



# The Cross-Coupling Reactions of Merging Photoredox with Nickel Catalysis

Lili Zhang

2022.3.18

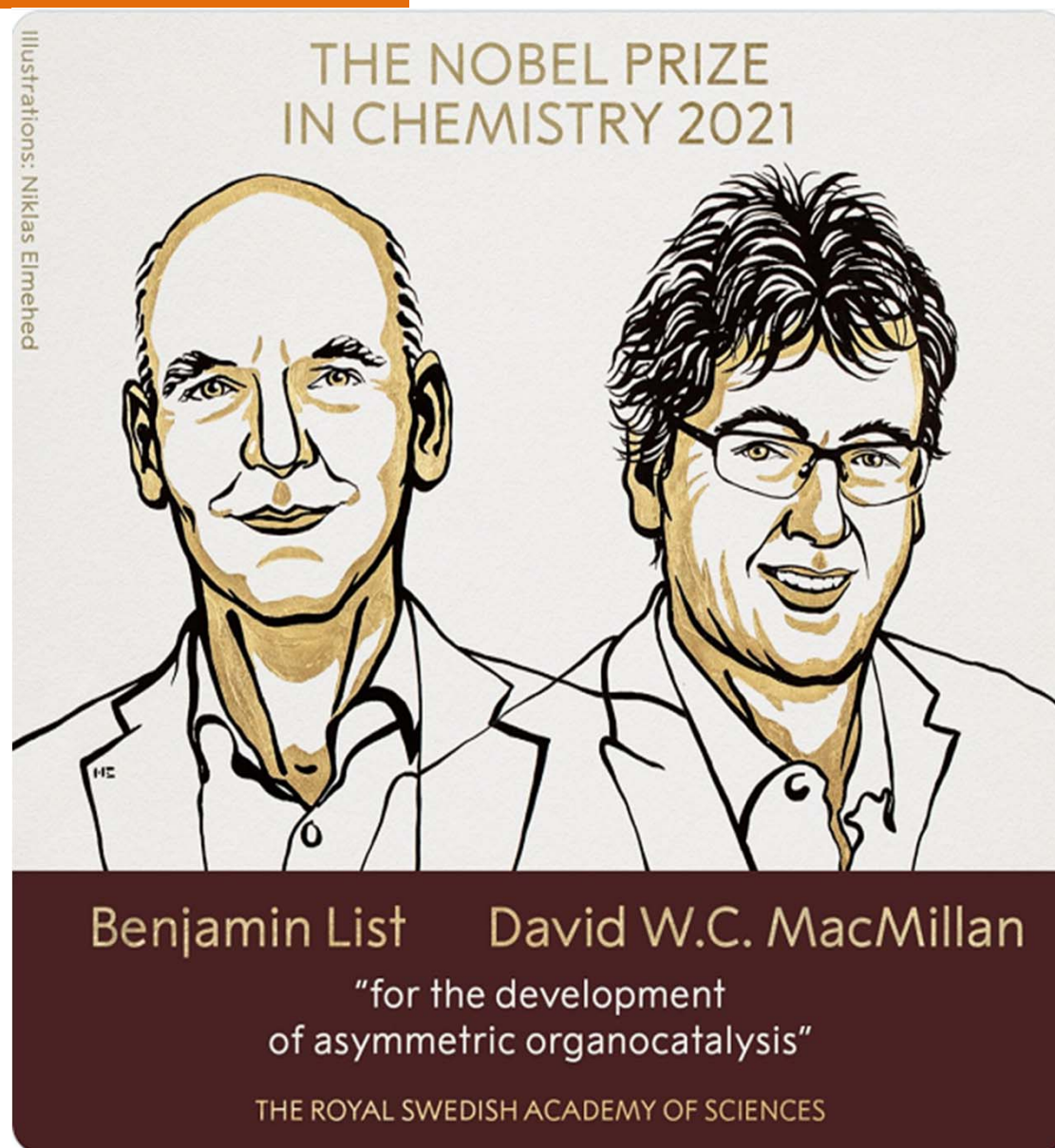
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# 目 录

- 背景
  - 作者介绍 P3-4
  - 光催化剂和早期的经典反应介绍 P5-11
- 光/镍催化构建C-C键（按自由基产生方式分类）
  - 氧化脱羧 P12-40
  - 奎宁环介导的HAT P41-51
  - TBADT介导的HAT P51-55
  - 硅自由基介导的XAT P56-66
- 光/镍催化构建C-O键 P67-75
- 光/镍催化构建C-N键 P76-80
- 光/镍催化同位素标记甲基化 P81-82

# Author Introduction



# Author Introduction



1968年 出生于苏格兰

1990年格拉斯哥大学毕业

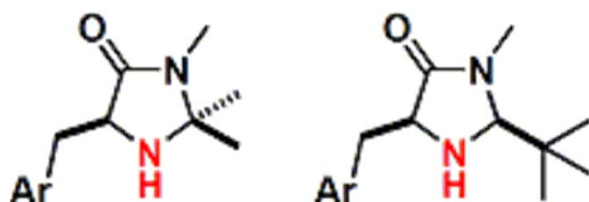
1996年加州大学欧文分校博士学位 (L.E.Overman教授)

1998年哈佛大学 博士研究生 (D.A.Evans教授)

1998年加州大学伯克利分校 任职

2000年加州理工学院

2006年普林斯顿大学



MacMillan's Catalyst

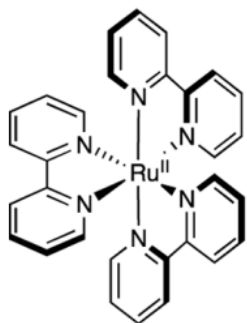
Organocatalysis

*Science* 2007, 316, 582.



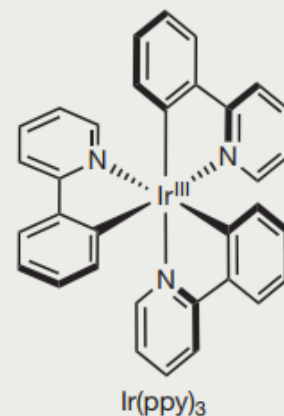
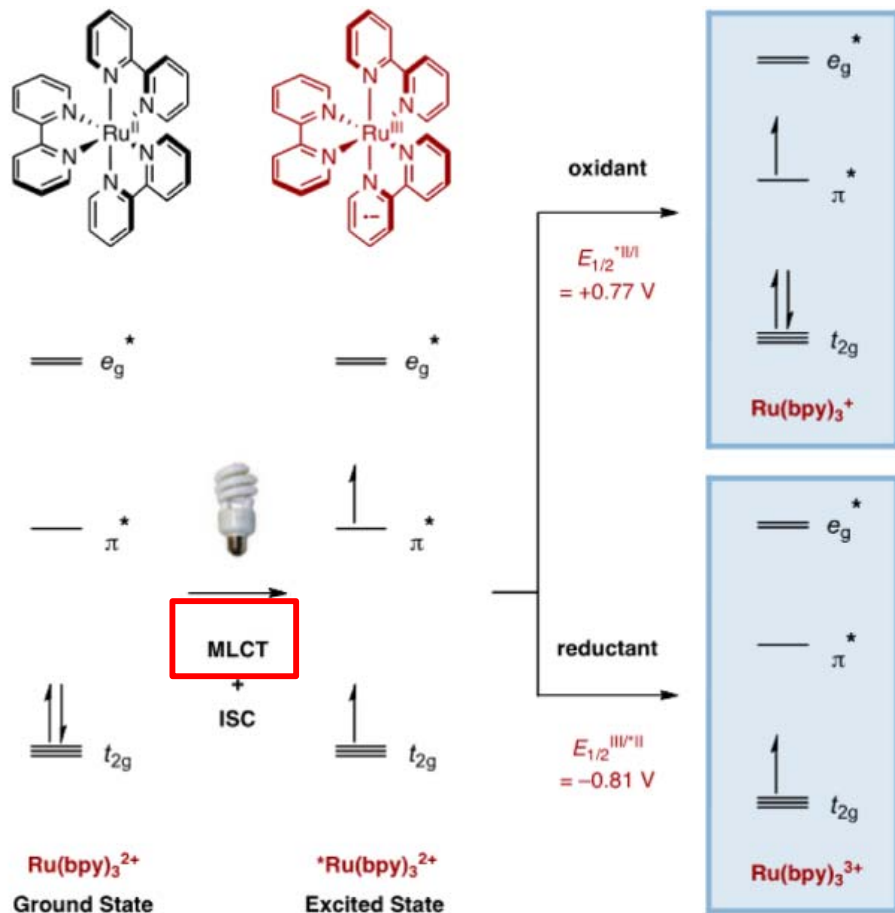
Metallaphotoredox  
catalysis

# Background



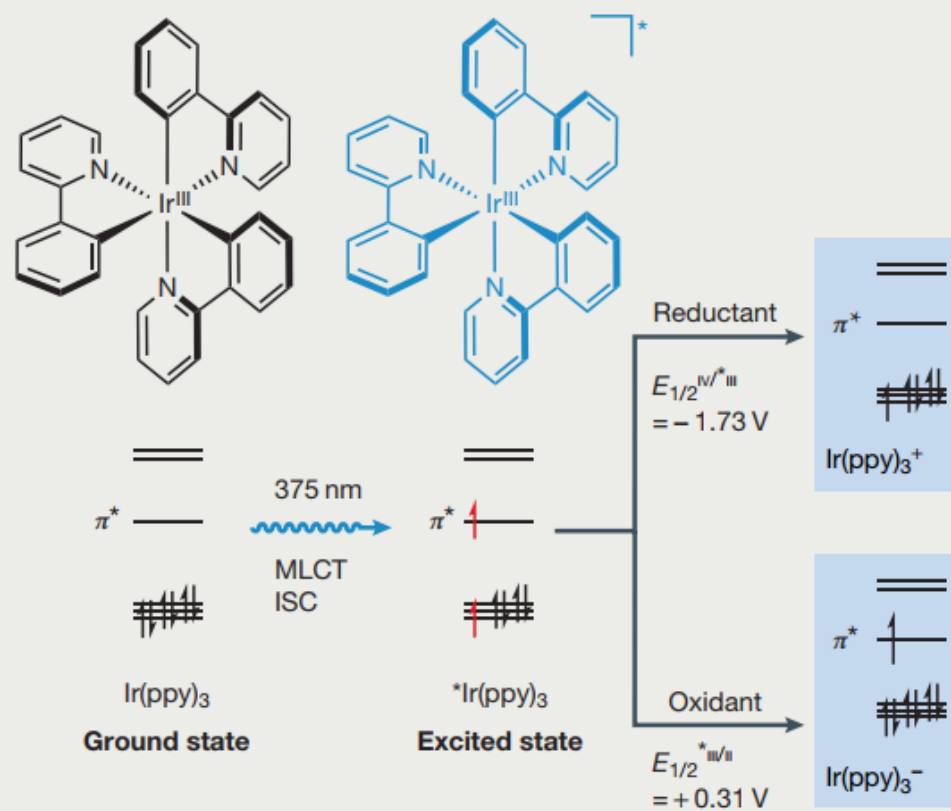
- Absorption at 452 nm (visible light)
- Stable, long-lived excited state ( $\tau = 1100$  ns)
- Single electron transfer (SET) catalyst
- Effective excited state oxidant and reductant

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

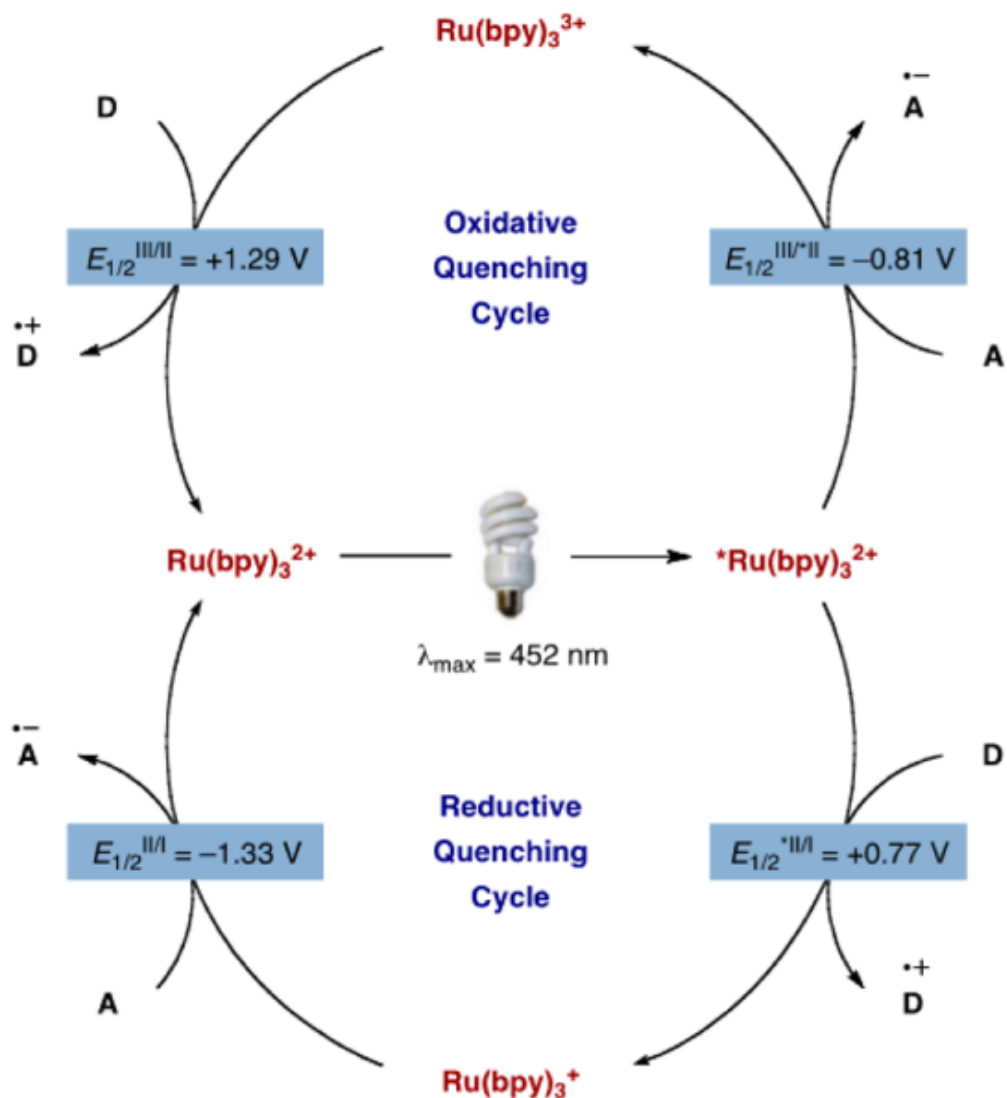


- Maximum absorption at 375 nm (visible light)
- Single-electron-transfer catalyst
- Effective oxidant and reductant
- Triplet energy of  $56$  kcal mol $^{-1}$
- Long-lived excited state ( $\tau = 1.9$   $\mu\text{s}$ )

$\text{Ir}(\text{ppy})_3$



# Background



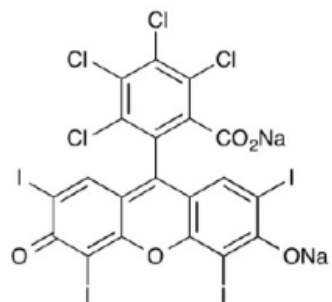
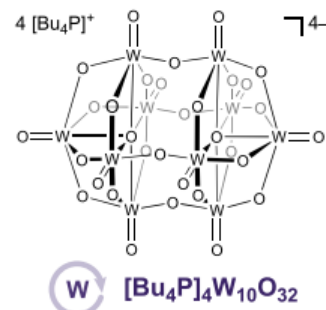
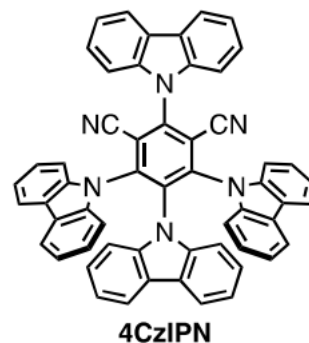
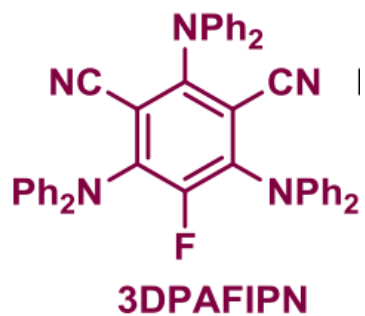
➤ 在无机和材料化学中被广泛研究和应用，例如水的光解；二氧化碳还原；太阳能电池；有机发光二极管；引发聚合反应等。

➤ 光反应优势：

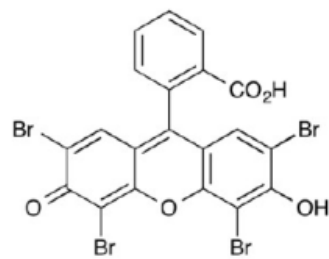
- ①独特的单电子氧化还原特性；
- ②高反应性和选择性；
- ③氧化和还原过程即时即地发生；
- ④条件相对温和，光催化剂本身惰性，可减少副产物。

对自由基化学的影响具有革命性！

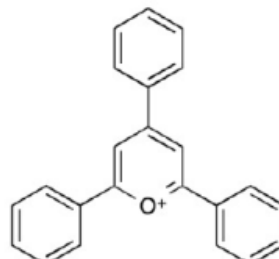
# Background



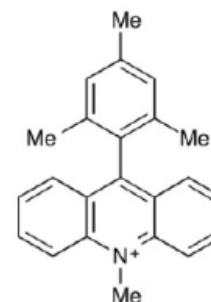
**Rose Bengal**



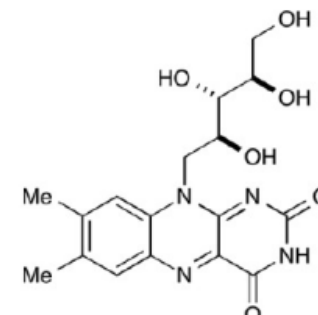
**Eosin Y**



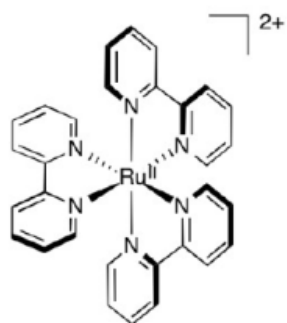
**TPP+**



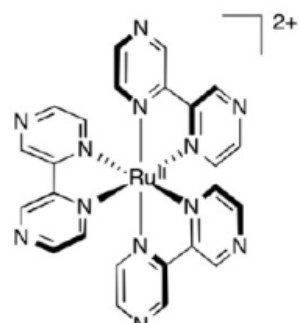
**Mes-Acr+**



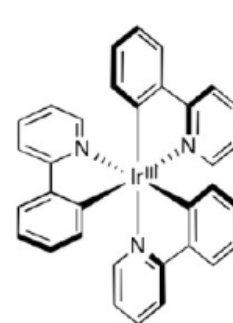
**Riboflavin**



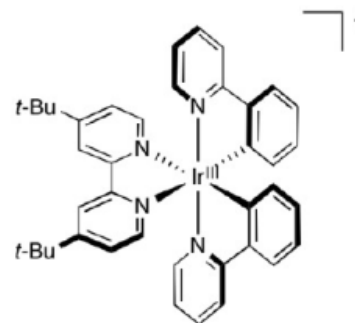
**Ru(bpy)<sub>3</sub><sup>2+</sup>**



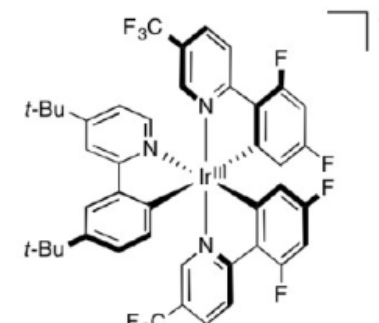
**Ru(bpz)<sub>3</sub><sup>2+</sup>**



**Ir(ppy)<sub>3</sub>**



**Ir(ppy)<sub>2</sub>(dtbbpy)<sup>+</sup>**



**Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)<sup>+</sup>**

# Background

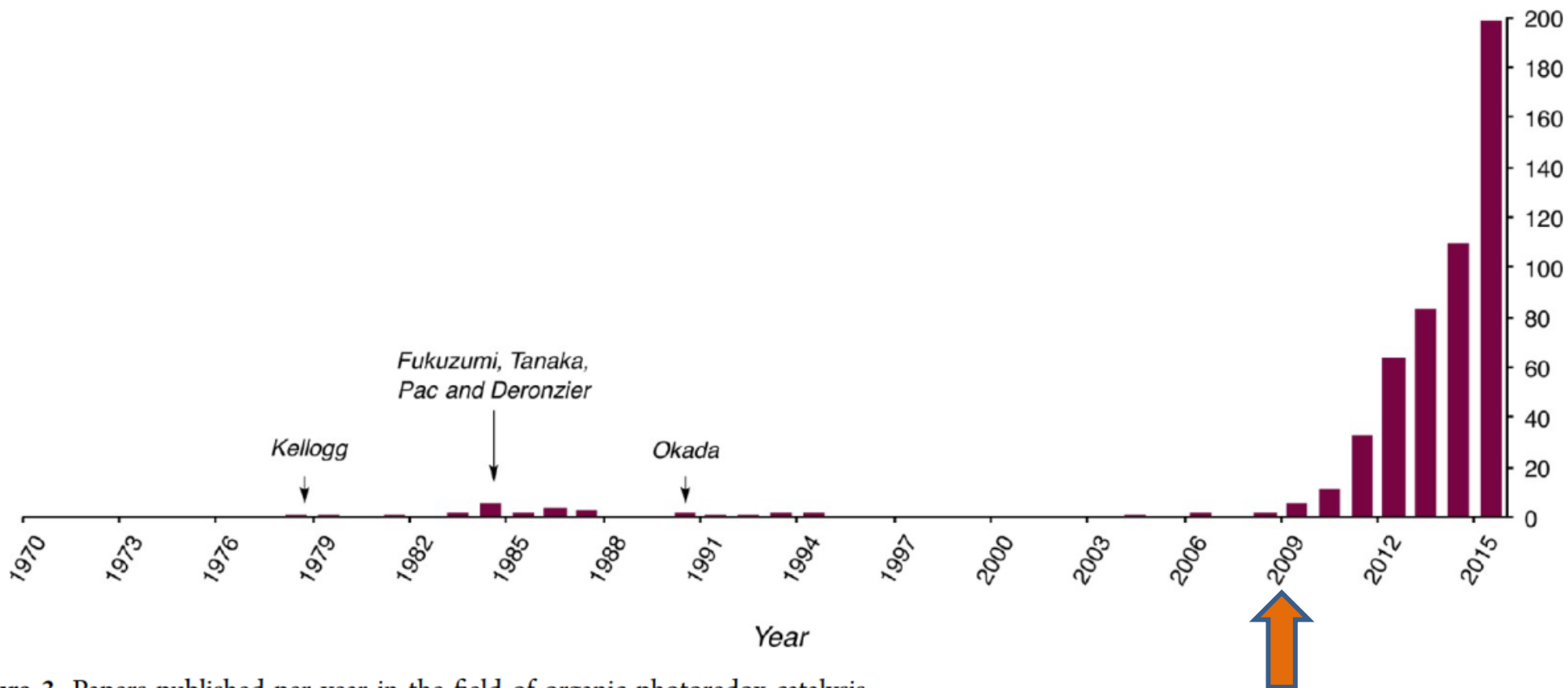


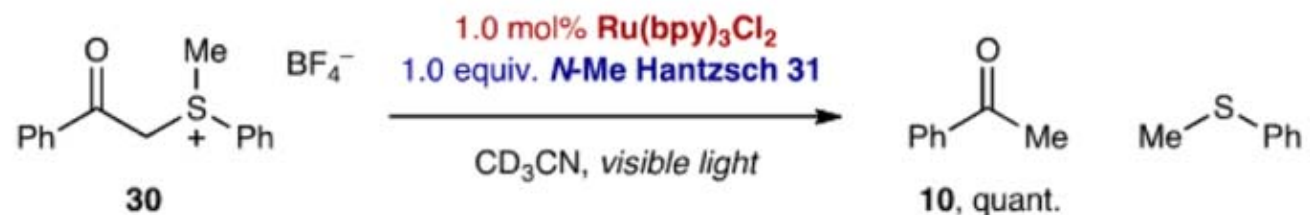
Figure 3. Papers published per year in the field of organic photoredox catalysis.

**MacMillan<sup>2008</sup>**  
**Yoon<sup>2008</sup>**  
**Stephenson<sup>2009</sup>**



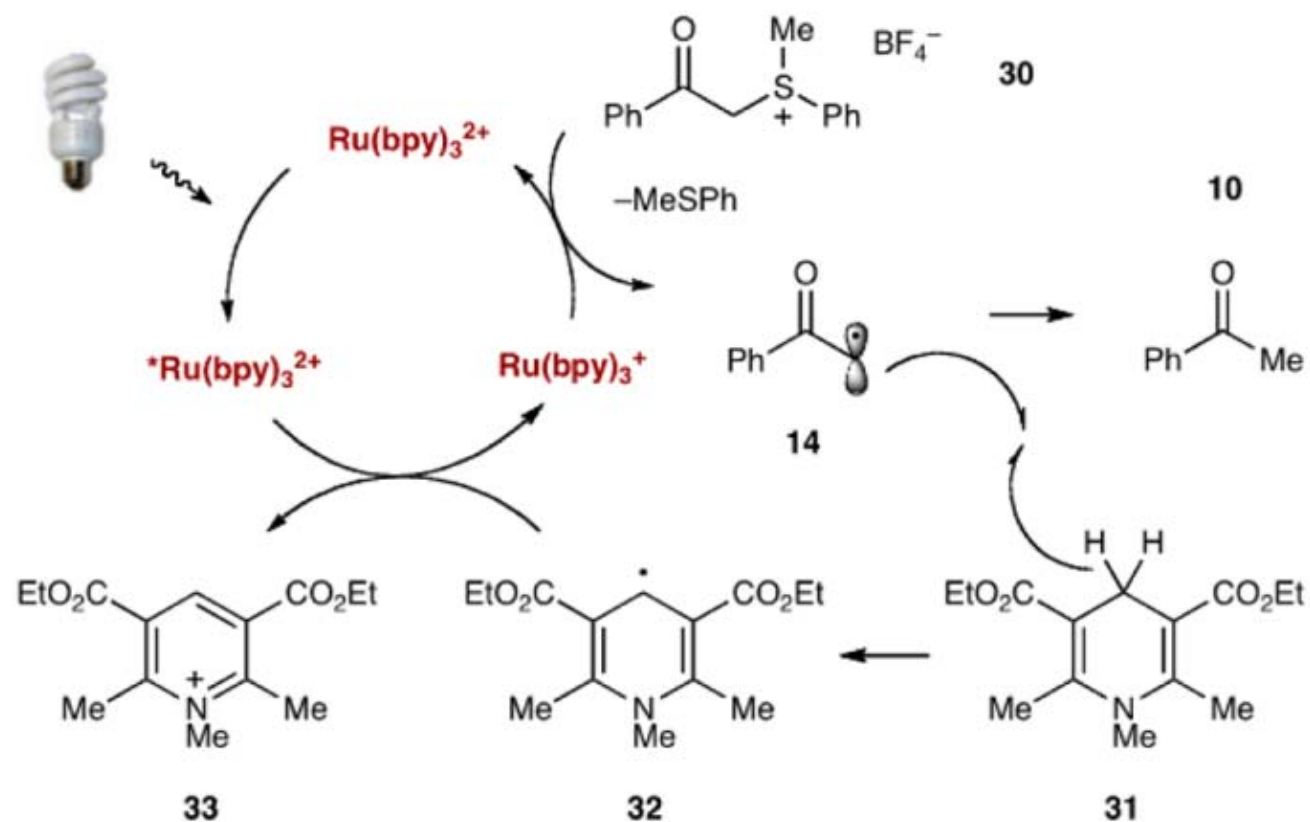
# Background

## Kellogg's work<sup>1978</sup>



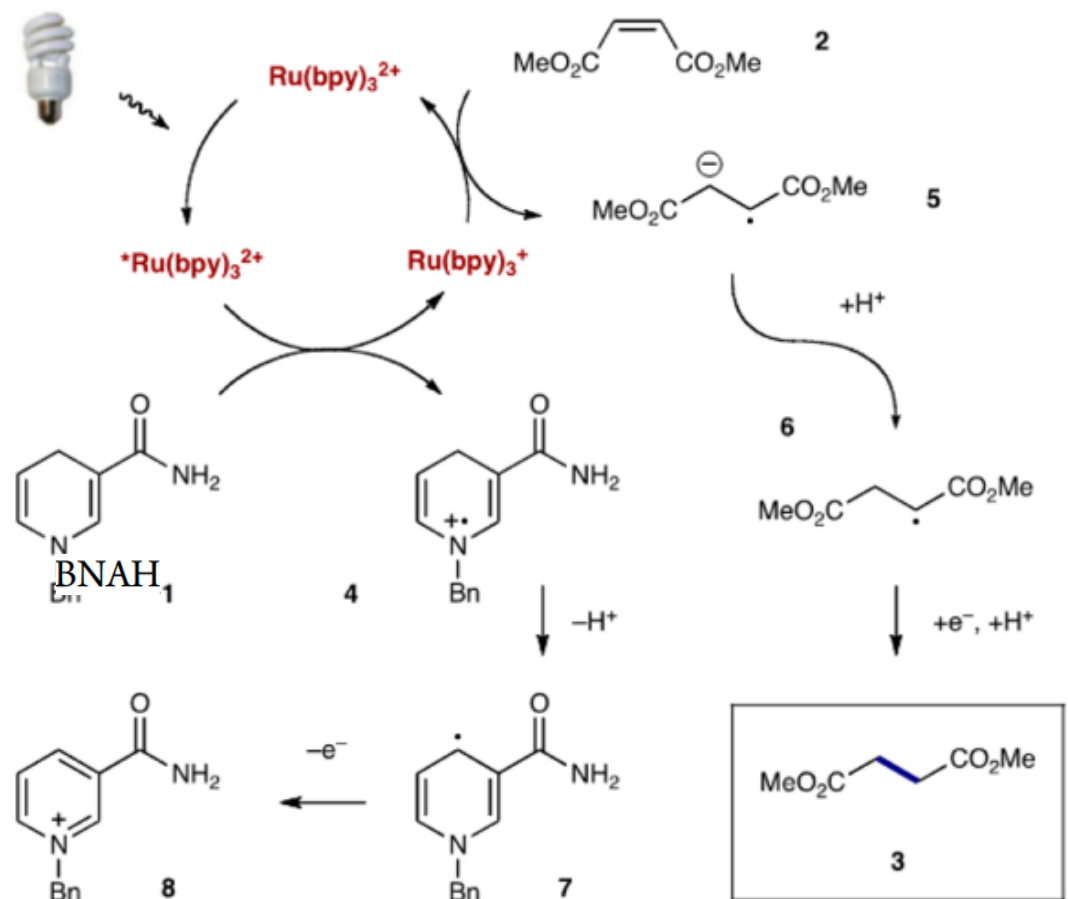
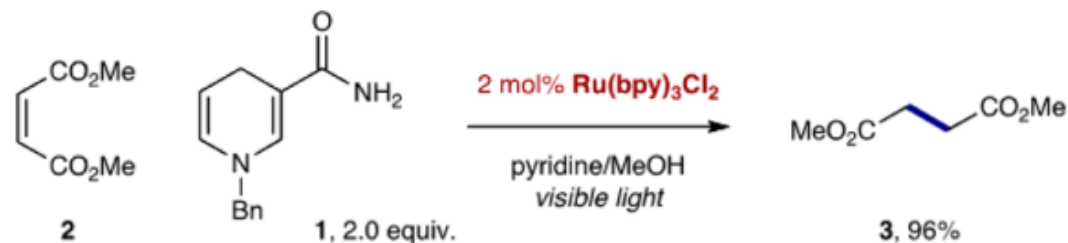
➤ 光氧化还原催化  
有机分子转化的  
最早的例子

➤ 激发态钌被还原  
猝灭；



# Background

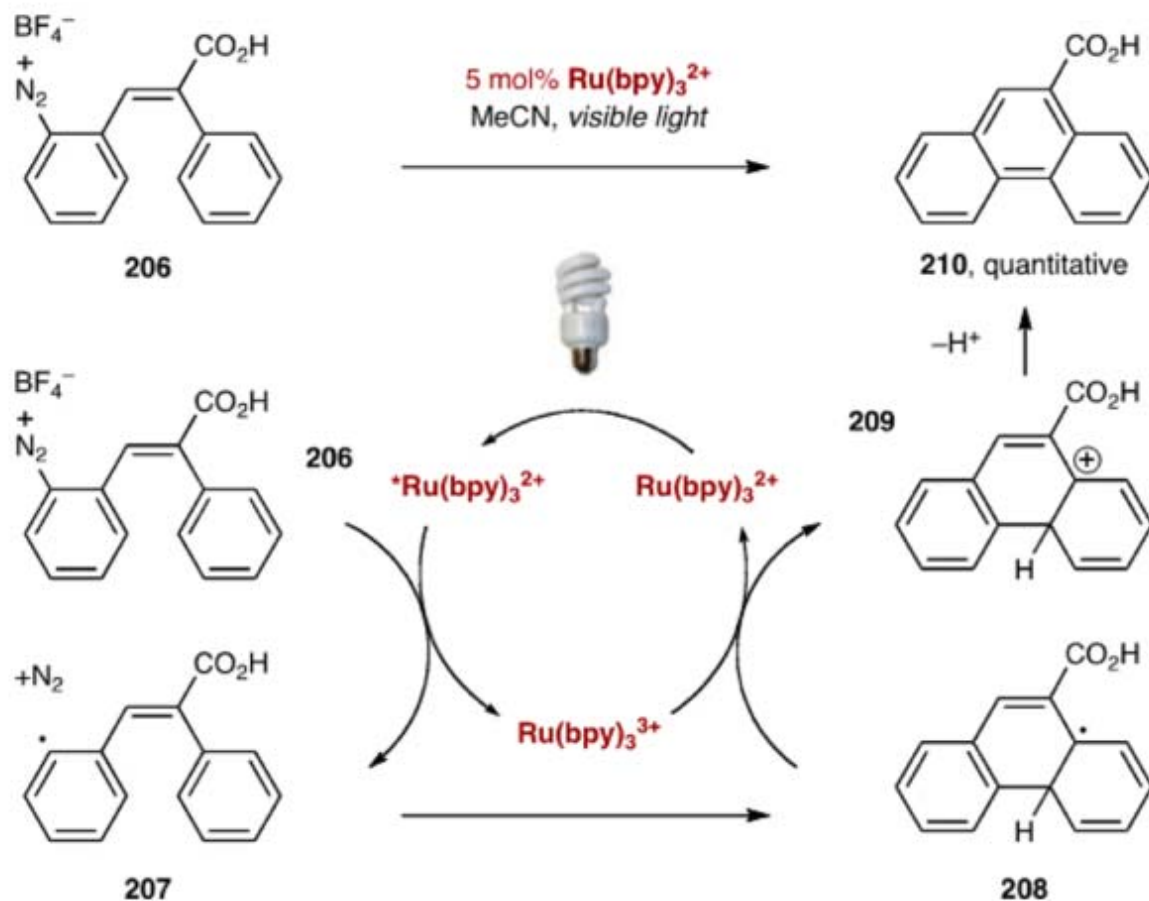
## Pac's work<sup>1981</sup>



- **BNAN**既当还原剂，也充当氢供体；
- **6**物种的还原剂可能 $\text{Ru}(\text{bpy})_3^+$ 也可能是**7**物种；
- 激发态钌被还原猝灭；

