@MelchiorreGroup

Tutorial Session – Frontiers in Organic Chemistry

Enhancing the Potential of Organocatalysis with Light

Paolo Melchiorre

ICREA Research Professor

Institute of Chemical Research of Catalonia (ICIQ)

Barcelona Institute of Science & Technology

Tarragona – SPAIN

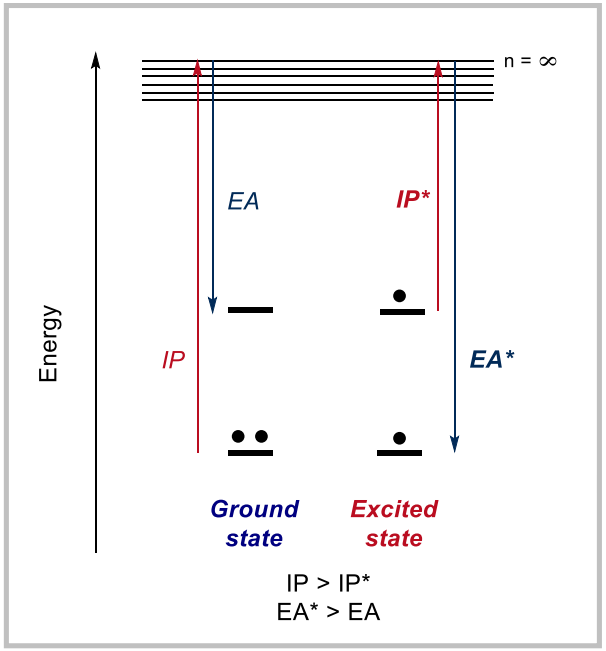
pmelchiorre@iciq.es

Ischia Advanced School of Organic Chemistry | IASOC

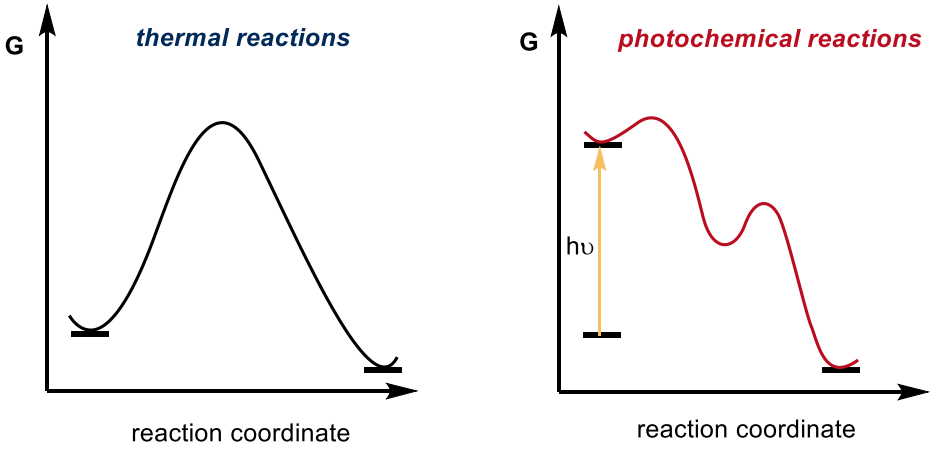
21 Sept 2018

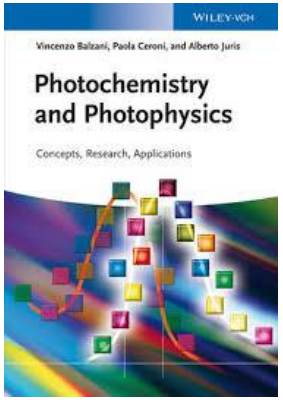
Photochemistry and Excited-State Reactivity

a molecule in the **excited state** is both a better ***reductant*** and a better ***oxidant*** than in the ground state



excited-state reactivity unlocks unconventional reaction pathways

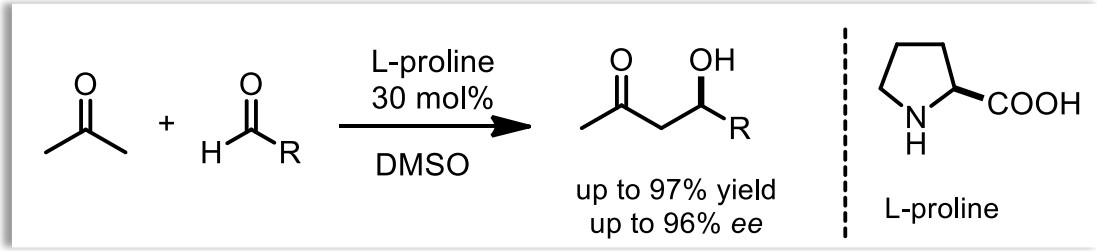




V. Balzani, P. Ceroni, A. Juris, in *Photochemistry and Photophysics*, Wiley-VCH, 2014
P. Klán, J. Jacob, in *Photochemistry of Organic Compounds*, John Wiley & Sons, 2010

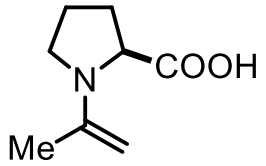
Activation Modes in Aminocatalysis

- Proline-catalyzed intermolecular aldol reaction



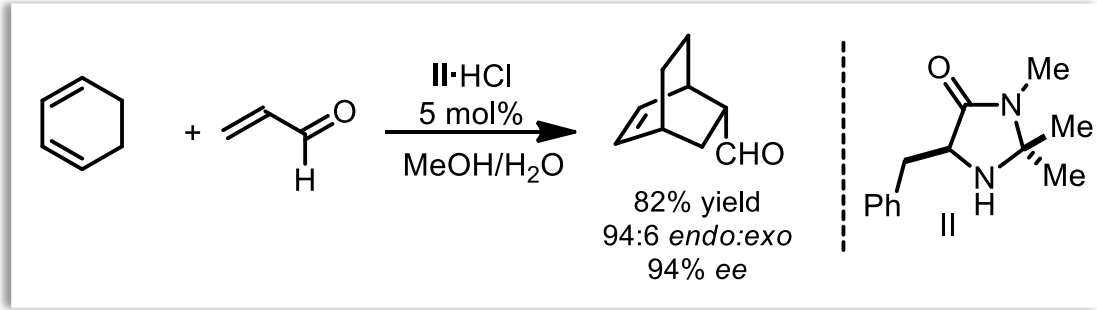
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Enamine Catalysis



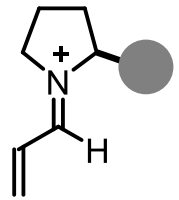
HOMO-Raising Activation

- Iminium ion catalyzed asymmetric Diels-Alder of enals



K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

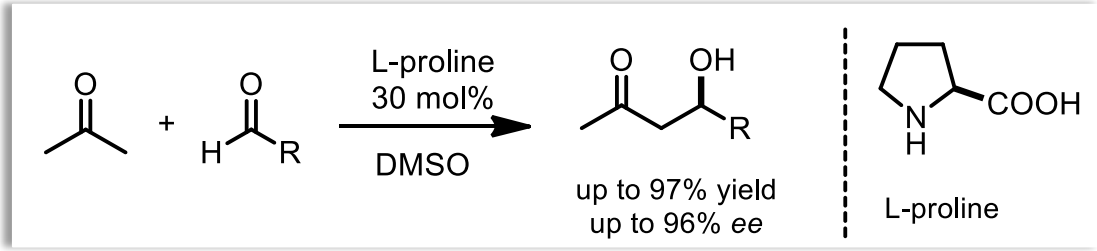
Iminium-Ion Catalysis



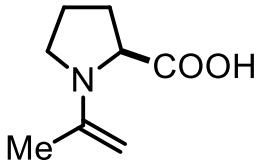
LUMO-Lowering Activation

Enamine in the Ground State

- Proline-catalyzed intermolecular aldol reaction



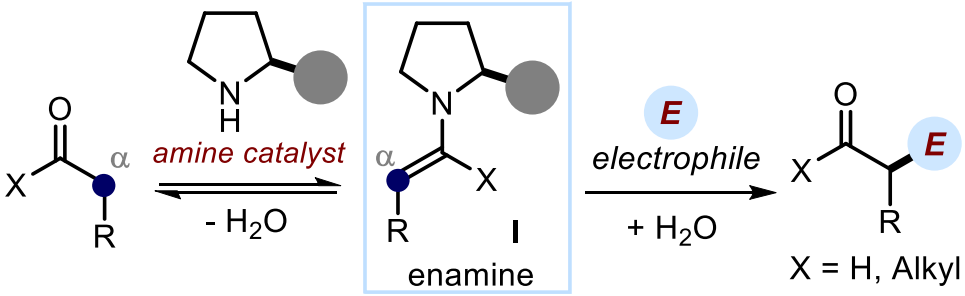
Enamine Catalysis



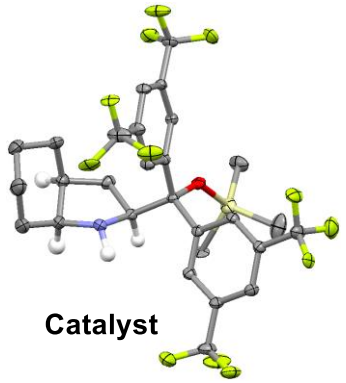
HOMO-Raising Activation

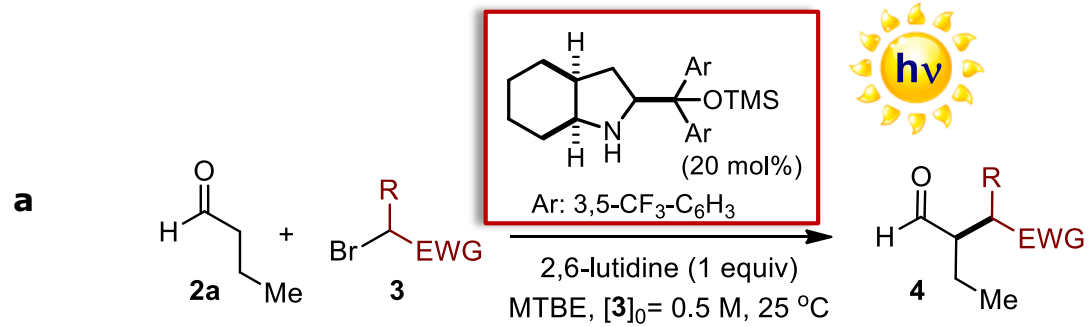
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

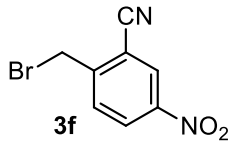
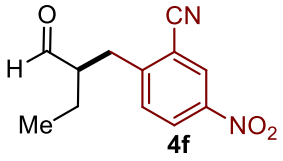
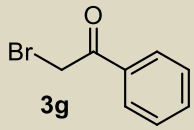
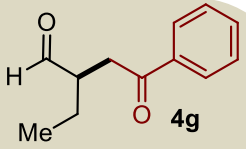
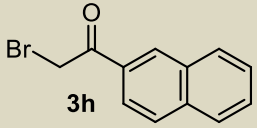
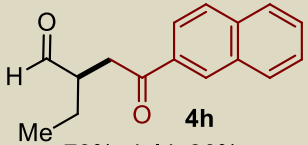
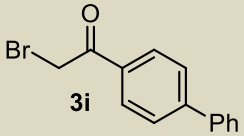
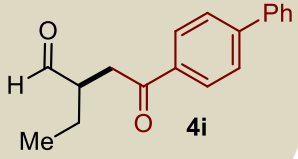
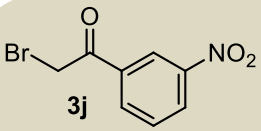
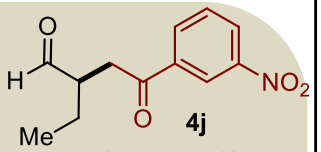
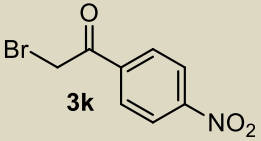
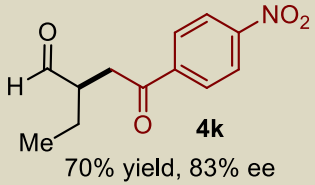
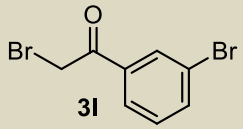
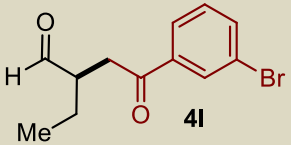
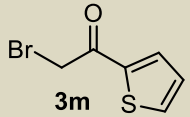
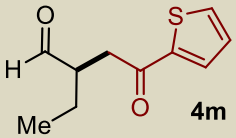
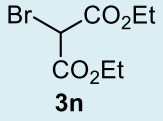
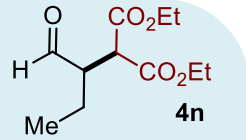
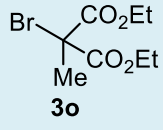
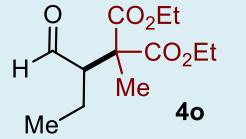
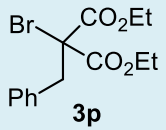
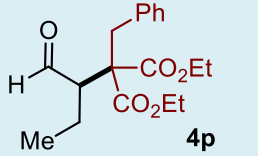
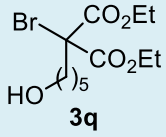
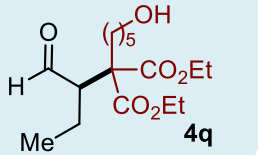
enamine-mediated catalysis



Photochemical Asymmetric Alkylation of Aldehydes



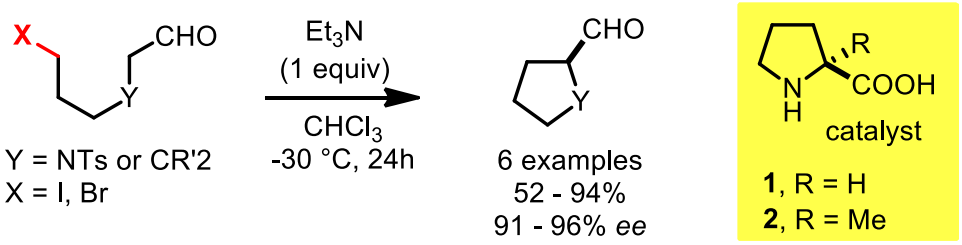


entry	alkyl-bromide	product	
1			95% yield, 84% ee
2			95% yield, 93% ee
3			70% yield, 86% ee
4			94% yield, 86% ee
5			86% yield, 86% ee
6			70% yield, 83% ee
7			96% yield, 87% ee
8			92% yield, 87% ee
9			65% yield, 84% ee
10*†			98% yield, 91% ee
11*			75% yield, 85% ee
12*			77% yield, 90% ee

For a pertinent precedent, see: D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77

with E. Arceo, I. Jurberg, A. Alvarez
Nature Chemistry, **2013**, *5*, 750-756

α-Alkylation of Aldehydes

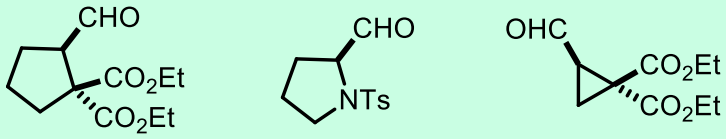


Y = NTs or CR'2
X = I, Br

6 examples
52 - 94%
91 - 96% *ee*

1, R = H
2, R = Me

Selected Products:



92% , 95% *ee*

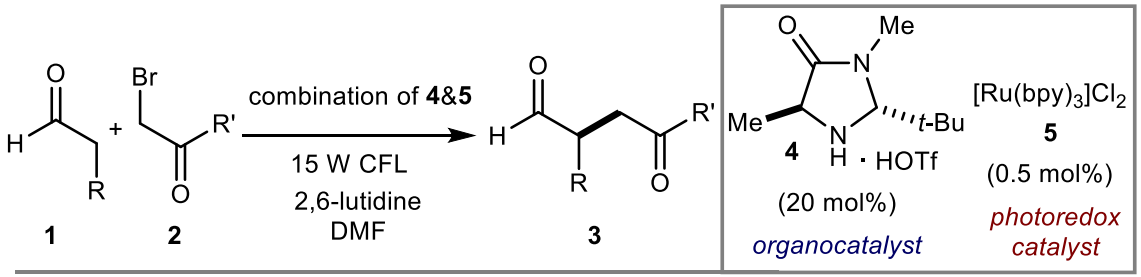
52% , 91% *ee*

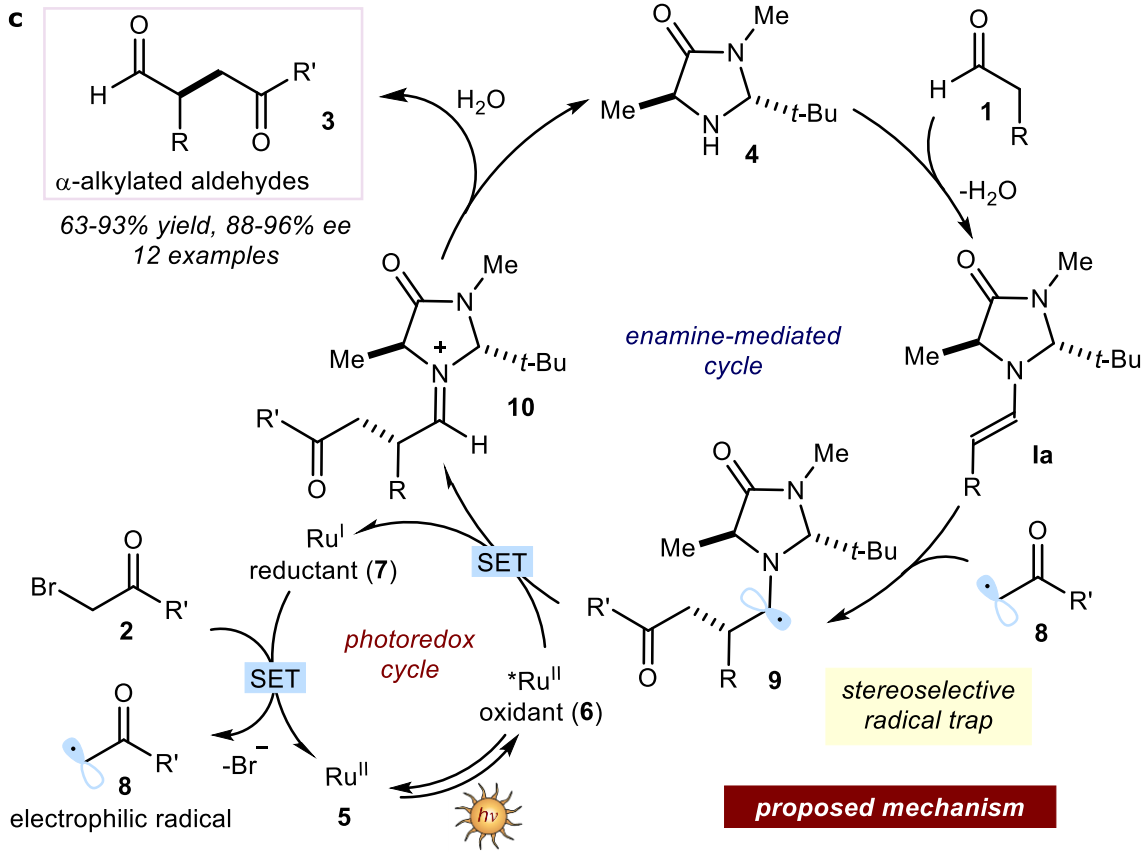
70% , 86% *ee*

Intramolecular S_N2 type Reaction

N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451

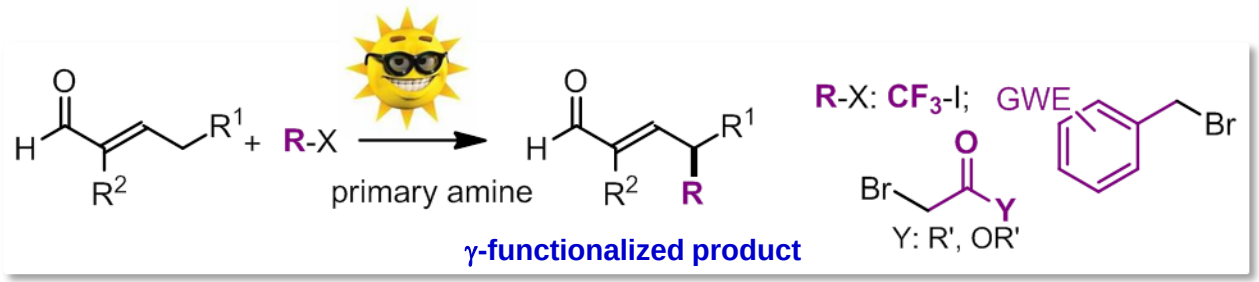
The Solution: Merging Photoredox- and Enamine-catalysis

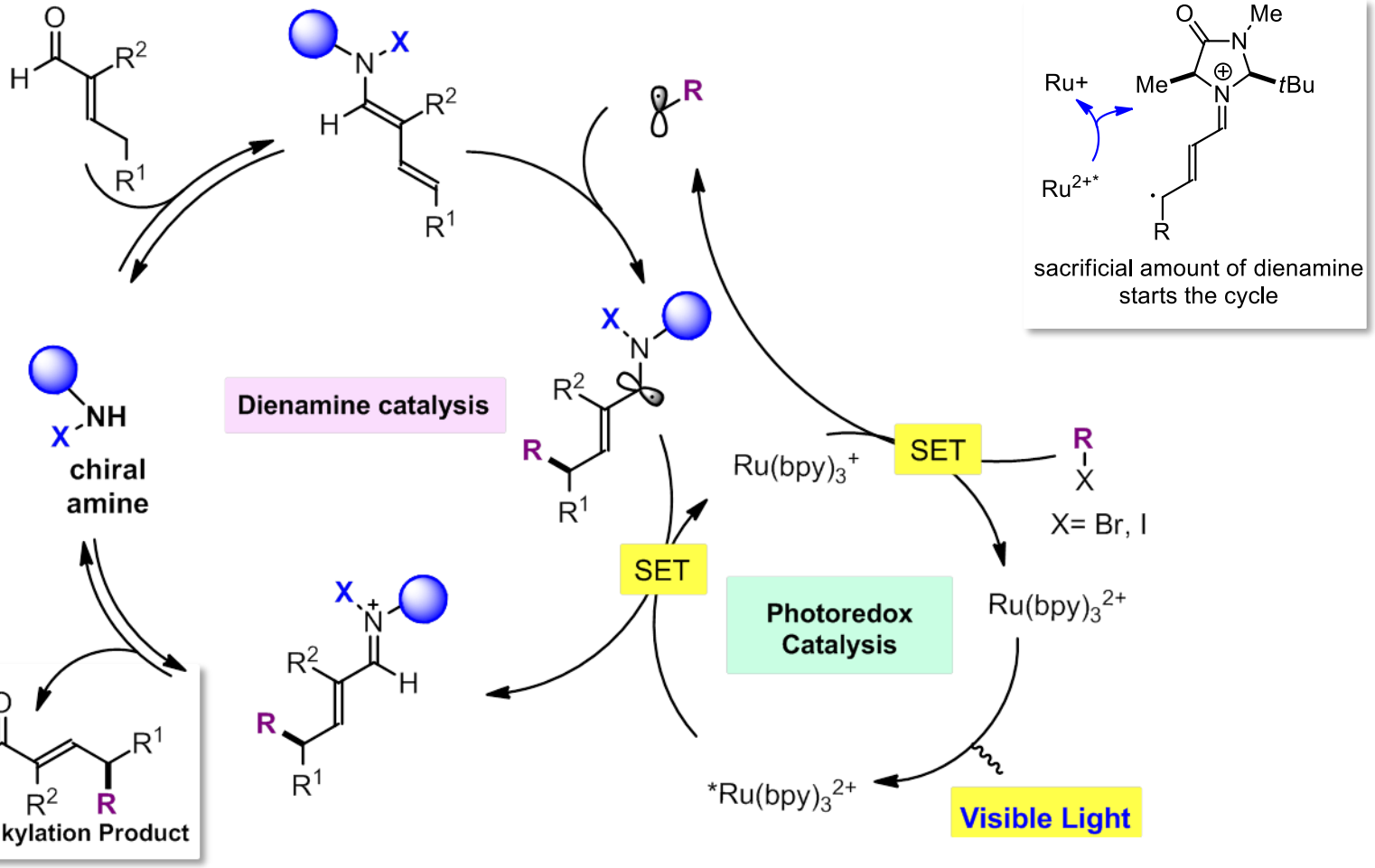




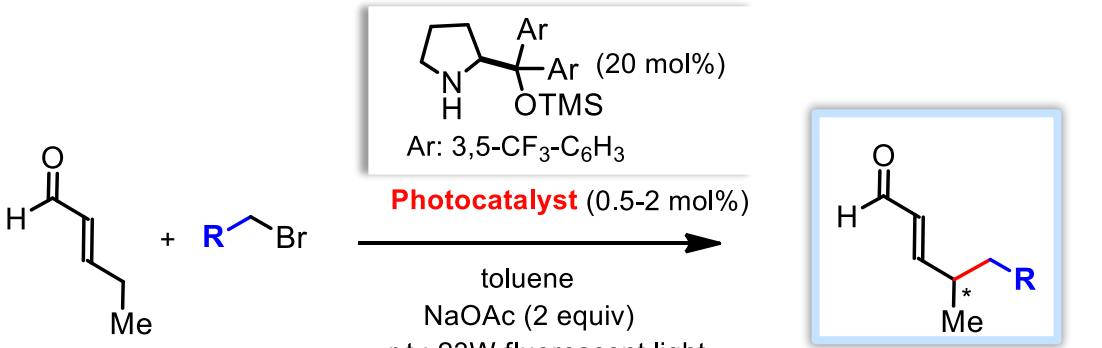
D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77

Merging Photoredox- and Amino-Catalysis

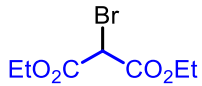
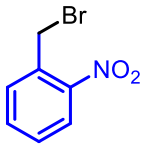
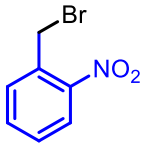




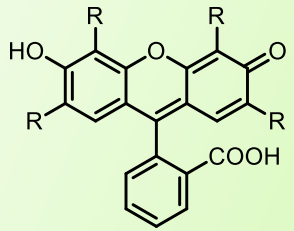
Vinylogous Reactivity in Radical Pathways



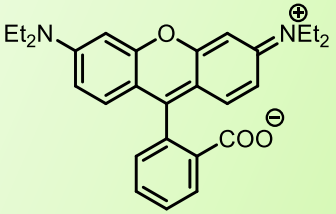
γ-functionalized product

	Photocatalyst	time	conv. R'Br	ee
	**Fluorescein**	48 h	100	**50 %**
	**$[Ru(bpy)_3]Cl_2$**	45 h	88	**64 %**
	**$[Ru(bpy)_3]Cl_2$**	40 h	75	**66 %**
	**$[Ru(bpy)_3]Cl_2$**	**14 h**	100	**64 %**

organic dyes

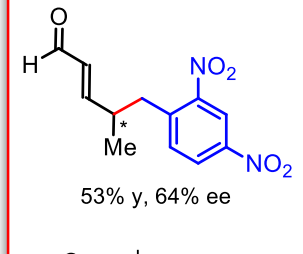


R: H; fluorescein
R: Br; eosin Y

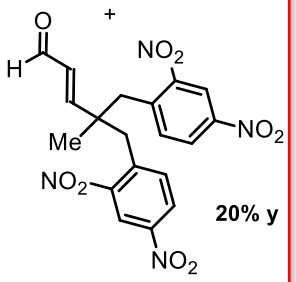


rhodamine B

K. Zeitler *et al.*,
ACIE **2011**, *50*, 951



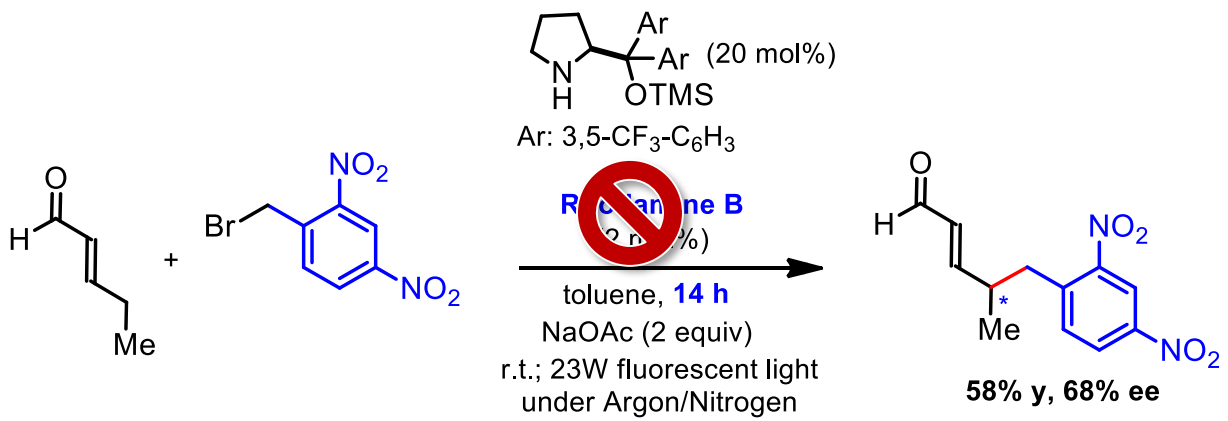
53% y, 64% ee



20% y

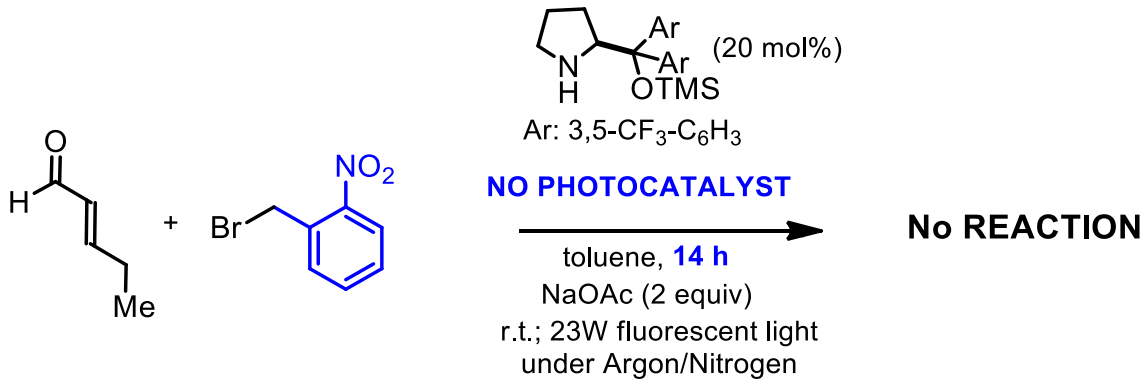
Vinylogous Reactivity in Radical Pathways

Elena Arceo

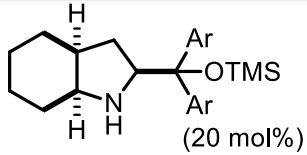


Control Experiment

The reaction works without any Photo-redox catalyst!

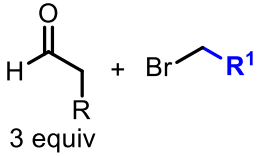


Expanding the Scope



(20 mol%)

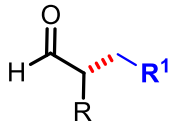
Ar: 3,5-CF_3-C_6H_3



3 equiv

Visible Light (23W)

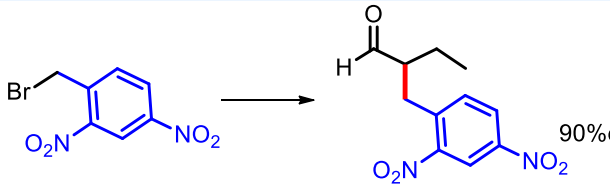
2,6-lutidine (1 equiv)
MTBE, 0.5 M, r.t.



