Proton Coupled Electron Transfer (PCET): Physical Organic Analysis and Applications

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Purpose

- Define proton coupled electron transfer (PCET).
- Analyze the physical organic properties required for elementary step identification.
- Apply the PCET mechanistic concepts to known applications in synthetic organic chemistry.
- Apply PCET mechanistic concepts to more complex reactions in biological and material applications.

Outline and Opportunities

Physical Organic Analysis

- ❑ Definitions
- ❑ Thermodynamic Equations
- ❑ Mechanism Determination

Synthetic Organic Applications

- ❑ Nitrogen Centered Radicals
- ❑ Oxygen Centered Radicals

Biological and other Applications

- ❑ Photosynthesis: Photosystem II
- ❑ Molecular Wires
- ❑ Conclusion

Decreased Reaction Barriers

Minimized High Energy Intermediates

Lowered Charge Buildup

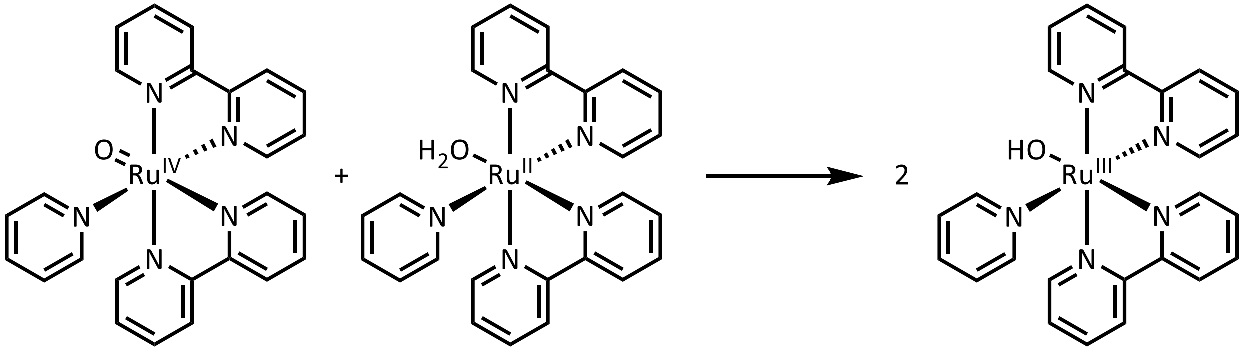
Possibility of Multi-Electron Multi-Proton Reactions

Defining PCET

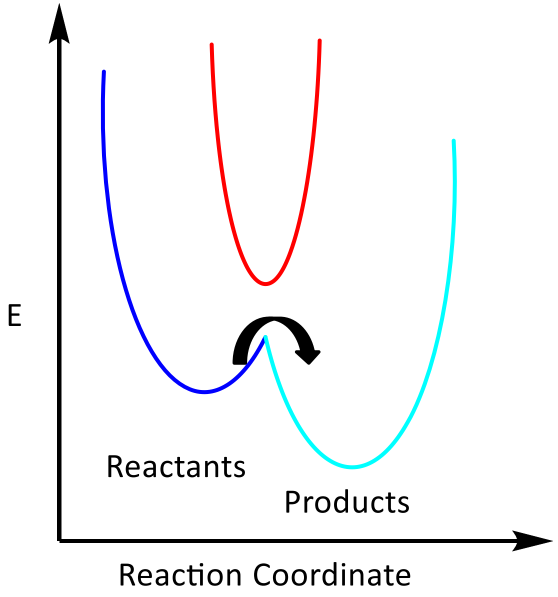
In History: A process in which an electron and a proton are transferred in a single kinetic step.

Most Current: A process in which an electron and a proton are transferred without regard for mechanism.

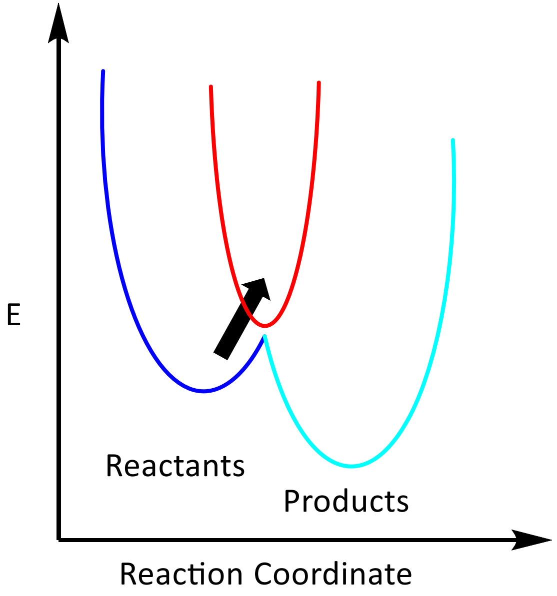
History:



Adiabatic or Nonadiabatic



Adiabatic



Non Adiabatic

Most Current:

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

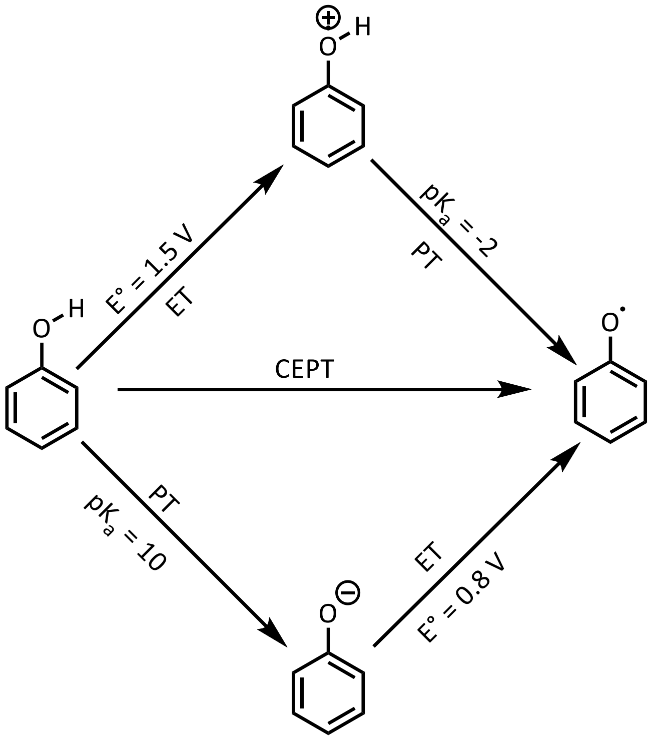
$$4H^+ + 4e^- \longrightarrow 2H_2$$

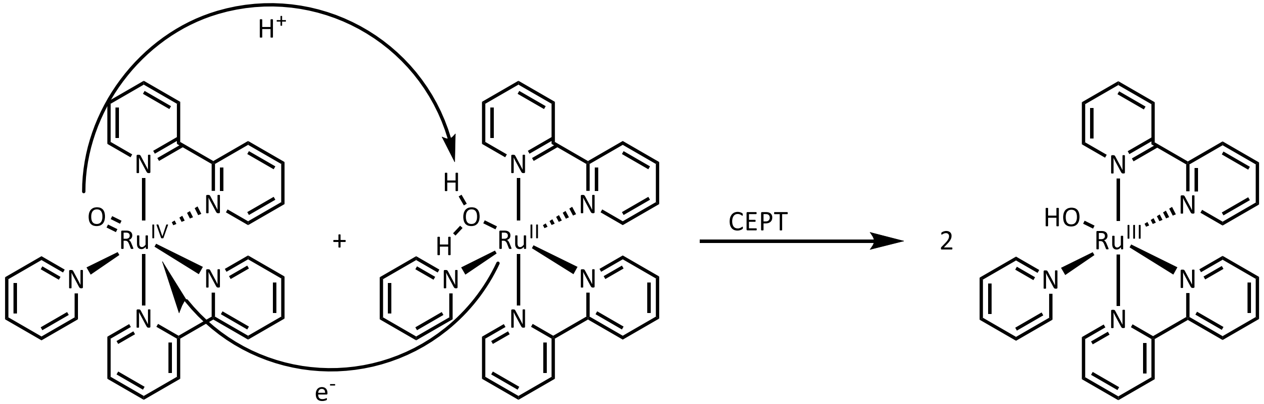
$$2H_2O \longrightarrow O_2 + 2H_2$$

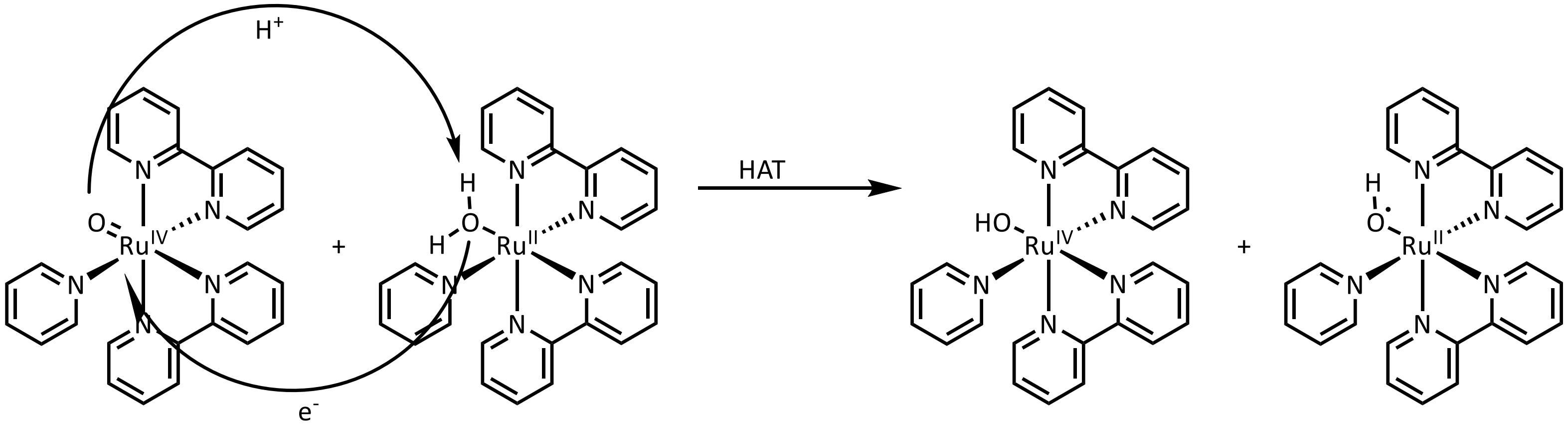
Moyer, B. A.; Meyer, T. J. J. Am. Chem. Soc. **1978**, *100*, 11, 3601–3603; *Binstead, R. A.; Moyer, B. A.; Samuels, G. J.; Meyer, T. J. J. Am. Chem. Soc.* **1981**, *103*, 10, 2897–2899; Bard, A. J.; Faulkner, L. R. Kinetics and Electrode Reactions. In Electrochemical Methods: Fundamentals and Applications, 2nd ed.; John Wiley & Sons, 2001; pp 130-131

The Elementary Steps

Electron Transfer (ET)
Proton Transfer (PT)
Concerted Electron-Proton Transfer (CEPT)
Hydrogen Atom Transfer (HAT)
Multi-Site Electron-Proton Transfer (MS-PCET)
Hydride Transfer (HT)







Tyburski, R.; Liu, T.; Glover, S. D.; Hammerström. J. Am. Chem. Soc. **2021**, *143*, 560–576. Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016-4093

Mathematical Description of ET

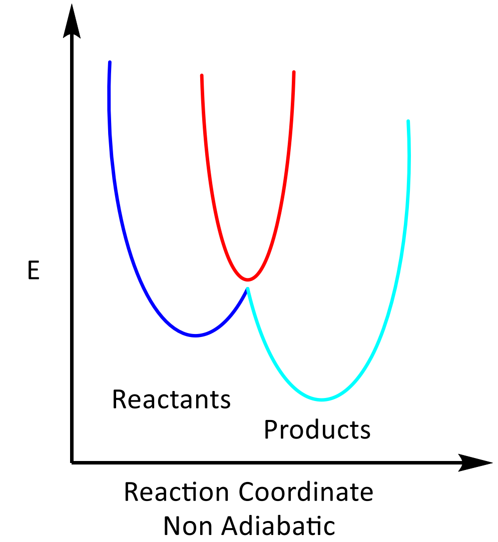
$$k_{ET} = v_{ET}(4\pi RT\lambda)^{-1/2} e^{-\left[\frac{(\Delta G_{ET}+\lambda)^2}{4\lambda RT}\right]}$$

Key Takeaways:

Exponent: The energy state required for electron transfer (intersection of reactant and product energy barriers)

Pre-exponential term: Classical density of states or the fraction of molecules at that energy

Therefore:
Rate is dependent on the number of molecules with the energy necessary to transfer an electron.



Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016-4093

Mathematical Description of CEPT

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

μ and ν = donor and acceptor vibrational states

P_{μ} = Boltzmann distribution of states for the reactants

V_{el} = electronic coupling constant

$S_{\mu\nu} r_{PT}$ = distance–dependent Franck–Condon overlap between reactant and product proton vibrational wavefunctions

r_{PT} = proton tunneling distance

Important Takeaways:

- Concerted electron-proton transfer is dependent on many factors.
    - Proton tunneling distance
    - Solvent
    - Temperature (discussed later)
    - Pressure (discussed later)
- The equation can be applied to explain the kinetic isotope effect of CEPT.
- This equation is for non-adiabatic CEPT. Adiabatic systems would be treated differently.

Tyburski, R.; Liu, T.; Glover, S. D.; Hammerström. *J. Am. Chem. Soc.* **2021**, *143*, 560–576

Temperature and Pressure Dependence

Dependencies can sometimes assist with determining if the mechanism is concerted.

Temperature Dependence:

Rate constant and KIE may change based on temperature, arising from:

$P_\mu =$
Boltzmann population of reactant proton vibrational states

$S_{\mu\nu}(r_{PT}) =$
Thermal distribution of proton tunneling distances

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

A change in pressure can have an impact on which mechanism is operative.

In certain cases, changes in pressure can be used to experimentally determine the mechanism.

Maxwell relation

$$A + B \rightleftharpoons C \qquad \frac{\Delta \ln K}{\Delta P} = -\frac{\Delta V}{RT}$$

$$\Delta V = V_C - (V_A + V_B)$$

$$A + B \rightleftharpoons [AB]^{\ddagger} \rightarrow C \qquad \frac{\Delta \ln k}{\Delta P} = -\frac{\Delta V^{\ddagger}}{RT}$$

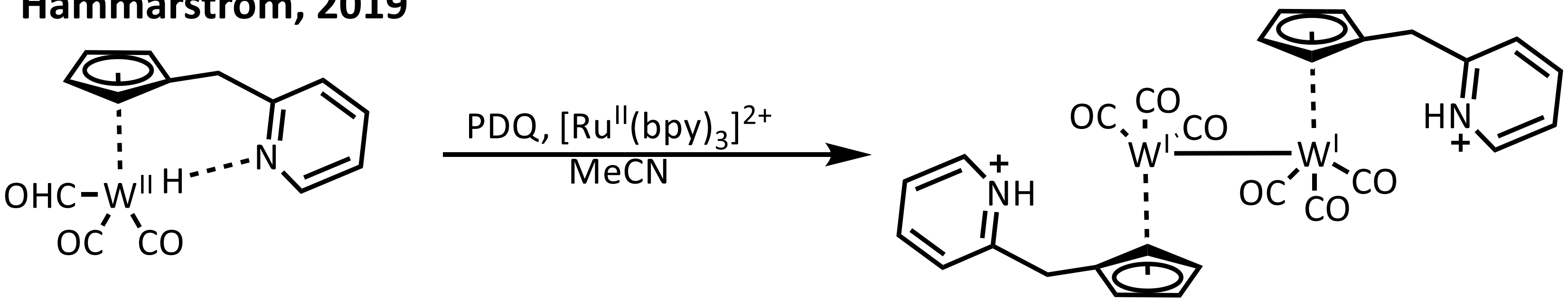
$$\Delta V = V_{[AB]^{\ddagger}} - (V_A + V_B)$$

$$k_{PCET} = k_{ETPT} + k_{PTET} + k_{CEPT}$$

Tyburski, R.; Liu, T.; Glover, S. D.; Hammerström. J. Am. Chem. Soc. **2021**, *143*, 560–576 Liu, T.; Tyburski, R.; Want, S.; Fernández-Terán, R.; Ott, S.; Hammarström. *J. Am. Chem. Soc.* **2019** *141*, 17245-17259

Pressure Dependent Mechanism Determination

Hammarström, 2019



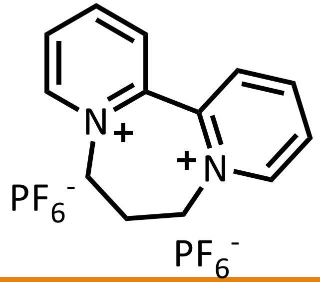
ETPT: initial decrease in charge decreases solvation($+\Delta V$)

CEPT: $\Delta V^{\ddagger} < \Delta V$.

PTET: initial increase in charge increases solvation($-\Delta V$)

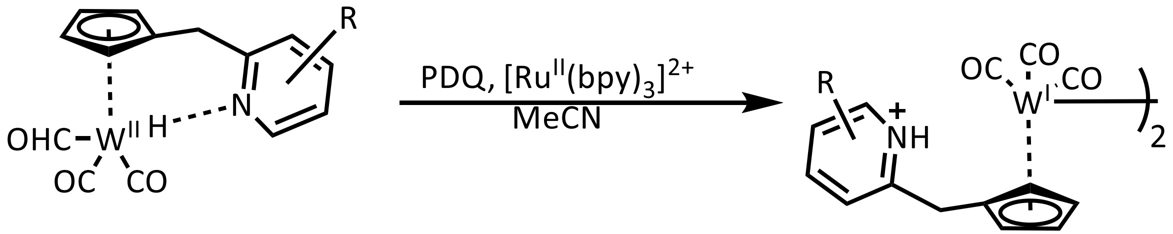
*An increase in pressure may increase tunneling in a CEPT mechanism and therefore the rate.

PDQ =



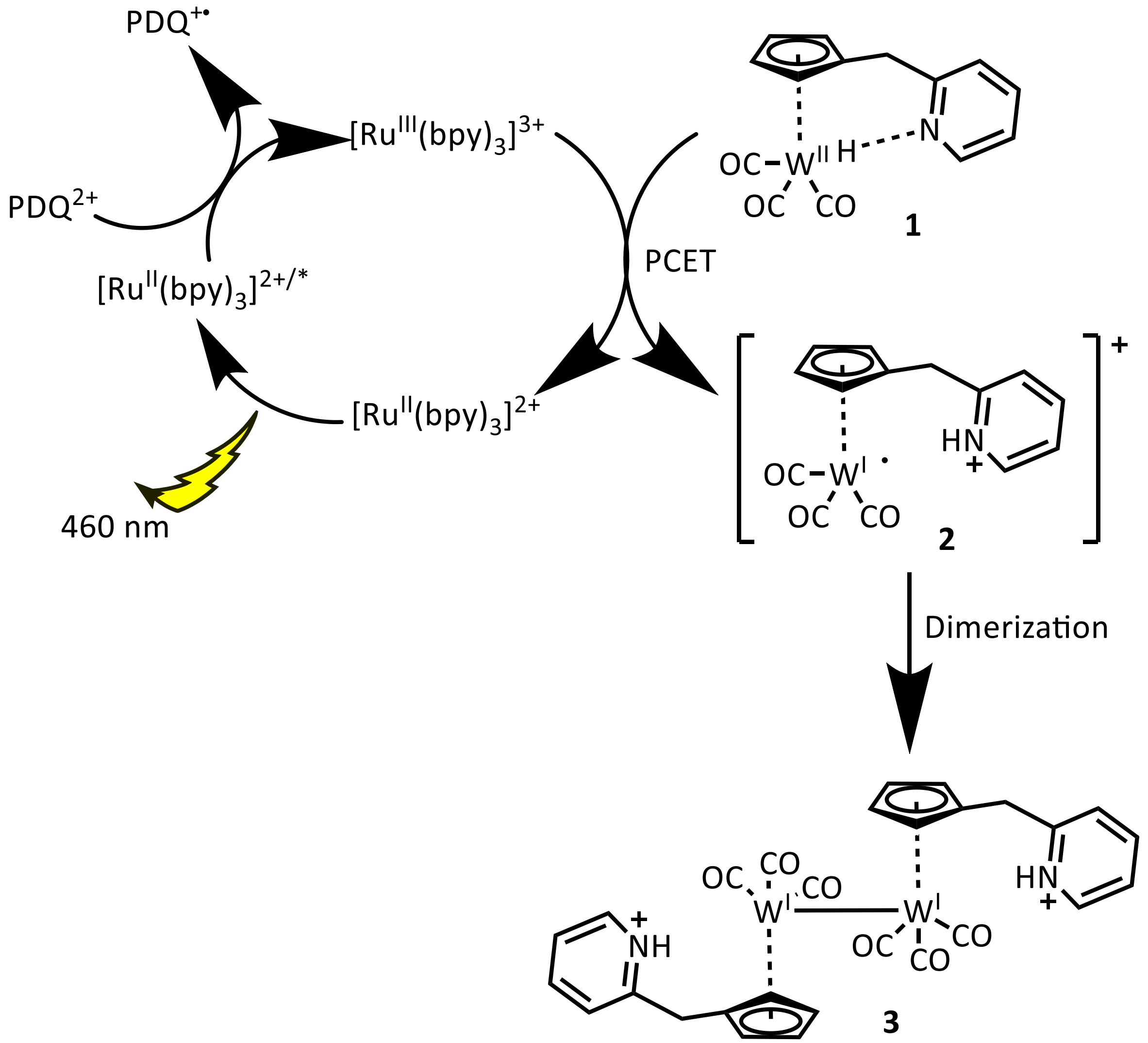
Liu, T.; Tyburski, R.; Want, S.; Fernández-Terán, R.; Ott, S.; Hammarström. *J. Am. Chem. Soc.* **2019** *141*, 17245-17259

Results of Mechanistic Analysis



R	$\Delta V^\ddagger$ (cm³/mol) W-H	$\Delta V^\ddagger$ (cm³/mol) W-D	KIE (1 bar)
3-CF_3	3.6	4.0	1.1
2-OMe	5.2	4.1	1.1
H	3.0	2.1	1.3
2-Me	-4.8	0.65	0.87
4-OMe	-0.54	-0.44	0.76

An increase in pressure resulted in a change in the KIE values.
All three mechanisms are attainable with variation of pressure.



