

Photoredox Organocatalysis

Literature seminar#2

M1 Hiromu Fuse

2017/07/15(Sat)

Introduction



Nicewicz, D. A. *et al. Science* **2015**, 349, 1326.

- ***Organic photoredox catalyzed reaction!***
- ***Direct C-H amination!***
- ***Access to simple aniline derivatives from ammonium***

 **What stage did
the photoredox achieve?**

Introduction

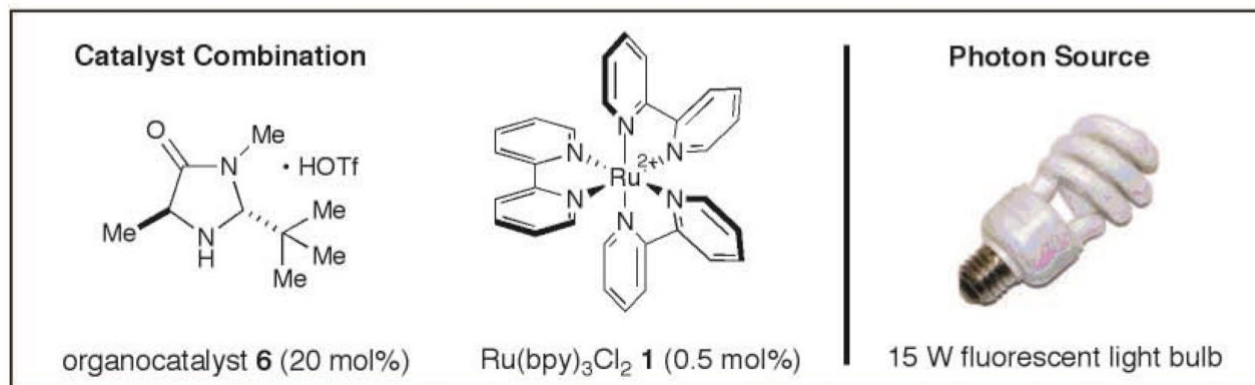
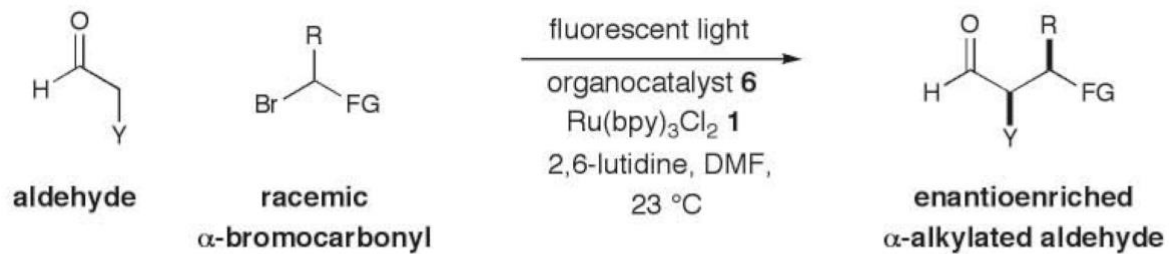


Dave was born and raised in central New Jersey. He completed his B.S. (2000) and M.S. (2001) in Chemistry at the University of North Carolina at Charlotte under the direction of Craig Ogle. Dave then went on to the University of North Carolina at Chapel Hill, where he did his Ph.D. studies under the tutelage of Jeffrey Johnson. Under Jeff's direction, Dave investigated the use of the Brook rearrangement in synthetic methodology and its application to the total synthesis of zaragozic acid C. Upon completion of his Ph.D. studies in 2006, Dave returned to his native New Jersey where he was a Ruth L. Kirschstein National Institutes of Health Postdoctoral Researcher in the laboratories of Professor David MacMillan at Princeton University. While in MacMillan's lab, Dave helped develop the budding area of photoredox organocatalysis. In July of 2009, Dave returned to UNC as an Assistant Professor of Chemistry.

<http://www.chem.unc.edu/people/faculty/nicewicz/group/biography.html>

The pioneer of Photoredox Catalysis!

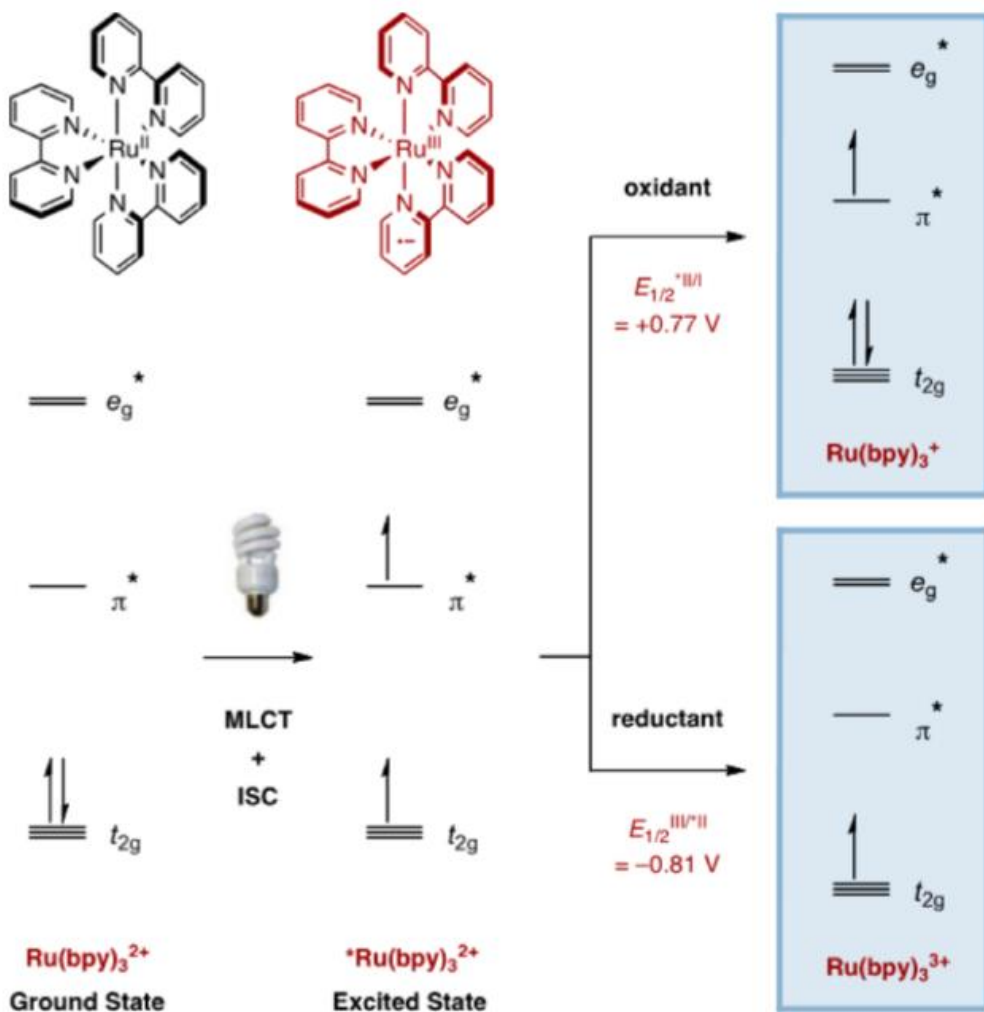
Introduction



Nicewicz, D. A.; MacMillan, D. W. C. *Science*. 2008, 322, 77.

The pioneer of Photoredox Catalysis!

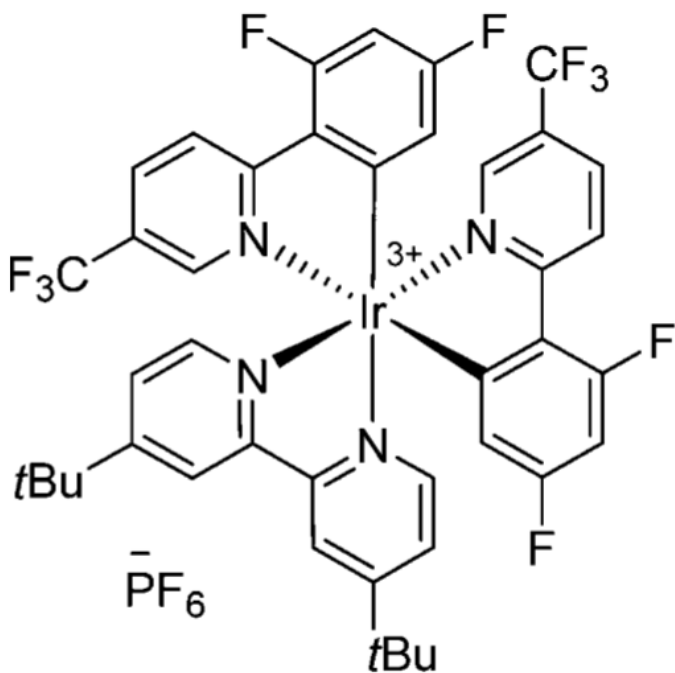
Photoredox catalysis



- ***MLCT and ISC give long-lived triplet photoexcited state.***
- ***Photoredox catalyst can work as both strong oxidant and strong reductant.***

MLCT: metal to ligand charge transfer
ISC: intersystem crossing

High potential of Mes-Acr+

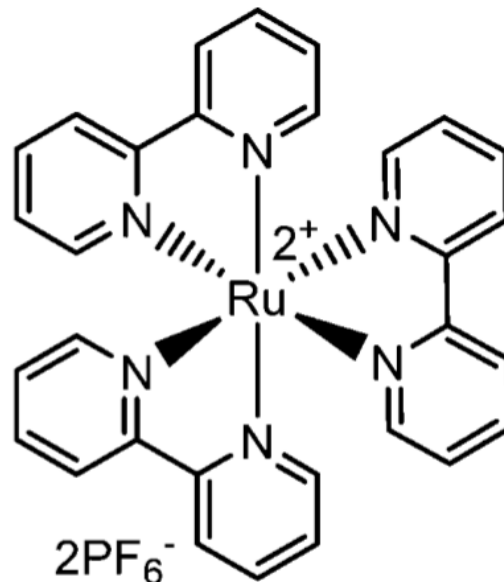


$\text{Ir}(\text{III})^*/\text{Ir}(\text{II}) = 1.21 \text{ V}$

$\text{Ir}(\text{IV})/\text{Ir}(\text{III}) = 1.69 \text{ V}$

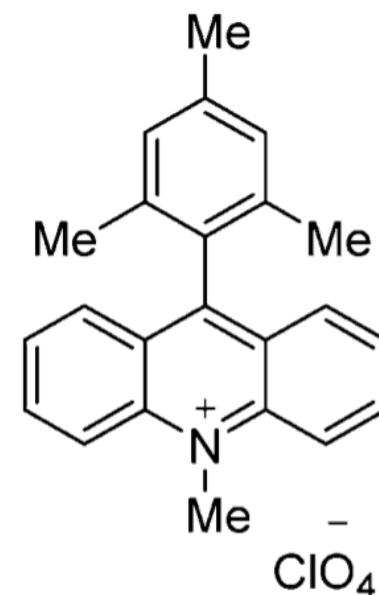
ex. $\text{S}_2\text{O}_8^{2-} = 1.85 \text{ V}$

$\text{HOCl} = 1.39 \text{ V}$



$\text{Ru}(\text{II})^*/\text{Ru}(\text{I}) = 0.77 \text{ V}$

$\text{Ru}(\text{III})/\text{Ru}(\text{II}) = 1.29 \text{ V}$



Et (S*/S) = 2.06 V

<http://chemlabs.princeton.edu/macmillan/photoredox/>

Today's Content

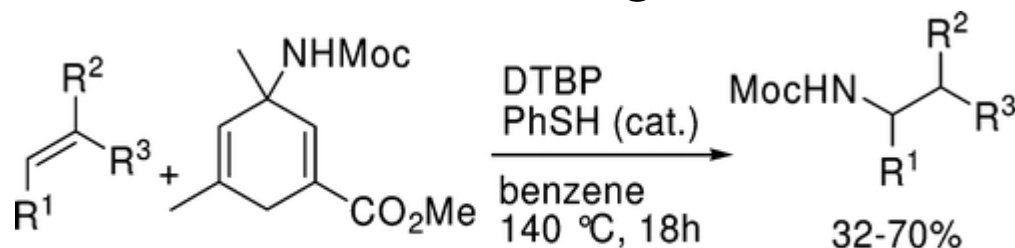
- 1. Mechanistic study of Mes-Acr⁺ catalyzed anti-Markovnikov hydro-functionalization***
- 2. Direct C-H amination***

Today's Content

- 1. Mechanistic study of Mes-Acr⁺ catalyzed anti-Markovnikov hydro-functionalization***
- 2. Direct C-H amination*

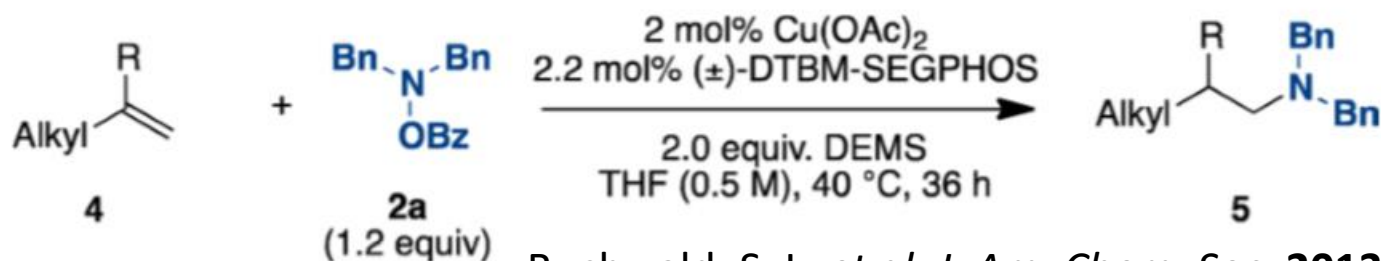
Anti-Markovnikov hydro-functionalization

- **Although anti-Markovnikov hydro-functionalization was developed, there is no general way.**
- **In many cases, substrates are limited such as vinylarenes or prefunctionalized heteroatom reagents.**



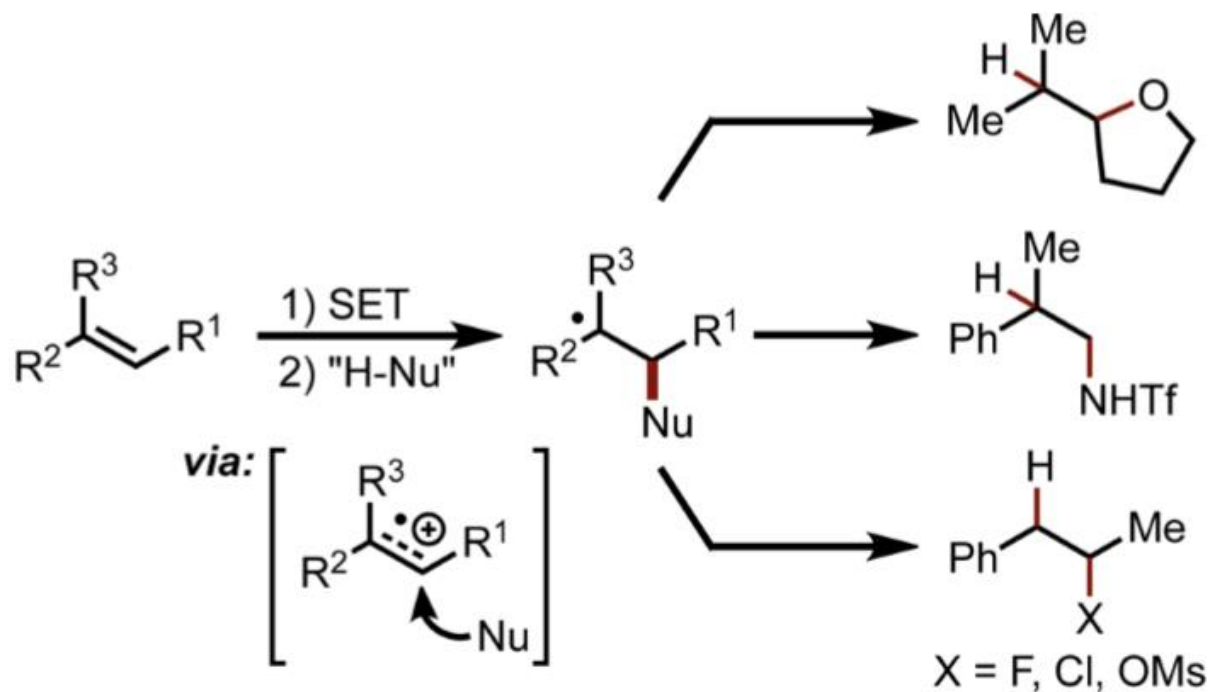
(25 examples)

Studer, A. *et al. J. Am. Chem. Soc.* **2007**, 129, 4498.

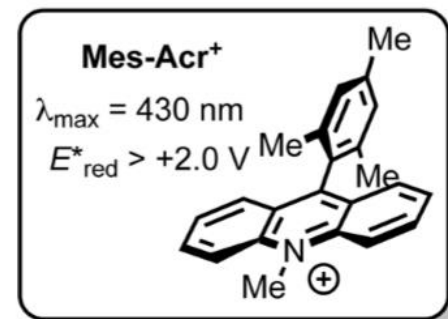


Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2013**, 135, 15746.

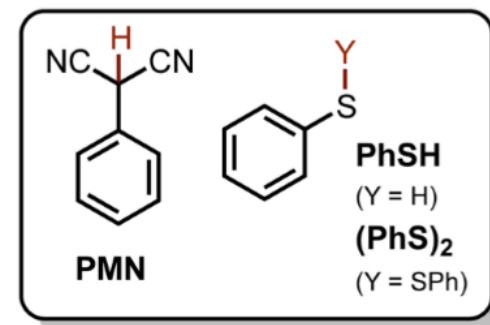
Photoredox-catalyzed anti-Markovnikov hydro-functionalization



photoredox catalyst



HAT catalysts



Nicewicz, D. A. *et al.* *J. Am. Chem. Soc.* **2012**, *134*, 18577.

Nicewicz, D. A. *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 10334.

