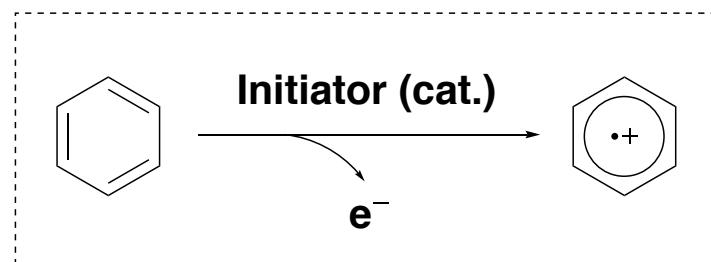


Initiators for radical cation-induced [2+2] and [4+2] cycloaddition reactions



2021/10/16 (Sat)
Haruna Kato

Contents

1. Introduction

2. Chemical oxidant-initiated cycloadditions

3. Electrochemical-initiated cycloadditions

4. Photoredox catalyst-initiated cycloadditions

5. Proposal

1. Introduction

1-1. Pericyclic reaction

• Cycloaddition reaction



• Electrocyclic reaction



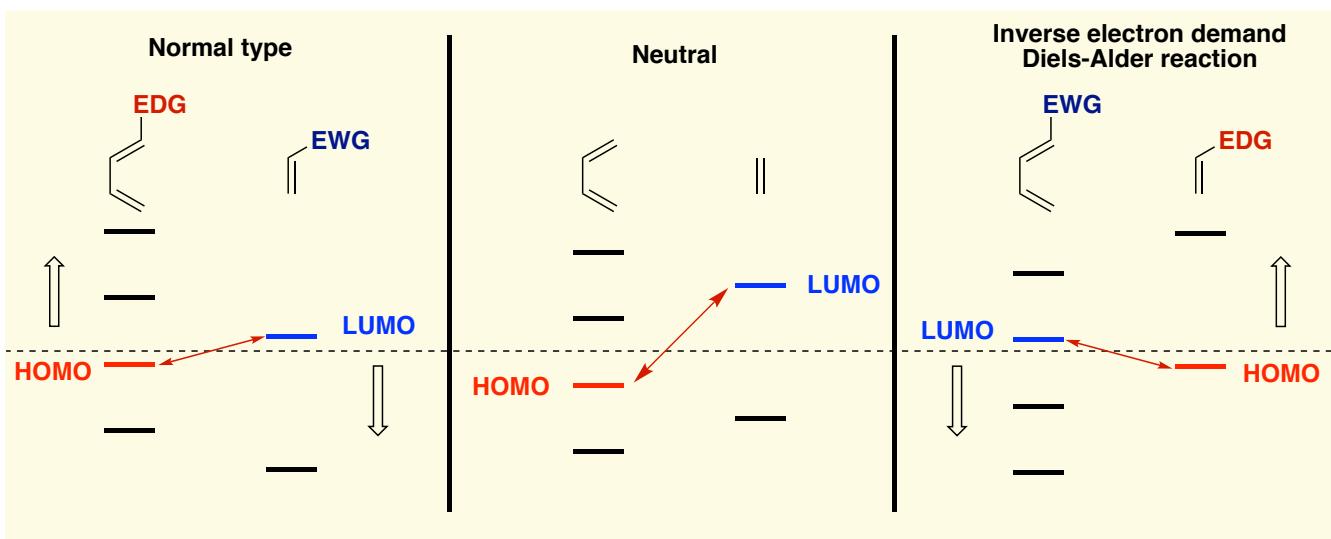
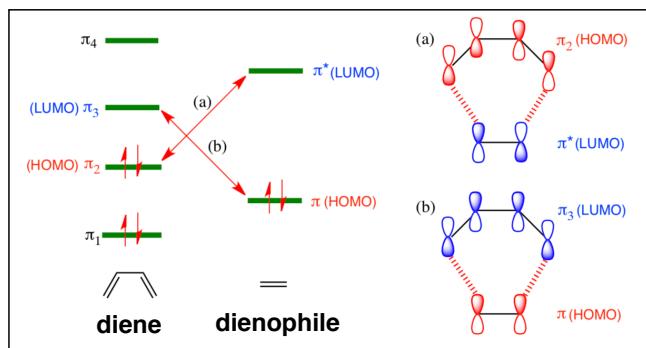
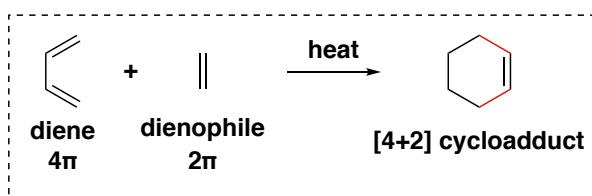
• Sigmatropic rearrangement



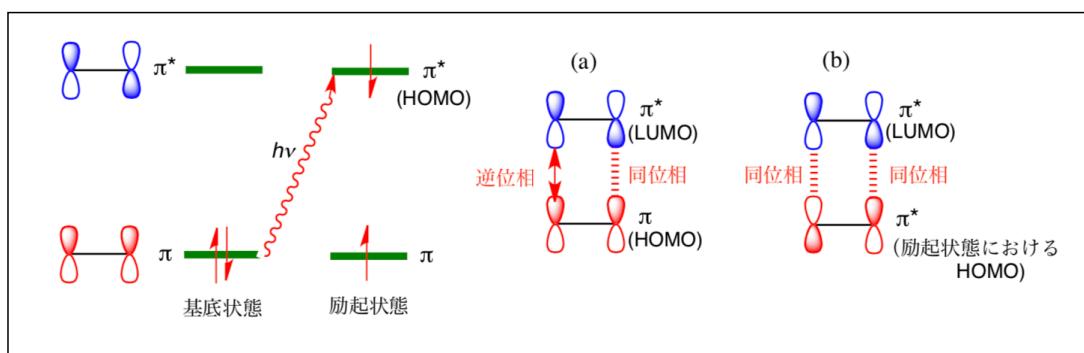
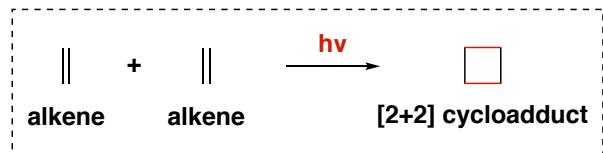
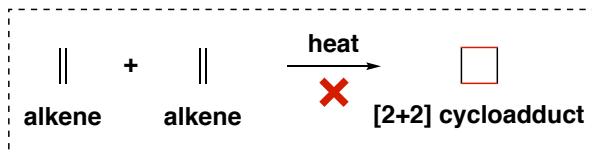
1-2. cycloaddition reaction

[4+2] cycloaddition

• Diels-Alder reaction



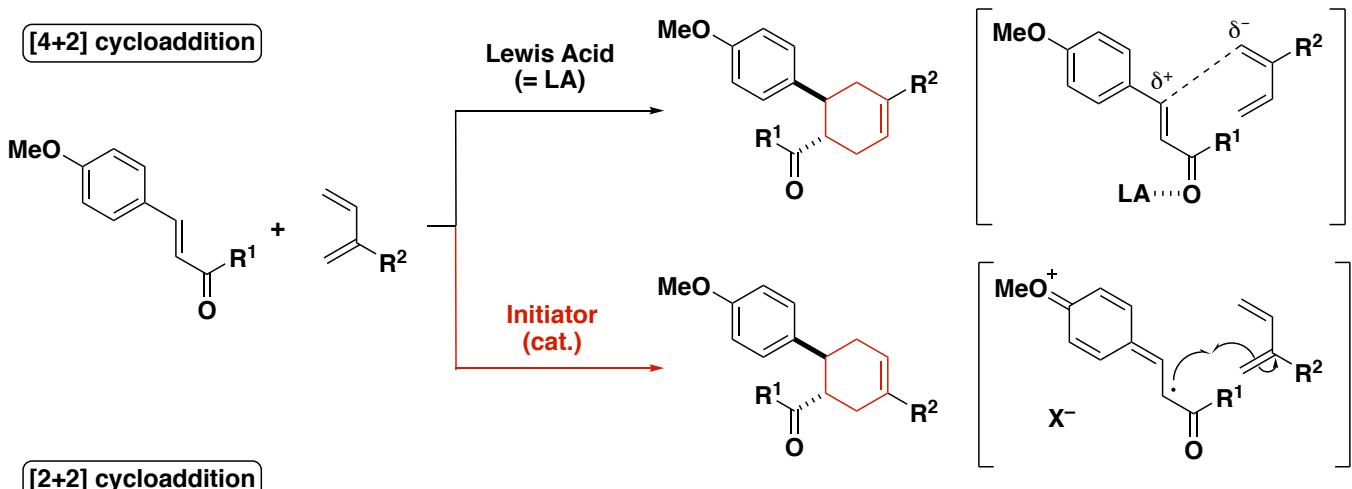
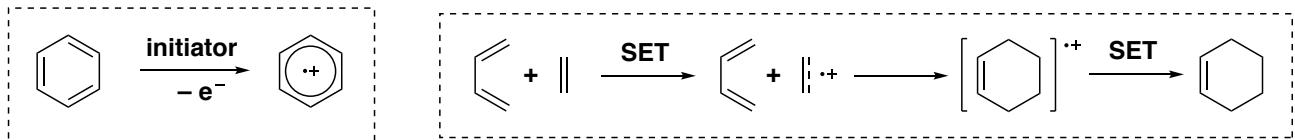
[2+2] cycloaddition



