

# **Photoinduced Copper-Catalyzed C–N Couplings**

**B4 Yu Irie**

2021/11/17 (Wed)

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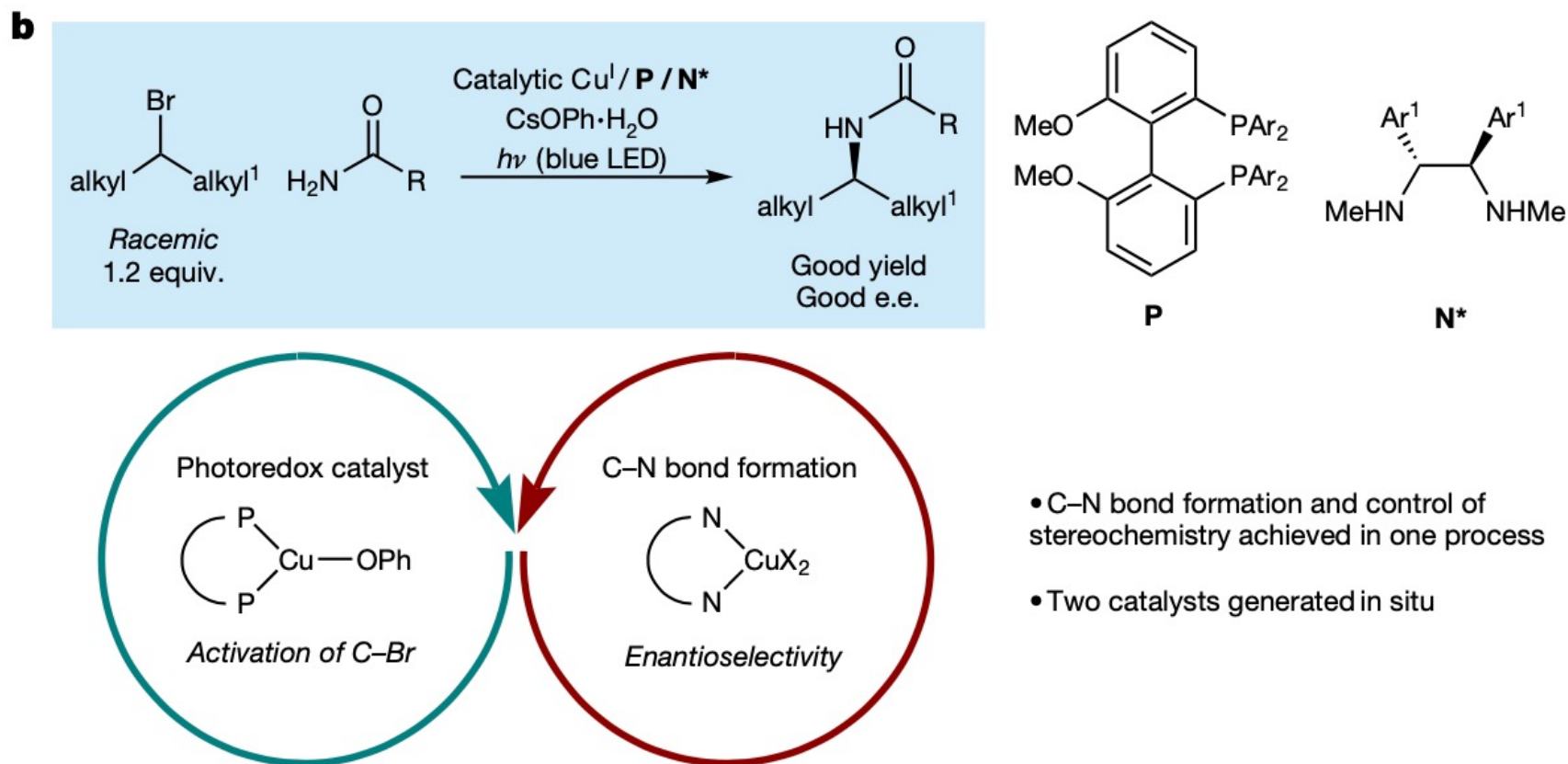
- 1. Introduction**
- 2. Enantioconvergent C–N couplings from carbazoles**
- 3. C–N couplings independent of nucleophiles by designing a ligand**
- 4. Enantioconvergent C–N couplings independent of nucleophiles by using 3 ligands**
- 5. Summary and perspective**

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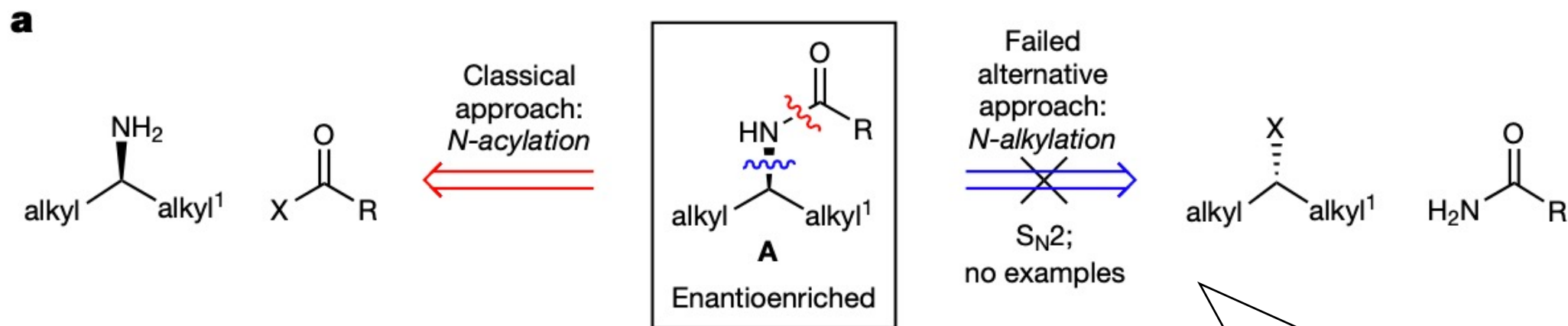
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- 1. Introduction**
2. Enantioconvergent C–N couplings from carbazoles
3. C–N couplings independent of nucleophiles by designing a ligand
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5. Summary and perspective

# Enantioconvergent Synthesis of Amides via Radical Intermediates



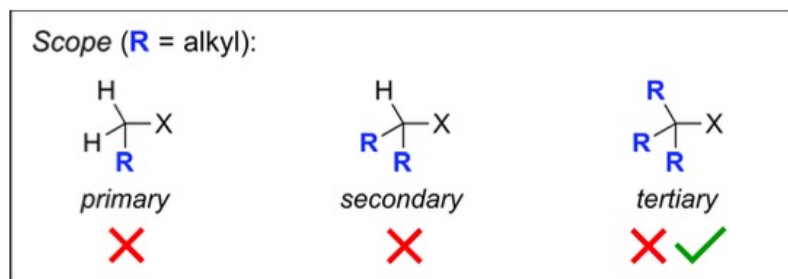
# Synthesis of Enantioenriched Amides



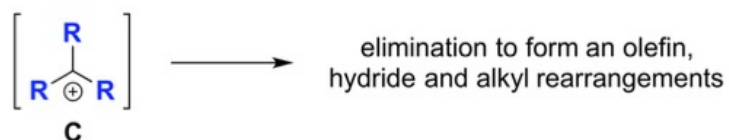
**\*Both strategies require enantiopure substrates.**

**Expanding the scope by *N*-alkylation via classical pathways ( $S_N1$  or  $S_N2$ ) is challenging.**

# Limitations of Approach via N-alkylation



Side reactions of carbocation **C**:



Limited scope with respect to the nucleophile ( $\text{Nu}^-$ ):

Deactivation by Brønsted acid ( $\text{H}^+$ ) or Lewis acid (LA) activators:

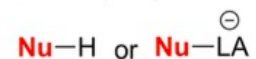
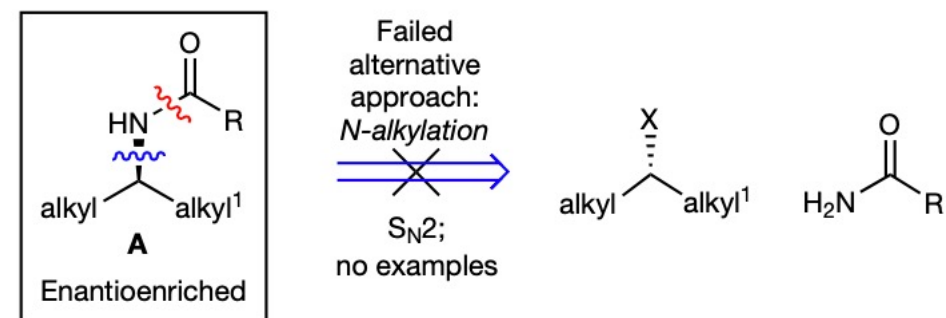


Figure 2. Limitations of the  $\text{S}_{\text{N}}1$  reaction.



Scope ( $R = \text{alkyl}$ ):

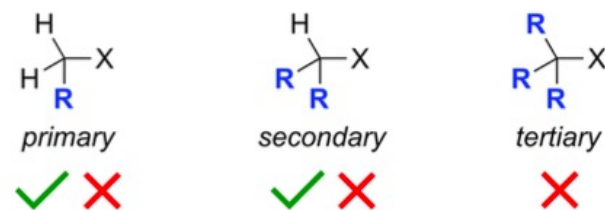
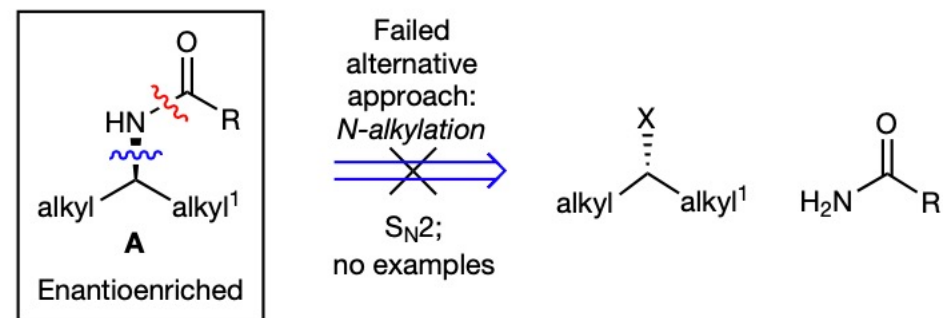
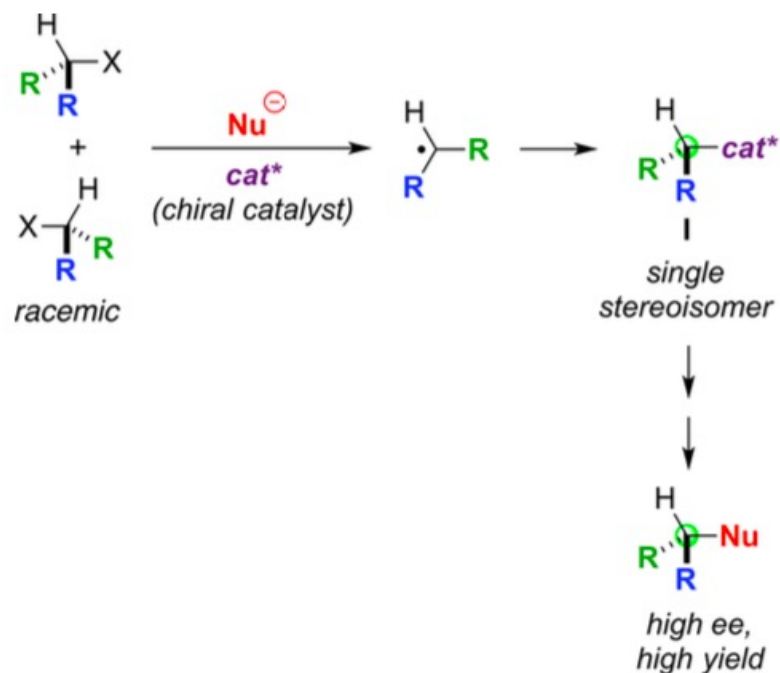


Figure 3. Limitations of the  $\text{S}_{\text{N}}2$  reaction.

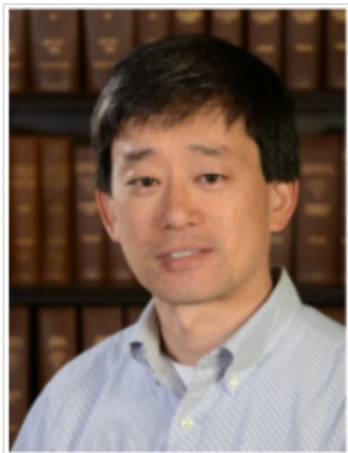
**+ Stereoselectivity problems:  $\text{S}_{\text{N}}1$  reaction gives racemic products, and  $\text{S}_{\text{N}}2$  reaction requires pure enantiomers as SM.**

# Approach via Radical Intermediate



**Transition-metal catalysis via radical intermediates could enable enantioconvergent reactions of racemic halides.**

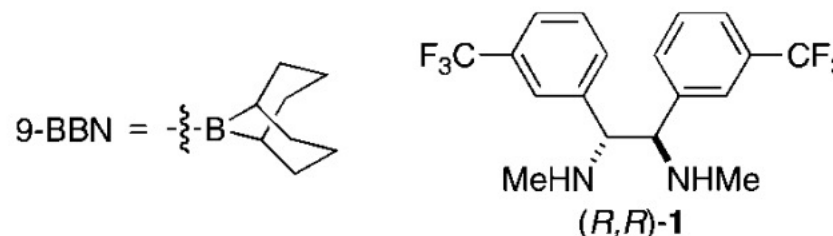
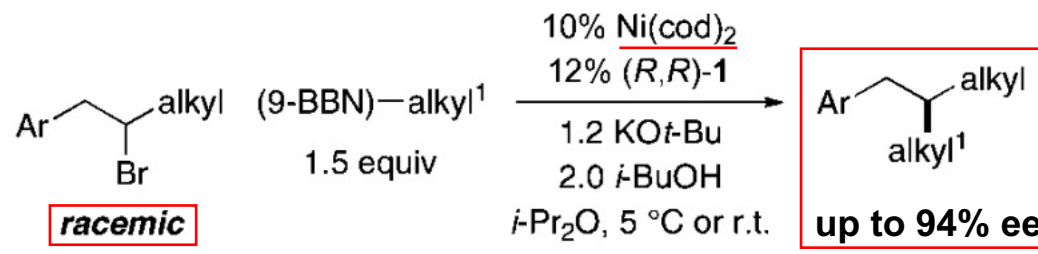
# About the Authors (G. C. Fu)



**Gregory C. Fu**  
Caltech  
(Professor of Chemistry)

**Enantioconvergent reaction  
from racemic alkyl halides  
via radical intermediate**

- **Nickel Catalysis: Metal-catalyzed coupling reactions of alkyl electrophiles**



G. C. Fu *et al.* *J. Am. Chem. Soc.* **2008**, *130*, 6694.

- **Copper Catalysis: Couplings of nitrogen nucleophiles with alkyl electrophiles (with Peters group)**



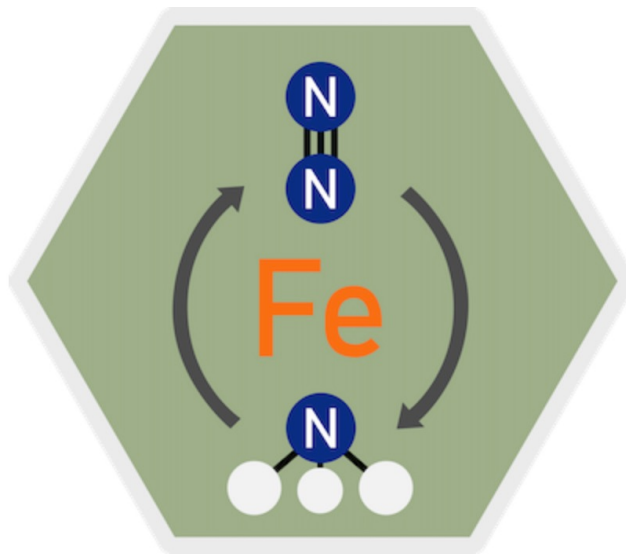
# About the Authors (J. C. Peters)

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- Photoinduced Copper-Catalyzed C–N Coupling
- **Investigation of Iron-Catalyzed Nitrogen/Ammonia Cycling** etc.

## Iron-Catalyzed Nitrogen/Ammonia Cycling

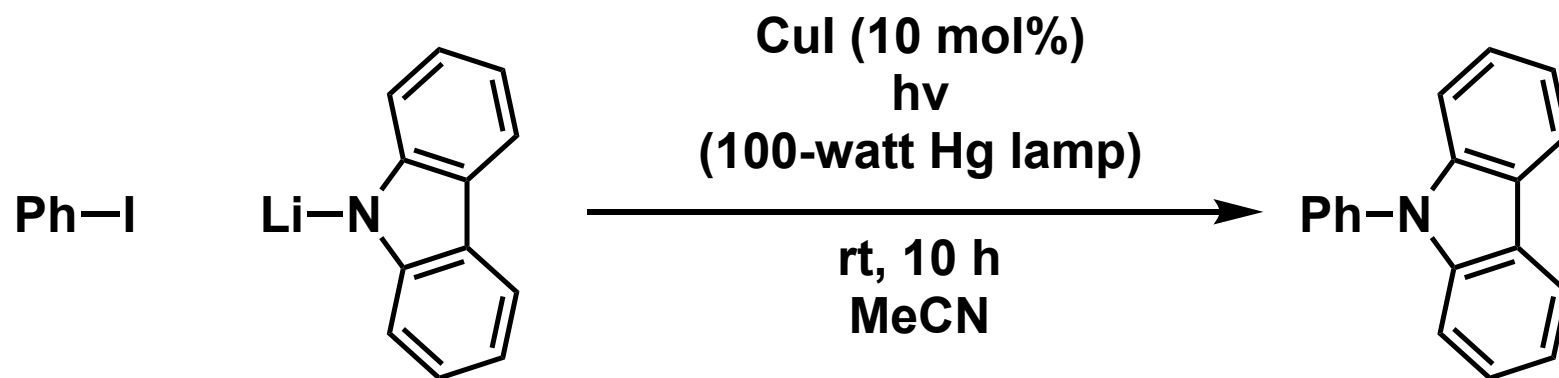
Nitrogen fixation to ammonia ( $N_2RR$ ) and its reverse, ammonia oxidation (AO), are key challenges in catalysis that offer the promise of low- or zero-carbon fuels and fertilizers. Well-defined coordination complexes offer a means to constrain mechanistic hypotheses in enzymatic catalysis (e.g., nitrogen fixation by nitrogenase enzymes), and to develop new catalysts well suited to detailed mechanistic studies in their own right. Our group continues to discover fascinating iron and other metal catalyst systems in this vein with sample rich mechanistic landscapes that we continue to explore.



