The Chemistry of Prof. Paolo Melchiorre

Radical Chemistry

Supervisor: Prof. Yong Huang
Reporter: Pengfei Yuan
Date: May. 31th, 2017

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Curriculum Vitae

Paolo Melchiorre

educational & **professional career**

- 1993-1999, MSc, University of Bologna (Italy);
- 2000-2003, PhD, University of Bologna;
- 2002, Research Period at Centre for Catalysis, University of Århus (DK);
- 2003-2006, Postdoctoral Fellow in Chemistry, University of Bologna;
- 2007-2009, Assistant Professor, University of Bologna;
- 2009 Sept –present, Research Professor, ICIQ – Tarragona (Spain).

Awards & Distinctions

2007 - Recipient of the ***"G. Ciamician" Gold Medal*** of the Italian Chemical Society

2008 - Recipient of the ***Liebig Lectureship*** awarded by the German Chemical Society

2009 - ***Thieme*** Journal Prize

2011 - ***ERC Starting Grant*** to carry out the 5-year project "ORGA-NAUT: Exploring Chemical Reactivity with Organocatalysis"

2013 - ***JSPS Fellowship*** under the FY2013 Program for Research in Japan

2014 - ***Erdtman Lecture 2014*** – Stockholm (Sweden)

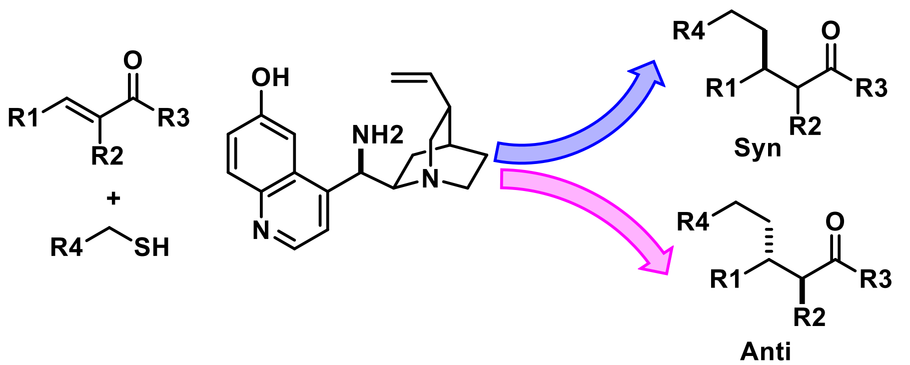
2015 - ***Thieme Lecture –*** *DOMINOCAT SYMPOSIUM* – Aachen (Germany)

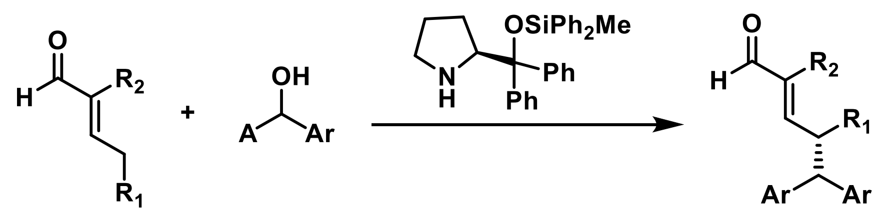
2015 - ***ERC Consolidator Grant*** to carry out the 5-year project "CATA-LUX"

2016 - Prize for Scientific Excellence from the Royal Spanish Chemical Society (**RSEQ**)

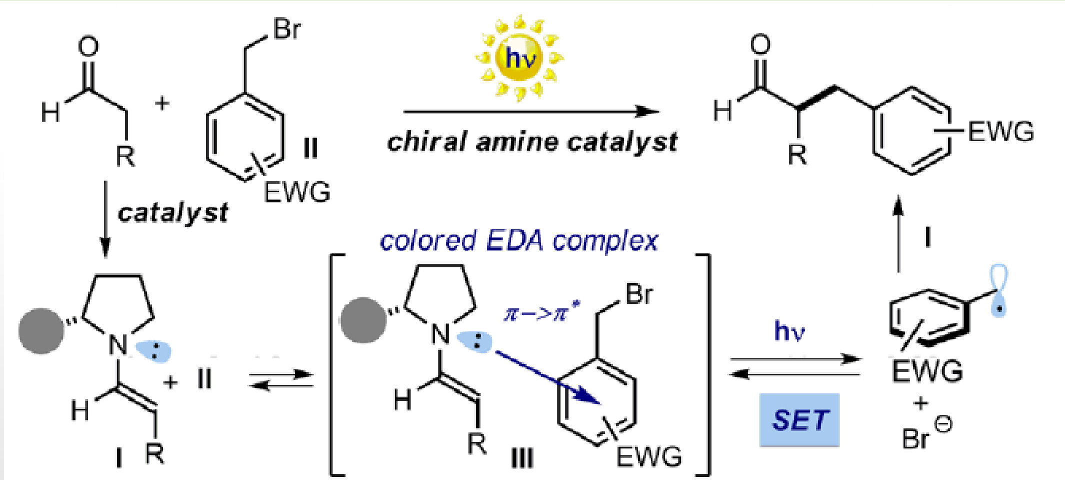
Research Interests

2009-2013, Discovery and mechanistic elucidation of new asymmetric organocatalytic processes and their application in drug discovery research





2013-present, Lie on the discovery and mechanistic elucidation combine new asymmetric organocatalytic with photochemical processes



P. Melchiorre, *Nat. Chem.*, **2013**, *5*, 750.

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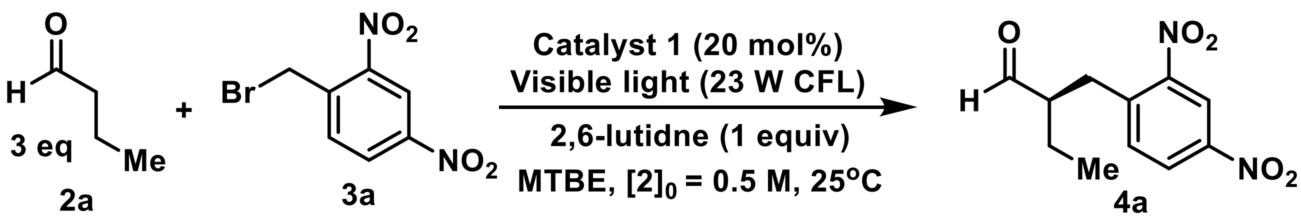
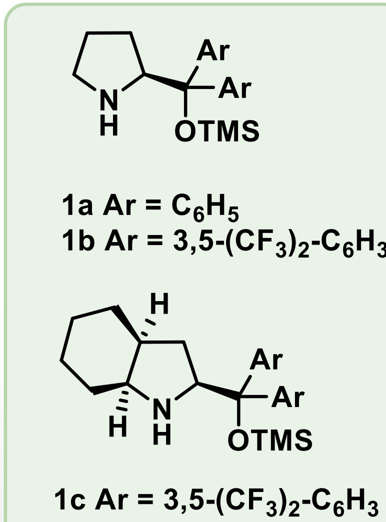
Photoactivation of EDA Complex

Photochemical activity of EDA (electron donor–acceptor) complexes drive stereoselective catalytic a-alkylation of aldehydes



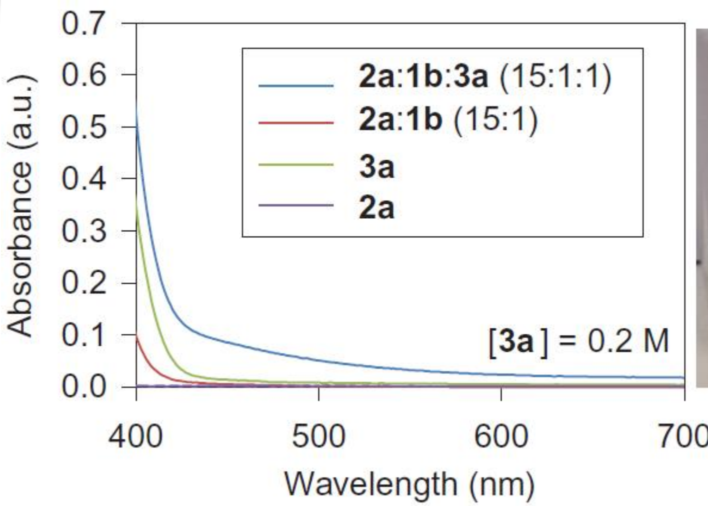
Entry	Catalyst	Light	Time	Yield (%)	e.e. (%) 4a
1	1a	ON	6 h	98	75
2	1b	ON	6 h	98	83
3*	1b	ON	6 h	94	82
4	1b	OFF	48 h	0	-
5	1b	OFF, 50 °C	48 h	0	-
6	-	ON	48 h	0	-
7	1b	ON, LED†	16 h	89	82
8	1b	ON, in air	40 h	78	84
9	1c	ON	48 h	87	92

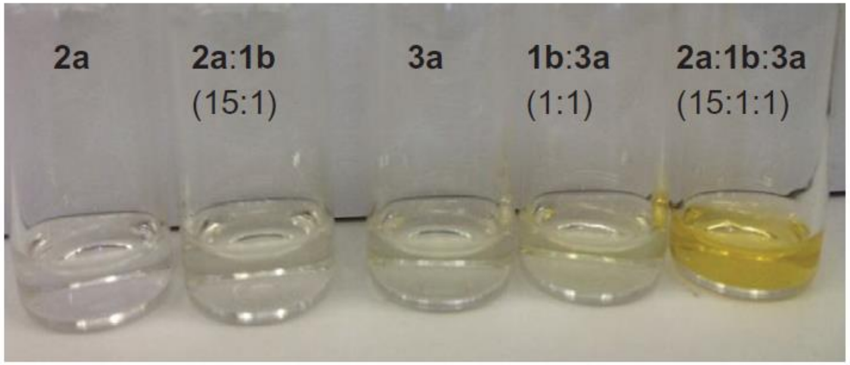


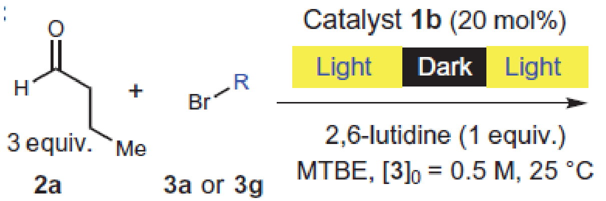
*Reaction performed using 1 equiv. NaOAc instead of 2,6-lutidine. 460 nm LED

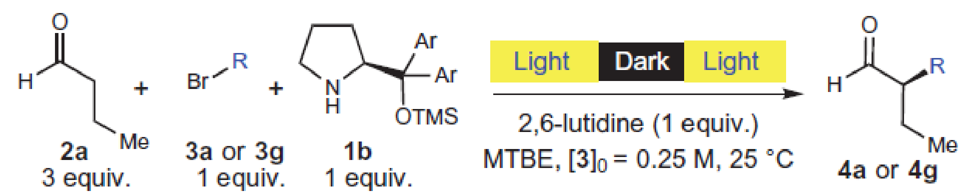
P. Melchiorre, *Nat. Chem.*, **2013**, *5*, 750.

