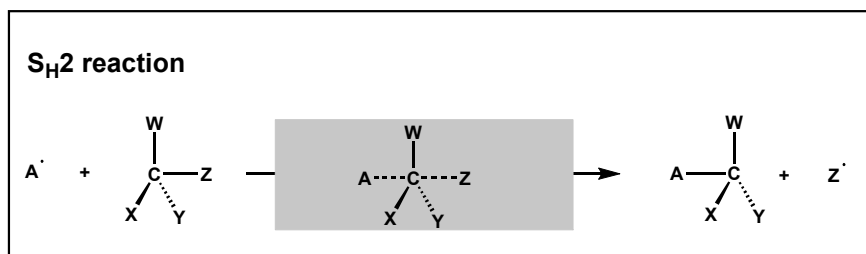
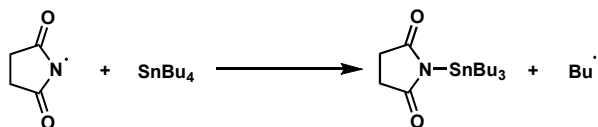
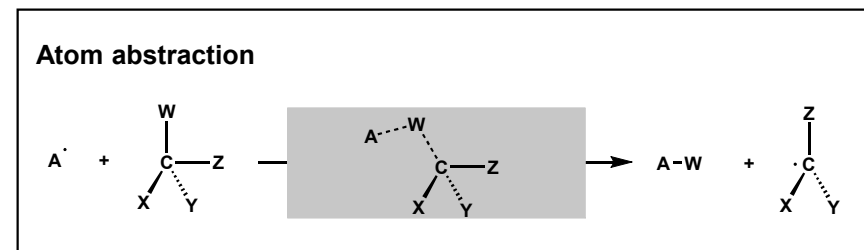


Introduction "S_H2 reactions occur very commonly in multivalent (non)metallic centers"



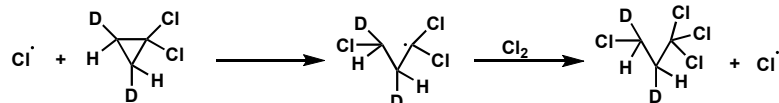
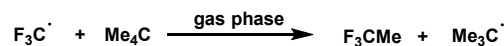
VS



Roberts, B. P. *Nat. Phys. Sci.* **1971**, 229, 221

S_H2 in the early years:

- ♣ Heteroatom as attacker, metallic center as acceptor.
- ♣ Mechanistic study was more favored
- ♣ Few C-X or C-C bond formation reported



"Seldom postulated, rarely discussed, frequently discarded as improbable, but potentially of immense interest in synthetic organic chemistry"

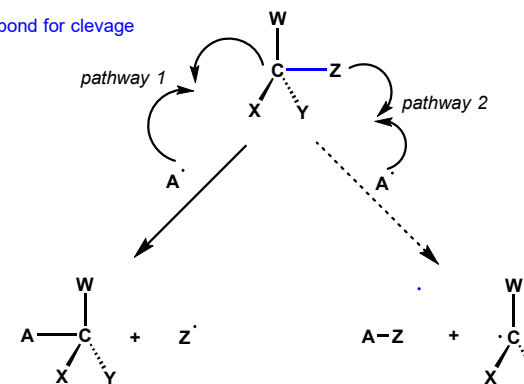
Johnson, M. D. *Acc. Chem. Res.* **1983**, 16, 343

Why is homolytic substitution of saturated carbon so arduous?

- ♣ Homolytical substitution at other centers (atom abstraction)
- ♣ Other side reaction like radical addition, homocoupling etc.

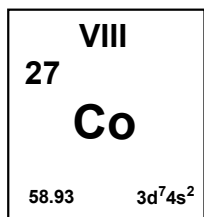
Solutions

- ♣ weak C-Z bond for cleavage



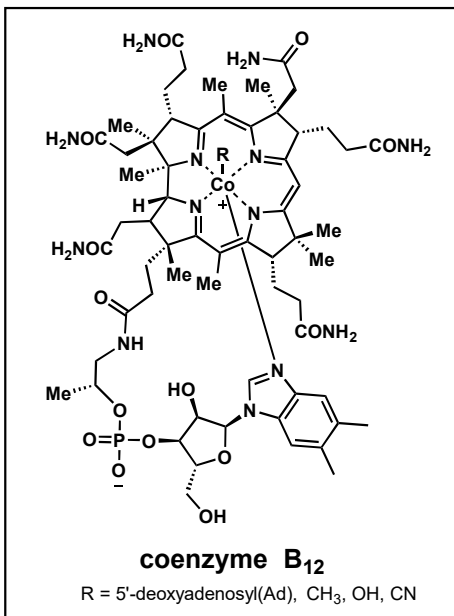
- ♣ prevent Z being attacked by A (steric hindrance)

- ♣ impede homocoupling (Persistent Radical Effect, radical sorting)



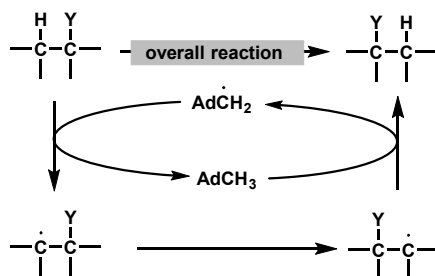
BDE

B ₁₂ Co-Me	37 kcal/mol
C-H	99 kcal/mol
C-C	79 kcal/mol

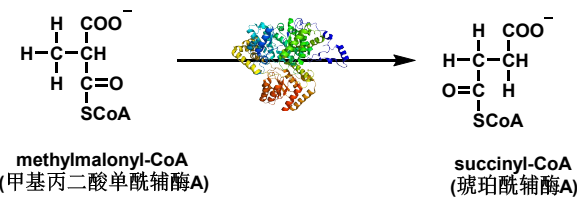


1. Intramolecular rearrangement

alkyl radical could be stabilized with coenzyme B₁₂



eg. methylmalonyl-CoA mutase (甲基丙二酸单酰辅酶A变位酶)

