

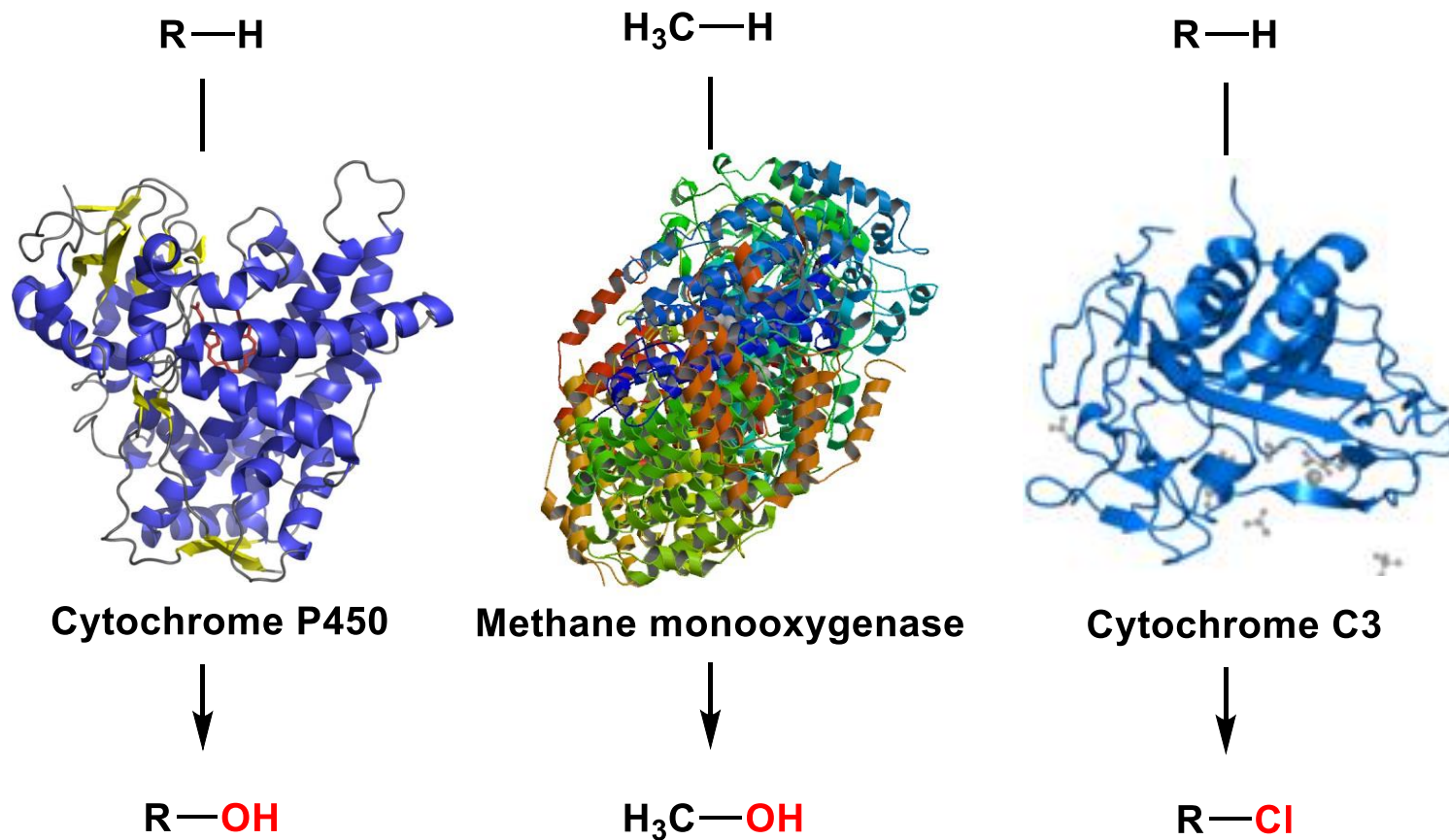
Literature Seminar

# **Bio-inspired C-H functionalization by metal-oxo complexes**

2016. 7. 23.

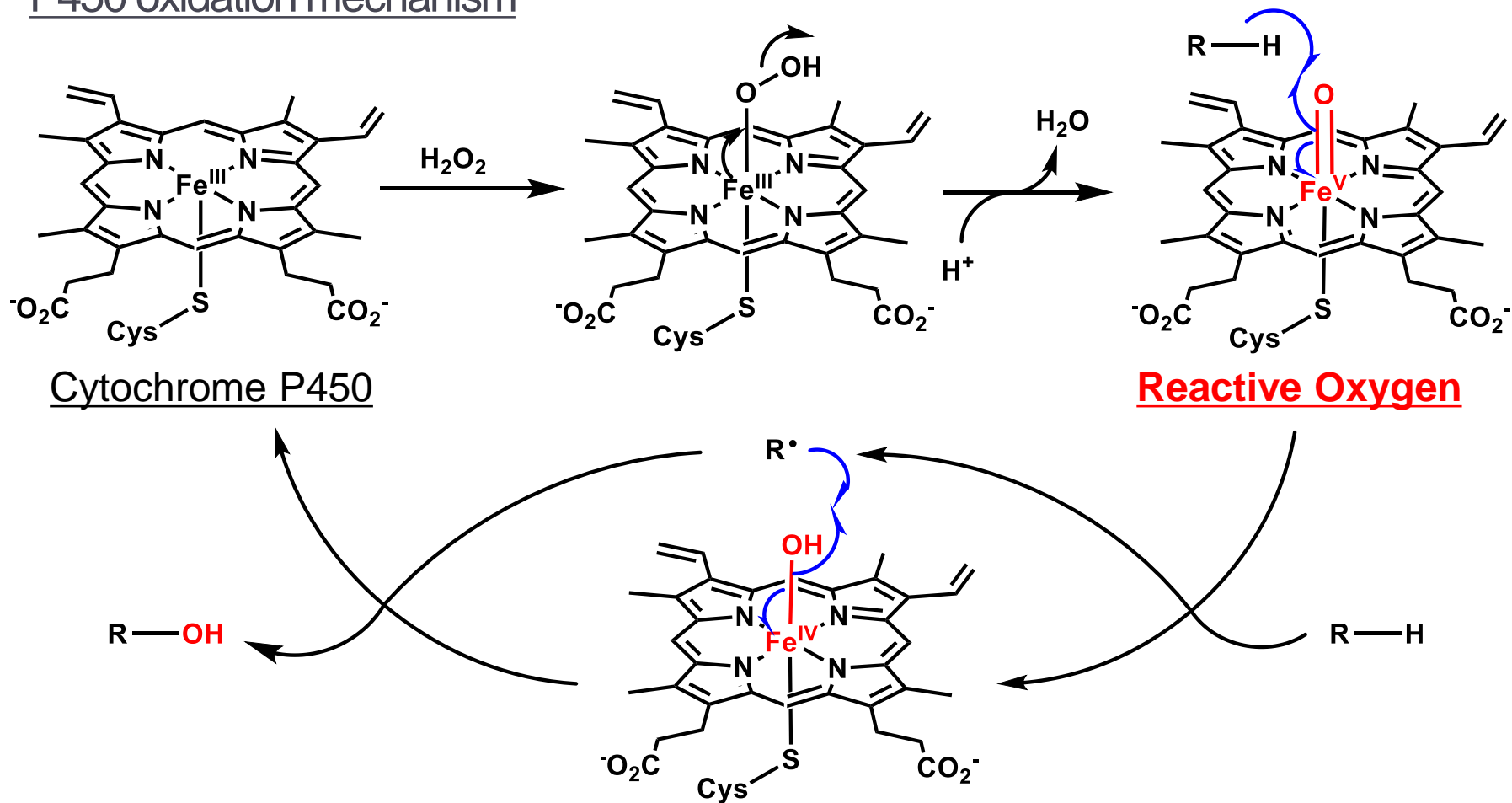
Nagashima Nozomu

## C-H functionalization by enzymes



**Enzymes enable aliphatic C-H functionalization**

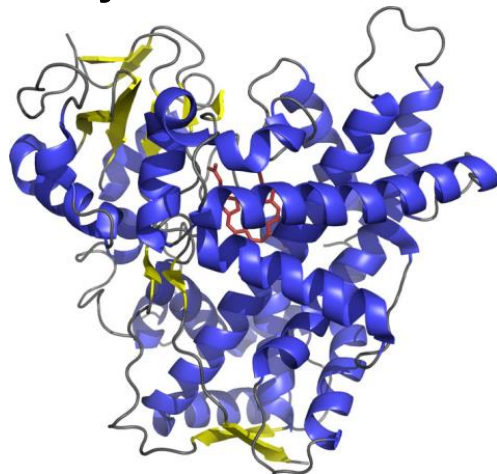
## P450 oxidation mechanism



- Cytochrome P450 makes reactive oxygen species.
- P450 can activate aliphatic C-H Bond.

These enzymes functions can be mimicked?

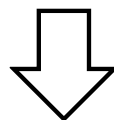
**Cytochrome P450**



**Cytochrome C3**



**Methane monooxygenase**



**Today's topic: Make enzyme-like reaction by metal catalysts**

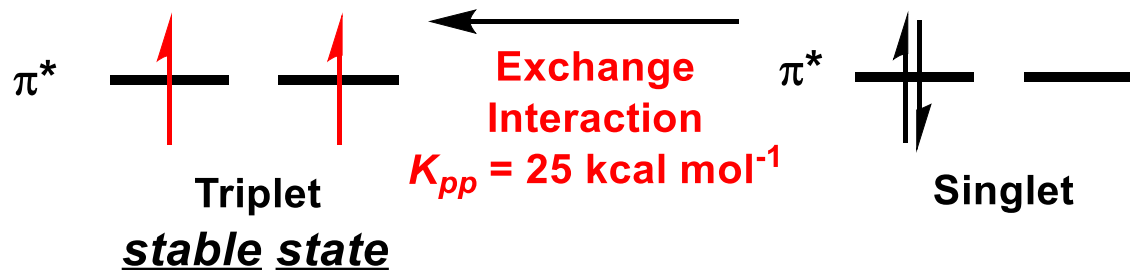
1. Why nature uses Fe for C-H functionalization?

## Spin chemistry and reactivity

### □ Exchange interactions

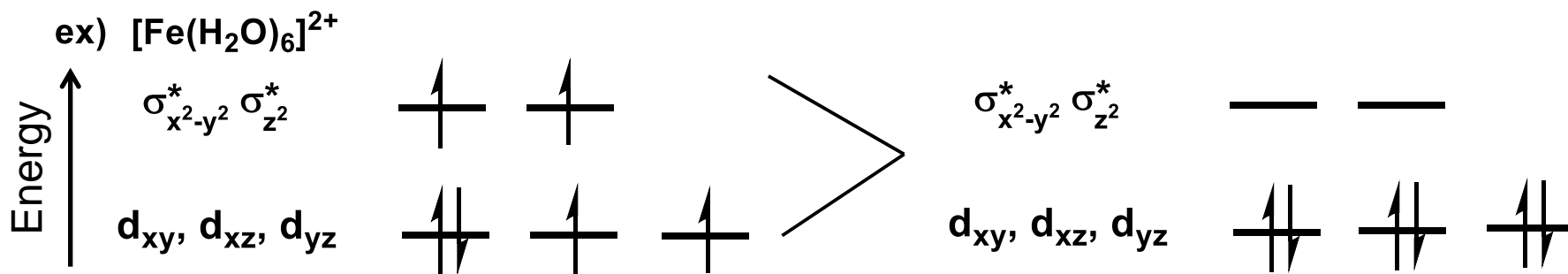
Interactions between two electrons whose spins are parallel.

ex)  $\text{O}=\text{O}$



Metal's spin state depends on

- 1) Orbital energies
- 2) Exchange interaction



Exchange interaction:  $4C_2 \equiv 6$  interaction

**More Stable**

## Exchange Interaction

### □ Table of metal's exchange interaction

Atoms	Sc	Ti	V	Cr	Mn	Fe	Co	Ni
$K_{dd'} (M^+)$	11.3	14.2	15.9	17.4	18.7	19.8	21.0	22.2
$K_{\pi^*\pi^*} (MO^+)$				17.2	17.7	13.6	11.4	13.2
	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd
$K_{dd'} (M^+)$	9.3	11.2	12.6	13.8	14.8	15.1	16.6	17.5
$K_{\pi^*\pi^*} (MO^+)$					13.6	11.9	8.7	13.1

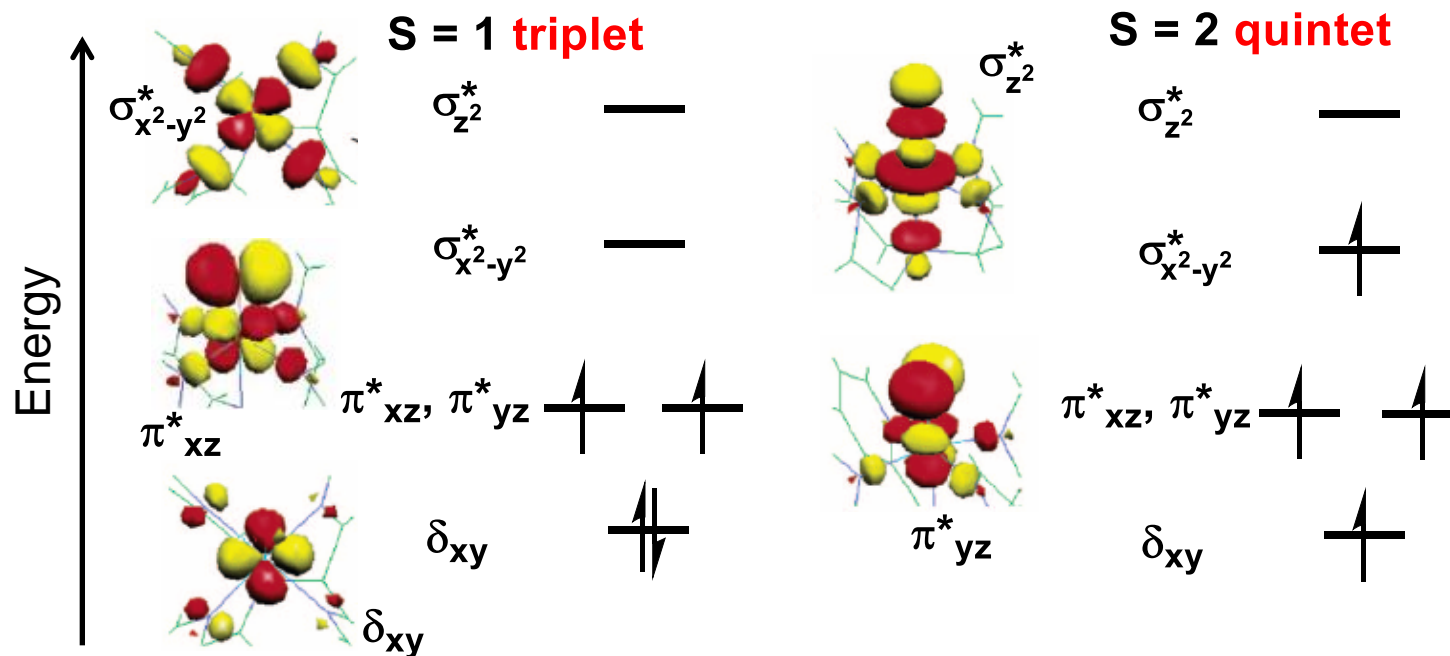
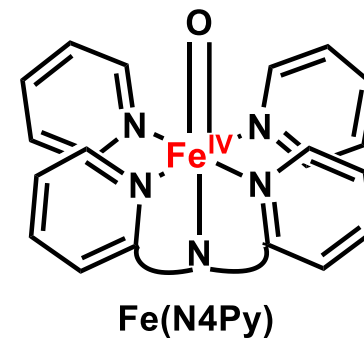
- As the atom size shrinks, the average electron-electron distance decreases and the exchange interaction increases.
- Cr, Mn, Fe, Co, and Ni show high exchange interaction and they show high reactivity.

