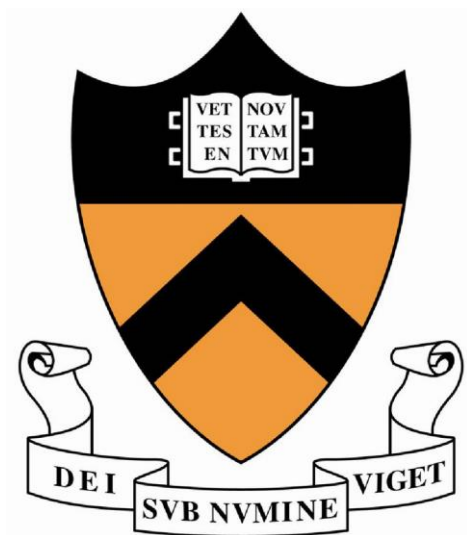


Mechanistic Understanding of Proton-Coupled Electron Transfer and Deracemization



Guanqi Qiu, PhD

Research Talk

Nov 12, 2021

About Me

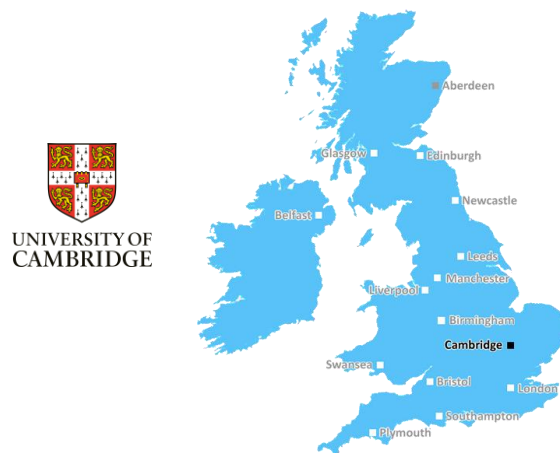
bis 2008



High school



B.A (Oct 2012 – Jun 2015)



Ph.D Sep 2016 – Jun 2021



Research in the Knowles Lab



Robert R. Knowles, Ph.D.

Doctor of Philosophy, California Institute of Technology
Advisor: David MacMillan (July 2003 – Oct. 2008)

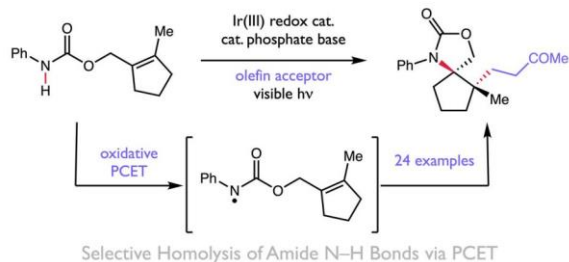
NIH NRSA Postdoctoral Fellow, Harvard University
Advisor: Eric Jacobsen (Dec. 2008 – June 2011)

Assistant Professor of Chemistry, Princeton University
(July 2011 – Mar. 2017)

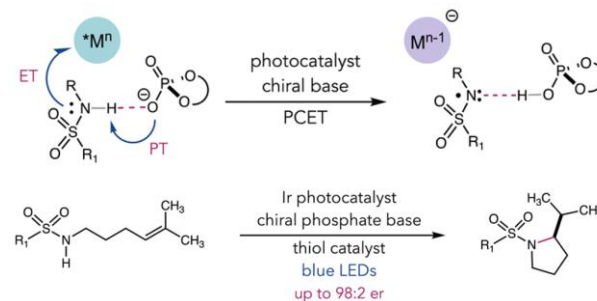
Professor of Chemistry, Princeton University
(Mar. 2017 – present)

Research in the Knowles Lab

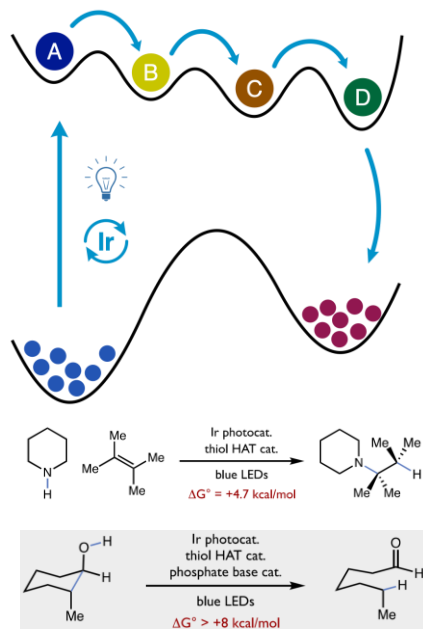
Organic Synthesis Enabled by Proton-Coupled Electron Transfer



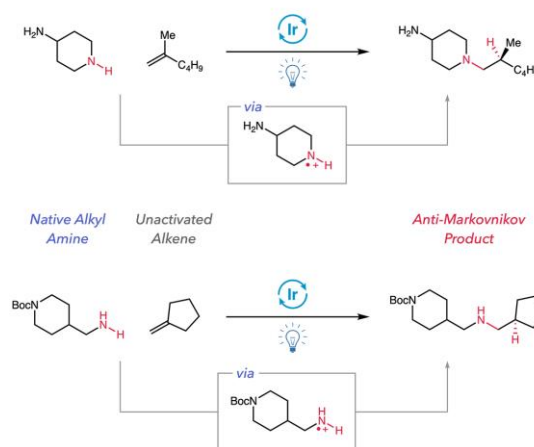
ASYMMETRIC CATALYSIS VIA RADICAL INTERMEDIATES



OUT-OF-EQUILIBRIUM TRANSFORMATIONS

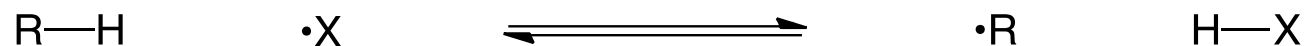


RADICAL METHODS FOR OLEFIN HYDROAMINATION

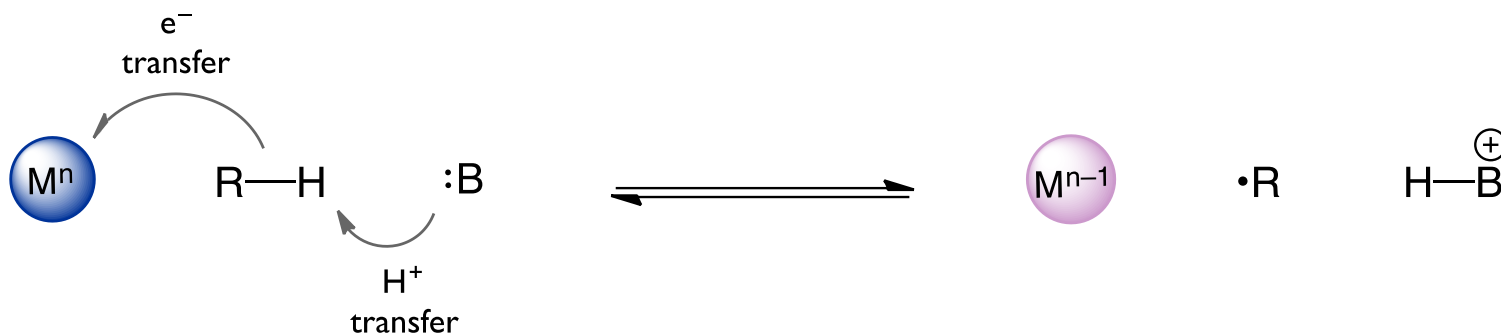


Mechanisms for Homolytic Bond Activation

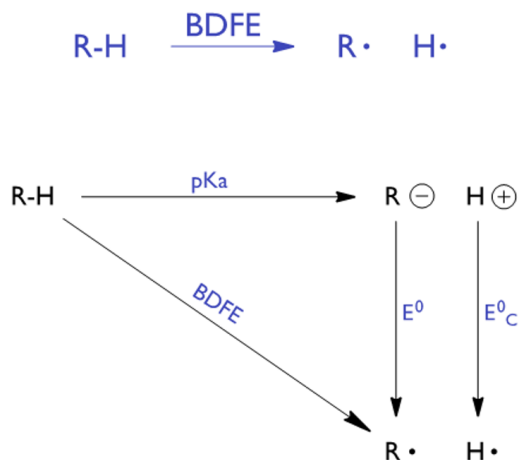
Hydrogen atom transfer (HAT)



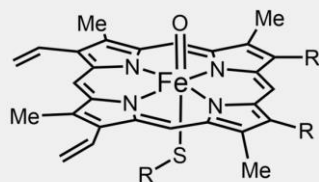
Proton-coupled electron transfer (PCET)



Challenges in Expanding Catalysis of Hydrogen Atom Transfer



Bordwell, F.G. *Acc. Chem. Res.* **1993**, 26, 510

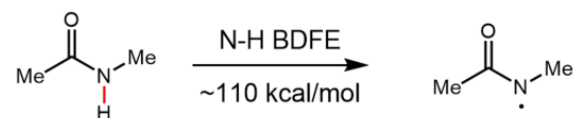
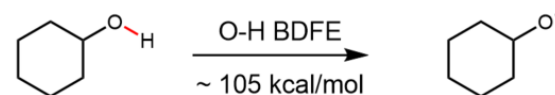
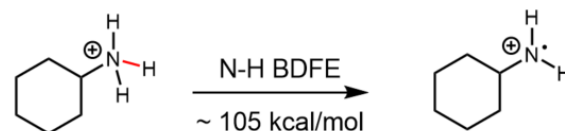


cytochrome P450

O-H (red. form) ~ 98 kcal/mol

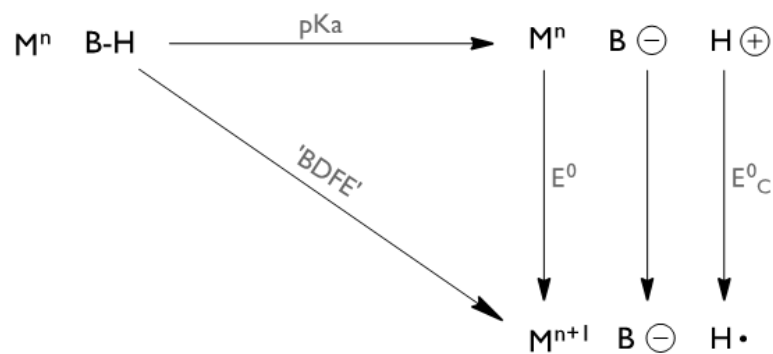
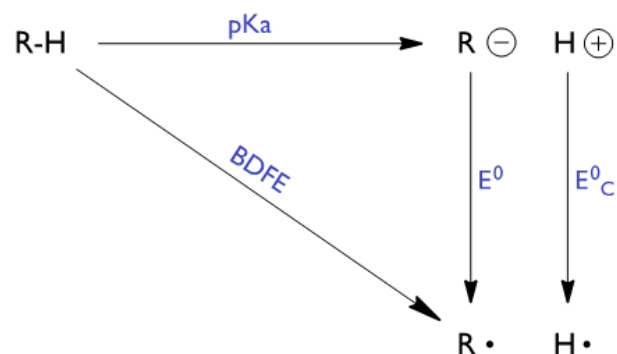
Green, M. T. *Science* **2004**, 304, 1653

Oxidative HAT



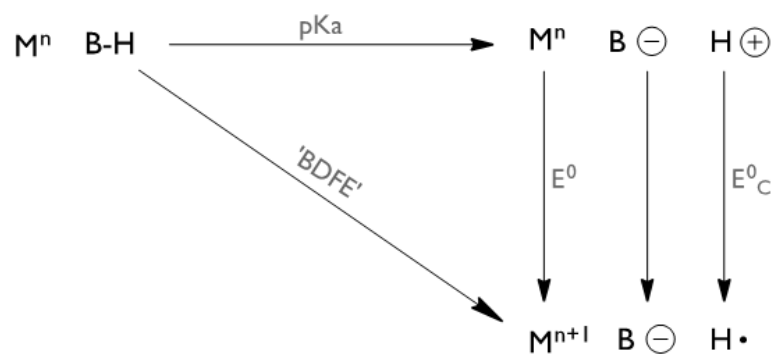
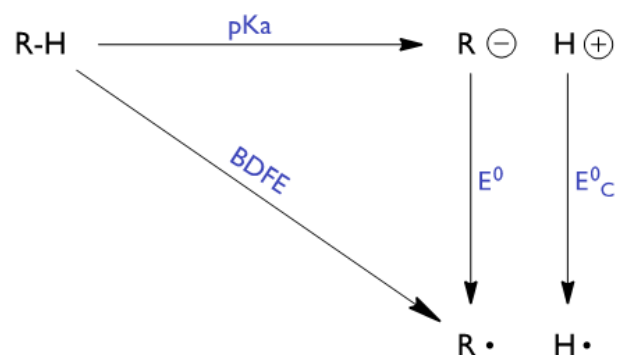
How can we homolytically activate stronger bonds?

Thermodynamic Modularity of PCET



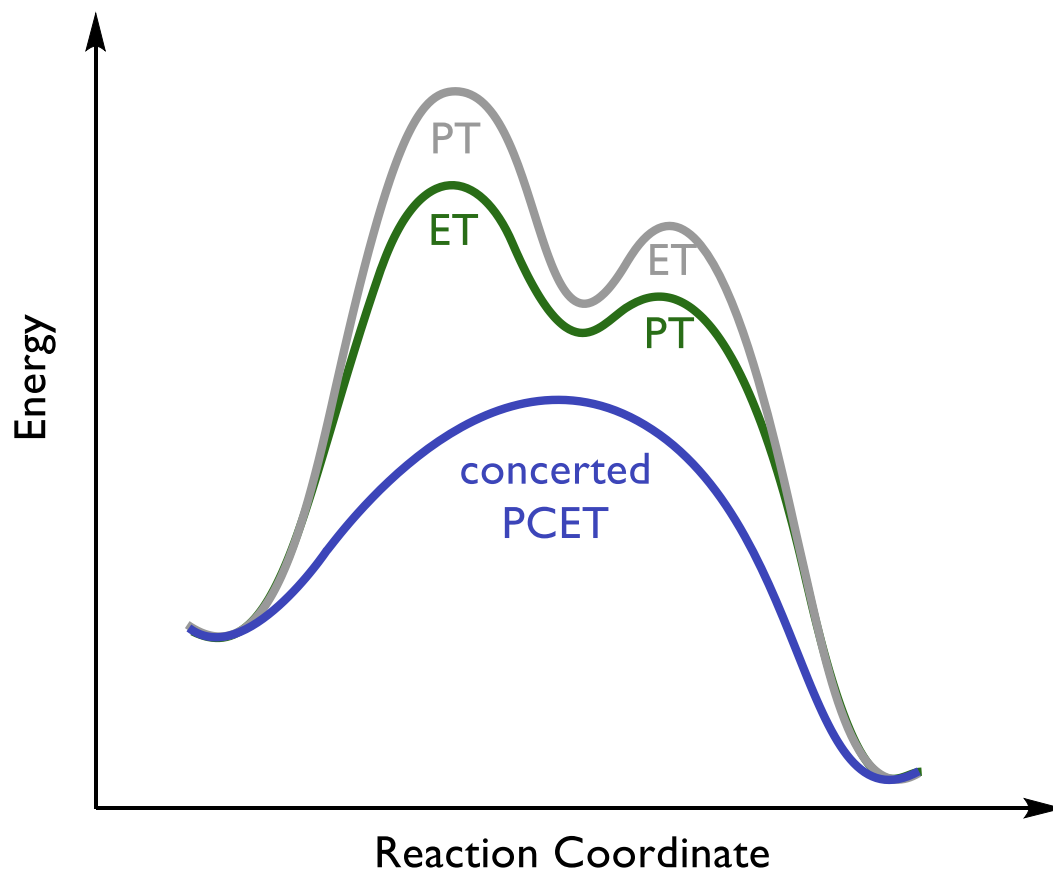
$$\text{BDFE (kcal/mol)} = 1.37 \text{ pK}_a + 23.06 \text{ E}^0 + 54.9 \text{ kcal/mol (RT in MeCN)}$$

Thermodynamic Modularity of PCET

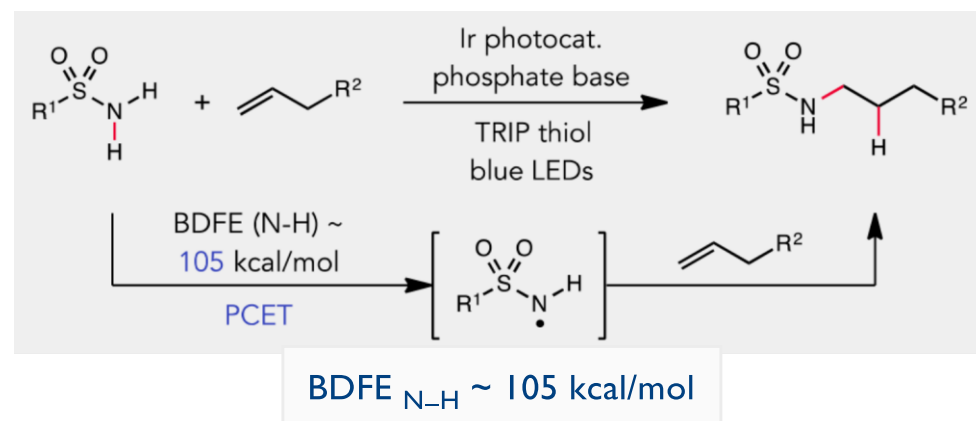
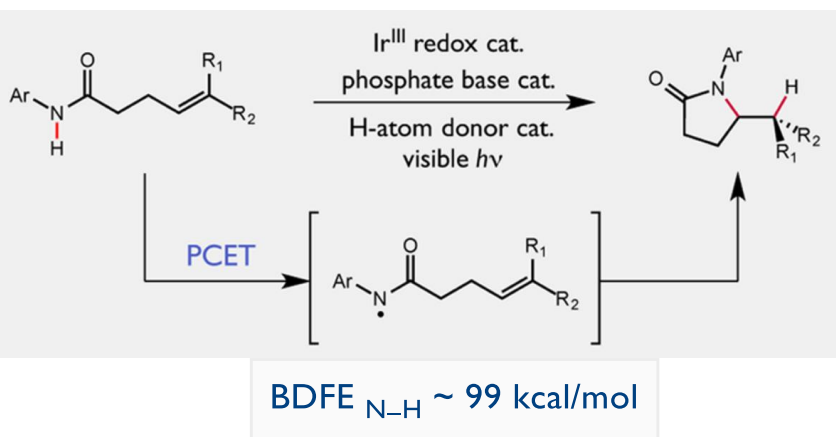
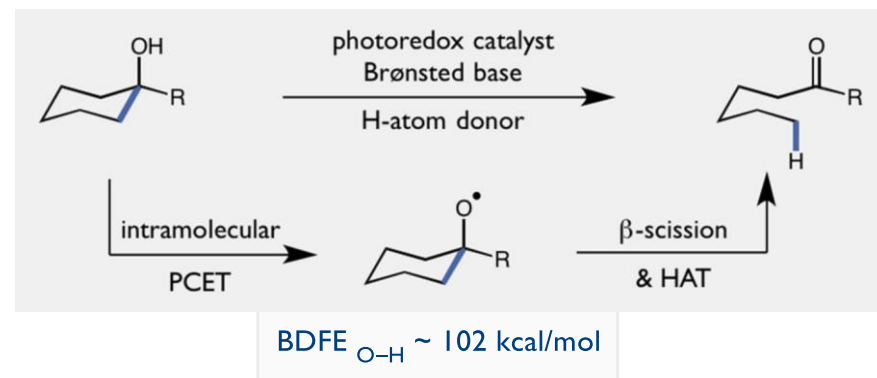
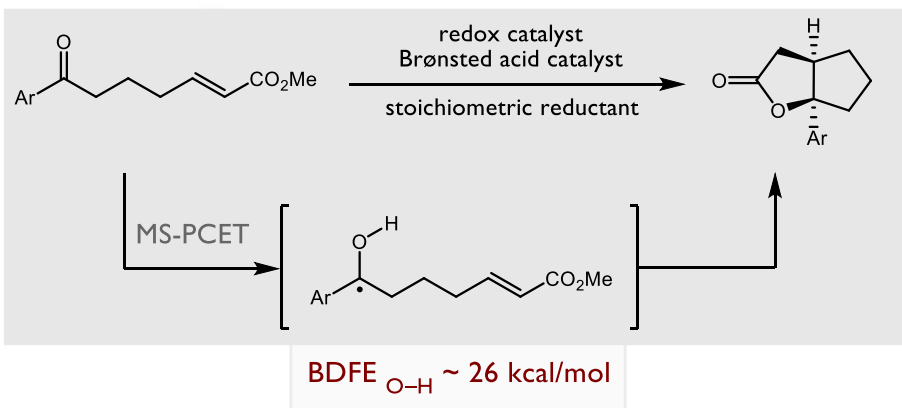
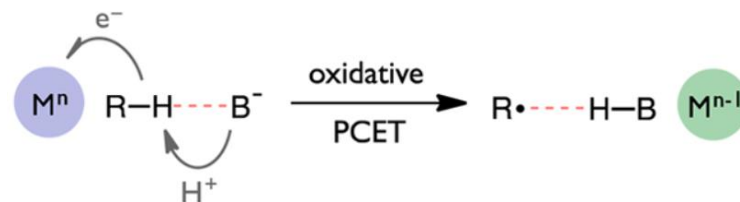
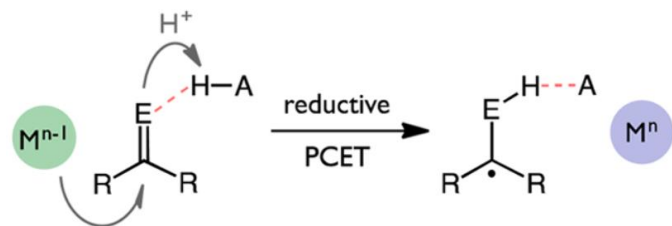


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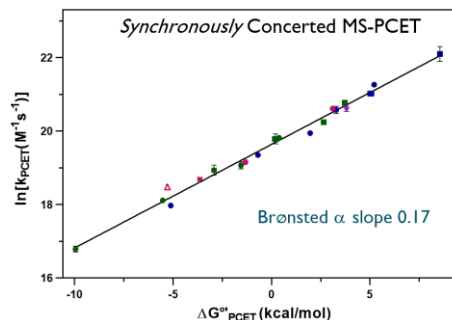
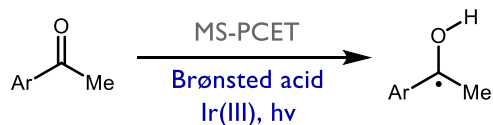
Kinetic Advantage of PCET



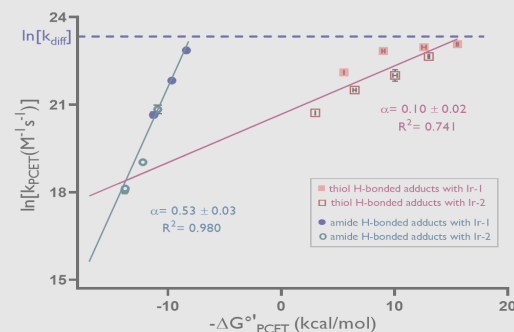
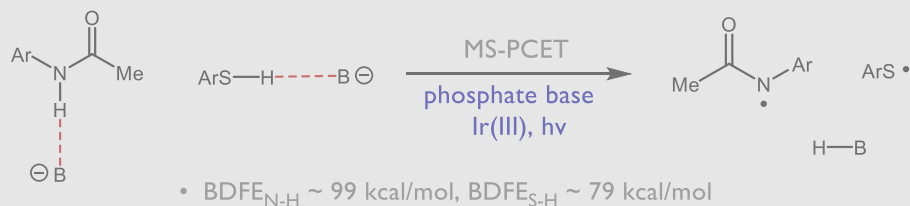
Kinetic Advantage of PCET



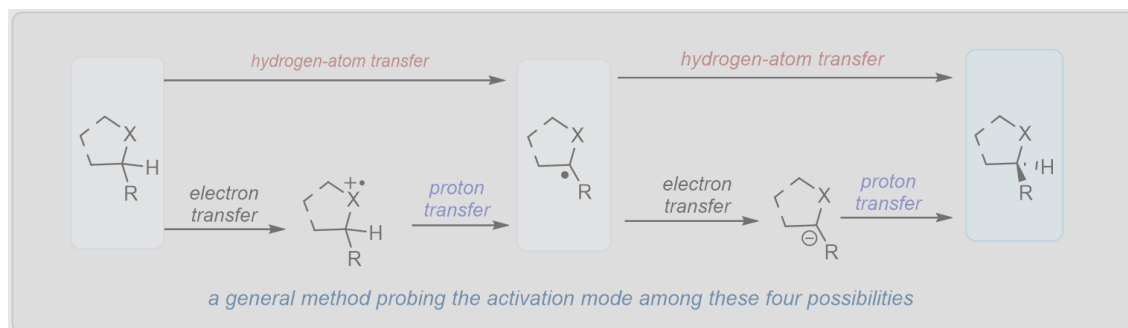
I. Kinetics and Mechanism of Multi-Site PCET



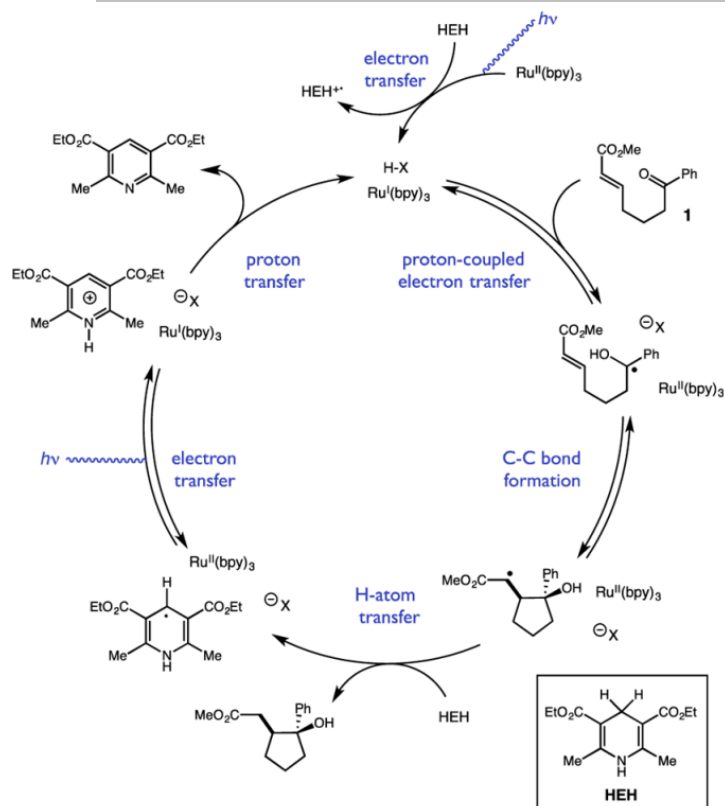
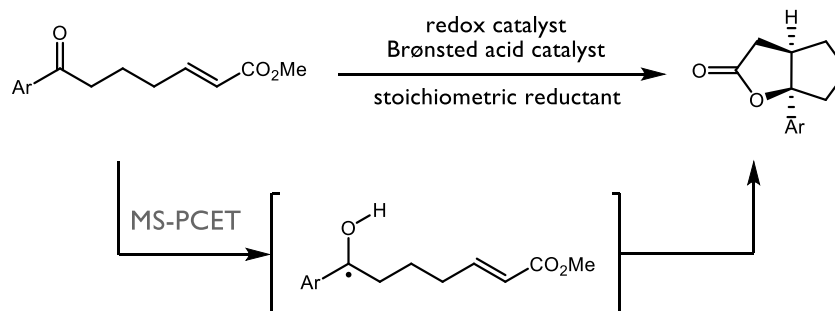
2. Chemoselectivity in Competitive Multi-Site PCET



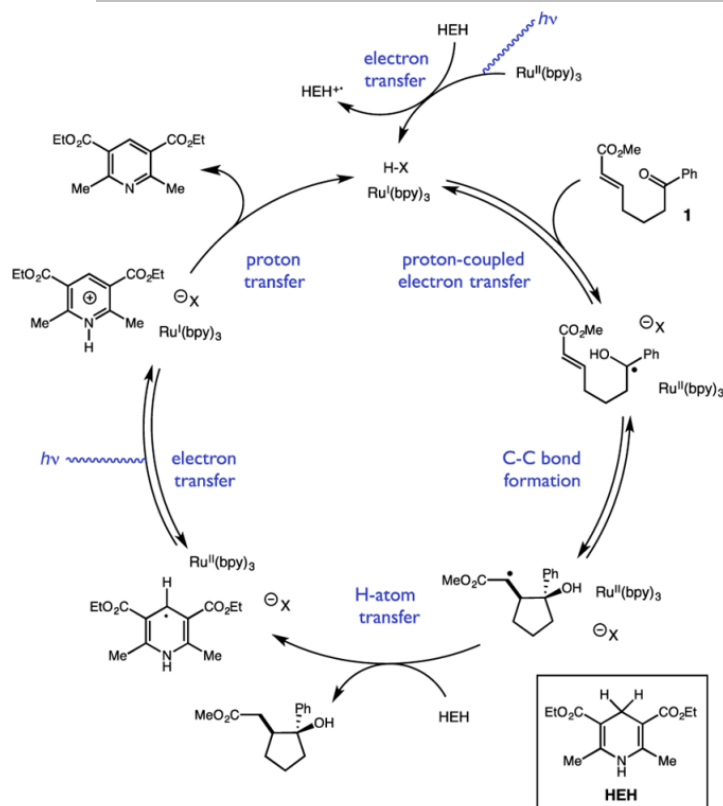
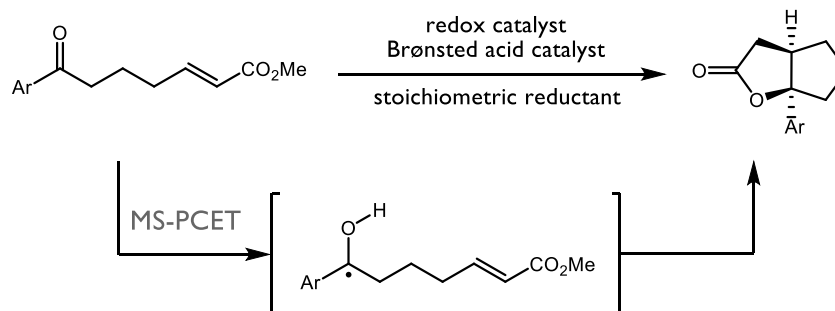
3. Probing Photocatalytic C–H Activation Mode



Thermodynamic Cut-off for PCET



Thermodynamic Cut-off for PCET

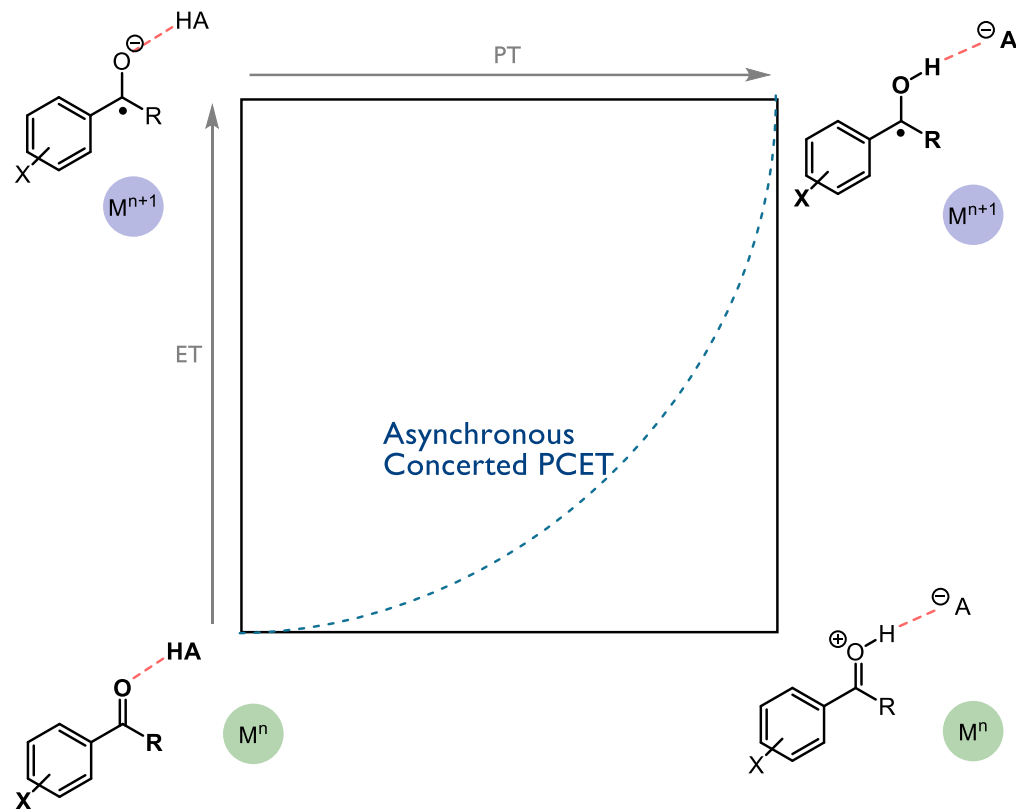


$$\text{BDFE}_{\text{O-H}} = 26 \text{ kcal/mol}$$

redox cat	Brønsted Acid	'BDFE'	% conv
$\text{Ru}^{\text{I}}(\text{bpy})_3$	none	—	0
$\text{Ru}^{\text{I}}(\text{bpy})_3$	PhCO_2H	45	0
$\text{Ir}^{\text{II}}(\text{ppy})_2\text{dtbpy}$	$\text{NEt}_3 \cdot \text{HBF}_4$	37	0
$\text{Ru}^{\text{I}}(\text{bpy})_3$	$\text{lutidine} \cdot \text{HBF}_4$	35	0
$\text{Ru}^{\text{I}}(\text{bpy})_3$	$(\text{PhO})_2\text{P}(\text{O})\text{OH}$	33	>95
$\text{Ir}^{\text{II}}(\text{ppy})_2\text{dtbpy}$	$\text{lutidine} \cdot \text{HBF}_4$	31	>95
$\text{Ir}^{\text{II}}(\text{ppy})_2\text{dtbpy}$	$(\text{PhO})_2\text{P}(\text{O})\text{OH}$	29	>95
$\text{Ru}^{\text{I}}(\text{bpy})_3$	$p\text{TSA}$	27	>95
$^*\text{Ir}^{\text{III}}(\text{ppy})_3$	$(\text{PhO})_2\text{P}(\text{O})\text{OH}$	24	>95

$$\Delta G^\circ (\text{kcal/mol}) = \text{'BDFE'} - \text{BDFE}_{\text{O-H}} = 1.37 \text{ p}K_{\text{a}} (\text{HA}) + 23.06 E^\circ (\text{M}^n/\text{M}^{n+1}) + 54.9 - \text{BDFE}_{\text{O-H}}$$

Nature of the Rate-Driving Force Relationship?

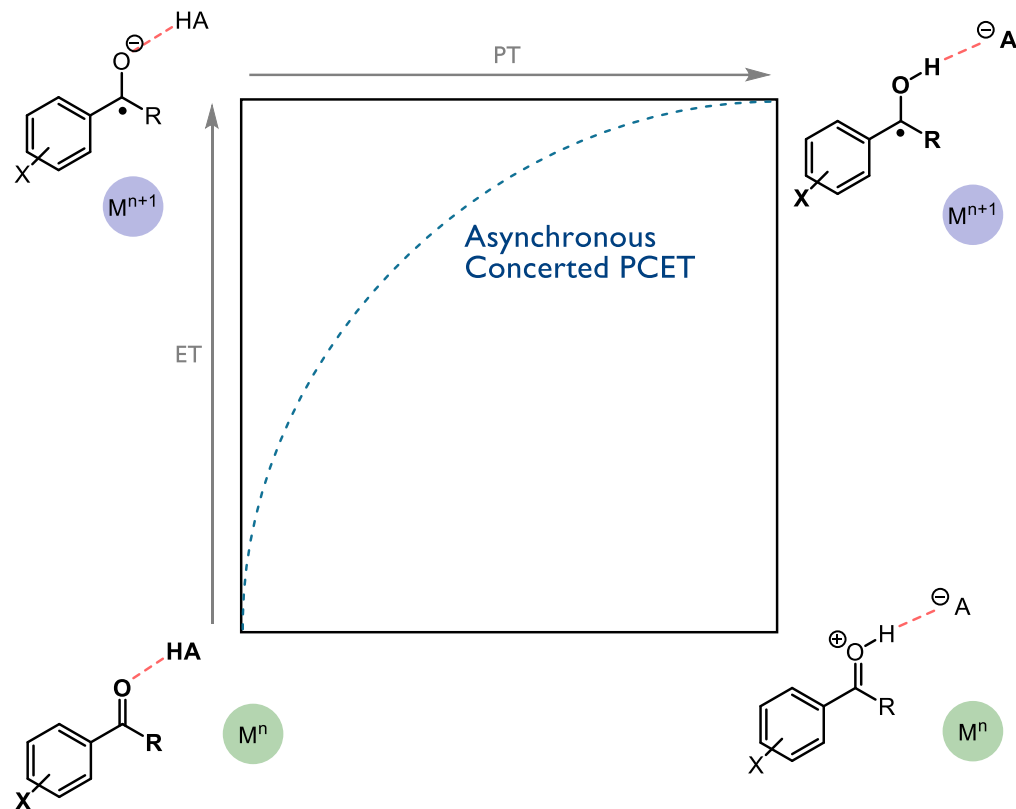


$$\Delta G^\circ \text{ (kcal/mol)} = \text{'BDFE'} - \text{BDFE}_{\text{O-H}} = 1.37 \text{ p}K_a(\text{HA}) + 23.06 E^\circ(\text{M}^n/\text{M}^{n+1}) + 54.9 - \text{BDFE}_{\text{O-H}}$$

$$k_{\text{PCET}} = f(\text{p}K_a) ?$$

$$k_{\text{PCET}} = f(E^\circ) ?$$

Nature of the Rate-Driving Force Relationship?

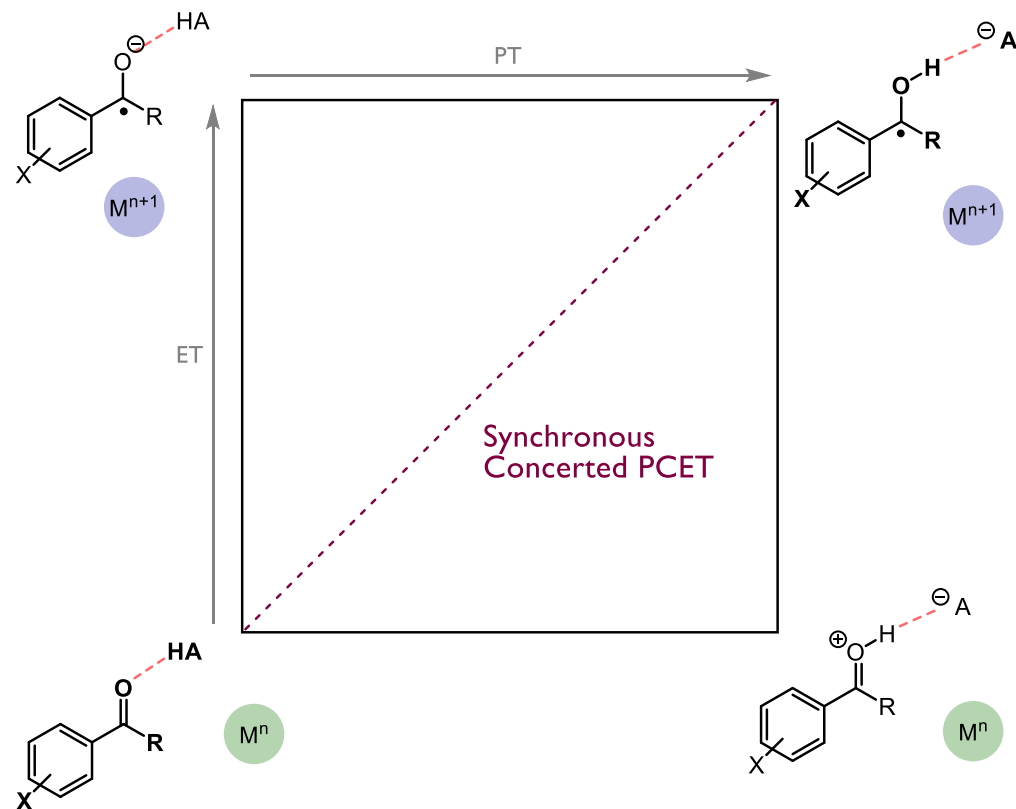


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$$k_{\text{PCET}} = f(\text{p}K_a) ?$$

$$k_{\text{PCET}} = f(E^\circ) ?$$

Nature of the Rate-Driving Force Relationship?

