

# **$\beta$ -C-H Alkylation of Carbonyls**

2021. 7. 3.  
Yusuke Imamura

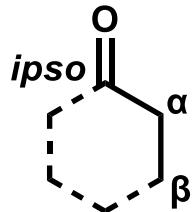
# **Contents**

**1. Introduction**

**2. C-H alkylation via enamine**

**3. C-H alkylation via enol silyl ether**

# **β-Functionalization of Carbonyls**



## ipso functionalization

Grignard reactions, Wittig reactions and reductive aminations...

## α functionalization

oxidations, alkylations, arylations and halogenations...

## β functionalization

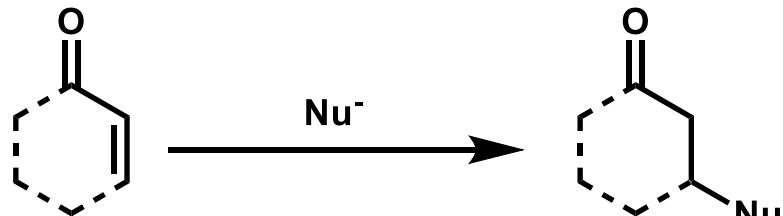
### 1. transition metal mediated reaction

- a. C-H activation via direction from carbonyl
- b. In situ formation of enone

### 2. photoredox reaction of enol

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Otherwise, 1,4 addition for enone, which was converted by oxidation.



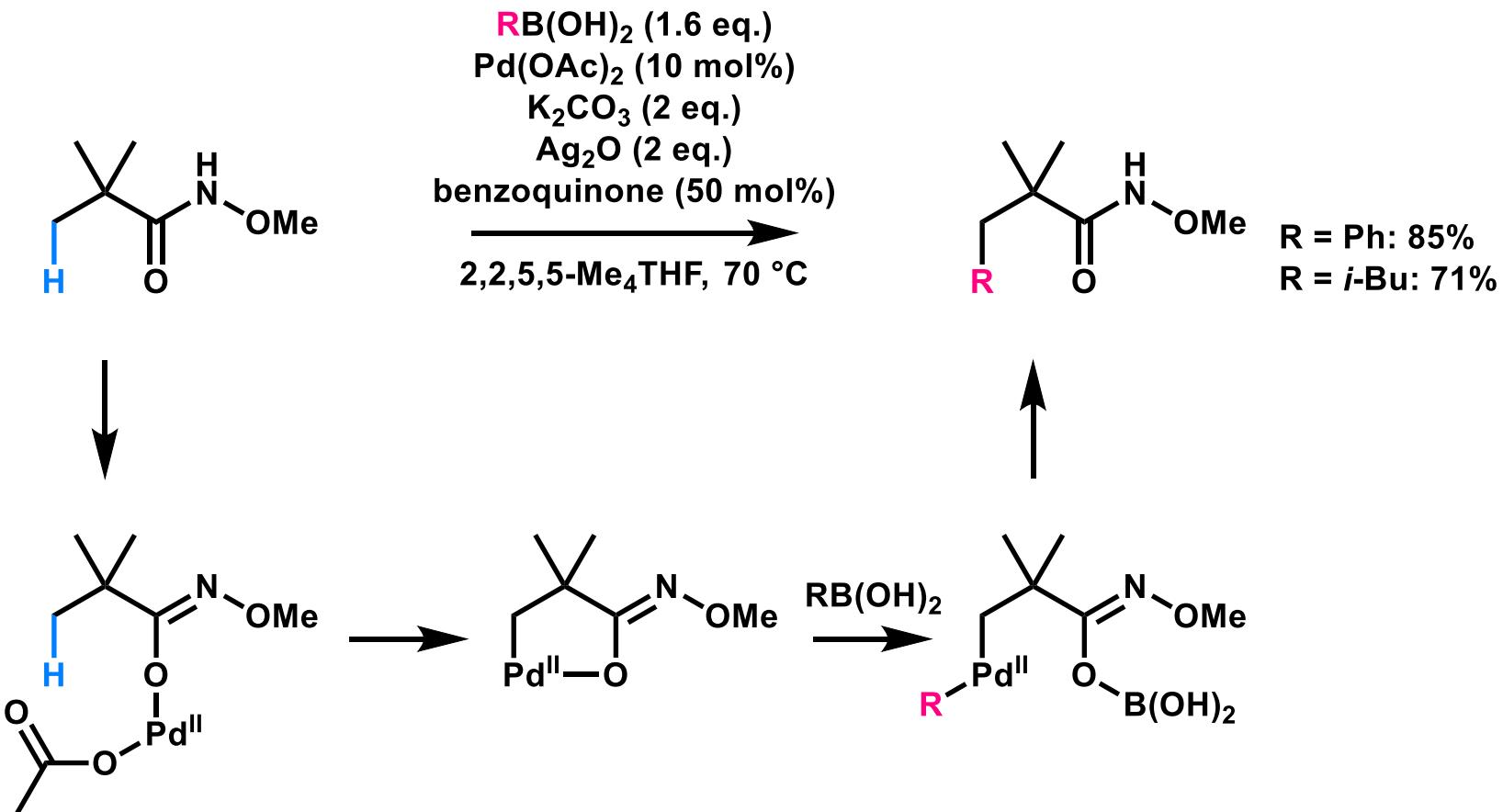
## advantage

- o reliable
- o asymmetric reaction available

## drawback

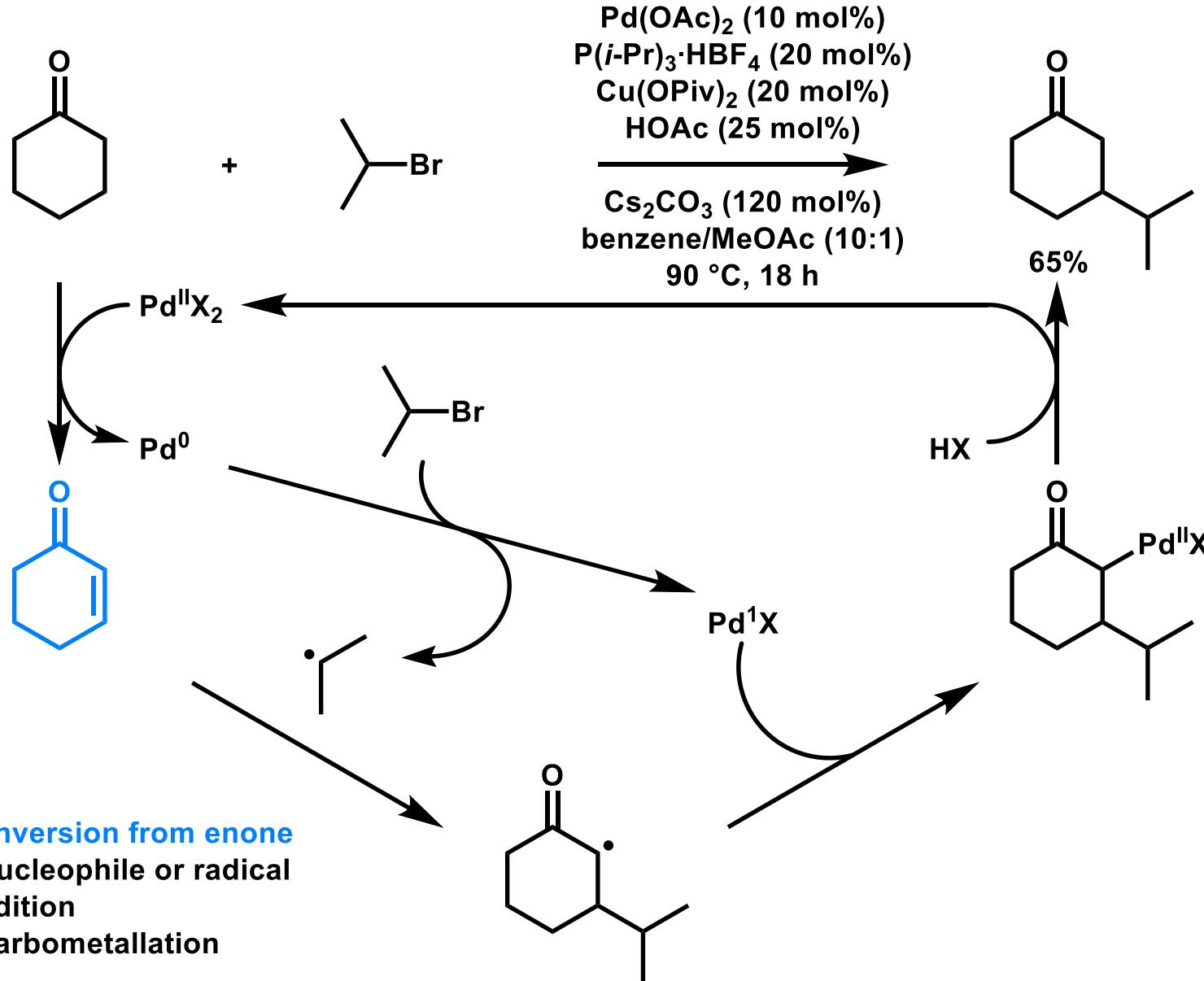
- x 1-2 steps to oxidize
- x atom efficiency

# C-H Activation via Direction from Carbonyl

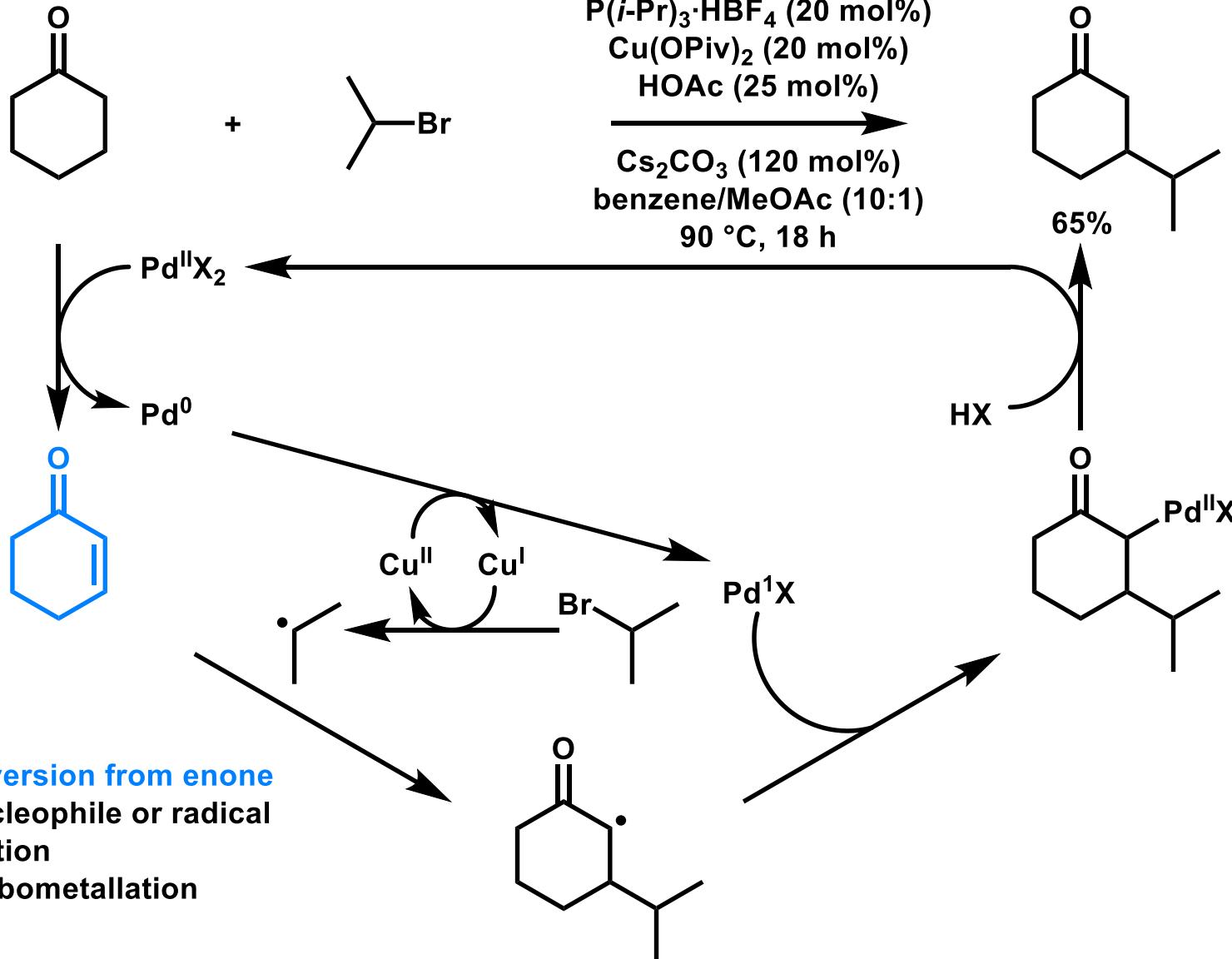


- Strong coordinating group (amide) are needed.
  - Appropriate conformation are needed.