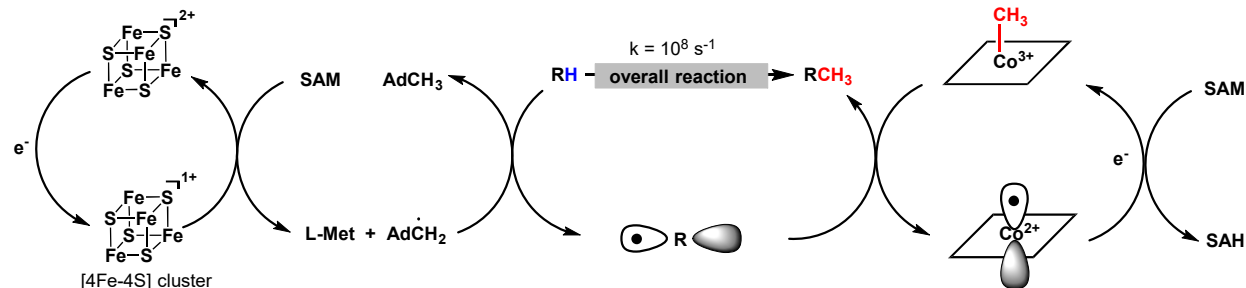


Halpern, J. *Science* 1985, 227, 869

2. Methyl transfer

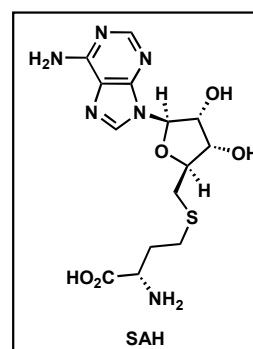
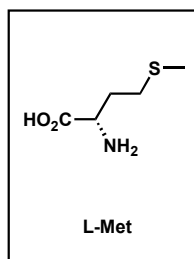
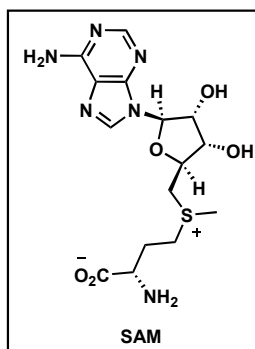
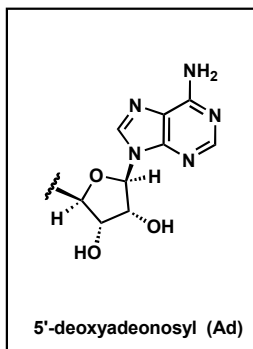
simple alkyl (methyl) group could undergo bimolecular (intermolecular) substitution reaction

eg. class B radical SAM methyltransferases (RSMTs)



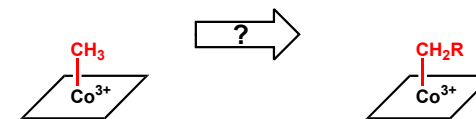
Liu, W. *Acc. Chem. Res.* 2012, 45, 555
Booker, S. J. *J. Biol. Chem.* 2015, 290, 3995

3. Ribonucleotide reduction

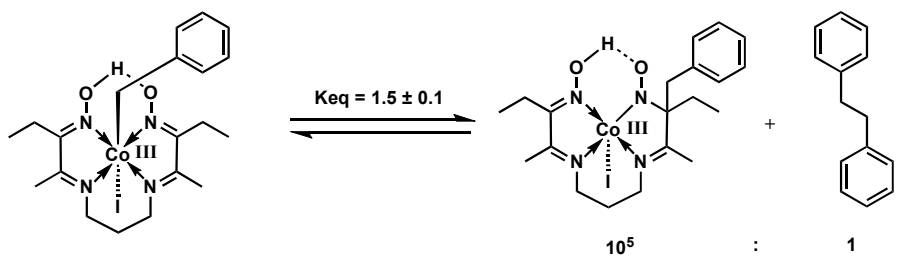


methyl transfer

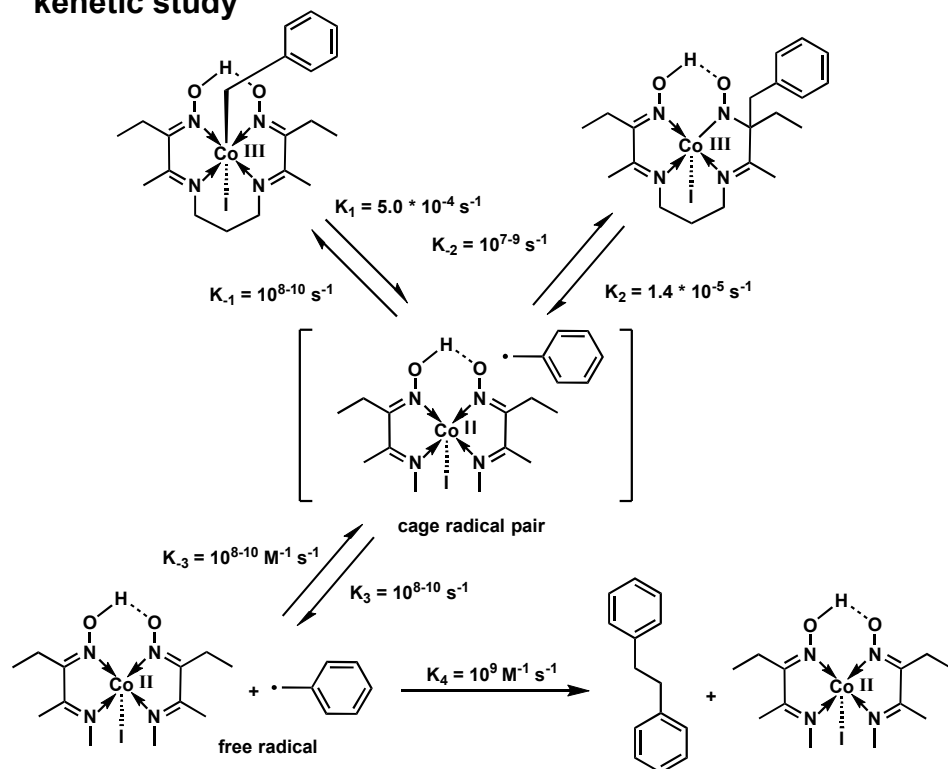
alkyl group transfer



Persistent Radical Effect



kinetic study



♣ A term coined by Finke in 1992

♣ Demonstrate the **necessary conditions** for high selectivity of intermolecular radical reaction

- one of the radical intermediates formed during the course of the reaction must be more persistent than the others.
- the persistent and transient radicals must be generated with equal rates.
- the persistent radical can't undergo homocoupling.

