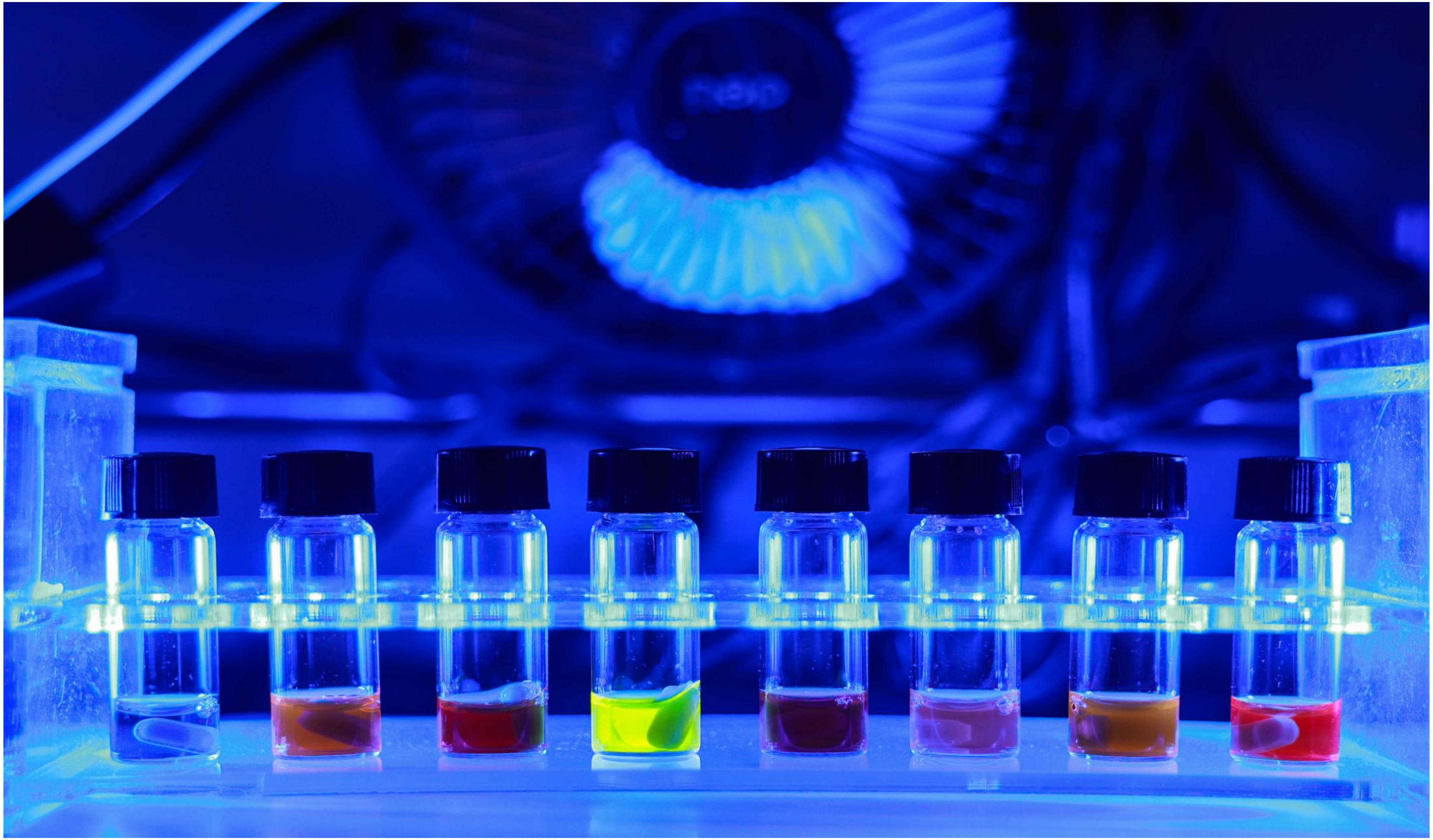
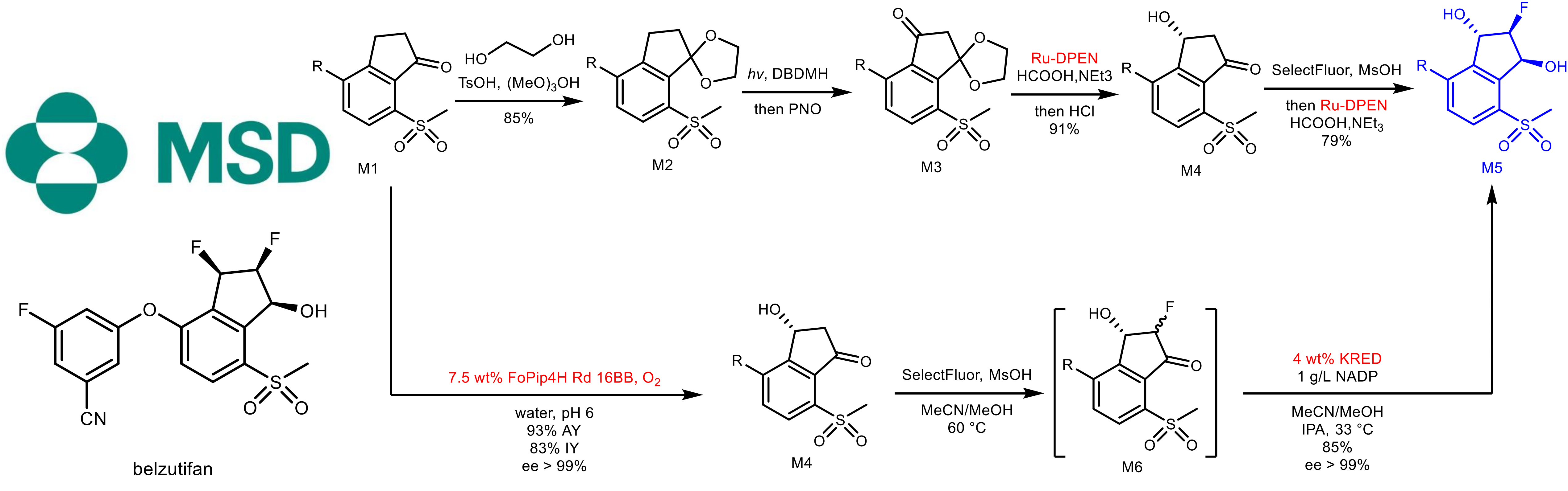
Literature Report