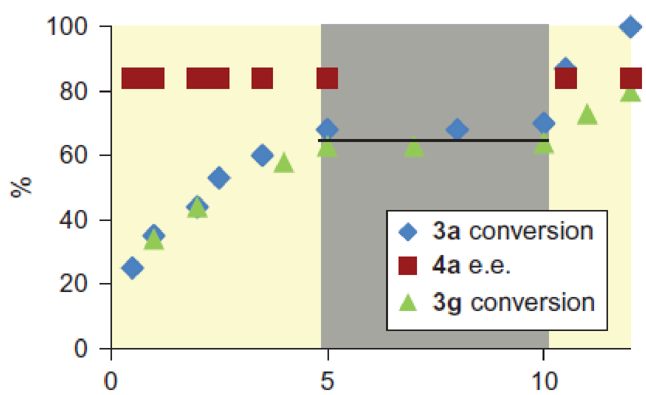
Mechanistic investigations

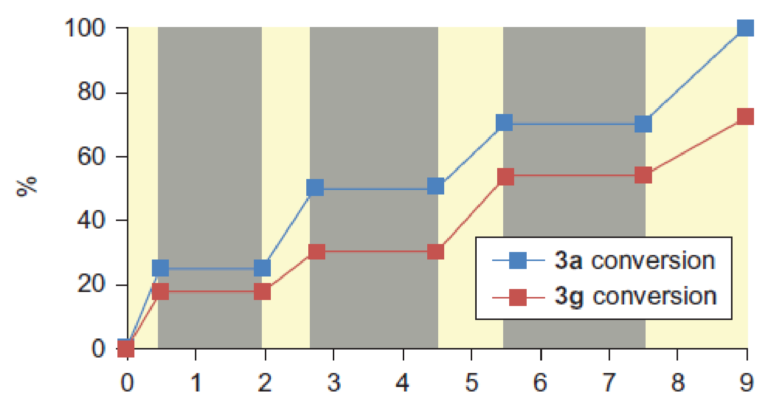










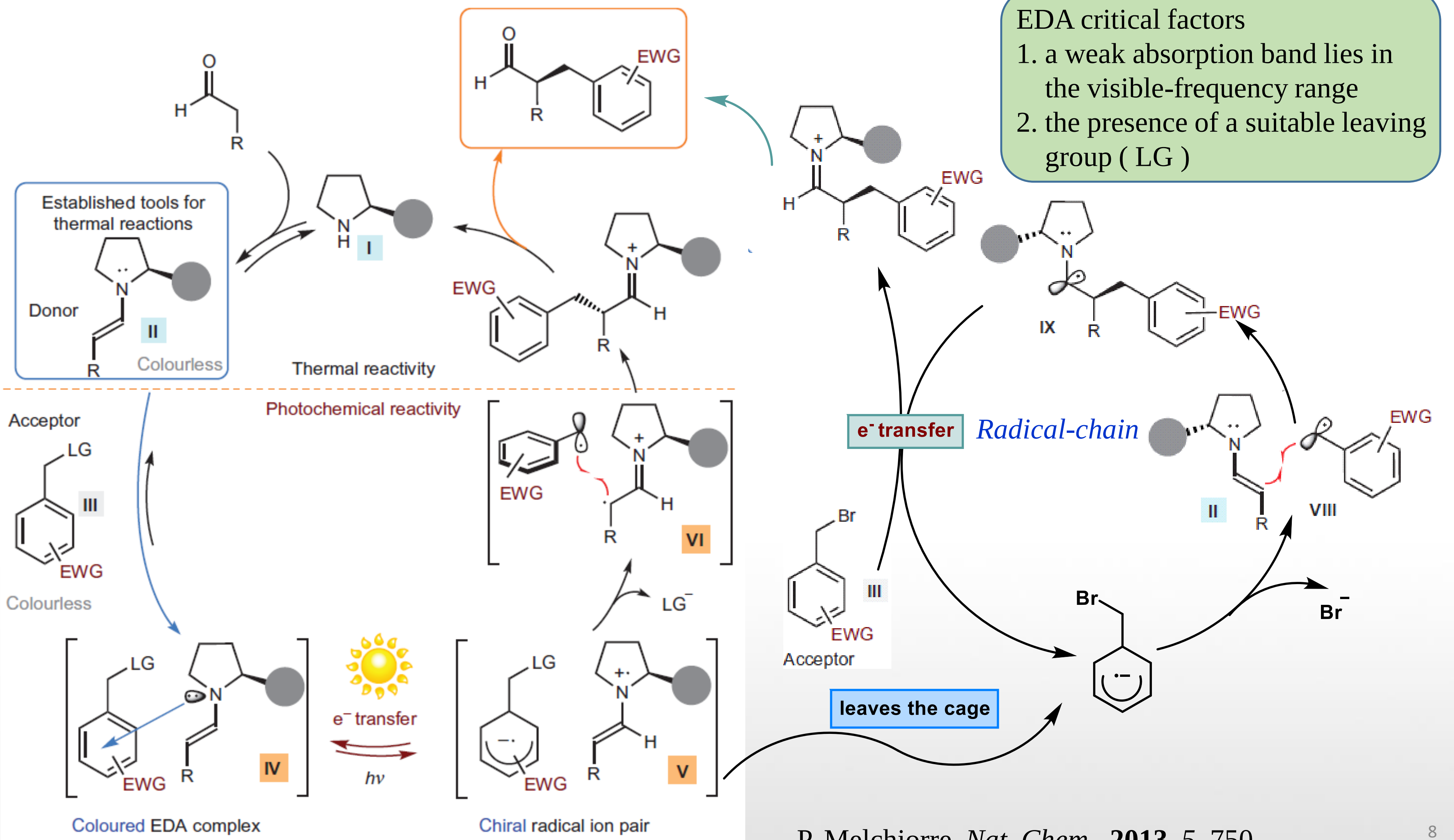


Photoactivation of EDA Complex

Mechanistic proposal for asymmetric catalytic photochemical processes

EDA critical factors

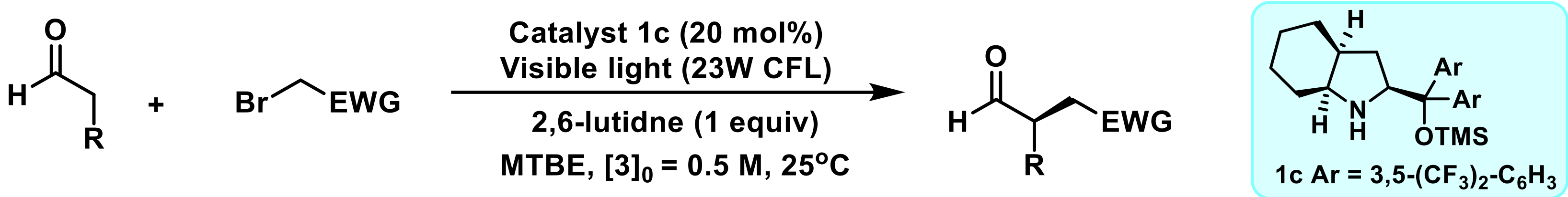
1. a weak absorption band lies in the visible-frequency range
2. the presence of a suitable leaving group (LG)

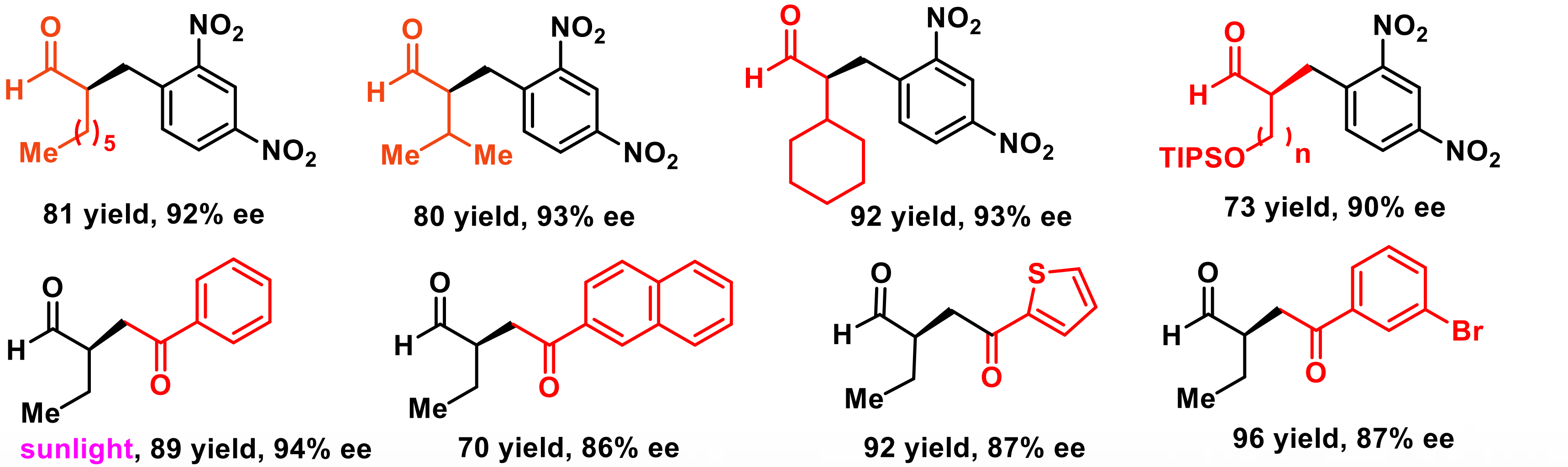


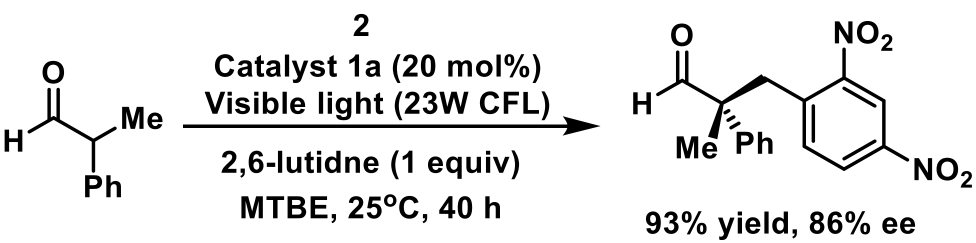
P. Melchiorre, *Nat. Chem.*, **2013**, *5*, 750.

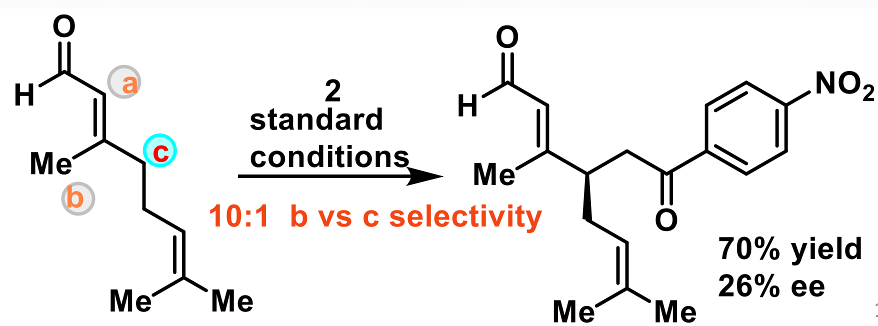
Photoactivation of EDA Complex

Evaluating the scope and the strategy's potential to address synthetically relevant problems



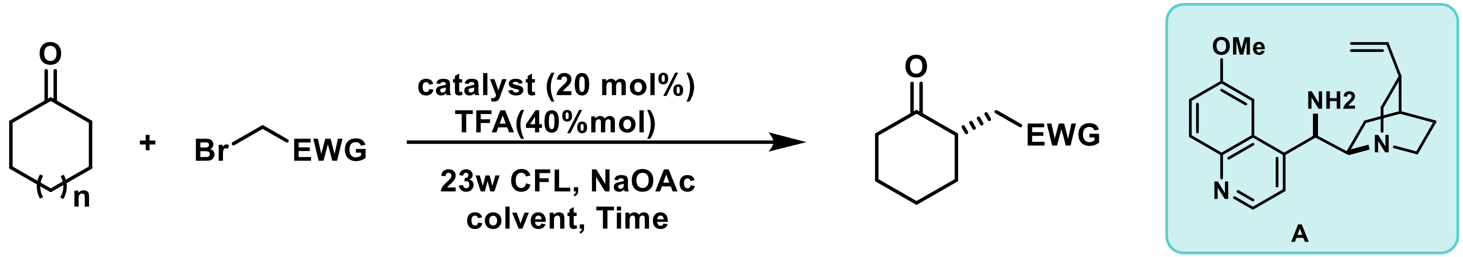






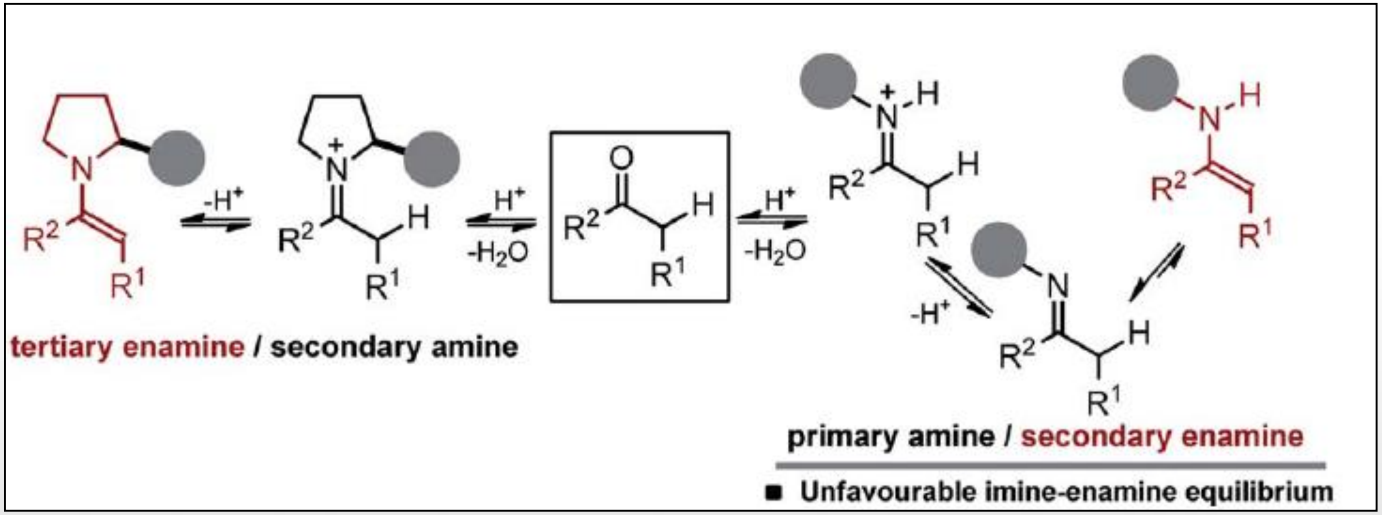
Photoactivation of EDA Complex

Enantioselective direct a-alkylation of cyclic ketones by photo-organocatalysis



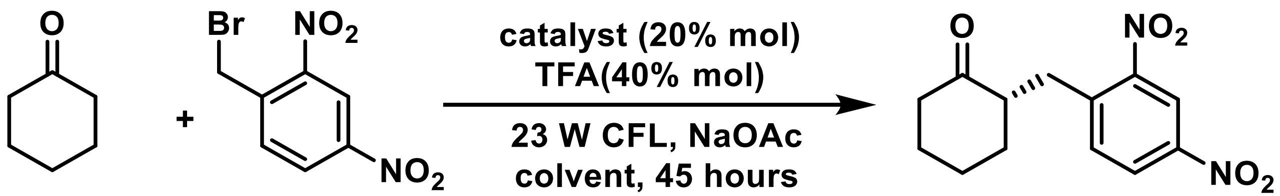
Concerns:

1. increased steric impediments which significantly limit the use of chiral secondary amine catalysts.
2. the resulting secondary enamine, which should have a suitable ionization potential (IP).
3. Have capable of conferring a high level of stereocontrol during the carbon–carbon bond forming event.



