Mechanistic Aspects of Organic Proton-Coupled Electron Transfer

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Supervisor： Prof. Lu

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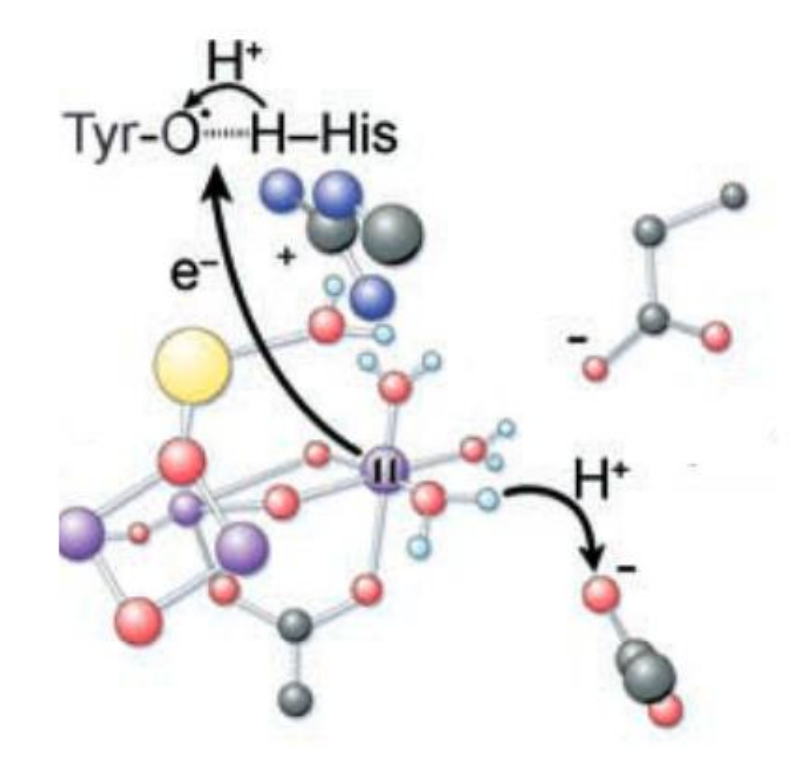
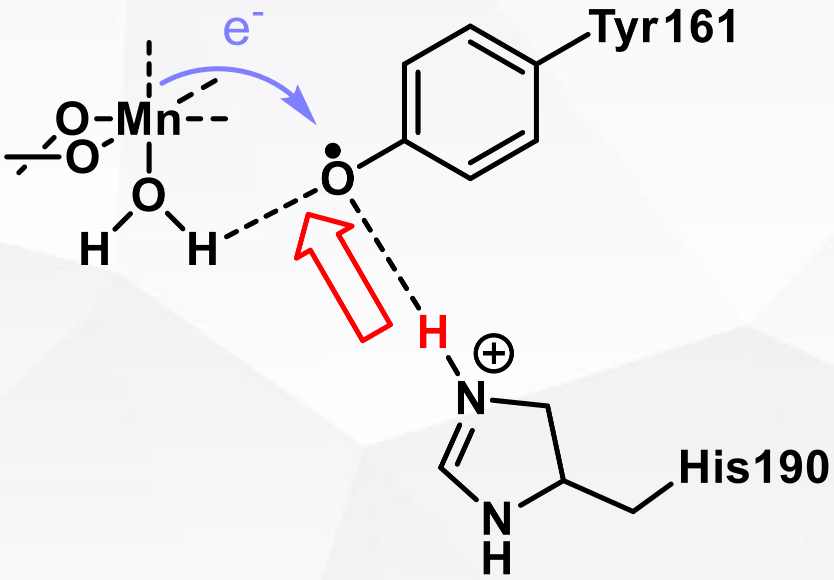
Theory of PCET

Proton-Coupled Electron Transfer (PCET)

$$6CO_2 + 6H_2O \xrightarrow{hv} C_6H_{12}O_6 + 6O_2 \qquad \Delta G^0 = -675\ \text{kcal/mol}$$

$$2H_2O \xrightarrow{hv} O_2 + 4e^- + 4\ H^+$$



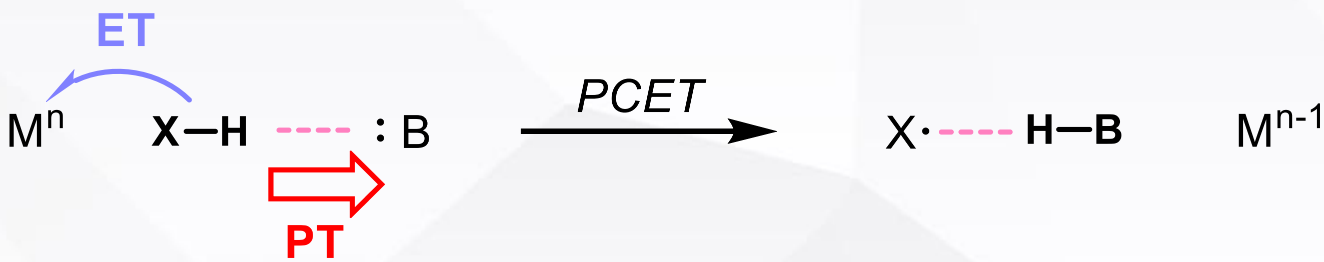


Meyer, T. J. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 5284 – 5304

Hydrogen Atom Transfer (HAT)

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

Proton-Coupled Electron Transfer

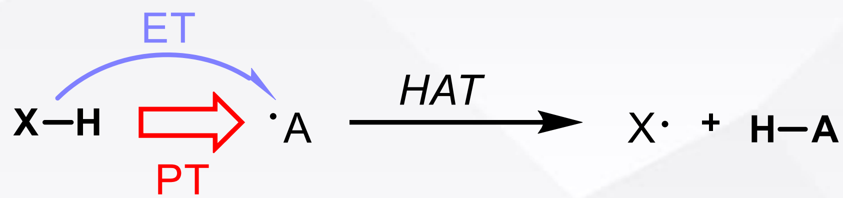


Concerted or stepwise transfer of the proton and electron

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

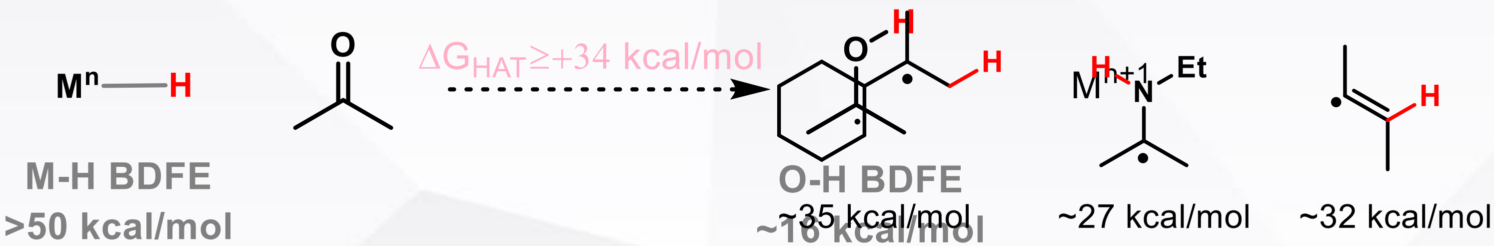
Proton **H^+** ***Hydrogen*** **H·** ***Hydride*** **H^-**

Hydrogen Atom Transfer (HAT)

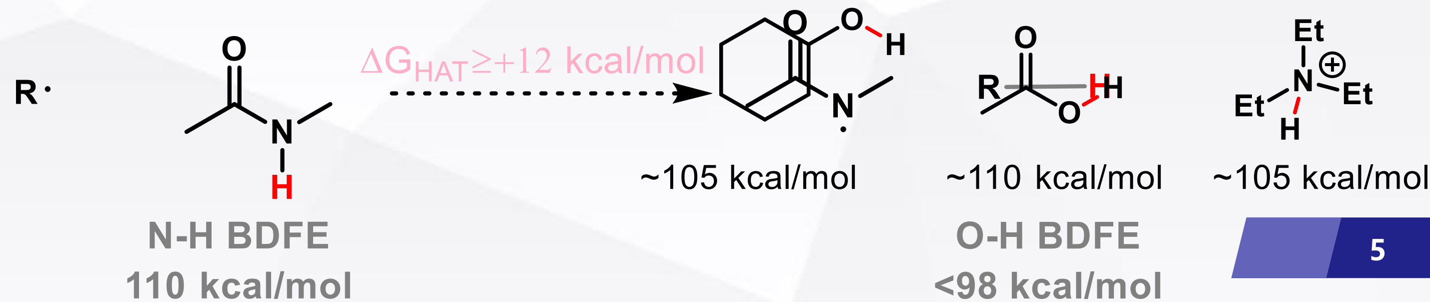


Concerted transfer of a proton and an electron from one H-X *bond*

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



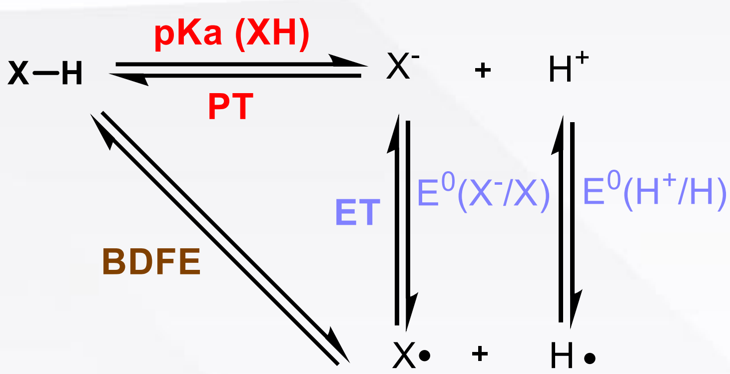
Oxidative HAT: R· too weak to break strong E-H bond



Norton, J. R. *et al.*, *J. Am. Chem. Soc.* **2008**, *130*, 4250−4252.
Gray, H. B. *et al.*, *Science* **2004**, *304*, 1653−1656.

BDFE: Bond Dissociation Free Energy

Bond Dissociation



At 298 K

$\Delta G^0_{PT} = -RT\ln(Ka) = -2.303RT\,pKa(X\text{-}H)$
$= -(1.37\ \text{kcal mol}^{-1})\,pKa(X\text{-}H)$

$\Delta G^0_{ET} = -FE^0 = -(23.06\ \text{kcal mol}^{-1}\,V^{-1})E^0$
$= -(23.06\ \text{kcal mol}^{-1}\,V^{-1})\,(E^0(X^-/X) + E^0(H^+/H))$

BDFE (kcal/mol) = 1.37pK*a*(X-H)+23.06 $E^0(X^-/X)$ +23.06$E^0(H^+/H)$

Adjustable

Contradictory

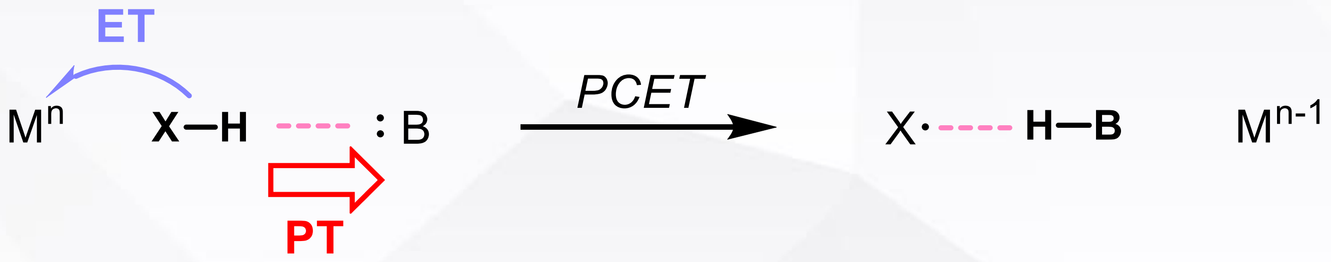
Constent

Bordwell, F. G. *et al., J. Am. Chem. Soc.* **1988**, *110*, 1229−1231.

Hydrogen Atom Transfer (HAT)

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

Proton-Coupled Electron Transfer

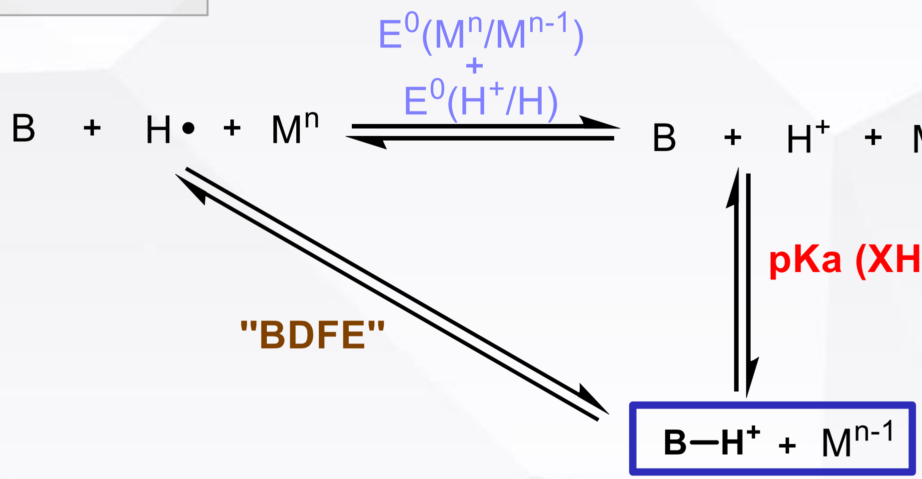


Concerted or stepwise transfer of the proton and electron

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

BDFE: Bond Dissociation Free Energy

Bond Generalization



Oxidant-base pair
or
Reductant-acid pair

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

Adjustable

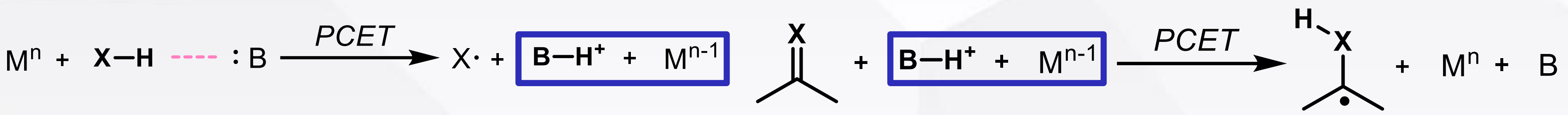
Unrelated

Mayer, J. M. *et al., Chem. Rev.* **2010**, *110*, 6961−7001.

