

C-H activation via Multiple-site Concerted Proton-Electron Transfer

Literature Seminar #1

2023/8/24

M1 Arii

1. Introduction

- 1-1. PCET and CPET · Marcus Cross Relation
- 1-2. Example of *Canonical HAT, Separated CPET, Multi-Site CPET*
- 1-3. Importance of Hydrogen Bond in MS-CPET

2. Contents

- 2-1. Intramolecular C-H activation via MS-CPET
- 2-2. Intramolecular C-H activation with photocatalyst via MS-CPET
- 2-3. Intermolecular C-H activation via MS-CPET

3. Summary

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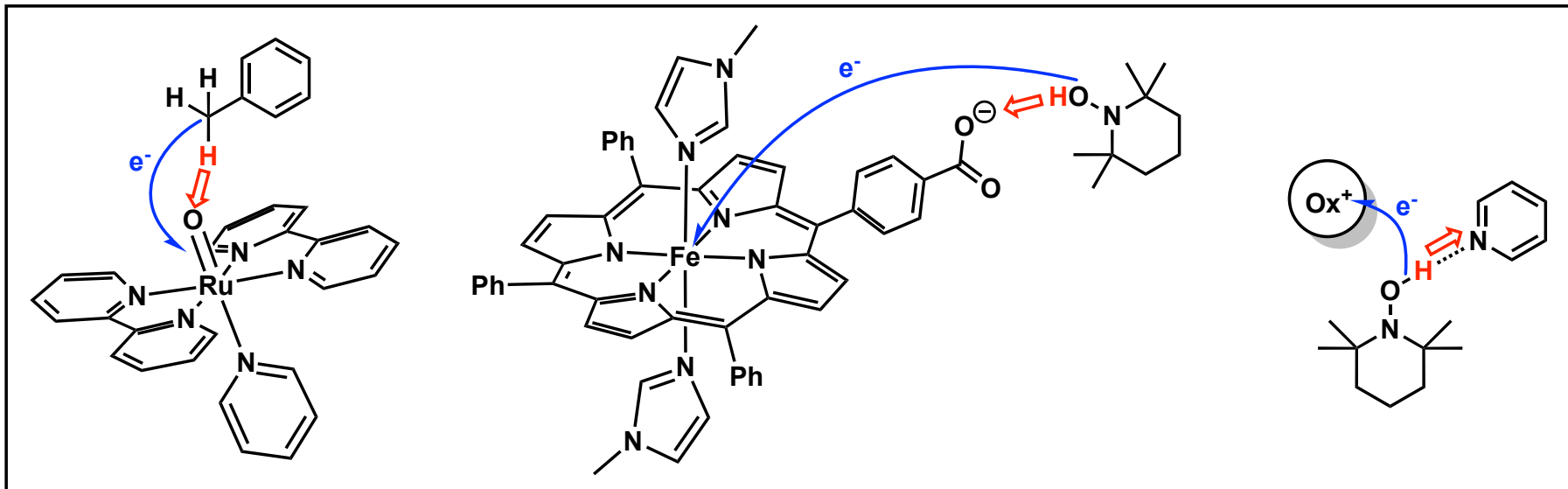
PCET : Proton-Coupled Electron Transfer

↳ Reaction which proton transfer (PT) and electron transfer (ET)

CPET : Concerted Proton Electron Transfer

↳ Reaction in which one proton and one electron transfer **concertedly**

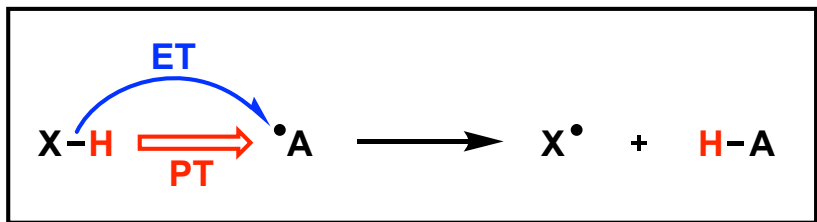
- CPET with different mechanisms exist.
- However, their classification is **ambiguous** and **continuous**.



All the reactions listed above are CPET.

Although there is no clear classification, CPET can be divided into **three main categories**.

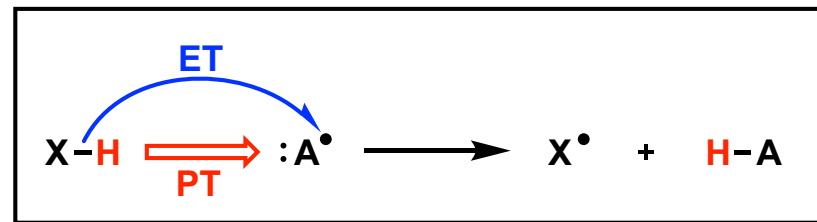
① *Canonical HAT*



► Proton and electron transfer as **hydrogen atom**.

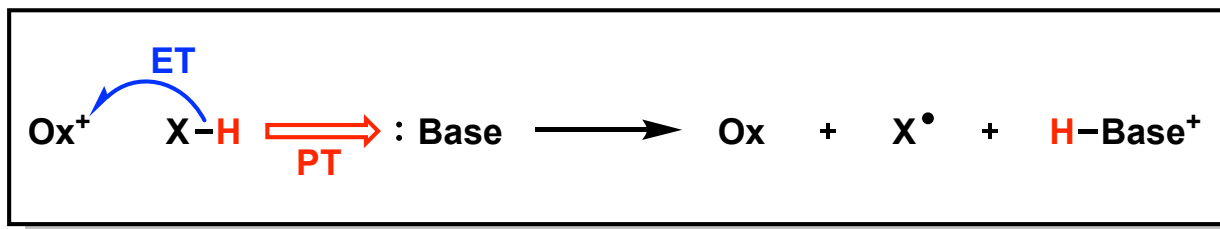
⇒ Protons and electrons transfer **into the same bond**.

② *Separated CPET*



► Proton and electron transfer **to another atom in the same molecule**.

③ *Multiple Site CPET*



► Proton and electron transfer to **completely separate molecules**.

Darcy, J. W.; Koronkiewicz, B.; Parada, G. A.; Mayer, J. M., *Acc. Chem. Res.* **2018**, *51*, 2391–2399

Marcus crossover equation can be used to understand the reaction rate of CPET.

When the reaction proceeds in CPET, $|\Delta G^\circ| \ll \lambda$ is established.

$$\textcircled{1} \quad \log(k) = \alpha \log(K_{\text{eq}}) + \beta$$

Brønsted catalysis law

$$\textcircled{2} \quad \Delta G^\ddagger = \alpha \Delta G^\circ + \beta'$$

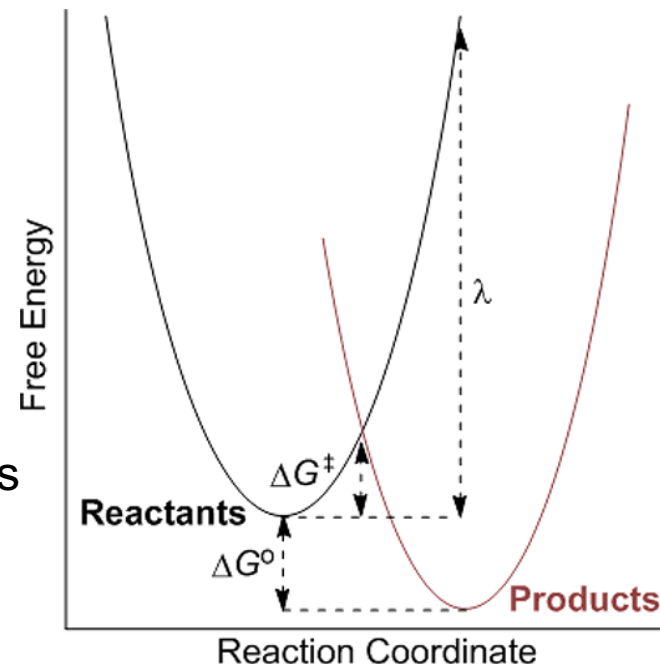
Eyring equation

$$\textcircled{3} \quad \Delta G^\ddagger = \frac{(\Delta G^\circ + \lambda)^2}{4\lambda}$$

Equation for the intersection of parabolas

$$\textcircled{4} \quad \alpha = \frac{\partial(\Delta G^\ddagger)}{\partial(\Delta G^\circ)} = \frac{2(\Delta G^\circ + \lambda)}{4\lambda} = \frac{1}{2} + \frac{\Delta G^\circ}{2\lambda}$$

$$\textcircled{5} \quad \alpha = \frac{1}{2} \left(1 + \frac{\Delta G^\circ}{\lambda} \right) \simeq \frac{1}{2} \quad \left(\because |\Delta G^\circ| \ll \lambda \Leftrightarrow \frac{\Delta G^\circ}{\lambda} \ll 1 \right)$$



Basically, the reactions that proceed in **CPET** have an **α of 0.5**

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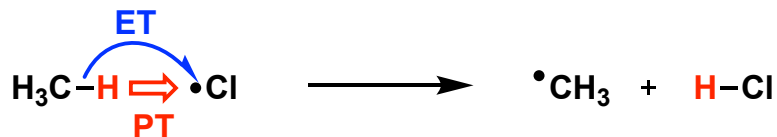
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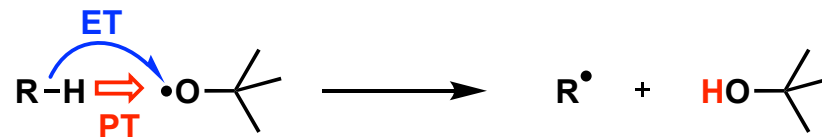
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Example of *Canonical HAT*

radical-chain chlorination

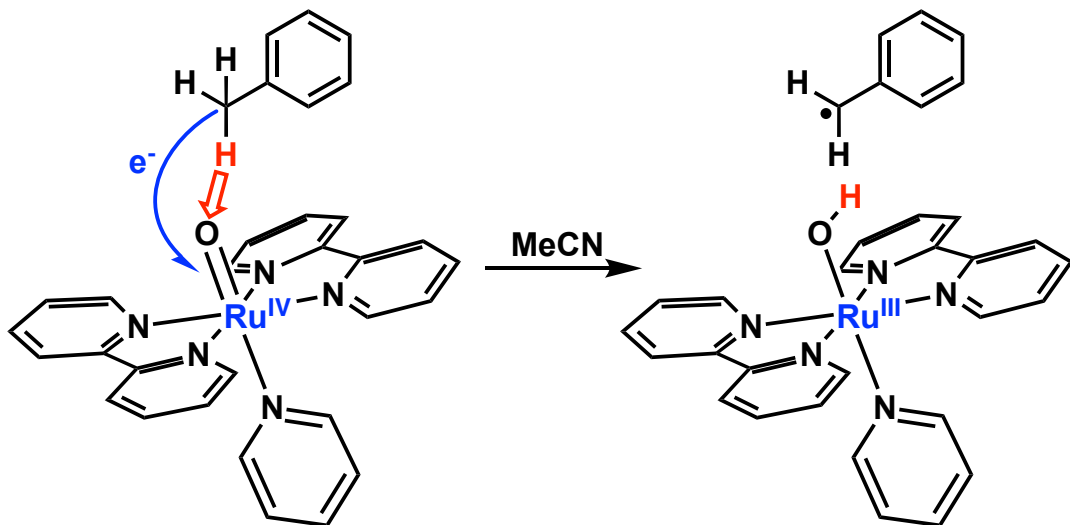


Alkane oxidation by *t*-BuO[•] radical



Darcy, J. W.; Koronkiewicz, B.; Parada, G. A.; Mayer, J. M., *Acc. Chem. Res.* **2018**, *51*, 2391–2399

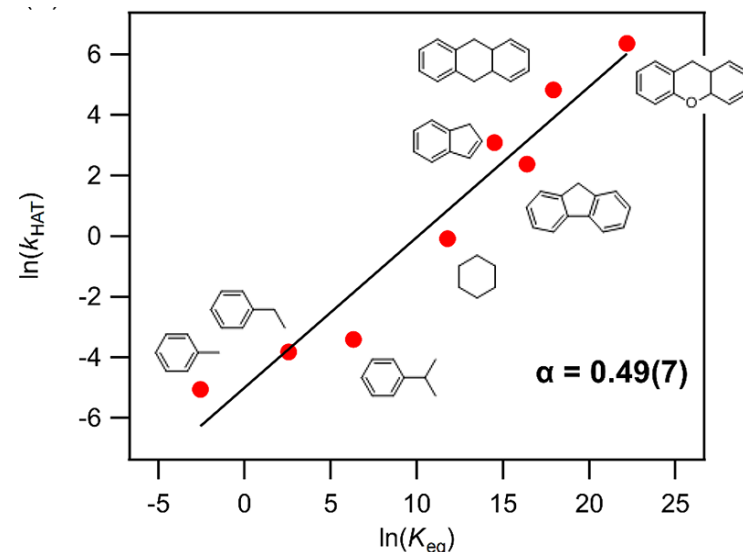
Hydrogen atom abstraction by a Ruthenium-oxo complex



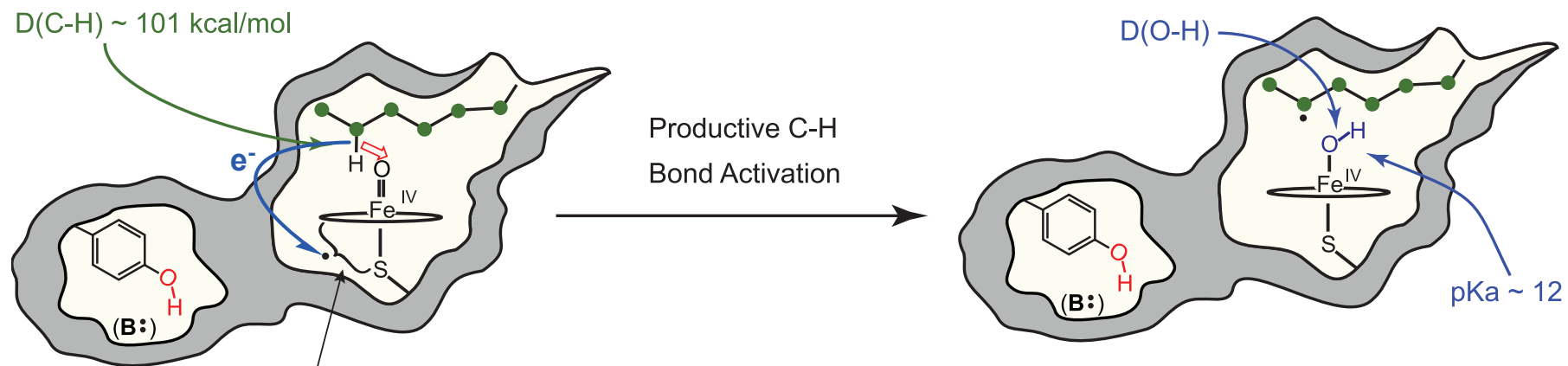
Bryant, J. R.; Mayer, J. M., *J. Am. Chem. Soc.* **2003**, *125*, 10351–10361

- Electron may have transferred to ruthenium as ruthenium is ultimately reduced.
- However, since the electrons are in **Ru-O π* orbital**, the transferred electrons may also **form O-H bond**.

Evidence of progress in CPET mechanism



Alkane oxidation by compound I in Cytochrome P450s



the mixture of porphyrin radical cation and thiyl radical

Yosca, T. H., *et al.*, *Science*, **2013**, 342, 825.