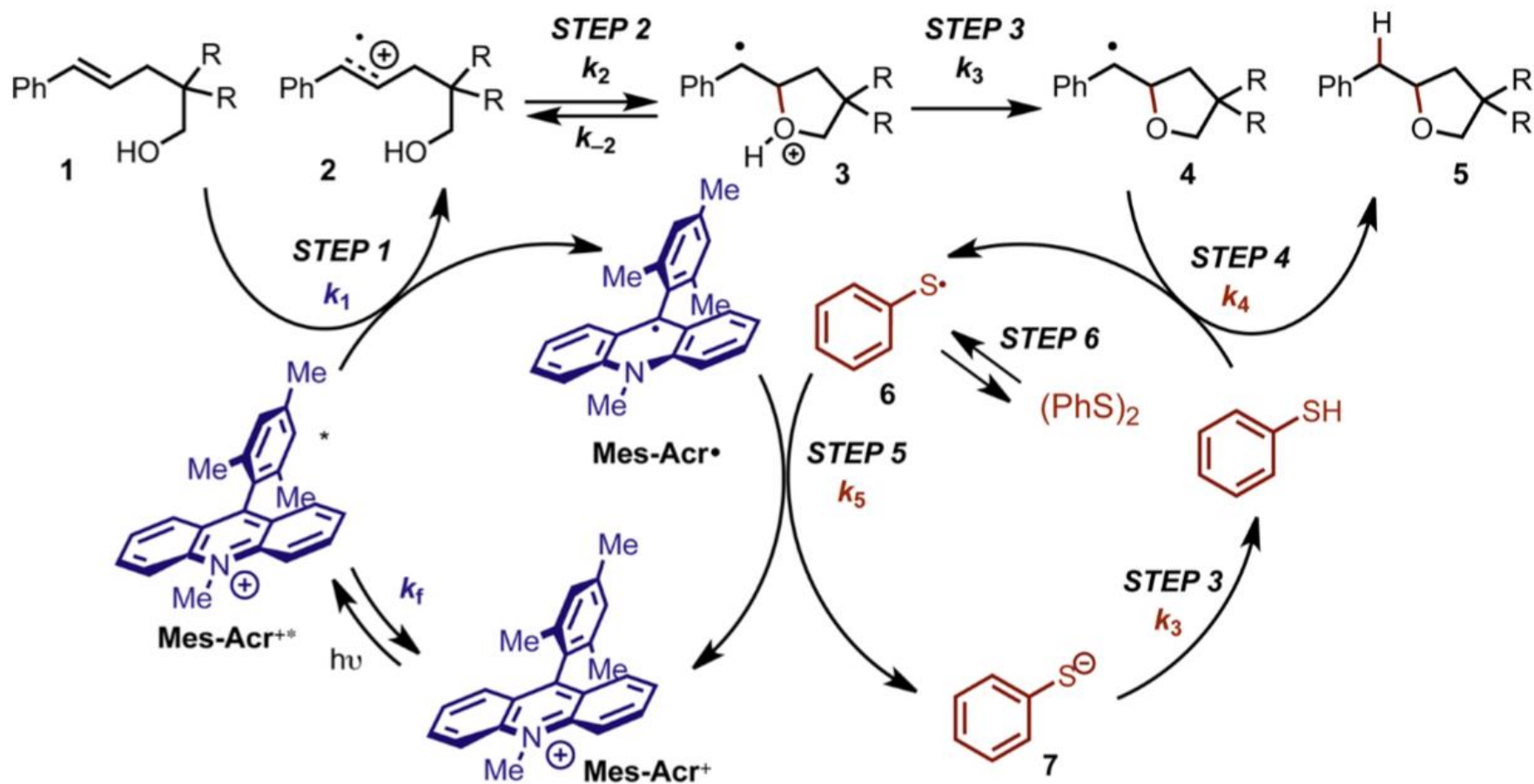
Nicewicz, D. A. *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 9588.

Nicewicz, D. A. *et al.* *Angew., Chem. Int. Ed.* **2014**, *53*, 6198.

Nicewicz, D. A. *et al.* *Nat. Chem.* **2014**, *6*, 720.

Nicewicz, D. A. *et al.* *Chem. Sci.* **2013**, *4*, 3160.

Proposed mechanism



How does this reaction proceed?

Difficulty of mechanistic study

1. Multicomponent catalytic systems

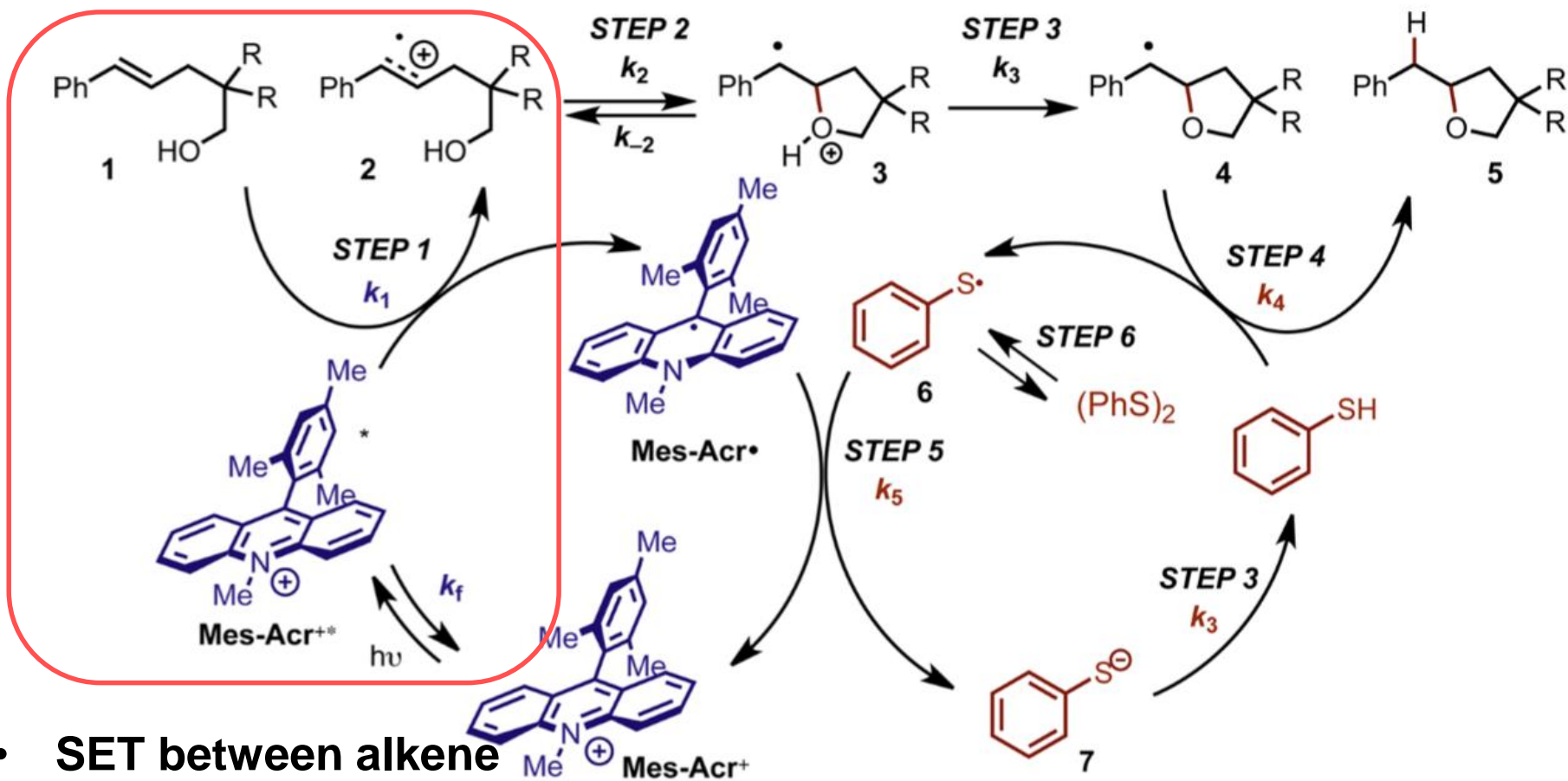
2. Short-lived intermediate

3. SET (Single Electron Transfer)



Spectroscopic study was employed.

Proposed mechanism

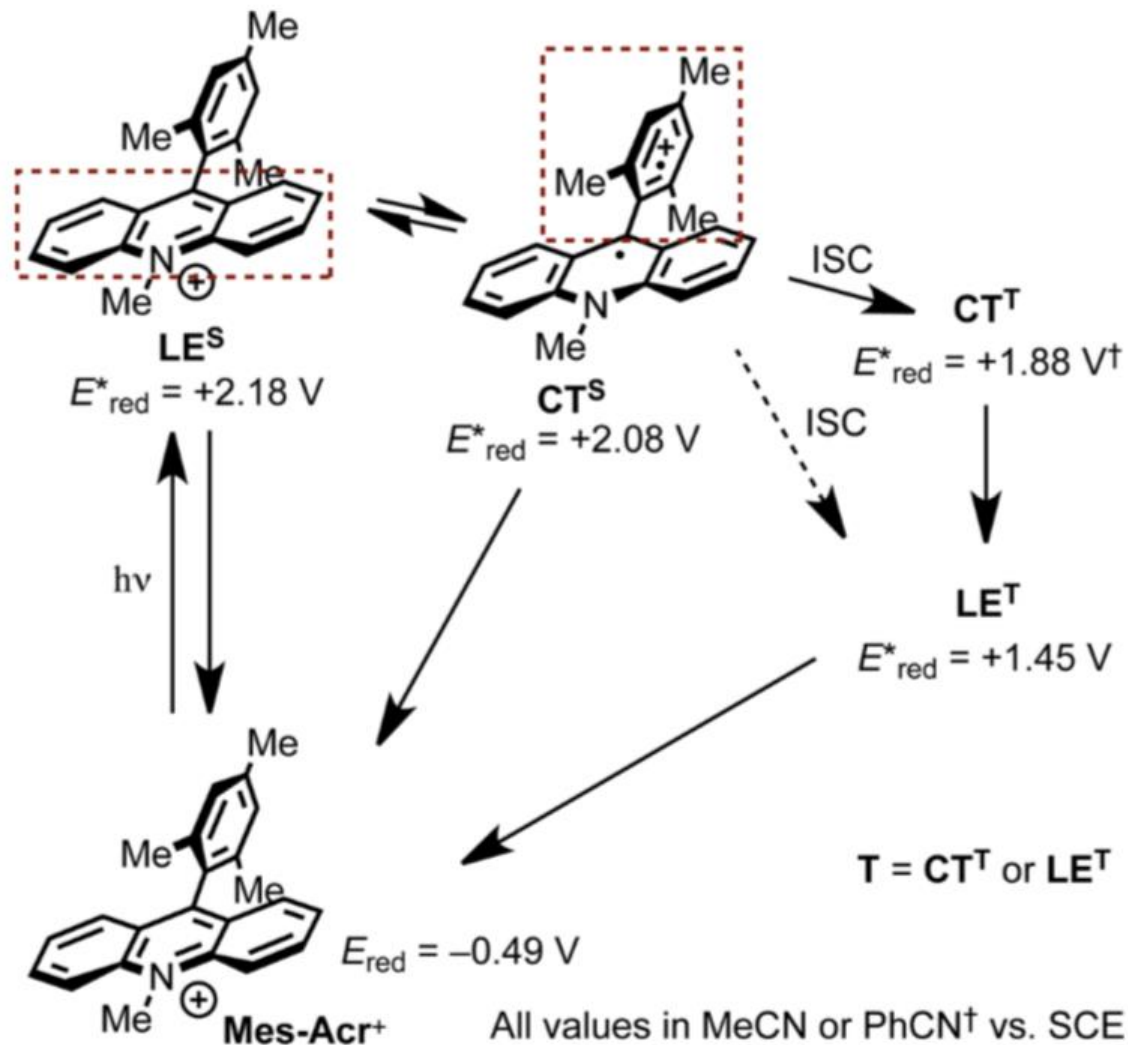


- SET between alkene and Mes-Acr⁺
- State of Mes-Acr⁺



How does this reaction proceed?

The state of Mes-Acr⁺

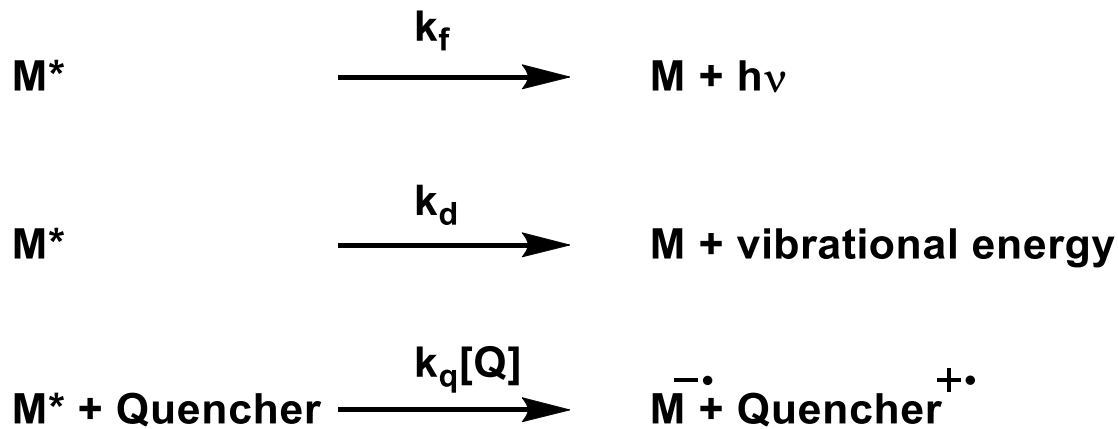
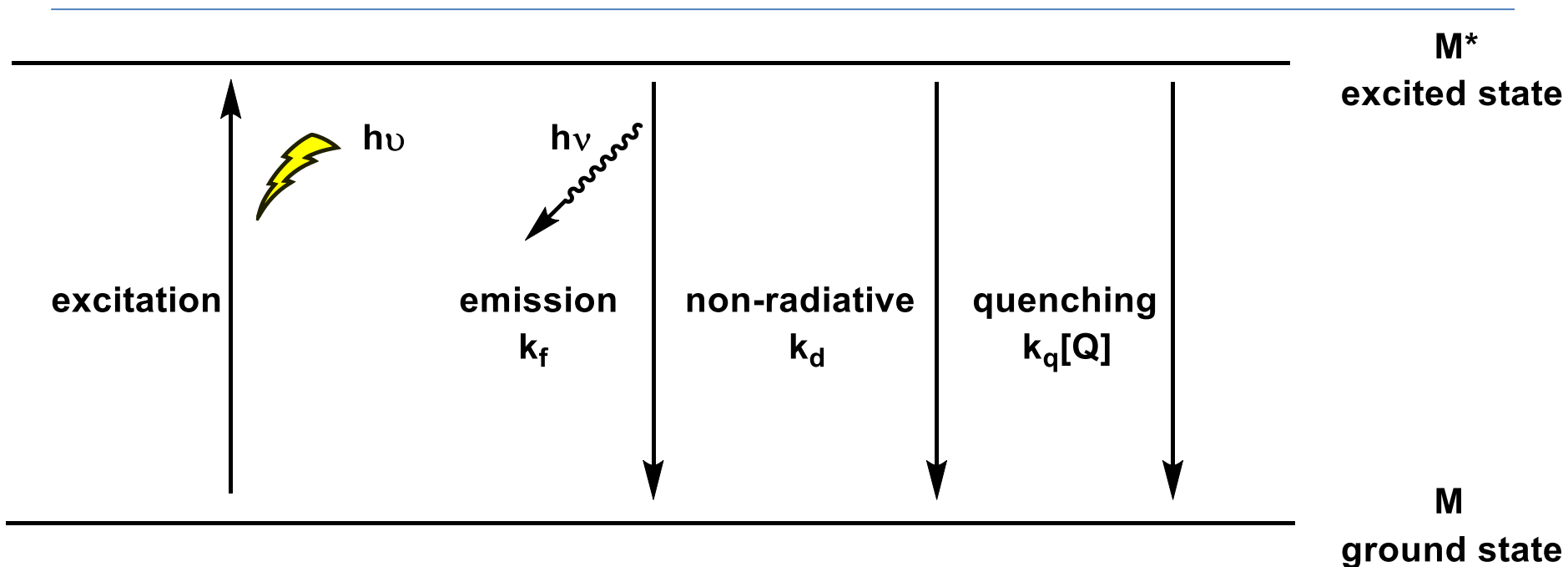


Which state was involved?