Proton-Coupled Electron Transfer

Oxidative Process

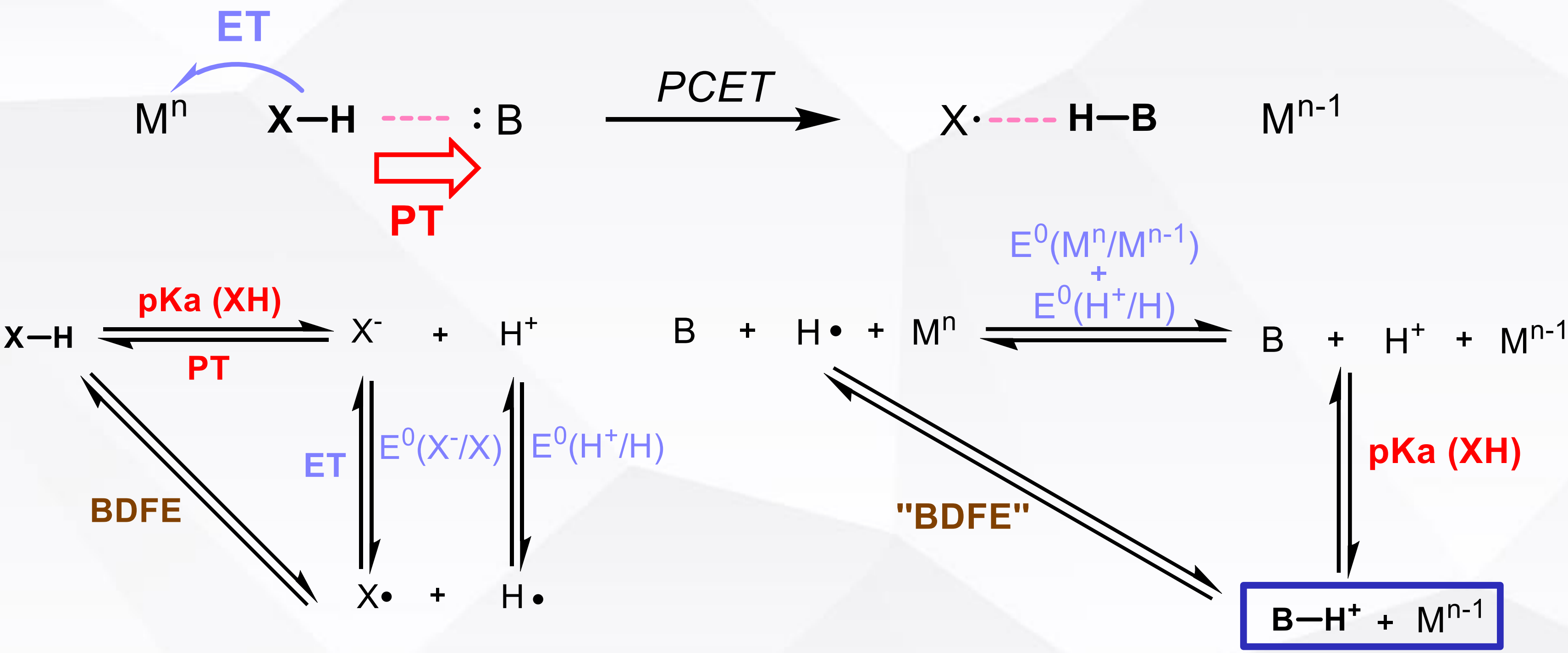
Reductive Process



Hydrogen Atom Acceptor Pairs					Hydrogen Atom Donor Pairs				
Oxidant	Base	E^0 (V)	pKa	'BDFE'	Reductant	Acid	E^0 (V)	pKa	'BDFE'
$Fe^{III}(bpy)_3$	pyridine	0.70	12.5	87	Cp_2Co	$PhCO_2H$	–1.34	21.5	54
$^*Ru^{II}(bpy)_3$	acetate	0.39	23.5	96	$(CpMe_5)_2Co$	lutidinium	–1.47	14.1	40
$^*Ru^{II}(bpz)_3$	lutidine	1.07	14.1	100	$Ru^{I}(bpy)_3$	pyridinium	–1.71	12.5	33
$^*Ir^{III}(dF(CF_3)ppy)_2(bpy)$	DMAP	1.0	18	103	$Ru^{I}(bpy)_3$	PTSA	–1.71	8.6	27

Knowles, R. R. *et al.*,*Top Curr Chem (Z)* **2016**, *374*, 30

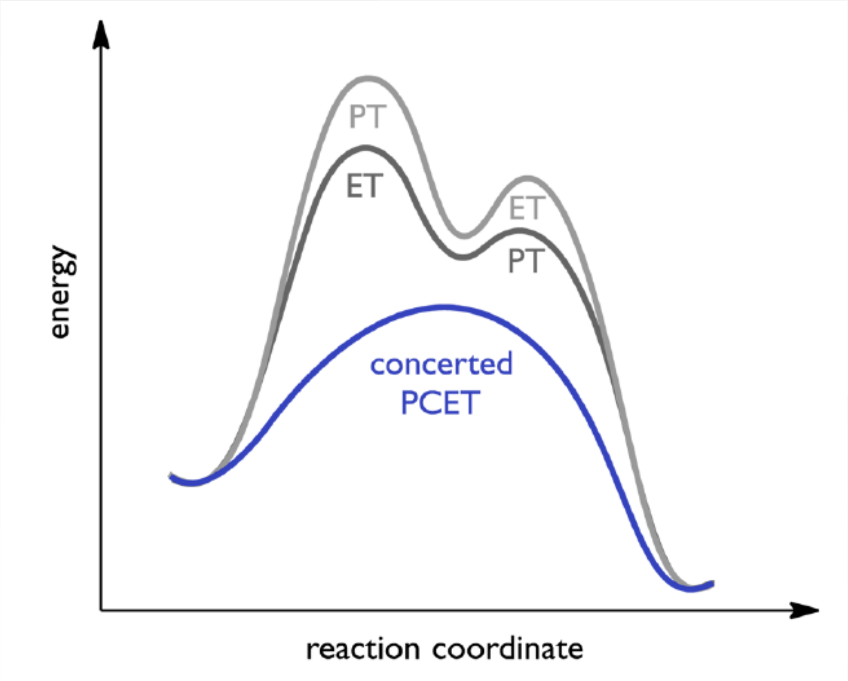
Proton-Coupled Electron Transfer

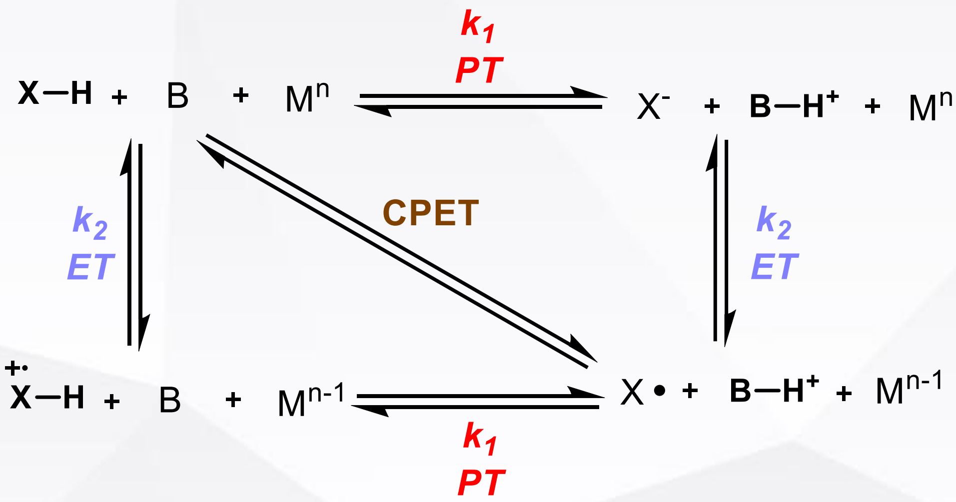


Δ G(PCET) = BDFE - "BDFE"

Mayer, J. M. *et al.*, *Chem. Rev.* **2010**, *110*, 6961−7001.

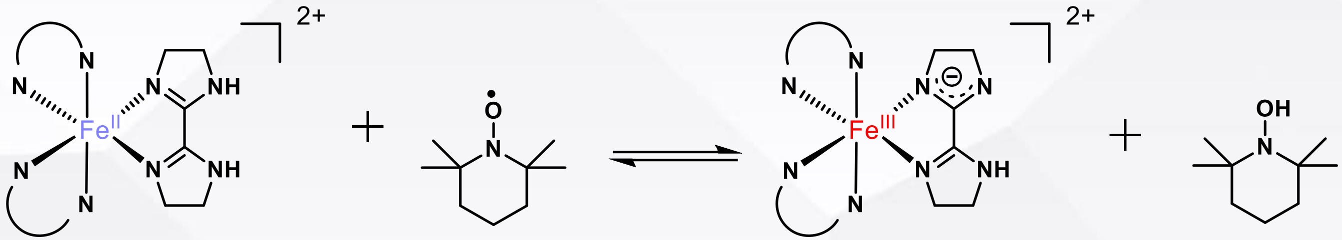
Kinetic Advantages of CPET



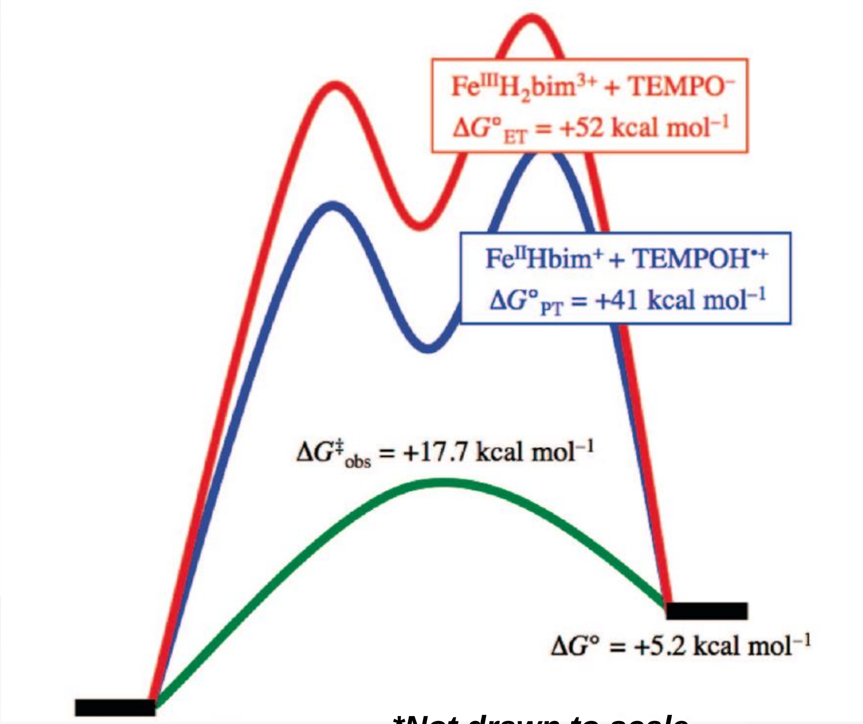


Hammes-Schiffer, S., *Acc. Chem. Res.* **2001**, *34*, 273-281
Knowles, R. R. *et al., Acc. Chem. Res.* **2016**, *49*, 1546−1556

Kinetic Advantages of CPET



$Fe^{II}H_2bim^{2+}$ TEMPO $Fe^{III}Hbim^{2+}$ TEMPOH



Not drawn to scale

ET : $Fe^{II}H_2bim^{2+}$ + TEMPO → $Fe^{III}H_2bim^{2+}$ + $TEMPO^-$

$\Delta G^0_{ET} = -FE^0$

$= -(23.06\ \text{kcal mol}^{-1}\ \text{V}^{-1})\ [\ (E^0(XH^{+/0}) + E^0(Y^{0/-})\ ]$

PT : $Fe^{II}H_2bim^{2+}$ + TEMPO → $Fe^{II}Hbim^{2+}$ + $TEMPOH^{\cdot+}$

$\Delta G^0_{PT} = -RT\ \ln(Ka)$

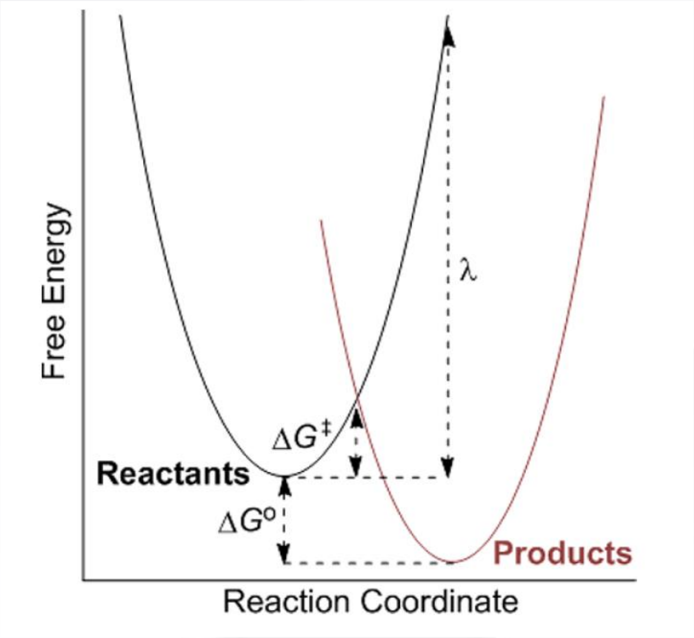
$= -(1.37\ \text{kcal mol}^{-1})\ \ [pKa(YH^+) - pKa(XH)]$

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

$\Delta G^0 < \Delta G^{\ddagger}$

Mayer, J. M. *et al.*, *Chem. Rev.* **2010**, *110*, 6961−7001.

One-Dimensional Marcus treatment



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

$\Delta G^{\ddagger} = \alpha\, \Delta G^{0} + \beta'$ **Eyring Equation**

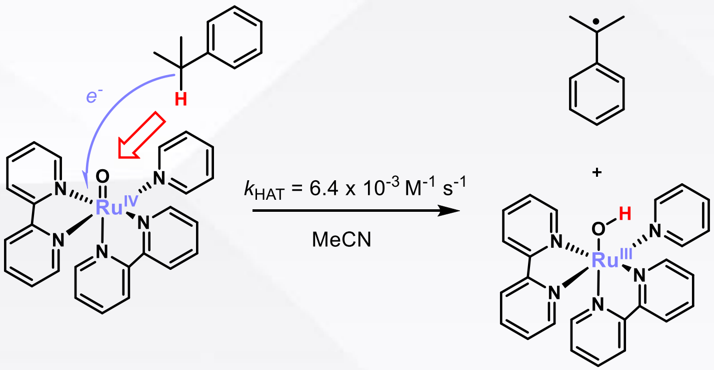
$\Delta G^{\ddagger} = \frac{(\Delta G^{0} + \lambda)^2}{4\lambda}$ **Marcus Equation**

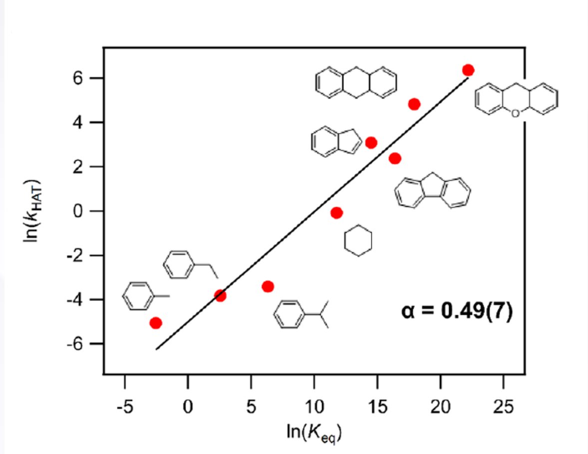
$\alpha = \frac{\partial(\Delta G^{\ddagger})}{\partial(\Delta G^{0})} = \frac{1}{2} + \frac{\Delta G^{0}}{2\lambda} \approx 0.5$ **when meets** $|\Delta G^{0}| \ll 2\lambda$

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

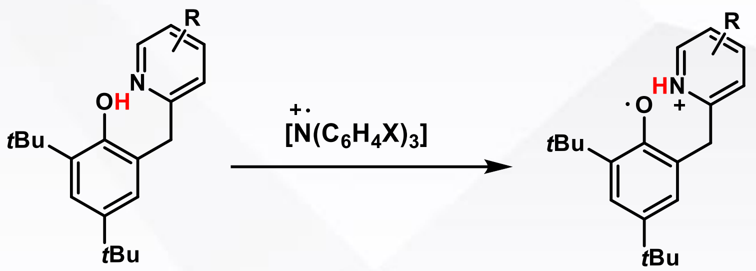
Mayer, J. M., Acc. Chem. Res. 2018, 51, 2391−2399