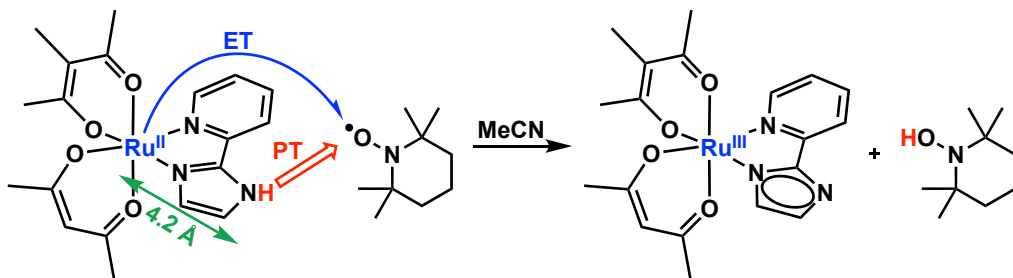
- The **proton** adds to the **oxo** forming a hydroxo ligand.
- The **electron** transfers a “hole” (= porphyrin radical cation or thiyl radical) away from the oxo.



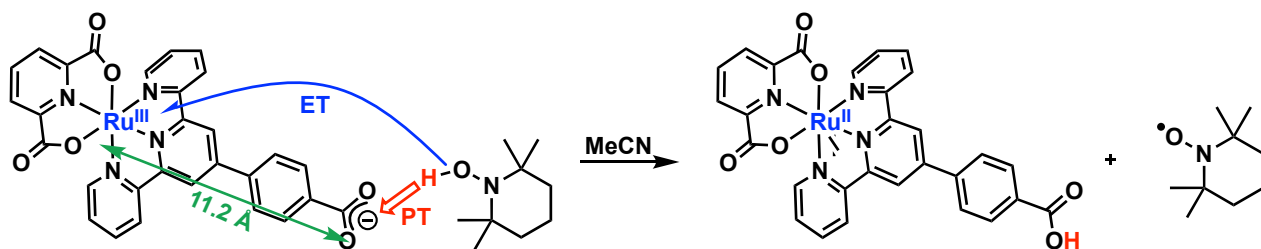
Separated CPET

Example of *Separated CPET*

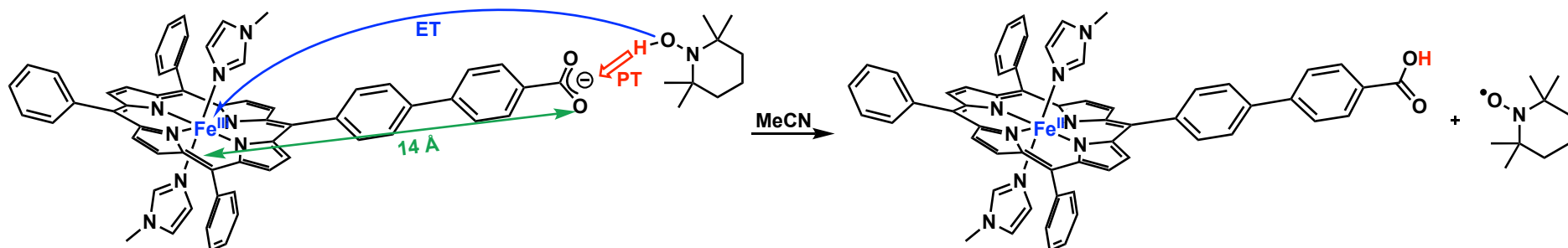
CPET with the long distance between redox and basic site



Wu, A.; Masland, J.; Swartz, R. D.; Kaminsky, W.; Mayer, J. M., *Inorg. Chem.* **2007**, 46, 11190–11201



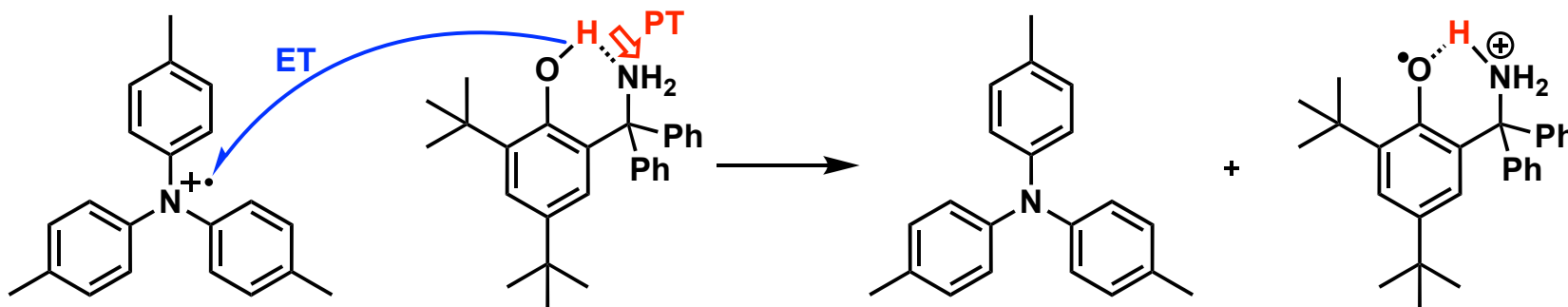
Manner, V. W.; Mayer, J. M., *J. Am. Chem. Soc.* **2009**, 131, 9874–9875



Warren, J. J.; Menzeleev, A. R.; Kretchmer, J. S.; Miller, T. F.; Gray, H. B.; Mayer, J. M., *J. Phys. Chem. Lett.* **2013**, 4, 519–523

Concerted proton electron transfer proceeds although the reduction and base fields are too **far** apart to interact with each other.

One-Electron Oxidation of a Phenol Coupled with an Intramolecular Amine-Driven Proton Transfer



Mayer, J. M.; Rhile, I. J., *J. Am. Chem. Soc.* **2004**, 126, 12718-12719.

Evidence of progress in CPET mechanism

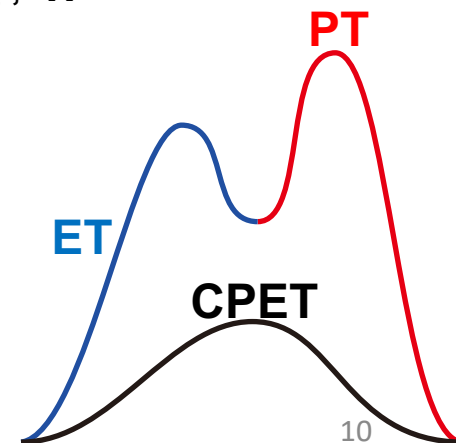
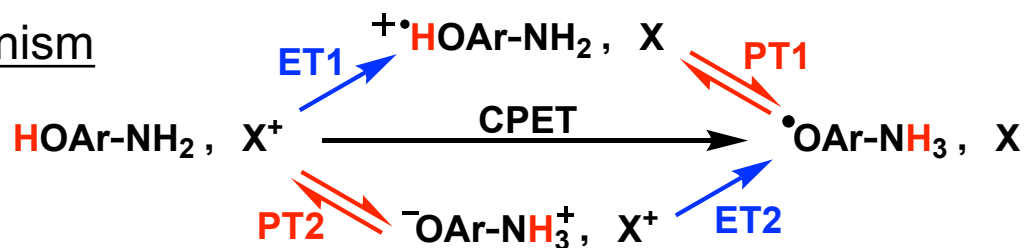
- ① A primary kinetic isotope effect

$$k_H/k_D = 2.4 \pm 0.2$$

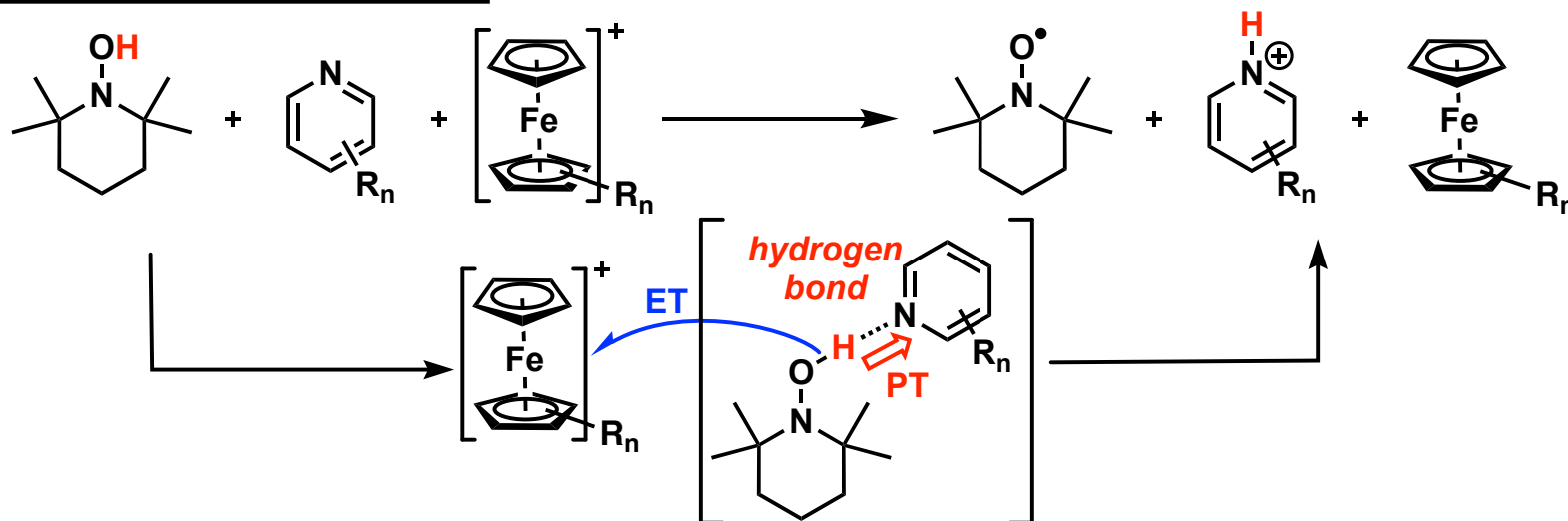
☞ **Protons** are involved in **the rate-limiting step**.

- ② The reaction rate is too fast to go through a high-energy intermediate. (→ Appendix)

- ③ $\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ = 0.53$



Three-Component MS-CPET Reactions

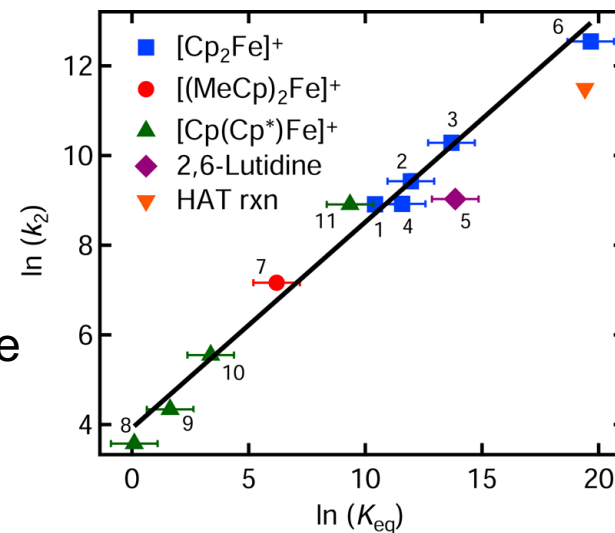


Morris, W. D.; Mayer, J. M., *J. Am. Chem. Soc.* **2017**, 139, 10312–10319.

Evidence of progress in CPET mechanism

- ① $\Delta G^\circ_{\text{ET1}}$ and $\Delta G^\circ_{\text{PT2}}$ are each **larger** than ΔG^\ddagger .
 ☞ **The reaction is not via ET1, PT2.** (→ Appendix)

- ② $\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ = \ln(k_2) / \ln(K_{\text{eq}}) = 0.46$
 Changing the E of the oxidant or the pK_a of the base will result in an α of 0.5. (→ Appendix)



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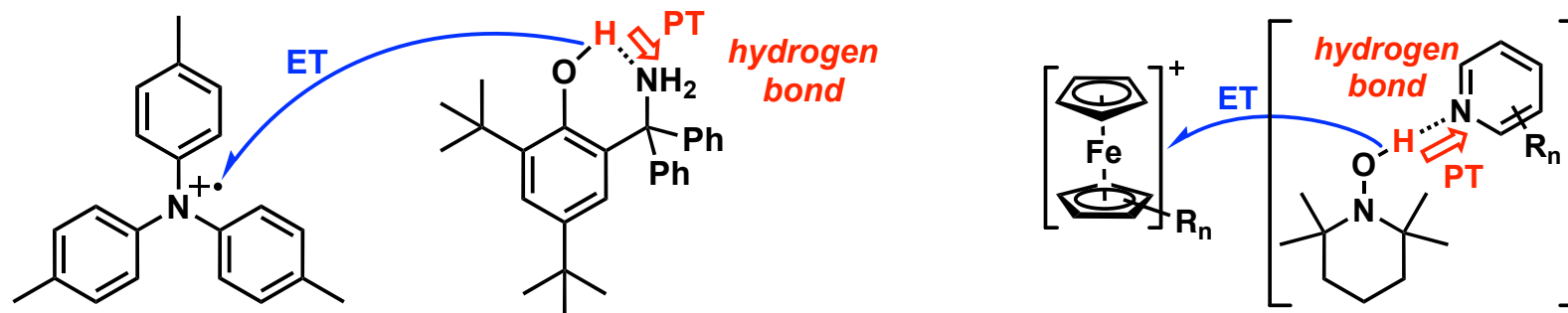
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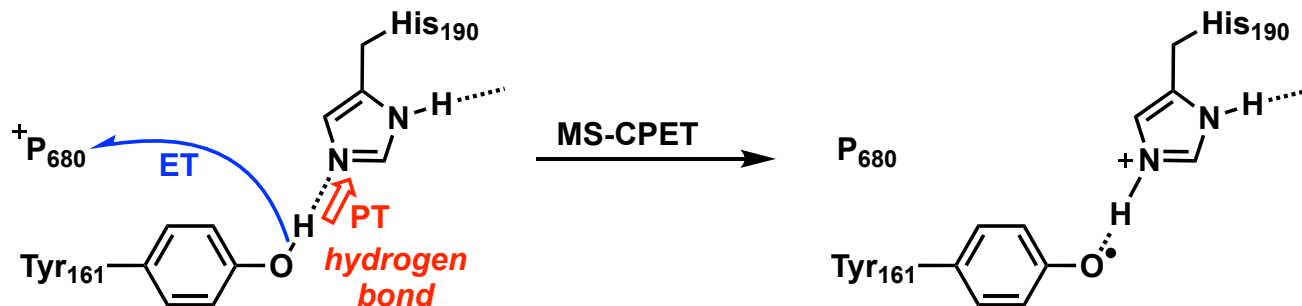
MS-CPET requires **fixing** the reaction coordinates of **a proton** in advance.



Hydrogen bond is the key



Tyrosine oxidation in Photosystem II



J. L. Dempsey, J. R. Winkler, H. B. Gray, *Chem. Rev.* **2010**, *110*, 7024–7039.

Enzymes also use hydrogen bond to proceed MS-CPET.

C-H bond **cannot form hydrogen bonds**. **C-H activation using MS-CPET is difficult.**

However, what if we could **fix the C-H bond on the PT reaction coordinates** in advance?