# Background

## Deronzier's work<sup>1984</sup>

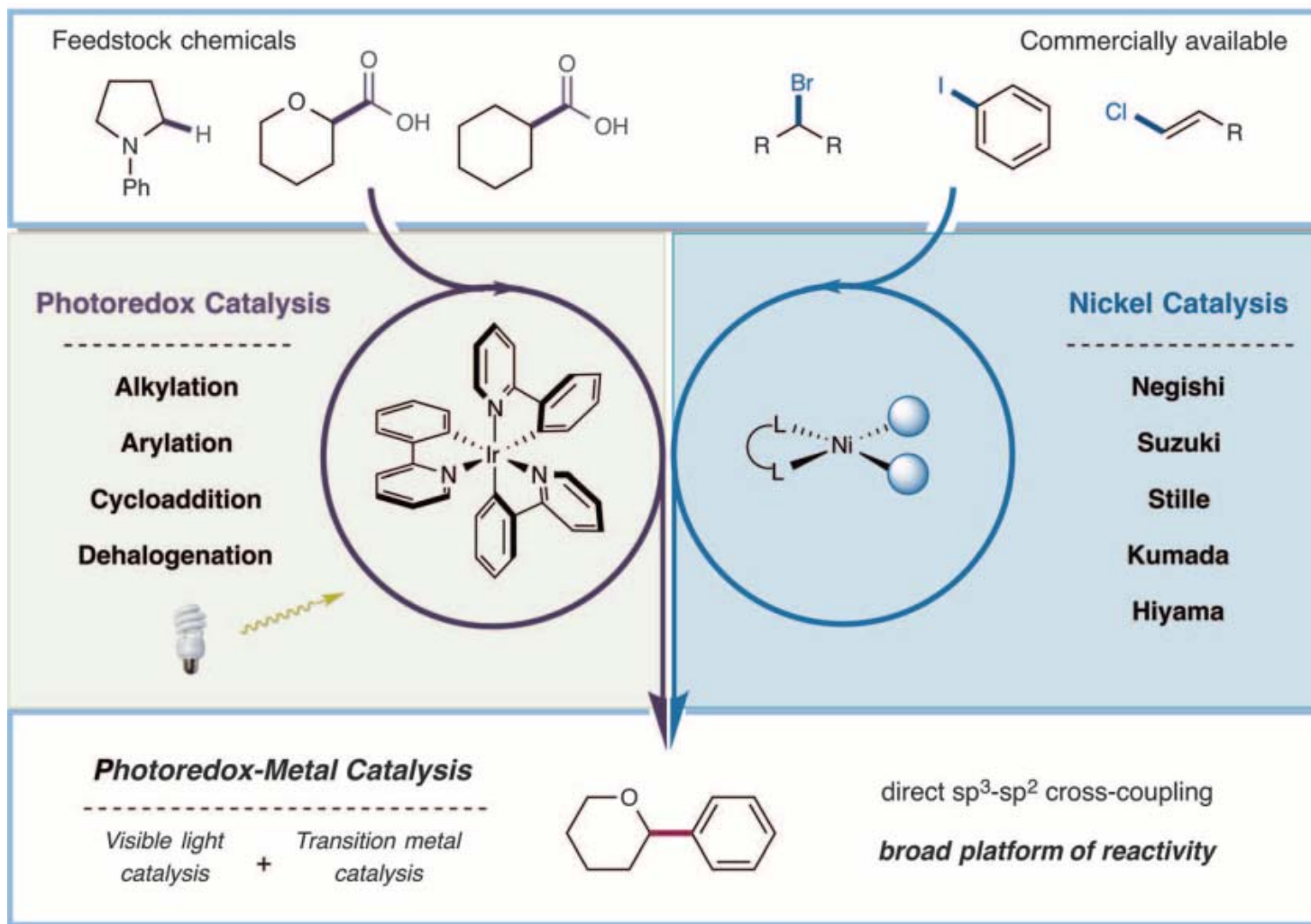


- **BNAN**既当还原剂，也充当氢供体；
- **6**物种的还原剂可能 **$\text{Ru}(\text{bpy})_3^{3+}$** 也可能是**7**物种；
- 激发态钌被氧化猝灭；

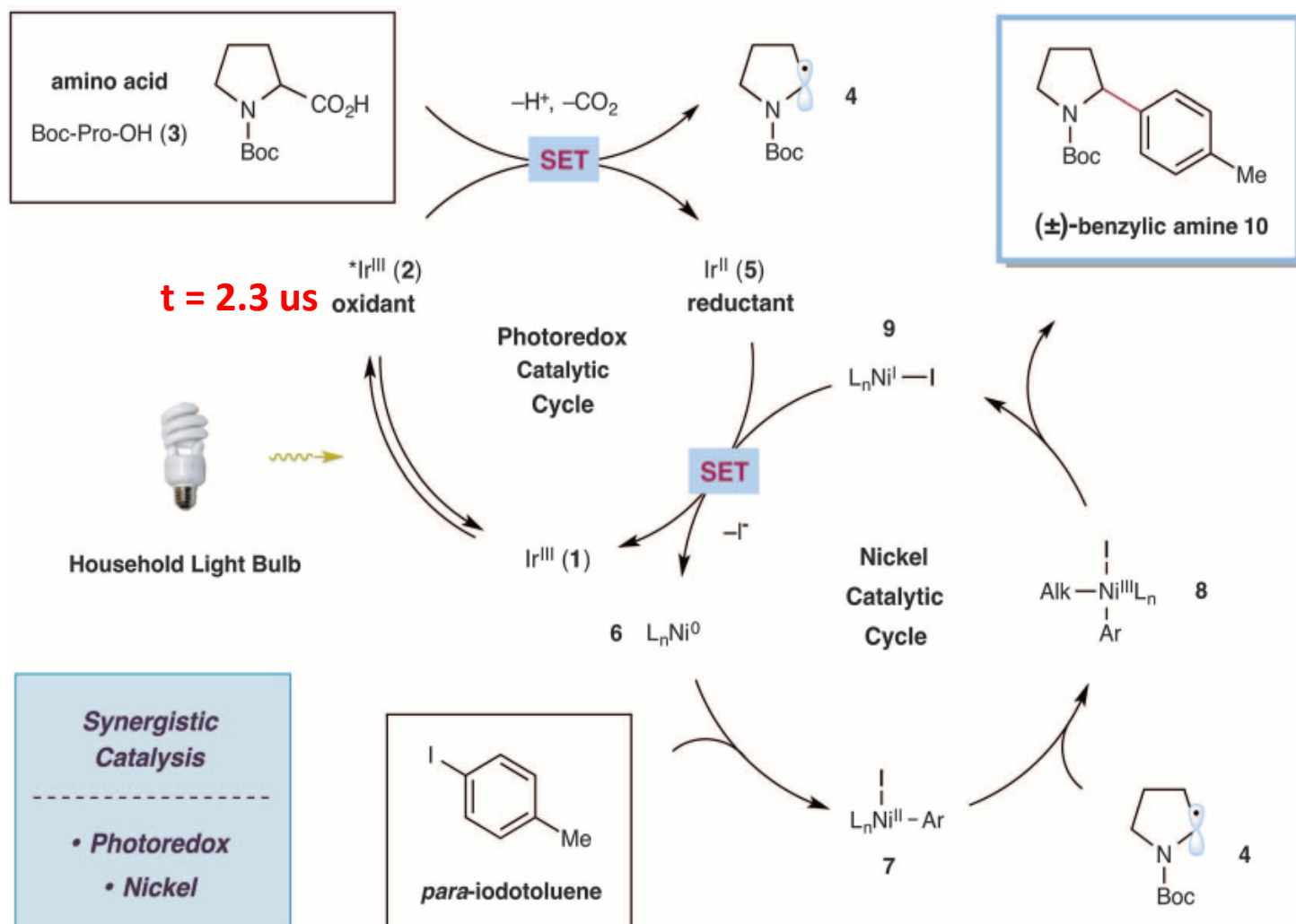


# Merging Photoredox with Nickel Catalysis: Coupling of $\alpha$ -Carboxyl $sp^3$ -Carbons with Aryl Halides

Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan  
**Science, 345, 437-440 (2014)**



# Proposed Mechanism



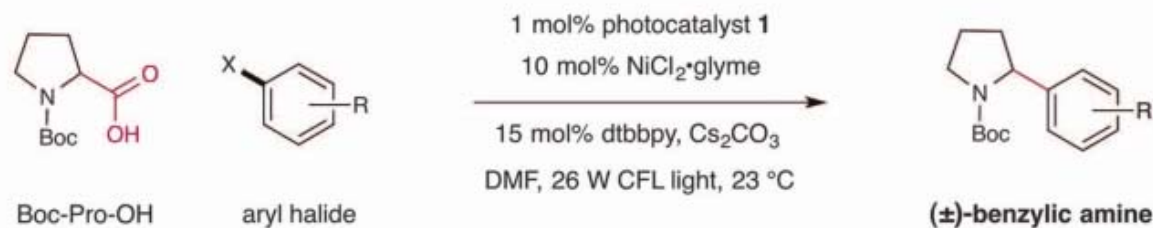
- 自由基产生
- 与碱脱质子化
- 脱CO<sub>2</sub>，氧化
- 氧化加成是否从Ni<sup>I</sup>开始?
- Ni<sup>0</sup>更容易OA
- Ni<sup>II</sup>可快速捕捉sp<sup>3</sup>自由基
- PC是否还原Ni<sup>II</sup>ArX物种?

铱与镍的还原电位:

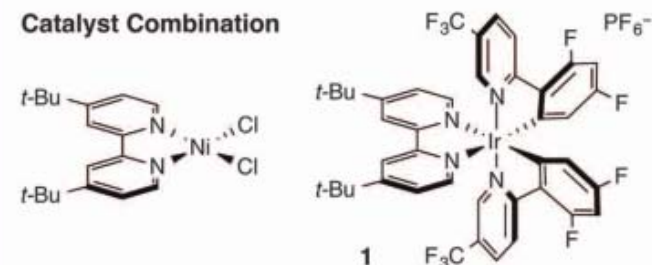
$$E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}\text{ArX}/\text{Ni}^{\text{I}}\text{Ar}] = -1.7 \text{ V vs SCE}$$

$$E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V vs SCE}$$

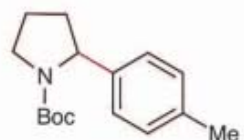
# Scope of substrates



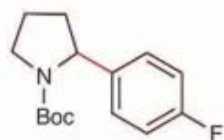
## Catalyst Combination



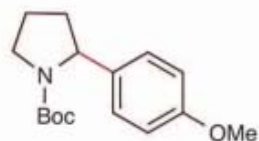
### iodoarenes X = I



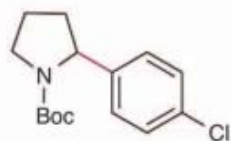
(±)-10 78% yield



(±)-11 65% yield

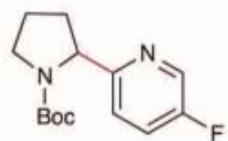


(±)-12 74% yield

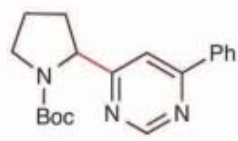


(±)-13 77% yield

### chloroarenes X = Cl

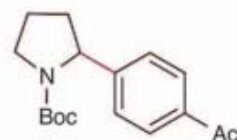


(±)-23 64% yield

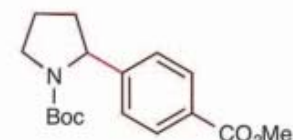


(±)-24 65% yield

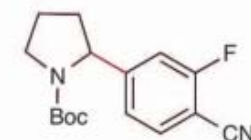
### bromoarenes X = Br



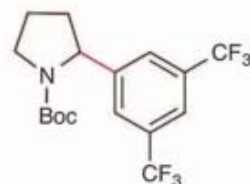
(±)-14 86% yield



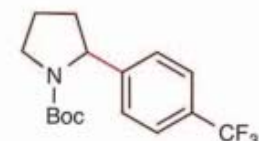
(±)-15 90% yield



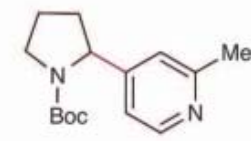
(±)-16 75% yield



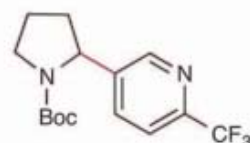
(±)-17 87% yield



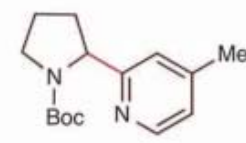
(±)-18 88% yield



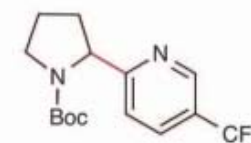
(±)-19 85% yield



(±)-20 82% yield



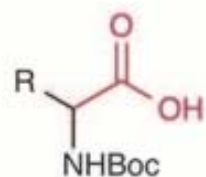
(±)-21 67% yield



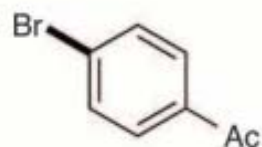
(±)-22 60% yield

# Scope of substrates

A



amino acid



1-acetyl-4-bromobenzene

1 mol% photocatalyst 1

10 mol% NiCl<sub>2</sub>·glyme

15 mol% dtbbpy, Cs<sub>2</sub>CO<sub>3</sub>

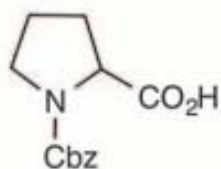
DMF, 23 °C

blue LEDs

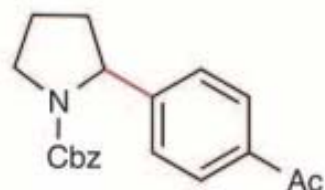


amino acid

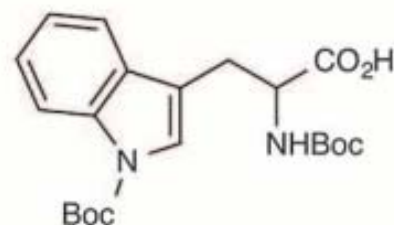
product



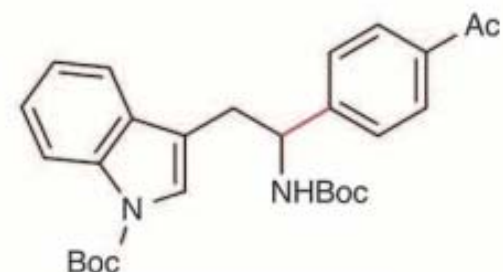
Cbz-Pro-OH



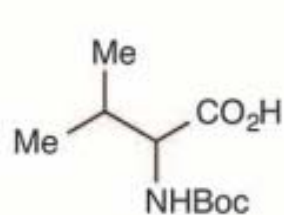
(±)-**25** 93% yield



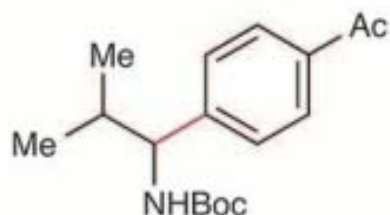
Boc-Trp(Boc)-OH



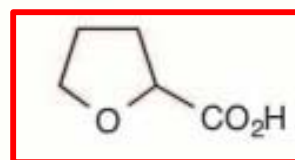
(±)-**29** 83% yield



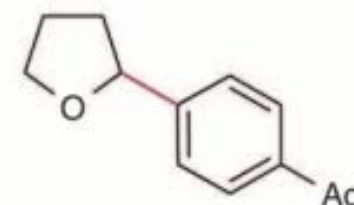
Boc-Val-OH



(±)-**28** 72% yield

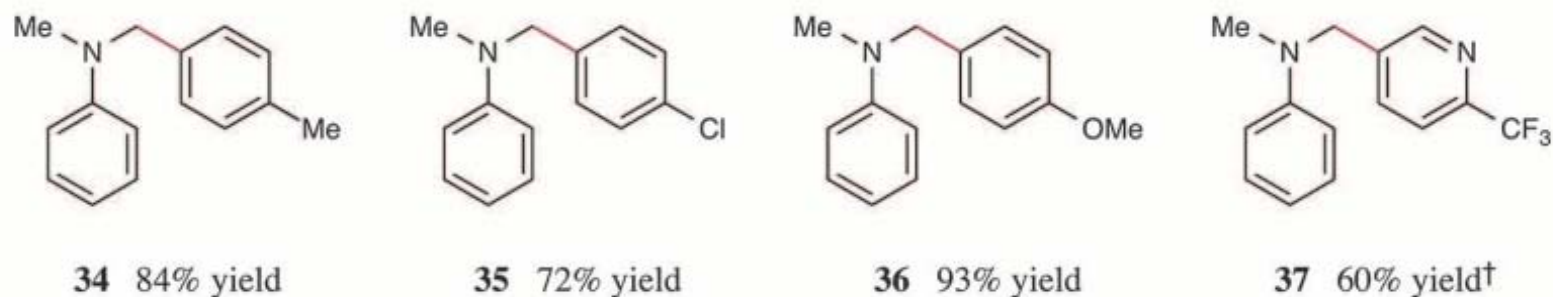
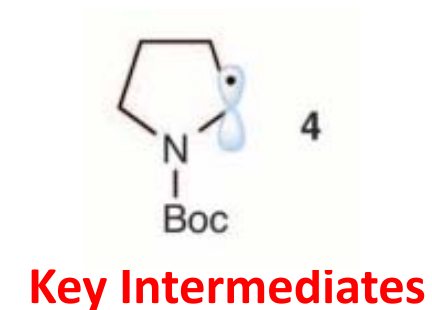
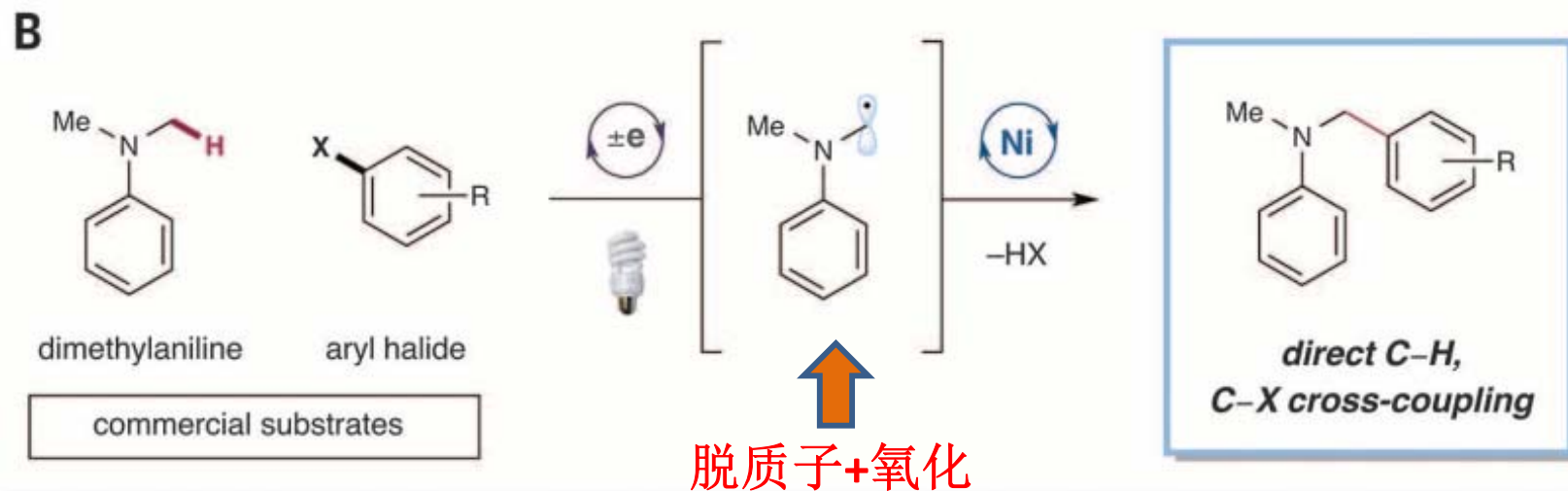


Tetrahydro-2-furoic acid



(±)-**33** 82% yield

# The direct Csp<sup>3</sup>-H, C-X cross-coupling



(B) are as follows: photocatalyst **1** [1 mole % (mol %)]; NiCl<sub>2</sub>·glyme (10 mol %), dtbbpy (15 mol %), **KOH** (3 equiv.), DMF, 23°C, 26-W light. \*Iodoarenes used as aryl halide, X = I. †Bromoarene used, X = Br.



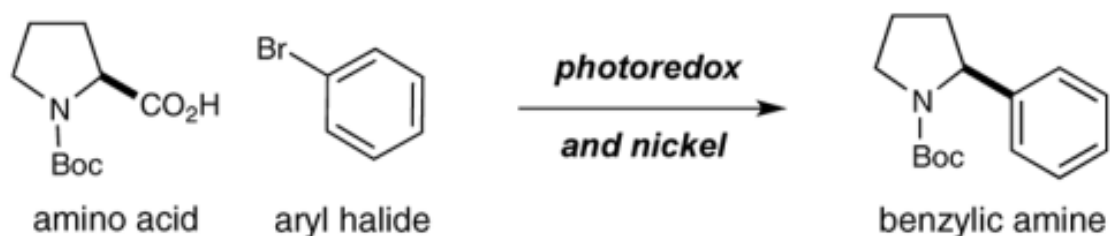
J. Am. Chem. Soc. 2015, 137, 624–627

# Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides

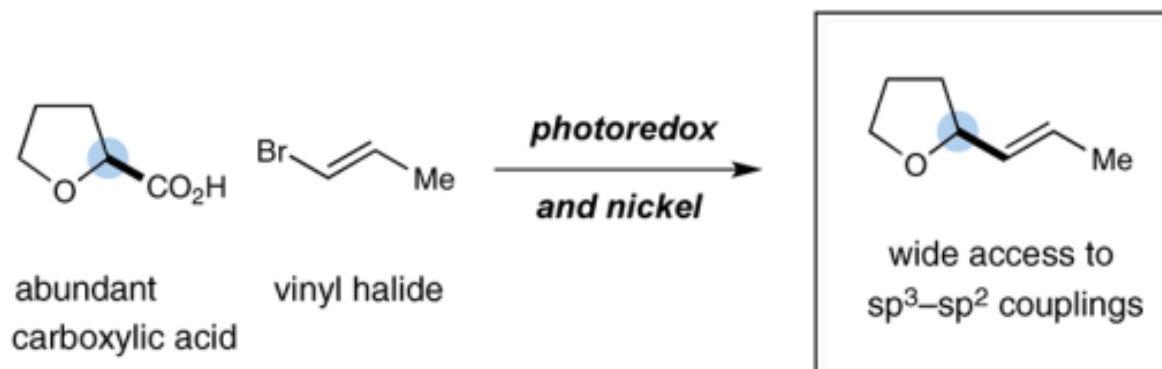
Adam Noble, Stefan J. McCarver, and David W. C. MacMillan\*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

## Decarboxylative Arylation with Nickel and Photoredox Catalysis (Eq 1)

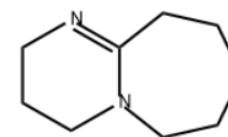
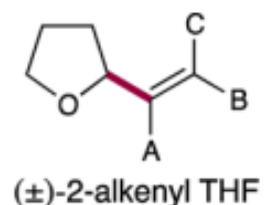
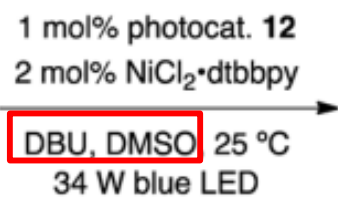
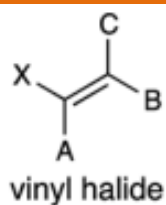
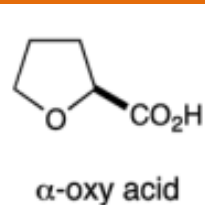


## Expanding this New $sp^3$ - $sp^2$ Coupling: Decarboxylative Olefination (Eq 2)



烯基化

# Scope of substrates



**DBU**  
**1,8-二氮杂二环**

entry	product, % yield	entry	product, % yield
1	(±)-13 90%	2	(±)-14 78%
3 <sup>b</sup>	(±)-15 74%	4	(±)-16 77%
5	(±)-17 68%	6 <sup>b</sup>	(±)-18 67%
7 <sup>b</sup>	(±)-19 84%	8 <sup>c</sup>	(±)-20 71%
9 <sup>c</sup>	(±)-21 73%	10 <sup>c</sup>	(±)-22 60%

$\alpha$ -oxy acids	product, % yield
	(±)-23 92%
	27 77%
$\alpha$ -amino acids	
	(±)-29 90%
alkyl carboxylic acids	
	34 78% <sup>b</sup>

*J. Am. Chem. Soc.* 2016, 138, 6, 1832–1835

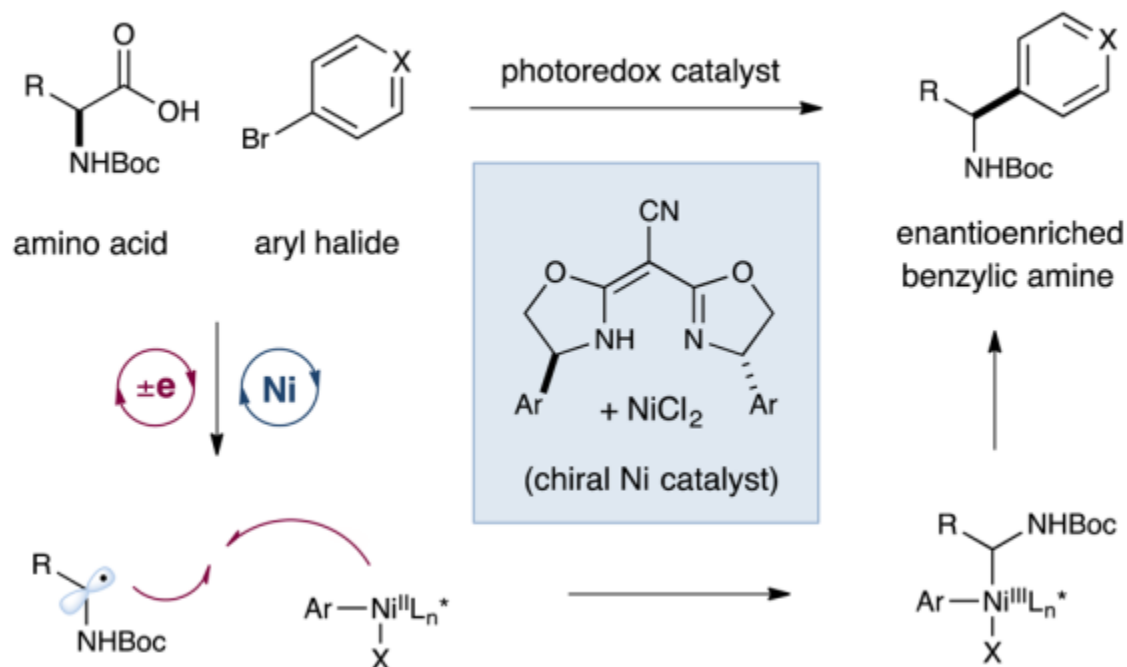
# Enantioselective Decarboxylative Arylation of $\alpha$ -Amino Acids via the Merger of Photoredox and Nickel Catalysis

Zhiwei Zuo,<sup>†,§</sup> Huan Cong,<sup>‡,§</sup> Wei Li,<sup>†</sup> Junwon Choi,<sup>‡</sup> Gregory C. Fu,<sup>\*,‡</sup> and David W. C. MacMillan<sup>\*,†</sup>

<sup>†</sup>Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States

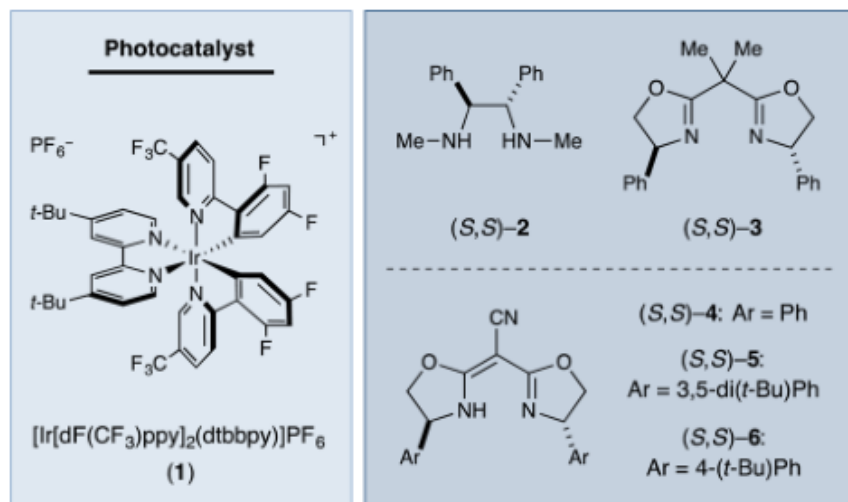
<sup>‡</sup>Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

## C Asymmetric Decarboxylative C<sub>sp3</sub>-C<sub>sp2</sub> Cross-Coupling (this work)

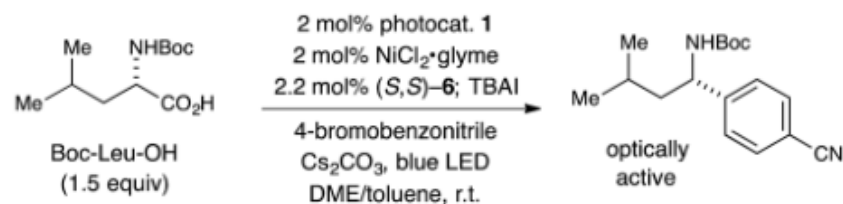
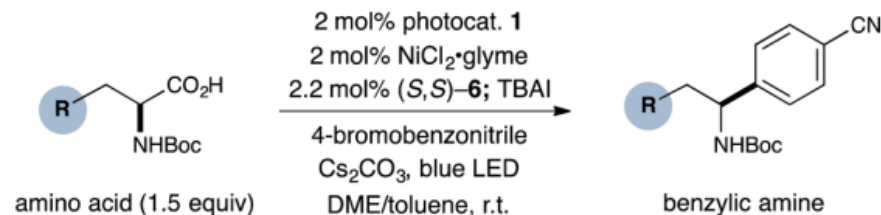


- 自由基产生
- 脱质子化
- 脱CO<sub>2</sub>, 氧化

# Reaction condition optimization and scope of substrates



**Table 2. Scope of the  $\alpha$ -Amino Acid<sup>a</sup>**



entry	variation from standard conditions	ee (%)	yield (%) <sup>b</sup>
1	(S,S)-2 instead of (S,S)-6	—	<2
2	(S,S)-3 instead of (S,S)-6	9	28
3	(S,S)-4 instead of (S,S)-6	77	34
4	(S,S)-5 instead of (S,S)-6	86	59
5	none	92	69
6	no NiCl <sub>2</sub> ·glyme	—	<2
7	no (S,S)-6	—	<2
8	no photocat. <b>1</b>	—	0
9	no light	—	0
10	(R,R)-6 instead of (S,S)-6	-91	72

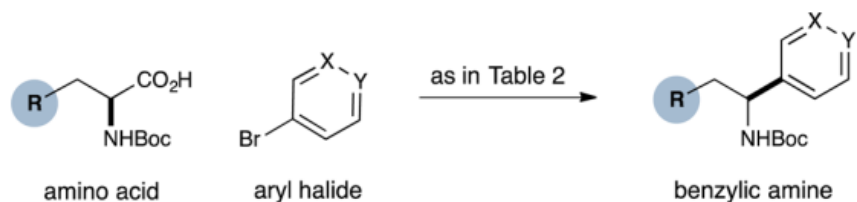
## 配体筛选

entry	product	entry	product
<b>1</b>		<b>2</b>	
<b>3</b>		<b>4</b>	
<b>9</b>		<b>10</b>	
<b>11</b>		<b>12</b>	

<sup>a</sup>All data are the average of two experiments. <sup>b</sup>Yields determined by <sup>1</sup>H NMR spectroscopy using 1,3-bis(trifluoromethyl)-5-bromobenzene as an internal standard.

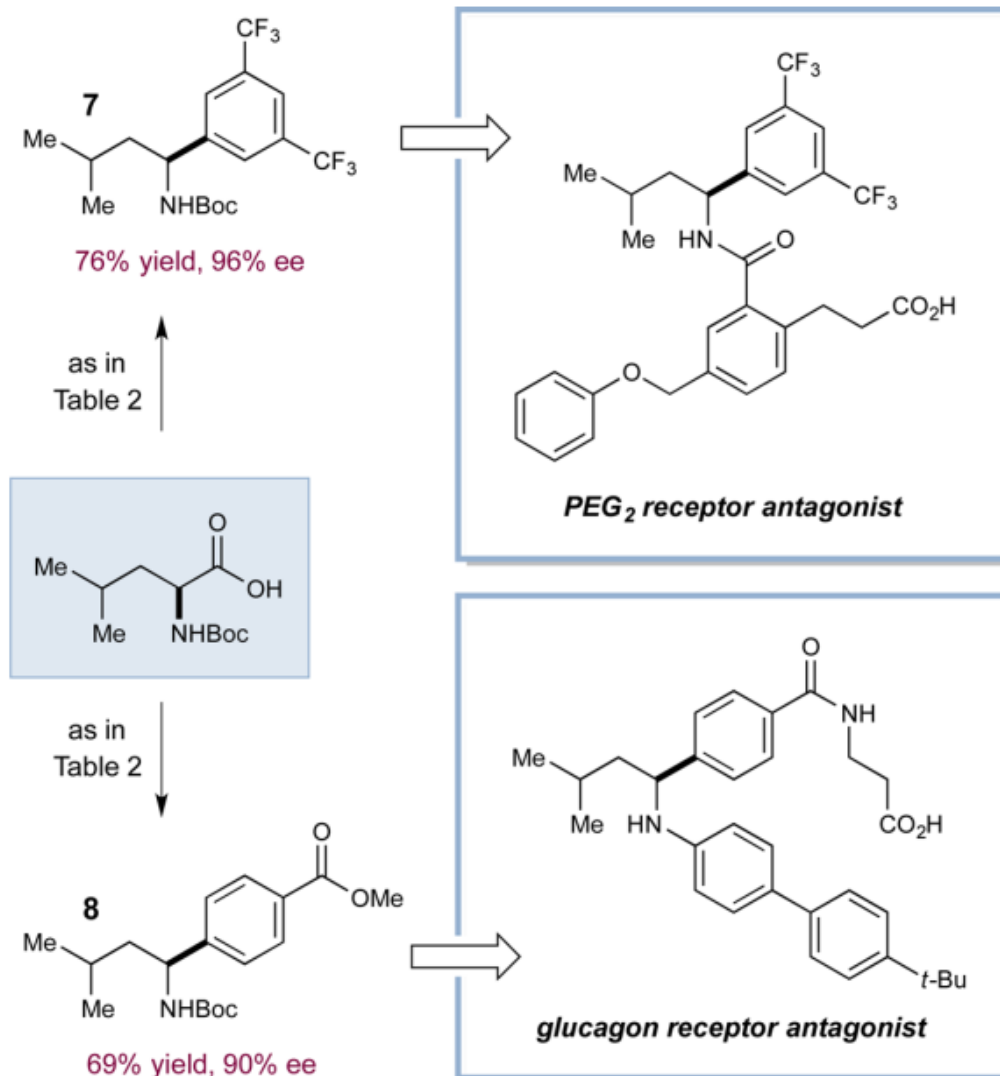
# Scope of substrates and synthesis of drugs

Table 3. Scope of the Aryl Halide<sup>a</sup>



entry	product	entry	product
1		2	
3		4	
9		10	
11		12	

Scheme 2. Catalytic Asymmetric Coupling To Produce Pharmacophores



VIP Dual Catalysis Very Important Paper

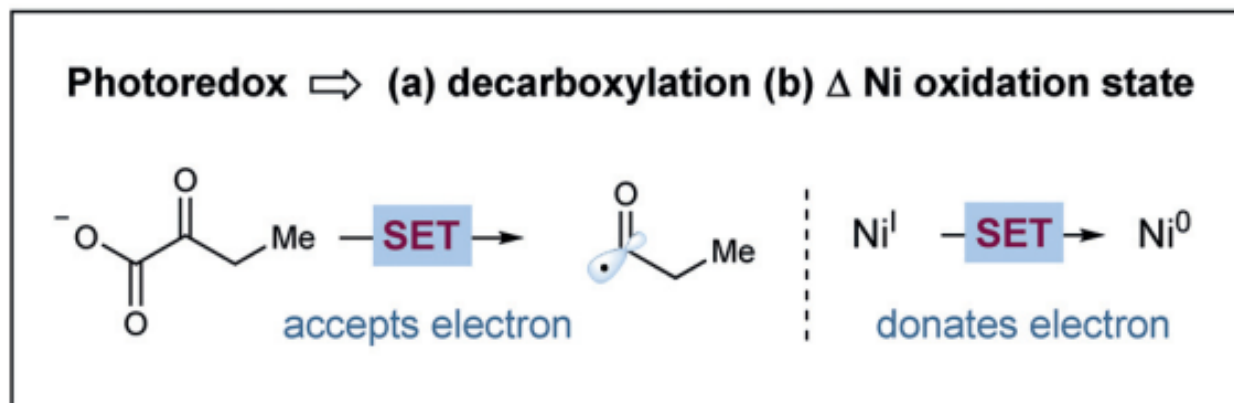
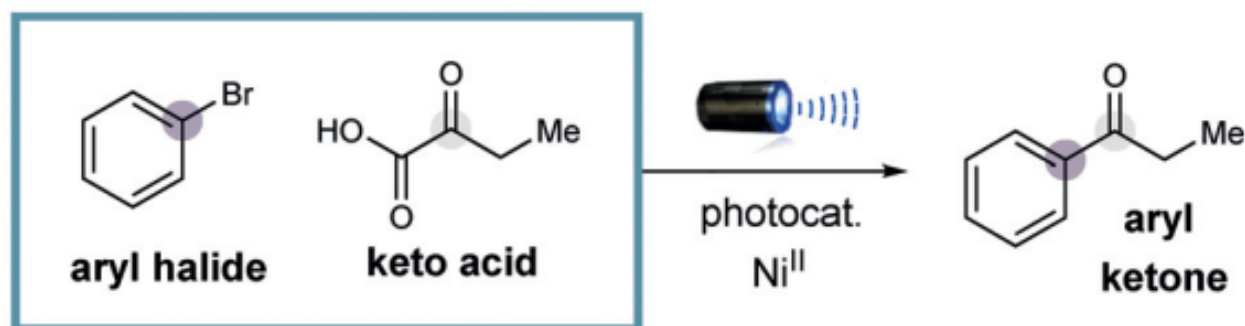
International Edition: DOI: 10.1002/anie.201501908

German Edition: DOI: 10.1002/ange.201501908

## Merging Photoredox and Nickel Catalysis: The Direct Synthesis of Ketones by the Decarboxylative Arylation of $\alpha$ -Oxo Acids\*\*

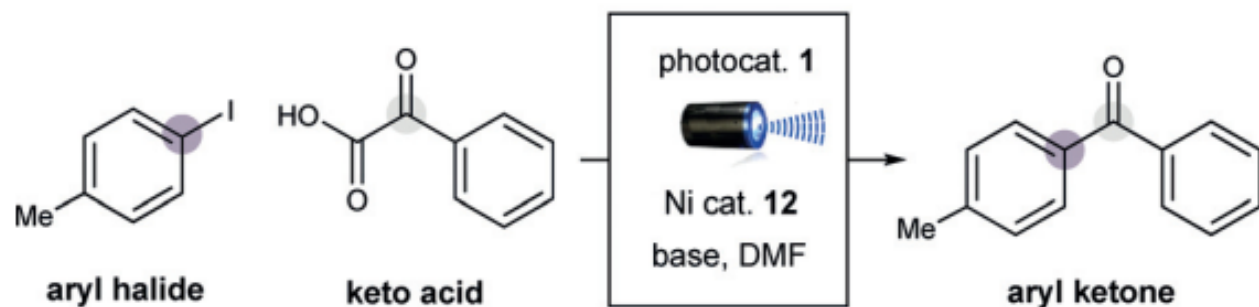
Lingling Chu, Jeffrey M. Lipshultz, and David W. C. MacMillan\*

### b) Metallaphotoredox decarboxylative keto acid arylation



脱质子+氧化  $\Rightarrow$  酰基自由基

# Reaction condition optimization



“presumably owing to protonolysis of the putative Ni<sup>II</sup> aryl complex at high H<sub>2</sub>O concentration”

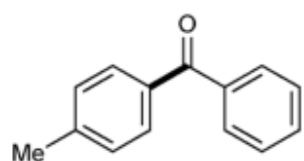
“可能是由于假定的Ni<sup>II</sup>芳基配合物在高H<sub>2</sub>O浓度下发生质子分解”

Entry	Base	Light source	H <sub>2</sub> O [equiv]	Yield [%]
1	Cs <sub>2</sub> CO <sub>3</sub>	blue LED strips	0	13
2	Li <sub>2</sub> CO <sub>3</sub>	blue LED strips	0	38
3	Li <sub>2</sub> CO <sub>3</sub>	34 W blue LED	0	60
4 <sup>[b]</sup>	Li <sub>2</sub> CO <sub>3</sub>	34 W blue LED	0	74
5 <sup>[b]</sup>	Li <sub>2</sub> CO <sub>3</sub>	34 W blue LED	2	84
6 <sup>[b]</sup>	Li <sub>2</sub> CO <sub>3</sub>	34 W blue LED	8	54
7 <sup>[b,c]</sup>	Li <sub>2</sub> CO <sub>3</sub>	34 W blue LED	2	88

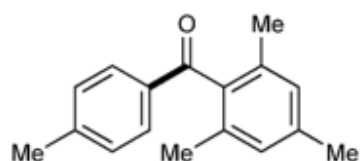
?