**Jonas C. Peters**  
**Caltech**  
**(Professor of Chemistry)**

# Photoinduced C–N Ullmann Coupling

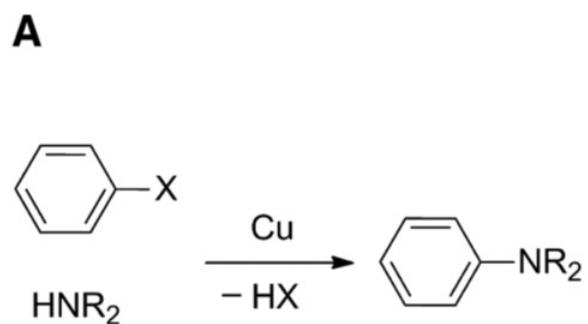
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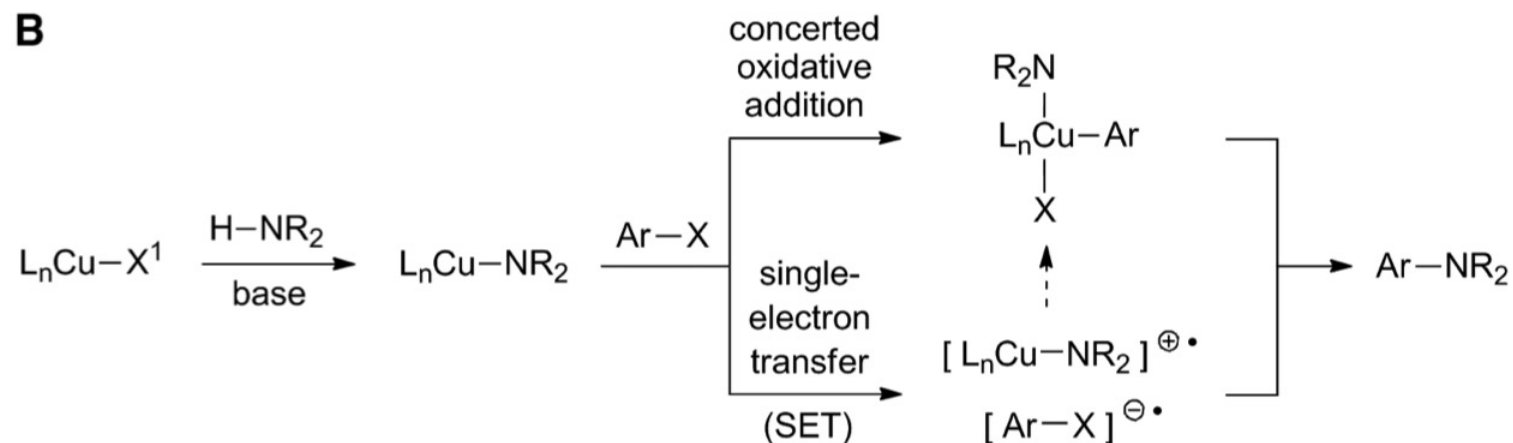
Using the light energy, the reaction proceeds under unusually mild conditions (room temperature or even  $-40\text{ }^{\circ}\text{C}$ ).

# Classical Ullmann Coupling

## General scheme of C–N Ullmann coupling

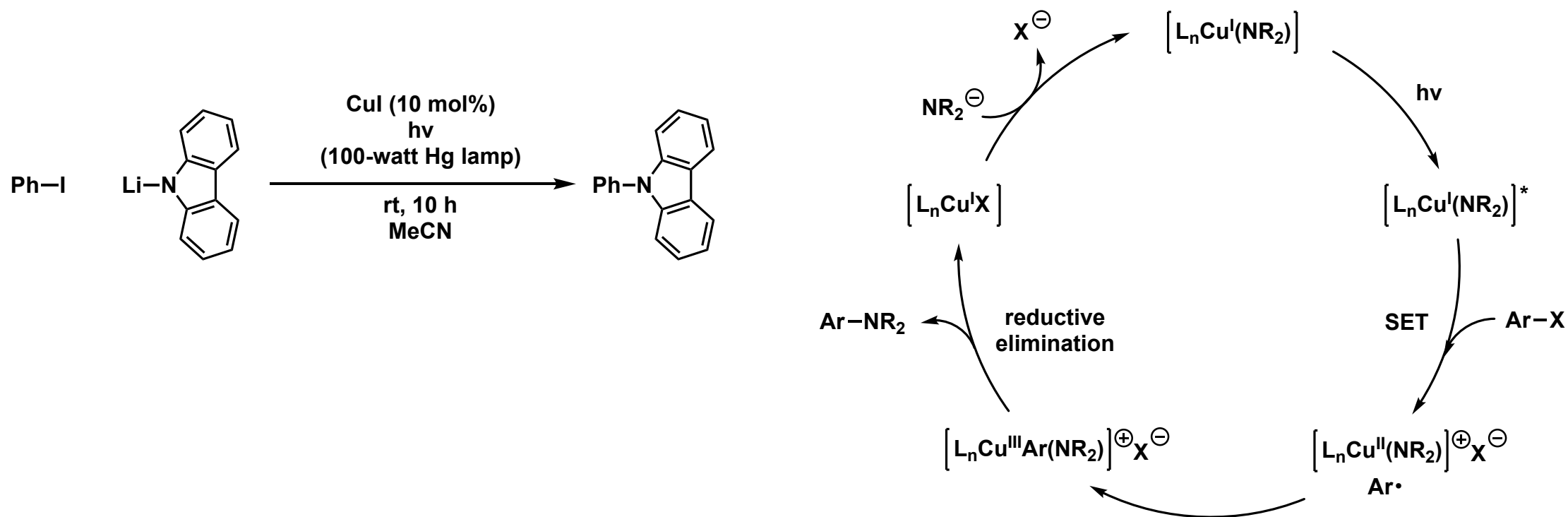


## Two possible pathways for Ullmann C–N bond formation



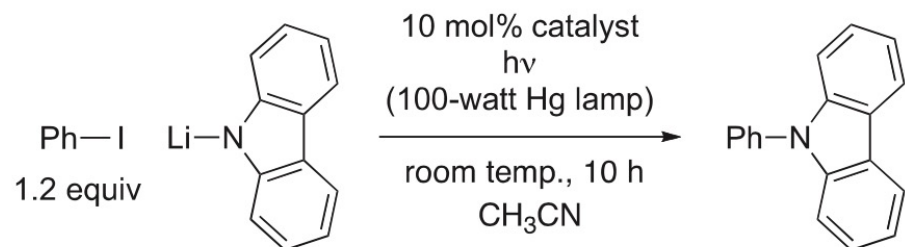
**Photoinduced C–N coupling was thought to proceed via SET pathway.**

# Possible Pathway for Photoinduced C–N Coupling

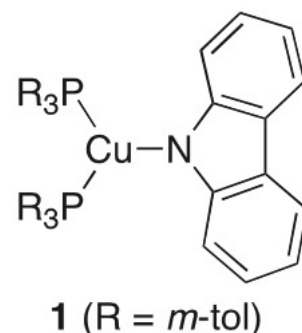


# Effects of Changes in Reaction Parameters

B



Entry	Catalyst	Conditions	Yield (%)
1	<b>1</b>	Standard conditions	64 (52)
2	<b>1</b>	dark	<1
3	None	Standard conditions	3
4	<b>1</b>	-40 °C	45
5	1.5 mol% <b>1</b>	Standard conditions	30
6	CuI	Standard conditions	65 (58)
7	CuI	dark	<1



\*Yields of purified product are in parentheses.

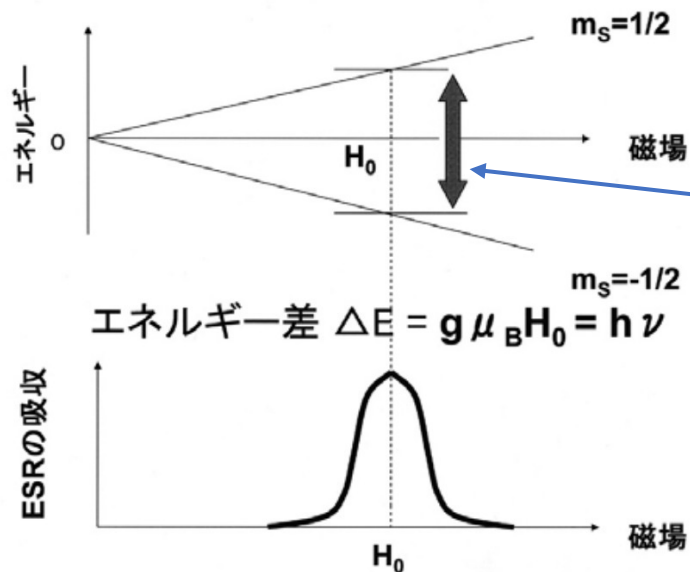
**Entry 2,3: Light and catalyst are necessary for the reaction to proceed.**

**Entry 6: CuI also serves as a catalyst. (The reaction proceeds likely via electron transfer from a luminescent copper-carbazolate complex generated in situ.)**

**Results of several experiments (X-band EPR spectrum/Cyclization in a photoinduced condition/Stereochemical study) are consistent with the pathway via radical intermediates.**

# Confirmation of a Radical Pathway: About X-band EPR Spectra

EPR is the observation of the resonance when unpaired electrons of a paramagnetic substance absorb the microwaves (especially on X-band) during spin transition.

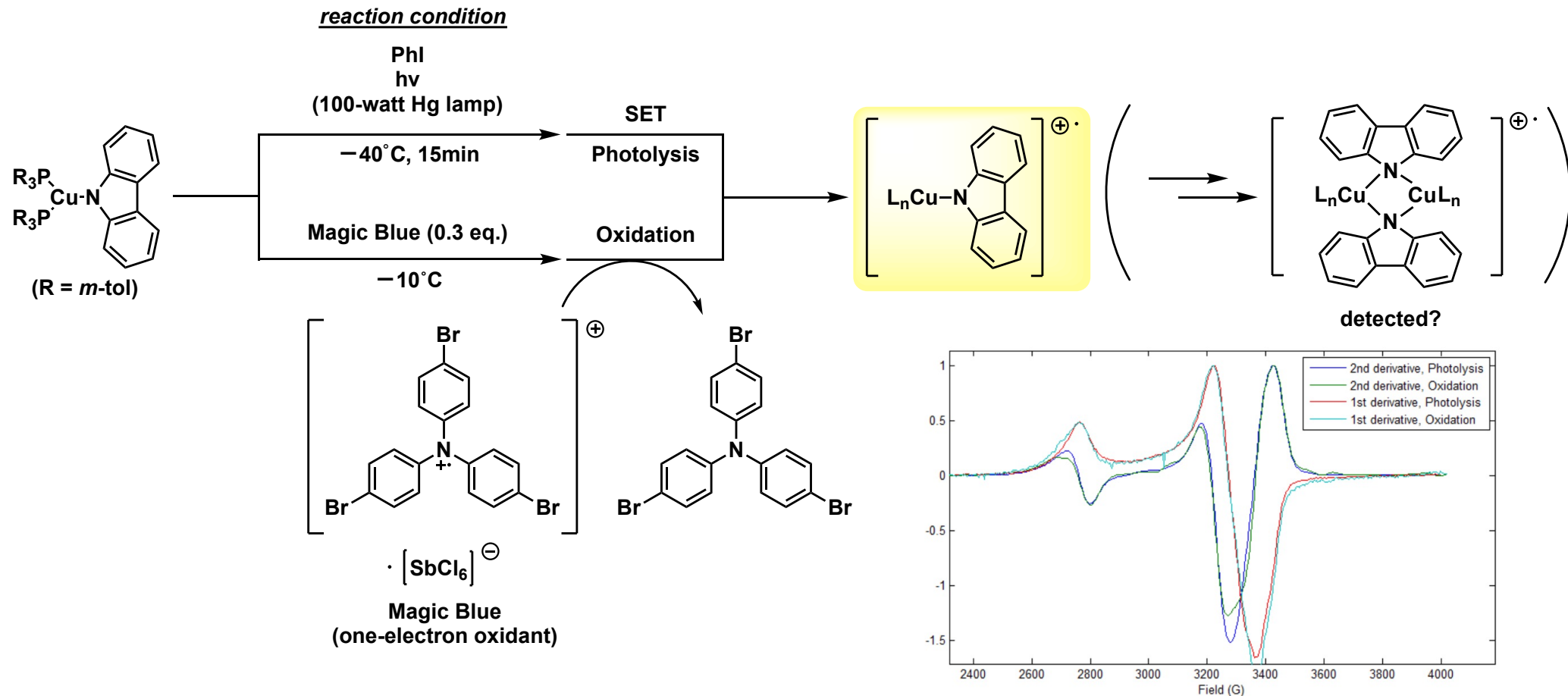


When the energy difference corresponds to the energy of microwaves, electrons absorb the energy of them.

<https://www.jaima.or.jp/jp/analytical/basic/magneticresonance/esr/>

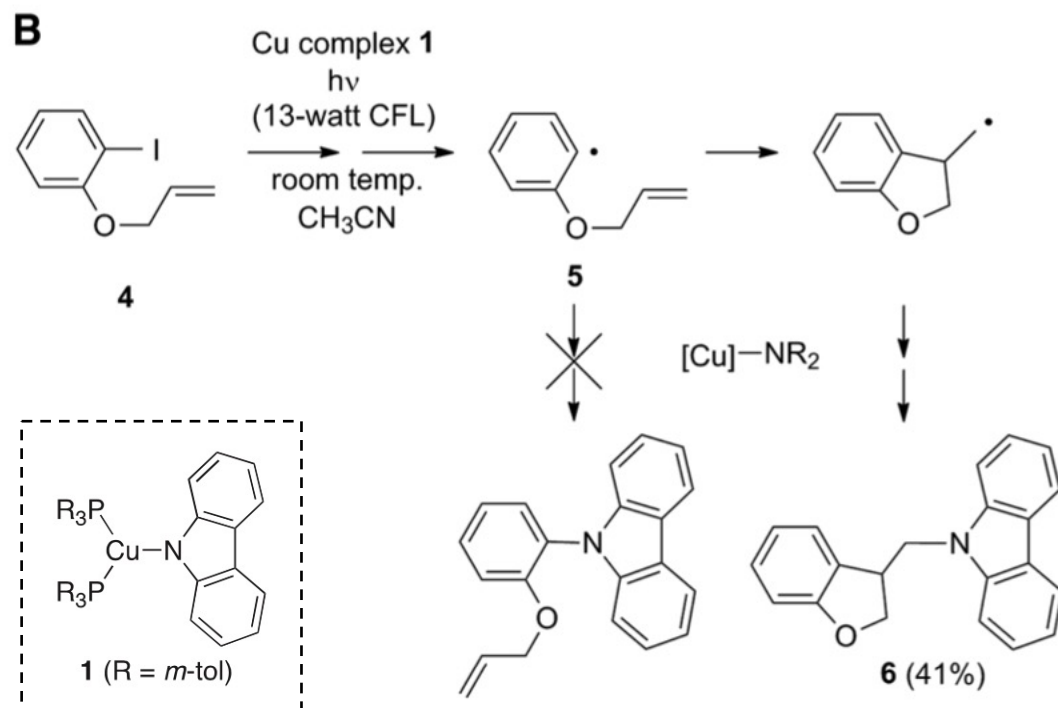
[https://www.oceanochemistry.org/publications/TRIOC/PDF/trioc\\_2006\\_19\\_113.pdf](https://www.oceanochemistry.org/publications/TRIOC/PDF/trioc_2006_19_113.pdf)

# Confirmation of a Radical Pathway: X-band EPR Spectrum



The same radical species can be generated by chemical and by photoinduced oxidation.