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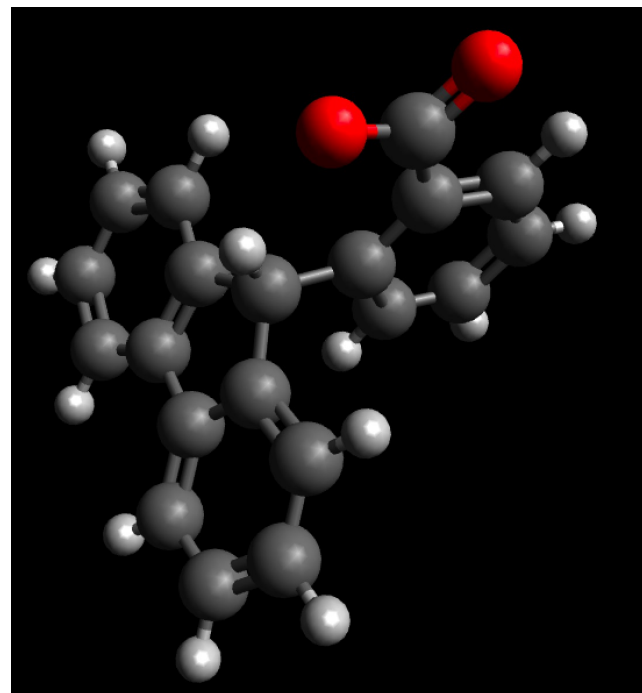
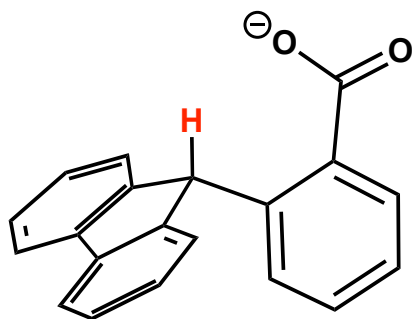
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Conditions for molecules designed by DFT calculations

- ☞ **A base positioned near a relatively weak C–H bond**



2-(9H-fluoren-9-yl)benzoate



Steric interactions between the **rigid** fluorene and the benzoate



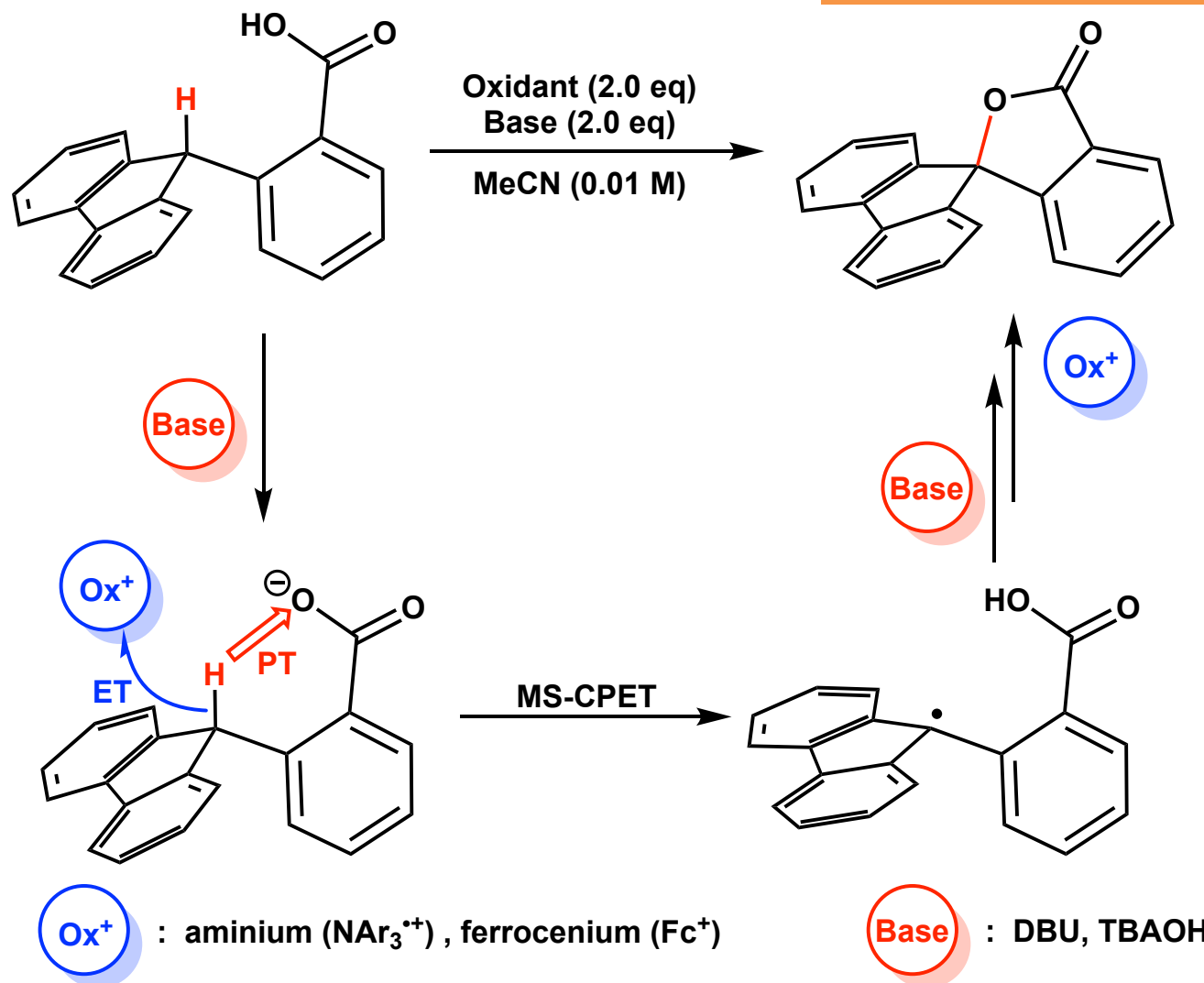
Keeping the rings nearly perpendicular



Positioning the base near the weak benzylic C–H bond

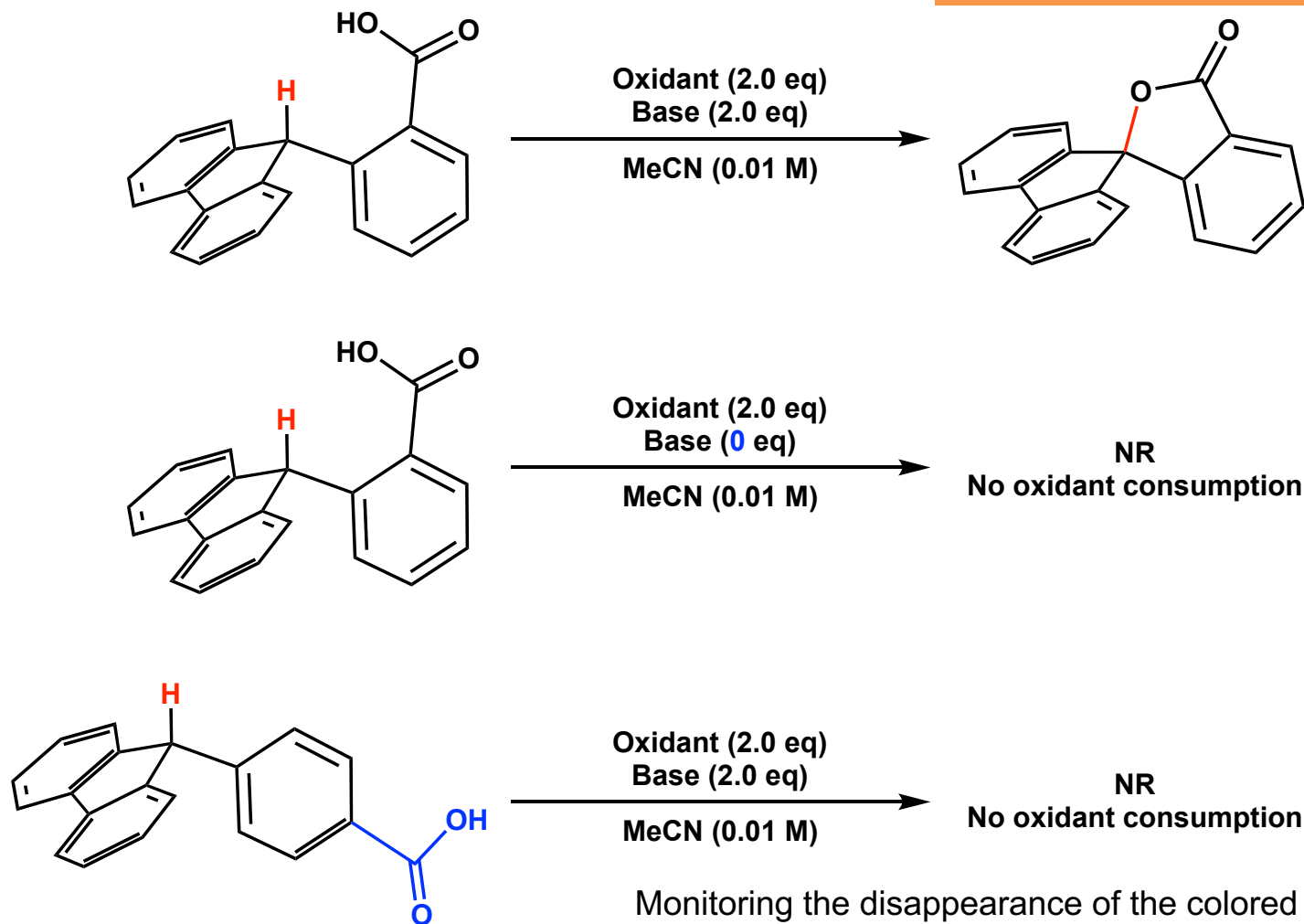
Lactone Formation in C-H activation via MS-CPET

Intramolecular C-H activation via MS-CPET



Comparison with Regioisomers

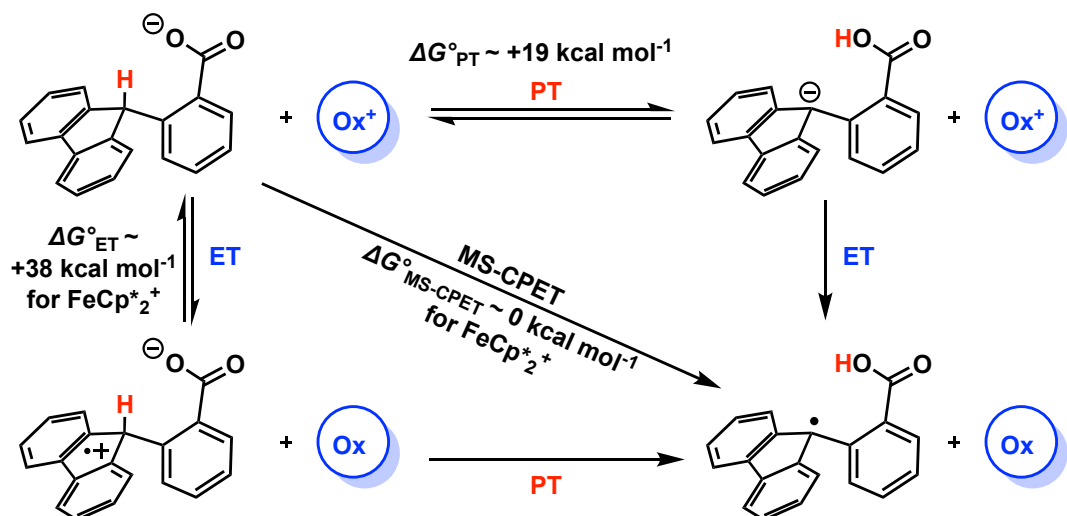
Intramolecular C-H activation via MS-CPET



Monitoring the disappearance of the colored oxidants
Markle, T. F.; Darcy, J. W.; Mayer, J. M., *Sci. Adv.* **2018**, *4*, eaat5776

The **presence** and **positioning** of the base are **crucial** for MS-CPET.

Stepwise reaction = (ET + PT) vs One-step reaction = MS-CPET



Evidence of progress in MS-CPET

- ① Reaction proceeds at an oxidant with $\Delta G^\circ_{\text{MS-CPET}}$ near 0, and no further decrease in oxidizing power will prevent the reaction from progressing.



Proceeding via MS-CPET

- ② $k_{\text{MS-CPET}}$ is dependent on

the strength of oxidant = E_{ox}

&

H/D substitution



ET and PT occurring in the rate-limiting step.

entry	Oxidant* ¹	E_{ox} (V) * ²	$k_{\text{MS-CPET}}$ ($\text{M}^{-1} \text{s}^{-1}$)	KIE ($k_{\text{H}}/k_{\text{D}}$)
1	$\text{N}(\text{Ar}_{\text{Br}})_3^{*+}$	0.67	7.2×10^5	~ 4.5
2	$\text{N}(\text{Ar}_{\text{OMe}})(\text{Ar}_{\text{Br}})_2^{*+}$	0.48	5.4×10^4	—
3	$\text{N}(\text{Ar}_{\text{OMe}})_2(\text{Ar}_{\text{Br}})^{*+}$	0.32	1.9×10^4	2.4
4	$\text{N}(\text{Ar}_{\text{OMe}})_3^{*+}$	0.16	9.5×10^3	3.7
5	FeCp_2^+	0.00	1.9×10^3	—
6	FeCp^*Cp^+	-0.27	3.8×10^2	1.6
7	FeCp_2^{*+}	-0.48	2.3×10^1	—
8	CoCp_2^+	-1.33	NR	n/a

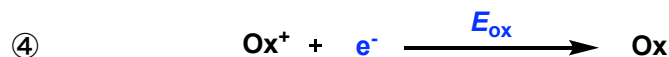
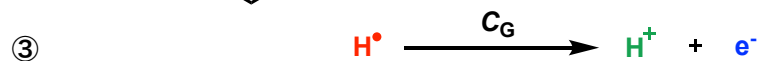
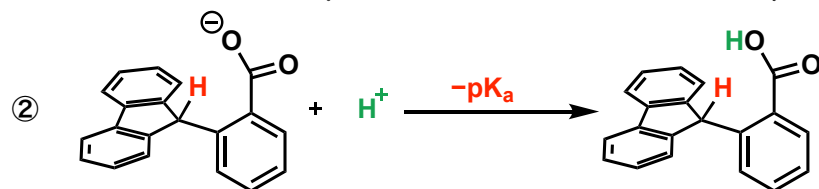
*¹ $\text{Ar}_X = p\text{-C}_6\text{H}_4\text{-X}$

*² $E_{1/2} = \text{versus FeCp}_2^{+/0}$ in MeCN

Stepwise reaction = (ET + PT) vs One-step reaction = MS-CPET

③ The value of $\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ = \Delta\ln(k_2) / \Delta\ln(K_{\text{eq}})$