α-alkylated products

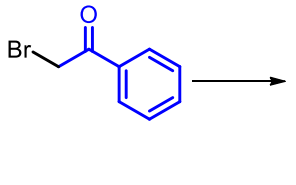
Igor Jurberg

Elena Arceo

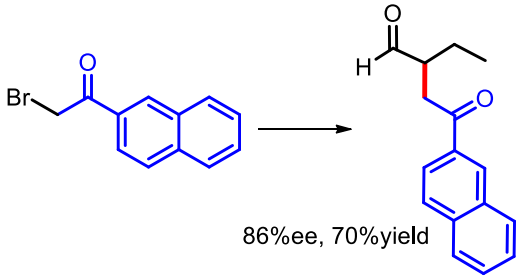


90%ee, 87%yield, 65h

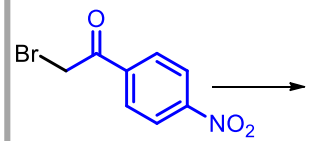
Benzylation

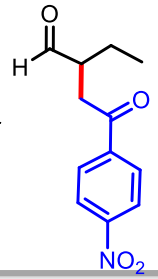


94%ee, 95%y, 72h



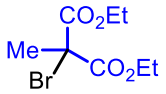
86%ee, 70%yield

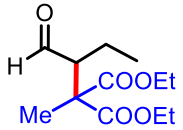




84%ee, 70%yield, 68h

Benzoylation

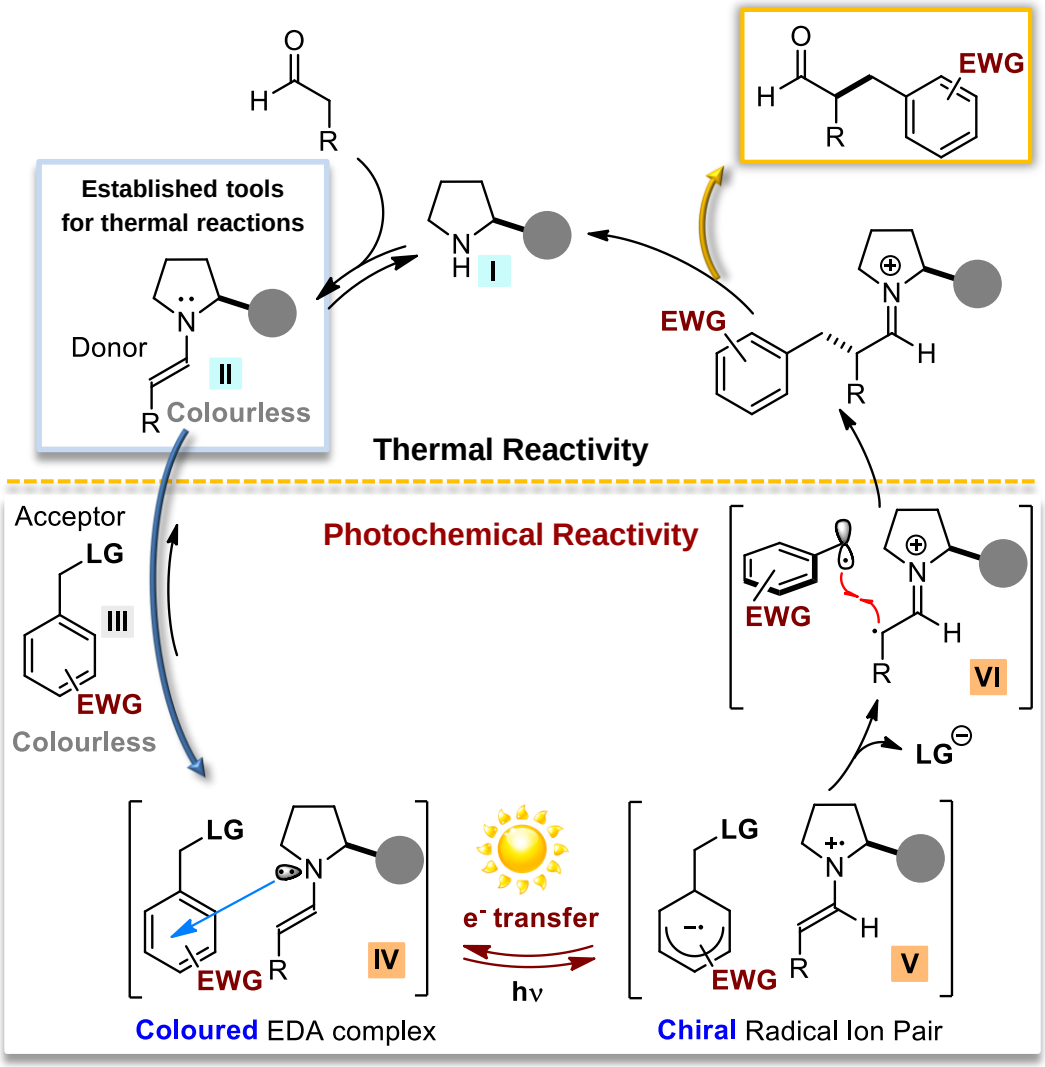




90% ee, 98% yield, 24h

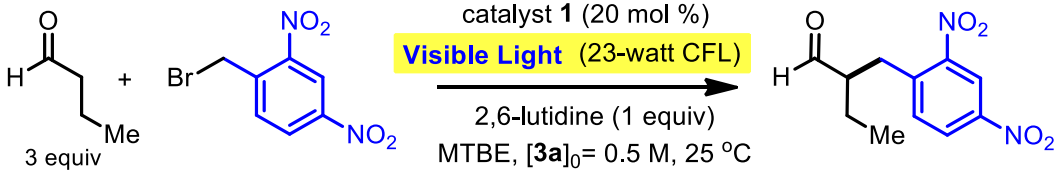
Alkylation

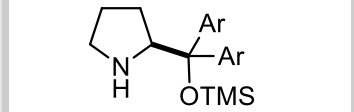
Photochemical Mechanism



EDA complexes and Charge Transfer theory
R. S. Mulliken, *J. Phys. Chem.* **1952**, *56*, 801

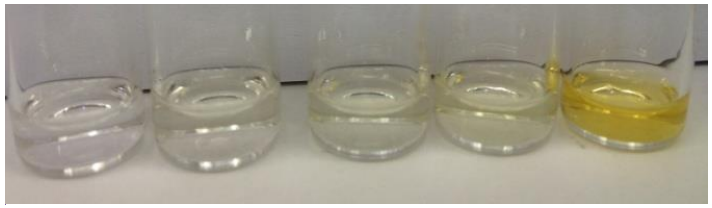
Electron Donor-Acceptor (EDA) Complex

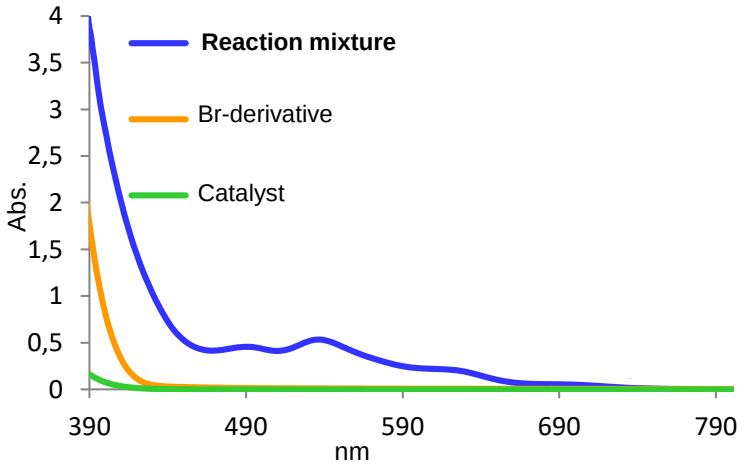


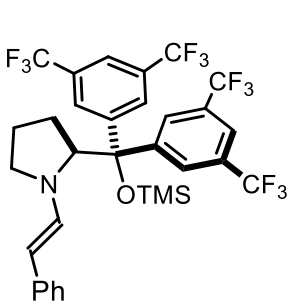


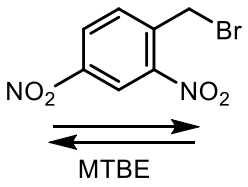
about Serendipity & Observations

visual observation

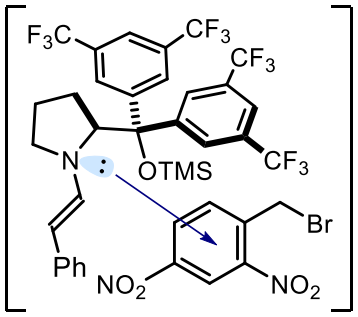








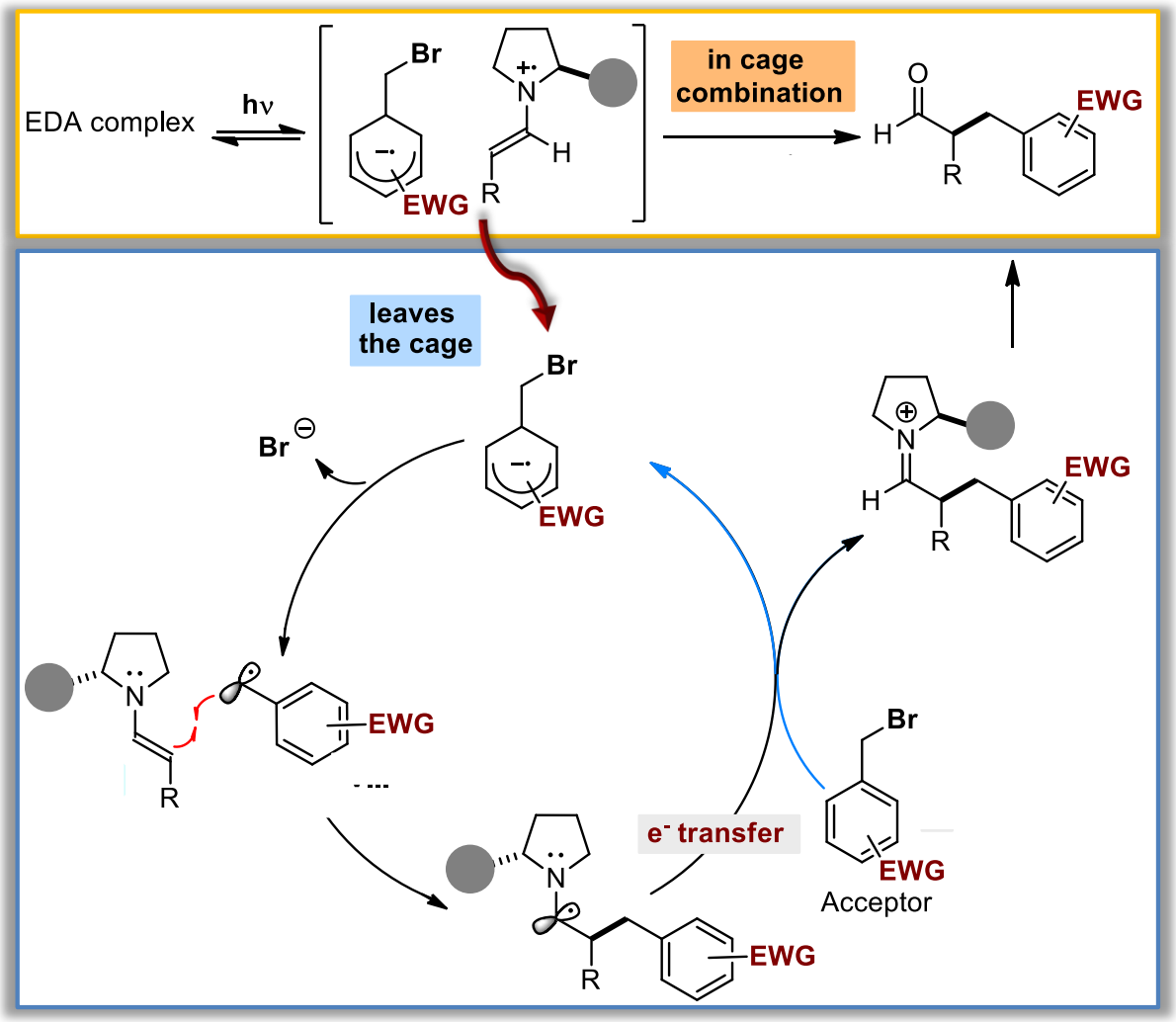
K_{EDA} = 11.6 M^{-1}



EDA Complex

For mechanistic studies (with Ana Bahamonde)
J. Am. Chem. Soc. **2016**, *138*, 8019–8030

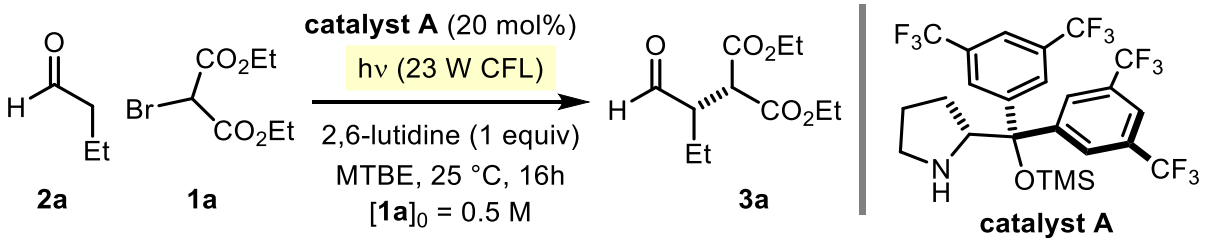
an Alternative Path: *Chain Mechanism*

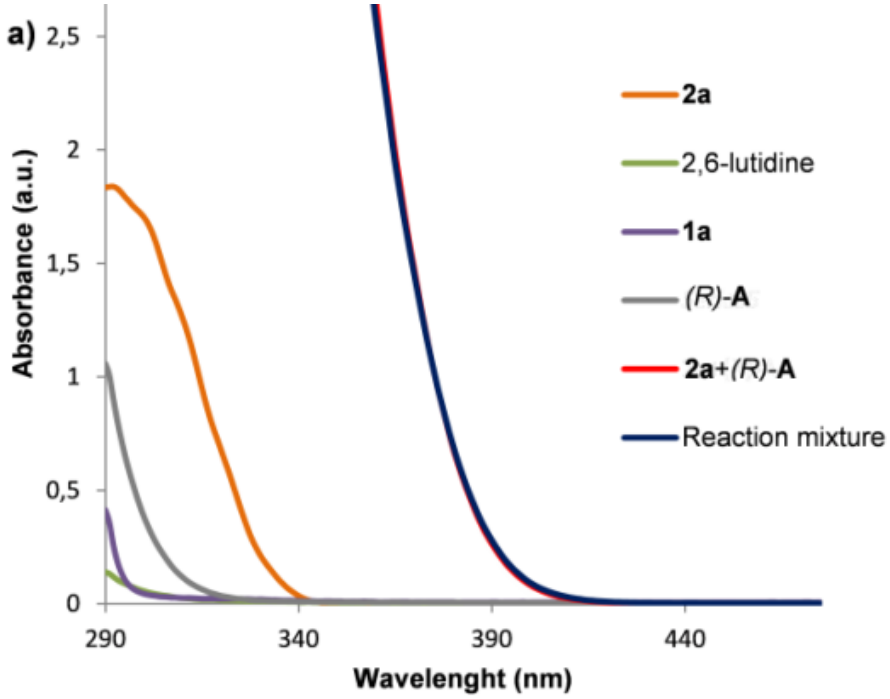


A quantum yield (Φ) of 25 was determined (λ = 450 nm)

for mechanistic studies (with Ana Bahamonde)
J. Am. Chem. Soc. **2016**, *138*, 8019–8030

