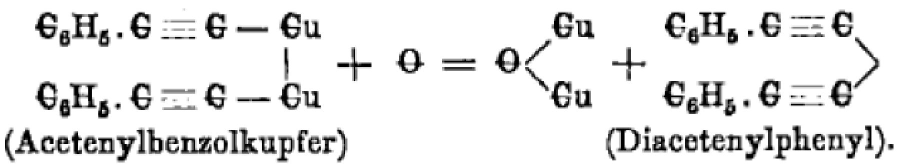
The OLDEST and the NEWEST metal Copper's rapid ascent in visible-light photoredox catalysis

- Bioinspired oxidations and oxygenations (e.g., hydroxylation of C−H bonds, dehydrogenation of alcohols, etc.)
- Cu-nitrene, Cu-H
- organometallic-like transformations (e.g., Ullman-like coupling reactions and C−H activation).

Jinteng Che
Peking-Tsinghua Center for Life Sciences
Academy for Advanced Interdisciplinary Studies
Peking University
Oct. 26th, 2019

Timeline of Achievements in Copper Chemistry

- **First cross-couplings**



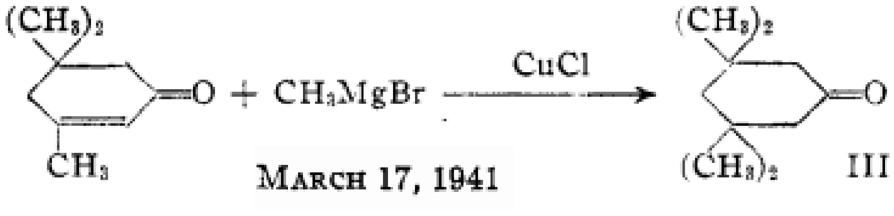
Glaser, C. *Ann. D. Chemie U. Pharm*, **1869**, *2*, 137–171

- **Ullmann–Goldberg reaction**

C-O、C-N、C-S

- **Copper organometallic reagents**

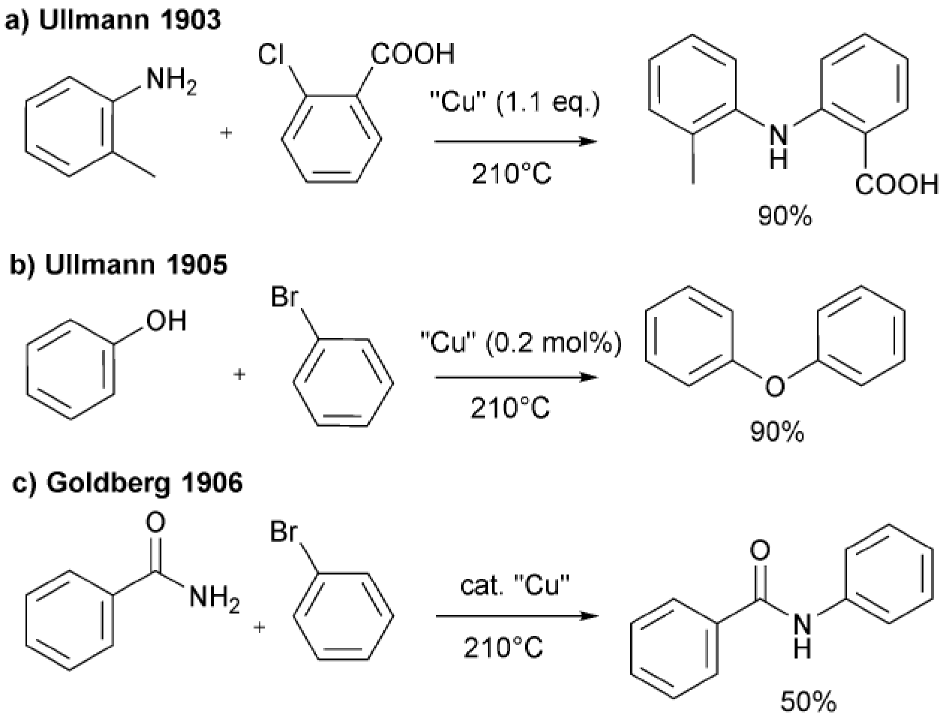
C-C

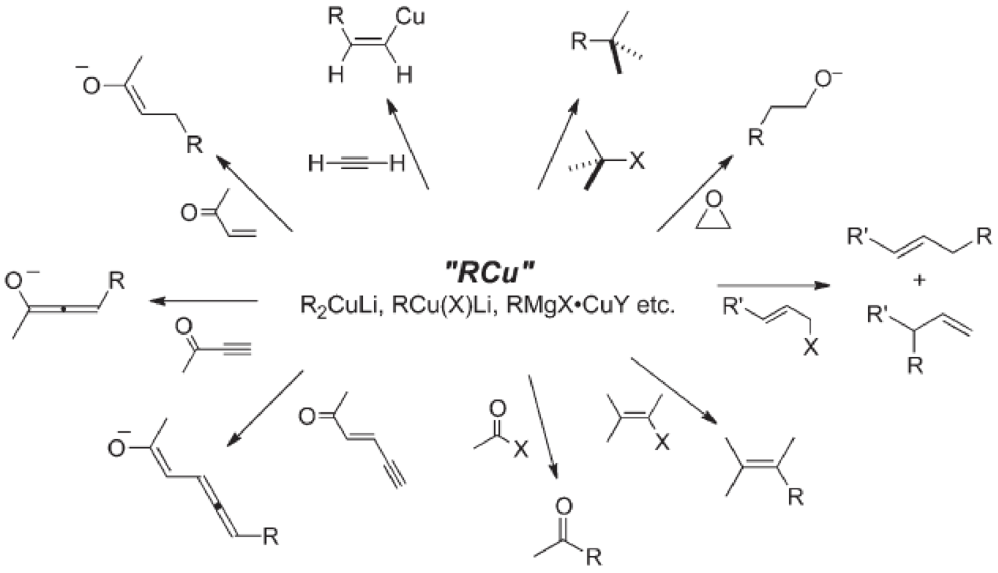


Kharasch, M. S.; Tawney, P. O. *JACS*. **1941**, 63, 2308.

$$2\ CH_3Li + 2\ CuCl_2 \rightarrow C_2H_6 + Cu_2Cl_2 + 2\ LiCl$$
$$2\ CH_3Li + Cu_2Cl_2 \rightarrow 2[CH_3Cu] + 2\ LiCl$$

Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem*, **1952**, *17*, 1630–1634





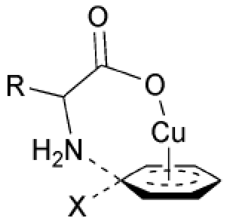
Review: *Chem. Rev*. **2012**, 112, 2339–2372.

Timeline of Achievements in Copper Chemistry

■ The post-Ullmann chemistry C-heteroatom (N, O, S, P, Se)、C-C

The classical Ullmann-Goldberg reactions had kept an unshakable position.

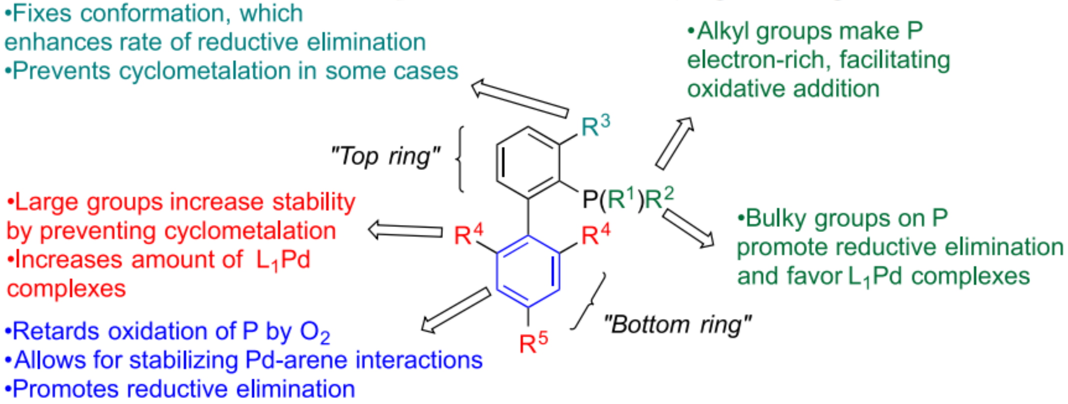
- **Harsh reaction conditions (high temperatures and strong bases)**
- **Limited substrate scope**
- **The use of large excess amounts of copper reagents.**



until late 1990s…

Palladium based Buchwald–Hartwig reaction

the clearest cases of transition-metal-catalyzed processes controlled by ligand design.



•Fixes conformation, which enhances rate of reductive elimination
•Prevents cyclometalation in some cases

•Alkyl groups make P electron-rich, facilitating oxidative addition

•Large groups increase stability by preventing cyclometalation
•Increases amount of L_1Pd complexes

•Bulky groups on P promote reductive elimination and favor L_1Pd complexes

•Retards oxidation of P by O_2
•Allows for stabilizing Pd-arene interactions
•Promotes reductive elimination

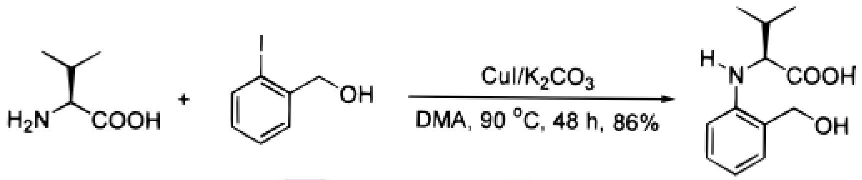
Ligand development and precatalyst design led to significant advances!!

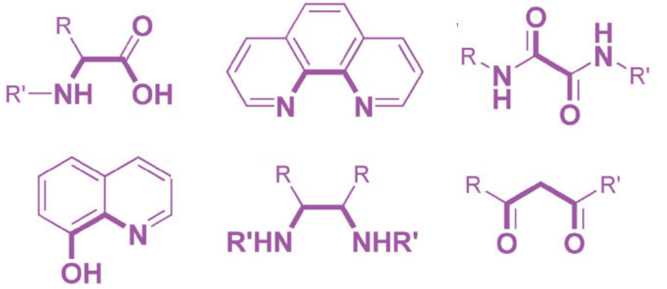
Broad substrate scopes: Cl, Br, I, OTf
Mild conditions: many reactions work well at r.t
Catalyst loadings: some reactions need 0.1-0.001 mol% of catalyst

Review: *Chem. Sci.*, **2011**, 2, 27
ACS Catal. **2015**, 5, 1386.

The use of bidentate ligands for copper.

Dawei Ma et al. J. Am. Chem. Soc. **1998**, 120, 12459.
H. B. Goodbrand et al. *J. Org. Chem*. **1999**, 64, 670.
Hauptman, Buchwald, Taillefer et al.





Broad substrate scopes: Cl, Br, I
Mild conditions: 80-100°C for many reactions
Catalyst loadings: 5-20 mol% in most cases

Review: *Angew. Chem. Int. Ed.* **2003**, 42, 5400.
Angew. Chem. Int. Ed. **2017**, 56, 16136.

Timeline of Achievements in Copper Chemistry

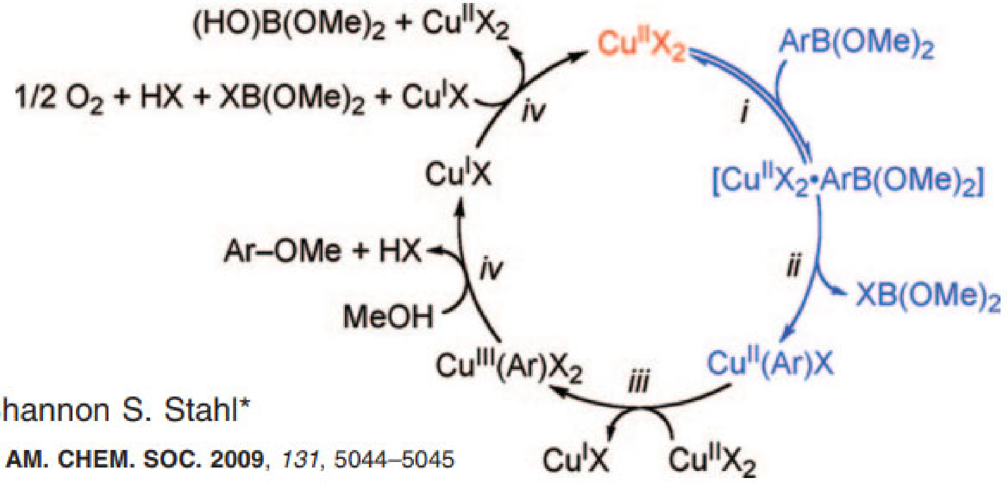
Chan-Evans-Lam Coupling

$$Ar{-}B(OH)_2 + Nu{-}H + 1/2\ O_2 \xrightarrow{[Cu]} Ar{-}Nu + B(OH)_3$$

Nu–H = alcohol, nitrogen nucleophile

C-C

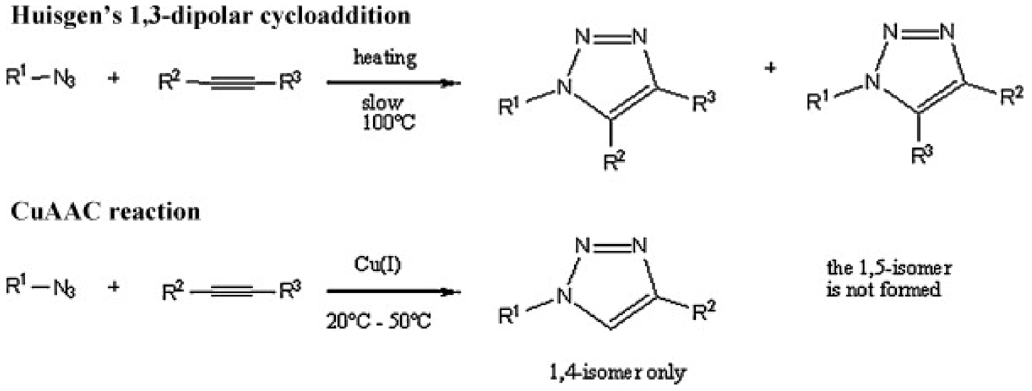
Chan, D. M. T. et al. Tetrahedron Lett. 1998, 39, 2933–2936.
Evans, D. A. et al. Tetrahedron Lett. 1998, 39, 2937–2940.
Lam, P. Y. S. et al. Tetrahedron Lett. 1998, 39, 2941–2944.