[a] Yield determined by <sup>1</sup>H NMR spectroscopy using 1,3-bis(trifluoromethyl)-5-bromobenzene as an internal standard. [b] Reaction time: 72 h. [c] 2 mol% of the photocatalyst.

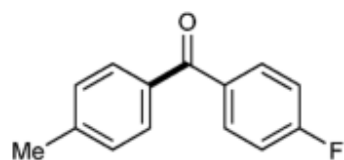
# Scope of substrates



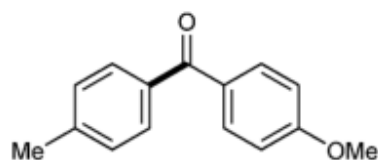
**13** 88% yield



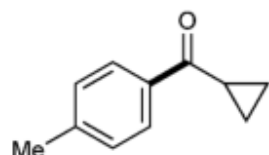
**14** 92% yield



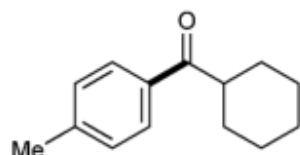
**15** 60% yield



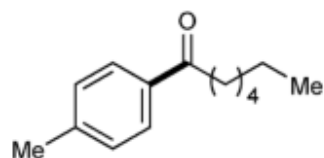
**16** 65% yield



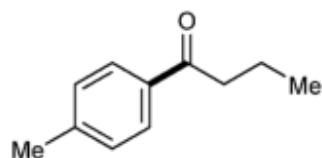
**17** 88% yield



**18** 80% yield

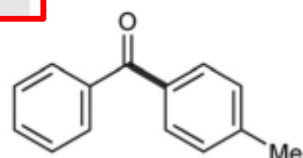


**19** 90% yield

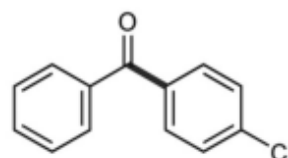


**20** 91% yield

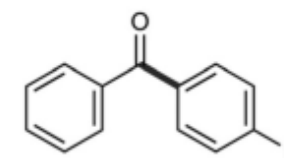
X = I



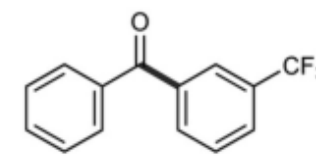
**13** 88% yield



**25** 90% yield

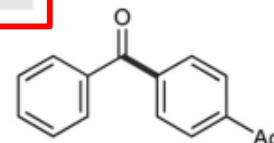


**24** 70% yield<sup>[b]</sup>

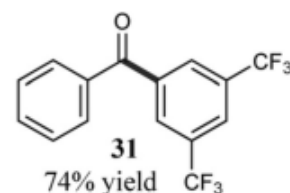


**26** 88% yield

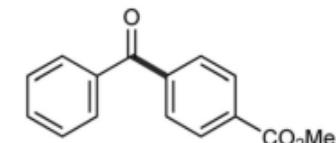
X = Br



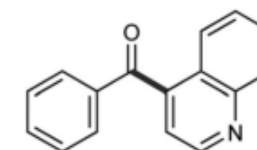
**29** 73% yield



**31** 74% yield



**30** 81% yield

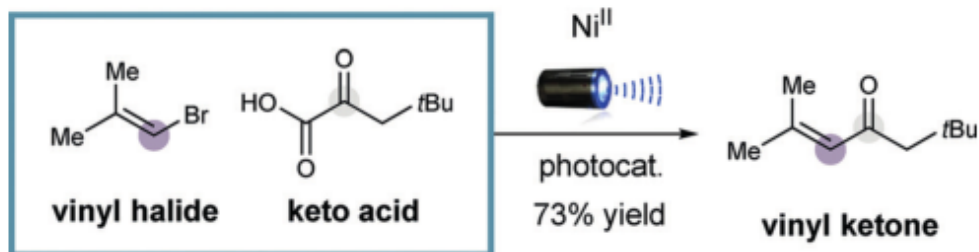


**32** 80% yield



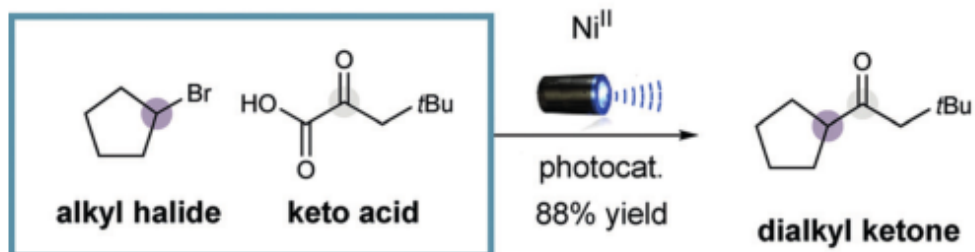
# Metallaphotoredox decarboxylation and its application.

## a) Carbonyl C(sp<sup>2</sup>)-Olefin Coupling to Generate Vinyl Ketones



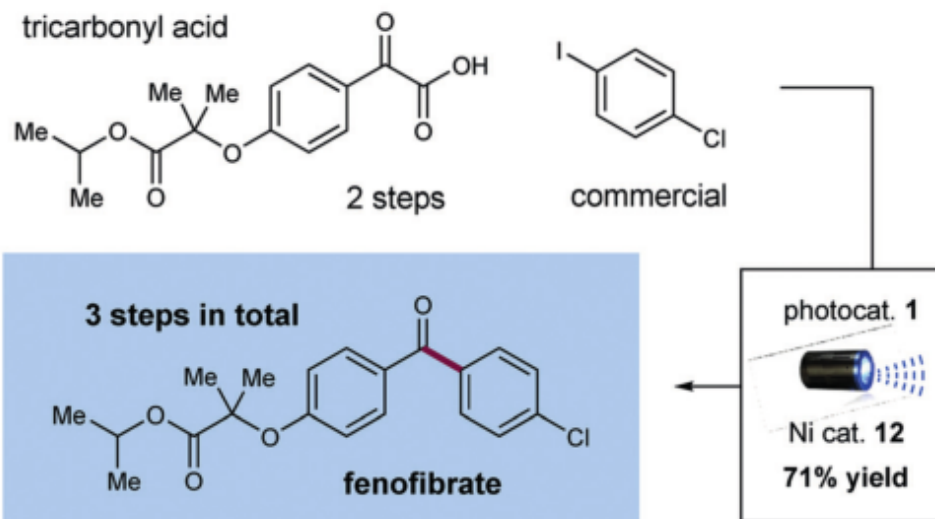
烯基溴

## b) Carbonyl C(sp<sup>3</sup>)-Alkyl Halide Coupling $\Rightarrow$ Dialkyl Ketones



烷基溴

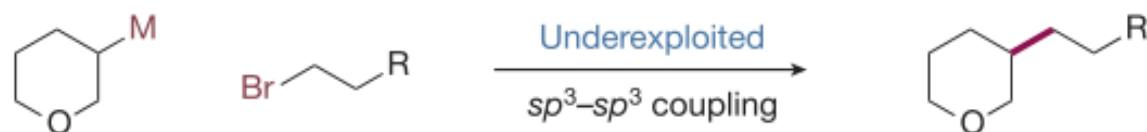
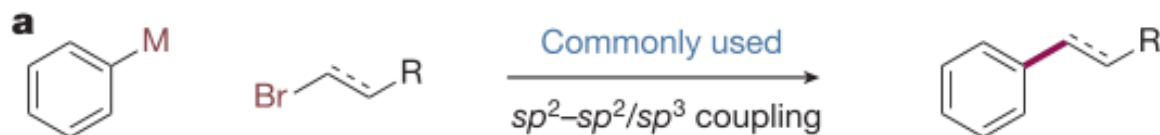
## c) Metallaphotoredox Decarboxylative Coupling $\Rightarrow$ Fenofibrate



非诺贝特：治疗高血脂

# Metallaphotoredox-catalysed $sp^3-sp^3$ cross-coupling of carboxylic acids with alkyl halides

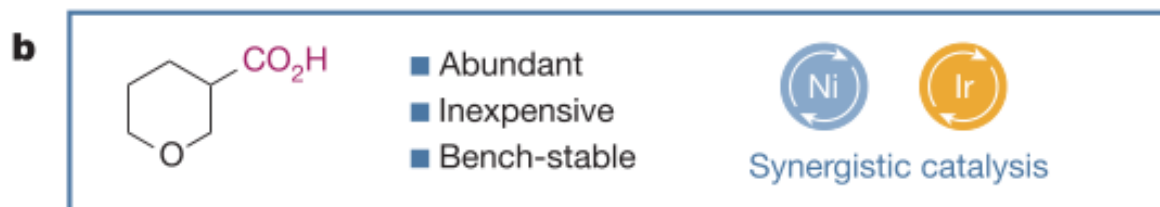
Craig P. Johnston<sup>1\*</sup>, Russell T. Smith<sup>1\*</sup>, Simon Allmendinger<sup>1</sup> & David W. C. MacMillan<sup>1</sup>



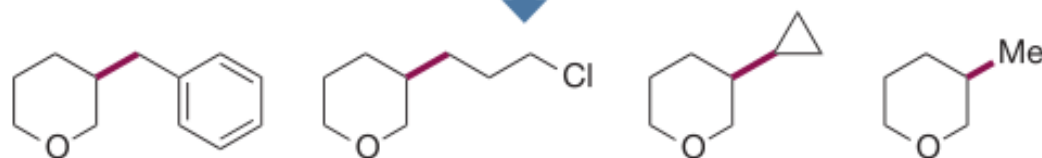
构建 $sp^3-sp^3$ 键的困境:

➤  $\beta$ -H消除

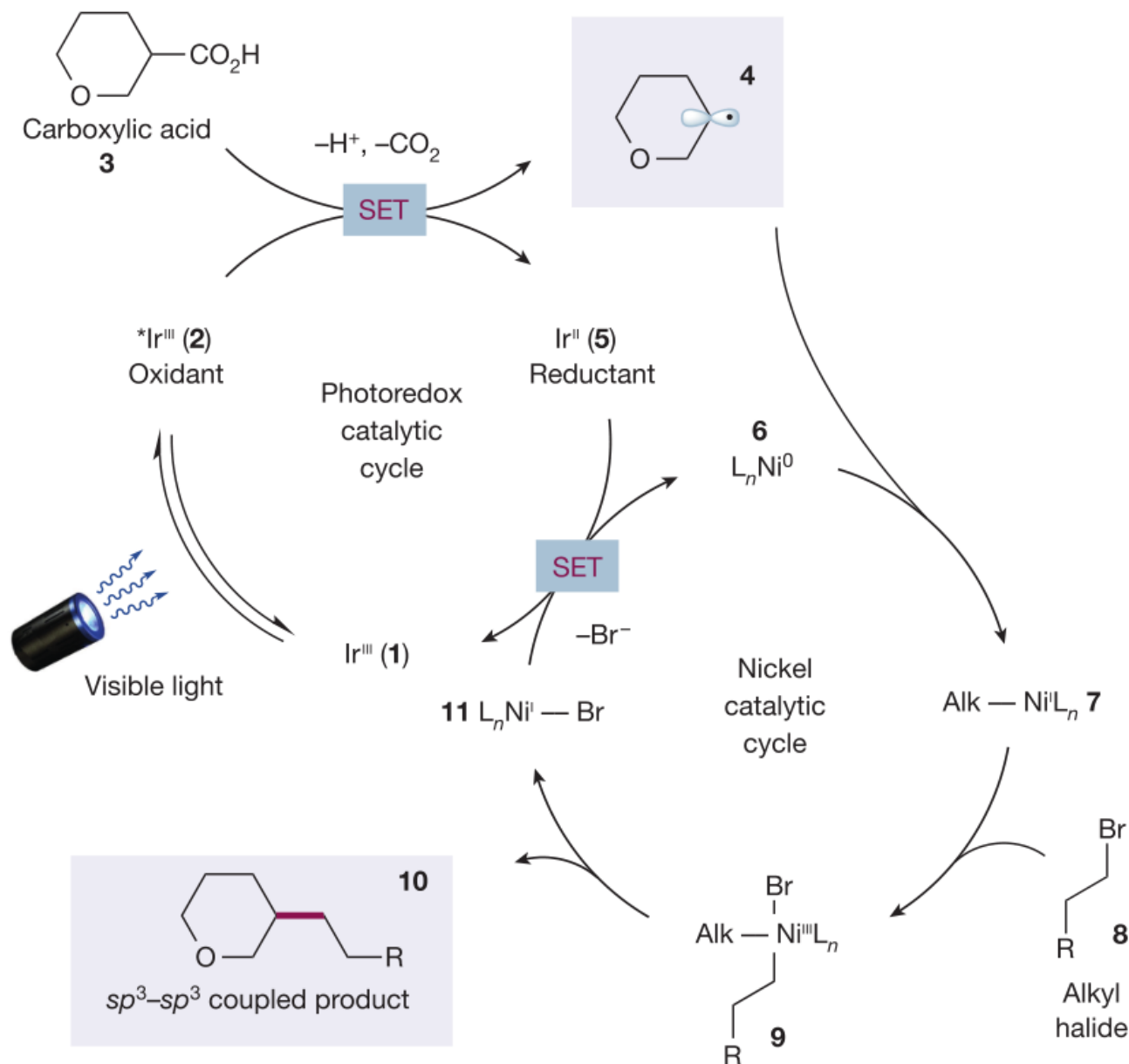
➤ OA困难



Ni vs Pd



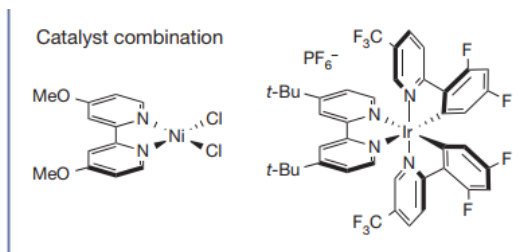
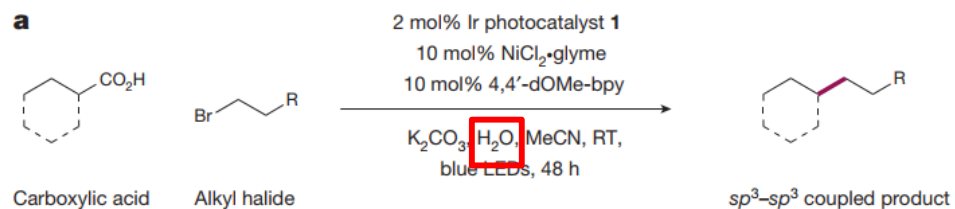
# Proposed mechanism



“At present, we cannot rule out the possibility of an alternative mechanism that involves Ni<sup>0</sup>-mediated oxidative addition and trapping of the alkyl radical **4** by a Ni<sup>II</sup> species”

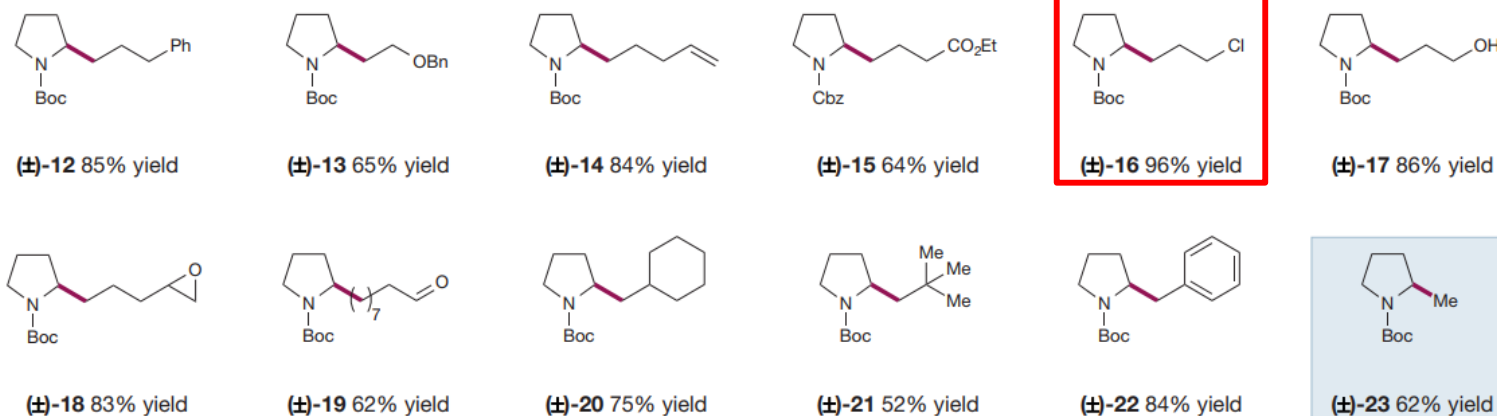
不排除先氧化加成的可能

# Scope of substrates



**20 eq H<sub>2</sub>O: 减少酯的形成?**

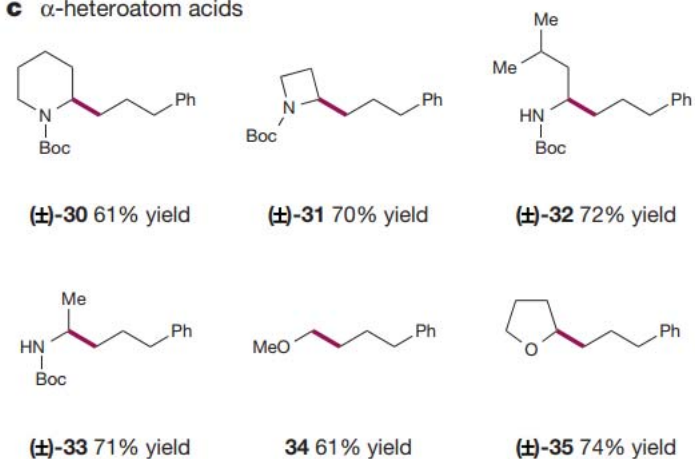
**b** Alkyl halides



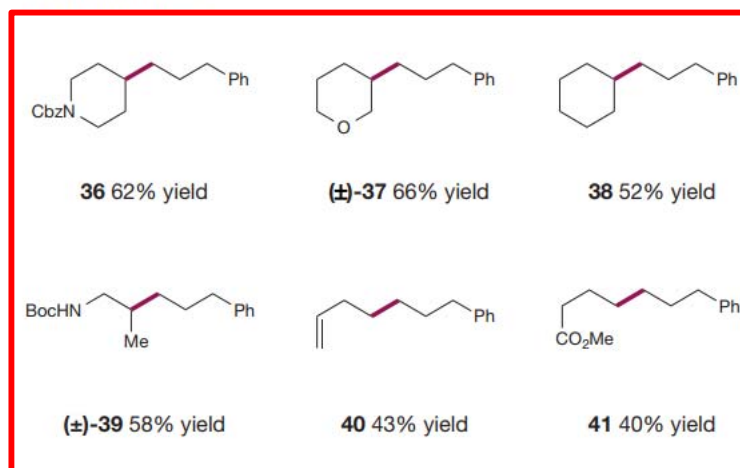
选择性高

**α-杂原子虽有益，但不是必须的**

**c** α-heteroatom acids



**d** α-alkyl acids




# Alcohols as Latent Coupling Fragments for Metallaphotoredox Catalysis: $sp^3-sp^2$ Cross-Coupling of Oxalates with Aryl Halides

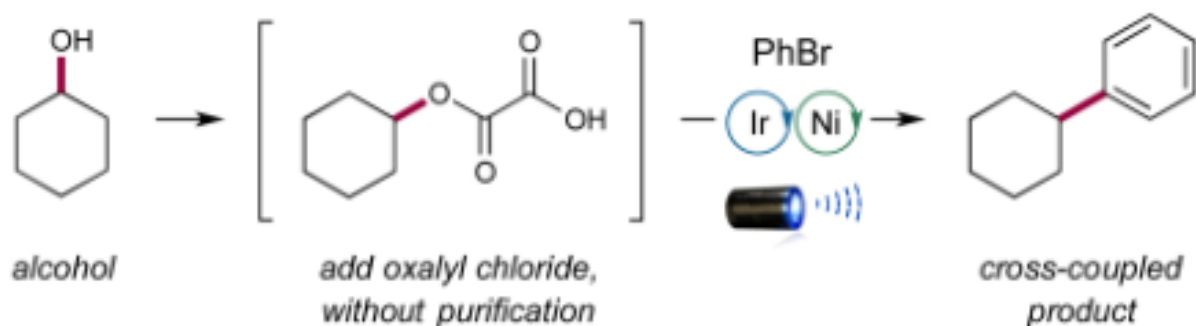
Xiaheng Zhang and David W. C. MacMillan\*

J. Am. Chem. Soc. 2016, 138, 13862-13865

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

 Supporting Information

## Metallaphotoredox-mediated alcohol cross-coupling via oxalates

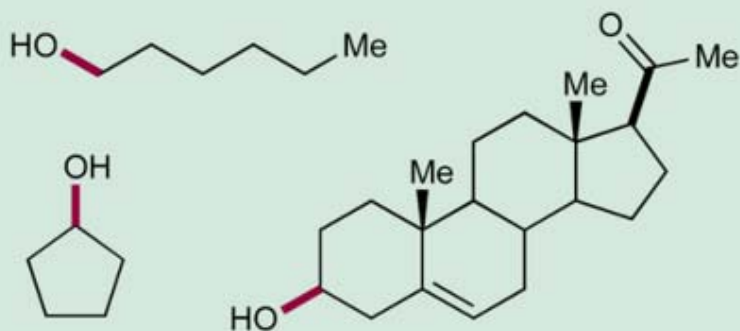


- Light-mediated C–O Bond Cleavage
- No Purification Needed for Oxalate
- Broad Scope in Alcohol
- Naturally Occurring Functionality

草酸为预制备，而非原位生成

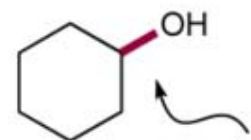
# Background

## Alcohols as a class of native nucleophiles



■ simple   ■ abundant   ■ commercial

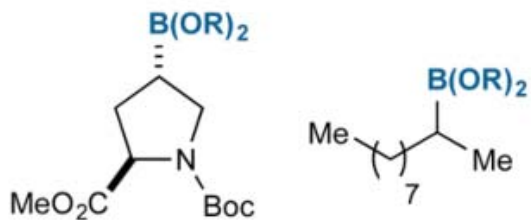
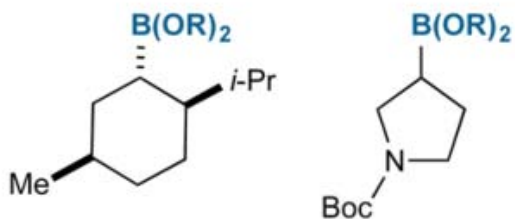
## Challenge: C–O bond activation



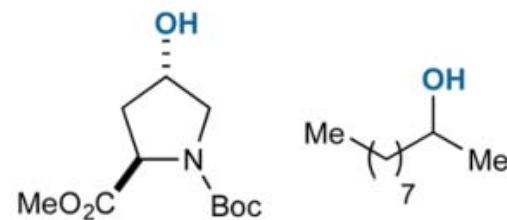
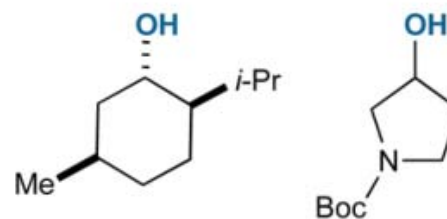
96 kcal/mol

high energetic barrier  
to cleavage

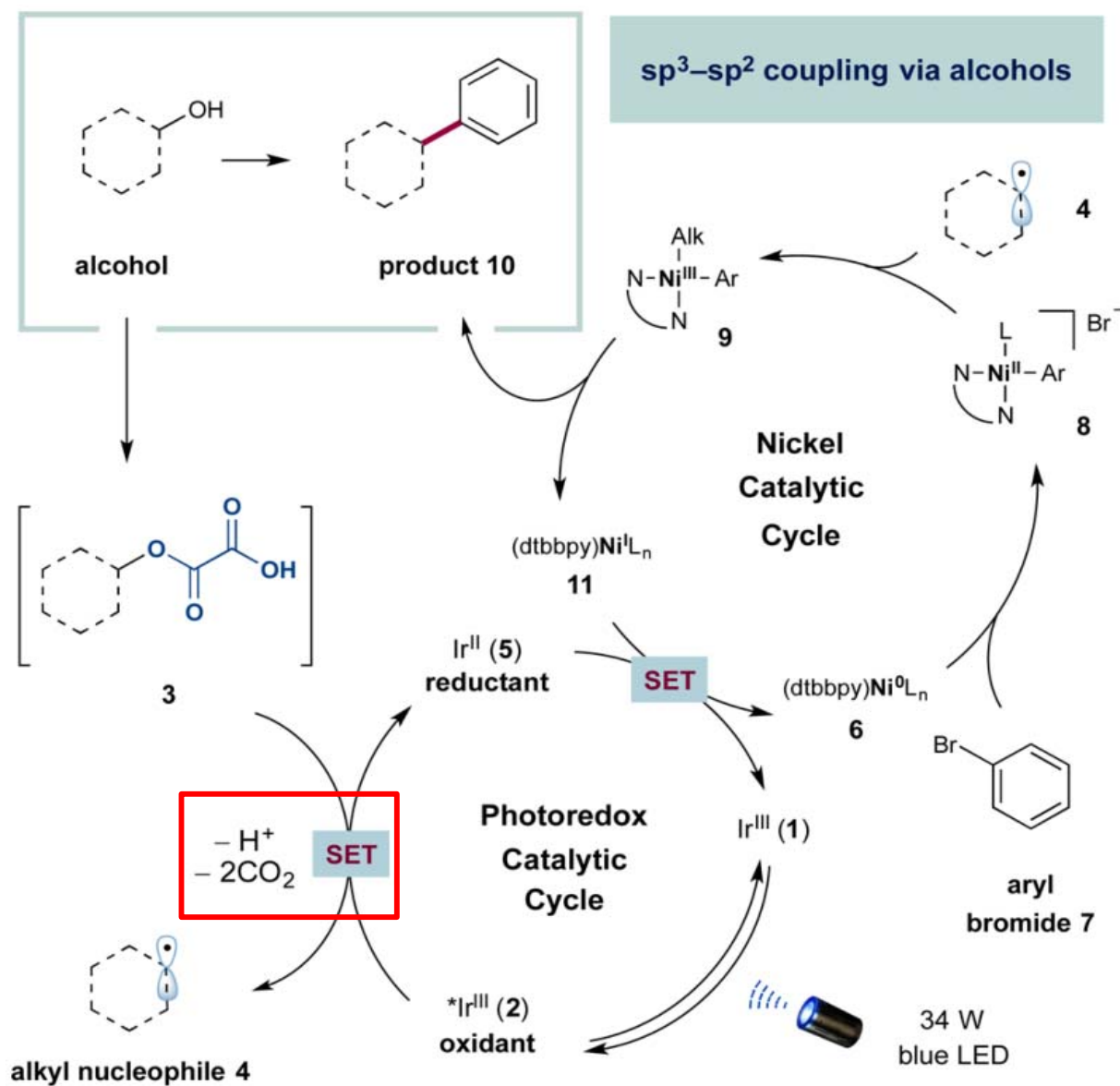
### Not yet commercial



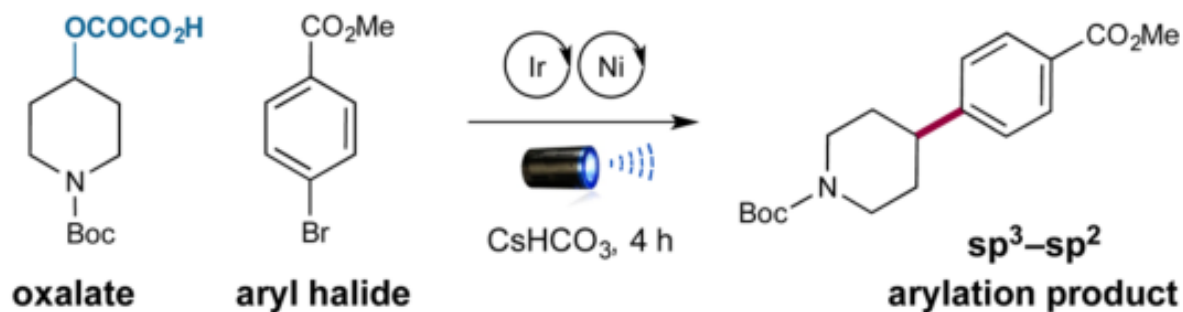
### Commercially available



# Proposed mechanism

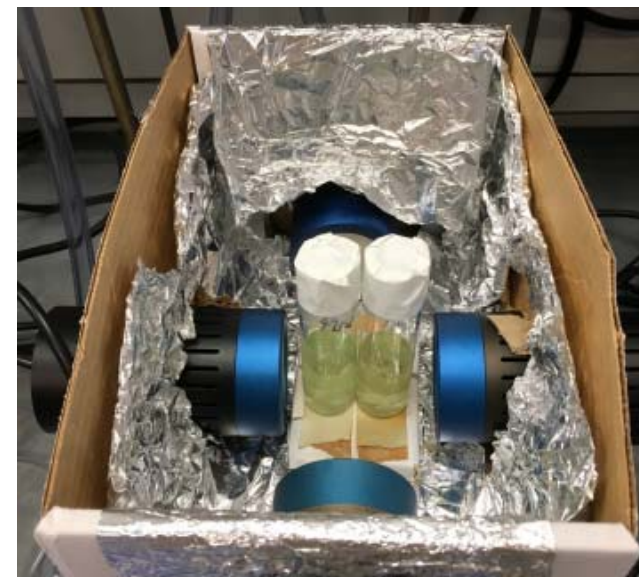


# Reaction Condition Optimization



- 升温对双脱羧步骤至关重要，否则生成大量酯；
- 光照、PC、Ni、碱均是必须的；
- 此温度在光反应中少见。

entry	conditions	solvent	temp. (°C)	yield (%) <sup>b</sup>
1	as shown	DMSO	25	0
2	as shown	THP	25	8
3	as shown	THP/DMSO 5:1	25	39
4	as shown	THP/DMSO 5:1	50	52
5	as shown	THP/DMSO 5:1	70	65
6	as shown	dioxane/DMSO 5:1	70	62
7	no photocatalyst	THP/DMSO 5:1	70	0
8	no Ni catalyst	THP/DMSO 5:1	70	0
9	no base	THP/DMSO 5:1	70	0
10	no light	THP/DMSO 5:1	70	0



四灯：80 °C；两灯：70 °C；

<sup>a</sup>Performed with photocatalyst **1** (1 mol %), NiBr<sub>2</sub>·dtbbpy **12** (5 mol %), aryl halide (1.0 equiv), oxalate (1.3 equiv) and CsHCO<sub>3</sub> (1.5 equiv). <sup>b</sup>Yields were obtained by <sup>1</sup>H NMR analysis of the crude reaction mixtures using an internal standard.