Liu, T.; Tyburski, R.; Want, S.; Fernández-Terán, R.; Ott, S.; Hammarström. *J. Am. Chem. Soc.* **2019** *141*, 17245-17259

Applying the equations for CEPT mechanism determination

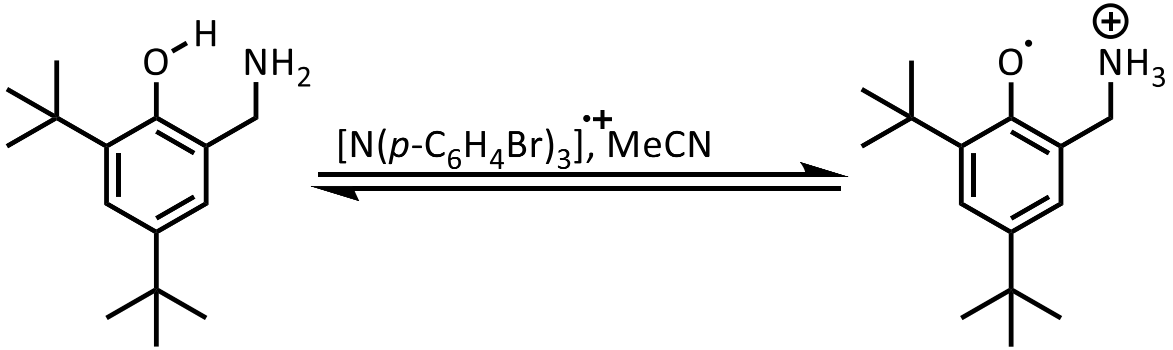
Issue 1:

An intermediate may or may not be present in non-concerted processes

Solution:

Thermodynamic calculations can be compared to experimental results

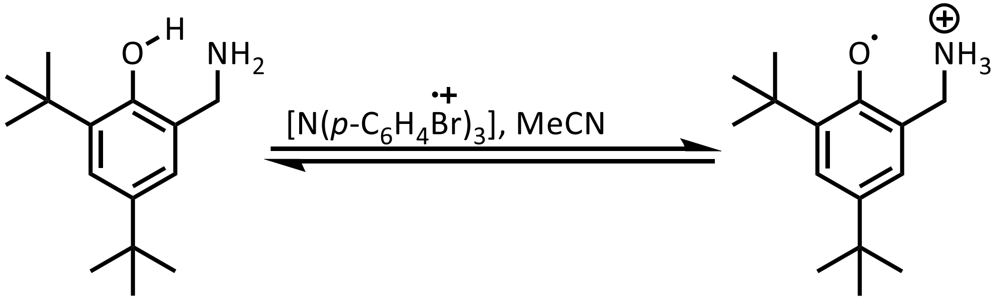
Ex. Previous studies observed fluorescence under UV irradiation



KIE = 1.6 – 2.8 with varying oxidant and phenol

Rhile, I. J.; Markle, T. F.; Nagao, H.; DiPasquale, A. G.; Lam, O. P.; Lockwood, M. A.; Rotter, K.; Mayer, J. M. *J. Am. Chem. Soc.* **2006**, 128, 18, 6075-6088

Complete Mechanism Analysis



Mechanism	E (V)	ΔG ($\mathrm{kcal\ mol^{-1}}$)	K ($\mathrm{M^{-1}\ s^{-1}}$)	k ($\mathrm{M^{-1}\ s^{-1}}$)
ETPT (calc.)	-0.71	16	10^{-12}	
ETPT (obs.)	-0.51	11		10^{5}
PTET (calc.)	N/A	N/A	10^{-4}	
PTET (obs.)	N/A	N/A		10^{-7}

$$\mathrm{K_{ET}} = \frac{\mathrm{k_{ET}}}{\mathrm{k_{-ET}}} \qquad \mathrm{K_{PT}} = \frac{\mathrm{k_{PT}}}{\mathrm{k_{ET}}}$$

ETPT observed rate implies $\mathrm{k_{-ET}} = 10^{17}\ \mathrm{M^{-1}\ s^{-1}}$
With $\mathrm{k_{-ET}}$ much larger than previously calculated diffusion limit in MeCN, ETPT is unlikely.
Similarly, PTET observed rate implies $\mathrm{k_{ET}} = 10^{11}\ \mathrm{M^{-1}\ s^{-1}}$ again larger than the calculated diffusion limit in MeCN, PTET is unlikely.

Determination of Mechanism (cont'd)

Issue 2:

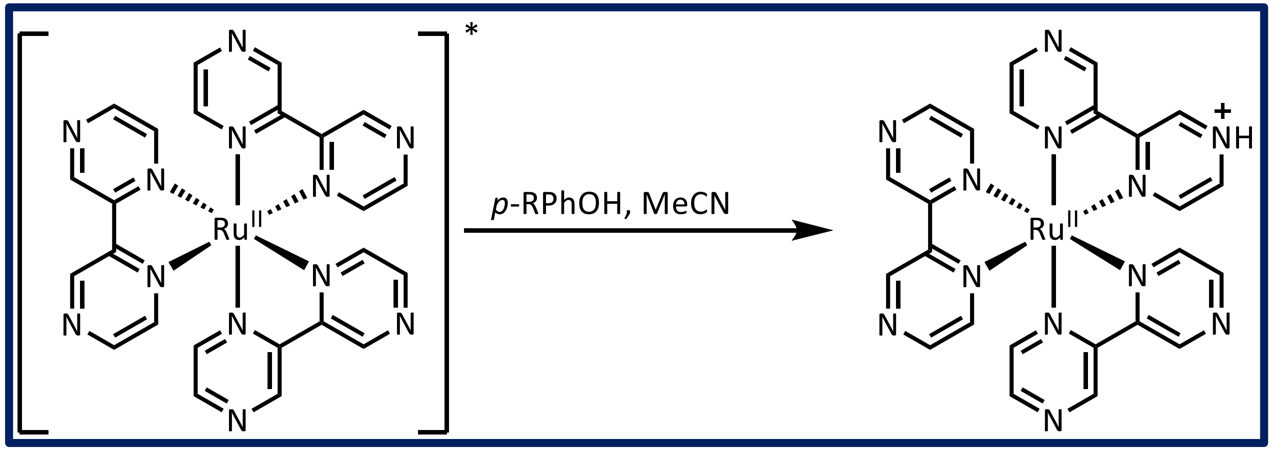
Many concerted mechanisms provide large KIE values, but if they don't, mechanism determination can become more difficult.

Solution:

Variation of the driving force combined with comparison to KIE.

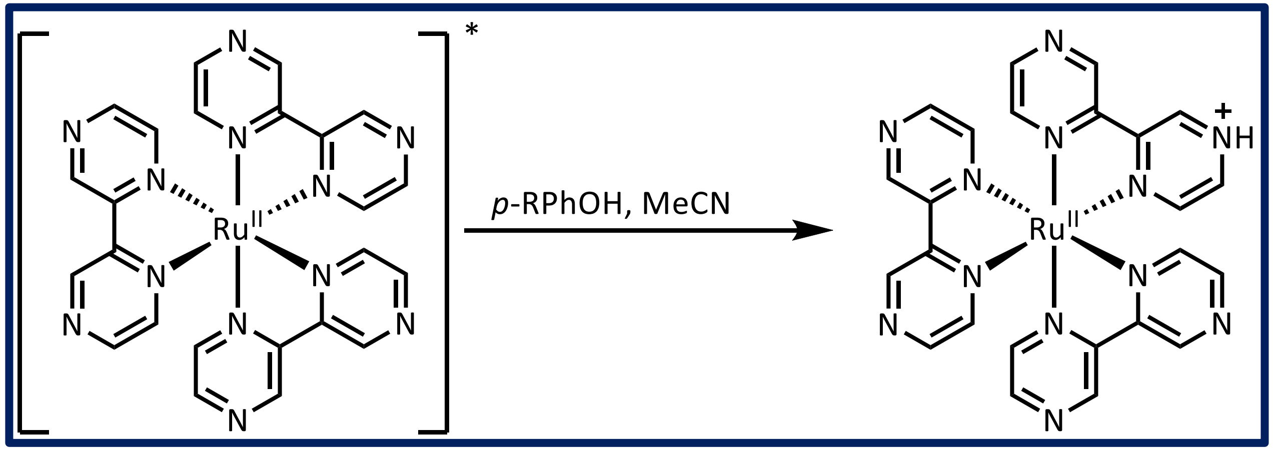
Driving force: the energy required to proceed from reactants to products (i.e. ΔG)

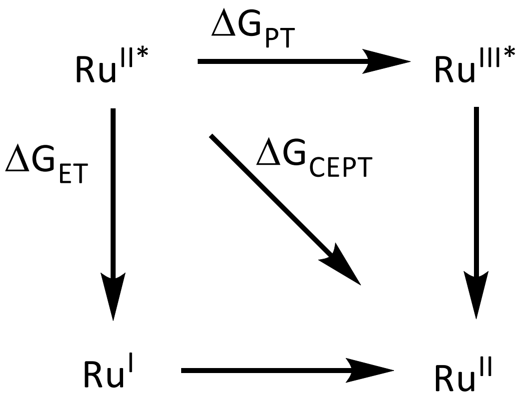
Ex. Similar to the previous example, luminescence was observed with these Ru complexes.



Sirimanne, C. T.; Kerrigan, M. M.; Martin, P. D.; Kanjolia, R. K.; Elliott, S. D.; Winter, C. H. *Inorg. Chem.* ***2015****, 54, 7,* 3680-3687. Bronner, C.; Wenger, O. S. *J. Phys. Chem. Lett.* **2012**, *3*, *1*, 70-74

Ruthenium Complex Quenching with Phenol





R	BDFE (kcal/mol)	$\Delta G_{ET,calc}$ (eV)	$\Delta G_{PT,calc}$ (eV)	$\Delta G_{CEPT,calc}$ (eV)	KIE
OMe	82.8	0.13	1.69	-0.06	1.03 ± 0.1
Me	86.3	0.24	1.68	0.15	1.66 ± 0.7
H	88.3	0.33	1.63	0.02	2.91 ± 0.3
Cl	88.3	0.33	1.56	-0.17	3.41 ± 0.4
Br	89.1	0.31	1.54	-0.05	7.75 ± 1.1
CN	92.7	0.48	1.35	-0.13	10.18 ± 0.1

In General:

$$\mathrm{KIE}_{\mathrm{ETPT}} \cong 1$$
$$1 \leq \mathrm{KIE}_{\mathrm{PTET}} \leq 2$$
$$\mathrm{KIE}_{\mathrm{CEPT}} > 1$$

Sirimanne, C. T.; Kerrigan, M. M.; Martin, P. D.; Kanjolia, R. K.; Elliott, S. D.; Winter, C. H. *Inorg. Chem.* ***2015****, 54, 7,* 3680-3687. Bronner, C.; Wenger, O. S. *J. Phys. Chem. Lett.* **2012**, *3*, *1*, 70-74

Driving Force Dependence

$$TyrOH + Os(bpy)_3^{3+} \xrightarrow[\text{phosphate buffer}]{\text{Indium Tin Oxide (ITO) electrodes}} Tyr\dot{O} + Os(bpy)_3^{2+}$$

