

C(sp³) - C(sp³) bond formation via S_H2 Reaction

Literature Seminar #1

2024/11/21

B4 Yusuke Nakamura

Contents

1. Introduction

2. Main

- Biomimetic Approach (Fe catalyzed)**
- Combination of S_H2 and MHAT (Co catalyzed)**
- Expansion of substrate scope (Ni catalyzed)**

3. Summary

Contents

1. Introduction

2. Main

- Biomimetic Approach (Fe catalyzed)
- Combination of S_H2 and MHAT (Co catalyzed)
- Expansion of substrate scope (Ni catalyzed)

3. Summary and Perspective

C(sp³) - C(sp³) Bond Formation

C(sp³) - C(sp³) Bond
→ Ubiquitous in bioactive molecules

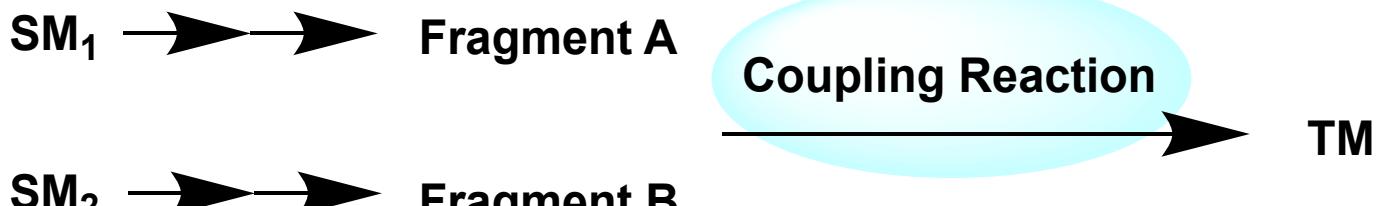
- **C(sp³) rich compounds have ...**

1. Three-dimensional structure
2. Increased water solubility
3. Low melting point



High probability of being drug

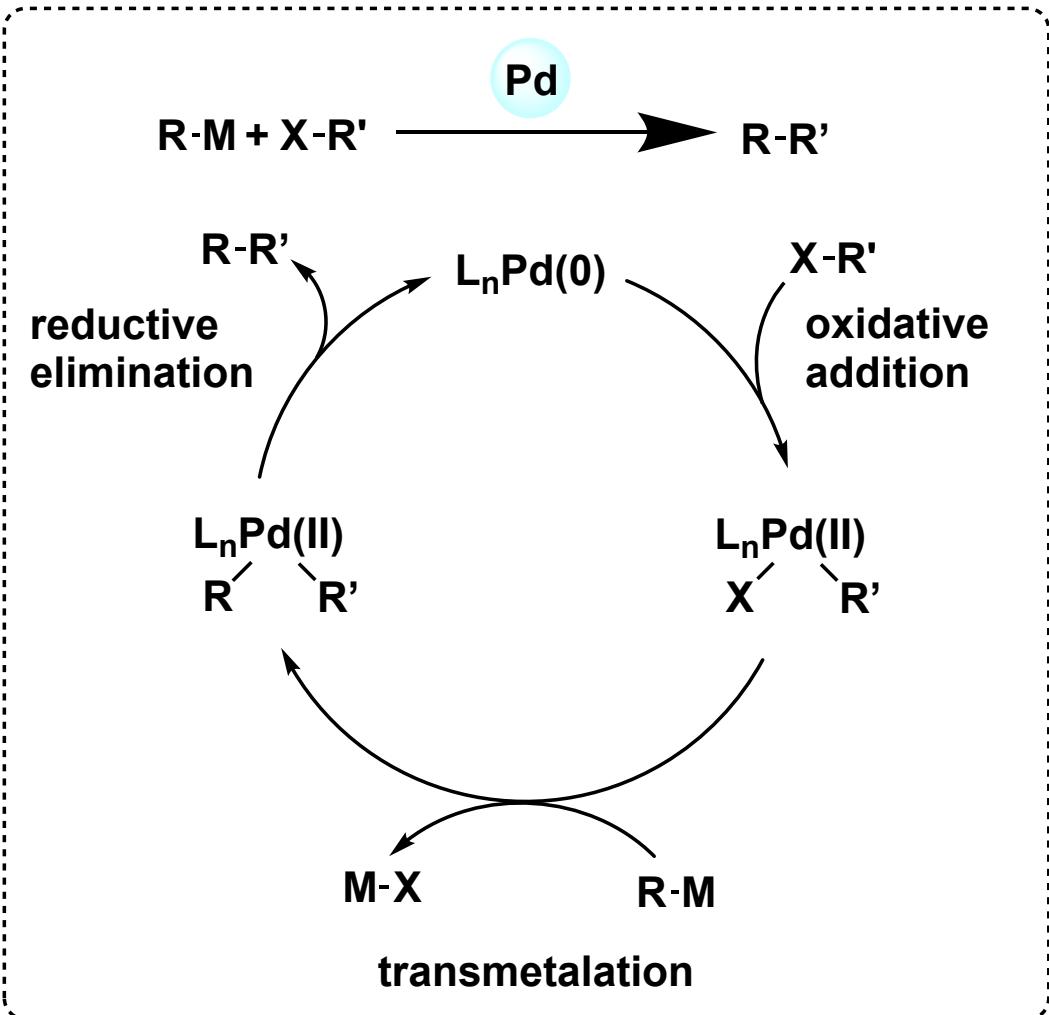
- **Convergent synthesis**



C(sp³) - C(sp³) coupling reactions available at the late stage are important.

Conventional Cross Coupling Reactions

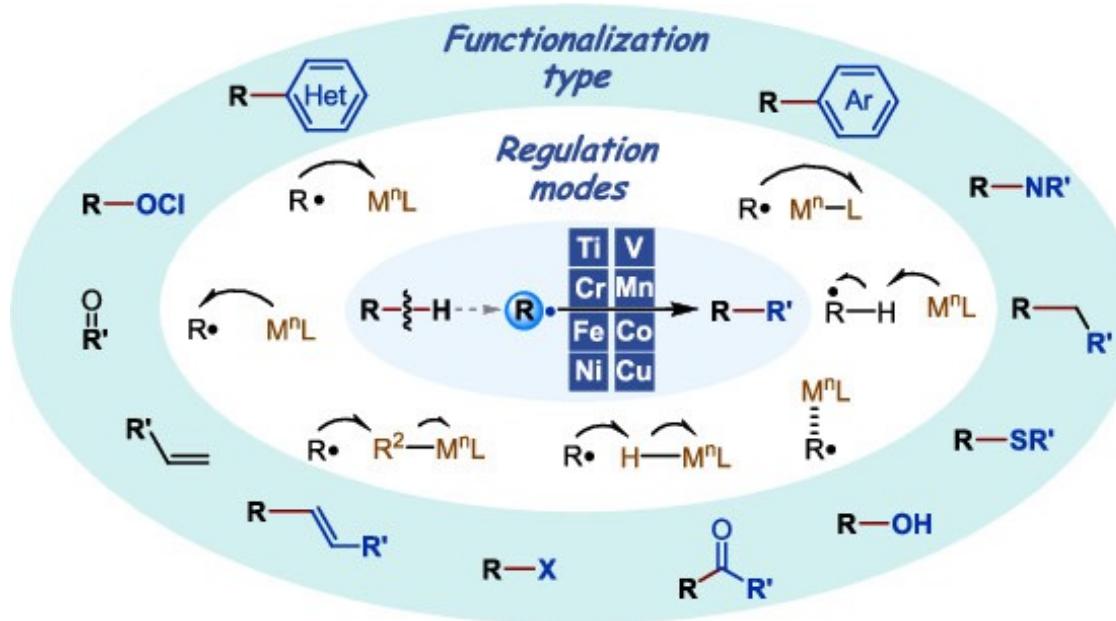
Example ... Pd based cross coupling
(Suzuki-Miyaura coupling, Negishi coupling etc...)



Challenges

- 1. Expensive and toxic Pd cat**
- 2. Rapid β -H elimination in Pd-alkyl complex**
→ mainly used for $C(sp^2) - C(sp^2)$ or $C(sp^2) - C(sp^3)$ bond forming

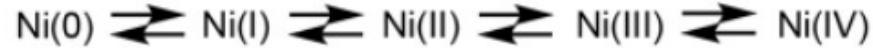
First-Row Transition Metals



Characteristics

- Earth-abundant and less toxic
- Lower electron negativity than Pd
- Variable oxidation states (ex $\text{Ni(I)} \sim \text{Ni(IV)}$)
→ single electron pathway

ex

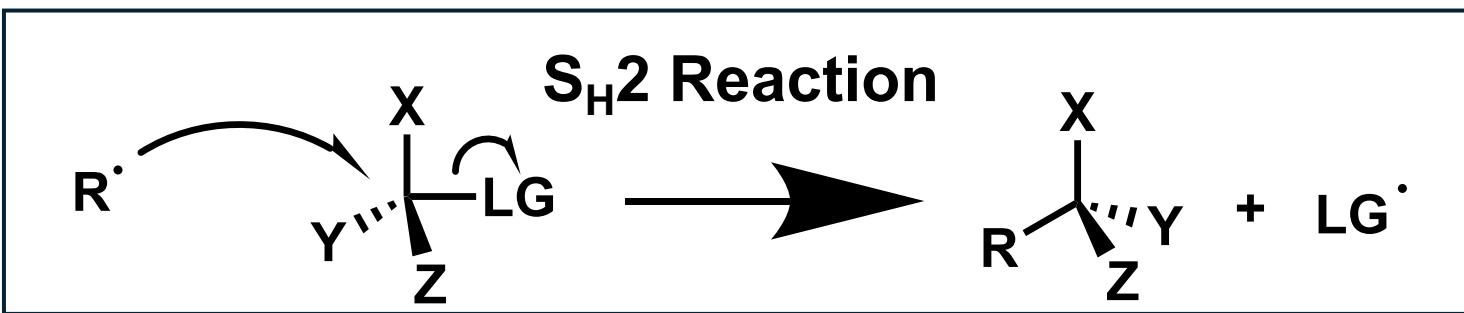


Often paramagnetic

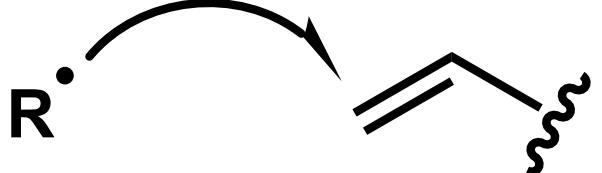


Usually diamagnetic

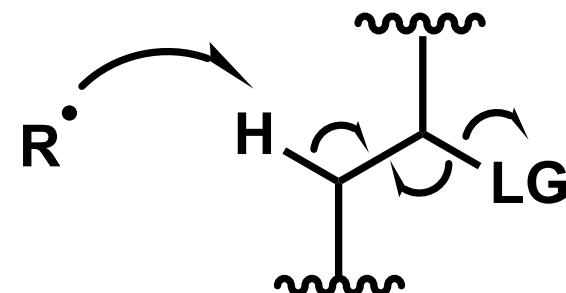
Bimolecular Homolytic Substitution (S_H2) Reaction



- A fundamental step in radical chemistry
- Past examples of synthetic applications were limited.
← Homolytic displacements at other centers are usually favored.



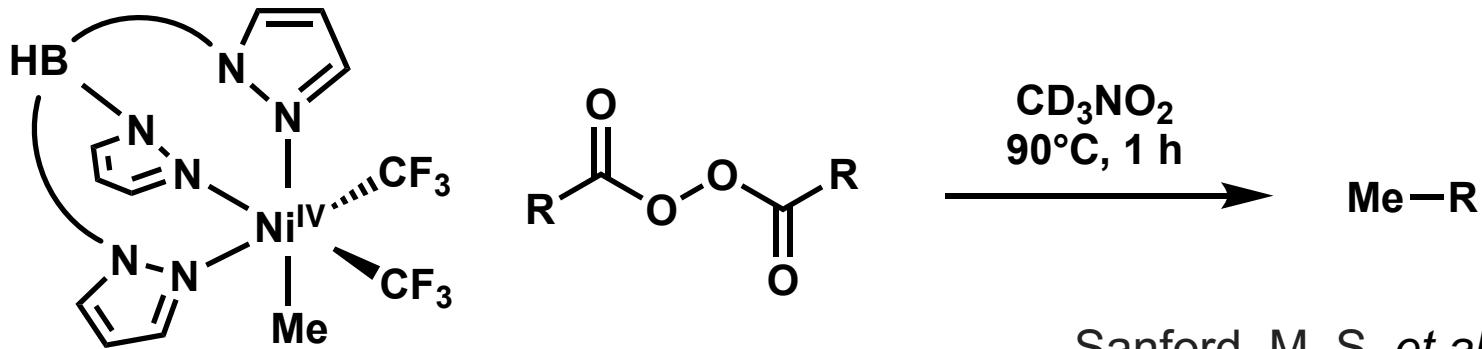
addition to unsaturated bond



withdrawal of hydrogen atom

Integration Transition Metal and S_H2 Reaction (Past)

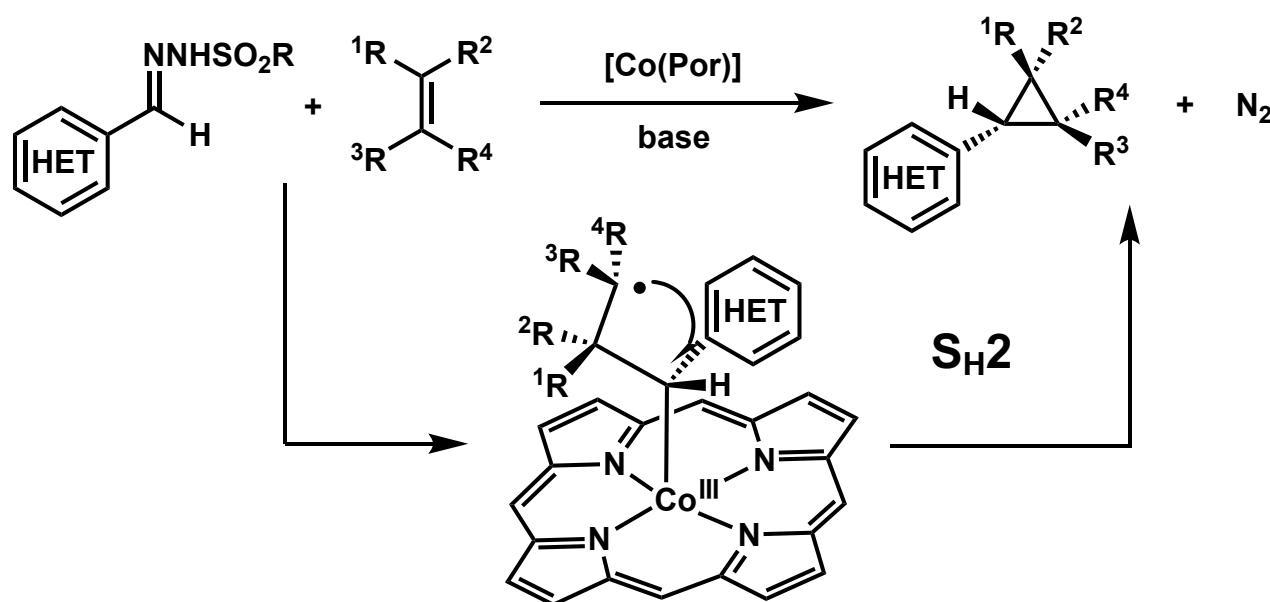
Example 1. Sanford Group



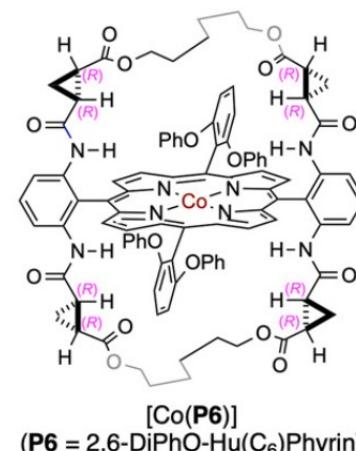
- High-valent Ni
- Requires 1 equivalent of Ni
- Limited substrate scope

Sanford, M. S. et al.; *J. Am. Chem. Soc.* 2019, 141, 8914

Example 2. Zhang Group



- Co(II)-based metalloradical catalysis (MRC)
- Intramolecular reaction
- Need multi-step to synthesize cobalt porphyrin cat

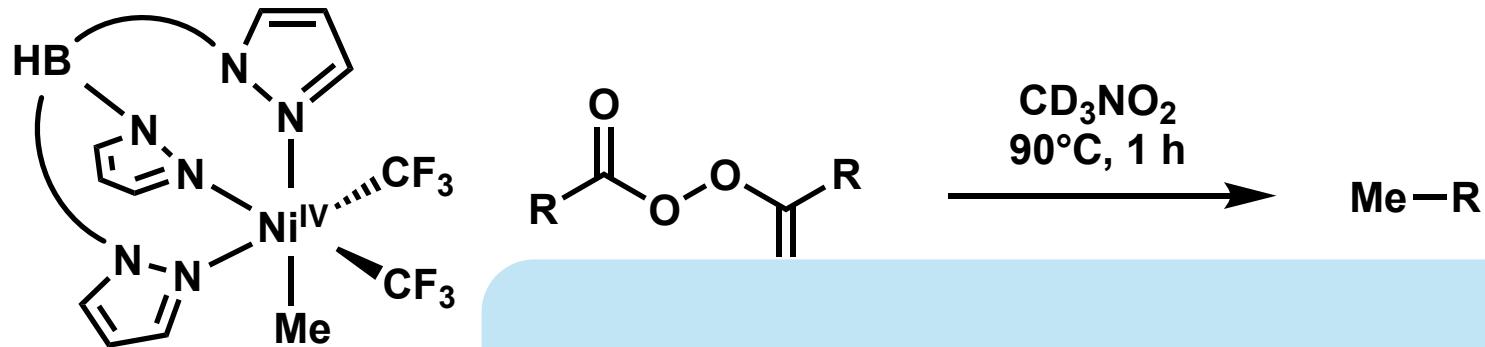


← cobalt porphyrin cat

Zhang, X. P. et al.; *J. Am. Chem. Soc.* 2021, 143, 11121.

Integration Transition Metal and S_H2 Reaction (Past)

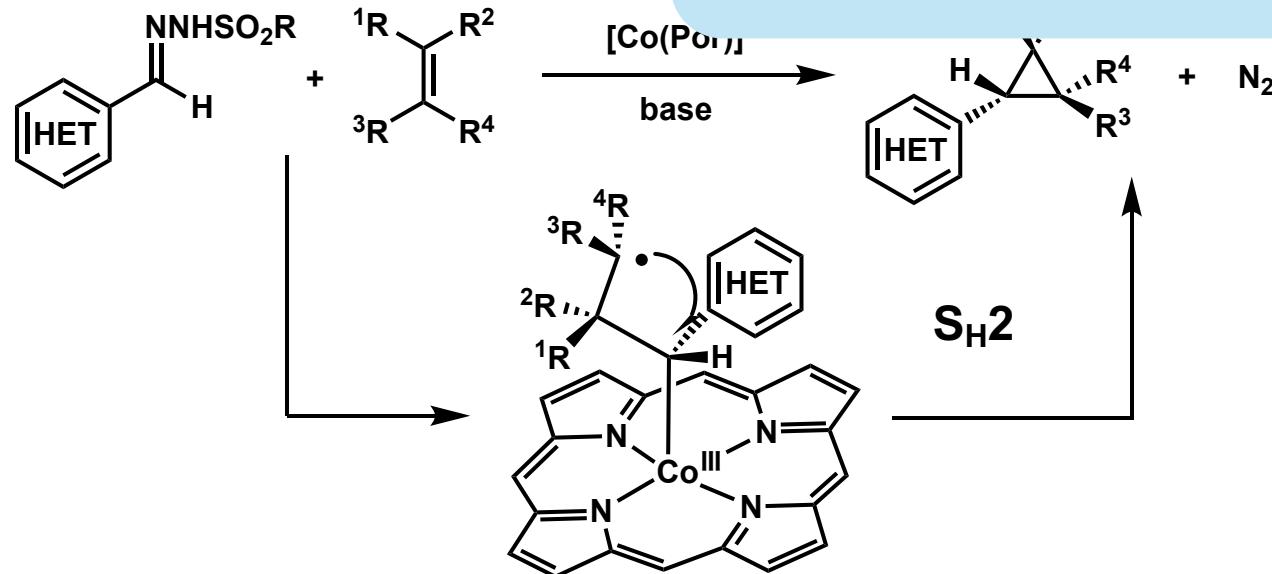
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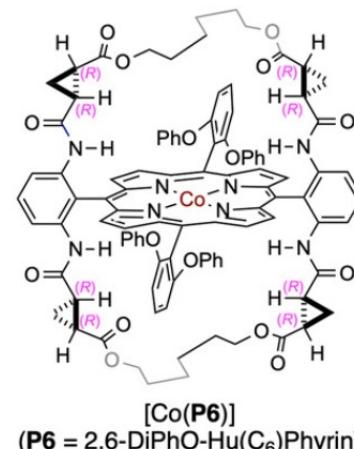
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J. Am. Chem. Soc. 2019, 141, 8914

Example 2. Zhang Group



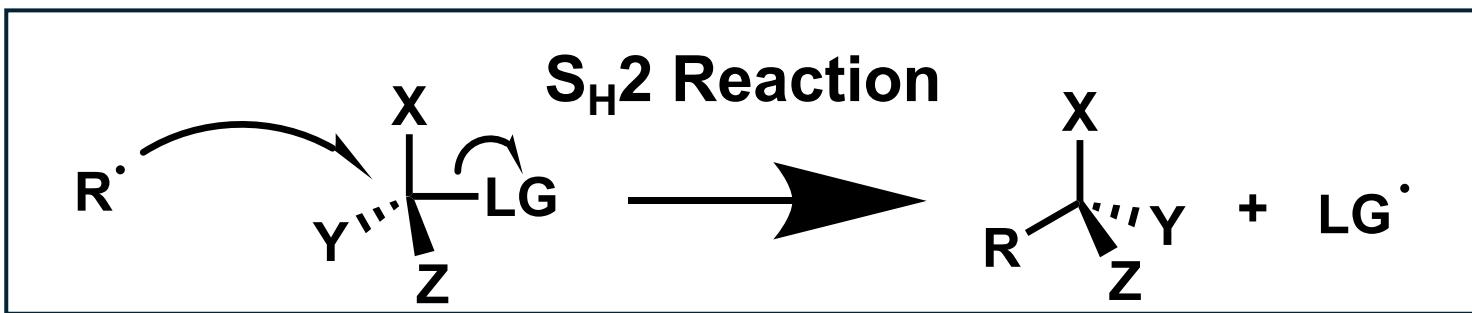
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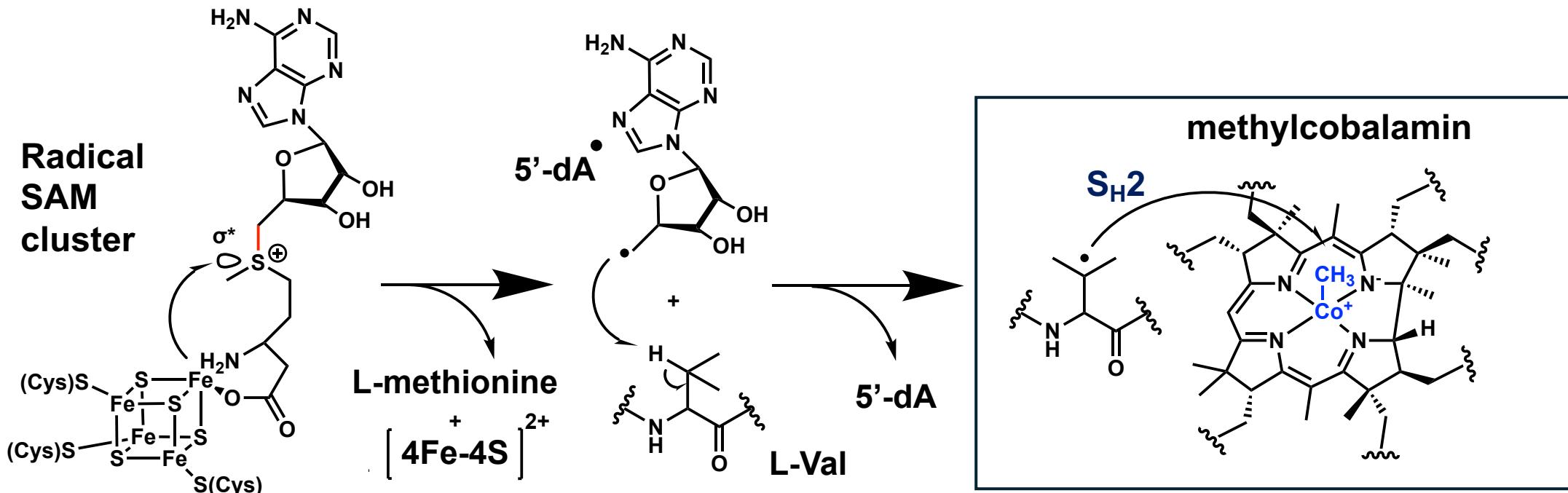
← cobalt porphyrin cat

Zhang, X. P. et al.; J. Am. Chem. Soc. 2021, 143, 11121.