P. Melchiorre, *Chem. Sci.*, **2014**, *5*, 2438.

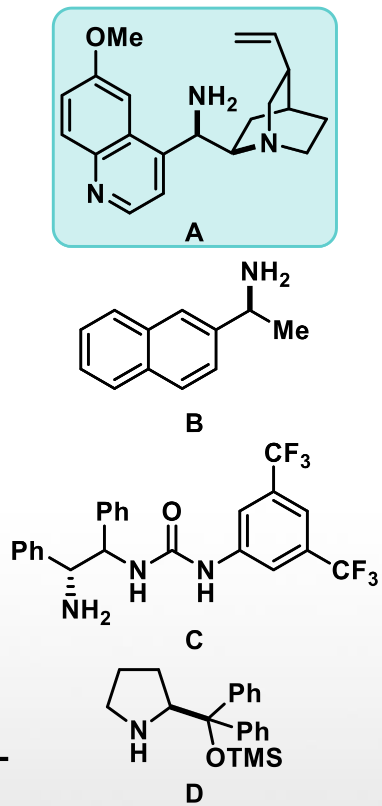
Explorative studies



Entry	Catalyst	Solvent	T (°C)	Conv.[b] (%)	ee[c] (%)
1[d]	**D**	Toluene	25	<5	n.d.
2	**A**	Toluene	25	45	88
3[e]	**C**	Toluene	25	45	42
4[e]	**B**	Toluene	25	90	18
5	**A**	$CHCl_3$	25	<5	n.d.
6	**A**	MTBE	25	19	68
7	**A**	DMSO	25	<5	n.d.
8	**A**	Toluene	0	60[f]	90
9	**E**	Toluene	0	50[f]	90[g]
10[h]	**A**	Toluene	40	<5	n.d.
11	—	Toluene	25	<5	n.d.
12[i]	**A**	Toluene	0	<5	n.d.

h: Reaction performed in the dark. i: Reaction performed in air.