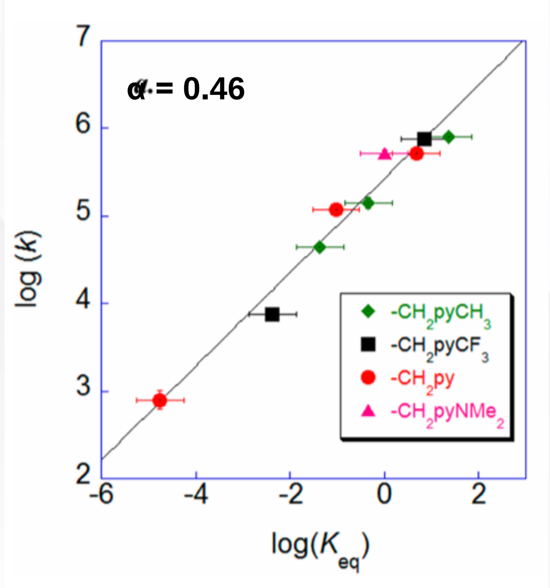
A Canonical CPET (HAT) Process





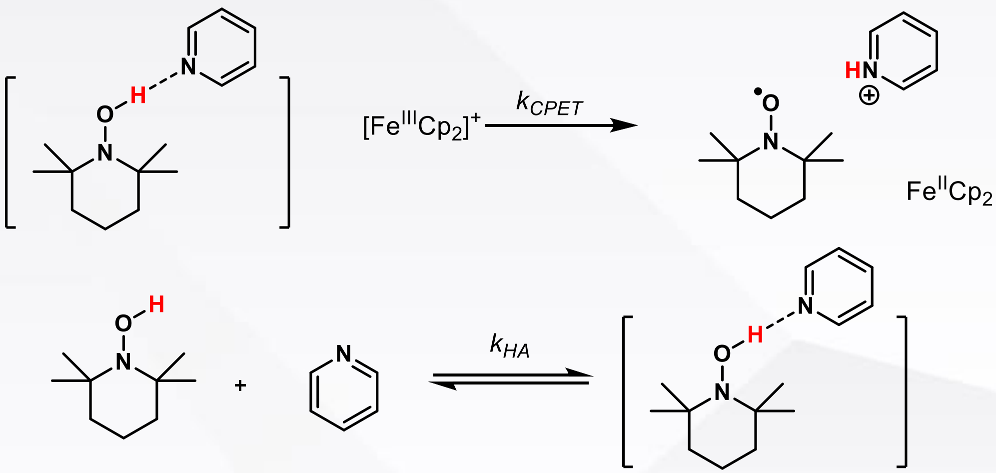
An Intramolecular Multisite CPET process

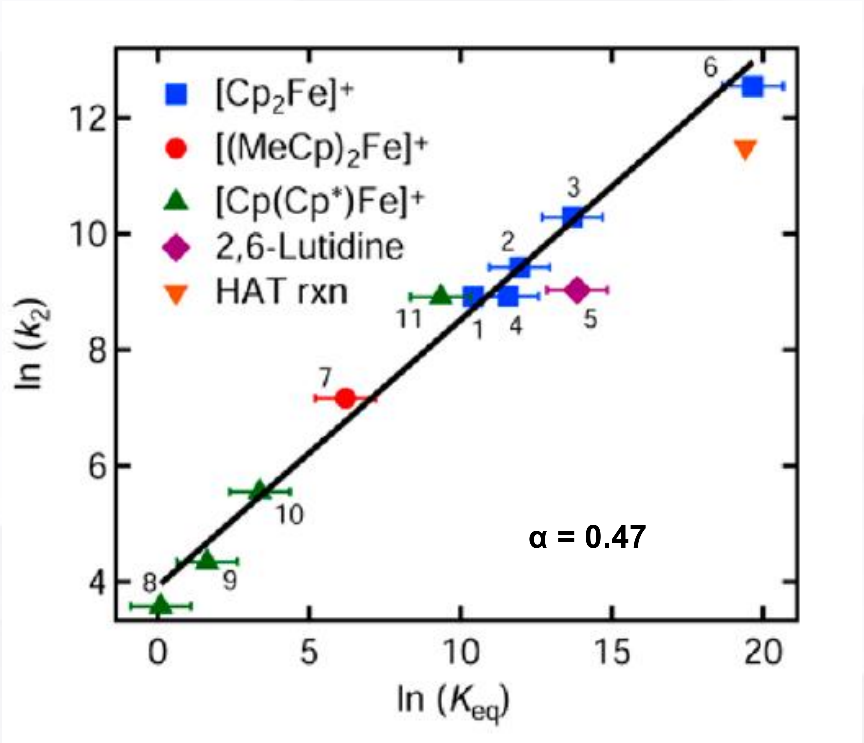




Mayer, J. M. *et al., J. Am. Chem. Soc.* **2003**, *125*, 10351−10361.
Mayer, J. M. *et al., J. Phys. Chem. A* **2012**, *116*, 12249−12259.

A Termolecular MS-CPET Process



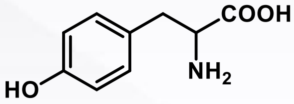


Mayer, J. M. *et al., J. Am. Chem. Soc.* **2003**, *125*, 10351−10361.
Mayer, J. M. *et al., J. Phys. Chem. A* **2012**, *116*, 12249−12259.

2

Mechanistic Study of PCET in Organic Synthesis

Mechanistic Study – Long range PT/ET

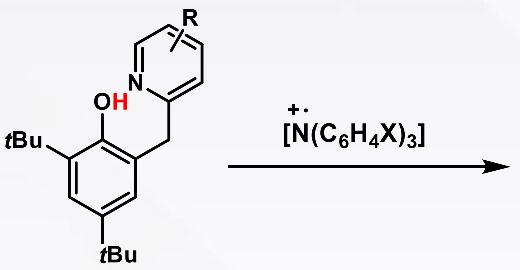


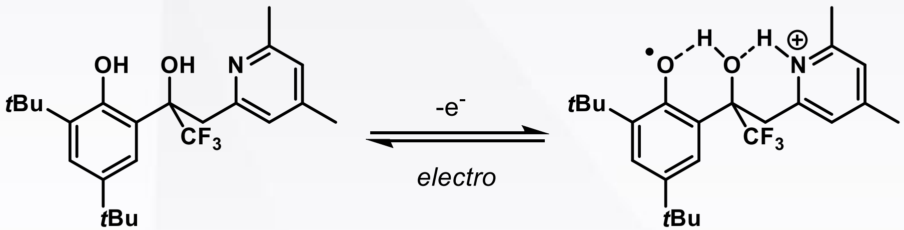
Tyrosine

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

Long range transfer

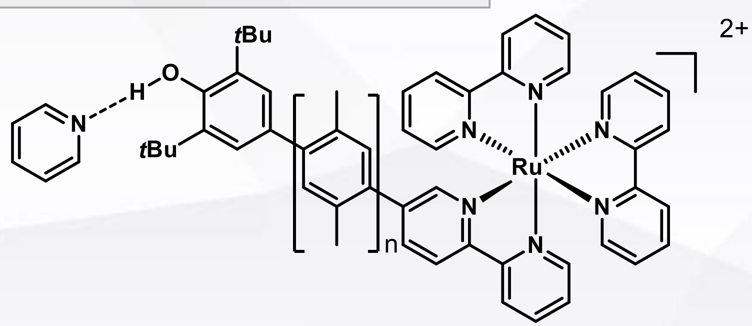
A Long range PT Process





long range proton transfer

A Long range ET Process

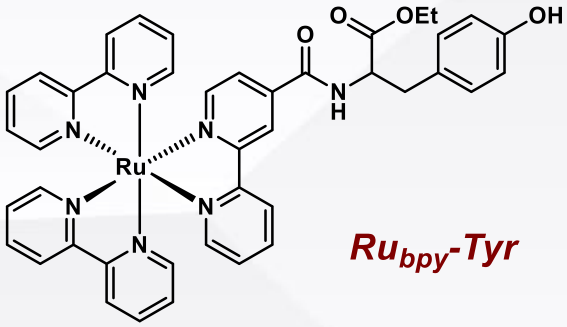


n	R_{DA} (Å)	k_{PCET} (s^{-1})
1	12.2	1.07×10^{9}
2	16.5	3.35×10^{8}
3	20.8	3.41×10^{6}

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

long range electron transfer

Mayer, J. M. *et al.*, *J. Phys. Chem. A* **2012**, *116*, 12249−12259
Wenger, O. S. *et al.*, *Chem. Eur. J.* **2014**, *20*, 4098–4104
Saveant, J. M.*et al.*, *Angew Chem Int Ed.* **2010**, *49*, 3803–3806



Ru_{bpy}-Tyr

$$Ru^{III}\text{-TyrOH} \longrightarrow Ru^{II}\text{-TyrO}^{\cdot} + H^{+}$$

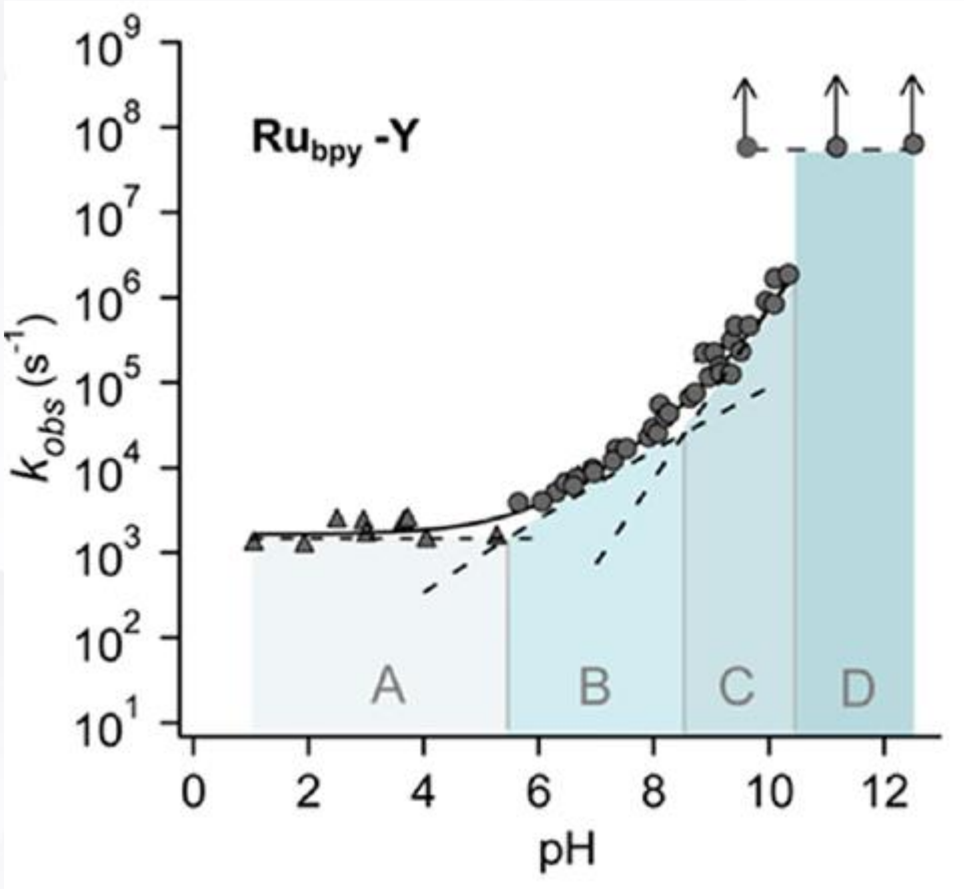
$$k_{PCET} = k_1 + k_2 \times 10^{0.5pH} + k_3 \times 10^{pH}$$

