PCET策略在惰性键活化中的应用

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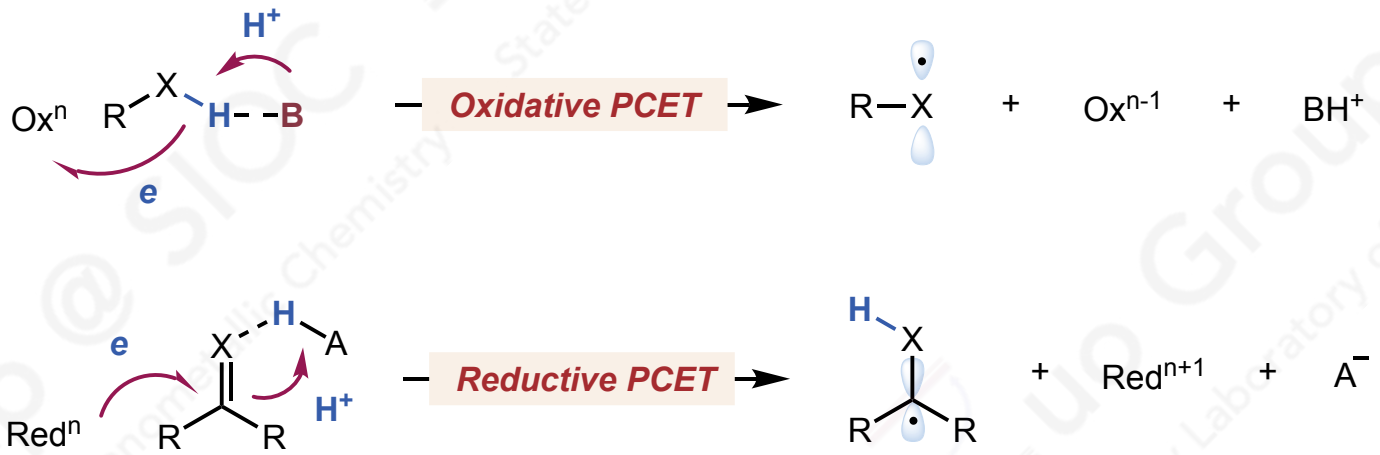
Proton-coupled electron transfer (PCET)

elementary step (or series of elementary steps) in which both a proton and an electron are exchanged.



- firstly proposed by Thomas Meyer in 1981
- ubiquitous chemical activation strategy in biological systems
- emerging synthetic strategy with intriguing catalytic transformations

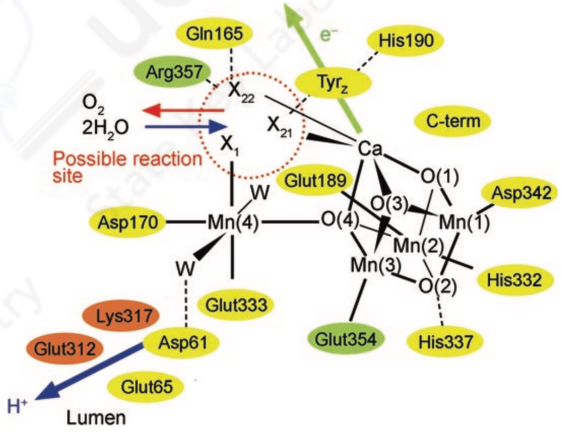
PCET在生物化学过程中的体现

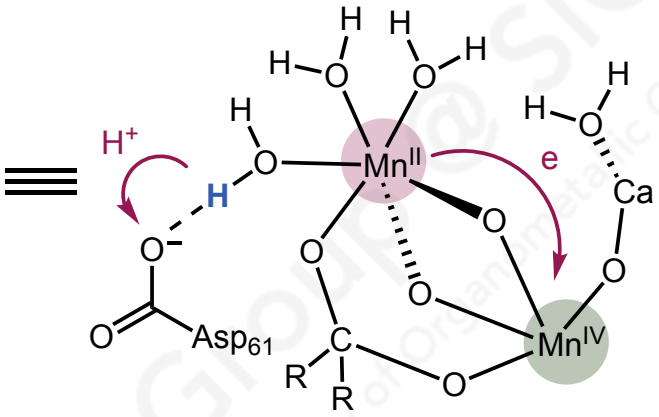
❑ 光合作用中水的氧化

$$O_2 + 4H^+ + 4e \longrightarrow 2H_2O$$

E^o = 0.815 V (vs NHE), pH = 7

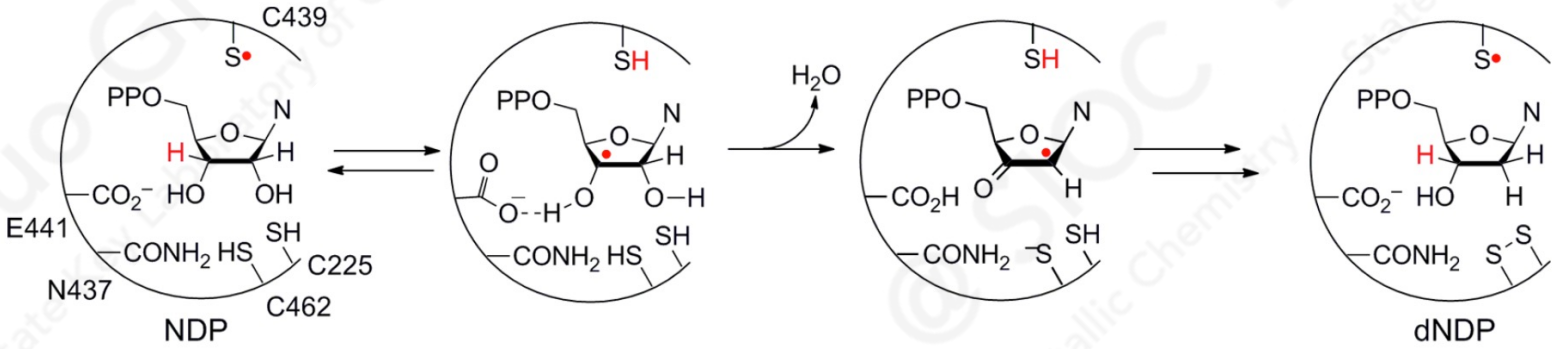
p$K_a(H_3O^+)$ = -1.74





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

❑ 核糖还原酶远程PCET还原

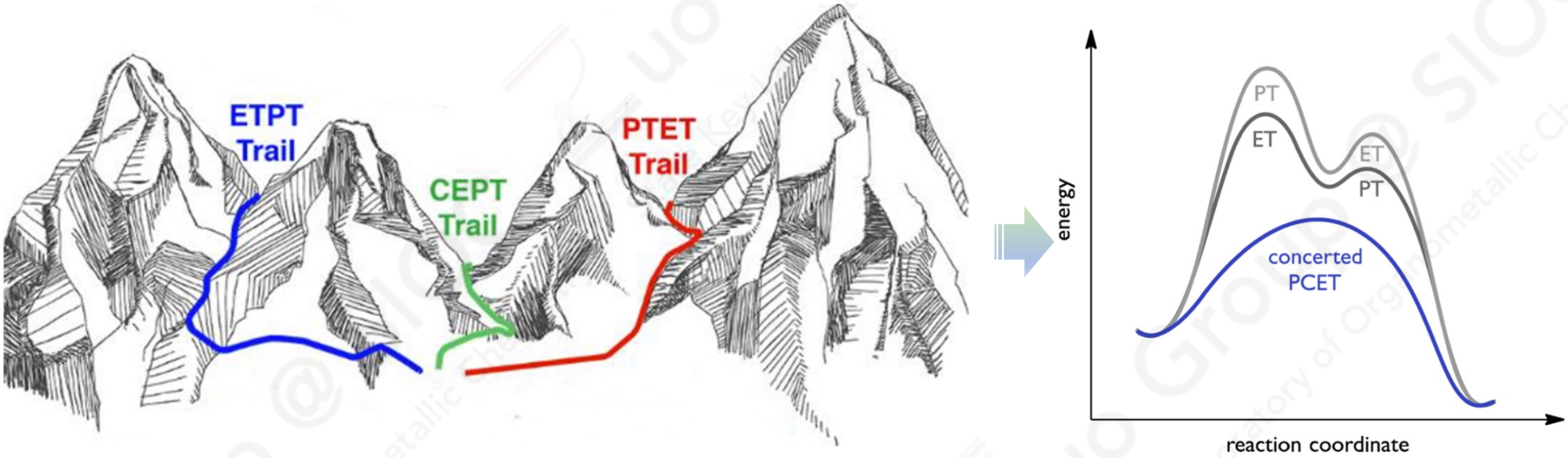


over 35 Å PCET

Stubbe J. et al. *Acc. Chem. Res.* **2013**, *46*, 2524–2535.

PCET过程在反应坐标中的表现

❑ 相比于分步的ET、PT过程，PCET通常需要克服的能垒更低



Leif H. et al. *J. Am. Chem. Soc.* **2019**, *141*, 17245−17259.

❑ PCET倾向于产生杂原子中心自由基

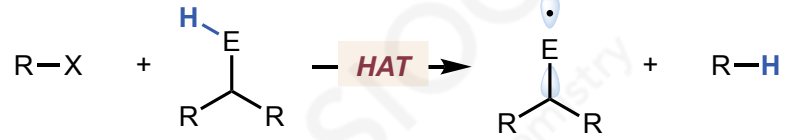
Baran P. S. et al. *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714.

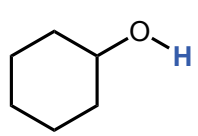
传统HAT反应的限制因素

❑ HAT反应在热力学上可能存在难度

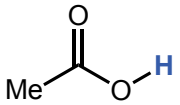
BDFE: Bond Dissociation Free Energy

化学键异裂所需的能量+将所得负离子单电子氧化所需能量+将质子单电子还原所需能量

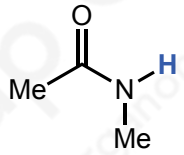




O—H BDFE
~ 105 kcal/mol

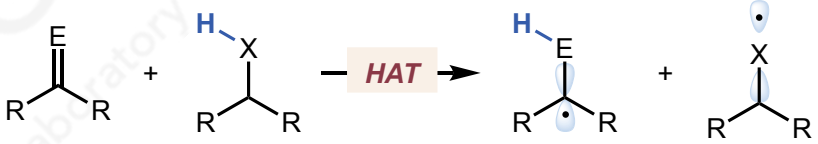


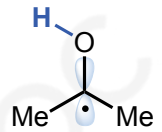
O—H BDFE
~ 110 kcal/mol



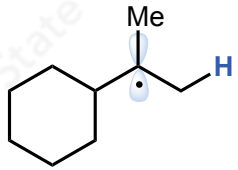
N—H BDFE
~ 110 kcal/mol

氧化型HAT反应中破坏X—H键需要形成一个键能更强的X'—H键

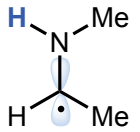




O—H BDFE
~ 17 kcal/mol



C—H BDFE
~ 35 kcal/mol



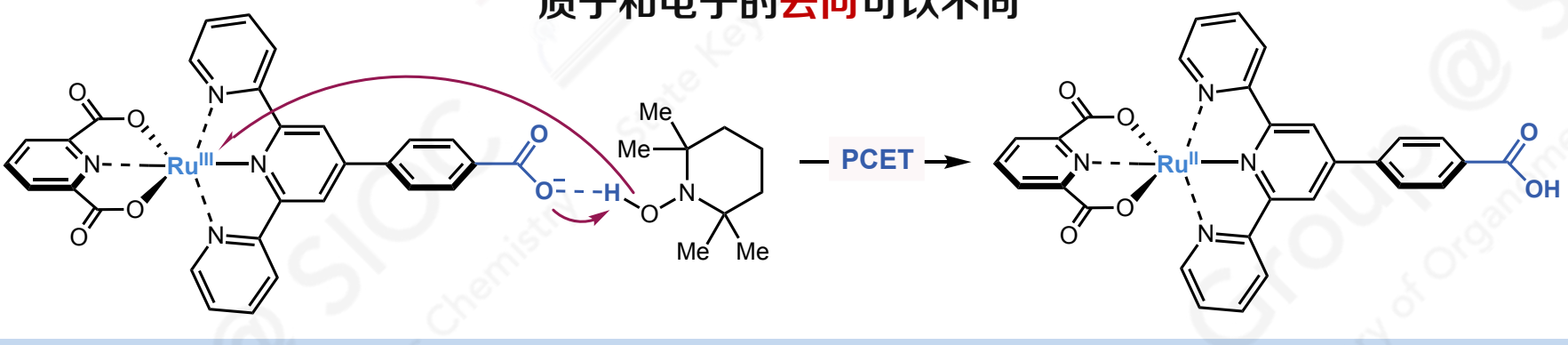
N—H BDFE
~ 27 kcal/mol

还原HAT反应往往缺少合适的H供体

PCET与HAT的表观区别

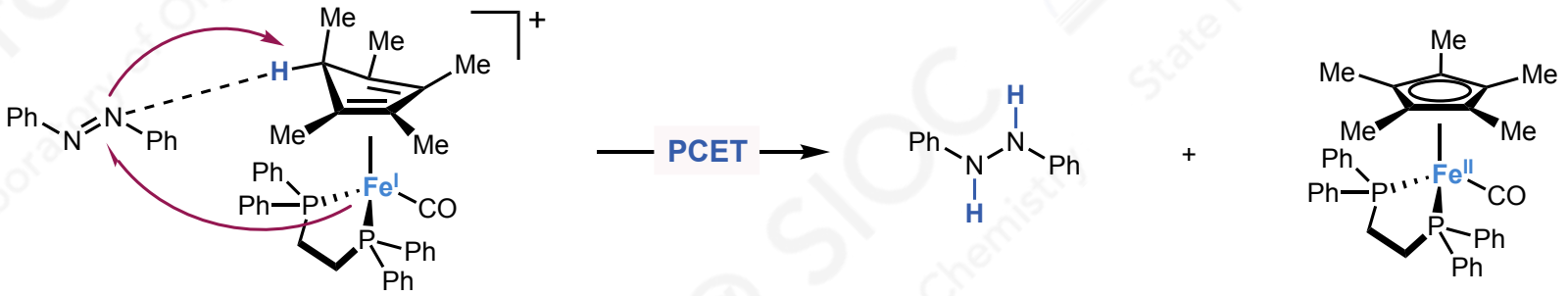
- **The proton and electron in a PCET process need not originate from the same bond, or even the same molecule**

质子和电子的去向可以不同



Mayer J. M. et al. *J. Am. Chem. Soc.* **2009**, *131*, 29, 9874–9875.