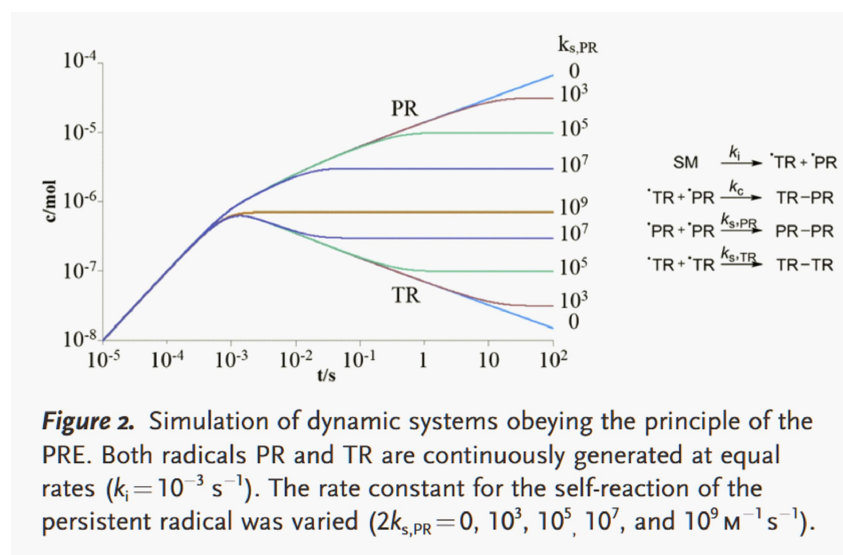


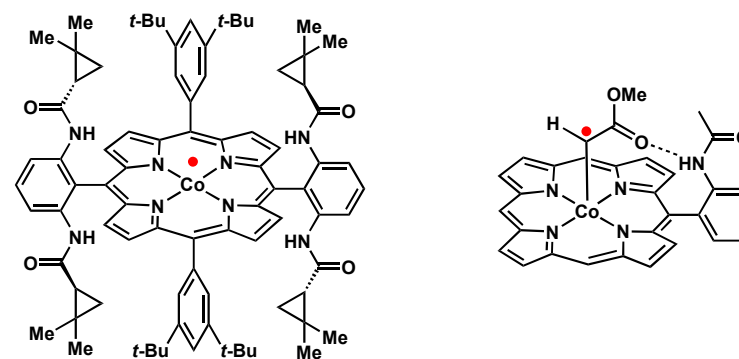
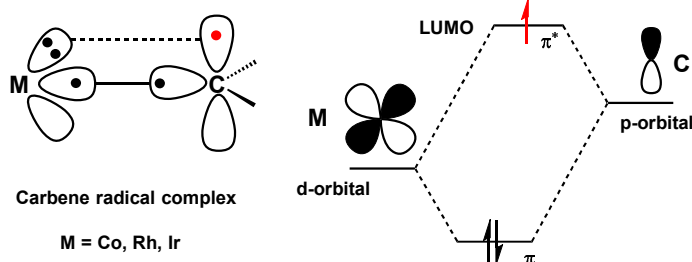
Figure 2. Simulation of dynamic systems obeying the principle of the PRE. Both radicals PR and TR are continuously generated at equal rates ($k_i = 10^{-3} \text{ s}^{-1}$). The rate constant for the self-reaction of the persistent radical was varied ($2k_{s,PR} = 0, 10^3, 10^5, 10^7, \text{ and } 10^9 \text{ M}^{-1} \text{ s}^{-1}$).

for systematically learning, see Studer, A. *Angew. Chem. Int. Ed.* **2020**, 59, 74

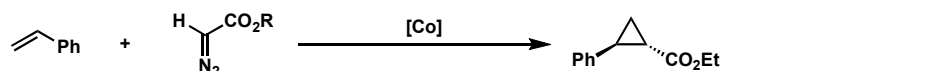
Metal-carbene radical species



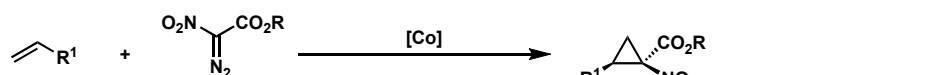
Xiang Peter Zhang
Department of Chemistry
Boston College



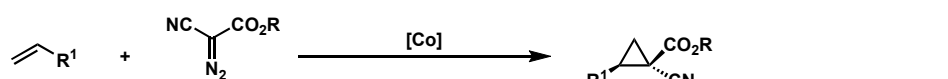
Asymmetric cyclopropanation



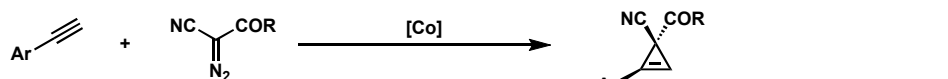
J. Am. Chem. Soc. **2004**, 126, 14718



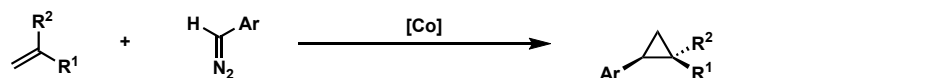
Angew. Chem. Int. Ed. **2008**, 47, 8460