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

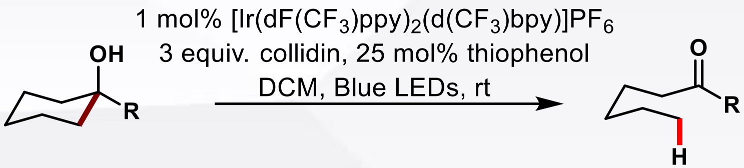
A region : ET-limited ETPT

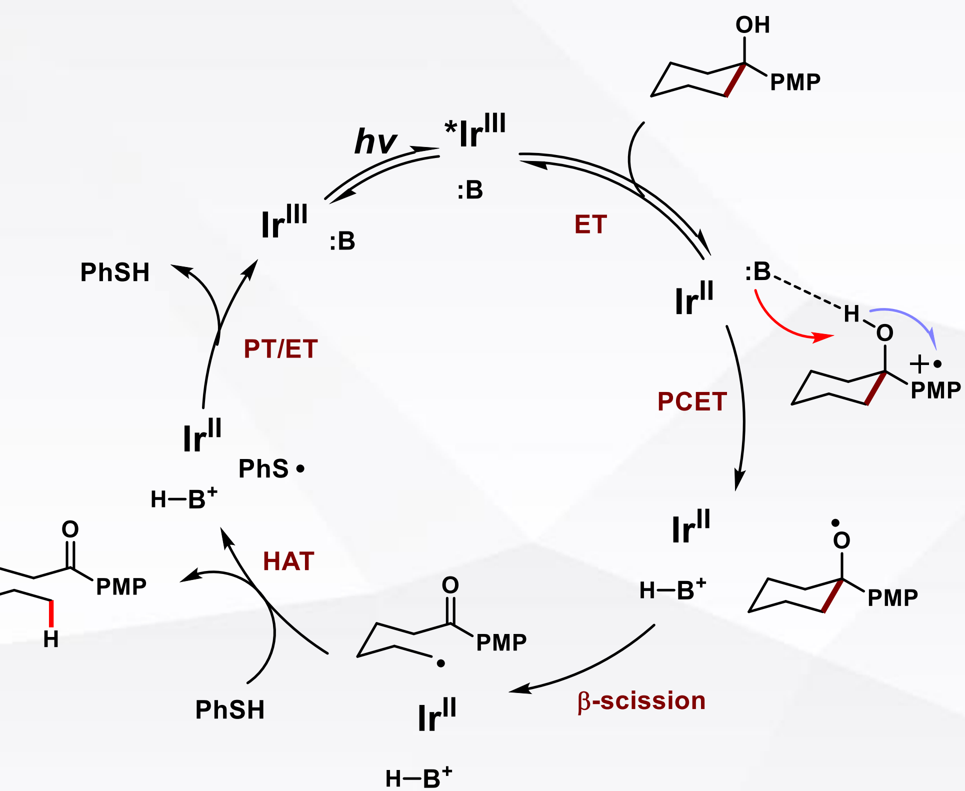


Hammarström, L *et al., J. Am. Chem. Soc.* **2012**, *134*, 16247−16254

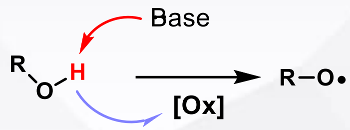
Mechanistic Study - Alcohols

Ring-Opening of Cyclic Alcohols





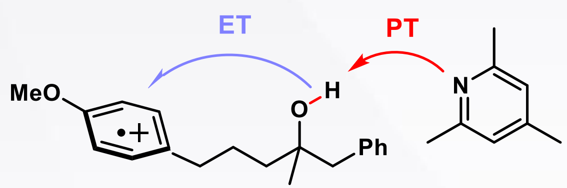
Alcohols



Strong bond ~ 105 kcal

Low acidicity

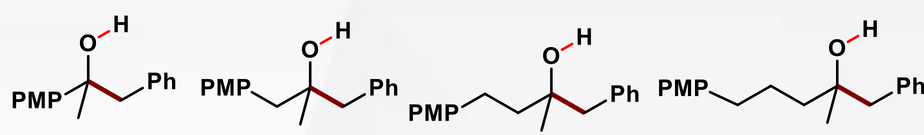
Difficult to selective homolysis



ΔG^0_{PT} ~ + 34 kcal/mol

ΔG^0_{PCET} ~ + 1 kcal/mol

long-range PCET

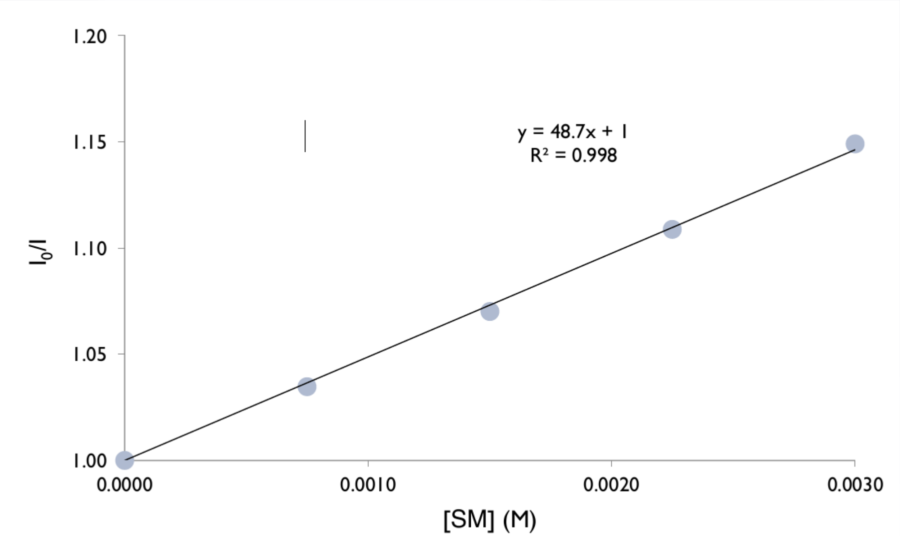


88% | 94% 17:1 rr | 89% | 6%

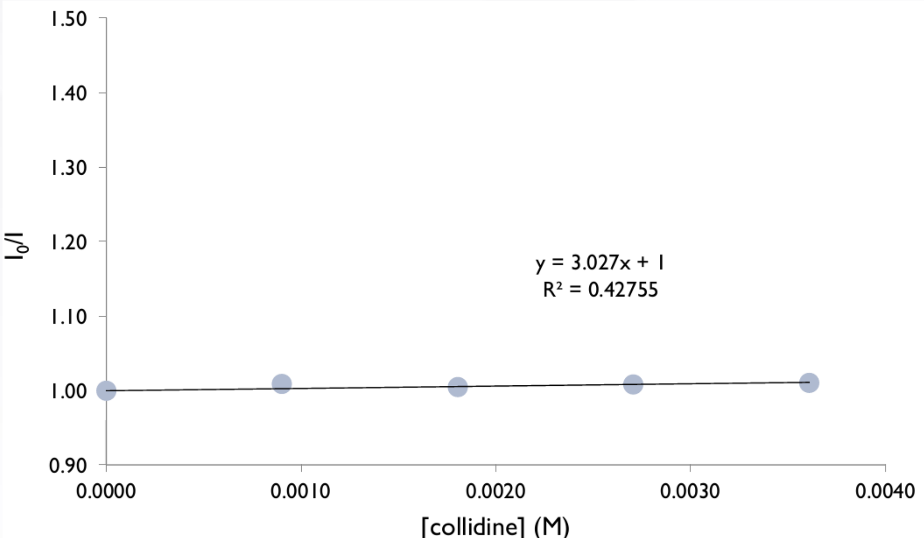
Knowles, R. R. *et al.*,*J. Am. Chem. Soc.* **2016**, *138*, 10794−10797F

Mechanistic Study - Alcohols

Stern-Volmer Studies

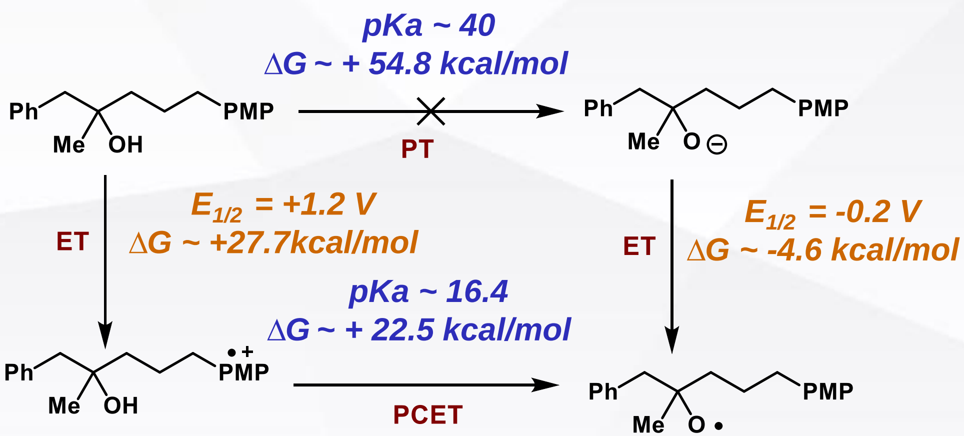


Starting Material



Collidine

Investigating Long-range PCET



pKa (collidine H$^+$) = 15.0

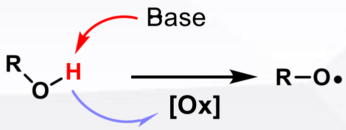
$E_{1/2}$ (Ir^{II}/Ir^{III}) = -1.07 V vs Fc/Fc$^+$

$E_{1/2}$ ($^*Ir^{III}/Ir^{II}$) = +1.30 V vs Fc/Fc$^+$

Knowles, R. R. *et al.*,*J. Am. Chem. Soc.* **2016**, *138*, 10794−10797F

Mechanistic Study - Alcohols

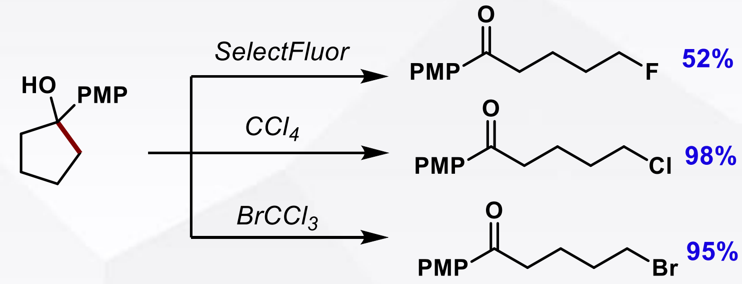
Alcohols



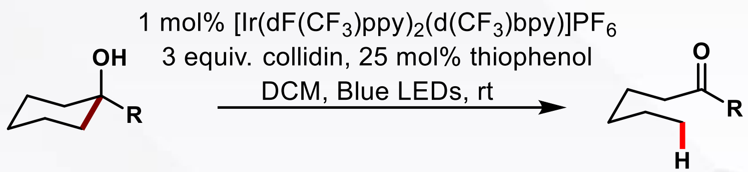
Strong bond ~ 105 kcal

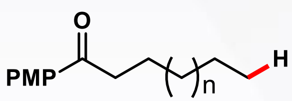
Low acidicity

Difficult to selective homolysis

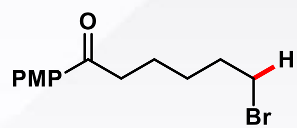


Ring-Opening of Cyclic Alcohols

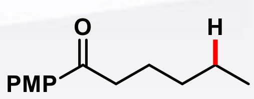




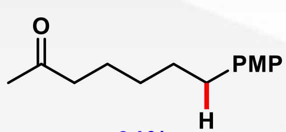
n = 1	71%
n = 2	86%
n = 3	89%
n = 4	90%
n = 5	81%
n = 6	92%
n = 7	85%



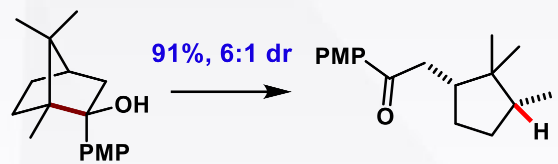
63%

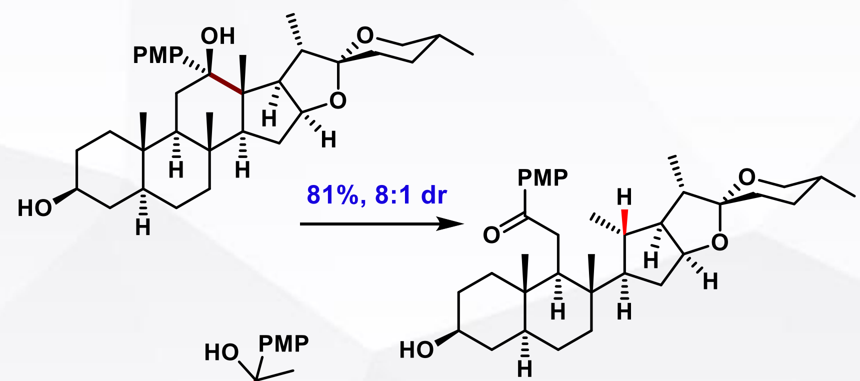


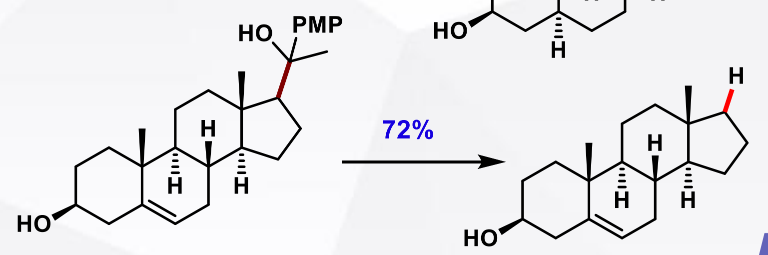
97%



91%



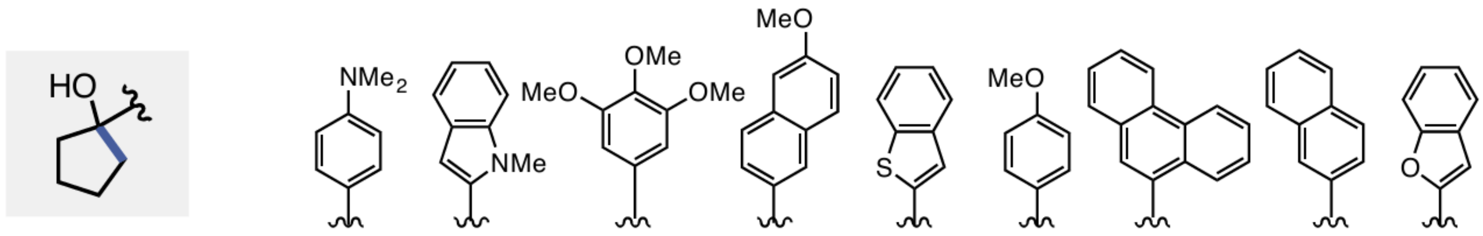




Knowles, R. R. *et al.*,*J. Am. Chem. Soc.* **2016**, *138*, 10794−10797F

Mechanistic Study - Alcohols

Effective BDFE Correlations with Reactivity

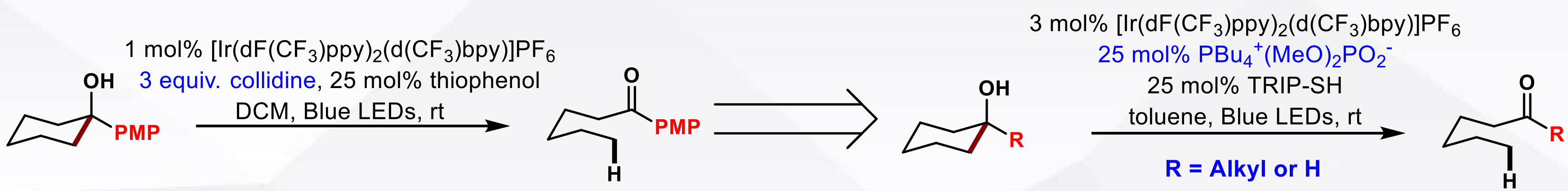


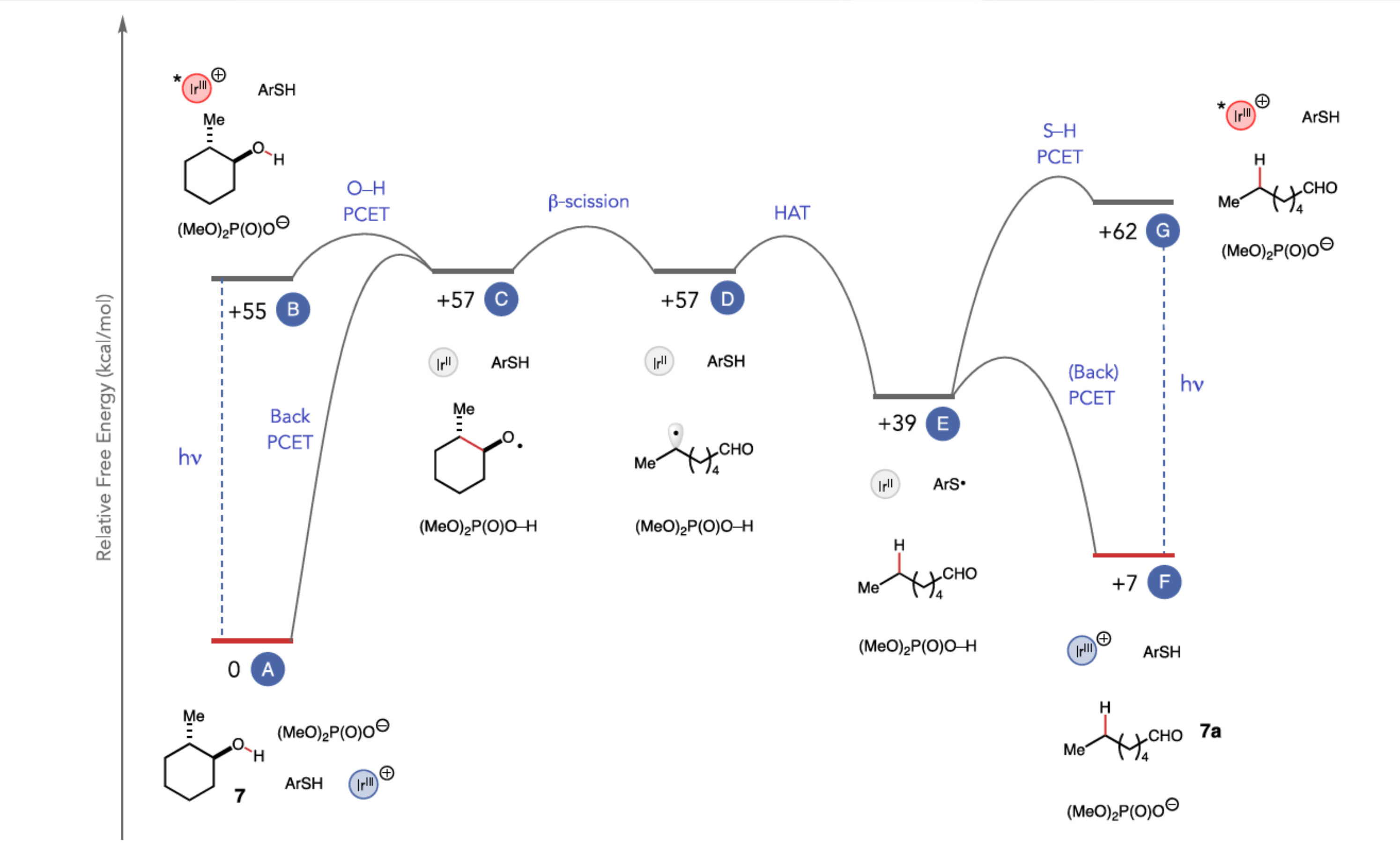
Base	$E_{p/2}$ (V)	0.39	0.69	0.92	0.96	1.18	1.22	1.22	1.24	1.27
2-MeO-pyridine	'BDFE'	77	84	90	91	96	97	97	97	98
pK_a = 9.9	Yield (%)	0	0	0	0	0	0	0	<5	8
pyridine	'BDFE'	81	88	93	94	99	100	100	101	101
pK_a = 12.5	Yield (%)	0	0	0	<5	6	16	14	5	19
CF_3COO^-	'BDFE'	81	88	93	94	99	100	100	101	101
pK_a = 12.5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

