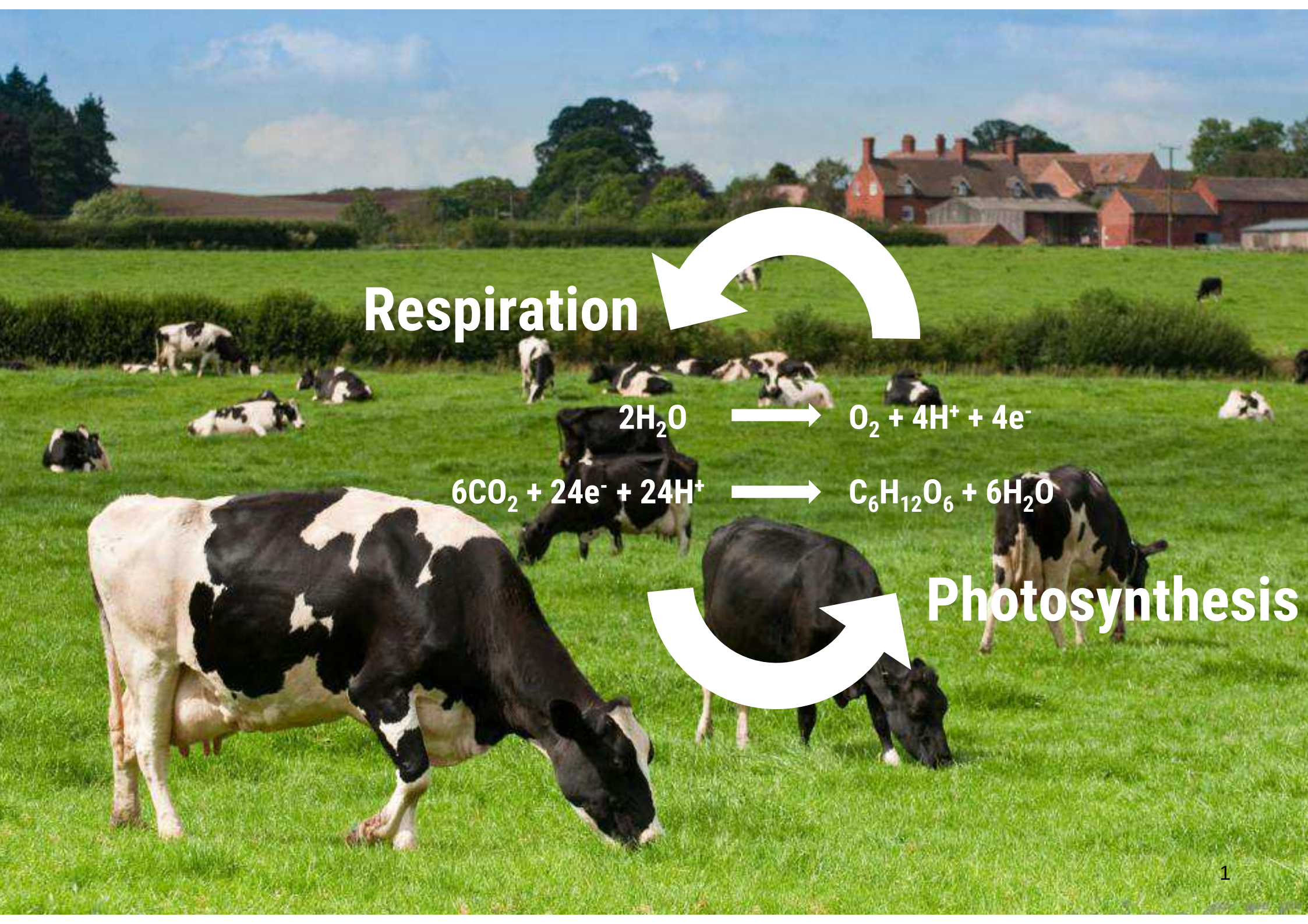
Proton Coupled Electron Transfer

Literature Seminar #3

2015.8.22 (Sat.)

Yusuke Shimizu (M2)


Respiration
$2H_2O \rightarrow O_2 + 4H^+ + 4e^-$
$6CO_2 + 24e^- + 24H^+ \rightarrow C_6H_{12}O_6 + 6H_2O$
Photosynthesis

Today's Topics

0. Introduction

1. Backgrounds of PCET

   Brief introduction of definition and thermodynamics of PCET,

   avoiding quantum mechanical discussion (difficult to understand for many of organic chemists!)

2. PCET in Biological Events

   Some representative biological PCET will be highlighted

3. PCET in Organic Chemistry

   Synthetic application of PCET, today's main topic

4. Summary

Backgrounds of PCET

Nernst Equation

Nernst equation

$$Ox + ze^- = Red$$

$$E = E^\circ + \frac{RT}{zF} \ln \frac{a_{Ox}}{a_{Red}}$$

E°: standard potential

R : universal gas constant

T : abusolute temperature

F : Faradey constant

a : activity

Redox reaction with dissociable proton (1 atm, 298K)

$$Ox + e^- + H^+ \longrightarrow Red\text{-}H$$

$$E = E^\circ + 0.059 \ln \frac{a_{Ox} a_{H^+}}{a_{Red\text{-}H}}$$

Nernst equation predicts the involvement of protons in redox potentials

pH-Dependent Thermodynamics

- Variation of redox potential with pH for cis-$[Ru^{II}(bpy)_2(py)(H_2O)]^{2+}$

For the $Ru^{III/II}$ couple

($RuOH_2^{3+}$: pKa^{III} = 0.85 $RuOH_2^{2+}$: pKa^{II} = 10.6)

1) pH < pKa^{III} : $0H^+/1e^-$ pH independent

$$Ru^{III}OH_2^{3+} + e^- \longrightarrow Ru^{II}OH_2^{2+}$$

2) pKa^{III} < pH < pKa^{II} : $1H^+/1e^-$ pH dependent

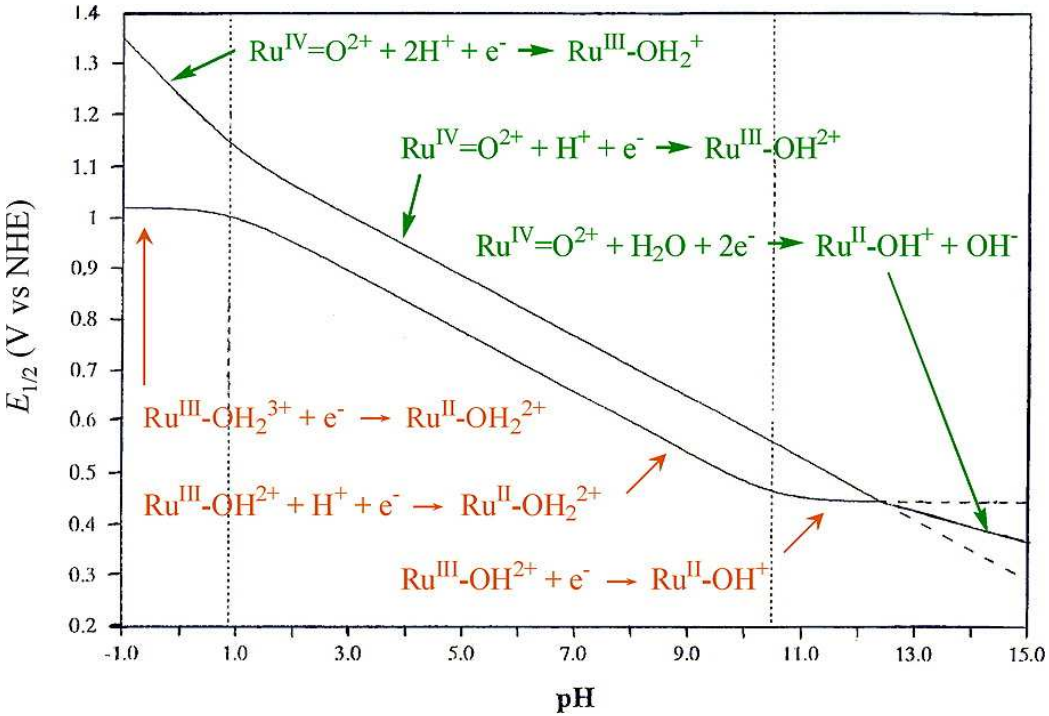
$$Ru^{III}OH^{2+} + e^- + H^+ \longrightarrow Ru^{II}OH_2^{2+}$$

$E°'(Ru^{III/II}) = E°'(RuOH_2^{3+/2+}) - 0.059(pH - pKa^{III})$

E°': formal potential

3) pKa^{II} < pH : $0H^+/1e^-$ pH independent

$$Ru^{III}OH^{2+} + e^- \longrightarrow Ru^{II}OH^{+}$$



Binstead, R. A. and Meyer, T. J. *J. Am. Chem. Soc*. **1987**, *109*, 3287

(Figure) Huynh, M. H. and Meyer, T. J. *Chem. Rev*. **2007**, *107*, 5004

Generally, in the redox reaction $Ox + mH^+ + ne^- \longrightarrow Red(H)_m^{(m-n)}$

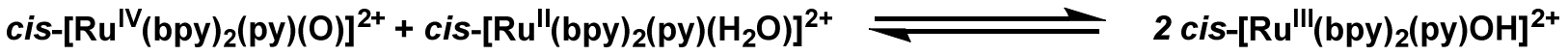
pH dependency can be described as $-0.059\frac{m}{n}pH$

e.g. E°' decreases by 118 mV/pH in pH < pKa^{III} region for the $Ru^{IV/III}$ couple ($2H^+/1e^-$)

Proton-Coupled Electron Transfer

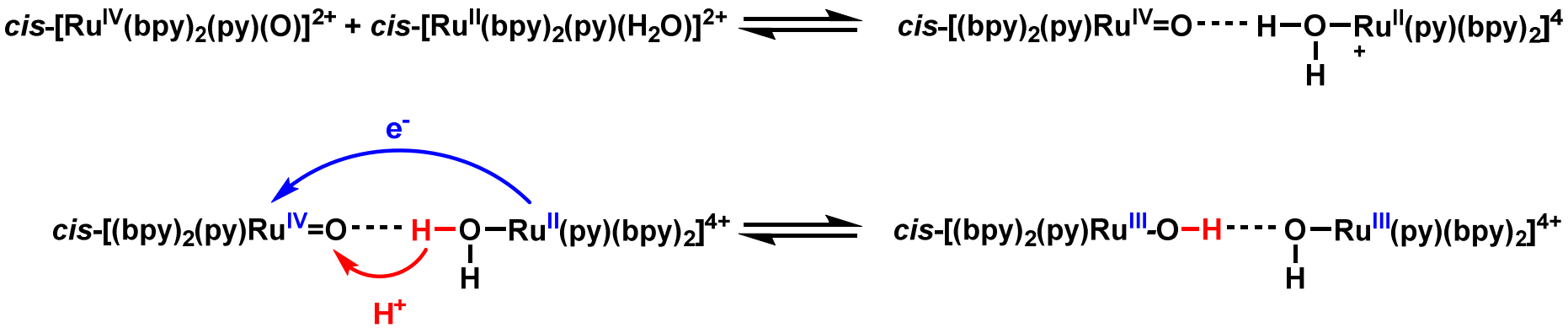
- Comproportionation reaction between $Ru^{IV/II}$

Meyer first coined the term “Proton-Coupled Electron Transfer” and applied it to the reaction below.



Meyer. T. J.*et al. J. Am. Chem. Soc*. **1981**, *103*, 2987

Proposed Mechanisms (pH 2-9)



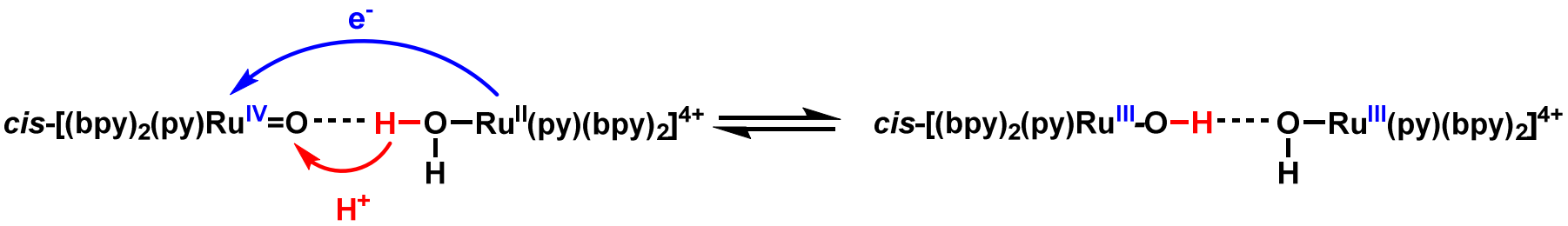
proton transfer is coupled with electron transfer

The term PCET was used to distinguish it from sequential ET-PT or PT-ET, and H-Atom Transfer

Termiology

The term PCET has come to be used more broadly to describe reactions and half reactions in which both electrons and protons are transferred without regard to mechanism.

Now, the new term to describe the concerted mechanism is needed.

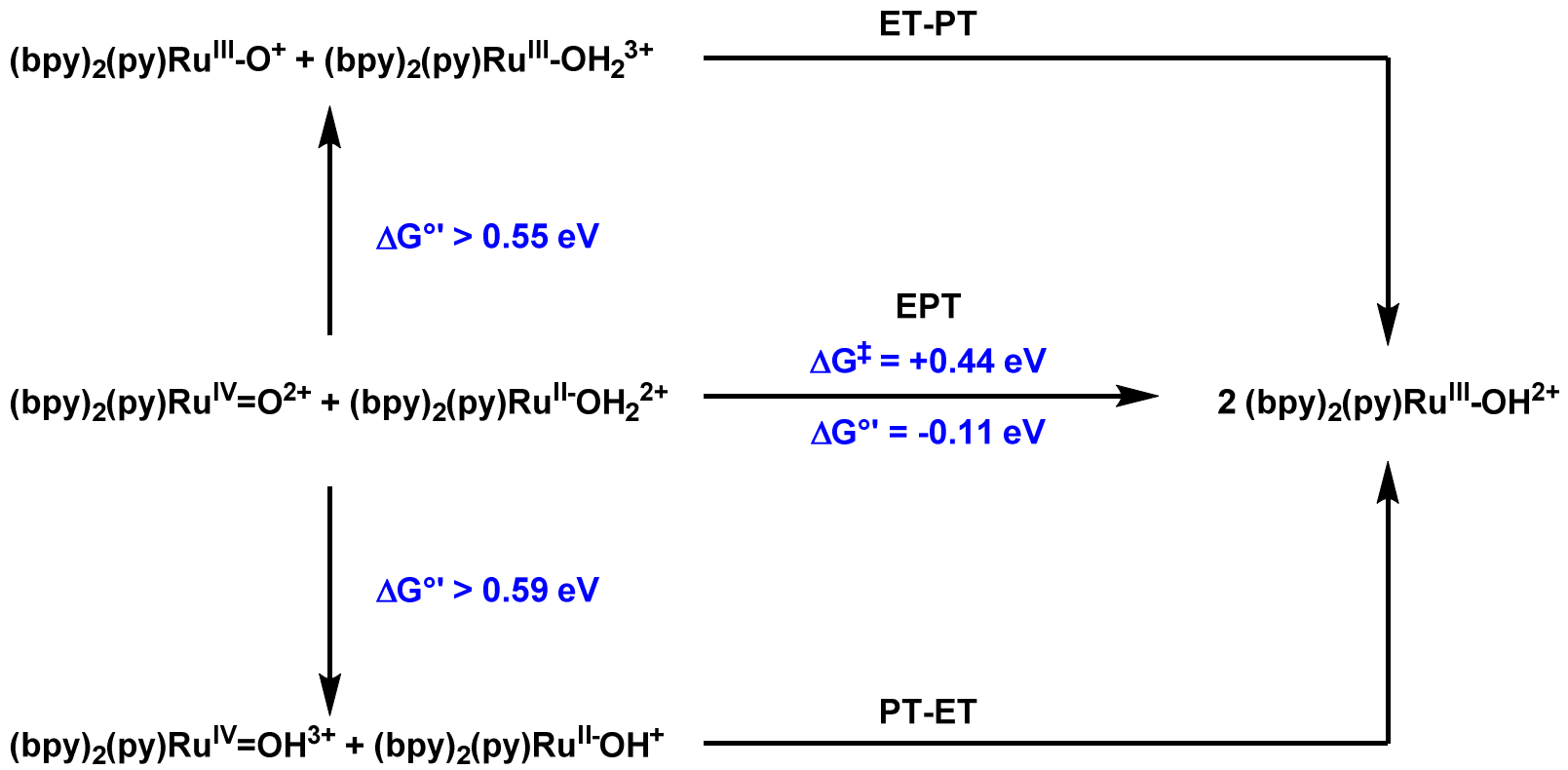


Unfortunately, the nomenclature has not been standardized yet

- concerted proton-electron transfer (CPET)
  Cukier, R. I. and Nocera, D. G. *Annu. Rev. Phys. Chem*. **1998**, *49*, 337
- concerted electron-proton transfer (CEP)
  Hammarström, L *et al. J. Am. Chem. Soc.* **2005**, *127*, 3855
- electron transfer proton transfer (ETPT)
  Saveant, J. M. *et al. J. Am. Chem. Soc*. **2001**, *123*, 4886
- **electron-proton transfer (EPT)** EPT will be used in this seminar
  Decornez, H. and Hammes-Schiffer, *S. J. Phys. Chem. A,* **2000**,*104*, 9370

Sequential vs Concerted

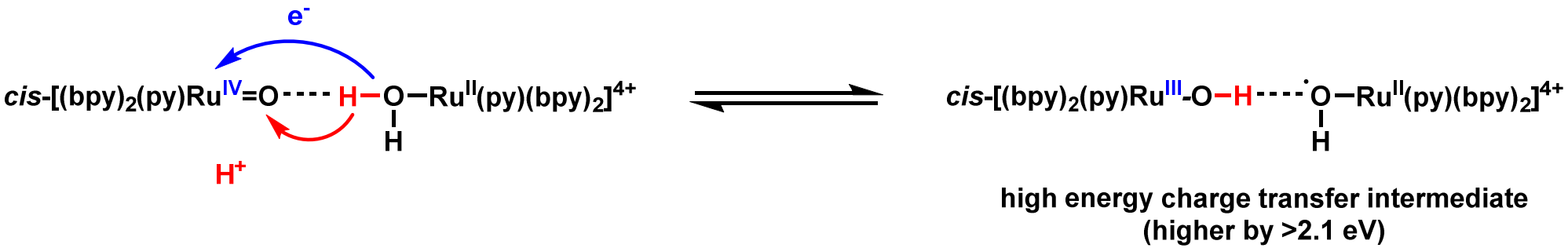
- Comproportionation reaction between $Ru^{IV/II}$ (at pH 7)



- Both ET-PT and PT-ET impose high reaction barrier in initial steps
- ΔG°' in ET-PT and PT-ET are lager than experimental free energy of activation (ruling these mechanisms out as major contribution)
- EPT has a significant advantage in avoiding high energy intermediate

HAT vs EPT

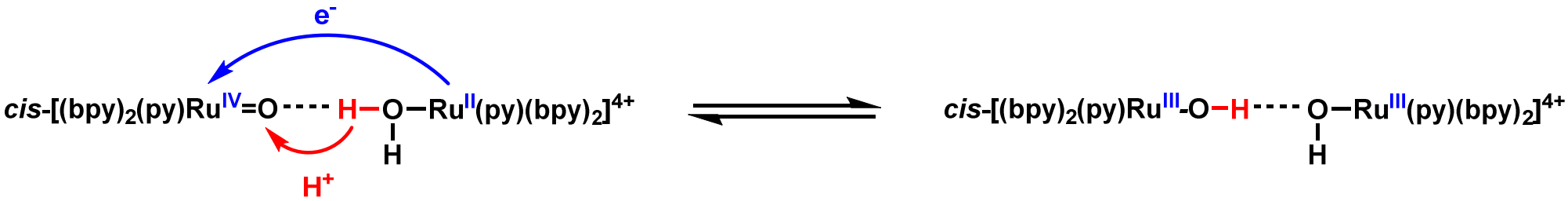
- Alternative concerted pathway, H-atom transfer (HAT)



high energy charge transfer intermediate (higher by >2.1 eV)

Both transferring e^-/H^+ come from the same bond

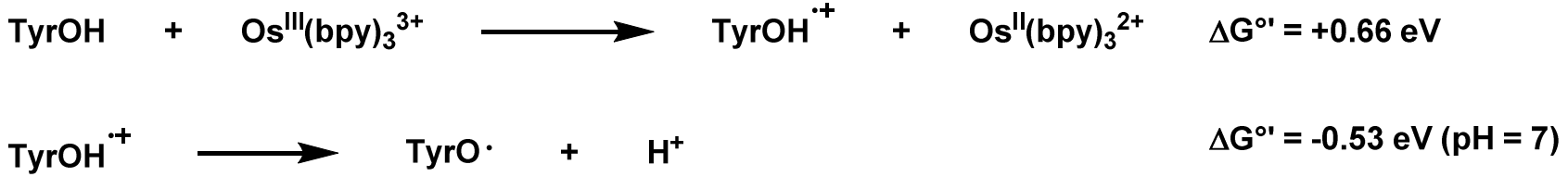
- EPT



e^-/H^+ transfer from different orbitals on the donor to different orbitals on the acceptor

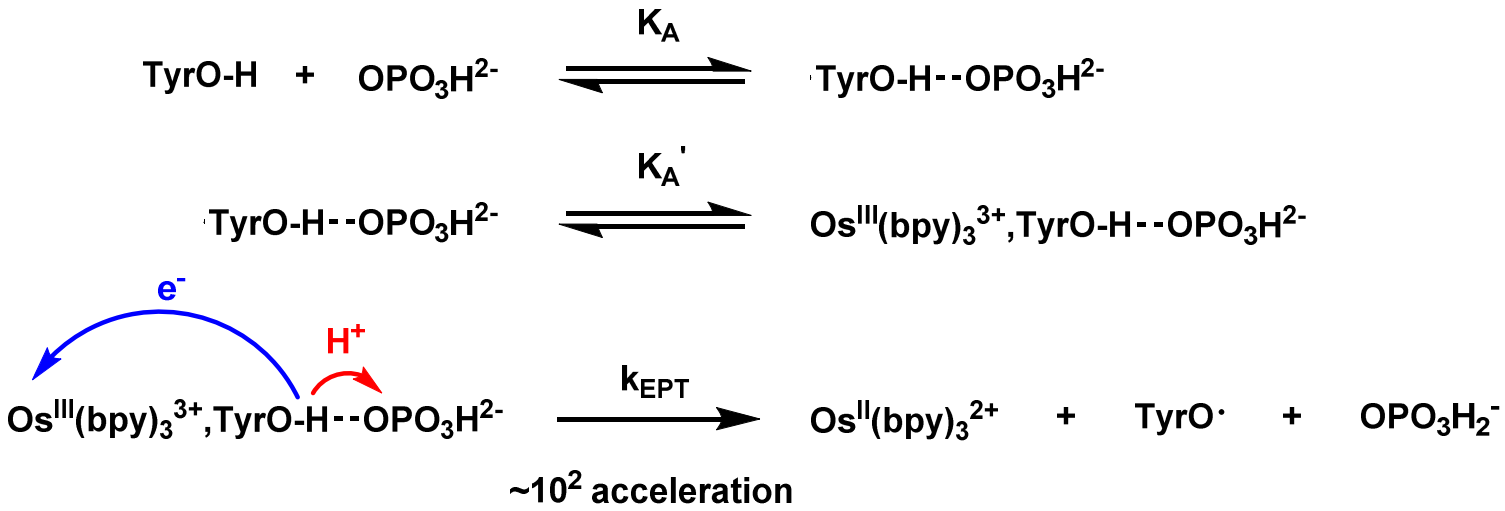
MS-EPT

- Oxidation of Tyrosine



ET-PT is slow because of high energy intemediate (k_{ET-PT} = 1.7 × 10^2 $M^{-1}s^{-1}$)

