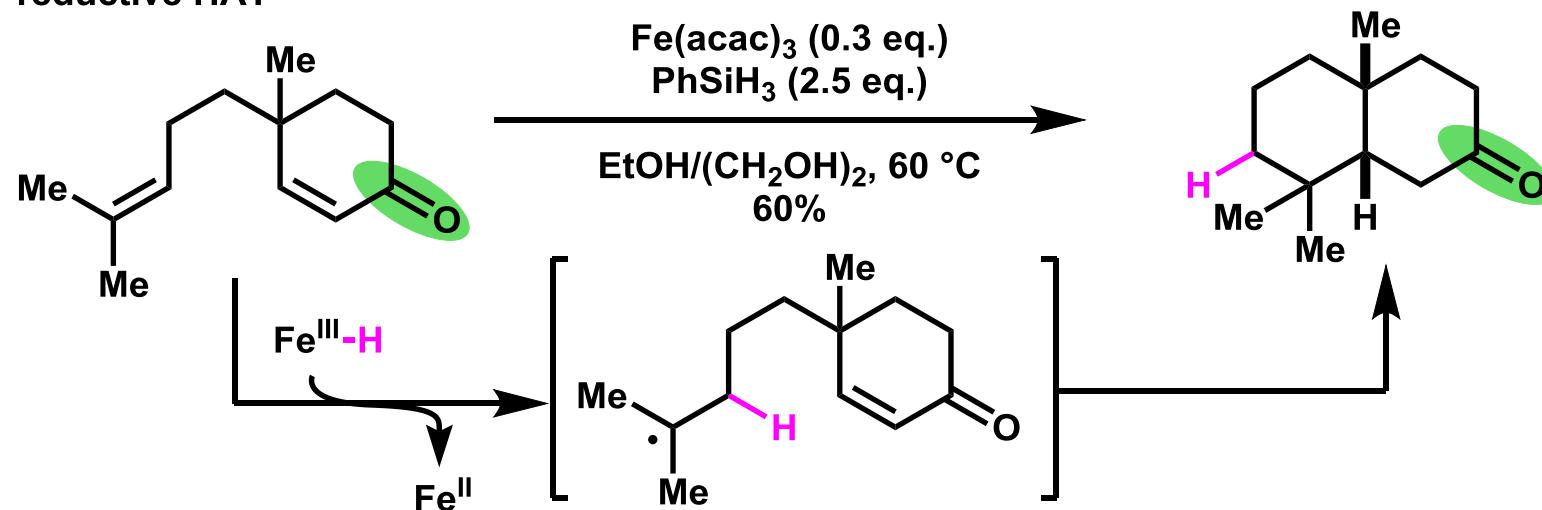


Proton-Coupled Electron Transfer (PCET) in Organic Chemistry

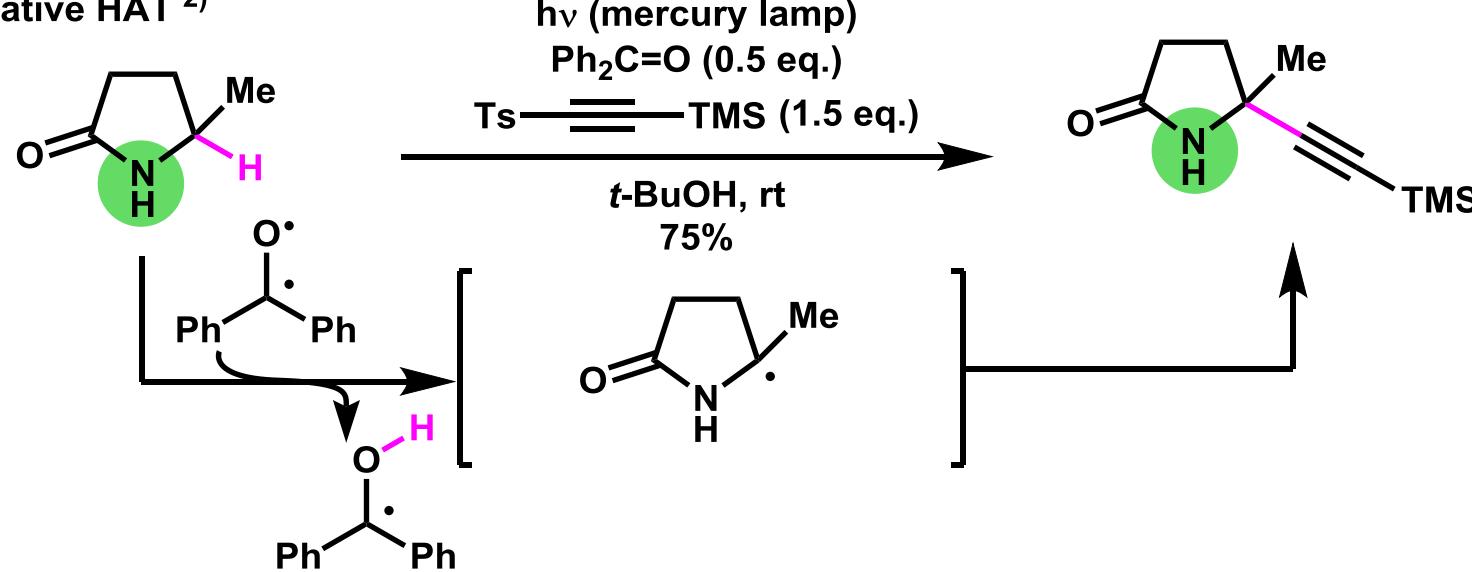
**LS 2016/9/24
Shun Yoshioka**

2. Hydrogen Atom Transfer (HAT) Reactions

- reductive HAT ¹⁾



- oxidative HAT ²⁾

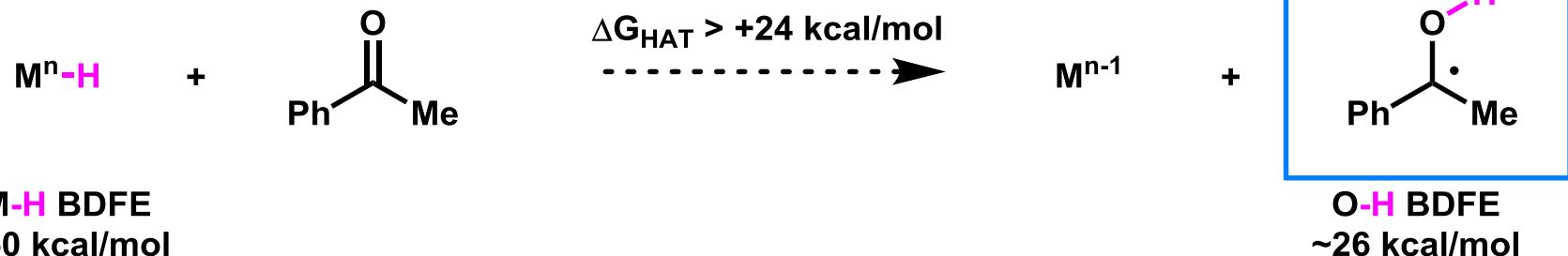


(1) a) Lo, J. C.; Yabe, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 1304. b) Shenvi, R. A. et al. *Chem. Rev.* **2016**, *116*, 8912. c) LS 2015.9.5 (Dr. Nagatomo)

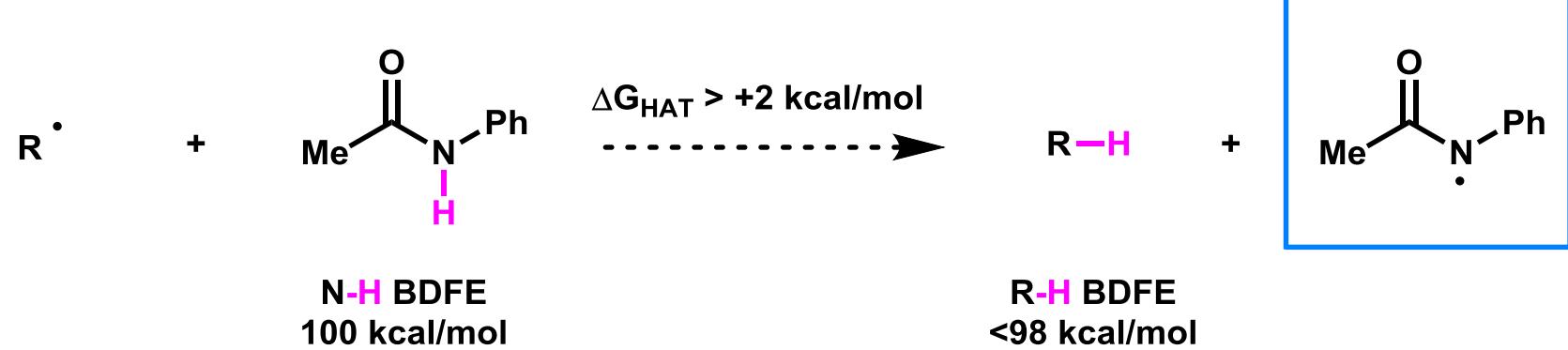
(2) Hoshikawa, T.; Kamijo, S.; Inoue, M. *Org. Biomol. Chem.* **2013**, *11*, 164.

3. Challenges of Hydrogen Atom Transfer

- reductive HAT to C=O π -bond



- oxidative HAT from N-H σ -bond



How can we generate these radicals?

BDFE = bond dissociation free energy

4. Contents

1. introduction of PCET

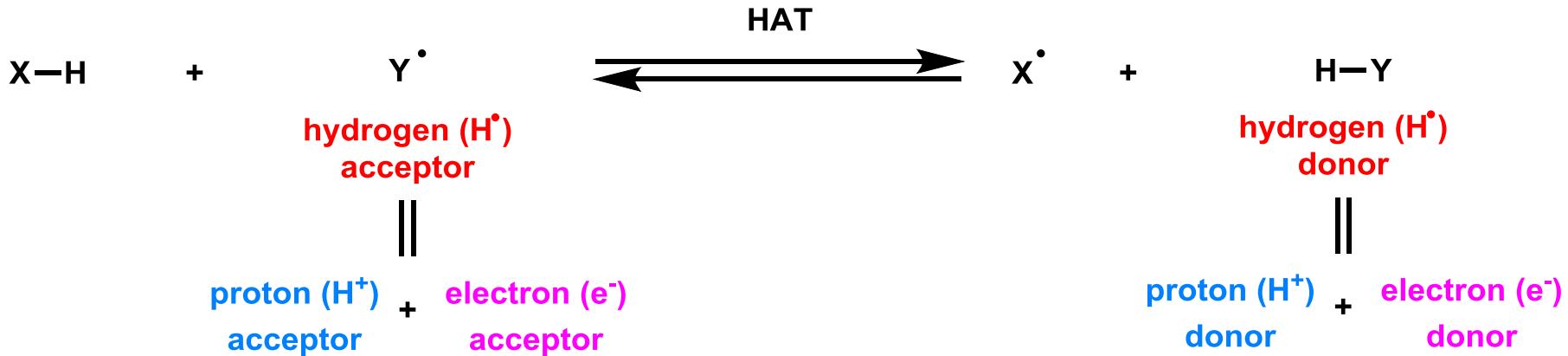
2. ketyl radical-mediated transformation

3. amidyl radical-mediated transformation

**4. oxyl radical-mediated transformation
(main paper)**

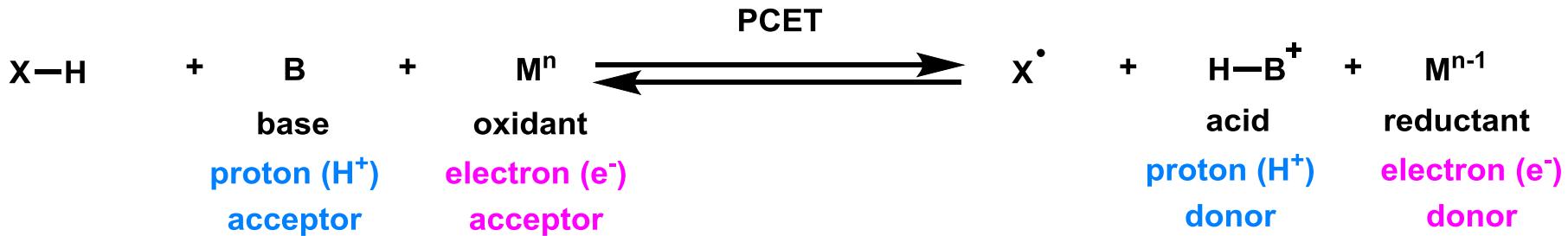
5. Proton-Coupled Electron Transfer (PCET)

(1) hydrogen atom transfer



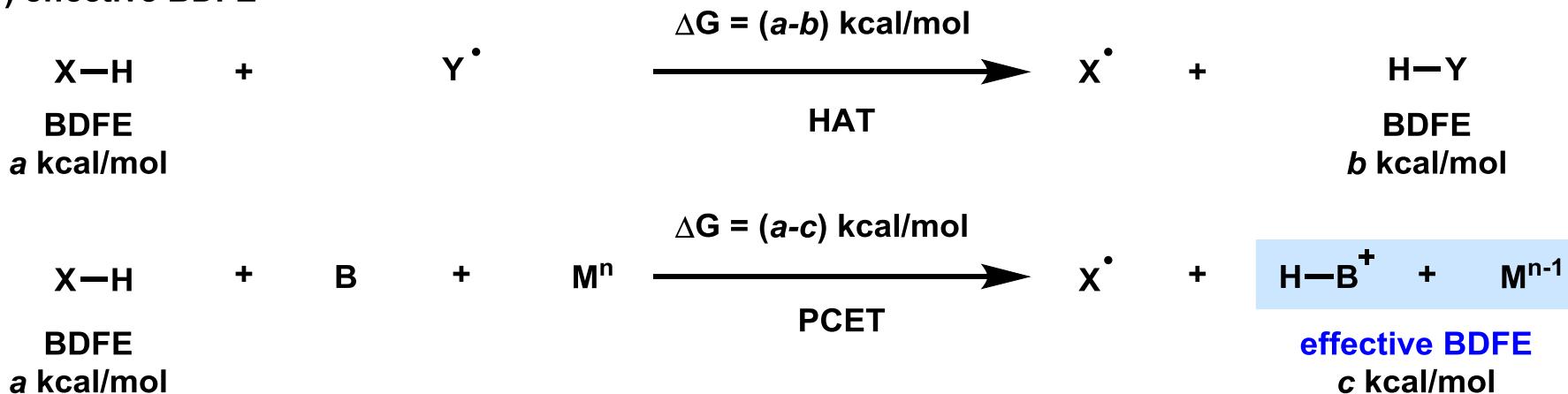
(2) proton-coupled electron transfer

"redox events in which an electron and proton are exchanged in a concerted elementary step"