# Confirmation of a Radical Pathway: Cyclization in a Photoinduced Condition



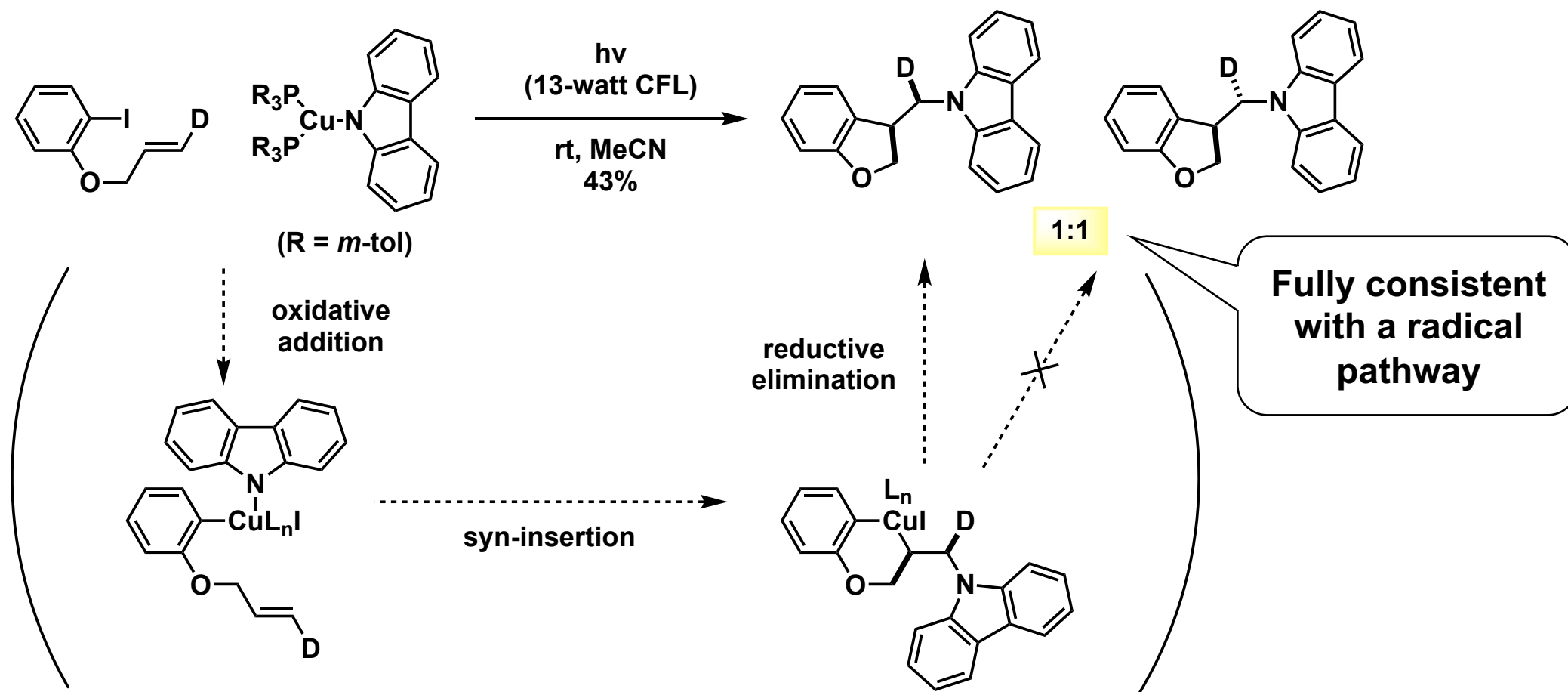
Radical 5 is known to cyclize  
very rapidly  
[rate constant ( $k$ ) =  $9.6 \times 10^9$   
 $s^{-1}$  in dimethyl sulfoxide].

Consistent with a  
radical pathway

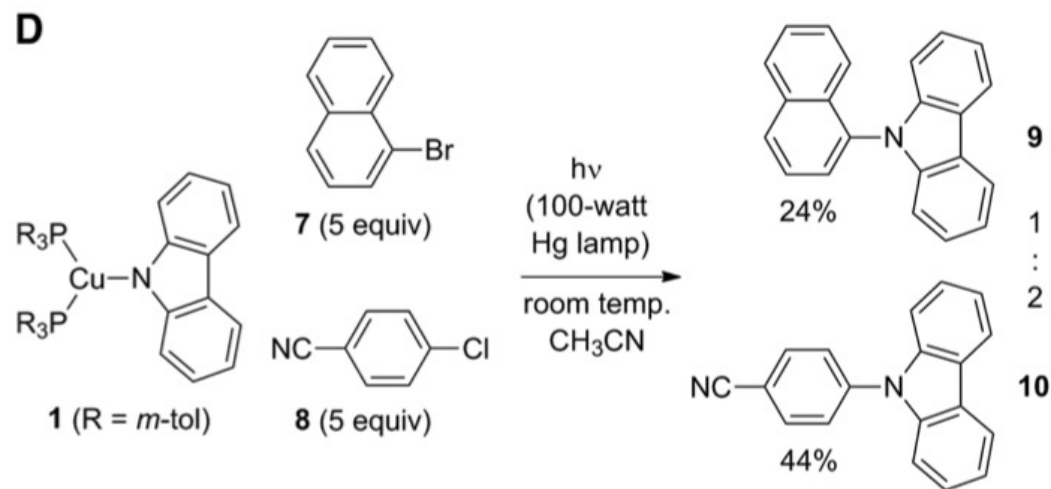
\*This product can be generated via  
concerted oxidative addition of 4 to form  
an aryl-copper reagent, followed by syn-  
insertion and reductive elimination.  
→ ***Needs further investigation***



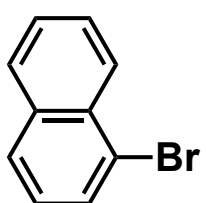
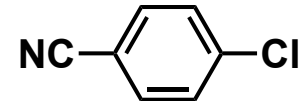
# Confirmation of a Radical Pathway: Stereochemical Study



# Substrate-Competition Study to Confirm a Pathway Involving SET

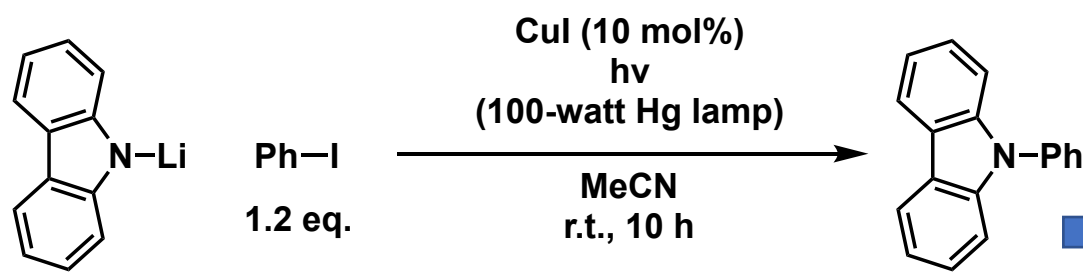


→ Consistent with a radical-based SET pathway for C–N bond formation

	oxidative addition	SET (reduction potential)
	○	△ (–2.17 V)
	△	○ (–2.03 V)

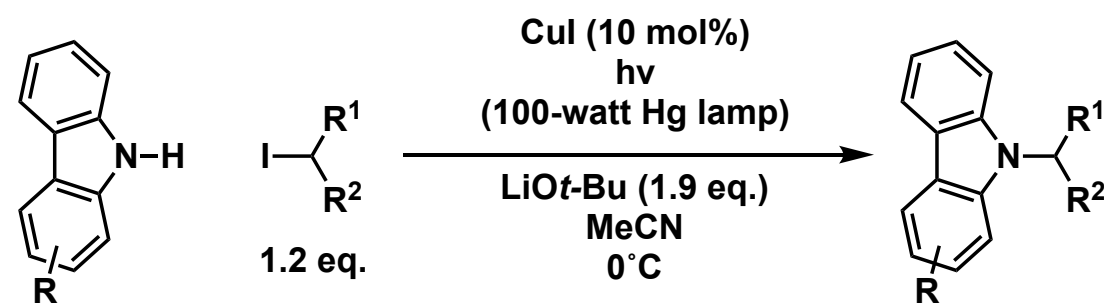
\*reduction potential: versus SCE in DMF

# Expansion of Substrate Scope of Photoinduced C–N Coupling



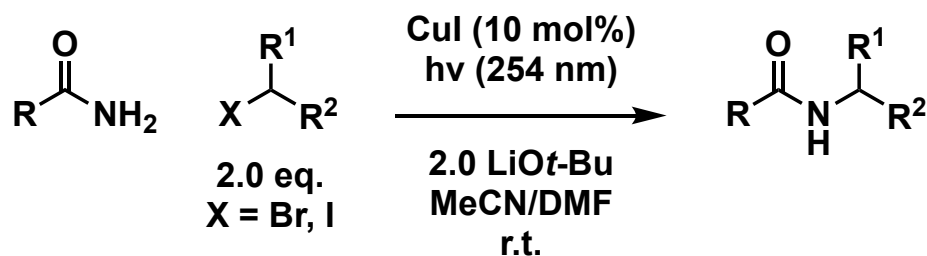
J. C. Peters, G. C. Fu *et al. Science*. **2012**, *338*, 647.

## • Carbazoles + Alkyl halides



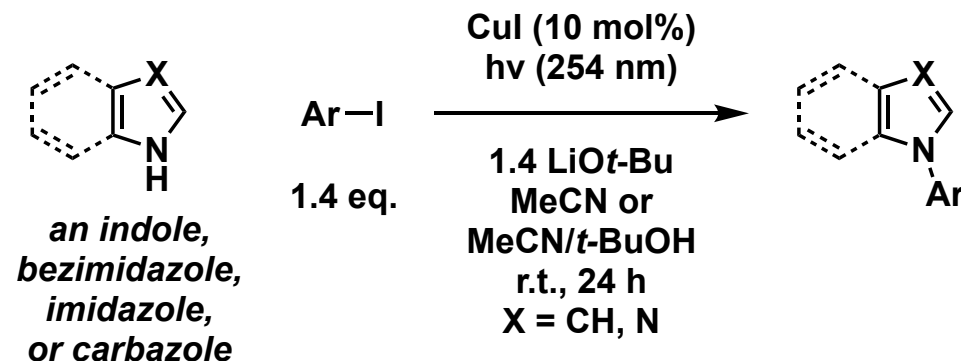
J. C. Peters, G. C. Fu *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 5129.

## • Amides + Alkyl halides



J. C. Peters, G. C. Fu *et al. J. Am. Chem. Soc.* **2014**, *136*, 2162.

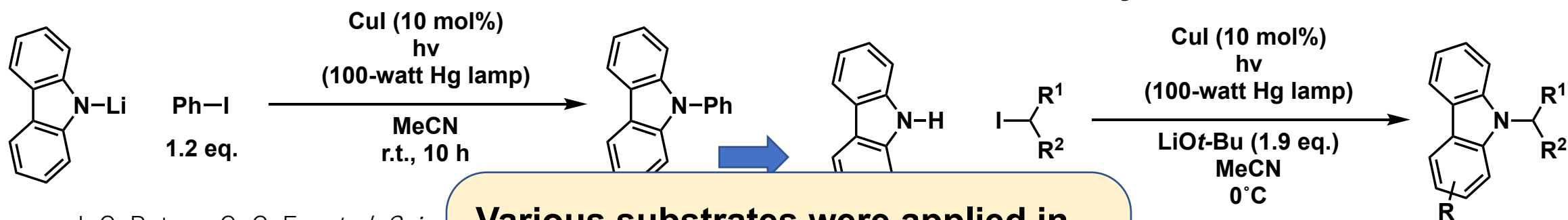
## • Various nitrogen nucleophiles + Aryl halides



J. C. Peters, G. C. Fu *et al. J. Am. Chem. Soc.* **2013**, *135*, 13107.

# Expansion of Substrate Scope of Photoinduced C–N Coupling

## • Carbazoles + Alkyl halides

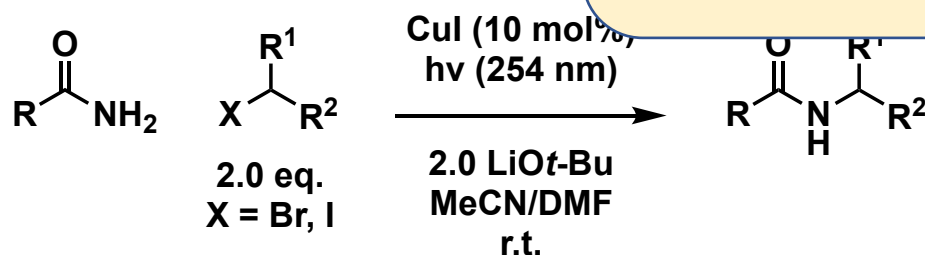


J. C. Peters, G. C. Fu *et al. Science*

Various substrates were applied in the reaction with similar mechanism.  
 → The next challenge is enantioconvergent reaction.

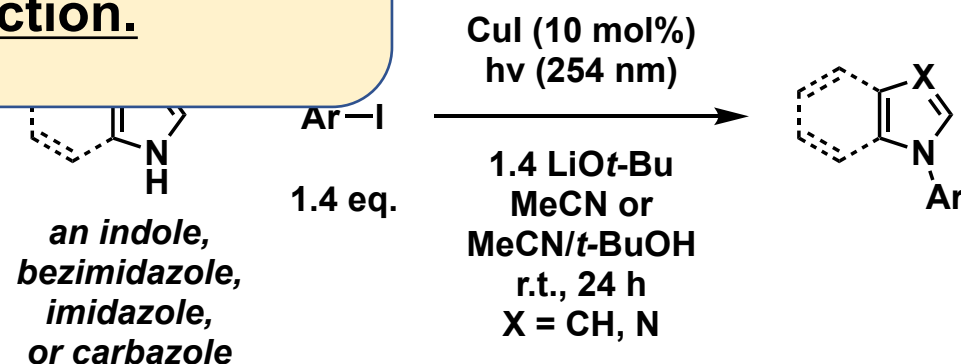
*Angew. Chem. Int. Ed.* **2013**, *52*, 5129.

## • Amides + Alkyl halides



J. C. Peters, G. C. Fu *et al. J. Am. Chem. Soc.* **2014**, *136*, 2162.

## nucleophiles + Aryl halides



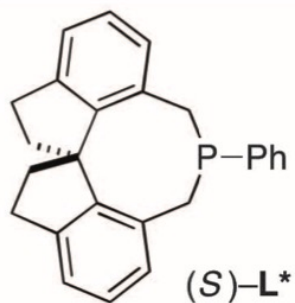
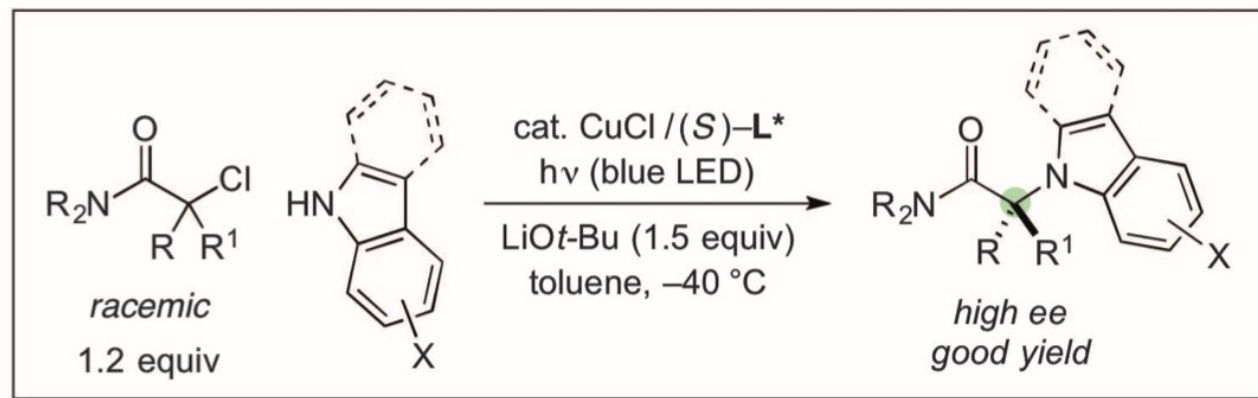
J. C. Peters, G. C. Fu *et al. J. Am. Chem. Soc.* **2013**, *135*, 13107.

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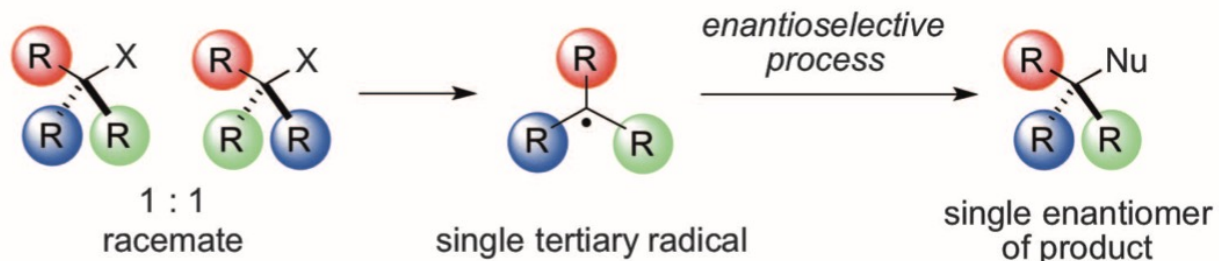
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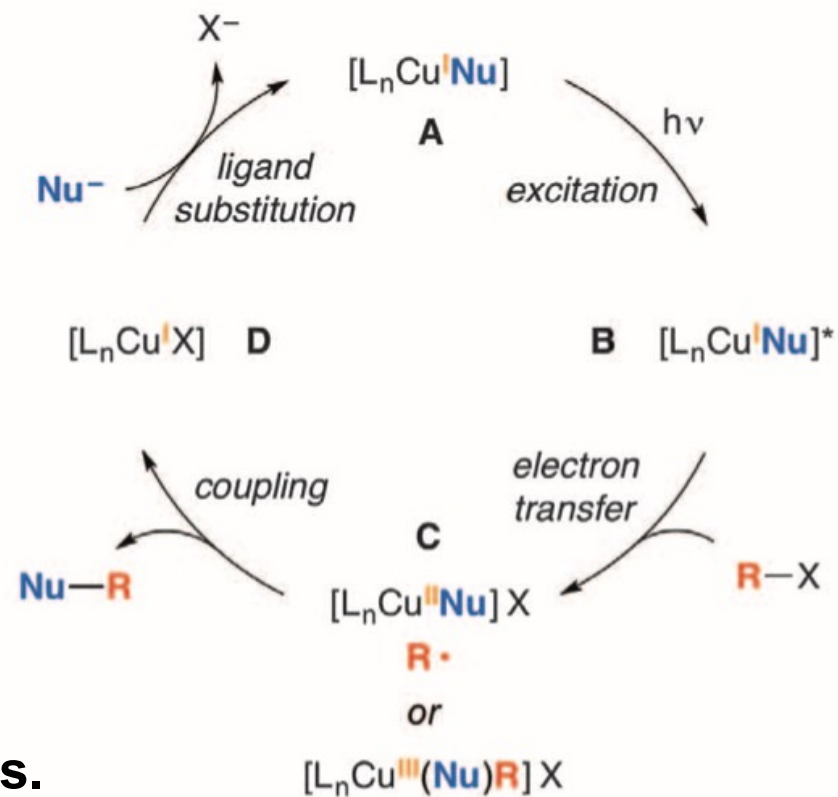
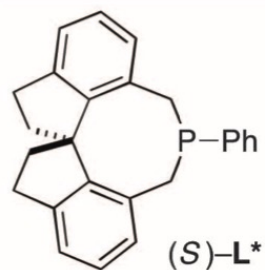
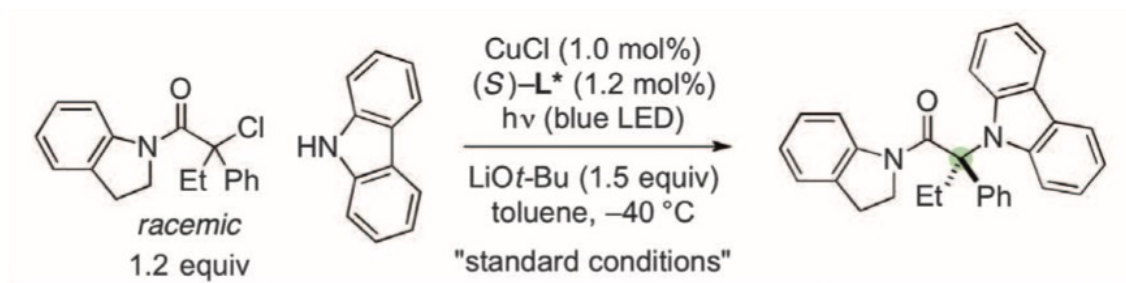
# Enantioconvergent C–N Couplings from Carbazoles



