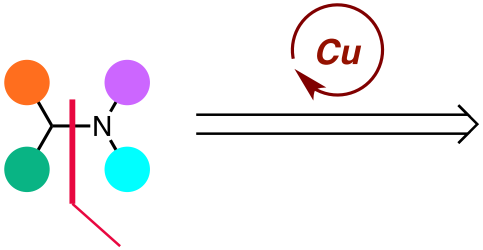
Construction C(sp^3)–N Bonds with Copper Catalysis



Yufan Liang
MacMillan Group Meeting
July 06, 2017

C(sp²)–N Bond Formation

Buchwald-Hartwig reaction

aryl halide *N*-nucleophile

Ullman coupling

aryl halide *N*-nucleophile

Chan-Evans-Lam coupling

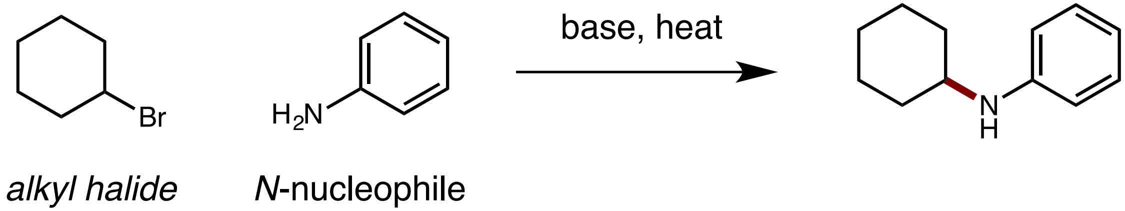
aryl boronic acid *N*-nucleophile

Buchwald **Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions** *Chem. Rev.* **2016**, *116*, 12564–12649.

Beletskaya **The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions** *Organometallics* **2012**, *31*, 7753–7808.

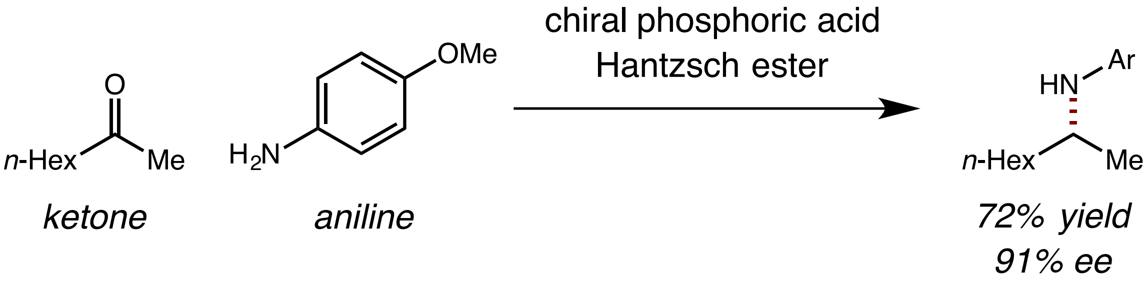
C(sp^3)–N Bond Formation: Other Classic Methods

Nucleophillic substitution



- Overalkylation
- Elimination
- Harsh conditions

Reductive amination



- Sensitive to sterically bulkyl substrates

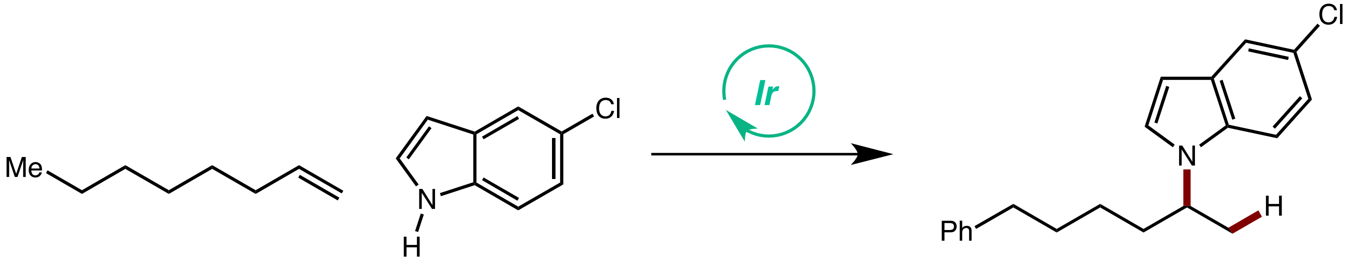
Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.
Kaga, A.; Chiba, S. *ACS Catal.* **2017**, *7*, 4697.

C(sp^3)–N Bond Formation: Transition-Metal Other than Copper

Other transition-metal catalysts

Ar = 3-CF$_3$-Ph

78% yield



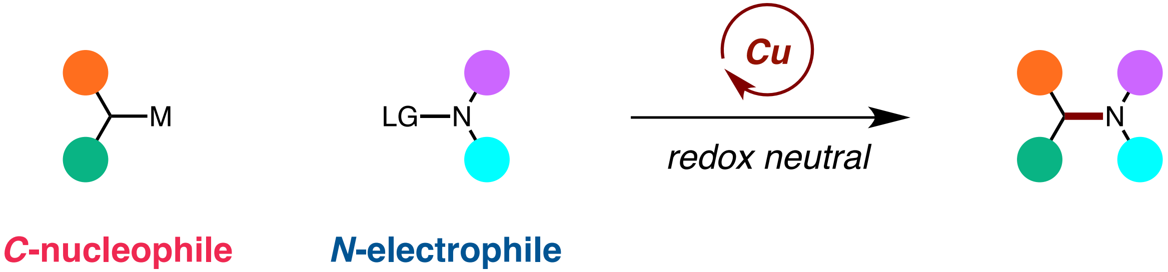
87% yield
>20:1 r.r.

74% yield
>20:1 r.r.

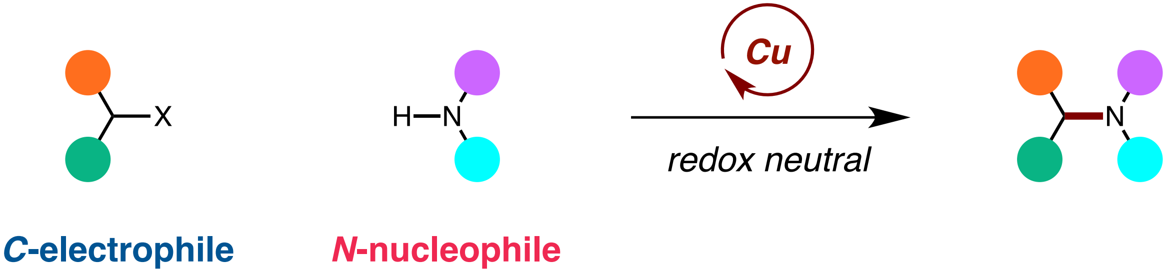
Peacock, D. M.; Roos, C. B.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 647.
Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200.
Ensign, S. C.; Vanable, E. P.; Kortman, G. D.; Weir, L. J.; Hull, K. L. *J. Am. Chem. Soc.* **2015**, *137*, 13748.

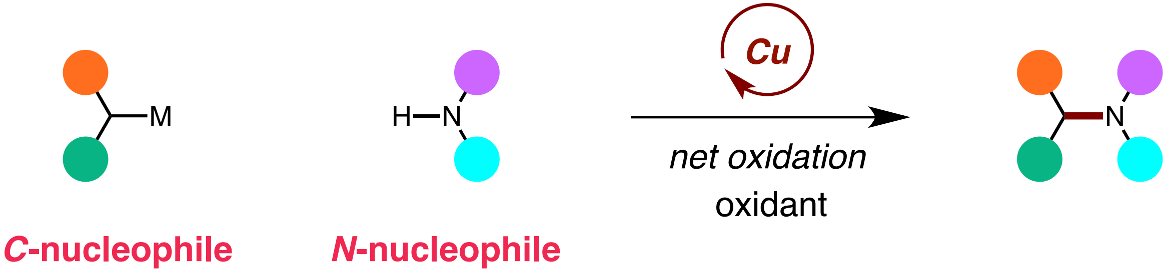
Outline

■ *N*-electrophiles



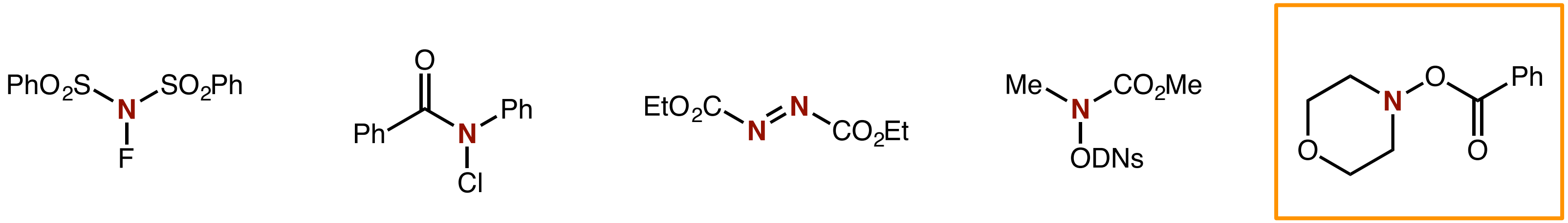
■ *N*-nucleophiles



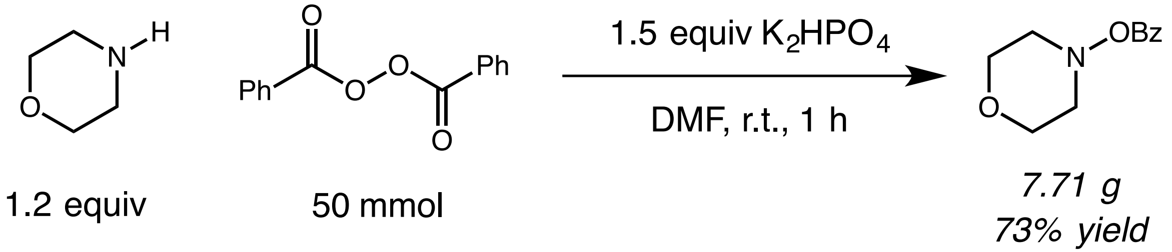


Electrophillic Aminating Reagents

Commonly used *N*-electrophiles



O-Benzoyl Hydroxylamines

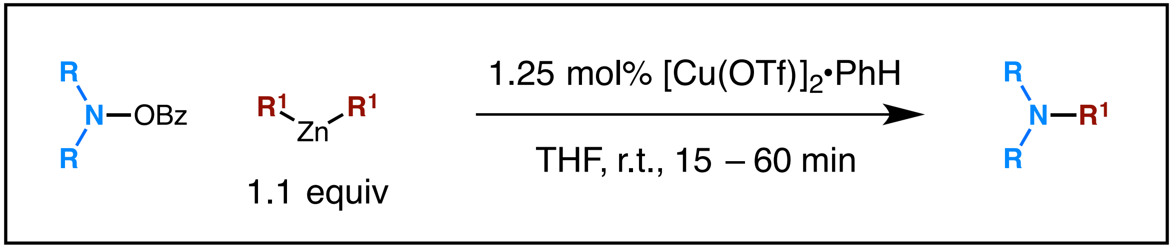


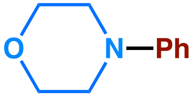
- Applicable to 1° and 2° amines
- Hinderd substrates also work (such as (*i*-Pr)$_2$NH)
- Bench stable compound, can be purifived via chromatography
- Not applicable to certain *N*-heterocycles

Starkov, P.; Jamison, T. F.; Marek, I. *Chem. Eur. J.* **2015**, *21*, 5278.
Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.

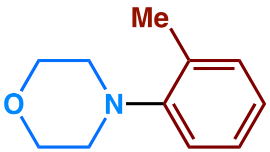
Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

- Seminal report from Prof. Jeffery Johnson in 2004

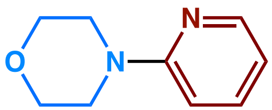




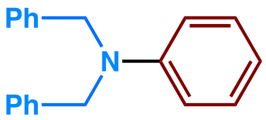
91% yield



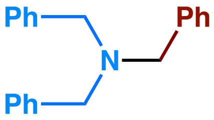
94% yield



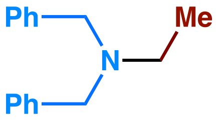
71% yield



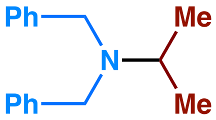
94% yield



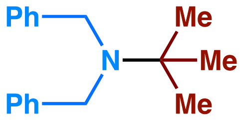
91% yield



91% yield



77% yield

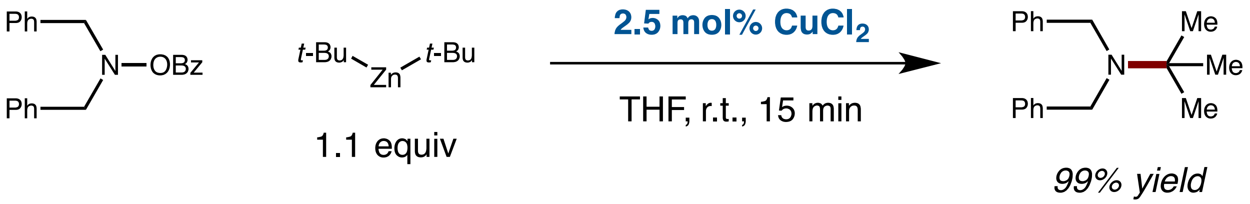


98% yield

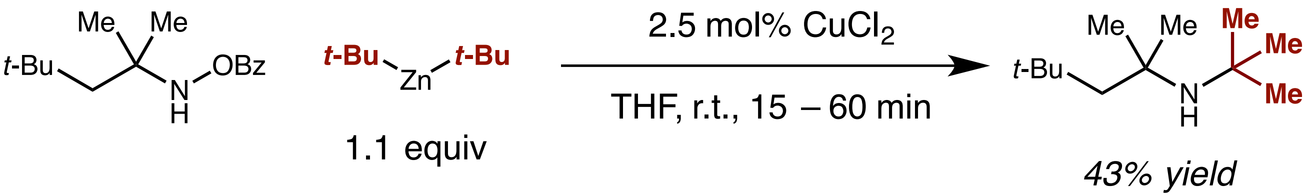
Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680.

Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

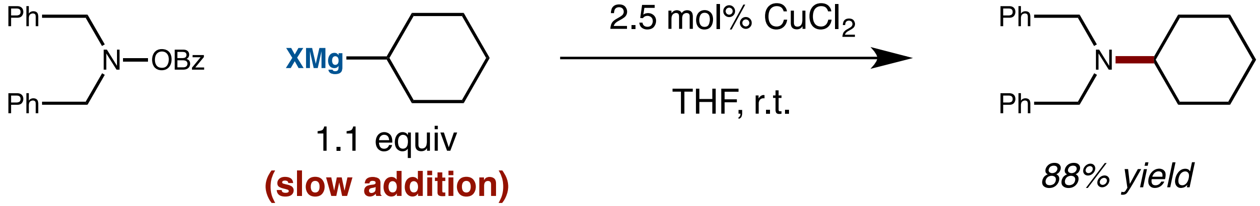
- Employing Cu(II) catalyst



- Primary amine N-OBz derivative



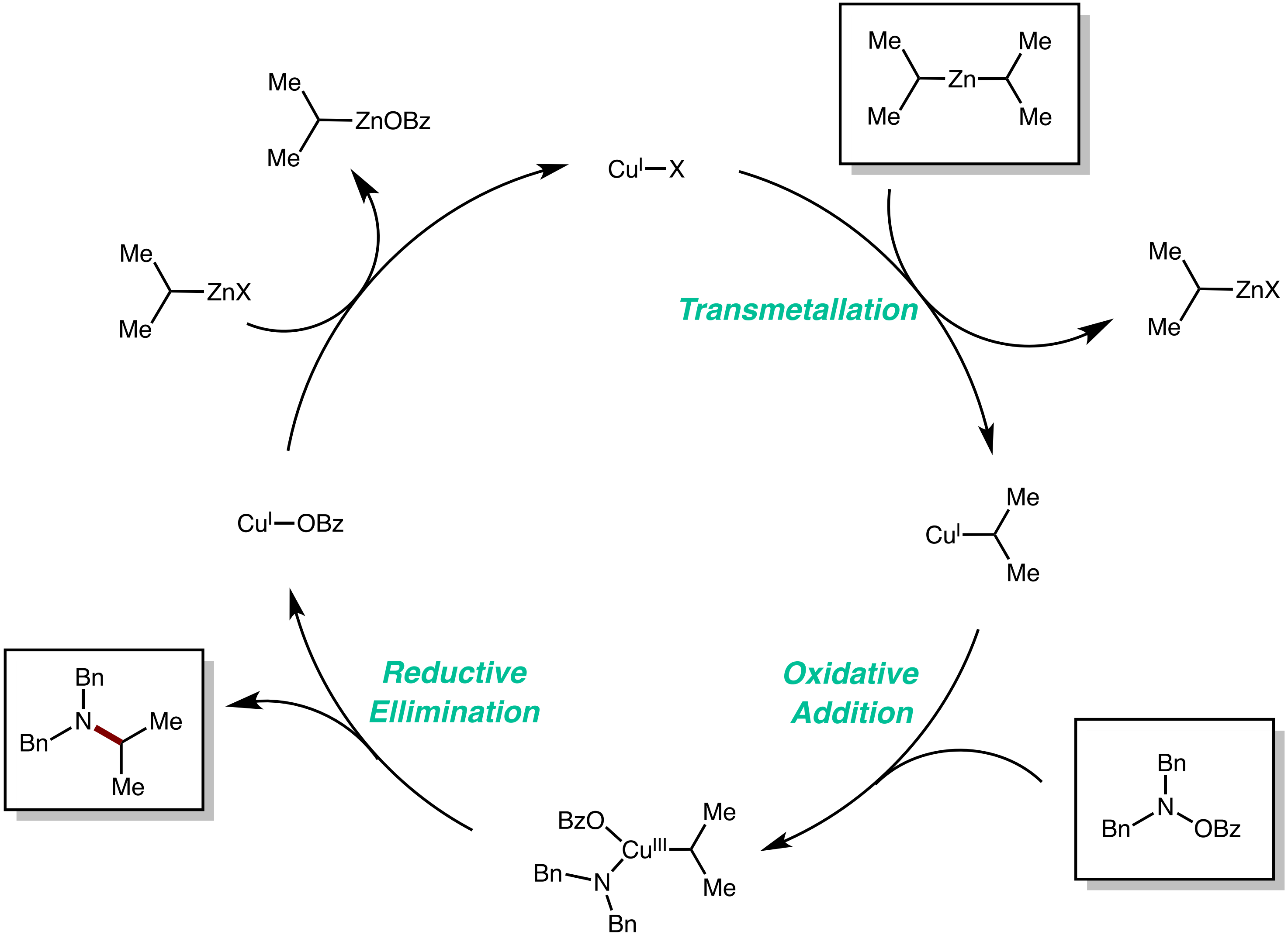
- Grignard reagents as nucleophiles



Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219.
Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

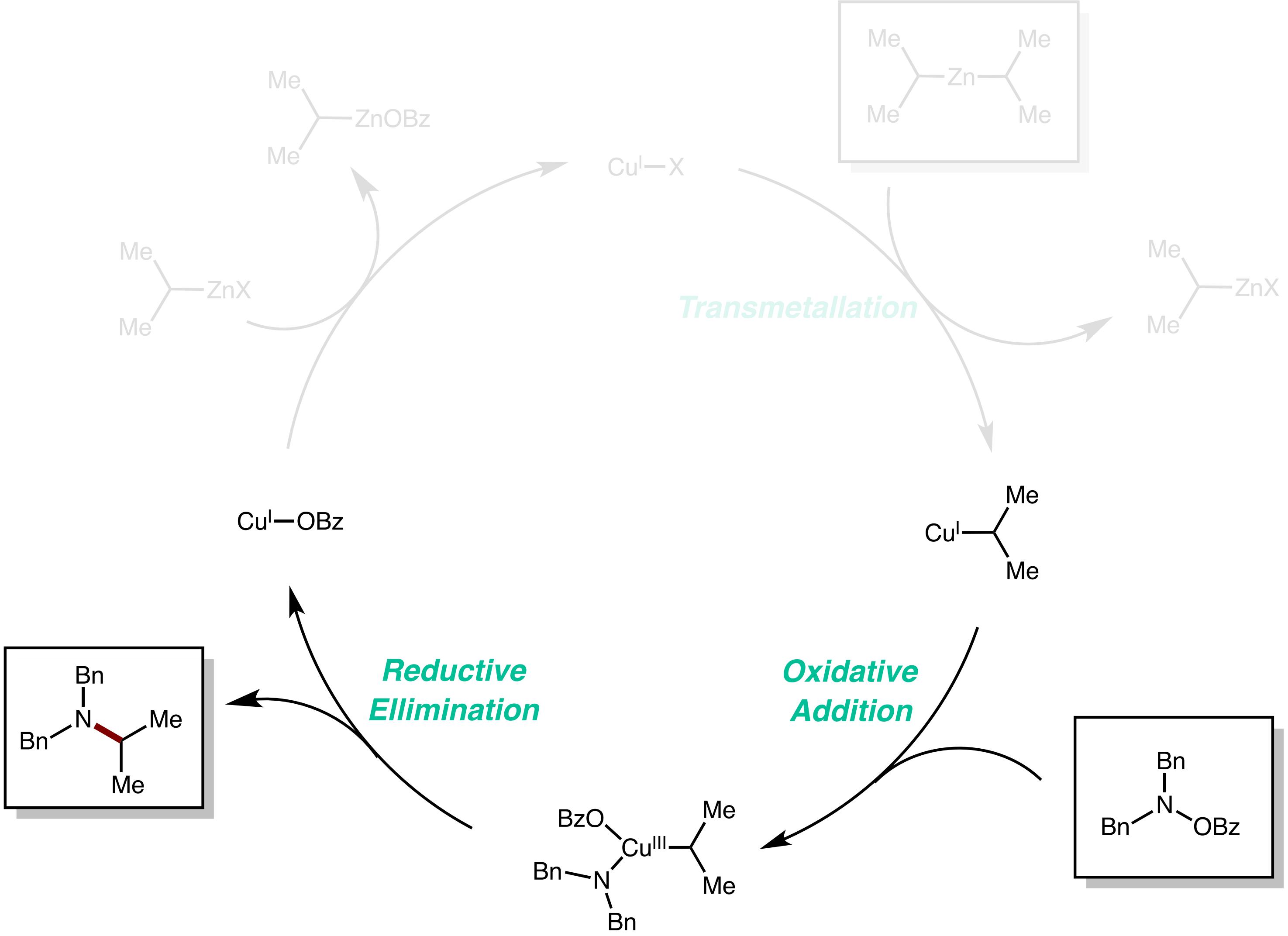
Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