**Confirm potential
of Mes-Acr⁺**

Fate of excited state



In today's case,
M: Mes-Acr+
Q: alkenes

Stern-Volmer Plot

$$\Phi_f^0 = \frac{k_f}{k_f + k_d} = \frac{k_f}{\frac{1}{\tau_0}} = k_f \tau_0$$

In absence of quencher

$$\Phi_f = \frac{k_f}{k_f + k_d + k_q [Q]} = \frac{k_f}{\frac{1}{\tau_0} + k_q [Q]}$$

In presence of quencher

$$\frac{\Phi_f^0}{\Phi_f} = \frac{\frac{k_f}{\frac{1}{\tau_0}}}{\frac{k_f}{\frac{1}{\tau_0} + k_q [Q]}} = 1 + k_q \tau_0 [Q]$$

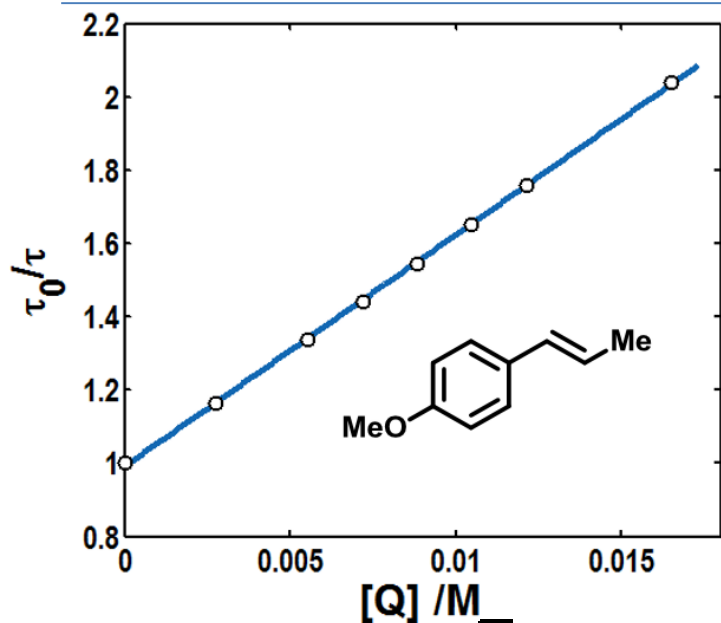
Dividing these equations

$$\frac{\Phi_f^0}{\Phi_f} = \frac{I_f^0}{I_f} = \frac{\tau_0}{\tau} = 1 + k_q \tau_0 [Q] \quad \text{Stern-Volmer Equation}$$

$K_{SV} = k_q \tau_0$
(K_{SV} : Stern-Volmer constant)

grow linearly with [Q]

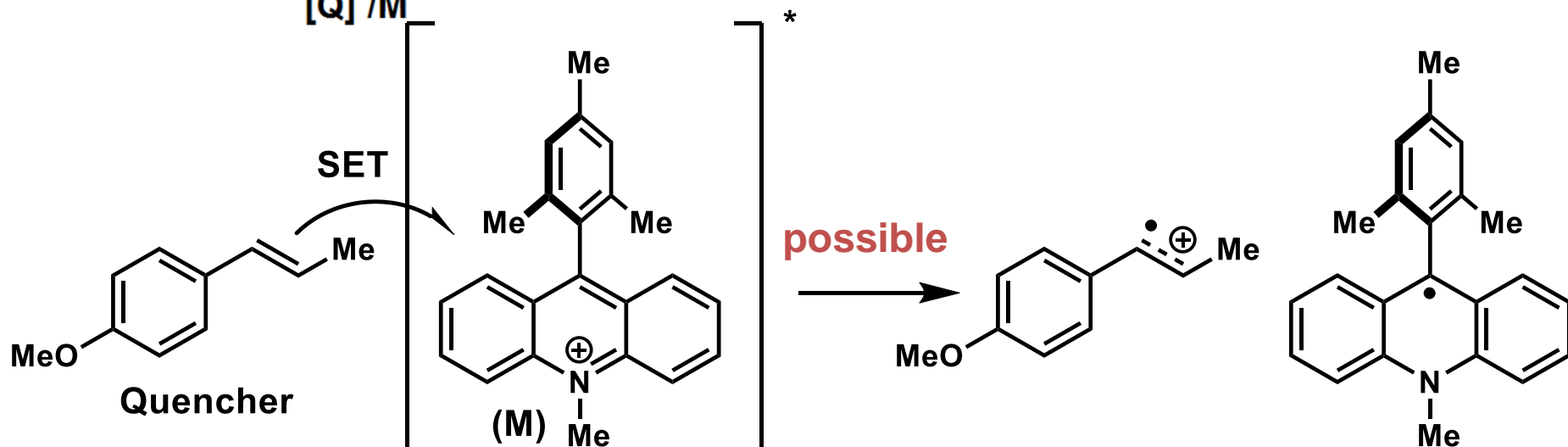
Stern-Volmer Plot



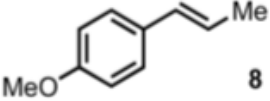
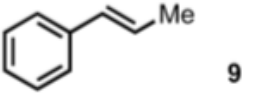
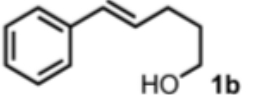
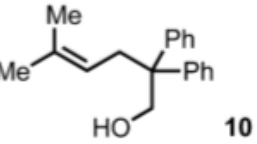
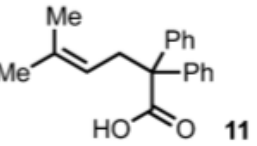
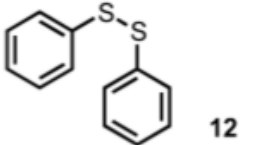
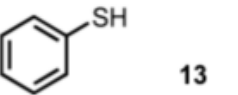
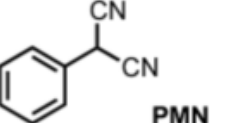
k_q (rate of deactivation by quencher)
 τ : lifetime of M^* (excited state of M)
 K_{SV} : Stern-Volmer constant

$$\tau_0/\tau = 1 + k_q[Q]\tau_0 = 1 + K_{SV}[Q]$$

$$k_q = K_{SV} / \tau_0$$



Rate of quenching

quencher	$K_{SV} (M^{-1})^a$	$k_1 (M^{-1}s^{-1})^b$	$E_{p/2}^c$
 8	63.2	9.85×10^9	1.34
 9	44.4 (136) ^d	6.92×10^9 (7.84×10^9) ^d	1.77
 1b	37.5	5.85×10^9	1.86
 10	7.53	1.18×10^9	2.09
 11	3.88	6.10×10^8	2.18
<hr/>			
 12	40.5	6.40×10^9	1.71
 13	53.5	8.47×10^9	1.60
 PMN	–	–	–

$k_1 = k_q$ (rate of deactivation by quencher)

K_{SV} : Stern-Volmer constant

$$k_1 = k_q = K_{SV} / \tau_0$$

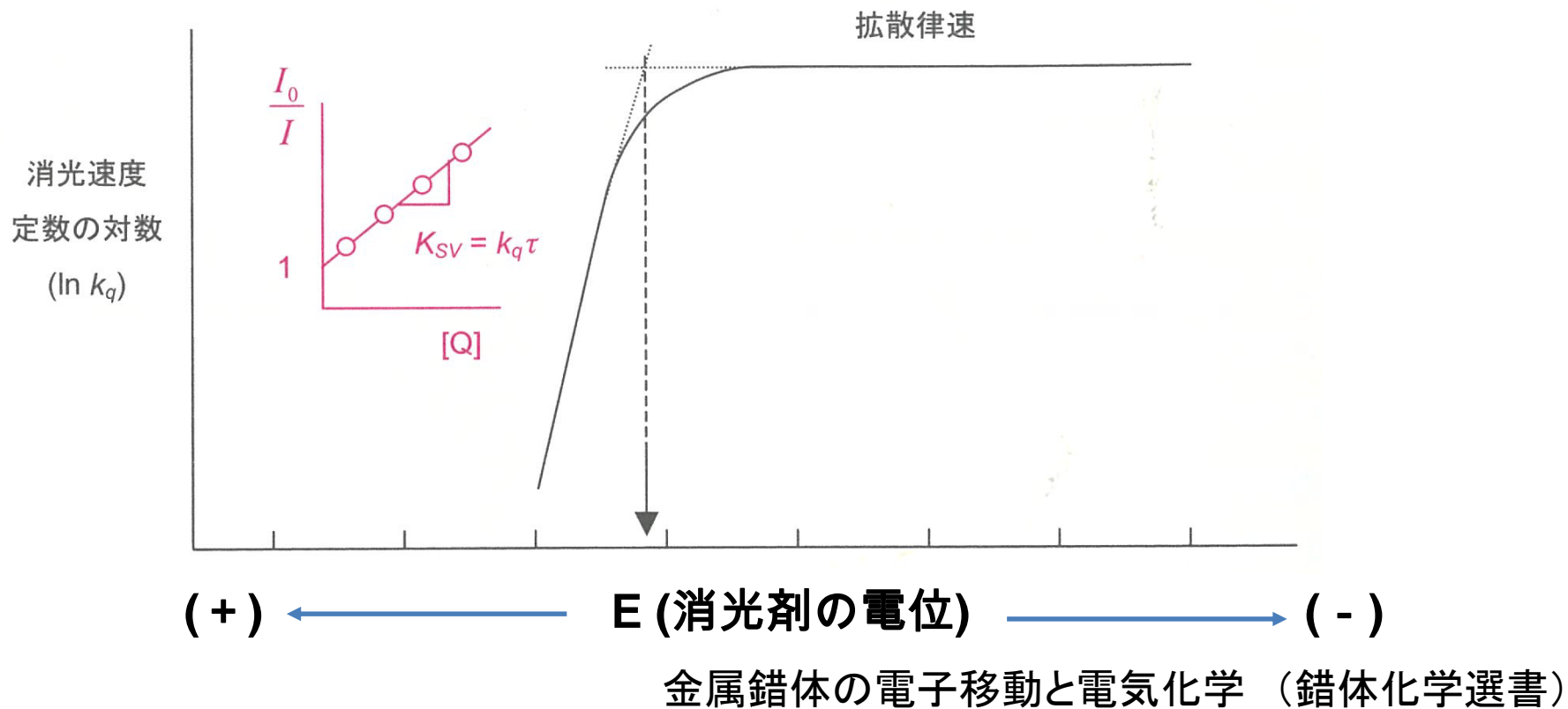
➡ SET is possible.

How to confirm potential of excited state?

- ***Rehm-Weller plot***
 - *Experimental techniques*

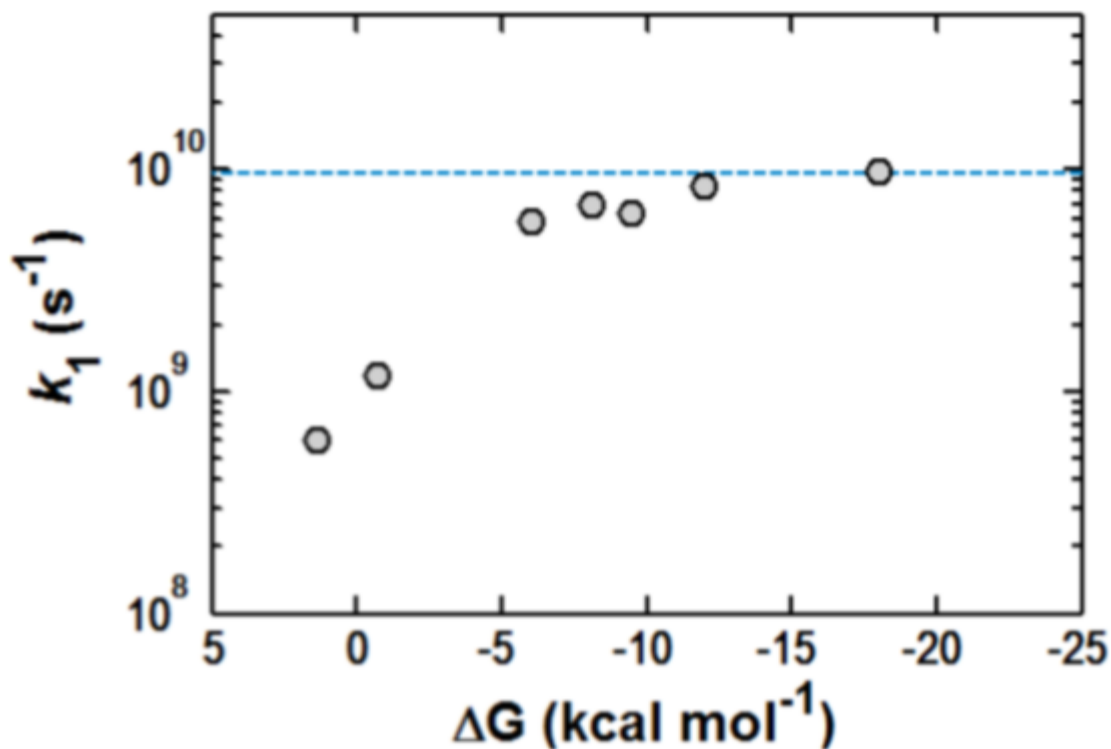
- **$E_{red}^* = E_{0,0} + E_{red}$**
 - *Calculation approach*

Rehm-Weller plot



- **Potential could be revealed by Rehm-Weller plot.**

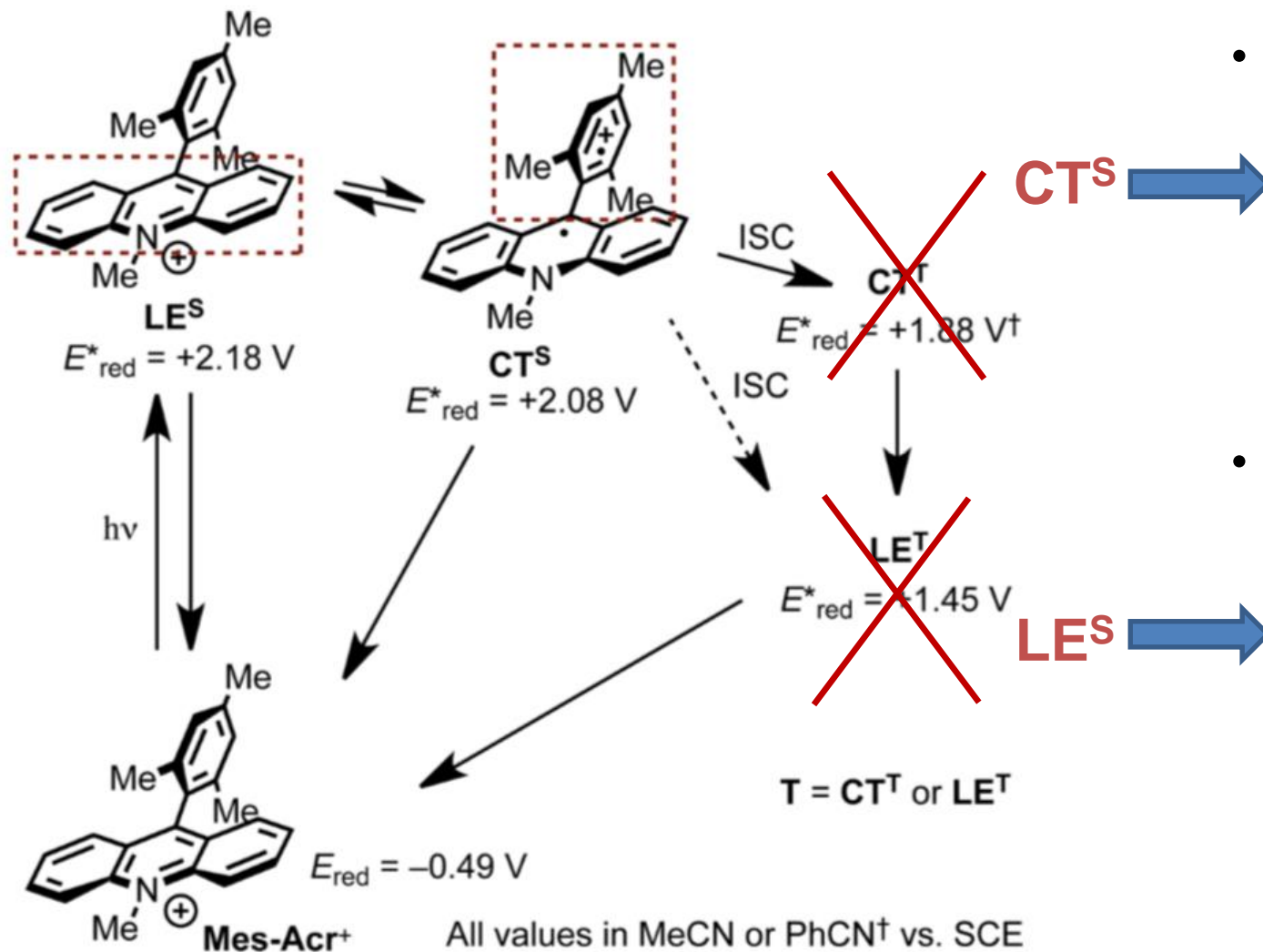
Rehm-Weller plot



- **Potential of Singlet State was needed.**

➡ Which is the dominant state, LE^S or CT^S?

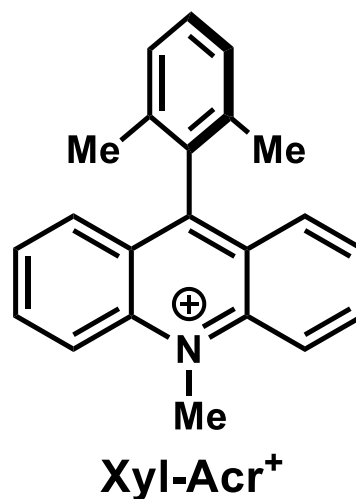
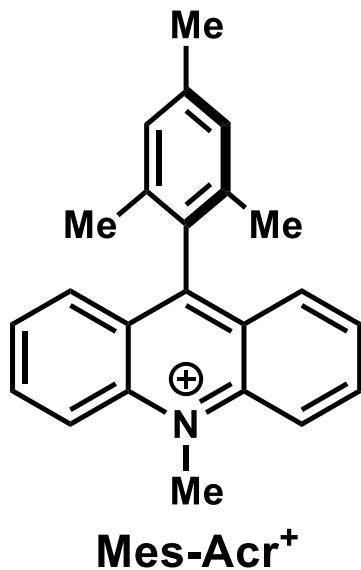
What is the motivation?



- *mesityl radical cation is limited to redox potential.*

- *Suppressing intramolecular charge transfer could lead more oxidizing acridinium catalyst.*

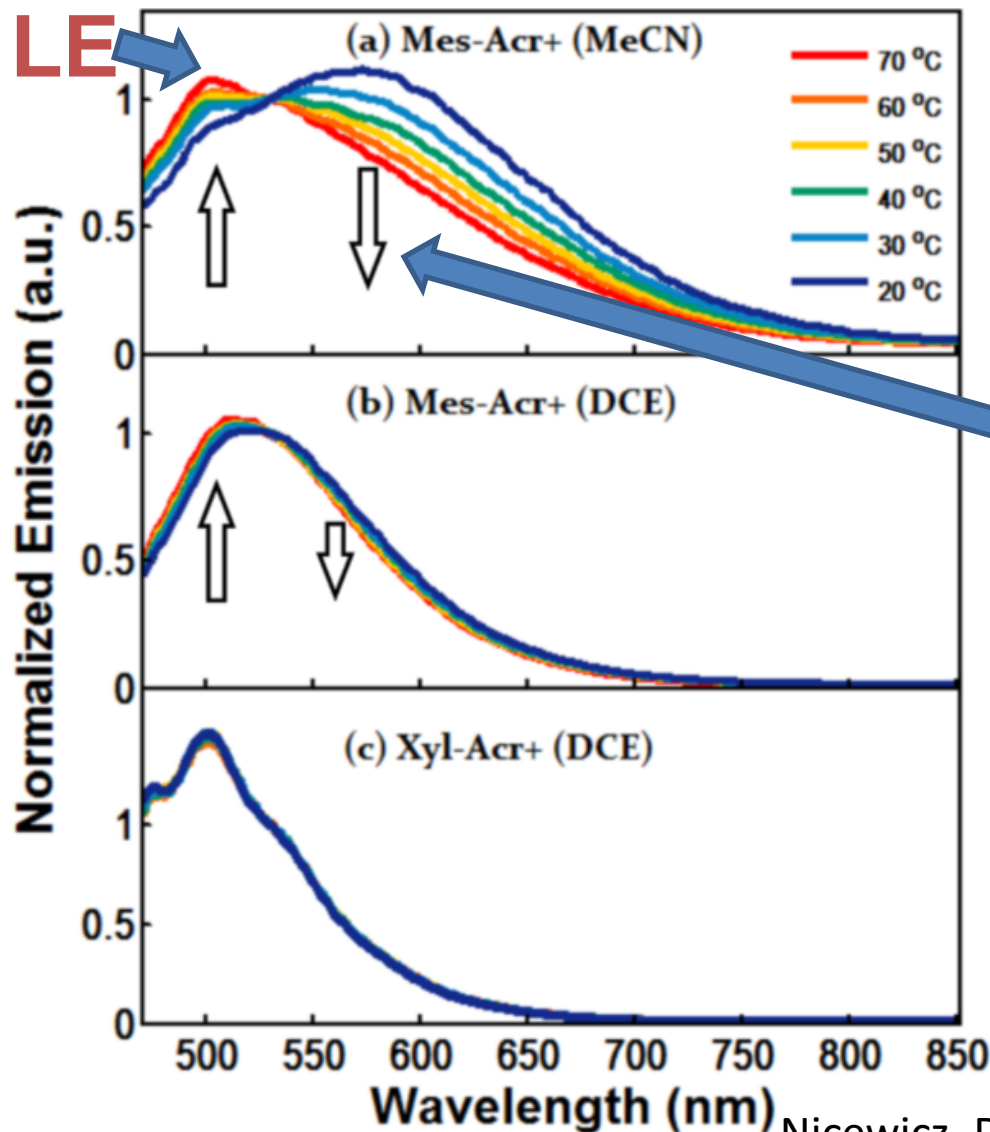
How to confirm?