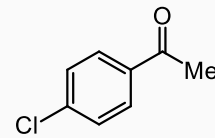
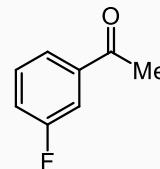
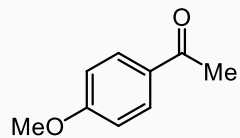
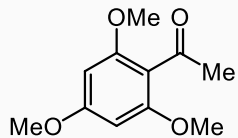
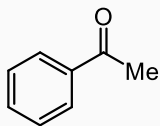


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$$k_{\text{PCET}} = f(\Delta G^\circ) ?$$

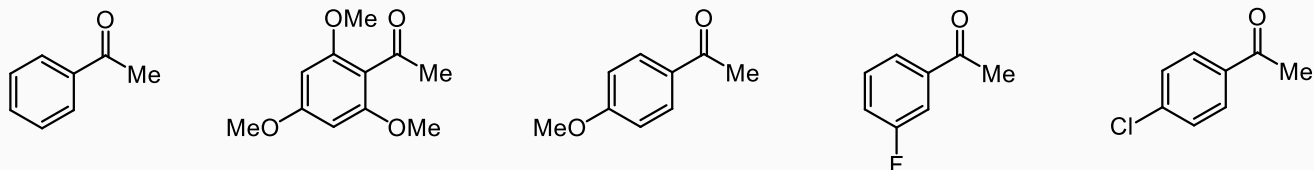
Ketone Substrate, Photo-reductant, and Brønsted Acid Scope

BDPE O_2H

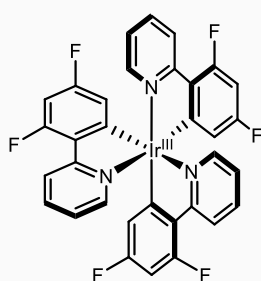


Ketone Substrate, Photo-reductant, and Brønsted Acid Scope

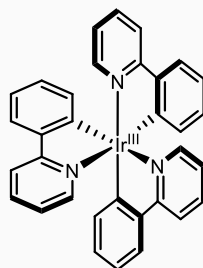
BDFE_{O-H}



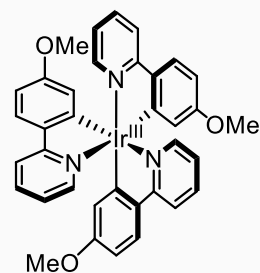
23.06 $E^\circ(M^n/M^{n+1})$



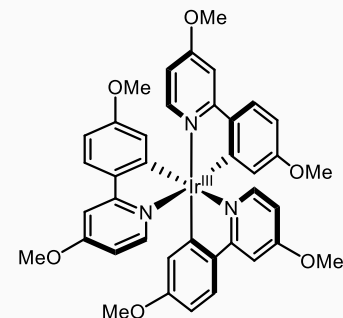
$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = -1.92 \text{ V (Fc}^+/\text{Fc)}$$



$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = -2.13 \text{ V (Fc}^+/\text{Fc)}$$



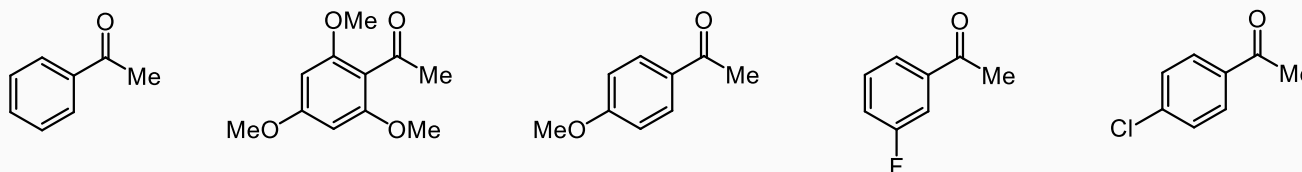
$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = -2.21 \text{ V (Fc}^+/\text{Fc)}$$



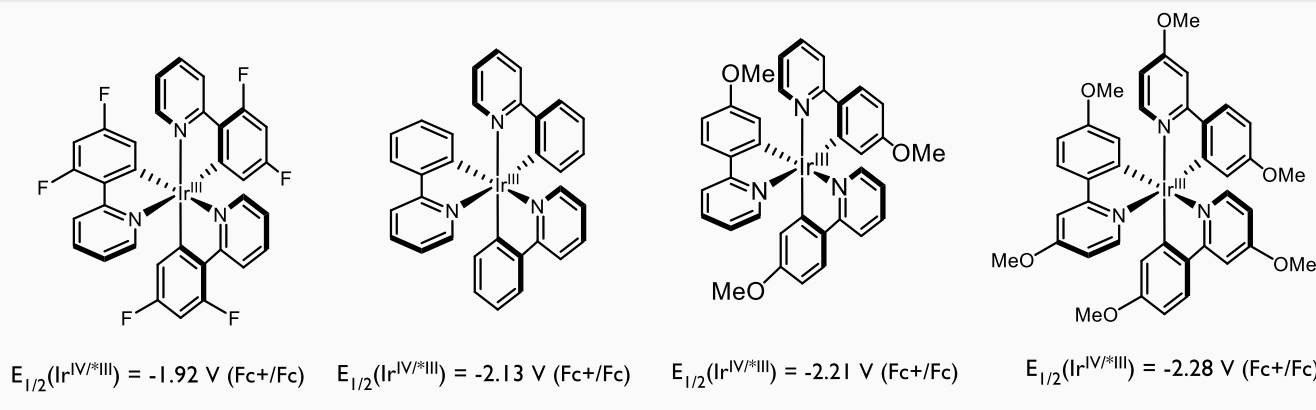
$$E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = -2.28 \text{ V (Fc}^+/\text{Fc)}$$

Ketone Substrate, Photo-reductant, and Brønsted Acid Scope

BDFE_{O-H}



23.06 $E^\circ(M^n/M^{n+1})$

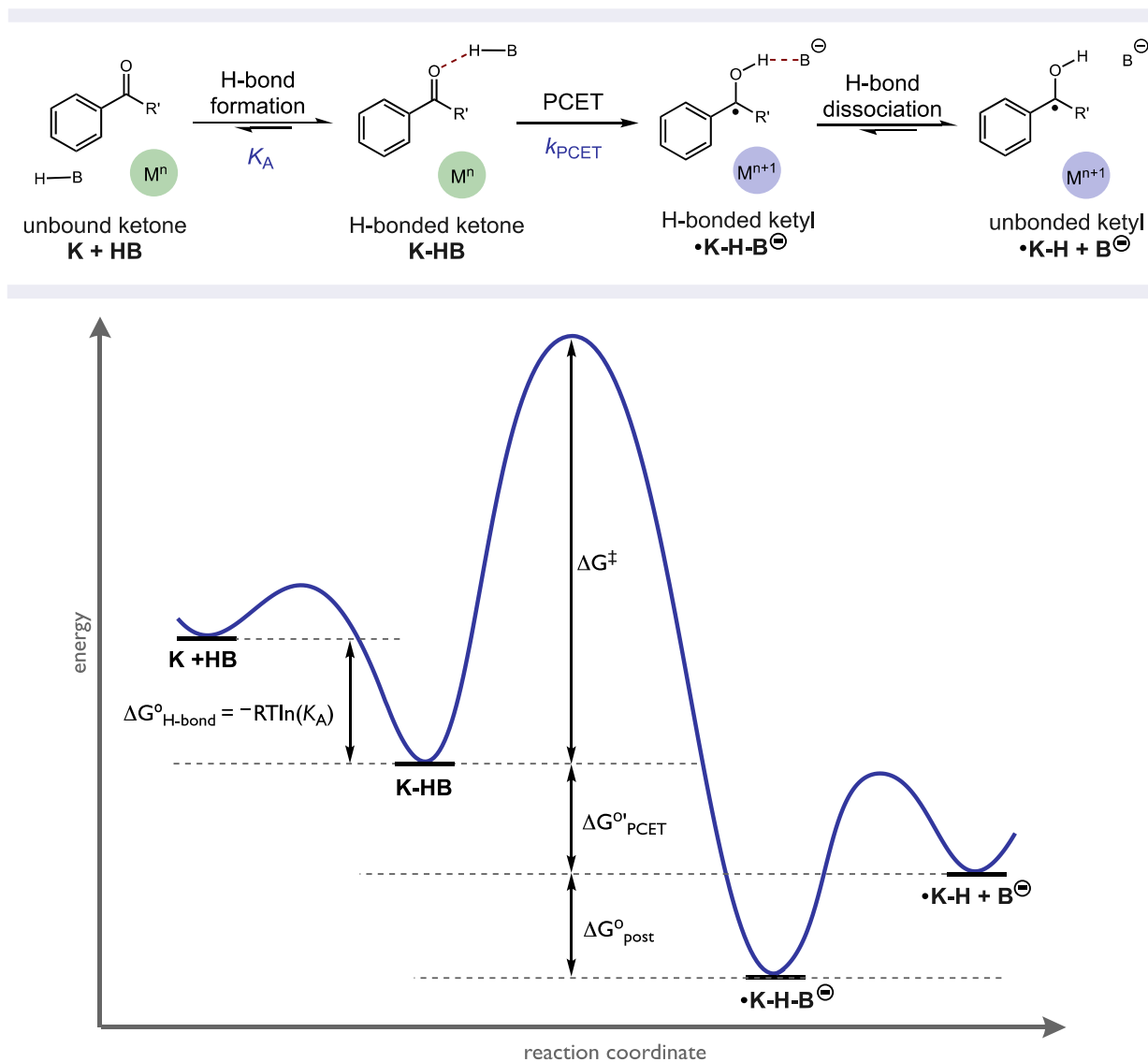


1.37 pK_a (HA)

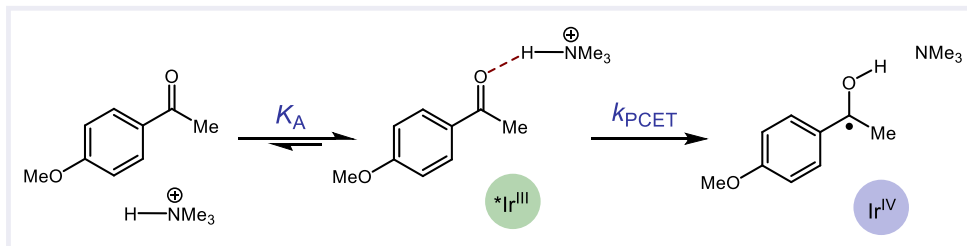
Brønsted acids: $(\text{PhO})_2\text{POOH}$ ($\text{pK}_a=13$), $p\text{-TsOH}$ ($\text{pK}_a=8.6$), NMe_3HBF_4 ($\text{pK}_a=17.6$), NEt_3HBF_4 ($\text{pK}_a=18.8$)

- Each component is varied independently
- Driving force range $\sim 20 \text{ kcal/mol}$

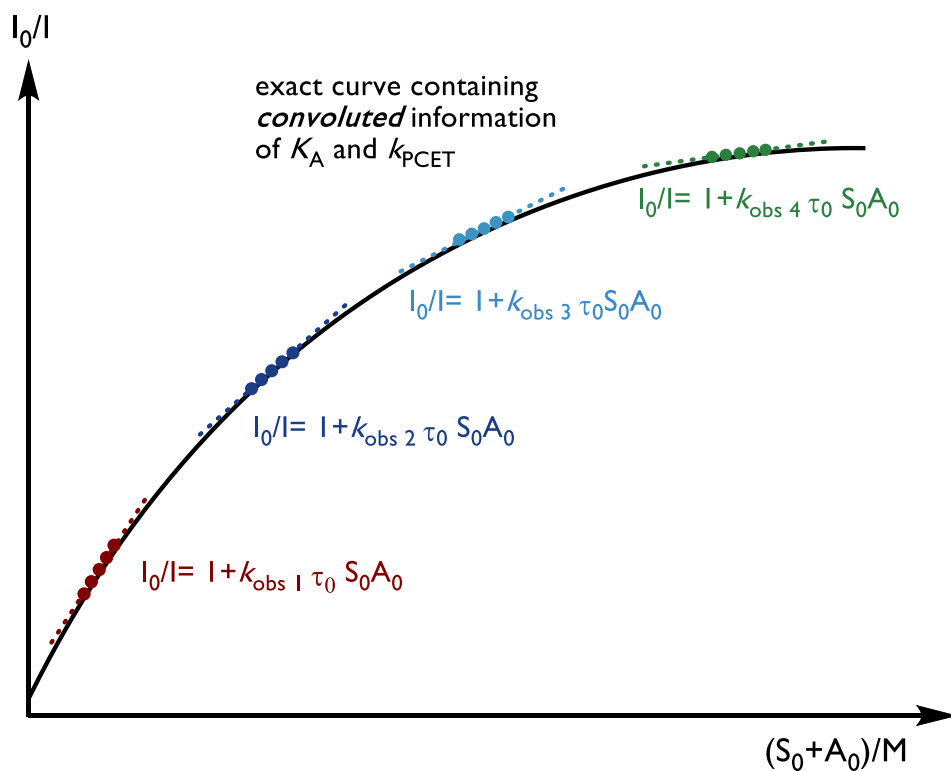
Free Energy Surface for the Hydrogen-bonding Mediated PCET



A Simple Experimental Method to Extract K_A and k_{PCET}

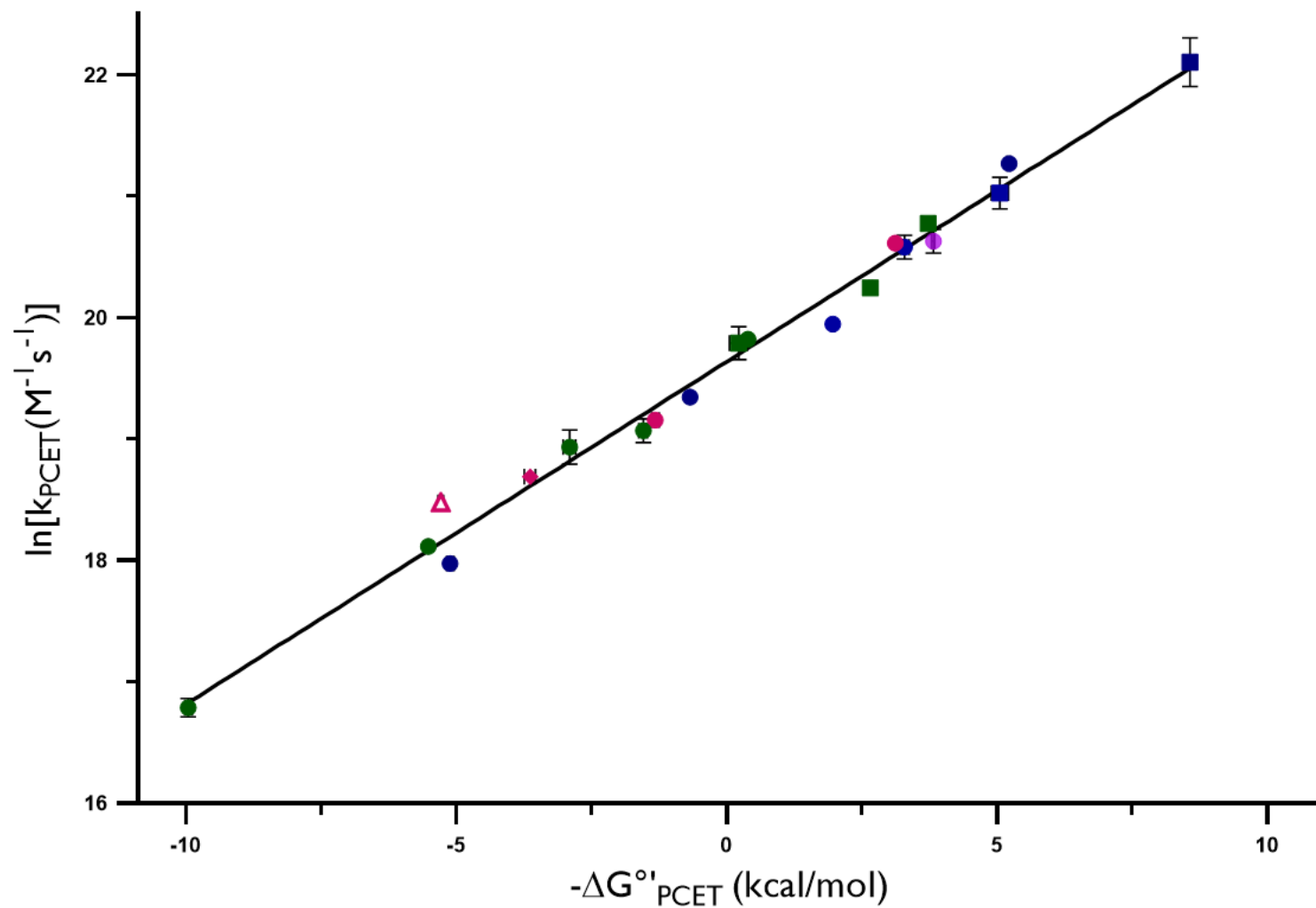


$$K_A = \frac{x}{(S_0 - x)(A_0 - x)}$$

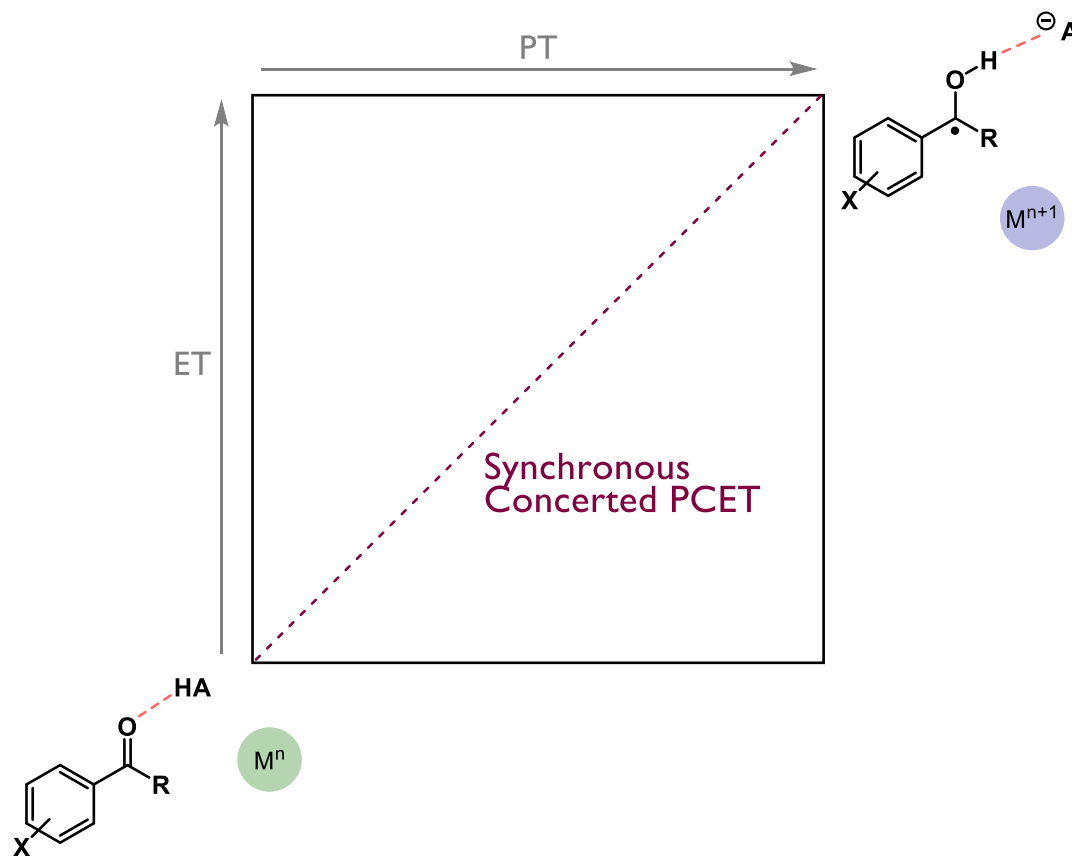


pre-PCET H-bonding equilibrium constant (K_A) and PCET rate constant (k_{PCET}) are extracted simultaneously

PCET is *Synchronous* Concerted

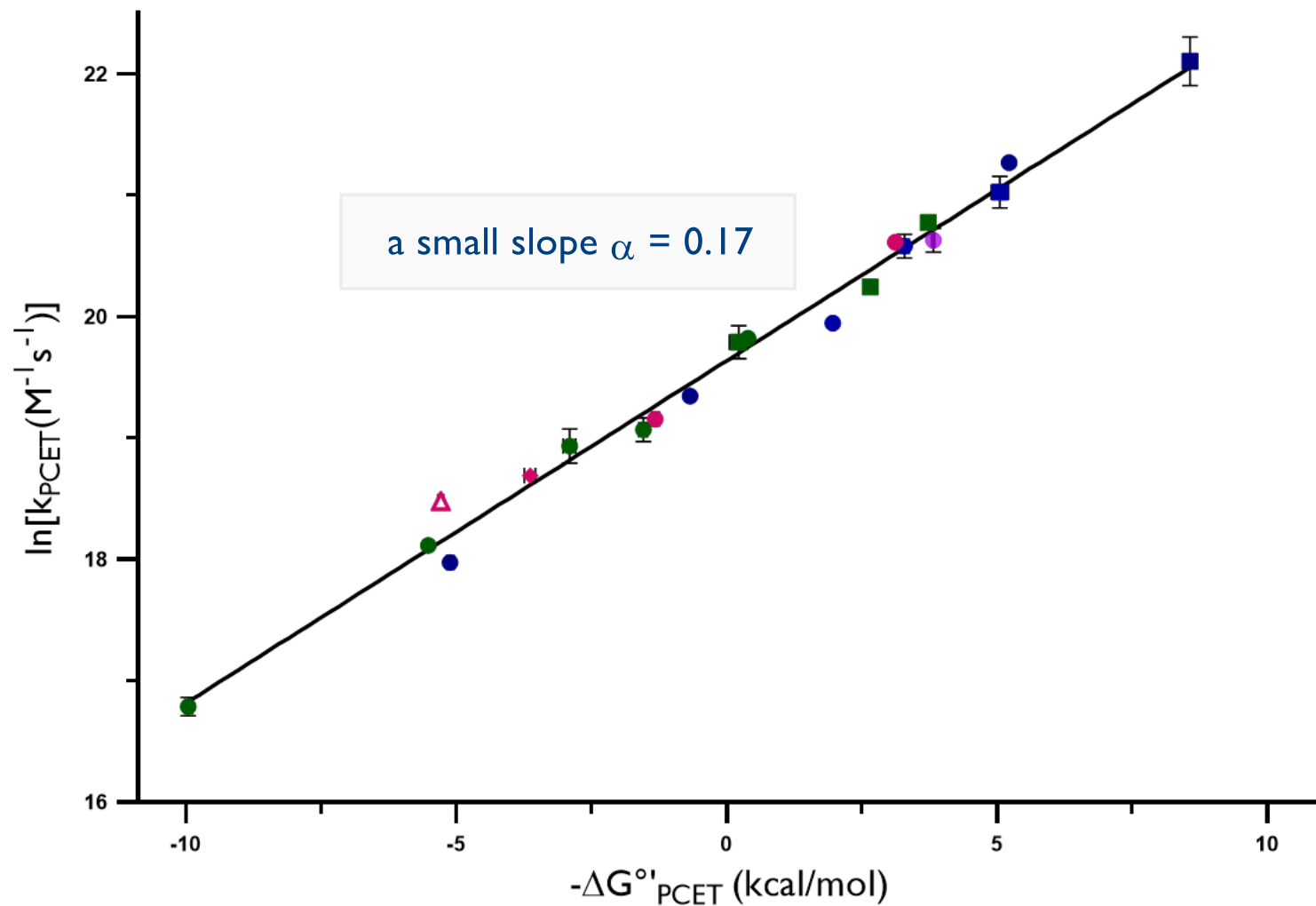


PCET is *Synchronous* Concerted



$$k_{\text{PCET}} = f(\Delta G^\circ)$$

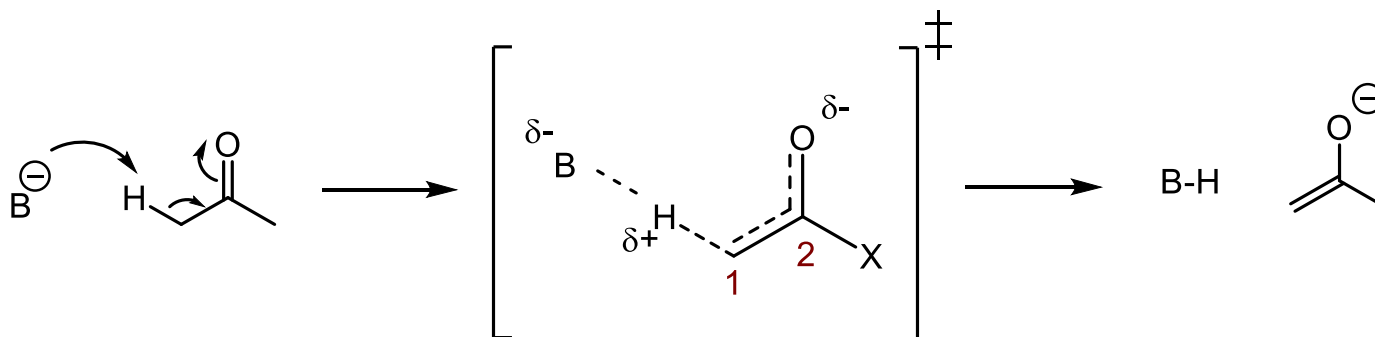
Slope Significantly Deviated from Classical Prediction



Explanation for the Small Slope : Principle of Non-Perfect Synchronization

Principle of Non-Perfect Synchronization (NPS): a product-stabilizing factor, the development of which at the transition state lags behind bond changes, increases the intrinsic barrier of a reaction, but lowers it if it develops ahead of bond changes.

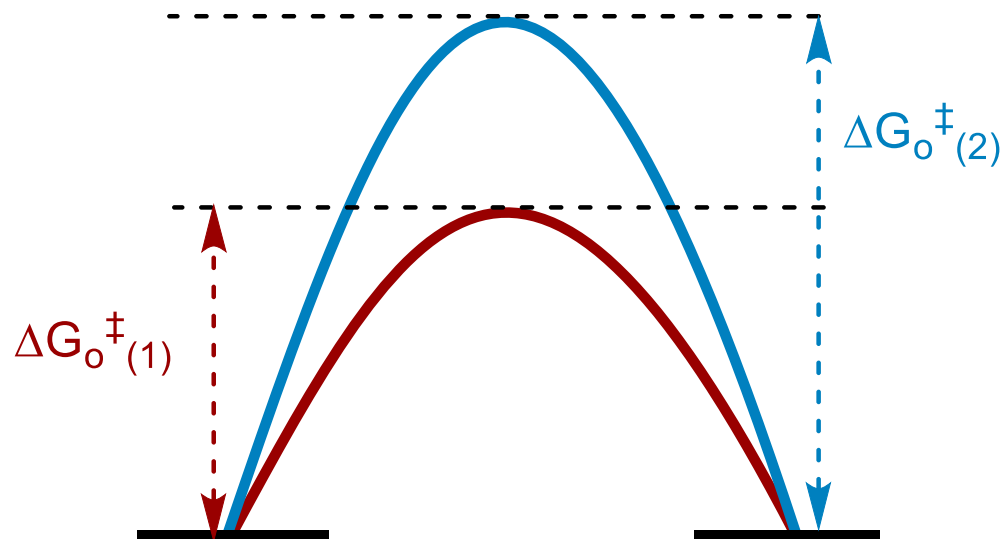
- Claude F. Bernasconi



Transition state does not benefit from the product stabilization
→ additional component of **intrinsic barrier**

What is Intrinsic Barrier

Intrinsic barrier is the reaction barrier at zero driving force. This reaction barrier is **independent** of the thermodynamics

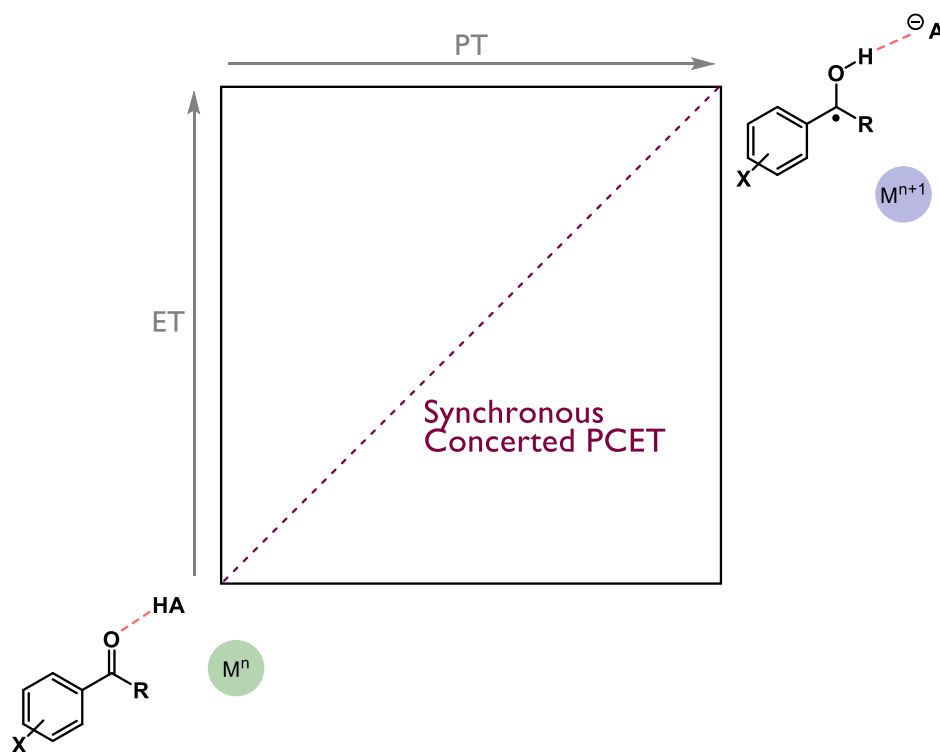


$$\Delta G^\circ = 0 \quad \Delta G_o^\ddagger(1) < \Delta G_o^\ddagger(2)$$

Explanation for the Small Slope : Principle of Non-perfect Synchronization

primary molecular processes:

concerted proton and electron exchange

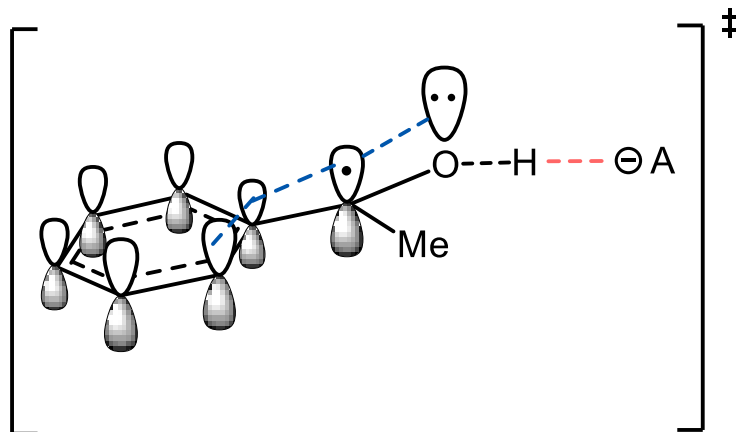


Imbalanced transition state: primary and secondary molecular processes are not progressed to the same extent at the transition state, affecting the responsiveness of the reaction barrier to the driving force.

Explanation for the Small Slope : Principle of Non-perfect Synchronization

secondary molecular processes (stabilizing/destabilizing factors):

- Resonance
- Solvation Change
- Hyperconjugation
- Inner-sphere geometric distortion
- Steric hindrance
- Hydrogen-bonding framework

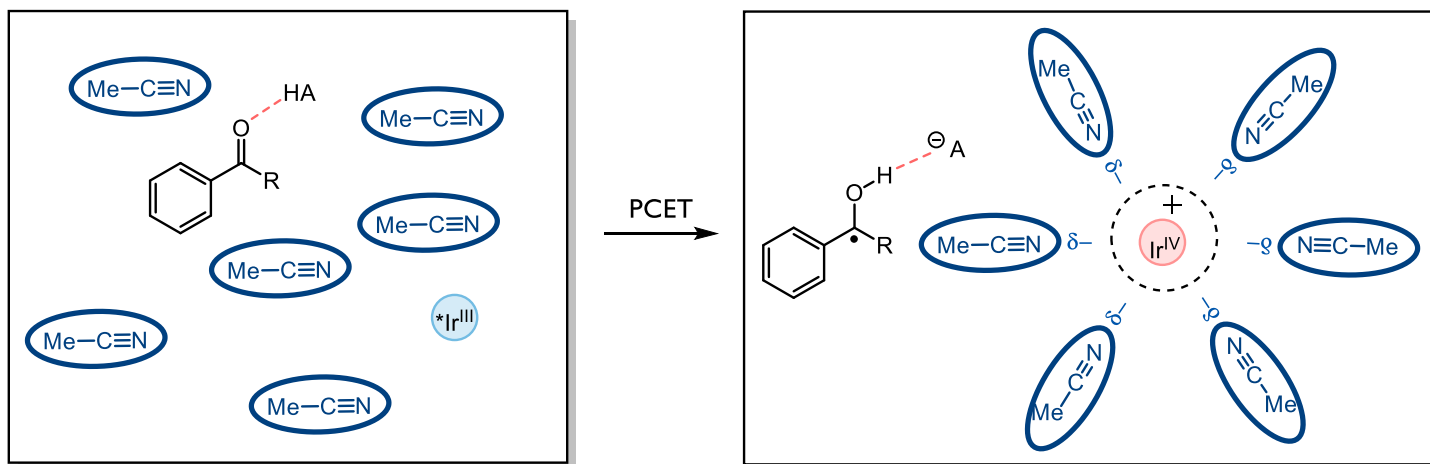


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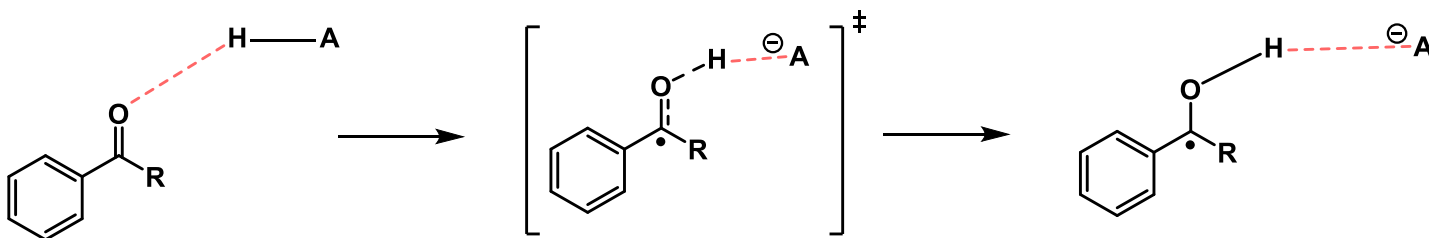


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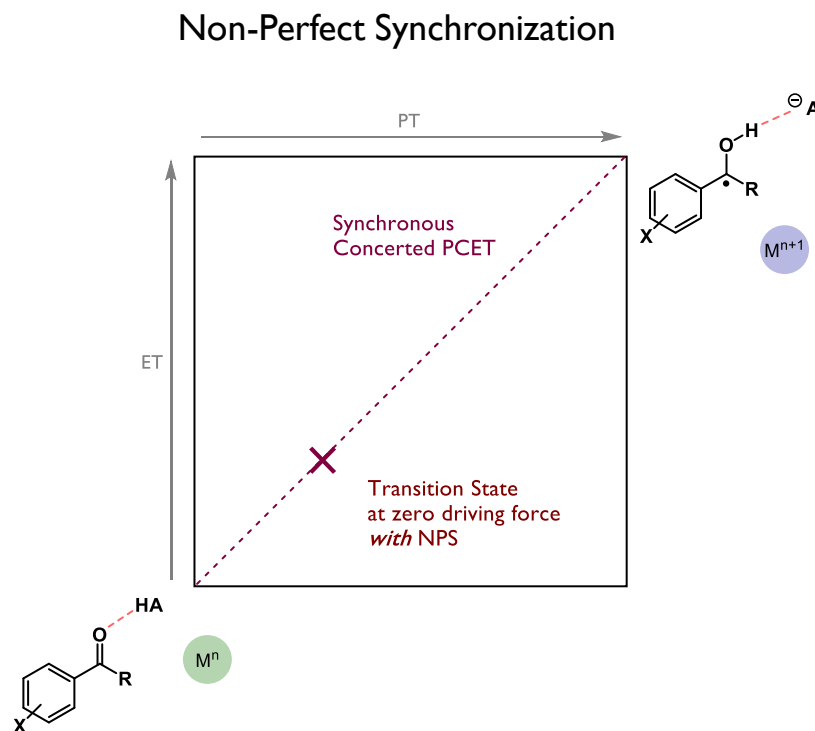
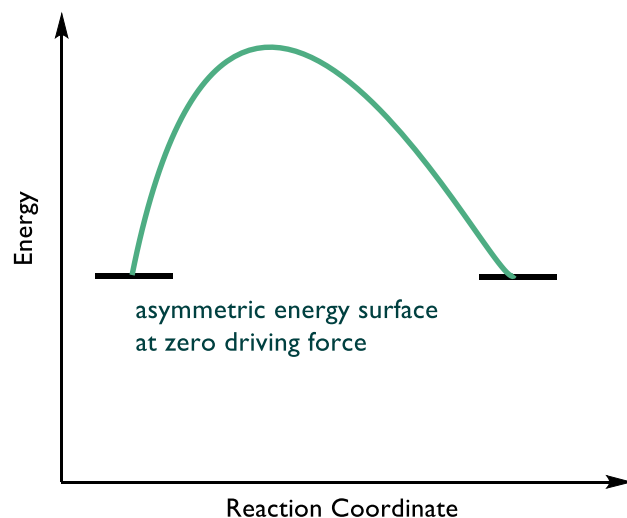
H-bond contract at the transition state

Imbalanced transition state: primary and secondary molecular processes are not progressed to the same extent at the transition state, affecting the responsiveness of the reaction barrier to the driving force.

Principle of Non-perfect Synchronization

Principle of Non-Perfect Synchronization (NPS): a product-stabilizing factor, the development of which at the transition state lags behind bond changes, increases the intrinsic barrier of a reaction, but lowers it if it develops ahead of bond changes.

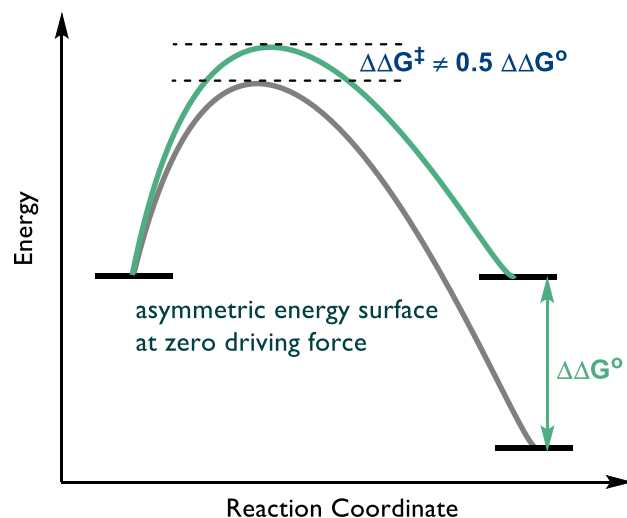
- Claude F. Bernasconi



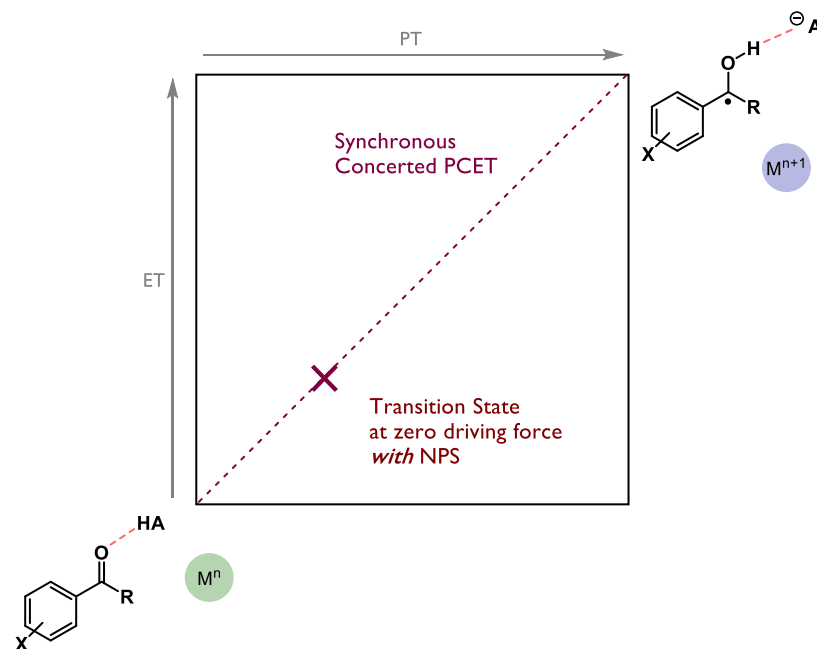
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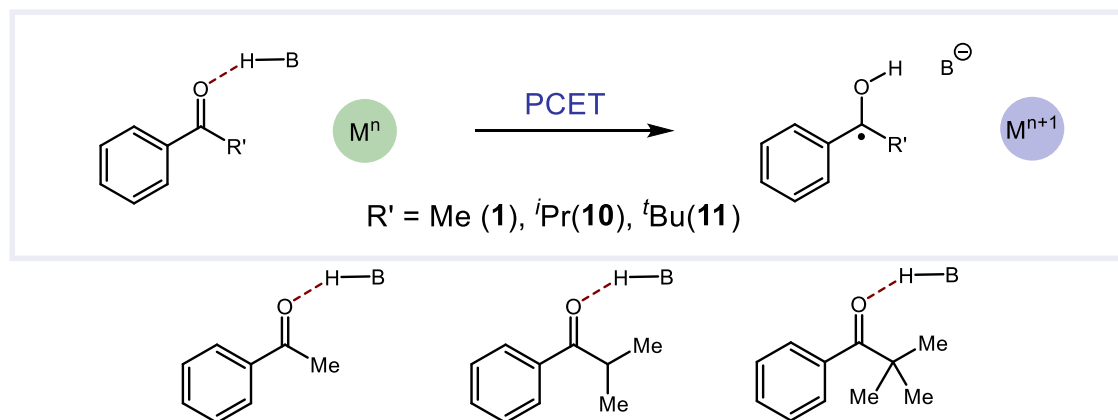
- Claude F. Bernasconi



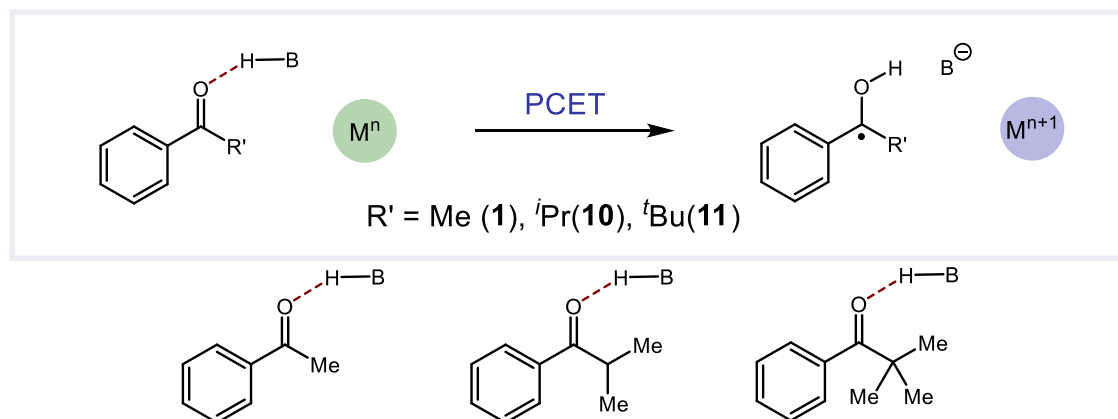
Non-Perfect Synchronization



Attempts to Push the System to Attain a Different Intrinsic Barrier

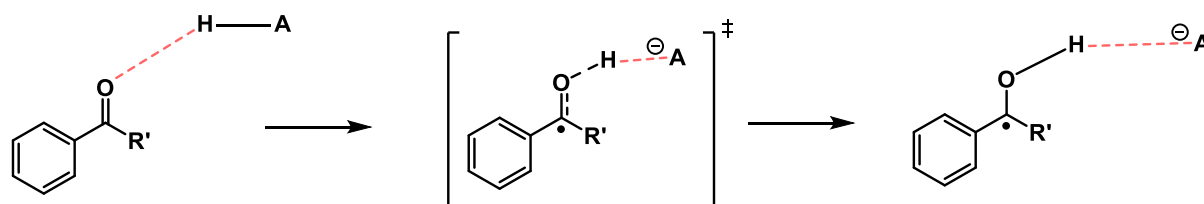
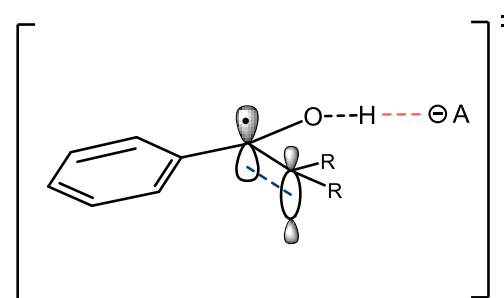


Attempts to Push the System to Attain a Different Intrinsic Barrier



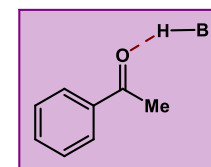
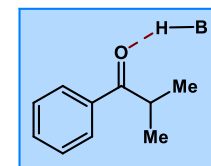
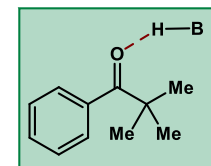
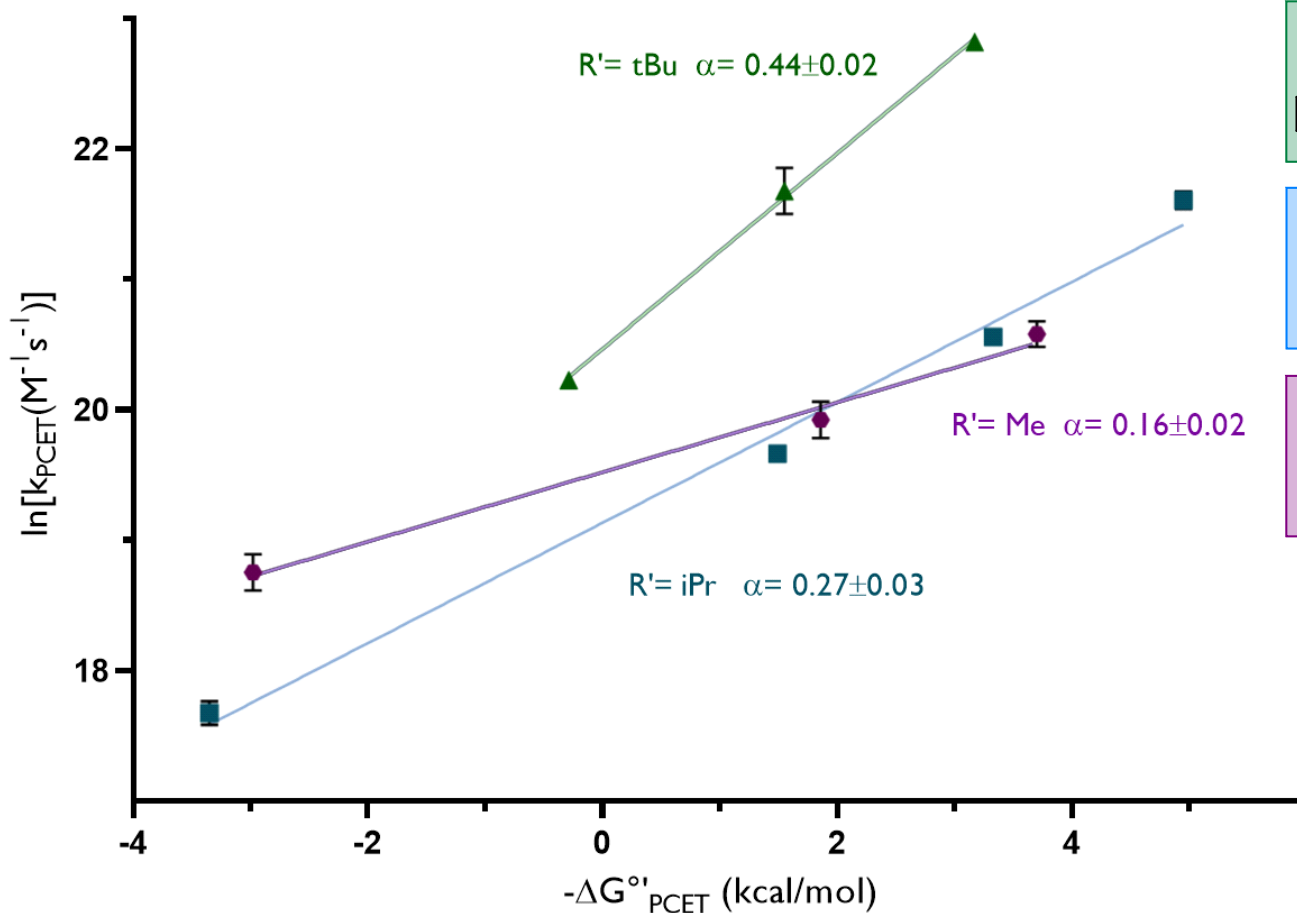
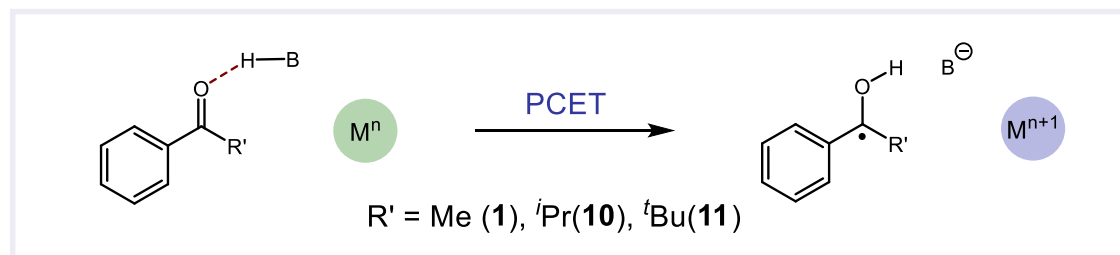
Possible differential secondary molecular processes:

- Resonance
- Solvation Change
- Hyperconjugation
- Inner-sphere geometric distortion
- Steric hindrance
- Hydrogen-bonding framework

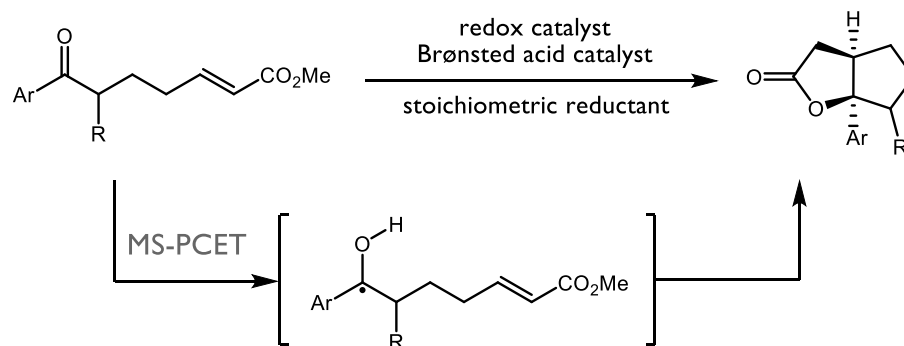


H-bond contracts at the transition state

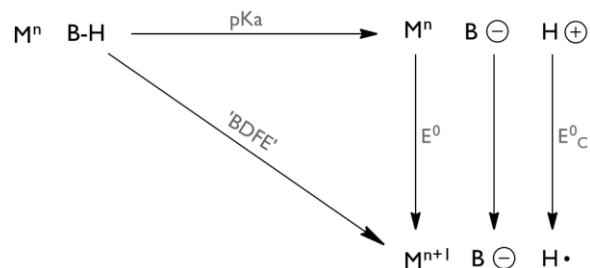
Attempts to Push the System to Attain a Different Intrinsic Barrier



Synthetic Implications



kinetics of ketone PCET activation vary linearly with driving force, and agnostic to identities of reagents

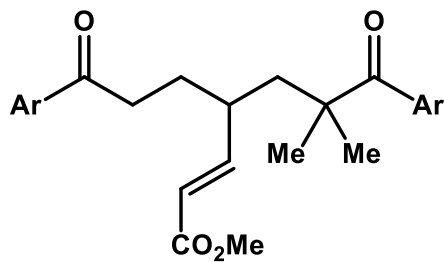
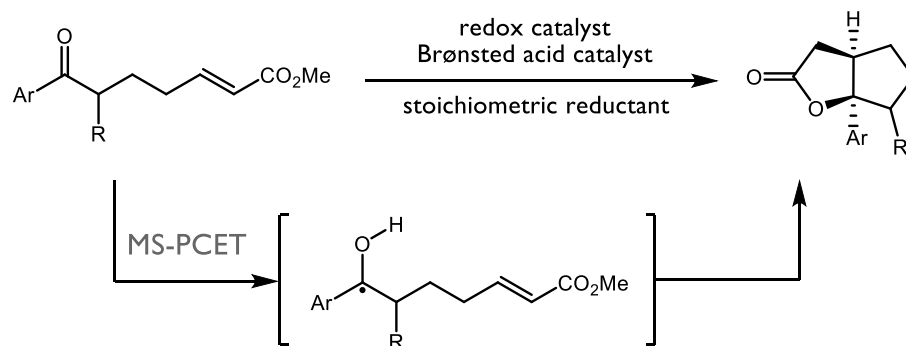


weaker reductant + stronger acid

weaker acid + stronger reductant

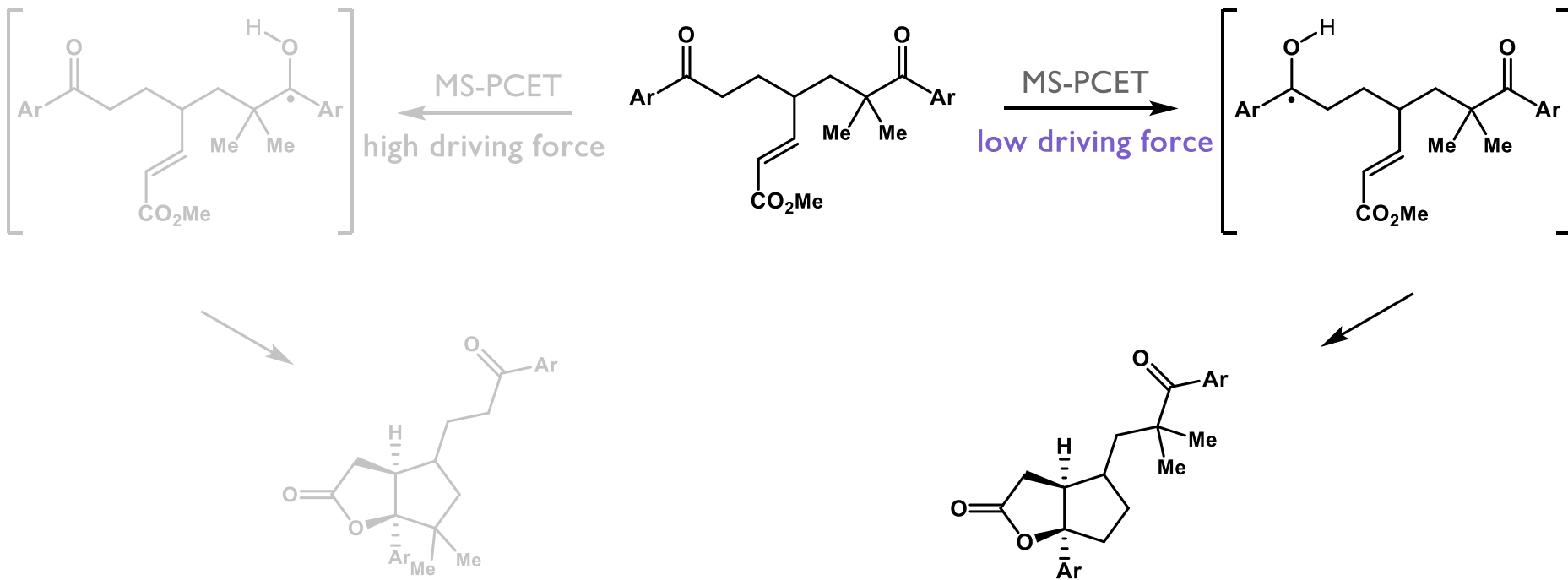
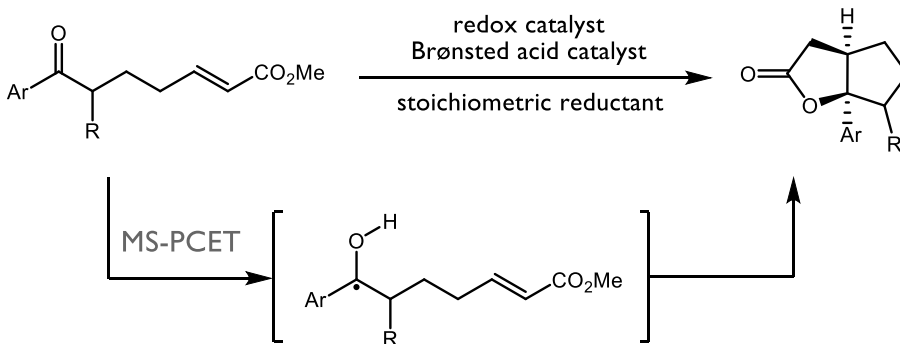
$$\text{BDFE (kcal/mol)} = 1.37 \text{ pK}_a + 23.06 \text{ E}^0 + 54.9 \text{ kcal/mol}$$

Synthetic Implications

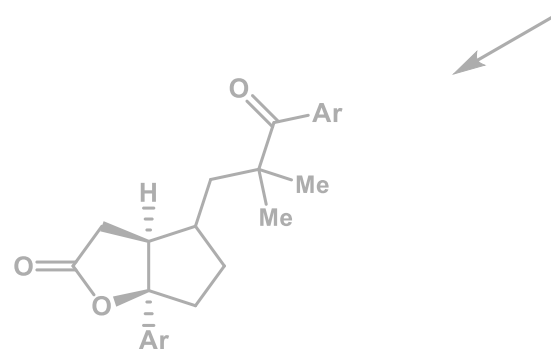
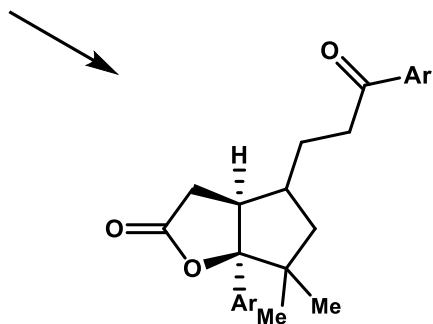
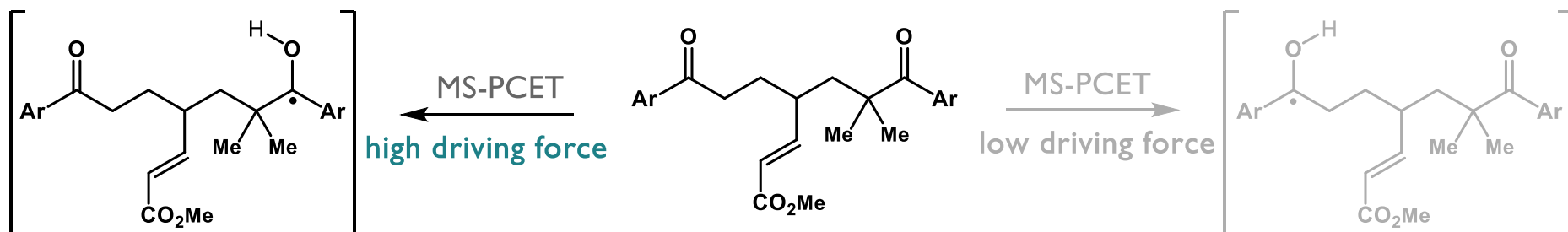
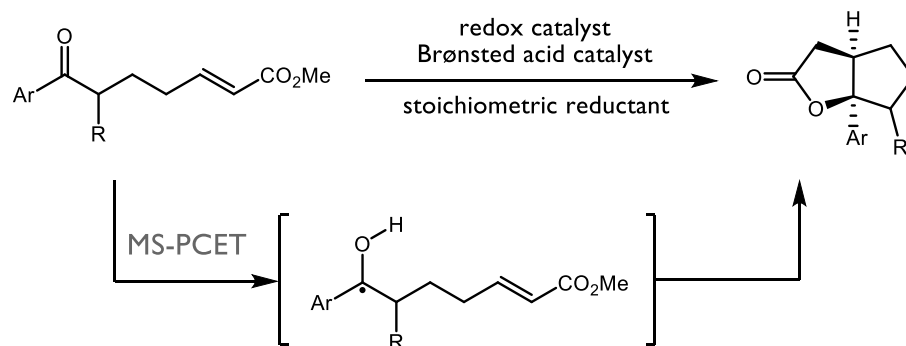


Can we *selectively* activate *each* of the two ketone sites?

Synthetic Implications

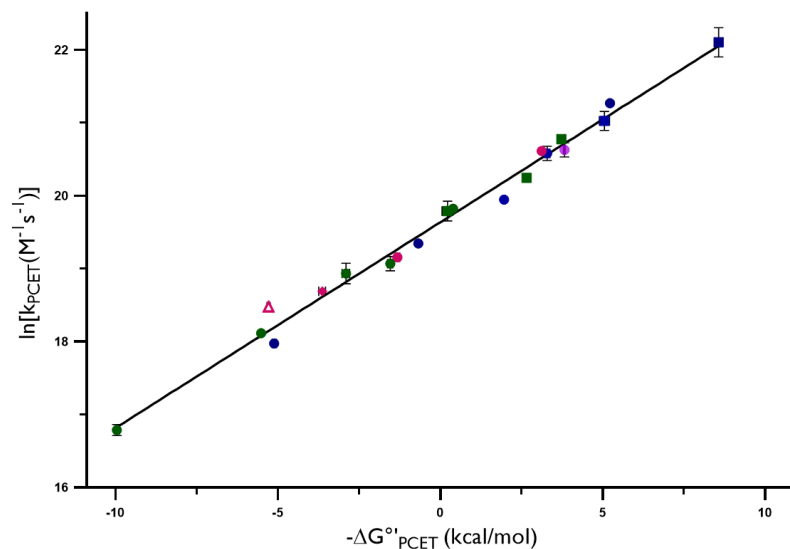


Synthetic Implications



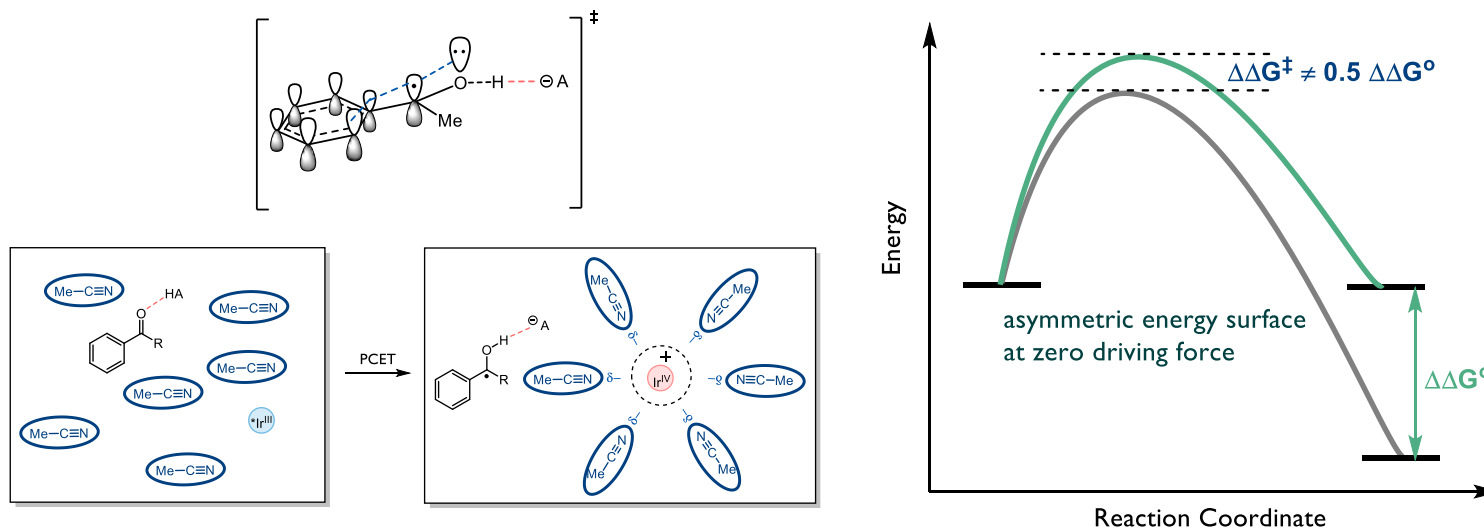
Summary

- The termolecular reductive MS-PCET is synchronous concerted, kinetics determined by the total driving force and agnostic to identities of catalysts
- The small Brønsted slope α is attributed to the non-perfect synchronization
- Thermodynamics is not the only factor that determines the rate, steric hindrance in H-bonding could change the intrinsic reactivity



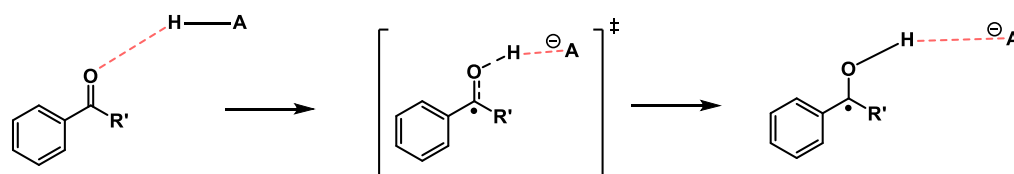
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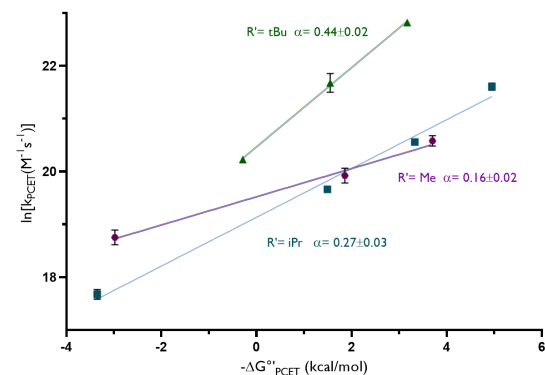
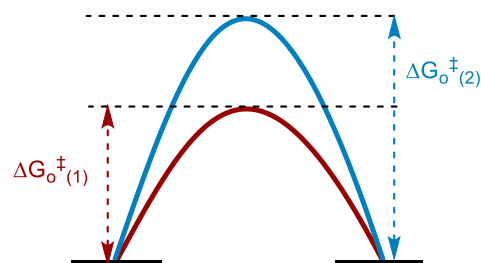


Summary

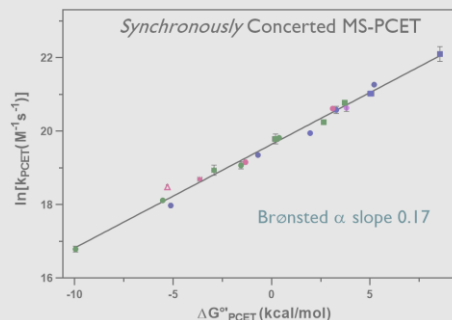
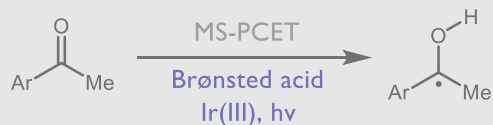
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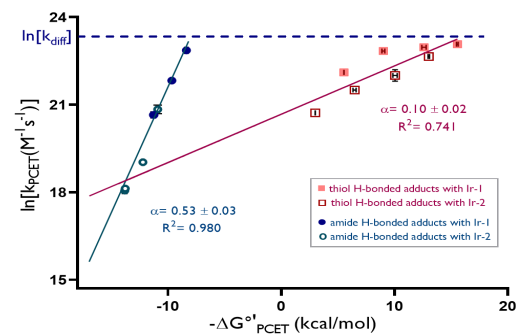
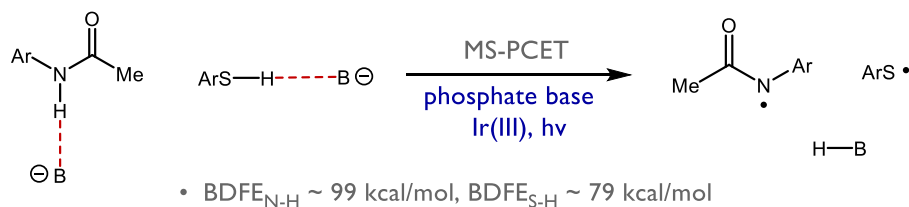
H-bond contracts at the transition state



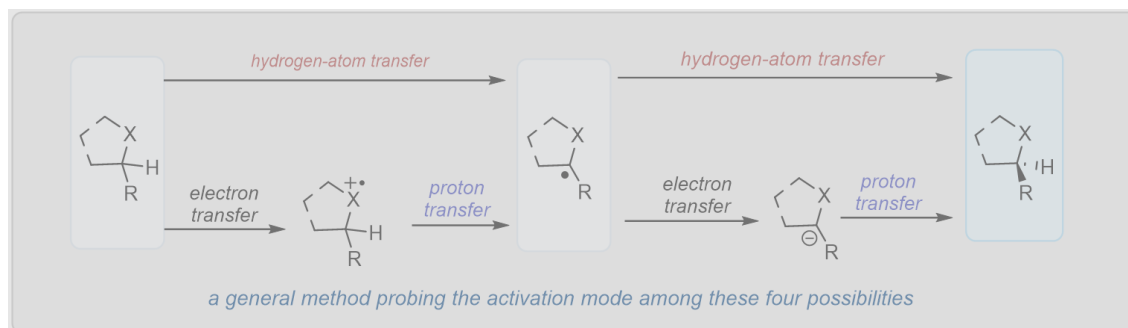
I. Kinetics and Mechanism of Multi-Site PCET



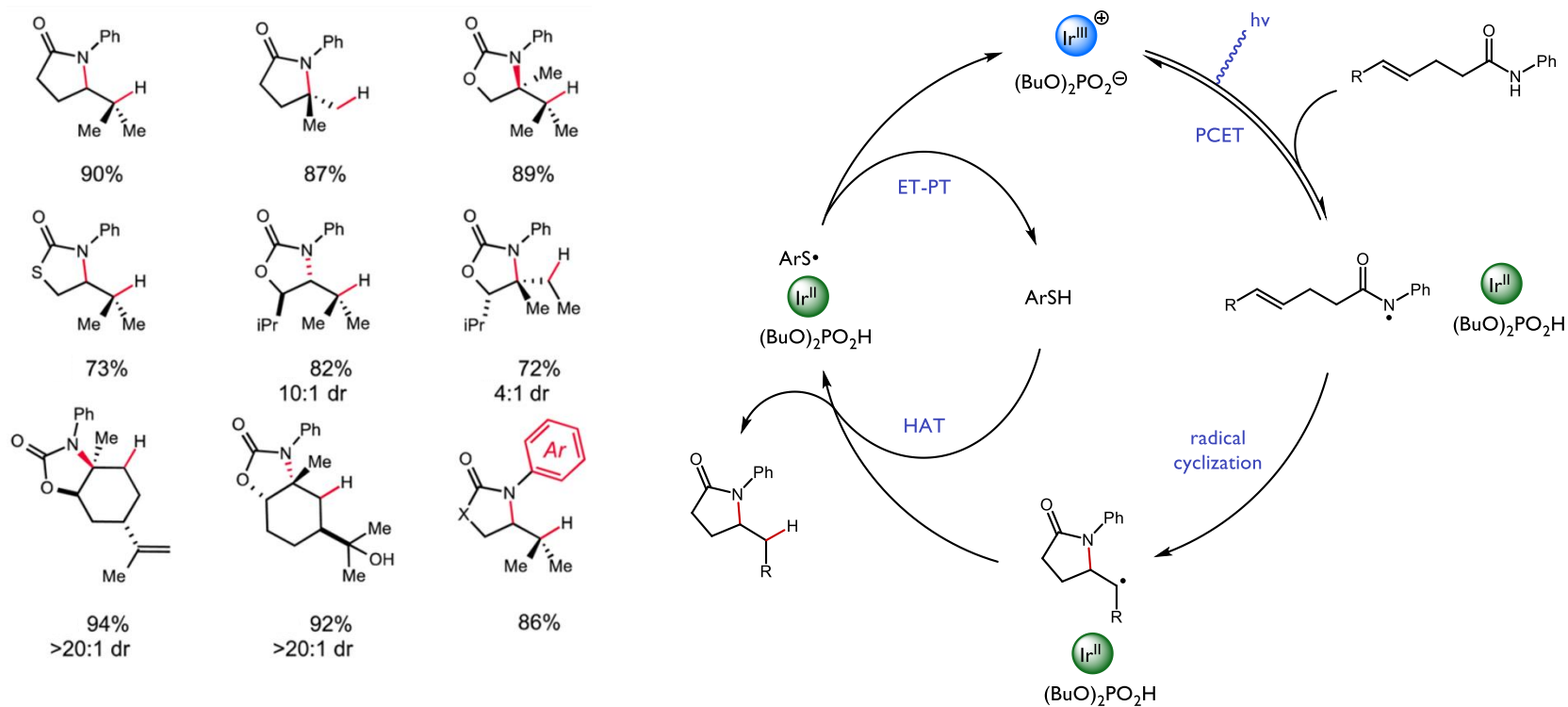
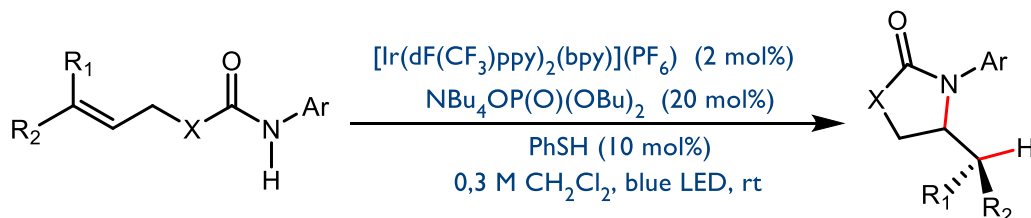
2. Chemoselectivity in Competitive Multi-Site PCET



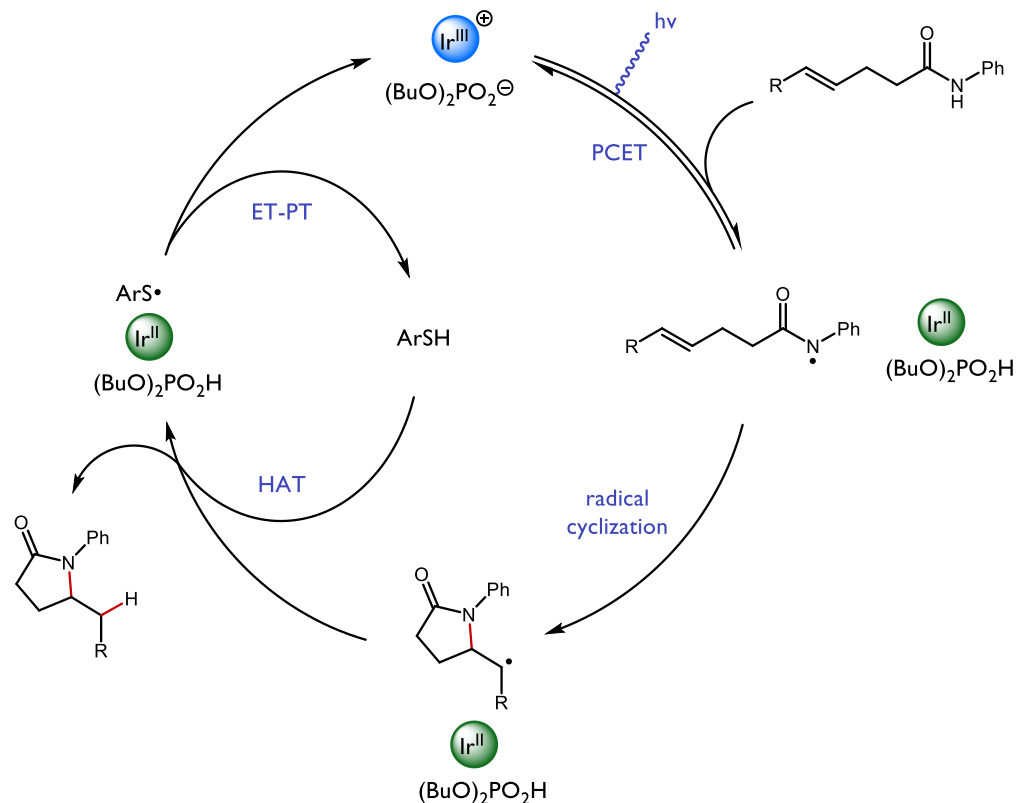
3. Probing Photocatalytic C–H Activation Mode



Account for the Unexpected PCET Chemoselectivity under Large Thermodynamic Bias

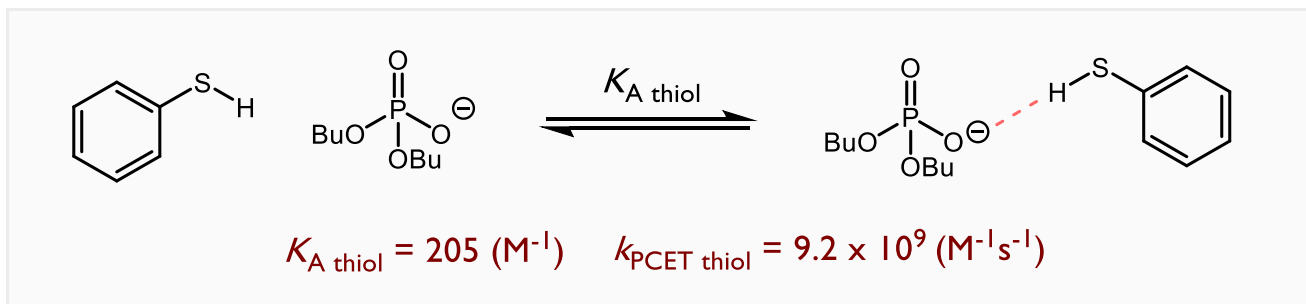
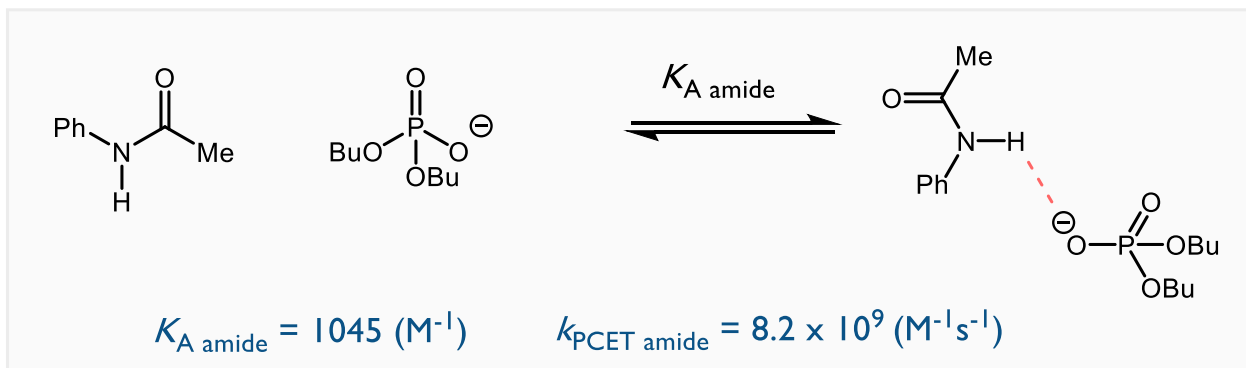


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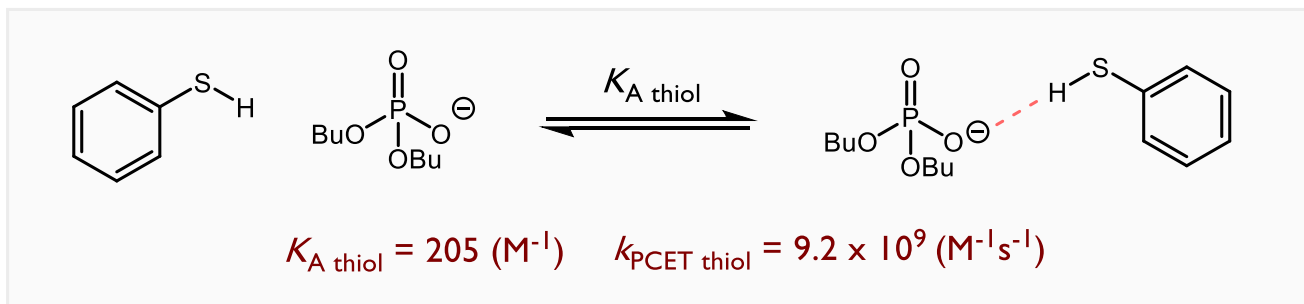
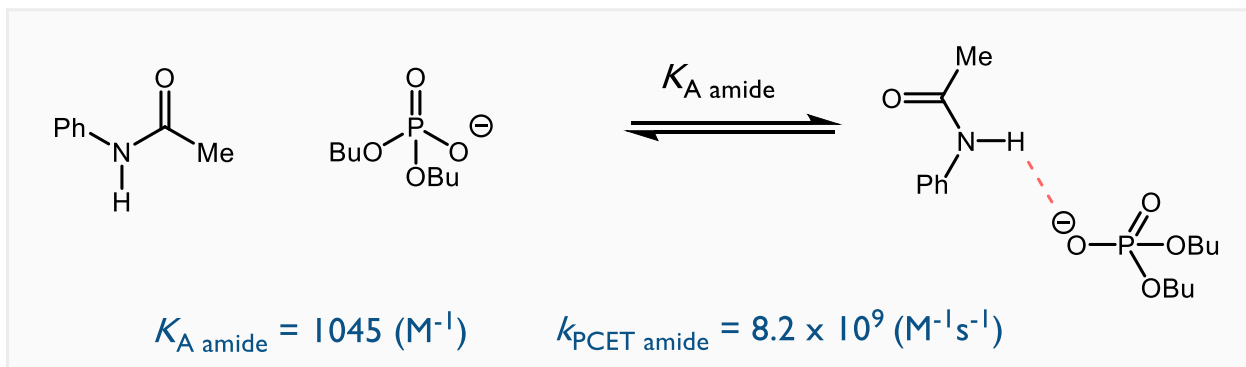


- Both amide and thiol are known substrates for H-bond mediated MS-PCET
 - BDFE N-H ~ 99 kcal/mol, BDFE S-H ~ 79 kcal/mol
- How does generation of amidyl radical succeed despite 20 kcal/mol thermodynamic disadvantage?

Preliminary Experimental Results

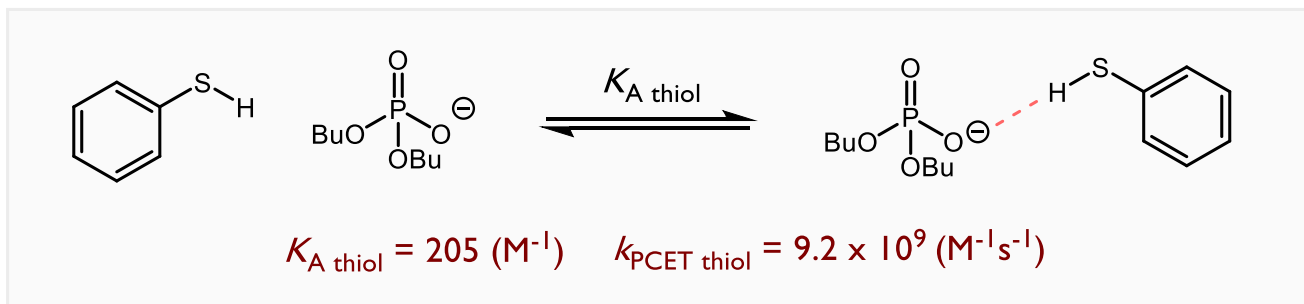
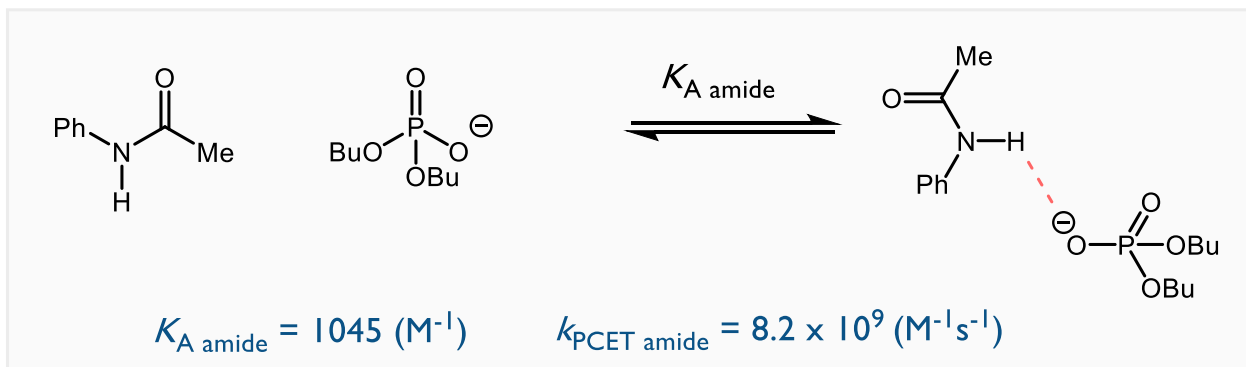


Preliminary Experimental Results



Both k_{PCET} rate constants ~ diffusion rate limit.
Thus, 20 kcal/mol thermodynamic advantage is nullified

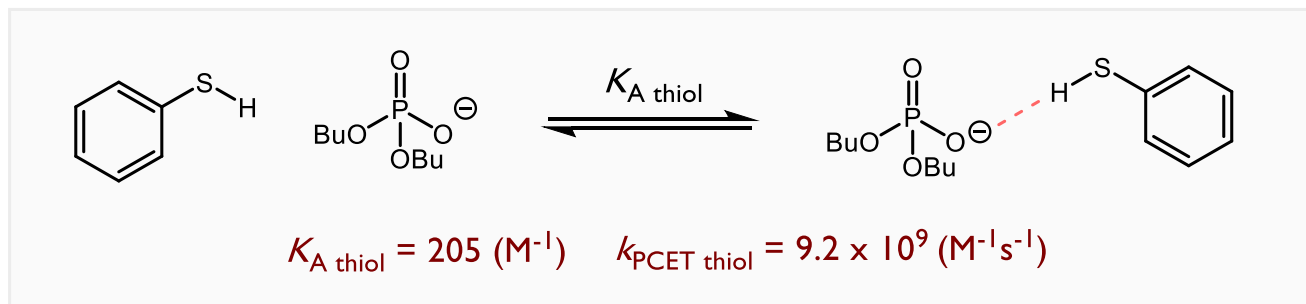
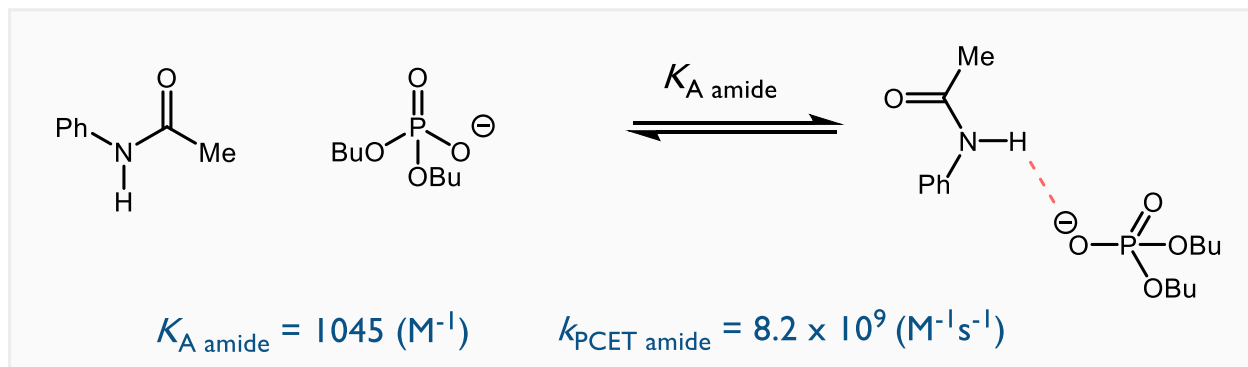
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At hydroamidation condition, [amide-base adduct]
~50 × [thiol-base adduct]

Preliminary Experimental Results



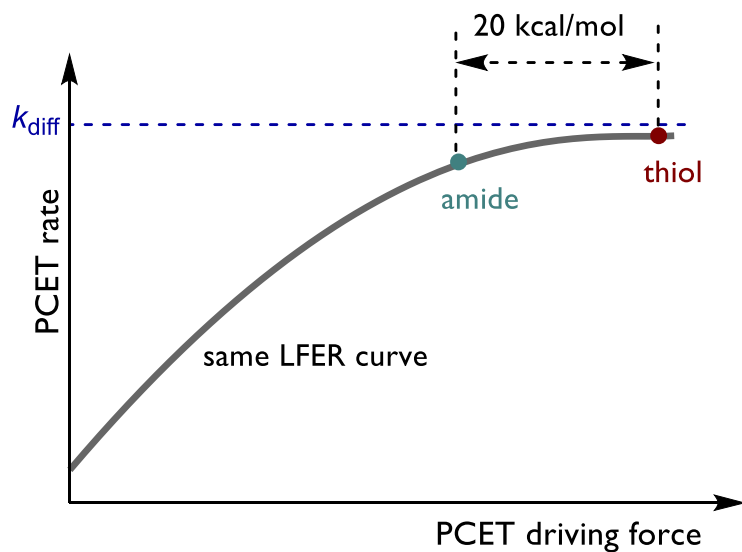
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At hydroamidation condition, [amide-base adduct]
~50 × [thiol-base adduct]

Difference in H-bonded adduct concentration dominates the PCET selectivity

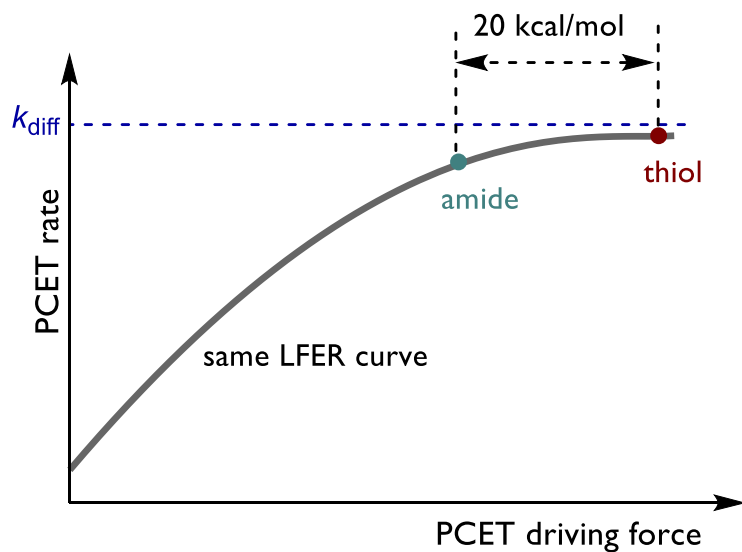
More about the Role of Thermodynamic Bias

How would the MS-PCET rate constant of amide and thiol *each* depend on the driving force?
Is driving force the only factor that dictates the MS-PCET rate constant?

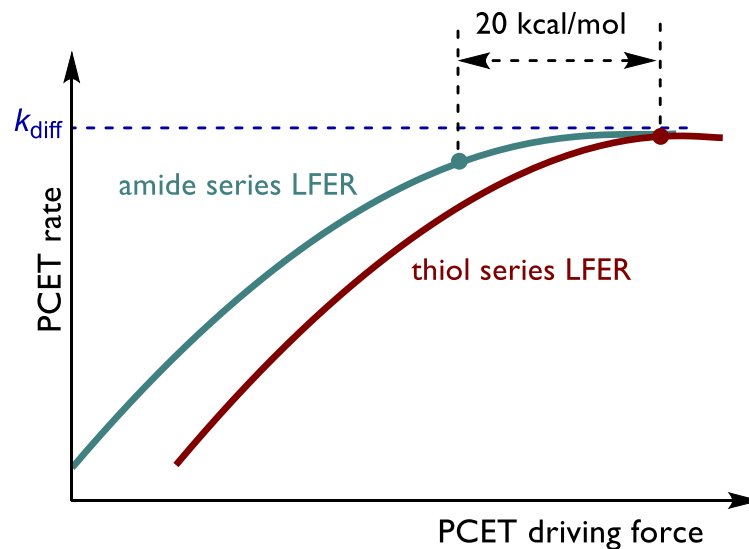


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VS

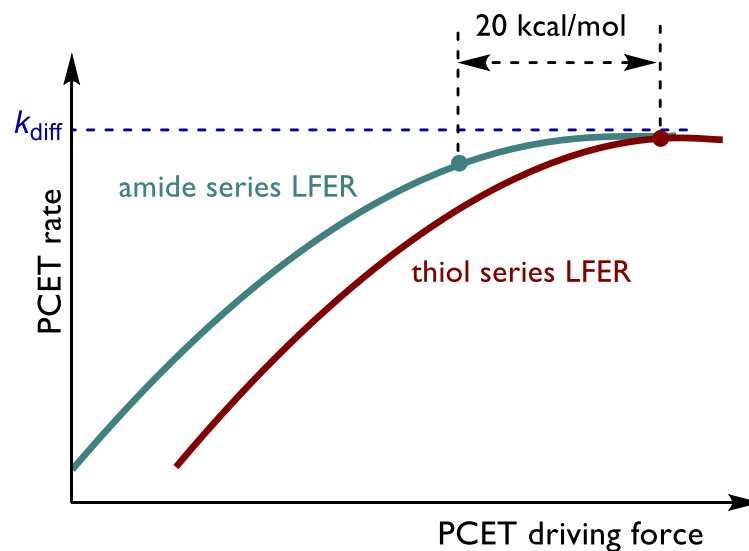


More about the Role of Thermodynamic Bias

Will the rate constant of different MS-PCET systems display same sensitivity to the driving force?

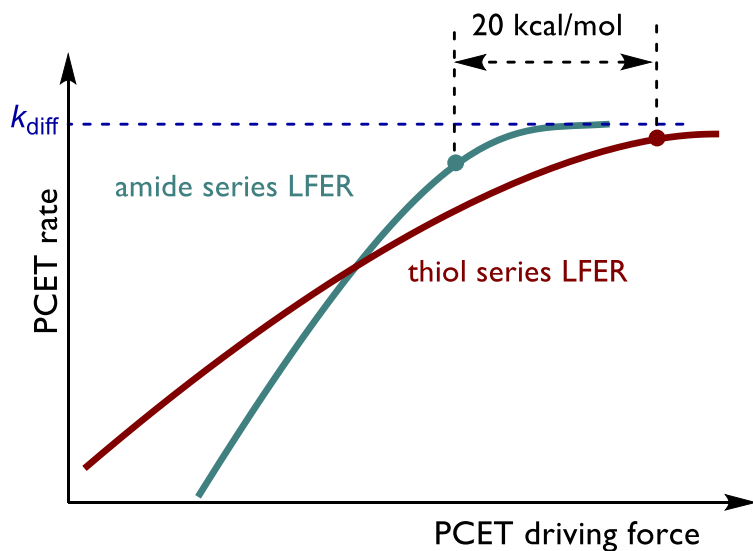
Could the chemoselectivity ever been reversed?