## Non-heam Fe = O species spin state

### □ Interaction of d orbitals in tetra-coordinated metal

$$d_{xy} < d_{xz, yz} < d_{x^2-y^2} < d_{z^2}$$

### □ Triplet and quintet state of iron-oxo species

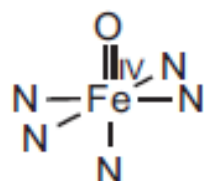
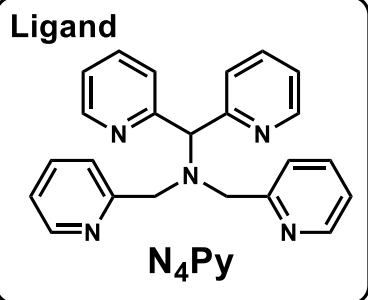
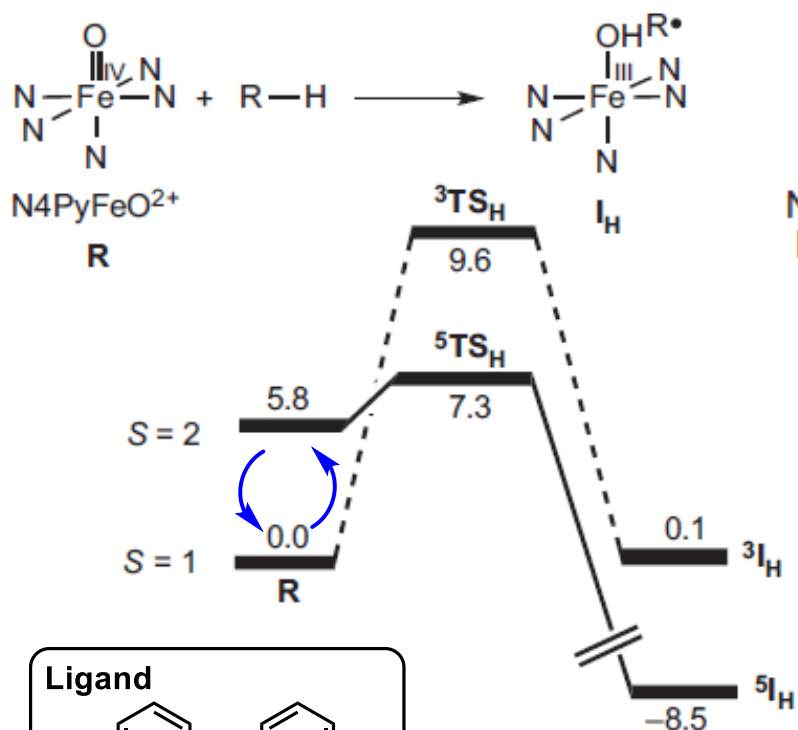


**Fe can make two states, S = 1 triplet and S = 2 quintet.**

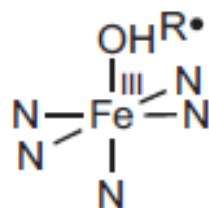
**Both states are related to the high reactivity of iron-oxo species.**



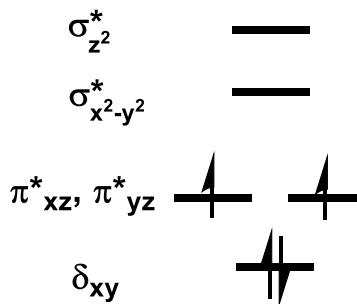
# C-H abstraction by non-haem iron



After Reaction



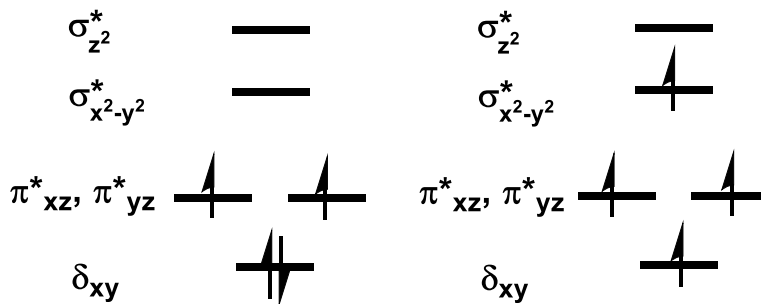
S = 1 triplet



Ground State

Excited State

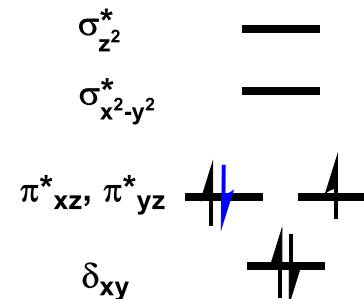
S = 2 quintet



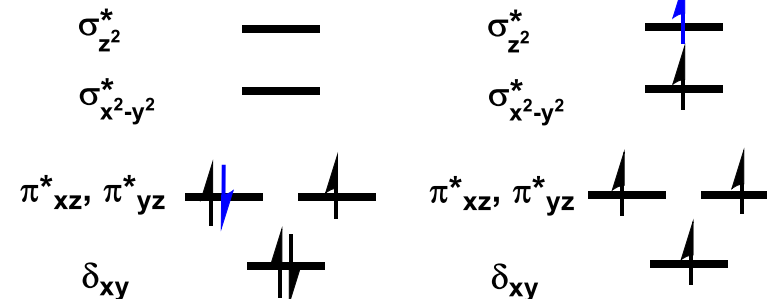
Excited State

Ground State

S = 1 triplet



S = 2 quintet



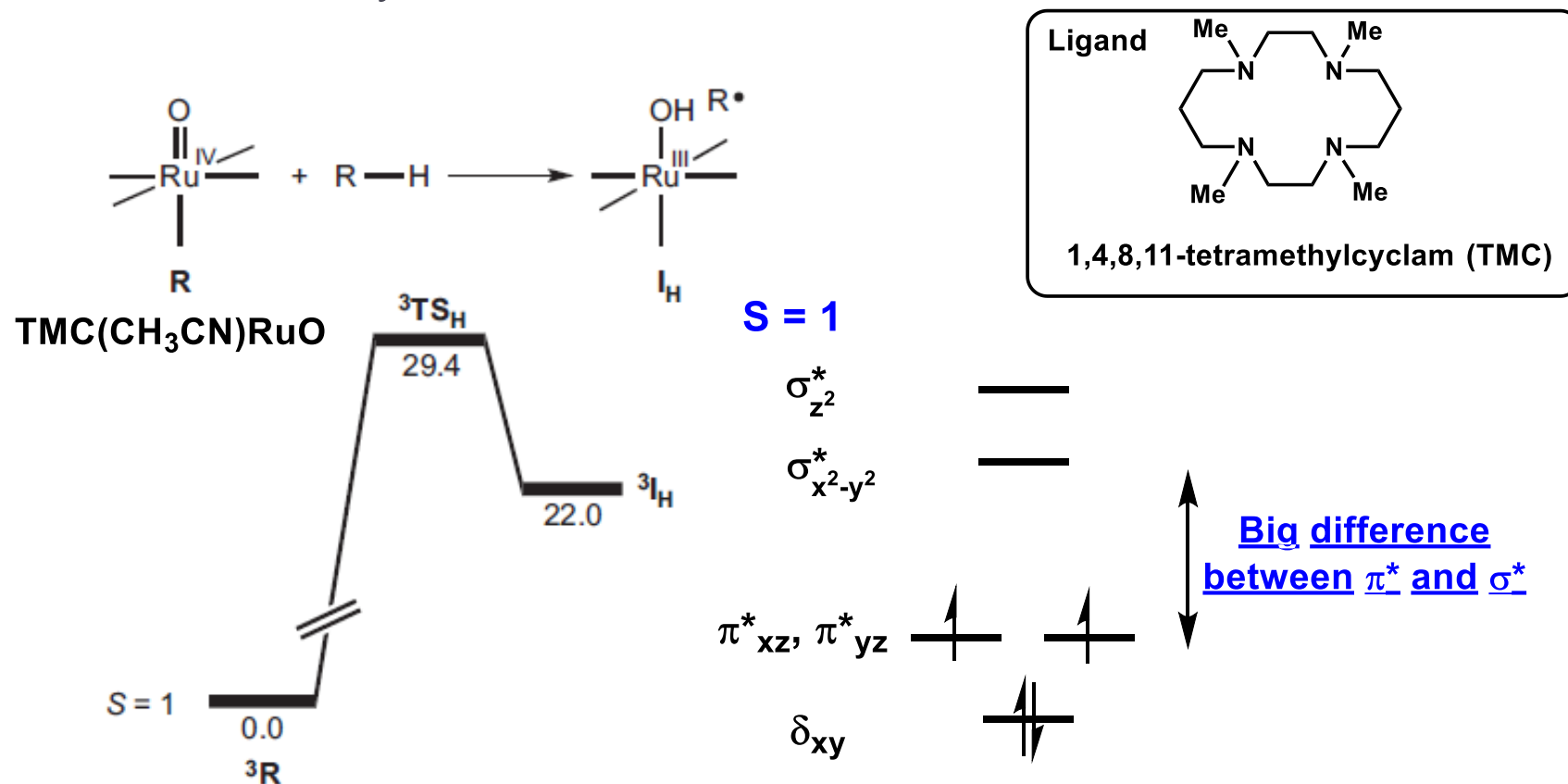
Exchange interaction stabilizes transition state of S = 2.

S = 2 can cleave C-H bonds easily.

Shaik, S. *et al.* *J. Am. Chem. Soc.* **2006**, 128, 8590.

Shaik, S. *et al.* *Nat. Chem.* **2011**, 3, 19.

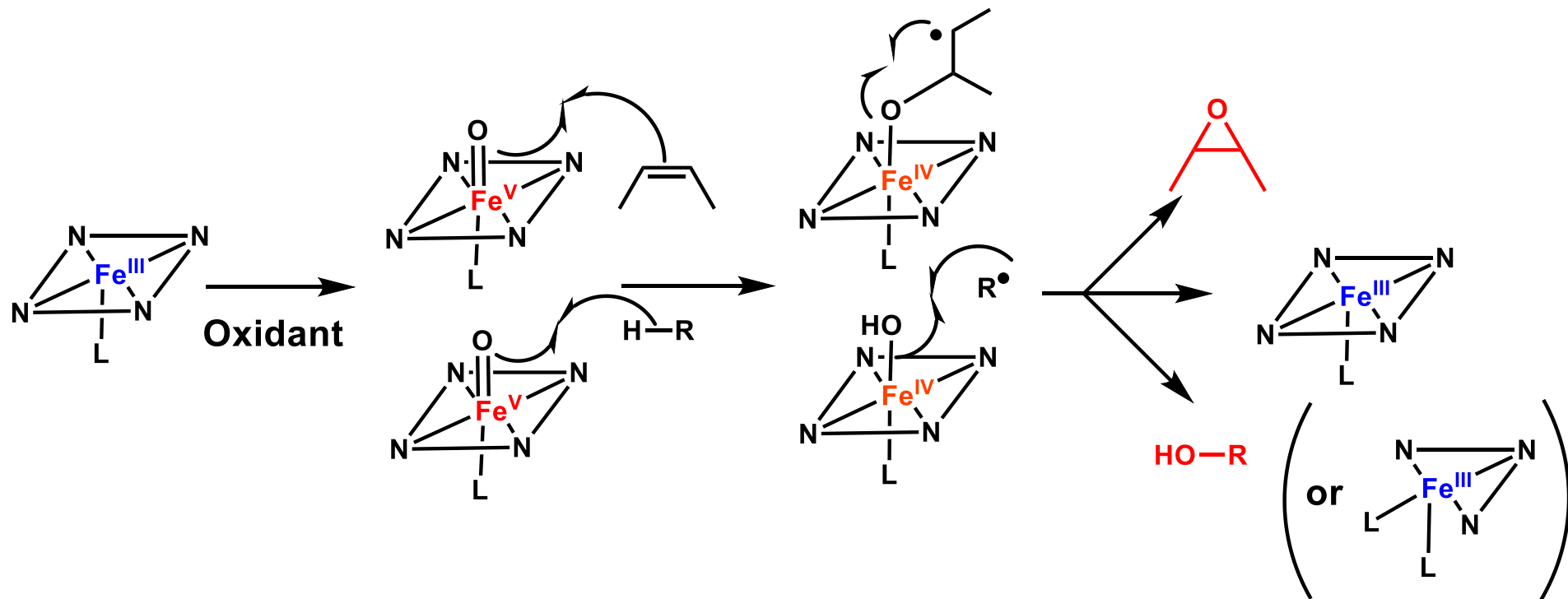
## C-H abstraction by ruthenium



1. The exchange interaction of ruthenium is lower than that of iron
  2. Ruthenium binds to ligand more strongly than iron
- **d orbitals are more delocalized and raise  $S = 2$  state.**

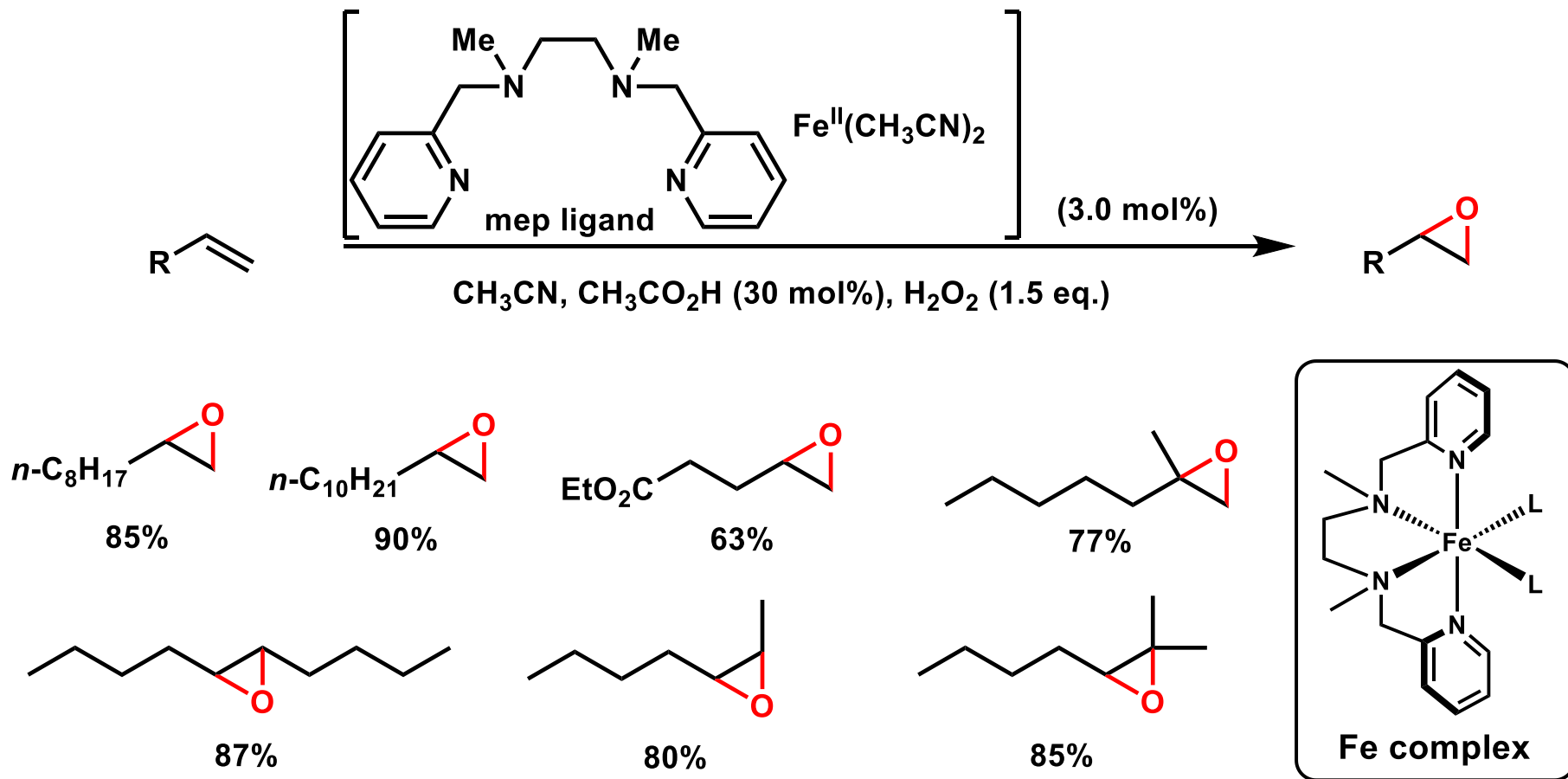
## 2. Oxygen atom transfer by iron-oxo species

