

Evolution of organocatalyst ~focused on MacMillan's work~

2015.5.9 (Sat)
Takumi Matsueda (M1)
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1. Introduction

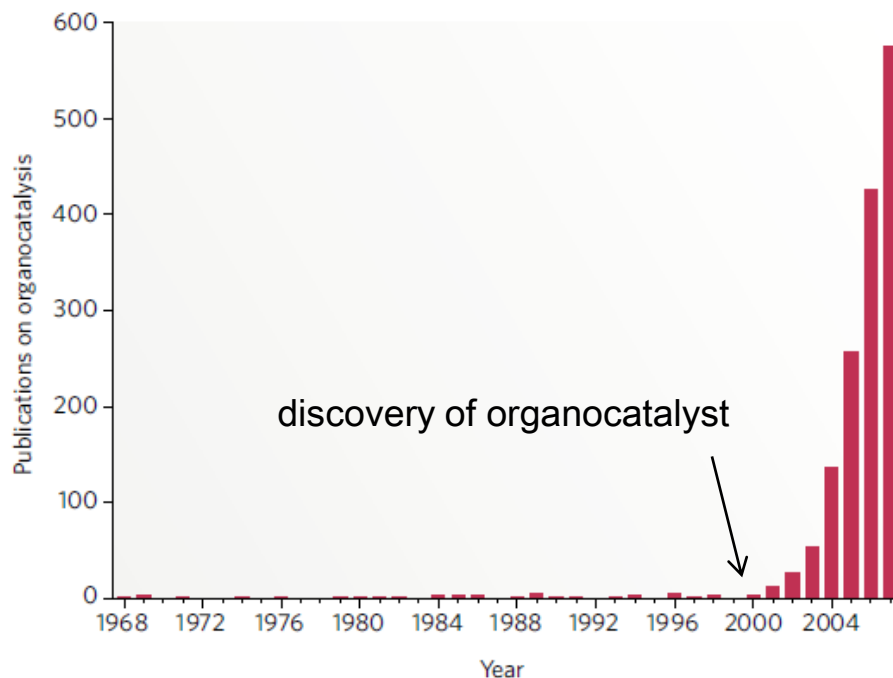
2. HOMO, LUMO-activation

3. SOMO-activation

4. Metal-free SOMO-activation

5. Summary

An explosion of interest in organocatalyst



Enantioselective organocatalyst was found in 2000 (by MacMillan)



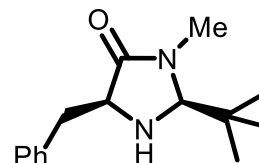
Organocatalyst is one of the most important catalyst in organic chemistry

MacMillan, D. C. *Nature*, 2008, 455, 304-308

- ✓ Inensitive to oxygen & moisture
- ✓ Non-toxic
- ✓ Inexpensive and easy to prepare
- ✓ A wide variety of organic reagent

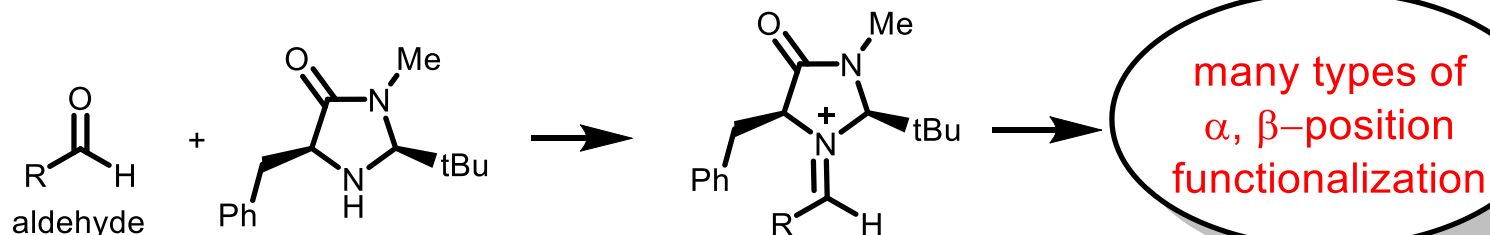


The pioneer of organocatalyst



MacMillan catalyst

= enantioselective C=O activation



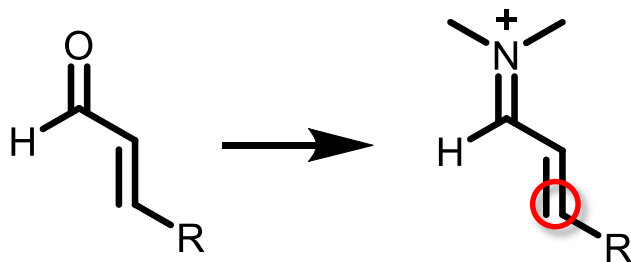
Career

1987-1991 Undergraduate degree in chemistry at the University of Glasgow
1991-1996 Doctoral studies at the University of California (Prof. Larry E. Overman)
1996-1998 Postdoctoral research fellow at Harvard University (Prof. David A. Evans)
1998-2000 His independent research career at the University of California, Berkeley
2000-2006 the Department of Chemistry at the California Institute of Technology
2006-2011 the Department of Chemistry at Princeton University
2011-present James S. McDonnell Distinguished University Professor of the Department of Chemistry at Princeton University

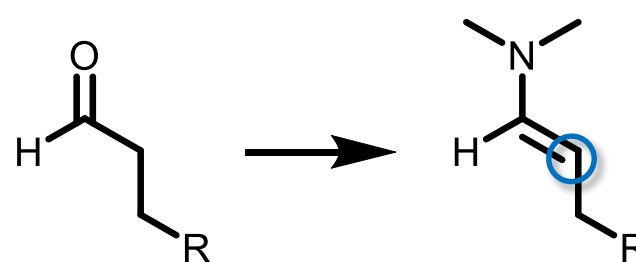
Aldehyde activation

4 main types of aldehyde activation

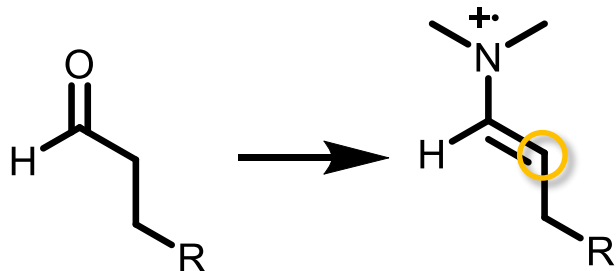
LUMO-activation



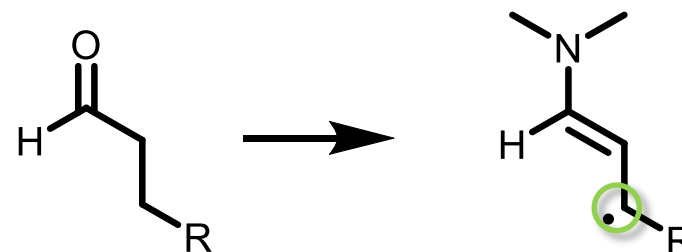
HOMO-activation



SOMO-activation



SOMO- β -activation



1. Introduction

2. HOMO, LUMO-activation

3. SOMO-activation

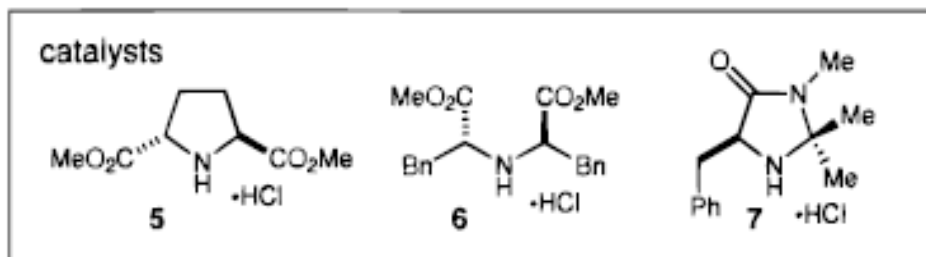
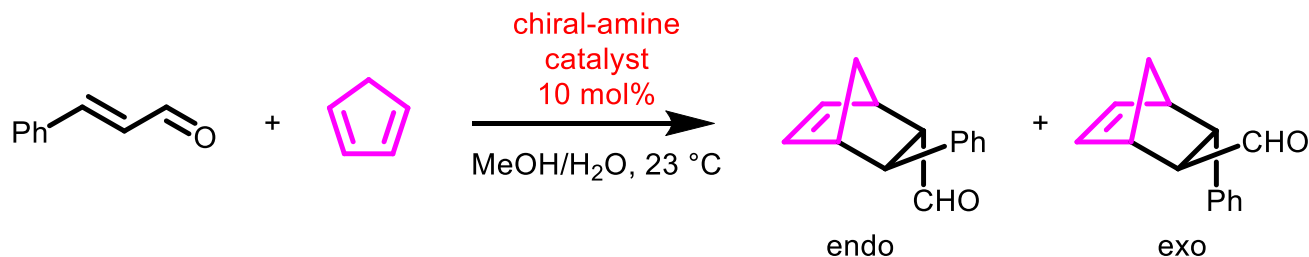
4. Metal-free SOMO-activation

5. Summary

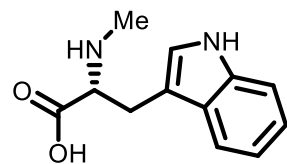
The birth of MacMillan catalyst

2. HOMO, LUMO-activation

LUMO-activated Diels-Alder reaction

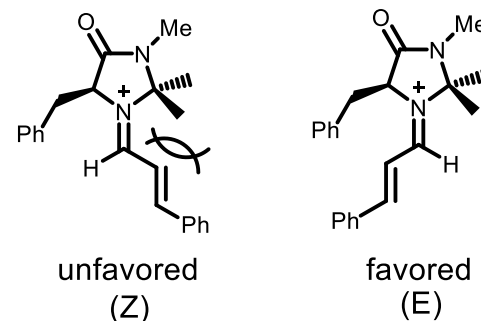


entry	catalyst	time (h)	yield (%)	exo:endo	exo ee (%) ^{a,b}
1	(<i>S</i>)-Pro-OMe·HCl	27	81	2.7:1	48 (<i>2R</i>)
2	(<i>S</i>)-Abr-OMe·HCl	10	80	2.3:1	59 (<i>2S</i>)
3	5	23	92	2.6:1	57 (<i>2R</i>)
4	6	84	82	3.6:1	74 (<i>2R</i>)
5	7	8	99	1.3:1	93 (<i>2S</i>) ^c



(*S*)-Abrine

*5 mol% cat. (entry 5)

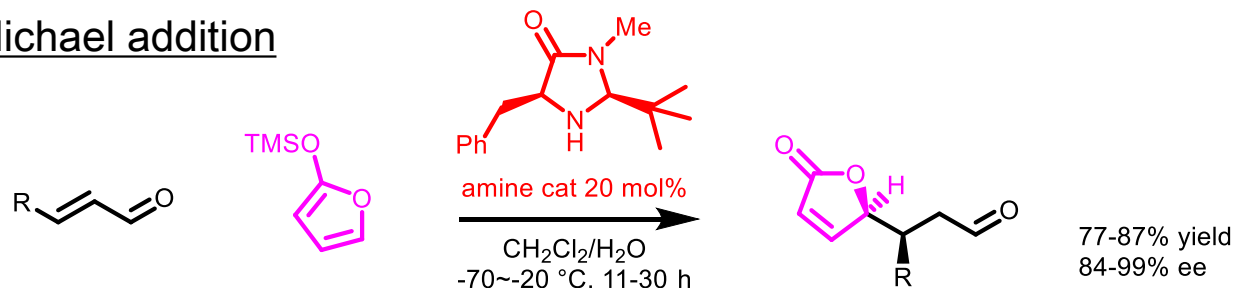


Selectivity of iminium cation formation

LUMO-activation by imidazolidinone

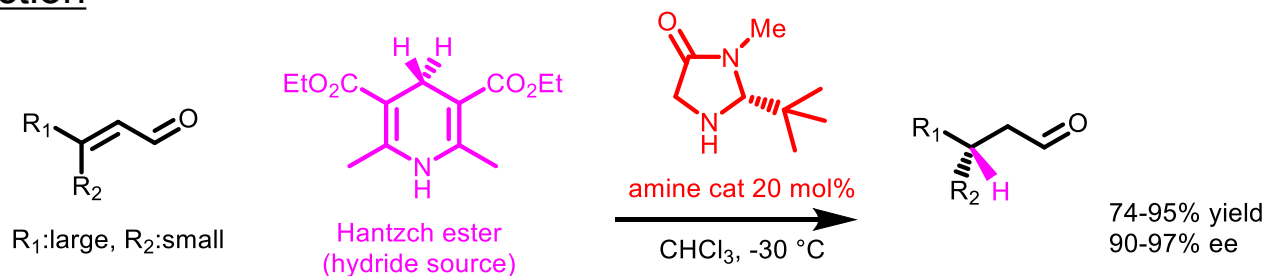
2. HOMO, LUMO-activation

Mukaiyama Michael addition



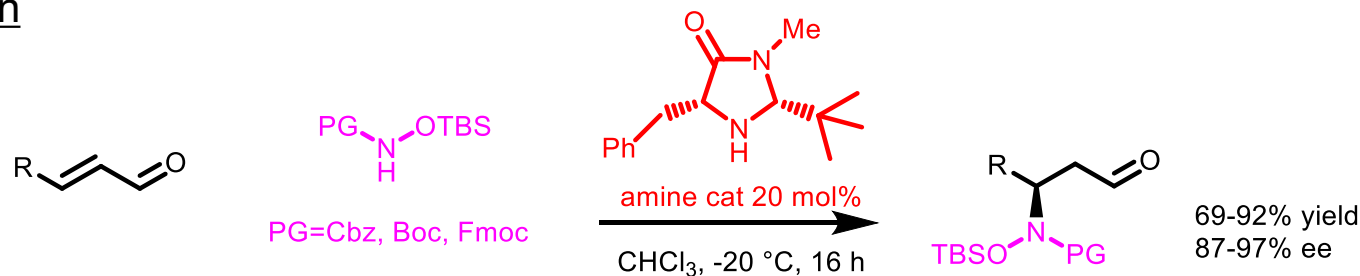
MacMillan, *et al.*, *J. Am. Chem. Soc.*, **2003**, *125*, 1192-1194

Hydride reduction



MacMillan, *et al.*, *J. Am. Chem. Soc.*, **2005**, *127*, 32-33

Amine addition

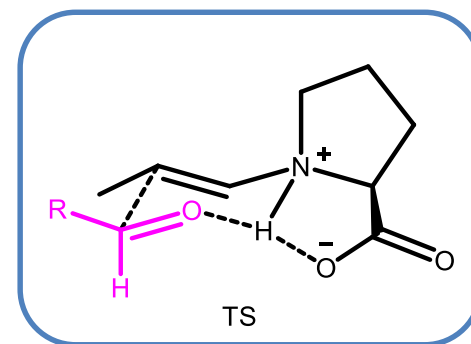
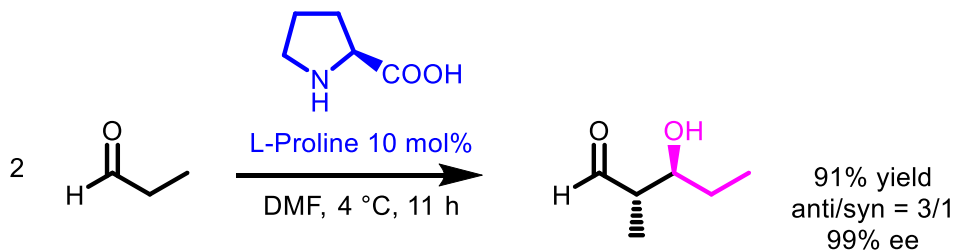


MacMillan, *et al.*, *J. Am. Chem. Soc.*, **2006**, *128*, 9328-9329

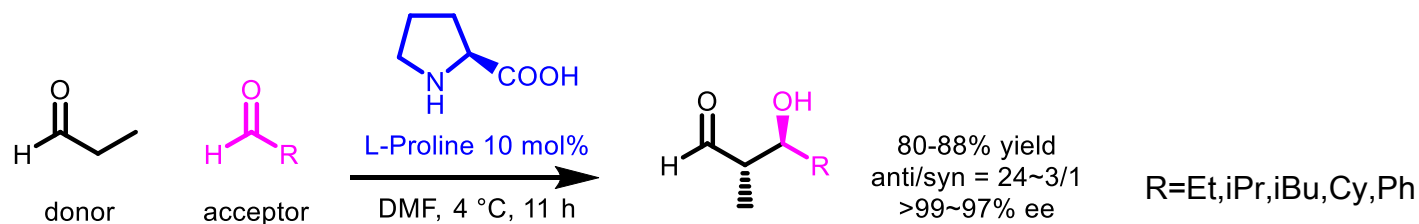
HOMO-activation by proline

2. HOMO, LUMO-activation

Homo aldol

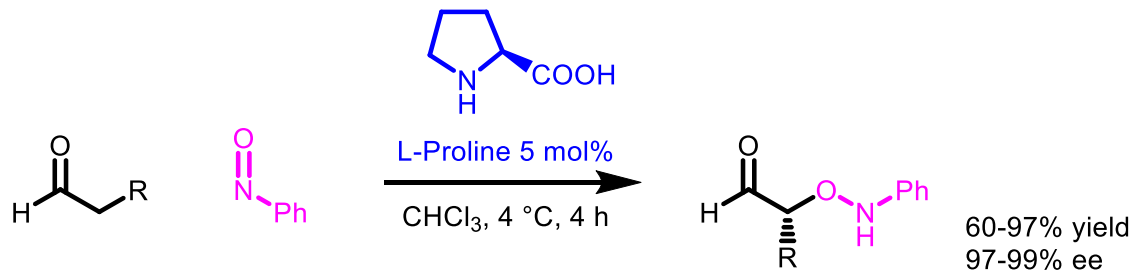


Cross aldol



MacMillan, *et al.*, *J. Am. Chem. Soc.*, **2002**, *124*, 6798-6799

Oxidation

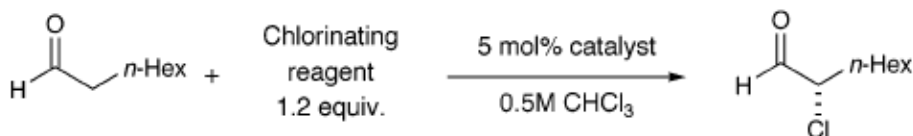


MacMillan, *et al.*, *J. Am. Chem. Soc.*, **2003**, *125*, 10808-10809

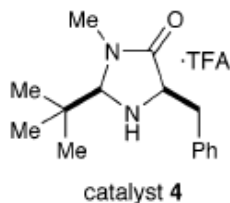
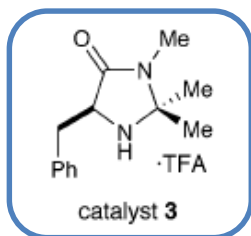
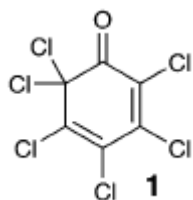
HOMO-activation by imidazolidinone

2. HOMO, LUMO-activation

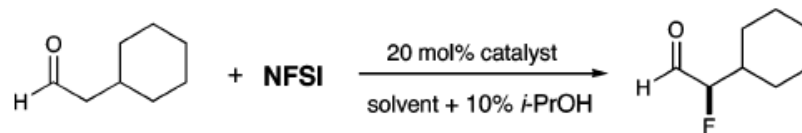
Chlorination



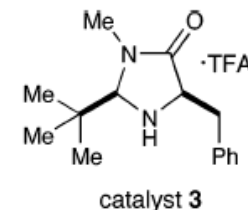
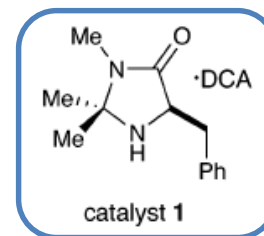
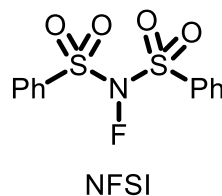
entry	catalyst	reagent	temp (°C)	time (h)	% conversion ^a	% ee ^b
1	L-proline	NCS	4	6	99	2
2	3	NCS	4	6	20	19
3	4	NCS	4	6	60	10
4	L-proline	1	4	12	44	2
5	L-proline	1	-30	30	NR	NA
6	3	1	-30	8	91	92
7	4	1	-30	6	78	42



Fluorination



entry	catalyst	solvent	temp (°C)	time (h)	% convrsn ^a	% ee ^b
1	L-proline	THF	23	4	79	26
2	3	THF	23	0.3	96	63
3	1	THF	23	0.5	73	98
4	1	CH ₃ CN	23	3	75	96
5	1	EtOAc	23	0.5	84	96
6	1	acetone	23	1	89	97
7	1	CHCl ₃	23	1	73	96
8	1	THF	4	6	97	98
9	1	THF	-10	12	98	98

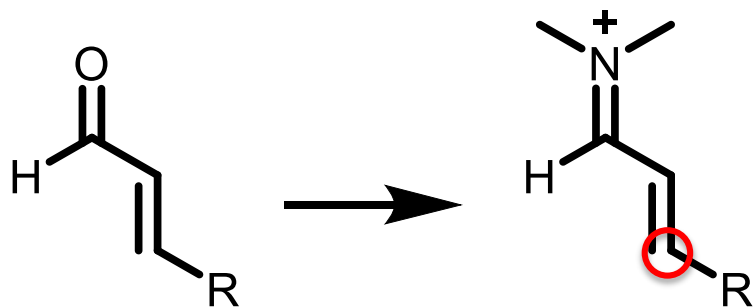


not 6-membered ring TS
... imidazolidinone catalyst

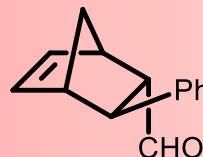
HOMO, LUMO-activation

2. HOMO, LUMO-activation

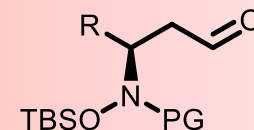
LUMO-activation



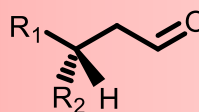
enantioselective ...