Bimolecular Homolytic Substitution (S_H2) Reaction



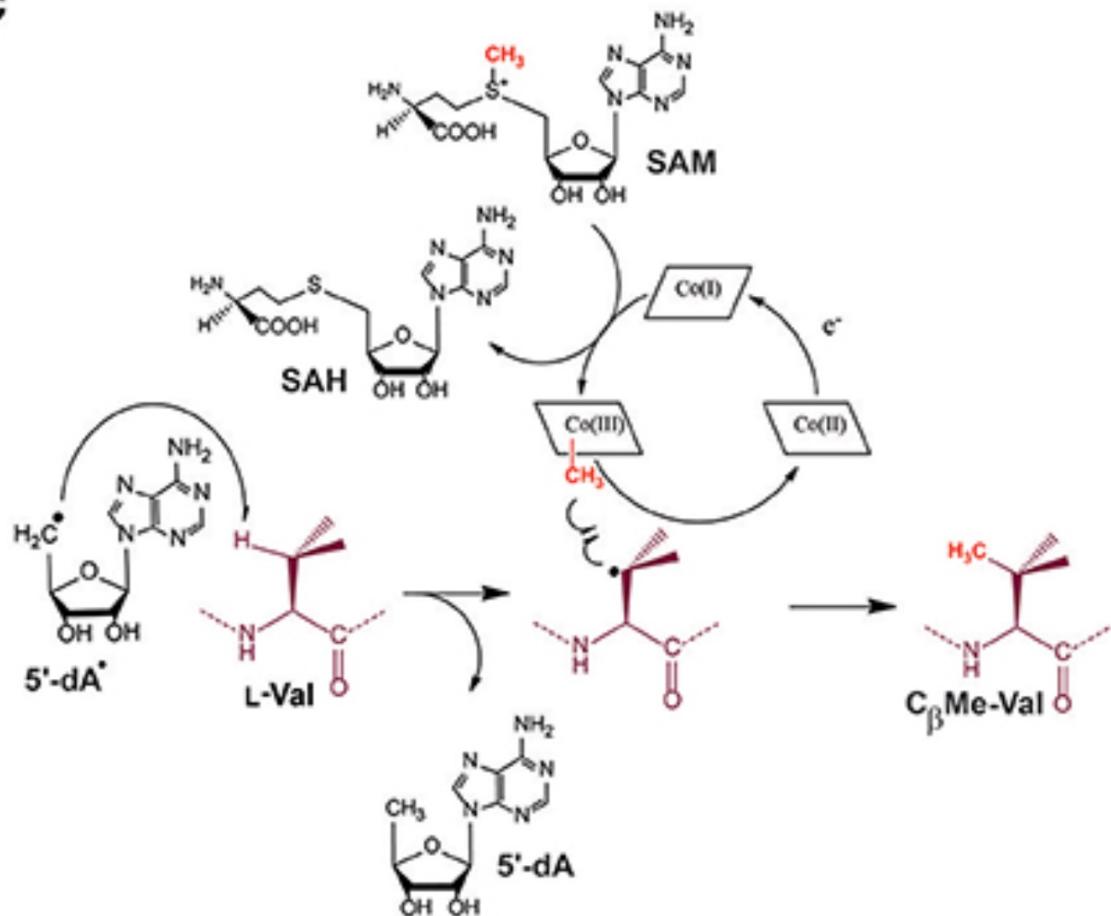
Example ... Cobalamin dependent radical SAM (ex ... Poy C)



$S_{H}2$ Reaction in Biosynthesis

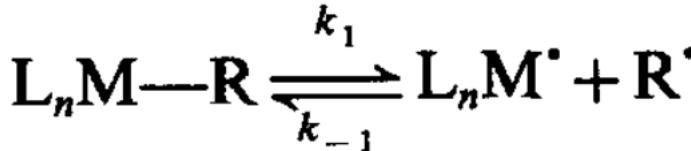
Biosynthesis of C_{β} -Me Val (PoyC)

c



Points

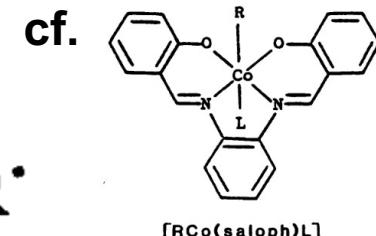
1. Activate each coupling substrate independently
2. Weak Me – Co bond (BDE = ~37 kcal/mol)
→ Rapid $S_{H}2$ Reaction
3. Metal-alkyl bonds are in equilibrium. Forming Co - methyl bonds are more favorable than forming methyl radical.



→ heteroselective carbon-carbon bond formation

Parameters to Consider for S_H2 Reaction

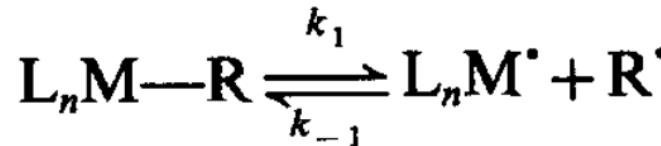
1. Selectivity of radical trapping



BDEs of R-Co bond

entry	Cobalt alkyl	BDE (kcal/mol)
1	CH ₃ CH ₂ CH ₂ -Co(Saloph)(py)	25
2	(CH ₃) ₂ CH-Co(Saloph)(py)	20
3	(CH ₃) ₃ CCH ₂ -Co(Saloph)(py)	18
4	C ₆ H ₅ CH ₂ -Co(Saloph)(py)	22

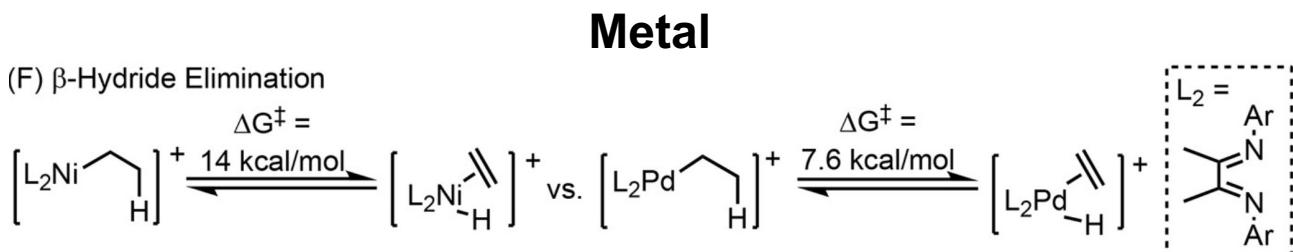
Halpern, J. *Science*, 1985, 227, 869.



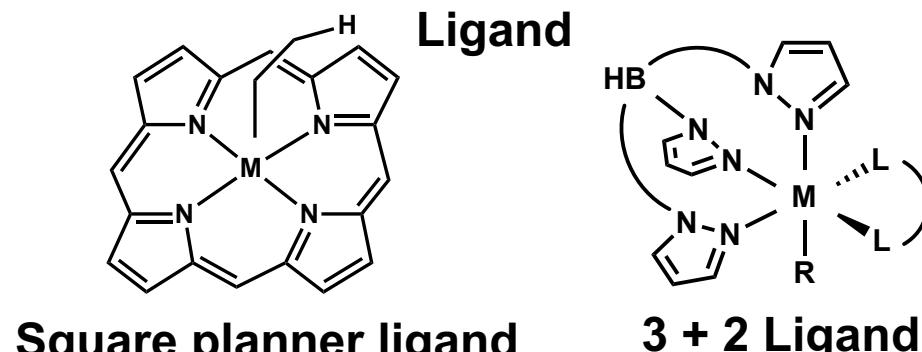
Radicals with less steric hindrance and less stability are more trapped.

Halpern, J. *Polyhedron*. 1988, 7, 1483.

2. Inhibition of side reactions (β -H elimination)



Rotation of M-C bond and BDE of M-H bond



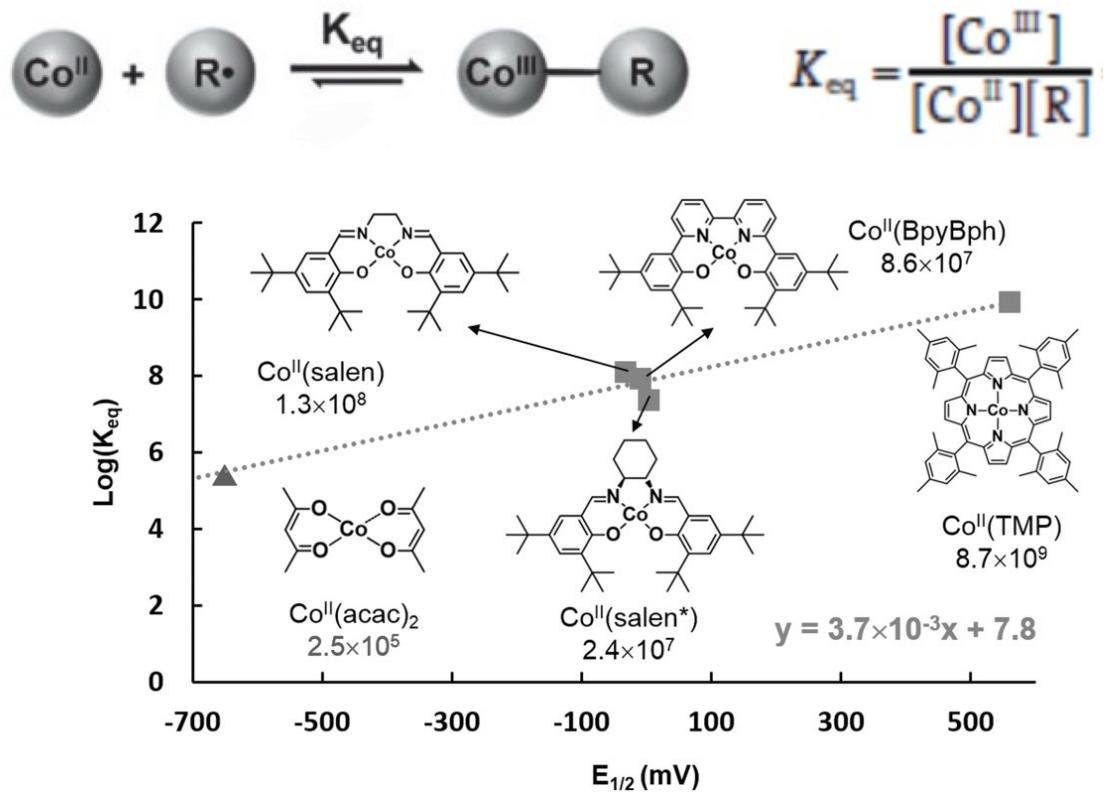
Diao, T. et al.; *Accounts Chem. Res.* 2020, 53, 906.

Tilset, M. *Comprehensive Organometallic Chemistry III*, 2007, 279.

Parameters to Consider for S_H2 Reaction

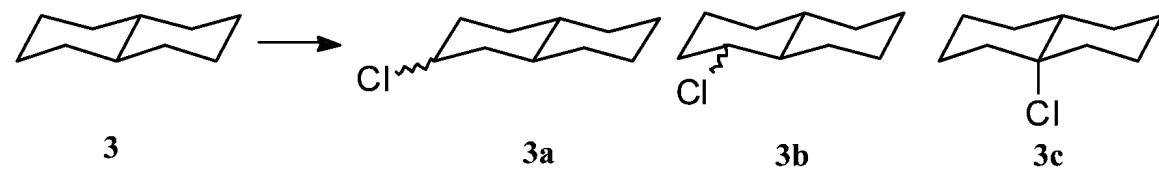
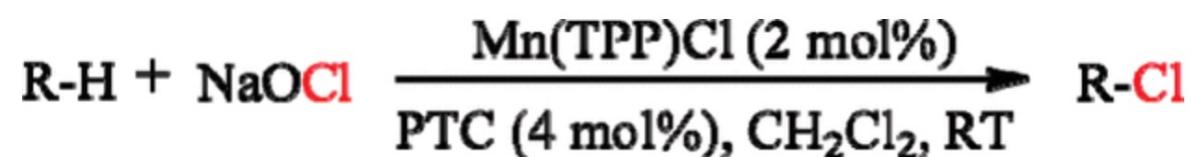
3. Electron density and steric environment of metal-ligand complex

The Correlation of E_{1/2} and K_{eq} of Cobalt Complexes



Electron-poor Co → more Co-Alkyl complex

Influence of the steric environment



	yield	distribution	
Mn(TPP)Cl/NaOCl	55%	38%	58%
Mn(TMP)Cl/NaOCl	51%	76%	19%

*TPP ... meso-Tetraphenylporphine

Steric environment on the ligand might affect reactivity and selectivity of the reaction.

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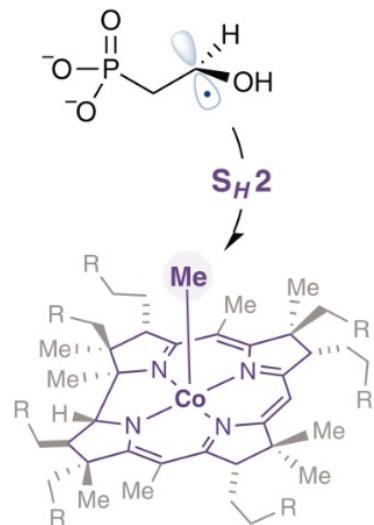
3. Summary and Perspective

Biomimetic Approach

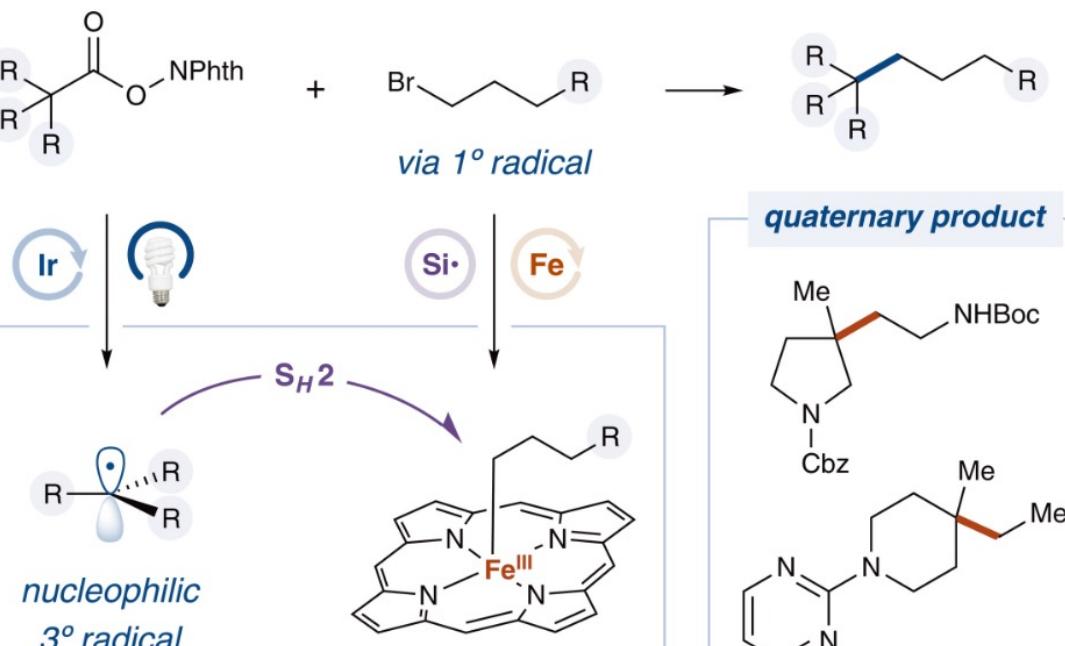
Fe porphyrin ... Weak metal-alkyl bonds similar to cobalt porphyrins

→ It could “sort” different radicals generated at the same time.

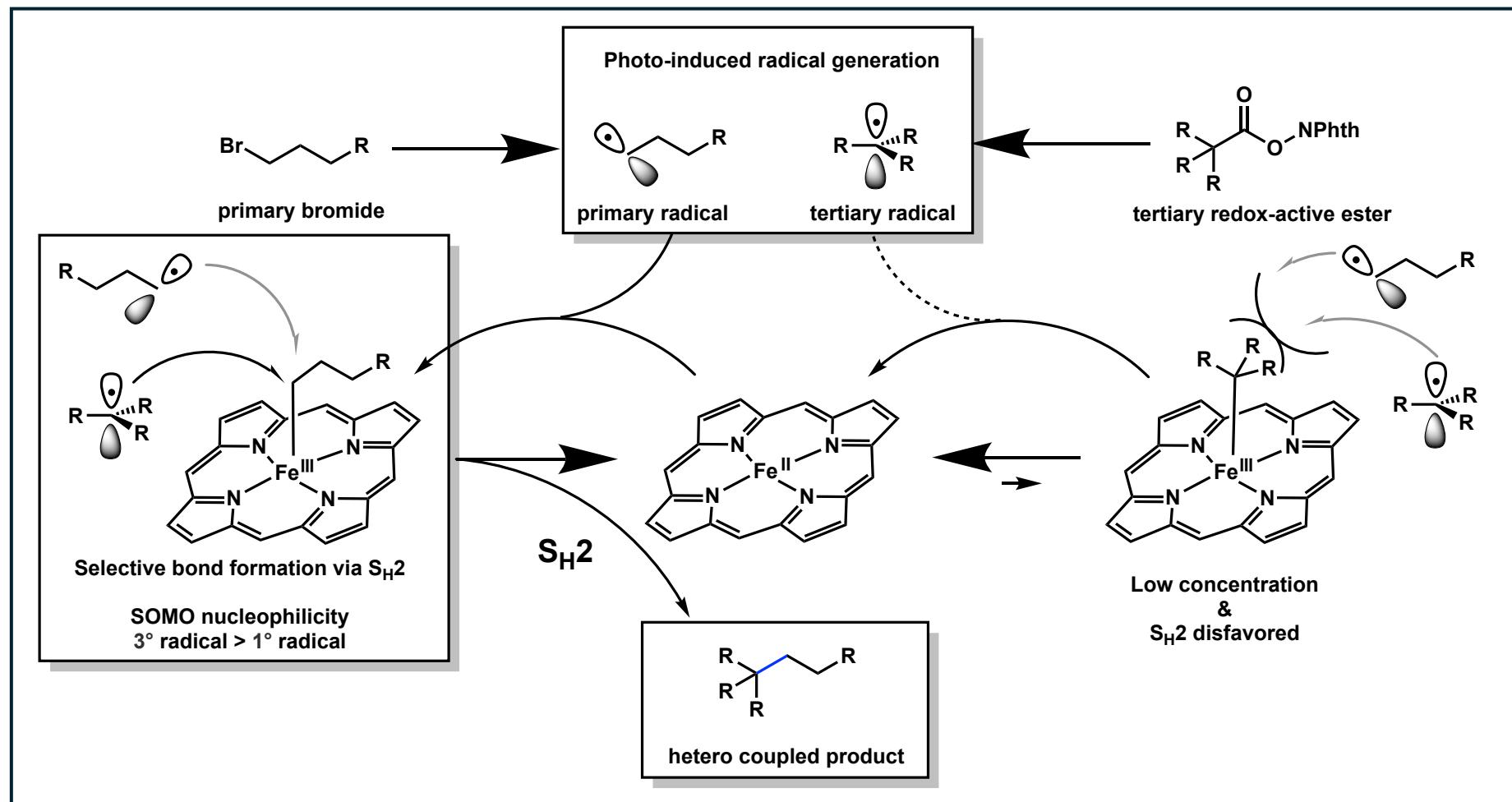
B biological methylation



C a biomimetic approach to $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ cross-coupling



Reaction Design (Selectivity)

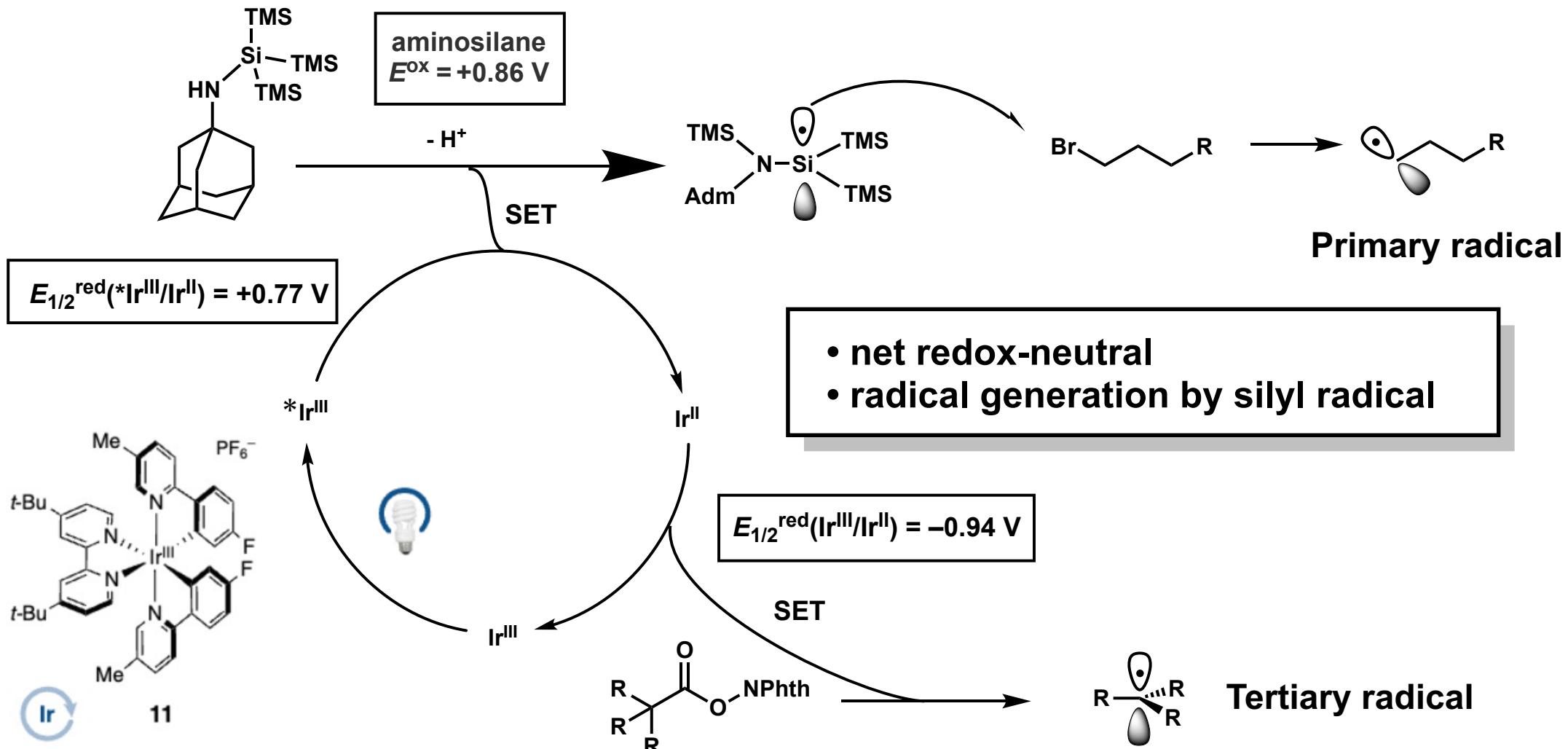


Fe porphyrin stabilizes primary radical and suppresses side reactions.