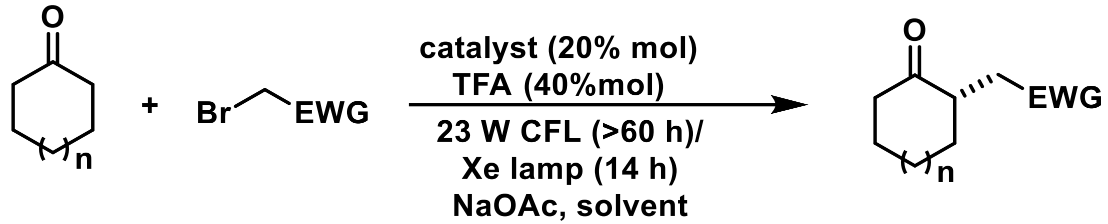
Catalysts

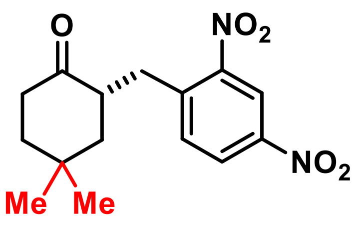


P. Melchiorre, *Chem. Sci.*, **2014**, *5*, 2438.

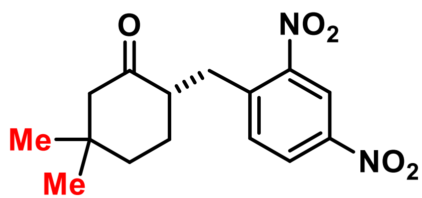
Photoactivation of EDA Complex

Scope of the photochemical ketone a-alkylation

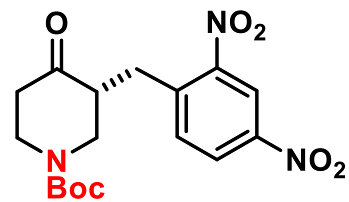




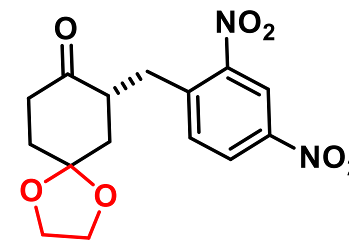
65% yield, 82% ee



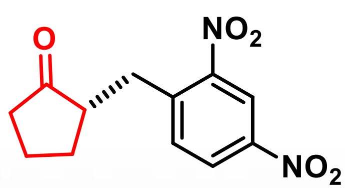
57% yield, 94% ee



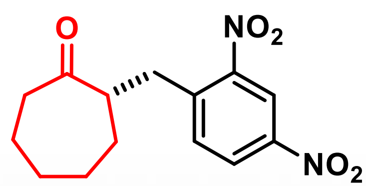
69% yield, 94% ee



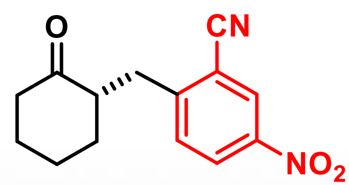
70% yield, 95% ee



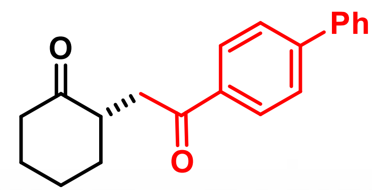
44% yield, 62% ee



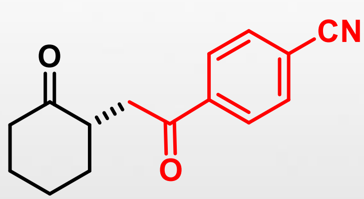
38% yield, 74% ee



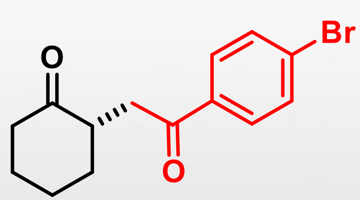
45% yield, 88% ee



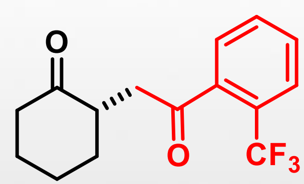
42% yield, 86% ee



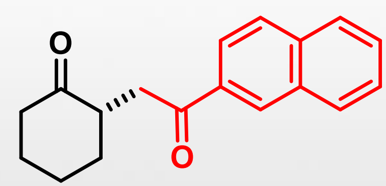
42% yield, 88% ee



52% yield, 86% ee

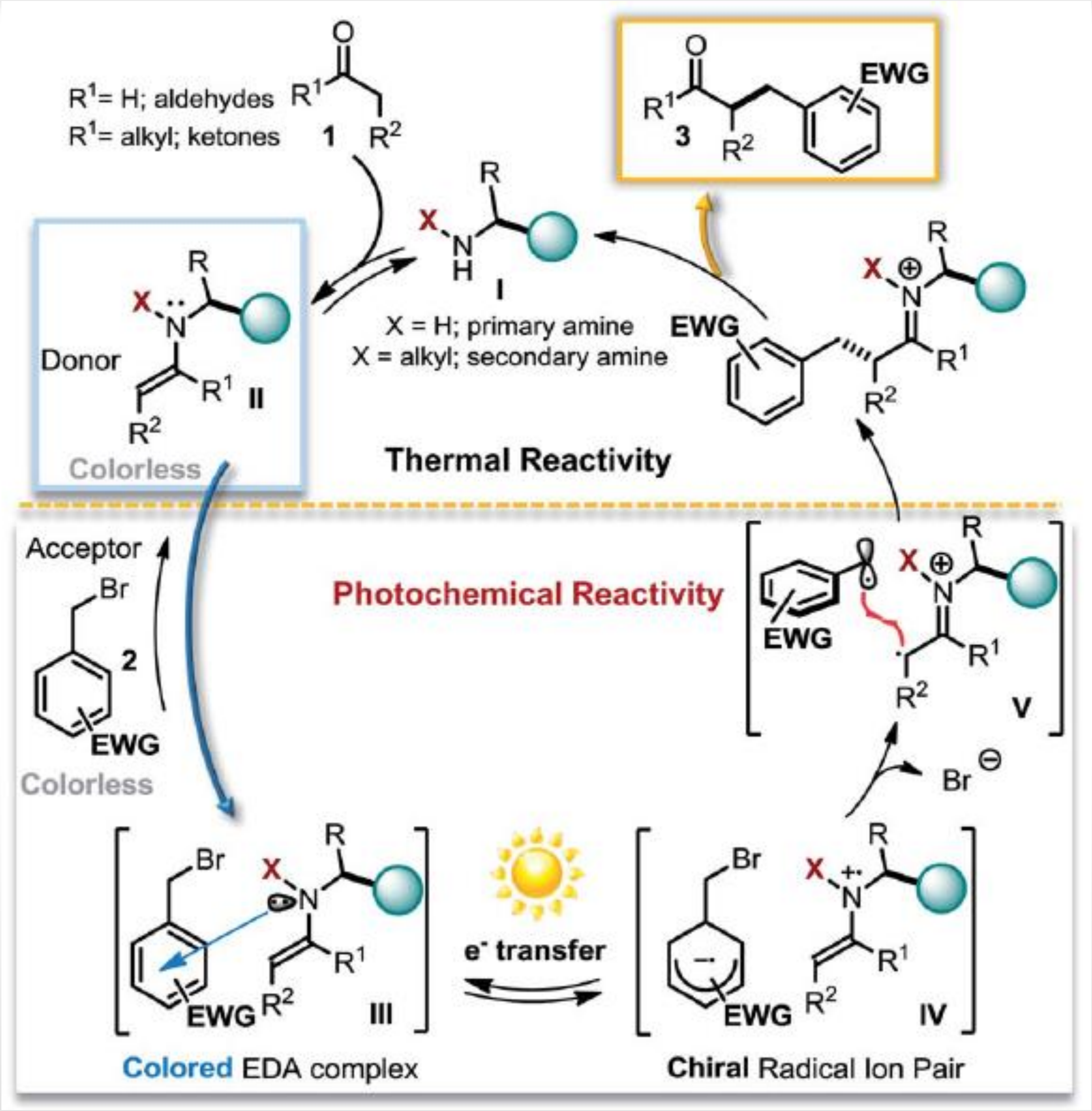


50% yield, 76% ee



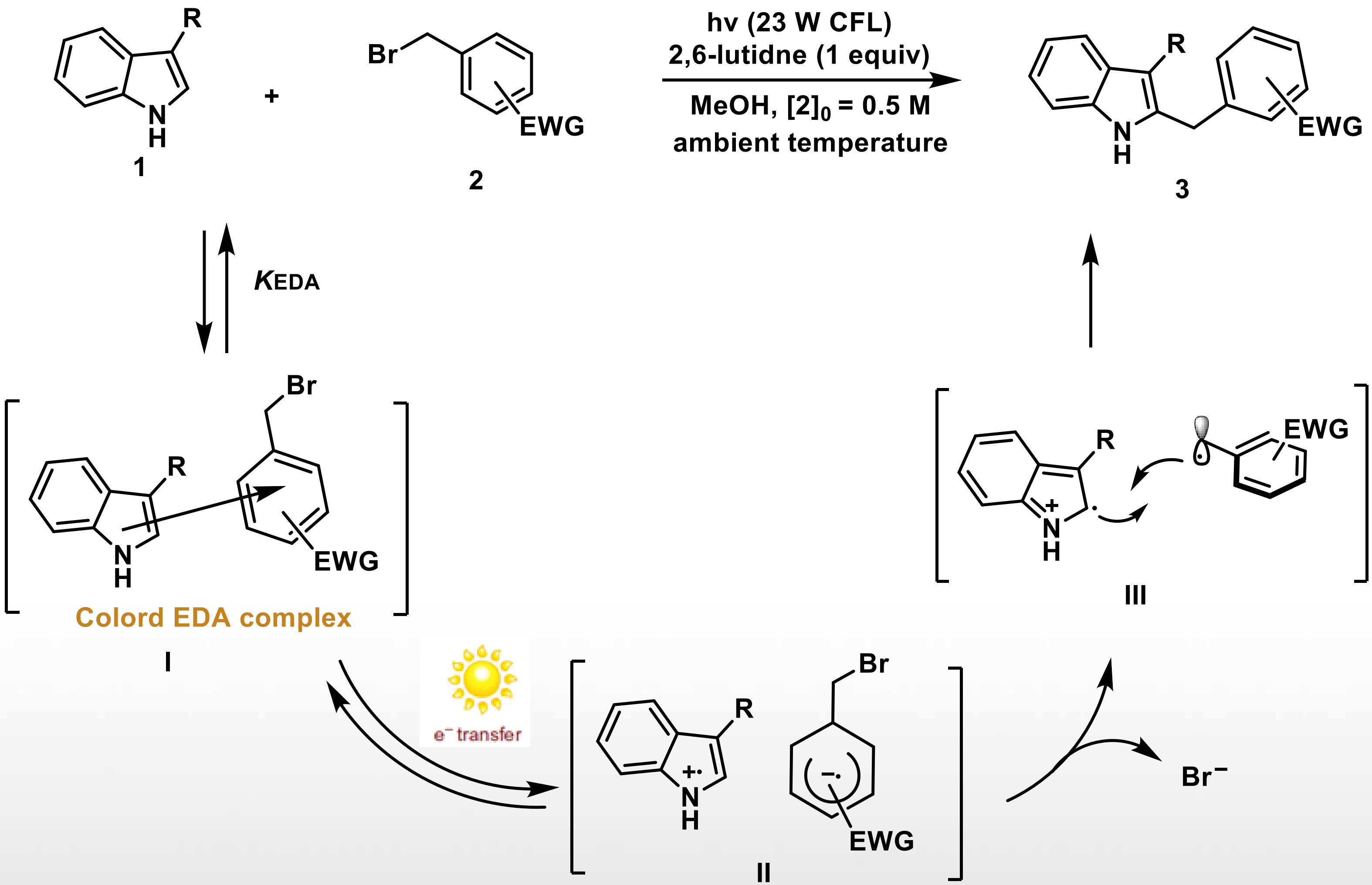
73% yield, 92% ee

Photoactivation of EDA Complex



Photoactivation of EDA Complex

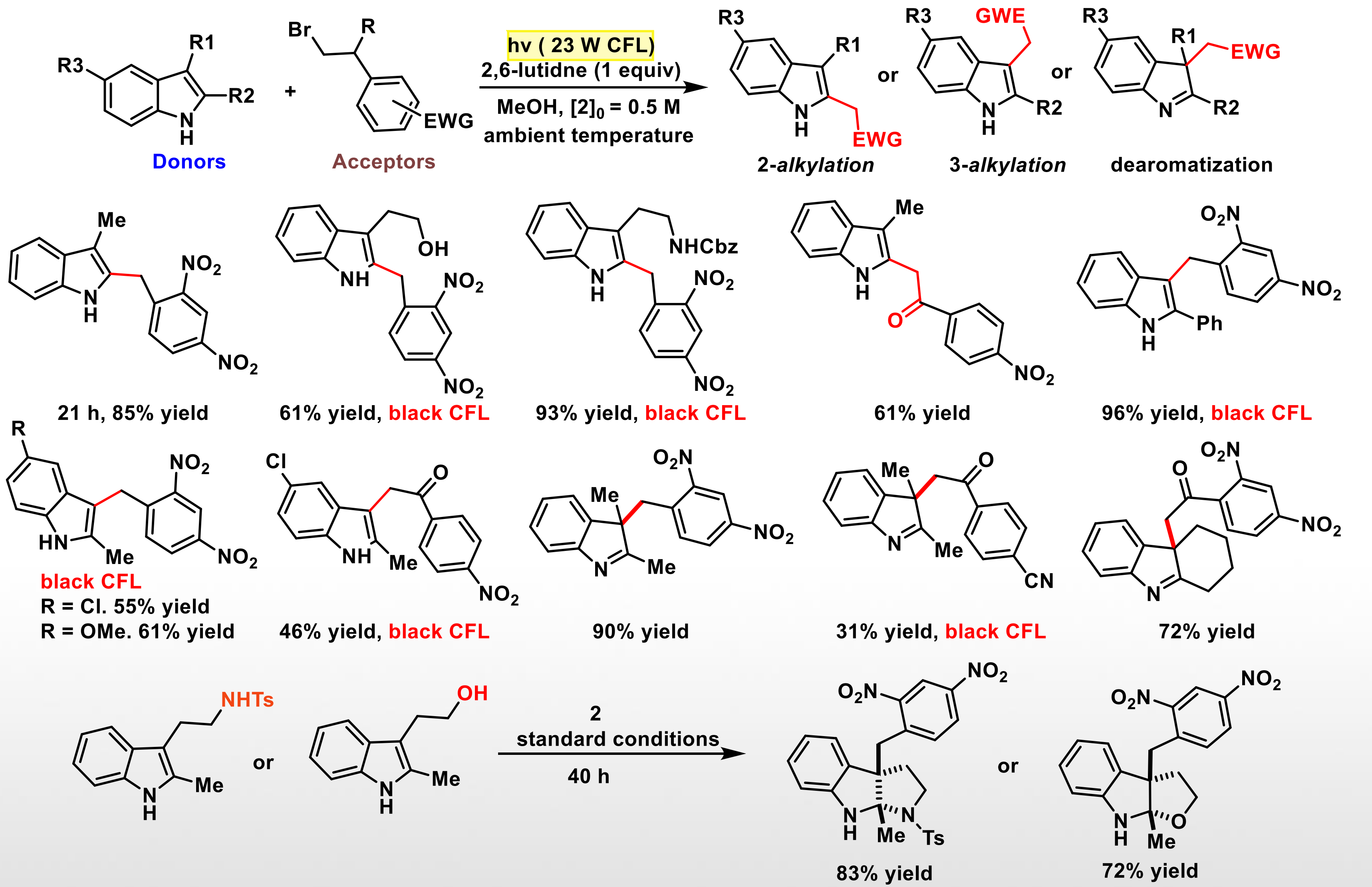
Electron Donor–Acceptor Complex that Drives the Photochemical Alkylation of Indoles



P. Melchiorre, *Angew. Chem. Int. Ed.* **2015**, *54*, 1485.

Photoactivation of EDA Complex

Evaluation of the scope of the photochemical indole alkylation strategy



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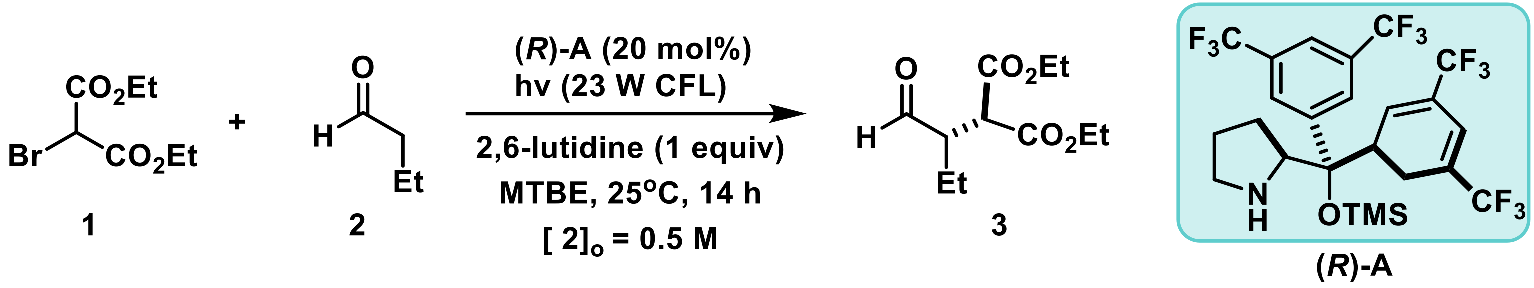
Photoactivation of Enamines

Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines

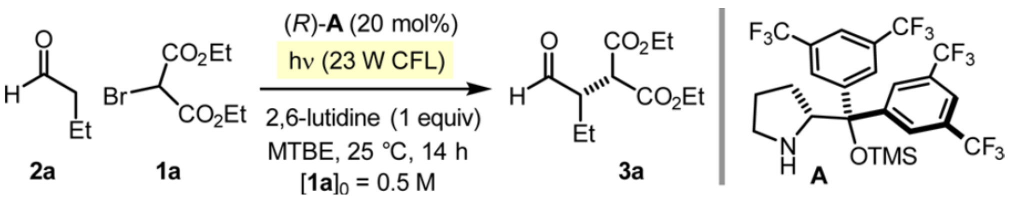


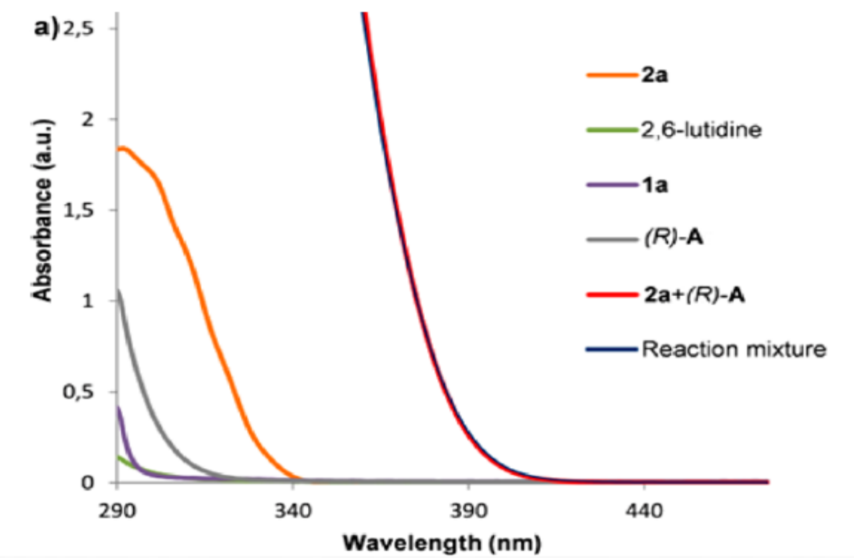
entry	deviation from standard conditions	% yield	% ee[b]
1	4 h reaction time	94[c]	83
2	in the dark	<5	
3	in air	<5	
4	TEMPO (1 equiv)	<5	
5	2 h, 10 mol % **A**	33	83
6	2 h, 10 mol % **A**, 0.5 mol % $Ru(bpy)_3^{2+}$	74	83
7[d]	cut off @ 385 nm	>95[e]	83
8[d]	band-pass @ 400 nm	>95[e]	83
9[d]	band-pass @ 450 nm	<5	

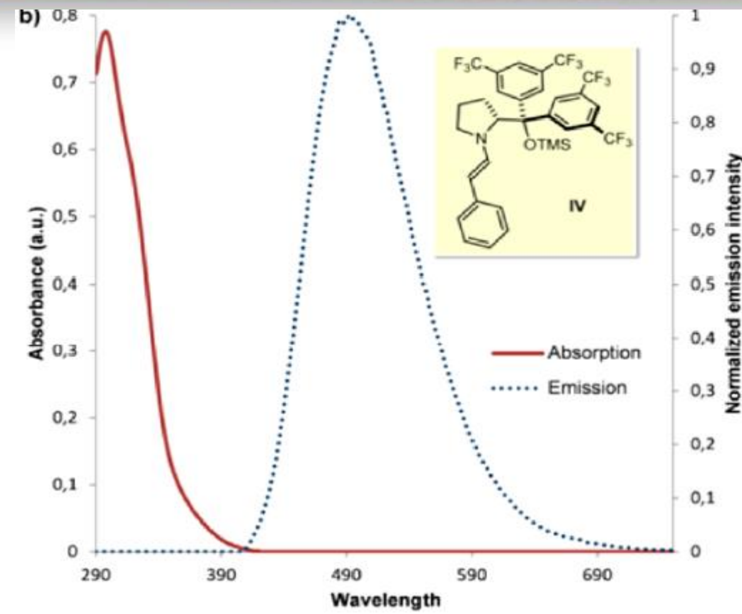
d : using a 300 W xenon lamp

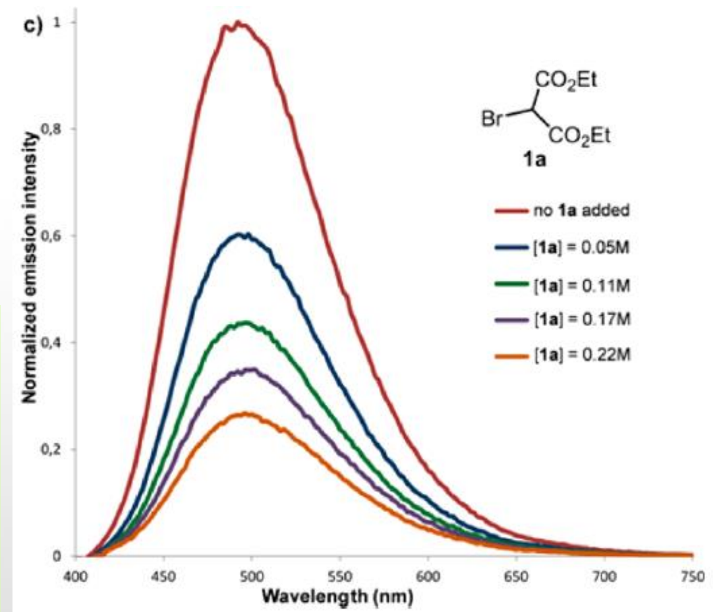
P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120.