- One possible catalytic cycle involves Cu^I/Cu^{III}



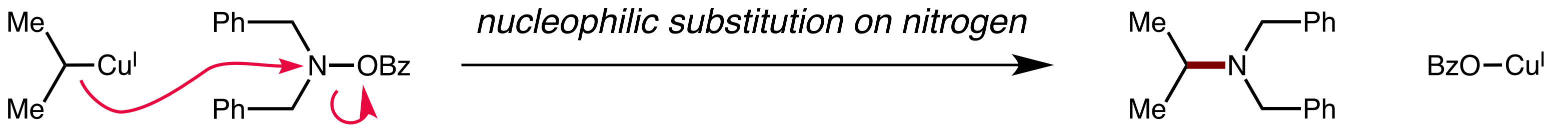
Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

- One possible catalytic cycle involves Cu^I/Cu^{III}

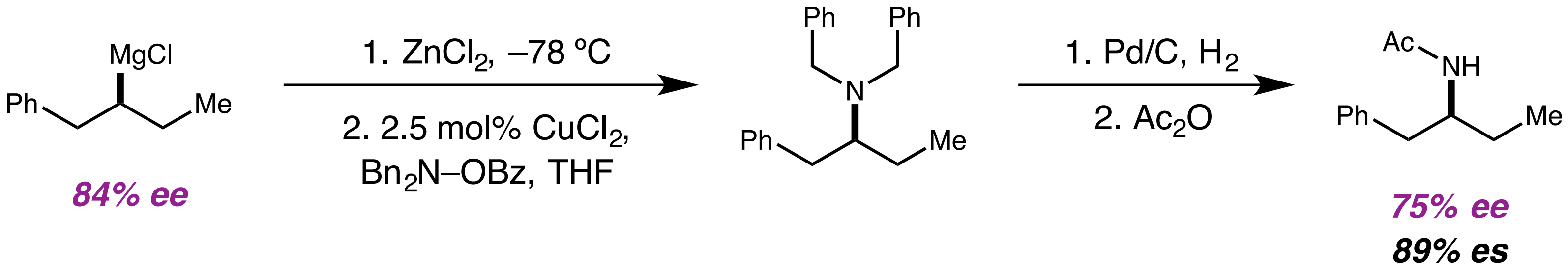


Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

An alternative C–N formation mechanism



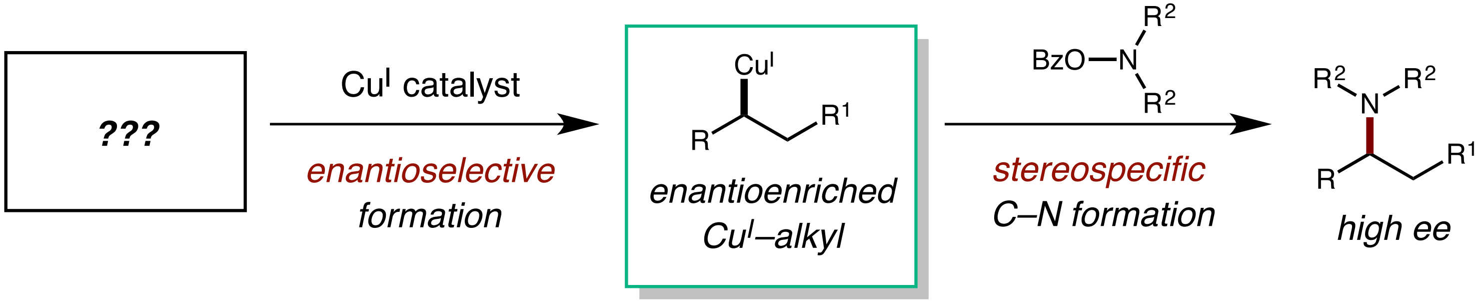
Stereospecific C–N formation step



Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

Enantioselective C–N formation



???

Cu^I catalyst

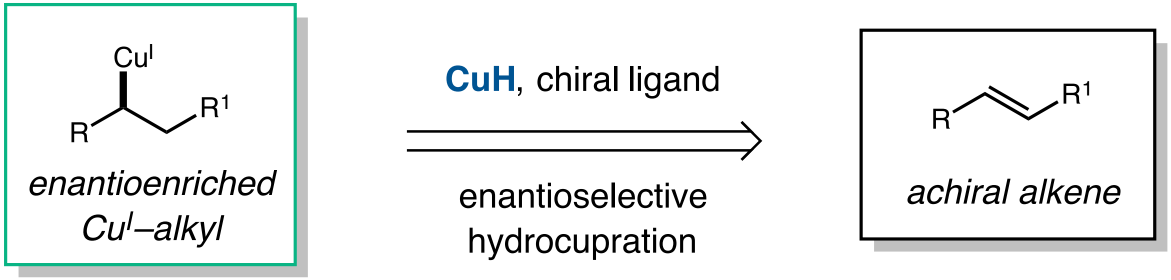
enantioselective formation

enantioenriched Cu^I–alkyl

stereospecific C–N formation

high ee

Enantioselective CuH-catalyzed hydrocupration



enantioenriched Cu^I–alkyl

CuH, chiral ligand

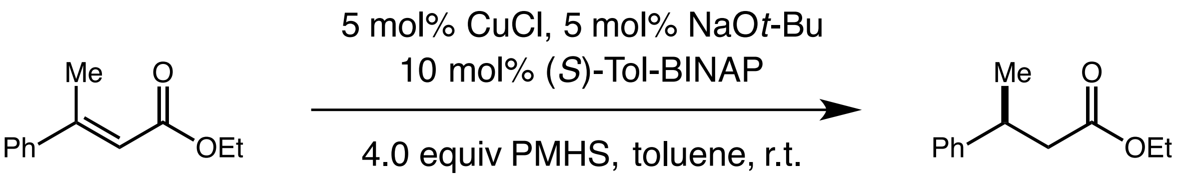
enantioselective hydrocupration

achiral alkene

Pirnot, M. T. Wang, Y.-M. Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48.

Copper-Catalyzed C–N Formation Using N-OBz Electrophiles

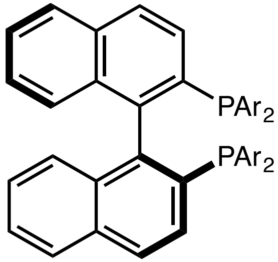
■ Enantioselective CuH-catalyzed hydrocuperation



5 mol% CuCl, 5 mol% NaO*t*-Bu
10 mol% (*S*)-Tol-BINAP

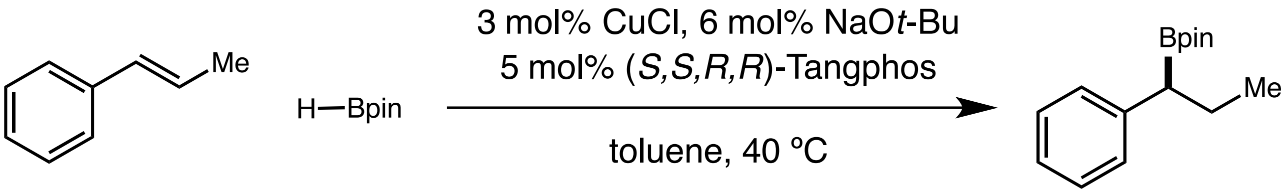
4.0 equiv PMHS, toluene, r.t.

*85% yield, **90% ee***



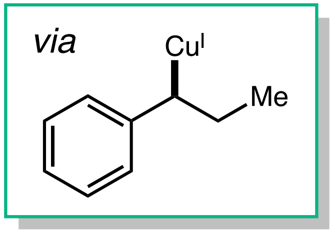
Ar = 4-MeC_6H_4
(*S*)-Tol-BINAP

■ Enantioselective Cu-catalyzed hydroboration

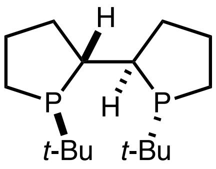


3 mol% CuCl, 6 mol% NaO*t*-Bu
5 mol% (*S,S,R,R*)-Tangphos

toluene, 40 °C



*71% yield, **95% ee***

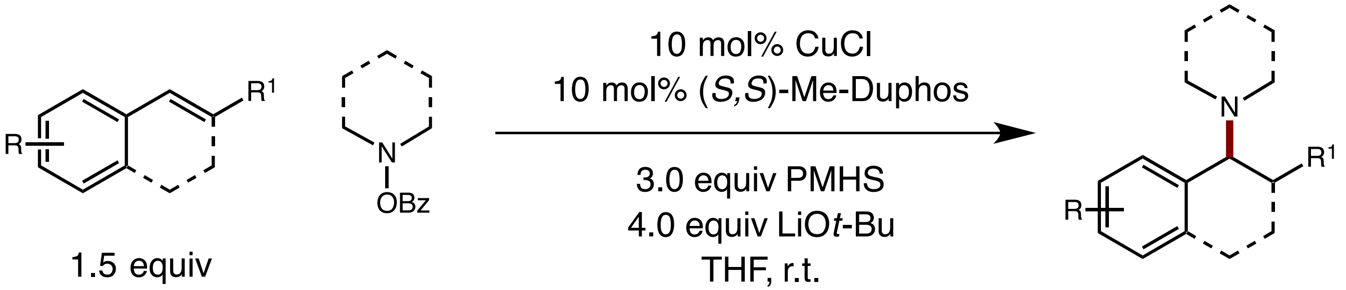


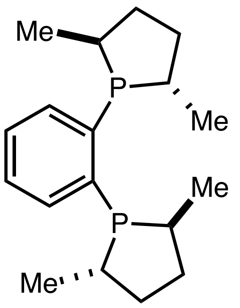
(*S,S,R,R*)-Tangphos

Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473.
Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6062

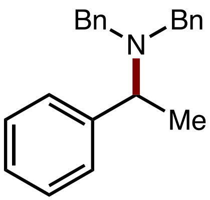
Enantioselective CuH-Catalyzed Hydroamination

■ Seminal report by Prof. Masahiro Miura

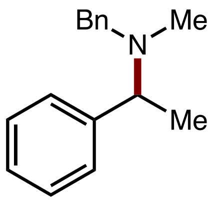




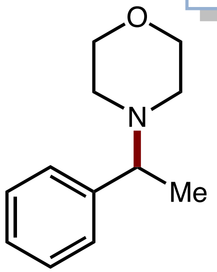
(*S,S*)-Me-Duphos



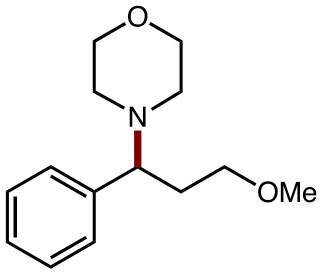
65% yield, ***74% ee***



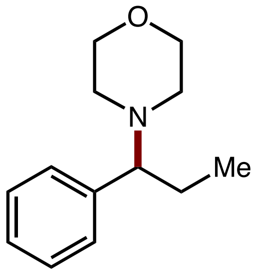
76% yield, ***86% ee***



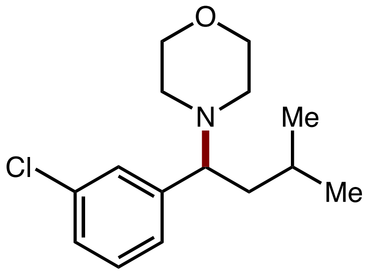
82% yield, ***76% ee***



66% yield, ***86% ee***



50% yield, ***90% ee***

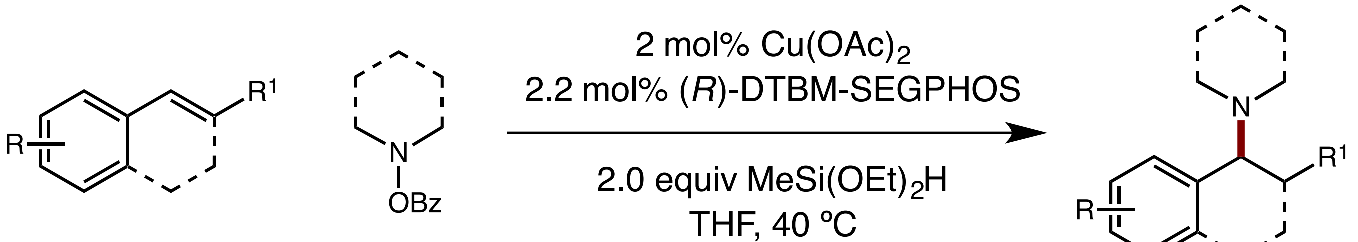


51% yield, ***66% ee***

Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830.

Enantioselective CuH-Catalyzed Hydroamination

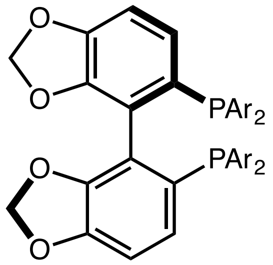
■ Seminal report by Prof. Steve Buchwald



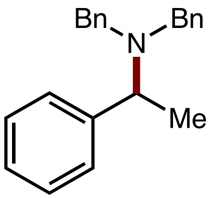
1.2 equiv

2 mol% $Cu(OAc)_2$
2.2 mol% (*R*)-DTBM-SEGPHOS

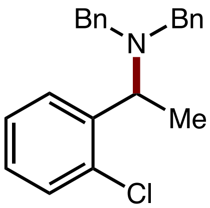
2.0 equiv $MeSi(OEt)_2H$
THF, 40 ºC



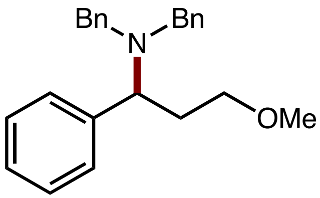
Ar = 3,5-*t*-Bu-4-MeOC_6H_2
(*R*)-DTBM-SEGPHOS



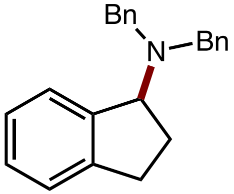
*91% yield, **96% ee***



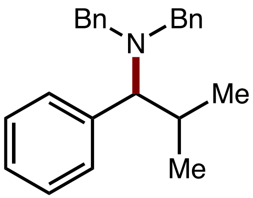
*86% yield, **92% ee***



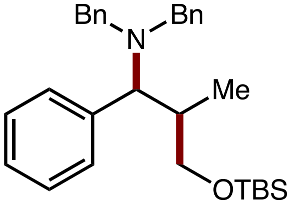
*95% yield, **98% ee***



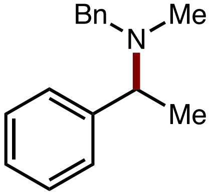
*84% yield, **97% ee***



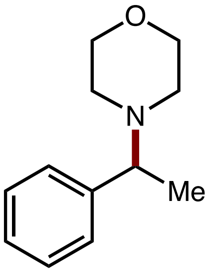
*77% yield, **>99% ee***



*83% yield, **>99% ee***
single diastereomer



*87% yield, **94% ee***

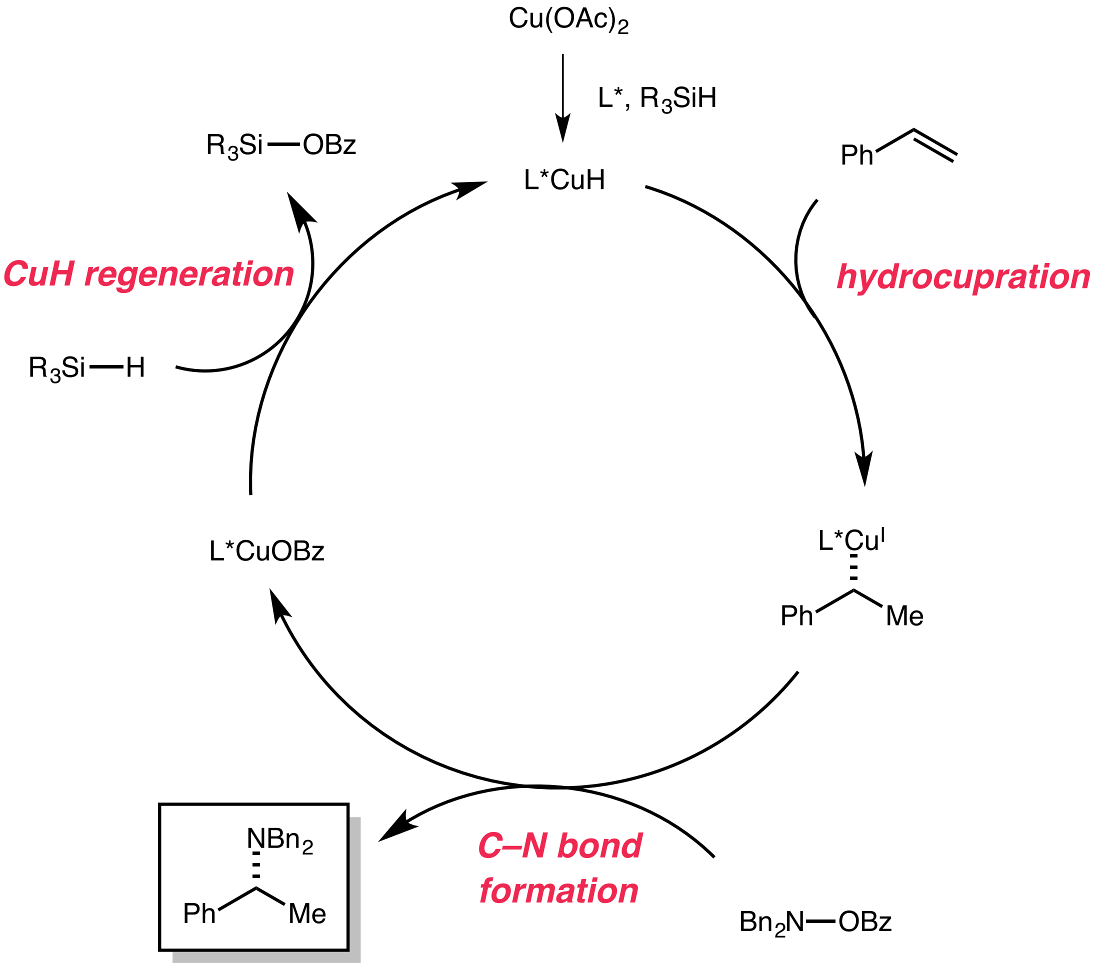


*87% yield, **95% ee***

Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746.