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

Knowles, R. R. *et al.*,*J. Am. Chem. Soc.* **2016**, *138*, 10794−10797F

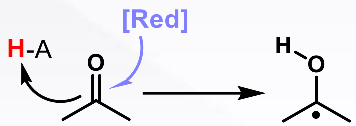
Mechanistic Study - Alcohols





Knowles, R. R. *et al., J. Am. Chem. Soc.* **2019**, *141*, 1457-1462

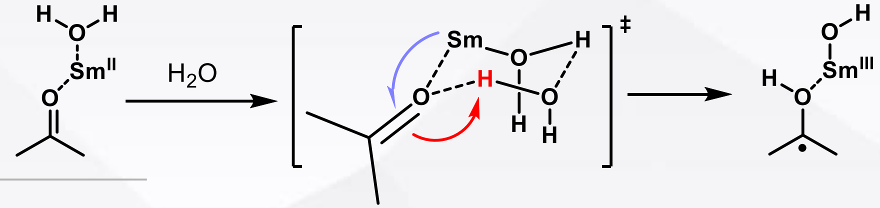
Ketone



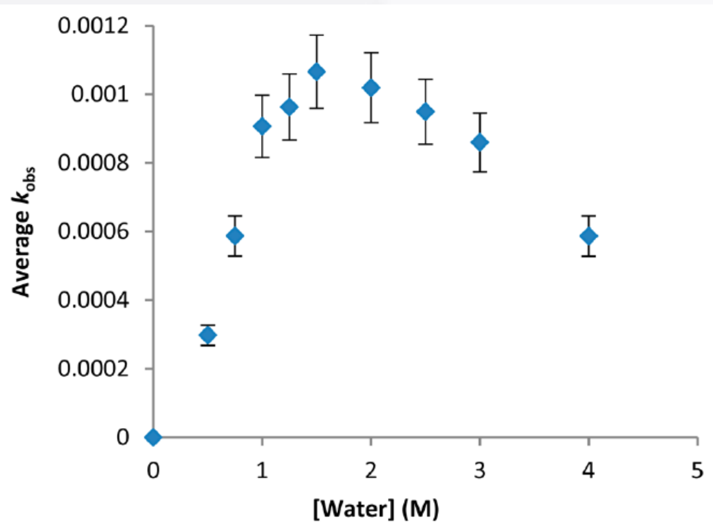
Ketyl radical

High reductive potential

Weak O-H bond



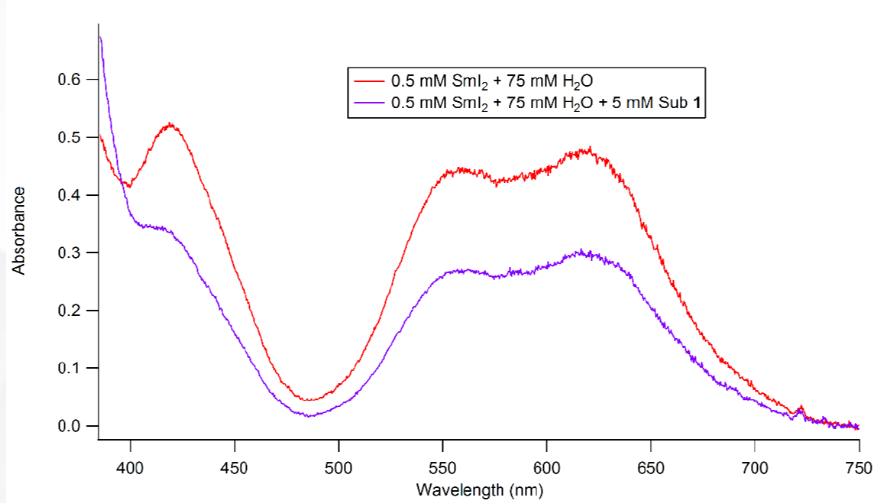
Reduction of Heptaldehyde By SmI_2



substrate	rate constant ($M^{-3}\ s^{-1}$)	rate orders H_2O	rate orders substrate	rate orders SmI_2
Heptaldehyde	$(4.2 \pm 0.3) \times 10^4$	2	1.0 ± 0.1	1
Cyclohexanone	570 ± 70	2	1.1 ± 0.1	1
5-Decanolide	0.18 ± 0.01	2	0.9 ± 0.1	1

$[H_2O]$ (0−1M) and constant $[SmI_2]$ (10 mM) and [substrate] (100 mM)

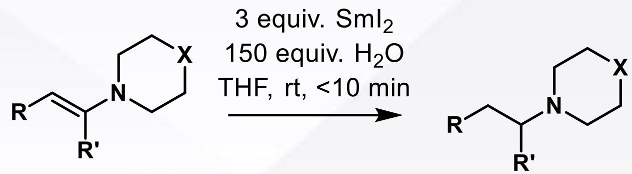
UV-Vis Spectra

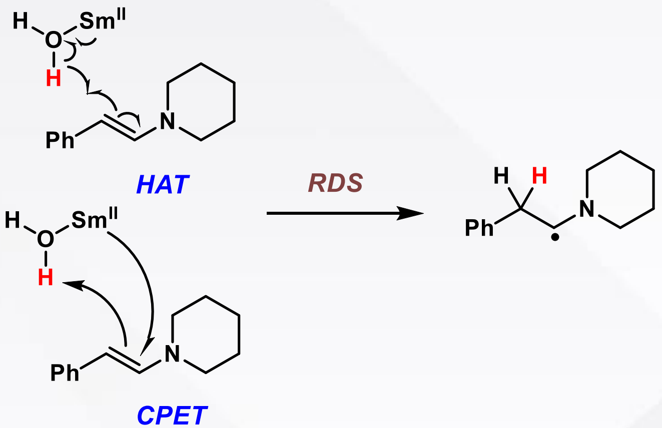


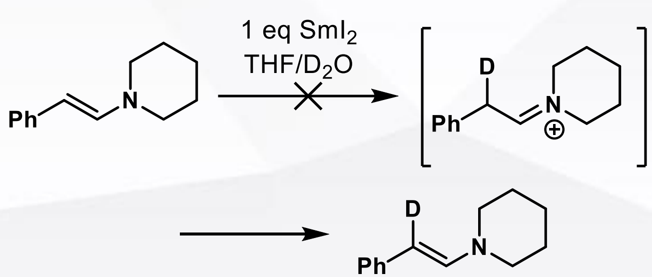
carbonyl coordination to Sm(II)

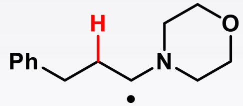
Flowers II, R. A. *et al., J. Am. Chem. Soc.* **2016**, *138*, 8738−8741

Enamines









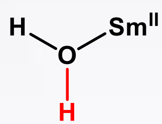
BDFE ~ 32 kcal/mol

$$Sm^{2+}\,(aq) \longrightarrow Sm^{3+}\,(aq) + e^- \qquad E = -E^o = 1.55V$$

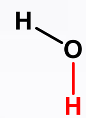
$$Sm^{3+}\,(aq) \longrightarrow Sm(OH)^{2+}\,(aq) + H^+ \qquad pKa \cong 3.3 \text{ for } Eu^{3+}$$

$$H^+ + e^- \longrightarrow H\bullet \qquad C_G = 57.6 \text{ kcal/mol}$$

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



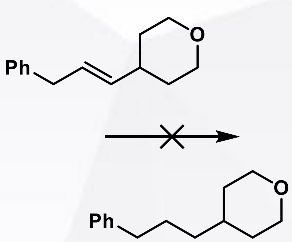
BDFE = 26 kcal/mol



BDFE = 110 kcal/mol

$$2Sm(H_2O)_n^{2+}\,(aq) \not\longrightarrow 2Sm(H_2O)_{n-1}(OH)^{2+}\,(aq) + H_2$$

$2Sm(H_2O)_n^{2+}$ (aq) +



+ $2Sm(H_2O)_{n-1}(OH)^{2+}$ (aq)

$\Delta G° < 0$

Mayer, J. M. *et al., J. Am. Chem. Soc.* **2017**, *139*, 10687−10692

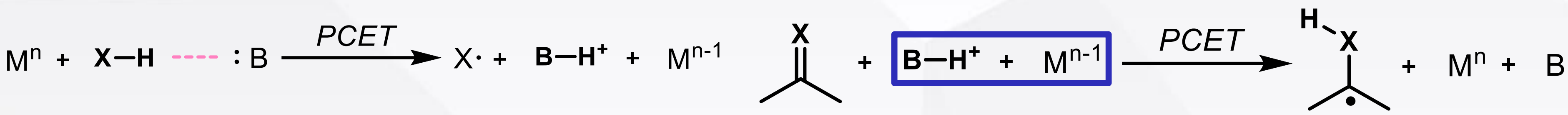
3

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

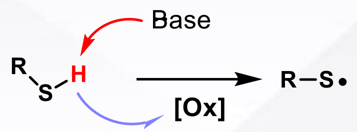
- **Enantioselective PCET catalysis**
- **Selectively C-H homolysis**
- **Application in total synthesis**
- **……**

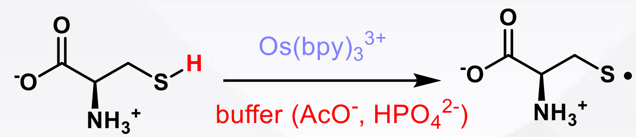
Thank you!