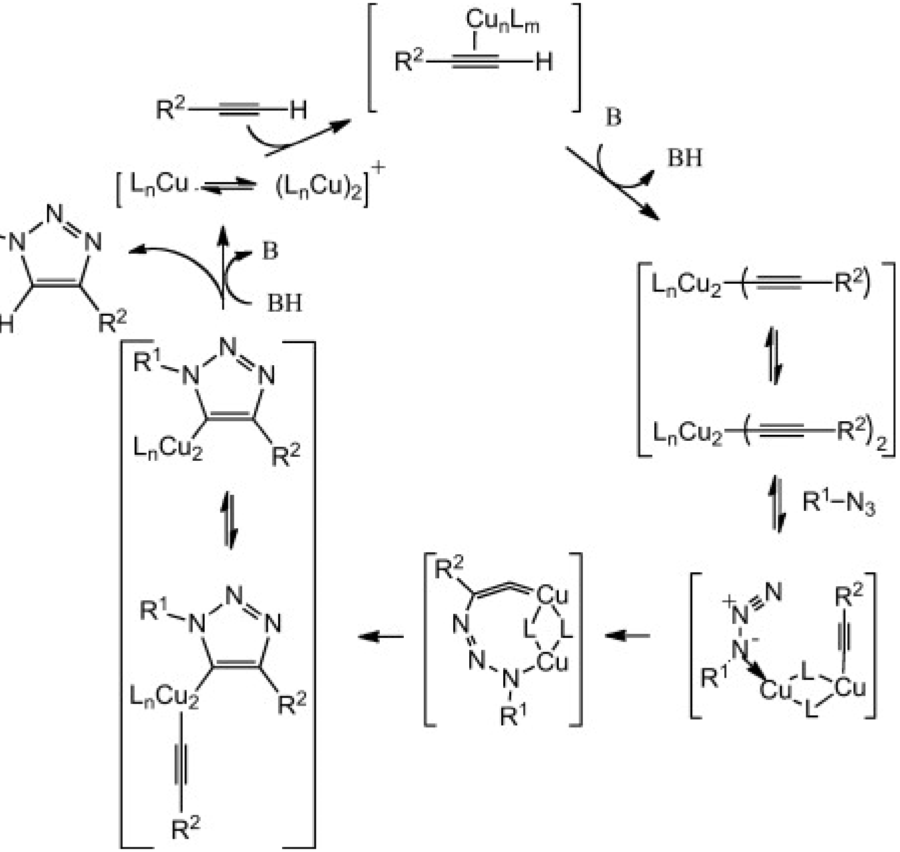


Shannon S. Stahl*
J. AM. CHEM. SOC. 2009, *131*, 5044–5045

Copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction

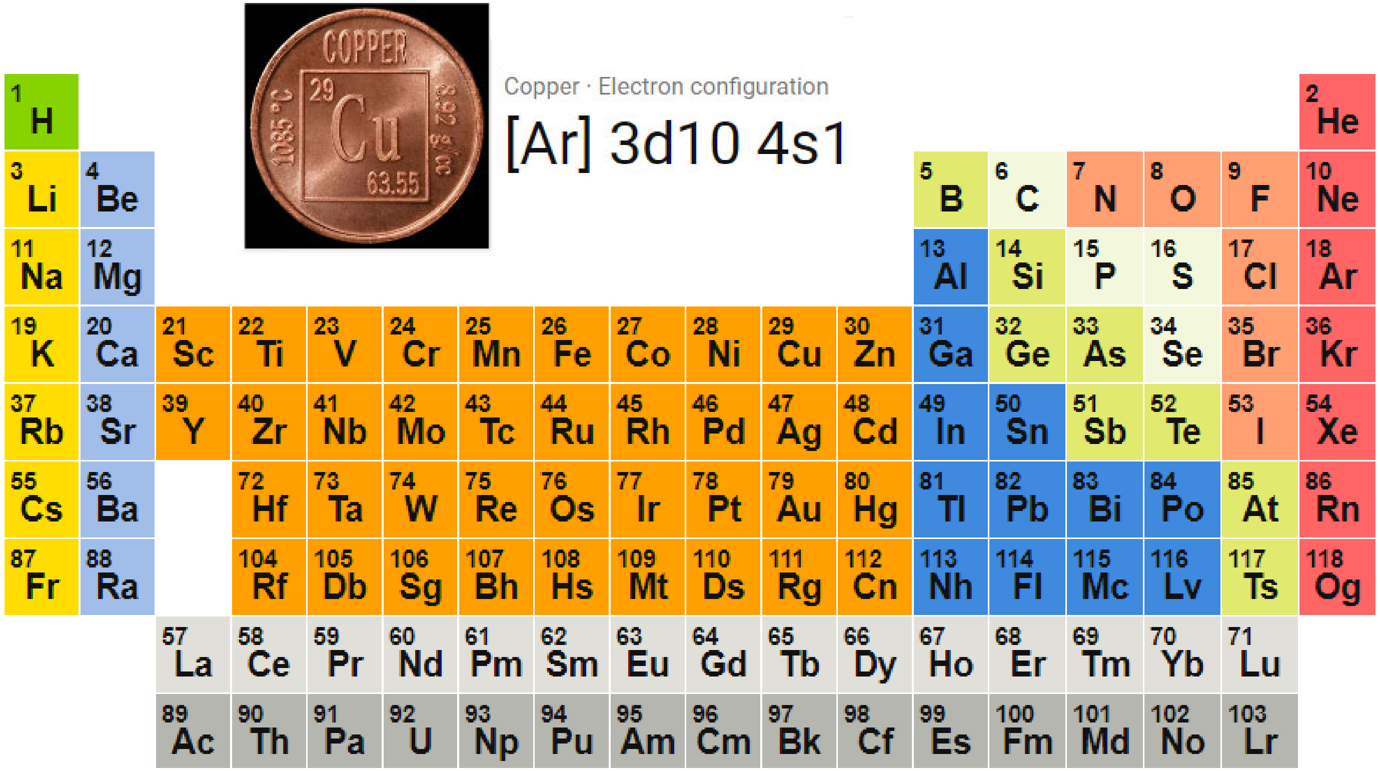
Huisgen, R. *Proc. Chem Soc.*, **1961**, 357–396
K. Barry Sharpless* *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021
K. Barry Sharpless* *Angew. Chem. Int. Ed.* **2002**, *41*, 2596
Morten Meldal* *J. Org. Chem.* **2002**, *67*, 3057–3064





Review: *Coord. Chem.Rev*. **2011**, 255, 2933–2945

Electronic Properties of Copper



Copper · Electron configuration

[Ar] 3d10 4s1

1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba		72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra		104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Nh	114 Fl	115 Mc	116 Lv	117 Ts	118 Og
		57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	
		89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr	


pubs.acs.org/organometallics

NOVEMBER 26, 2012 VOL. 31 · ISSUE 22

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PRESENTING COPPER IN ORGANOMETALLIC CHEMISTRY

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2012, vol 31, issue 22.

$$\mathrm{Cu^{I}} \overset{E_{1/2}=0.16\,\mathrm{V}}{\rightleftharpoons} \mathrm{Cu^{II}} \overset{E_{1/2}=2.4\,\mathrm{V}}{\rightleftharpoons} \mathrm{Cu^{III}}$$

d^{10} — d^{9} — d^{8}, metal cation

isoelectronic with Ni(0) Pd(0)

isoelectronic with Pd(II)

Nickel	Palladium
−1 **0** **+1** **+2** **+3** +4	**0** +1 **+2** +3 **+4**
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Facile β-migratory insertion	Facile β-hydride elimination
Radical pathways more accessible	

Nature **2014**, 509, 299.

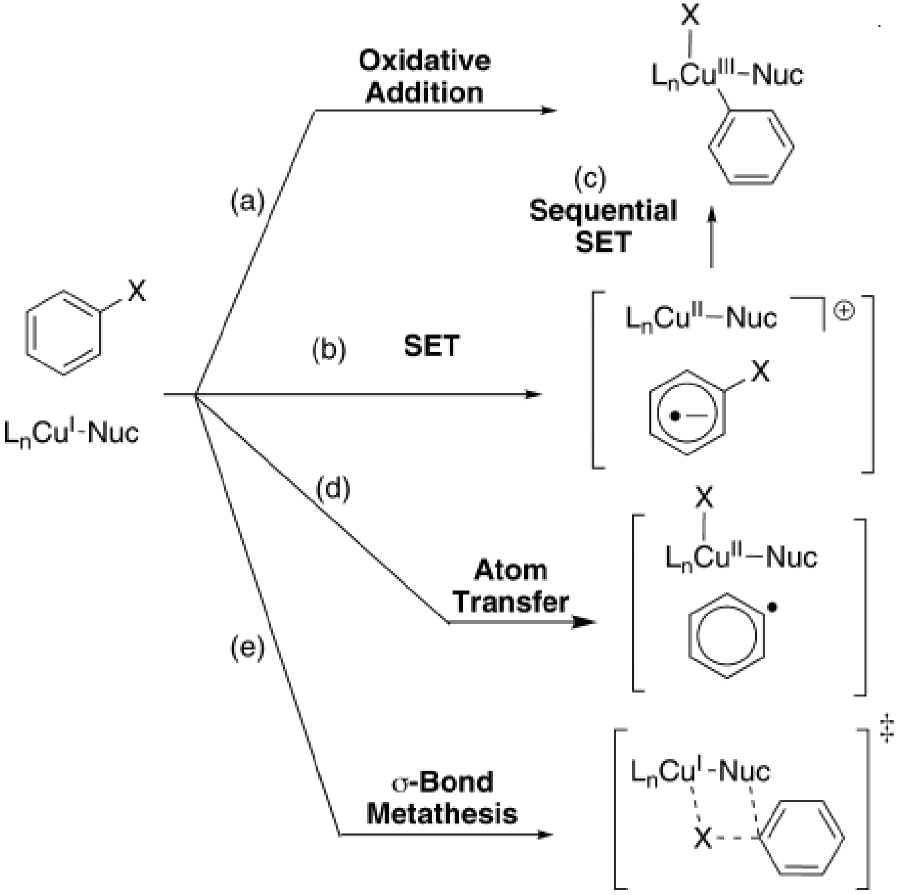
- forms shorter bonds than Pd
- harder Lewis acidity than Pd
- higher affinity for O, N ligands
- smaller coordination shell can not accomodate large ancillary ligands

- highly electrophilic and unstable
- potent oxidizer
- requires highly stabilizing ligands
- unstable towards the reverse reductive elimination
- requires the nucleophile to be in the coordination sphere prior to oxidative addition

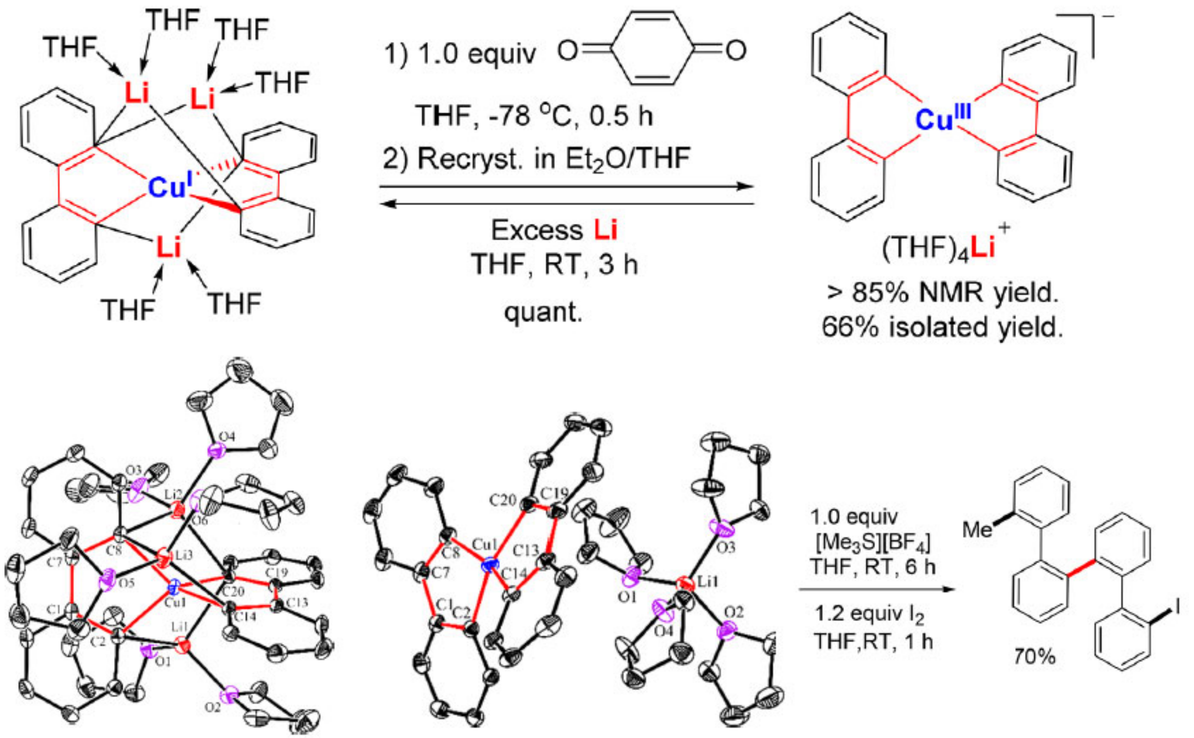
no useful guidelines in ligand design

Mechanism of Copper-catalysed cross-coupling

- Three oxidation states (0, I, and II) are found to be effective in cross coupling ($CuBr_2$,$CuCl_2$, $Cu(OAc)_2$, CuX, Cu powder). Cu(I) species are the primary active catalysts.
- Most of available experimental data favor the proposal that the nucleophile is coordinated to the Cu(I) prior to activation of the aryl halide. (fast and irreversible)
- The most frequently invoked activation mode of aryl halides by Cu complexes
- A Cu^I/Cu^{III} cycle.



- For Cu(III) complexes: *Chem. Sci.*, **2013**, 4, 2301
  Xi et al. *JACS*. **2017**, 139, 13688. ref.

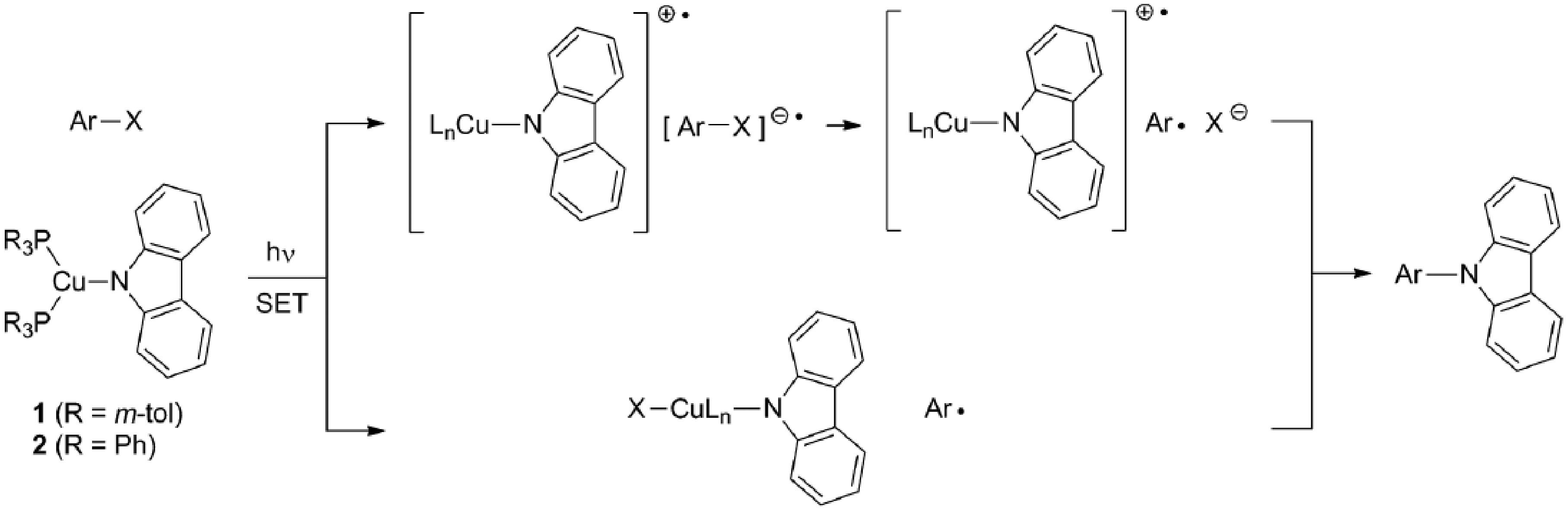


Mechanism of Ullmann-Goldberg can vary

Photoinduced Ullmann C–N Coupling: Demonstrating the Viability of a Radical Pathway

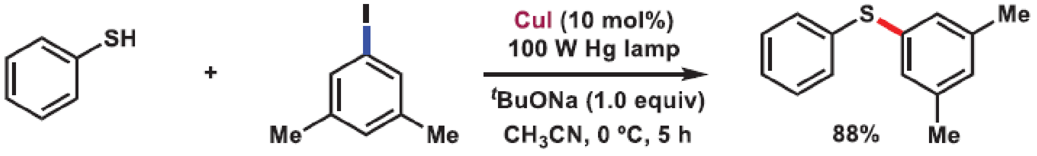
Sidney E. Creutz,[1]* Kenneth J. Lotito,[1]* Gregory C. Fu,[1,2]† Jonas C. Peters[1]†

SCIENCE VOL 338 2012 **647**



1 (R = *m*-tol)
2 (R = Ph)

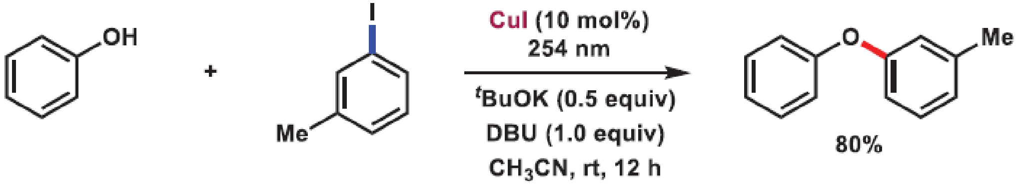
Fu and Peters, 2013



UV-light-absorbing species

$[Cu(SPh)_2]^-$
+
$[Cu_2(SPh)_3]^-$

Fu and Peters, 2014

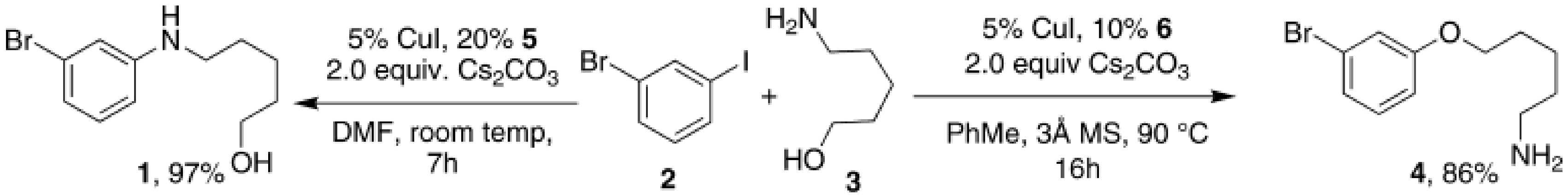


$[Cu(OPh)_2]^-$

Mechanism of Ullmann-Goldberg can vary

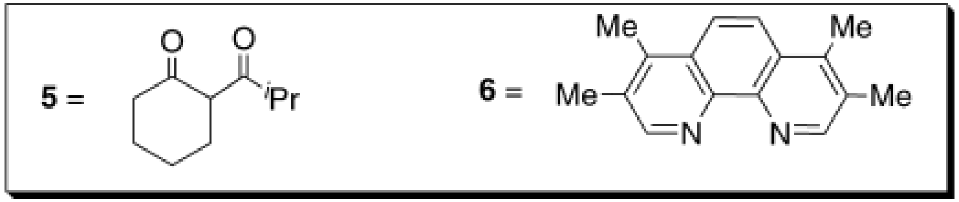
■ Single-electron transfer (SET) *VS* iodine atom transfer (IAT)

Buchwald et al. *JACS*. **2010**, 132, 6205.