How would MS-PCET selectivity affect the catalytic reaction outcome?

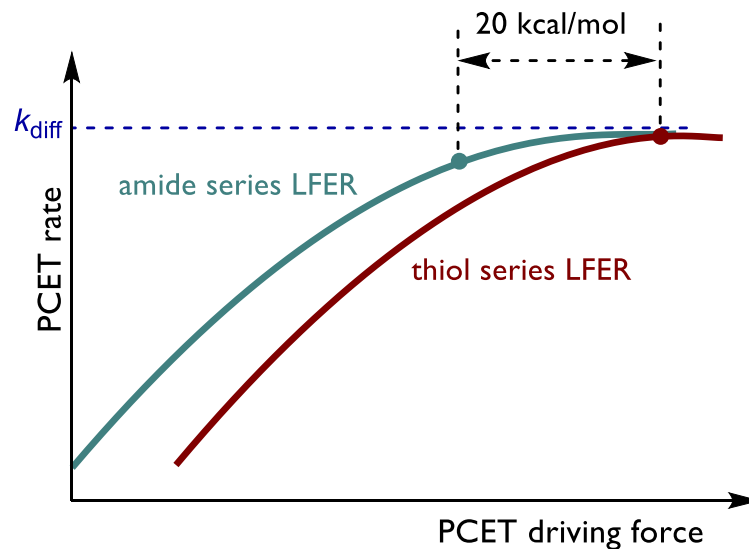


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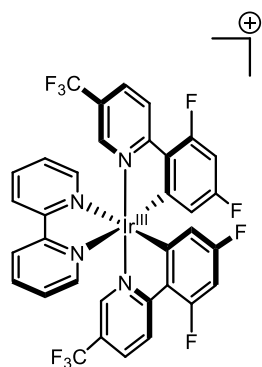
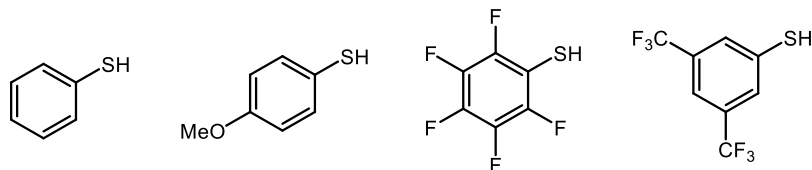
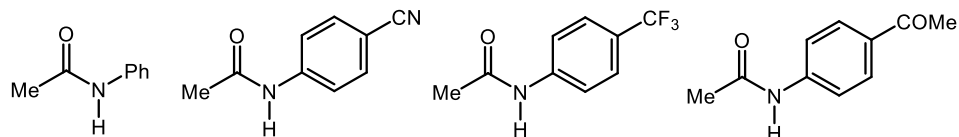


VS

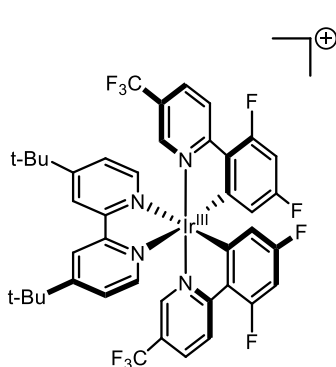


More about the Role of Thermodynamic Bias: Rate-Driving Force Correlation

Base $\text{NBu}_4\text{OP(O)(OBu)}_2$

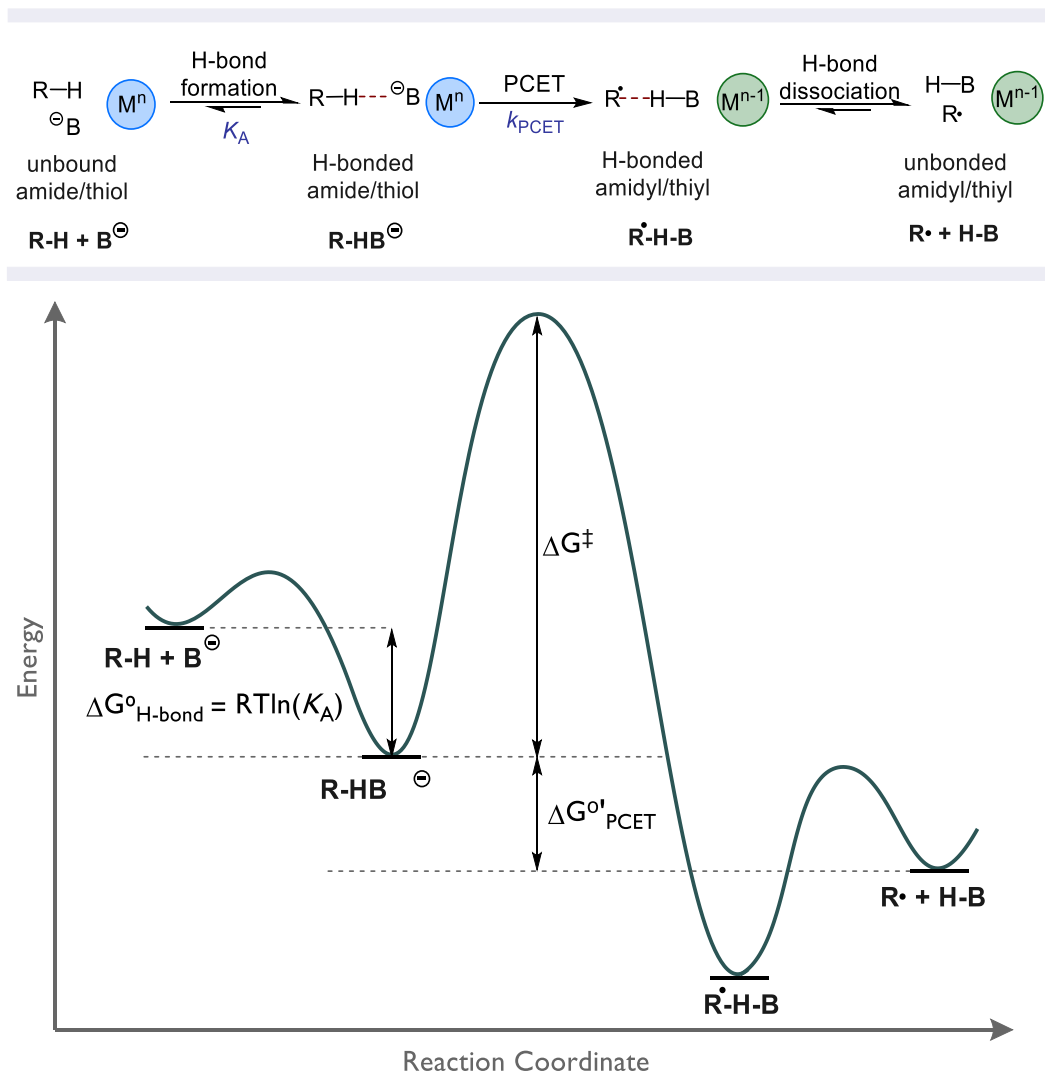


$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})\text{PF}_6$
 $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.32\text{V SCE}$

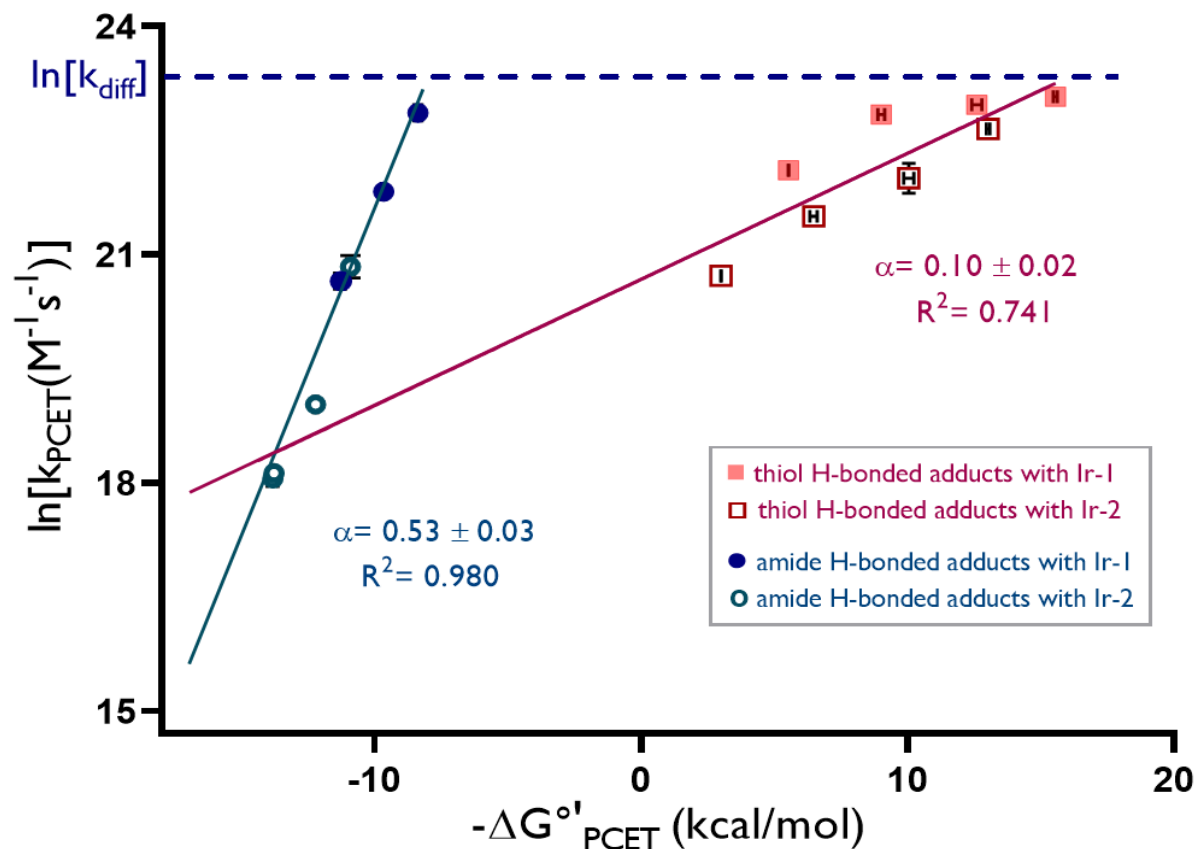


$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})\text{PF}_6$
 $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.21\text{V SCE}$

More about the Role of Thermodynamic Bias: Rate-Driving Force Correlation



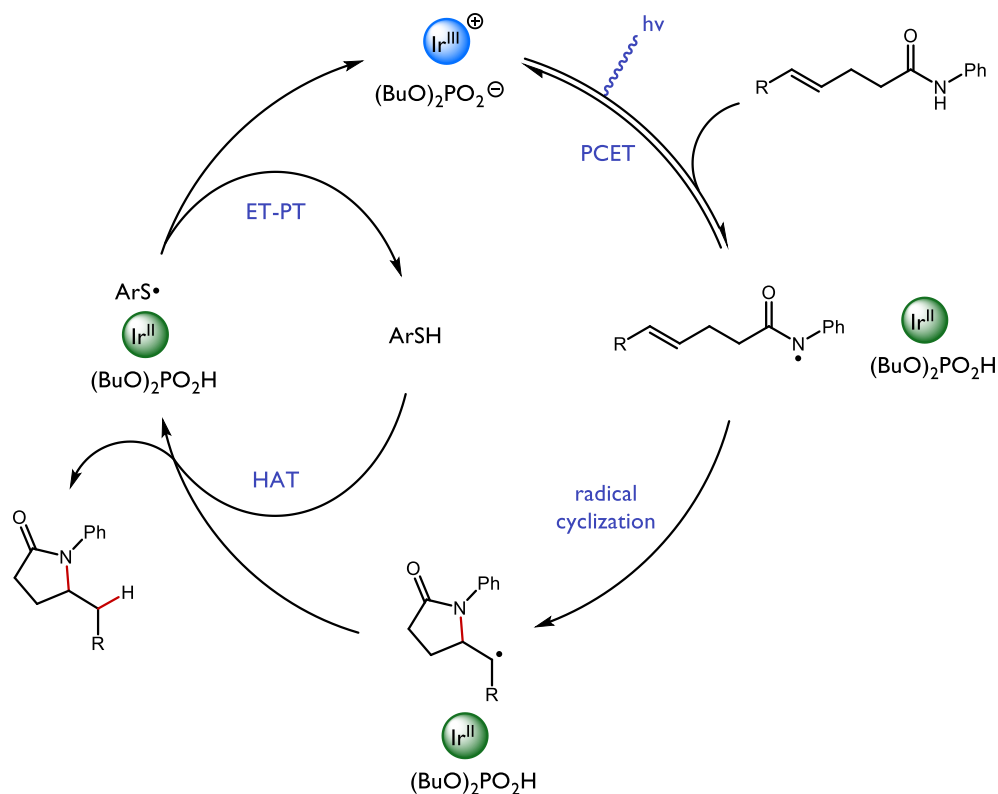
More about the Role of Thermodynamic Bias: Rate-Driving Force Correlation



- Amide and Thiol kinetic-thermodynamic correlation lines do not overlay
- The two series of PCET reaction display different intrinsic reactivities

New Hypothesis for Origin of PCET Selectivity

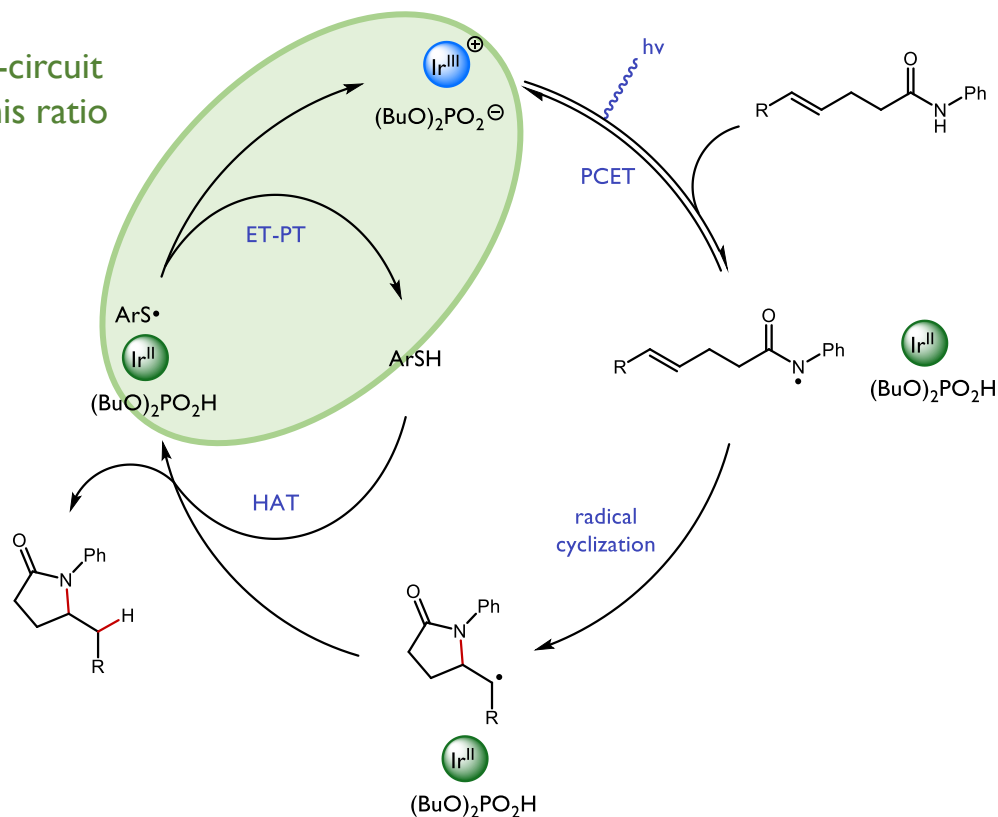
$$Q = \frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$



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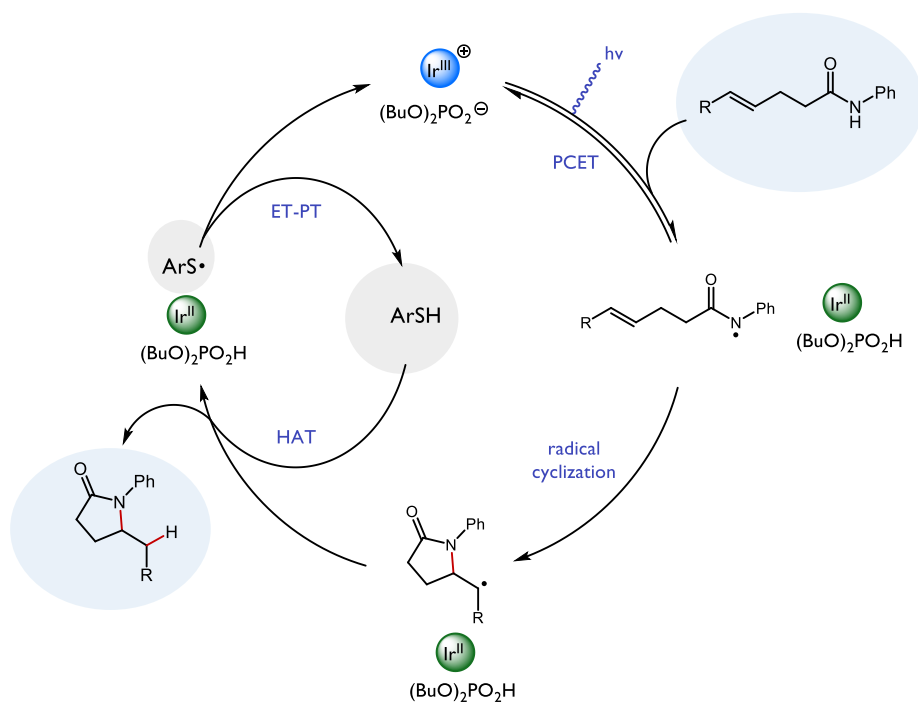
$$Q = \frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$

The thiol cycle will short-circuit the catalytic reaction if this ratio is too small



Correlation between PCET Selectivity and Hydroamidation Yield

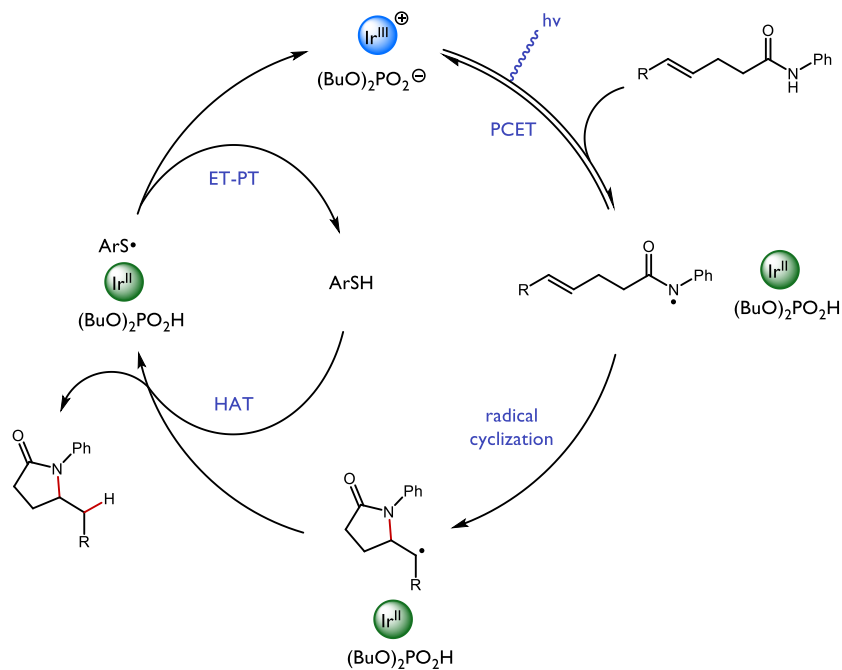
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- In the hydroamidation reaction system, amide is the substrate, thiol is a catalyst
- $\Rightarrow$ Amide is being stoichiometrically consumed

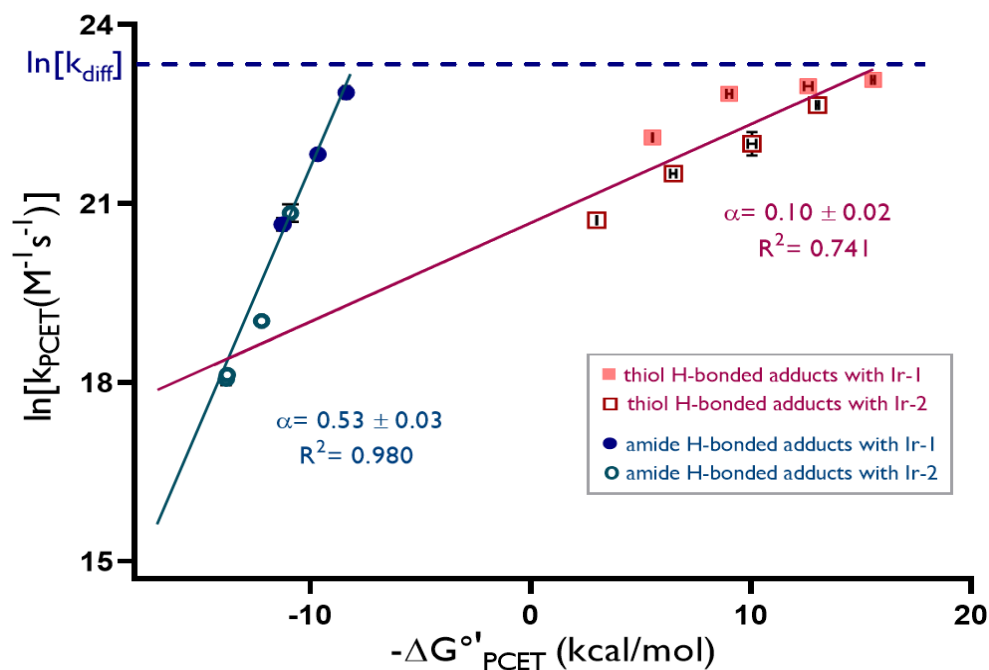
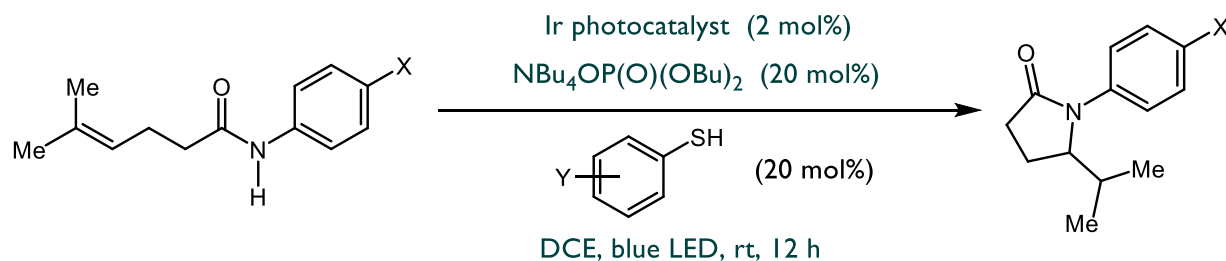
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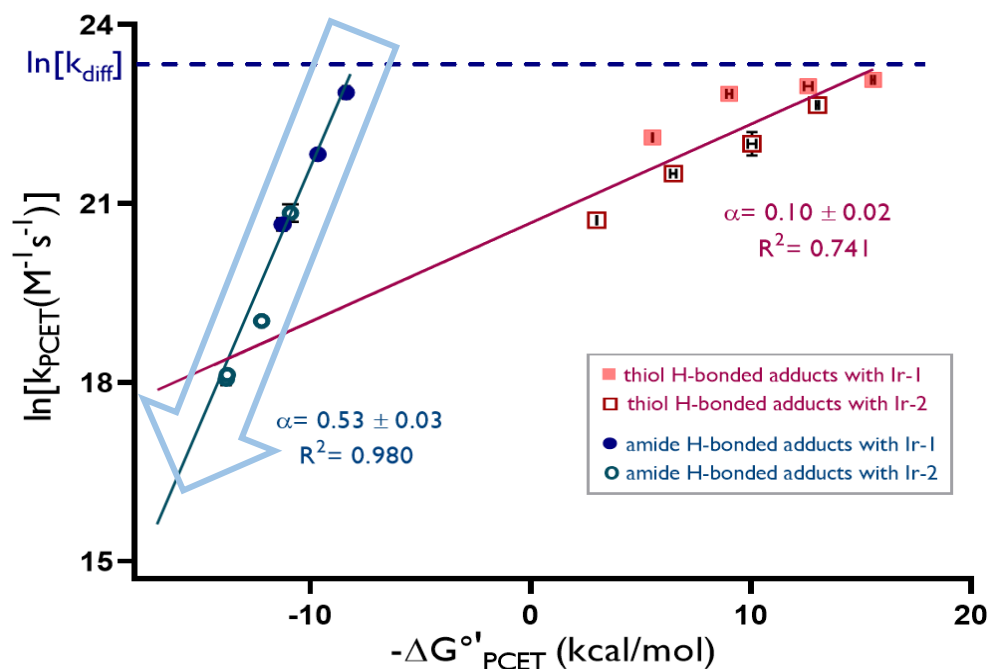
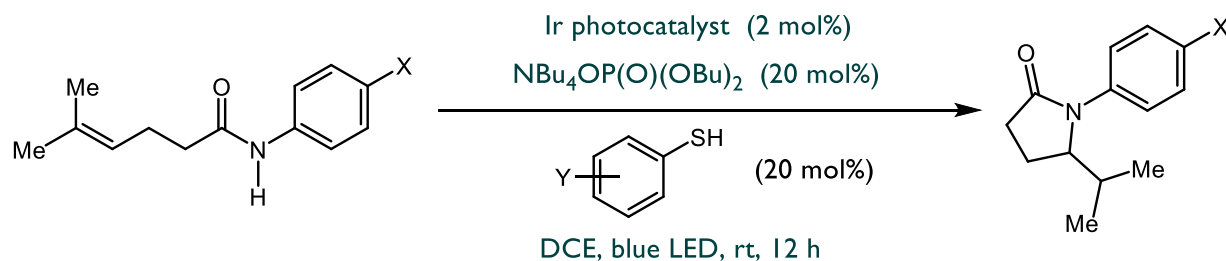
- In the hydroamidation reaction system, amide is the substrate, thiol is a catalyst
- $\Rightarrow$ Amide is being stoichiometrically consumed
- $[\text{amide adduct}]$ is decreasing, $[\text{thiol adduct}]$ is increasing
- $\Rightarrow Q$ is decreasing
- $\Rightarrow Q_0$ (initial value of Q) reflects how much "excess amide" is available to be consumed

Electron-Withdrawing Group on Amide



$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Electron-Withdrawing Group on Amide

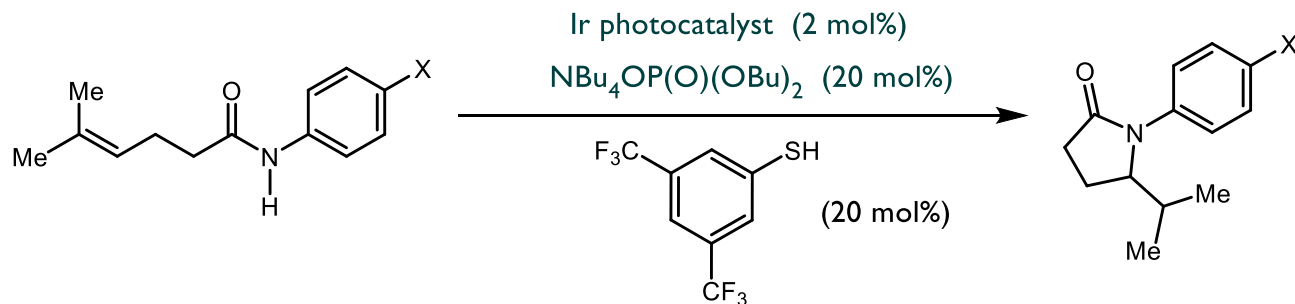


$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Stronger N-H bond: lower $k_{\text{PCET amide}}$
 Stronger H-bond donor: higher $K_{\text{A amide}}$
 Rate is sensitive to driving force

} Q_0 decreases

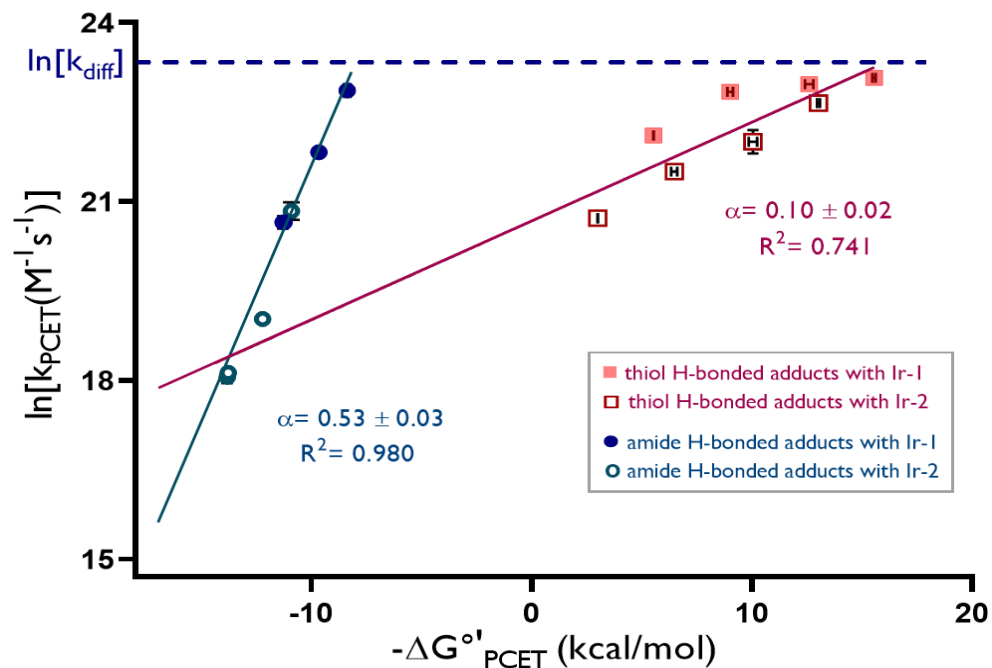
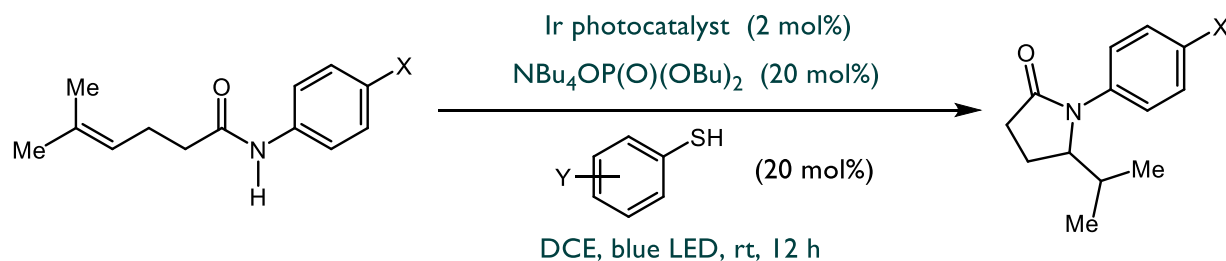
Electron-Withdrawing Group on Amide



	$K_{\text{A amide}}$	$k_{\text{PCET amide}}$	Q_0	% yield
<chem>CC(C)=CC(=O)Nc1ccccc1</chem>			64 : 36	85
<chem>CC(C)=CC(=O)Nc1ccc(C(=O)C)cc1</chem>			23 : 77	10
<chem>CC(C)=CC(=O)Nc1ccc(C#N)cc1</chem>			18 : 82	0

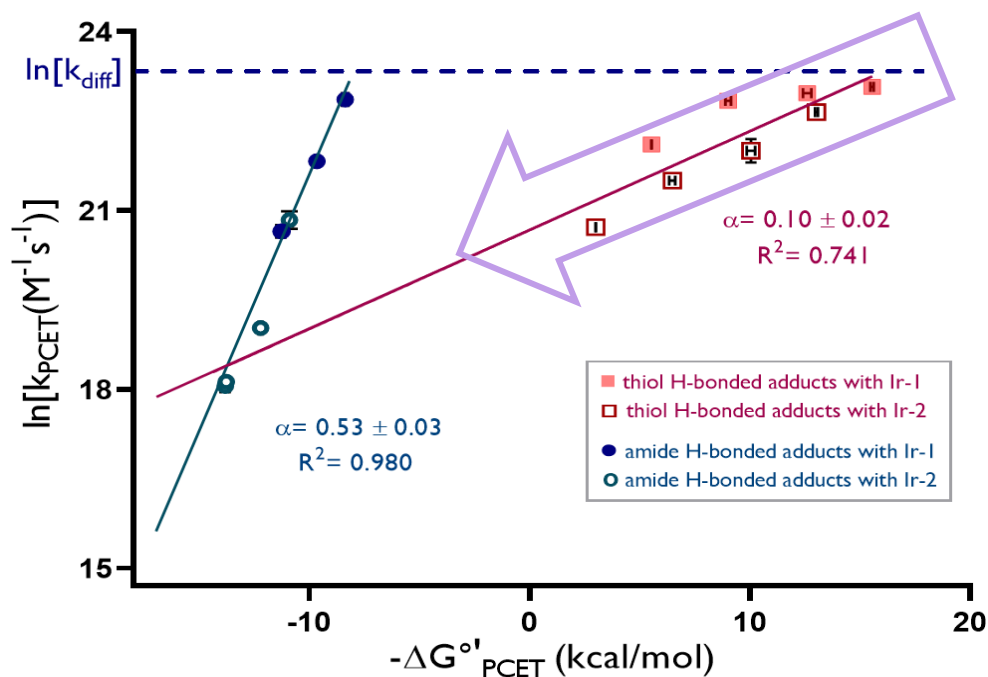
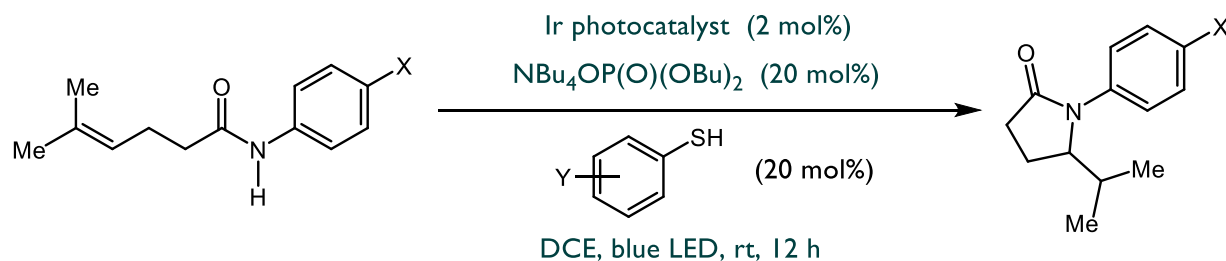
$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Electron-Withdrawing Group on Thiol



$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Electron-Withdrawing Group on Thiol

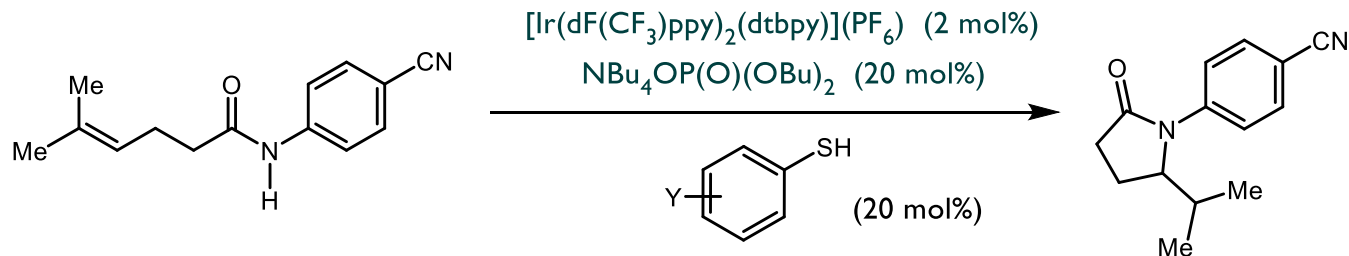


$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Stronger S-H bond: lower $k_{\text{PCET thiol}}$
 Stronger H-bond donor: higher $K_{\text{A thiol}}$
 Rate is insensitive to driving force

Q_0 decreases

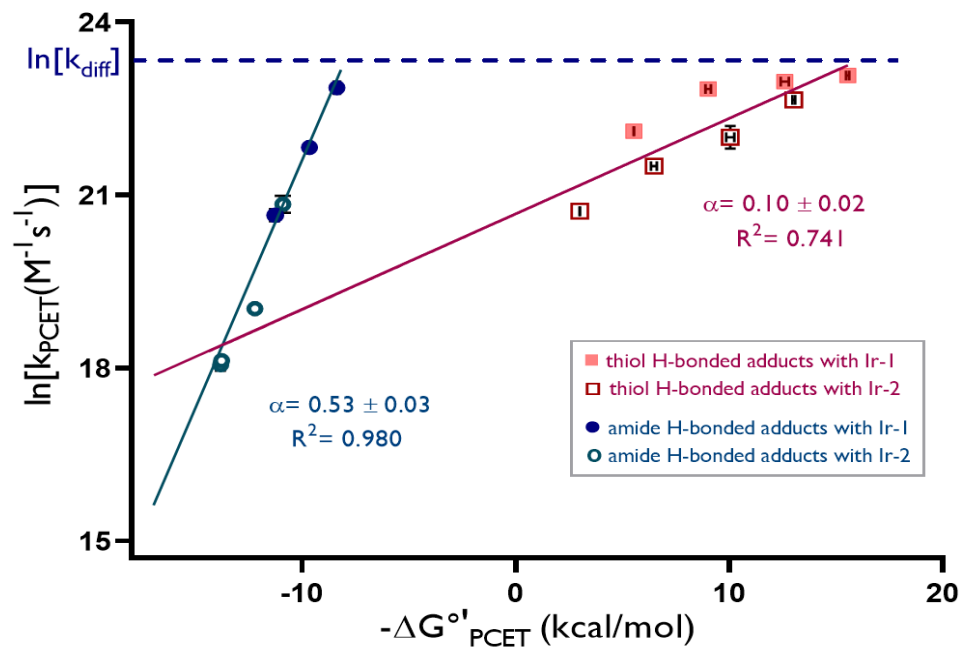
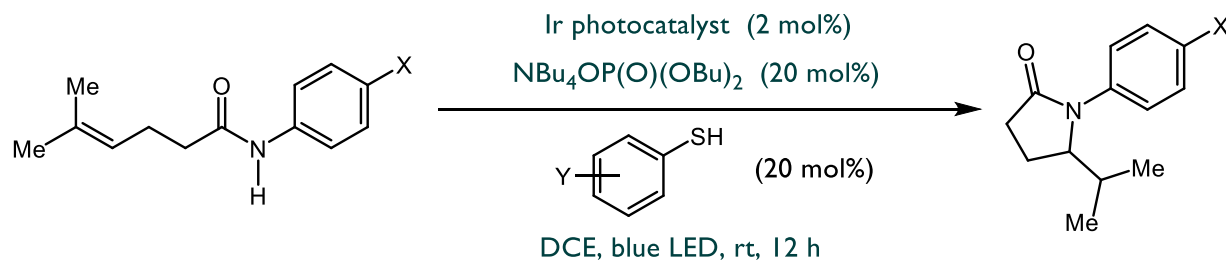
Electron-Withdrawing Group on Thiol



	$K_{\text{A thiol}}$	$k_{\text{PCET thiol}}$	Q_0	% yield
<chem>c1ccccc1S</chem>			87 : 13	100
<chem>FC(F)(F)c1ccc(S)cc1C(F)(F)F</chem>			47 : 53	13
<chem>Fc1c(F)c(S)c(F)c(F)c1F</chem>			44 : 56	3

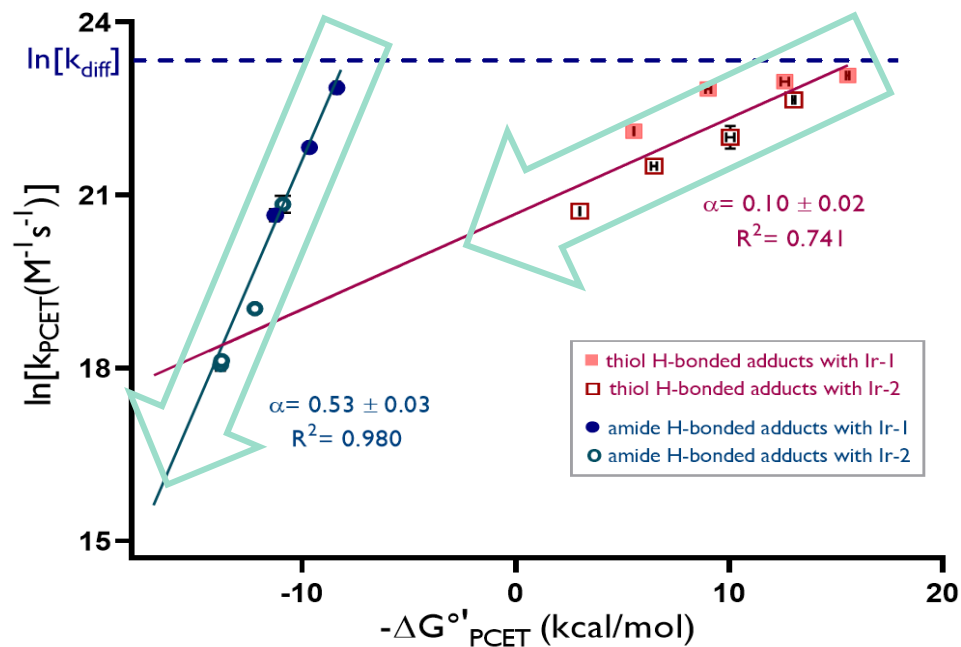
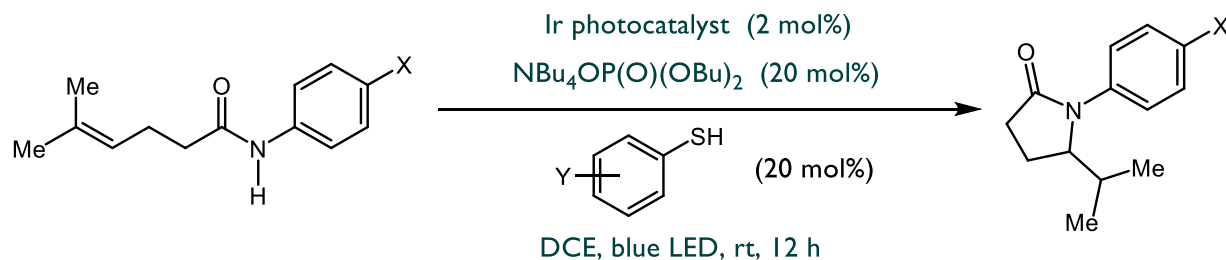
$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Weaker Photo-oxidant



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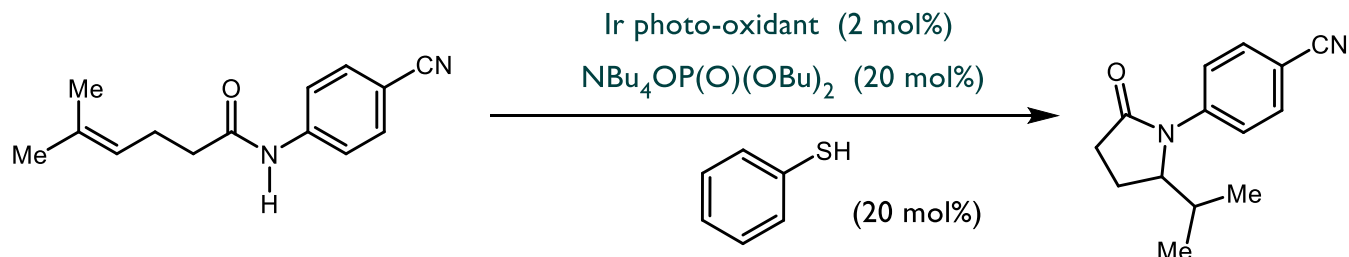
Weaker Photo-oxidant



$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Both $k_{\text{PCET amide}}$ and $k_{\text{PCET thiol}}$ decrease
 $k_{\text{PCET amide}}$ is sensitive to driving force
 $k_{\text{PCET thiol}}$ is insensitive to driving force
 } Q_0 decreases