Reporter：Zhou Qiang
Supervisor： Prof. Lu

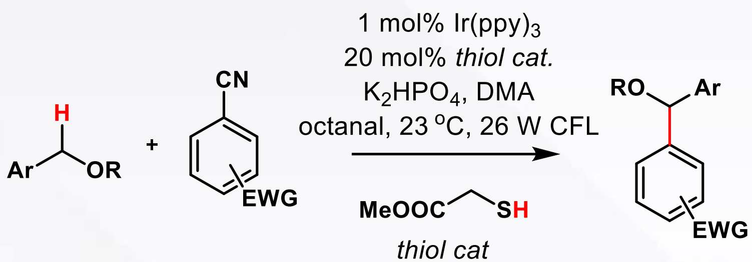
Oxidative PCET - Thiols

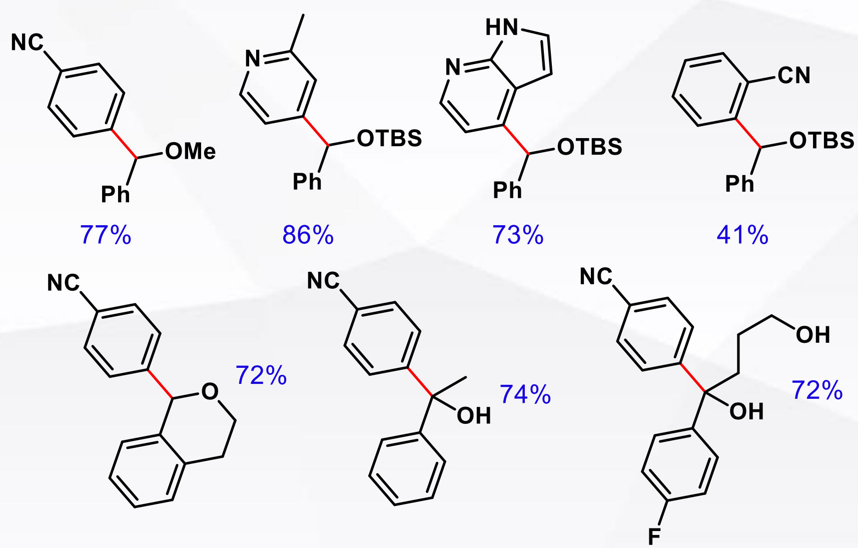
Thiols

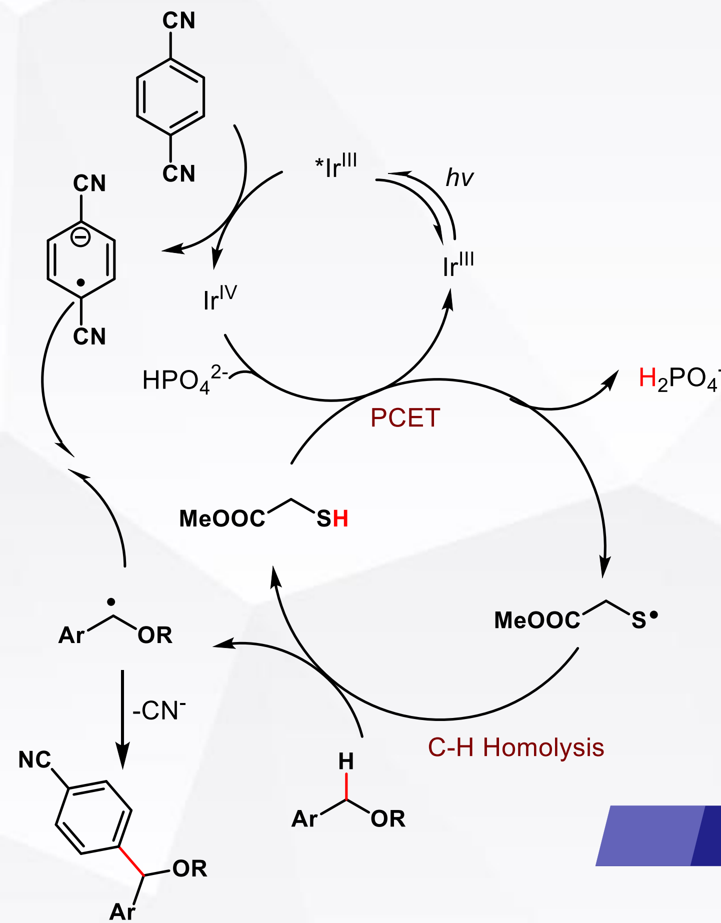




C–H bond Abstraction



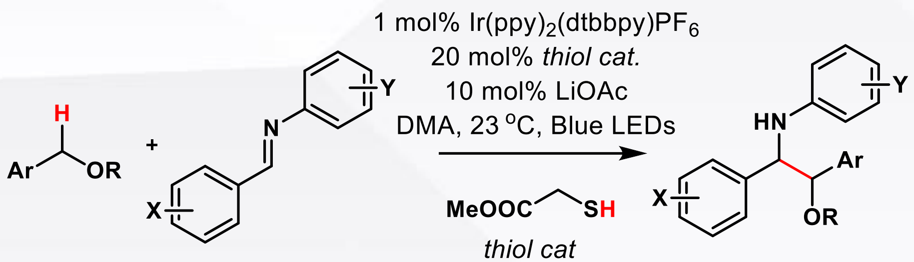


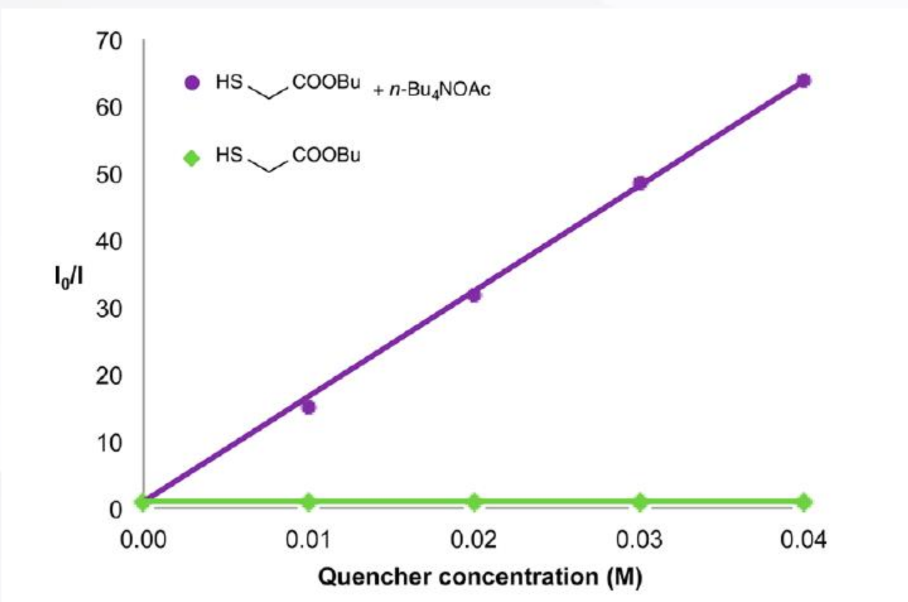


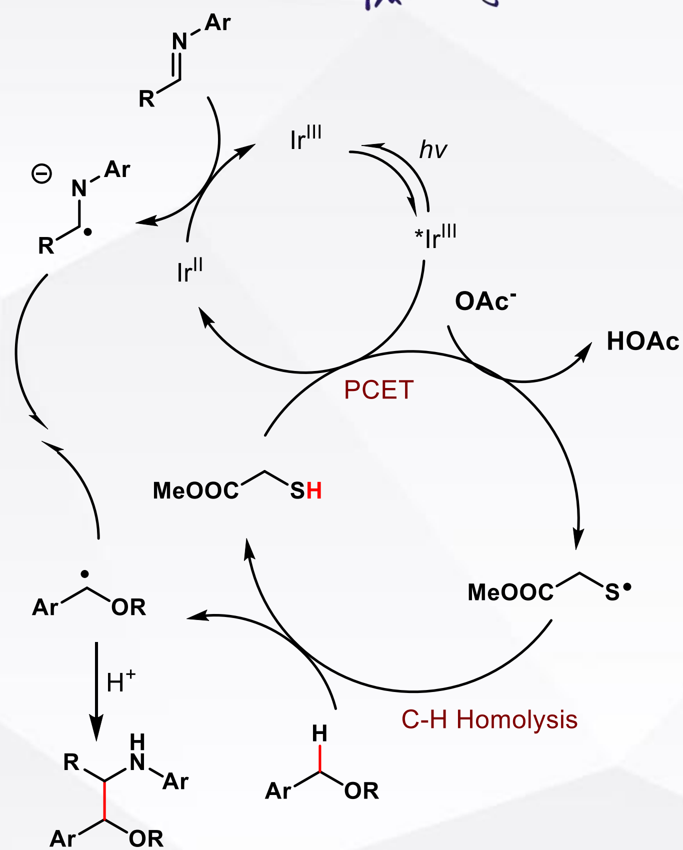
MacMillan, W. C., *et al., J. Am. Chem. Soc.* **2014**, *136*, 626−629

Oxidative PCET - Thiols

C–H bond Abstraction







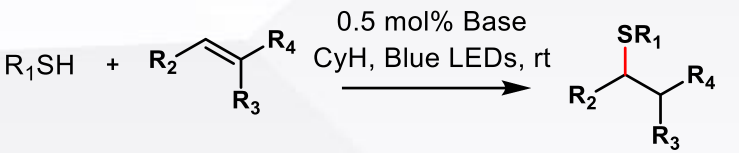
Stern–Volmer quenching experiment

PT/ET OR **CPET**

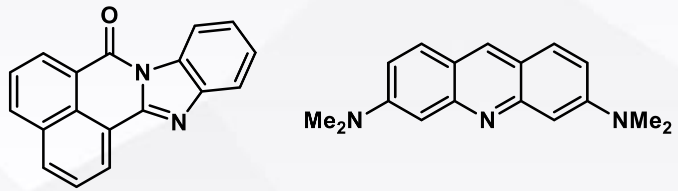
MacMillan, W. C., *et al., J. Am. Chem. Soc.* **2014**, *136*, 16986−16989

Oxidative PCET - Thiols

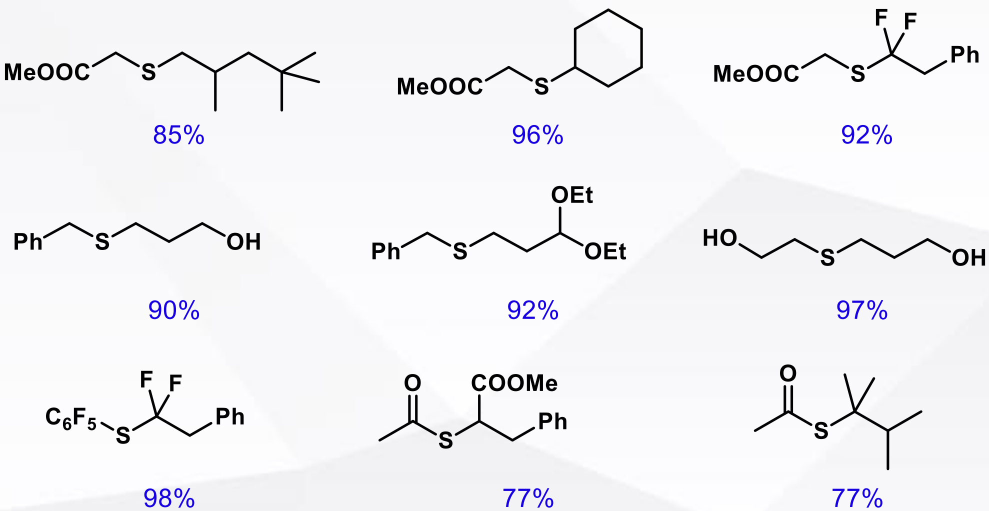
Thiol-Ene Reaction

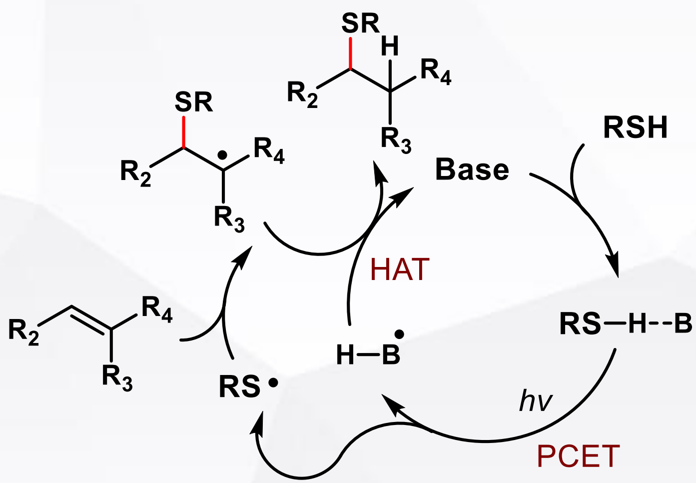


Base:



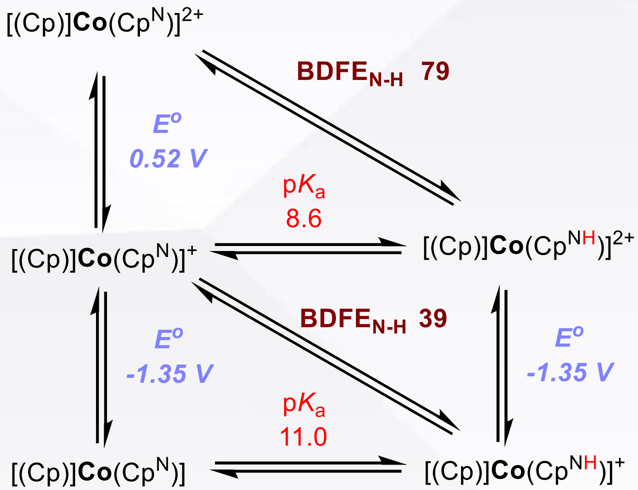
1 2



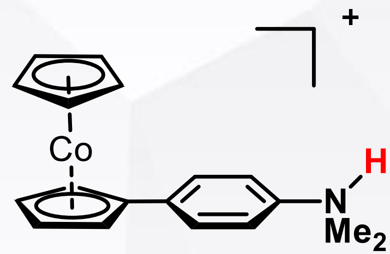


Dilman, A. D., *et al., J. Org. Chem.* **2019**, *84*, 8337-8343

Reductive PCET - Ketone



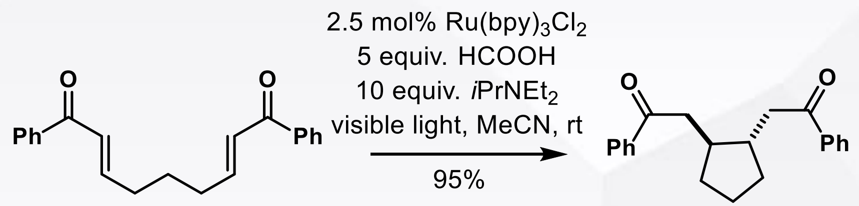
Electrocatalytic CPET

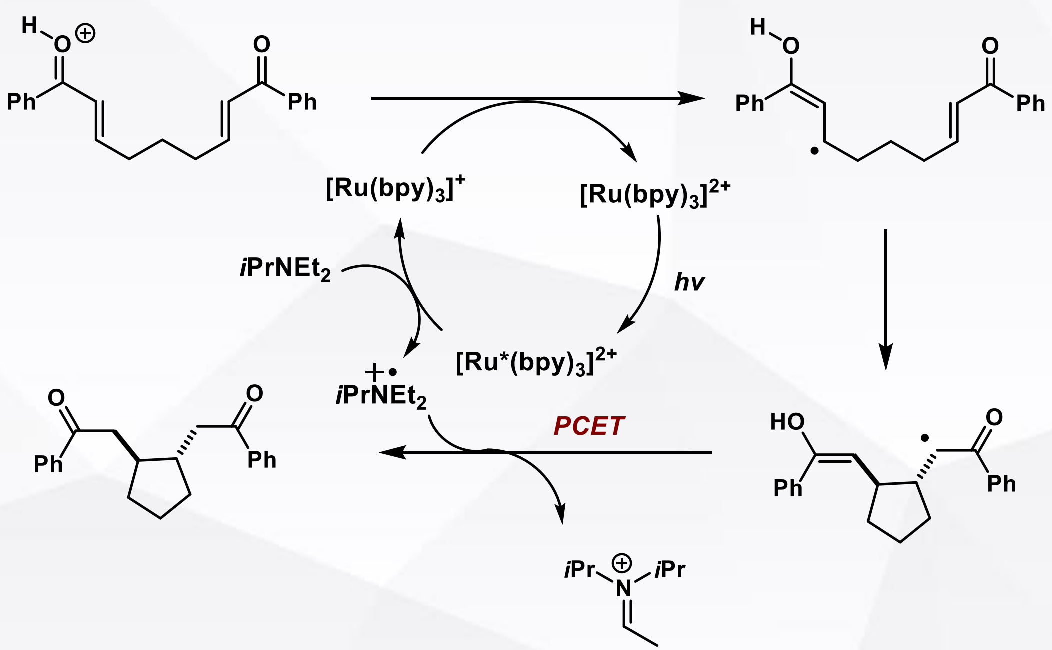


Reduction weakens bond by 40 kcal/mol !