## Target reaction by metal catalysts



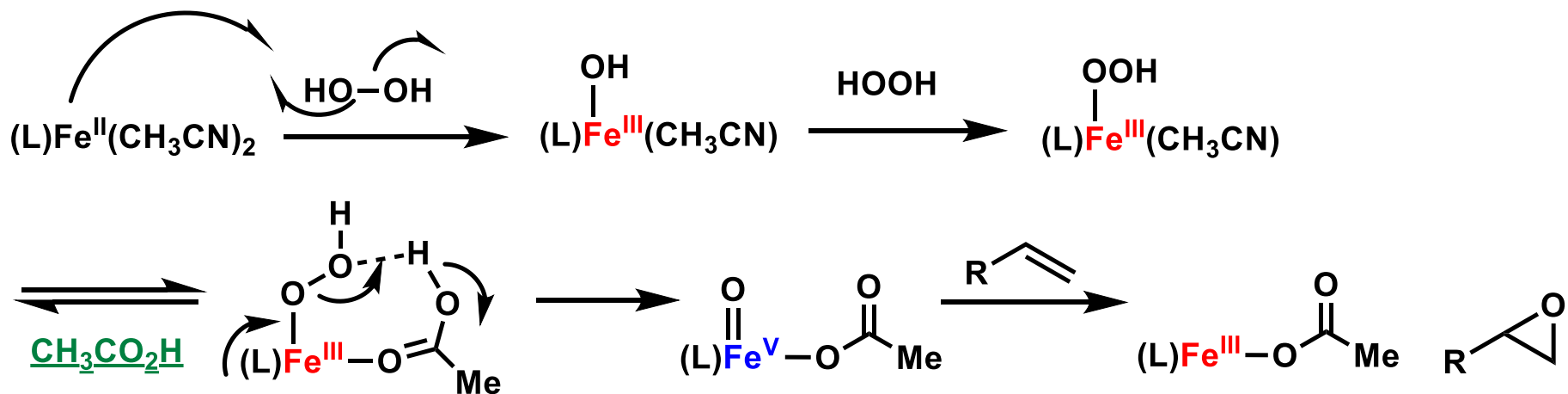
**Epoxidation and hydroxylation should be achieved by using tetra-coordinated or tri-coordinated metal catalysts**

# Alkene epoxidation by $\text{Fe}(\text{mep})(\text{CH}_3\text{CN})_2$

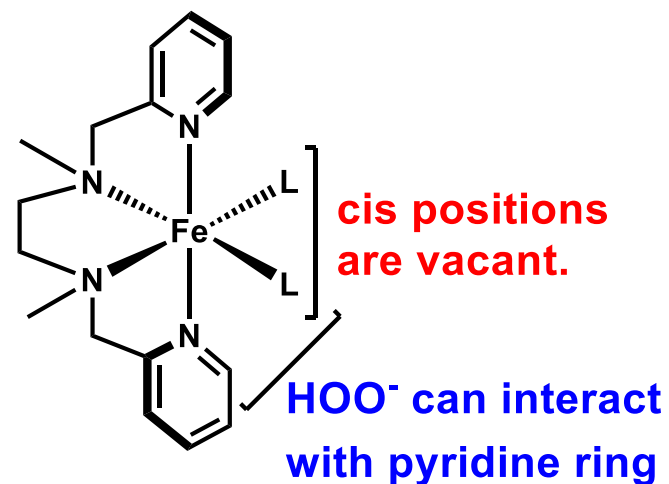
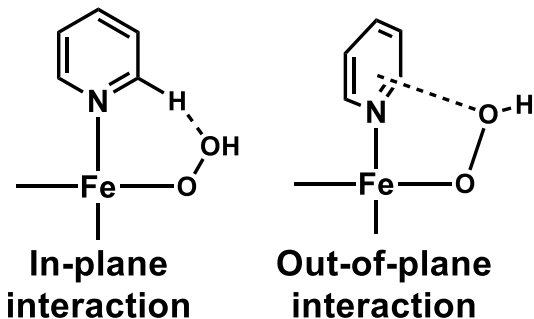


*mep*:  $N,N'$ -dimethyl- $N,N'$ -bis(2-pyridylmethyl)-ethane,1,2-diamine

## Fe(mep)(CH<sub>3</sub>CN)<sub>2</sub> activation by acetic acid

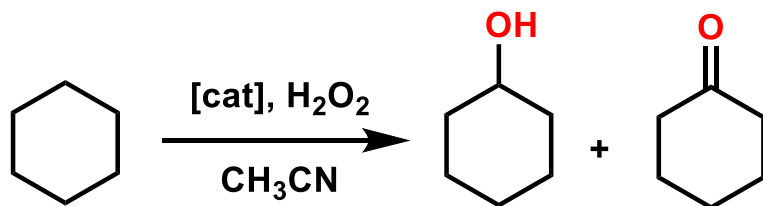


- 1) The addition of acid promotes O-O bond cleavage.
- 2) Ligand structure enables both generation of Fe<sup>V</sup>=O species and activation of Fe.
- 3) Pyridine ring also interacts with H<sub>2</sub>O<sub>2</sub> and promotes O-O bond cleavage.

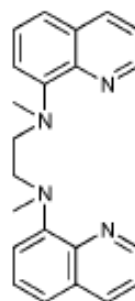


Jacobsen, E. N. *et al.* *J. Am. Chem. Soc.* **2001**, *123*, 7194.  
 Que-Jr. L. *et al.* *J. Am. Chem. Soc.* **2007**, *129*, 15964.  
 Nishida, Y. *et al.* *Dalton Trans.* **1997**, 3547.

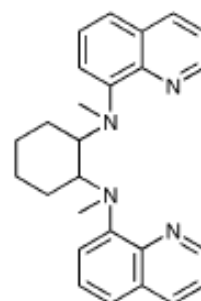
## Ligand structure of Iron for C-H functionalization



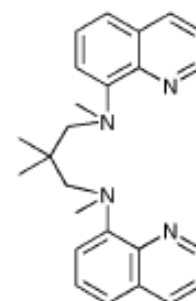
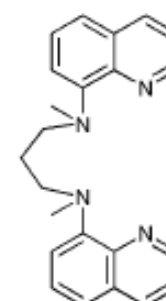
Entry	[cat]	A + K(%)
1	Fe(1)(OTf) <sub>2</sub>	51
2	Fe(2)(OTf) <sub>2</sub>	16
3	Fe(3)(OTf) <sub>2</sub>	49
4	Fe(4)(OTf) <sub>2</sub>	34
5	Fe(5)(OTf) <sub>2</sub>	5
6	Fe(mep)(OTf) <sub>2</sub>	65



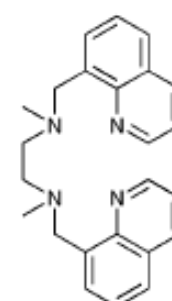
BQEN 1



BQCN 2

BQMe<sub>2</sub>PN 3

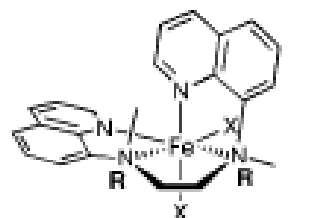
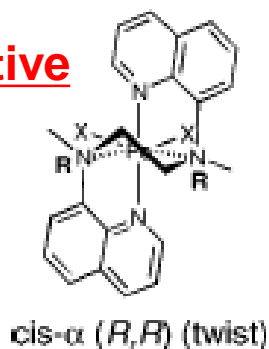
BQPN 4



BQMEN 5

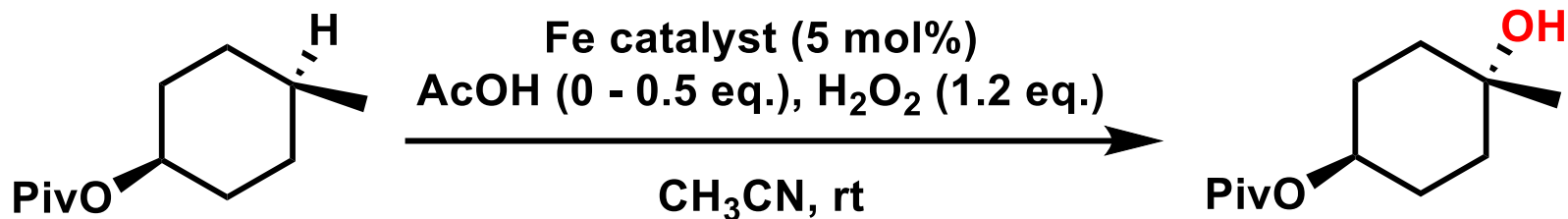
mep: Jacobsen's iron ligand

**Most reactive**



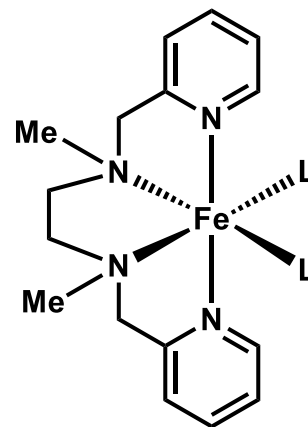
They showed the rigidity and the stabilization of *cis-α* (twist) complex were important in C-H functionalization

## C-H hydroxylation by Iron catalyst

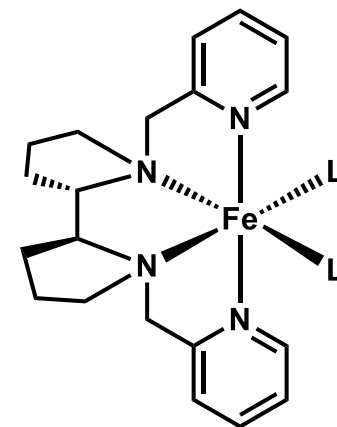


Entry	Cat.	AcOH	Yield	Select.**
1	1	0	7	56
2	1	0.5	26	62
3	2	0.5	38	90
4*	2	0.5	51	-

4\*: Reagents were added three times iteratively  
 Select.\*\*: Selectivity for desired product.



Conventional cat.  
 1. Fe(mep)(CH<sub>3</sub>CN)<sub>2</sub>

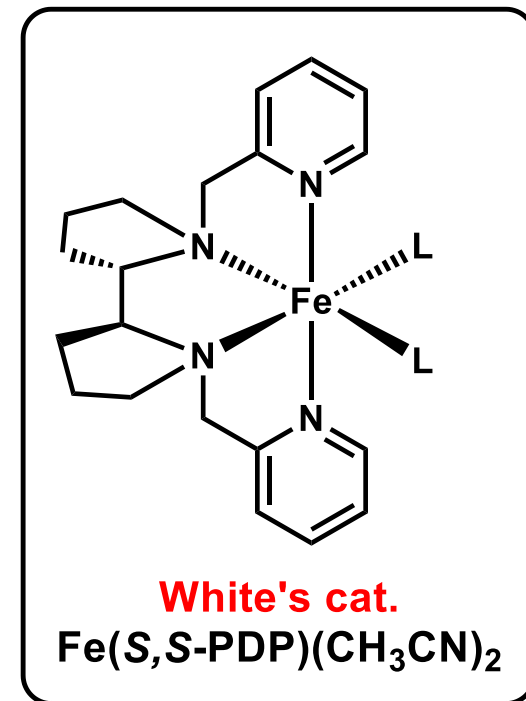
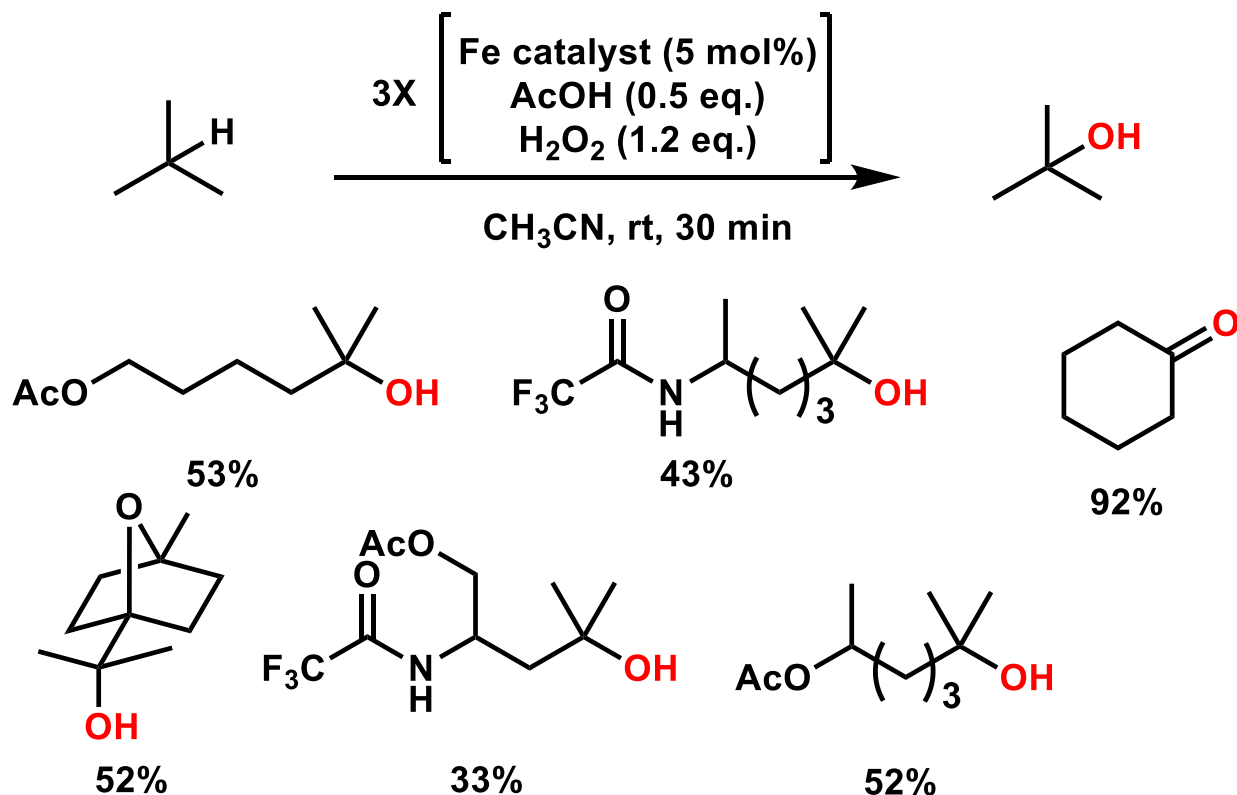


White's cat.  
 2. Fe(S,S-PDP)(CH<sub>3</sub>CN)<sub>2</sub>

- White's new iron catalyst enabled C-H hydroxylation highly selectively.
- Selectivity increased by the inhibition of decomposition of catalysts.

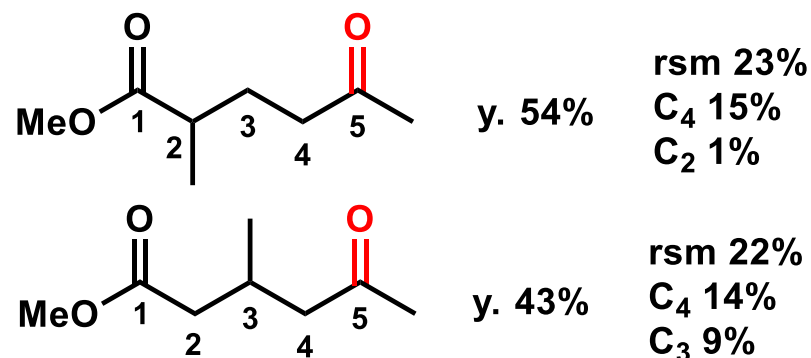
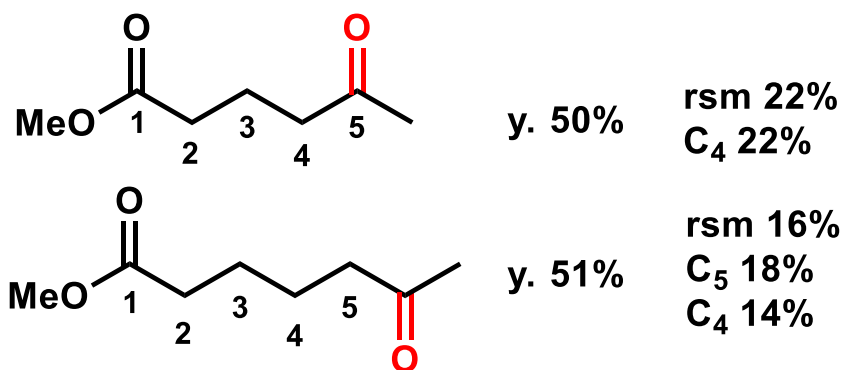
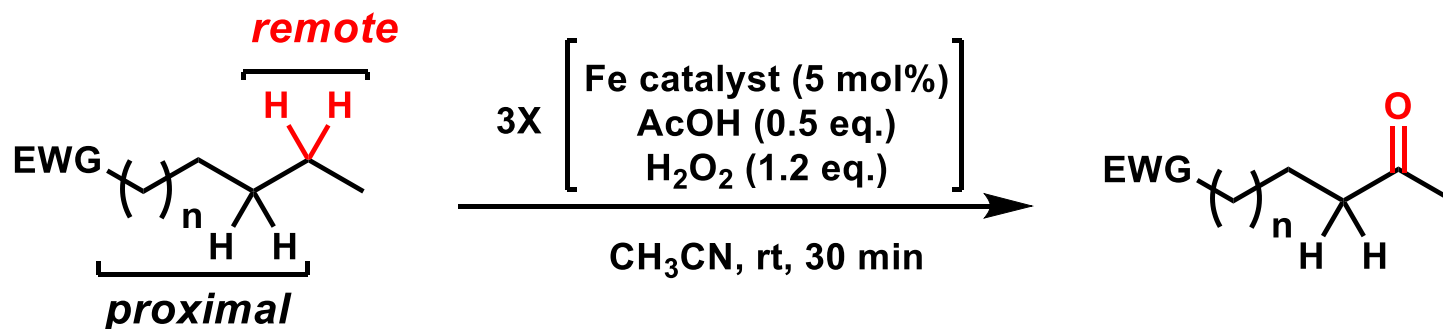
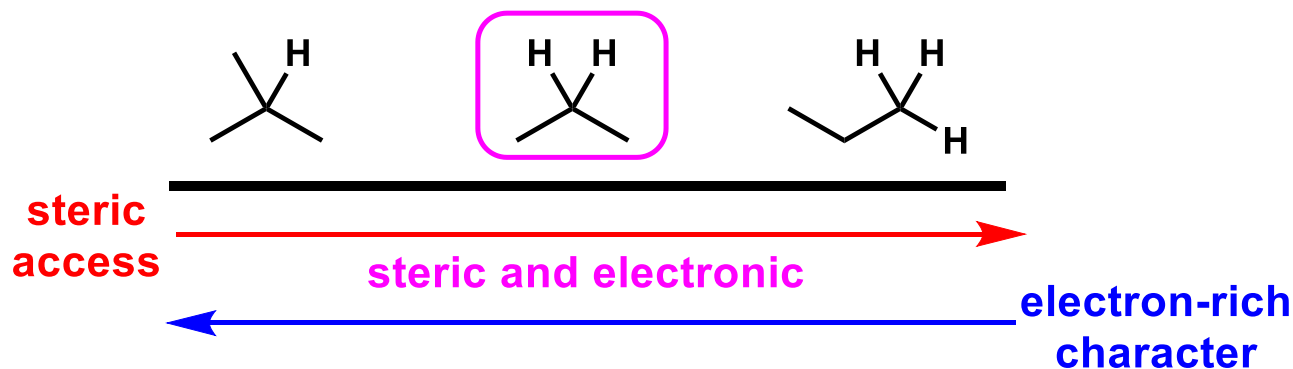