Content

The application of enzymatic catalysis in Pharmaceutical Research



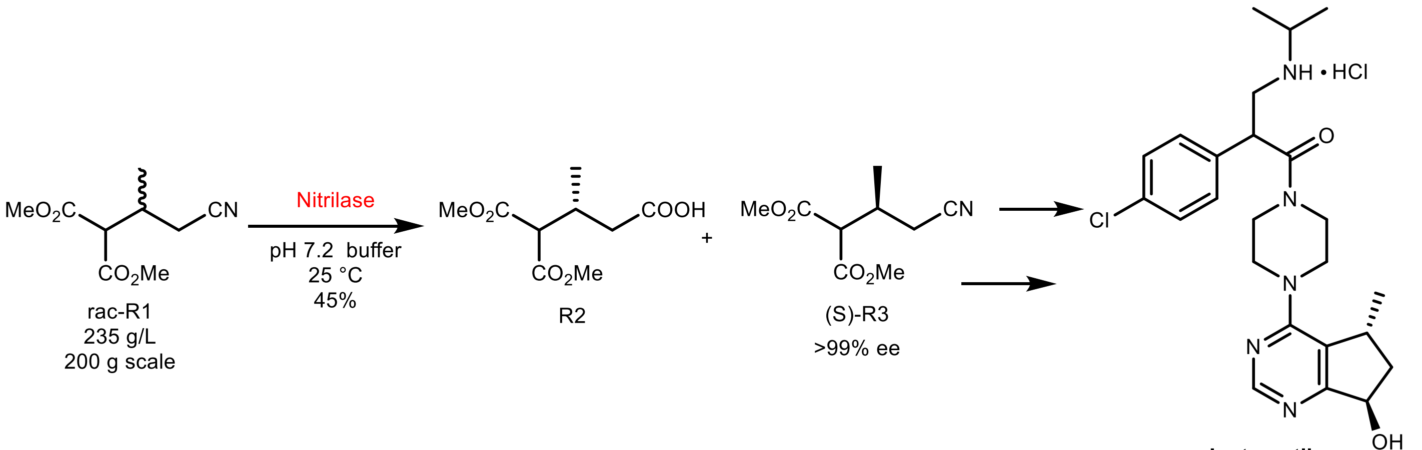
4 kg scale

From 16 steps (4%) to 9 steps (26%)

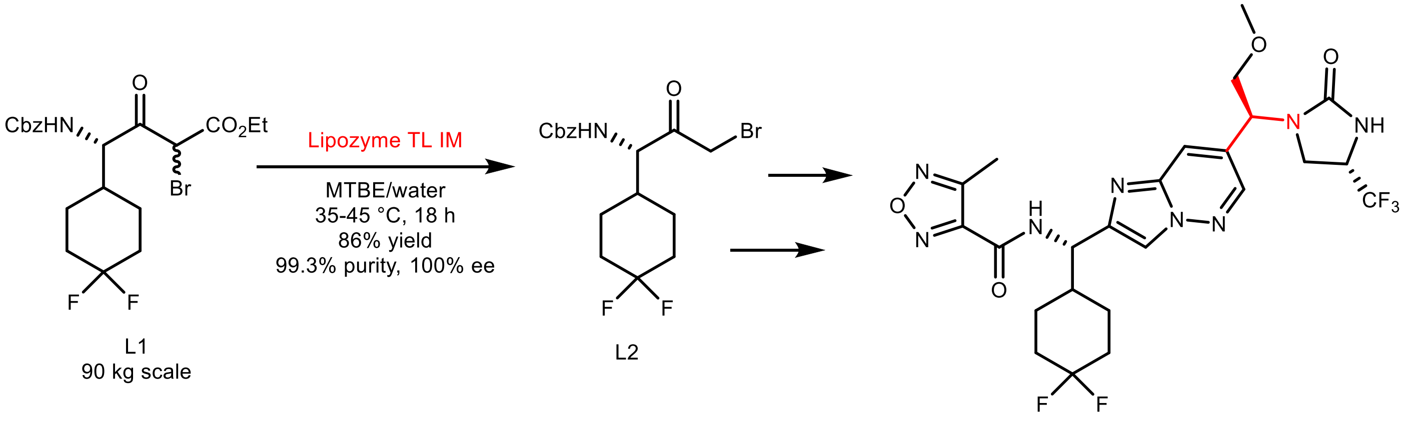
Daniel A. D. et al. *Org. Process Res. Dev.* **2024**, *28*, 404−412

The application of enzymatic catalysis in Pharmaceutical Research

Roche

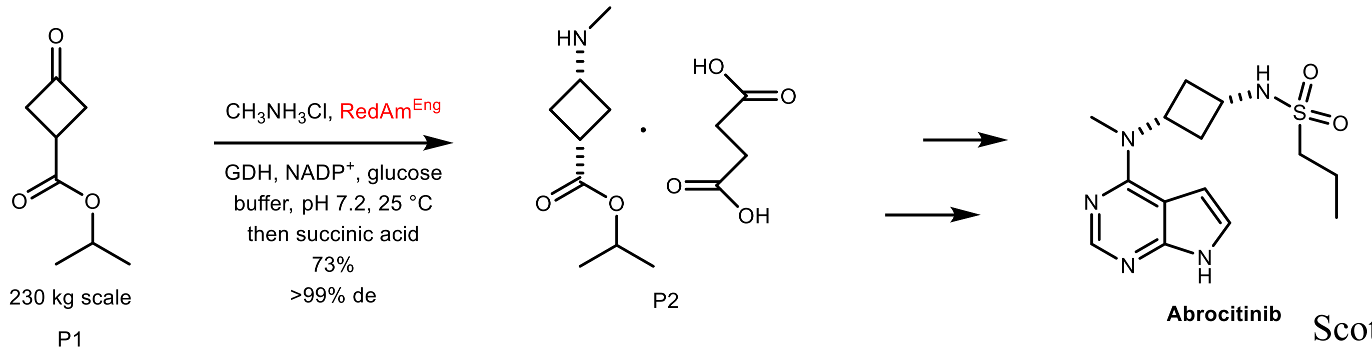


Ipatasertib



LY3509754

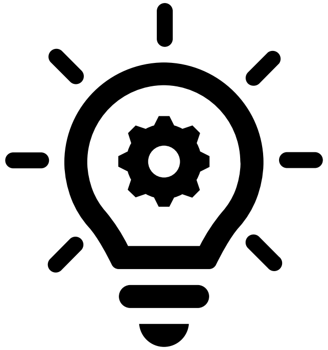
1. Shorter steps
2. Mild conditions
3. Free precious metal
4. Atom economy
5. … …

