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Mechanistic Aspects of Organic Proton-Coupled Electron Transfer

Reporter : Zhou Qiang

Supervisor : Prof. Lu

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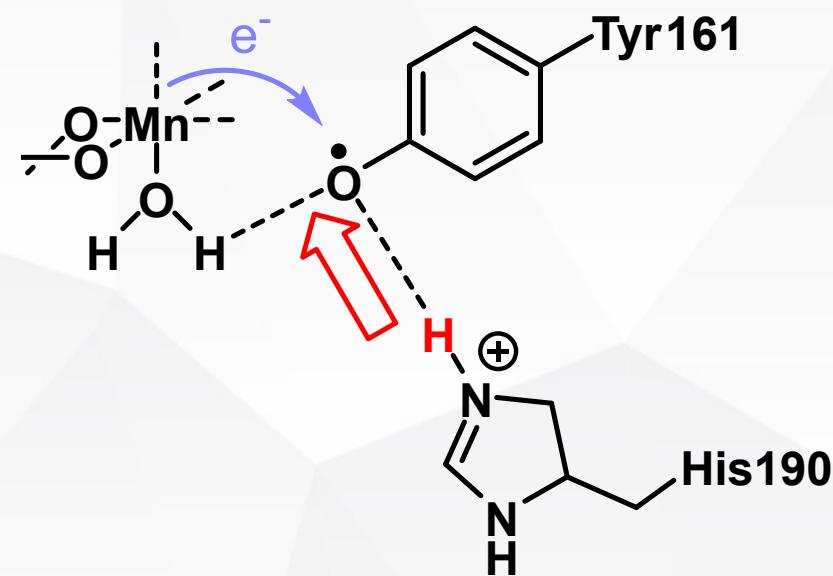
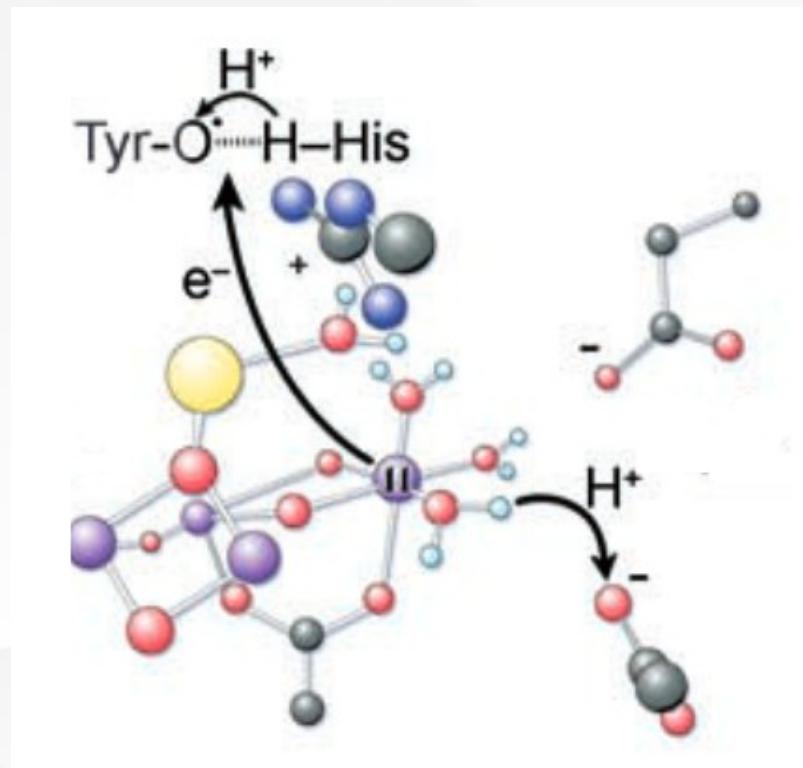
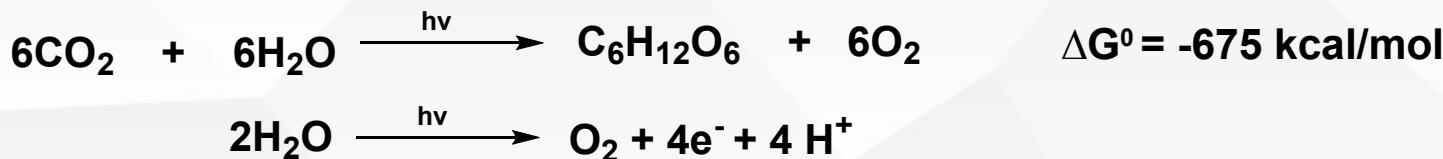
03

Summary

1

Theory of PCET

Proton-Coupled Electron Transfer (PCET)

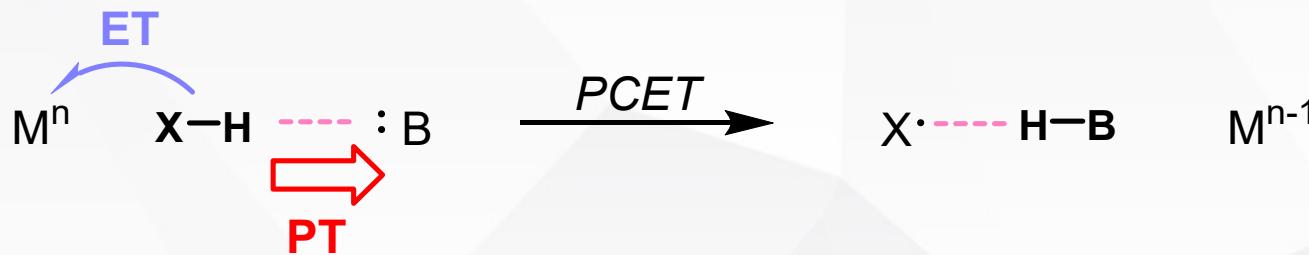


Hydrogen Atom Transfer (HAT)



*Concerted transfer of a proton and an electron from **one** H-X bond*

Proton-Coupled Electron Transfer



Concerted or stepwise transfer of the proton and electron

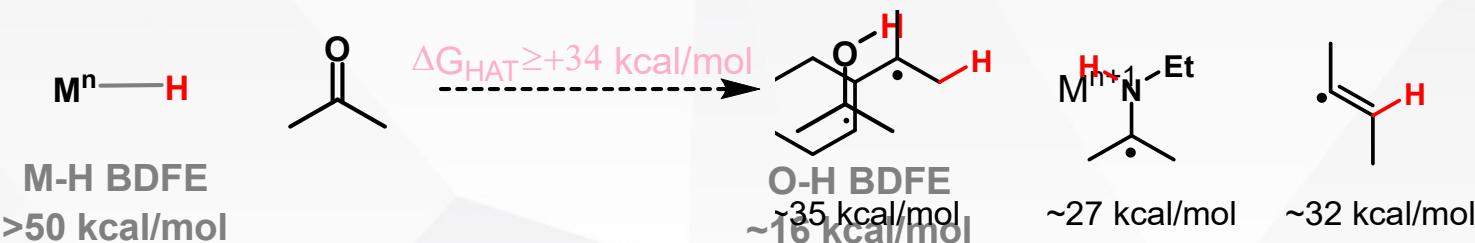
No need to originate from the same bond, or even the same molecule

Hydrogen Atom Transfer (HAT)

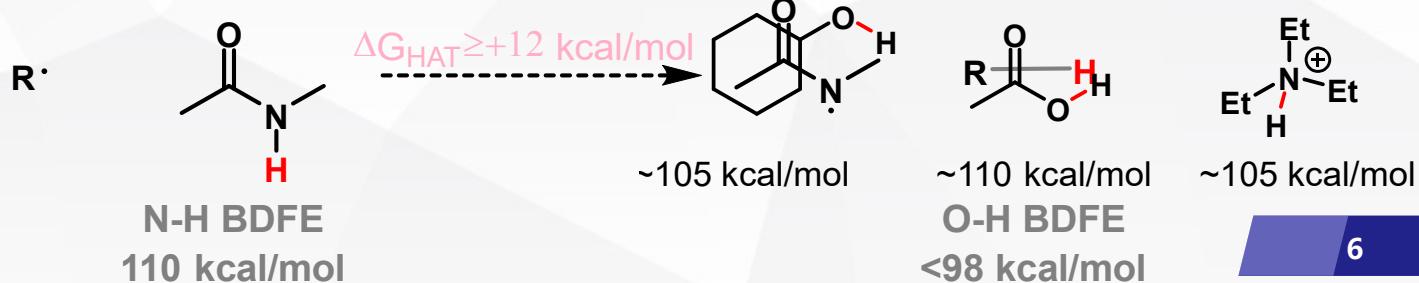


*Concerted transfer of a proton and an electron from **one** H-X bond*

Reductive HAT: M-H too strong to form weak E-H bond

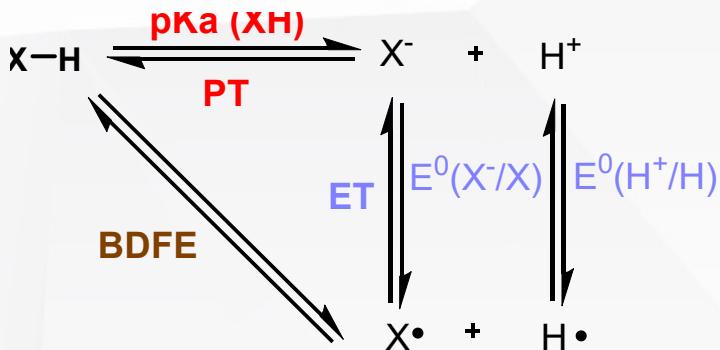


Oxidative HAT: R· too weak to break strong E-H bond



BDFE: Bond Dissociation Free Energy

Bond Dissociation



At 298 K

$$\begin{aligned}\Delta G_{PT}^0 &= -RT \ln(Ka) = -2.303RT \text{ pKa(X-H)} \\ &= -(1.37 \text{ kcal mol}^{-1}) \text{ pKa(X-H)}\end{aligned}$$

$$\begin{aligned}\Delta G_{ET}^0 &= -FE^0 = -(23.06 \text{ kcal mol}^{-1} \text{ V}^{-1})E^0 \\ &= -(23.06 \text{ kcal mol}^{-1} \text{ V}^{-1})(E^0(\text{X}/\text{X}) + E^0(\text{H}/\text{H}))\end{aligned}$$

$$\text{BDFE (kcal/mol)} = 1.37 \text{ pKa(X-H)} + 23.06 E^0(\text{X}/\text{X}) + 23.06 E^0(\text{H}/\text{H})$$



Adjustable
Contradictory



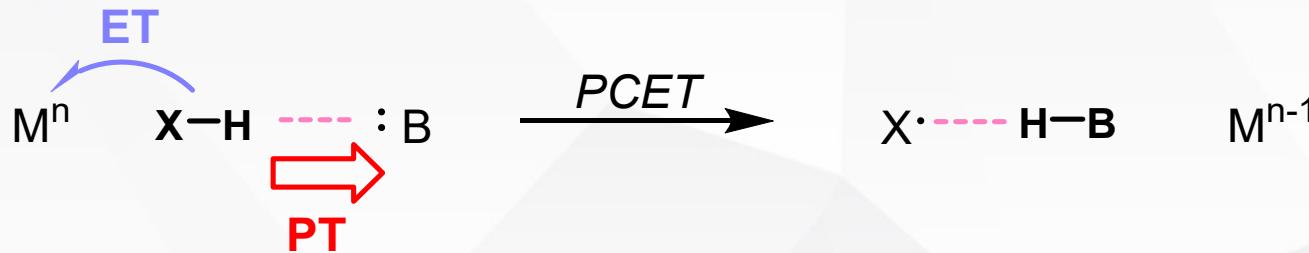
Constant

Hydrogen Atom Transfer (HAT)



*Concerted transfer of a proton and an electron from **one** H-X bond*

Proton-Coupled Electron Transfer

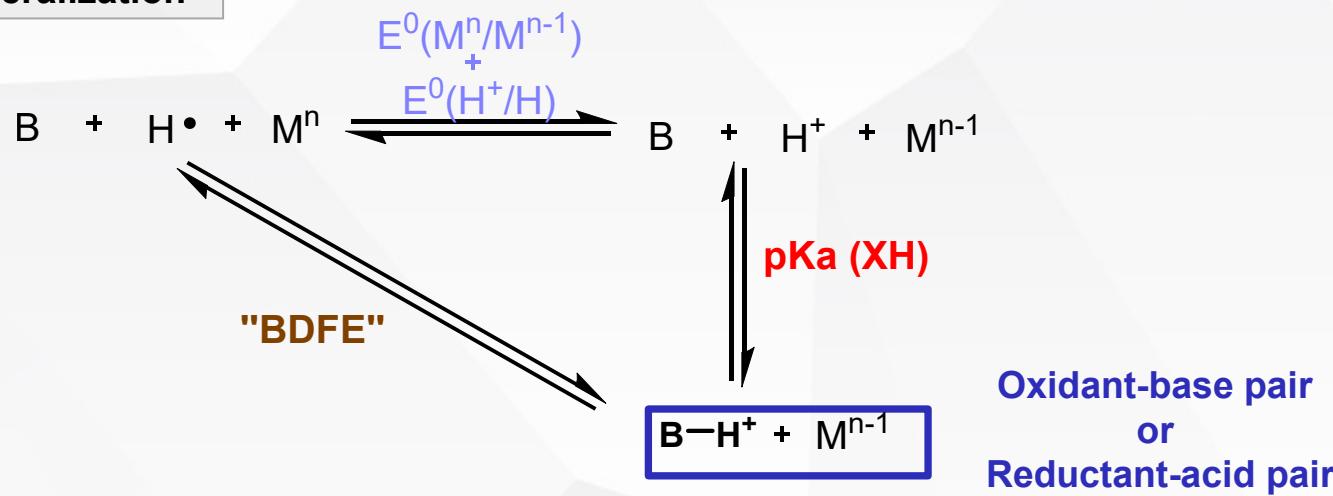


Concerted or stepwise transfer of the proton and electron

No need to originate from the same bond, or even the same molecule

BDFE: Bond Dissociation Free Energy

Bond Generalization



$$\text{"BDFE"} \text{ (kcal/mol)} = 1.37\text{pKa}(B-H^+) + 23.06 E^0(M^{n-1}/M^n) + 23.06E^0(H^0/H)$$