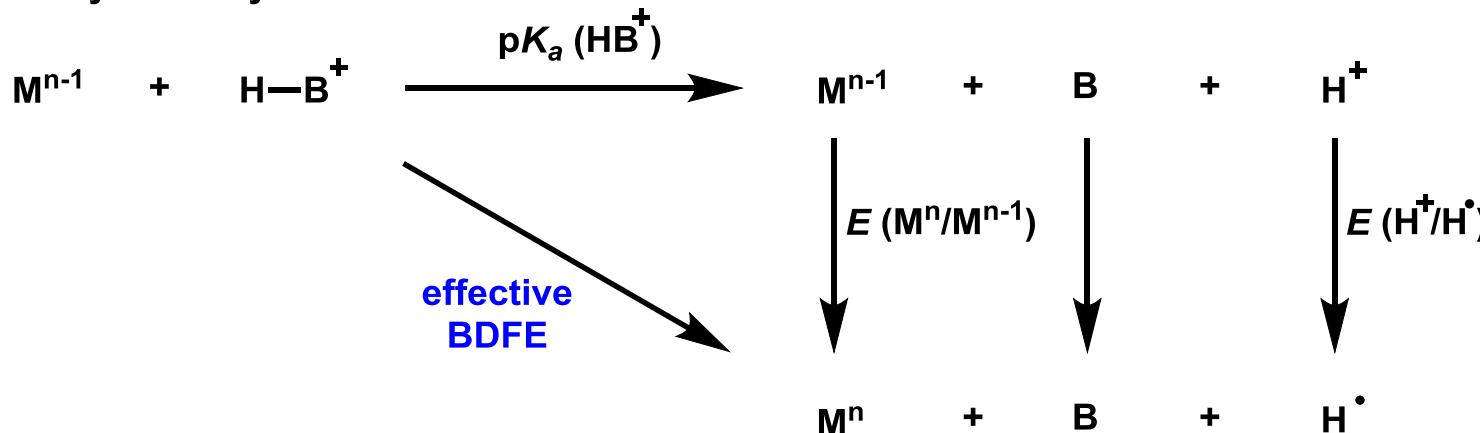


6. Thermochemistry of PCET

(1) effective BDFE



(2) thermodynamic cycle



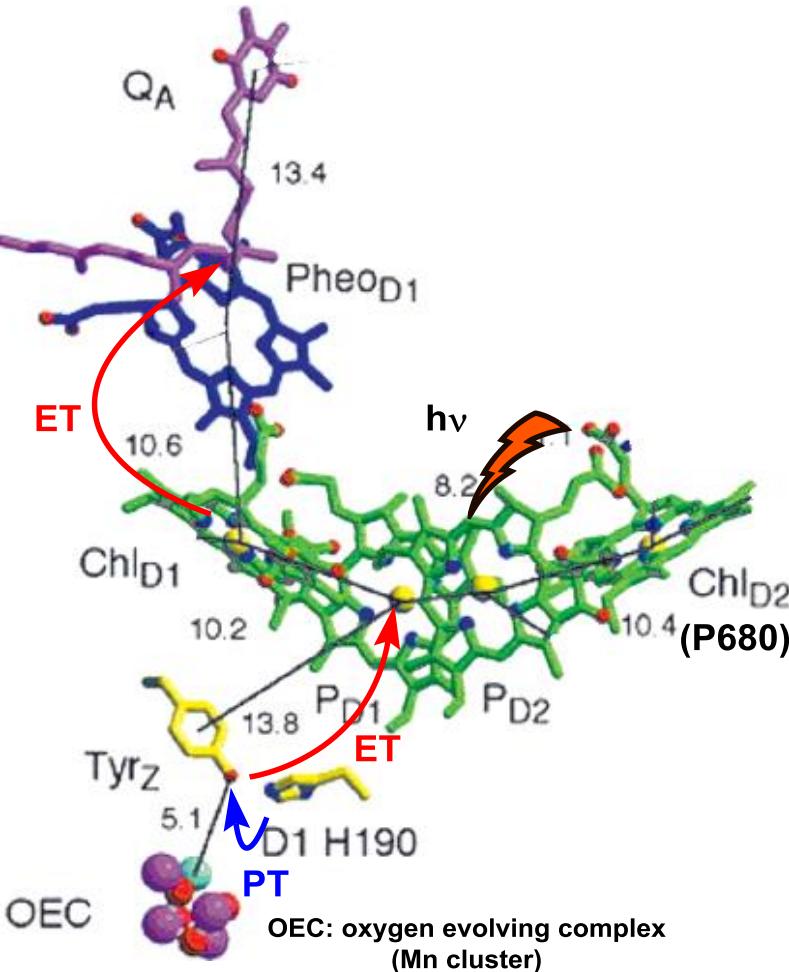
$$\text{effective BDFE (kcal/mol)} = -RT \ln(K_a(\text{HB}^+)) + FE(\text{M}^n/\text{M}^{n-1}) - FE(\text{H}^+/\text{H}^\bullet)$$

$$= 1.37 \text{ p}K_a(\text{HB}^+) + 23.06 E(\text{M}^n/\text{M}^{n-1}) + C_{\text{solv}} \text{ (at 298 K)}$$

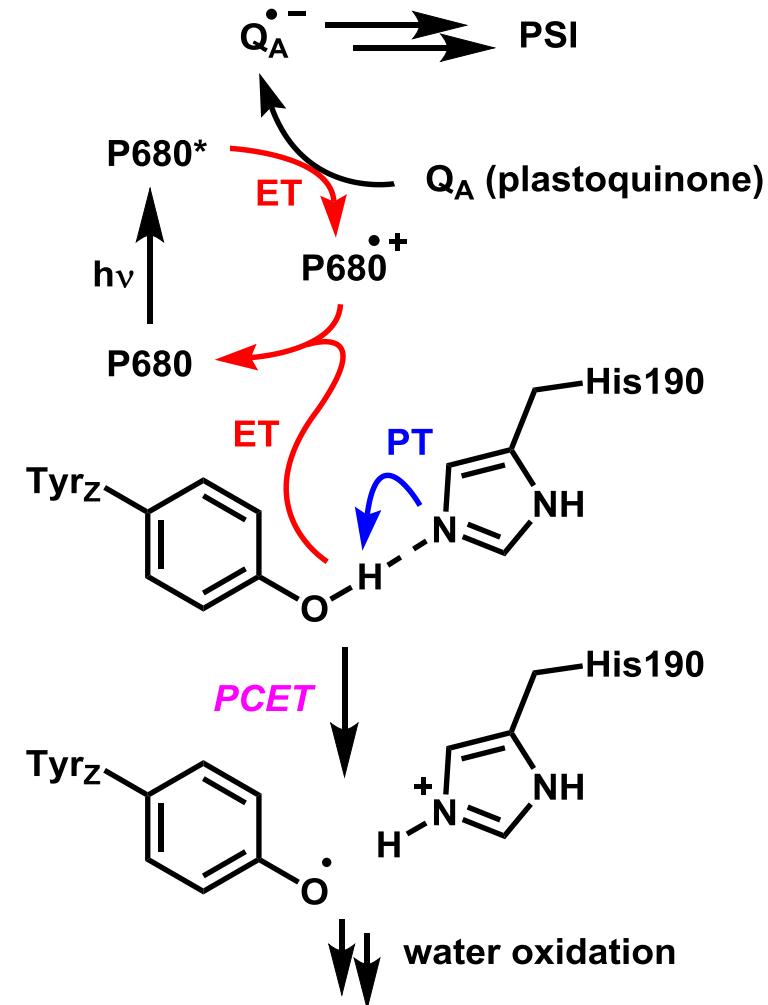
7. PCET in Photosystem II



(1) reaction center of PSII



(2) electron transport



8. Asst. Prof. Robert R. Knowles



CV:

2003: B.S. College of William and Mary
2008: Ph.D. California Institute of Technology (Prof. David MacMillan)
2008-2011: Postdoctoral Fellow, Harvard Univ. (Prof. Eric Jacobsen)
2011-: Assistant Professor, Princeton Univ. (PI)

Awards:

2012: Thieme Journal Prize
2014: Alfred P. Sloan Foundation Research Fellowship

Research:

organic synthesis and catalysis, photochemistry

"One area of recent focus has been exploring the synthetic applications of proton-coupled electron transfer (PCET) reactions. [...] Among the primary goals of this work is to establish concerted PCET as a general mechanism for homolytic bond activation that is complementary to and broader in scope than conventional hydrogen atom transfer (HAT) chemistry."

9. Contents

1. introduction of PCET

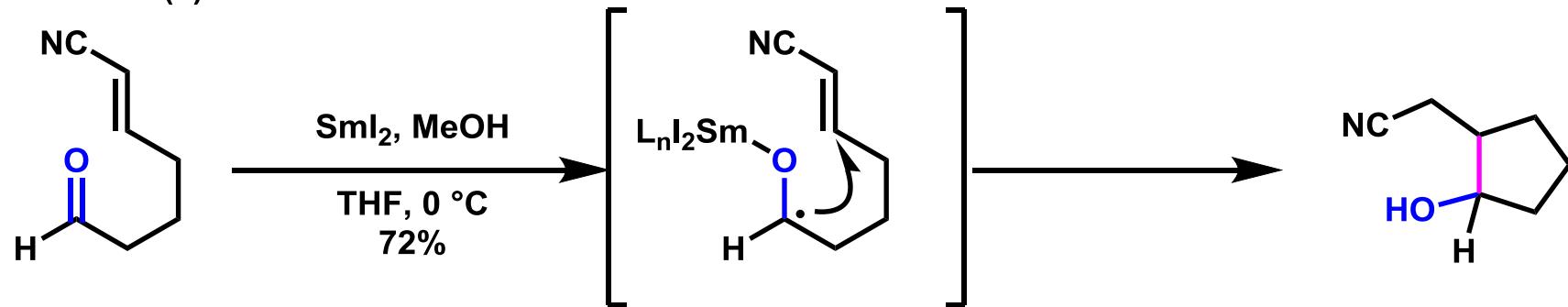
2. ketyl radical-mediated transformation

3. amidyl radical-mediated transformation

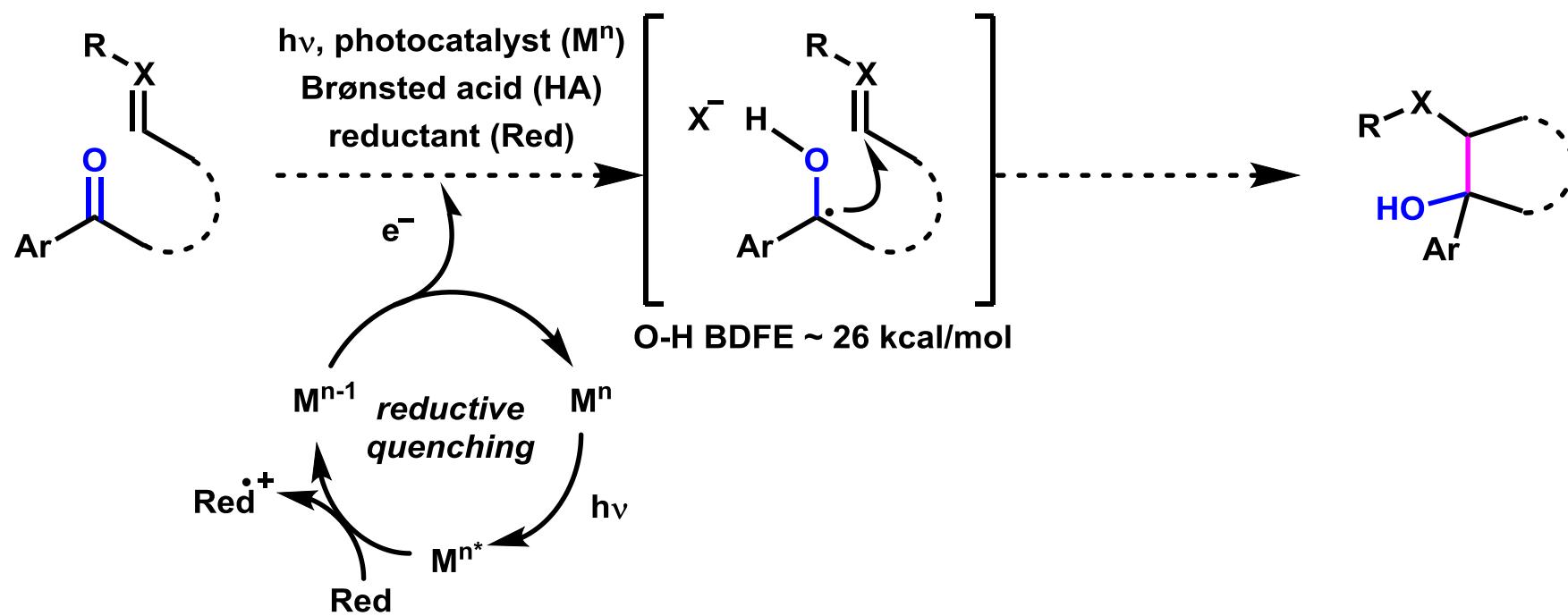
**4. oxyl radical-mediated transformation
(main paper)**

10. Reductive PCET for Ketyl Generation

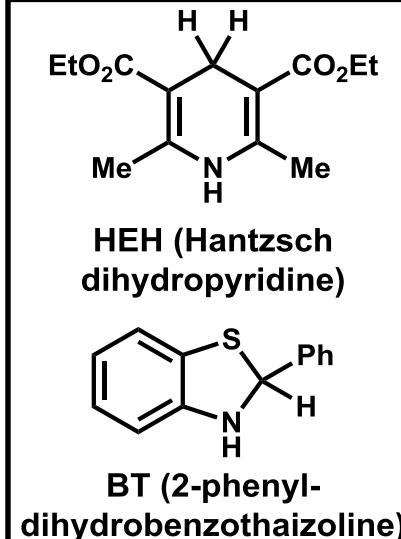
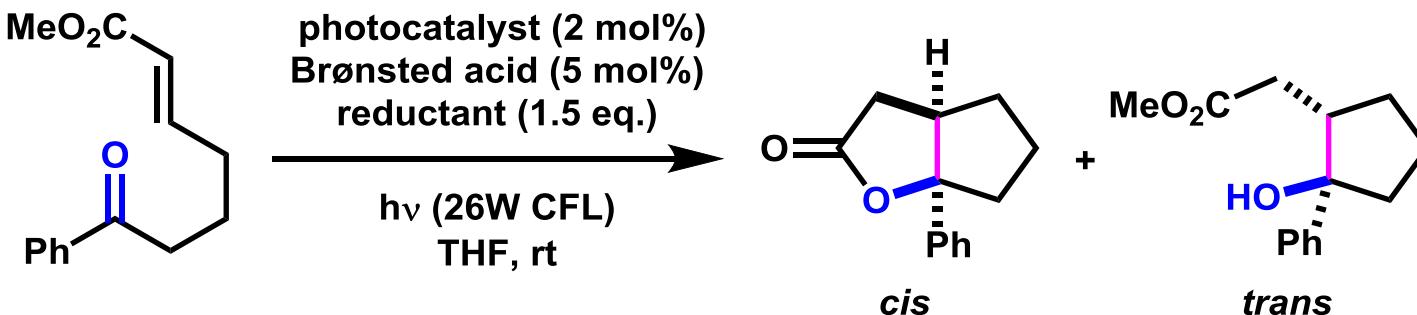
(1) samarium(II) iodide ¹⁾



(2) reductive PCET activation ²⁾



11. Optimization of Reaction Conditions

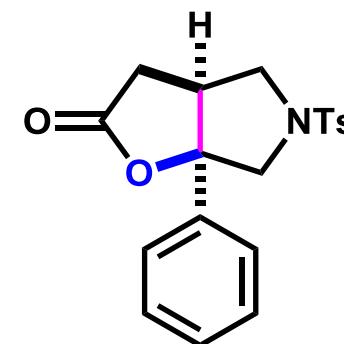
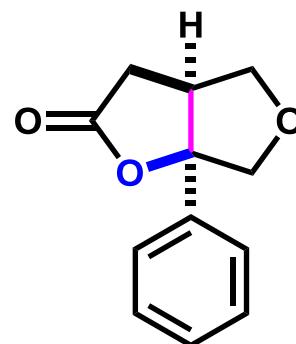
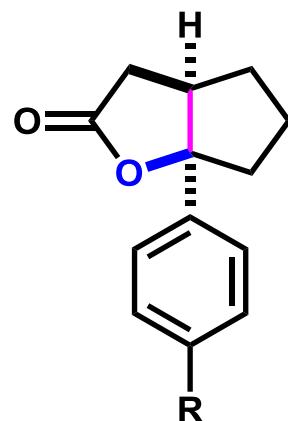
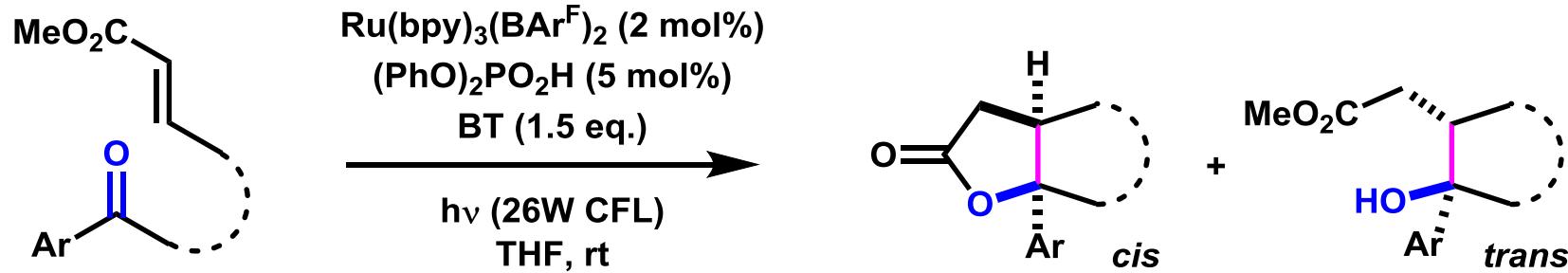


photocatalyst	Brønsted acid cat	reductant	yield, %	<i>cis:trans</i>	effective BDFE, kcal/mol ^a
Ru(bpy) ₃ (BAr ^F) ₂	none	HEH	0	-	-
Ru(bpy) ₃ (BAr ^F) ₂	PhCO ₂ H	HEH	0	-	45
Ru(bpy) ₃ (BAr ^F) ₂	lutidine•HBF ₄	HEH	0	-	35
Ru(bpy) ₃ (BAr ^F) ₂	(PhO) ₂ PO ₂ H	HEH	78	4.6:1	33
Ru(bpy) ₃ (BAr ^F) ₂	(PhO) ₂ PO ₂ H	BT	89	10:1	33

