ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

@MelchiorreGroup

Melchiorre Group

Photochemistry, Organocatalysis & Enzymes

New Radical Opportunities

Ischia Advanced School of Organic Chemistry

IASOC 2024

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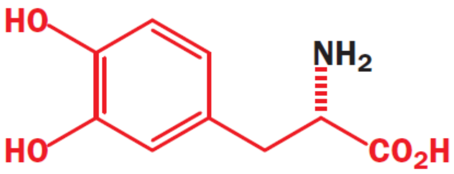
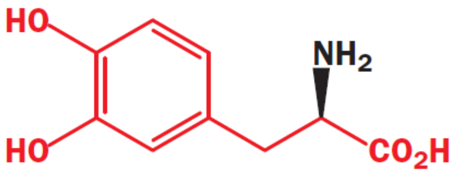
Bologna University
Industrial Chemistry Department *'Toso Montanari'*

Nature's inherent chirality requires us to create chiral molecules in enantiomerically pure form in order to interact with or modify our world

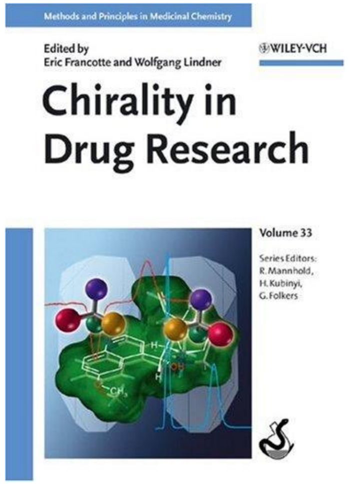


L-dopa
marketed as a single enantiomer



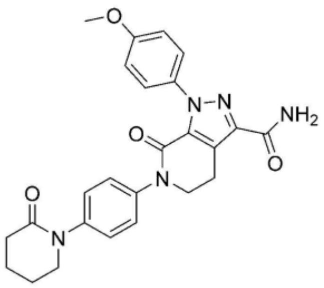
D-dopa
toxic

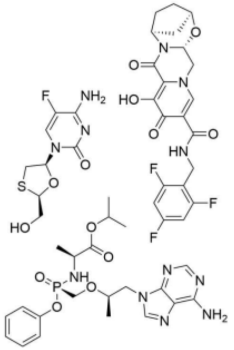
Stereochemistry is an essential dimension in drug discovery

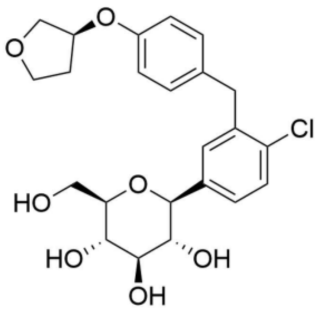


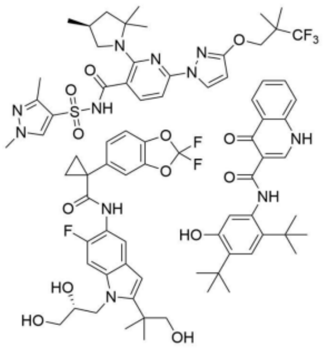
Top 200 Small Molecule Drugs by Retail Sales in 2023

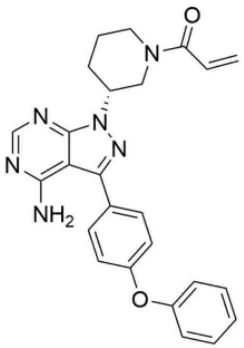
Compiled and Produced by Ryan E. Williams and Hayden M. Leatherwood from the Njarðarson Group (The University of Arizona)

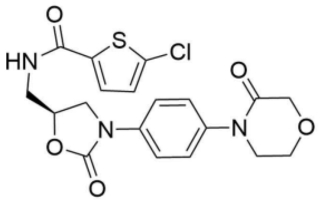
1 Eliquis
(Apixaban)

$18.953 Billion
Cardiology/Vascular Diseases

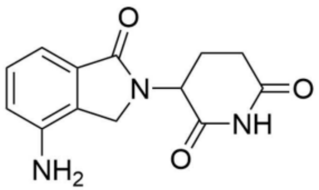
2 Biktarvy
(Bictegravir/Emtricitabine/Tenofovir Alafenamide)

$11.850 Billion
Infectious Diseases

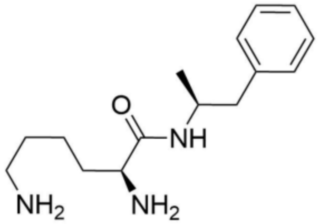
3 Jardiance
(Empagliflozin)

$10.600 Billion
Diabetes

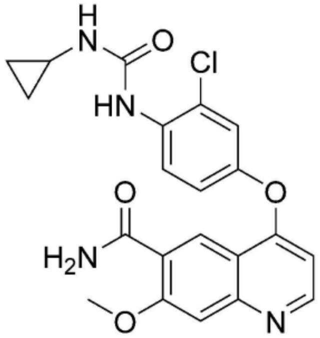
4 Trikafta
(Elexacaftor/Tezacaftor/Ivacaftor)

$8.944 Billion
Genetic Diseases

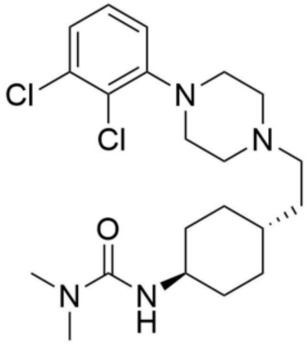
5 Imbruvica
(Ibrutinib)

$6.860 Billion
Oncology

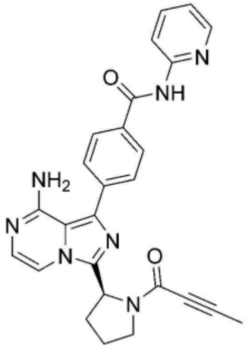
6 Xarelto
(Rivaroxaban)

$6.793 Billion
Cardiology/Vascular Diseases

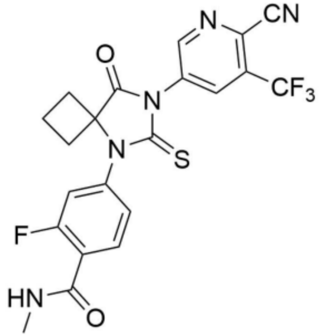
7 Revlimid
(Lenalidomide)

$6.179 Billion
Oncology

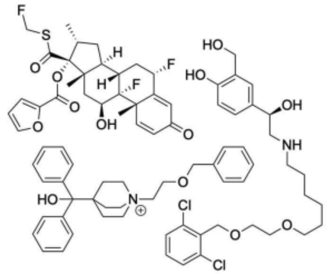
21 Vyvanse
(Lisdexamfetamine)

$2.978 Billion
Neurology

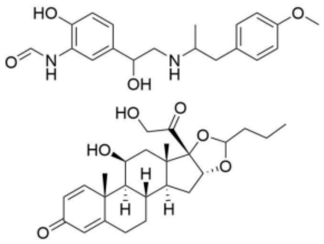
22 Lenvima
(Lenvatinib)

$2.868 Billion
Oncology

23 Vraylar
(Cariprazine)

$2.759 Billion
Neurology

24 Calquence
(Acalabrutinib)

$2.514 Billion
Oncology

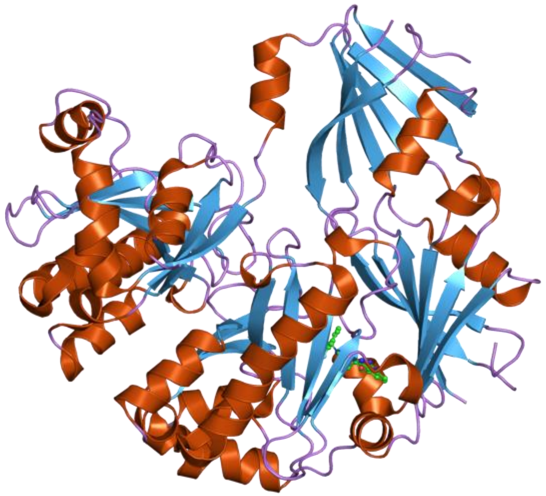
25 Erleada
(Apalutamide)

$2.387 Billion
Oncology

26 Trelegy Ellipta
(Fluticasone Furoate/Vilanterol Trifenatate/Umeclidinium)

$2.376 Billion
Respiratory Diseases

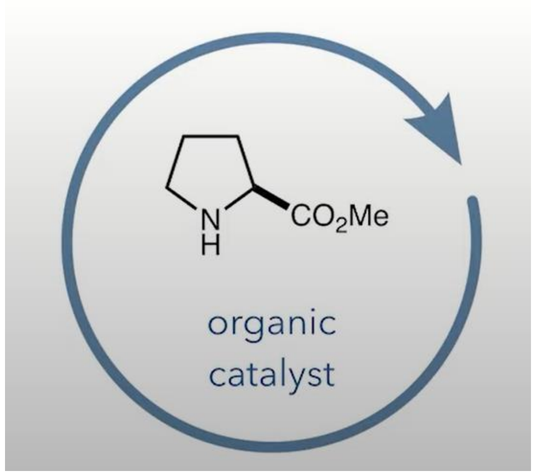
27 Symbicort
(Budesonide/Formoterol)

$2.362 Billion
Respiratory Diseases

Catalysis *makes existing reactions easier, faster, and allows new chemical reactions*

metal catalysis



biocatalysis



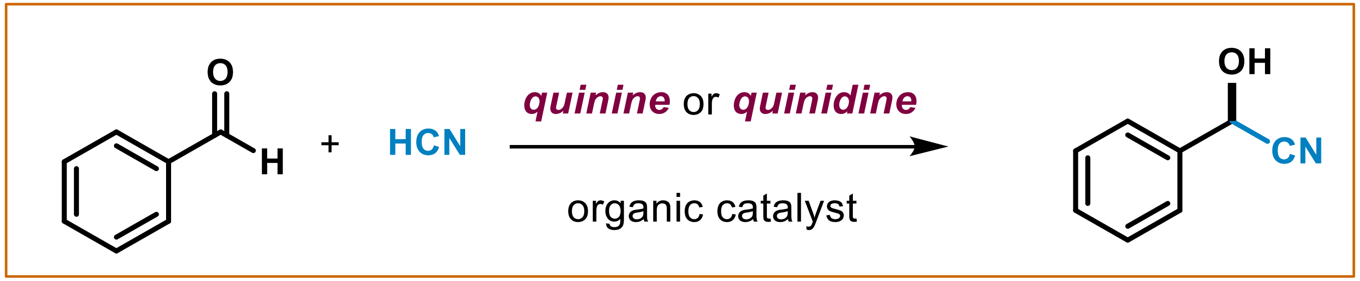
organocatalysis

Enantioselective Catalysis

Most economical, energy-saving, and environmentally benign approach to achieve stereocontrol

Noyori, R. Synthesizing our future. *Nature Chemistry* 1, 5–6 (2009)

Asymmetric Cyanation & Organocatalysis



ee less than 10%

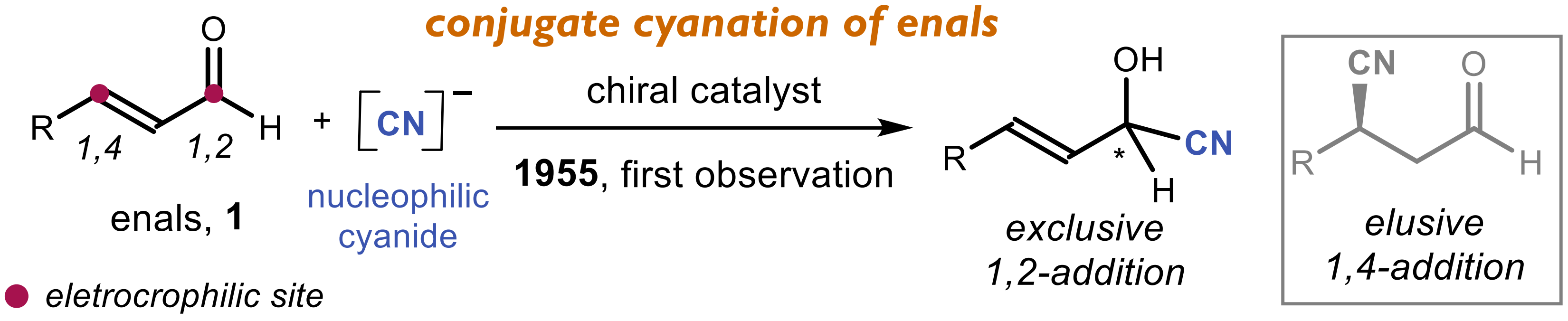
Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7–23

first example of non-enzymatic asymmetric catalysis ever developed by chemists

Kagan, H. B.
Historical perspectives, in *Comprehensive Asymmetric Catalysis*,
ed. Jacobsen, E. N., Pfaltz A. & Yamamoto, H. Springer-Verlag, Berlin (1999), vol. 1, p. 4-22

But when it comes to conjugate cyanation…

Problem number 1



*how to override the intrinsic 1,2-chemoselectivity of **1** to favour a conjugate 1,4-cyanation?*

Prelog, V. & Wilhelm, M. *Helv. Chim. Acta* **37**, 1634–1660 (1954).

How to develop a chemoselective conjugate cyanation process?

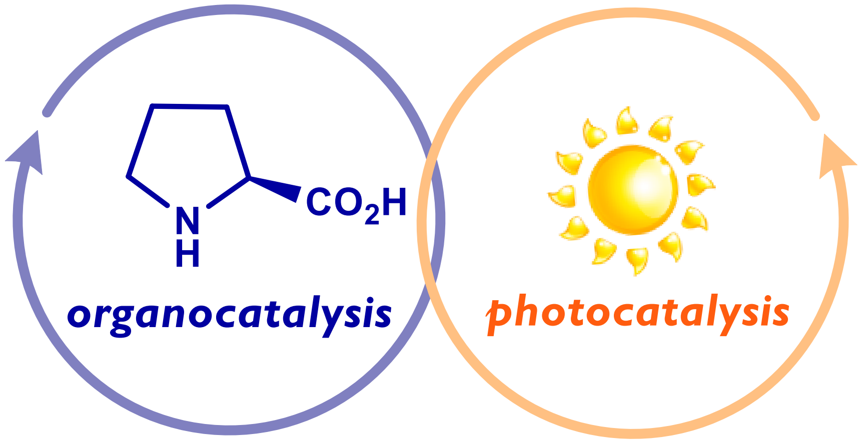
no example of 1,4 cyanation of enals
even in the racemic regime

But when it comes to conjugate cyanation…

Problem number 1

How to develop a chemoselective conjugate cyanation process?

Our approach

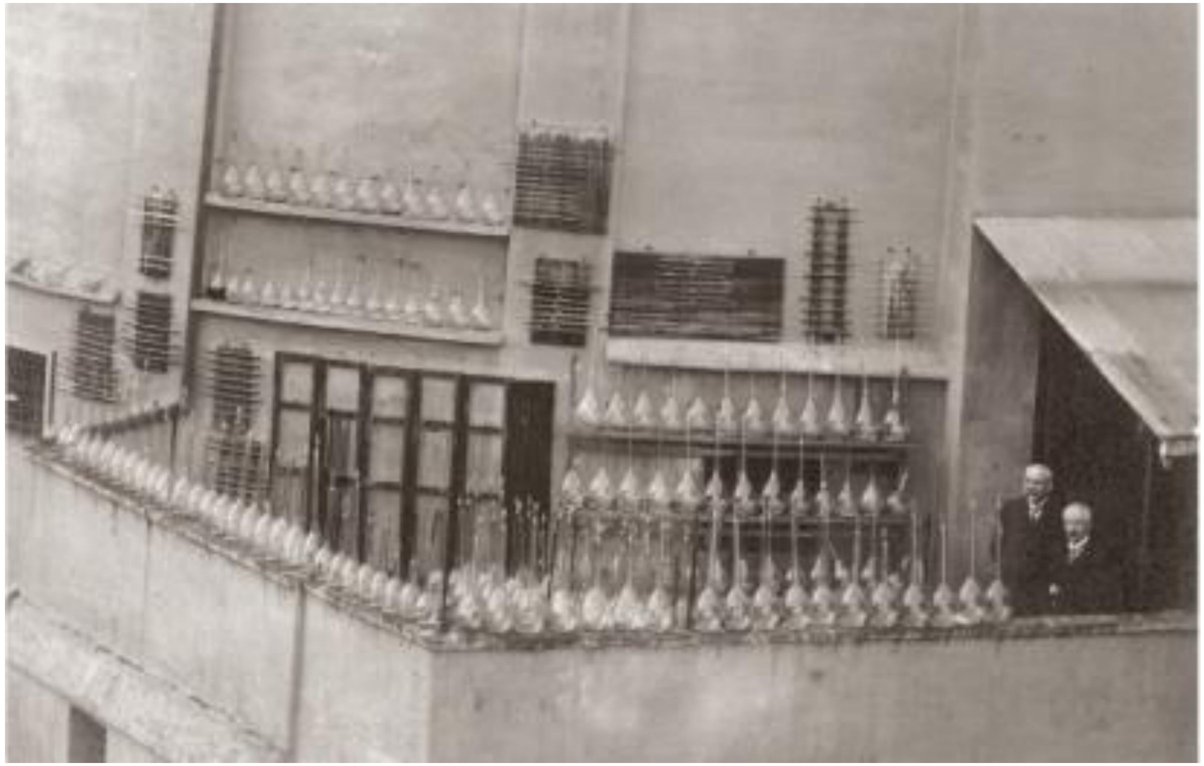


the Father of Photochemistry

Giacomo Ciamician (1857-1922)

'The Photochemistry of the Future'
Science **1912**, *36*, 385–394

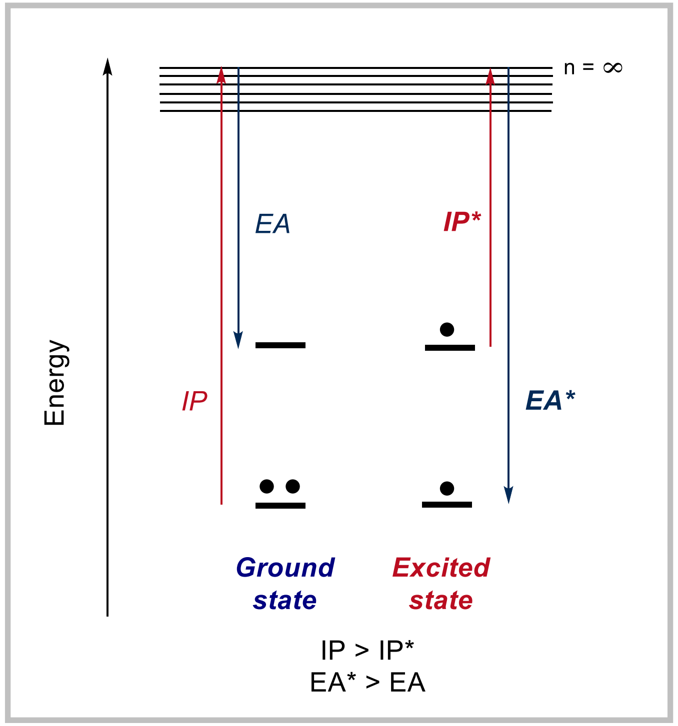
"… and if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilization will continue as long as the sun shines!"



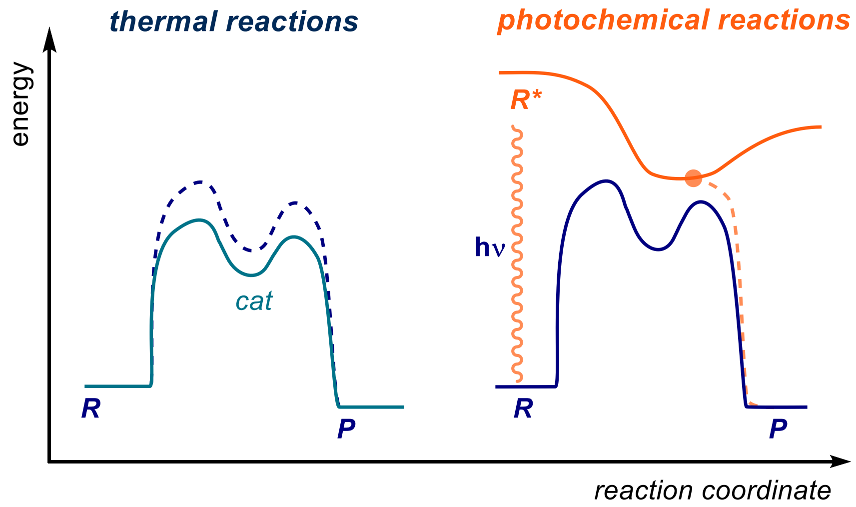
on the roof of the Chemistry Department in Bologna (Italy)

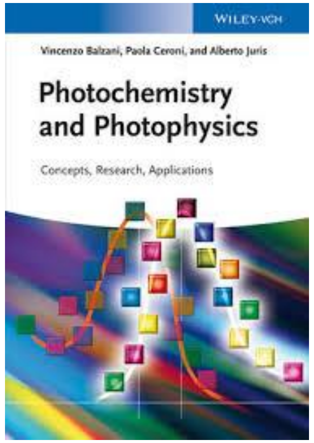
Photochemistry and Excited-State Reactivity

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



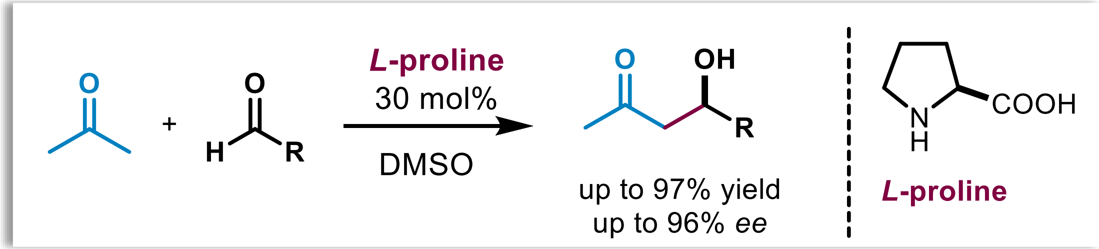
excited-state reactivity unlocks unconventional reaction pathways





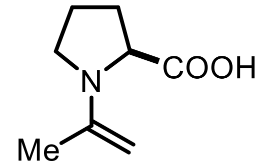
Organocatalysis

- Proline-catalyzed intermolecular aldol reaction



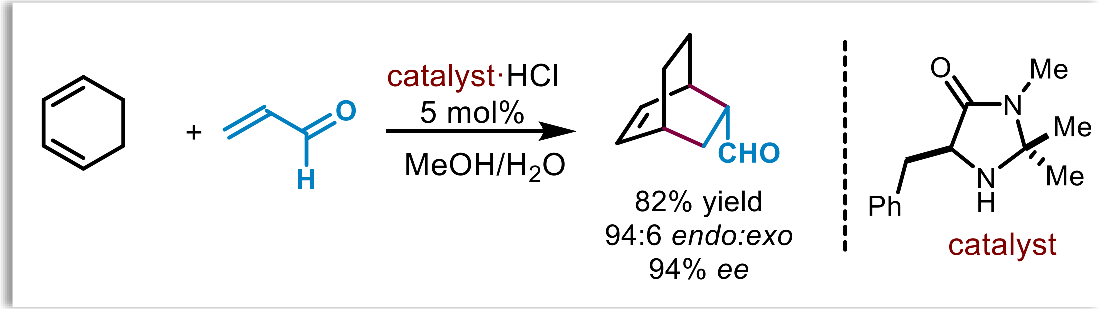
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Enamine Catalysis



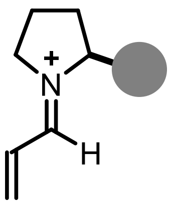
HOMO-Raising Activation

- Iminium ion catalyzed asymmetric Diels-Alder of enals



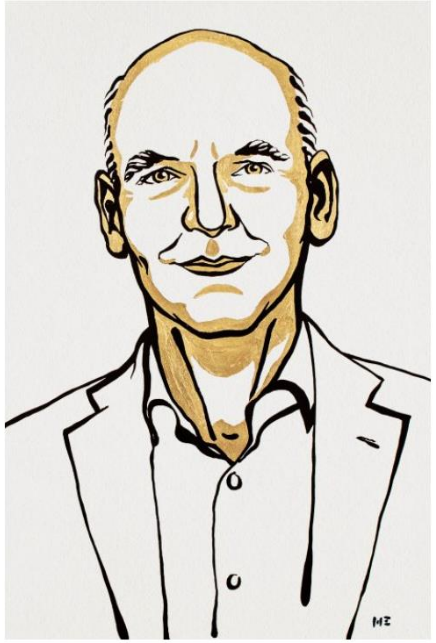
K. A. Ahrendt, C. J. Borths, **D. W. C. MacMillan**, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

Iminium-Ion Catalysis



LUMO-Lowering Activation

Where we are now



Ill. Niklas Elmehed © Nobel Prize Outreach.

Benjamin List

Prize share: 1/2

Ill. Niklas Elmehed © Nobel Prize Outreach.

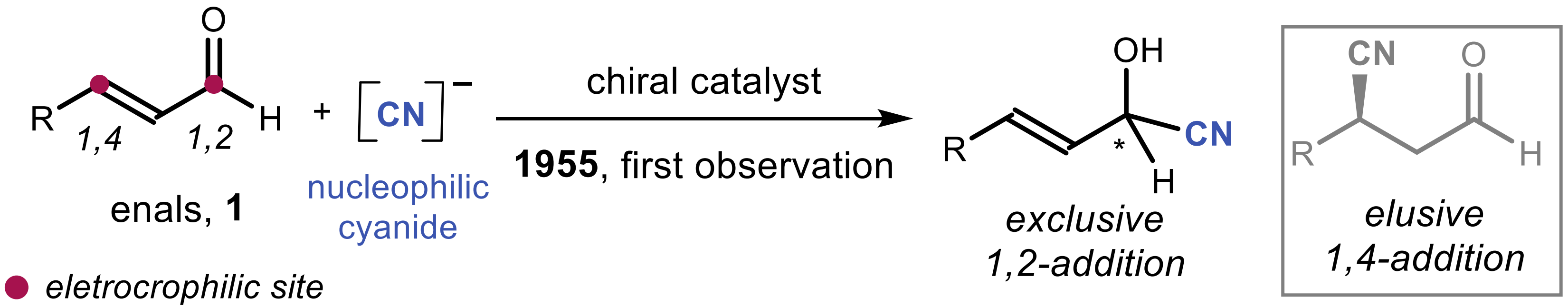
David W.C. MacMillan

Prize share: 1/2

The Nobel Prize in Chemistry 2021 was awarded jointly to Benjamin List and David W.C. MacMillan "for the development of asymmetric organocatalysis."