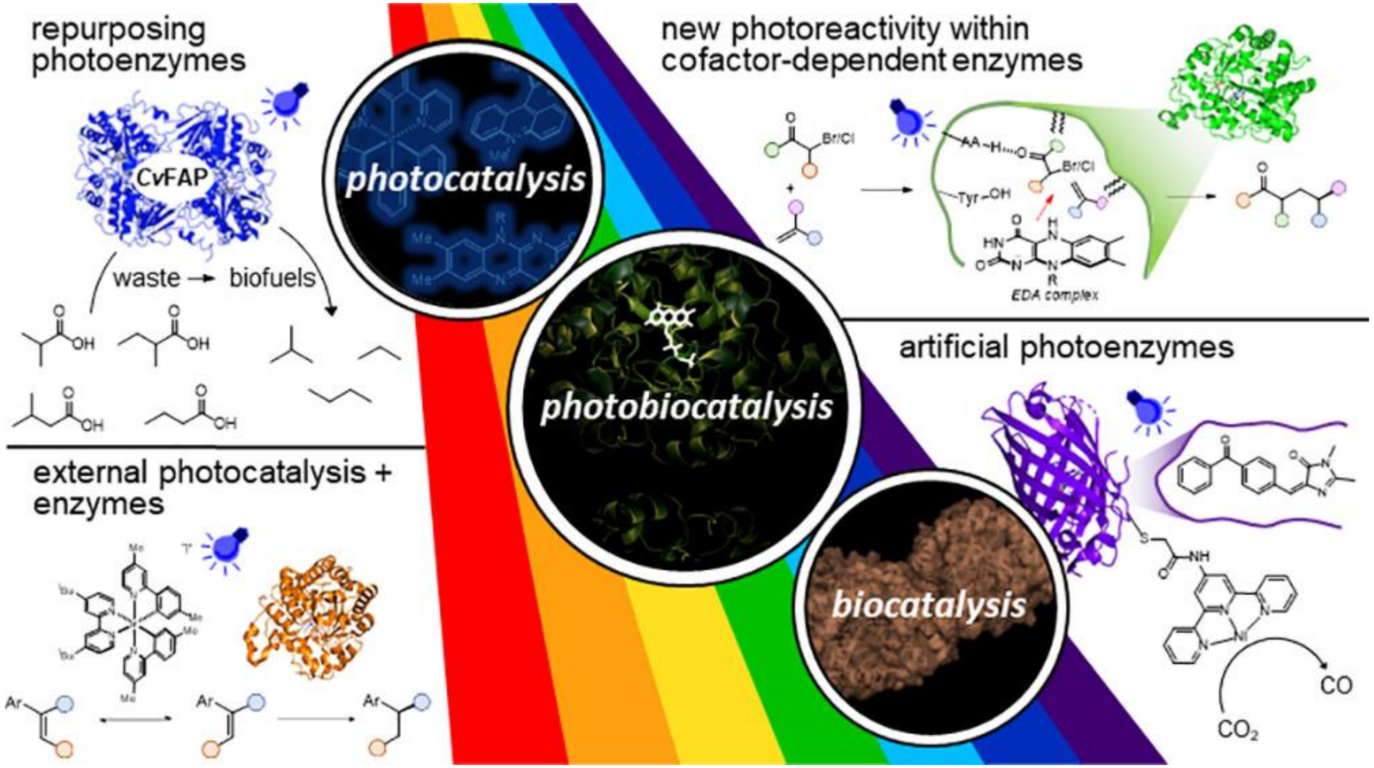


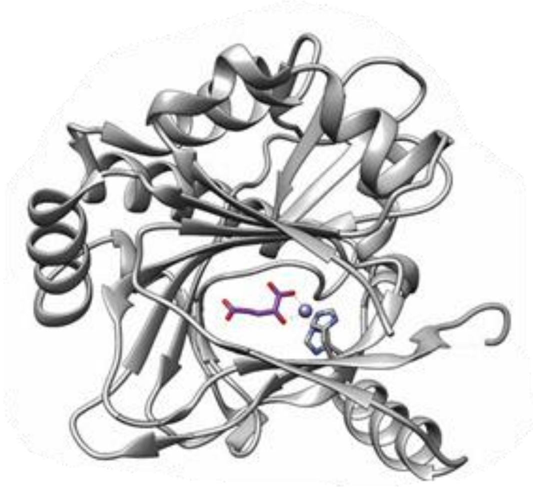
Abrocitinib

Scott P. F. et al. *JACS Au* **2023**, *3*, 715−735

The combination photocatalysis with enzymatic catalysis







Photocatalysis:
Mild reaction conditions
Renewability
Strong reactivity

Poor selectivity

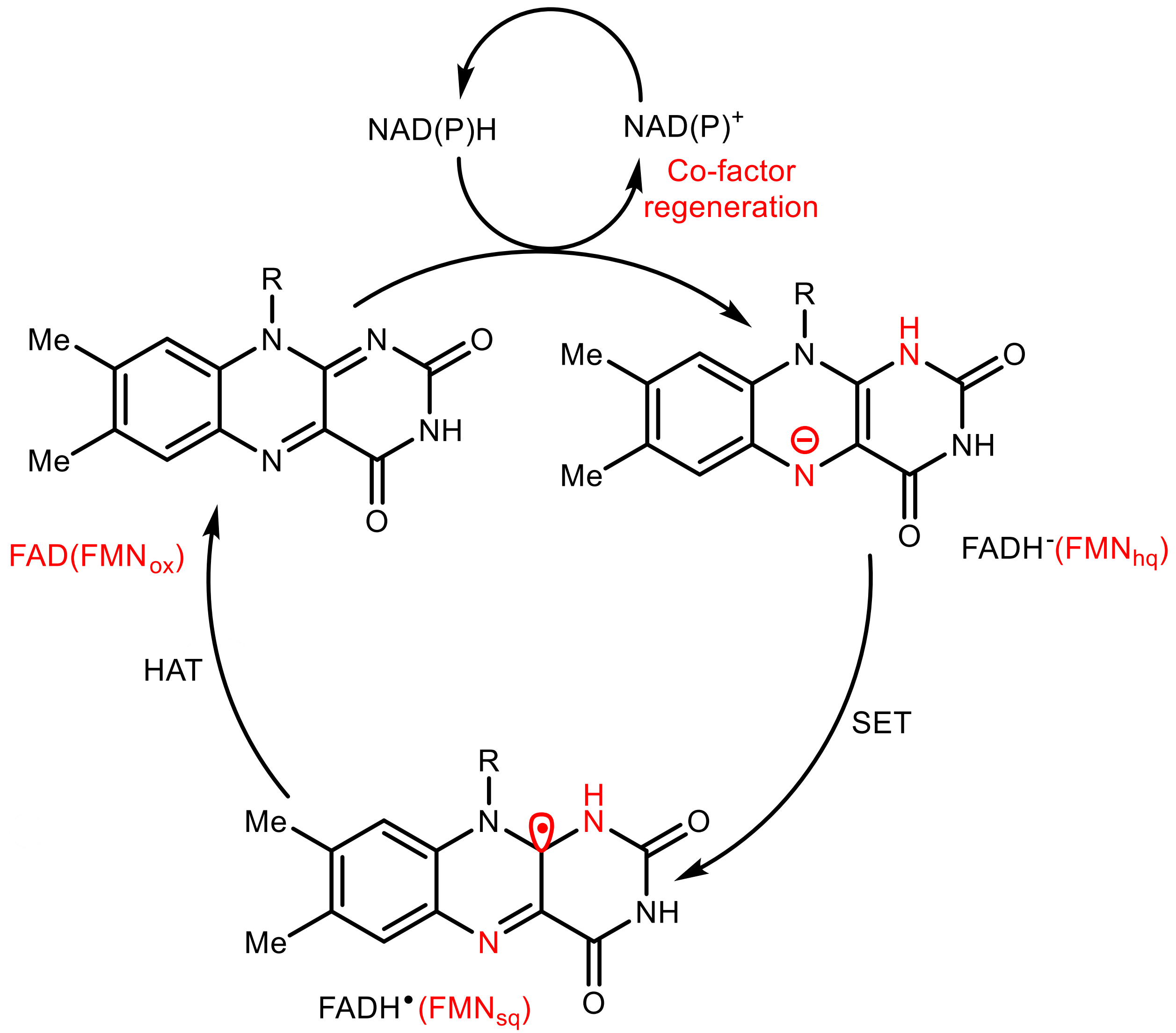
Enzymatic catalysis:
High specificity
High selectivity