No CT in DCE

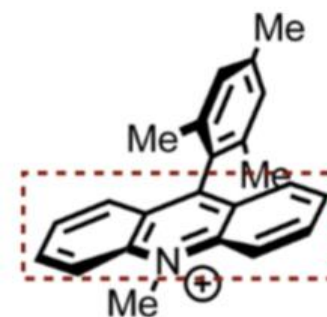
→ compare the spectrums of these two species

Comparing spectrum



- *There was possibility that CT was not necessary?*

CT

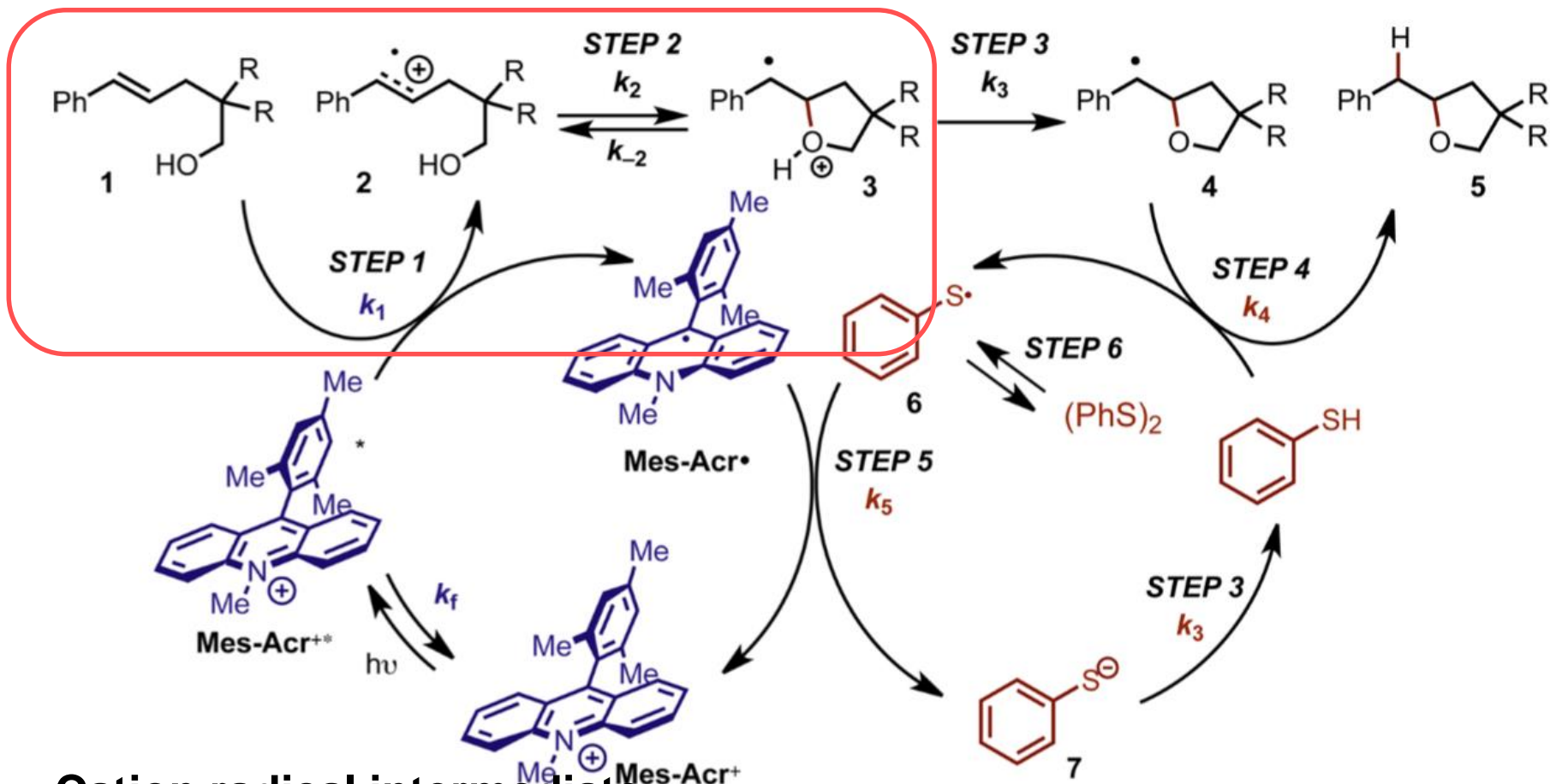


LE^s

$$E^*_{\text{red}} = +2.18 \text{ V}$$

dominant species?

Proposed mechanism

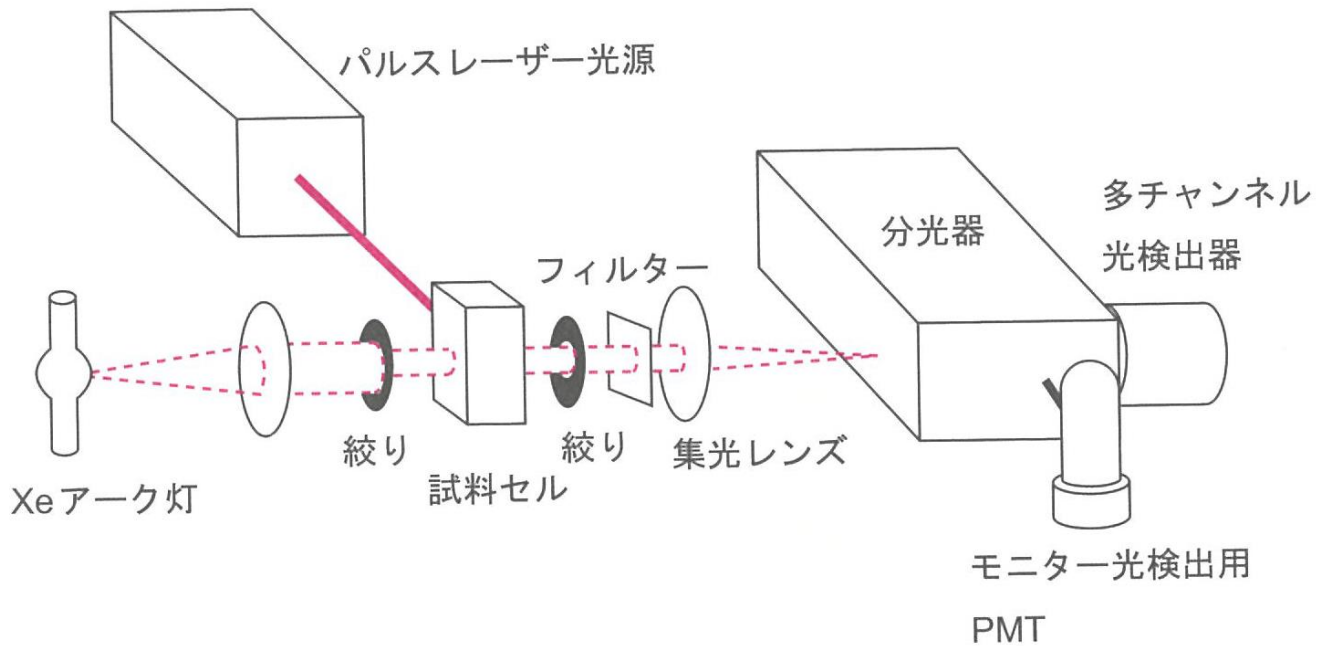


- Cation radical intermediate
- k_2 (rate of cyclization)



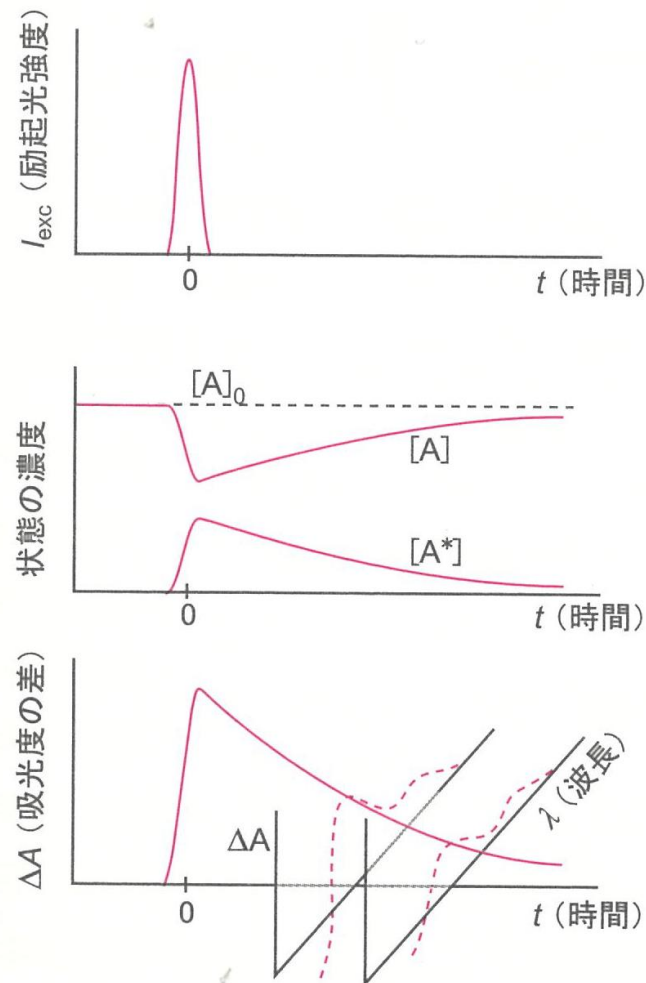
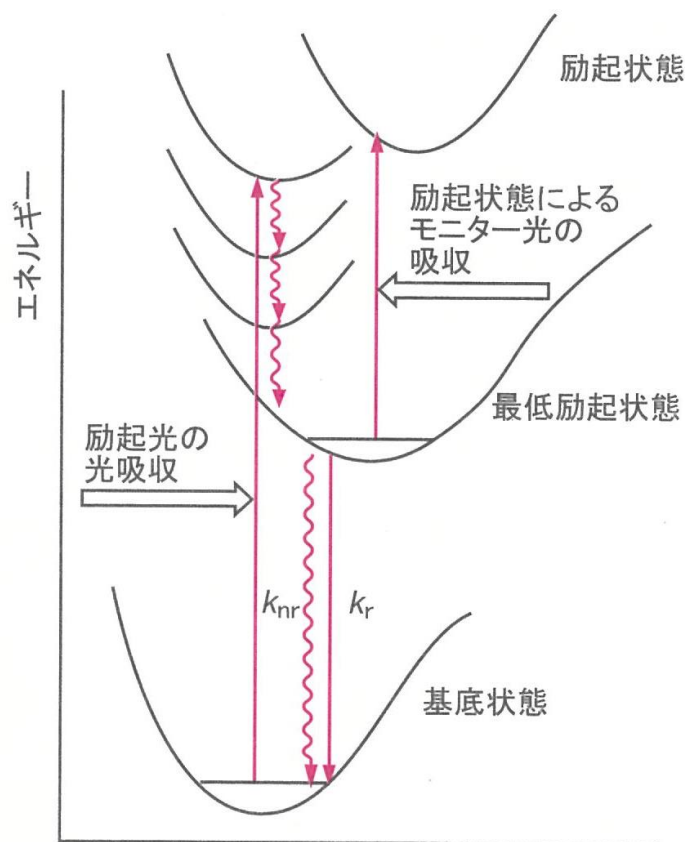
How does this reaction proceed?

Transient absorption spectroscopy



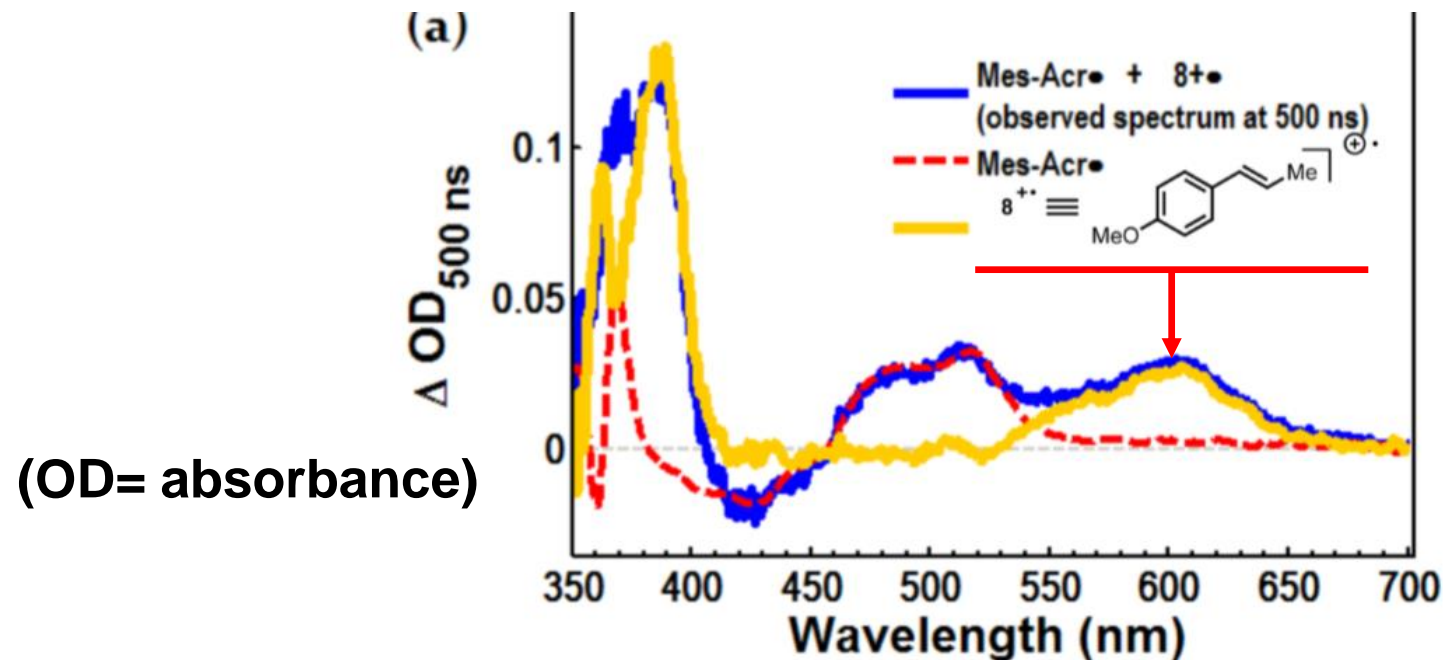
- ***It can detect the chemicals which have short life.***

Transient absorption spectroscopy

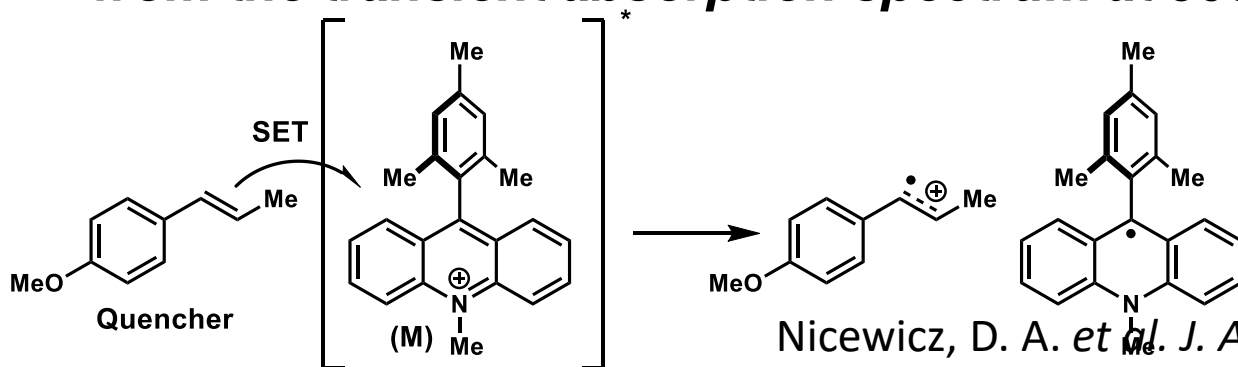


- ***It can detect the chemicals which have short life.***

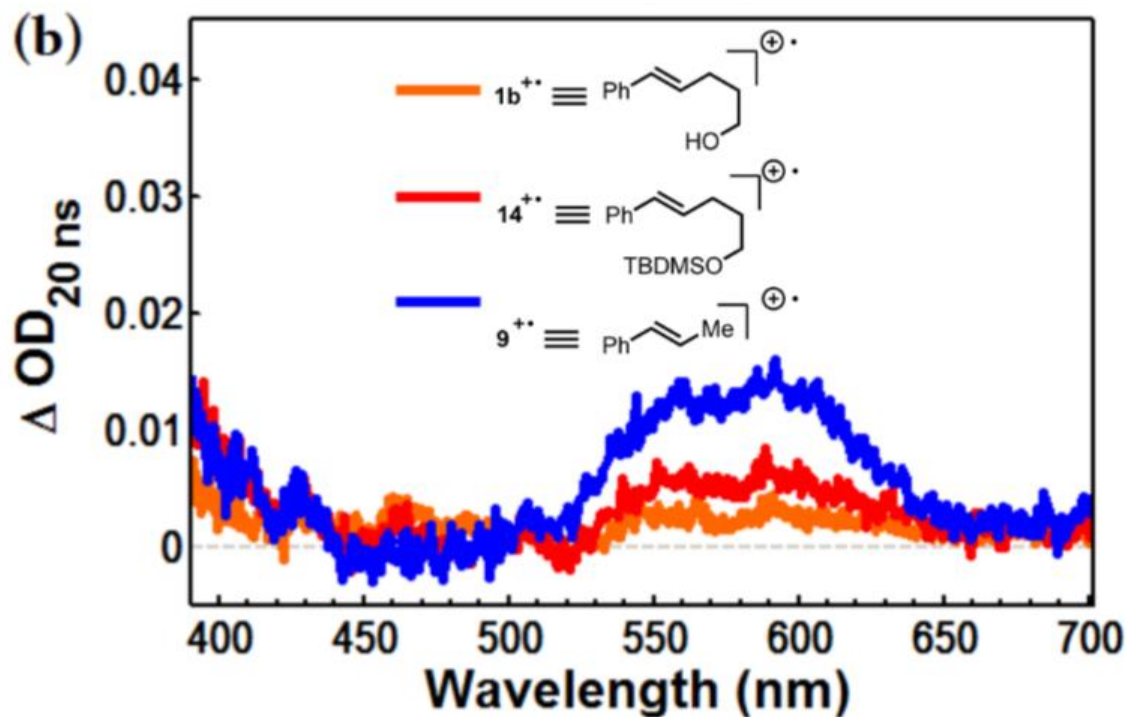
Detection of cation radical intermediate