Enantioselective CuH-Catalyzed Hydroamination

Proposed catalytic cycle

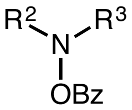


Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

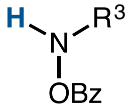
Enantioselective CuH-Catalyzed Hydroamination

alkene *amine derivative*

Amine derivative

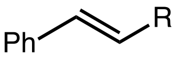


2° amine derivative

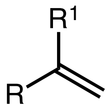


1° amine derivative

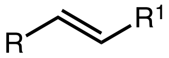
Alkene



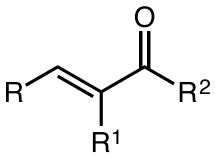
styrene



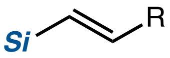
1,1-disubstitued alkene



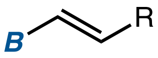
unactivated internal alkene



enal/enone



alkenylsilane

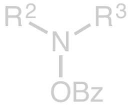


alkenylborate

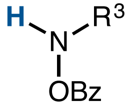
Enantioselective CuH-Catalyzed Hydroamination

alkene *amine derivative*

Amine derivative

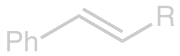


2° amine derivative

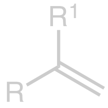


1° amine derivative

Alkene

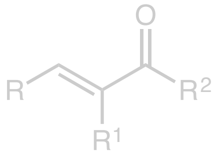


styrene

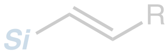


1,1-disubstitued alkene

unactivated internal alkene



enal/enone

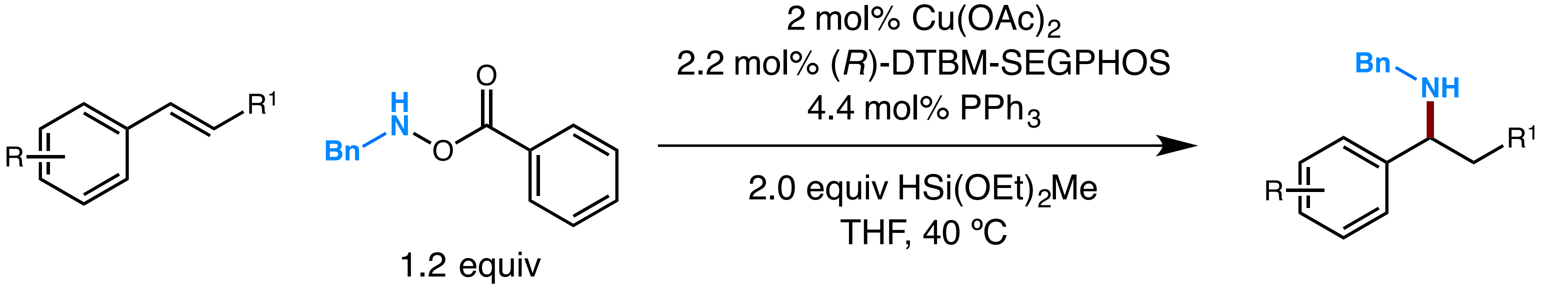


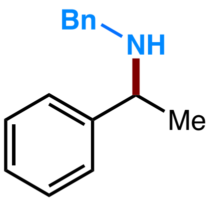
alkenylsilane

alkenylborate

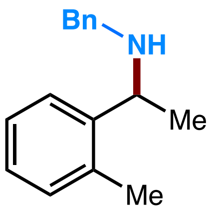
Enantioselective CuH-Catalyzed Hydroamination

■ Enantioselective hydroamination using 1° amine derivative

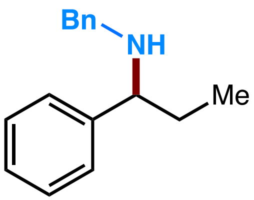




60% yield, 96% ee

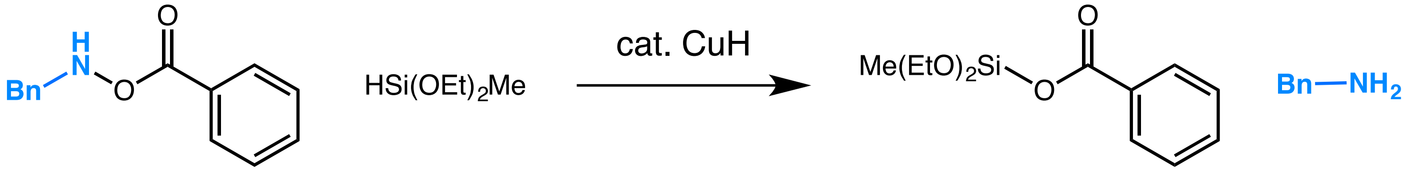


25% yield



<10% yield

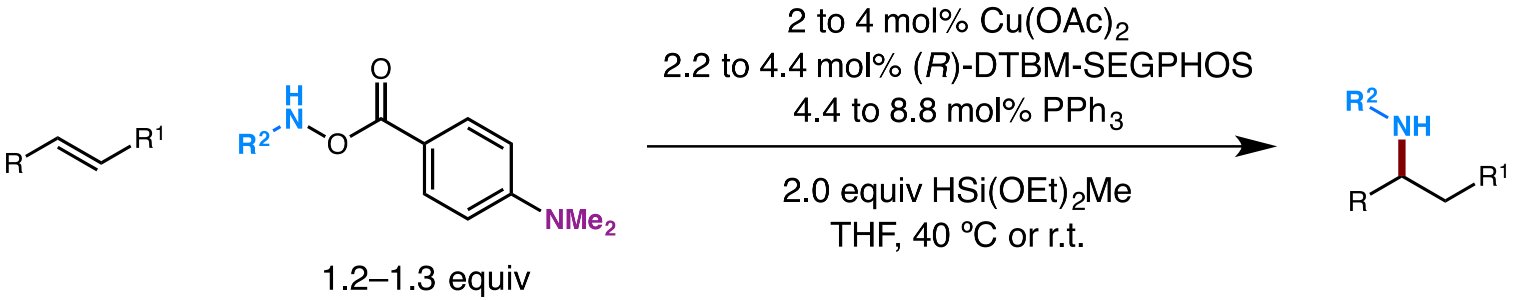
Competing side-reaction:



Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716.

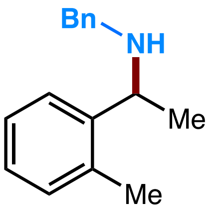
Enantioselective CuH-Catalyzed Hydroamination

- Modified amine transfer reagents

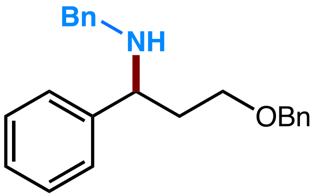

2 to 4 mol% $Cu(OAc)_2$
2.2 to 4.4 mol% (*R*)-DTBM-SEGPHOS
4.4 to 8.8 mol% PPh_3

2.0 equiv $HSi(OEt)_2Me$
THF, 40 ºC or r.t.

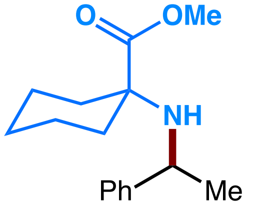
1.2–1.3 equiv



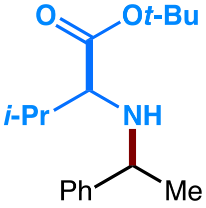
*84% yield, **94% ee***



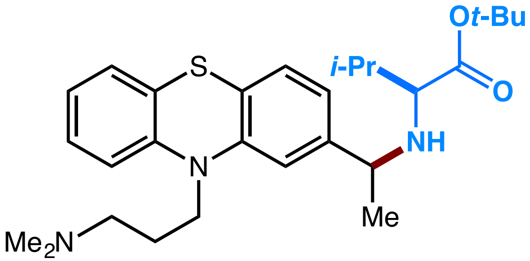
*88% yield, **96% ee***



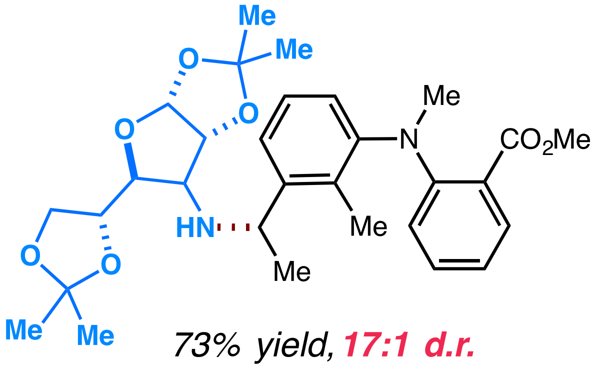
*92% yield, **95% ee***



*79% yield, **>20:1 d.r.***



*82% yield, **>20:1 d.r.***



*73% yield, **17:1 d.r.***

Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716.

Enantioselective CuH-Catalyzed Hydroamination

Competition experiments

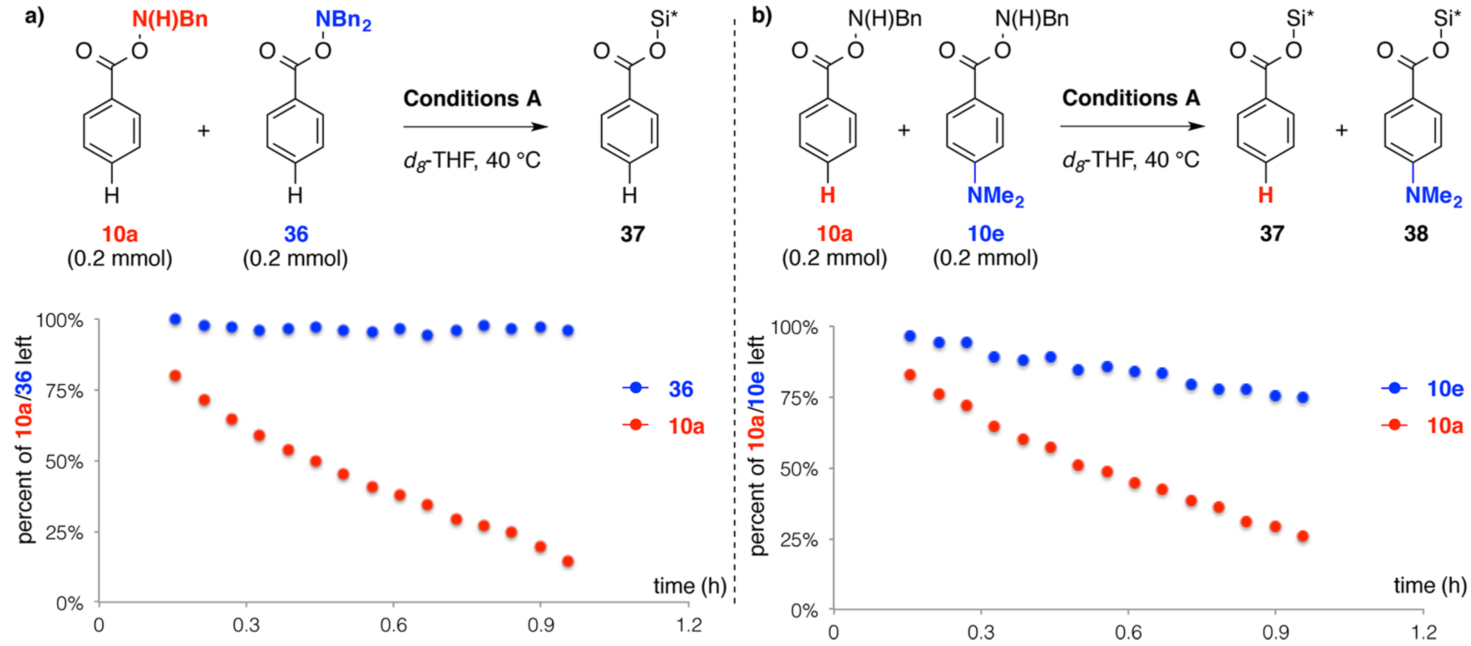


Figure 4. Relative rates of the reactions between LCuH and different amine transfer agents. Si* = $Si(OEt)_2Me$. **Conditions A**: a 0.6 mL of a stock solution made from $Cu(OAc)_2$ (3.6 mg), (*R*)-DTBM-SEGPHOS (26 mg), PPh_3 (11.6 mg), $HSi(OEt)_2Me$ (0.32 mL, 2.0 mmol), and THF-d_8 (1.0 mL) is used. The progress of these experiments was monitored by ^1H NMR.

- An electron-rich aromatic ring leads to more stable amine transfer reagents under CuH conditions

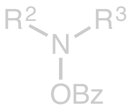
Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716.

Enantioselective CuH-Catalyzed Hydroamination

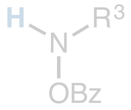
alkene

amine derivative

Amine derivative

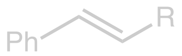


2° amine derivative

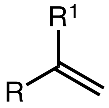


1° amine derivative

Alkene

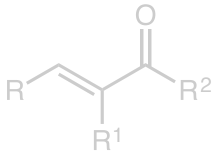


styrene

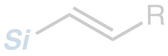


1,1-disubstitued alkene

unactivated internal alkene



enal/enone

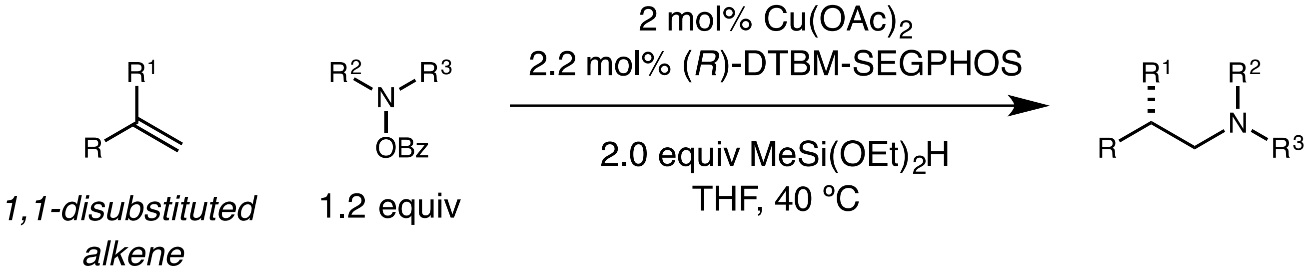


alkenylsilane

alkenylborate

Enantioselective CuH-Catalyzed Hydroamination

■ 1,1-Disubstituted alkenes as substrates

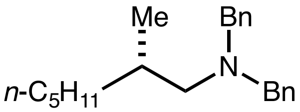


1,1-disubstituted alkene

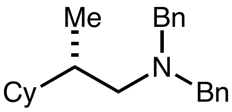
1.2 equiv

2 mol% $Cu(OAc)_2$
2.2 mol% (*R*)-DTBM-SEGPHOS

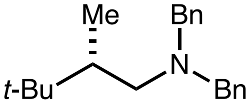
2.0 equiv $MeSi(OEt)_2H$
THF, 40 °C



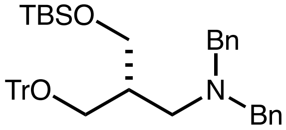
90% yield, ***59% ee***



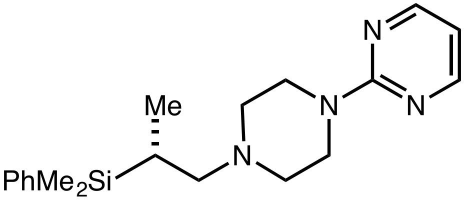
88% yield, ***95% ee***



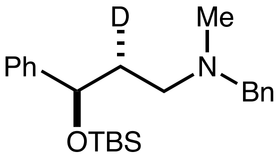
86% yield, ***92% ee***



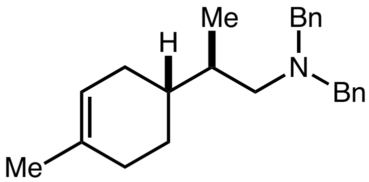
94% yield, ***77% ee***



90% yield, ***96% ee***



86% yield, ***12:1 d.r.***
*with (S)-**L**, 85% yield,* ***1:15 d.r.***



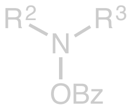
96% yield, ***14:1 d.r.***
*with (S)-**L**, 92% yield,* ***1:17 d.r.***

Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913.

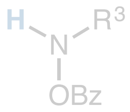
Enantioselective CuH-Catalyzed Hydroamination

alkene *amine derivative*

Amine derivative

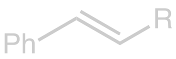


2° amine derivative

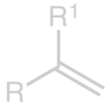


1° amine derivative

Alkene

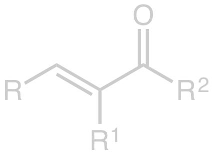


styrene

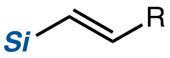


1,1-disubstitued alkene

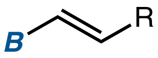
unactivated internal alkene



enal/enone



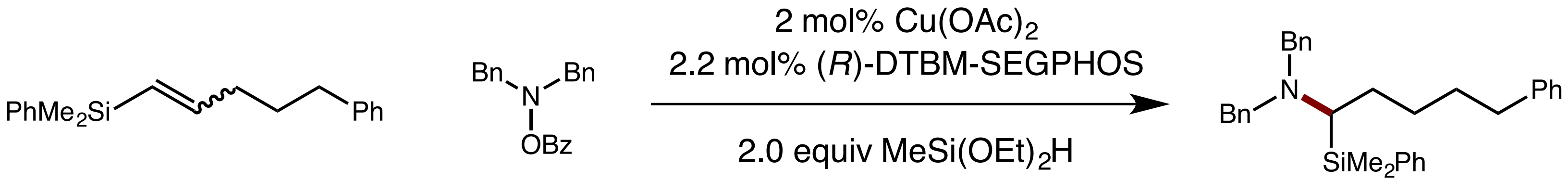
alkenylsilane



alkenylborate

Enantioselective CuH-Catalyzed Hydroamination

■ Alkenylsilanes as substrates



2 mol% Cu(OAc)$_2$
2.2 mol% (*R*)-DTBM-SEGPHOS

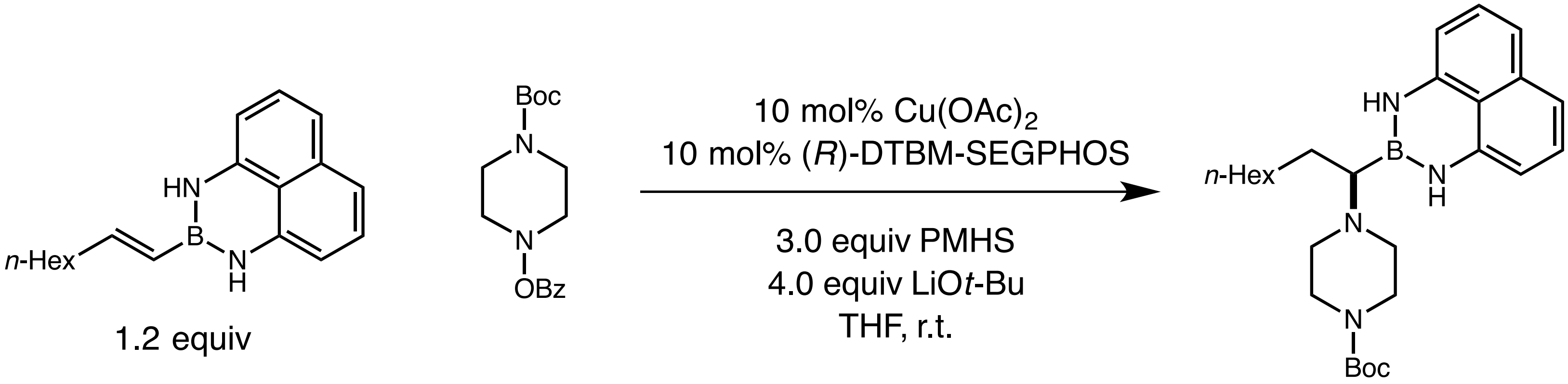
2.0 equiv MeSi(OEt)$_2$H
THF, 40 °C

(Z)- or (E)-alkenylsilanes

1.2 equiv

*(Z)-SM, 80% yield, **93% ee***
*(E)-SM, 92% yield, **99% ee***

■ Alkenylborates as substrates



10 mol% Cu(OAc)$_2$
10 mol% (*R*)-DTBM-SEGPHOS

3.0 equiv PMHS
4.0 equiv LiO*t*-Bu
THF, r.t.

1.2 equiv

*81% yield, **97% ee***

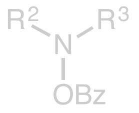
Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638.
Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620.

Enantioselective CuH-Catalyzed Hydroamination

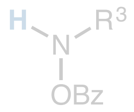
alkene

amine derivative

Amine derivative

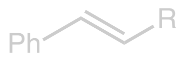


2° amine derivative

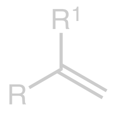


1° amine derivative

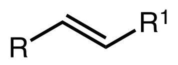
Alkene



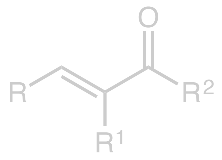
styrene



1,1-disubstitued alkene

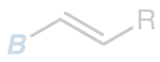


unactivated internal alkene



enal/enone

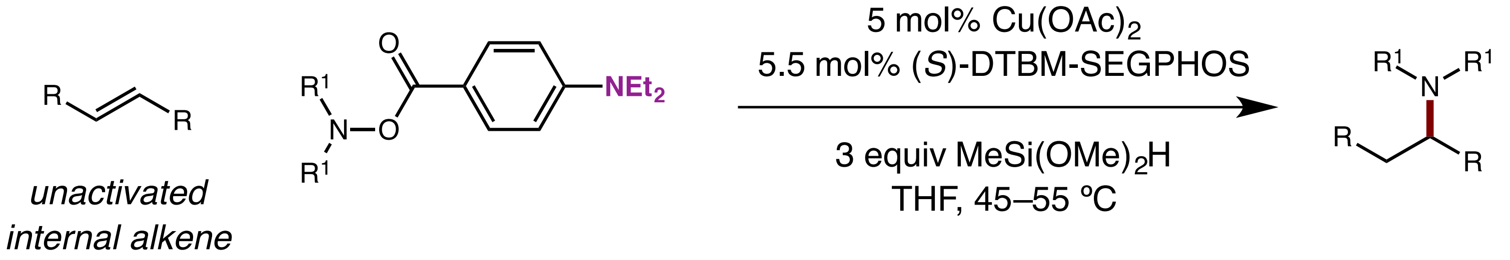
alkenylsilane



alkenylborate

Enantioselective CuH-Catalyzed Hydroamination

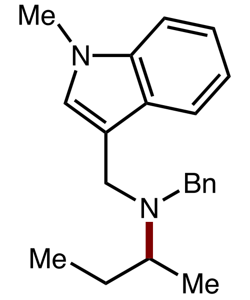
Unactivated internal alkenes



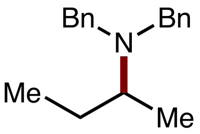
5 mol% $Cu(OAc)_2$
5.5 mol% (*S*)-DTBM-SEGPHOS

3 equiv $MeSi(OMe)_2H$
THF, 45–55 ºC

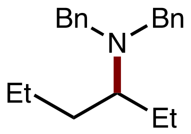
unactivated internal alkene



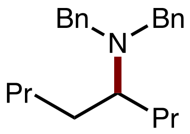
*76% yield, **97% ee***



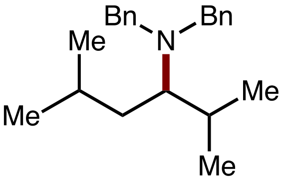
*76% yield, **98% ee***



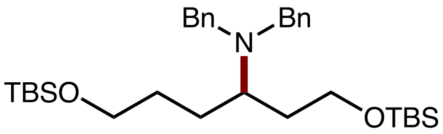
*83% yield, **98% ee***



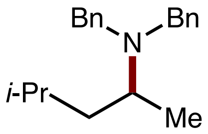
*82% yield, **98% ee***



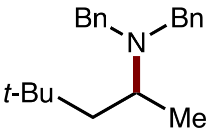
*65% yield, **99% ee***



*94% yield, **97% ee***



*70% yield, **99% ee***
rr = 82:18



*66% yield, **99% ee***
rr = 85:15

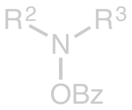
Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.