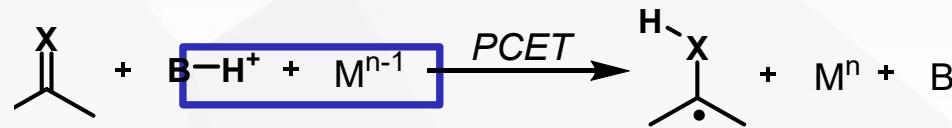
Adjustable
Unrelated

Proton-Coupled Electron Transfer

Oxidative Process



Reductive Process



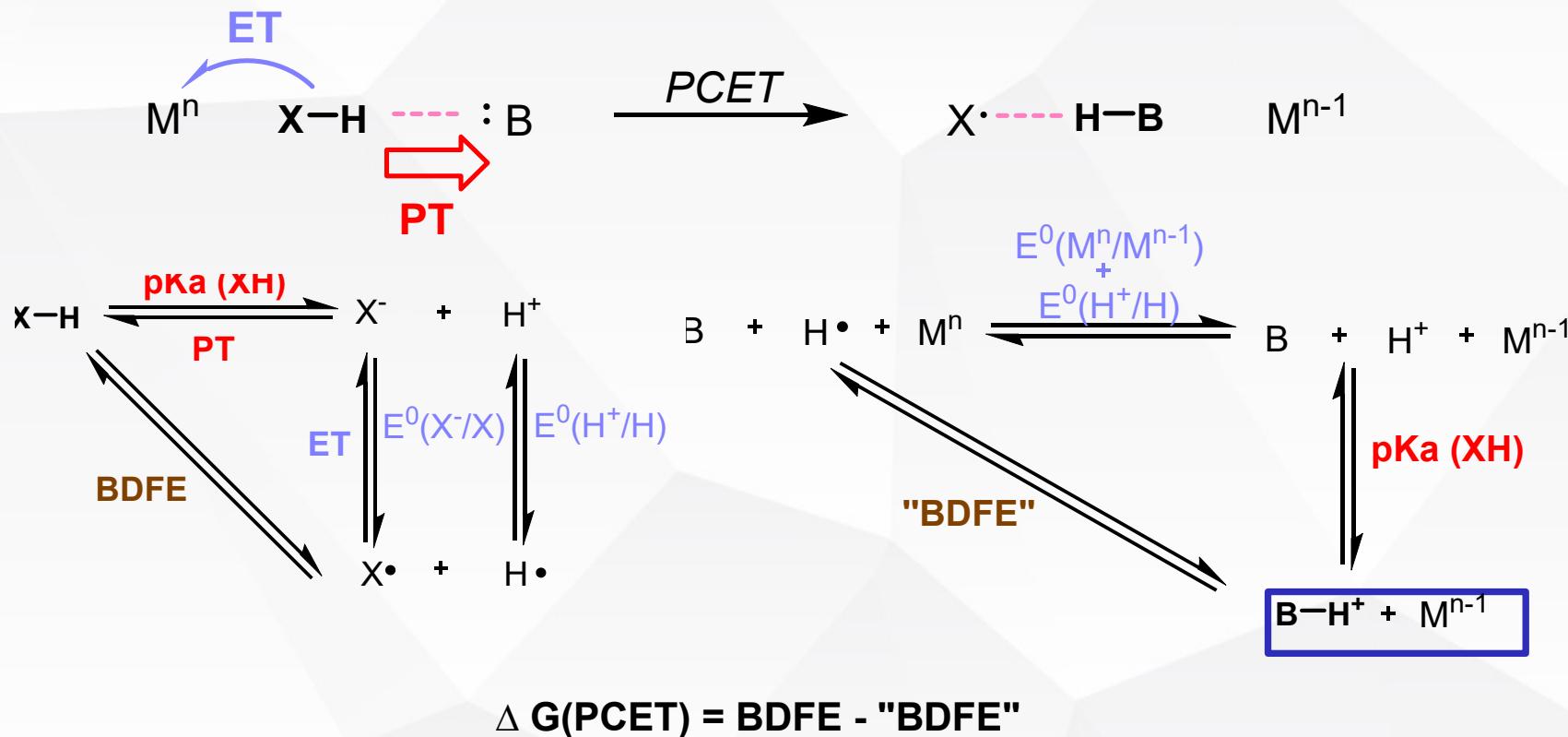
Hydrogen Atom Acceptor Pairs

Oxidant	Base	E^0 (V)	pKa	'BDFE'
Fe ^{III} (bpy) ₃	pyridine	0.70	12.5	87
*Ru ^{II} (bpy) ₃	acetate	0.39	23.5	96
*Ru ^{II} (bpz) ₃	lutidine	1.07	14.1	100
*Ir ^{III} (dF(CF ₃)ppy) ₂ (bpy)	DMAP	1.0	18	103

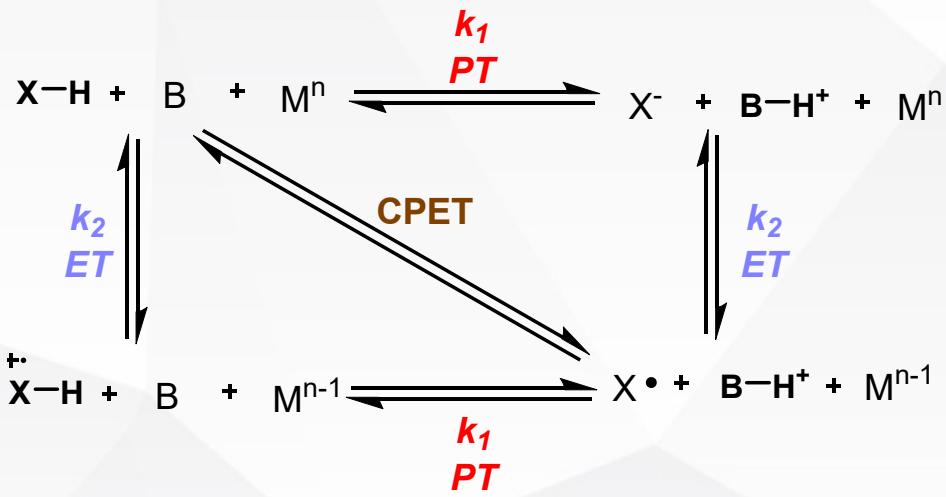
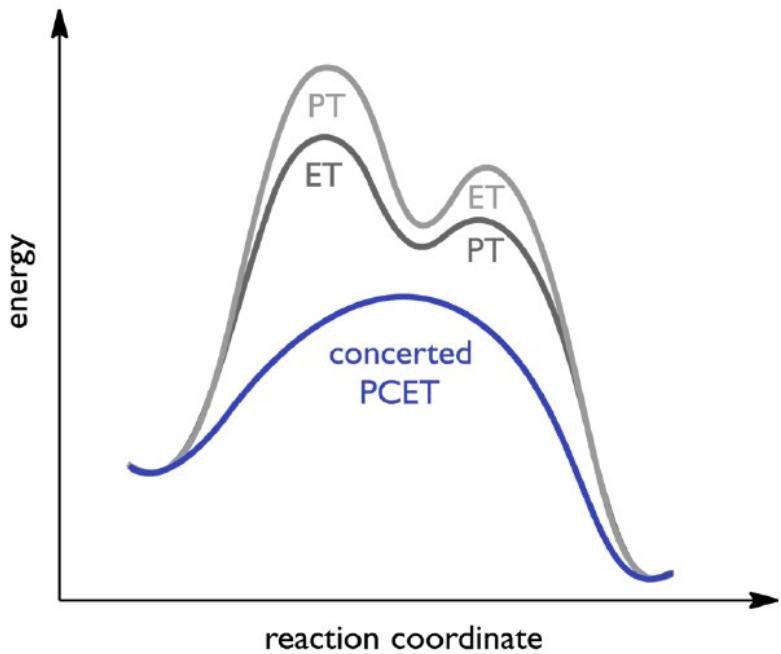
Hydrogen Atom Donor Pairs

Reductant	Acid	E^0 (V)	pKa	'BDFE'
Cp ₂ Co	PhCO ₂ H	-1.34	21.5	54
(CpMe ₅) ₂ Co	lutidinium	-1.47	14.1	40
Ru ^I (bpy) ₃	pyridinium	-1.71	12.5	33
Ru ^I (bpy) ₃	PTSA	-1.71	8.6	27

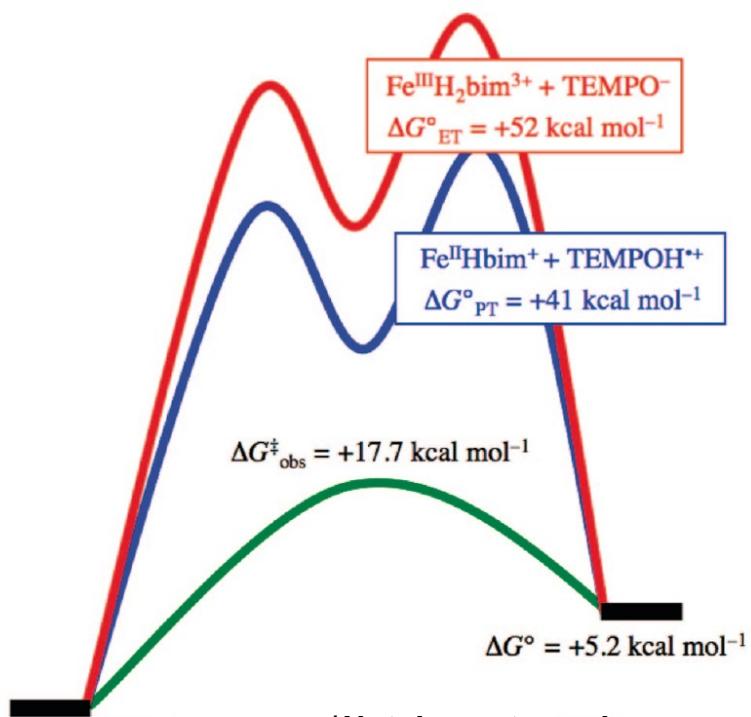
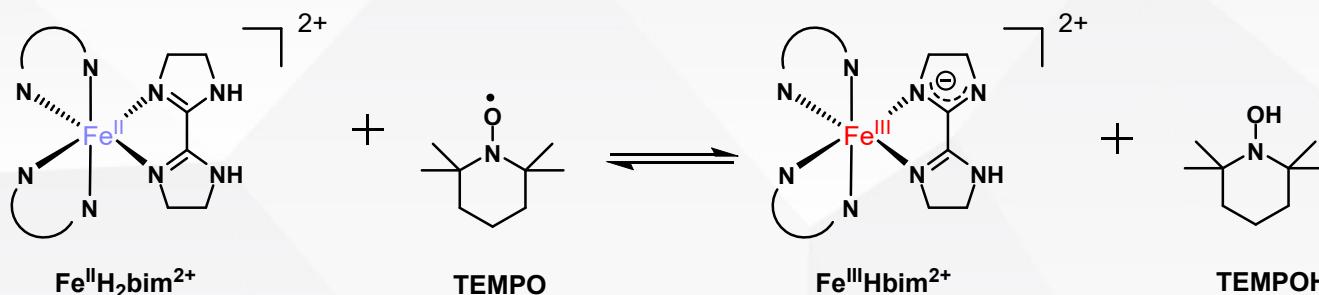
Proton-Coupled Electron Transfer



Kinetic Advantages of CPET



Kinetic Advantages of CPET



$$\begin{aligned}\Delta G^{\circ}_{\text{ET}} &= -FE^{\circ} \\ &= -(23.06 \text{ kcal mol}^{-1} \text{ V}^{-1}) [(E^{\circ}(\text{XH}^{+/0}) + E^{\circ}(\text{Y}^{0/-})) \end{aligned}$$

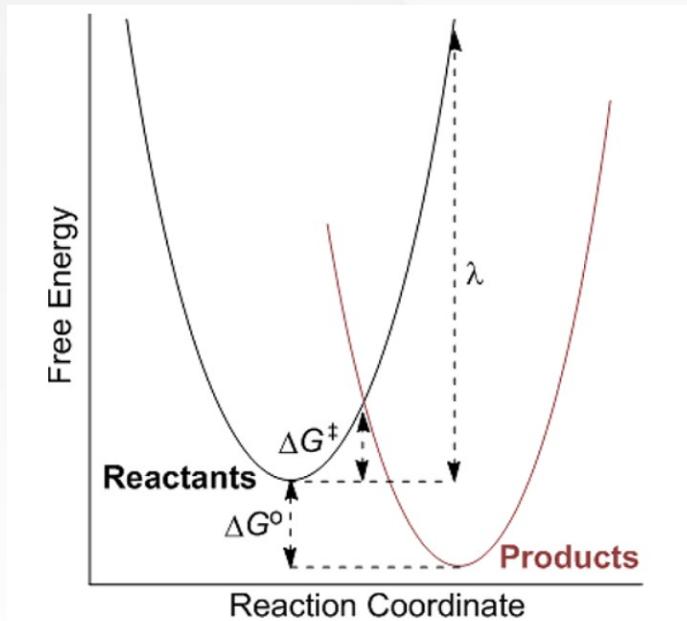


$$\begin{aligned}\Delta G^{\circ}_{\text{PT}} &= -RT \ln(K_a) \\ &= -(1.37 \text{ kcal mol}^{-1}) [\text{p}K_a(\text{YH}^+) - \text{p}K_a(\text{XH})] \end{aligned}$$

