



同濟大學  
TONGJI UNIVERSITY

# 双分子均裂取代 (SH2) 与自由基配体转移 (RLT) 作为自由基转化中的新兴反应

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时间：2026.05.17

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作者简介

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课题提出及初步尝试

03

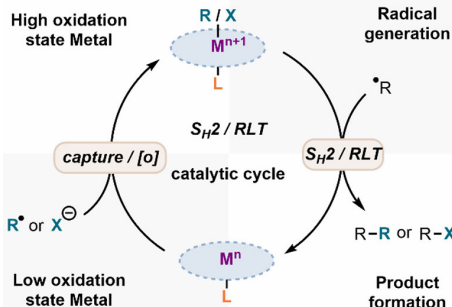
底物拓展

04

未来展望



# 1 S<sub>H</sub>2和RLT催化循环



## S<sub>H</sub>2 催化循环

- 1 起始状态: 低价金属配合物  $M^{(n)}$
- 2 自由基捕获:  $M^{(n)}$  捕获瞬态烷基自由基  $R^\bullet$  形成烷基金属中间体  $R-M^{(n+1)}$
- 3 SH2 反应: 烷基金属中间体与持久自由基伴侣  $R'$  进行双分子均裂取代
- 4 产物形成: 生成 C-C 键偶联产物  $R-R'$ , 金属回到  $M^{(n)}$  状态
- ★ 关键特征: 通过自由基分选实现选择性偶联

## RLT 催化循环

- 1 起始状态: 高价金属配合物  $M^{(n+1)}-X$ ,  $X$  为可转移配体
- 2 配体转移:  $M^{(n+1)}-X$  与烷基自由基  $R^\bullet$  反应,  $X$  直接转移到  $R^\bullet$
- 3 过渡态: 在  $X$  原子处的均裂取代, 异步协同离子-电子转移 cIET
- 4 产物形成: 生成 C-X 键产物  $R-X$ , 金属被还原为  $M^{(n)}$
- Ⓒ 金属再氧化:  $M^{(n)}$  经氧化和配体配位回到  $M^{(n+1)}-X$  完成循环

## 2.1 RLT (Radical Ligand Transfer, 自由基配体转移)

RLT: 一个杂原子配体 ( $X^-$ ) 从氧化还原活性的金属中心 ( $M^{n+1}-X$ ) 直接转移到一个烷基自由基 ( $R\cdot$ ) 上, 形成新的 C-X 键, 同时金属被还原为低价态  $M^n$ 。该过程也称为 **氧化性配体转移 (OLT)**

## 关键研究发现

## 1 首次报道 (Kochi group)

杂原子配体直接从氧化活性金属中心  $M^{(n+1)}-X$  转移到烷基自由基  $R\cdot$ 。

## 2 过渡态特征

在 X 原子处的均裂取代, 形成新的 C-X 键, 同时生成还原态金属  $M^{(n)}$ 。

## 3 异步协同的离子-电子转移 (CIET) 框架 (Srnc group等)

计算研究揭示 RLT 步骤通过异步协同离子-电子转移进行, 电子转移与离子转移在单一过渡态中同时发生。

## 4 Groves group 实验验证

氟和氯自由基转移最好描述为从底物自由基到铁的异步电子转移, 随后在同一过渡态中晚期配体转移到底物。

## 5 配体选择性

配体身份而非其在配合物上的配位位点优先决定 RLT 选择性, 氧化态和配体支架影响 RLT 行为。

**电子转移 (ET)**: 从烷基自由基转移到金属中心。  
**离子转移 (IT)**: 配体  $X^-$  从金属转移到自由基碳  
这两个事件在同一个过渡态中发生, 但并不同步。

CIET mechanism



"Radical Ligand Transfer"

"Radical Rebound"

"Oxidative Ligand Transfer"

## 1. RLT定义与机制

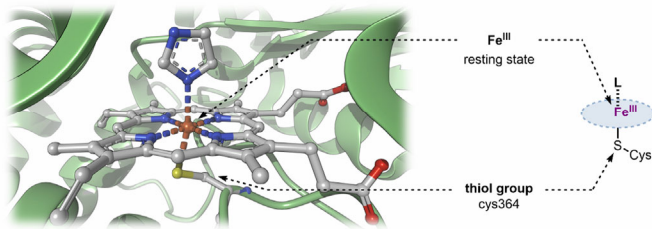
### 2.1.1 细胞色素 P450 的 HAT – 自由基回弹机制

 自然原型：细胞色素 P450 是 RLT 机制的生物原型。

 活性物种：高价  $\text{Fe(IV)=O}$  物种 (Cpd-I) 执行 HAT。

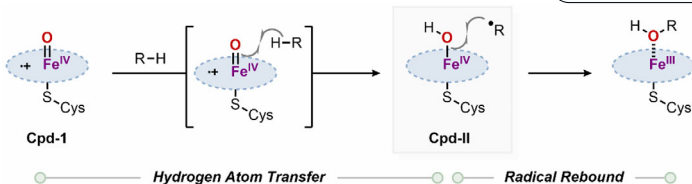
 中间体生成：生成  $\text{Fe(IV)-OH}$  (Cpd-II) 和烷基自由基。

 反弹步骤：羟基配体快速反弹生成羟基化产物。



 理论支持：Groves 最初提出自由基反弹机制，Shaik 等人开发双态反应性 (TSR) 原理提供理论支持。

 动力学模拟：Houk 和 Ess 的分子动力学模拟阐明了自由基对中间体在自由基反弹之前的多种可能。



## 2.2 S<sub>H</sub>2 (Bimolecular Homolytic Substitution) 双分子均裂取代

S<sub>H</sub>2: 低氧化态金属捕获一个自由基, 与另一个自由基发生均裂取代, 形成 C-C 键

特点: 两个自由基同时存在时, 金属优先结合亲核性、体积较小的烷基自由基(如一级烷基自由基)。

第二个自由基通常是亲电性、持久性自由基(如三级烷基自由基)。

### *Backside homolytic substitution*



"S<sub>H</sub>2"

"Bimolecular  
homolytic substitution"

#### 命名来源

Eliel 首次提出 S<sub>H</sub>2。类似于 Ingold' s S<sub>N</sub>2 的分类。

#### 反应特征

直接、协同的均裂取代反应, 伴随 Walden 反转

#### 实验支持

烷基钴配合物与自由基反应时观察到构型完全反转

#### MacMillan 创新

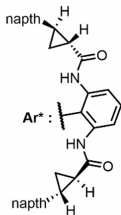
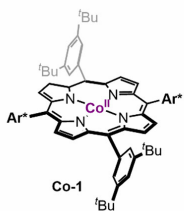
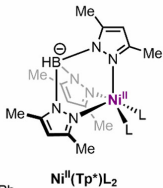
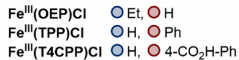
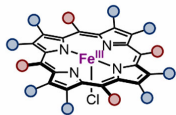
利用低价金属 (Fe(II) 和 Ni(II)) 捕获和稳定烷基自由基, 类似维生素 B12 钴胺素配合物

#### 应用突破

通过关键 S<sub>H</sub>2 步骤实现空间拥挤的季碳中心构建, 为创新交叉偶联奠定基础



## 3 $S_H2$ 催化策略关键和应用

3.1 关键的金属催化剂(S<sub>H</sub>2)**Fe 卟啉配合物 Fe(OEP)Cl**

MacMillan 团队 2021 年报告, 用于光氧化还原和铁介导的 S<sub>H</sub>2 催化交叉偶联, 生成烷基 Fe 中间体进行 S<sub>H</sub>2 反应。

**Ni 螯型配合物**

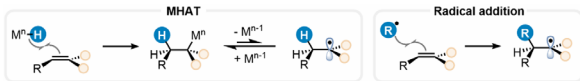
MacMillan 团队将其用于双脱羧交叉偶联反应和介导叔烷基和伯烷基溴化物等的交叉偶联策略。

**Co 卟啉配合物 Co-1**

Zhang 团队用于桥接 S<sub>H</sub>2 和金属自由基催化, 实现对映选择性环丙烷化, 通过 Co-卡宾自由基中间体进行分子内 S<sub>H</sub>2 步骤。

- 1, 低氧化态金属能够通过“金属中心捕获”机制与自由基结合, 形成相对稳定的金属-烷基中间体
- 2, 配体环境(如大环卟啉或螯型多齿氮配体)对金属的电子和立体环境有强烈调控作用
- 3, 它们在SH2步骤中能够与另一个持久性自由基发生双分子均裂取代, 实现选择性的C-C偶联

### 3.1.1 S<sub>H</sub>2催化协同使用的关键策略



#### 自由基分选 (Radical Sorting)

基于自由基性质差异 (亲电/亲核性) 进行选择反应的通用逻辑。



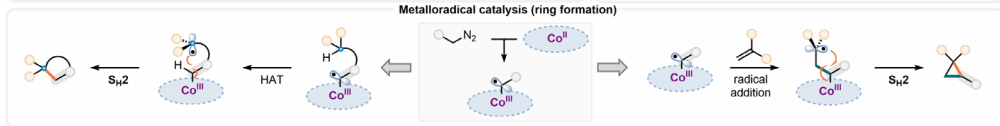
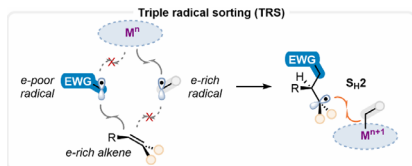
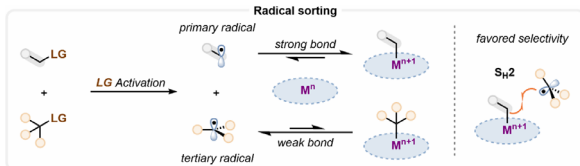
#### 三重自由基分选 (TRS)

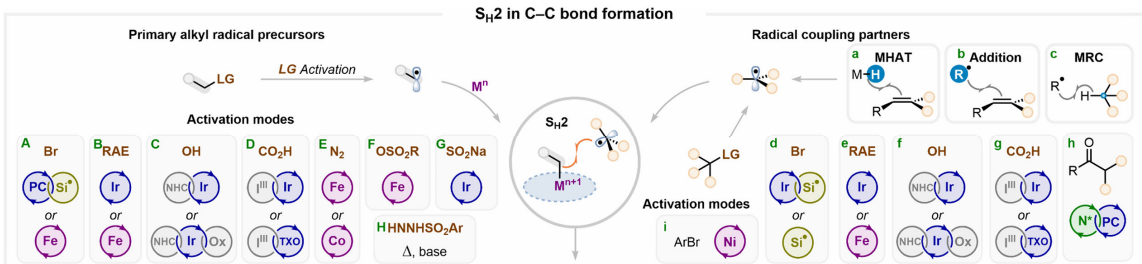
分选的级联应用, 通过三步不同性质的自由基, 将三种组分有序组合, 构建复杂结构。

产生烷基自由基的方式

#### 金属自由基催化 (ring formation)

催化剂自身形成金属-烷基自由基, 通过分子内的S<sub>H</sub>2关环。



3.1.2 S<sub>H</sub>2协同催化构建C-C键

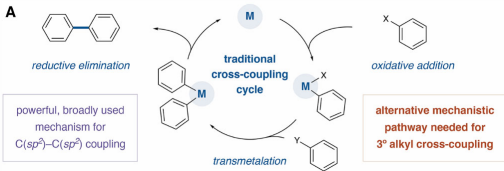
- 自由基来源广泛**: 它兼容来自RAE、醇、卤代物、烯烃、甚至简单羧酸的多种自由基前体。
- 金属催化剂多样**: 铁(卟啉)、镍(螯型)、钴(卟啉)等都能找到各自最优的反应模式。
- 策略高度协同**: 它极易与XAT、MHAT、光催化、有机催化甚至生物催化等策略整合, 形成强大的级联或协同催化体系。
- 选择性与能力卓越**: 从构建拥挤的季碳中心, 到实现高度的化学、区域、对映选择性, 再到复杂天然产物的后期修饰, S<sub>H</sub>2都展现了其作为C-C键构建核心工具。

### 3.2 铁催化的S<sub>H</sub>2构建C-C键

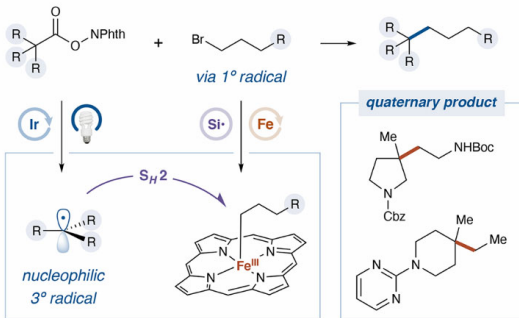
# A biomimetic S<sub>H</sub>2 cross-coupling mechanism for quaternary sp<sup>3</sup>-carbon formation

Wei Liu<sup>1†</sup>, Marissa N. Lavagnino<sup>1†</sup>, Colin A. Gould<sup>1</sup>, Jesús Alcázar<sup>2</sup>, David W. C. MacMillan<sup>1\*</sup>

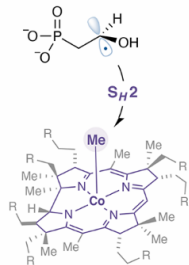
MacMillan, D. W. C. *Science* **2021**, 374, 1258.



**C** a biomimetic approach to C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross-coupling

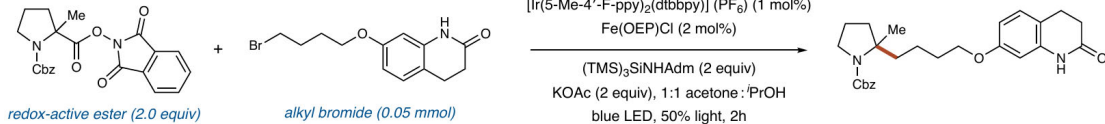


**B** biological methylation

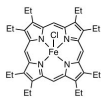
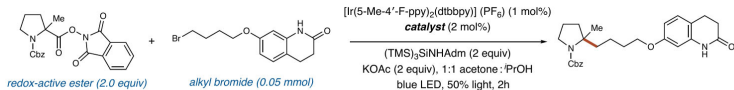


methylcobalamin

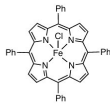
nature's free radical carrier



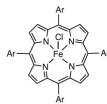
<i>Deviations</i>	<i>Yields</i>
none	86%
without [Fe]	13%
without KOAc	75%
without photocatalyst	0%
without aminosilane	0%
ambient light	0%



Fe(OEP)Cl  
86% yield

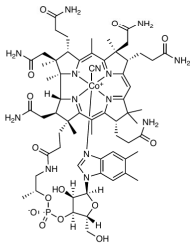


Fe(TPP)Cl  
6% yield

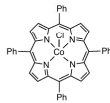


Fe(*p*-MeOTPP)Cl  
8% yield

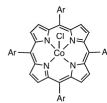
Ar:



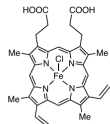
Vitamin B12  
7% yield



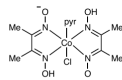
Co(TPP)Cl  
3% yield



Co(*p*-MeOTPP)Cl  
8% yield



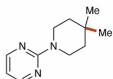
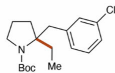
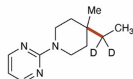
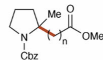
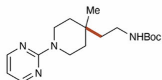
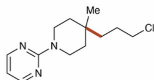
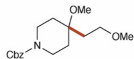
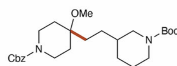
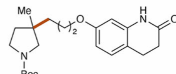
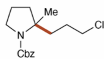
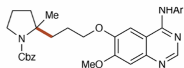
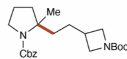
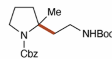
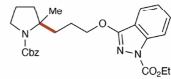
Fe(III) Protoporphyrin IX  
18% yield



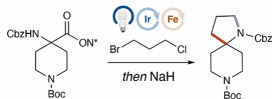
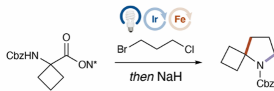
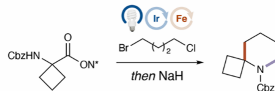
Chloro(pyridine)cobaloxime (III)  
3% yield

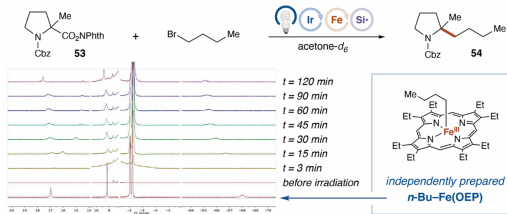
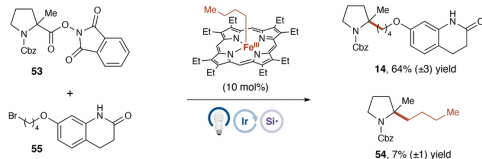
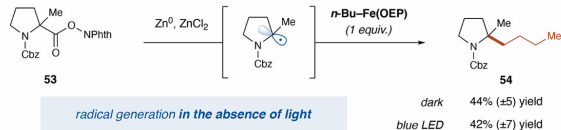
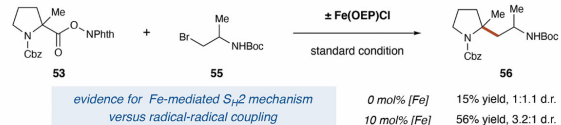


## alkyl bromides

(±)-**30**, 59% yield<sup>S,II</sup>**31**, 84% yield<sup>S,II</sup>(±)-**32**, 71% yield**33**, 63% yield(±)-**34**, n = 1, 33% yield(±)-**35**, n = 3, 76% yield**36**, 70% yield**37**, 52% yield<sup>‡</sup>**38**, 47% yield(±)-**39**, 74% yield(±)-**40**, 70% yield(±)-**41**, 75% yield(±)-**42**, 52% yield(±)-**43**, 65% yield<sup>II</sup>(±)-**44**, 68% yield(±)-**45**, 63% yield

## accelerated access to spirocyclic saturated heterocycles

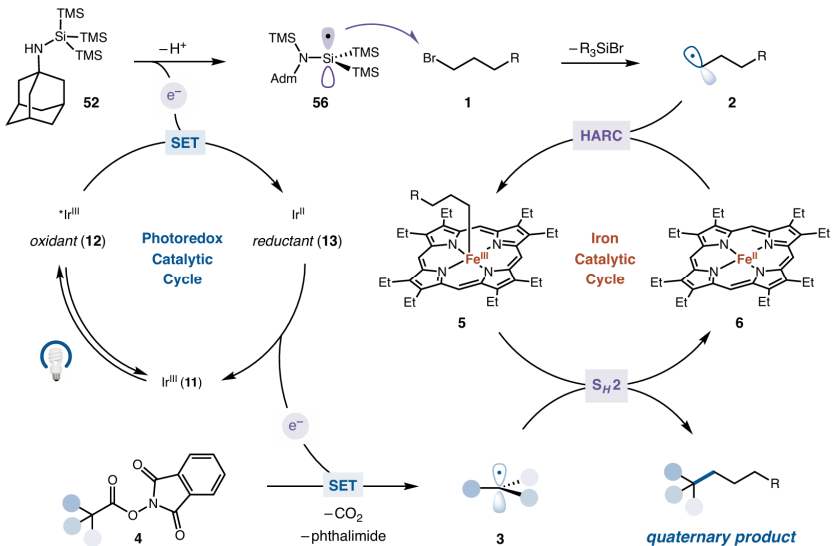
**46**, 66% yield **47**, 98% yield<sup>II</sup>**48**, 62% yield<sup>†</sup> **49**, 99% yield<sup>II</sup>**50**, 55% yield<sup>†</sup> **51**, 85% yield<sup>II</sup>

**A** — PhotoNMR experiment to directly observe *n*-Bu-Fe(OEP) complex in situ

**B** — Direct use of *n*-Bu-Fe(OEP) complex as precatalyst

**C** — Light is not required for C–C bond formation

**D** — Iron-dependent diastereoselectivity in C–C bond formation


## Slide 18

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**6h1** 66619 honey, 2026/5/13



## 铁催化的SH2

# Rapid and Modular Access to Quaternary Carbons from Tertiary Alcohols via Bimolecular Homolytic Substitution

Colin A. Gould, Andria L. Pace, and David. W. C. MacMillan\*



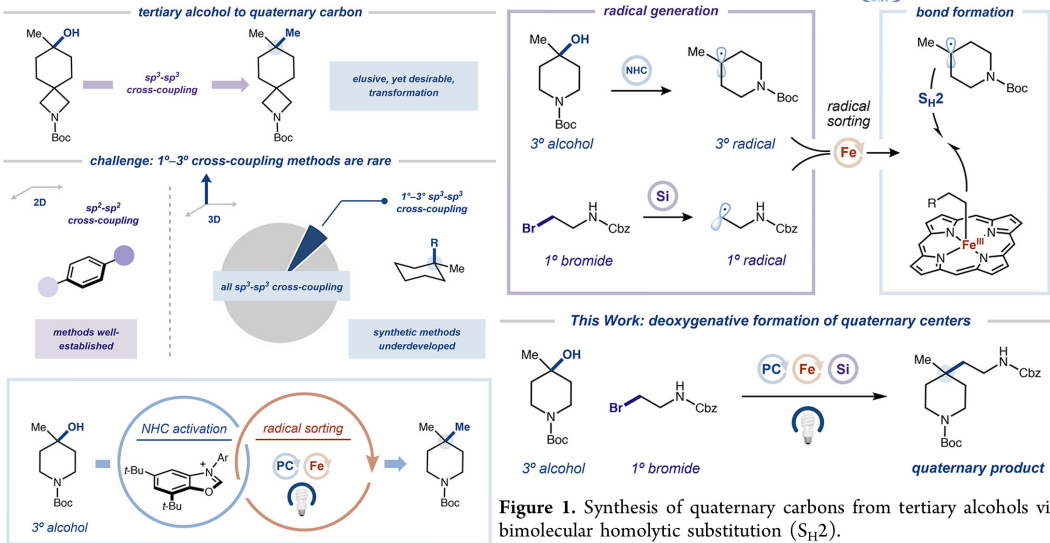
Cite This: *J. Am. Chem. Soc.* 2023, 145, 16330–16336



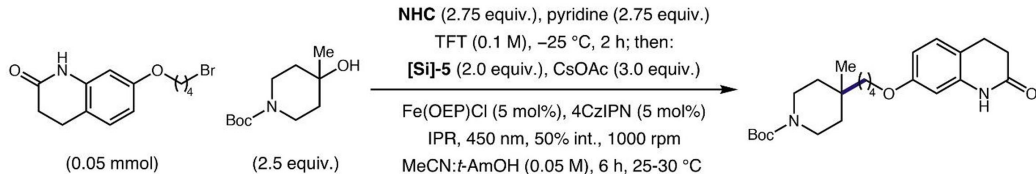
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通过双分子均裂取代从三级醇快速模块化构建季碳

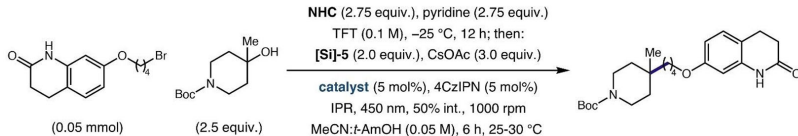
MacMillan, D. W. C., *J. Am. Chem. Soc.* **2023**, 145, 16330–16336.