But when it comes to conjugate cyanation…

conjugate cyanation of enals



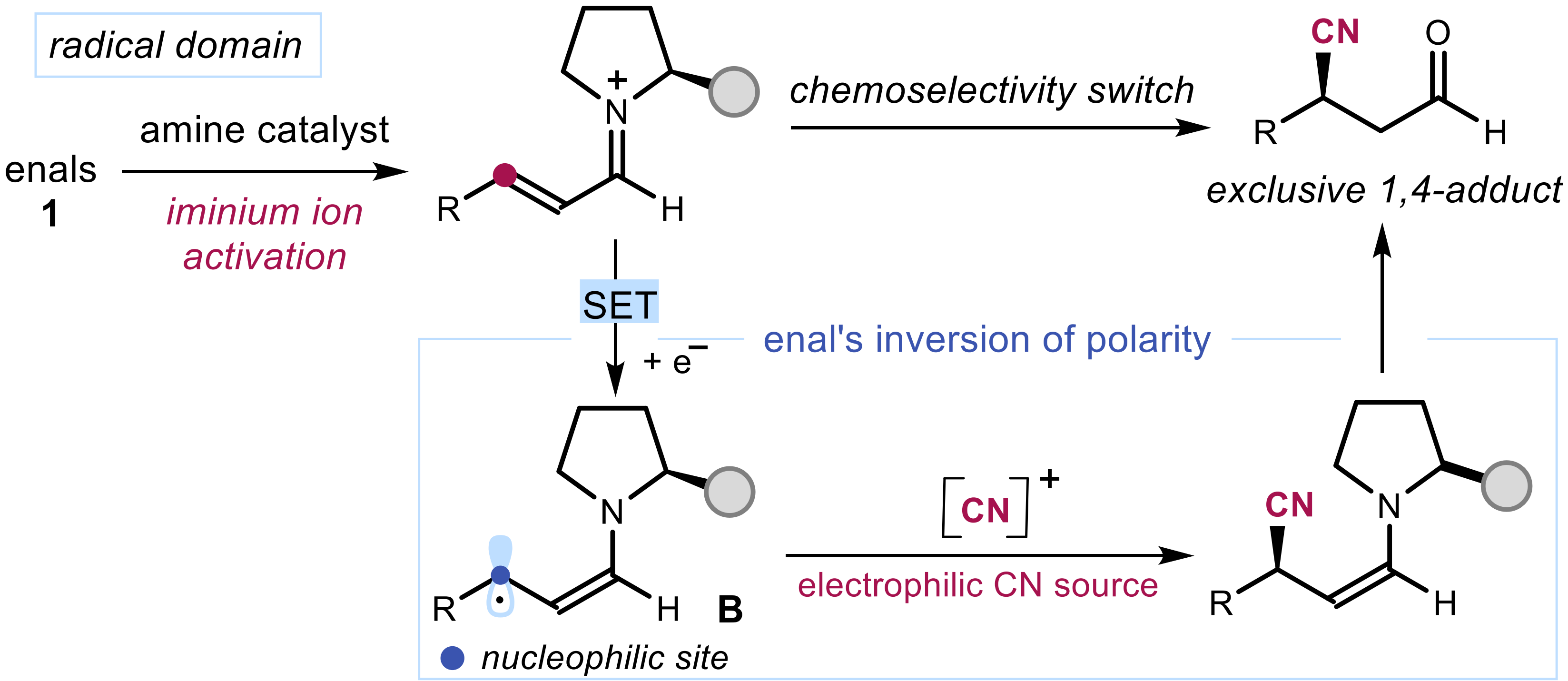
*how to override the intrinsic 1,2-chemoselectivity of **1** to favour a conjugate 1,4-cyanation?*

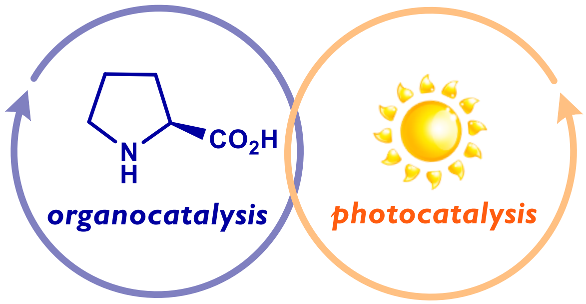
Prelog, V. & Wilhelm, M. *Helv. Chim. Acta* **37**, 1634–1660 (1954).

iminium ion catalysis could not achieve this target

no example of 1,4 cyanation of enals
even in the racemic regime

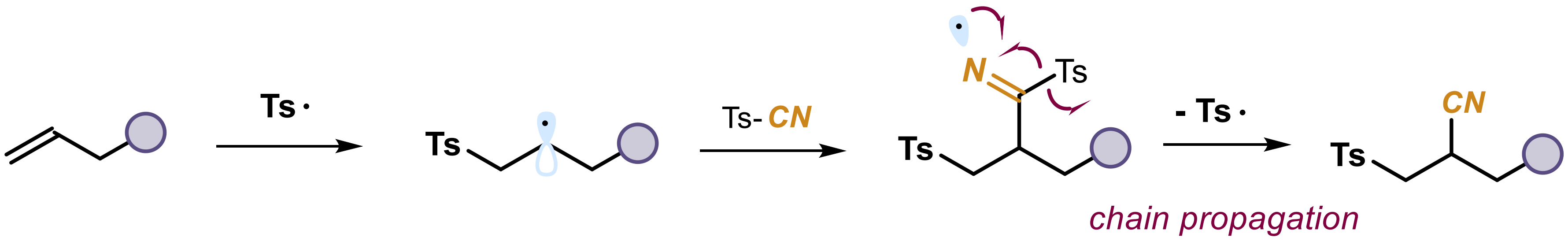
Our Idea..


radical domain
enals
1
amine catalyst
iminium ion
activation
chemoselectivity switch
CN
O
R
H
exclusive 1,4-adduct
SET
+ e⁻
enal's inversion of polarity
N
B
nucleophilic site
[CN]+
electrophilic CN source


N
H
CO2H
organocatalysis
photocatalysis

Asymmetric Conjugate Cyanation

electrophilic CN source



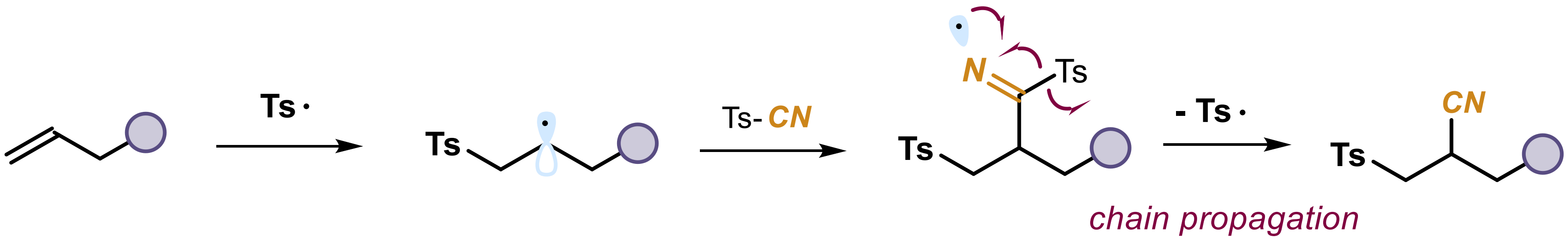
Martin Berger

Barton Cyanation - nitrile transfer to carbon radicals

Radical nitrile transfer with methanesulfonyl cyanide or p-toluenesulfonyl cyanide to carbon radicals
Tetrahedron Lett. **1991**, *32*, 3321

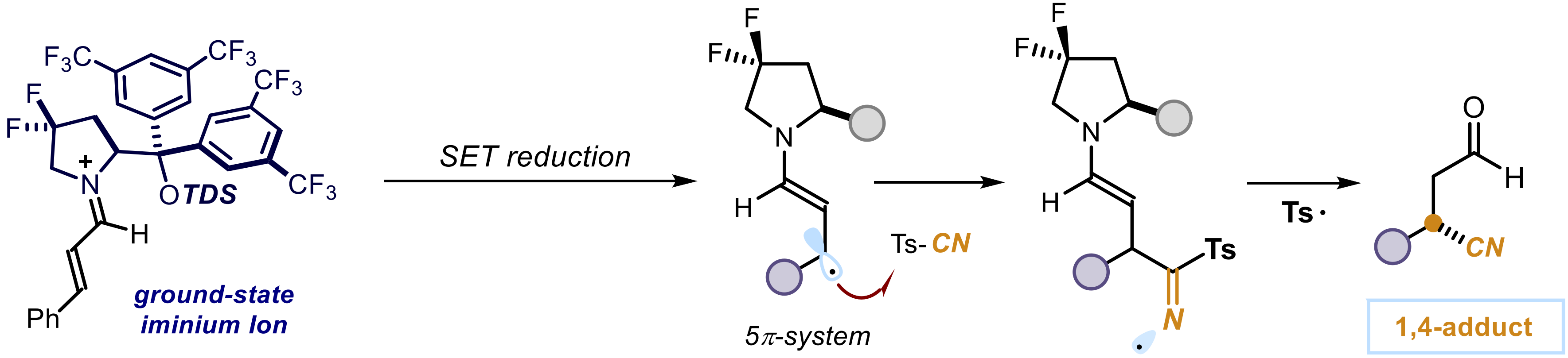
Asymmetric Conjugate Cyanation

electrophilic CN source

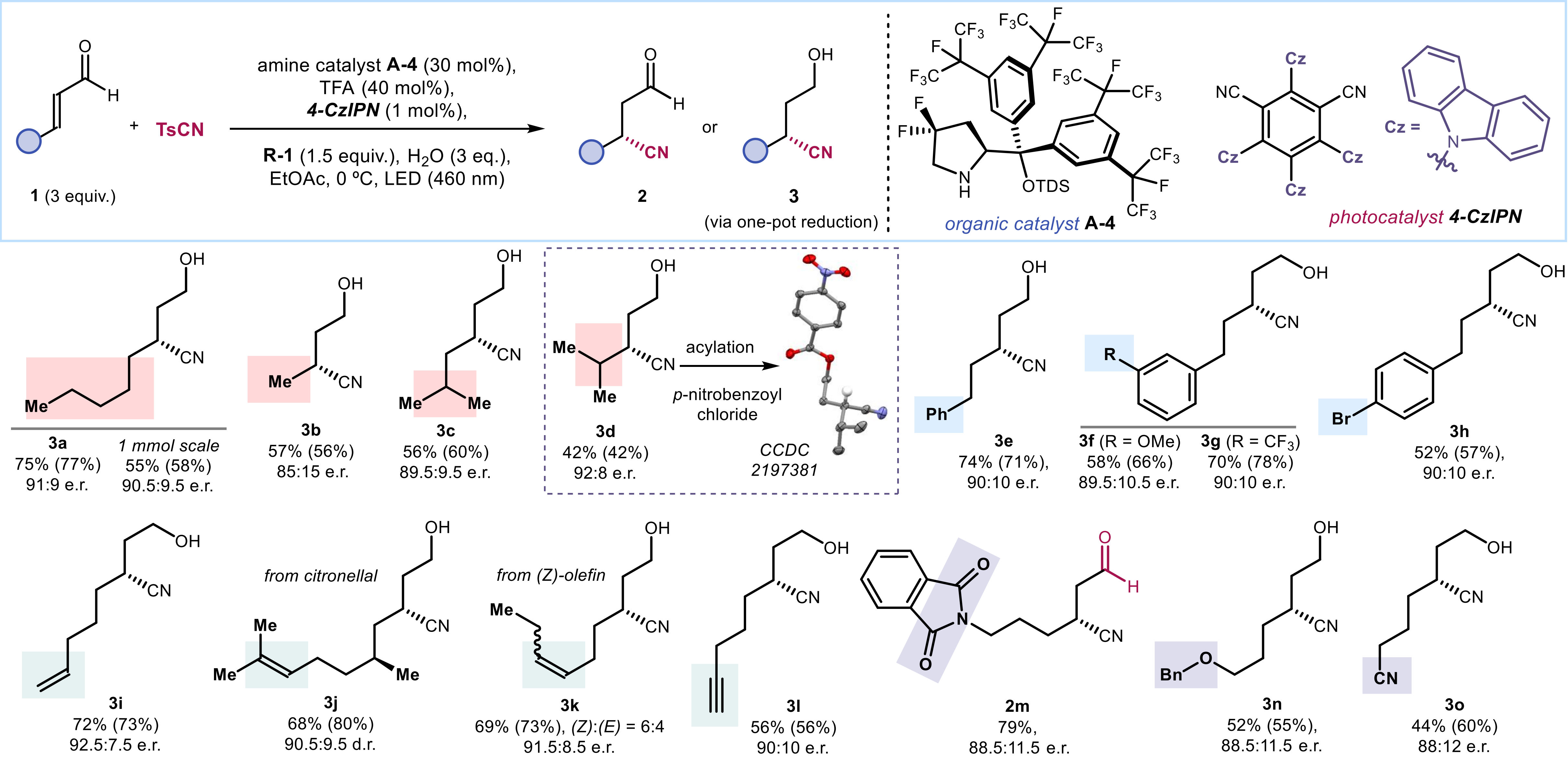


Martin Berger

Barton Cyanation - nitrile transfer to carbon radicals



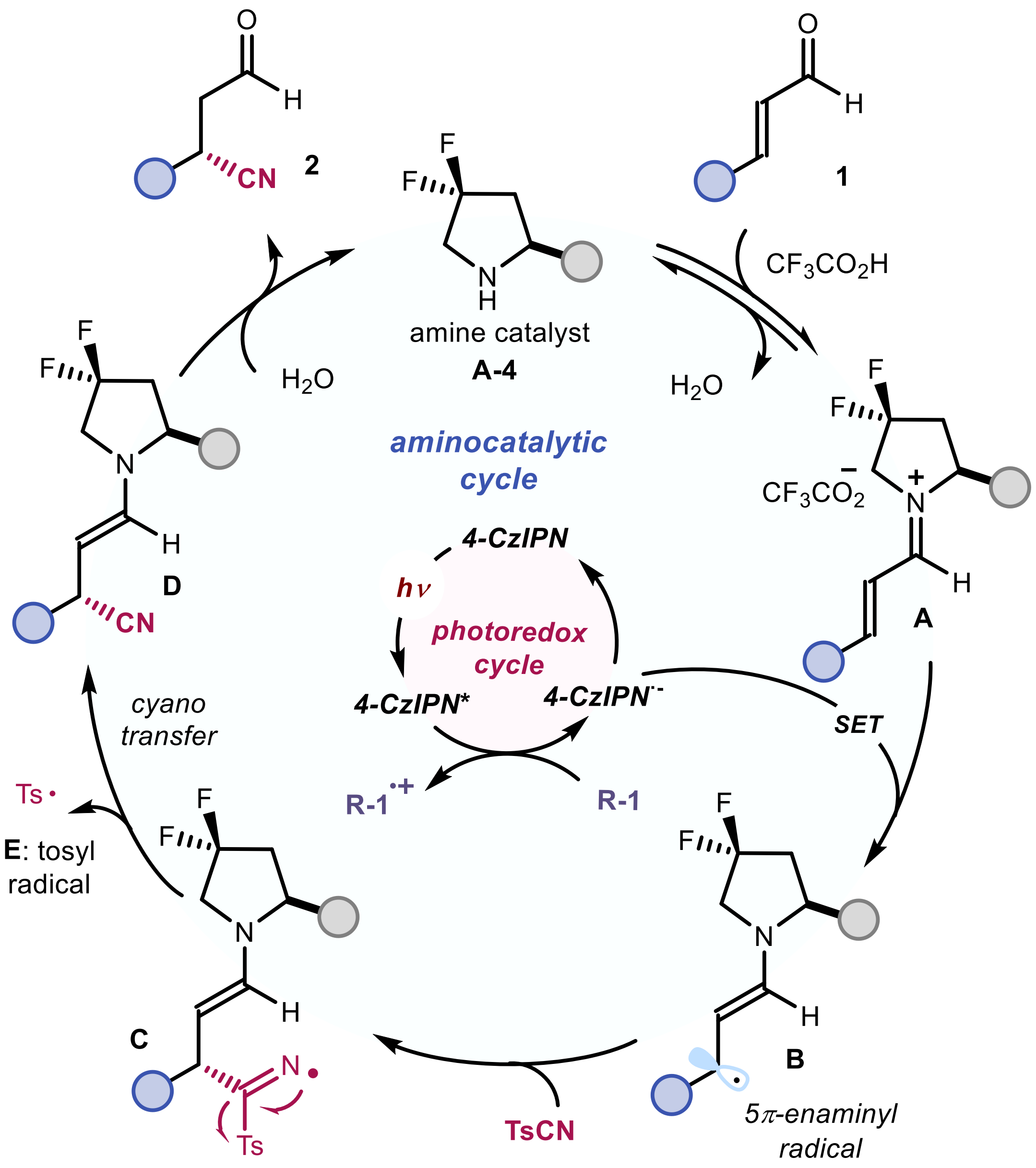
Asymmetric Conjugate Cyanation

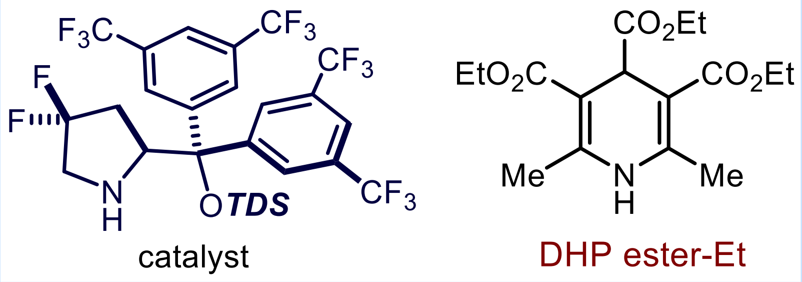


with M. Berger, D. Ma, Y. Baumgartner, T. Wong
Nat Catal. **2023**, *6*, 332–338

Asymmetric Conjugate Cyanation

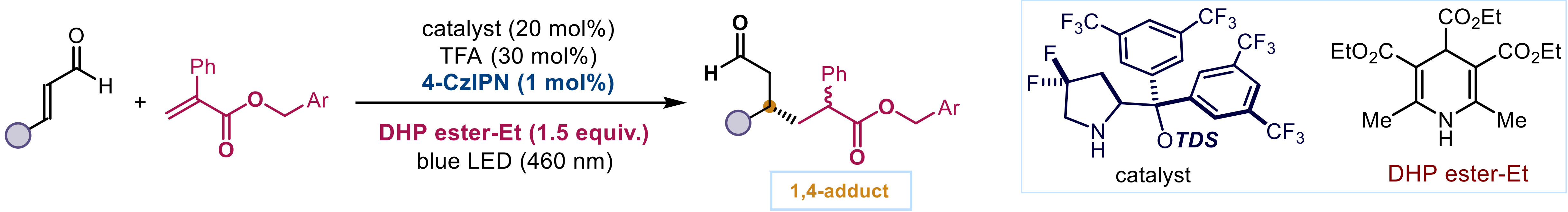
Proposed catalytic cycle

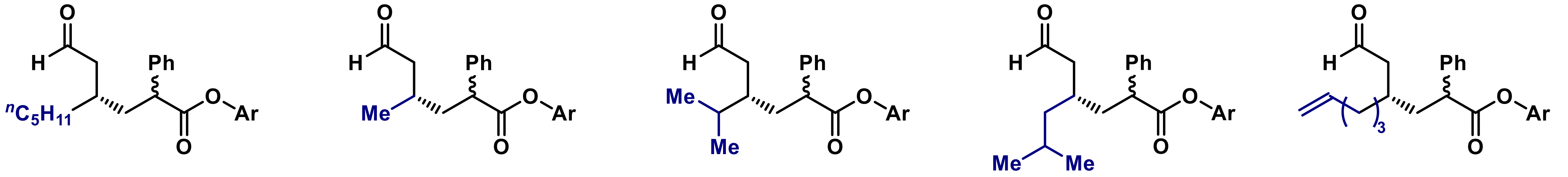




with M. Berger, D. Ma, Y. Baumgartner, T. Wong
Nat Catal. **2023**, *6*, 332–338

Asymmetric Conjugate β-Alkylation of Enals





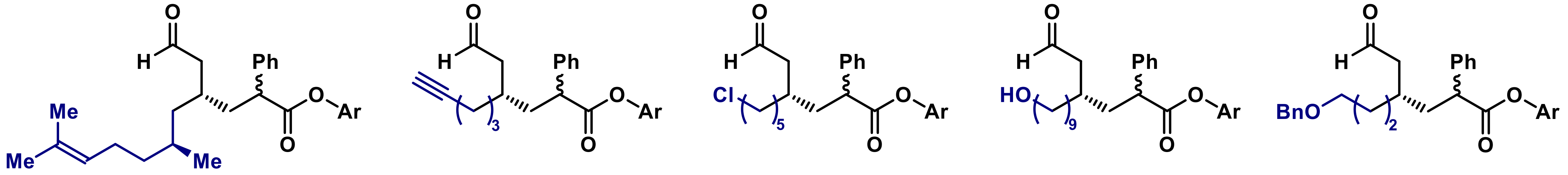
93% yield, 1:1 dr
90% ee, 82% ee

71% yield, 1:1 dr
75% ee, 60% ee

46% yield, 1.1:1 dr
87% ee, 75% ee

56% yield, 1.1:1 dr
87% ee, 78% ee

82% yield, 1.2:1 dr
89% ee, 74% ee



67% yield, 1.6:1 dr
72% ee, 77% ee

65% yield, 1:1 dr
82% ee, 70% ee

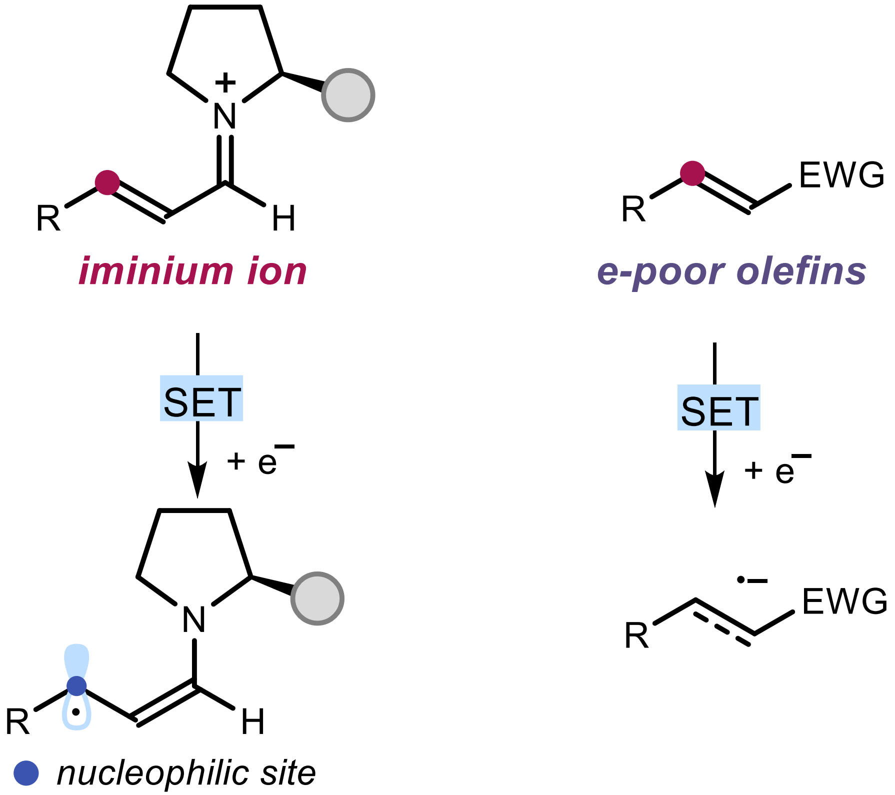
65% yield, 1.1:1 dr
90% ee , 72% ee

72% yield, 1:1 dr85% ee ,
85% ee, 68% ee

71% yield, 1.1:1 dr
87% ee, 73% ee

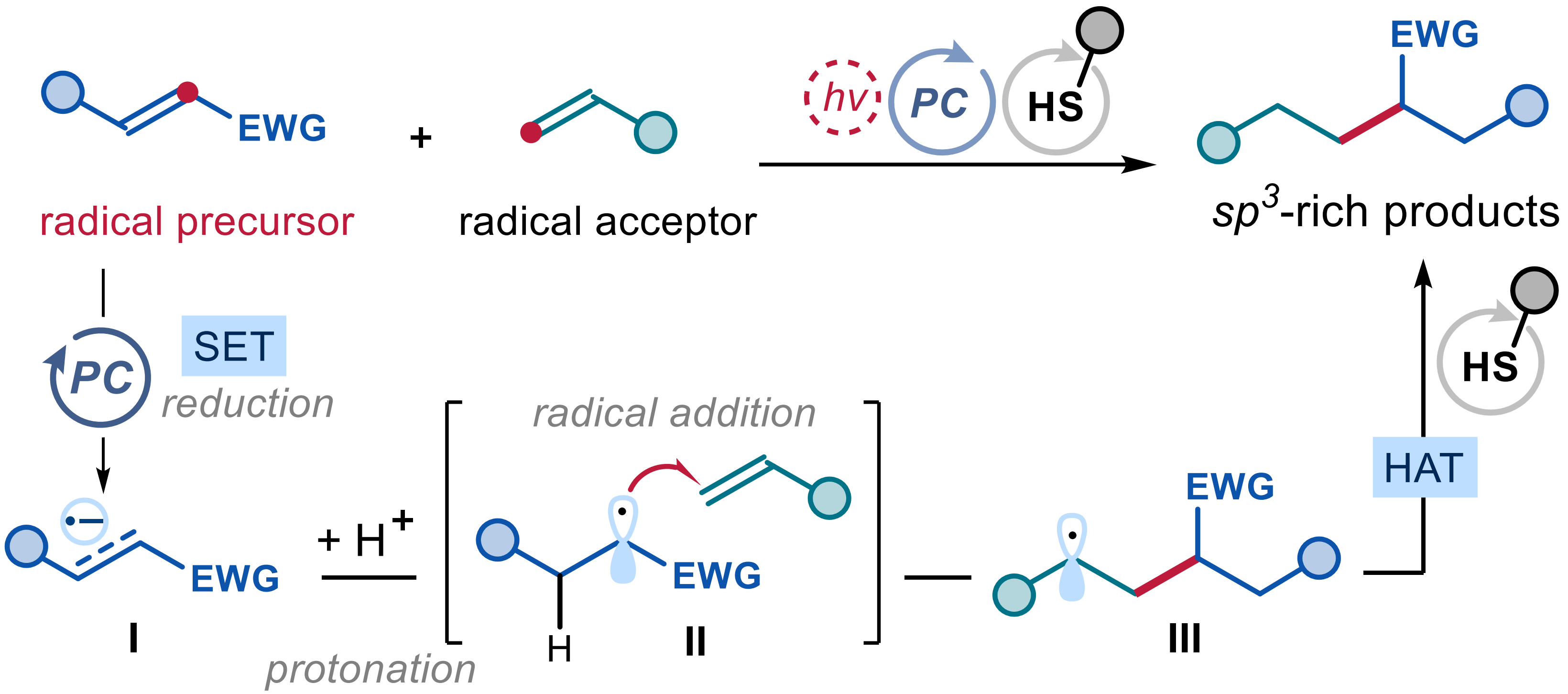
with M. Berger, D. Ma, Y. Baumgartner, T. Wong
Nat Catal. **2023**, *6*, 332–338

How to further expand the idea of SET activation of electron-poor π-systems



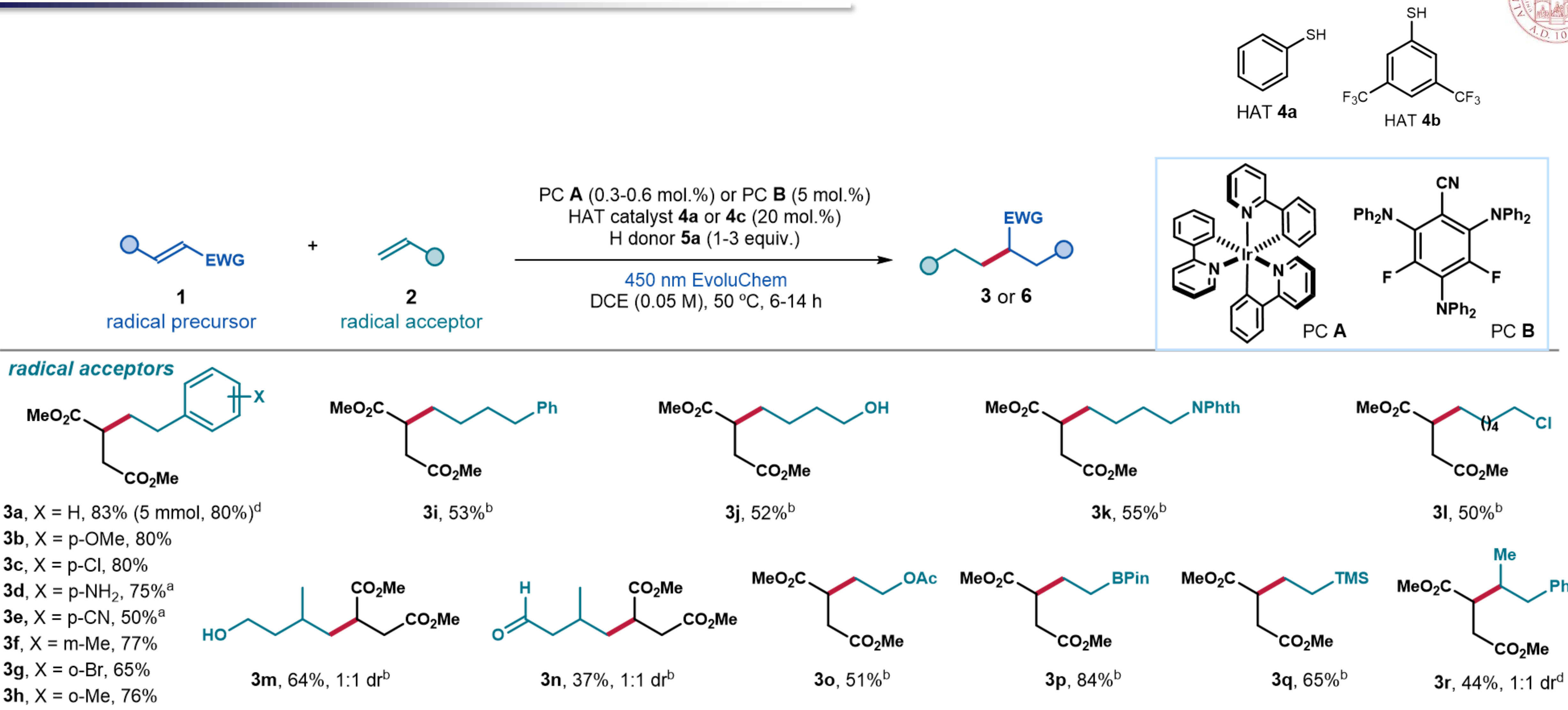
Reductive Cross-Coupling of Olefins

Reductive cross-coupling of olefins with opposite connectivity (*this work*)



with W. Zhuo, I.A. Dmitriev,
J. Am. Chem. Soc. **2023**, *145*, 25098-25102

Reductive Cross-Coupling of Olefins



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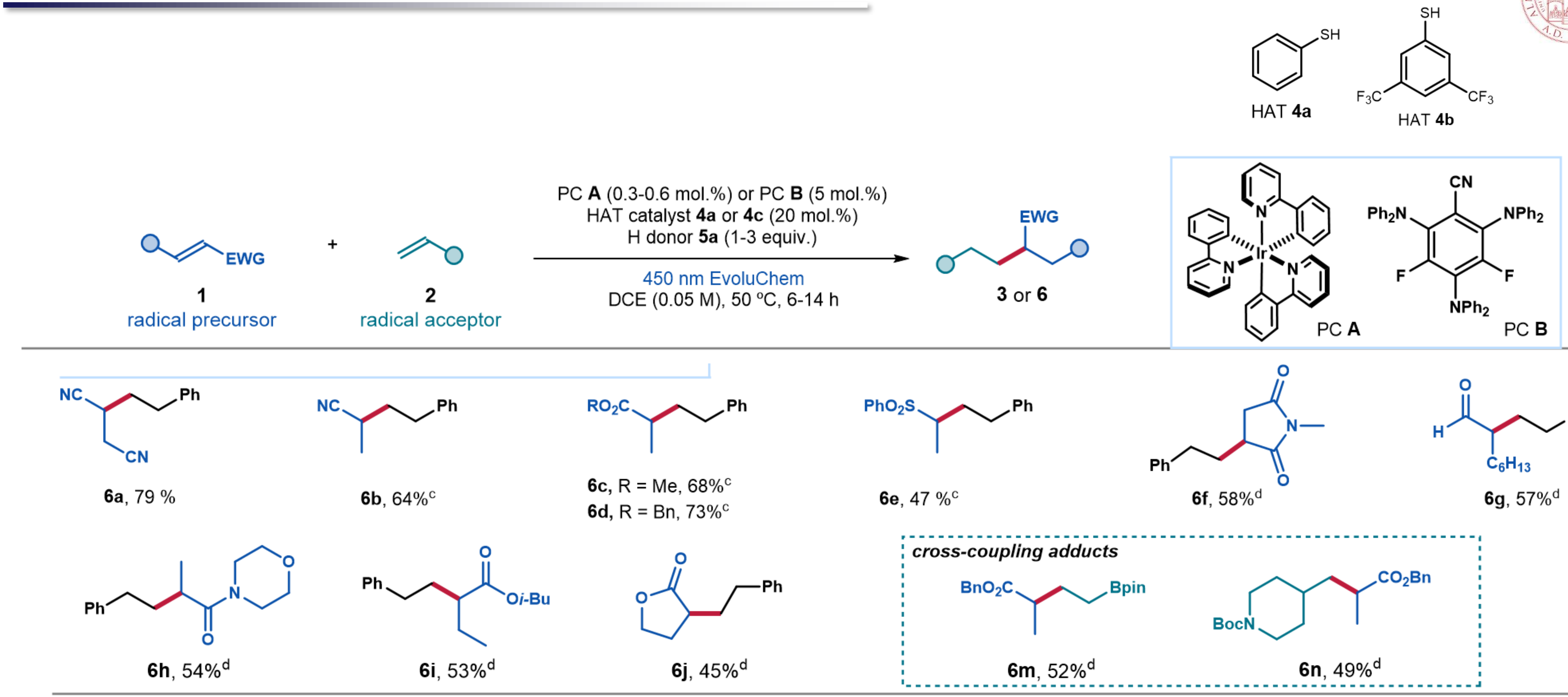
Reductive Cross-Coupling of Olefins