- photochemistry and enantioselectivity via a single transition metal (copper)
- enantioconvergent C–N cross-couplings of racemic alkyl electrophiles
- high enantioselectivities with tertiary electrophiles

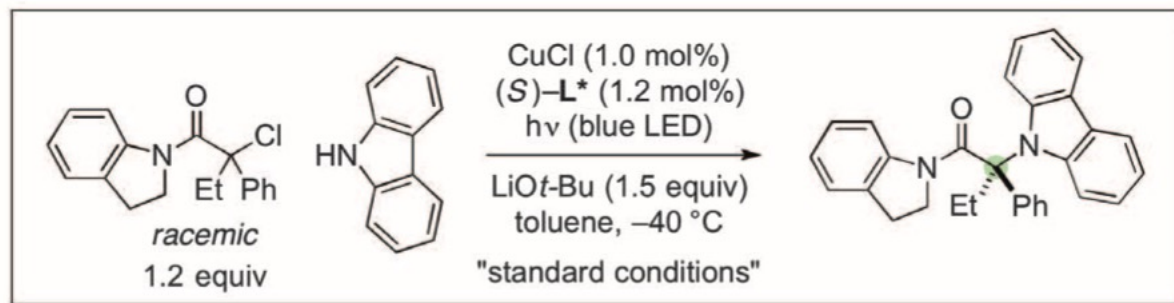


# Possible Reaction Pathway

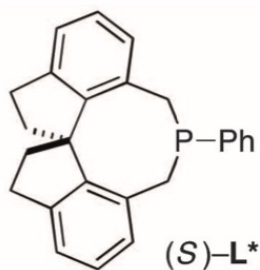


It is almost the same with the previous reactions.

# Effect of Changes in Reaction Parameters



entry	change from the "standard conditions"	yield (%)	ee (%)
1	<b>none</b>	<b>95</b>	<b>95</b>
2	CuCl (0.25 mol%), ( <i>S</i> )-L* (0.30 mol%)	77	95
3	no CuCl	<1	–
4	no hν	<1	–
5	no ( <i>S</i> )-L*	3	0
6	added water (0.10 equiv)	83	94

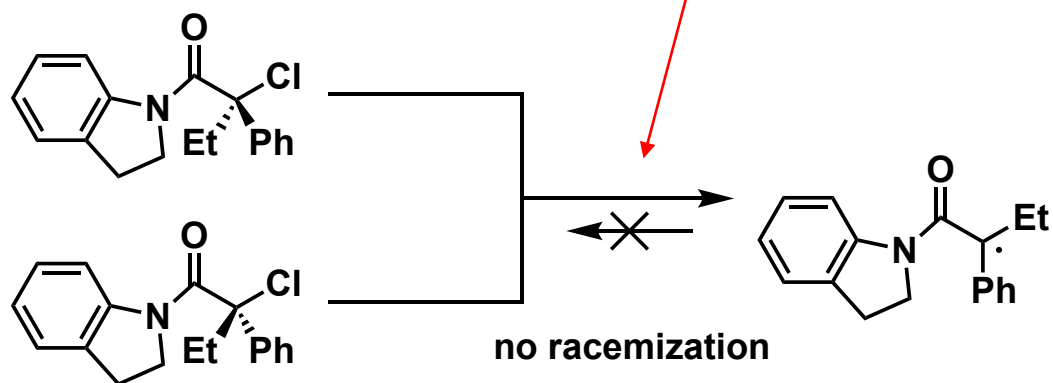
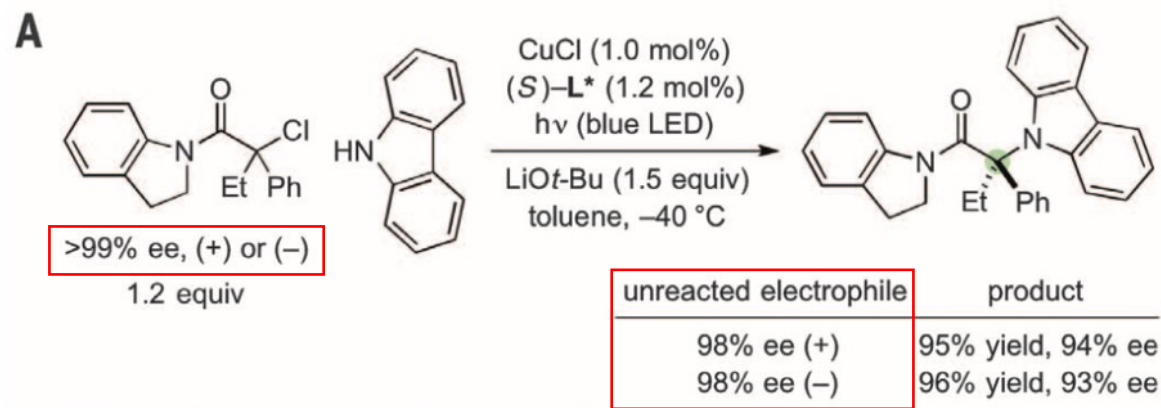


High ee was achieved by adding the chiral ligand, thereby proving that a phosphine (L\*) binds to a copper in the presence of the nucleophiles which are also likely to bind to a copper.

\*They are taking advantage of the photocatalyst, which doesn't work without phosphine binding to a copper (entry 5).

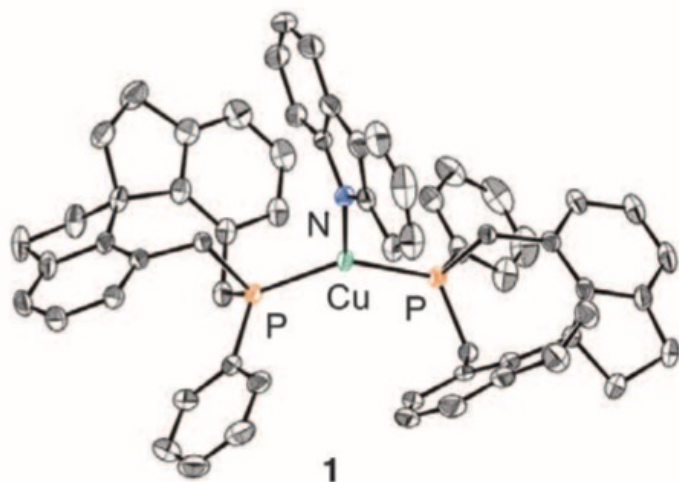
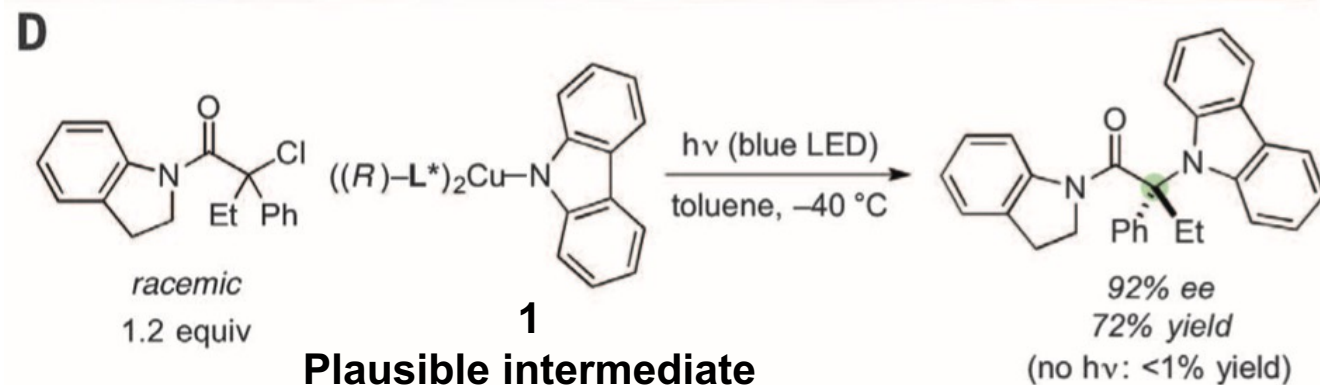


# Investigation of Kinetic Resolution



The chiral ligand determines the absolute configuration of the stereochemistry very effectively, and C–Cl bond cleavage is irreversible.

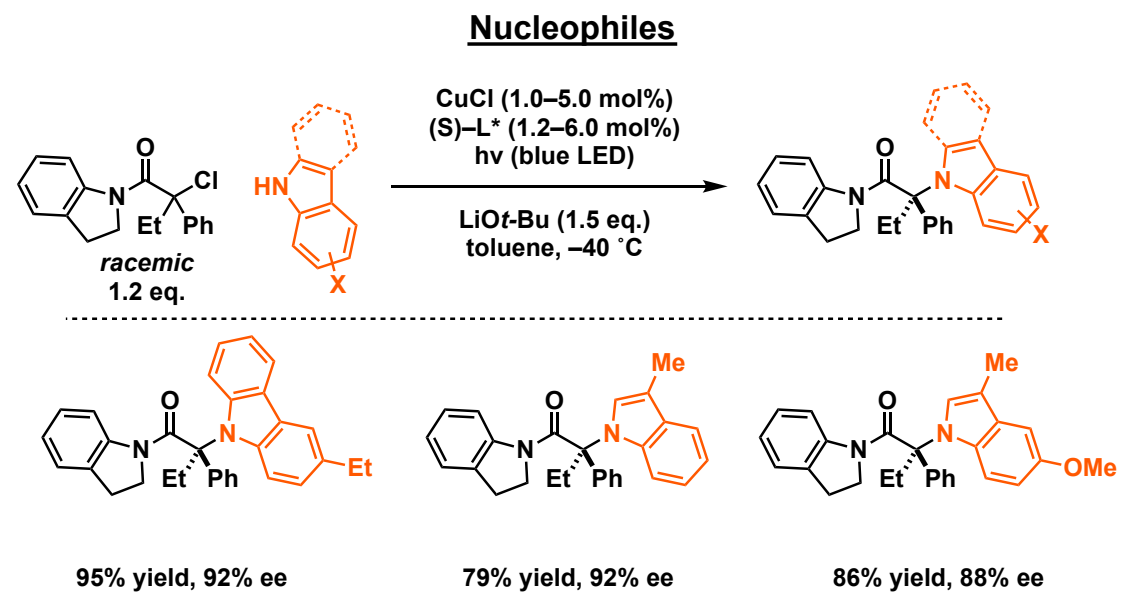
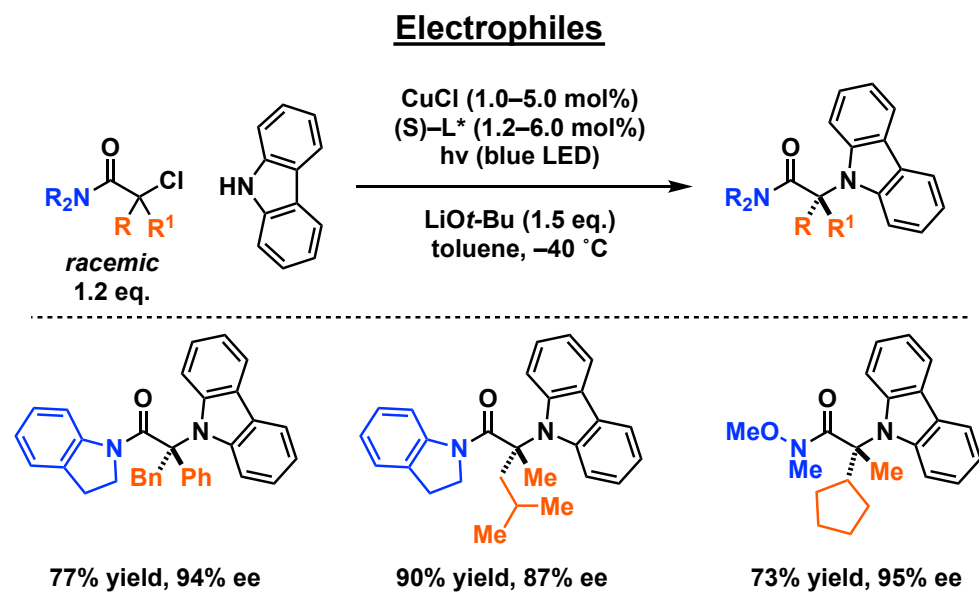
# Plausible Intermediate in the Catalytic Cycle



**Plausible intermediate**

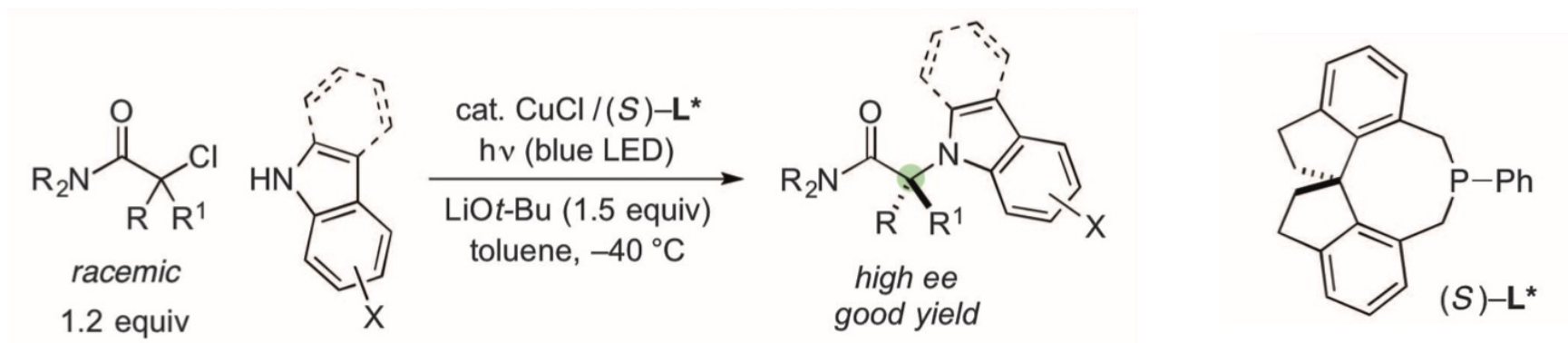
Irradiation of complex **1** in the presence of a racemic tertiary alkyl halide leads to C–N bond formation in good yield and with enantioselectivity.