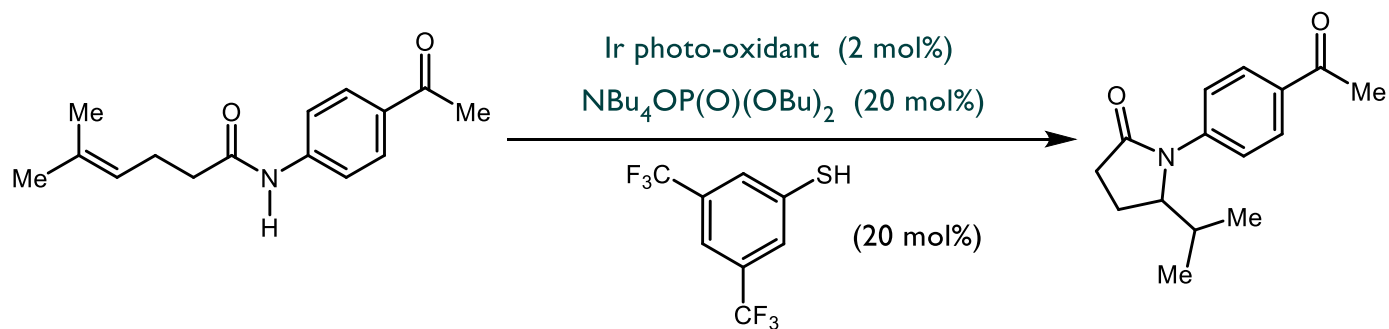
Weaker Photo-oxidant



	$k_{\text{PCET amide}}$	$k_{\text{PCET thiol}}$	Q_0	% yield
$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})](\text{PF}_6)$ $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.32\text{V SCE}$	↑	↑	87 : 13	100
$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})](\text{PF}_6)$ $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.21\text{V SCE}$			57 : 43	8

$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Weaker Photo-oxidant

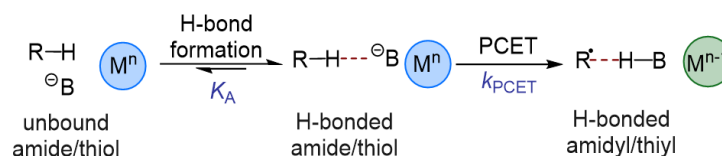


	$k_{\text{PCET amide}}$	$k_{\text{PCET thiol}}$	Q_0	% yield
$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})](\text{PF}_6)$ $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.32\text{V SCE}$	↑	↑	56 : 44	60
$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})](\text{PF}_6)$ $E_{1/2}(\text{Ir}^{*\text{III/II}}) = +1.21\text{V SCE}$			23 : 77	10

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Summary and General Principles

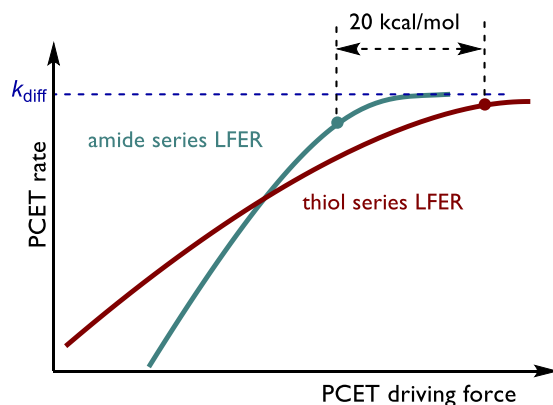
- Selectivity of MS-PCET is determined by H-bonded adduct concentration and its rate constant
- MS-PCET of amide and thiol display different intrinsic barriers: kinetics respond to thermodynamics with different sensitivities
- PCET reaction barrier is well separated into intrinsic barrier and thermodynamics. (kinetic VS thermodynamic control)
- eg. the 20 kcal/mol thermodynamic disadvantage for acetinilide N-H bond is compensated by its lower intrinsic barrier.
- Selectivity in MS-PCET could be made to switch, thus catalytic reactions could be manipulated



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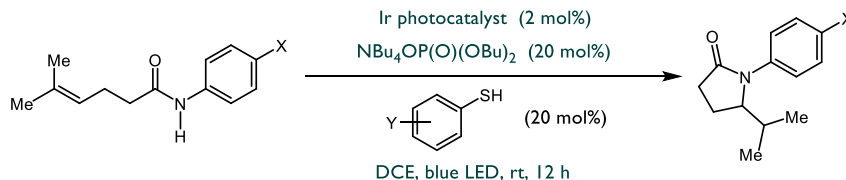
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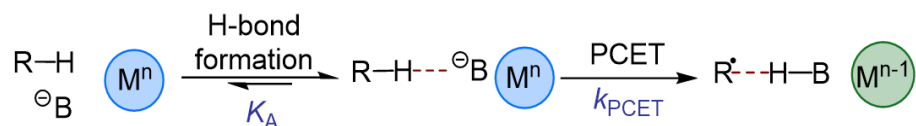


$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0}$$

Q_0	% yield
78 : 22	95
64 : 36	85
56 : 44	60
47 : 53	13
23 : 77	10
18 : 82	0

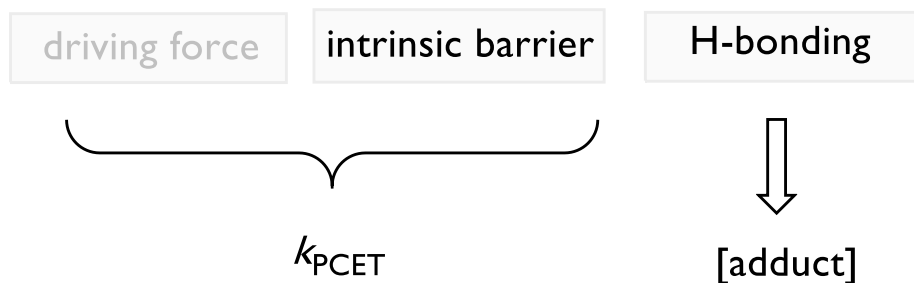
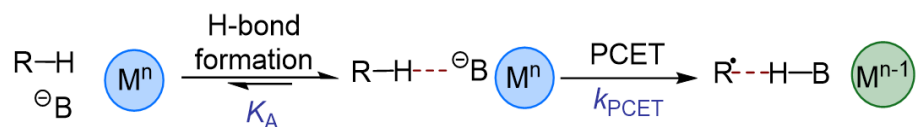
General Implications in Organic Synthesis

- EDG/EWG : H-Bond K_A thus [H-bonded adduct]; driving force thus k_{PCET}
- $\text{p}K_a$ of Brønsted acid/base: H-Bond K_A thus [H-bonded adduct]; driving force thus k_{PCET}
- Steric effects: H-Bond K_A thus [H-bonded adduct]; perhaps intrinsic barrier thus α value
- Outer-sphere oxidant/reductant: driving force thus k_{PCET}
- Which effect dominant affected by α value



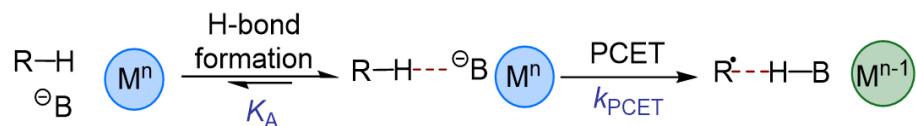
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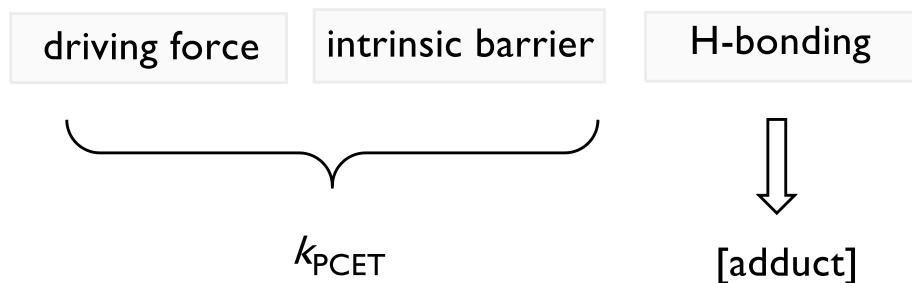
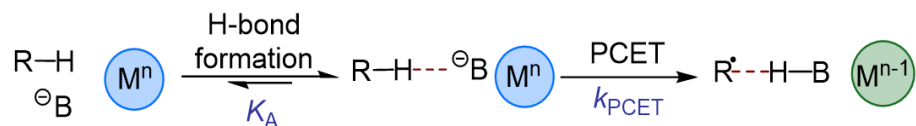
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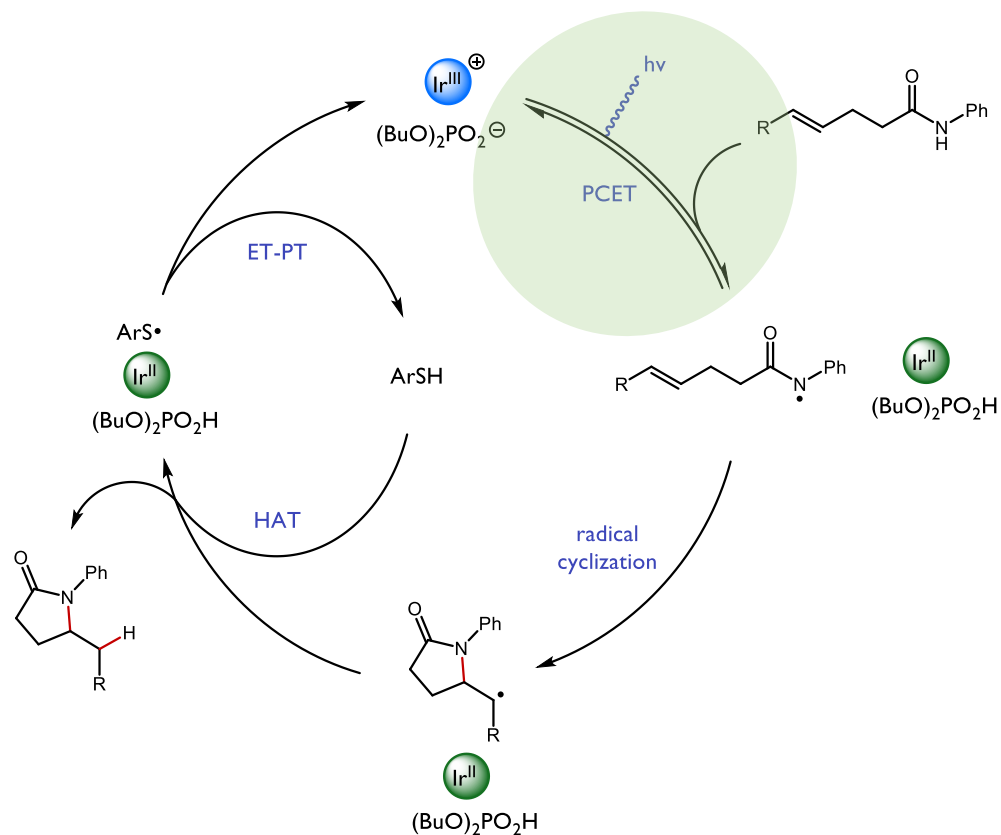


General Implications in Organic Synthesis

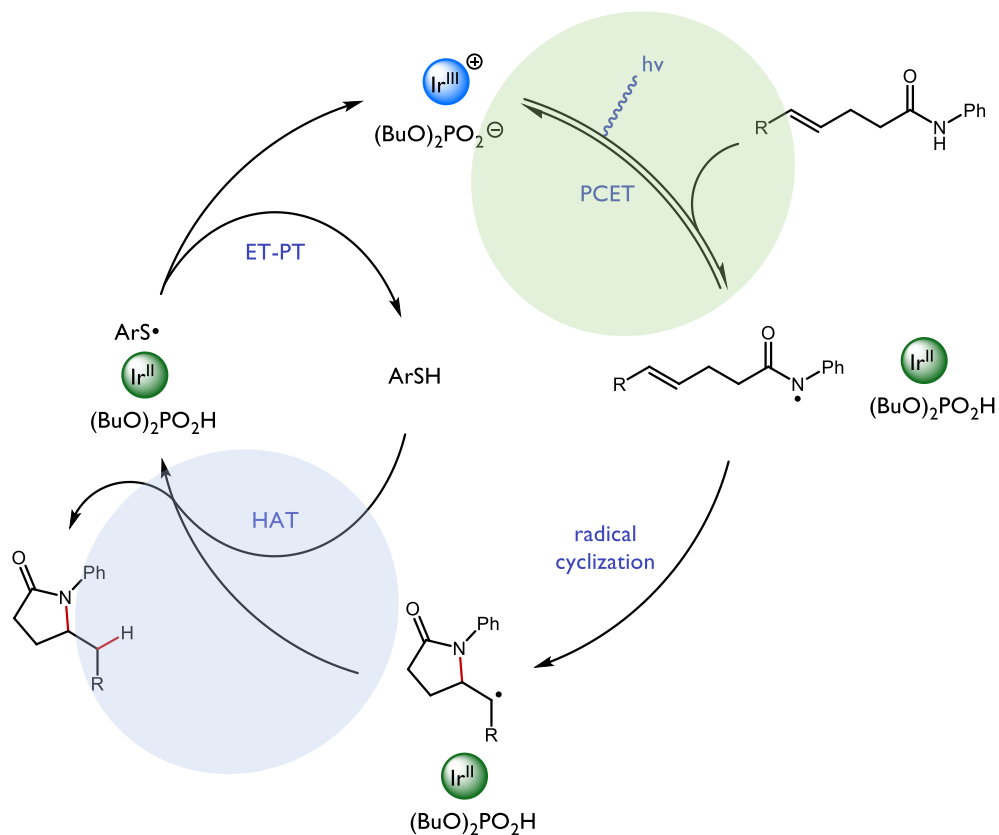
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MS-PCET kinetics and chemoselectivity determine the fate of the *upstream* of the catalytic cycle.

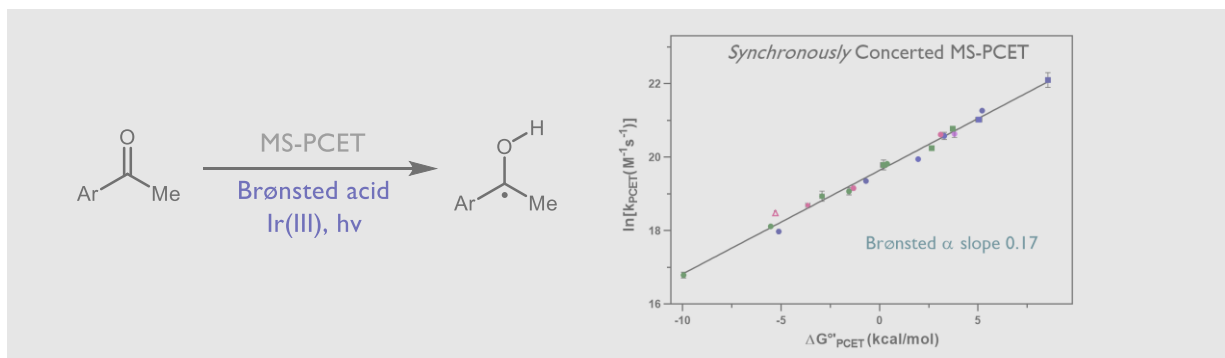


MS-PCET kinetics and chemoselectivity determine the fate of the *upstream* of the catalytic cycle.

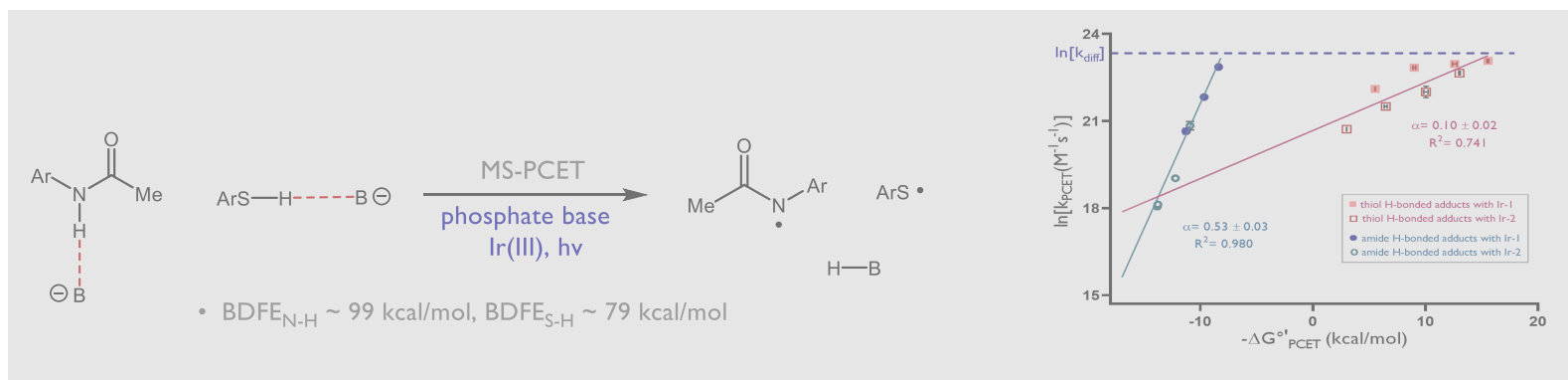


How could the *downstream* of the catalytic cycle be probed?

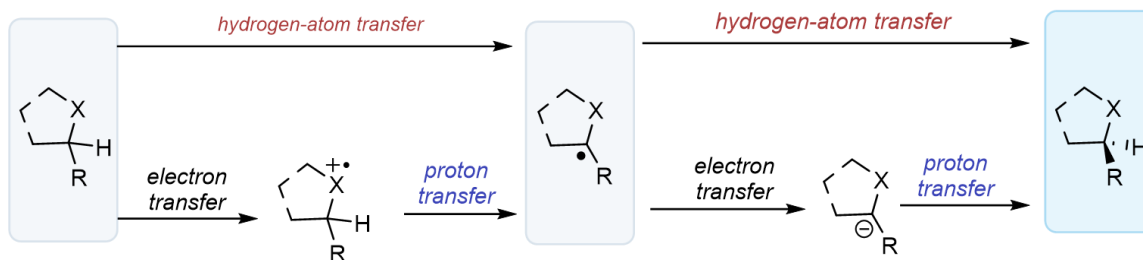
I. Kinetics and Mechanism of Multi-Site PCET



2. Chemoselectivity in Competitive Multi-Site PCET

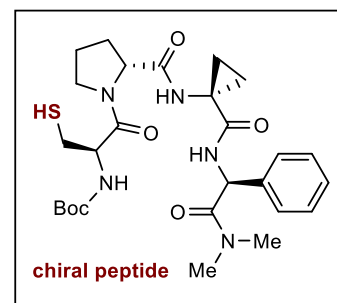
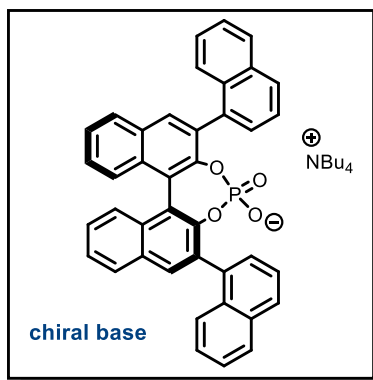
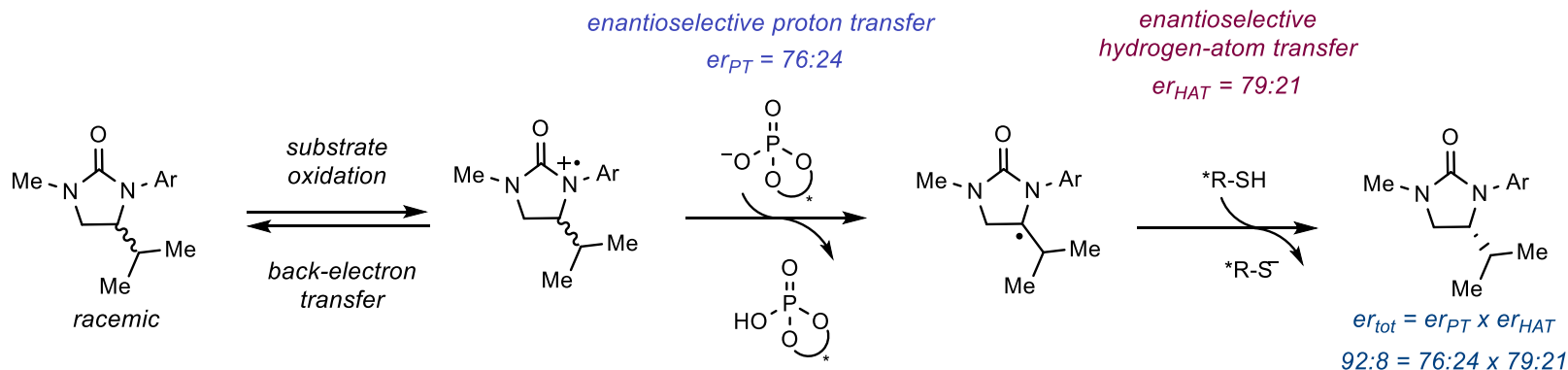


3. Probing Two-Step C–H Activation Mode



a general method probing the activation mode among these four possibilities

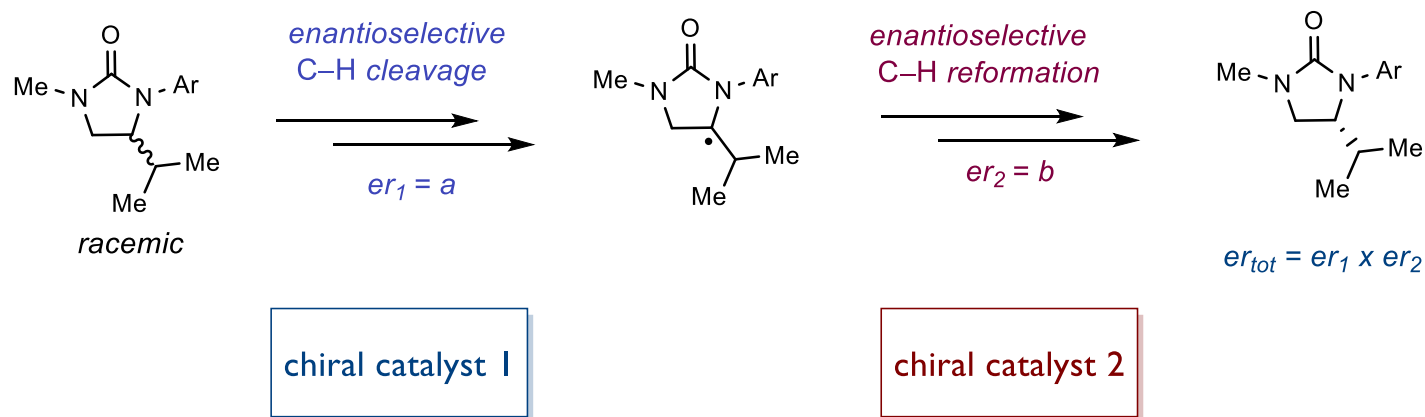
Probing the Activation Mode for Sequential Cleavage-Reformation of C–H Bond



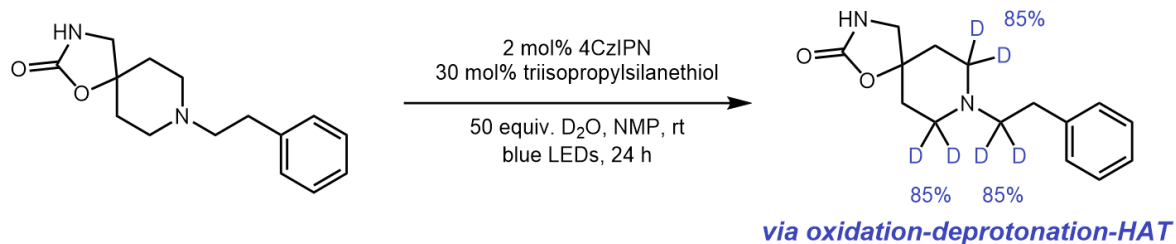
overall C–H activation mechanism: ETPT-HAT

there are other possibilities in general

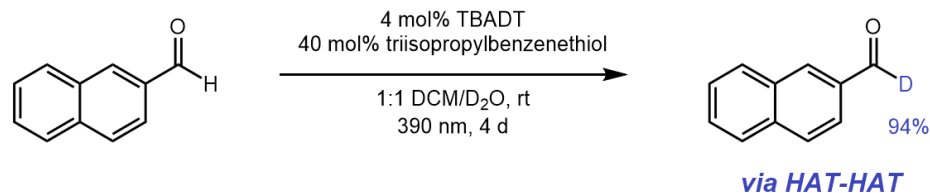
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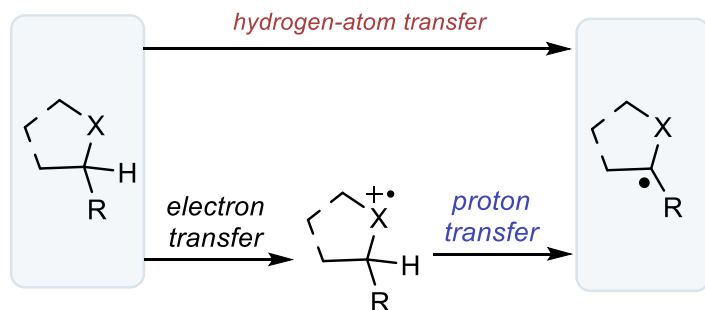
(MacMillan, 2017)



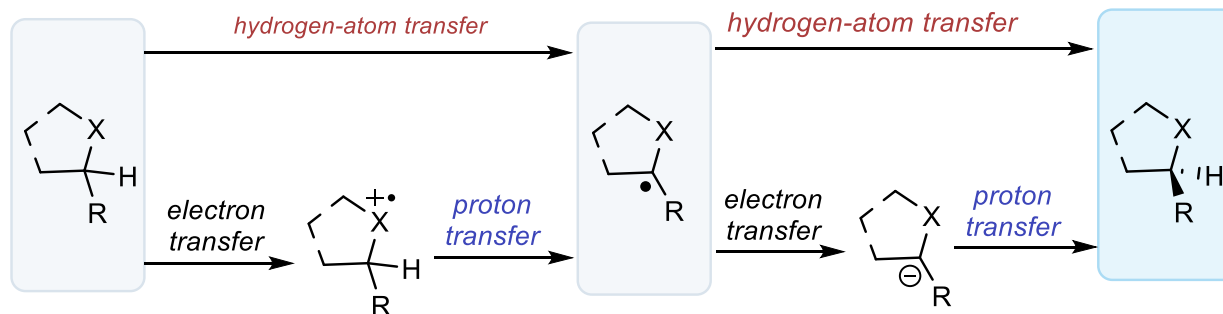
(Wang, 2019)



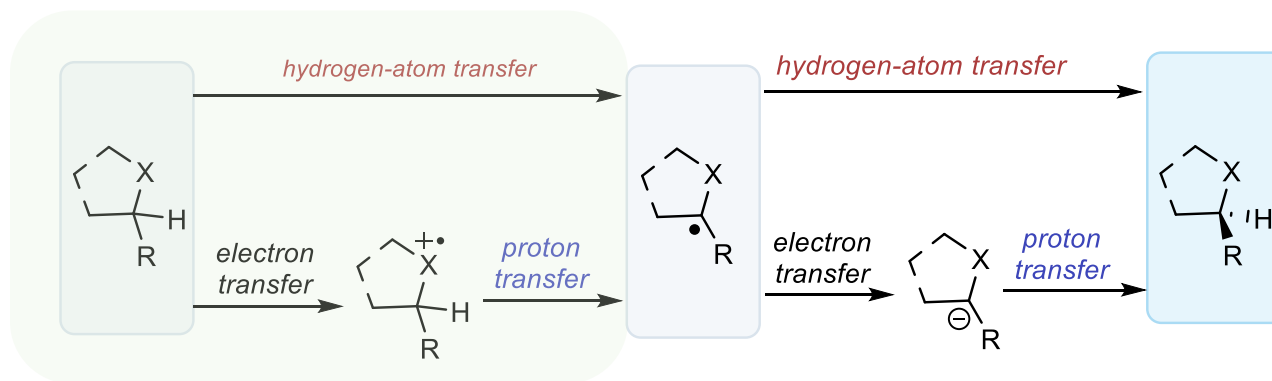
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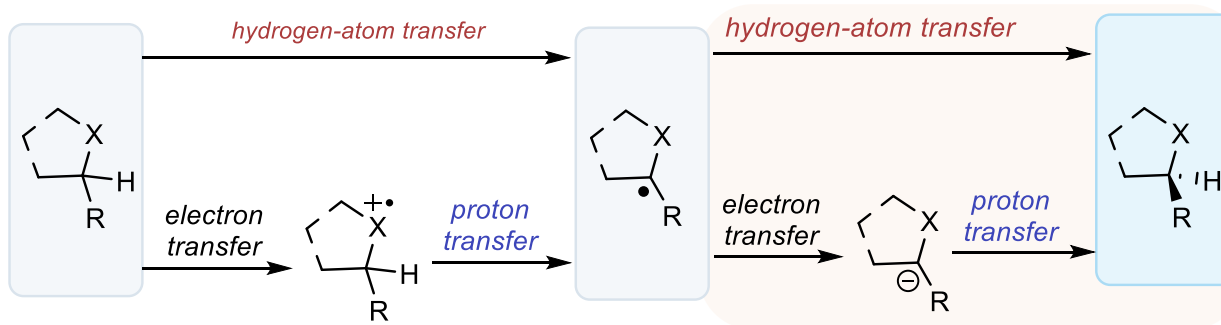


Probing the Activation Mode for Sequential Cleavage-Reformation of C–H Bond



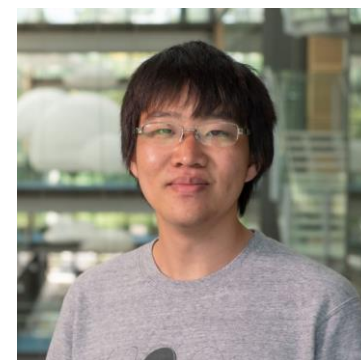
substrate/thiol activation could be probed directly

Probing the Activation Mode for Sequential Cleavage-Reformation of C–H Bond



How to probe the fate of the reactive intermediate?

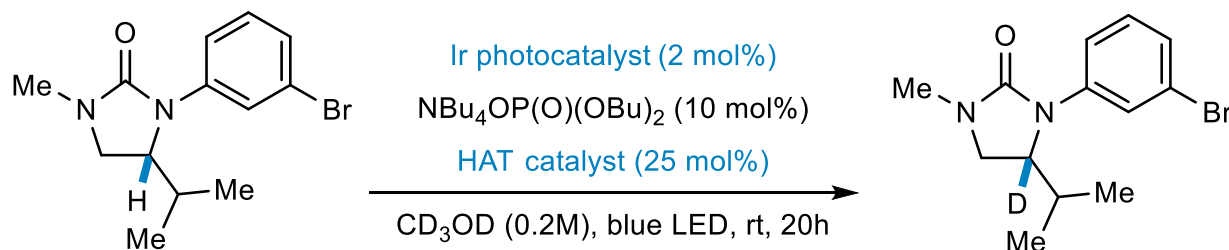
This work: Fractionation Slope of Gradual Deuteration



Chi-Li Ni

H/D Isotopic Exchange as the Readout for C–H Activation

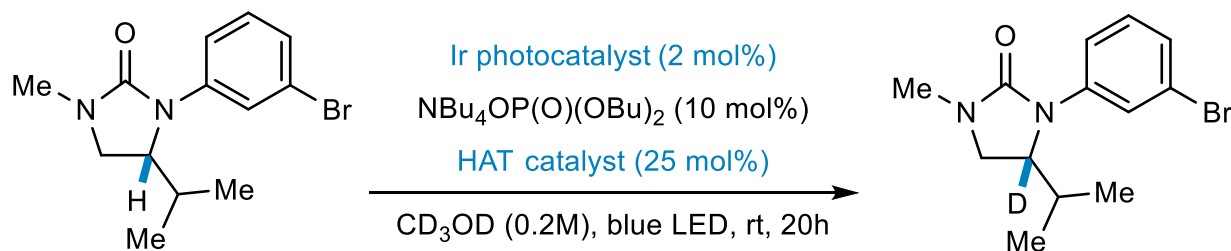
Interplay between (very common) catalysts



Ir photocatalyst	HAT catalyst	deuterium incorporation
Ir(dF(CF ₃)ppy) ₂ dtbpy)PF ₆	thioacetic acid	96% D
Ir(dF(CF ₃)ppy) ₂ dtbpy)PF ₆	thiophenol	0% D
Ir(dF(CF ₃)ppy) ₂ (3,3'-d(CO ₂ Me)bpy)PF ₆	thiophenol	92% D (48h)

De-optimization!

Interplay between (Very Common) Catalysts



BDFE (C–H) ~ 90 kcal/mol

Ir photocatalyst

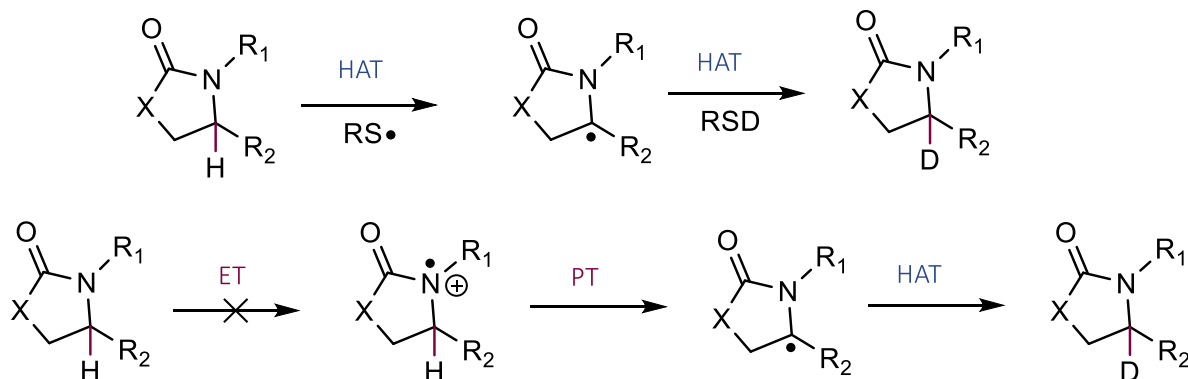
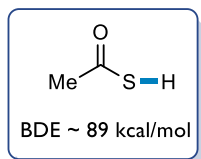
HAT catalyst

deuterium incorporation

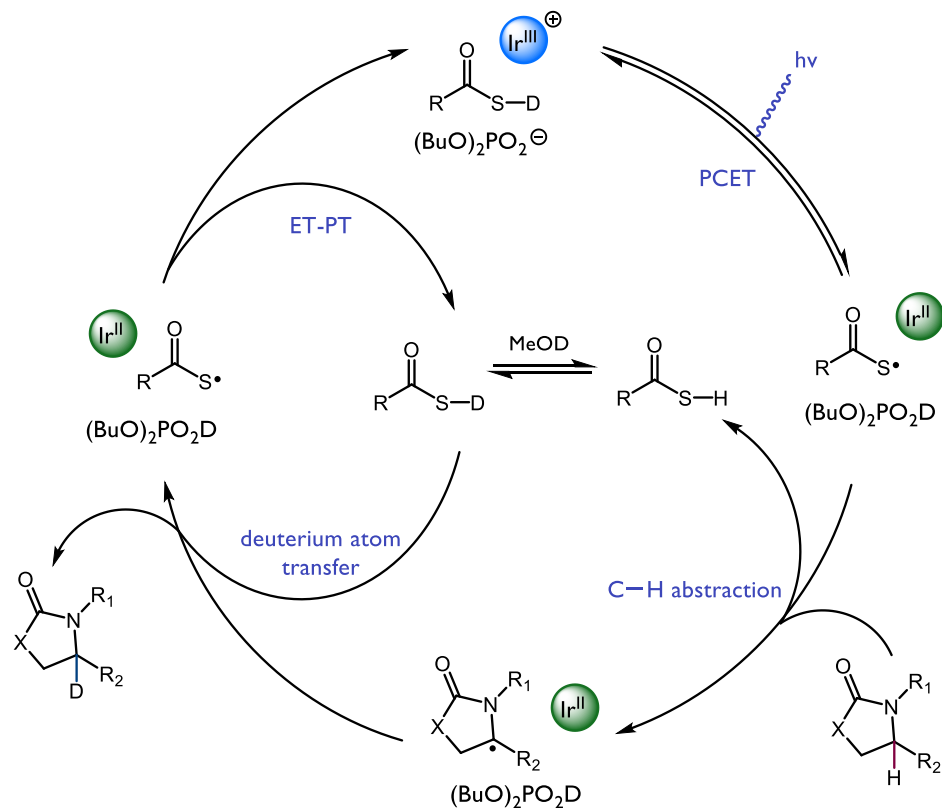
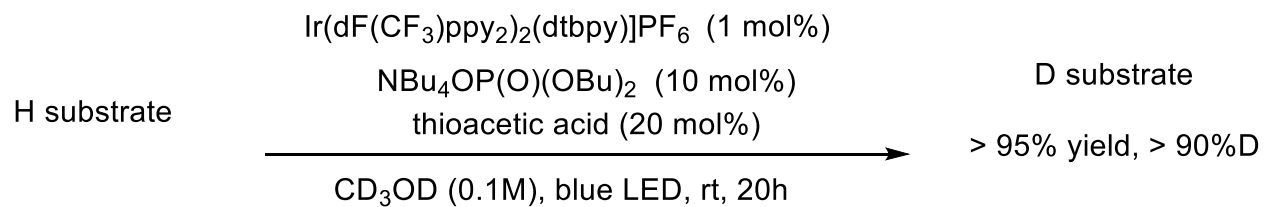
Ir(dF(CF₃)ppy)₂dtbpy)PF₆

thioacetic acid

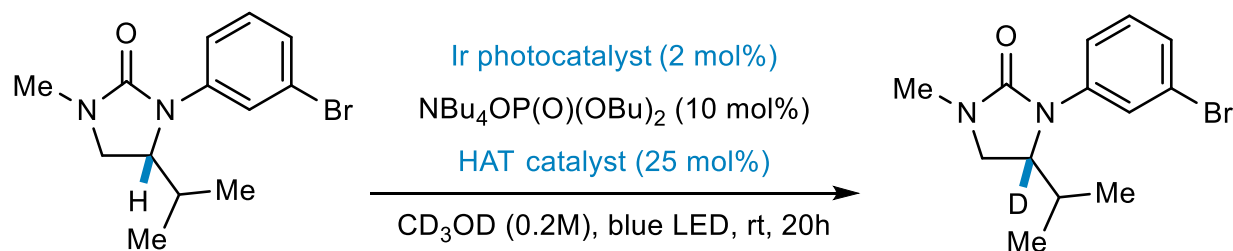
96% D



HAT-HAT Deuteration

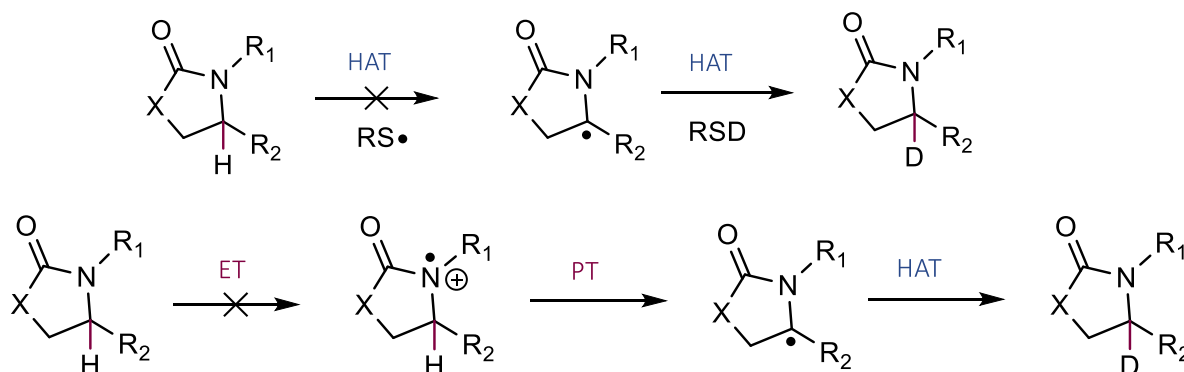
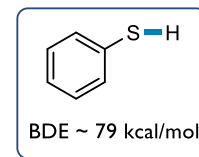


Interplay between (Very Common) Catalysts

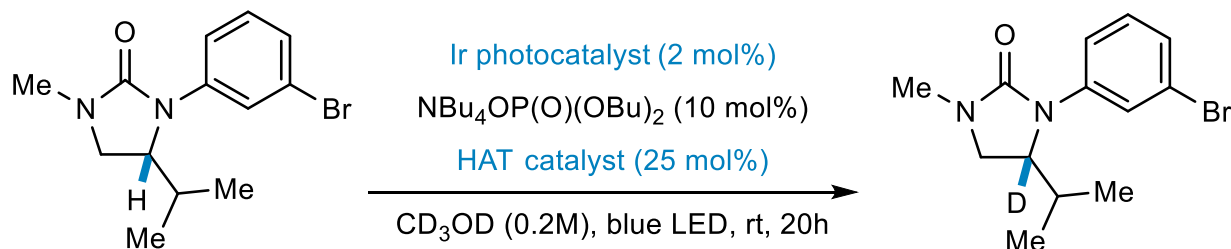


BDFE (C–H) ~ 90 kcal/mol

	Ir photocatalyst	HAT catalyst	deuterium incorporation
$E_{1/2}(\text{Ir}^{\text{III/II}}) = +0.83\text{V vs Fc}^+/\text{Fc}$	$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2\text{dtbpyPF}_6$	thioacetic acid	96% D
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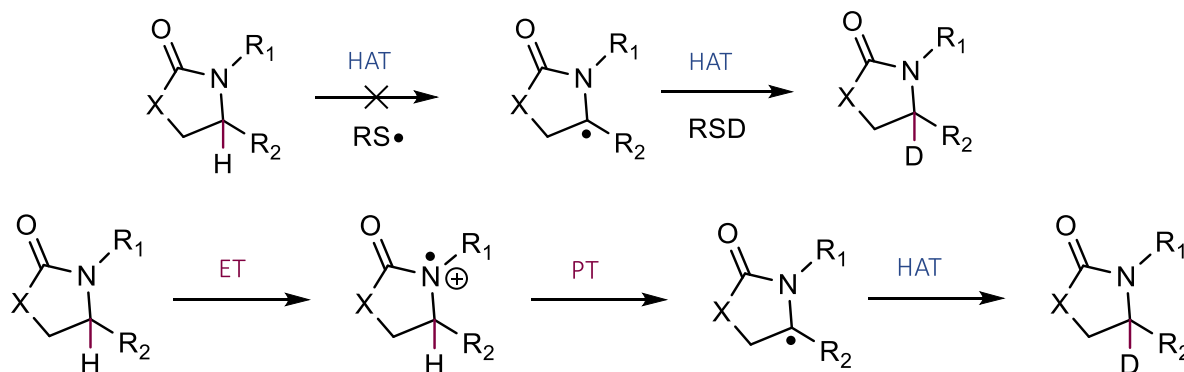
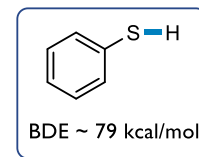


Interplay between (Very Common) Catalysts



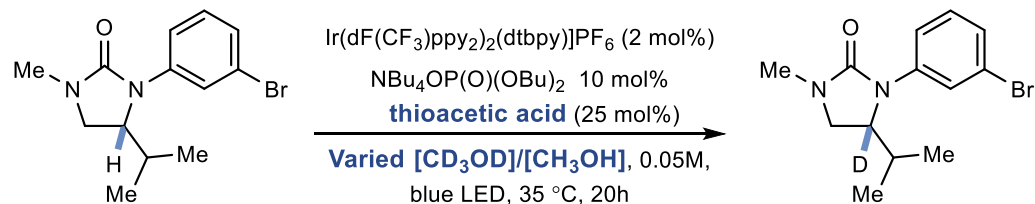
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$E_{1/2}(\text{Ir}^{IV/III}) = +1.26\text{V vs Fc}^+/\text{Fc}$	$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(3,3'\text{-d}(\text{CO}_2\text{Me})\text{bpy})\text{PF}_6$	thiophenol	92% D (48h)



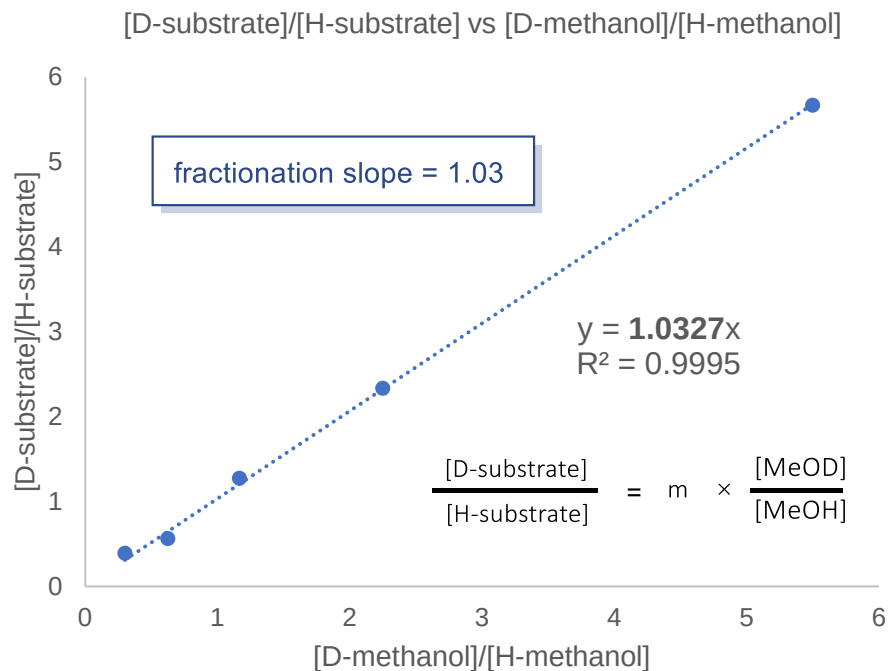
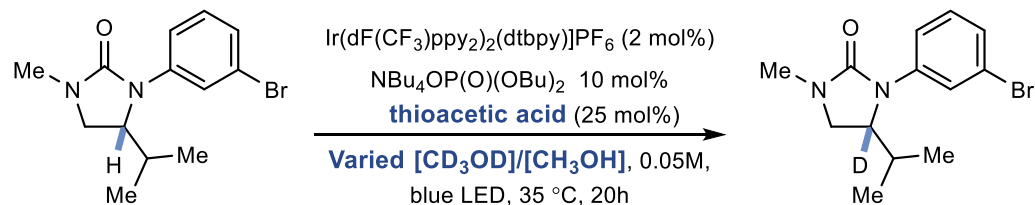
The Method of Isotope Fractionation