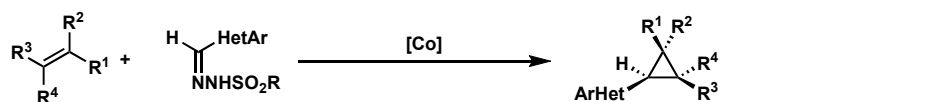
J. Am. Chem. Soc. **2010**, 132, 12796



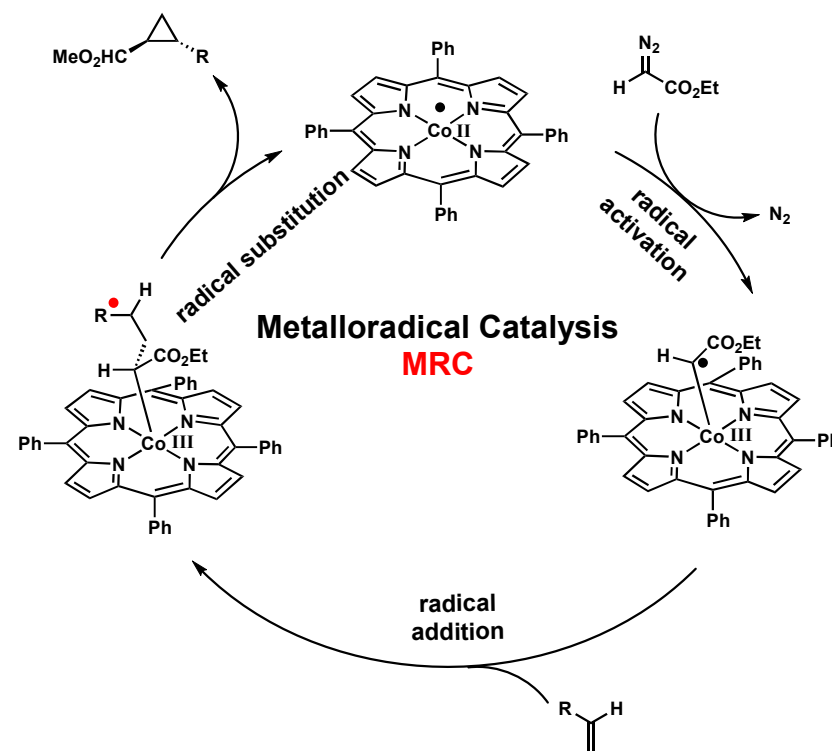
J. Am. Chem. Soc. **2011**, 133, 3304



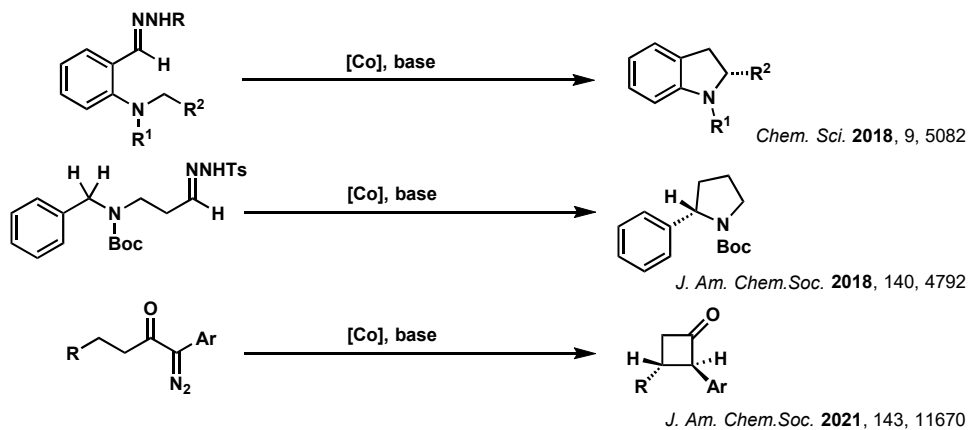
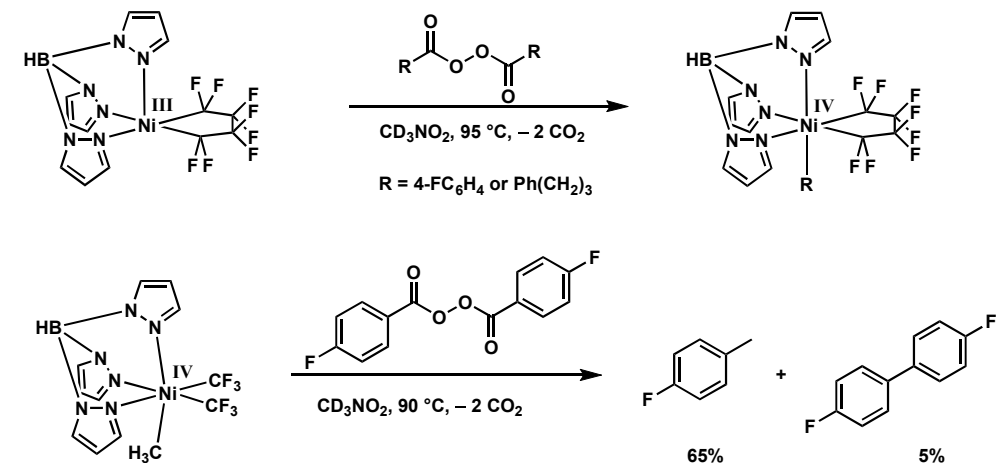
J. Am. Chem. Soc. **2017**, 139, 1049



J. Am. Chem. Soc. **2021**, 143, 11141



Asymmetric intramolecular cyclization

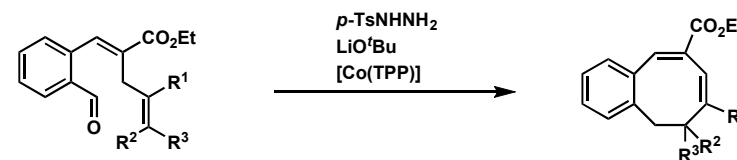
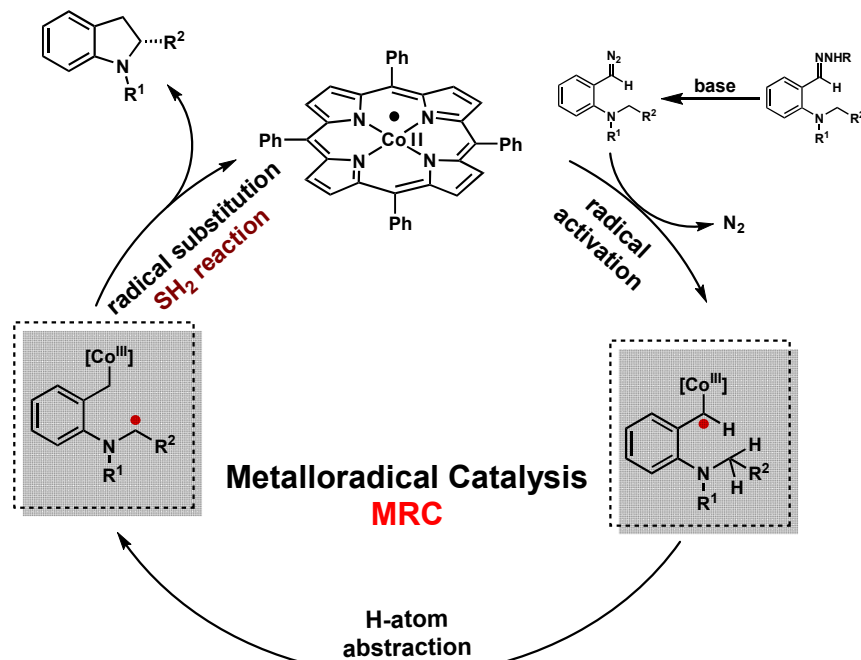
Other intermolecular S_H2-related reaction