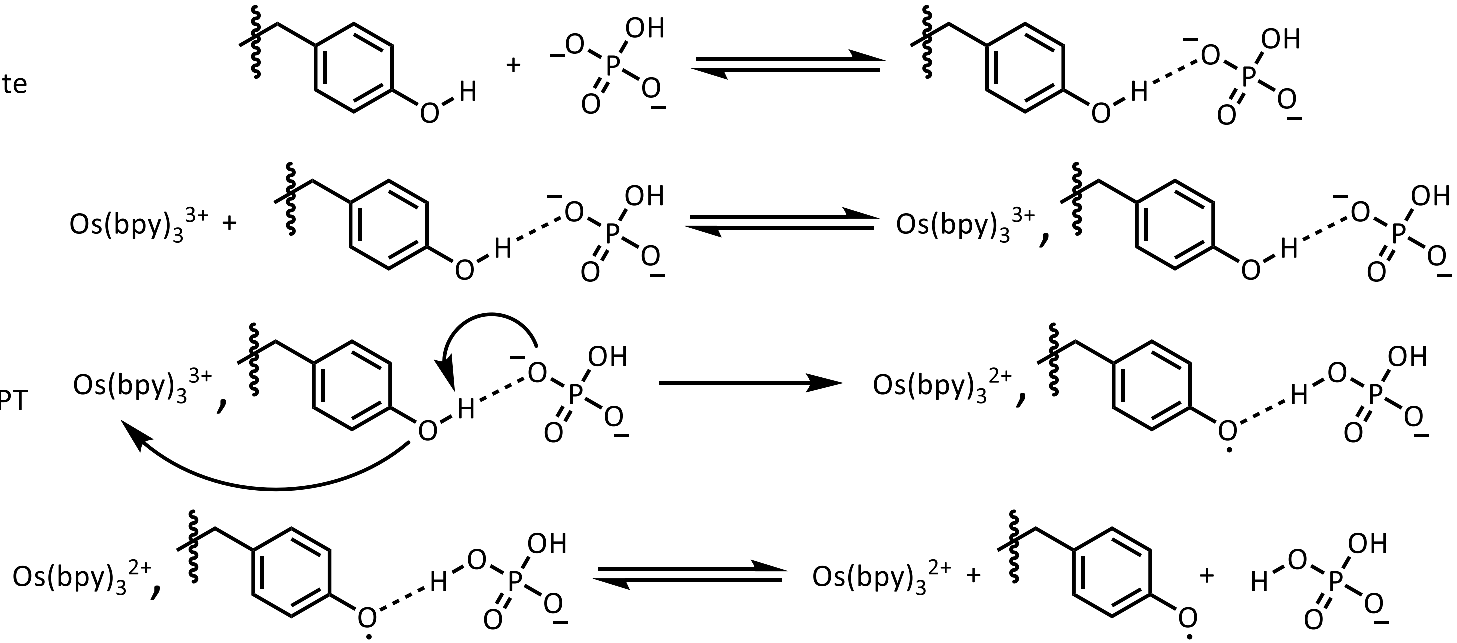
Changes in driving force can involve: strength of oxidant/reductant, acid/base, or the pH

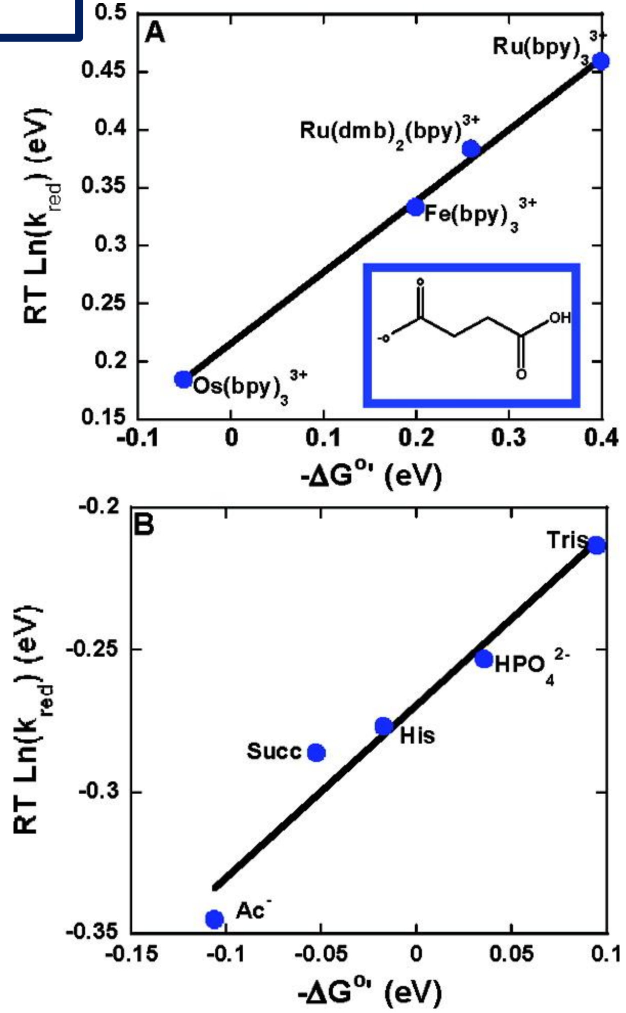
1) Hydrogen Bonding of phenol and phosphate

2)Interaction of Os catalyst to H-bond complex

3)PCET through MS-CEPT

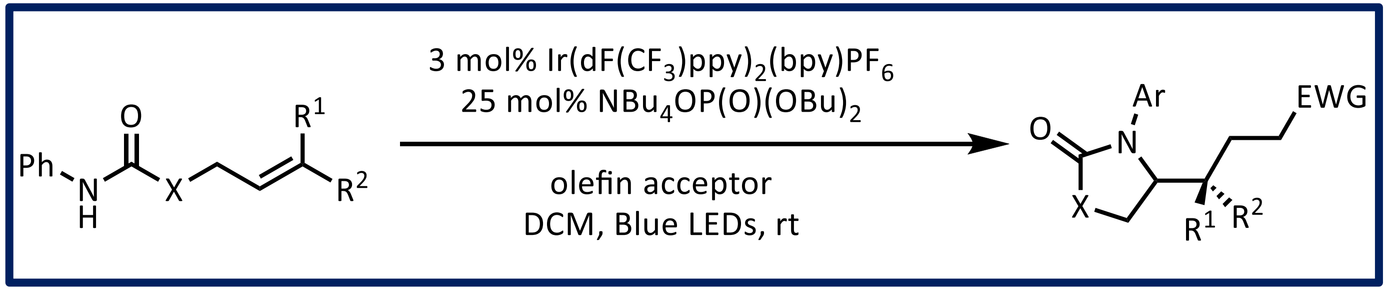
4)Release of all components

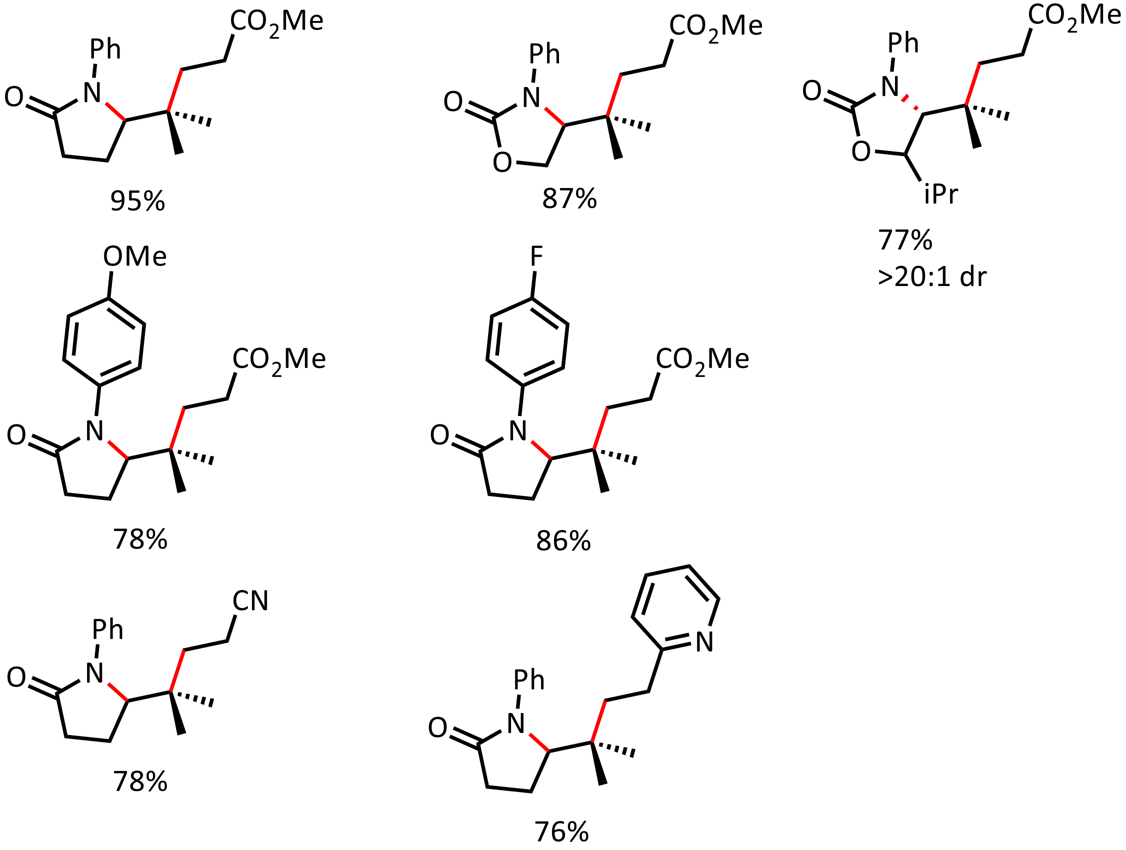




Fecenko, C. J.; Thorp, H. H.; Meyer, T. J. . *J. Am. Chem. Soc.* **2007** *129*, 15098-15099 Reused with permissions from ACS