^a calculated from pK_a and potential data in MeCN ($C = 54.9$ kcal/mol)

$$\text{effective BDFE (kcal/mol)} = 1.37 \text{ p}K_a(\text{HA}) + 23.06 E (\text{Ru}^{II}/\text{Ru}^I) + C_{\text{solv}} \text{ (at 298 K)}$$

12. Ketyl-Olefin Coupling -Substrate Scope-

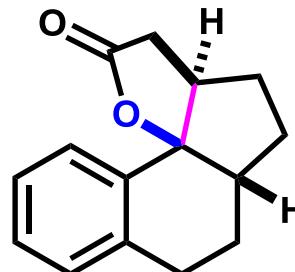
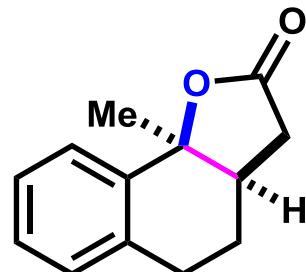


R = Me: 86% (*cis:trans* = 6:1)

R = OMe: 78% (*cis:trans* = 12:1)

87% (*cis:trans* = 4.8:1)

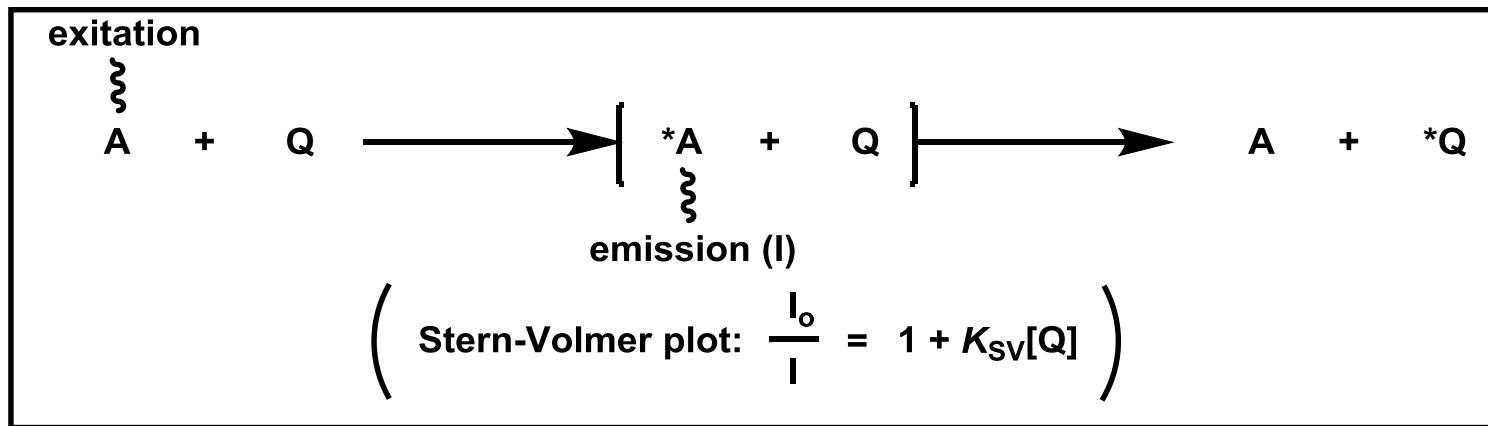
80% (*cis:trans* = 3.4:1)



78% (*cis:trans* = 1.2:1)

82% (*cis:trans* = 16:1)

13. Luminescence Quenching Studies

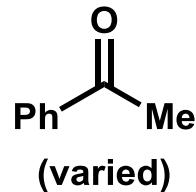


$\text{Ir(ppy)}_3 : 2.0 \times 10^{-6} \text{ M}$

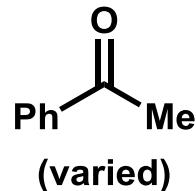
Ex: 390 nm, Em: 518 nm

$\text{Ru(bpy)}_3(\text{BAr}^F)_2 : E (\text{Ru}^{II}/\text{Ru}^I) = -1.71 \text{ V vs Fc/Fc}^+$

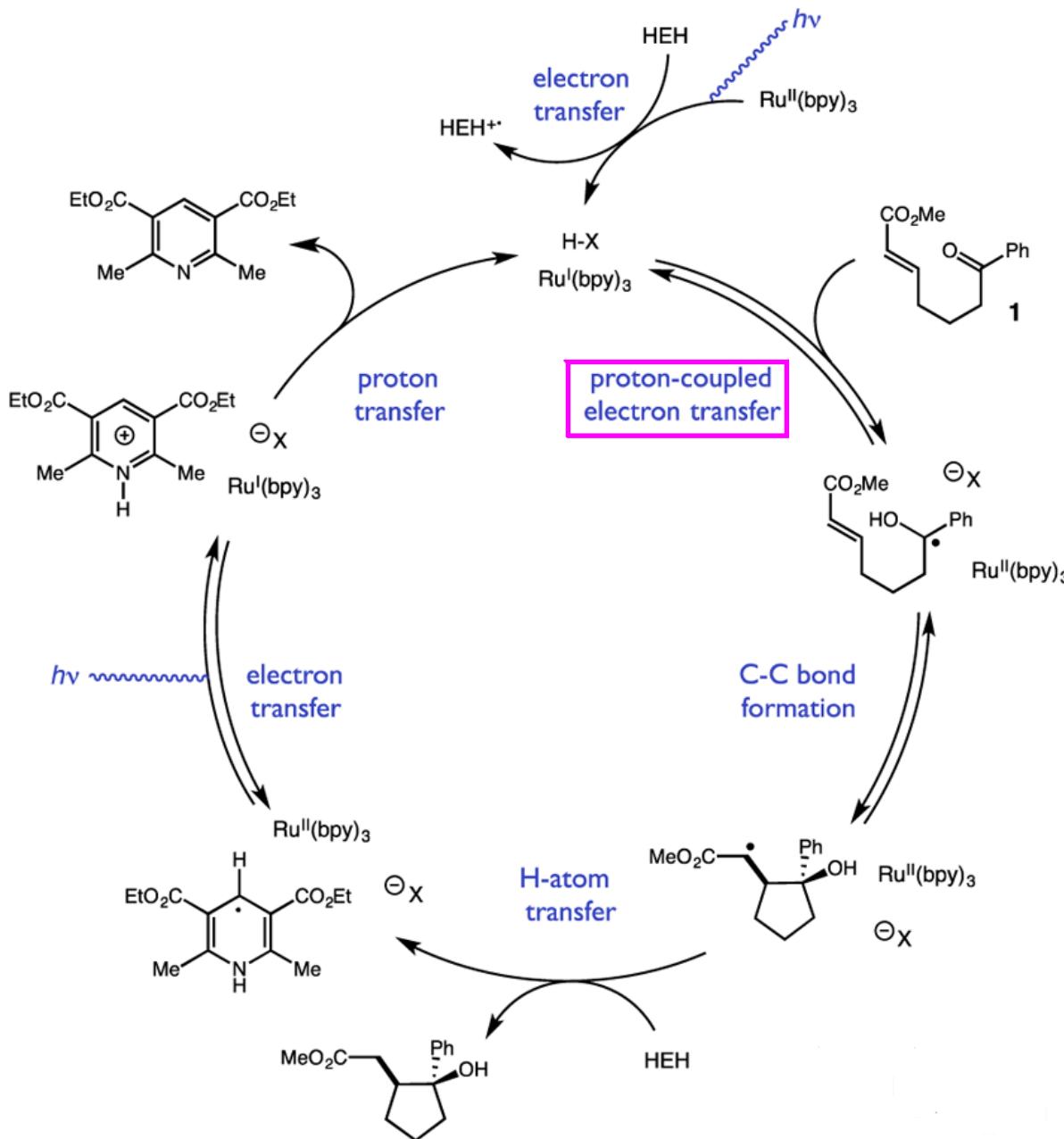
$\text{Ir(ppy)}_3 : E (\text{Ir}^{IV}/*\text{Ir}^{III}) = -2.11 \text{ V vs Fc/Fc}^+$



reaction mechanism



14. Proposed Catalytic Cycle



15. Contents

1. introduction of PCET

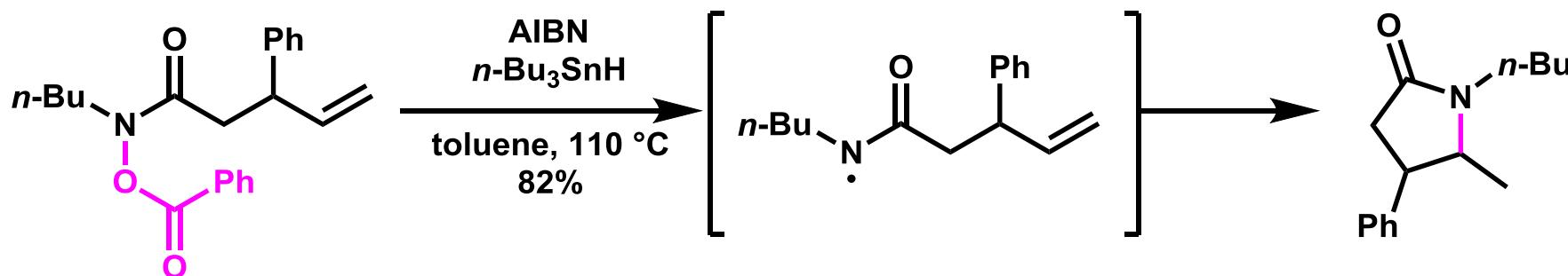
2. ketyl radical-mediated transformation

3. amidyl radical-mediated transformation

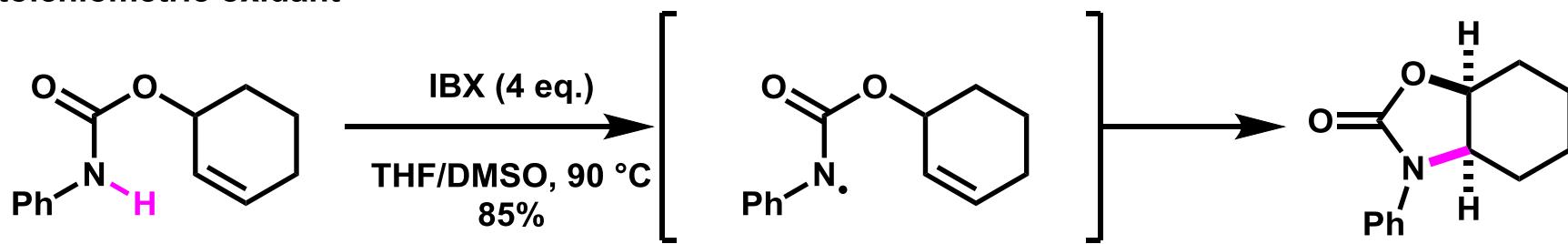
**4. oxyl radical-mediated transformation
(main paper)**

16. Oxidative PCET for Amidyl Generation

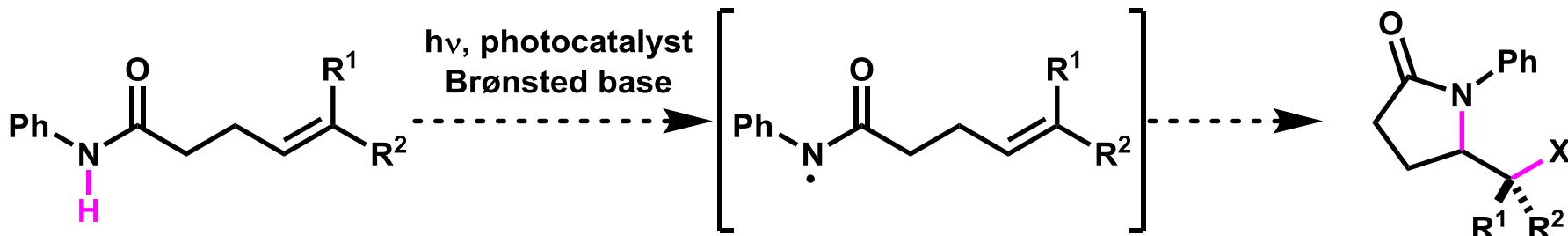
(1) prefunctionalization ¹⁾



(2) stoichiometric oxidant ²⁾



(3) oxidative PCET activation ³⁾

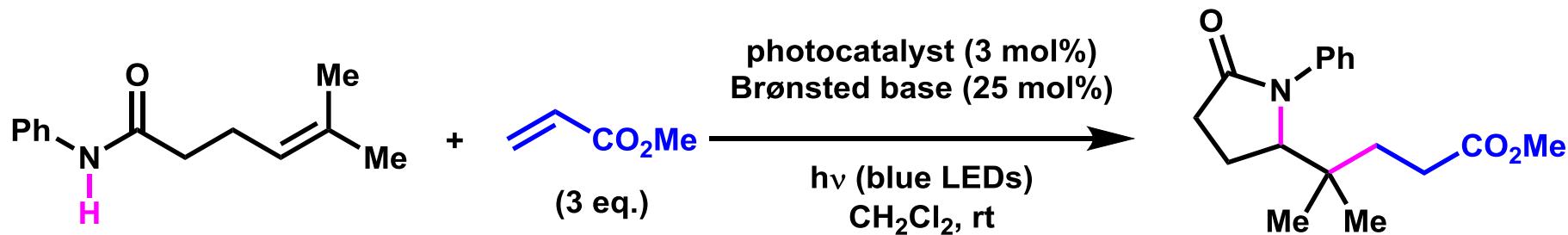


N-H BDFE ~ 100 kcal/mol

(1) Clark, A. J.; Peacock, J. L. *Tetrahedron Lett.* **1998**, 39, 6029. (2) Nicolaou, K. C. et al. *J. Am. Chem. Soc.* **2002**, 124, 2233.