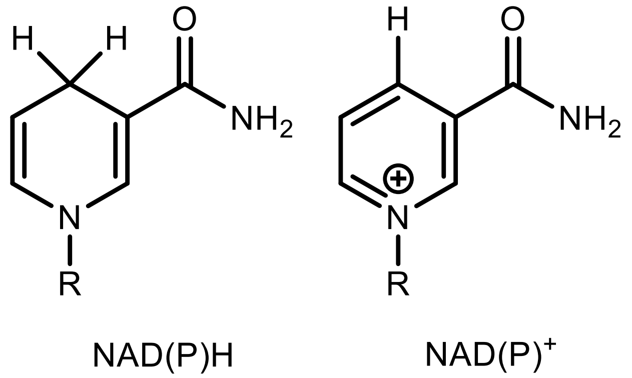
Limited reaction
Narrow substrate scope

Zhao, H. M. et al. *Acc. Chem. Res.* **2022,** *55*, 1087−1096

The enzymes and cofactors

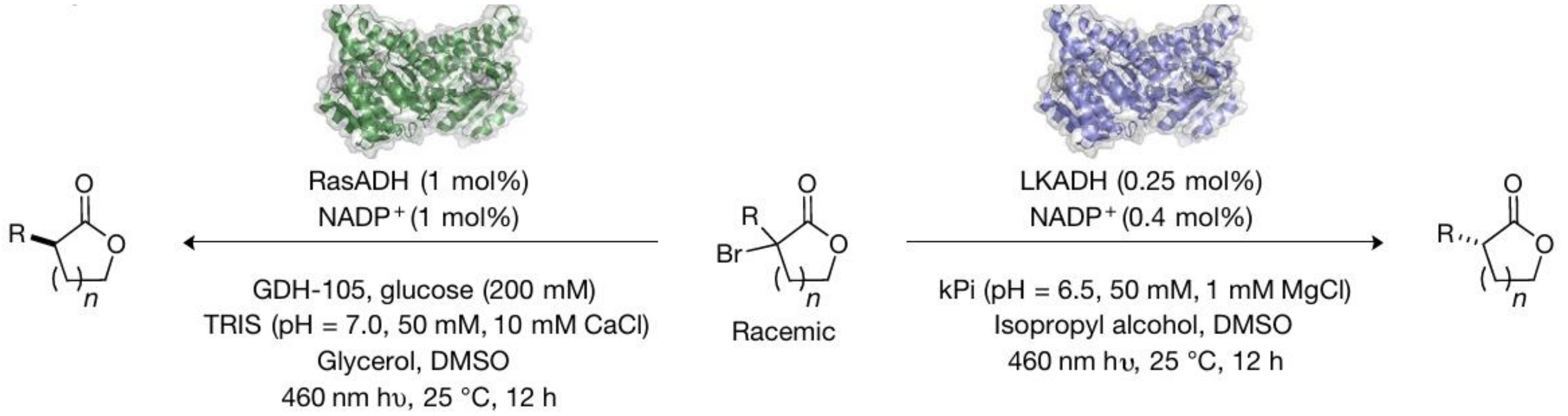
KREDs (Ketoreductases) and EREDs (ene-reductases)

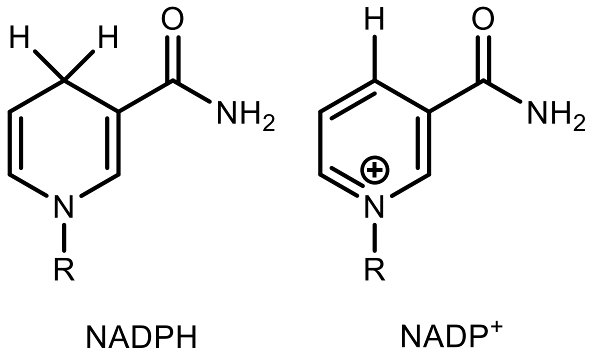




The development of photoenzymatic catalysis

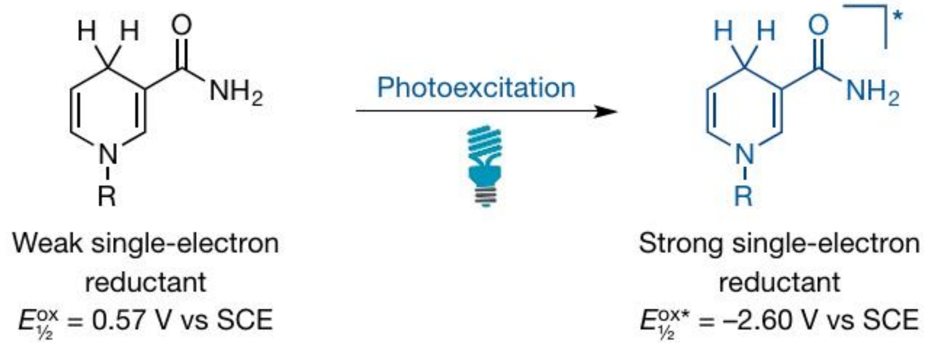
Non-natural reaction of highly enantioselective radical dehalogenation