Nitrogen Radical: Carboamination

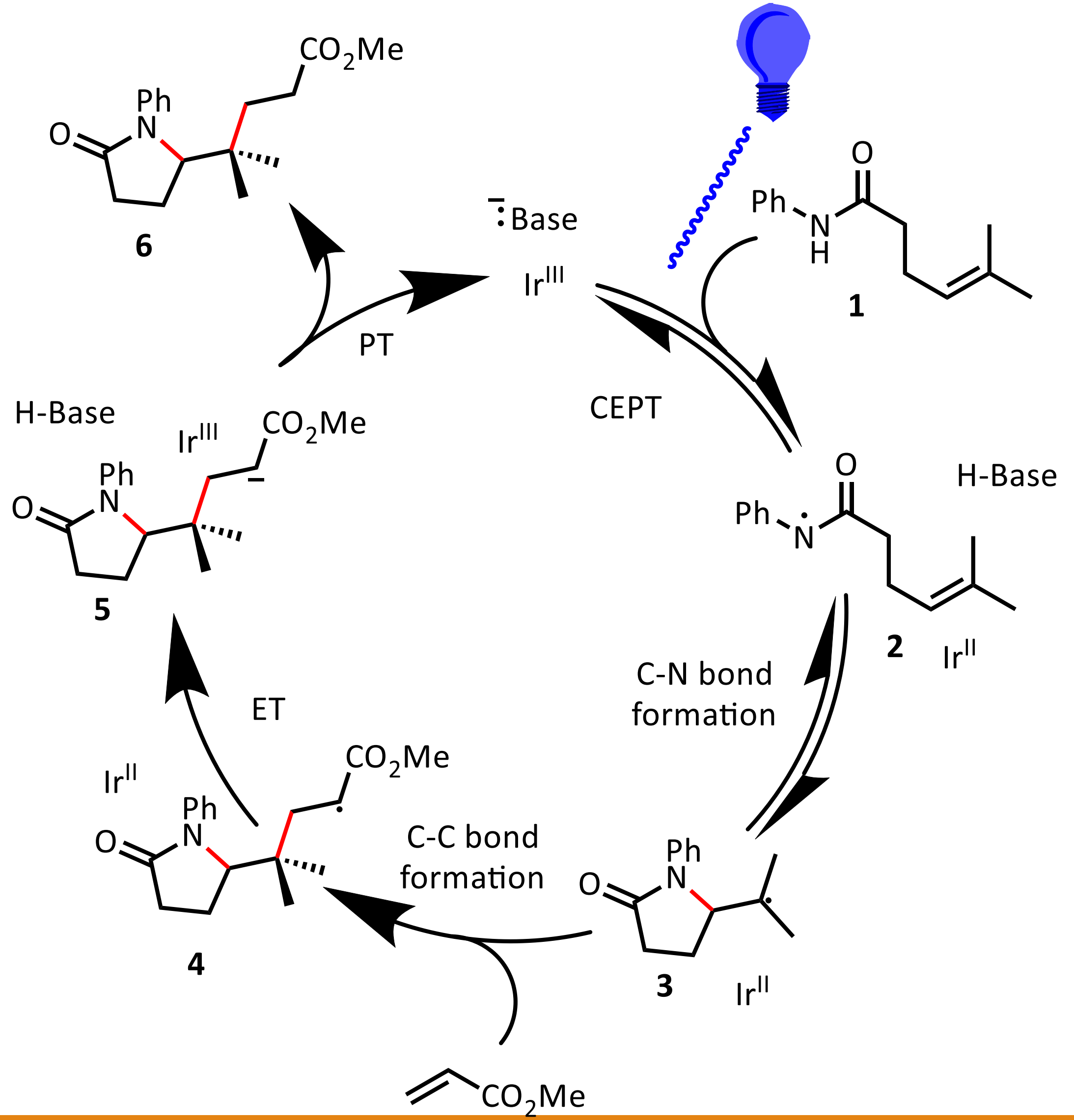




N-H bonds have hydrogen bond properties that could be utilized to decrease the tunneling distances required for PCET reactions.

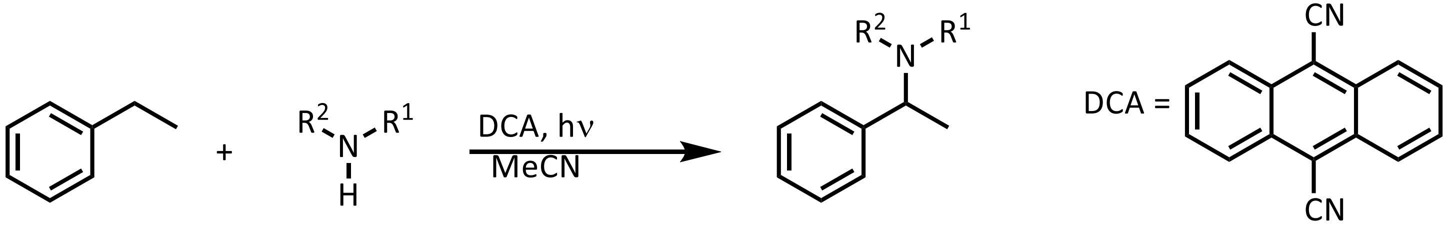
Choi, G. J.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226-9229

Carboamination Mechanistic Analysis



1) Stern-Volmer analysis indicated only acetanilide fluorescently quenching the Iridium catalyst.
2) Observed KIE = 1.15 ± 0.04
   - Mechanism is likely PTET or CEPT
3) $\Delta \mathrm{pK_a}$ ~ 20 between the amide and phosphate
   - PTET is unlikely

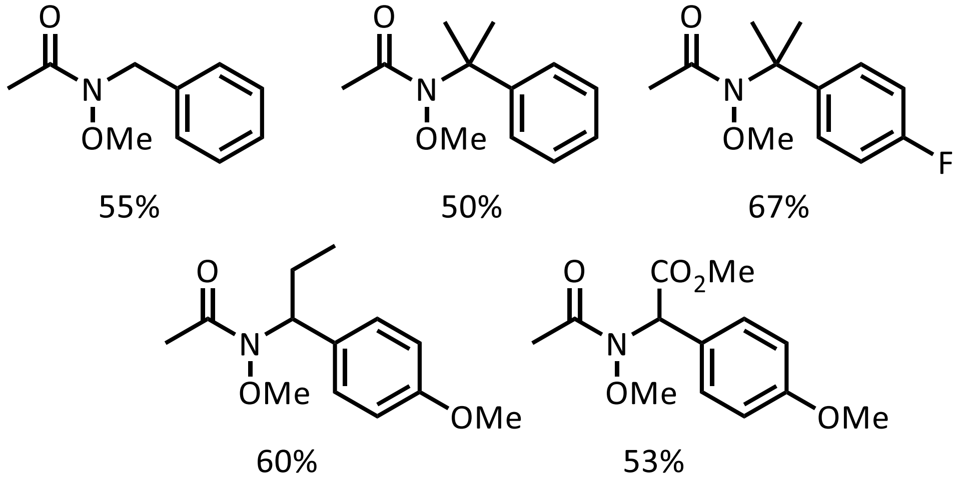
Organic Photocatalysis



PCET reactions are also able to perform in the presence of organic photocatalysts.

Previously: 1,4-dicyanonaphthalene C-O bond formation conditions failed when C-N bond formation was attempted

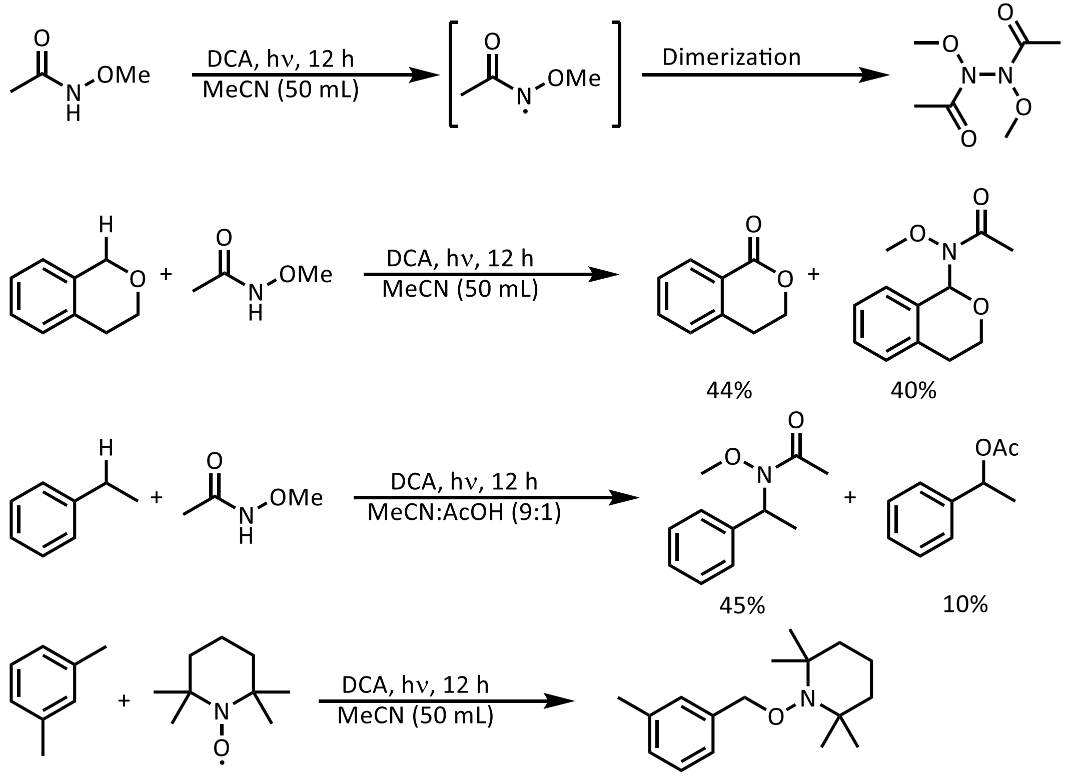
Hypothesis: Induction of the radical using N-methoxyacetamide may prevent the competing electron-transfer that was observed.

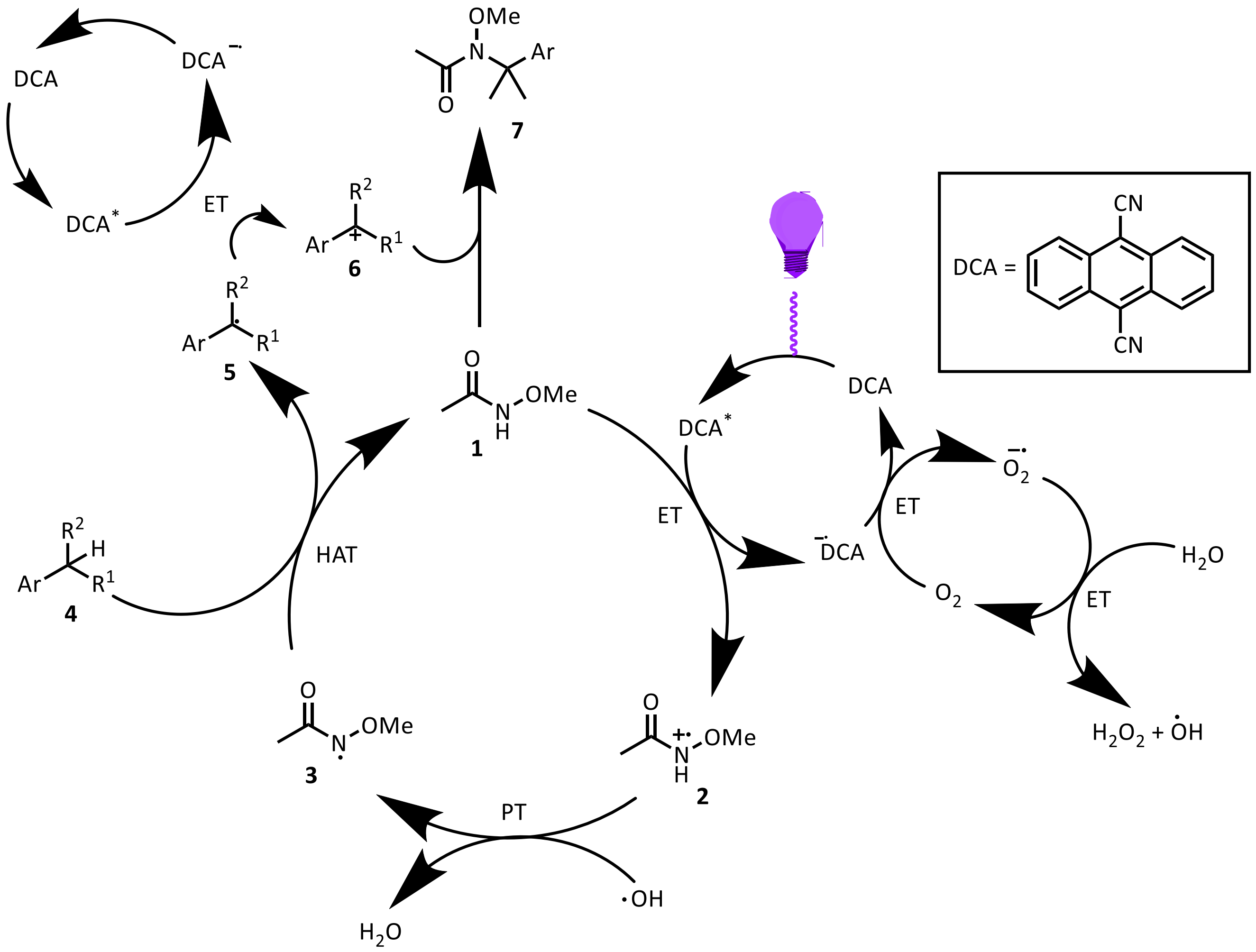


Photocatalytic Mechansim

Product and Side Product Mechanistic Studies:

i) Acetamide dimerization
ii) Radical trapping
iii) Radical trapping
iv) TEMPO Radical Trapping