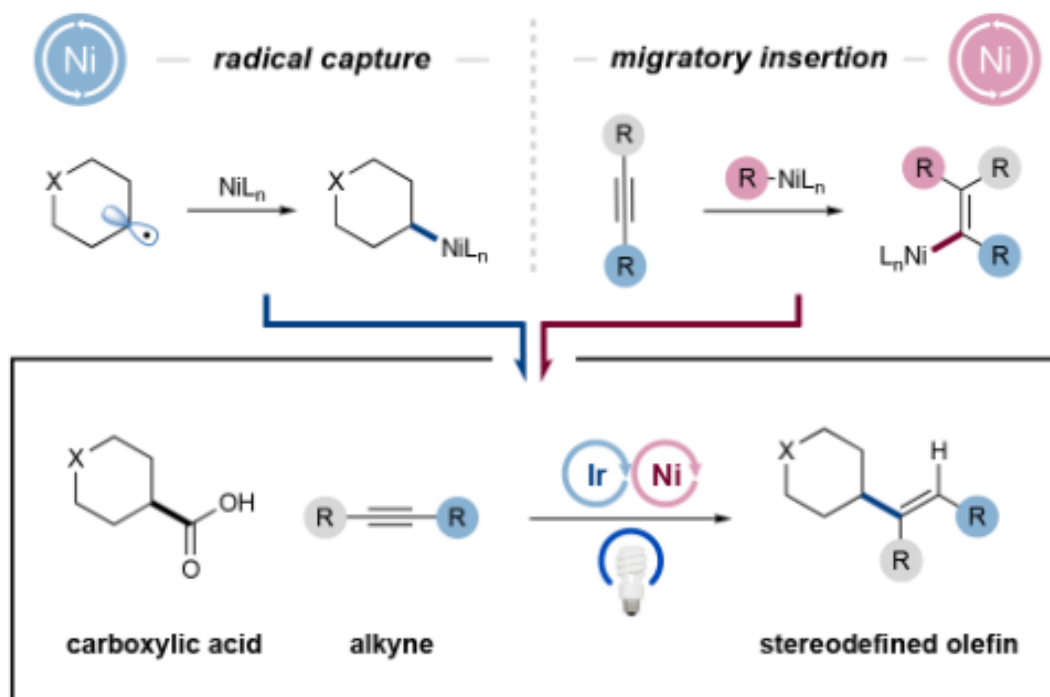


## Decarboxylative Hydroalkylation of Alkynes

Nicholas A. Till, Russell T. Smith, and David W. C. MacMillan\*<sup>id</sup>

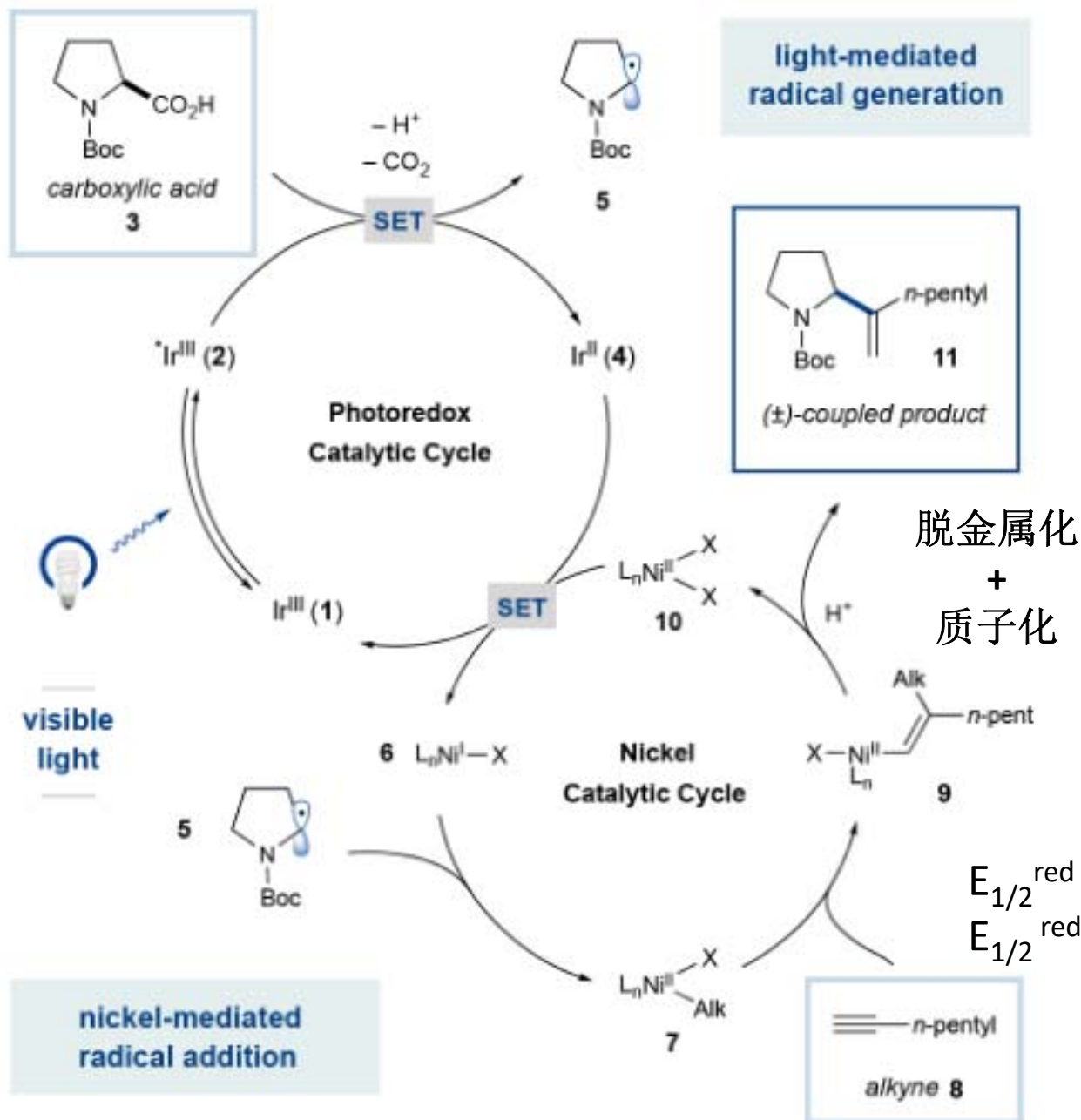
Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

*this work: stereoselective radical addition to unactivated alkynes*



炔基自由基加氢烷基化

# Proposed mechanism

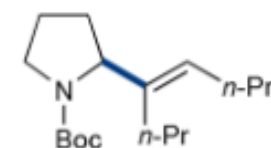


立体选择性:

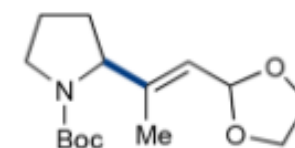
碳-镍键在构型上是稳定，另一侧可能发生自由基快速反转 ( $K_{inv}=10^9 s^{-1}$ ,  $-133^\circ C$ )，但反转不占主要地位。

区域选择性:

镍定位在电子密度较大的 C(sp) 位置。



(±)-21, 60% yield  
>20:1 E:Z



(±)-22, 71% yield  
>20:1 r.r.

$$E_{1/2}^{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37 \text{ V vs SCE in MeCN}$$

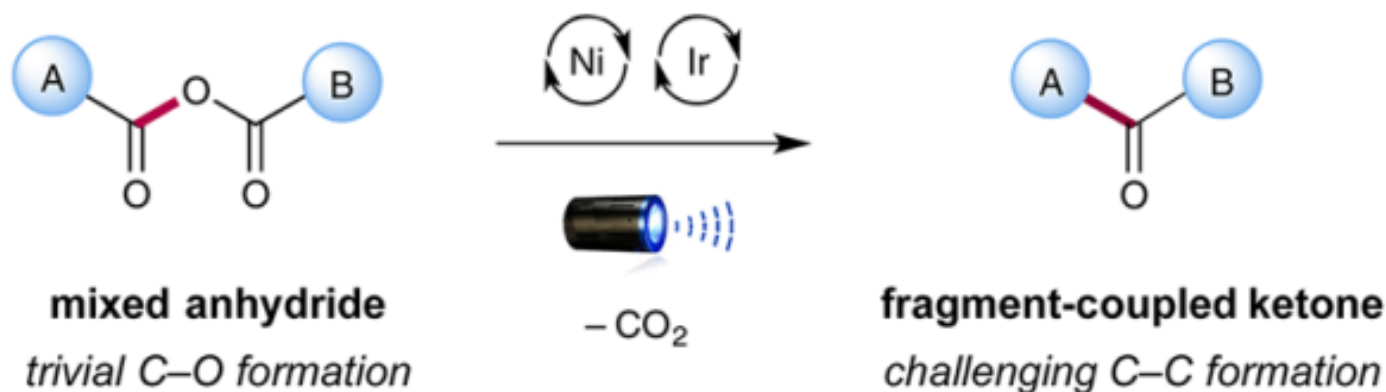
$$E_{1/2}^{\text{red}} [\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2 \text{ V vs SCE in DMF}$$

# Fragment Couplings via CO<sub>2</sub> Extrusion–Recombination: Expansion of a Classic Bond-Forming Strategy via Metallaphotoredox

Chi “Chip” Le and David W. C. MacMillan\*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States

## Metallaphotoredox: Anhydrides to Ketones using CO<sub>2</sub>ExR (Eq 4)

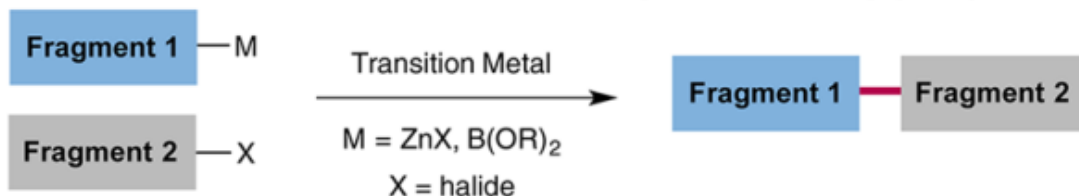


原位生成酸酐

Metal insertion–decarboxylation–recombination

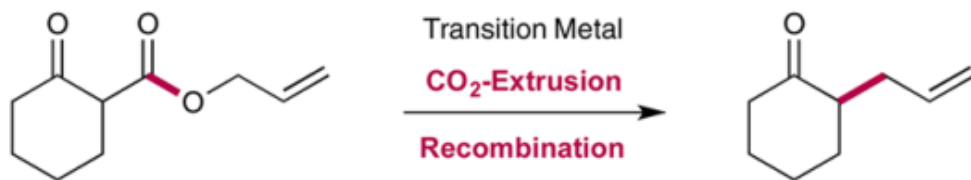
# Background

## Conventional Metal-mediated $sp^2$ - $sp^2$ Fragment Coupling (Eq 1)



1980

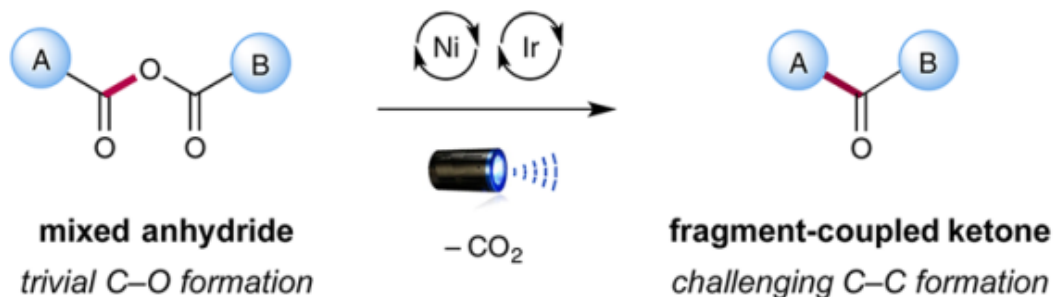
## Tsuji-Saegusa $CO_2$ -Extrusion-Recombination: Enolate Allylation (Eq 2)



## General $CO_2$ -Extrusion-Recombination ( $CO_2$ ExR) Coupling (Eq 3)



## Metallaphotoredox: Anhydrides to Ketones using $CO_2$ ExR (Eq 4)

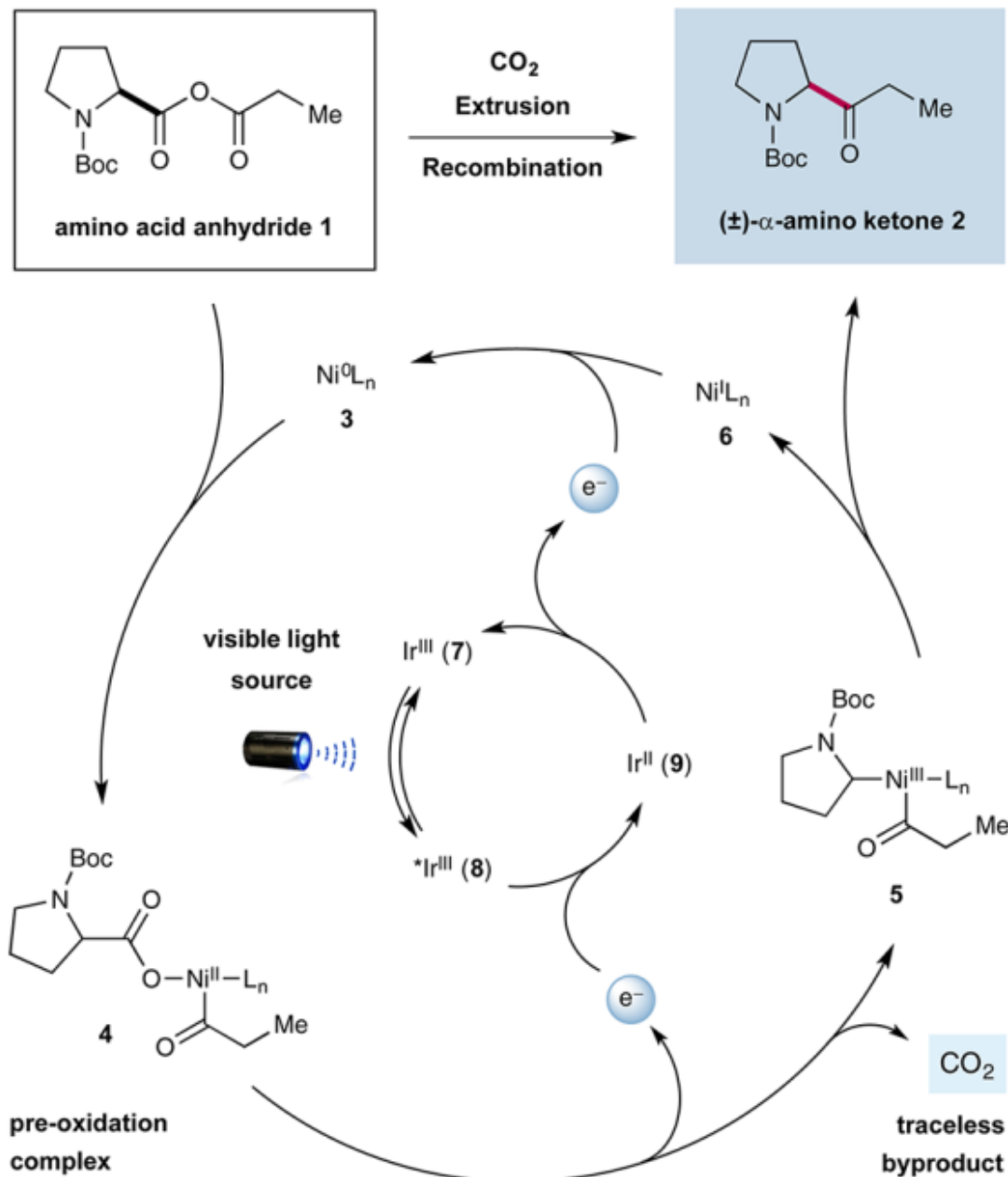


烯醇的烯丙基化

一般策略：原位形成酸酐、酯、氨基甲酸酯

重组酰基化反应

# Proposed mechanism

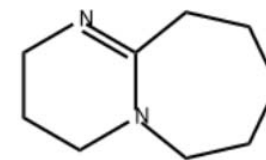
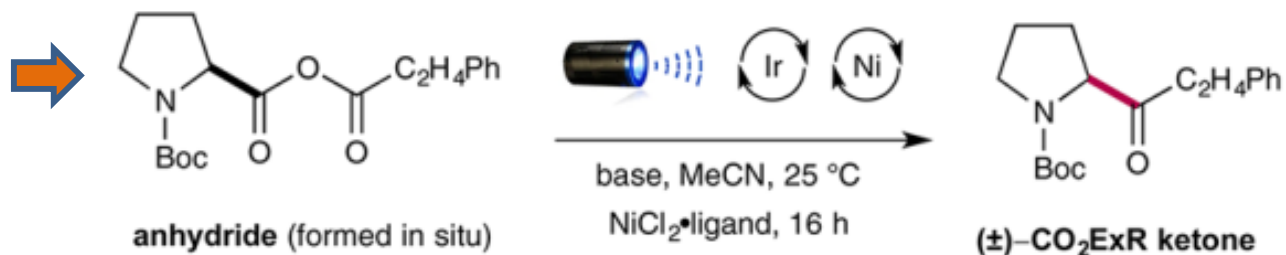


$$E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V vs SCE in MeCN}$$

激发态\*Ir<sup>III</sup>具有强氧化性，可攫取Ni<sup>0</sup>的电子，诱导氧化脱羧以形成相应的烷基酰基Ni<sup>III</sup>络合物

# Proposed Mechanism

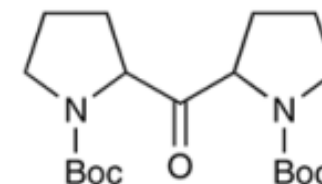
羧酸  
+  
酰氯



DBU  
二氮杂二环

entry	conditions	base	ligand	byproduct 10 <sup>b</sup>	ketone
1	as shown	Cs <sub>2</sub> CO <sub>3</sub>	11	20%	40%
2	as shown	DBU	11	14%	70%
3	as shown	DBU	12	3%	84%
4	no photocatalyst	DBU	12	0%	0%
5	no Ni catalyst	DBU	—	0%	0%
6	no base	—	12	0%	0%
7	no light	DBU	12	0%	0%
8 <sup>c</sup>	as shown	DBU	12	5%	73%

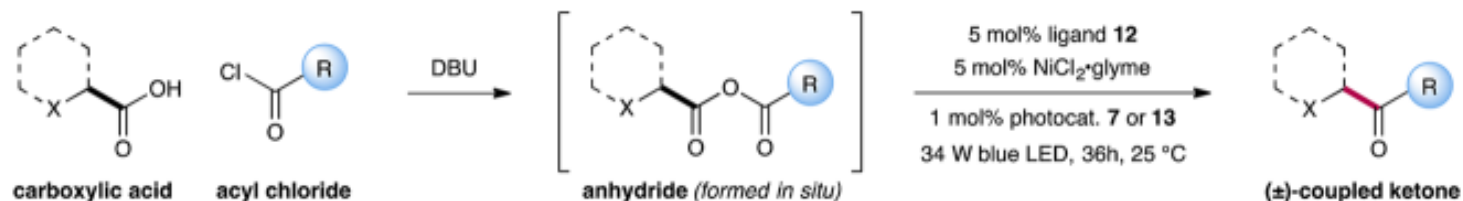
Initial experiment



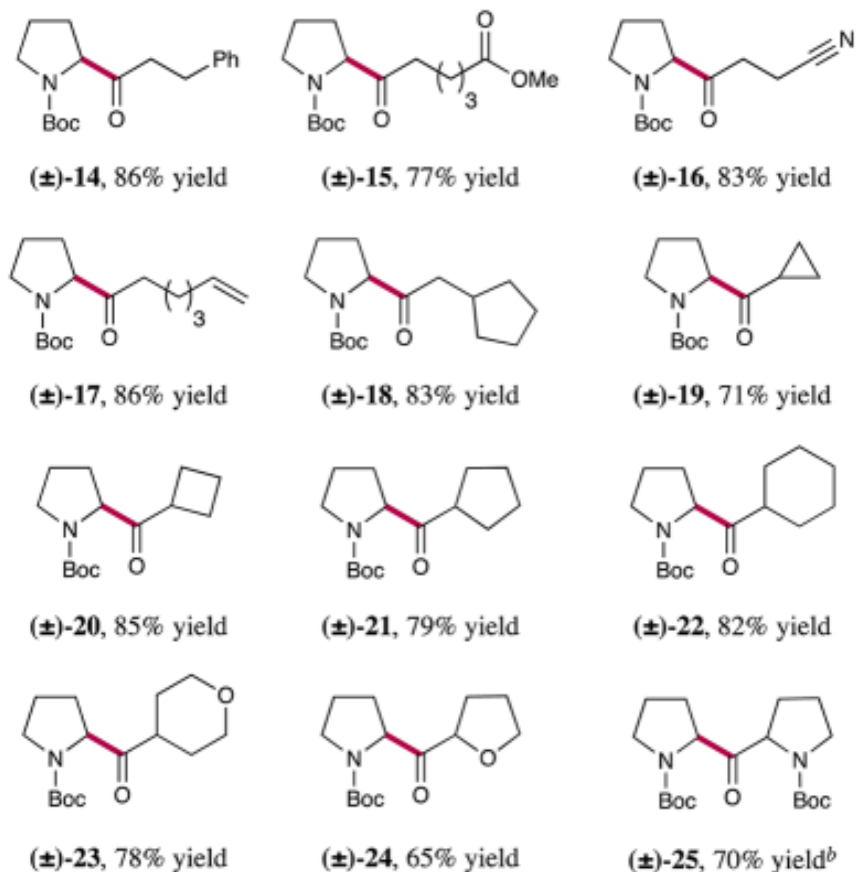
byproduct (10)

如何生成?

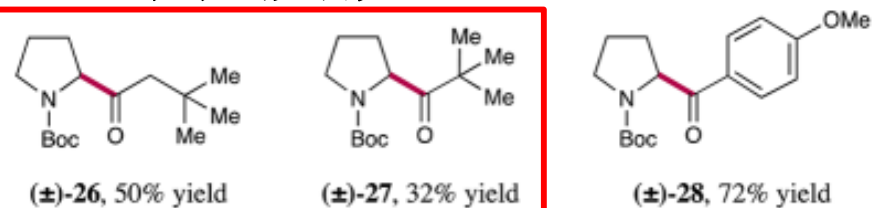
<sup>a</sup>Reactions performed using photocatalyst 7 (1 mol%), NiCl<sub>2</sub>·glyme (5 mol%), bipyridine ligand (5 mol%), hydrocinnamoyl chloride (0.10 mmol), *N*-Boc-*L*-proline (0.13 mmol), and base (0.13 mmol). Yields determined by GC analysis using an internal standard. <sup>b</sup>Major byproduct. <sup>c</sup>Anhydride was synthesized and isolated prior to reaction.



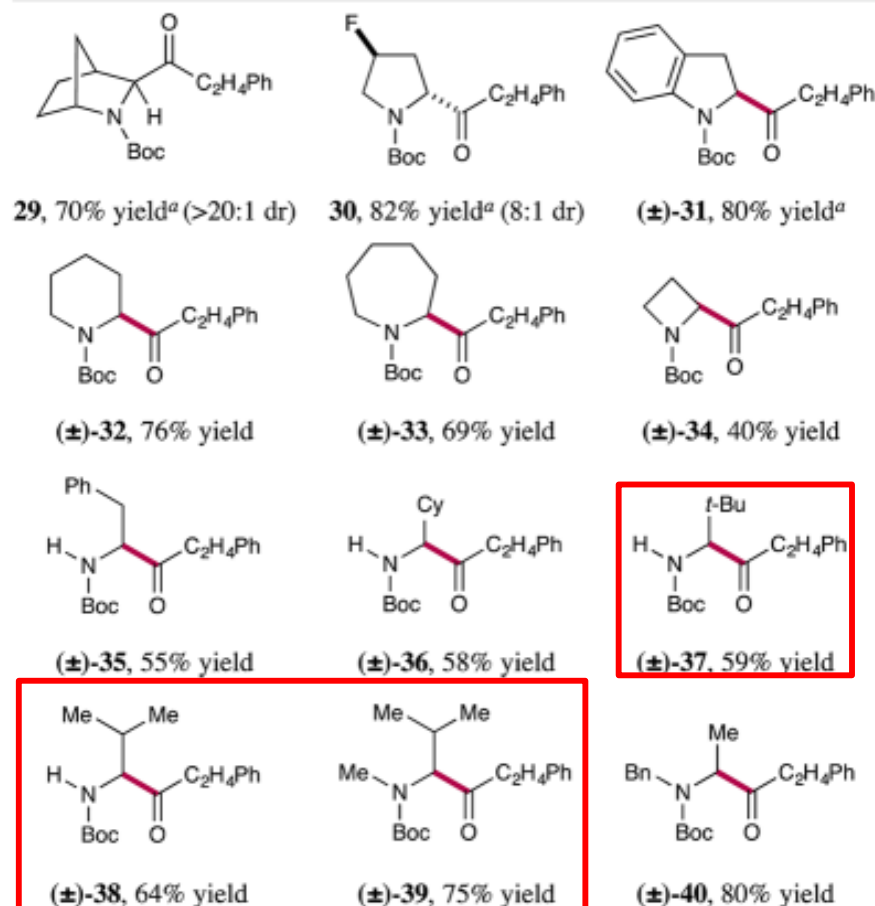
acyl chloride scope with *N*-Boc-L-proline<sup>a</sup>



位阻影响大

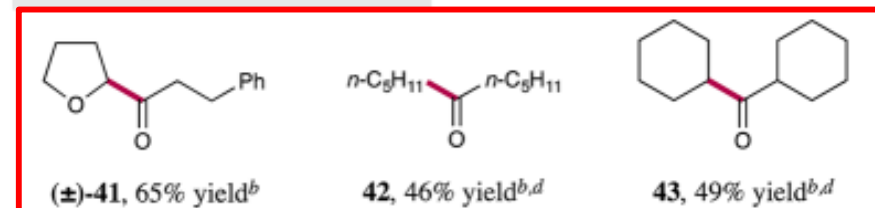


amino acid scope with hydrocinnamoyl chloride<sup>c</sup>



位阻影响小

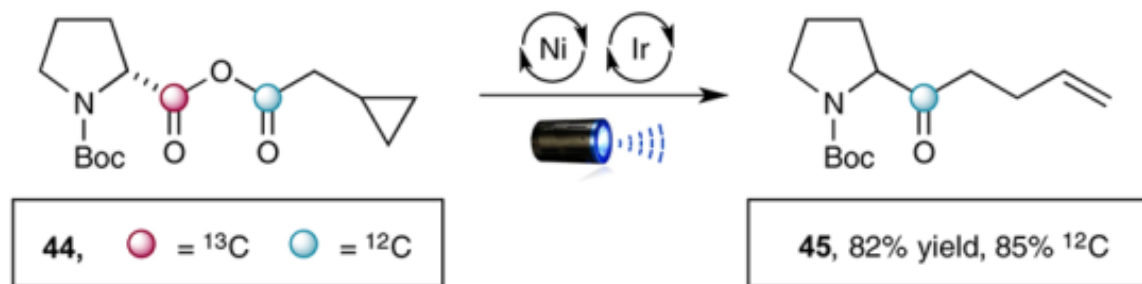
other compatible dialkyl substrates



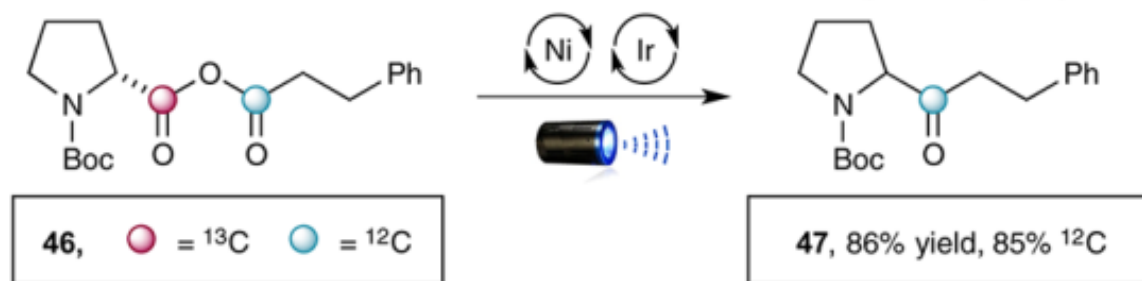
非氨基酸

# Mechanism research

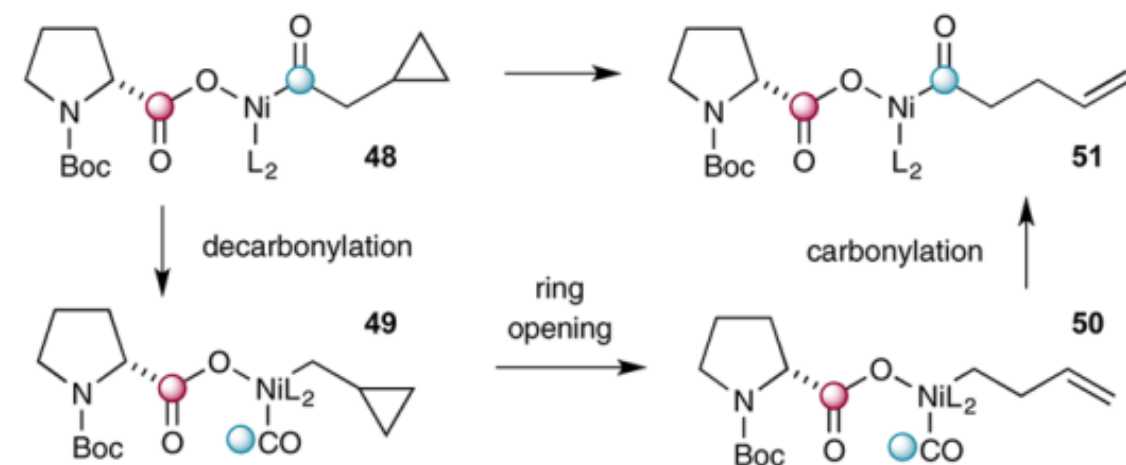
## Rearrangement of Cyclopropylacetic Anhydride Substrate (Eq 5)



## Extrusion Recombination with ${}^{13}\text{C}$ -labeled Mixed Anhydride (Eq 6)



## Proposed Mechanism Based on Cyclopropyl ${}^{13}\text{C}$ -labeling Studies (Eq 7)



- 同位素标记证明了金属插入的位置。实际上，插入反应可能是可逆的和非区域选择性的，两者经历动态动力学选择过程，最终脱羧反应发生在氨基酸一侧。

- 机理推测：经历脱羰基-再羰基化过程，此过程此前有报道。

➔ 自由基开环重排

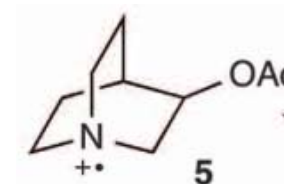
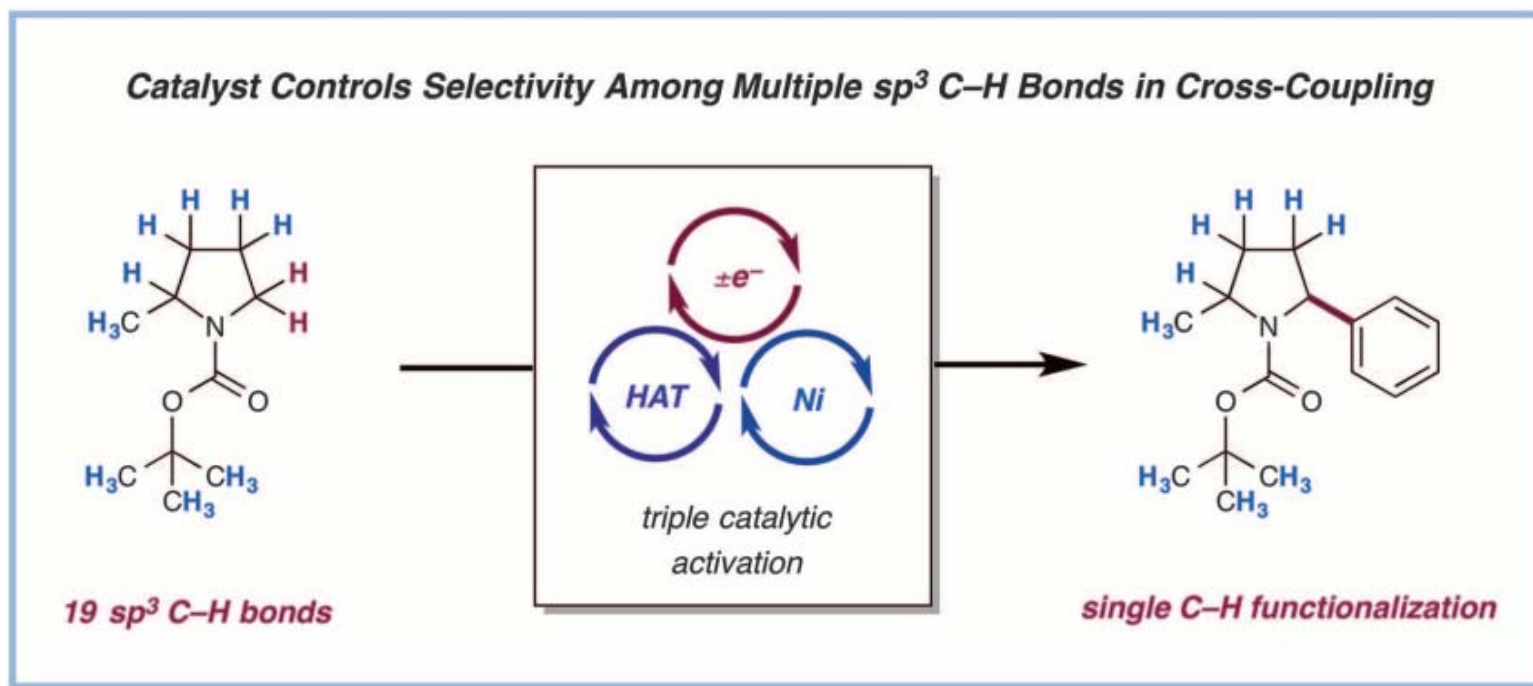


# 奎宁环闪亮登场!

## Native functionality in triple catalytic cross-coupling: $sp^3$ C-H bonds as latent nucleophiles

Science, 352, 1304-1308 (2016)

Megan H. Shaw,\* Valerie W. Shurtleff,\* Jack A. Terrett,\*  
James D. Cuthbertson, David W. C. MacMillan†

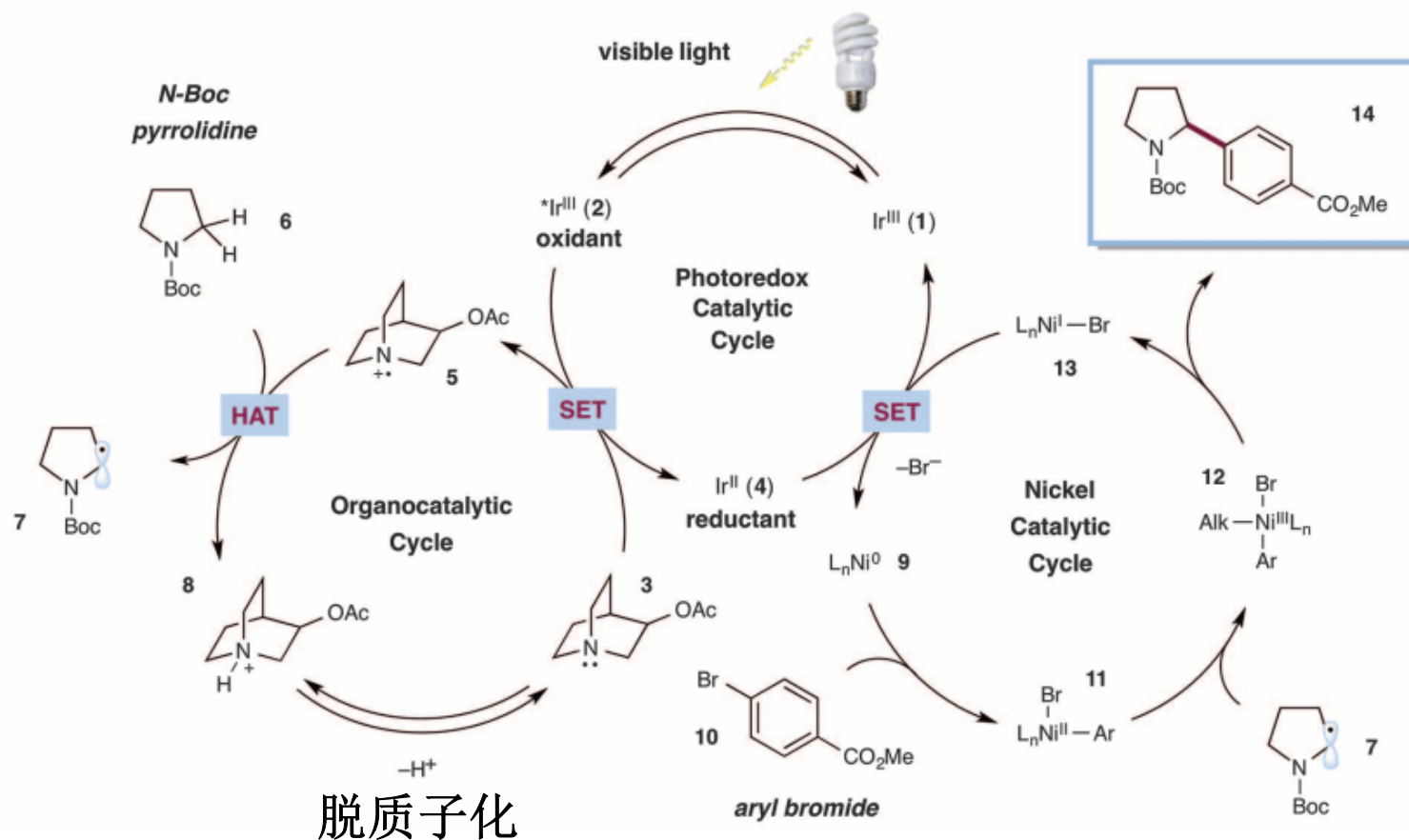
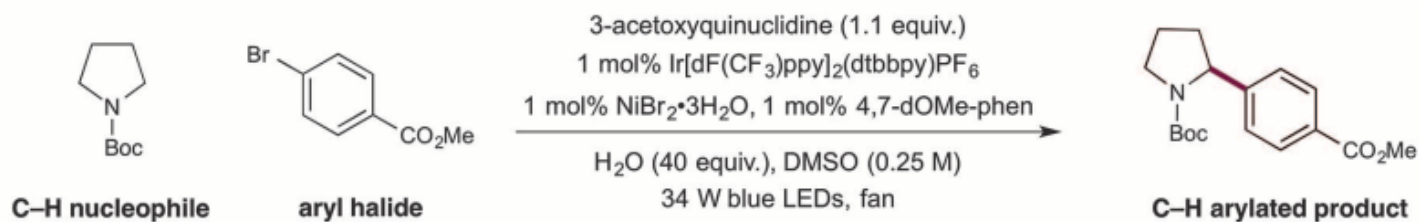
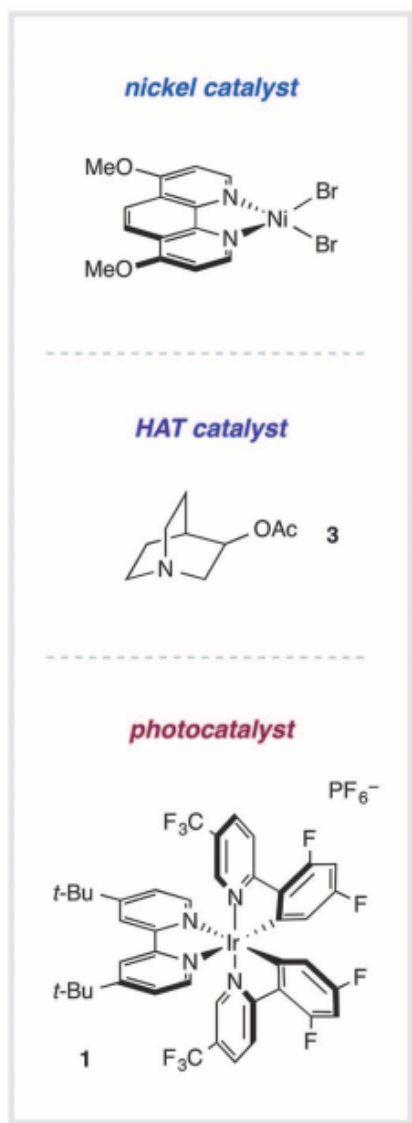


electrophilic nature

selective abstraction of electron-rich C-H bonds

Photoredox, HAT, and nickel-catalyzed cross-coupling

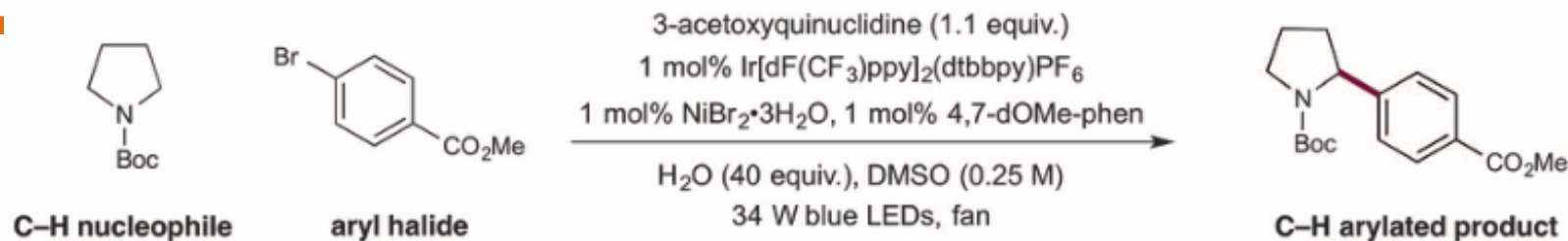
# Proposed mechanism



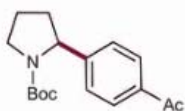
$$E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

$$E_{1/2}^{\text{red}} \text{ quinuclidine} = +1.1 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

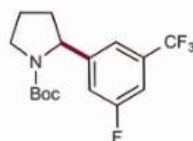
# Scope of substrates



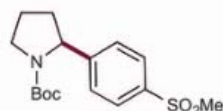
*aryl bromides*



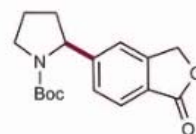
(±)-15 84% yield



(±)-16 71% yield

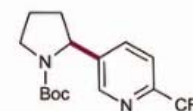


(±)-17 78% yield



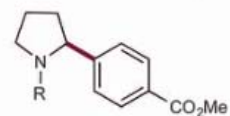
(±)-18 76% yield

*aryl chlorides*

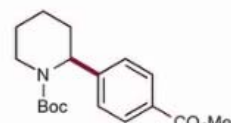


(±)-27 81% yield

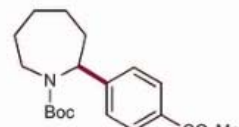
*amines*



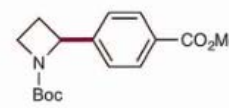
(±)-14 R = Boc 81% yield  
(±)-30 R = Piv 79% yield



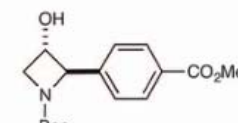
(±)-33 42% yield



(±)-34 69% yield

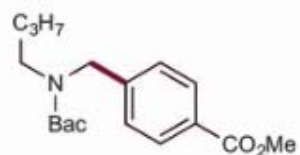


(±)-35 58% yield



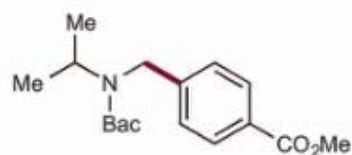
(±)-36 45% yield, >20:1 d.r.