Typical Experiment: *Gradual Deuteration*



The Method of Isotope Fractionation

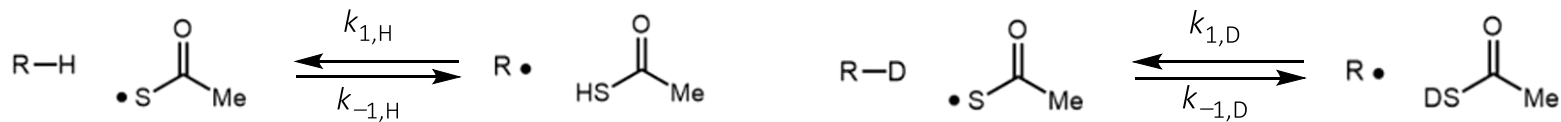
Typical Experiment: *Gradual Deuteration*



Key: the fractionation slope m as an indicator for C–H activation mechanism, **HAT-HAT** is the “reference mechanism”

The Method of Isotope Fractionation

Reference Mechanism HAT-HAT

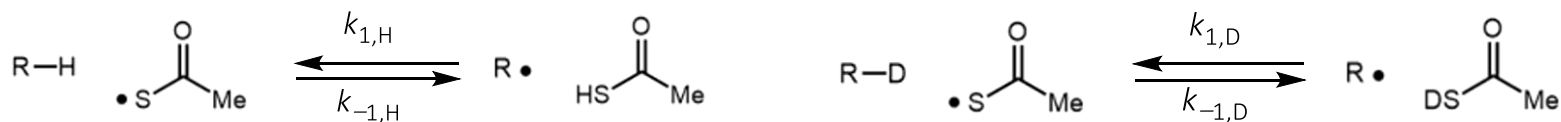


rate of formation of D-substrate: $(k_{1,\text{H}}) \times (k_{-1,\text{D}}) \times [\text{RS-D}]$

rate of formation of H-substrate: $(k_{1,\text{D}}) \times (k_{-1,\text{H}}) \times [\text{RS-H}]$

The Method of Isotope Fractionation

Reference Mechanism HAT-HAT



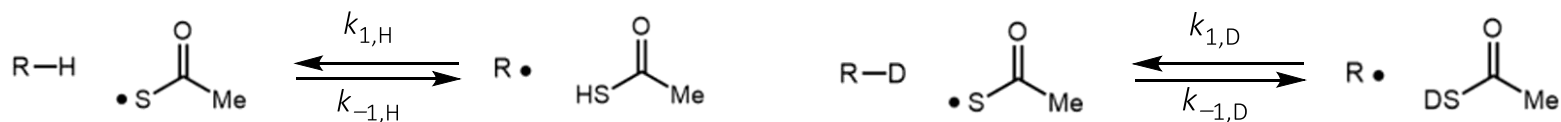
rate of formation of D-substrate: $(k_{1,H}) \times (k_{-1,D}) \times [\text{RS-D}]$

rate of formation of H-substrate: $(k_{1,D}) \times (k_{-1,H}) \times [\text{RS-H}]$

At the photodynamic equilibrium formation of D- and H-substrate at the same rate:

The Method of Isotope Fractionation

Reference Mechanism HAT-HAT



rate of formation of D-substrate: $(k_{1,H}) \times (k_{-1,D}) \times [\text{RS-D}]$

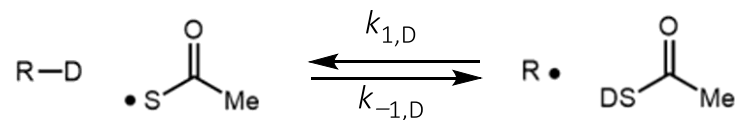
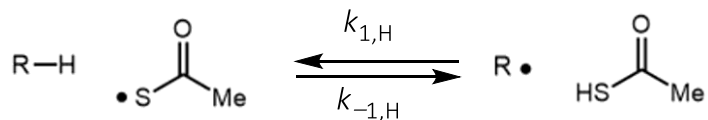
rate of formation of H-substrate: $(k_{1,D}) \times (k_{-1,H}) \times [\text{RS-H}]$

At the photodynamic equilibrium,

$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = \frac{k_{1,H}}{k_{1,D}} \times \frac{k_{-1,D}}{k_{-1,H}} \times \frac{[\text{RS-D}]}{[\text{RS-H}]}$$

The Method of Isotope Fractionation

Reference Mechanism HAT-HAT



rate of formation of D-substrate: $(k_{1,\text{H}}) \times (k_{-1,\text{D}}) \times [\text{RS-D}]$

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At the photodynamic equilibrium,

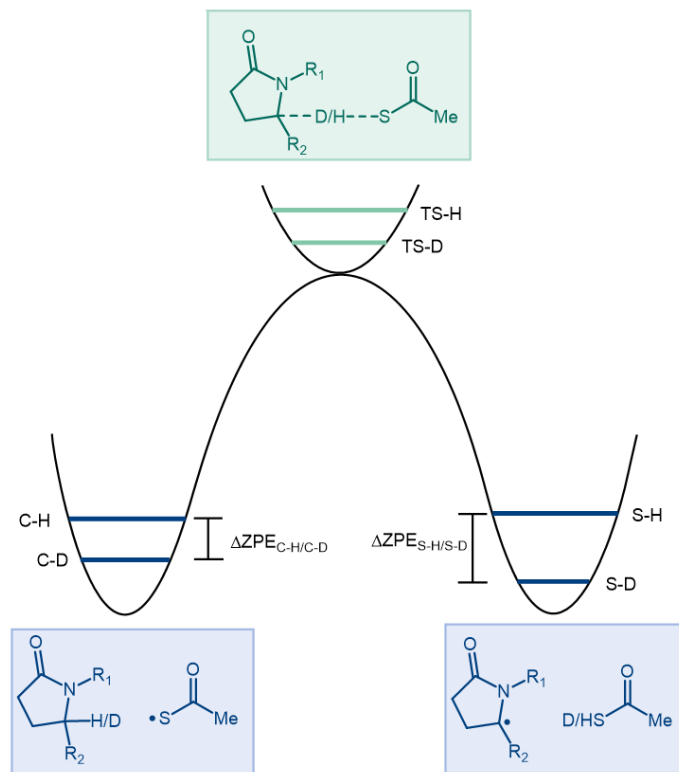
$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = \frac{k_{1,\text{H}}}{k_{1,\text{D}}} \times \frac{k_{-1,\text{D}}}{k_{-1,\text{H}}} \times \frac{[\text{RS-D}]}{[\text{RS-H}]}$$

$$\frac{k_{1,\text{H}}}{k_{1,\text{D}}} = e^{\Delta\text{ZPE}/RT} (\text{substrate})$$

$$\Delta\text{ZPE} (\text{substrate}) = 0.5 (v_{\text{R-H}} - v_{\text{R-D}})$$

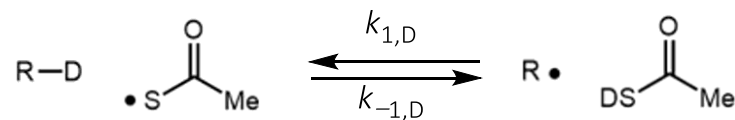
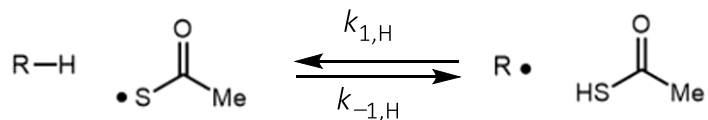
$$\frac{k_{-1,\text{H}}}{k_{-1,\text{D}}} = e^{\Delta\text{ZPE}/RT} (\text{thiol})$$

$$\Delta\text{ZPE} (\text{thiol}) = 0.5 (v_{\text{S-H}} - v_{\text{S-D}})$$



The Method of Isotope Fractionation

Reference Mechanism HAT-HAT



rate of formation of D-substrate: $(k_{1,\text{H}}) \times (k_{-1,\text{D}}) \times [\text{RS-D}]$

rate of formation of H-substrate: $(k_{1,\text{D}}) \times (k_{-1,\text{H}}) \times [\text{RS-H}]$

At the photodynamic equilibrium,

$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = \frac{k_{1,\text{H}}}{k_{1,\text{D}}} \times \frac{k_{-1,\text{D}}}{k_{-1,\text{H}}} \times \frac{[\text{RS-D}]}{[\text{RS-H}]}$$

$$\frac{k_{1,\text{H}}}{k_{1,\text{D}}} = e^{\Delta\text{ZPE}/RT} (\text{substrate})$$

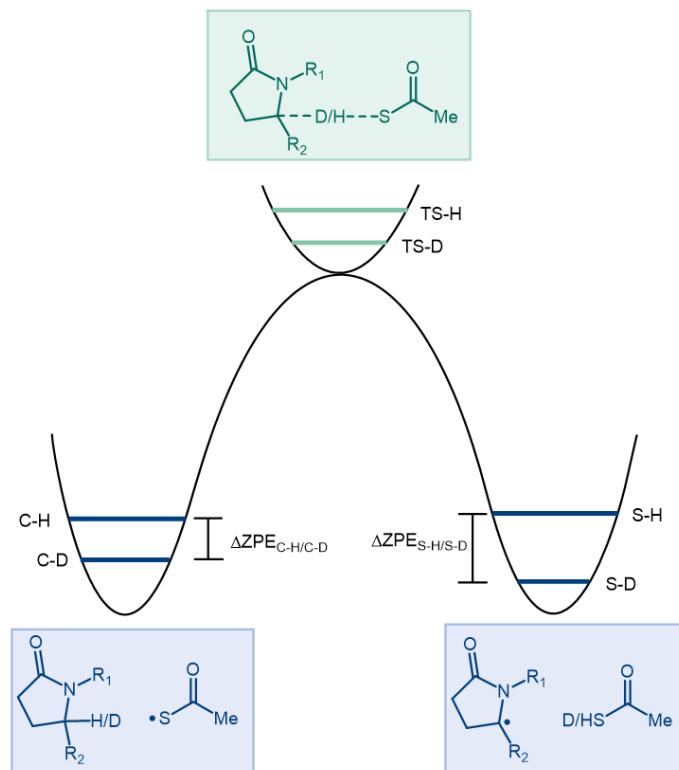
$$\Delta\text{ZPE} (\text{substrate}) = 0.5 (v_{\text{R-H}} - v_{\text{R-D}})$$

$$\frac{k_{-1,\text{H}}}{k_{-1,\text{D}}} = e^{\Delta\text{ZPE}/RT} (\text{thiol})$$

$$\Delta\text{ZPE} (\text{thiol}) = 0.5 (v_{\text{S-H}} - v_{\text{S-D}})$$

$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = e^{\Delta\Delta\text{ZPE}/RT} \times \frac{[\text{RS-D}]}{[\text{RS-H}]}$$

$$\approx e^{\Delta\Delta\text{ZPE}/RT} \times \frac{[\text{MeOD}]}{[\text{MeOH}]}$$

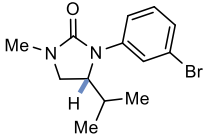
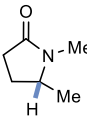
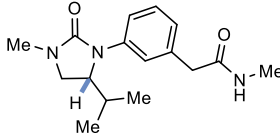
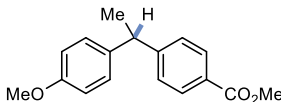
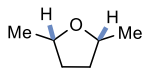
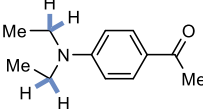


$$\Delta\Delta\text{ZPE} = \Delta\text{ZPE}_{\text{R-H/R-D}} - \Delta\text{ZPE}_{\text{S-H/S-D}}$$

Calculated Isotope Fractionation Slope for HAT-HAT Mechanism

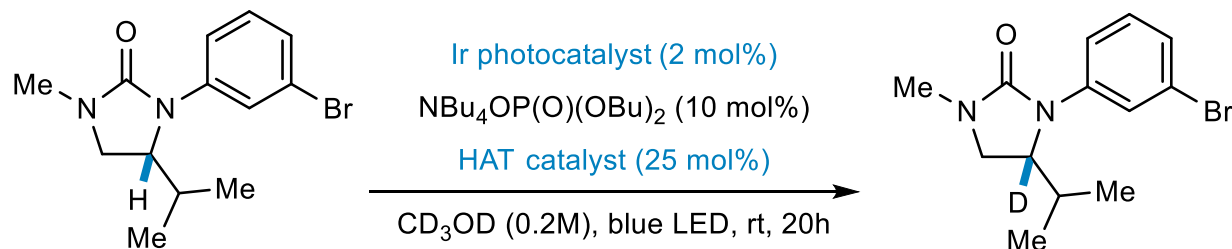
$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = e^{\Delta\Delta\text{ZPE}/RT} \times \frac{[\text{MeOD}]}{[\text{MeOH}]}$$

$$\Delta\Delta\text{ZPE} = \Delta\text{ZPE}_{\text{R-H/R-D}} - \Delta\text{ZPE}_{\text{S-H/S-D}}$$

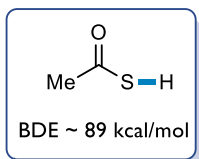
Substrate	C-H BDFE (kcal/mol)	HAT catalyst	exp($\Delta\Delta\text{ZPE}/RT$)
	89	MeC(O)SH	1.11
		PhSH	1.12
	81	MeC(O)SH	1.10
	90	MeC(O)SH	1.04
	89	MeC(O)SH	1.11
	84	MeC(O)SH	1.09
	92	MeC(O)SH	1.05
	91	MeC(O)SH	1.17

Experimental fractionation slope values lie between 0.95 - 1.20 suggest HAT-HAT mechanism, values significantly deviated suggest different consecutive elementary steps (transition state no longer cancel).

Fractionation Slope and Mechanism

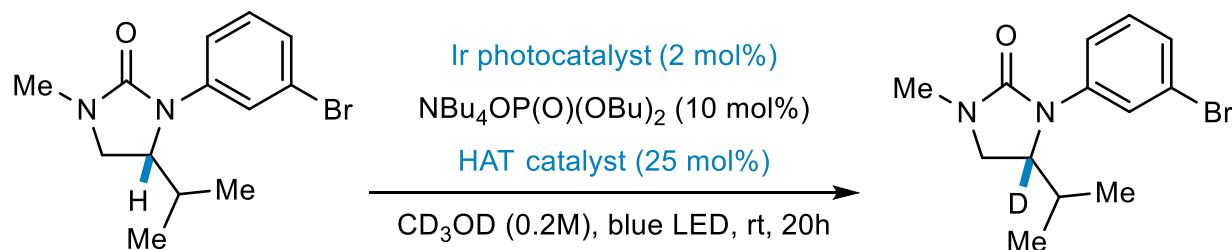


BDFE (C–H) ~ 90 kcal/mol

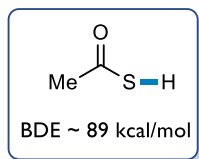


Ir photocatalyst	HAT catalyst	deuterium incorporation	
$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{dtbpy)PF}_6$	thioacetic acid	96% D	HAT-HAT
$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{dtbpy)PF}_6$	thiophenol	0% D	
$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{(3,3'-d(CO}_2\text{Me)bpy)PF}_6$	thiophenol	92% D (48h)	ETPT-HAT

Fractionation Slope and Mechanism

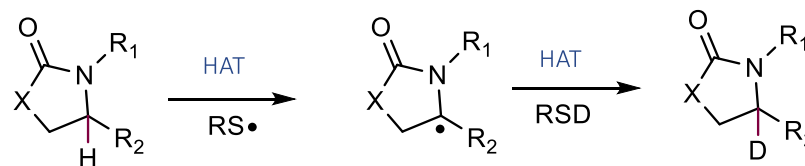
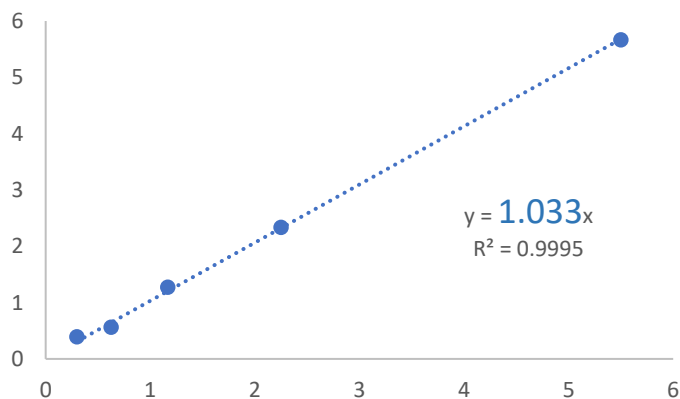


BDFE (C-H) ~ 90 kcal/mol



Ir photocatalyst	HAT catalyst	deuterium incorporation	
Ir(dF(CF ₃)ppy) ₂ dtbpy)PF ₆	thioacetic acid	96% D	HAT-HAT
Ir(dF(CF ₃)ppy) ₂ dtbpy)PF ₆	thiophenol	0% D	
Ir(dF(CF ₃)ppy) ₂ (3,3'-d(CO ₂ Me)bpy)PF ₆	thiophenol	92% D (48h)	ETPT-HAT

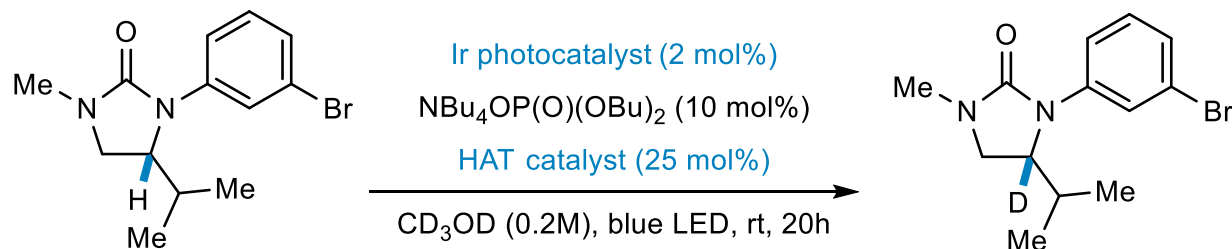
Product [D]/[H] vs [CD₃OD]/[CH₃OH]



Fractionation slope ~ 1.11

Suggest HAT-HAT

Fractionation Slope and Mechanism



BDFE (C–H) ~ 90 kcal/mol

Ir photocatalyst

HAT catalyst

deuterium incorporation

$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{dtbpy)PF}_6$

thioacetic acid

96% D

HAT-HAT

$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{dtbpy)PF}_6$

thiophenol

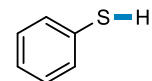
0% D

$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{(3,3'-d(CO}_2\text{Me)bpy)PF}_6$

thiophenol

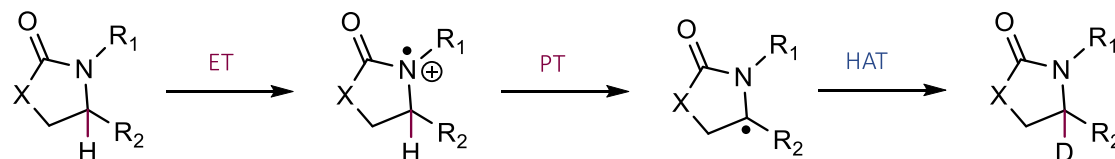
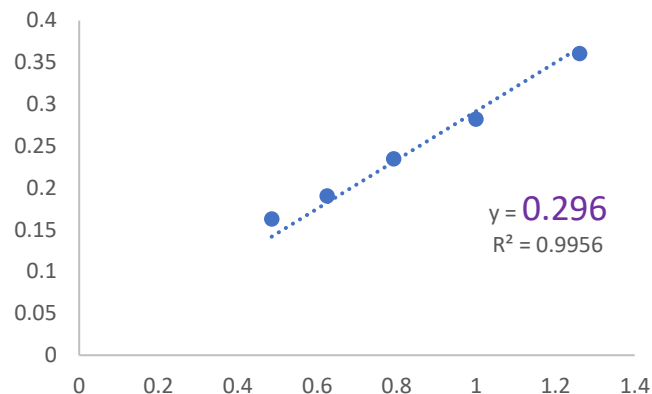
92% D (48h)

ETPT-HAT



BDE ~ 79 kcal/mol

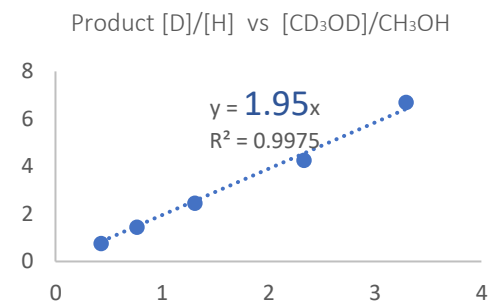
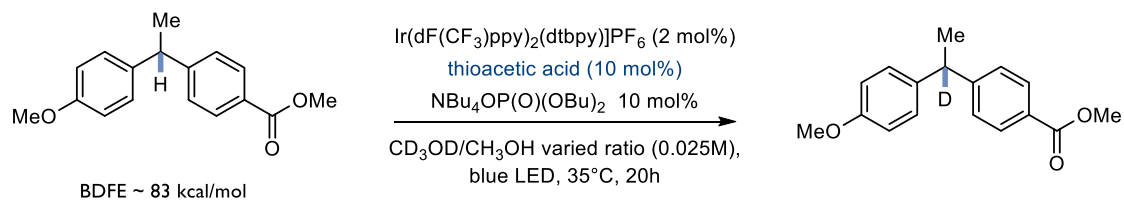
Product [D]/[H] vs $[\text{CD}_3\text{OD}]/[\text{CH}_3\text{OH}]$



Fractionation slope very different from I.I.I

Suggest ETPT-HAT

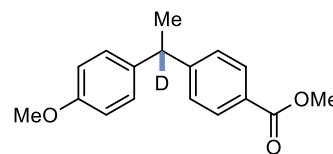
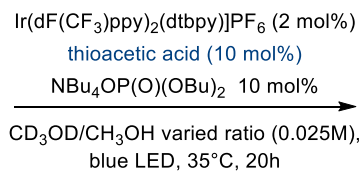
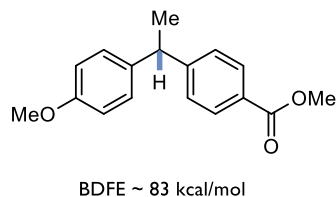
Fractionation Slope and Mechanism



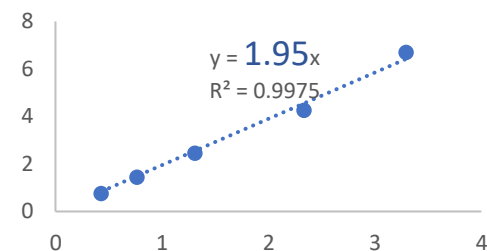
Suggest HAT - ETPT

Fractionation slope very different from 1.09

Fractionation Slope and Mechanism

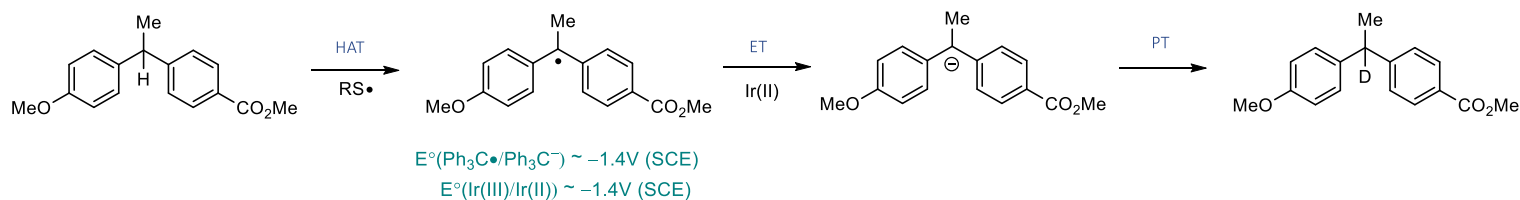
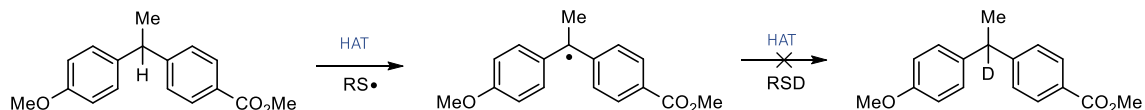
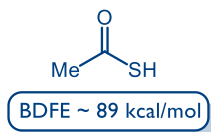


Product [D]/[H] vs $[\text{CD}_3\text{OD}]/[\text{CH}_3\text{OH}]$

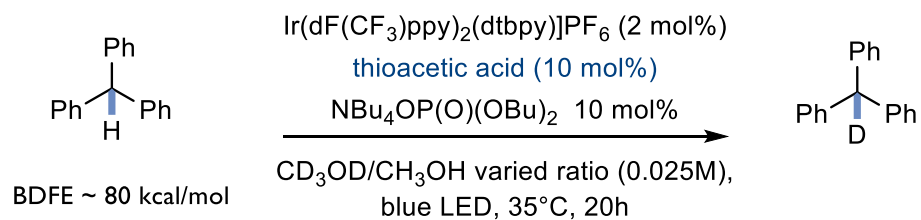


Suggest HAT - ETPT

Fractionation slope very different from 1.09



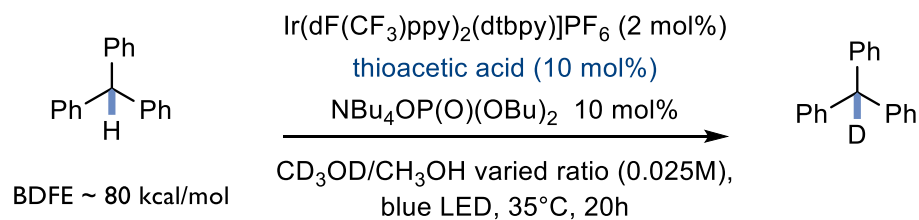
Fractionation Slope and Mechanism



Fractionation slope is 2.00, very different from 1.11

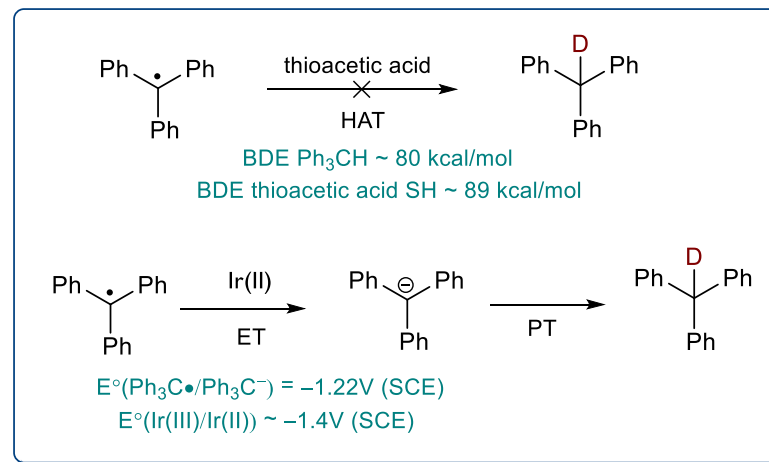
Suggest HAT - ETPT

Fractionation Slope and Mechanism

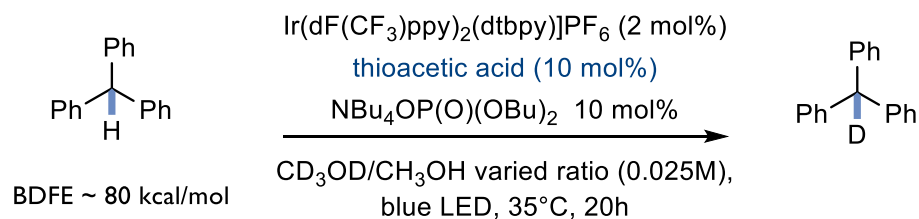


Fractionation slope is 2.00, very different from 1.11

Suggest HAT - ETPT

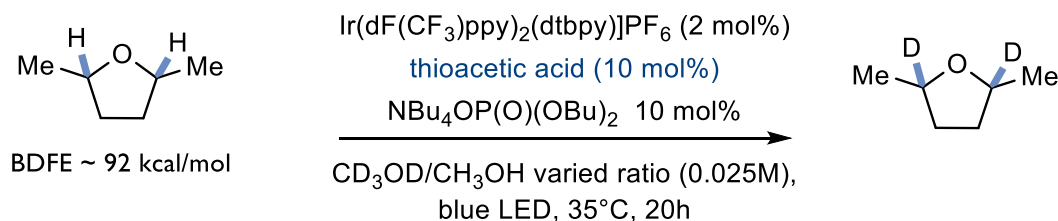
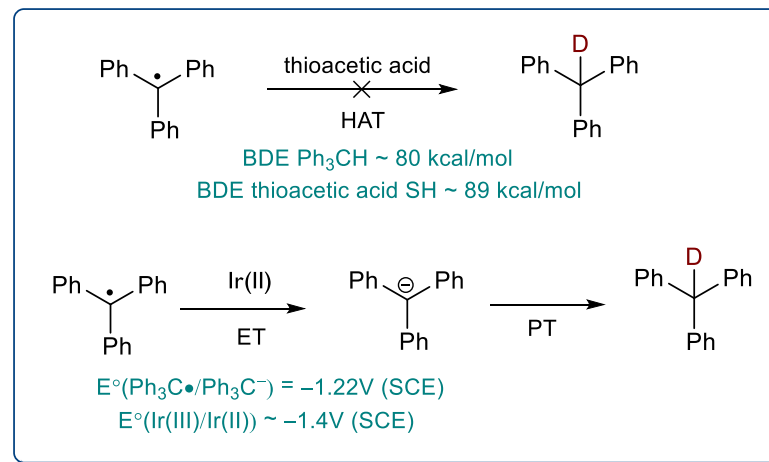


Fractionation Slope and Mechanism



Fractionation slope is 2.00, very different from 1.11

Suggest HAT - ETPT

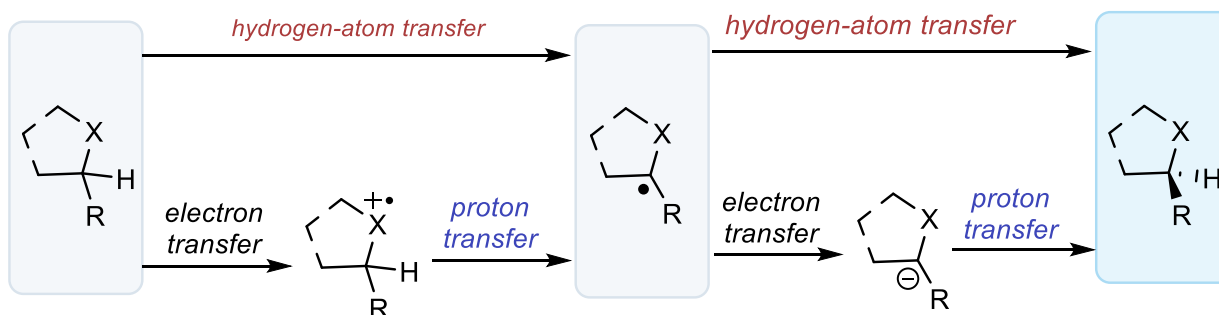


Fractionation slope is 1.02, excellent agreement with 1.05

Suggest HAT - HAT

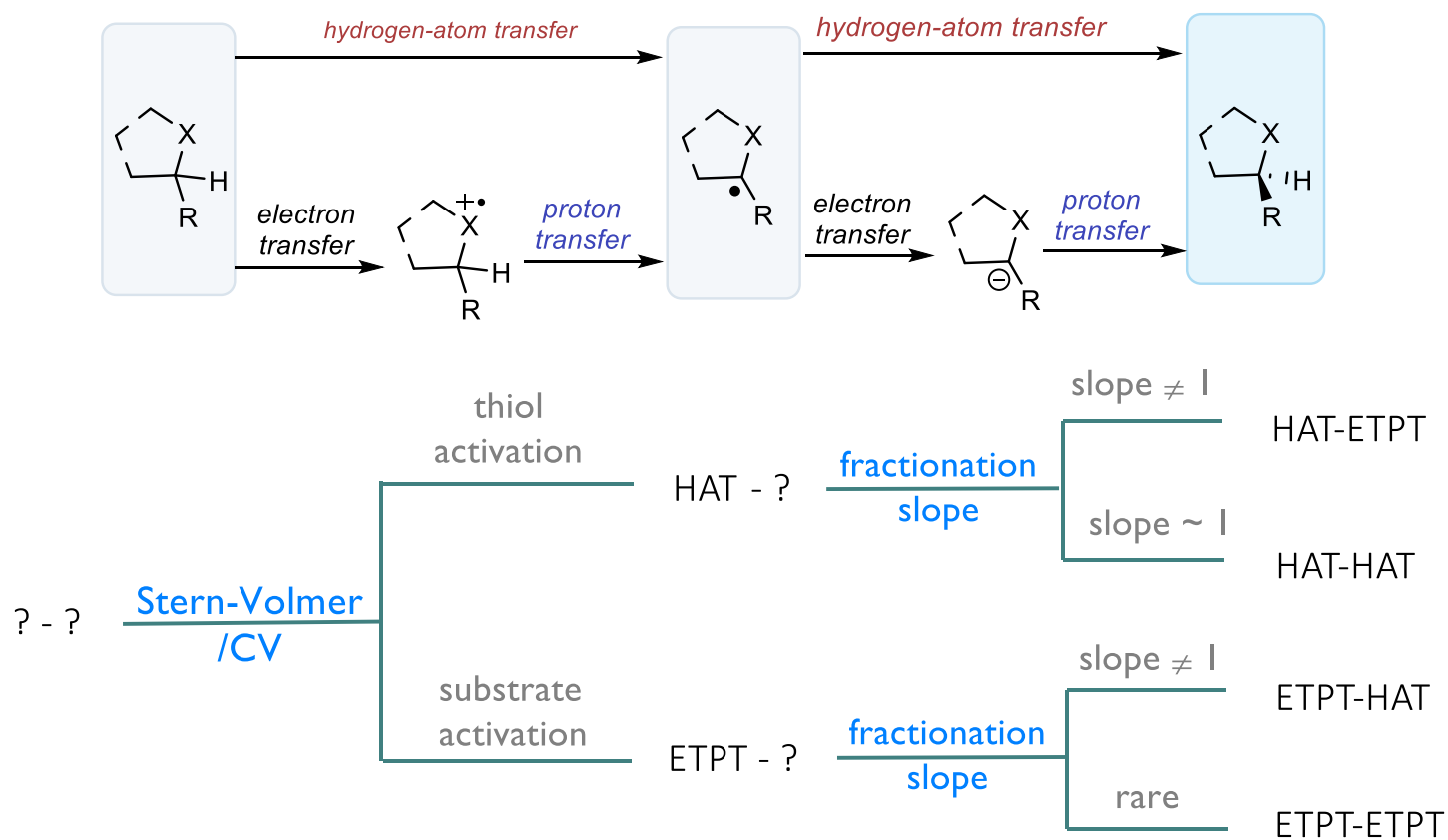
Summary – Rule of Thumb

- Mechanism determined by this fractionation slope method in excellent agreement with that predicted by the known properties of substrate, intermediate, and catalysts
- This fractionation slope method can determine the activation mode for reactions wherein the mechanism is not trivial to predict

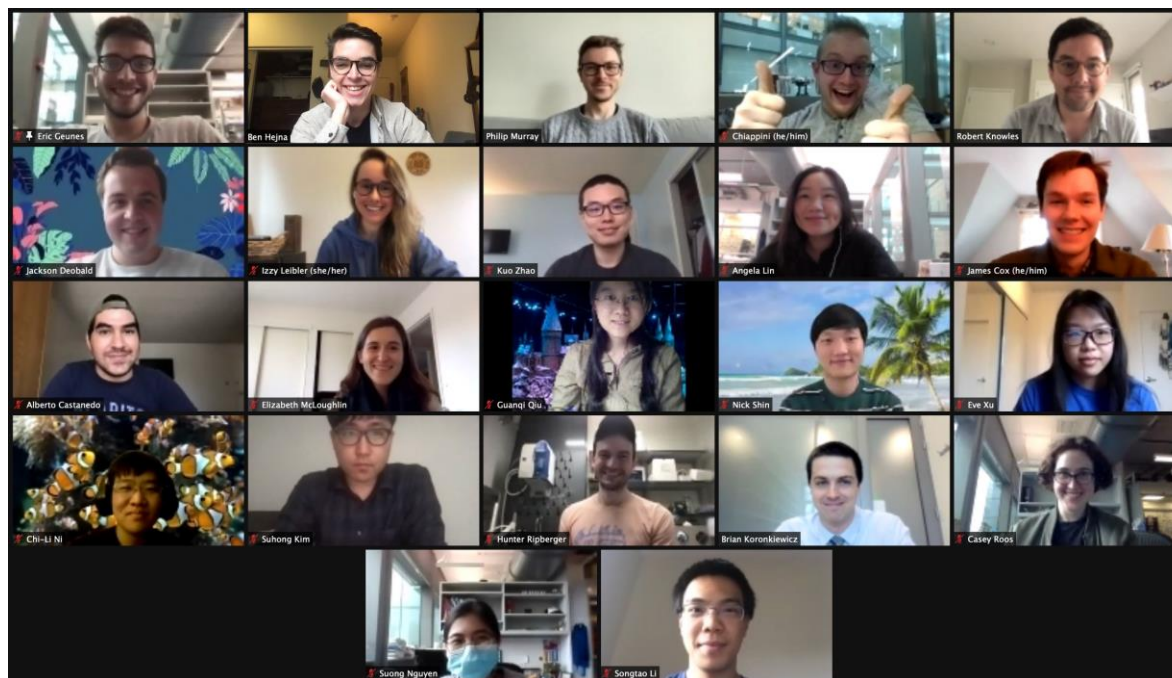


Summary – Rule of Thumb

- Mechanism determined by this fractionation slope method in excellent agreement with that predicted by the known properties of substrate, intermediate, and catalysts
- This fractionation slope method can determine the activation mode for reactions wherein the mechanism is not trivial to predict



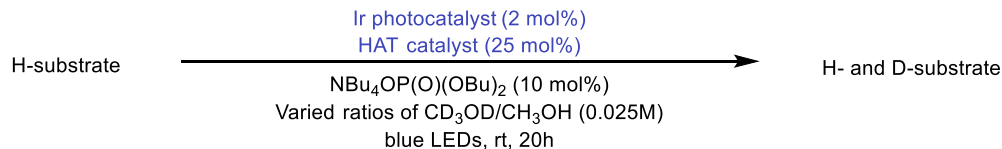
Acknowledgement



Prof. Robert Knowles Chi-Li Ni The Knowles Group

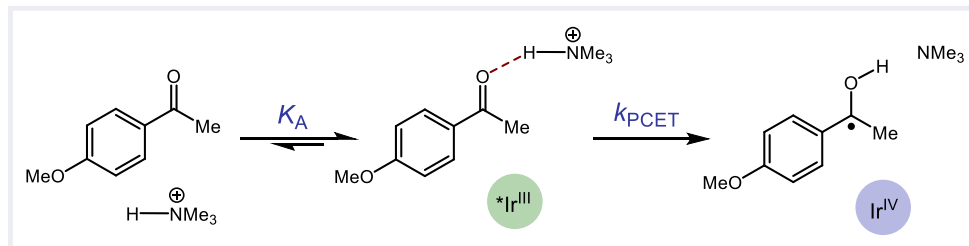
Prof. Abigail Doyle Prof. Erik Sorensen Kelsey Lovering Taylor Fellowship
Prof. John Groves Prof. David MacMillan Meredith LaSalle-Tarantin Patchett Fellowship

Fractionation Slope and Mechanism

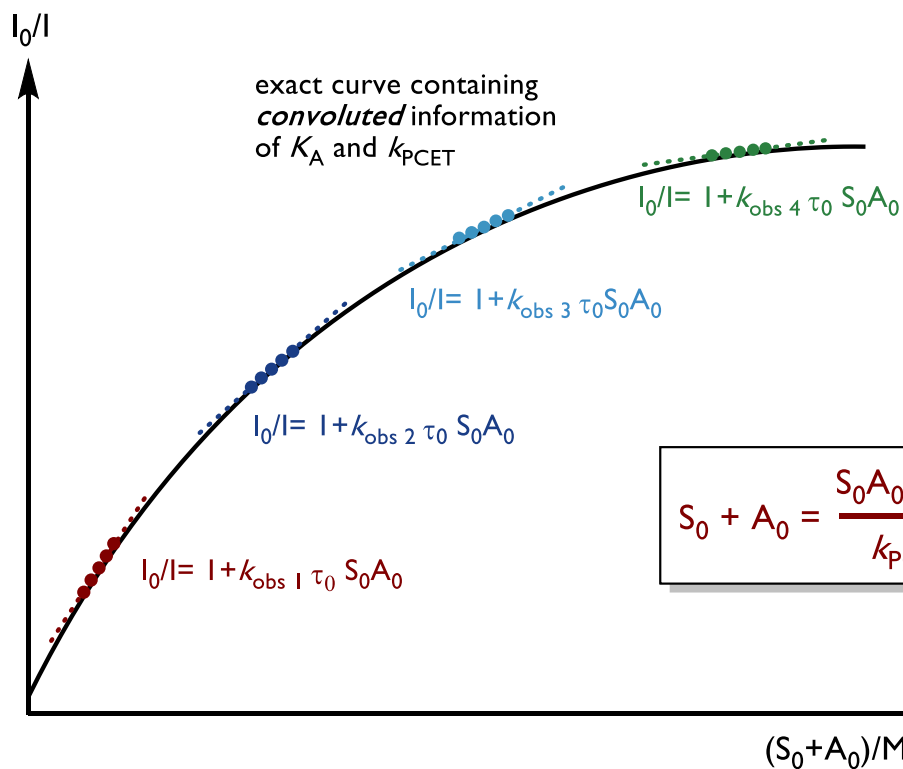


Substrate	Entry	Ir photocatalyst and HAT catalyst	fractionation slope expected for HAT-HAT mechanism ^a	Substrate oxidation ^b	thiyl C–H abstraction ^c	C• S–H abstraction ^c	experimental fractionation slope	C–H homolysis mechanism suggested
	1	Ir-2 MeC(O)SH	1.11	No	Yes	Yes	1.03	HAT - HAT
	2 ^d	Ir-3 PhSH	1.12	Yes	No	Yes	0.39	ETPT - HAT
	3 ^d	Ir-4 PhSH	1.12	Yes	No	Yes	0.31	(ETPT + PCET _{C–H}) - HAT
	4	Ir-1 MeC(O)SH	1.10	No	Yes	No	1.95	HAT - ETPT
	5	Ir-1 MeC(O)SH	1.04	No	Yes	Yes	1.09	HAT - HAT
	6	Ir-2 MeC(O)SH	1.09	No	Yes	borderline	2.05	HAT - ETPT
	7	Ir-1 MeC(O)SH	1.05	No	Yes	Yes	1.00	HAT - HAT
	8	Ir-5 MeC(O)SH	1.11	No	Yes	Yes	1.12	HAT - HAT
	9	Ir-3 PhSH	1.12	Yes	No	Yes	0.46	ETPT - HAT
	10	Ir-3 MeC(O)SH	1.11	Yes	Yes	Yes	0.24	ETPT - HAT
	11 ^e	Ir-5 MeC(O)SH	1.17	Yes	Yes	Yes	1.01	HAT - HAT
	12 ^e	Ir-3 MeC(O)SH	1.17	Yes	Yes	Yes	0.61	(HAT + ETPT) - HAT
	13 ^{c,f}	Ir-3 MeC(O)SH (1eqv)	1.17	Yes	Yes	Yes	0.82	(HAT + ETPT) - HAT

A Simple Experimental Method to Extract K_A and k_{PCET}



$$K_A = \frac{x}{(S_0 - x)(A_0 - x)}$$



$$S_0 + A_0 = \frac{S_0 A_0 k_{\text{obs}} \tau_0}{k_{\text{PCET}} \tau_0} + \frac{k_{\text{PCET}} \tau_0}{k_{\text{obs}} \tau_0} - (1/K_A)$$

pre-PCET H-bonding equilibrium constant (K_A) and PCET rate constant (k_{PCET}) are extracted simultaneously

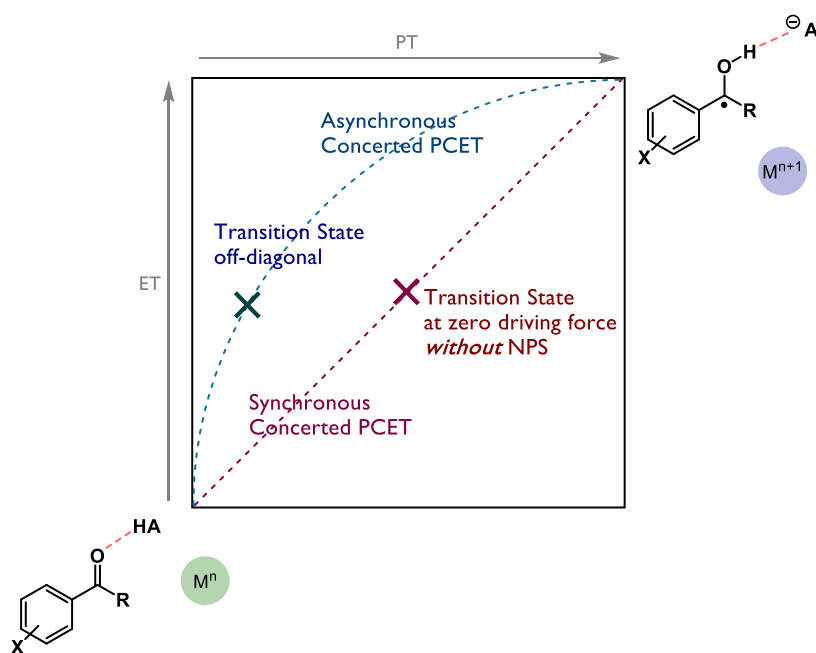
Principle of Non-perfect Synchronization

Contrast: Non-Perfect Synchronization versus Asynchronous

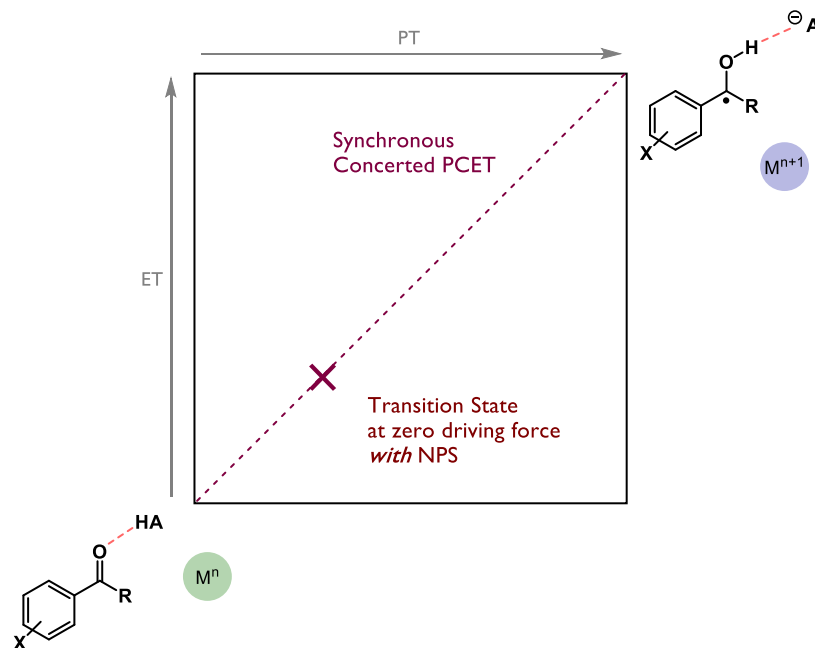
Principle of Non-Perfect Synchronization (NPS): a product-stabilizing factor, the development of which at the transition state lags behind bond changes, increases the intrinsic barrier of a reaction, but lowers it if it develops ahead of bond changes.