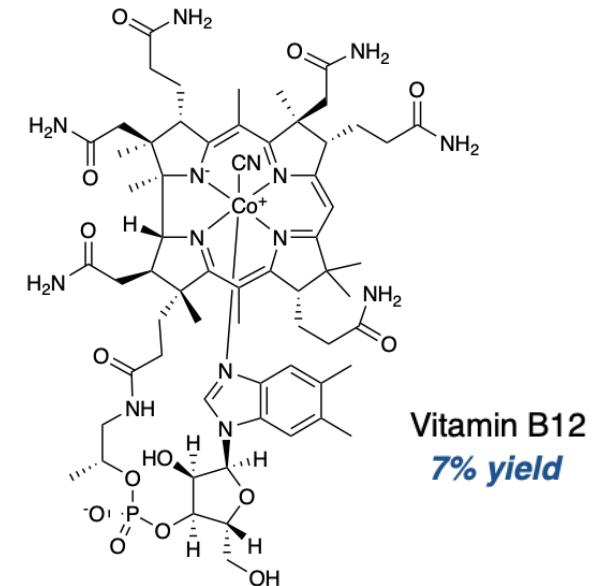
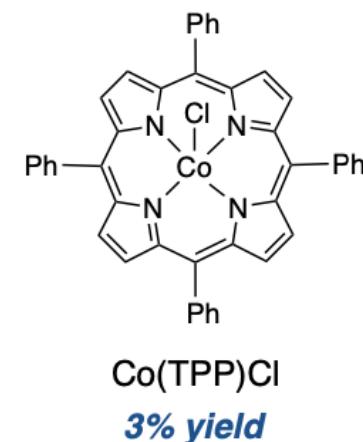
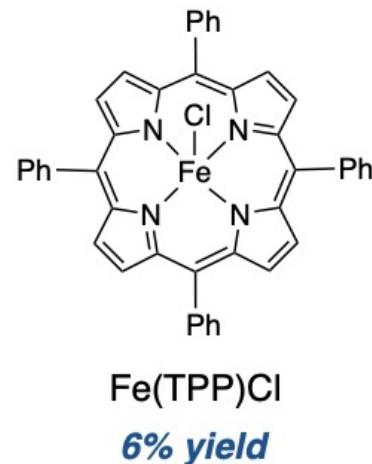
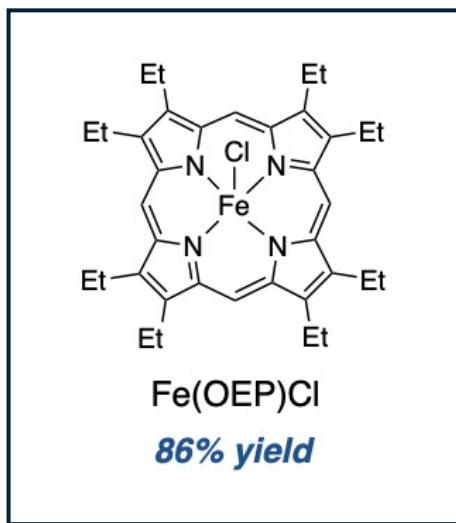
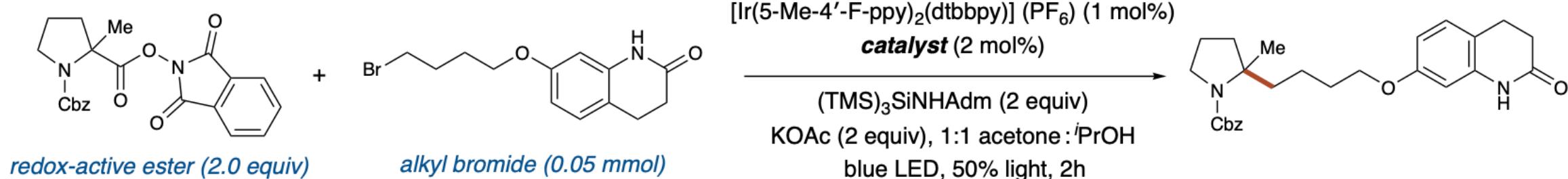
MacMillan, D. W. et al.; *Science*, 2021, 374, 1258.

Reaction Design

Fe – alkyl complexes ... heat and O₂ sensitive
→ Radical generation under mild condition is needed.



Reaction Design ... M-Ligand Optimization (Excerpt)



1. Steric environment of reactive center
(Substituent at meso-position)

2. Strength of M-C bond
(OEP > TPP)

3. Physical properties of catalyst (Solubility)

4. Identity of metal
(Co catalysts generated alkenes as side products.)

Proposed Reaction Mechanism

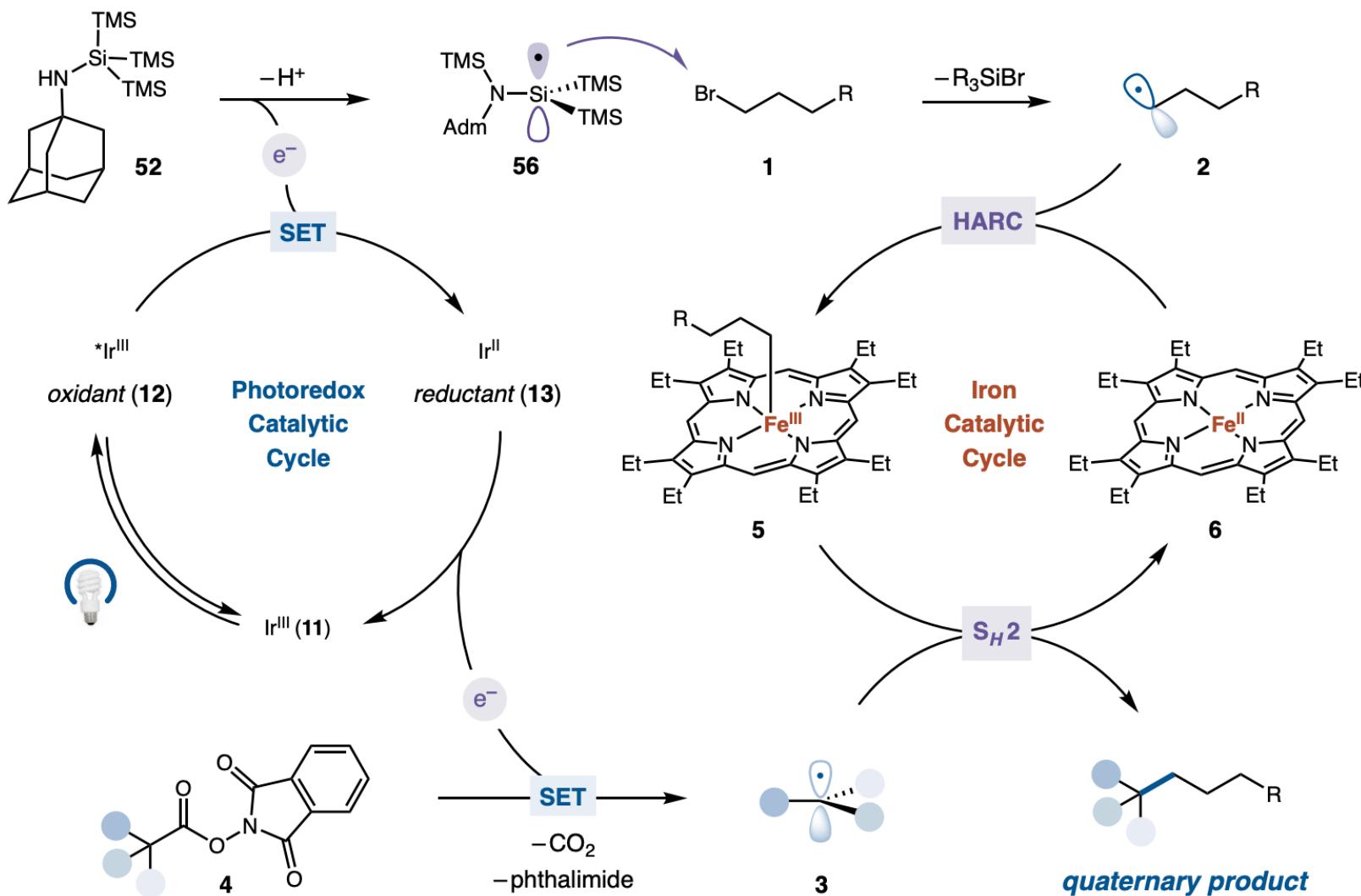
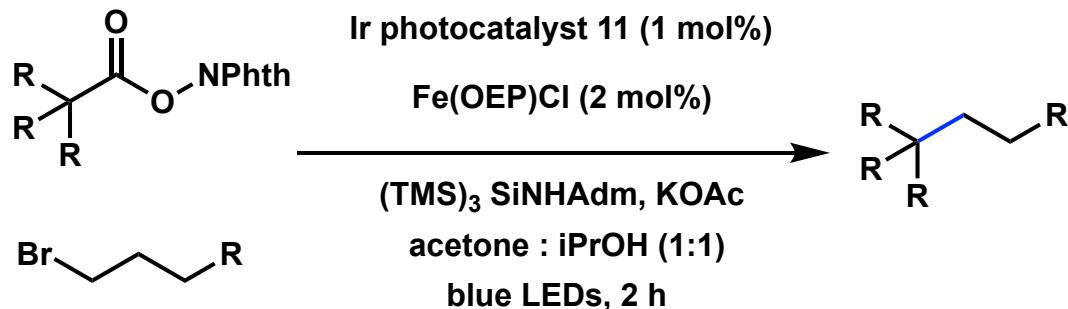
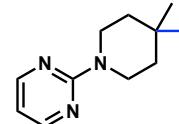


Figure S1. Proposed reaction mechanism of iron metallaphotoredox $C(sp^3)-C(sp^3)$ cross-coupling

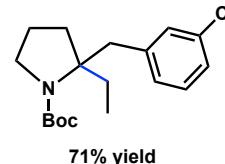
Substrate Scope (Excerpt)



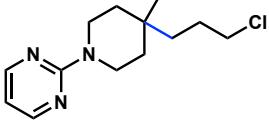
Primary bromides



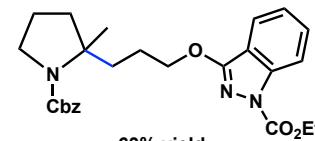
84% yield
(With 2 equivalents of methyl p-toluenesulfonate and tetrabutylammonium bromide and Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ as the photocatalyst)



71% yield

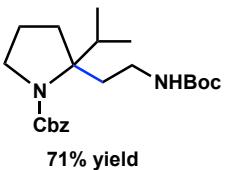


52% yield
(Ir(ppy)₂ (dtbbpy)PF₆ as the photocatalyst)

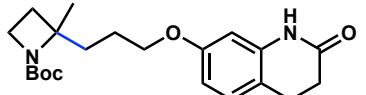


63% yield

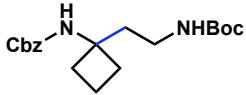
Redox-active esters



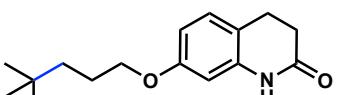
71% yield



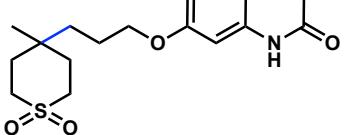
46% yield
(With KOAc and Zn(OAc)₂ as bases)



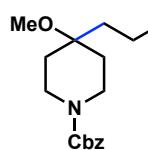
69% yield
(With Zn(OAc)₂ as the base and Ir(ppy)₂ (dtbbpy)PF₆ as the photocatalyst)



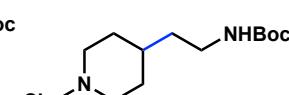
47% yield



60% yield

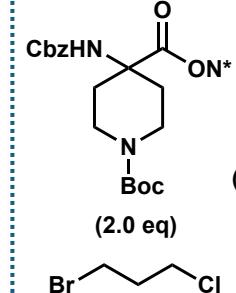


68% yield

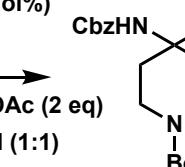


65% yield

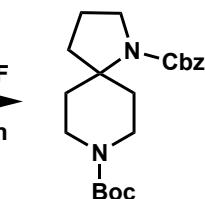
Synthesis of spirocycles



Ir photocatalyst 11 (10 mol%)
Fe(OEP)Cl (2 mol%)
(TMS)₃SiNHAdm (2.5 eq), KOAc (2 eq)
acetone / t-amyl alcohol (1:1)
blue LEDs, 3 h



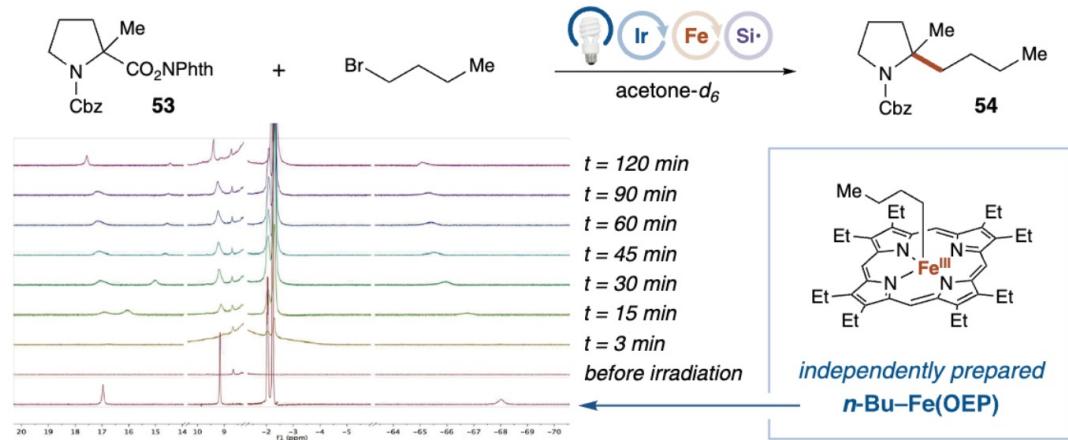
66% yield



98% yield

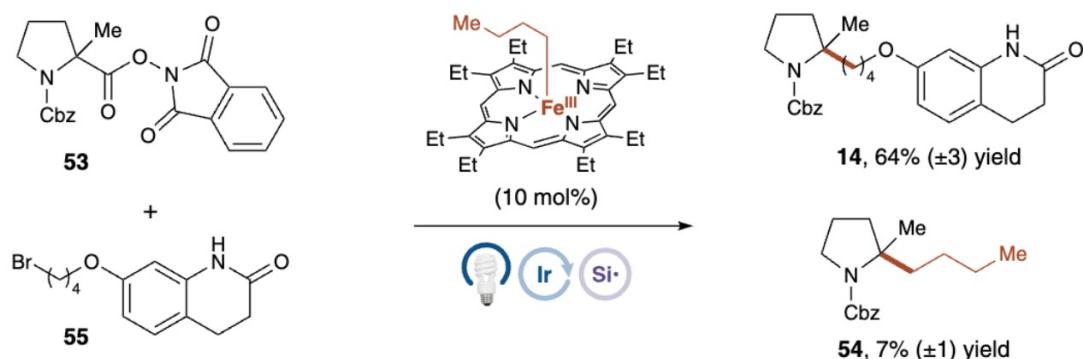
Mechanistic Studies

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



Monitoring of the reaction
→ slow increase of n-Bu–Fe(OEP) complex

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

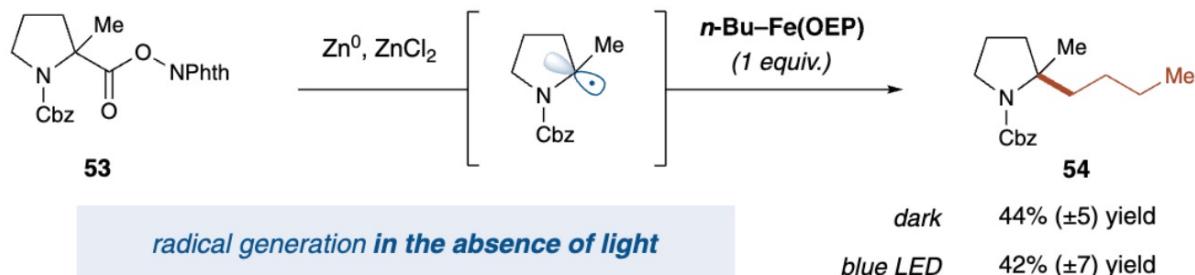


Use of n-Bu–Fe(OEP) complex instead of Fe(OEP)Cl
↓
Similar yield and
n-Bu incorporated product were observed.

Mechanistic Studies

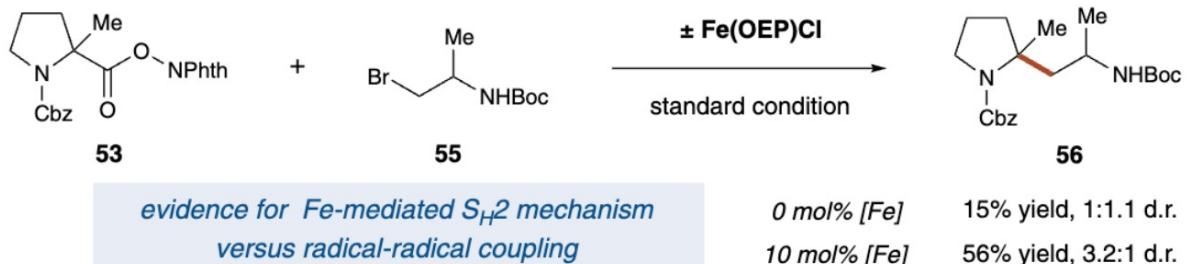
Alkyl - Fe bond homolyze under light irradiation.
→ Coupling between free radicals is a possibility.

C — Light is not required for C-C bond formation



When radical is generated by single electron reductant, There is no change in yield with or without light irradiation.
→ Blue light is required for photoredox cycle.

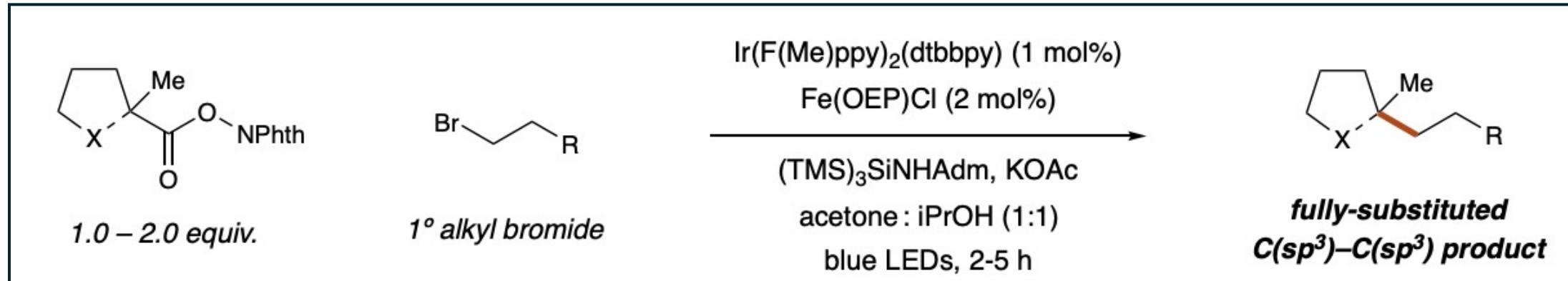
D — Iron-dependent diastereoselectivity in C-C bond formation



Yield and diastereomeric ratio increases depending on the presence or absence of Fe(OEP)Cl.

Short Summary

By biomimetic approach, a C(sp³) - C(sp³) coupling reaction was achieved.



Based on this concept, a variety of reactions are being developed.