# Substrate Scope



# Short Summary

- **Enantioconvergent C–N couplings were attained.**
- **Substrates are limited to carbazoles and indoles (since visible light is used for irradiation).**



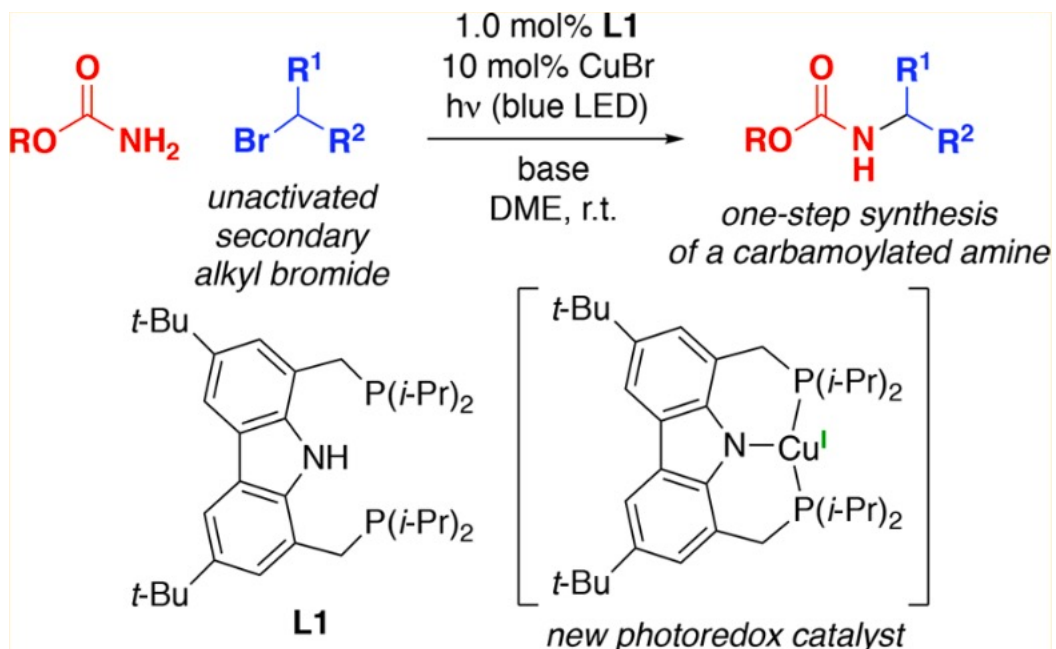
- **Expansion of the nucleophile scope requires new strategy.**

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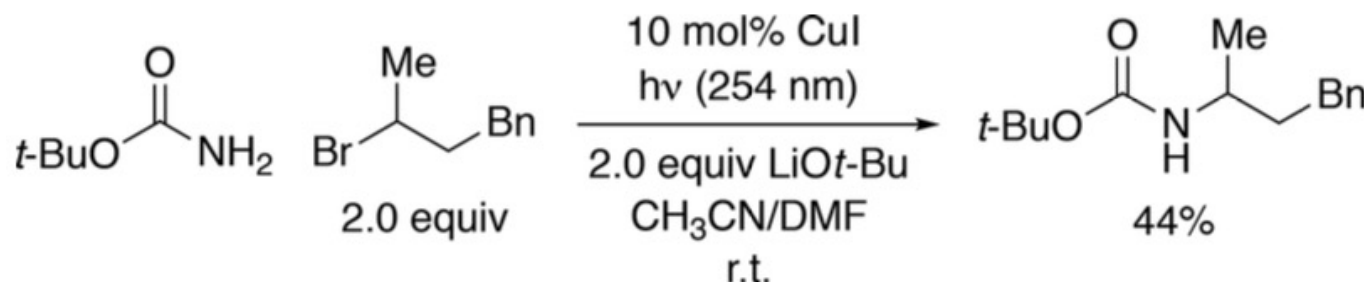
# Expanding Nucleophile Scope by Designing a Ligand



**This reaction can be applied not only to carbazoles and indoles but also to carbamates.**

**\*Not enantioconvergent**

# Selective Mono-Alkylation of a Primary Carbamate

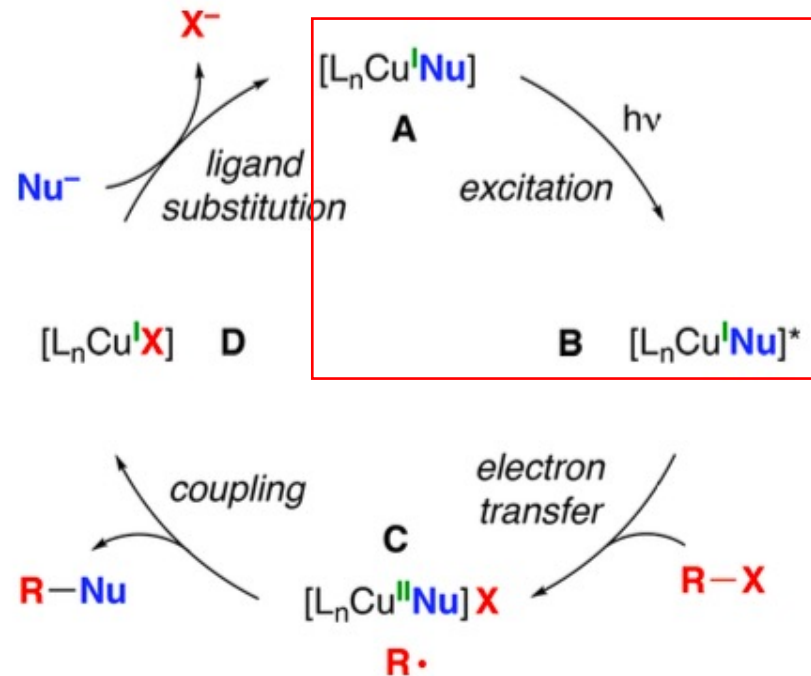


cf. J. C. Peters, G. C. Fu *et al.* *J. Am. Chem. Soc.* **2014**, *136*, 2162.

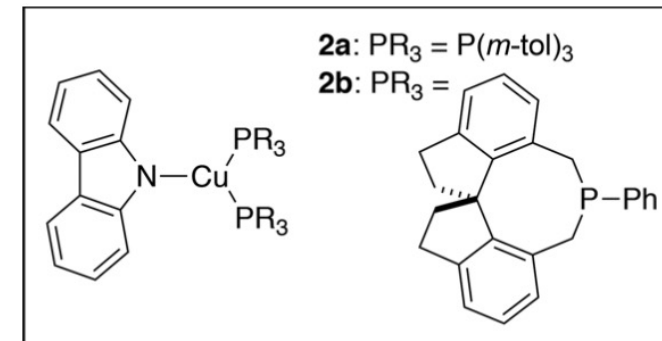
- Inefficiency of the alkylation
- Need for high-energy ultraviolet irradiation
- Use of an excess of the electrophile

→ To enhance the reactivity under a mild condition, using visible light (though the substrate is limited so far) may be effective.

# Limitations on Substrates in Previous Approach Using Visible Light



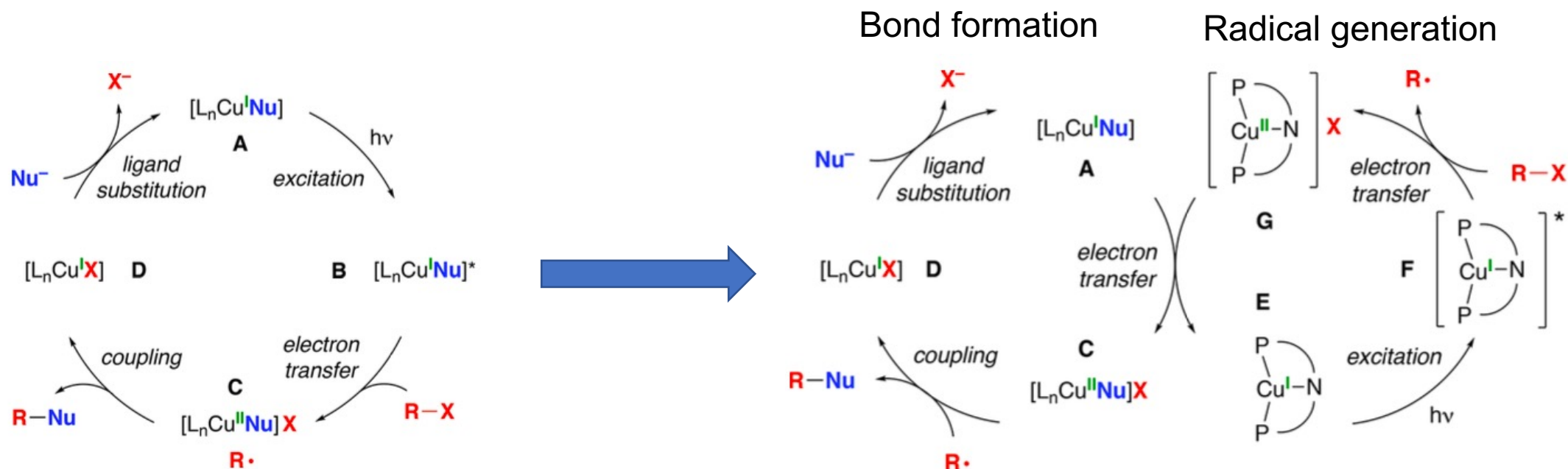
The photophysical properties of the copper-nucleophile complex are dependent on the structure of the nucleophile (only carbazoles and indoles are applicable so far).



\*Example of the complexes that can absorb relatively long-wavelength lights



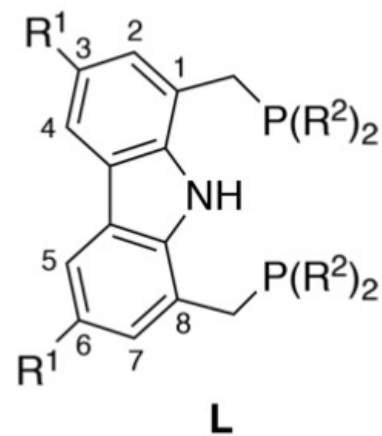
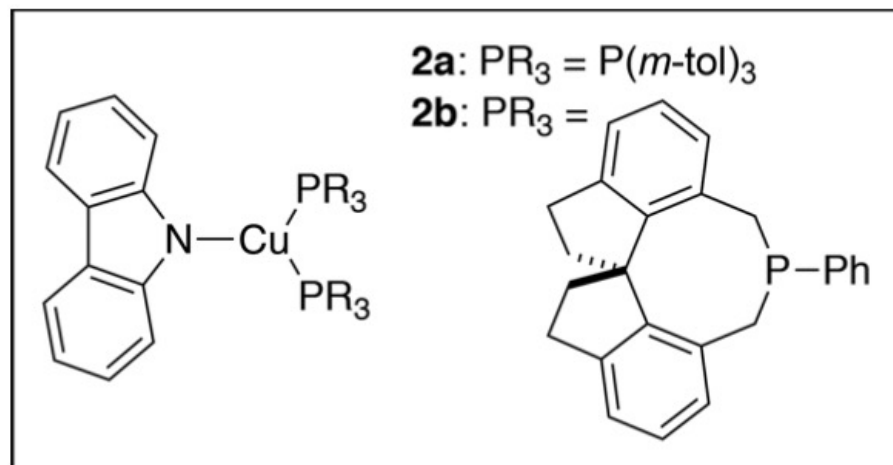
# Solution: Development of a Photocatalyst



Two different types of copper catalysts would be generated in situ:

1. Catalyst (E) that serves as a photoredox catalyst ← designed this time
2. Catalyst (A) that facilitates the bond formation

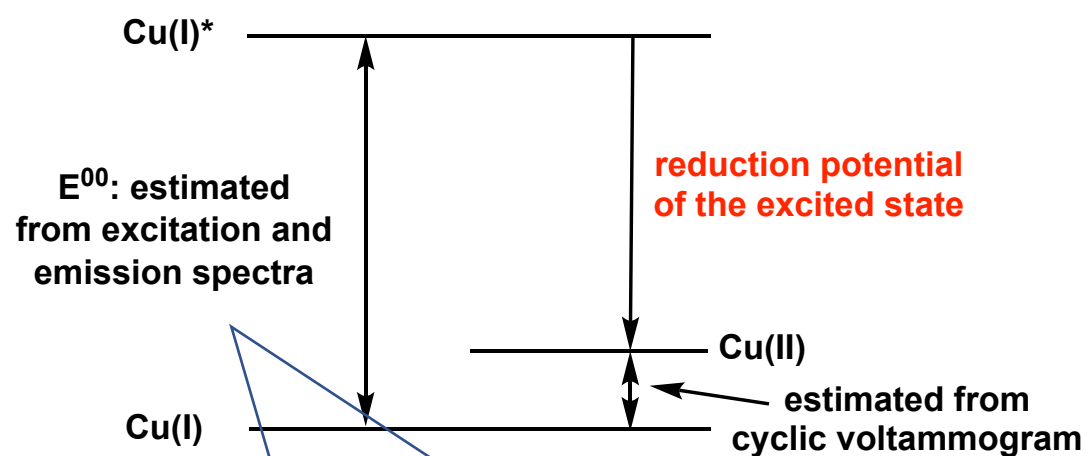
# Design of a New Photocatalyst



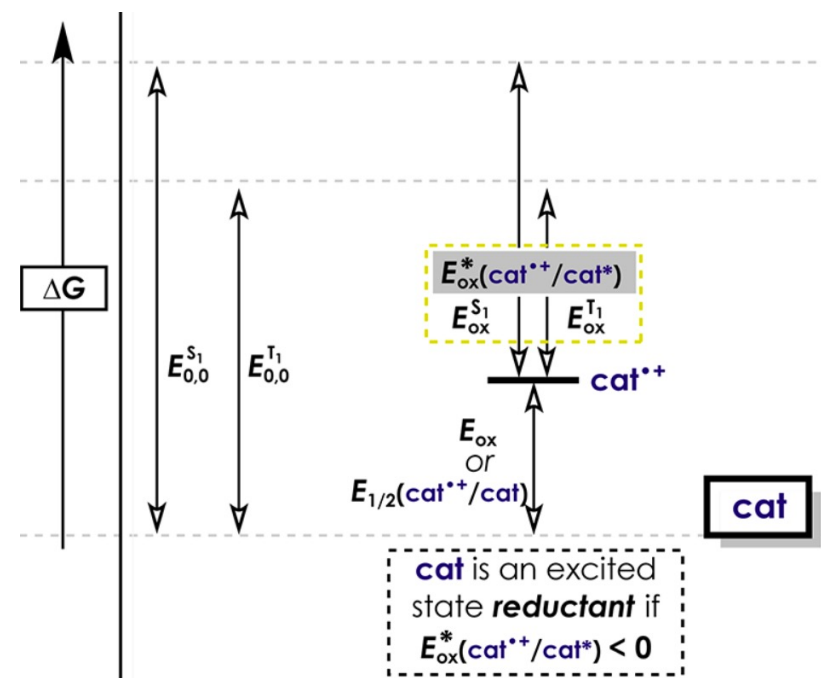
**\*Catalysts such as 2a (2012 Science) and 2b (2016 Science) can react to form C–N bonds upon irradiation with relatively long-wavelength light.**

- Linking these ligands, they made a copper complex which
- is stable to ligand substitution
  - can serve as an effective photocatalyst which works upon exposure to visible light independent of the nucleophile.

# Estimation of the Reduction Potential of the Excited State: The Method



The transition energy between the lowest energy vibrational state ( $\nu = 0$ ) of  $S_1$  to  $\nu = 0$  of  $S_0$



# Estimation of the Reduction Potential of the Excited State: Estimation of $E^{00}$

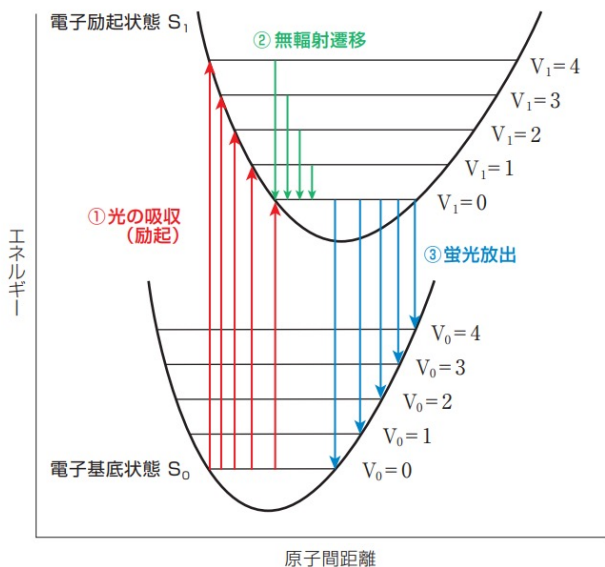


図6 エネルギー準位と吸収・蛍光

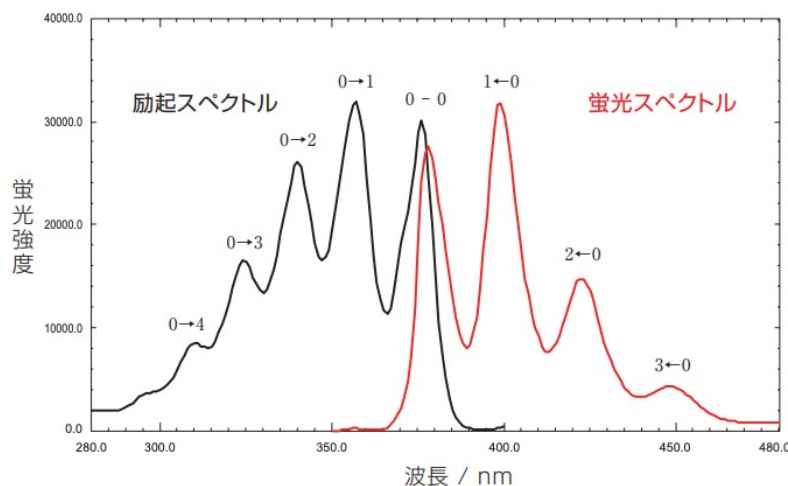
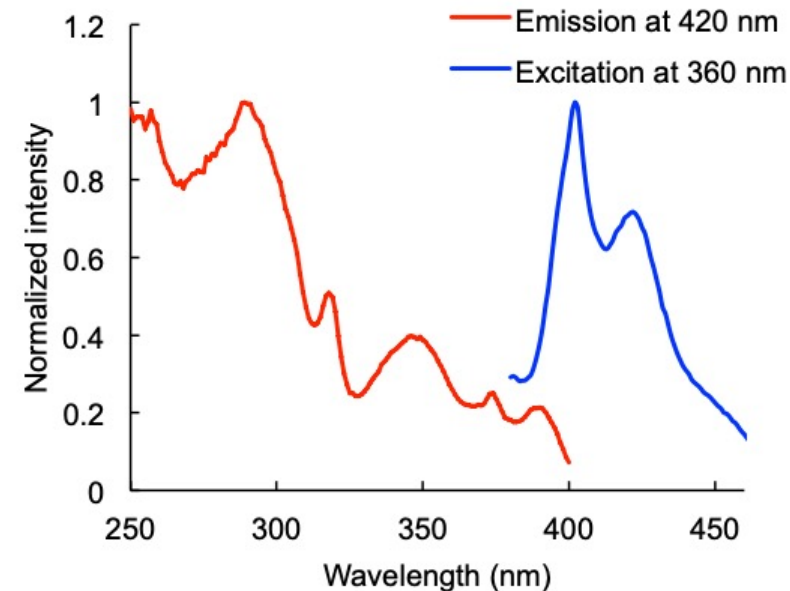


図7 アントラセン(シクロヘキサン溶液)の励起・蛍光スペクトル



In this case,  $E^{00}$  seems to have been estimated from the fluorescence maximum: 400 nm  
→ corresponds to 3.1 eV

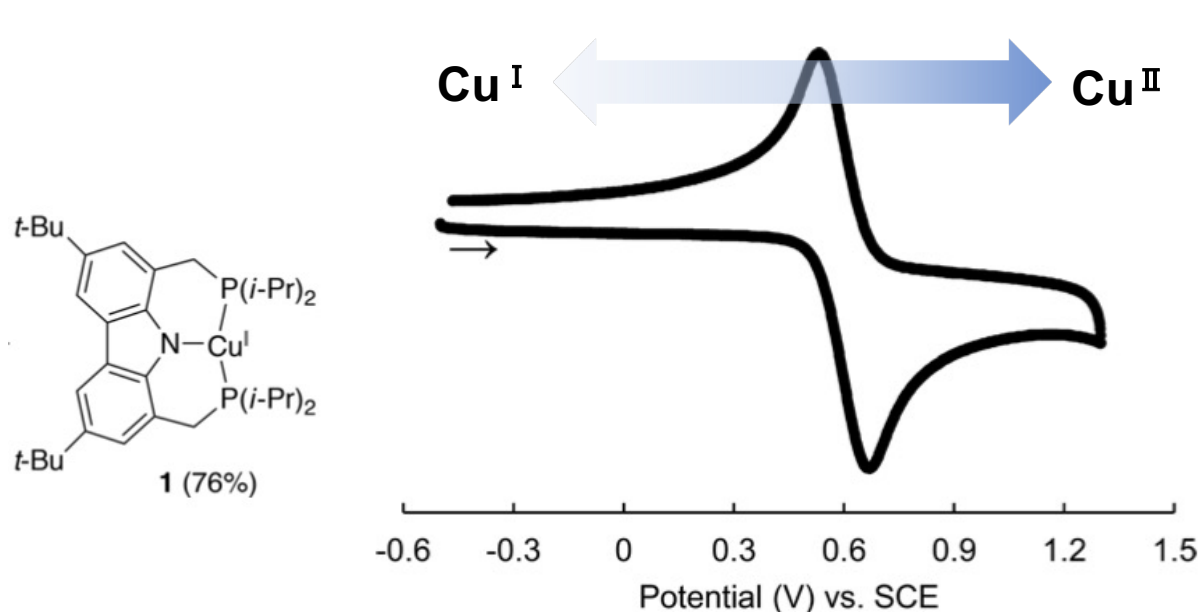
$E^{00}$  is normally estimated at the intersection between normalized symmetrical absorbance and emission spectra.