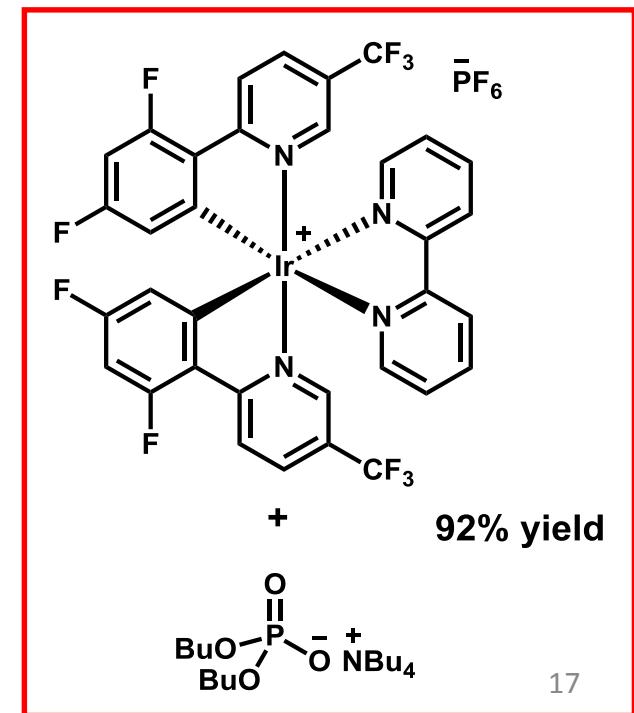
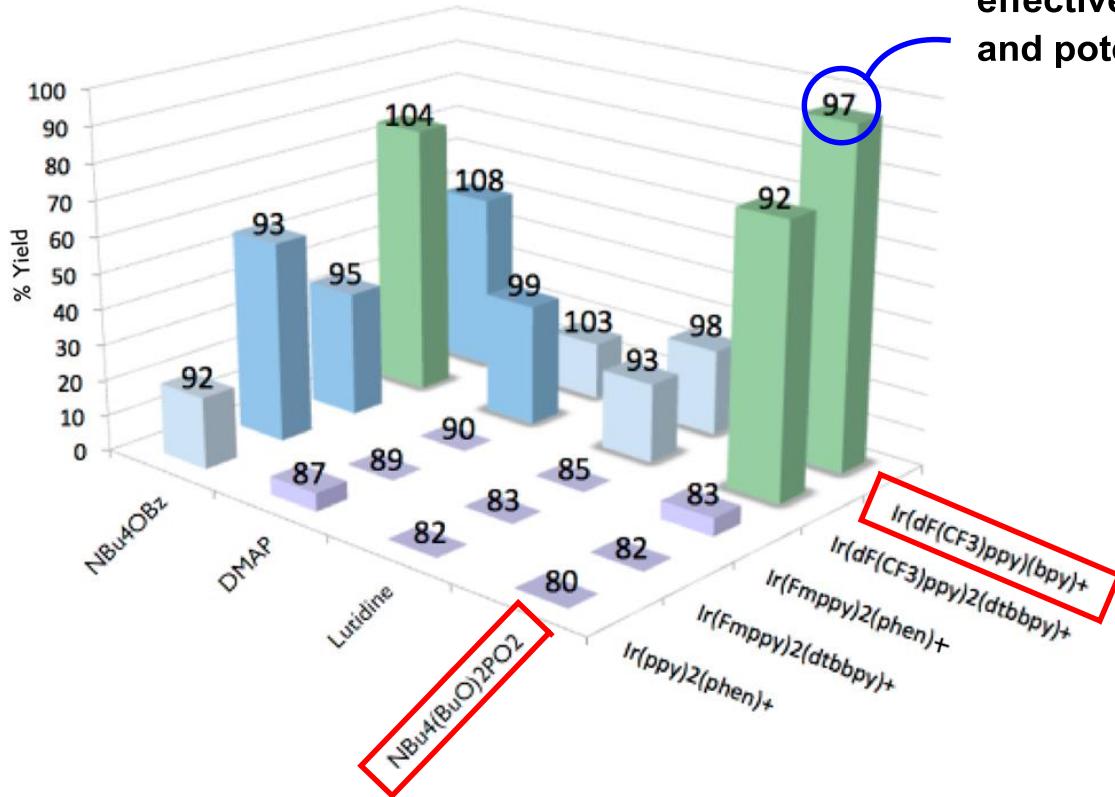
(3) Choi, G. J.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, 137, 9226.

17. Optimization of Reaction Conditions

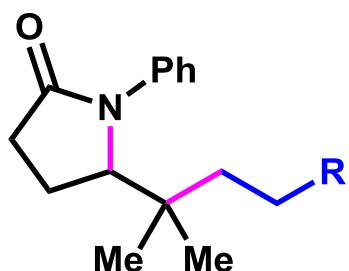
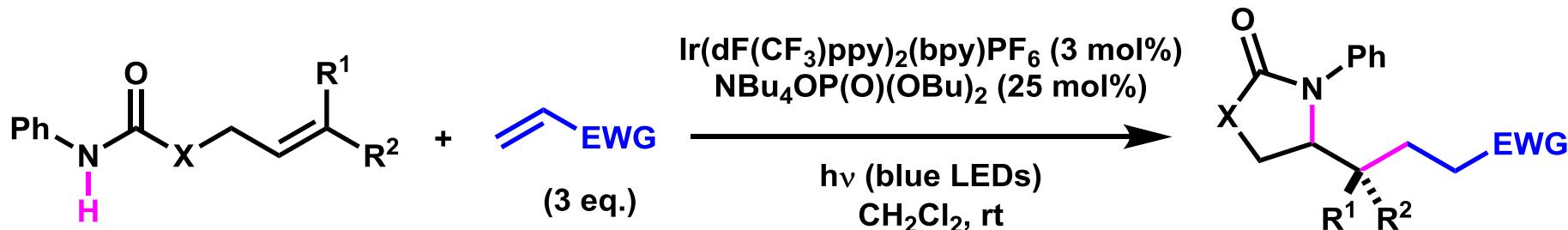


$$1.37 \text{ p}K_a(\text{HB}) + 23.06 E (\text{*Ir}^{\text{III}}/\text{Ir}^{\text{II}}) + C_{\text{solv}} \text{ (at 298 K)}$$

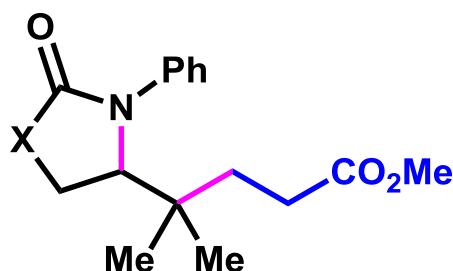
effective BDFE (kcal/mol) calculated from $\text{p}K_a$ and potential data in MeCN ($C = 54.9 \text{ kcal/mol}$)



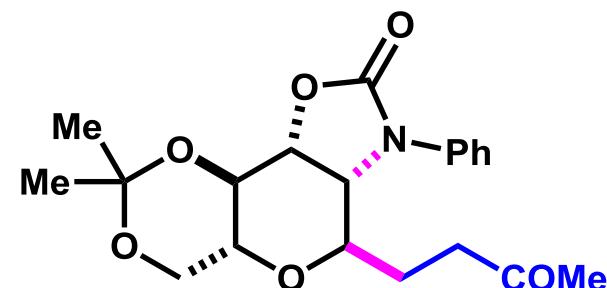
18. Carboamidation -Substrate Scope-



$R = \text{COMe}$	94%
$R = \text{CHO}$	50%
$R = \text{CN}$	78%

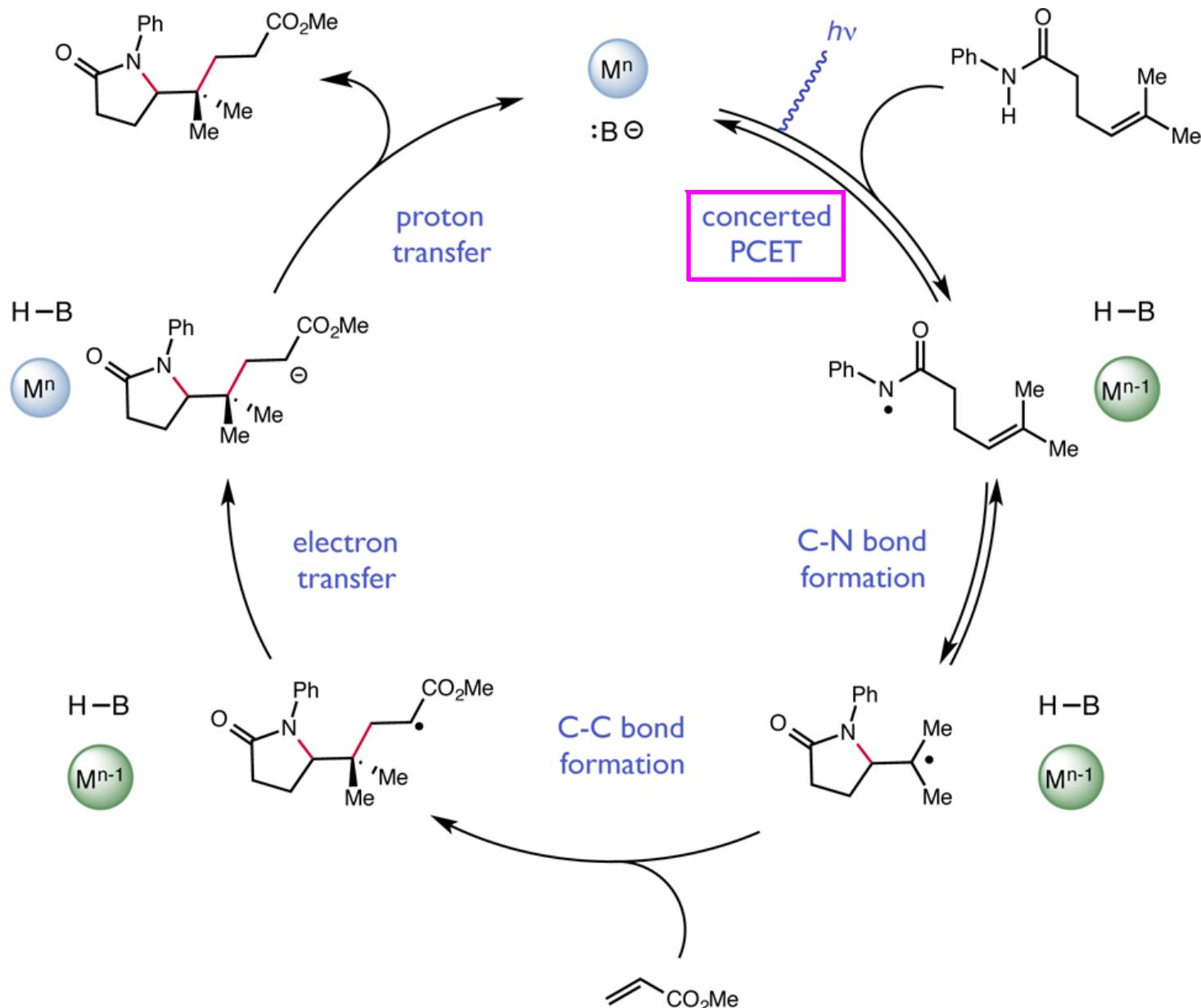


$X = \text{O}$	87%
$X = \text{NMe}$	63%
$X = \text{S}$	72%



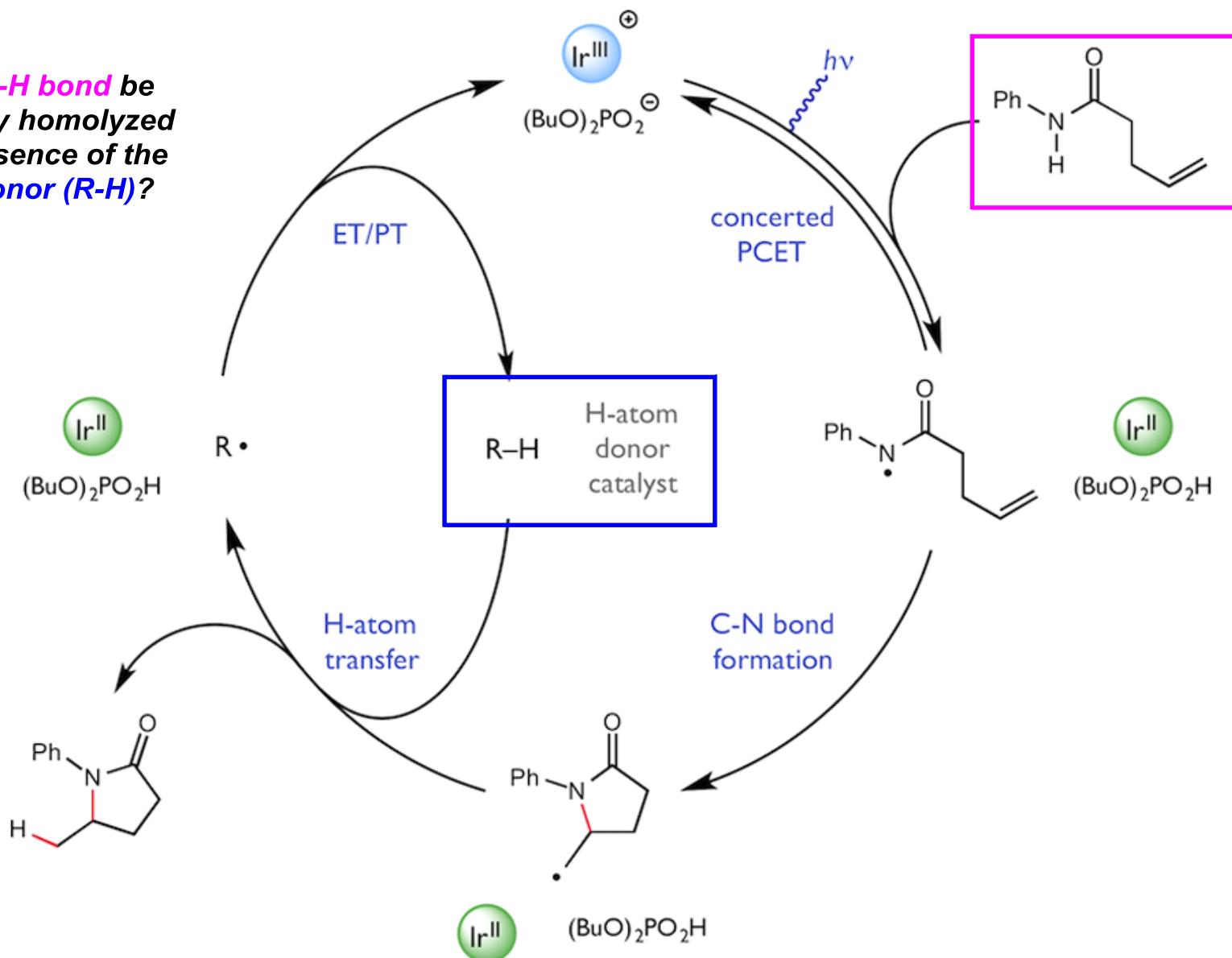
63%
(d.r. >20:1)

19. Proposed Catalytic Cycle

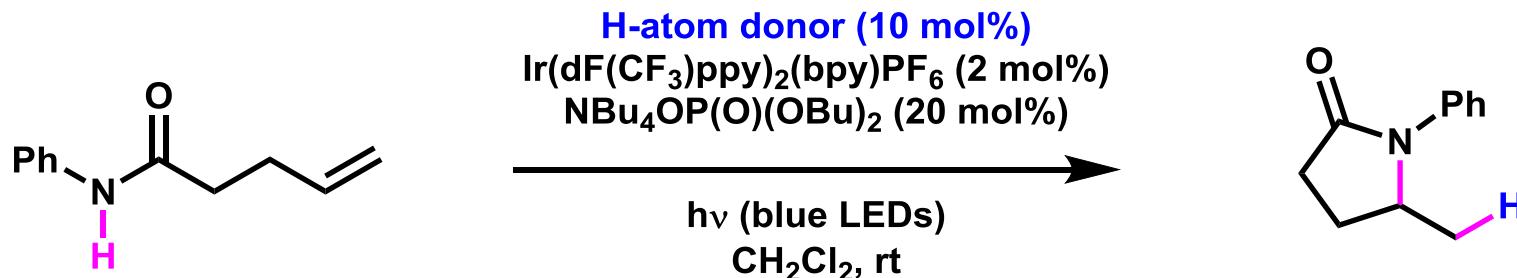


20. Task for Catalytic Hydroamidation

Can the **N-H bond** be selectively homolyzed in the presence of the **H-atom donor (R-H)**?