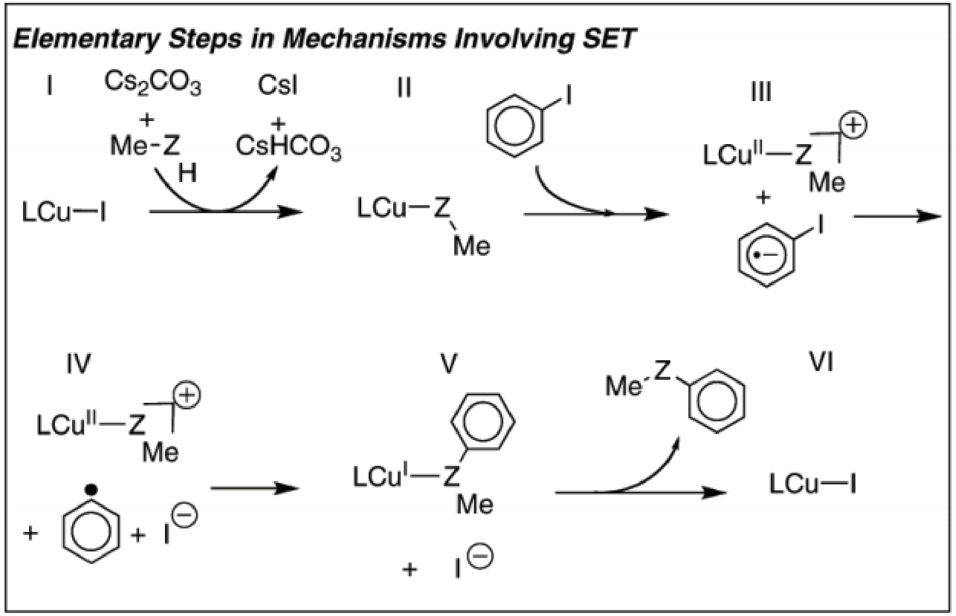


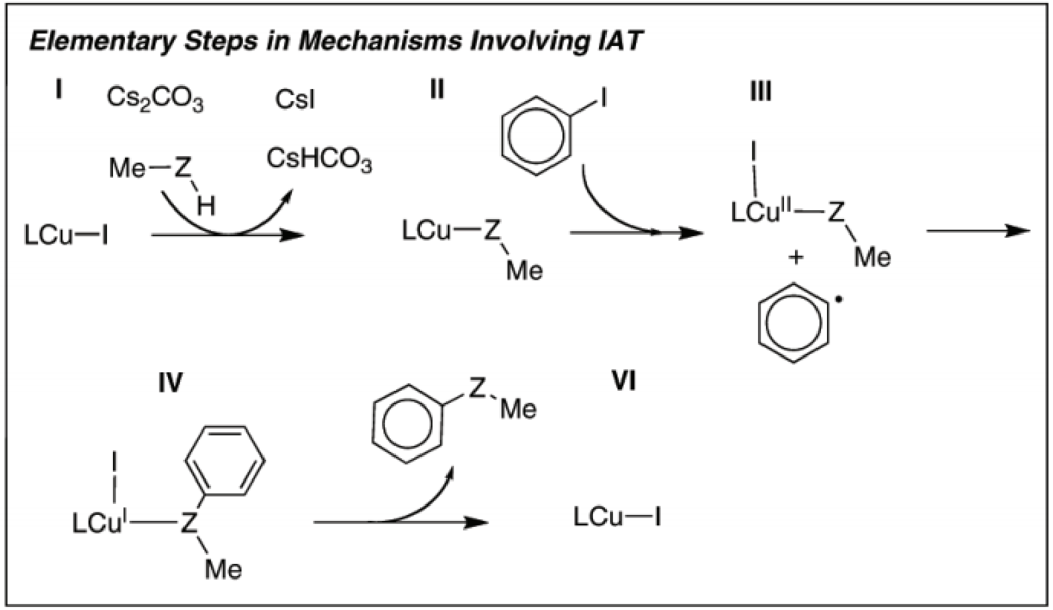
1, 97% **2** **3** **4**, 86%

Ket (5)	SET	IAT
O-bound	27.2	32.9
N-bound	26.2	41.1



Phen (6)	SET	IAT
O-bound	43.6	34
N-bound	35.1	39.6


Elementary Steps in Mechanisms Involving SET

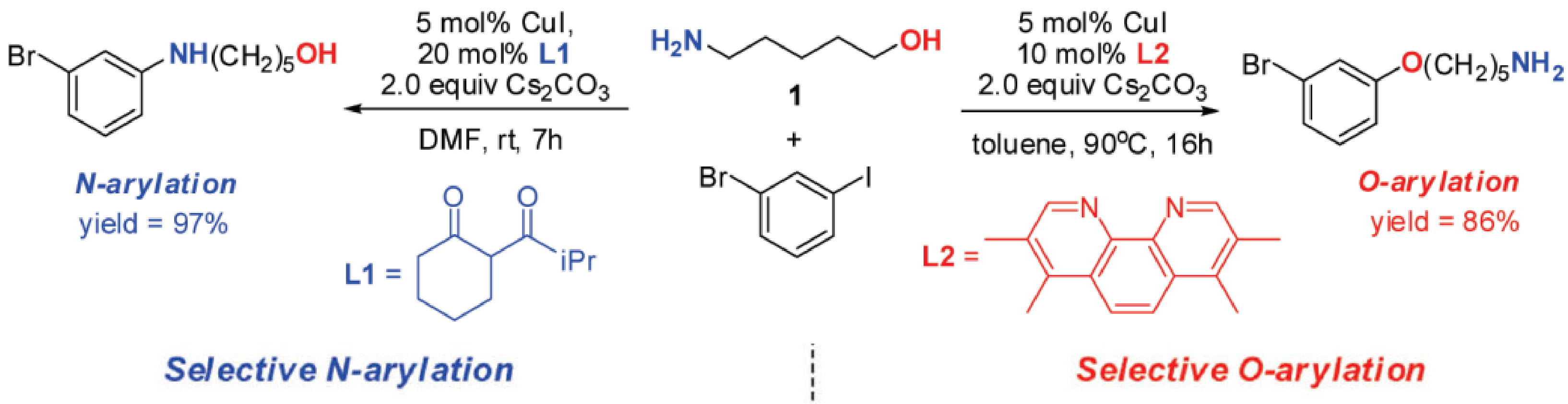

Elementary Steps in Mechanisms Involving IAT

- **Mechanisms involving either oxidative addition/reductive elimination or σ-bond metathesis are disfavored in this case.**

Mechanism of Ullmann-Goldberg can vary

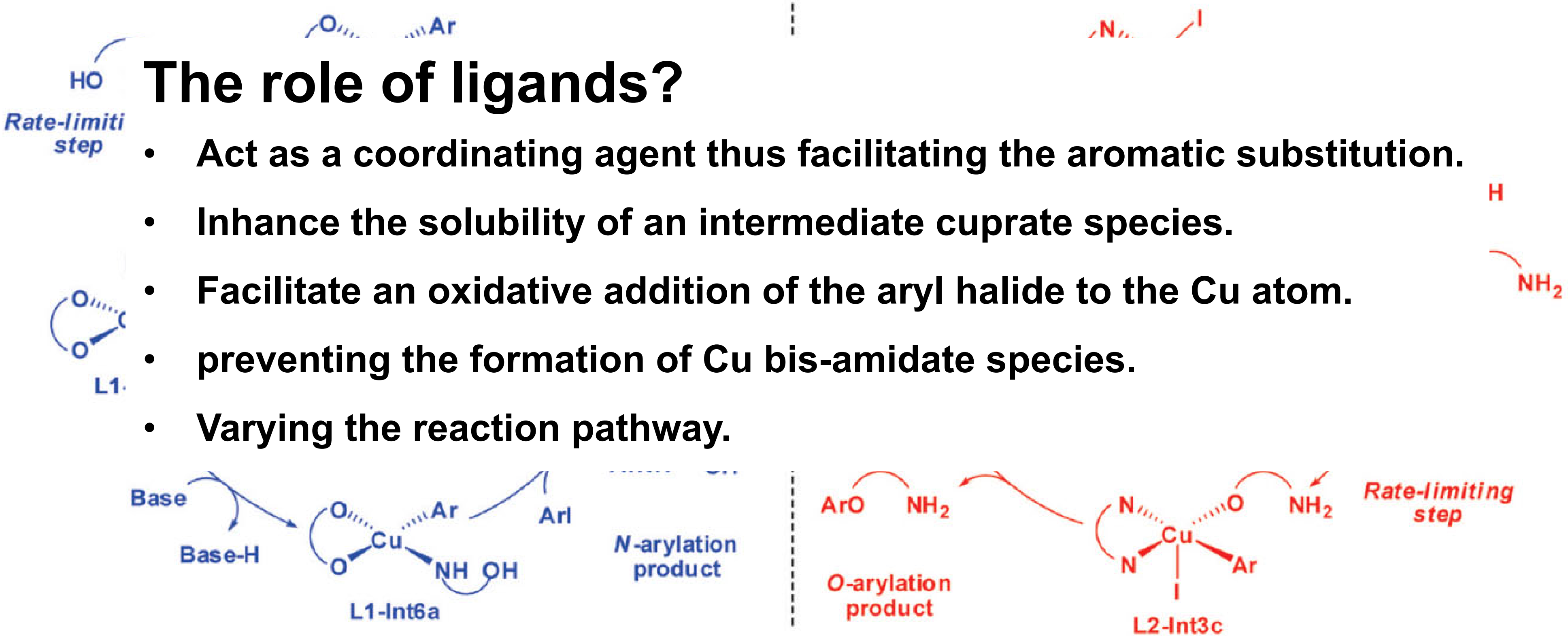
- **Oxidative addition/reductive elimination mechanism**

Yao Fu et al. *JACS*. **2010**, 132, 18078.



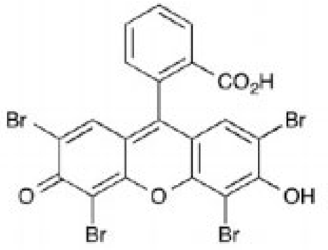
The role of ligands?

- **Act as a coordinating agent thus facilitating the aromatic substitution.**
- **Inhance the solubility of an intermediate cuprate species.**
- **Facilitate an oxidative addition of the aryl halide to the Cu atom.**
- **preventing the formation of Cu bis-amidate species.**
- **Varying the reaction pathway.**

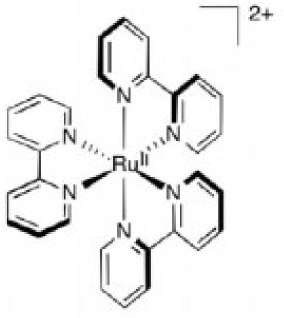


Asymmetric photoredox transition-metal catalysis

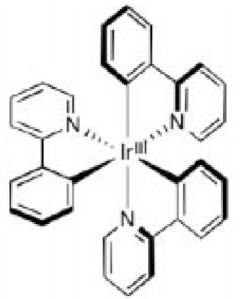
- **Catalysts that can straightforwardly direct photoredox processes in their inner sphere, and thereby control reactions through their ligand environment are desirable.**



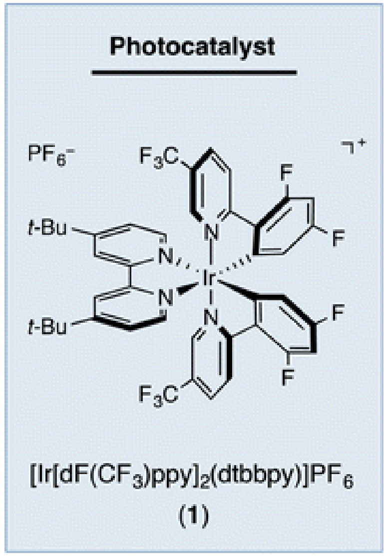
Eosin Y



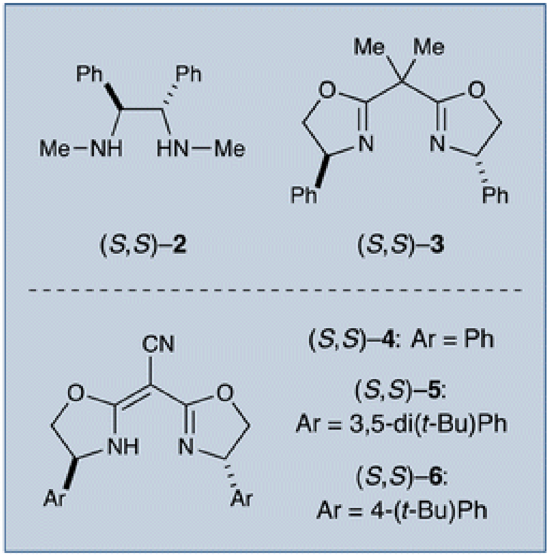
Ru(bpy)$_3$$^{2+}$



Ir(ppy)$_3$



[Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$
(**1**)



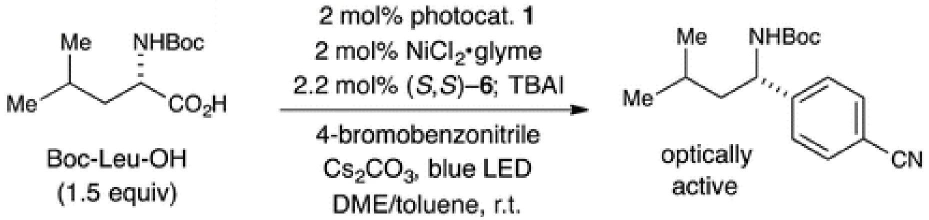
(*S*,*S*)–**2**

(*S*,*S*)–**3**

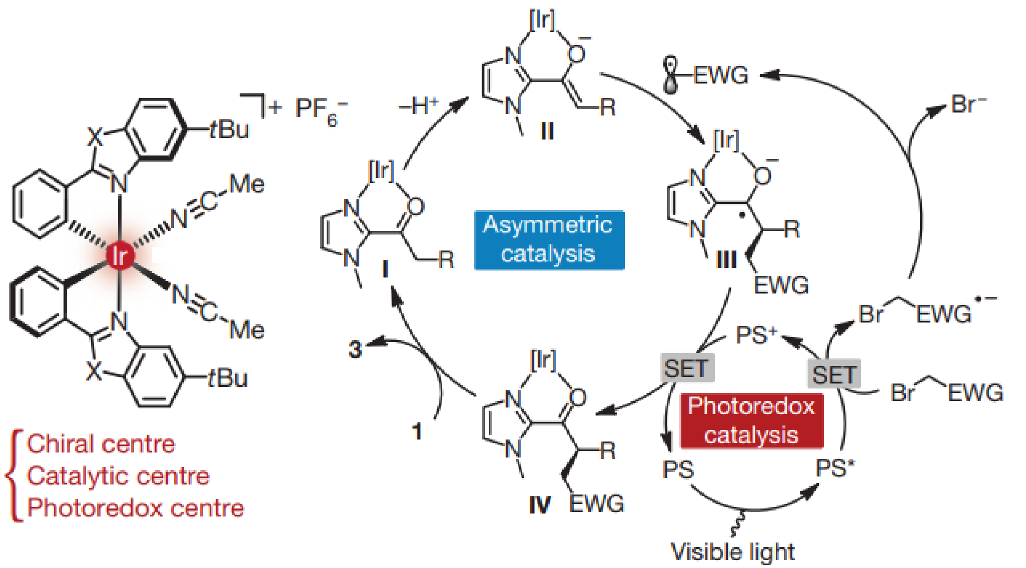
(*S*,*S*)–**4**: Ar = Ph

(*S*,*S*)–**5**: Ar = 3,5-di(*t*-Bu)Ph

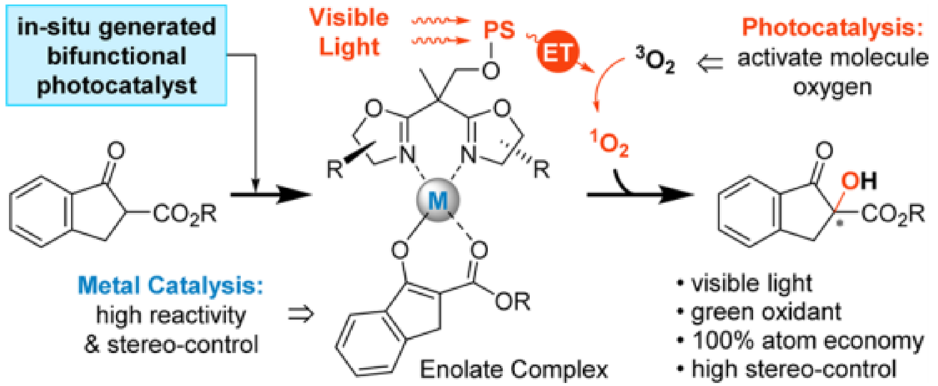
(*S*,*S*)–**6**: Ar = 4-(*t*-Bu)Ph



Eric Meggers et al. *Nature* **2014**, 515, 100



Wenjing Xiao et al. *J. Am. Chem. Soc.* **2017**, 139, 63.