with W. Zhuo, I.A. Dmitriev,
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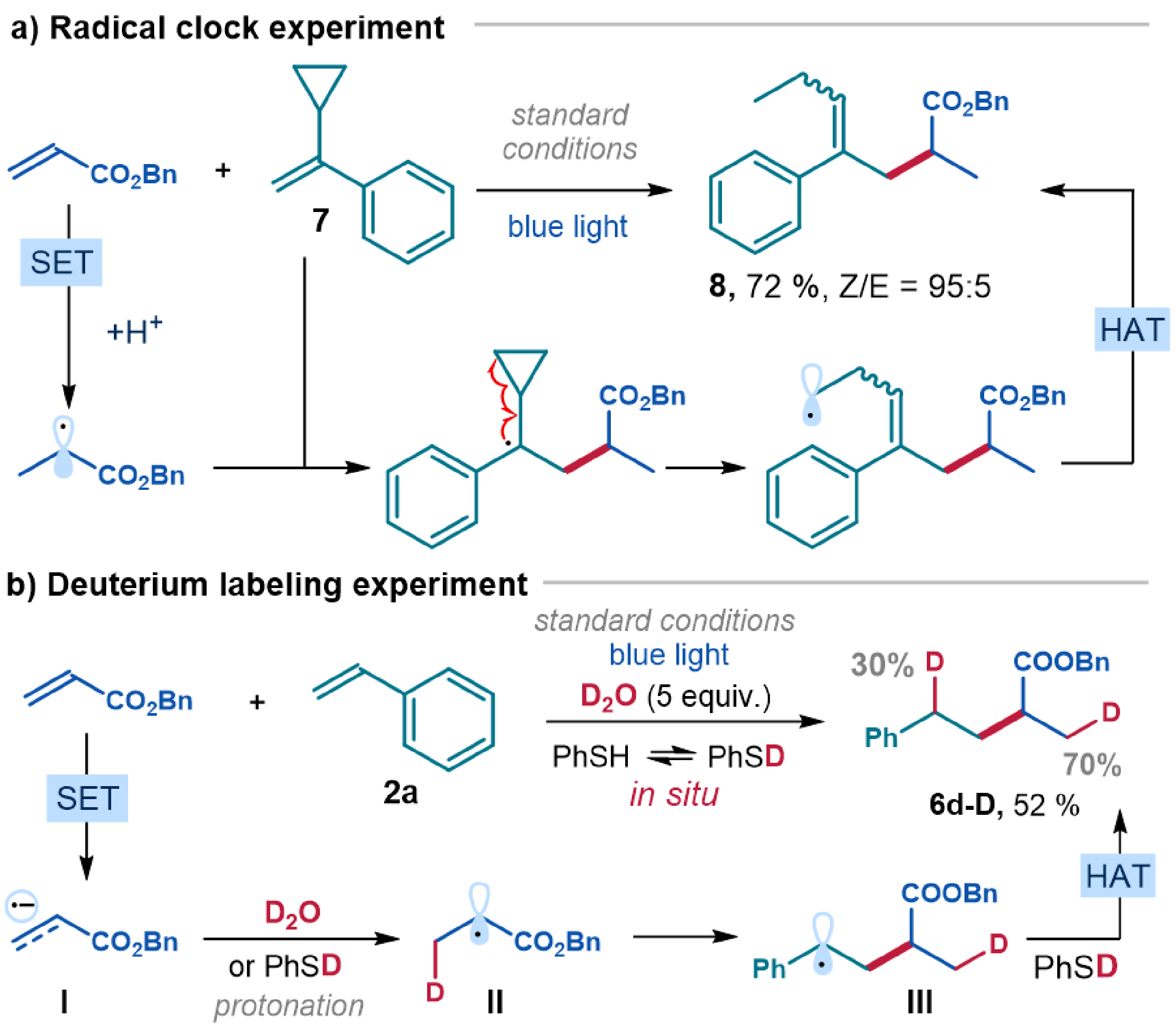
Reductive Cross-Coupling of Olefins



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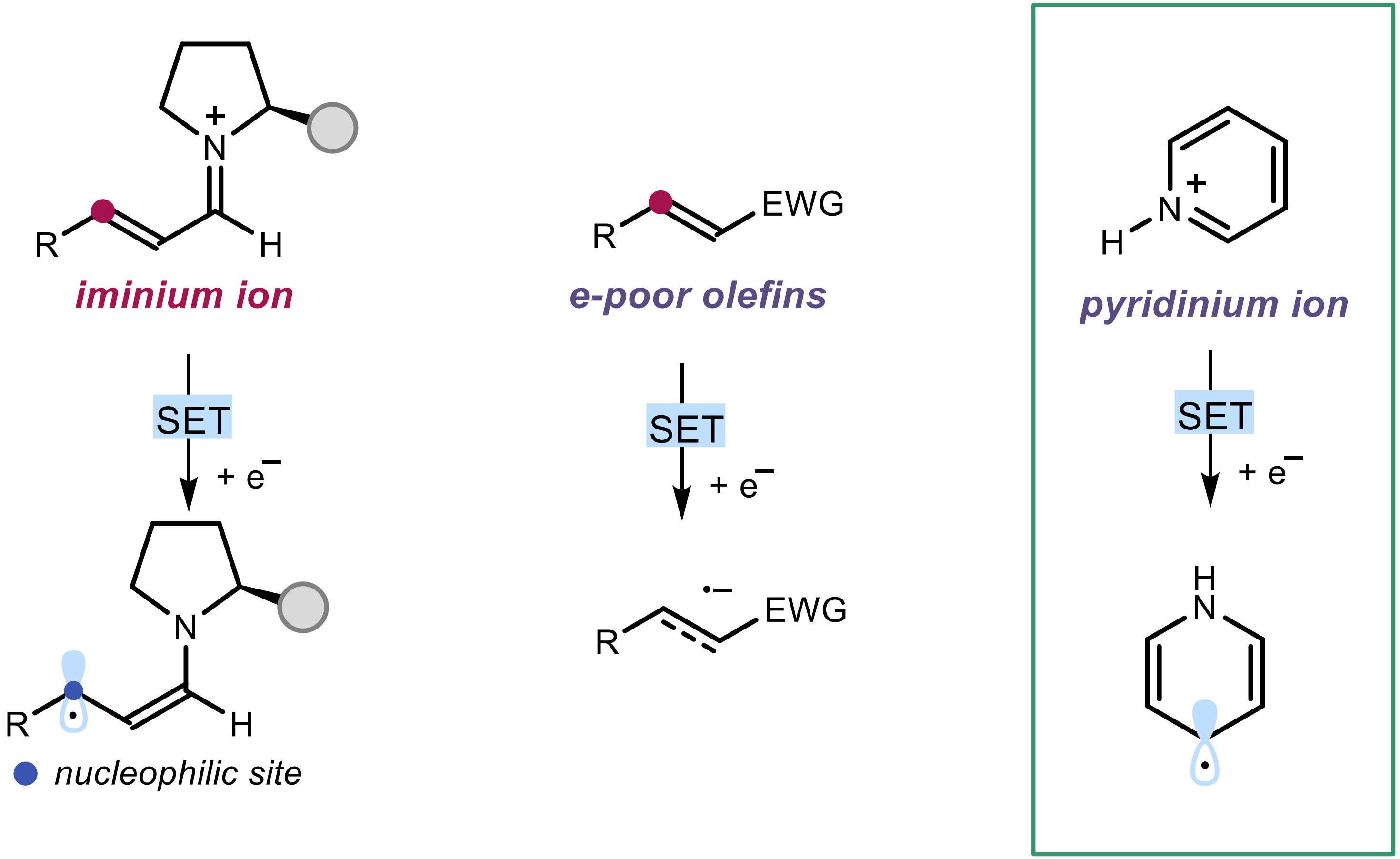
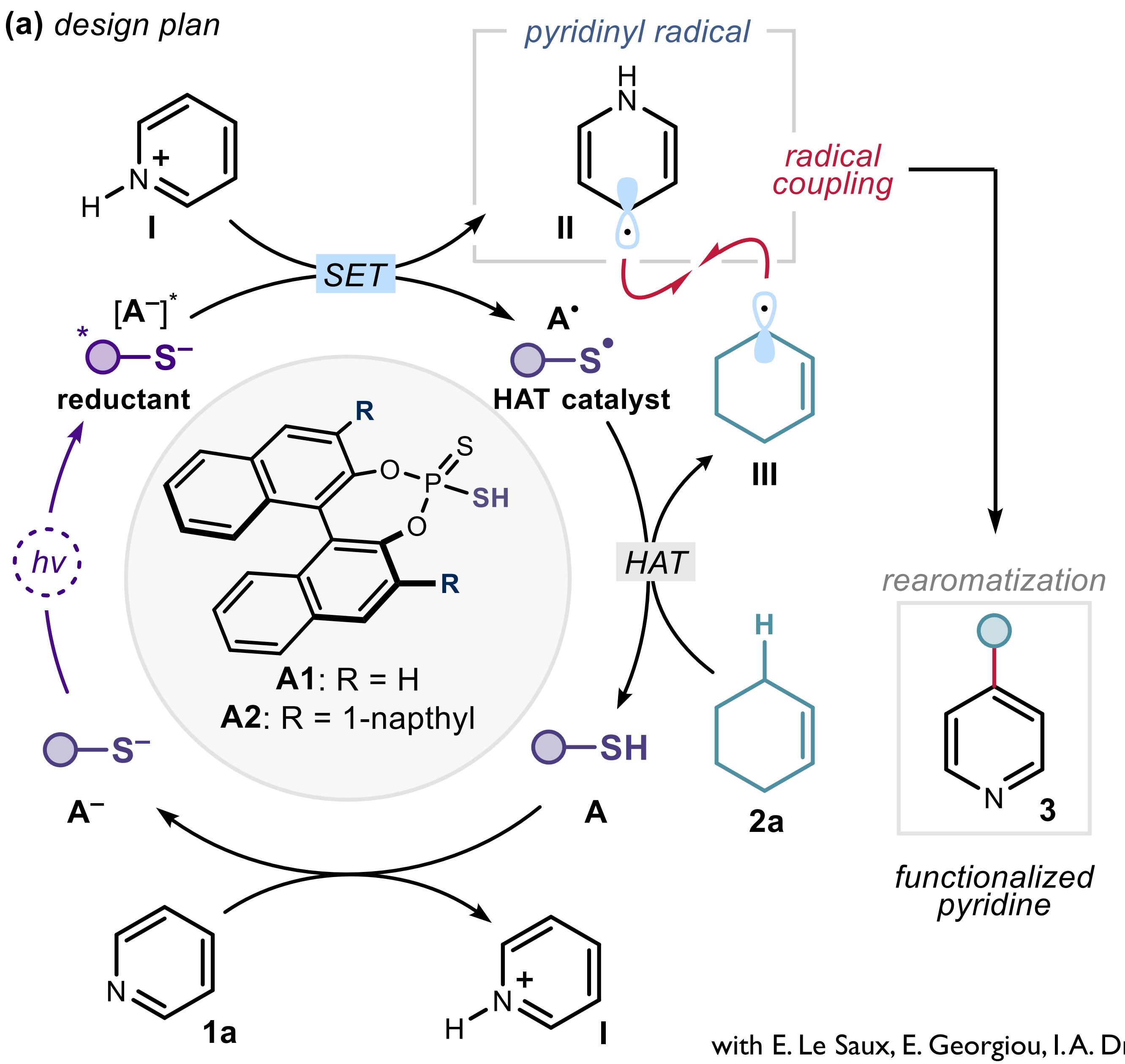
How to further expand the idea of SET activation of electron-poor π-systems



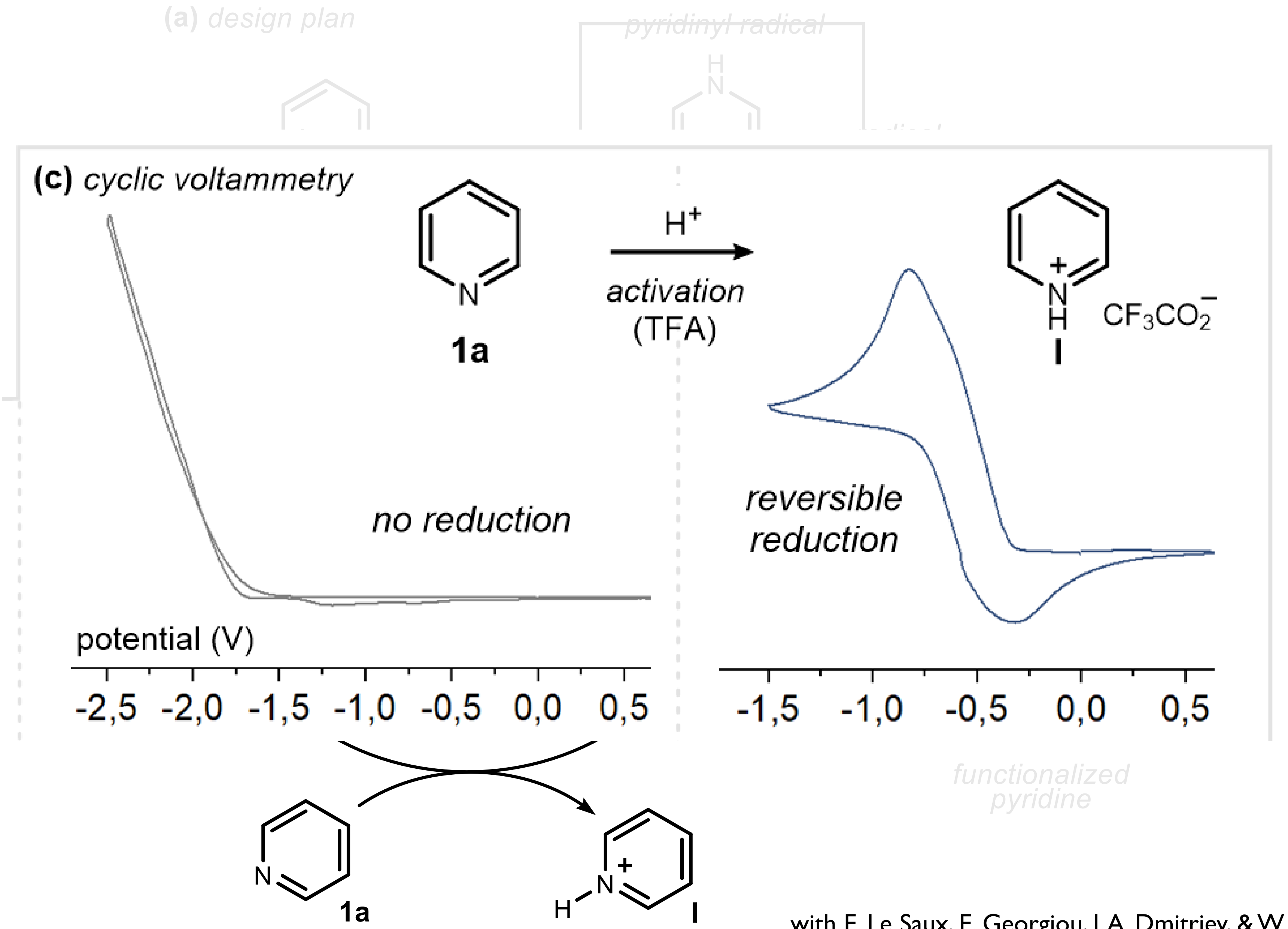
Functionalization of Pyridines via Pyridinyl Radicals



Emilien Le Saux

with E. Le Saux, E. Georgiou, I.A. Dmitriev, & W. C. Hartley, *JACS* **2023**, *145*, 47–52

Functionalization of Pyridines via Pyridinyl Radicals



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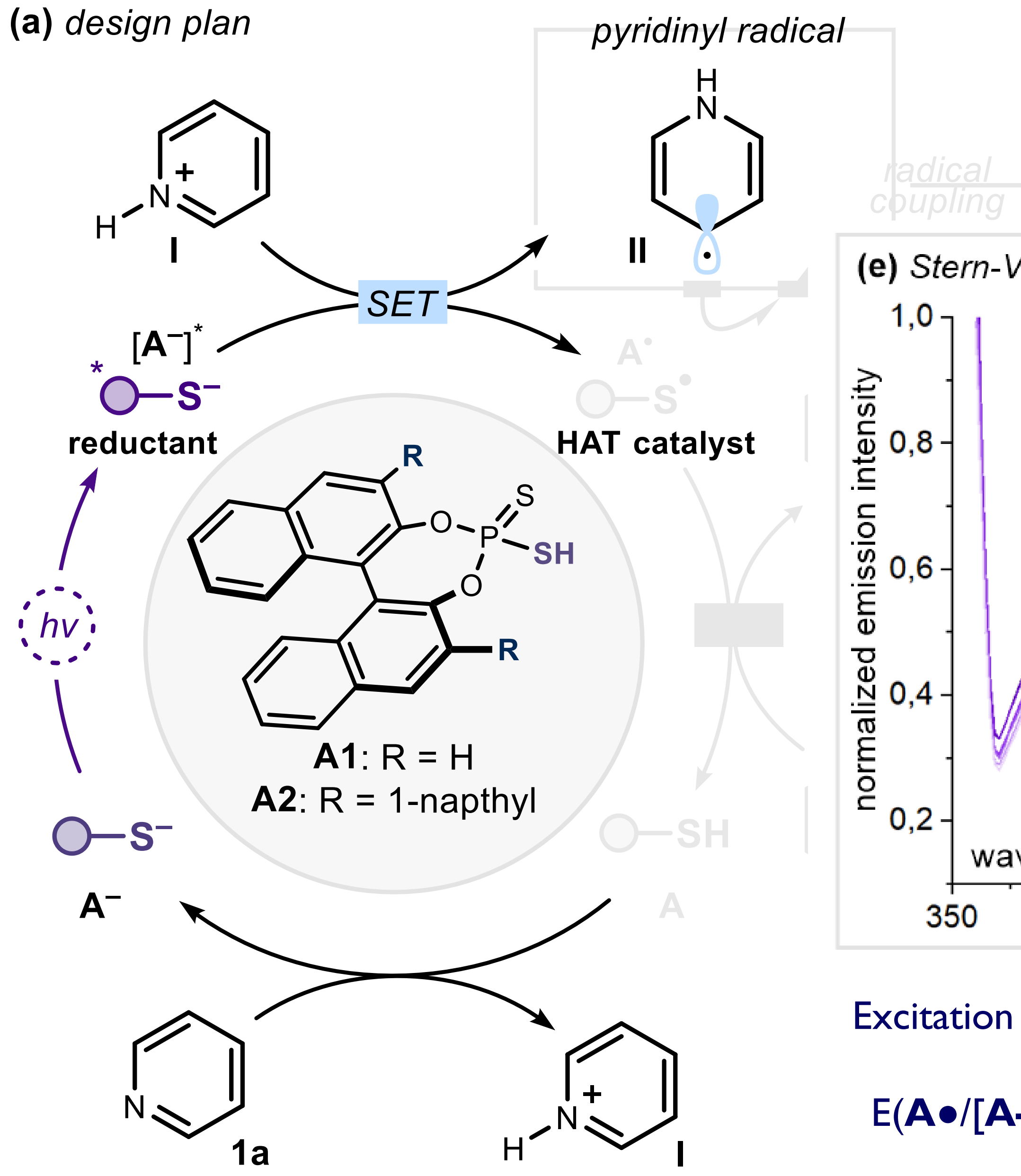
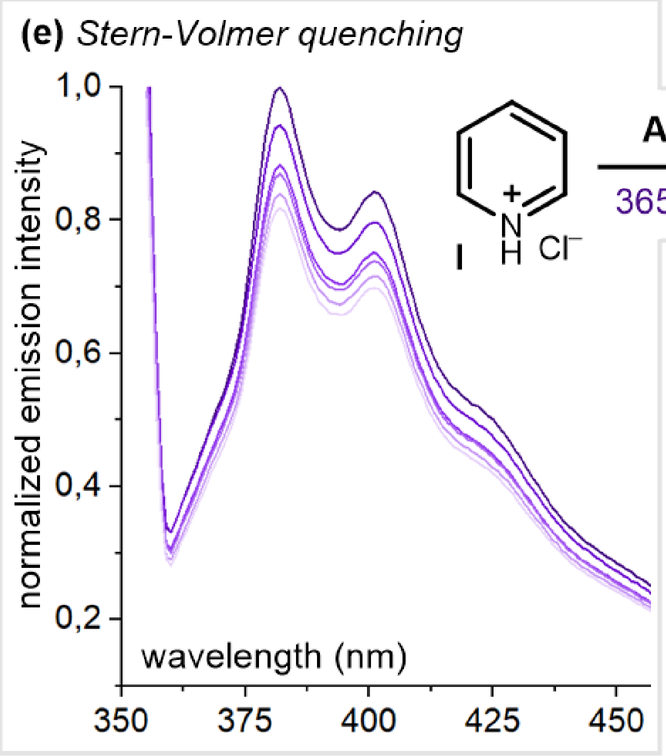
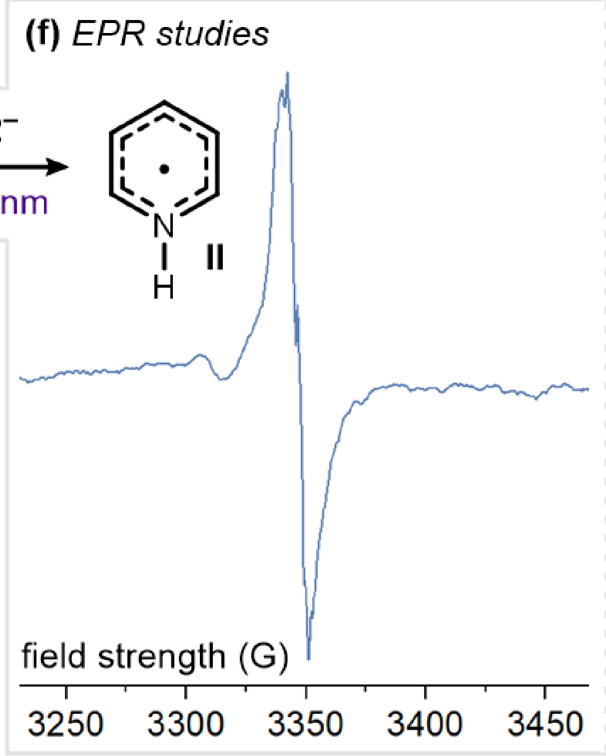




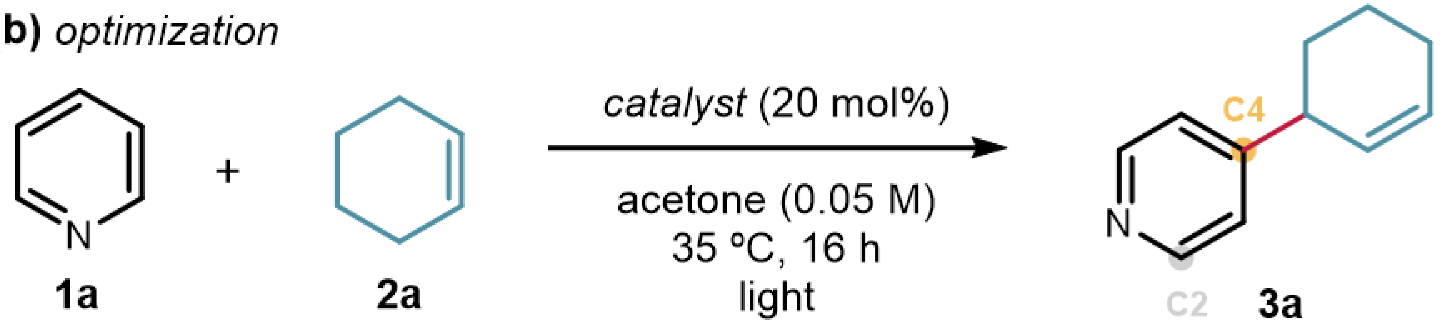


Excitation at 350 nm, Emission at 385 nm

E(**A•**/[**A–**]*)] estimated as **–2.23 V** (vs Ag+/Ag in CH3CN

Functionalization of Pyridines via Pyridinyl Radicals

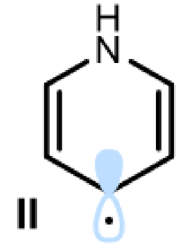
(b) *optimization*



entry	catalyst	light	additive	yield (%)	**3a** (*C4*:*C2*)
1	**A1**	455 nm	-	n.d.	n.d.
2	**A1**	365 nm	-	17	8:1
3	**A1**	365 nm	collidine	41	4:1
4	**A2**	365 nm	collidine	67 (55)	6:1 (> 20:1)
5	**A2**	455 nm	Ir-PC (1 mol%)	79 (65)	4:1 (> 20:1)
6[a]	**A2**	365 nm	collidine	68 (51)	3:1 (> 20:1)
7	-	365 nm	collidine	n.d.	n.d.
8	**A2**	-	collidine	n.d.	n.d.

with E. Le Saux, E. Georgiou, I. A. Dmitriev, & W. C. Hartley, *JACS* **2023**, *145*, 47−52

Functionalization of Pyridines via Pyridinyl Radicals



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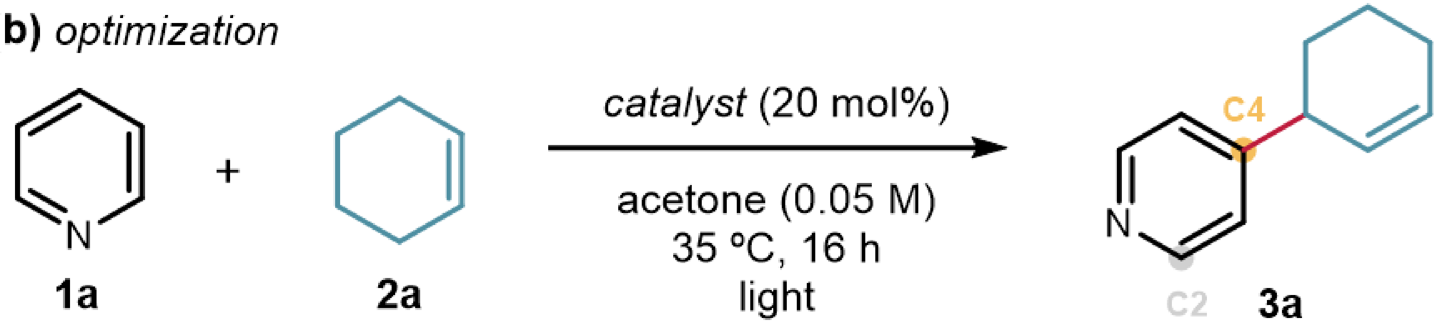

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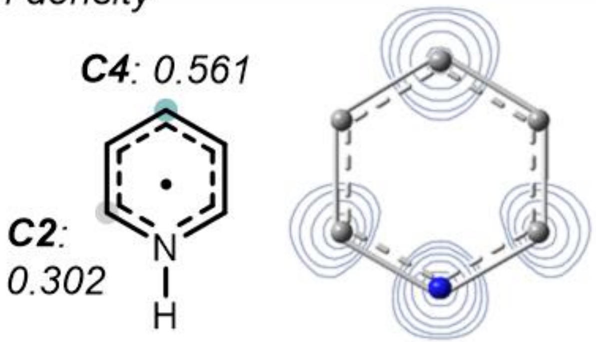
7	-	365 nm	collidine	n.d.	n.d.
8	**A2**	-	collidine	n.d.	n.d.