Contents

1. Introduction

2. Main

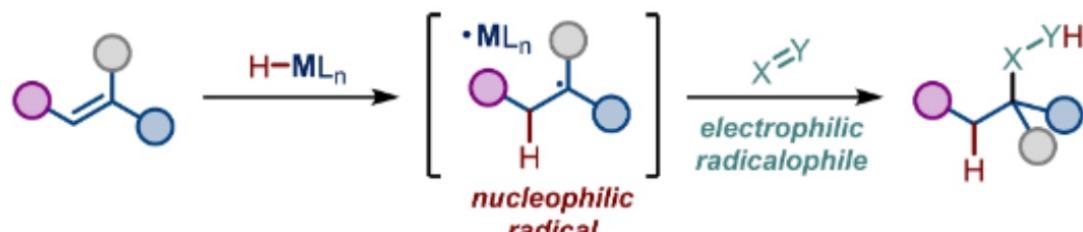
- Biomimetic Approach (Fe catalyzed)
- Combination of SH2 and MHAT (Co catalyzed)**
- Expansion of substrate scope (Ni catalyzed)

3. Summary and Perspective

Metal – Hydride Hydrogen Atom Transfer (MHAT)

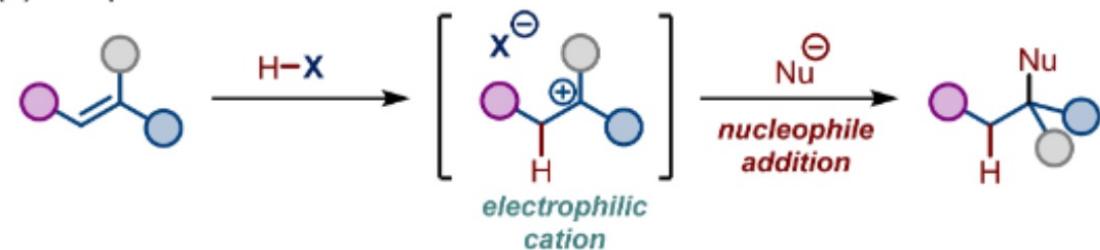
MHAT from high-valent, first-row transition metal hydride

(a) General principle of metal hydride catalysed hydrogen atom transfer catalysis



- Widely available or easy to prepare alkene starting materials
- Predictable catalytic radical generation
- Metal can tune reactivity of radical

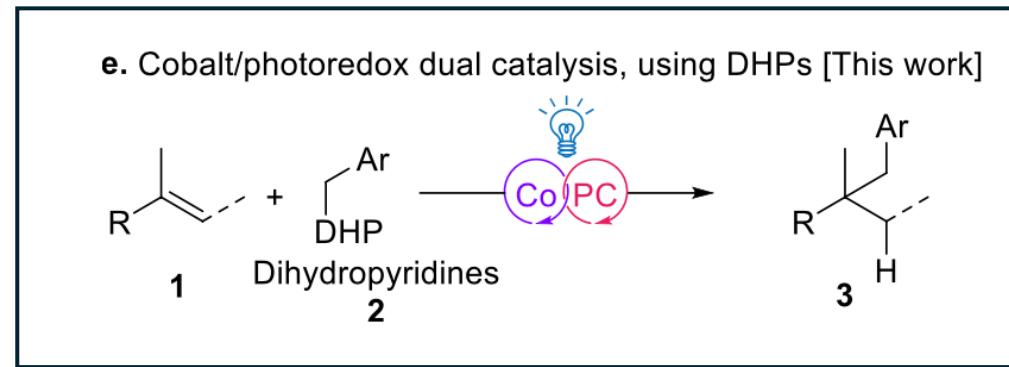
(b) Comparison to Brønsted acid mediated reactions



Characteristics

- Orthogonal reactivity and mild condition in contrast to Brønsted acid mediated reactions
- Markovnikov selective radical generation

Reaction Design (Combination of MHAT and S_H2)

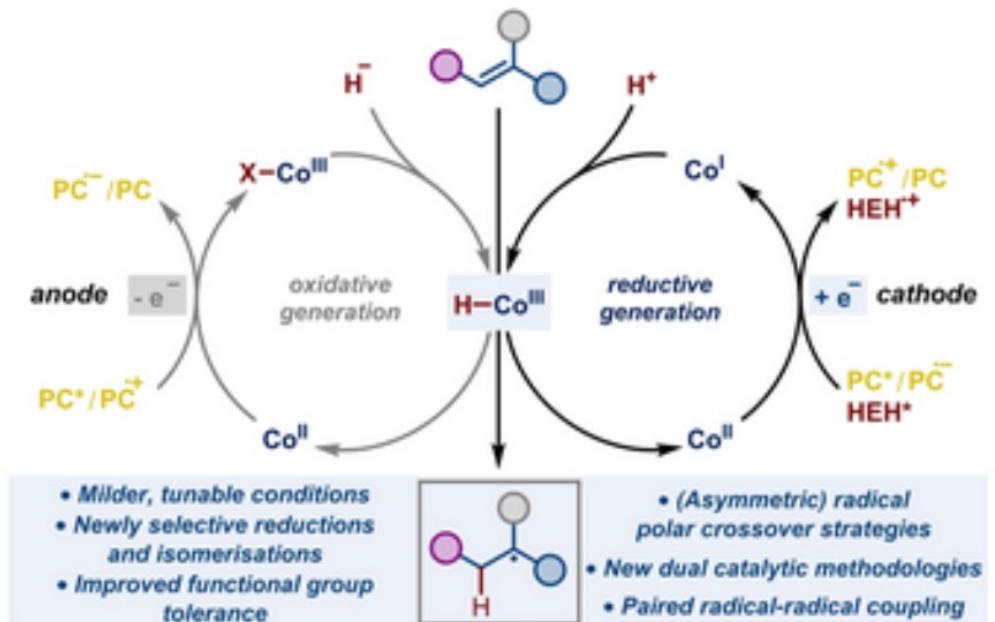


1. Reductive generation of Co-H

- Oxidative generation of Co-H
(Oxidation of Co^{II} & reduction of Co^{III})

- Reductive generation of Co-H
(Reduction of Co^{II} & protonation of Co^I)

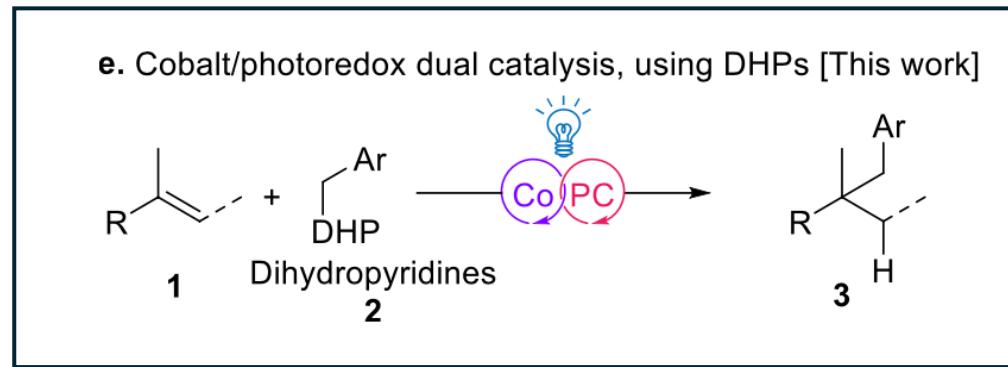
→ No need for oxidant and H⁻



Matsunaga, S. et al.; Org. Lett. 2024

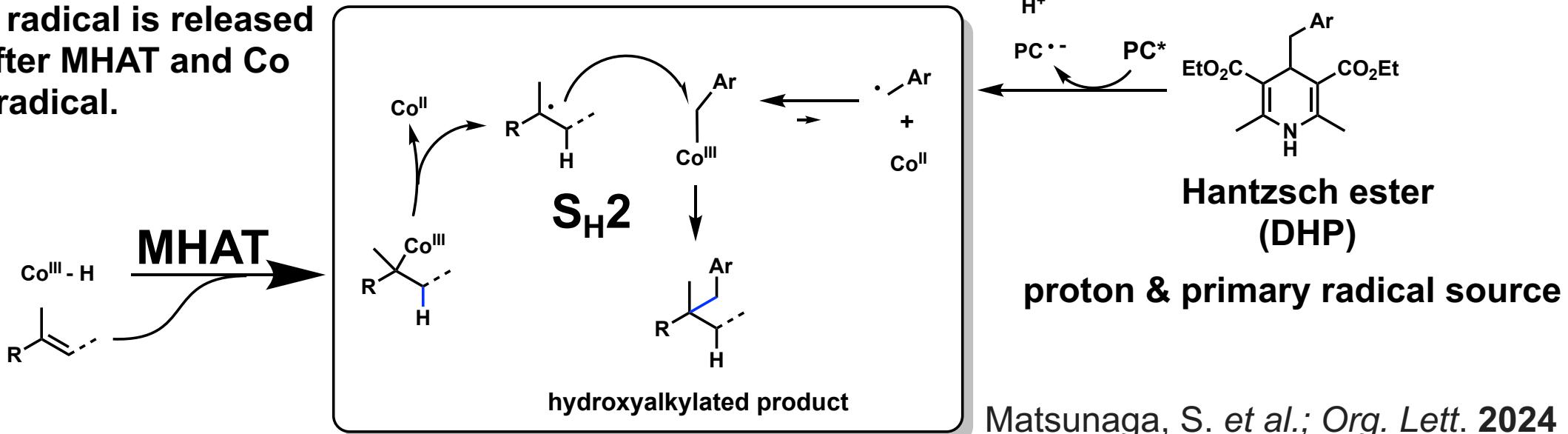
Teskey, C. J. et al.; Angew. Chem. Int. 2023, 62, e202304882.

Reaction Design (Combination of MHAT and S_H2)



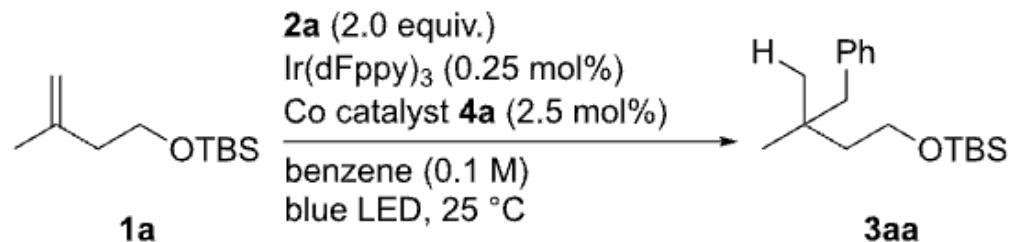
2. Combination of MHAT and S_H2

- Tertiary alkyl radical is released immediately after MHAT and Co traps primary radical.



Catalyst Optimization and Control Experiments

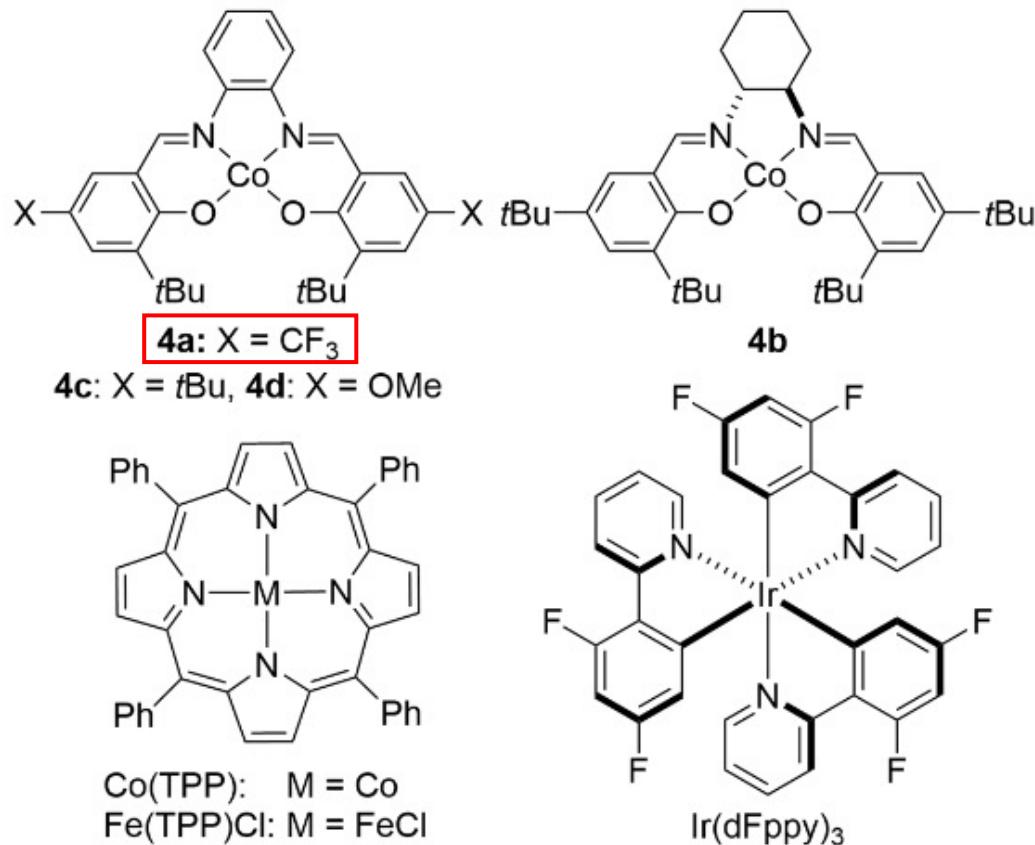
Table 1. Optimized Conditions and Their Variations



entry	deviation from the above conditions	% yield ^a ^b
1	none	80 (85)
2	Co cat. 4b instead of 4a	45
3	Co cat. 4c instead of 4a	70
4	Co cat. 4d instead of 4a	61
5	Co(TPP) instead of 4a	37
6	Fe(TPP)Cl instead of 4a	13
7	without PC	N.D.
8	without Co catalyst	N.D.
9	without blue LED irradiation (dark)	N.D.

^aDetermined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. ^bIsolated yield after purification by column chromatography.

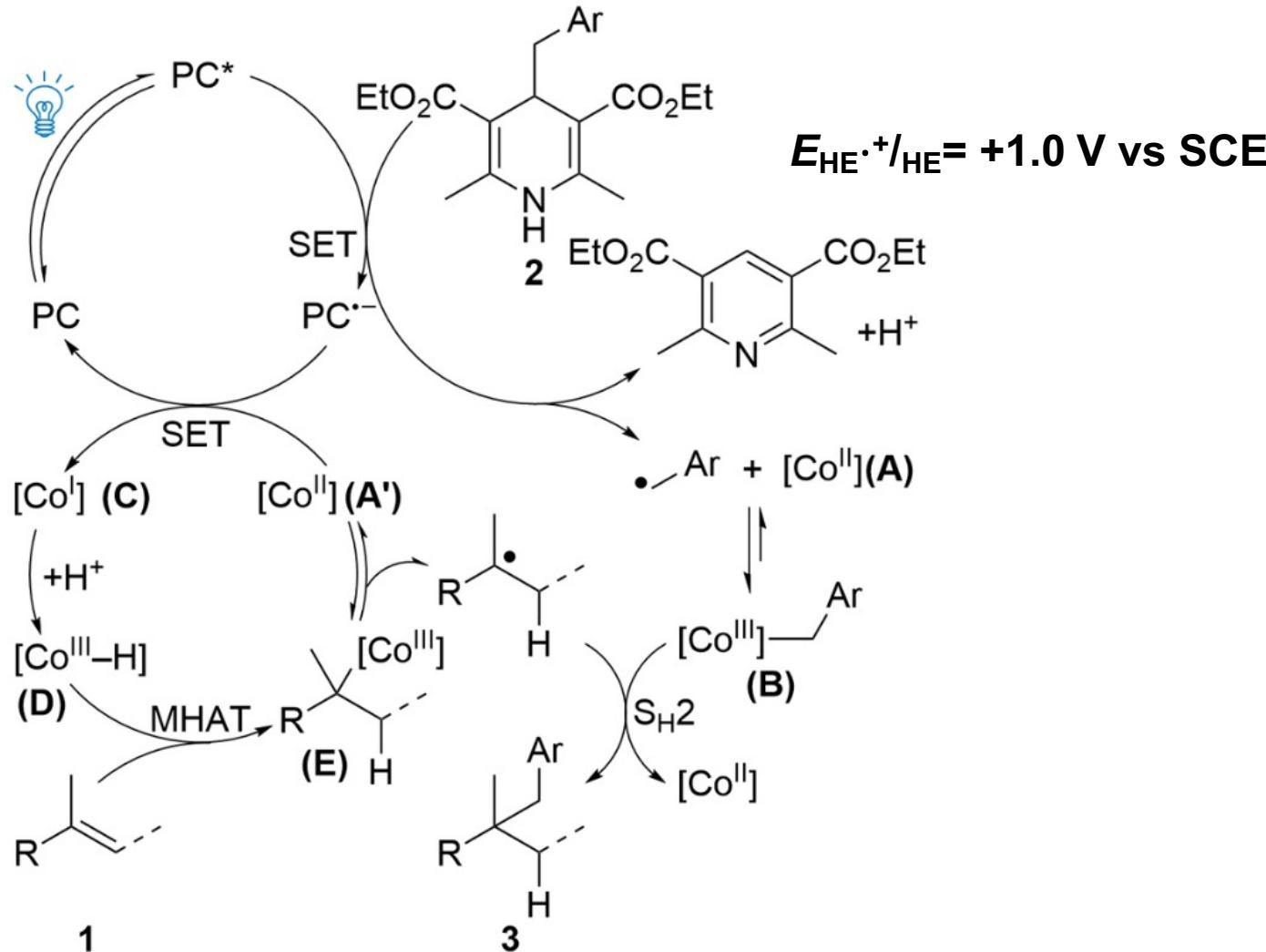
b. Catalysts in this study



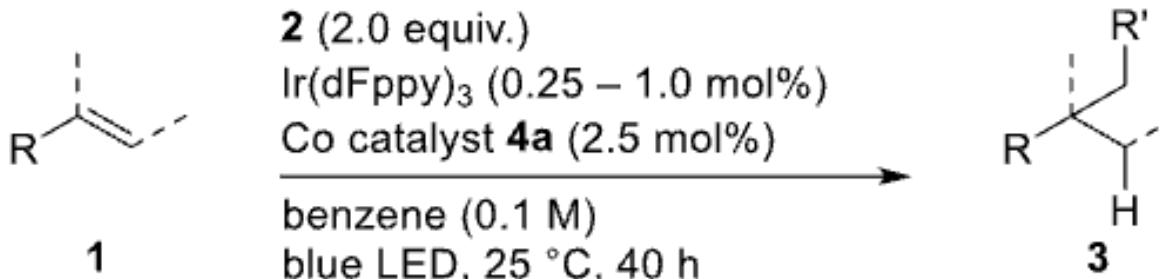
- **4a ~ 4c ... Electron-poor Co → improved yield**
- **Co(TPP) and Fe(TPP)Cl ... difficult to form M-H or solubility?**
- **PC, Co cat, Light irradiation are all needed.**

Reaction Mechanism

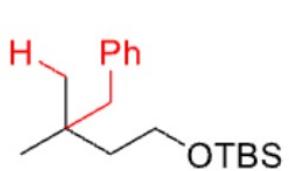
a. Hypothetical catalytic cycle



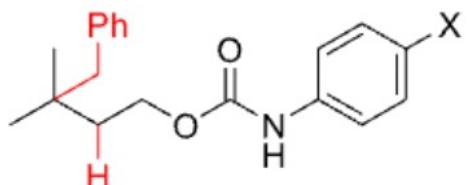
Substrate Scope



Variation of Alkene

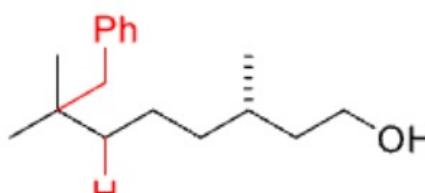


3aa, 85%^b(77%)^c

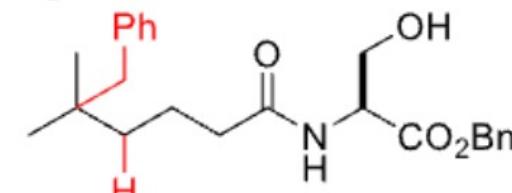


X = H: 3ba, 62% Ac: 3ga, 58%
Me: 3ca, 57%^d CN: 3ha, 58%
OMe: 3da, 63% Cl: 3ia, 62%
OBn: 3ea, 56% Br: 3ja, 63%
CF₃: 3fa, 60%

Natural products

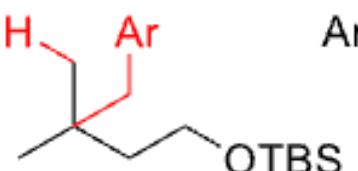


3ka, 46% (from β-citronellol)



3la, 58% (from L-Ser)

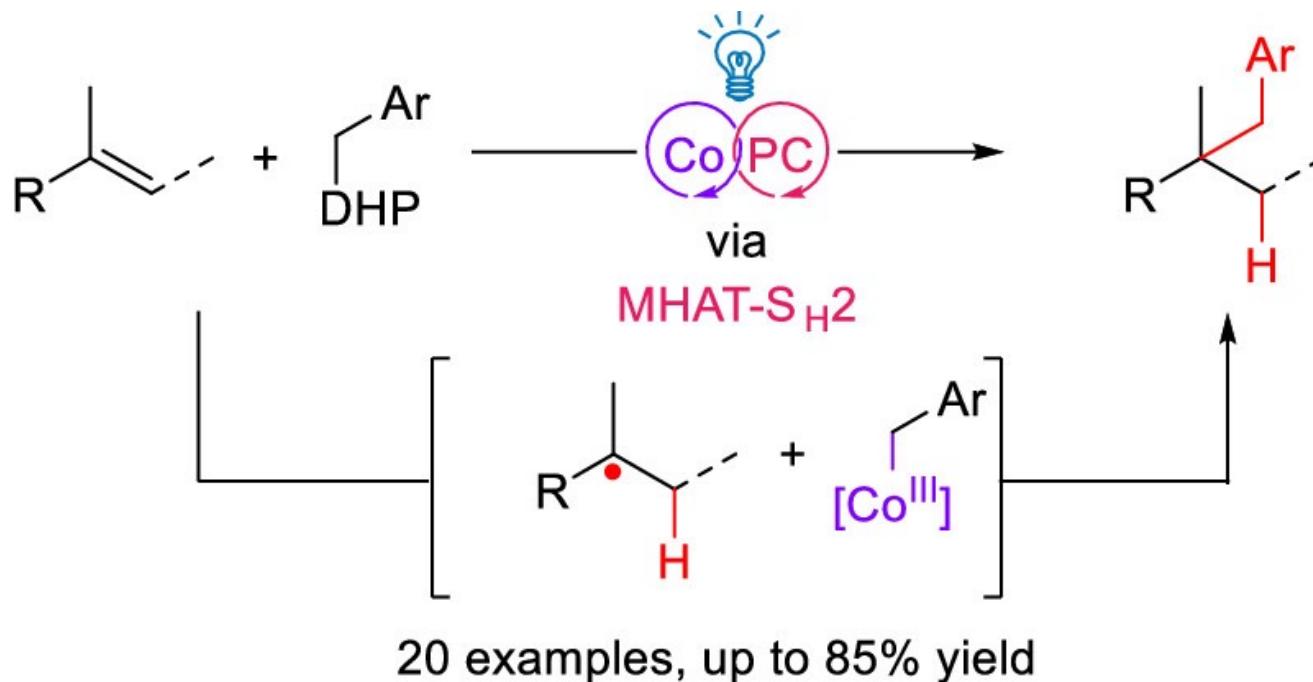
Variation of DHP



Ar = 4-MeC₆H₄: 3ab, 58%^b 3-CIC₆H₄: 3af, 47%
4-FC₆H₄: 3ac, 57%^b 2-CIC₆H₄: 3ag, 65%
4-BrC₆H₄: 3ad, 43% 4-OMeC₆H₄: 3ah, 51%^e
4-CIC₆H₄: 3ae, 61% 3-OMeC₆H₄: 3ai, 56%

Short Summary

- MHAT and S_{H2} processes enabled Markovnikov-selective hydrobenzylation of di/trisubstituted alkenes affording products with a quaternary carbon center in a redox-neutral manner.



- Each coupling fragment had to be activated in a different way.

Contents

1. Introduction

2. Main

- **Biomimetic Approach (Fe catalyzed)**
- **Combination of SH2 and MHAT (Co catalyzed)**
- Expansion of substrate scope (Ni catalyzed)**

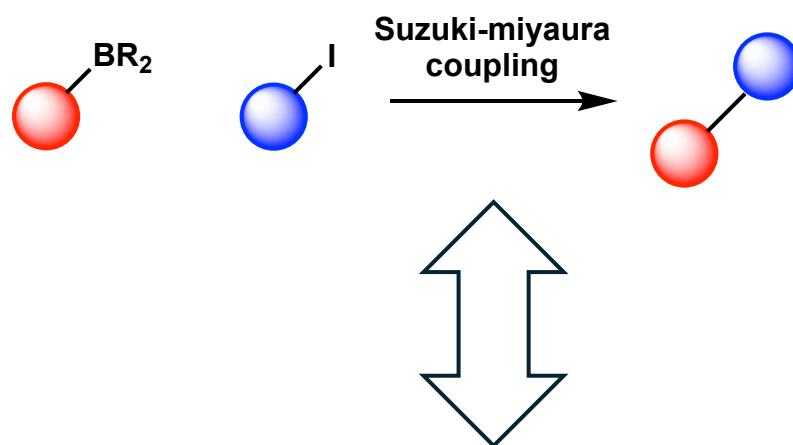
3. Summary and Perspective

Single Functional Group Cross Coupling

- Advantage of single functional group coupling

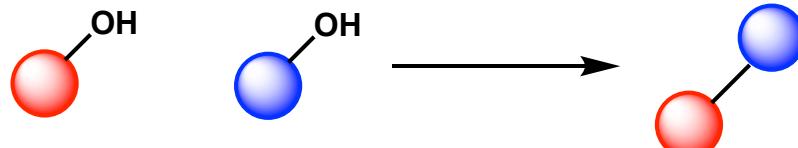
In many coupling reactions, two functional groups must be activated in an orthogonal manner.