$\Delta G^{\ddagger}_{\text{CPET obs}} = +17.7 \text{ kcal/mol}$

$\Delta G^{\circ} < \Delta G^{\ddagger}$

One-Dimensional Marcus treatment



$$\ln(k) = \alpha \ln(K_{eq}) + \beta$$

$$\Delta G^\ddagger = \alpha \Delta G^0 + \beta'$$

Eyring Equation

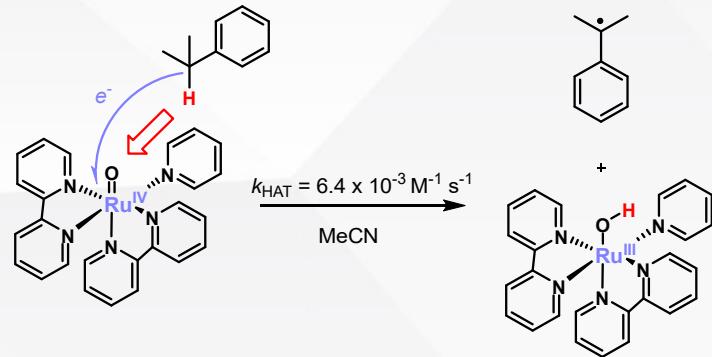
$$\Delta G^\ddagger =$$

Marcus Equation

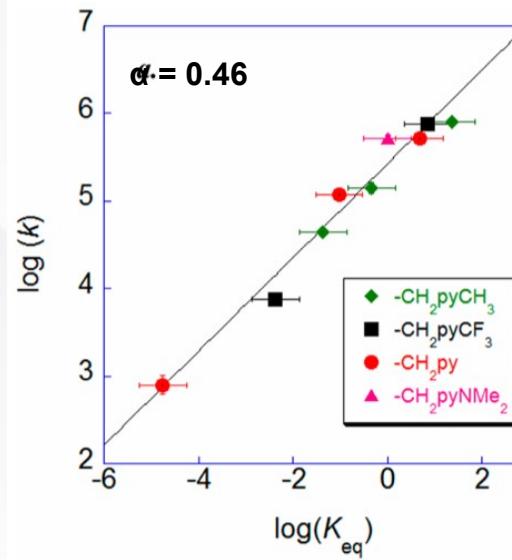
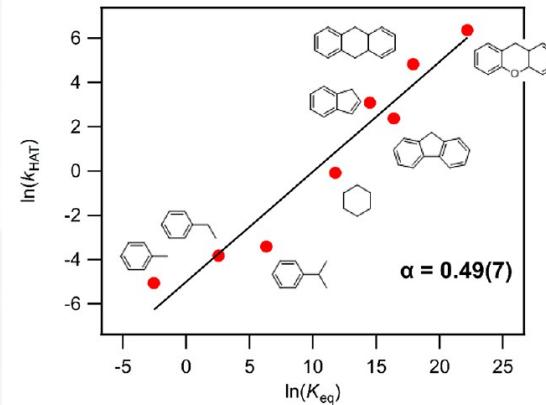
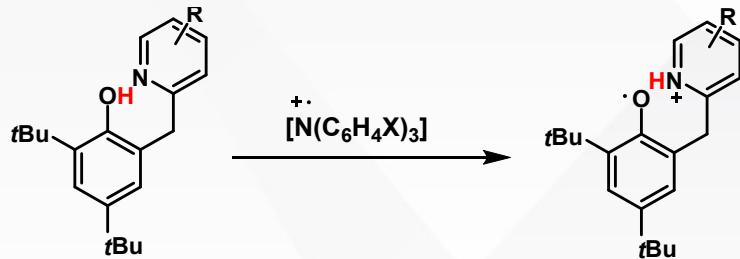
$$\alpha = = \approx 0.5 \text{ when } \lambda \ll 2$$

Linear correlation of rate constant (k) vs equilibrium constant (K_{eq}) is the important evidence for concerted e^- and H^+ transfer.

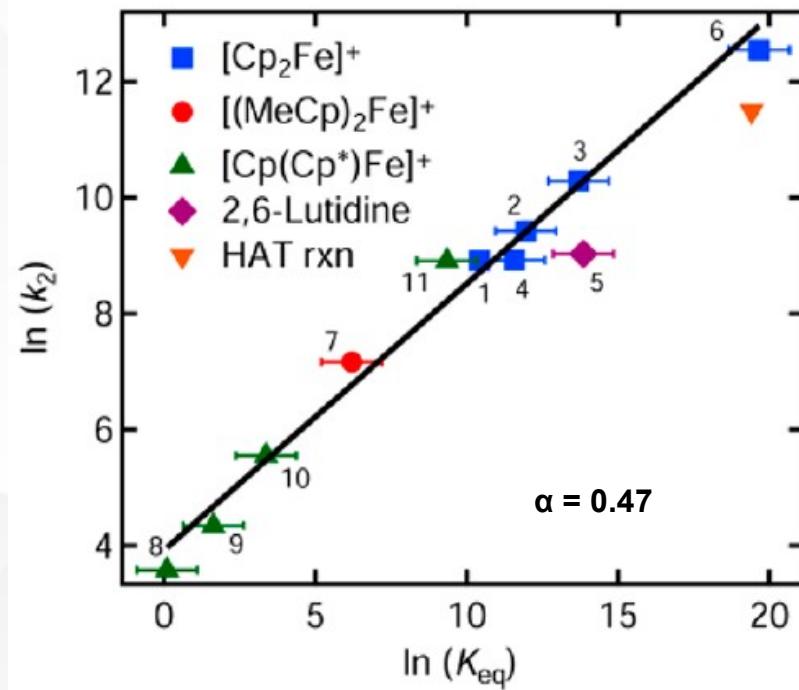
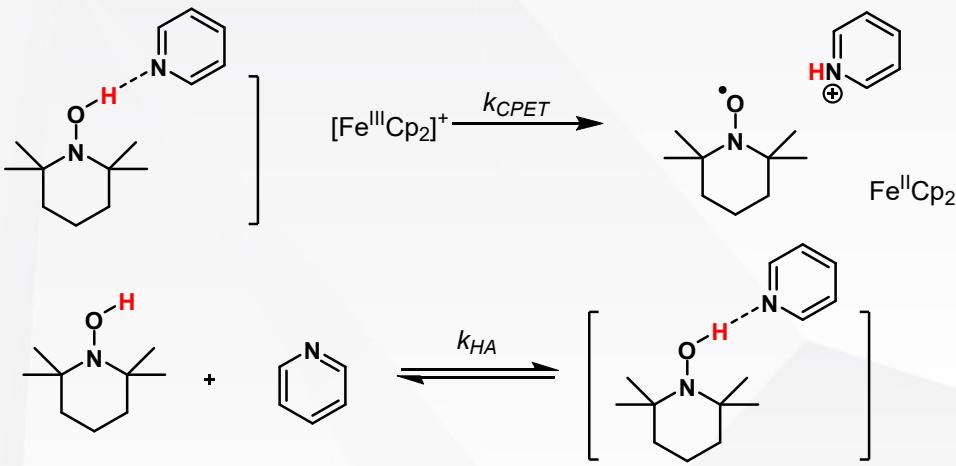
A Canonical CPET (HAT) Process



An Intramolecular Multisite CPET process



A Termolecular MS-CPET Process





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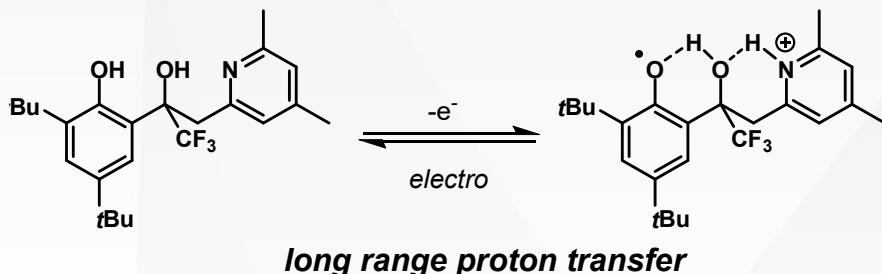
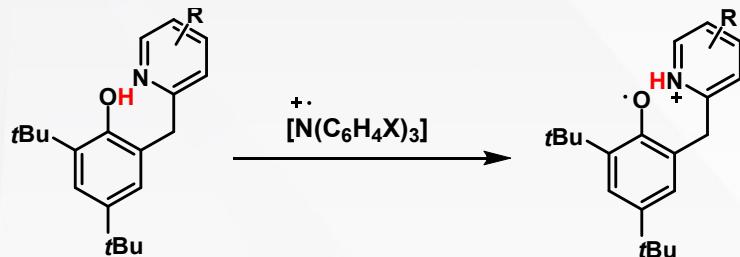
Mechanistic Study of PCET in Organic Synthesis



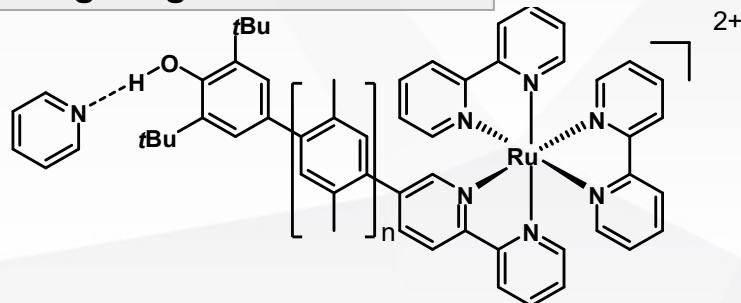
Bacteriophage T4-induced ribonucleotide
Photosystem II
Prostaglandin endoperoxide synthase-2
...

Long range transfer

A Long range PT Process



A Long range ET Process



long range electron transfer

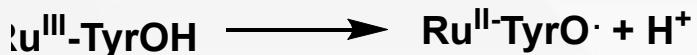
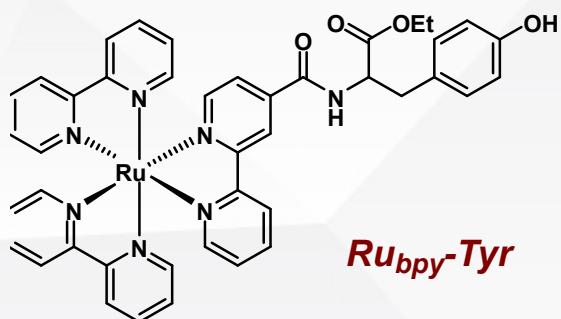
n	R _{DA} (Å)	k _{PCET} (s ⁻¹)
1	12.2	1.07x10 ⁹
2	16.5	3.35x10 ⁸
3	20.8	3.41x10 ⁶

Photosystem II	~10 Å
R1 subunit of RNR	~7 Å
Prostaglandin-H synthase-2	~7 Å

Mechanistic Study – The influence of pH



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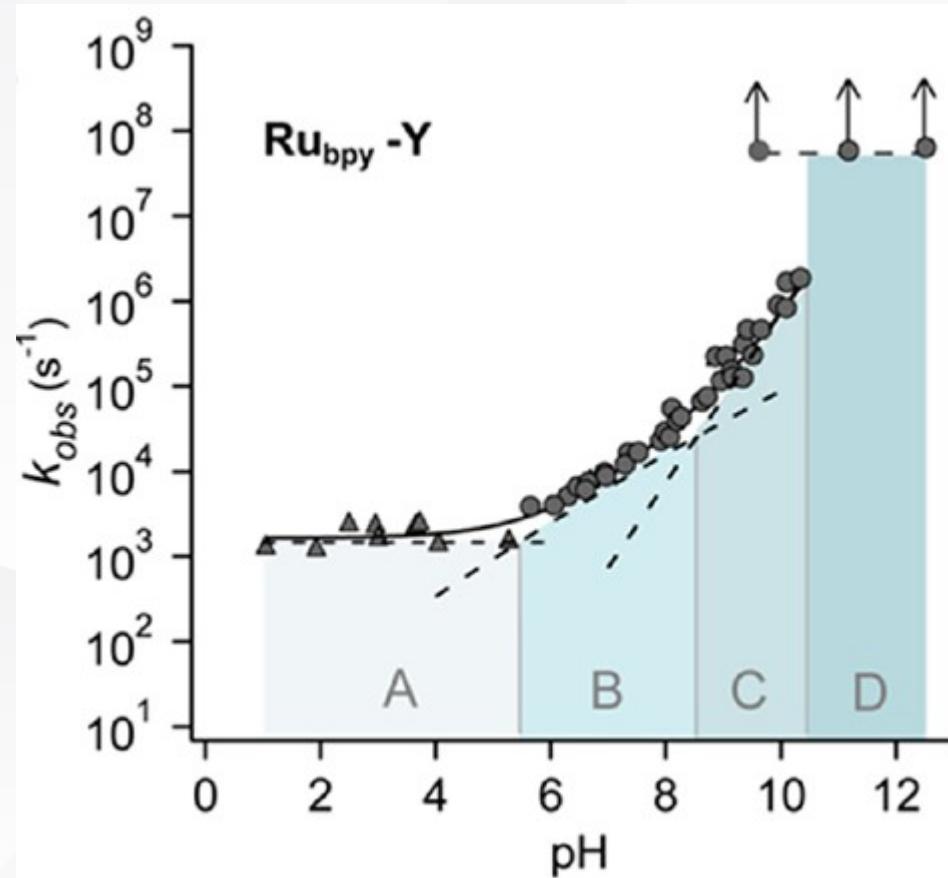


$$k_{PCET} = k_1 + k_2 \times 10^{0.5\text{pH}} + k_3 \times 10^{\text{pH}}$$

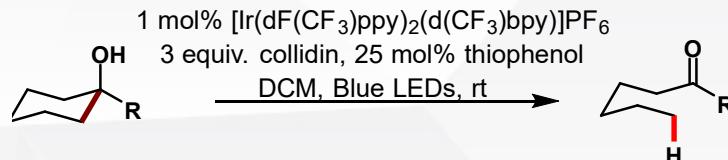
D region : A pure ET from TyrO[·]

C region : PT-limited PTET with OH⁻ as proton acceptor around

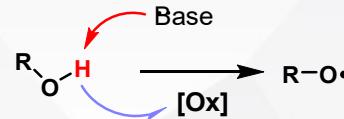
B region : CPET around pH = 7 with water as proton acceptor