With buffer base HPO_3^{2-}

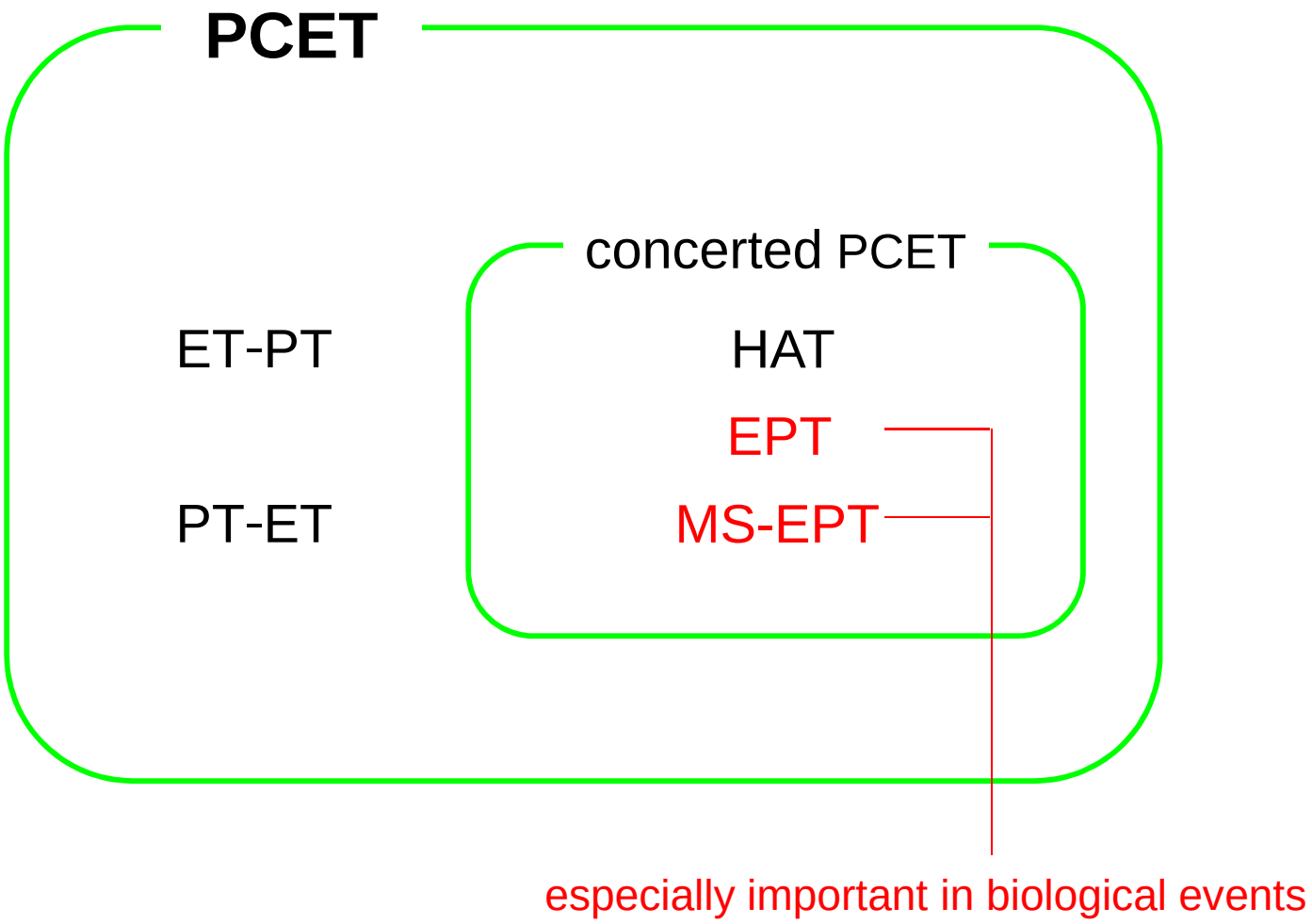


An electron−proton donor transfers e^-/H^+ to spatially separated acceptors

Multiple Site Electron-Proton Transfer (MS-EPT)

Thorp, H. H. *et al. J. Am. Chem. Soc*. **2006**, *128*, 11020

Short Summary



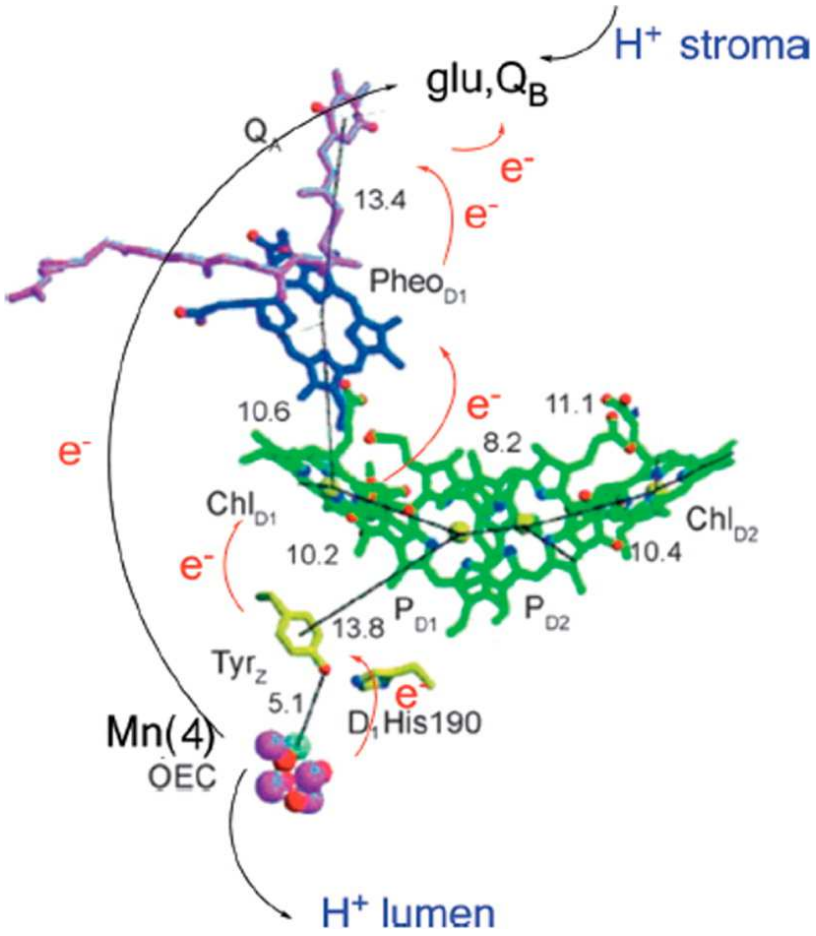
Concerted PCET have advantage in avoinding high-energy intermediate

PCET in Biological Events

Photosystem II

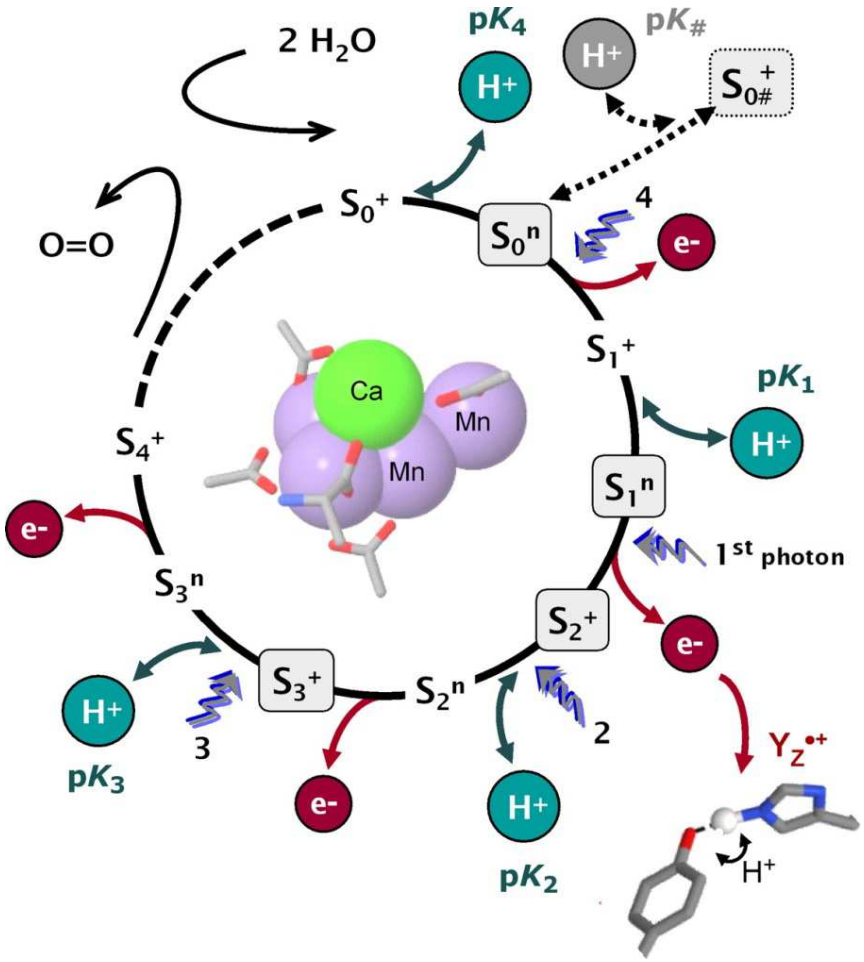
Key function of PS II is water oxidation

$$2H_2O + 4h\nu \longrightarrow O_2 + 4e^- + 4H^+$$



Iwata, S. *et al. Science,* **2004**, *303*, 1831

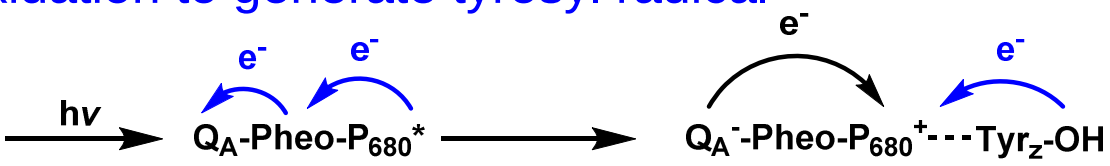
Photooxidation catalyzed by Oxygen-evolving complex (Kok cycle)



Dau, H. *et. al. J. Biol. Chem.* **2011**, *286*, 18222

PCET in Photosystem II

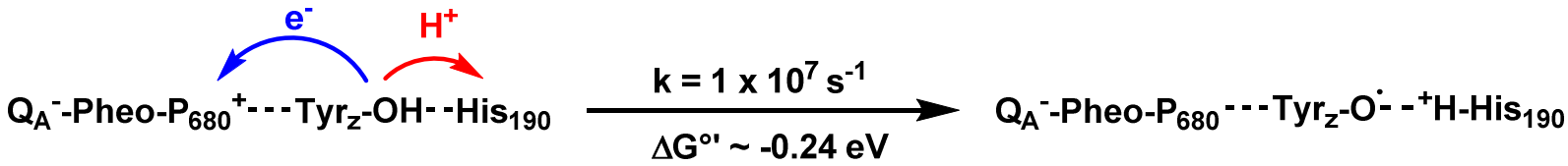
- Y_z oxidation to generate tyrosyl radical



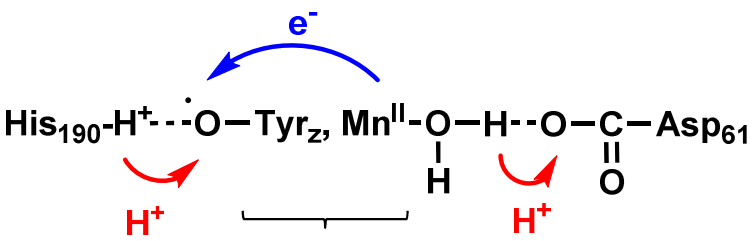
$k \sim 7 \times 10^3\ s^{-1}$

$\Delta G^{\circ\prime} \sim +0.20$ eV

too slow to compete with back electron transfer



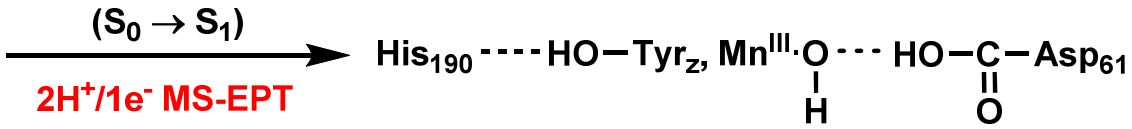
- S_0-S_1 transition (H-atom abstraction from $CaMn_4$ cluster)

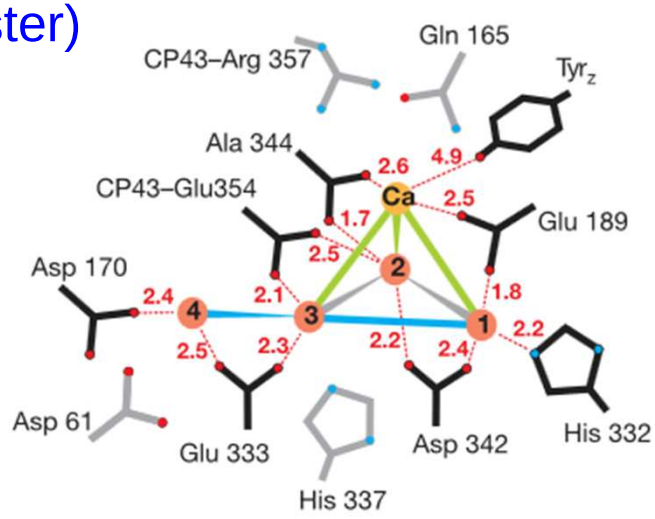


Too far for H^+ transfer (>7Å)

H^+ have short range nature

e^- have relatively long range nature

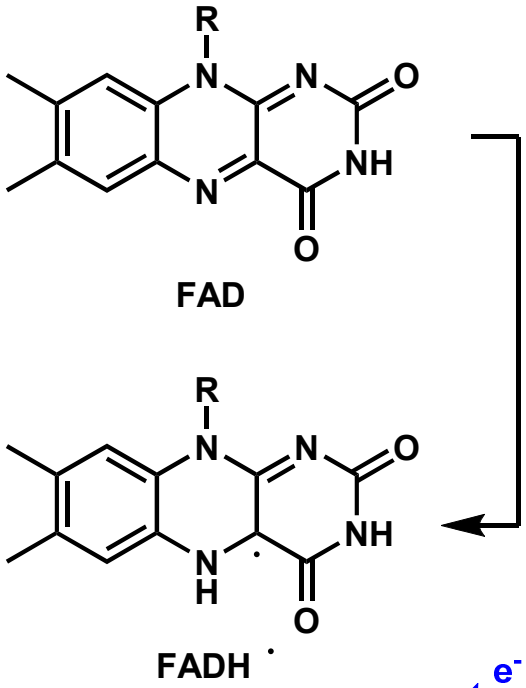


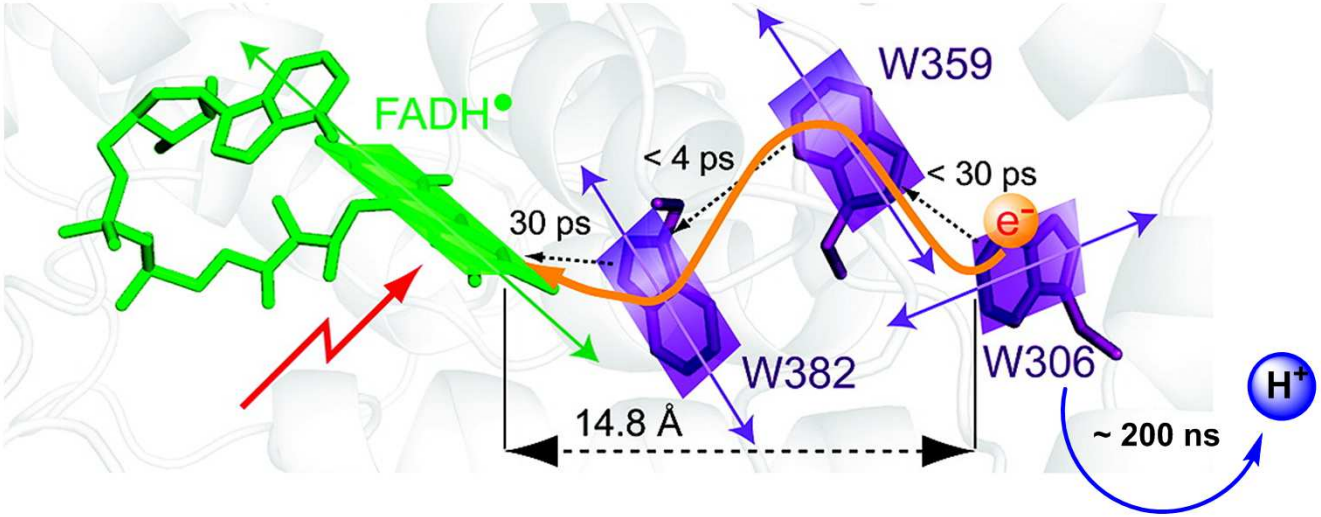


Biesiadka, J. *et al. Nature,* **2005**, *438*, 1040

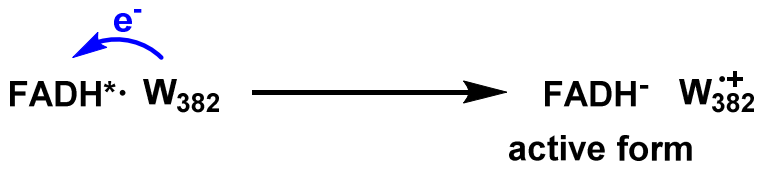
DNA Photolyase

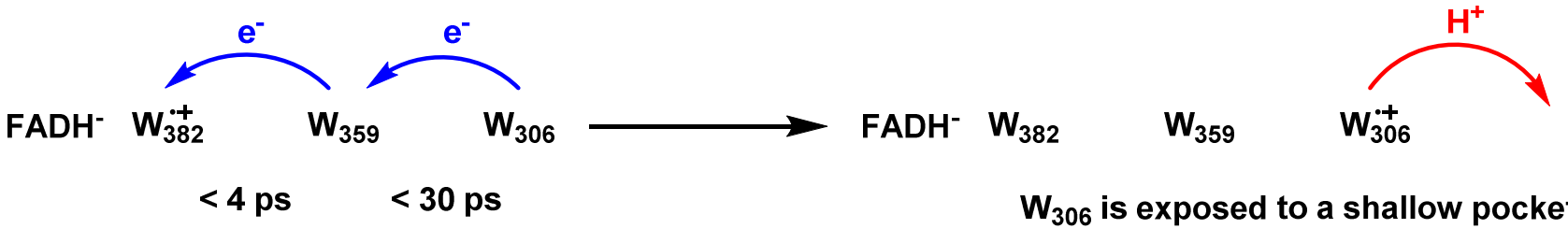
- Photoactivation of *Escherichia coli* DNA photolyase





Vos, M. H. *et al. J. Am. Chem. Soc*. **2008**, *130*, 14394





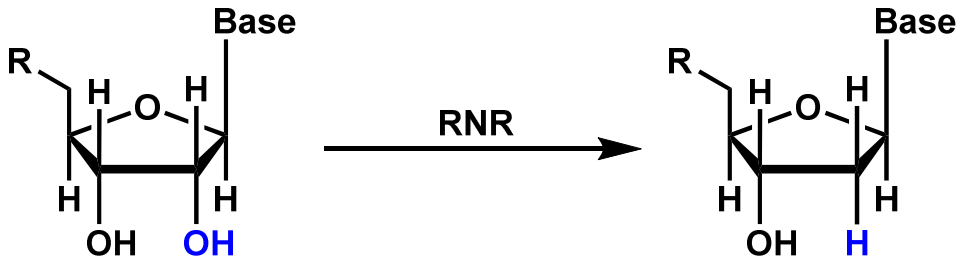
W_{306} is exposed to a shallow pocket open to solvent

Trp chain works as a "wire" to transfer electron

Class I Ribonucleotide Reductase

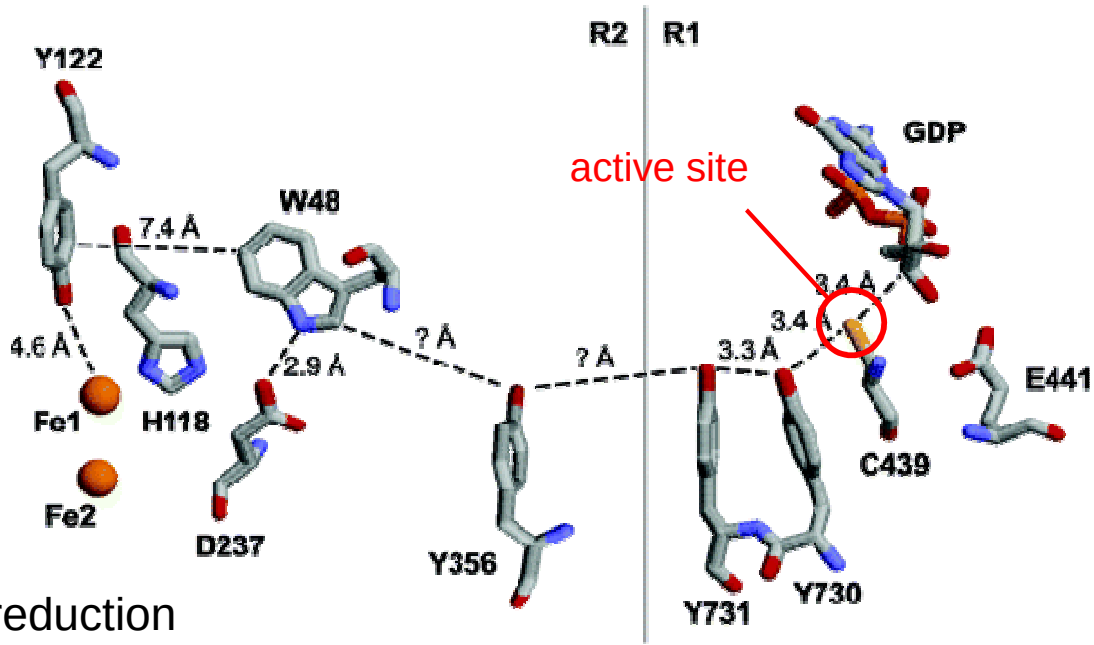
- Long-range EPT “shuttle”