Ex.

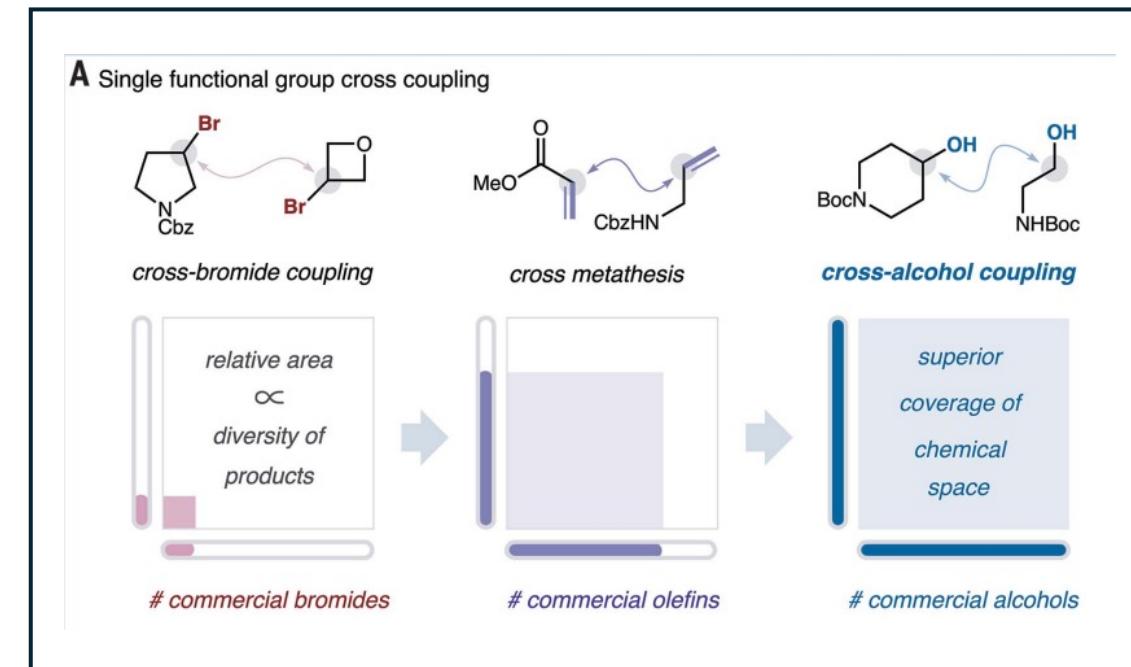


Single functional group cross coupling
→ A single activation mode is needed.

Ex.

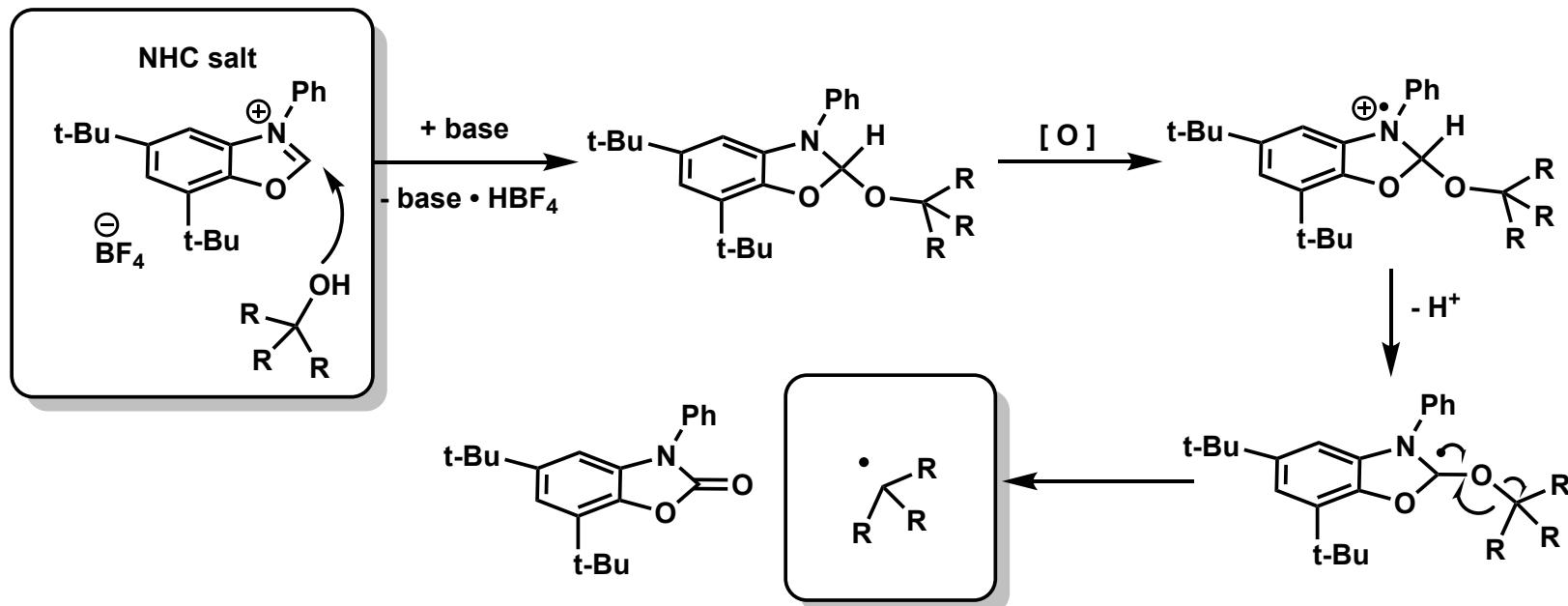
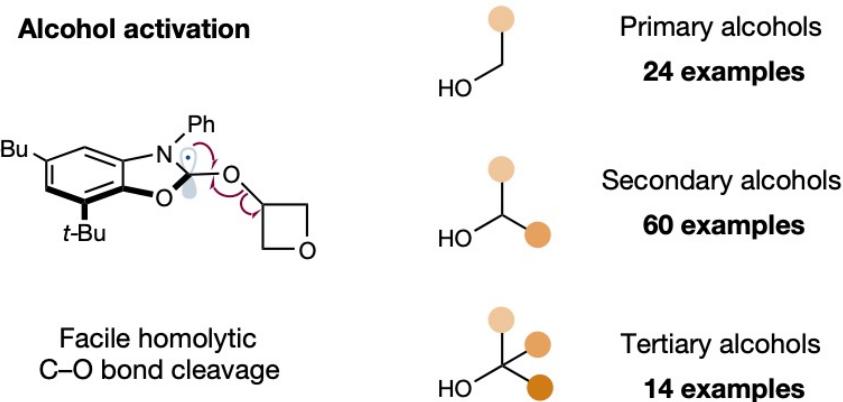


- Alcohol-alcohol cross-coupling



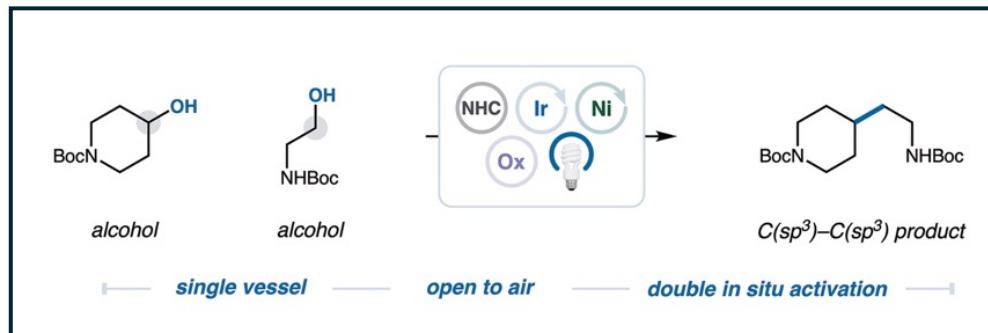
Broader substrate scope

Activation of Alcohol by NHC salt



1. Electron-rich anilinic nitrogen atom is easily oxidized.
2. Exothermic pathway for the formation of a benign aromatic byproduct.

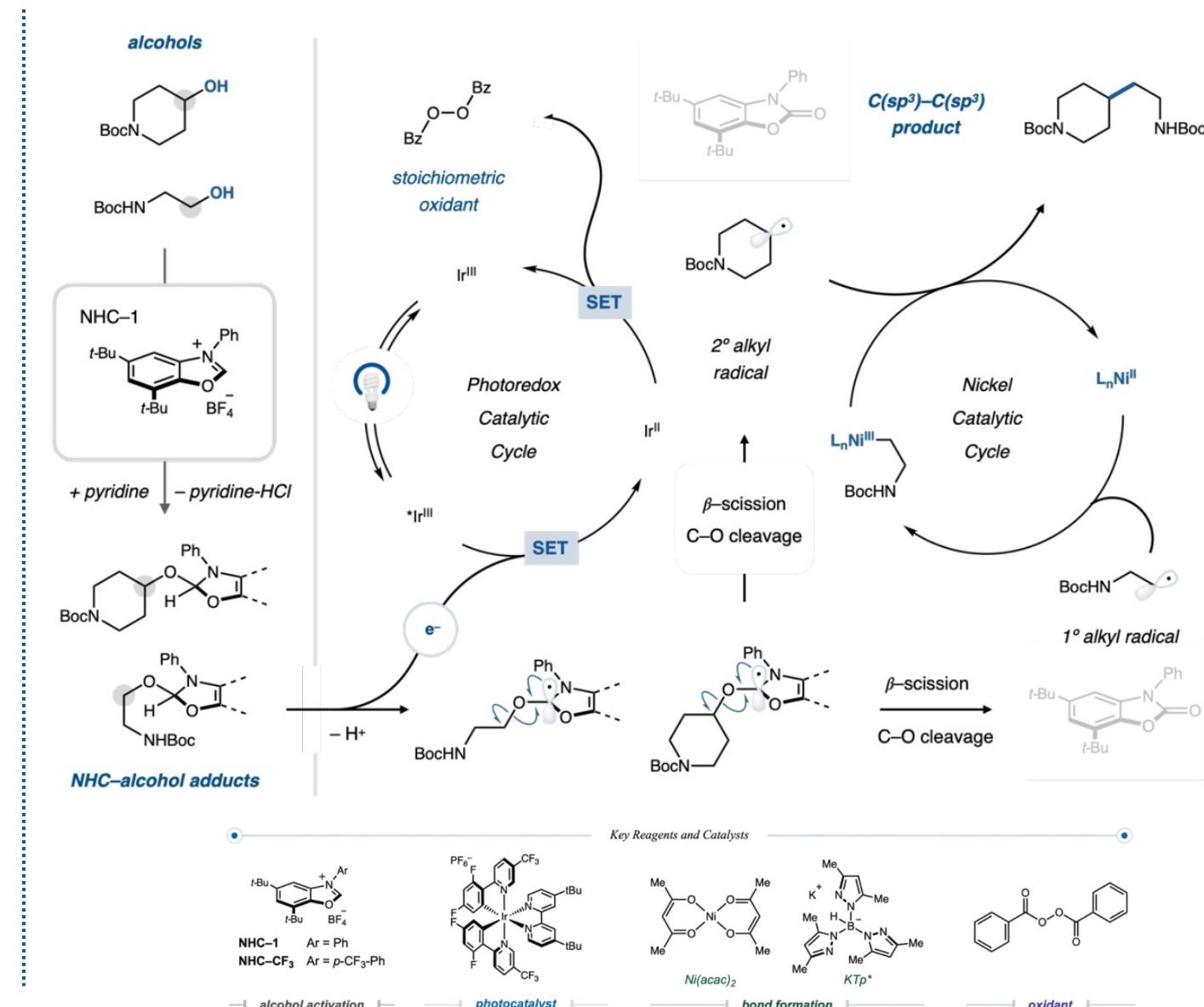
Reaction Design and Proposed Reaction Mechanism



Simultaneously generated free radicals usually complex mixtures of recombination and disproportionation products.

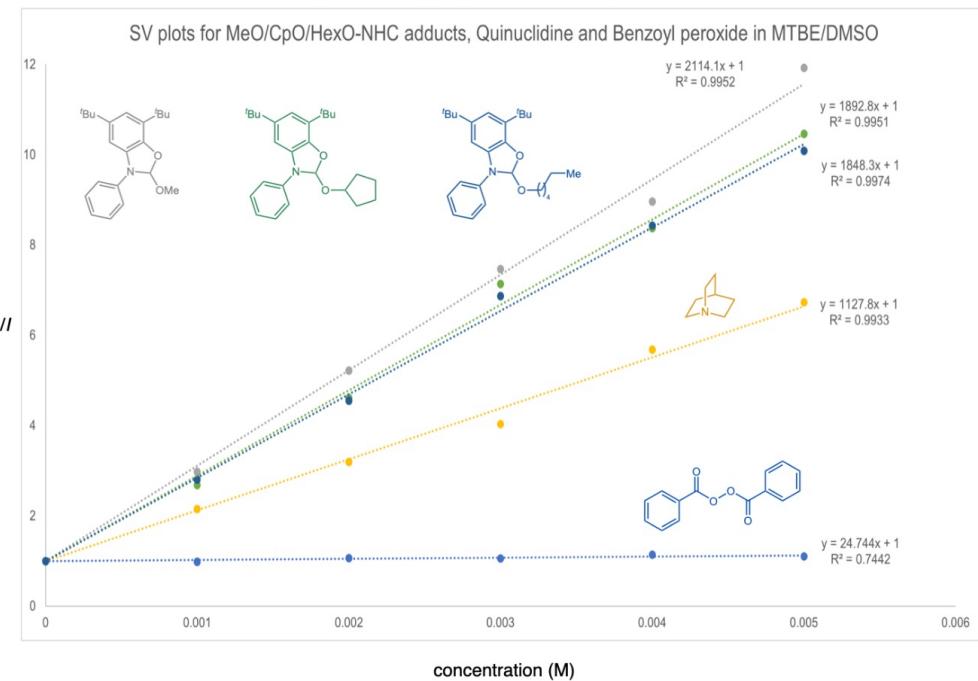
↓

Sorted by Ni and coupled via S_{H2}



Mechanistic Studies

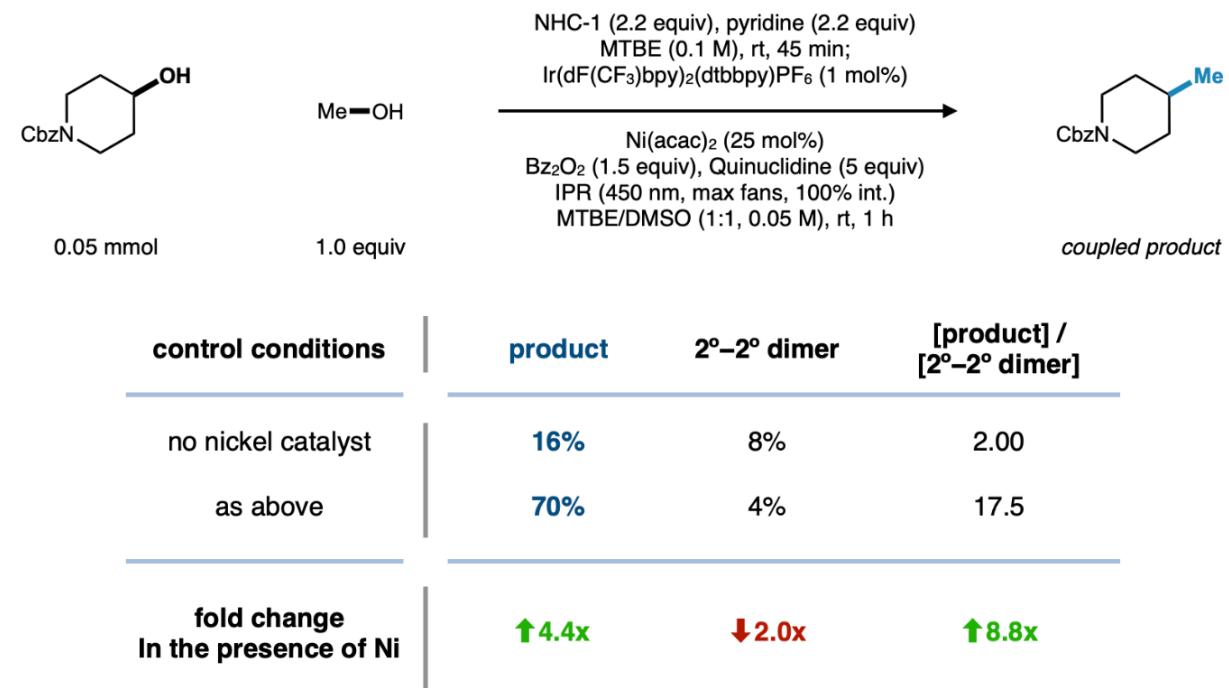
Stern-Volmer plots



NHC-alcohol adducts rapidly quench the excited state of a photocatalyst regardless of alcohol substitution pattern.

→ prevents preferential consumption of one coupling partner over another

Ni radical sorting is operative.

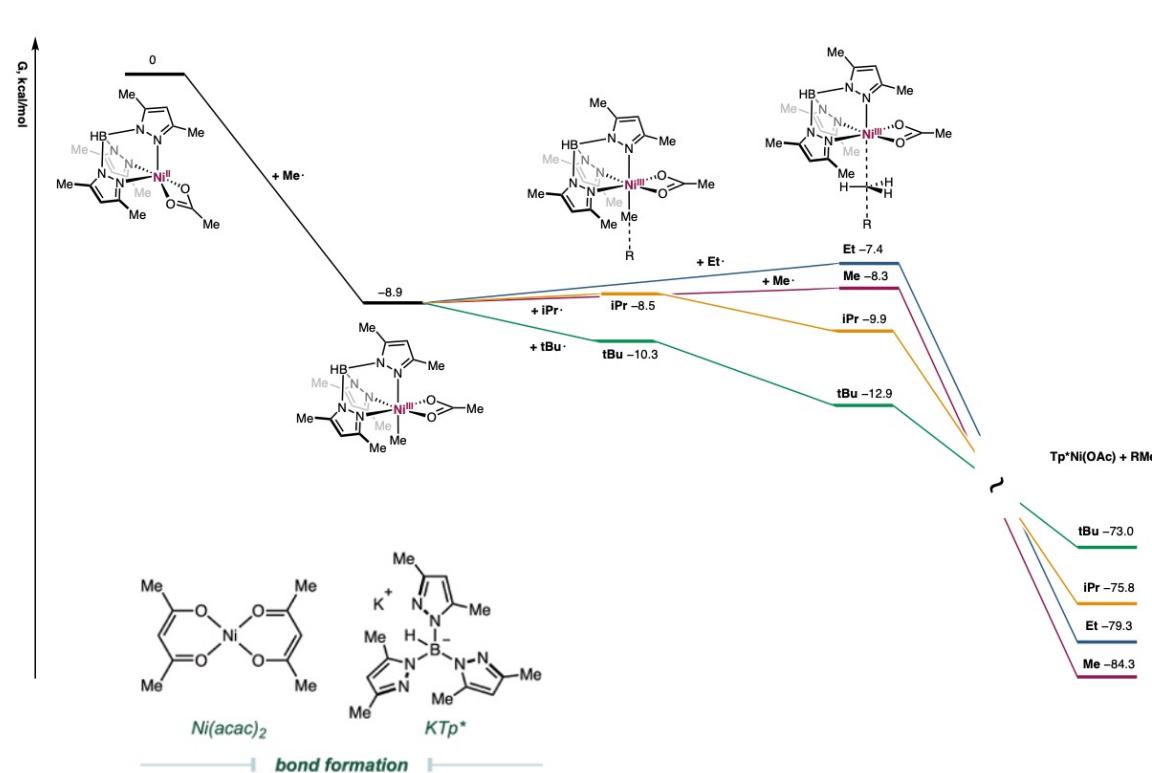


S_H2 Reaction by $KTp^*Ni(OAc)$

DFT calculation ... S_H2 process rather than radical addition.