# *in situ* Formation of Enone (author proposal)



# *in situ* Formation of Enone (another explanation)



# Redox Potentials

## Oxidative quenching cycle

Oxidation potential of activated catalyst:  $*E_{\text{Ox}}(\text{cat}^+/\text{cat}^*)$

reduction potential of acceptor:  $E_{\text{red}}(\text{A}^n/\text{A}^{n-1})$

If  $*E_{\text{Ox}}(\text{cat}^+/\text{cat}^*) < E_{\text{red}}(\text{A}^n/\text{A}^{n-1})$  oxidative cycle starts.

Oxidation potential of ground state catalyst:  $E_{\text{Ox}}(\text{cat}^+/\text{cat})$

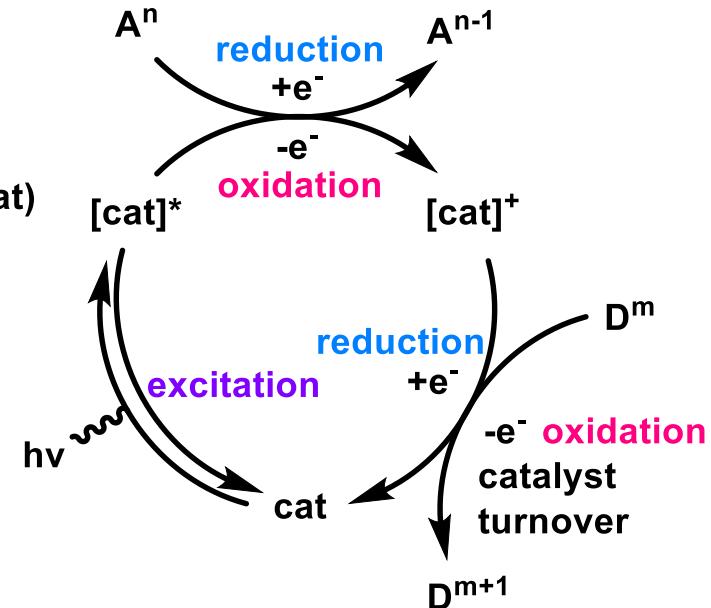
Oxidation potential of donor:  $E_{\text{Ox}}(\text{D}^{m+1}/\text{D}^m)$

If  $E_{\text{Ox}}(\text{cat}^+/\text{cat}) > E_{\text{Ox}}(\text{D}^{m+1}/\text{D}^m)$  oxidative cycle turns.

### definitions

$*E_{\text{Ox(red)}}$ : Generated electric potential when excited catalyst was oxidized(reduced).

$E_{\text{Ox(red)}}$ : Necessary electric potential to oxidize(reduce) the substrate.



## Reductive quenching cycle

reduction potential of activated catalyst:  $*E_{\text{red}}(\text{cat}^*/\text{cat})$

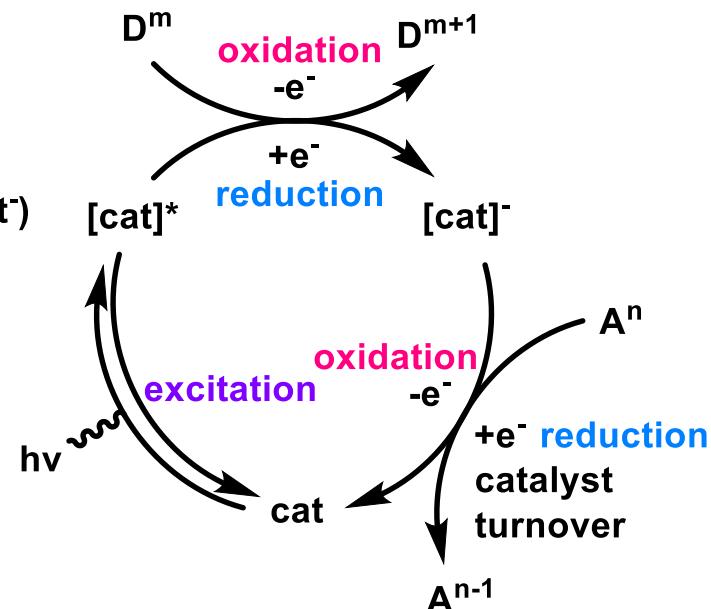
Oxidation potential of acceptor:  $E_{\text{Ox}}(\text{D}^{m+1}/\text{D}^m)$

If  $*E_{\text{red}}(\text{cat}^*/\text{cat}) > E_{\text{Ox}}(\text{D}^{m+1}/\text{D}^m)$  oxidative cycle starts.

reduction potential of ground state catalyst:  $E_{\text{red}}(\text{cat}/\text{cat}^-)$

reduction potential of donor:  $E_{\text{red}}(\text{A}^n/\text{A}^{n-1})$

If  $E_{\text{red}}(\text{cat}/\text{cat}^-) < E_{\text{red}}(\text{A}^n/\text{A}^{n-1})$  oxidative cycle turns.



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## 3. C-H alkylation of enol silyl ether



Communication

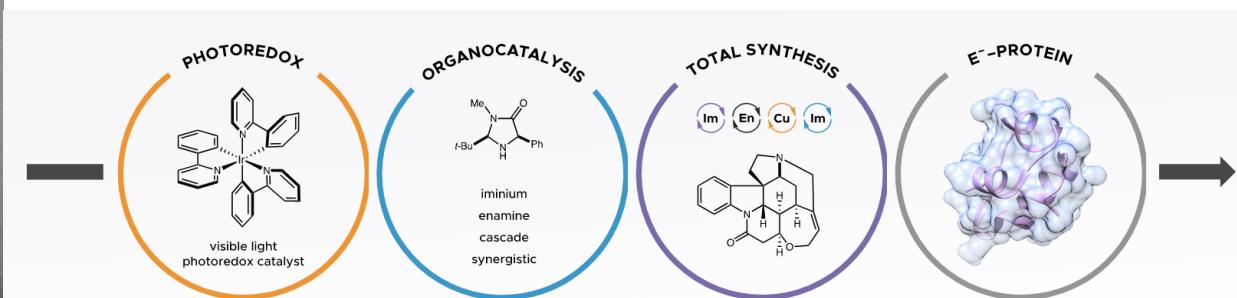
[pubs.acs.org/JACS](https://pubs.acs.org/JACS)

### Direct $\beta$ -Alkylation of Aldehydes via Photoredox Organocatalysis

Jack A. Terrett, Michael D. Clift, and David W. C. MacMillan\*

Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States

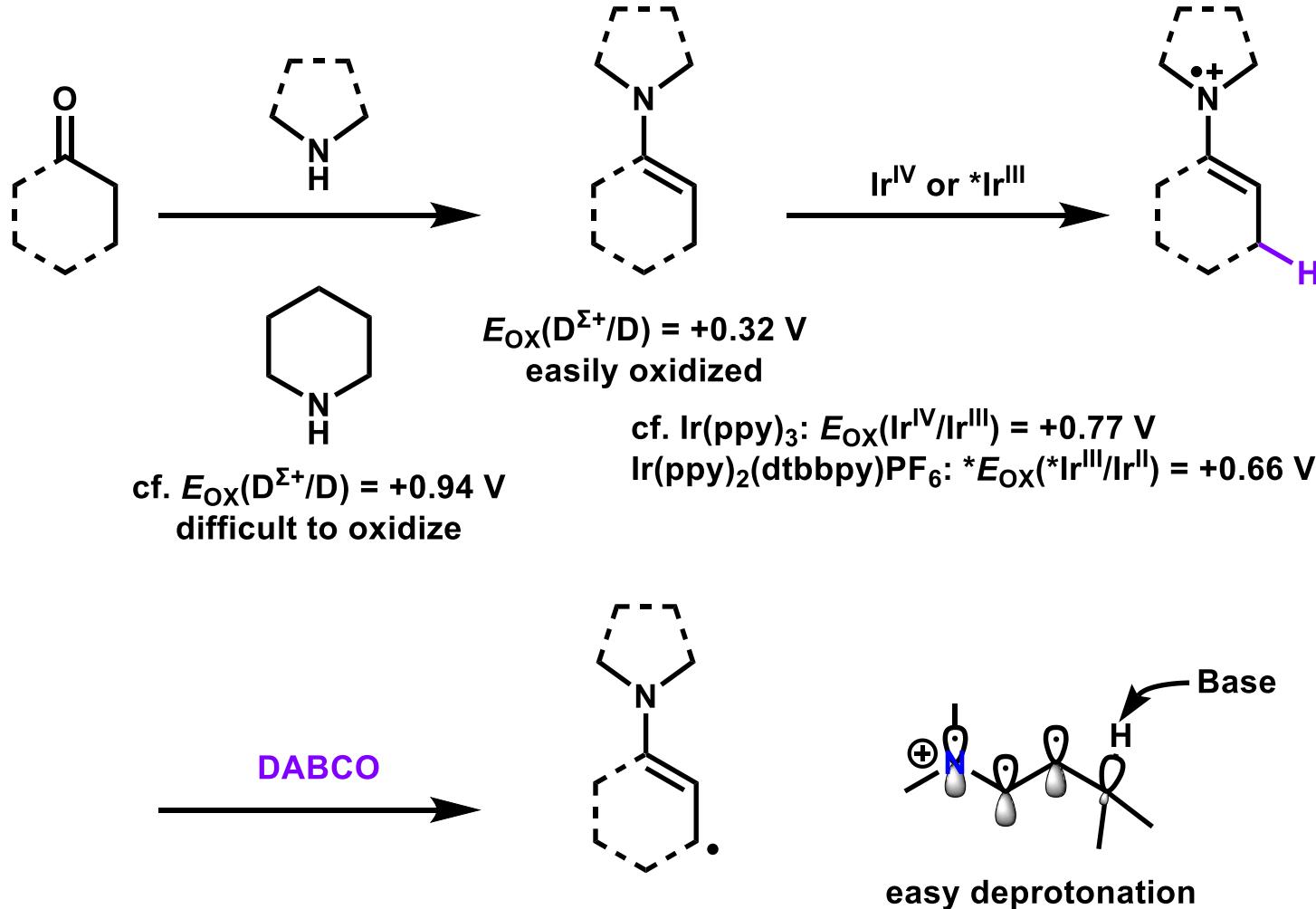
# Prof. David W. C. MacMillan



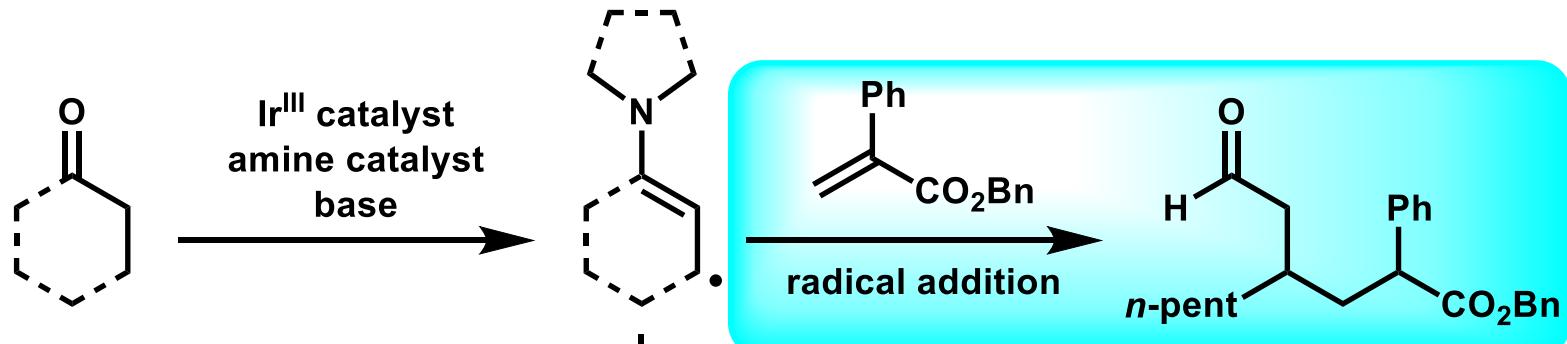
- 1991 B.S. @ University of Glasgow
- 1996 Ph.D @ the University of California, Irvine  
(Prof. Larry E. Overman, "Total synthesis of 7-(-)-deacetoxyalcyonin acetate")
- 1996- Postdoctoral fellow
  - @ Harvard University (Prof. David A. Evans, "the design and development of Sn(II) box")
  - @ the University of California, Berkeley
  - @ the California Institute of Technology
- 2004 Professor @ the California Institute of Technology
- 2006 Professor @ Princeton University
- 2011 Distinguished professor @ Princeton University

Research topic: photoredox, organocatalysis, total synthesis, e<sup>-</sup> protein

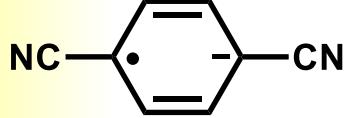
# $\beta$ -Enamine Radical



# Application of $\beta$ -Enamine Radical

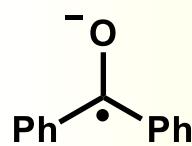


radical-radical coupling



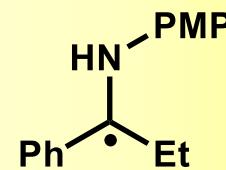
cyanoarene

Science, 2013, 339, 1593.