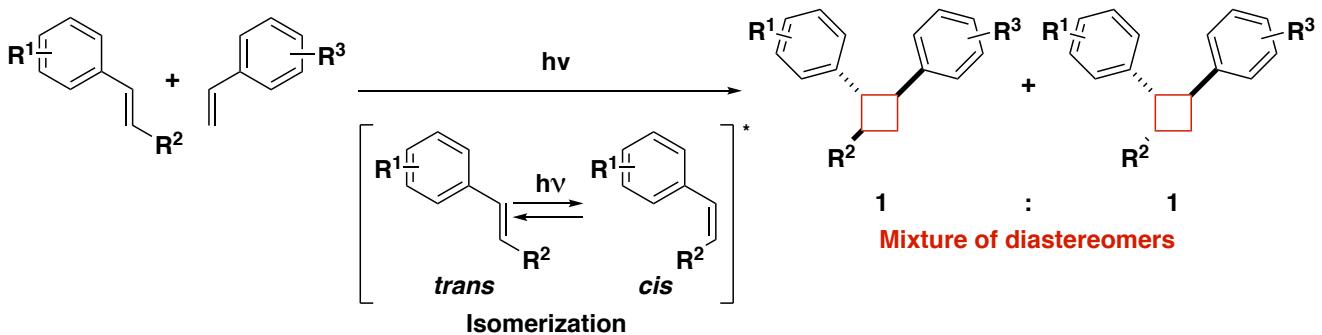
1. Introduction

1-3. Radical cation-induced cycloaddition reaction

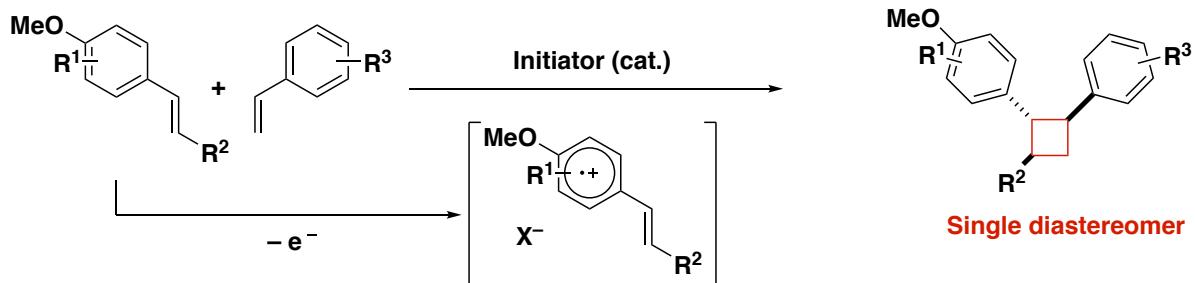
• Radical cation



• Photocyclization (triplet sensitization)



• Radical cation-induced cycloaddition



1-4. Initiators for radical cation-induced cycloaddition reaction

a) Chemical method

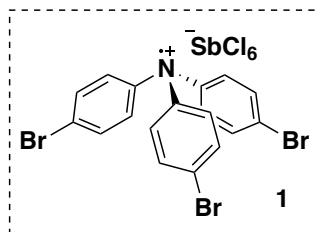
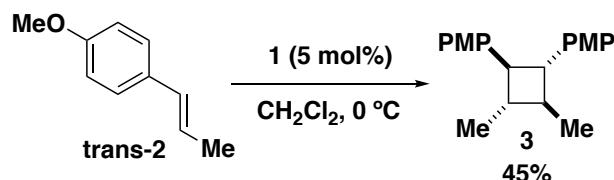
b) Electrochemical oxidation

c) Photochemical method

2. Chemical Oxidant-initiated cycloadditions

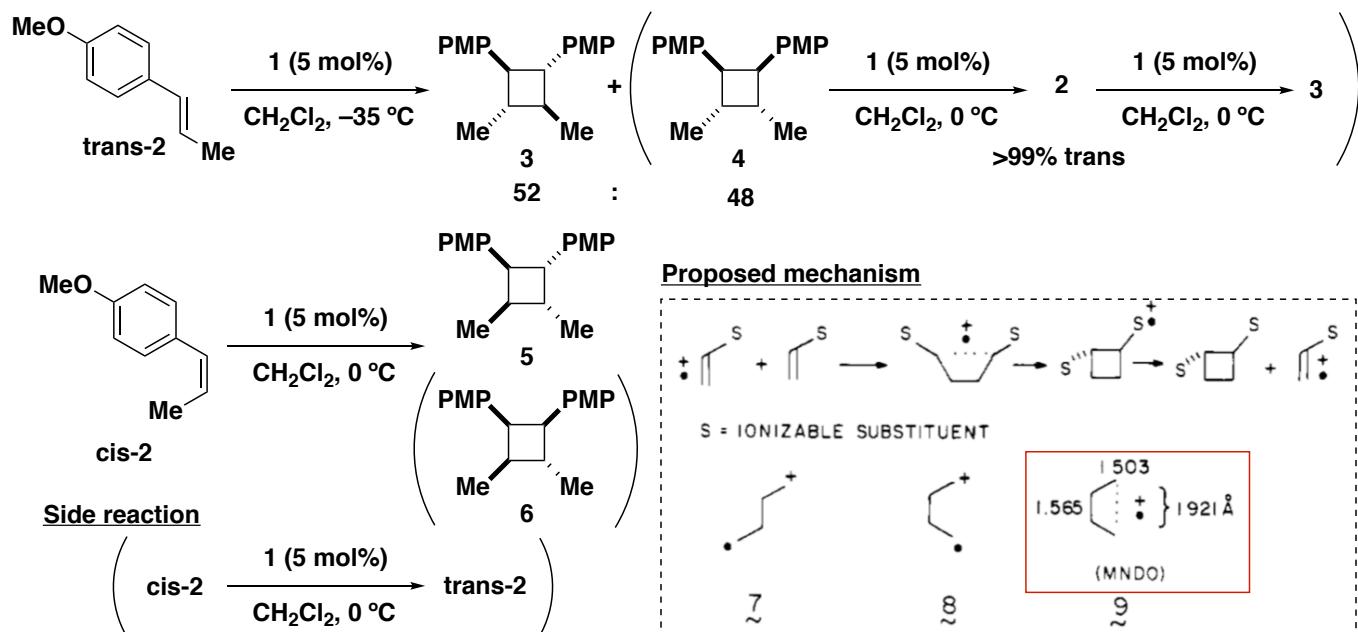
2-1. Aminium radical cation (Bauld)

Homo [2+2] cycloaddition (1983)



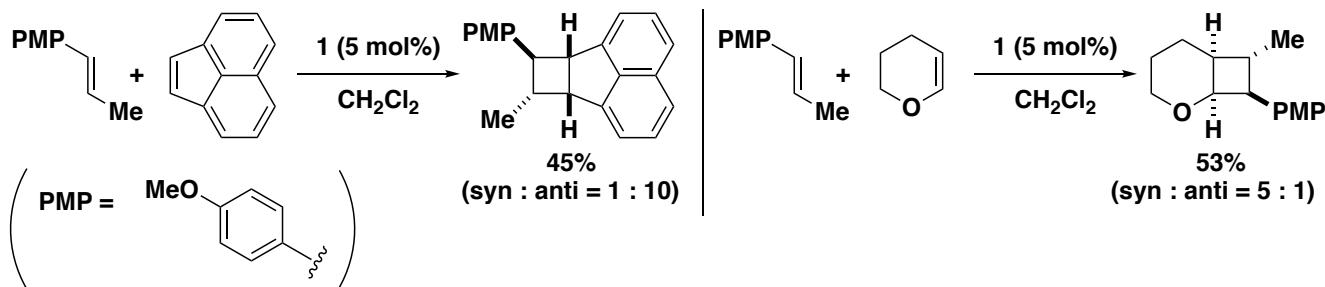
Bauld, N. L.