Enantioselective CuH-Catalyzed Hydroamination

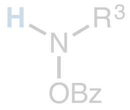
alkene

amine derivative

Amine derivative

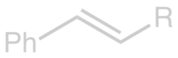


2° amine derivative

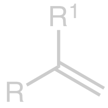


1° amine derivative

Alkene

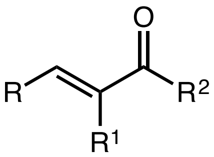


styrene

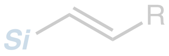


1,1-disubstitued alkene

unactivated internal alkene



enal/enone

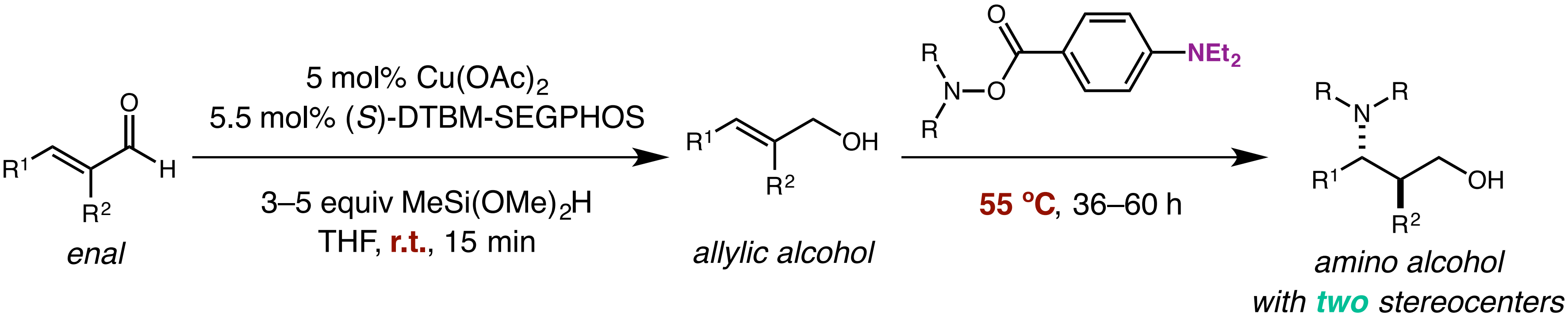


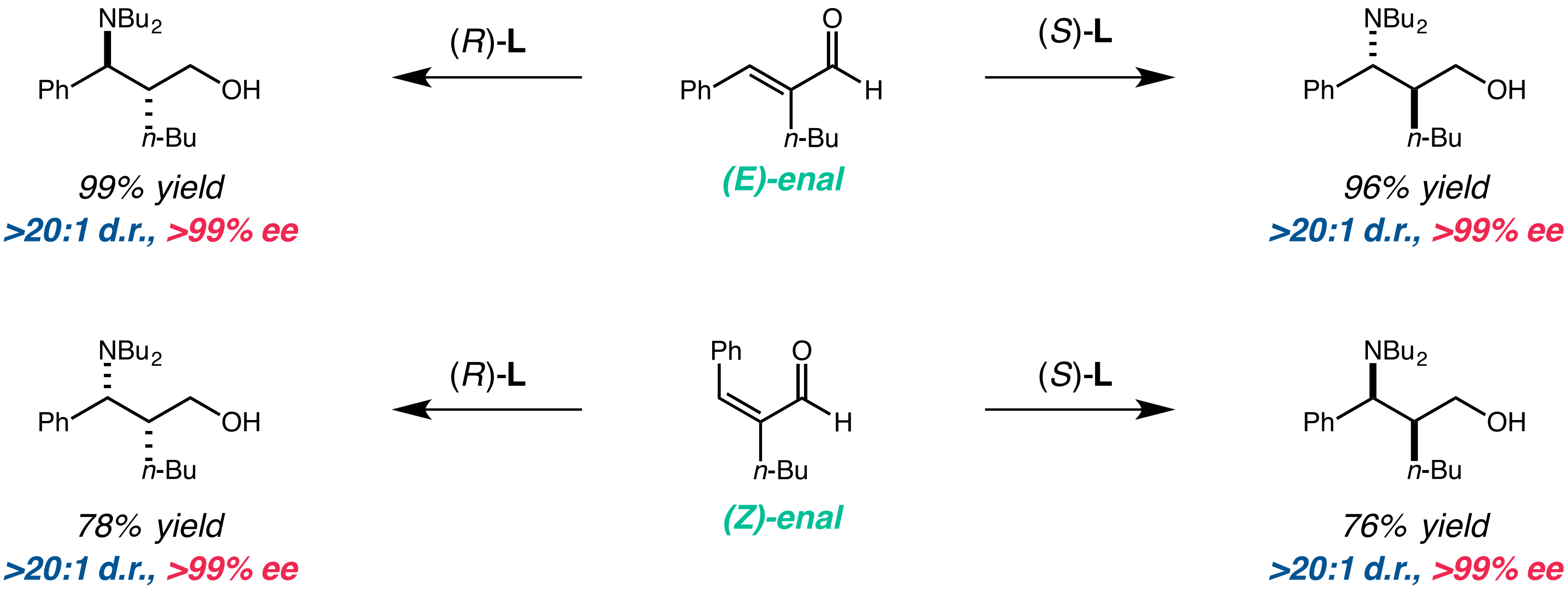
alkenylsilane

alkenylborate

Enantioselective CuH-Catalyzed Hydroamination

- Enal as substrate: stereodivergent synthesis of all diastereomers

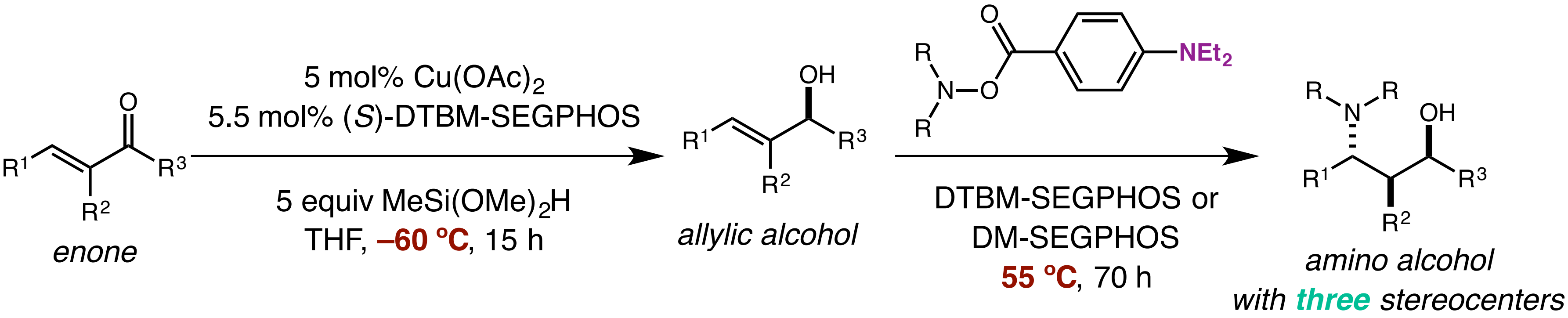


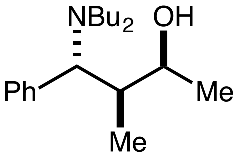


Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353

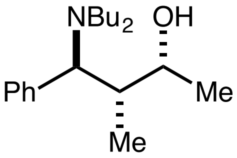
Enantioselective CuH-Catalyzed Hydroamination

- Enone as substrate: stereodivergent synthesis of all diastereomers

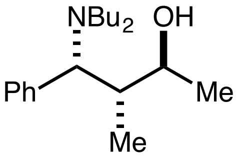




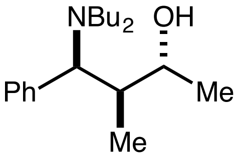
76% yield
>20:1 d.r., >99% ee



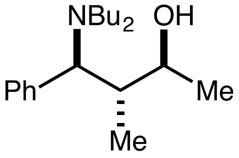
75% yield
>20:1 d.r., >99% ee



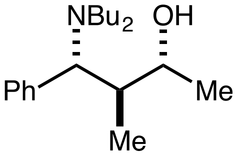
64% yield
>20:1 d.r., >99% ee



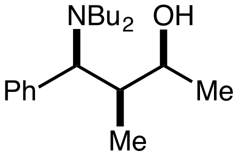
62% yield
>20:1 d.r., >99% ee



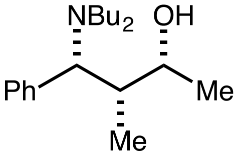
60% yield
13:1 d.r., >99% ee



61% yield
13:1 d.r., >99% ee



33% yield
7:1 d.r., >99% ee

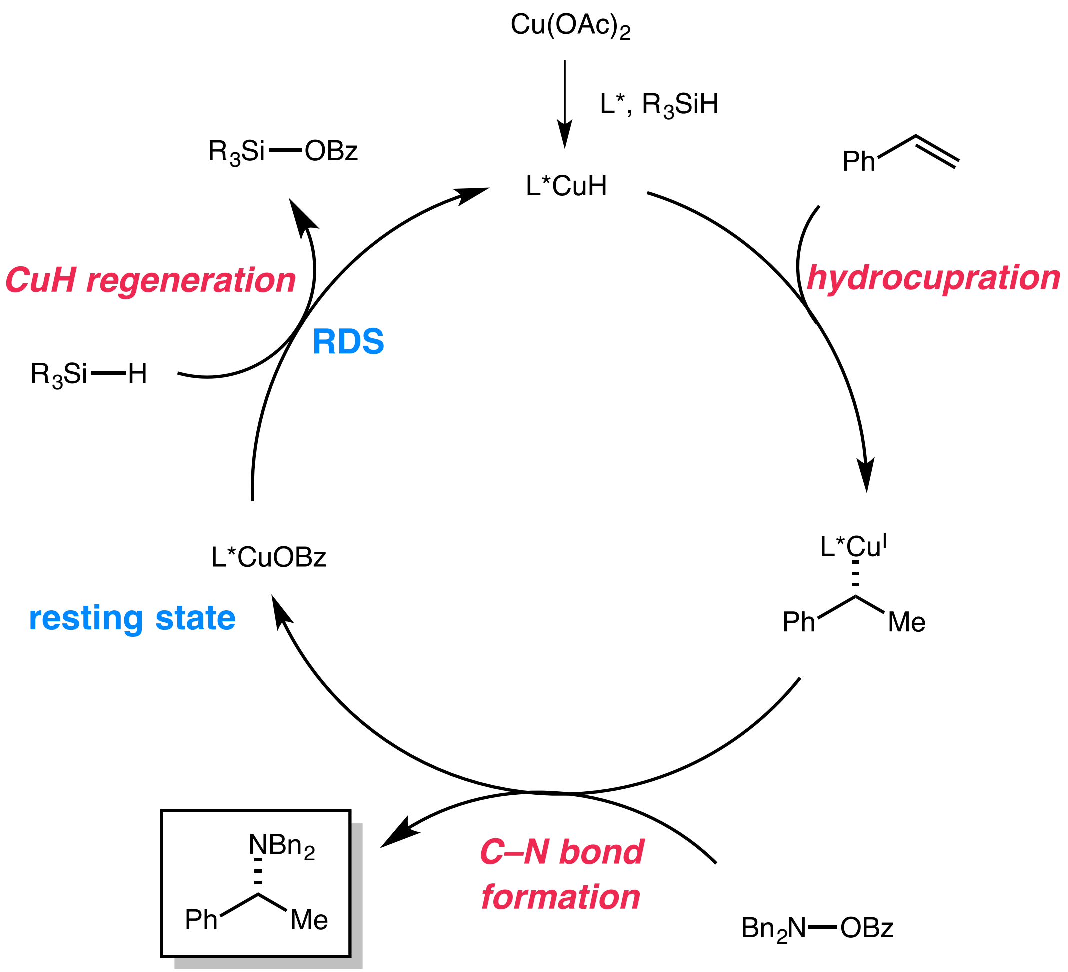


33% yield
7:1 d.r., >99% ee

Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353

Enantioselective CuH-Catalyzed Hydroamination

Mechanistic studies: proposed catalytic cycle



Kinetics:

- Zero order in alkene and Bn_2NOBz
- First order in silane
- Fractional order in $Cu(OAc)_2$+**L**

Resting state

- ^{31}P NMR shows that resting state of catalyst is **L*CuOBz**

Nonlinear effect

- Active catalyst is a monomeric species

Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Enantioselective CuH-Catalyzed Hydroamination

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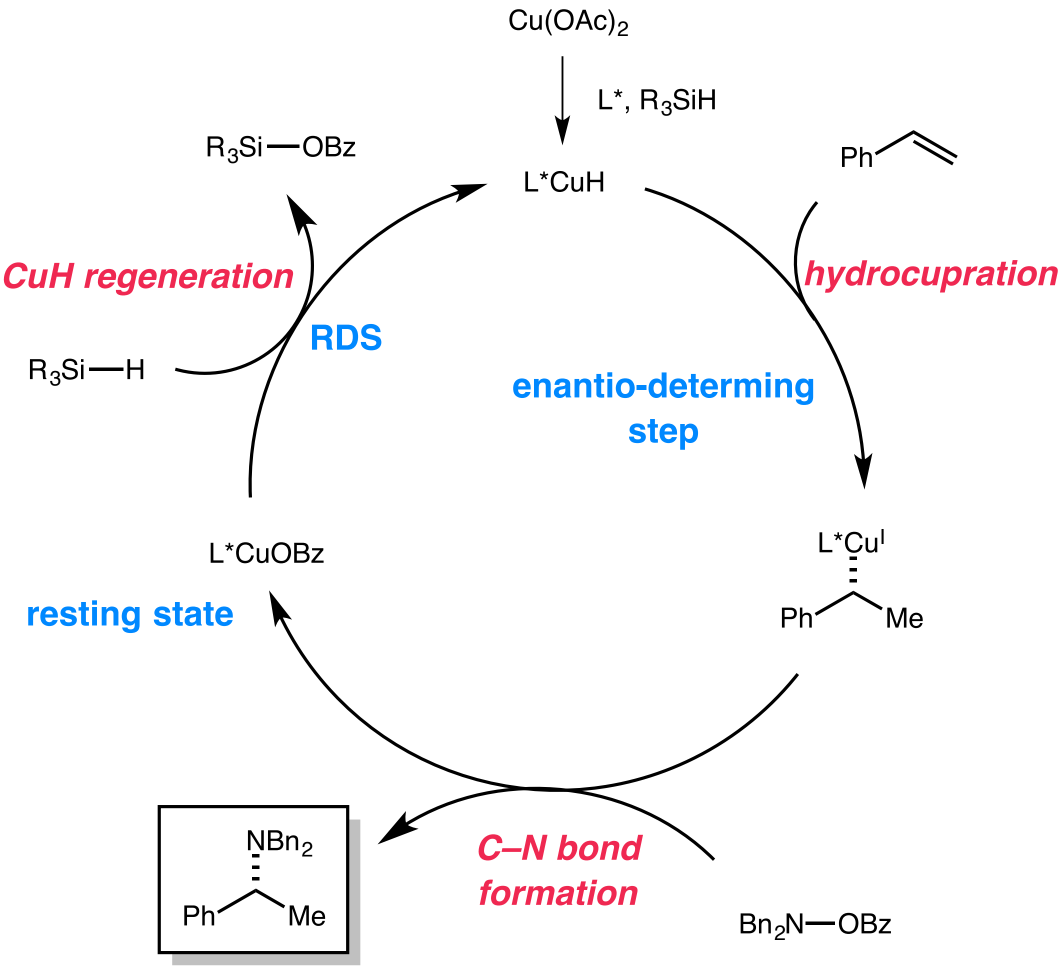

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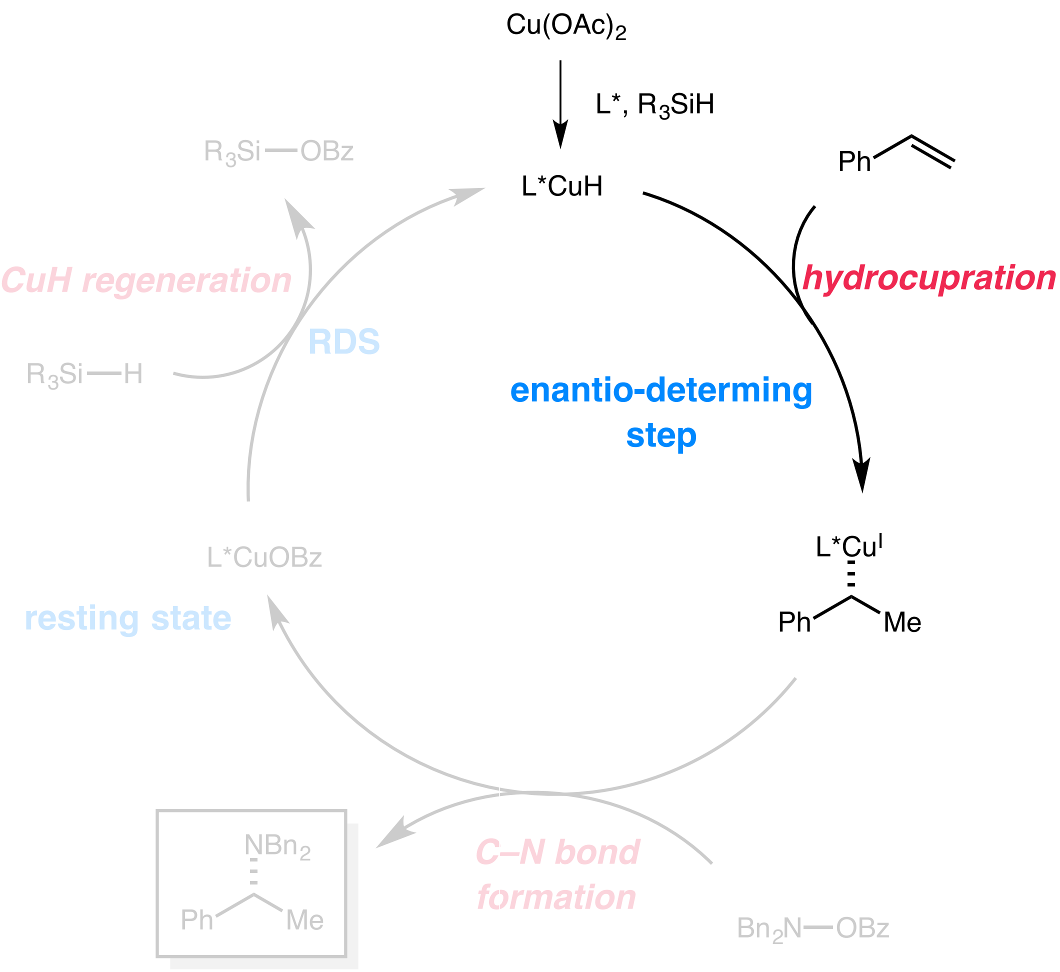
Electronic effect on styrene
- E-deficient styrene gives lower *ee*
- Electronic effect on styrene has no effect on reaction rate

Other observations:
- Different silanes give similar *ee*
- Different carboxylates of amine give similar *ee*

Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Enantioselective CuH-Catalyzed Hydroamination

Mechanistic studies: proposed catalytic cycle



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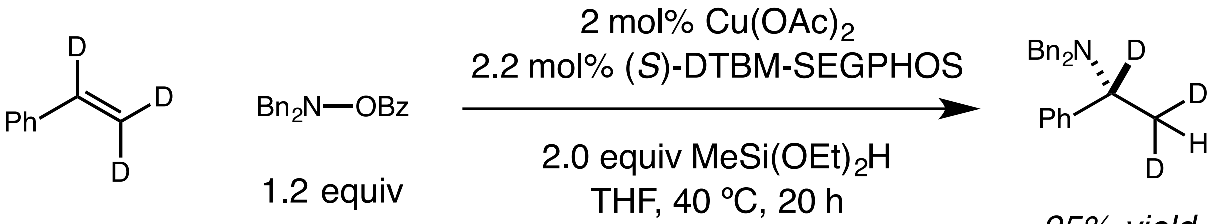
Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Enantioselective CuH-Catalyzed Hydroamination

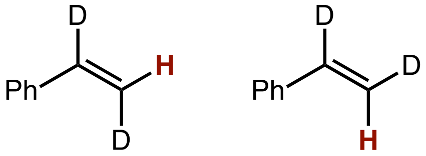
- Hydrocupration: enantio-determing step, irreversible



1.2 equiv

95% yield

Not observed:



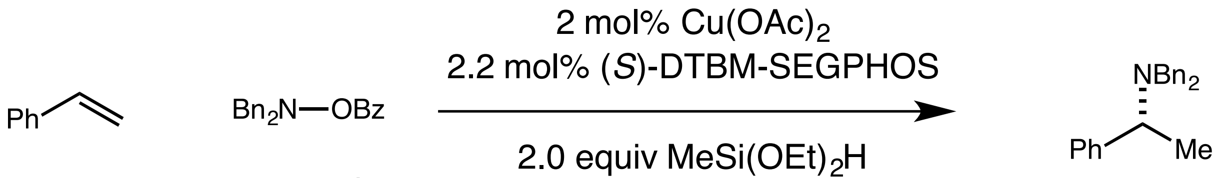
CuH hydrocupration:

- Enantio-determing step
- Irreversible
- No β-hydride elimination
- No chain-walking

Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Enantioselective CuH-Catalyzed Hydroamination

First-generation condition



Bn_2N—OBz

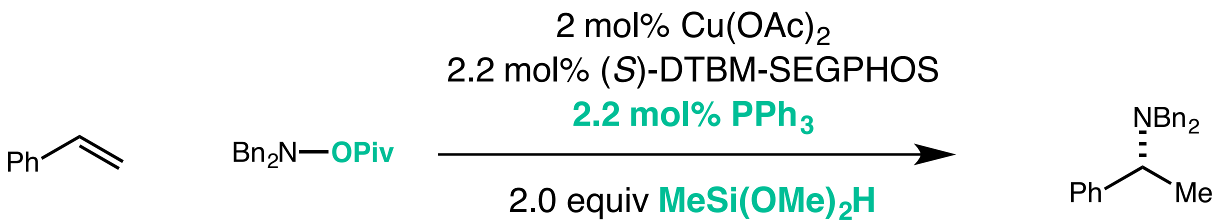
1.2 equiv

2 mol% $Cu(OAc)_2$
2.2 mol% (*S*)-DTBM-SEGPHOS

2.0 equiv $MeSi(OEt)_2H$
THF, 40 ºC, **9 h**

91% yield, ***96% ee***

Second-generation condition



Bn_2N—**OPiv**

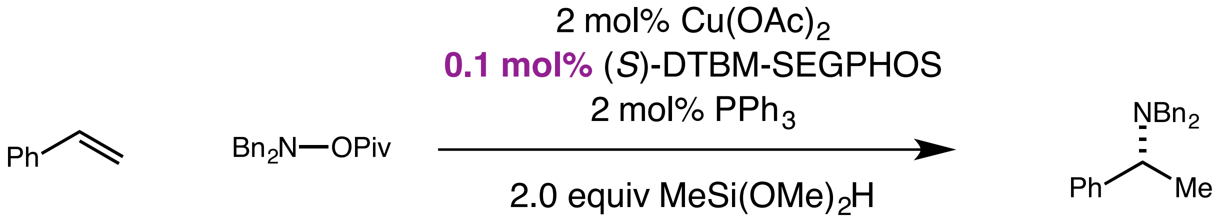
1.2 equiv

2 mol% $Cu(OAc)_2$
2.2 mol% (*S*)-DTBM-SEGPHOS
2.2 mol% PPh_3

2.0 equiv **$MeSi(OMe)_2H$**
THF, 40 ºC, **1 h**

99% yield, ***96% ee***

Low-loading chiral ligand



Bn_2N—OPiv

1.2 equiv

2 mol% $Cu(OAc)_2$
0.1 mol% (*S*)-DTBM-SEGPHOS
2 mol% PPh_3

2.0 equiv $MeSi(OMe)_2H$
THF, 60 ºC, **24 h**

88% yield, ***92% ee***

Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Enantioselective CuH-Catalyzed Hydroamination

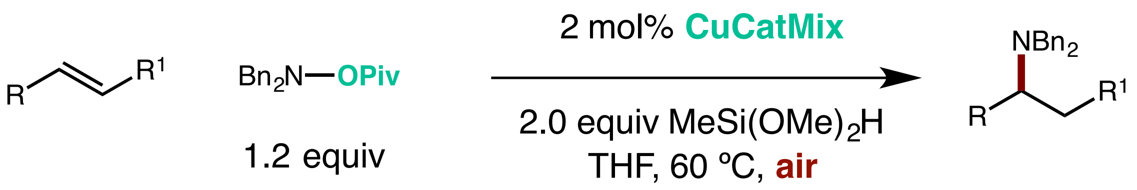
■ Preparation of precatalyst

$\mathrm{Cu(OAc)_2}$ (*S*)-DTBM-SEGPHOS $\mathrm{PPh_3}$ $\xrightarrow{\text{THF, r.t., 30 min}}$ **CuCatMix**

1.1 equiv 1.1 equiv

air-stable free-flowing powder

■ Under air conditions with CuCatMix

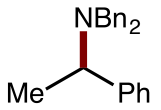


1.2 equiv

2 mol% **CuCatMix**

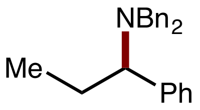
2.0 equiv $\mathrm{MeSi(OMe)_2H}$

THF, 60 ºC, **air**



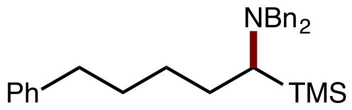
*91% yield, **95% ee***

10 min



*89% yield, **98% ee***

20 min



*88% yield, **99% ee***

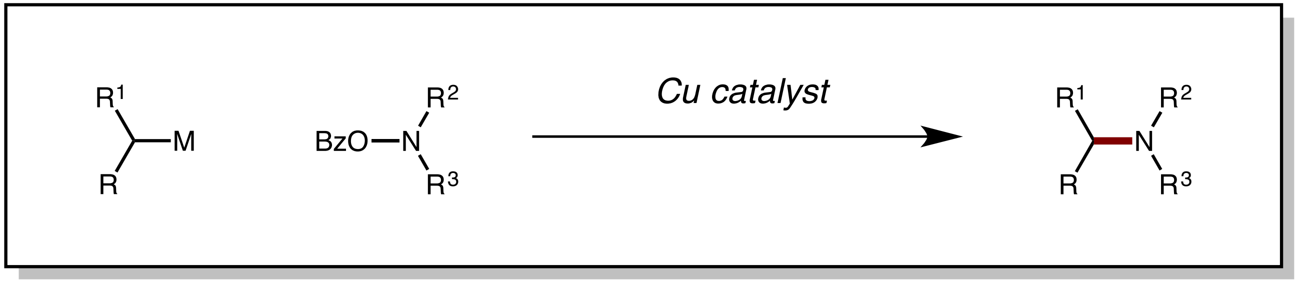
15 min

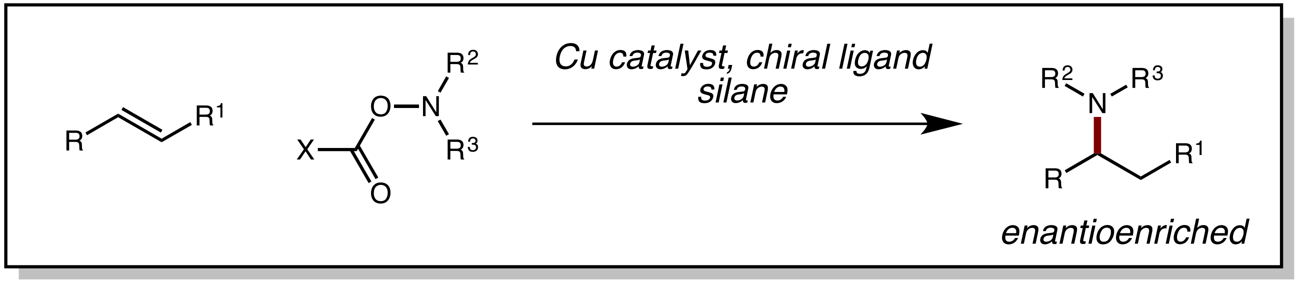
Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

Summary: Part 1

- *N*-electrophiles

C-nucleophile **N-electrophile**





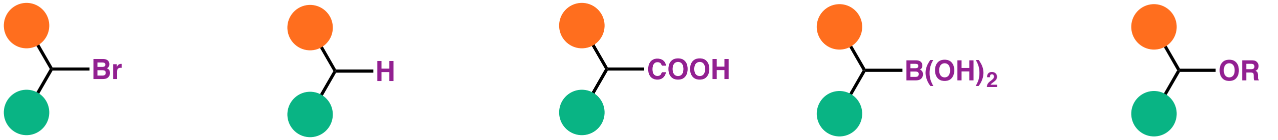
Copper-Catalyzed C–N Formation Using N-Nucleophiles

■ *N*-nucleophiles

***C*-electrophile**
or *C*-nucleophile

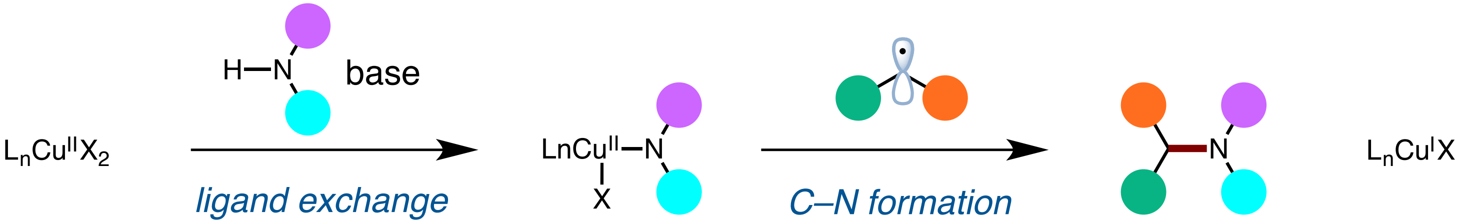
***N*-nucleophile**

■ Coupling partners



alkyl halide *C–H nucleophile* *carboxylic acid* *boronic acid* *alcohol derivative*

■ One common working hypothesis of C–N formation



ligand exchange

C–N formation

Copper-Catalyzed C–N Formation Using N-Nucleophiles

■ *N*-nucleophiles

***C*-electrophile**
or *C*-nucleophile

***N*-nucleophile**

■ Coupling partners

alkyl halide *C–H nucleophile* *carboxylic acid* *boronic acid* *alcohol derivative*

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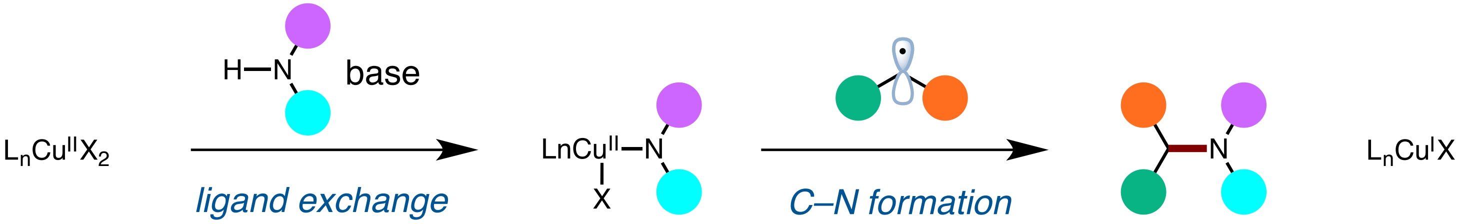
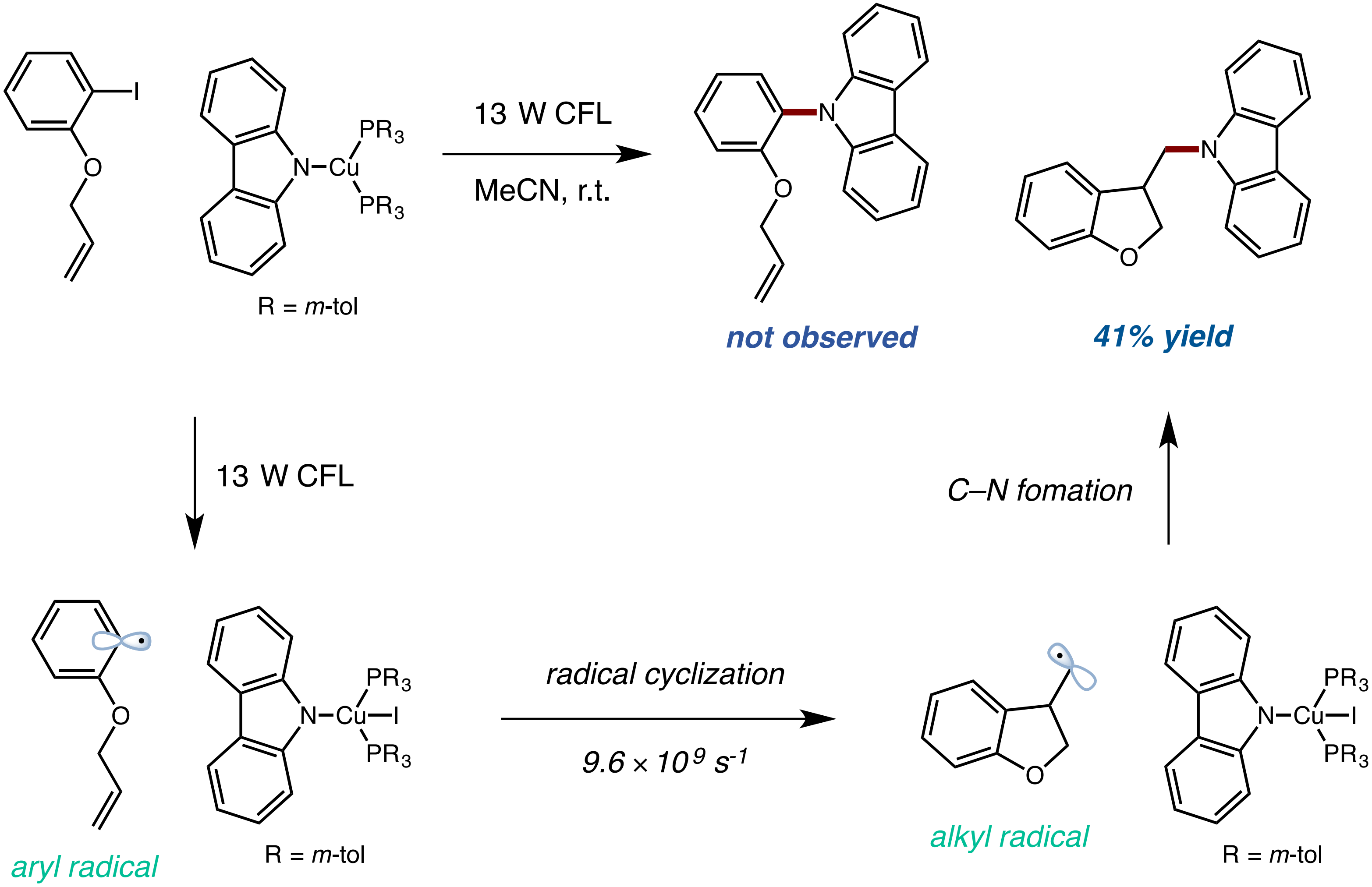


Copper-Catalyed C–N Formation using Alkyl Halides

- Seminal report from Prof. Greg Fu and Prof. Jonas Peters



Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647.

Copper-Catalyed C–N Formation using Alkyl Halides

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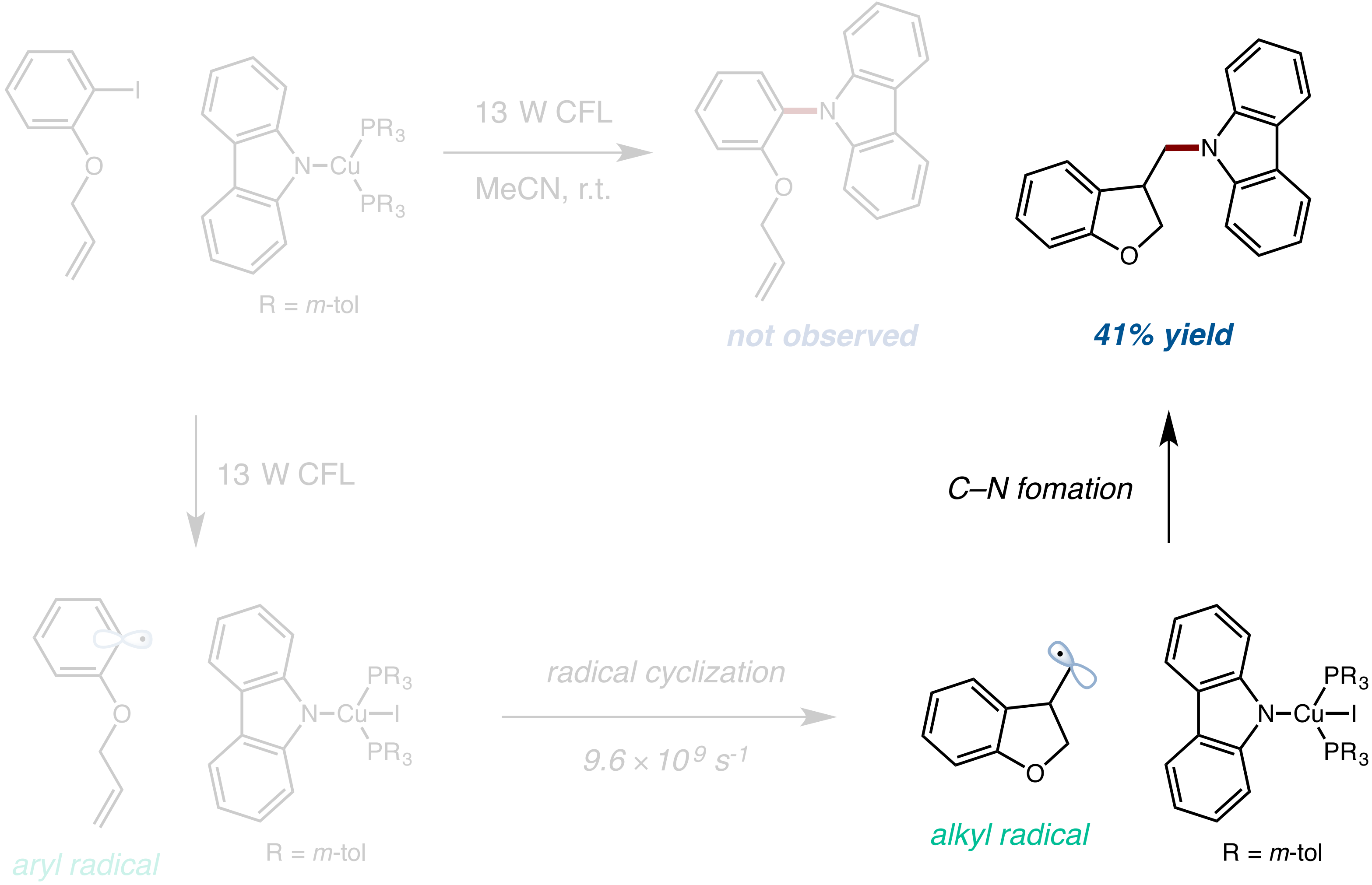
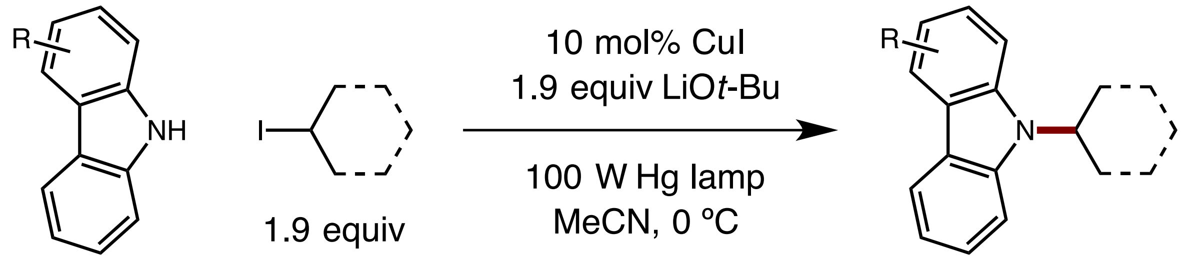


Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647.