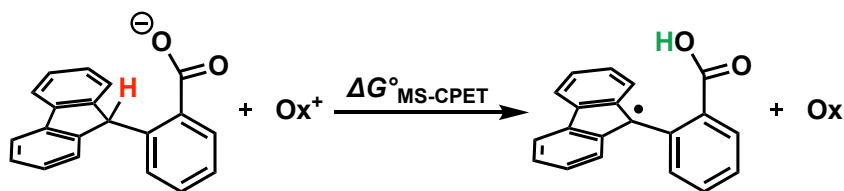
Determining K_{eq} { HAT reaction \rightarrow the difference in BDEs
MS-CPET \rightarrow Combination of acid-base and oxidation reactions



$$\Delta G^\circ_{\text{MS-CPET}} = \text{BDE}_{\text{C-H}} - 1.37\text{pK}_a - 23.06E_{\text{ox}} - C_G$$

$$\Delta\log(K_{\text{eq}}) = -\Delta G^\circ_{\text{MS-CPET}} / 2.303RT$$

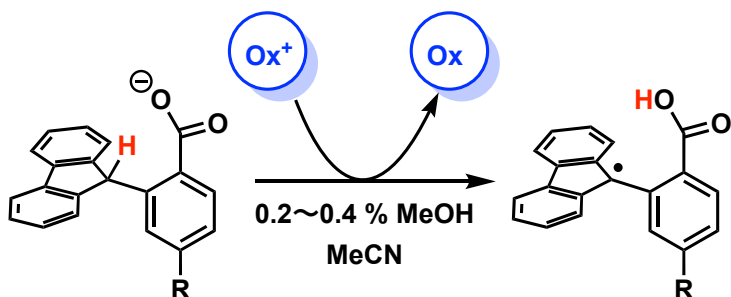
$$\Delta\log(k_{\text{MS-CPET}}) = \alpha\Delta\log(K_{\text{eq}})$$



Markle, T. F.; Darcy, J. W.; Mayer, J. M., *Sci. Adv.* **2018**, 4, eaat5776

Julia W. Darcy, Scott S. Kolmar, and James M. Mayer, *J. Am. Chem. Soc.* **2019**, 141, 10777–10787

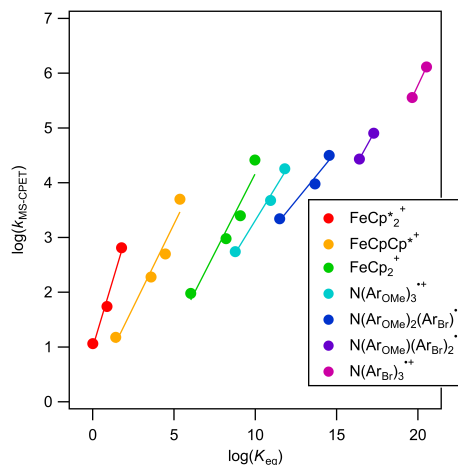
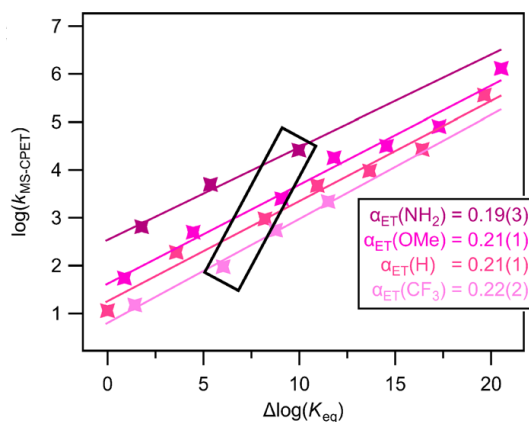
③ The value of $\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ = \ln(k_2) / \ln(K_{\text{eq}})$



entry	R	pKa(CO ₂ H) expt	Δ pKa(CO ₂ H) expt	Δ BDE _{C-H} (CO ₂ ⁻) (kcal mol ⁻¹)
1	NH ₂	22.0	+0.8	-0.06
2	OMe	21.5	+0.3	0.22
3	H	21.2	0	0
4	CF ₃	20.3	-0.9	0.83

α_{ET} : Fixed substituents, **changing reduction potential**

Brønsted α : Fixed reduction potential, **changing substituents**



Oxidant	Brønsted α
N(ArBr) ₃ ⁺⁺	0.64
N(ArOMe)(ArBr) ₂ ⁺⁺	0.54
N(ArOMe) ₂ (ArBr) ⁺⁺	0.36 ± 0.07
N(ArOMe) ₃ ⁺⁺	0.48 ± 0.05
FeCp ₂ ⁺	0.58 ± 0.10
FeCp [*] Cp ⁺	0.61 ± 0.09
FeCp [*] ₂ ⁺	0.99 ± 0.12

- $\alpha_{\text{ET}} = 0.19 \sim 0.22$ \rightarrow **Not sensitive to changes in E_{ox}**
- Brønsted $\alpha =$ about 0.50 \rightarrow **Sensitive to changes in substituents**

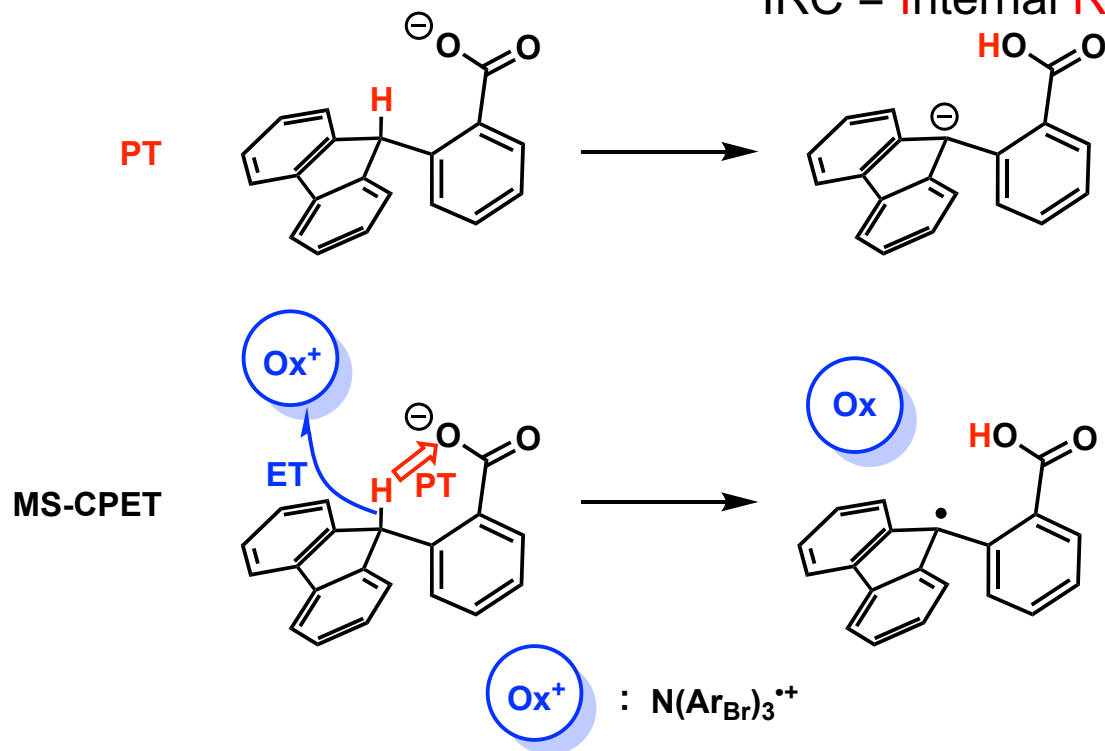
Changing substituents $\left\{ \begin{array}{l} \text{pK}_a \quad \leftarrow \text{large effect} \\ \text{BDE} \quad \leftarrow \text{small effect} \end{array} \right. \quad (\rightarrow \text{Appendix})$

DFT Calculated Potential Energy Surfaces

Intramolecular C-H activation via MS-CPET

Comparison of changes in IRC between PT and MS-CPET

IRC = Internal Response Coordinates



PT coordinate : the distance between the fluorenyl proton and carboxylate oxygen
the extent of ET (only MS-CPET) : the change on the nitrogen atom of the oxidant

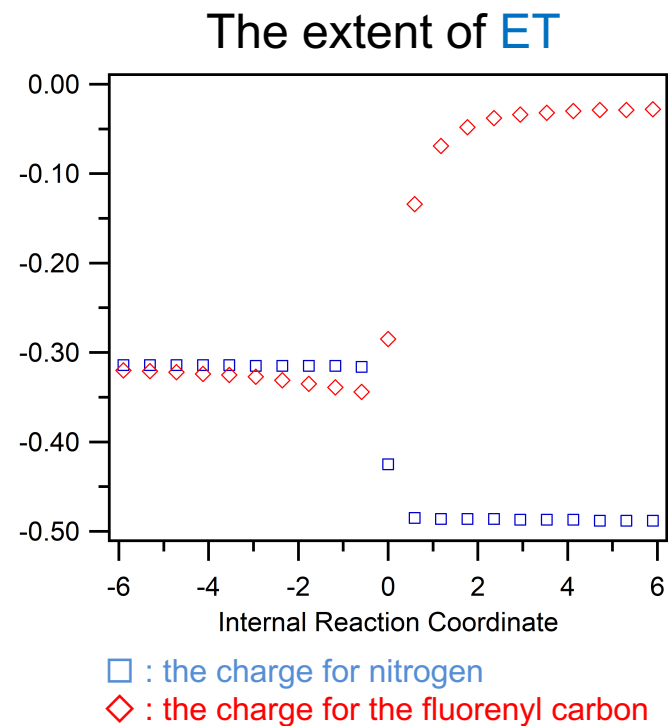
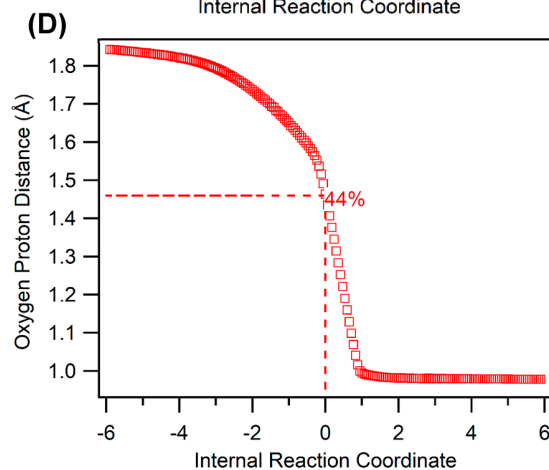
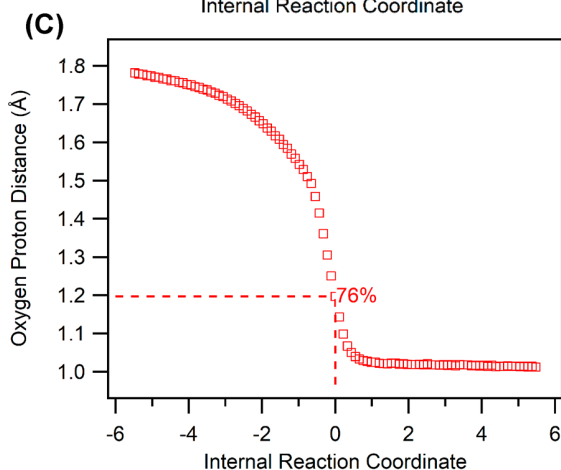
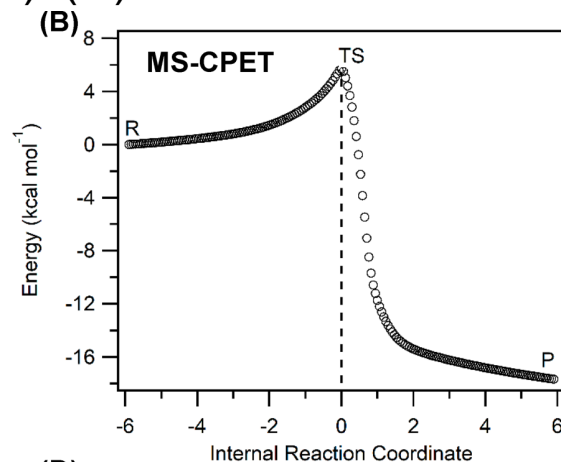
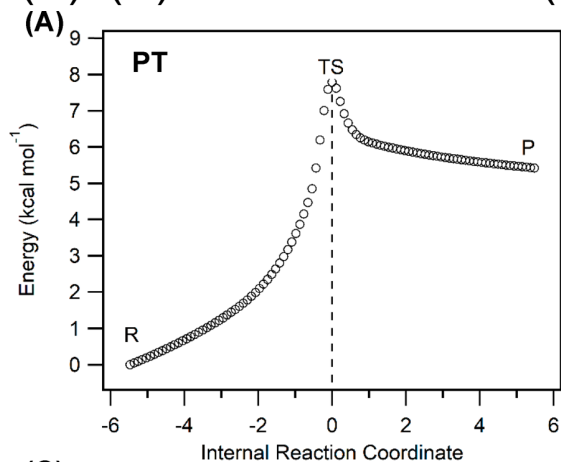
Julia W. Darcy, Scott S. Kolmar, and James M. Mayer, *J. Am. Chem. Soc.* **2019**, *141*, 10777–10787

DFT Calculated Potential Energy Surfaces

Intramolecular C-H activation via MS-CPET

(A) • (B) : IRC and TS

(C) • (D) : IRC and Distance of protons to oxygen



- “PT in MS-PCET” is slower than PT in TS.
- **PT precedes ET in MS-PCET.**
- **In MS-CPET, ET occurs at once in TS.**



The electron transfer "switch" is triggered by the transfer of a proton to a transition state.

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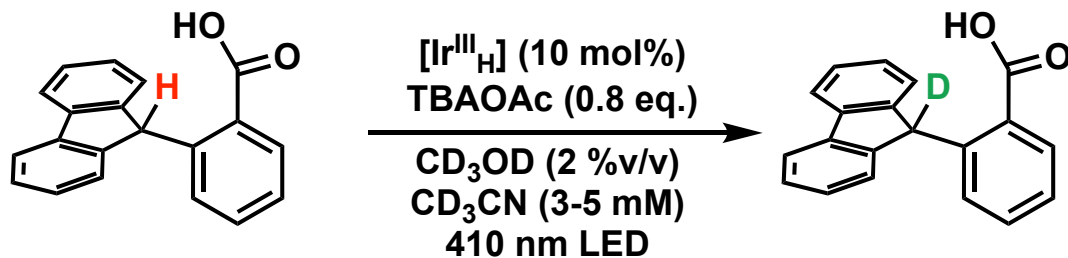
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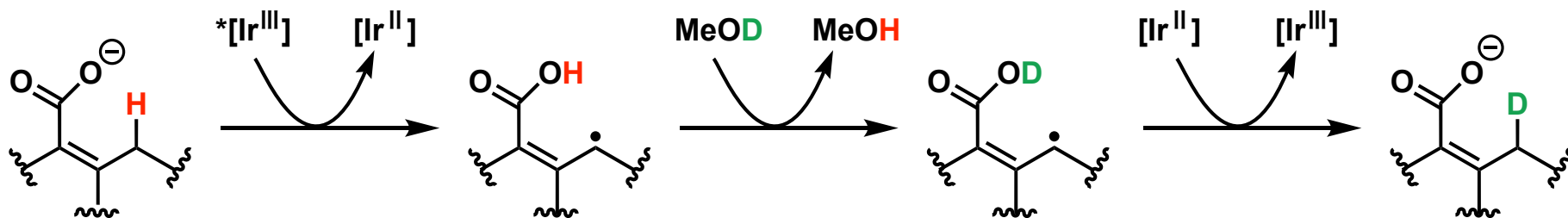
Markers of Iridium-Catalyzed C-H Activation

Intramolecular C-H activation with photocatalyst via MS-CPET

However, **the blue path (Net neutral conditions)** also occurs in the system.