Control experiments

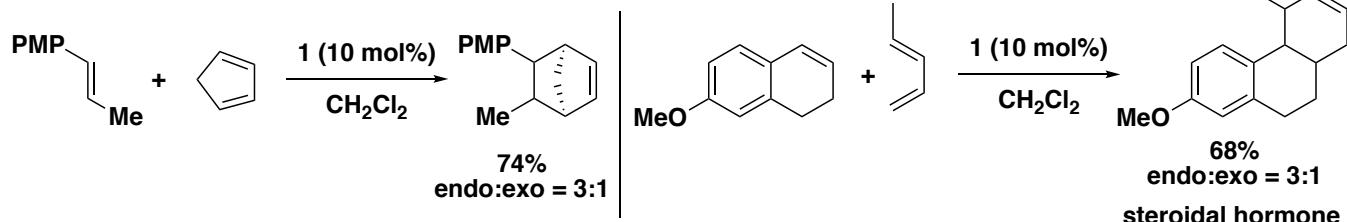


→ The cyclodimerization of 1 is inherently **stereospecific**

Hetero [2+2] cycloaddition (1983)



[4+2] cycloaddition (1983)



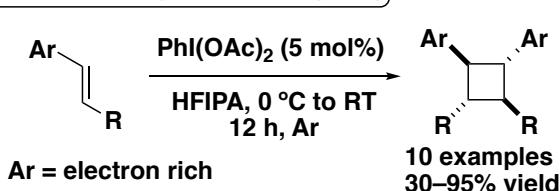
1) Bauld, N. L. et al. *J. Am. Chem. Soc.* 1983, 105, 633.

2) Bauld, N. L. et al. *J. Am. Chem. Soc.* 1983, 105, 5158.

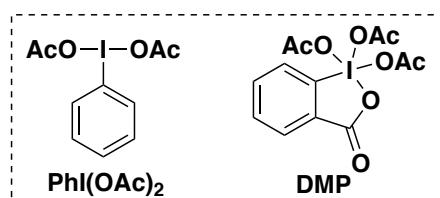
2. Chemical Oxidant-initiated cycloadditions

2-2. Hypervalent iodine (Donohoe)

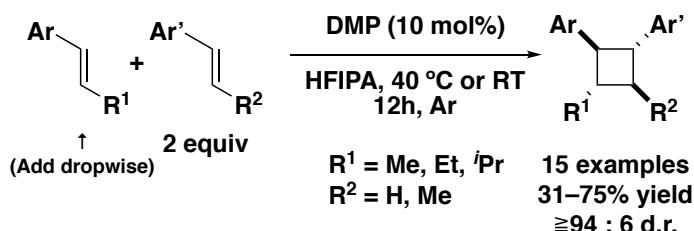
Homo [2+2] cycloaddition (2016)



Ar = electron rich



Hetero [2+2] cycloaddition (2016)



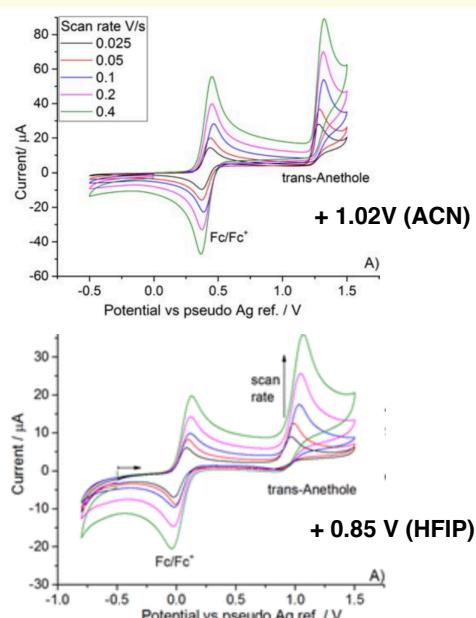
Effect of HFIP (2016)

[2+2] cycloaddition with Hypervalent iodine proceeds only in HFIP solvents

a) Voltammetric response

	ACN	HFIP
trans-anethole (1), $E_{p,a}$	1.02	0.85
PIDA (2), $E_{p,c}$	-1.32	-0.47
$\Delta E_{p,p}$	-2.35	-1.31

→ The strong enhancement of the oxidizing abilities of PIDA in HFIP



Optimization

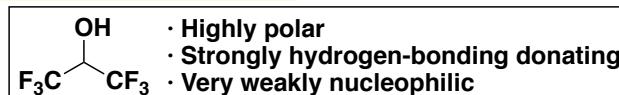
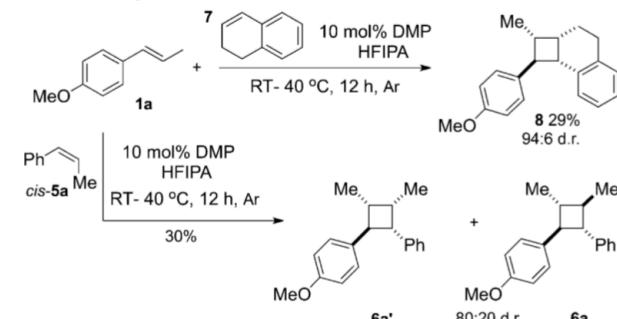
Entry	Catalyst	T [°C]	Yield of 2a [%] ^[a]
1	10 mol % IBX	RT	39
2	10 mol % DMP	RT	33
3	10 mol % PhI(O ₂ CCF ₃) ₂	RT	22
4	10 mol % PhI(OAc) ₂	RT	51
5 ^[b]	10 mol % PhI(OAc) ₂	RT	34
6	5 mol % PhI(OAc) ₂	RT	63
7	1 mol % PhI(OAc) ₂	RT	39
8	5 mol % PhI(OAc) ₂	0-RT	76
9	no catalyst	RT	0

[a] The product 2a was isolated as a single (racemic)^[14] diastereoisomer ($\geq 95:5$ d.r.) according to NMR spectroscopy. [b] Reaction run in CF₃CH₂OH. DMP = Dess–Martin periodinane, IBX = o-iodoxybenzoic acid.



Donohoe, T. J.

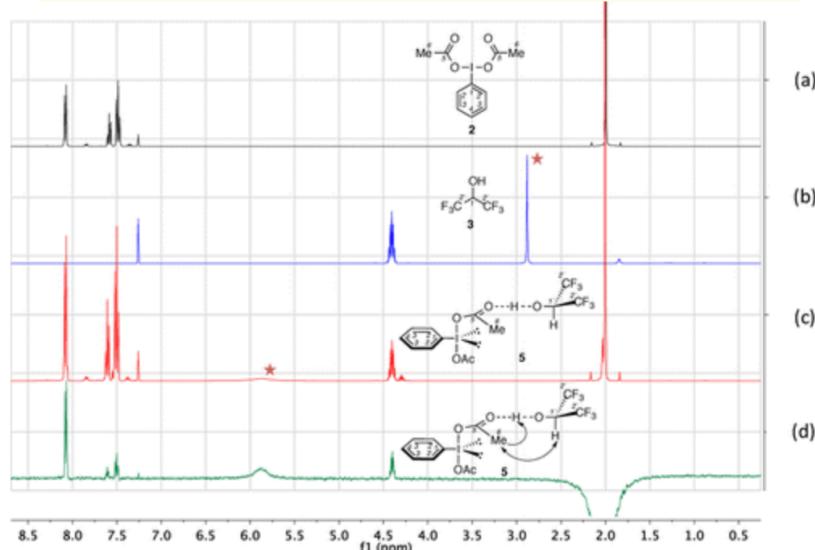
Control experiment



b) MS and NMR

HRMS: without the observation of any new formed species
→ No ligand exchange (the low nucleophilicity of the solvent)

NMR: OH signal in HFIP from 2.88 to 5.88 ppm in the 1:1 adduct
→ Formation of a H-bonded adduct between the HFIP and PIDA



3) Donohoe, T. J. et. al. *Angew. Chem. Int. Ed.* **2016**, *55*, 4748.

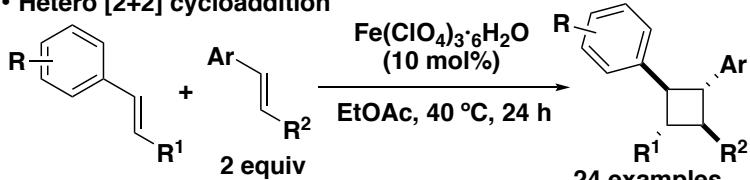
4) Donohoe, T. J. et. al. *J. Am. Chem. Soc.* **2016**, *138*, 8855.