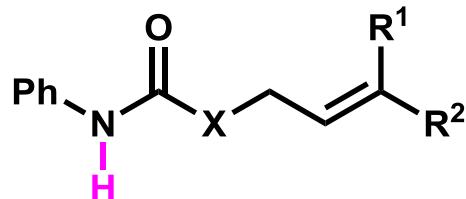


21. Screening of H-atom Donor

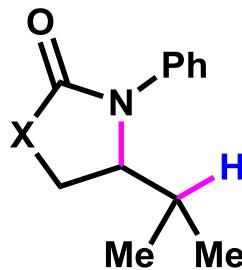
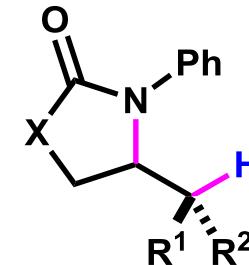


none		28%		18%		16%		95%
24%								

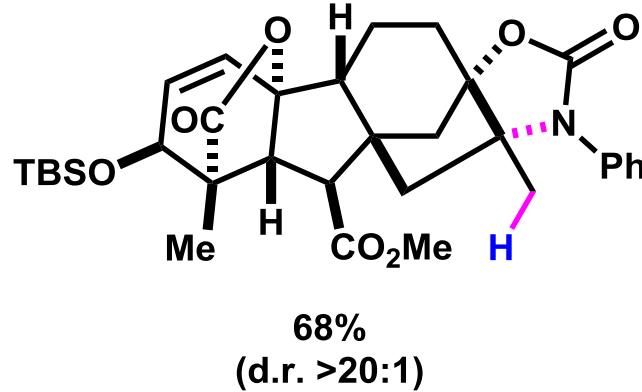
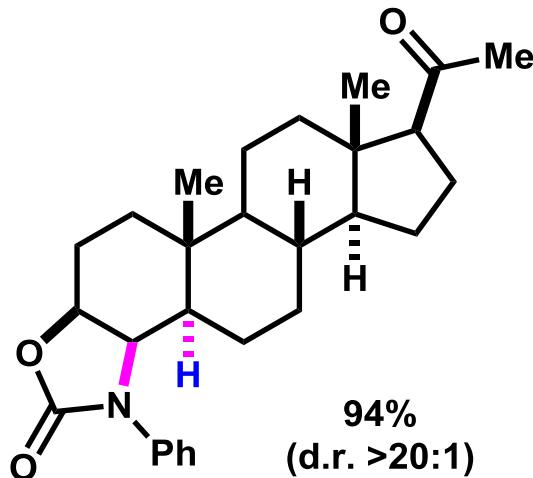
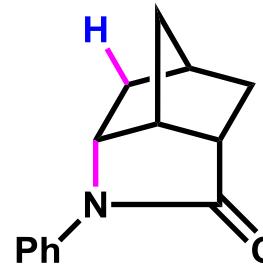
22. Hydroamidation –Substrate Scope-



PhSH (10 mol%)
Ir(dF(CF₃)ppy)₂(bpy)PF₆ (2 mol%)
NBu₄OP(O)(OBu)₂ (20 mol%)
 $\xrightarrow{h\nu \text{ (blue LEDs)}, \text{CH}_2\text{Cl}_2, \text{rt}}$



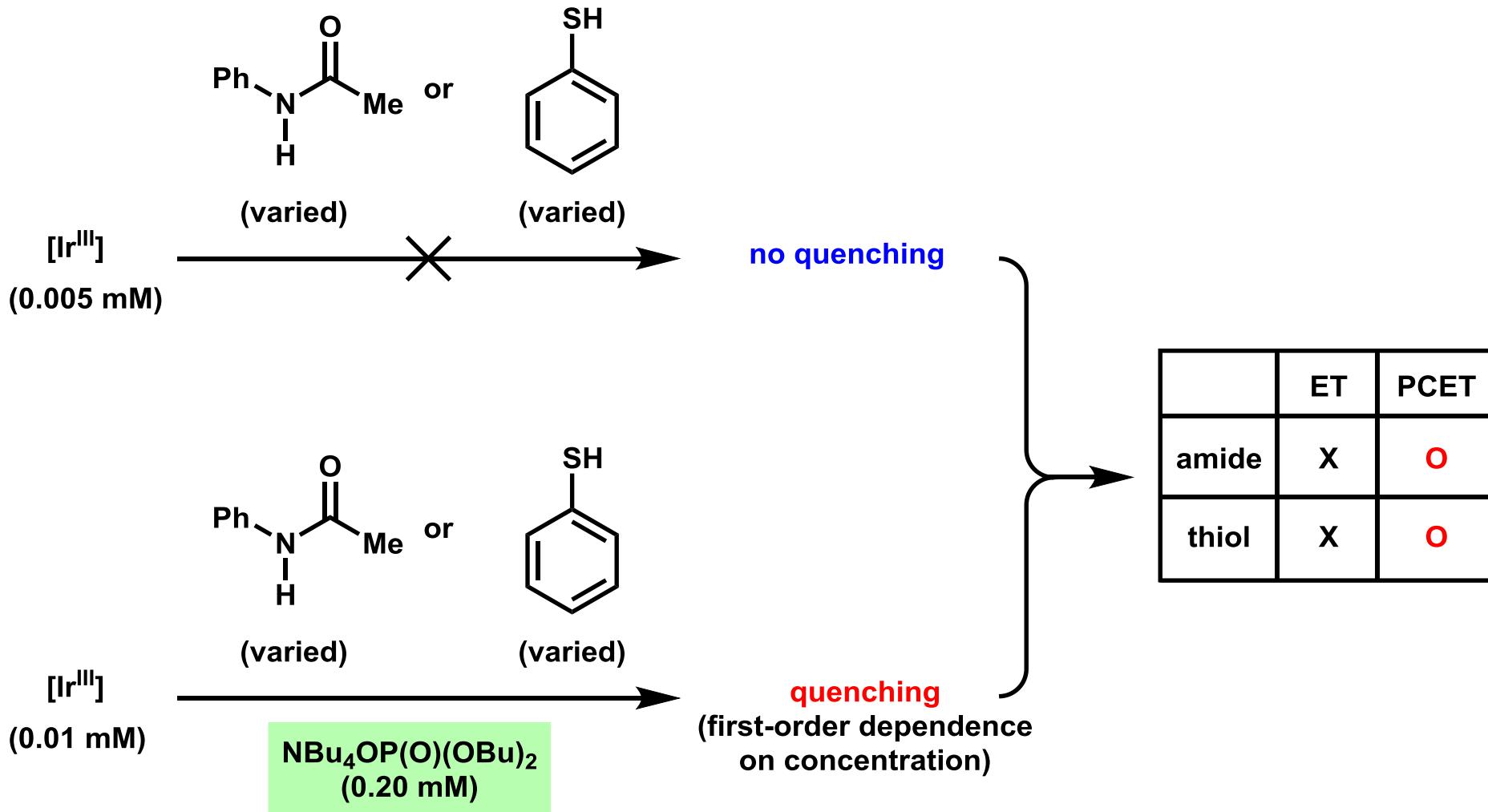
X = O 89%
X = NMe 90%
X = S 73%



23. Luminescence Quenching Studies

$[\text{Ir}^{\text{III}}] = \text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})\text{PF}_6$: $E^{(\text{*Ir}^{\text{III}}/\text{Ir}^{\text{II}})} = 0.94 \text{ V vs Fc/Fc}^+$

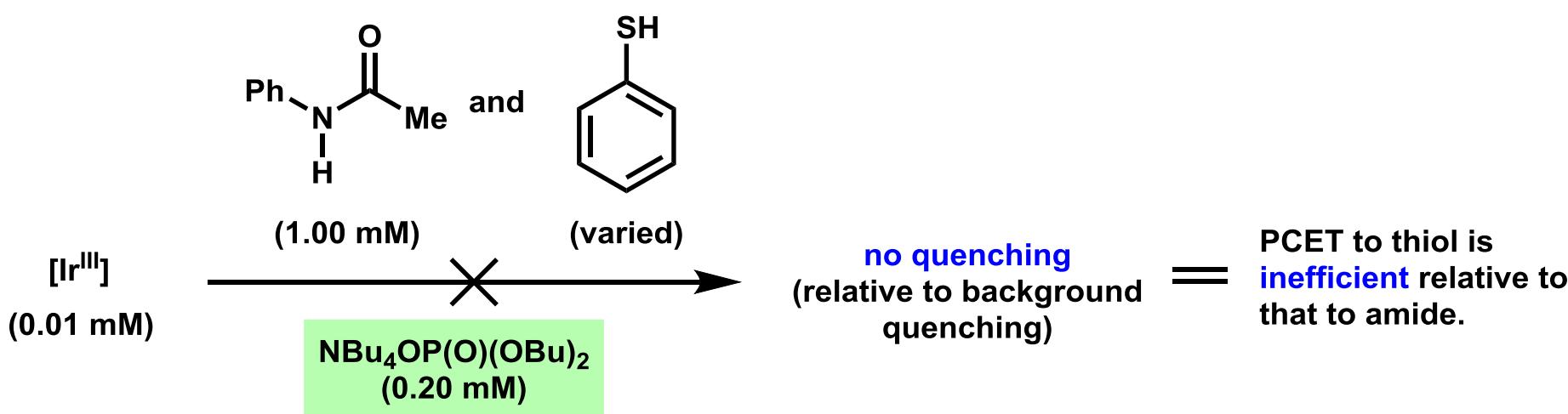
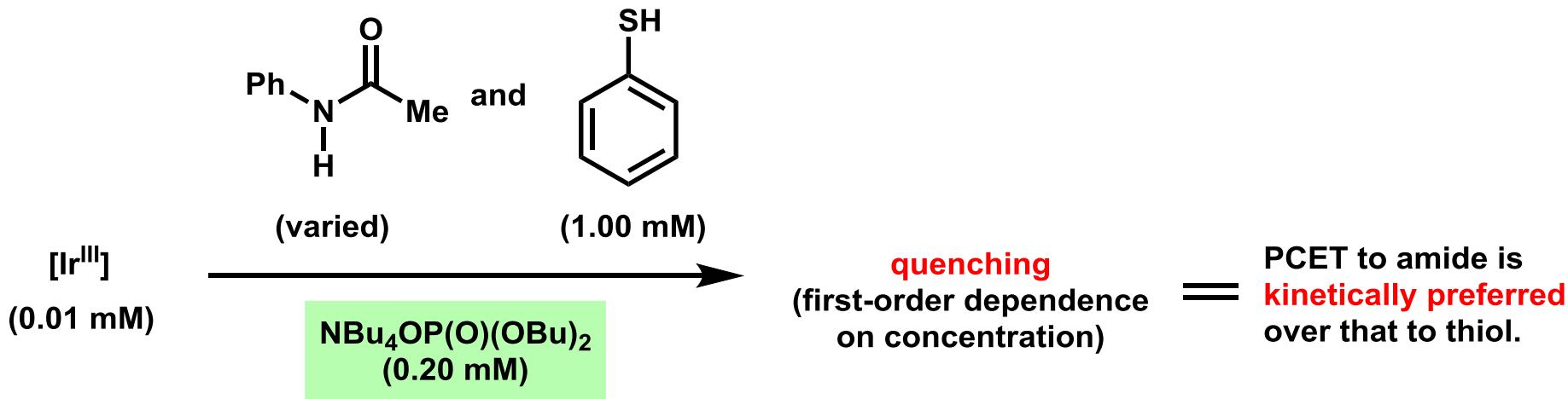
Ex: 370 nm, Em: 498 nm



24. Competition-Qenching Studies

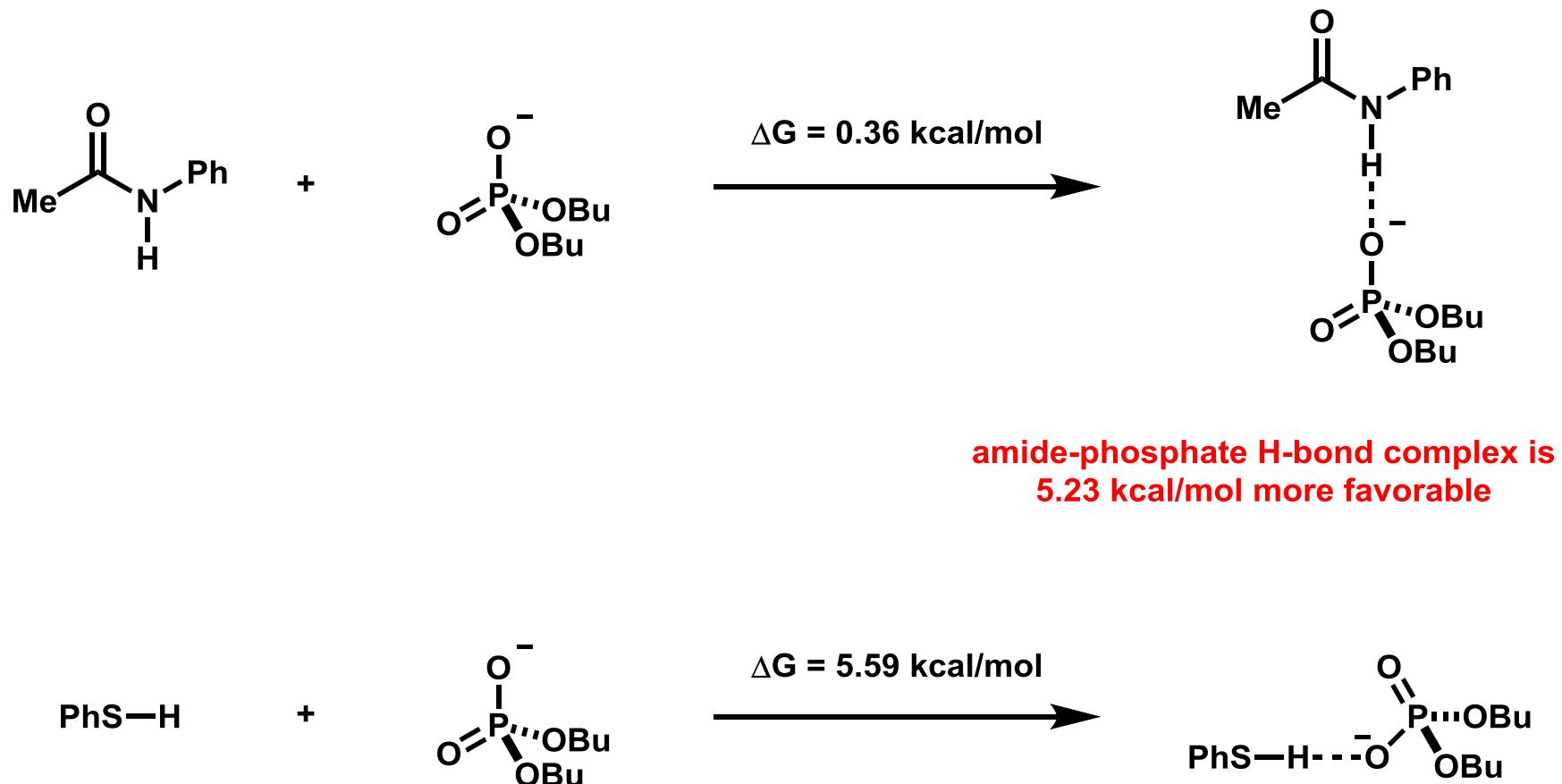
$[Ir^{III}] = Ir(dF(CF_3)ppy)_2(bpy)PF_6$: $E(^*Ir^{III}/Ir^{II}) = 0.94 \text{ V vs Fc/Fc}^+$