**Figure 1.** Synthesis of quaternary carbons from tertiary alcohols via bimolecular homolytic substitution ( $S_H2$ ).



Changes from above	Yield*
none	<b>71%</b>
no Fe(OEP)Cl	<b>2%</b>
no 4CzIPN	-
no CsOAc	-
no silane	<b>6%</b>
no light	-



catalyst

Yield\*

Fe(OEP)Cl

72%

Fe(TPP)Cl

31%

Fe(Pc)

7%

Ni(acac)<sub>2</sub>

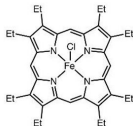
3%

Ni(TMHD)<sub>2</sub>

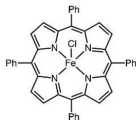
2%

Cu(TMHD)<sub>2</sub>

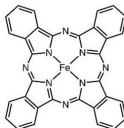
3%



Fe(OEP)Cl

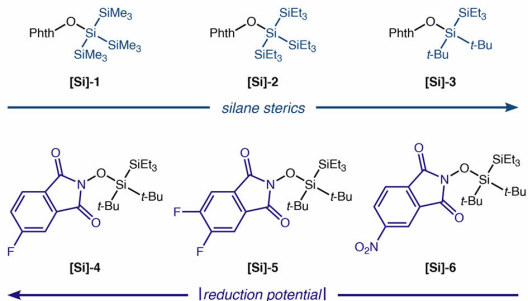
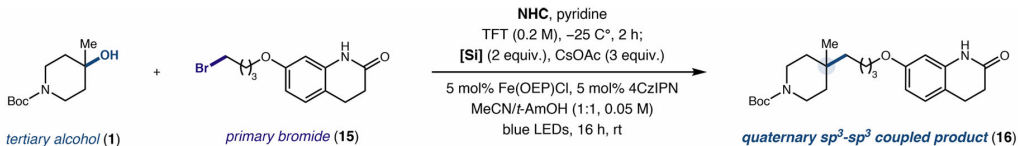


Fe(TPP)Cl

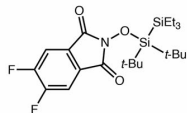


Fe(Pc)

Ni(acac)<sub>2</sub>Ni(TMHD)<sub>2</sub>Cu(TMHD)<sub>2</sub>



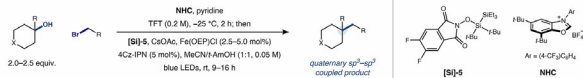
entry	silane reagent	yield
1	none	6%
2	[Si]-1	17%
3	[Si]-2	12%
4	[Si]-3	60%
5	[Si]-4	67%
6	[Si]-5	71%
7	[Si]-6	0%



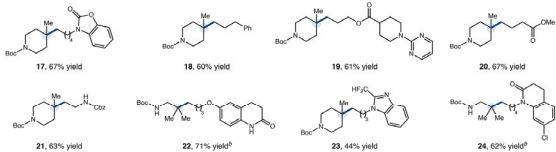
air-stable, crystalline solid

decagram-scale synthesis

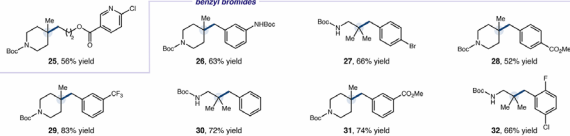
alkyl or aryl bromide activation



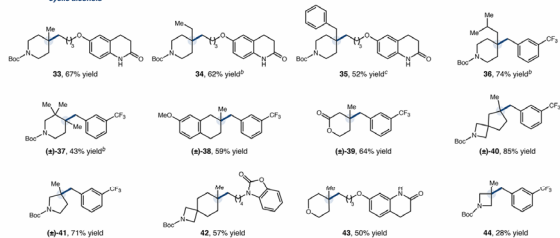
## alkyl bromides



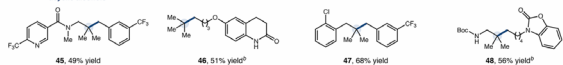
## benzyl bromides



## cyclic alcohols

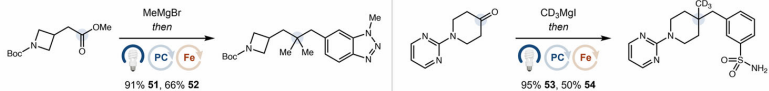
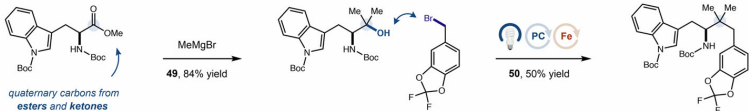


## acyclic alcohols



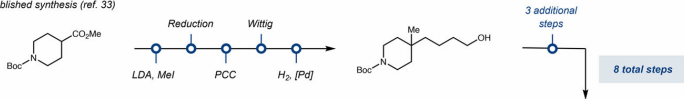
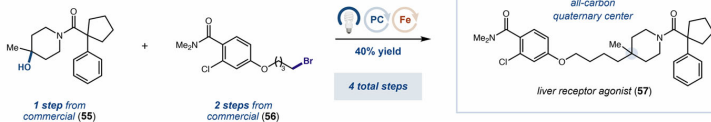
<sup>a</sup>Reactions were performed on a 0.5 mmol scale with alcohol (2.0–2.5 equiv), NHC (1.1 equiv, with respect to alcohol), pyridine (1.1 equiv, with respect to alcohol), TFT (0.2 M), 2 h, -25 °C; alkyl bromide (1.0 equiv), [Si]-5 (2.0 equiv, for alkyl bromides; 0.0 equiv, for benzyl bromides), CsOAc (2.5–3.0 equiv), 4CzIPN (5 mol %), Fe(OEP)Cl (2.5–5.0 mol %), 1:1 MeCN/*t*-AmOH (0.05 M), blue LEDs, 9–16 h. All yields are isolated. <sup>b</sup>3.0 equiv. alcohol. <sup>c</sup>3.5 equiv. alcohol. <sup>d</sup>4.0 equiv. alcohol.

## modular construction of all-carbon quaternary centers



## expedited synthesis of bioactive molecules

published synthesis (ref. 33)

*sp*<sup>3</sup>-*sp*<sup>3</sup> fragment coupling



镍催化的 $S_{H2}$ 

# Nickel Catalysis via $S_{H2}$ Homolytic Substitution: The Double Decarboxylative Cross-Coupling of Aliphatic Acids

Artem V. Tsymbal,<sup>†</sup> Lorenzo Delarue Bizzini,<sup>†</sup> and David W. C. MacMillan\*

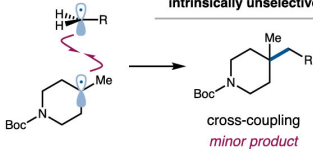
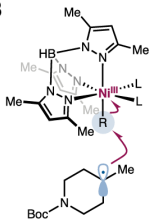


Cite This: *J. Am. Chem. Soc.* 2022, 144, 21278–21286

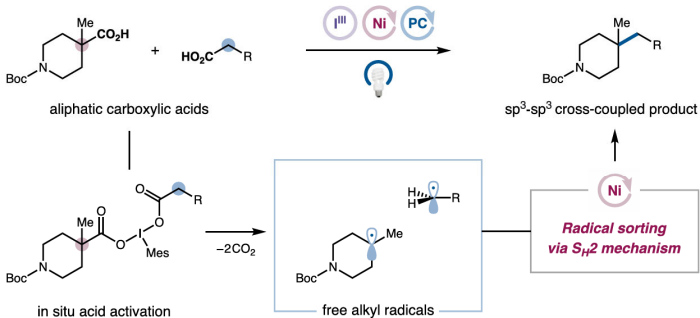


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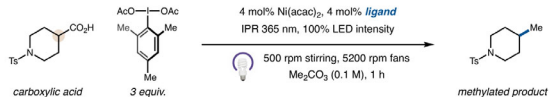
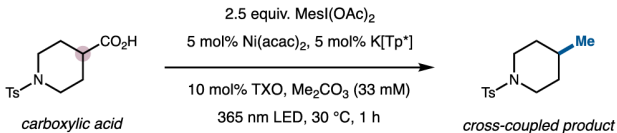
通过 $S_{H2}$ 自由基取代的镍催化：脂肪酸的双脱羧交叉偶联

**A** **Recombination of free radicals intrinsically unselective**

**B** **Homolytic S<sub>H</sub>2 substitution new catalysis mode**


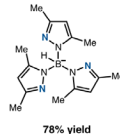
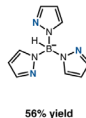
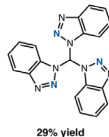
*Can S<sub>H</sub>2 at nickel enable catalytic cross-coupling of free radicals?*

**C** **Decarboxylative cross-coupling of aliphatic carboxylic acid – an elusive transformation**


■ mild conditions    ■ commercial reagents    ■ operationally simple    ■ > 50 examples



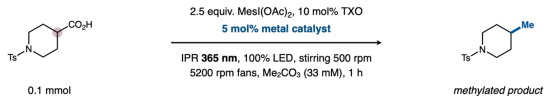
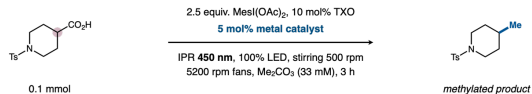
## Scorpionate ligands



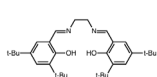
entry <sup>a</sup>	deviation	yield <sup>b</sup> (%)
--------------------	-----------	------------------------

1	none	85
2	no Ni(acac) <sub>2</sub> , no K[TP*]	37
3	no K[TP*]	51
4	no TXO	82
5	no light	0

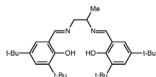
<sup>a</sup>0.1 mmol scale. <sup>b</sup>UPLC yields vs acetanilide as an internal standard. See the [Supporting Information](#) for further details. Ts, *para*-toluenesulfonyl.

Table S4. Evaluation of iron and cobalt S<sub>H</sub>2 catalysts under UV light protocol.Table S5. Evaluation of iron and cobalt S<sub>H</sub>2 catalysts under visible light protocol.

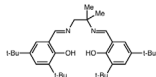
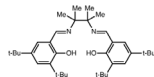
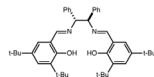
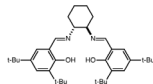
Entry	Metal catalyst	SM, %	AY, %	Entry	Metal catalyst	SM, %	AY, %
1	no-metal control	8	37	9	Co <sup>II</sup> (TPP)	16	37
2	Ni(acac) <sub>2</sub> /KTp*	7	88	10	Vitamin B <sub>12</sub>	7	38
3	Co <sup>II</sup> (salen)	7	34	11	[Fe <sup>III</sup> Cl(OEP)]	68	8
4	Co <sup>II</sup> (Me-salen)	7	34	12	[Fe <sup>III</sup> Cl(TPP)]	87	trace
5	Co <sup>II</sup> (Me <sub>2</sub> -salen)	6	38	13	[Fe <sup>III</sup> Cl(T <sup>†</sup> PP)]	—	13
6	Co <sup>II</sup> (Me <sub>4</sub> -salen)	11	42	14	[Fe <sup>III</sup> Cl(PC)]	71	20
7	Co <sup>II</sup> (threo-Ph <sub>2</sub> -salen)	7	34	15	Fe <sup>II</sup> (PC)	90	10
8	[Co <sup>III</sup> (Cy-salen)(OTs)]·H <sub>2</sub> O	8	35	16	[Fe <sup>III</sup> Cl(salen)]	8	32



salen

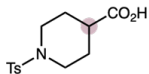


Me-salen

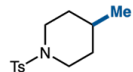
Me<sub>2</sub>-salenMe<sub>4</sub>-salenthreo-Ph<sub>2</sub>-salen

Cy-salen

Entry	Metal catalyst	SM, %	AY, %	Entry	Metal catalyst	SM, %	AY, %
1	no-metal control	8	18	9	Co <sup>II</sup> (TPP)	87	trace
2	Ni(acac) <sub>2</sub> /KTp*	4	93	10	Vitamin B <sub>12</sub>	11	18
3	Co <sup>II</sup> (salen)	29	7	11	[Fe <sup>III</sup> Cl(OEP)]	48	5
4	Co <sup>II</sup> (Me-salen)	21	7	12	[Fe <sup>III</sup> Cl(TPP)]	66	1
5	Co <sup>II</sup> (Me <sub>2</sub> -salen)	39	13	13	[Fe <sup>III</sup> Cl(T <sup>†</sup> PP)]	—	7
6	Co <sup>II</sup> (Me <sub>4</sub> -salen)	42	20	14	[Fe <sup>III</sup> Cl(PC)]	41	15
7	Co <sup>II</sup> (threo-Ph <sub>2</sub> -salen)	21	10	15	Fe <sup>II</sup> (PC)	47	10
8	[Co <sup>III</sup> (Cy-salen)(OTs)]·H <sub>2</sub> O	17	9	16	[Fe <sup>III</sup> Cl(salen)]	29	10



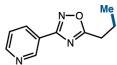
0.1 mmol

2.5 equiv. MesI(OAc)<sub>2</sub>, 10 mol% TXO**5 mol% metal source**, 5 mol% KTP\*
 IPR 365 nm, 100% LED, stirring 500 rpm  
 5200 rpm fans, Me<sub>2</sub>CO<sub>3</sub> (33 mM), 1 h
*methylated product*

Entry	Metal source	SM, %	AY, %
1	no-metal control	8	37
2	Ni(acac) <sub>2</sub>	7	88
3	V(acac) <sub>3</sub>	10	26
4	CrCl <sub>2</sub>	7	36
5	MnCl <sub>2</sub>	8	38

Entry	Metal source	SM, %	AY, %
6	Fe(acac) <sub>3</sub>	5	37
7	Co(acac) <sub>2</sub>	74	4
8	Co(acac) <sub>3</sub>	80	3
9	Cu(acac) <sub>2</sub>	62	26
10	BiCl <sub>3</sub>	29	8

## Primary Acids



9  
 ● 67% yield  
 ○ 59% yield

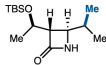


10  
 ● 80% yield  
 ○ 66% yield

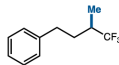
## Secondary Acids



11  
 ● 57% yield  
 ○ 75% yield



12  
 ● 85% yield  
 ○ 80% yield



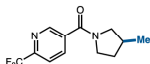
13  
 ● 90% yield<sup>a</sup>  
 ○ 74% yield



14  
 ● 70% yield  
 ○ 70% yield



15  
 ● 69% yield, 3.3:1 d.r.  
 ○ 70% yield, 3.0:1 d.r.



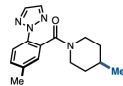
16  
 ● 83% yield  
 ○ 73% yield



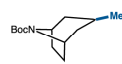
17  
 ● 85% yield  
 ○ 82% yield



18  
 ● 84% yield, 1.3:1 d.r.  
 ○ 82% yield, 1.3:1 d.r.

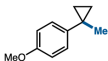


19  
 ● 66% yield  
 ○ 60% yield



20  
 ● 81% yield, 2.2:1 d.r.  
 ○ 61% yield, 2.0:1 d.r.

## Tertiary Acids



21  
 ● 68% yield  
 ○ 56% yield



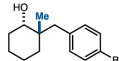
22  
 ● 73% yield  
 ○ 55% yield



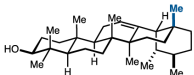
23  
 ● 79% yield  
 ○ 80% yield



24  
 ● 86% yield  
 ○ 40% yield



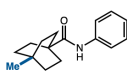
25  
 ● 91% yield, 2.3:1 d.r.  
 ○ 70% yield, 2.3:1 d.r.



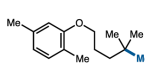
26  
 ● 74% yield, >20:1 d.r.  
 ○ 42% yield, >20:1 d.r.



27  
 ● 59% yield  
 ○ 54% yield



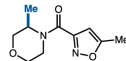
28  
 ● 0% yield<sup>a</sup>  
 ○ 40% yield<sup>b,c</sup>



29  
 ● 78% yield  
 ○ 53% yield

 $\alpha$ -Amino/Oxy Acids

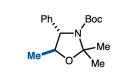
30  
 ● 72% yield  
 ○ 44% yield



31  
 ● 64% yield  
 ○ 65% yield

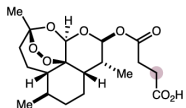


32  
 ● 61% yield  
 ○ 52% yield

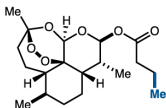


33  
 ● 76% yield, 8:1 d.r.  
 ○ 81% yield, 8:1 d.r.

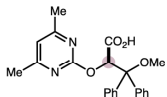
## Late-Stage Functionalization



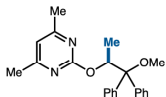
Artesunate



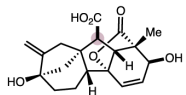
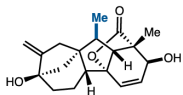
**34**  
 ● 0% yield<sup>a</sup>  
 ○ 44% yield<sup>b</sup>



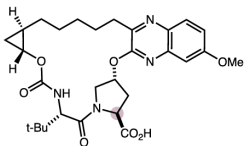
Ambrisentan



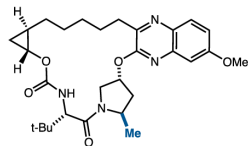
**36**  
 ● 89% yield  
 ○ 48% yield

Gibberellin A<sub>3</sub>

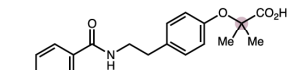
**38**  
 ● 76% yield, 19:1 d.r.  
 ○ 57% yield, 9:1 d.r.



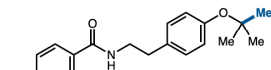
Grazoprevir precursor



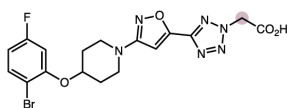
**35**  
 ● 60% yield, 2:1 d.r.  
 ○ 45% yield, 2:1 d.r.