♣ stoichiometric organonickel methylation

♣ priorly prepared sensitive nickel(IV) complex

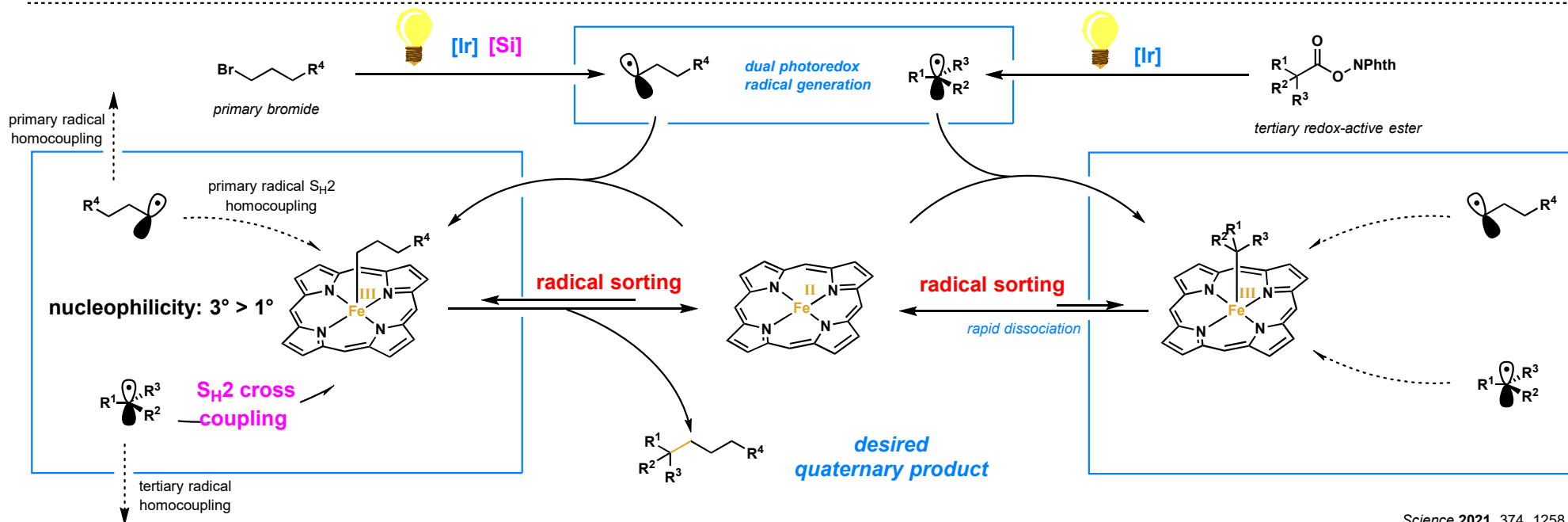
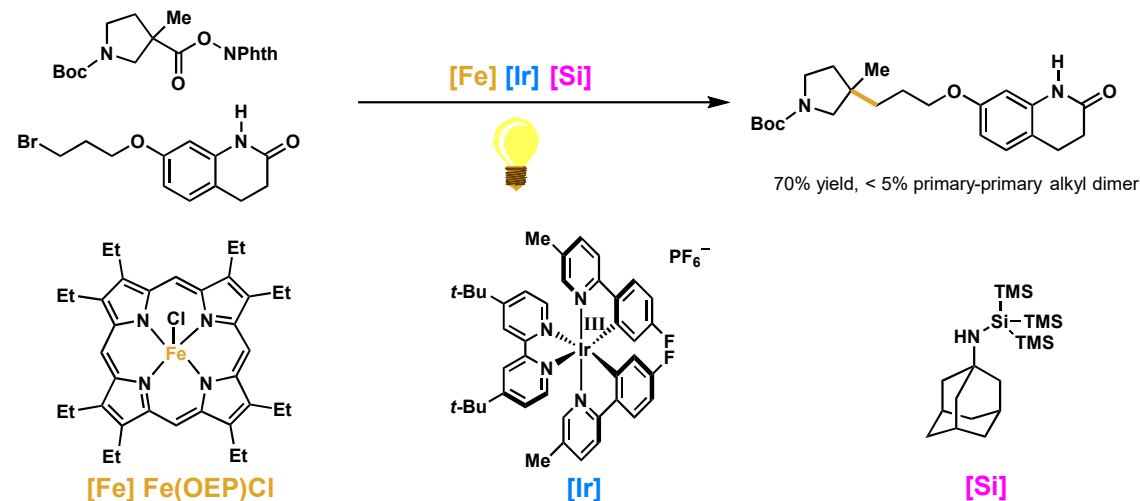
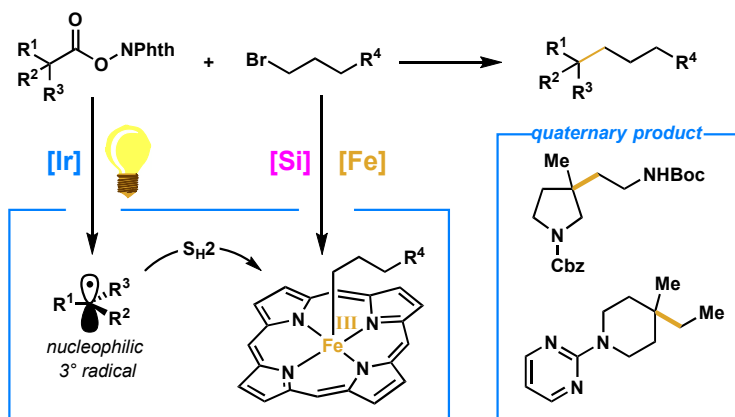
♣ homocoupling exists

♣ limited radical scope

Sanford, M. S. *J. Am. Chem. Soc.* 2019, 141, 8914De Bruin, B. *Angew. Chem. Int. Ed.* 2020, 59, 11073♣ intramolecular S_H2 reaction

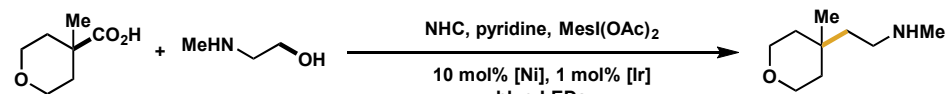
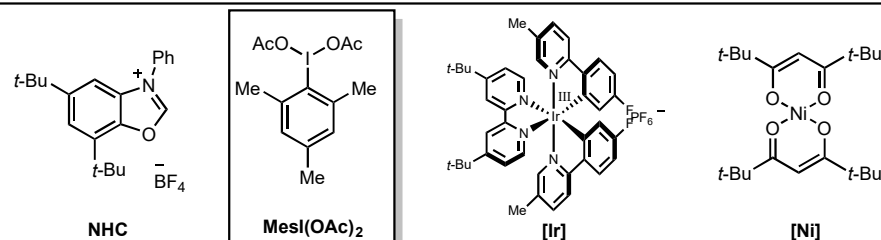
♣ diazo-compound as radical precursor