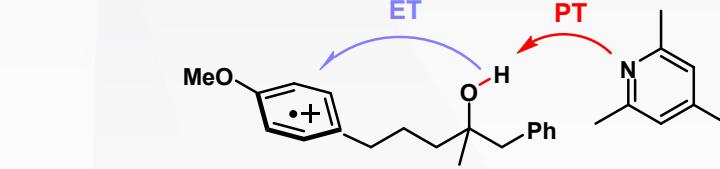
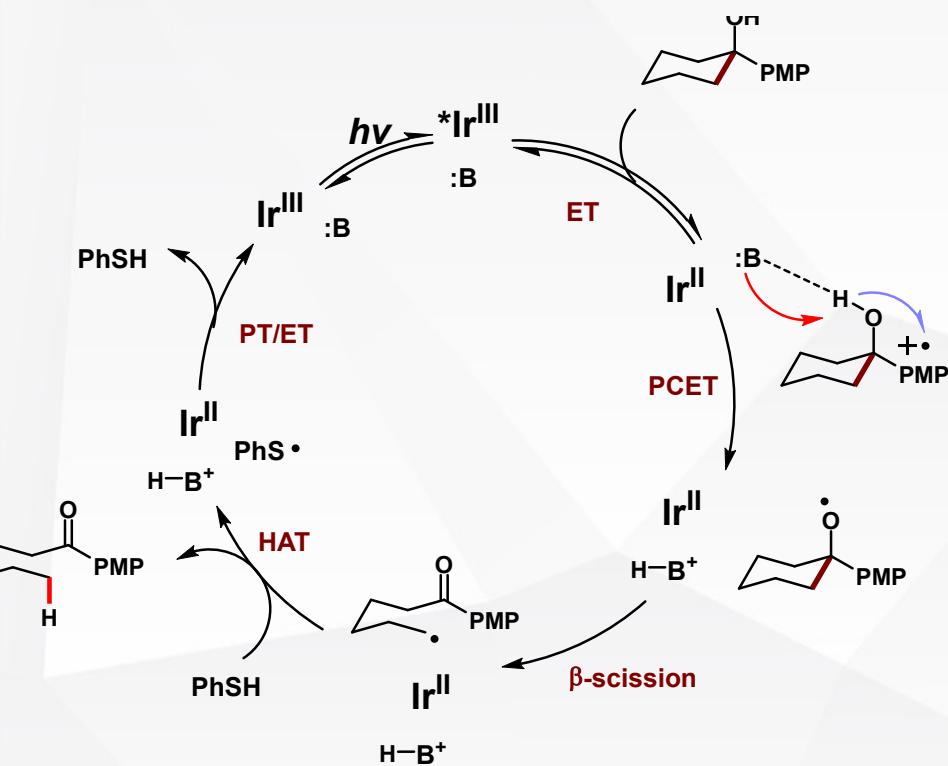
Ring-Opening of Cyclic Alcohols



Alcohols

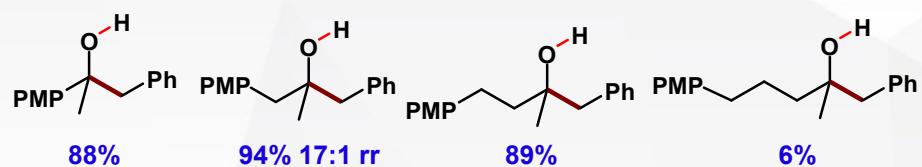


Strong bond ~ 105 kcal
Low acidity
Difficult to selective homolysis

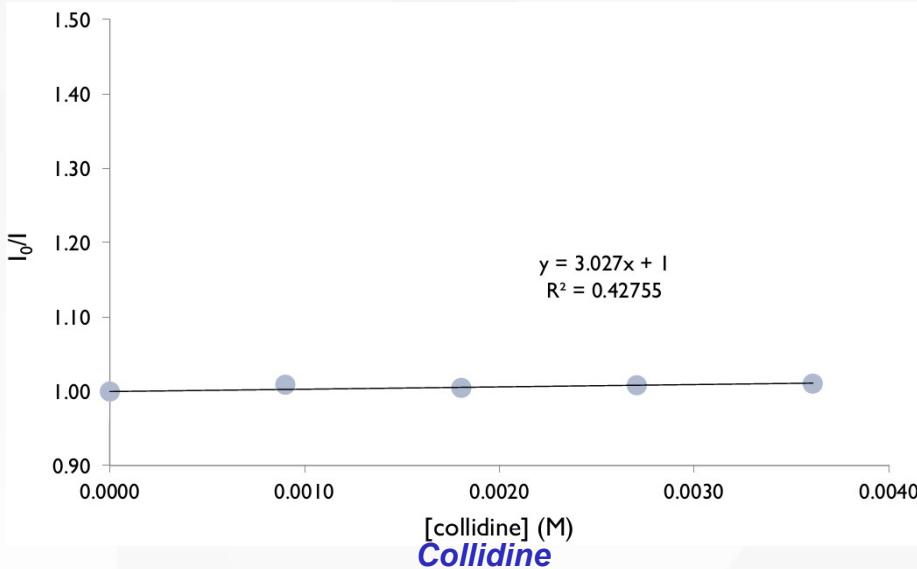
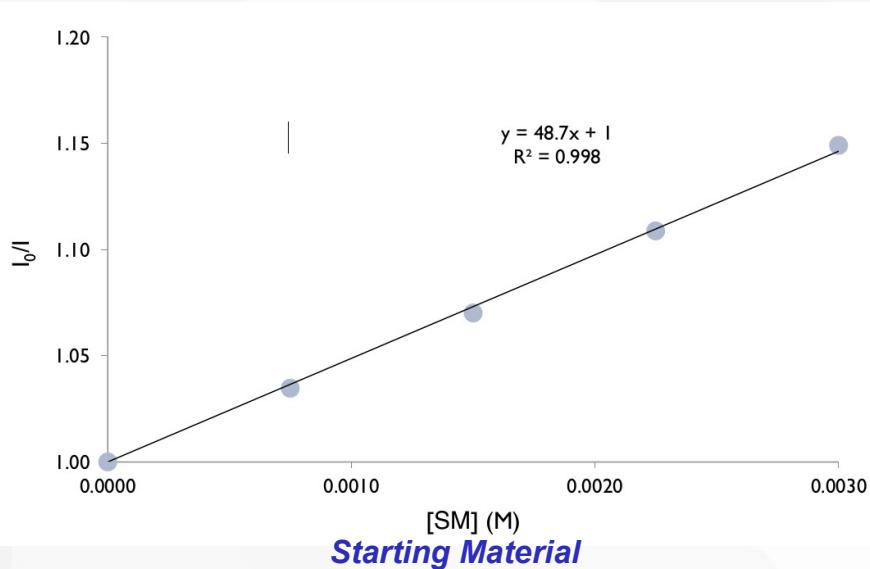


$\Delta G^0_{\text{PT}} \sim + 34 \text{ kcal/mol}$
 $\Delta G^0_{\text{PCET}} \sim + 1 \text{ kcal/mol}$

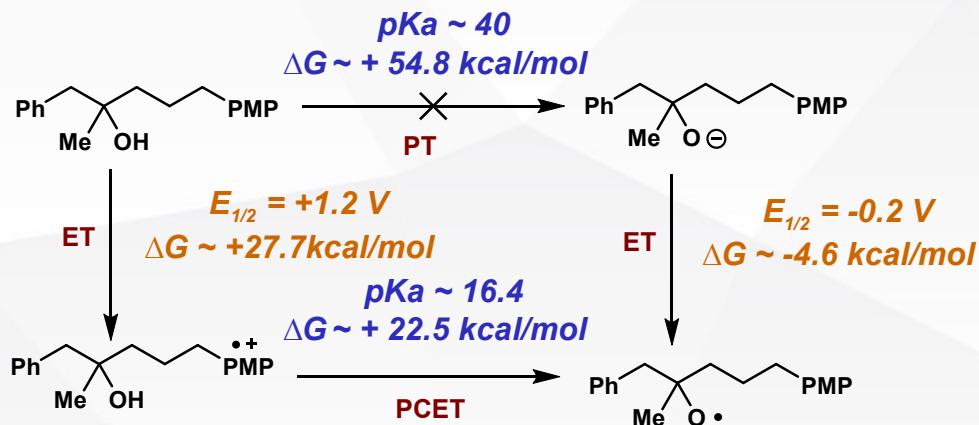
long-range PCET



Stern-Volmer Studies

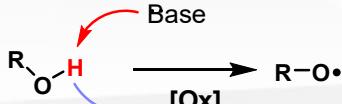


Investigating Long-range PCET



$pK_a (\text{collidine H}^+) = 15.0$
 $E_{1/2} (\text{Ir}^{II}/\text{Ir}^{III}) = -1.07 \text{ V vs Fc/Fc}^+$
 $E_{1/2} (*\text{Ir}^{III}/\text{Ir}^{II}) = +1.30 \text{ V vs Fc/Fc}^+$

Alcohols

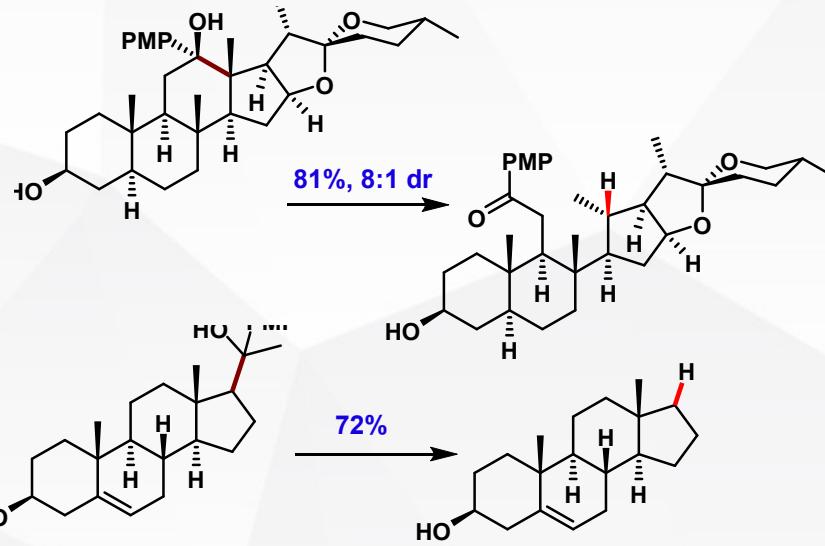
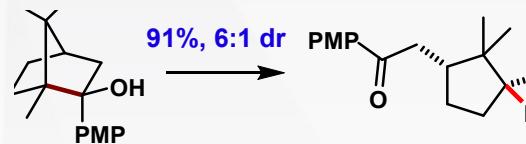
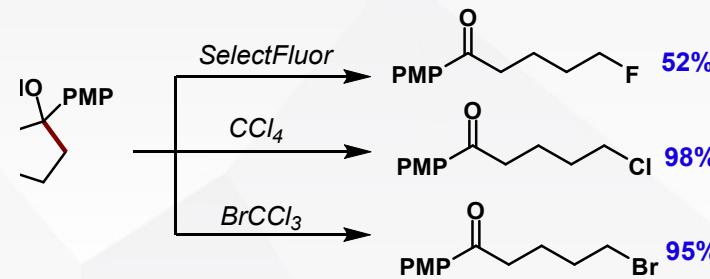
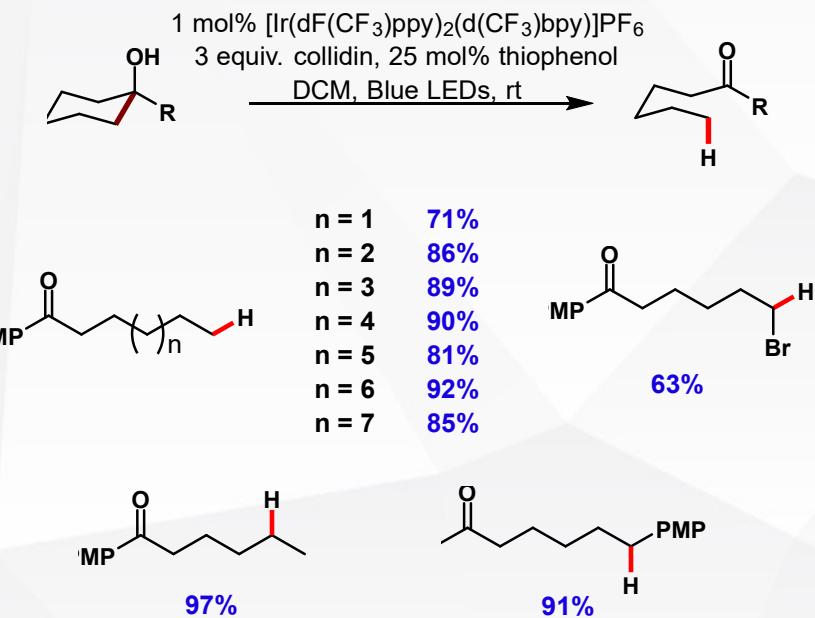


Strong bond ~ 105 kcal

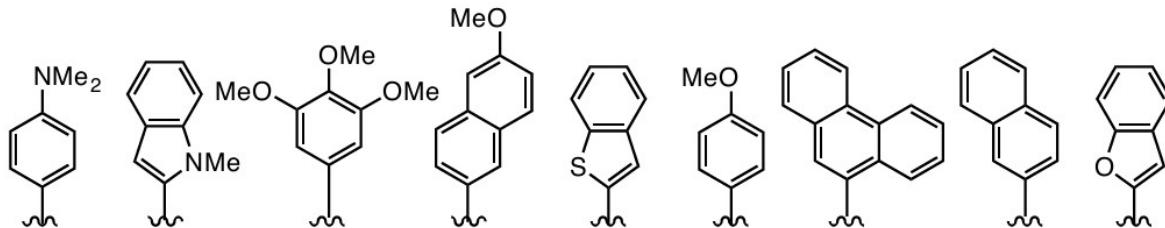
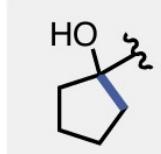
Low acidity