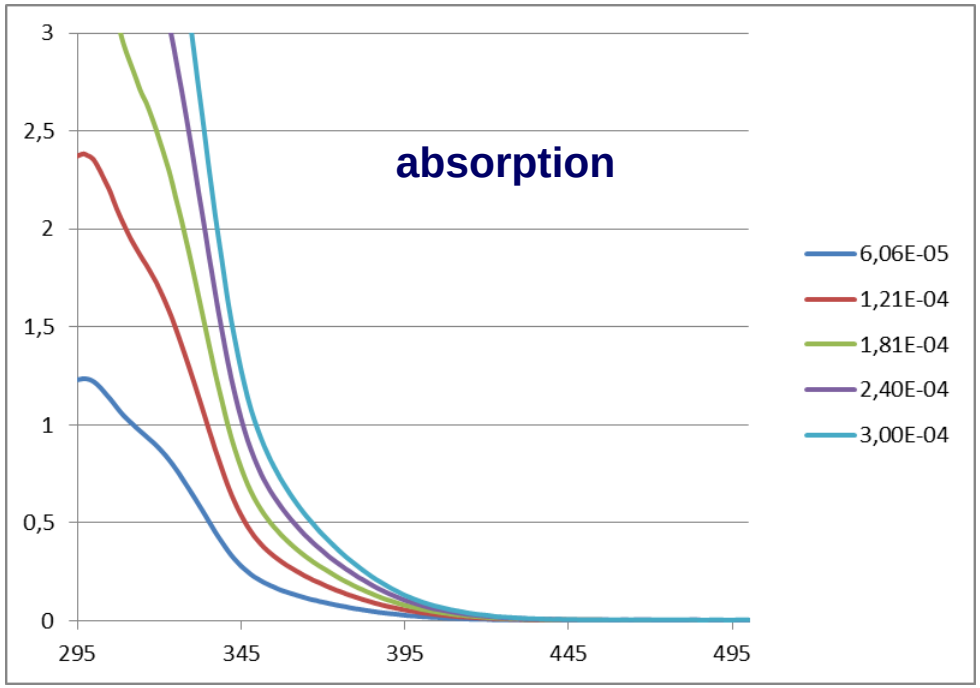
Asymmetric Photochemical Alkylation



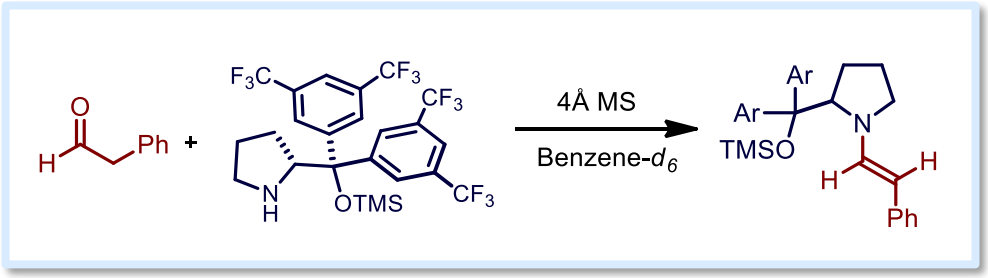


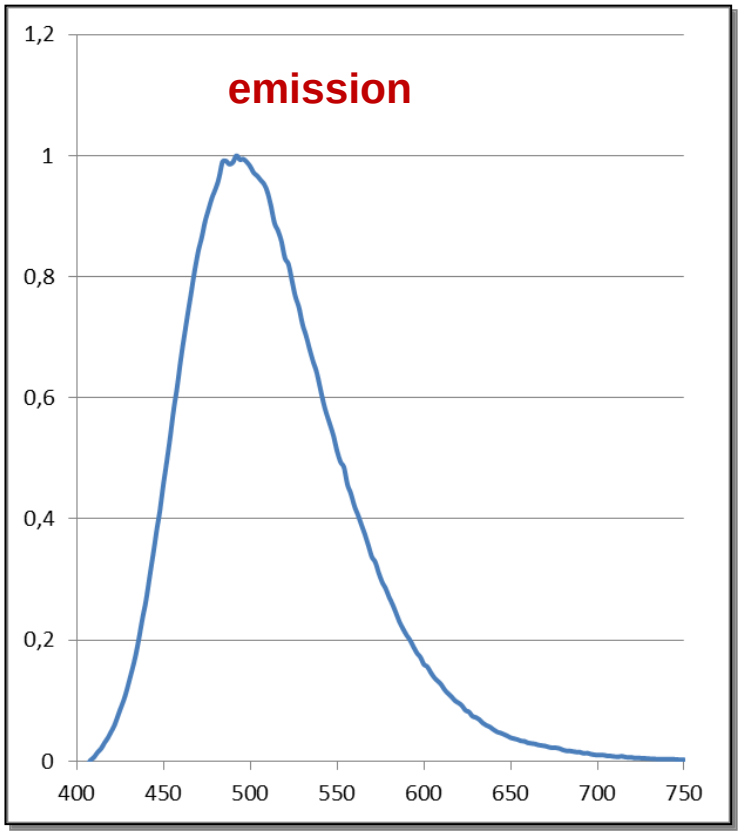
the enamine weakly absorbs visible light

Direct Excitation of Enamines

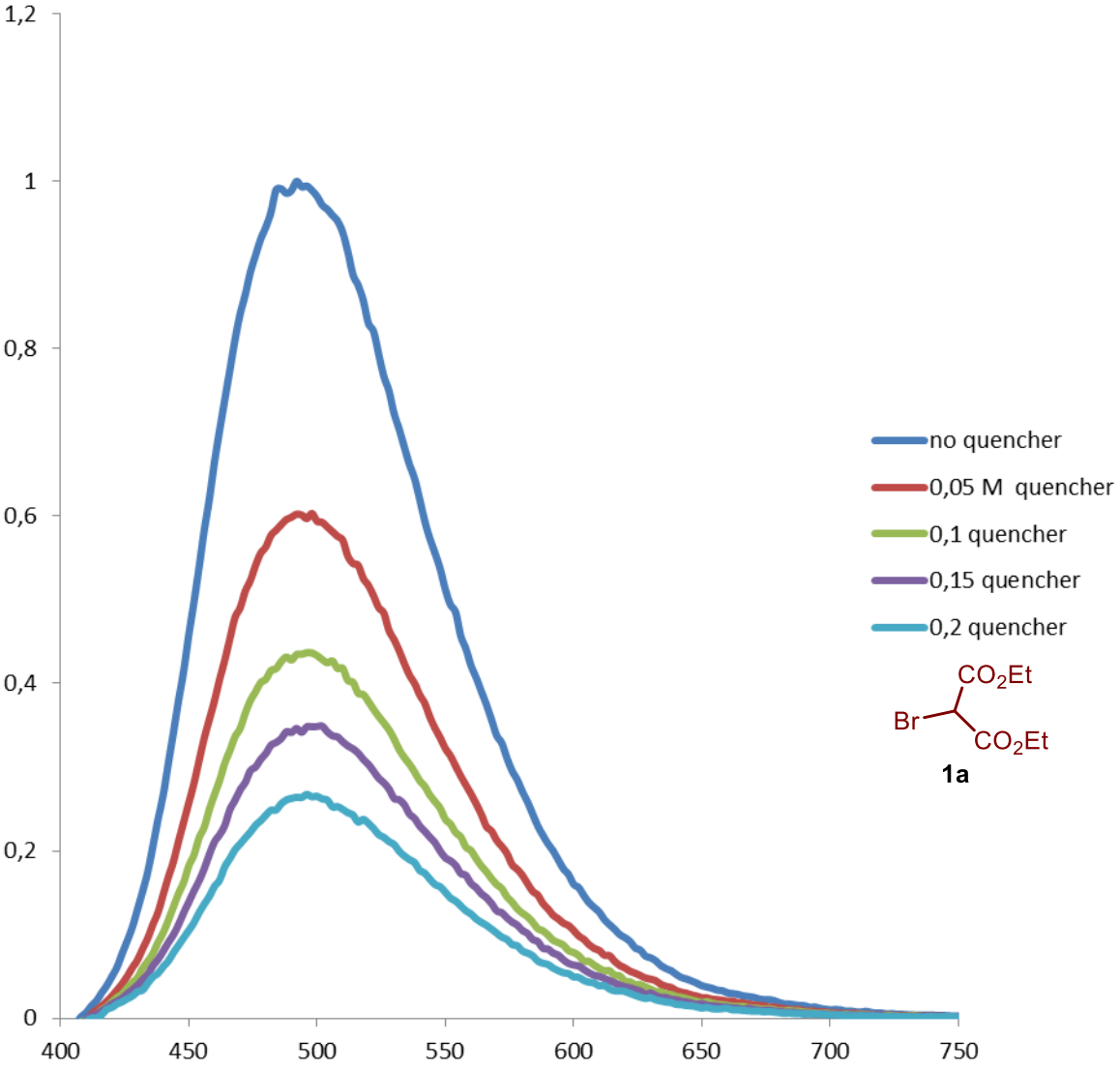


Mattia Silvi

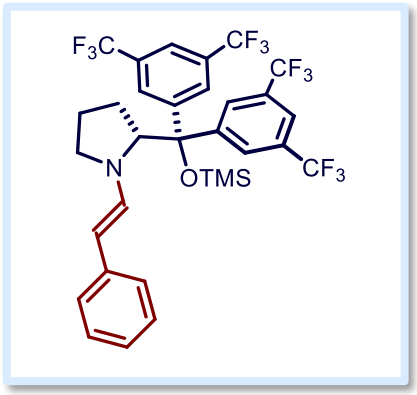




Direct Excitation of Enamines



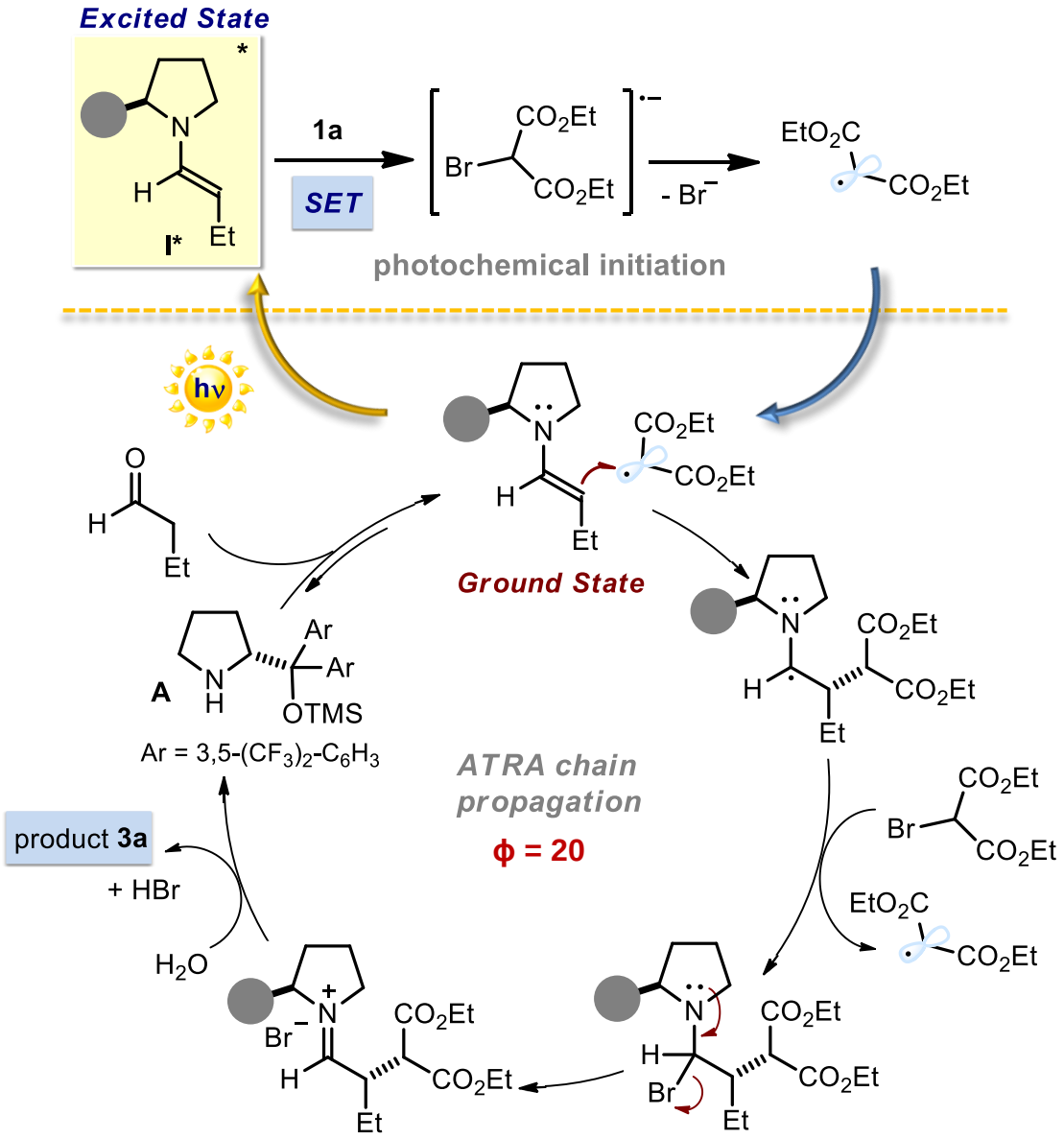
1a



Stern−Volmer quenching studies

Mattia Silvi

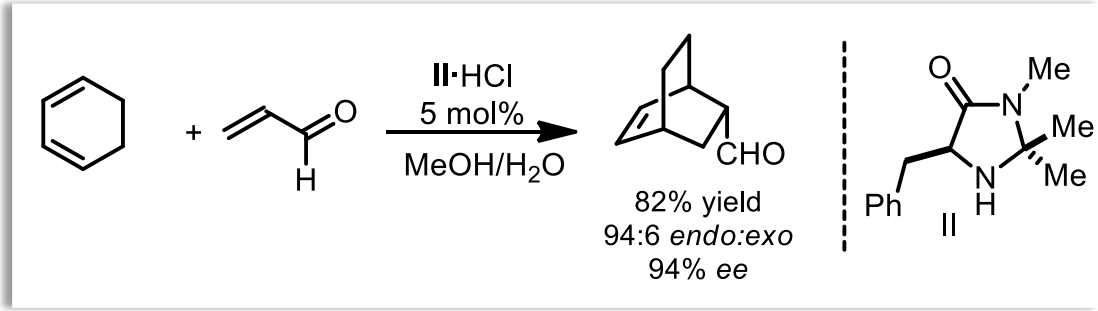
Photo-Excitation of Enamines



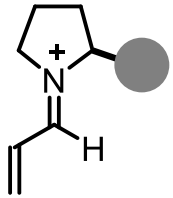
with M. Silvi, E. Arceo, I. Jurberg, C. Cassani
J. Am. Chem. Soc. **2015**, *137*, 6120-6123