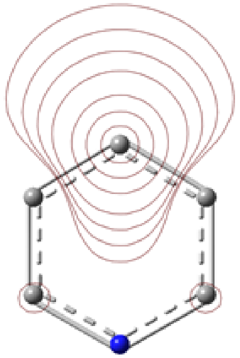
spin density



NBO analysis

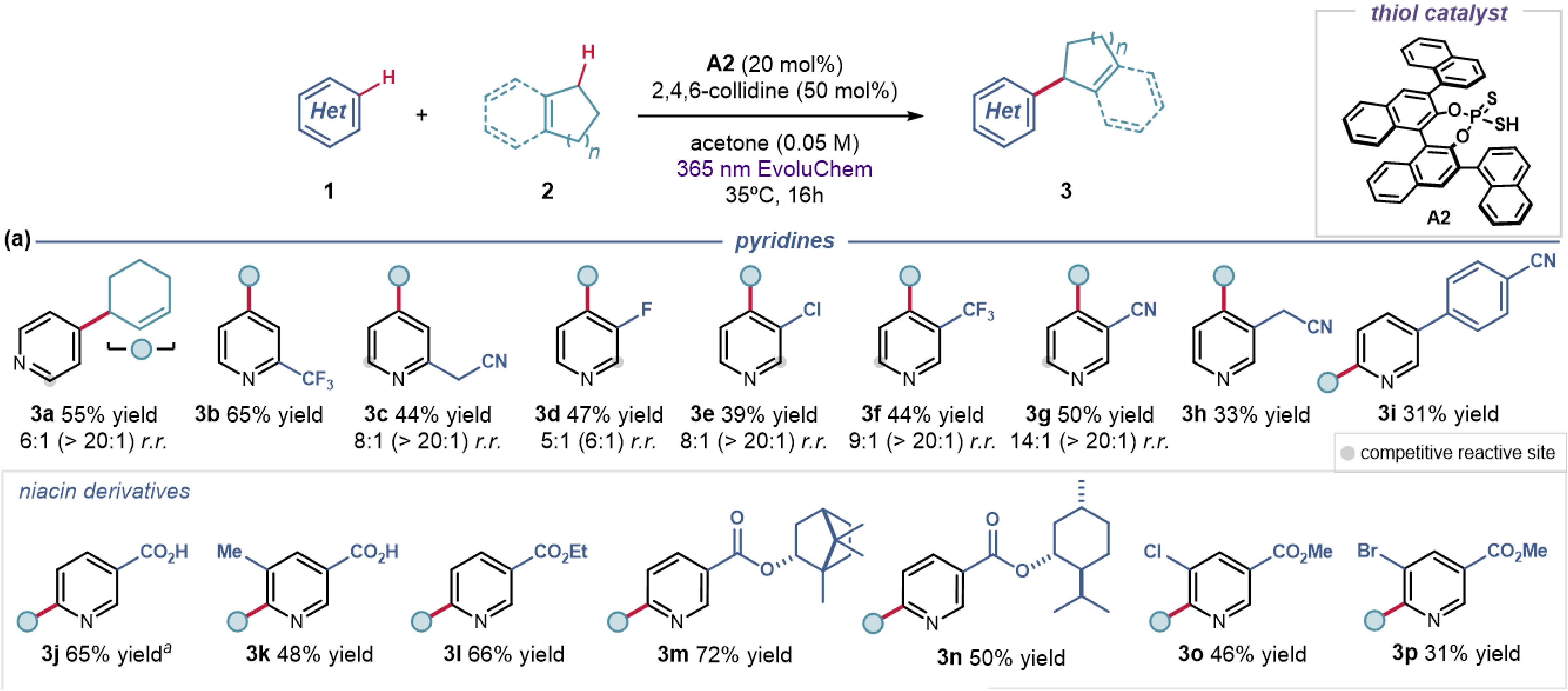
localization of **SOMO**

radical at C4



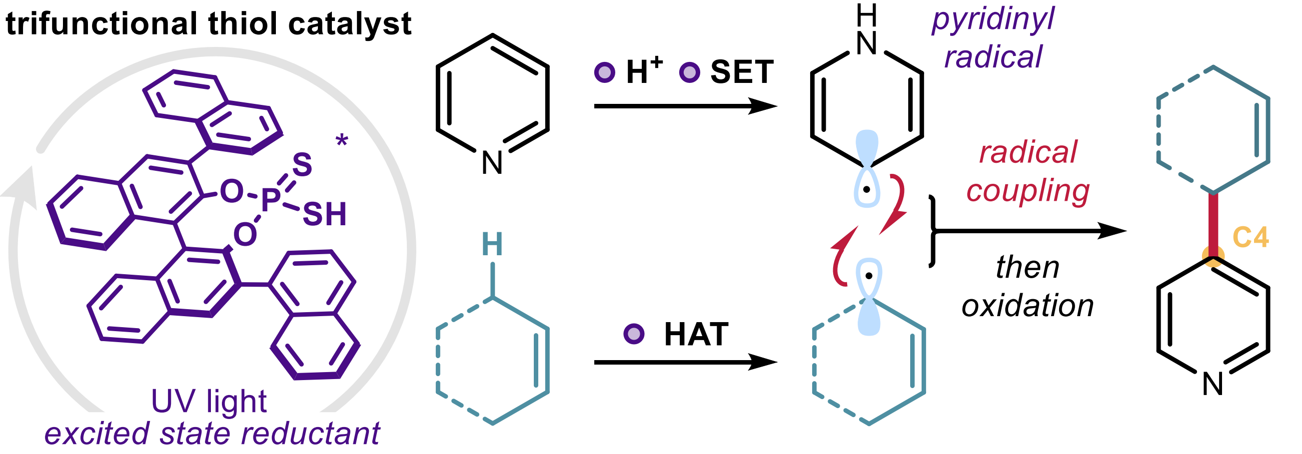
with E. Le Saux, E. Georgiou, I. A. Dmitriev, & W. C. Hartley, *JACS* **2023**, *145*, 47−52

Functionalization of Pyridines via Pyridinyl Radicals



with E. Le Saux, E. Georgiou, I. A. Dmitriev, & W. C. Hartley, *JACS* **2023**, *145*, 47−52

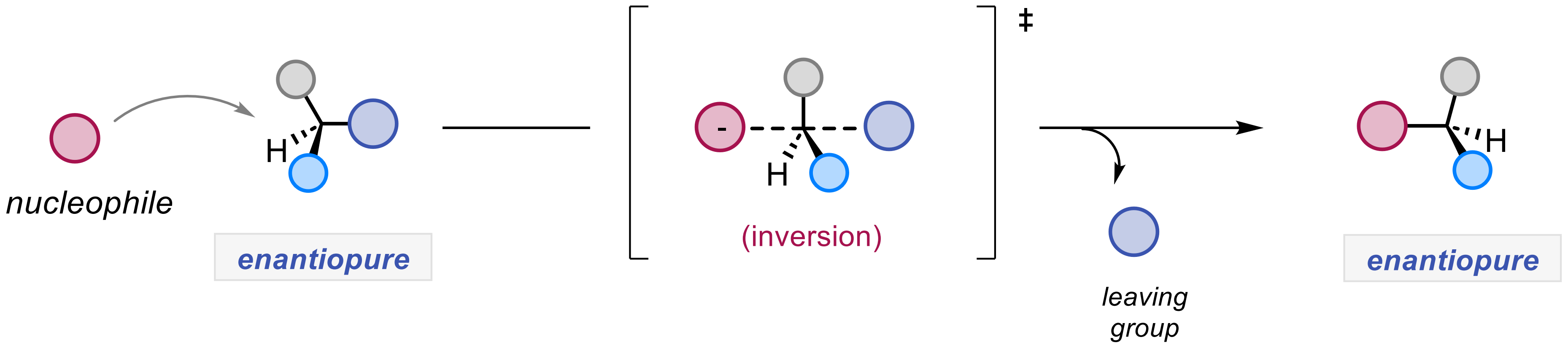
Functionalization of Pyridines via Pyridinyl Radicals



with E. Le Saux, E. Georgiou, I. A. Dmitriev, & W. C. Hartley, *JACS* **2023**, *145*, 47−52

'Classic' approaches: stereospecific reactions

Problem number 2

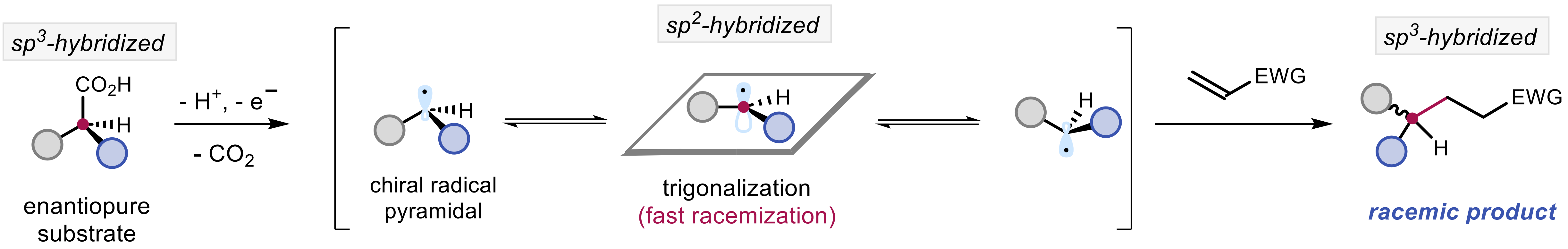


S_N2 *processes*

Transferring the stereochemical information from chiral substrates into the products

But when it comes to radical chemistry…

Problem number 2



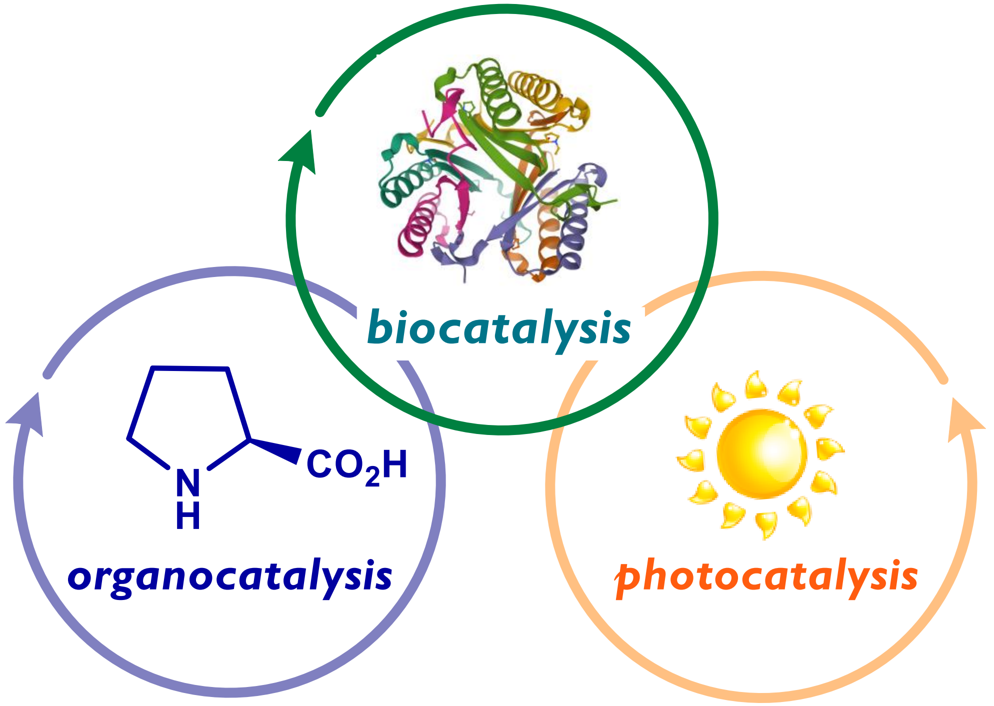
How to transfer stereochemical information when chiral radicals are formed?

But when it comes to radical chemistry…

Problem number 2

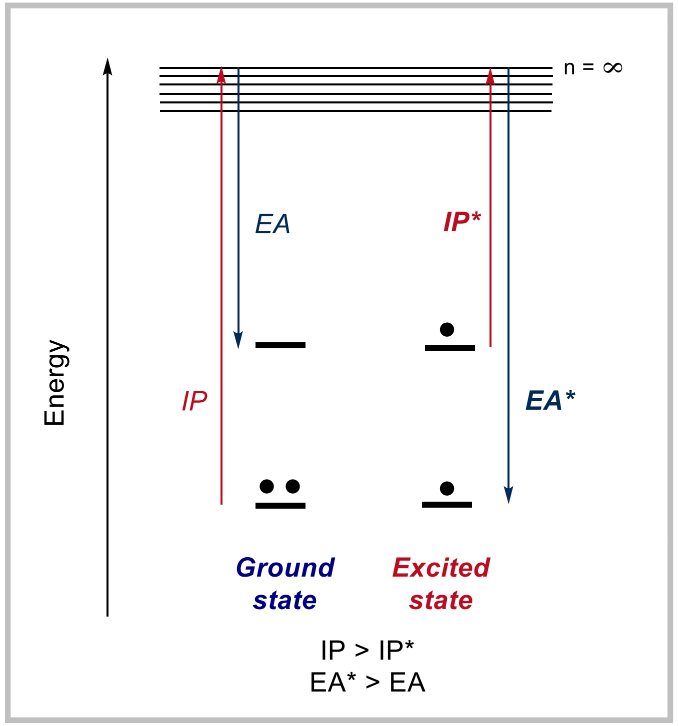
How to transfer stereochemical information when chiral radicals are formed?

Our approach

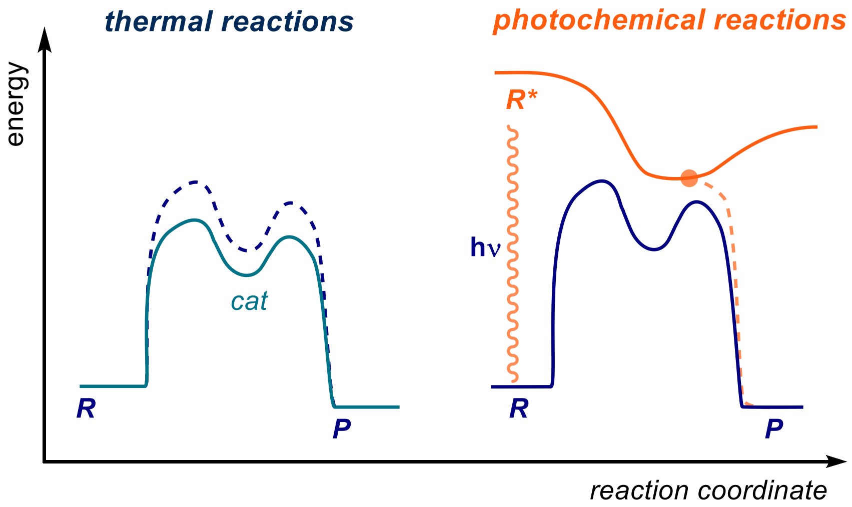


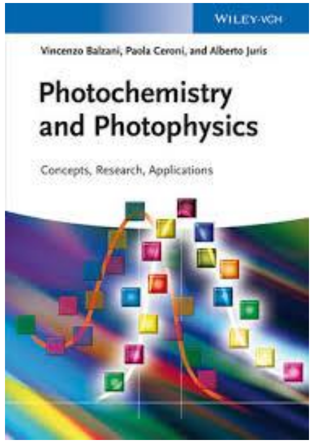
Why Photochemistry and Excited-State Reactivity

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



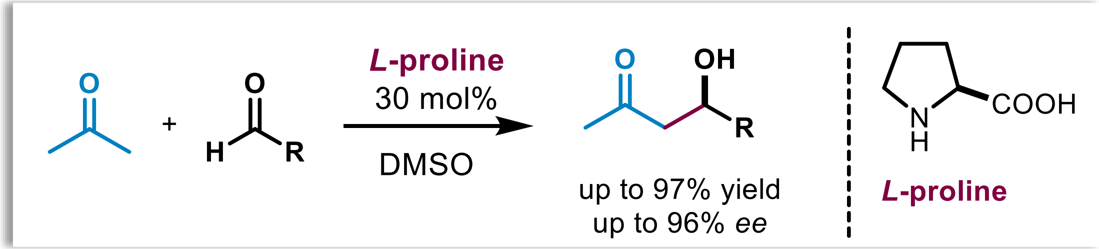
excited-state reactivity unlocks unconventional reaction pathways





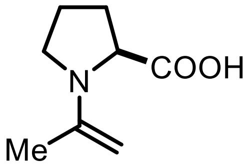
And what about Organocatalysis

- Proline-catalyzed intermolecular aldol reaction



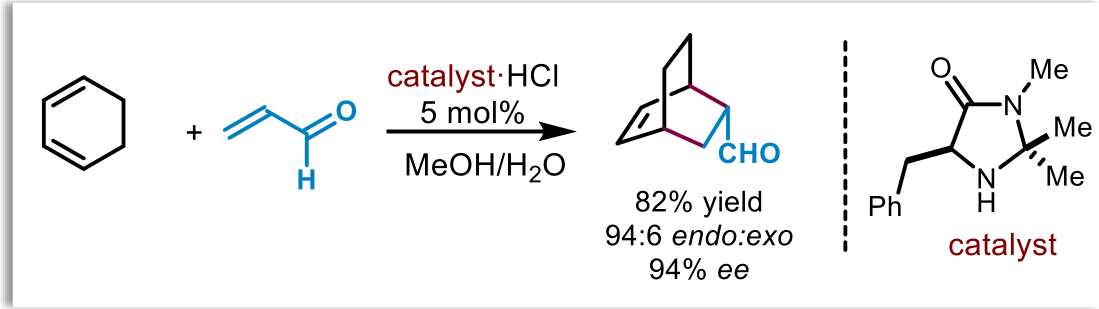
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Enamine Catalysis



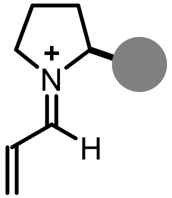
HOMO-Raising Activation

- Iminium ion catalyzed asymmetric Diels-Alder of enals



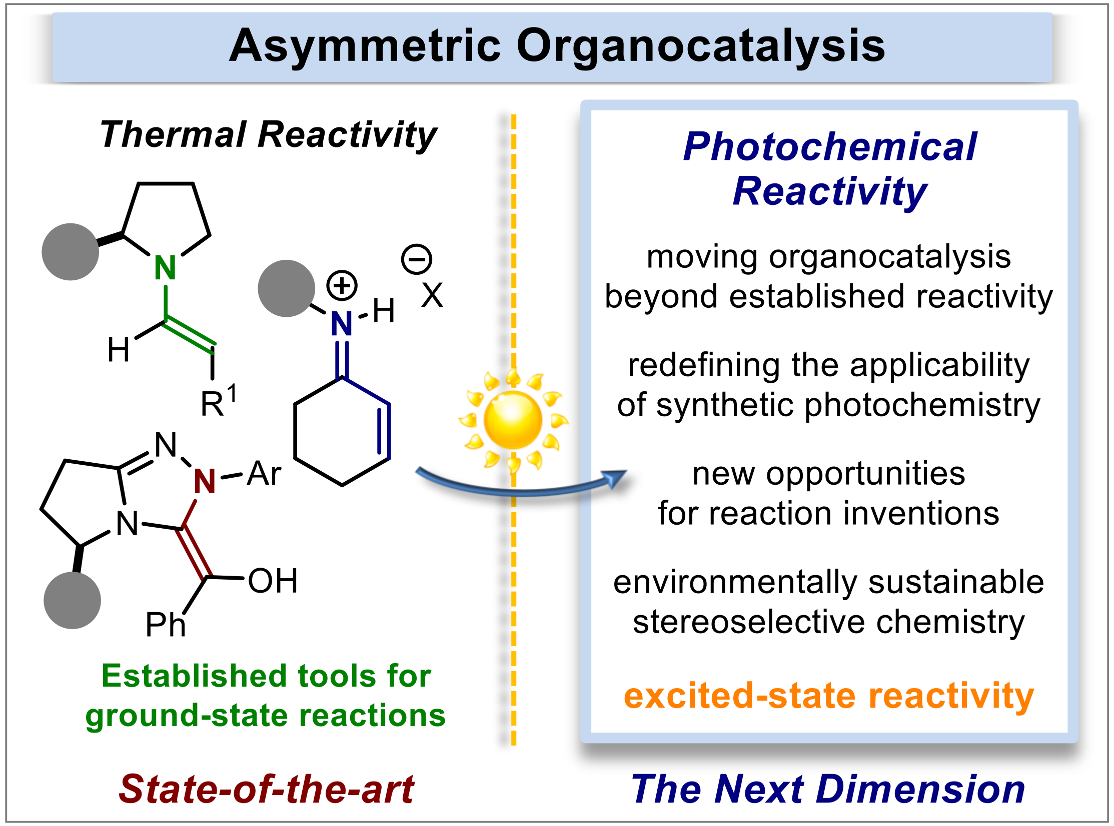
K. A. Ahrendt, C. J. Borths, **D. W. C. MacMillan**, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

Iminium-Ion Catalysis



LUMO-Lowering Activation

Expanding the Potential of Organocatalysis with Light



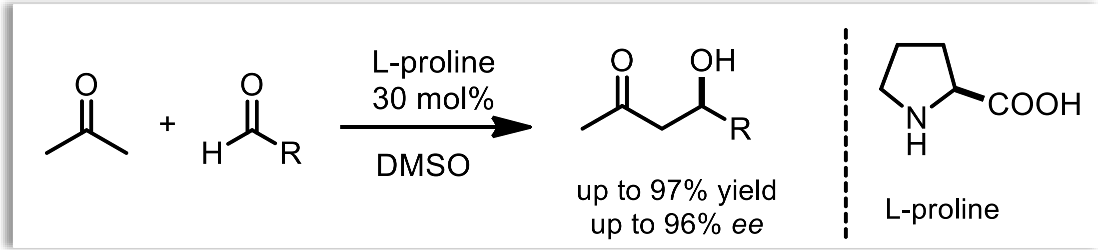
Review

Mattia Silvi & Paolo Melchiorre, "Enhancing the potential of enantioselective organocatalysis with light" *Nature* **554**, 41–49 (2018)

'Following the light of the sun, we left the Old World'
Cristoforo Colombo

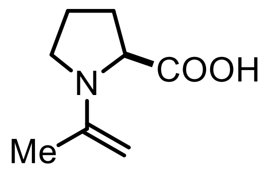
Enamines in the Ground State

- Proline-catalyzed intermolecular aldol reaction



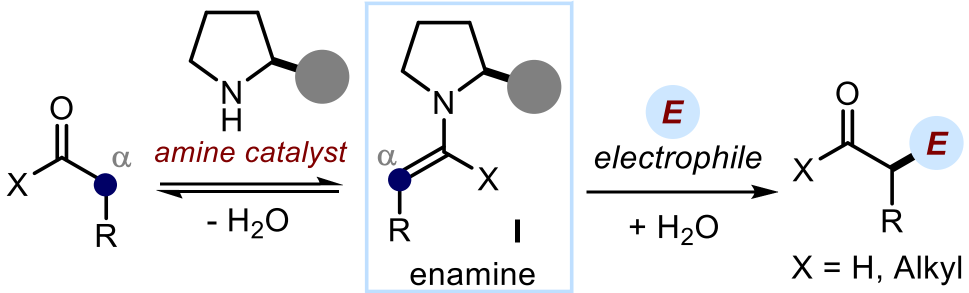
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396

Enamine Catalysis



HOMO-Raising Activation

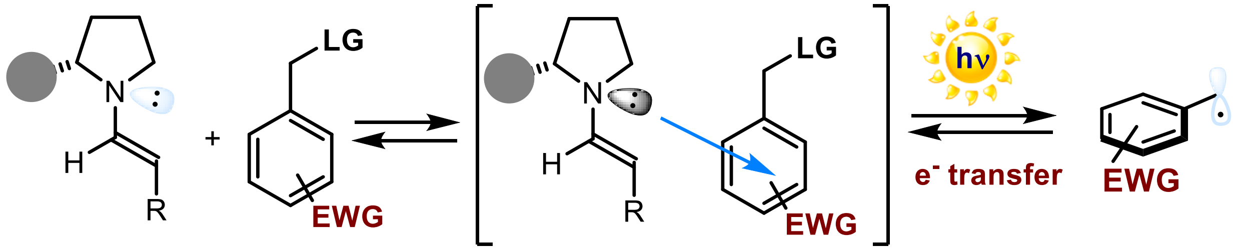
enamine-mediated catalysis



Nucleophilicity of enamines: Gilbert Stork, et al. *J. Am. Chem. Soc.* **1963**, *85*, 207−222

Electron Donor-Acceptor (EDA) Complex

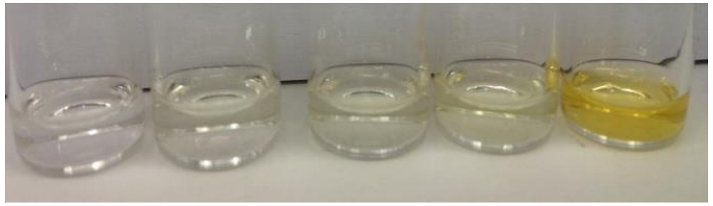
Enamines as Donors in Photo-Active EDA-Complexes in the Ground State

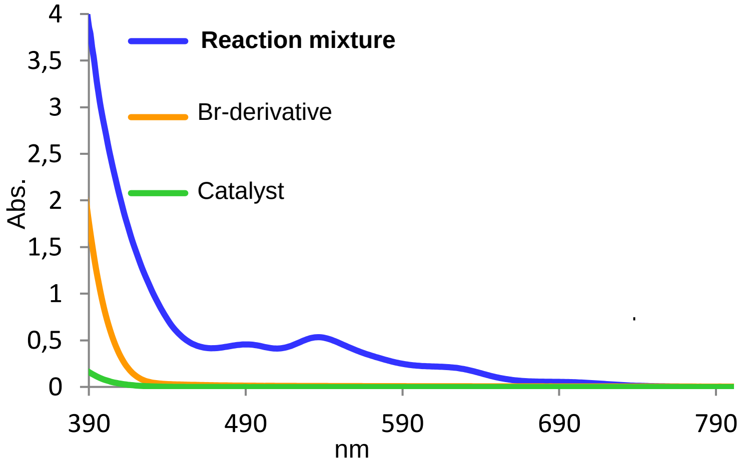


Coloured EDA complex in the ***Ground State***

Nature Chemistry, **2013**, *5*, 750-756
Chem. Science **2014**, *5*, 2438-2442
J. Am. Chem. Soc. **2016**, *138*, 8019-8030

visual observation

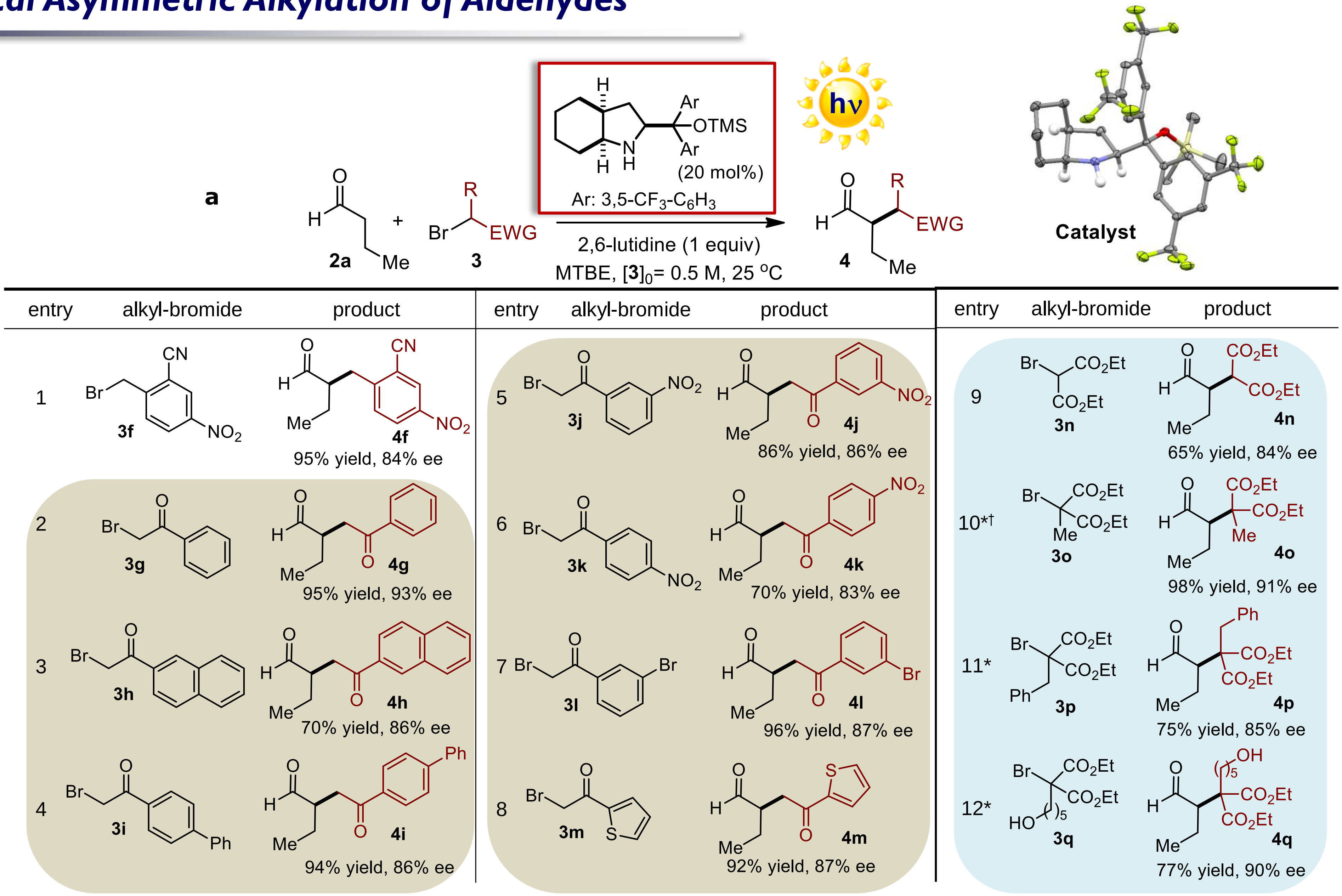




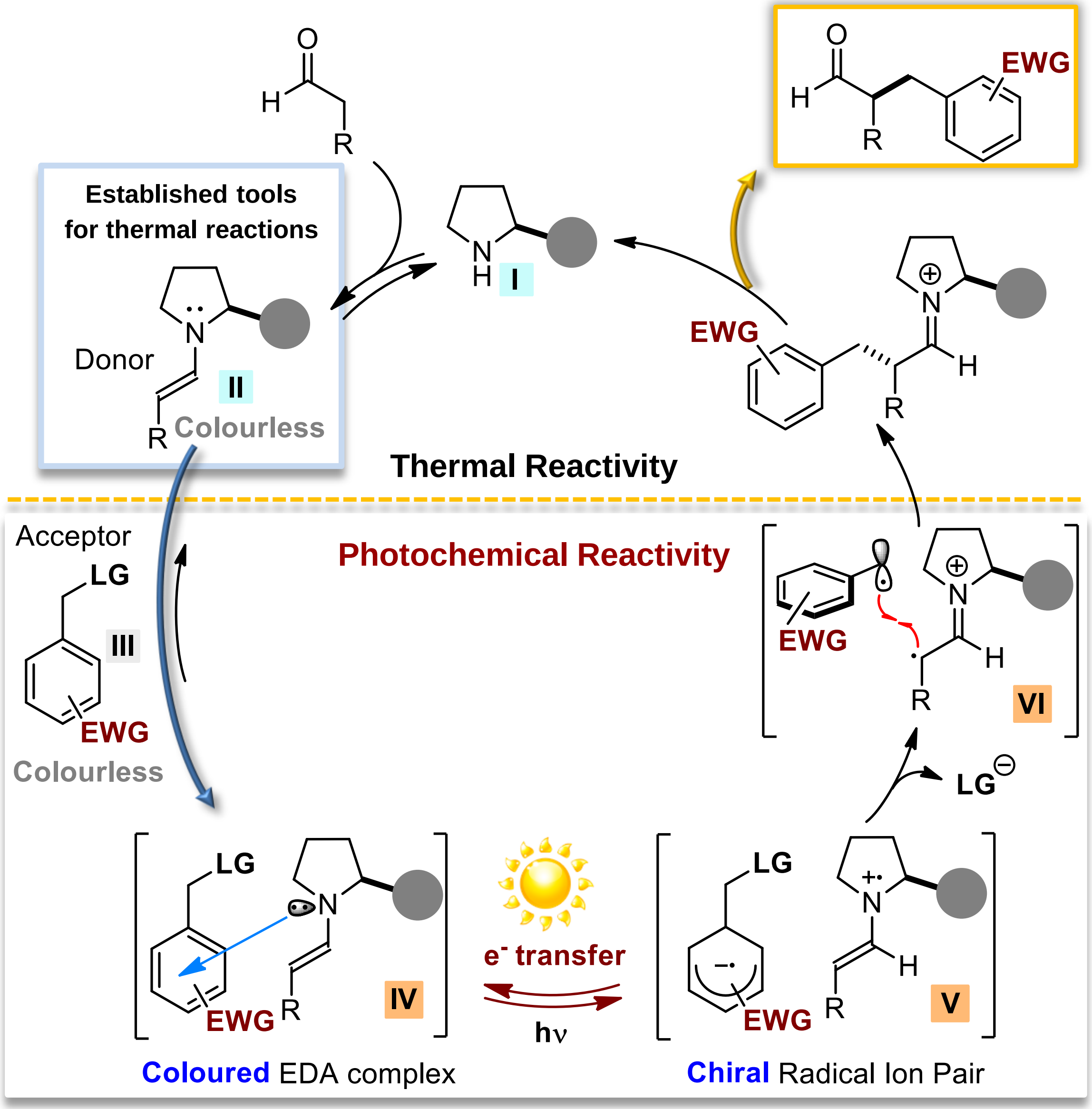
EDA complexes and Charge Transfer theory
R. S. Mulliken, *J. Phys. Chem.* **1952**, *56*, 801