Difficult to selective homolysis

Ring-Opening of Cyclic Alcohols



Effective BDFE Correlations with Reactivity



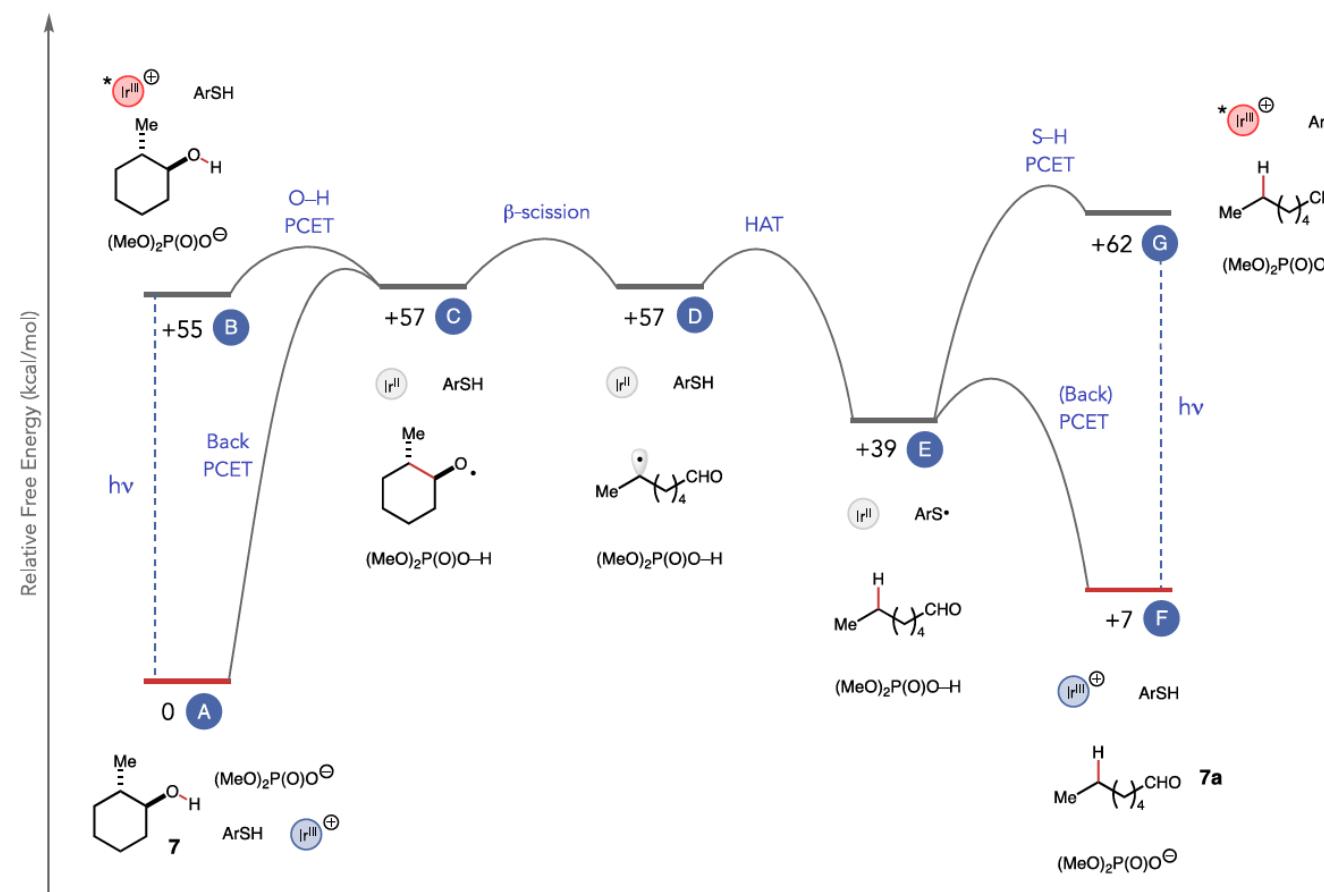
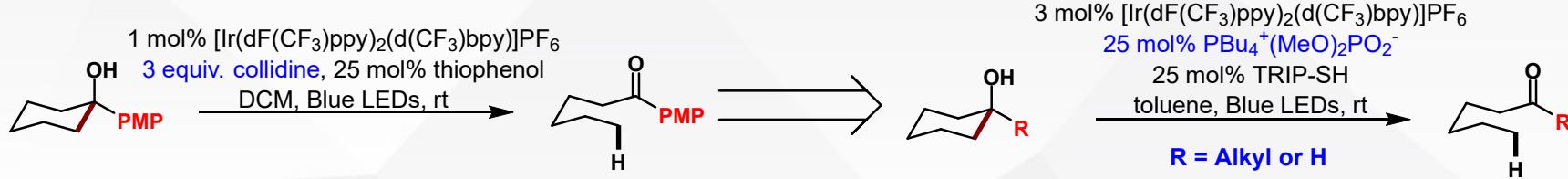
Base	$E_{p/2}$ (V)	0.39	0.69	0.92	0.96	1.18	1.22	1.22	1.24	1.27
2-MeO-pyridine $pK_a = 9.9$	'BDFE'	77	84	90	91	96	97	97	97	98
	Yield (%)	0	0	0	0	0	0	0	<5	8
pyridine $pK_a = 12.5$	'BDFE'	81	88	93	94	99	100	100	101	101
	Yield (%)	0	0	0	<5	6	16	14	5	19
CF_3COO^- $pK_a = 12.5$	'BDFE'	81	88	93	94	99	100	100	101	101
	Yield (%)	0	0	0	0	23	87	79	97	18
collidine $pK_a = 15$	'BDFE'	84	91	97	98	103	104	104	104	105
	Yield (%)	0	0	<5	7	86	86	82	41	84

$$\text{'BDFE'} = 23.06 E_{1/2}(\text{Ar}^{0/+}) + 1.37 \text{ pKa (base)} + 54.9 \text{ (rt in MeCN)}$$

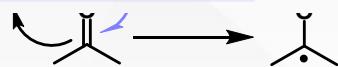
Mechanistic Study - Alcohols



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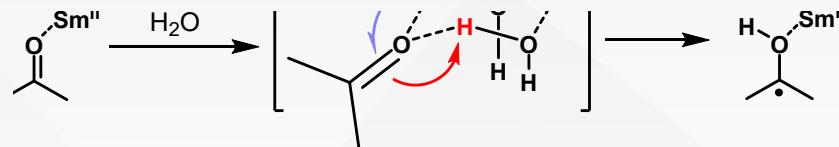
Ketone



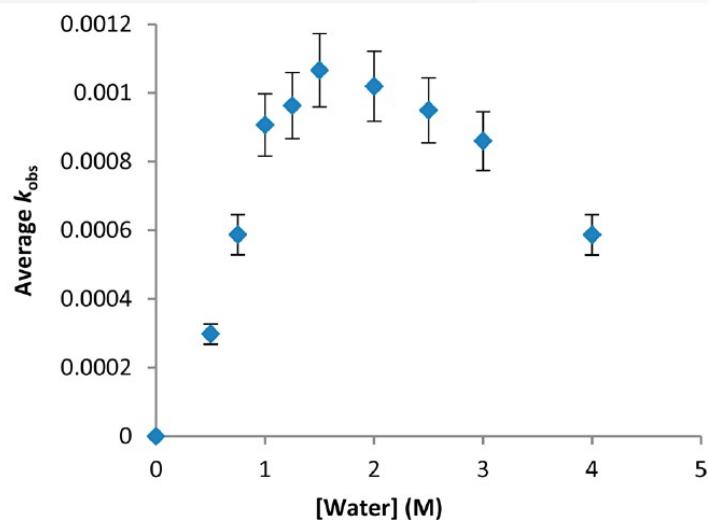
Ketyl radical

High reductive potential

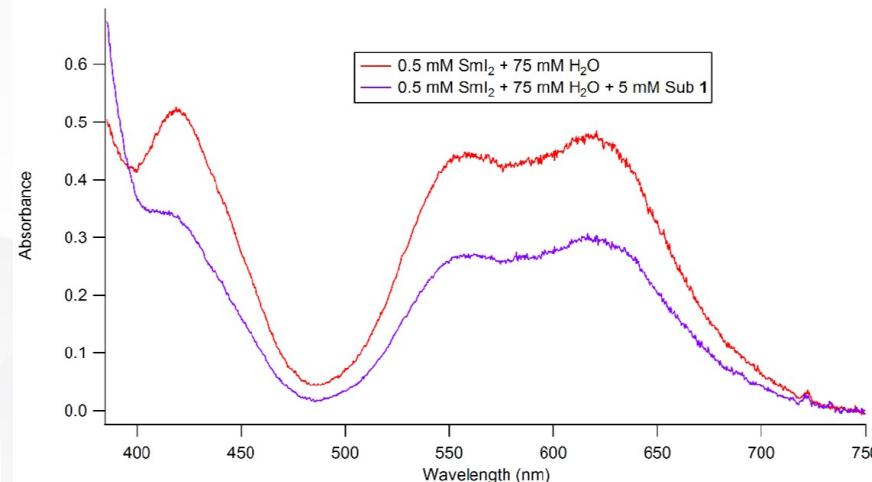
Weak O-H bond



Reduction of Heptaldehyde By SmI_2



UV-Vis Spectra



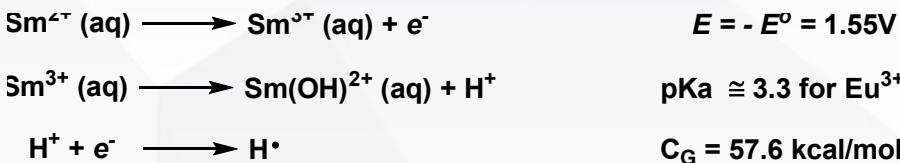
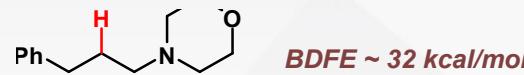
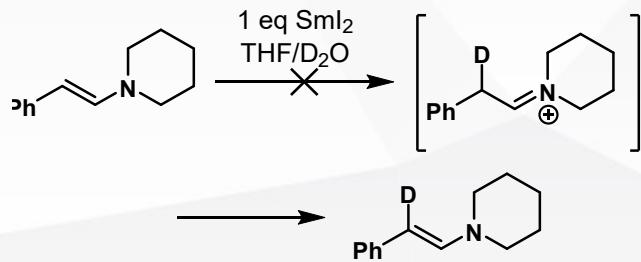
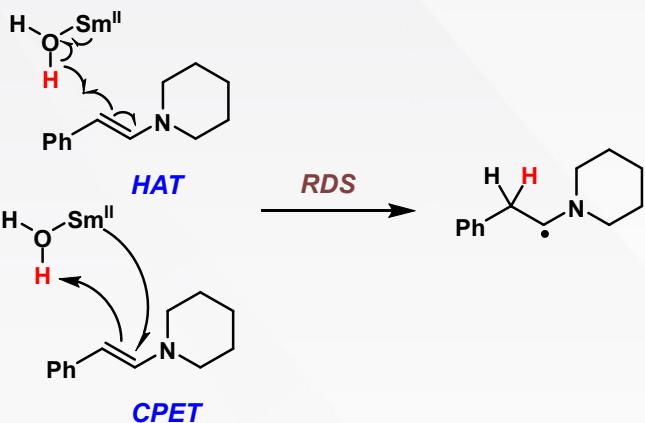
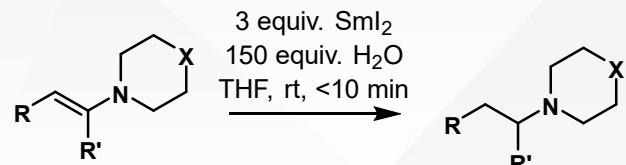
carbonyl coordination to Sm(II)

substrate	rate constant ($\text{M}^{-3} \text{s}^{-1}$)	rate orders	
		H_2O	$\text{SmI}_2^{\cdot-}$
Heptaldehyde	$(4.2 \pm 0.3) \times 10^4$	2	1.0 ± 0.1
Cyclohexanone	570 ± 70	2	1.1 ± 0.1
5-Decanolide	0.18 ± 0.01	2	0.9 ± 0.1

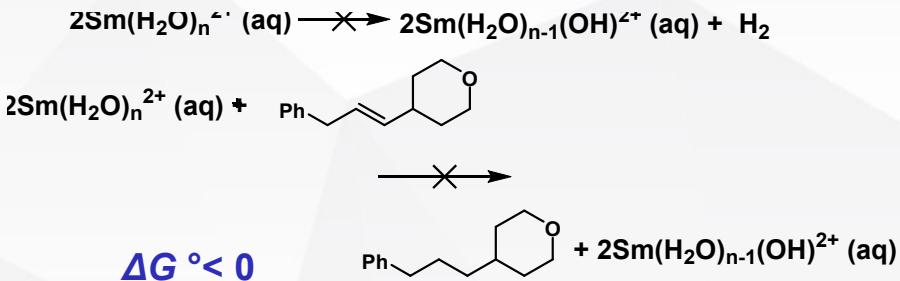
$[\text{H}_2\text{O}] (0-1\text{M})$ and constant $[\text{SmI}_2]$ (10 mM) and $[\text{substrate}]$ (100 mM)

Flowers II, R. A. et al., J. Am. Chem. Soc. 2016, 138, 8738–8741

Enamines



$$\text{BDDE} = 23.06 E + 1.37 \text{ pKa} + C_G = 26 \text{ kcal/mol}$$





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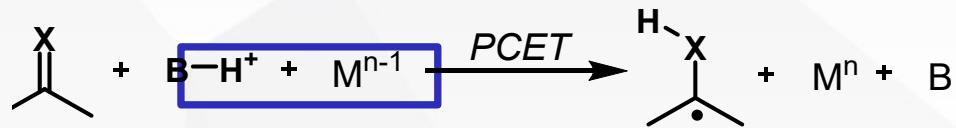
Summary

Proton-Coupled Electron Transfer

Oxidative Process



Reductive Process



A strong strategy for homolytic activation

Thermodynamical Advantages

Adjustable effective BDFE

Kinetic Advantages

Lower barrier

Enable the direct homolytic activation of many common organic functional groups

Prospect

Theory

- Detailed mechanism study in bioprocess
- Kinetic barrier
-

Application

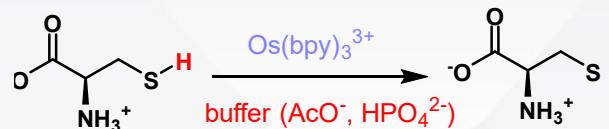
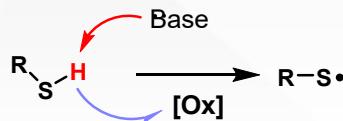
- Enantioselective PCET catalysis
- Selectively C-H homolysis
- Application in total synthesis
-

Thank you!