<https://www.an.shimadzu.co.jp/sites/an.shimadzu.co.jp/files/ckeditor/uv/support/lib/uvtalk/pdf/vol17.pdf>

J. C. Peters, G. C. Fu *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 18101.

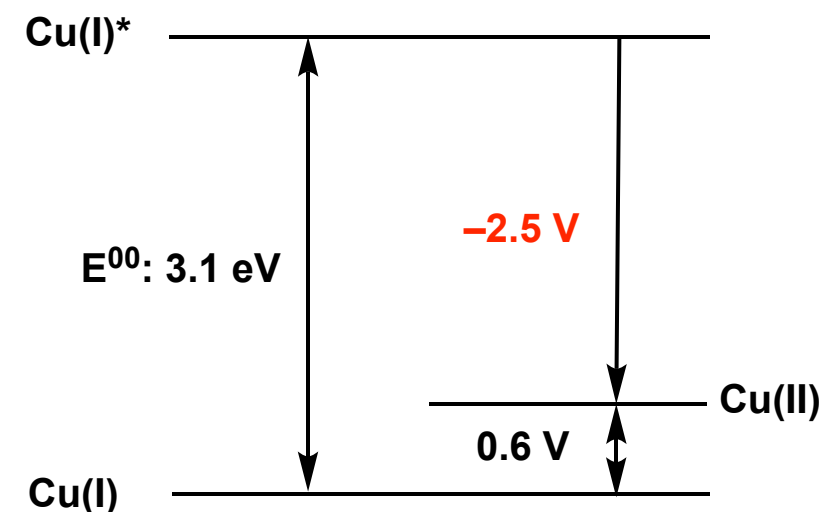
D. A. Nicewicz *et al.* *Chem. Rev.* **2016**, *116*, 10075.

# Estimation of the Reduction Potential of the Excited State: Estimated Results



Cyclic voltammogram of copper complex 1 in THF (100 mV/s scan rate; 0.1 M in TBAPF6)

A cyclic voltammogram shows a reversible wave at ~0.6 V (vs. SCE).

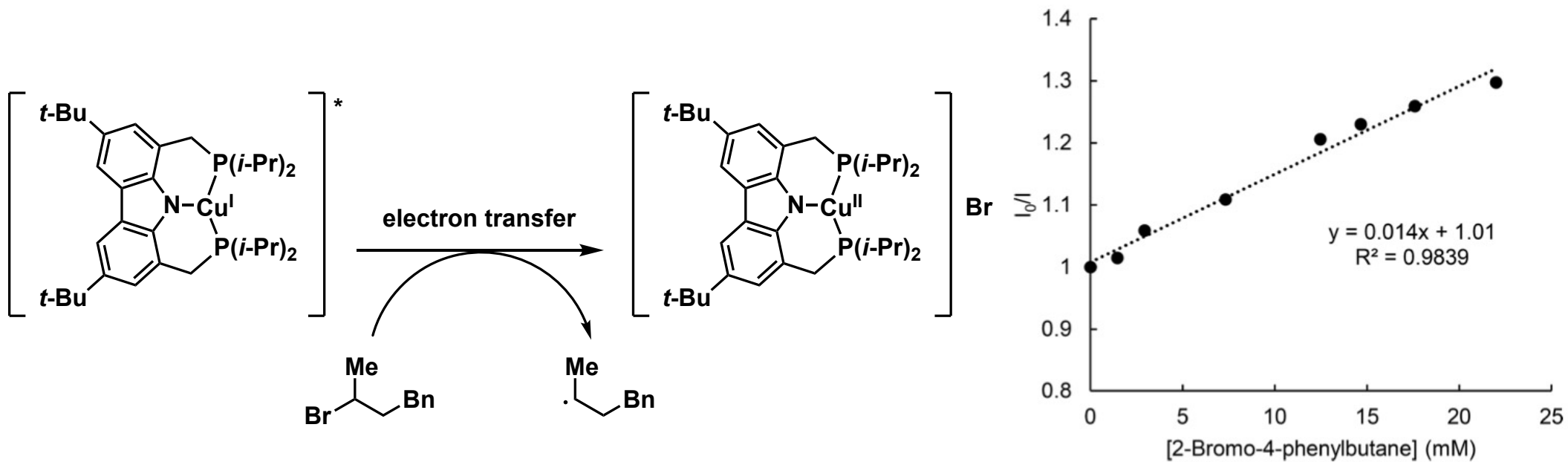


$E^{00}: 3.1 \text{ eV}$

Ground-state redox couple : ~0.6 V

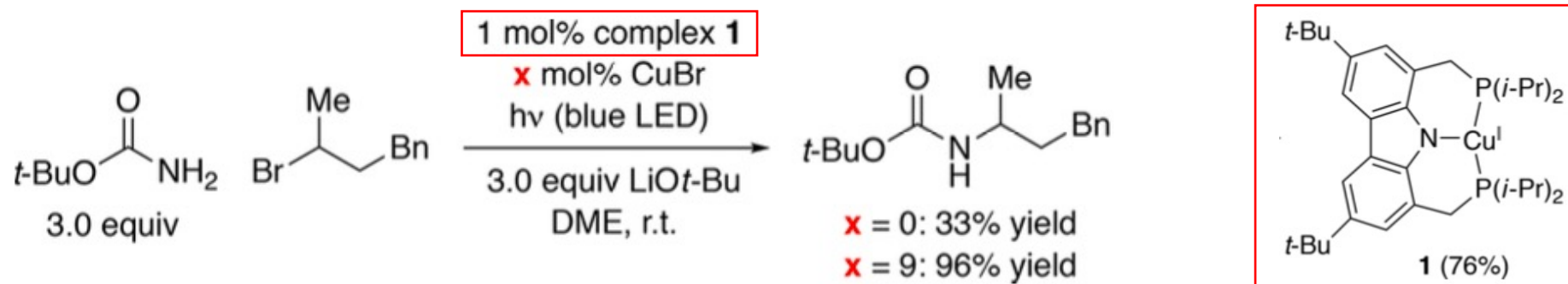
Predicted reduction potential :  
-2.5 V (vs. SCE)  $\cong$  -2.6 V (complex 2a)

# Stern-Volmer Luminescence Quenching

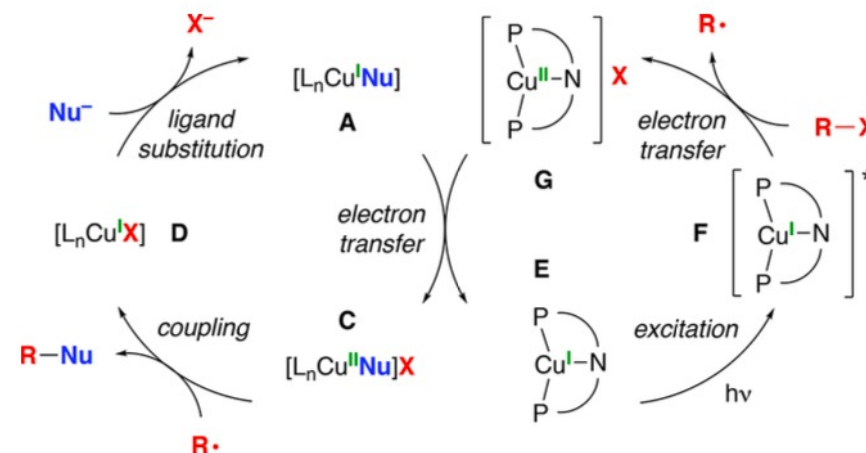


The quenching of the emission at 427 nm was confirmed.  
→ The excited state of the designed photocatalyst is capable of reducing the alkyl bromide.

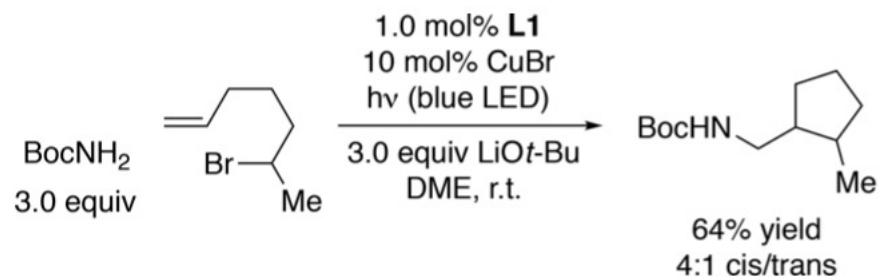
# The Role of the Designed Photocatalyst



**Excess CuBr → Copper complex 1 may be serving the typical role of photoredox catalysts and not directly involved in the key bond-forming process.**

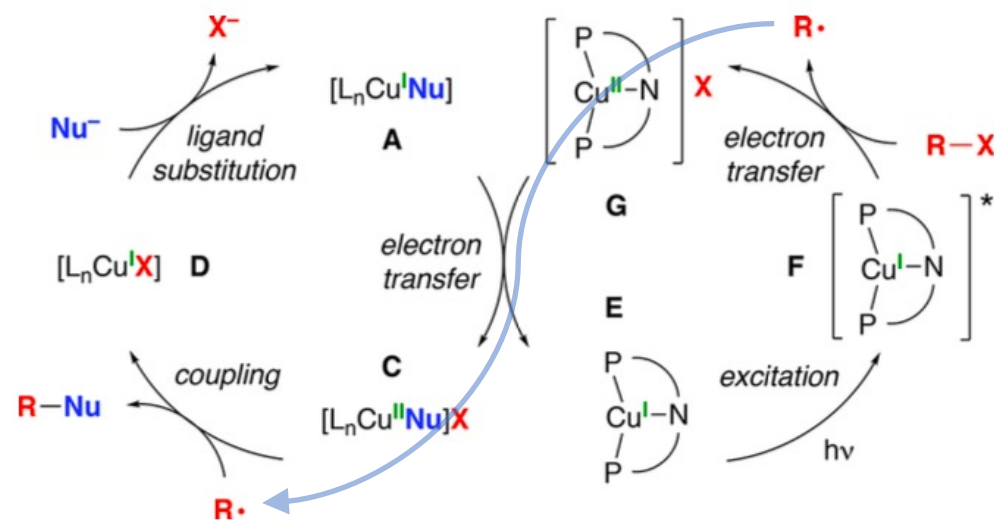


# Radical Cyclization Experiment



The same stereoselectivity with the cyclization of the secondary alkyl radical

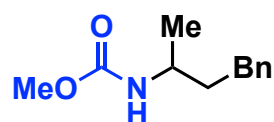
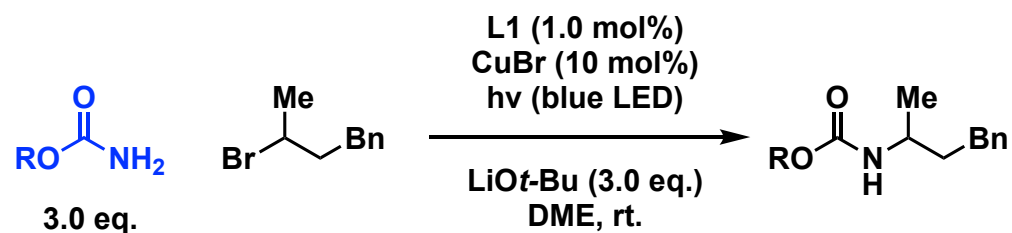
The rate constant of the cyclization of alkyl radical:  $1.0 \times 10^5 \text{ s}^{-1}$   
< Typical rates of diffusion: more than  $10^8 \text{ s}^{-1}$   
→ Consistent with the proposed mechanism showing that after radical being generated, it diffuses before coupling



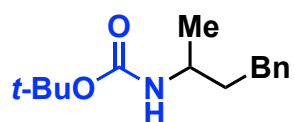


# Substrate Scope

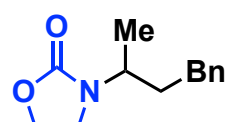
## Carbamates



90% yield

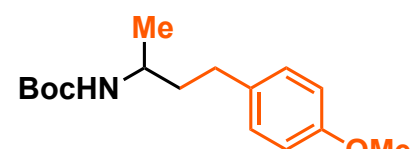
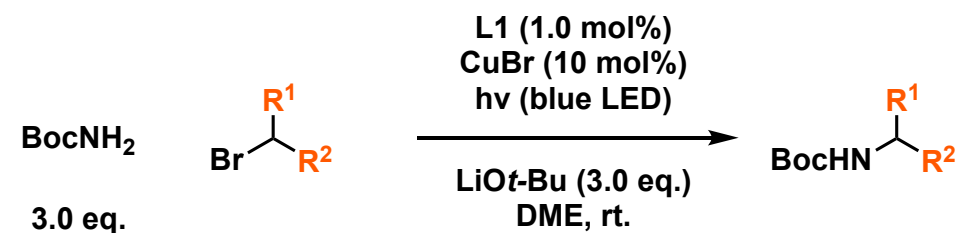


87% yield

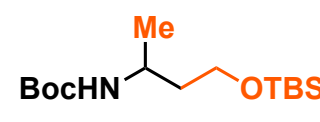


74% yield

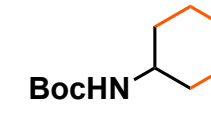
## Electrophiles



81% yield



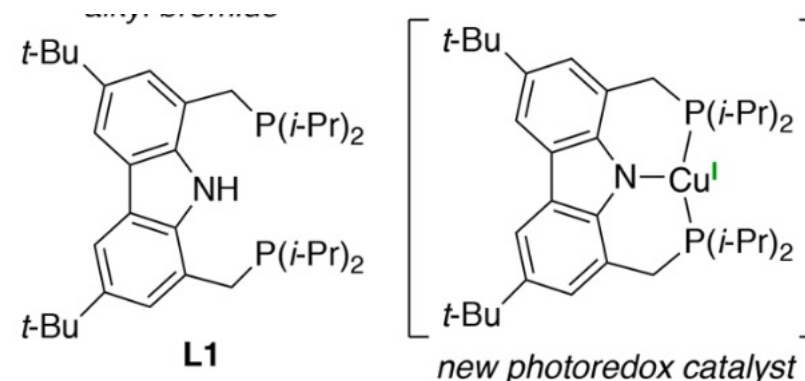
72% yield



81% yield

# Short Summary

- By designing a ligand, nucleophile scope were expanded to carbamates other than carbazoles and indoles.
- The newly designed photocatalyst can work independently as a photocatalyst, and basically does not participate in bond forming process.