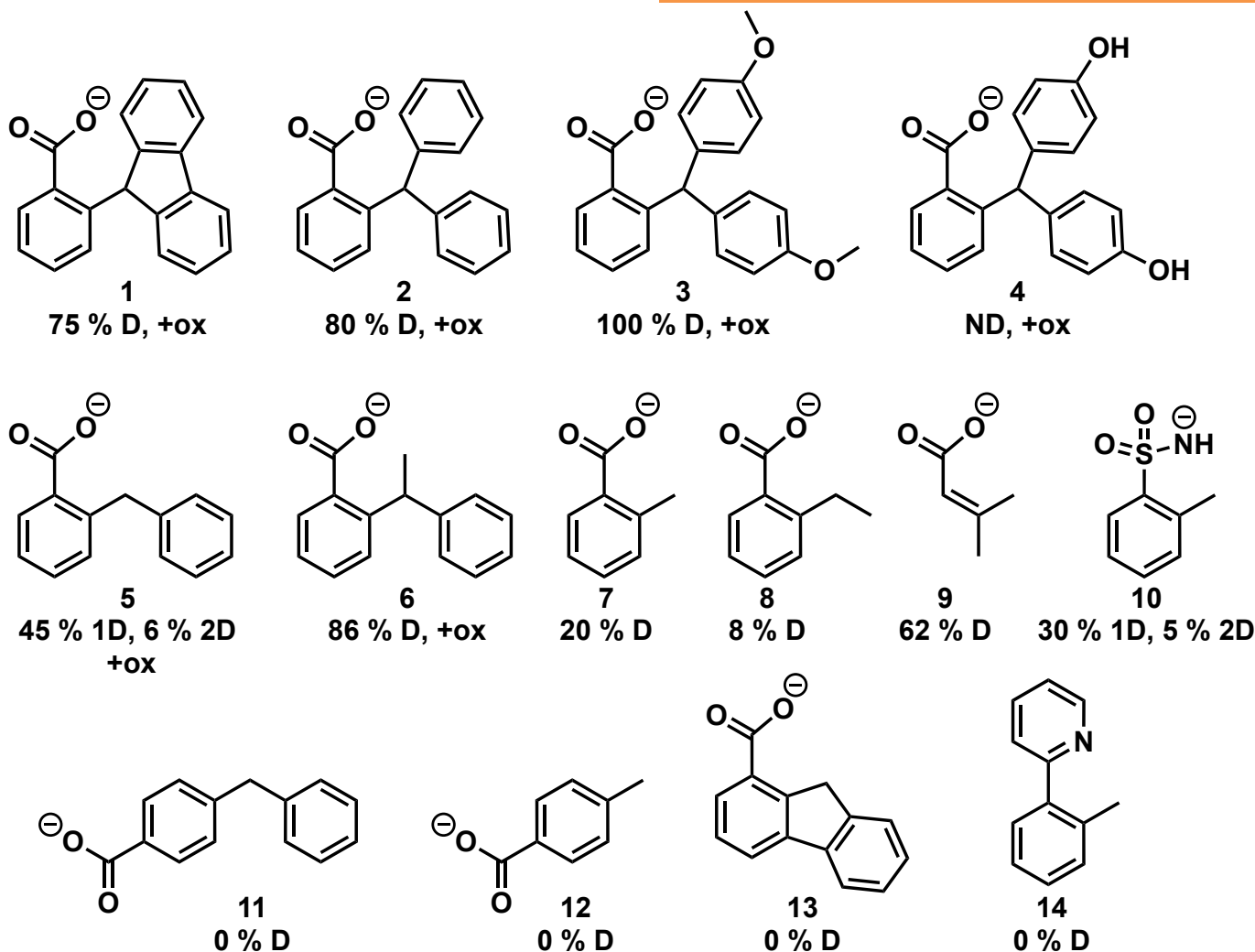
entry	[Ir ^{III} _H]	410 nm LED	1-d Substituent (%)
1	-	-	0
2	+	+	80



Deuterium incorporation can be used as **a marker for transient C-H activation** by *[Ir^{III}].

Substrate Scope of Iridium-Catalyzed C-H Activation

Intramolecular C-H activation with photocatalyst via MS-CPET



+ox : Lactone is also formed when catalyst and oxidant are added

Photoredox C-H activation occurs for a variety of benzylic substrates with internal carboxylates.

“ET + HAT” vs MS-CPET

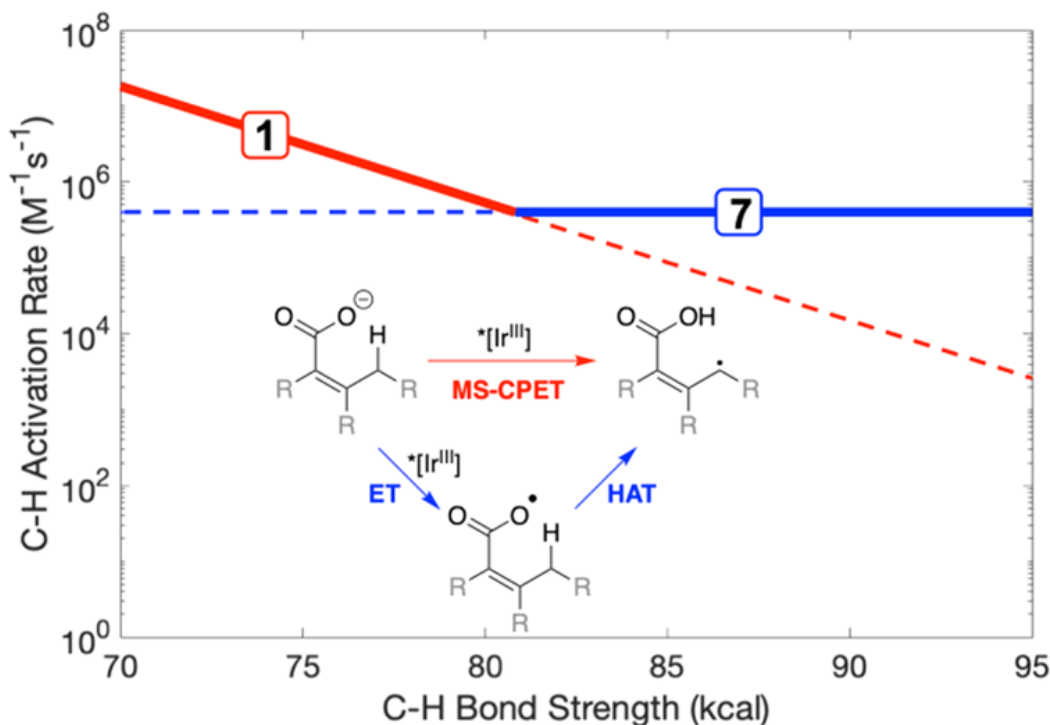
Intramolecular C-H activation with photocatalyst via MS-CPET

redox couple	$E_{1/2}$ (V)	references
$E_{1/2}$ ($\text{Ir}_H^{\text{IV}}/\text{Ir}_H^{\text{III}}$)	~1.38	estimated here ^a
$E_{1/2}$ ($\text{Ir}_{\text{tBu}}^{\text{IV}}/\text{Ir}_{\text{tBu}}^{\text{III}}$)	~1.35	estimated here ^a
$E_{1/2}$ ($^*\text{Ir}_H^{\text{III}}/\text{Ir}_H^{\text{II}}$)	~1.05	estimated here ^b
$E_{1/2}$ ($^*\text{Ir}_{\text{tBu}}^{\text{II}}/\text{Ir}_{\text{tBu}}^{\text{II}}$)	~0.95	estimated here ^b
$E_{1/2}$ ($\text{RCO}_2^\bullet/\text{RCO}_2^-$)	~0.9	3a, 4a, 19

$[\text{Ir}_R]$ can oxidize carboxylates **directly**.



Some molecules may proceed with **“ET+HAT”** instead of **MS-CPET**



MS-CPET

→ the C-H bond is **weak**
the proton acceptor is **basic** and **difficult to oxidize**.

“ET+HAT”

→ the C-H bond is **stronger**
the proton acceptor is **easy to oxidize**.

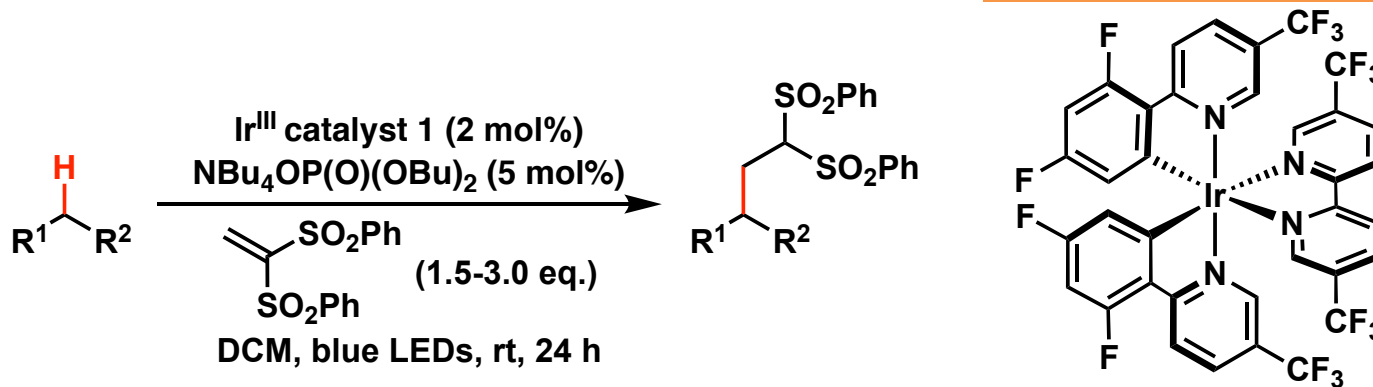
1. Introduction

- 1-1. PCET and CPET · Marcus Cross Relation
- 1-2. Example of *Canonical HAT, Separated CPET, Multi-Site CPET*
- 1-3. Importance of Hydrogen Bond in MS-CPET

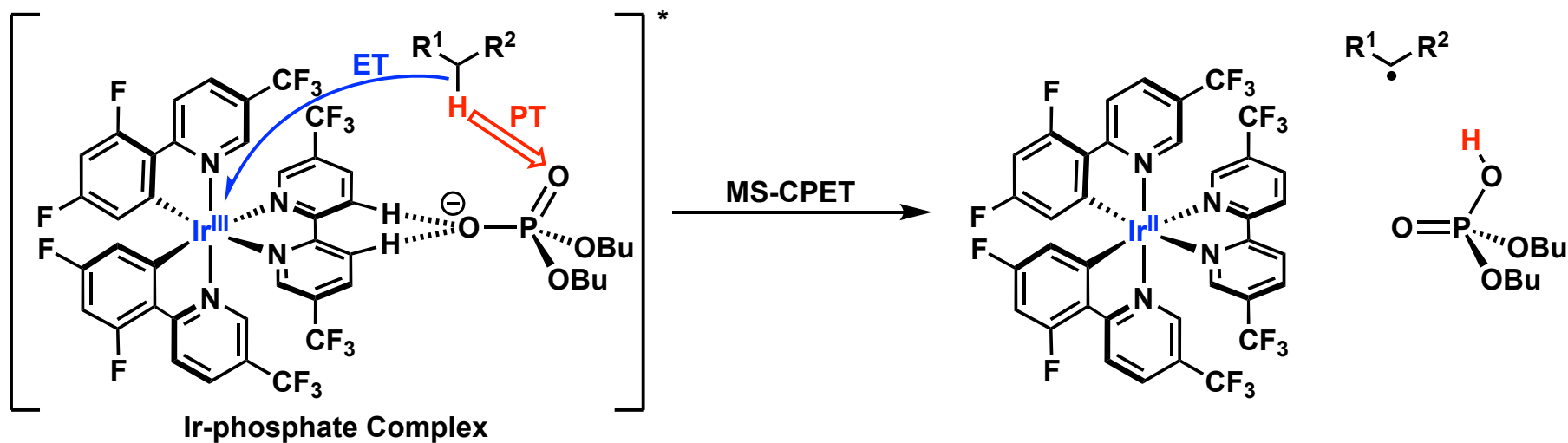
2. Contents

- 2-1. Intramolecular C-H activation via MS-CPET
- 2-2. Intramolecular C-H activation with photocatalyst via MS-CPET
- 2-3. Intermolecular C-H activation via MS-CPET**

3. Summary



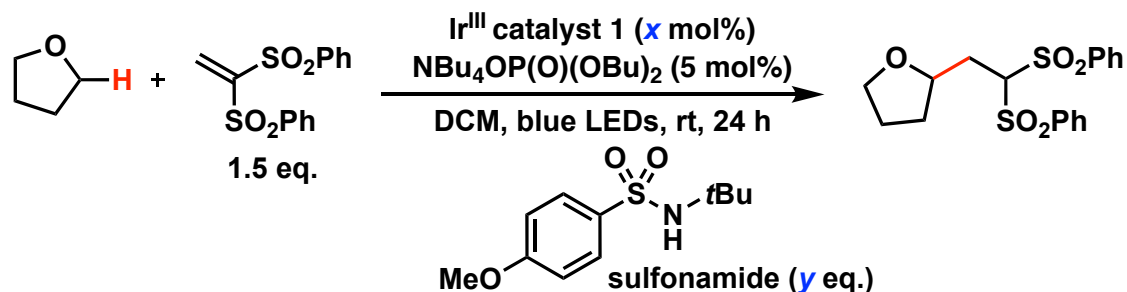
transition state



Carla M. Morton, *et al.*, *J. Am. Chem. Soc.* **2019**, *141*, 13253–13260

Intermolecular aliphatic C-H activation via **MS-CPET** was achieved.

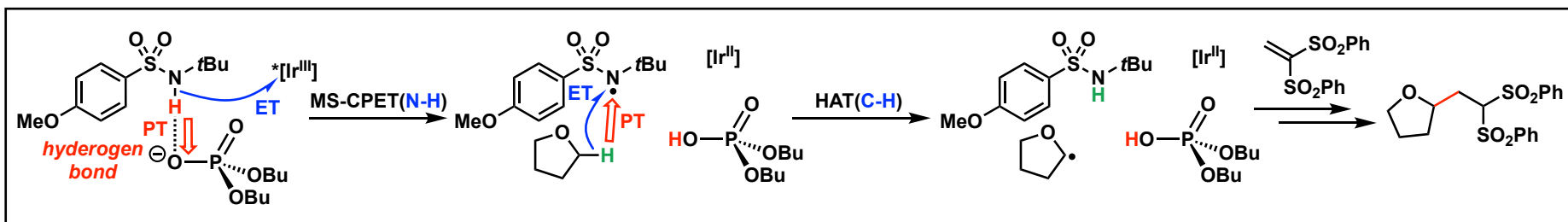
Development of Conditions for C-H Alkylation



Intermolecular C-H activation via MS-CPET

entry	<i>x</i> mol%	<i>y</i> eq.	yield (%)
1	5	1.0	75
2	5	0	66
3	2	0	92

The mechanism that the authors were designing



The authors' initial approach was to **generate heteroatom-centered radicals** via **MS-CPET**, followed by **HAT** of hydrocarbons.