*methyl vs. methylene*



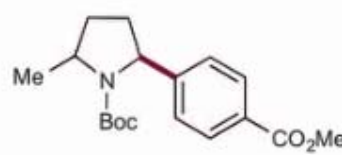
48 78% yield  
4:1 r.r.‡

*methyl vs. methine*



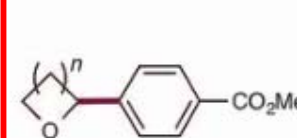
49 82% yield  
single regioisomer

*methylene vs. methine*



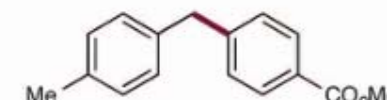
(±)-50 62% yield, 1:1 d.r.  
single regioisomer

*ethers*



(±)-51 n = 2 76% yield  
(±)-52 n = 1 53% yield

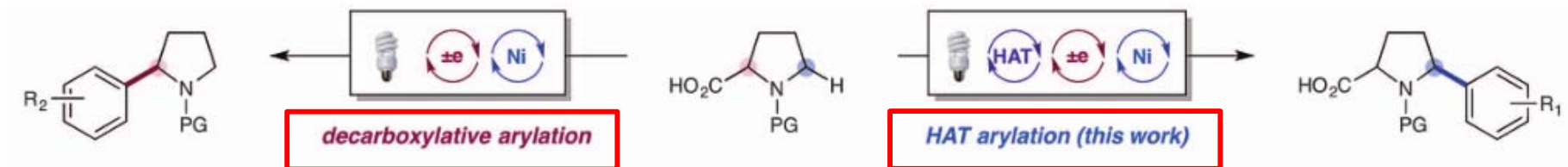
*benzylic C-H*



53 54% yield§

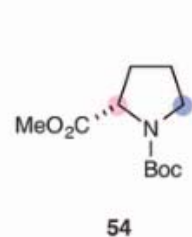
- 不对称胺底物具有区域选择性
- α-氧基和苄基C-H的底物也适用

# Application

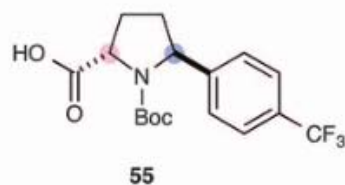


1 mol% photocatalyst 1  
10 mol% NiCl<sub>2</sub>·glyme  
15 mol% dtbbpy, Cs<sub>2</sub>CO<sub>3</sub>  
DMF, 26 W CFL light, 23 °C

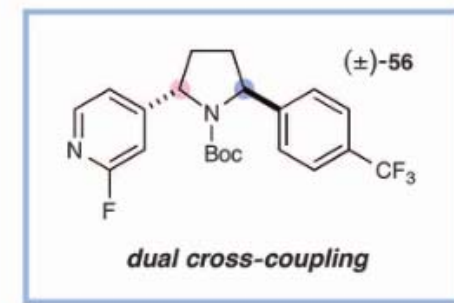
3-acetoxyquinuclidine (1.1 equiv.)  
1 mol% Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub>  
1 mol% NiBr<sub>2</sub>·3H<sub>2</sub>O, 1 mol% 4,7-dOMe-phen  
H<sub>2</sub>O (40 equiv.), DMSO (0.25 M)  
34 W blue LEDs, fan



HAT arylation  
66% yield, 4:1 d.r.  
then LiOH, H<sub>2</sub>O/THF  
90% yield, 6:1 d.r.

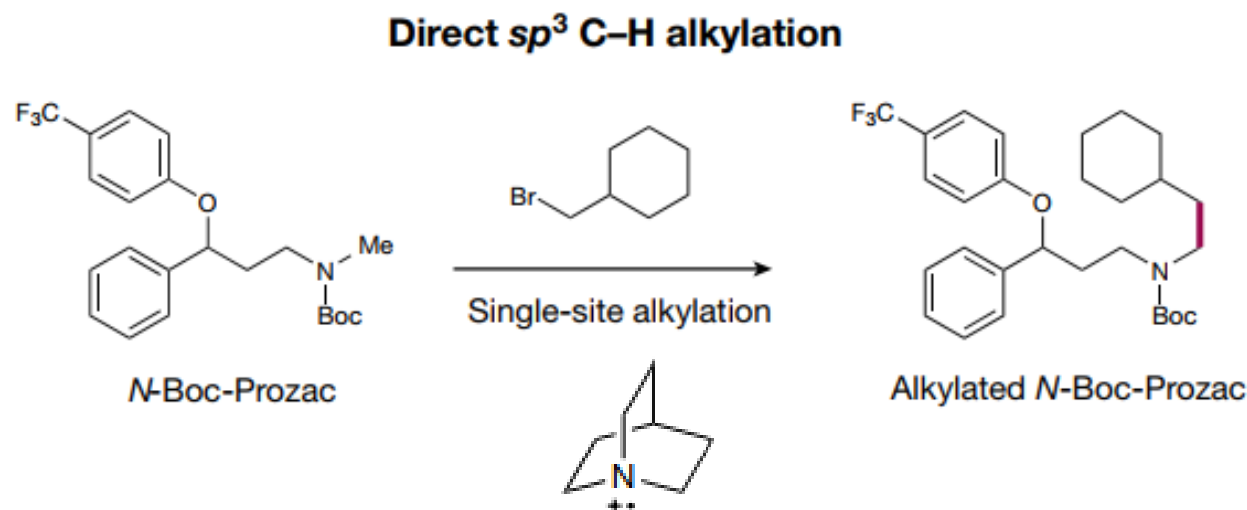


decarboxylative  
arylation  
73% yield, 4:1 d.r.



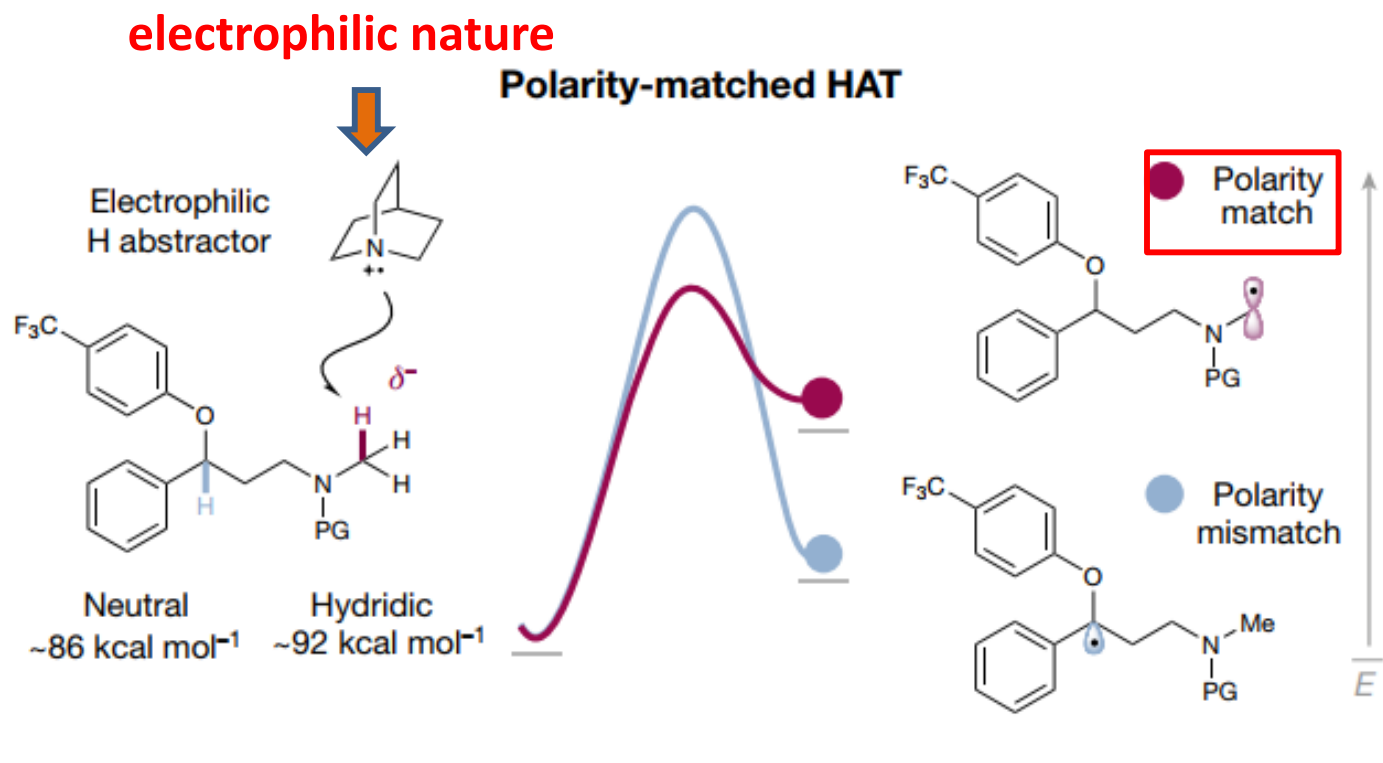
# Selective $sp^3$ C–H alkylation via polarity–match–based cross–coupling

Chip Le<sup>1\*</sup>, Yufan Liang<sup>1\*</sup>, Ryan W. Evans<sup>1\*</sup>, Ximing Li<sup>1</sup> & David W. C. MacMillan<sup>1</sup>



**Polarity-matched** hydrogen-atom transfer (HAT), alkyl halide oxidative addition, and reductive elimination to enable alkyl–alkyl fragment coupling.

# Polarity-matched hydrogenatom transfer (HAT)

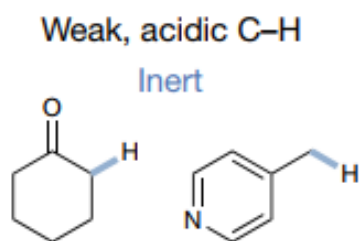


**极性匹配?**

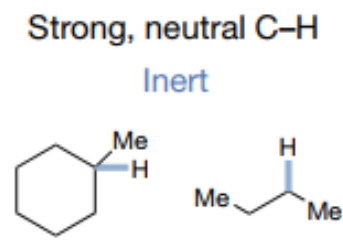
指C-H键和HAT催化剂电子极性的匹配，跟键的强度和热力学上的驱动力相关性弱。

**强碳氢键?**

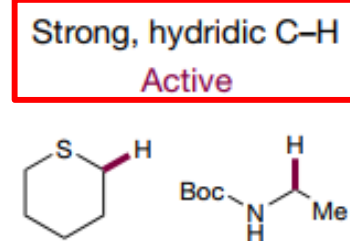
这里指富电子的C-H键。



缺电子



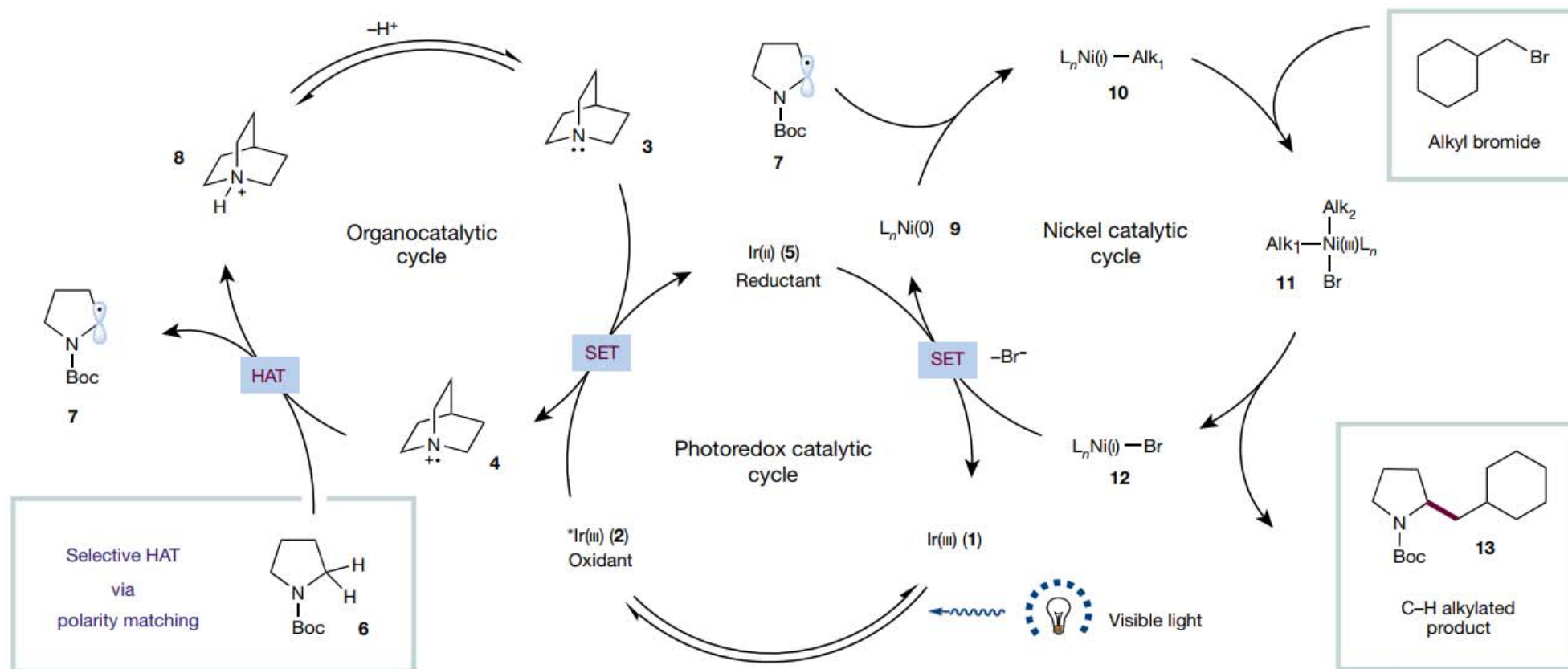
中性



富电子

**极性匹配效应给一个非选择性的HAT过程带来高度的动力学选择性!**

# Proposed mechanism



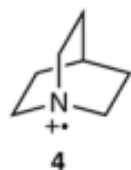
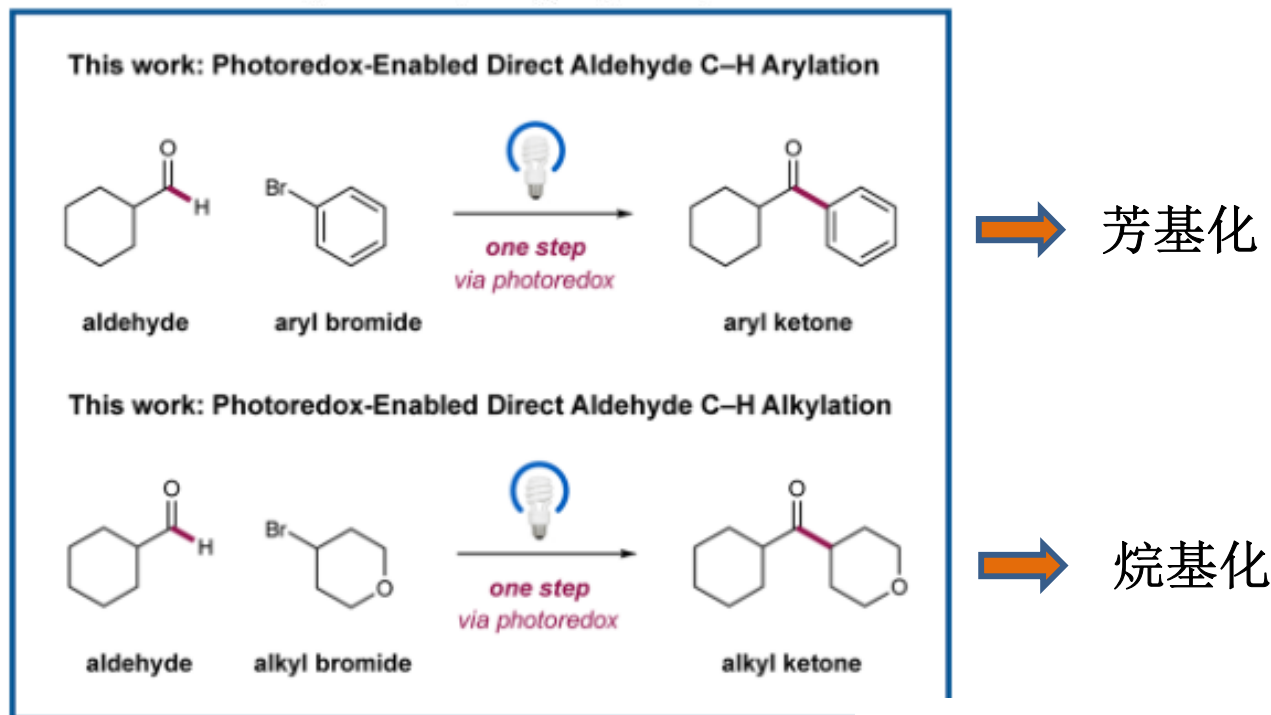
$$E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

$$E_{1/2}^{\text{red}} \text{ quinuclidine} = +1.1 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

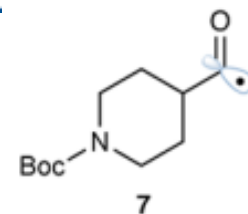
# Direct Aldehyde C–H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis

Xiaheng Zhang and David W. C. MacMillan\*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States



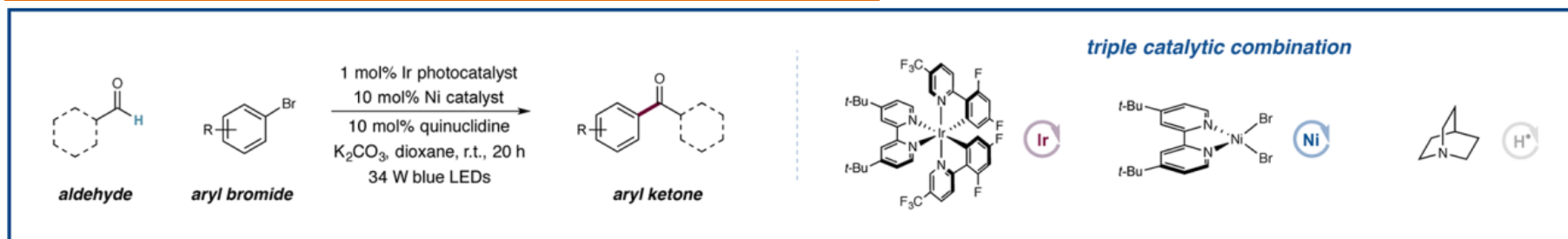
**Polarity-matched HAT**



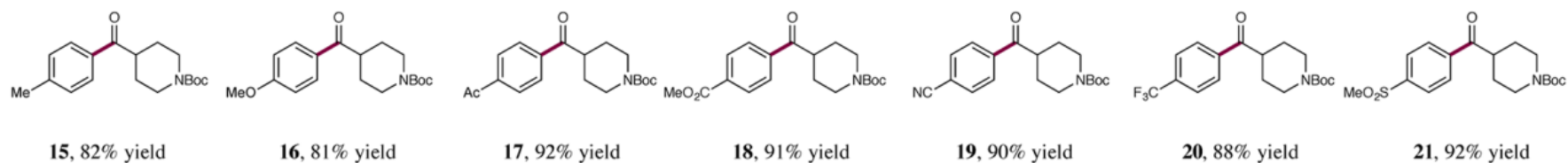
酰基自由基



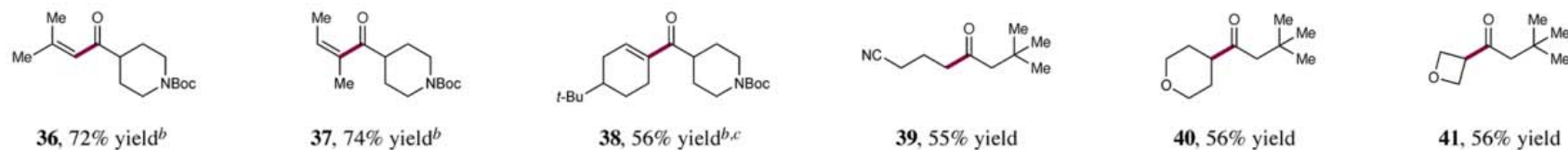
# Scope of substrates



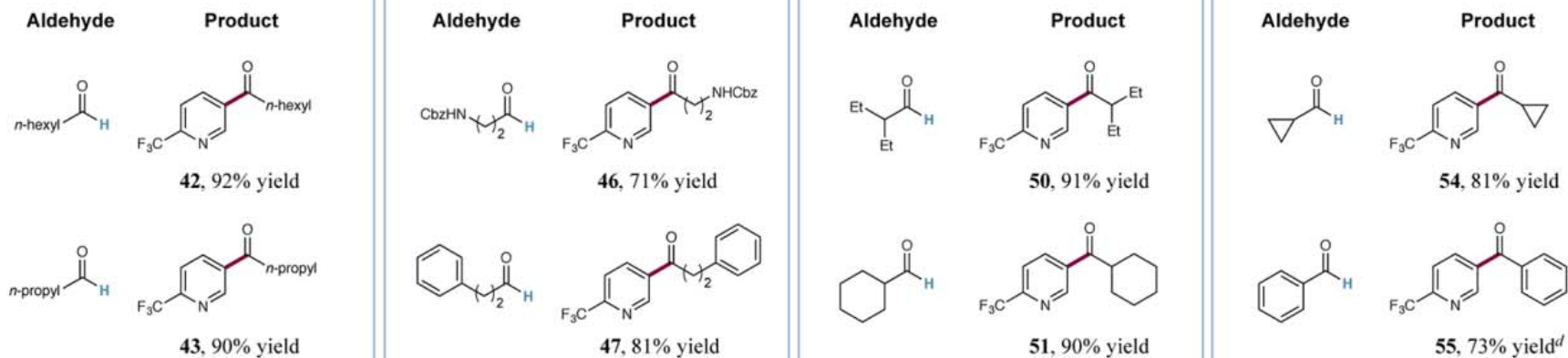
## Aryl Bromide Scope



## Vinyl and Alkyl Bromide Scope



## Aldehyde Scope



烯基溴  
烷基溴

烷基醛  
芳香醛

**Photoredox Catalysis** Hot Paper

International Edition: DOI: 10.1002/anie.201800749

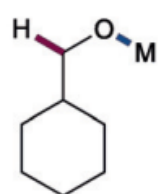
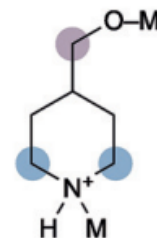
German Edition: DOI: 10.1002/ange.201800749

# Selective Hydrogen Atom Abstraction through Induced Bond Polarization: Direct $\alpha$ -Arylation of Alcohols through Photoredox, HAT, and Nickel Catalysis

Angew. Chem. Int. Ed. 2018, 57, 5369–5373

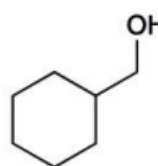
*Jack Twilton, Melodie Christensen, Daniel A. DiRocco, Rebecca T. Ruck, Ian W. Davies, and David W. C. MacMillan\**

## In Situ Metal Alkoxide Activation

**C-H over O-H**  
activationactivation of  
alcohol C-H ●  
over  
amine C-H ●

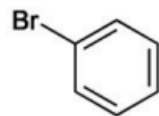
极性匹配

## This work: Lewis acid-mediated alcohol C-H activation



alcohol

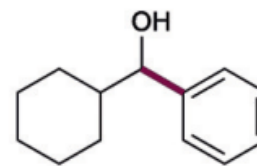
+



aryl bromide

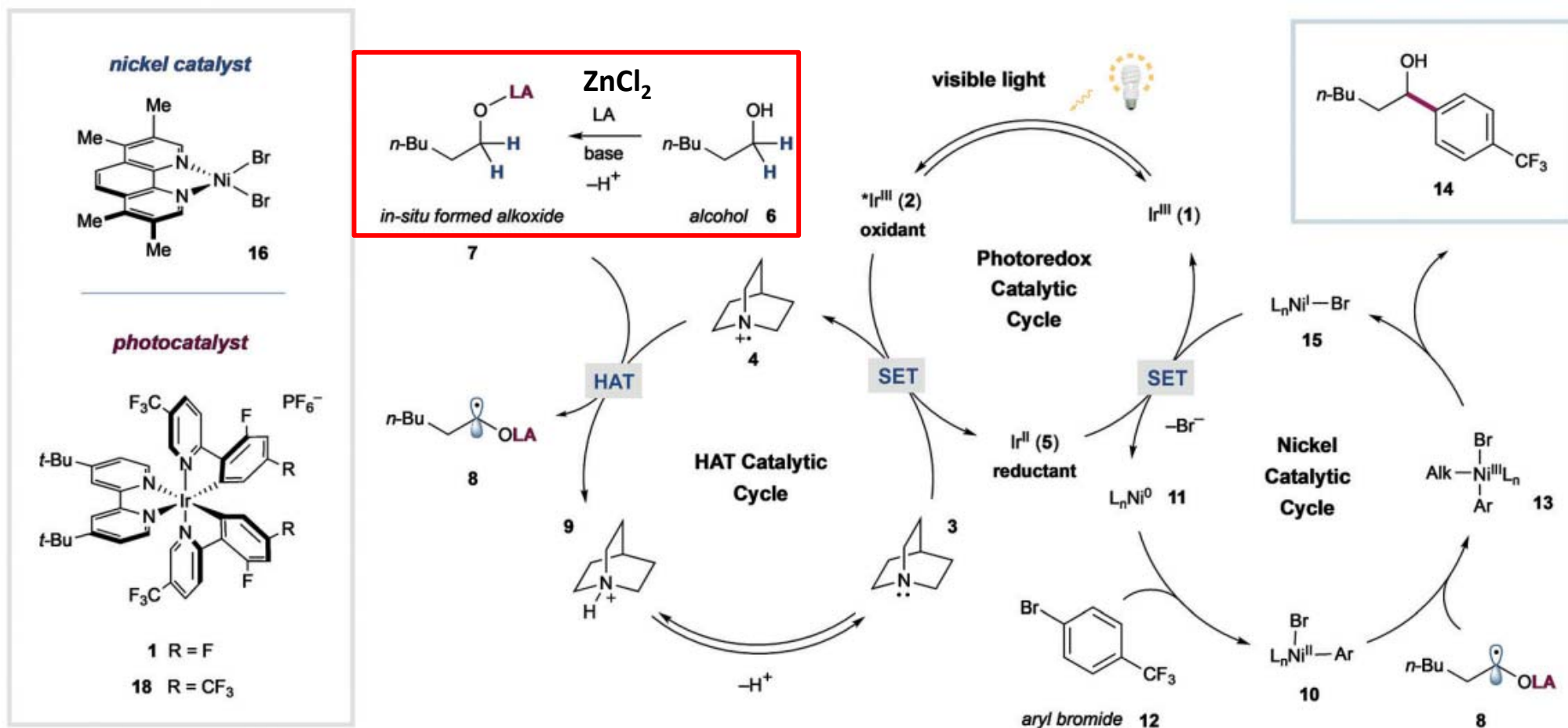


Lewis Acid

 $\text{ZnCl}_2$   $\alpha$ -C-OH coupled product

增强氢的负电性

# Proposed mechanism



## 路易斯酸活化模式

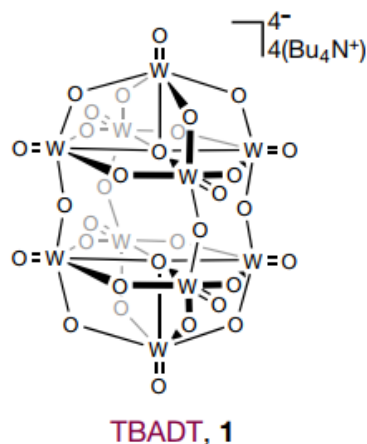
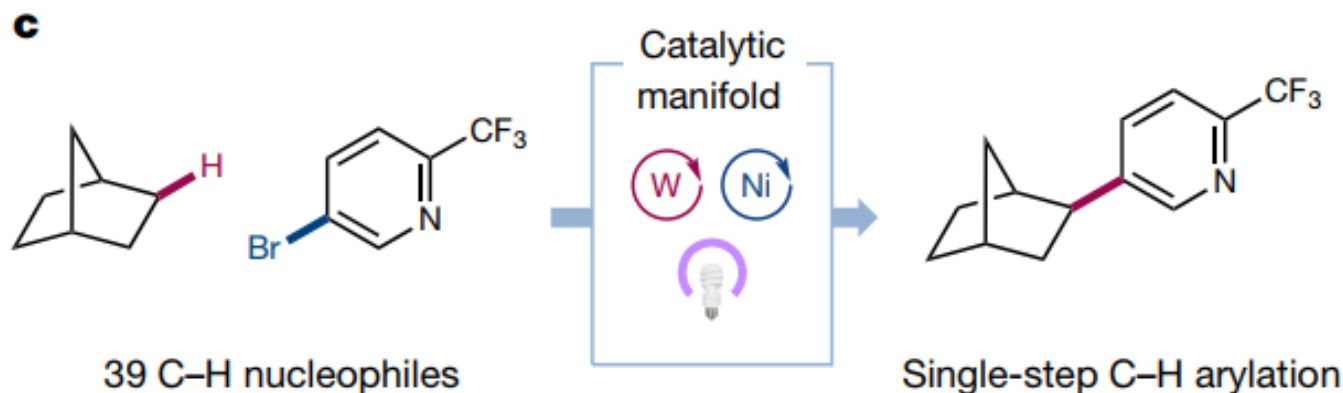
形成：路易斯酸与羟基配位后脱质子  
作用：

- ①激活羟基 $\alpha$ 位C-H (hydridic character)；
- ②抑制镍与羟基配位成键；
- ③使其他氢键失活，如 $\alpha$ -氨基和 $\alpha$ -氧基的C-H。

物种7与镍发生金属交换进而形成碳氧键？

## Direct arylation of strong aliphatic C–H bonds

Ian B. Perry<sup>1,3</sup>, Thomas F. Brewer<sup>1,3</sup>, Patrick J. Sarver<sup>1</sup>, Danielle M. Schultz<sup>2</sup>, Daniel A. DiRocco<sup>2</sup> & David W. C. MacMillan<sup>1\*</sup>



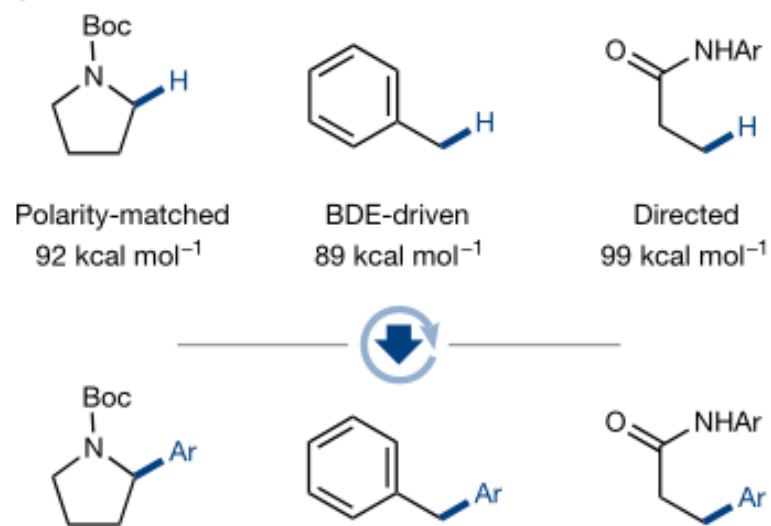
四丁基铵十钨酸盐（**tetrabutylammonium decatungstate, TBADT**）是一种多金属氧酸盐（**polyoxometalates, POMs**）。作为高效的HAT光催化剂，具有高能激发态，键离解能高达**100 kcal mol<sup>-1</sup>**，激发态寿命**55 ns**，被用于各种氧化、脱氢、共轭加成等反应。

首次与过渡金属偶联结合

# Background

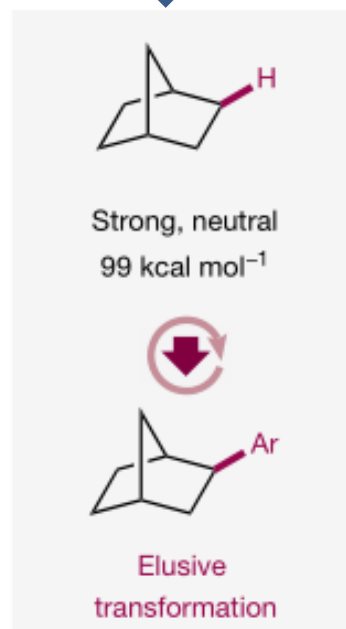
未活化中性C-H

**a**

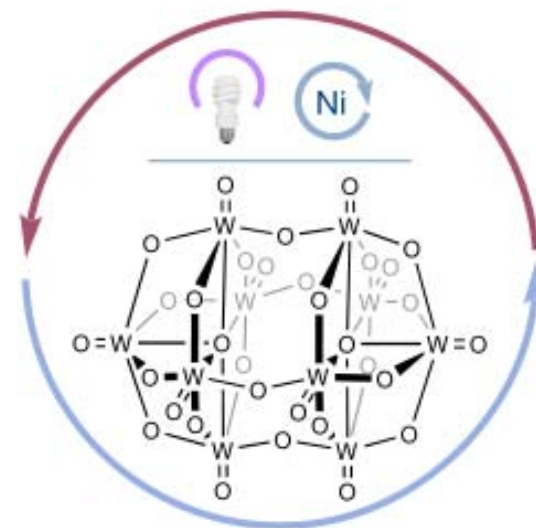


极性匹配

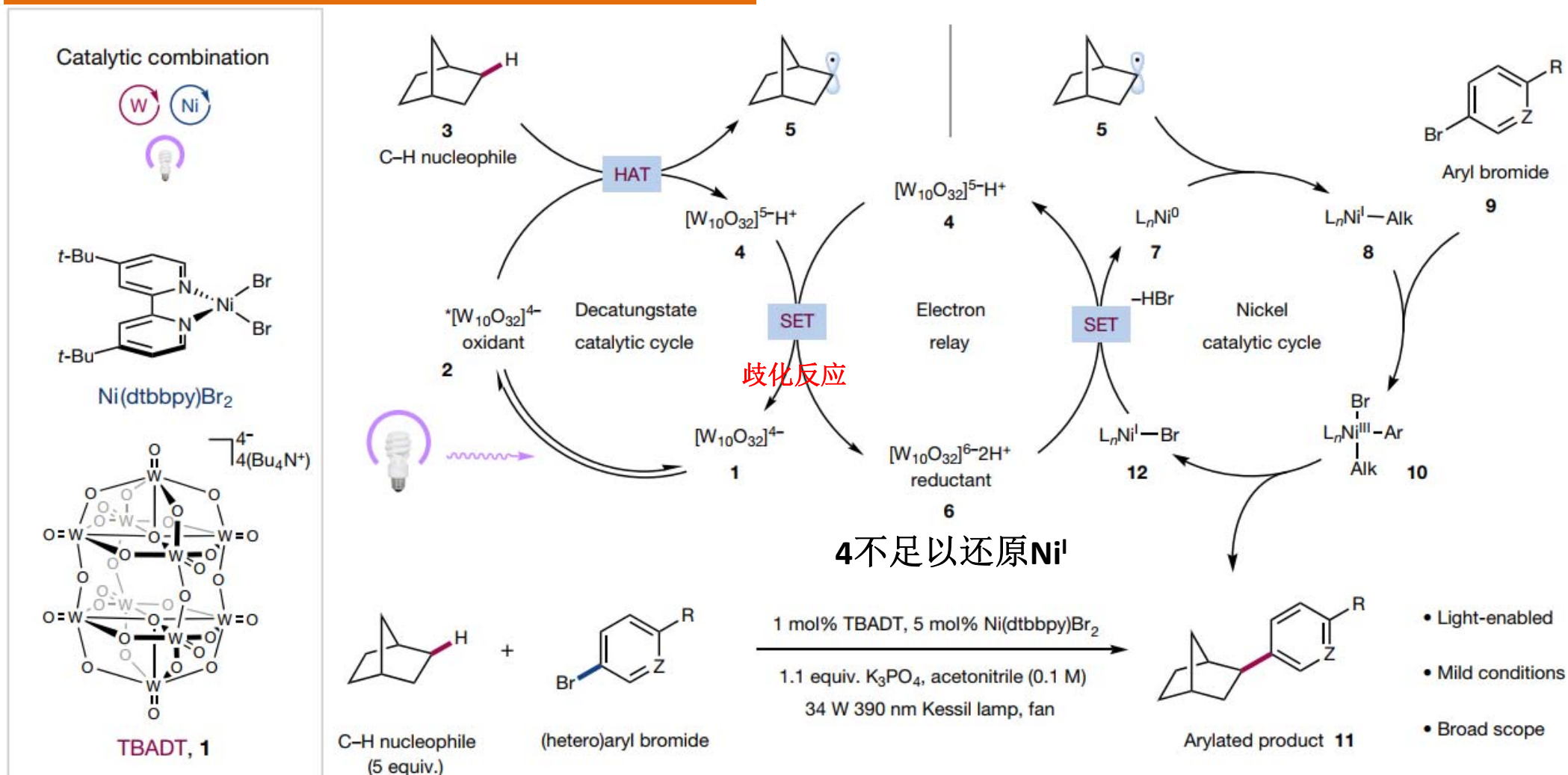
解离能低



反应性?  
选择性?