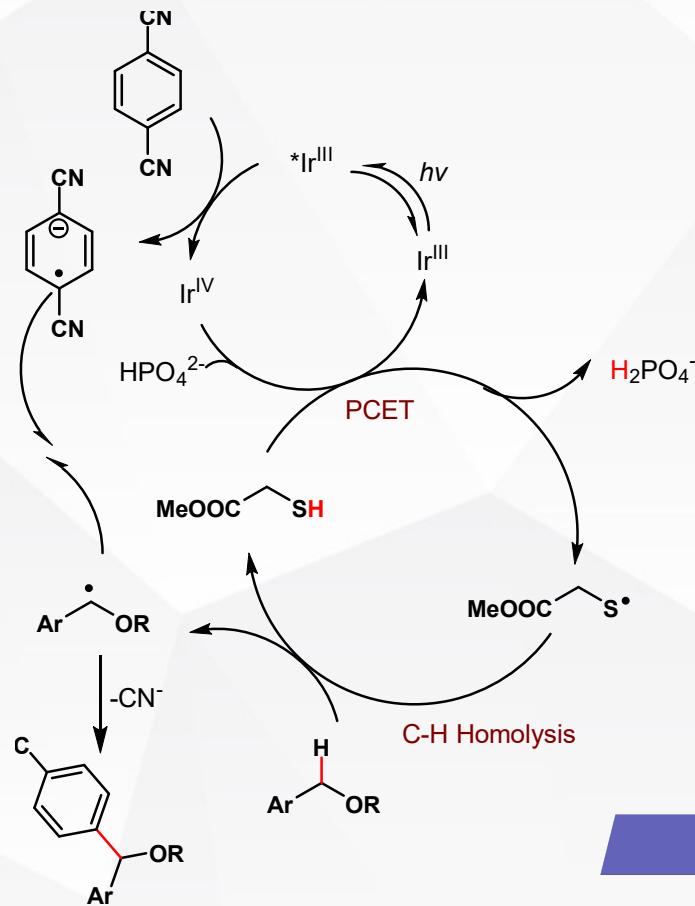
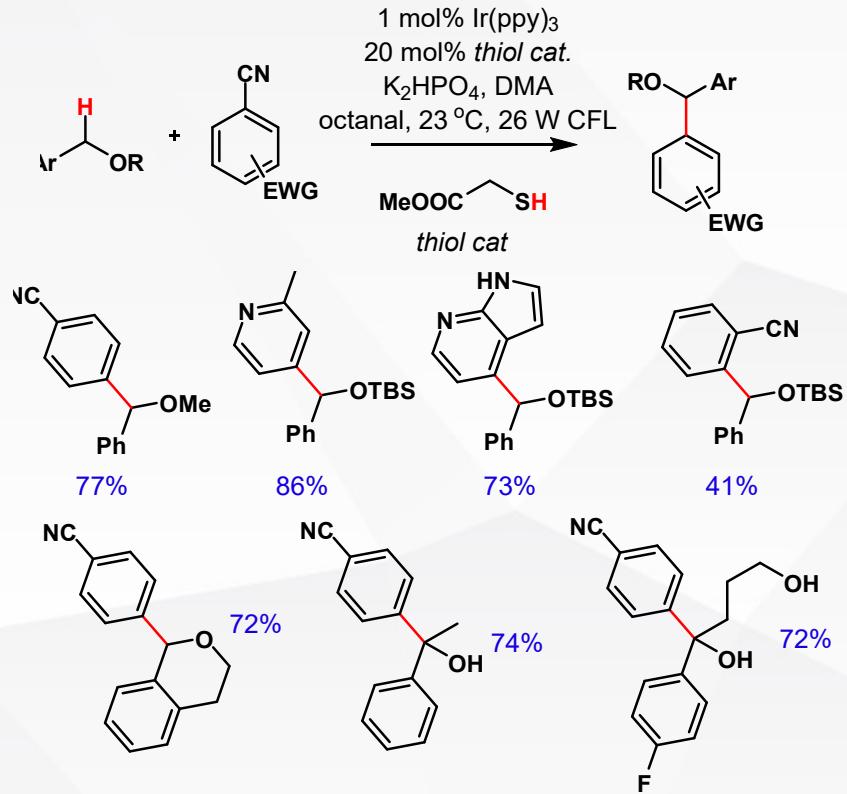
Reporter : Zhou Qiang

Supervisor : Prof. Lu

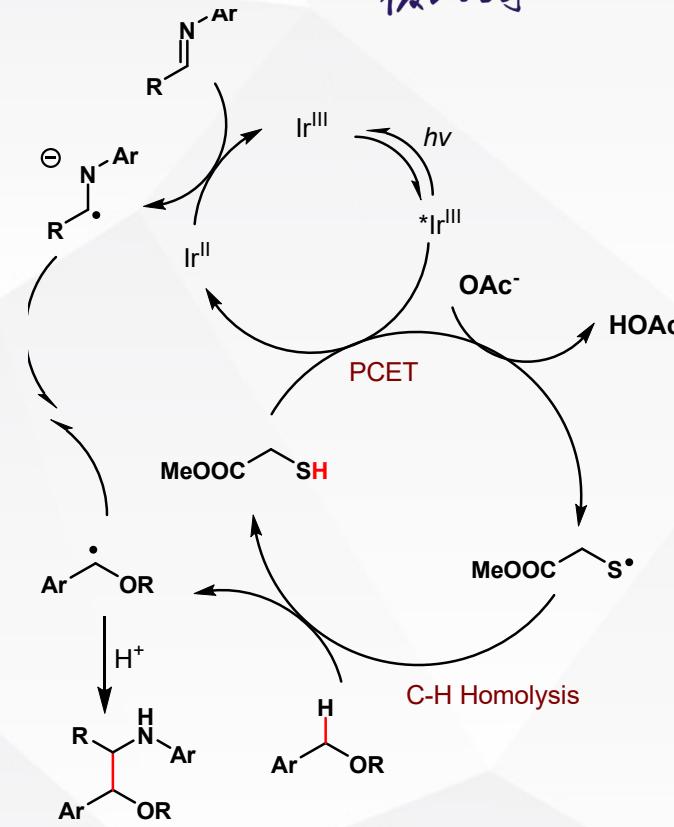
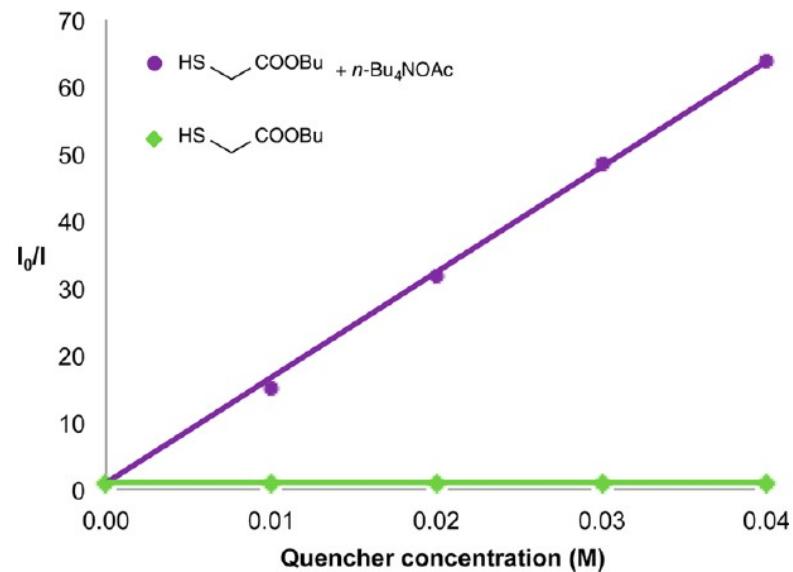
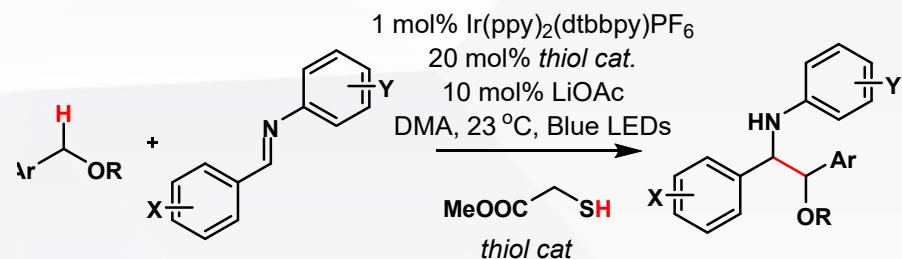
Thiols



C–H bond Abstraction



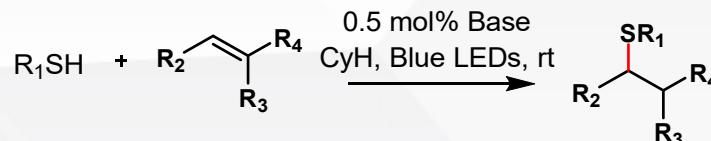
C–H bond Abstraction



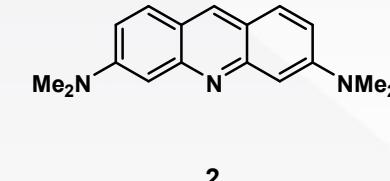
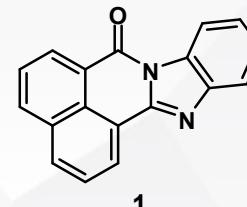
Stern–Volmer quenching experiment

PT/ET OR CPET

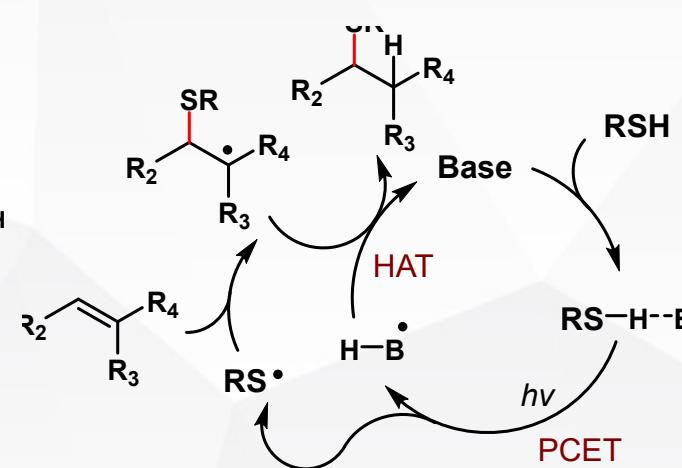
Thiol-Ene Reaction

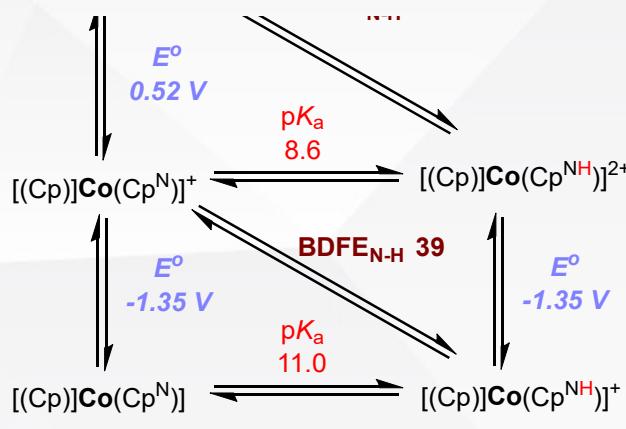


Base:

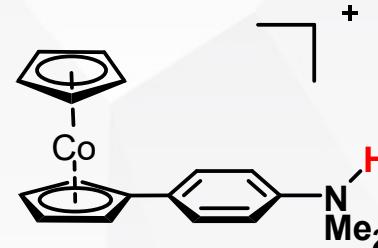


Ph-CH2-CH2-OH	Ph-CH2-CH2-C(OEt)2	HO-CH2-CH2-OH
90%	92%	97%
98%	77%	

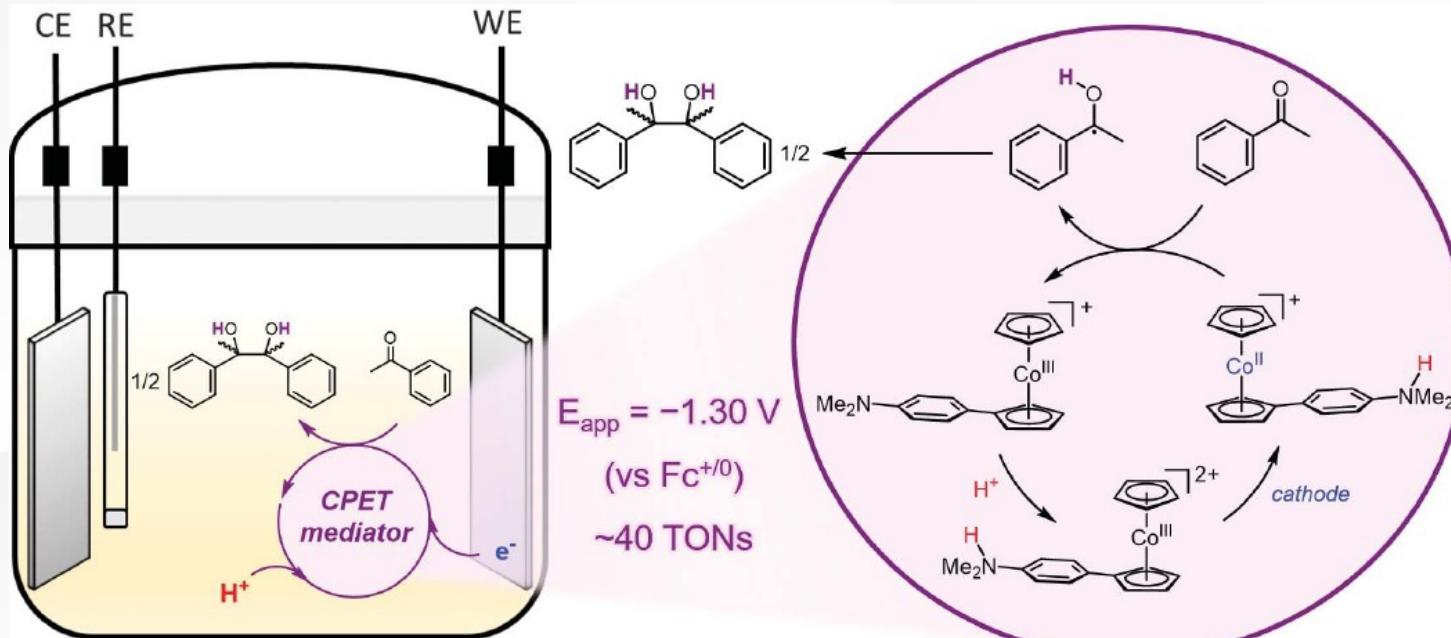




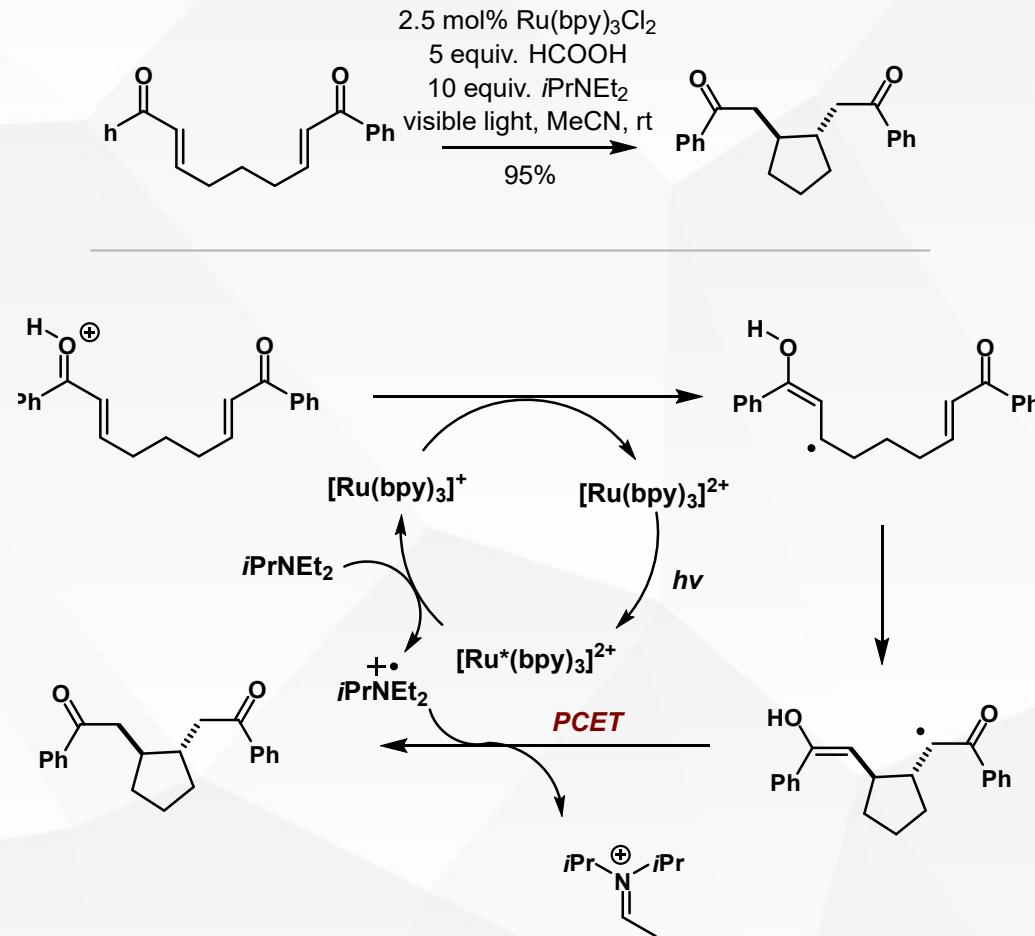
Electrocatalytic CPET



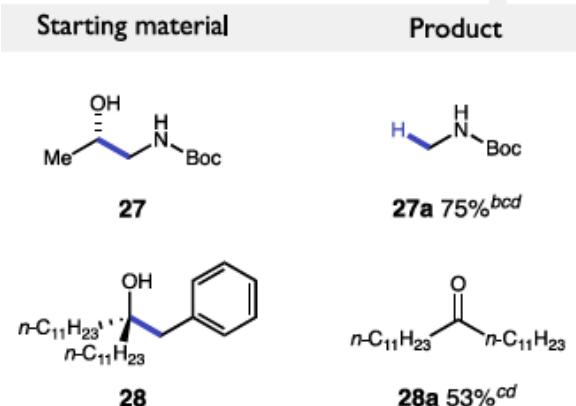
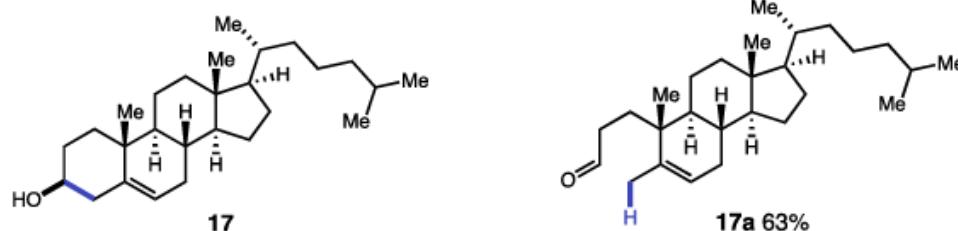
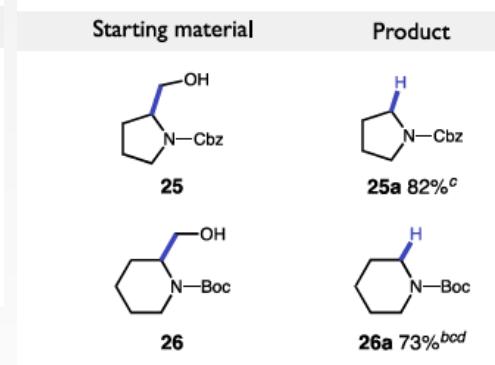
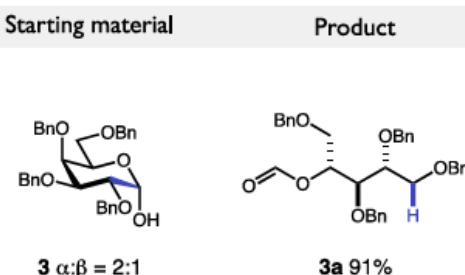
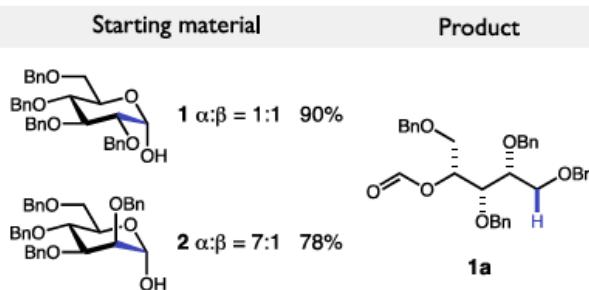
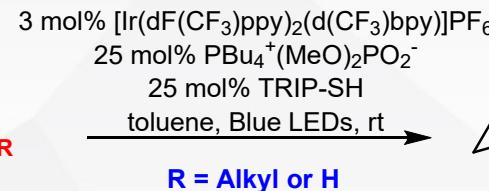
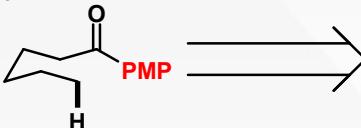
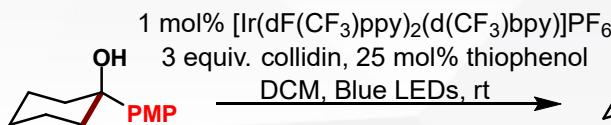
Reduction weakens bond by 40 kcal/mol !



Enones



Ring-Opening of Cyclic Alcohols

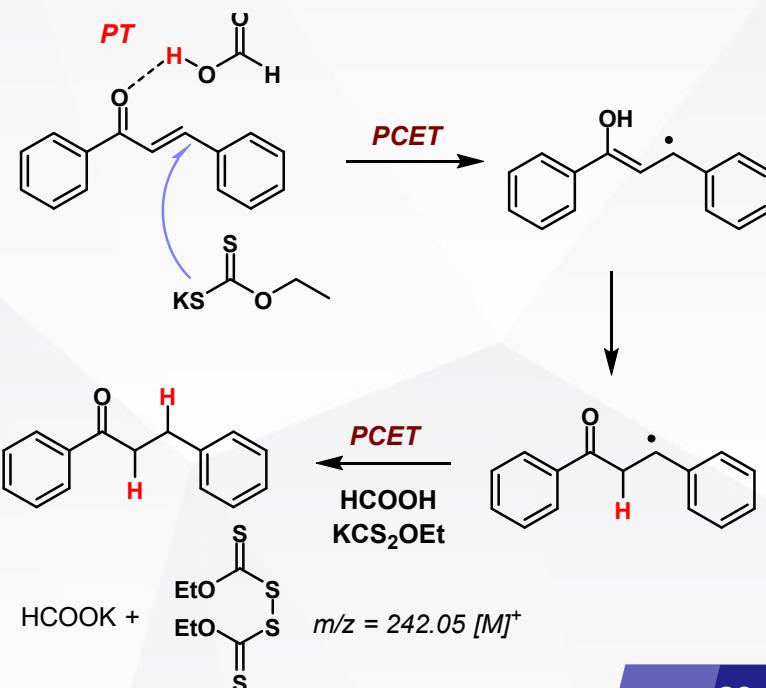
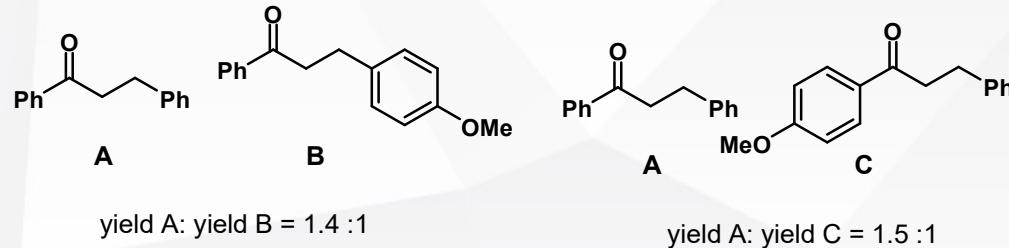
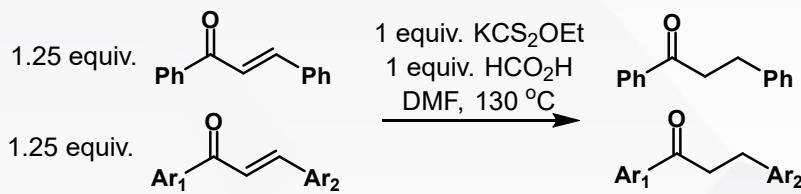
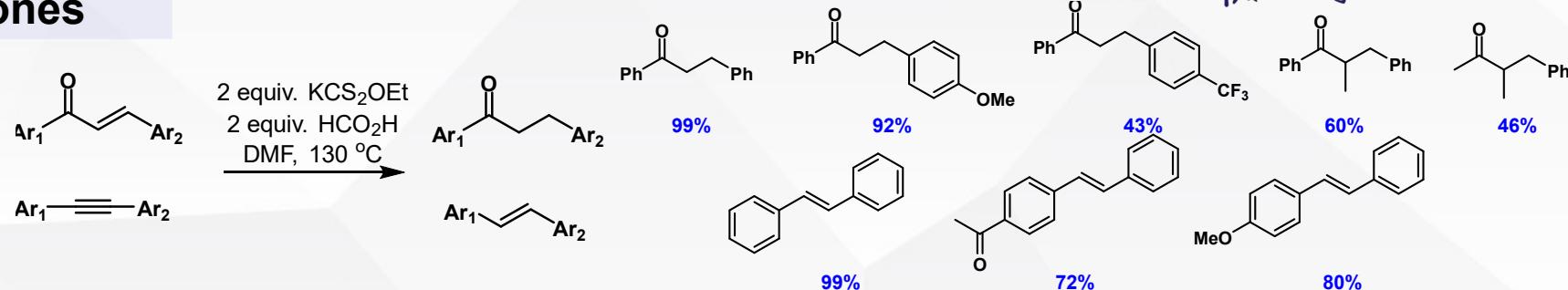


Reductive PCET - Enones

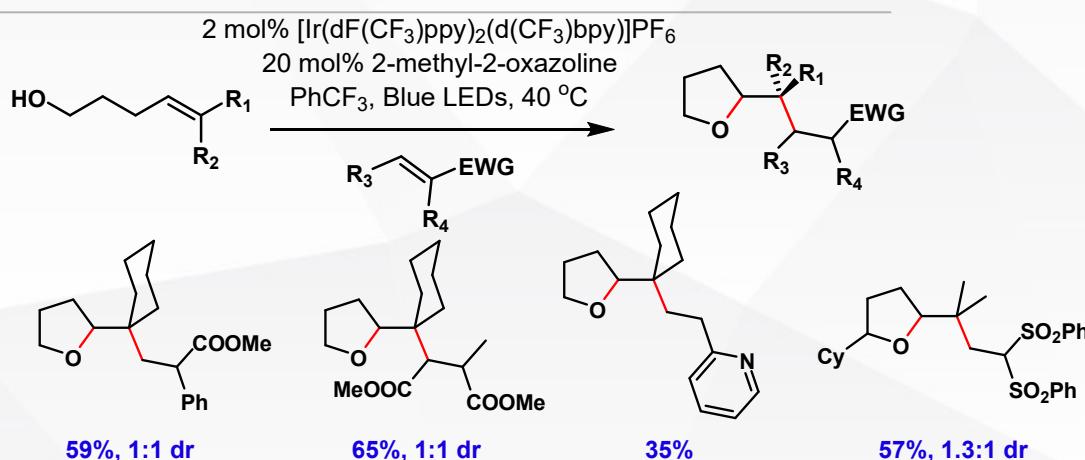
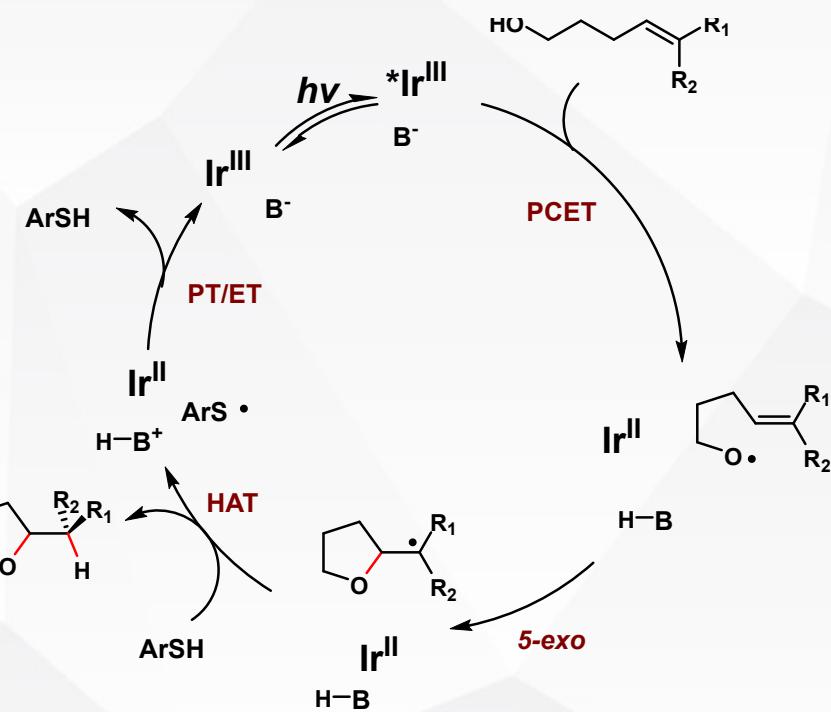
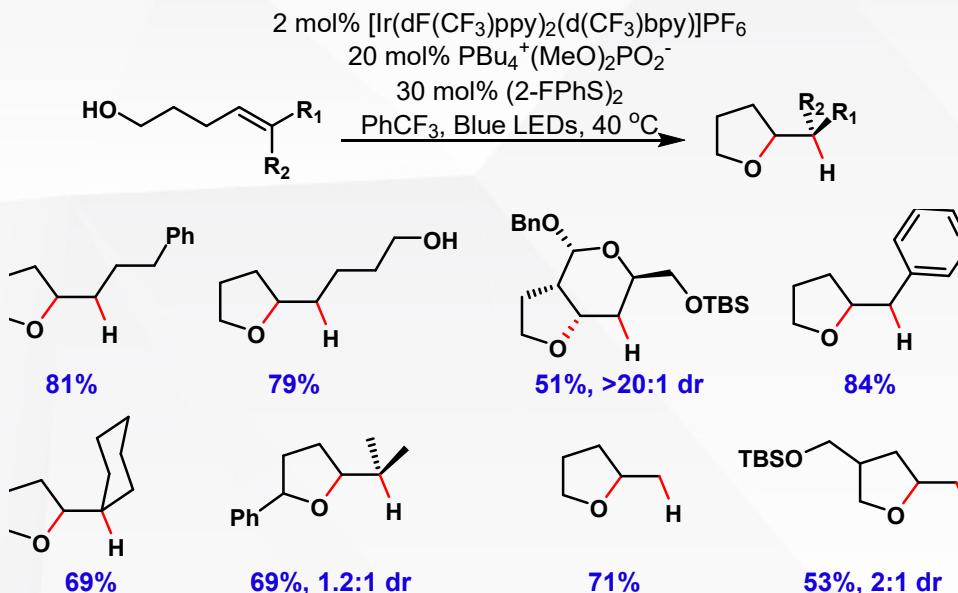