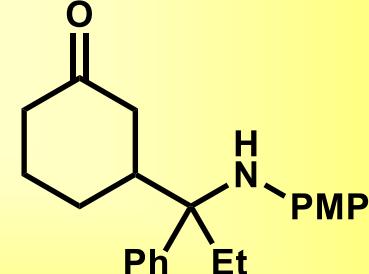
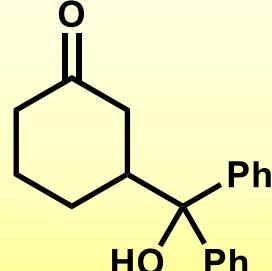
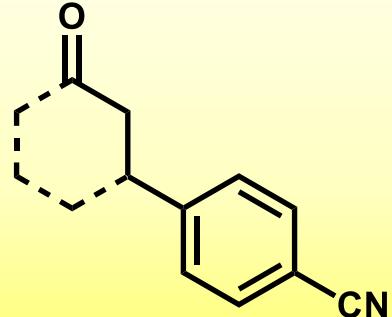
aryl ketone

JACS, 2013, 135, 18323.



aryl imine

JACS, 2015, 137, 8404.



# Initial Studies

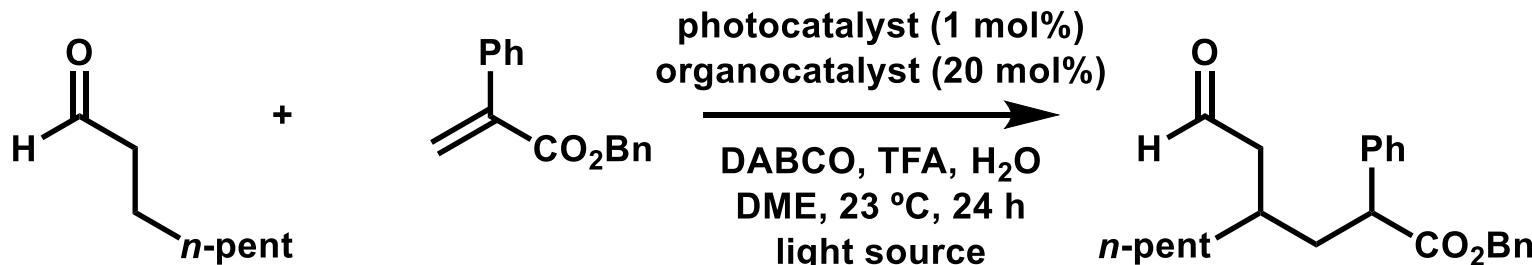
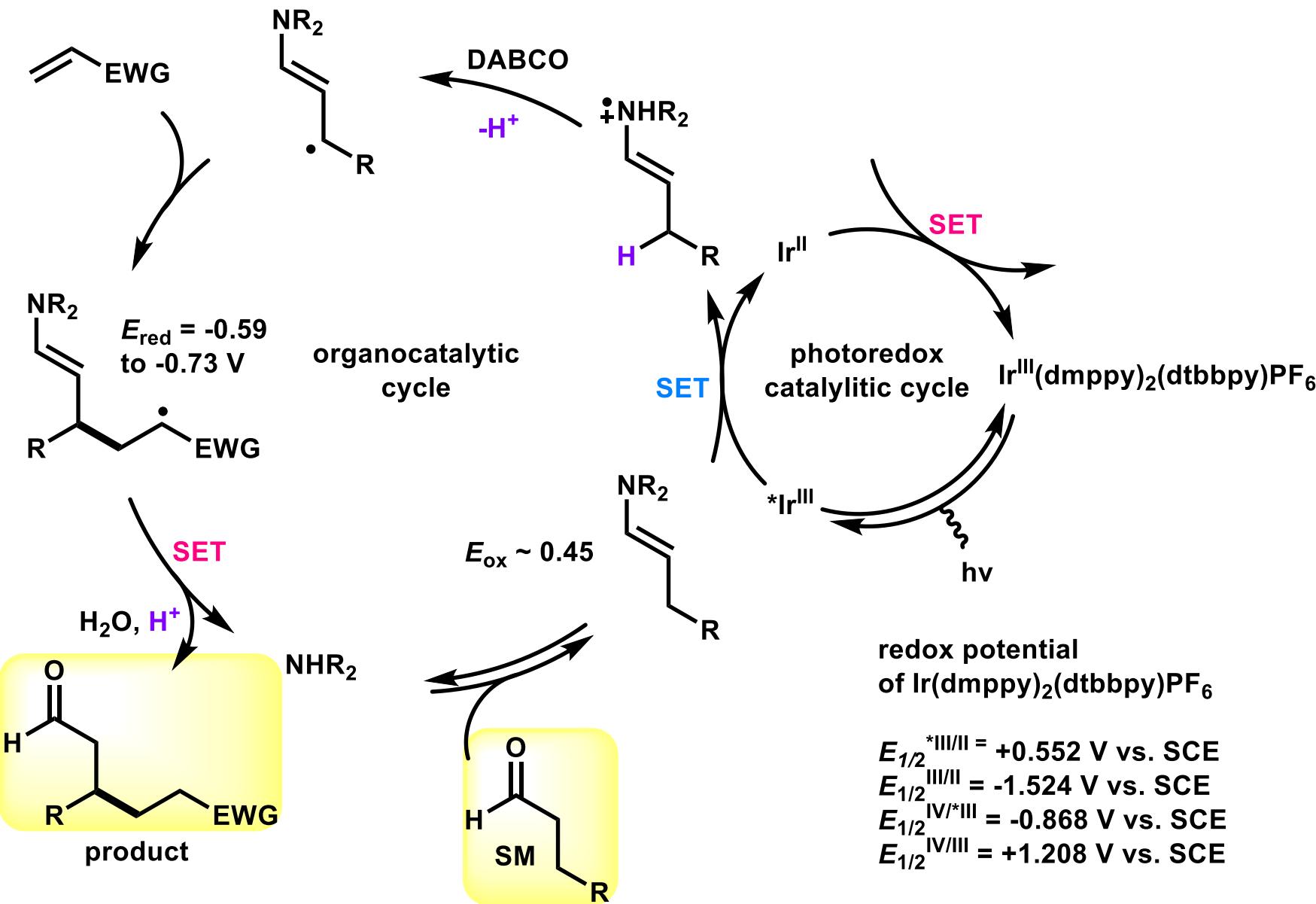


photo-entry	catalyst	organo-catalyst	light source	yield	cf. redox potential vs. SCE <sup>1</sup>
			photocatalyst	*E <sub>red</sub>	E <sub>red</sub>
1	Ir(ppy) <sub>3</sub>	i-Bu <sub>2</sub> NH	26W CFL	7	Ir(ppy) <sub>3</sub> 0.31 -2.19
2	Ru(bpy) <sub>3</sub> Cl <sub>2</sub>	i-Bu <sub>2</sub> NH	26W CFL	50	Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub> 0.77 -0.81
3	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	i-Bu <sub>2</sub> NH	26W CFL	52	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub> 0.66 -1.51
4	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	i-Bu <sub>2</sub> NH	blue LED	64	E <sub>OX</sub> of enamine ~ 0.45
5	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	pyrrolidine	blue LED	6	
6	Ir(ppy) <sub>2</sub> (dtbpy)PF <sub>6</sub>	Cy <sub>2</sub> NH	blue LED	80	

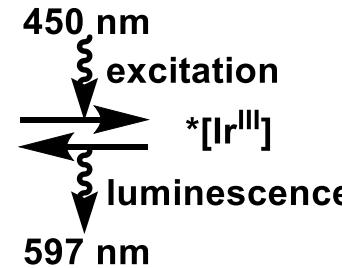
# Proposed Mechanism



# Stern–Volmer Experiment

$\text{Ir}(\text{dmppy})_2(\text{dtbbpy})\text{PF}_6$   
0.5 mM in DME

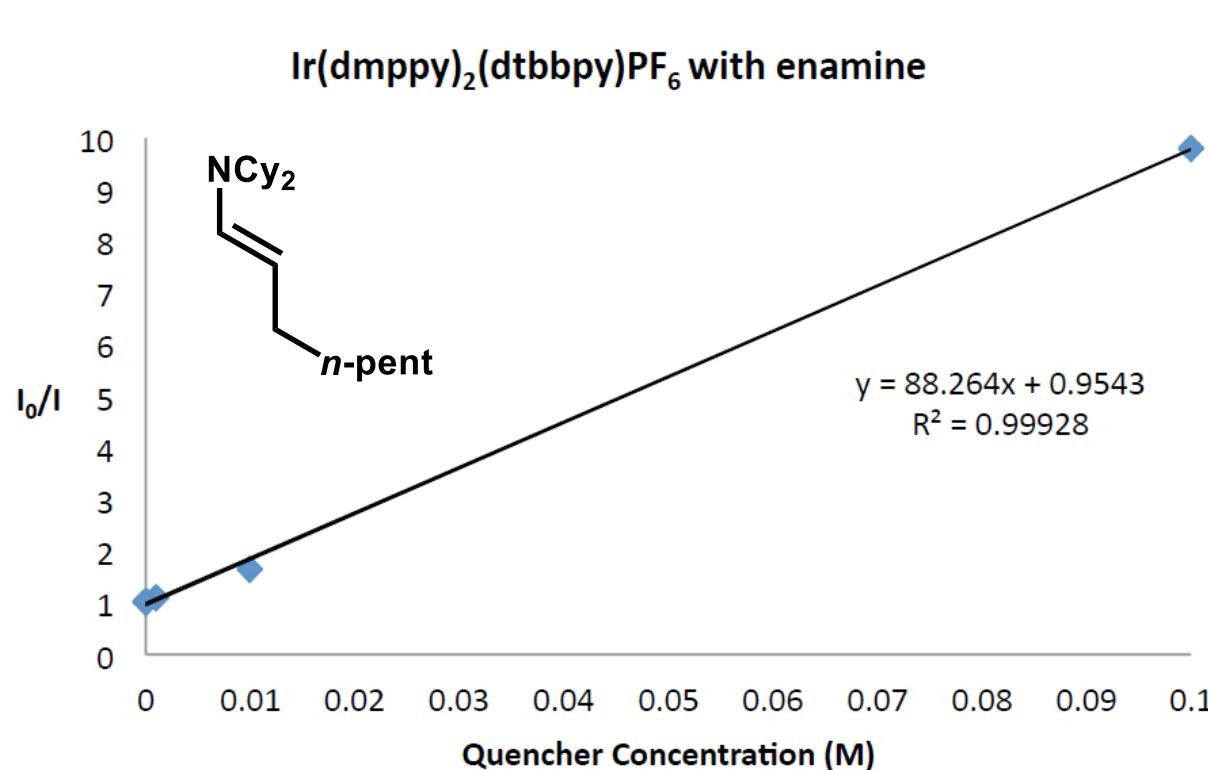
+ quencher



$I_0$ : emission intensity without quencher

$I$ : emission intensity (variable)

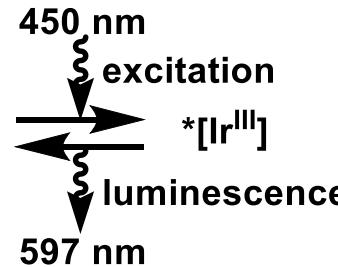
$I_0/I$  should increase if the quencher affected the excited photocatalyst.



\*Enamine was formed *in situ* from octanal and dicyclohexylamine (15:1 ratio).  
Quencher concentration assumes complete conversion to enamine.