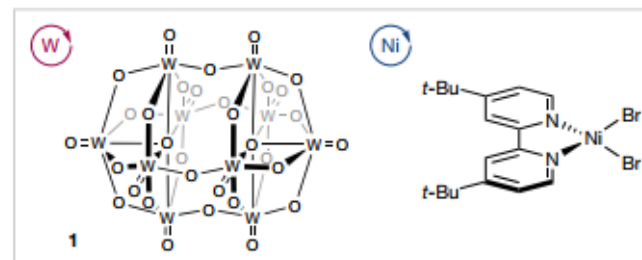
# Proposed mechanism



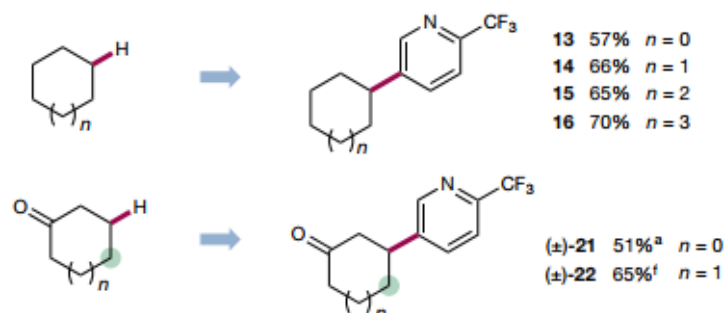
$$E_{1/2 \text{ red}}([\text{W}_{10}\text{O}_{32}]^{5-}/[\text{W}_{10}\text{O}_{32}]^{6-}) = -1.52 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

$$E_p(\text{Ni}^{\text{III}}/\text{Ni}^0) = -1.47 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

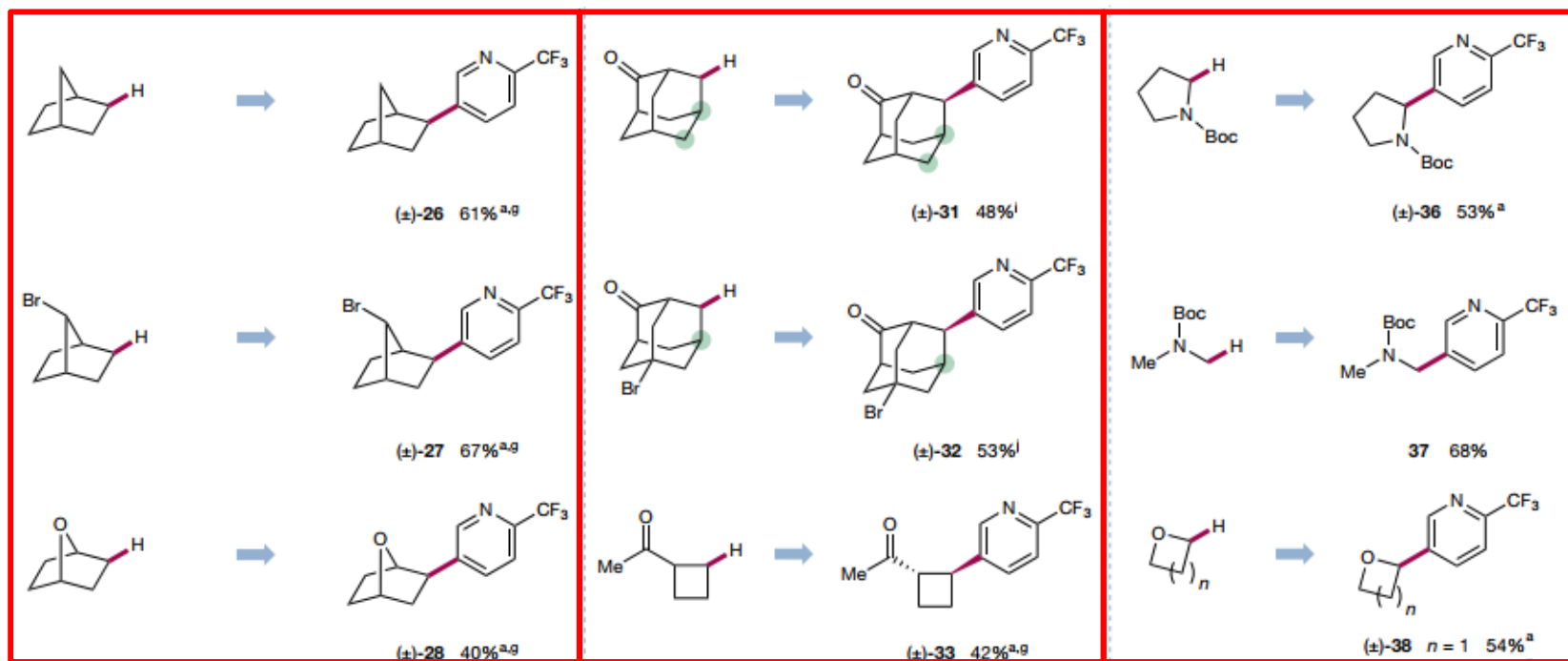
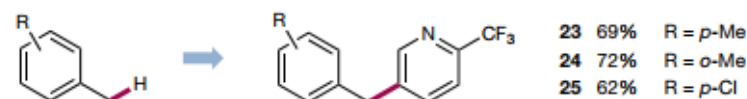
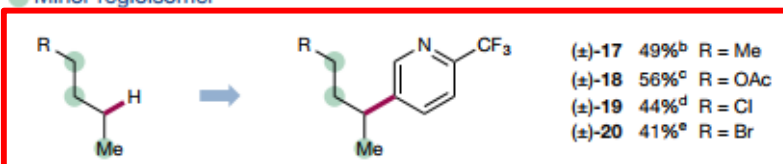
# Scope of substrates



C-H nucleophiles



Minor regioisomer



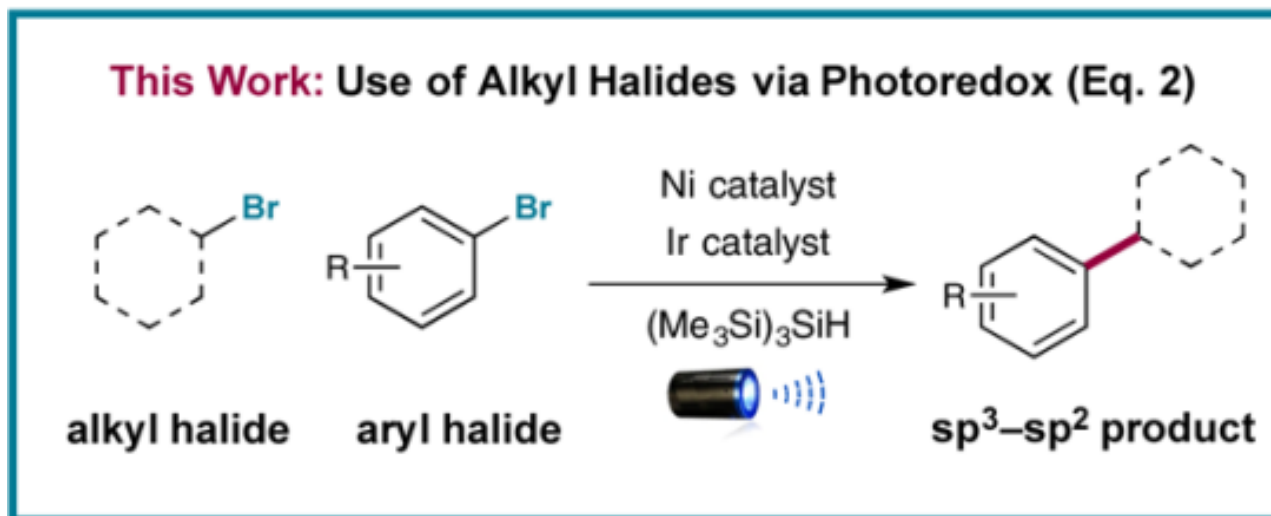
选择性:  
电子效应  
位阻效应

- 1、线性烷烃主要在2号位;
- 2、桥联双环烷烃主要在位阻小的亚甲基上;
- 3、酮类化合物主要在羰基的 $\beta$ 位;
- 4、 $\alpha$ -杂原子底物高选择性的活化 $\alpha$ 位的C-H。

# Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling

Patricia Zhang, Chi “Chip” Le, and David W. C. MacMillan\*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, United States



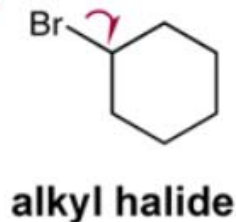
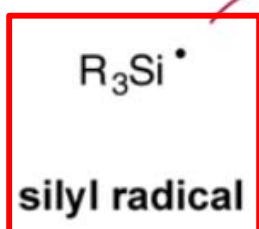


# Background

如何产生硅  
自由基?

Known Halogen Atom Abstraction via Silyl Radical (Eq. 1)

偶氮二异丁腈或过氧化物



$Csp^3-Br$   
BDE = 69 kcal/mol

Fast and Efficient  
Activation of Alkyl Halides

$\sim 10^8 M^{-1}s^{-1}$

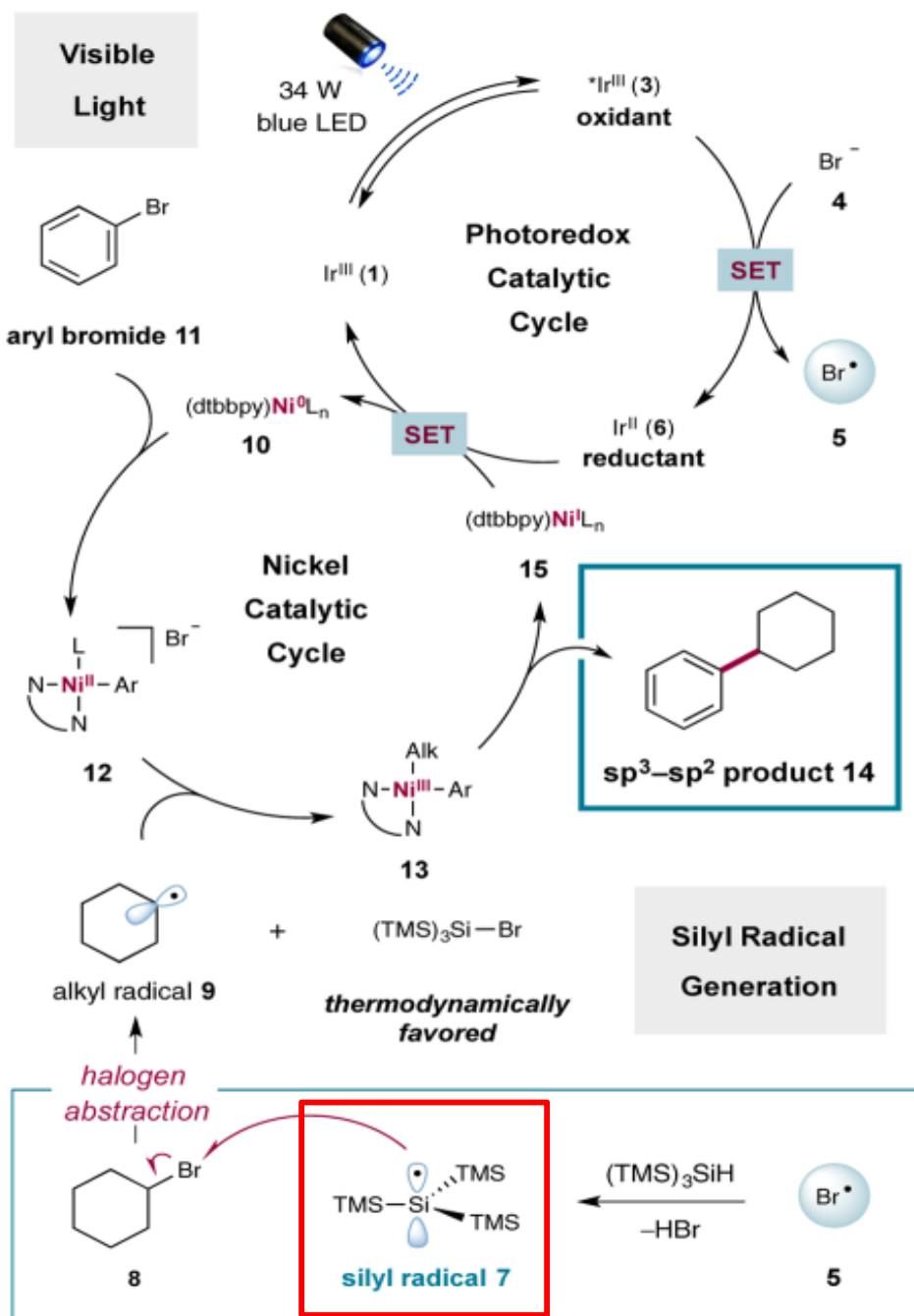
可行, 快速,  
不可逆

$R_3Si-Br$   
BDE = 96 kcal/mol



nucleophilic  
carbon-centered  
radical

# Proposed mechanism

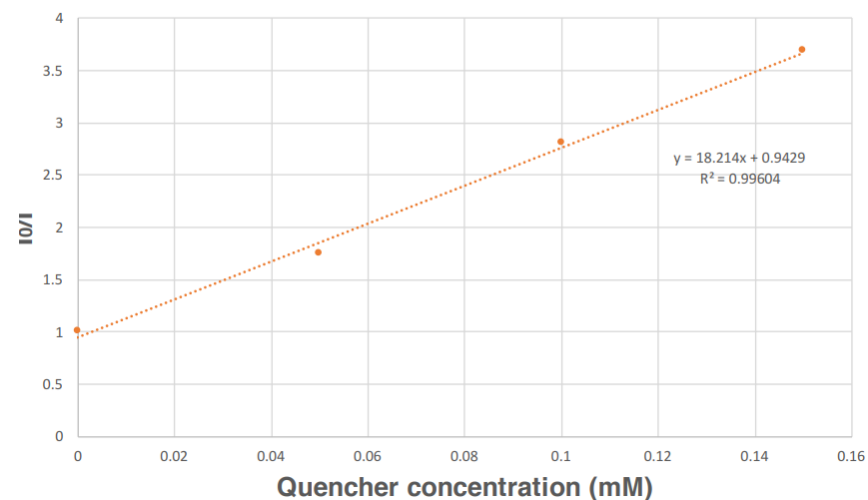


$$E_{1/2}^{\text{red}}[*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V vs Ag/AgCl in CH}_3\text{CN}$$

$$E_{1/2}^{\text{red}}[\text{Br}^-/\text{Br}\cdot] = +0.80 \text{ V vs SCE in DME}$$

亲电溴自由基一旦产生，便能从Si-H键中迅速提取氢原子

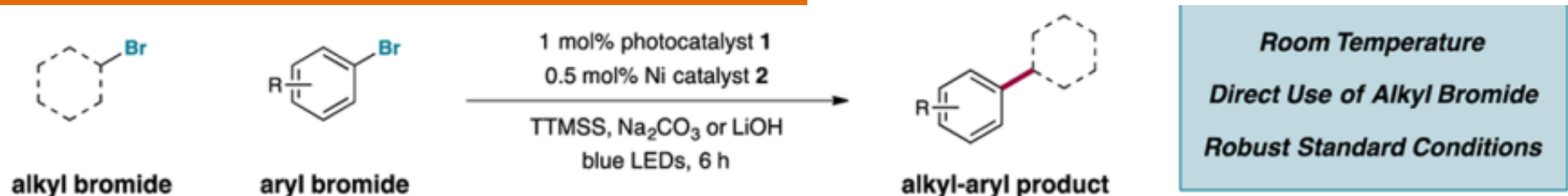
Emission Quenching of <sup>\*</sup>Ir(III) by LiBr



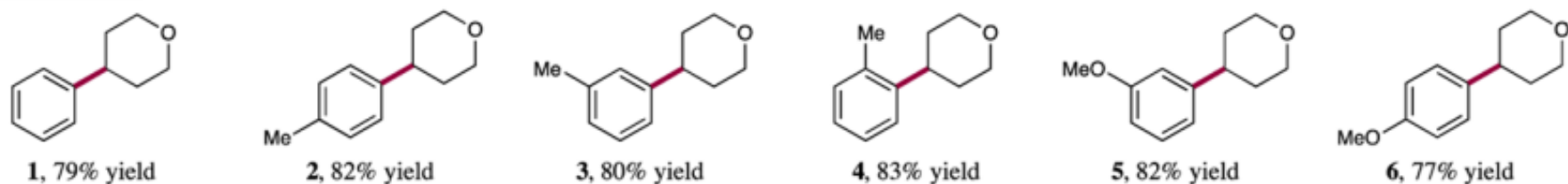
## 荧光猝灭实验

不能确认硅自由基的存在，但观察到反应效率与Si-H键能的相关性，符合HAT机制。机理在进一步研究。

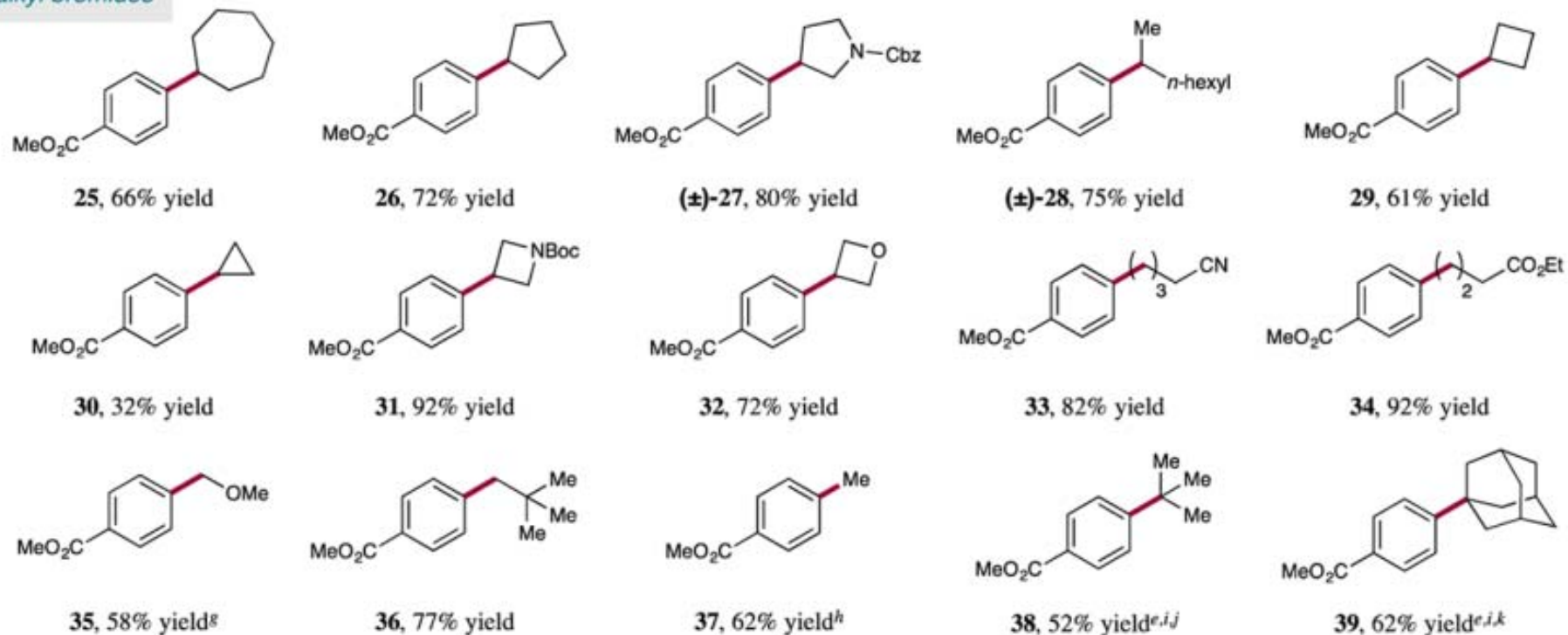
# Scope of substrates



## aryl bromides



## alkyl bromides



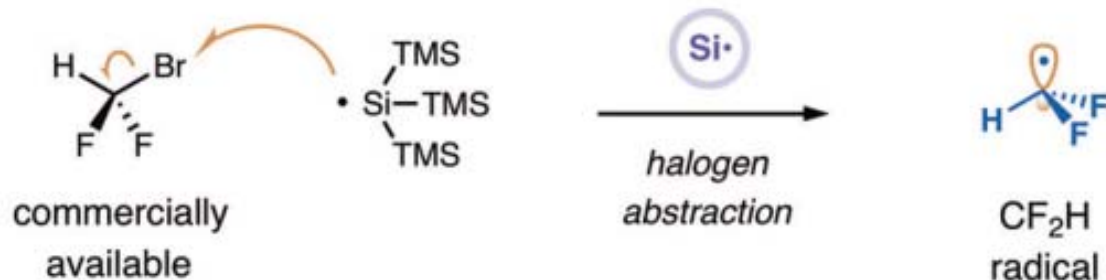
**Difluoromethylation**

International Edition: DOI: 10.1002/anie.201807629

German Edition: DOI: 10.1002/ange.201807629

**Metallaphotoredox Difluoromethylation of Aryl Bromides**

Vlad Bacauanu<sup>+</sup>, Sébastien Cardinal<sup>+</sup>, Motoshi Yamauchi<sup>+</sup>, Masaru Kondo, David F. Fernández, Richard Remy, and David W. C. MacMillan\* **Angew. Chem. Int. Ed.** 2018, 57, 12543–12548



C-Br: BDE = 69 kcalmol<sup>-1</sup>  
Si-Br: BDE = 96 kcalmol<sup>-1</sup>

**Silane-Mediated Difluoromethylation of Aryl Bromides**

1 mol% Ir photocatalyst 1  
5 mol% NiBr<sub>2</sub>·dtbbpy

(TMS)<sub>3</sub>SiH, 2,6-lutidine  
DME, blue LEDs, 18 h

二氟甲基化

## Cooperative Catalysis

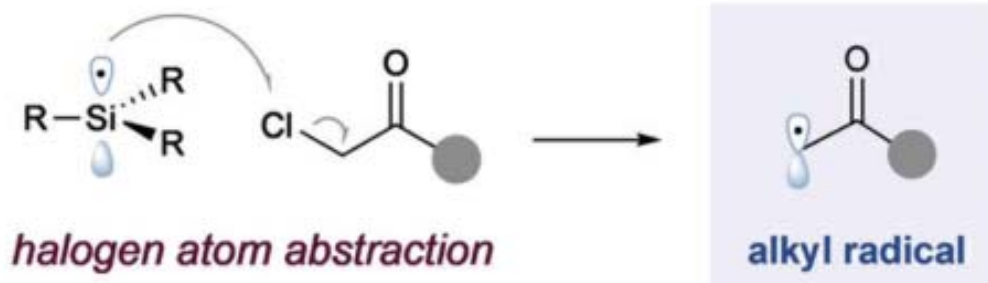
International Edition: DOI: 10.1002/anie.201909072

German Edition: DOI: 10.1002/ange.201909072

A Metallaphotoredox Strategy for the Cross-Electrophile Coupling of  $\alpha$ -Chloro Carbonyls with Aryl Halides

Tiffany Q. Chen and David W. C. MacMillan\*

Angew. Chem. Int. Ed. 2019, 58, 14584 –14588



narrow range of C–Cl BDEs for activated alkyl halides

Si-Cl: BDE > 80 kcalmol<sup>-1</sup>

## Cross-Electrophile Coupling of Unactivated Alkyl Chlorides

Holt A. Sakai,<sup>†</sup> Wei Liu,<sup>†</sup> Chi “Chip” Le, and David W. C. MacMillan\*

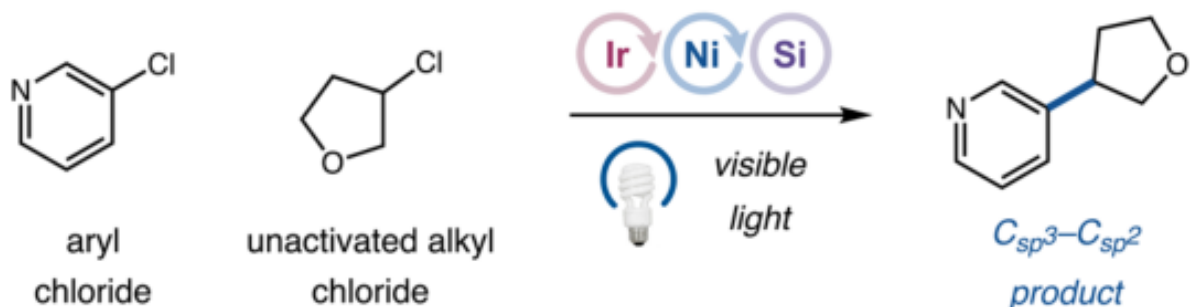


Cite This: *J. Am. Chem. Soc.* 2020, 142, 11691–11697

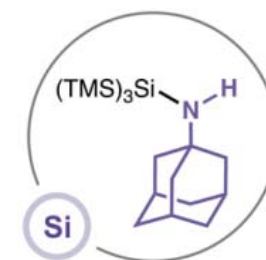


Read Online

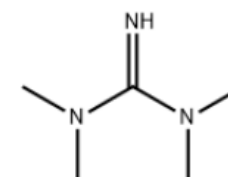
**Previously unknown:** cross-electrophile coupling of organochlorides



■ alkyl chlorides: broadly underutilized      ■ bench-stable reagents & substrates



金刚烷氨基硅



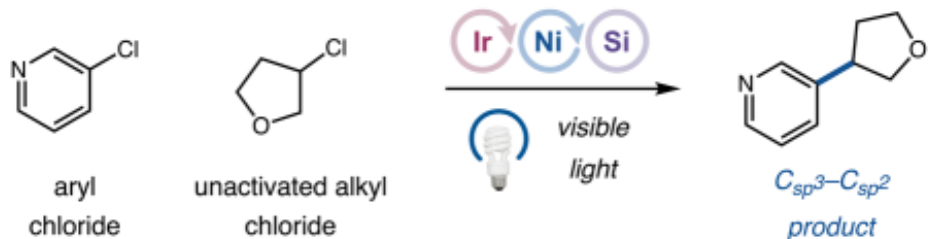
TMG

未活化的氯代烷烃亲电偶联

# Background

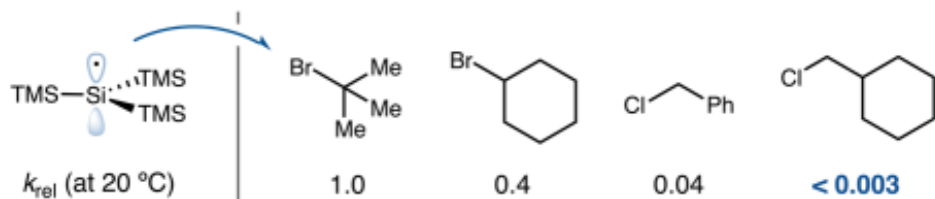
## 极性匹配策略克服氯原子转移的热力学屏障

Previously unknown: cross-electrophile coupling of organochlorides

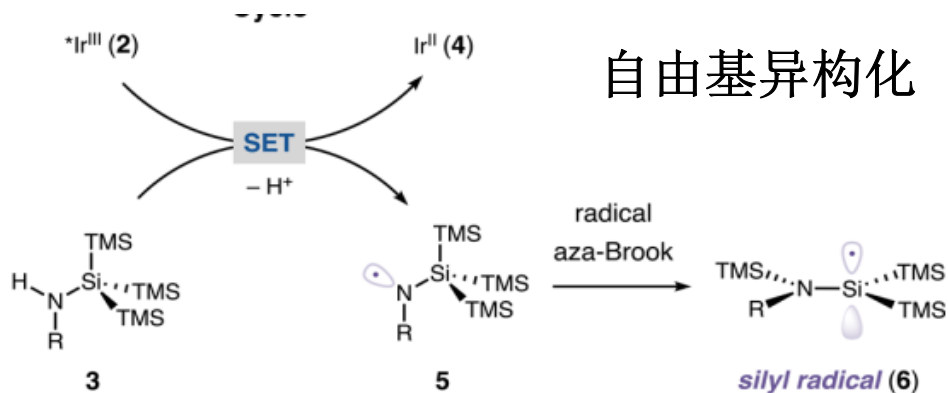


■ alkyl chlorides: broadly underutilized ■ bench-stable reagents & substrates

Unactivated  $C(sp^3)-Cl$  bonds are generally inert toward activation

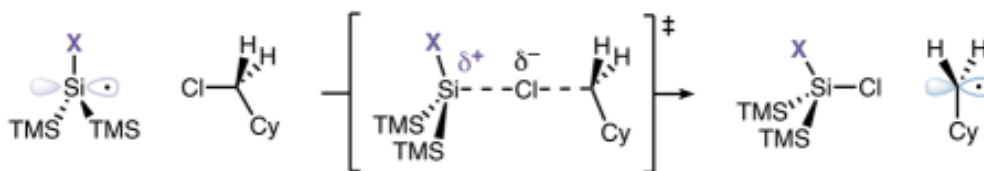


challenging silane-mediated abstraction of unactivated alkyl chlorides



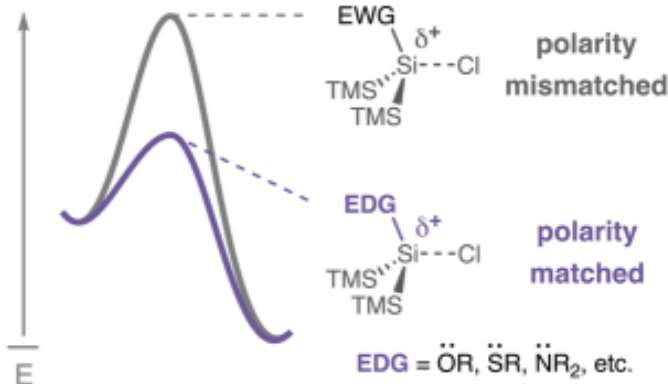
改造取代基降低硅自由基的正电性

Engaging unactivated alkyl chlorides via polarity-matching

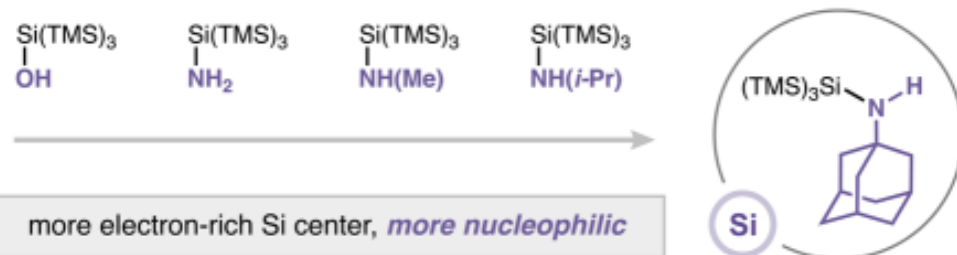


favorable thermodynamics ( $\Delta G^\circ \approx -30$  kcal/mol)

How can we overcome this kinetic barrier?



reagent design:  $\pi$ -donating EDG stabilizes charge buildup in TS

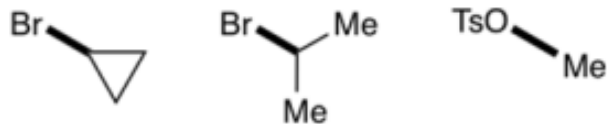
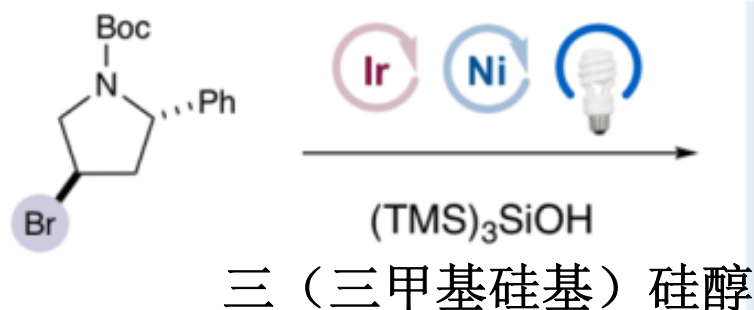


**J. Am. Chem. Soc. 2018, 140, 17433–17438**

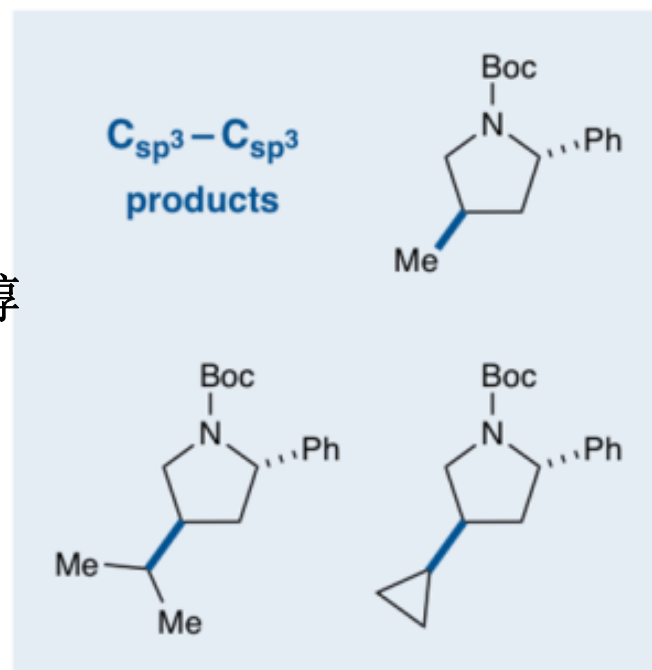
# Metallaphotoredox-Catalyzed Cross-Electrophile $C_{sp^3}-C_{sp^3}$ Coupling of Aliphatic Bromides

Russell T. Smith,<sup>†,§</sup> Xiaheng Zhang,<sup>†,§</sup> Juan A. Rincón,<sup>\*,‡</sup> Javier Agejas,<sup>‡</sup> Carlos Mateos,<sup>‡</sup> Mario Barberis,<sup>‡</sup> Susana García-Cerrada,<sup>‡</sup> Oscar de Frutos,<sup>‡</sup> and David W. C. MacMillan<sup>\*,†</sup>