Class I RNRs found in *E. coli* catalyze reduction of nucleotides



$Y_{122}^{\bullet}$ W_{48} Y_{356} Y_{731} Y_{730} C_{439}

radical transfer over 35 Å



thiyl radical generation to initiate nucleotide reduction

Stubbe, J. *et al. J. Am. Chem. Soc.* **2006**, *128*, 1562

PCET in Organic Chemistry

Robert R. Knowles

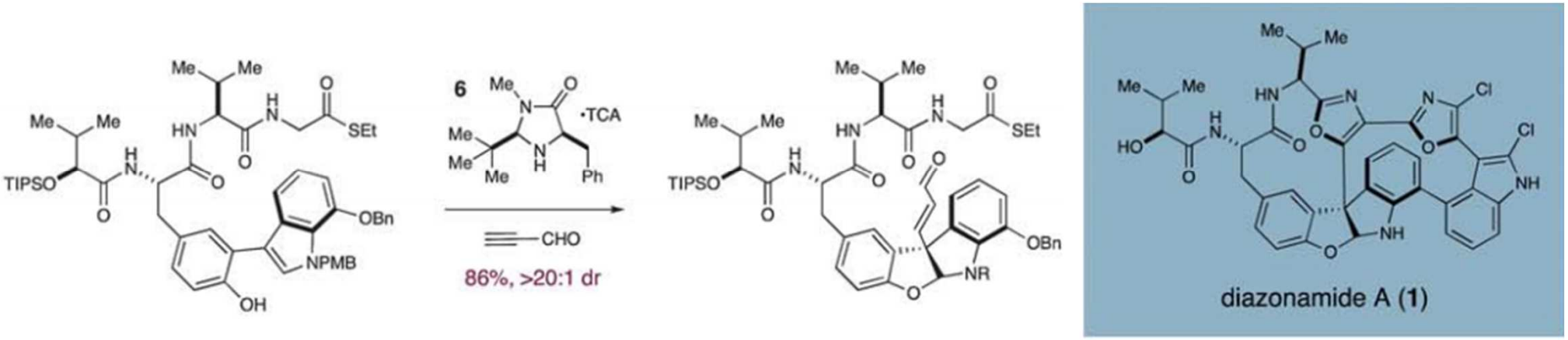
2003 B.S. in Chemistry, College of William and Mary

2008 Ph.D. with David MacMillan, Caltech

NIH Postdoctoral Fellow with Eric Jacobsen, Harvard University

2011 Assistant Professor of Chemistry, Princeton University

- **Total Synthesis of Diazonamide A**



Knowles, R. R.; MacMillan D. W. C. *et al. Chem. Sci*. **2011**, *2*, 308

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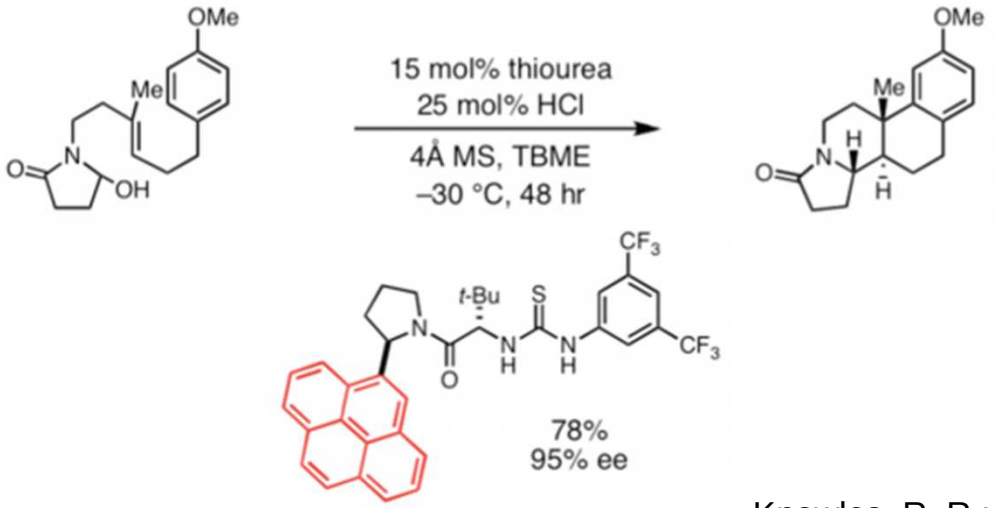
2003 B.S. in Chemistry, College of William and Mary

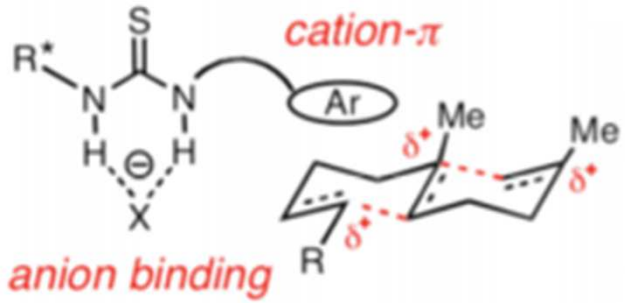
2008 Ph.D. with David MacMillan, Caltech

NIH Postdoctoral Fellow with Eric Jacobsen, Harvard University

2011 Assistant Professor of Chemistry, Princeton University

Enantioselective Thiourea-Catalyzed Cationic Polycyclizations





Noncovalent interactions

Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2010**, *132*, 5030

Robert R. Knowles

2003 B.S. in Chemistry, College of William and Mary

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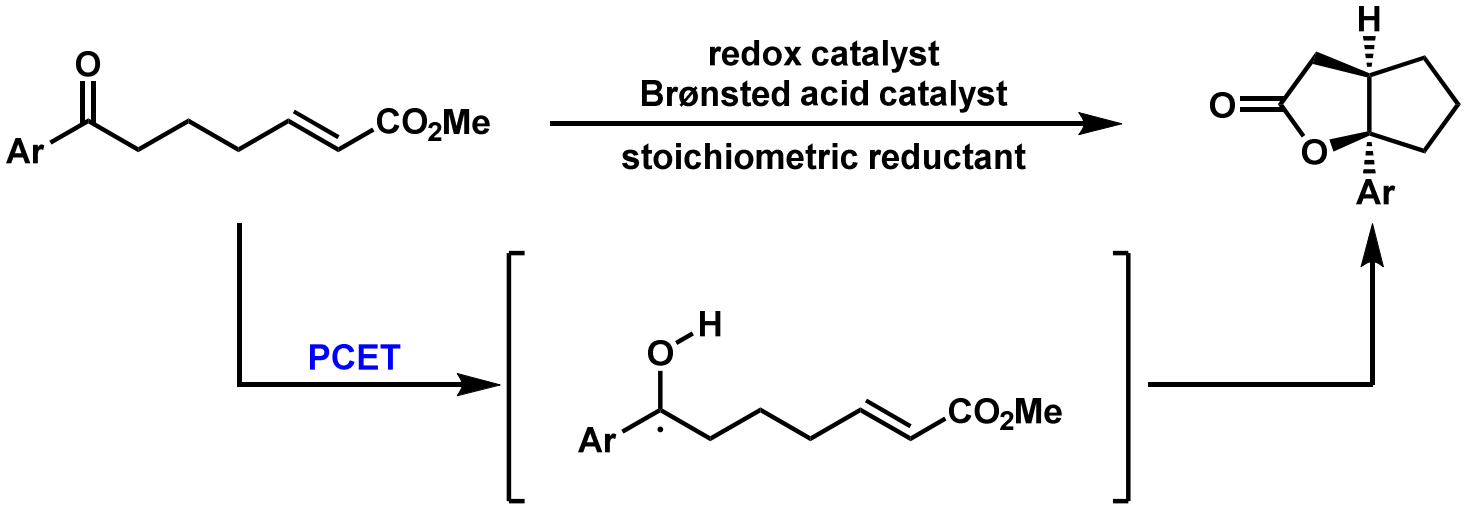
NIH Postdoctoral Fellow with Eric Jacobsen, Harvard University

2011 Assistant Professor of Chemistry, Princeton University

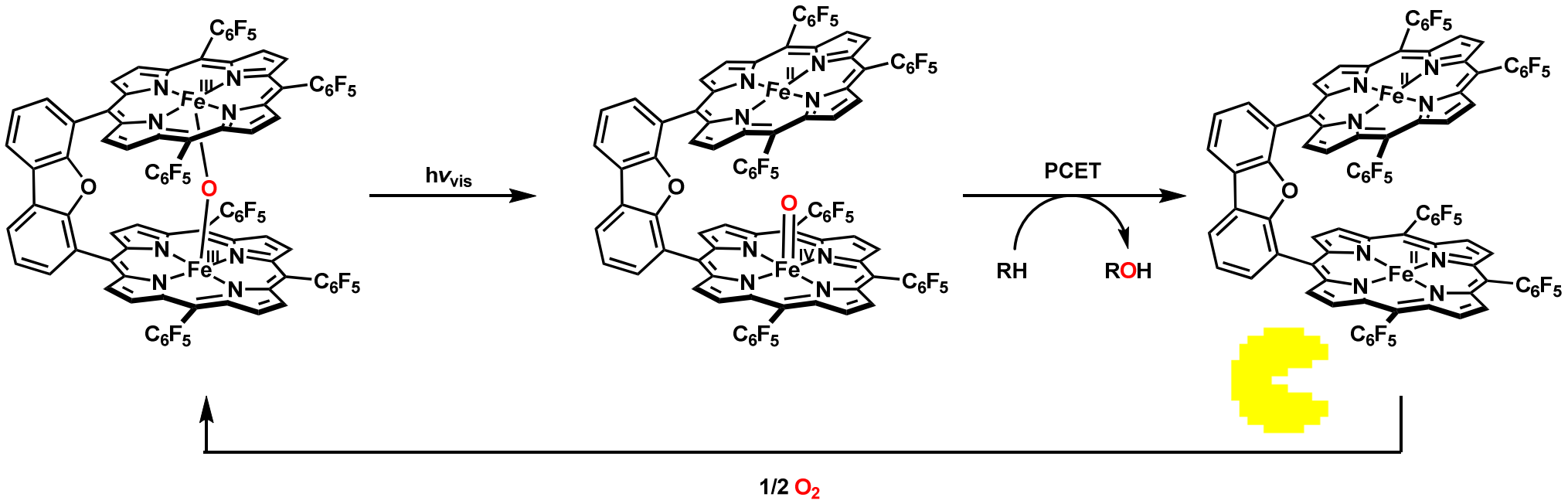
- **Synthetic Application of PCET (Today's Topic)**



Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc*. **2013**, *135*, 10022

Precedent

- Aerobic C-H oxidation with Pacman system



substrate	product	IE (eV)	k_{ox} (M-1s-1)
fluorene	fluorenone	1.52×10^{-2}	1.36×10^{7}
diphenylmethane	benzophenone	2.76×10^{-3}	2.41×10^{6}
cumene	acetophenone cumyl alcohol	1.99×10^{-3}	1.74×10^{6}
toluene	benzaldehyde	1.51×10^{-3}	1.32×10^{6}
toluene-d_8		9.79×10^{-4}	8.53×10^{5}

IE-k_{ox} correlation and KIE suggest asynchronous PT-ET rather than HAT

Nocera, D. G. *et al. J. Am. Chem. Soc.* **2006**, *128*, 6546

Advantages of concerted PCET

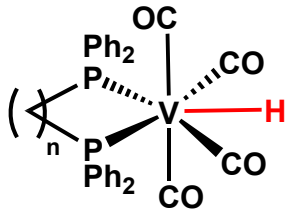
How can we utilize concerted PCET for the development of catalyst system?

- Bond dissociation free energy

HAT reactivity can be described by BDFE

$$BDFE = 1.37\ pKa + 23.06\ E^{\circ} + C_{solv}$$

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



V-H BDFE
55~58 kcal/mol

Unfortunately, pKa and E° are interdependent and inversely correlated

⟶ BDFE range is limited

Norton, J. R. *et al. J. Am. Chem. Soc*. **2008**, *130*, 4250

(Even with one of the weakest HAT donor, BDFE > 50 kcal/mol)

- "Effective" bond dissociation free energy

BDFE formalism can be applied to MS-EPT,

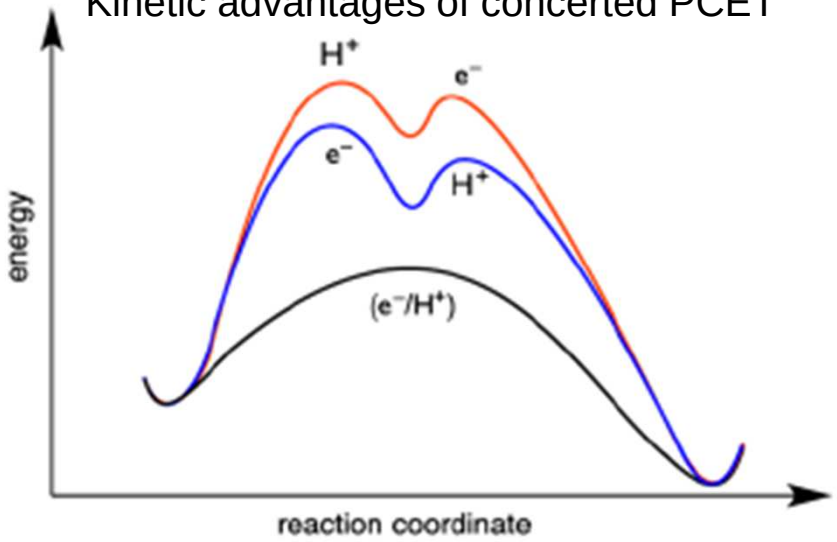
while no bond is homolytically cleaved

$$\text{'BDFE'} = 1.37\ pKa(HX) + 23.06\ E^{\circ}(Red) + C_{solv}$$

pKa and E° are independent with each other

⟶ 'BDFE' < 50 kcal/mol can be achieved?

Kinetic advantages of concerted PCET



Knowles, R. R. *et al. J. Am. Chem. Soc*. **2013**, *135*, 10022

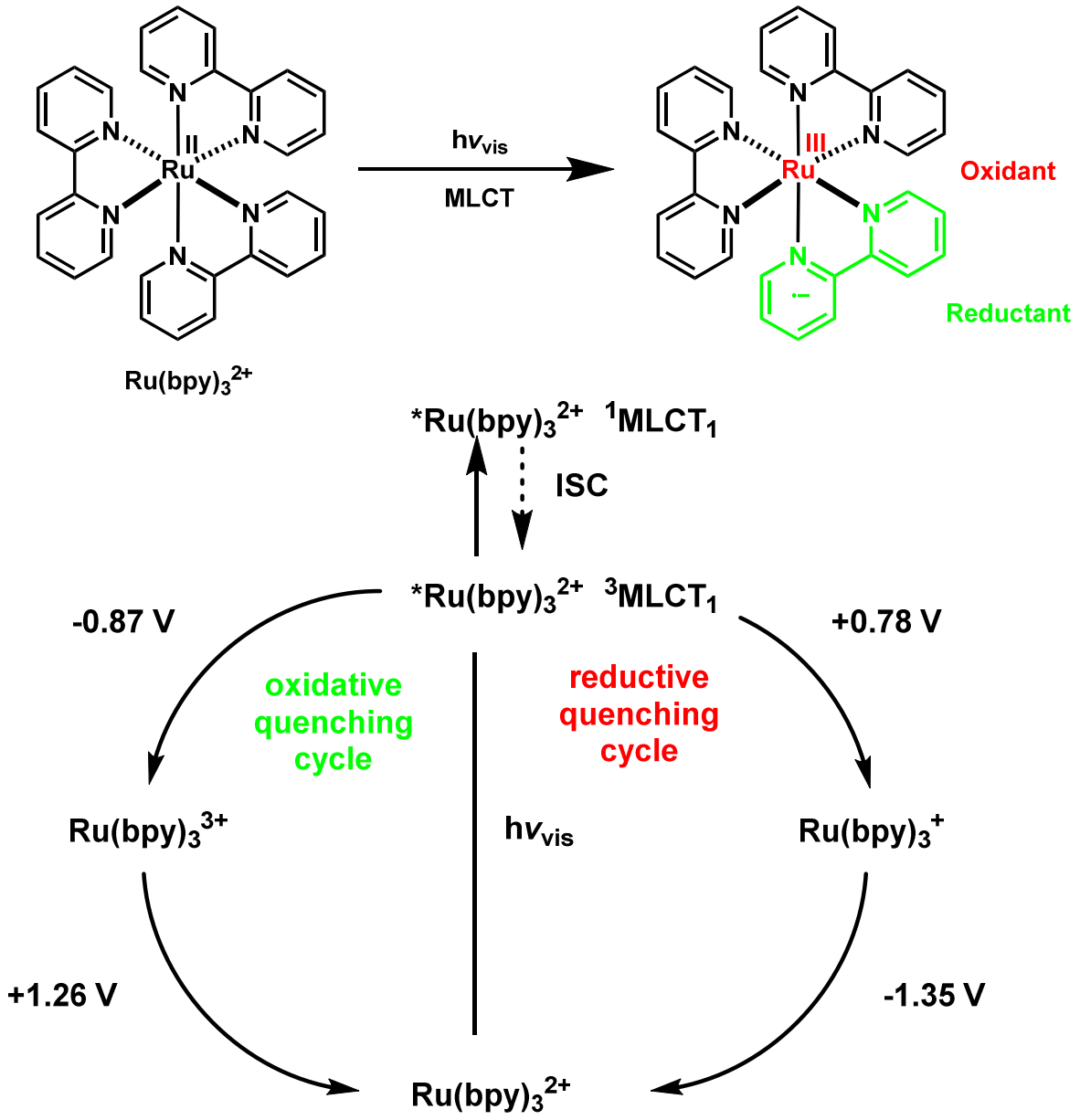
With kinetic advantage and 'BDFE', PCET can generate the radicals inaccessible by HAT?

Photoredox Catalysis

×

PCET

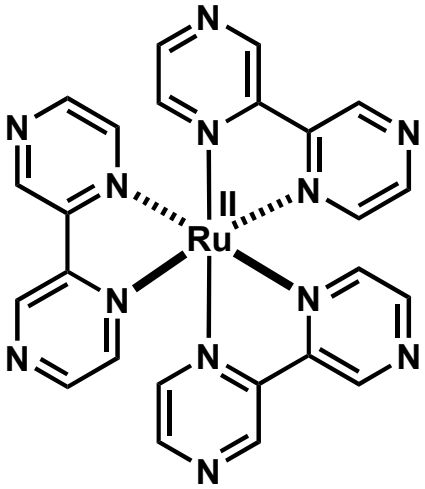
Photoredox Catalyst



Tucker, J. W. and Stephenson, C. R. J. *J. Org. Chem*. **2012**, *77*, 1617

Photoredox Catalyst

Redox potential can be tuned by changing metal and ligands



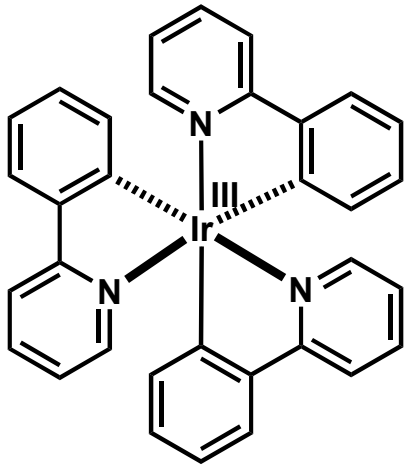
Ru(bpz)$_3^{2+}$

Redox potential (vs SCE)

$E_{1/2}(Ru^{III/II})$ = +1.86 V

strong oxidant

$E_{1/2}(Ru^{II/I})$ = -0.80 V



***fac*-Ir(ppy)$_3$**

Redox potential (vs SCE)

$E_{1/2}(Ir^{IV/III})$ = +0.77 V

$E_{1/2}(Ir^{III/II})$ = -2.19 V

strong reductant

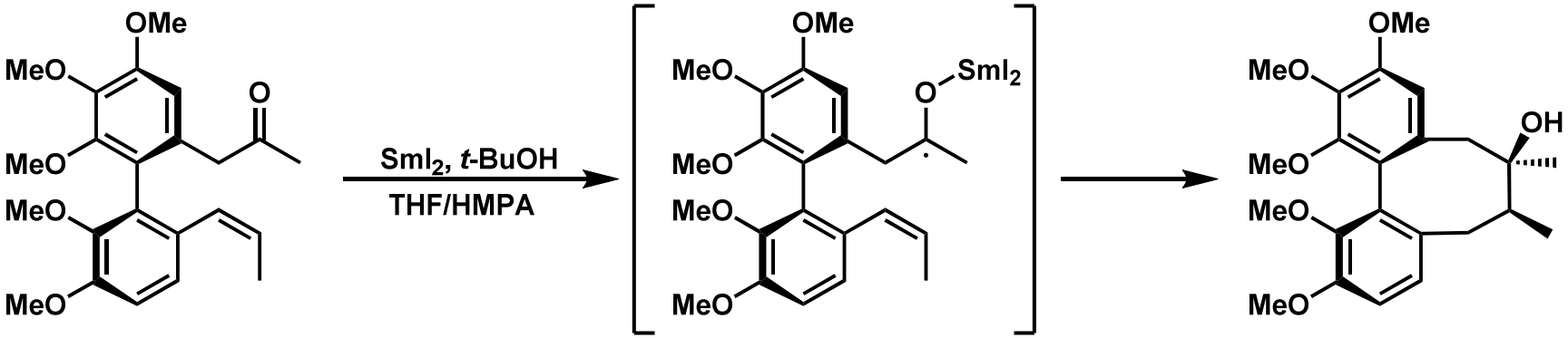
Tunable redox potential = Tunable 'BDFE'

'BDFE' = 1.37 pKa(HX) + 23.06 E°(Ox) + C_{solv}

Photoredox catalysts are ideal partner for PCET!