- The spectrum of cation radical is obtained by subtraction of Mes-Acr• from the transient absorption spectrum at 500 ns.**



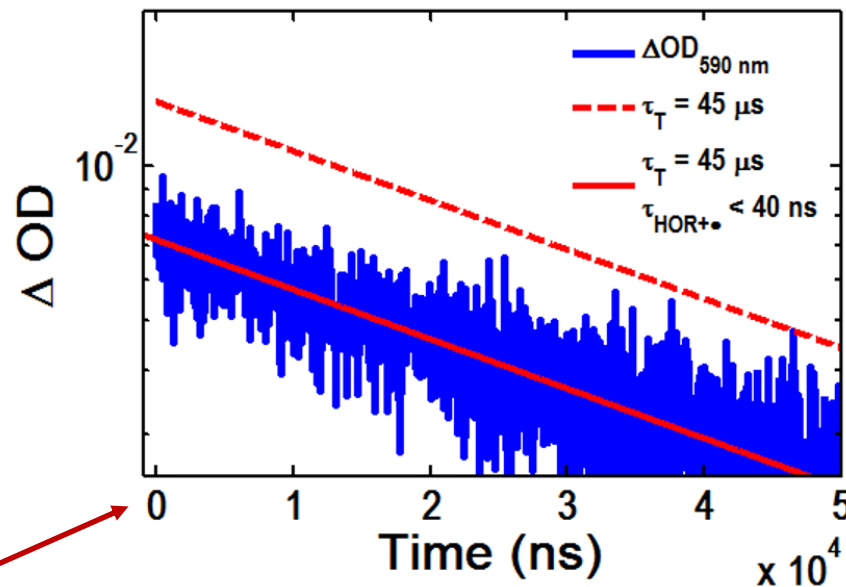
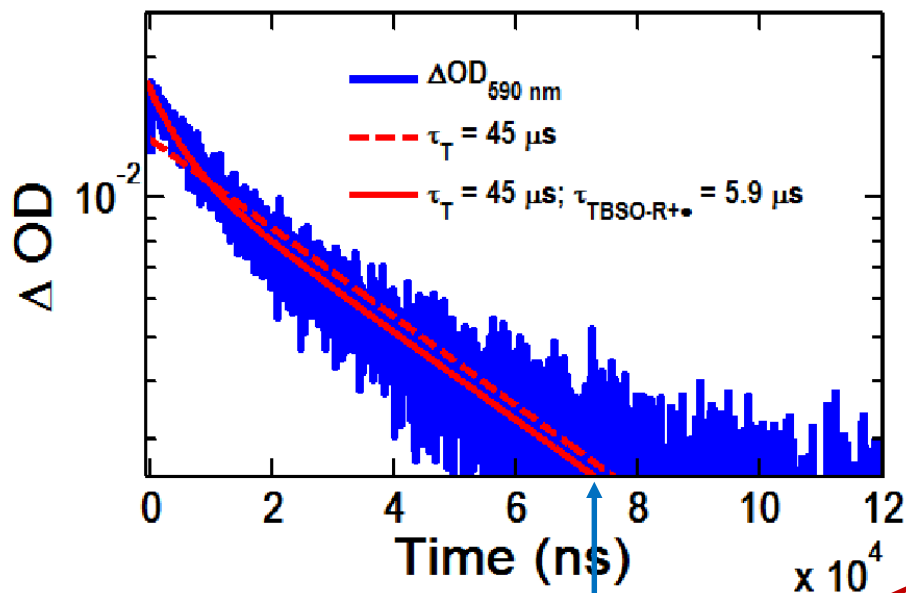
Detection of cation radical intermediate



- *Each cation radical could be observed.*

Detection of cation radical intermediate

- Transient absorption spectroscopy at 40 ns



$$\Delta OD_{590}(t) = \alpha_T e^{-\frac{t}{\tau_T}} + \alpha_{CR} e^{-\frac{t}{\tau_{CR}}}$$

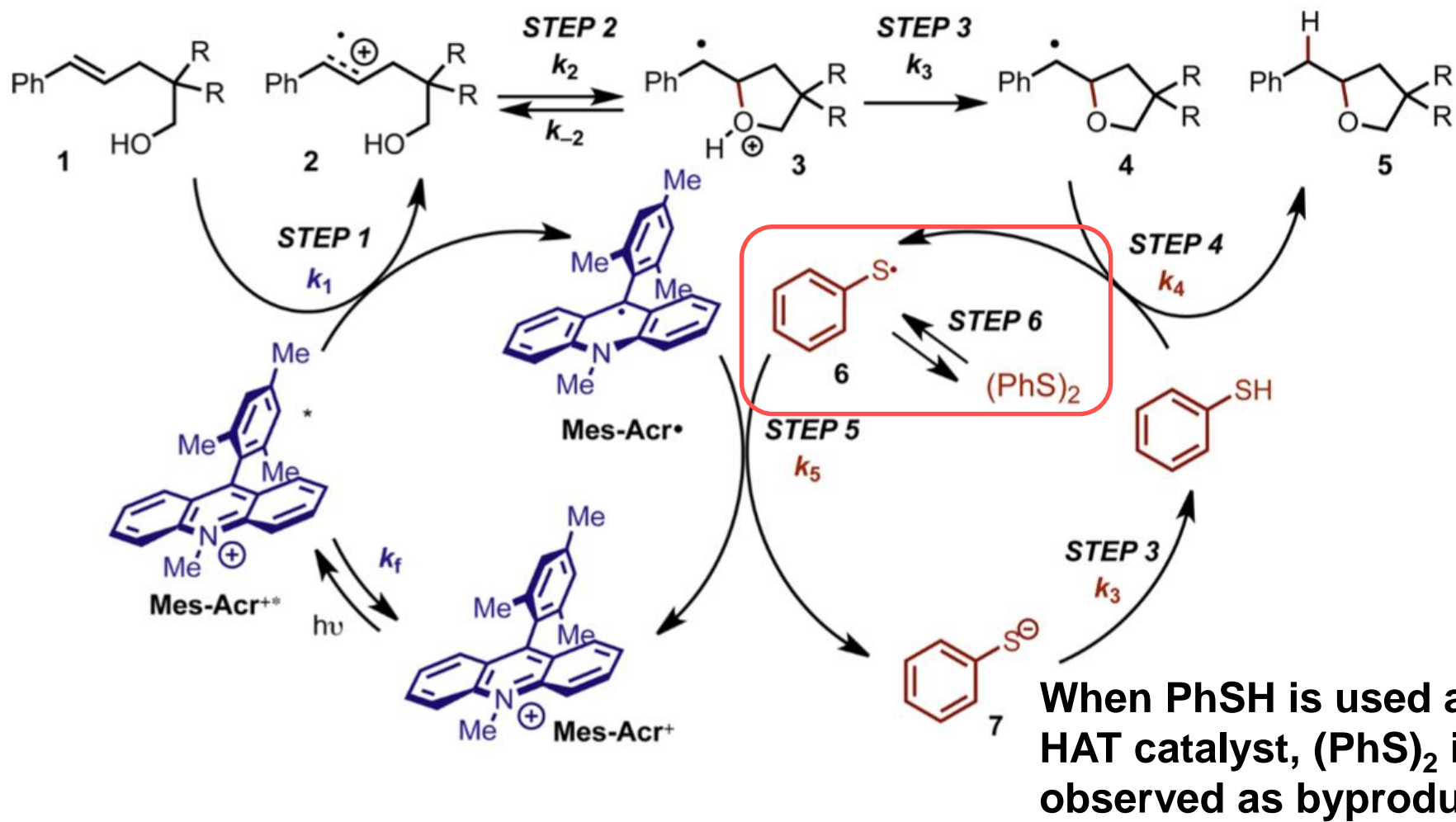
T: triplet state of Mes-Acr⁺

CR: cation radical



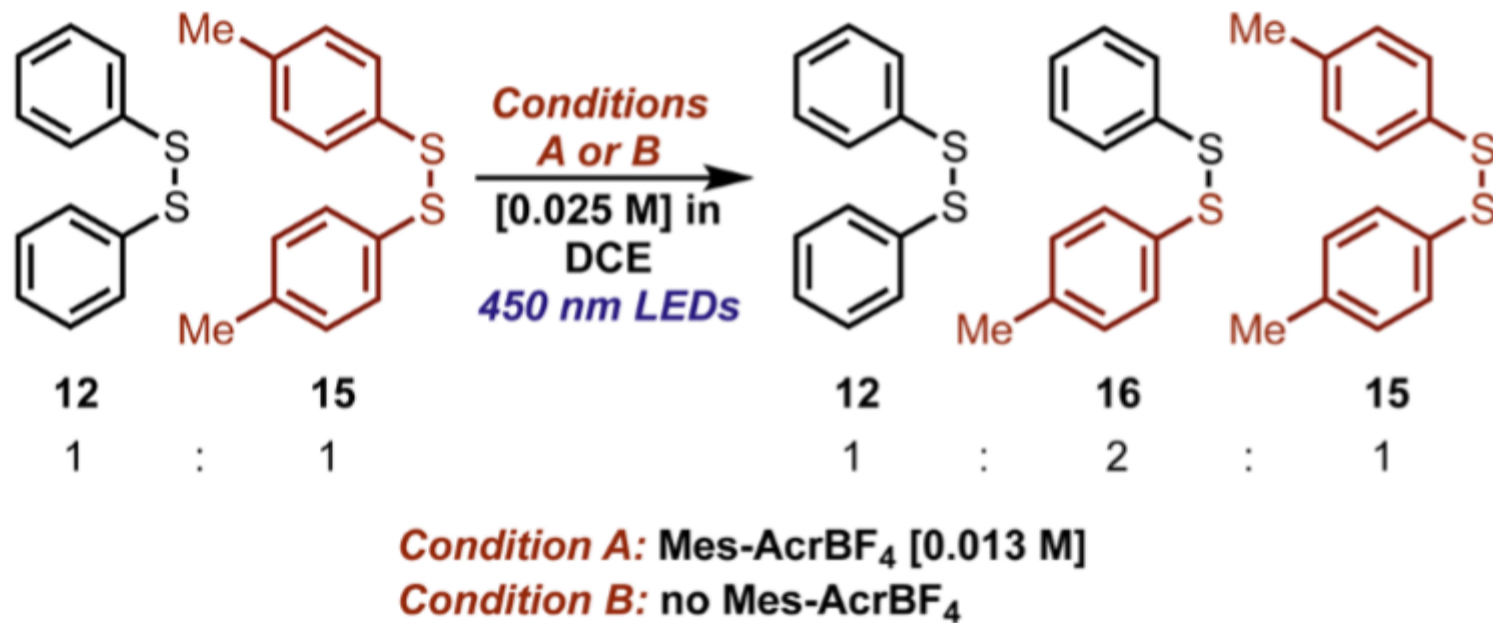
- In 40 ns, cyclization was finished. $\Rightarrow k_2 > 2.5 \times 10^7 \text{ s}^{-1}$

Proposed mechanism



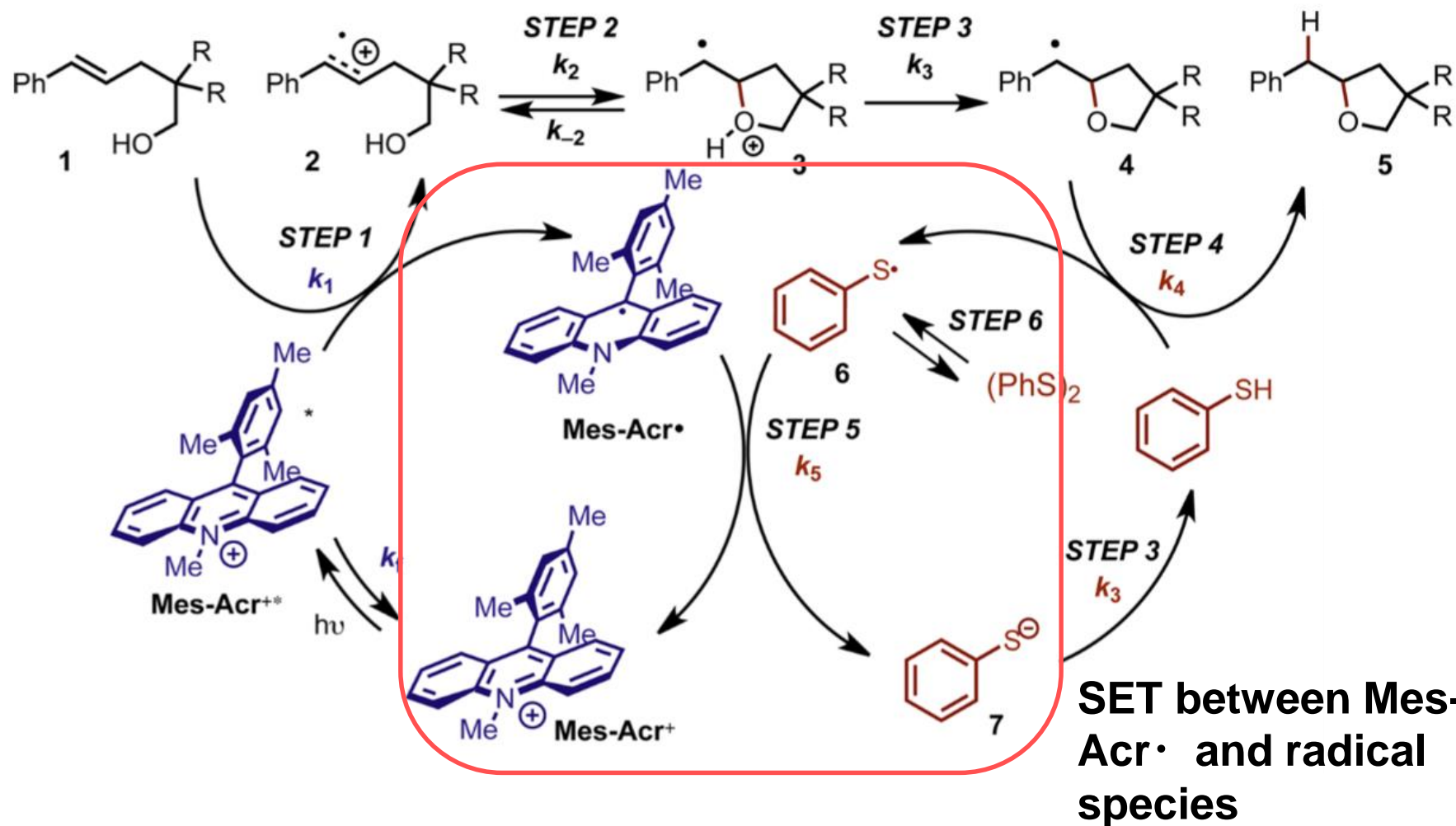
➡ **How does this reaction proceed?**

Disulfide crossover experiment



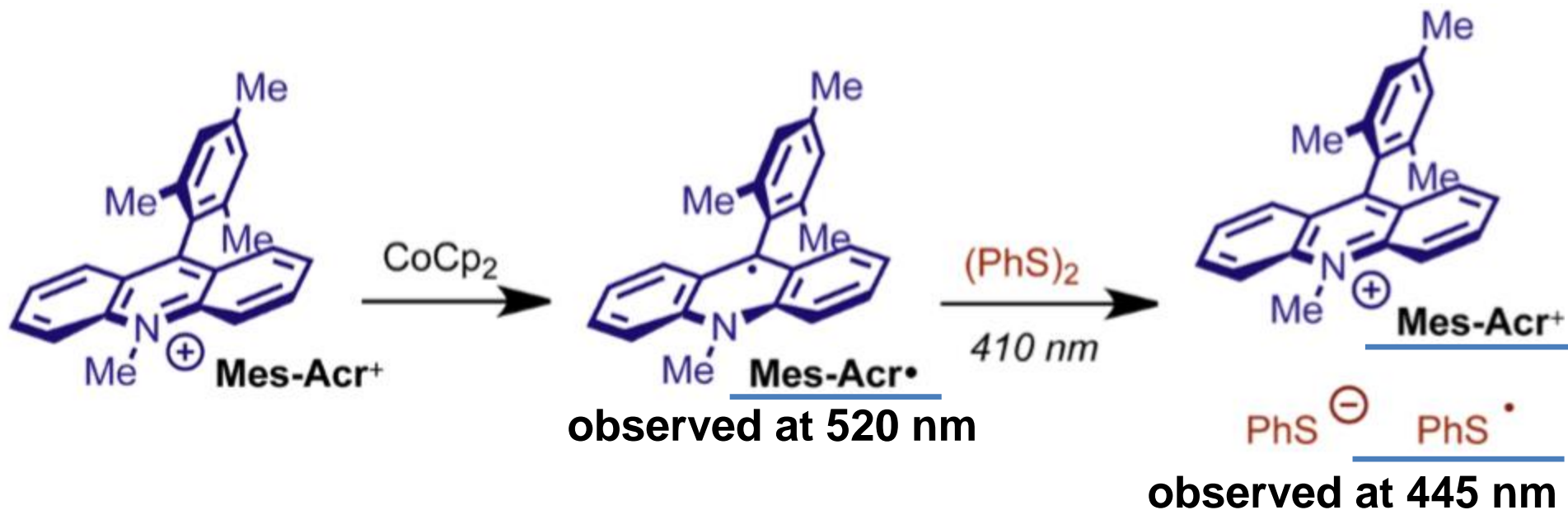
- *Disulfides were competent HAT catalysts .*
- *Disulfide bond was cleaved by visible light irradiation.*