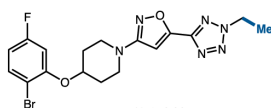
Bezafibrate



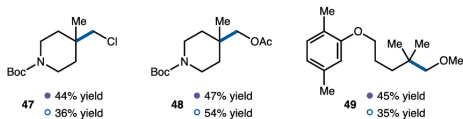
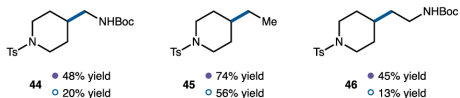
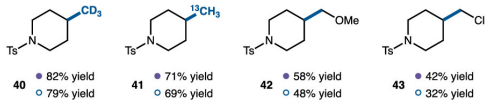
**37**  
 ● 63% yield  
 ○ 84% yield



MK-8245 SCD inhibitor



**39**  
 ● 40% yield  
 ○ 26% yield





no Ni source background reaction	→	34% yield d.r. 1.5:1
5 mol% Ni(acac) <sub>2</sub> 5 mol% K[TP]	→	63% yield d.r. 2.4:1
5 mol% Ni(acac) <sub>2</sub> 5 mol% K[TP*]	→	81% yield d.r. 3.0:1

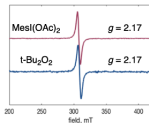
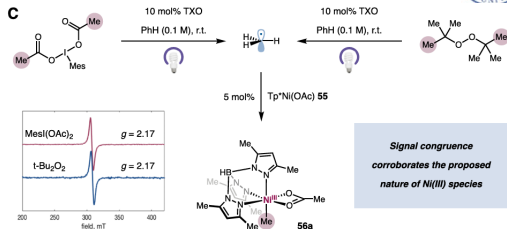
*Ni mediates C–C bond formation*



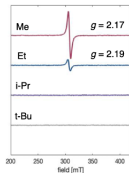
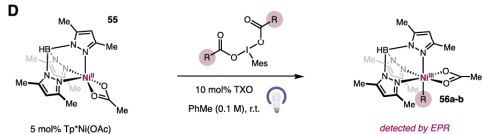
standard reaction conditions	↓	85% yield
+ 3 equiv. 53	↓	84% yield
+ 3 equiv. 54	↓	83% yield

aryl halides are fully recovered

*Intermediacy of Ni(0) and Ni(I) is unlikely*



*Signal congruence corroborates the proposed nature of Ni(III) species*

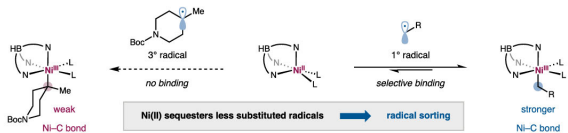
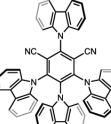
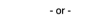
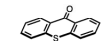
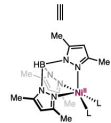
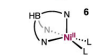
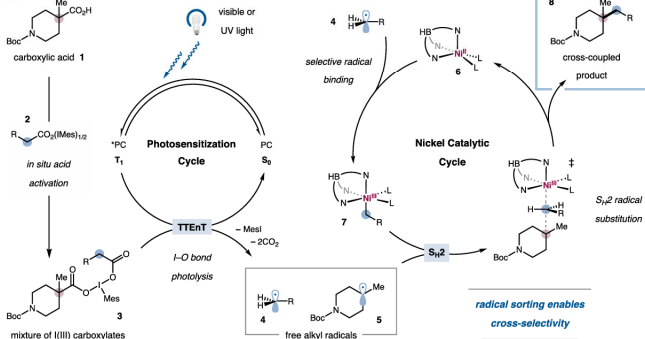


R	Ni-R BDFE
Me	9.5 kcal/mol
Et	1.1 kcal/mol
i-Pr	-1.9 kcal/mol
t-Bu	-9.8 kcal/mol

*Only methyl and 1° alkyl bind to the nickel complex*



*Radical sorting*

**A** Less substituted free radical sequestered by Ni(II) and turned into persistent Ni(III)-Alk species

**B**


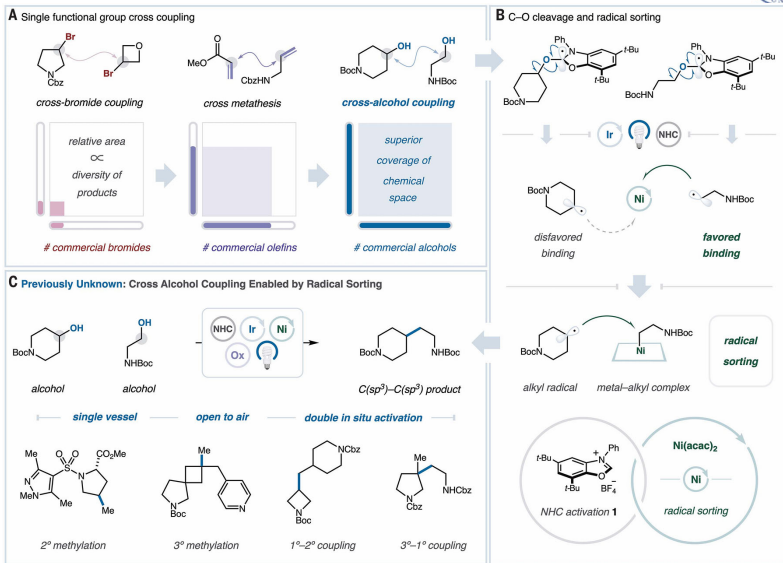
镍催化的 $S_H2$

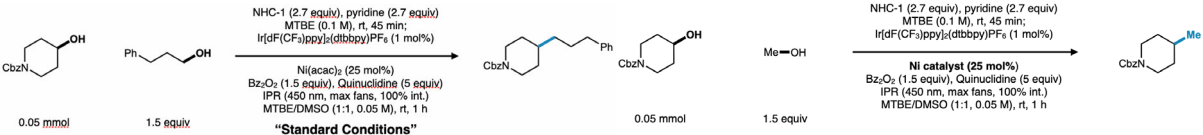
# Alcohol-alcohol cross-coupling enabled by $S_H2$ radical sorting

Ruizhe Chen<sup>1†</sup>, Nicholas E. Intermaggio<sup>1†</sup>, Jiaxin Xie<sup>1†</sup>, James A. Rossi-Ashton<sup>1†</sup>, Colin A. Gould<sup>1</sup>, Robert T. Martin<sup>1</sup>, Jesús Alcázar<sup>2</sup>, David W. C. MacMillan<sup>1\*</sup>

由  $S_H2$  自由基分选促进的醇-醇交叉偶联

MacMillan, D. W. C., *Science* **2024**, 383, 1350–1357.





## Deviation from "Standard Conditions"

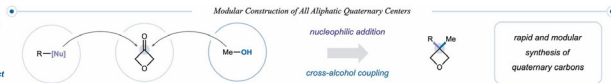
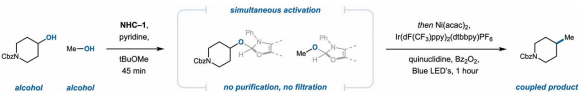
## UPLC Assay Yield

None	54%
No photocatalyst	0%
No base	0%
No peroxide (under air)	13%
No blue LEDs (ambient light)	0%
No Ni catalyst	17%

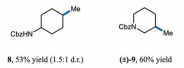
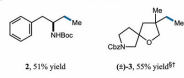
## Ni Catalysts

## UPLC Assay Yield

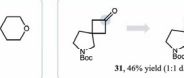
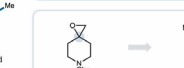
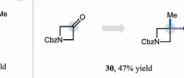
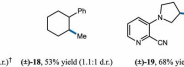
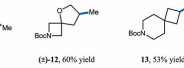
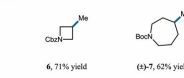
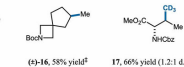
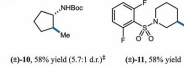
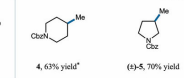
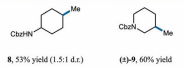
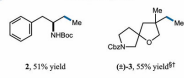
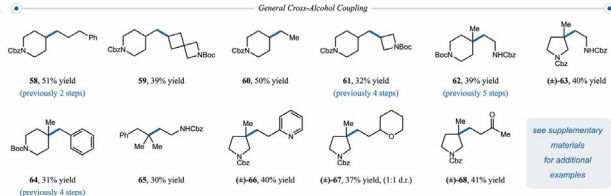
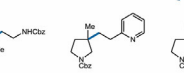
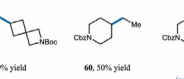
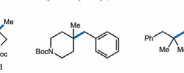
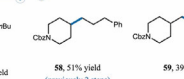
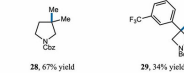
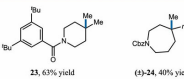
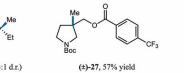
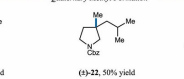
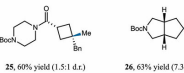
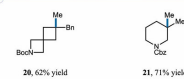
Ni(acac) <sub>2</sub>	68%
Ni(TMHD) <sub>2</sub>	57%
Ni(acac) <sub>2</sub> /KTP <sup>+</sup>	60%
Ni(dtbbpy)Cl <sub>2</sub>	13%
NiBr <sub>2</sub> (glyme)	33%
Ni(OEP)	9%



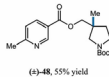
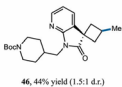
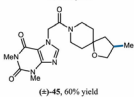
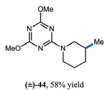
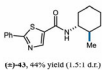
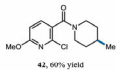
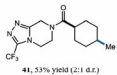
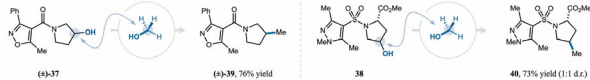
## Primary Methylation



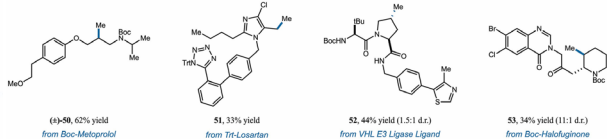
## Secondary Methylation

Quaternary Methyl Formation<sup>†</sup>

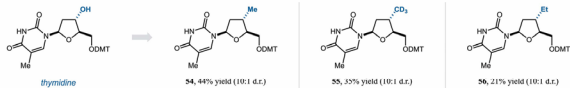
## Heterocyclic Alcohols



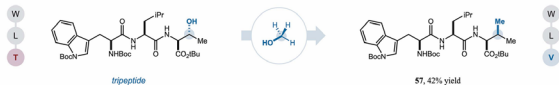
## Derivatization of Biologically Active Molecules



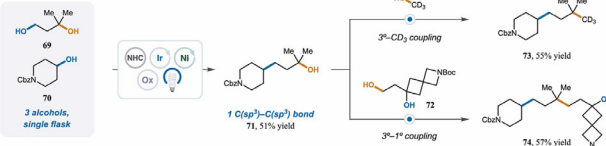
## Nucleoside Library Synthesis



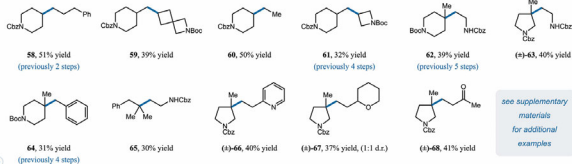
## Peptide Editing



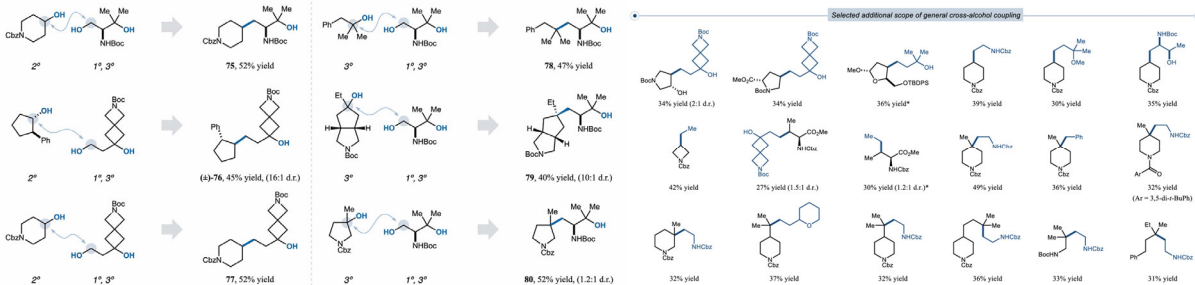
## Functionalization of Diols



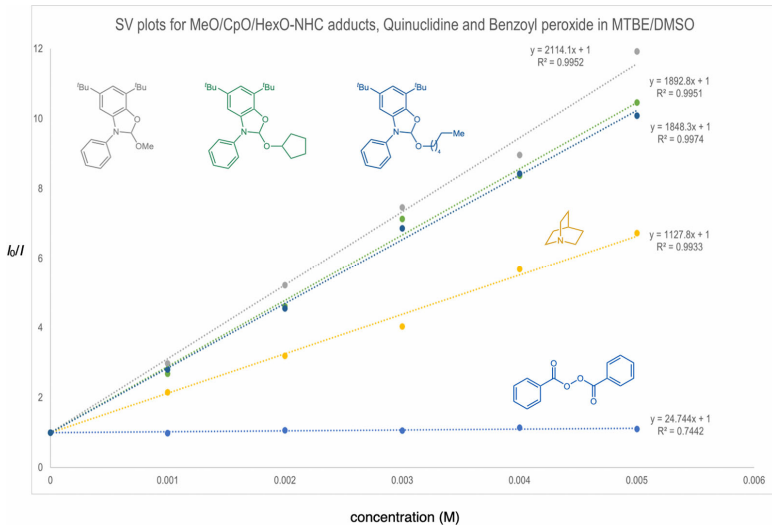
## General Cross-Alcohol Coupling

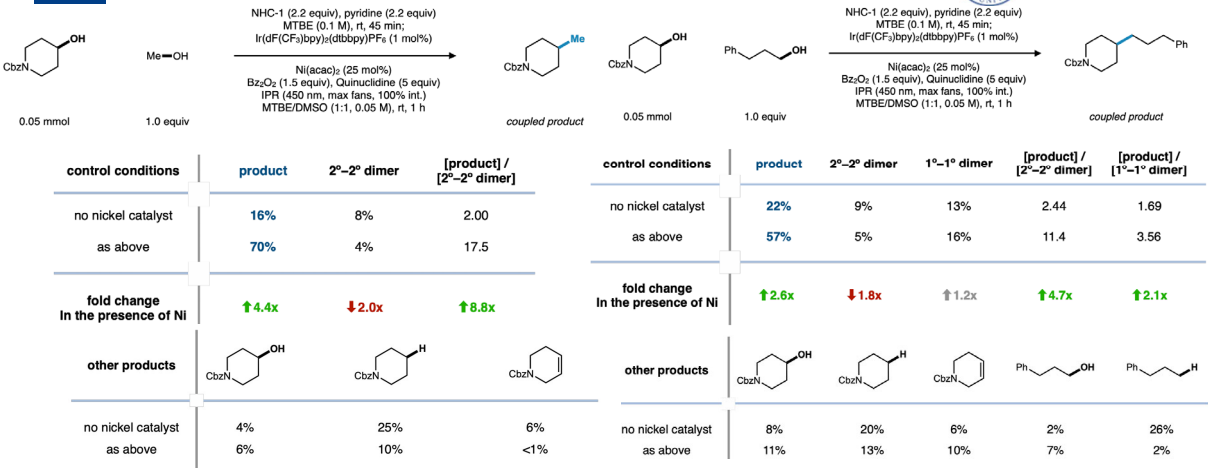


## Selected additional scope of general cross-alcohol coupling



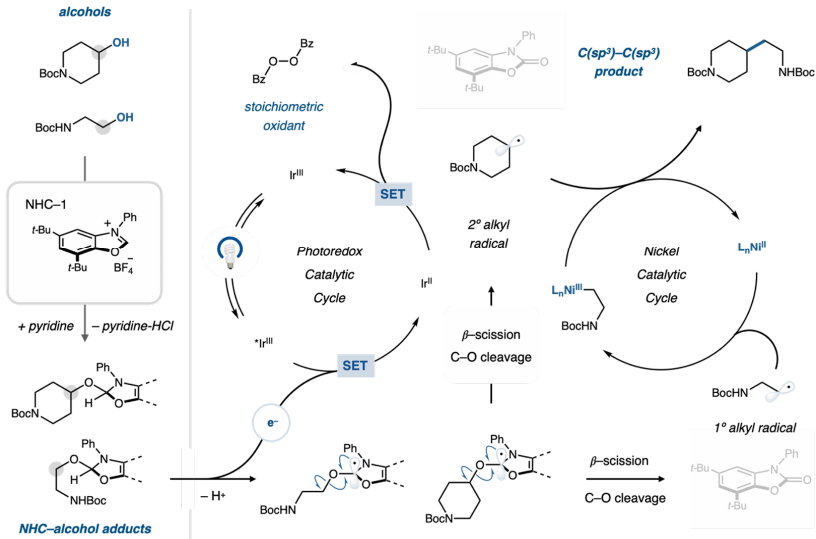
## Stern-Volmer Quenching Experiments





因此，这些实验观察结果有力地支持了一种由镍介导的自由基分选效应：它能让两个短暂的烷基自由基以显著更高的效率偶联在一起，远超那种单纯的、统计随机性的自由基-自由基重组，也进一步支持镍介导的自由基分选效应在这些醇-醇交叉偶联反应中是可行的。

## 4) Proposed Reaction Mechanism



铁催化的MHAT-SH2

# Carbon quaternization of redox active esters and olefins by decarboxylative coupling

Xu-cheng Gan<sup>1†</sup>, Benxiang Zhang<sup>1†</sup>, Nathan Dao<sup>1†</sup>, Cheng Bi<sup>1</sup>, Maithili Pokle<sup>1</sup>, Liyan Kan<sup>1,2</sup>, Michael R. Collins<sup>3</sup>, Chet C. Tyrol<sup>4</sup>, Philippe N. Bolduc<sup>5</sup>, Michael Nicastrì<sup>5</sup>, Yu Kawamata<sup>1\*</sup>, Phil S. Baran<sup>1\*</sup>, Ryan Shenvi<sup>1\*</sup>

氧化还原活性酯和烯烃经脱羧偶联的构建季碳反应

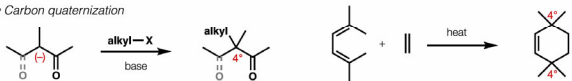
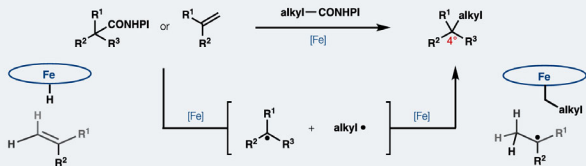
Shenvi, R. A, *Science* **2024**, 384, 113–118

**A** Conventional quaternization (polar or pericyclic)

## • Nitrogen quaternization



## • Carbon quaternization

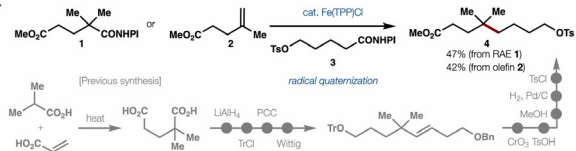

**B** This work: radical quaternization using abundant feedstock chemicals


• Single [Fe] catalyst

• Chemoselective

• Simple protocol

• Broad scope

**C** Quick routes to high Fsp<sup>3</sup> materials


子图

内容要点

A

对比氮季碳化（简单）与碳季碳化（复杂），提出研究动机

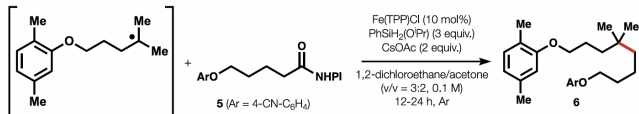
B

本文开发的自由基季碳化策略：烯烃 + 羧酸（RAE）→ 季碳

C

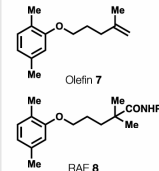
应用示例：10步传统路线 → 1步本方法，显著简化合成

## B Reaction optimization



Entry	3° radical precursor	Deviations from above	Yield
1	Olefin 7	None	58%
2	Olefin 7	no base	trace
3	Olefin 7	KOAc instead of CsOAc	50%
4	Olefin 7	sealed under air	48%
5	Olefin 7	1,2-dichloroethane as solvent	14%
6	Olefin 7	+ 10 mol% Fe(acac) <sub>3</sub>	32%
7	Olefin 7	PhSiH <sub>3</sub> instead of PhSiH <sub>2</sub> (O'Pr)	45%
8	Olefin 7	PhSiH <sub>3</sub> + <sup>i</sup> PrOH (2 eq) + KOAc	52%
9	RAE 8	None	9%
10	RAE 8	20 mol% Fe(TPP)Cl	24%
11 <sup>*</sup>	RAE 8	Zn instead of PhSiH <sub>2</sub> (O'Pr)	37%
12 <sup>*</sup>	RAE 8	Zn in 1,2-dichloroethane/acetone = 7/4	42%
13 <sup>*†</sup>	RAE 8	Zn/KOAc instead of PhSiH <sub>2</sub> (O'Pr)/CsOAc	44%
14 <sup>*†</sup>	RAE 8	Addition of Et <sub>3</sub> N·HCl (20 mol%) to entry 13	61%
15 <sup>*†</sup>	Olefin 7	Conditions in entry 14	n.d.