质子和电子的来源可以不同

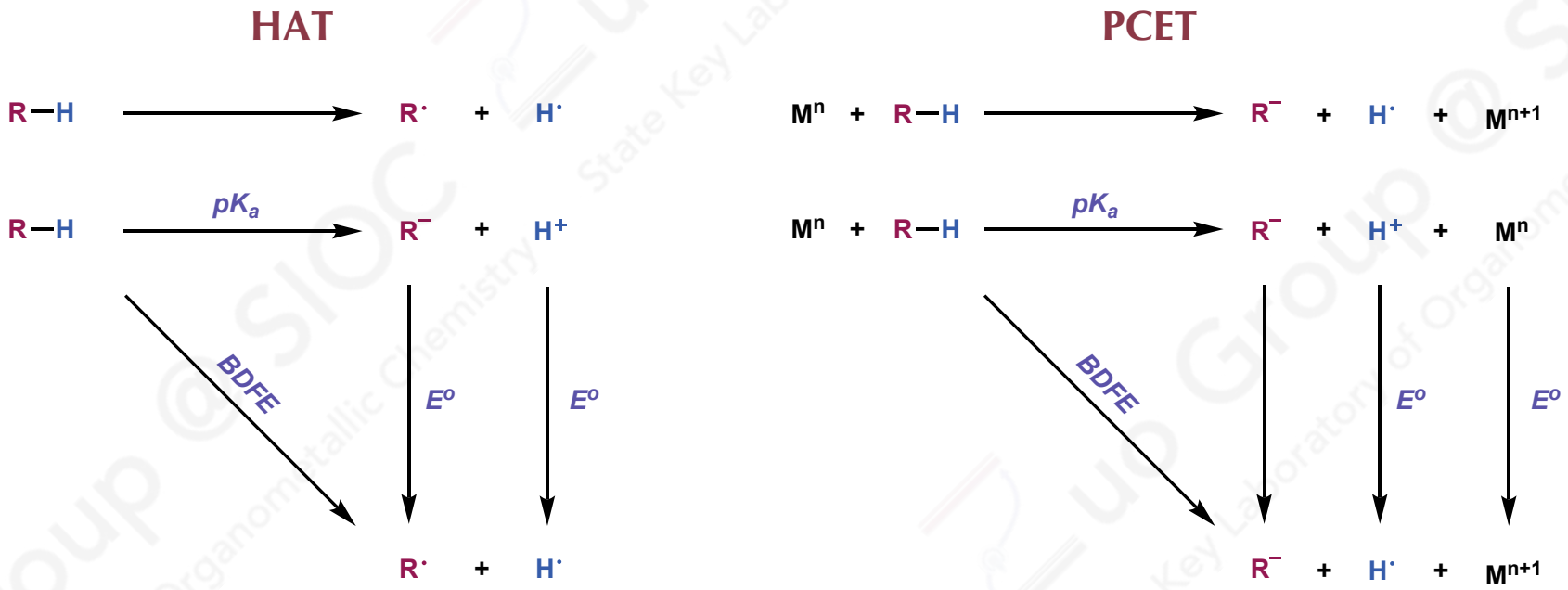


Peters J. C. et al. *J. Am. Chem. Soc.* **2020**, *142*, 44, 18963–18970.

HAT is definitely a kind of PCET, ET and PT from the same bond.

PCET与HAT的热力学区别

❑ 与HAT相比，PCET活化能力的调节范围往往更大



$BDFE(kcal/mol) = 1.37pK_a + 23.06E^o(R^-/R^\bullet) + 23.06E^o(H^+/H^\bullet)$

同一分子的pKa和Eº往往呈负相关
难以调节（HAT试剂发展的困难）

$BDFE(kcal/mol) = 1.37pK_a + 23.06E^o(M^n/M^{n+1}) + 23.06E^o(H^+/H^\bullet)$

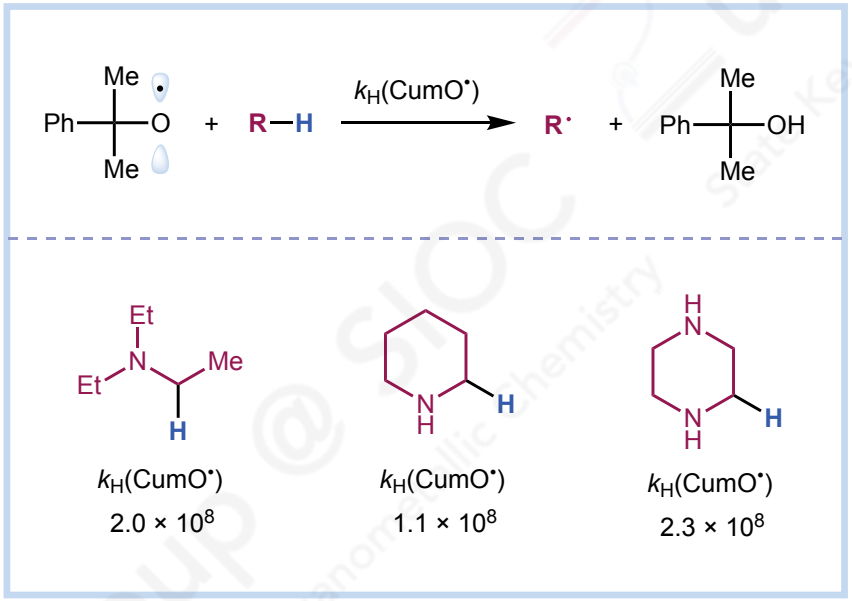
来自于两个不同组分，调节范围更大

Knowles R. R. et al. *Acc. Chem. Res.* **2016**, *49*, 1546–1556.

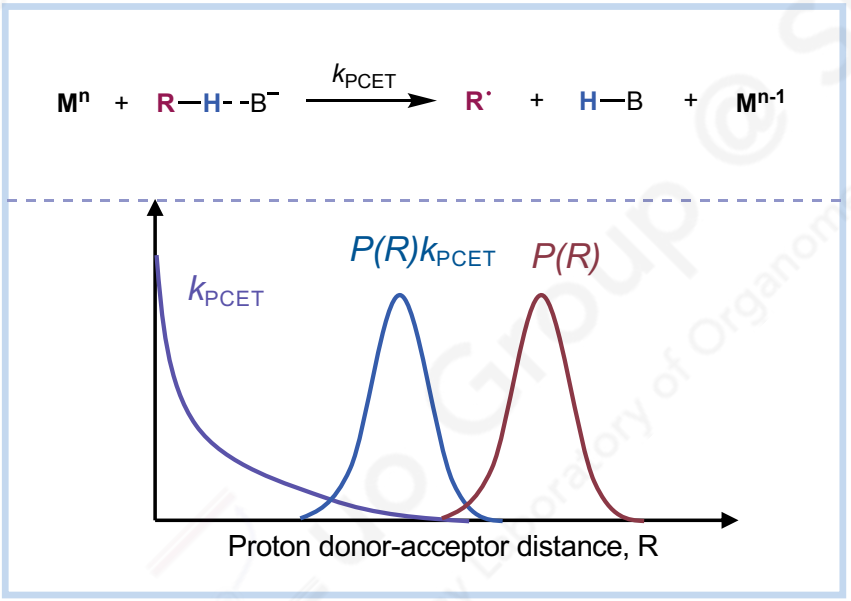
PCET选择性与HAT的区别

❑ PCET与HAT存在正交的选择性

HAT



PCET



While electrons tunnel readily over large distances (10 A˚), heavier protons can only travel over relatively small distances (1–2 A˚).

HAT反应往往优先发生在键能较弱的C–H键

PCET反应往往优先发生在较易形成H键但键能更强的X–H键

Bietti M. et al. *Acc. Chem. Res.* **2015**, *48*, 2895–2903.

Hammes Schiffer H. et al. *Chem. Rev.* **2014**, *114*, 3466–3494.

PCET机理的证明方法

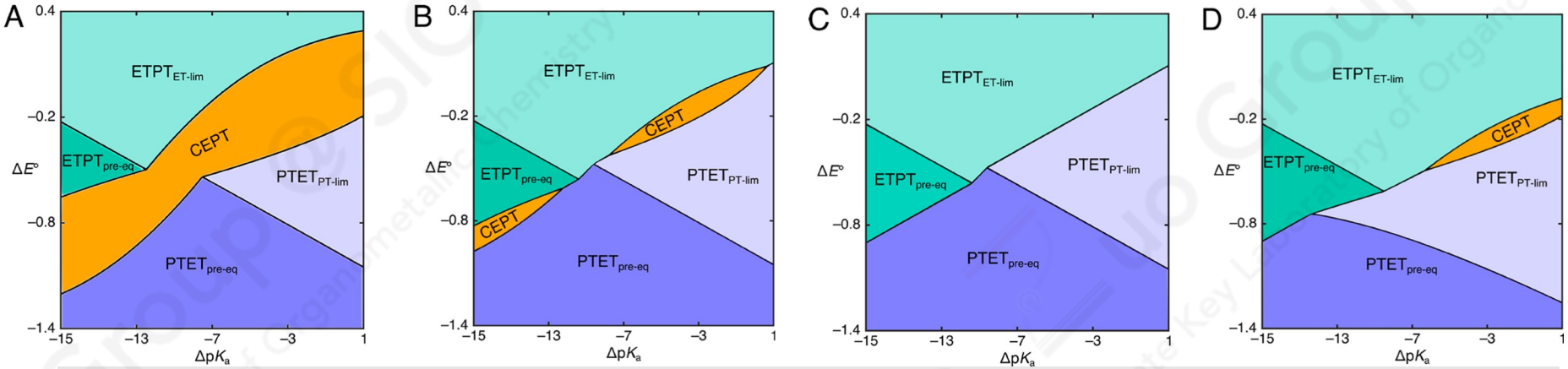
❑ PCET与ETPT、PTET存在竞争关系

$$k_{ET} = \frac{|V_{el}|^2}{\hbar}\sqrt{\frac{\pi}{\lambda k_B T}}\exp\left[\frac{-(\Delta G^\circ_{ET} + \lambda)^2}{4\lambda k_B T}\right]$$

$$k_{CEPT}(r_{PT}) = \sum_\mu P_\mu \sum_\nu \frac{|V_{el}|^2 |S_{\mu\nu}(r_{PT})|^2}{\hbar}\sqrt{\frac{\pi}{\lambda k_B T}} \times \exp\left[\frac{-(\Delta G^\circ_{\mu\nu} + \lambda)^2}{4\lambda k_B T}\right]$$

λ : 反应重组能

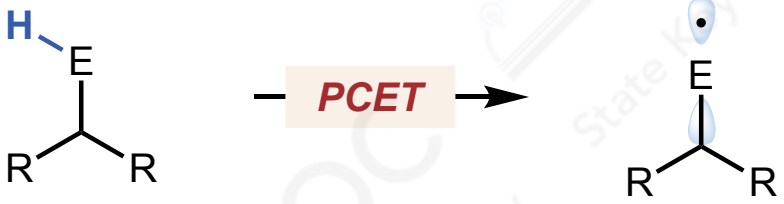
A : 指前因子



	A		B		C		D	
	λ (eV)	A (au)	λ (eV)	A (au)	λ (eV)	A (au)	λ (eV)	A (au)
k_{PT1}	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.01
k_{ET1}	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
k_{PT2}	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
k_{ET2}	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
k_{CEPT}	1.65	0.01	1.65	0.001	1.65	0.0001	1.65	0.0001

Hammarström L. et al. *J. Am. Chem. Soc.* **2021**, *143*, 560–576.