Proposed mechanism



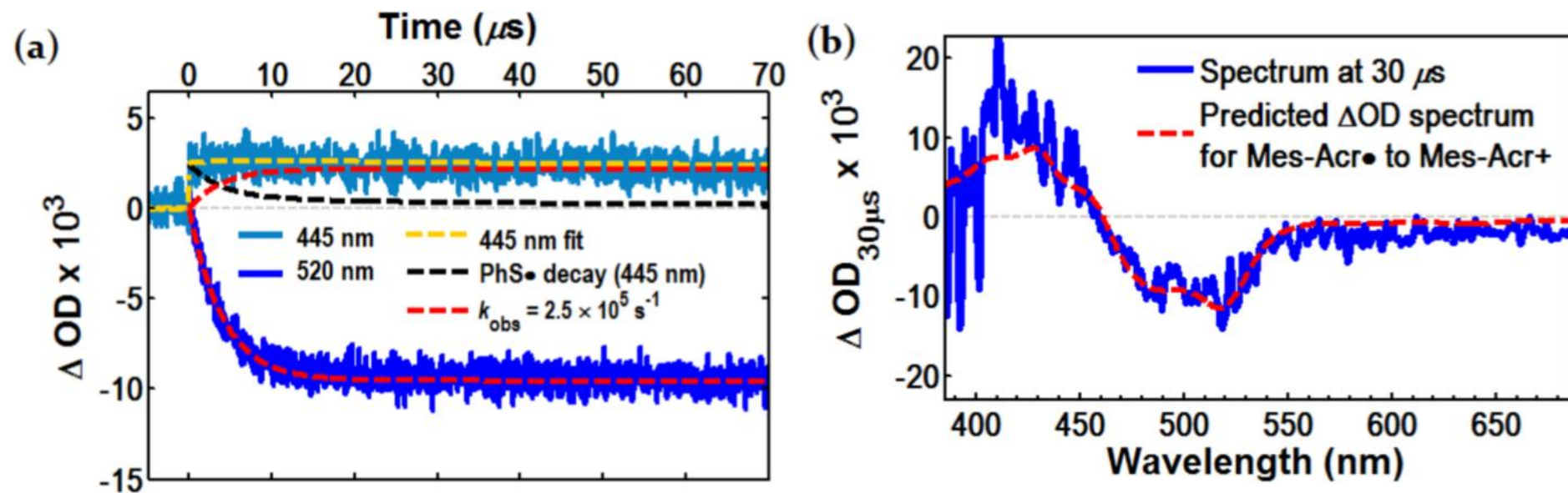
➡ **How does this reaction proceed?**

How to confirm?



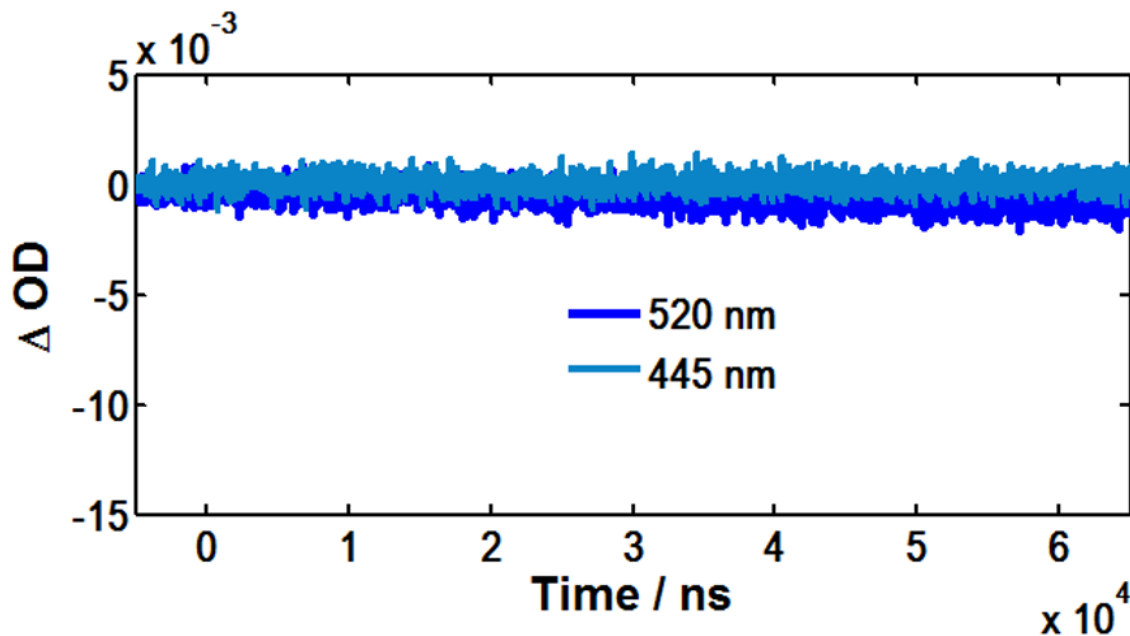
- *Reduction by CoCp₂ produces Mes-Acr[•].*
- *$\lambda_{\text{ex}} = 410 \text{ nm}$, where Mes-Acr[•] absorption is at a minimum.*

Transient absorption spectroscopy



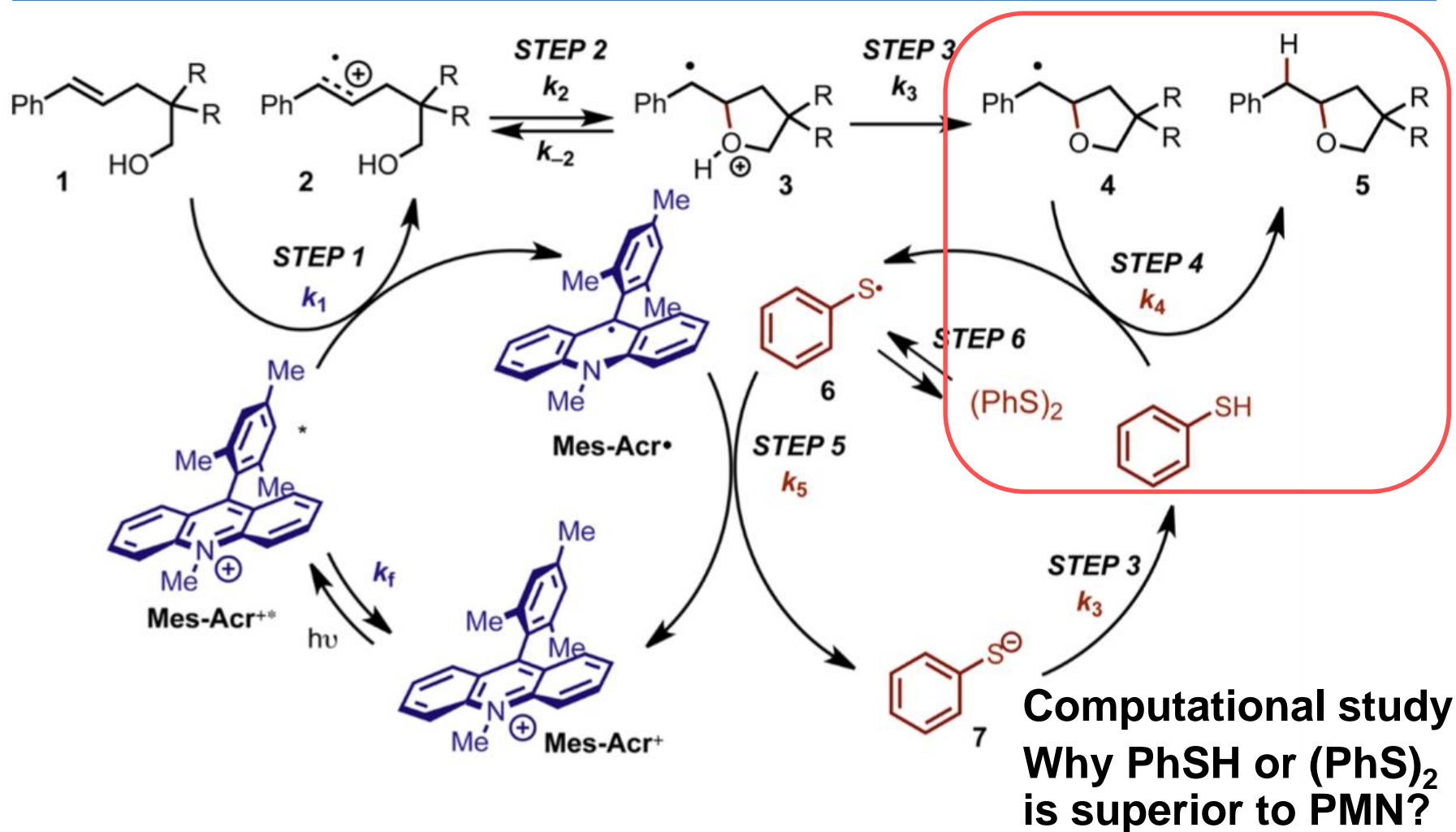
- ***520 nm indicates Mes-Acr• .***
- ***445 nm indicates a combination of Mes-Acr+ growth and PhS• decay.***
- ***k_{obs} confirms that MesAcr+ grows in at the same rate that Mes-Acr• disappears.***

Control experiment



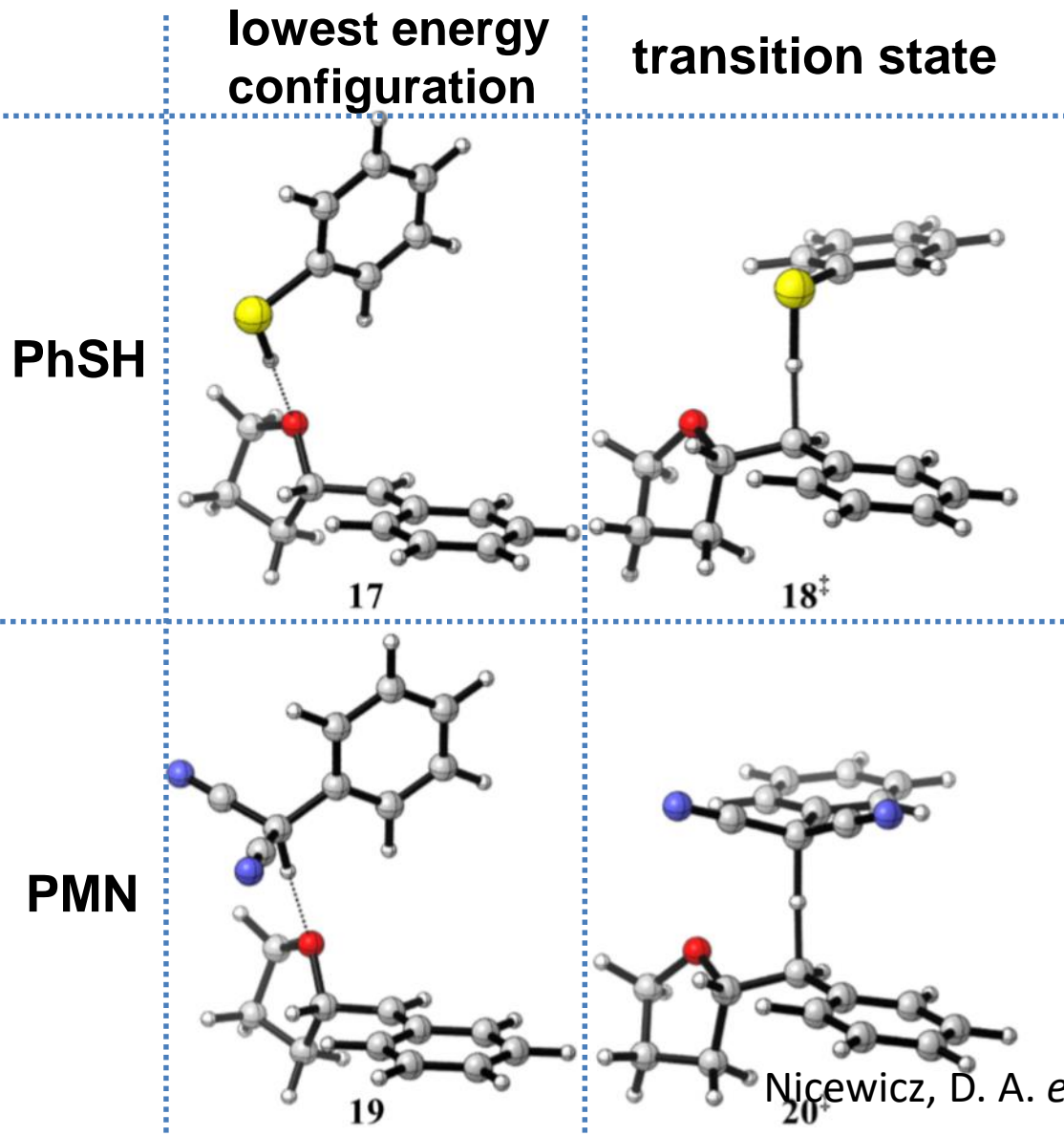
- ***In the absence of $(PhS)_2$, no change was confirmed.***

Proposed mechanism



How does this reaction proceed?

HAT process

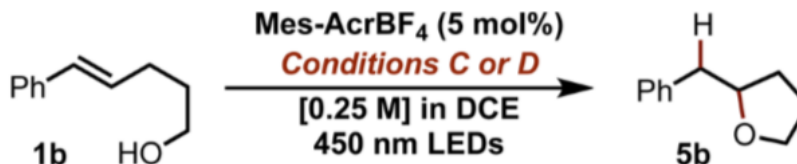


- *The calculated activation free energy barrier for HAT is 9.5 kcal mol⁻¹ for PhSH, as compared with 15.1 kcal mol⁻¹ for PMN.*



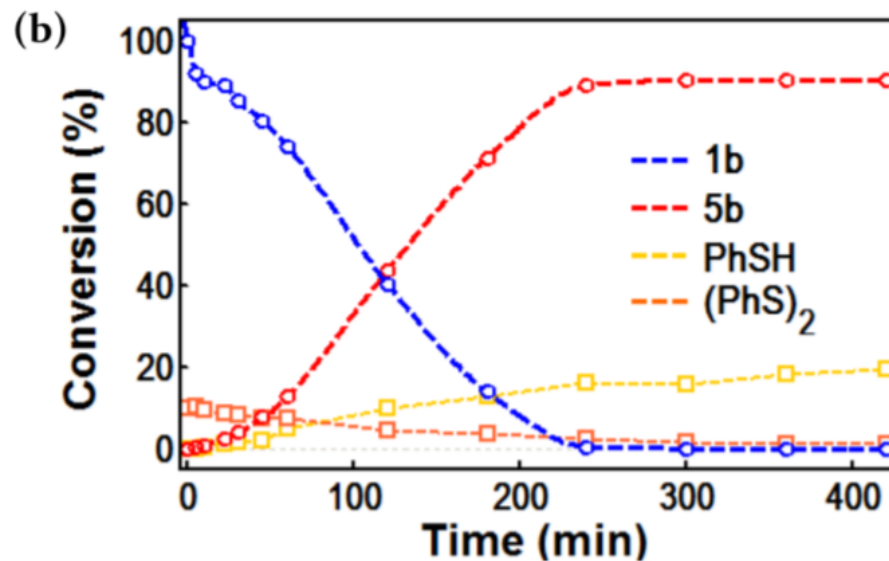
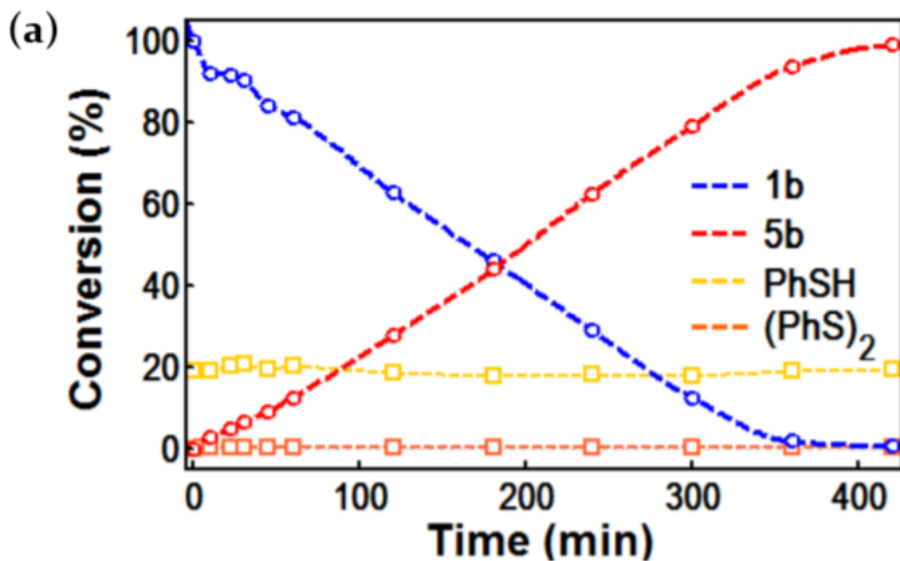
- *Owing to structure reorganization, HAT process is less costly for PhSH.*
- *k_4 for PhSH is $6.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ (for PMN is $5.0 \times 10^1 \text{ M}^{-1} \text{ s}^{-1}$)*

Preparative scale reaction kinetics



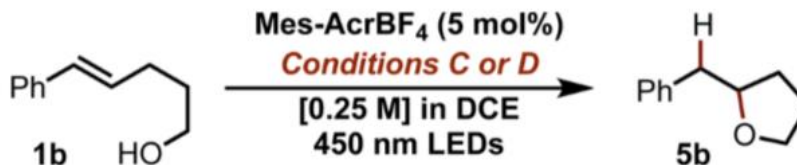
Condition C: PhSH (20 mol %)

Condition D: (PhS)₂ (10 mol %)