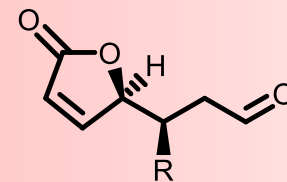
cyclo addition



amine addition

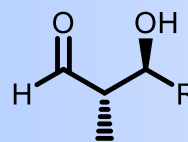
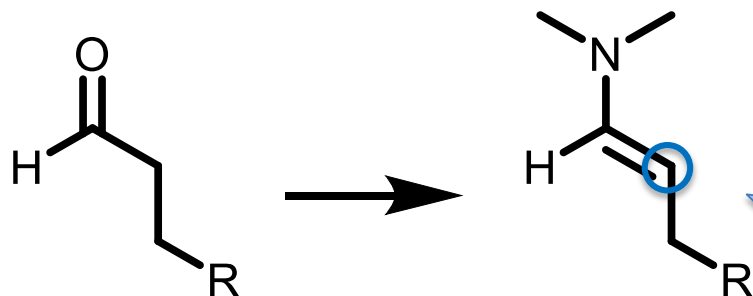


hydride reduction

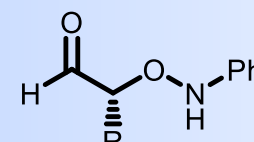


Mukaiyama-Michael addition

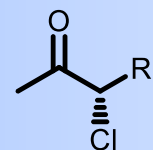
HOMO-activation



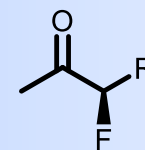
cross aldol



oxidation



chlorination

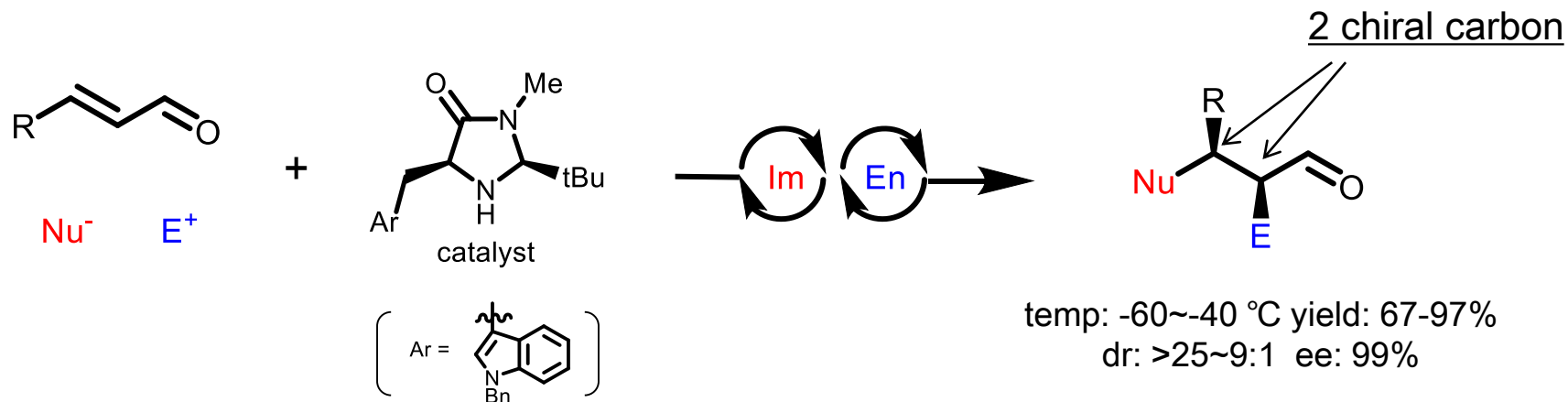


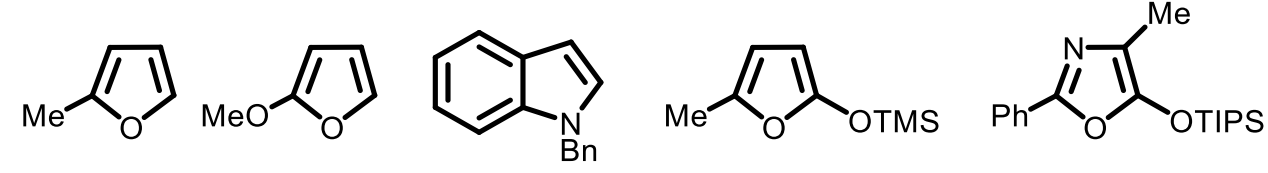
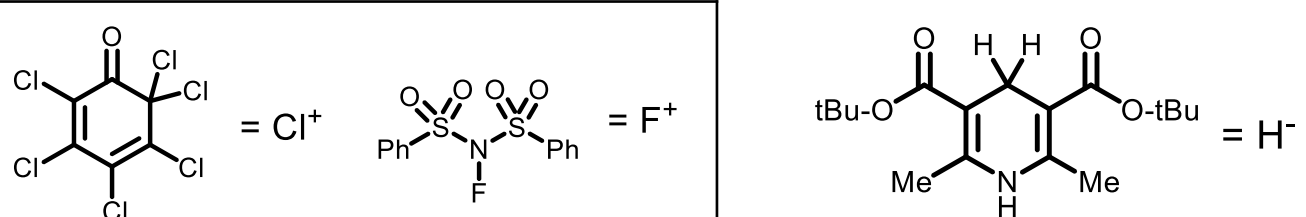
fluorination

Organocascade reaction

2. HOMO, LUMO-activation

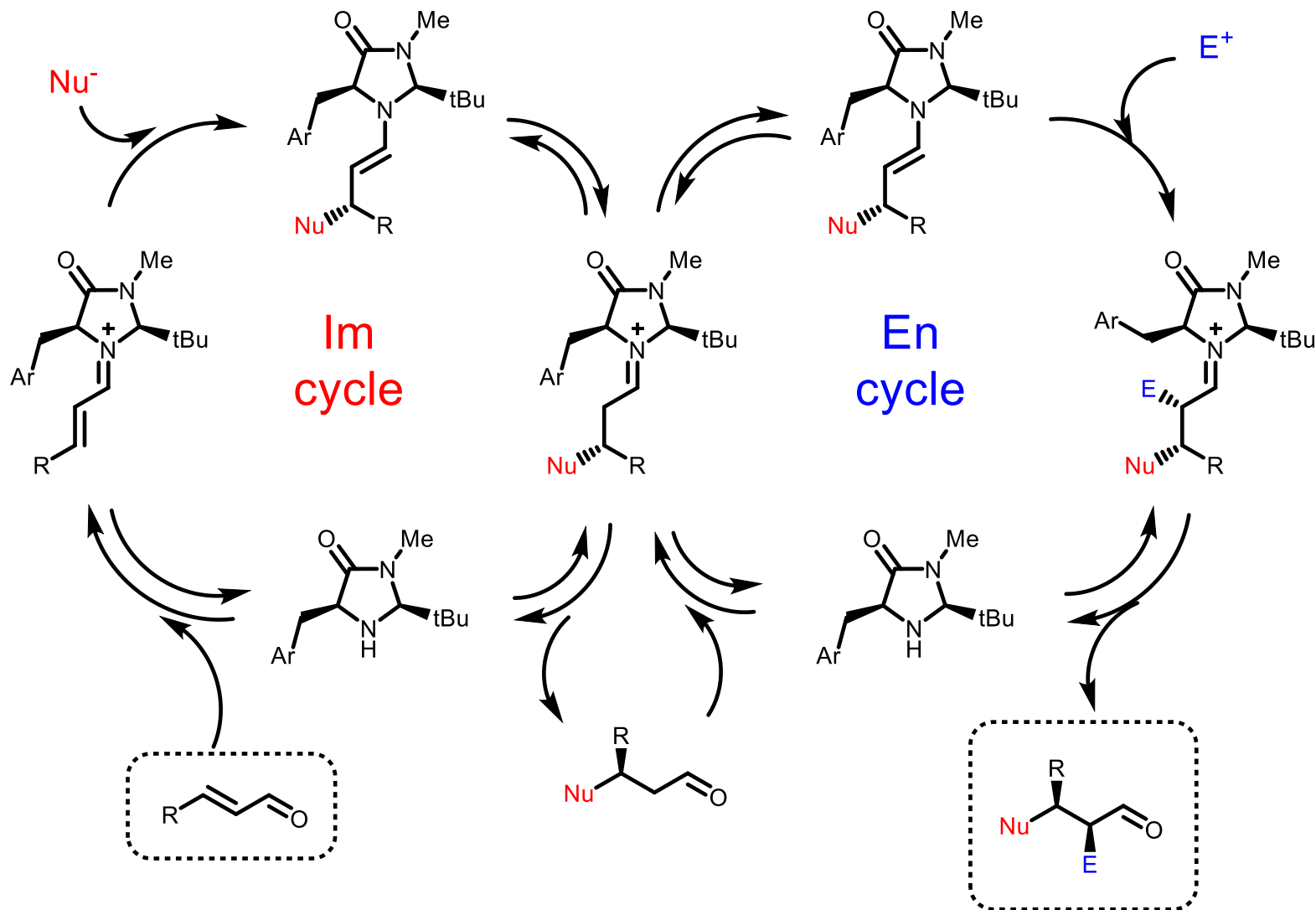
enantioselective C-Nu and C-E bond formation in one-pot reaction



Nu⁻	
E⁺	

Cascade cycle

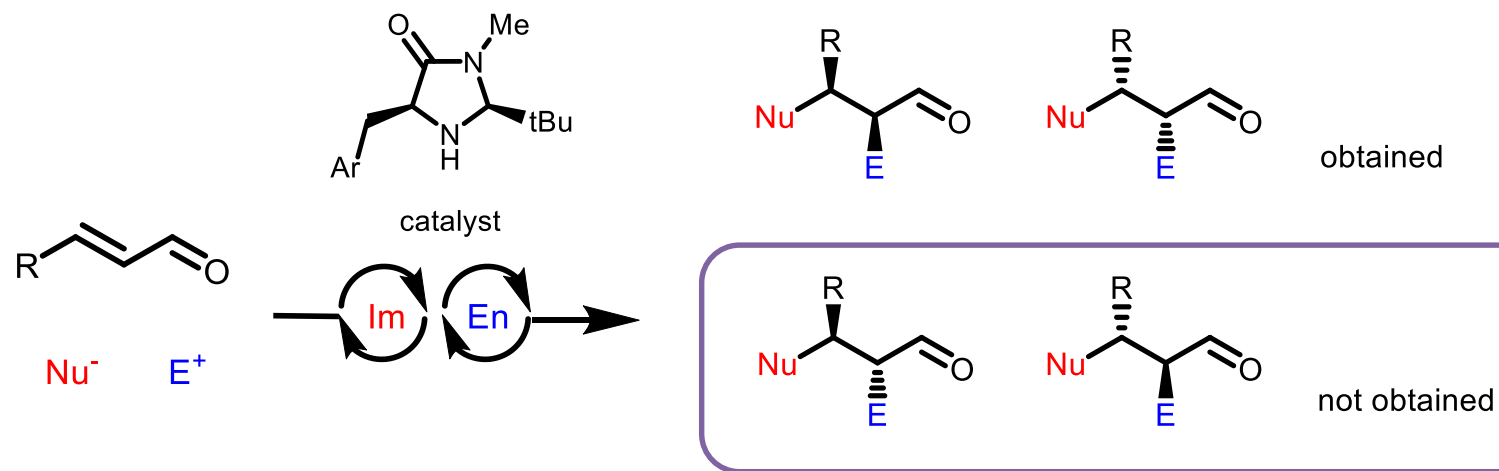
2. HOMO, LUMO-activation



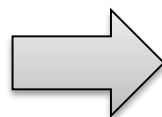
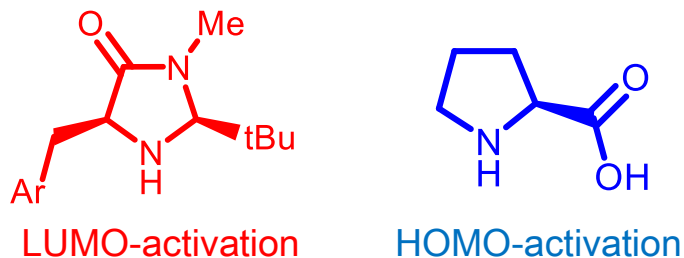
Problem of organocascade reaction

2. HOMO, LUMO-activation

Problem: diastereoselectivity

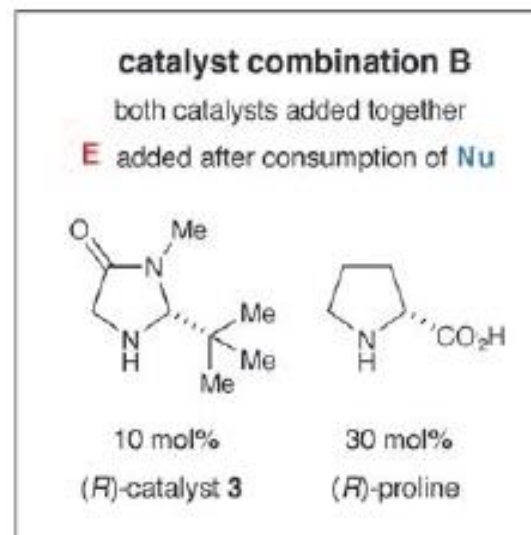
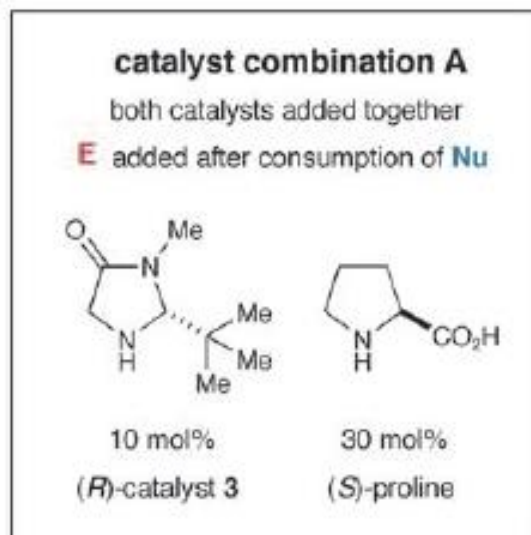
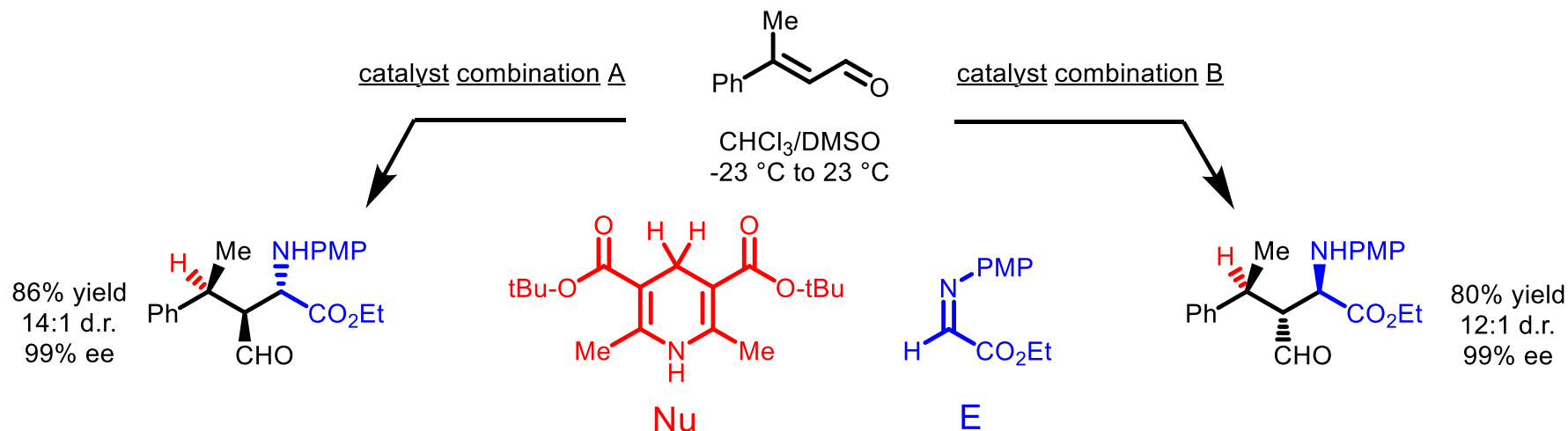


Solution: use different catalyst at respective cycle



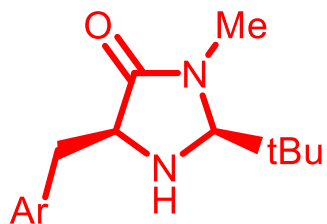
Cycle specific
organocascade reaction

Cycle-specific organocascade reaction ². HOMO, LUMO-activation

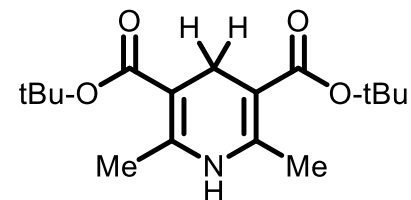
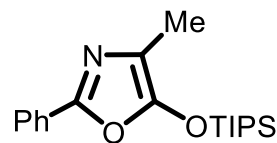
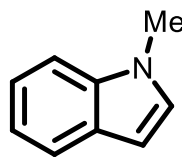
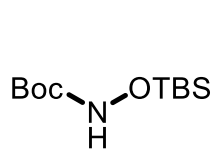