S_H2 process

Bimolecular homolytic S_H2 substitution at Ni(III) methyl complex



Radical addition

Sequential radical binding to generate high-valent Ni(IV) dialkyl complexes

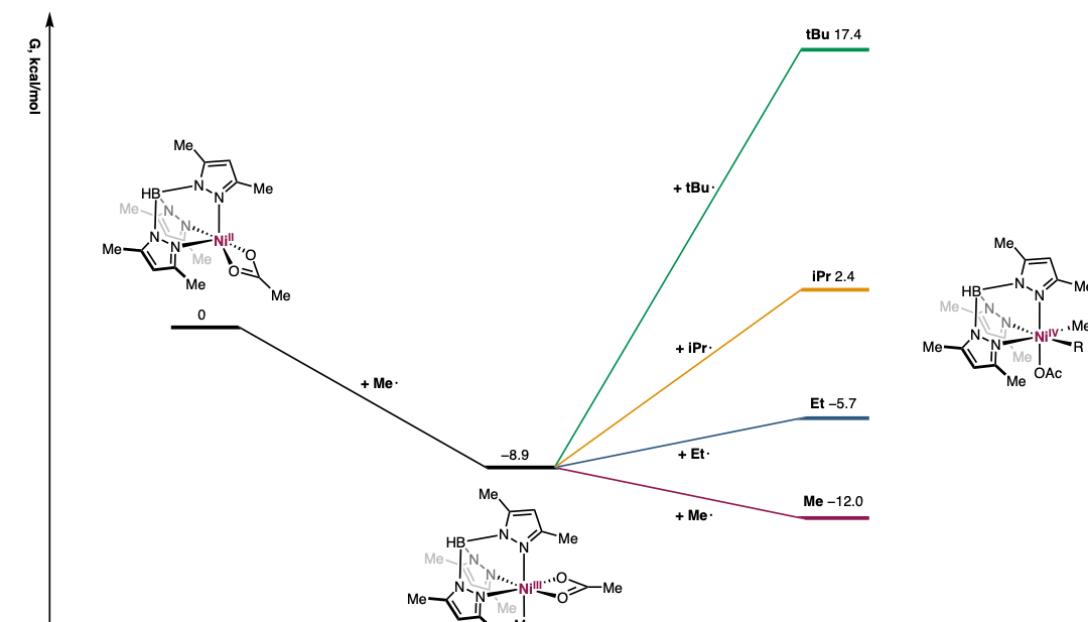
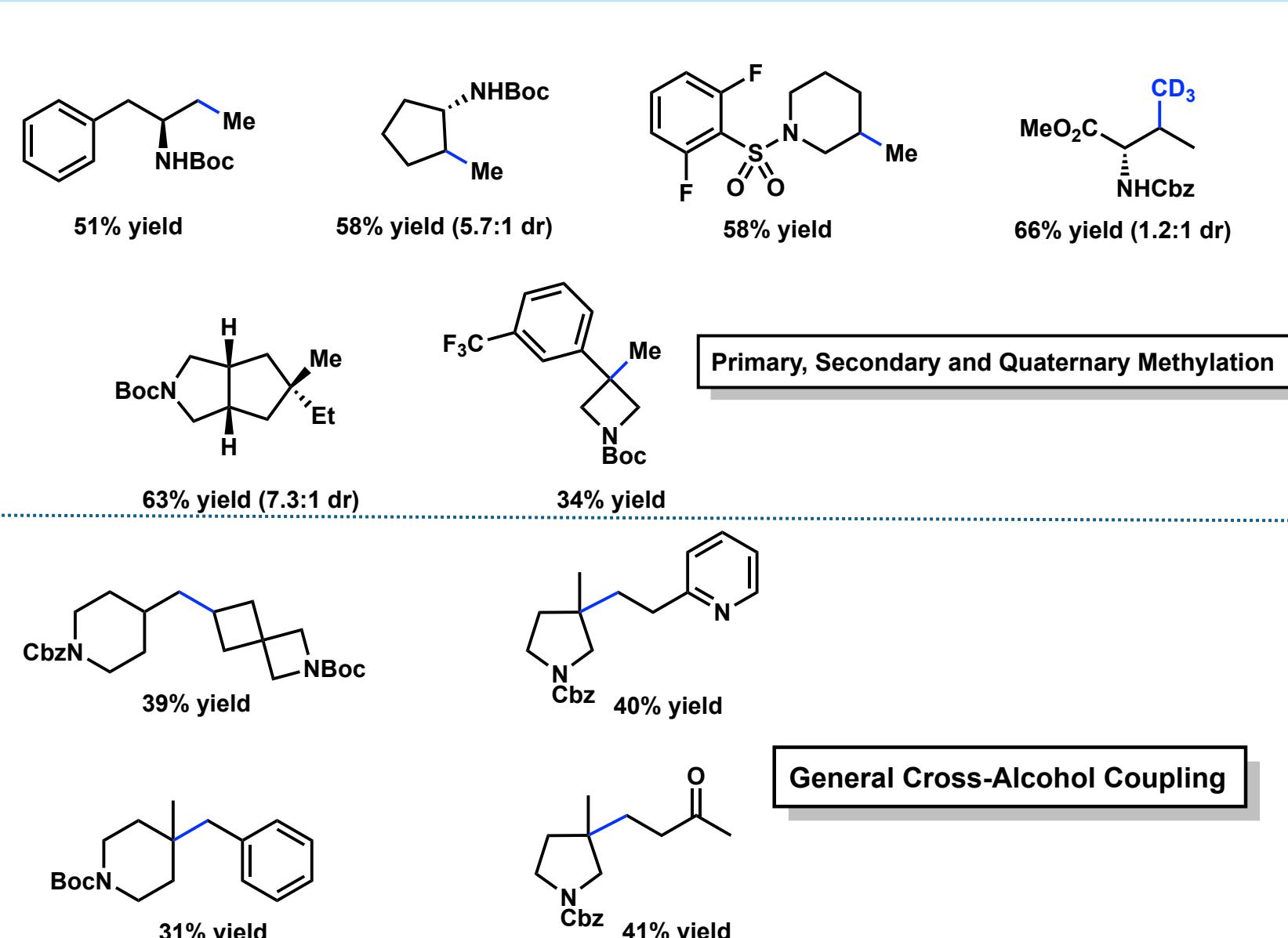
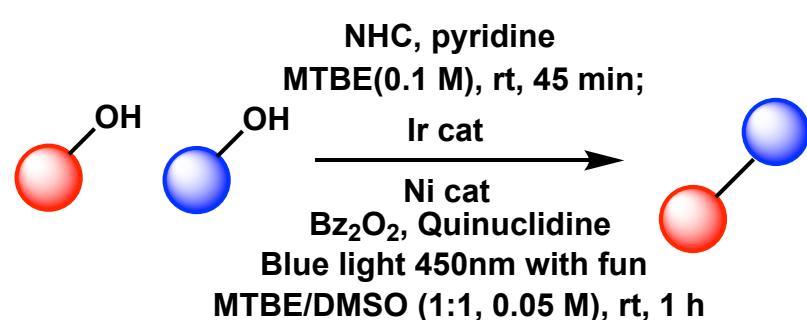


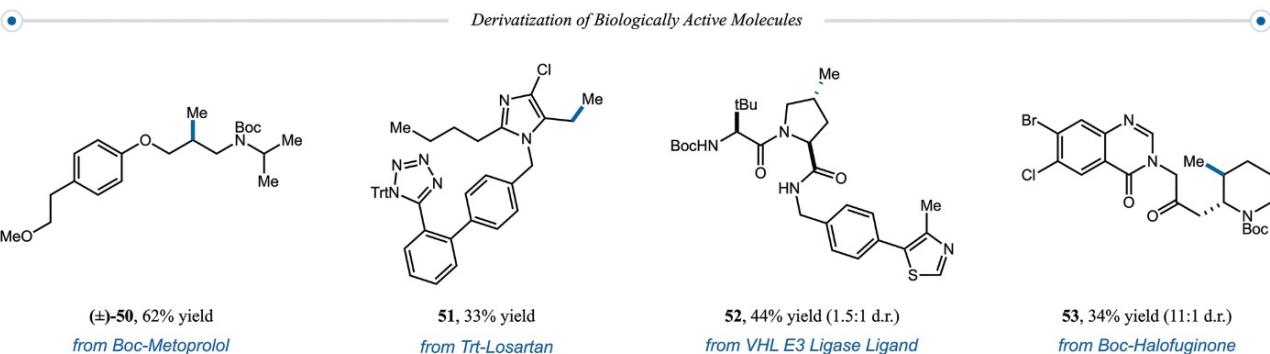
Figure S27. Sequential radical binding to generate Ni(IV) dialkyl complexes.

Substrate Scope (Excerpt)



Substrate Scope (Applications)

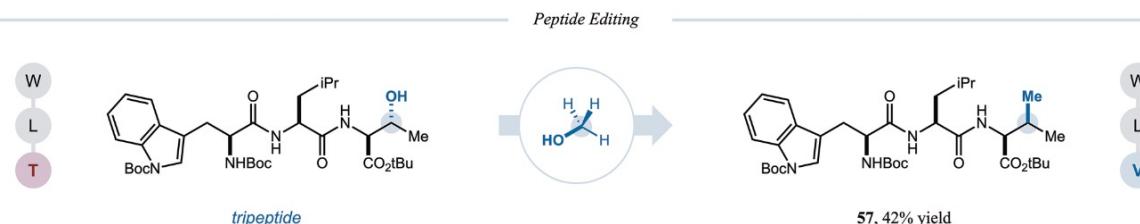
Complex molecules



Selective coupling of diols



Peptide



The rate of condensation between an alcohol and a NHC salt is governed by sterics.
(MeOH > 1° > 2° >> 3°)

Contents

1. Introduction

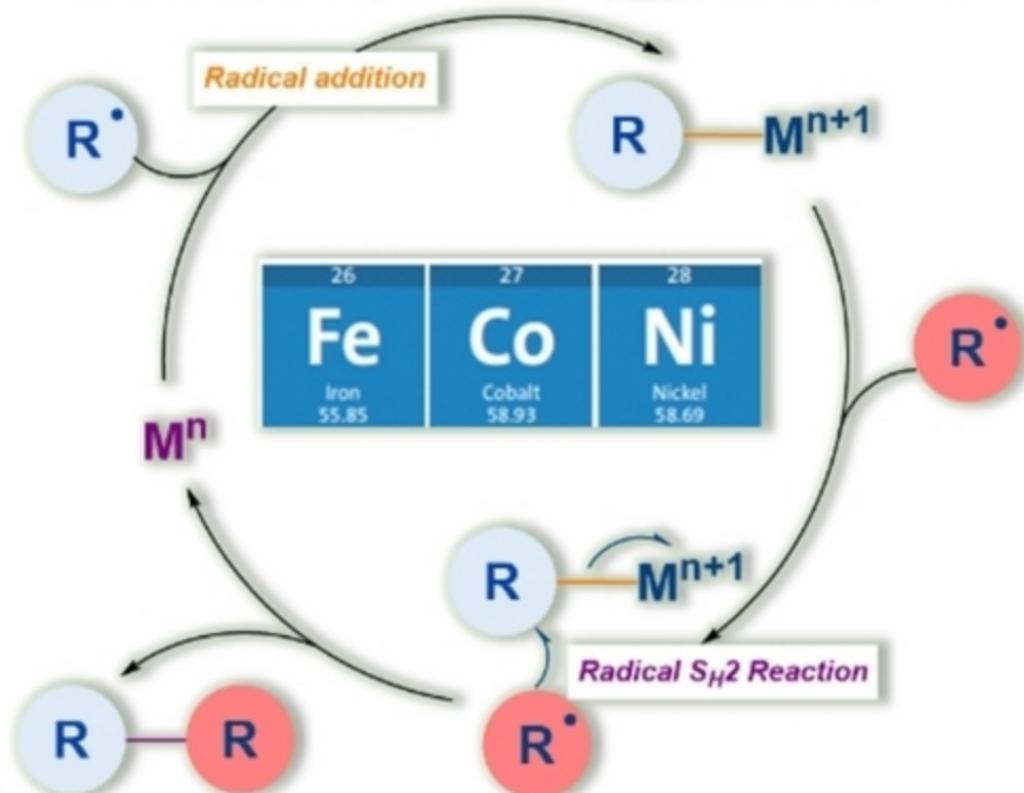
2. Main

- Biomimetic Approach (Fe catalyzed)
- Combination of SH2 and MHAT (Co catalyzed)
- Expansion of substrate scope (Ni catalyzed)

3. Summary and Perspective

Summary and Perspective

■ Bimolecular Homolytic Substitution (S_H2) at A Transition Metal



Summary

Utilizing S_H2 Reaction at a transition metal, various types of $C(sp^3) - C(sp^3)$ cross coupling reactions were realized.

Perspective

- Other transition metals (Cu, Cr, Mn etc ...)
- Application for synthesis of complex organic molecules
- Asymmetric reactions
- Merging of S_H2 reactions with other catalytic strategies

Appendix

$C(sp^3)$ rich compounds

Figure 6

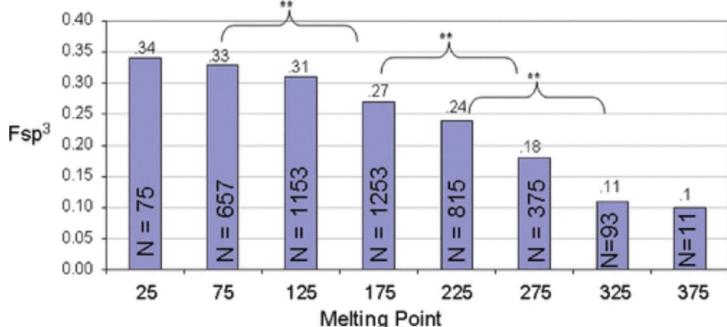


Figure 6. F_{sp^3} as a function of melting point. ** P value <0.001.

Figure 5

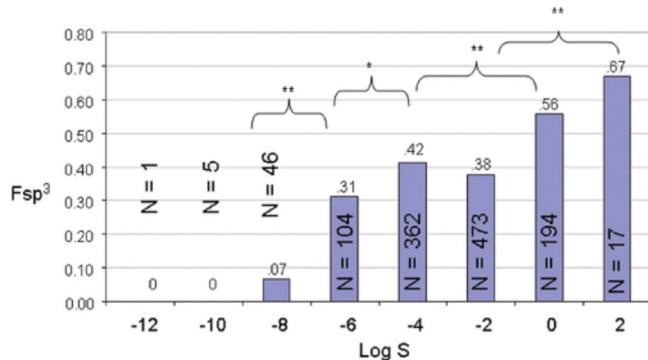


Figure 5. F_{sp^3} as a function of log S. * P value <0.01. ** P value <0.001.

Figure 3

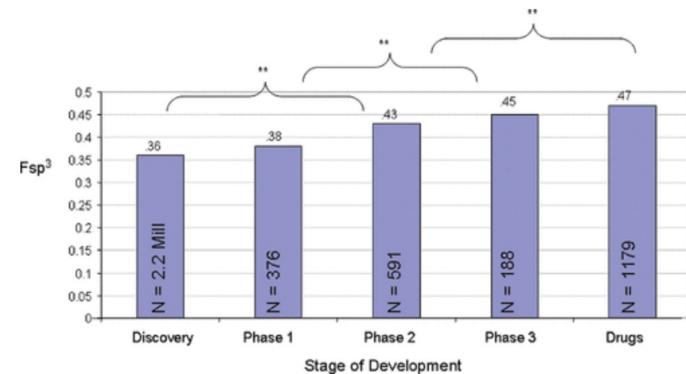


Figure 3. Mean F_{sp^3} for compounds in different stages of development. ** P value <0.001.

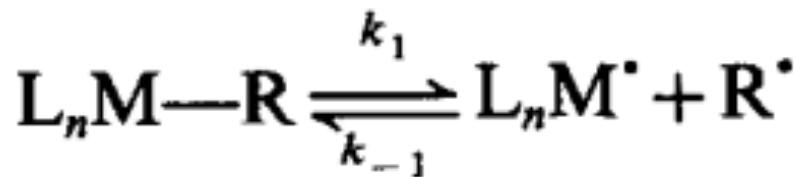
• $C(sp^3)$ rich compounds have ...

1. Three-dimensional structure
2. Increased water solubility
3. Low melting point



High probability of being drug

Method for Calculation of BDEs of M-C bond

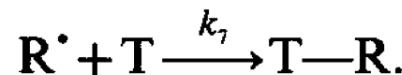
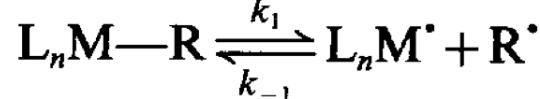


$$D_{M-R} = \Delta H_1^\ddagger - \Delta H_{-1}^\ddagger.$$

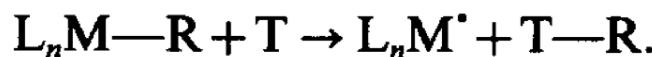
$$\Delta H_1^\ddagger \Delta H_{-1}^\ddagger$$

... Activation energies of the forward and reverse reactions

① ΔH_1^\ddagger



Overall:



$$\frac{-d[L_nM-R]}{dt} = \frac{k_1 k_7 [L_nM-R][T]}{k_{-1}[L_nM^\cdot] + K_7[T]}.$$

(Estimate k_1)

② ΔH_{-1}^\ddagger

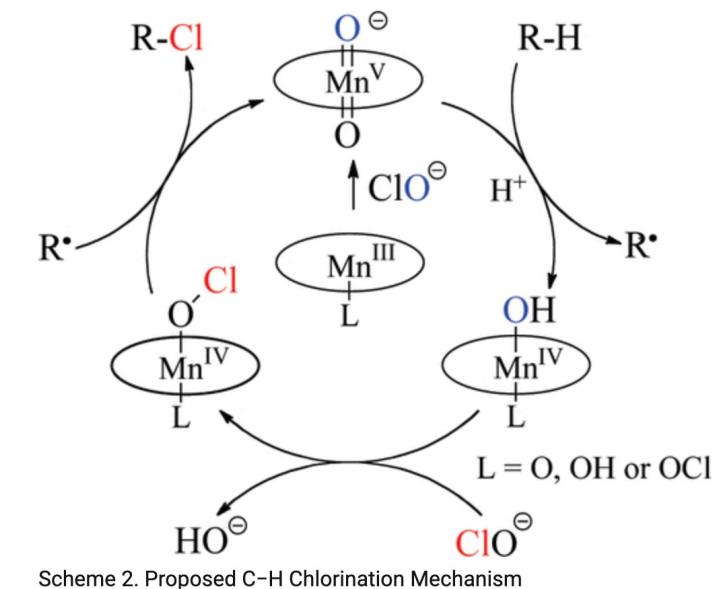
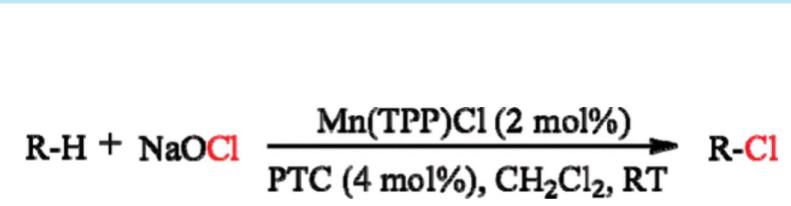
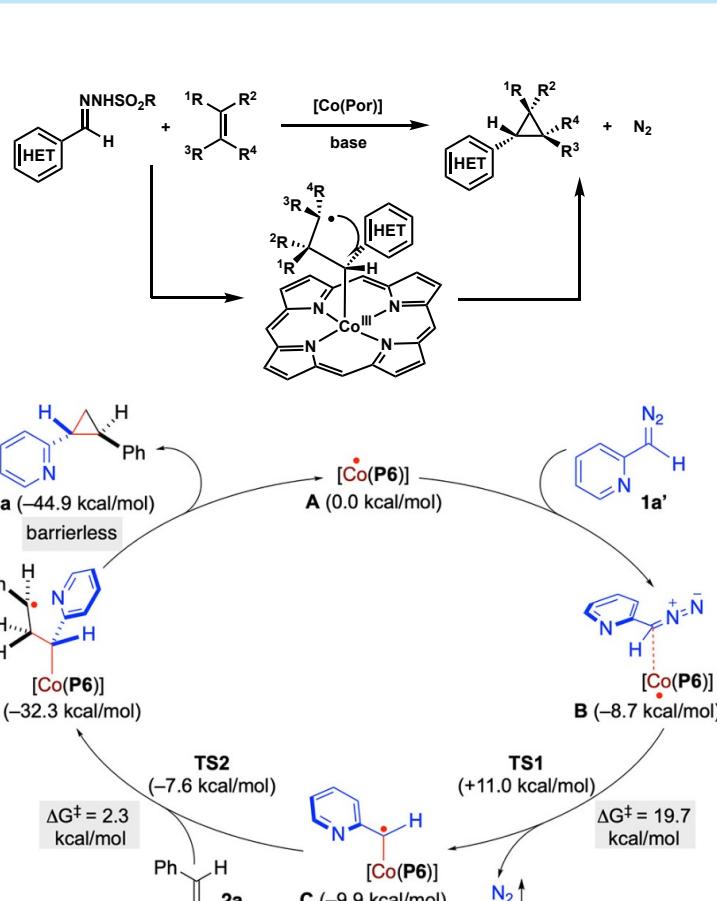
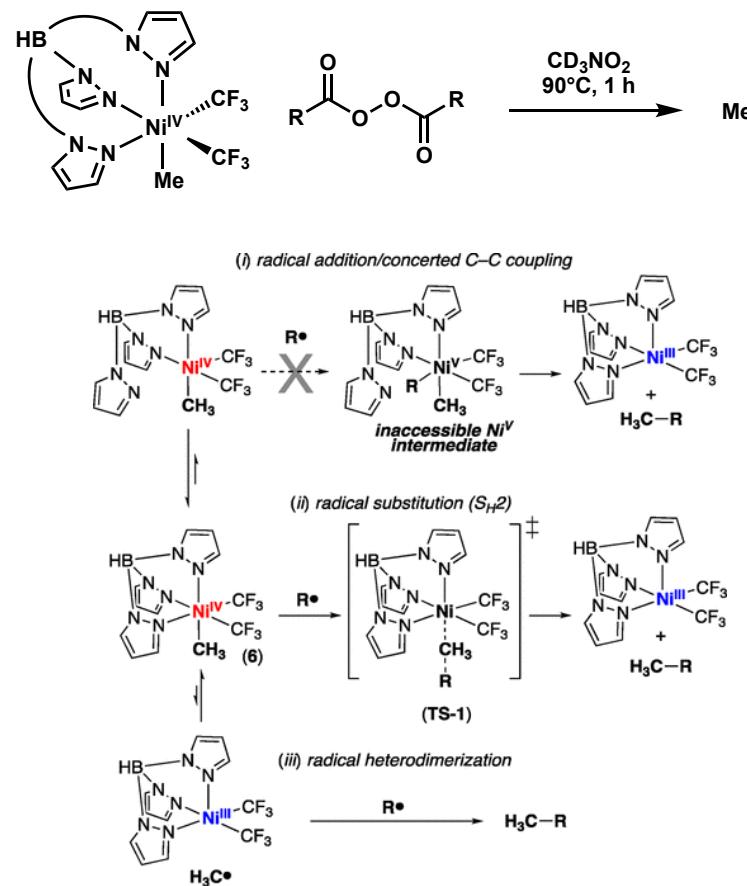
- (1) Direct measurement by photoexcitation of M-R and recombination
- (2) Competition with compounds with known rate constants

(Estimate k_{-1})

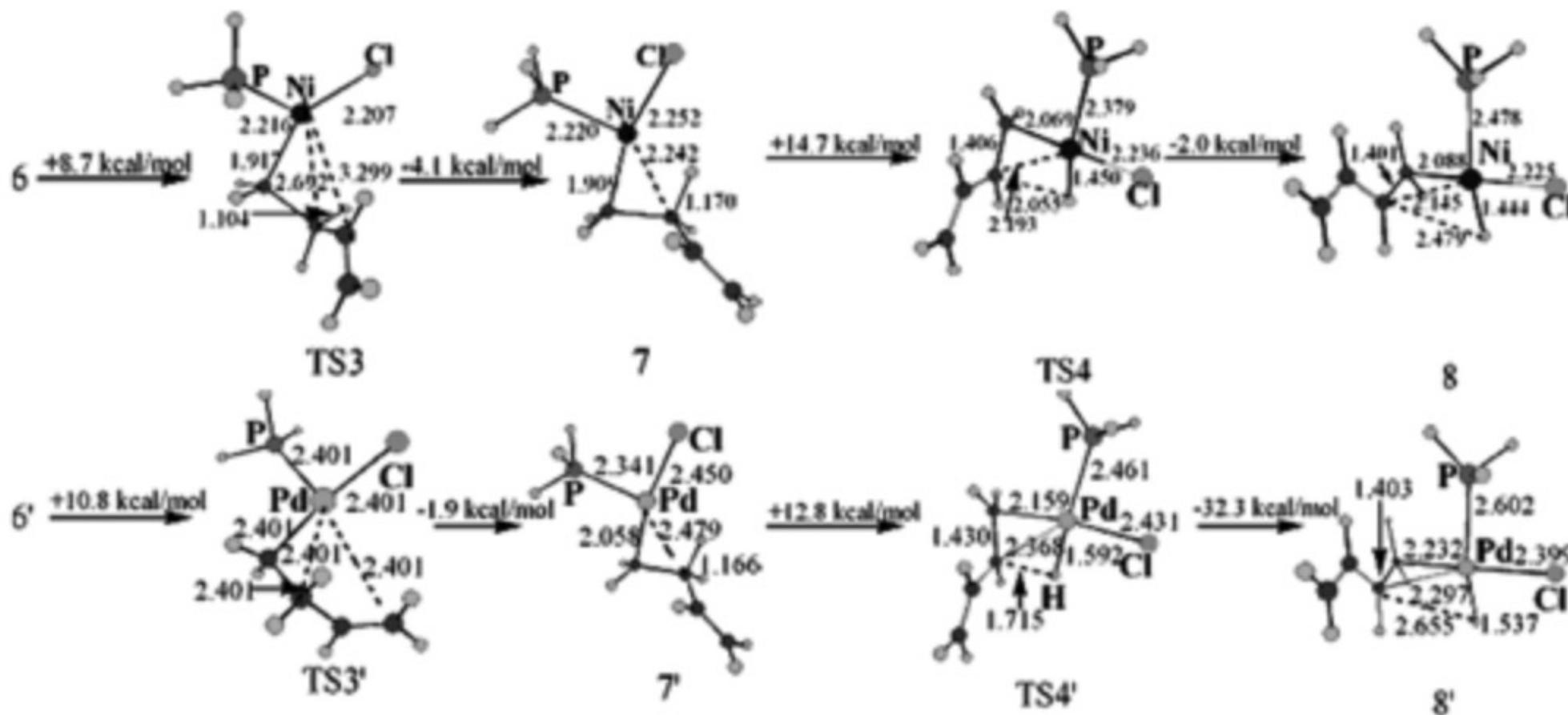
③ Arrhenius equation

$$k = A e^{\frac{-E_a}{RT}}$$

Proposed Reaction Mechanisms



β -H Elimination (Computational Calculation)



Light Absorption of Fe - Porphyrin

5. UV-Vis Spectra of Catalysts

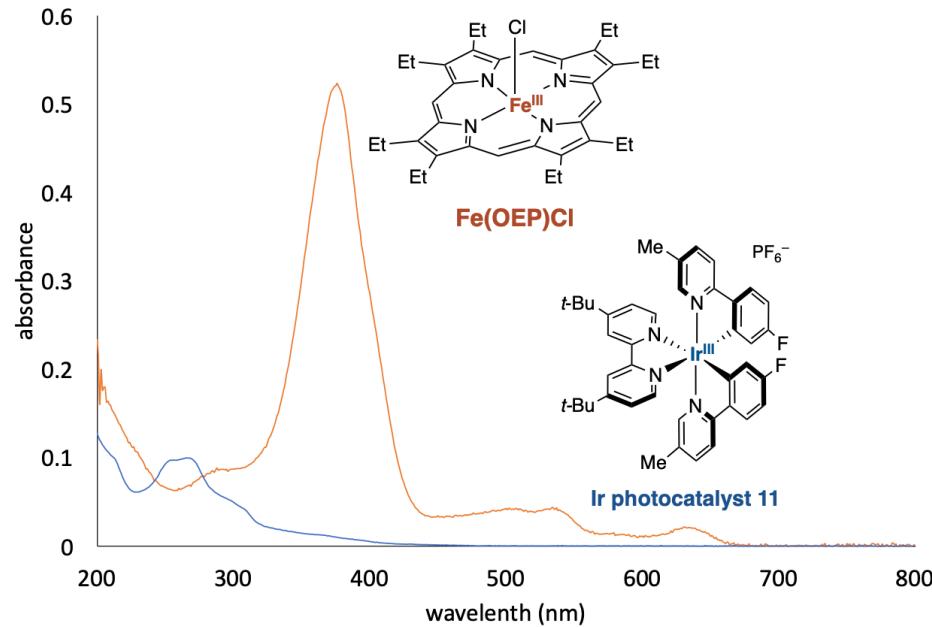


Figure S8. UV-Vis spectra of iron porphyrin catalyst Fe(OEP)Cl and Ir photocatalyst **11** in acetone. Relative scale of spectra reflects the relative concentration of each catalyst in solution under initially optimized conditions (5:1 iron:iridium). At 450 nm, iron porphyrin catalyst absorbs approximately 28 times more light than iridium photocatalyst.