Ketyls

- SmI_2 mediated keyl-olefine cyclization

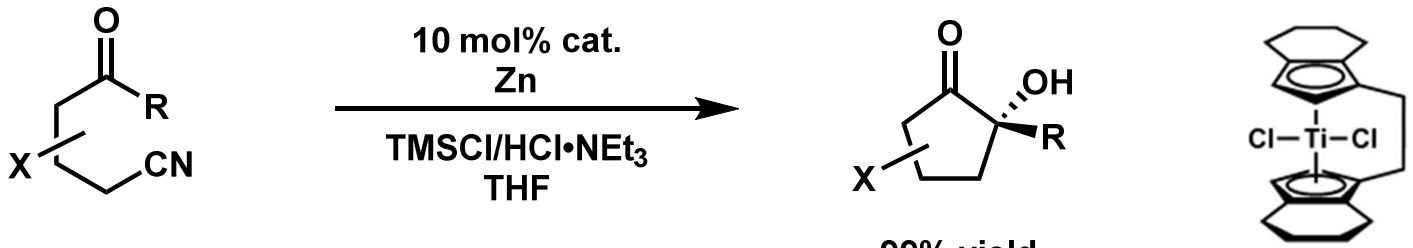


(+)-isoschizandrin

85%, dr >18:1

Molander, G. A. *et al. J. Org. Chem.*, 2003, 68, 9533

- Titanocene catalyzed enantioselective cyclization



~99% yield

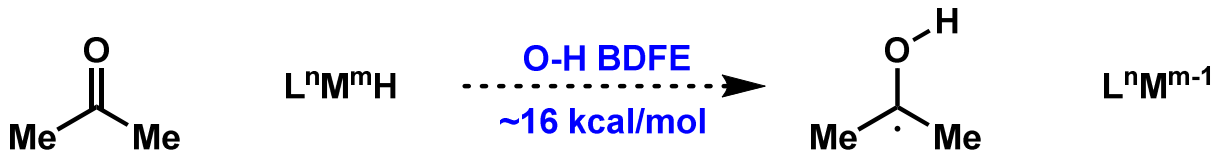
~94% *ee*

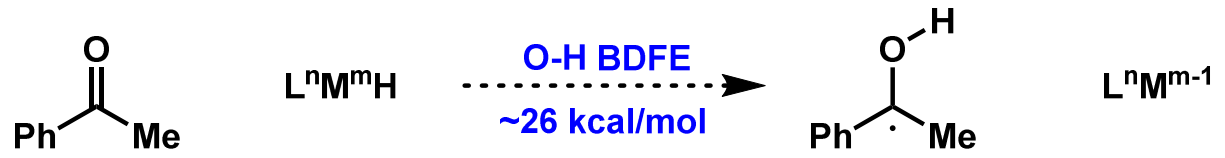
Gellrich, U. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 8661

Ketyls are versatile radical intemediate

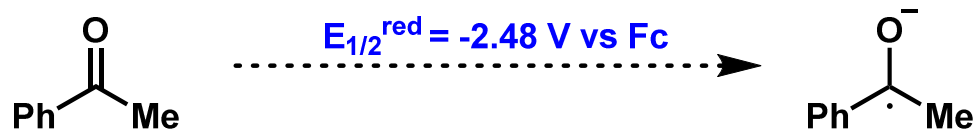
Challenges in Ketyl Generation

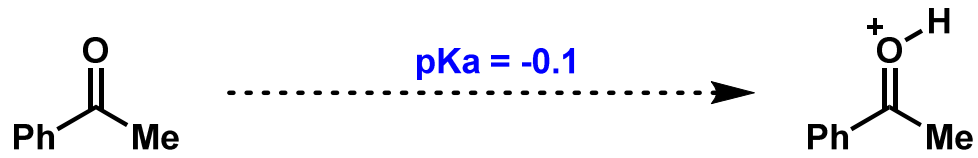
- Thermodynamic challenges in reductive HAT





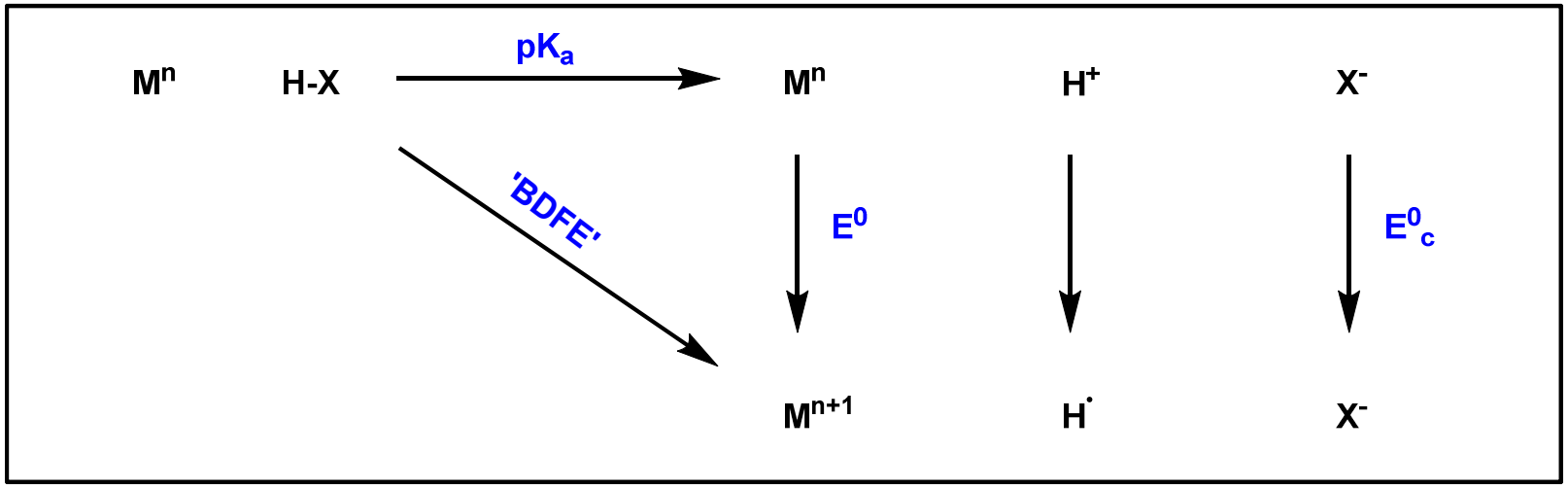
- Thermodynamic challenges in sequential PCET

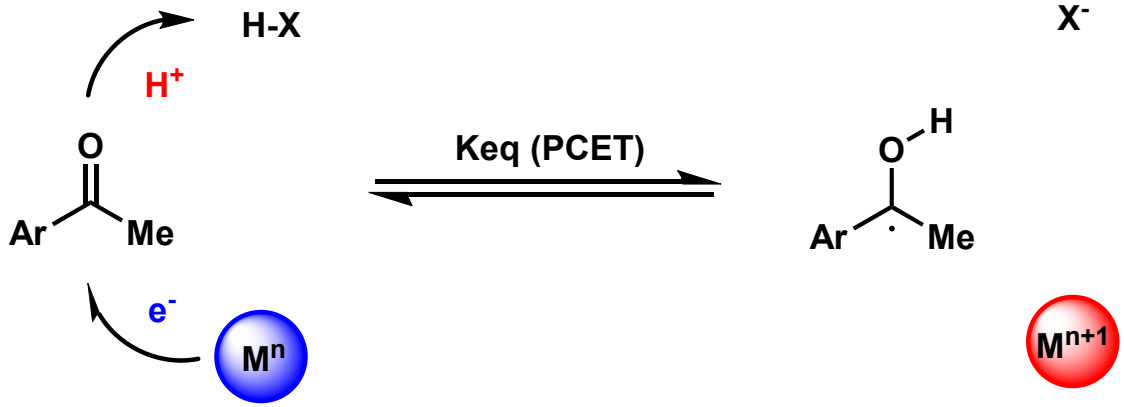




Both HAT and sequential PCET are highly demanding

Reaction Design

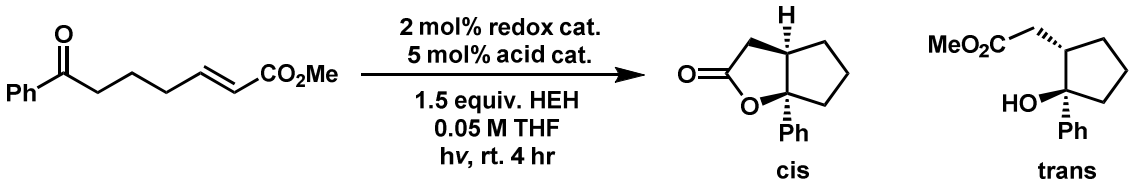




'BDFE' (kcal/mol) =
$2.3RTpK_a(HX) + 23.06E^0(M^n) + C_{solv}$

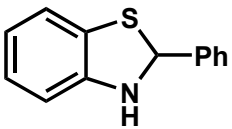
O-H BDFE ~26 kcal/mol

Optimization

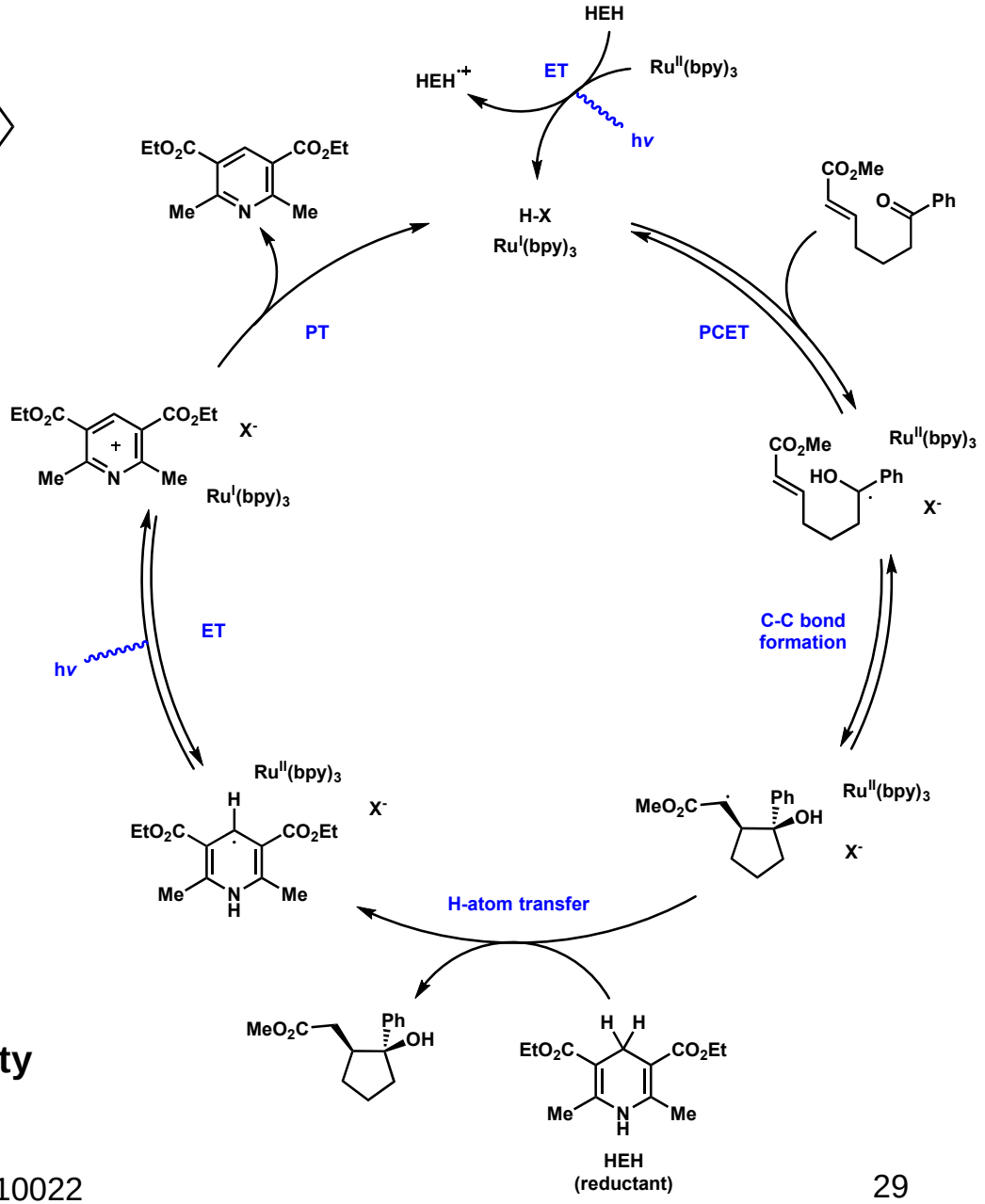


entry	acid catalyst	redox catalyst	'BDFE' (MeCN)	% yield	cis:trans
1	none	$Ru(bpy)_3(BAr^F)_2$	—	0	—
2	BzOH	$Ru(bpy)_3(BAr^F)_2$	45	0	—
3	NEt_3•HBF_4	$Ru(bpy)_3(BAr^F)_2$	41	0	—
4	lutidine•HBF_4	$Ru(bpy)_3(BAr^F)_2$	35	0	—
5	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	33	78	4.6:1
6	*p*TSA	$Ru(bpy)_3(BAr^F)_2$	27	74	4.3:1
7	$(PhO)_2PO_2H$	$Ir(ppy)_2(dtbpy)PF_6$	29	93	4.8:1
8	$(PhO)_2PO_2H$	*fac*-$Ir(ppy)_3$	24	92	4.8:1
9	lutidine•HBF_4	$Ir(ppy)_2(dtbpy)PF_6$	33	74	4.9:1
10[a]	$(PhO)_2PO_2H$	$Ru(bpy)_3(BAr^F)_2$	31	89	10:1

[a]BT was used in place of HEH

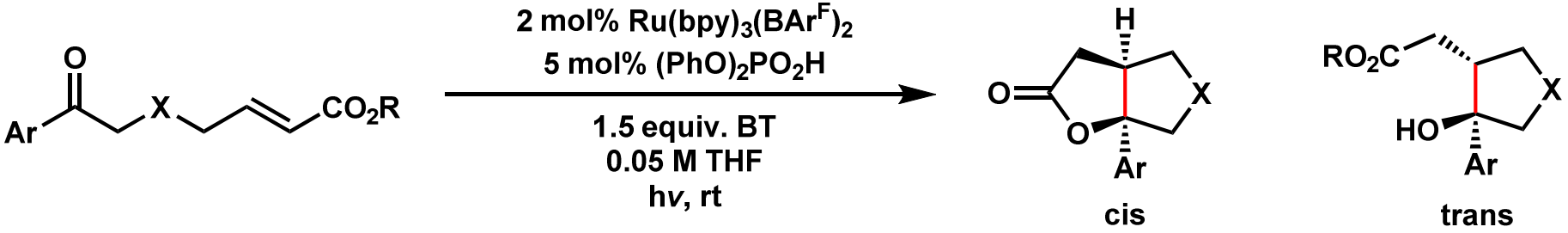


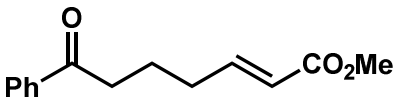
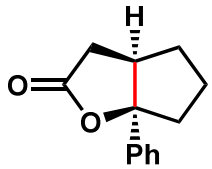
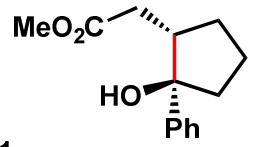
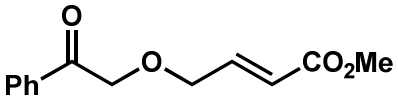
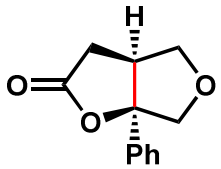
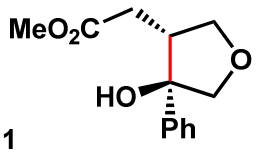
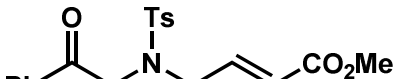
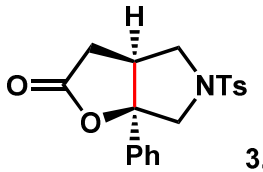
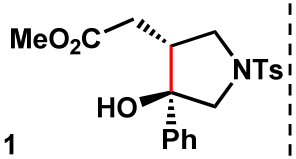
SmI_2 shows reversed selectivity

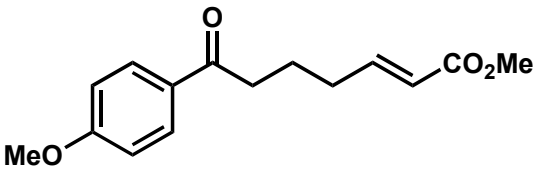
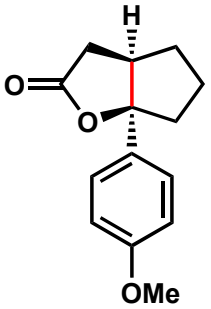
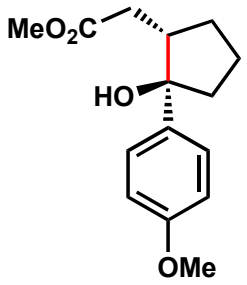
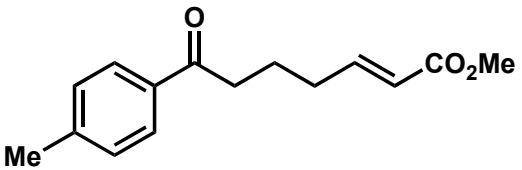
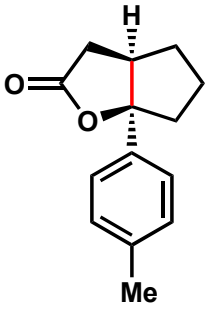
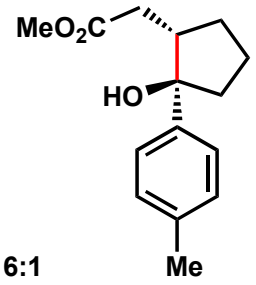


Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc*. **2013**, *135*, 10022

Substrate Scope



substrate	products		
			11:1 73%
			4.8:1 87%
			3.4:1 80%

substrate	products		
			12:1 78%
			6:1 86%

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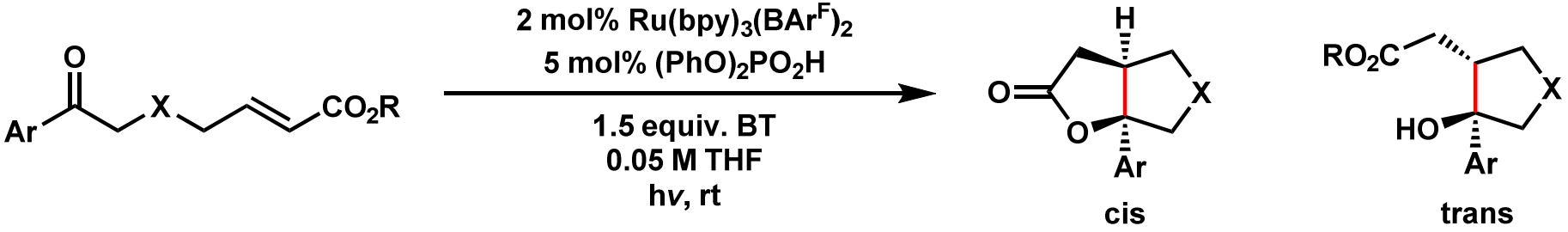
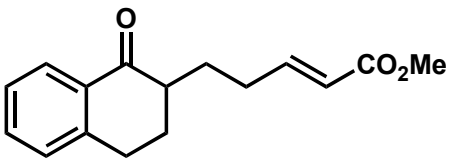
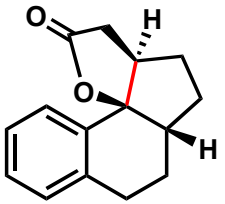
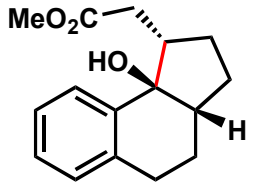
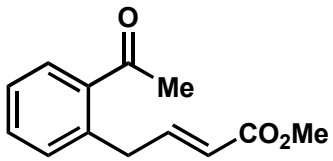
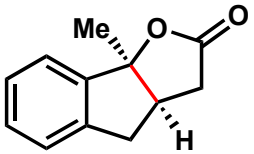
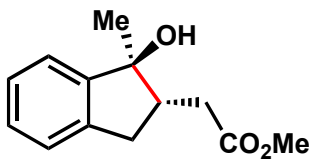
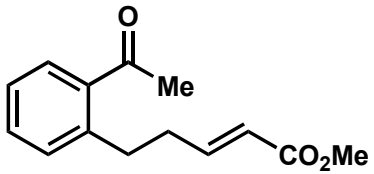
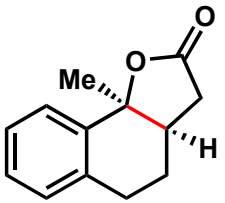
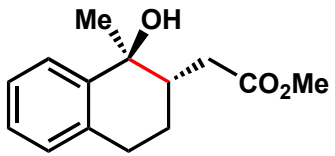
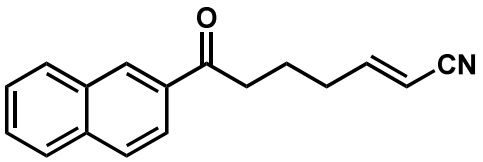
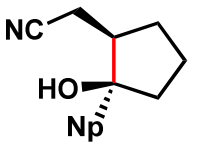
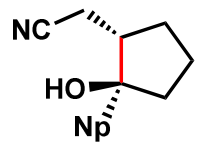
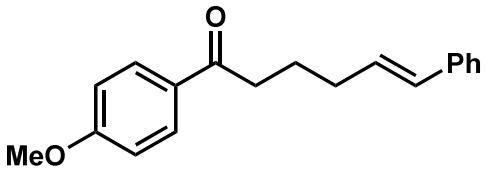
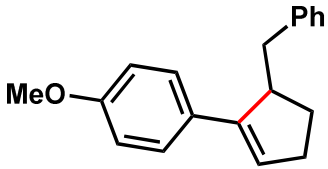
Substrate Scope



substrate	products	
		
	16:1 82%	
		
	2:1 96%	
		
	1.2:1 78%	

substrate	products	
		
	10:1 64%	
		
	68%	

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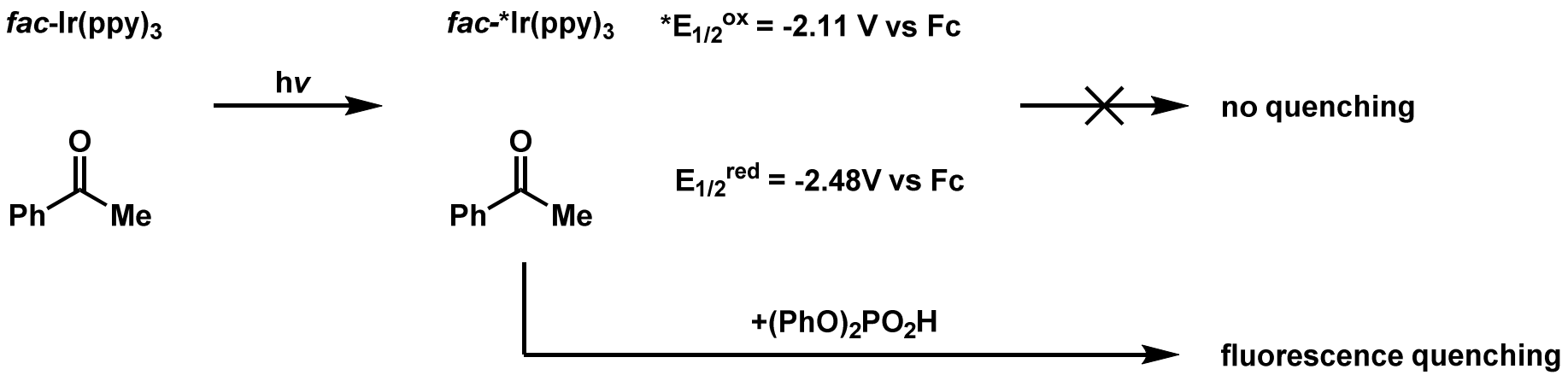
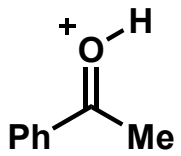
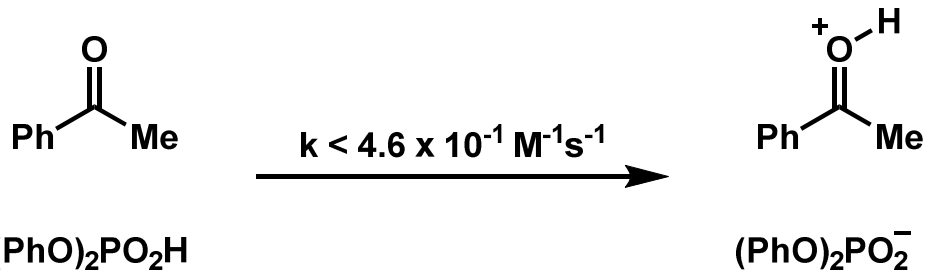
Mechanism