Limitation of electrophile

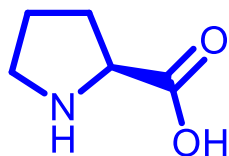
2. HOMO, LUMO-activation



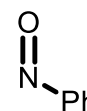
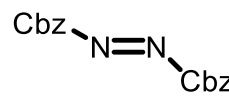
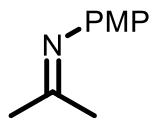
LUMO-activation



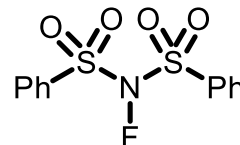
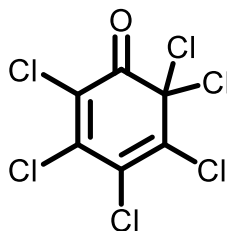
wide range of nucleophile



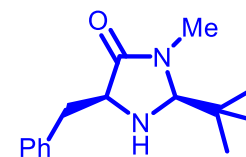
HOMO-activation



6-membered TS electrophile



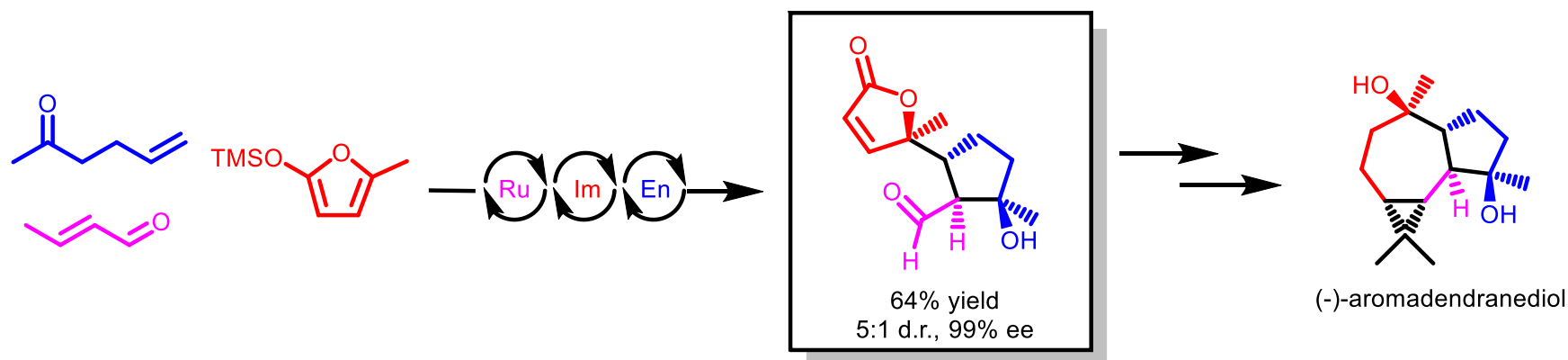
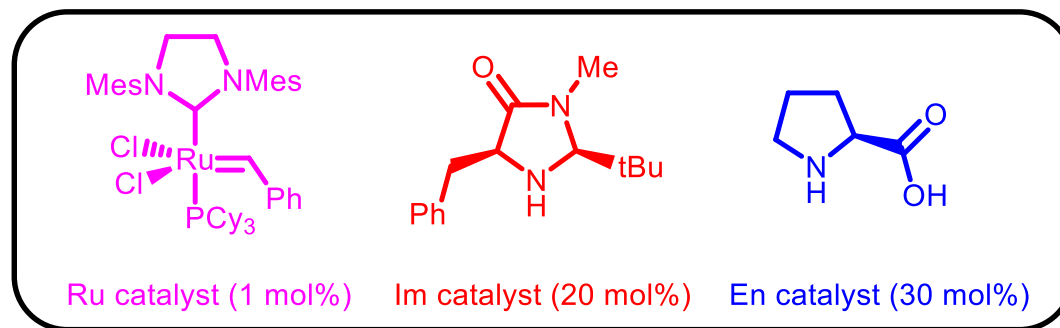
not 6-membered TS



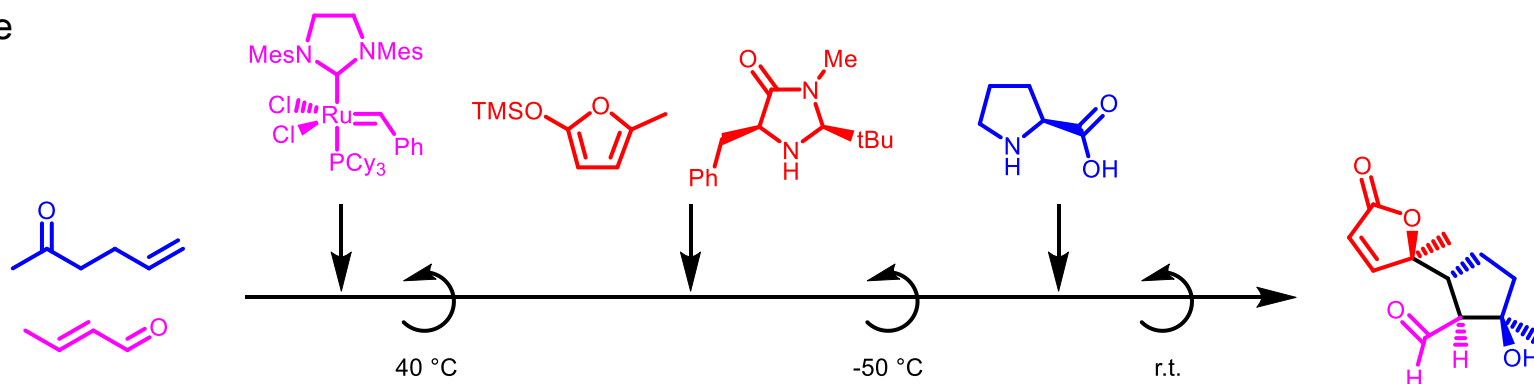
imidazolidinone
HOMO-activation

Application of cascade reaction

2. HOMO, LUMO-activation

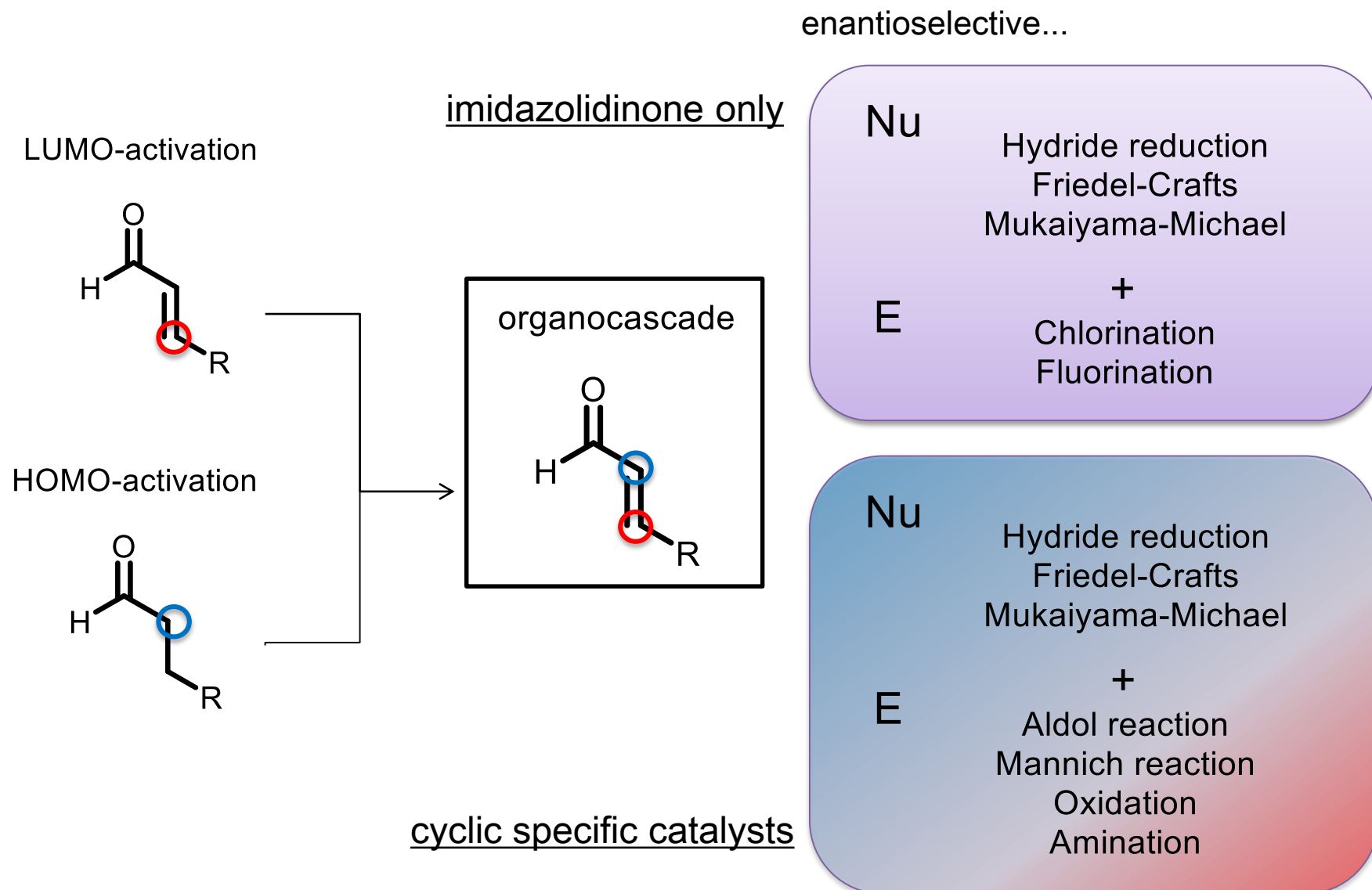


Timeline



Summary of organocascade reaction

2. HOMO, LUMO-activation



1. Introduction

2. HOMO, LUMO-activation

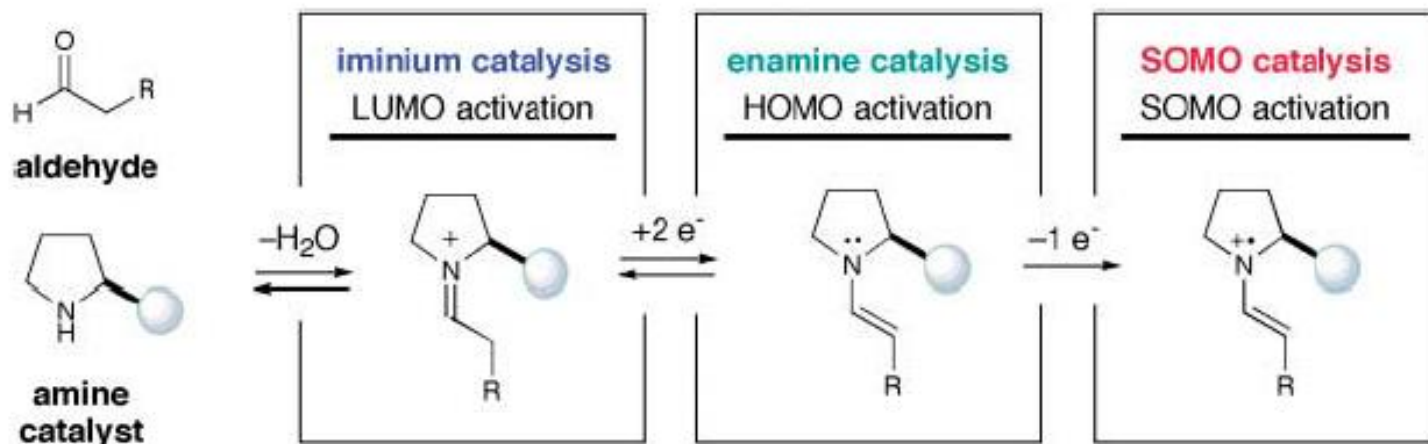
3. SOMO-activation

4. Metal-free SOMO-activation

5. Summary

The concept of SOMO-activation

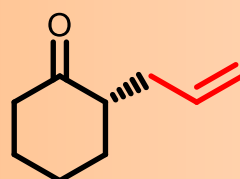
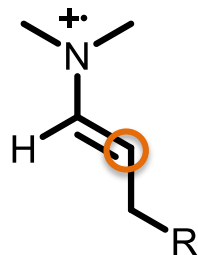
3. SOMO activation



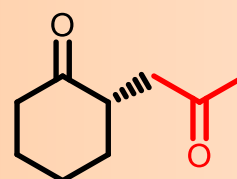
low ionization potential of enamine ... 3π electron system and radicalic addition

MacMillan, *et al.*, *Science*, 2007, 316, 582-585

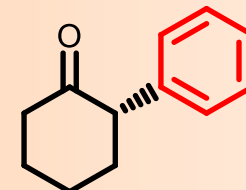
SOMO-activation



allylation



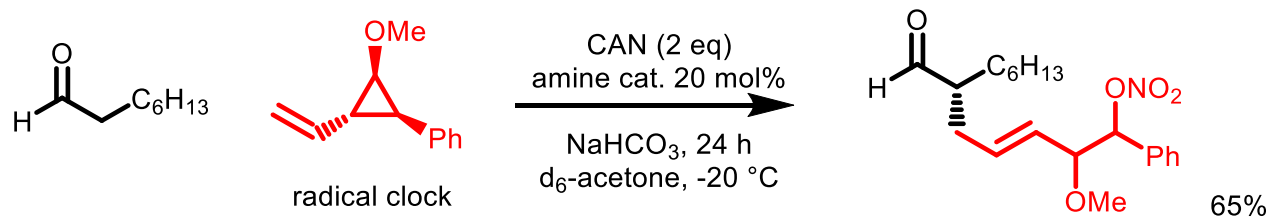
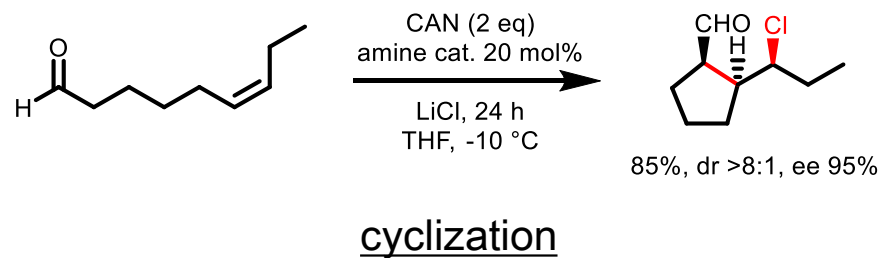
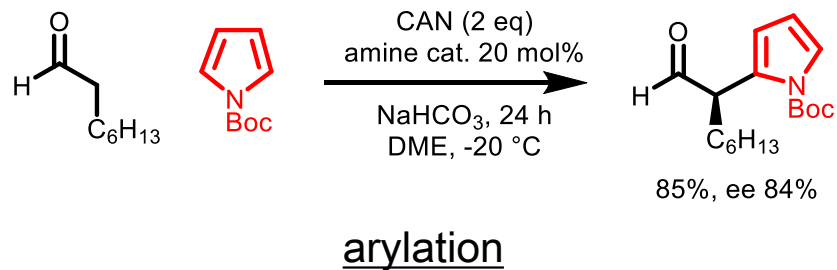
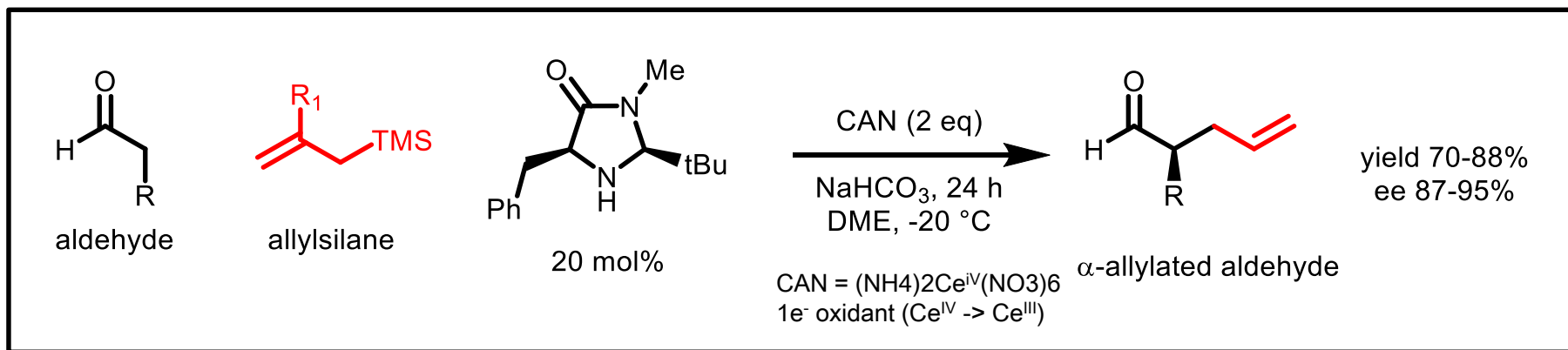
enolation



arylation

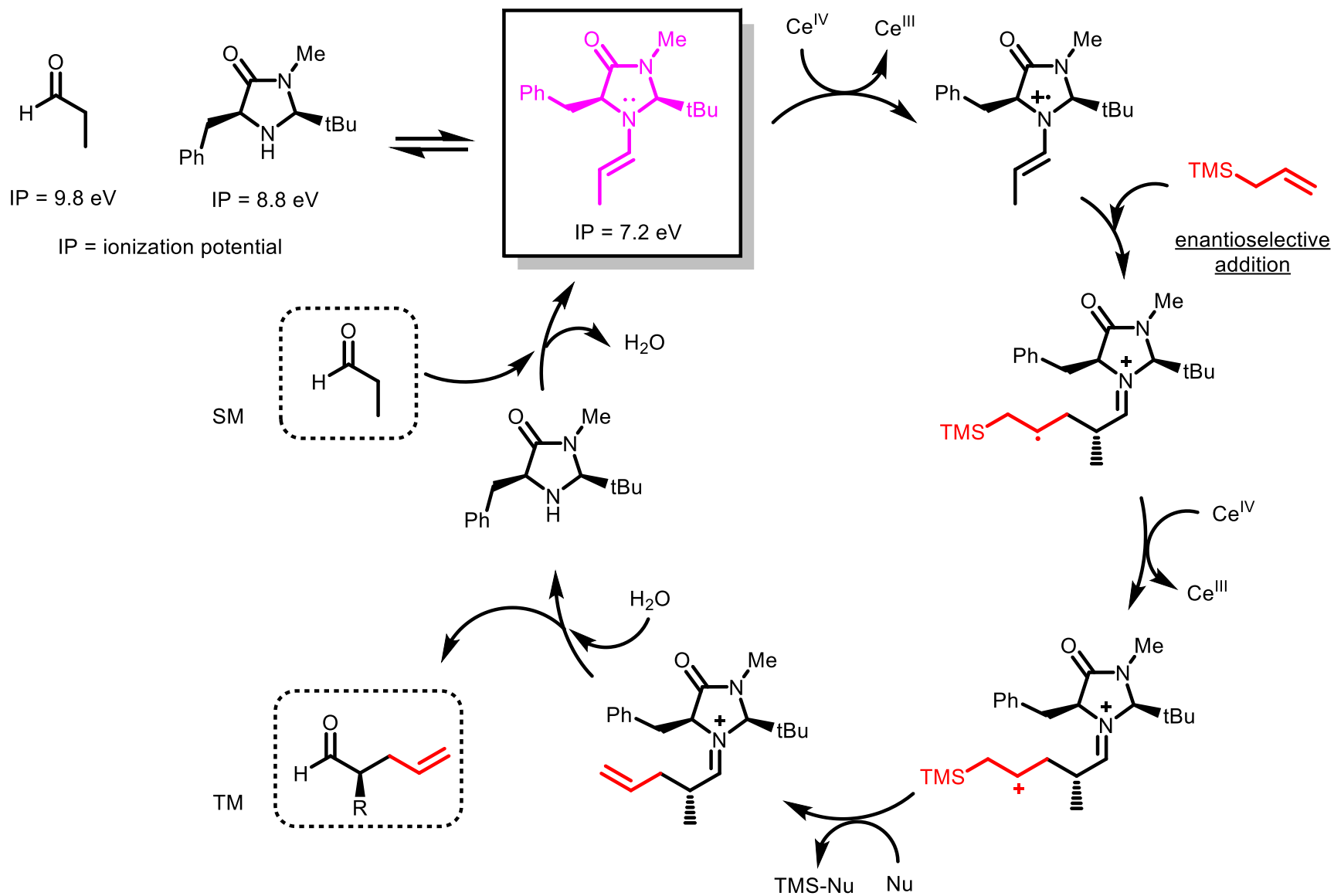
SOMO-activation by CAN

3. SOMO activation



Catalytic cycle of SOMO-activation

3. SOMO activation



Mechanistic study

3. SOMO activation

3 features of SOMO-activation by CAN

- Enamine selective oxidation
- Water concentration is critical (2 eq is good)
- Kinetic role of CAN is masked (heterogeneous)