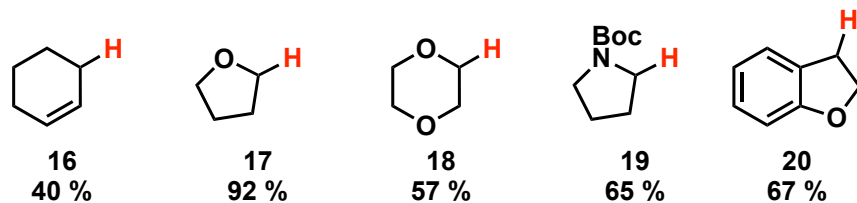
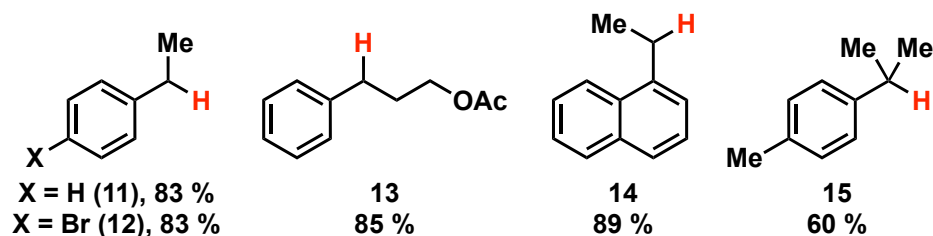
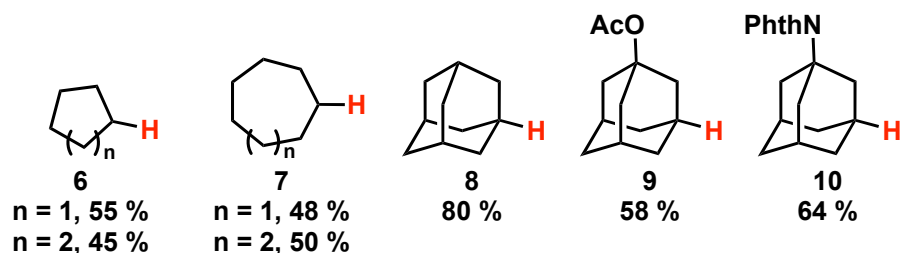
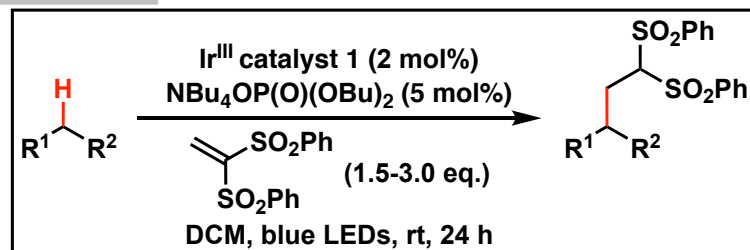


However, alkylation proceeded **without sulfonamide**, as represented in entry 3.

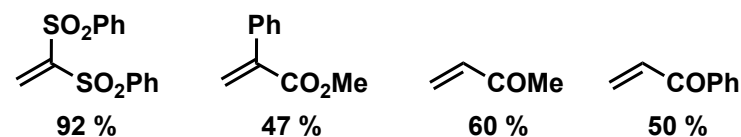
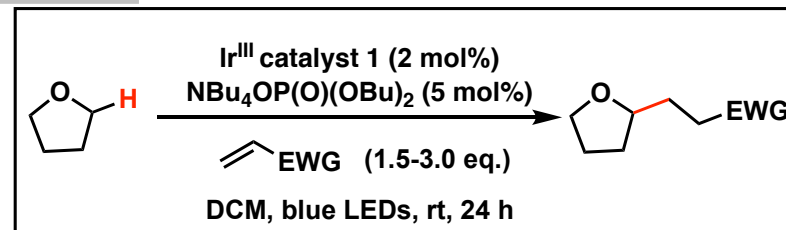
Substrate Scope / Alkene Scope

Intermolecular C-H activation via MS-CPET

Substrate Scope



Alkene Scope



Substrate Scope

Reaction proceeds selectively with weaker C-H bonds as seen in HAT.

Alkene Scope

Reactions with alternative alkenes also proceeded in moderate yields.

Mechanism Analysis (Formation of Complex)

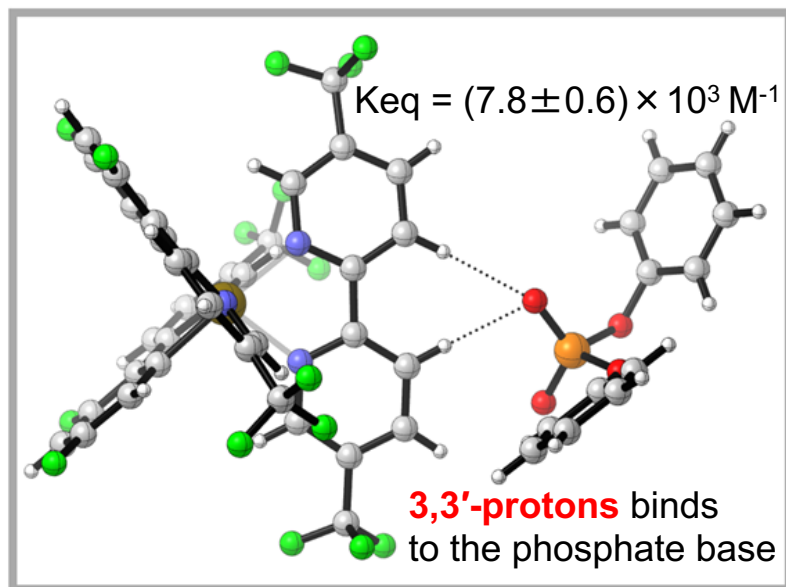
Intermolecular C-H activation via MS-CPET

① : The association of the **phosphate base** and **iridium photocatalyst**

Titration of the base into a solution containing the Ir^{III} catalyst

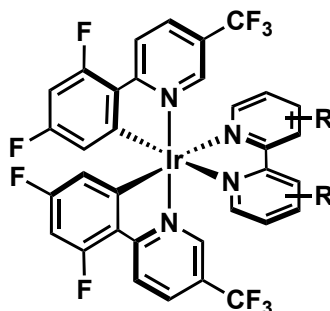
☞ Downfield shifts in the ¹H NMR spectrum of **all protons of the bipyridine ligand**

↳ Especially, **3,3'-protons**



The crystal structure of the Ir^{III} catalyst and diphenyl phosphate base

entry	Ir photocat.	E_{ox} (V vs. Fc+/Fc)	K_{eq} (M^{-1})	yield (%)
1	5,5'-d(CF ₃)bpy	1.30	$(7.8 \pm 0.6) \times 10^3$	73
2	bpy	0.94	$(1.0 \pm 0.1) \times 10^3$	37
3	4,4'-dtbbpy	0.83	$(3.4 \pm 0.2) \times 10^2$	45
4	3,3'-F-5,5'-d(CF ₃)bpy	1.59	–	–
5	3,3'-d(CO ₂ CH ₃)bpy	1.28	–	–



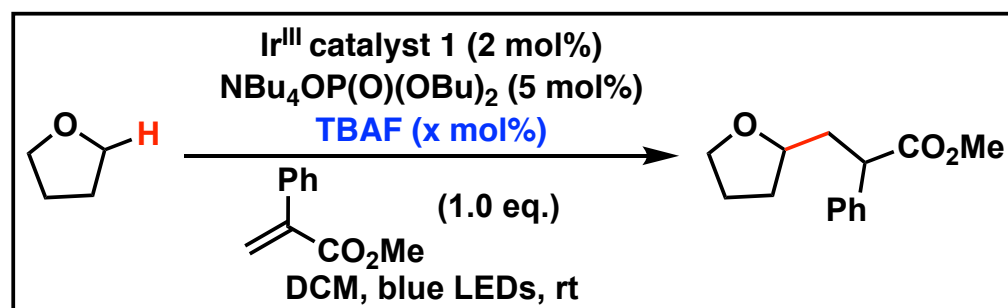
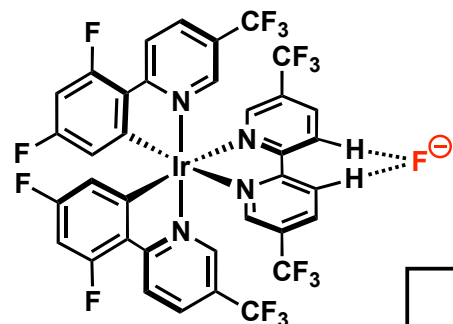
Loss of 3,3'-proton prevents binding to phosphate base

Carla M. Morton, *et al.*, *J. Am. Chem. Soc.* **2019**, *141*, 13253–13260

① : The association of the **phosphate base** and **iridium photocatalyst**

Experimentally, it was found that the K_{eq} is comparable to that of phosphate bases. $K_{eq} = (6.9 \pm 0.4) \times 10^3 \text{ M}^{-1}$

Competitive experiments confirm the need for complex.



0 mol% TBAF

Entry	Time (min)	[Product] (M)
1	0	0
2	30	0.00622
3	105	0.0412
4	180	0.0852
5	240	0.112
6	300	0.130

2.5 mol% TBAF

Entry	Time (min)	[Product] (M)
1	0	0
2	30	0.00187
3	105	0.0175
4	180	0.0377
5	240	0.0555
6	300	0.0684

5 mol% TBAF

Entry	Time (min)	[Product] (M)
1	0	0
2	30	0
3	105	0.00966
4	180	0.0218
5	240	0.0259
6	300	0.0296

8 mol% TBAF

Entry	Time (min)	[Product] (M)
1	0	0
2	30	0
3	105	0.00585
4	180	0.0177
5	240	0.0202
6	300	0.0230

Reaction efficiency was maintained when TBAF was added to the N-H PCET reaction.

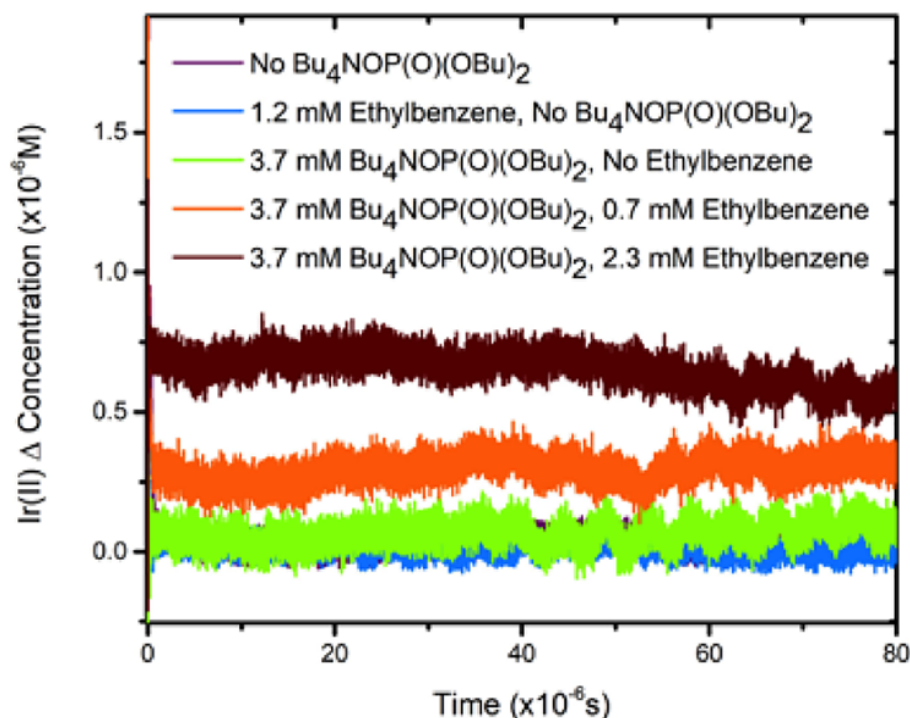
Complex is required for C-H activation.

② : ET also requires **substrate**

A signal for monoreduced Ir^{II} could be observed by transient absorption spectroscopy.



The formation of Ir^{II} can determine if electron transfer has occurred.



- Electron transfer is occurring only when **both substrate and phosphate base are present.**
- Electron transfer is **proportional to substrate concentration.**



MS-CPET proceeds only when all three elements are present.

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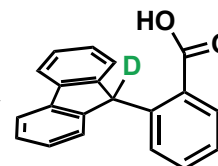
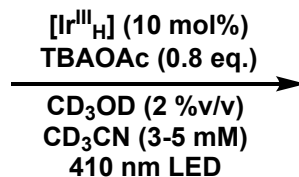
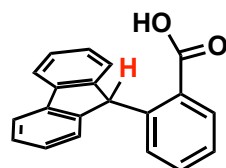
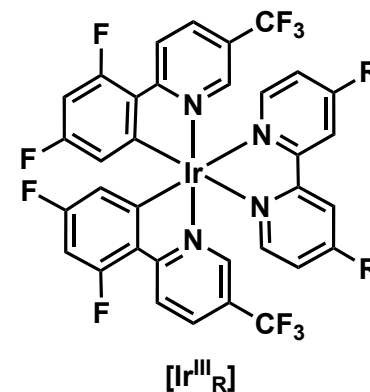
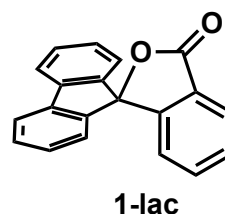
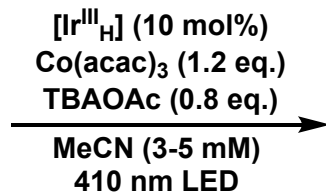
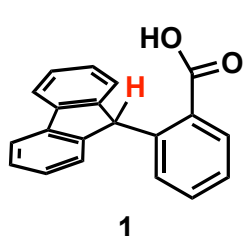
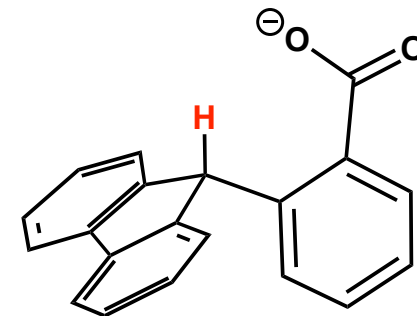
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- 2-3. Intermolecular C-H activation via MS-CPET

3. Summary

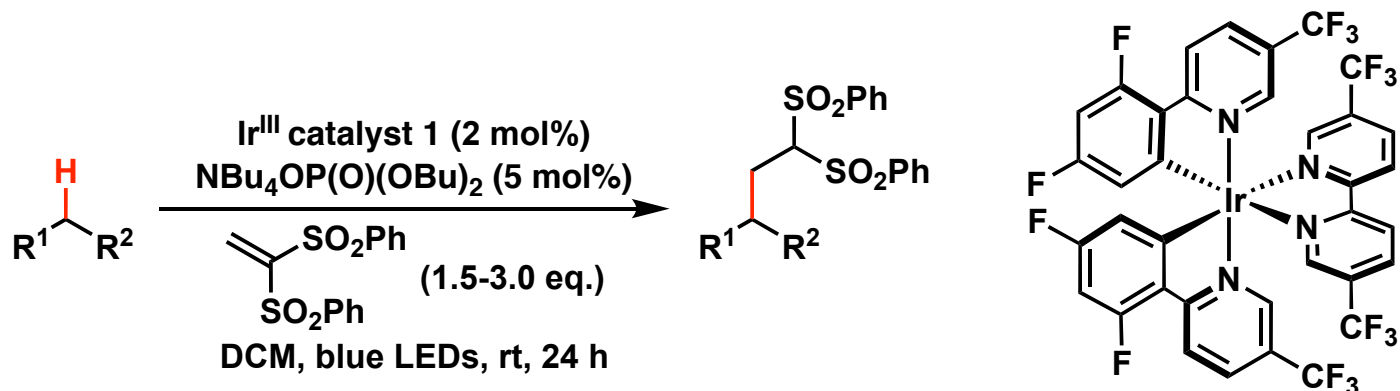
Summary

- By designing the molecule, intramolecular C-H activation proceeded via MS-CPET, which normally requires hydrogen bond.
- By using mechanism analysis experiments and computational chemistry, it was also confirmed that ET and PT proceed **concertedly**.
- The introduction of the photocatalyst facilitated the study of C-H activation via MS-CPET and expanded the substrate.