# Stern–Volmer Experiment

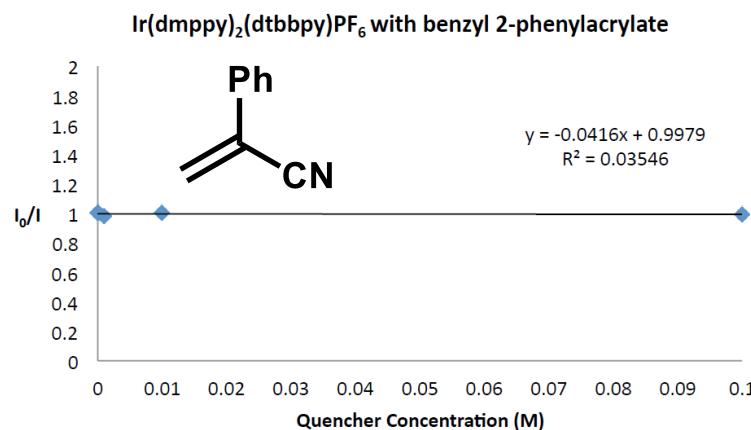
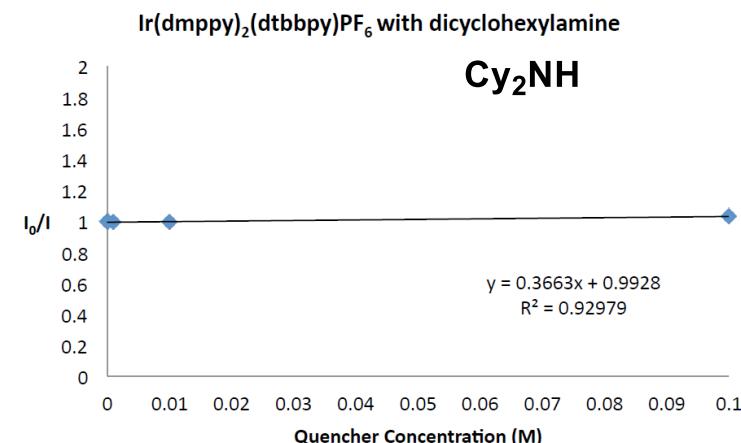
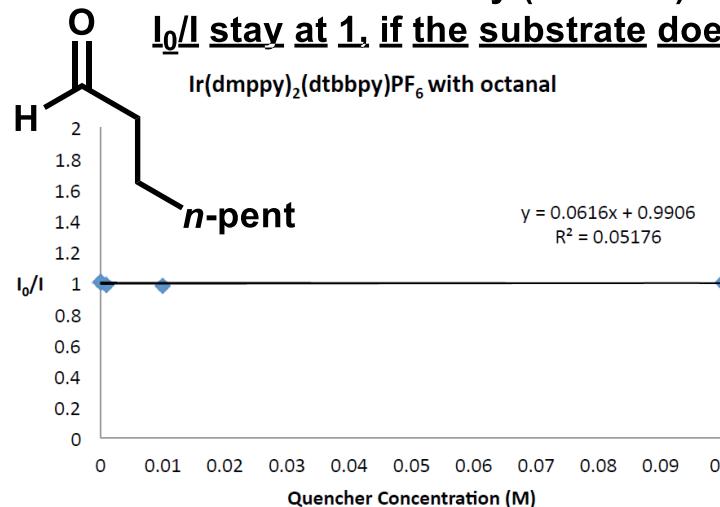
$\text{Ir}(\text{dmppy})_2(\text{dtbbpy})\text{PF}_6$   
0.5 mM in DME + quencher



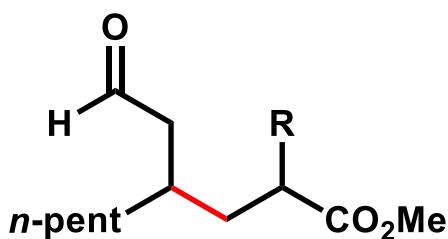
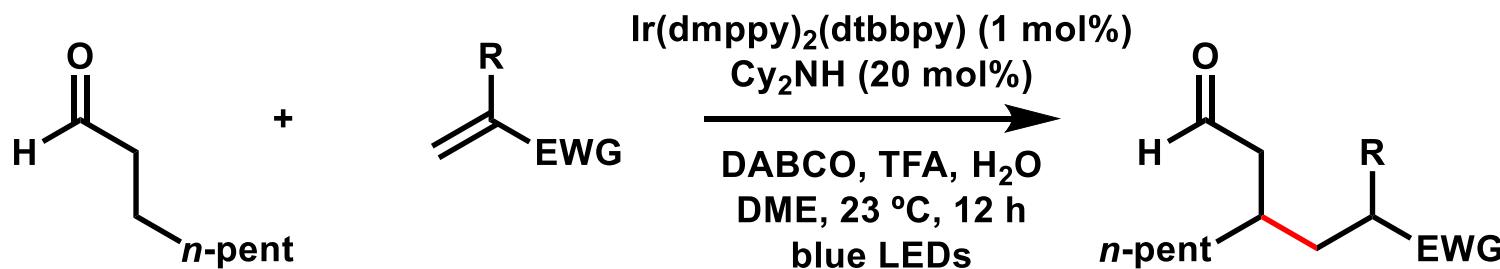
$I_0$ : emission intensity without quencher

$I$ : emission intensity (variable)

$I_0/I$  stay at 1, if the substrate doesn't quench excited photocatalyst.



# Substrate Scope of Michael Acceptor



R = H: 60%

R = Ph: 79%

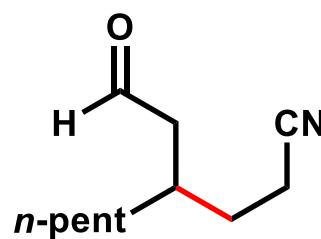
R = naphthyl: 77%

R = o-Br-C<sub>6</sub>H<sub>4</sub>: 69%

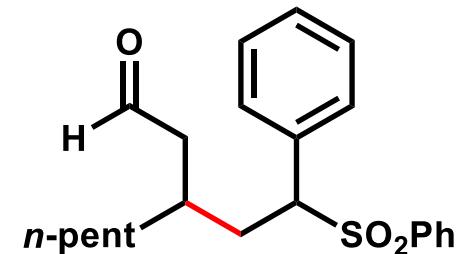
R = p-OMe-C<sub>6</sub>H<sub>4</sub>: 69%

R = p-F-C<sub>6</sub>H<sub>4</sub>: 79%

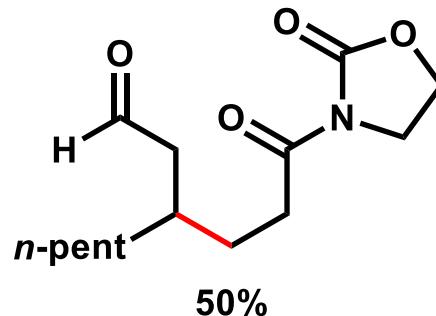
R = p-Cl-C<sub>6</sub>H<sub>4</sub>: 71%



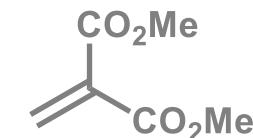
80%



61%

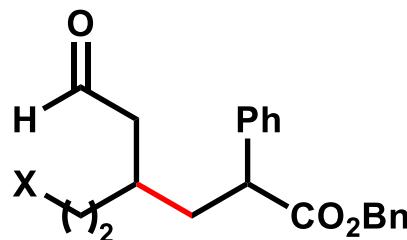
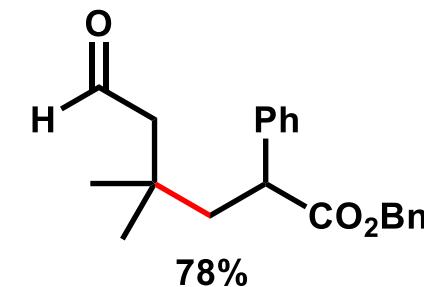
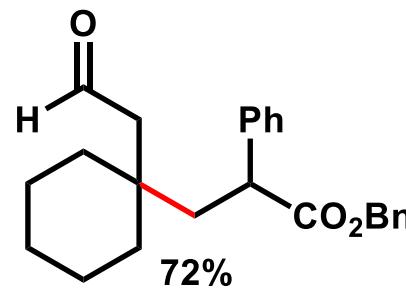
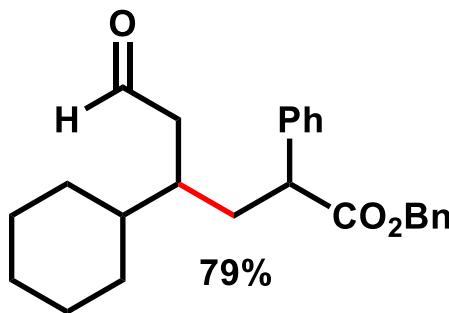
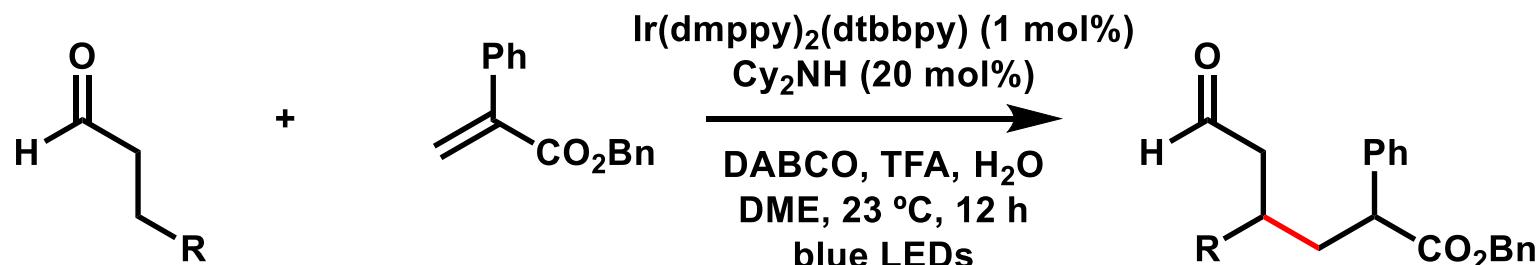


50%

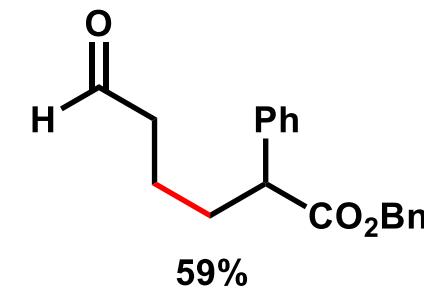


only  $\alpha$ -alkylation

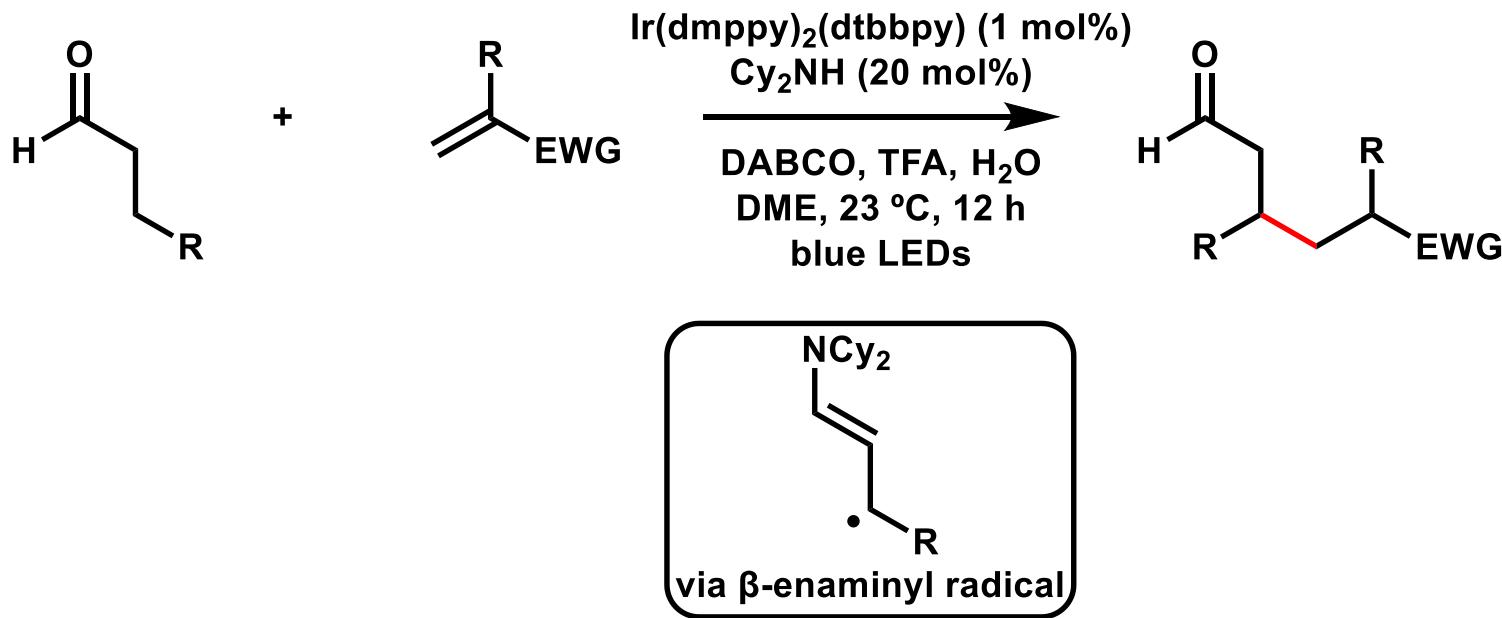
# Substrate Scope of Aldehyde



$X = \text{CO}_2\text{Et}$ : 83%  
 $X = \text{vinyl}$ : 72%



# Short Summary



## advantages

- One-pot  $\beta$ -alkylation of fully saturated aldehydes
- Redox-neutral
- Atom-economical
- Different reaction mode from enone