2. Chemical Oxidant-initiated cycloadditions

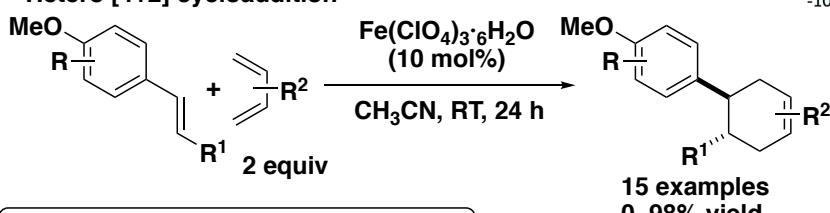
2-3. Iron(III) (Zhong, Kang)

(Fe(ClO₄)₃ with O₂ (2018, Zhong))

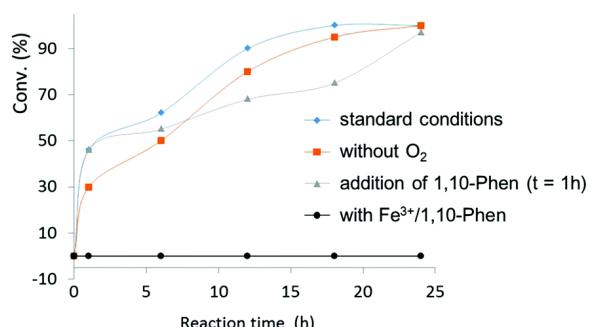
- Hetero [2+2] cycloaddition



- Hetero [4+2] cycloaddition



Control experiment



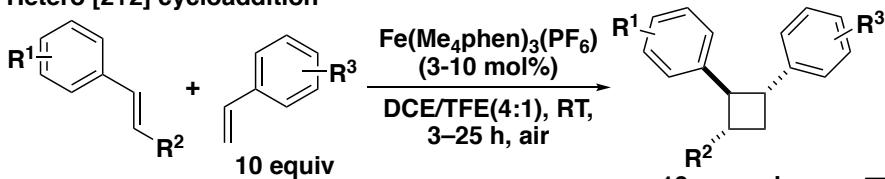
→ Fe(II) salt might be oxidized by O₂ to regenerate Fe(III) initiator



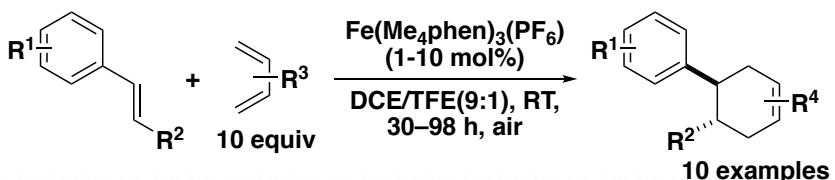
Zhong, F.

(Fe(III)-propyridyl complexes (2018, Kang))

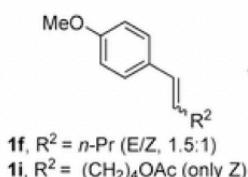
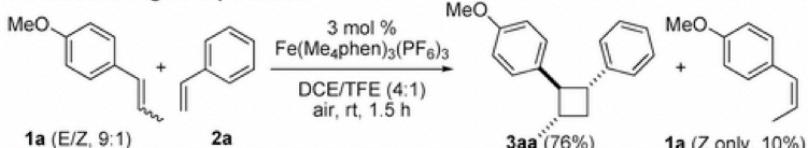
- Hetero [2+2] cycloaddition



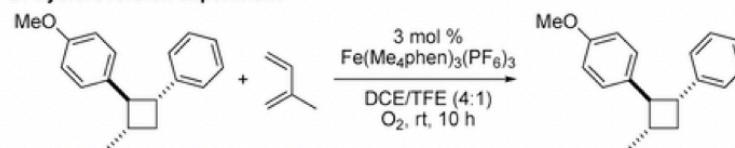
- Hetero [4+2] cycloaddition



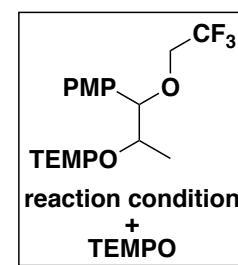
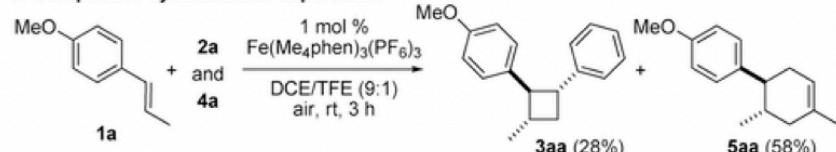
A. Stereoconvergent experiments



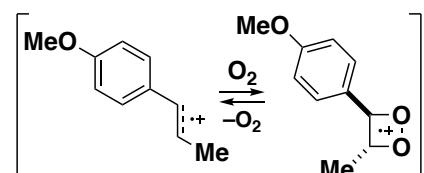
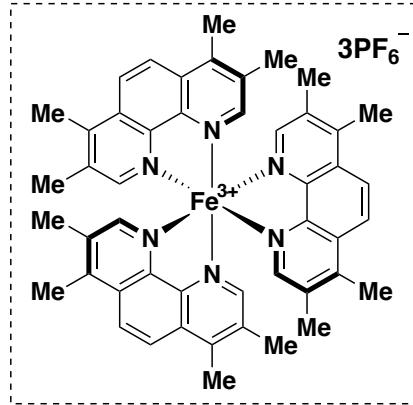
B. Cycloreversion experiment



C. Competitive cycloaddition experiment



Kang, E. J.



→ Oxygen may be stabilizing the radical cation intermediates

6) Zhong, F. et al. *Green. Chem.* 2018, 20, 1743.

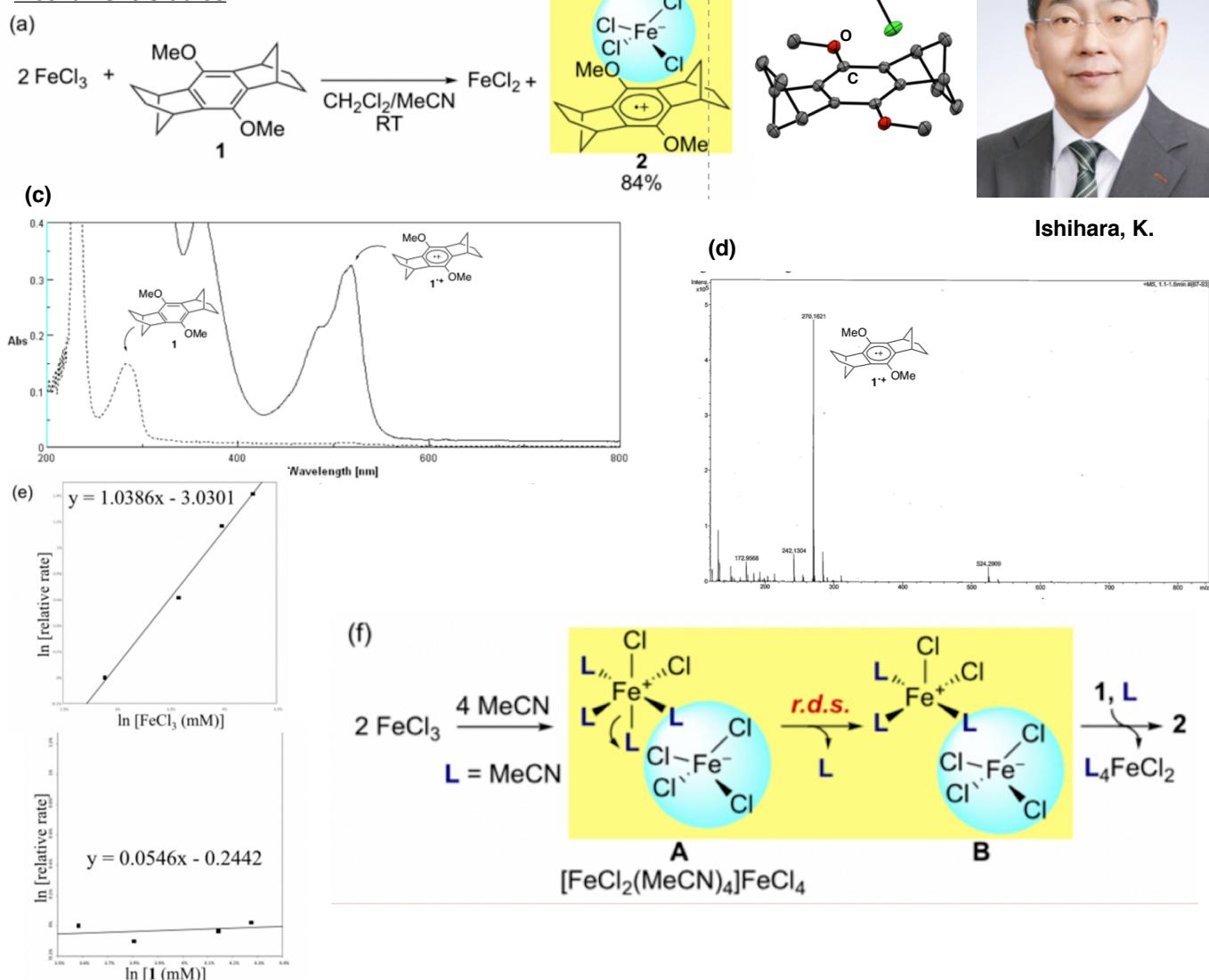
7) Kang, E. J. et al. *Org. Lett.* 2018, 20, 5872.