Ex: 370 nm, Em: 498 nm



25. Computational Evaluation of Hydrogen Bonding

¹⁾ ωB97XD / 6-31G++(2d,2p) in CH₂Cl₂



26. Contents

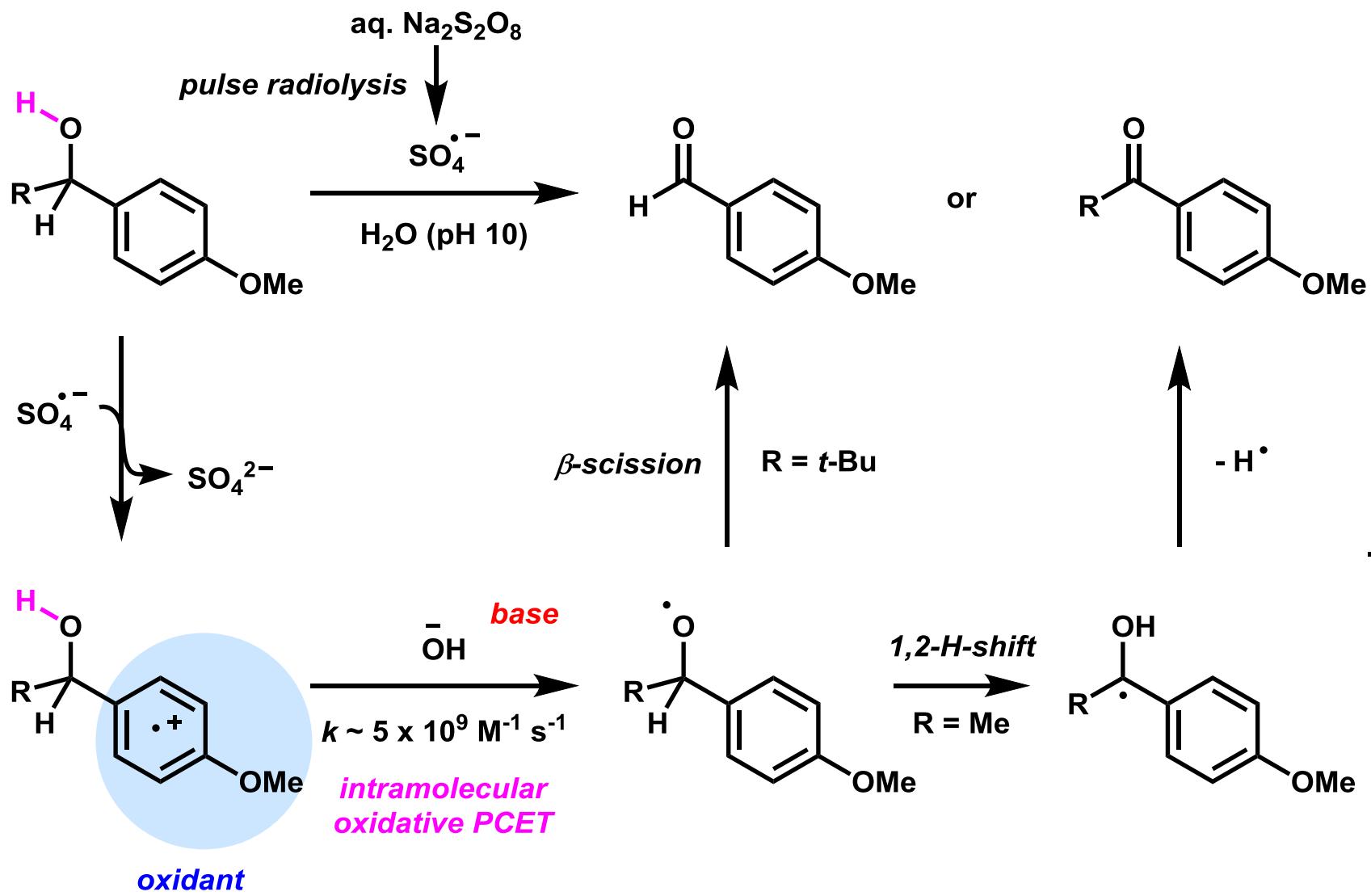
1. introduction of PCET

2. ketyl radical-mediated transformation

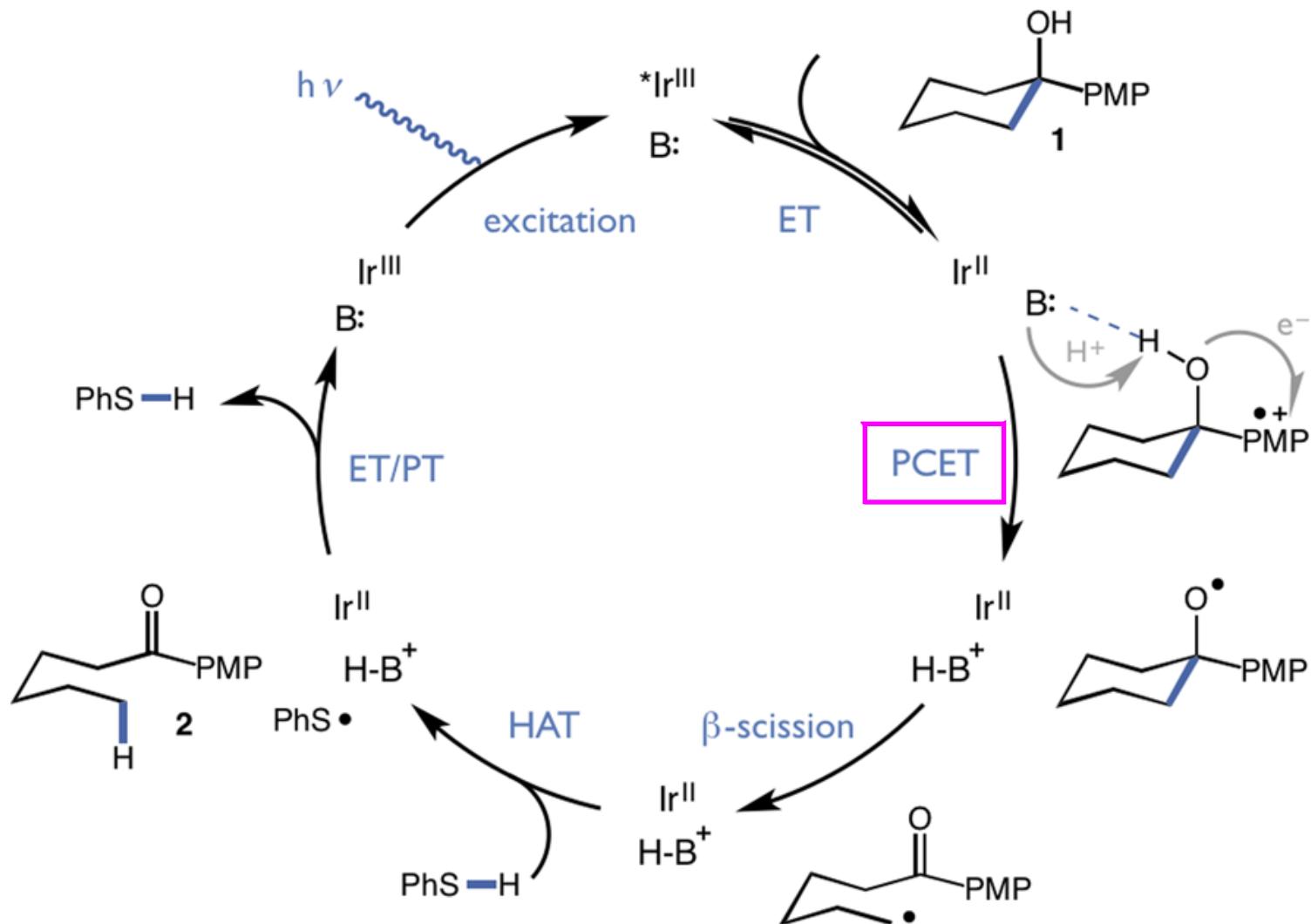
3. amidyl radical-mediated transformation

**4. oxyl radical-mediated transformation
(main paper)**

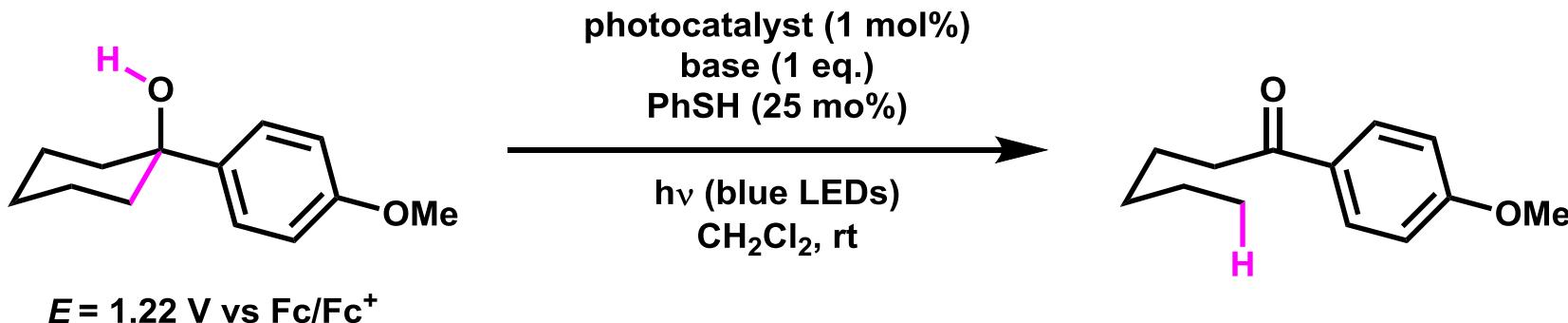
27. Intramolecular PCET



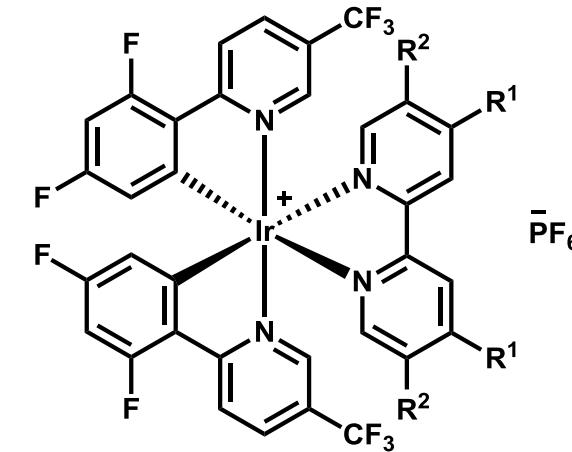
28. Design of Ring-Opening Reaction



29. Optimization Reaction Conditions

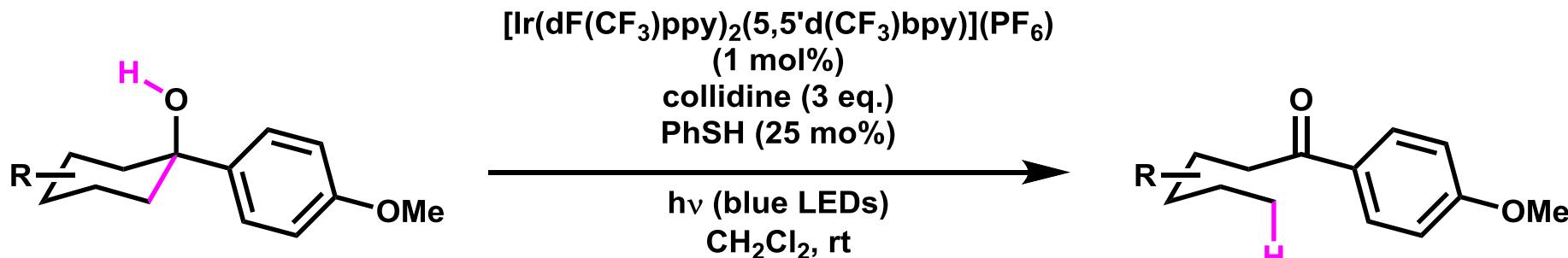


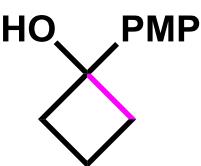
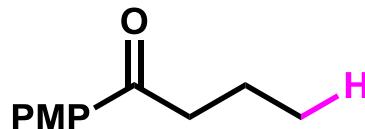
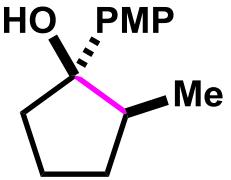
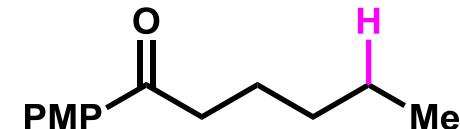
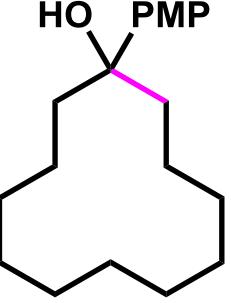
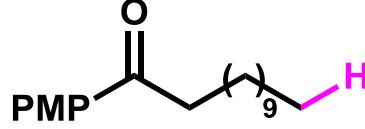
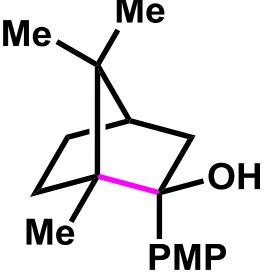
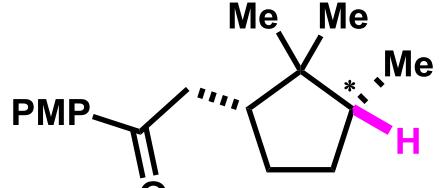
photocatalyst	base	yield, %
A	collidine	0
B	collidine	9
C	collidine	79
C	collidine (3 eq.)	91
C	pyridine	6
C	none	0



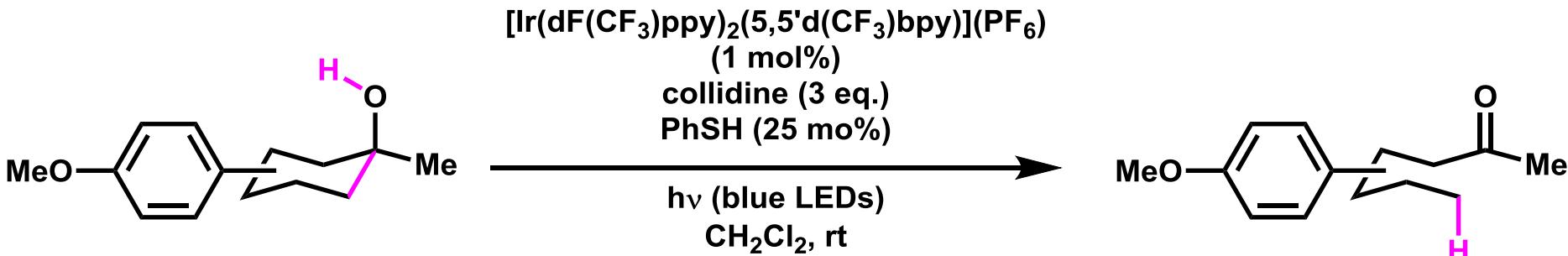
	R ¹	R ²	$E (^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}})$ vs Fc/Fc ⁺
A	t-Bu	H	0.83 V
B	H	H	0.94 V
C	H	CF ₃	1.30 V

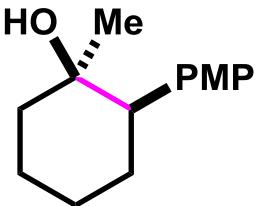
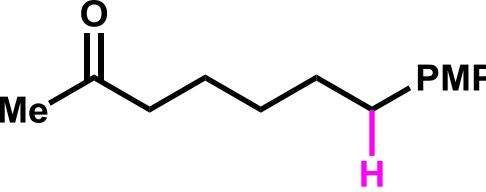
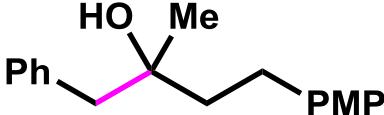
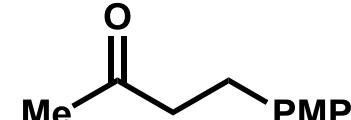
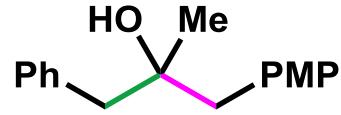
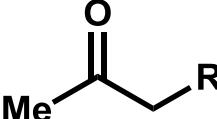
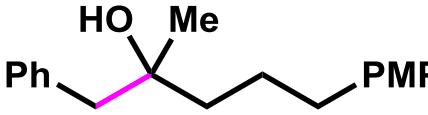
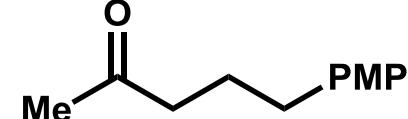
30. Ring-Opening Reaction –Substrate Scope–



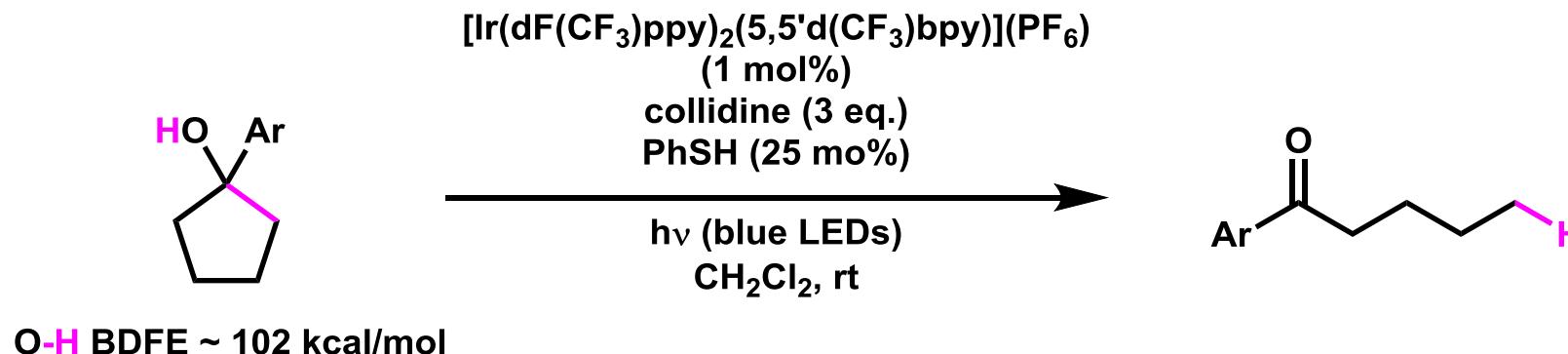
substrate	product	substrate	product
	 71%		 97%
	 85%		 91% (d.r. = 6:1)