## drawbacks

- Only aldehydes for carbonyl part
- Racemic

# Contents

## 1. Introduction

## 2. C-H alkylation of enamine

## 3. C-H alkylation of enol silyl ether

ARTICLE

<https://doi.org/10.1038/s41467-019-10641-y>

OPEN

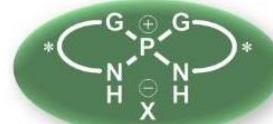
Direct allylic C-H alkylation of enol silyl ethers enabled by photoredox-Brønsted base hybrid catalysis

Kohsuke Ohmatsu<sup>1</sup>, Tsubasa Nakashima<sup>1</sup>, Makoto Sato<sup>1</sup> & Takashi Ooi<sup>1,2</sup>

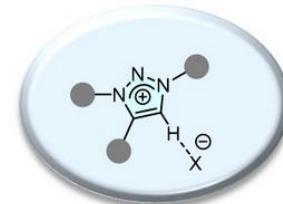
# Prof. Takashi Ooi



アミノホスホニウム塩



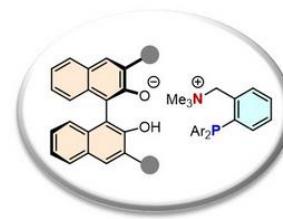
1,2,3-トリアゾリウム塩



アンモニウムベタイン



アンモニウムホスフィン

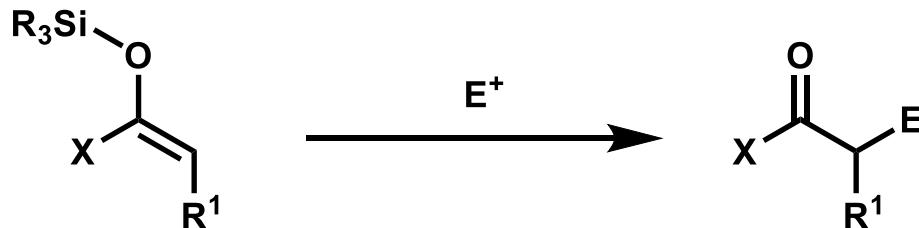


- 1989 名古屋大学工学部応用化学及び合成化学科卒業  
1991 名古屋大学大学院工学研究科博士前期課程応用化学専攻修了  
1994 名古屋大学大学院工学研究科博士後期課程応用化学専攻修了 博士(工学) (山本尚教授)  
("Selective Activation of Epoxides and Aldehydes by Modified Organoaluminum Reagents")  
1994 米国MIT博士研究員 (Prof. J. Rebek. Jr.)  
1995 北海道大学大学院理学研究科助手 (丸岡啓二教授)  
1998 同上講師 (丸岡啓二教授)  
2001 京都大学大学院理学研究科助教授 (丸岡啓二教授)  
2006- 名古屋大学大学院工学系研究科教授 (応用有機化学口座有機反応化学研究グループ)  
2013- 名古屋大学トランスフォーマティブ生命分子研究所 (WPI-ITbM) PI

Research topic: application of “Organic Ion Pair”

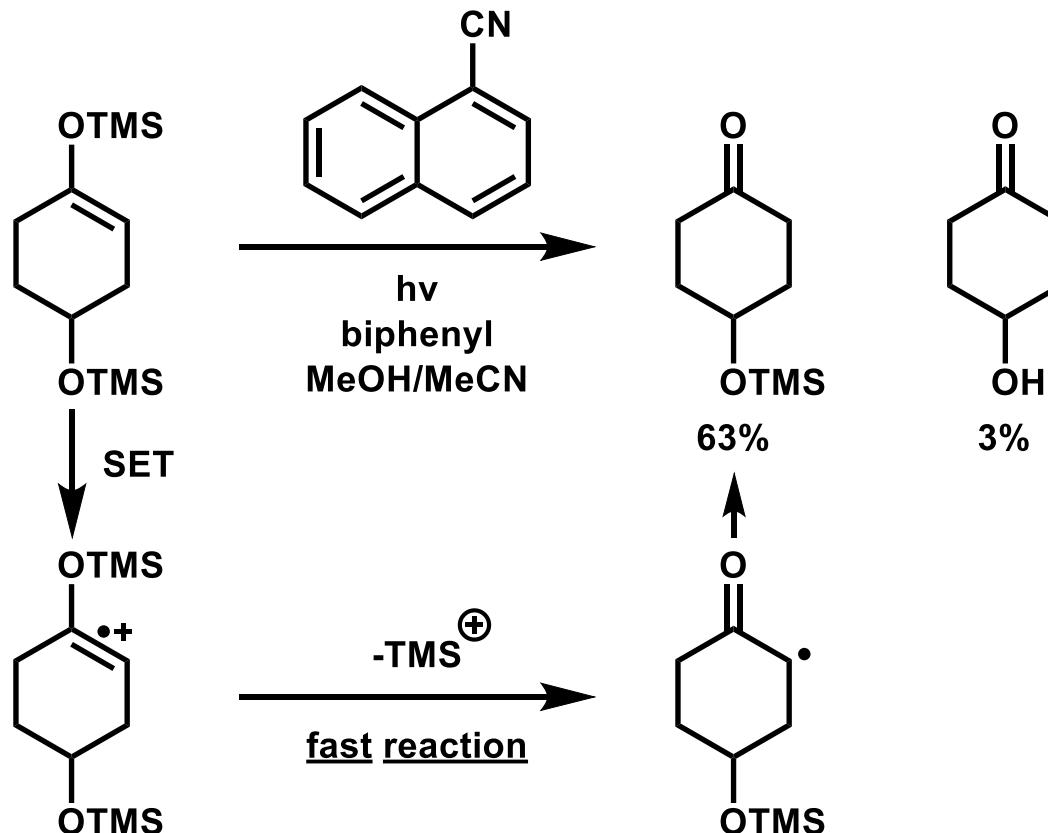
# Reaction of Enol Silyl Ether

- General reaction of enol silyl ether

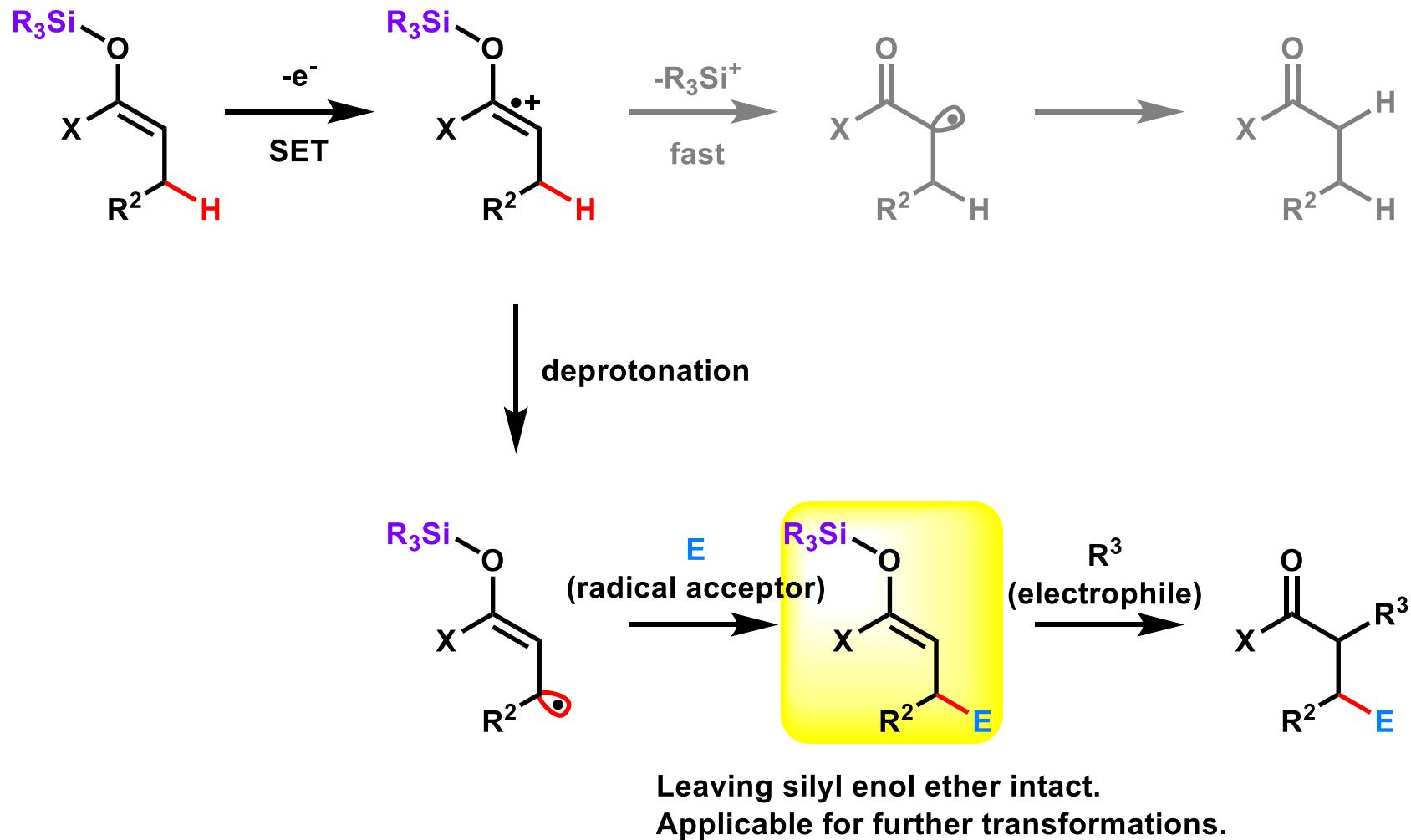


- Electron transfer-induced desilylation

(Gassman, P. G.; Bottorff, K. J. *J. Org. Chem.* 1988, 53, 1097.)

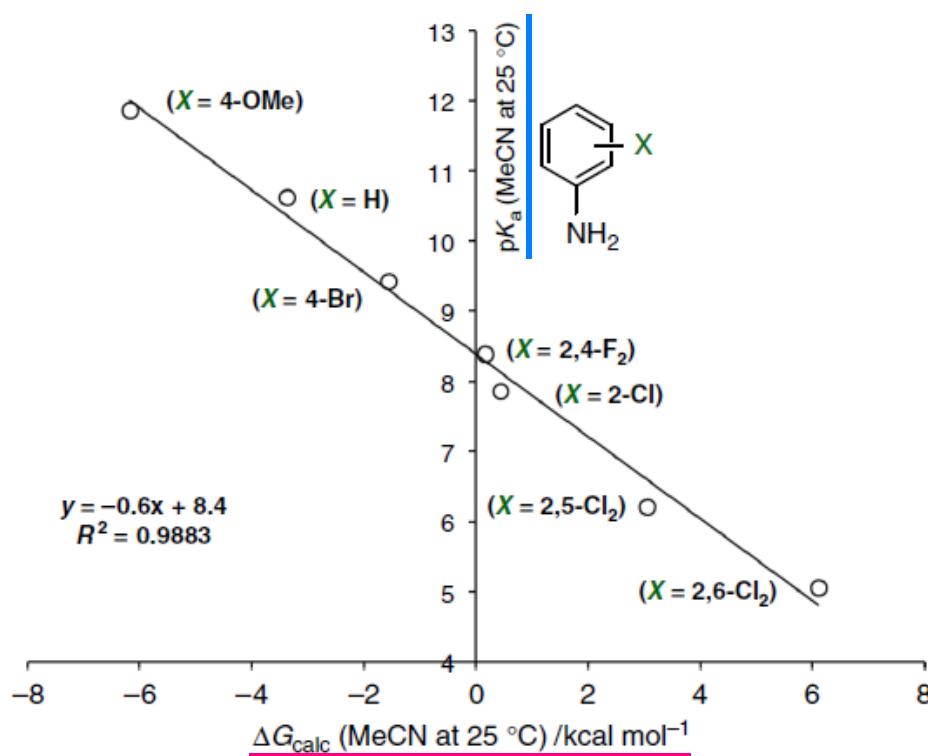
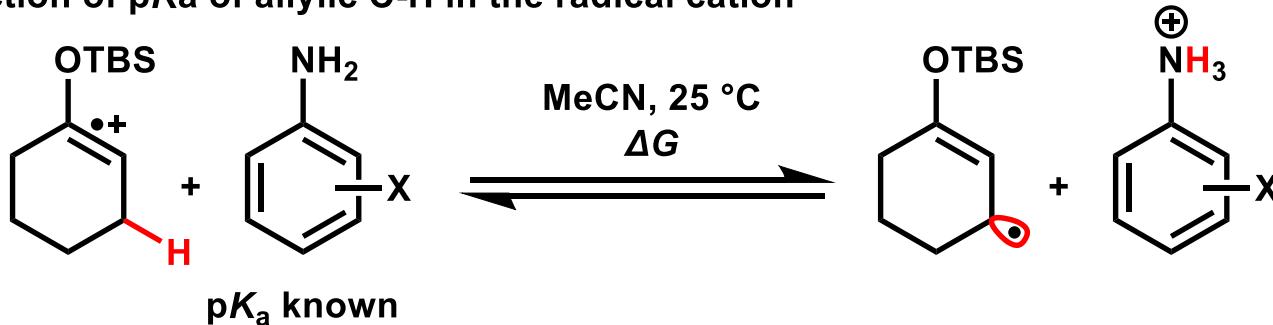