一、氧化型PCET反应



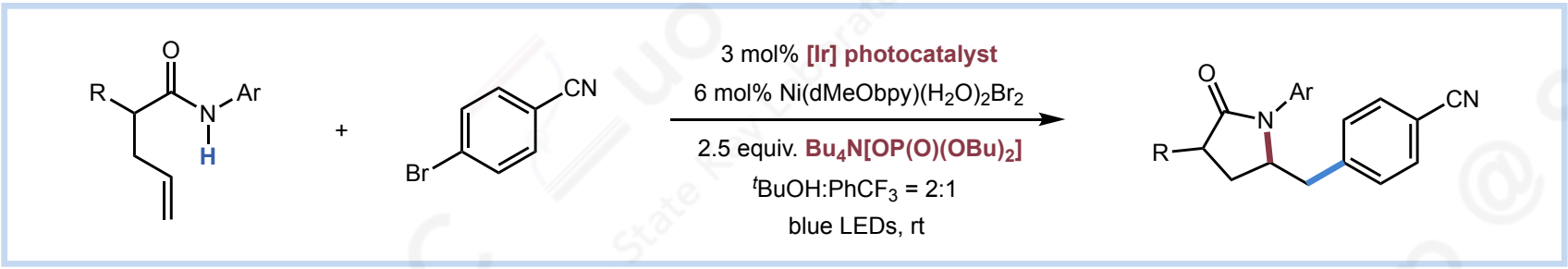
- N–H Bonds
- S–H Bonds
- O–H Bonds
- C–H Bonds

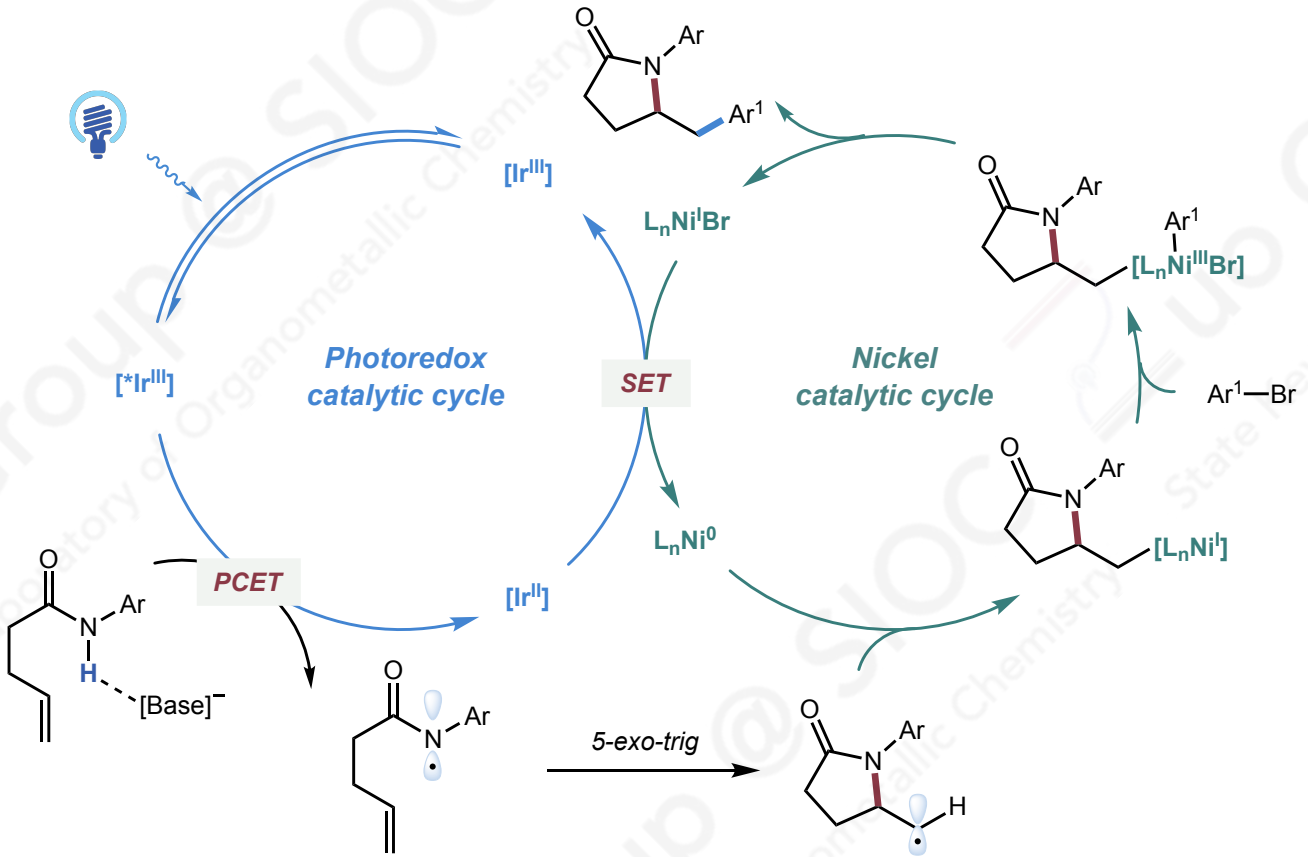
二、还原型PCET反应

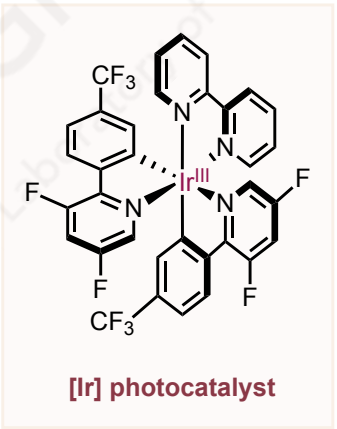
- C=N Bonds
- C=C Bonds
- C=O Bonds
- S• Radicals

PCET: N-Centered Radical Generation from N–H Bonds

■ *Photoredox PCET Cascade Amidoarylation of Unactivated Olefins*



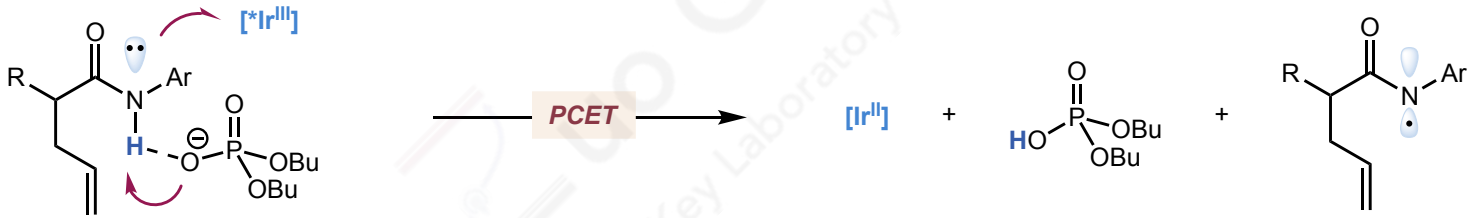




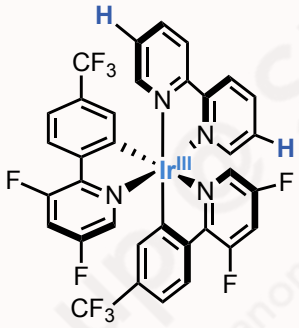
I. *PCET*
II. *5-exo-trig*
III. *coupling*

Molander. G. A. et al. *Chem*. **2019**, *5*, 339–352.

PCET: N-Centered Radical Generation from N–H Bonds

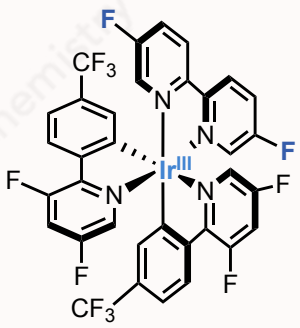


■ 氧化电势对PCET速率的影响



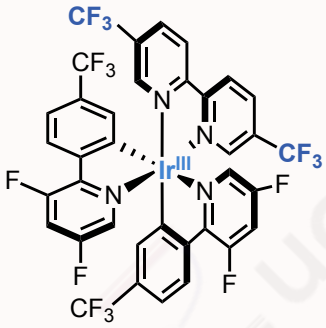
E_{PC^*/PC^-} = 1.32 V (SCE)

29% yield



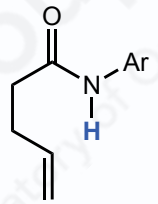
E_{PC^*/PC^-} = 1.61 V (SCE)

25% yield



E_{PC^*/PC^-} = 1.68 V (SCE)

0% yield



N—H

pK_a = 21

E^o = 1.78 V (SCE)

■ pKa对PCET速率的影响

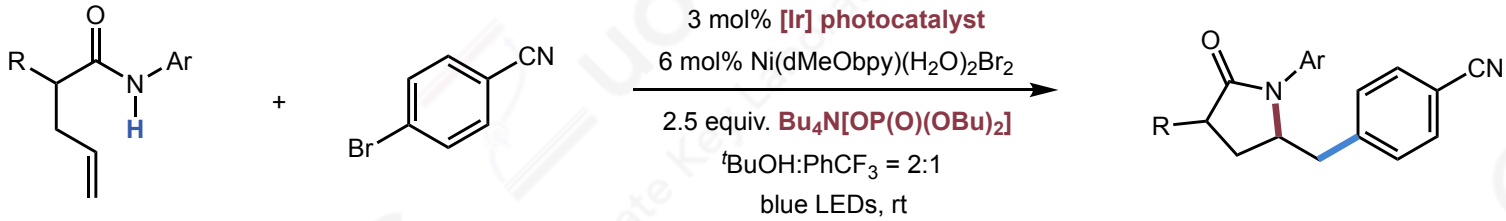
$Bu_4N[OP(O)(OBu)_2]$ pK_a = 1.72	29% yield
^{t}BuOK pK_a = 17	0% yield

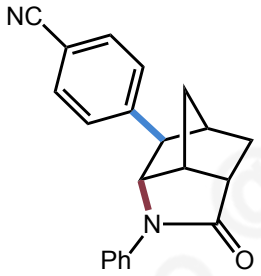
■ 溶剂极性影响H键形成从而影响PCET速率

DCE as solvent	^{t}BuOH as solvent	^{t}BuOH:PhCF_3 = 2:1 as solvent
29% yield	68% yield	78% yield

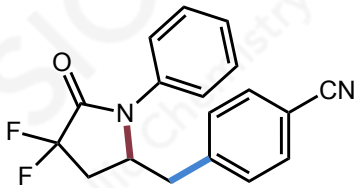
PCET: N-Centered Radical Generation from N–H Bonds

Scope of substrates

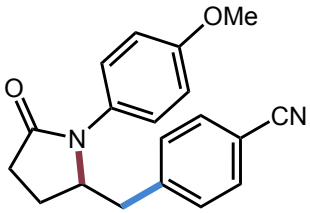




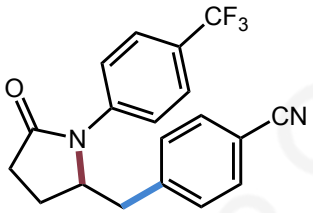
72% yield
> 20:1 dr



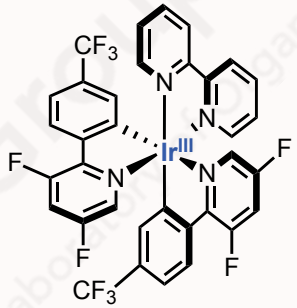
49% yield



58% yield

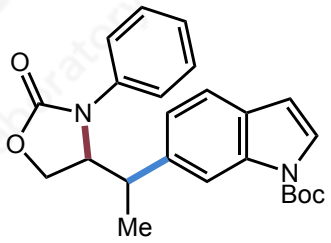


29% yield
E_{amide} = 2.03 V (SCE)

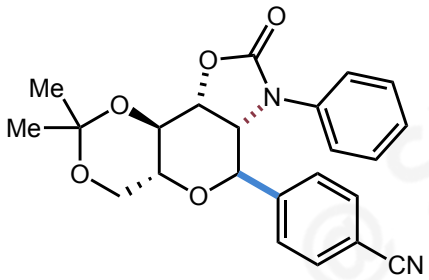


[Ir]-1
$E_{PC*/PC-}$ = 1.32 V (SCE)

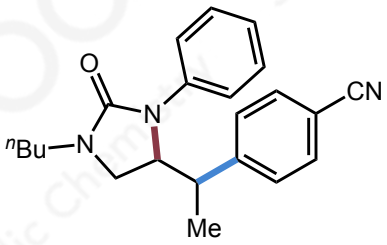
Synthesis application



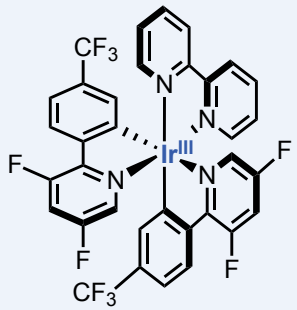
55% yield
Zolmitriptan core



83% yield, >20:1 dr
C-Aryl-Amino Glycosides



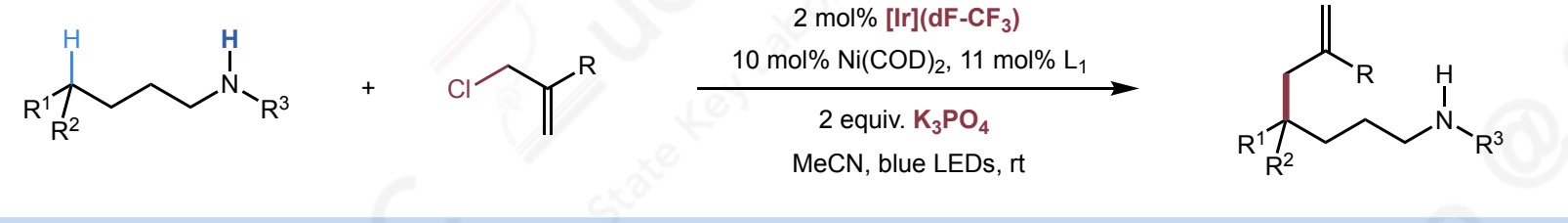
58% yield

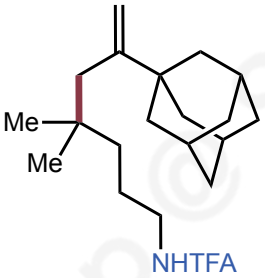


[Ir]-2
$E_{PC*/PC-}$ = 1.61 V (SCE)

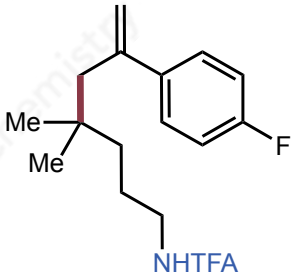
PCET: N-Centered Radical Generation from N–H Bonds