- *In condition D, reaction proceeded faster.*
- *In both conditions, PhSH is dominant species.*

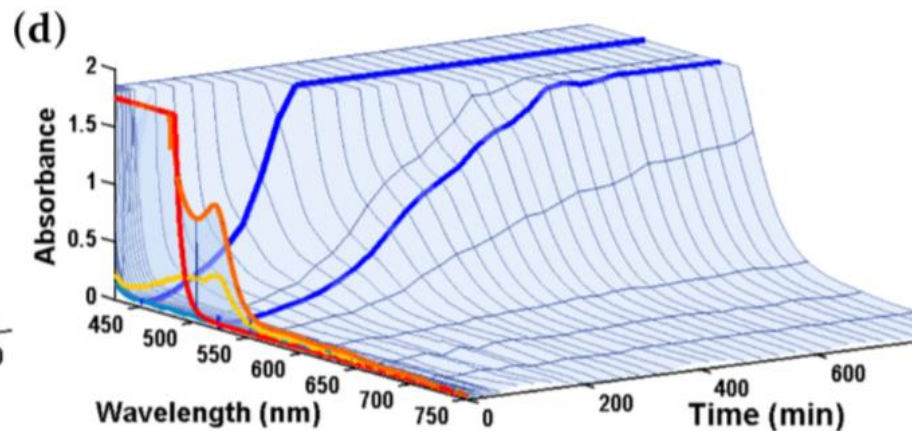
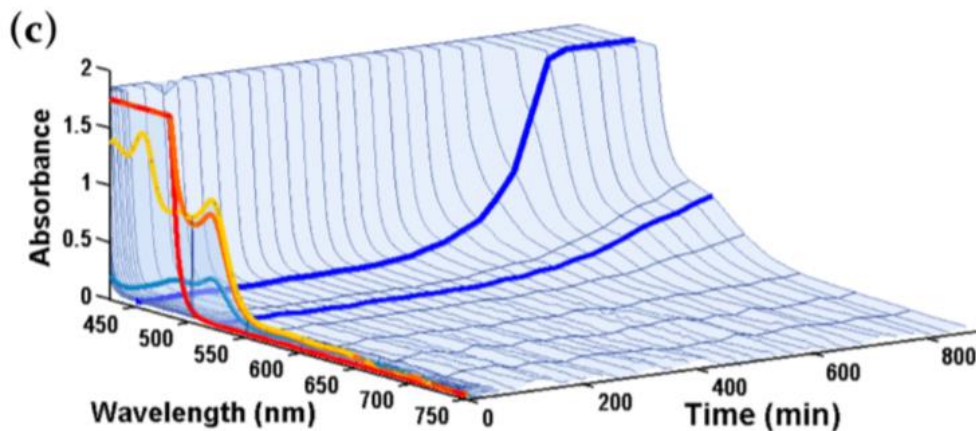
Preparative scale reaction kinetics



Condition C: PhSH (20 mol %)

Condition D: (PhS)₂ (10 mol %)

UV-vis spectroscopy

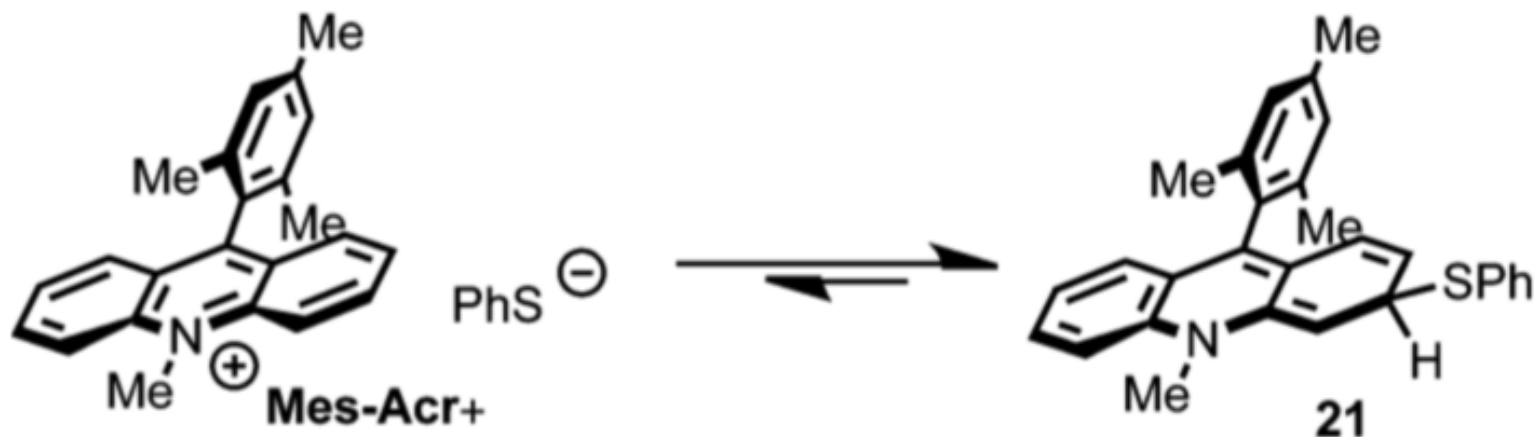


Red= 0 min, Orange= 1 min, Yellow= 2 min, Cyan= 3 min

Time traces of absorbance at 450 nm (Mes-Acr⁺) and 520 nm (Mes-Acr[•]) are highlighted in blue.

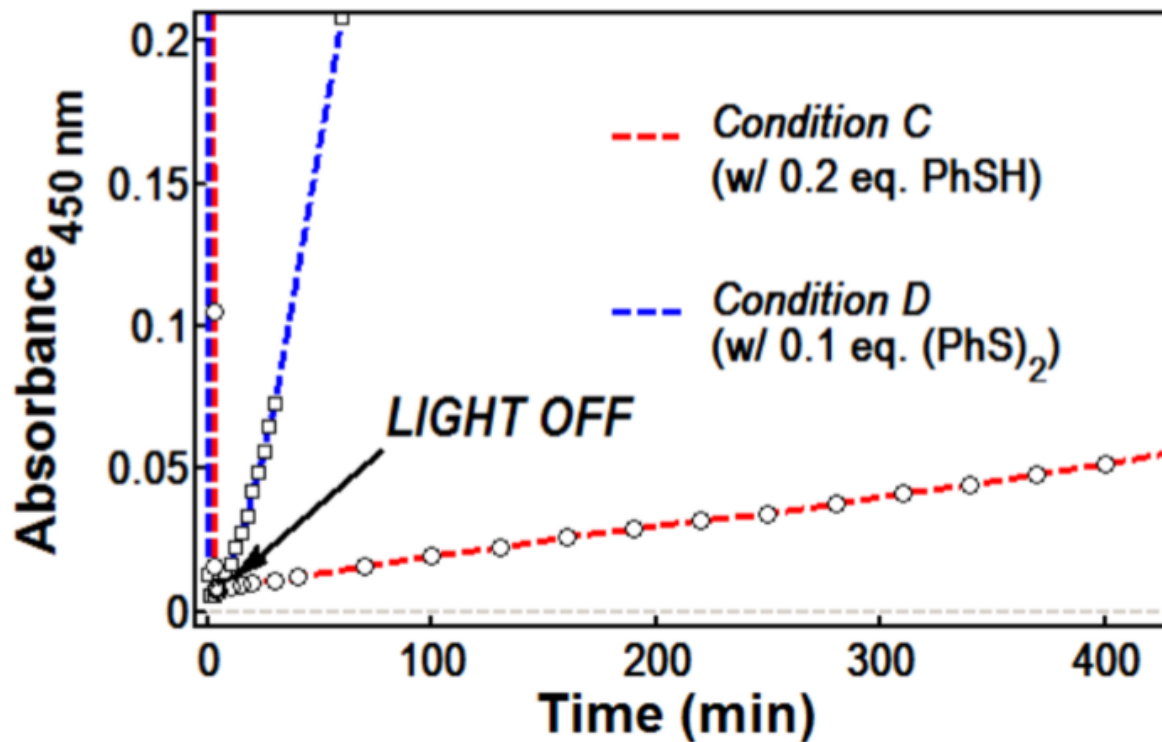
- In both cases, Mes-Acr⁺ and Mes-Acr[•] were not detectable in early stages.*

Resting state of Mes-Acr⁺



- ***Reversible adduct can explain that absorption for both Mes-Acr⁺ and Mes-Acr[·] was not detectable, but Mes-Acr⁺ could be isolated after reaction was completed.***

Recovery of Mes-Acr+



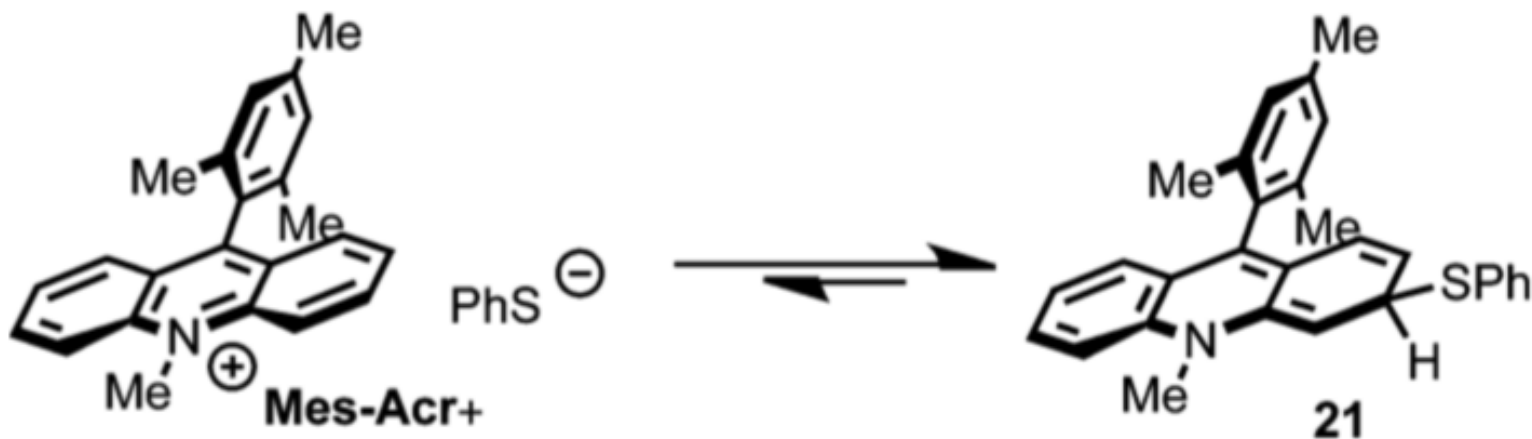
- ***Recovery of Mes-Acr+ was observed.***

Rate-limiting factors

1. Deprotonation step has rate-limiting effect?

- $(\text{PhS})_2$ does not depend on HAT for generation of thiyl radical.
- PhSH is required to encounter radical 4 (benzyl radical).

2. Off-cycle intermediate



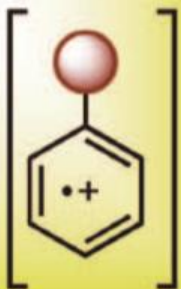
Today's Content

- 1. Mechanistic study of Mes-Acr⁺ catalyzed anti-Markovnikov hydro-functionalization*
- 2. Direct C-H amination**

Direct C-H amination



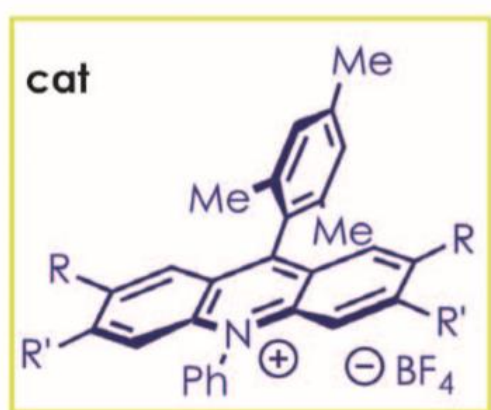
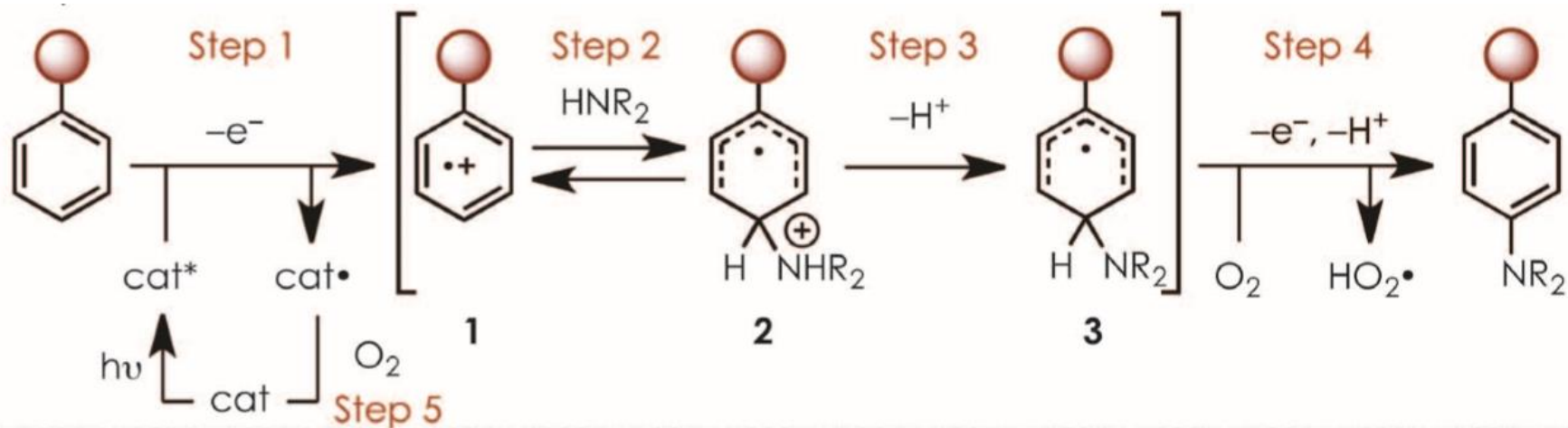
via:



- Arene as limiting reagent
- Diverse amine scope including azoles and ammonia
- Good to excellent site selectivity
- Easily tunable organic catalyst system
- General method for arene C-H functionalization

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Outline of arene C-H amination

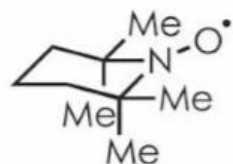


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Photoredox-Catalyzed Reaction



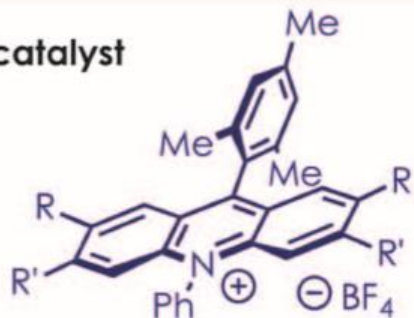
additive



TEMPO

- **Improve yield**
- **Diminish byproduct**

catalyst



A; R = R' = H; $E^*_{red} = +2.20$ V

B; R = Me; R' = H; $E^*_{red} = +2.09$ V

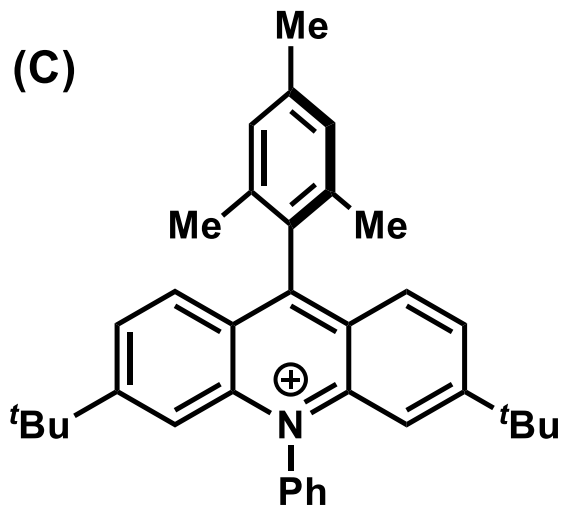
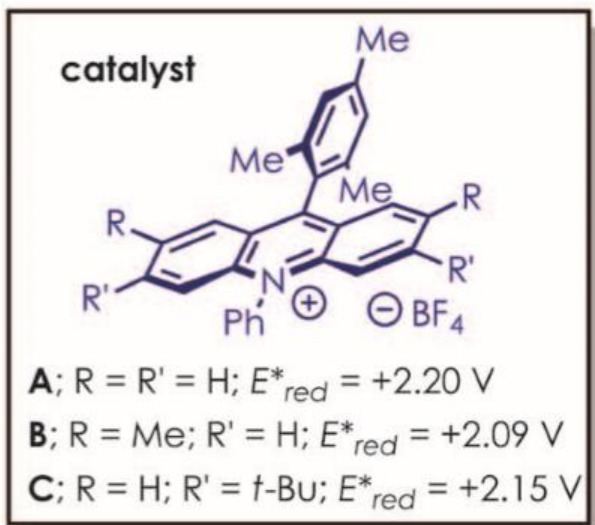
C; R = H; R' = *t*-Bu; $E^*_{red} = +2.15$ V

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Optimization of Mes-Acr+

entry	additive	catalyst	solvent [M]	yield	p:o
14	TEMPO (0.2 eq.)	A	DCM[0.1]	61%	6.8:1
15	TEMPO (0.2 eq.)	B	DCM[0.1]	79%	6.7:1
16	TEMPO (0.2 eq.)	C	DCM[0.1]	88%	6.9:1

In initial study, cat A or cat B could not be observed in crude NMR.