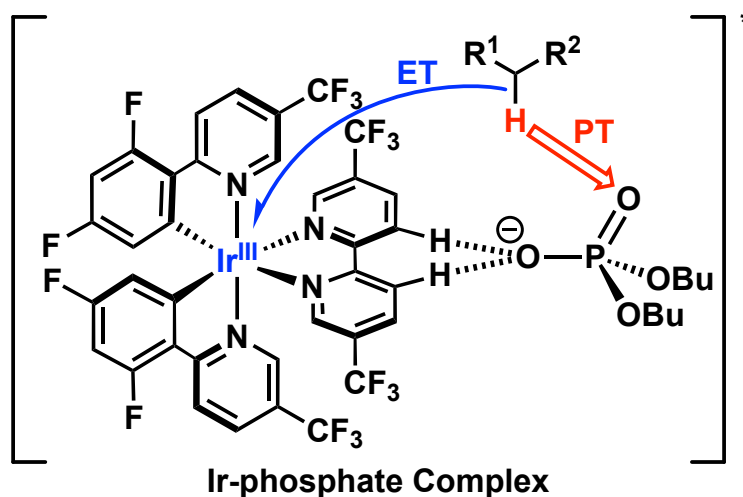


Summary

- A system for **C-H activation via intermolecular MS-CPET** has been discovered and can be applied to **many aliphatic C-H bond**.

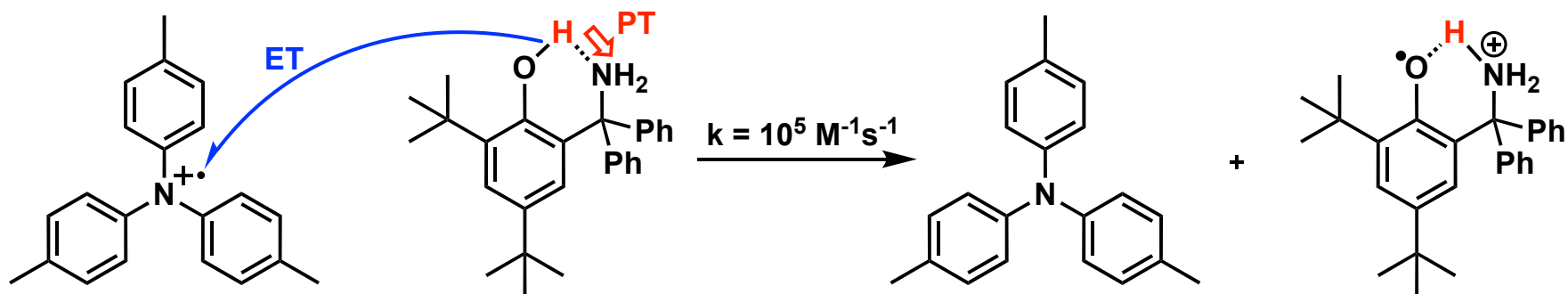


transition state



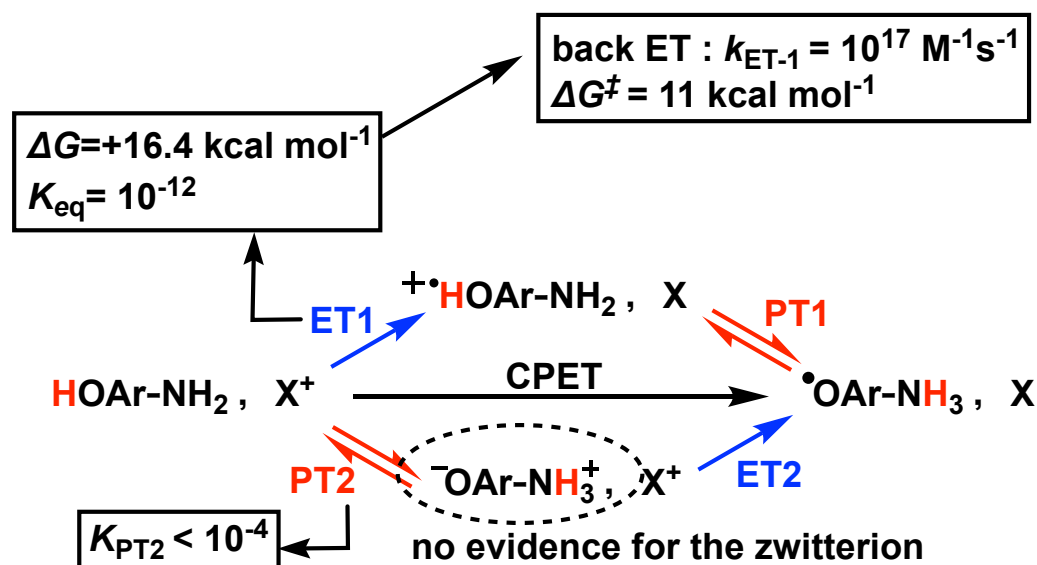
Appendix

Example of *Multi-Site CPET*



Mayer, J. M.; Rhile, I. J., *J. Am. Chem. Soc.* **2004**, 126, 12718-12719.

Evidence of progress in CPET mechanism ② : high-energy intermediates



Example of *Multi-Site CPET*

Three-Component MS-CPET Reactions

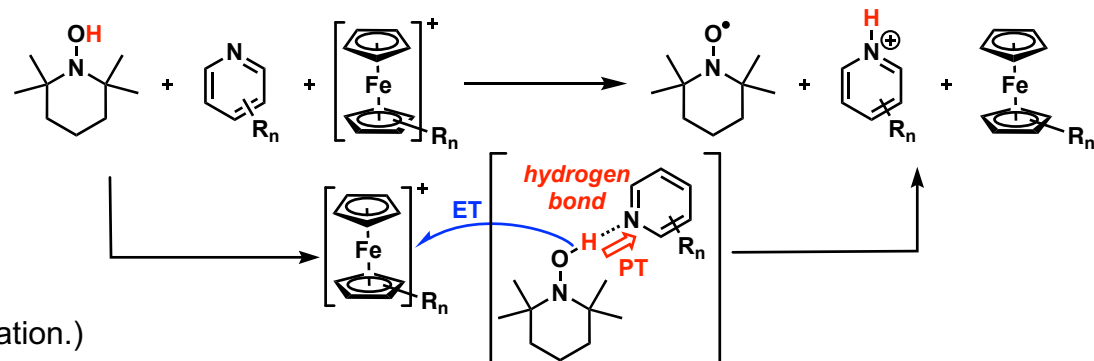
$$\Delta G^{\circ}_{\text{ET1}} = +16 \text{ kcal mol}^{-1}$$

$$\Delta G^{\circ}_{\text{PT1}} = +31 \text{ kcal mol}^{-1}$$

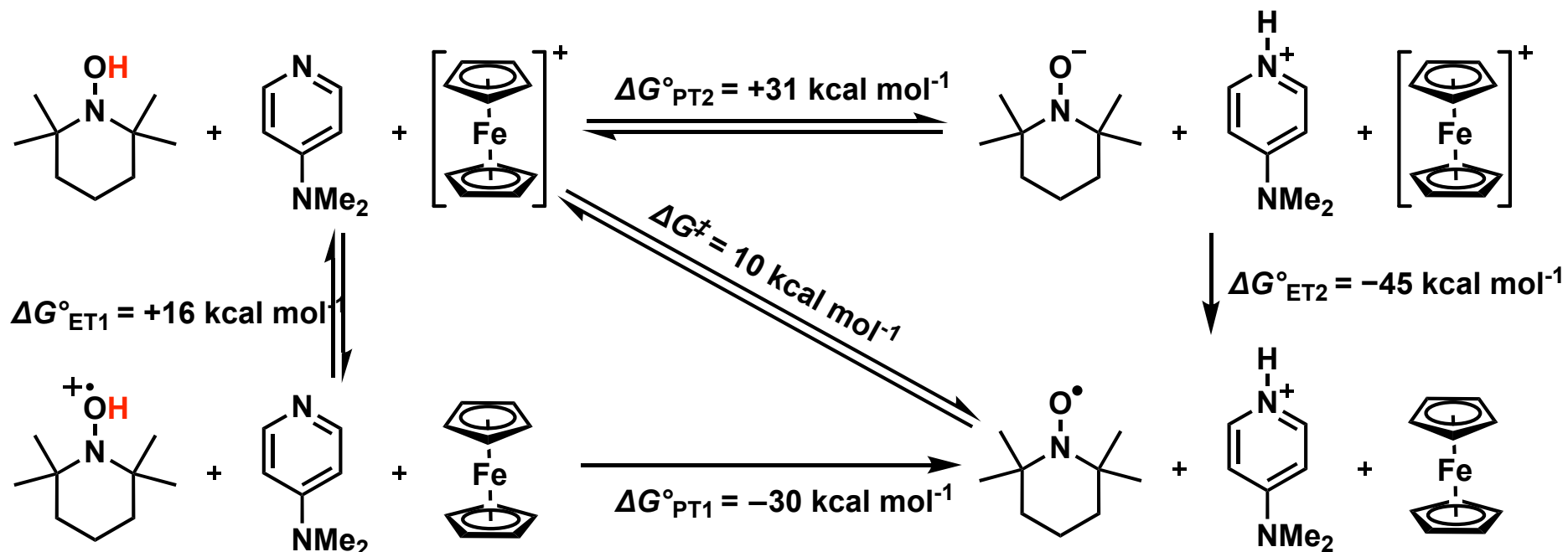
∇

$$\Delta G^{\ddagger} = 10 \text{ kcal mol}^{-1}$$

(ΔG^{\ddagger} is given from the measured k_2 and the Eyring equation.)



☞ The reaction is not via ET1, PT2.



Morris, W. D.; Mayer, J. M., *J. Am. Chem. Soc.* **2017**, *139*, 10312–10319.

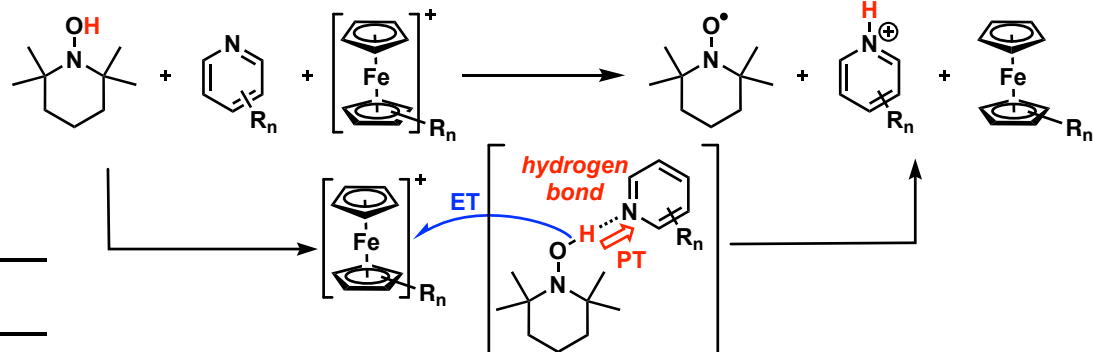
Example of *Multi-Site CPET*

Three-Component MS-CPET Reactions

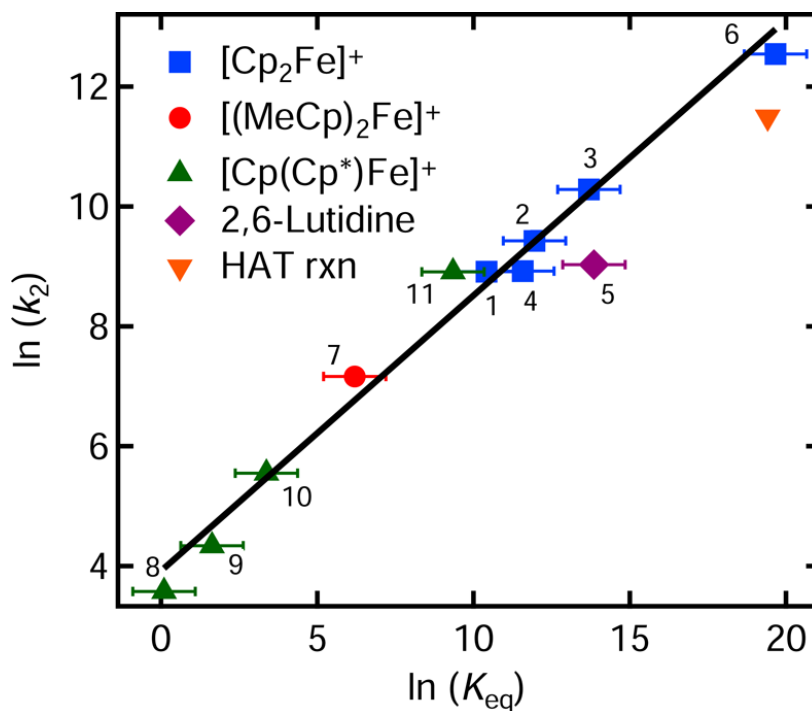
$$\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ$$

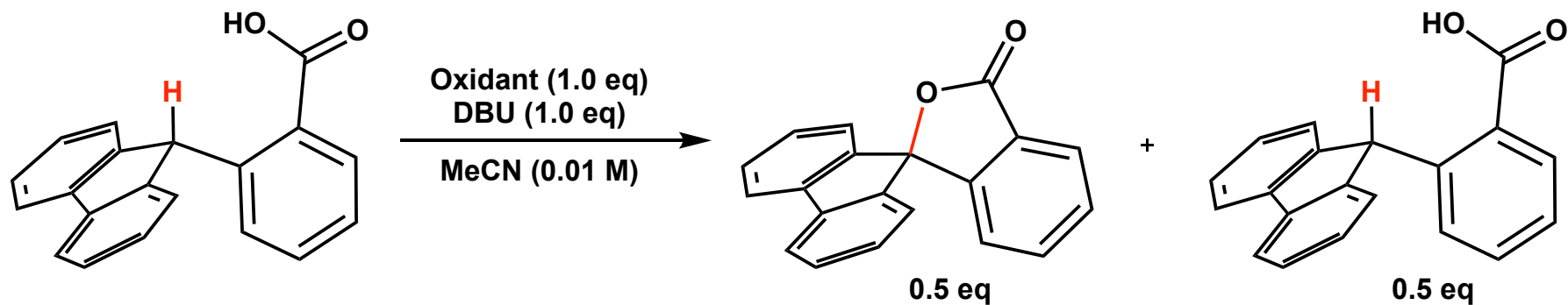
$$= \ln(k_2) / \ln(K_{\text{eq}}) = 0.46$$

entry	oxidant	base
1	[Cp ₂ Fe]BF ₄	py
2	[Cp ₂ Fe]BF ₄	4-Me-py
3	[Cp ₂ Fe]BF ₄	4-MeO-py
4	[Cp ₂ Fe]BF ₄	4-Me-py
5	[Cp ₂ Fe]BF ₄	2,6-lutidine
6	[Cp ₂ Fe]BF ₄	4-Me ₂ N-py
7	[(MeCp) ₂ Fe]PF ₆	py
8	[Cp(Cp*)Fe]PF ₆	py
9	[Cp(Cp*)Fe]PF ₆	4-Me-py
10	[Cp(Cp*)Fe]PF ₆	4-MeO-py
11	[Cp(Cp*)Fe]PF ₆	4-Me ₂ N-py