3° radical precursors



Olefin 7

RAE 8

Optimal conditions

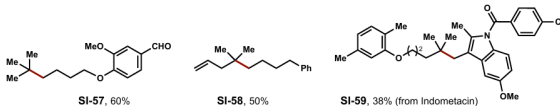
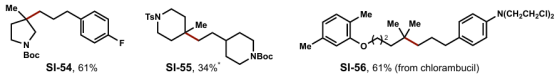
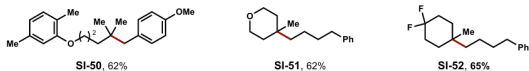
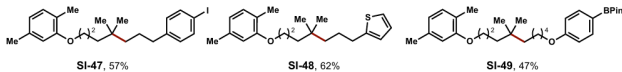
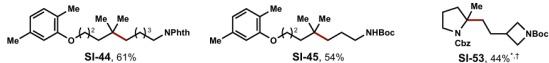
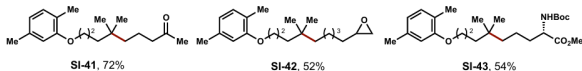
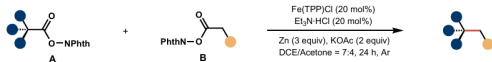
**Conditions A (olefin-RAE)**

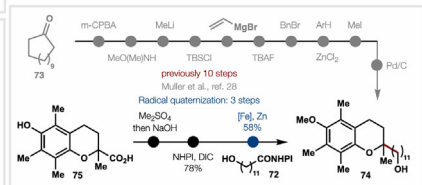
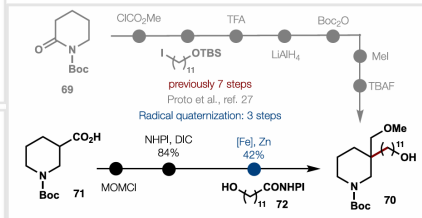
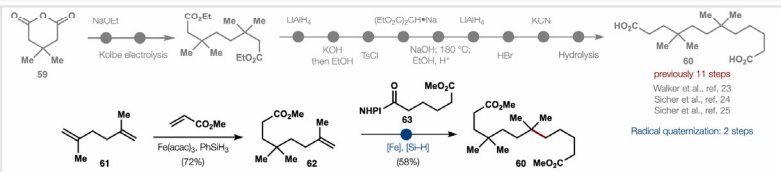
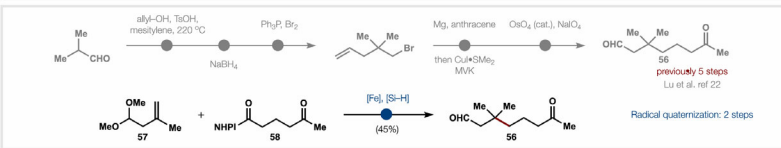
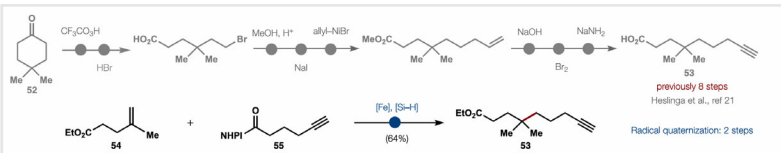
Fe(TPP)Cl (10 mol%)  
PhSiH<sub>2</sub>(O'Pr) (3 equiv)  
CsOAc (2 equiv)  
1,2-dichloroethane/acetone=3:2  
(0.1 M) 24 h, Ar

**Conditions B (RAE-RAE)**

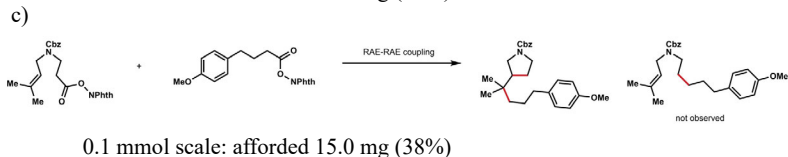
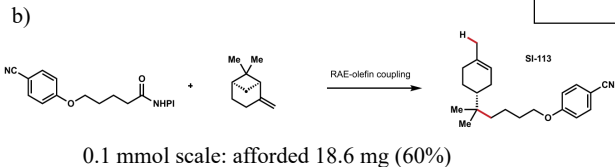
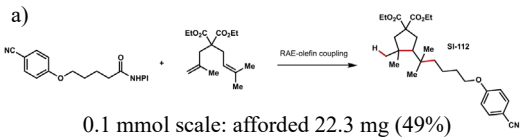
Fe(TPP)Cl (20 mol%)  
Et<sub>3</sub>N·HCl (20 mol%)  
Zn (3 equiv)  
KOAc (2 equiv)  
1,2-dichloroethane/acetone=7:4  
(0.1 M) 24 h, Ar



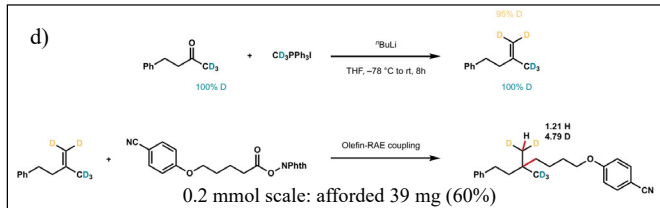




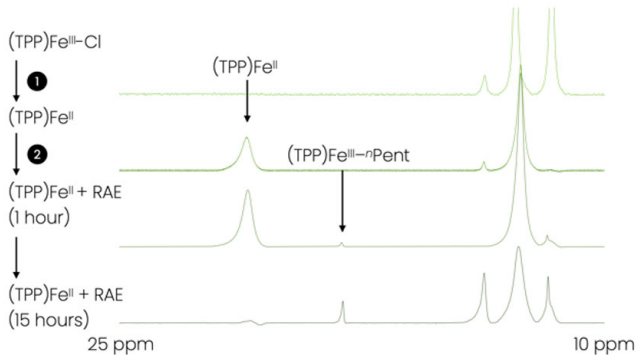
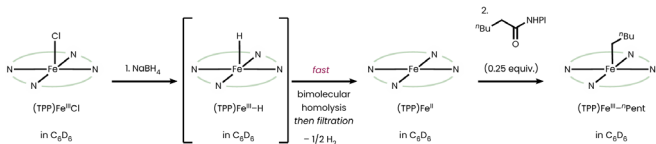
## 1) Cyclization/Ring-opening Reactions(环化/开环反应)



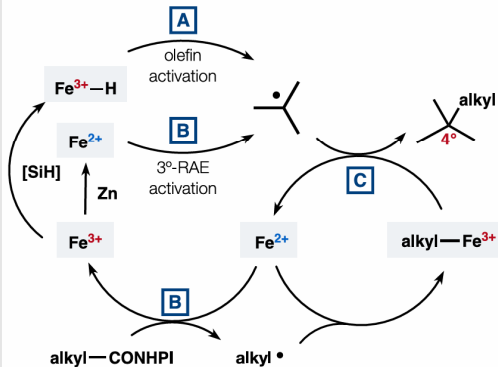
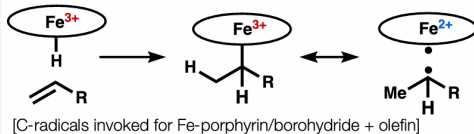
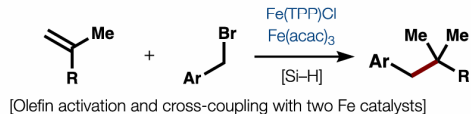
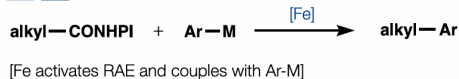
## 2) Deuterium labeling



## 化学计量实验(Stoichiometric Experiment)



**A** Reaction design and relevant literature precedent

*Convergent catalytic cycles from alkenes and redox-active esters?*

**A** Setsune et al., ref. 12; Neta et al., ref. 13

**A C** Shenvi and co-workers, ref. 15

**B C** Baran and co-workers, ref. 16


## 铁催化的MHAT-SH2

# Alkene Hydrobenzylation by a Single Catalyst That Mediates Iterative Outer-Sphere Steps

Lingran Kong,<sup>§</sup> Xu-cheng Gan,<sup>§</sup> Vincent A. van der Puyl Lovett,<sup>§</sup> and Ryan A. Shenvi\*



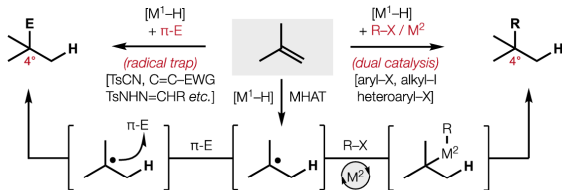
Cite This: *J. Am. Chem. Soc.* 2024, 146, 2351–2357



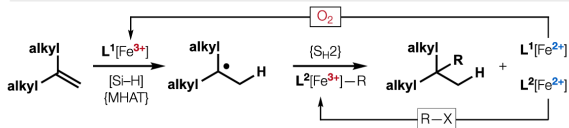
Read Online

单一催化剂介导迭代外球步骤的烯烃氢苯基化反应

a. Quaternization by radical additions, e.g. MHAT alkene hydrofunctionalization

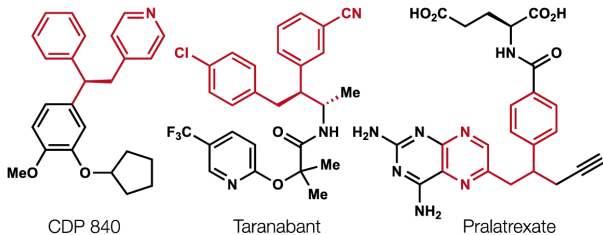


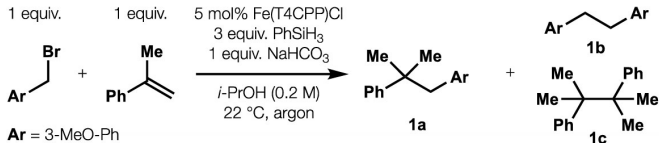
b. [prior work] Two catalysts and exogenous oxidant



a: 此前的方法要么限于  $\pi$ -亲电体, 要么需要两个不同的催化剂协同工作。  
 b: 该体系需要  $\text{O}_2$  来再生  $\text{Fe}^{3+}$ , 限制了放大规模。

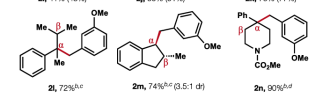
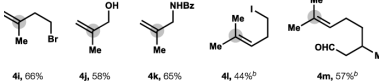
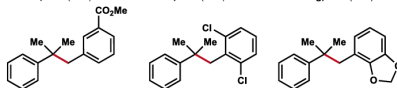
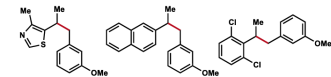
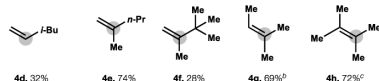
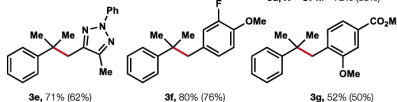
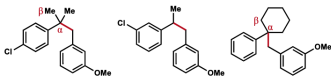
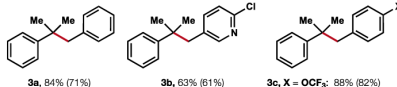
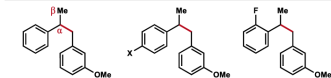
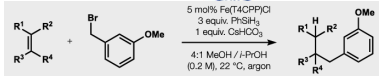
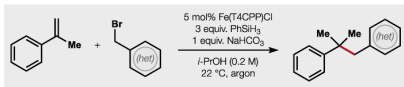
d. Dibenzyl (1,2-diarylethane) motifs are common among drug substances



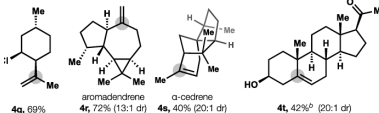
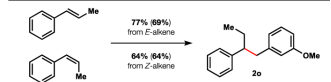


entry	variation <sup>a</sup>	% <b>1a</b> <sup>b</sup>	% <b>1b</b>	% <b>1c</b>
1	none	87	8	2
2	Fe(TPP)Cl not Fe(T4CPP)Cl	14	1	6
3	Fe(T4SPP)Cl not Fe(T4CPP)Cl	10	5	2
4	Fe(acac) <sub>3</sub>	nd	nd	nd
5	CsHCO <sub>3</sub> not NaHCO <sub>3</sub>	45	5	2
6	no NaHCO <sub>3</sub>	36	3	2
7	NaBH <sub>4</sub> not PhSiH <sub>3</sub>	65	5	9
8	2 mol % Fe(T4CPP)Cl	52	7	2

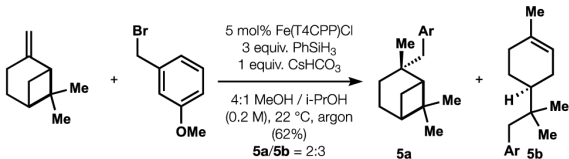
<sup>a</sup>T4CPP = tetra(4-carboxyphenyl)porphyrin; TPP = tetraphenylporphyrin; T4SPP = tetra(4-sulfoxyphenyl)porphyrin. <sup>b</sup>Values determined by <sup>1</sup>H NMR; theoretical yield of **1a**, **1b**, and **1c** are 100%, 50%, and 50%.



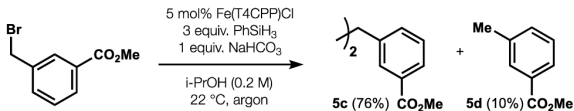
<sup>a</sup>With 0.2 mmol of alkene and 0.2 mmol of bromide. <sup>b</sup><sup>1</sup>H NMR yield (isolated yield)



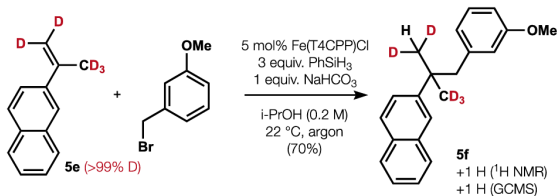
a. alkene is converted to C-centered radical



b. Alkene outcompetes background homodimerization



c. MHAT is irreversible



d. C–C bond formation occurs with different dr than R\*•R\*• coupling

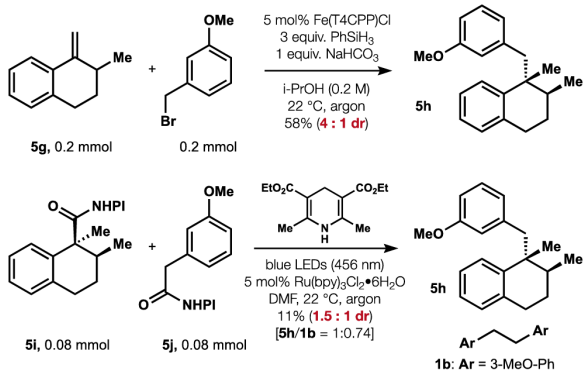
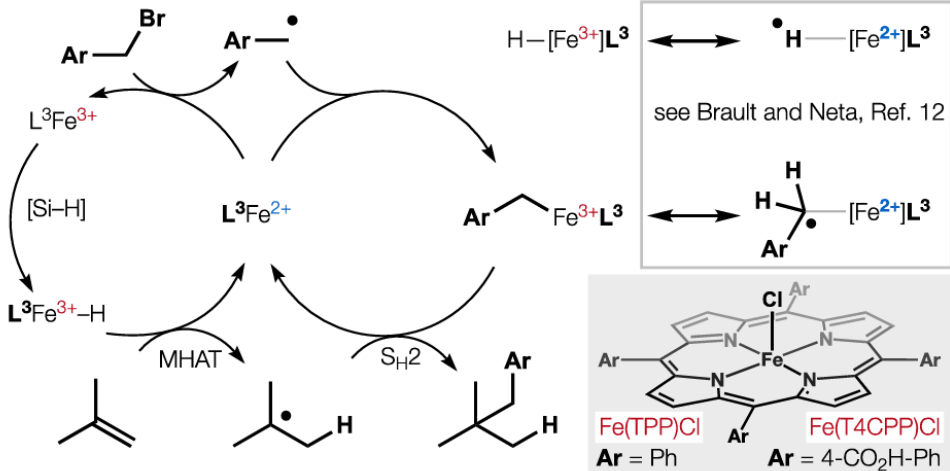


Figure 2. Experiments relevant to the mechanism of C–C bond formation.



## 锰催化的MHAT,镍的SH2

# Engaging Alkenes in Metallaphotoredox: A Triple Catalytic, Radical Sorting Approach to Olefin-Alcohol Cross-Coupling

Qinyan Cai,<sup>‡</sup> Iona M. McWhinnie,<sup>‡</sup> Nathan W. Dow,<sup>‡</sup> Amy Y. Chan, and David W. C. MacMillan\*

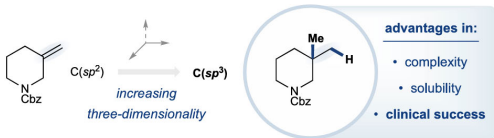
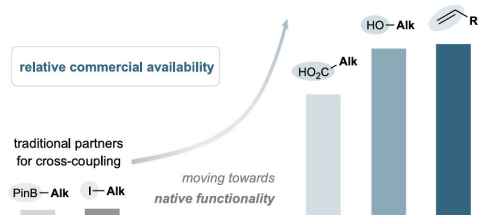
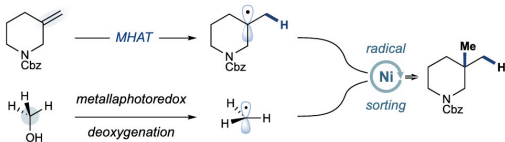
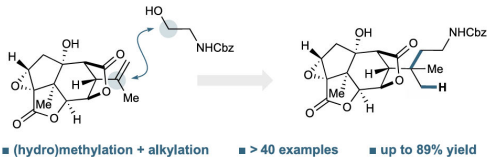


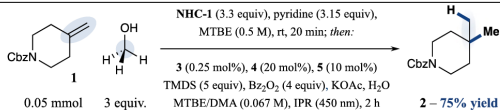
Cite This: *J. Am. Chem. Soc.* 2024, 146, 12300–12309



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在金属光催化中活化烯烃：一种三重催化、自由基分类的烯烃-醇交叉偶联方法

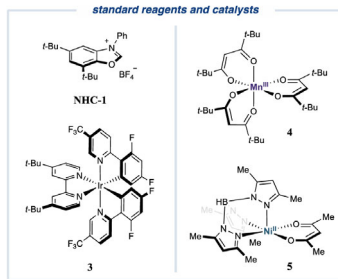
**A. Building C(sp<sup>3</sup>) quaternary carbons from C(sp<sup>2</sup>) functionality**

**B. Abundance and diversity of potential alkyl fragments**

**C. Radical sorting enables previously elusive cross-couplings**

**D. This work: cross-coupling of alkenes and alcohols**


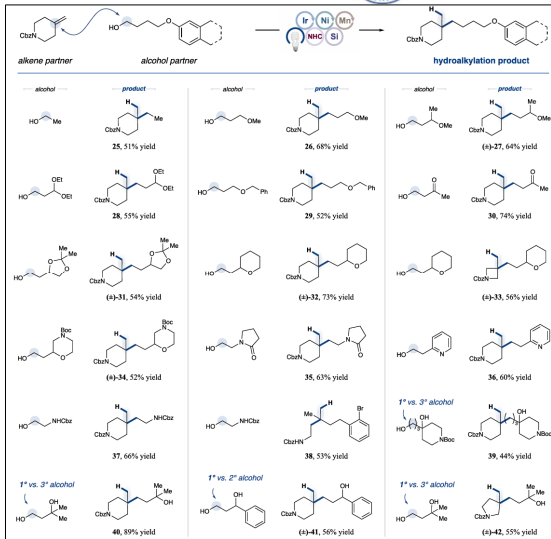
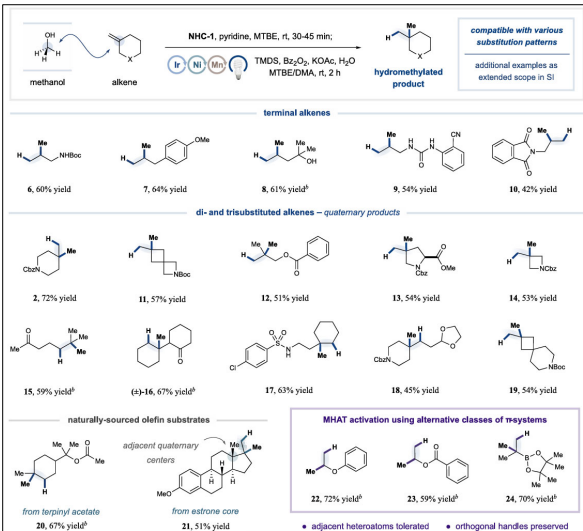


entry	deviation	yield <sup>b</sup>
1	none	75%
2	in absence of base (KOAc)	65%
3	in absence of H <sub>2</sub> O additive	65%
4	Fe(OEP)Cl instead of 5	2%
5	no Ni catalyst 5	10%
6	Ni(acac) <sub>2</sub> instead of 5	67%
7	Fe(acac) <sub>3</sub> instead of 4	9%
8	Co(acac) <sub>2</sub> or Co(salen) instead of 4	4%
9	no Mn catalyst 4	0%
10	no light	5%
11	no photocatalyst 3	19%
12	no TMSD	0%
13	no oxidant	0%

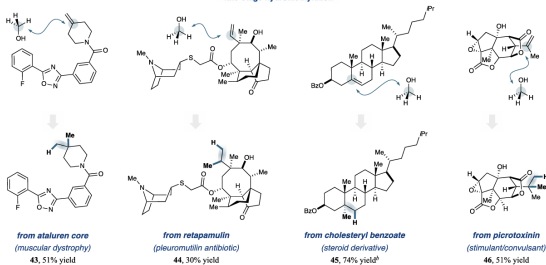
<sup>a</sup>Typically performed with 0.5 equiv. KOAc, 5 equiv. H<sub>2</sub>O and 4:1 MTBE/DMA. See SI for experimental details. <sup>b</sup>Yield determined by <sup>1</sup>H NMR. Ac, acetyl; Acac, acetylacetonate; Bz, benzoyl; Cbz, benzyloxycarbonyl; DMA, N,N-dimethylacetamide; MTBE, methyl *tert*-butyl ether; OEP, 2,3,7,8,12,13,17,18-octaethyl-21H,23H-porphine.