Mechanistic Investigations



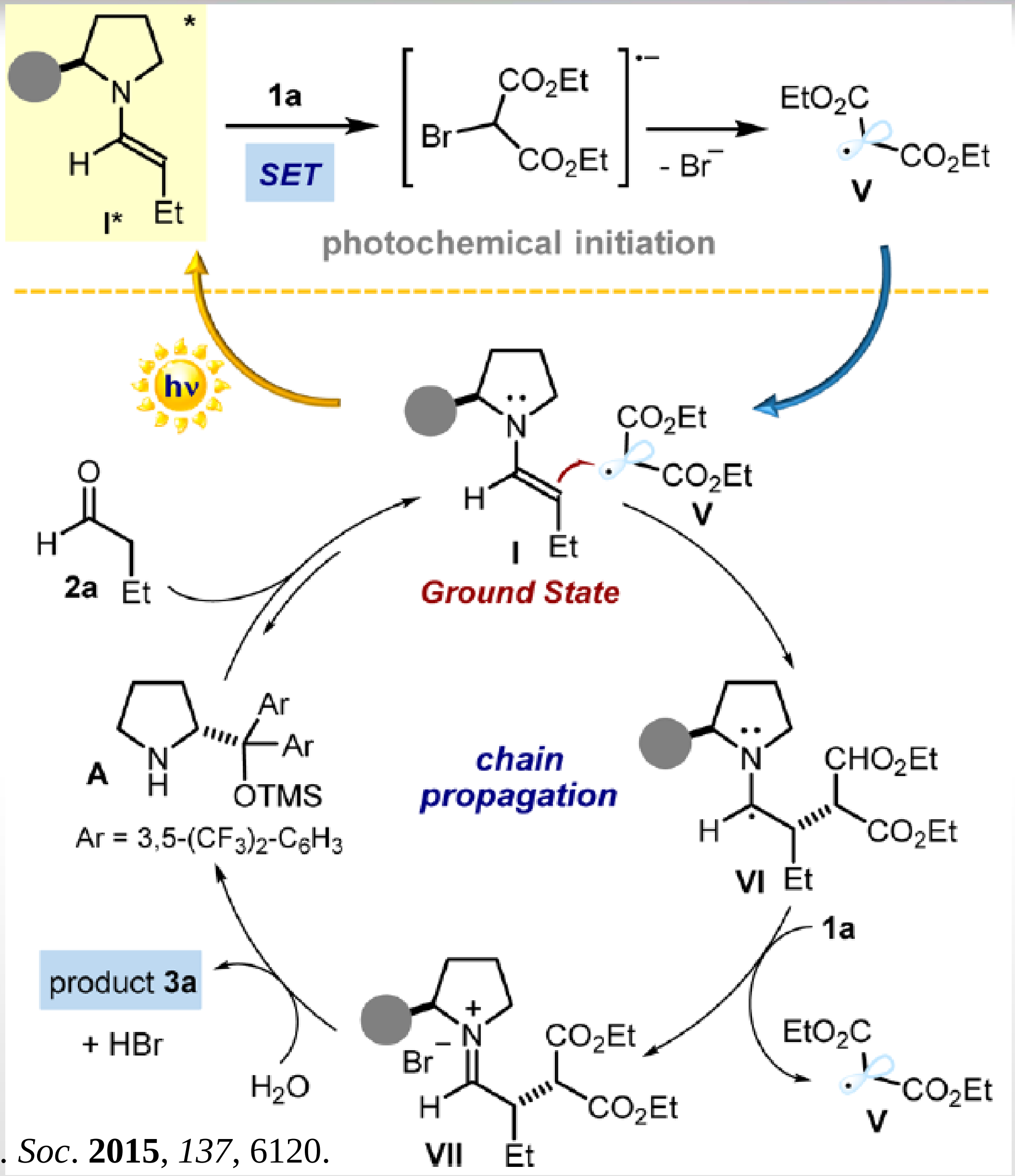






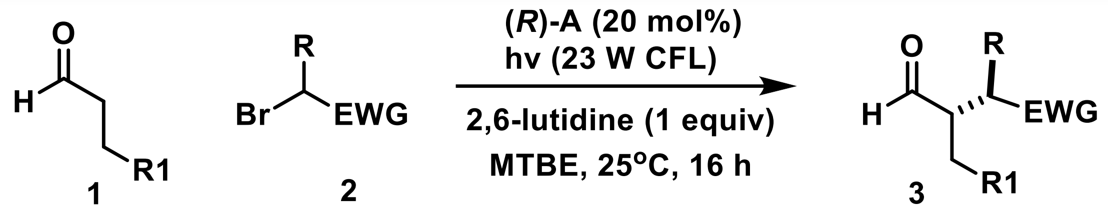
a: Excluding any EDA association in the ground state
b: Absorption band until 415 nm
c: Stern−Volmer quenching Studies revealed that bromomalonate 1a effectively quenched the excited state of enamine **IV**