Copper’s rapid ascent in Visible-light photoredox catalysis

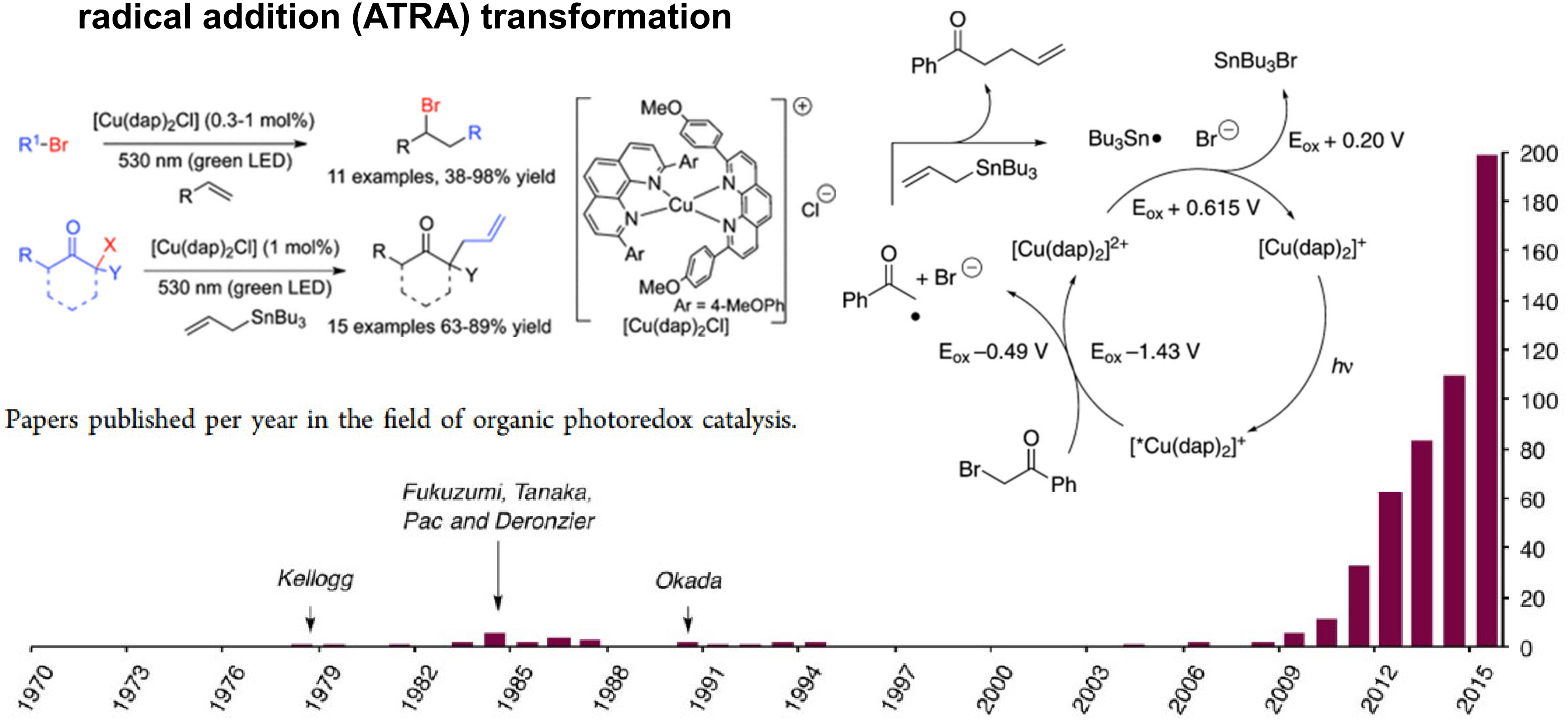
Photoassisted C–C Coupling *via* Electron Transfer to Benzylic Halides by a Bis(di-imine) Copper(I) Complex

J. CHEM. SOC., CHEM. COMMUN., 1987

Jean-Marc Kern[a] and Jean-Pierre Sauvage[b]

[a] Laboratoire d’Electrochimie Organique and [b] Laboratoire de Chimie Organo-Minérale, Institut de Chimie, 1, rue Blaise Pascal, F-67000 Strasbourg, France

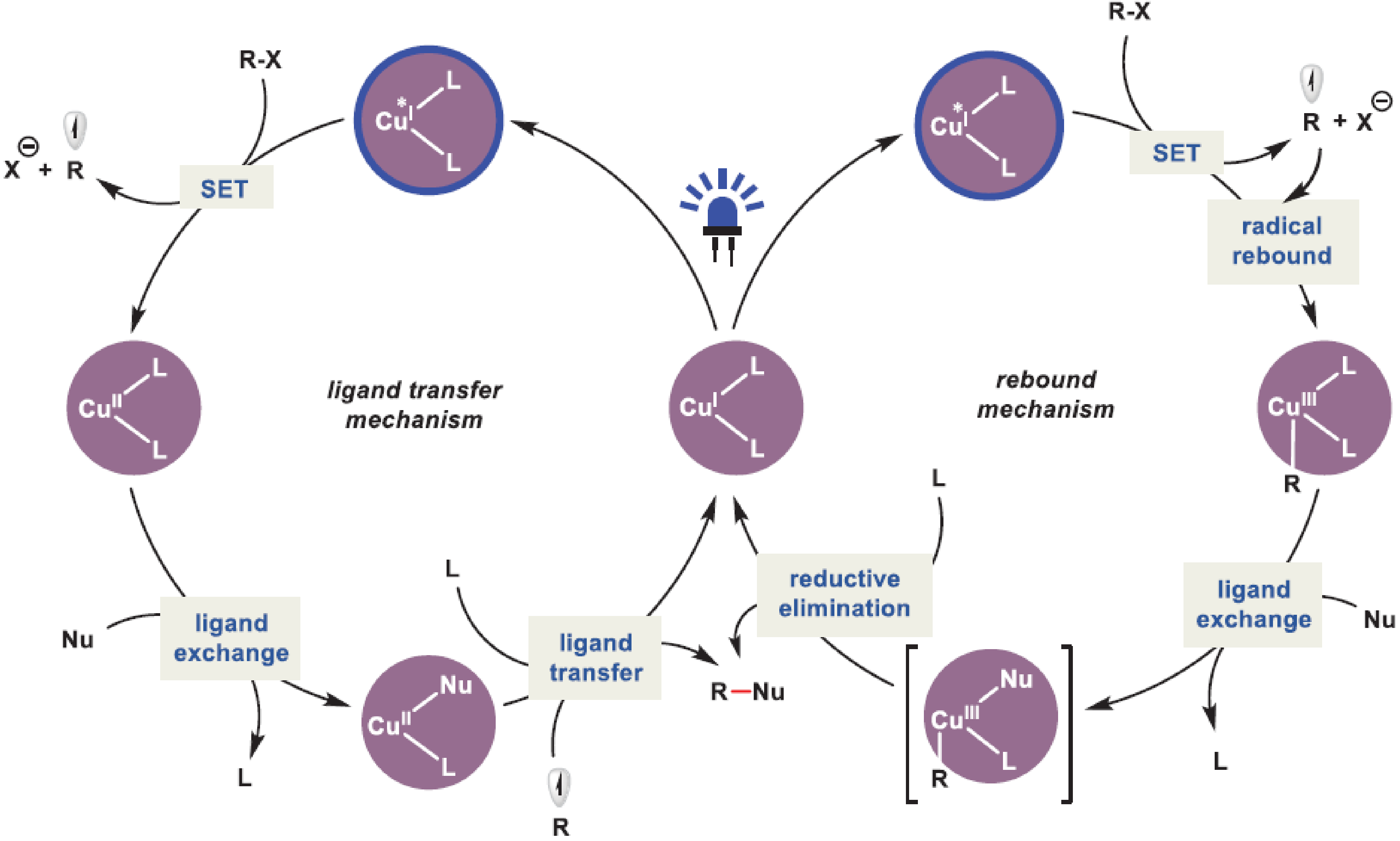
- **Resuscitated in 2012 for a C–C bond-forming atom transfer radical addition (ATRA) transformation**



Papers published per year in the field of organic photoredox catalysis.

The mechanistic paradigm of Cu(I) photocatalysts

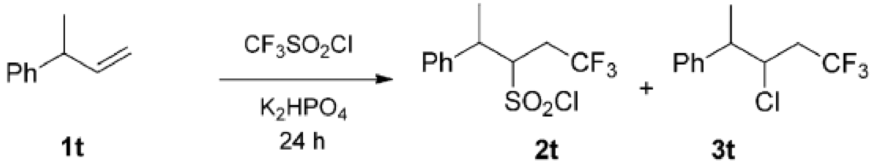
- **Cu(I)/Cu(II) catalytic cycle involve sequential elementary steps—SET, ligand exchange, and ligand transfe.**
- **Cu(I)/Cu(II)/Cu(III) catalytic cycle involve SET, radical rebound, ligand exchange, and reductive elimination steps.**



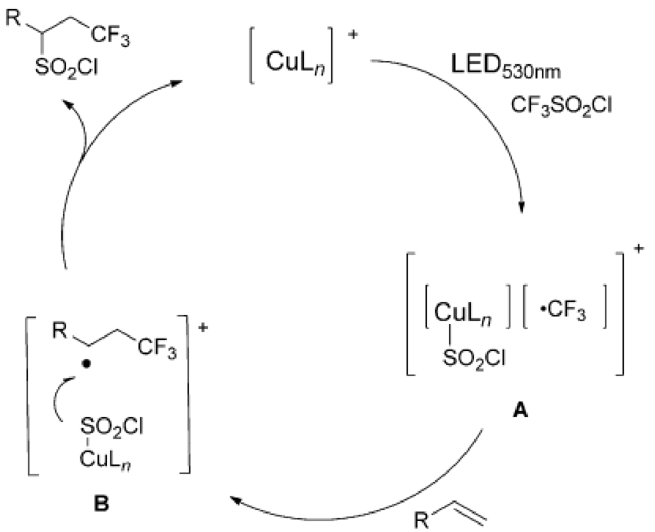
Bifunctionalization of olefins

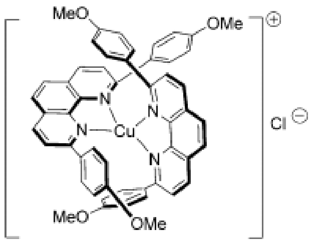
Trifluoromethylchlorosulfonylation of Alkenes: Evidence for an Inner - Sphere Mechanism by a Copper Phenanthroline Photoredox Catalyst†

Oliver Reiser et al., *Angew. Chem. Int. Ed.* **2015**, 54, 6999

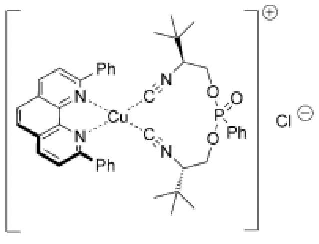


$[Cu(dap)_2]Cl$ (1 mol %), 530 nm	3:1, 79%
$[Cu(dpp)(binc)]Cl$ (1 mol %), 530 nm	9:1, 83%
$[Ru(bpy)_3]Cl_2$ (1 mol %), 455 nm	<1:>99, 77%





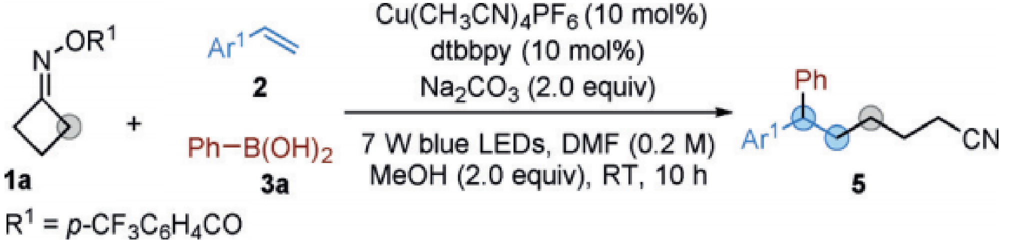
$[Cu(dap)_2]Cl$

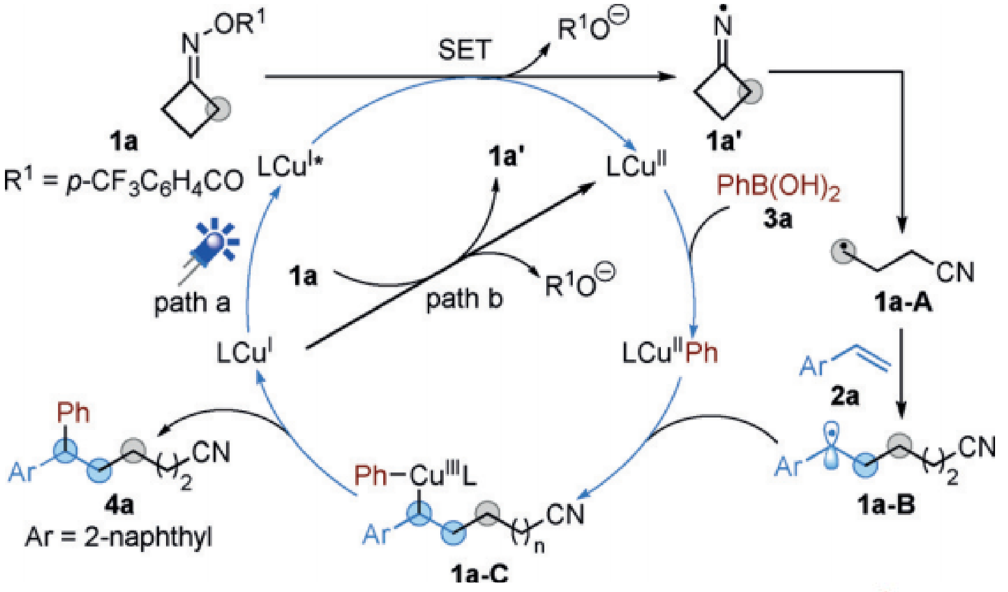


$[Cu(dpp)(binc)]Cl$

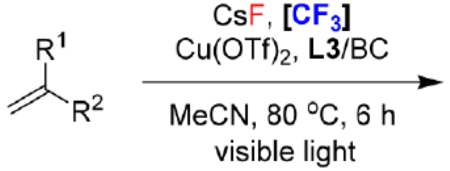
Copper-Catalyzed Radical Cross-Coupling of Redox-Active Oxime Esters, Styrenes, and Boronic Acids

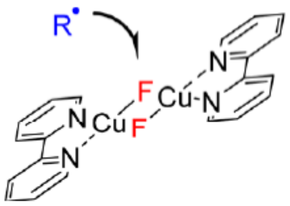
Angew. Chem. Int. Ed. **2018**, *57*, 15505–15509



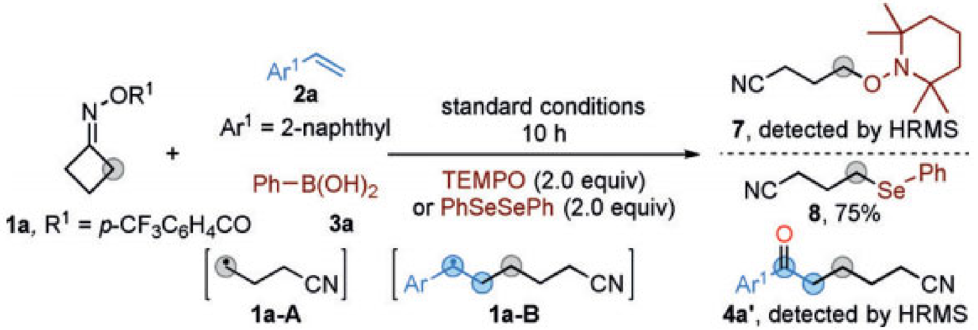


Fluorotrifluoromethylation of Alkenes





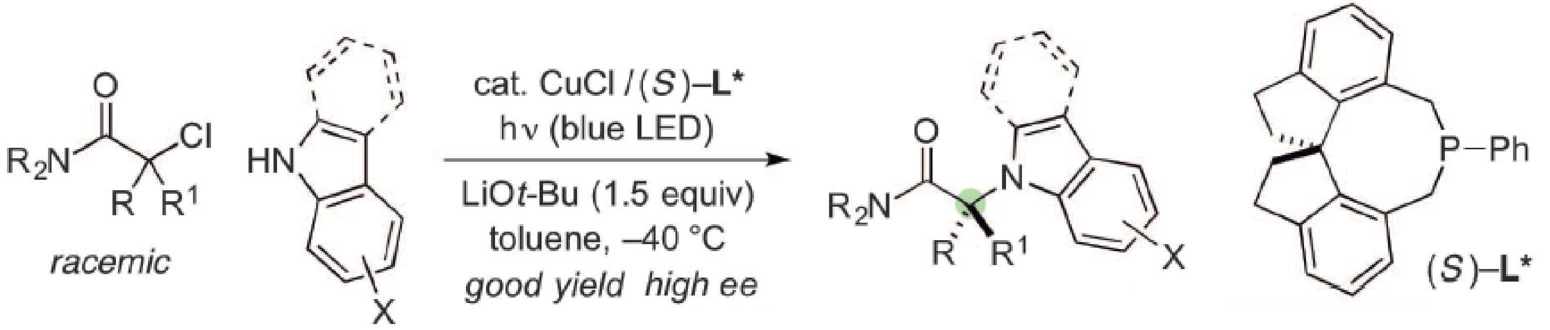
Chaozhong Li et al. *J. Am. Chem. Soc.* **2018**, 140, 6169