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Enones



Hydroetherification



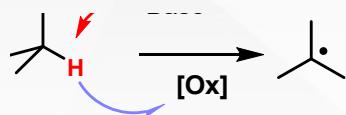
Intramolecular hydroetherification of unactivated alkenes

Oxidative PCET - C-H bond

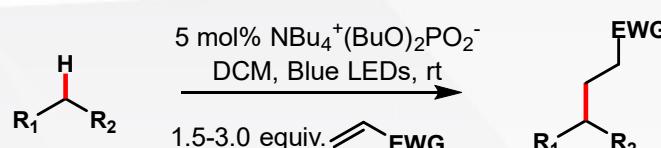
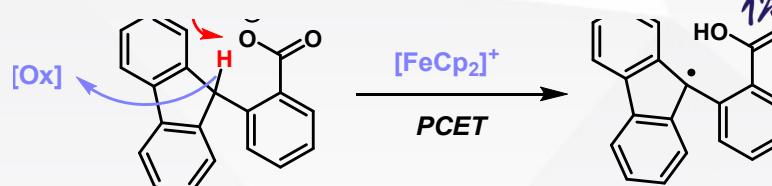


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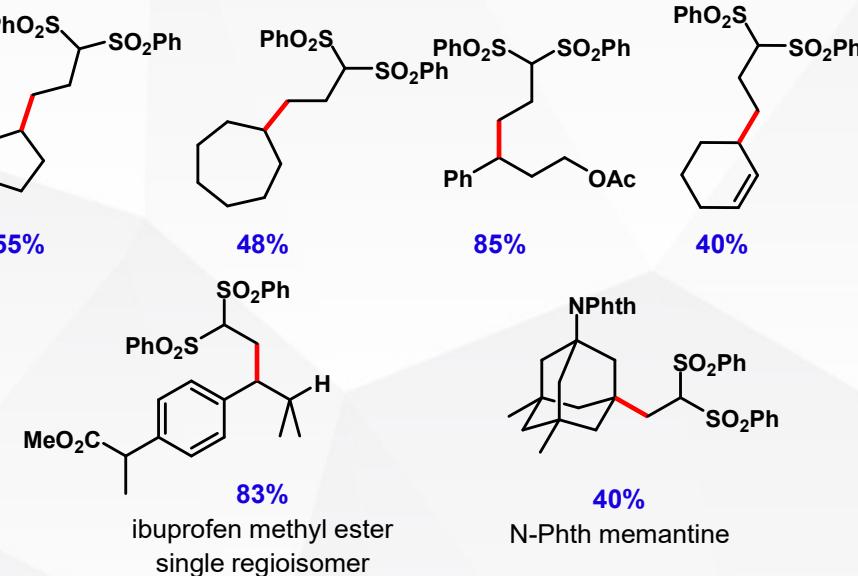
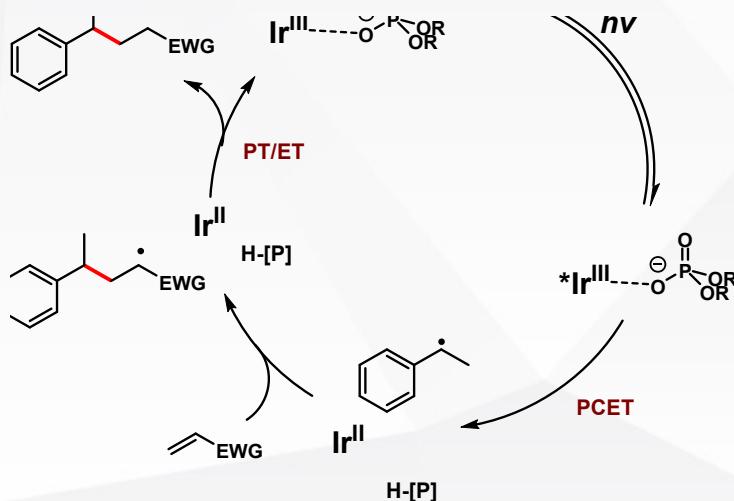
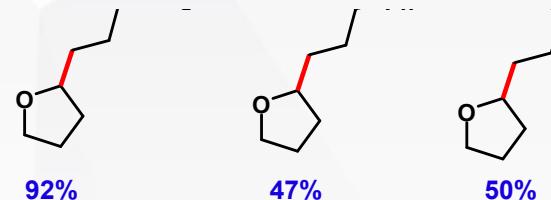
C-H Bond



*Strong bond
Low acidity
Non-polar*



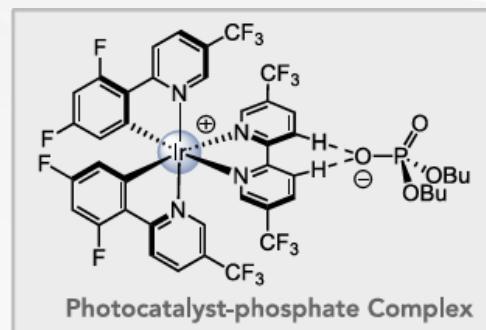
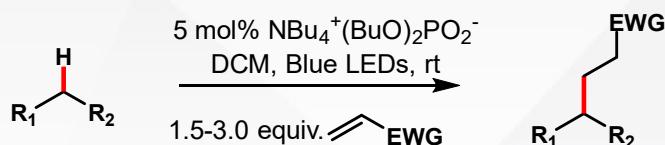
$\Delta G^\ddagger = 0$, BDFE ~74 kcal



Oxidative PCET - C-H bond

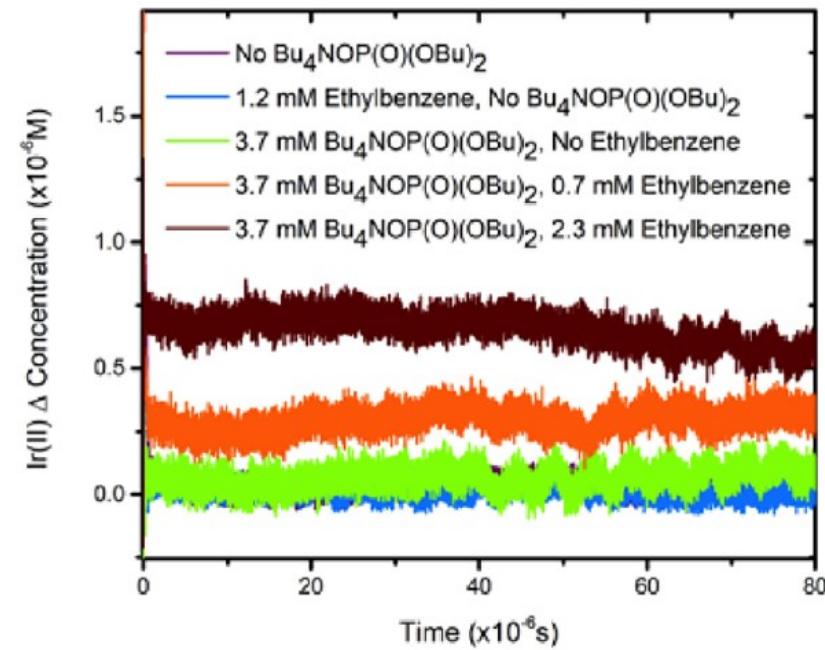
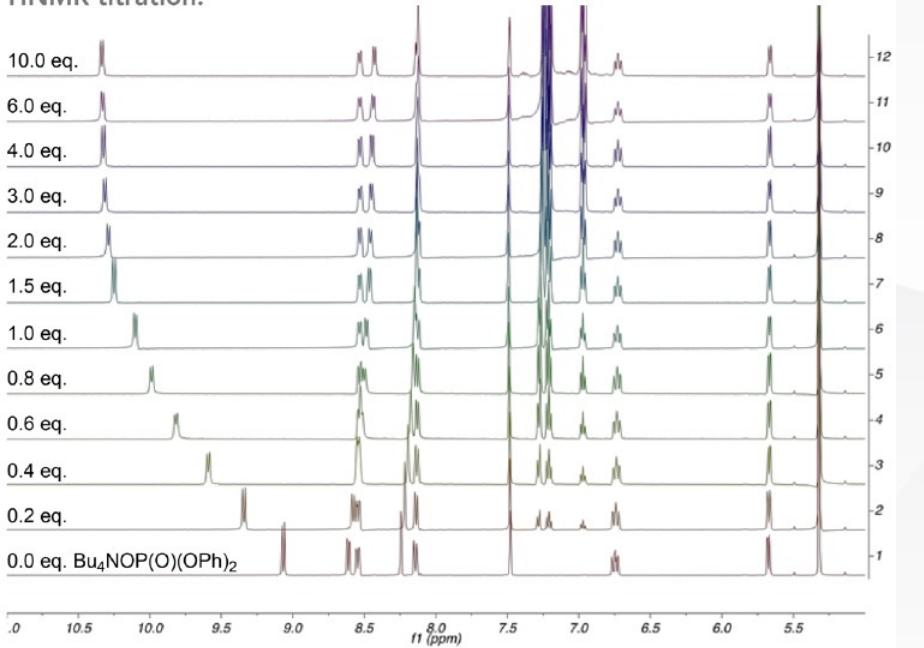


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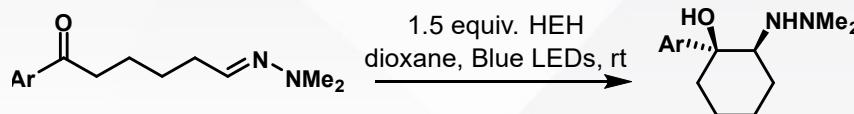


"BDFE" ~ 105 kcal/mol

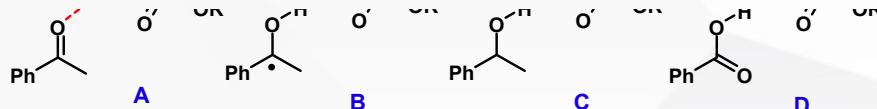
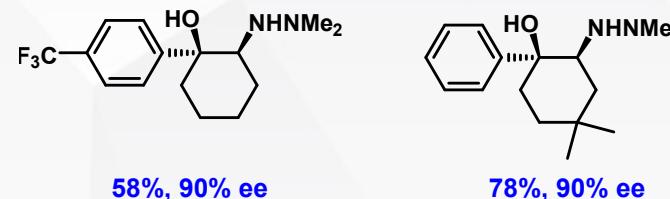
HNMR titration:



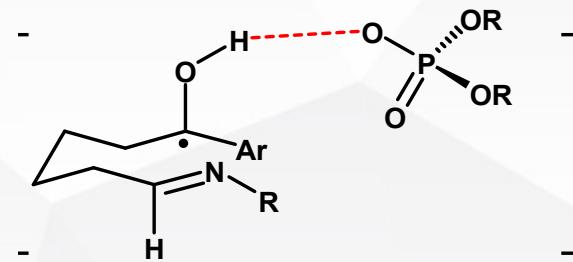
Asymmetric Aza-Pinacol Cyclization



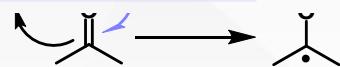
ET $\Delta G^\circ = +13.6 \text{ kcal/mol}$
 PCET $\Delta G^\circ = +3.1 \text{ kcal/mol}$



complex	$\Delta E_{\text{H-bond}}^{\text{a},\text{b}}$	$d \text{ OH}\cdots\text{O} (\text{\AA})^{\text{a}}$	O-H pK _a (MeCN)	Mulliken charge (H) ^a
A	-9.2	1.642	13	0.39
B	-14.4	1.629	20	0.59
C	-10.4	1.737	$\sim 38^{\text{c}}$	0.51
D	-12.6	1.551	21.5	0.60



Ketone



Ketyl radical

High reductive potential

Weak O-H bond