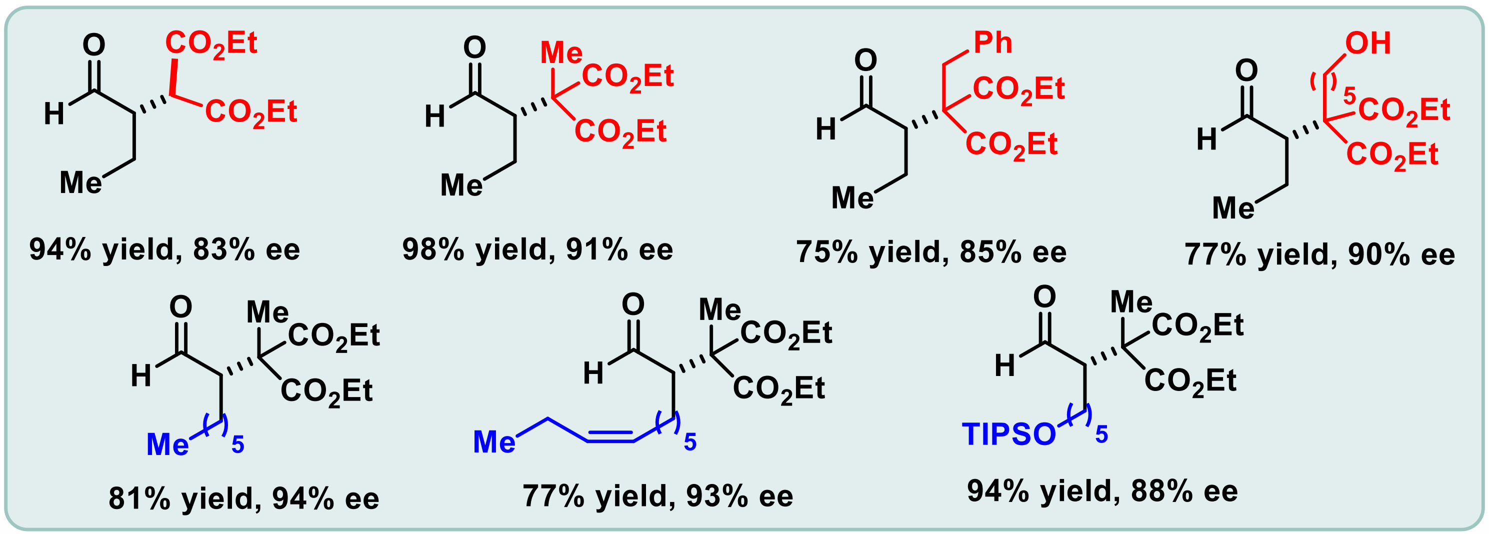
Proposed Mechanism

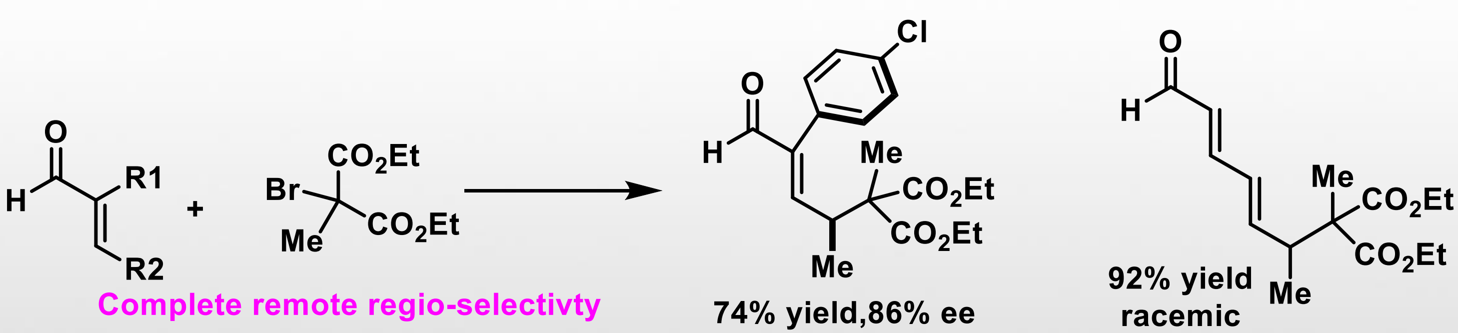


P. Melchiorre, *J. Am. Chem. Soc*. **2015**, *137*, 6120.

Substrate Scope

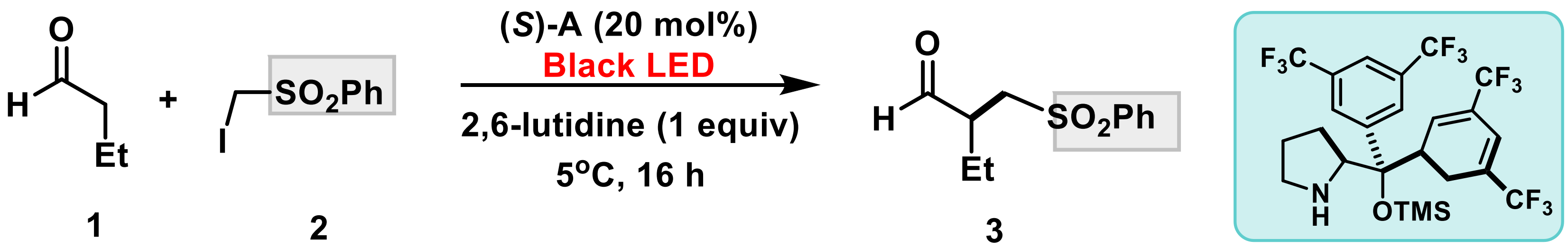






Photoactivation of Enamines

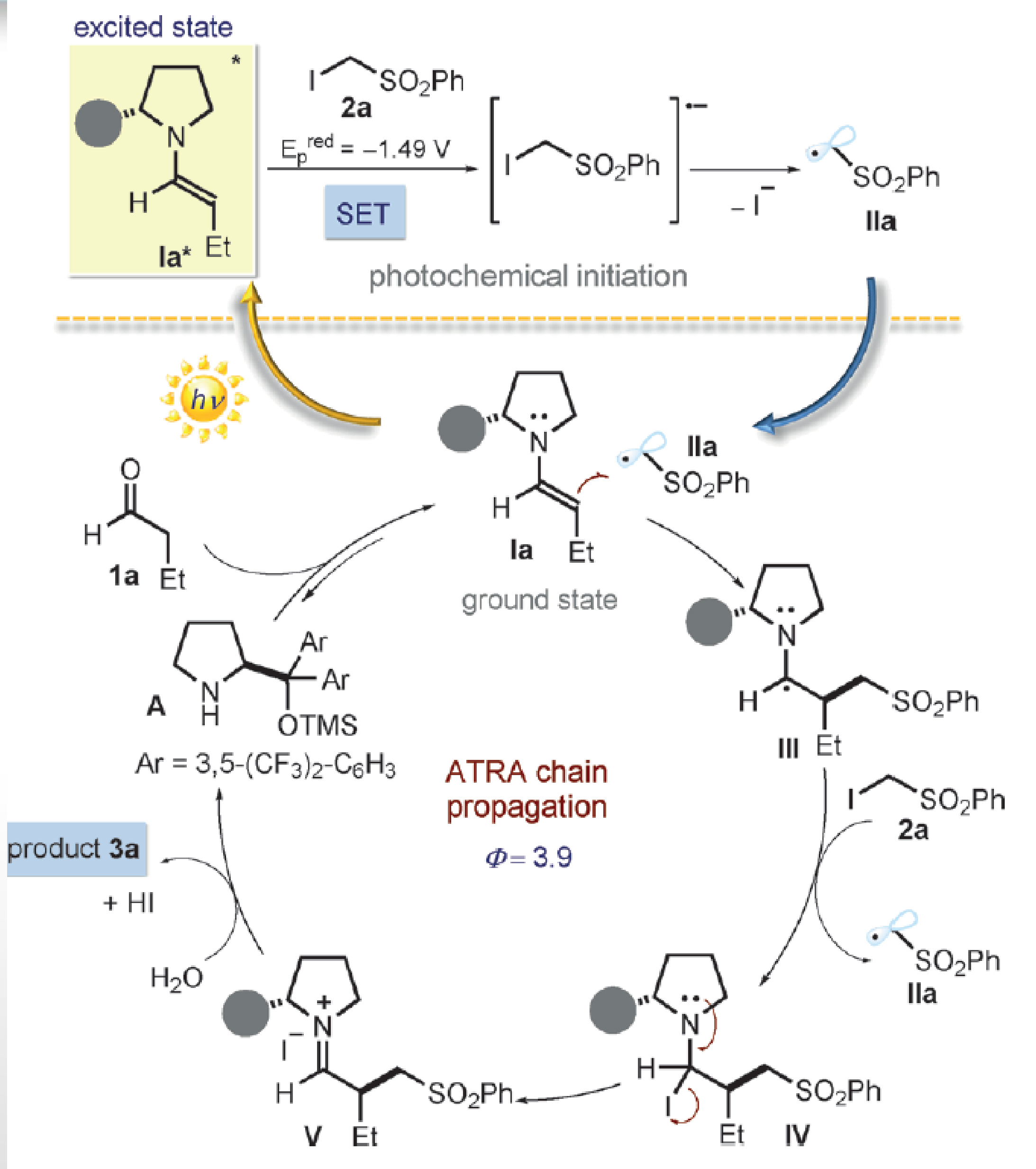
Enantioselective Formal a-Methylation or Benzylation by Means of Photo-Organocatalysis



Entry	Solvent	Additives and Conditions	Yield [%][b]	*ee* [%][c]
1	toluene	–	43	80
2	toluene	I_2 (10 mol%)	13	80
3	toluene	$Na_2S_2O_3$ (10 mol%)	50	80
4	toluene/hexanes/H_2O (1:1:2 ratio)	$Na_2S_2O_3$ (50 mol%)	99 (76)[d]	82 (80)
5	toluene/hexanes/H_2O (1:1:2 ratio)	$Na_2S_2O_3$ (50 mol%), in the dark	< 5	–
6	toluene/hexanes/H_2O (1:1:2 ratio)	$Na_2S_2O_3$ (50 mol%), O_2 or TEMPO (1 equiv)	< 5	–
7	toluene/hexanes/H_2O (1:1:2 ratio)	$Na_2S_2O_3$ (50 mol%), band pass @ 400 nm	92	82

P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 4447.

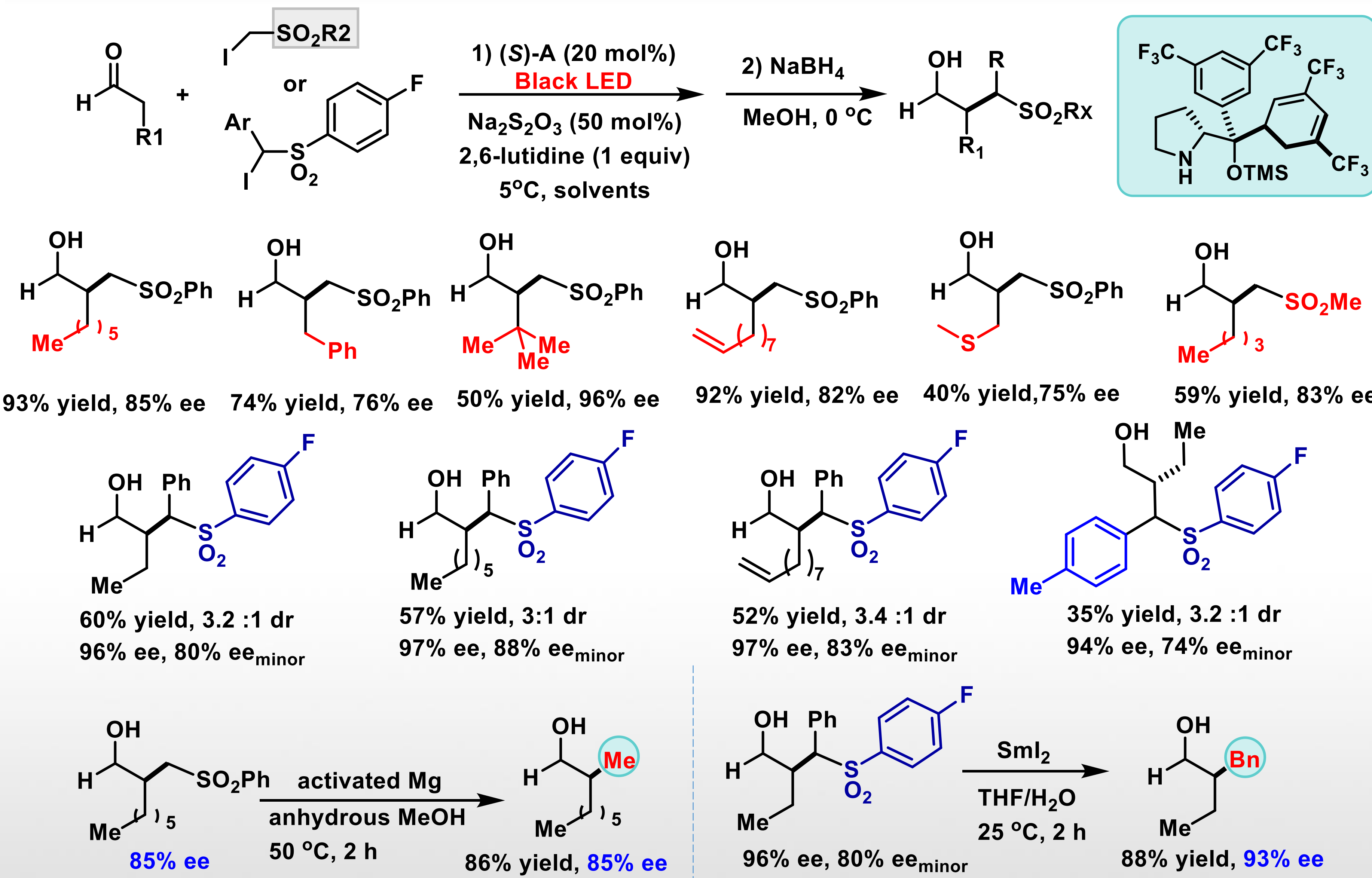
Proposed Mechanism



Ep^{red} V/III = -0.95 V

Ep ^{red} 2a = -1.49 V

Substrate Scope



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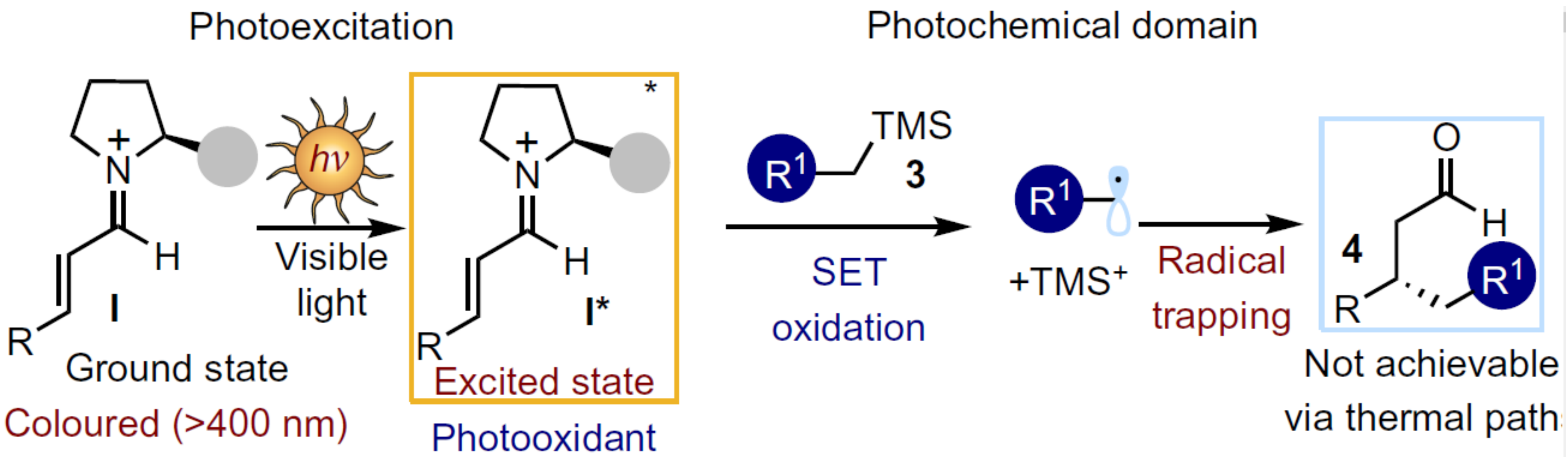
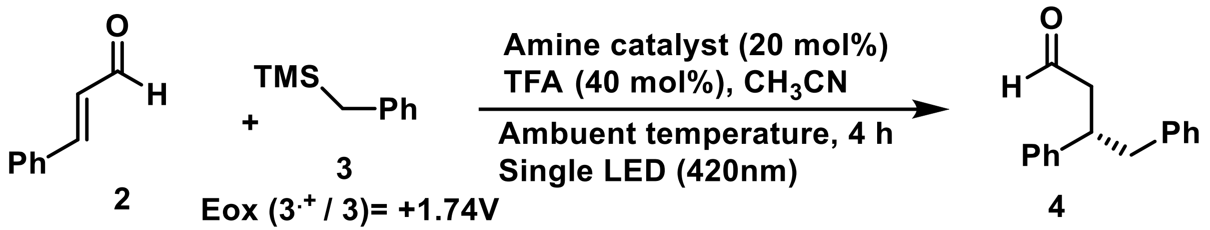
Phexcitation of Iminium Ions



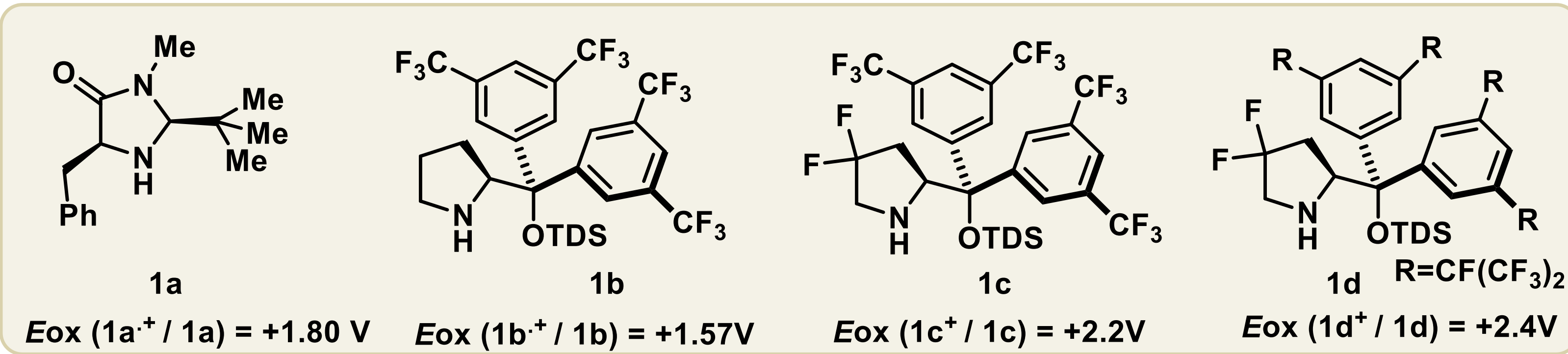
P. Melchiorre, *Nature Chem.*, **2017**, DOI: 10.1038/nchem.2748.