# Working Hypothesis



# Estimation of Reaction

- prediction of  $pK_a$  of allylic C-H in the radical cation

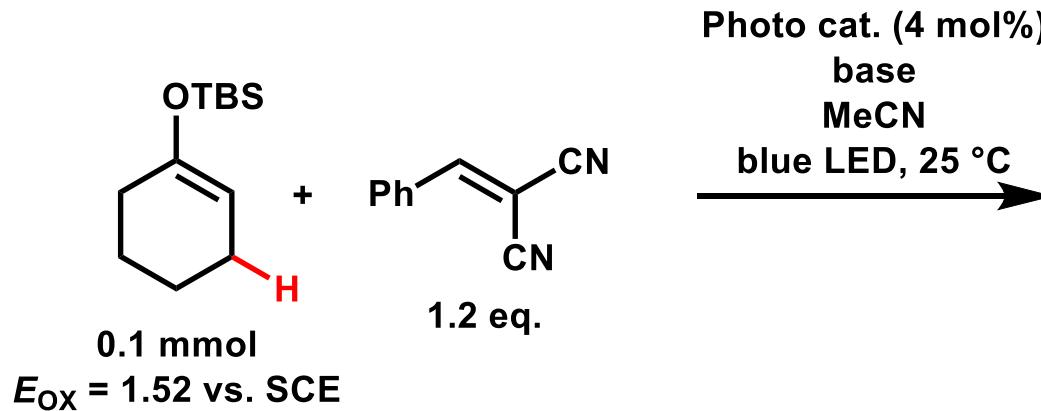


$pK_a$  of the radical cation was estimated by calculation.

Experimentally known  $pK_a$  and calculated free energy of deprotonation was plotted.

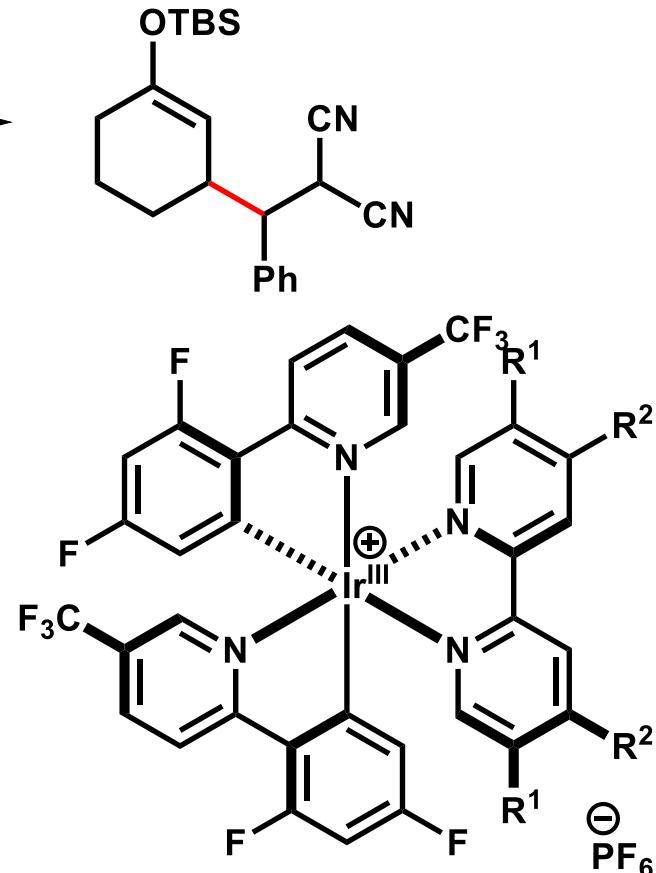
The value was estimated to be 8.4

# Screening of Reaction



entry	PC	Base (mol%)	Yield (%), dr)
1	a	2,4,6-collidine (100)	78, (1.7:1)
2	a	<u>DTBMP (100)</u>	27, (1.7:1)
3	a	<u>K<sub>3</sub>PO<sub>4</sub> (100)</u>	0
4	b	2,4,6-collidine (100)	14, (1.7:1)
5	c	2,4,6-collidine (100)	0
6*	a	2,4,6-collidine (10)	96 (1.8:1)

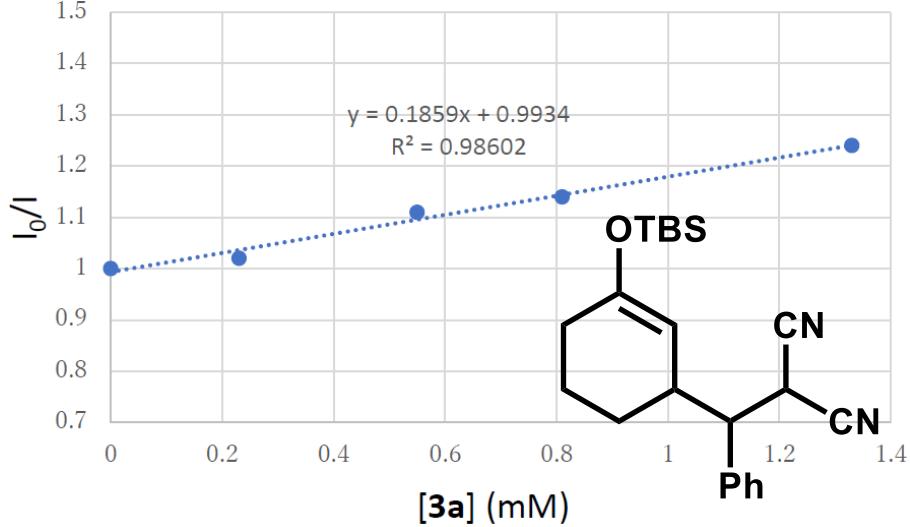
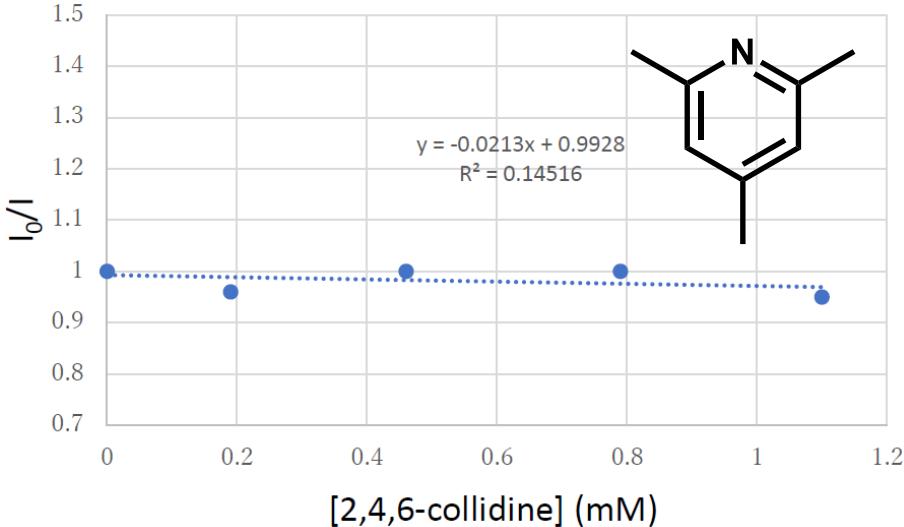
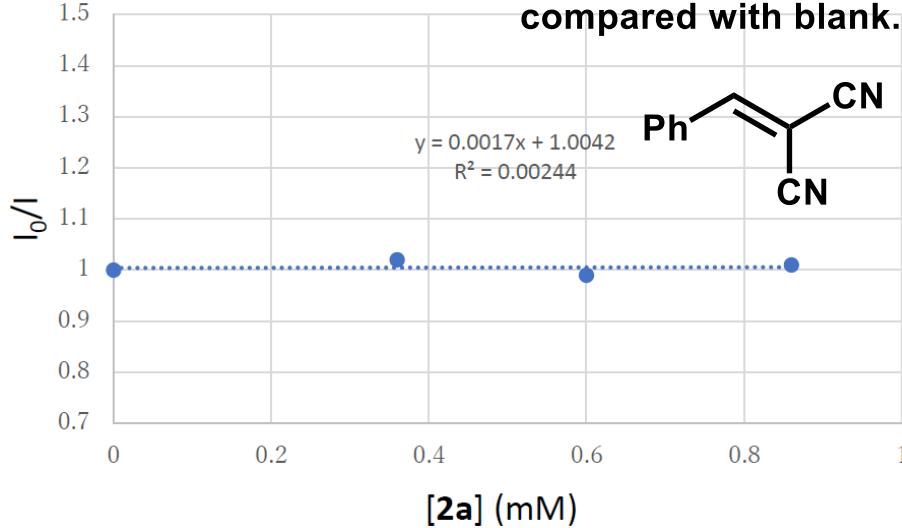
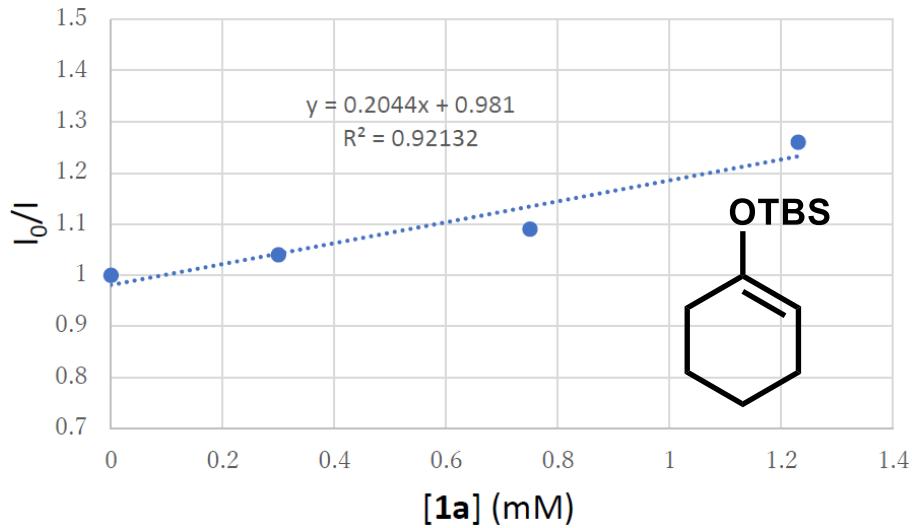
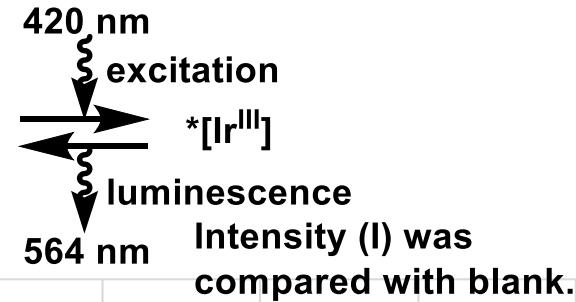
\* 2.0 mmol (0.42 g) scale, optimized conditions  
isolated yield