Enamine formation

+ : Lewis acidity of Cerium cation

- : hydrolysis by H₂O

CAN
Ce(NO₃)₃ · 6H₂O } same reactivity for enamine formation

concentration of CAN: 0.03M (anhydrous), 0.39M (water 2 eq)

The role of water: hydrolysis of enamine, solve CAN

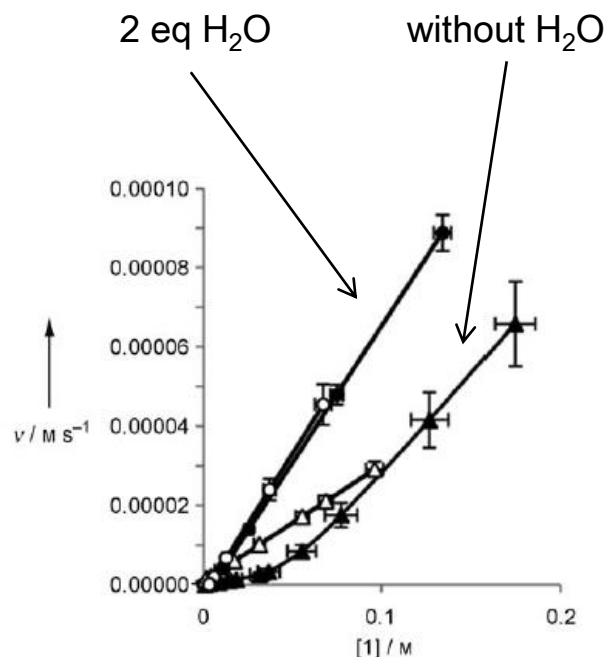
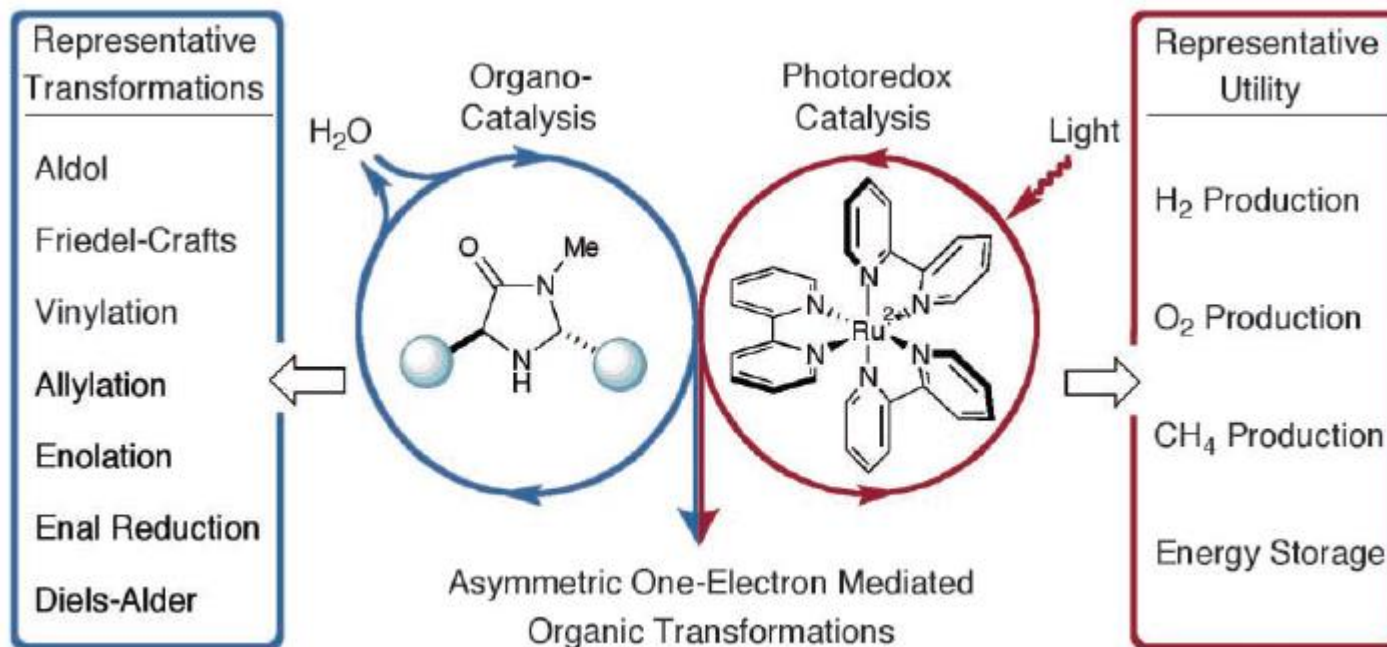


Figure 1. Rate vs. concentration of 1 for anhydrous same excess experiments for run 1 (▲) and run 2 (△) and same excess experiments with H₂O for run 3 (●) and run 4 (○).

Combination with photoredox catalyst

3. SOMO activation

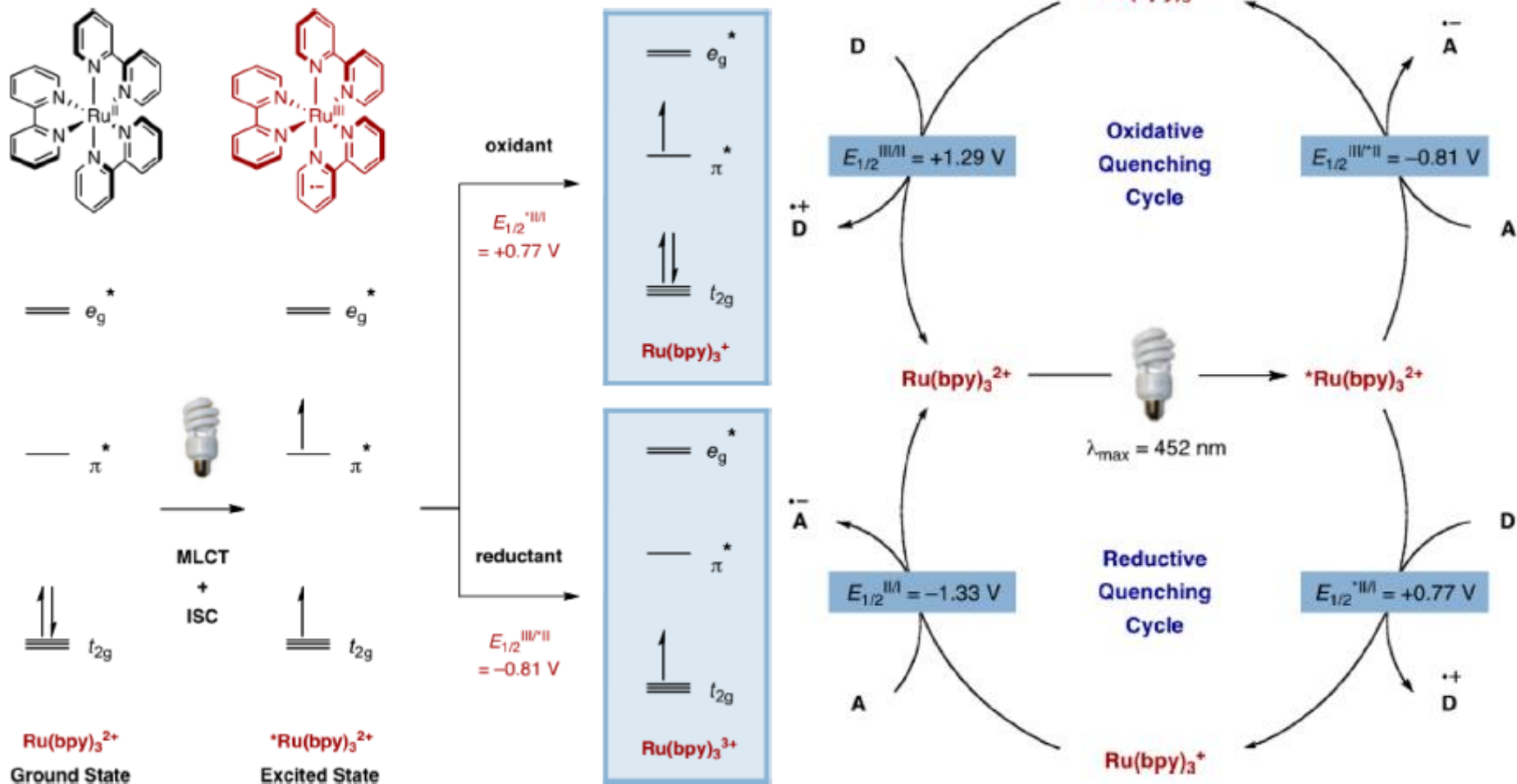


- ✓ First report of photoredox catalyst in organic chemistry
- ✓ Catalytic amount of redox reagent (CAN: 2 eq)

About photoredox catalyst

3. SOMO activation

activation by visible light and 2 types of quenching route

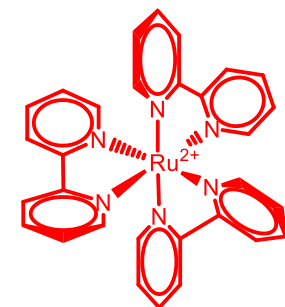
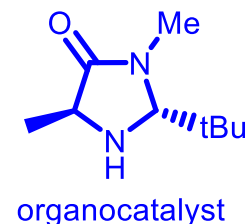
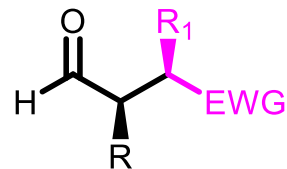
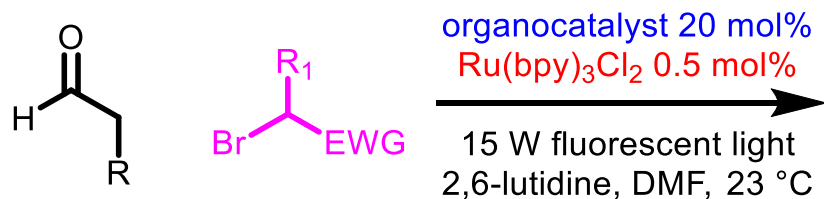


A=1e⁻ acceptor, D=1e⁻ donor

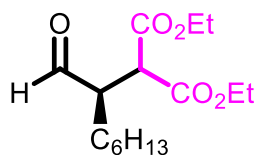
MLCT=metal to ligand charge transfer
ISC=intersystemcrossing

α -alkylation

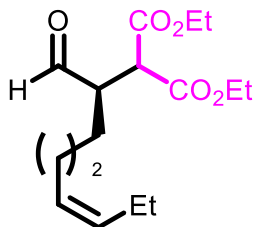
3. SOMO activation



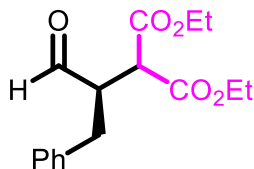
photoredox catalyst



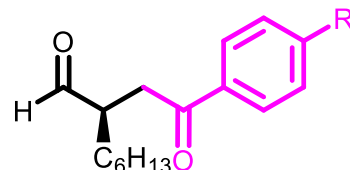
93%, 90% ee



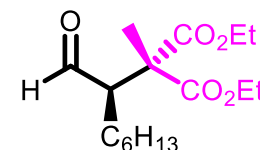
86%, 90% ee



92%, 90% ee



R=H 84%, 96% ee
R=OMe 87%, 96% ee
R=NO₂ 84%, 95% ee



80%, 88% ee

- ✓ Olefin, benzyl tolerate (Ru cat don't produce allylic radical and benzyl radical)
- ✓ Wide scope of substituent of phenyl moiety
- ✓ Addition of tertially alkyl moiety to α -position of C=O

Catalytic cycle

3. SOMO activation

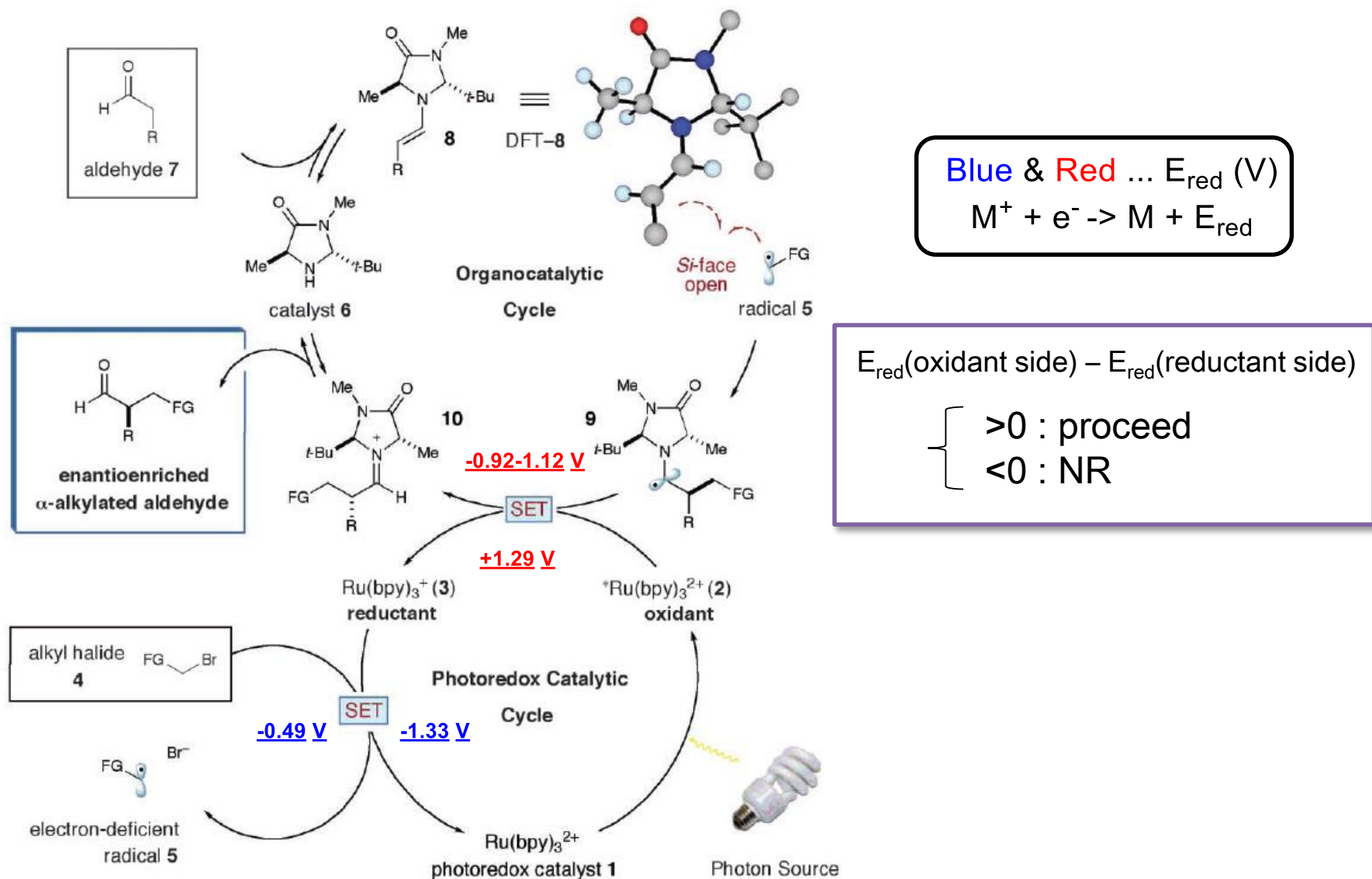
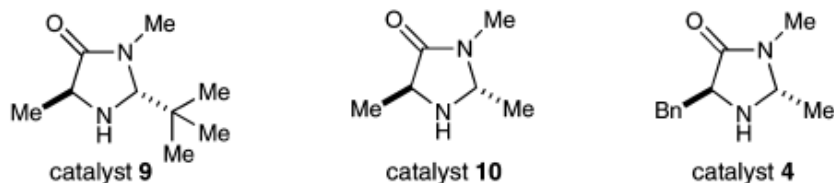
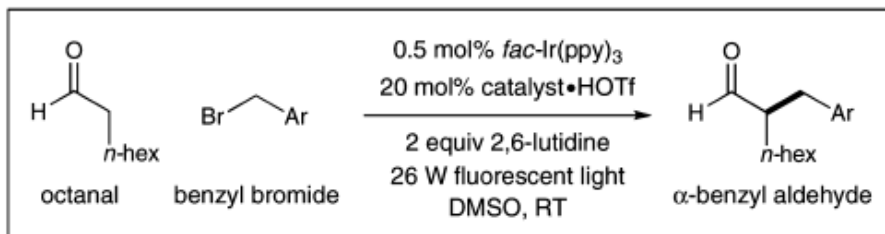


Fig. 2. Merging photoredox catalysis with organocatalysis. Proposed mechanism. *t*-Bu, *tert*-butyl.

Ir(ppy)₃ catalyst

3. SOMO activation

Ir cat. passes reductive quenching route



entry	Ar	catalyst	% yield ^a	% ee ^b
1	Phenyl	9	0	ND
2	2,4-(NO ₂) ₂ C ₆ H ₃	9	74	97
3	2,4-(NO ₂) ₂ C ₆ H ₃	10	93	82
4	2,4-(NO ₂) ₂ C ₆ H ₃	4	94	92
5 ^c	4-Pyridinyl	9	0	ND
6 ^c	4-Pyridinyl	10	81	78
7 ^c	4-Pyridinyl	4	86	90

^a Isolated yields. ^b Enantiomeric excess determined by chiral HPLC.

^c 4-(Bromomethyl)pyridine added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine.