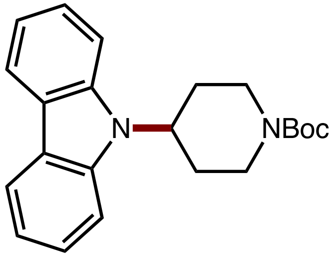
Copper-Catalyed C–N Formation using Alkyl Halides

N-alkylation of carbazoles

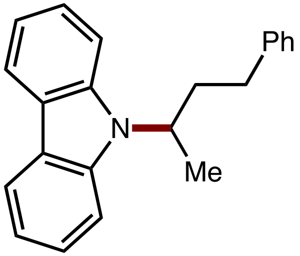


10 mol% CuI
1.9 equiv LiO*t*-Bu

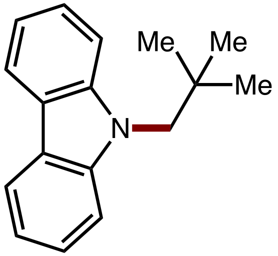
100 W Hg lamp
MeCN, 0 ºC



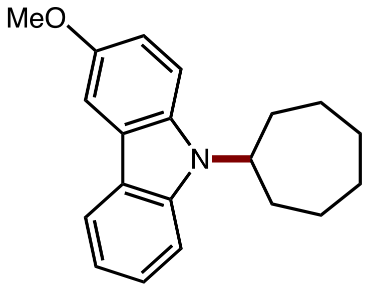
61% yield



80% yield

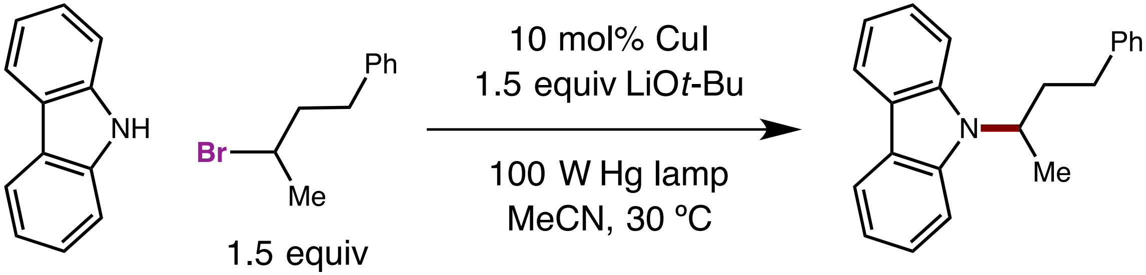


61% yield



59% yield

Alkyl bromide as electrophile



10 mol% CuI
1.5 equiv LiO*t*-Bu

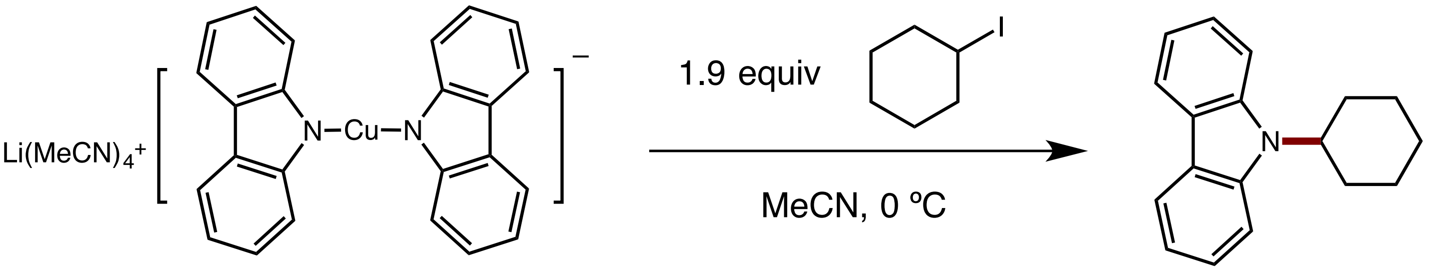
100 W Hg lamp
MeCN, 30 ºC

88% yield

Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129.

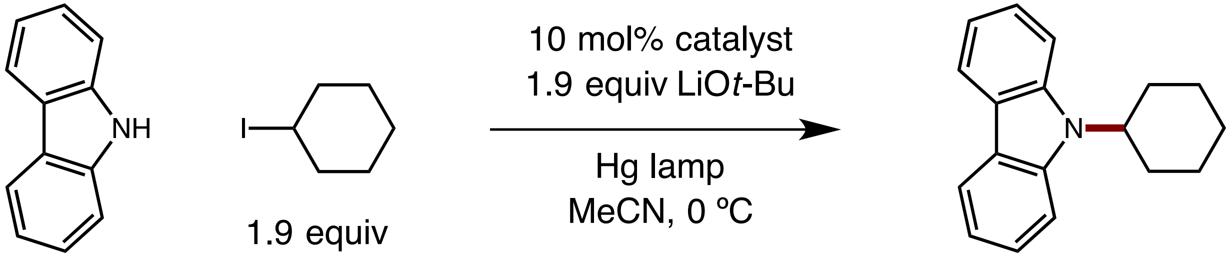
Copper-Catalyed C–N Formation using Alkyl Halides

Mechanistic studies



Complex A

no light: 0%
with Hg lamp: 68%

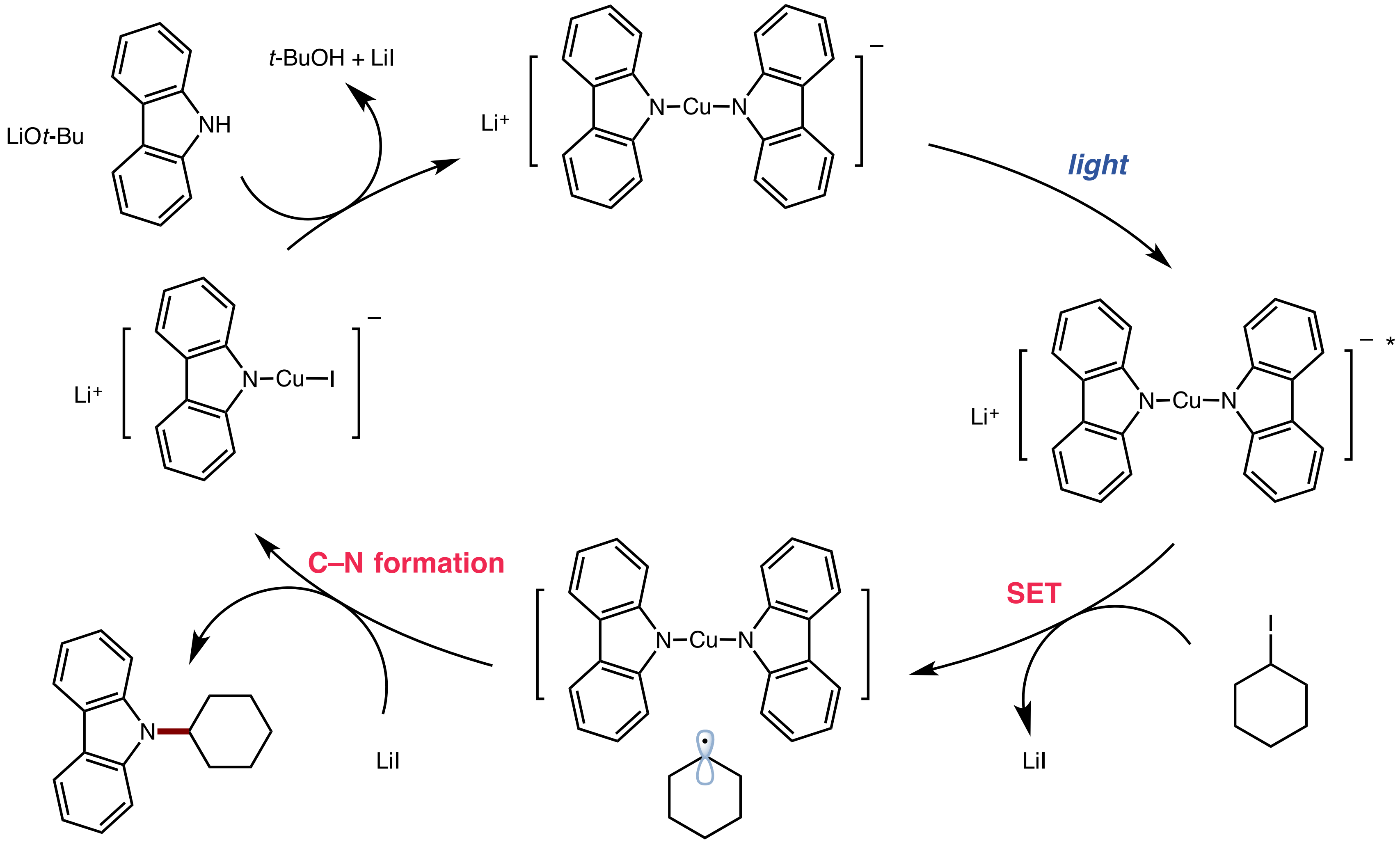


10 mol% CuI: 74% yield
10 mol% **A**: 81% yield

Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129.

Copper-Catalyed C–N Formation using Alkyl Halides

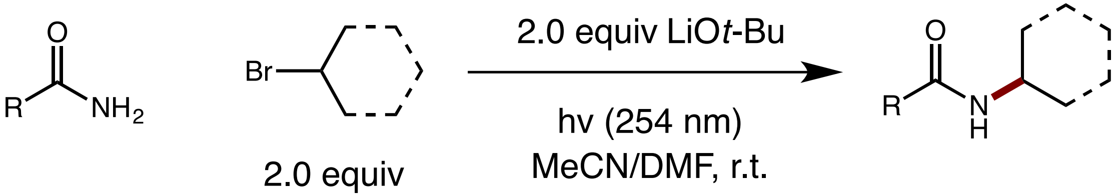
- One possible catalytic cycle

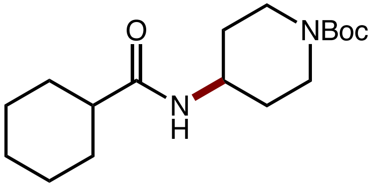


Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129.

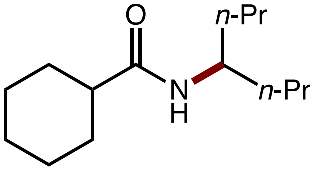
Copper-Catalyed C–N Formation using Alkyl Halides

■ *N*-alkylation of amides

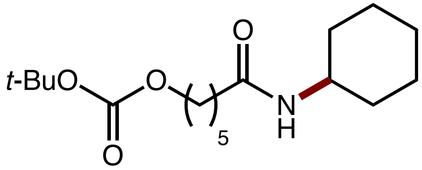




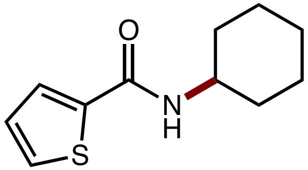
90% yield



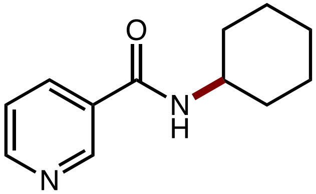
65% yield



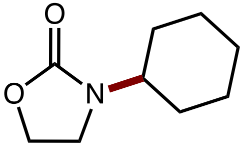
89% yield



72% yield



83% yield

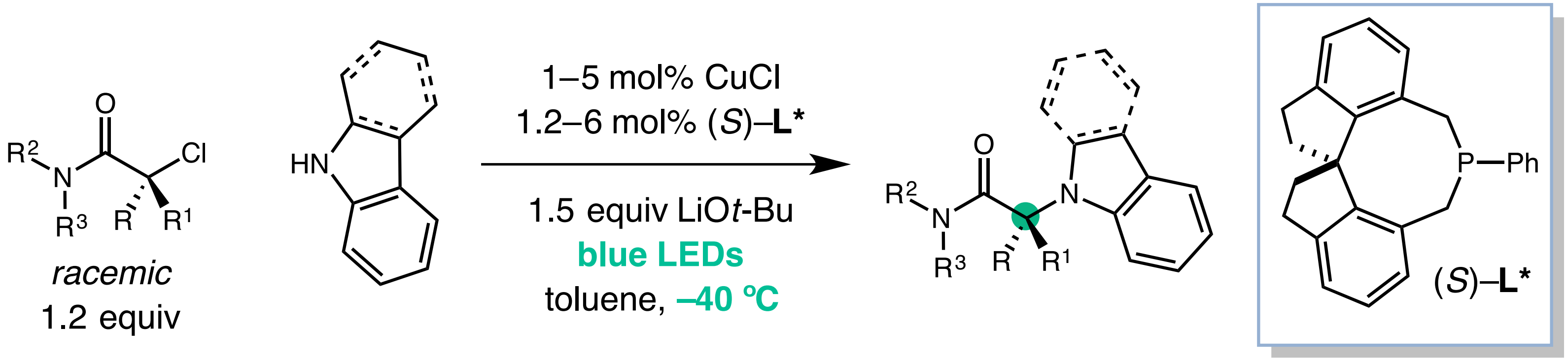


90% yield

Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162.

Copper-Catalyed C–N Formation using Alkyl Halides

Enantioselective alkylation with tertiary alkyl chlorides

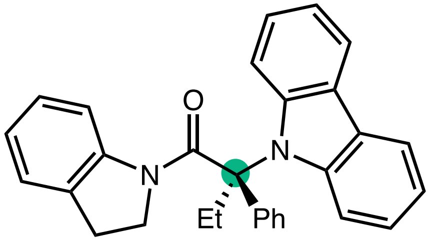


racemic
1.2 equiv

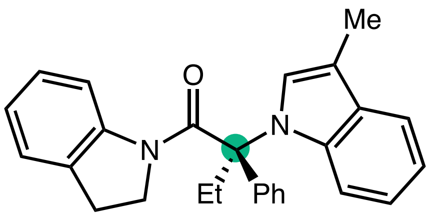
1–5 mol% CuCl
1.2–6 mol% (*S*)–**L***

1.5 equiv LiO*t*-Bu
blue LEDs
toluene, **–40 ºC**

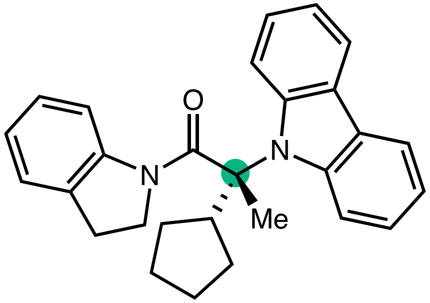
(*S*)–**L***



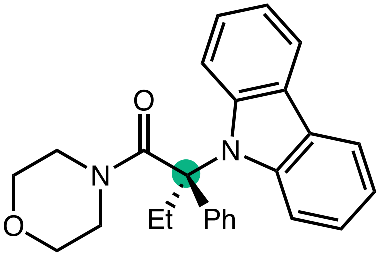
*95% yield, **92% ee***



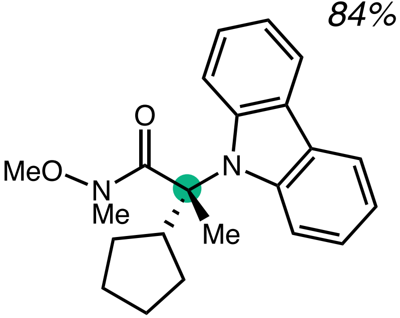
*79% yield, **92% ee***



*84% yield, **98% ee***



*74% yield, **90% ee***

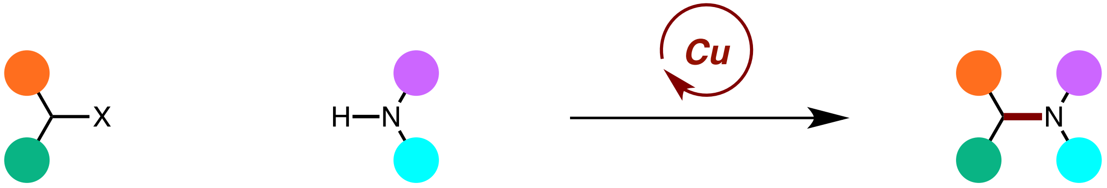


*73% yield, **95% ee***

Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681.

Copper-Catalyzed C–N Formation Using N-Nucleophiles

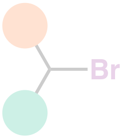
■ *N*-nucleophiles



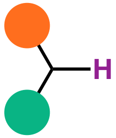
***C*-electrophile**
or *C*-nucleophile

***N*-nucleophile**

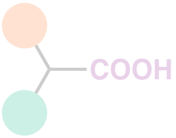
■ Coupling partners



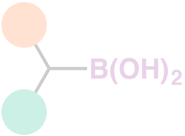
alkyl halide



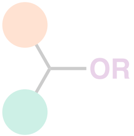
C–H nucleophile



carboxylic acid



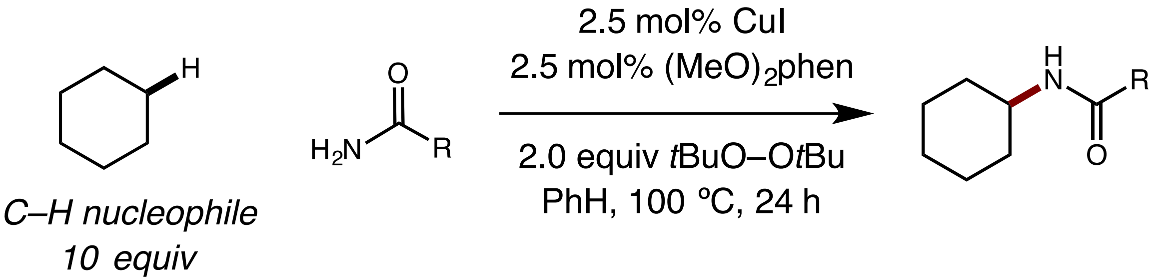
boronic acid

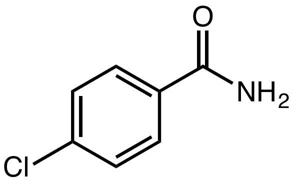


alcohol derivative

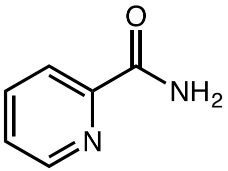
Copper-Catalyed C–N Formation using C–H Nucleophiles

- Seminal report from Prof. John Hartwig

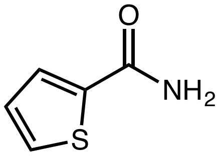




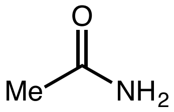
82% yield



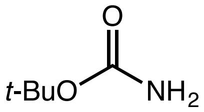
84% yield



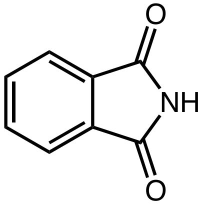
47% yield



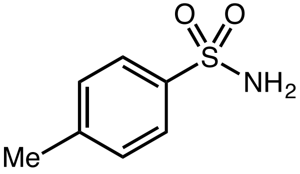
38% yield



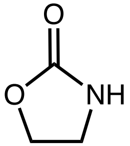
75% yield



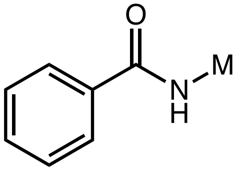
75% yield



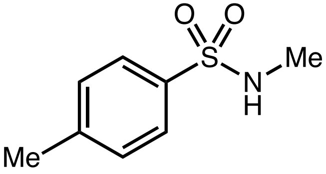
55% yield



46% yield



<10% yield

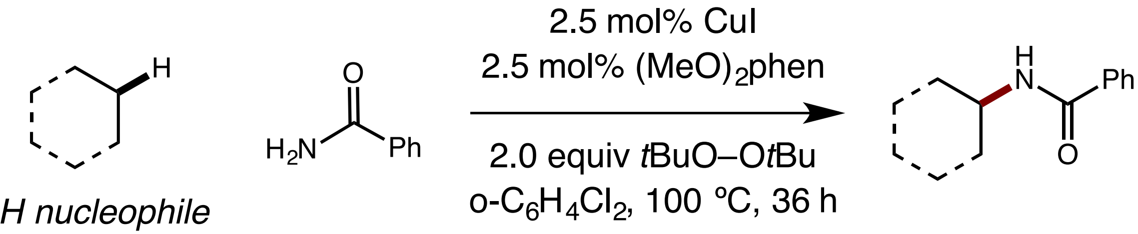


30% yield

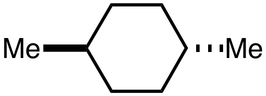
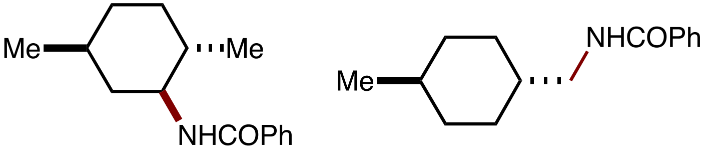
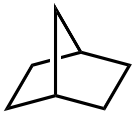
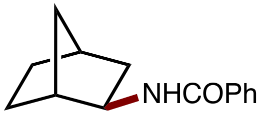
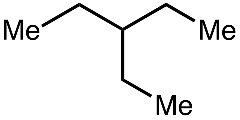
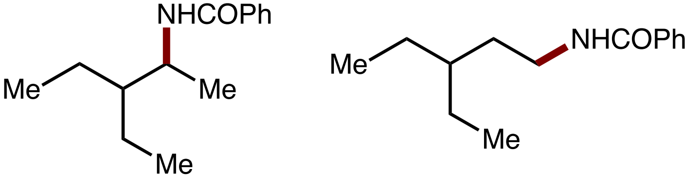
Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

C–H nucleophile scope



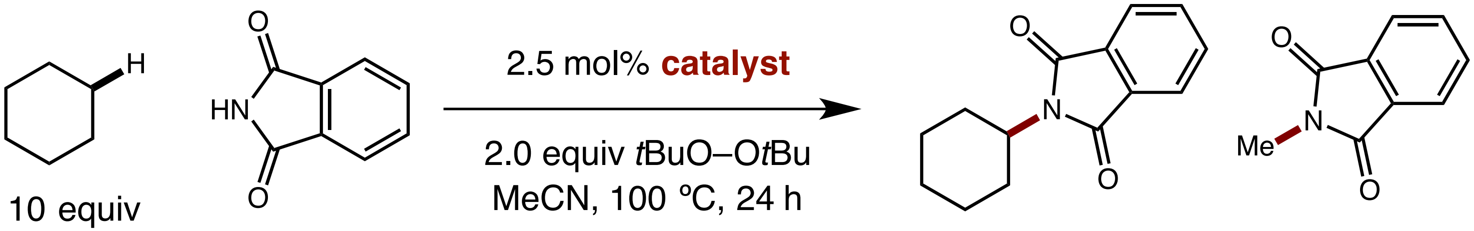
C–H nucleophile
10–17 equiv

substrate	product	yield
		*69% yield* *(>10:1 r.r.)*
		*81% yield* *(>10:1 d.r.)*
		*54% yield* *(2:1 r.r.)*

Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

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

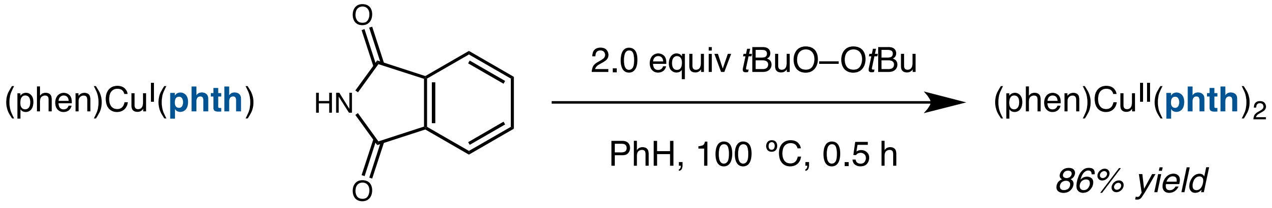


10 equiv

2.5 mol% **catalyst**

2.0 equiv *t*BuO–O*t*Bu
MeCN, 100 ºC, 24 h

2.5 mol% (phen)Cu$^{\mathrm{I}}$(**phth**)	*80% yield*	*20% yield*
2.5 mol% (phen)Cu$^{\mathrm{II}}$(**phth**)$_2$	*54% yield*	*13% yield*



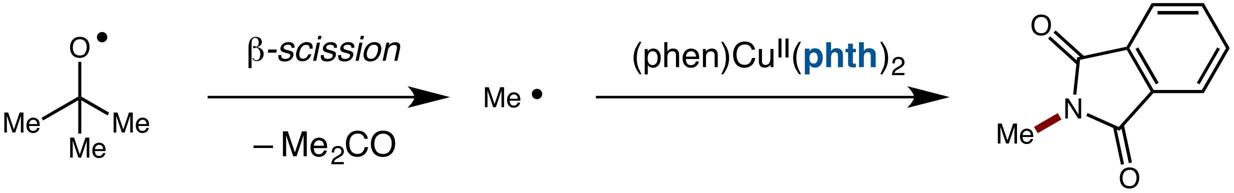
(phen)Cu$^{\mathrm{I}}$(**phth**) + phthalimide (1.5 equiv) → (phen)Cu$^{\mathrm{II}}$(**phth**)$_2$

2.0 equiv *t*BuO–O*t*Bu
PhH, 100 ºC, 0.5 h

86% yield

1.5 equiv

Formation of the *N*-Me side product: β-scission of *t*-BuO• radical



β-*scission*
– Me$_2$CO

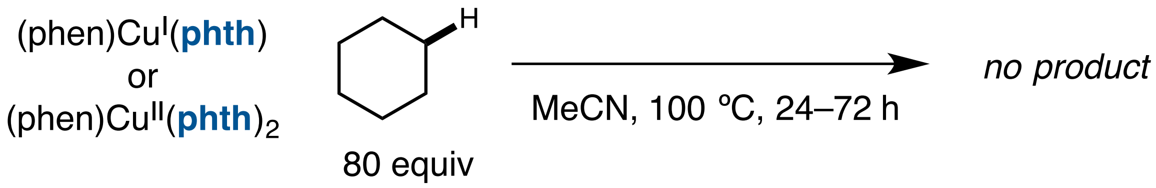
Me •

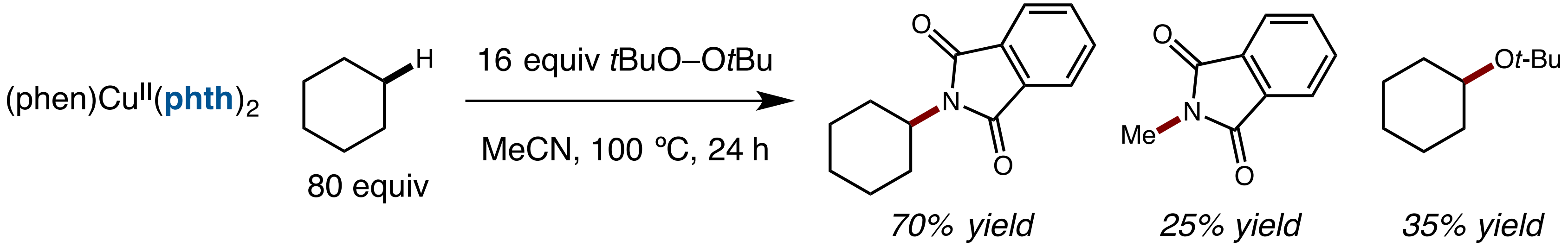
(phen)Cu$^{\mathrm{II}}$(**phth**)$_2$

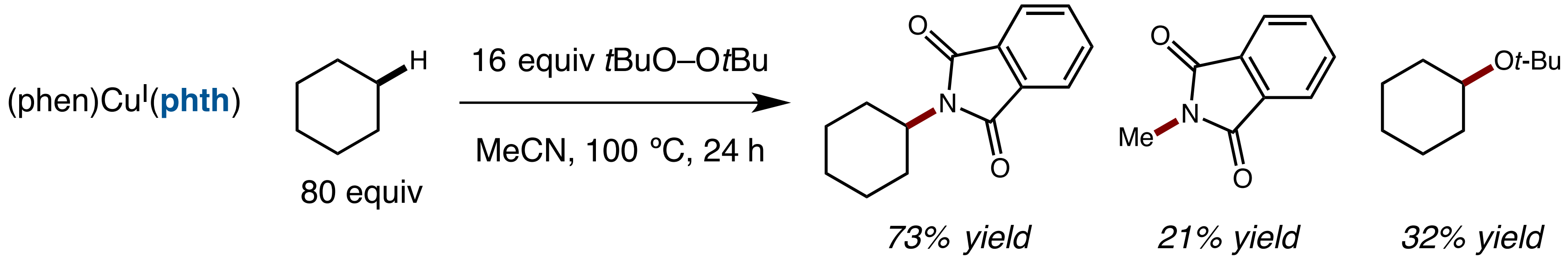
Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

Stoichiometric reactions: the role of *t*-BuOO*t*-Bu



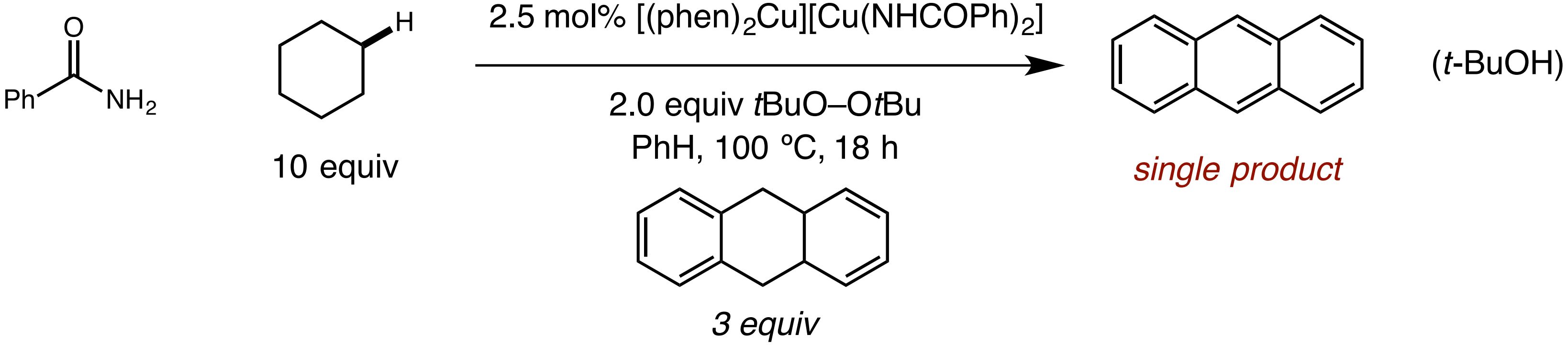




Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

Radical trapping experiments



10 equiv

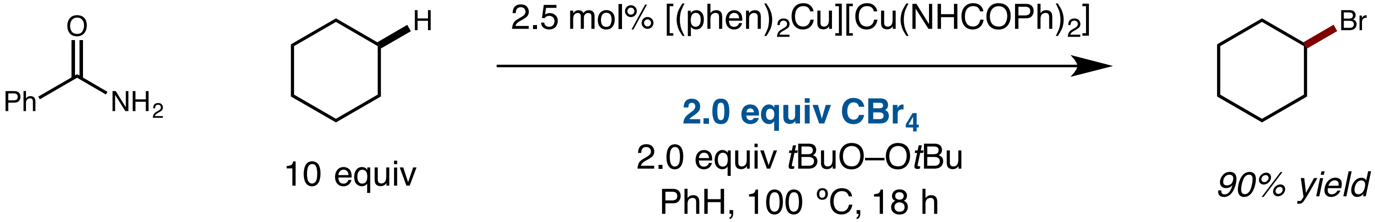
2.5 mol% $[(phen)_2Cu][Cu(NHCOPh)_2]$

2.0 equiv *t*BuO–O*t*Bu
PhH, 100 °C, 18 h

3 equiv

single product

(*t*-BuOH)



10 equiv

2.5 mol% $[(phen)_2Cu][Cu(NHCOPh)_2]$

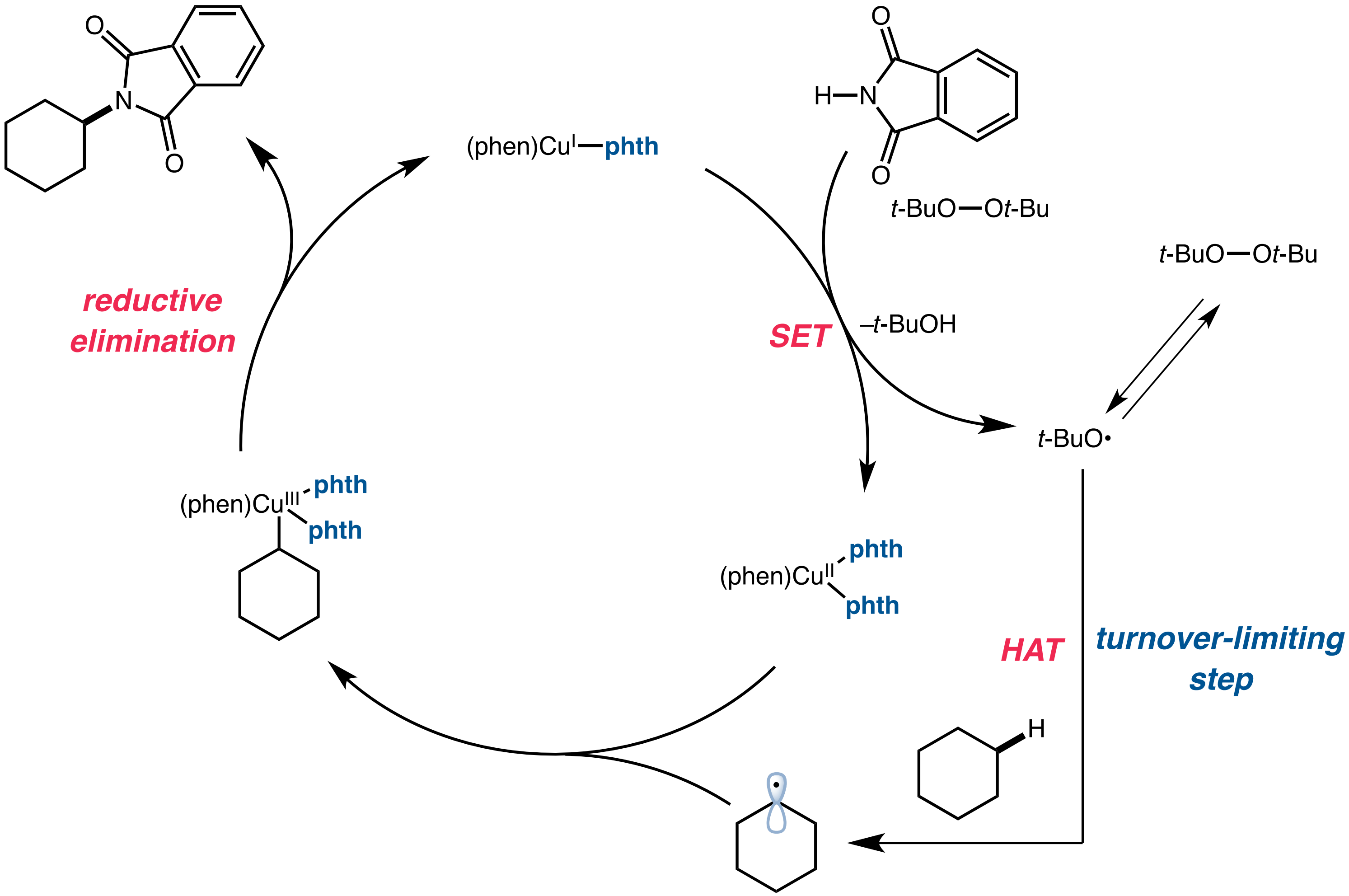
2.0 equiv CBr_4
2.0 equiv *t*BuO–O*t*Bu
PhH, 100 °C, 18 h

90% yield

Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

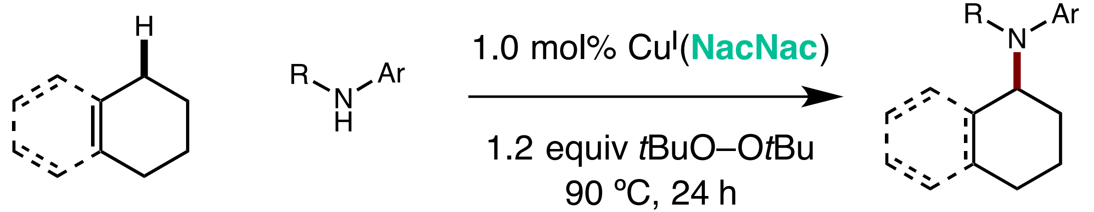
Proposed mechanism



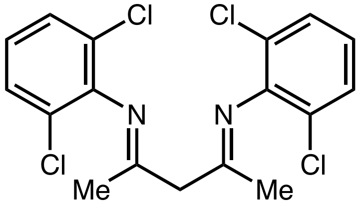
Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

Copper-Catalyed C–N Formation using C–H Nucleophiles

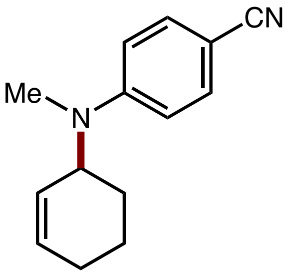
Benzylic and allylic C–H amination



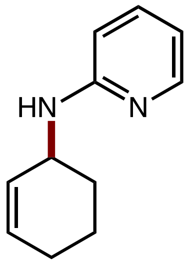
C–H nucleophile
10 equiv or solvent



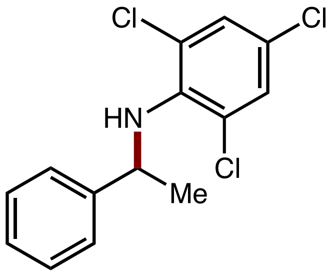
H–NacNac



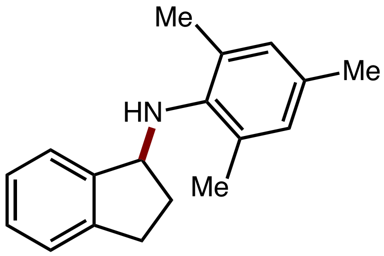
64% yield



75% yield



99% yield

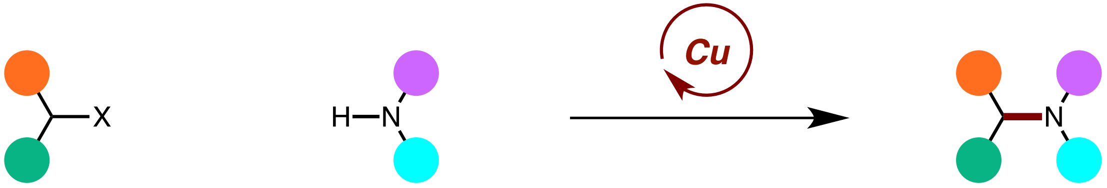


85% yield

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–N Formation Using N-Nucleophiles

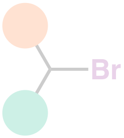
■ *N*-nucleophiles



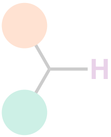
***C*-electrophile**
or *C*-nucleophile

***N*-nucleophile**

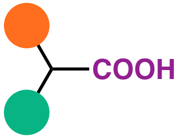
■ Coupling partners



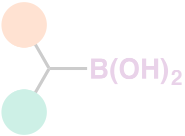
alkyl halide



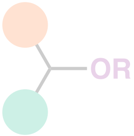
C–H nucleophile



carboxylic acid



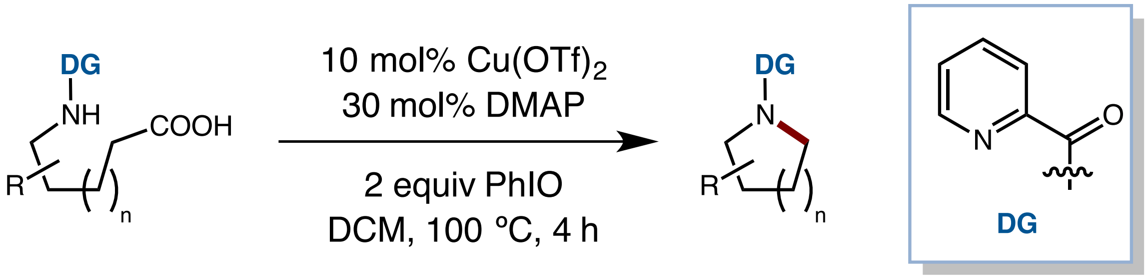
boronic acid

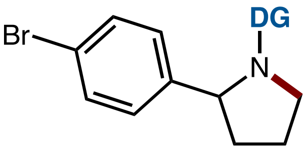


alcohol derivative

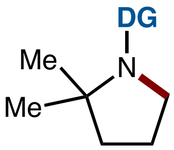
Copper-Catalyed C–N Formation using Carboxylic Acids

■ Intramolecular decarboxylative C–N formation

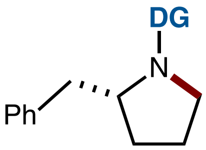




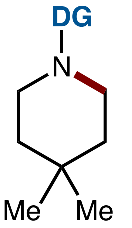
71% yield



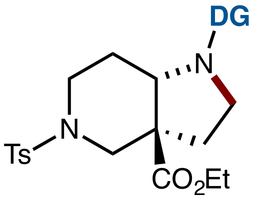
67% yield



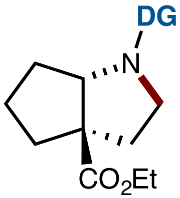
80% yield
(99% ee)



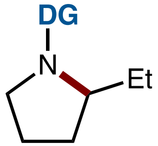
57% yield



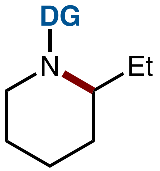
69% yield



80% yield



43% yield

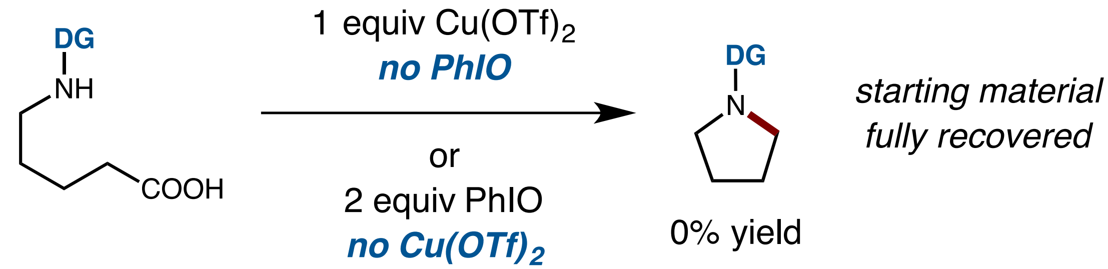


trace

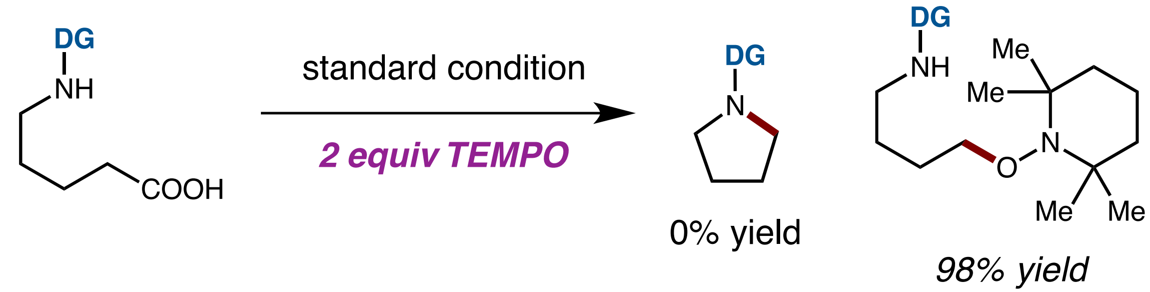
Liu, Z.-J.; Lu, X.; Wang, G.; Li, L.; Jiang, W.-T.; Wang, Y.-D.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 9714.