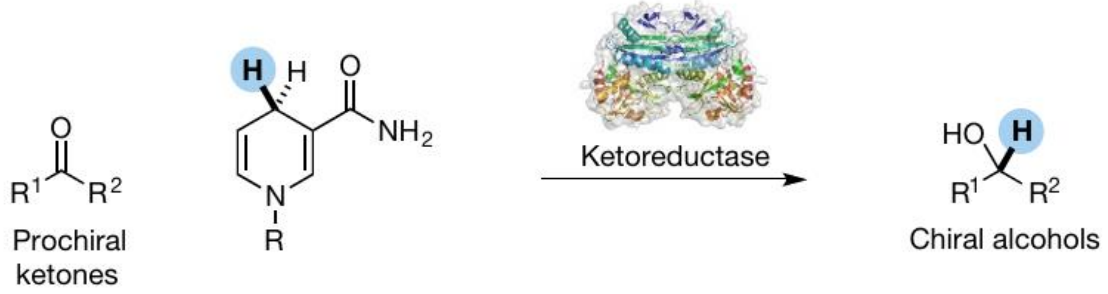


Nicotinamide-dependent ketoreductases (KREDs)

a

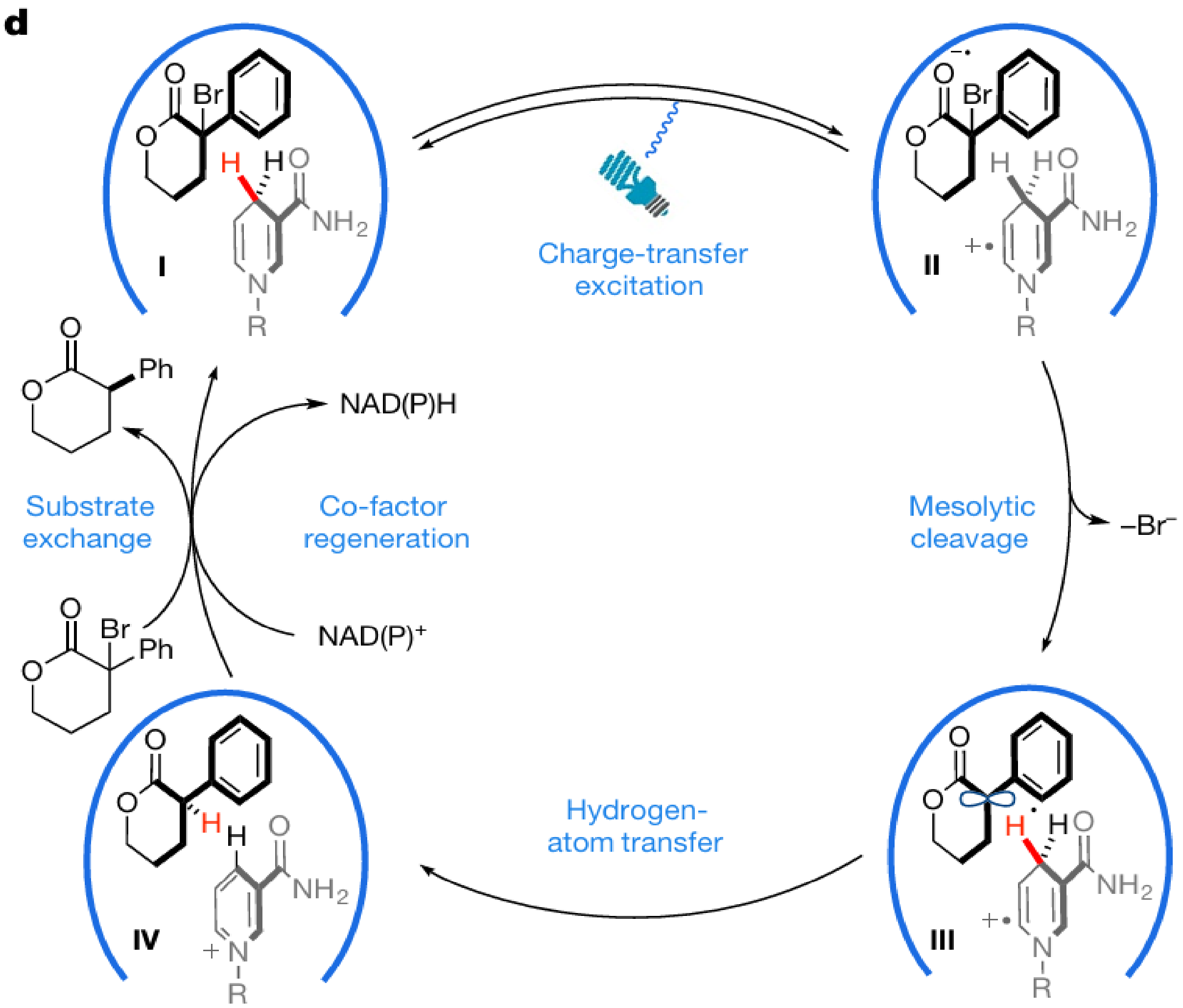


b



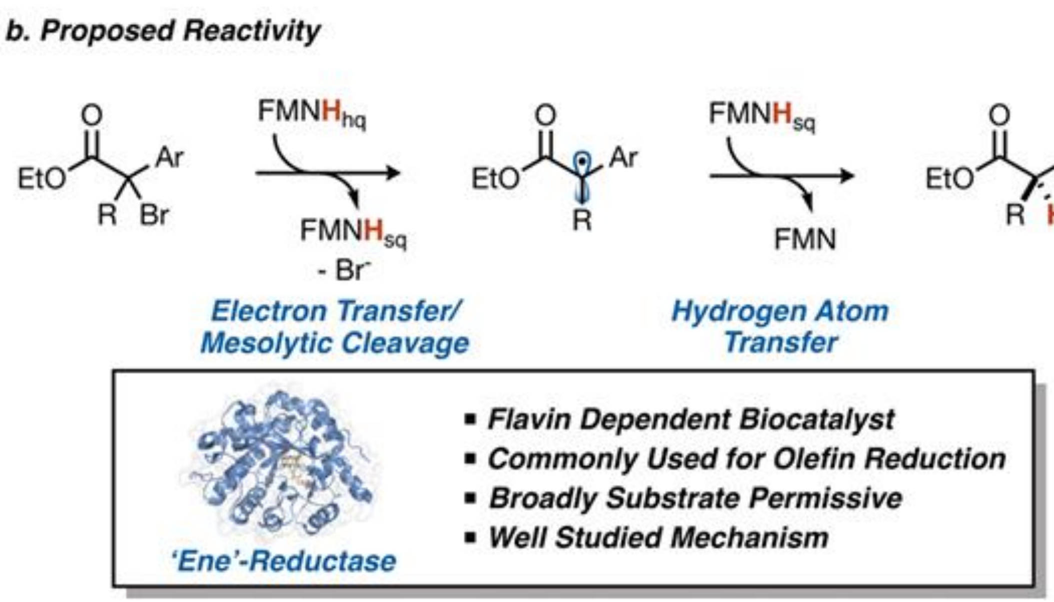
Hyster, T. K. et al. *Nature* **2016**, *540*, 414–417