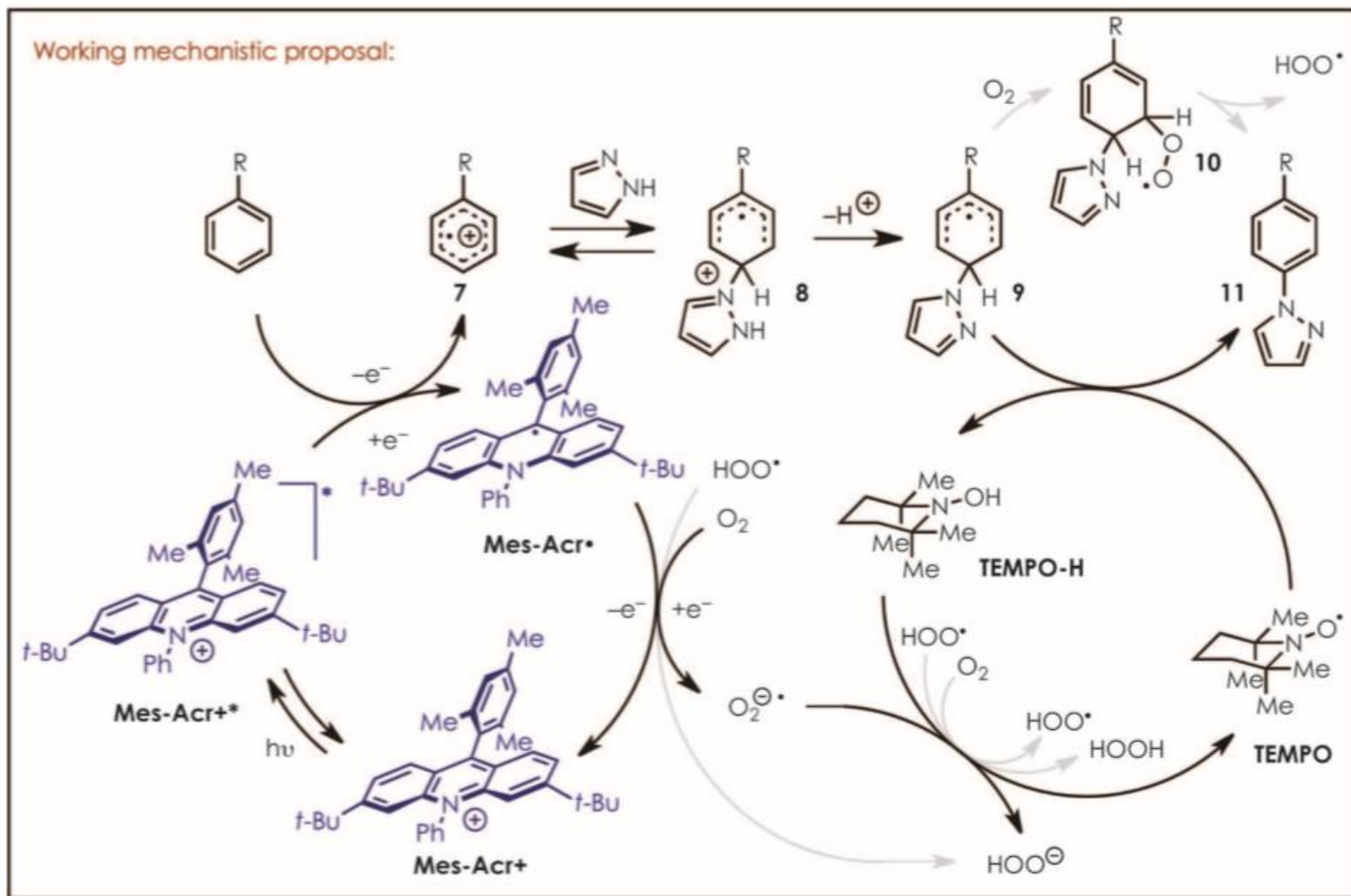


Stable against addition of nucleophiles and radicals

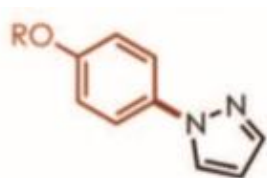
photoredox catalyst designed originally!!

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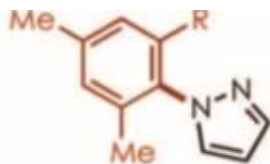
Plausible catalytic cycle



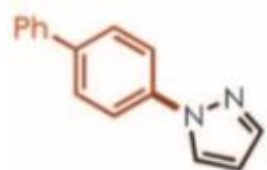
Substrate scope for arenes



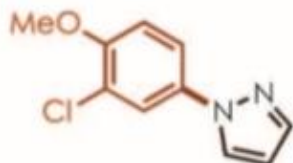
- 6; R = -OMe; 88% yield; 8.8:1 p:o
 12; R = -OMOM; 52% yield; 7.8:1 p:o
 13; R = -OTBS; 74% yield; 9.3:1 p:o
 14; R = -Ot-Bu; 63% yield; 6:1 p:o
 15; R = -OPh; 86% yield; 11:1 p:o



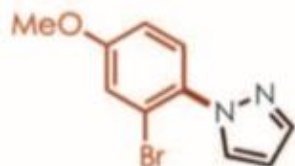
- 16 (R = -Me)
 82% yield*
 17 (R = -H)
 36% yield*



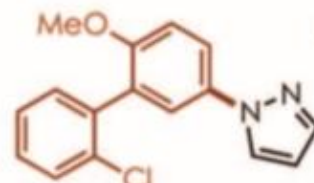
- 18
 56% yield; 7.9:1 p:o



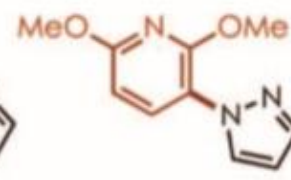
- 19
 70% yield
 single regioisomer



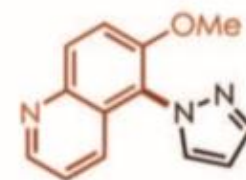
- 20
 54% yield
 single regioisomer



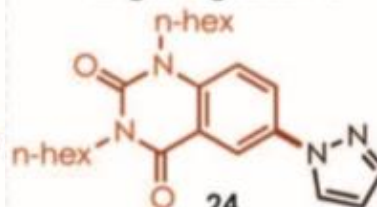
- 21
 75% yield
 single regioisomer



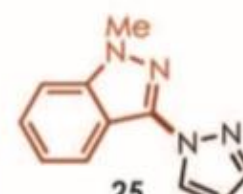
- 22
 45% yield
 single regioisomer



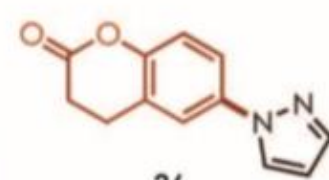
- 23
 60% yield
 single regioisomer



- 24
 43% yield
 >15:1 regioselectivity



- 25
 43% yield
 single regioisomer



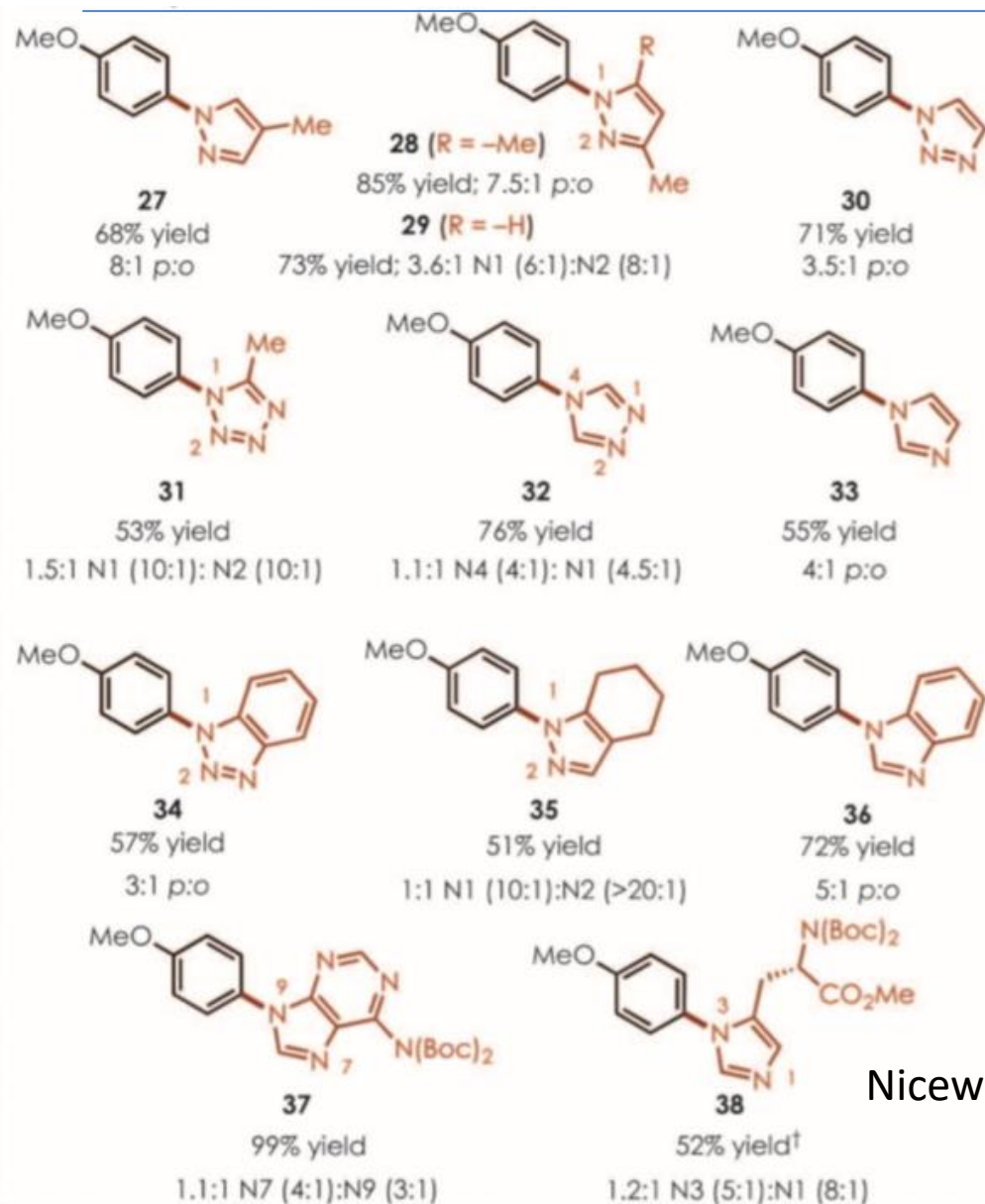
- 26
 30% yield
 single regioisomer

For 16 and 17, reactions run with 2.0 equivalents of arene, 1.0 equivalent of amine, and 1.0 equivalent of TEMPO under an N₂ atmosphere for 44 hours.

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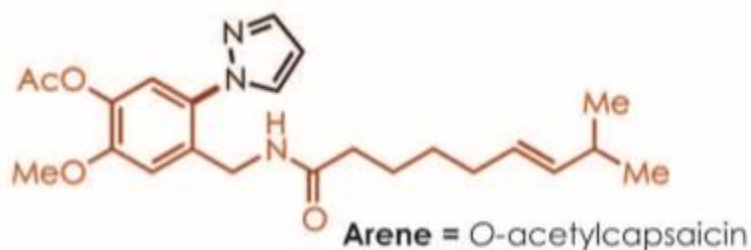
Substrate scope for amines

For 38, a reaction run under N_2 with 1.0 equivalent of TEMPO.



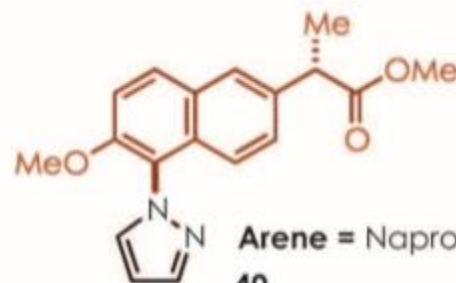
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Application for late-stage functionalization



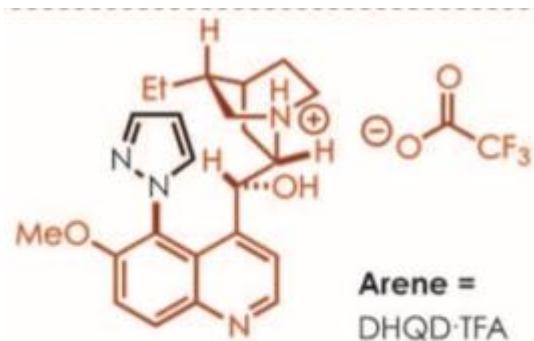
39

66% yield
single regioisomer



40

26% yield
single regioisomer

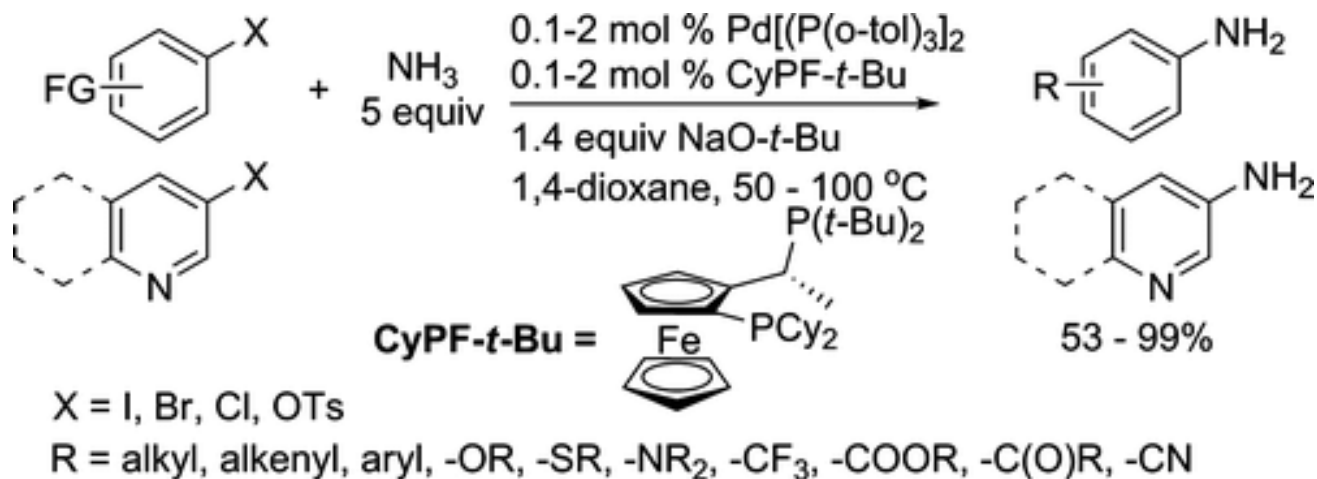


41

53% yield
single regioisomer

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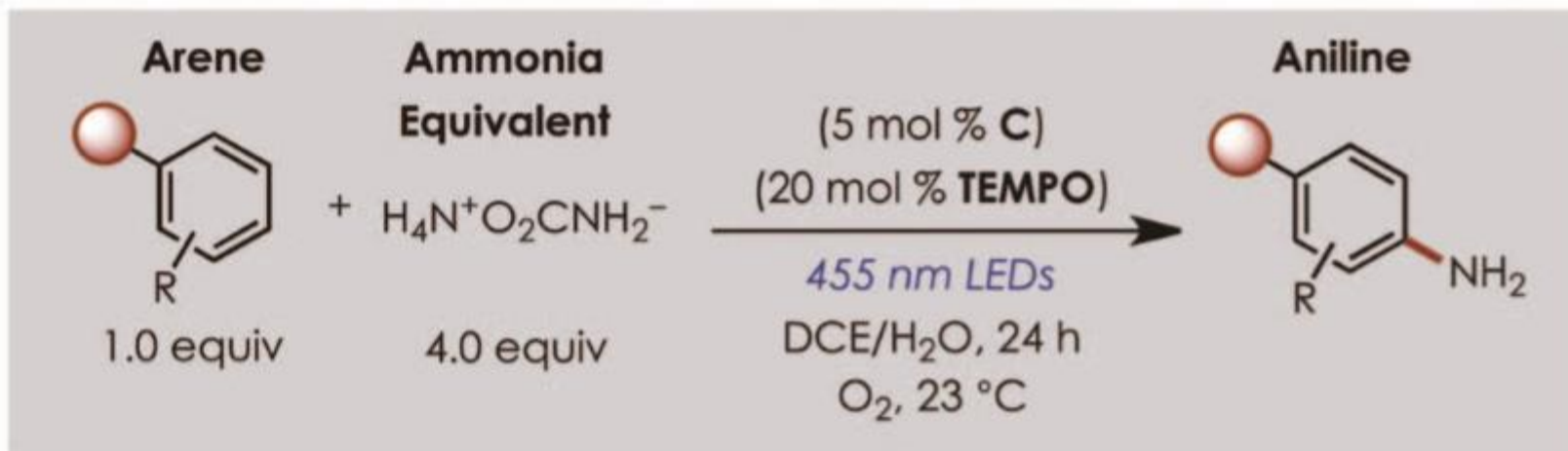
Synthesis of aniline from ammonia



Hartwig, J. F. *et al.* *J. Am. Chem. Soc.* **2009**, *131*,11049.

- ***Ammonia is one of the most abundant N1 sources.***
- ***However, metal-catalyzed amination using ammonia is very rare.***

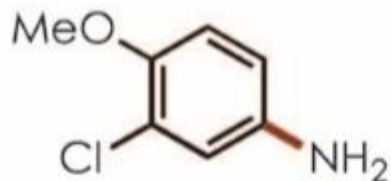
Synthesis of aniline



- ***Benchmark-stable solid salt which is less costly on a molar basis than liquid ammonia could be used as N1 source.***

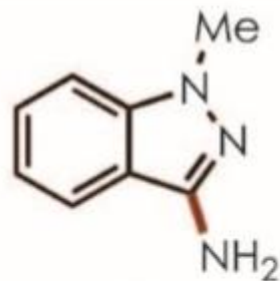
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Substrate scope for aniline



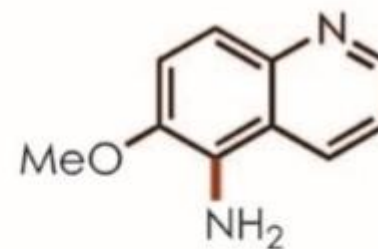
47

33% yield
single regioisomer



48

61% yield
>6:1 regioselectivity



49

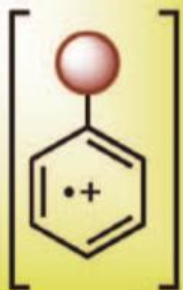
36% yield
single regioisomer

Nicewicz, D. A. *et al. Science* **2015**, *349*, 1326.

Direct C-H amination



via:



- Arene as limiting reagent
- Diverse amine scope including azoles and ammonia
- Good to excellent site selectivity
- Easily tunable organic catalyst system
- General method for arene C-H functionalization

Nicewicz, D. A. *et al. Science* **2015**, 349, 1326.

The photoredox organocatalyst

1. *High potential in catalytic amount*

- *Access to unstable intermediate*

2. *Easily tunable system*

- *Changing stability and redox potential based on organic structure*