实验编号	变更条件 (Deviation)	结果 (Yield)	结论
Entry 4	用 Fe 催化剂代替 Ni (5)	2%	<b>Ni 的关键性:</b> Fe 催化剂无法有效进行“自由基分选 (Radical Sorting)”以形成 C-C 键。
Entry 5	不加 Ni 催化剂	10%	证明 Ni 是偶联步骤的核心, 没有它反应几乎停止。
Entry 6	仅用 Ni(acac) <sub>2</sub> (无配体)	67%	虽然有一定活性, 但证明了配体 (Tp*) 对 Ni 催化剂的重要性。
Entry 7	用 Fe 代替 Mn (4)	9%	<b>Mn 的关键性:</b> Fe-H 体系无法像 Mn-H 那样高效地活化端炔。
Entry 8	用 Co 代替 Mn (4)	4%	Co-H 体系同样不适用。
Entry 9	不加 Mn 催化剂	0%	证明 Mn 是端炔活化 (MHAT 过程) 的必要条件。

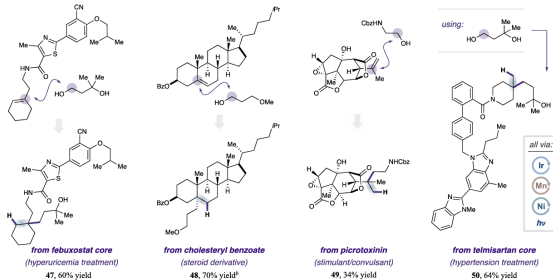




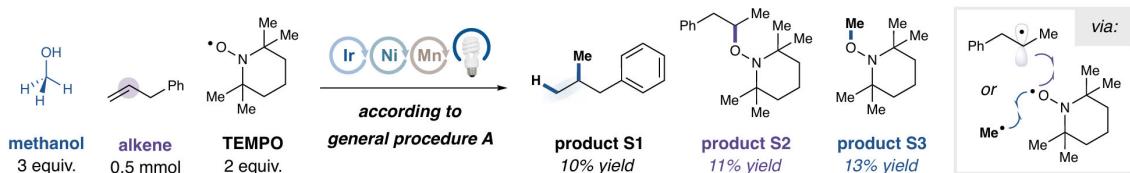
## late-stage hydromethylation



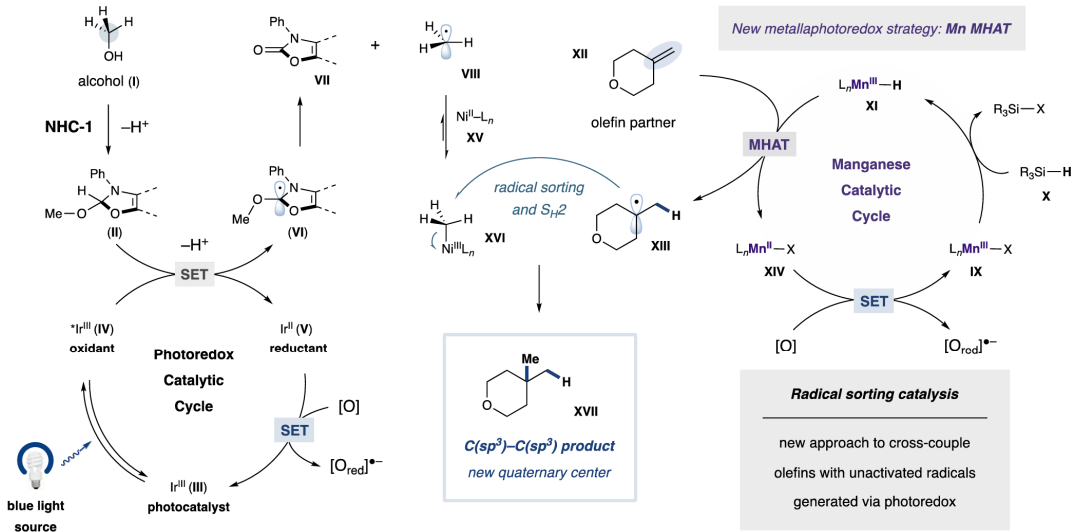
## late-stage hydroalkylation



## Radical trapping experiments(自由基捕获实验)



这些数据与详细描述合理机理一致，并且与MHAT及NHC-1介导的光氧化去氧化反应作为烯烃-醇交叉偶联的有效活化方式相符。



自由基加成-镍催化的SH2

Article

# Alkene dialkylation by triple radical sorting

通过三重自由基分选的烯烃二烷基化

<https://doi.org/10.1038/s41586-024-07165-x>

Johnny Z. Wang<sup>1,2</sup>, William L. Lyon<sup>1,2</sup> & David W. C. MacMillan<sup>1</sup>✉

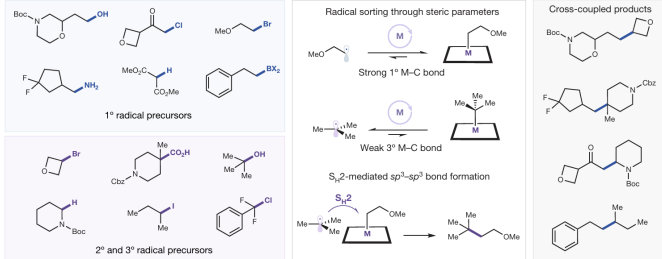
Received: 20 November 2023

Accepted: 5 February 2024

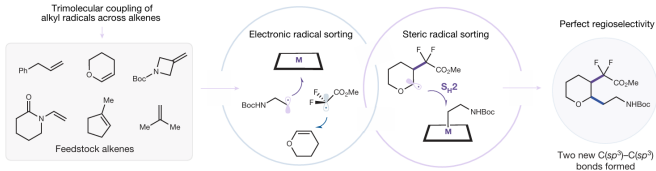
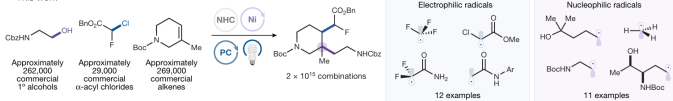
Published online: 13 February 2024

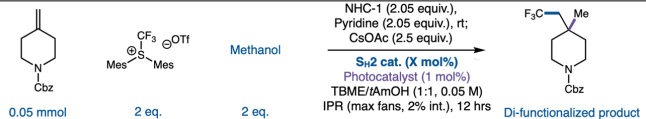
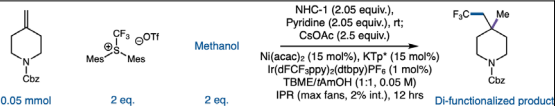
 Check for updates

Macmillan, D. W. C. *Nature* **2024**, 628, 104–109.

**a**  $S_{1,2}$  as a platform for radical sorting

**b**  $S_{1,2}$ -enabled trimolecular cross-coupling

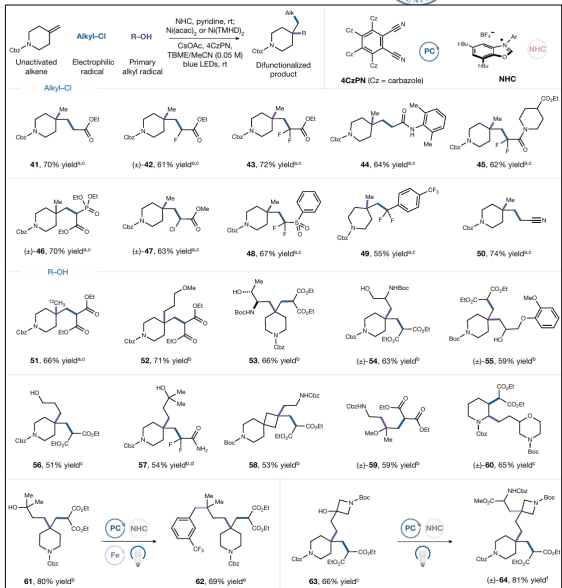
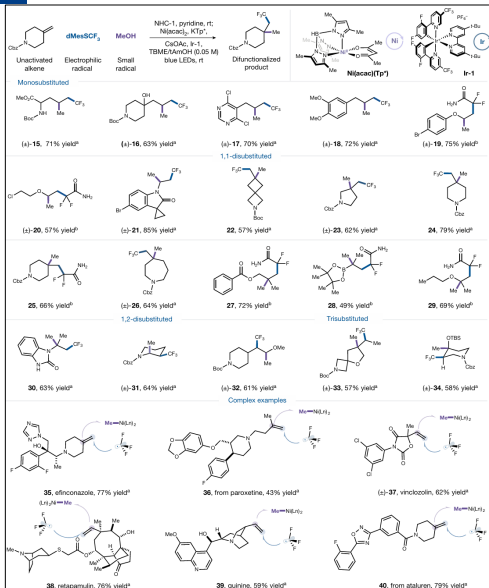
Trimolecular coupling of alkyl radicals across alkenes


**c** This work




entry	deviation	yield
1	none	84%
2	No CsOAc	< 5%
3	No light	0%
4	No photocat.	0%
5	No Nickel	< 5%
6	No sparge	22%
7	100% light int. (15 mins)	71%

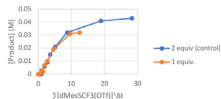
S <sub>H</sub> 2 Catalyst	Photocatalyst			
	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	Ir(dFMeppey) <sub>2</sub> (dtbpy)PF <sub>6</sub>	Ir(dFCF <sub>3</sub> ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	4CzPN
Ni(acac) <sub>2</sub> (25 mol%)	75%	74%	66%	63%
Ni(acac) <sub>2</sub> (15 mol%)	73%	72%	74%	60%
Ni(acac) <sub>2</sub> + KTP* (25 mol%)	79%	79%	81%	71%
Ni(acac) <sub>2</sub> + KTP* (15 mol%)	81%	82%	84%	65%



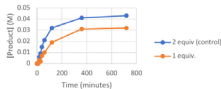
## 动力学级数实验(VTNA)

dMesSCF<sub>3</sub>(OTf) VTNA

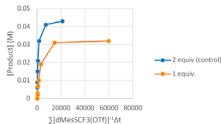
First Order



Zero Order

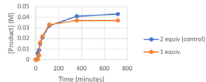


-1 Order

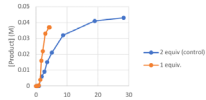
the reaction is first order in dMesSCF<sub>3</sub>(OTf).

MeOH-NHC adduct VTNA

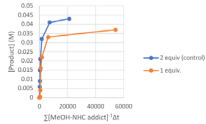
Zero Order



First Order



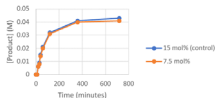
-1 Order



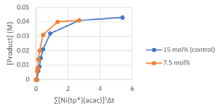
the reaction is zero order in MeOH-NHC adduct.

Ni(tp\*)(acac) VTNA

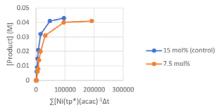
Zero Order



First Order



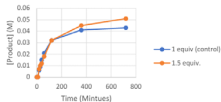
-1 Order



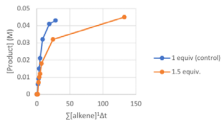
the reaction is zero order in Ni(Tp\*)(acac).

Alkene VTNA

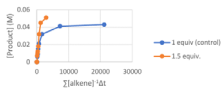
Zero Order



First Order



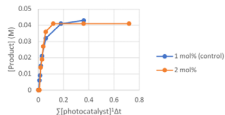
-1 Order



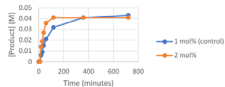
the reaction is zero order in alkene.

Photocatalyst VTNA

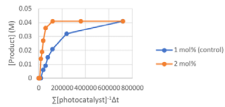
First Order



Zero Order

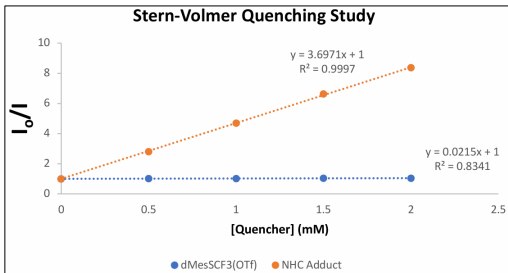


-1 Order

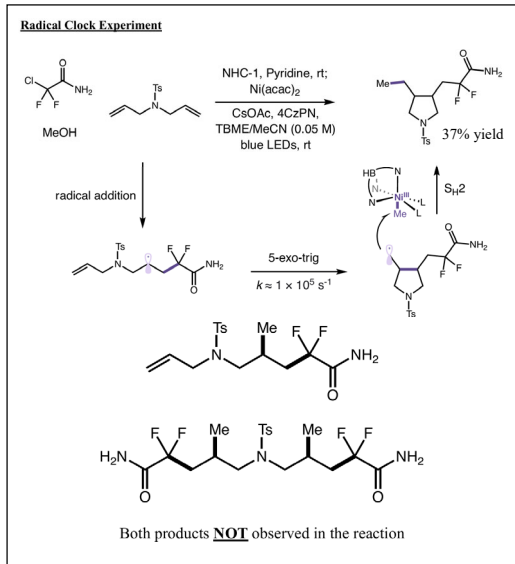


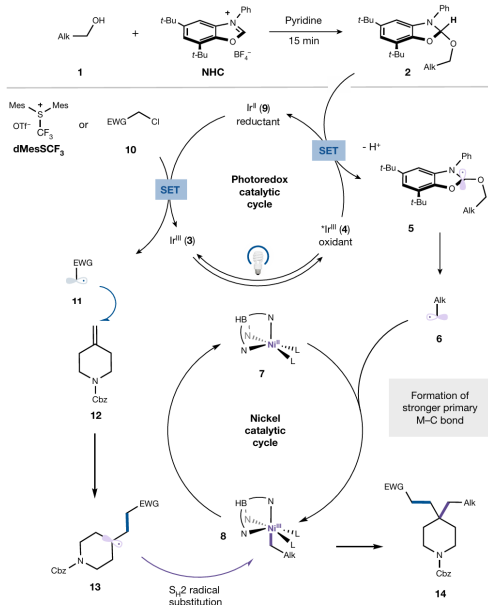
the reaction is first order in photocatalyst.

反应级数由观察产物形成曲线的重叠情况来确定。



这表明双分子SH<sub>2</sub>过程与单分子5-exo-trig环化过程不具有竞争性





## MRC-钴催化的SH2

### Article

# Asymmetric radical cyclopropanation of dehydroaminocarboxylates: Stereoselective synthesis of cyclopropyl $\alpha$ -amino acids

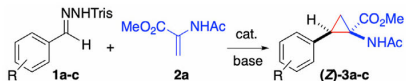
Wan-Chen Cindy Lee,<sup>1</sup> Duo-Sheng Wang,<sup>1</sup> Congzhe Zhang,<sup>1</sup> Jingjing Xie,<sup>1</sup> Bo Li,<sup>1</sup> and X. Peter Zhang<sup>1,2,\*</sup>

脱氢氨基酸酯的不对称自由基环丙烷化：环丙基 $\alpha$ -氨基酸的立体选择性合成

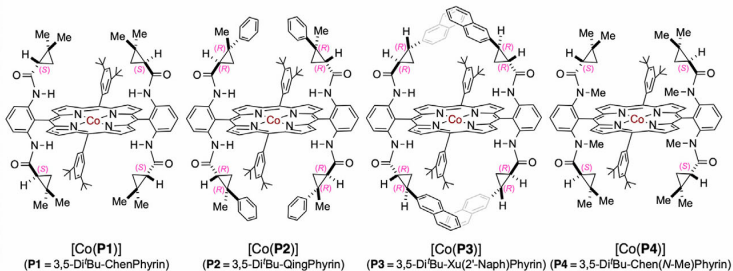
Zhang, X. P. *Chem.* **2021**, *7*, 1588–1601.

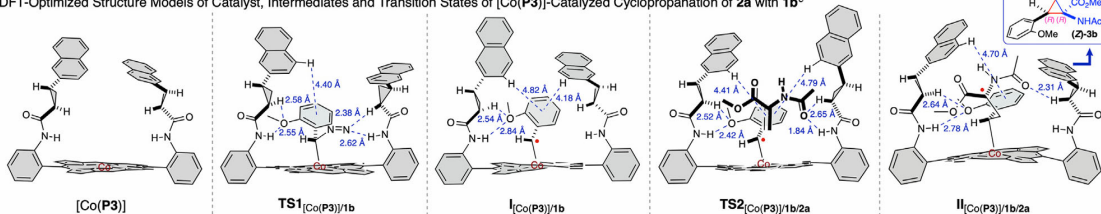


逻辑板块	核心议题	主要内容概述	关键挑战/突破点
背景与现状	自由基化学与立体控制	自由基反应因条件温和、官能团耐受性好而备受关注, 但控制其立体选择性 (特别是对映选择性) 是长期难题。	如何在保持自由基高反应活性的同时, 实现精准的立体控制?
技术手段	金属自由基催化 (MRC)	MRC 利用金属中心自由基生成并稳定有机自由基。Co(II) 配合物 (基于 $D_2$ -对称手性酰胺卟啉) 能有效活化重氮化合物, 生成 Co(III)-烷基自由基, 实现环丙烷化的立体控制。	Co(II) 体系此前主要适用于单取代烯烃 (如苯乙烯), 在 1,1-二取代烯烃上的应用尚不成熟。
研究对象	脱氢氨基酸酯 (Dehydroamino acid esters)	这是一类重要的 1,1-二取代烯烃, 是合成非蛋白源性氨基酸的关键前体。	由于其独特的空间和电子特性, 是否适合 Co(II) 自由基环丙烷化尚属未知, 且面临多重挑战 (见下表)。
具体难点	反应中的四大挑战	针对该底物与原位生成的 $\alpha$ -芳基重氮甲烷反应, 存在以下具体困难:	<ol style="list-style-type: none"> <li><b>空间位阻:</b> 两个偕位取代基 (氨基和酯基) 阻碍自由基加成。</li> <li><b>对映选择性:</b> 氨基和酯基大小相似, 难以区分烯烃的前手性面。</li> <li><b>非对映选择性:</b> 后续的 3-exo-tet 环化过程难以控制。</li> <li><b>电子效应:</b> 三级自由基中间体的稳定性及潜在的氢键干扰。</li> </ol>
现有局限	传统催化体系的不足	现有的金属催化 (如 Rh(II) 卡宾) 体系通常涉及亲电性金属卡宾, 与缺电子的脱氢氨基酸酯存在电子不兼容性。	现有方法通常立体选择性差, 或需要多步操作 (如硫叶立德法), 缺乏一种通用的、高对映选择性的直接催化体系。
本研究策略	配体设计与目标	旨在通过设计具有特定电子、空间和手性环境的 $D_2$ -对称手性酰胺卟啉配体, 来调控 Co(II) 催化过程。	<b>目标:</b> 开发首个能直接催化脱氢氨基酸酯与重氮化合物进行不对称环丙烷化的体系, 合成具有 (Z)-非对映选择性的手性环丙烷 $\alpha$ -氨基酸衍生物。



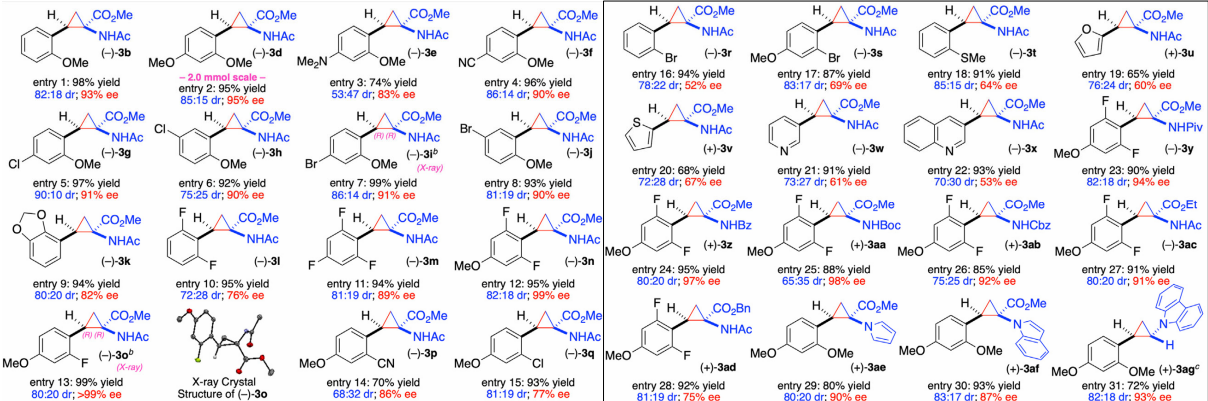
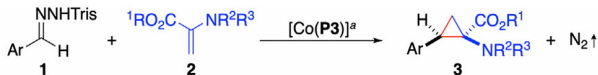
entry <sup>a</sup>	R	cat.	product	yield (%) <sup>b</sup>	dr (Z/E) <sup>c</sup>	ee (%) <sup>d</sup>
1	H	–	<b>3a</b>	18	17/83	–
2	H	[Co( <b>P1</b> )]	<b>3a</b>	65	64/36	–
3	H	[Co( <b>P1</b> )]	<b>3a</b>	66	59/41	–36
4	H	[Co( <b>P2</b> )]	<b>3a</b>	69	53/47	16
5	H	[Co( <b>P3</b> )]	<b>3a</b>	80	68/32	43
6	2-OMe	[Co( <b>P3</b> )]	<b>3b</b>	98	82/18	93
7	2-Et	[Co( <b>P3</b> )]	<b>3c</b>	81	67/33	37
8	2-OMe	[Co( <b>P1</b> )]	<b>3b</b>	68	87/13	–65
9	2-OMe	[Co( <b>P4</b> )]	<b>3b</b>	62	83/17	–12



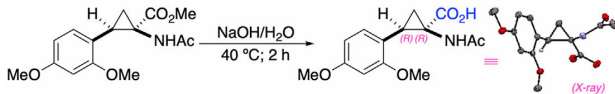
DFT-Optimized Structure Models of Catalyst, Intermediates and Transition States of [Co(P3)]-Catalyzed Cyclopropanation of **2a** with **1b**<sup>6</sup>

关键指标	简单/无配体 (如Entry 1-2)	优化后的 [Co(P3)] 配体 (Entry 6)	说明
产率 (Yield)	较低 (18% - 65%)	极高 (98%)	催化剂显著提升了反应效率
非对映选择性 (d r)	差, 甚至生成反向异构体	82:18 (Z型为主)	解决了传统方法难以控制立体构型的问题
对映选择性 (ee)	无或很低 (<40%)	93%	实现了手性分子的精准合成
核心作用力	无控制/热力学控制	氢键 + $\pi$ 堆积	解释了选择性来源的机理