- Claude F. Bernasconi

Without Non-Perfect Synchronization



Non-Perfect Synchronization

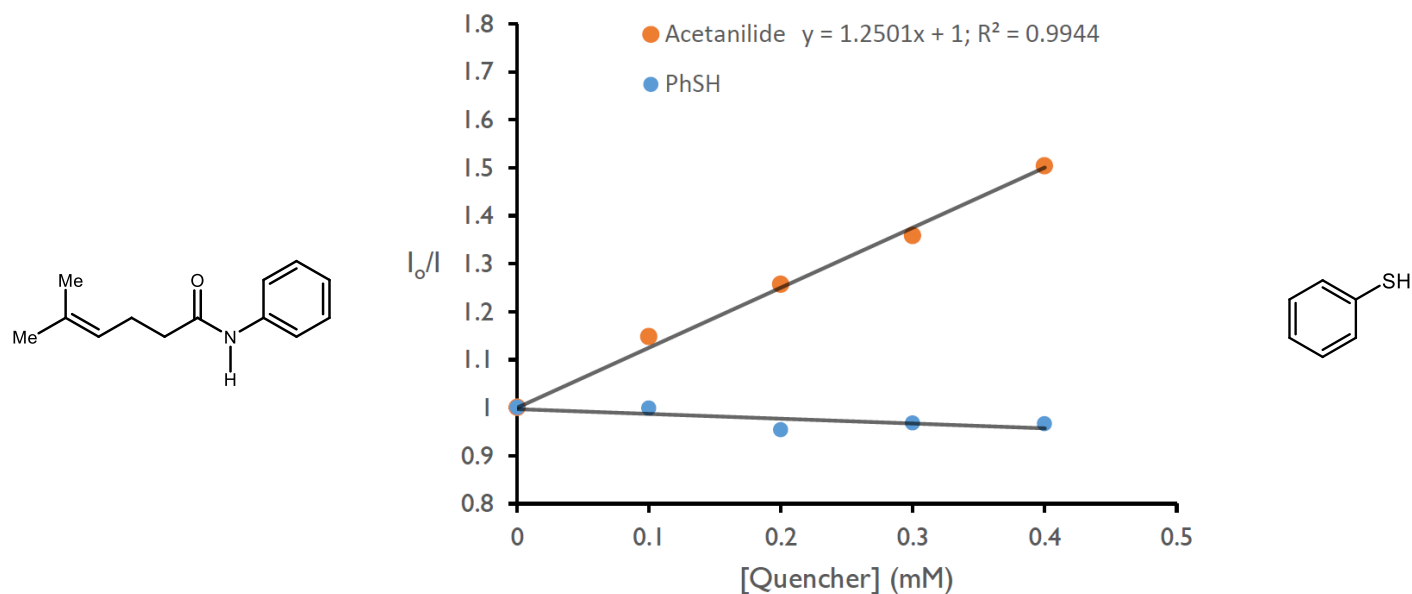


New Hypothesis for Origin of PCET Selectivity

$$Q = \frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$

Species	Concentration (mM)
[Ir(dF(CF ₃)ppy) ₂ (bpy)](PF ₆)	0.01
Bu ₄ N ⁺ (BuO) ₂ PO ₂ ⁻	0.20
Thiophenol	1.00
Acetanilide	Varied

Species	Concentration (mM)
[Ir(dF(CF ₃)ppy) ₂ (bpy)](PF ₆)	0.01
Bu ₄ N ⁺ (BuO) ₂ PO ₂ ⁻	0.20
Thiophenol	Varied
Acetanilide	1.00

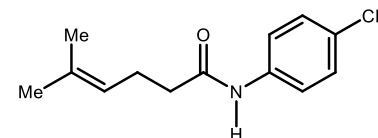
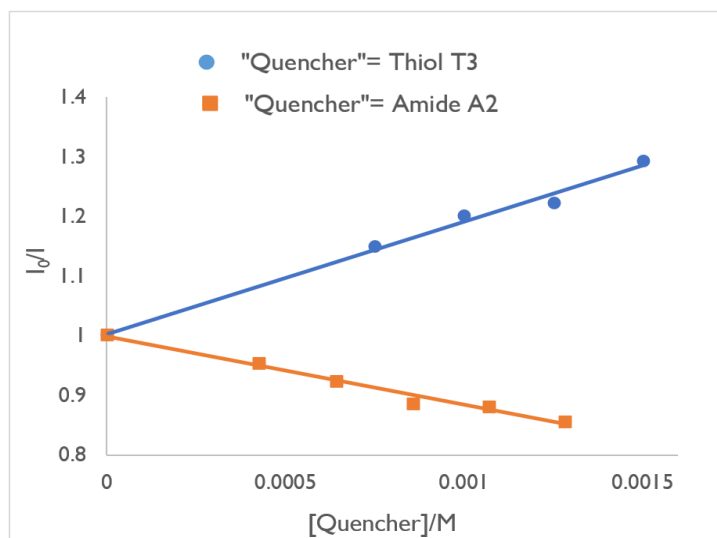
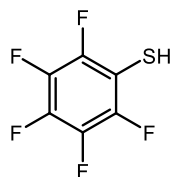


Hydroamidation reaction yield: 100%

New Hypothesis for Origin of PCET Selectivity

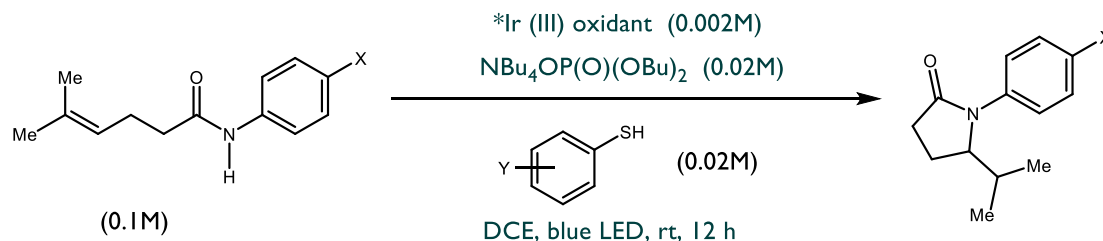
$$Q = \frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$

Blue		Orange	
Species	Concentration (M)	Species	Concentration (M)
Oxidant Ir-2	0.00001	Oxidant Ir-2	0.00001
Bu ₄ N ⁺ (BuO) ₂ PO ₂ ⁻	0.00015	Bu ₄ N ⁺ (BuO) ₂ PO ₂ ⁻	0.0001
Thiol T3	0.001	Thiol T3	Varied
Amide A2	Varied	Amide A2	0.001



Hydroamidation reaction yield: 0%

Correlate PCET Selectivity with Hydroamidation Efficiency

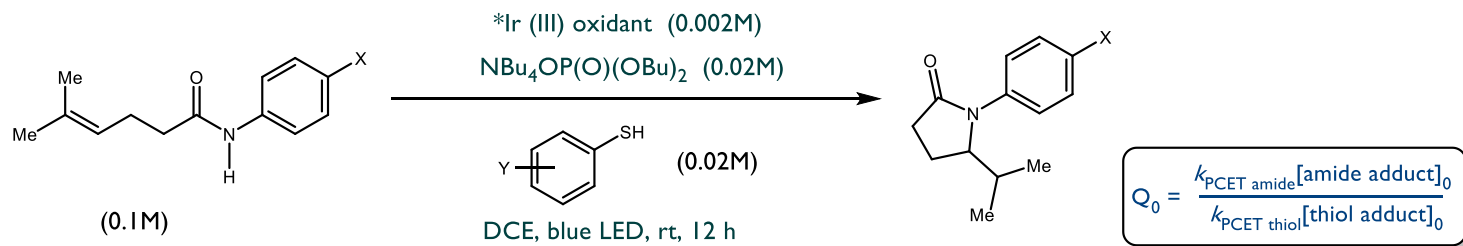


$$Q_0 = \frac{k_{\text{PCET amide}}[\text{amide adduct}]_0}{k_{\text{PCET thiol}}[\text{thiol adduct}]_0}$$

entry	thiol	amide X=	*Ir (III)	$k_{\text{PCET amide}}(\text{M}^{-1}\text{s}^{-1})$	$K_{\text{A amide}}(\text{M}^{-1})$	$k_{\text{PCET thiol}}(\text{M}^{-1}\text{s}^{-1})$	$K_{\text{A thiol}}(\text{M}^{-1})$	Q_0	% yield ^b	% recovery ^b
1	PhSH	H	Ir-1	8.4×10^9	1050	9.5×10^9	200	96 : 4	100	0
2	PhSH	COMe	Ir-1	3.0×10^9	1500	9.5×10^9	200	91 : 9	100	0
3	PhSH	CN	Ir-1	9.3×10^8	3550	9.5×10^9	200	87 : 13	100	0
4	PhSH	H	Ir-2	1.1×10^9	1050	3.6×10^9	200	86 : 12	100	0
5	PhSH	COMe	Ir-2	1.8×10^8	1500	3.6×10^9	200	62 : 38	80	9
6	PhSH	CN	Ir-2	6.8×10^7	3550	3.6×10^9	200	57 : 43	8	85
7	3,5-(CF ₃) ₂ C ₆ H ₃ SH	H	Ir-1	8.4×10^9	1050	8.3×10^9	2100	78 : 22	95	0
8	3,5-(CF ₃) ₂ C ₆ H ₃ SH	H	Ir-2	1.1×10^9	1050	2.2×10^9	2100	64 : 36	85	0
9	3,5-(CF ₃) ₂ C ₆ H ₃ SH	COMe	Ir-1	3.0×10^9	1500	8.3×10^9	2100	56 : 44	60	30
10	3,5-(CF ₃) ₂ C ₆ H ₃ SH	CN	Ir-1	9.3×10^8	3550	8.3×10^9	2100	47 : 53	13	62
11	3,5-(CF ₃) ₂ C ₆ H ₃ SH	COMe	Ir-2	1.8×10^8	1500	2.2×10^9	2100	23 : 77	10	47
12	3,5-(CF ₃) ₂ C ₆ H ₃ SH	CN	Ir-2	6.8×10^7	3550	2.2×10^9	2100	18 : 82	0	84
13	C ₆ F ₅ SH	H	Ir-1	8.4×10^9	1050	4.0×10^9	5600	75 : 25	91	0
14	C ₆ F ₅ SH	H	Ir-2	1.1×10^9	1050	1.0×10^9	5600	61 : 39	61	23
15	C ₆ F ₅ SH	COMe	Ir-1	3.0×10^9	1500	4.0×10^9	5600	56 : 44	17	70
16	C ₆ F ₅ SH	CN	Ir-1	9.3×10^8	3550	4.0×10^9	5600	44 : 56	3	54
17	C ₆ F ₅ SH	COMe	Ir-2	1.8×10^8	1500	1.0×10^9	5600	24 : 76	trace	54
18	C ₆ F ₅ SH	CN	Ir-2	6.8×10^7	3550	1.0×10^9	5600	18 : 82	0	88
In the following two entries, [thiol] = 0.04M, [base] = 0.005M										
19	PhSH	H	Ir-2	1.1×10^9	1050	3.6×10^9	200	81 : 19	100	0
20	C ₆ F ₅ SH	H	Ir-2	1.1×10^9	1050	1.0×10^9	5600	35 : 65	15	50

^a All reactions are on the scale of 0.05mmol. ^b Each percentage yield and starting material recovery was taken after 12 hours of reaction time, by NMR relative to internal standard. There was no further product formation upon prolonged reaction time.

Correlate PCET Selectivity with Hydroamidation Efficiency



entry	thiol	amide X=	*Ir (III)	$k_{\text{PCET amide}} (\text{M}^{-1}\text{s}^{-1})$	$K_{\text{A amide}} (\text{M}^{-1})$	$k_{\text{PCET thiol}} (\text{M}^{-1}\text{s}^{-1})$	$K_{\text{A thiol}} (\text{M}^{-1})$	Q_0	% yield ^b	% recovery ^b
1	PhSH	H	Ir-1	8.4×10^9	1050	9.5×10^9	200	96 : 4	100	0
2	PhSH	COMe	Ir-1	3.0×10^9	1500	9.5×10^9	200	91 : 9	100	0
3	PhSH	CN	Ir-1	9.3×10^8	3550	9.5×10^9	200	87 : 13	100	0
4	PhSH	H	Ir-2	1.1×10^9	1050	3.6×10^9	200	86 : 12	100	0
5	PhSH	COMe	Ir-2	1.8×10^8	1500	3.6×10^9	200	62 : 38	80	9
6	PhSH	CN	Ir-2	6.8×10^7	3550	3.6×10^9	200	57 : 43	8	85
7	3,5-(CF ₃) ₂ C ₆ H ₃ SH	H	Ir-1	8.4×10^9	1050	8.3×10^9	2100	78 : 22	95	0
8	3,5-(CF ₃) ₂ C ₆ H ₃ SH	H	Ir-2	1.1×10^9	1050	2.2×10^9	2100	64 : 36	85	0
9	3,5-(CF ₃) ₂ C ₆ H ₃ SH	COMe	Ir-1	3.0×10^9	1500	8.3×10^9	2100	56 : 44	60	30
10	3,5-(CF ₃) ₂ C ₆ H ₃ SH	CN	Ir-1	9.3×10^8	3550	8.3×10^9	2100	47 : 53	13	62
11	3,5-(CF ₃) ₂ C ₆ H ₃ SH	COMe	Ir-2	1.8×10^8	1500	2.2×10^9	2100	23 : 77	10	47
12	3,5-(CF ₃) ₂ C ₆ H ₃ SH	CN	Ir-2	6.8×10^7	3550	2.2×10^9	2100	18 : 82	0	84
13	C ₆ F ₅ SH	H	Ir-1	8.4×10^9	1050	4.0×10^9	5600	75 : 25	91	0
14	C ₆ F ₅ SH	H	Ir-2	1.1×10^9	1050	1.0×10^9	5600	61 : 39	61	23
15	C ₆ F ₅ SH	COMe	Ir-1	3.0×10^9	1500	4.0×10^9	5600	56 : 44	17	70
16	C ₆ F ₅ SH	CN	Ir-1	9.3×10^8	3550	4.0×10^9	5600	44 : 56	3	54
17	C ₆ F ₅ SH	COMe	Ir-2	1.8×10^8	1500	1.0×10^9	5600	24 : 76	trace	54
18	C ₆ F ₅ SH	CN	Ir-2	6.8×10^7	3550	1.0×10^9	5600	18 : 82	0	88
In the following two entries, [thiol] = 0.04M, [base] = 0.005M										
19	PhSH	H	Ir-2	1.1×10^9	1050	3.6×10^9	200	81 : 19	100	0
20	C ₆ F ₅ SH	H	Ir-2	1.1×10^9	1050	1.0×10^9	5600	35 : 65	15	50

^a All reactions are on the scale of 0.05mmol. ^b Each percentage yield and starting material recovery was taken after 12 hours of reaction time, by NMR relative to internal standard. There was no further product formation upon prolonged reaction time.

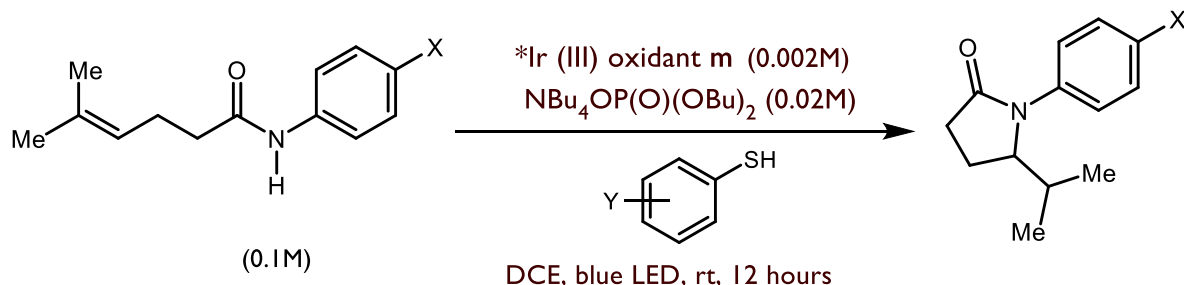
Q₀ and Medium Yields Span



entry	[amide]/M	[thiol]/M	[base]/M	Q ₀	% yield	% recovery
1	0.05	0.02	0.005	75 : 25	88	4
2	0.05	0.02	0.02	68 : 32	81	0
3	0.05	0.02	0.04	51 : 49	74	4
4	0.05	0.02	0.06	38 : 62	48	14
5	0.05	0.09	0.01	39 : 61	62	25
6	0.05	0.09	0.03	28 : 72	50	45
7	0.05	0.09	0.05	19 : 81	40	60
8	0.05	0.09	0.07	10 : 90	22	66

All reactions are on the scale of 0.05mmol. Each percentage yield was taken after 12 hours of reaction time, by NMR. There was no further product formation upon prolonged reaction time.

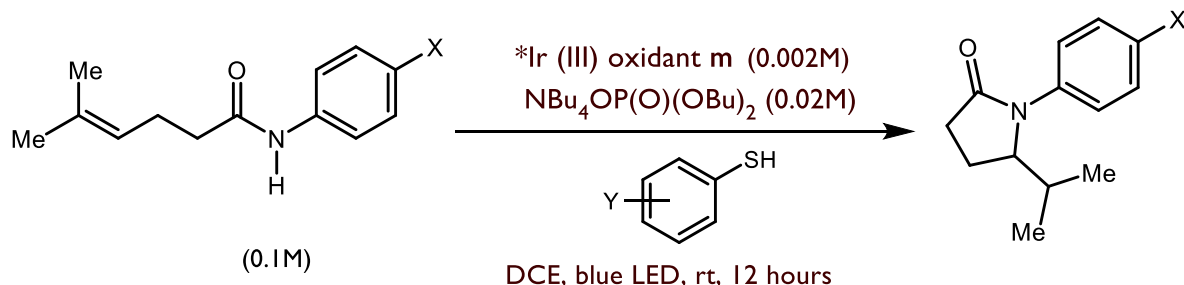
Deconvolution of PCET Selectivity Effect on Reaction Efficiency



entry	amide X=	thiol(s)	[thiol(s)]/M	ratio Q_0	% yield
1	CN	PhSH	0.02	90 : 10	100
2	CN	F ₅ -PhSH	0.02	38 : 62	3
3	CN	3,5-(CF ₃) ₂ PhSH	0.02	44 : 56	20
4	CN	PhSH + F ₅ -PhSH	0.02+0.02	< 38 : 62	4
5	CN	PhSH + 3,5-(CF ₃) ₂ PhSH	0.02+0.02	< 44 : 56	20
6	COMe	PhSH	0.02	90 : 10	100
7	COMe	F ₅ -PhSH	0.02	56 : 44	17
8	COMe	3,5-(CF ₃) ₂ PhSH	0.02	60 : 40	60
9	COMe	PhSH + F ₅ -PhSH	0.02+0.02	< 56 : 44	30
10	COMe	PhSH + 3,5-(CF ₃) ₂ PhSH	0.02+0.02	< 60 : 40	77

All reactions are on the scale of 0.05mmol. Each percentage yield was taken after 12 hours of reaction time, by NMR. There was no further product formation upon prolonged reaction time.

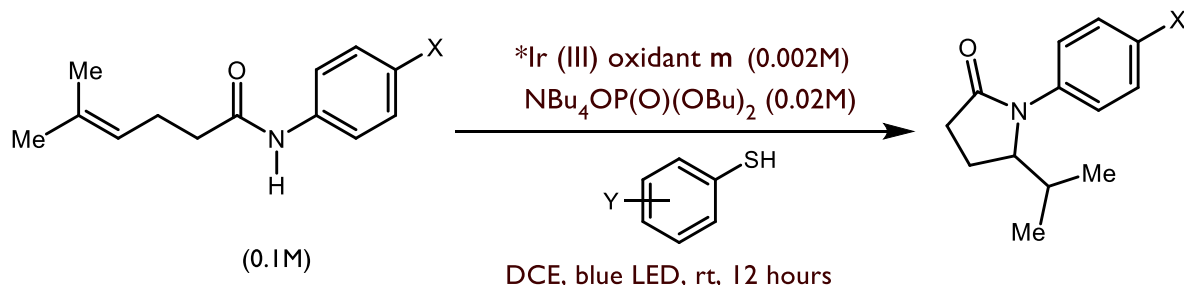
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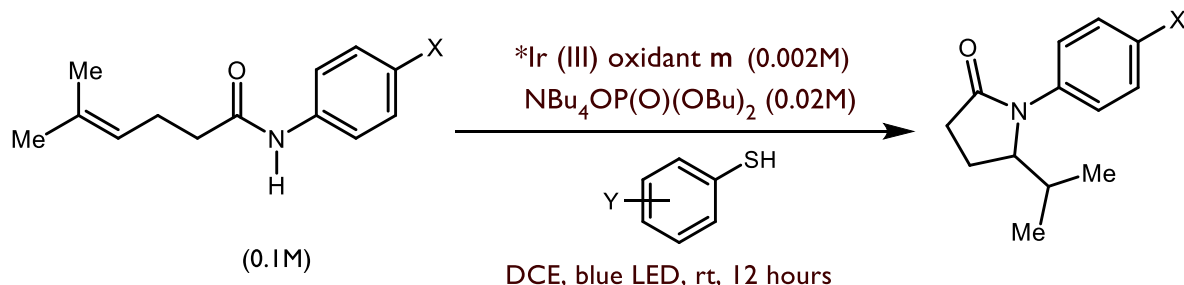
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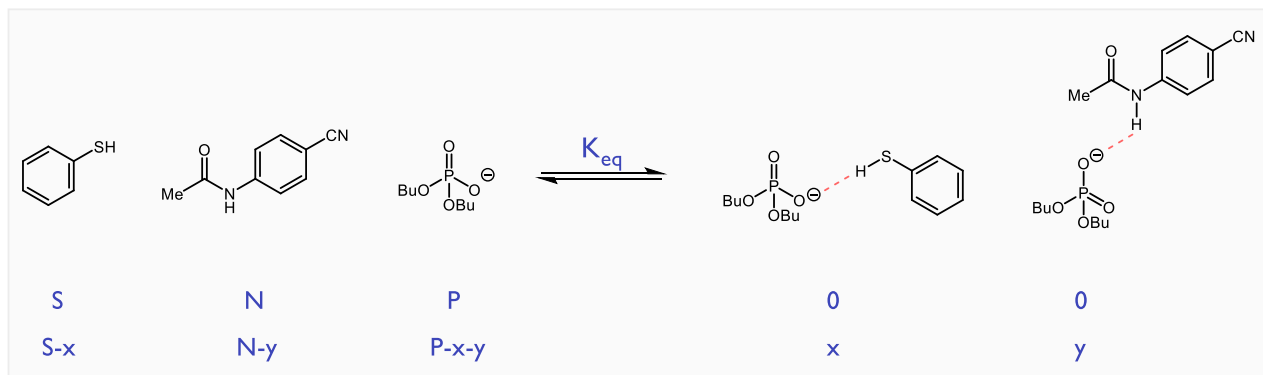
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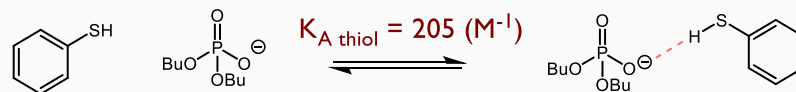
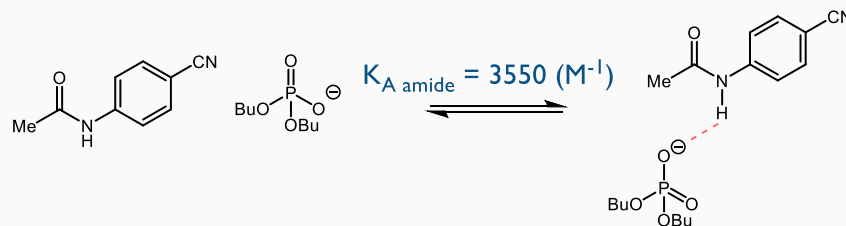
Test of the New Hypothesis: Predicted Quenching Constant



Another two equilibria co-established. $K_{A \text{ amide}}$ and $K_{A \text{ thiol}}$ were pre-determined via our experimental method

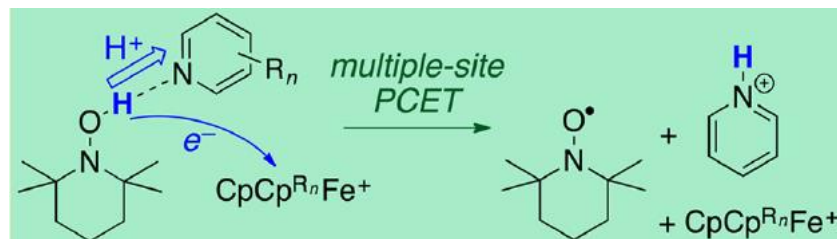
$$K_{A \text{ amide}} = 3550 = \frac{y}{(N-y)(P-x-y)}$$

$$K_{A \text{ thiol}} = 205 = \frac{x}{(S-x)(P-x-y)}$$

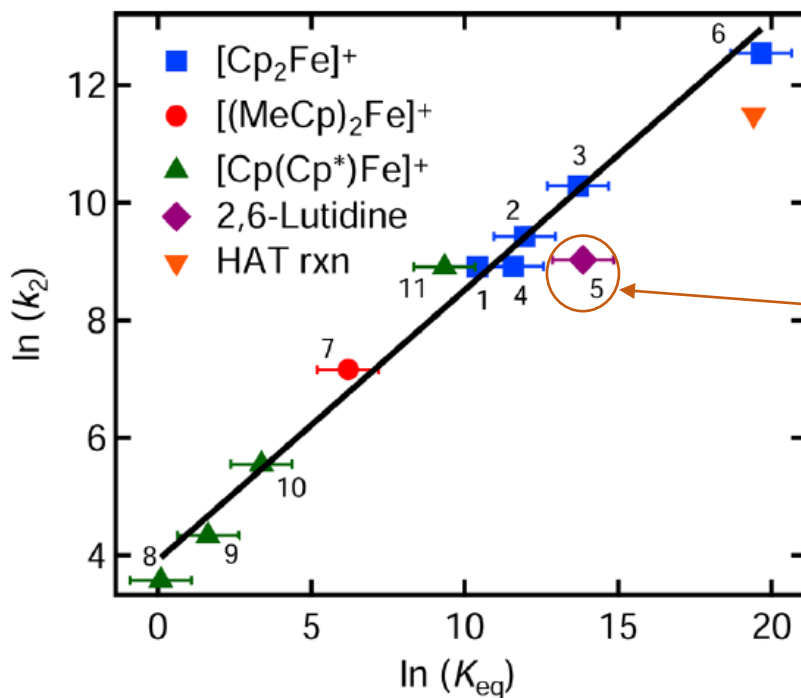
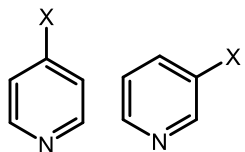


From this simultaneous equation, x and y will be known, given initial concentrations of amide, thiol, and base

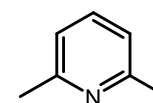
Precedented evidence of Changes in Intrinsic Barrier



On the linear
correlation line

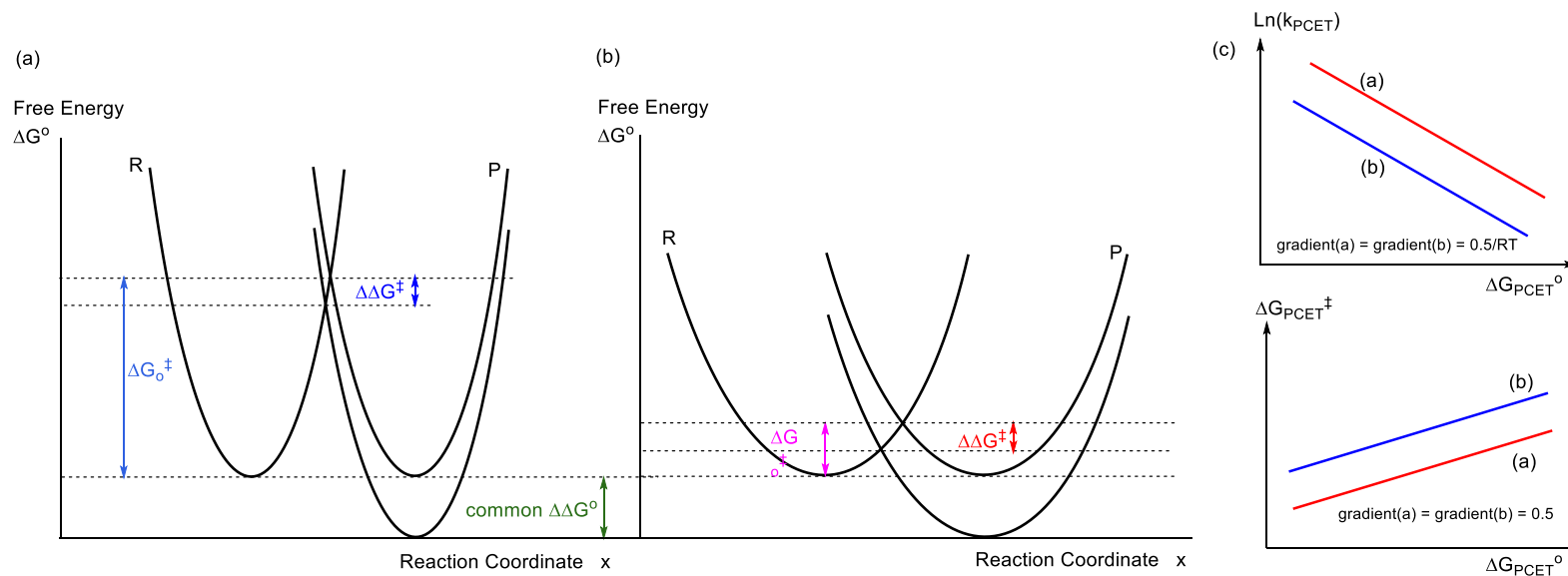


Outlier

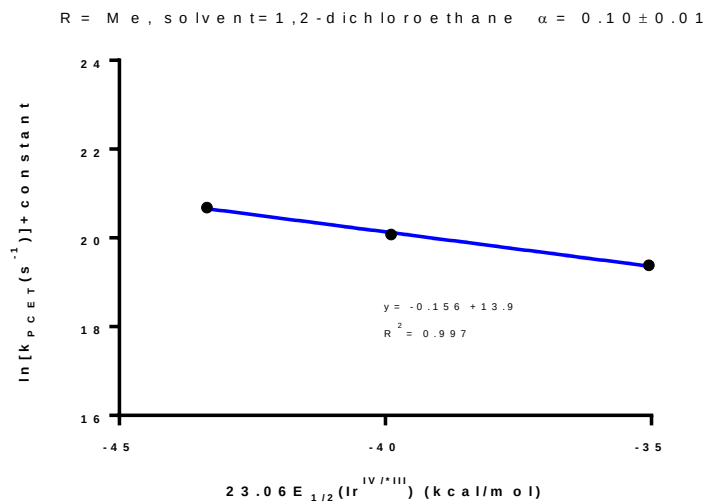
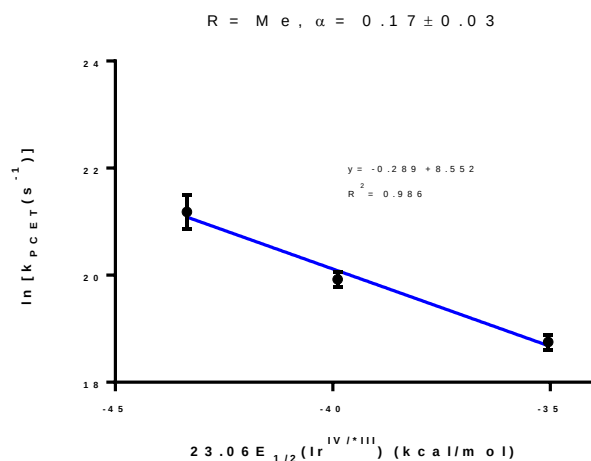
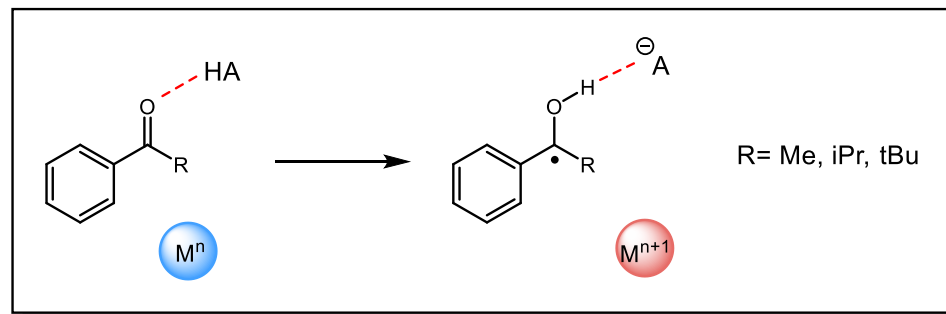


Steric effect in hydrogen-bonding → different intrinsic barrier

Physical meaning of identical Marcus parabolae

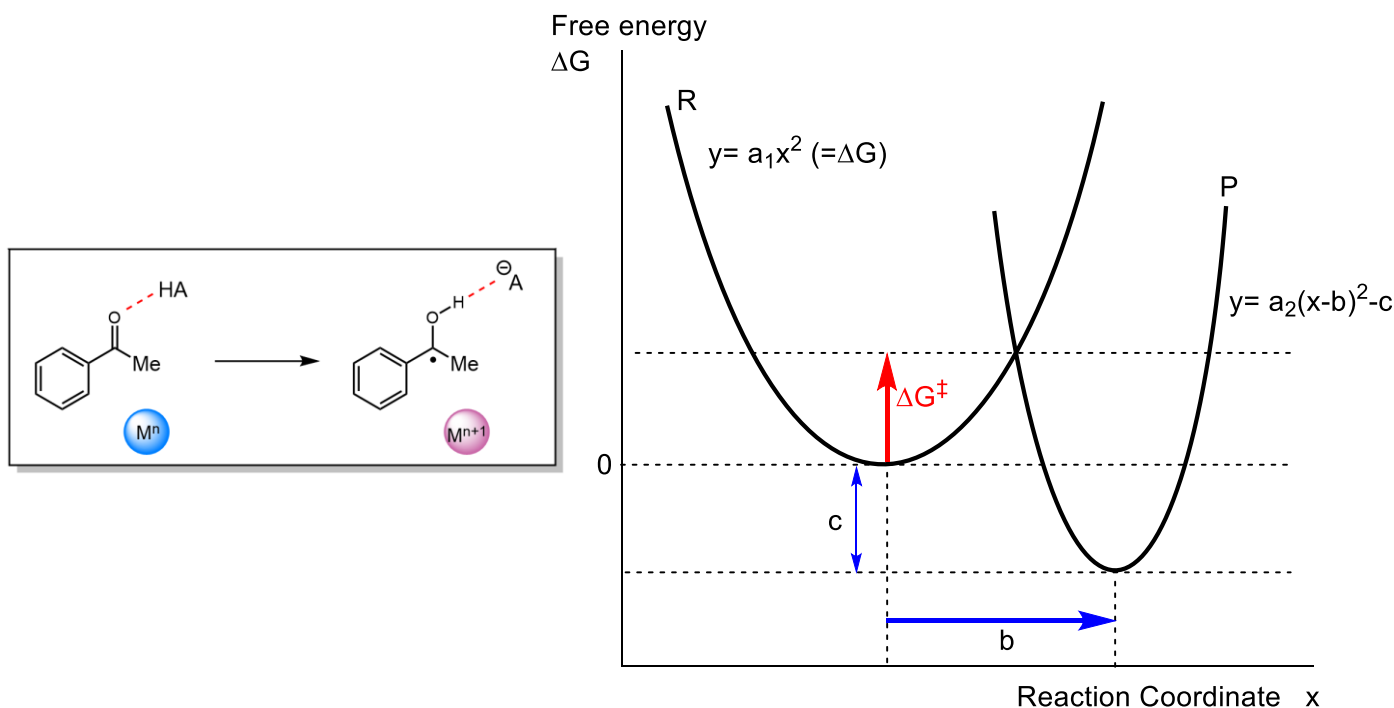


More evidence: Solvational Non-Perfect Synchronization



MeCN: $\epsilon = 37.5$ $\mu = 3.45$
 DCE: $\epsilon = 10.4$ $\mu = 1.86$

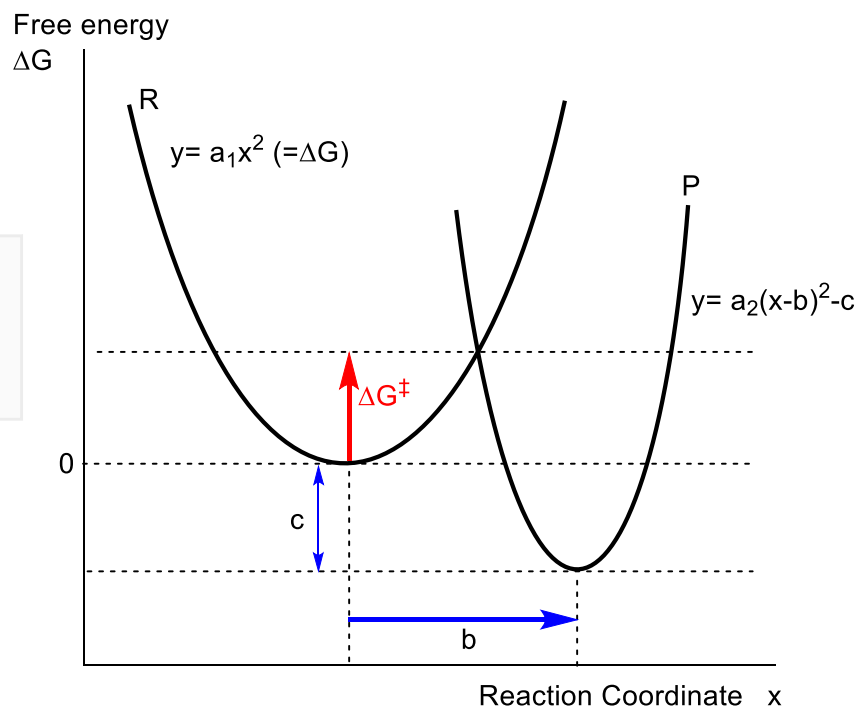
Our Hypothesis: Parabolae of pre-PCET State and post-PCET State are NOT Identical



- Product State gain one electron from outer sphere
- The intramolecular vibration and solvation is very possible to be different from that of the reactant state

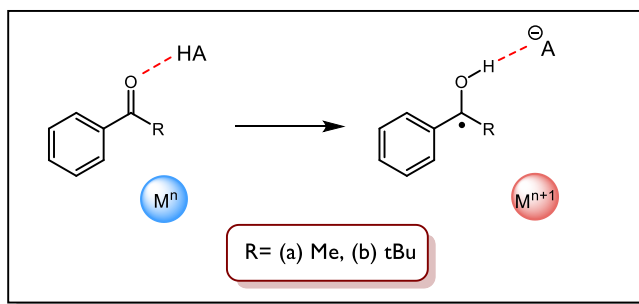
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different *Intrinsic Barrier* from if the parabolae are identical

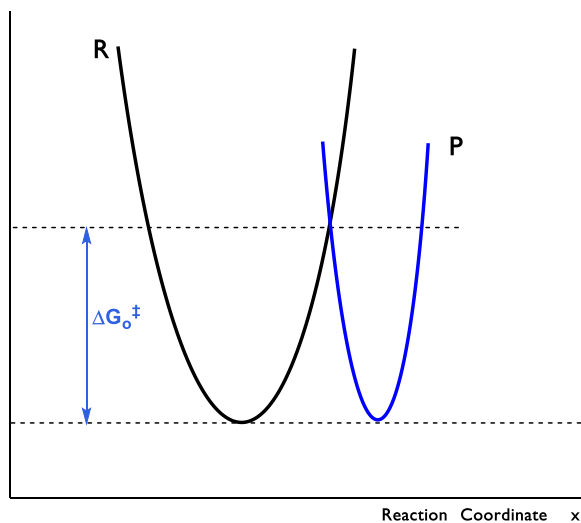


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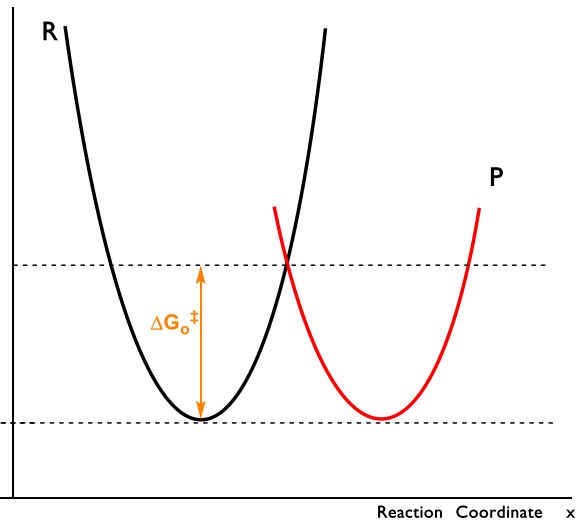
Non-Identical Marcus Parabola and Brønsted Slope