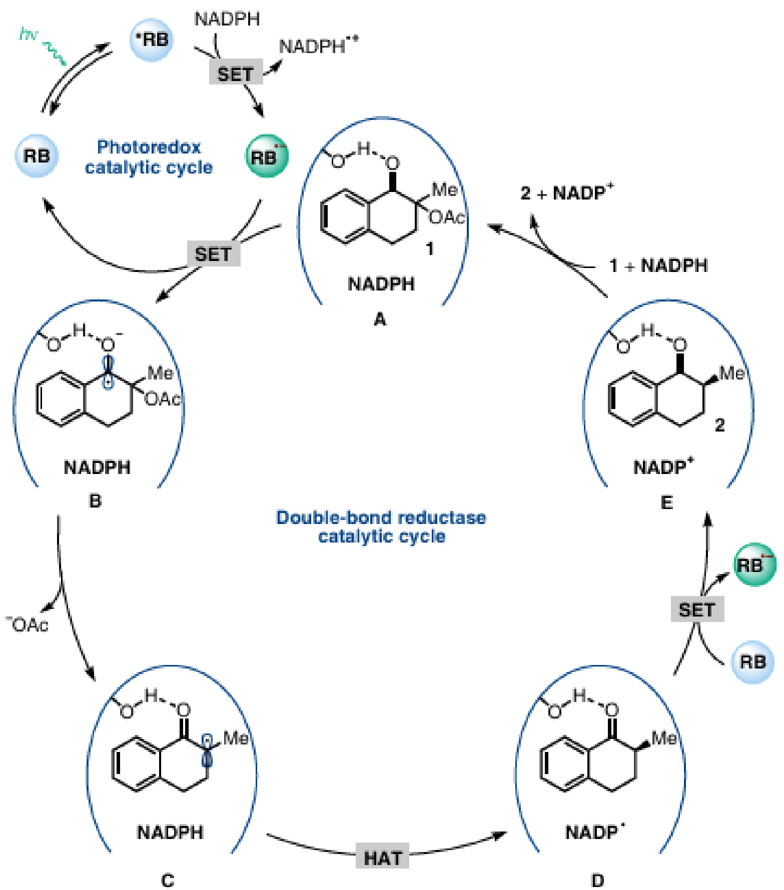
The development of photoenzymatic catalysis



The mechanism of photo-induced enantioselective radical dehalogenation catalyzed by KREDs

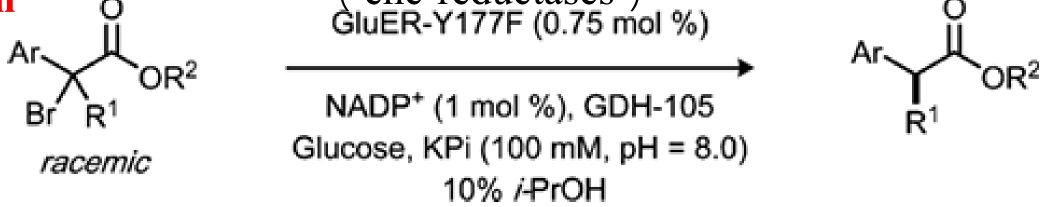
The development of photoenzymatic catalysis



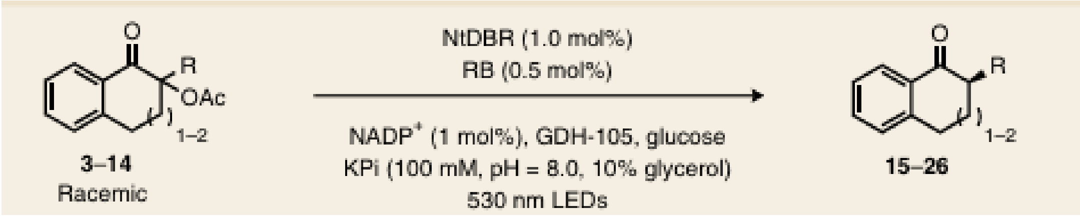


2016
Hyster
KREDs
Dehalogenation

2017
Hyster
EREDs
(ene-reductases)

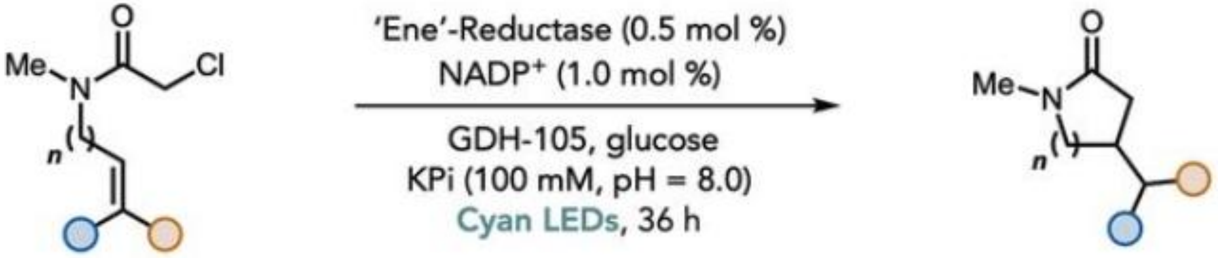


2018
Hyster
DBRs
(Nicotinamide-dependent double-bond reductases)
Decarboxylation



Hyster, T. K. et al. *J. Am. Chem. Soc.* **2017**, *139*, 11313-11316
Hyster, T. K. et al. *Nat. Chem.* **2018**, *10*, 770-775

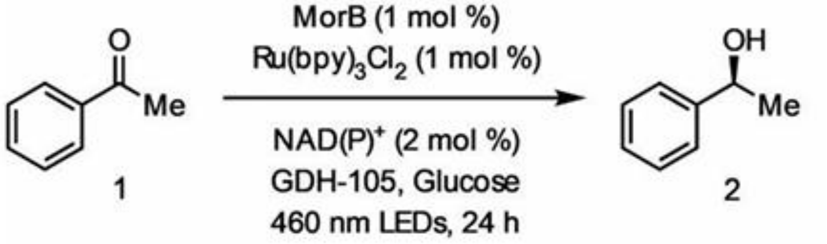
The development of photoenzymatic catalysis