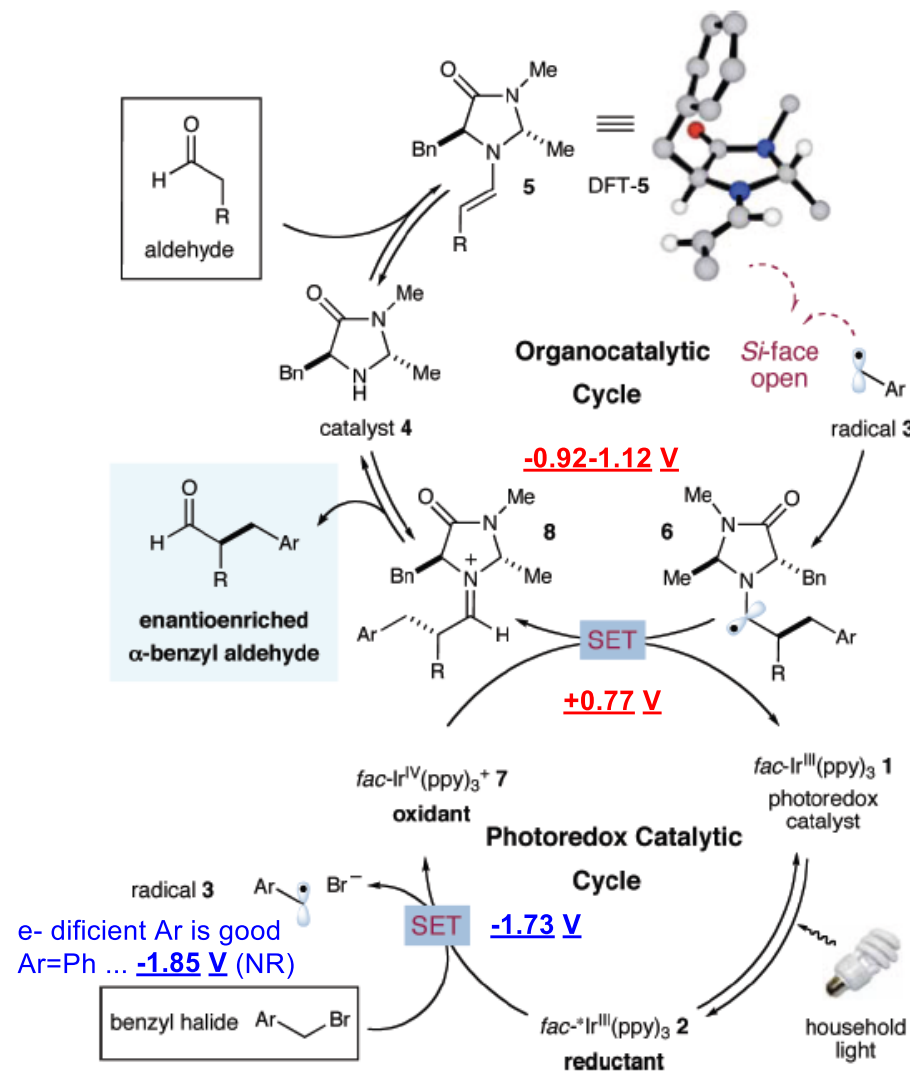
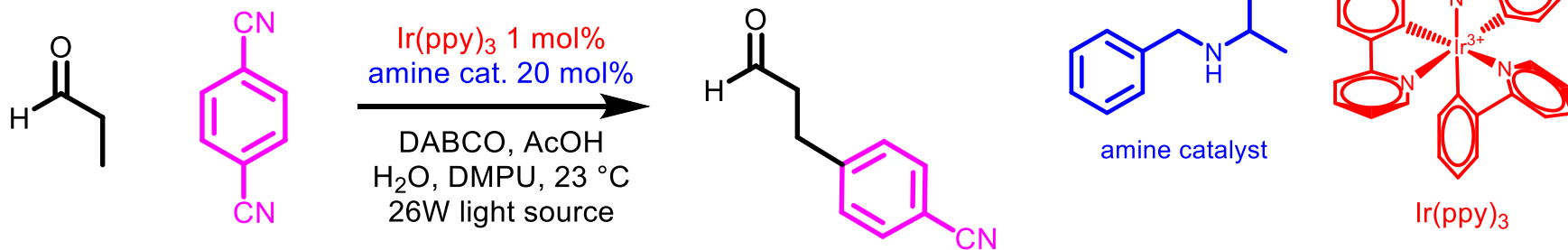


Figure 1. Proposed catalytic cycle for aldehyde α-benylation.

SOMO- β -activation

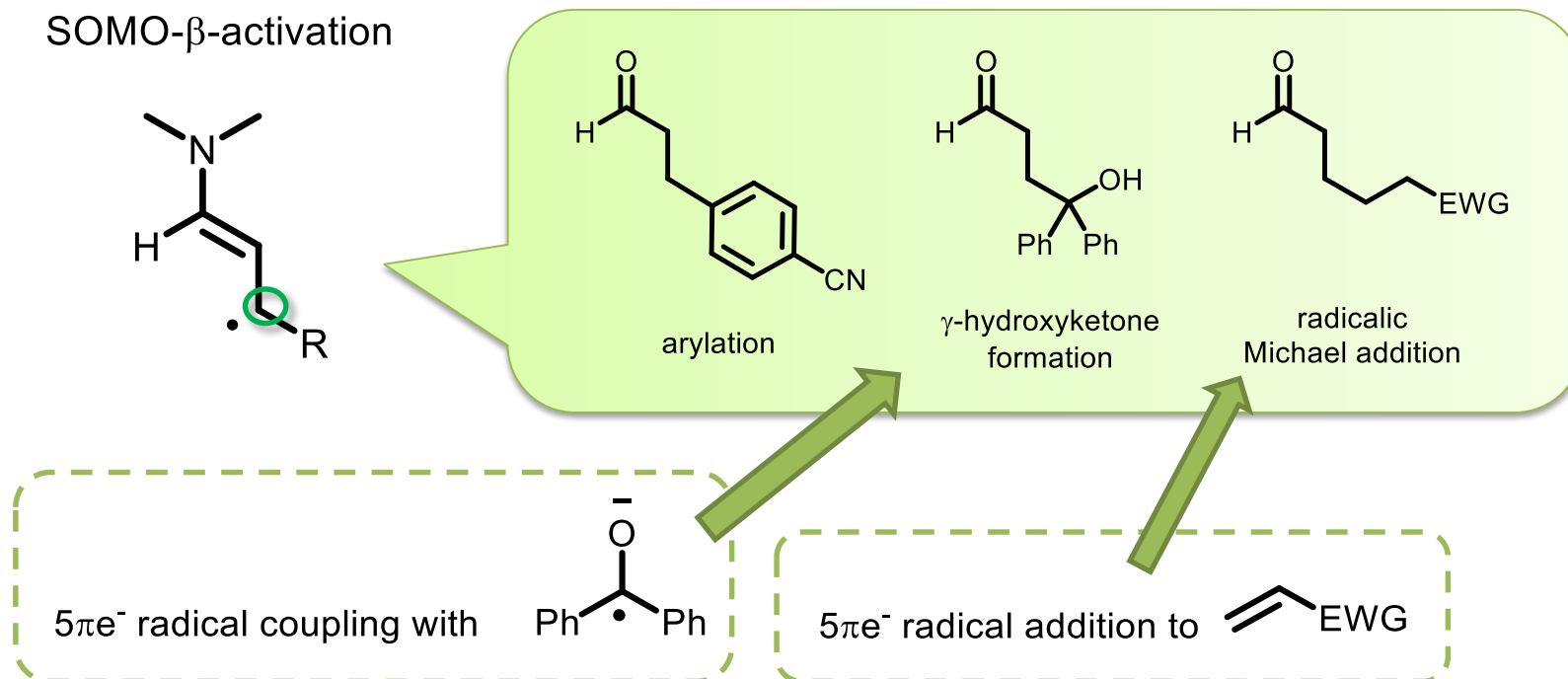
3. SOMO activation

New type of enamine activation



MacMillan, *et al.*, *Science*, 2013, 339, 1593-1596

SOMO- β -activation



β -allylation - mechanism

3. SOMO activation

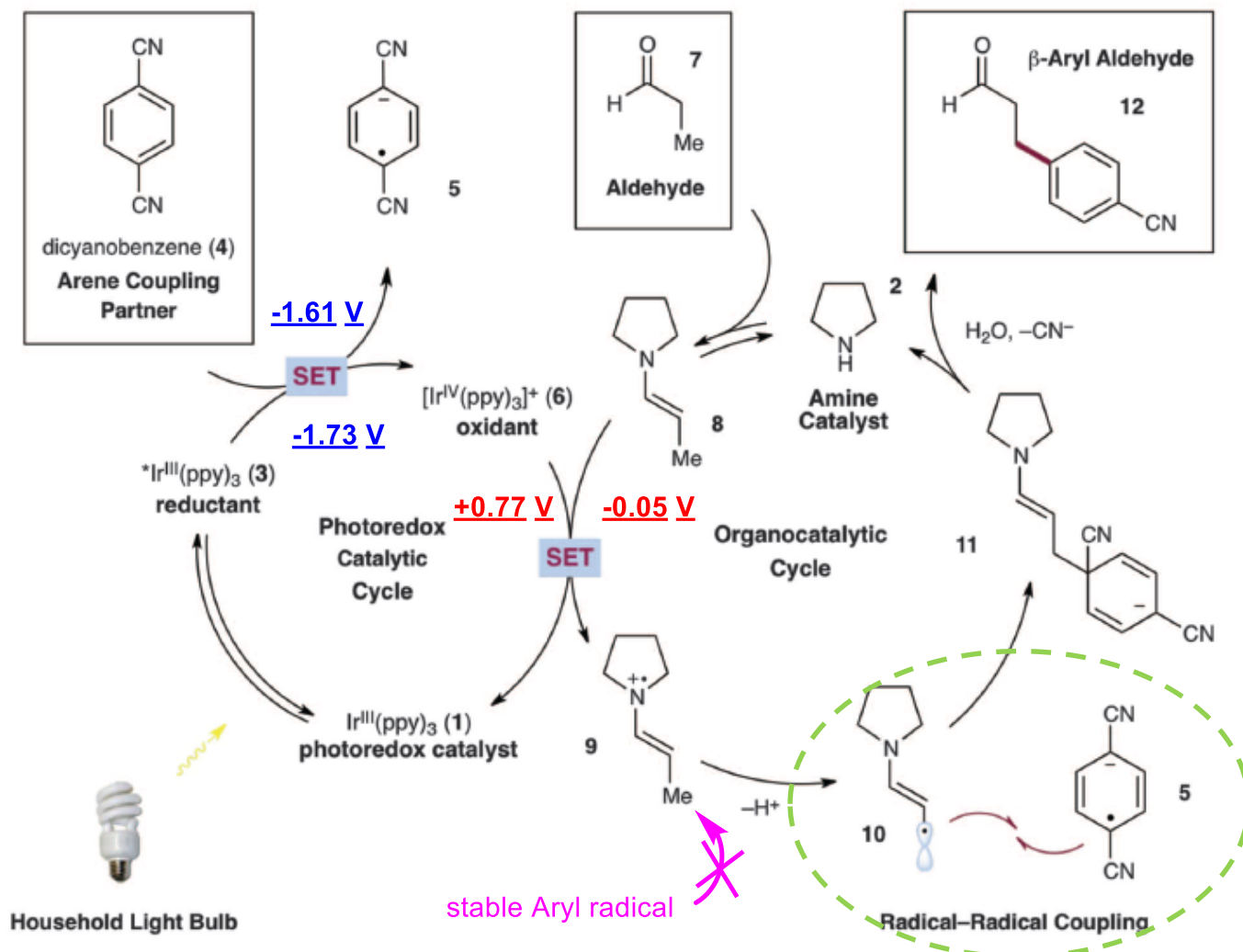
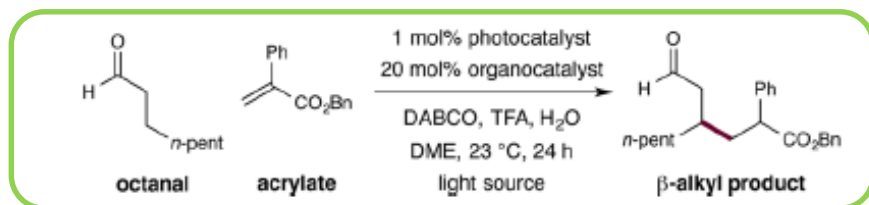


Fig. 2. Photoredox C-H β -arylation: Proposed mechanistic pathway (Me, methyl).

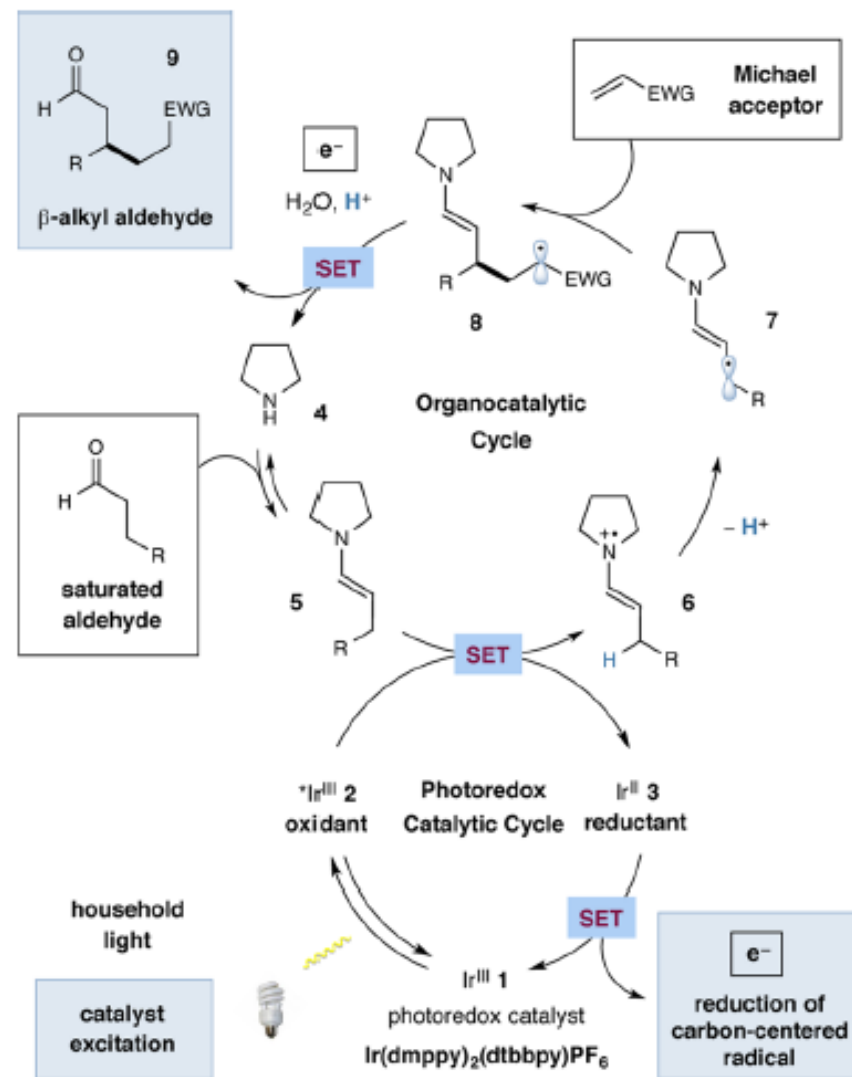
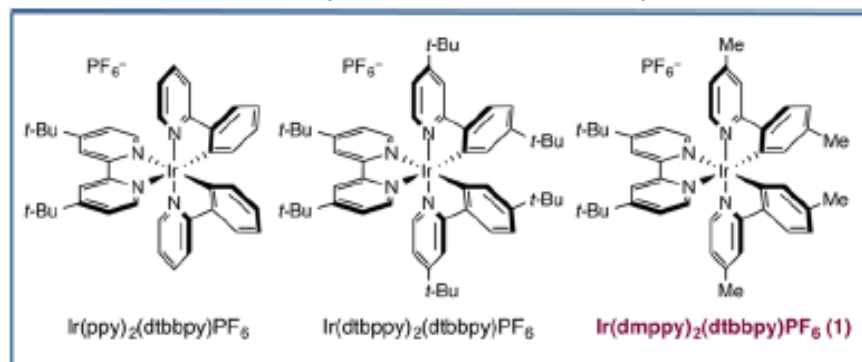
Michael addition of SOMO- β -activation

3. SOMO activation



entry	photocatalyst	organocatalyst	light source	yield ^a (%)
1	Ir(ppy) ₃	<i>i</i> -Bu ₂ NH	26 W CFL	7
2	Ru(bpy) ₃ Cl ₂	<i>i</i> -Bu ₂ NH	26 W CFL	50
3	Ir(ppy) ₂ (dtbbpy)PF ₆	<i>i</i> -Bu ₂ NH	26 W CFL	52
4	Ir(ppy) ₂ (dtbbpy)PF ₆	<i>i</i> -Bu ₂ NH	blue LEDs	64
5	Ir(ppy) ₂ (dtbbpy)PF ₆	pyrrolidine	blue LEDs	6
6	Ir(ppy) ₂ (dtbbpy)PF ₆	<i>i</i> -Pr ₂ NH	blue LEDs	77
7	Ir(ppy) ₂ (dtbbpy)PF ₆	Cy ₂ NH	blue LEDs	80
8	Ir(dtbbpy) ₂ (dtbbpy)PF ₆	Cy ₂ NH	blue LEDs	56
9 ^b	Ir(dmppy) ₂ (dtbbpy)PF ₆	Cy ₂ NH	blue LEDs	84
10 ^c	Ir(dmppy) ₂ (dtbbpy)PF ₆	Cy ₂ NH	blue LEDs	0
11	Ir(dmppy) ₂ (dtbbpy)PF ₆	Cy ₂ NH	none	0
12	none	Cy ₂ NH	blue LEDs	0
13	Ir(dmppy) ₂ (dtbbpy)PF ₆	none	blue LEDs	0

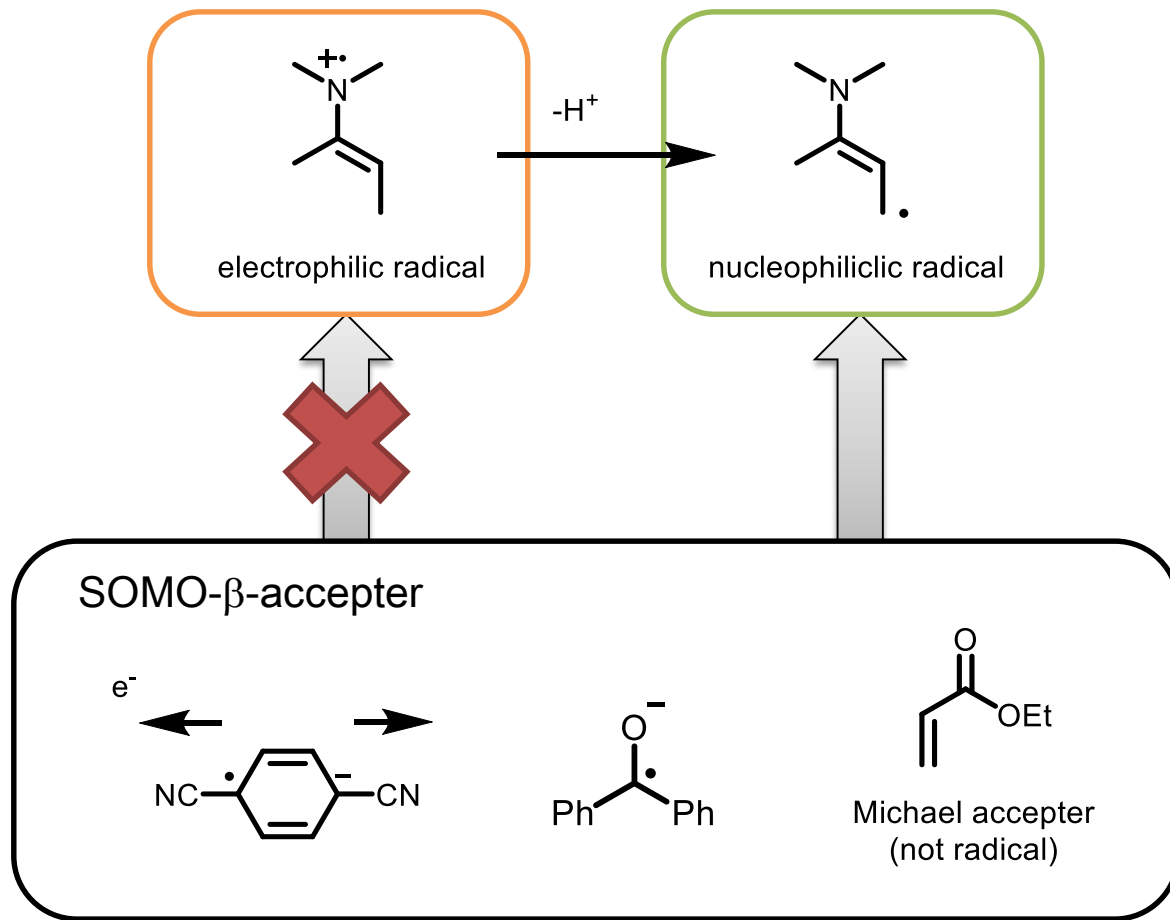
entry9: reaction time 12 h / entry10: without DABCO