2. Chemical Oxidant-initiated cycloadditions

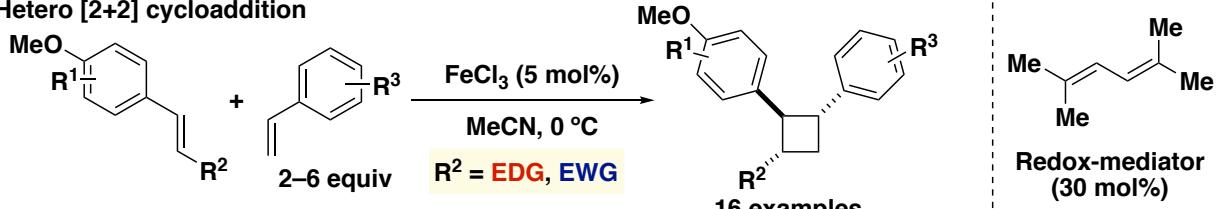
2-3. Iron(III) (Ishihara)

$\text{FeCl}_3, \text{Fe}(\text{OTf})_3$ (2019-2020)

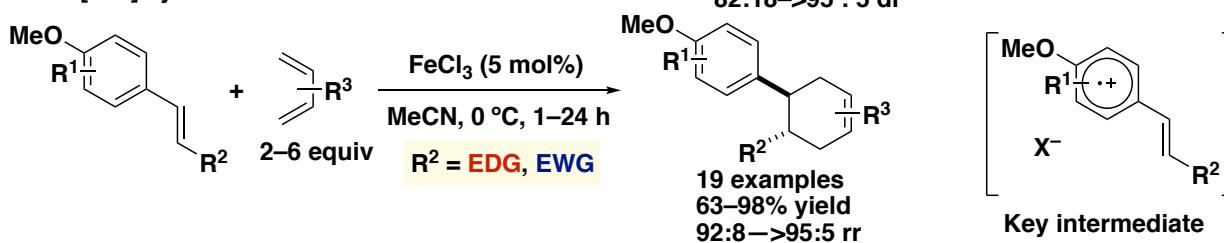
Mechanistic studies



• Hetero [2+2] cycloaddition



• Hetero [4+2] cycloaddition



8) Ishihara, K. et al. *J. Am. Chem. Soc.* 2019, 141, 1877.

9) Ishihara, K. et al. *Adv. Synth. Catal.* 2020, 362, 960.

10) Ishihara, K. et al. *Asian. J. Org. Chem.* 2020, 9, 395.

3. Electrochemical-initiated cycloadditions

3-1. Characteristics of electrolytic reaction

Electrolytic reaction

- The reaction is carried out by receiving electrons directly from the electrodes.
- Electrolytic reactions can provide much more energy to a substrate than thermal reactions.

○ Mild conditions, High yield, High selectivity

- Reactions does not require heavy metals

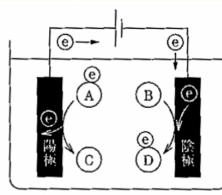
○ Eco-friendly

- Oxidation and reduction reactions occur in different places
→ Electron transfer can be done separately

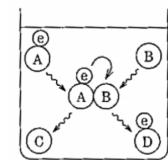
Normal reaction condition

- High temperature conditions are required
- Side reactions, substrate degradation, decreased selectivity

- Oxidation and reduction reactions occur in the same place



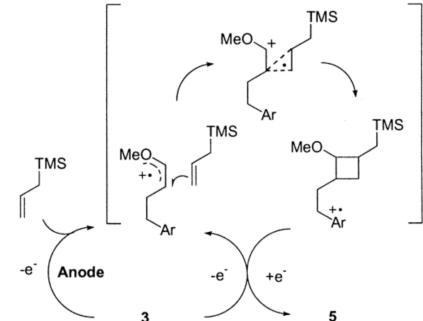
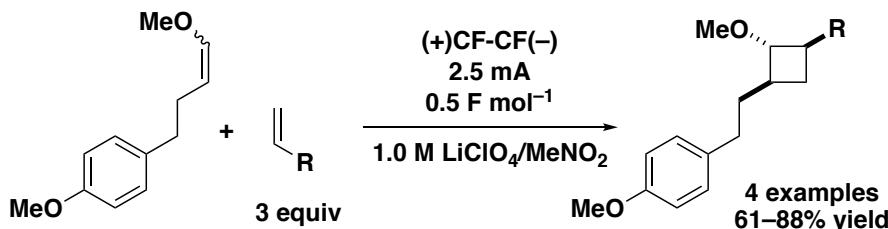
Electrolytic reaction



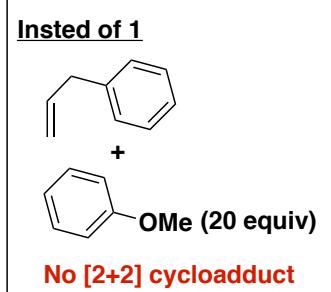
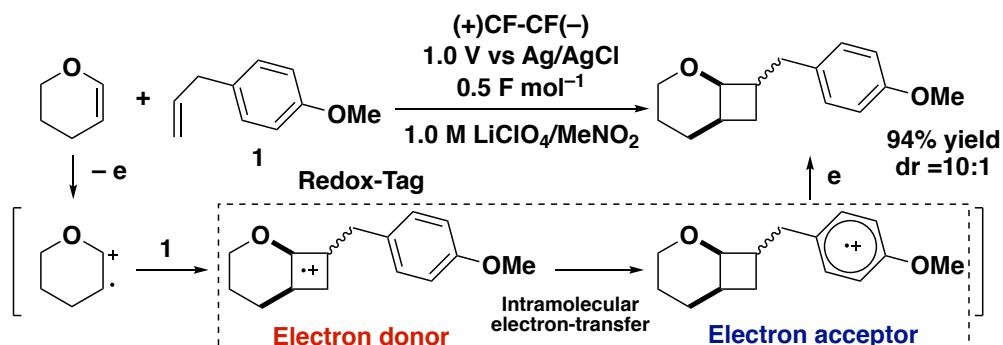
Normal reaction

3-2. Aromatic “Redox Tag” Strategy (Chiba)

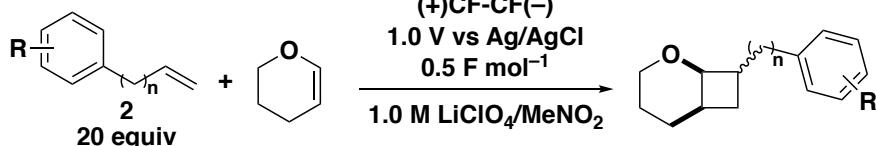
A pioneering work on intermolecular [2+2] cycloaddition (2001)



Intramolecular electron transfer (2009-2011)

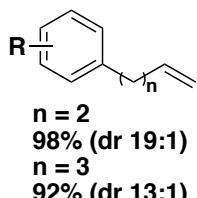
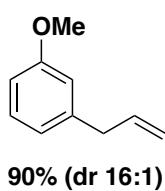


Substrate scope

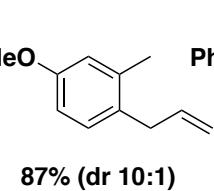


Chiba, K.

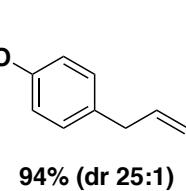
2, yield, dr



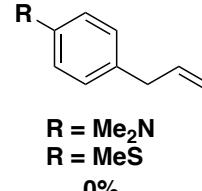
n = 2
98% (dr 19:1)
n = 3
92% (dr 13:1)



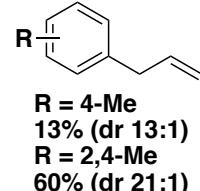
87% (dr 10:1)



94% (dr 25:1)



R = Me₂N
R = MeS
0%



R = 4-Me
13% (dr 13:1)
R = 2,4-Me
60% (dr 21:1)
R = 2,4,6-Me
84% (dr 22:1)

11) Chiba, K. et al. *J. Am. Chem. Soc.* 2001, 123, 11314.