Remote Allylation of Unactivated C(sp^3)–H Bonds

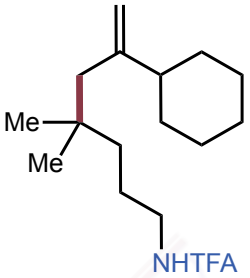




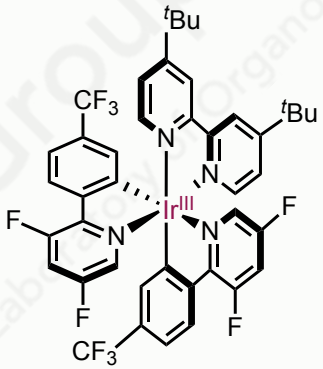
64% yield



76% yield

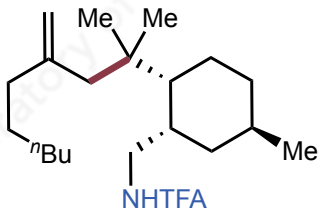


70% yield



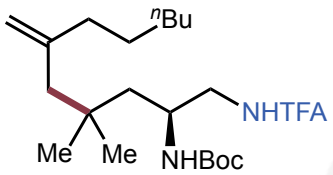
[Ir](dF-CF_3)

E_{PC^*/PC^-} = 1.21 V (SCE)



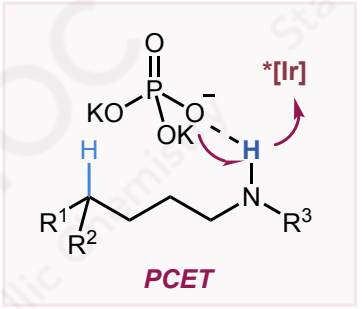
from (*L*)-menthol

64% yield

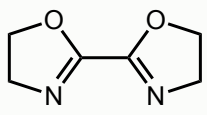


from (*S*)-leucine

68% yield



PCET

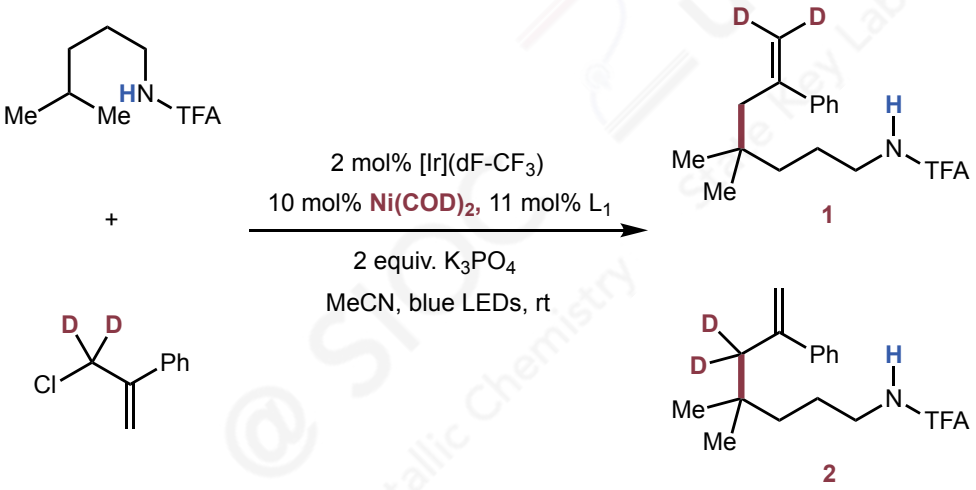


L_1

Tambar U. K. et al. *ACS Catal.* **2019**, *9*, 4627–4631.

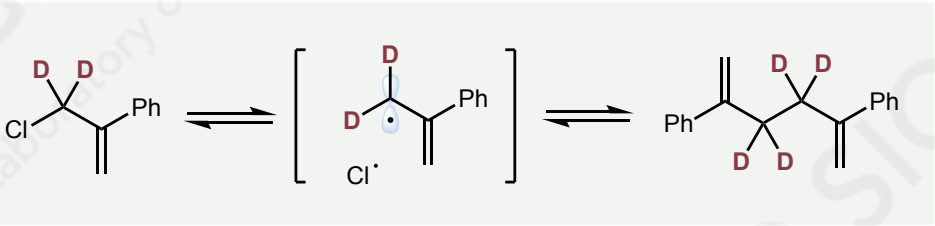
PCET: N-Centered Radical Generation from N–H Bonds

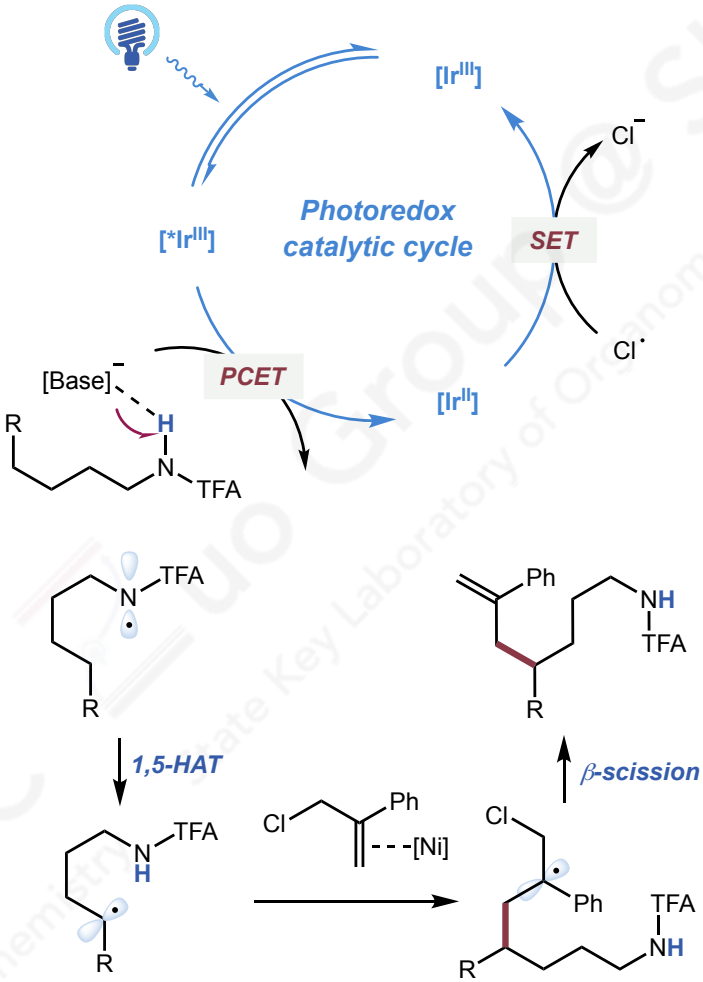
Proposed Mechanism



Optimal result: 72% yield, 1:2 = 88:12

No $Ni(COD)_2/L_1$: 45% yield, 1:2 = 88:12

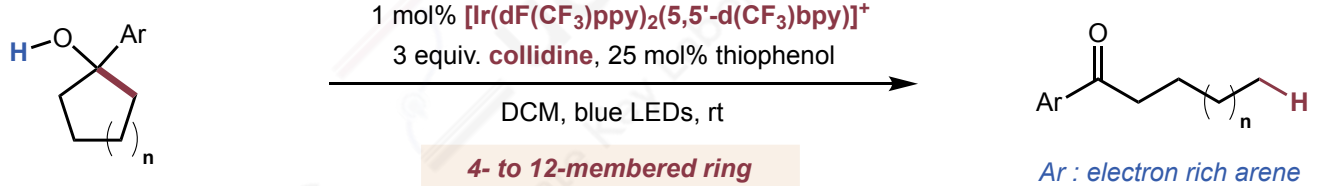


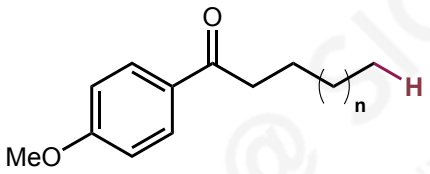


Tambar U. K. et al. *ACS Catal.* **2019**, *9*, 4627–4631.

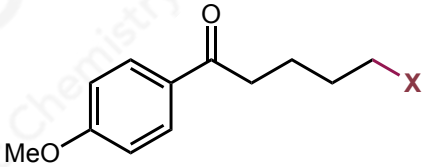
PCET: O-Centered Radical Generation from O–H Bonds

Ring-Opening of Cyclic Alcohols Enabled by PCET

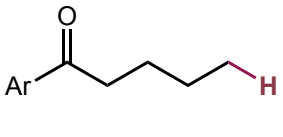




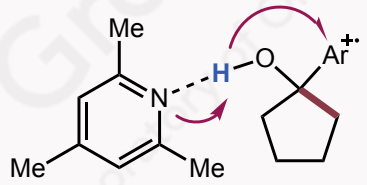
n = 0, 71% yield
n = 1, 86% yield
n = 8, 85% yield



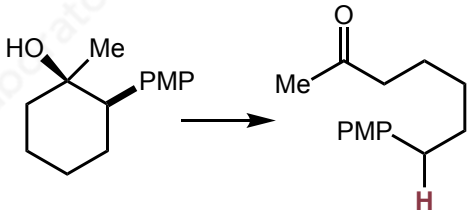
with SelectFluor, X = F, 52% yield
with CCl_4, X = Cl, 98% yield
with $BrCCl_3$, X = Br, 95% yield



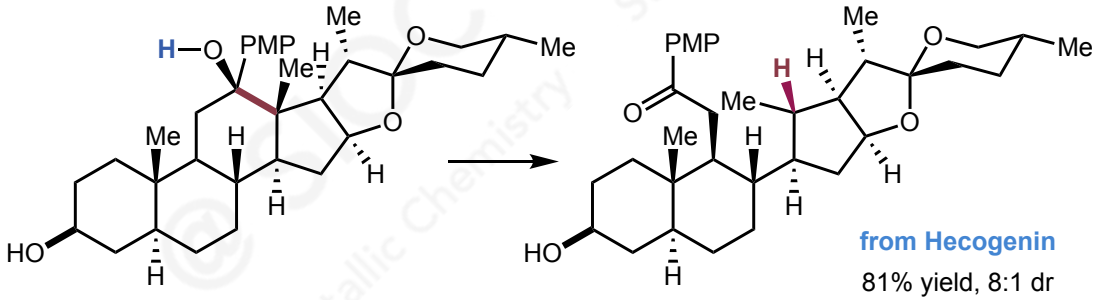
Ar = benzofuran, 84% yield
Ar = naphthalene, 41% yield



PCET



91% yield

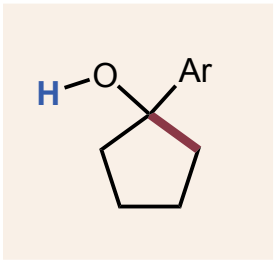


from Hecogenin
81% yield, 8:1 dr

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

PCET: O-Centered Radical Generation from O–H Bonds

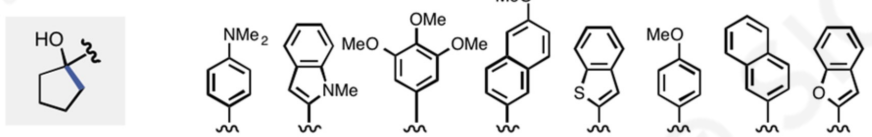
❑ BDFE: bond dissociation free energy



O—H BDE :
~ 105 kcal/mol (MeOH)
based on calculations

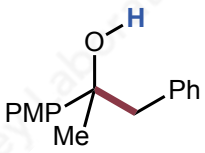
O—H BDFE
~ 102 kcal/mol

$$BDFE(kcal/mol) = 1.37pK_a + 23.06E^o(M^n/M^{n+1}) + 23.06E^o(H+H^{\cdot})$$

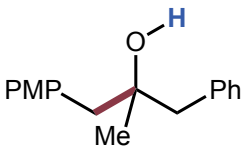


Base	$E_{p/2}$ (V)	0.39	0.69	0.92	0.96	1.18	1.22	1.24	1.27
2-MeO-pyridine	'BDFE'	77	84	90	91	96	97	97	98
pK_a = 9.9	Yield (%)	0	0	0	0	0	0	<5	8
pyridine	'BDFE'	81	88	93	94	99	100	101	101
pK_a = 12.5	Yield (%)	0	0	0	<5	6	16	5	19
CF_3COO^-	'BDFE'	81	88	93	94	99	100	101	101
pK_a = 12.5	Yield (%)	0	0	0	0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