Iminium Ion in the Ground State

- Iminium ion catalyzed asymmetric Diels-Alder of enals



Iminium-Ion Catalysis



LUMO-Lowering Activation

K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

iminium ion-mediated catalysis

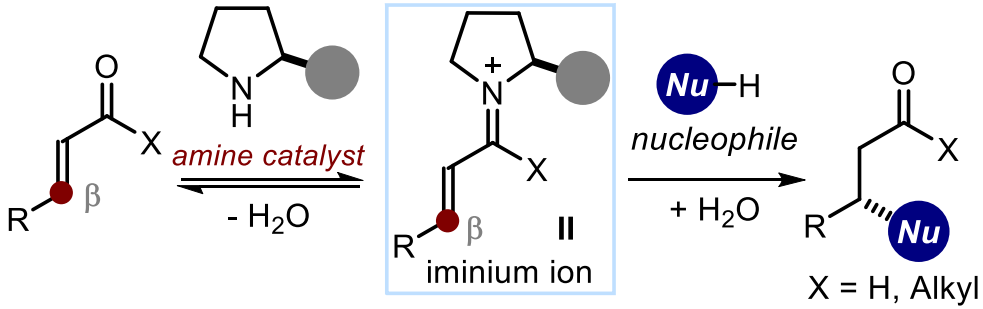
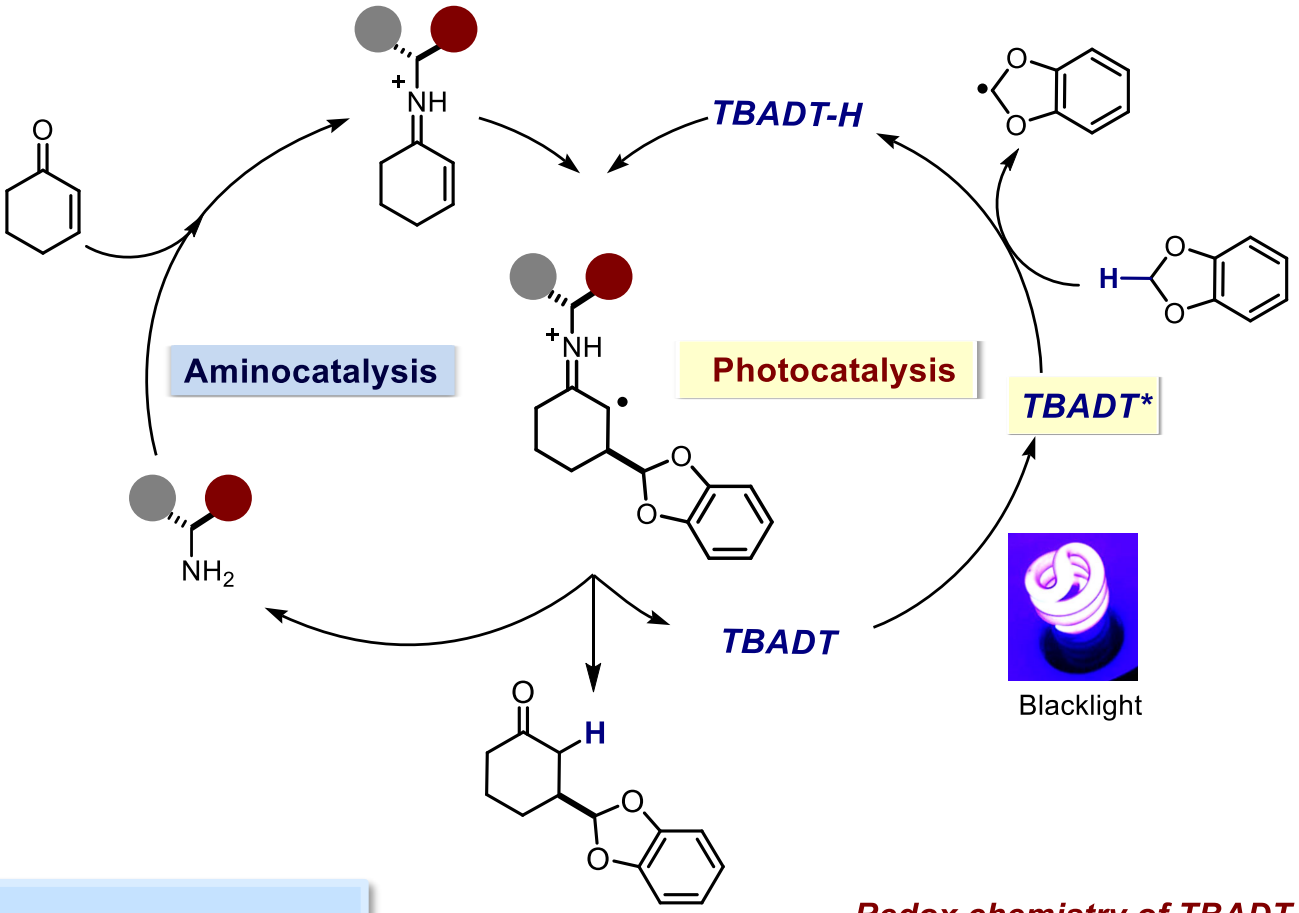


Photo-Organocatalytic Radical Conjugate Additions

HAT: Hydrogen Atom Transfer mechanism



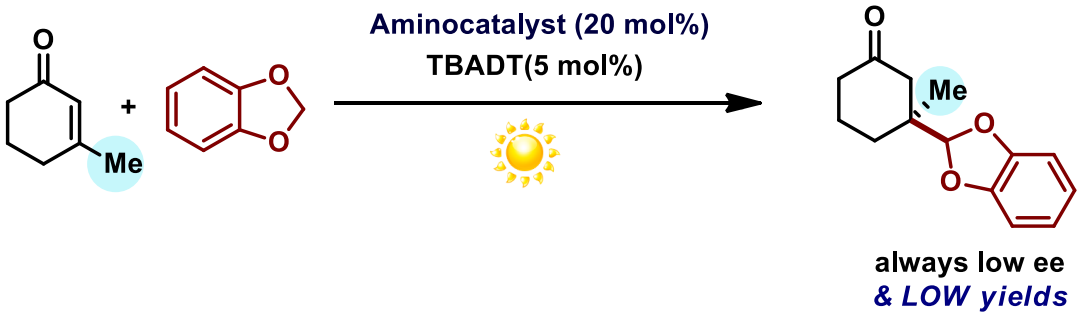
collaboration with Maurizio Fagnoni
Università di Pavia (Italy)

Redox chemistry of TBADT

$W_{10}O_{32}^{4-} \longrightarrow W_{10}O_{32}^{5-}$ -1.30 eV in DMF

$W_{10}O_{32}^{5-} \longrightarrow W_{10}O_{32}^{4-} + W_{10}O_{32}^{6-}$

Photo-Organocatalytic Radical Conjugate Additions



always low ee
& LOW yields

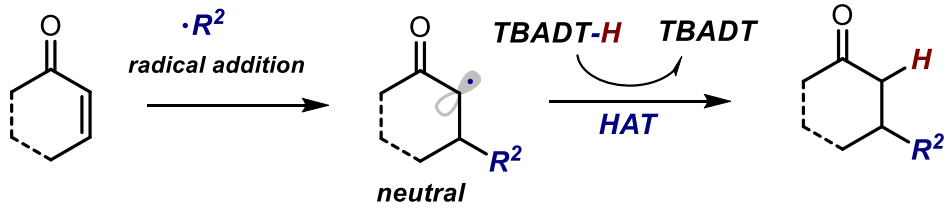
Quaternary carbon stereocentre

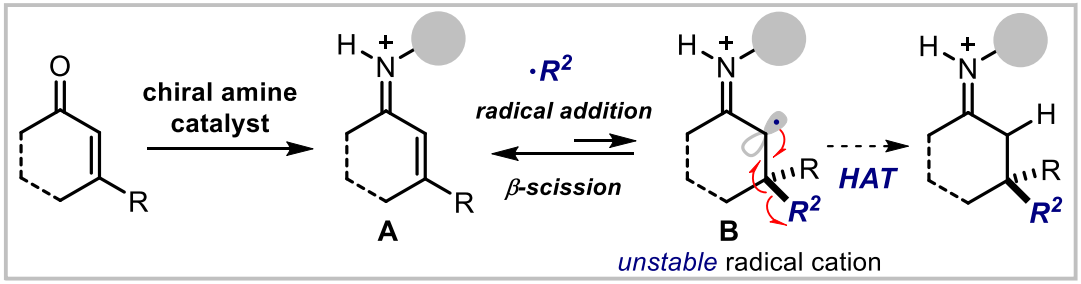
David Bastida

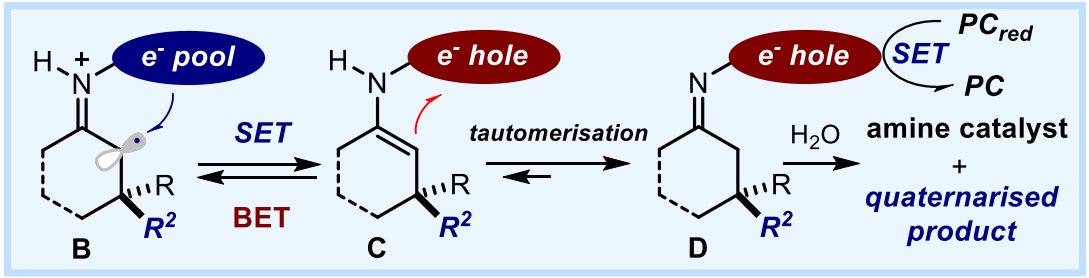
John Murphy

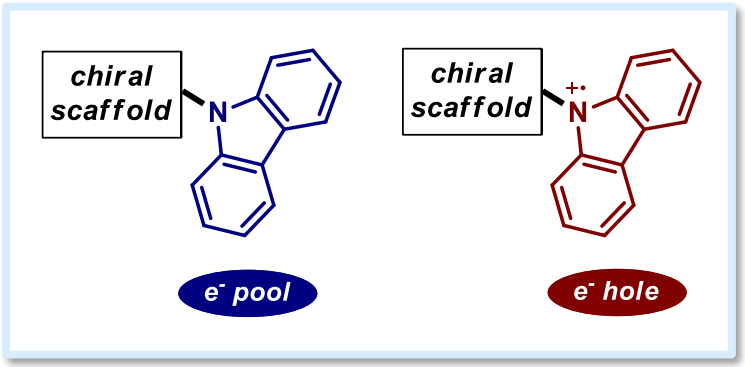
For pertinent precedents on enantioselective catalytic radical conjugate additions
T. P. Yoon et al. *J. Am. Chem. Soc.* **2015**, *137*, 2452
M. P. Sibi et al. *J. Am. Chem. Soc.* **2006**, *128*, 13346

Identifying the Problem

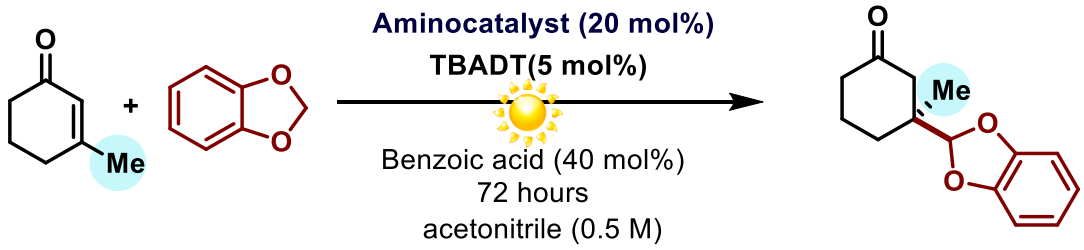


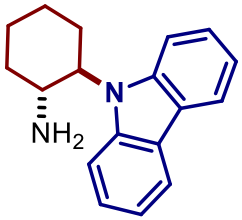






Catalyst Design

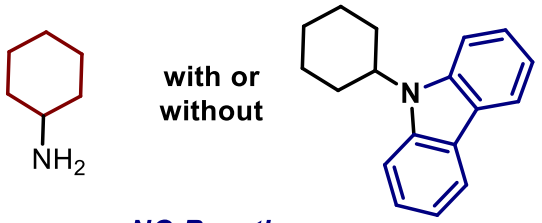




52% yield
80% ee

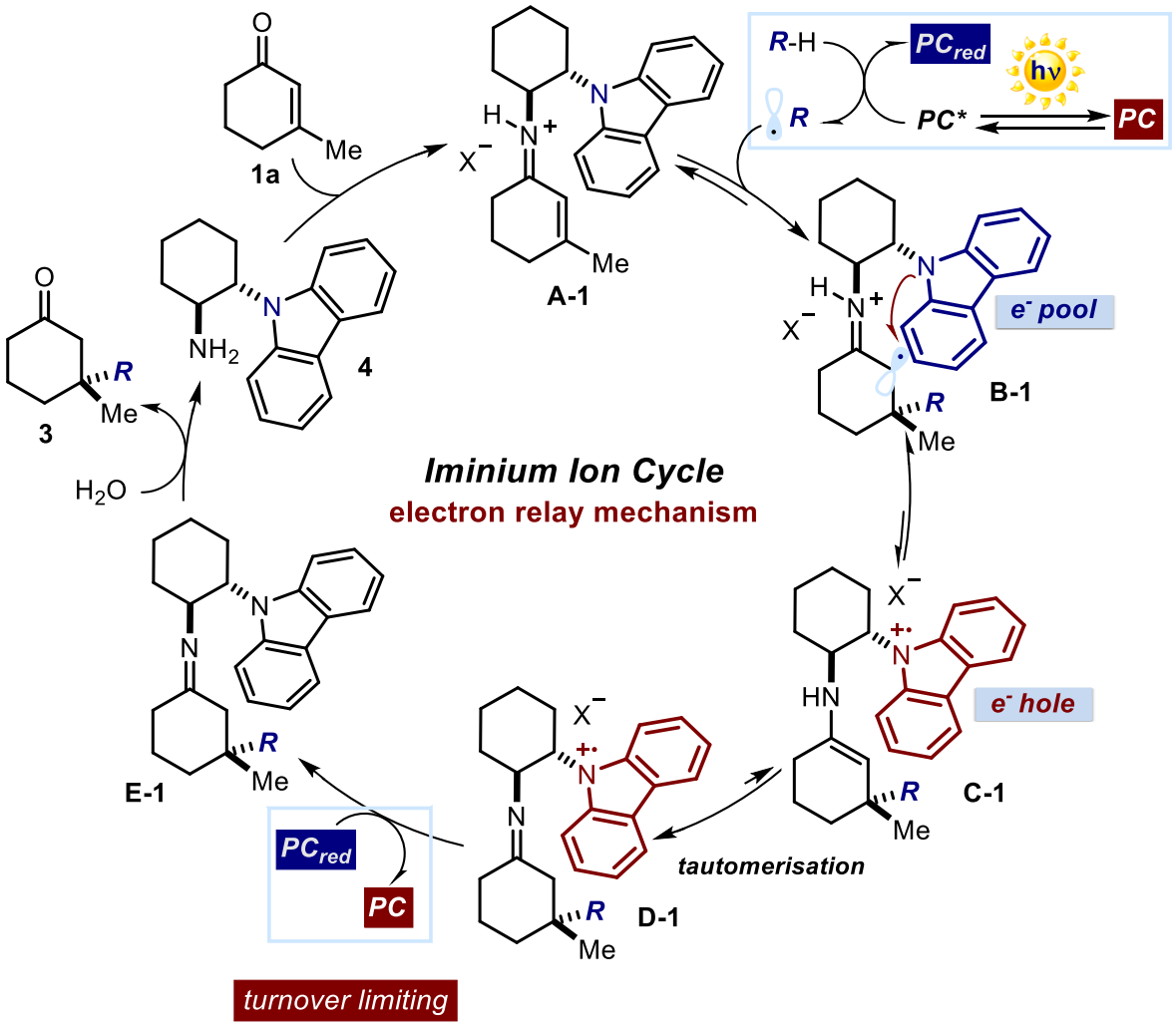
David Bastida

John Murphy



NO Reaction

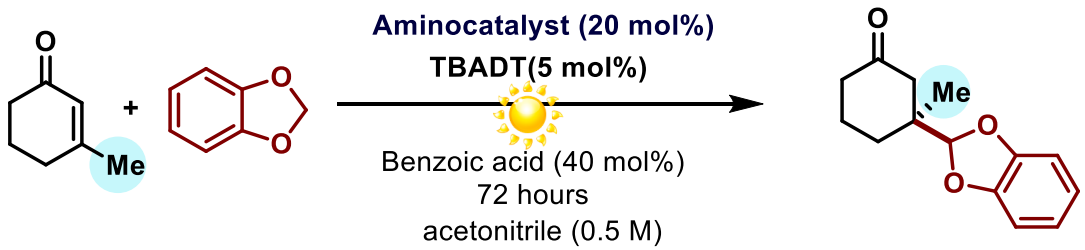
Electron-relay Mechanism



Mechanistic studies with Ana Bahamonde and John J. Murphy

J. Am. Chem. Soc. **2017**, *139*, 4559−4567

Catalyst Development



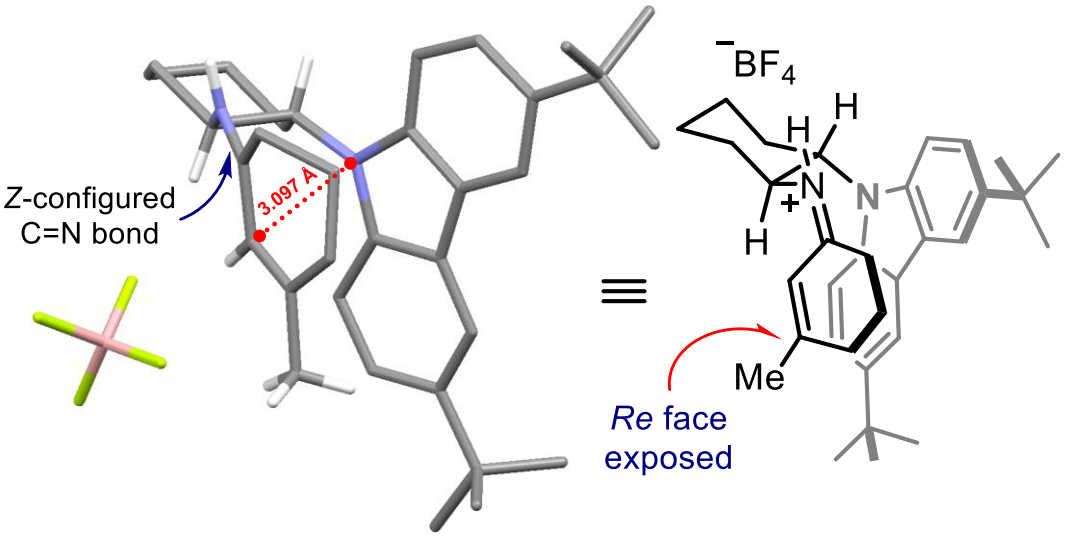
the Beast
copyright: J.J. Murphy

David Bastida

John Murphy

with J.J. Murphy, D. Bastida, S. Paria, M. Fagnoni
Nature **2016**, *532*, 218–222