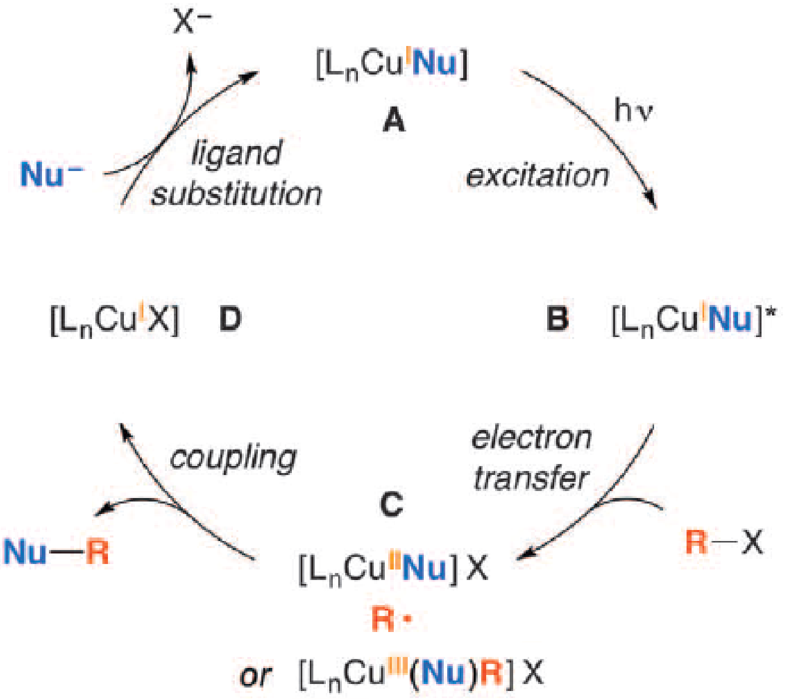


C(sp^3/sp^2)- heteroatom cross-coupling

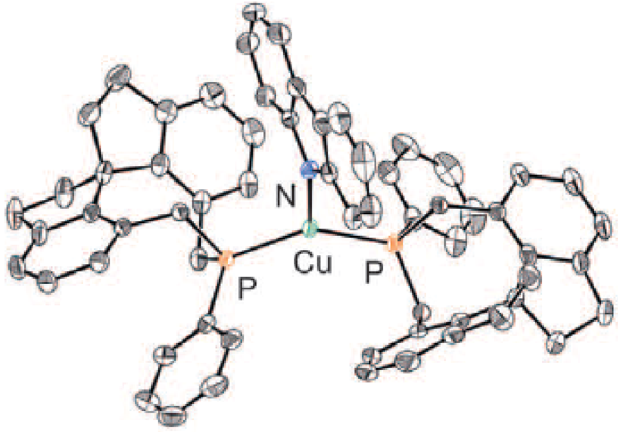
Asymmetric copper-catalyzed C-N cross-couplings induced by visible light

Quirin M. Kainz, Carson D. Matier, Agnieszka Bartoszewicz, Susan L. Zultanski,
Jonas C. Peters,* Gregory C. Fu* *Science* **351** (6274), 681-684. 2016





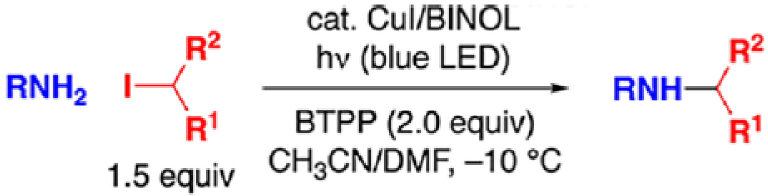
- photochemistry and enantioselectivity via a single transition metal (copper)
- enantioconvergent C–N cross-couplings of racemic alkyl electrophiles
- high enantioselectivities with tertiary electrophiles

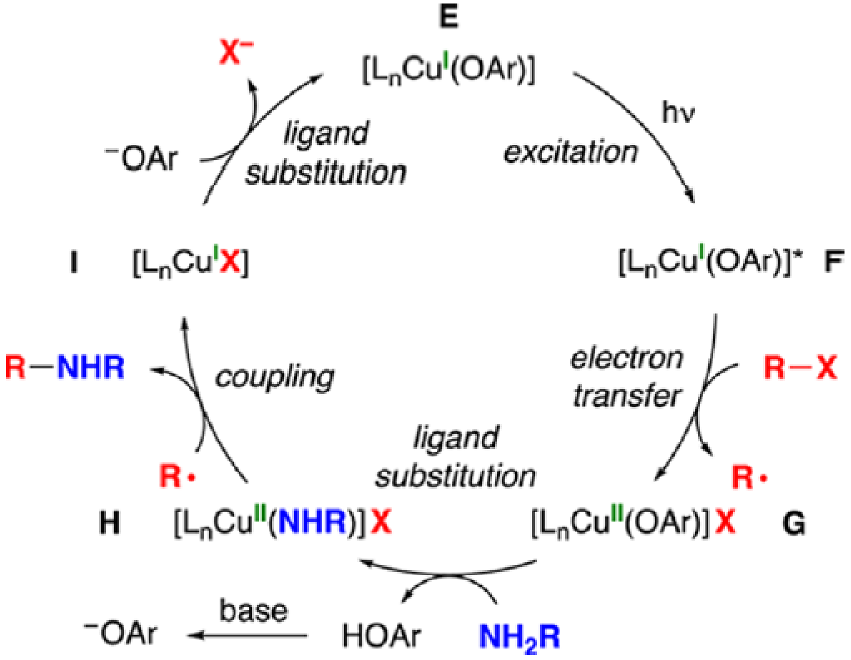


All of reported couplings have employed nucleophiles wherein the nucleophilic site is part of a π system.

“out-of-cage” nucleophiles

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





E

$[L_nCu^I(OAr)]$

hν

excitation

$[L_nCu^I(OAr)]^*$ F

electron transfer

R—X

R•

$[L_nCu^{II}(OAr)]X$ G

ligand substitution

H $[L_nCu^{II}(NHR)]X$

NH_2R

HOAr

base

^-OAr

R•

coupling

R—NHR

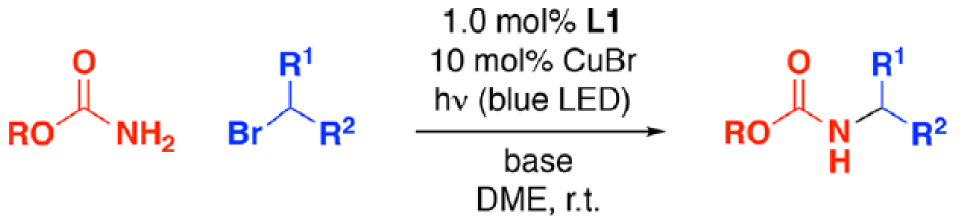
I $[L_nCu^IX]$

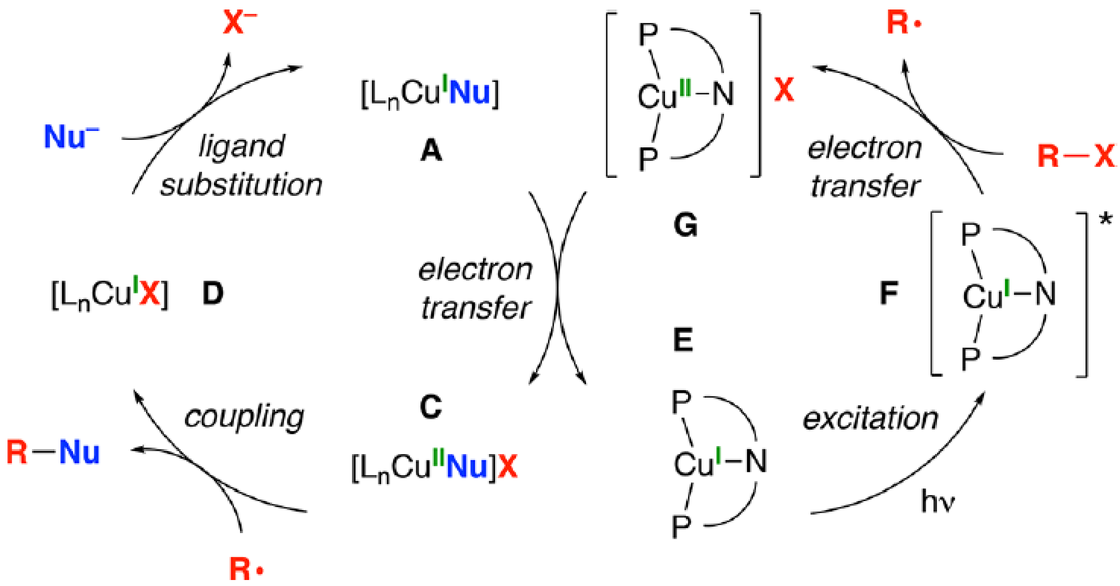
^-OAr

ligand substitution

X^-

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





X^-

Nu^-

ligand substitution

$[L_nCu^INu]$

A

$[P_2Cu^{II}–N]X$

G

R•

electron transfer

R—X

F

$[P_2Cu^I–N]^*$

$[L_nCu^IX]$ D

electron transfer

E

$P_2Cu^I–N$

C

$[L_nCu^{II}Nu]X$

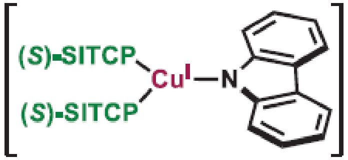
coupling

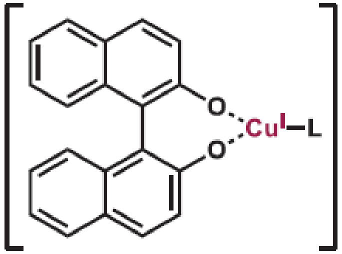
R—Nu

R•

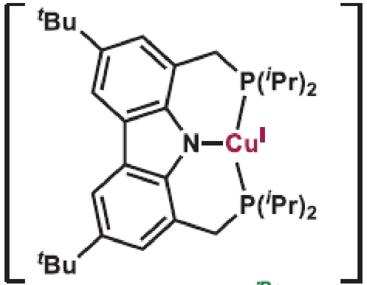
excitation

hν





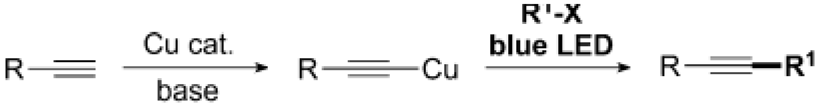
Cu(I)-binaphtholate



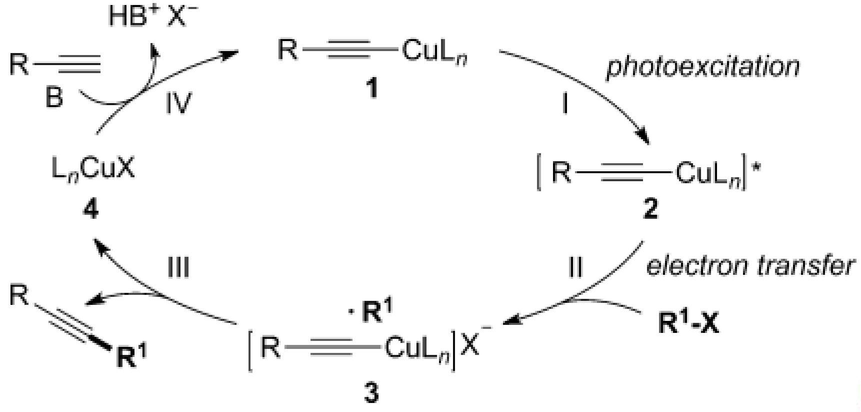
$Cu(Cbzdiphos^{iPr})$

Cu(I)-phenylacetylide species

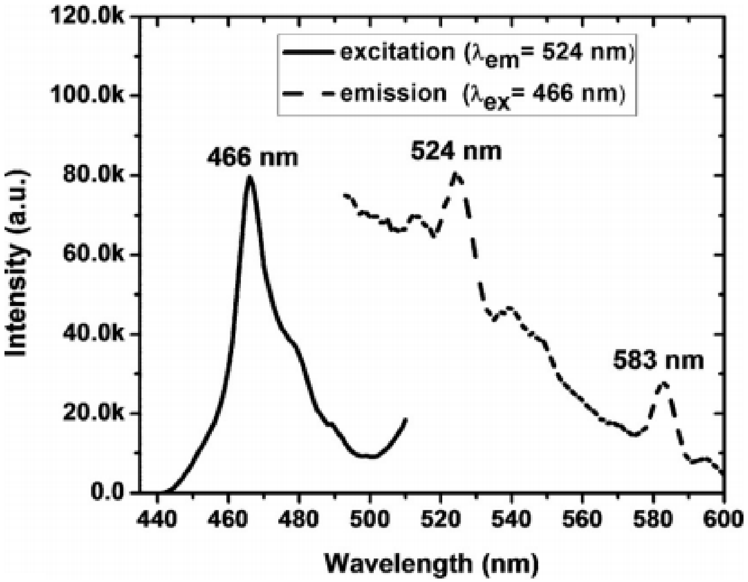
Angew. Chem. Int. Ed. **2018**, 57, 5492



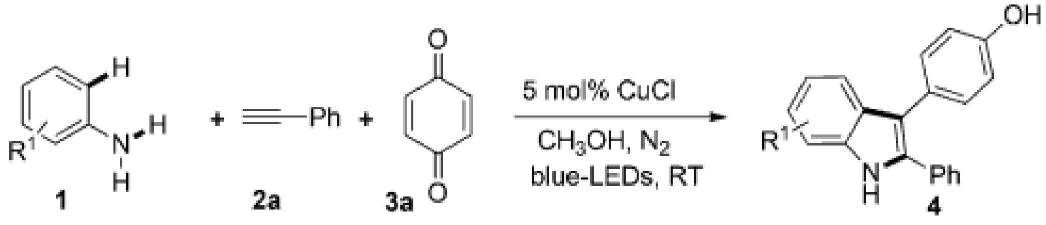
R^1-X = primary, secondary, and bridgehead tertiary alkyl iodides



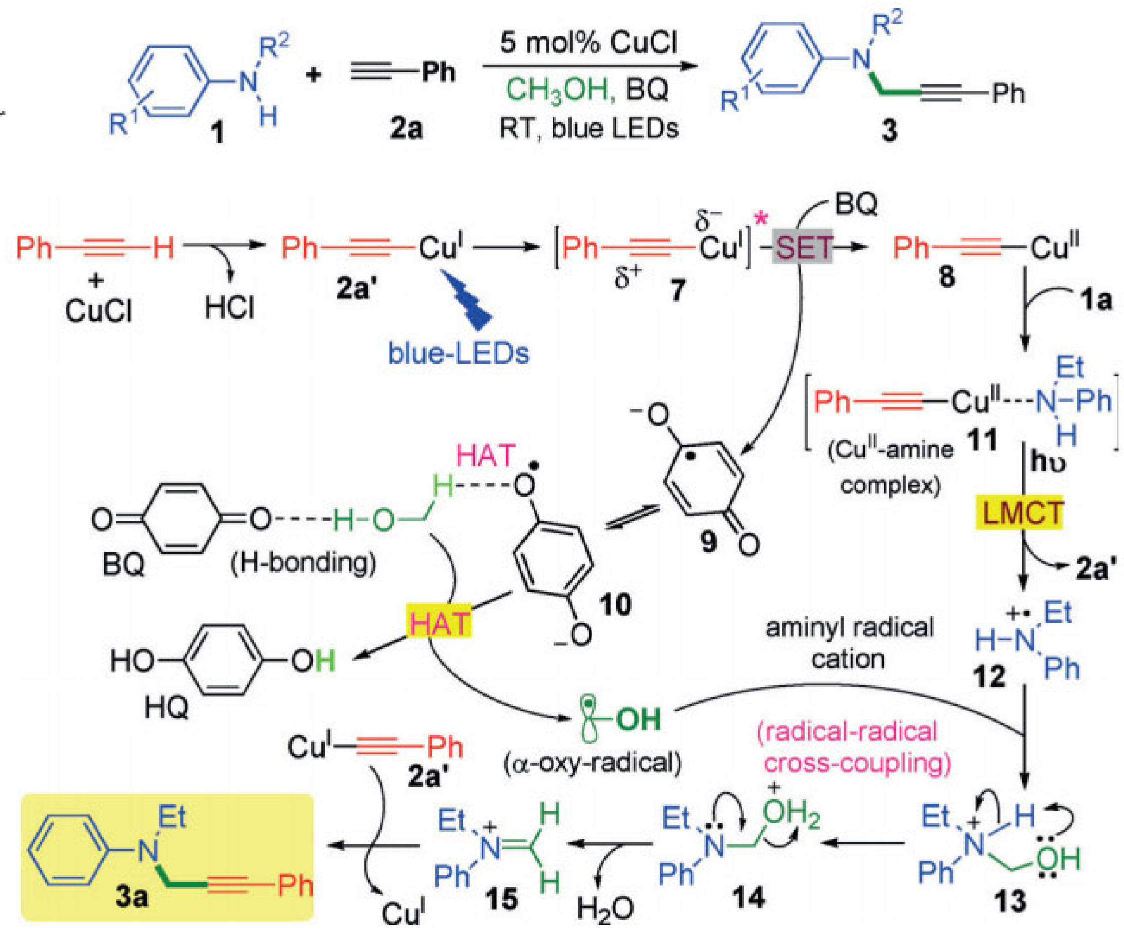
Excitation and emission spectra of in situ generated $Ph-C\equiv C-Cu$ in CH_3OH.