- Flueorescenece quenching technique



- pK_a difference

	pK_a in MeCN
	-0.1
$(PhO)_2PO_2H$	13



too slow considering 1.9 μs lifetime of Ir^{III} excited state

✕ET-PT ✕PT-ET ○MS-EPT

Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc*. **2013**, *135*, 10022

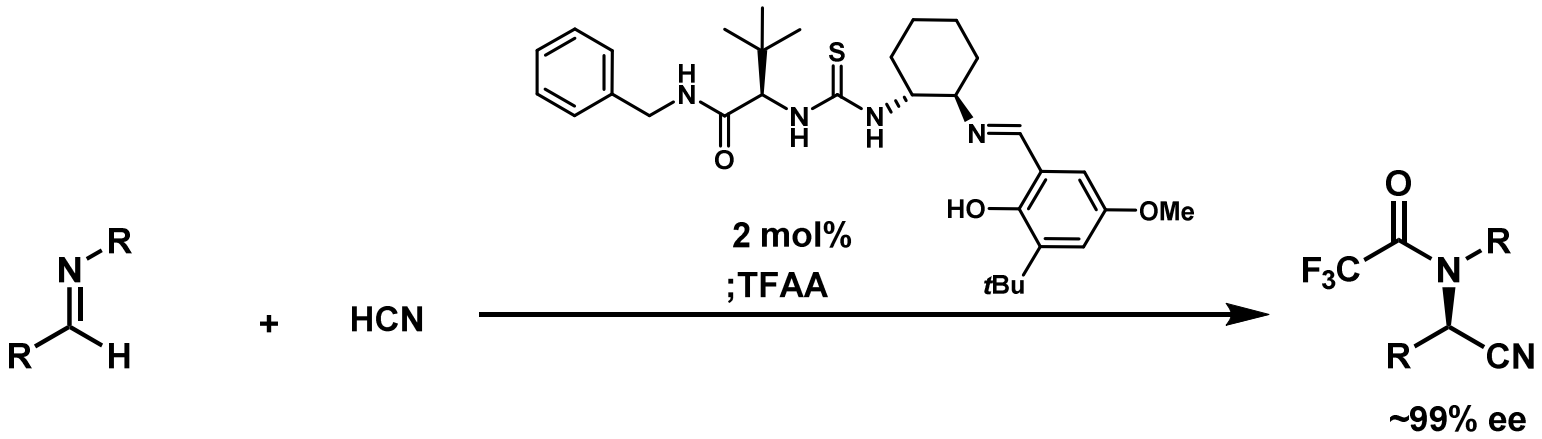
Chiral Brønsted Acid Chemistry

×

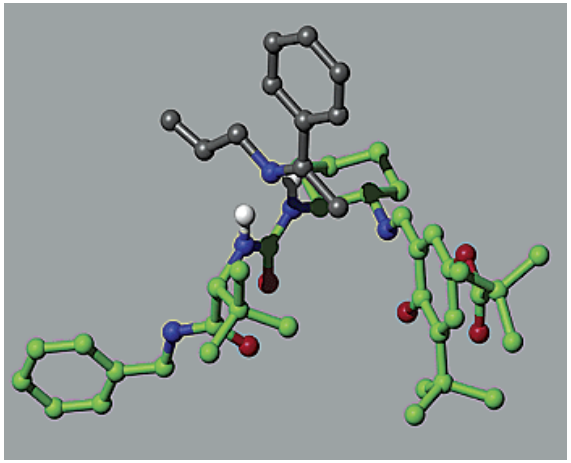
PCET

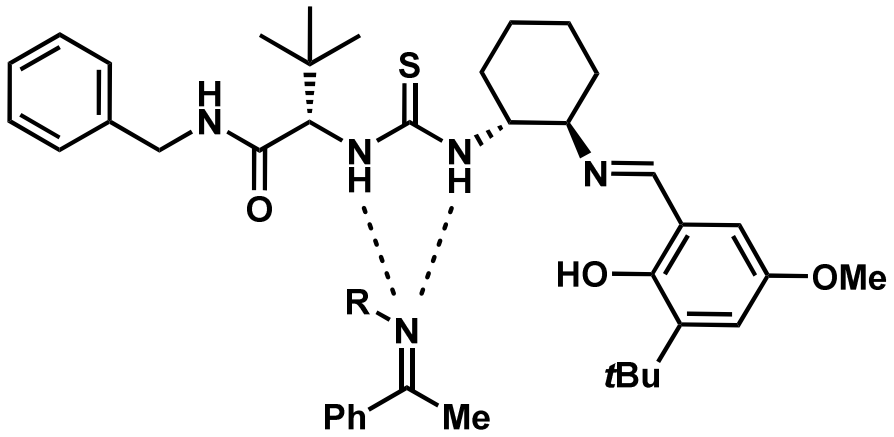
Chiral Brønsted Acid Chemistry

- Ground-breaking thiourea catalyzed asymmetric Strecker reaction



Sigman, M. S. and Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 4901
Vachal, P. and Jacobsen, E. N. *Org. Lett*. **2000**, *2*, 867
Sigman, M. S. and Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2000**, *39*, 1279

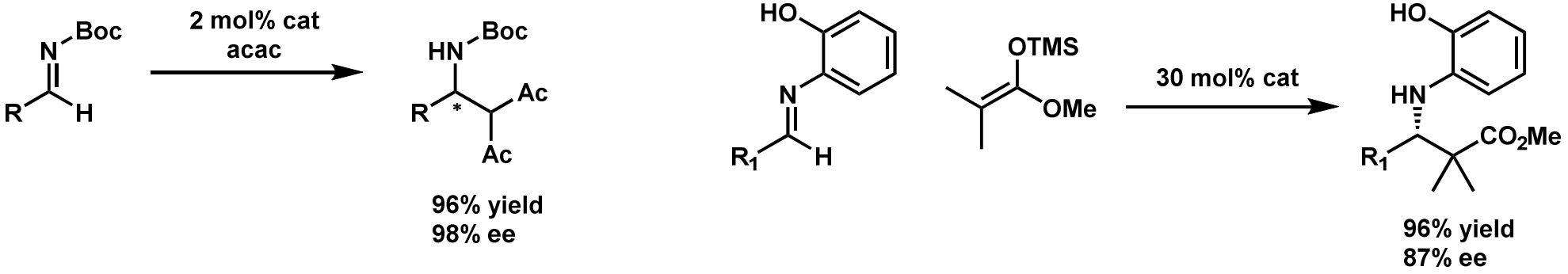




Vachal, P. and Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, 1*24*, 10012

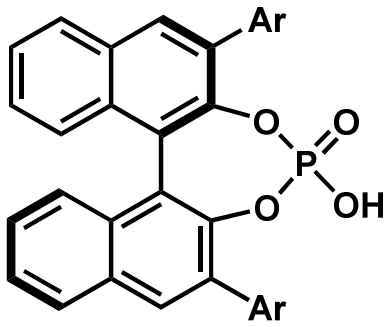
Chiral Brønsted Acid Chemistry

- Another Class of Chiral Brønsted Acid – Phosphoric Acid Catalyst

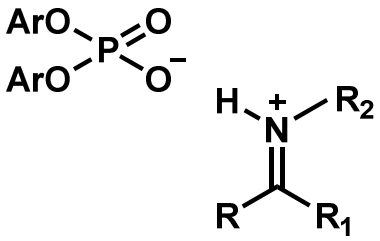


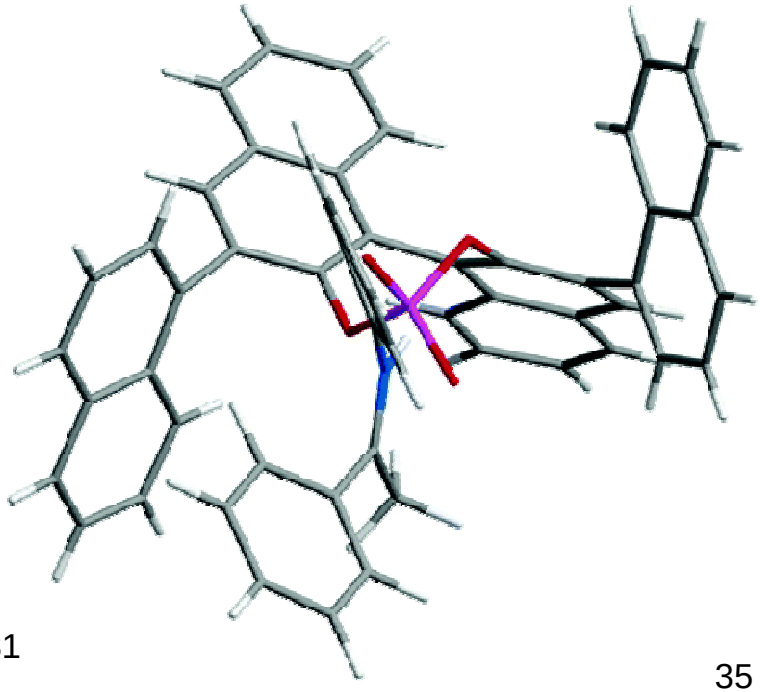
Uraguchi, D. and Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356

Akiyama, T. *et al. Angew. Chem. Int. Ed*. **2004**, *43*, 1566



cat.

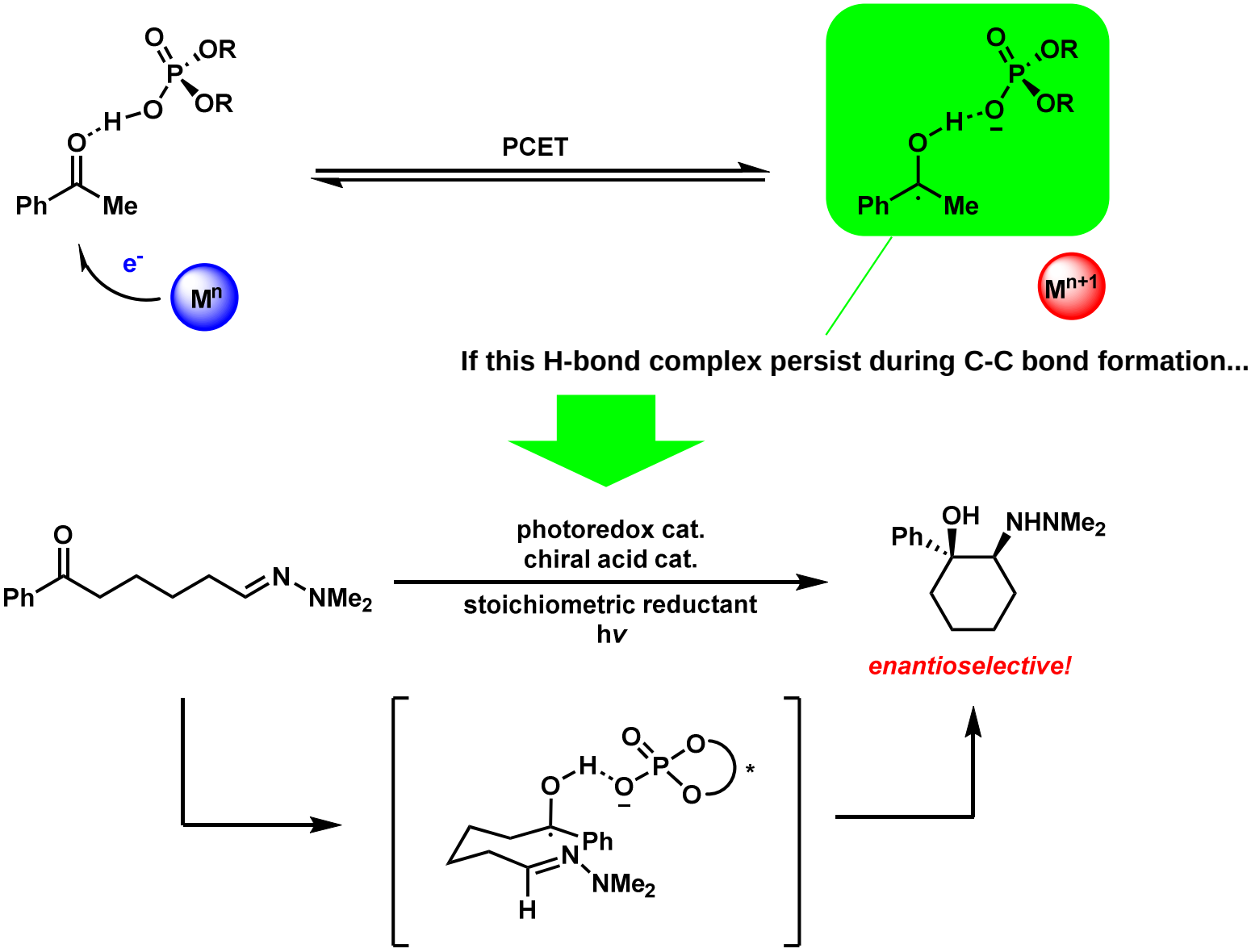




Rueping, M. et al. *Org. Lett*. **2005**, *7*, 3781

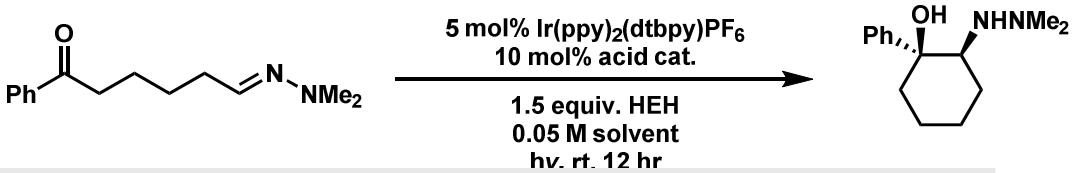
Enantioselective Aza-Pinacol Cyclization

- Working Hypothesis



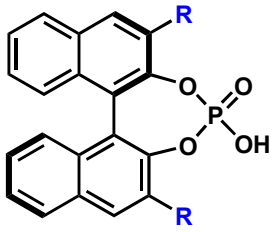
Knowles, R. R. *et al. J. Am. Chem. Soc*. **2013**, *135*, 17735

Optimization Study

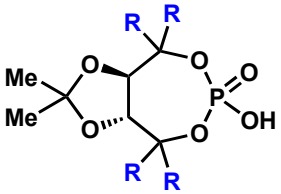


entry	acid catalyst	solvent	% yield	% ee
1	$(PhO)_2PO_2H$	THF	91	—
2	1	THF	89	0
3	2	THF	84	30
4	3	THF	96	58
5	4	THF	80	68
6	5	THF	84	82
7	6	THF	92	89
8	7	THF	90	0
9	8	THF	85	0
10	6	DME	90	88
11	6	C_6H_6	30	86
12	6	CH_2Cl_2	99	88
13	6	MeCN	77	81
14	6	dioxane	94	92
15[b]	6	dioxane	90	92

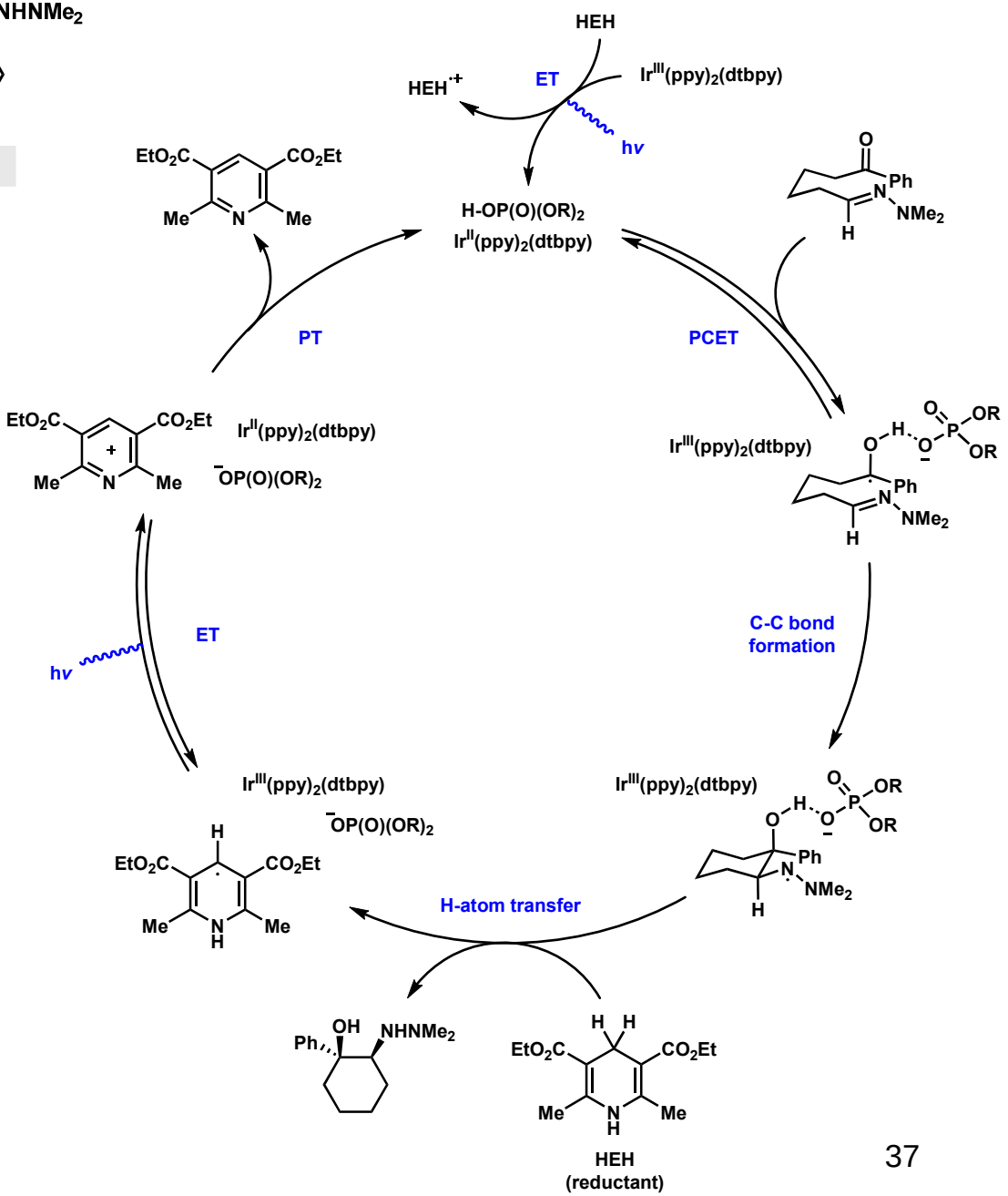
[b] 3 hr, 2 mol% photocatalyst



1 R = H
2 R = 2-naphtyl
3 R = Mesityl
4 R = 2,4,6-*i*Pr$_3$C$_6$H$_2$
5 R = *i*Pr$_3$Si
6 R = Ph$_3$Si

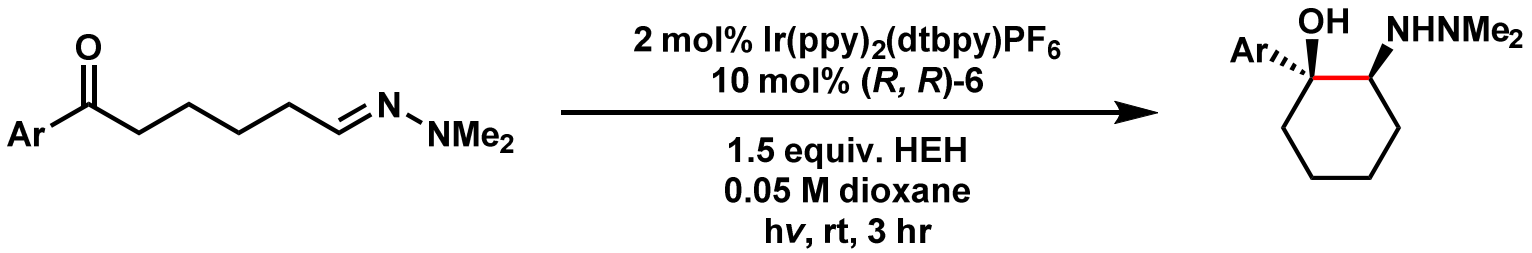


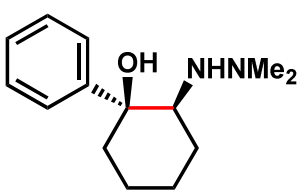
9 R = Ph
10 R = 2-naphtyl



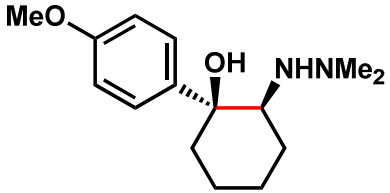
Knowles, R. R. *et al. J. Am. Chem. Soc*. **2013**, *135*, 17735