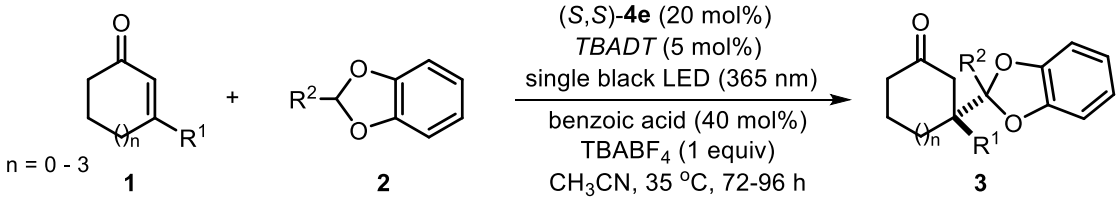
Origin of the Stereocontrol

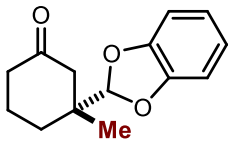


CCDC 1437991

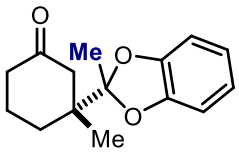
with J.J. Murphy, D. Bastida, S. Paria, M. Fagnoni
Nature **2016**, *532*, 218–222

Results

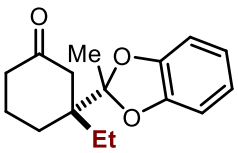




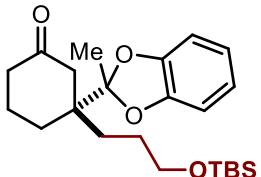
75% yield
93% ee



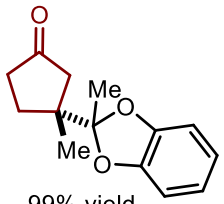
69% yield
97% ee



56% yield
96% ee

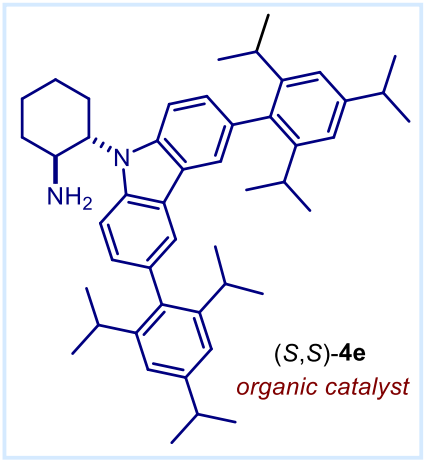


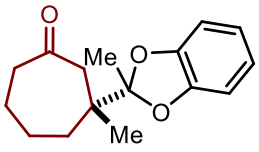
57% yield
85% ee



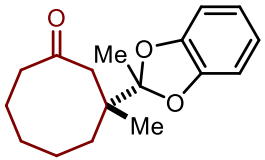
99% yield
88% ee

Photoredox system 1
TBADT - HAT mechanism

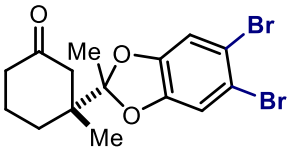




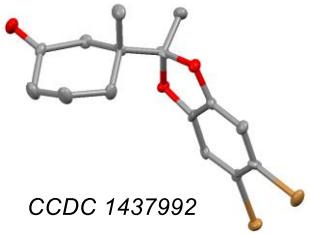
70% yield
94% ee



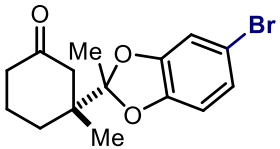
63% yield
91% ee



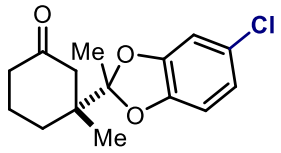
49% yield
91% ee



CCDC 1437992



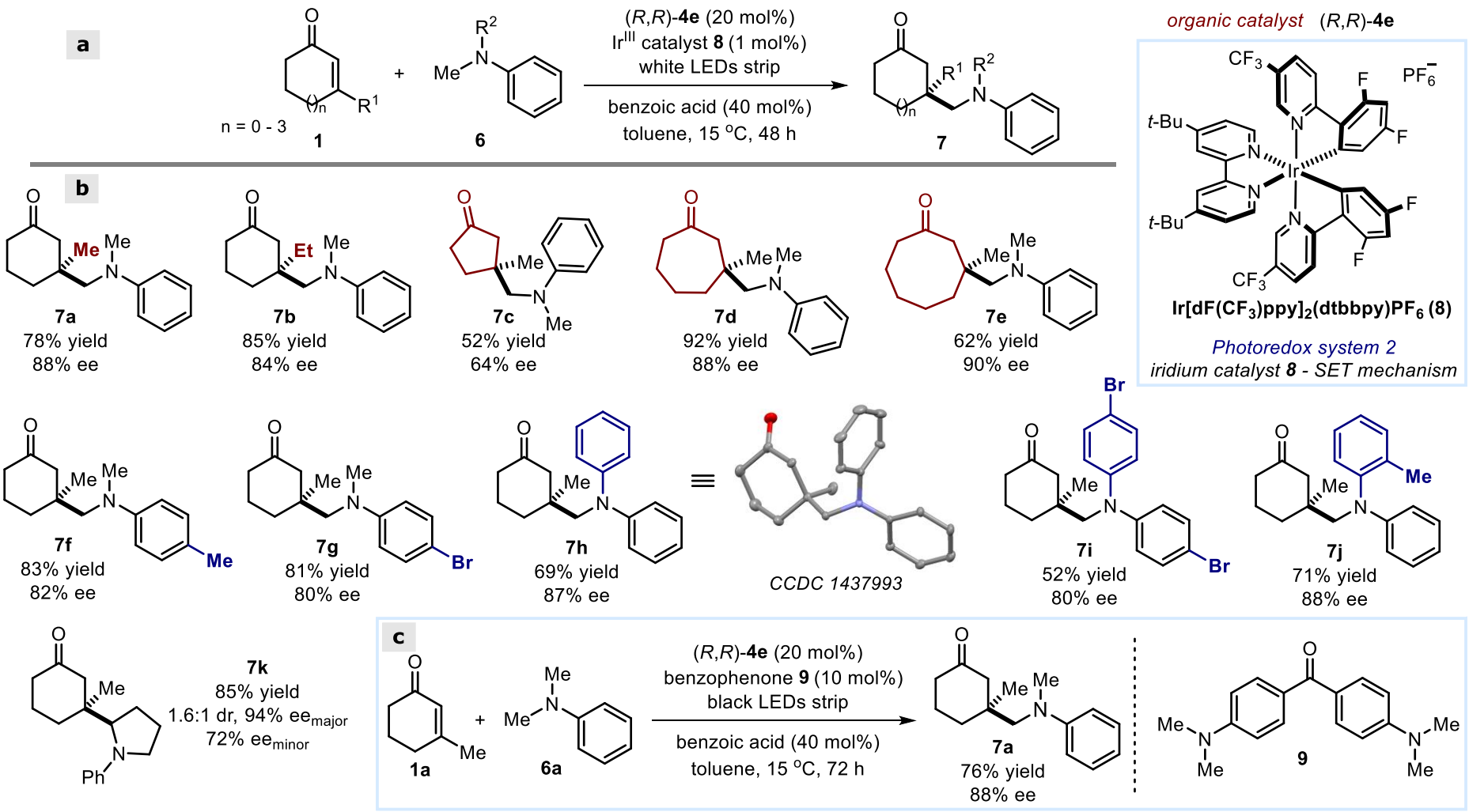
67% yield
1.5:1 dr, 98% ee



61% yield
1:1 dr, 98% ee

with J.J. Murphy, D. Bastida, S. Paria, M. Fagnoni
Nature **2016**, *532*, 218–222

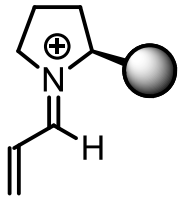
Results



with J.J. Murphy, D. Bastida, S. Paria, M. Fagnoni
Nature **2016**, *532*, 218–222

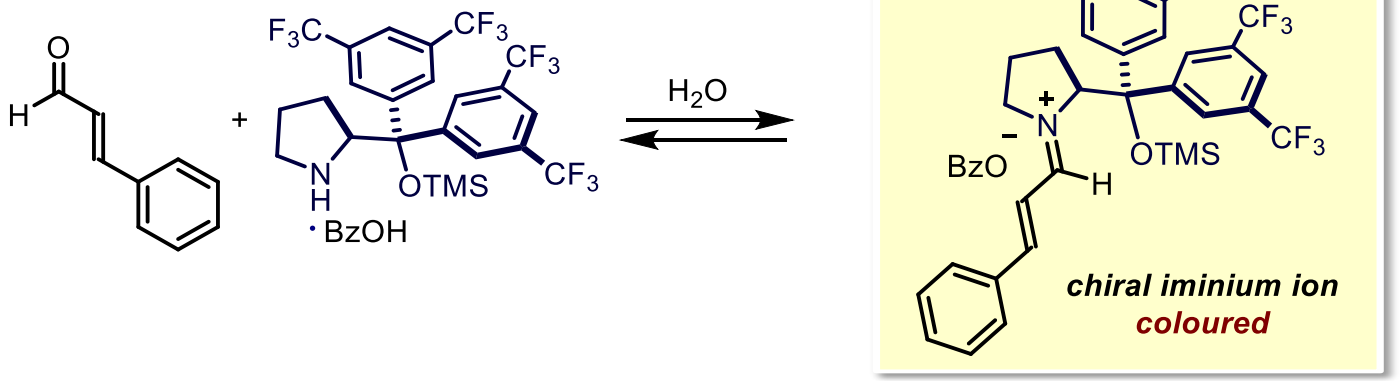
Iminium Ion Activation and Photochemistry

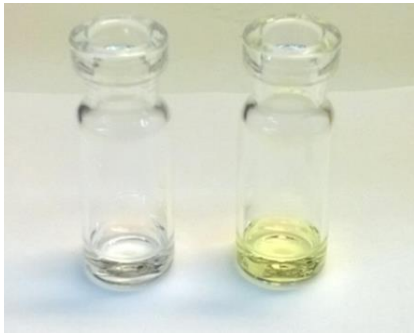
Iminium-Ion Catalysis

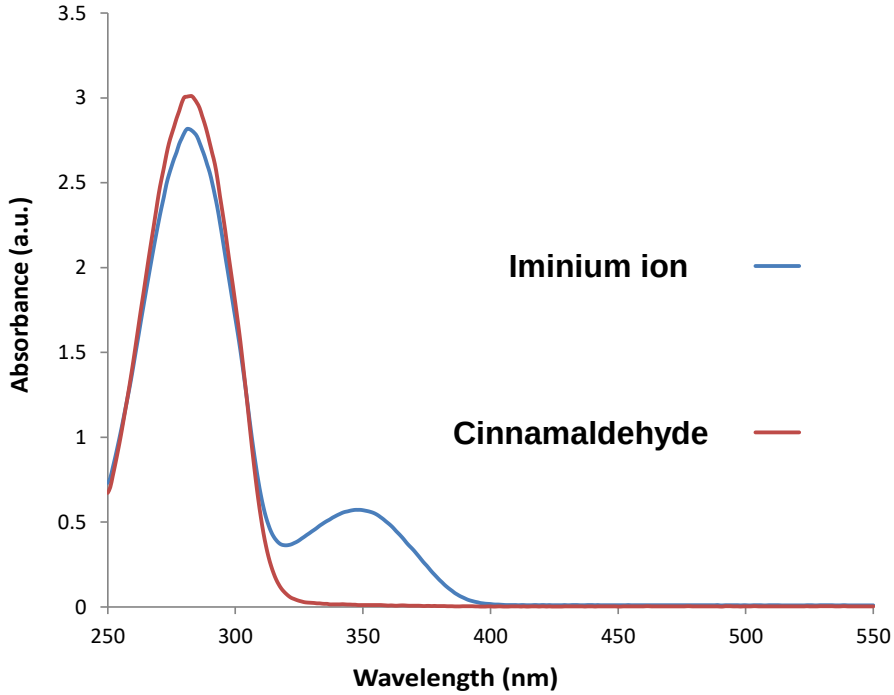


LUMO-Lowering Activation

the Photochemistry of Iminium Ions

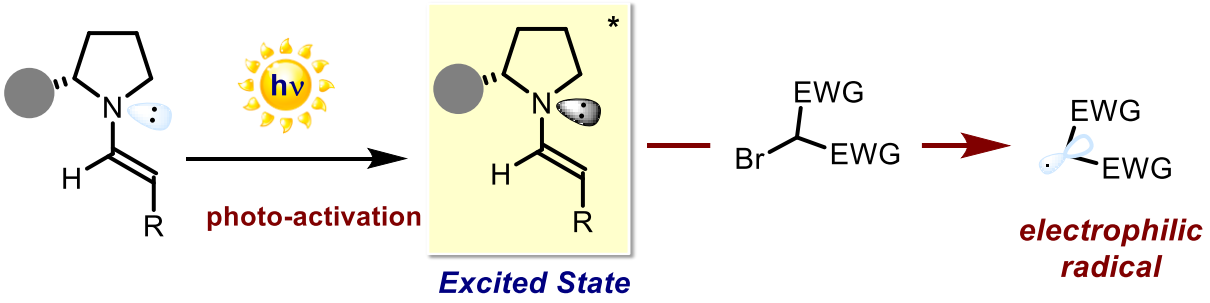






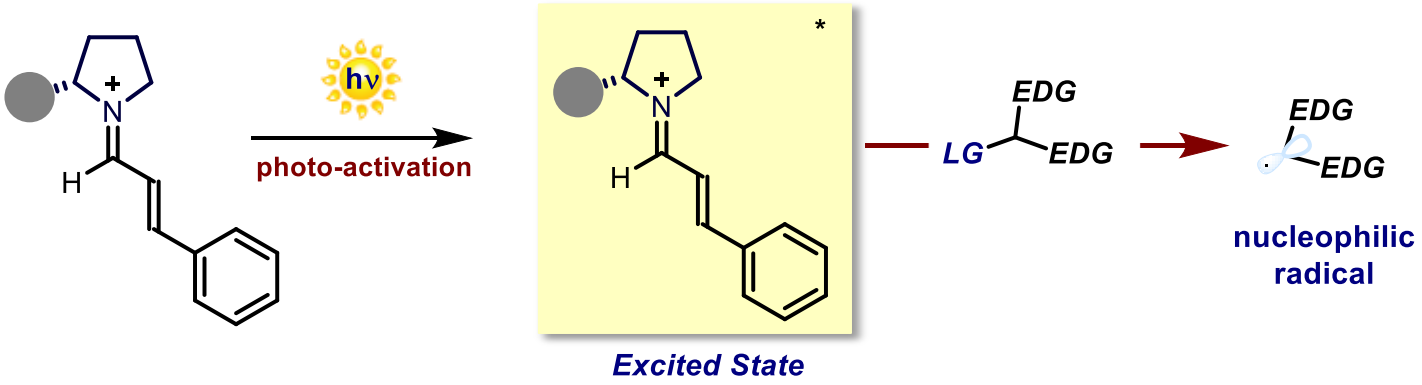
Photochemistry of *Enamines* in the Excited State

Strong reductant

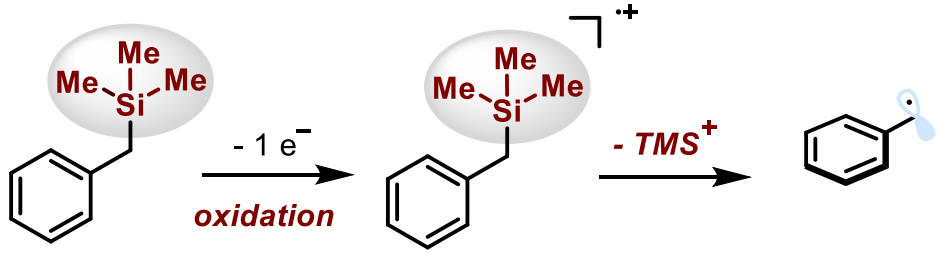


Photochemistry of *Iminium Ions* in the Excited State

Strong oxidant?