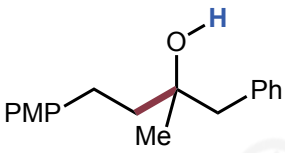
❑ 热力学计算数值在PCET反应中准确度较高



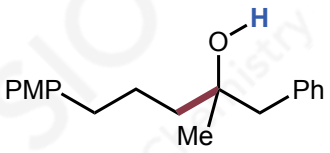
88% yield



94% yield



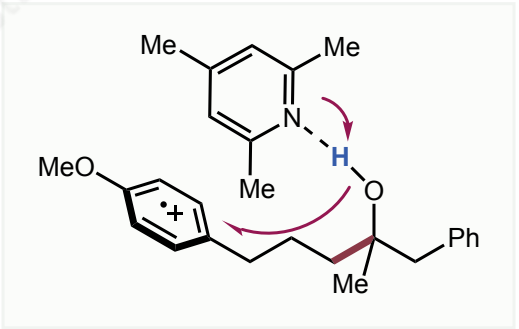
89% yield



6% yield

ΔG^o_{PT} = +34 kcal/mol

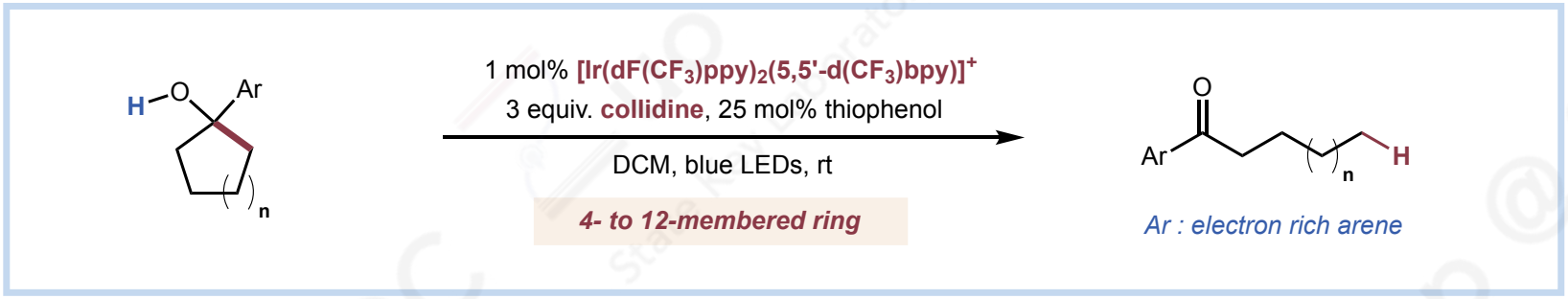
$\Delta G^o_{\text{charge recombination}}$ = -53 kcal/mol

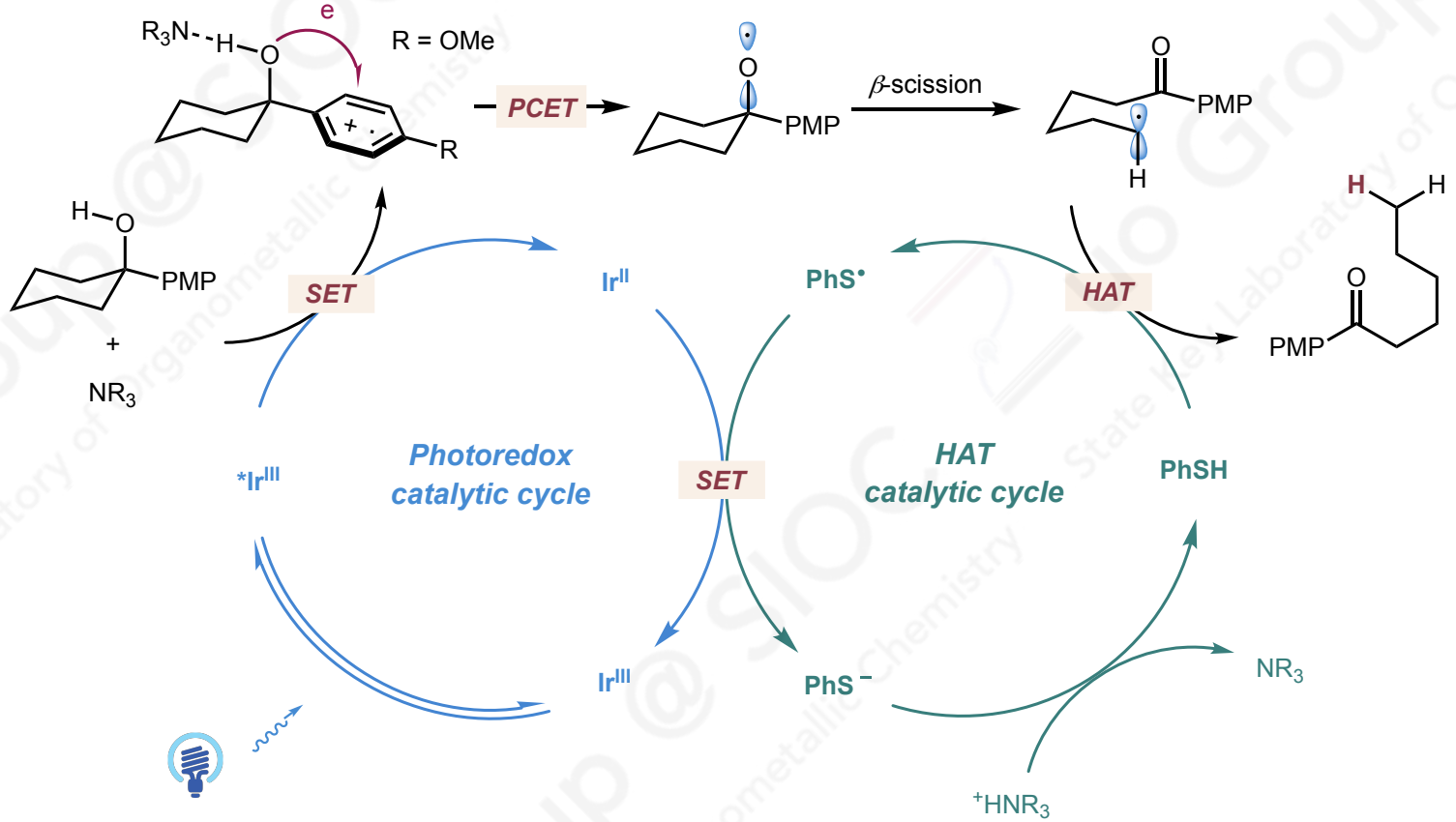


ΔG^o_{PCET} = -1 kcal/mol

PCET: O-Centered Radical Generation from O–H Bonds

Proposed Mechanism

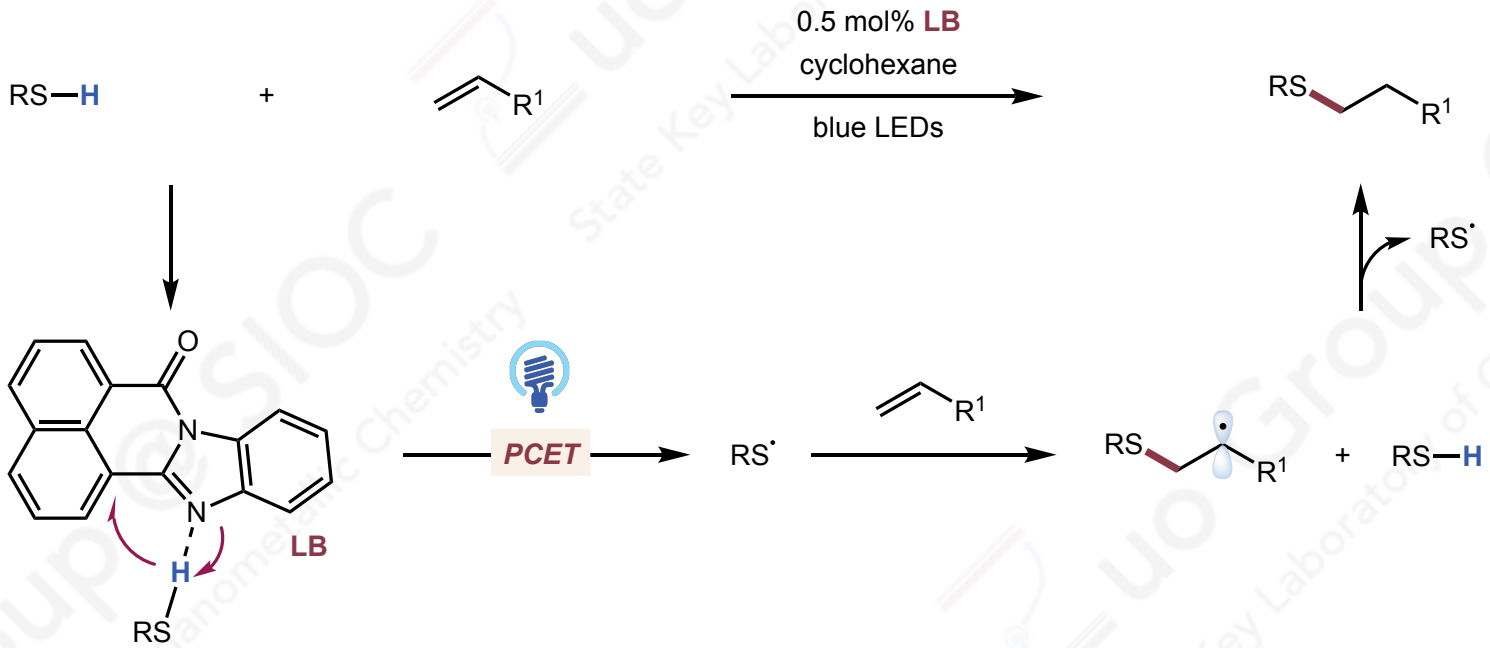




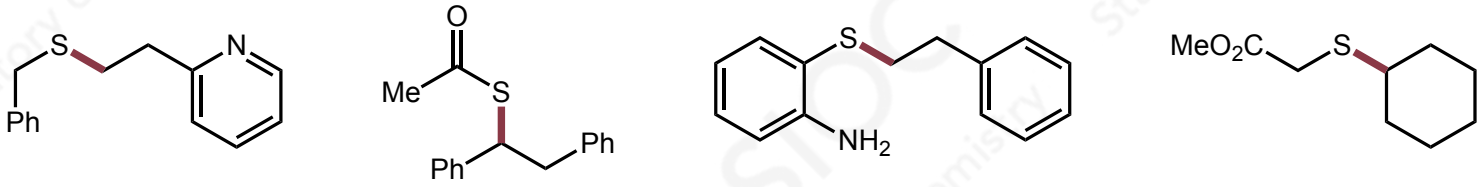
Knowles R. R. et al. *J. Am. Chem. Soc.* **2016**, *138*, 10794–10797.

PCET: S-Centered Radical Generation from S–H Bonds

Visible-Light-Mediated Organocatalyzed Thiol–Ene Reaction



Scope of substrates

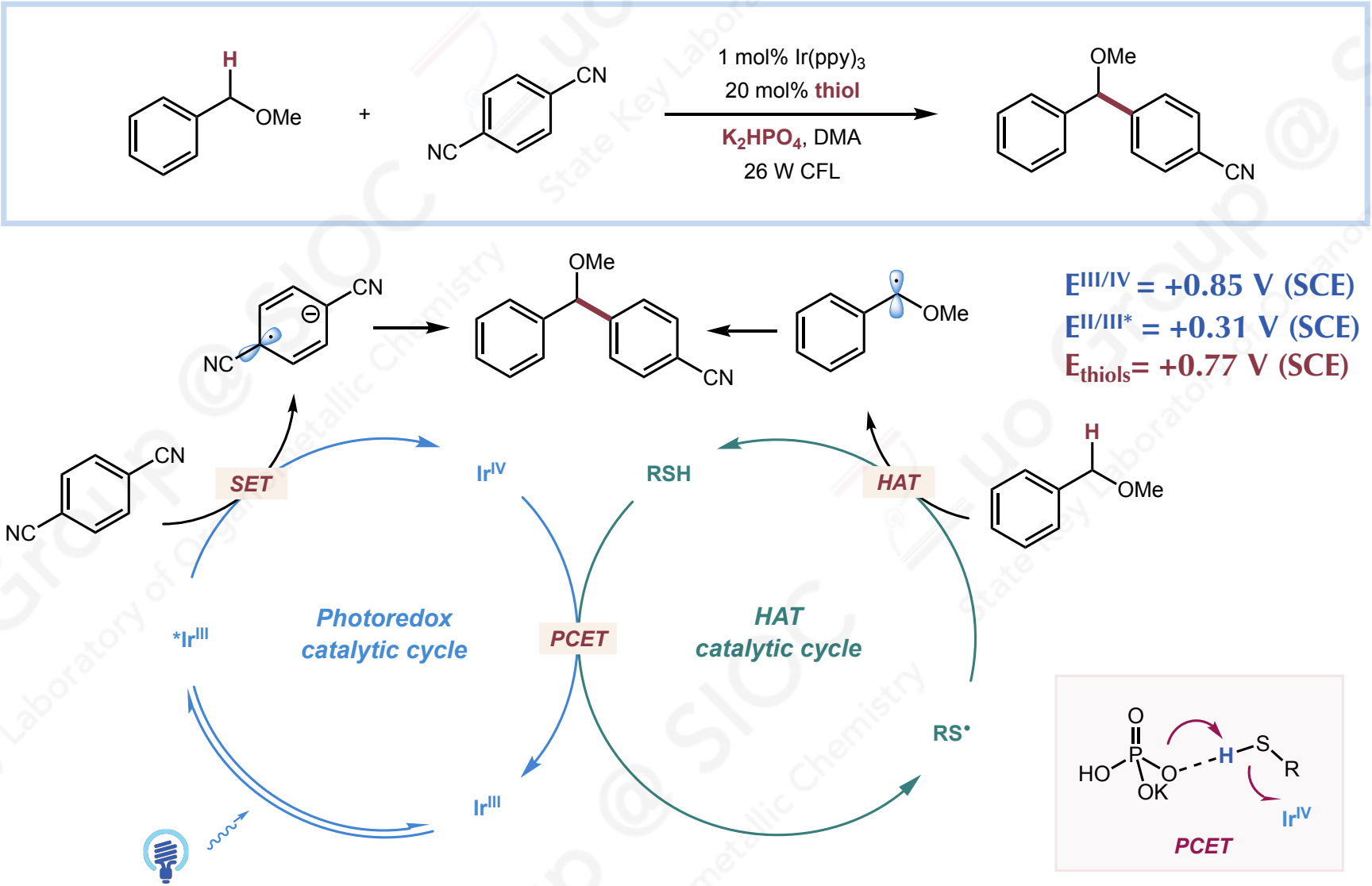


58% yield | 90% yield | 92% yield | 96% yield

Dilman D. A. *J. Org. Chem.* **2019**, *84*, 8337–8343.