Substrate Scope

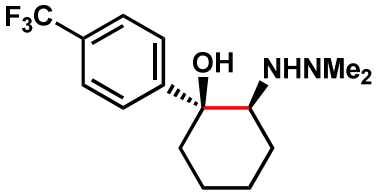




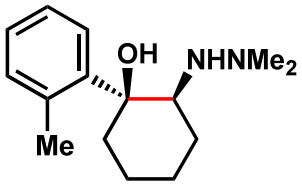
83%, 93% ee



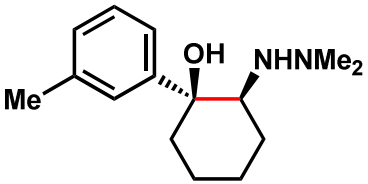
86%, 94% ee



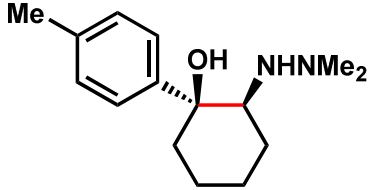
58%, 90% ee



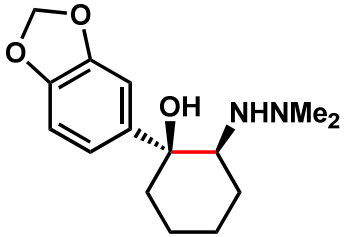
[a]63%, 94% ee



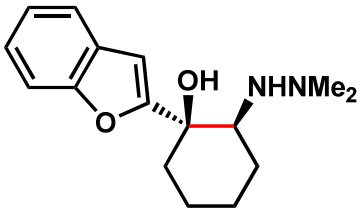
78%, 90% ee



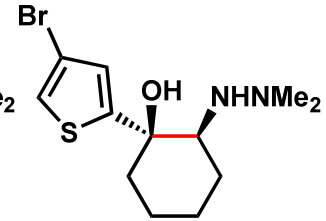
81%, 95% ee



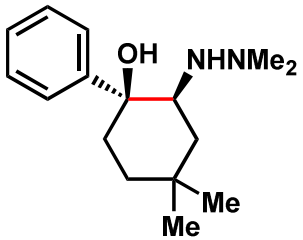
96%, 94% ee



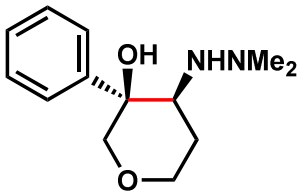
53%, 82% ee



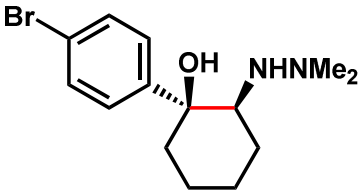
69%, 85% ee



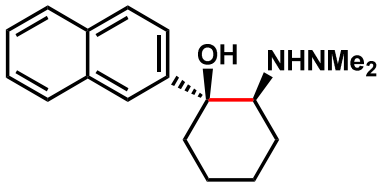
78%, 90% ee



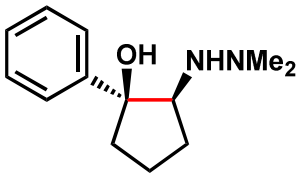
[b]85%, 83% ee



77%, 95% ee



[c]45%, 91% ee



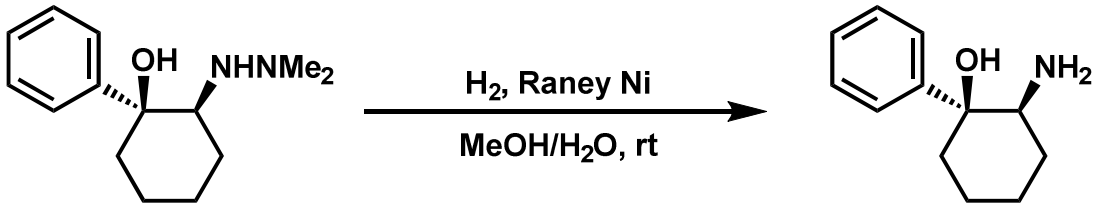
[d]71%, 77% ee

[a] 18 hr
[b] -30 °C, 44 hr,
20 mol% catalyst 6, 1 mol% Ir.
[c] 0 °C, THF, 6 hr
[d] -20 °C, THF, catalyst 4, 48 hr

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

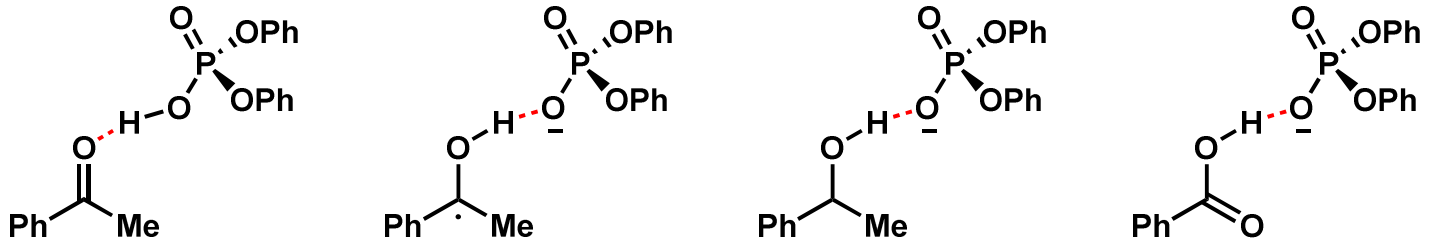
Further Study

- Cleavage of N-N Bond



96% yield

- DFT Evaluation of Ketyl-phosohate H-bonding



A B C D

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

*Calculated at UB3LYP/6-311+g(d, p)

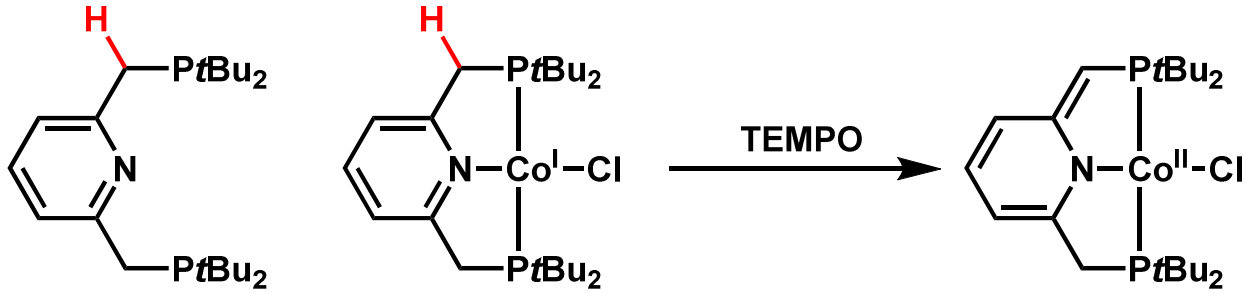
Knowles, R. R. *et al. J. Am. Chem. Soc*. **2013**, *135*, 17735

Bond-Weakening Chemistry

×

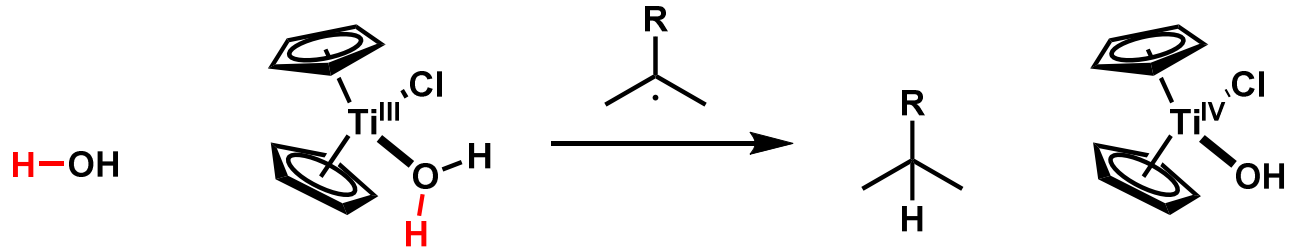
PCET

Bond Weakening Chemistry



C-H BDFE **79.8 kcal/mol** **49.9 kcal/mol**

Chirick, P. J. *et al. J. Am. Chem. Soc*. **2014**, *136*, 9211

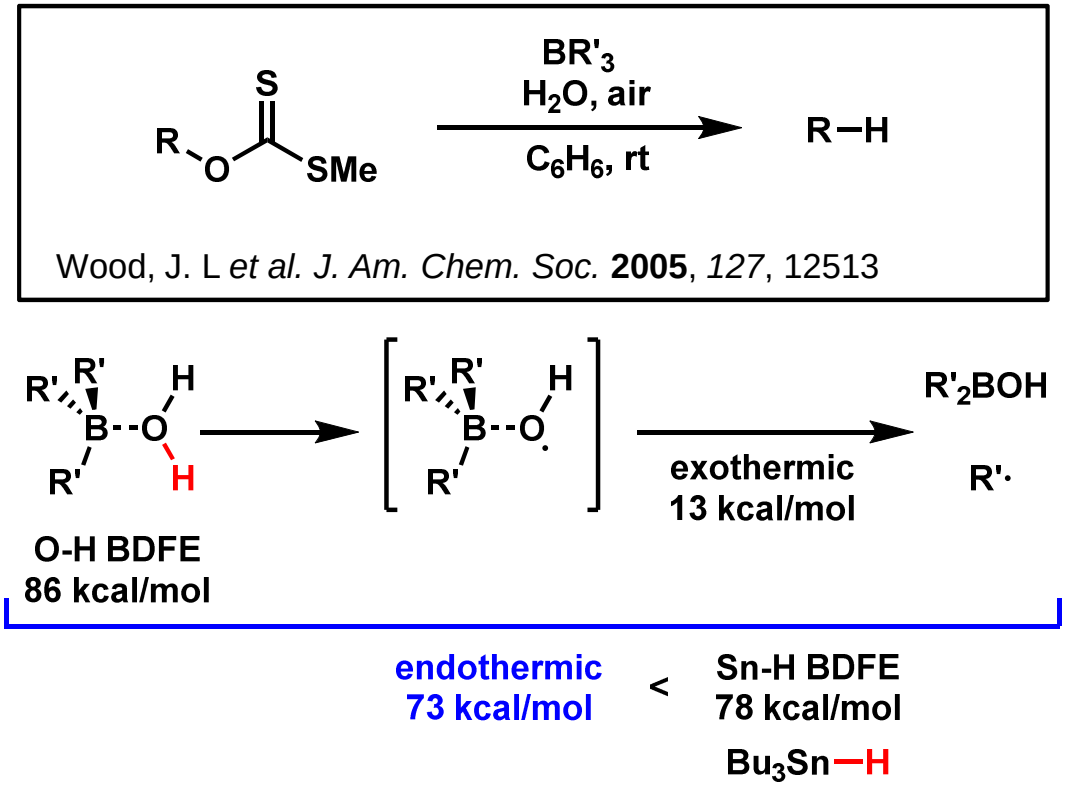


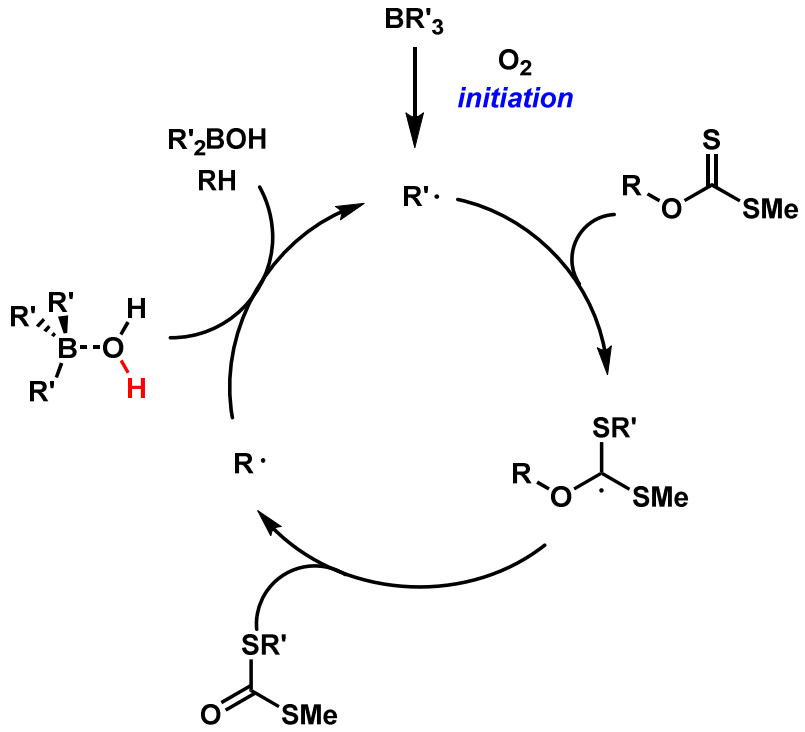
O-H BDFE **108.1 kcal/mol** **49.4 kcal/mol**

Cuerva, J. M. *et al. Angew. Chem. Int. Ed*. **2006**, *45*, 5522

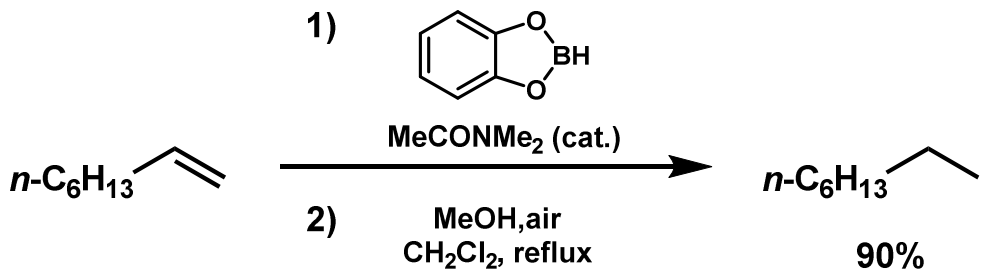
Bond-Weakening Catalysis

Tin-free Barton-McCombie Deoxygenation





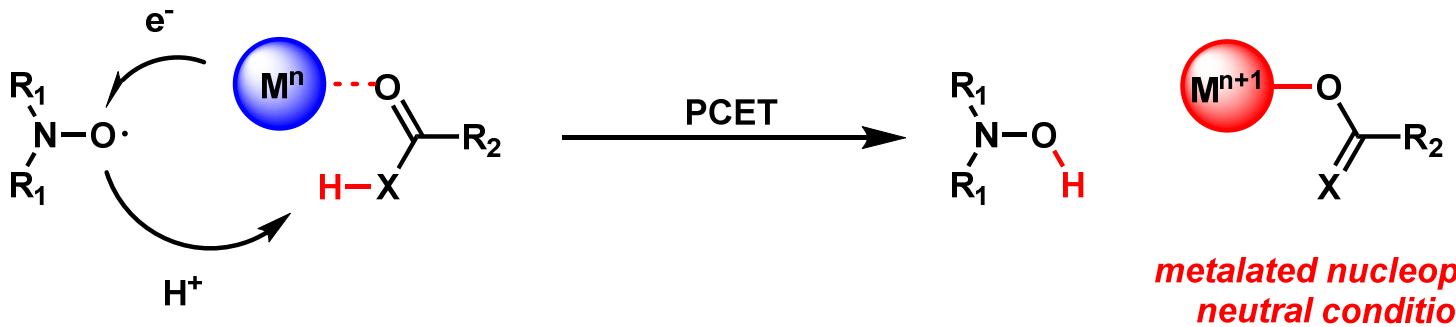
Reduction of *B*-Alkylcatecholboranes to Alkanes



Renaud, P. *et al. J. Am. Chem. Soc.* **2005**, *127*, 14204

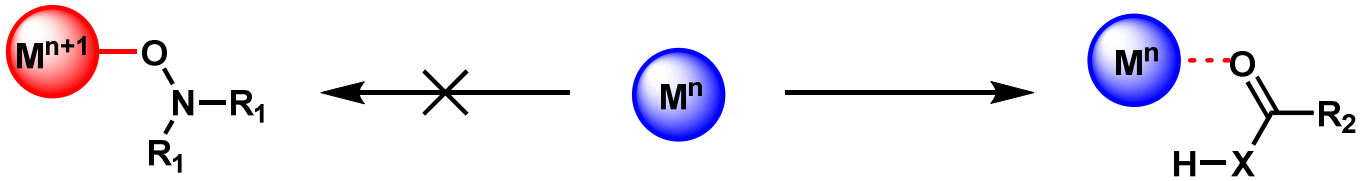
Reaction Design

Working Hypothesis



Homolytic activation of strong X-H bond with a weak H-atom acceptor

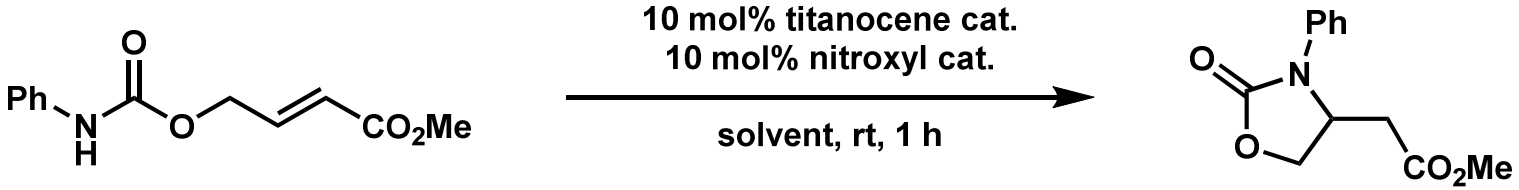
Requirement



complex formation with a large N-oxyl ligand

coordination to a less hindered substrate

Optimization Study



entry	Ti catalyst	nitroxyl catalyst	solvent	% yield
1	Cp_2TiCl	TEMPO	MeCN	0
2	$(t\text{-BuCp})_2TiCl$	TEMPO	MeCN	0
3	$Cp_2Ti^{IV}Cl(TEMPO)$	TEMPO	MeCN	0
4	Cp(Cp*)TiCl	TEMPO	MeCN	95
5	Cp^*_2TiCl	TEMPO	MeCN	98
6	Cp^*_2TiCl	TEMPO	DMF	96
7	Cp^*_2TiCl	TEMPO	C_6H_6	15
8	Cp^*_2TiCl	TEMPO	THF	25
9	Cp^*_2TiCl	TEMPO	DCM	20
10	Cp^*_2TiCl	AZADO	MeCN	96
11	—	TEMPO	MeCN	0
12	Cp^*_2TiCl	—	MeCN	0
13	$Cp^*_2Ti^{IV}Cl_2$	TEMPO	MeCN	0
14[a]	Cp^*_2TiCl	TEMPO	MeCN	95

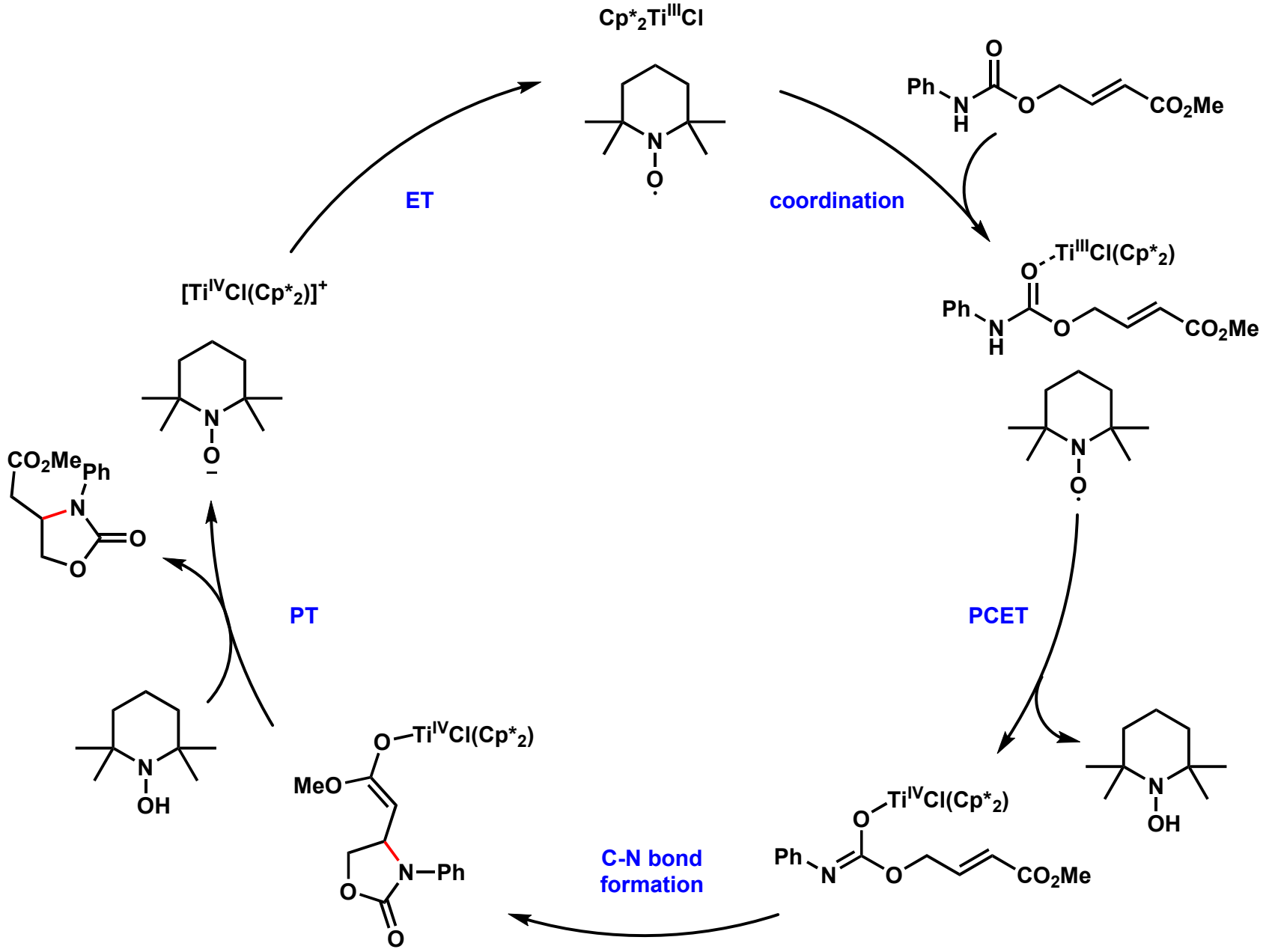
× less bulky

○ sufficiently bulky

[a] 1 mol% Cp^*_2TiCl, 1 mol% TEMPO

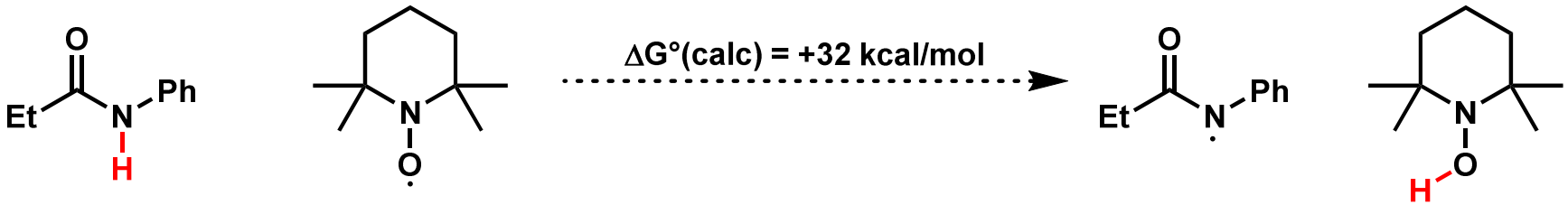
Knowles. R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440