## C-H hydroxylation of tertiary alcohols

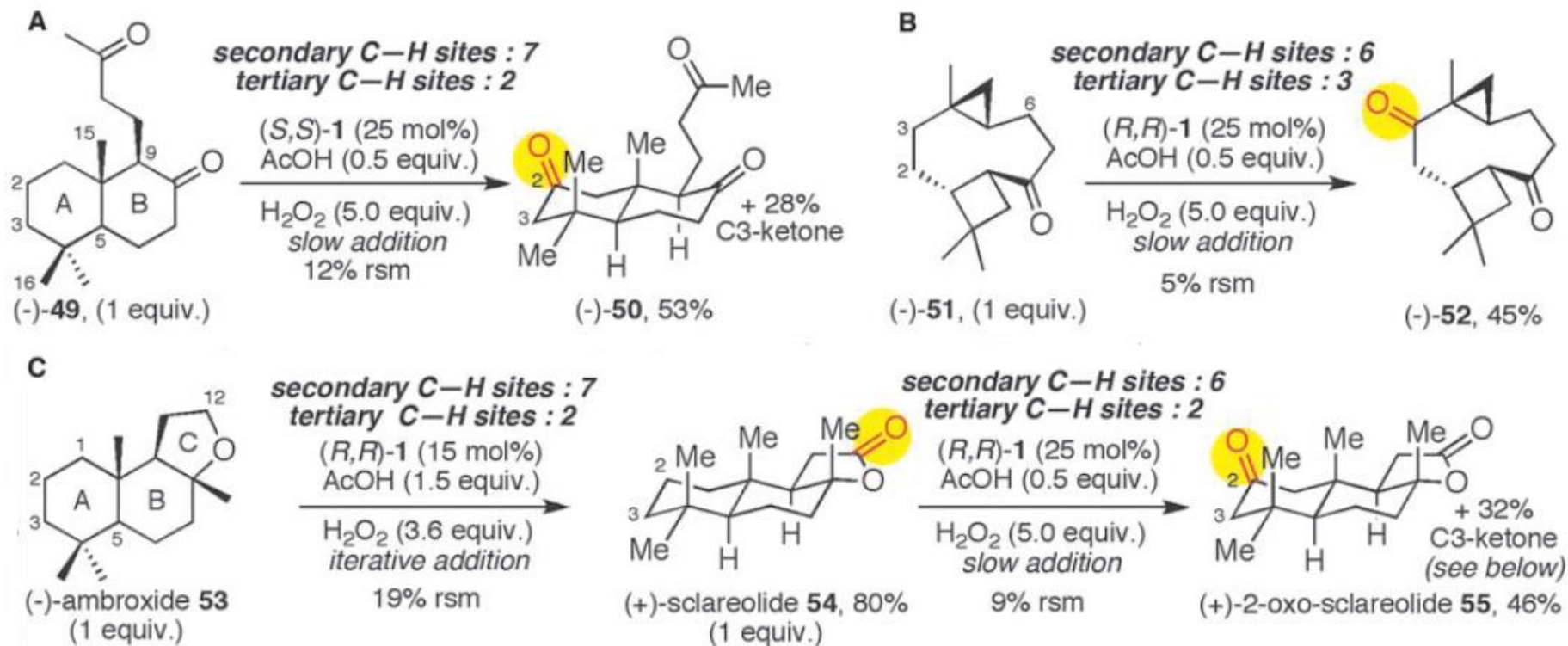


**Fe(S,S-PDP)(CH<sub>3</sub>CN)<sub>2</sub> promoted C-H oxidation 1) electron-rich or 2) sterically accessible site selectively.**

# Methylene oxidation by White's catalysts

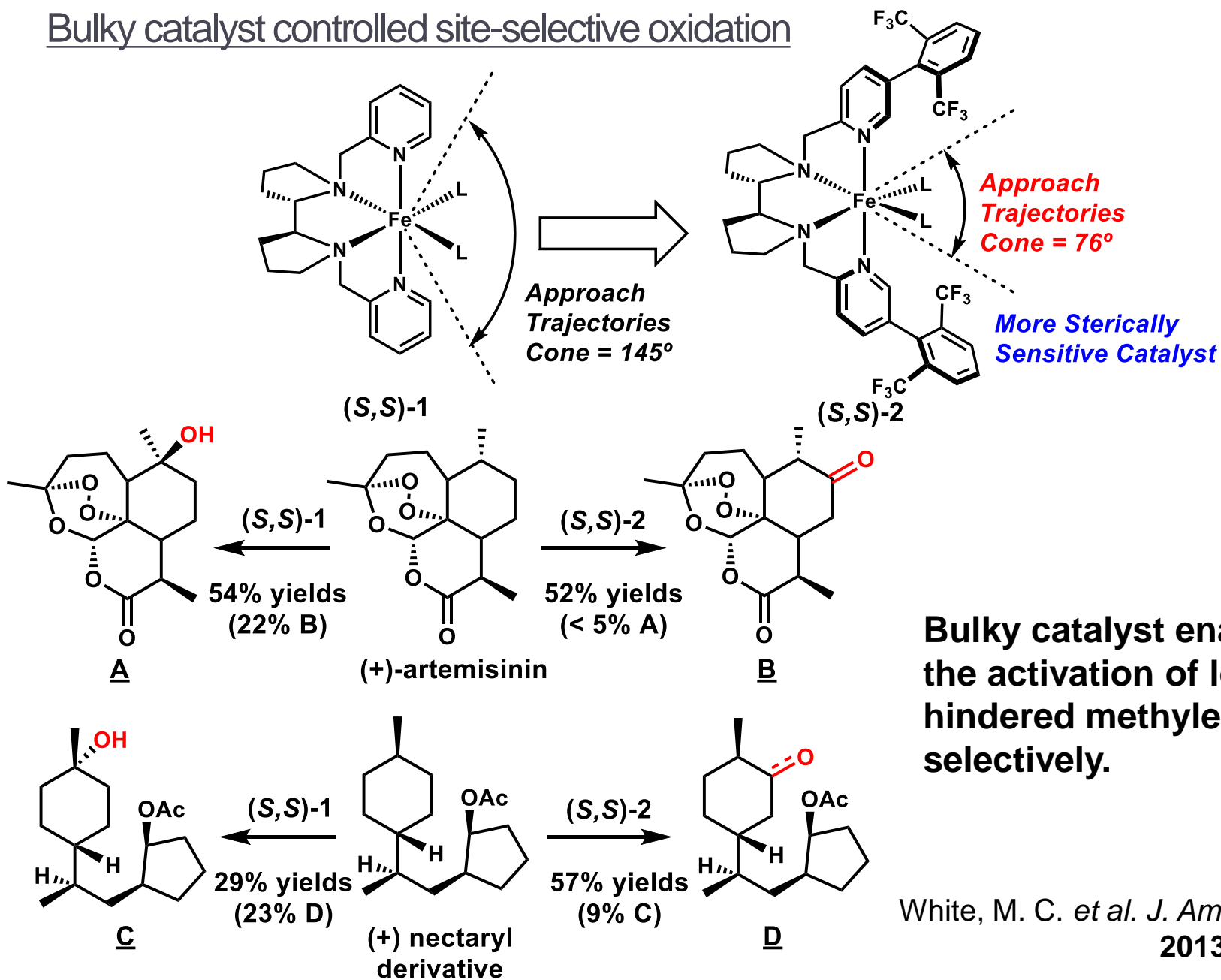


## C-H bond oxidations of terpenoids

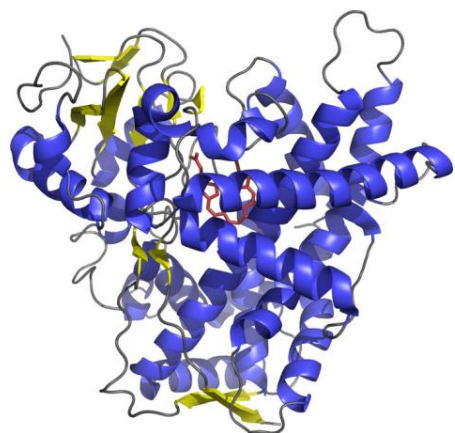


- It enabled C-H oxidation sterically accessible and electron-rich position selectively.
- Methylene selectivity was sometimes not perfect because it depended on the substrate structures.

# Bulky catalyst controlled site-selective oxidation

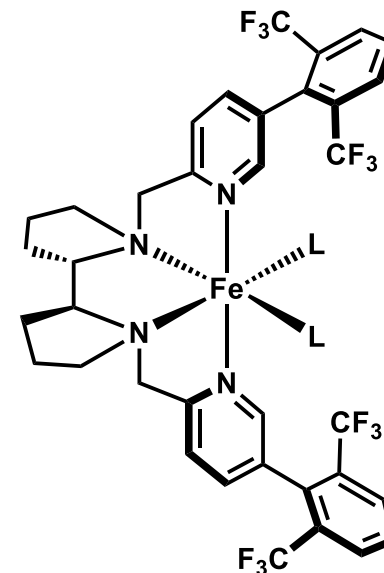
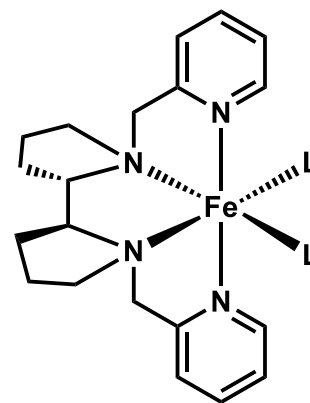
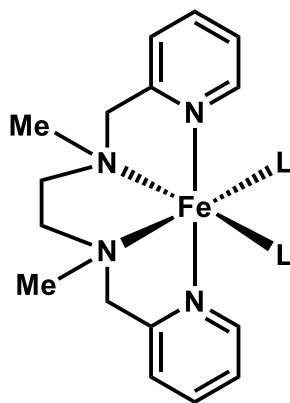


## C-H functionalization by iron catalyst

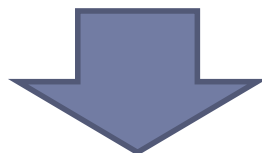


P450

**Reactivity**  
→  
**mimic**



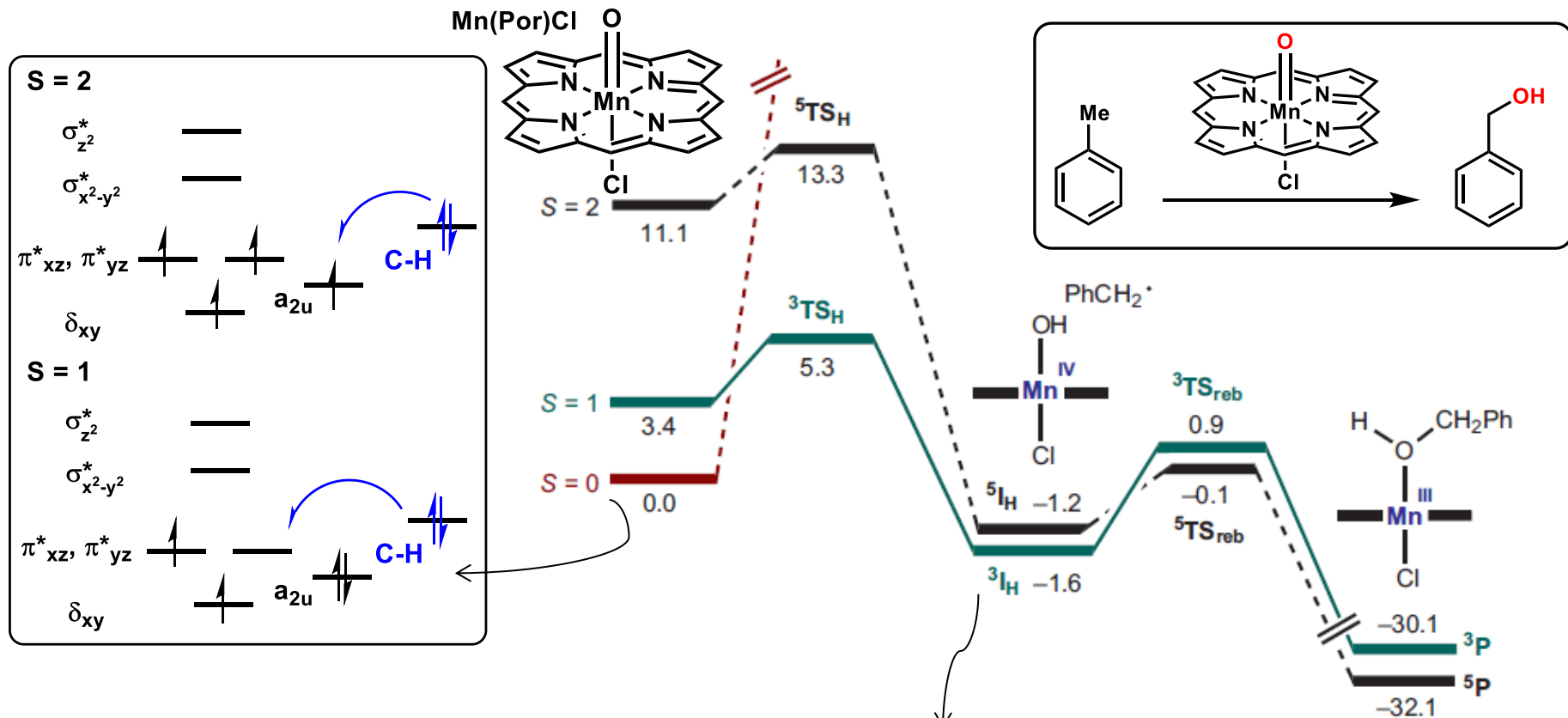
They enabled C-H epoxidation and hydroxylation