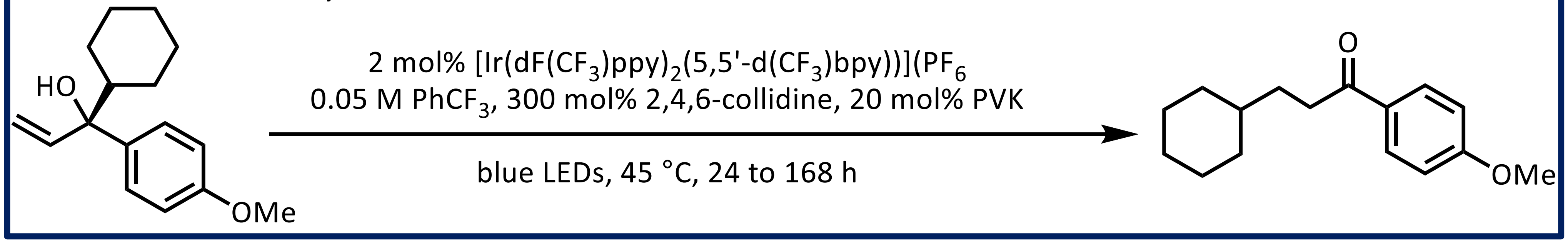




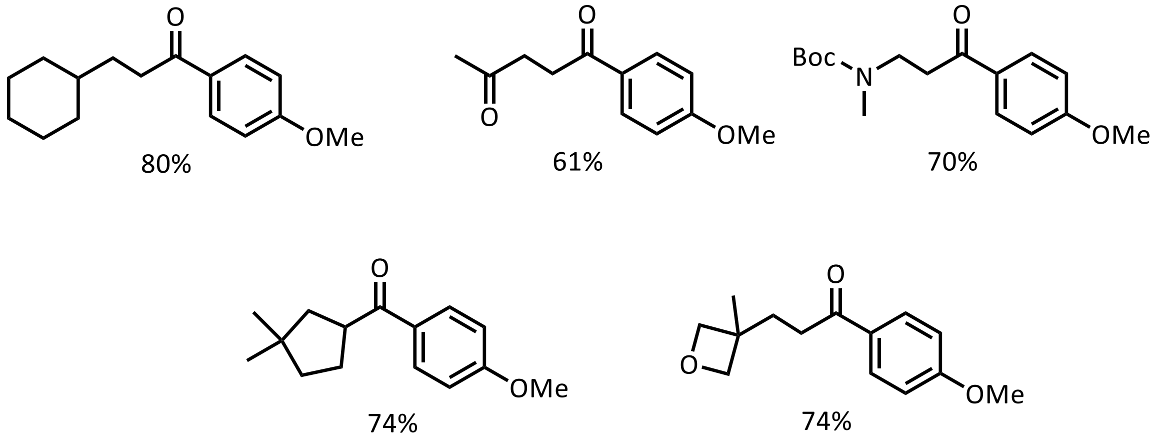
Pandey, G.; Laha, R. *Angew. Chem. Int. Ed.* **2015** *54*, 14875-14879

Oxygen Radical: 1,3-alkyl Transposition

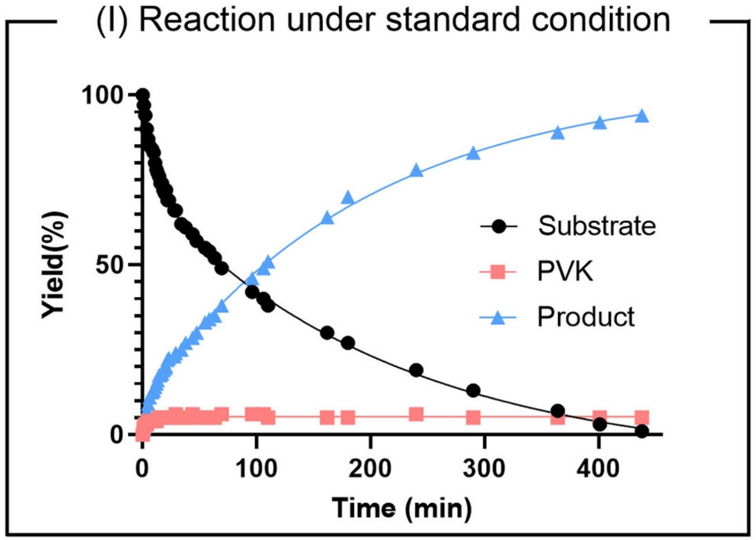
Knowles, 2021

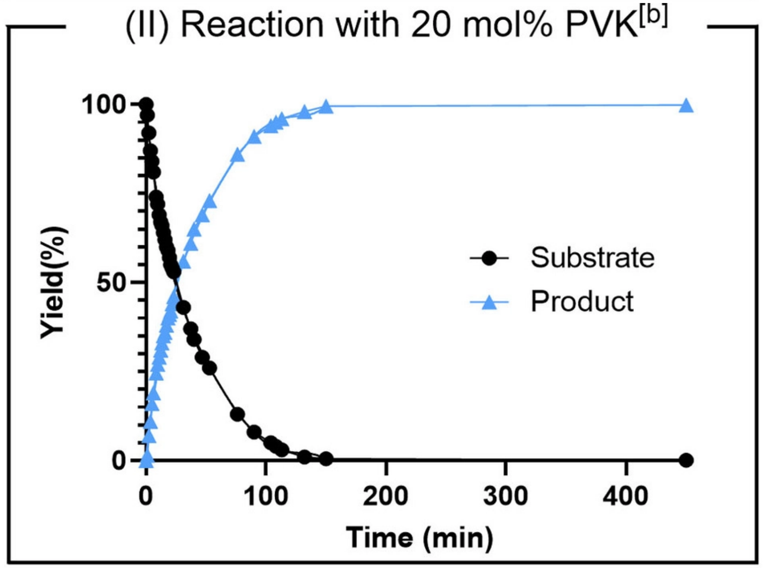


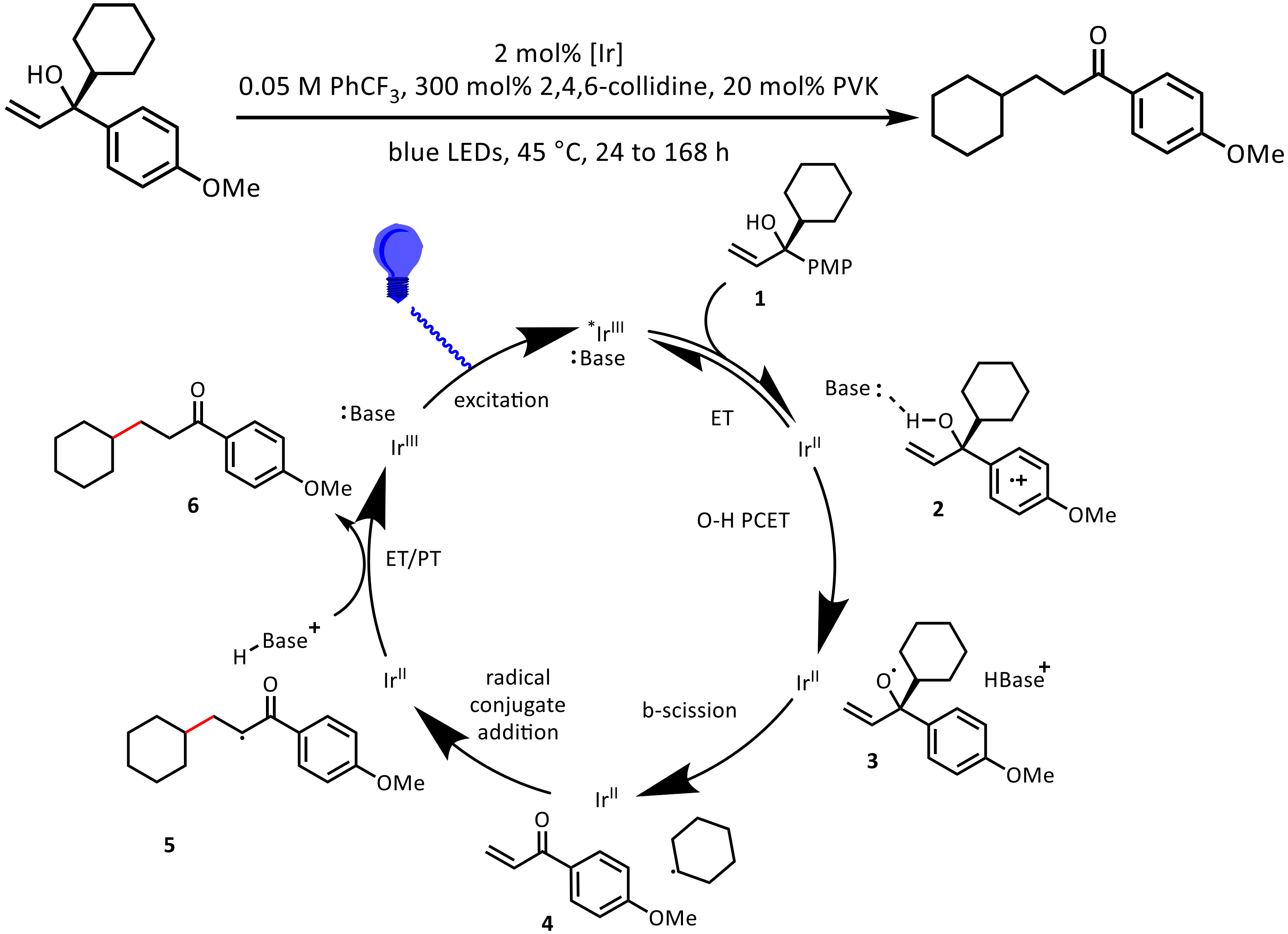
Previous work from the Knowles group had shown oxygen centered radicals in PCET reactions.
Initial yields were generally below 50% likely due to a reduced and inactive state of the catalyst.
Crossover experiments with an external olefin acceptor resulted in recovery of *p*-methoxy vinyl ketone.