MacMillan, *et al.*, *J. Am. Chem. Soc.*, 2014, 136, 6858-6861

Limitation of β -allylation

3. SOMO activation



- Acceptor should stabilize radical anion. (EWG aryl / ketyl radical)
- Not radical acceptor (alkylation)

1. Introduction

2. HOMO, LUMO-activation

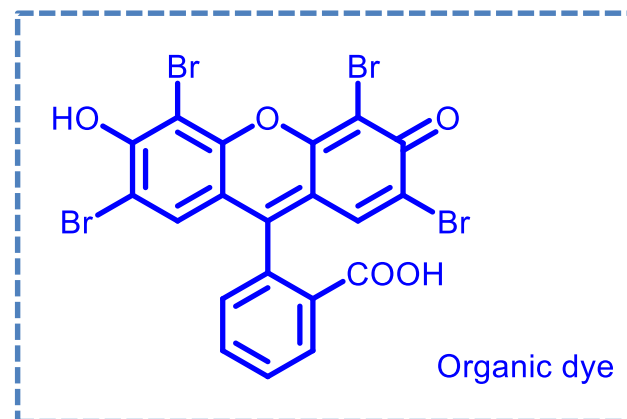
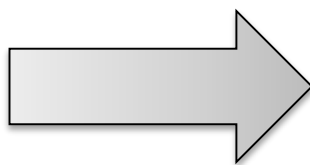
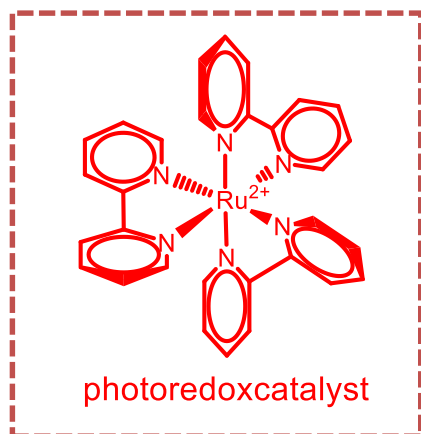
3. SOMO-activation

4. Metal-free SOMO-activation

5. Summary

- HOMO, LUMO-activation ... imidazolidinone or proline catalyst (organocatalyst)
- SOMO-activation ... imidazolidinone + photoredoxcatalyst (Ru, Ir)

potentially toxic for environment

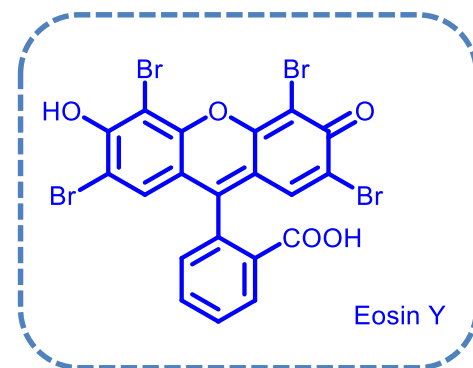
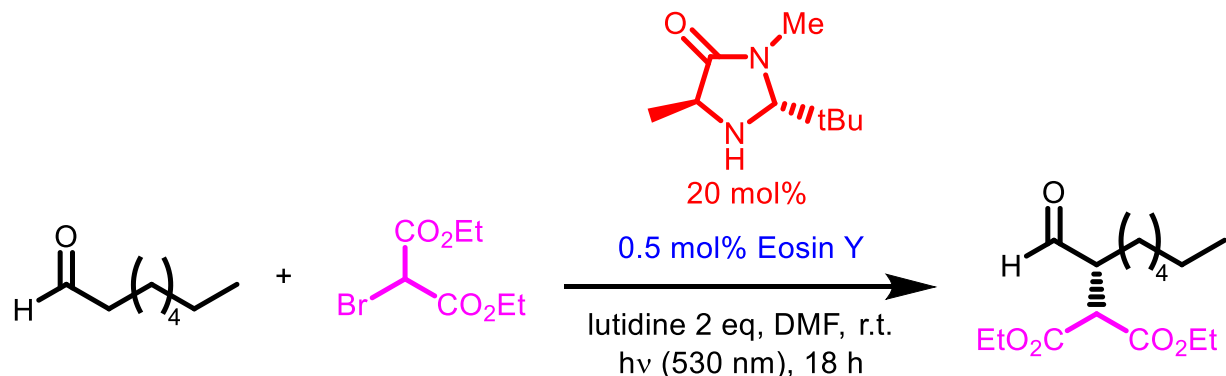


Use organic dye for photoredox catalyst

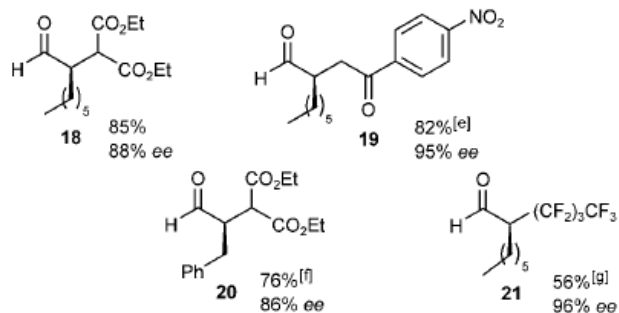
- ✓ low cost
- ✓ non toxic (= environmental friendly)
- ✓ activated by visible light (especially green light)

Alkylation by organic dye catalyst

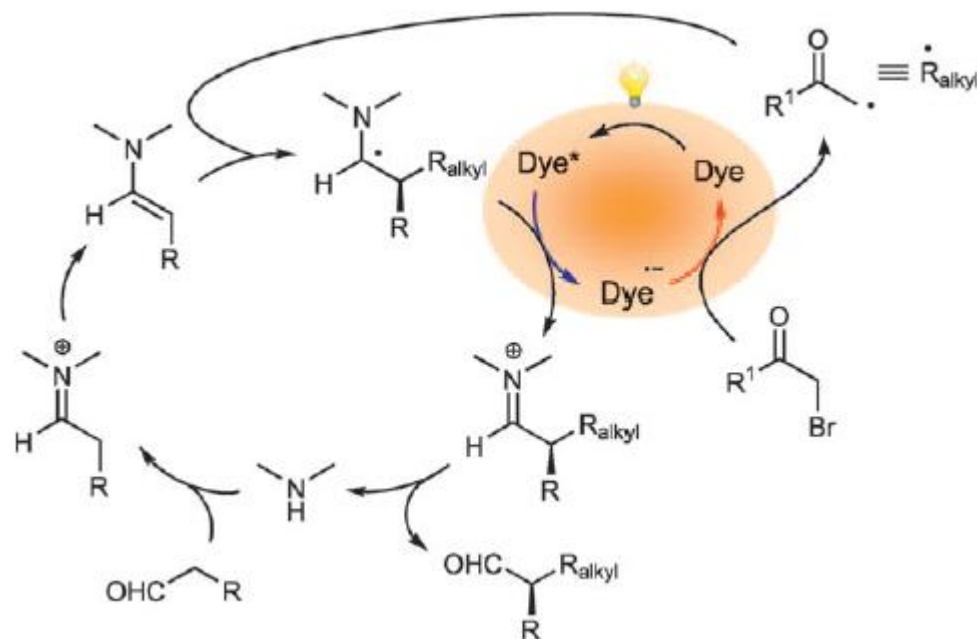
4. Metal-free SOMO activation



Entry	Variation from the standard conditions ^[a]	Yield [%] ^[b]	ee [%] ^[d]
1	none	63	77
2	23 W fluorescent bulb instead of LED	78	80
3	23 W fluorescent bulb instead of LED and [Ru(bpy) ₃]Cl ₂ (8)	75	76
4	T = 0 °C	70	81
5	T = -5 °C	85	88
6	sunlight (T ≈ 30 °C) ^[d]	77	76



[a] Standard conditions as described above. [b] Yield of isolated products. [c] Enantiomeric excess was determined as reported in Ref. [8a]. [d] Full conversion was reached after approximately 4 h. [e] Reaction was performed at +5 °C; *p*-NO₂-phenacyl bromide was used. [f] Phenylpropionaldehyde was used instead of octanal. [g] Reaction was performed at -15 °C; 1-iodoperfluorobutane was used instead of diethyl bromomalonate.



Consecutive PET

4. Metal-free SOMO activation

PDI gains high reductivity from photoactivation by two photons

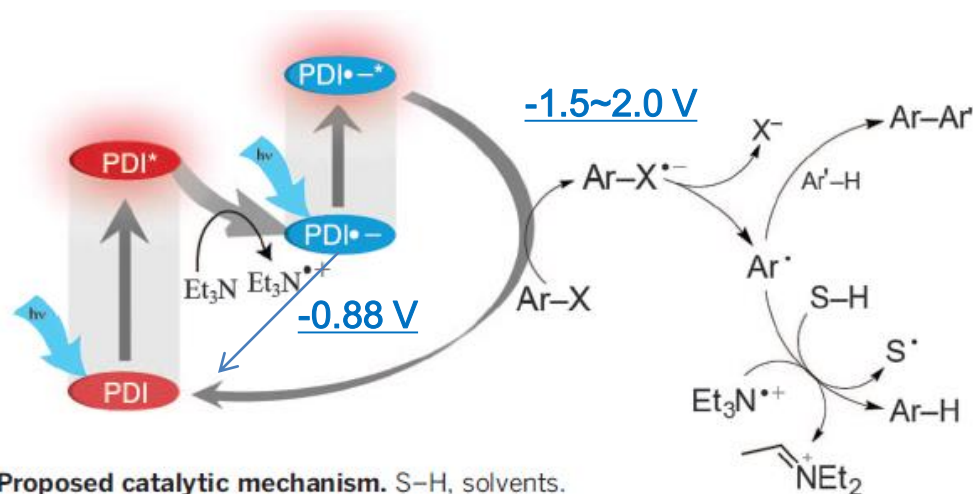
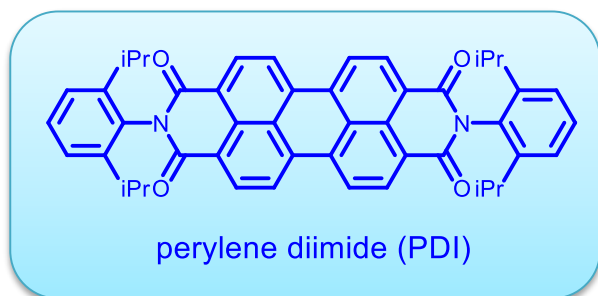
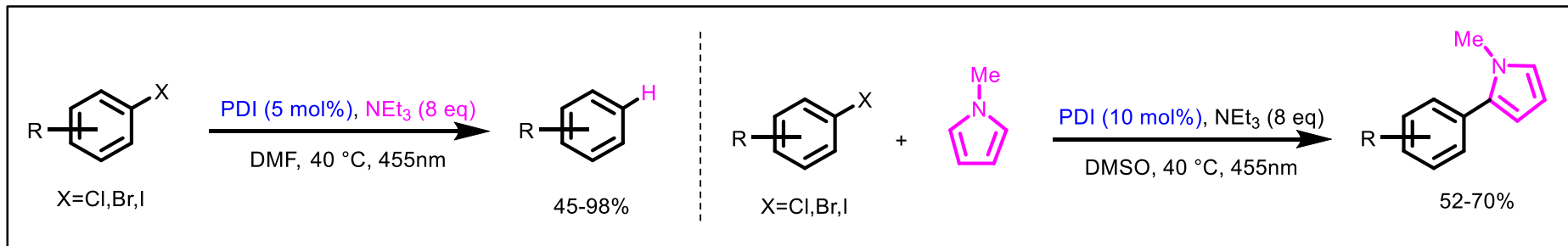


Fig. 4. Proposed catalytic mechanism. S-H, solvents.

- Stability of $\text{PDI}^{\bullet-}$ is important for second activation
- Exceeds reduction energy of $\text{PDI}^{\bullet-}$ to Ar-Cl (high reduction energy)
- Potential to stronger photoredox catalyst than Ru, Ir
- R = EWG only

1. Introduction

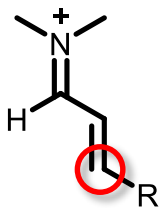
2. HOMO, LUMO-activation

3. SOMO-activation

4. Metal-free SOMO-activation

5. Summary

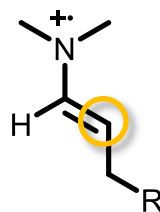
LUMO-activation



Imidazolidinone activation

Diels-Alder,
Hydride reduction
Mukaiyama-Michael

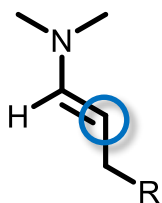
SOMO-activation



CAN (2 eq) activation
low IP of enamine
addition of water
allylation

Photoredox
 $\text{Ru}(\text{bpy})_2\text{Cl}_2$, $\text{Ir}(\text{ppy})_3$
alkylation

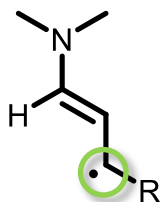
HOMO-activation



Proline activation
(6-membered ring TS)

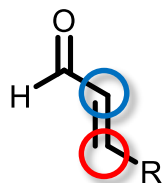
Imidazolidinone activation
(not 6-membered ring TS)

SOMO- β -activation



$\text{Ir}(\text{ppy})_3$
stable radical anion partner
 β -arylation
 γ -hydroxyketone
radical Michael addition

organocascade

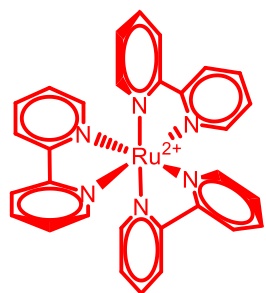


Imidazolidinone only
 $\rightarrow \text{HCl}$, HF addition

Cyclic specific catalyst
 \rightarrow Hydride reduction
+aldol, oxidation, amination

Summary-2

photoredox catalyst

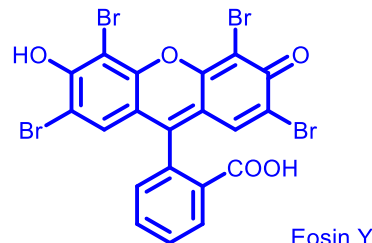


$\text{Ru}(\text{bpy})_3\text{Cl}_2$

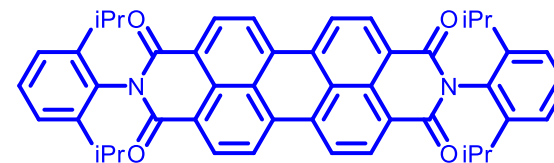


$\text{Ir}(\text{ppy})_3$

Metal photoredox



Eosin Y



perylene diimide (PDI)

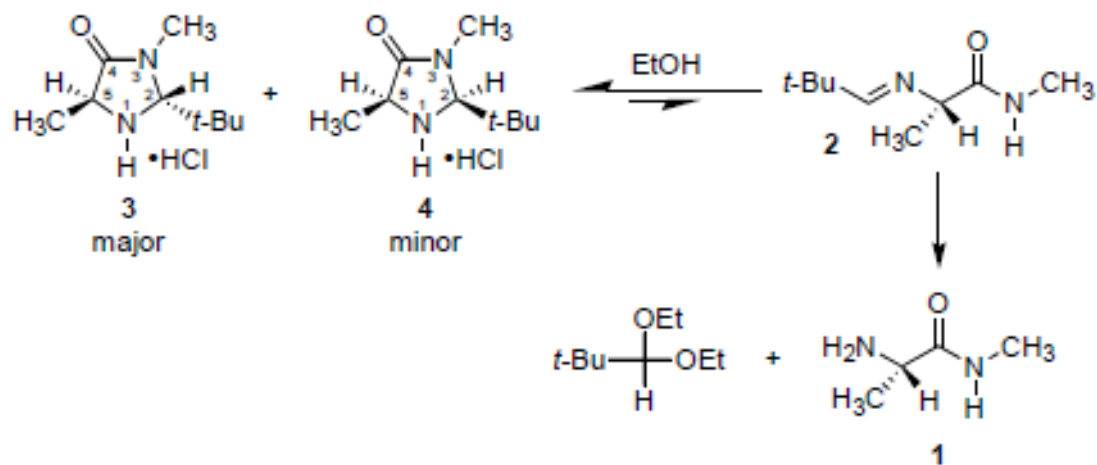
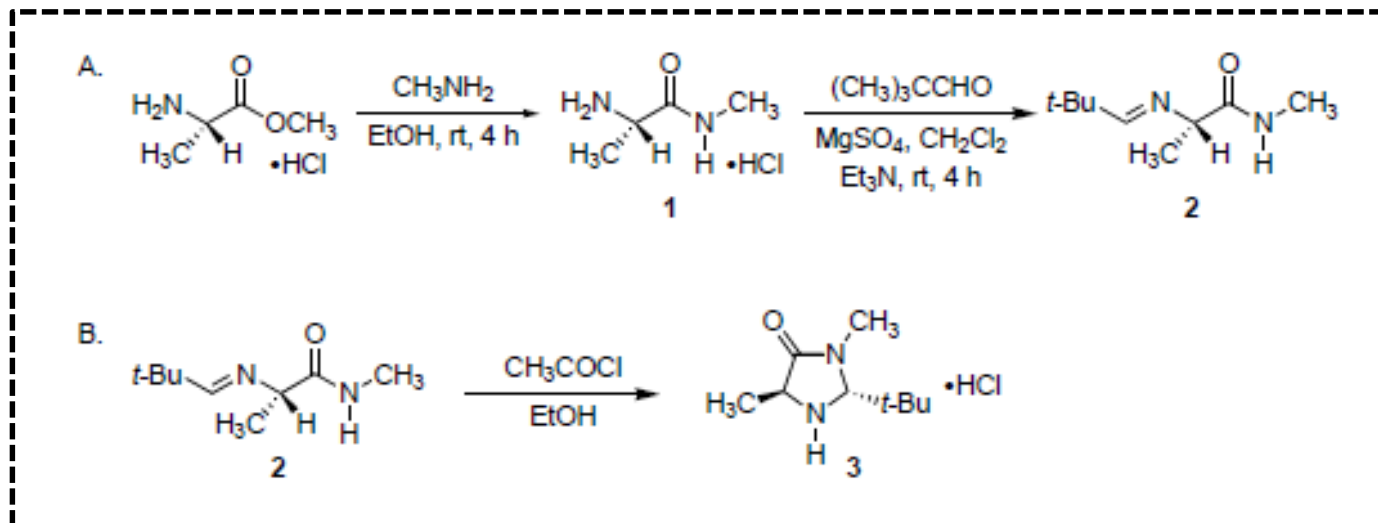
Metal-free photoredox

- ✓ high reactivity
- ✓ easy to change reactivity (ligand modification)
- high cost
- potential toxic