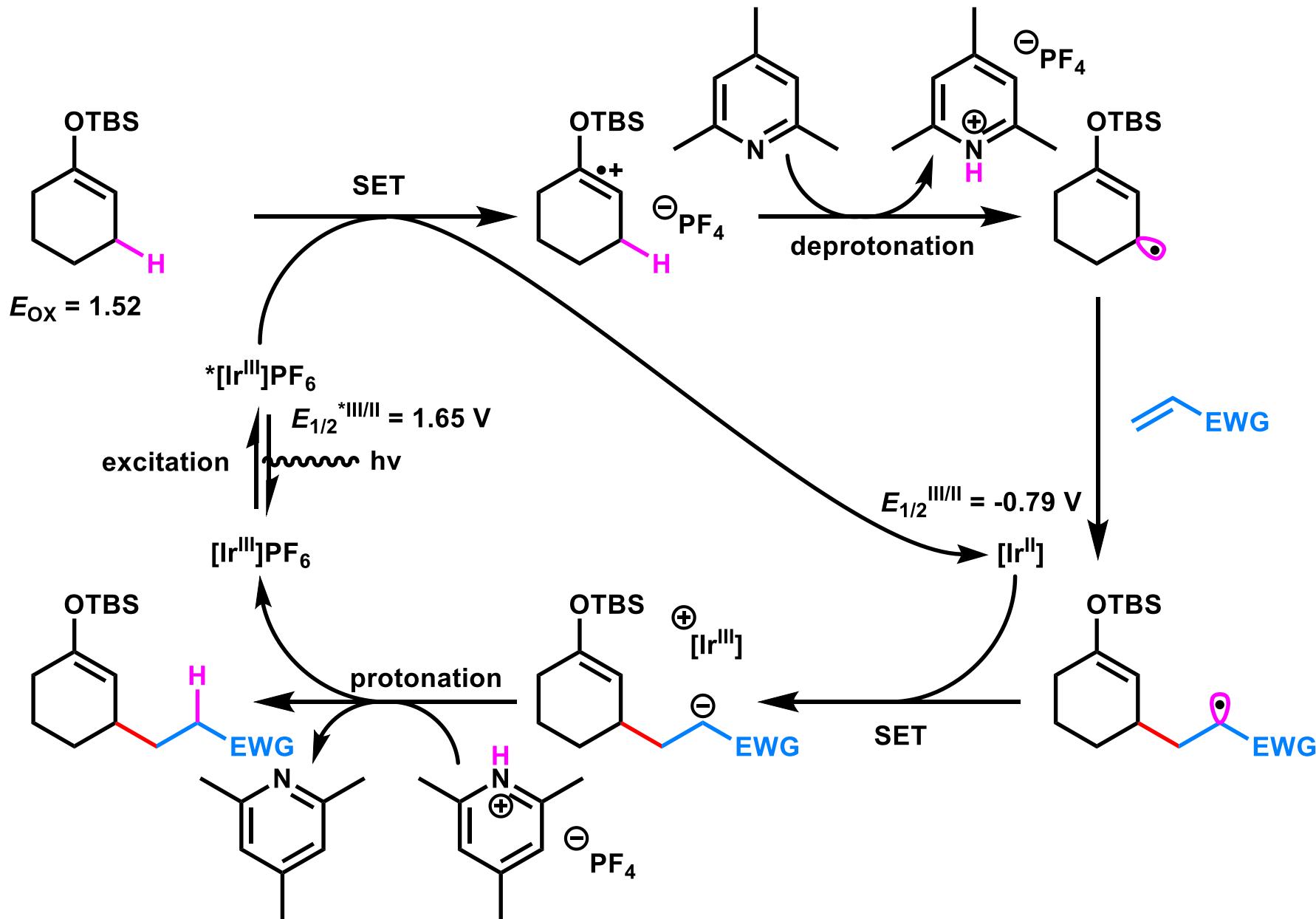
- a ( $R^1 = H, R^2 = CF_3$ ):  
 $E_{1/2}^{*III/II} = 1.65 \text{ V}, E_{1/2}^{III/II} = -0.79 \text{ V}$ ,
- b ( $R^1 = F, R^2 = H$ ):  
 $E_{1/2}^{*III/II} = 1.61 \text{ V}, E_{1/2}^{III/II} = -1.16 \text{ V}$ ,
- c ( $R^1 = H, R^2 = t\text{-Bu}$ ):  
 $E_{1/2}^{*III/II} = 1.21 \text{ V}, E_{1/2}^{III/II} = -1.37 \text{ V}$ ,  
 vs. SCE

# Stern–Volmer Experiment

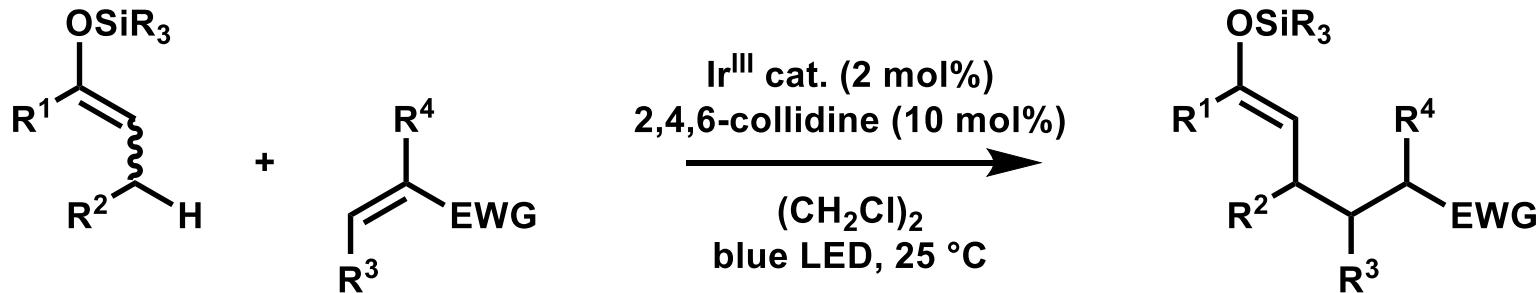
$[\text{Ir}^{\text{III}}(\text{dF}(\text{CF}_3)\text{ppy})_2(4,4'\text{-dCF}_3\text{bpy})]\text{PF}_6$  + various quencher  
0.1 mM in  $(\text{CH}_2\text{Cl})_2$



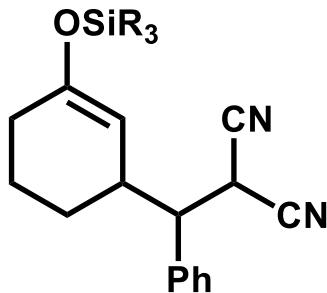
# Proposed Reaction Mechanism



# Substrate Scope (1)

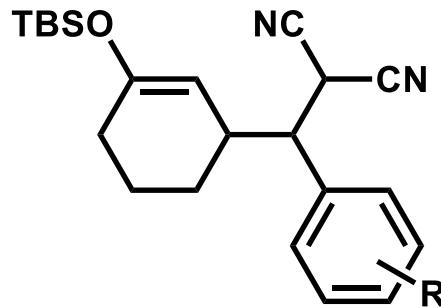


## bulkiness of Si group



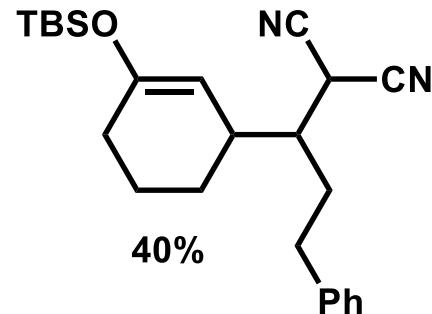
$R_3Si = TBS: 96\%$   
 $R_3Si = TES: 83\%$   
 $R_3Si = TMS: 77\%$

## arylidene malononitriles

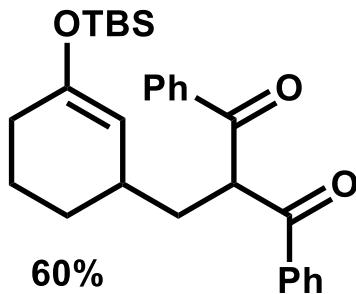


$R = p-CF_3: 77\%$   
 $R = p-OMe: 73\%$   
 $R = o-I: 84\%$

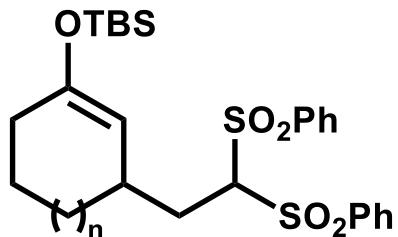
## alkylidene malononitriles



## other EWGs

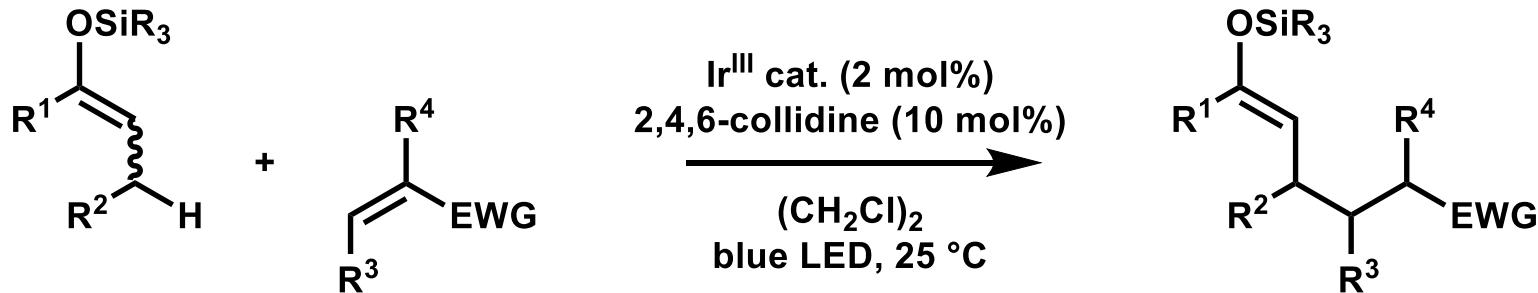


## ring sizes

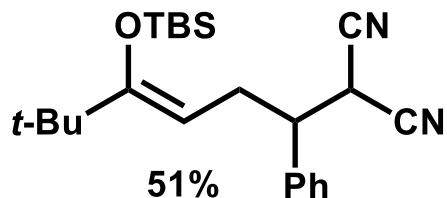


$n = 1: 83\%$   
 $n = 2: 64\%$   
 $n = 3: 68\%$

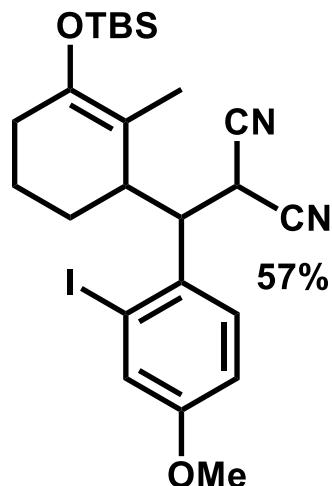
# Substrate Scope (2)



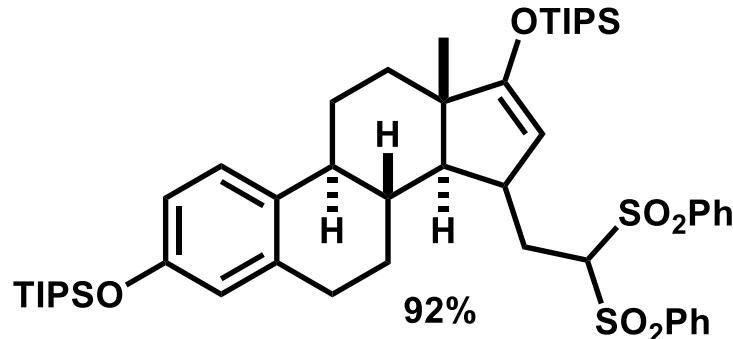
**1° radical**



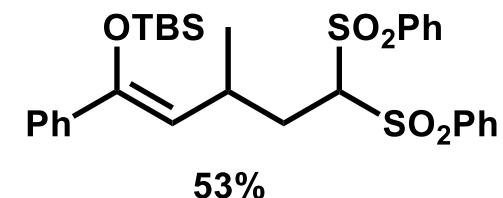
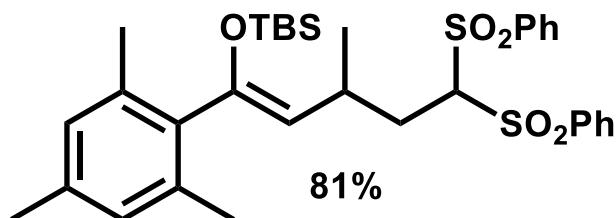
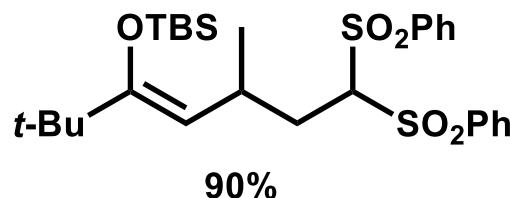
**1° vs. 2° radical**



**estrone derivative**



**effect of R<sup>1</sup>**



# Difference in Reactivity



[a]<sup>•</sup> ( $R^1 = t\text{-Bu}$ )

[b]<sup>•</sup> ( $R^1 = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$ )

[c]<sup>•</sup> ( $R^1 = \text{Ph}$ )

allylic radical	Spin density		SOMO <sup>a</sup> (eV)	$\Delta G^\ddagger_b$ (kcal/mol)	Yield (%) of the reaction
	C1	C3			
[a] <sup>•</sup>	0.75	0.70	-5.77	21.2	90
[b] <sup>•</sup>	0.62	0.64	-5.77	21.6	81
[c] <sup>•</sup>	0.58	0.51	-5.77	23.3	53

<sup>a</sup> Calculated at (U)CAM-B3LYP/6-311+G(d,p)

<sup>b</sup> Calculated at SMD(DCE)-(U)CAM-B3LYP/6-311+G(d,p)

SOMO levels were almost the same in all the substrate.