Proposed Catalytic Cycle



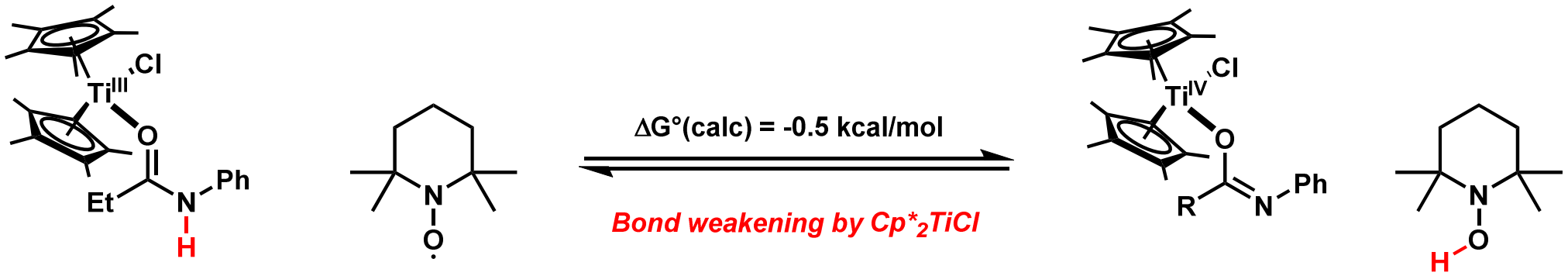
Knowles. R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440

DFT Calculations



N-H BDFE 99 kcal/mol

O-H BDFE 67 kcal/mol

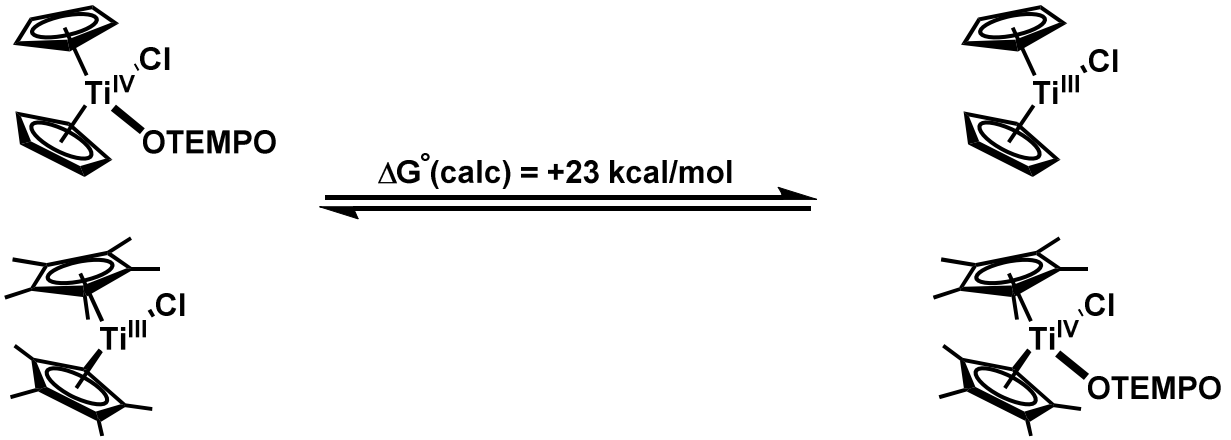


N-H BDFE 66 kcal/mol

Knowles. R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440

Compatibility of Cp^*_2TiCl & TEMPO

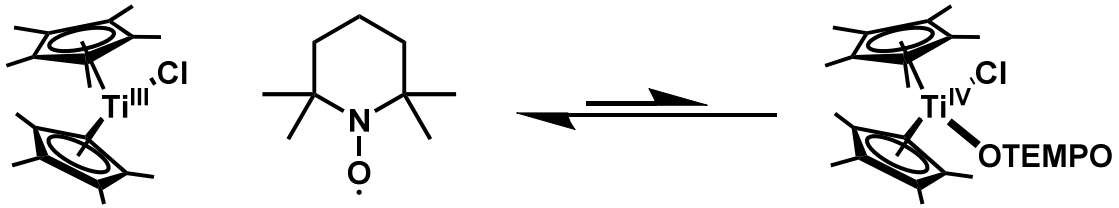
- Isodesmic Estimation



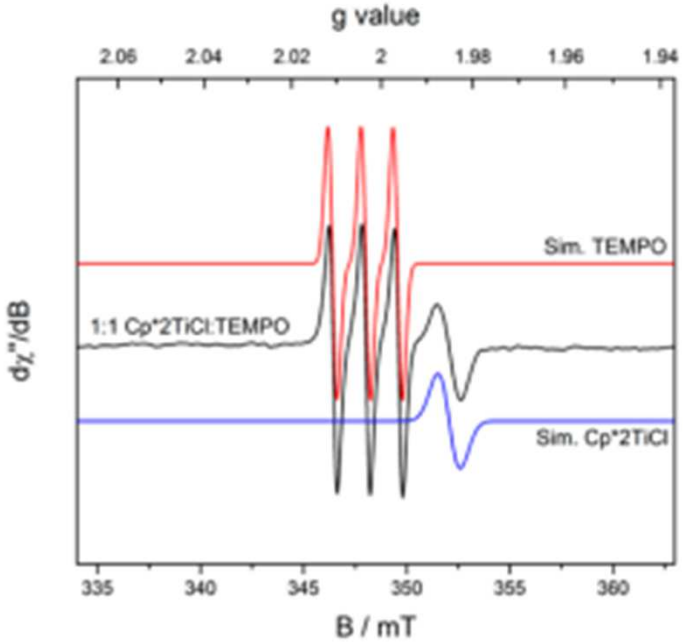
Ti-O BDFE = 25 kcal/mol

Ti-O BDFE = 2 kcal/mol

- EPR Spectra

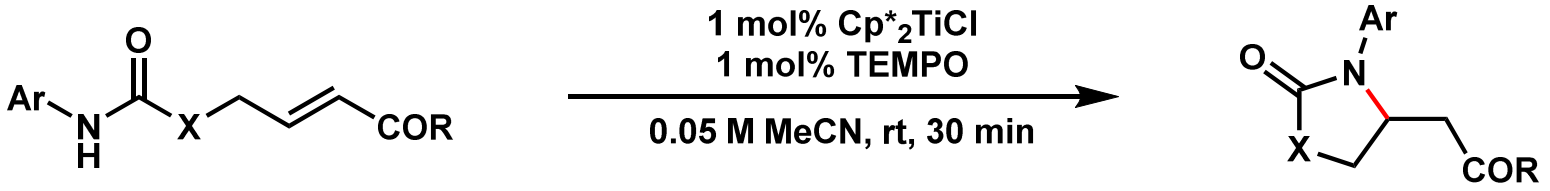


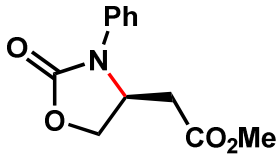
1 e⁻ parallel to Flustrated Lewis Pair



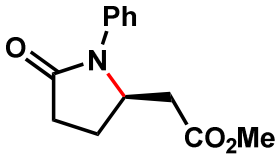
Knowles. R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440

Substrate Scope

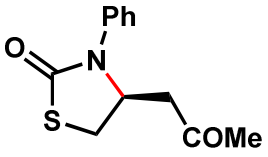




94%



87%



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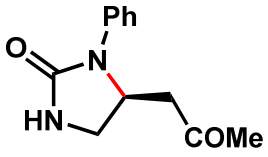

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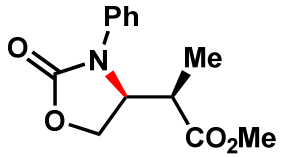

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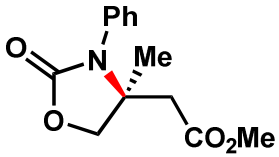

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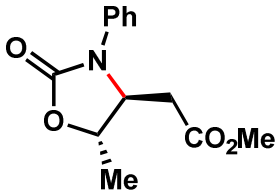

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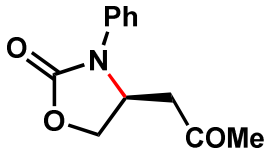

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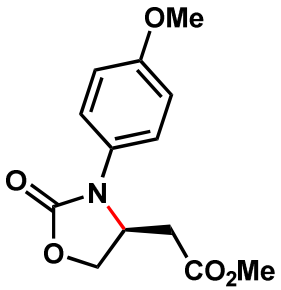

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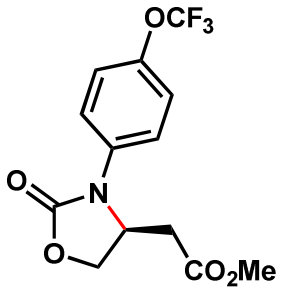

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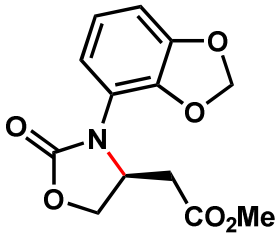

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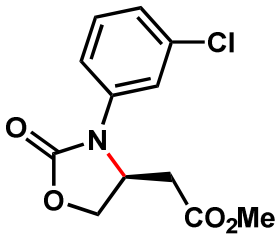

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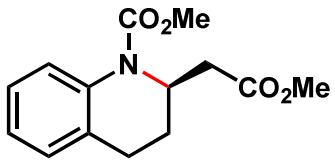

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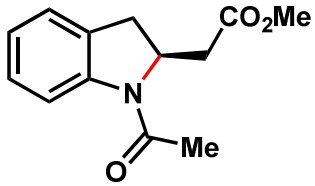

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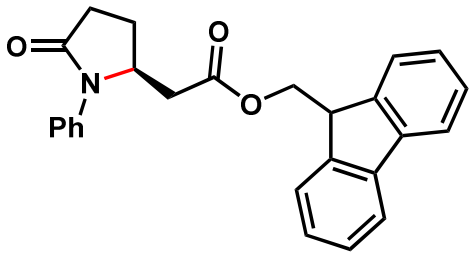

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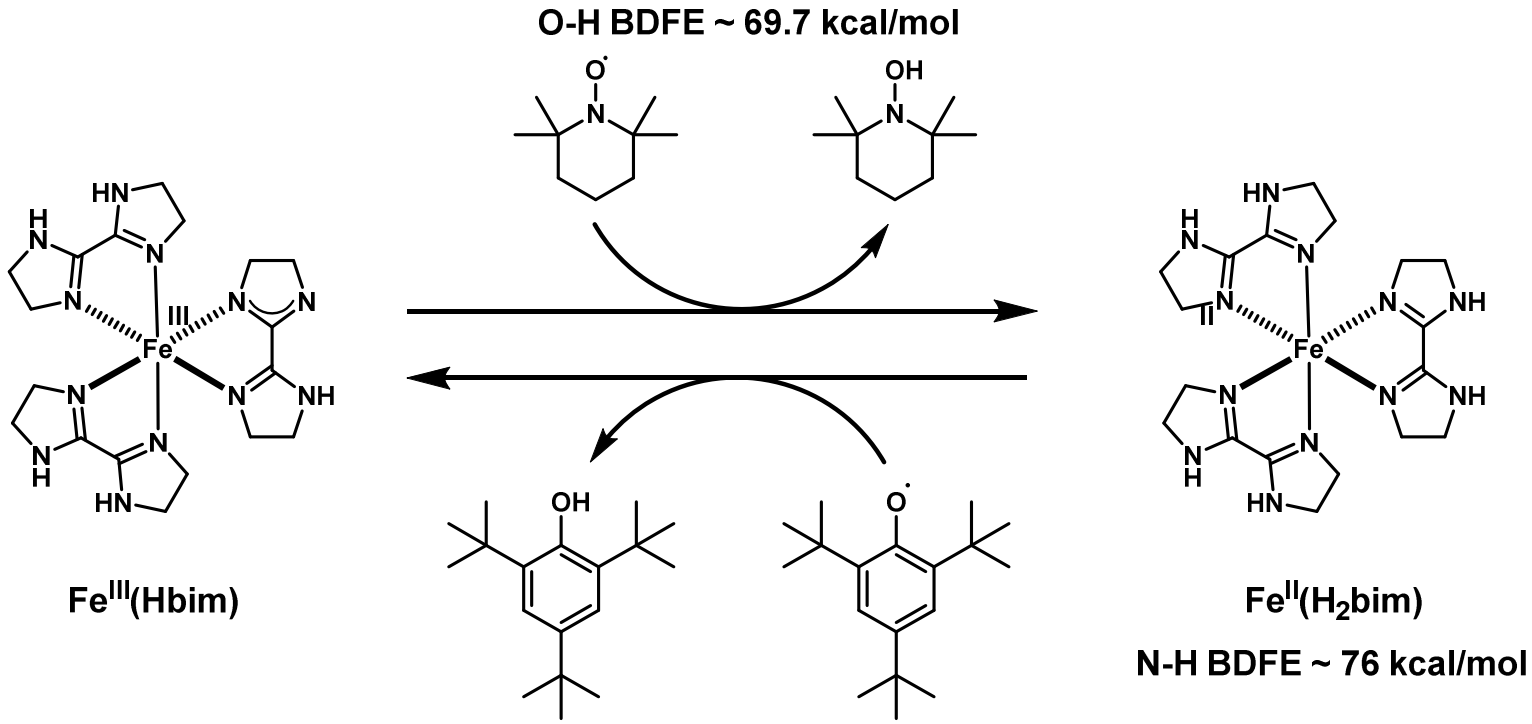
Knowles. R. R. *et al. J. Am. Chem. Soc.* **2015**, *137*, 6440

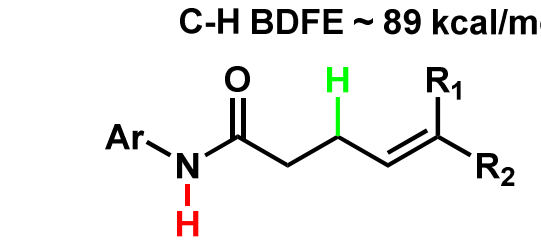
Hydrogen Atom Transfer
vs
PCET

Limitation of HAT activation

Reactivity of HAT donor is highly correlated with BDFE of broken bond



Mayer, J. M. *et al. Science*, **2001**, *294*, 2524

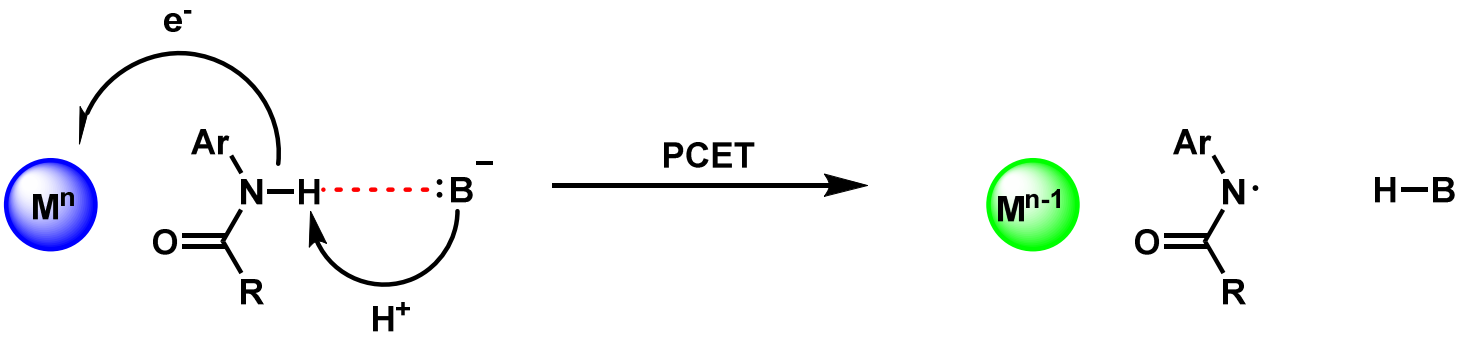


Homolytic activation of strong N-H bond

in the presence of weaker C-H bond by HAT is difficult

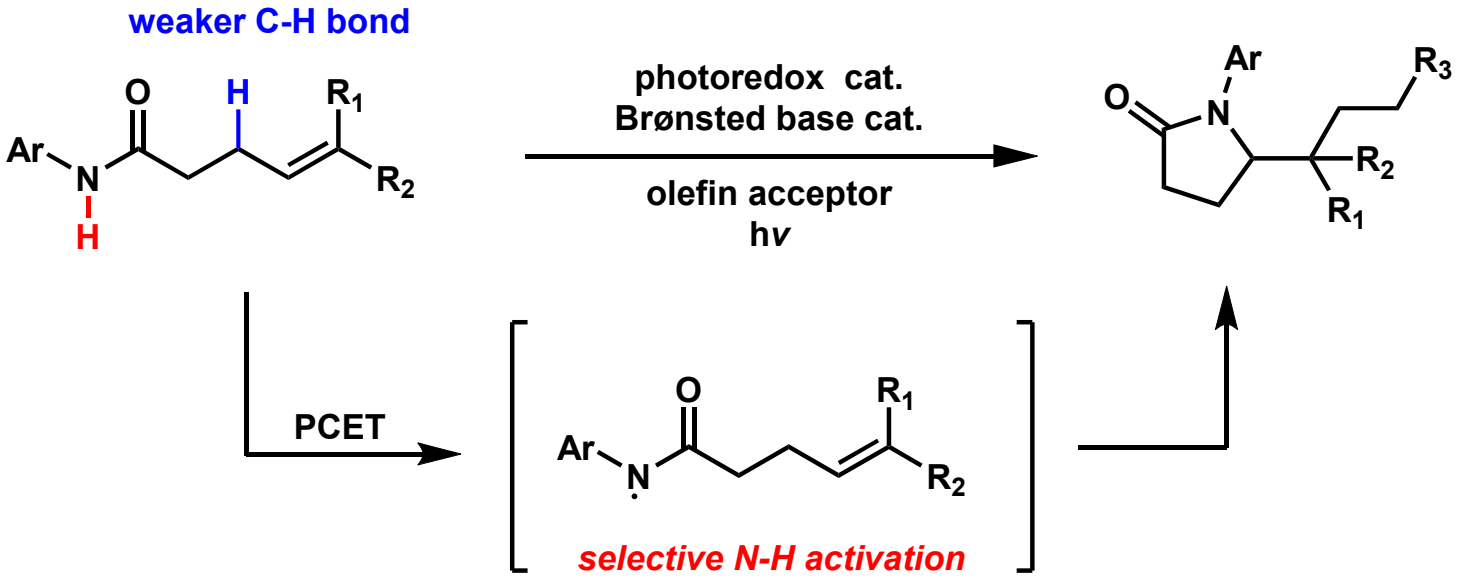
Carboamination

- Working Hypothesis

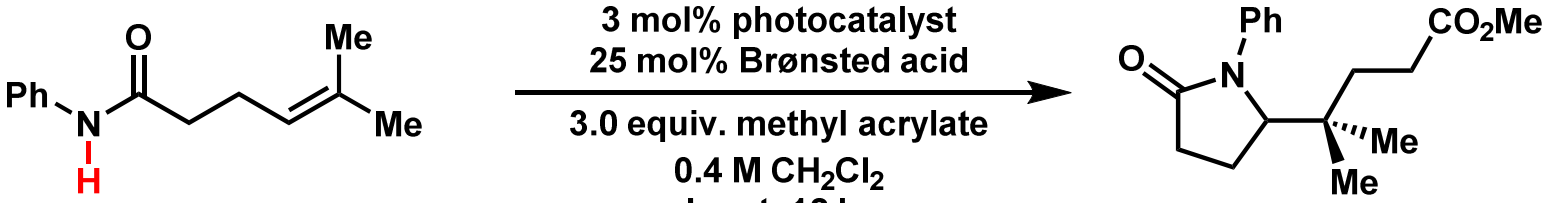


N-H BDFE for N-aryl amide ~ 100 kcal/mol

'BDFE' (kcal/mol) = 1.37 pK_a(H-B) + 23.06 $E(M^n)$ + C_{solv}



Optimization Study



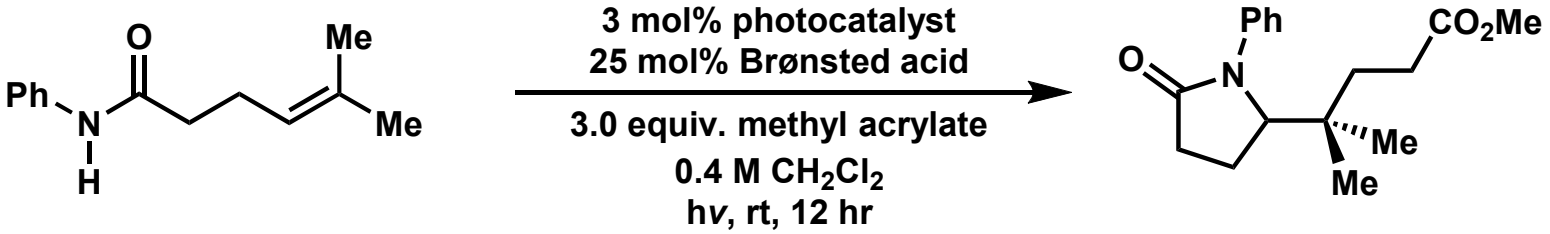
N-H BDFE = 99 kcal/mol

entry	photocatalyst	base	'BDFE'	% yield
1	$Ir(ppy)_2(phen)PF_6$	$NBu_4OP(O)(OBu)_2$	80	0
2	$Ir(ppy)_2(phen)PF_6$	lutidine	82	0
3	$Ir(Fmppy)_2(dtbbpy)PF_6$	$NBu_4OP(O)(OBu)_2$	82	0
4	$Ir(Fmppy)_2(dtbbpy)PF_6$	lutidine	83	0
5	$Ir(Fmppy)_2(phen)PF_6$	$NBu_4OP(O)(OBu)_2$	83	trace
6	$Ir(Fmppy)_2(phen)PF_6$	lutidine	85	0
7	$Ir(ppy)_2(phen)PF_6$	DMAP	87	trace
8	$Ir(Fmppy)_2(dtbbpy)PF_6$	DMAP	89	0

'BDFE' < N-H BDFE

Choi. G. J. and Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226

Optimization Study



entry	photocatalyst	base	'BDFE'	% yield
9	$Ir(Fmppy)_2(phen)PF_6$	DMAP	90	6
10	$Ir(ppy)_2(phen)PF_6$	NBu_4OBz	92	20
11	$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$	$NBu_4OP(O)(OBu)_2$	92	76
12	$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$	lutidine	93	22
13	$Ir(Fmppy)_2(dtbbpy)PF_6$	NBu_4OBz	93	56
14	$Ir(Fmppy)_2(phen)PF_6$	NBu_4OBz	95	35
15	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	$NBu_4OP(O)(OBu)_2$	97	92
16	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	lutidine	98	24
17	$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$	DMAP	99	34
18	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	DMAP	103	16
19	$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$	NBu_4OBz	104	76
20	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	NBu_4OBz	108	50