PCET: S-Centered Radical Generation from S–H Bonds

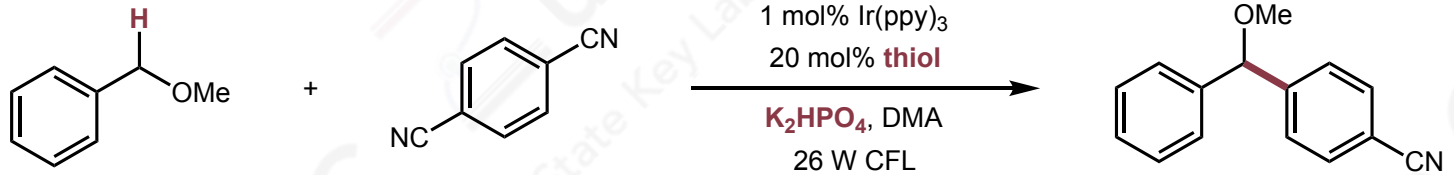
■ *Direct Arylation of Benzylic Ethers*

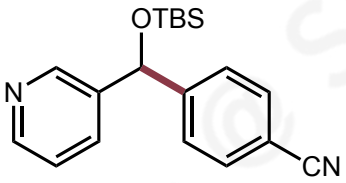


MacMillan. D. W. C. et al. *J. Am. Chem. Soc.* **2014**, *136*, 626–629.

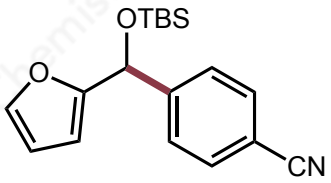
PCET: S-Centered Radical Generation from S–H Bonds

Scope of substrates

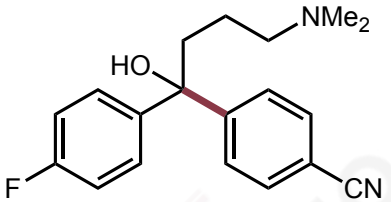




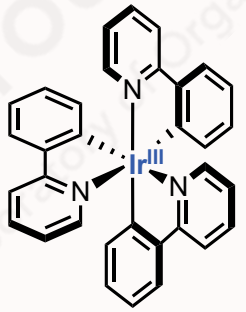
61% yield



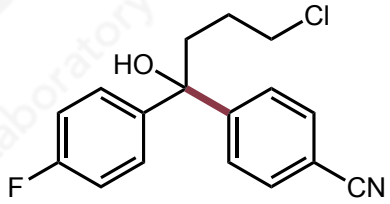
64% yield



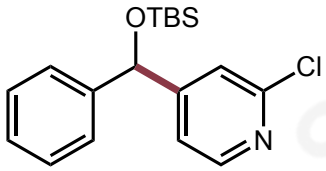
75% yield



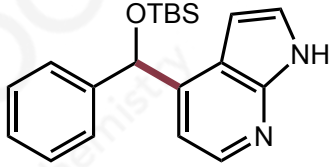
Ir(ppy)$_3$



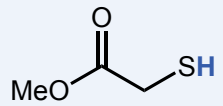
70% yield



51% yield



73% yield



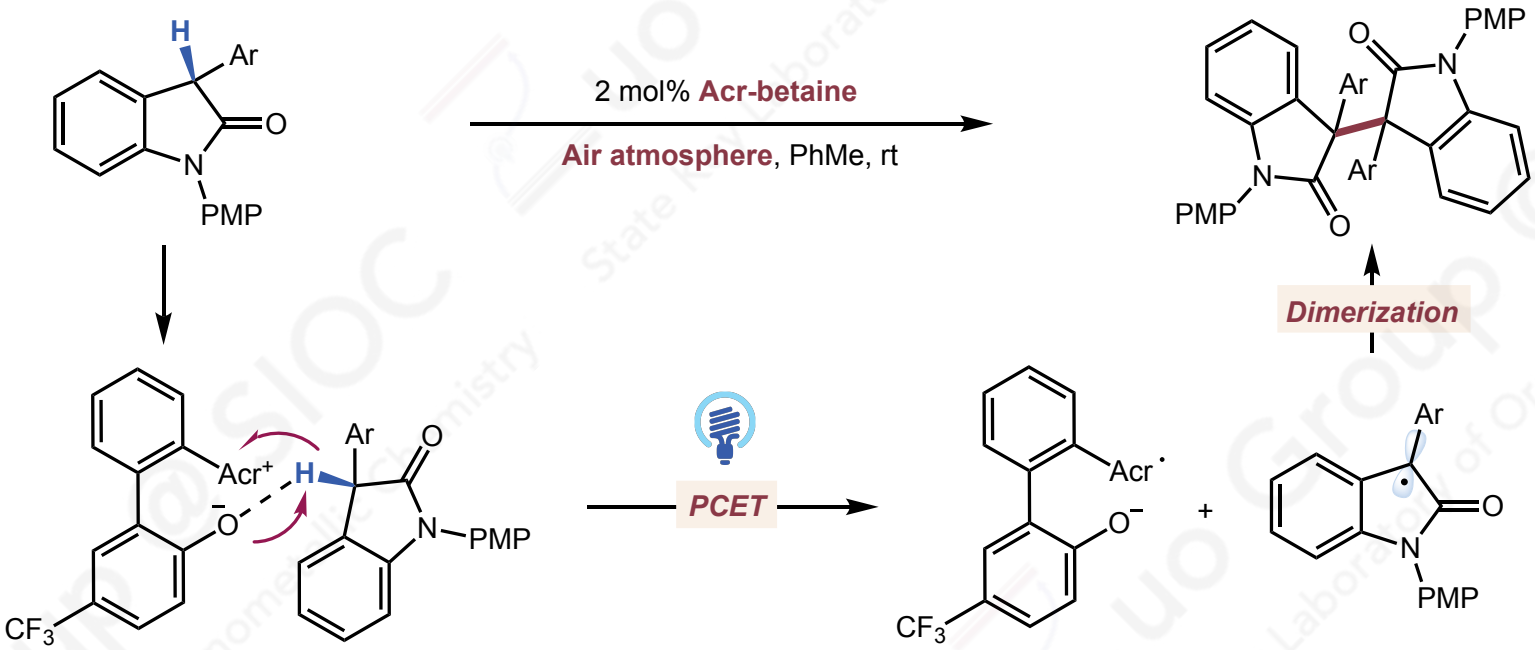
S—H BDE = 87 kcal/mol

αC—H BDE = 85.8 kcal/mol

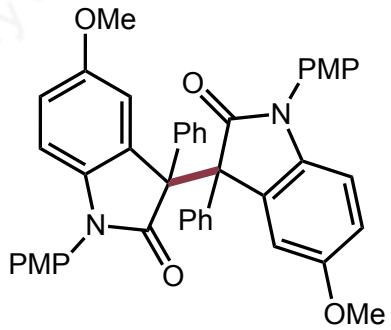
MacMillan. D. W. C. et al. *J. Am. Chem. Soc.* **2014**, *136*, 626–629.

PCET: C-Centered Radical Generation from C–H Bonds

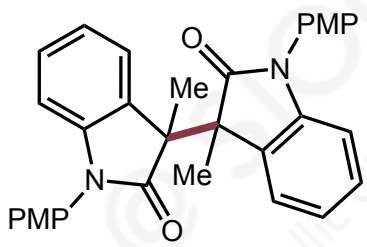
Dimerization of Oxindoles with Acridinium Betaine as Catalyst



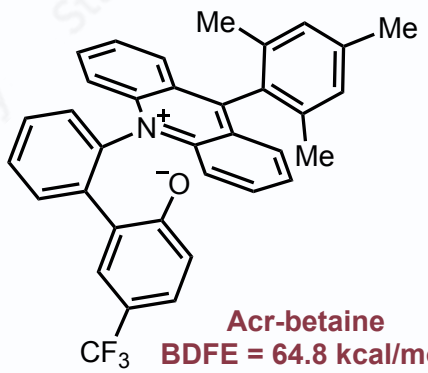
Scope of substrates



64% yield



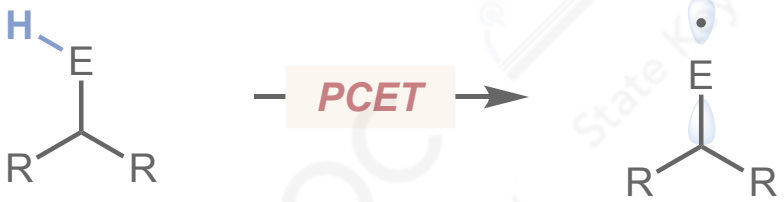
not detected



Acr-betaine
BDFE = 64.8 kcal/mol

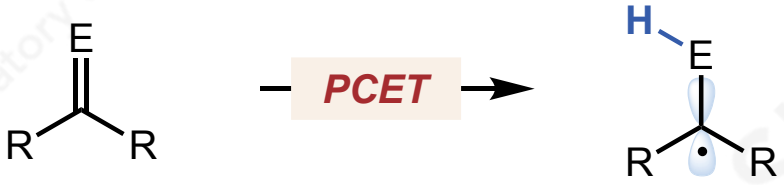
Ooi T. et al. *ACS Catal.* **2017**, *7*, 2765–2769.

一、氧化型PCET反应



- N–H Bonds
- S–H Bonds
- O–H Bonds
- C–H Bonds

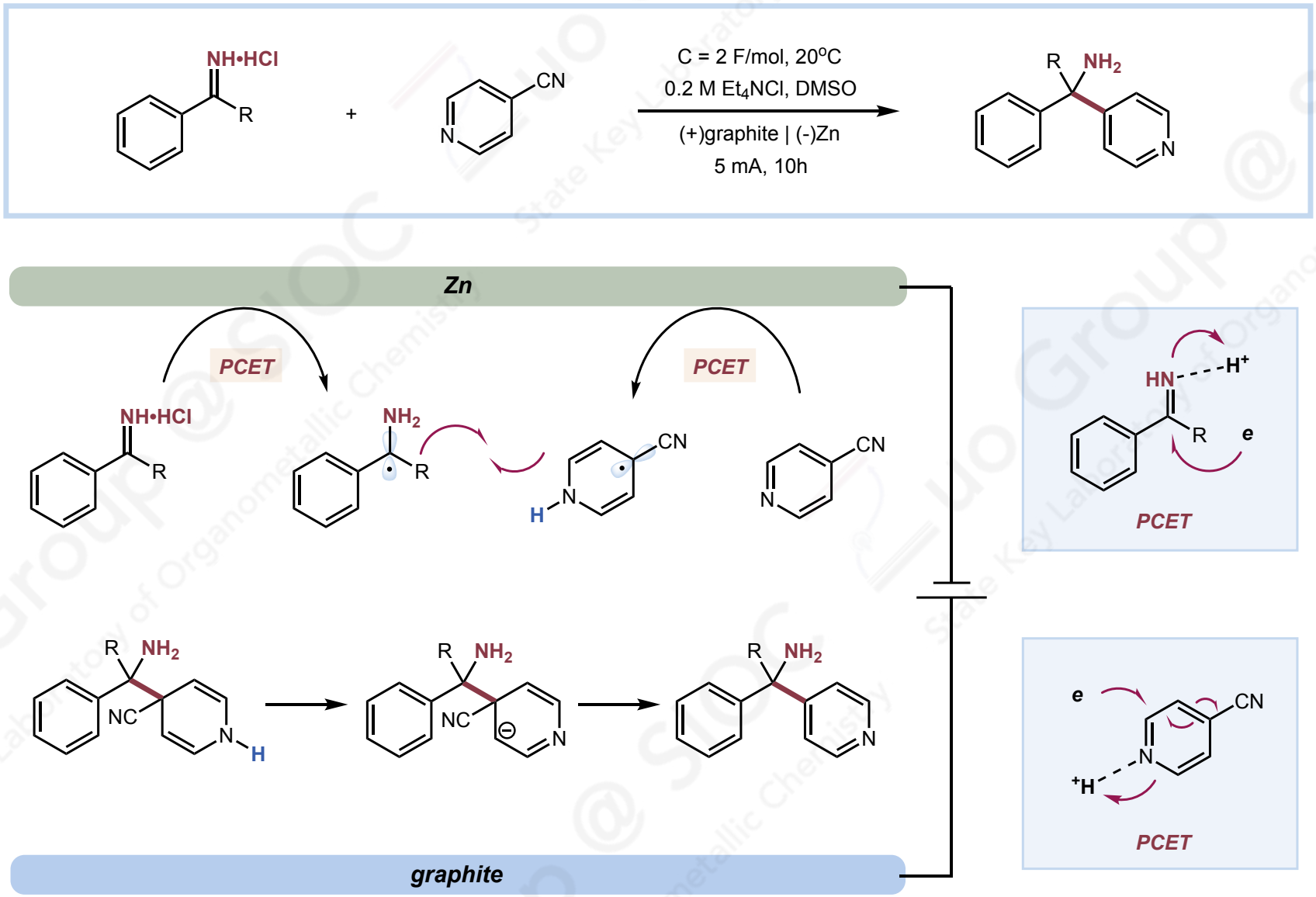
二、还原型PCET反应



- C=N Bonds
- C=C Bonds
- C=O Bonds
- S• Radicals

PCET: Reductive Transformations of Imines (C=N)

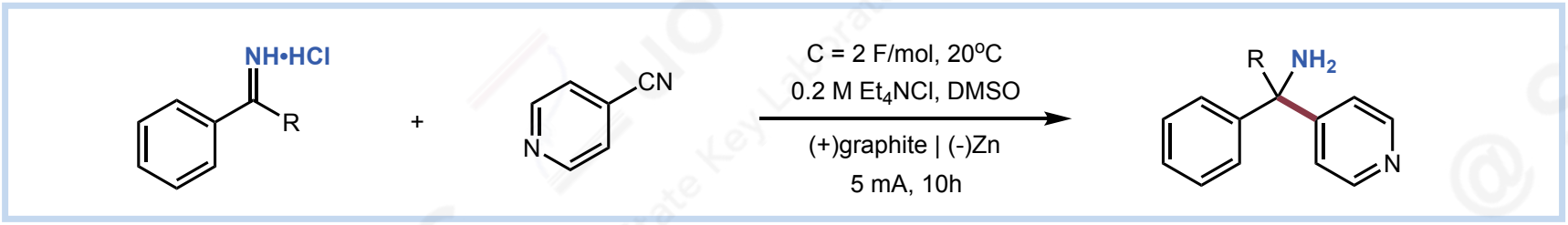
Electrochemical Synthesis of Hindered Primary and Secondary Amines

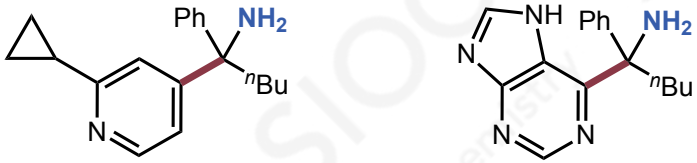


Rovis T. et al. *J. Am. Chem. Soc.* **2020**, *142*, 468–478.