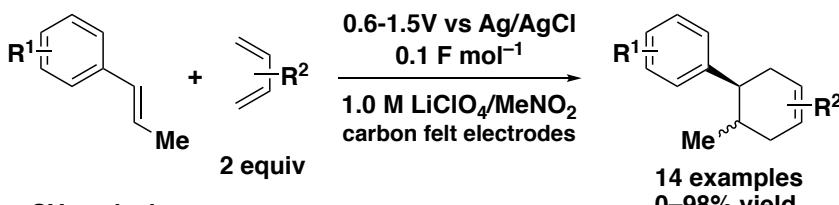
12) Chiba, K. et al. *Org. Lett.* 2009, 11, 1033.

13) Chiba, K. et al. *J. Org. Chem.* 2011, 76, 3470.

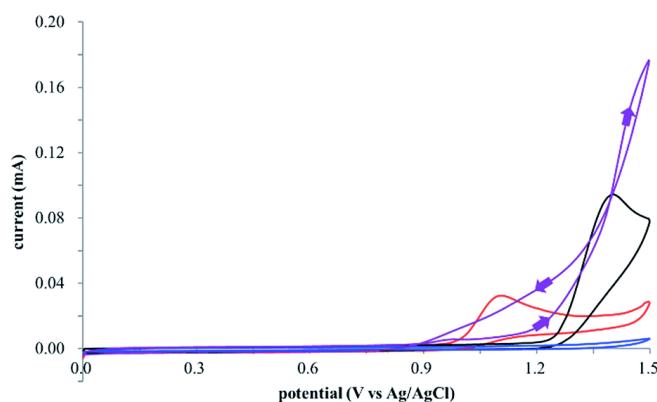
3. Electrochemical-initiated cycloadditions

3-2. Aromatic “Redox Tag” Strategy (Chiba)

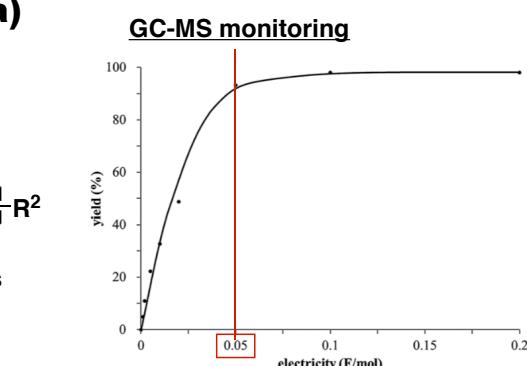
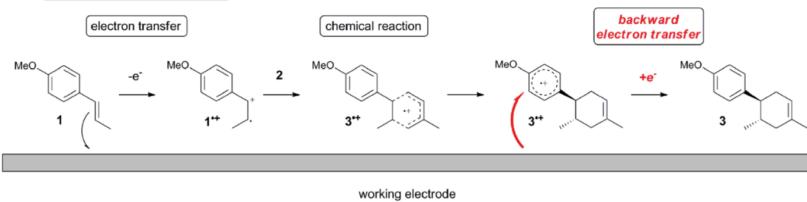
Diels-Alder reactions by electrocatalysis (2016)



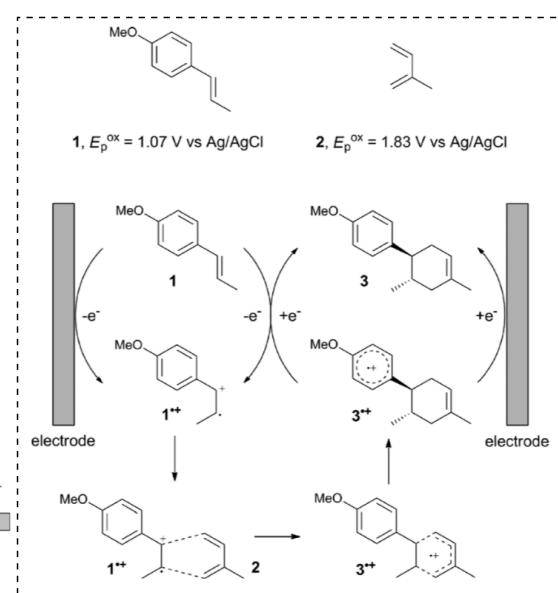
CV analysis



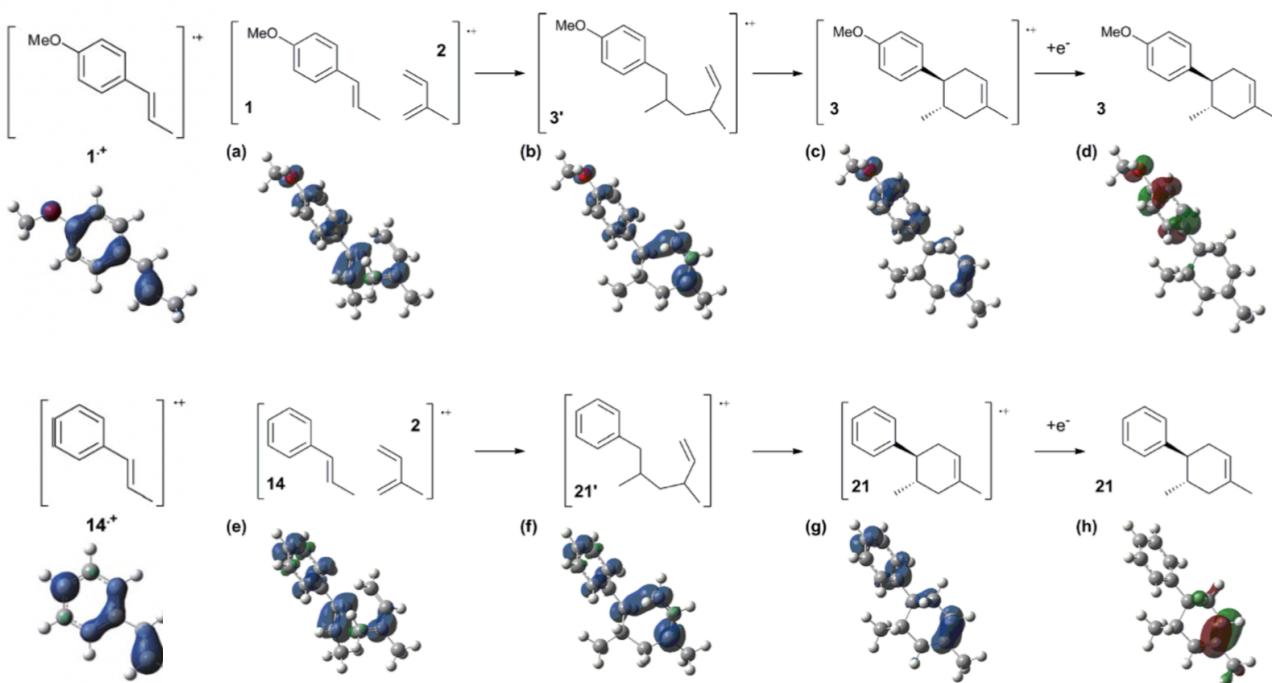
EC-backward-E



Reaction mechanism



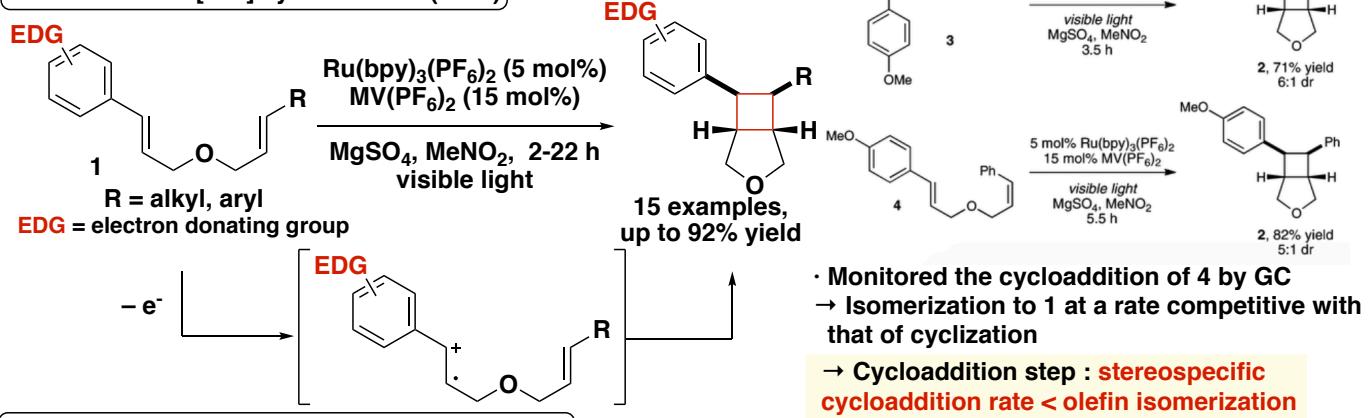
Spin densities (DFT calculations)