Peters, J. C. *et al.*, *Science* **2020**, *369*, 850–854

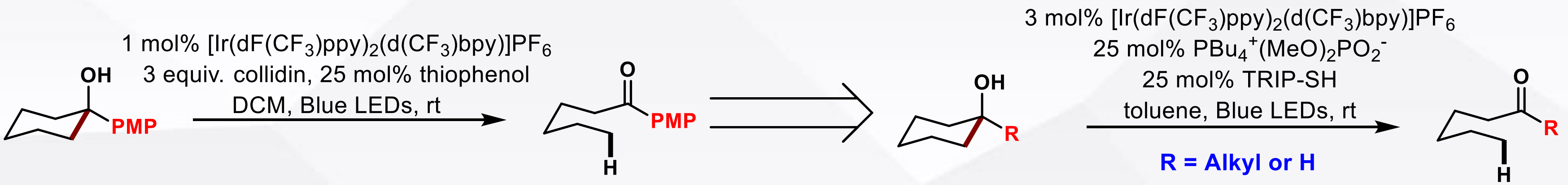
Enones

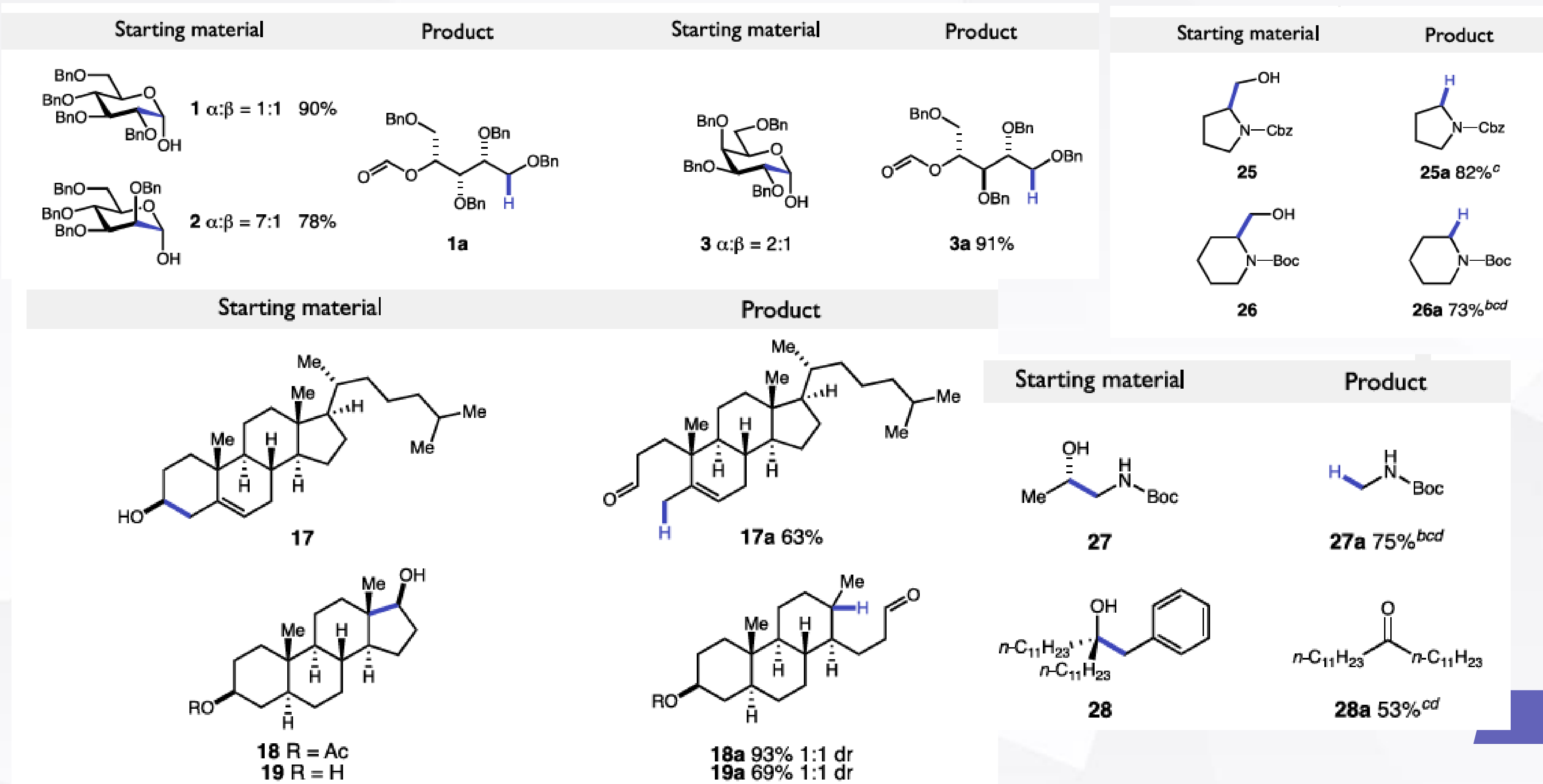




Yoon, T. P. *et al.*, *Chem. Sci.*, **2011**, *2*, 2115 - 2119

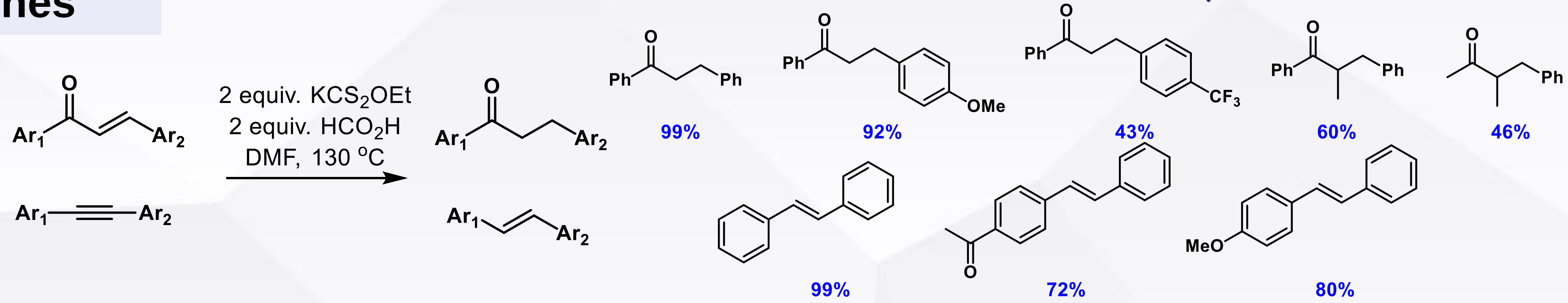
Ring-Opening of Cyclic Alcohols

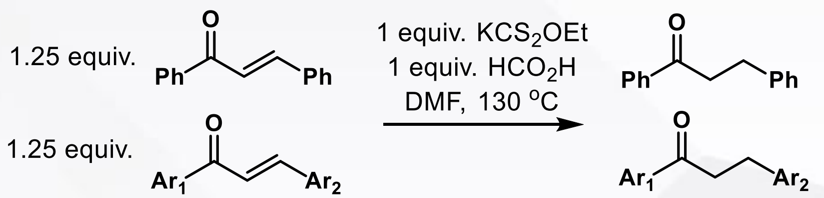


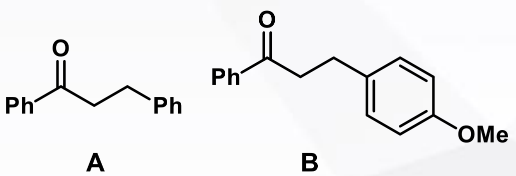


Knowles, R. R. *et al., J. Am. Chem. Soc.* **2019**, *141*, 1457-1462

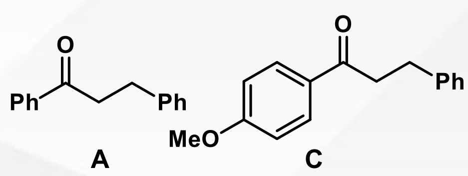
Enones



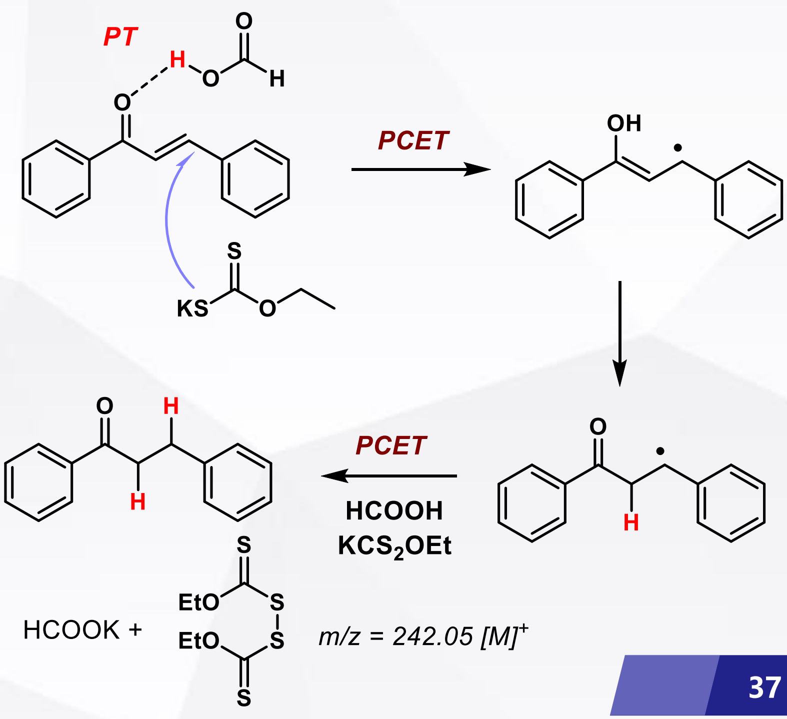




yield A: yield B = 1.4 :1



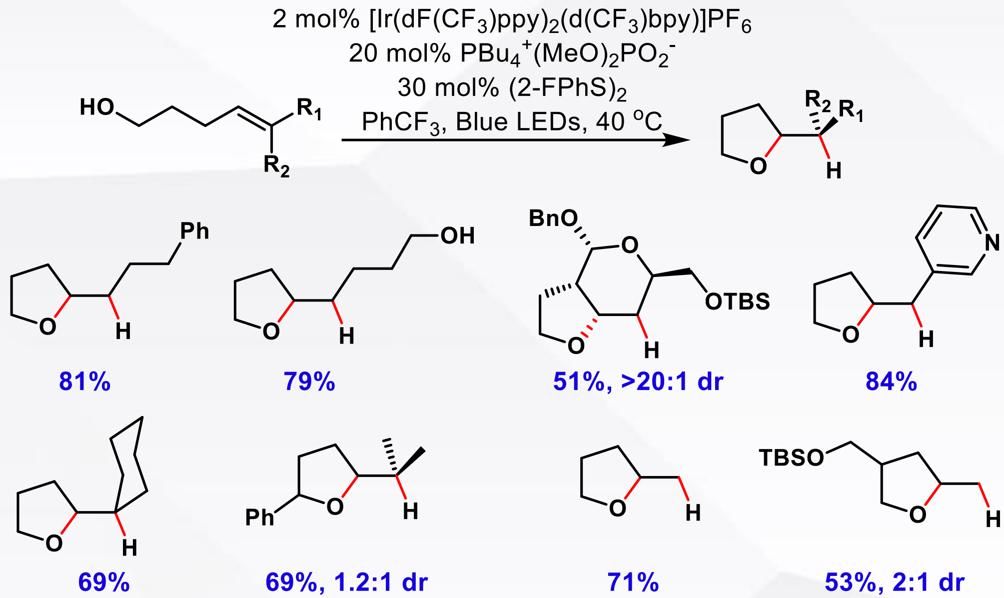
yield A: yield C = 1.5 :1

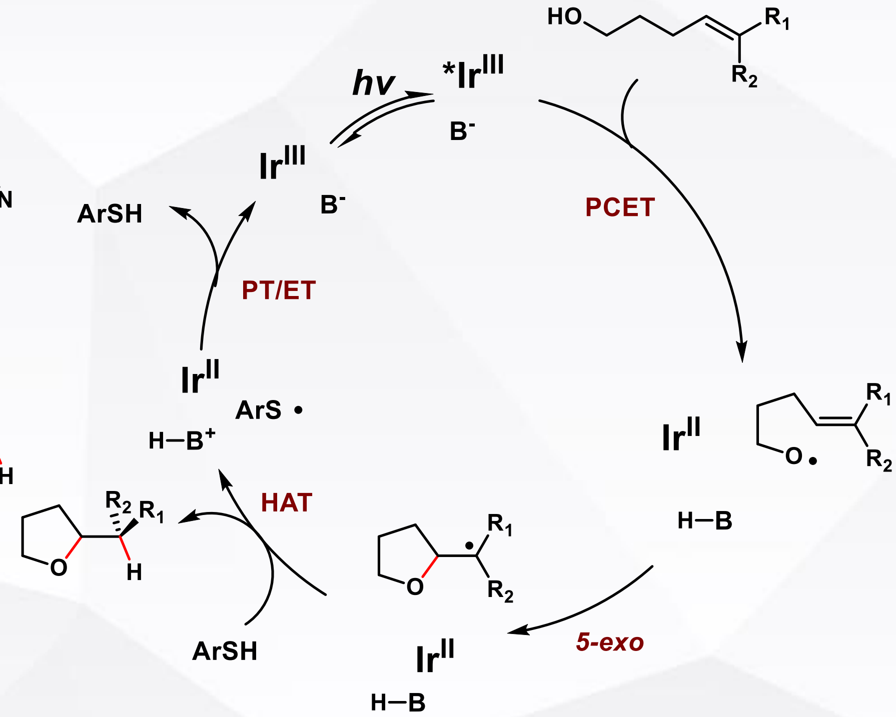


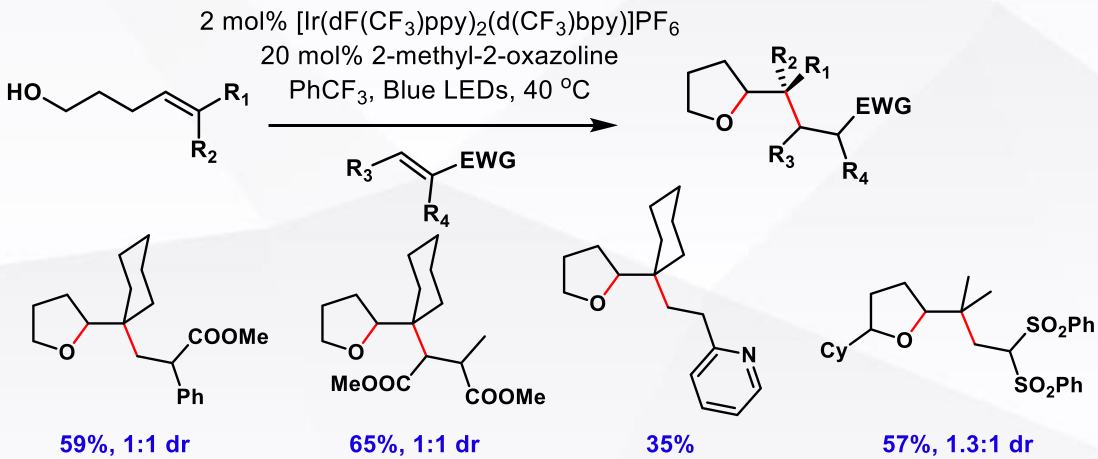
Sekar, G. *et al.*, *Org. Lett.* **2019**, *21*, 2650-2653

Oxidative PCET - Alcohols

Hydroetherification





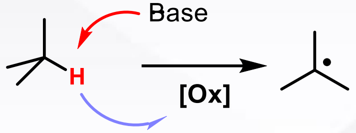


Intramolecular hydroetherification of unactivated alkenes

Knowles, R. R. *et al.*, *Angew. Chem. Int. Ed.* **2020**, *59*, 11845–11849

Oxidative PCET - C-H bond

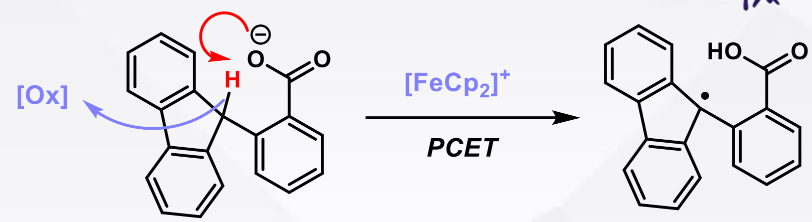
C-H Bond



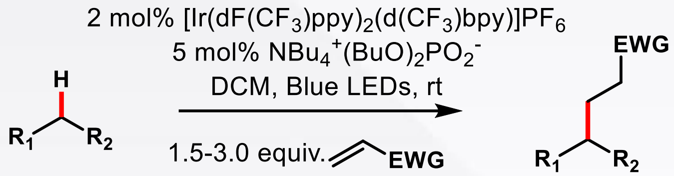
Strong bond

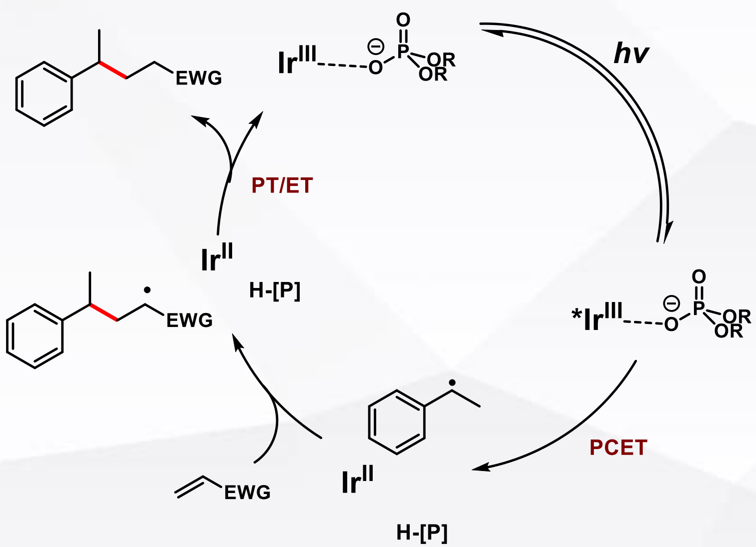
Low acidicity

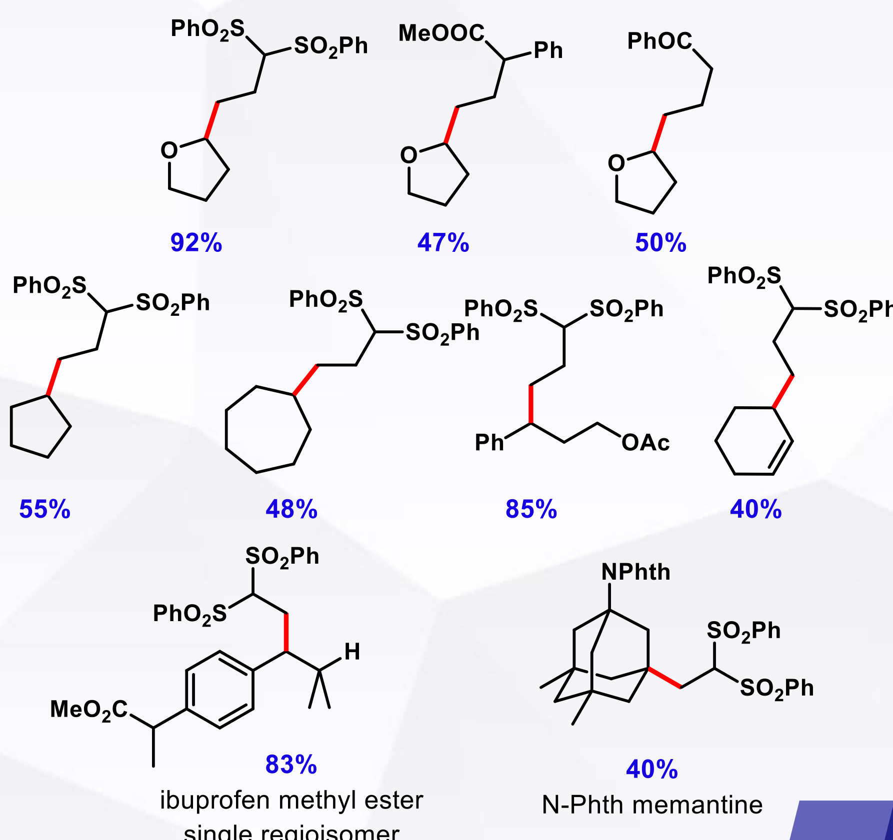
Non-polor



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

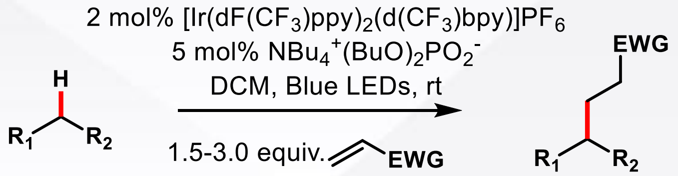


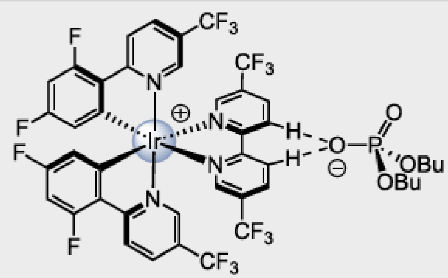




Mayer, J. M. *et al.*, *Sci. Adv.* **2018**, *4*, *eaat5776*
Alexanian, E. J. *et al.*, *J. Am. Chem. Soc.* **2019**, *141*, 13253−13260