R. S. Mulliken

Photochemical Asymmetric Alkylation of Aldehydes



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

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Perspective

Synthetic Methods Driven by the Photoactivity of Electron Donor–Acceptor Complexes

Giacomo E. M. Crisenza,# Daniele Mazzarella,# and Paolo Melchiorre*

Cite This: *J. Am. Chem. Soc.* 2020, 142, 5461−5476

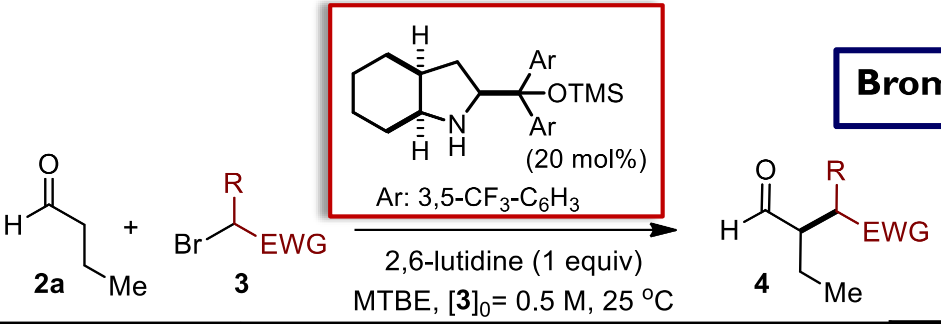
Read Online

Review on EDA complex photochemistry

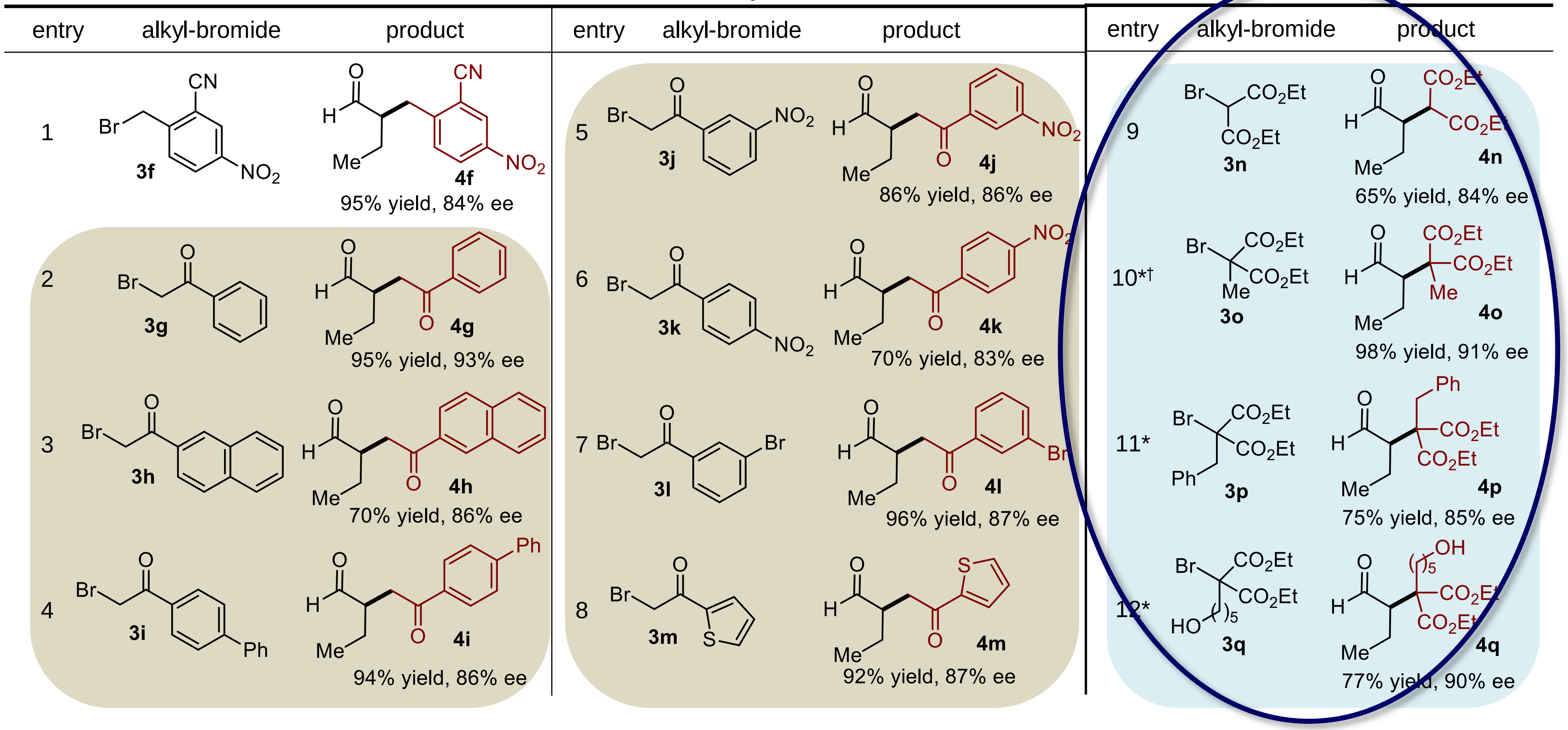
G. Crisenza, D. Mazzarella, P. Melchiorre, *JACS* **2020,** *142*, 5461

The growing field of EDA-complex-mediated synthetic photochemistry:
Aggarwal, Chatani, Glorius, Hyster, Molander, König, Lakhdar, Leonori, Miyake…

the Bromomalonate Conundrum

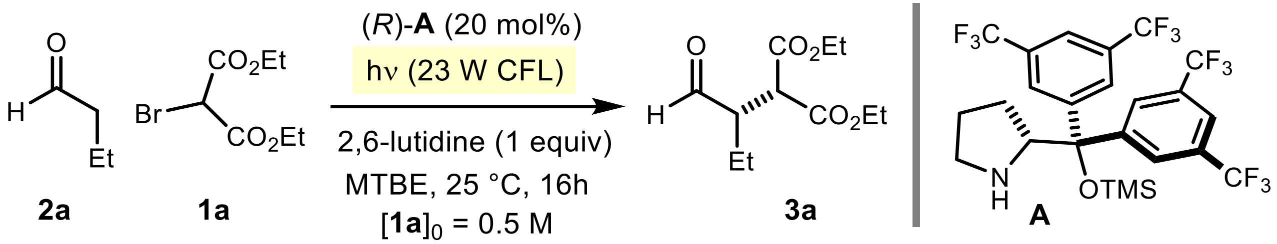


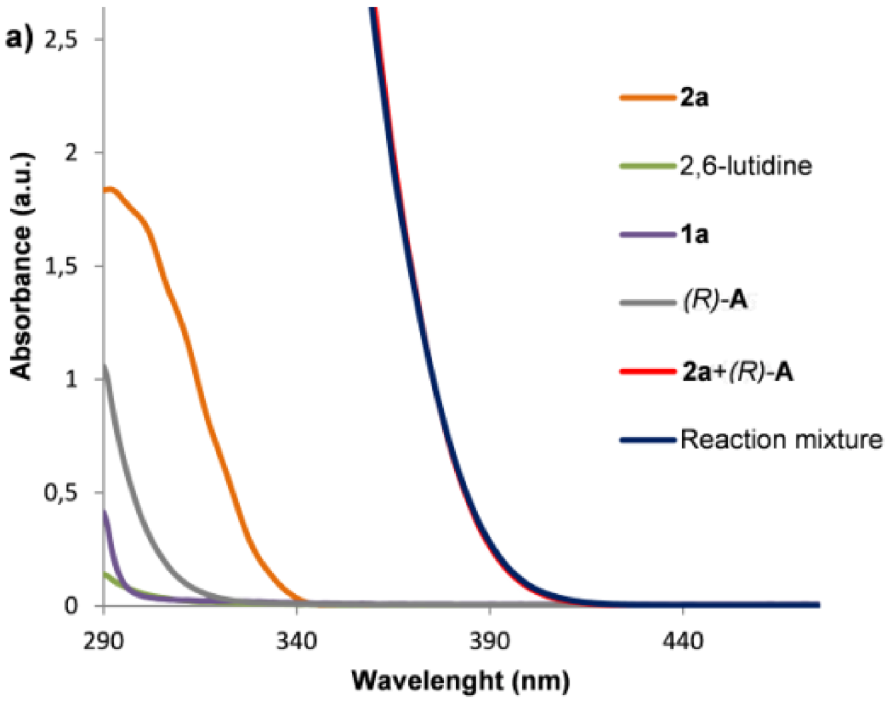
Bromo malonates work! how??



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

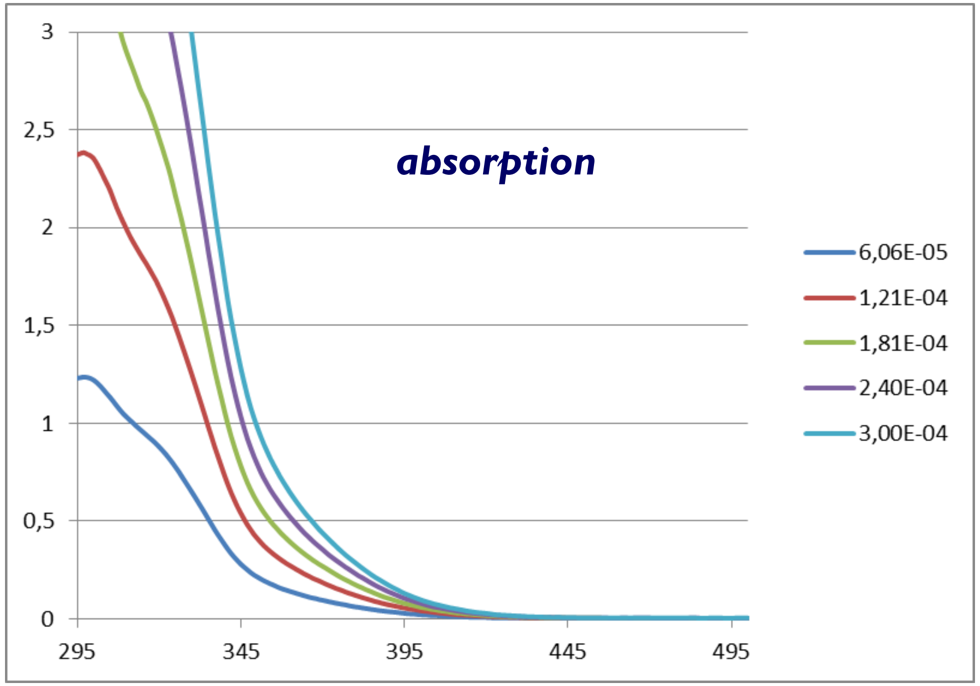
Asymmetric Photochemical Alkylation



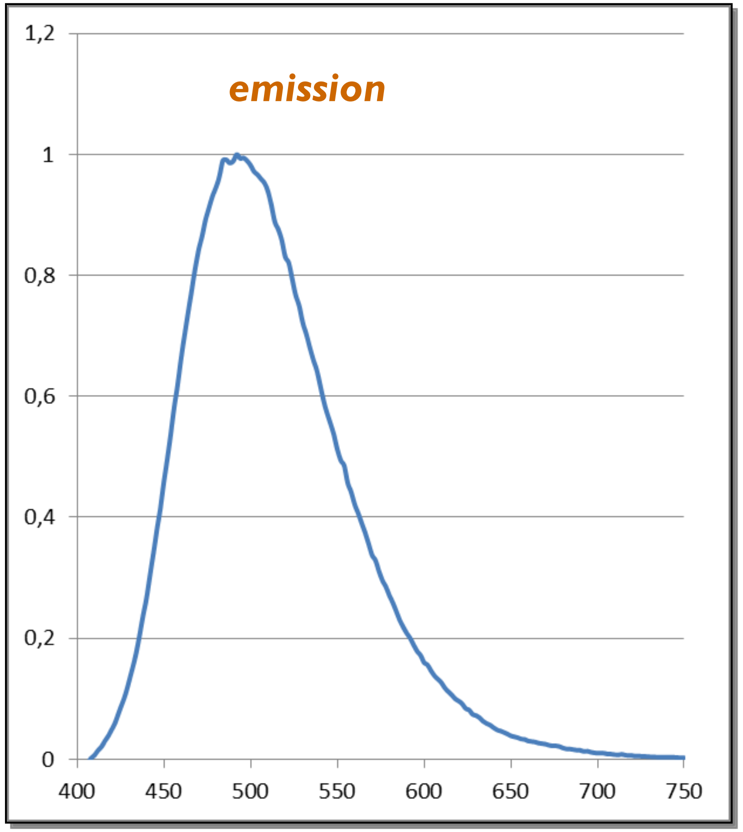


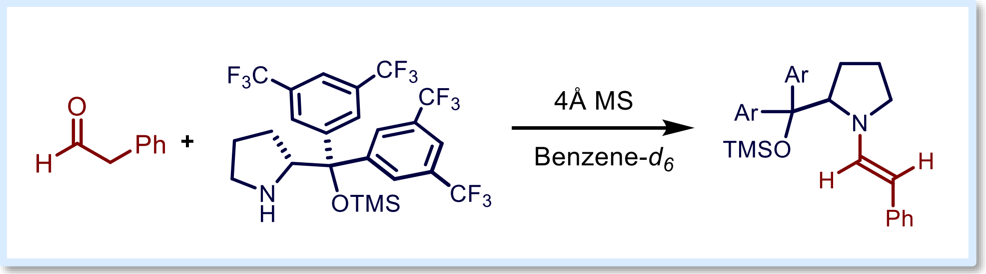
the enamine weakly absorbs visible light

Direct Excitation of Enamines

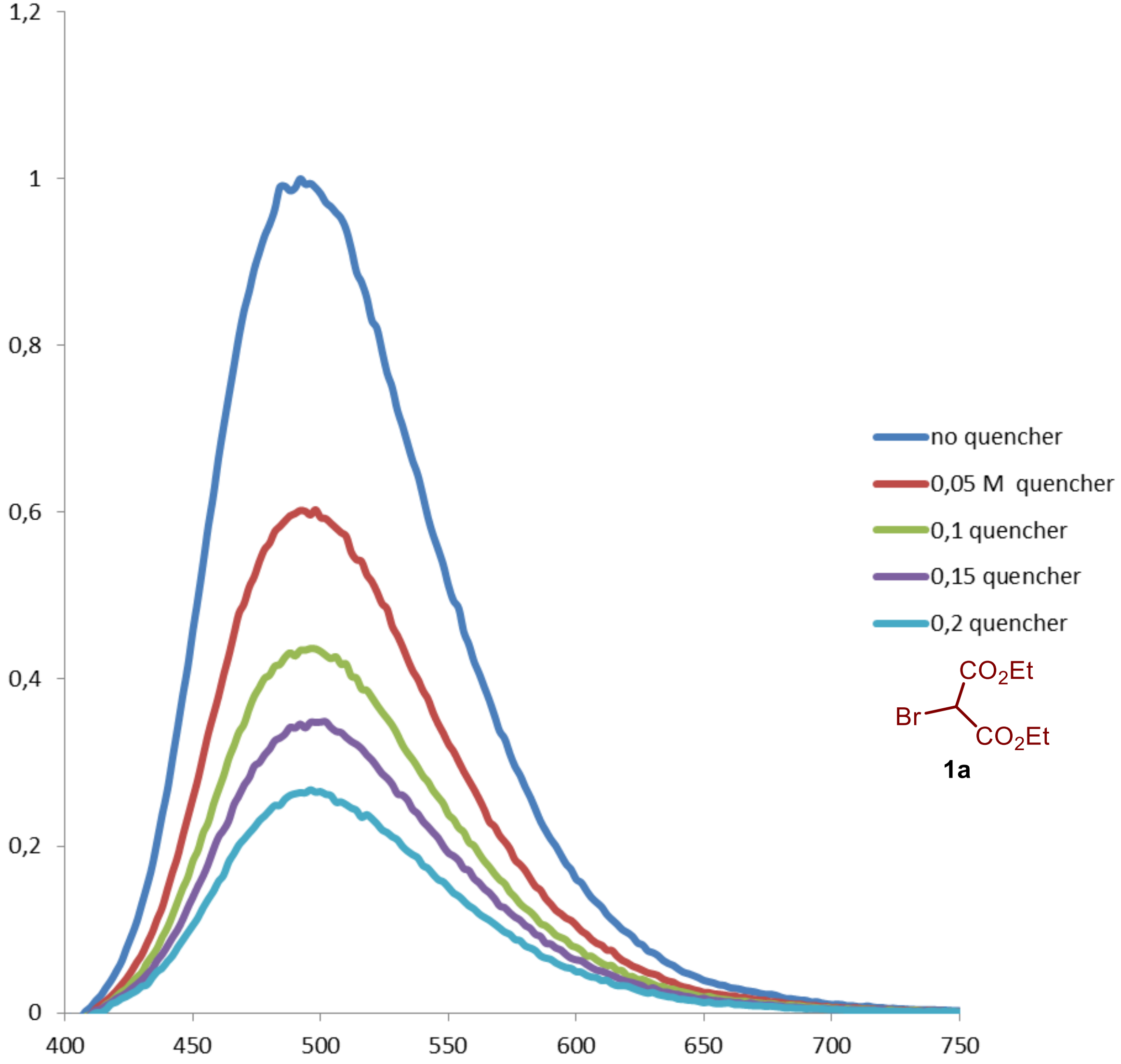


Mattia Silvi



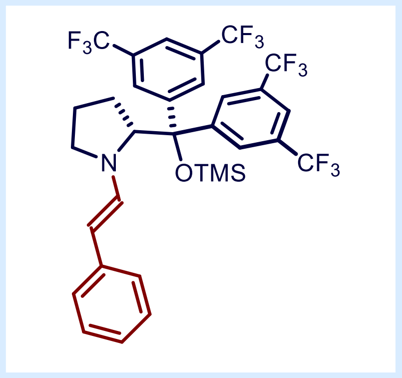


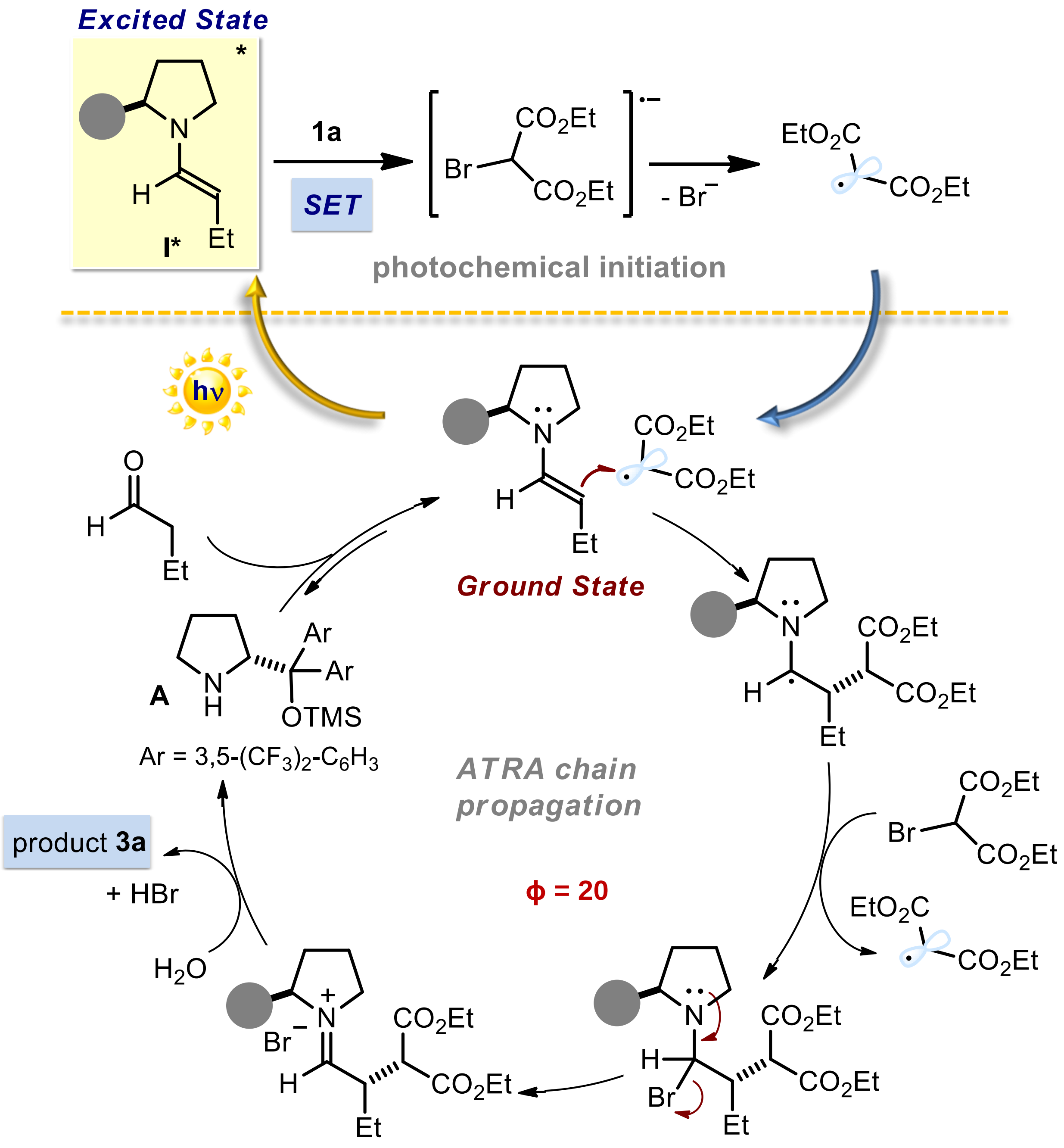
Direct Excitation of Enamines



Stern−Volmer quenching studies

Mattia Silvi

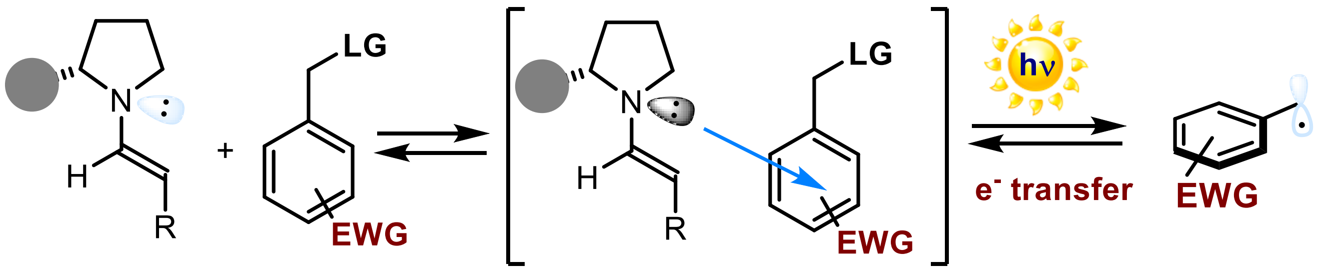




with M. Silvi, E. Arceo, I. Jurberg, C. Cassani
J. Am. Chem. Soc. **2015**, *137*, 6120-6123

Excited-state reactivity of chiral enamines

Enamines as Donors in Photo-Active EDA-Complexes in the Ground State



Coloured EDA complex in the ***Ground State***

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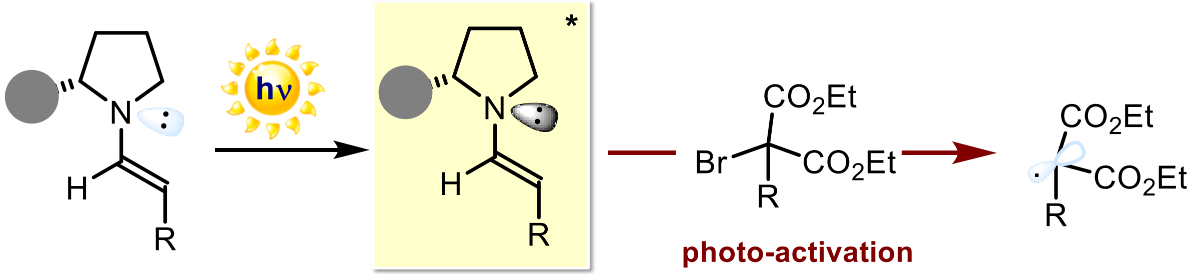
Chem. Sci. **2014**, *5*, 2438-2442
J. Am. Chem. Soc. **2016**, *138*, 8019-8030

Photochemistry of Enamines in the Excited State

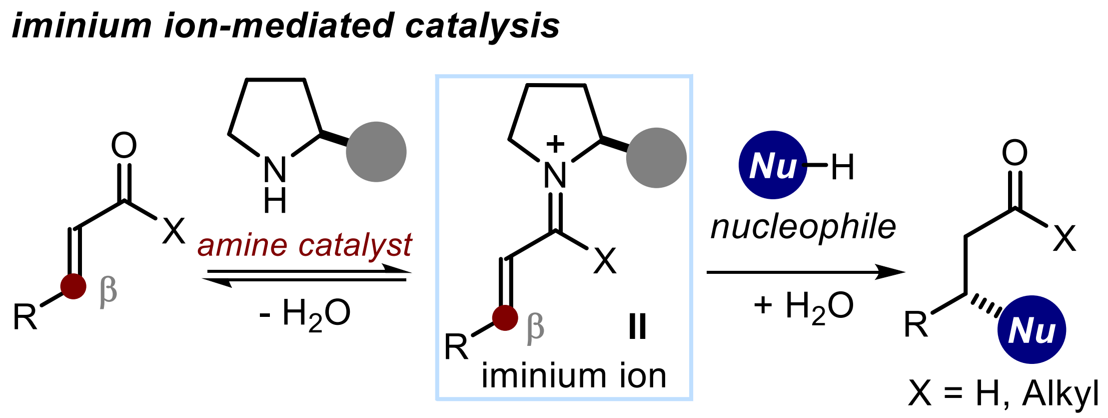


Excited State

J. Am. Chem. Soc. **2015**, *137*, 6120
Angew. Chem. Int. Ed. **2017**, *56*, 4447-4451

Review
Mattia Silvi & Paolo Melchiorre, "Enhancing the potential of enantioselective organocatalysis with light" *Nature* **554**, 41–49 (2018)

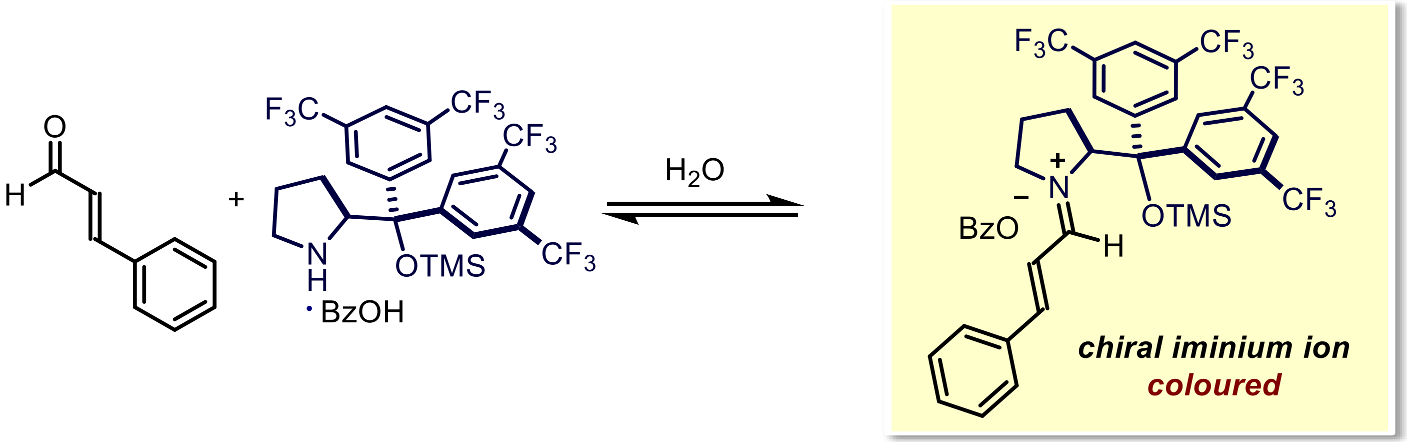
Iminium Ions in the Ground State

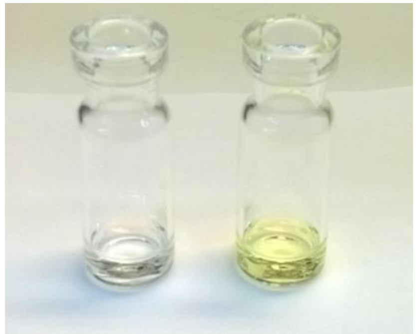


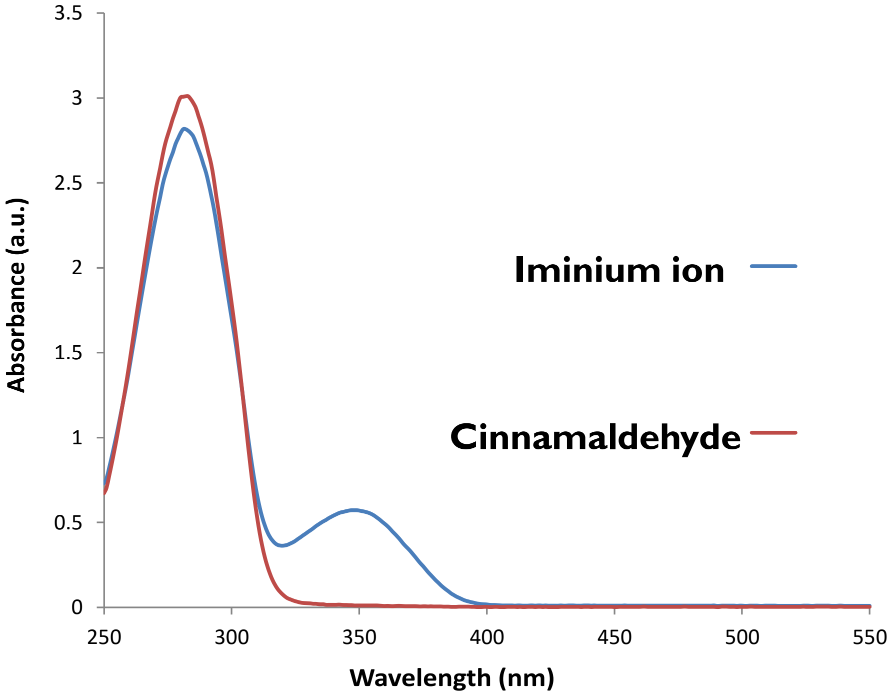
Asymmetric iminium ion-mediated catalysis:

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

the Photochemistry of Iminium Ions



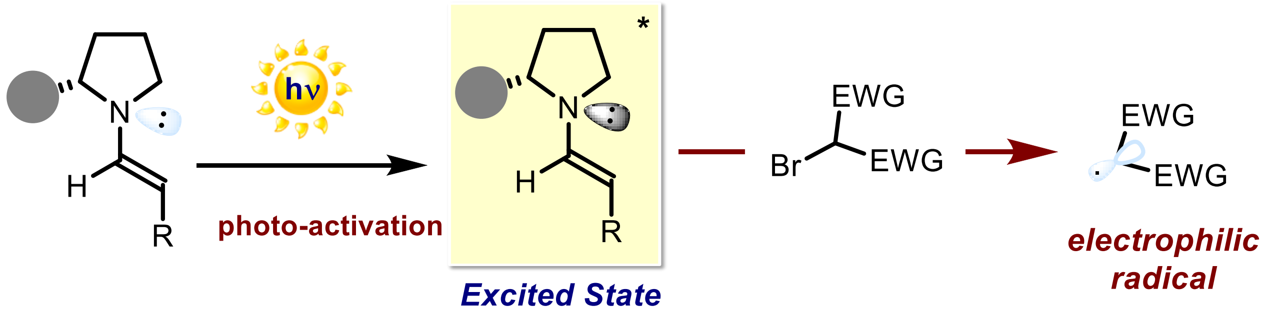




the Question…

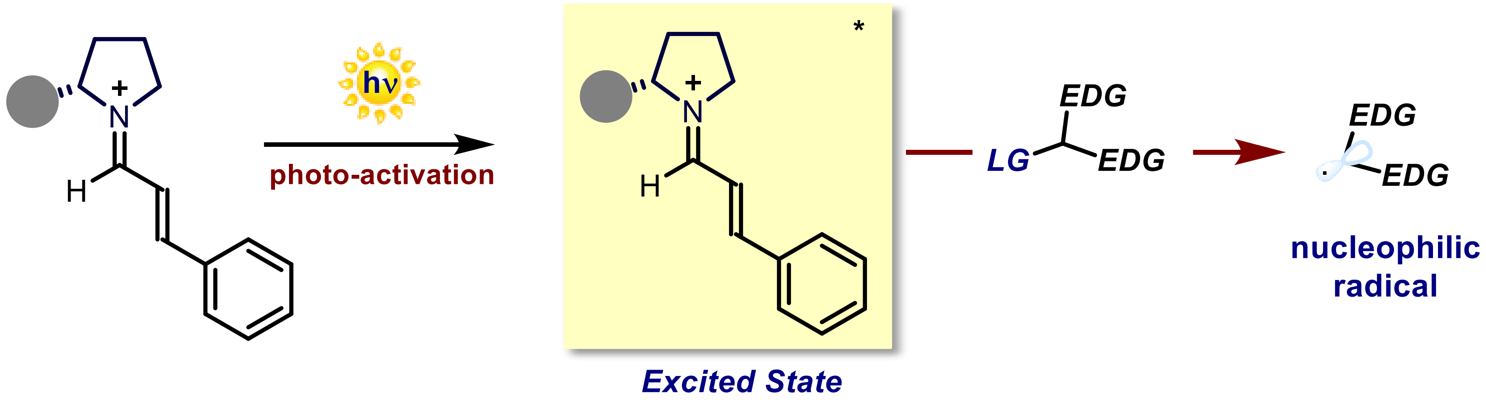
Photochemistry of *Enamines* in the Excited State

Strong reductant



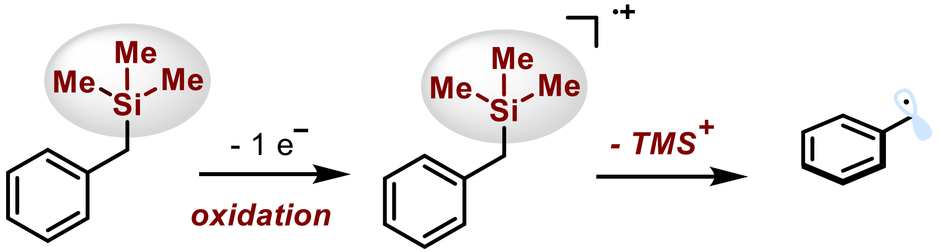
Photochemistry of *Iminium Ions* in the Excited State

Strong oxidant?



Nature Chem. **2017**, 9, 868
Angew. Chem. Int. Ed. **2018**, *57*, 1068
Angew. Chem. Int. Ed. **2018**, *57*, 12819
J.Am. Chem. Soc. **2018,** *140*, 8439
Angew. Chem. Int. Ed. **2021**, *60*, 5357

Searching for a suitable substrate



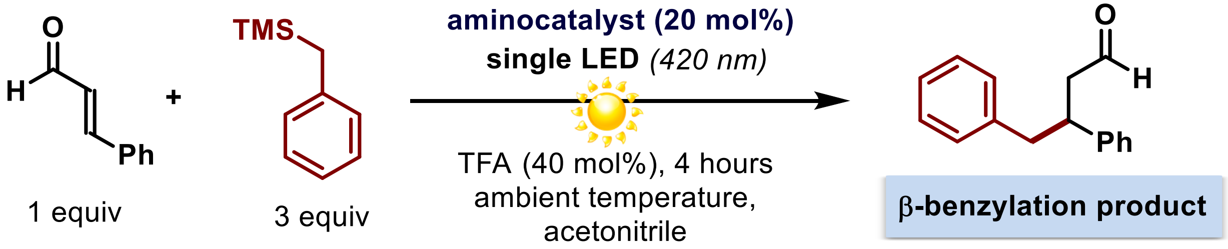
SILANE

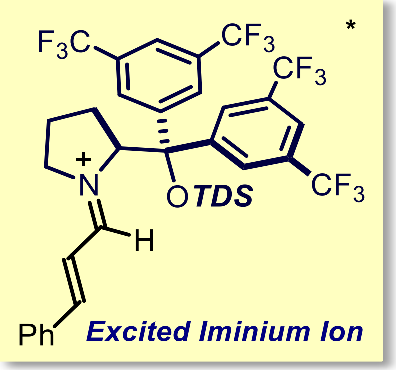
- ✓ **Low reduction potentials** (E_{ox} = +1.4 – 1.7 V)
- ✓ **Can easily fragment realeasing free radicals**
- ✓ **Cheap, easy to synthesize, low toxicity**

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

Mattia Silvi

Photo-excitation of Iminium Ions

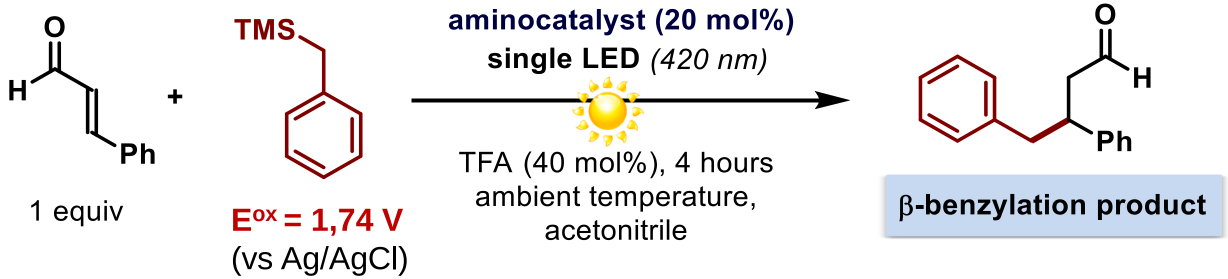


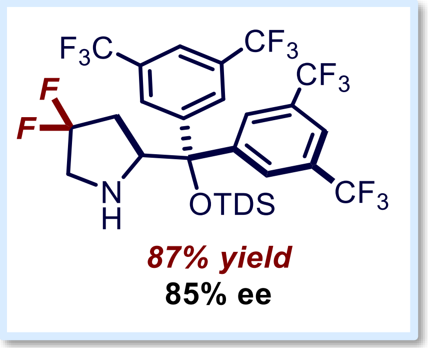


Mattia Silvi

Charlie Verrier

Photo-excitation of Iminium Ions





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

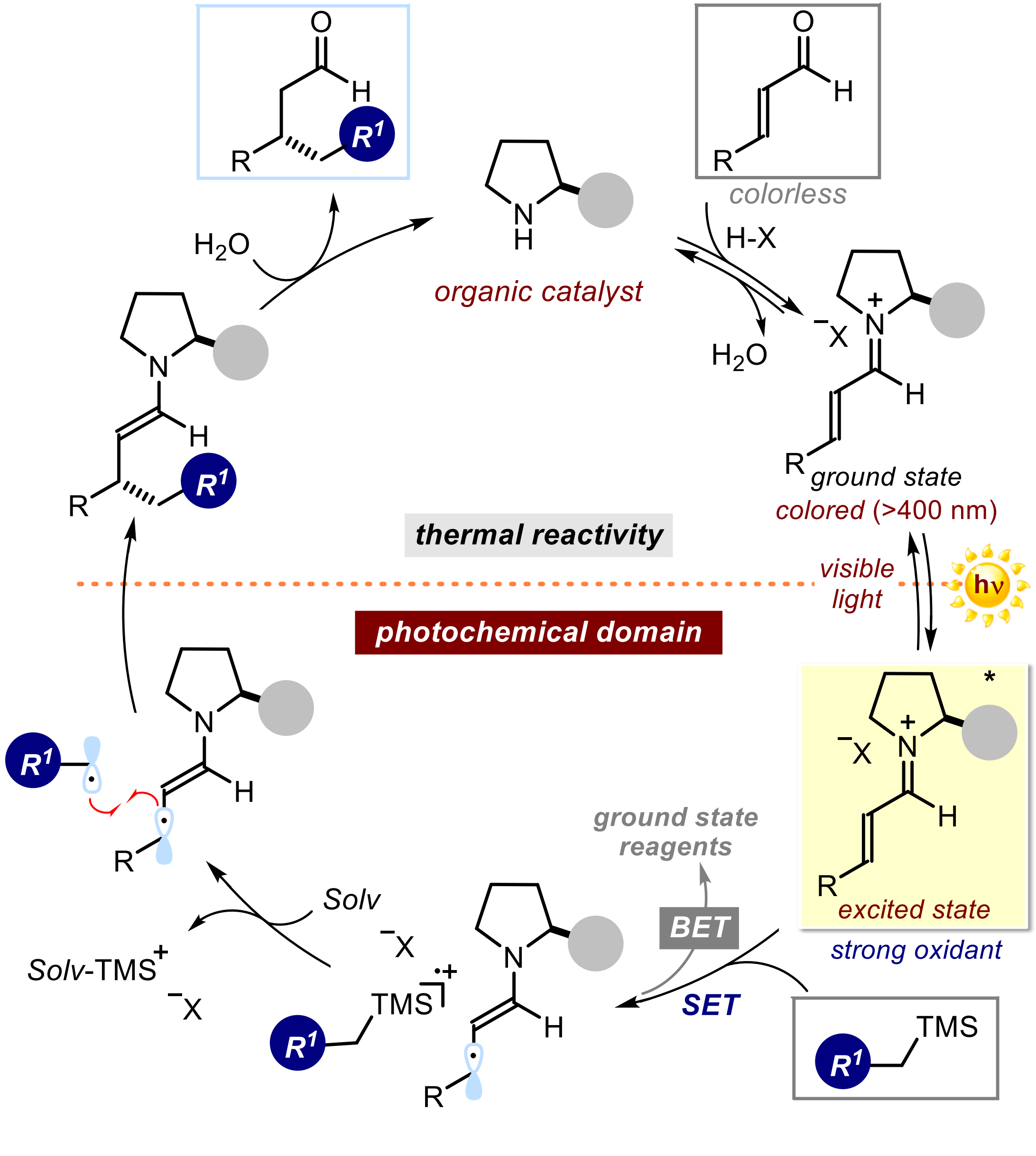
TDS: dimethylthexylsilyl

Yannick Rey

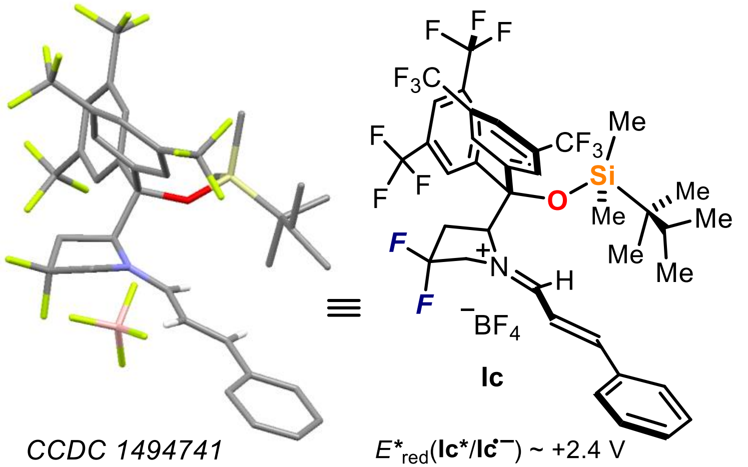
Charlie Verrier

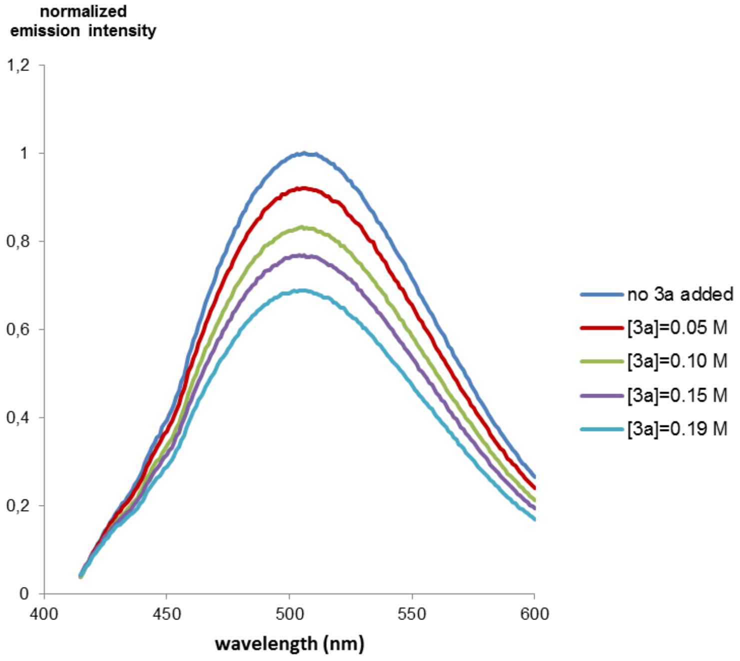
with M. Silvi, C. Verrier, Y. Rey, L. Buzzetti
Nature Chem. **2017**, 9, 868-873

Proposed mechanism



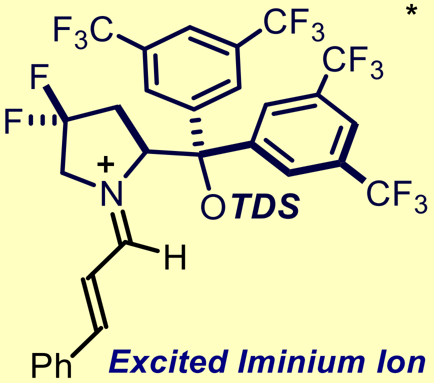
Φ (400 nm) = 0,04





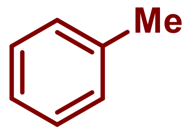
Nature Chem. **2017**, *9*, 868-873

Asymmetric Photocatalytic C-H Functionalization of Toluene

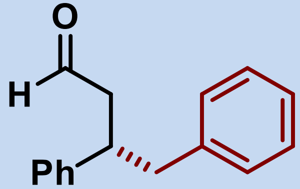


Excited Iminium Ion

Strong oxidant



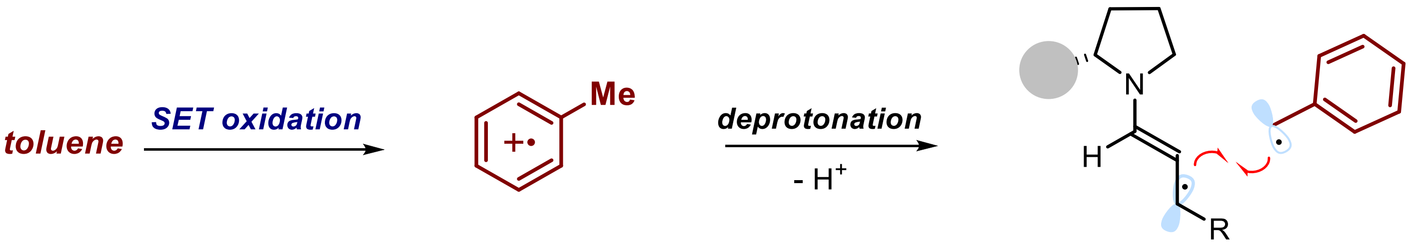
E_{ox} = + 2.2 V



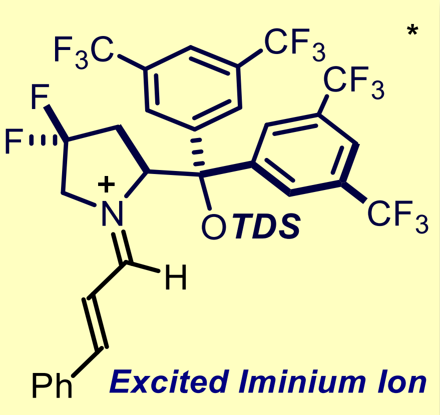
62% yield
85% ee

with D. Mazzarella, G. Crisenza,
J. Am. Chem. Soc. **2018,** *140*, 8439-8443

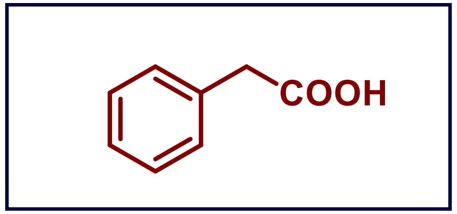
Mechanistic path



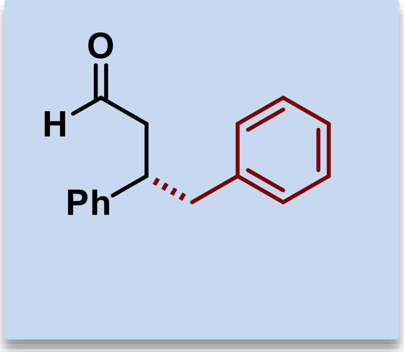
Something we could not do



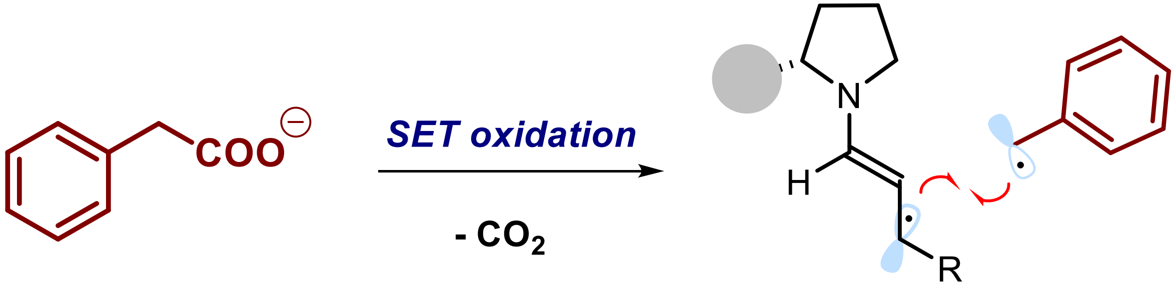
Strong oxidant



abundant



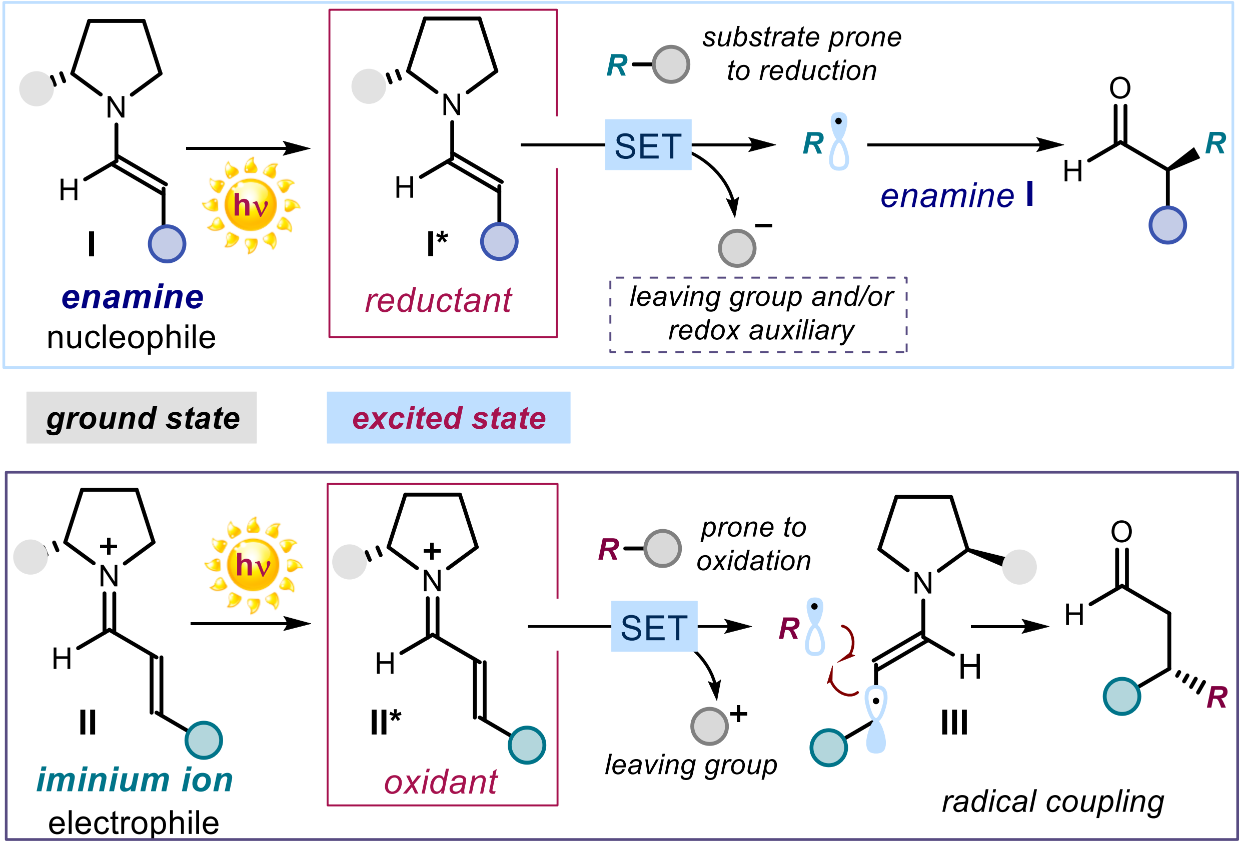
Mechanistic path



Why we failed:

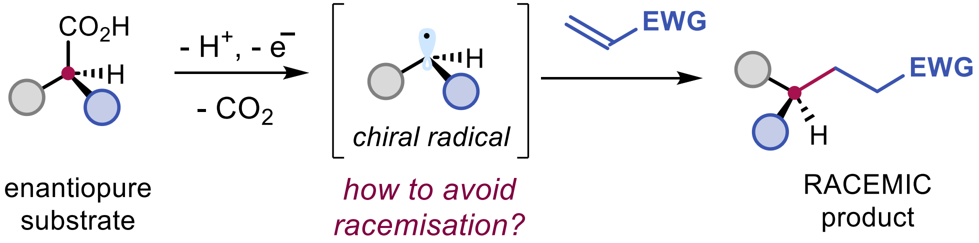
Acidic conditions of iminium ion formation are incompatible with carboxylate formation

Background



Open Challenge

- *Memory of Chirality in Asymmetric Radical Chemistry*



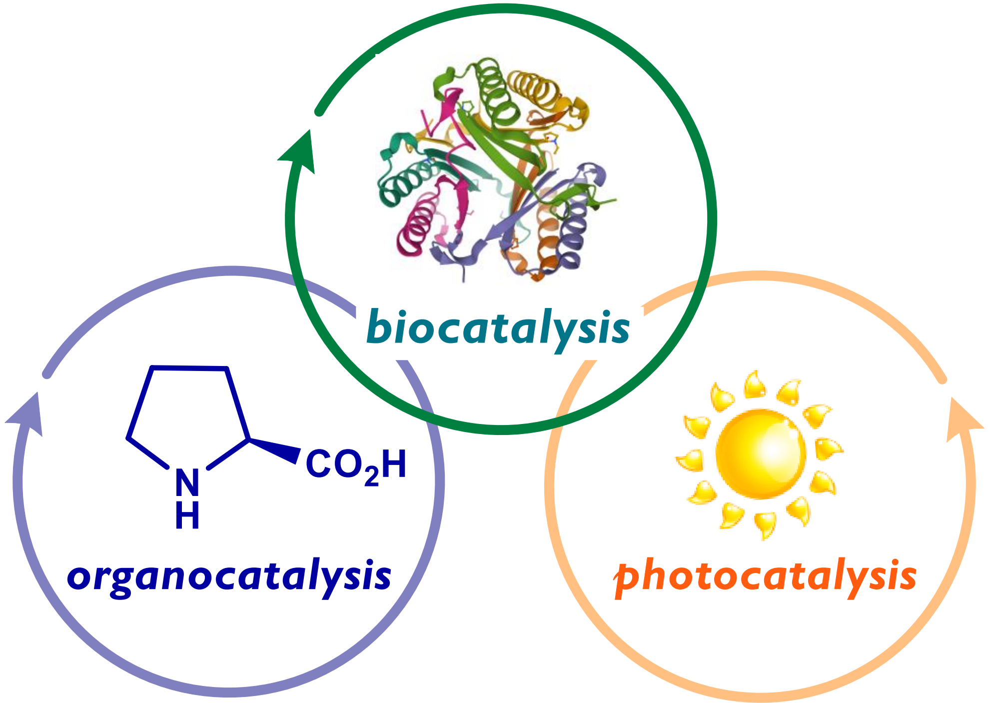
Enhancing the potential of enantioselective organocatalysis with light

Mattia Silvi[1] & Paolo Melchiorre[2,3]

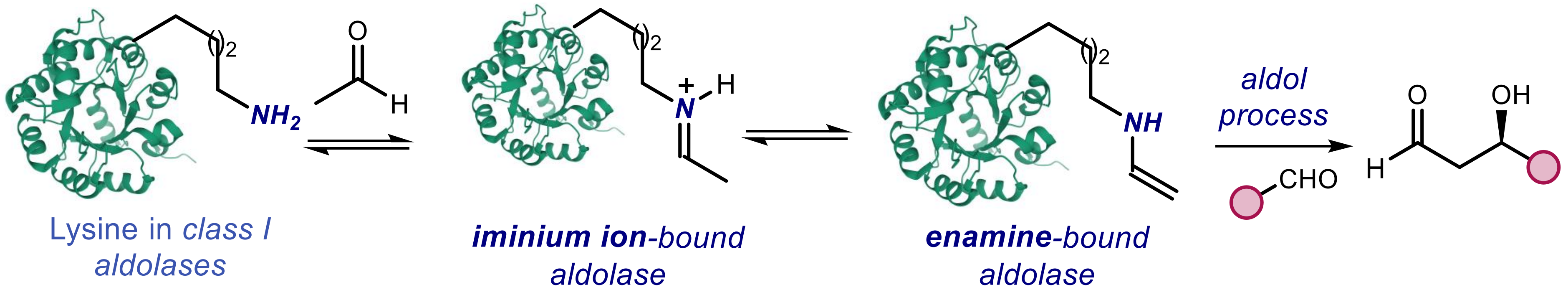
Review
Nature **554**, 41–49 (2018)