David Macmillan's work

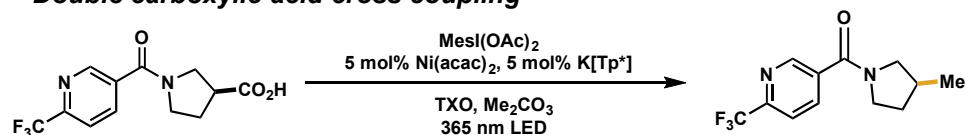
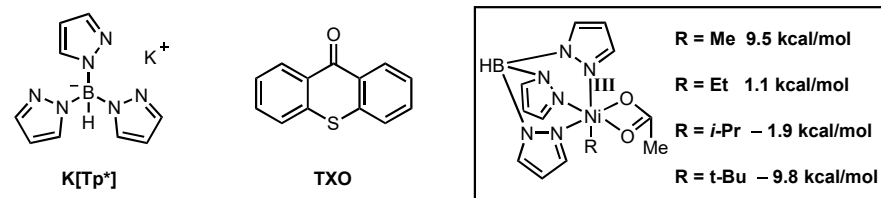
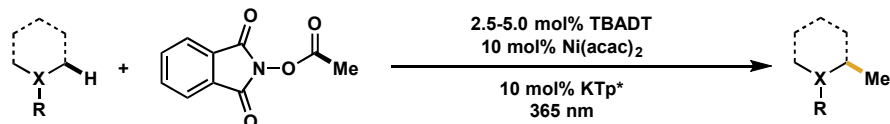
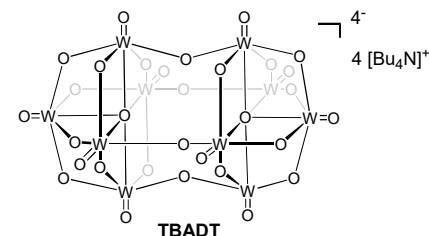


Science 2021, 374, 1258

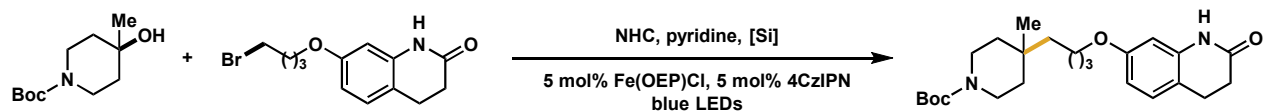
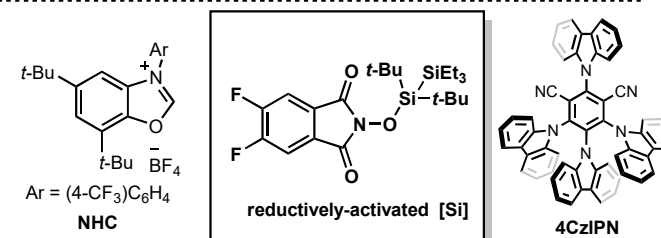
Carboxylic acid-alcohol cross coupling

*J. Am. Chem. Soc.* **2022**, 144, 6185

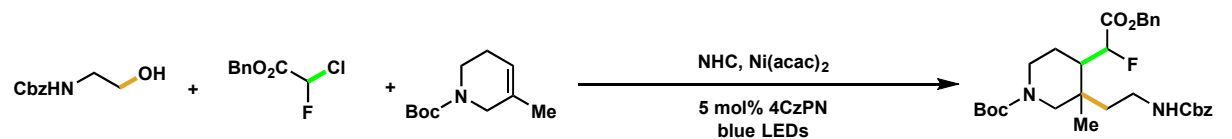
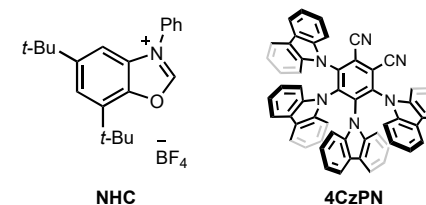
*Double carboxylic acid cross coupling

*J. Am. Chem. Soc.* **2022**, 144, 21278C(sp³)-H methylation*J. Am. Chem. Soc.* **2023**, 145, 2787