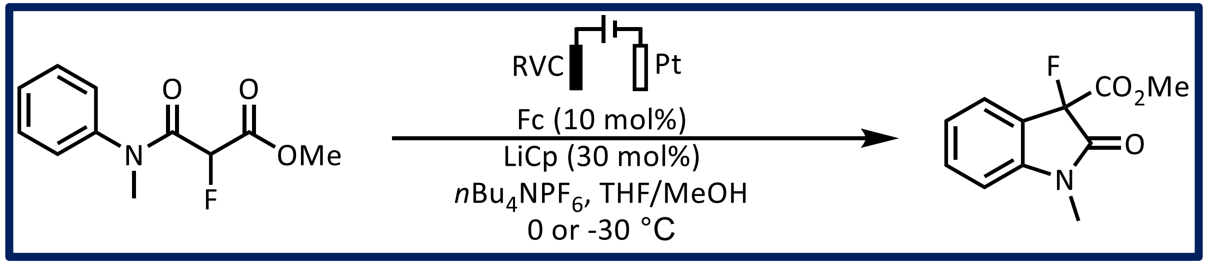
1,3-alkyl Transposition Mechanism





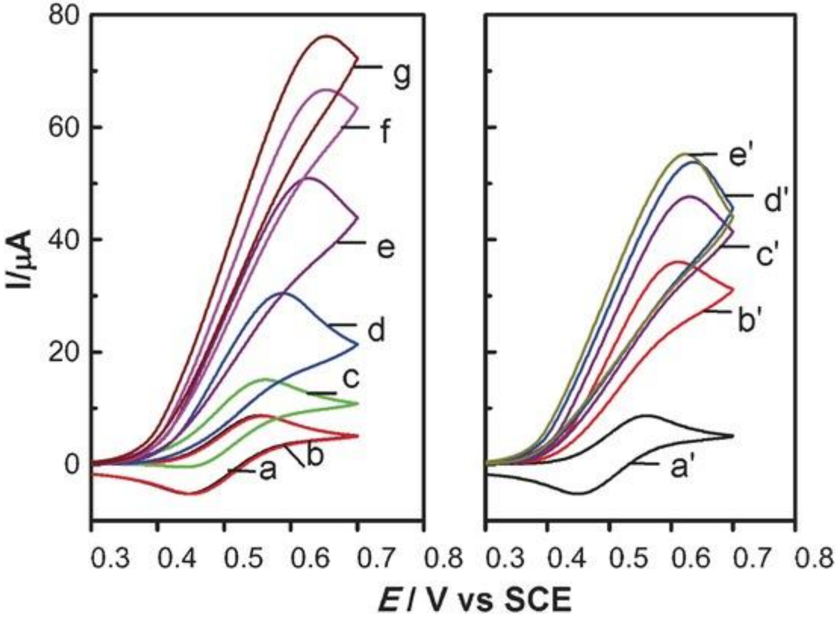


Electrochemical Oxygen Radical Formation



Similar reactions have been observed with strong oxidants.

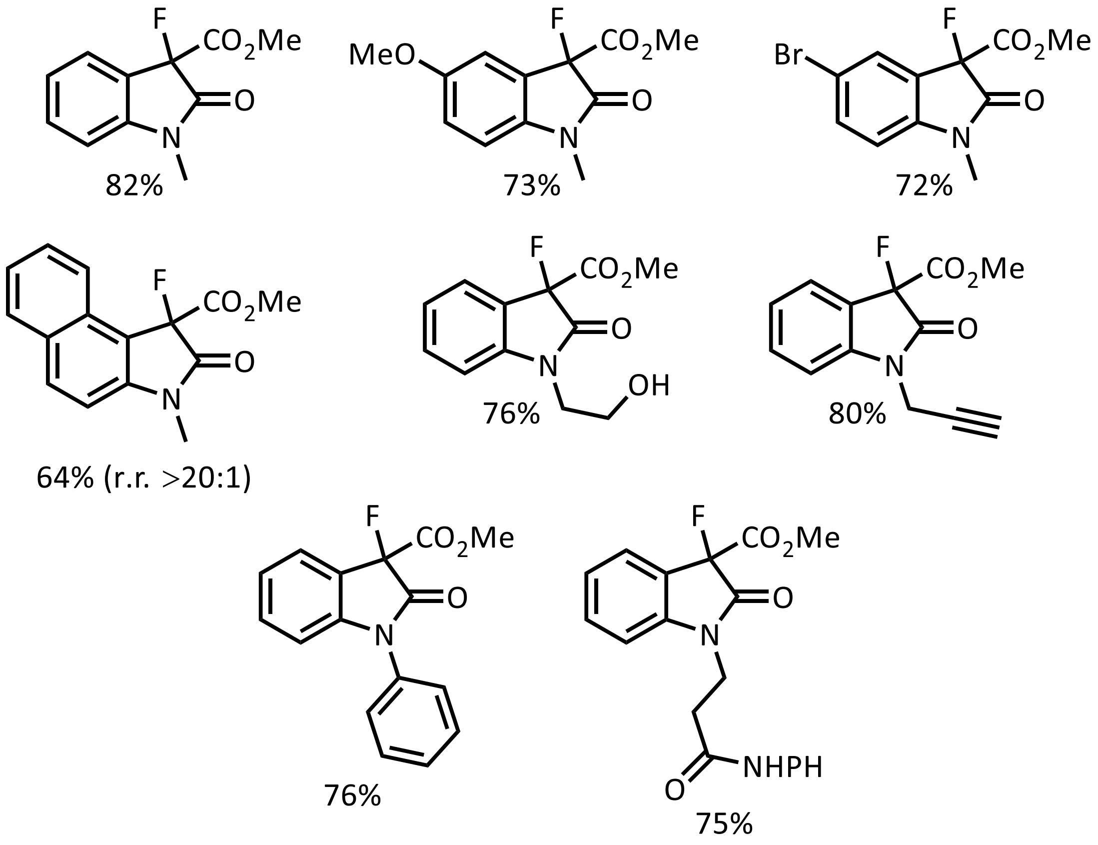
	Conditions
a	No LiCp or β-amido ester present
b	36 mM β-amido ester
c	b + 72 mM LiCp
d	b + 18 mM LiOMe
e	b + 36 mM LiOMe
f	b + 72 mM LiOMe
g	b + 108 mM LiOMe

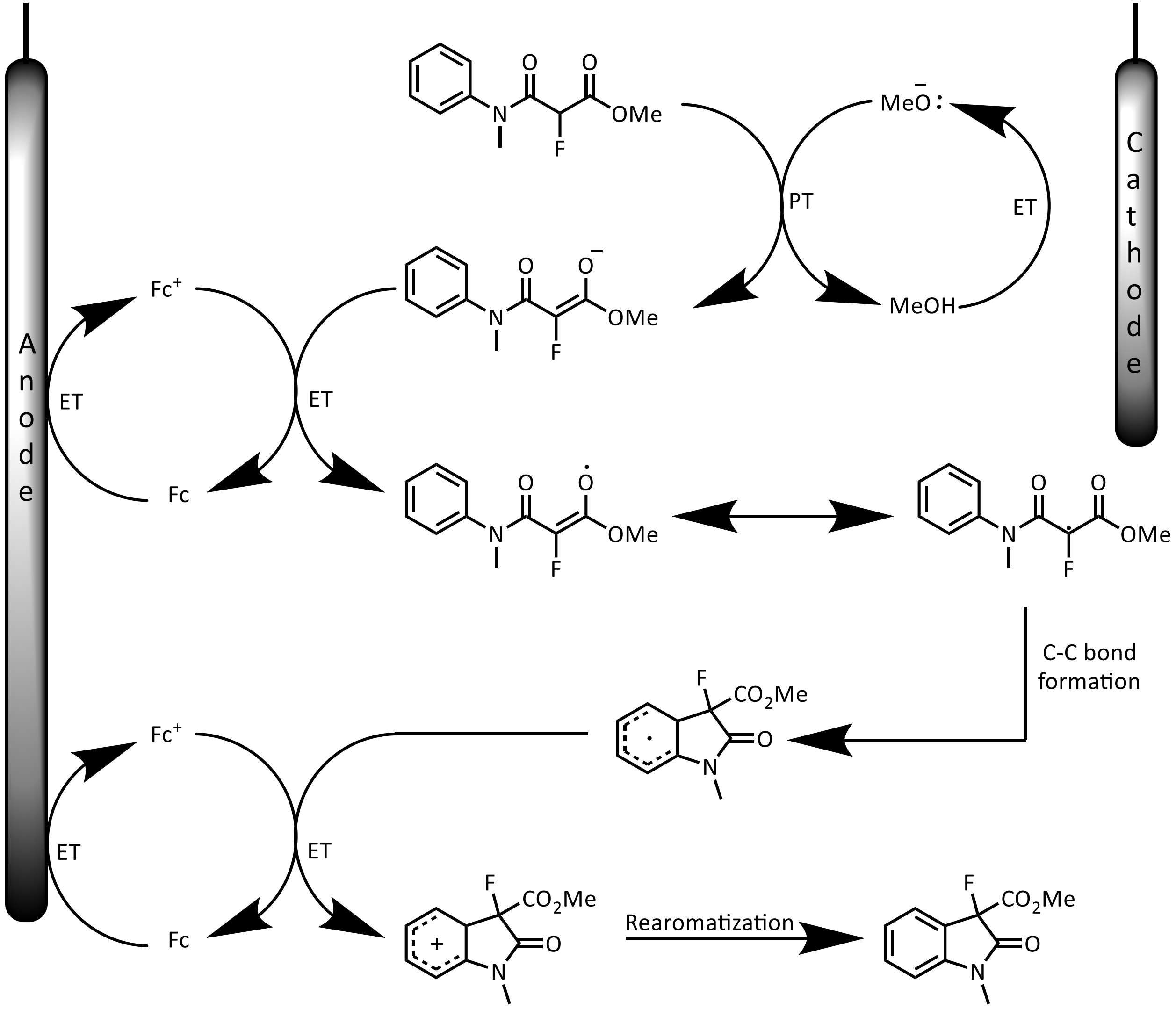


	Conditions
a’	No LiCp or β-amido ester present
b’	36 mM LiOMe 18 mM β-amido ester
c’	36 mM LiOMe 36 mM β-amido ester
d’	36 mM LiOMe 72 mM β-amido ester
e’	36 mM LiOMe 108 mM β-amido ester

Wu, Z.-J. Xu, H.-C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4734-4738 Reused with permissions from Wiley

Electrochemical Mechanism

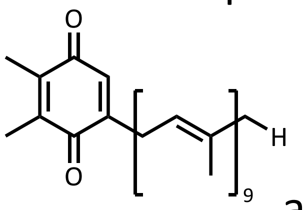


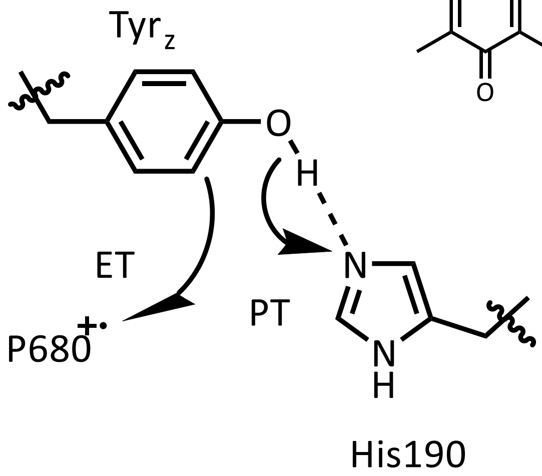


Biological Applications: Photosystem II

20 subunits for a total of 700 kDa in cyanobacteria
Multiple reactions occur for the complete oxidation of water.