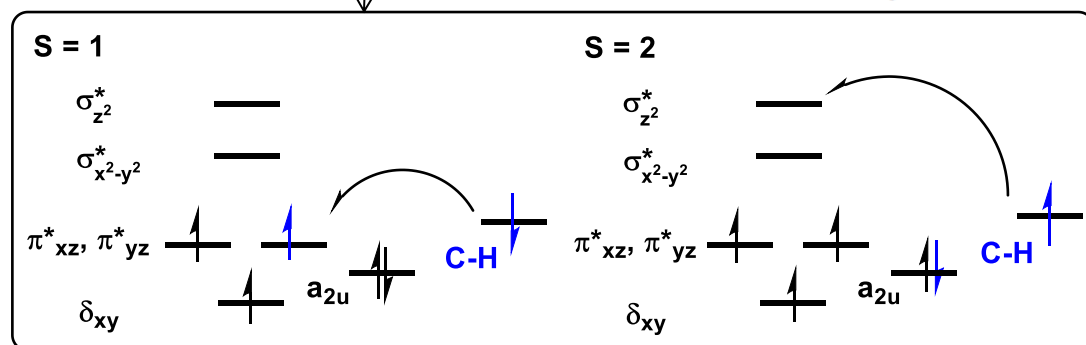
**How about other functionalization by metal-oxo species??**

### 3. Various C-H functionalization by manganese-oxo complexes

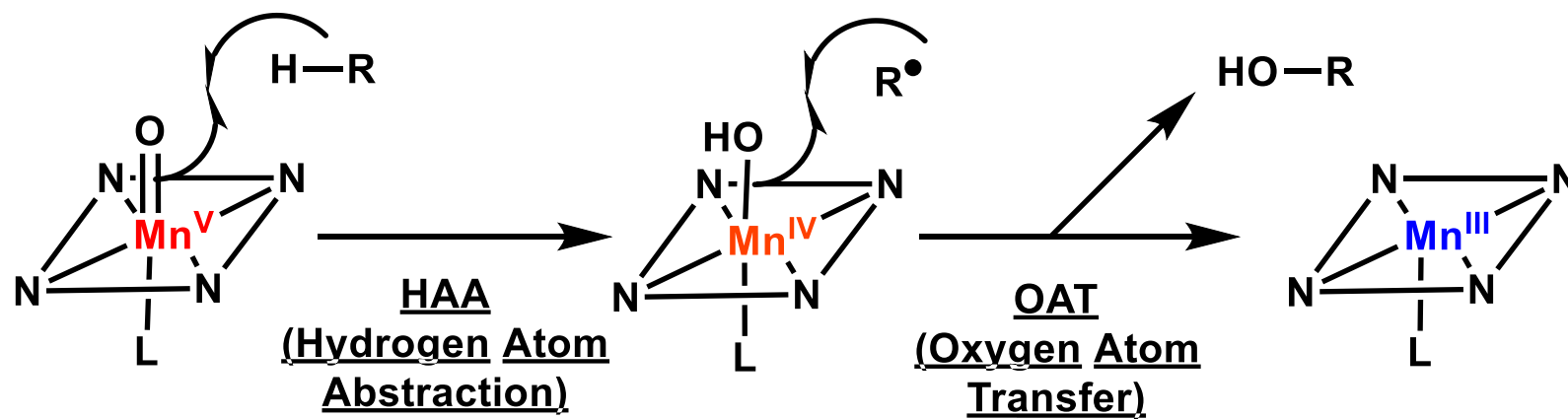
# C-H abstraction and oxygen transfer to toluene by heam manganese



- Hydrogen atom abstraction starts from S = 1 state, but both S=1 and S=2 show high reactivity in oxygen atom transfer.

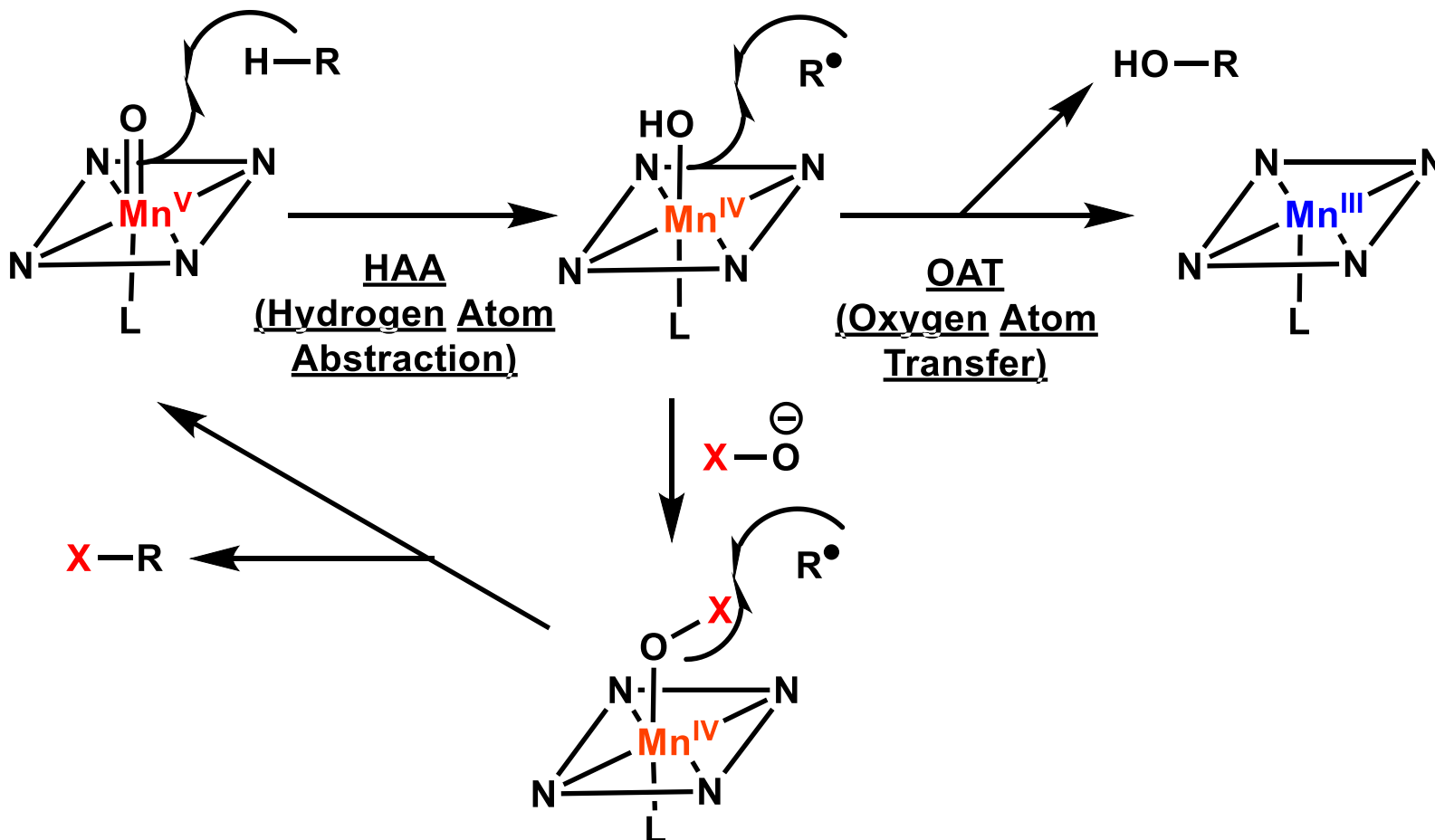


## C-H halogenation by metal-oxo species



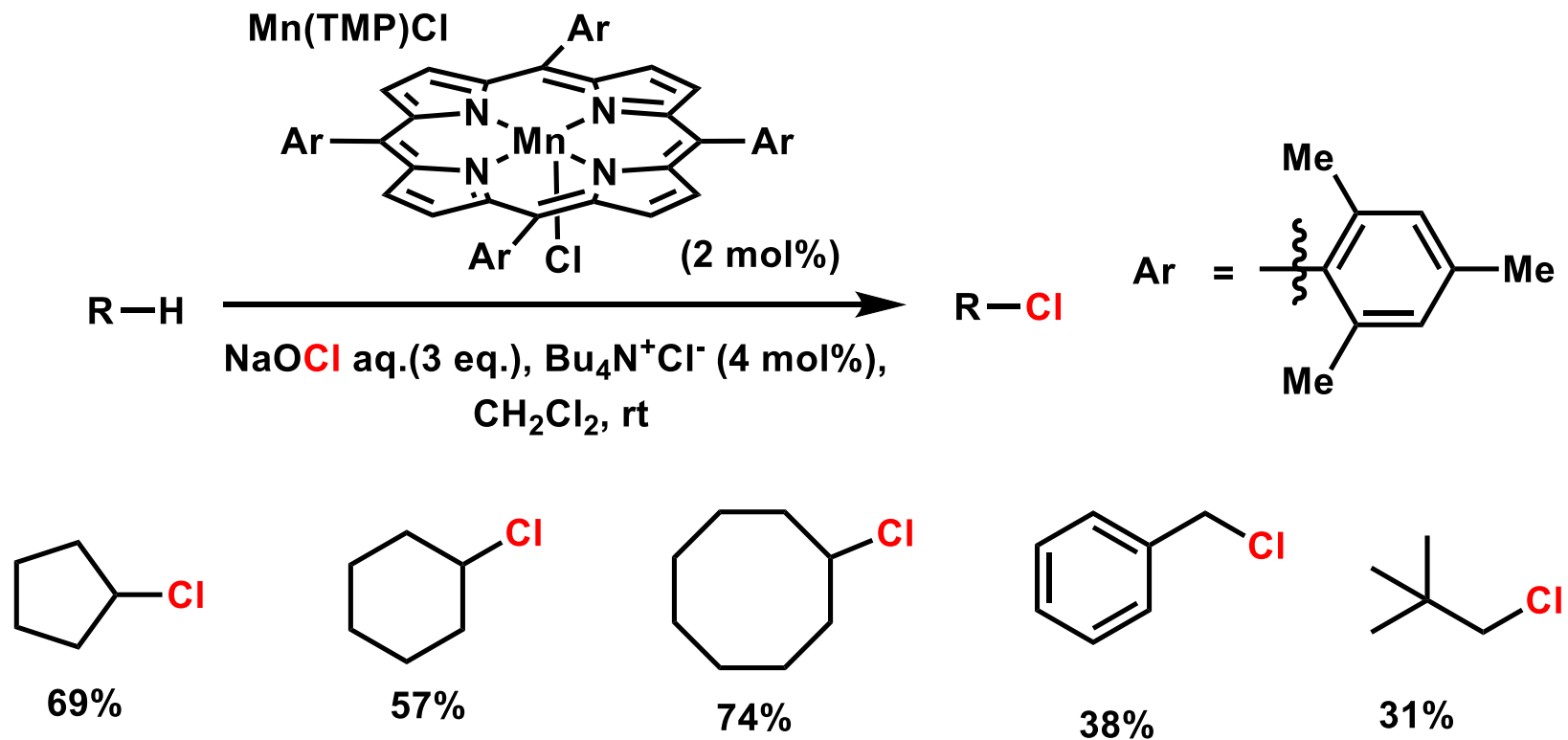


## C-H halogenation by metal-oxo species

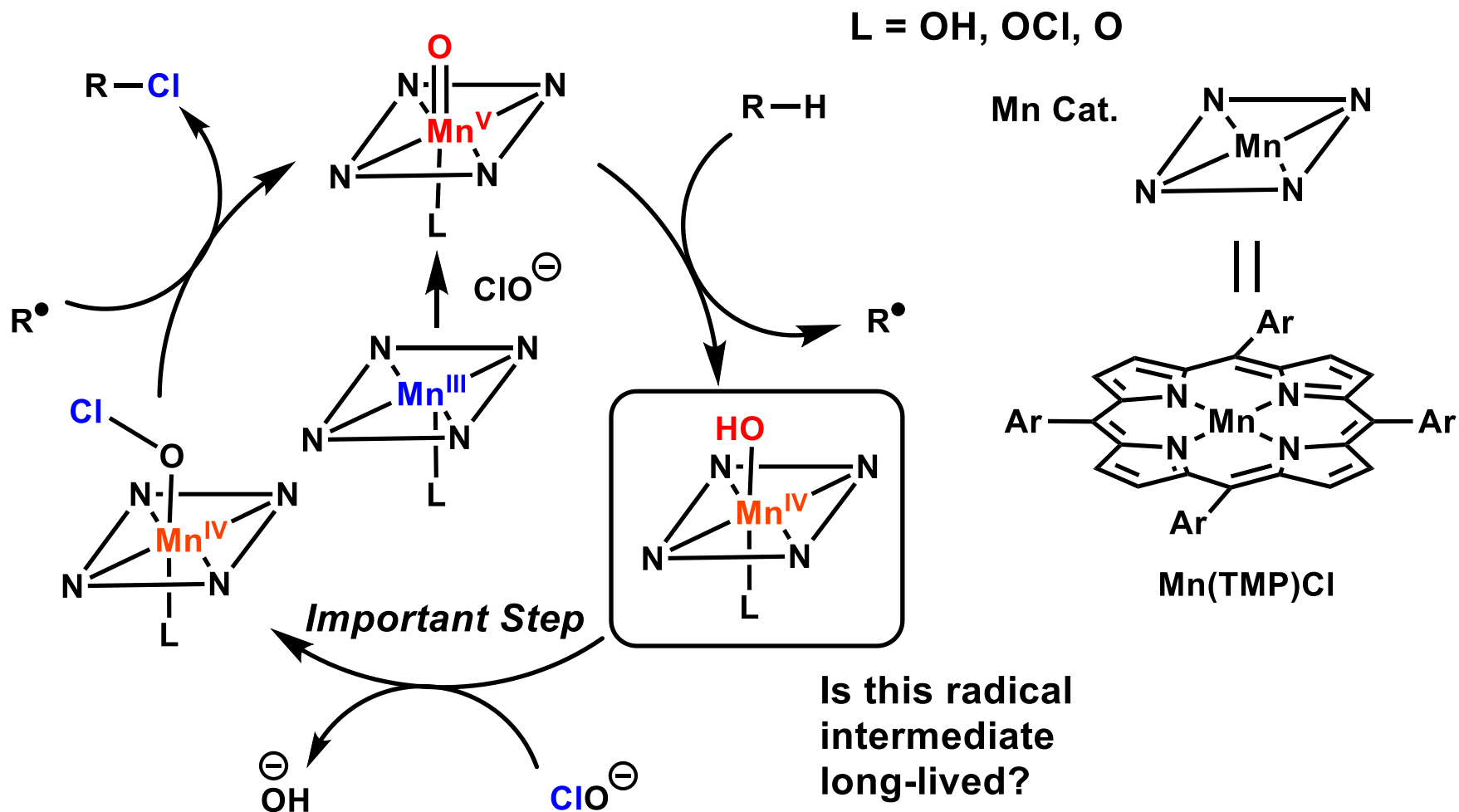


By trapping  $\text{R}^\bullet$  radical, C-H halogenation should be achieved.