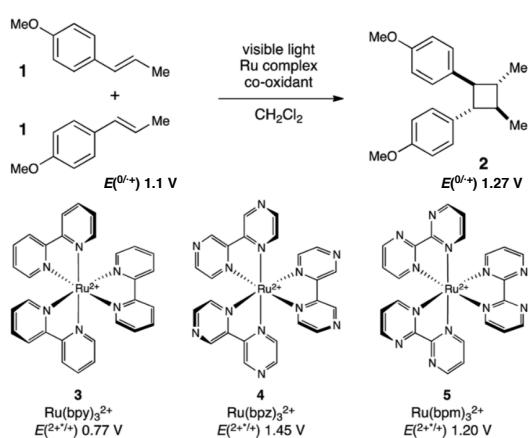
4. Photoredox catalyst-initiated cycloaddition

4.1-Ruthenium catalyst (Yoon)

Photooxidative [2+2] cycloaddition (2010)

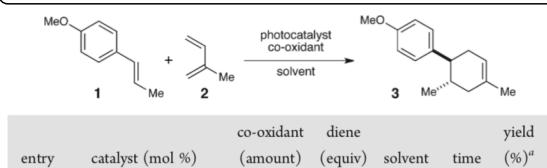


Cross intermolecular [2+2] cycloaddition (2012)

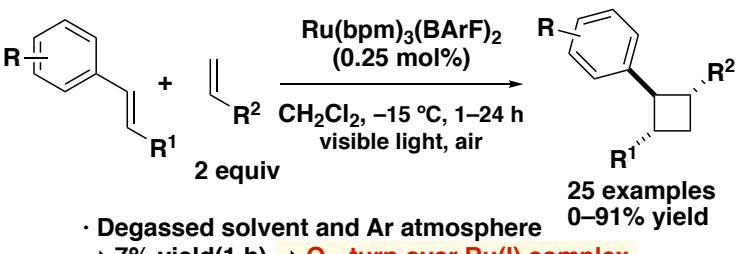


Entry ^b	Ru complex	Co-oxidant	Time	Yield ^c
1 ^d	Ru(bpy) ₃ (PF ₆) ₂	MV(PF ₆) ₂	24 h	9%
2	Ru(bpy) ₃ (BArF) ₂	Air	8 h	1%
3	Ru(bpz) ₃ (BArF) ₂	Air	2 h	57%
4	Ru(bpz) ₃ (BArF) ₂	Air	16 h	65%
5	Ru(bpm) ₃ (BArF) ₂	Air	2 h	72%
6 ^e	Ru(bpm) ₃ (BArF) ₂	Air	2 h	83% (81%) ^f

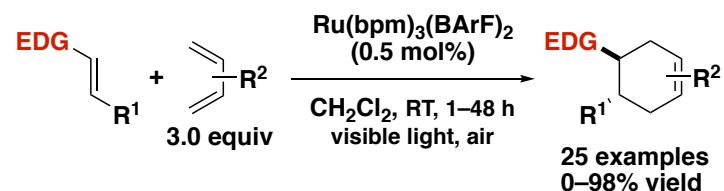
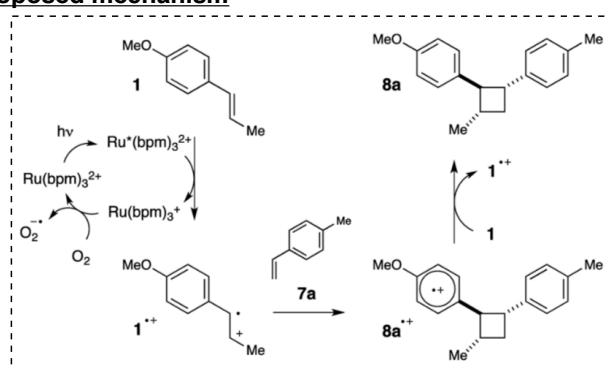
Cross intermolecular [4+2] cycloaddition (2011)



^a Yields were determined by ¹H NMR analysis using CH₂Br₂ as an internal standard, unless otherwise noted. ^b Conducted in the presence of 200 wt % MgSO₄. ^c Isolated yield.



Proposed mechanism



Control experiment

entry	conditions	time	yield (%)
1	standard conditions	1 h	98
2	no Ru(bpz) ₃ (PF ₆) ₂	1 h	0
3	no light	1 h	0
4	ambient sunlight instead of fluorescent lamp	1 h	98
5	no air (under N ₂)	1 h	46
6	Rose Bengal instead of Ru(bpz) ₃ ²⁺	1 h	0
7	9,10-dicyanoanthracene instead of Ru(bpz) ₃ ²⁺	1 h	0
8	triphenylpyriliun·BF ₄ instead of Ru(bpz) ₃ ²⁺	1 h	28



Yoon, T. P.

15) Yoon. et al. *J. Am. Chem. Soc.* 2010, 132, 8572.

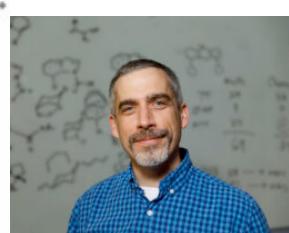
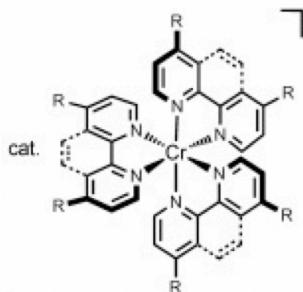
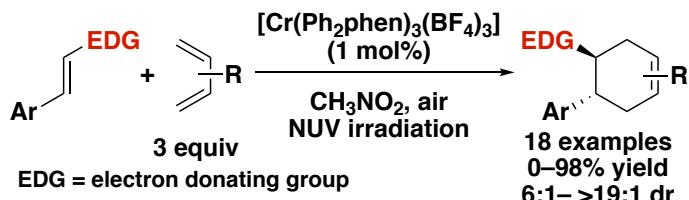
16) Yoon. et al. *Chem. Sci.* 2012, 3, 2807.

17) Yoon. et al. *J. Am. Chem. Soc.* 2011, 133, 19350.

4. Photoredox catalyst-initiated cycloaddition

4.2-Cr-Photoredox catalysis (Ferreira)

[4+2] cycloaddition of electron-rich olefins (2015)

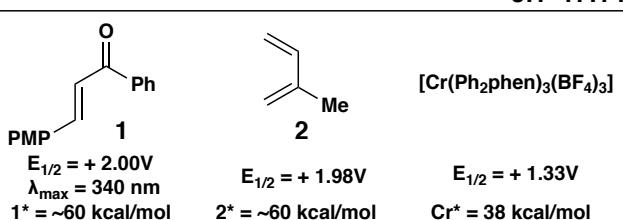
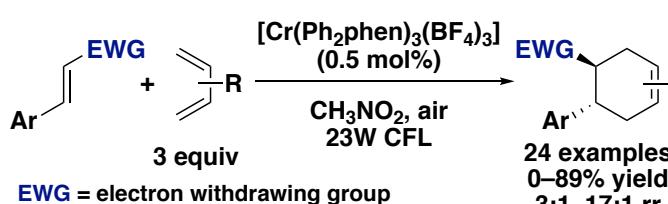


Ferreira, E. M.

Cr^{III} catalyst

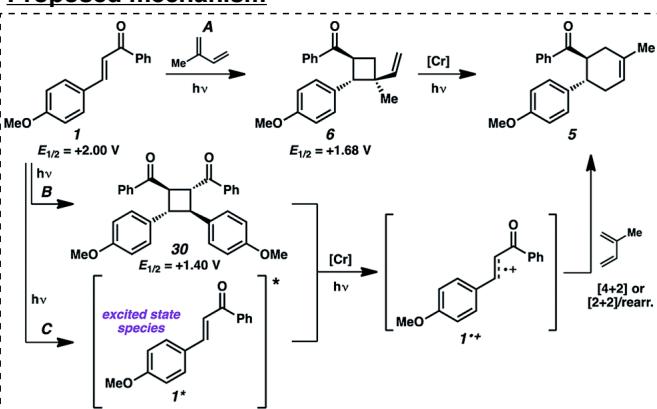
- Earth-abundant
- Comparatively higher excited state reduction potentials, ranging from +1.40 to +1.84 V
- The excited state lifetimes (t_{obs}^*) of the Cr^{III} species are substantially longer than those of the common Ru/Ir photocatalysts

[4+2] cycloaddition of electron-poor olefins (2017)



→ The oxidation potential of 1 is too positive to be oxidized by the $[\text{Cr}(\text{Ph}_2\text{phen})_3]^+$ catalyst

Proposed mechanism



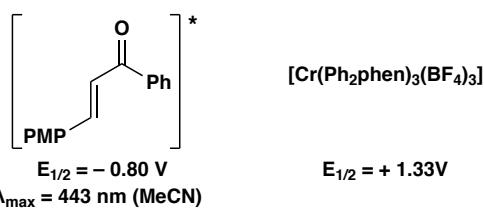
^a NMR yield with dodecyl acetate as internal standard. The remainder is recovered 30.