Looking for a suitable substrate



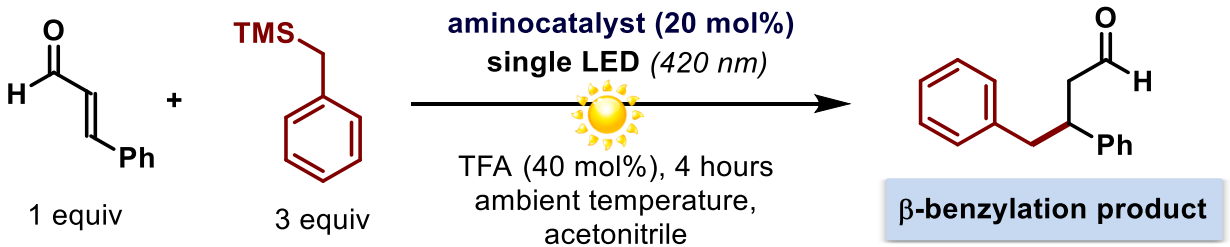
SILANE

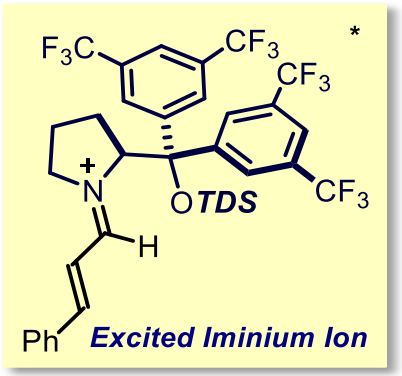
- ✓ **Low reduction potentials** (E_{ox} = +1.4 – 1.7 V)
- ✓ **Can easily fragment realeasing free radicals**
- ✓ **Cheap, easy to synthesize, low toxicity**

Mattia Silvi

For a pertinent precedent, see:
Ohga, K.; Mariano, P. S. *J. Am. Chem. Soc.* **1982**, *104*, 617

Photo-excitation of Iminium Ions

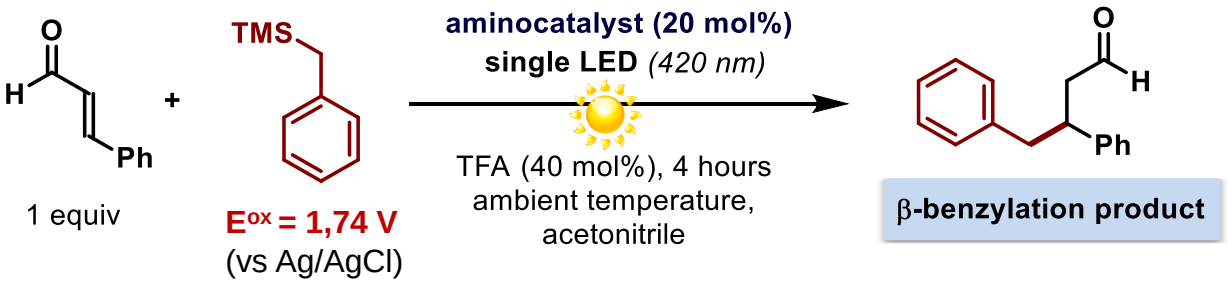




Mattia Silvi

Charlie Verrier

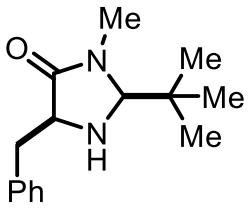
Photo-excitation of Iminium Ions



1 equiv

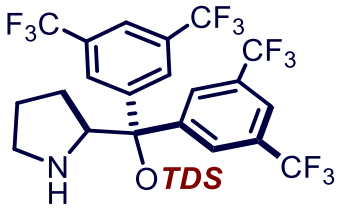
E^{ox} = 1,74 V
(vs Ag/AgCl)

β-benzylation product



79% yield
30% ee

E^{ox} = 1,80 V
(vs Ag/AgCl)

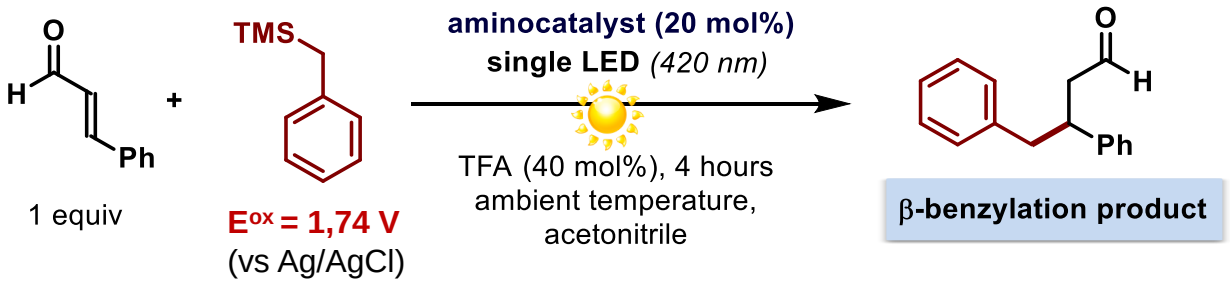


28% yield
76% ee

E^{ox} = 1,57 V
(vs Ag/AgCl)

TDS: dimethylthexylsilyl

Photo-excitation of Iminium Ions

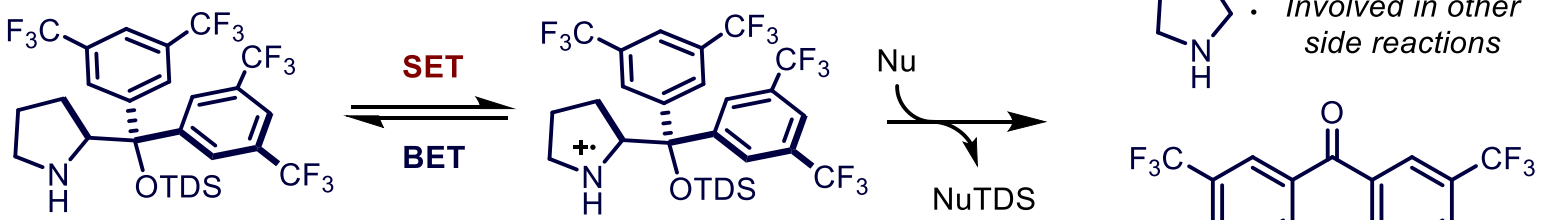


1 equiv

E^{ox} = 1,74 V
(vs Ag/AgCl)

β-benzylation product

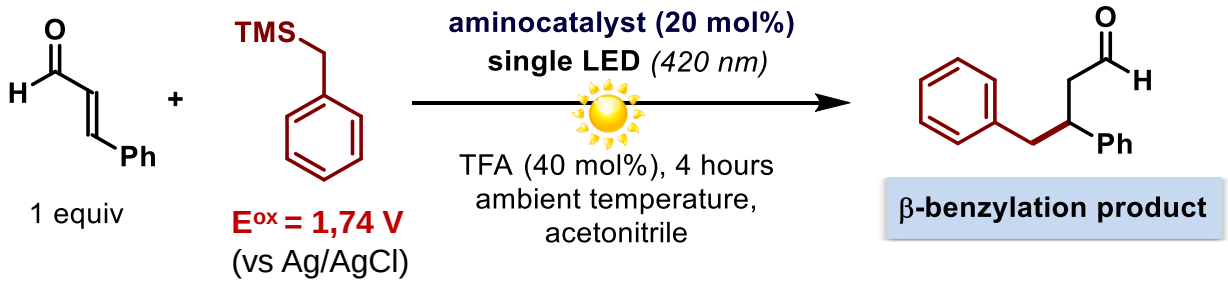
Plausible explanation



E^{ox} = 1,57 V
(vs Ag/AgCl)

Observed

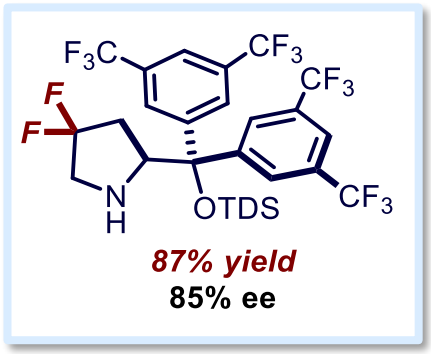
Photo-excitation of Iminium Ions



1 equiv

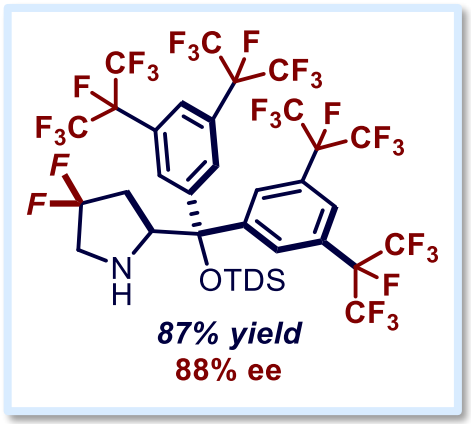
E^{ox} = 1,74 V
(vs Ag/AgCl)

β-benzylation product



87% yield
85% ee

E^{ox} = 2,20 V
(vs Ag/AgCl)



87% yield
88% ee

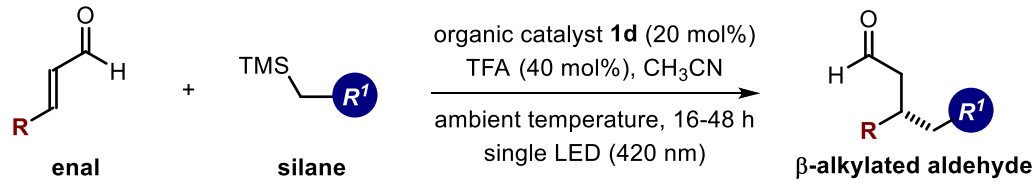
E^{ox} = 2,40 V
(vs Ag/AgCl)

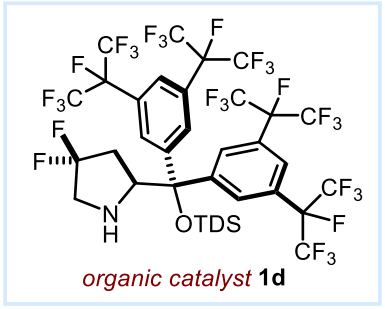
TDS: dimethylthexylsilyl

Charlie Verrier

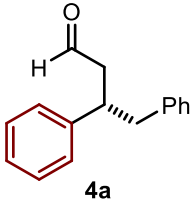
Yannick Rey

with M. Silvi, C. Verrier, Y. Rey, L. Buzzetti
Nature Chem. **2017**, 9, 868-873

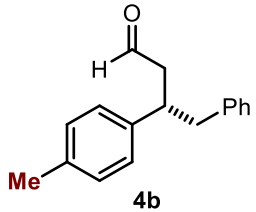




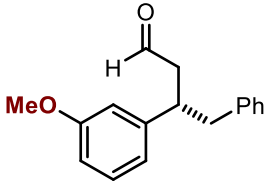
Enals



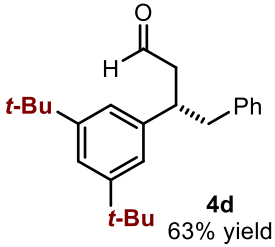
4a
87% (73%)* yield
88% (88%)* e.e.



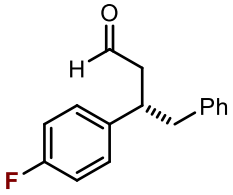
4b
74% yield
78% e.e.



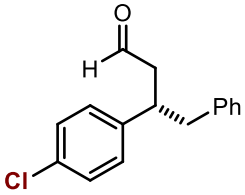
4c
62% yield
82% e.e.



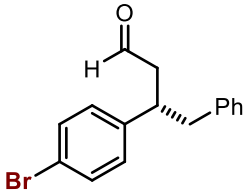
4d
63% yield
68% e.e.



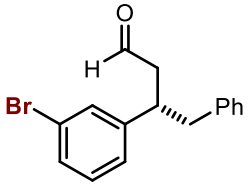
4e
76% yield
85% e.e.



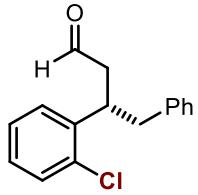
4f
75% yield
86% e.e.



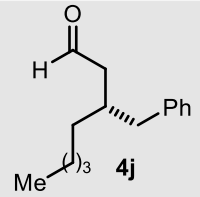
4g
74% yield
84% e.e.



4h
73% yield
86% e.e.

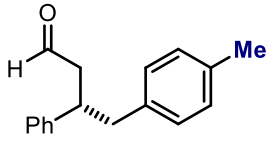


4i
75% yield
88% e.e.

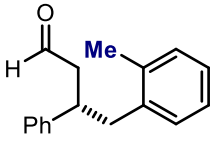


4j
not detected

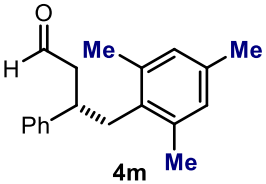
C Benzyl Silanes



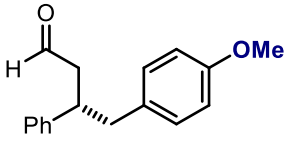
4k
90% yield
91% e.e.



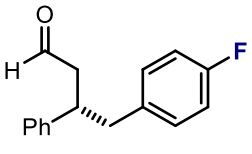
4l
85% yield
90% e.e.



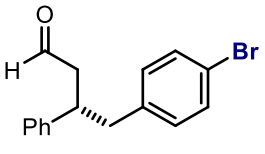
4m
93% yield
93% e.e.



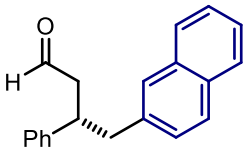
4n
77% yield
92% e.e.



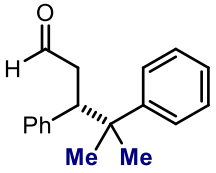
4o
80% yield
85% e.e.



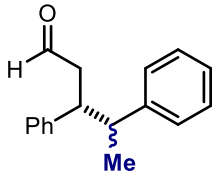
4p
66% yield
78% e.e.



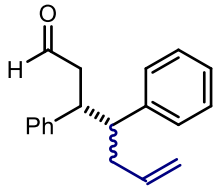
4q
77% yield
91% e.e.



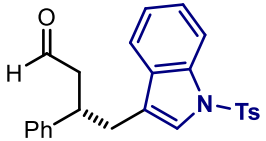
4r
46% yield
71% e.e.