[Co(P3)] 催化体系, 利用氢键和位阻的协同作用, 成功解决了脱氢氨基酸环丙烷化反应中立体选择性难以控制的难题, 实现了目标手性分子的高效、高选择性合成。

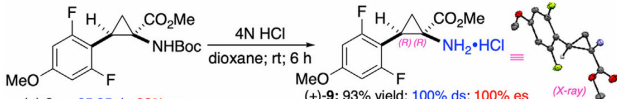


## 转化

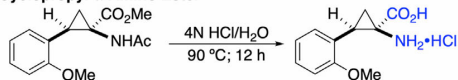
A Selective Hydrolysis of Ester Group in *N*-Protected Cyclopropyl  $\alpha$ -Amino Ester

(-)-3d: &gt; 20:1 dr; 95% ee

(-)-8: 92% yield; 100% ds; 100% es

B Selective Hydrolysis of Amide Group in *N*-Protected Cyclopropyl  $\alpha$ -Amino Ester

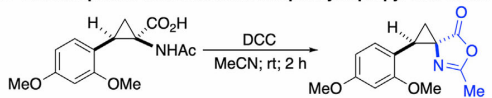
(+) -3aa: 65:35 dr; 98% ee

 (+)-9: 93% yield; 100% ds; 100% es  
 recrystallization: 56% yield; 92:8 dr; 99% ee (HCl was omitted)
C Full Hydrolysis of Both Ester and Amide Group in *N*-Protected Cyclopropyl  $\alpha$ -Amino Ester

(-)-3b: &gt; 20:1 dr; 93% ee

 (+)-10: 86% yield; 100% ds; 100% es  
 recrystallization: 69% yield; > 20:1 dr; 99% ee

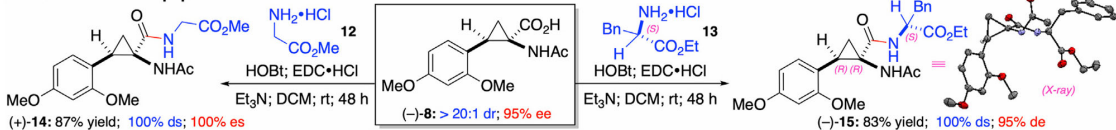
## D Enantiospecific Transformation to Spirocyclopropyl Oxazolone



(-)-8: &gt; 20:1 dr; 95% ee

(+) -11: 84% yield; 100% ds; 100% es

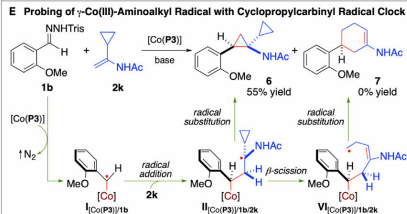
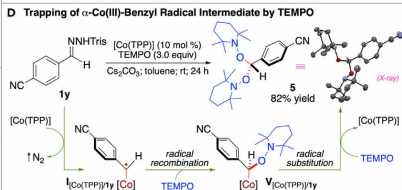
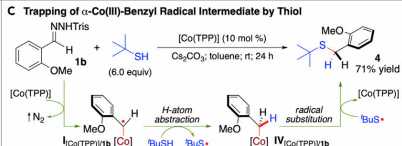
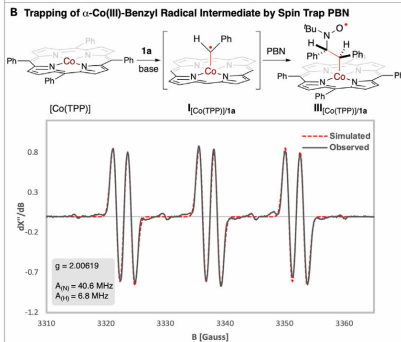
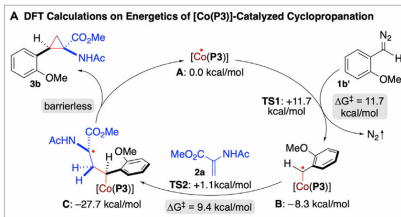
## E Construction of Dipeptides

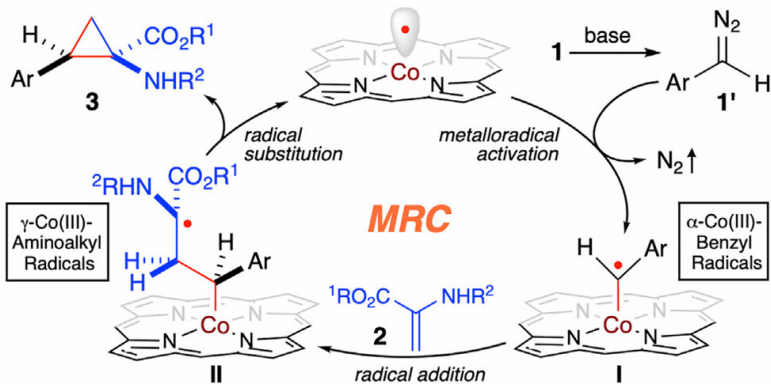
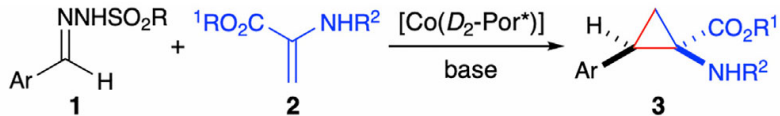


(+) -14: 87% yield; 100% ds; 100% es

(-)-8: &gt; 20:1 dr; 95% ee

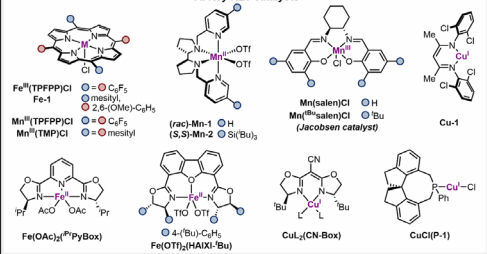
(-)-15: 83% yield; 100% ds; 95% de



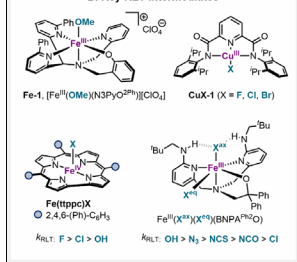


## 4 RLT催化策略关键和应用

## A. Key RLT catalysts

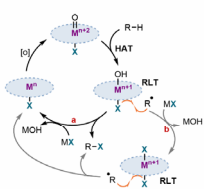


## B. Key RLT intermediates

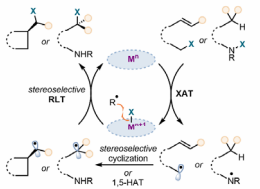


金属	催化剂 (Figure 4A)	催化的反应类型	反应描述与产物	原文实例编号
Mn	$\text{Mn}(\text{TMP})\text{Cl}$	C-H 氟化	直接对烷烃或苄位C-H键进行氟化, 以AgF为氟源。	28, 29
	Jacobsen 催化剂 (Mn-salen类)	苄位 C-H 氟化	对苄位C-H键进行氟化, 且表现出比烷基化更高的氟转移选择性。	29前体
	$(\text{rac})\text{-Mn1}$	C-H 羟基化/乙酰氧基化	在 $\text{H}_2\text{O}_2$ 和乙醚存在下, 对C-H键进行羟基化或乙酰氧基化。	25
	$(\text{S,S})\text{-Mn-2}$	对映选择性 C-H 内酯化	将羧酸的C-H键直接氧化为内酯, 实现分子内不对称氧化。	26
Fe	Fe-1 (Fe-porphyrin)	苄位 C-H 胺化	经由 $\text{Fe}(\text{III})(\text{N-Py})$ 类氮宾中间体, 对苄位C-H键进行胺化。	34
	$\text{Fe}(\text{OAc})_2(\text{iPrPyBox})$	三级 C-H 叠氮化	原位生成活性物种, 对叔碳C-H键进行叠氮化, 适用于复杂分子后期修饰。	36
	$\text{Fe}(\text{OTf})_2(\text{HAIXI-Bu})$	烯烃不对称双官能团化	催化烯烃的不对称碳叠氮化 (Carboazidation) 和氨基叠氮化 (Aminoazidation)。	42
Cu	$\text{CuCl}(\text{P-1})$ (手性Cu配合物)	光诱导不对称C-N偶联	通过光激发SET还原底物产生自由基, 再发生对映选择性的C-N键偶联。	44

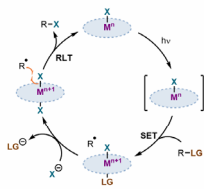
C. RLT catalysis via M=O HAT



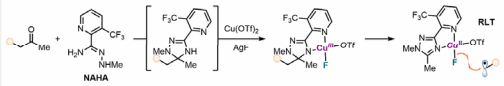
D. RLT catalysis via XAT



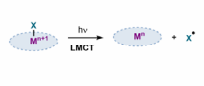
E. RLT catalysis via SET



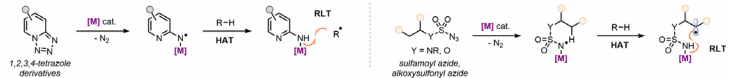
F. Deacylative approach



G. LMCT strategy



H. RLT via nitrene-like intermediates



策略模块

核心活化机制

4C. M=O 介导的 HAT-RLT

氢原子转移 (HAT)

4D. 通过 XAT 启动的 RLT

卤原子转移 (XAT)

4E. 通过 SET 启动的 RLT

单电子转移 (SET)

4F. 脱酰基氟化中的 RLT

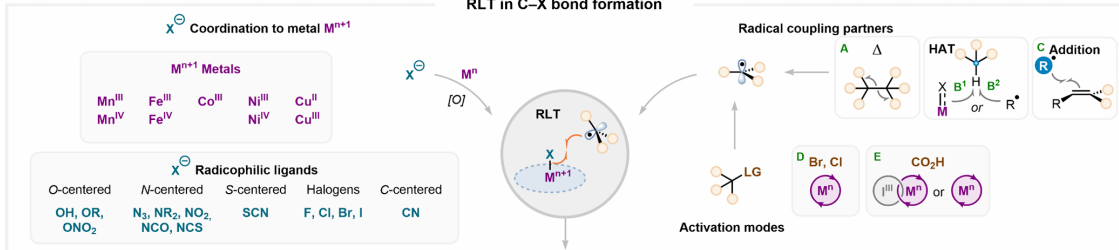
脱酰基产生自由基

4G. 通过 LMCT 启动的 RLT

配体-金属电荷转移 (LMCT)

4H. 通过类氮宾中间体的 RLT

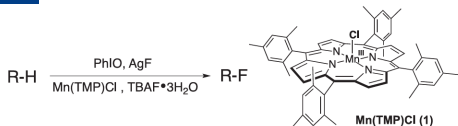
氢原子转移 (HAT) (源于氮宾自由基)



























锰催化的RLT构建C-F键

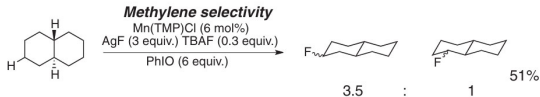
# Oxidative Aliphatic C-H Fluorination with Fluoride Ion Catalyzed by a Manganese Porphyrin

Wei Liu,<sup>1</sup> Xiongyi Huang,<sup>1</sup> Mu-Jeng Cheng,<sup>2</sup> Robert J. Nielsen,<sup>2</sup>  
William A. Goddard III,<sup>2</sup> John T. Groves<sup>1\*</sup>

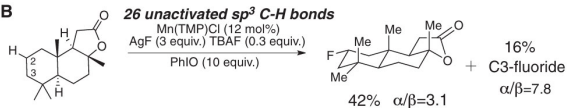


Entry	Substrate	Fluorination product	Entry	Substrate	Major fluorination product	Minor sites
1		 2, 49%	7		 8, 46% dr=6:1	C4 14%
2		 3, 51%	8		 9, 44% dr=8:1	C4 12%
3		 4, 55%	9		 10, 42%	C3 11%
4		 5, 53% 1:1.4	10		 11, 51% dr=1.5:1	C2 <2%
5		 6, 49% exo: endo=5.7	11		 12a, 30% cis/trans=1:1	12b, C3 27% cis/trans= 2:1
6		 7, 2:1*	12		 13, 49% dr=1.6:1†	C3 9%

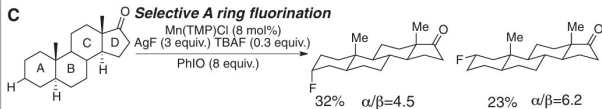
A



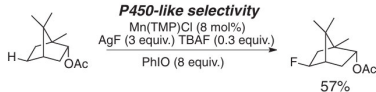
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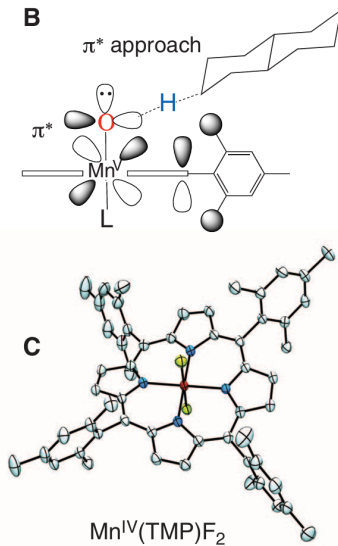
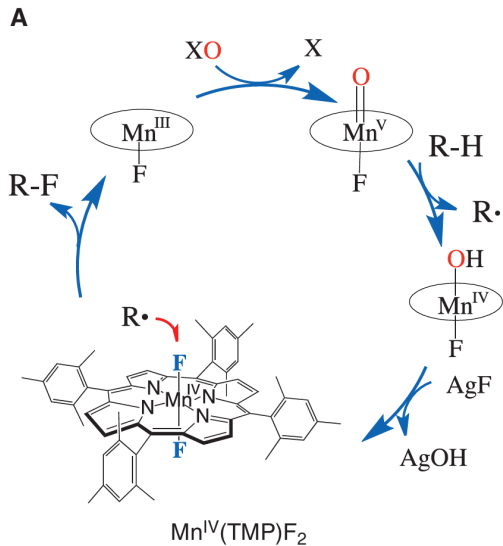


C



D





## 锰催化的RLT构建C-F键



J | A | C | S  
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

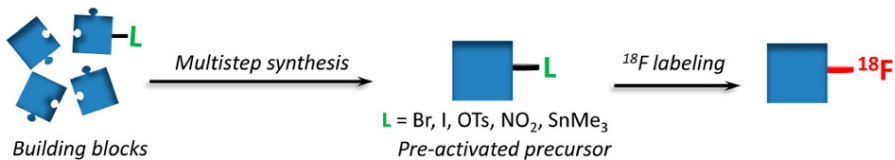
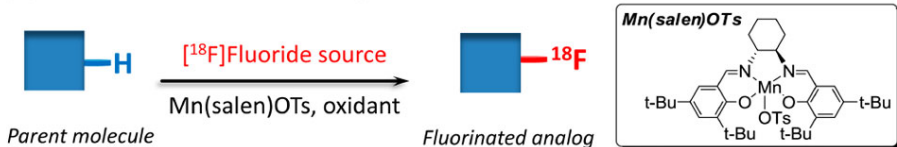
Communication

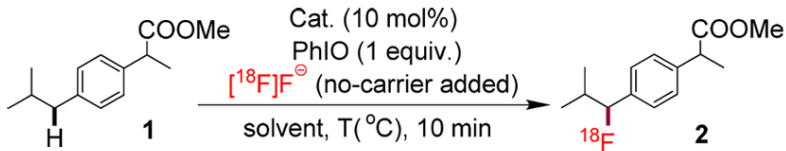
[pubs.acs.org/JACS](https://pubs.acs.org/JACS)

## Late Stage Benzylic C–H Fluorination with [ $^{18}\text{F}$ ]Fluoride for PET Imaging

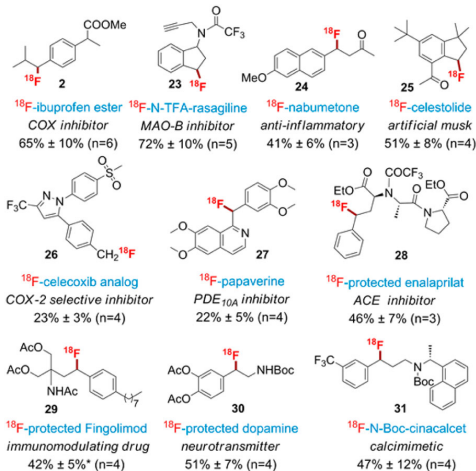
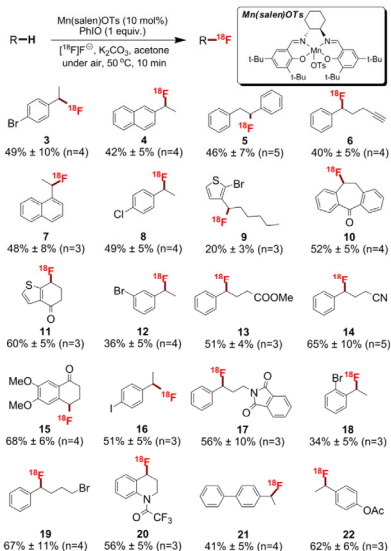
Xiongyi Huang,<sup>†,||</sup> Wei Liu,<sup>†,||</sup> Hong Ren,<sup>‡,§</sup> Ramesh Neelamegam,<sup>‡</sup> Jacob M. Hooker,<sup>\*,‡,§</sup>  
and John T. Groves<sup>\*,†</sup>

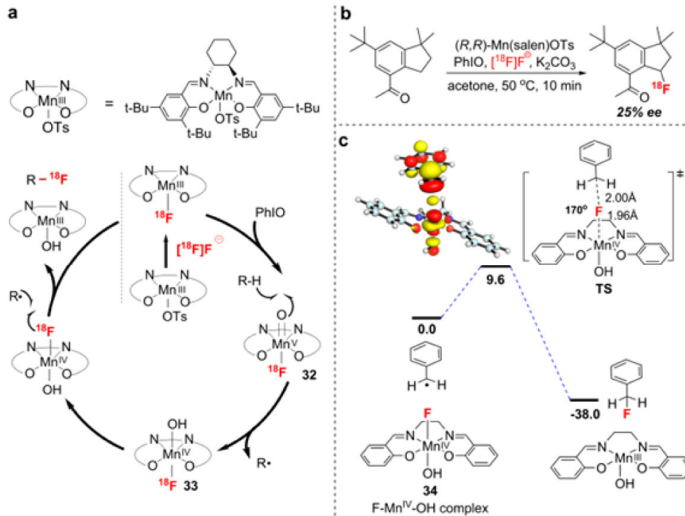
## (a) Traditional approaches: Pre-functionalization

(b) This work: Direct C-H  $^{18}\text{F}$  labeling



	catalyst	solvent	$T$	RCC
1	Mn(salen)Cl	CH <sub>3</sub> CN	50	trace
2	Mn(salen)OTf	CH <sub>3</sub> CN	50	16%
3	Mn(salen)ClO <sub>4</sub>	CH <sub>3</sub> CN	50	34%
4	Mn(salen)OTs	CH <sub>3</sub> CN	50	53%
5	Mn(salen)OTs	acetone	50	65%
6	Mn(salen)OTs	acetone	25	45%
7	Mn(salen)OTs	acetone	90	50%





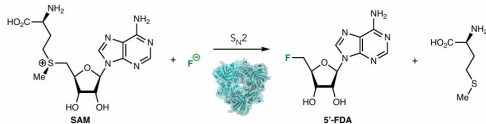
## 铁催化的RLT构建C-F键

### Biocatalytic asymmetric C(sp<sup>3</sup>)-H fluorination enabled by directed evolution of nonheme Fe enzymes

Liu-Peng Zhao<sup>1</sup>, Binh Khanh Mai<sup>2</sup>, Lida Cheng<sup>1</sup>, Fangqiu Gao<sup>1</sup>, Yunlong Zhao<sup>1</sup>, Rui Guo<sup>1</sup>, Hao Wu<sup>3</sup>, Yongda Zhang<sup>3</sup>, Peng Liu<sup>2\*</sup> and Yang Yang<sup>1,4\*</sup>

*[Nature Synthesis](#)*

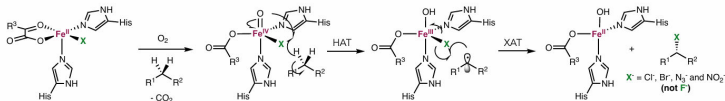
a The only known fluorinating enzyme: natural fluorinases



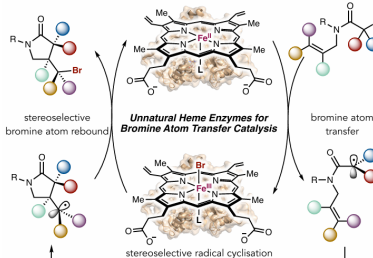
#### Challenges w/ Biocatalytic Fluorination

- Only one natural mechanism:  $S_N2$
- Limited substrate scope
- No metalloenzymes for fluorination
- Difficult asymmetric C-H fluorination

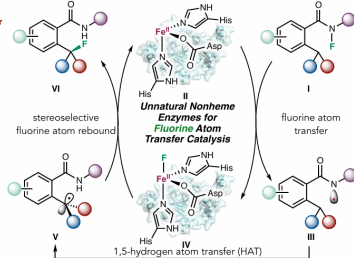
b  $\alpha$ KG-dependent nonheme Fe halogenases: natural halogenating enzymes using a radical rebound mechanism for C-X bond formation