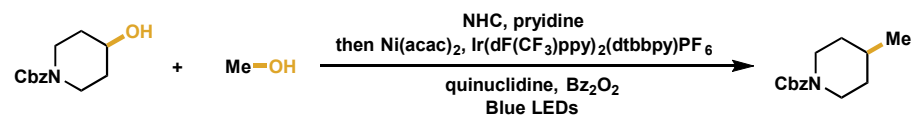
Tertiary alcohol-bromide coupling

*J. Am. Chem. Soc.* **2023**, 145, 16330

Triple radical coupling

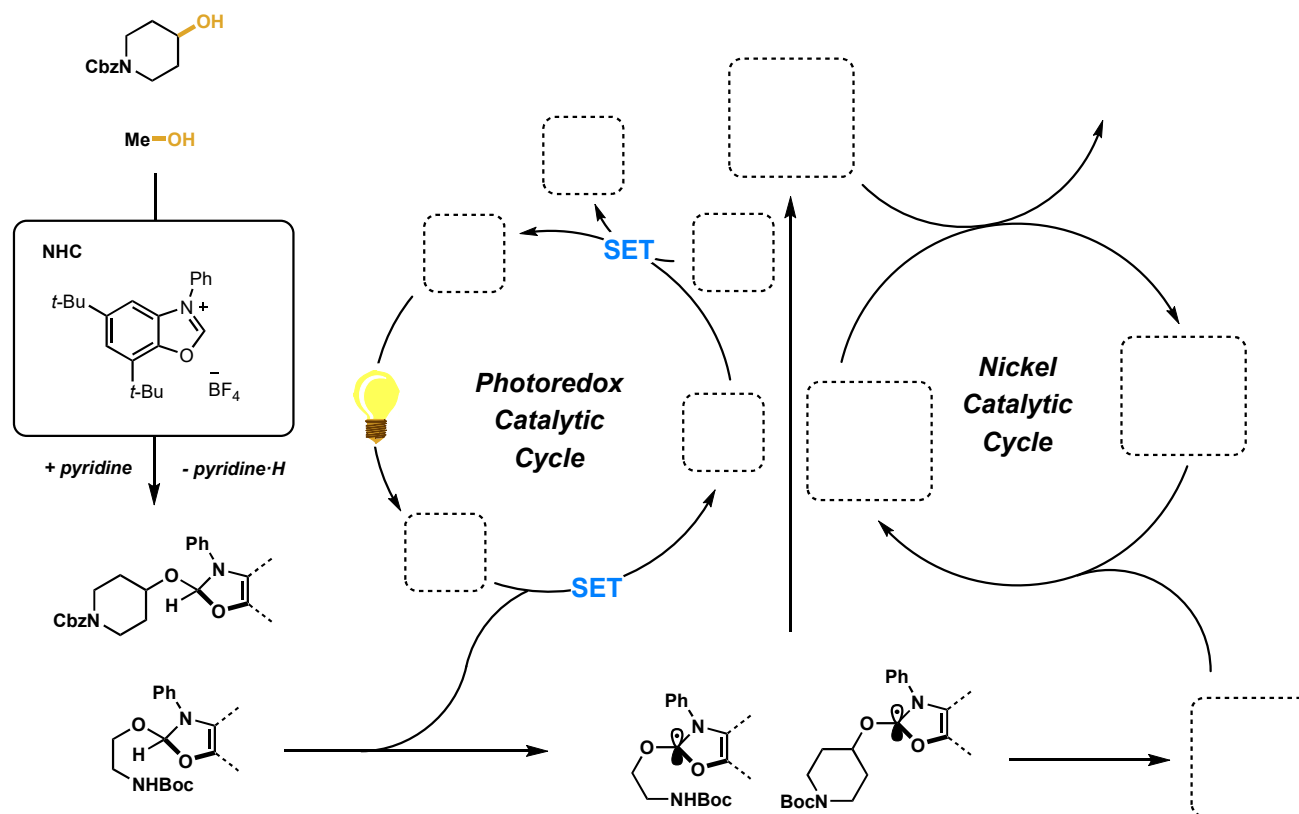
*Nature* **2024**, 628, 104

Double alcohol cross-coupling

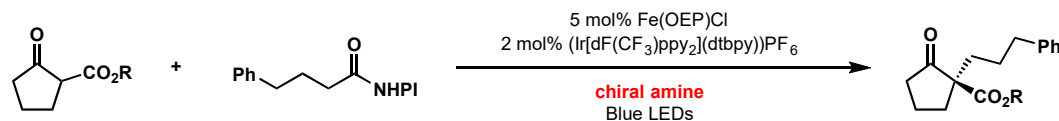
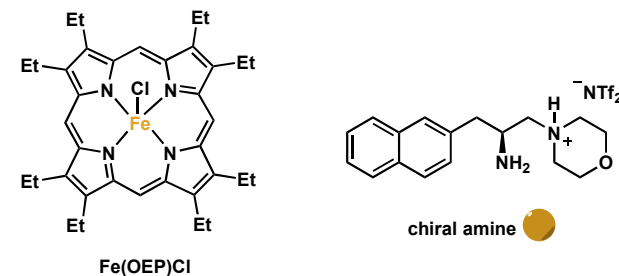


Science 2024, 383, 1350

Proposed Reaction Mechanism

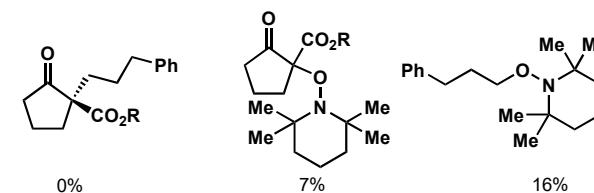


Primary amine catalyzed enantioselective quaternization

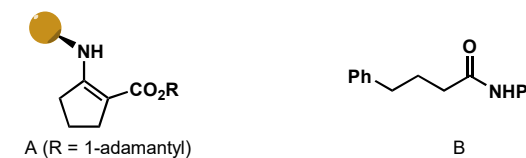
Yang, Z. P. *J. Am. Chem. Soc.* 2024, 146, 9404

Mechanistic Studies

1. radical trapping (2 equiv TEMPO was added):



2. CV analysis



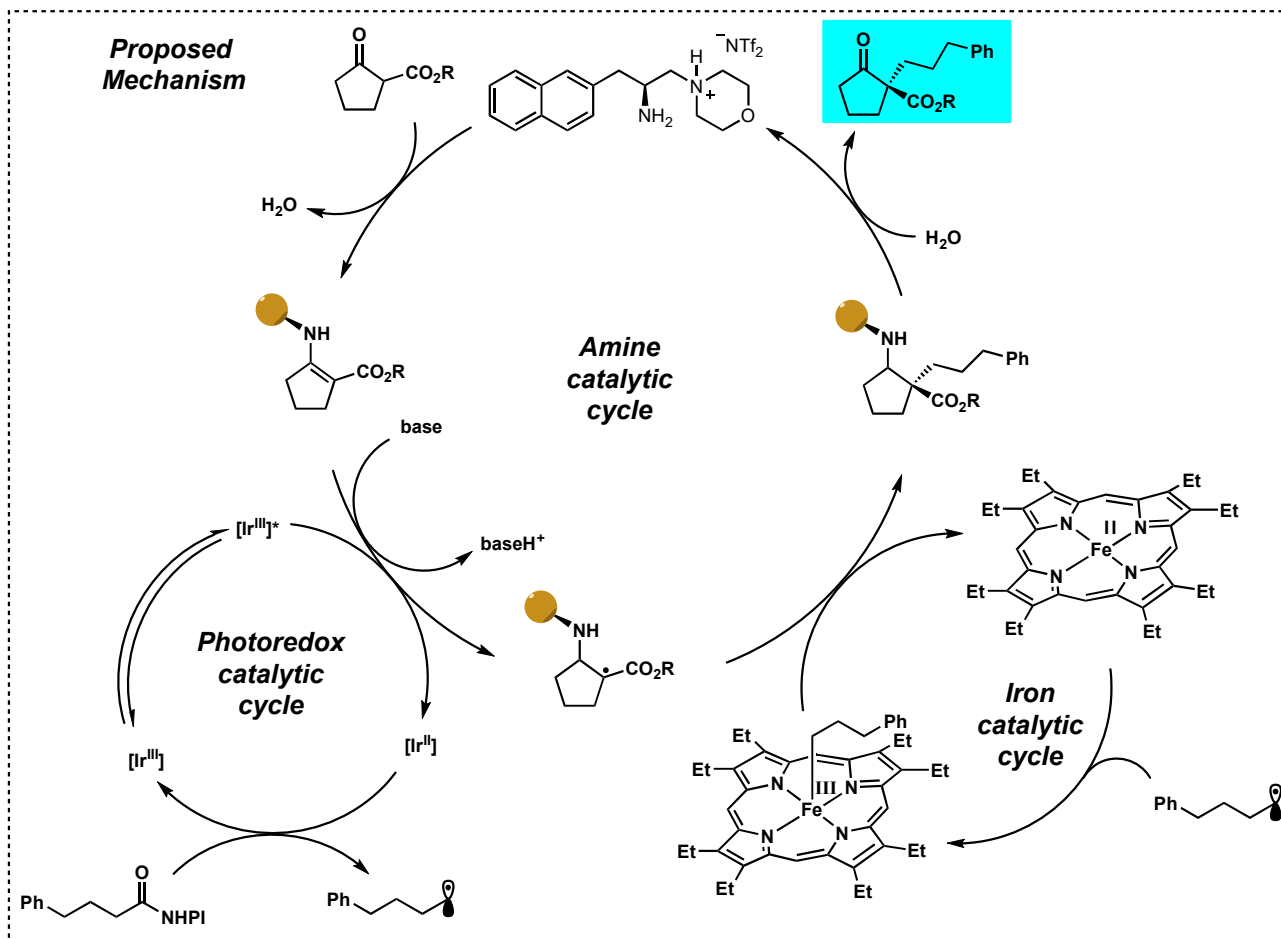
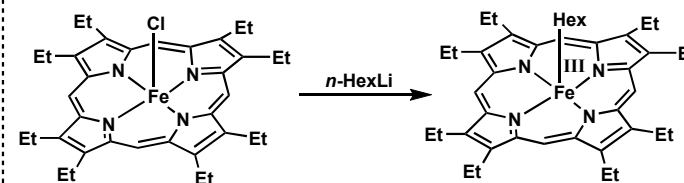
Reductive quenching:

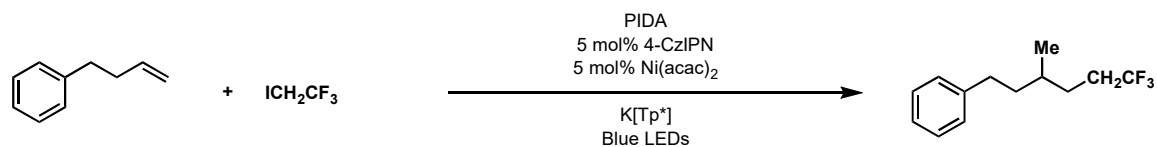
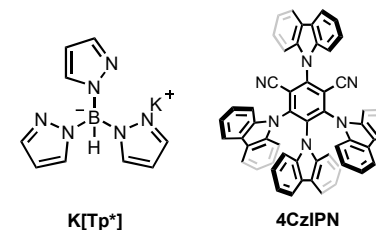
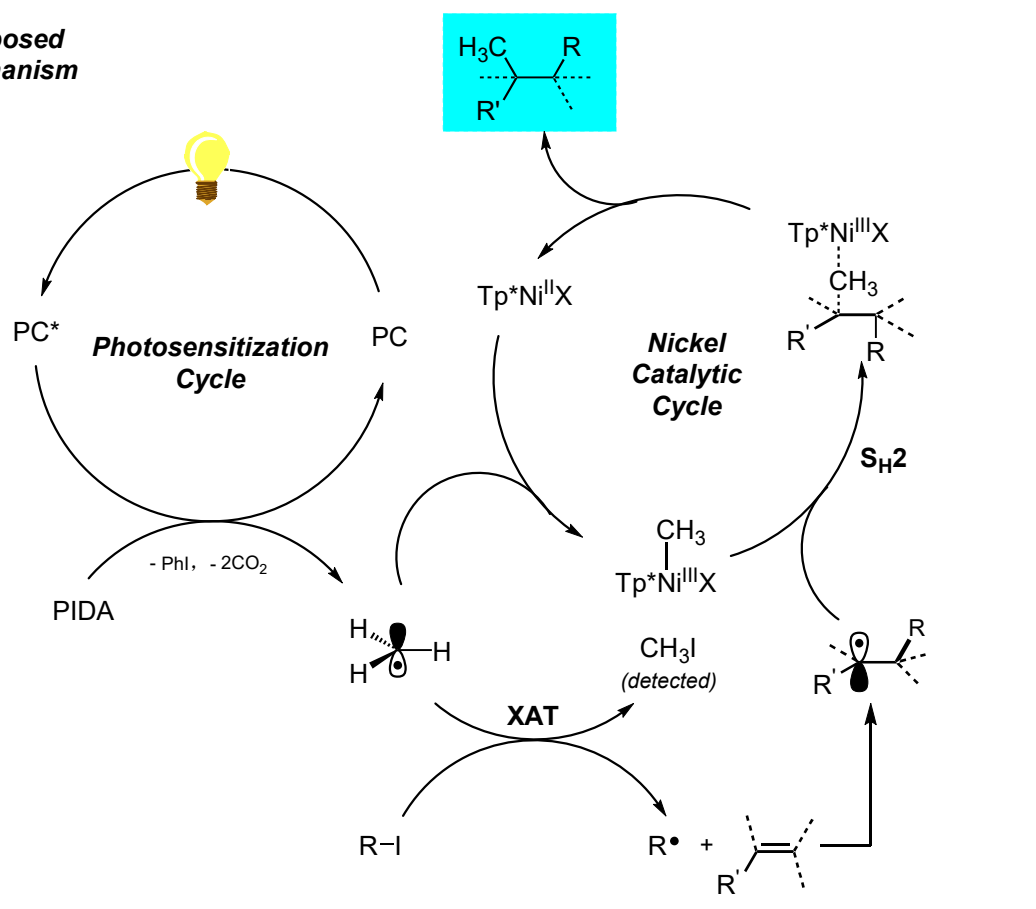
 $E_{1/2}(\text{PC}^*/\text{Pc}^-) = +1.21 \text{ V vs. SCE}$ $E_{1/2}(\text{PC}/\text{PC}^-) = -1.37 \text{ V vs. SCE}$

Oxidative quenching:

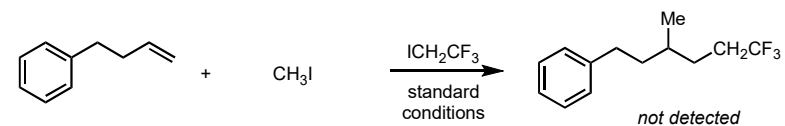
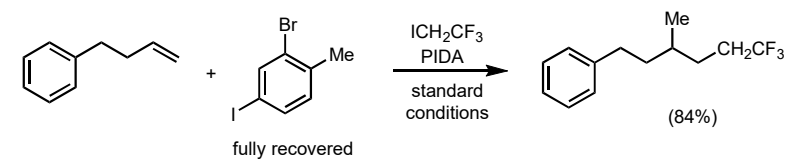
 $E_{1/2}(\text{PC}^*/\text{Pc}^*) = -0.89 \text{ V vs. SCE}$ $E_{1/2}(\text{PC}/\text{PC}^-) = -1.37 \text{ V vs. SCE}$

3. X-ray structure



Koh, M. J. *J. Am. Chem. Soc.* **2024**, 146, 10274**Proposed Mechanism****Mechanistic Studies**

1. Intermediacy of low-valent nickel species



2. Different methyl radical source