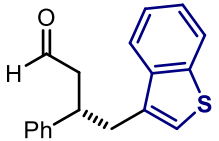
4s: 92% yield
1.2:1 d.r.; 92% e.e.$_{major}$
92% e.e.$_{minor}$



4t: 66% yield
1.5:1 d.r.; 92% e.e.$_{major}$
90% e.e.$_{minor}$

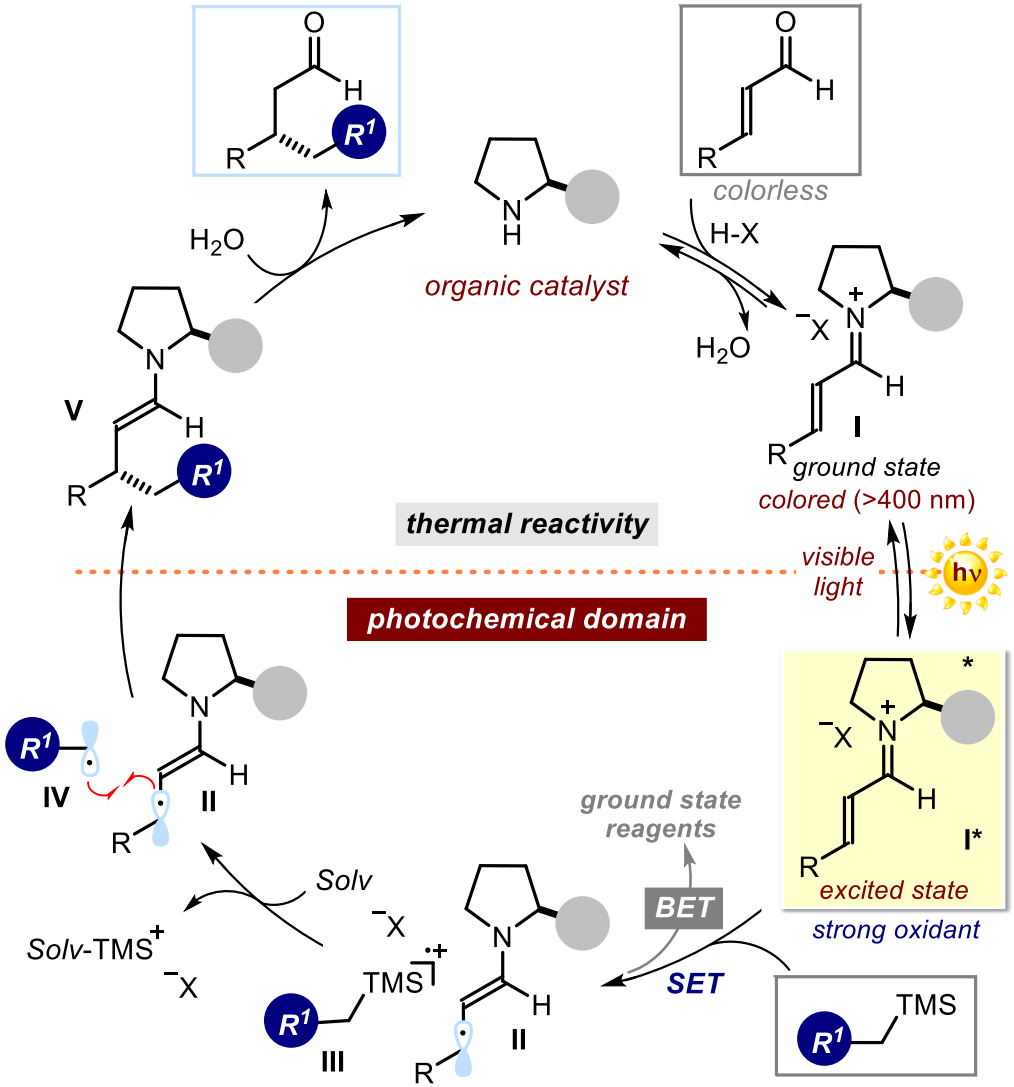


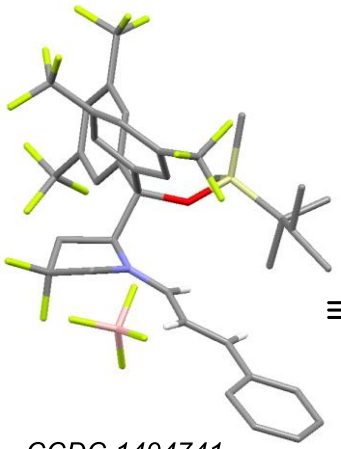
4u
52% yield
94% e.e.



4v
55% yield
87% e.e.†

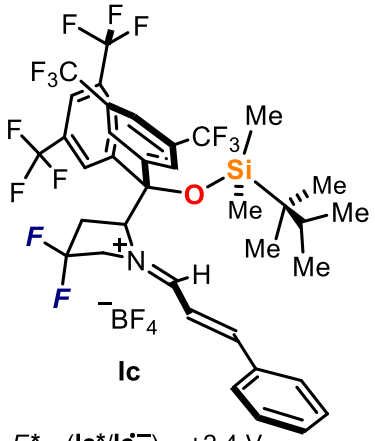
Proposed mechanism





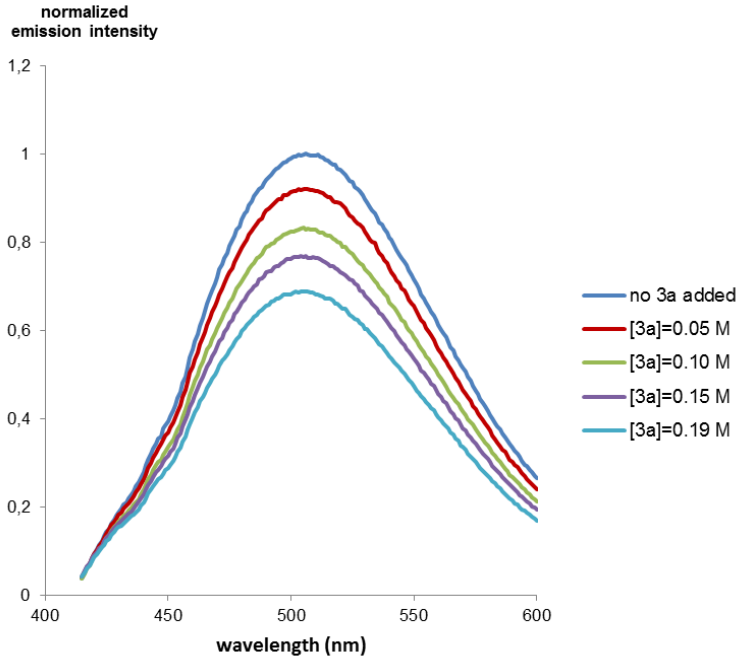
CCDC 1494741

≡



Ic

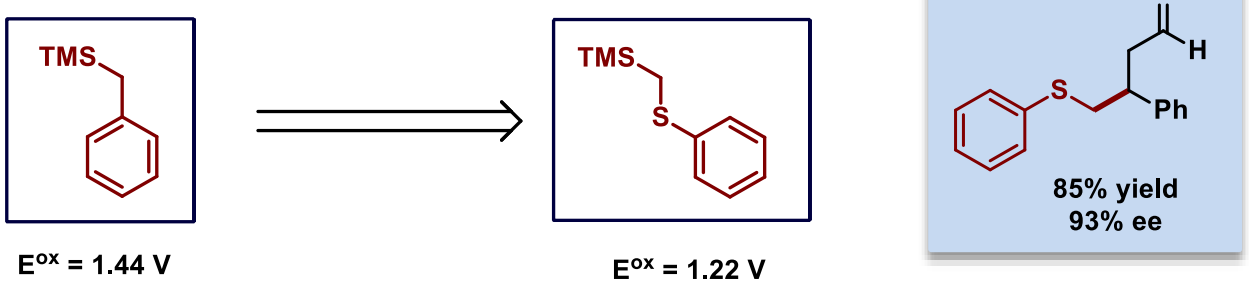
$E^*_{red}(Ic^*/Ic^{\bullet-})$ ~ +2.4 V



Φ (*400 nm*) = **0,04**

Nature Chem. **2017**, 9, 868-873

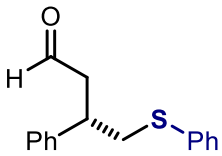
Photochemistry of Iminium Ions



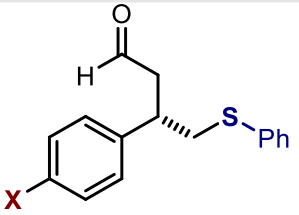
E^{ox} = 1.44 V

E^{ox} = 1.22 V

α-Heteroatom-substituted Organic Silanes

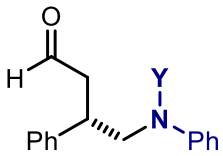


5a
73% yield
90% ee‡



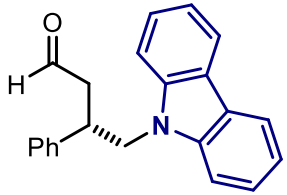
X = MeO: **5b**
81% yield
79% ee#

X = CF_3: **5c**
43% yield
81% ee#

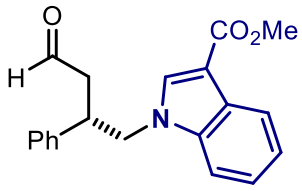


Y = Ph: **5d**
58% yield
75% ee‡

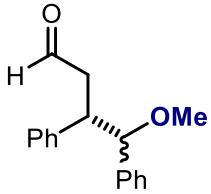
X = BOC: **5e**
63% yield
71% ee



5f
82% yield
81% ee



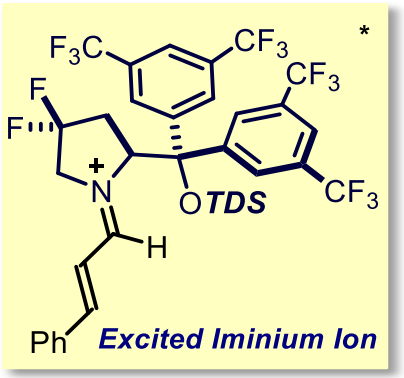
5g
64% yield
92% ee‡



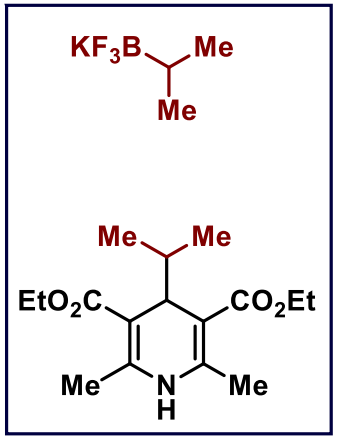
5h: 56% yield†
1.9:1 d.r.; 68% ee_{major}
61% ee_{minor}

with M. Silvi, C. Verrier, Y. Rey, L. Buzzetti
Nature Chem. **2017**, 9, 868-873

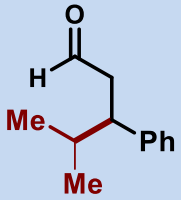
Photochemistry of Iminium Ions



Strong oxidant



65% yield
82% ee



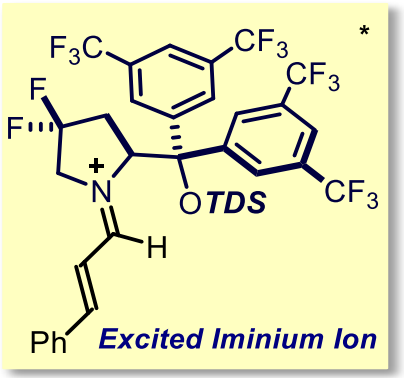
84% yield
86% ee

with Charlie Verrier, Nurtalya Alandini, Luca Buzzetti
ACS Catal. **2018**, *8,* 1062–1066

For pertinent precedents:

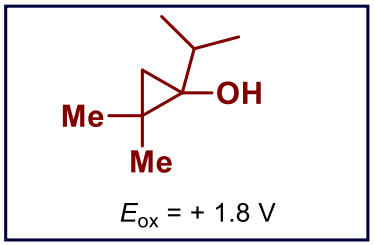
J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433–436
K. Nakajima, S. Nojima, K. Sakata, Y. Nishibayashi, *ChemCatChem* **2016**, 8, 1028–1032
G. A. Molander *et al., ACS Catal.* **2016**, *6*, 8004–8008

Asymmetric Organocatalytic Photo-Cascade

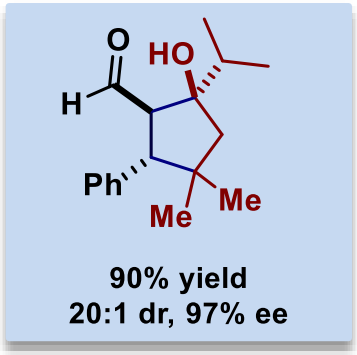


Excited Iminium Ion

Strong oxidant



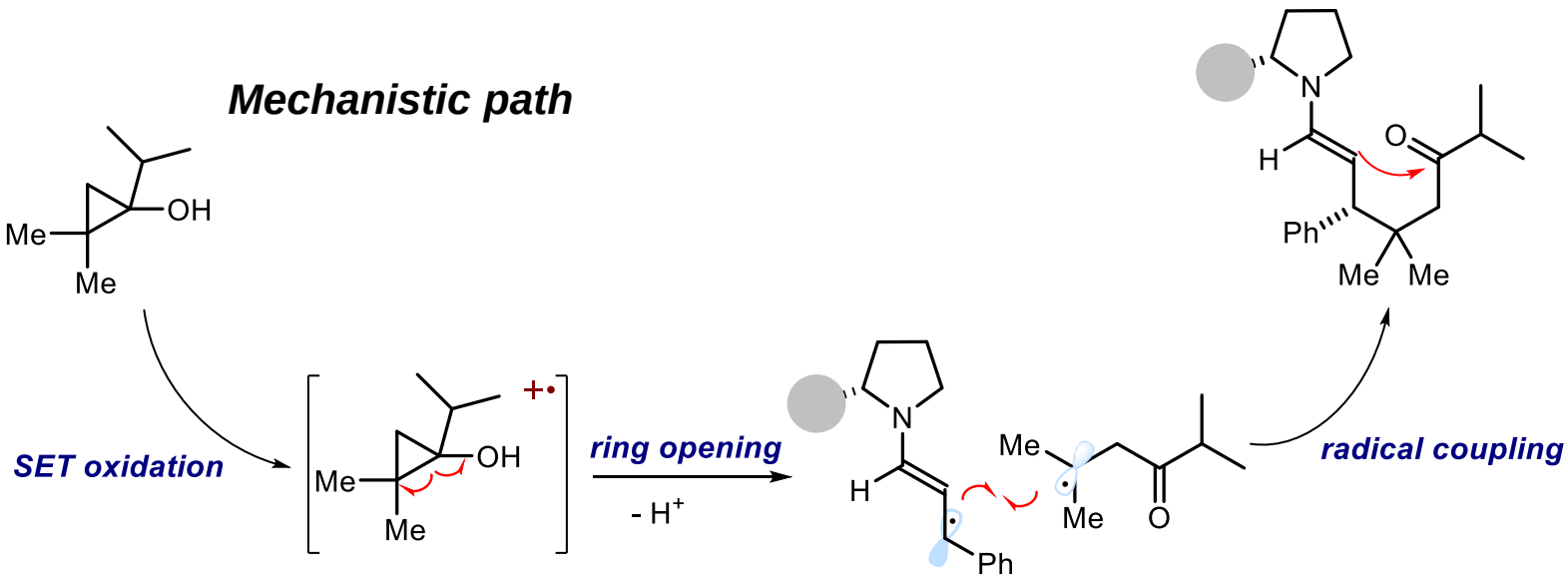
E_{ox} = + 1.8 V



90% yield
20:1 dr, 97% ee

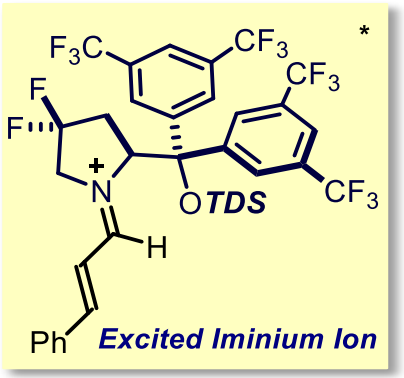
with Lukasz Wozniak & G. Magagnano,
Angew. Chem. Int. Ed. **2018**, *57*, 1068

Mechanistic path

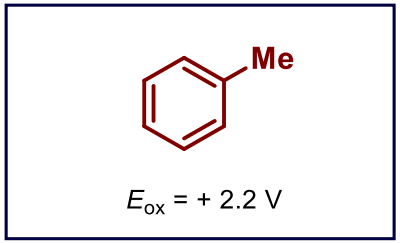


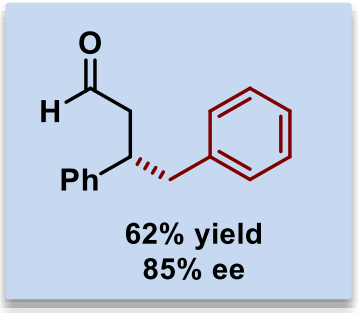
For a pertinent study, see:
P. Mariano, *Tetrahedron* **1981** *37*, 3385-3395

Asymmetric Photocatalytic C-H Functionalization of Toluene



Strong oxidant





with D. Mazzarella, G. Crisenza,
unpublished results

Mechanistic path