(a)
Free Energy ΔG°

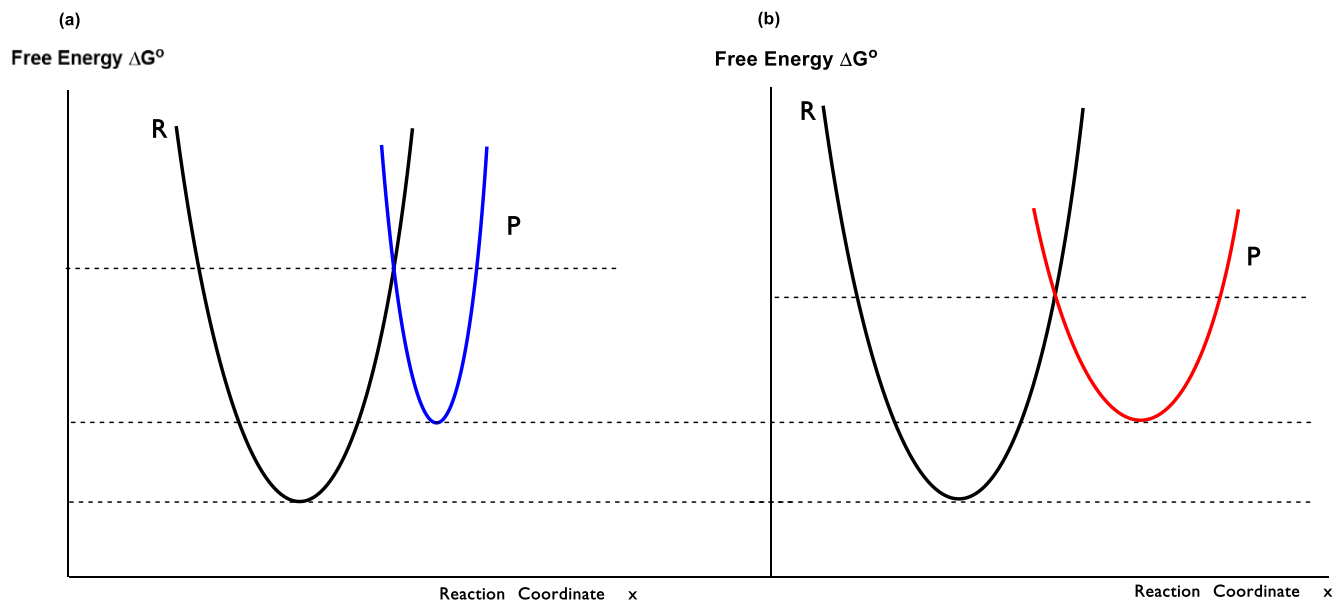
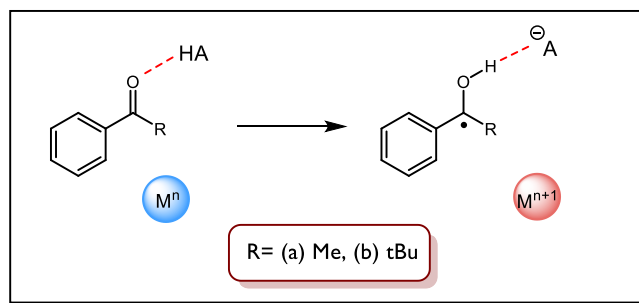


(b)
Free Energy ΔG°



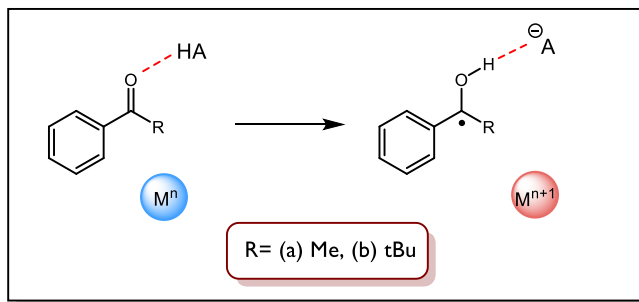
Two intrinsic barriers are different

Non-Identical Marcus Parabola and Brønsted Slope

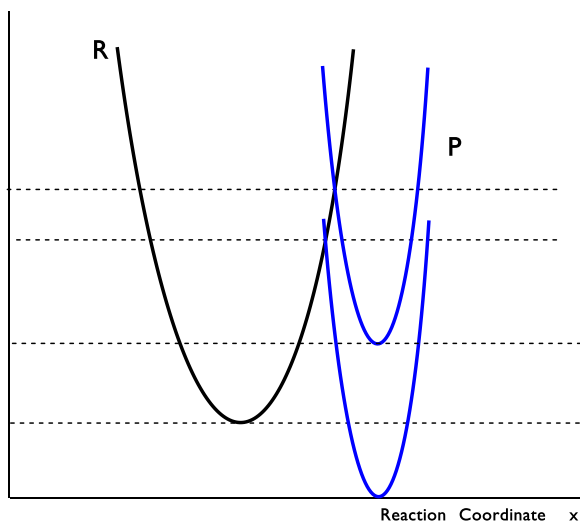


A common driving force for both

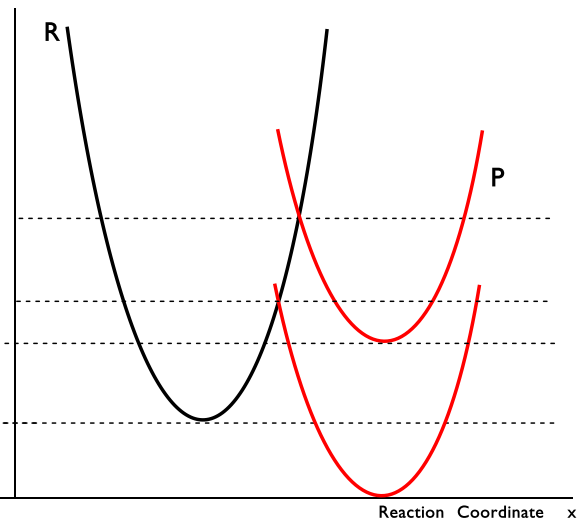
Non-Identical Marcus Parabola and Brønsted Slope



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Free Energy ΔG°

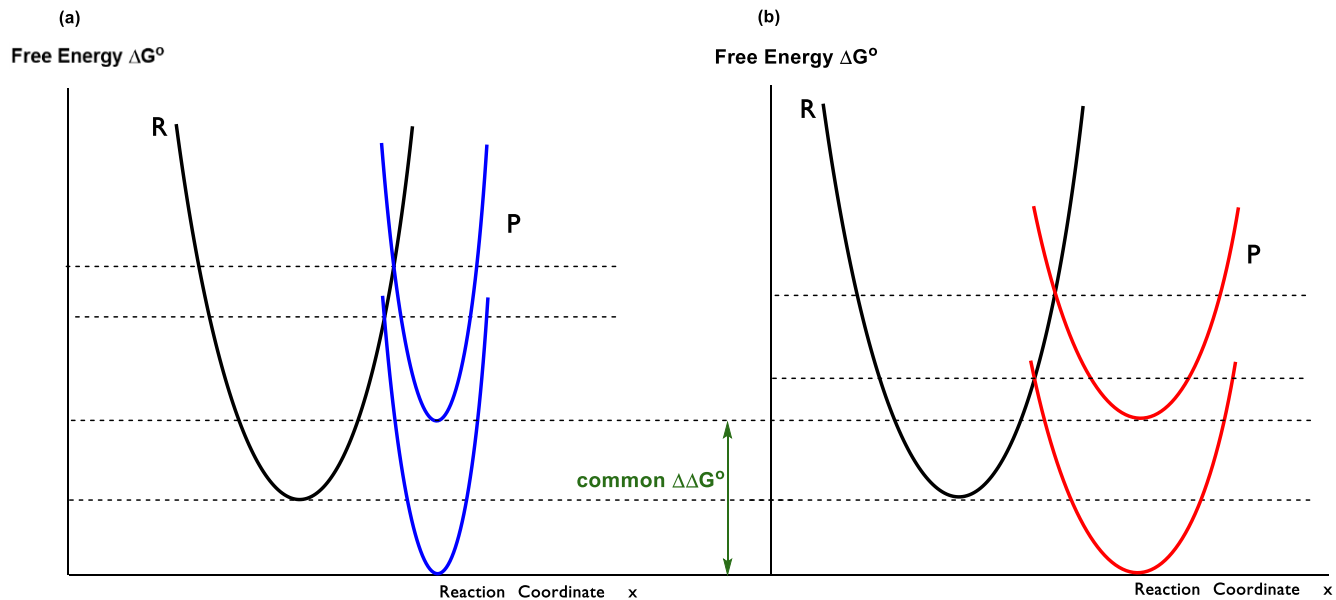
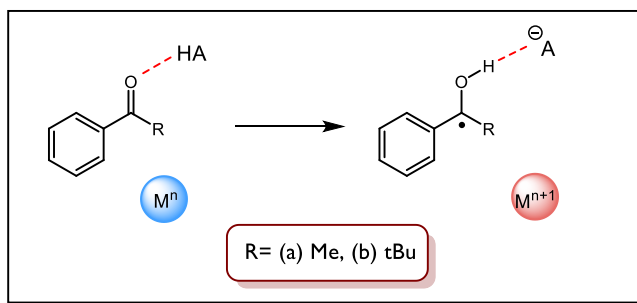


(b)
Free Energy ΔG°



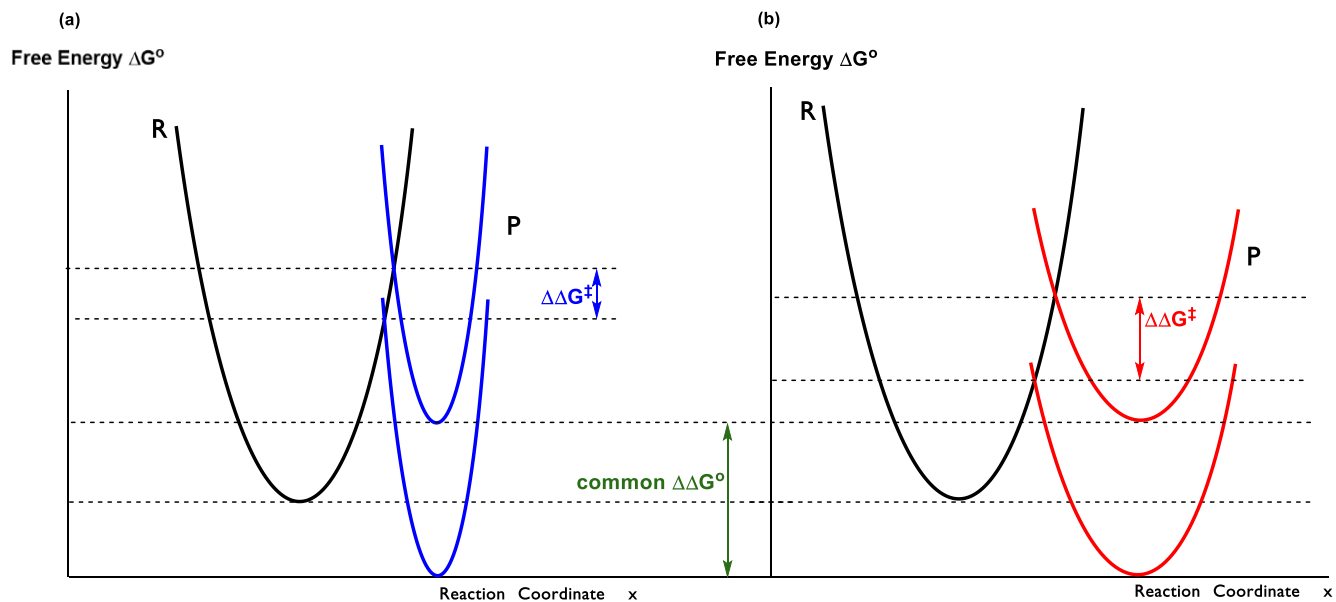
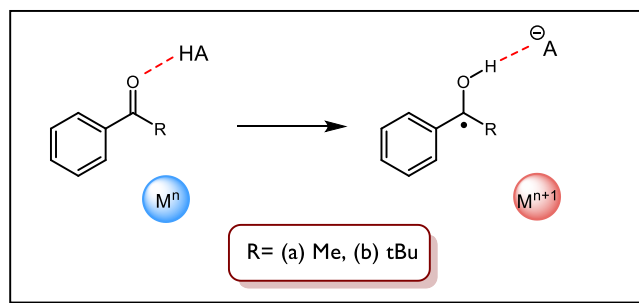
Another common driving force for both

Non-Identical Marcus Parabola and Brønsted Slope



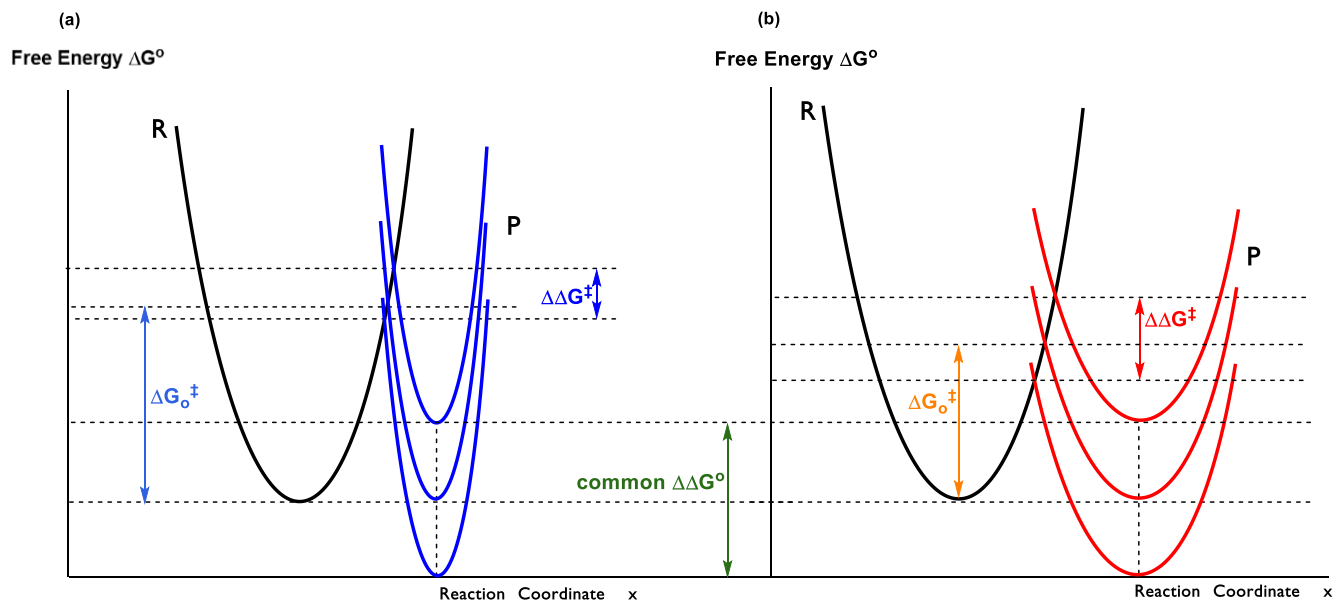
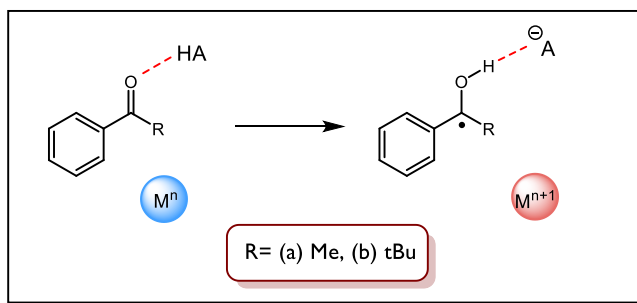
common CHANGE in driving force for both

Non-Identical Marcus Parabola and Brønsted Slope



The common change in driving force results in
DIFFERENT change in reaction barrier

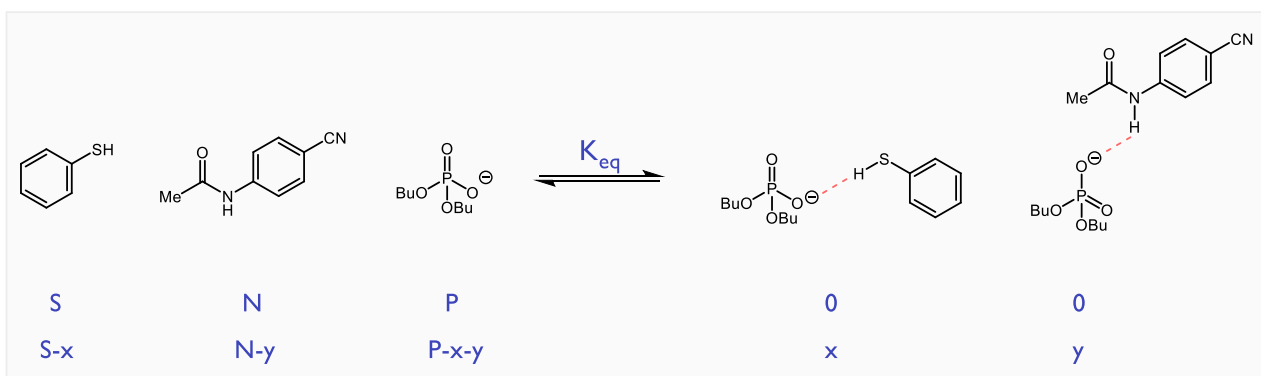
Non-Identical Marcus Parabola and Brønsted Slope



Because of different intrinsic barrier, the common change in driving force results in different change in reaction barrier. i.e. different α value

New Hypothesis for Origin of PCET Selectivity

$$\frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$

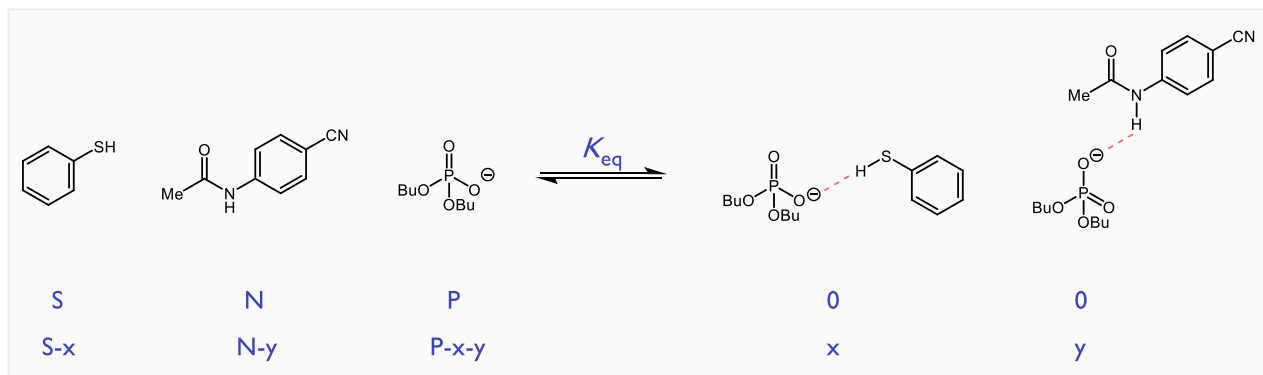


$$I_0/I = 1 + k_{\text{PCET thiol}} \tau_0(x) + k_{\text{PCET amide}} \tau_0(y)$$

$$I_0/I = 1 + \left(\frac{k_{\text{PCET thiol}} \tau_0(x) + k_{\text{PCET amide}} \tau_0(y)}{[\text{base}]_{\text{average}}} \right) [\text{base}]$$

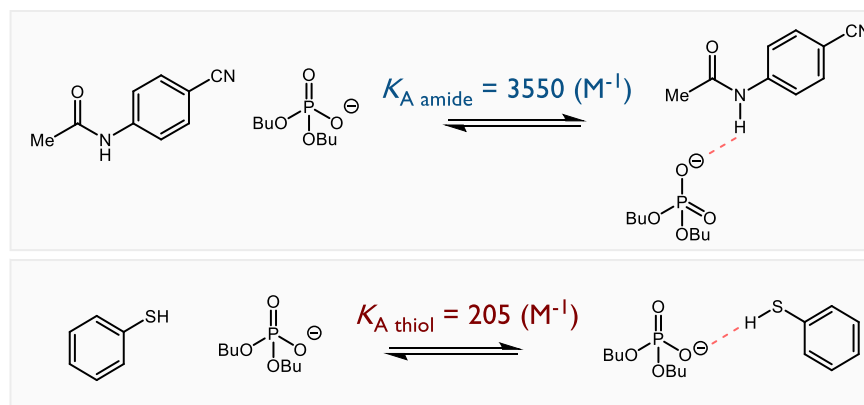
$k_{\text{PCET amide}}$ and $k_{\text{PCET thiol}}$ were pre-determined via our experimental method

Test of the New Hypothesis: Competitive Stern-Vomer Experiment

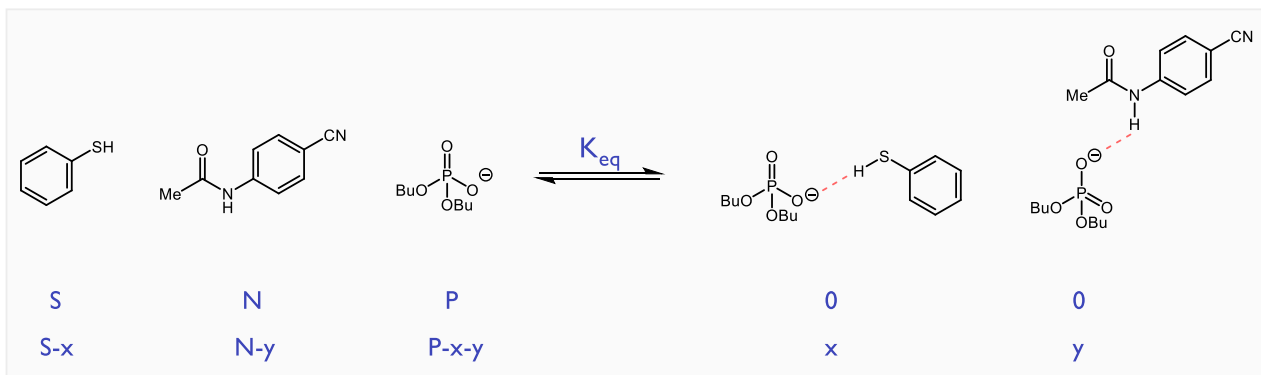


Another two equilibria co-established. $K_{A \text{ amide}}$ and $K_{A \text{ thiol}}$ were pre-determined via our experimental method

$$\left\{ \begin{array}{l} K_{A \text{ amide}} = 3550 = \frac{y}{(\text{N-y})(\text{P-x-y})} \\ K_{A \text{ thiol}} = 205 = \frac{x}{(\text{S-x})(\text{P-x-y})} \end{array} \right.$$



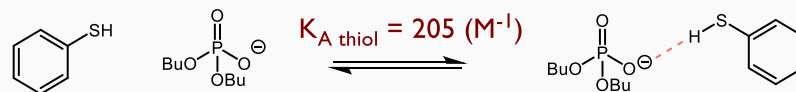
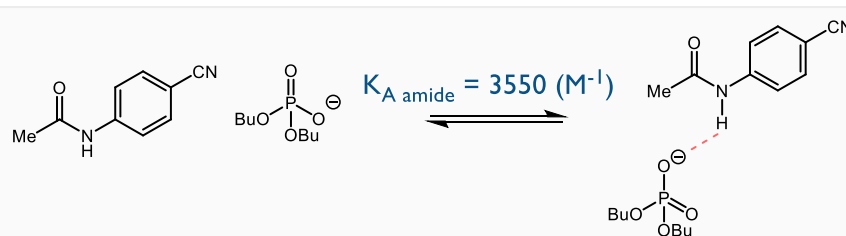
Test of the New Hypothesis: Predicted Quenching Constant



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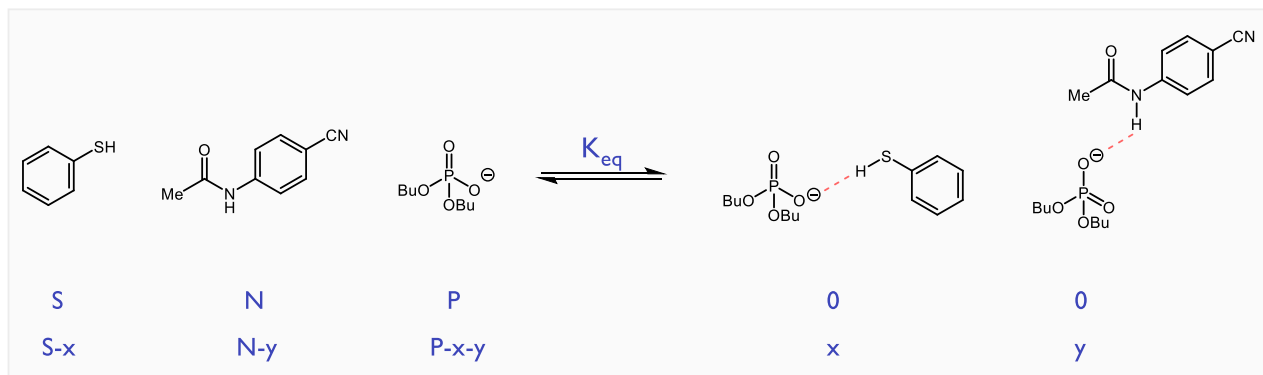
$$K_{A \text{ amide}} = 3550 = \frac{y}{(N-y)(P-x-y)}$$

$$K_{A \text{ thiol}} = 205 = \frac{x}{(S-x)(P-x-y)}$$



From this simultaneous equation, x and y will be known, given initial concentrations of amide, thiol, and base

Test of the New Hypothesis : Predicted Quenching Constant



Initial concentrations in competitive Stern-Volmer experiment:

- [amide] and [thiol] are constant at 0.001 M
- [base] is varied around the average value of 0.0001 M

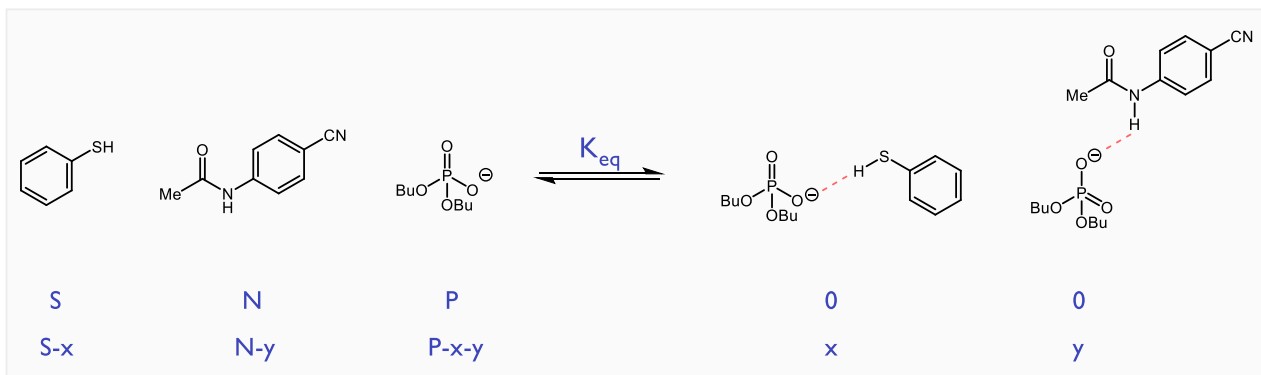
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$$y = 7.46 \times 10^{-5} \text{ M}$$

$$x = 4.30 \times 10^{-6} \text{ M}$$

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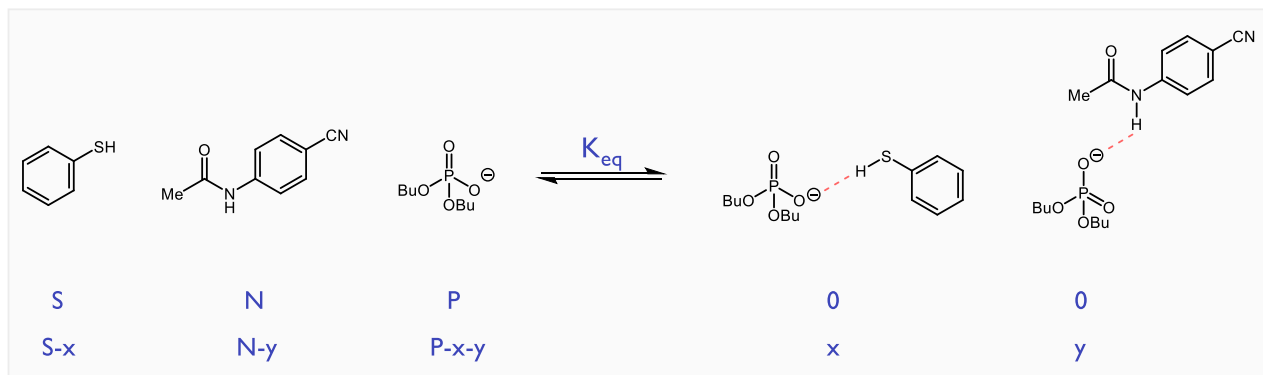
$$k_{\text{PCET amide}} \tau_0(y) = 1279$$

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$$k_{\text{obs predicted}} = 1600$$

Competitive Stern-Volmer Experiment: Predicted Quenching Rate vs Experimental Quenching Rate



Initial concentrations in competitive Stern-Volmer experiment:

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- [base] is varied around the average value of 0.0001 M

$$I_0/I = 1 + k_{SV} ([\text{amide}] + [\text{thiol}]) [\text{base}]$$

$$k_{\text{obs experimental}} = 1598$$

$$k_{\text{PCET amide}} \tau_0 (y) = 1279$$

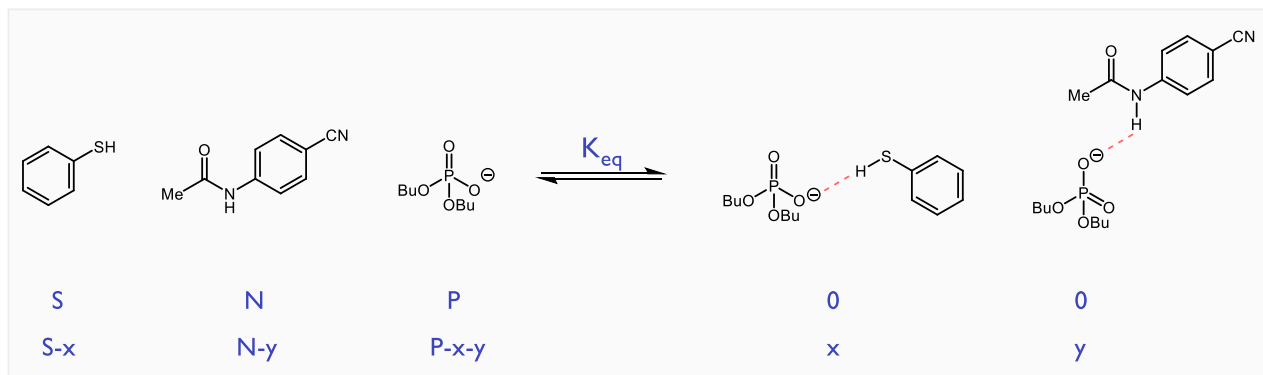
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$$\frac{k_{\text{PCET amide}} [\text{amide adduct}]}{k_{\text{PCET thiol}} [\text{thiol adduct}]}$$

is determinantal to PCET selectivity

$$k_{\text{PCET amide}} \tau_0 (\text{y}) = 1279$$

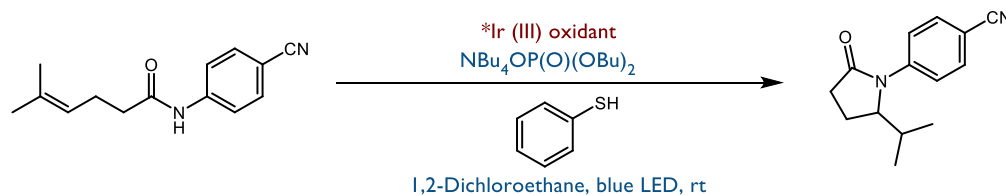
$$k_{\text{PCET thiol}} \tau_0 (\text{x}) = 16719$$

$$I_0/I = 1 + k_{\text{PCET thiol}} \tau_0 (\text{x}) + k_{\text{PCET amide}} \tau_0 (\text{y})$$

$$I_0/I = 1 + \left(\frac{k_{\text{PCET thiol}} \tau_0 (\text{x}) + k_{\text{PCET amide}} \tau_0 (\text{y})}{[\text{base}]_{\text{average}}} \right) [\text{base}]$$

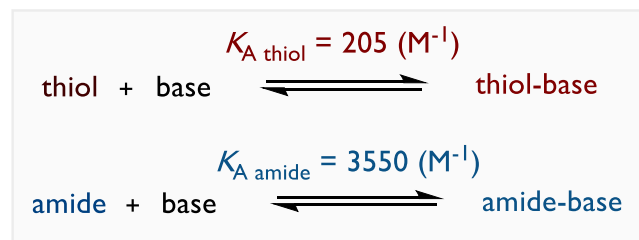
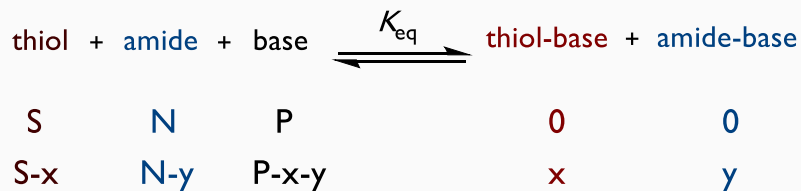
$$k_{\text{obs predicted}} = 1600$$

Determination of PCET Selectivity Factor in a Catalytic Reaction an example



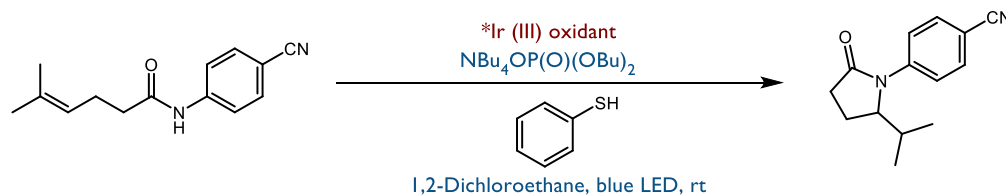
oxidant	[amide]/M	[PhSH]/M	[base]/M	[Ir(III)]/M	NMR yield
$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})\text{PF}_6$	0.1	0.016	0.017	0.002	100%

$$\left\{ \begin{array}{l} K_{\text{A amide}} = 3550 = \frac{y}{(\text{N}-y)(\text{P}-x-y)} \\ K_{\text{A thiol}} = 205 = \frac{x}{(\text{S}-x)(\text{P}-x-y)} \end{array} \right.$$



Change in adduct concentration via oxidant-base binding is negligible

Determination of PCET Selectivity Factor in a Catalytic Reaction an example



oxidant	[amide]/M	[PhSH]/M	[base]/M	[Ir(III)]/M	NMR yield
$\text{Ir(dF(CF}_3\text{)ppy)}_2\text{(bpy)PF}_6$	0.1	0.016	0.017	0.002	100%

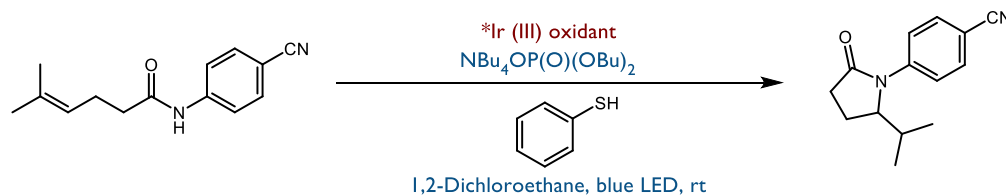
$$\left\{ \begin{array}{l} K_{\text{A amide}} = 3550 = \frac{y}{(\text{N}-y)(\text{P}-x-y)} \\ K_{\text{A thiol}} = 205 = \frac{x}{(\text{S}-x)(\text{P}-x-y)} \end{array} \right.$$

$$\left\{ \begin{array}{l} 3550 = \frac{y}{(0.1-y)(0.02-x-y)} \\ 205 = \frac{x}{(0.02-x)(0.02-x-y)} \end{array} \right.$$

$$\left\{ \begin{array}{l} y = 0.01676\text{M} \\ x = 0.00018\text{M} \end{array} \right.$$

Change in adduct concentration via oxidant-base binding is negligible

Determination of PCET Selectivity Factor in a Catalytic Reaction an example



oxidant	[amide]/M	[PhSH]/M	[base]/M	[Ir(III)]/M	NMR yield
$\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{bpy})\text{PF}_6$	0.1	0.016	0.017	0.002	100%

$$k_{\text{PCET amide}} = 7.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$$

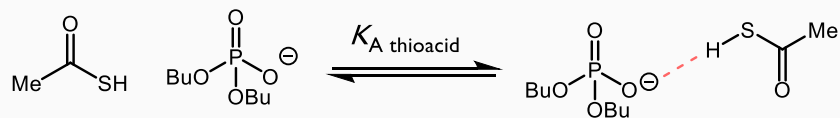
$$k_{\text{PCET thiol}} = 9.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

$$Q_0 = \frac{k_{\text{PCET amide}} [\text{amide adduct}]_0}{k_{\text{PCET thiol}} [\text{thiol adduct}]_0} = \frac{k_{\text{PCET amide}} y}{k_{\text{PCET thiol}} x} = 90 : 10 \quad \left\{ \begin{array}{l} y = 0.01676 \text{ M} \\ x = 0.00018 \text{ M} \end{array} \right.$$

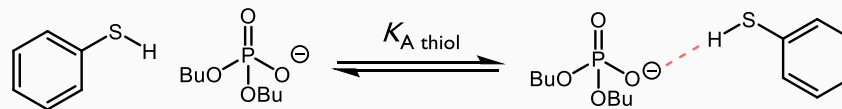
Thioacetic Acid as PCET Substrate



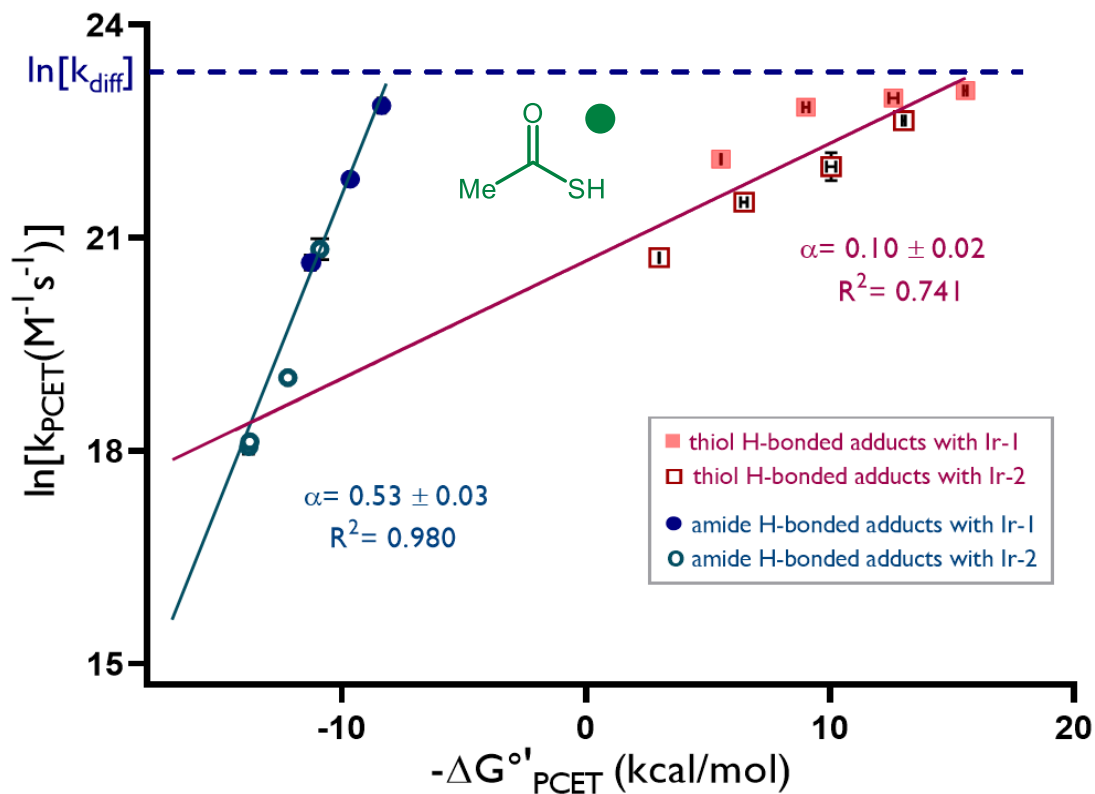
BDFE ~ 89 kcal/mol



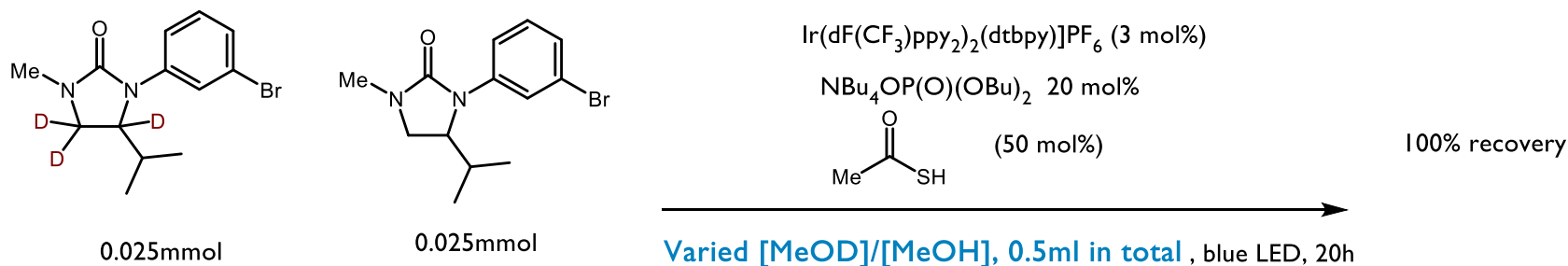
$$K_{\text{A thioacid}} = 2900 \text{ (M}^{-1}\text{)} \quad k_{\text{PCET thioacid}} = 6.8 \times 10^9 \text{ (M}^{-1}\text{s}^{-1}\text{)}$$



$$K_{\text{A thiol}} = 200 \text{ (M}^{-1}\text{)} \quad k_{\text{PCET thiol}} = 9.3 \times 10^9 \text{ (M}^{-1}\text{s}^{-1}\text{)}$$

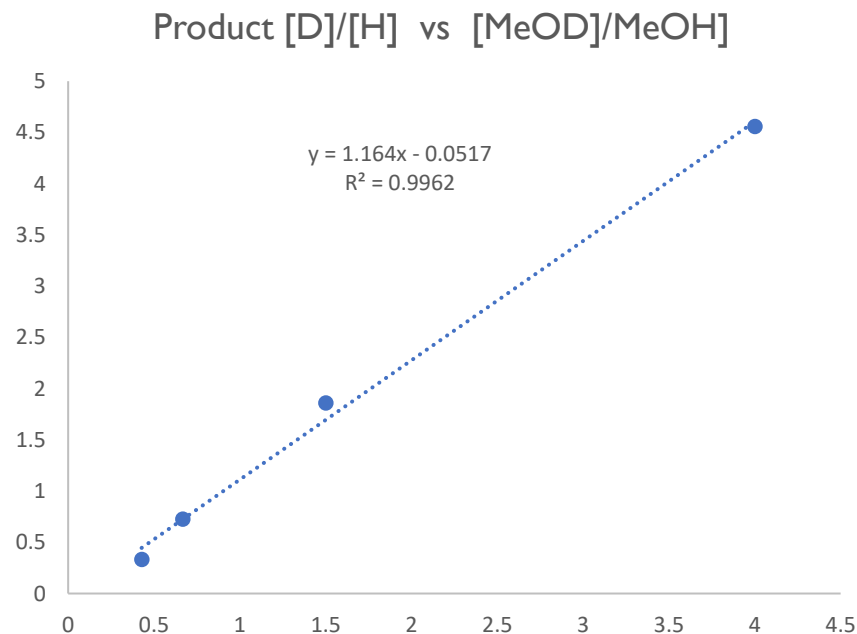


Evidence for HAT-DAT Mechanism: Downstream

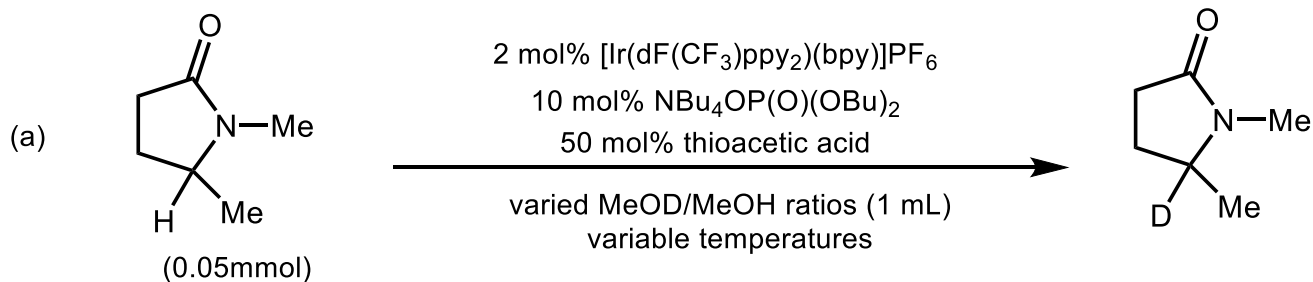


vol MeOD/ml	vol MeOH/ml	% of D product
0.4	0.1	82
0.3	0.2	65
0.2	0.3	42
0.15	0.35	25

Linear correlation with slope~1 → degree of deuteration solely limited by the downstream H/DAT, KIE cancelled

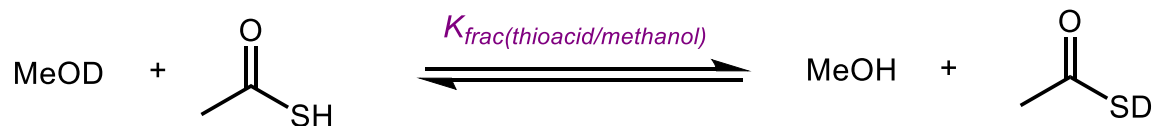


Fractionation between Thiol and Methanol



(b)

$$\frac{[\text{D-substrate}]}{[\text{H-substrate}]} = \overbrace{e^{\Delta\Delta\text{ZPE}/RT} \times K_{\text{frac}(\text{thioacid/methanol})}}^{\text{Fractionation Slope}} \frac{[\text{MeOD}]}{[\text{MeOH}]}$$



(c)

Temperature (°C)	-20	0	25	55
Fractionation Slope	0.67	1.12	1.04	1.06