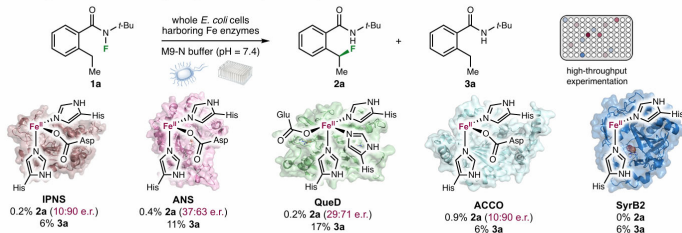
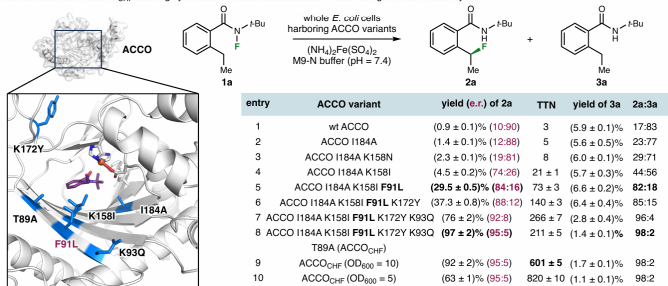
c Our new-to-nature heme-dependent bromine atom transferases (*Science* 2021)

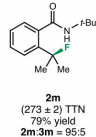
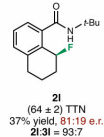
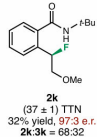
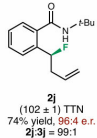
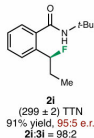
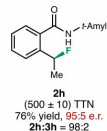
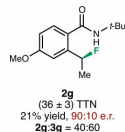
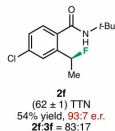
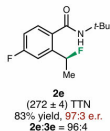
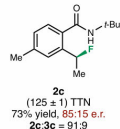
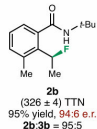
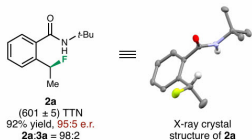
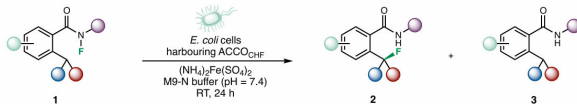


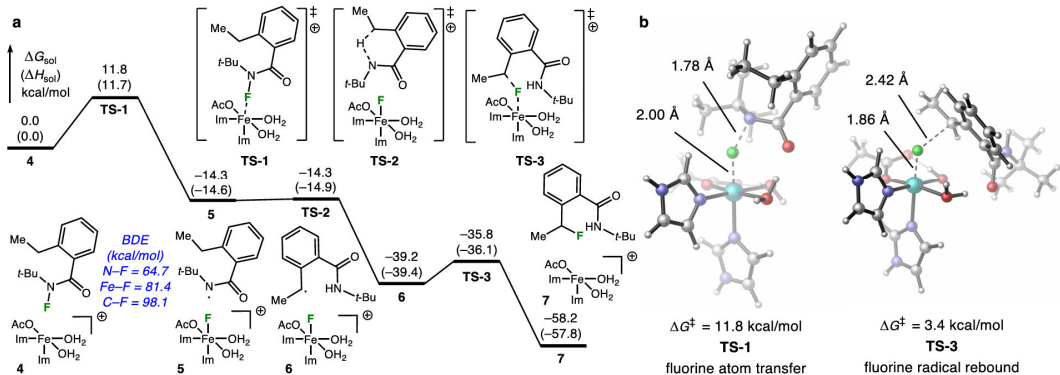
d This work: new-to-nature nonheme Fe fluorine atom transferases



## a Discovery of fluorine transfer activity among natural Fe-dependent enzymes

b Directed evolution of ACCO<sub>CHF</sub> as a highly chemo- and enantioselective C-H fluorinating nonheme Fe enzyme





## 铁催化的RLT构建C-N键

RLT via nitrene-like intermediates

# Iron-Catalyzed Intermolecular Amination of Benzylic C(sp<sup>3</sup>)-H Bonds

Hillol Khatua, Subrata Das, Sima Patra, Sandip Kumar Das, Satyajit Roy,  
and Buddhadeb Chattopadhyay\*

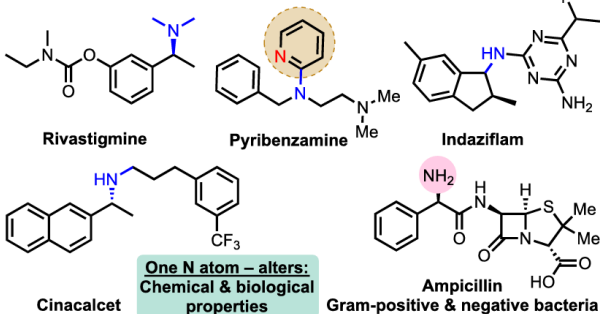
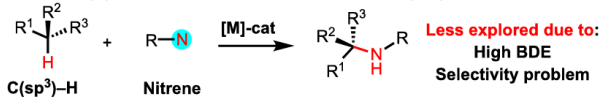
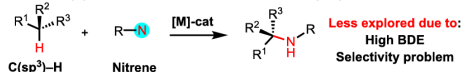


Cite This: *J. Am. Chem. Soc.* 2022, 144, 21858–21866

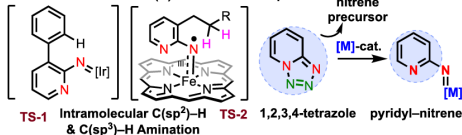
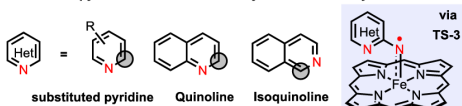
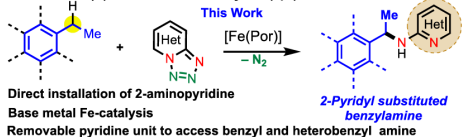


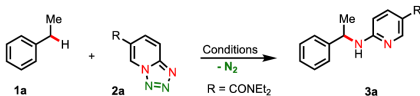
Read Online

## (A) Benzyl Amine Pharmaceuticals

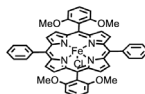
(B) Intermolecular Nitrene Insertion to C(sp<sup>3</sup>)-H Bond(B) Intermolecular Nitrene Insertion to C(sp<sup>3</sup>)-H Bond

## (C) Our Previous Reports

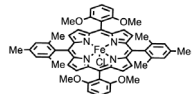
(D) Intermolecular Benzylic C(sp<sup>3</sup>)-H Amination



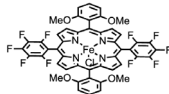
#	Catalyst (mol%)	Reductant (mol%)	Solvent	T °C	Time (h)	3a (%)
1	Fe(TPP)Cl (5)	Zn (20)	PhH	100	16	trace
2	Fe(TPP)Cl (10)	Zn (20)	PhH	100	16	15
3	Fe(TMP)Cl (10)	Zn(20)	PhH	100	16	22
4	Fe(TPFPP)Cl (10)	Zn (20)	PhH	100	16	trace
5	Fe(TDCPP)Cl (10)	Zn (20)	PhH	100	16	10
6	Fe(TMPP)Cl (10)	Zn (20)	PhH	100	16	30
7	Fe(por)cat-I (10)	Zn (20)	PhH	100	16	36
8	Fe(por)cat-II (10)	Zn (20)	PhH	100	16	25
9	Fe(por)cat-III (10)	Zn (20)	PhH	100	16	74
10	Fe(por)cat-III (10)	Zn (20)	PhH	70	74	
11	<b>Fe(por)cat-III (5)</b>	<b>Zn(20)</b>	<b>PhH</b>	<b>70</b>	<b>16</b>	<b>87(82)<sup>b</sup></b>
12	<b>Fe(por)cat-III (5)</b>	<b>Zn(20)</b>	<b>PhCl</b>	<b>70</b>	<b>16</b>	<b>83</b>
13	Fe(por)cat-IV (10)	Zn(20)	PhH	100	16	67
14	Fe(por)cat-III (10)	-	PhH	100	16	0
15	-	Zn(20)	PhH	100	16	0



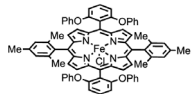
Fe(por)cat-I



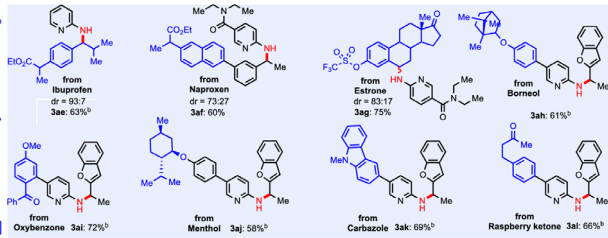
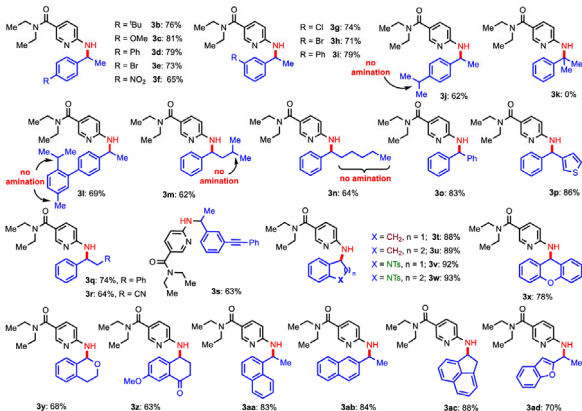
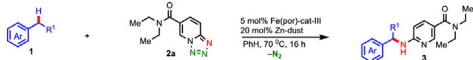
Fe(por)cat-III

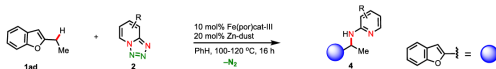


Fe(por)cat-II

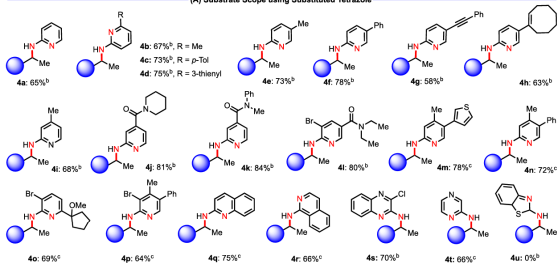


Fe(por)cat-IV

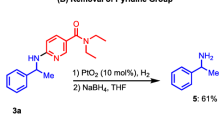




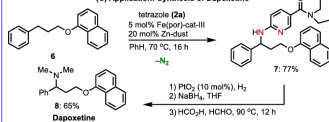
(A) Substrate Scope using Substituted Tetrazole



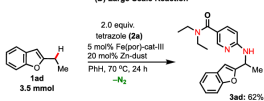
(B) Removal of Pyridine Group



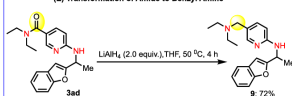
(C) Application: Synthesis of Dapoxetine

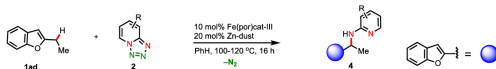


(D) Large Scale Reaction

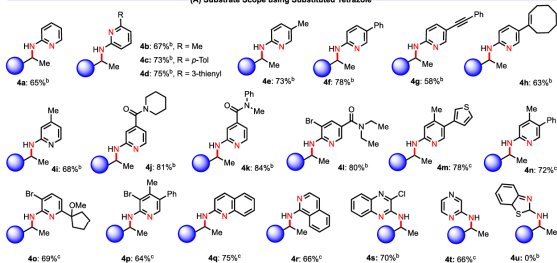


(E) Transformation of Amide to Benzyl Amine

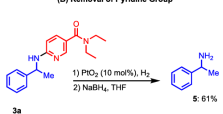




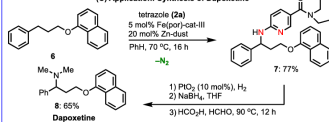
(A) Substrate Scope using Substituted Tetrazole



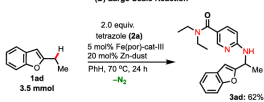
(B) Removal of Pyridine Group



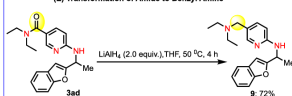
(C) Application: Synthesis of Dapoxetine



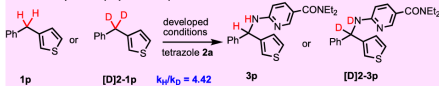
(D) Large Scale Reaction



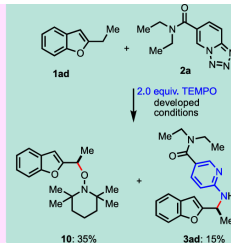
(E) Transformation of Amide to Benzyl Amine



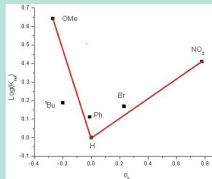
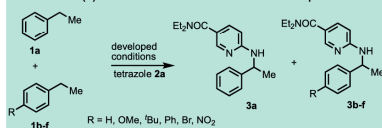
## Parallel competition (Separate Vial)



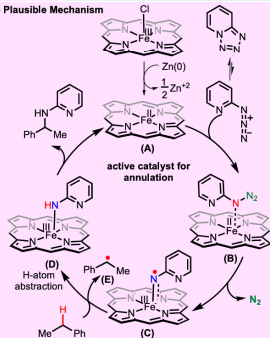
## Intramolecular Competition



## (B) Correlation of Products ratios with Hammett plot



## (D) Plausible Mechanism



## 铁催化的LMCT-RLT构建C-N键

nature communications






Article

<https://doi.org/10.1038/s41467-022-35560-3>

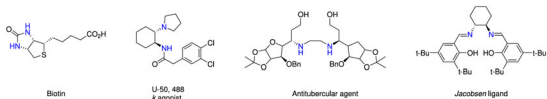
# Photochemical diazidation of alkenes enabled by ligand-to-metal charge transfer and radical ligand transfer

Received: 26 July 2022

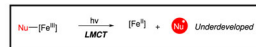
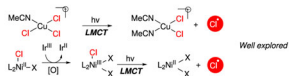
Accepted: 8 December 2022

Kang-Jie Bian<sup>1,2</sup>, Shih-Chieh Kao<sup>1,2</sup>, David Nemoto Jr. <sup>1</sup>, Xiao-Wei Chen<sup>1</sup> & Julian G. West <sup>1</sup> 

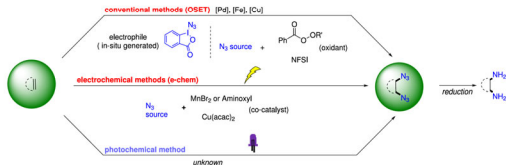
## a Vicinal diamines in pharmaceuticals/natural product and synthesis



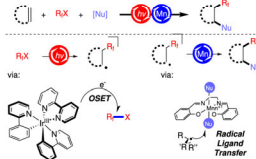
## c Radical generation via Ligand-to-Metal Charge Transfer (LMCT)



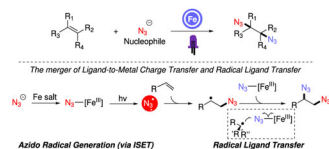
## b Accessing vicinal diamines from diazidation of alkenes via outer-sphere single electron transfer (OSET) or electrochemical method (e-chem)

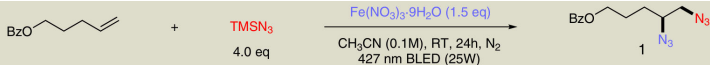


## d Modular difunctionalization via Radical Ligand Transfer (RLT)



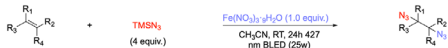
## e Alkene diazidation via LMCT and Ligand Transfer (this work)





Entry	Deviation from Standard Conditions	Yield (%) <sup>a</sup>
1	none	86 (84)
2 <sup>b</sup>	1.5 eq $\text{CuX}_2$ (X = Br, Cl) instead of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	ND
3 <sup>c</sup>	1.5 eq $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ instead of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	trace
4	1.5 eq $\text{Fe}(\text{acac})_3$ instead of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	trace
5	DCM	ND
6	THF	ND
7	EA	64
8	Acetone	60
9 <sup>d</sup>	0.2 M, 0.05 M	78, 82
10	2.0 eq $\text{TMSN}_3$	40
11	1.0 eq $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	80
12	CFL (26 W), 390 nm, 456 nm, 525 nm LED (25 W)	40–82
13	no iron salt	NR
14	in the dark	NR
15	under air	72
16 <sup>e</sup>	under air with 20% $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$	48

# RLT部分

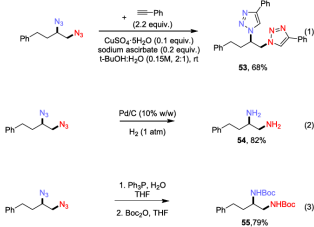


1. R = C <sub>6</sub> H <sub>13</sub> , 80%	5.56%	6.68%	*7.72%	8.64%
2. R = (CH <sub>2</sub> ) <sub>5</sub> Ph, 70%				
3. R = (CH <sub>2</sub> ) <sub>5</sub> Ph, 70%				
4. R = Cyclopentyl, 71%				
*9.58%	10.75%	11.62%	12.49%	13.63%
14.70%	15.87%	16.67%	17.61%	18.66%
19.74%	20.53%	21.55%	22. R = Ph, 76% 23. R = OPh, 74%	*24. 68% (1.3:1)
25.73% (1.3:1)	*26. 84% (1.6:1)	27. 70%	28. 72% (1:1)	29. R = Me, 72% 30. R = i-Pr, 67%
31. 64% (>20:1)	*32. 62% (4.4:1)	33. 78% (2.5:1)	34. 65% (1:1)	35. 68%
36. 74% (2:1)	37. 79% (1.4:1)	38. 61% (2.3:1)	39. 62% (2:1)	40. 70% (4.5:1)

Drugs/natural product derivatives + TMSN<sub>3</sub>  $\xrightarrow[\text{CH}_3\text{CN, RT, 24h 427 nm BLED (25w)}]{\text{Fe(NO}_3)_3 \cdot 9\text{H}_2\text{O (1.0 equiv.)}}$

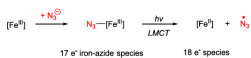
from ibuprofen 41. 60%	from Flurbiprofen 42. 79%	from Loxoprofen 43. 40%
from isoxepac 44. 64%	from Naproxen *45. 52%	from Flavone-derivative 46. 62%
from L-Menthyl 47. 70%	from (-)-Borneol 48. 72%	from D-Galactopyranosylamine 49. 62%
from 18β-Glycyrrhetic acid 50. 59%	from Oleic acid *51. 74%	from Mycophenolic acid *52. 48% (3.5:1)

A

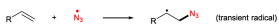


C

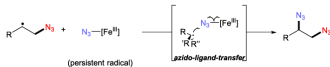
## Azido Radical Generation (Step 1)



## Radical Addition (Step 2)

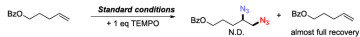


## Radical Ligand transfer (Step 3)

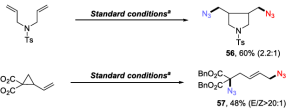


B

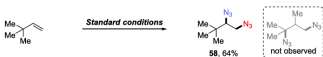
## 1. radical scavenger experiment



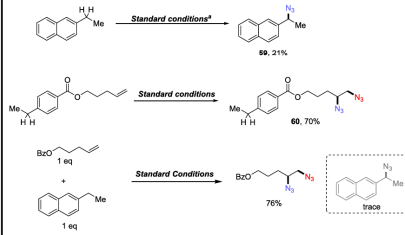
## 2. radical clock experiments



## 3. carboradical vs carbocation









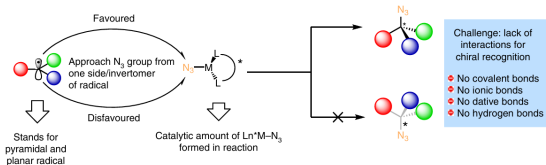
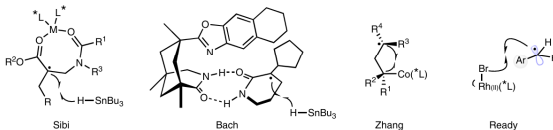
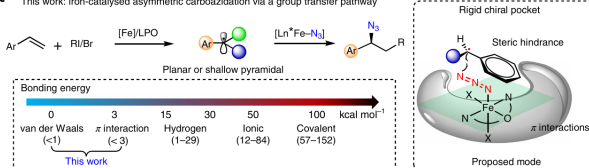
## 4. direct C-H azidation enabled by LMCT/RLT

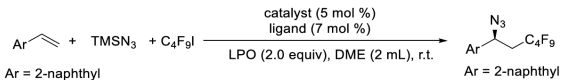


铁催化的RLT构建C-N键

# Iron-catalysed asymmetric carboazidation of styrenes

Liang Ge<sup>1,4</sup>, Huan Zhou<sup>1,4</sup>, Mong-Feng Chiou <sup>1,4</sup>, Heming Jiang<sup>2</sup>, Wujun Jian<sup>1</sup>, Changqing Ye<sup>1</sup>, Xiaoyan Li<sup>1</sup>, Xiaotao Zhu<sup>1</sup>, Haigen Xiong<sup>1</sup>, Yajun Li <sup>1</sup>, Lijuan Song<sup>2</sup>, Xinhao Zhang <sup>2</sup>  and Hongli Bao <sup>1,3</sup> 

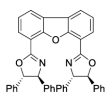
**a** Enantioselective azidation on untethered radical centre

**b** State-of-the-art stereocontrol on radical centres via atom/group transfer pathways

**c** This work: iron-catalysed asymmetric carboazidation via a group transfer pathway

 How does the chiral metal complex <sup>\*</sup>LnMN<sub>3</sub> recognize the free radicals? By π and van der Waals interactions.