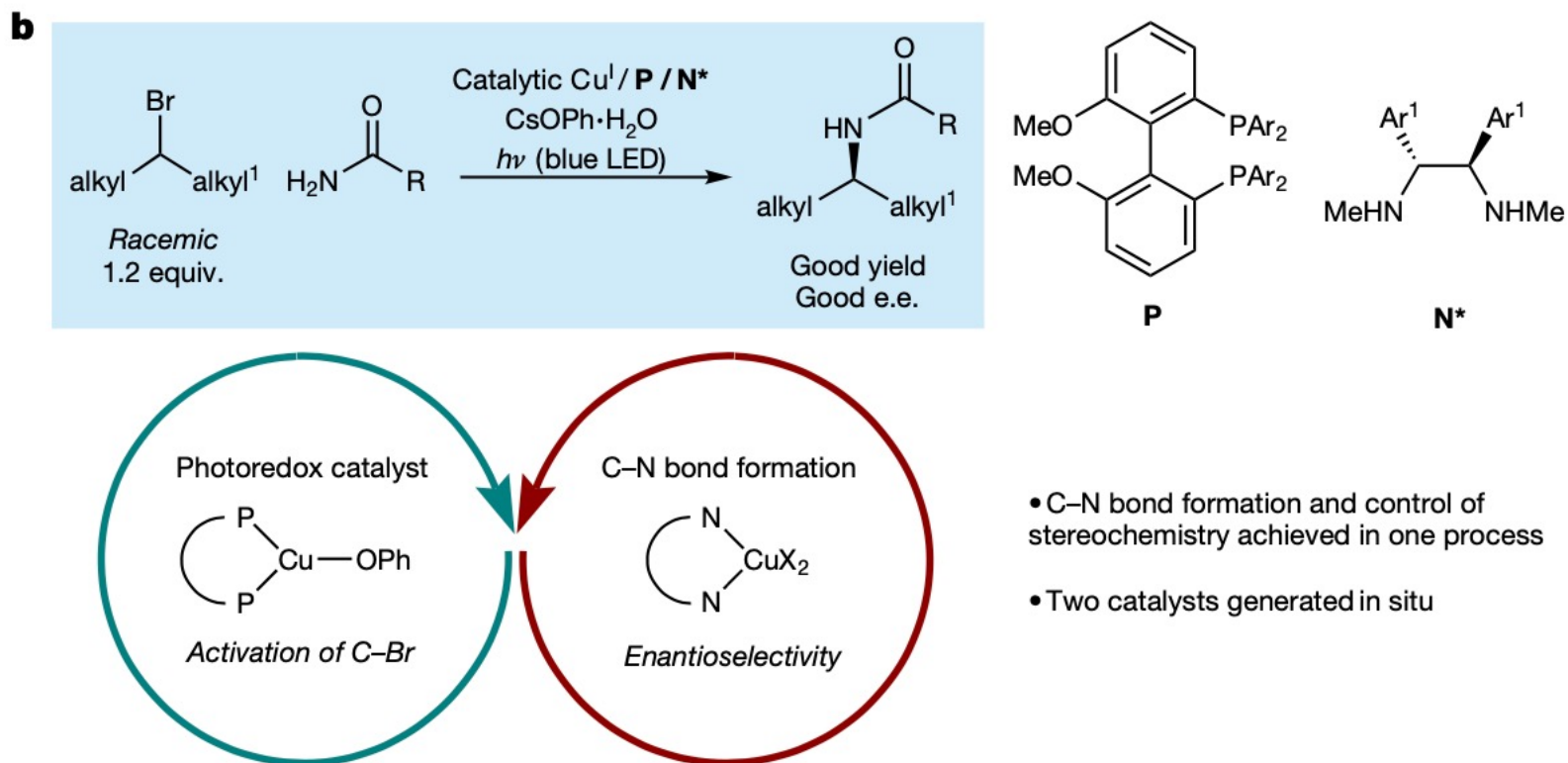
- Enantioselective reaction with expanded scope may be attained by developing a new strategy which includes a chiral catalyst.

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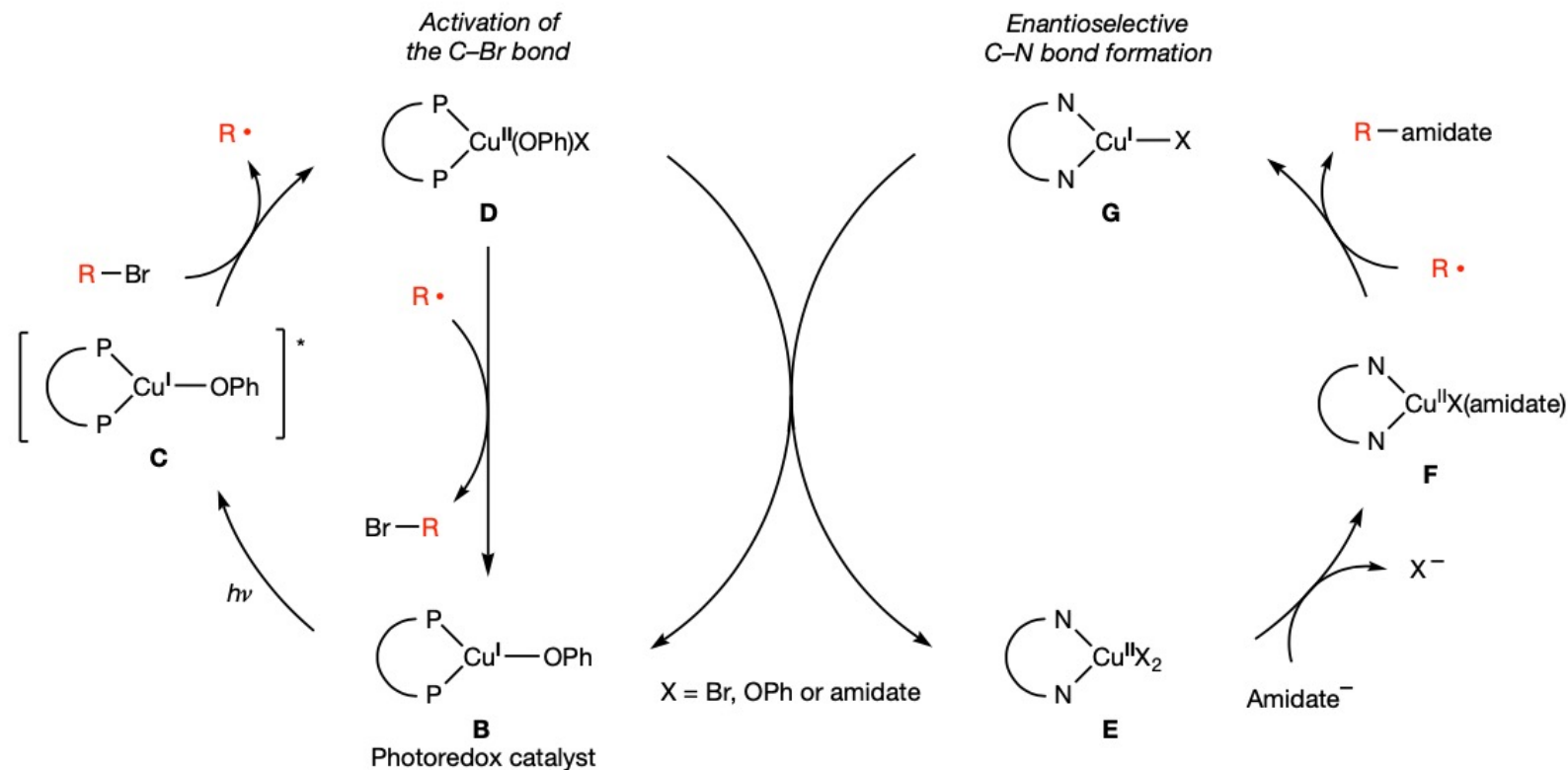
1. Introduction
2. Enantioconvergent C–N couplings from carbazoles
3. C–N couplings independent of nucleophiles by designing a ligand
4. **Enantioconvergent C–N couplings independent of nucleophiles by using 3 ligands**
5. Summary and perspective

# Enantioconvergent Reaction with Expanded Scope by Using 3 Ligands



They succeeded in developing an enantioconvergent reaction which is independent of the nucleophiles by using 3 ligands: a bisphosphine, a phenoxide and a chiral diamine.

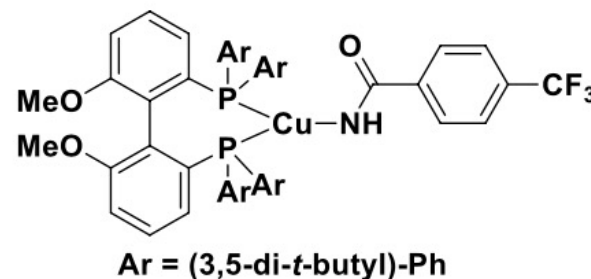
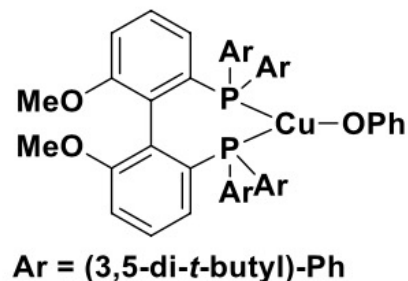
# Possible Catalytic Cycle



The reaction mechanism is similar to that of a previous reaction (cf. p.32, 2017 JACS).

# Investigation of Possible Photocatalysts

Possible photocatalysts: The electrophile is consumed in the absence of diamine N1\* but not in the absence of bisphosphine P. → PCuI(OPh) and PCuI(amidate)



To compare these two,

- Estimated excited-state reduction potentials
- Excited-state lifetime measurement
- Stern-Volmer luminescence quenching

were investigated.

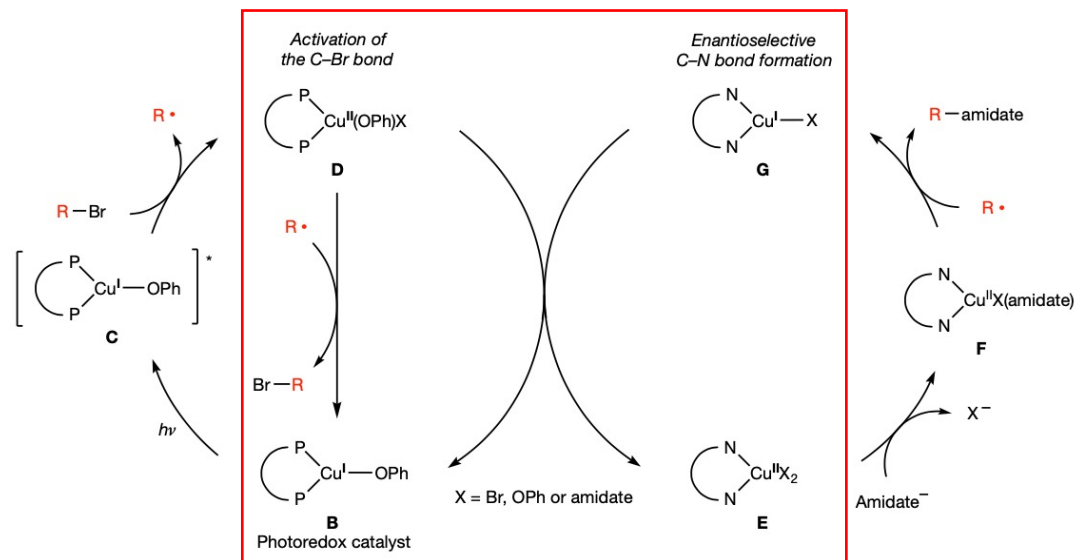
# Results of the Investigation of Possible Photocatalysts (PCu<sup>I</sup>(OPh) or PCu<sup>I</sup>(amidate))

	PCu <sup>I</sup> (OPh)	PCu <sup>I</sup> (amidate)
Estimated excited-state reduction potential* (vs Fc <sup>+</sup> /Fc)	-2.8 V	-2.3 V
Excited-state lifetime measurement	4.6 μs	2.4 μs
Stern-Volmer constant	189 M <sup>-1</sup>	25.2 M <sup>-1</sup>

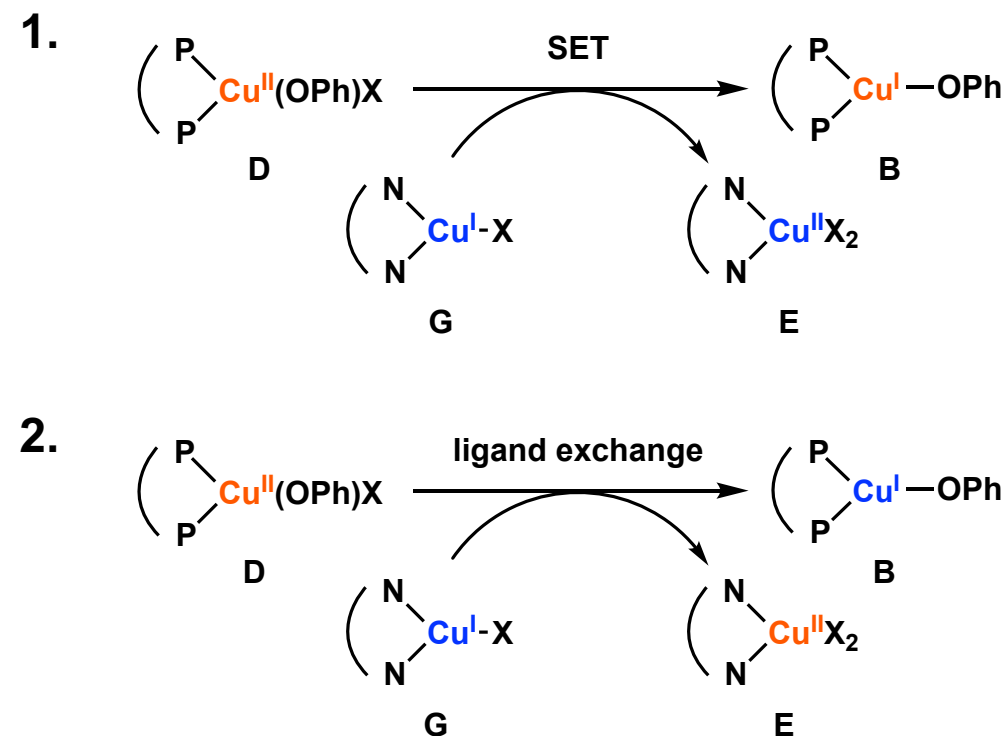
\*The estimated reduction potential of the representative electrophiles: -2.3 V and -2.4 V (vs Fc<sup>+</sup>/Fc)

**These results point to PCu<sup>I</sup>(OPh) complex as the more likely photocatalyst under the reaction condition.**

# Investigation of the Reaction where Two Catalytic Cycles Intersect (D&G→B&E)

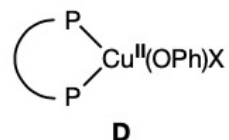


## Two plausible mechanisms

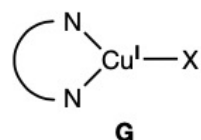




# 1. SET Mechanism: Prediction of Redox Potentials



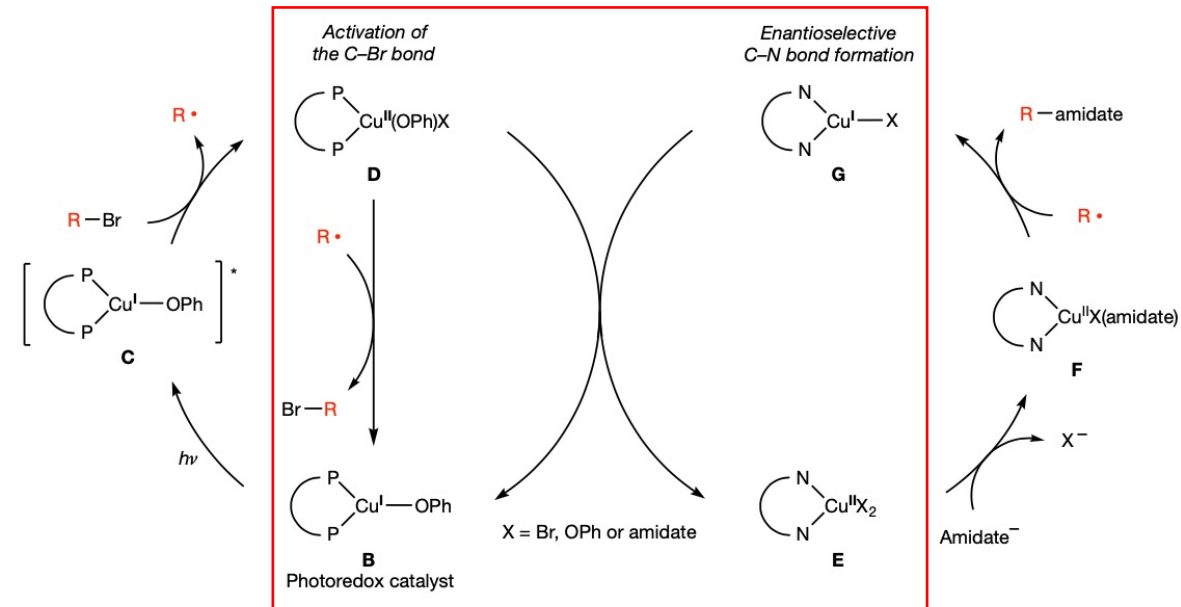
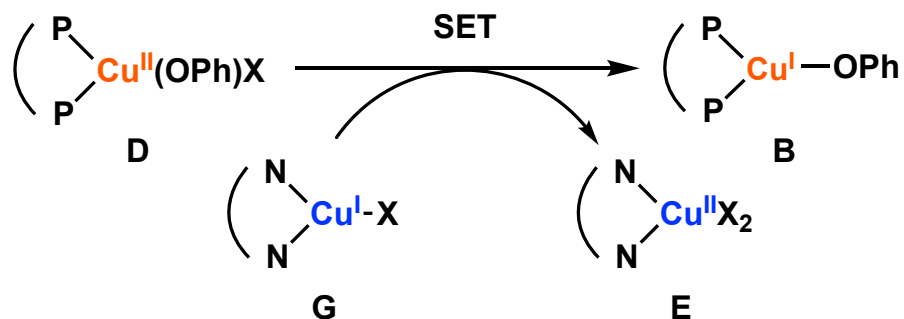
X = OPh: 1.3 V (calc.)  
X = Br: 1.2 V (calc.)