Phexcitation of Iminium Ions

Light excitation of iminium ions enables the enantioselective catalytic β-alkylation of enals



3: electron rich trimethylsilane reagents



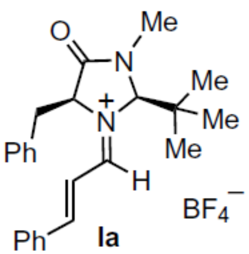
Entry	Catalyst	Light	3a yield (%)	e.e. (%)
1	1a	On	79	30
2	None	On	0	–
3	1a	Off	0	–
4	1b	On	28	76
5	1c	On	83	85
6	1d	On	87	88

E_{ox} for catalysts 1 measured by cyclic voltammetry versus Ag/Ag^{+} in CH_3CN.

(Ered* ($Ib^{*}/Ib^{\cdot-}$) = +2.3 V versus Ag/Ag+ in CH3CN)

P. Melchiorre, *Nature Chem.*, **2017**, DOI: 10.1038/nchem.2748.

Mechanistic investigation



E_{red}^{*} (Ia*/Ia·−) ~ +2.3 V

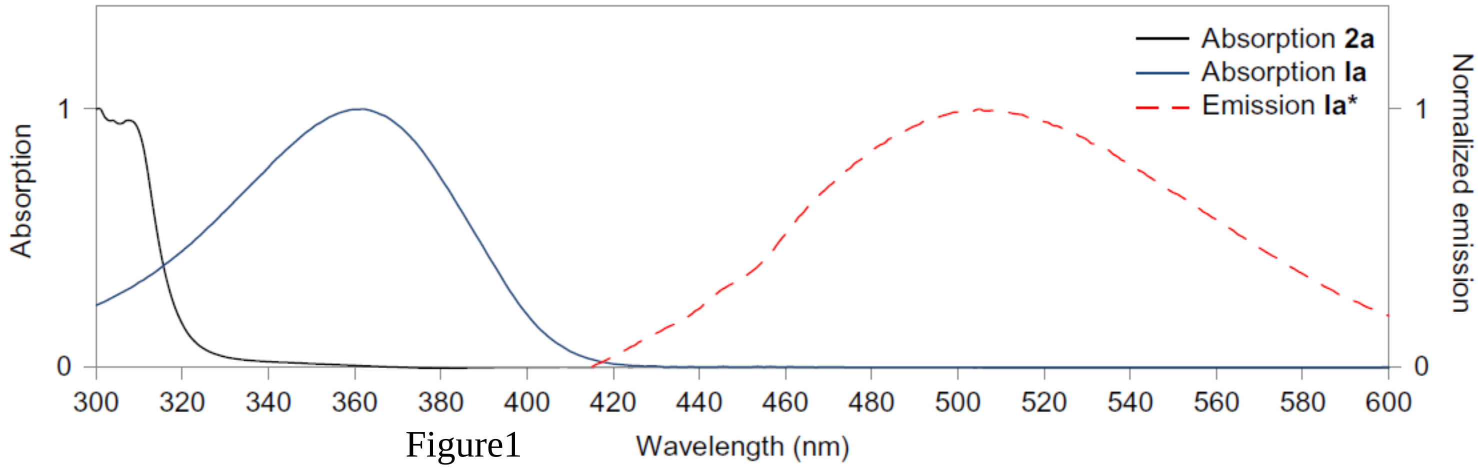
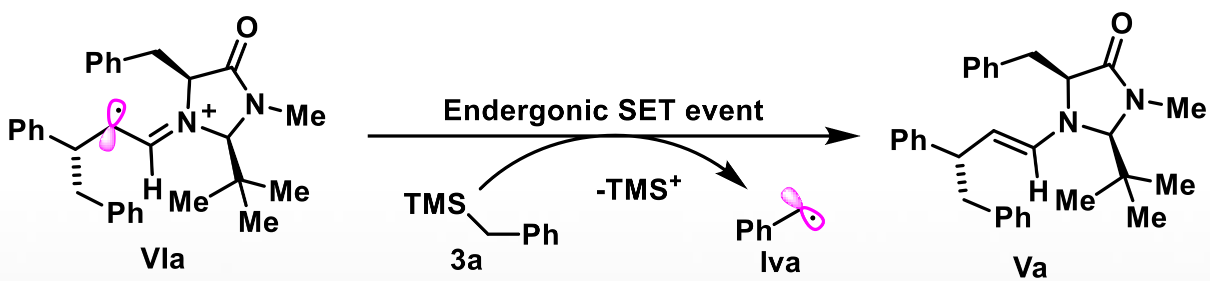


Figure1

Key step of a possible chain propagation manifold



E_{red} (VIa·+ / Va) = + 0.9V

E_{ox} (3a·+ / 3a) = + 1.74 V

Figure 2

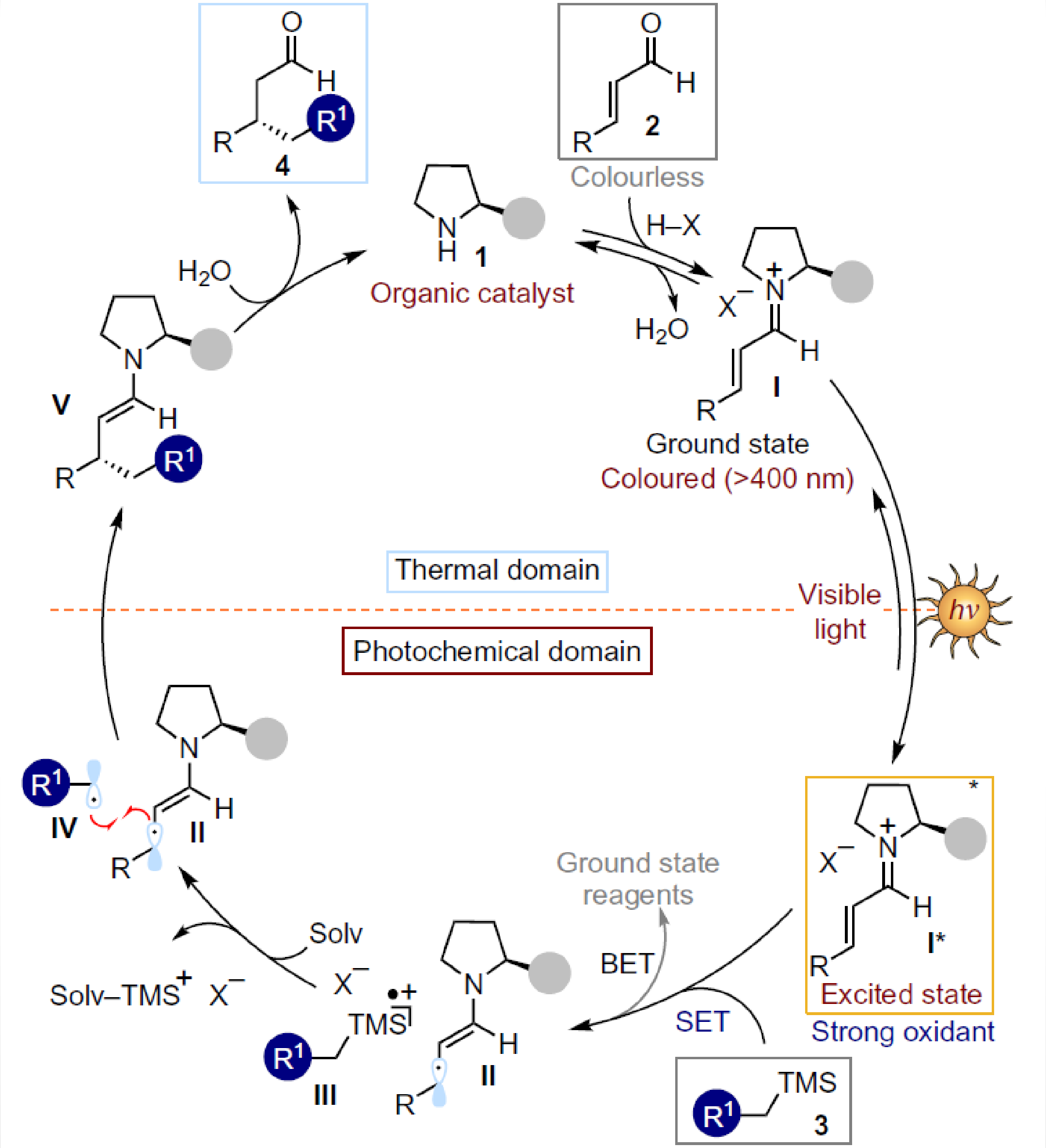
A chain propagation mechanism is unlikely for several reasons:

(i) the already-mentioned poor nucleophilicity of benzyl radicals

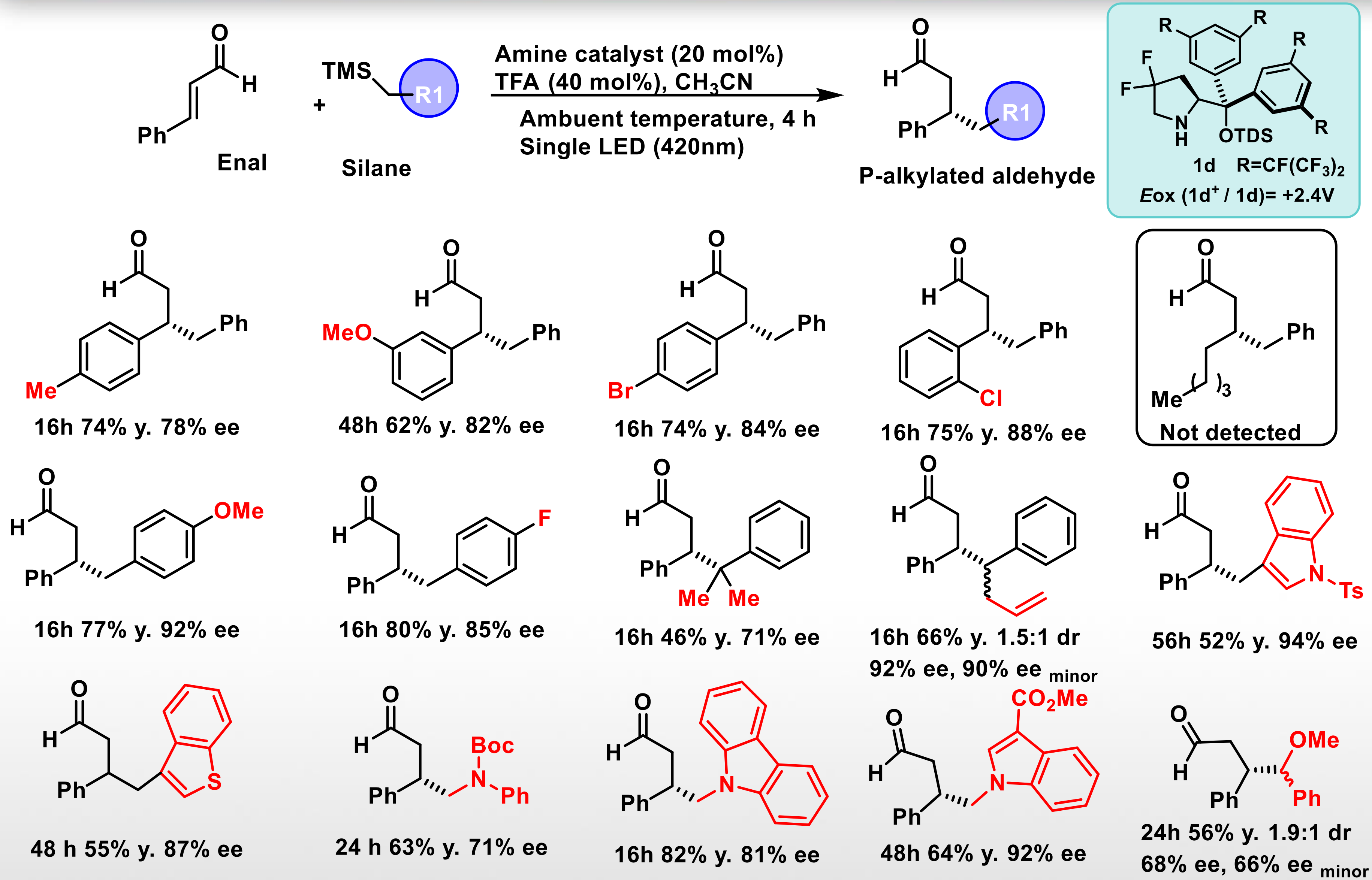
(ii) the low tendency of iminium ions to trap radicals

(iii) the endergonic SET in Fig. 2 is highly disfavoured when considering the redox potentials