PCET: Reductive Transformations of Imines (C=N)

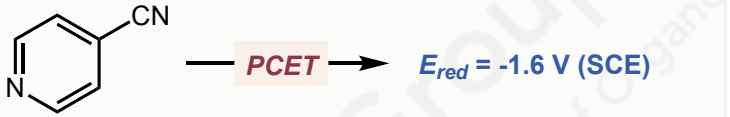
Electrochemical Synthesis of Hindered Primary and Secondary Amines

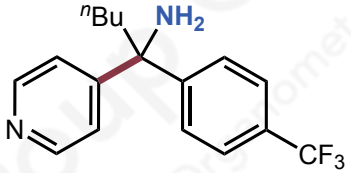




35% yield

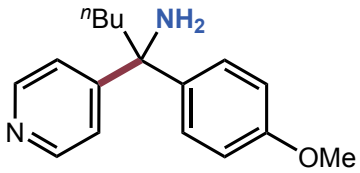
59% yield





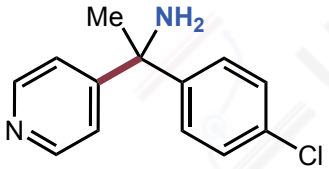
15% yield

E_{red} = -0.8 V (SCE)



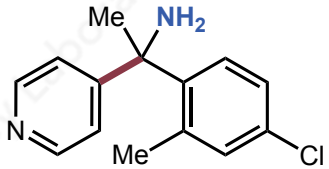
80% yield

E_{red} = -1.23 V (SCE)



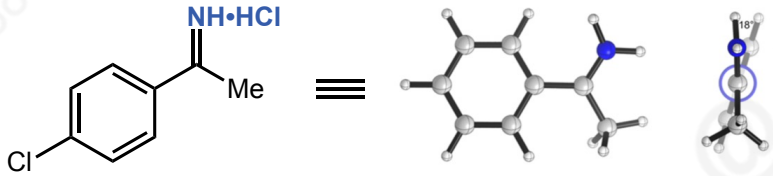
32% yield

E_{red} = -0.96 V (SCE)

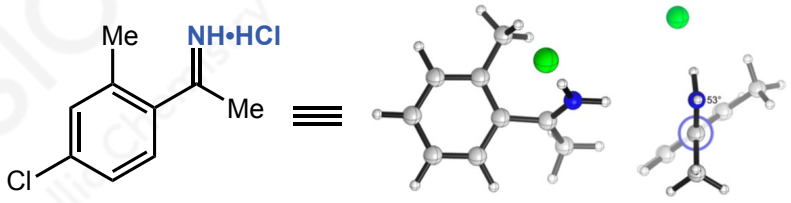


85% yield

E_{red} = -1.12 V (SCE)



E_{LUMO} = -1.56 eV

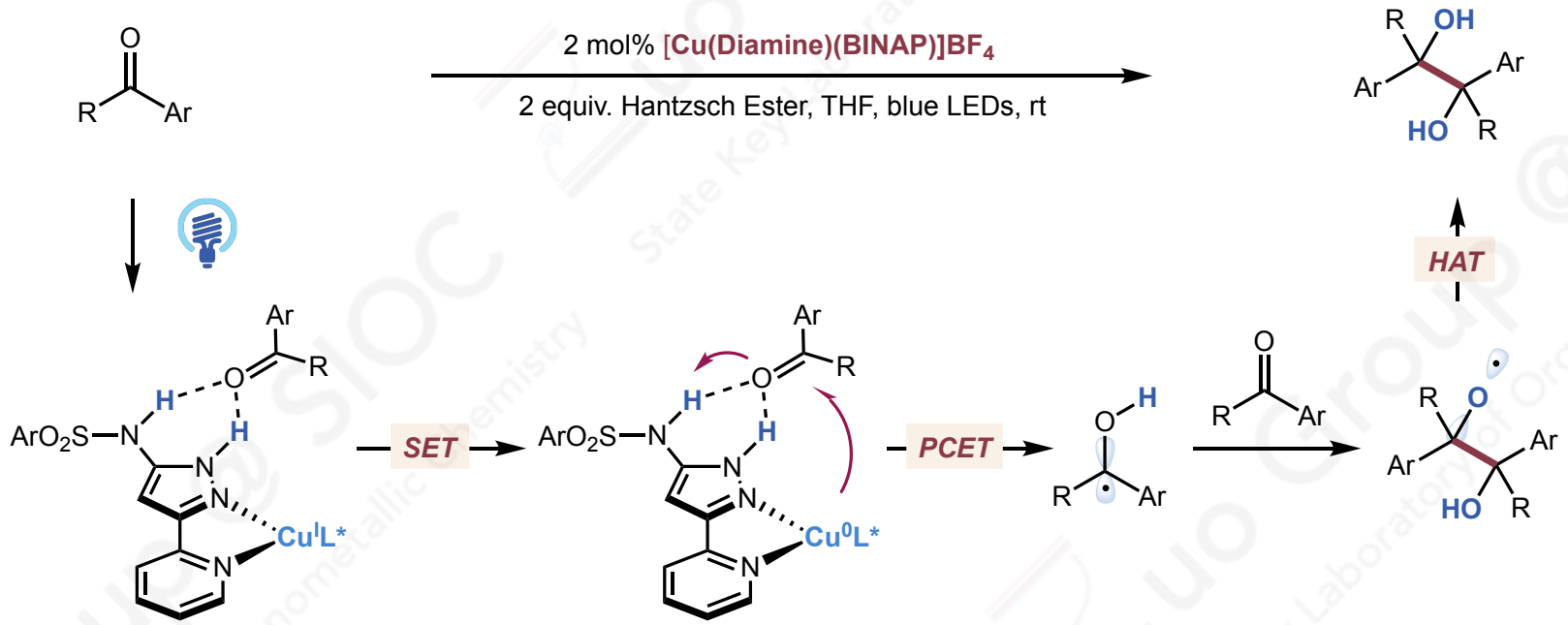


E_{LUMO} = -1.15 eV

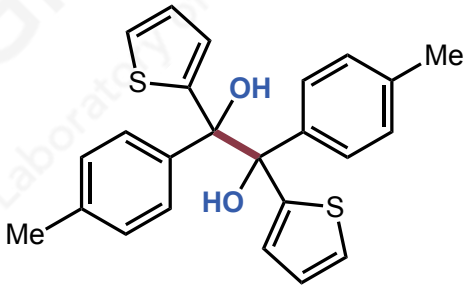
Rovis T. et al. *J. Am. Chem. Soc.* **2020**, *142*, 468–478.

PCET: Reductive Transformations of Carbonyls (C=O)

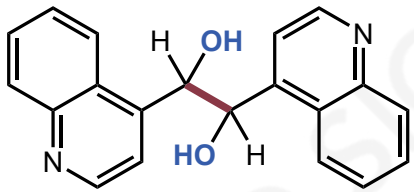
Reductive Pinacol-Type Couplings



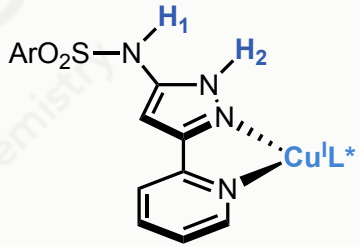
Scope of substrates



62% yield



68% yield



pK_{a1} = 14.2

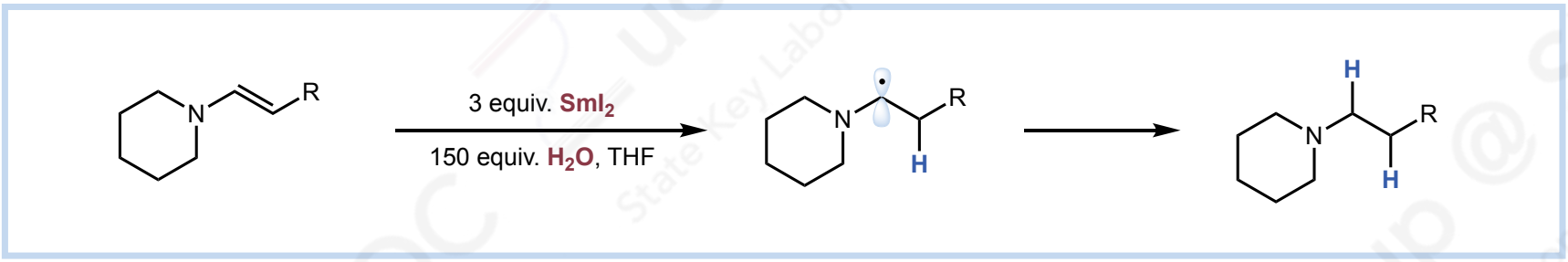
pK_{a2} = 16.1

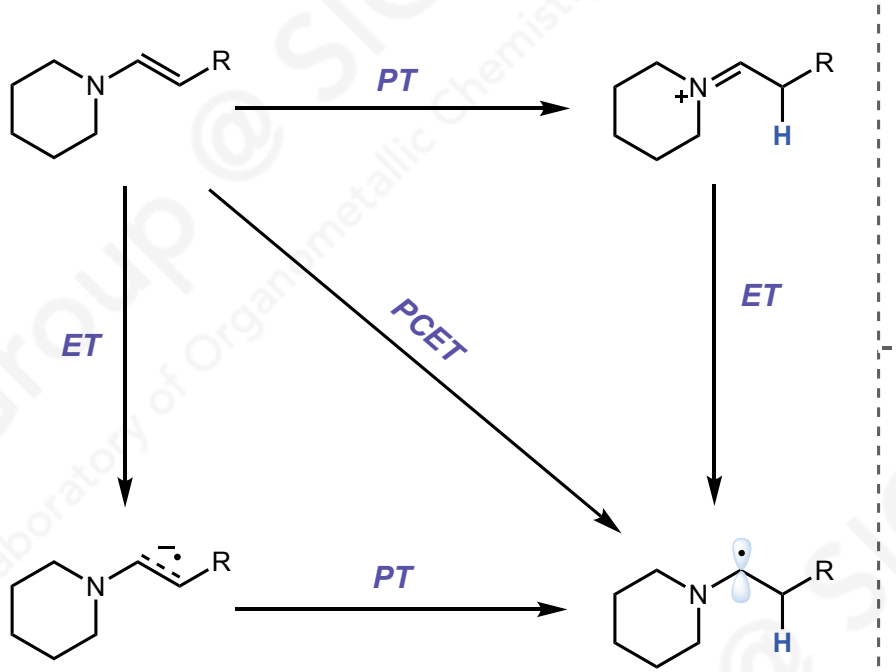
$pK_{a(dppa)}$ = 3.72

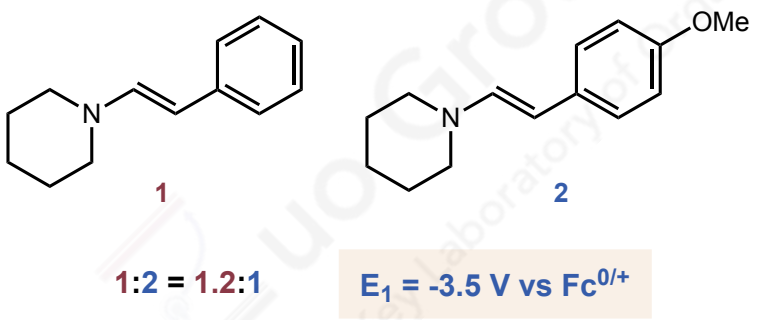
Collins. S. K. et al. *ACS Catal.* **2019**, *9*, 9458–9464.