2019
Hyster
FMN-EREDs
Ketone reduction

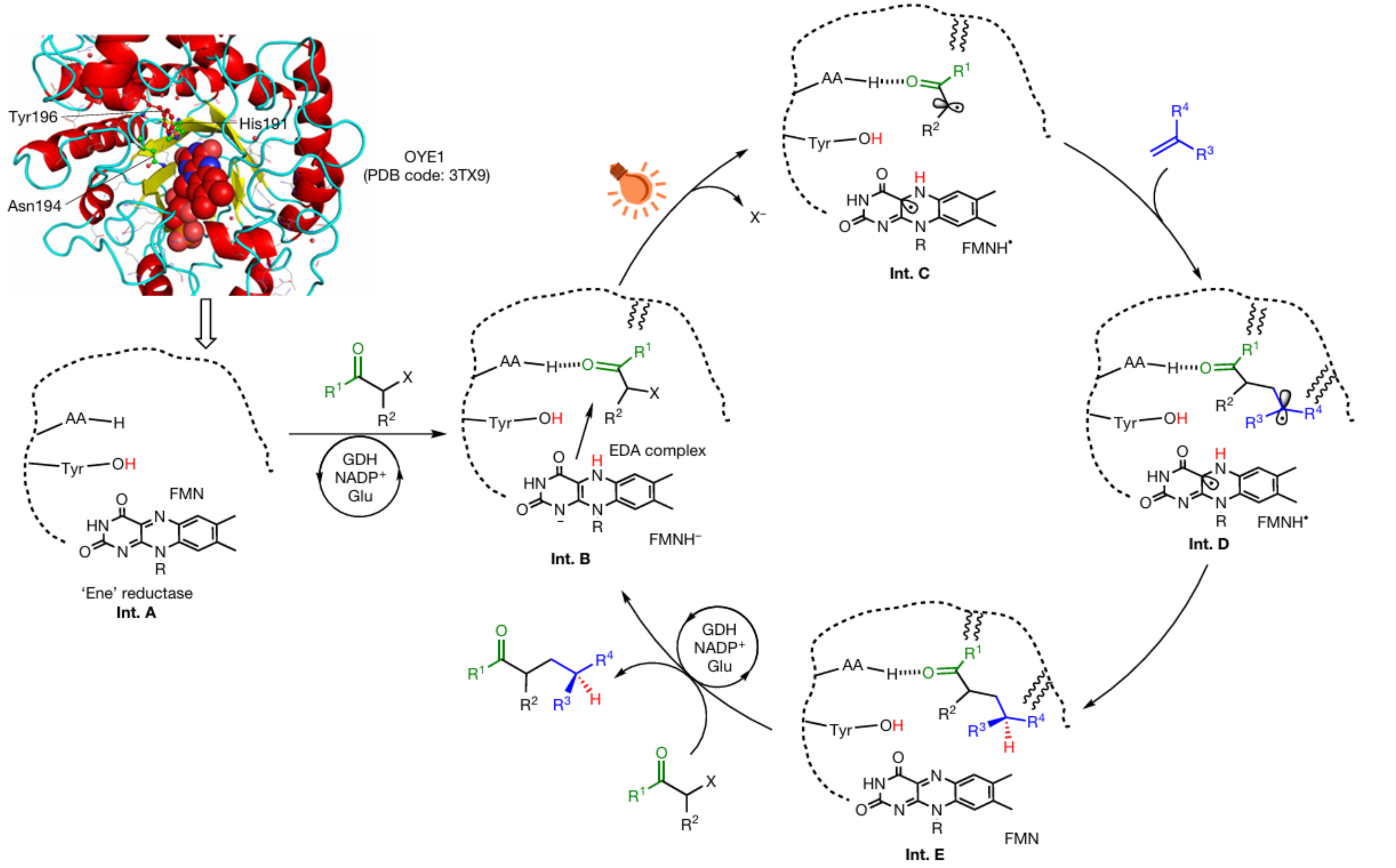
2019
Hyster
EREDs
Radical cyclization

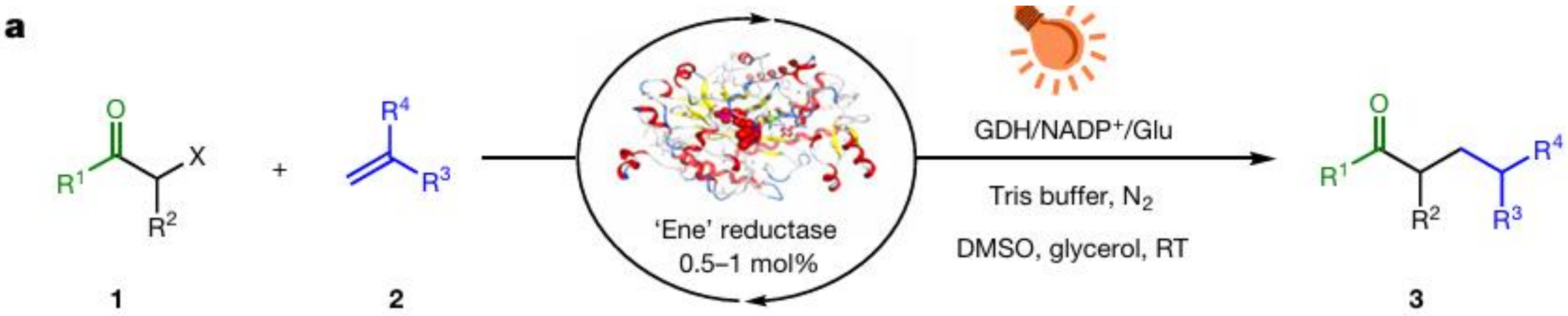
2020
Huimin Zhao
EREDs
Intermolecular radical hydroalkylation



Hyster, T. K. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 8714-8718
Hyster, T. K. et al. *Science*, **2019**, *364* , 1166-1169