^b Yield when reaction was performed without catalyst.

Enone dimer 30 was rarely formed without diene

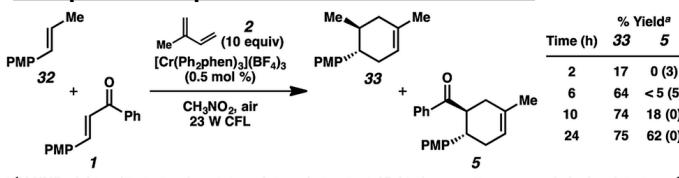
→ This pathway is a minor contributor at most

Mechanism C



- Lifetime of enone 1^* is long for oxidation by Cr catalyst
- 1^* can be oxidized by the $[\text{Cr}(\text{Ph}_2\text{phen})_3]^+$ catalyst

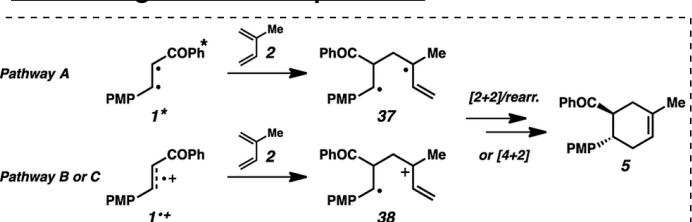
Competition experiment with trans-anethole



^a ^1H NMR yields with dodecyl acetate as internal standard. Yields in parentheses are of vinylcyclobutane 6.
 PMP = 4-MeOC₆H₄

→ This may implicate the intermediacy of the enone radical cation ($1^{\bullet+}$) in the overall process

General regiochemical explanation

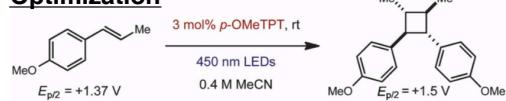


4. Photoredox catalyst-initiated cycloaddition

4.3-Triryl pyrillium catalyst (Nicewicz)

Homo [2+2] cycloaddition (2013)

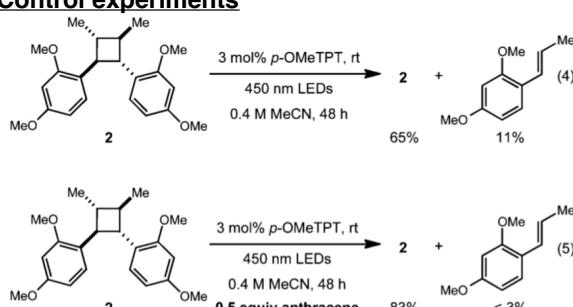
Optimization



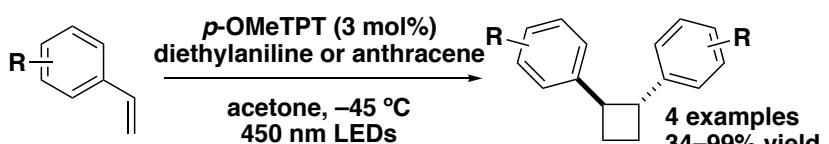
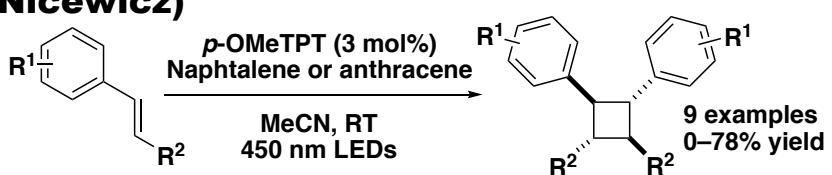
Entry	Electron relay ^b	Equivalents	Yield
1	None	None	0%
2	Anthracene (+1.21 V)	0.25	13%
3	Naphthalene (+1.61 V)	0.25	16%
4	Naphthalene	0.5	18%
5 ^c	Naphthalene	0.5	54%
6	NH ₃ (+0.91 V)	0.25	0%
7 ^d	Naphthalene	0.5	0%
8 ^e	Naphthalene	0.5	0%

^a Reactions were carried out for 24 h, unless otherwise noted. ^b ¹H NMR yields are reported. ^c Peak potentials of electron relay in parenthesis. ^d Reaction time was 5 days. ^e Reaction in the dark. ^f Reaction in the absence of p-OMeTPT.

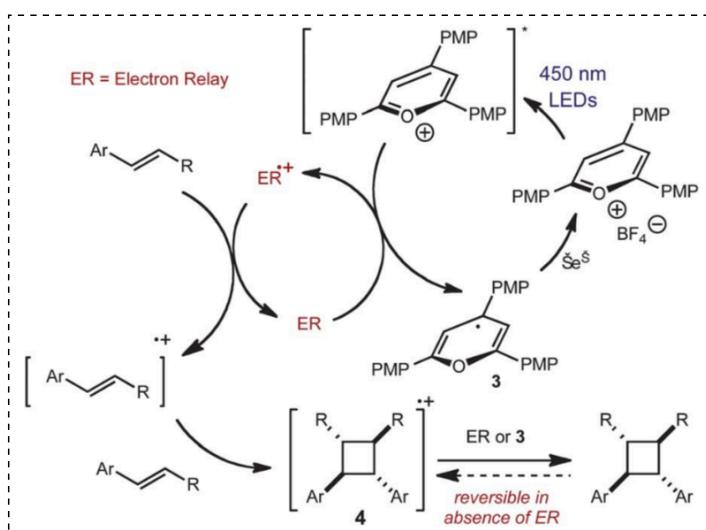
Control experiments



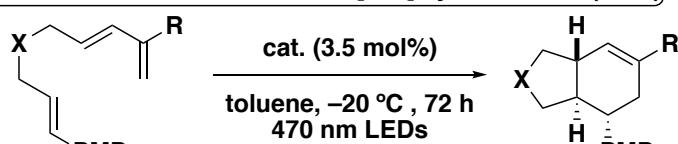
→ Anthracene suppressed cycloreversion by shielding the cyclobutane products



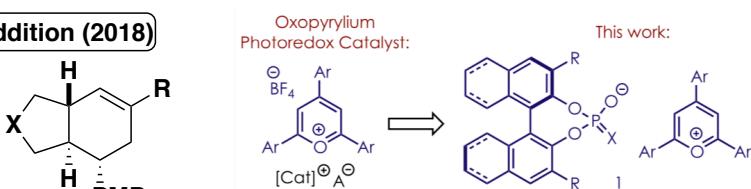
Proposed mechanism



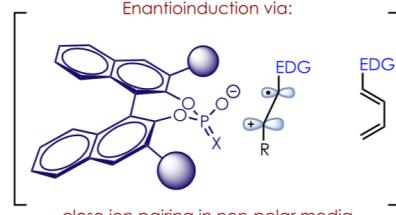
Enantio selective intramolecular [4+2] cycloaddition (2018)



PMP = $-C_6H_4(4\text{-OMe})$
 $(X = \text{O, TsN}$
 $R = i\text{-Pr, Cy, Bn, Me})$

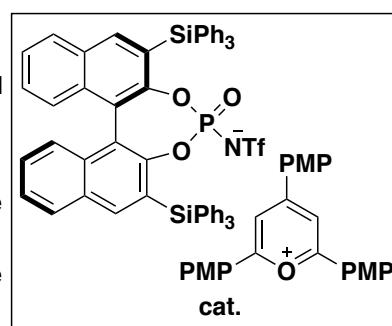
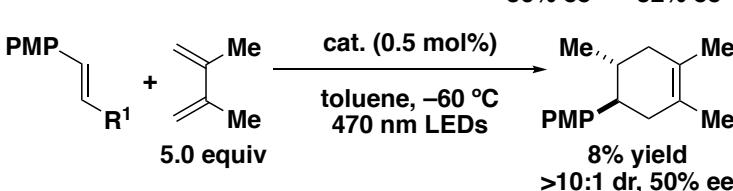
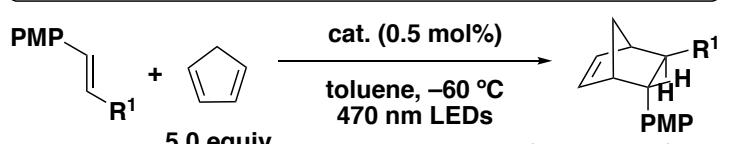


Enantioinduction via:



close ion pairing in non-polar media

Enantio selective intermolecular [4+2] cycloaddition (2018)



Nicewicz, D. A.

20) Nicewicz. et. al. *Chem. Sci.* 2013, 4, 2625.

21) Nicewicz. et. al. *Tetrahedron*. 2018, 74, 3266.