Kuo Chu Hwang et al. *Angew. Chem. Int. Ed.* **2015**, 54, 13896

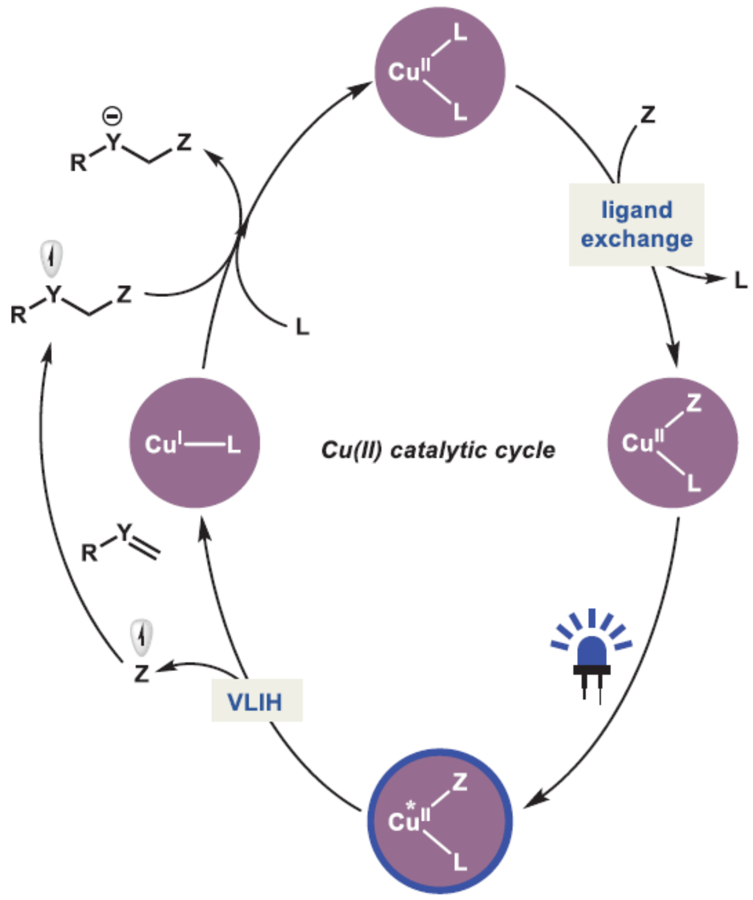


Kuo Chu Hwang et al. *Angew. Chem. Int. Ed.* **2019**, 58, 3838

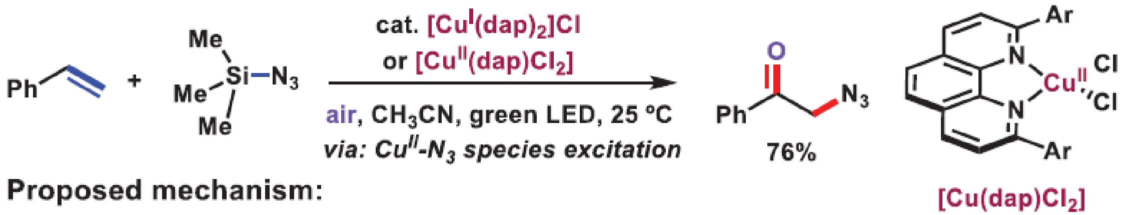


New avenue: light-accelerated Cu^{II} homolysis

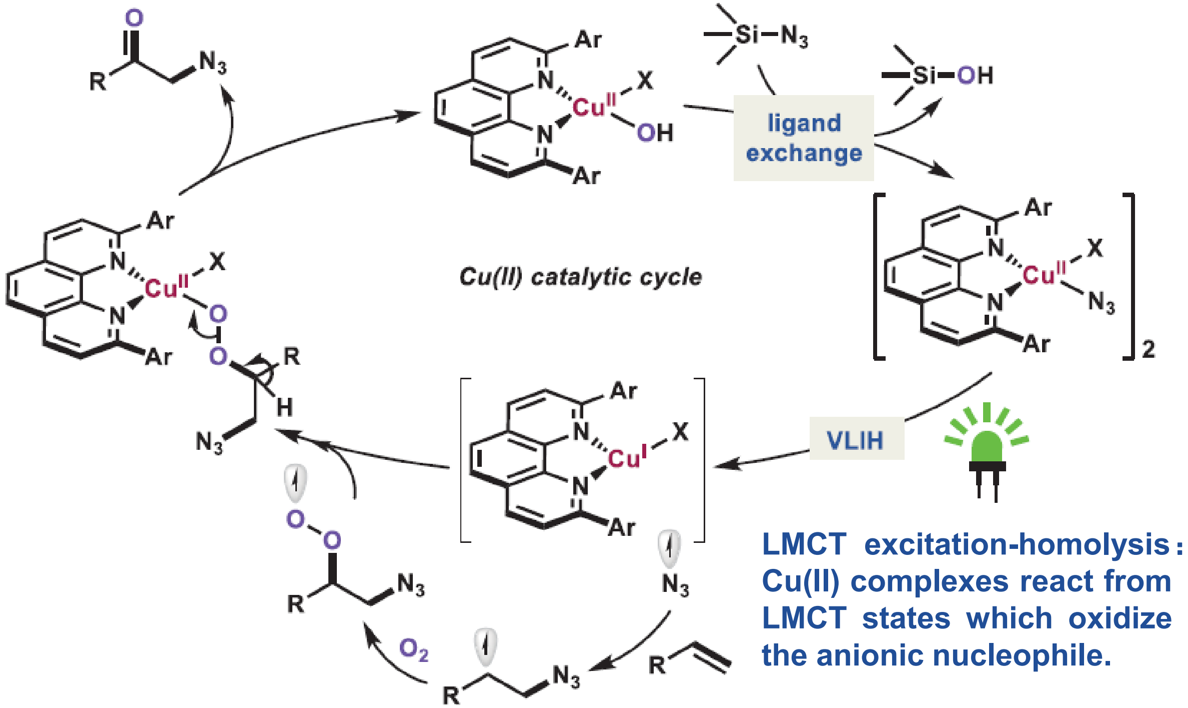
Mechanistic paradigm of Cu(II) photocatalysis



Oliver Reiser et al. *Angew. Chem. Int. Ed.* **2018**, 57, 8288.



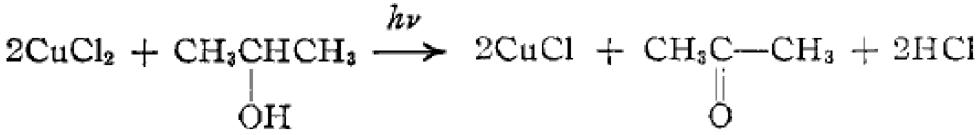
Proposed mechanism:



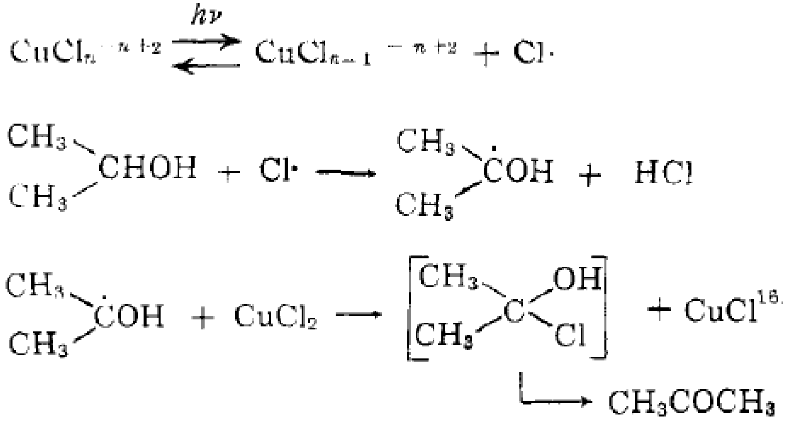
LMCT excitation-homolysis: Cu(II) complexes react from LMCT states which oxidize the anionic nucleophile.

Photolyses of Metal Compounds: Cupric Chloride in Organic Media

By Jay K. Kochi[1] *J. Am. Chem. Soc.* 1962, 84, 11, 2121



$$2CuCl_2 + CH_3\underset{\substack{|\\ OH}}{C}HCH_3 \xrightarrow{h\nu} 2CuCl + CH_3\underset{\substack{\|\\ O}}{C}{-}CH_3 + 2HCl$$



$$CuCl_n{}^{-n+2} \overset{h\nu}{\rightleftharpoons} CuCl_{n-1}{}^{-n+2} + Cl\cdot$$

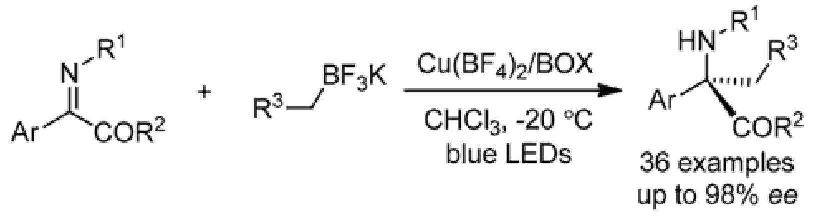
$$\begin{array}{l}CH_3\\CH_3\end{array}\!\!\!>CHOH + Cl\cdot \longrightarrow \begin{array}{l}CH_3\\CH_3\end{array}\!\!\!>\dot{C}OH + HCl$$

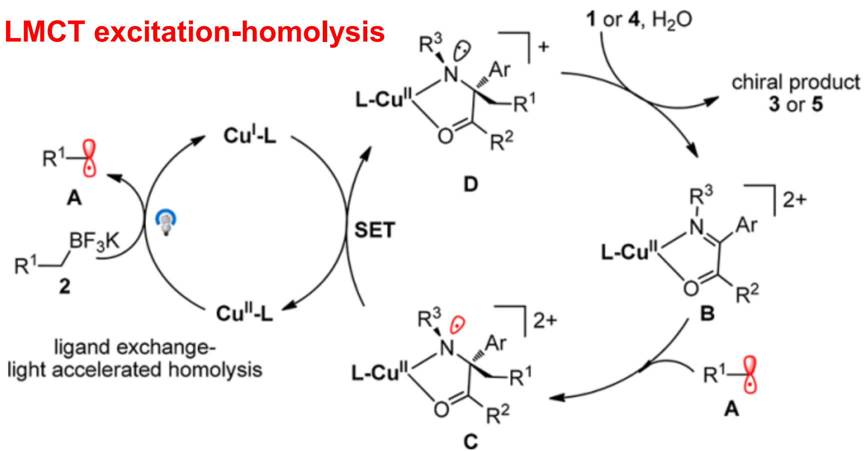
$$\begin{array}{l}CH_3\\CH_3\end{array}\!\!\!>\dot{C}OH + CuCl_2 \longrightarrow \left[\begin{array}{l}CH_3\\CH_3\end{array}\!\!\!>C<\!\!\!\begin{array}{l}OH\\Cl\end{array}\right] + CuCl^{16} \longrightarrow CH_3COCH_3$$

The activation of $Cu(II)X_2$ complexes endowed with suitable ligands to redshift absorption into the visible region can produce radicals X• that initiateproductive organic transformations!

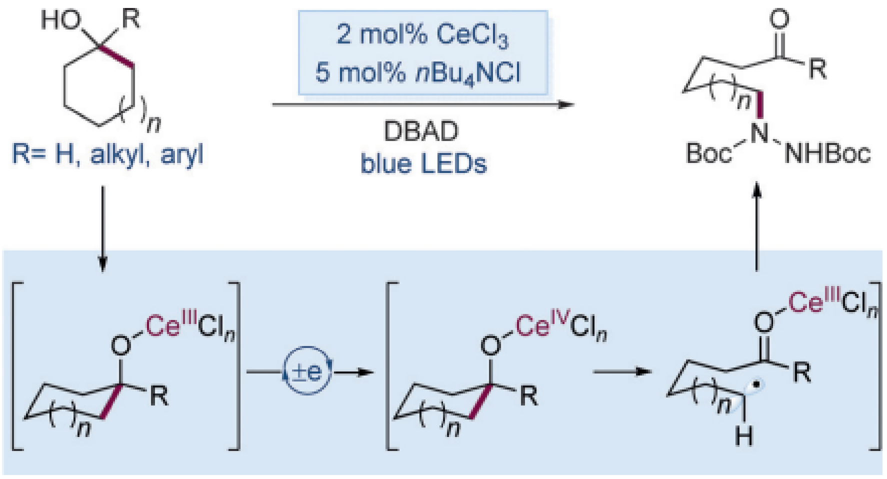
New avenue: light-accelerated Cu^{II} homolysis

Lei Gong et al. *J. Am. Chem. Soc.* **2018**, 140, 15850.

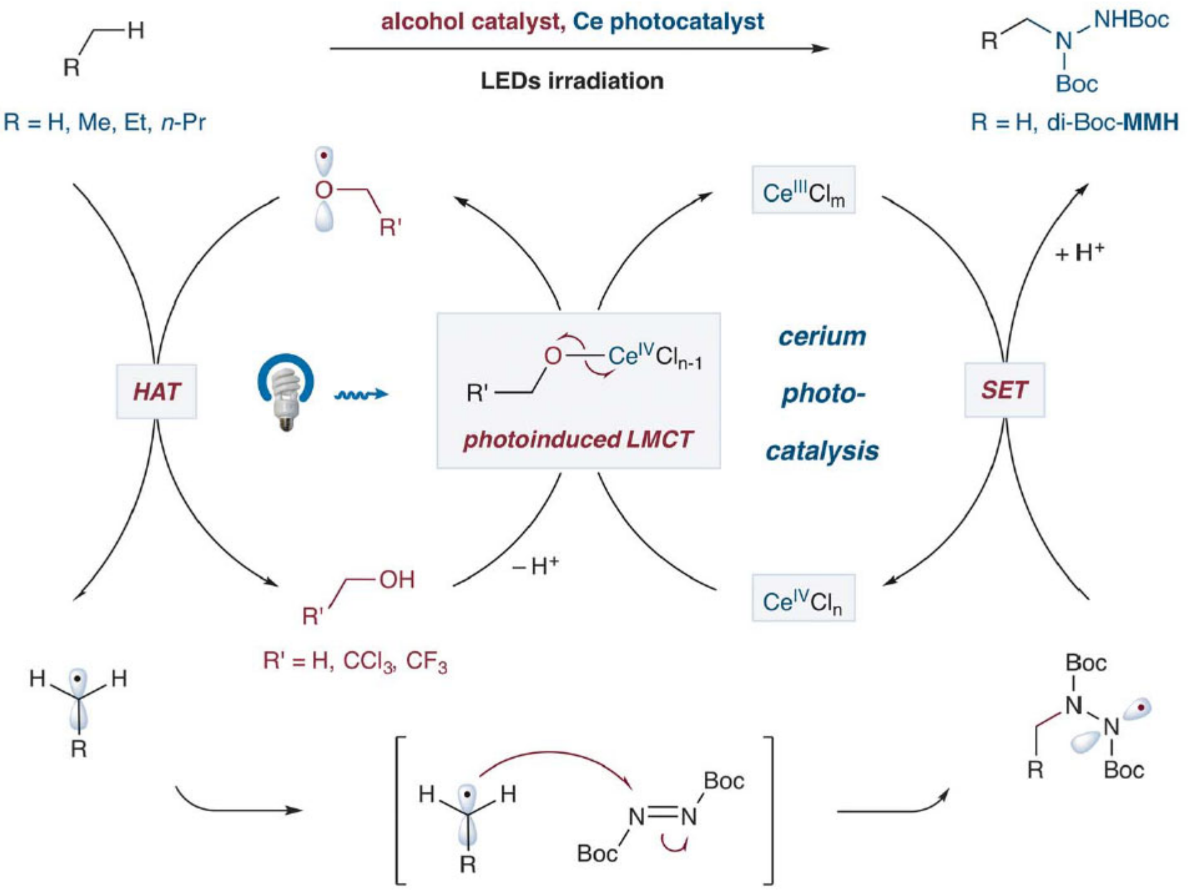




Zhiwei Zuo et al. *Angew. Chem. Int. Ed.* **2016**, 55, 15319.