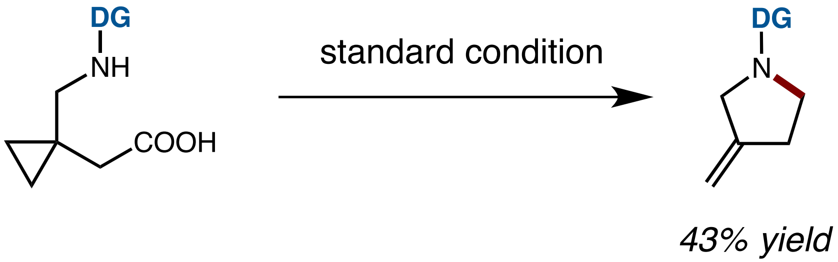
Copper-Catalyed C–N Formation using Carboxylic Acids

Mechanistic studies



starting material fully recovered

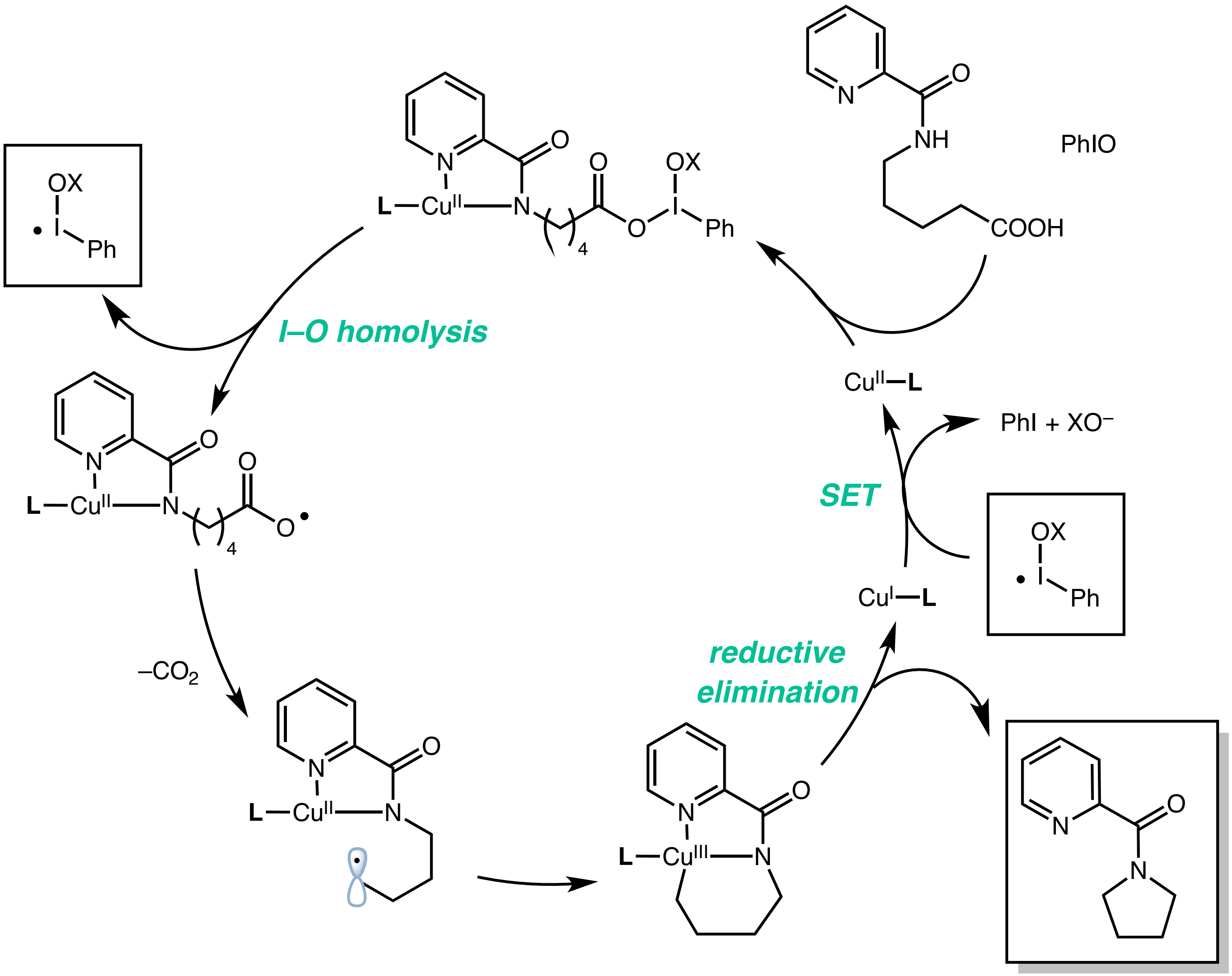




Liu, Z.-J.; Lu, X.; Wang, G.; Li, L.; Jiang, W.-T.; Wang, Y.-D.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 9714.

Copper-Catalyed C–N Formation using C–H Nucleophiles

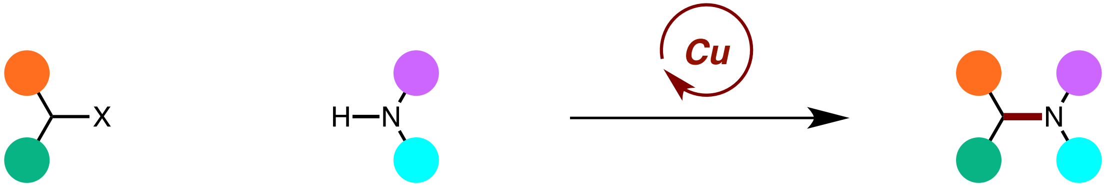
Proposed mechanism



Liu, Z.-J.; Lu, X.; Wang, G.; Li, L.; Jiang, W.-T.; Wang, Y.-D.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 9714.

Copper-Catalyzed C–N Formation Using N-Nucleophiles

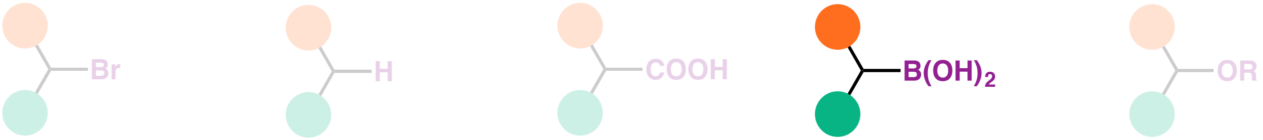
N-nucleophiles



***C*-electrophile**
or *C*-nucleophile

***N*-nucleophile**

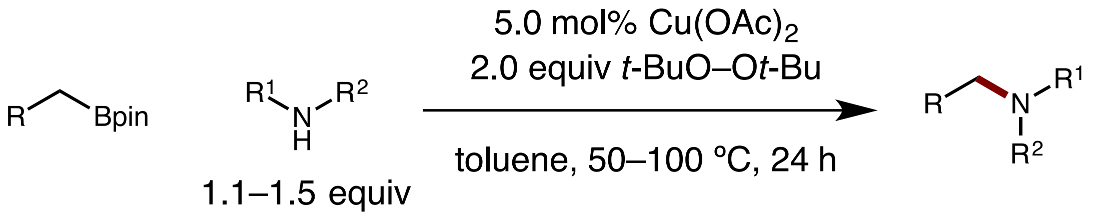
Coupling partners



alkyl halide *C–H nucleophile* *carboxylic acid* *boronic acid* *alcohol derivative*

Copper-Catalyed C–N Formation using Alkyl Boronic Acids

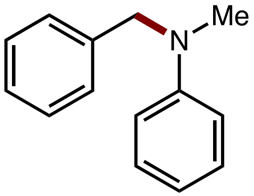
- Amine alkylations with primary alkyl boronic acid derivatives



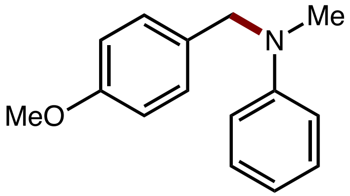
5.0 mol% $Cu(OAc)_2$
2.0 equiv *t*-BuO–O*t*-Bu

toluene, 50–100 ºC, 24 h

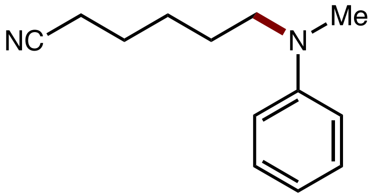
1.1–1.5 equiv



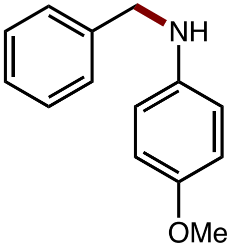
99% yield



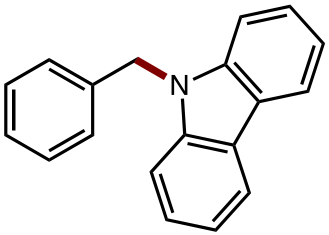
57% yield



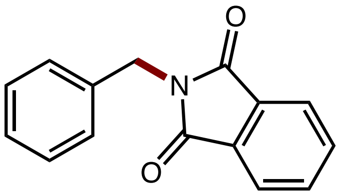
51% yield



78% yield



45% yield

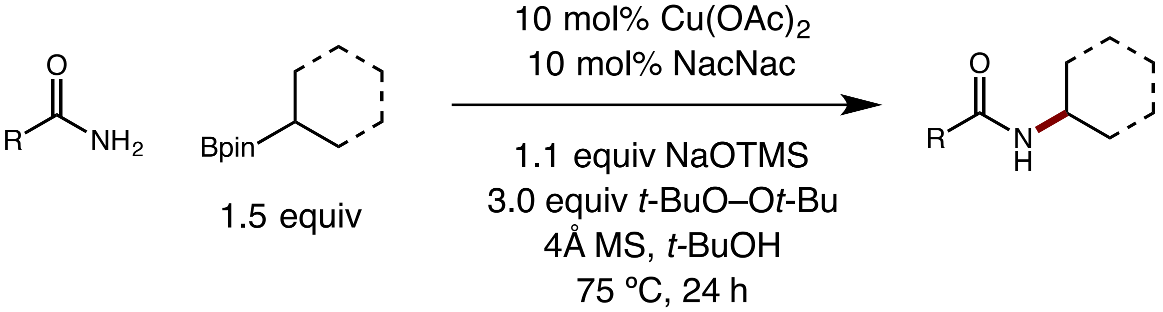


65% yield

Sueki, S.; Kuninobu, Y. *Org. Lett.* **2013**, *15*, 1544.

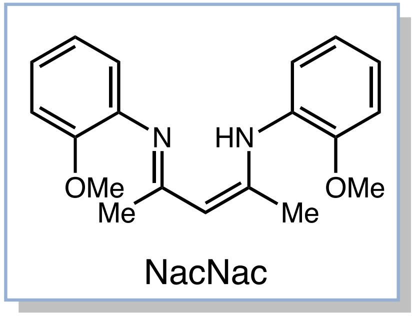
Copper-Catalyed C–N Formation using Alkyl Boronic Acids

- Amide alkylations with secondary alkyl boronic acid derivatives

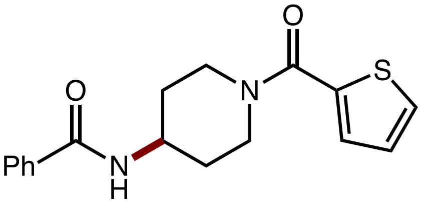


10 mol% $Cu(OAc)_2$
10 mol% NacNac

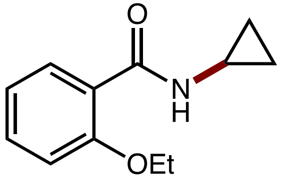
1.1 equiv NaOTMS
3.0 equiv *t*-BuO–O*t*-Bu
4Å MS, *t*-BuOH
75 ºC, 24 h



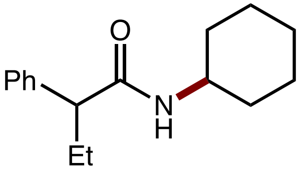
NacNac



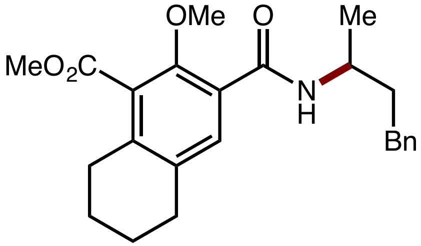
49% yield



56% yield



65% yield

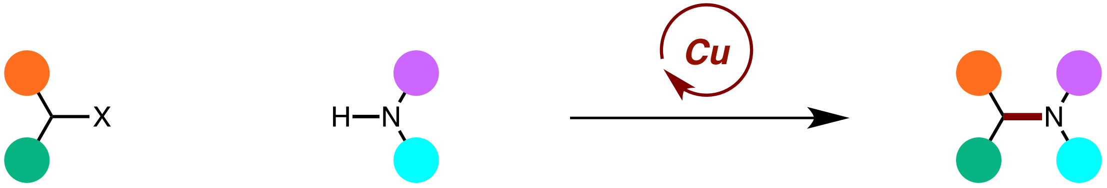


68% yield

Mori-Quiroz, L. M.; Shimkin, K. W.; Rezazadeh, S.; Kozlowski, R. A.; Watson, D. A. *Chem. Eur. J.* **2016**, *22*, 15654.

Copper-Catalyzed C–N Formation Using N-Nucleophiles

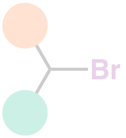
■ *N*-nucleophiles



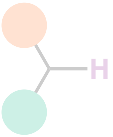
***C*-electrophile**
or *C*-nucleophile

***N*-nucleophile**

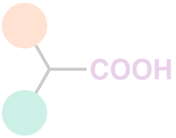
■ Coupling partners



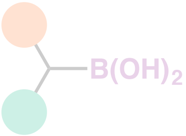
alkyl halide



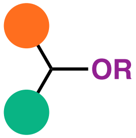
C–H nucleophile



carboxylic acid



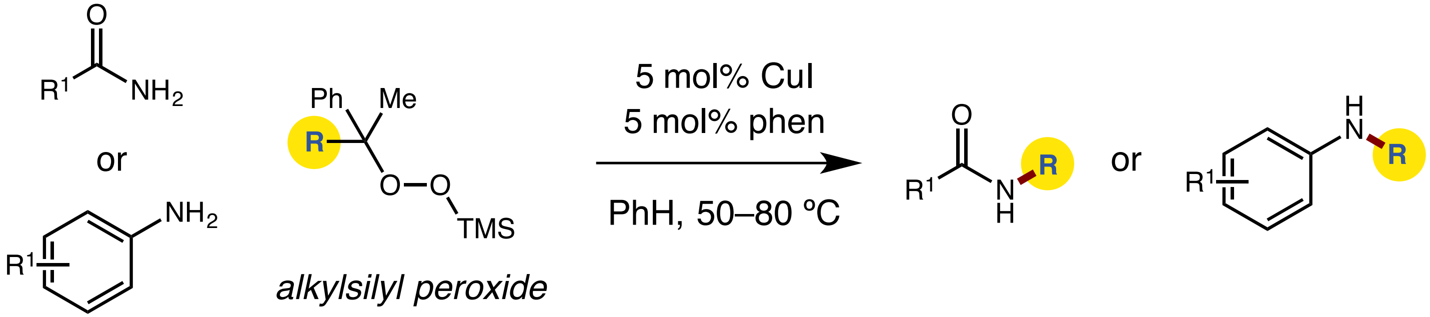
boronic acid



alcohol derivative

Copper-Catalyed C–N Formation using Alcohol Derivatives

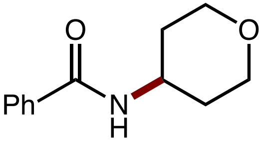
■ Alkylation with alkylsilyl peroxides



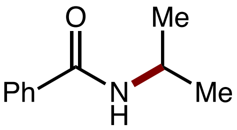
5 mol% CuI
5 mol% phen

PhH, 50–80 ºC

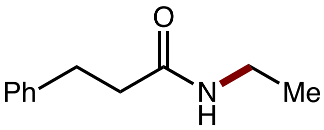
alkylsilyl peroxide
1.5 equiv



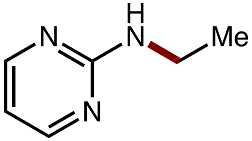
98% yield



94% yield

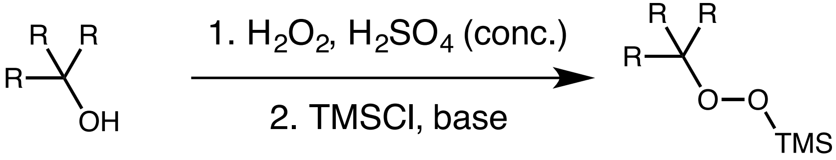


97% yield



68% yield

■ Preparation of alkylsilyl peroxides



1. H_2O_2, H_2SO_4 (conc.)

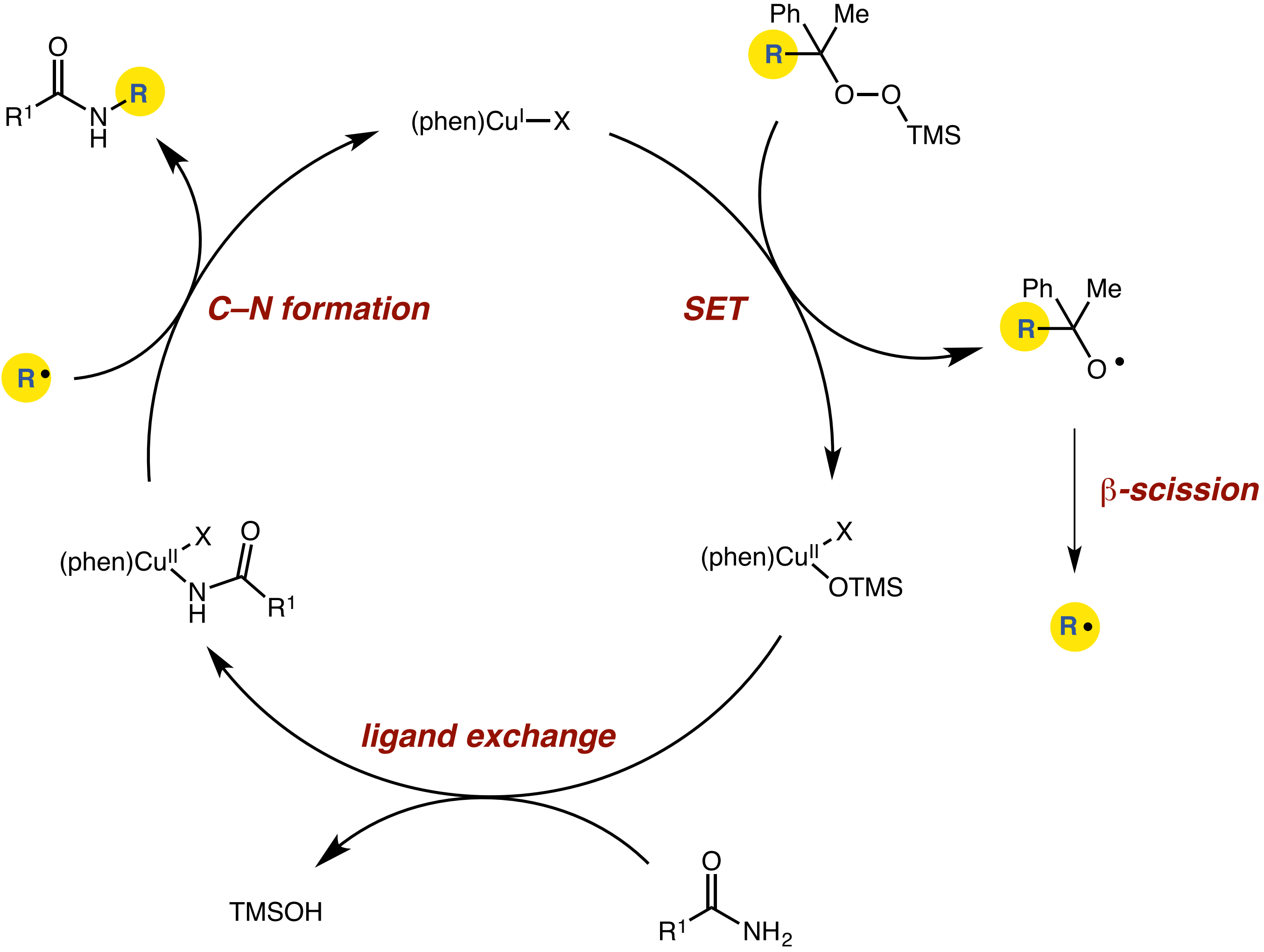
2. TMSCl, base

purified via
chromatography

Sakamoto, R.; Sakurai, S.; Maruoka, K. *Chem. Eur. J.* **2017**, ASAP, doi: 10.1002/chem.201702217

Copper-Catalyed C–N Formation using Alcohol Derivatives

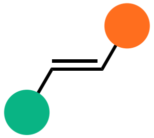
■ Proposed mechanism

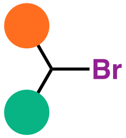


Sakamoto, R.; Sakurai, S.; Maruoka, K. *Chem. Eur. J.* **2017**, ASAP, doi: 10.1002/chem.201702217

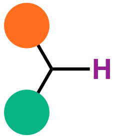
Summary and Future Direction

Coupling partners

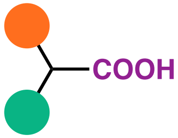

alkene



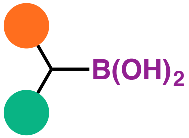
alkyl halide



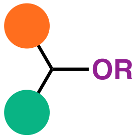
C–H nucleophile



carboxylic acid

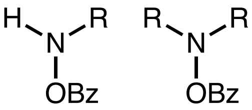


boronic acid

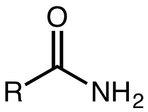


alcohol derivative

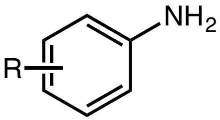
N-electrophiles and nucleophiles



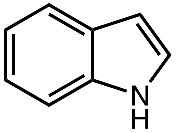
amine N–OBz



1° amide



1° aniline



N-heterocycle

Future directions

- Other types of *N*-nucleophiles
- Other families of alkyl precursors
- Tertiaryl alkyl substrates
- Enantioselective C–N formation