**This work:** development of cross-electrophile  $C_{sp^3}-C_{sp^3}$  coupling



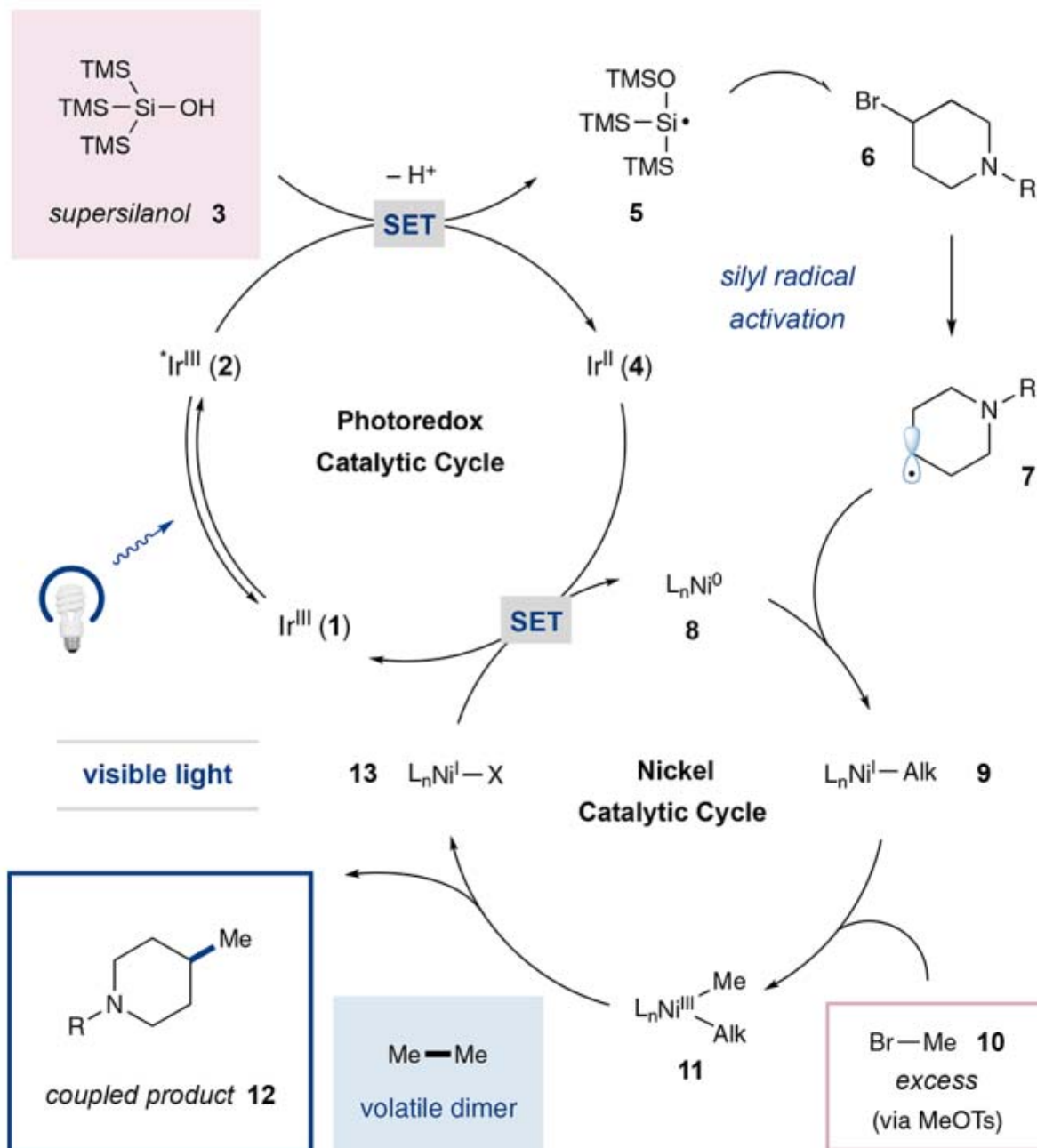
commercial alkyl electrophiles



烷基溴化物和对甲苯磺酸甲酯



# Proposed mechanism

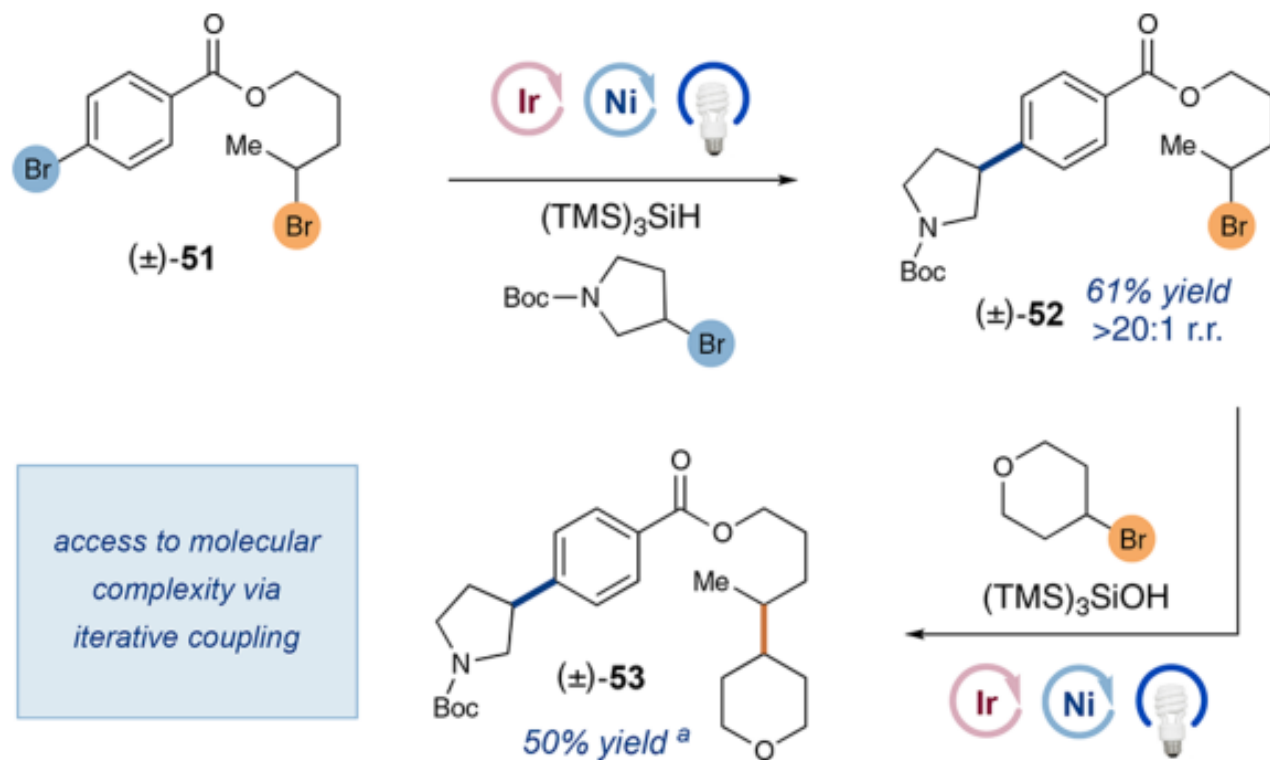


3 → 5

脱质子化+氧化+异构化

溴甲烷由对甲苯磺酸甲酯和四丁基溴化铵 (TBAB) 原位生成

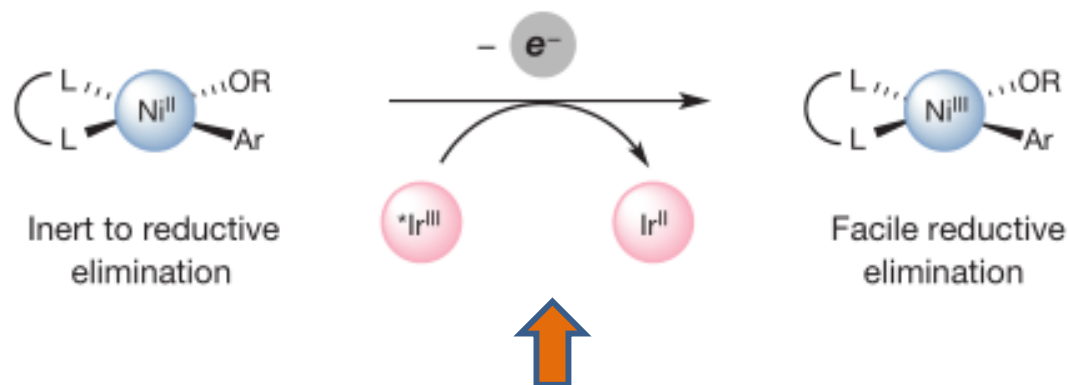
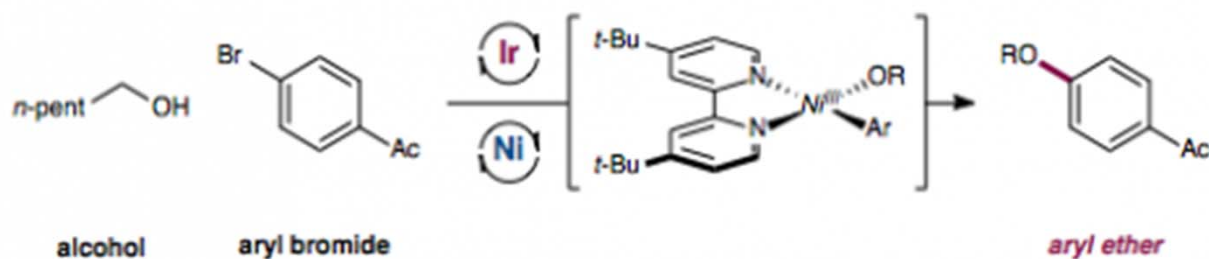
# Iterative Coupling Sequence



**51**包含芳香族和脂肪族溴通过两次选择性偶联得到目标产物

# Switching on elusive organometallic mechanisms with photoredox catalysis

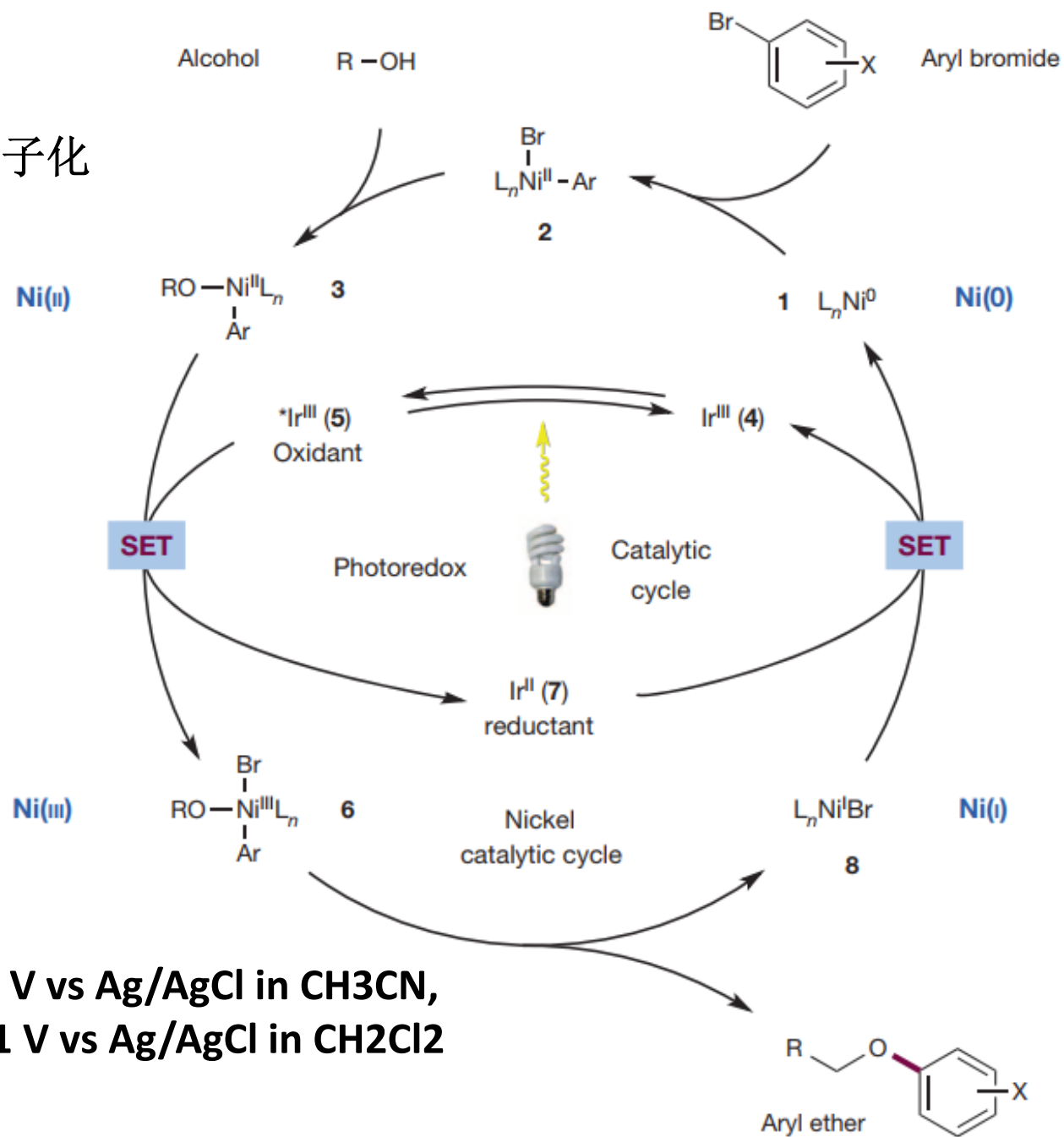
Jack A. Terrett<sup>1</sup>, James D. Cuthbertson<sup>1</sup>, Valerie W. Shurtleff<sup>1</sup> & David W. C. MacMillan<sup>1</sup>



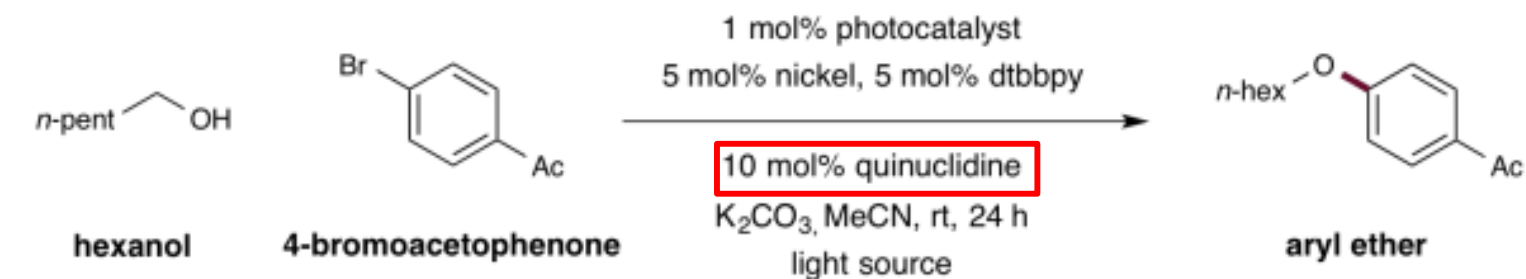
构建C-O键的挑战： $\text{Ni}^{\text{III}}$ 中间体的生成

# Proposed mechanism

配体交换随后脱质子化



# Reaction Condition Optimization



entry	photocatalyst	nickel source	light source	yield
1	None	Ni(COD) <sub>2</sub>	blue LEDs	0%
2 <sup>a</sup>	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	Ni(COD) <sub>2</sub>	blue LEDs	8%
3	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	Ni(COD) <sub>2</sub>	blue LEDs	86%
4	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiBr <sub>2</sub> •diglyme	blue LEDs	89%
5	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiCl <sub>2</sub> •glyme	blue LEDs	91%
6 <sup>a</sup>	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiCl <sub>2</sub> •glyme	blue LEDs	0%
7	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	None	blue LEDs	0%
8 <sup>b</sup>	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiCl <sub>2</sub> •glyme	blue LEDs	0%
9	None	NiCl <sub>2</sub> •glyme	blue LEDs	0%
10	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiCl <sub>2</sub> •glyme	None	0%
11	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	NiCl <sub>2</sub> •glyme	26W CFL	86%

amine base/reductant	yield
Ph <sub>3</sub> N	0%
DMAP	1%
<i>i</i> -Pr <sub>2</sub> NEt	29%
DABCO	34%
Cy <sub>2</sub> NEt	44%
Et <sub>3</sub> N	54%
quinuclidine	90%

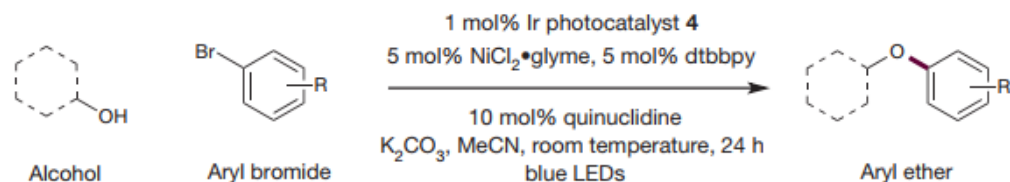
**As a sacrificial reductant and electron shuttle**

**奎宁环作用:**

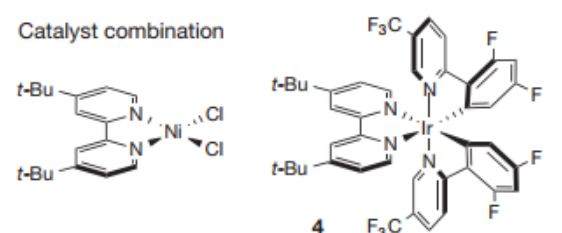
- 奎宁环与铱协同还原Ni<sup>II</sup>
- 协助电子转移

**Figure S1.** Optimization and control experiments in the photoredox–nickel catalyzed C–O coupling. Yields determined by <sup>1</sup>H NMR analysis using 1,3-benzodioxole as internal standard. Reactions performed using 1.5 equiv. hexanol on 0.25 mmol scale. **Reaction performed in the absence of quinuclidine.** <sup>b</sup>Reaction performed in the absence of 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

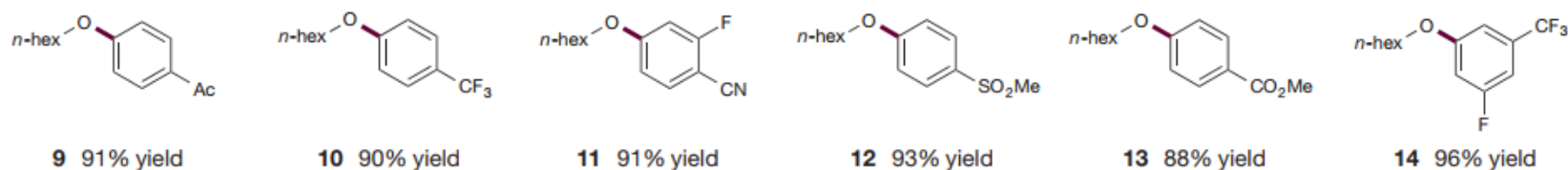
# Scope of substrates



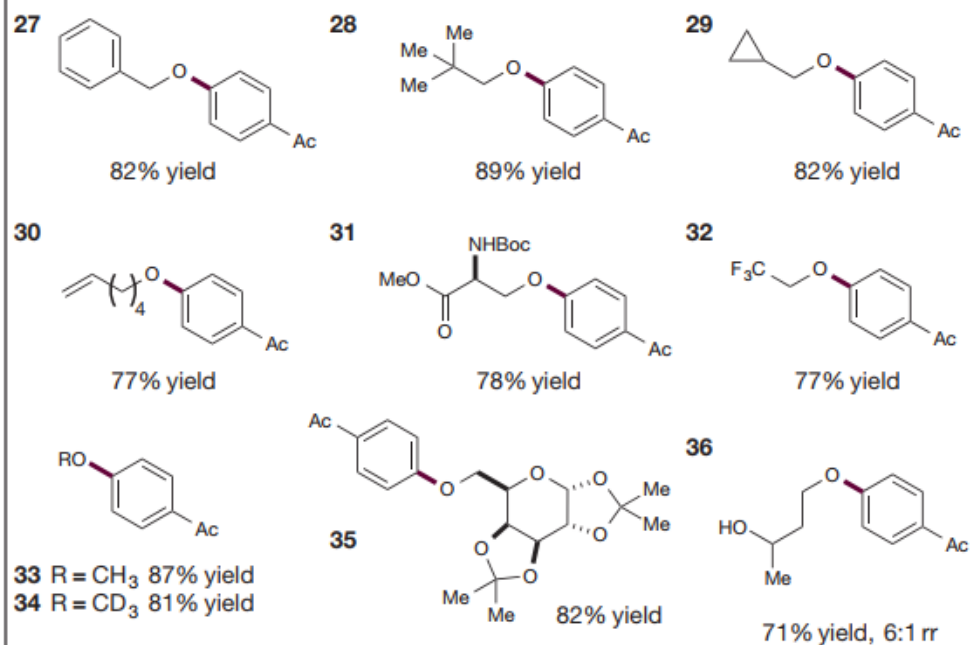
Catalyst combination



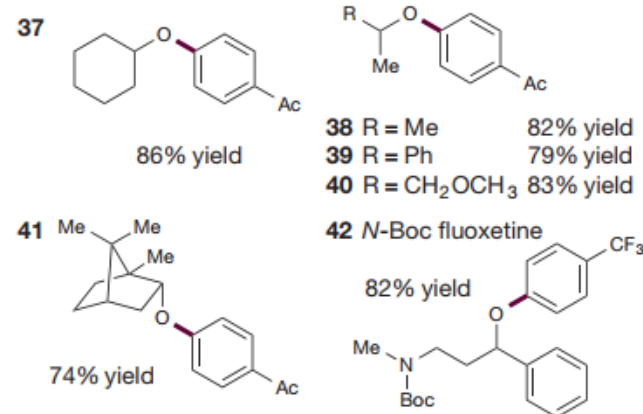
## Aryl bromides



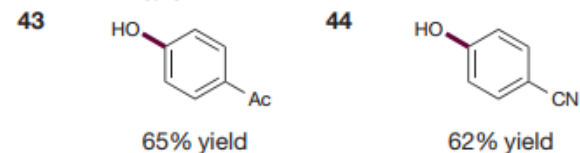
## Primary alcohols



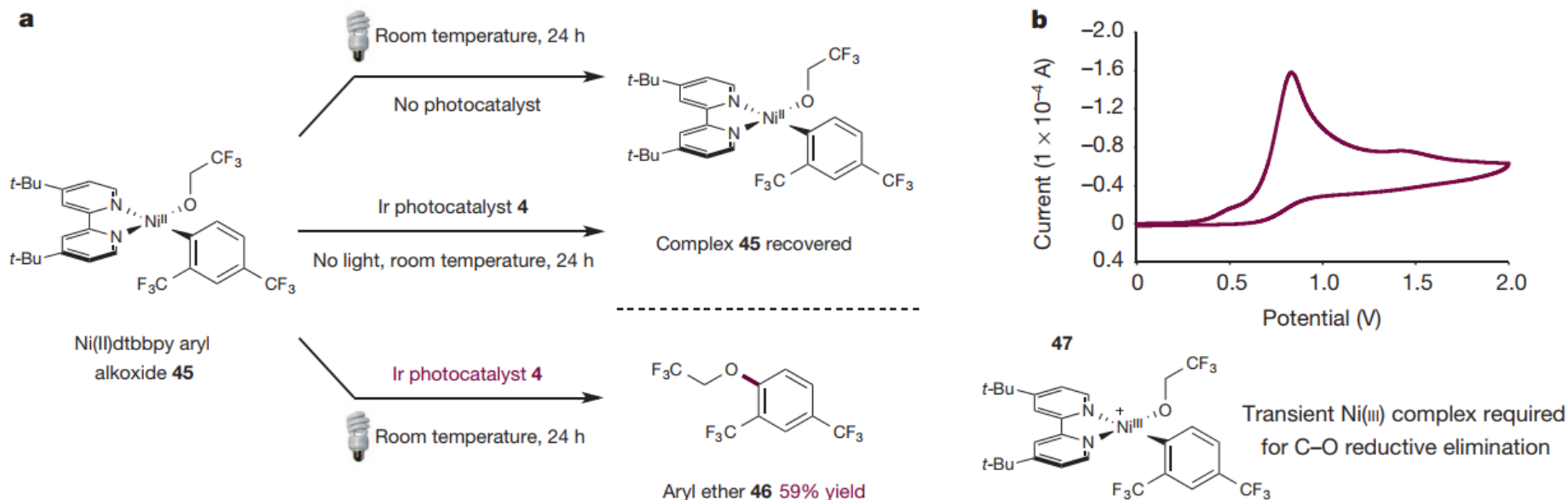
## Secondary alcohols



## Water



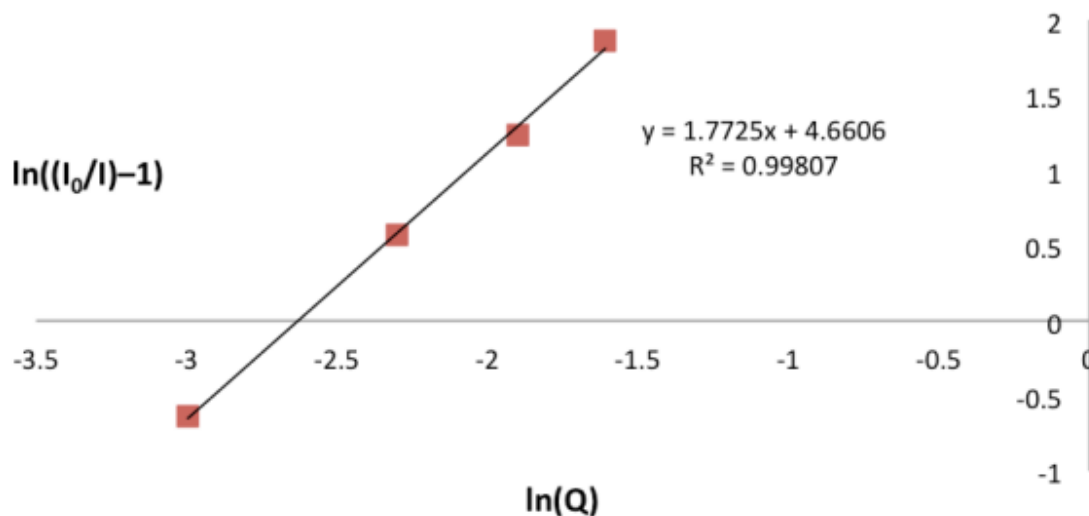
# Mechanistic studies



**Figure 4 | Mechanistic studies support the intermediacy of transient Ni(III) complex to enable C–O reductive elimination.** **a**, Reductive elimination to form C–O bond only occurs in the presence of photocatalyst and light. Reactions performed on 5.55  $\mu\text{mol}$  scale with 41 mol% photocatalyst **1** and blue

LEDs. See Supplementary Information for experimental details. **b**, Cyclic voltammogram of **45** shows Ni<sup>III</sup>/Ni<sup>II</sup> couple at **+0.83 V versus SCE in CH<sub>3</sub>CN** with 0.1 M tetrabutylammonium hexafluorophosphate as the supporting electrolyte at 100  $\text{mV s}^{-1}$ .

## Emission Quenching of \*Ir(III) by Ni Complex 45

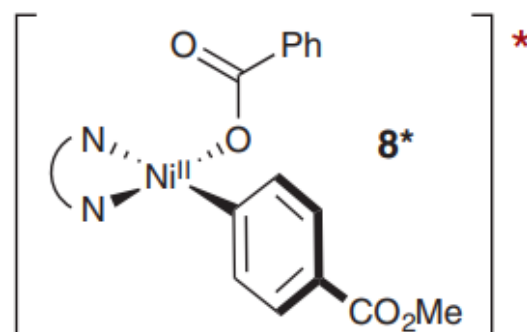
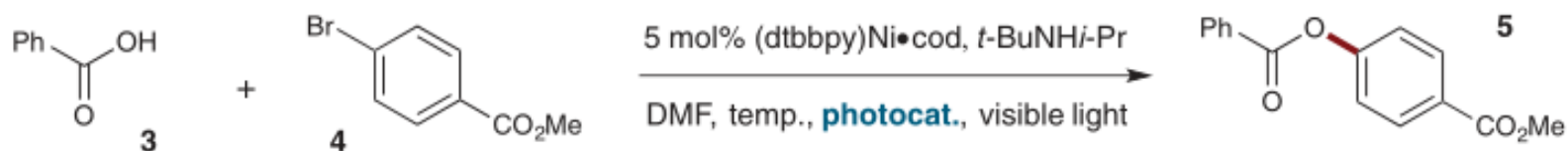


$$E1/2\text{red}[*\text{IrIII}/\text{IrII}] = +1.21 \text{ V vs SCE in CH}_3\text{CN}$$

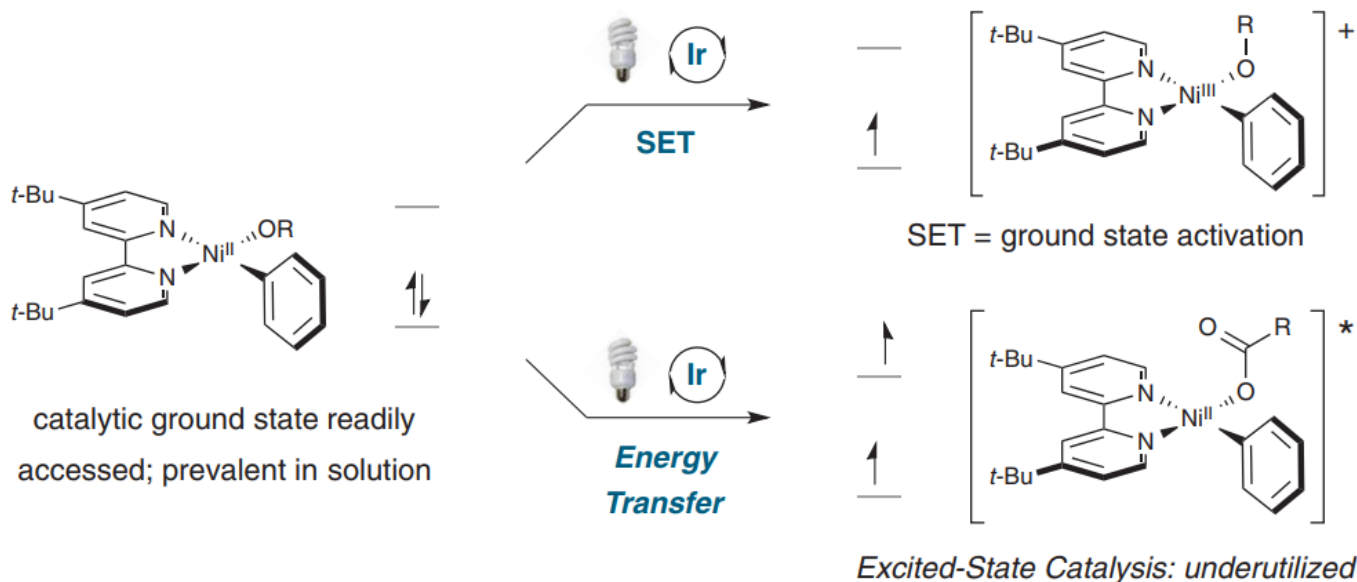
- 荧光猝灭实验证明：当NiIII络合物**45**浓度升高时，\*IrIII的发射强度降低。
- 三氟乙醇、4,4'-二叔丁基-2,2'-联吡啶和奎宁环做荧光猝灭实验，排除这些物质的影响。

# Photosensitized, energy transfer-mediated organometallic catalysis through electronically excited nickel(II)

Eric R. Welin,<sup>1</sup> Chip Le,<sup>1</sup> Daniela M. Arias-Rotondo,<sup>2</sup>  
James K. McCusker,<sup>2\*</sup> David W. C. MacMillan<sup>1\*</sup>



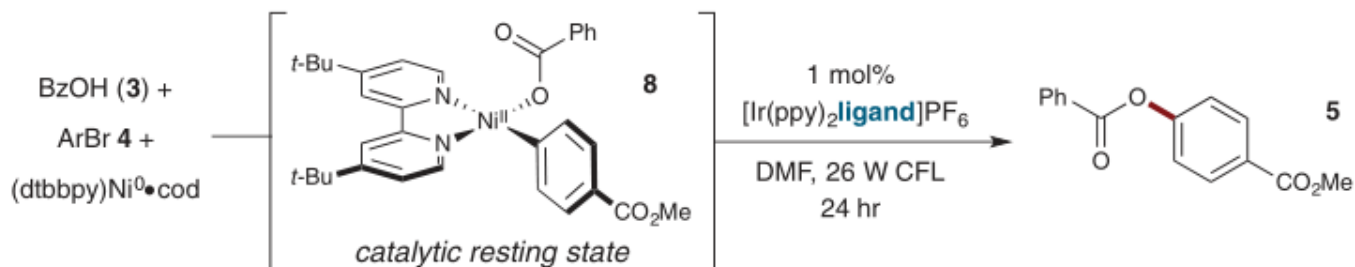




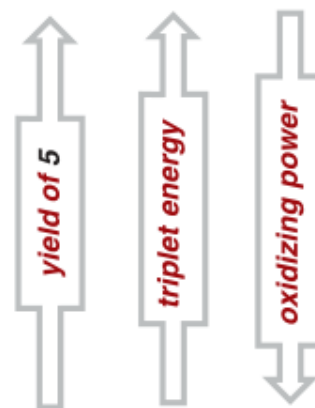
光催化剂能诱导产生Ni<sup>II</sup>激发态以实现催化偶联吗？



**C** Reactivity of arynickel(II) carboxylate is strongly dependent on photocatalyst  $E_T$



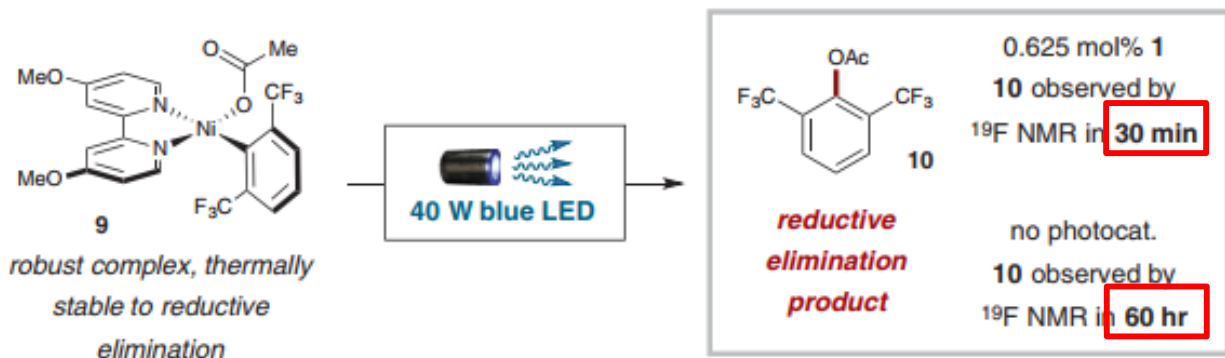
ligand	yield 5	$E_T$ (kcal)	$E_{1/2}^{II/III^*}$ (V)	$E_{1/2}^{III/IV}$ (V)
ppy (1)	85%	53.6	0.13	0.77
5,5'-Me <sub>2</sub> bpy	80%	49.0	0.61	1.26
4,4'-(MeO) <sub>2</sub> bpy	70%	47.7	0.58	1.22
4,4'-Me <sub>2</sub> bpy	65%	47.6	0.59	1.25
bpy	50%	46.3	0.61	1.28
4,4'-Cl <sub>2</sub> bpy	3%	42.6	0.72	1.32
4,4'-(CO <sub>2</sub> Me) <sub>2</sub> bpy	0%	39.7	0.70	1.34
4,4'-(F <sub>3</sub> C) <sub>2</sub> bpy	0%	39.2	0.74	1.37