# C-H chlorination by heam manganese

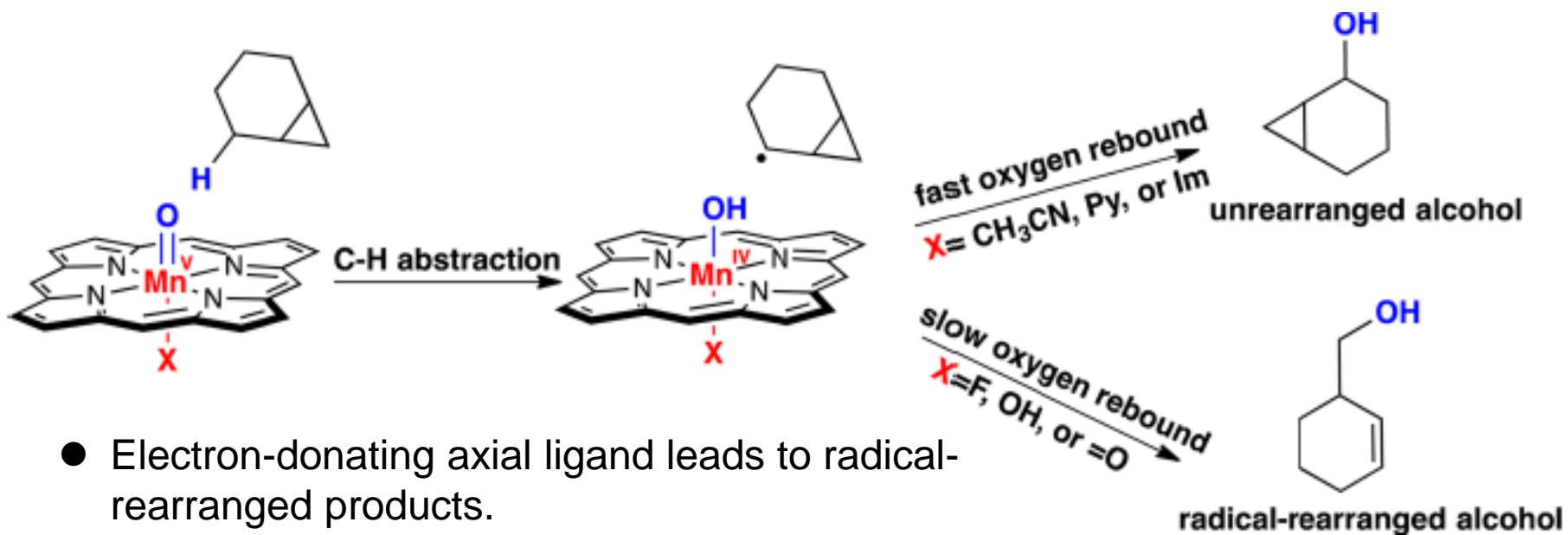
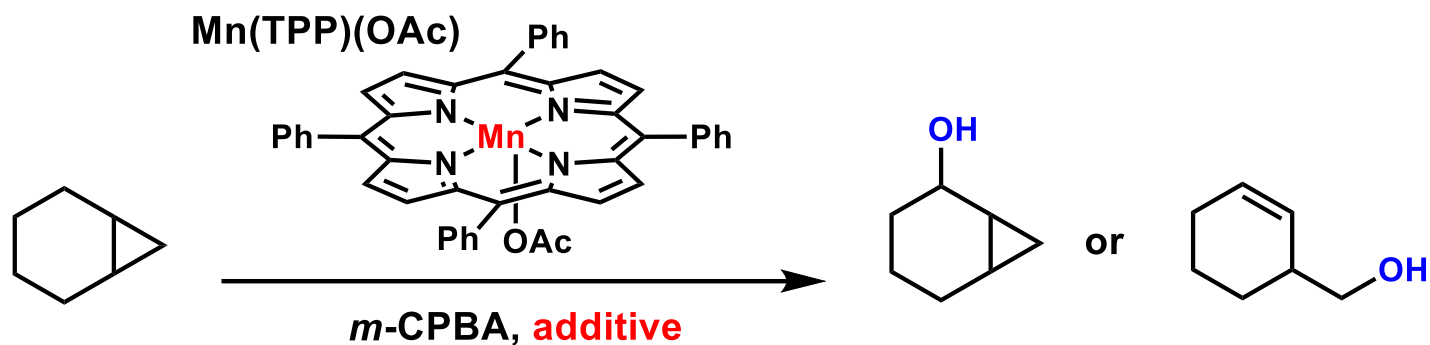


# Reaction mechanism



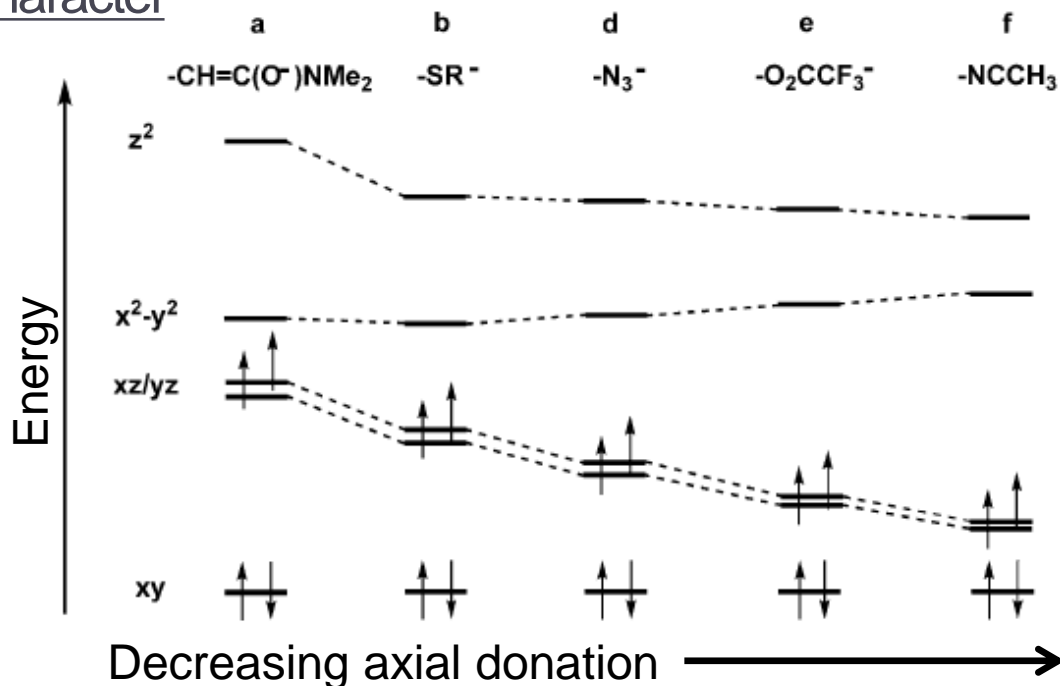
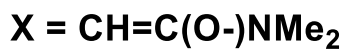
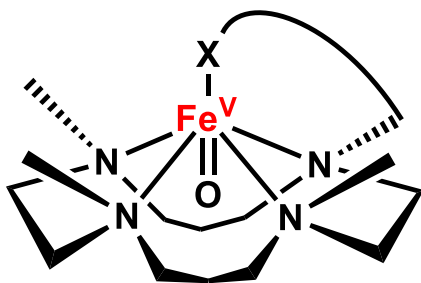
Groves, J. T. *et al. J. Am. Chem. Soc.* **2010**, *132*, 12847.  
 dioxo Mn(V): Groves, J. T. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12416.

## Axial ligands effect



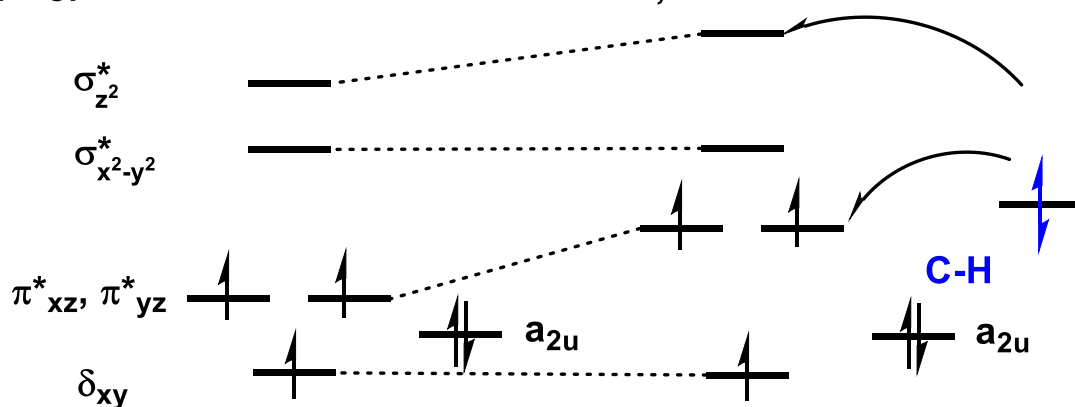
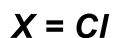
- Electron-donating axial ligand leads to radical-rearranged products.

## Axial ligands effect for radical character

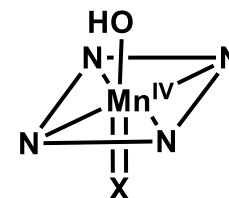


Ray, K. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 7632.

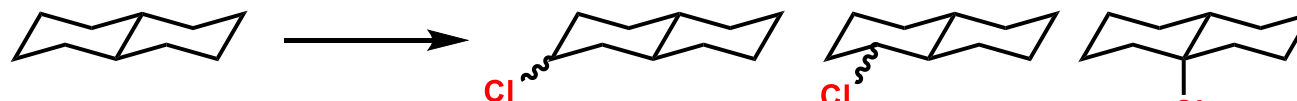
- OH<sup>-</sup> and OCl<sup>-</sup> made long-lived radical intermediate



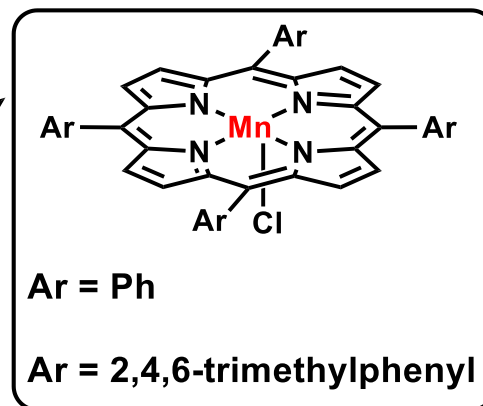
Increase in the energy of  $\sigma_{z^2}^*$  and  $\pi_{xz}^*$ ,  $\pi_{yz}^*$  decreased the reactivity of oxygen atom transfer.



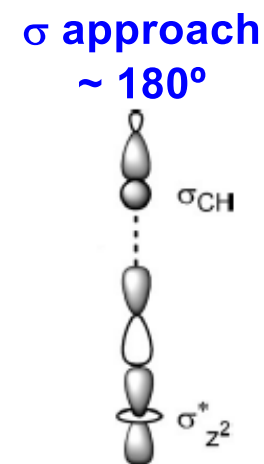
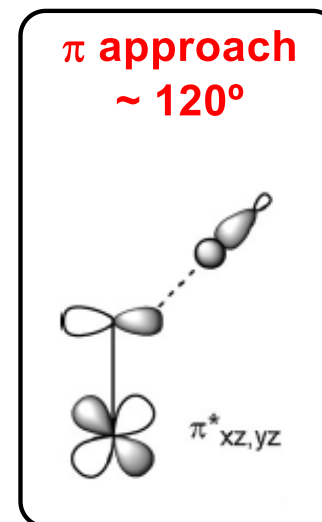
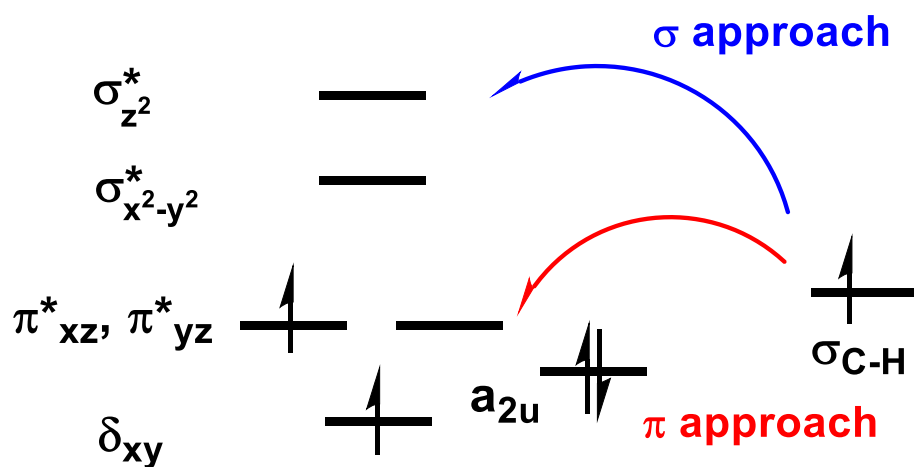
## Methylene selectivity of chlorination



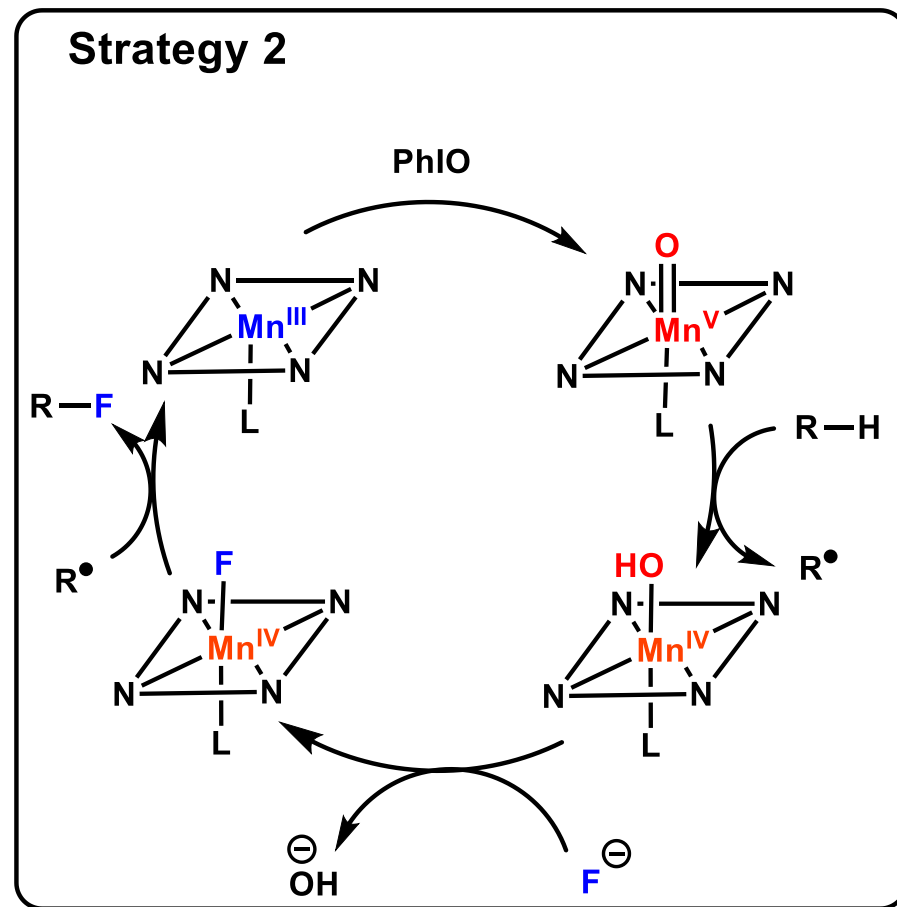
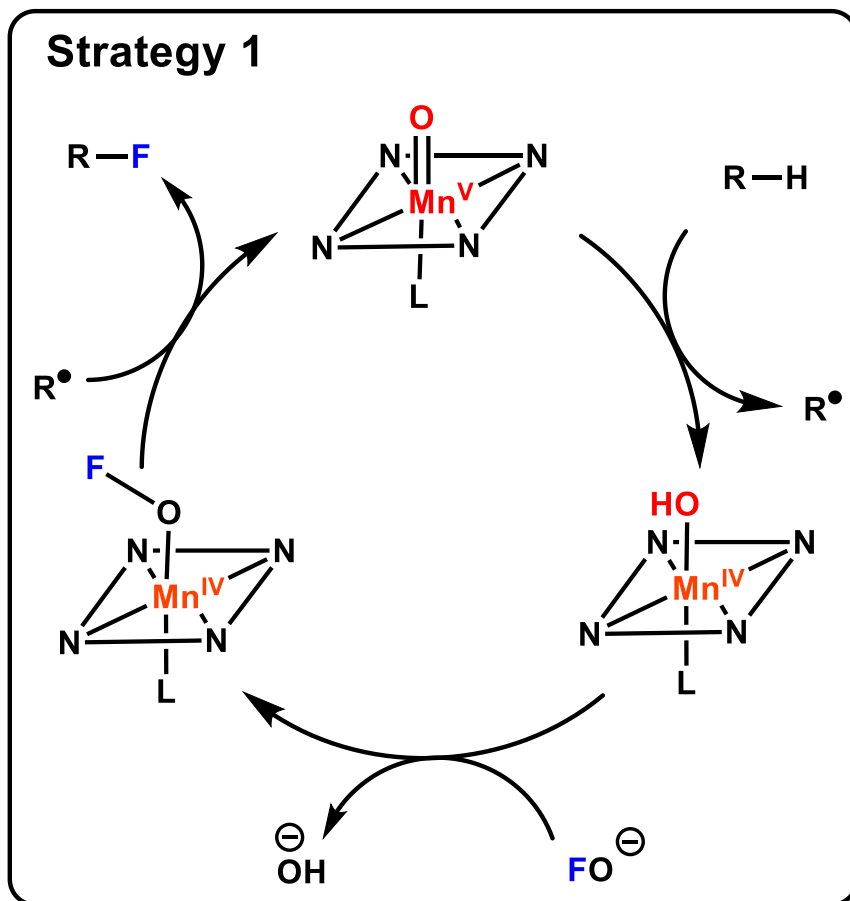
	Yield		Distribution	
<b>Mn(TPP)Cl</b> / NaOCl	55%	38%	58%	4%
<b>Mn(TMP)Cl</b> / NaOCl	51%	76%	19%	5%



Mn catalyst which has bulky substituents showed the selective chlorination to less-hindered methylene position.