Proposed Mechanism



Substrate Scope



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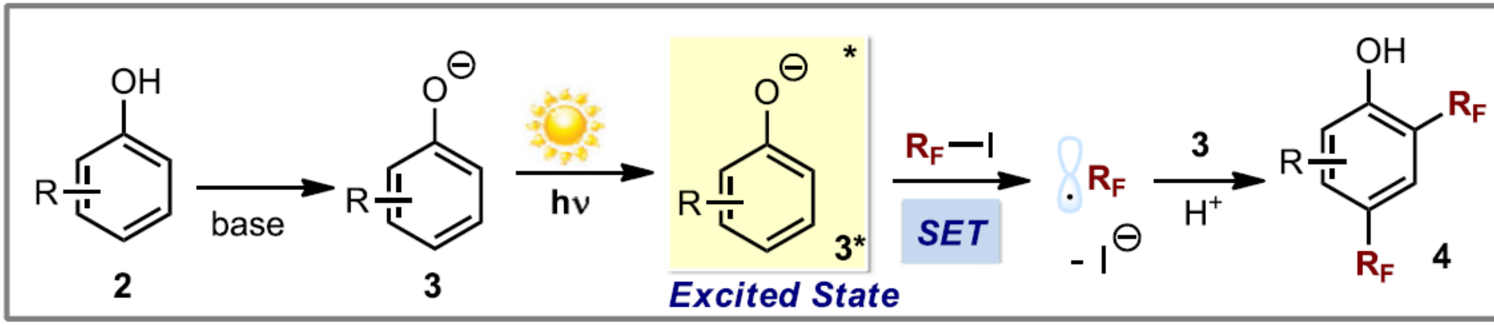
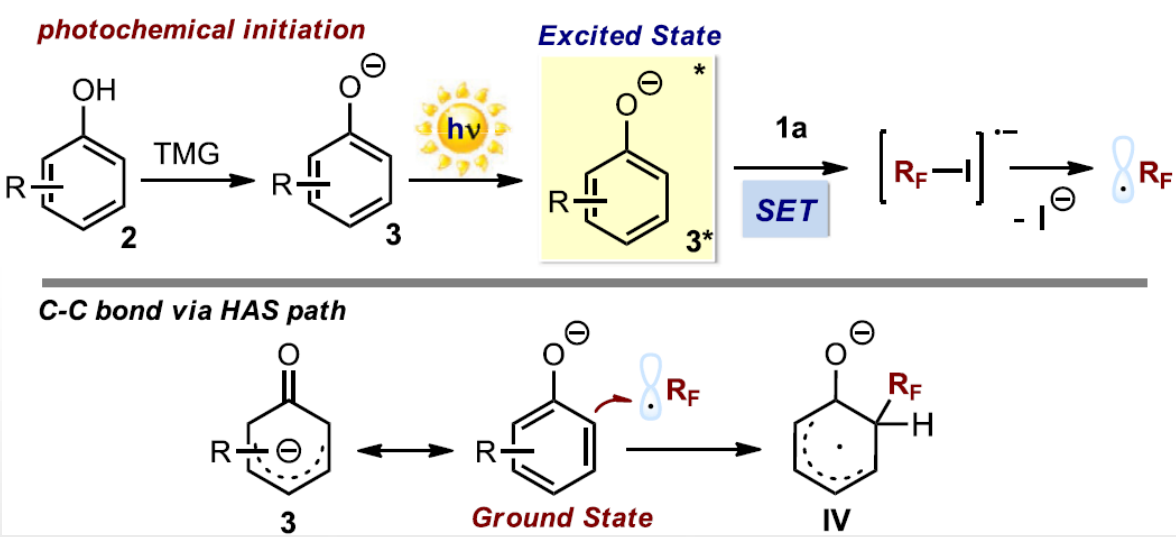
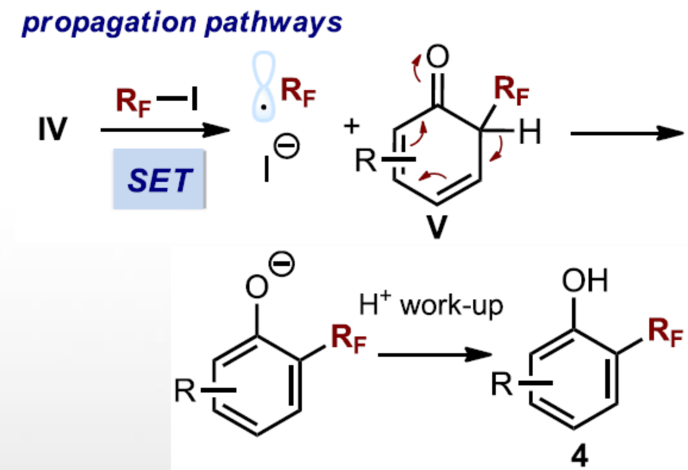
Other Methods of Photoactivation

Photochemical Direct Perfluoroalkylation of Phenol



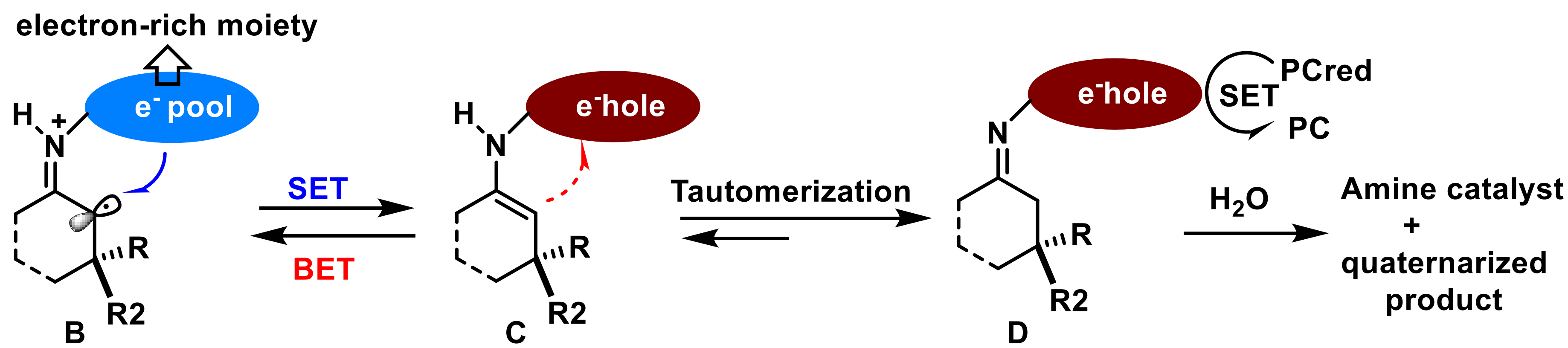


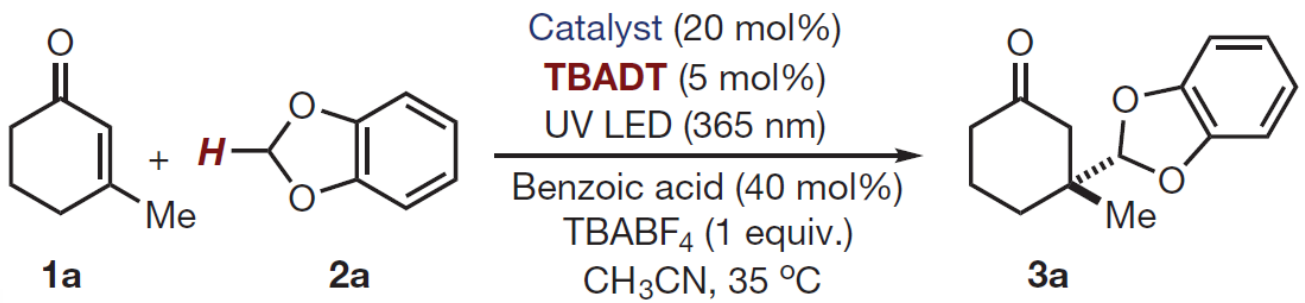


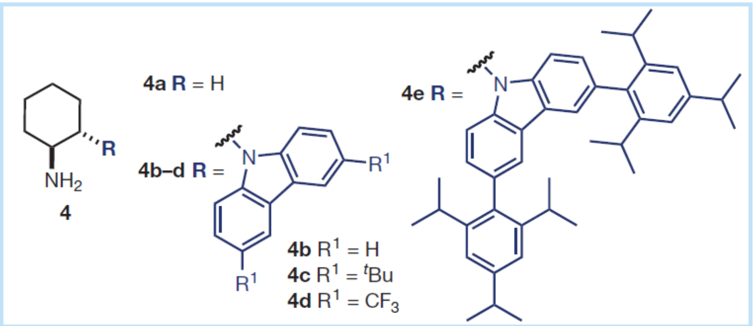
P. Melchiorre, *Tetrahedron*, **2015**, *71*, 4535.

Other Methods of Photoactivation

Electron-relay strategy to remove the short-lived α-iminyl radical cation (**B**) by reduction







P. Melchiorre, *Nature* **2016**, *532*, 218.

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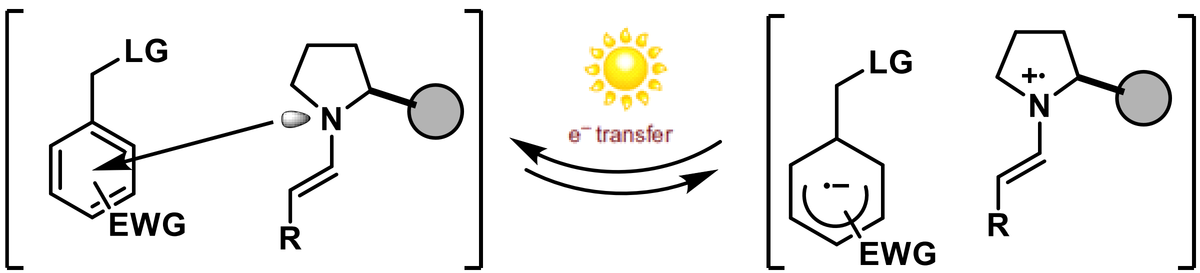
Summary

Combine organocatalytic with photochemical processes to realize metal-free asymmetric reaction under mild conditions

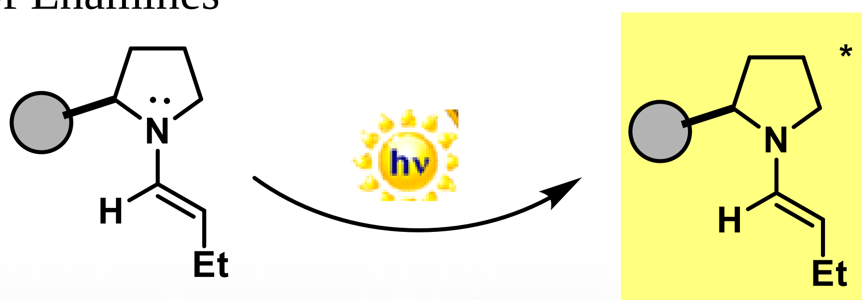
◆ Photoactivation of EDA complex



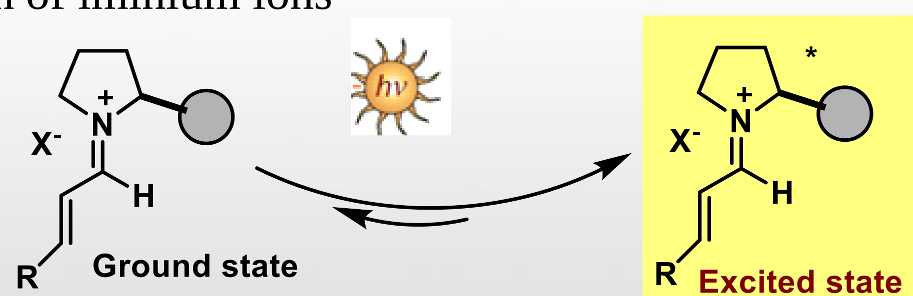
EDA complex

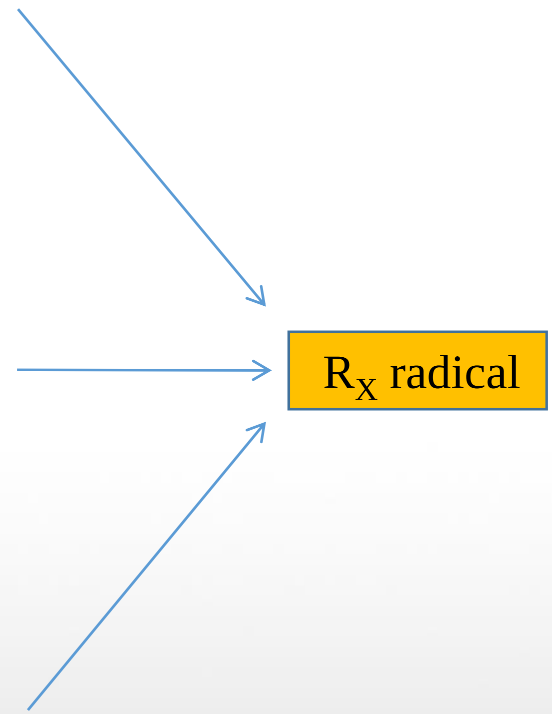
Chiral radical ion pair

◆ Photoexcitation of Enamines



◆ Photoexcitation of iminium ions





Acknowledgement

- ***Prof. Huang***
- ***Dr. Chen***
- ***All members here***

Thanks for your attention!