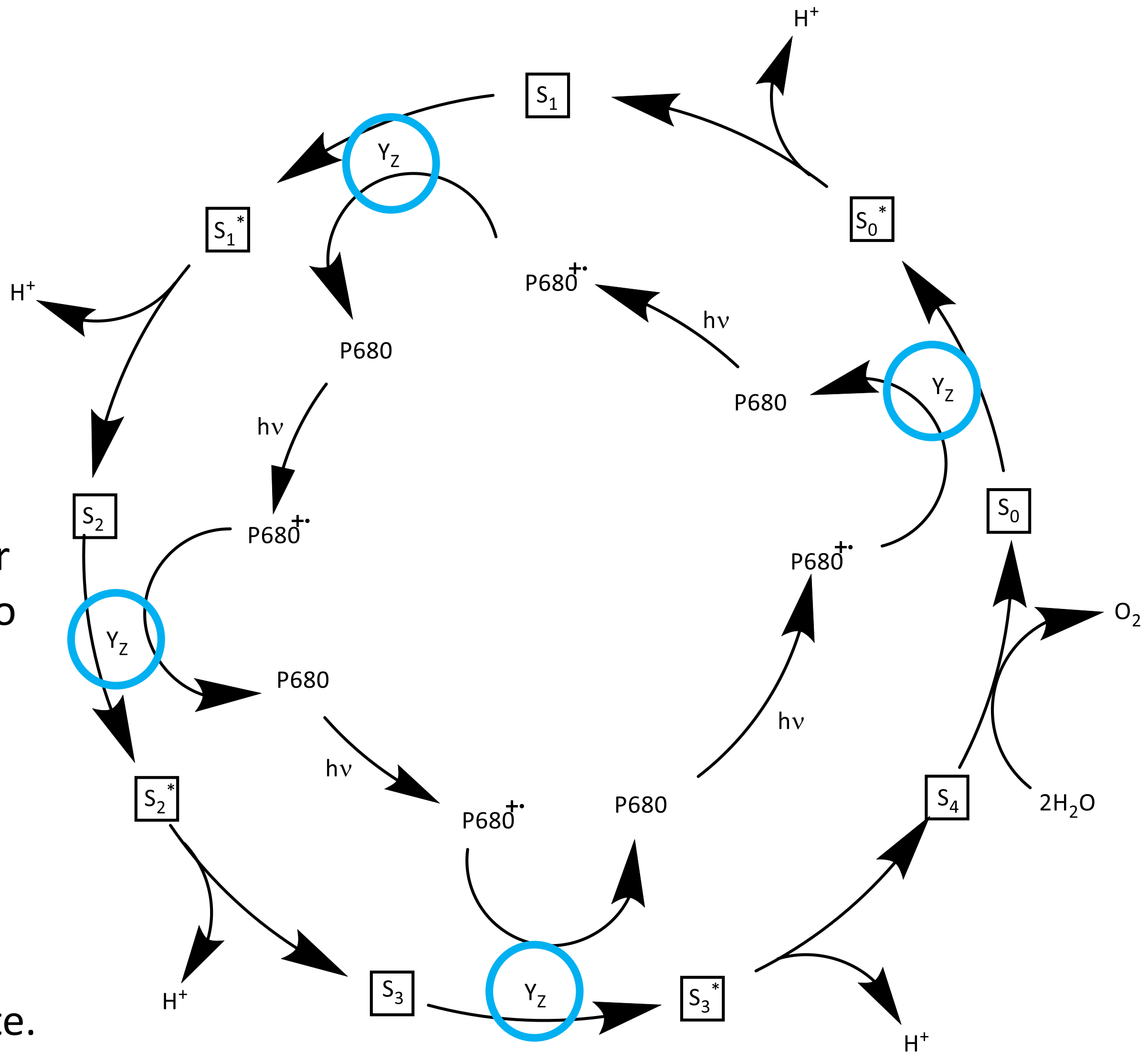
1) Light induced radical formation (green/blue)
2) PCET splitting of oxygen (red)
3) Quenching of the cation with plastoquinone (brown/purple)





Multi-Site PCET (MS-PCET) assists in the splitting of water in chlorophyl Photosystem II to produce oxygen.

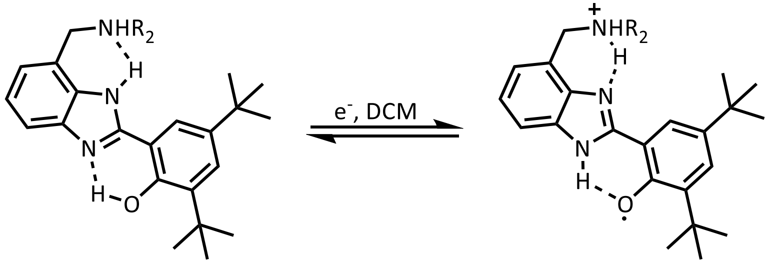
The metal cluster changes shape throughout the process of water oxidation.



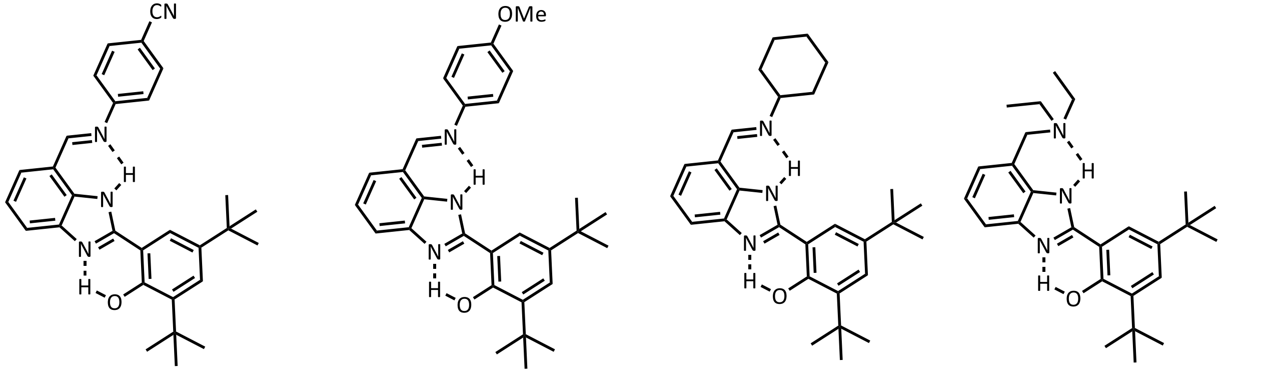
P680 is the structure of the chlorophylls that surround the active site.

Renger, G. *Biochimica et Biophysica Acta.* ***2012***, *1817, 8, 1164-1176*
Shen, J.-R. Annu. Rev. Plant Biol. ***2015***, *66, 23-48*

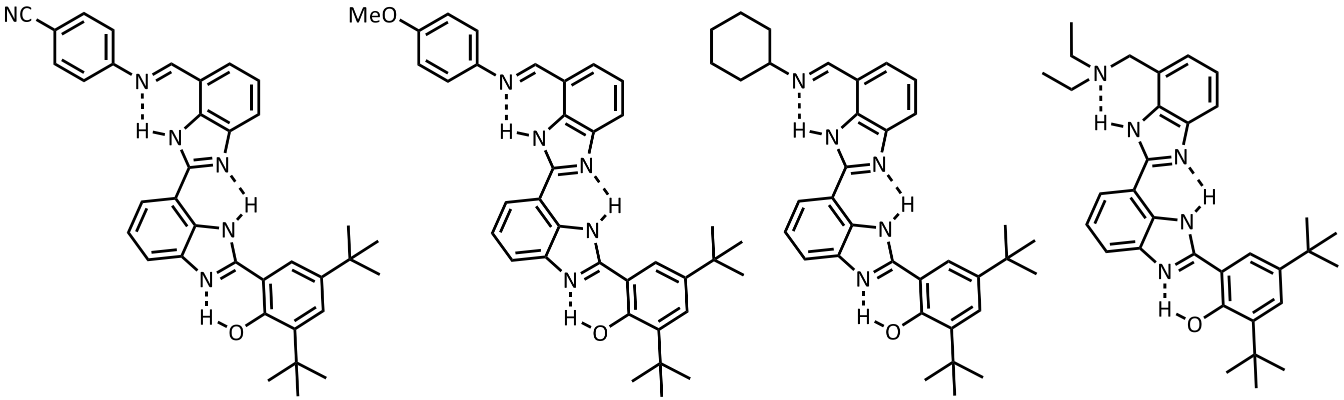
Using Photosystem II as a Model



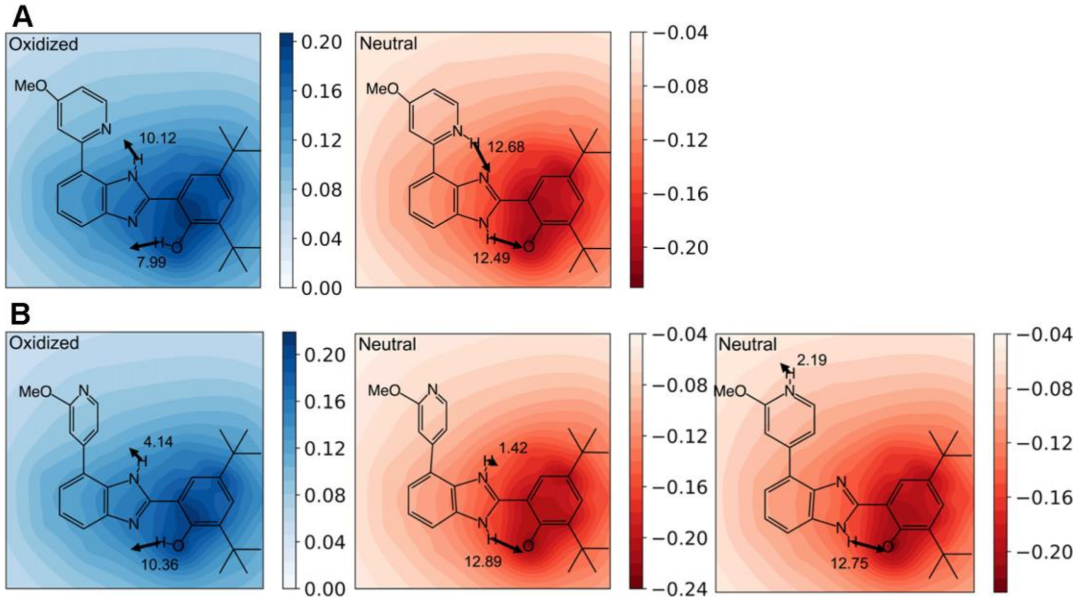
E2PT Substrates



E3PT Substrates



Multi-proton coupled electron transfer could be used for energy transfer.
Tyrosine-like and histidine-like residues proceed through similar mechanisms to photosystem II.



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Further Discussion of PCET

Today

- Physical analysis of PCET mechanism determination
- Samples of organic applications
- Biological and material applications

Further Explanation

- Carbon centered radical reactions
- Metal-free conditions

Recommended Reading

- Photochemical and Electrochemical Applications of Proton-Coupled Electron Transfer in Organic Synthesis (Citation Below)

Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Boos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. *Chem. Rev*. **2022**, *122*, 2017-2291