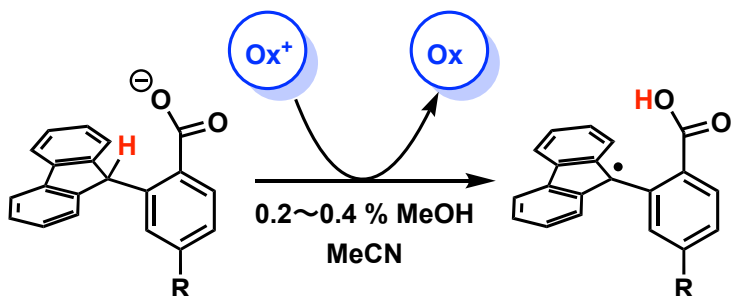
Appendix



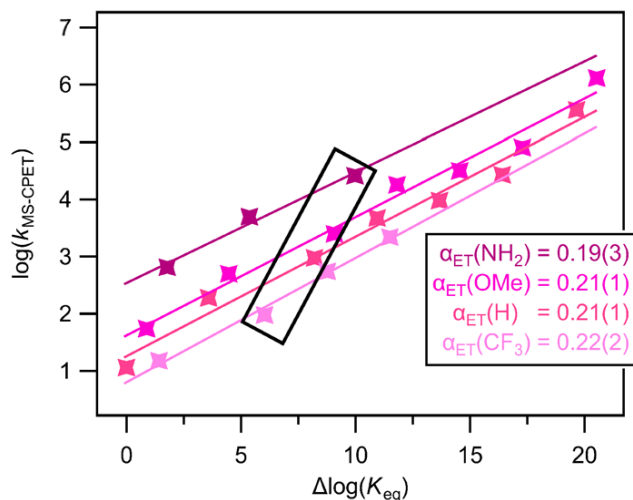


Markle, T. F.; Darcy, J. W.; Mayer, J. M., *Sci. Adv.* **2018**, *4*, eaat5776

③ The value of $\alpha = \Delta\Delta G^\ddagger / \Delta\Delta G^\circ = \ln(k_2) / \ln(K_{\text{eq}})$



entry	R	pKa(CO ₂ H) expt	Δ pKa(CO ₂ H) expt	Δ BDE _{C-H} (CO ₂ ⁻) (kcal mol ⁻¹)
1	NH ₂	22.0	+0.8	-0.06
2	OMe	21.5	+0.3	0.22
3	H	21.2	0	0
4	CF ₃	20.3	-0.9	0.83



①

Compare entry 1 and 4

$$\Delta\text{pK}_a = 1.7 \rightarrow \Delta G^\circ = 2.3 \text{ kcal mol}^{-1}$$

②

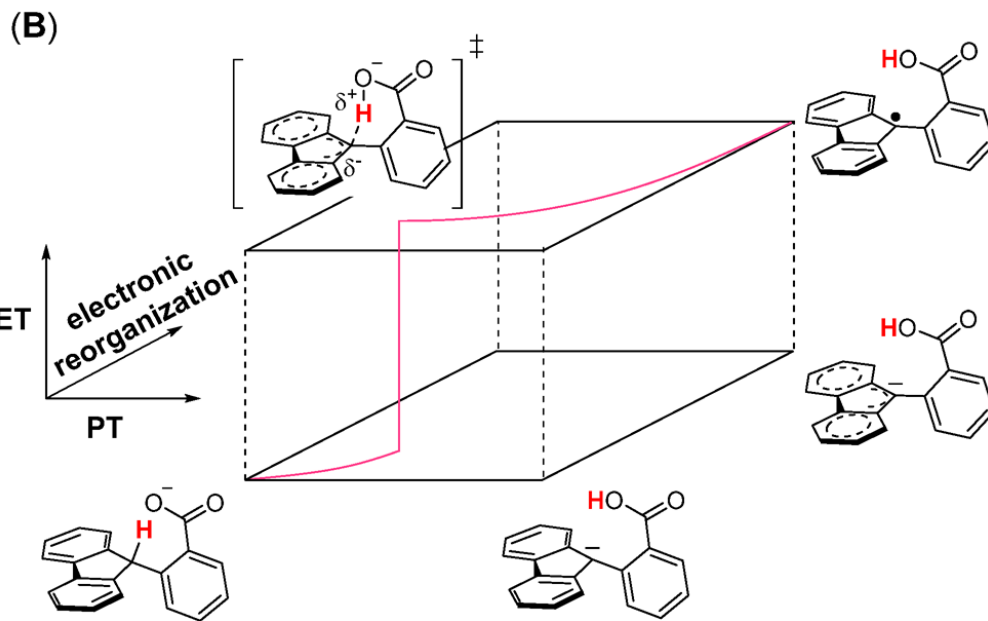
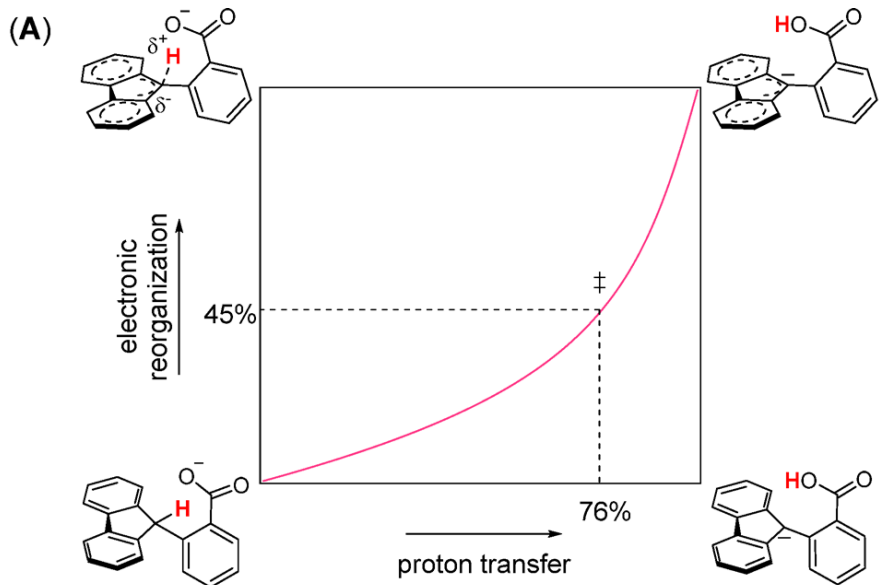
$$\Delta\text{BDE}_{\text{C-H}} = 0.9 \text{ kcal mol}^{-1}$$

☞ ΔpK_a has a greater impact.

- The R = OMe compound reacts **3 times faster** than the R = H compound.
- The R = OMe have **a slightly stronger C-H bond**.

☞ **The difference of BDE isn't the major contributor.**

Julia W. Darcy, Scott S. Kolmar, and James M. Mayer, *J. Am. Chem. Soc.* **2019**, *141*, 10777–10787
 James M. Mayer, et al., *J. Org. Chem.* **2022**, *87*, 2997–3006



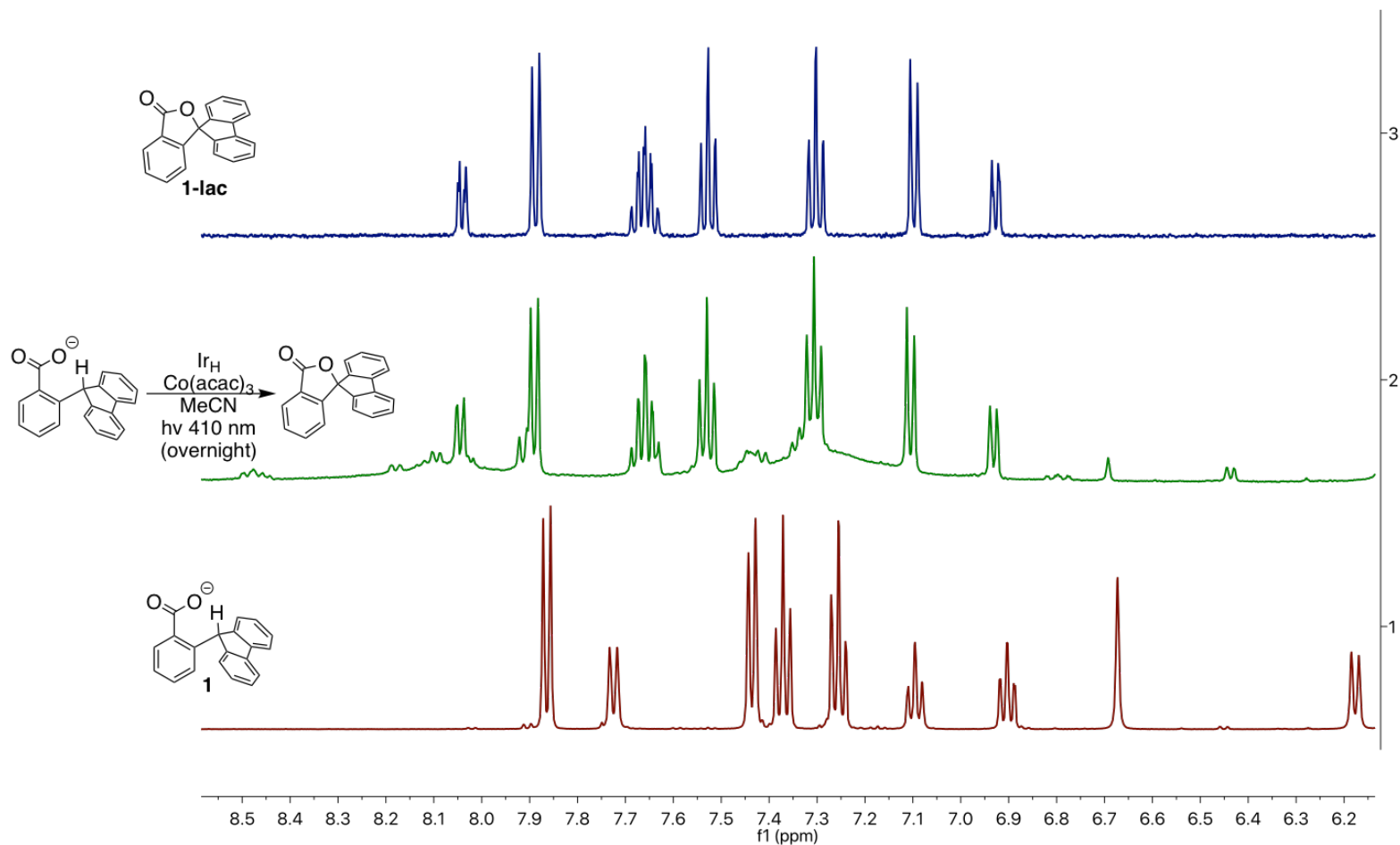
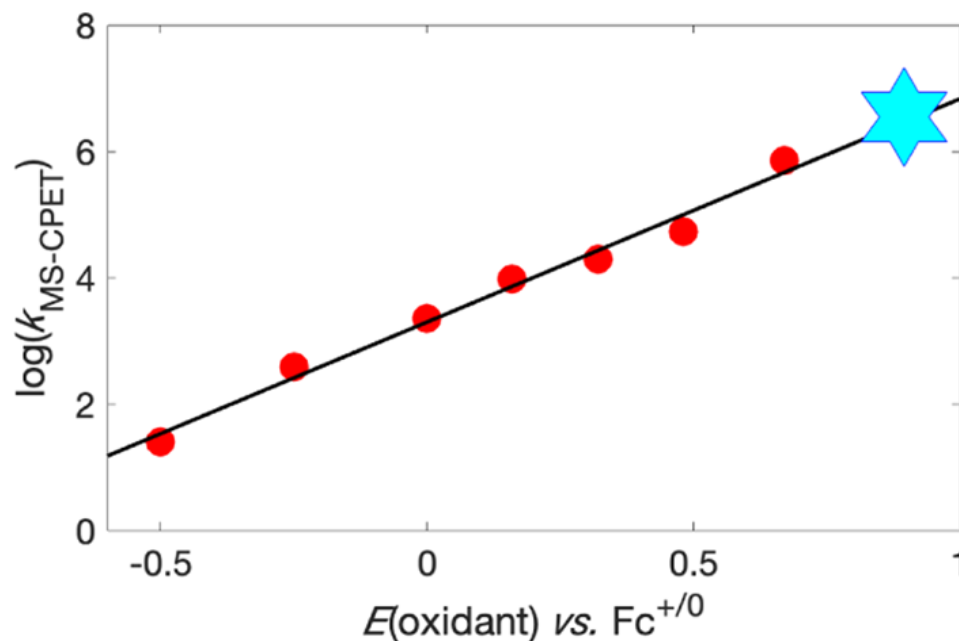


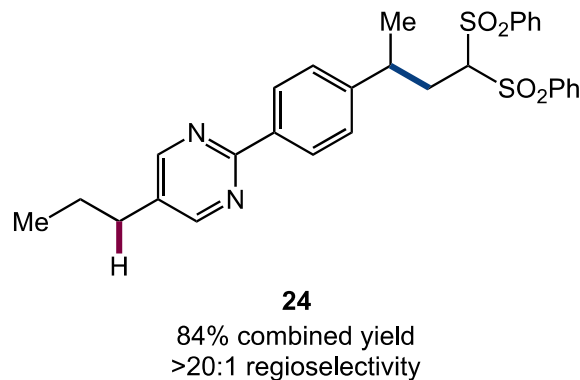
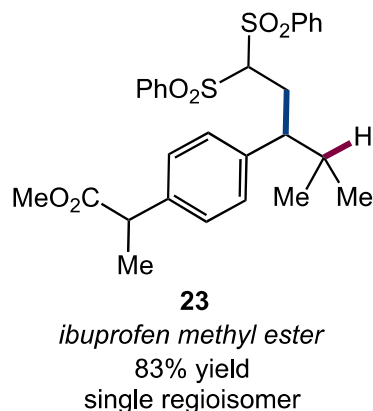
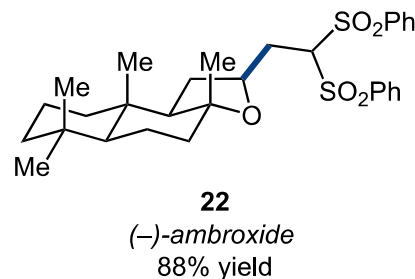
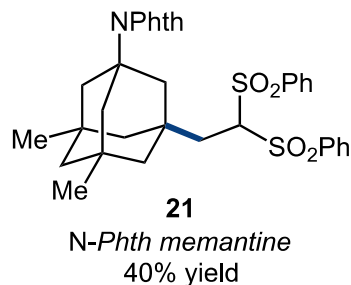
Figure S2. Red: Substrate **1** (deprotonated *in situ*). The singlet at 6.67 ppm corresponds to the fluorenyl proton. Green: Crude reaction mixture after overnight irradiation. Initial reaction mixture: 6 mM **1** with 0.8 eq TBAOAc, 7 mM $\text{Co}(\text{acac})_3$, 75 μM $[\text{Ir}_\text{H}]$, in d^3 -MeCN. Blue: **1-lac** generated by photoredox oxidation. The crude reaction mixture was filtered through a silica plug.



Maraia E. Ener, Julia W. Darcy, Fabian S. Menges, and James M. Mayer, *J. Org. Chem.* **2020**, *85*, 7175–7180

The fact that the photocatalytic system is also on the thermal MS-CPET correlation line suggests that iridium-catalyzed C-H activation also proceeds by MS-CPET.

Complex Substrates



The oxygen-centered radicals produced by phosphate oxidation showed low regioselectivity. Therefore, it is thought that a different mechanism is at work.