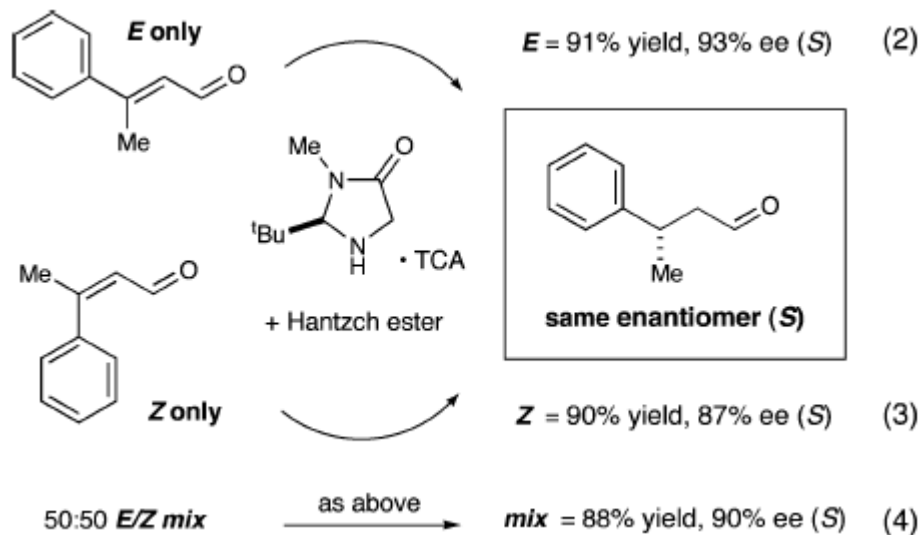
- ✓ low cost
- ✓ non toxic (= environmental friendly)
- stability (catalyst is radical reactant)

Appendix

Synthesis of imidazolidinone from amino acid



Hydride reduction of E/Z mixture

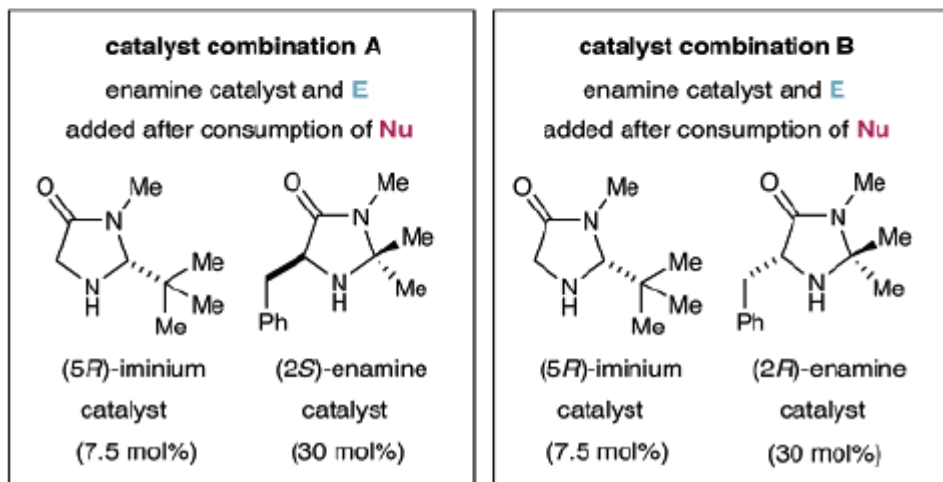
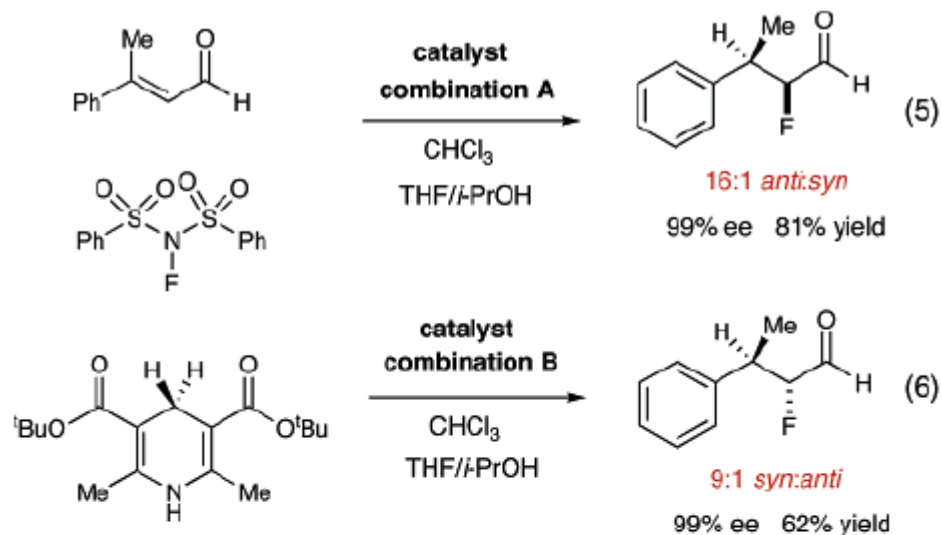


amine cat accelerate isomerization of E/Z intermediate

Table 3. Effect of Aldehyde Substituents on EOHR

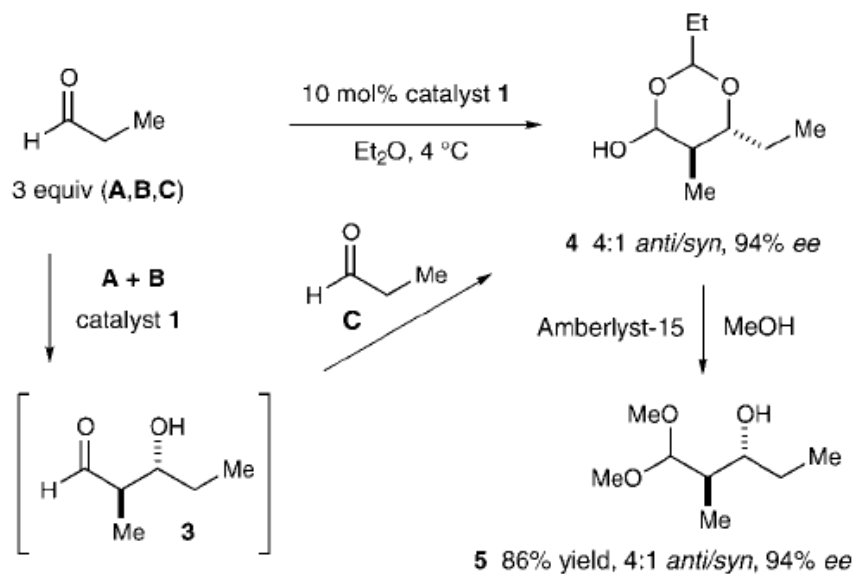
entry	E:Z substrate	product	time (h)	% yield	% ee ^a
1	> 20:1		23	91	93 ^b
2	> 20:1		48	79	94 ^{b,c}
3	> 20:1		16	74	94
4	> 20:1		16	92	97
5	5:1		10	91	96 ^b
6	3:1		23	95	91 ^c
7	> 20:1		26	83 ^d	91 ^f
8	> 20:1		72	74	90
9	> 20:1		0.5	95 ^d	97 ^e

Imidazolidinone & imidazolidinone cascade



-20 °C 30 h → -10 °C 12 h

Aldol reaction by imidazolidinone catalyst



Scheme 3. Imidazolidinone-catalyzed aldol reaction: initial results.

aldol reaction ... proceeds at 4 °C

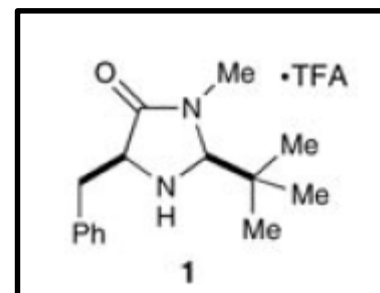


Table 1: Imidazolidinone-catalyzed direct aldol condensation: reaction scope.

Entry	R ¹	R ²	Product	Yield [%] ^[a]	<i>anti/syn</i> ^[b]	<i>ee</i> [%] ^[c,d]
1	Me	Me		86	4:1	94
2	Me	<i>i</i> Pr		90	5:1	95
3	Me	<i>c</i> -C ₆ H ₁₁		81	5:1	97
4	Me	Ph		61	4:1	93

Redox potential of photoredox catalysts

Table 1. Redox Potentials and Selected Photophysical Properties of Commonly Utilized Visible Light Photocatalysts^a

entry	photocatalyst	$E_{1/2}$ (M ⁺ /M [*])	$E_{1/2}$ (M [*] /M ⁻)	$E_{1/2}$ (M ⁺ /M)	$E_{1/2}$ (M/M ⁻)	excited-state lifetime, τ (ns)	excitation λ_{\max} (nm)	emission λ_{\max} (nm)	ref
1	Ru(bpm) ₃ ²⁺	-0.21	+0.99	+1.69	-0.91	131 ^b	454	639 ^b	161
2	Ru(bpz) ₃ ²⁺	-0.26	+1.45	+1.86	-0.80	740	443	591	55
3	Ru(bpy) ₃ ²⁺	-0.81	+0.77	+1.29	-1.33	1100	452	615	1, 3
4	Ru(phen) ₃ ²⁺	-0.87	+0.82	+1.26	-1.36	500	422	610 ^c	1, 129
5	Ir[dF(CF ₃) ppy] ₂ (dtbbpy) ⁺	-0.89	+1.21	+1.69	-1.37	2300	380	470	77
6	Ir(ppy) ₂ (dtbbpy) ⁺	-0.96	+0.66	+1.21	-1.51	557		581	58, 77
7	Cu(dap) ₂ ⁺	-1.43		+0.62		270		670 ^d	33
8	fac-Ir(ppy) ₃	-1.73	+0.31	+0.77	-2.19	1900	375	494 ^e	38

^aAll potentials are given in volts versus the saturated calomel electrode (SCE). Measurements were performed in acetonitrile at room temperature unless otherwise noted. ^bDetermined in propylene carbonate. ^cDetermined in aqueous solution. ^dDetermined in dichloromethane. ^eDetermined in 1:1 ethanol/methanol glass at 77 K.

MacMillan, *et al.*, *Chem. Rev.*, 2013, 113, 5322-5363

Ground state redox potentials obtained:

$$E_{1/2}^{\text{III/II}} = -1.479 \text{ V vs. Ag/AgCl } (-1.524 \text{ V vs. SCE})$$

cyclic voltammetry data of Ir(dmppy)₂(dtbbpy)₂

$$E_{1/2}^{\text{IV/III}} = +1.253 \text{ V vs. Ag/AgCl } (+1.208 \text{ V vs. SCE})$$

Excited state redox potentials calculated from ground-state potentials and $\lambda_{\max}(\text{emission}) = 597$ nm

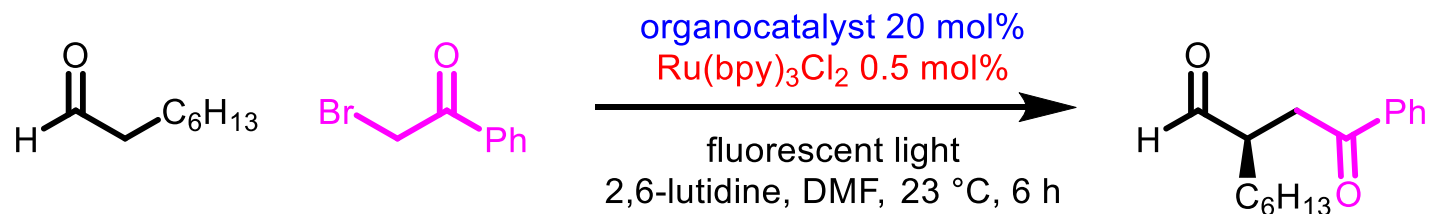
$$E_{0,0} = 2.076 \text{ eV}$$

$$E_{1/2}^{\text{*III/II}} = +0.552 \text{ V vs. SCE}$$

$$E_{1/2}^{\text{*IV/III}} = -0.868 \text{ V vs. SCE}$$

MacMillan, *et al.*, *J. Am. Chem. Soc.*, 2014, 136, 6858-6861

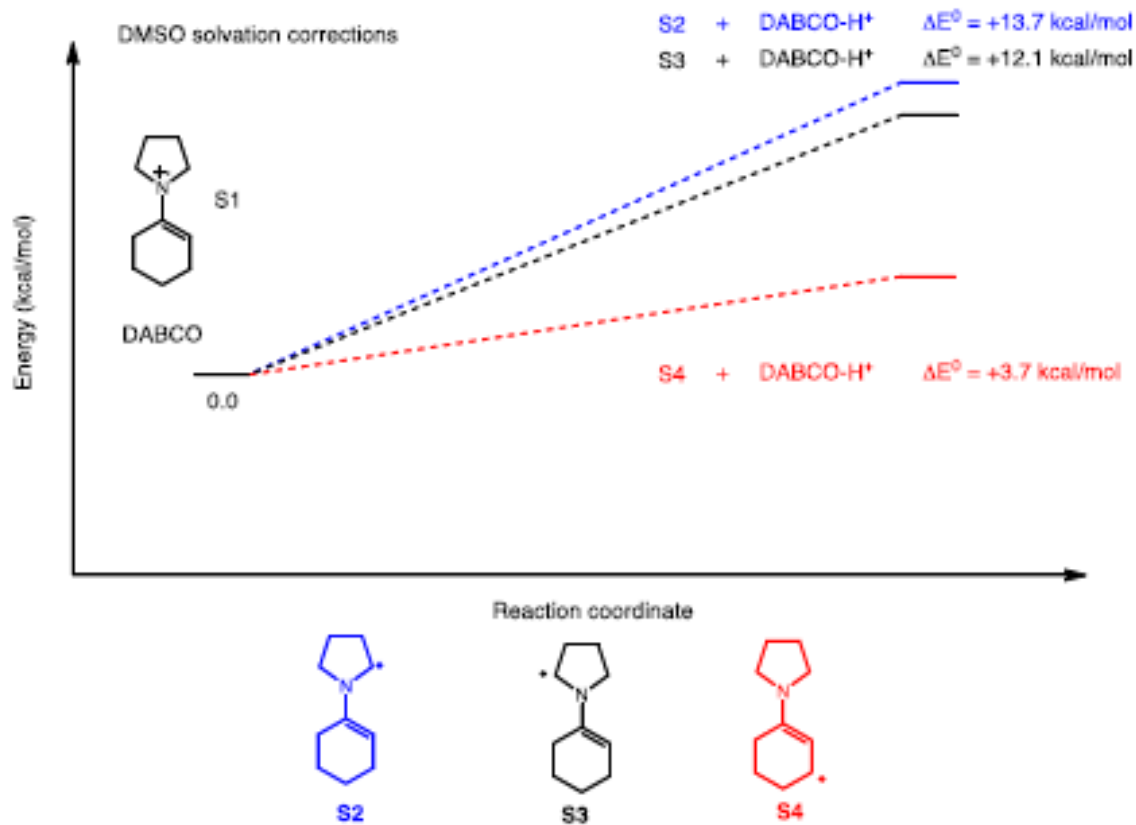
α -alkylation



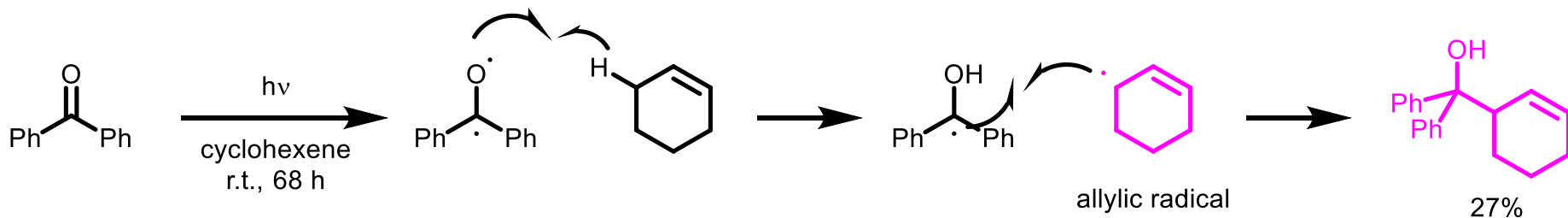
entry	light	Ru(bpy) ₃ Cl ₂	yield
1	15-W fluorescent bulb	○	84%
2	-	○	no rxn
3	15-W fluorescent bulb	-	<10%
4	UV (300-350 nm)	-	>80%
5	MLCT absorption band (465 nm)	○	84% *
6	MLCT absorption band	-	<5%

*90min

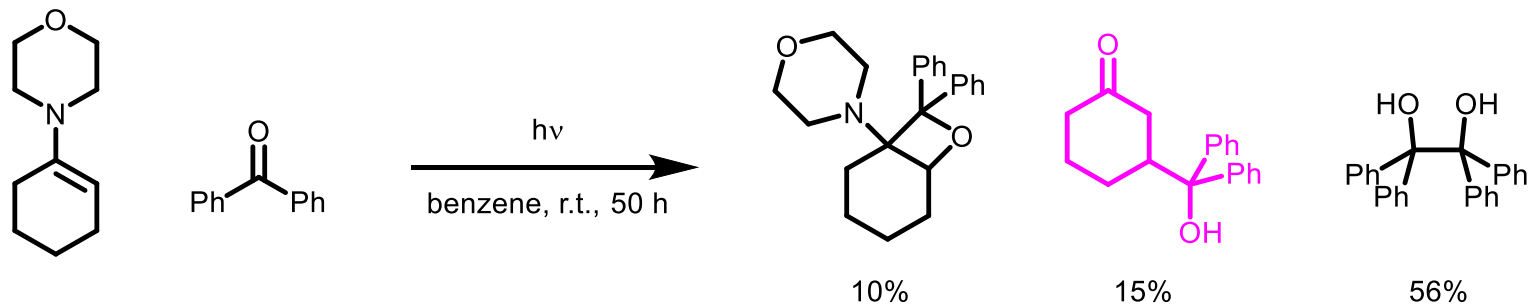
Deprotonation of β -position



Benzylol addition to allylic radical

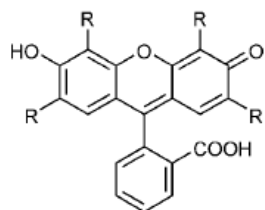


J. S. Bradshaw, *J. Org. Chem.*, **1966**, *31*, 237-240

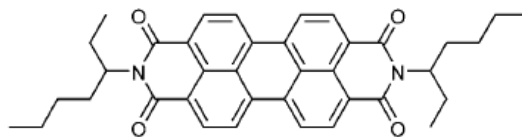


H. Nozaki, *et al.*, *Tetrahedron*, **1968**, *24*, 6557-6562

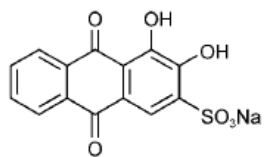
Searching for metal-free photoredox catalyst



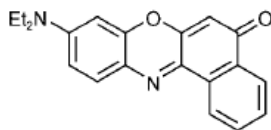
R = H fluorescein (1) $\lambda = 450 \text{ nm}$; $E^\circ = -1.22 \text{ V}$
 = Br eosin Y (2) $\lambda = 539 \text{ nm}$; $E^\circ = -1.06 \text{ V}$



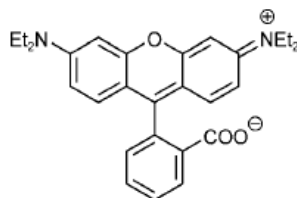
perylene 3
 $\lambda = 524 \text{ nm}$; $E^\circ \text{ ca. } -0.8 \text{ V}$



alizarin red S (4)
 $\lambda = 420 \text{ nm}$; $E^\circ = -0.28 \text{ V}$



Nile red (5)
 $\lambda = 543 \text{ nm}$; $E^\circ = -1.02 \text{ V}$



Rhodamine B (6)
 $\lambda = 524 \text{ nm}$; $E^\circ = -0.8 \text{ V}$

[Ru(bpy)₃]²⁺ $\lambda = 450 \text{ nm}$; $E^\circ = -1.33 \text{ V}$

[Ir(ppy)₂(dtb-ppy)]⁺ $\lambda = 416 \text{ nm}$; $E^\circ = -1.51 \text{ V}$

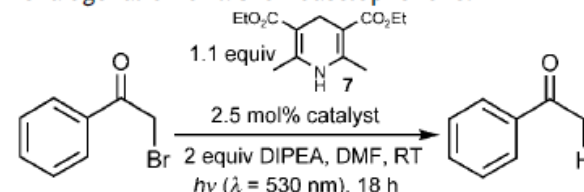
ちなみにお値段の方はmmol単位の値段で

Ru(bpy)₂Cl₂ \$62.5

Ir(ppy)₃ \$630

EosinY \$2.66

Table 1: Dehalogenation of α -bromoacetophenone.