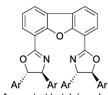
entry <sup>a</sup>	catalyst	yield <sup>b</sup> (%)	er
1	Fe(OTf) <sub>2</sub>	59	64:36
2	CoCl <sub>2</sub>	trace	/
3	MnC <sub>2</sub> O <sub>4</sub> ·2H <sub>2</sub> O	trace	/
4	Phthalocyanine iron	trace	/
5	FeCl <sub>2</sub>	15	55:45
6	iron powder	9	53:47
8	FeC <sub>2</sub> O <sub>4</sub>	trace	/
9	FeSO <sub>4</sub> ·7H <sub>2</sub> O	6	57:43



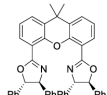
**L1**  
73% yield, 64:36 er



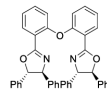
**L2 (HAI-XI-H)**  
79% yield, 82:18 er



Ar = *p*-*tert*-butylphenyl  
**L3 (HAI-XI-tBu)**  
80% yield, 94:6 er



**L4**, trace



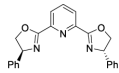
**L5**, trace



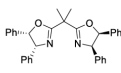
**L6 (boxmi)**, trace



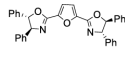
**L7**  
43% yield, 50:50 er



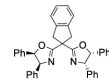
**L8 (pybox)**, trace



**L9**  
57% yield, 48:52 er



**L11**  
16.4% yield, 54:46 er



**L10**  
46% yield, 53.5:46.5 er



**L12**  
66% yield, 46:54 er



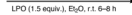
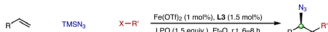
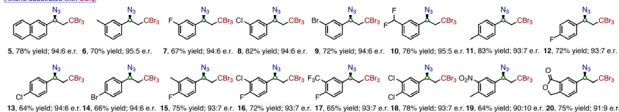
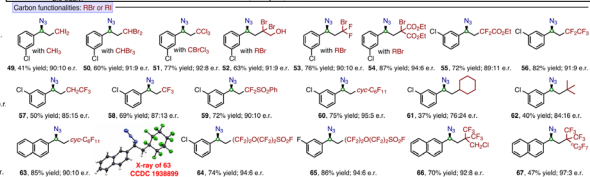
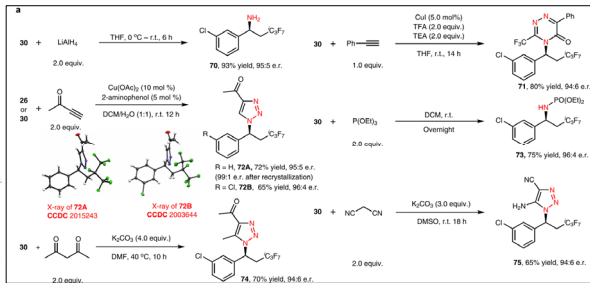
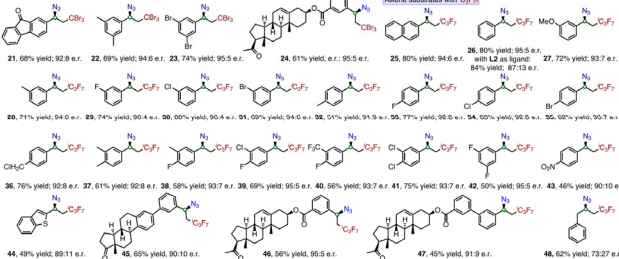
**L13**, trace

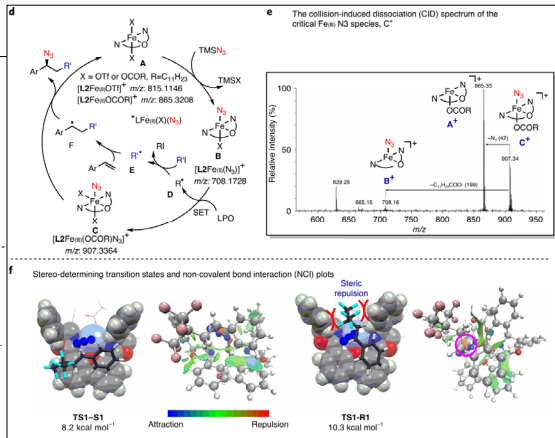
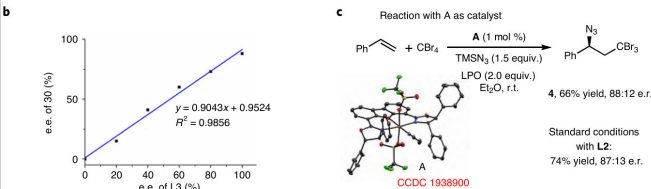
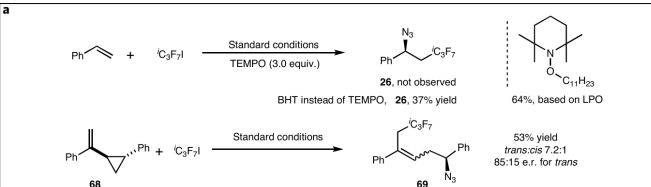


**L14**  
51% yield, 81:19 er



**L15** Ar = *p*-trimethylsilylphenyl, 95%, 90:10 er  
**L16** Ar = 3,5-dimethylphenyl, 42%, 64:36 er  
**L17** Ar = 3,5-di-*tert*-butylphenyl, 27%, 72:28 er

Alkene substrates with CBr<sub>3</sub>Alkene substrates with C<sub>2</sub>F<sub>5</sub>



铜催化自由基加成的RLT构建C-X键

# Kharasch-Type Haloalkylation of Alkenes by Photoinduced Copper Catalysis

Yuan Cai, Mahiob Dawor, Gaurav Gaurav, and Tobias Ritter\*

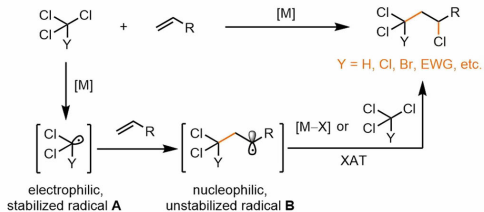


Cite This: *J. Am. Chem. Soc.* 2025, 147, 18438–18444

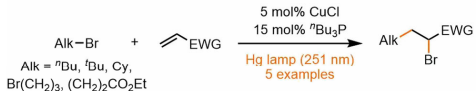


Read Online

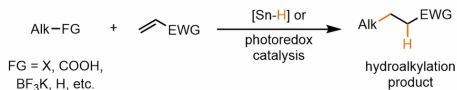
## a. Kharasch addition, since 1945, ref 1



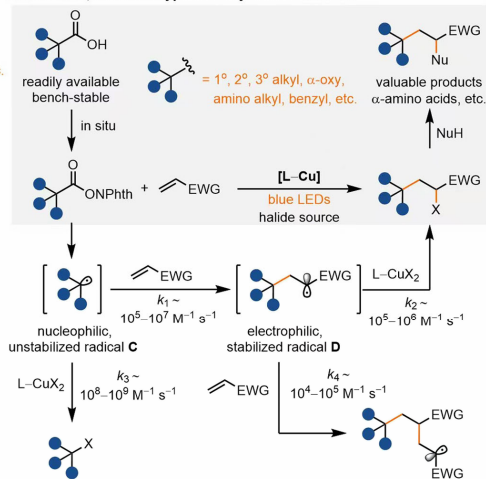
## b. Mitani, 1983, ref 10

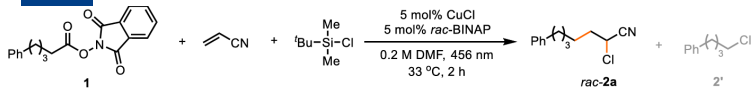


## c. Giese reaction, since 1983, ref 12

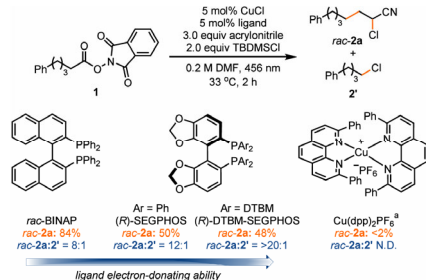


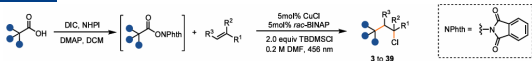
## d. This work, Kharasch-type haloalkylation of alkenes



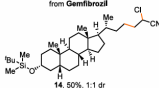
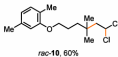


entry	variations	yield of <i>rac</i> -2a, 2' (%)	entry	variations	yield of <i>rac</i> -2a, 2' (%)
1	none	84, 10	12	<i>N</i> -isopropylacrylamide	30, 27
2	1 was generated in one pot	71, 18		<b>solvents</b>	
3	in air	78, 14	13	MeCN	10, 6
4	2.0 equiv 1 and 1.0 equiv acrylonitrile	93, 72	14	THF	18, 10
	<b>(psuedo)halide sources</b>		15	DCM	5, 2
5	Tetrabutylammonium chloride	3, 5	16	DMSO	<2, <2
6	Pyridine hydrochloride	61, 22	17	1,4-Dioxane	26, 20
7	TMSCl	69, 15		<b>ligands</b>	
8	TMSBr	41, 54	18 <sup>b</sup>	Cu(dpp) <sub>2</sub> PF <sub>6</sub>	<2, <2
9 <sup>a</sup>	TMSBr	85, 97	19	Xantphos	5, 3
10 <sup>a</sup>	TMSN <sub>3</sub>	6, <2	20	( <i>R</i> )-Segphos	50, 4
	<b>Michael acceptors</b>		21	( <i>R</i> )-DTBM-segphos	48, <2
11	Methyl acrylate	44, 22	22	DPPF	<2, <2

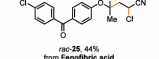
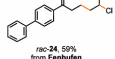
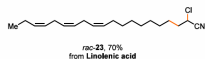
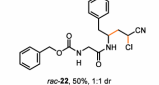
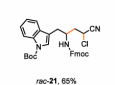
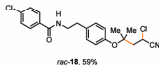
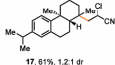
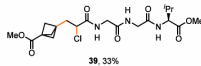
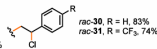


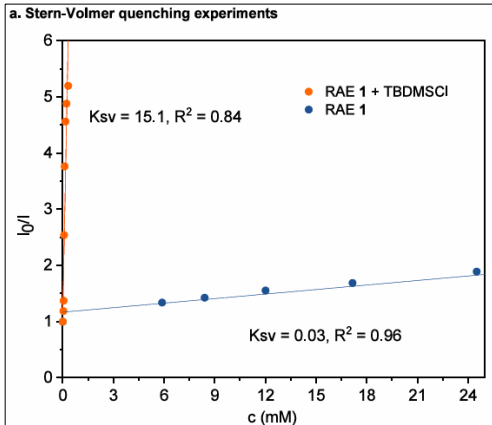


### Scope of carboxylic acids\*

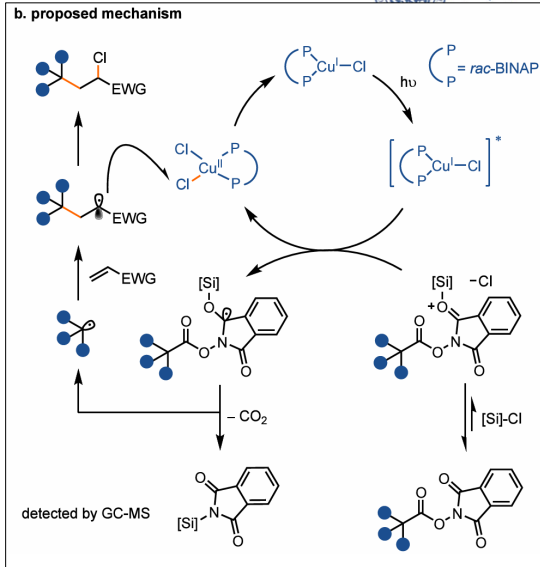


### Scope of alkenes<sup>b</sup>





这一观察结果与硅基加速反应速率,其通过降低RAE的还原电位实现。



锰催化自由基加成的RLT构建C-X键

## Modular Difunctionalization of Unactivated Alkenes through Bio-Inspired Radical Ligand Transfer Catalysis

Kang-Jie Bian, David Nemoto, Jr., Shih-Chieh Kao, Yan He, Yan Li, Xi-Sheng Wang,\*  
and Julian G. West\*

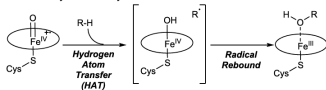


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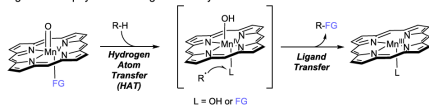


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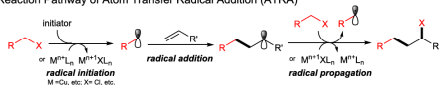
## a Oxidation of C-H Bonds by P450 Enzymes



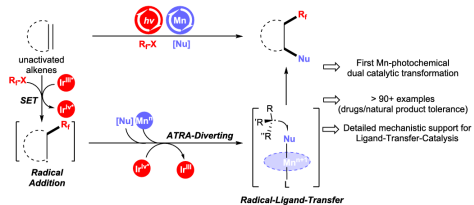
## b Manganese Porphyrin Mimicking P450 Enzymes in C-H Functionalization

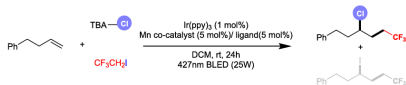


## c Reaction Pathway of Atom Transfer Radical Addition (ATRA)

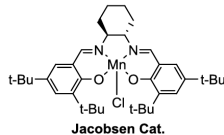
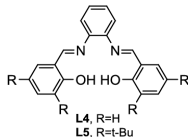
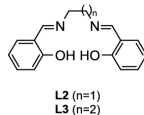
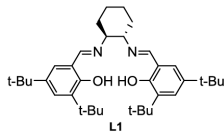


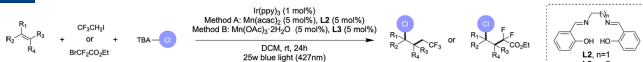
## d This work: Modular Difunctionalization via Radical Ligand Transfer Catalysis



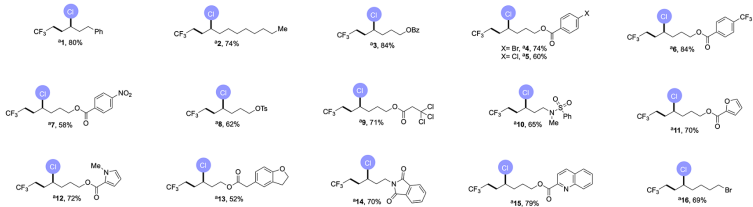


Entry	Mn cat.	Ligand	Solvent	Yield (%) <sup>a</sup>
1	Mn(OAc) <sub>3</sub> ·2H <sub>2</sub> O	L1	DCM	28
2	MnCl <sub>2</sub>	L1	DCM	12
3	Mn(OAc) <sub>2</sub> ·2H <sub>2</sub> O	L1	DCM	20
4 <sup>b</sup>	Jacobsen cat.	none	DCM	16
5	Mn(acac) <sub>2</sub>	L1	DCM	48
6	Mn(acac) <sub>2</sub>	L2	DCM	60
7	Mn(acac) <sub>2</sub>	L3	DCM	50
8	Mn(acac) <sub>2</sub>	L4	DCM	40
9	Mn(acac) <sub>2</sub>	L5	DCM	36
10	Mn(acac) <sub>2</sub>	none	DCM	32
11 <sup>c</sup>	Mn(acac) <sub>2</sub>	L2	DCM	28/30
12	Mn(acac) <sub>2</sub>	L2	MeCN	36
13	Mn(acac) <sub>2</sub>	L2	Dioxane	0/12
14	Mn(acac) <sub>2</sub>	L2	Toluene	trace
15	Mn(acac) <sub>2</sub>	L2	MeOH	24
16 <sup>d</sup>	Mn(acac) <sub>2</sub>	L2	DCM	60
17 <sup>e</sup>	Mn(acac) <sub>2</sub>	L2	DCM	56
18 <sup>f</sup>	Mn(acac) <sub>2</sub>	L2	DCM	64
19 <sup>g</sup>	Mn(acac) <sub>2</sub>	L2	DCM	40
20 <sup>h</sup>	Mn(acac) <sub>2</sub>	L2	DCM	72
21 <sup>f,h</sup>	Mn(acac) <sub>2</sub>	L2	DCM	82(80)
22 <sup>i</sup>	Mn(acac) <sub>2</sub>	L2	DCM	NR
23 <sup>j</sup>	Mn(acac) <sub>2</sub>	L2	DCM	NR
24 <sup>k</sup>	Mn(acac) <sub>2</sub>	L2	DCM	0/44
25 <sup>l</sup>	none	none	DCM	18

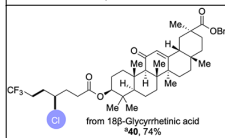
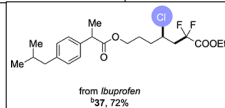
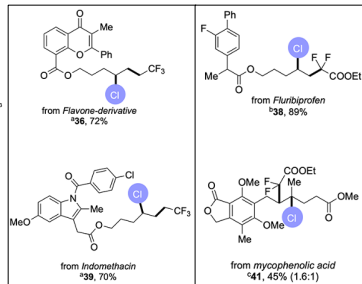
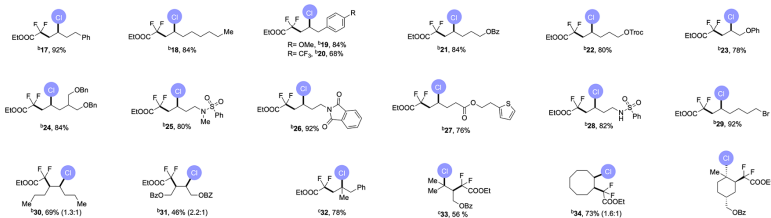




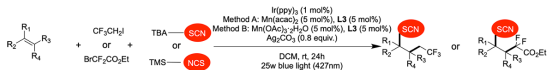
## Trifluoroethylation scope



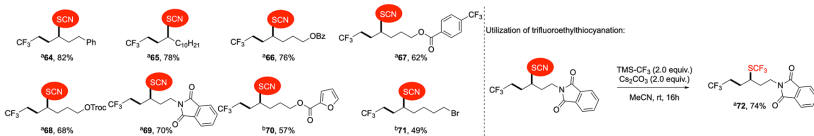
## Difluoroalkylation scope







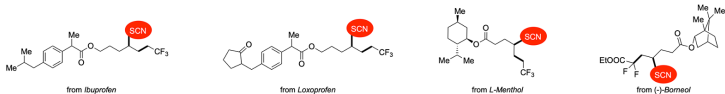
## Trifluoroethylation scope



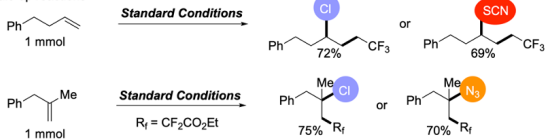
## Difluoroalkylation scope



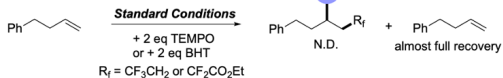
## Drugs/Natural product scope



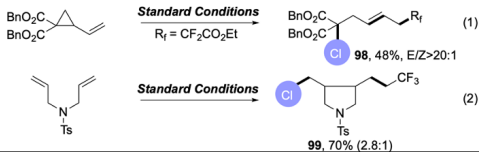
## a Scale-up reactions



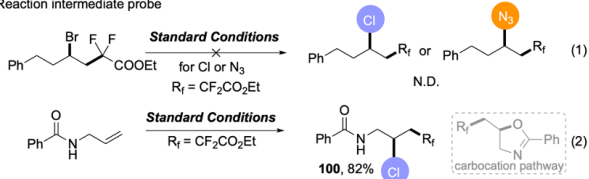
## b Radical scavenger trapping



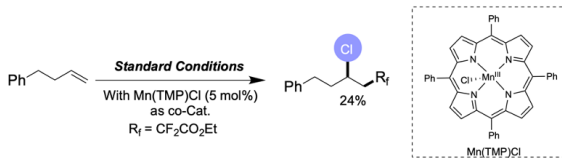
## c Radical clock experiments

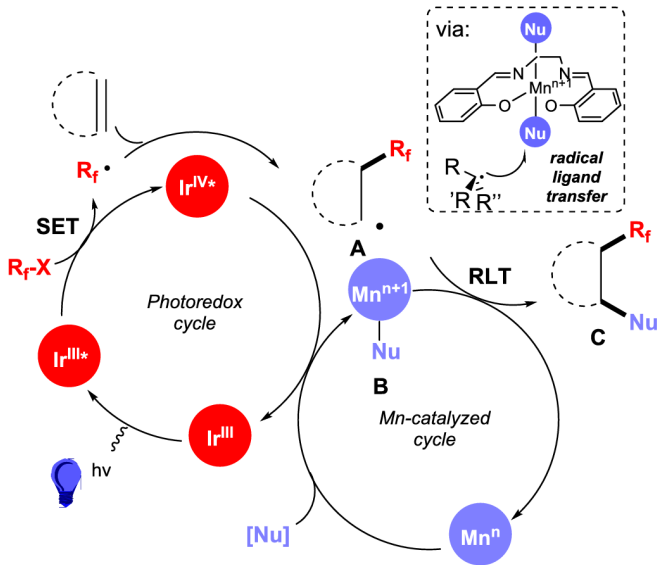


## d Reaction intermediate probe



## e Reductive elimination vs Radical oxidation







# Proposal