31. Effect of Remote PMP Group



substrate	product	substrate	product
	 91%		 89%
	 89% ($R = \text{Ph}$) 5% ($R = \text{PMP}$)		 6%

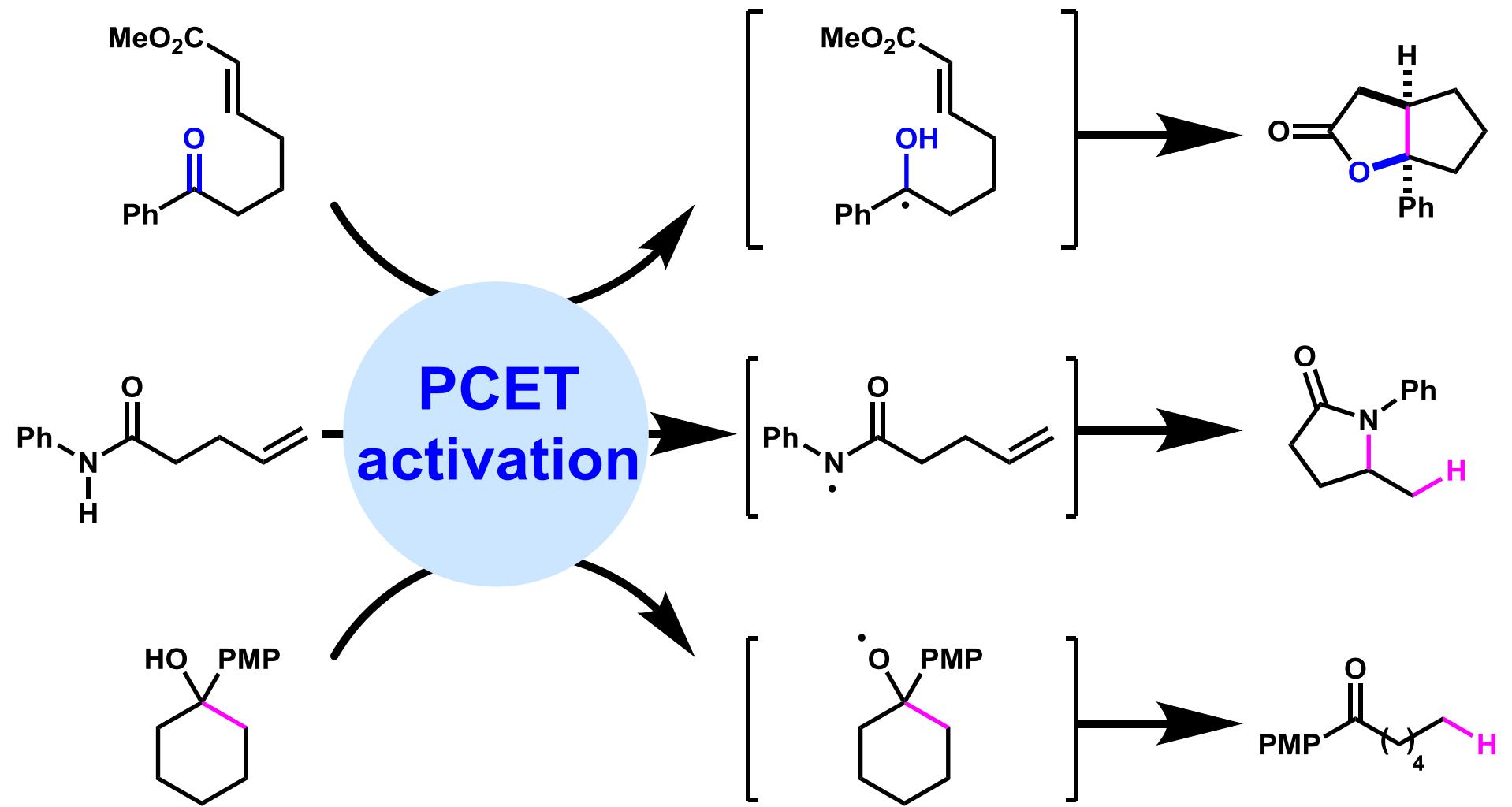
32. Effect of Proximal Aryl Group



$E(\text{Ar}^{\cdot+/0})$	0.92 V	0.96 V	1.18 V	1.22 V
effective BDFE (kcal/mol)	97	98	103	104
yield	<5%	7%	86%	86%
				84%

$$\text{effective BDFE (kcal/mol)} = 1.37 \text{ } pK_a(\text{HB}^+) + 23.06 \text{ } E(\text{Ar}^{\cdot+/0}) + 54.9 \text{ (at 298 K, MeCN)}$$

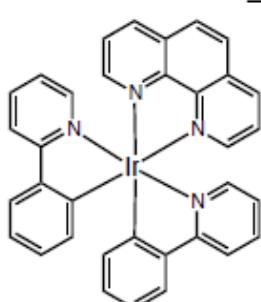
33. Summary



Appendix

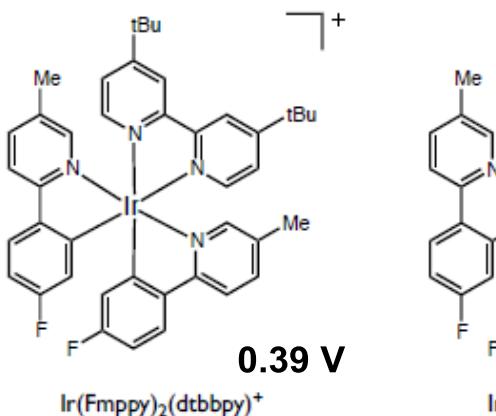
Redox Potential and pKa

E (*Ir^{III}/Ir^{II}) vs Fc/Fc⁺



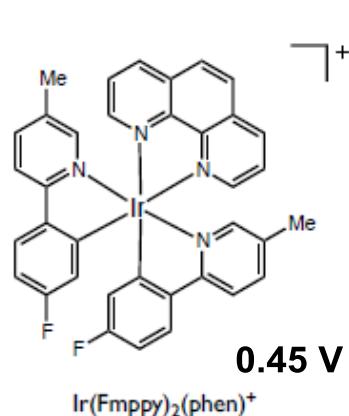
$\text{Ir}(\text{ppy})_2(\text{phen})^+$

0.32 V



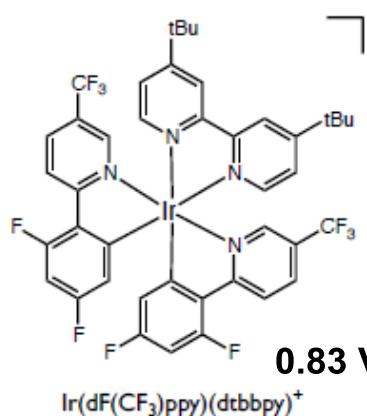
$\text{Ir}(\text{Fmppy})_2(\text{dtbbpy})^+$

0.39 V



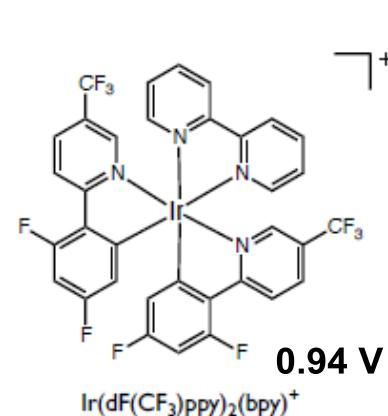
$\text{Ir}(\text{Fmppy})_2(\text{phen})^+$

0.45 V



$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})(\text{dtbbpy})^+$

0.83 V



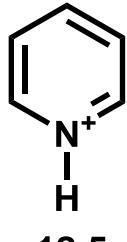
$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})^+$

0.94 V

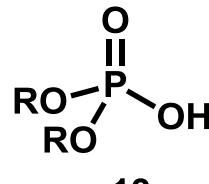
To convert the potentials from SCE (calomel) to Fc/Fc⁺ reference, 380 mV were subtracted from the measured values.

ex.) 1.68 V vs SCE = 1.30 V vs Fc/Fc⁺

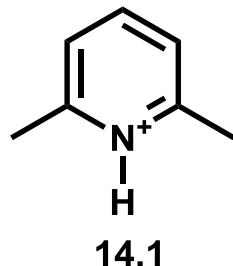
pK_a in MeCN



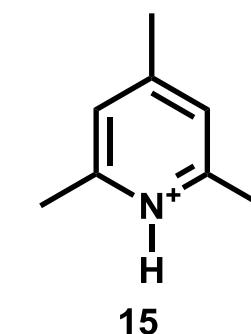
12.5



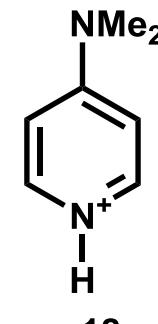
13



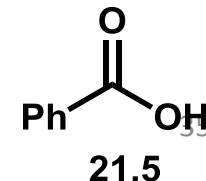
14.1



15

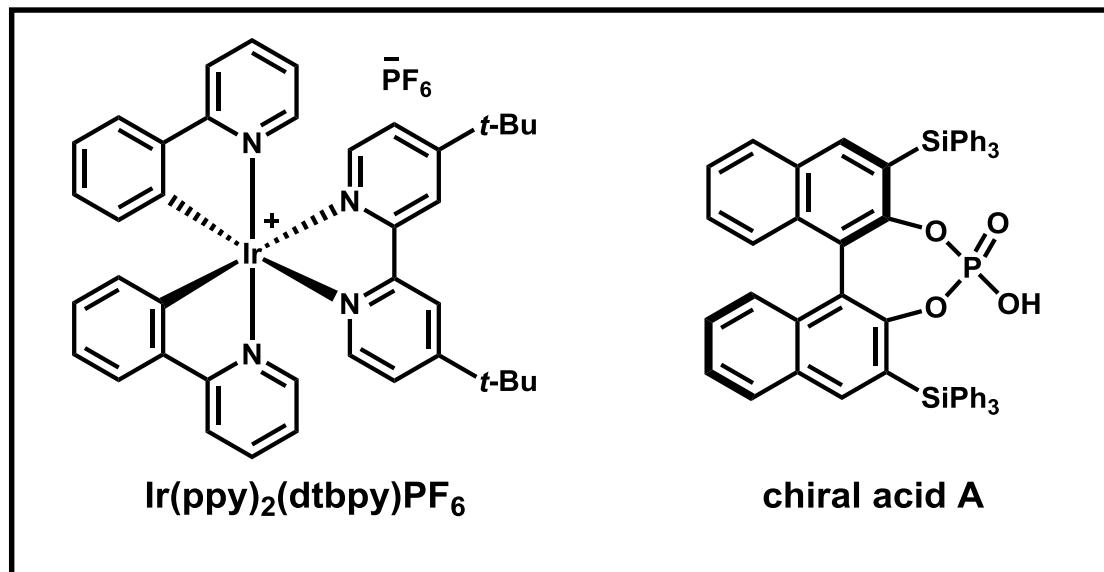
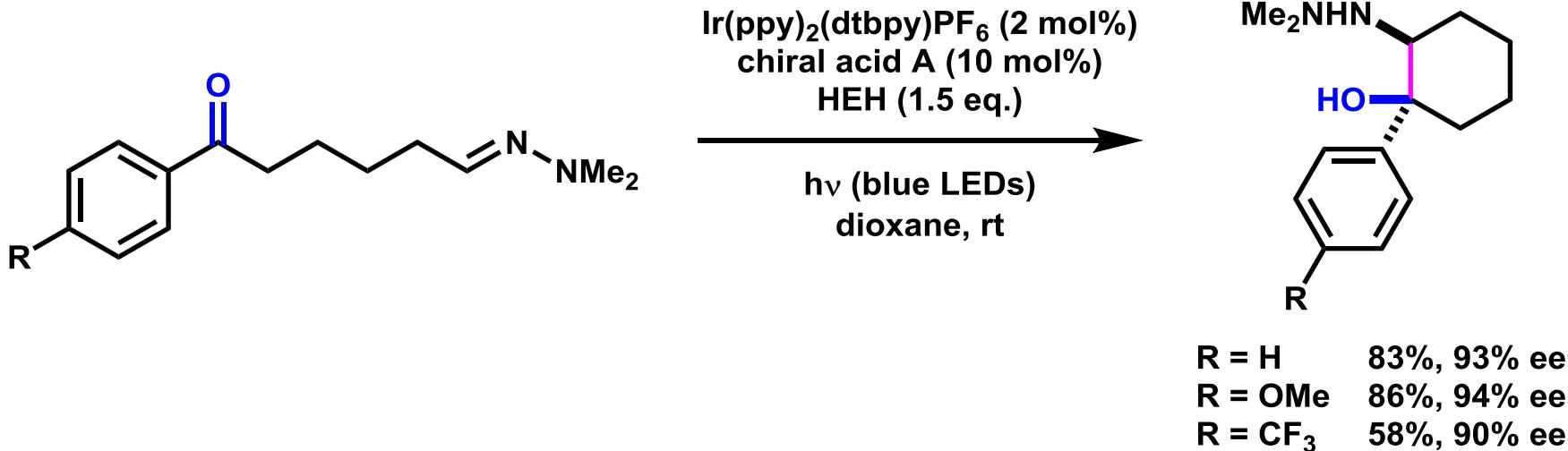