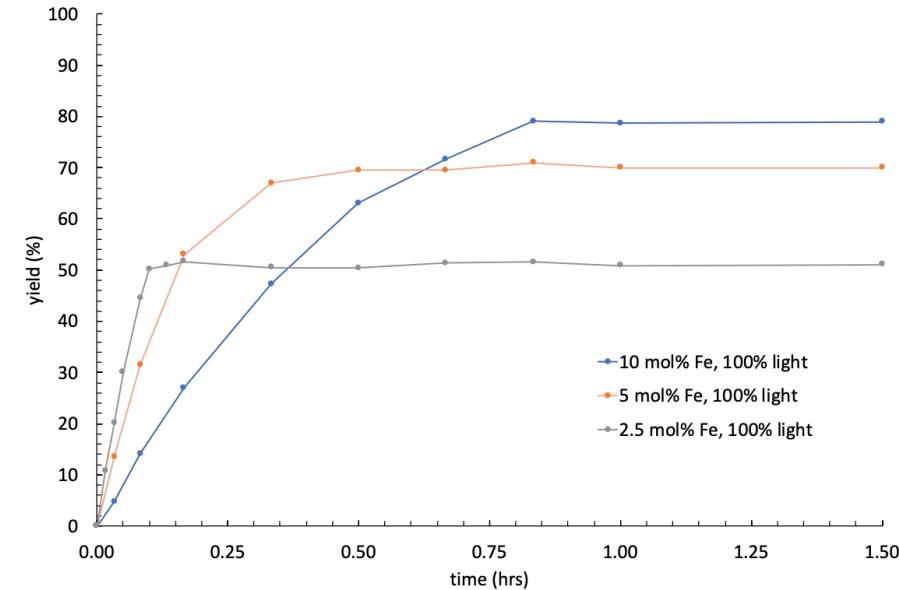
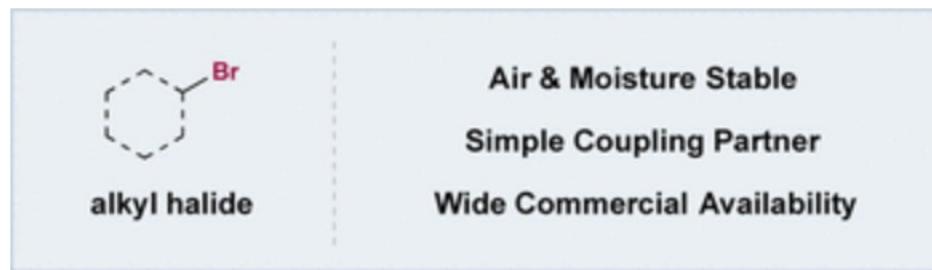
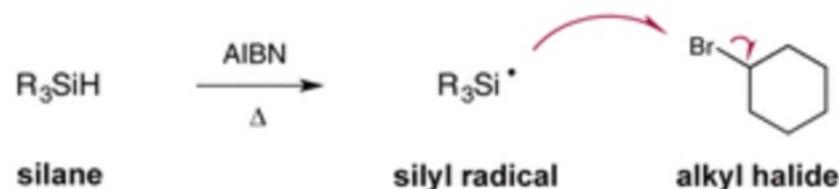


Figure S3. Reaction profile showing yield of C-C coupled product over time at different iron porphyrin catalyst loadings while *maintaining the same light intensity*. As catalyst loading is decreased, the rate of the reaction increases while the final yield of product decreases. Yields determined by UPLC.

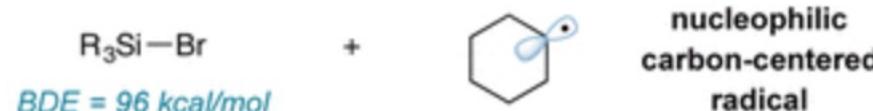
A Silyl Radical–Mediated Halogen Abstraction–Radical Capture



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

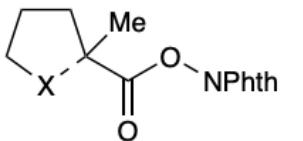


Fast and Efficient Activation of Alkyl Halides



Si–Br bond (96 kcal/mol for $\text{Me}_3\text{Si–Br}$) and the C_{sp}^3 –Br bond (69 kcal/mol for bromoethane)

Limitations



1.0 – 2.0 equiv.



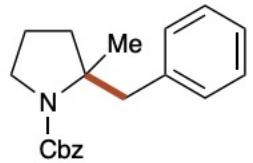
1° alkyl bromide

Ir(F(Me)ppy)₂(dtbbpy) (1 mol%)
Fe(OEP)Cl (2 mol%)
(TMS)₃SiNHAdm, KOAc
acetone : iPrOH (1:1)
blue LEDs, 2-5 h

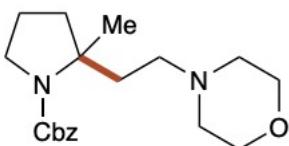


**fully-substituted
C(sp³)–C(sp³) product**

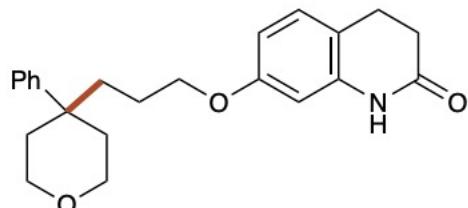
Limitations:



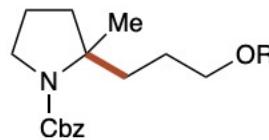
18% yield*



<5% yield*



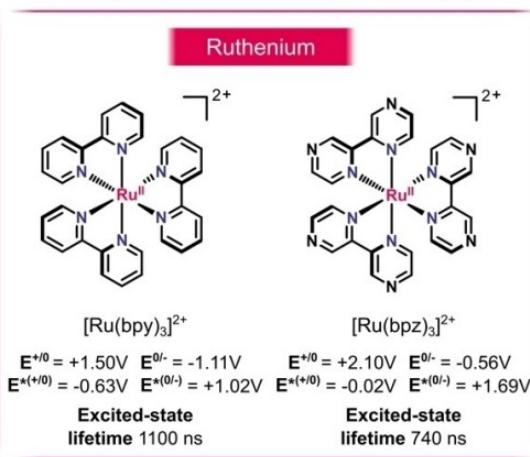
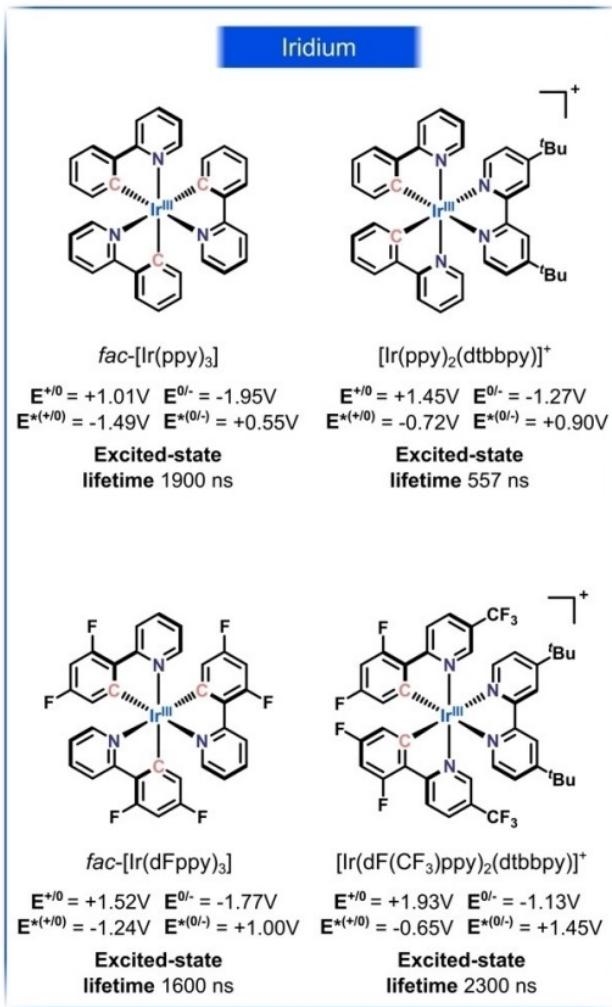
22% yield*



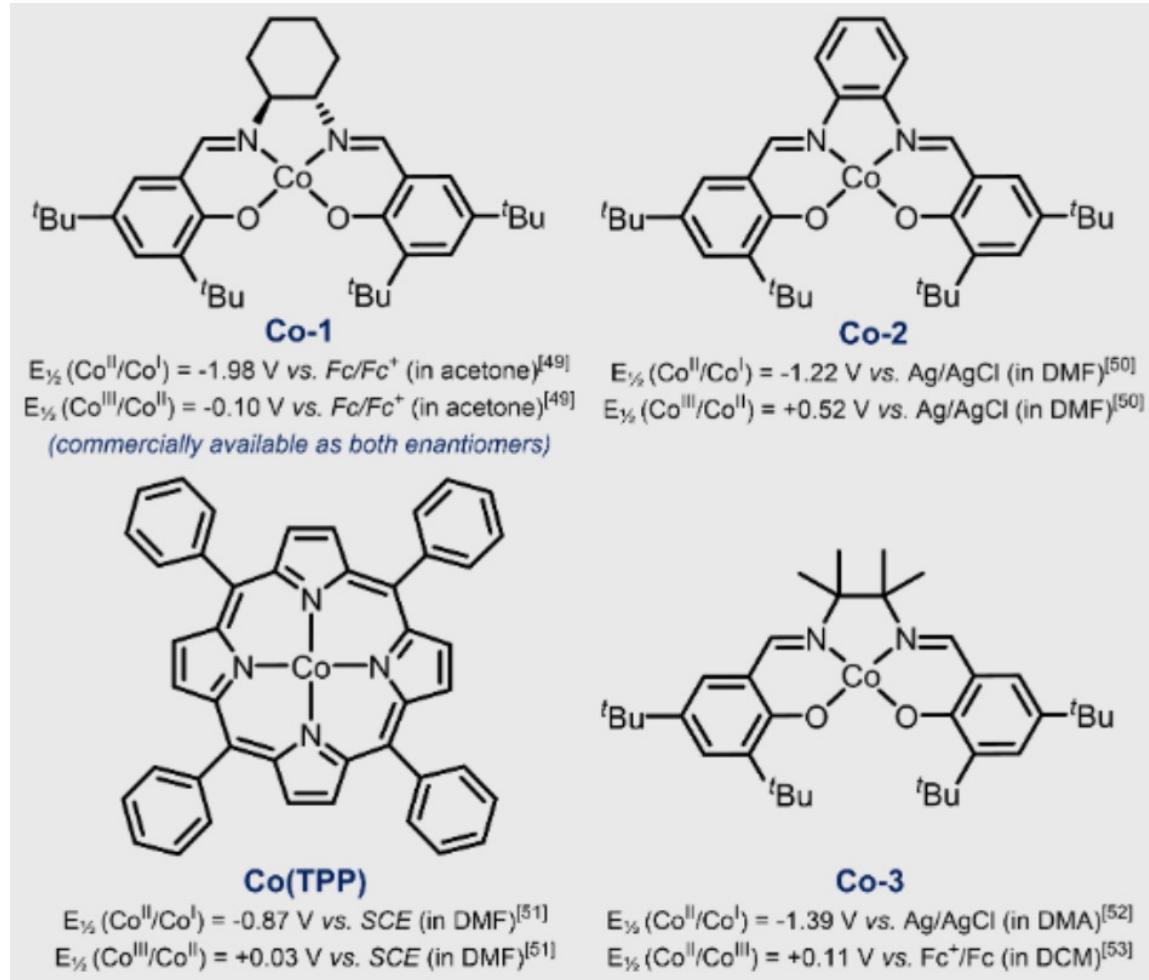
(±)-66, R = H, 30% yield*
(±)-67, R = Ac, 72% yield*

Reduction Potentials

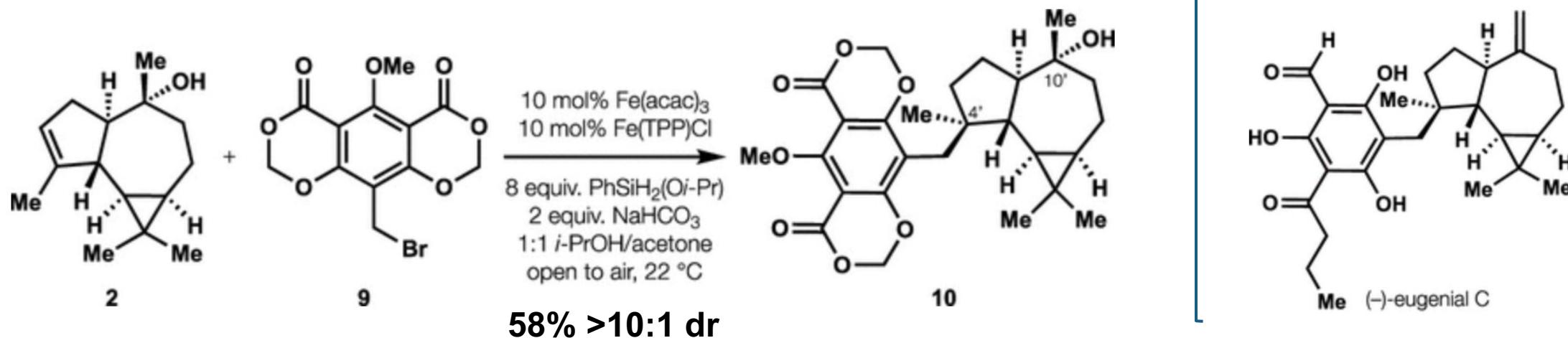
Photocatalyst (vs NHE)



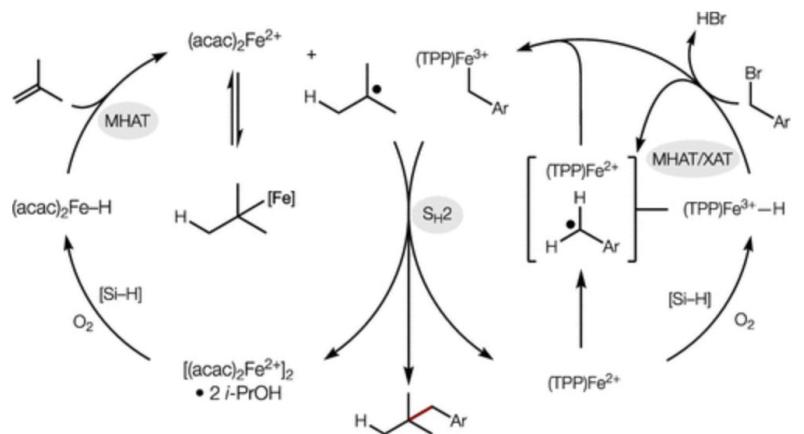
Co – Ligand complexes



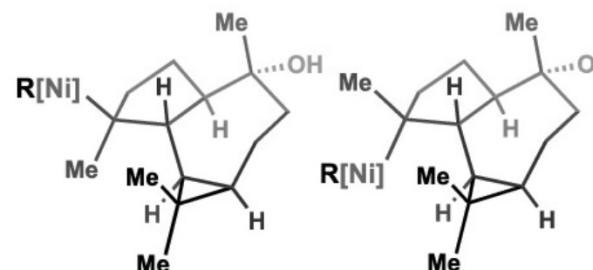
Application of $S_{H}2$ Reaction for Synthesis of Natural Product



Oxidative generation of Fe-H + $S_{H}2$



reductive elimination pathway did not distinguish diastereomers



can $S_{H}2$ favor C4' re-face approach due to geminal dimethyl repulsion?

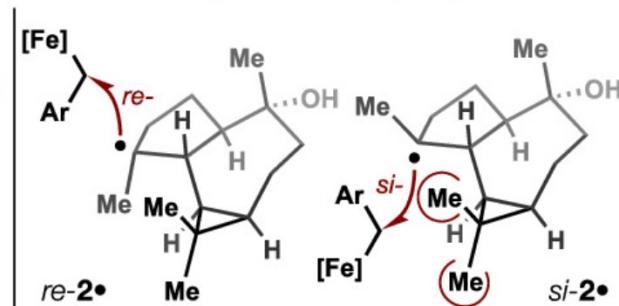
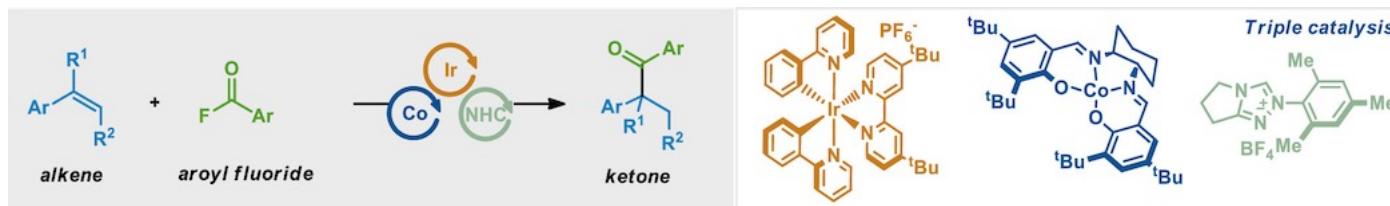
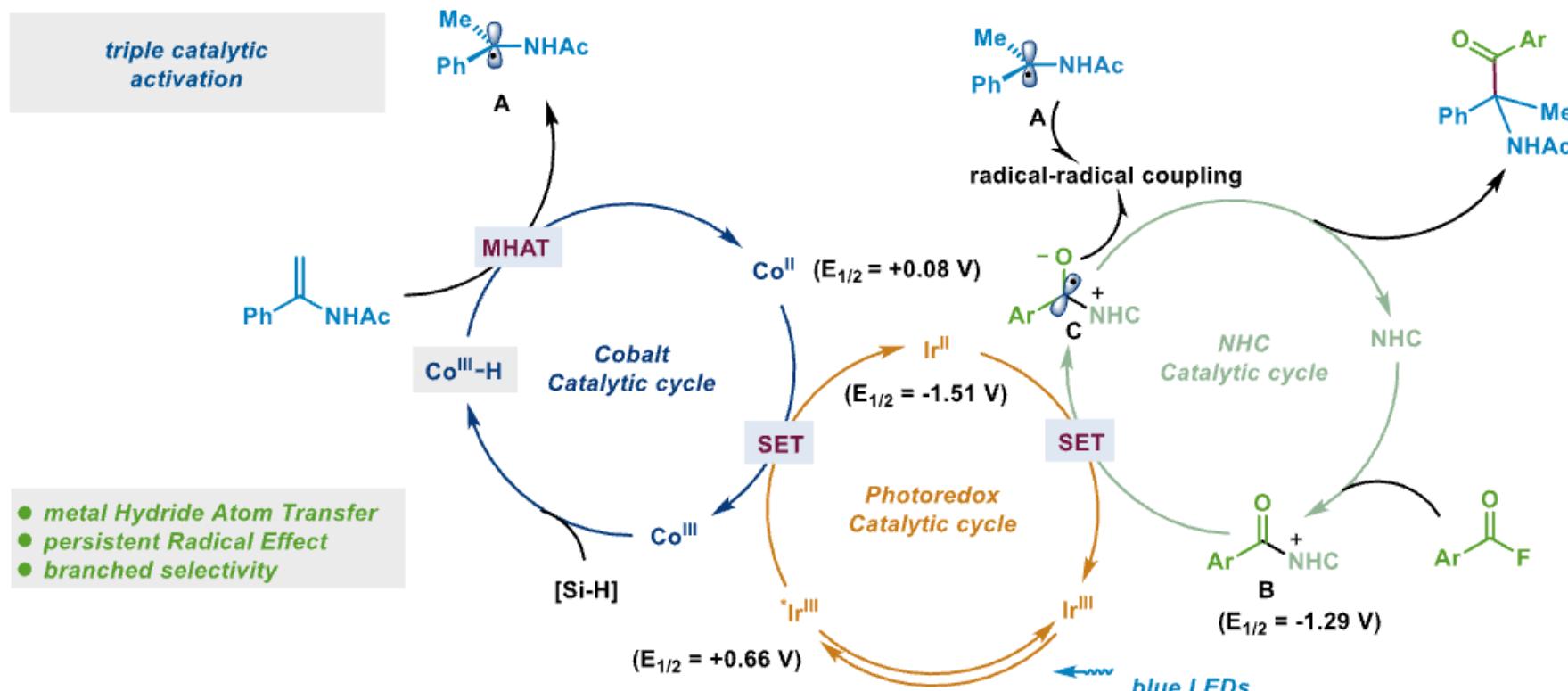


Figure 2. Proposed intersection of catalytic cycles. See the text for competing hypotheses.