Entry ^[a]	Dye catalyst	Yield [%] ^[b]
1	none	40
2	[Ru(bpy) ₃] ²⁺ (8) ^[d]	100
3	alizarin red S (4)	36
4	perylene 3	100
5	nile red (5)	100
6	fluorescein (1)	100
7	eosin Y (2)	100
8	eosin Y (2)	3 ^[d]
9	eosin Y (2)	80 ^[e]
10	rhodamine B (6)	80

[a] Standard conditions as described above. [b] GC yield determined using a calibrated internal standard. [c] A blue high-power LED ($\lambda \approx 455 \text{ nm}$) was used instead. [d] Reaction was performed in the dark. [e] Reaction was conducted in sunlight; full conversion was reached after 1 h of irradiation.

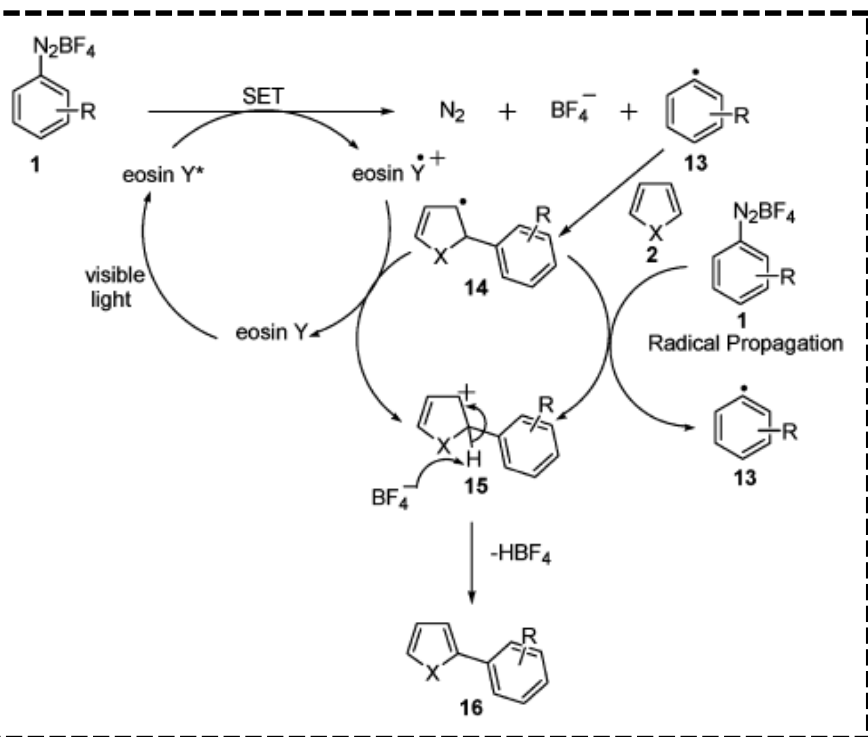
entry 3, 5, 10 ... degradation observed

entry 4, 6, 7-9 ... stable under light

エオシンが比較的高い反応性と安定性を有していることからエオシンをチョイスした

Metal-free catalytic SOMO-activation

Meerwein reaction



transition metals : CuCl, TiCl₃, Pd
mechanism : radicalic intermediate

R is electron rich ... low yield
electron poor ... high yield

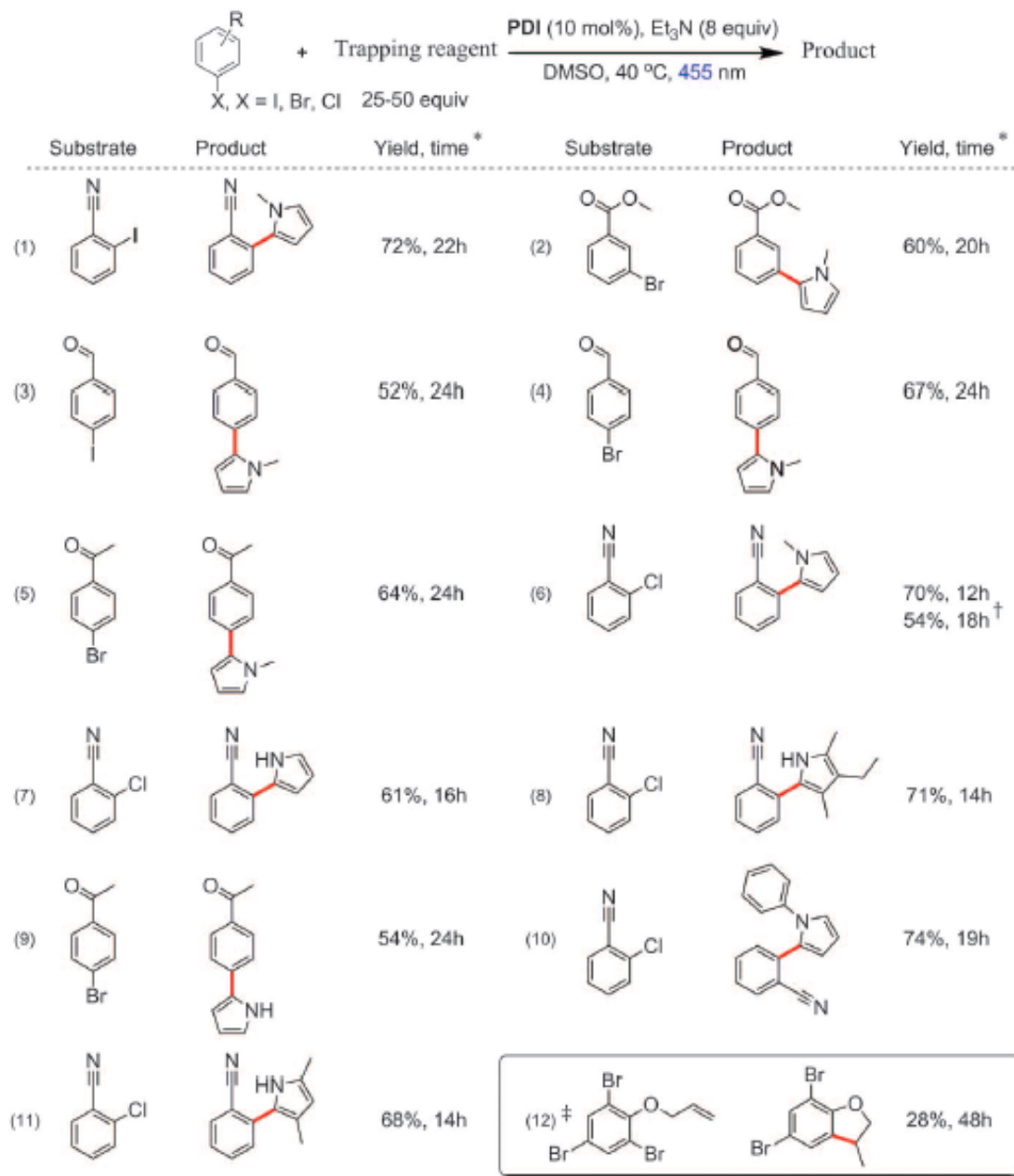
B. König, *et al.*, *J. Am. Chem. Soc.*, 2012, 134, 2958-2961

Reduction potential of aryl chloride

Table 2. Fragmentation Rate Constants and Standard Potentials for Aryl Chlorides in DMF

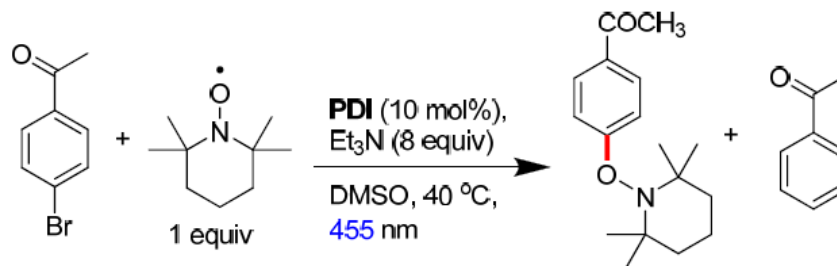
ArCl	log k_f (s ⁻¹)	$-E_{ArX/ArX^-}^0$ (V vs SCE)
2-chloronitrobenzene	-2.0 ± 0.1^a	0.99 ^a
4-chloronitrobenzene	-2.0 ± 0.1^a	1.05 ^a
9,10-dichloroanthracene	1.2 ± 0.1^b	1.47 ^b
4,4'-dichlorobenzophenone	0.8 ± 0.1^b	1.55 ^b
2-chlorobenzaldehyde	2.3 ± 0.1^b	1.56 ^b
3-chlorobenzophenone	1.65 ± 0.10^a	1.64 ^a
9-chloroanthracene	2.15 ± 0.03^c	1.71 ^a
1-chloroanthracene	0.90 ± 0.04^c	1.73 ^a
2-chloroanthracene	1.35 ± 0.04^c	1.80 ^a
3-chloroacetophenone	1.0 ± 0.1^a	1.83 ^a
4-[2-(4-chlorophenyl)ethenyl]-pyridine	1.5 ± 0.1^a	1.84 ^a
4-chloroquinoleine	5.8 ± 0.6^a	1.89 ^a
4'-chloroacetophenone	5.5 ± 0.6^a	1.90 ^a
2-chloroquinoleine	5.8 ± 0.6^a	1.92 ^a
ethyl 4-chlorobenzoate	7.1 ± 0.1^b	2.02 ^b
4-chlorobenzonitrile	8.2 ± 0.6^a	2.08 ^a
1-chloronaphthalene	$7.2 \pm 0.6^{a,d}$	2.26 ^a
2-chloronaphthalene	8.0 ± 0.6^a	2.30 ^a
	7.2 ^d	2.30 ^a
3-chloropyridine	9.5 ± 0.15^b	2.36 ^b
3-chlorobiphenyl	5.85 ^d	2.36 ^e
2-chloropyridine	9.6 ± 0.14^b	2.37 ^b
4-chlorobiphenyl	8.65 ± 0.02^d	2.43 ^e
2-chlorobiphenyl	10.85 ^d	2.59 ^e

PDI photocatalyst substrate



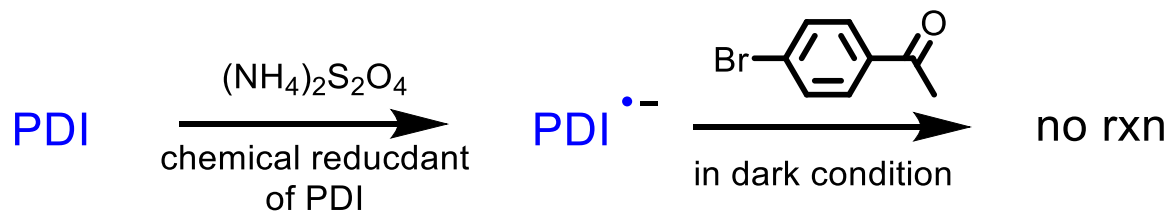
* Isolated yield. † Reaction was performed with commercially available catalyst. ‡ Reaction was performed in DMF.

radical trap by TEMPO



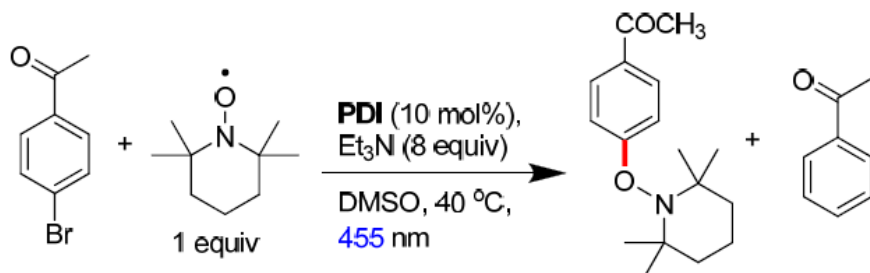
HRMS: calculated for [M+H]⁺ C₁₇H₂₆NO₂⁺ 276.1964; found 276.1959.

chemical production of PDI radical



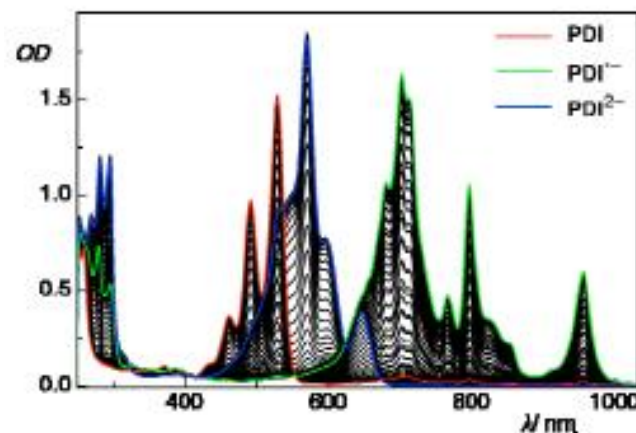
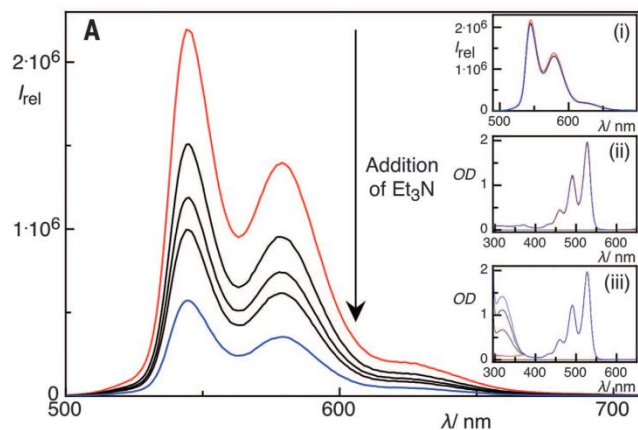
Evidence of PDI radical anion photoactivation

E° in DMF vs Fc/Fc^+ : $E^\circ(\text{PDI}^{\bullet-}/\text{PDI}) = -0.88 \text{ V}$, $E^\circ(\text{PDI}^{2-}/\text{PDI}^{\bullet-}) = -1.18 \text{ V}$.



Aryl radical trapping

HRMS: calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{26}\text{NO}_2^+$ 276.1964; found 276.1959.



PDI radical anion production by addition of $(\text{Et}_2\text{N})_4\text{S}_2\text{O}_4$ (= chemical reductant of PDI)
 ... no reduction of 4-Br-acetophenone

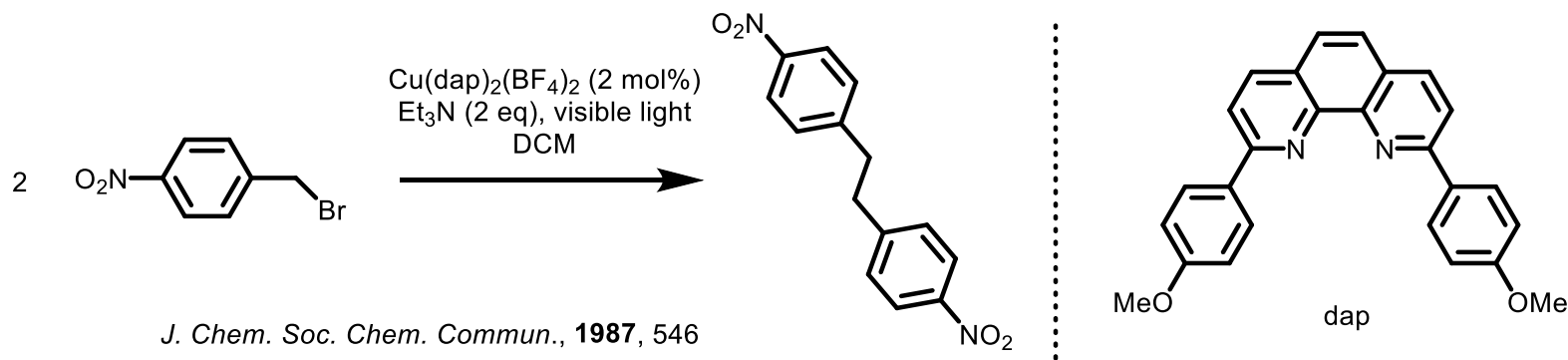
Q & A

この研究の最終目的は何か？

触媒量の金属のみの使用で酸化剤・還元剤を必要としない photoredox catalyst は atom economy や不要な副産物を生みにくいという点で環境負荷のない合成法を可能にしています。現在はそれらを用いた反応のバリエーションを増やしている段階だと考えられますが、最終的には全合成・医薬品合成においてクリーンな合成方法を確立することにあるのではないかなと思います。

Ru, Ir 以外で photoredox catalyst となる例はある？

Photoredox catalyst は Ru, Ir が使われる場合がほとんどで、それ以外のケースではエオシンのような色素が使われるケースもありますが、Cu を使った光酸化還元反応もあります。



p26でアルデヒドの α 位はラセミ化しないのか？

MacMillanらの結果をみるにラセミ化はあまり起こっていないことが分かります。その理由としてはamine catalystが置換後のアルデヒドに攻撃しにくくなっていることが挙げられるのではないかと考えられます。反応前のアルデヒドより立体的に混んでいる生成物がアミンの攻撃に耐性があるためイミンやエナミンの生成が妨げられ、結果としてラセミ体になりにくいという可能性が考えられます。

RuとIrの使い分け方

Appendixのp45の表を参考に光励起されてから酸化的パス(E^*/E^-)のエネルギー差と還元的パス(E^+/E^*)のエネルギー差を比べてみると、Ruは酸化的パスのエネルギーが大きく、Irは還元的パスのエネルギーが大きいです。そのため傾向と言えることは比較的酸化されにくい基質があるときはRuの方が適切で、還元されにくい基質があるときはIrが適切であるということです。例えばp28のSOMO-activationの例ではカップリングパートナーが還元されにくいいためRuは使えずIrで反応を回しています。

SOMO-activationとSOMO-β-activationの違いはどこに起因するのか？

SOMO-activationにおけるカップリングパートナーはphotoredox catalystによって一電子還元された不安定なラジカルでエナミンに対してすぐ反応してしまうと考えられます。一方でSOMO-β-activationの場合はカップリングパートナー側がラジカルを安定化するような置換基（電子求引基）を持つことでエナミンへの付加が抑制されることで、エナミン側に脱プロトンされる隙が生じたのではないかと考えられます。（つまり、基質依存ではないかと思えます）

また、SOMO-activationの場合においてエナミンの酸化に先立ってラジカルの付加が起こっているという実験結果からもラジカル自体の不安定さが反応性に影響していることが示唆されます。

SOMO-β-activationのβ位にラジカルが生じる機構は？

考えられる機構としては以下のようなものが挙げられます。