18

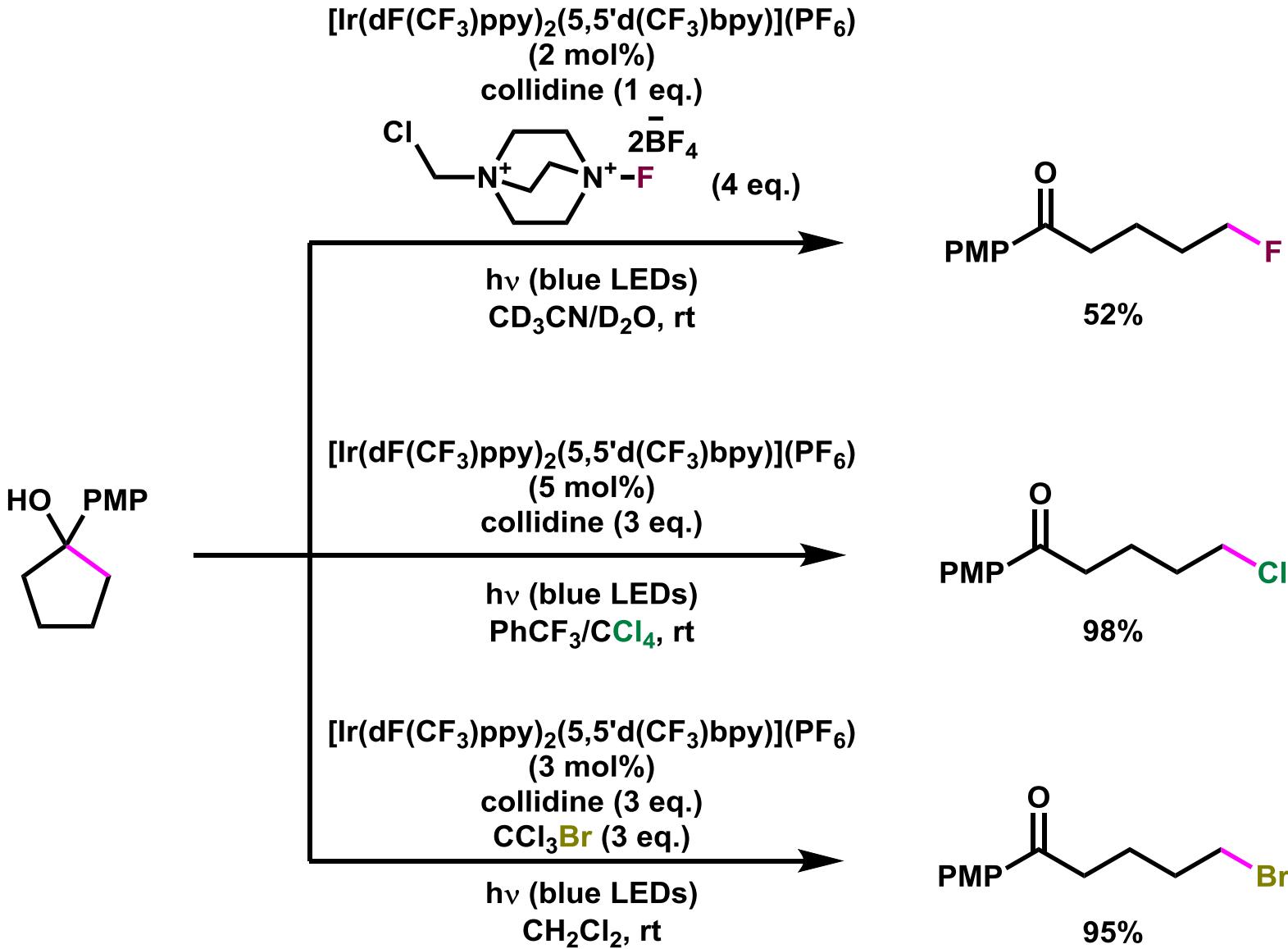


21.5

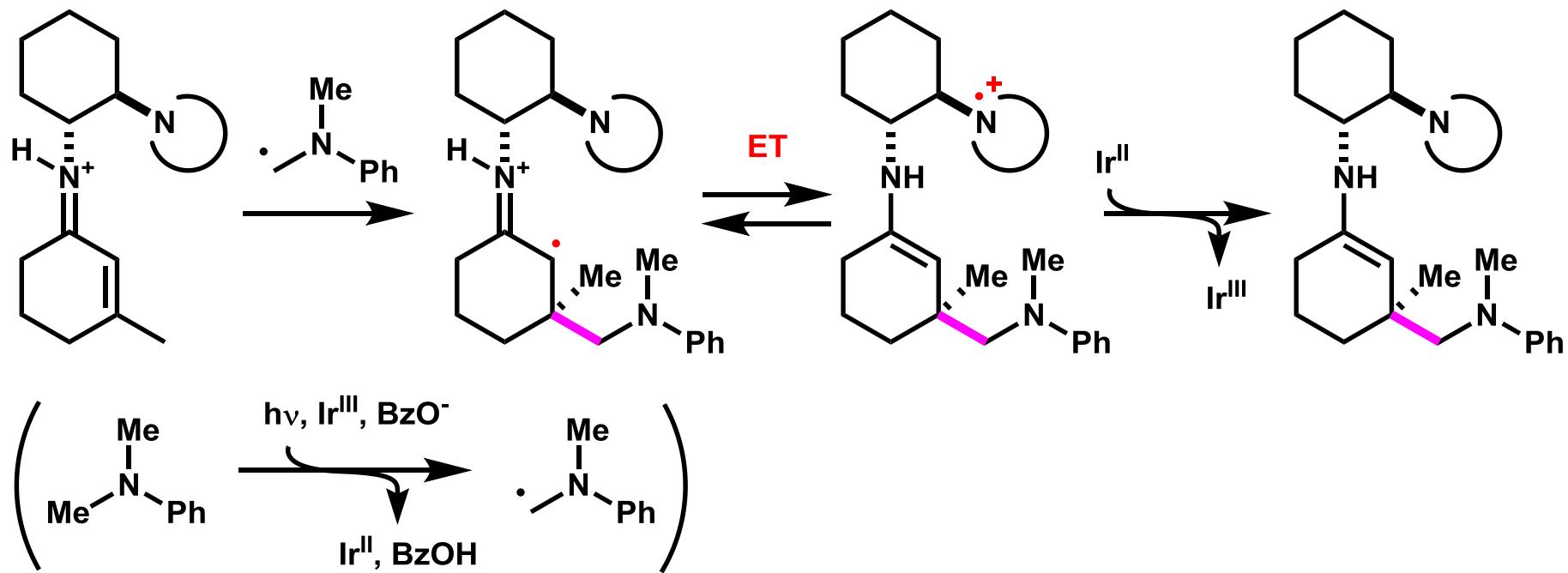
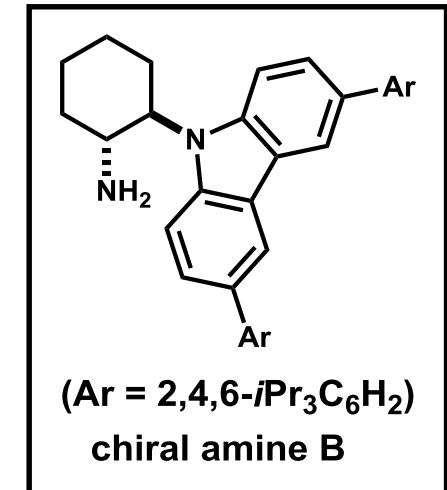
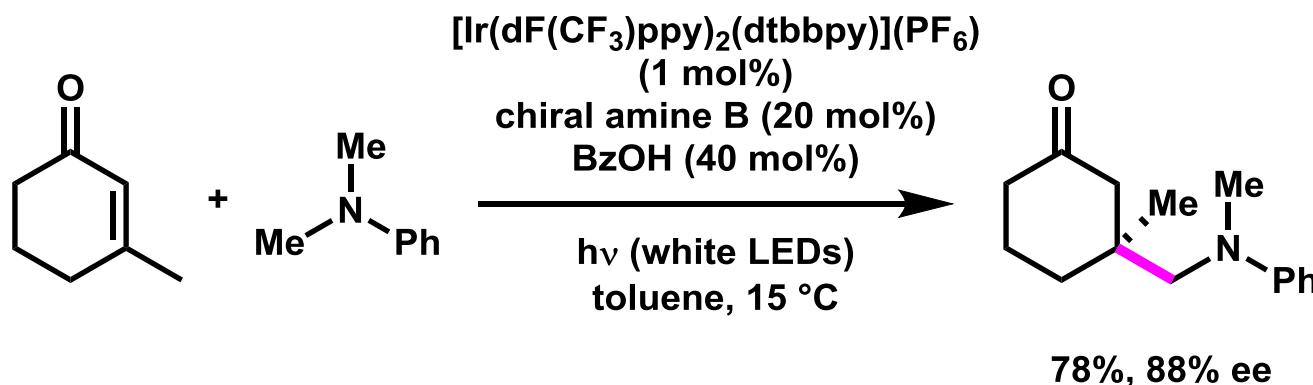
Asymmetric Aza-Pinacol Cyclization



Halogenation Reactions



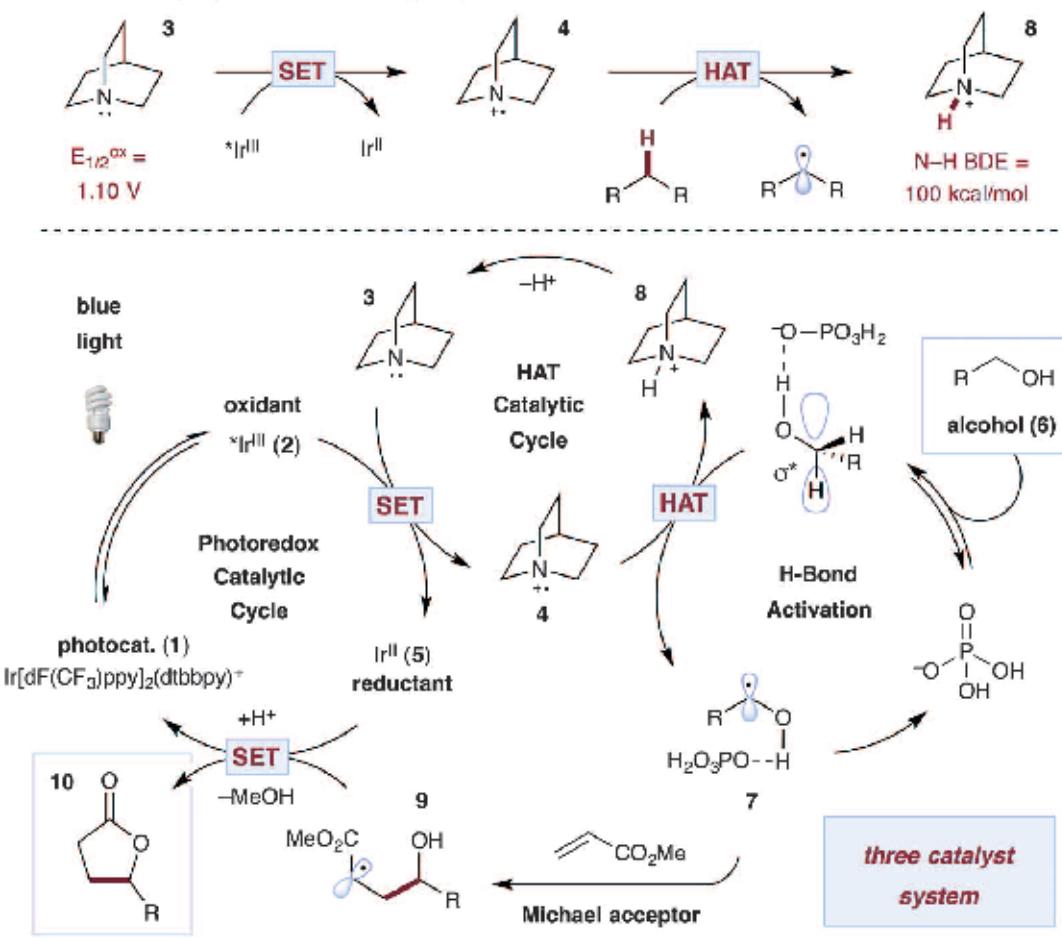
Intramolecular ET Strategy



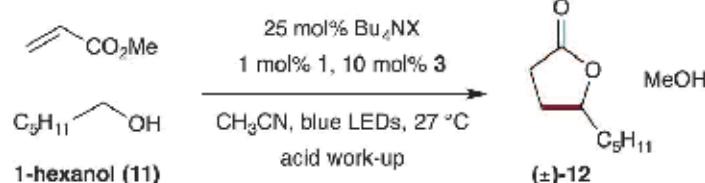
H-Bonding Promoted HAT

A

Harnessing a powerful HAT catalyst: quinuclidine

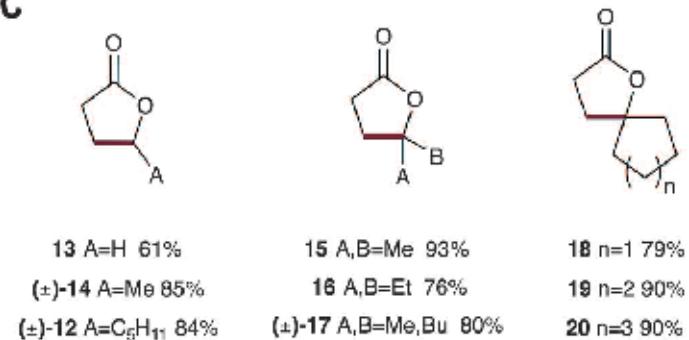


B



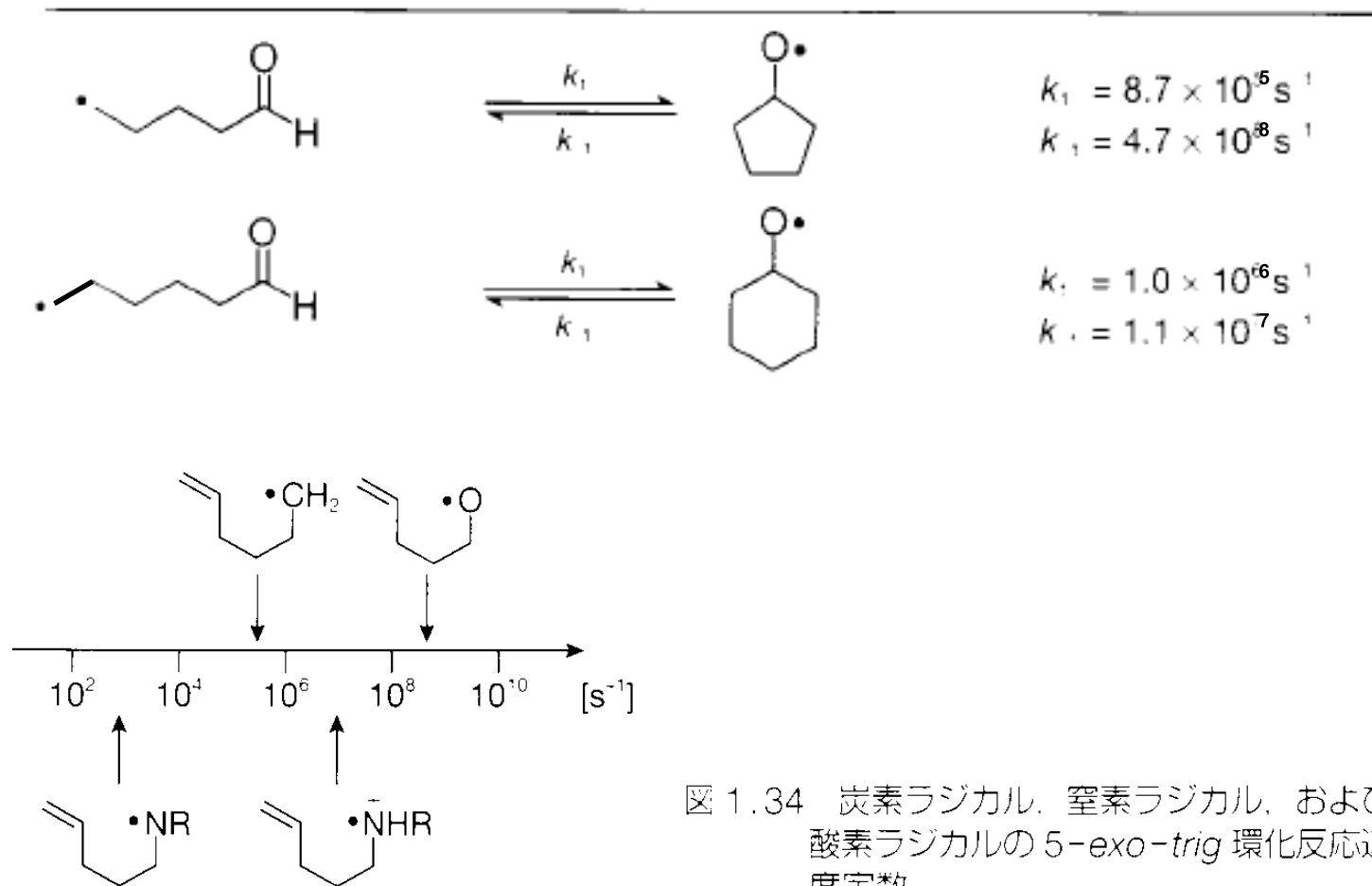
catalyst (Bu_4NX)	relative rate _{init}	yield lactone
—	1.0	67%
Bu_4NBF_4	1.0	71%
$\text{Bu}_4\text{NPO}_4\text{H}_2$	1.8	84%
$\text{Bu}_4\text{N}(\text{PhO})_2\text{PO}_2$	2.5	76%
$\text{Bu}_4\text{NCO}_2\text{CF}_3$	2.6	75%

C



Reaction Rate of Radical Cyclization

表 1.6 カルボニル基およびイミノ基への環化反応速度定数 (80 °C)



Kinetics of PCET (Marcus Theory)

$$k_{\text{CEPT}} = \sum_{\mu} P_{\mu} \sum_{\nu} \frac{1}{2\pi\hbar} |V_{\text{ET}}|^2 \sqrt{\frac{4\pi^3}{\lambda k_{\text{B}} T}} \exp\left[\frac{-\Delta G_{\mu\nu}^{\ddagger}}{k_{\text{B}} T}\right] \\ \times \int_{r=0}^{\infty} \left[\langle \phi_{\mu} | \phi_{\nu} \rangle_r^2 \frac{\exp(-E_x/k_{\text{B}} T)}{\int_{\Delta r=0}^{\infty} \exp(-E_x/k_{\text{B}} T)} \right]$$

$$\Delta G_{\mu\nu}^{\ddagger} = \frac{(\Delta G^\circ + \Delta E_{\mu\nu}^{\text{vib}} + \lambda)^2}{4\lambda}$$

$$E_n^{\text{vib}} = (n + 1/2)\hbar\omega - \frac{((n + 1/2)\hbar\omega)^2}{4D_{\text{e}}}$$

$$V_{\mu\nu} \approx V_{\text{ET}} \langle \phi_{\mu} | \phi_{\nu} \rangle$$

Crystal Structure of OEC