Oxidative Co-H Generation



C) Proposed mechanism



Limitations and Consideration

2-5. Limitations of Hydrobenzylat

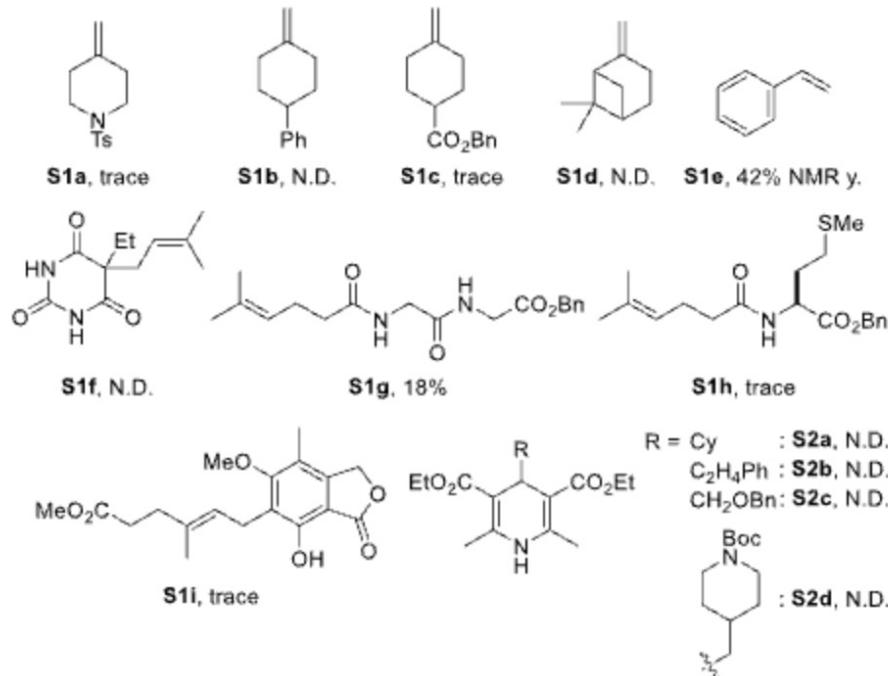


Table S1. Screening of Photocatalysts

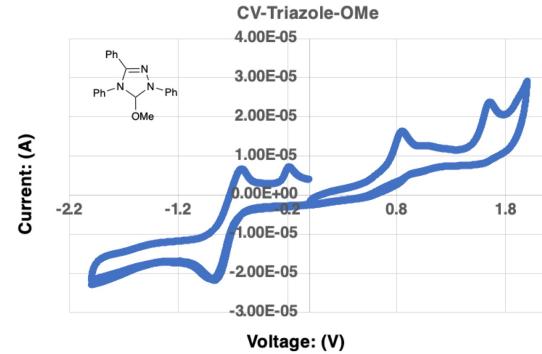
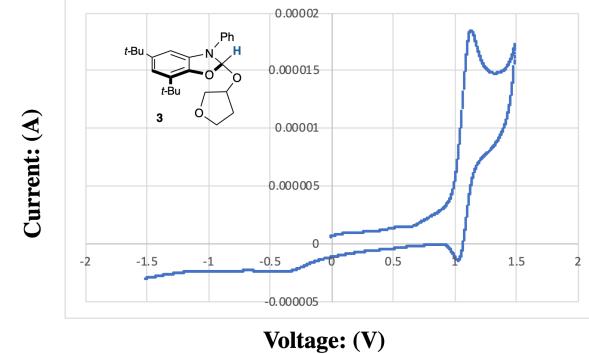
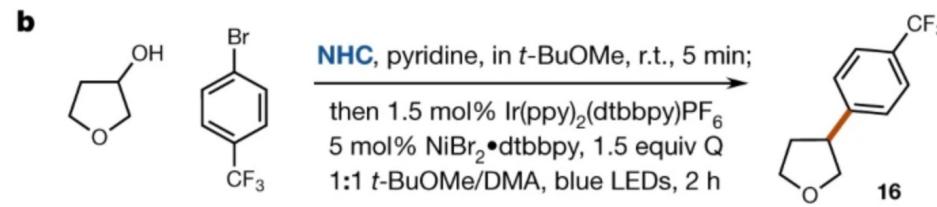
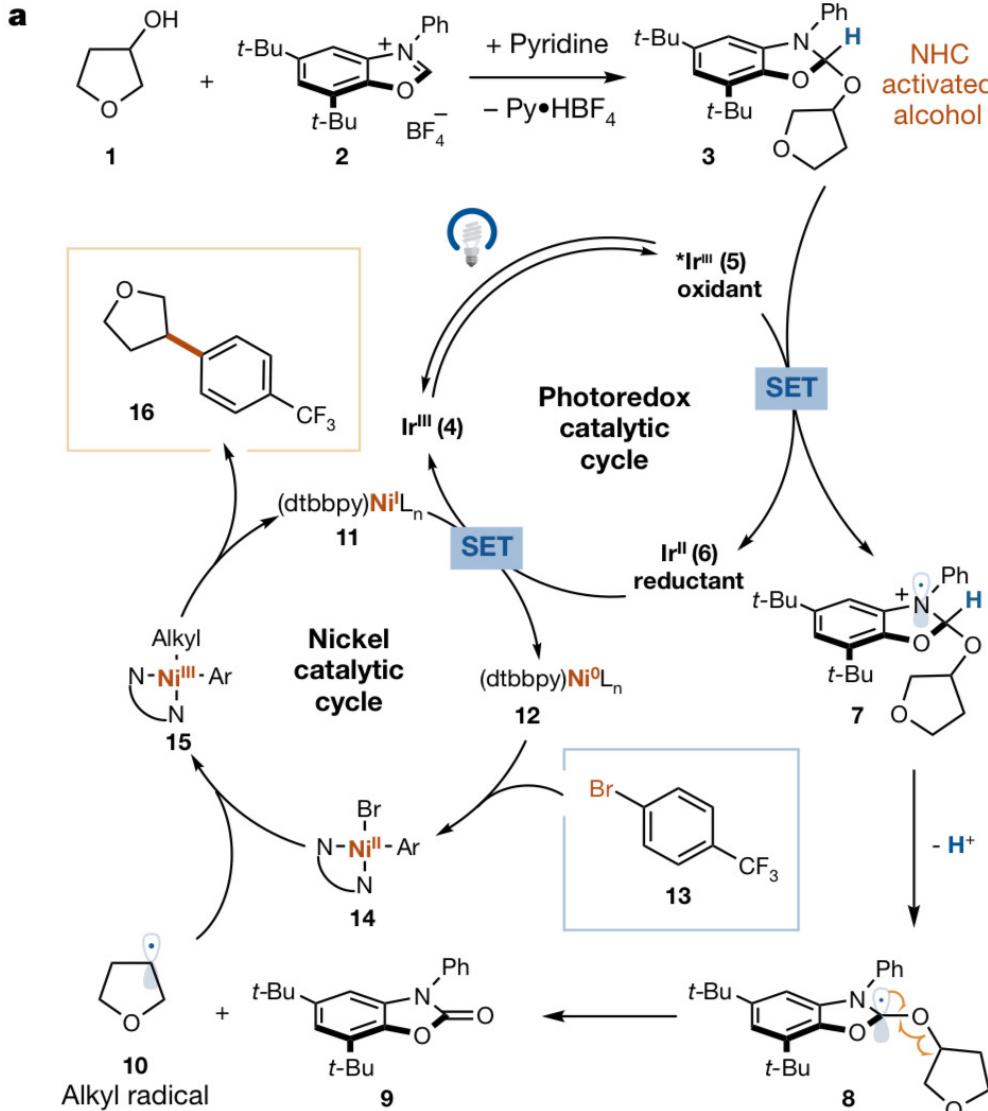
Entry	Photocatalyst	% yield ^a	E _{red} (PC/PC ⁺) [V vs. SCE]
			1a 2a (2.0 equiv.) PC (1.0 mol%) 4a (1.0 mol%) benzene (0.1 M) blue LED, 25 °C, 18 h 3aa
1	Ir(dFppy) ₃	74	-1.24
2	[Ir{dF(CF ₃)ppy} ₂ (dtbpy)](PF ₆)	46	-1.37
3	[Ir(ppy) ₂ (dtbpy)](PF ₆)	37	-1.51
4	Ru(bpy) ₃	N.D.	-1.33
5	4CzIPN	60	-1.21

^a Determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

The reaction efficacy might rely on factors other than the electronic properties of the photocatalysts.

(reaction rate of the SET, benzyl radical quenching process etc ...)

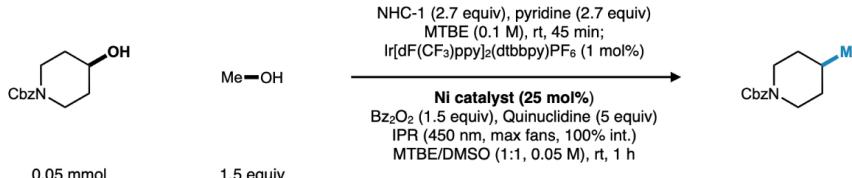
Deoxygenative Arylation of Alcohols



Optimization (Methylation)

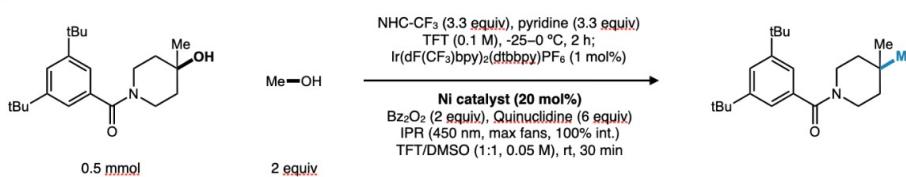
Ni cat

Table S9. Evaluation of Ni catalysts for cross-alcohol coupling with methanol



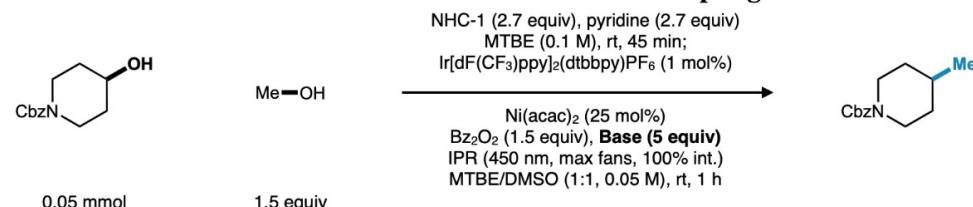
Ni Catalysts	UPLC Assay Yield
Ni(acac) ₂	68%
Ni(TMHD) ₂	57%
Ni(acac) ₂ /KTp*	60%
Ni(dtbbpy)Cl ₂	13%
NiBr ₂ (glyme)	33%
Ni(OEP)	9%

Table S14. Evaluation of Ni catalysts for cross-alcohol coupling of tertiary alcohol with methanol



Ni catalyst	UPLC Assay Yield
Ni(acac) ₂	56%
Ni(TMHD) ₂	47%
Ni(acac) ₂ /KTp*	67%

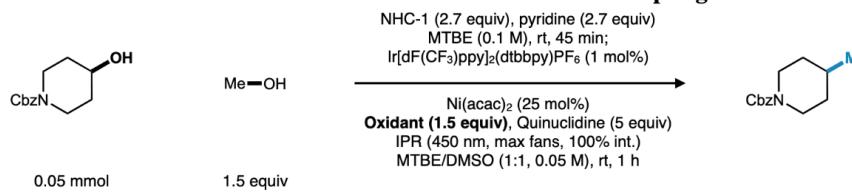
Table S11. Additional evaluation of bases for cross-alcohol coupling with methanol



Base

Base	UPLC Assay Yield
Quinuclidine	68%
KOAc	0%
NaOBz	19%
Cs ₂ CO ₃	4%
DABCO	0%

Table S10. Additional evaluation of oxidants for cross-alcohol coupling with methanol



Oxidant

Oxidant	UPLC Assay Yield
Bz ₂ O ₂	68%
K ₂ S ₂ O ₈	49%
SeO ₂	0%
CAN	0%
KIO ₃	37%
Oxone	51%

The Effect of Oxidation of Quinuclidine

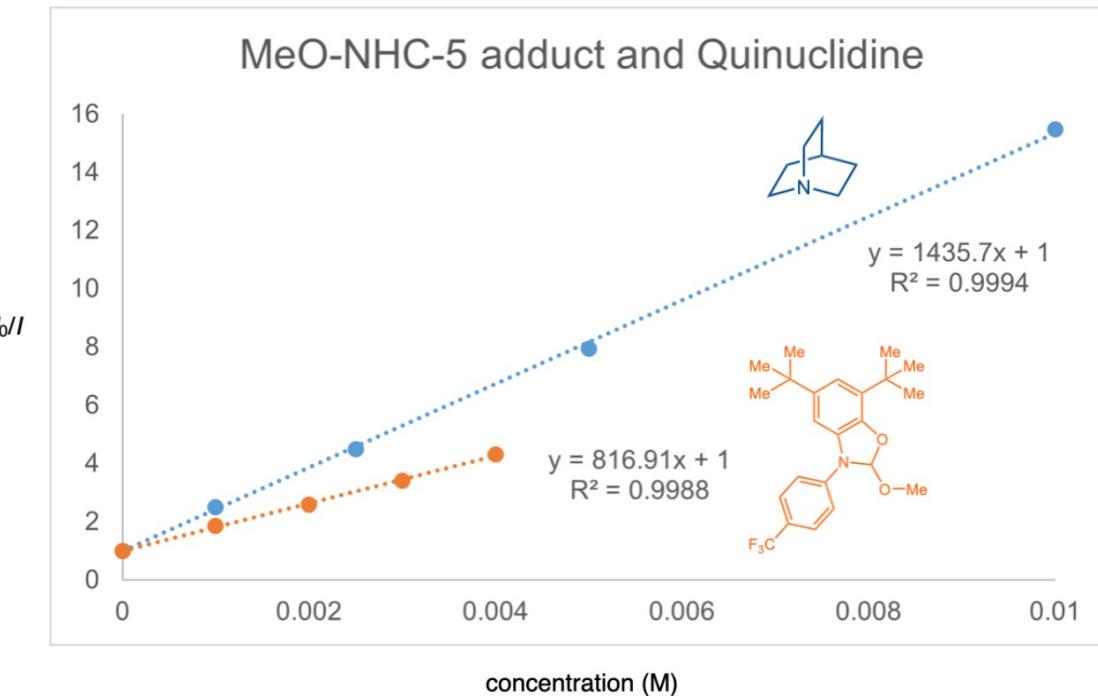


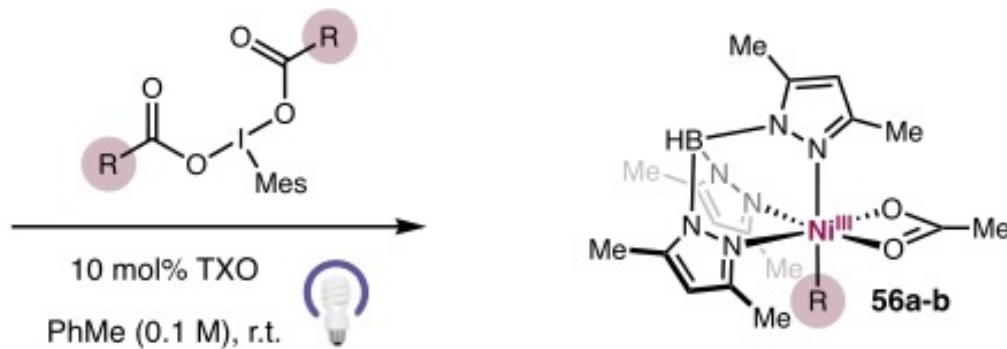
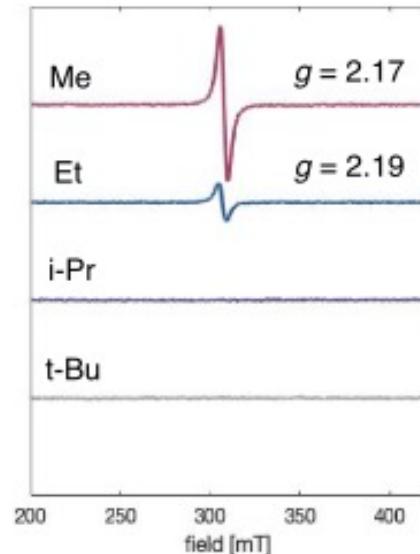
Table S17. A time study for cross-alcohol coupling of *tert*-butyl 3-hydroxy-3-methylpyrrolidine-1-carboxylate and methanol

Irradiation time	Results
10 min	57% yield
20 min	55% yield
30 min	53% yield
60 min	52% yield
90 min	49% yield
120 min	44% yield

LC trace/mass hit observed

Detection of Ni-Alkyl Complex

D



detected by EPR

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

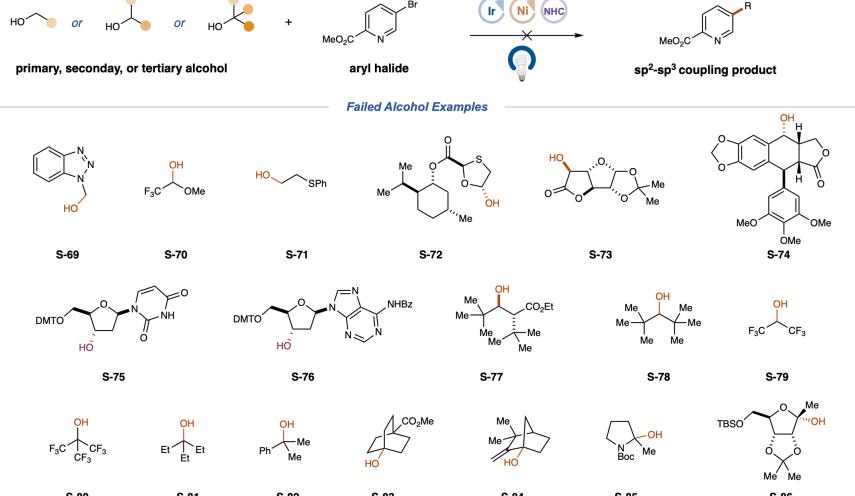
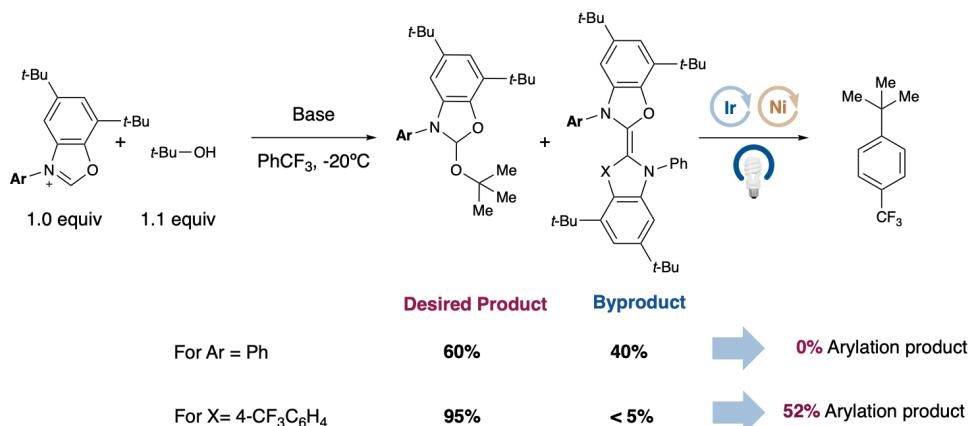
Only methyl and 1° alkyl bind
to the nickel complex

Radical sorting

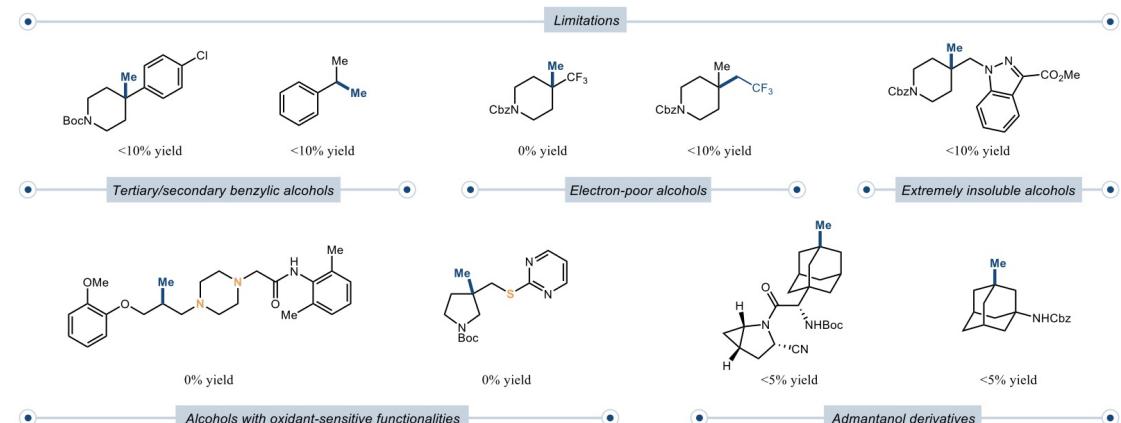
R = Me, Et ... Ni(III) was detected.
(consistent with BDFE calculated
by DFT)

Limitations

NHC activation

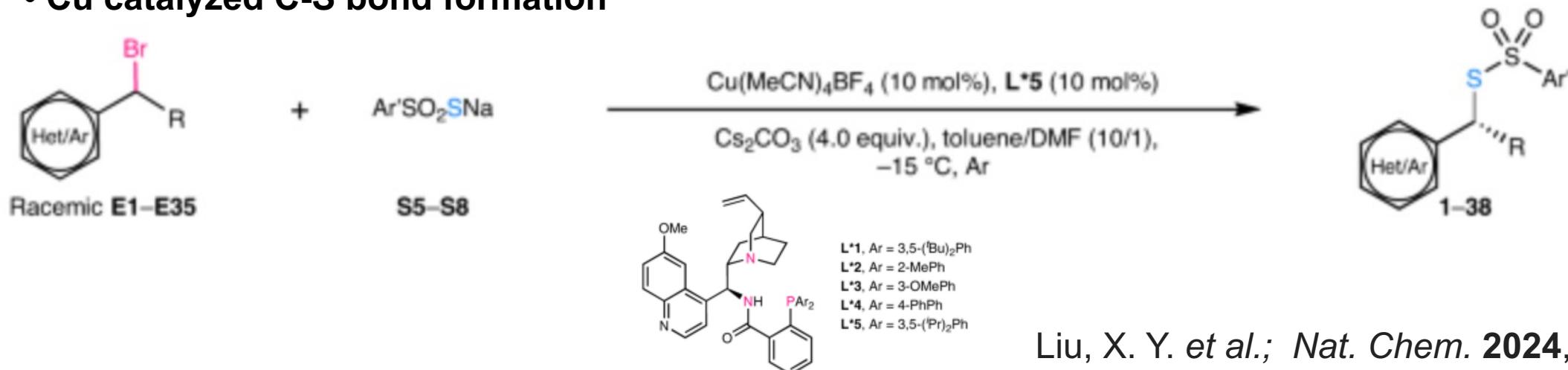


Alcohol-alcohol coupling



Examples of The Use of Other Transition Metals

- Cu catalyzed C-S bond formation



- Mn catalyzed difunctionalization of unactivated alkenes