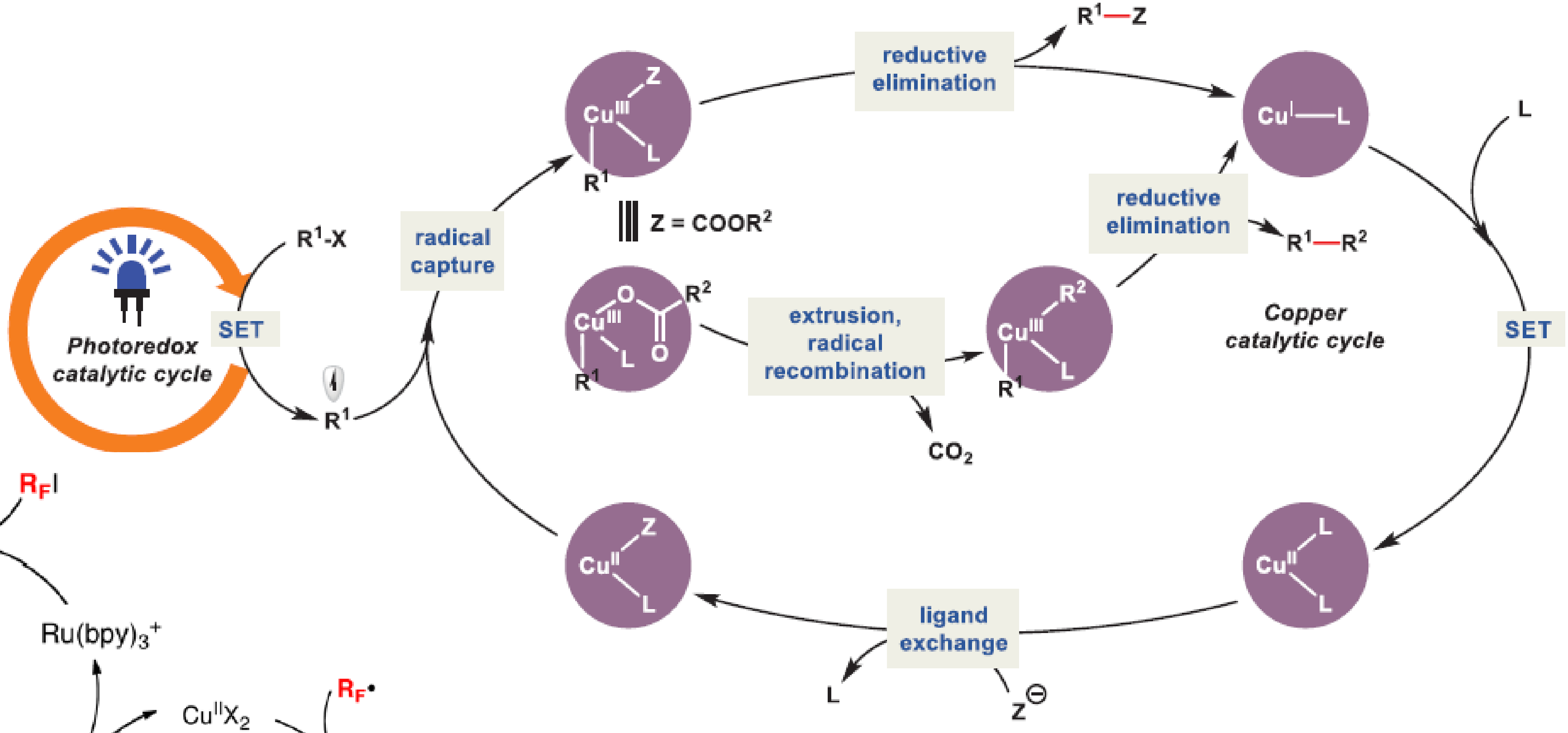
Such principle was also impressively demonstrated by Zuo and co-workers: Highly electrophilic alkoxy radicals, generated from simple alcohols via photoinduced LMCT(*Science* 2018, 361, 668).

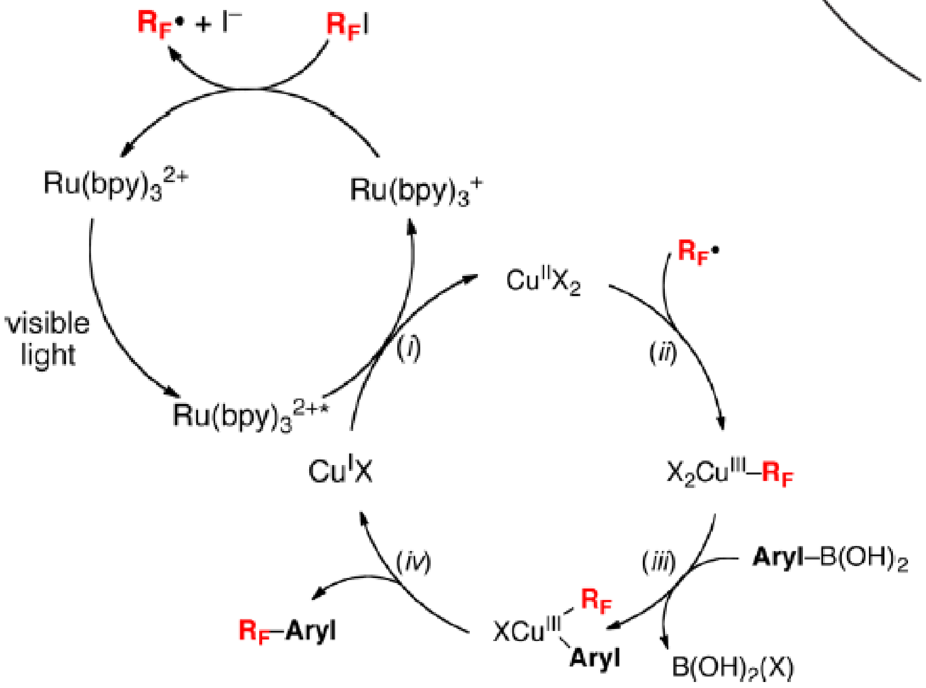


Cooperative photoredox dual catalysis

- **The radical capture by Cu(II) species gives rise to a high-valent Cu(III) intermediate that undergoes facile reductive elimination to furnish the cross-coupled product.**

Co-operative photoredox-copper catalysis: Capturing radicals with copper





$$\text{Aryl}-\text{B(OH)}_2 \;+\; \text{CF}_3\text{I} \xrightarrow[\text{DMF, 60 °C, 12h}]{\substack{\text{20 mol \% CuOAc} \\ \text{1 mol \% Ru(bpy)}_3\text{Cl}_2\bullet 6\text{H}_2\text{O} \\ \text{1 equiv K}_2\text{CO}_3 \\ \text{26 W light bulb}}} \text{Aryl}-\text{CF}_3$$

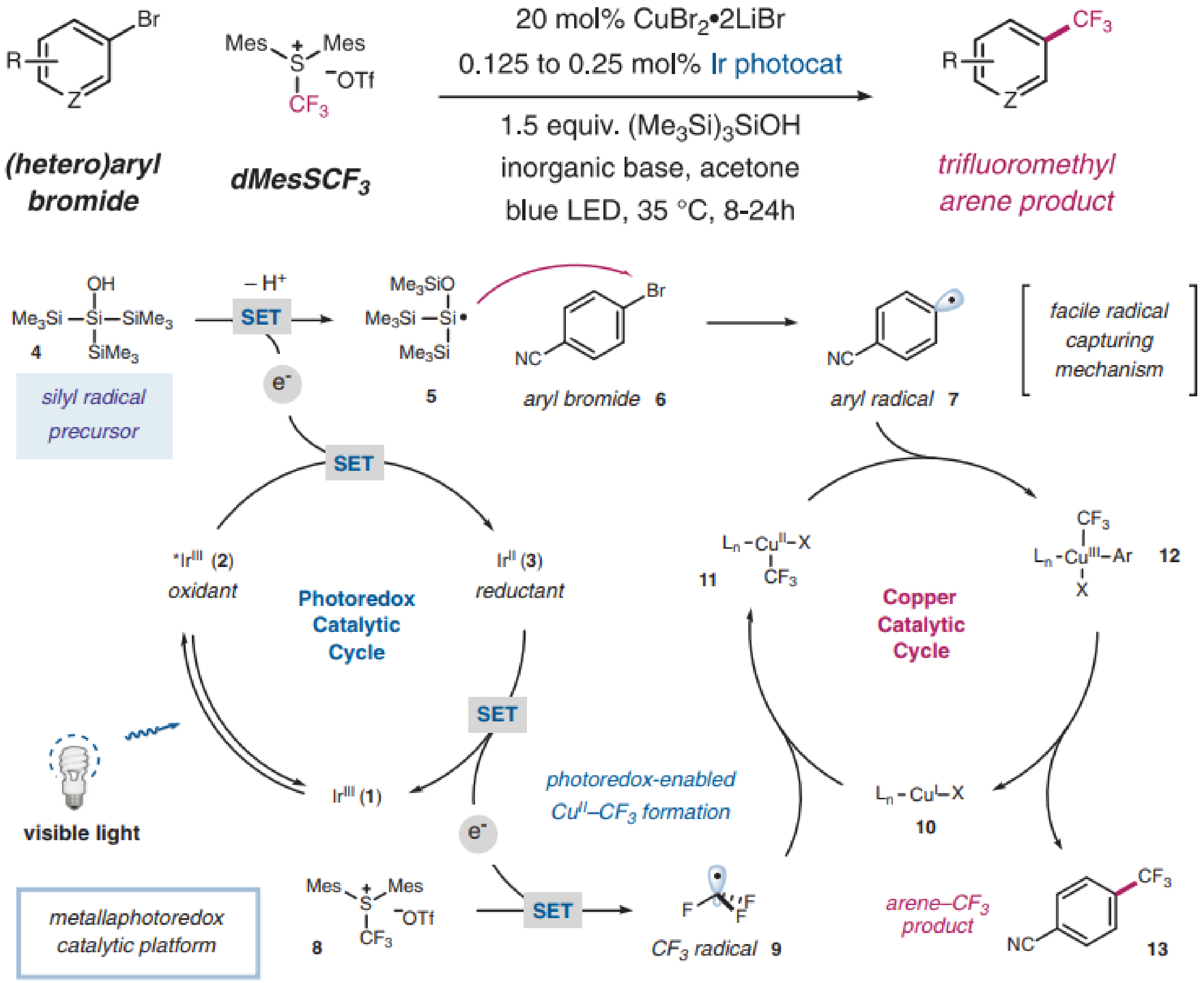
Sanford et al. *J. Am. Chem. Soc.* **2012**, 134, 9034.

Debromo/decarboxylative trifluoromethylation

Macmillan et al. *Science* **2018**, 360, 1010. J. Am. Chem. Soc. 2018, 140, 6522.

A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes

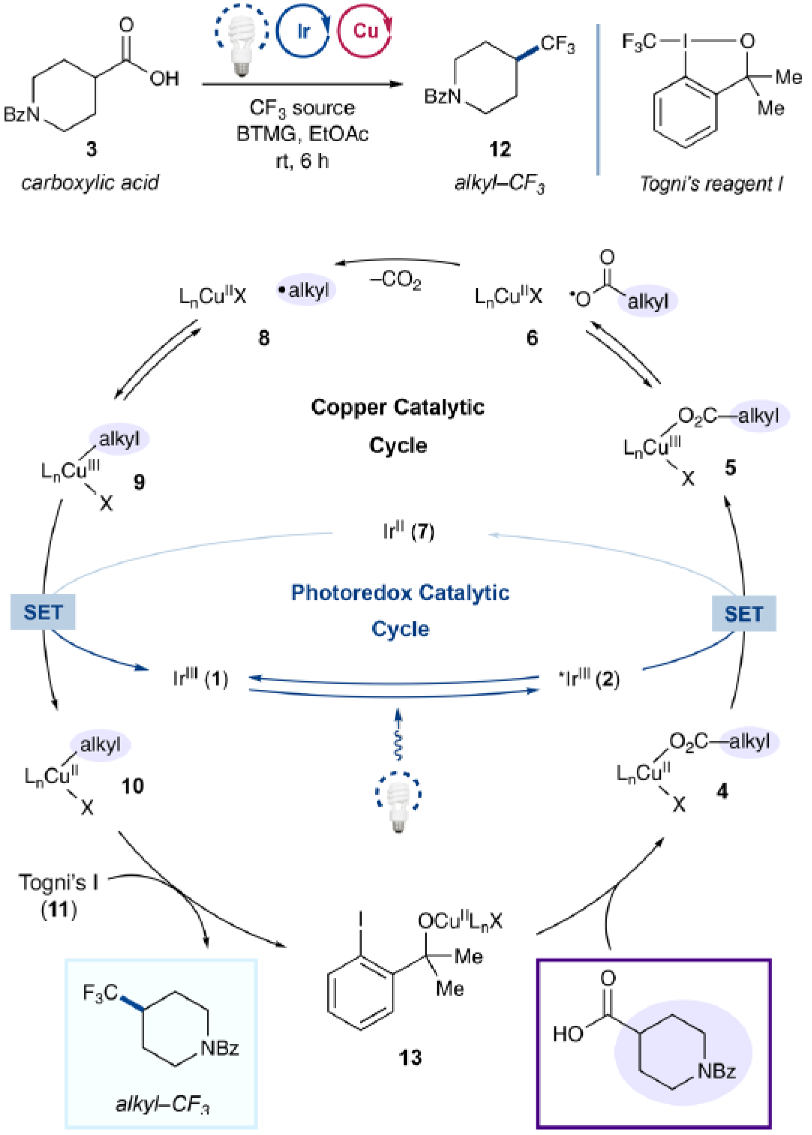
Chip Le,* Tiffany Q. Chen,* Tao Liang,* Patricia Zhang, David W. C. MacMillan†



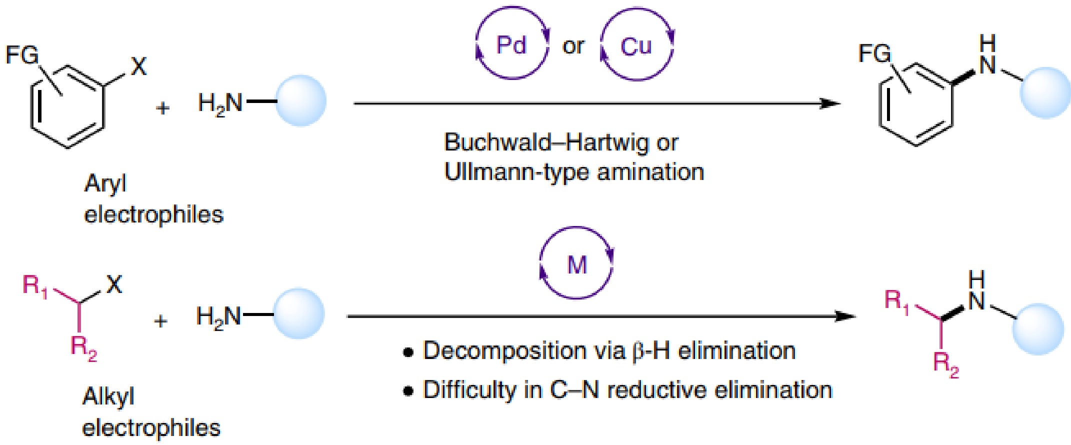
$\text{Aryl}-\text{B(OH)}_2 + \text{CF}_3\text{I} \longrightarrow \text{Aryl}-\text{CF}_3$

Aryl radical generated by single electron oxidation?

Alkyl radical?