'BDFE' ~ N-H BDFE

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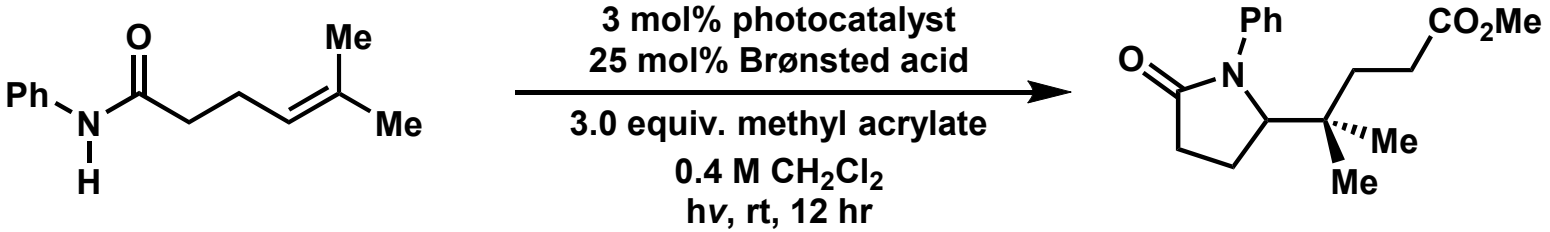
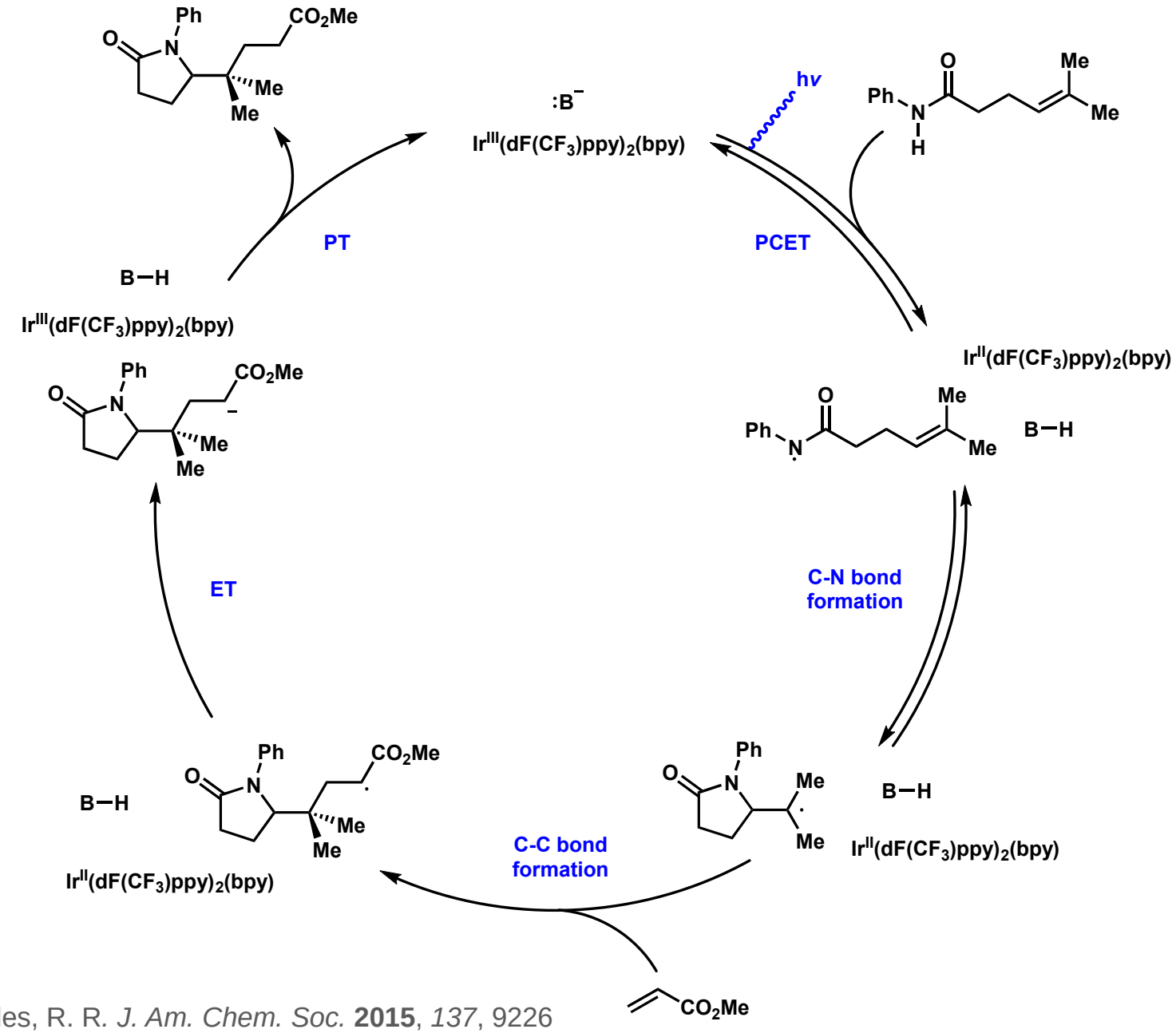
Optimization Study



entry	change from the best conditions (entry 15)	% yield
21	no light	0
22	no photocatalyst	0
23	no $NBu_4OP(O)(OBu)_2$	<5
24	1 mol% $Ir(dF(CF_3)ppy)_2(bpy)PF_6$	76
25	10 mol% $NBu_4OP(O)(OBu)_2$	78
26	1.1 equivalent of acrylate	68
27	0.1 M in CH_2Cl_2	80

Choi. G. J. and Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226

Proposed Catalytic Cycle



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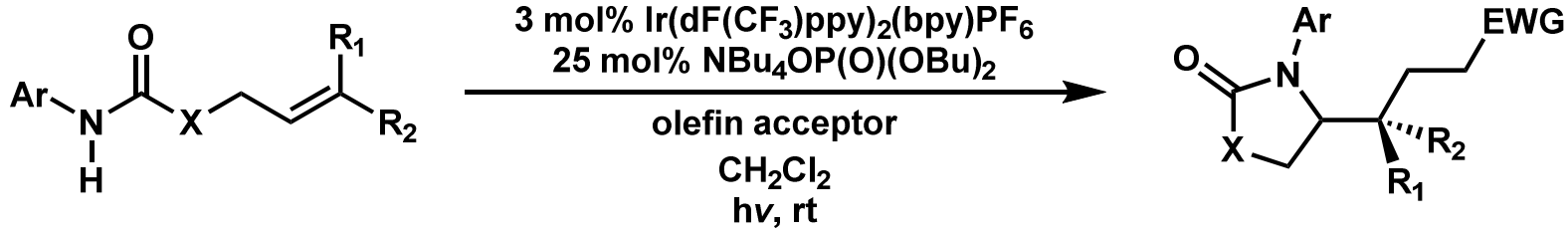
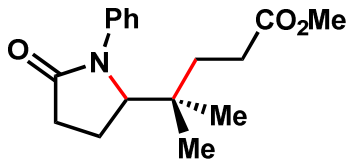
Substrate Scope





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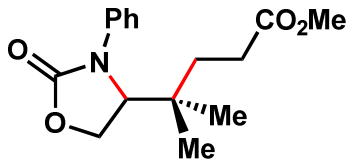

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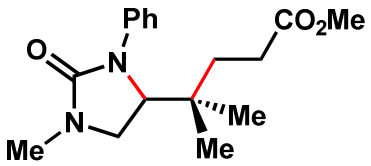

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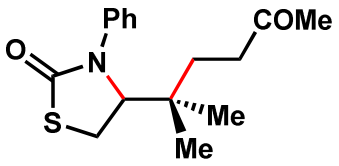

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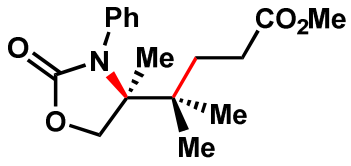

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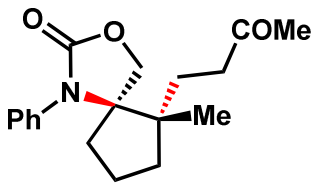

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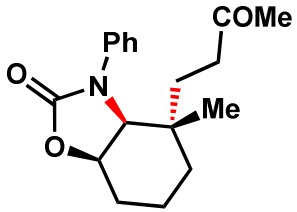

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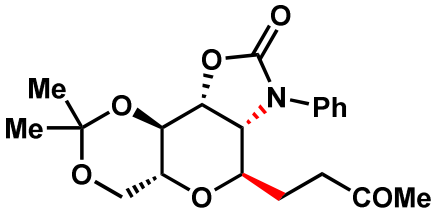

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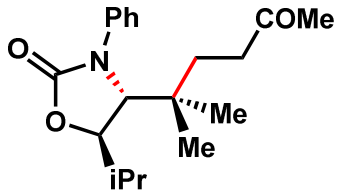

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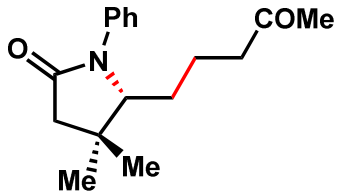

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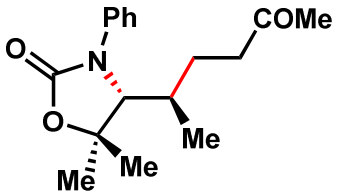

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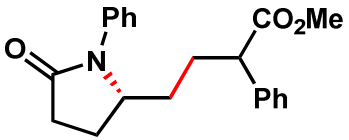

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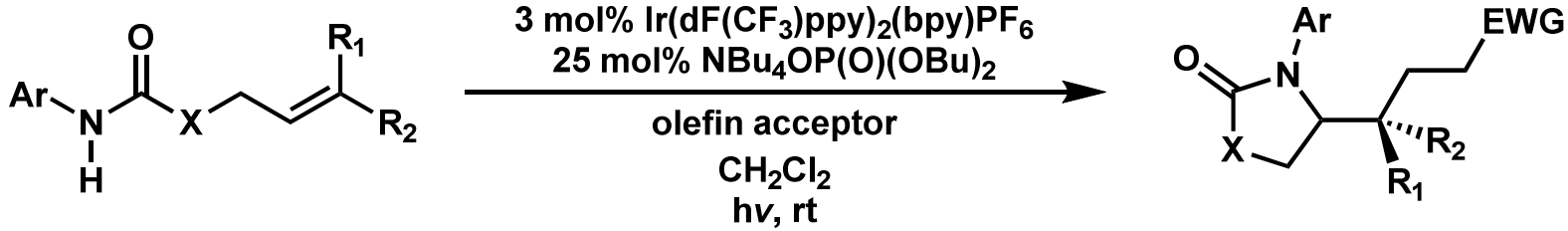
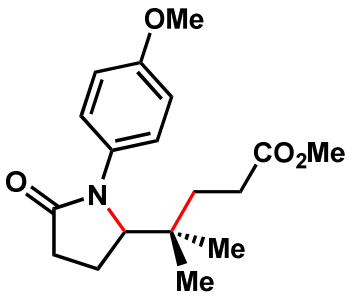
Substrate Scope





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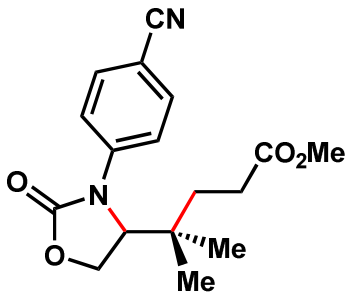

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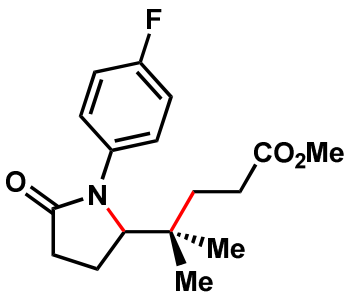

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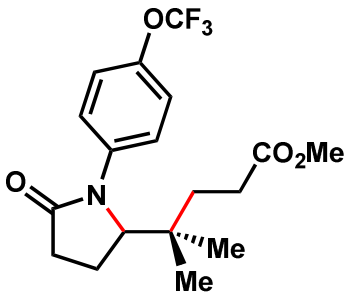

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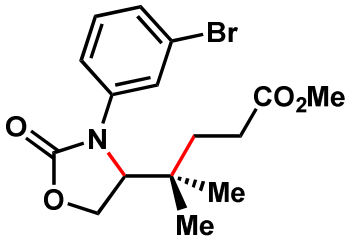

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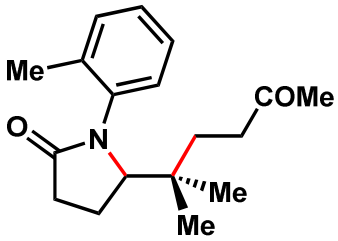

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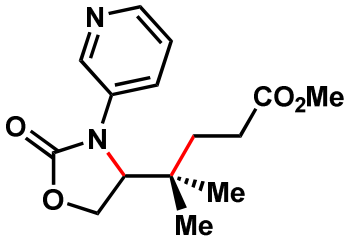

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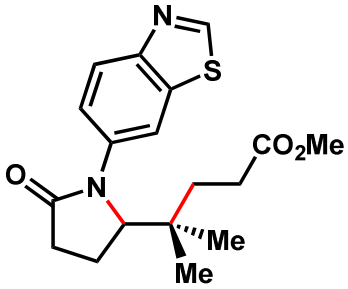

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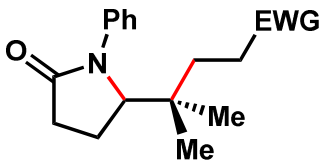

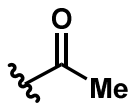

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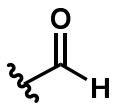

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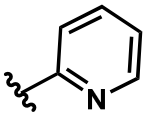

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Choi. G. J. and Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226

Summary

Summary

Photoredox Catalysis

Chiral Brønsted Acid
Bond-Weakening Chemistry

Well-established Chemistry

Proton Coupled Electron Transfer

Ubiquitous in biology

Studied over decades

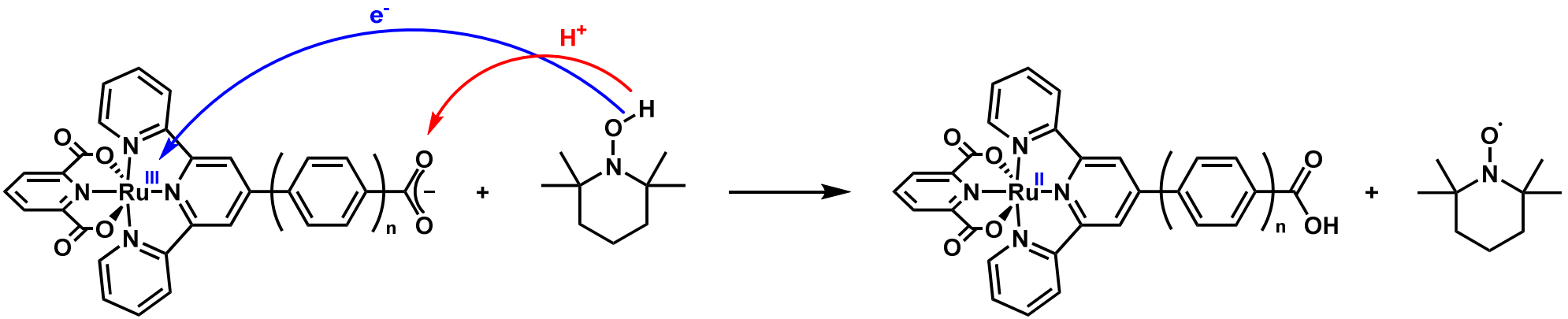
PCET Activation Chemistry

Novel catalysis platform

Providing catalytic access to valuable neutral free radical intermediates

Appendix

Ambiguity between HAT and EPT



Manner, V. W. and Mayer, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 9874

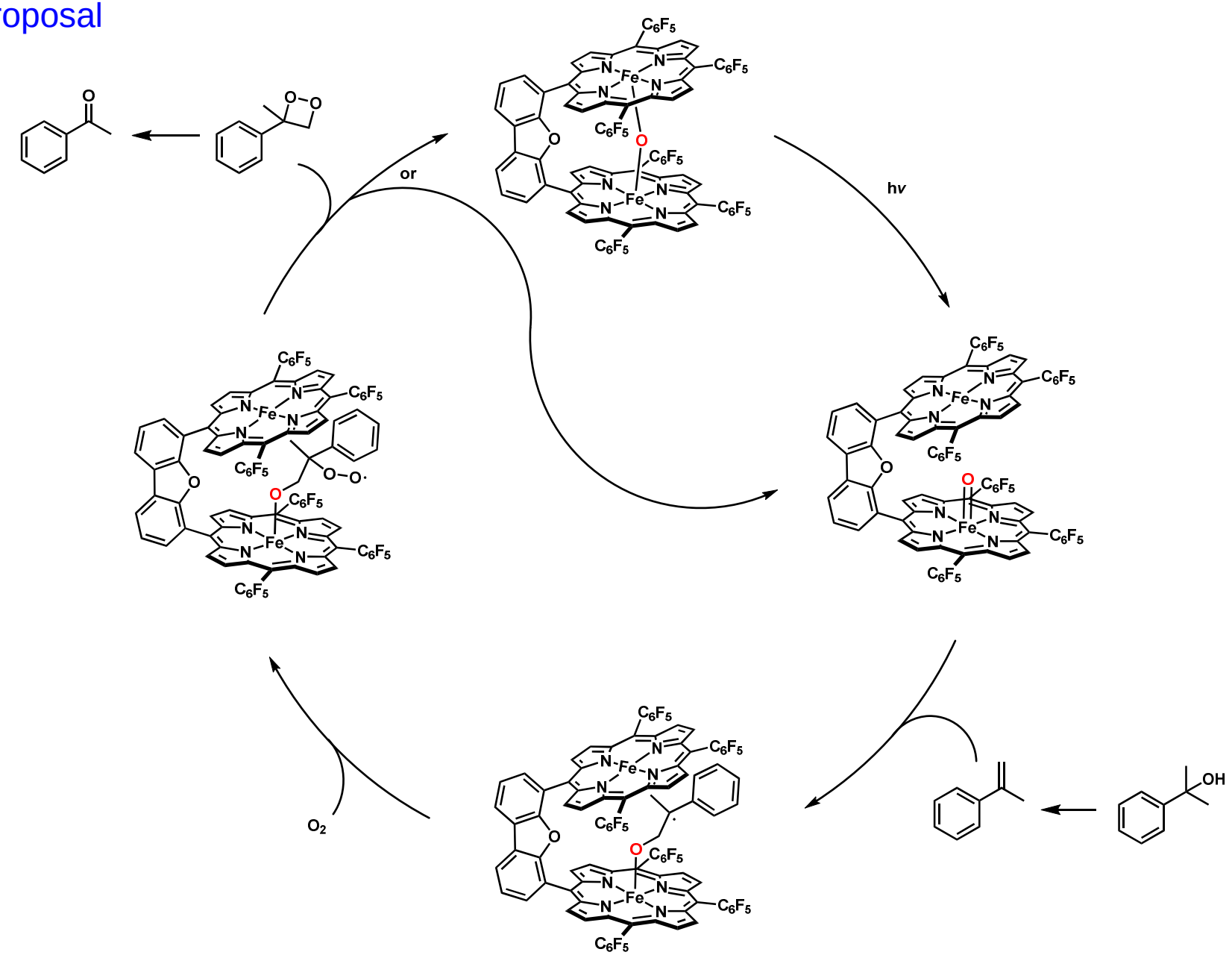
Essentially no communication between e^-/H^+ acceptor sites

MS-EPT character

Appendix

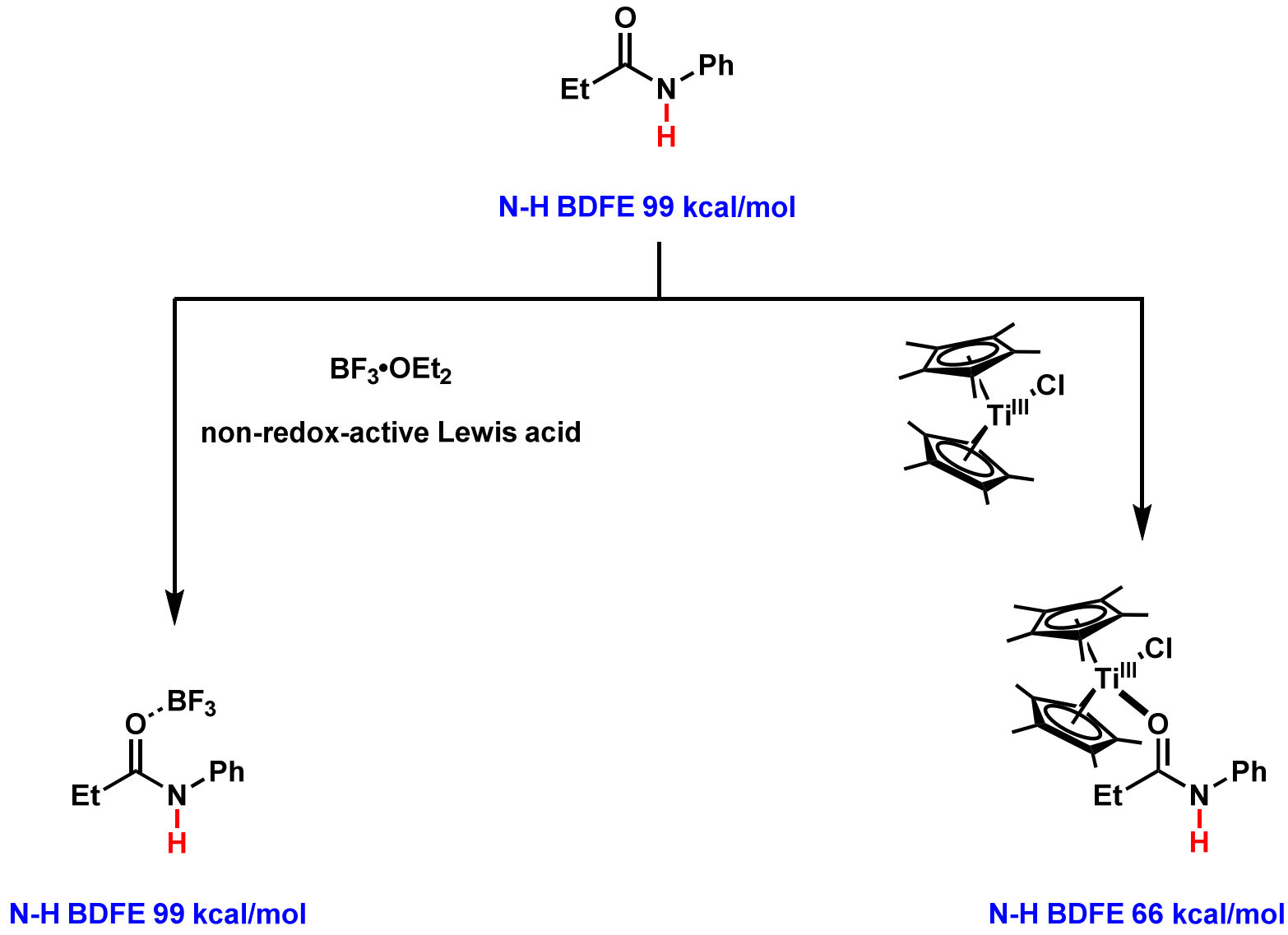
Oxidation of Cumyl Alcohol

- My Proposal



Appendix

Bond-Weakening Effect



Homolytic bond-weakening is not a simple Lewis-acid-mediated process