This Story

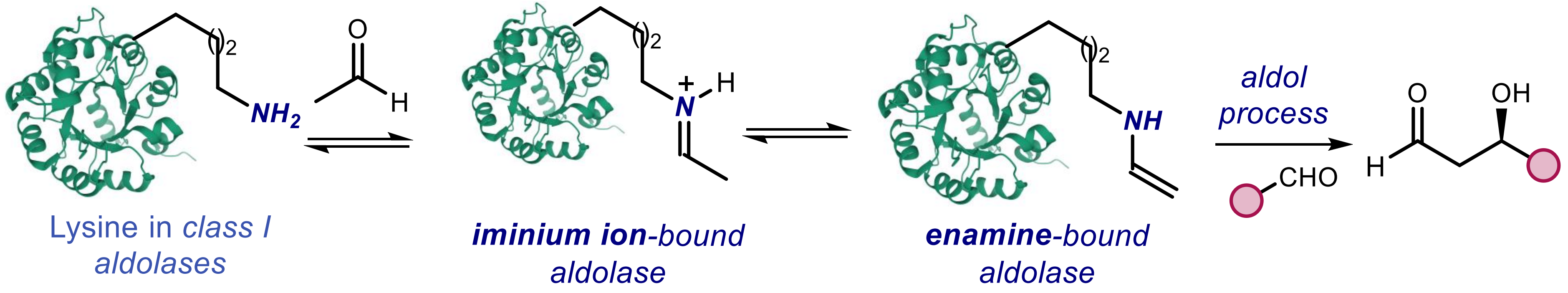
Organocatalysis, Light & Enzymes



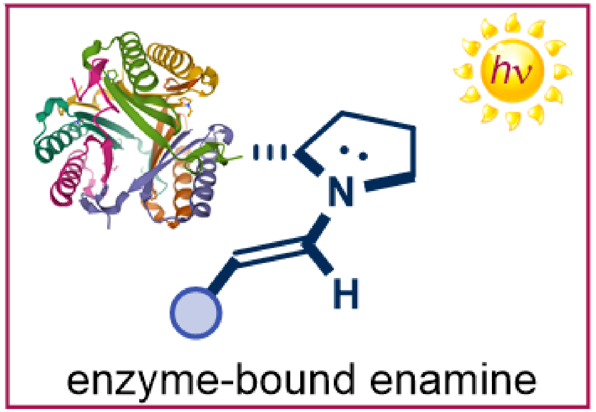
Why Moving into Biocatalysis

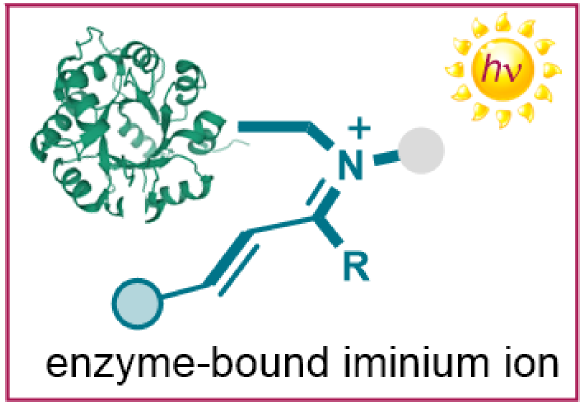


Photoenzymes for New Chemistry



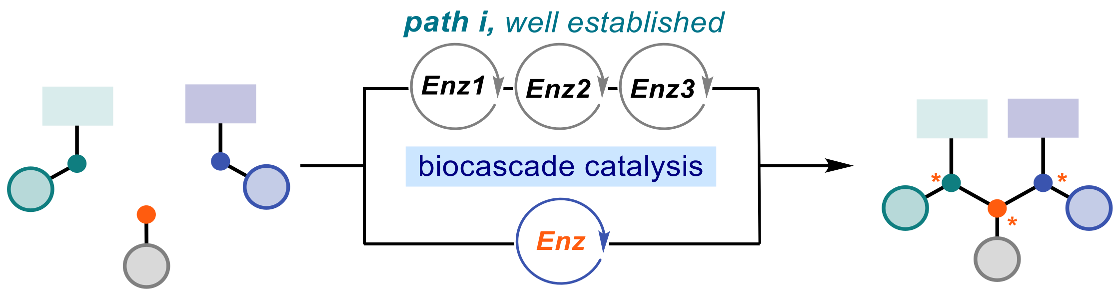
PHOTOZYME'S Tools





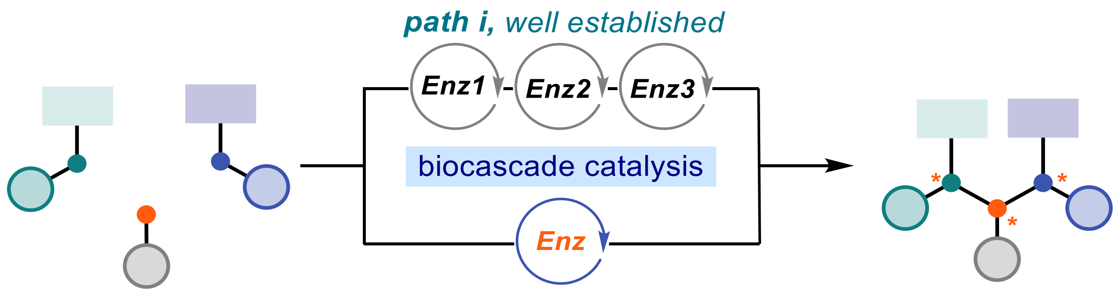
excitation of protein-bound catalytic intermediates

Biocatalysis



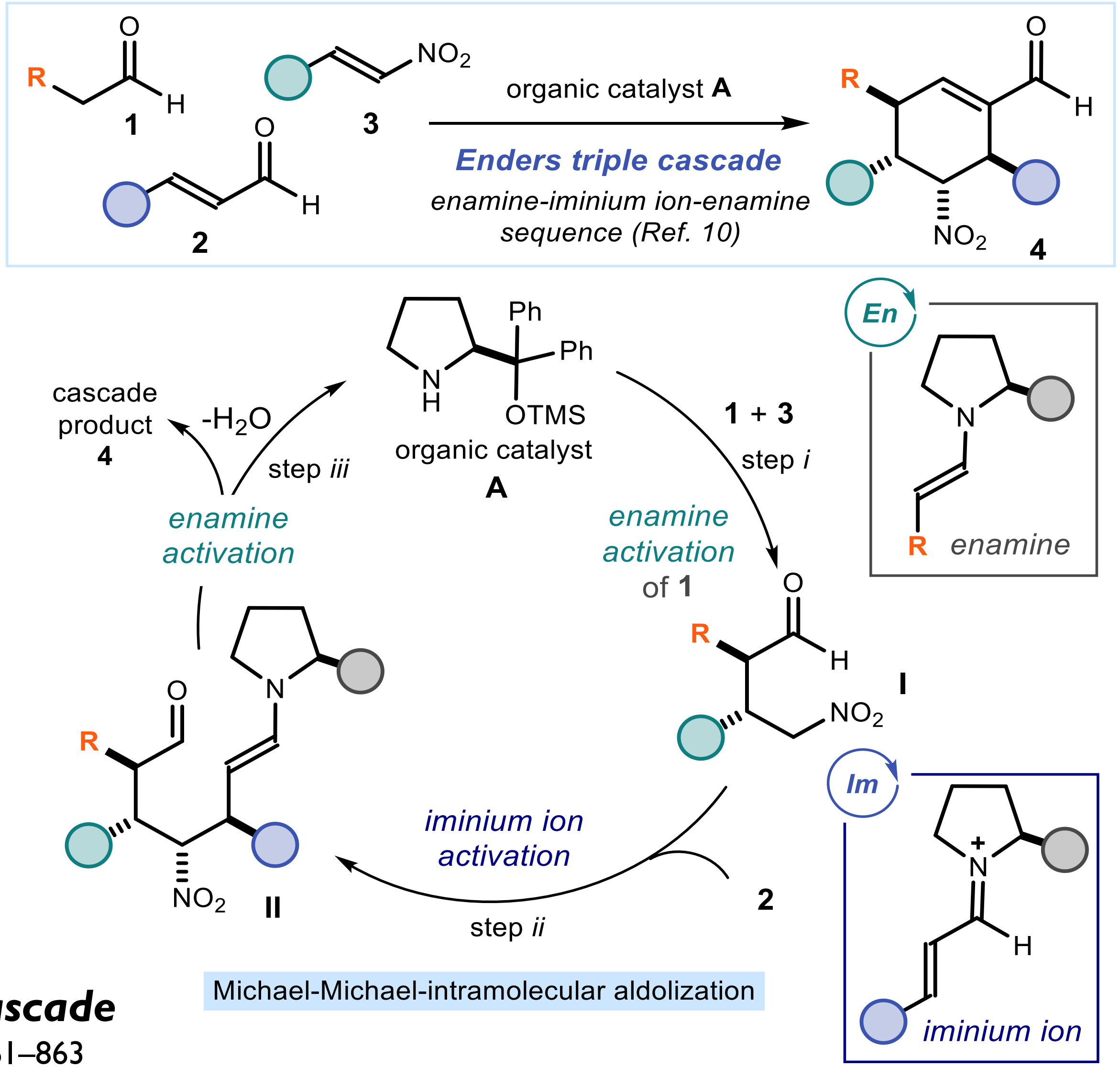
Established approach to design biocascade processes

Biocatalysis



Established approach to design biocascade processes

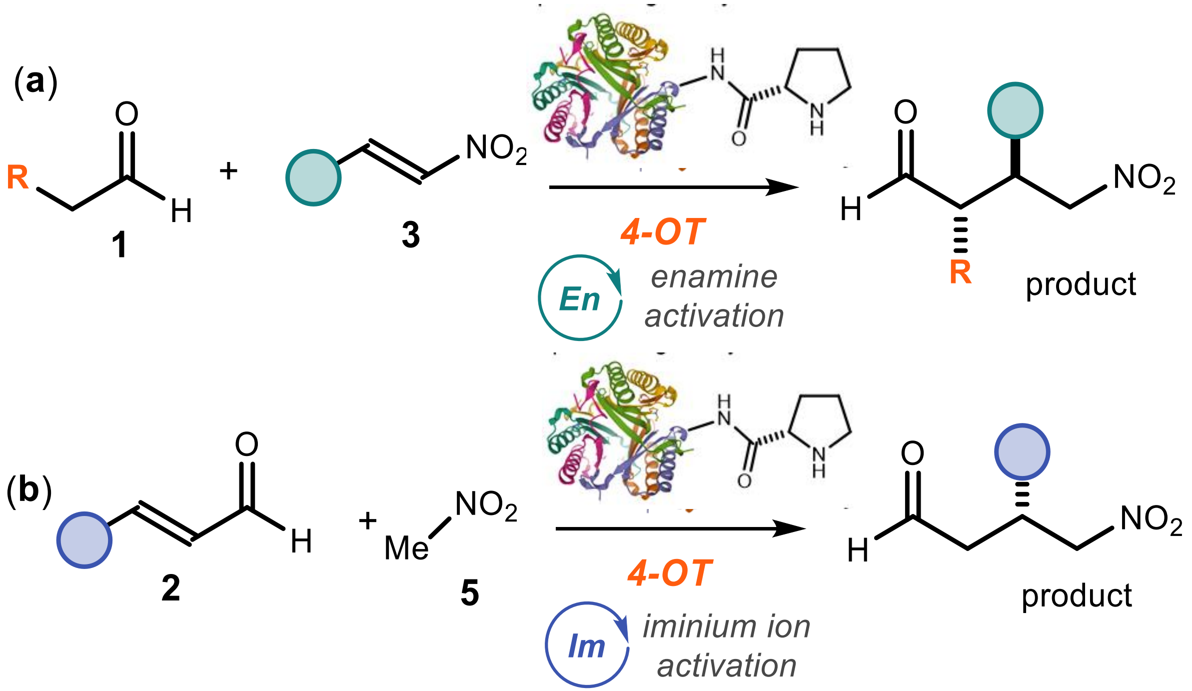
Organocatalysis



Enders Triple cascade

Nature **2006**, *441*, 861–863

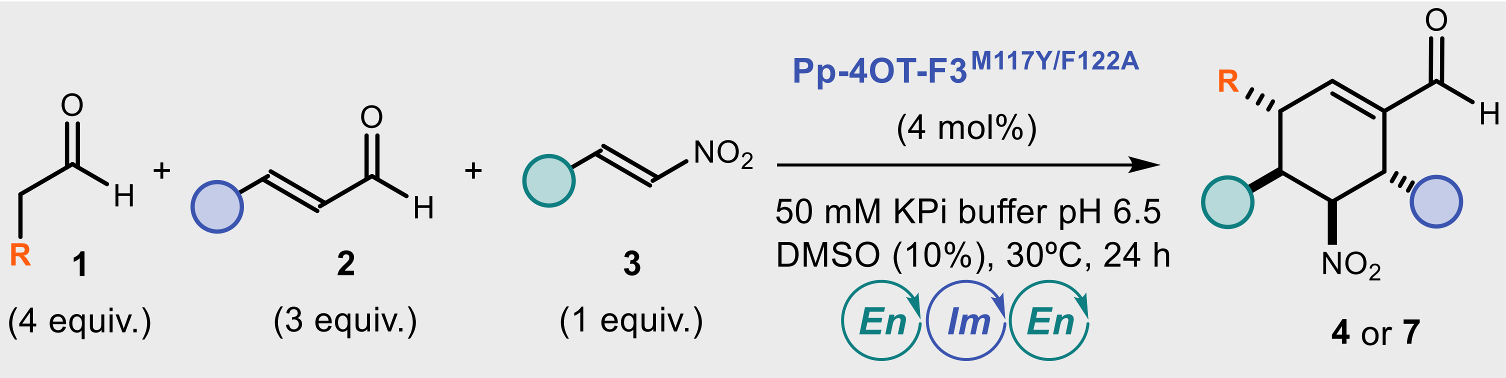
Pioneering works of Poelarends



4-Oxalocrotonate tautomerase (4-OT) enzymes can promote organocatalytic asymmetric processes

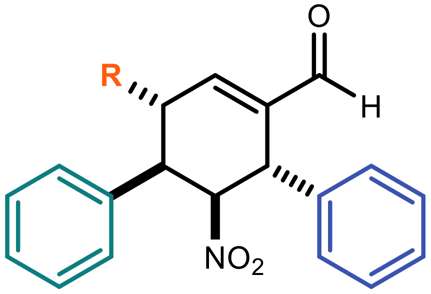
Poelarends, G. J. et al.:
(a) *Chem. Bio. Chem.* **2015**, *15*, 738–741. (b) *Angew. Chem. Int. Ed.* **2020**, *59*, 10374–10378. (c) *Angew. Chem. Int. Ed.* **2021**, *60*, 24059–24063.
(d) *Angew. Chem. Int. Ed.* 2022, e202203613

Biocatalytic Triple Cascade



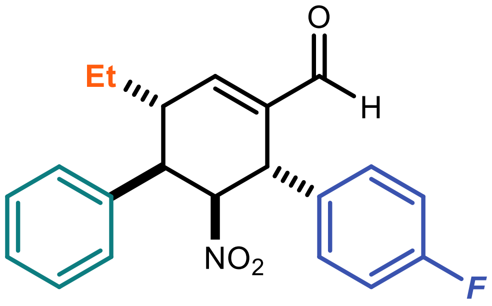
Vasilis Tseliou

scope of the triple biocascade

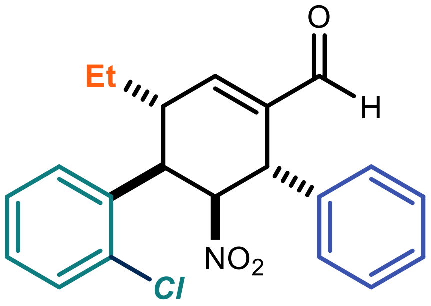


R = H: 4a*: 28% yield
>20:1 dr, >99% ee

R = Et: 7a: 50% yield
3.7:1 dr, >99% ee



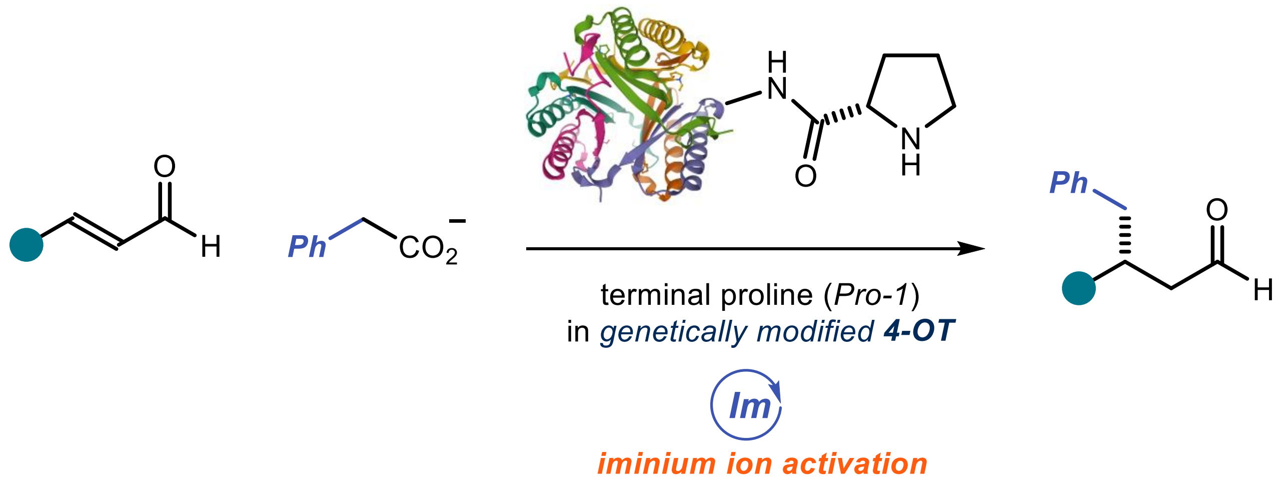
7b: 43% yield
6:1 dr, >99% ee



7c: 51% yield
4.7:1 dr, >99% ee
(23% yield isolated)

with V. Tseliou, A. Faraone, L. Kqiku, J. Vilím, G. Simionato
Angew. Chem. Int. Ed. **2022**, *e202212176*

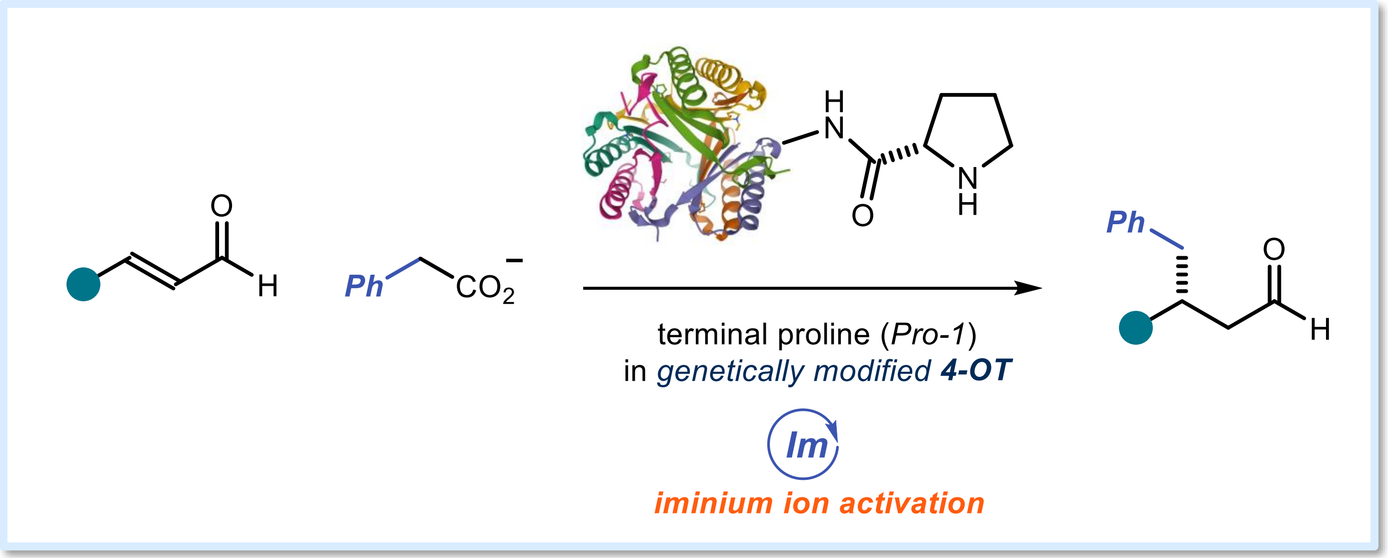
Biocatalysis, Organocatalysis, and Light



violet LED 15% yield, **99% ee**
No light: no reaction

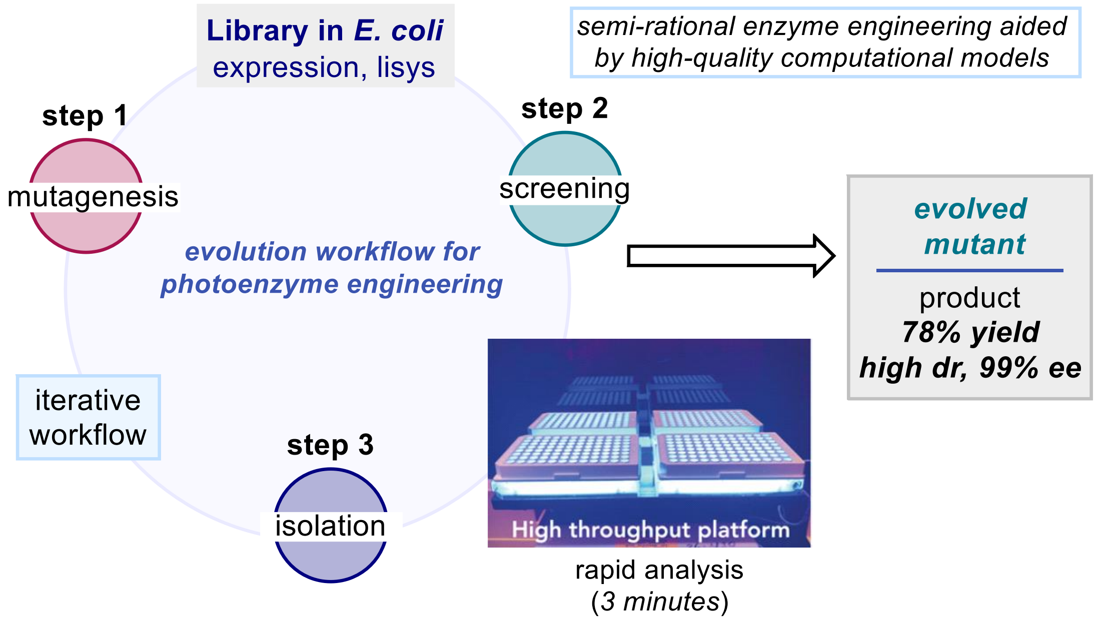
with V. Tseliou, L. Kqiku, M. Berger, T. Schiel

A Non-Natural Photodecarboxylase



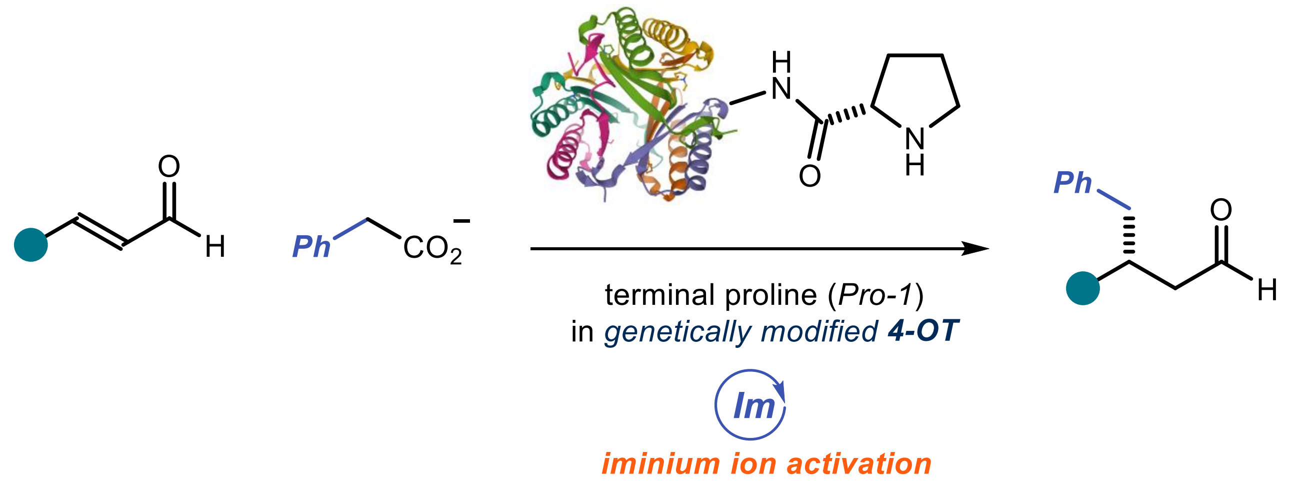
violet LED 15% yield, **99% ee**
No light: no reaction

with V. Tseliou, L. Kqiku, M. Berger, T. Schiel
unpublished



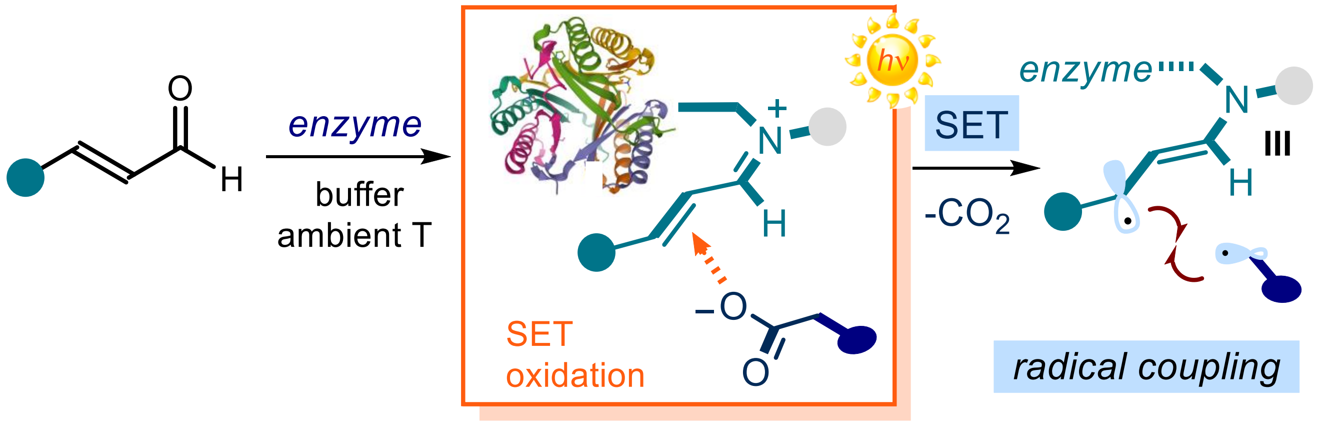
Iterative saturation mutagenesis by high-throughput experimentation (HTE)