Oxidative PCET - C-H bond

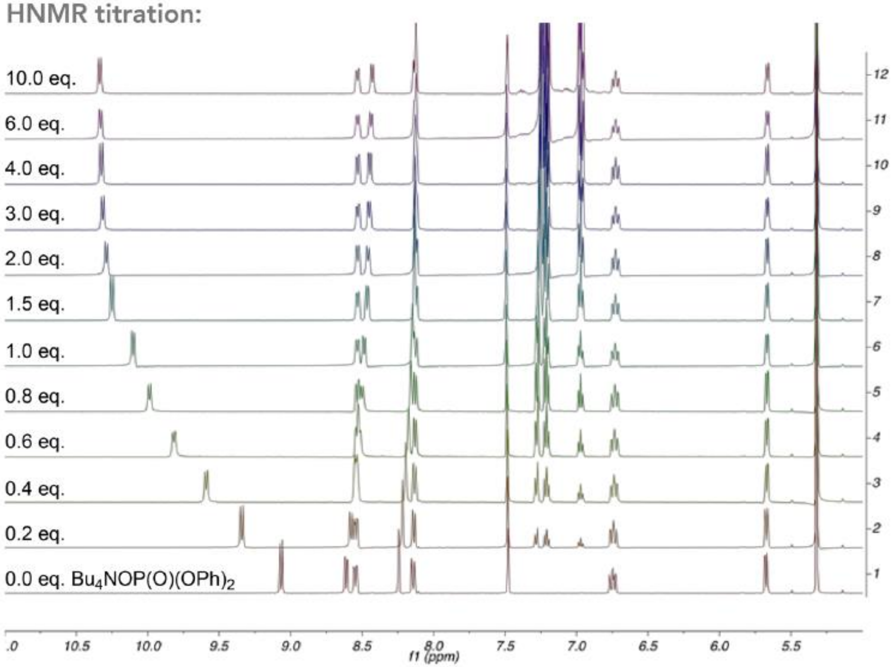


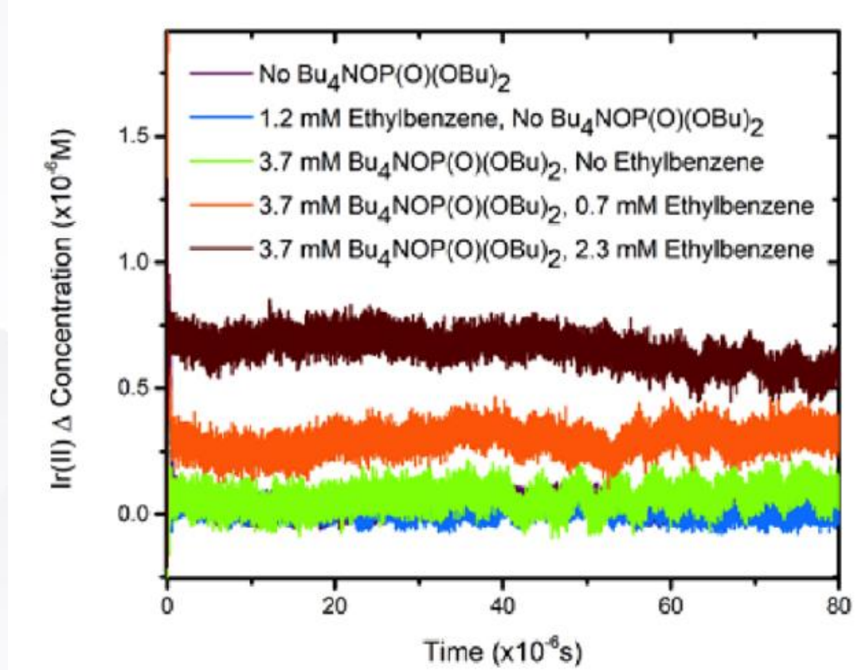


Photocatalyst-phosphate Complex

"BDFE" ~ 105 kcal/mol

HNMR titration:

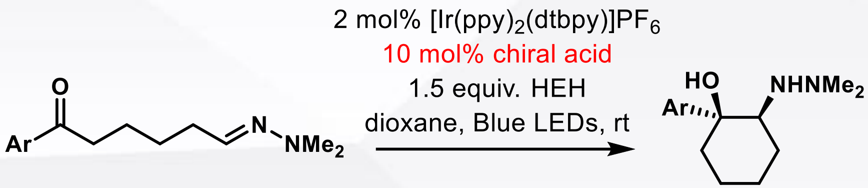


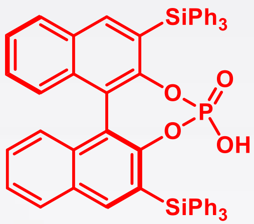


Alexanian, E. J. *et al*., *J. Am. Chem. Soc.* **2019**, *141*, 13253−13260

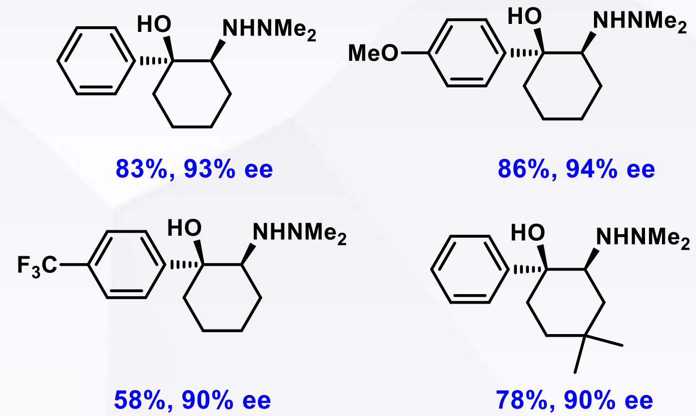
Reductive PCET - Ketone

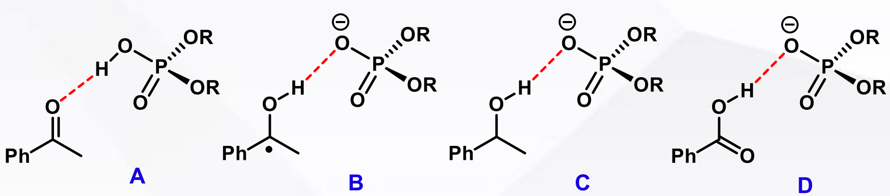
Asymmetric Aza-Pinacol Cyclization



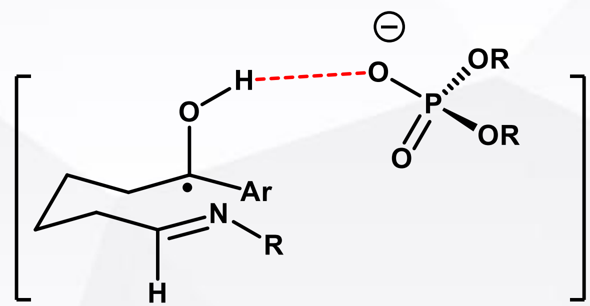


ET $\Delta G°$ = +13.6 kcal / mol
PCET $\Delta G°$ = +3.1 kcal / mol



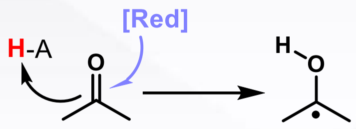


complex	$\Delta E_{H\text{-bond}}$[a,b]	d OH···O (Å)[a]	O–H pK_a(MeCN)	Mulliken charge (H)[a]
A	−9.2	1.642	13	0.39
B	−14.4	1.629	20	0.59
C	−10.4	1.737	~38[c]	0.51
D	−12.6	1.551	21.5	0.60



Knowles, R. R. *et al., J. Am. Chem. Soc. 2013, 135, 17735−17738.*

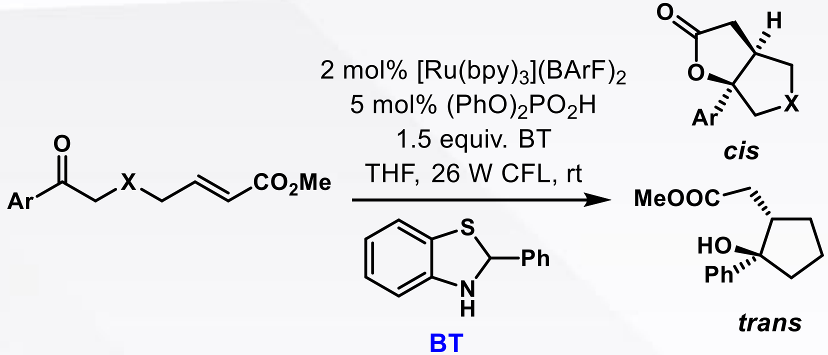
Ketone

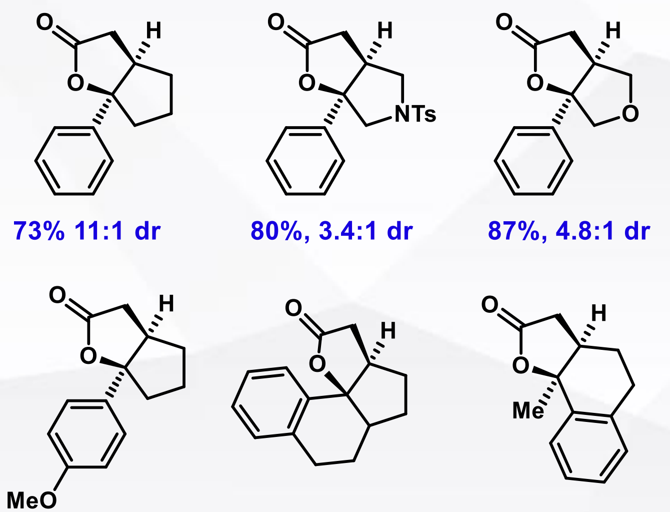


Ketyl radical

High reductive potential

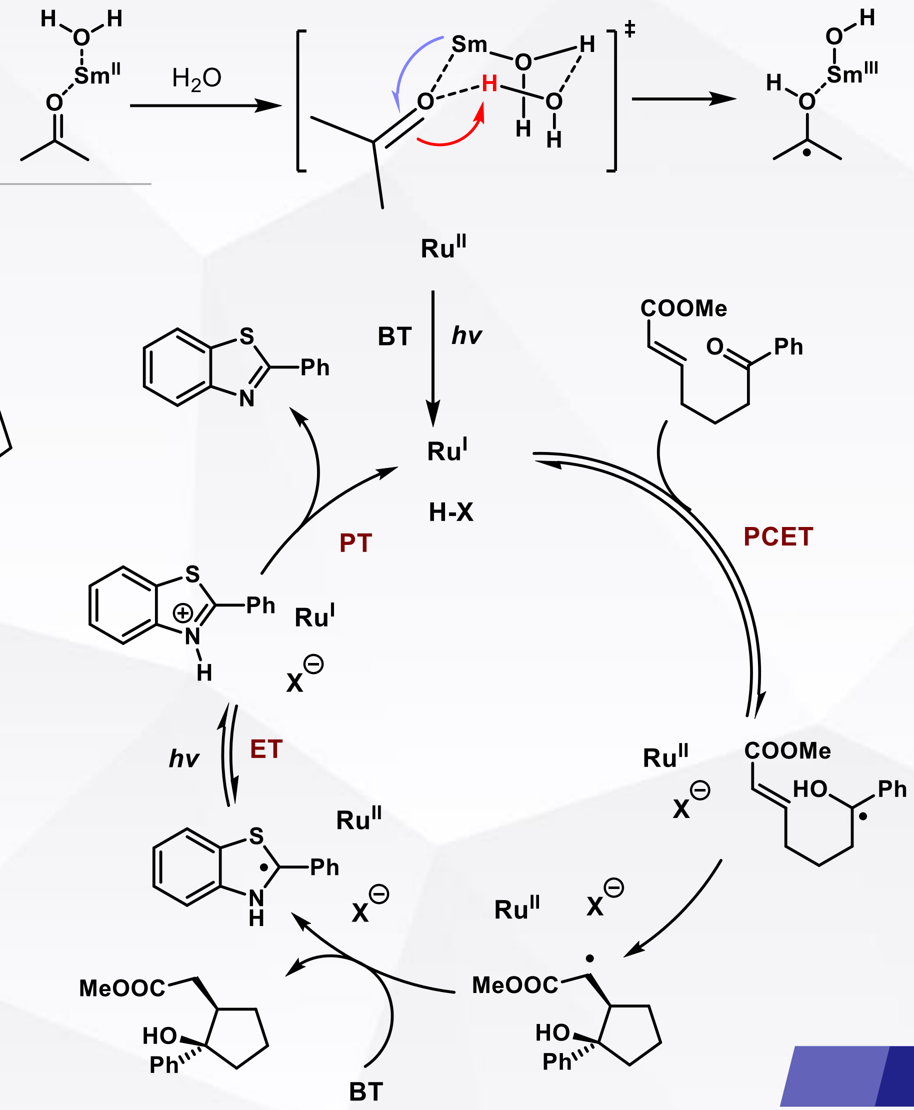
Weak O-H bond





73% 11:1 dr | **80%, 3.4:1 dr** | **87%, 4.8:1 dr**

78% 12:1 dr | **82%, 16:1 dr** | **78%, 1.2:1 dr**



Flowers II, R. A. *et al., J. Am. Chem. Soc.* **2016**, *138*, 8738−8741
Knowles, R. R. *et al., J. Am. Chem. Soc.* **2013**, *135*, 10022–10025