Decarboxylative sp^{3}C-N coupling



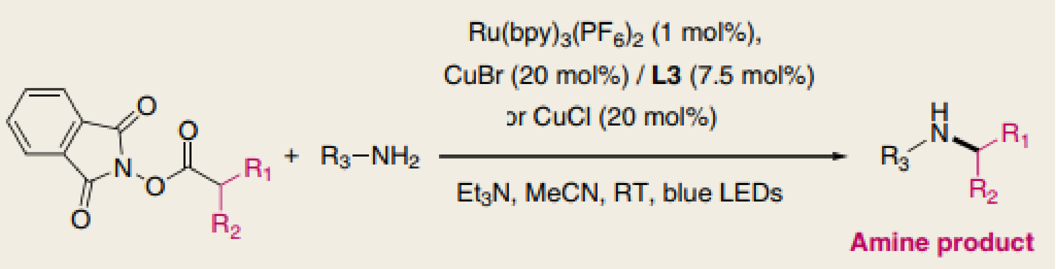
Well established

Under-developed

Aryl$-B(OH)_2$ + **CF_3**I ⟶ **Aryl**$-$**CF_3**

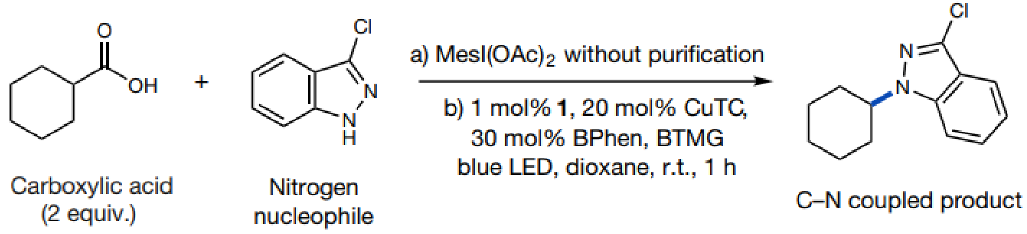
Alkyl radical generated by single electron reduction?

Xile Hu et al. *Nat. Catalys.* **2018**, 1, 120

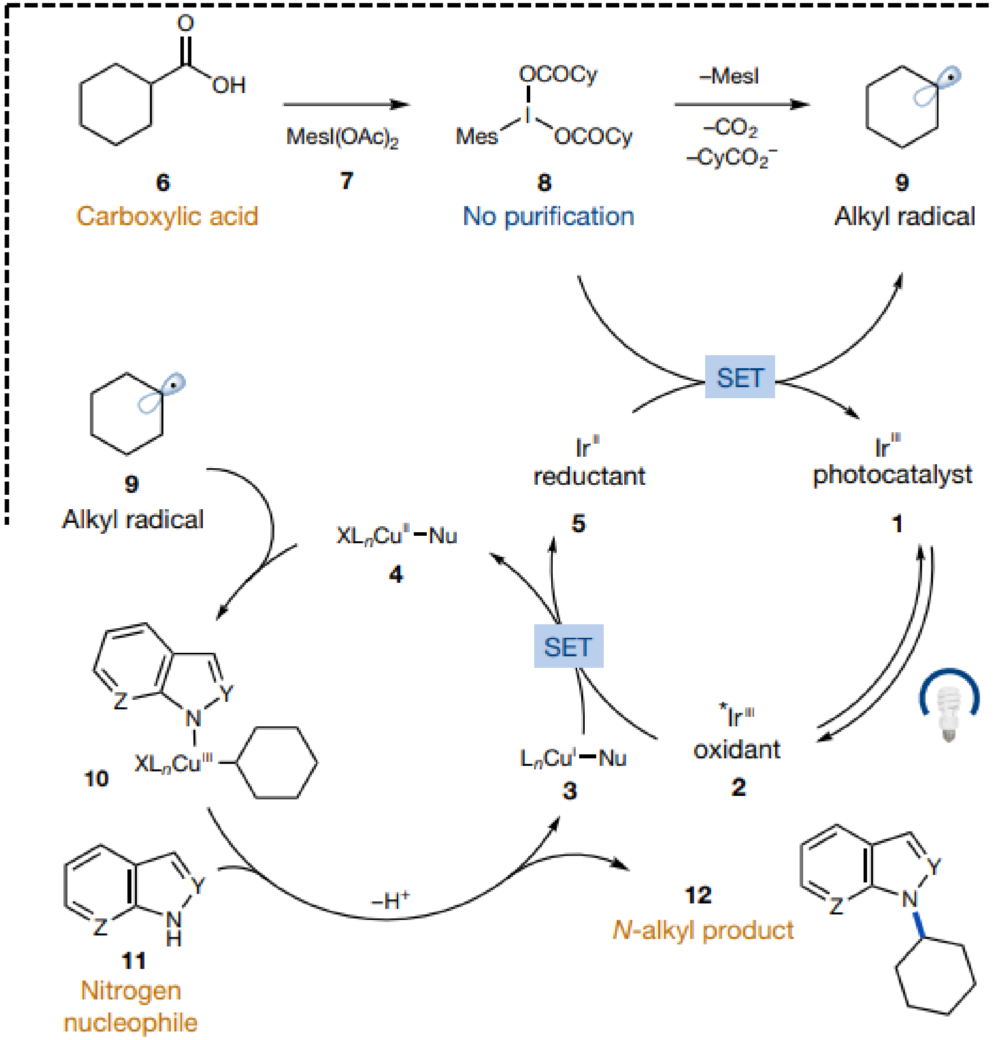


Primary, Secondary alkyl acids
aromatic amines

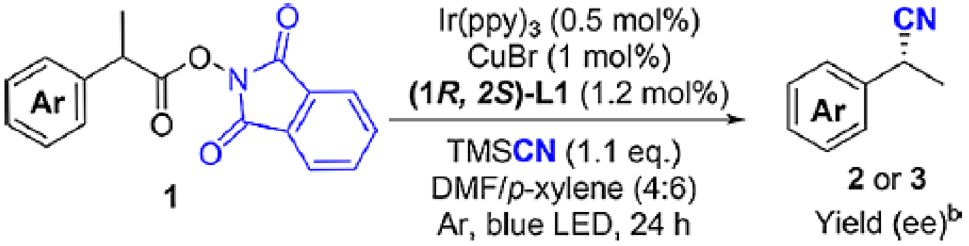
Macmillan et al. *Nature.* **2018**, 559, 83.

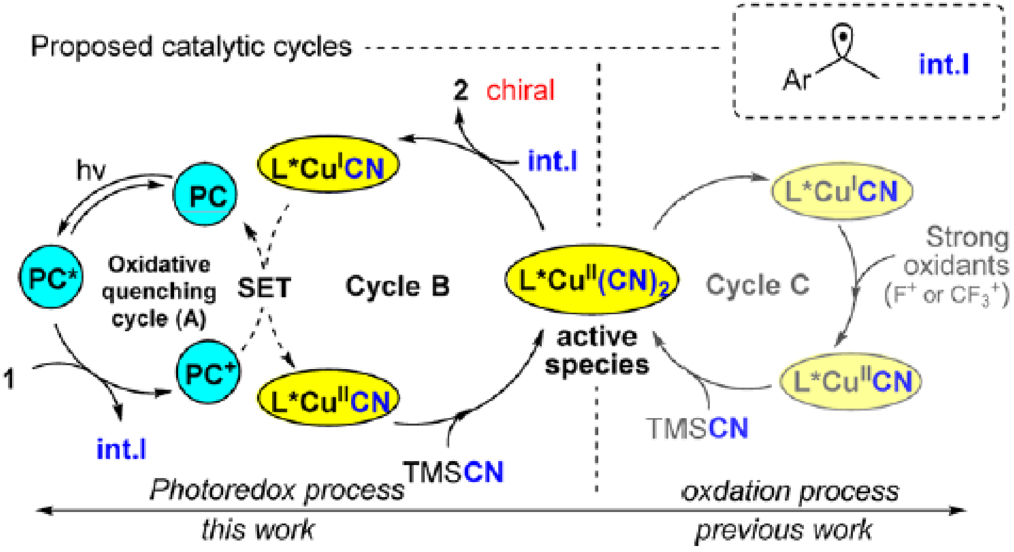


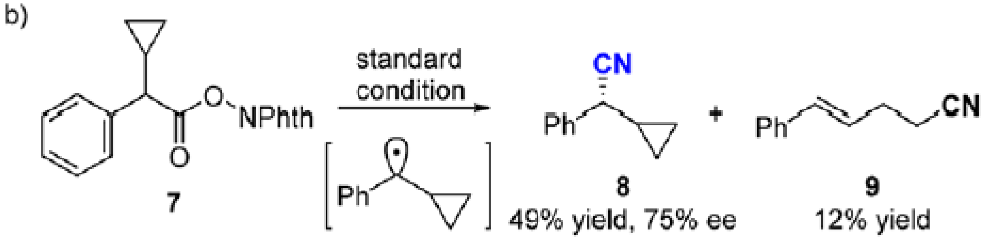
Primary, Secondary, Tertiary alkyl acids
Various nitrogen nucleophiles(most N-heterocycles)

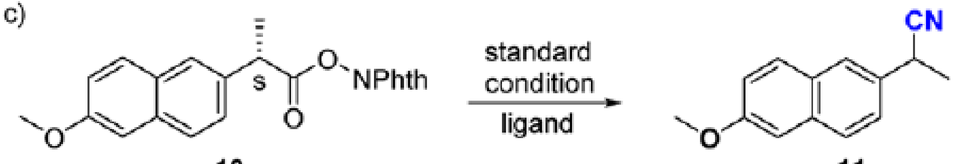


Enantioselective decarboxylative sp^3C-CN coupling







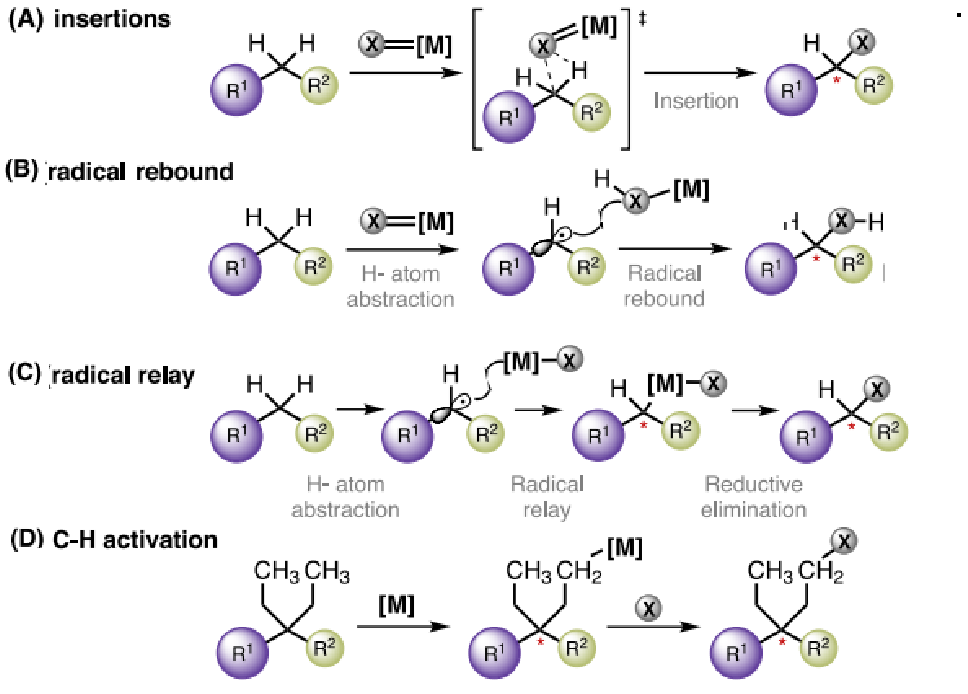


(1*R*,2*S*)-**L1** (*R*)-**11** 84% yield, 87% ee
(1*S*,2*R*)-**L1** (*S*)-**11** 85% yield, -88% ee

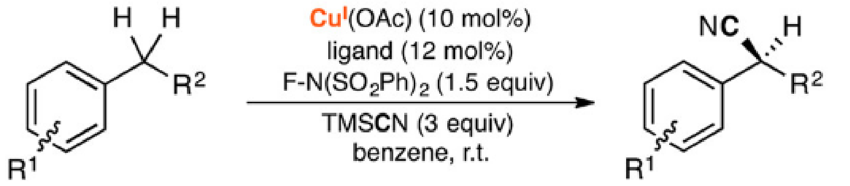
Guosheng Liu et al.
JACS. **2017**, 139, 15632

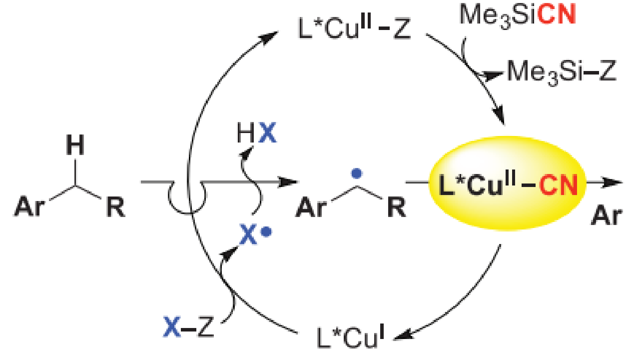
■ General Mechanisms for Transition Metal-Catalyzed C–H Bond Functionalization.

Chem. Rev. **2019**, 119, 2954−3031
Trends in Chemistry **2019**, 1, 471. *Tetrahedron Letters* **2019**, 60, 151225



Cu-Catalyzed Enantioselective C–H Cyanation via Radical Relay

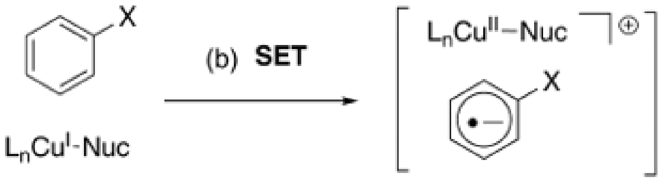




Guosheng Liu et al.
Science. **2016**, 353, 1014

Summary

- **Mechanism of Ullmann-Goldberg can vary**



$$\mathrm{Cu^{I}} \xrightleftharpoons{E_{1/2}= 0.16V} \mathrm{Cu^{II}} \xrightleftharpoons{E_{1/2}= 2.4V} \mathrm{Cu^{III}}$$

d^{10} — d^{9} — d^{8}, metal cation

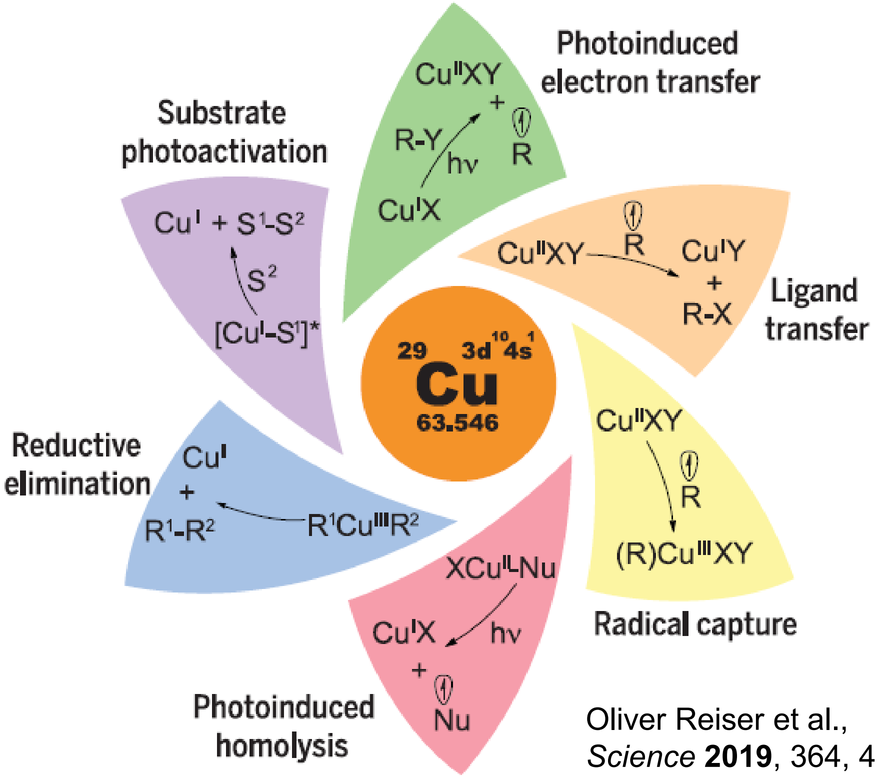
isoelectronic with Ni(0) Pd(0)

isoelectronic with Pd(II)

- forms shorter bonds than Pd
- harder Lewis acidity than Pd
- higher affinity for O, N ligands
- smaller coordination shell can not accomodate large ancillary ligands

- highly electrophilic and unstable
- potent oxidizer
- requires highly stabilizing ligands
- unstable towards the reverse reductive elimination
- requires the nucleophile to be in the coordination sphere prior to oxidative addition

- **Single-electron reduction from Cu(I)* complexes**
- **LMCT excitation-homolysis Cu(II) * complexes**
- **Cooperative photoredox dual catalysis: the radical capture by Cu(II) species gives rise to a high-valent Cu(III) intermediate that undergoes facile reductive elimination**



Oliver Reiser et al., *Science* **2019**, 364, 450.