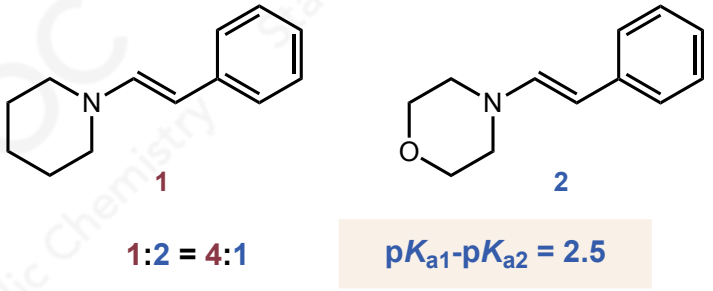
PCET: Reductive Transformations of C=C π-Bonds

$SmI_2(H_2O)_n$ Reduction of Electron Rich Enamines





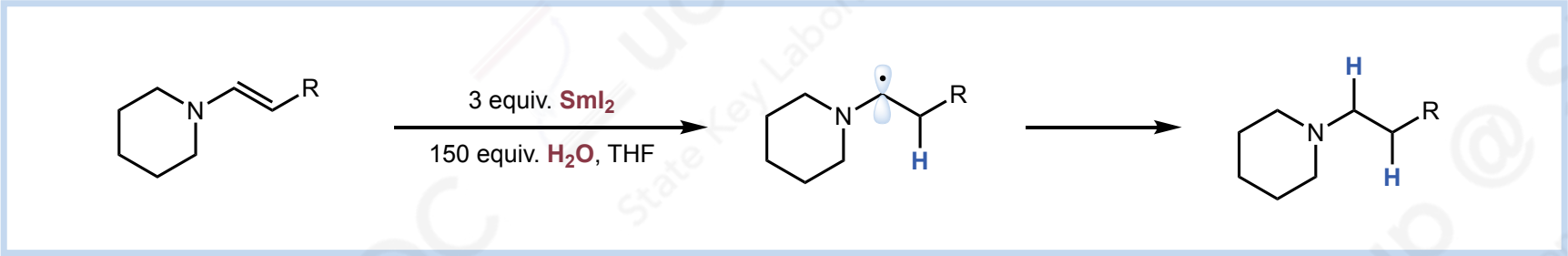


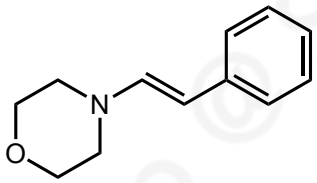


Mayer J. M. et al. *J. Am. Chem. Soc.* **2017**, *139*, 10687–10692.

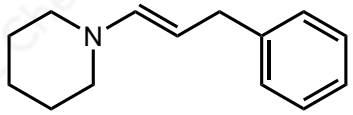
PCET: Reductive Transformations of C=C π-Bonds

$SmI_2(H_2O)_n$ Reduction of Electron Rich Enamines

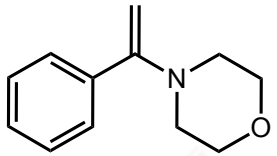




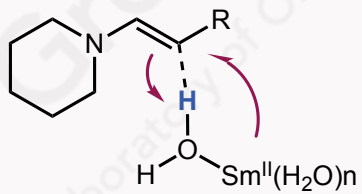
88% yield



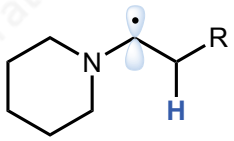
31% yield



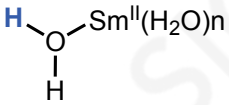
75% yield



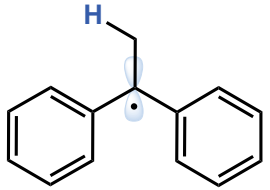
PCET



$BDFE_{C—H}$ = 32kcal/mol



$BDFE_{O—H}$ = 26kcal/mol



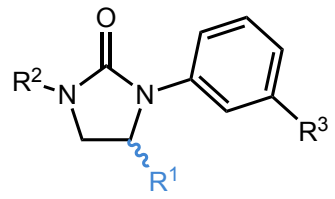
not observed

$BDFE_{C—H}$ = 30kcal/mol

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

PCET: Reductive Transformations of S• Radicals

Deracemization enabled by excited-state electron transfer



racemate

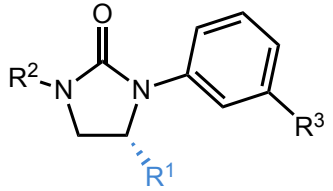
peptide thiol catalyst

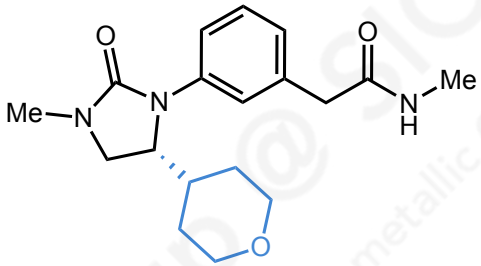
chiral phosphate base catalyst

2 mol% $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$

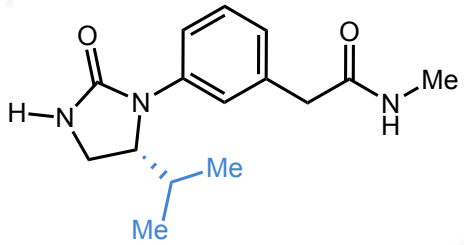
blue LEDs, 25° C

△G° = +0.42 kcal/mol

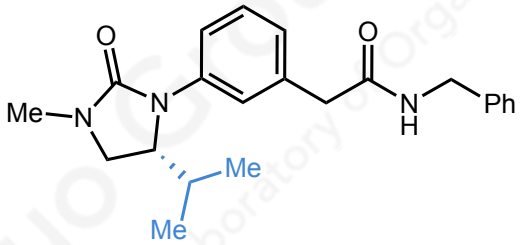




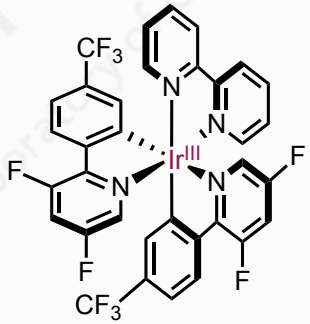
96% yield, 94:6 er



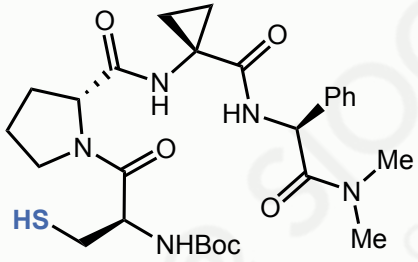
99% yield, 92:8 er



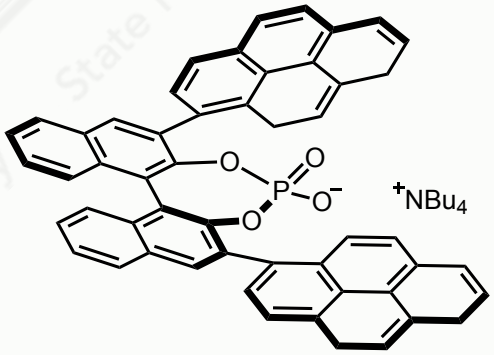
99% yield, 95:5 er



$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$



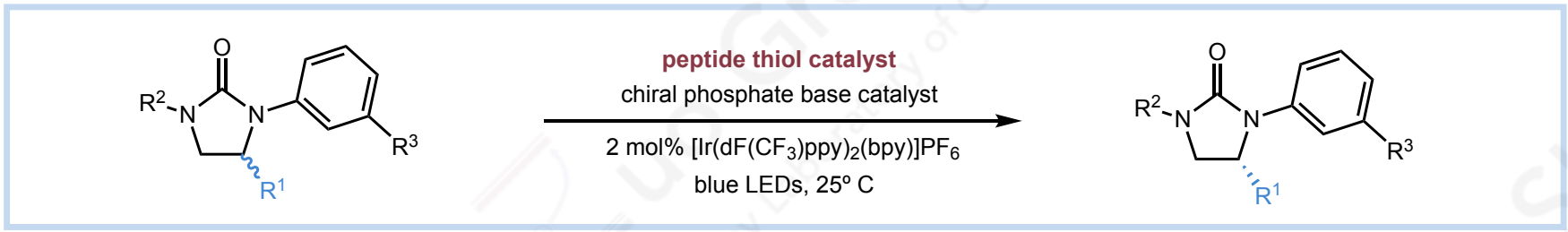
peptide thiol catalyst

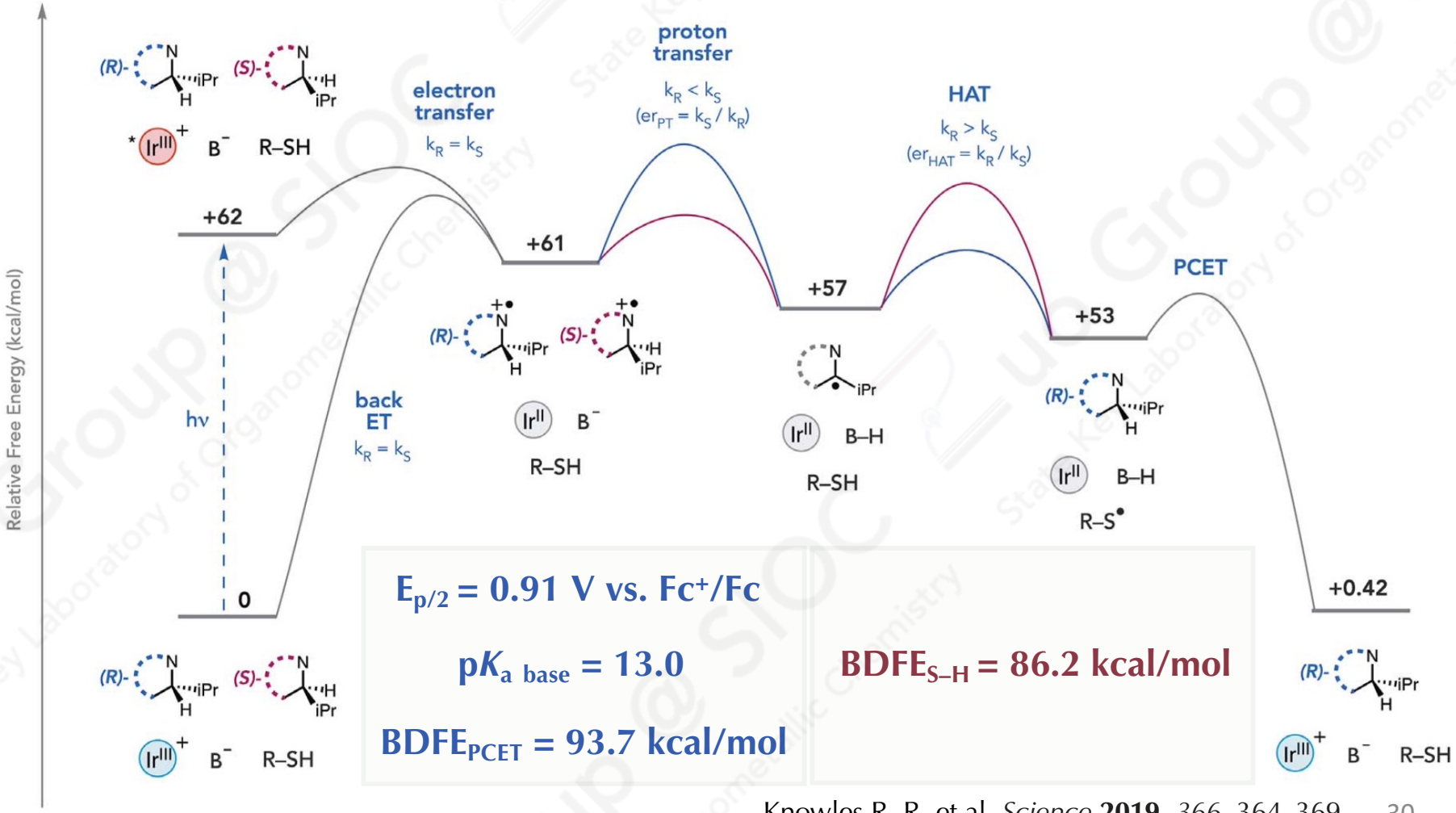


chiral phosphate base catalyst

Knowles R. R. et al. *Science* **2019**, *366*, 364–369.

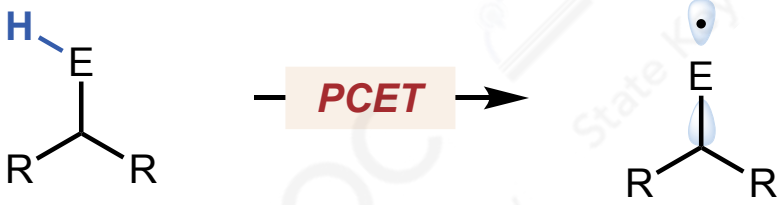
PCET: Reductive Transformations of S• Radicals





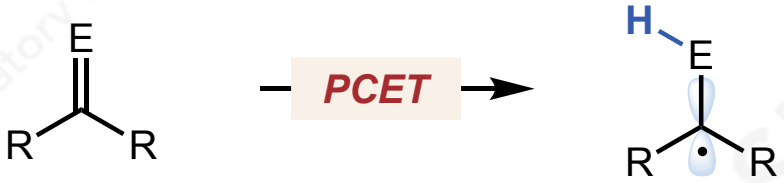
Knowles R. R. et al. *Science* **2019**, *366*, 364–369.

一、氧化型PCET反应



- N–H Bonds
- S–H Bonds
- O–H Bonds
- C–H Bonds

二、还原型PCET反应



- C=N Bonds
- C=C Bonds
- C=O Bonds
- S• Radicals

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10. Mayer J. M. et al. *J. Am. Chem. Soc*. **2017**, *139*, 10687–10692.
11. Knowles R. R. et al. *Science* **2019**, *366*, 364–369.