Spin density reflects the reactivity of the radical in that carbon.

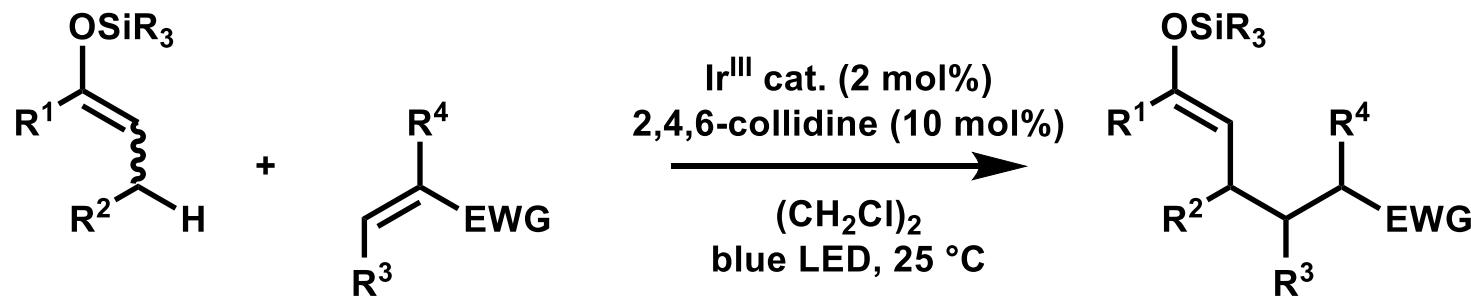
Spin density of C3 is decreased in [c]<sup>•</sup> because the radical can be delocalized over the phenyl group.

# Summary

MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* 2014



Ooi, T. et al. *Nat. Commun.* 2019

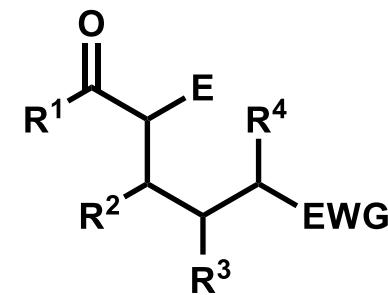


## advantages

- Further functionalization from silyl enol ether
- Redox-neutral
- Atom-economical
- Different reaction mode from enone
- Applicable for ketones

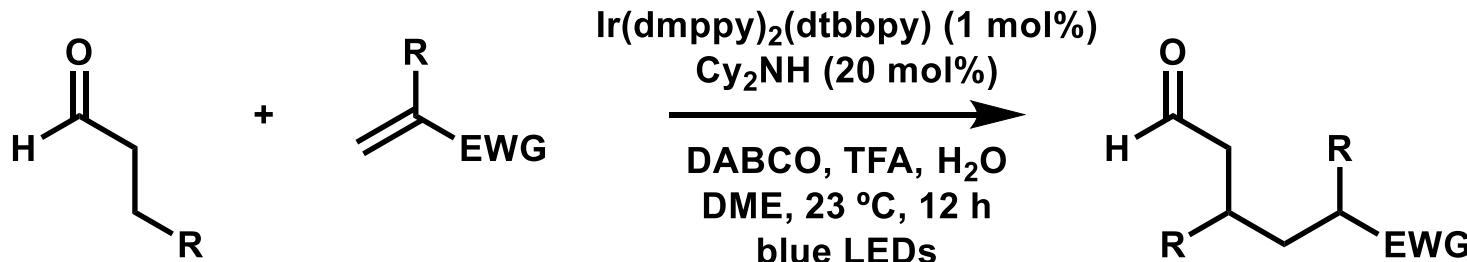
## drawbacks

- Preparation of silyl enol ether
- Racemic

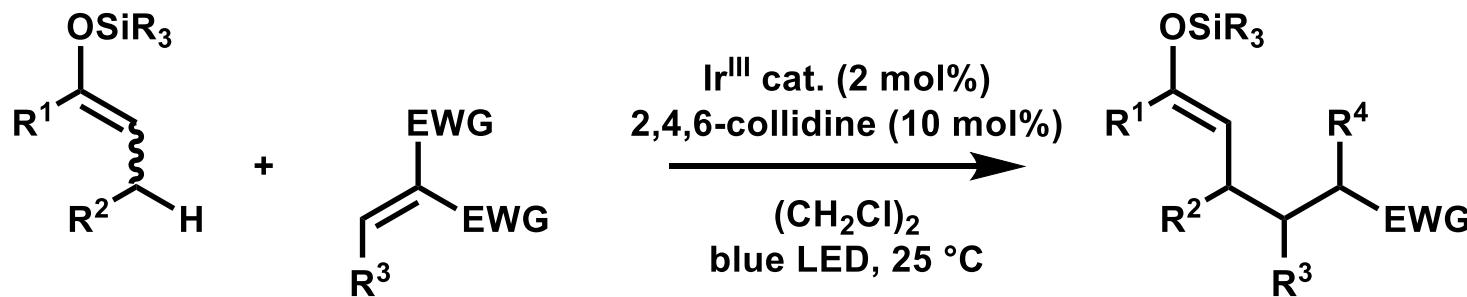


# Appendix 1. Difference in Reactivity

MacMillan, D. W. C. et al. *J. Am. Chem. Soc.* 2014



Ooi, T. et al. *Nat. Commun.* 2019



Macmillan used mono-activated Michael acceptor, while Ooi used double activated one. This might be because...

1. Difference in nucleophilicity of N-substituted allylic radical and O-substituted one.
2. Existence of acidic proton promoted reduction of radical.

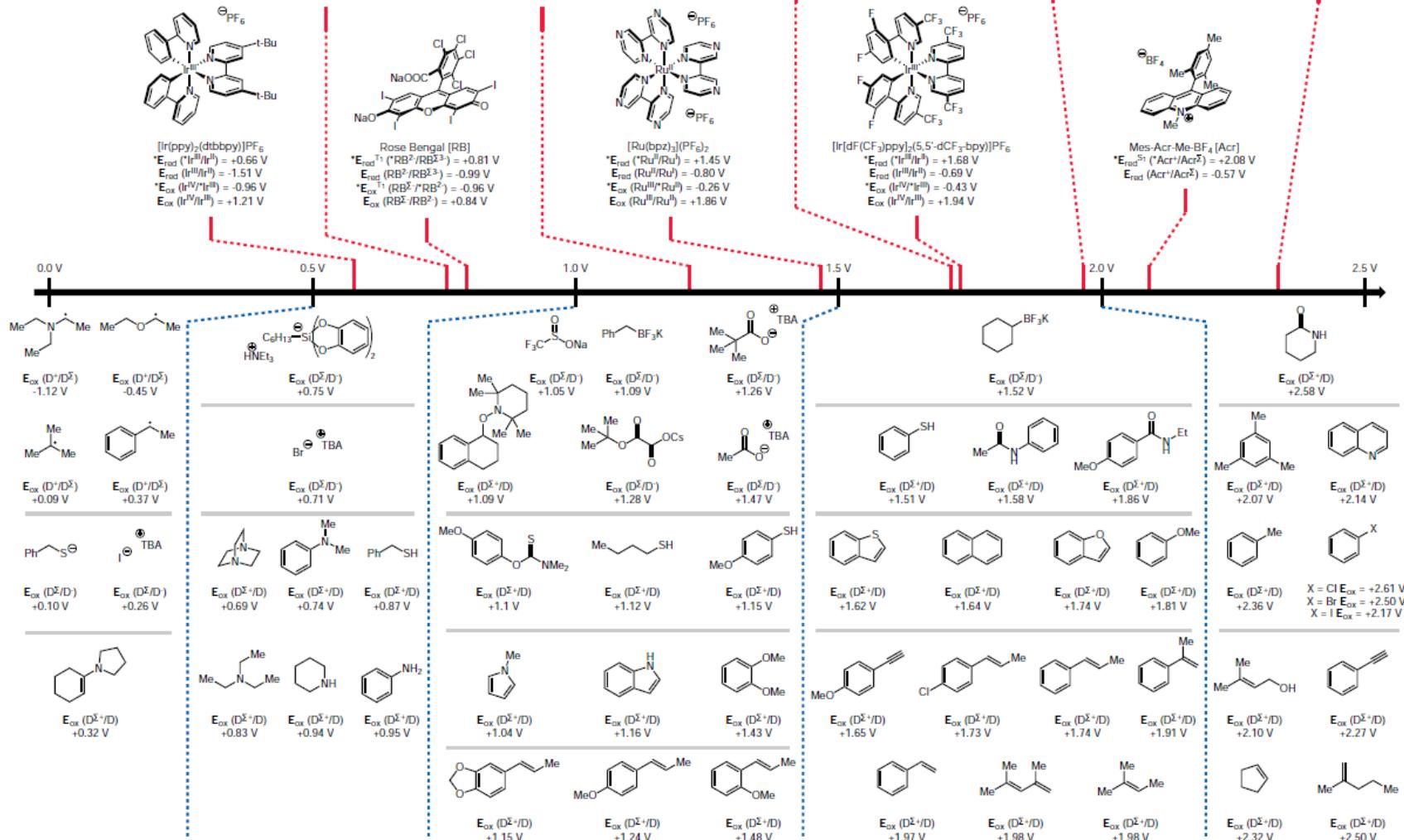
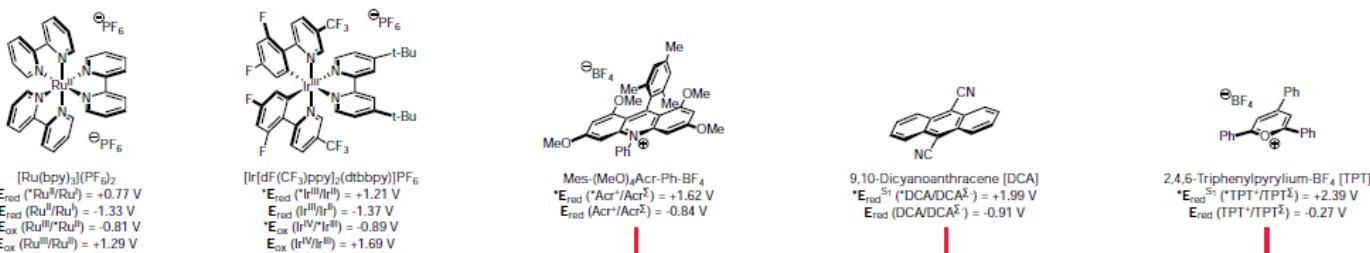
# **Excited state photooxidants**

**Table 2. Excited state photooxidants**

$$DG_{PET} = -nF[\epsilon E_{red} (\text{cat/cat}) - E_{ox} (D^{m+1}/D^m)]$$

Compiled redox potentials reported in volts (V) versus Saturated Calomel Electrode (SCE)

Compiled data represent measured  $E_{1/2}$  (half-wave),  $E_p$  (peak potential), or  $E_{p/2}$  (half-peak potential) values



# **Excited state photoreductants**

**Table 3. Excited state photoreductants**

$$\Delta G_{\text{PDT}} = -n F [E_{\text{red}}(A^n/A^{n-1}) - E_{\text{ox}}(\text{cat}^+/\text{cat})]$$

Compiled redox potentials reported in volts (V) versus Saturated Calomel Electrode (SCE)

Compiled data represent measured  $E_{1/2}$  (half-wave),  $E_p$  (peak potential), or  $E_{p1/2}$  (half-peak potential) values