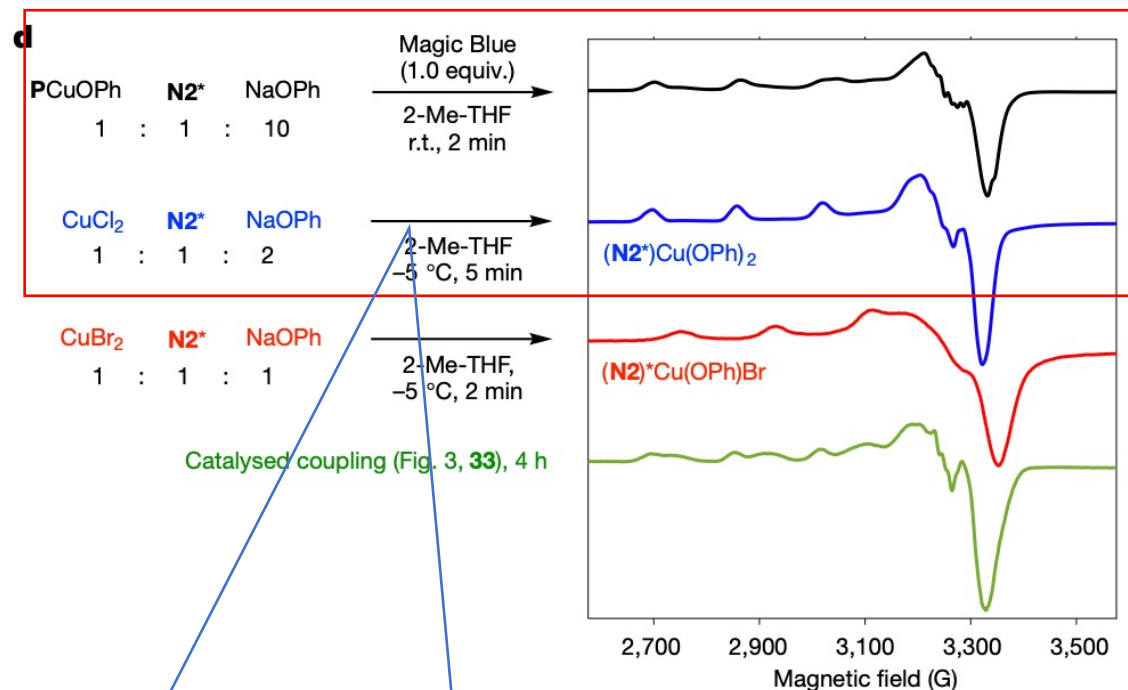
Cu<sup>I</sup>/Cu<sup>II</sup>

X = OPh: -0.6 V (calc.)  
X = amidate: -0.6 V (calc.)

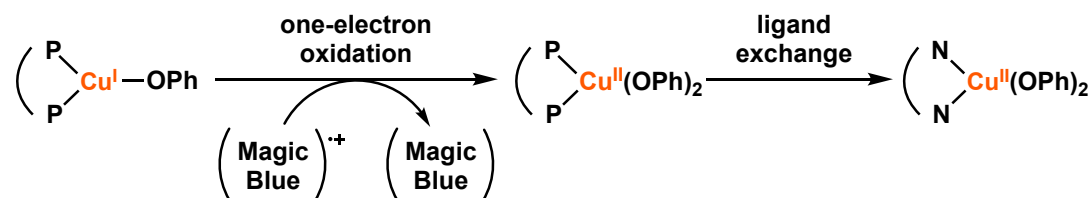
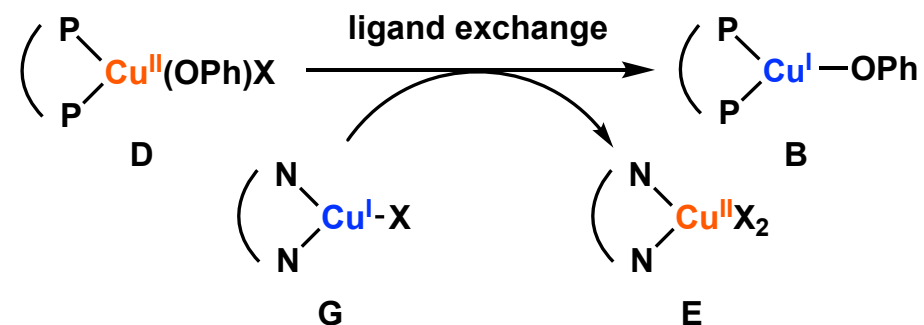
→ Consistent with SET mechanism



## 2. Ligand Exchange Mechanism: EPR Studies



→ Consistent with rapid ligand exchange (P → N2\*) upon oxidation of Cu<sup>I</sup> to Cu<sup>II</sup>

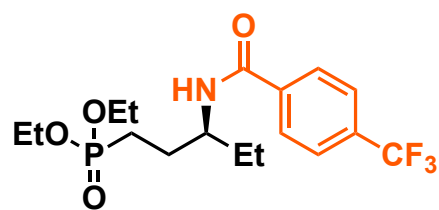
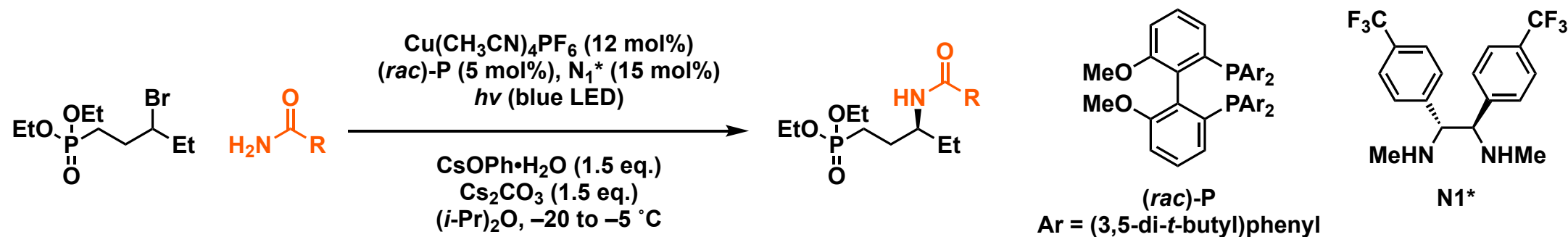


1. SET

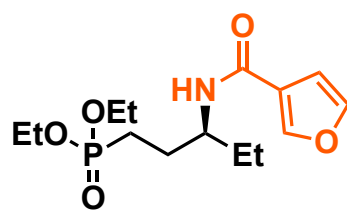
2. Ligand exchange

→ Either or both of these are operative.

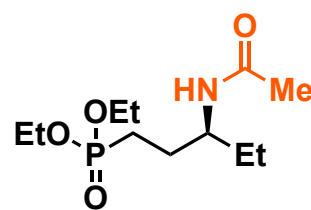
# Substrate Scope (Amides)



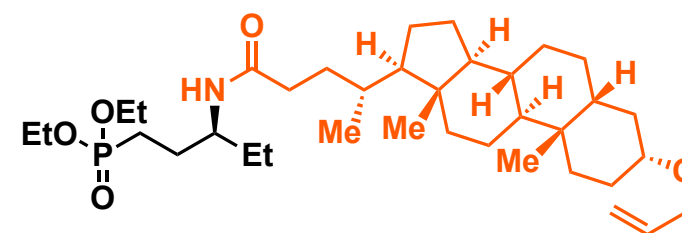
95% yield, 93% ee



76% yield, 90% ee

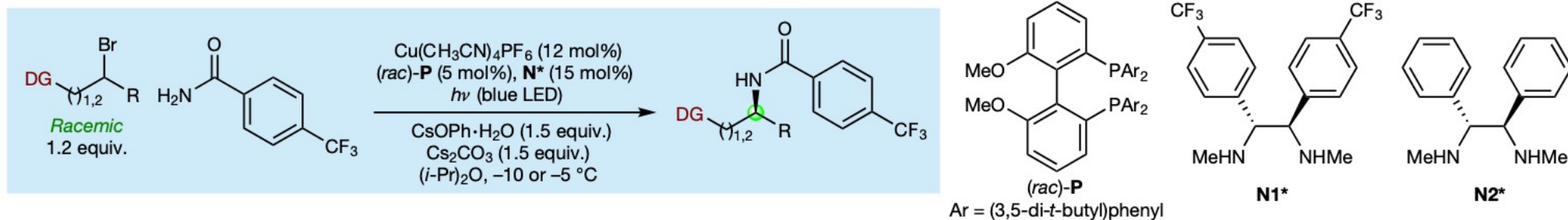


62% yield, 91% ee



Lithocolic acid derivative  
*(R,R)*- $\text{N1}^*$ : 78% yield, 93:7 d.r.  
[*(S,S)*- $\text{N1}^*$ : 73% yield, 5:95 d.r.]

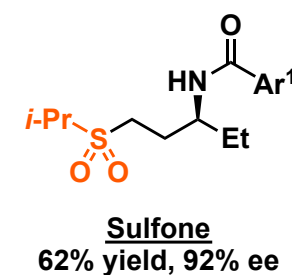
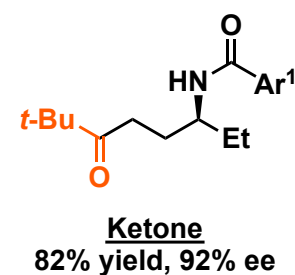
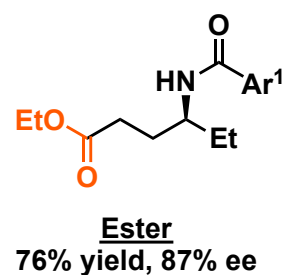
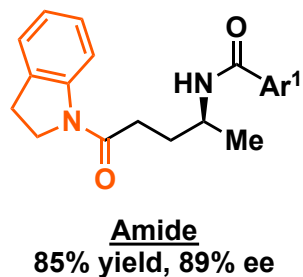
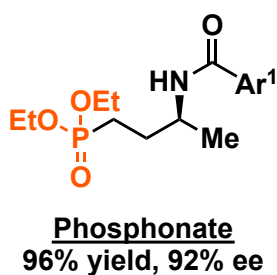
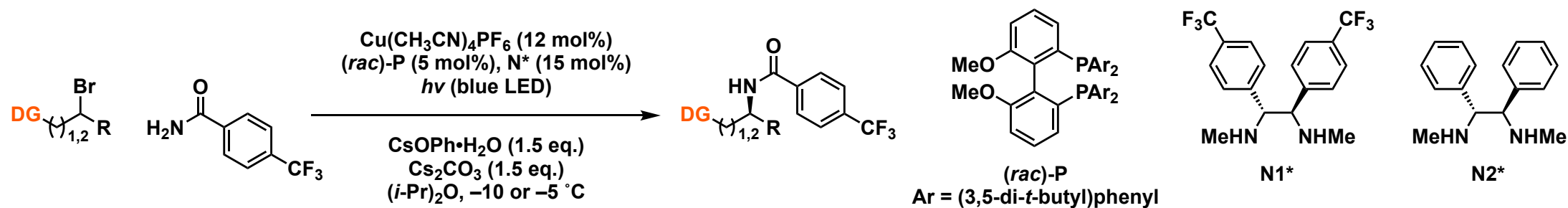
# A Strategy to Differentiate Between Two Similar Substituents



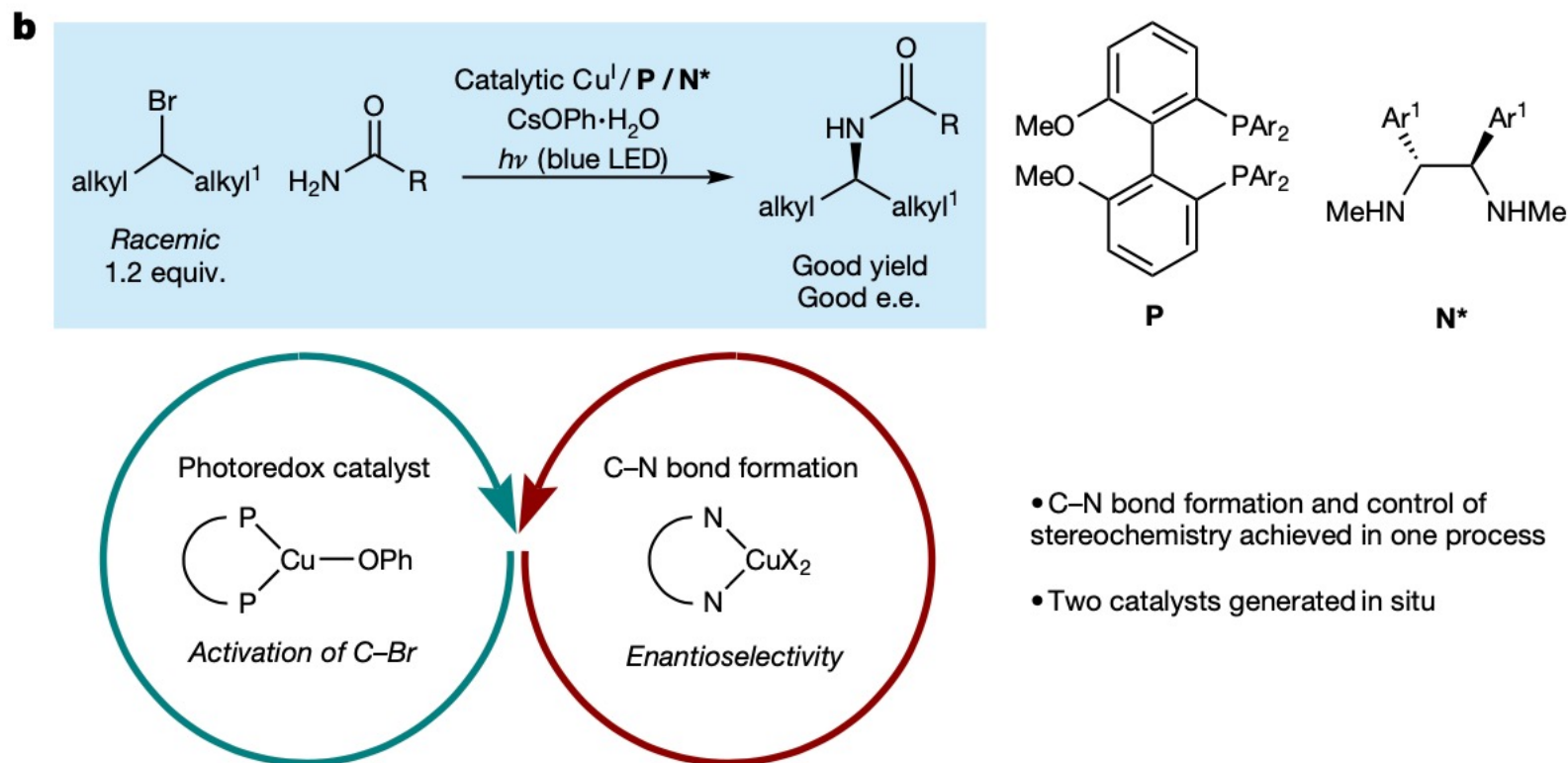
A Lewis-basic functional group of the alkyl halide provides a two-point interaction between the substrate and the chiral catalyst.

→ Other than phosphonate, an amide, ester, ketone, sulfone, sulfonamide and phosphine oxide can work as well.

# Substrate scope (Alkyl halides)



# Short Summary



**Enantioselective reaction with expanded scope was attained by exploiting three ligands.**

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# Summary

**Copper-catalyzed  
photoinduced C–N coupling**



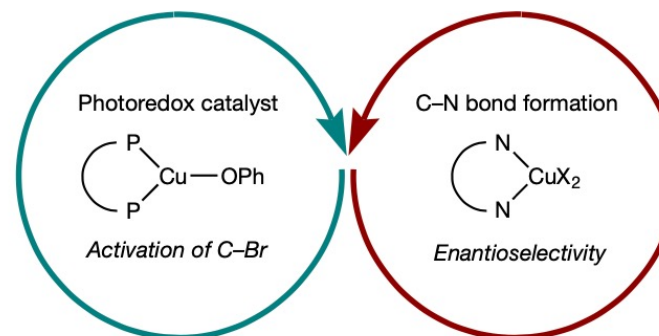
**Enantioconvergent reaction  
(restrictions on nucleophiles)**



**Nucleophile-independent  
reaction by designing a  
new photocatalyst**



**Enantioconvergent,  
nucleophile-independent  
C–N coupling by using 3  
ligands**

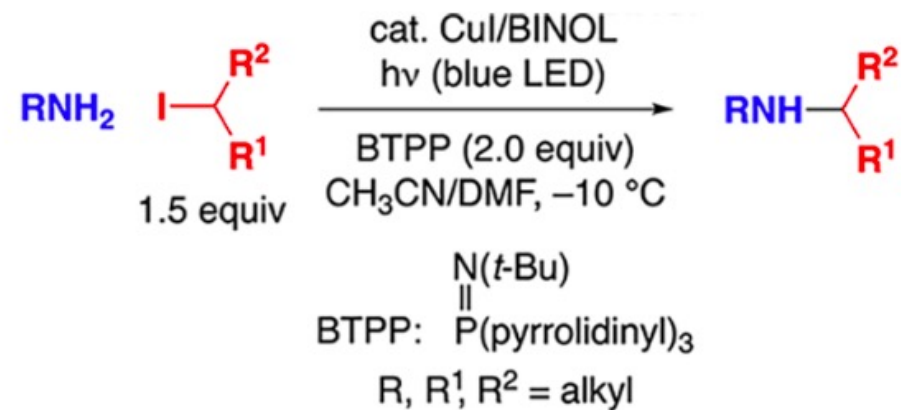




# Perspective

- Expansion of substrate scope
  - Other *N*-nucleophiles (e.g. aliphatic amines)

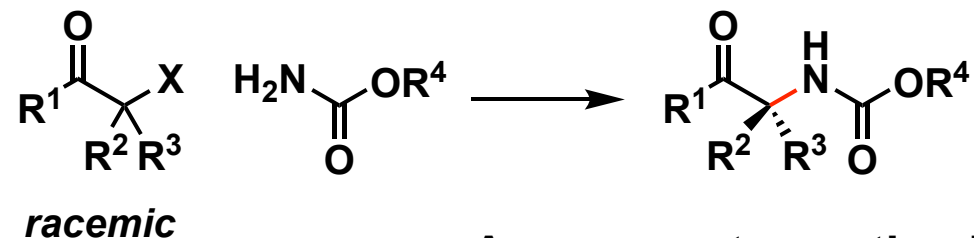
The bond-formation step which determines the stereochemistry may be challenging.



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

- *Tertiary* alkyl halides

Substrates which have electron-withdrawing groups (such as those used in 2016 Science) may be applied.



→ A new way to synthesize unnatural amino acids