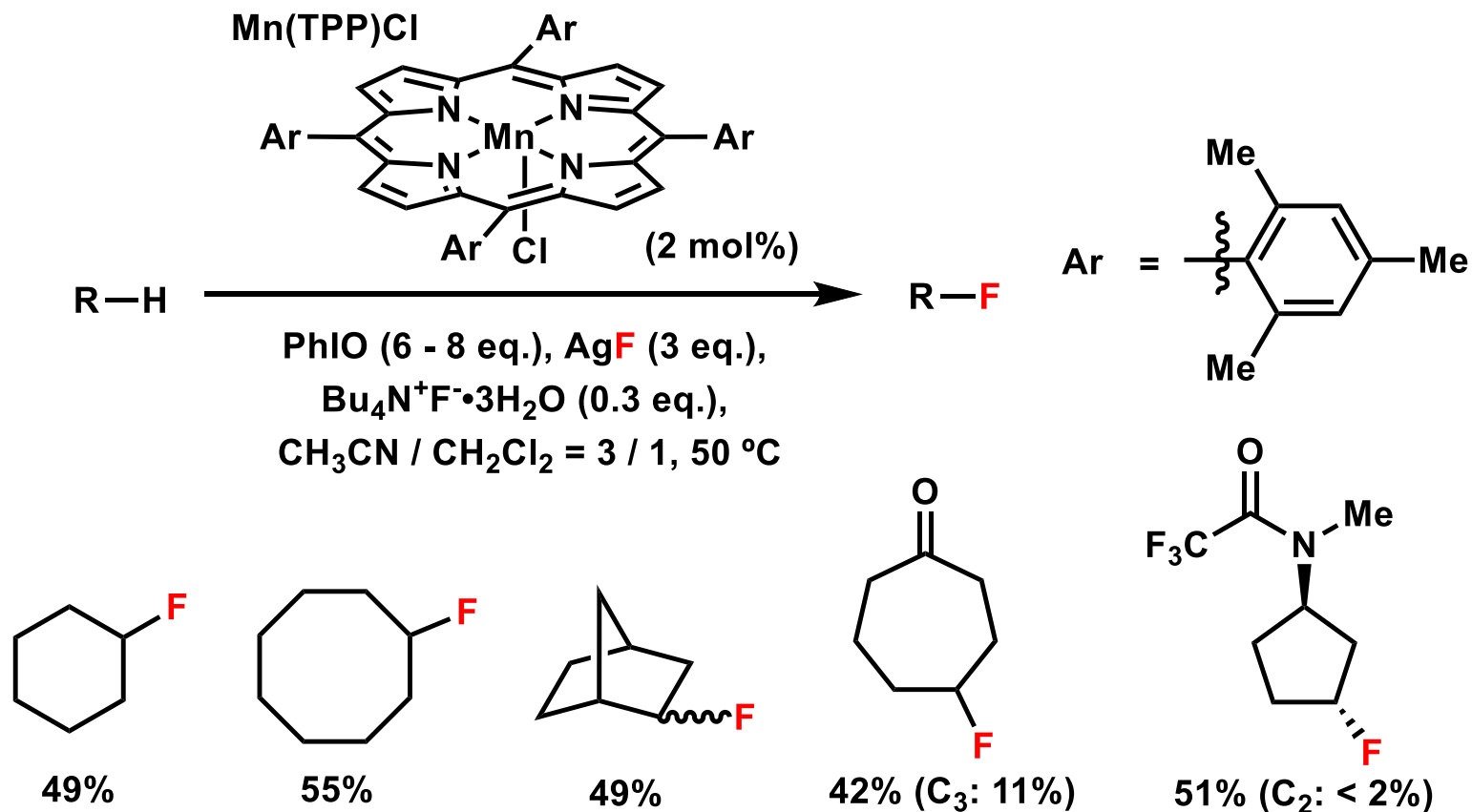


## Strategy for fluorination



- Strategy 1 failed (The reason was not mentioned in paper.)
- By using long-lived radical intermediate, strategy 2 should be achieved.

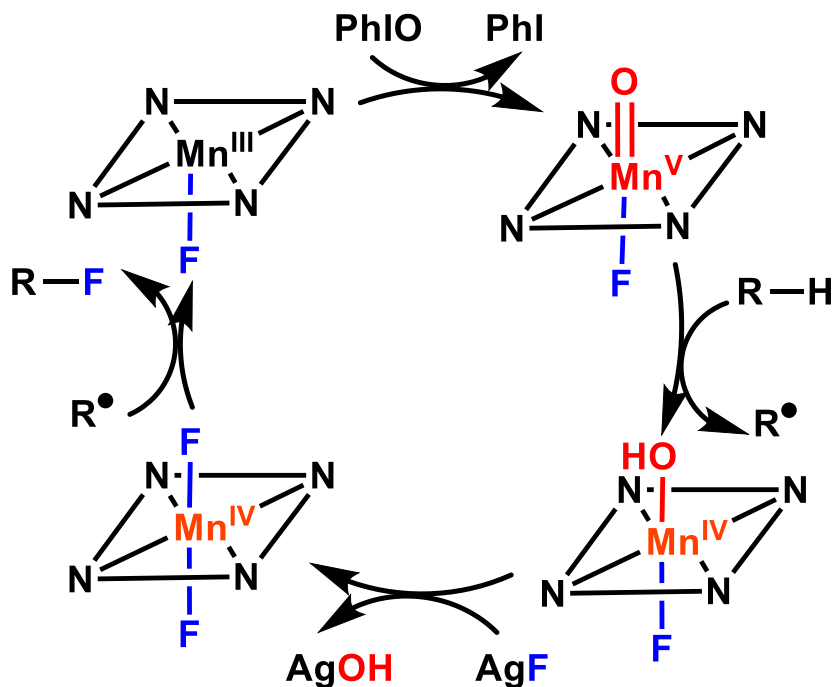
# C-H fluorination by heam manganese





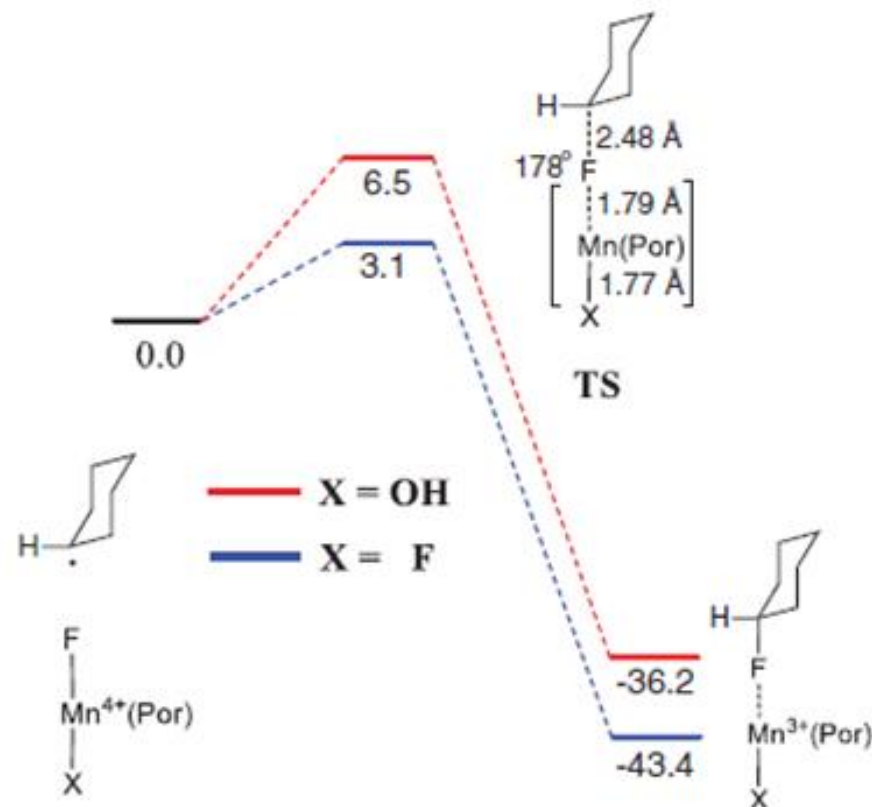
## Reaction mechanism of fluorination

### □ Catalytic cycle



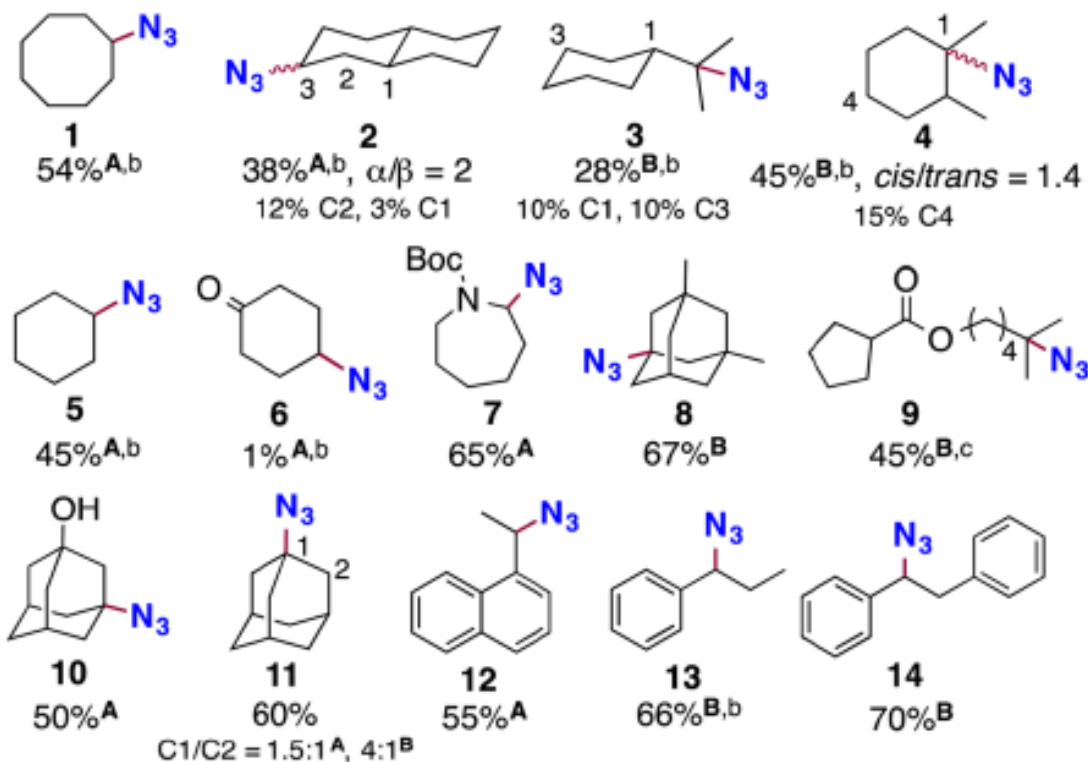
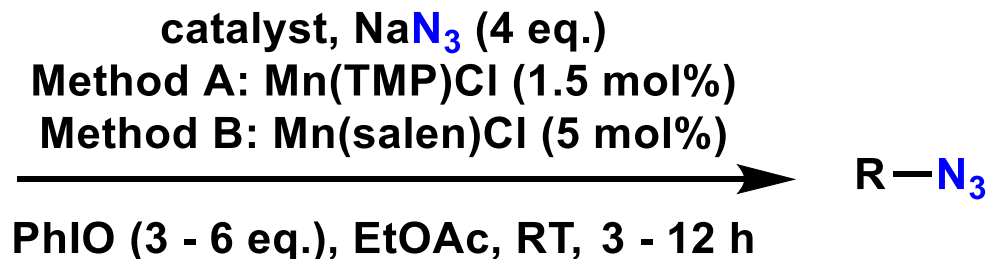
- Axial ligand controlled the reactivity of Mn-porphyrin.

### □ Energy landscape for F rebound

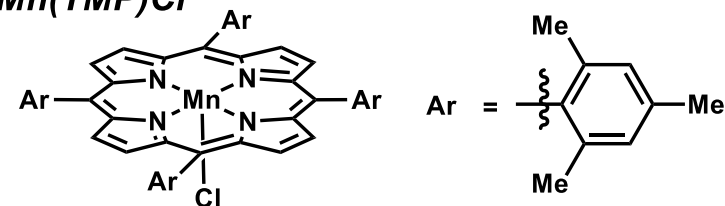


- The axial ligand of F makes the F rebound barrier lower.