A Non-Natural Photodecarboxylase

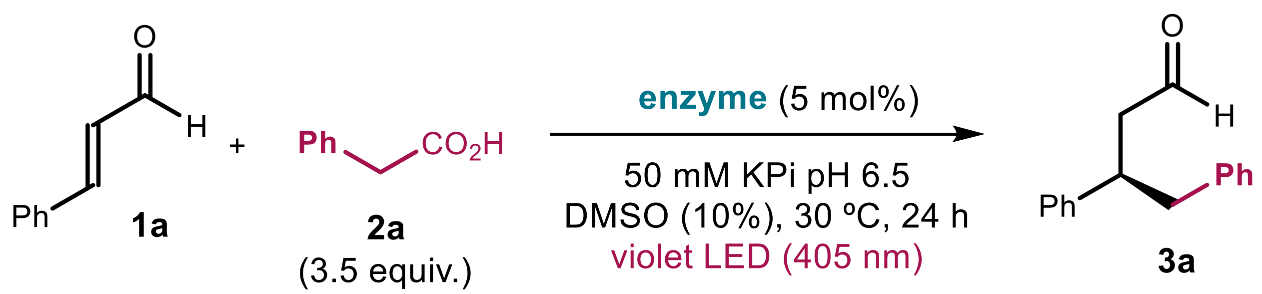


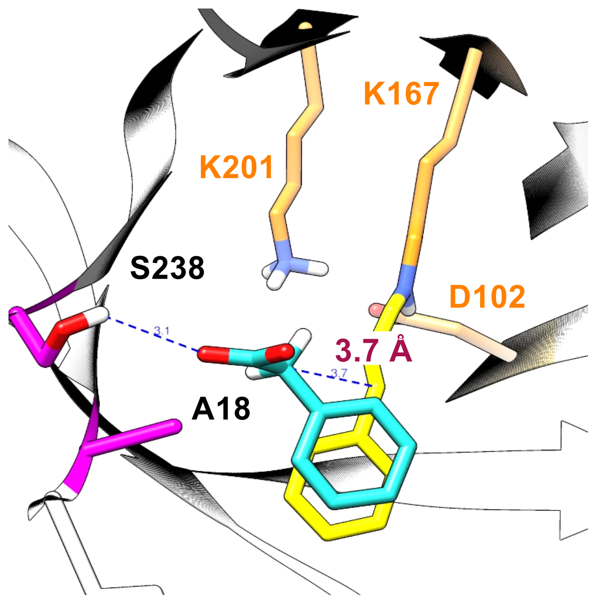
violet LED 15% yield, **99% ee**
No light: no reaction

with V. Tseliou, L. Kqiku, M. Berger, T. Schiel

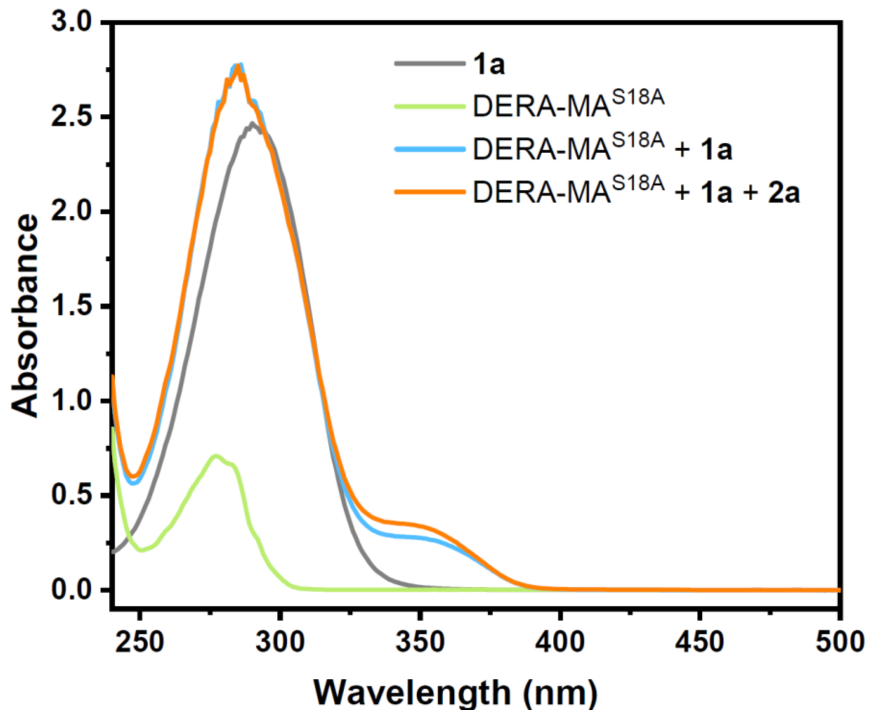


A Non-Natural Photodecarboxylase

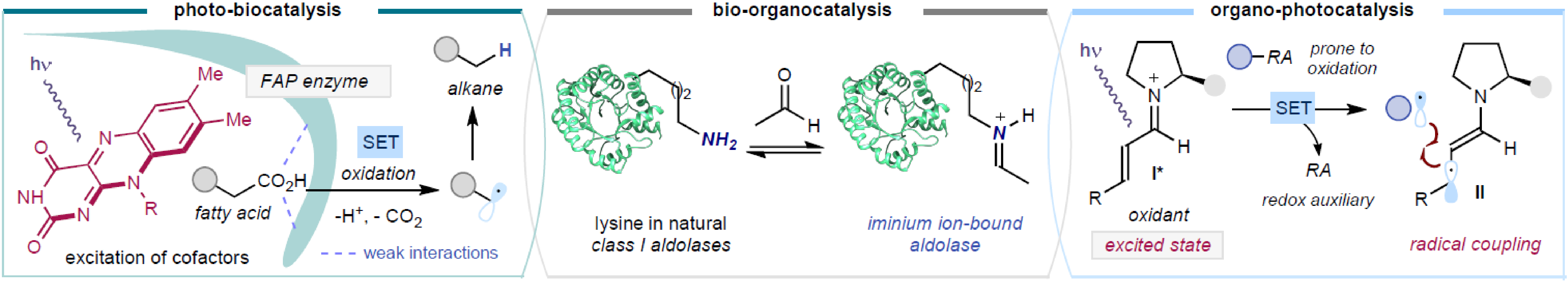




DERA-MA^{S18A}

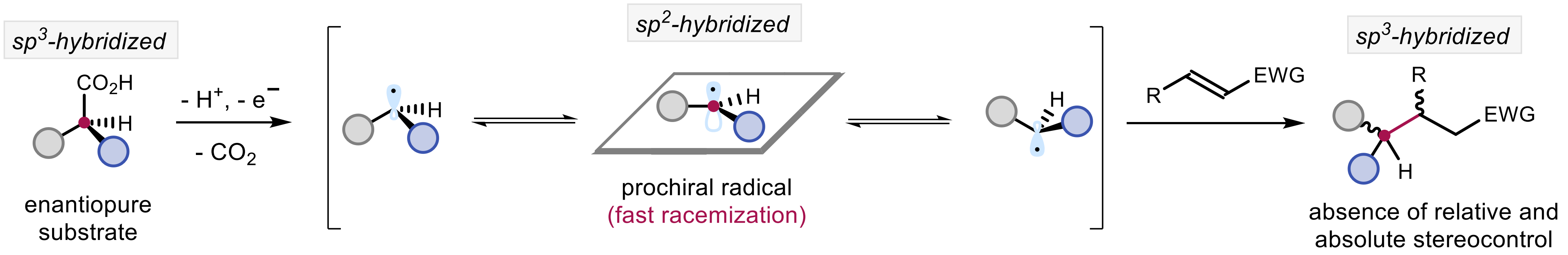


A Non-Natural Photodecarboxylase

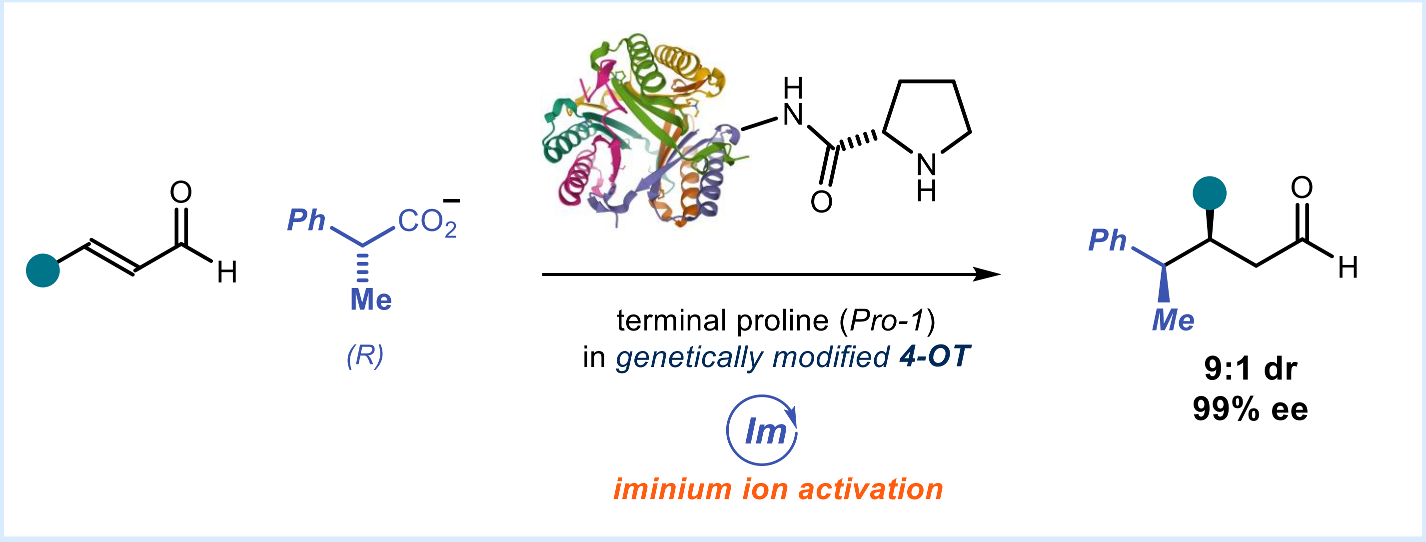


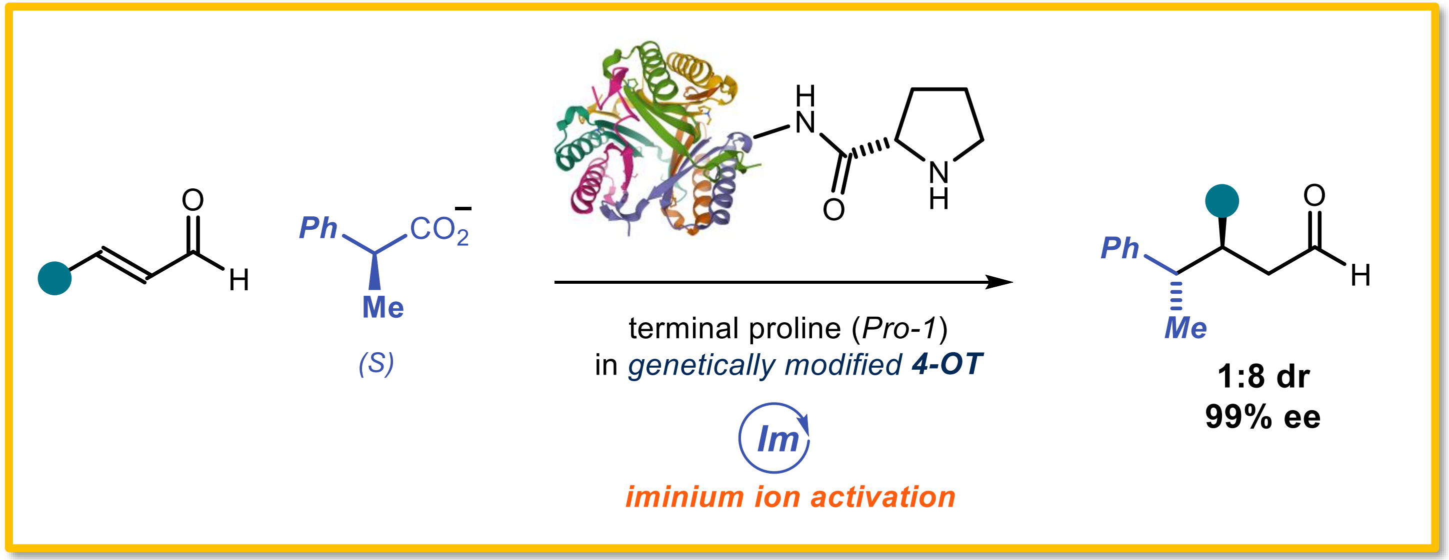
For the natural Fatty Acid Photodecarboxylase (FAP), see:
Beisson, F. et al. An algal photoenzyme converts fatty acids to hydrocarbons
Science **357**, 903−907 (2017).

About chiral radicals



The problem of chiral radicals

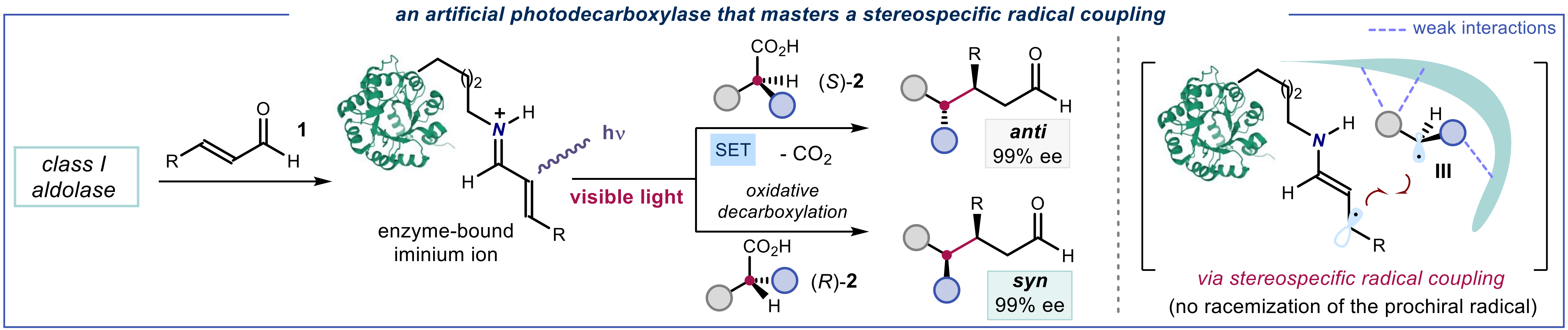


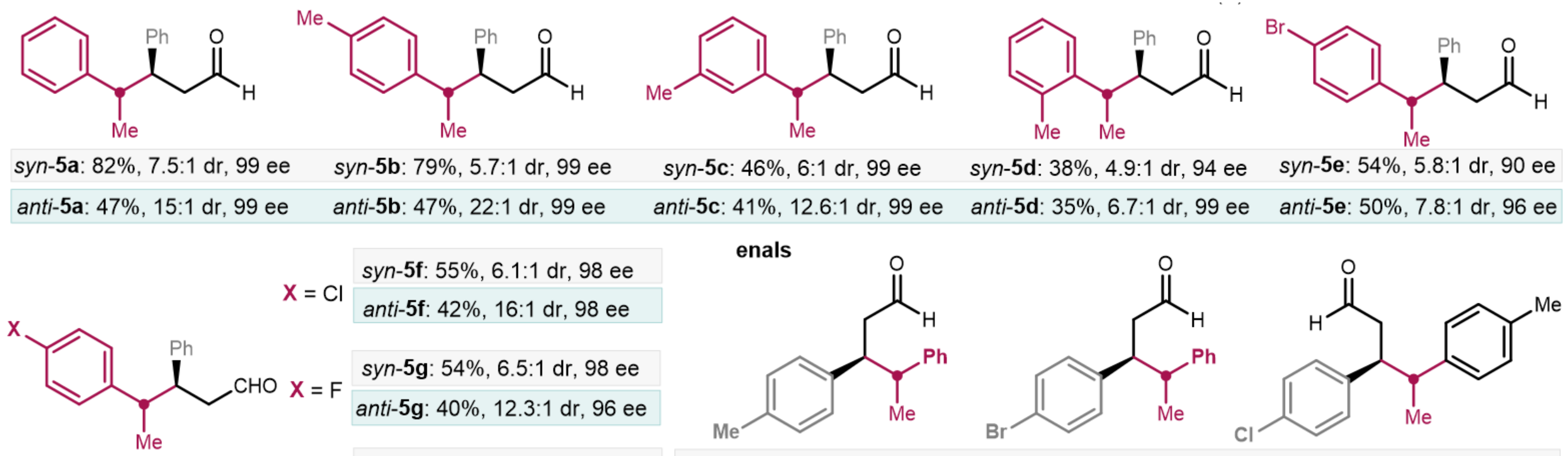


Memory of chirality

with V. Tseliou, L. Kqiku, M. Berger, T. Schiel
Nature **2024**, 10.1038/s41586-024-08004-9

Stereospecific Radical Coupling





syn-**5a**: 82%, 7.5:1 dr, 99 ee | *anti*-**5a**: 47%, 15:1 dr, 99 ee

syn-**5b**: 79%, 5.7:1 dr, 99 ee | *anti*-**5b**: 47%, 22:1 dr, 99 ee

syn-**5c**: 46%, 6:1 dr, 99 ee | *anti*-**5c**: 41%, 12.6:1 dr, 99 ee

syn-**5d**: 38%, 4.9:1 dr, 94 ee | *anti*-**5d**: 35%, 6.7:1 dr, 99 ee

syn-**5e**: 54%, 5.8:1 dr, 90 ee | *anti*-**5e**: 50%, 7.8:1 dr, 96 ee

X = Cl: *syn*-**5f**: 55%, 6.1:1 dr, 98 ee | *anti*-**5f**: 42%, 16:1 dr, 98 ee

X = F: *syn*-**5g**: 54%, 6.5:1 dr, 98 ee | *anti*-**5g**: 40%, 12.3:1 dr, 96 ee

X = OMe: *syn*-**5h**: 54%, 3.2:1 dr, 99 ee | *anti*-**5h**: 43%, 6.7:1 dr, 99 ee

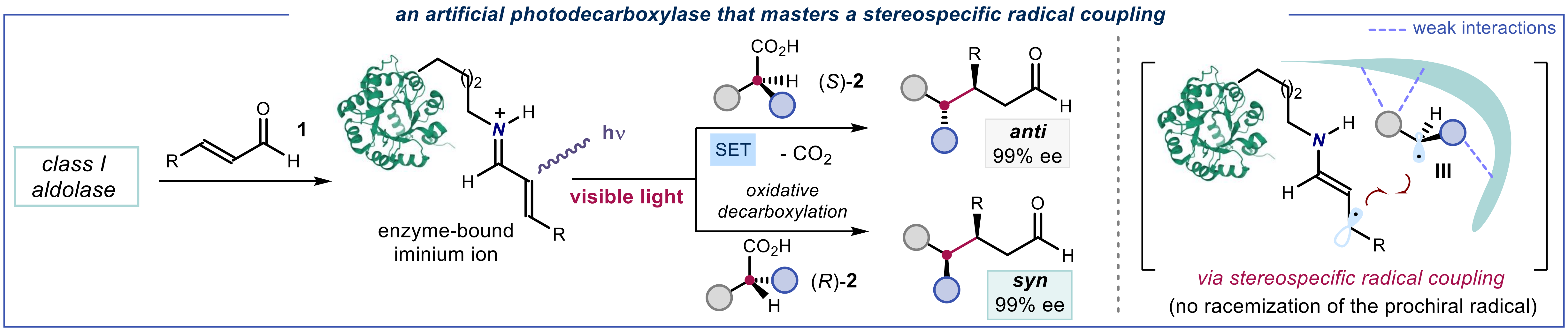
enals

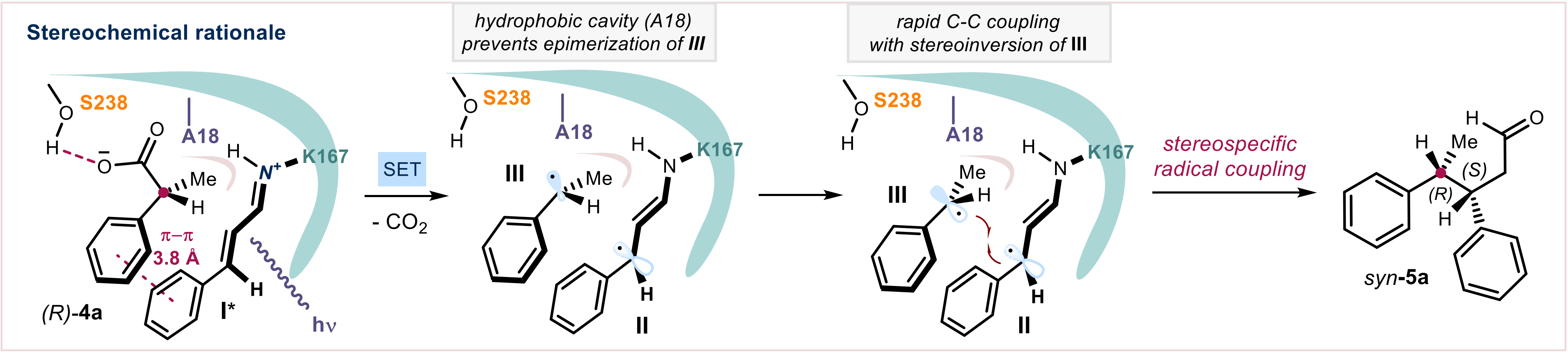
syn-**5i**: 65%, 7.7:1 dr, 99 ee | *anti*-**5i**: 37%, 13.8:1 dr, 99 ee

syn-**5j**: 38%, 6.9:1 dr, 99 ee | *anti*-**5j**: 26%, 12.7:1 dr, 99 ee

syn-**5k**: 39%, 7.6:1 dr, 99 ee | *anti*-**5k**: 48%, 22:1 dr, 99 ee

Stereospecific Radical Coupling

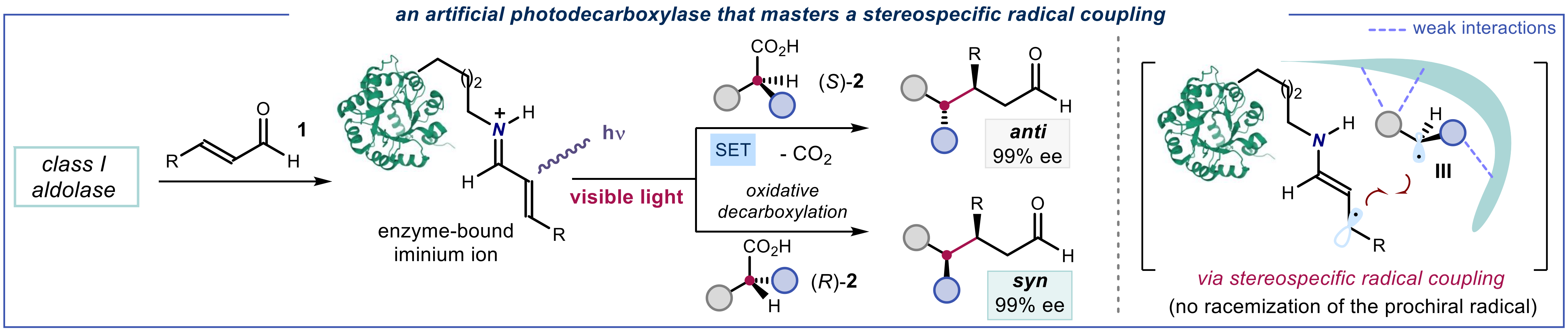


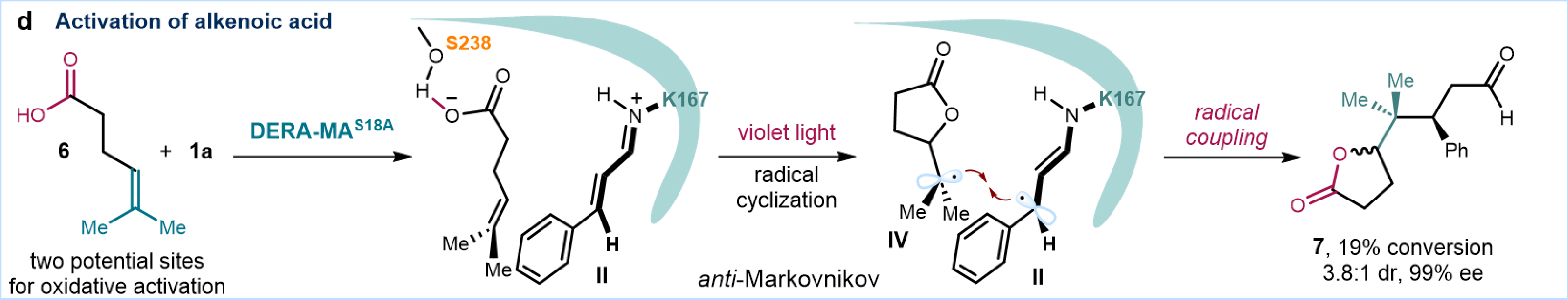


with V. Tseliou, L. Kqiku, M. Berger, T. Schiel

Nature **2024**, 10.1038/s41586-024-08004-9

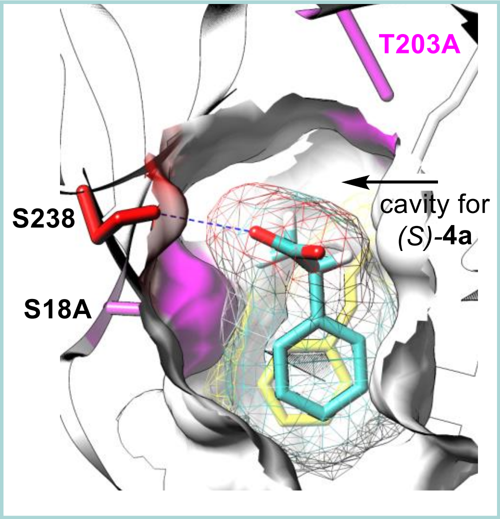
Stereospecific Radical Coupling



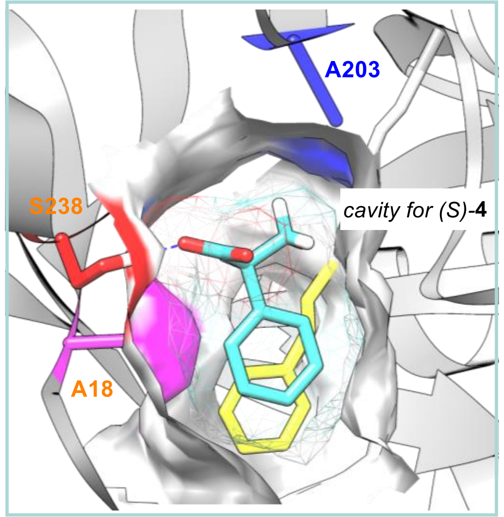


with V. Tseliou, L. Kqiku, M. Berger, T. Schiel
Nature **2024**, 10.1038/s41586-024-08004-9

Towards a Kinetic Resolution

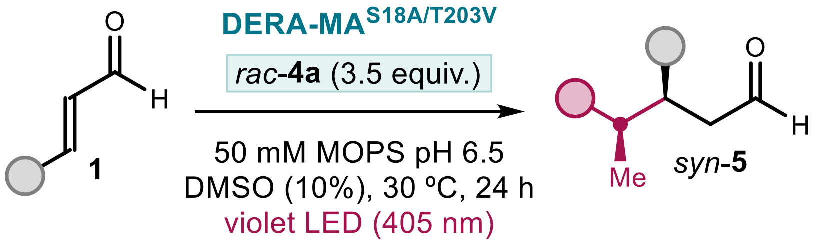


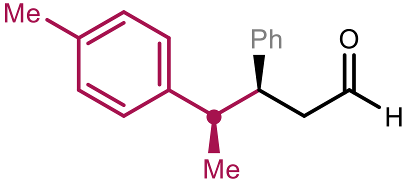
(R)-acid



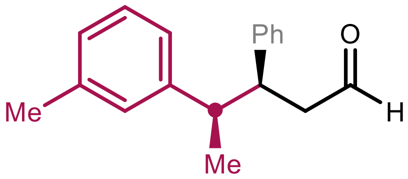
(S)-acid

Kinetic Resolution

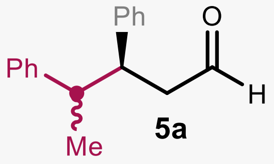




syn-**5b**: 76%, 5.5:1 dr, 99 ee



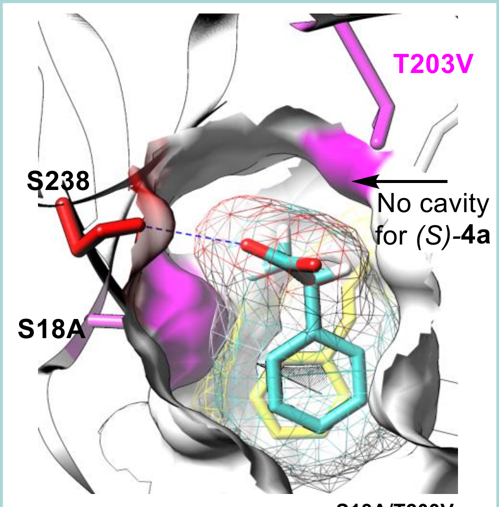
syn-**5c**: 49%, 3.1:1 dr, 95 ee



from *rac*-**4a**
syn-**5a,** 67%, **5.3:1 dr**, 99% ee

from (*R*)-**4a**
syn-**5a,** 70%, 8.3:1 dr, 99% ee

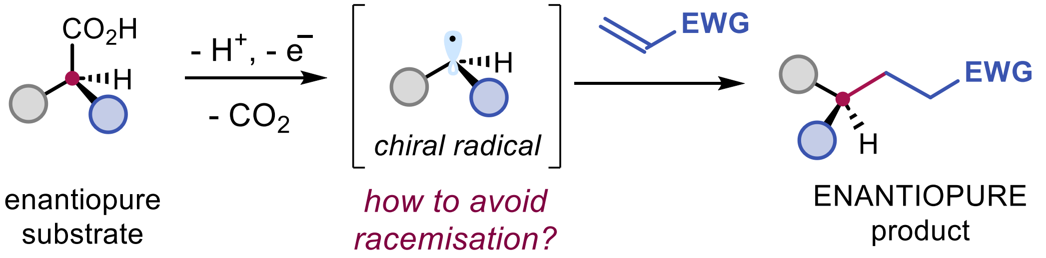
from (*S*)-**4a**
anti-**5a,** 9%, 4.3:1 dr, 99% ee



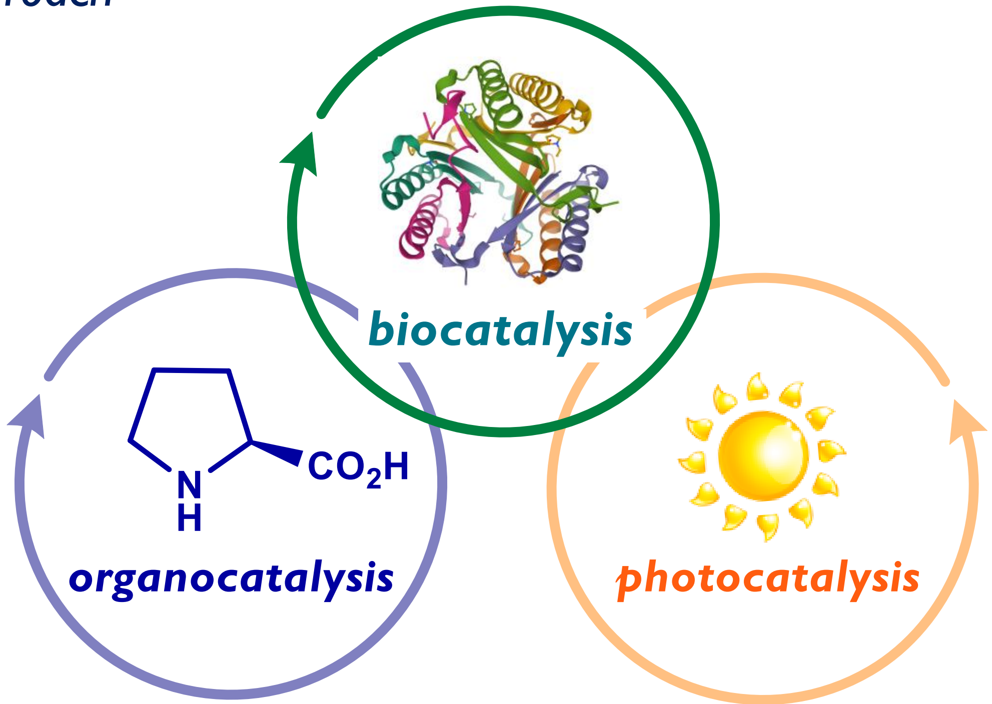
(*R*)-**4a** wihtin DERA-MA$^{S18A/T203V}$

with V. Tseliou, L. Kqiku, M. Berger, T. Schiel
Nature **2024**, 10.1038/s41586-024-08004-9

How to transfer stereochemical information when chiral radicals are formed?



Our approach



Moving back to UNIBO – Alma Mater

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Acknowledgements

Present members:

@ICIQ

Laura Kqiku
Shuo Wu
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Florian Schiel

@UNIBO

Dr. Sumit Mallik
Dr. Binlin Zhao
Dr. Andrea Palone
Dr. Bixiao Li
Hailong Wang
Su Huan
Roberta Coccia
Luca DiMartile
Enrico Sfreddo
Jacopo Mazzeo
Ramon Arora

Starting (2011-2016)
Consolidator (2016-2021)
Proof-of-Concept (2020)
Advanced (2023-2028)

MUR PRIN 2022 PNRR

"LIGHT CAT" P2022 RHMCM
supported by the Next Generation EU program