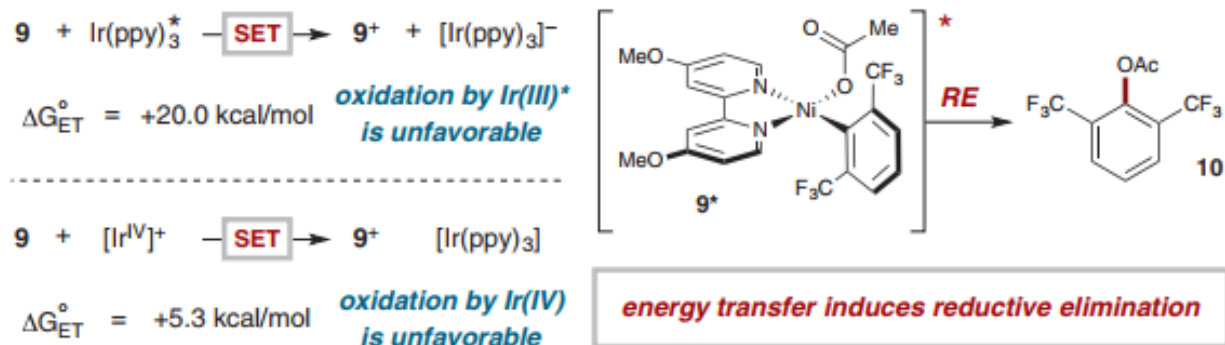
- 光催化剂三重态能量与产率正相关；
- 光催化剂三重态氧化能力与产率负相关。

# Mechanism studies

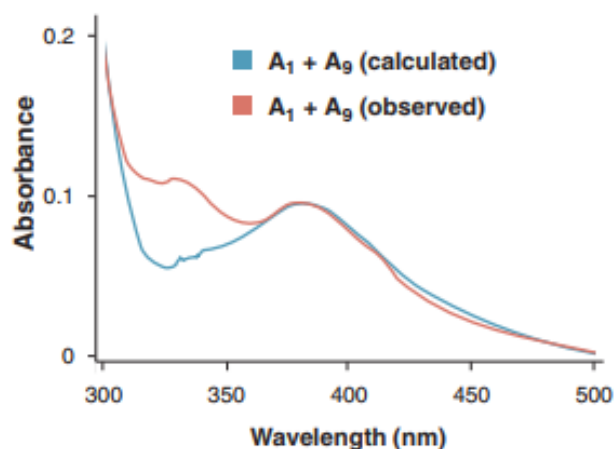
## A Stoichiometric studies with arylnickel(II) acetate complex 9



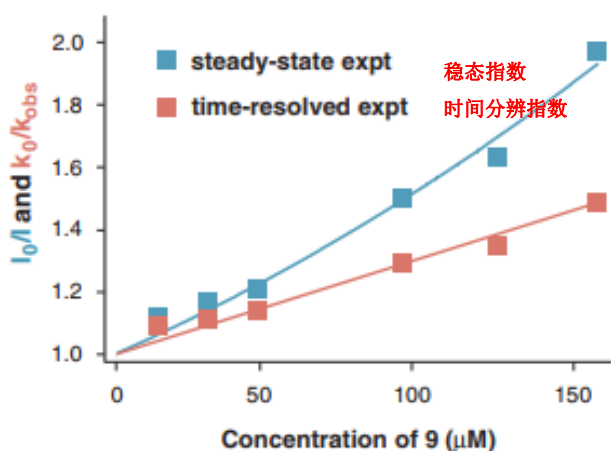
## B Determining the likelihood of a redox pathway



## C UV-Visible Spectrum (5:1 Ni:Ir)



## D Stern-Volmer Quenching Study



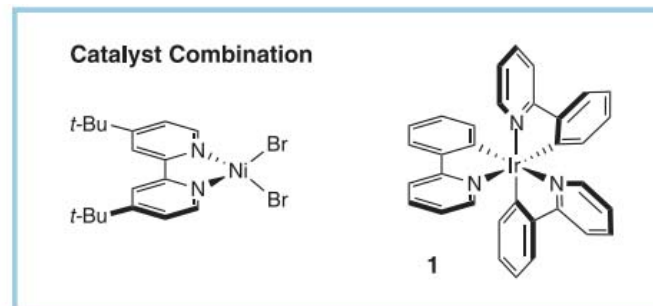
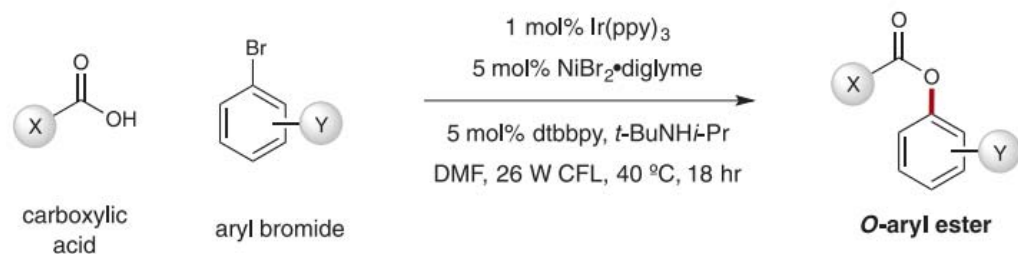
延长反应时间和升高温度，也可获得TM，但效率非常低。单纯光照效率低下，通过光催化剂介导的能量传递可产生大量的激发态Ni<sup>II</sup>物种。

Ir<sup>III</sup>\*和Ir<sup>IV</sup>通过SET氧化Ni<sup>II</sup>在热力学上是不利的。

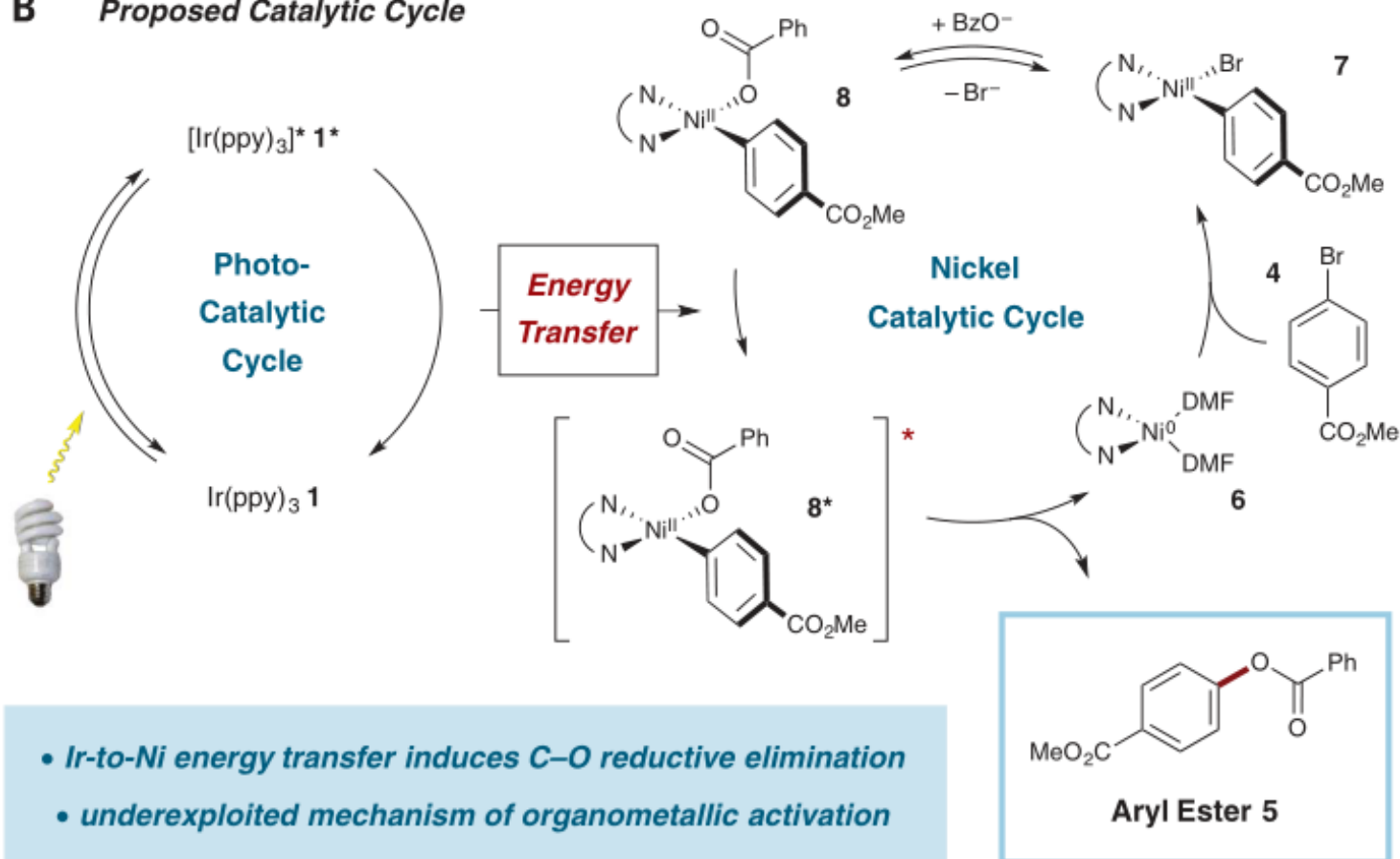
紫外吸收光谱在 330 nm 附近出现了吸收特征，这表明溶液中两种物质之间存在关联。

淬灭实验研究显示静态和动态淬灭的证据。

# Proposed mechanism



## B Proposed Catalytic Cycle



J. Am. Chem. Soc. 2020,  
142, 4555–4559

结论：还原消除机制是一个单分子过程，发生在Ni<sup>II</sup>络合物的长寿命激发态上

**Photocatalysis** Hot Paper

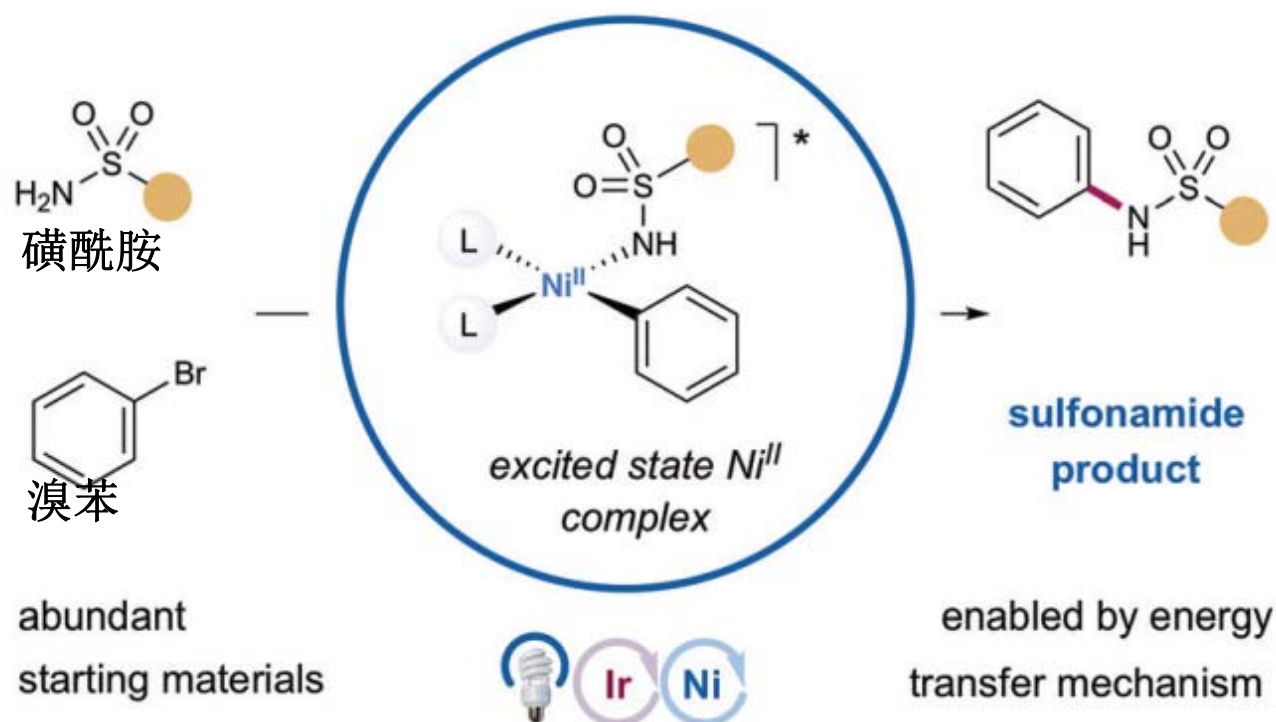
International Edition: DOI: 10.1002/anie.201800699

German Edition: DOI: 10.1002/ange.201800699

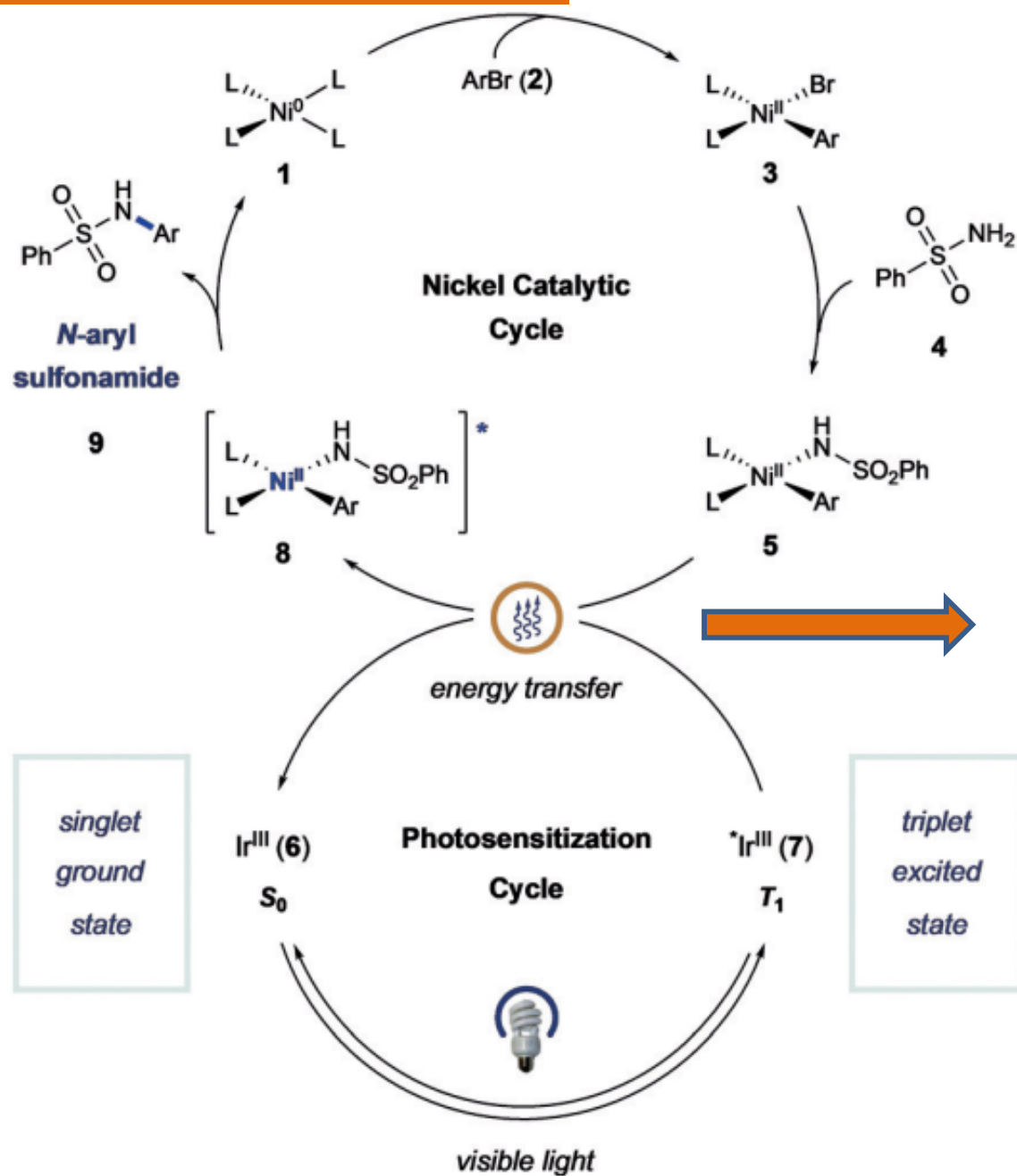
# Sulfonamidation of Aryl and Heteroaryl Halides through Photosensitized Nickel Catalysis

Angew. Chem. Int. Ed. 2018, 57, 3488–3492

Taehoon Kim<sup>+</sup>, Stefan J. McCarver<sup>+</sup>, Chulbom Lee, and David W. C. MacMillan\*



# Proposed mechanism



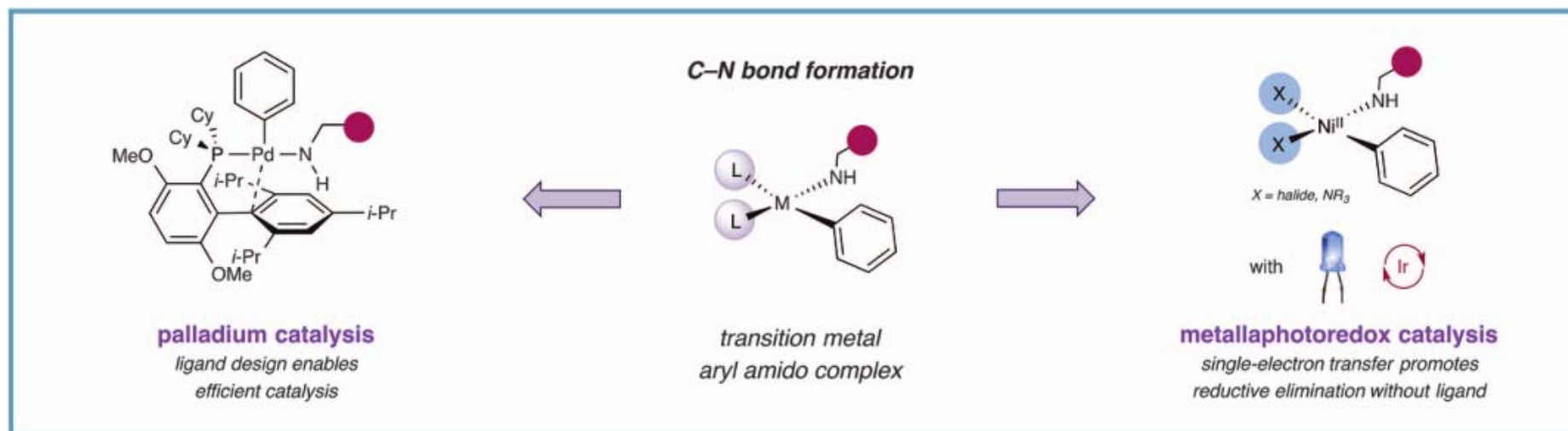
Mechanism studies:

Energy-transfer

Not SET

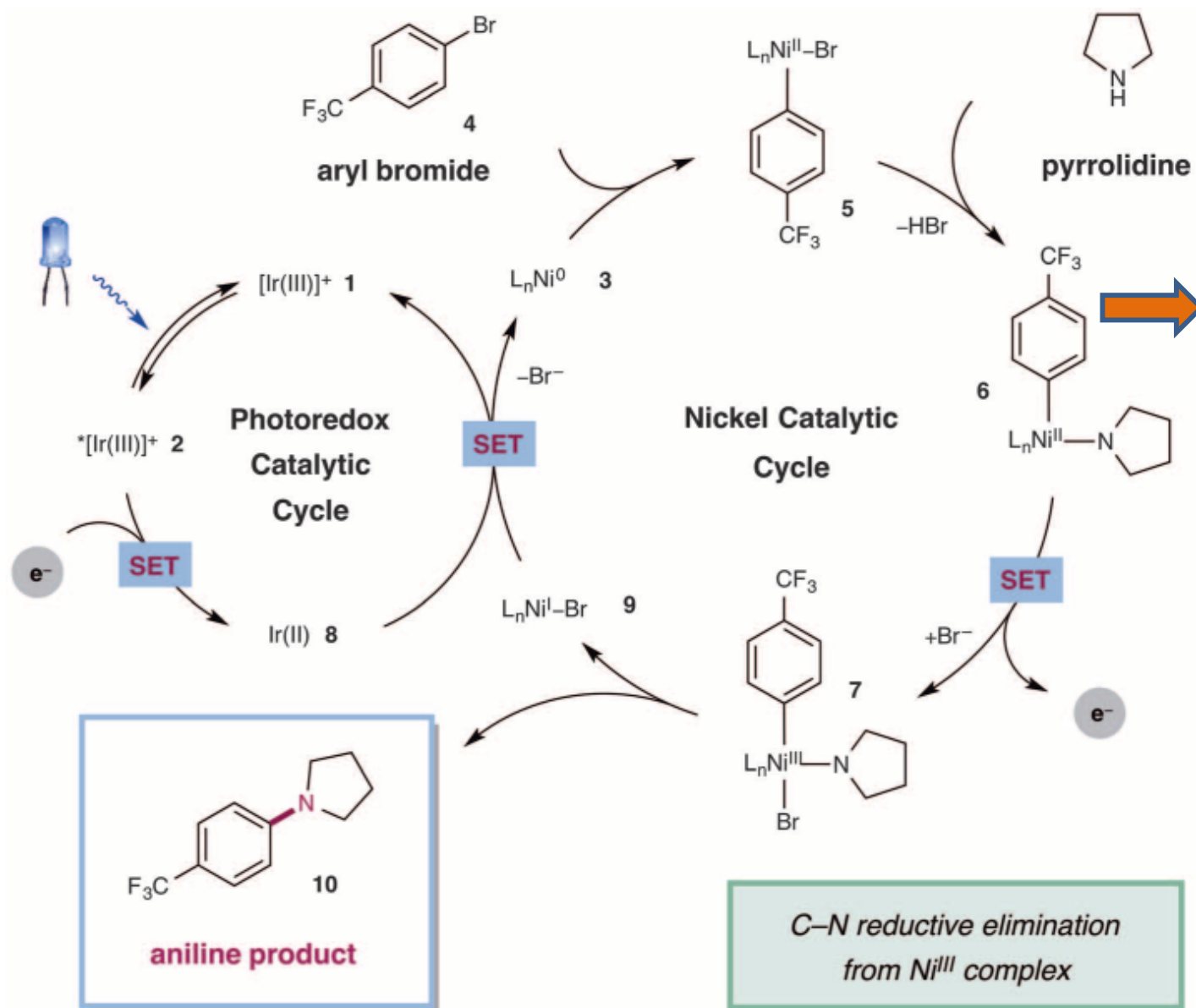
# Aryl amination using **ligand-free Ni(II)** salts and photoredox catalysis

Emily B. Corcoran,<sup>1</sup> Michael T. Pirnot,<sup>2</sup> Shishi Lin,<sup>3</sup> Spencer D. Dreher,<sup>3</sup>  
Daniel A. DiRocco,<sup>3</sup> Ian W. Davies,<sup>3</sup> Stephen L. Buchwald,<sup>2\*</sup> David W. C. MacMillan<sup>1\*</sup>



配体是一把双刃剑：一方面可调控反应的发生，另一方面降低反应的普适性。

# Proposed mechanism



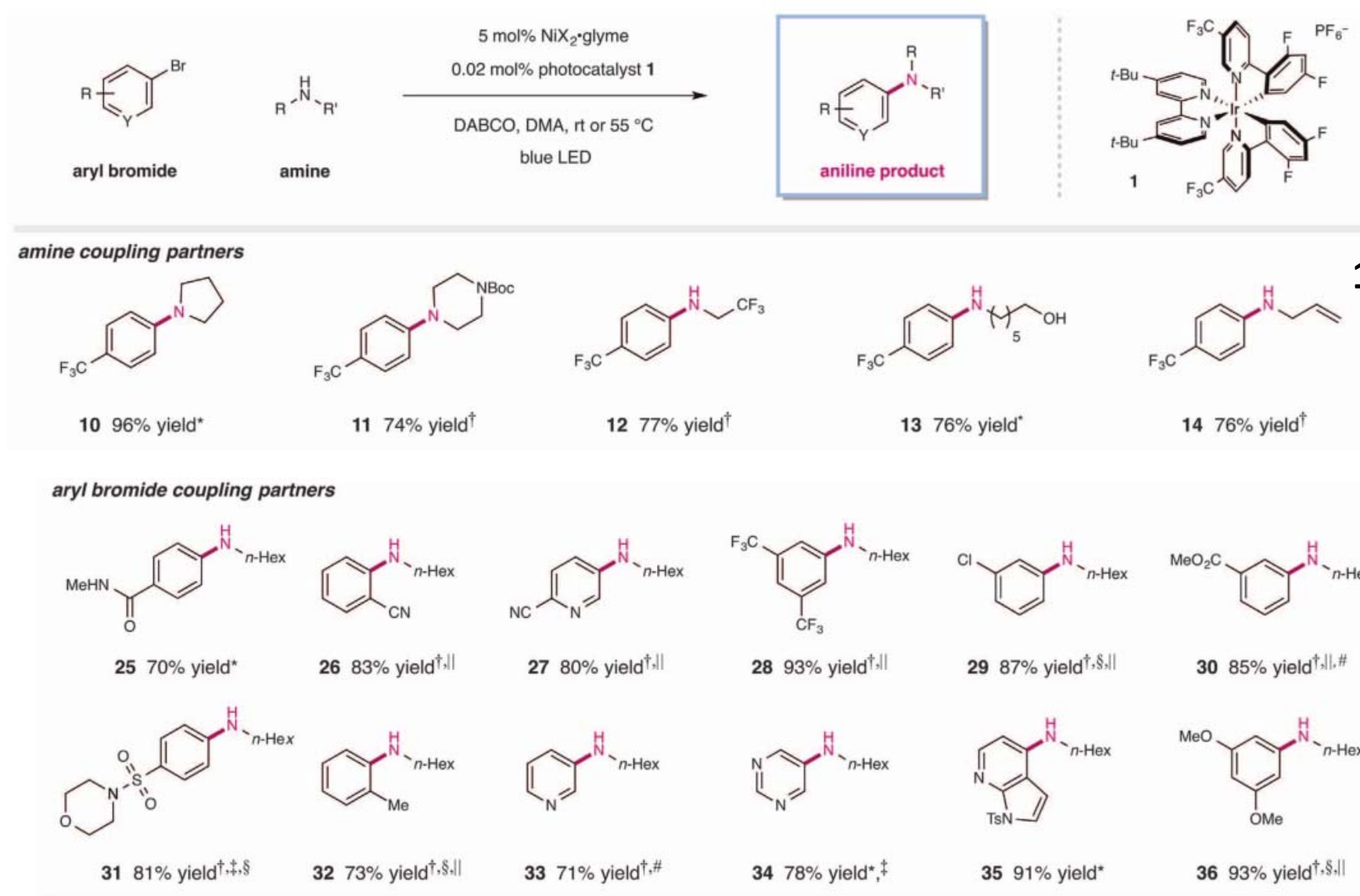
配体交换随后脱质子化

With ligand: 72% yield  
No ligand: 96% yield

J. Am. Chem. Soc. 2020,  
142, 15830-15841

结论：光催化在Ni<sup>I</sup>和Ni<sup>III</sup>  
中间体产生过程中起到关键作用。

# Scope of substrates



**DABCO**  
1,4-二氮杂二环

**Fig. 3. Metallaphotoredox-catalyzed amination: amine and arene scope.** For each entry number (in bold), data are reported as percent isolated yield. R: H, alkyl, or aryl substrate; Y: C, CH, or N; X: Cl or Br; DABCO: 1,4-diazabicyclo[2.2.2]octane; DMA, *N,N*-dimethylacetamide; rt, room temperature; LED: light-emitting diode; Me: methyl; *n*-pent: *n*-pentyl; Boc: *tert*-butoxycarbonyl. \*Run at ambient temperature. <sup>†</sup>Reaction heated to 55°C. <sup>‡</sup>DMSO (dimethyl sulfoxide) used as solvent. <sup>§</sup>MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) used as base. <sup>||</sup>0.002 mol % **1** used. <sup>¶</sup>10 mol % pyrrolidine included. <sup>#</sup>See supplementary materials for details.



# Metallaphotoredox aryl and alkyl radiomethylation for PET ligand discovery

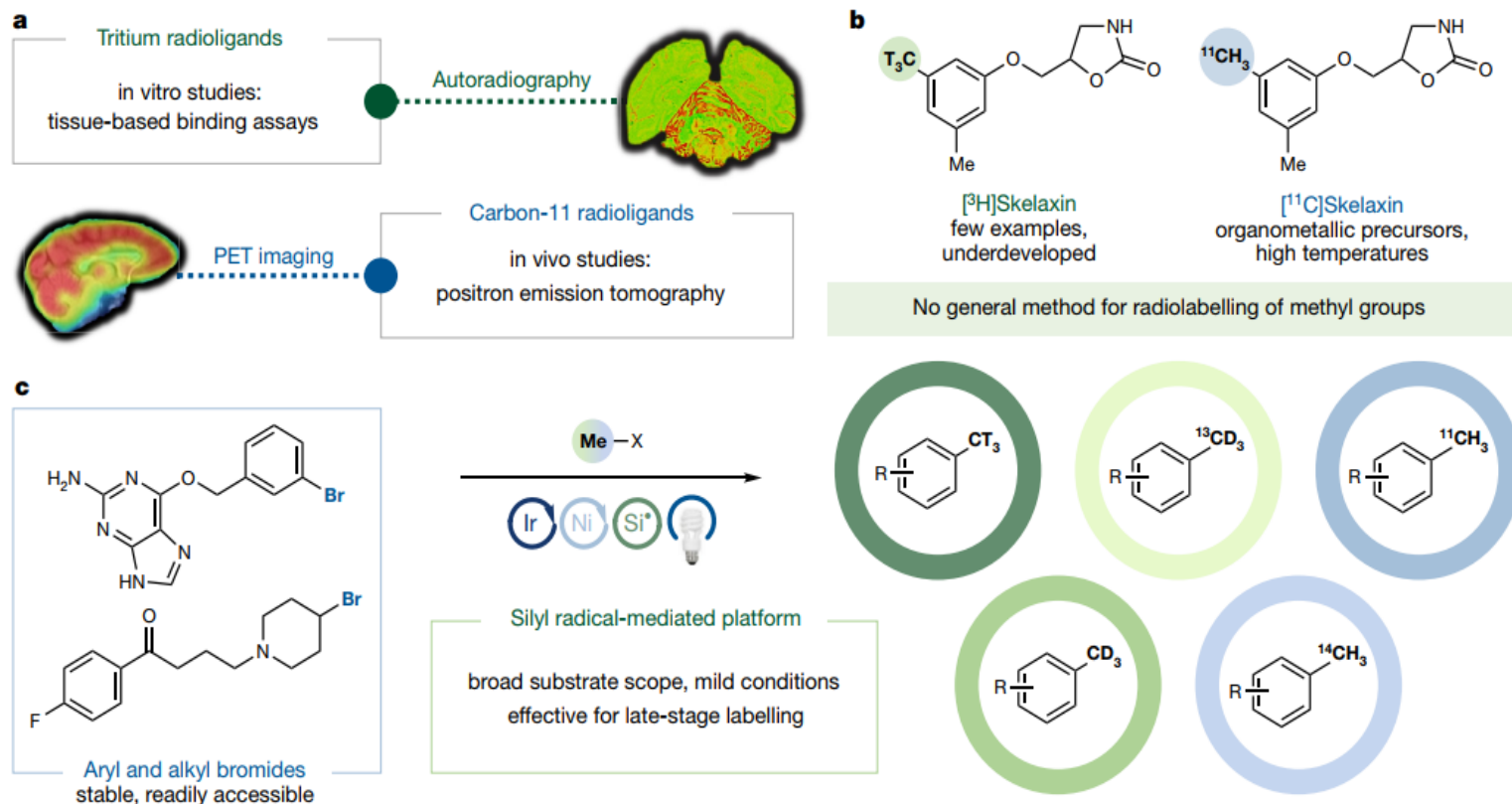
Nature 2021, 589, 542–547

<https://doi.org/10.1038/s41586-020-3015-0>

Received: 29 July 2020

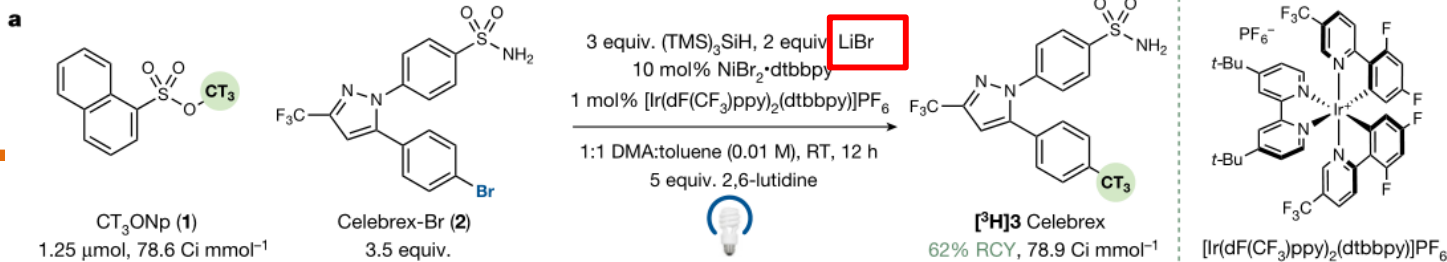
Accepted: 18 November 2020

Robert W. Pipal<sup>1</sup>, Kenneth T. Stout<sup>1</sup>, Patricia Z. Musacchio<sup>1</sup>, Sumei Ren<sup>2</sup>, Thomas J. A. Graham<sup>3</sup>, Stefan Verhoog<sup>4</sup>, Liza Gantert<sup>4</sup>, Talakad G. Lohith<sup>4</sup>, Alexander Schmitz<sup>3</sup>, Hsiaoju S. Lee<sup>3</sup>, David Hesk<sup>2,5</sup>, Eric D. Hostetler<sup>4</sup>, Ian W. Davies<sup>1</sup> & David W. C. MacMillan<sup>1</sup>✉

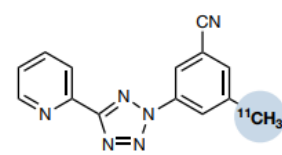
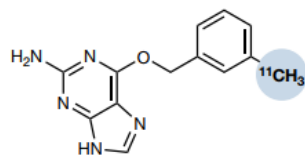
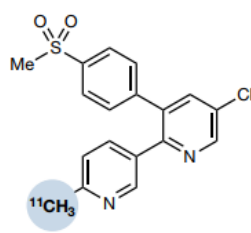
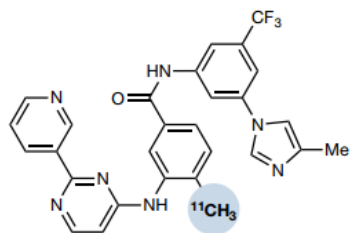
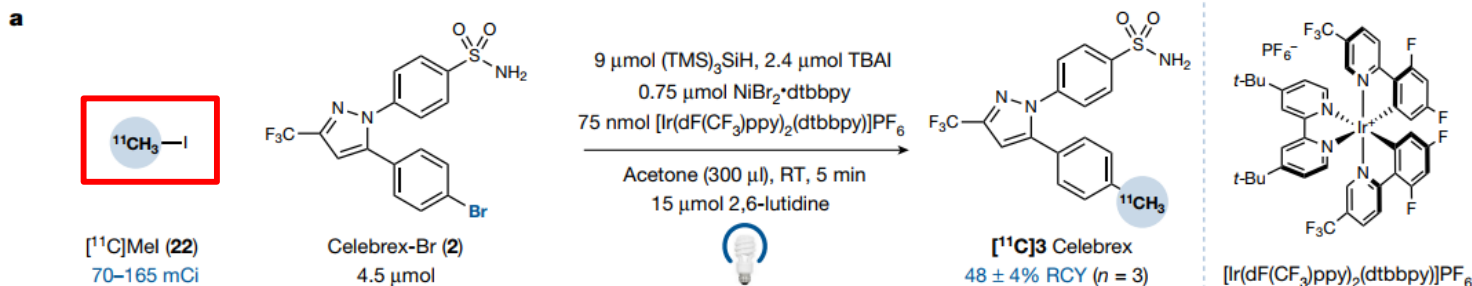
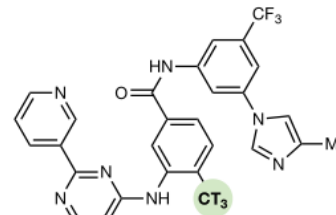
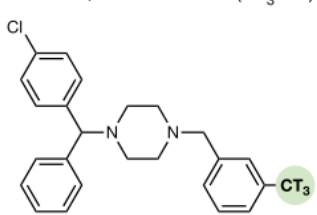
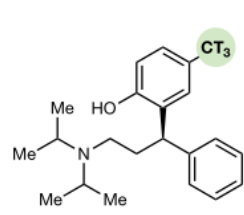
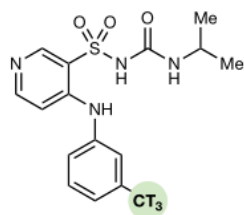
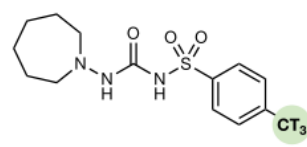
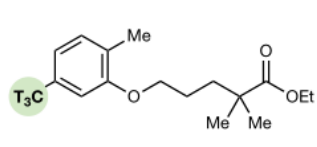
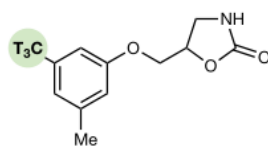
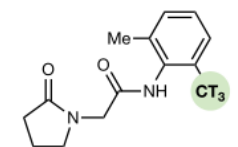


正电子发射断层扫描（PET）放射性配体（放射性标记的示踪化合物）对于中枢神经系统候选药物、神经退行性疾病和许多肿瘤靶点的体内表征非常有用。

本文通过硅自由基到产生甲基自由基策略，实现甲基化反应。应用于多种放射性配体的合成，标记元素包括碳-14、碳-13、碳-11、氘和氚。



## 甲基<sup>1</sup>-萘磺酸盐 (CT<sub>3</sub>ONp) 与溴化 锂原位生成溴甲烷



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Thanks!