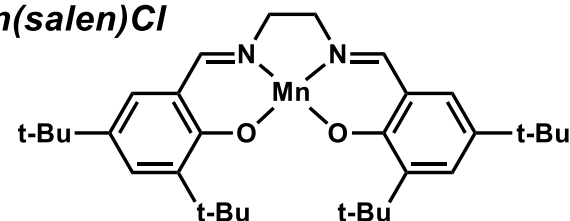
# C-H azidation by Mn-catalysts



*Mn(TMP)Cl*



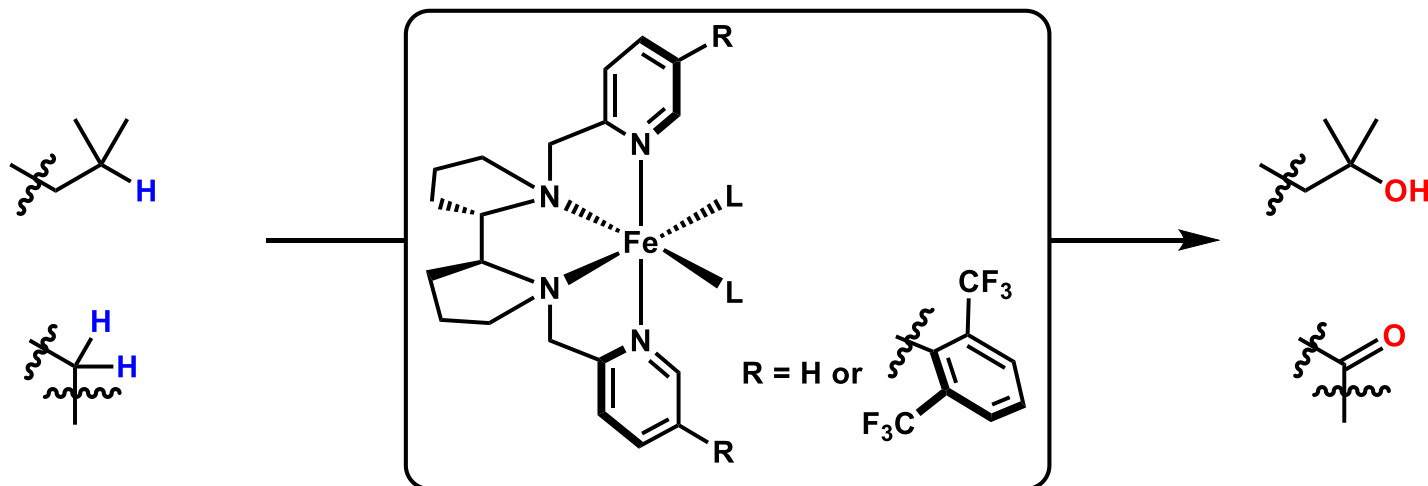
*Mn(salen)Cl*



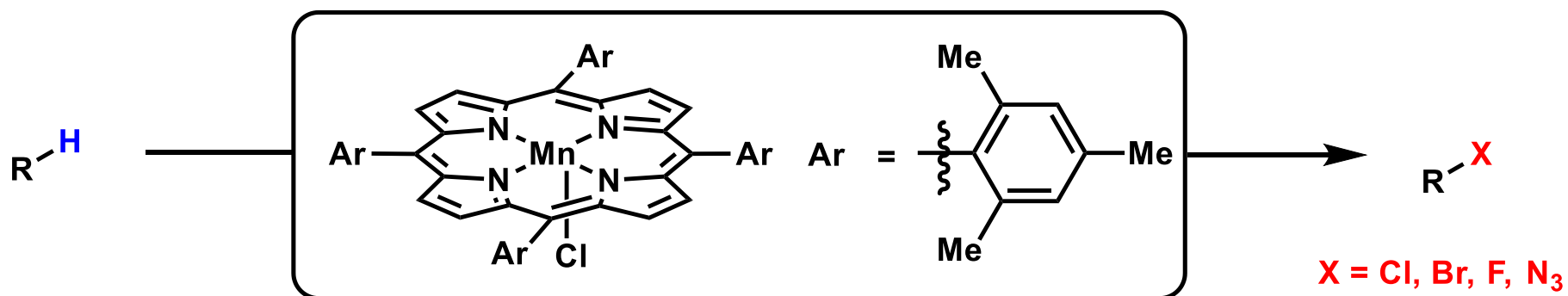
## 4. Summary

## Summary

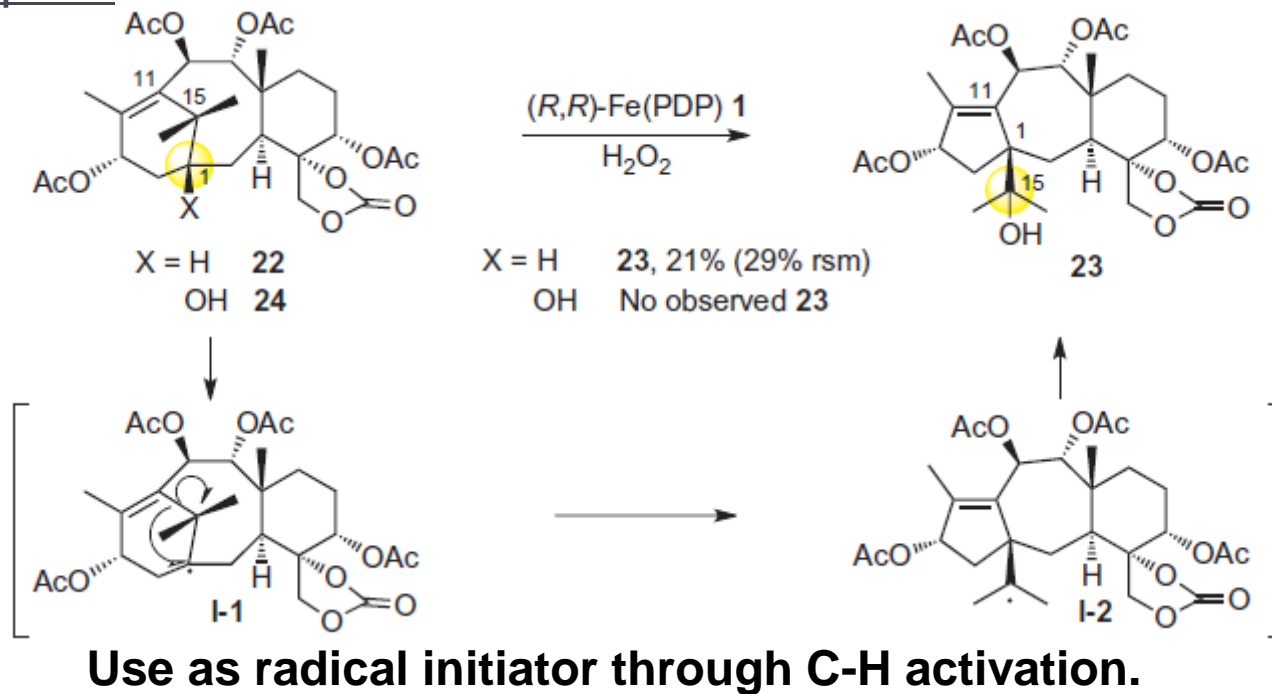
### 1. C-H hydroxylation by iron catalyst



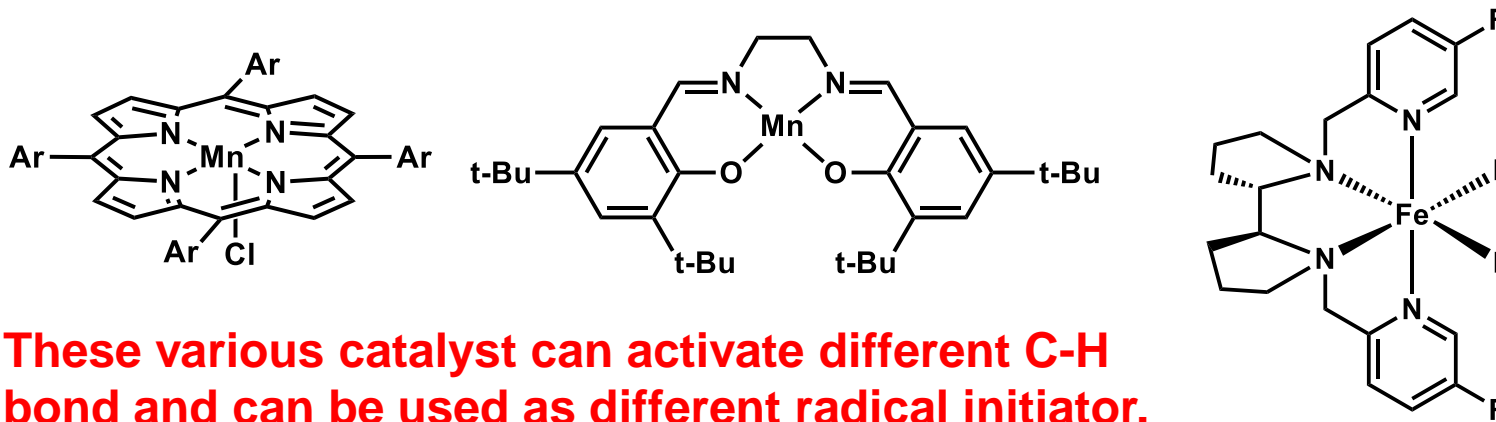
### 2. C-H functionalization by manganese catalyst



## Future prospects

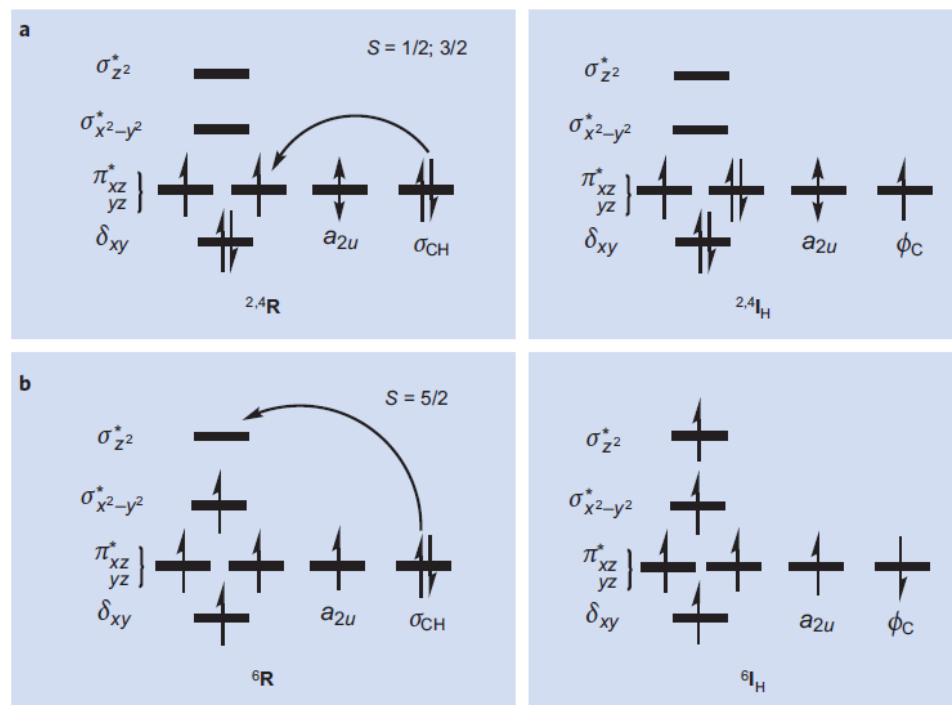
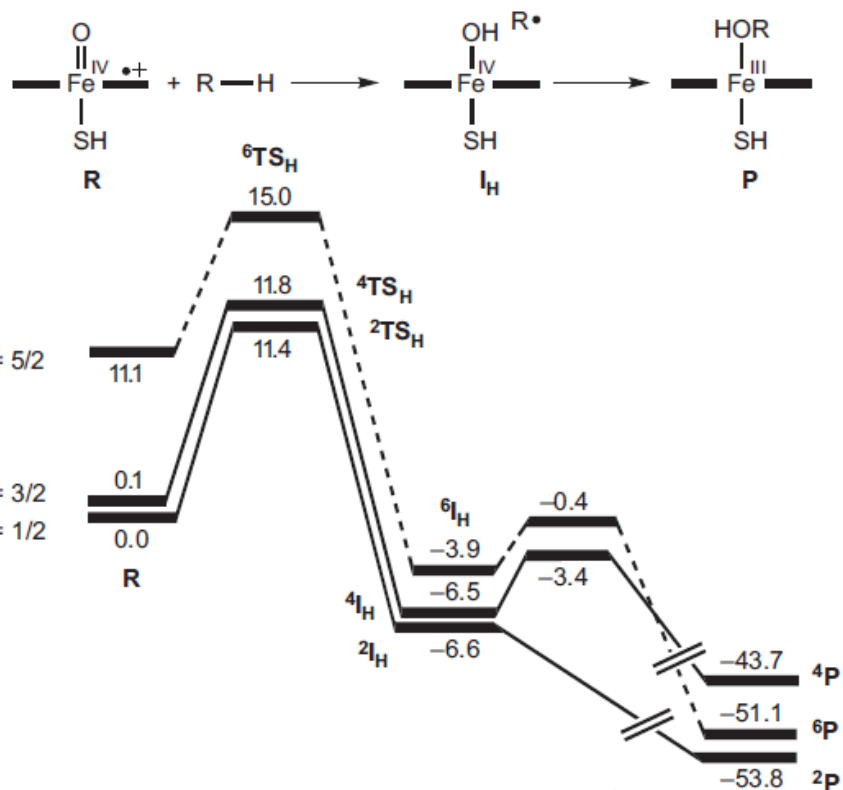


White, M. C. *et al. Nat. Chem.* **2011**, 3, 216.



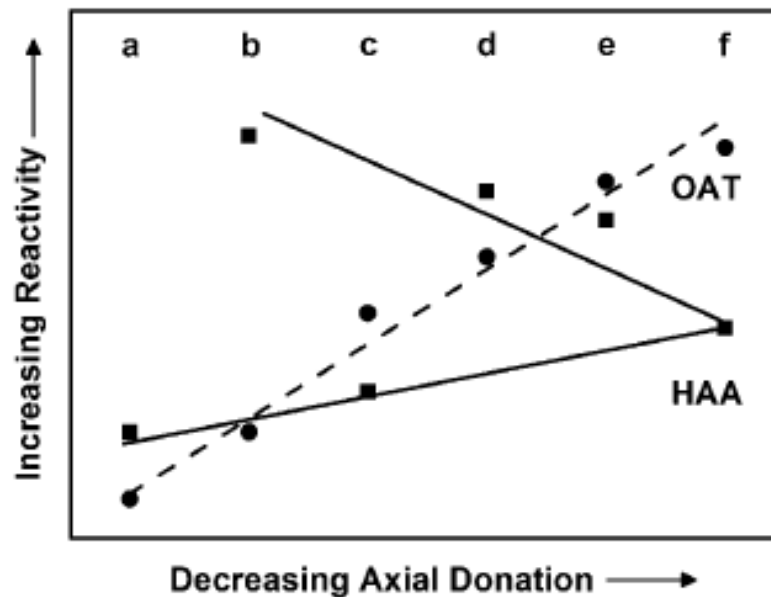
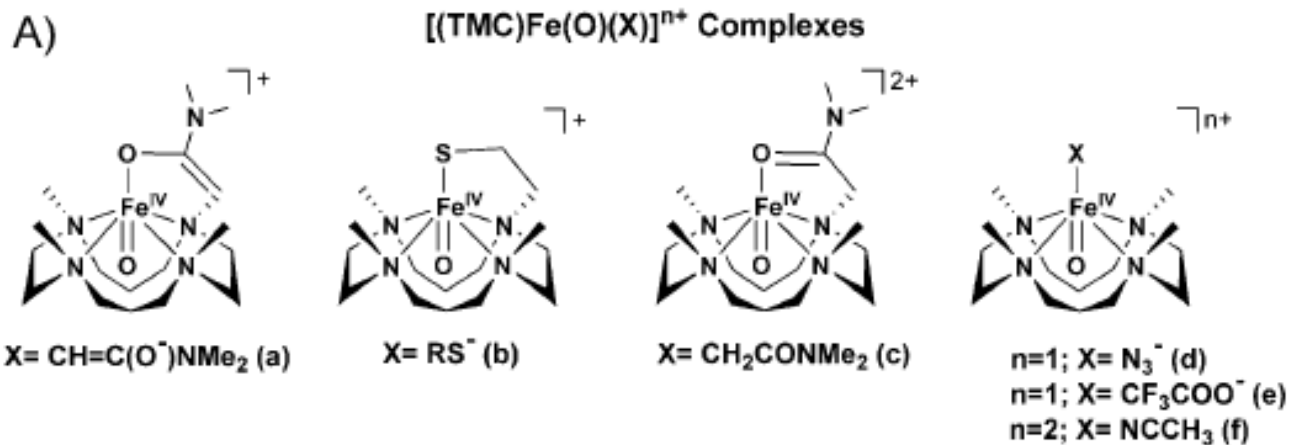
# Appendix

## C-H abstraction by heam iron



Iron shows high reactivity.

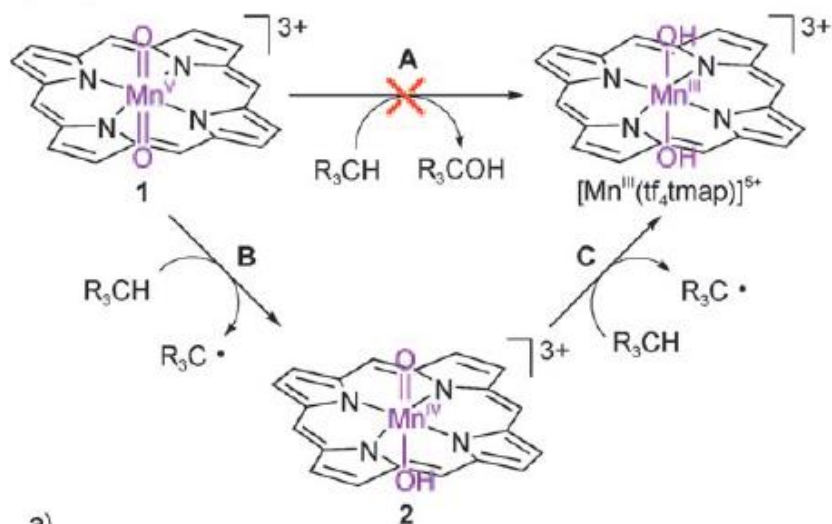
## Axial ligand and HAA, OAT



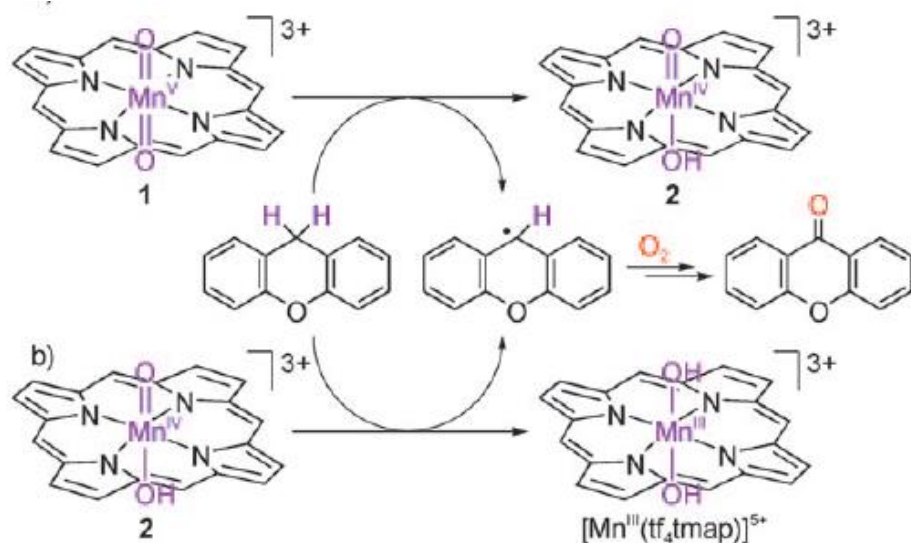


# Manganese reactivity

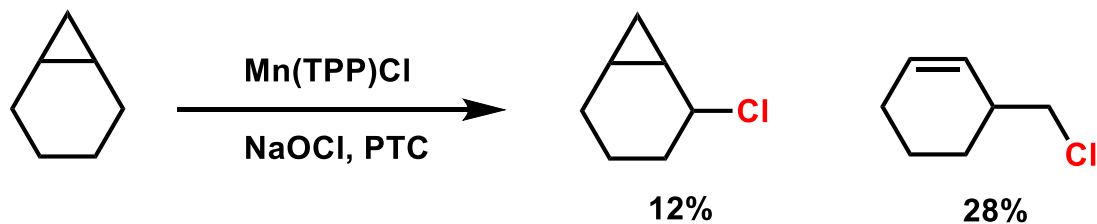
Hydrogen-atom abstraction



a)



Radical feature



Rearranged products indicated a long-lived radical intermediate.

## Rieske non-hem iron species