T

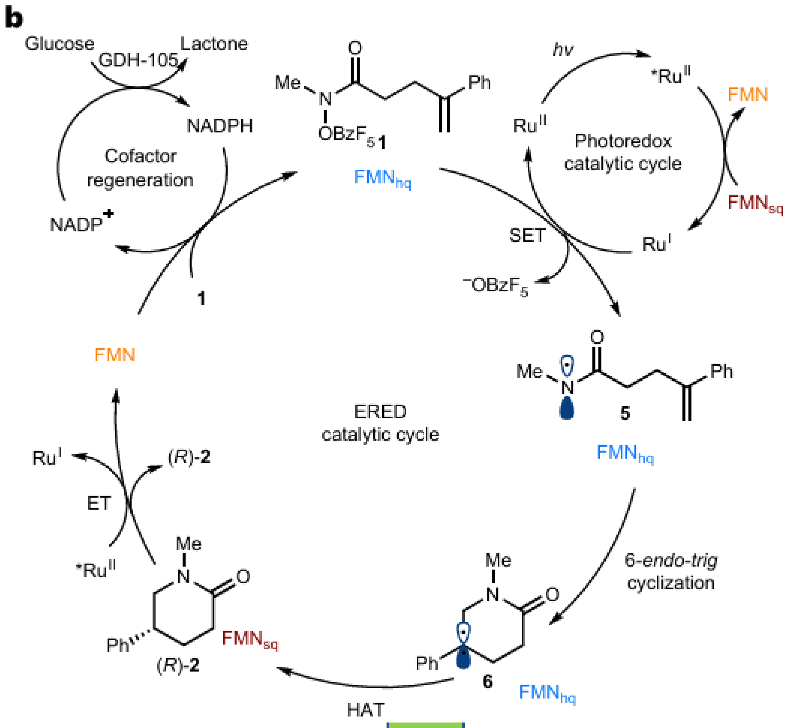


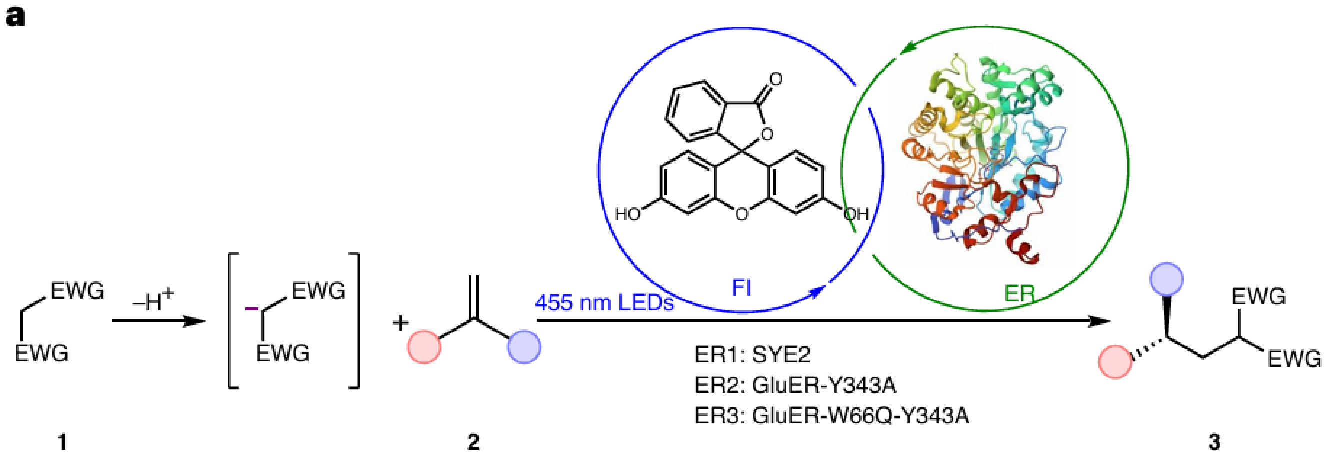


2020
Huimin Zhao
EREDs
Intermolecular radical hydroalkylation

Zhao, H. M. et al. *Nature*, **2020**, *584*, 69-74

The development of photoenzymatic catalysis



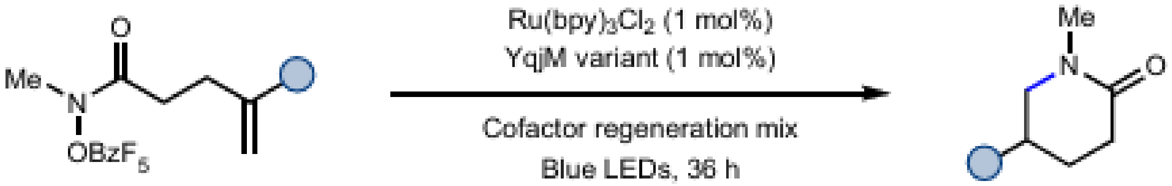


2022
Hyster
EREDs

2025
Yajie Wang
EREDs

C－N bond formation

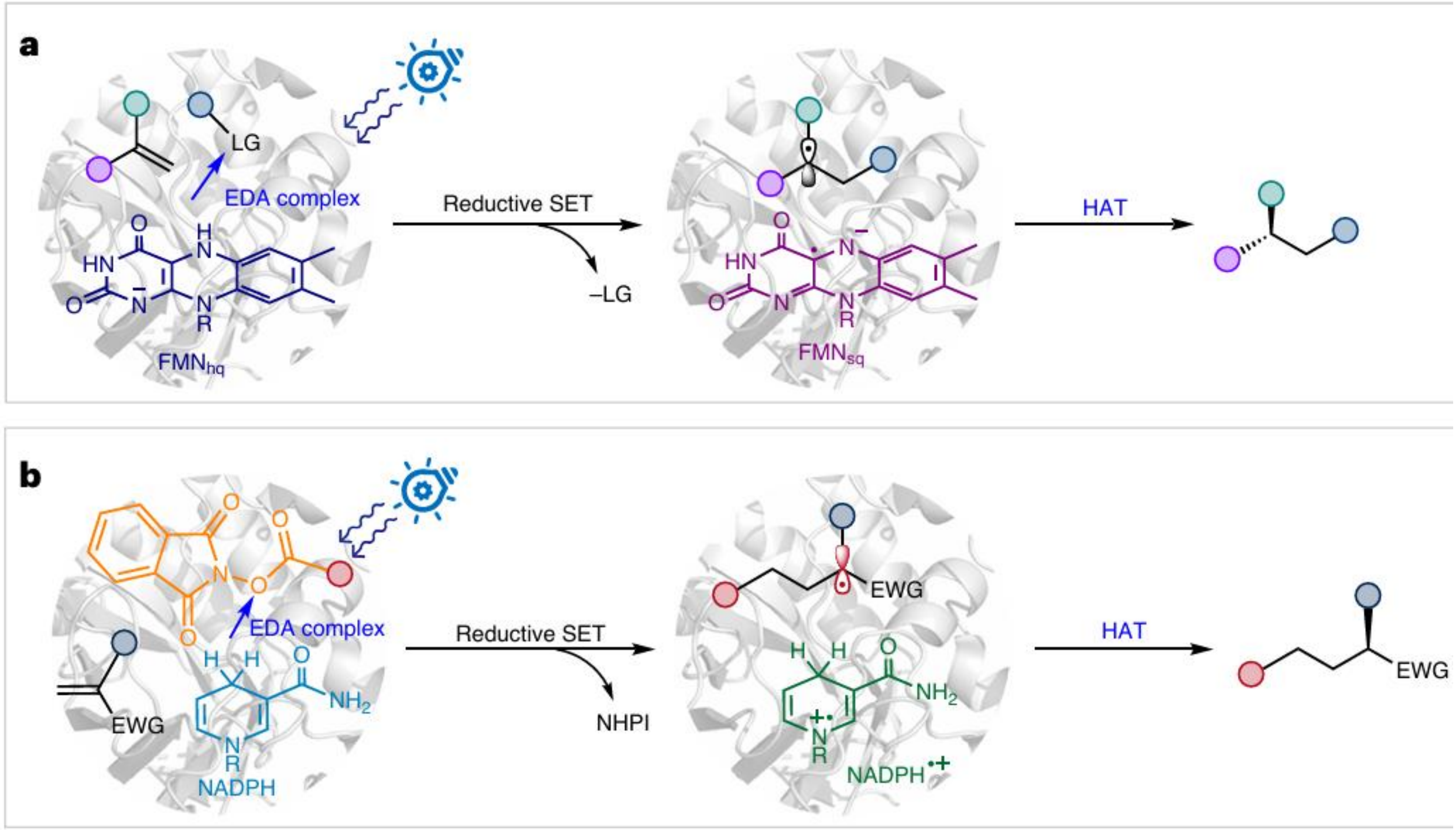
Enantioselective hydrofunctionalization



Hyster, T. K. et al. *Nat. Chem.* **2023**, *15*, 206-212
https://doi.org/10.1038/s41929-025-01434-2

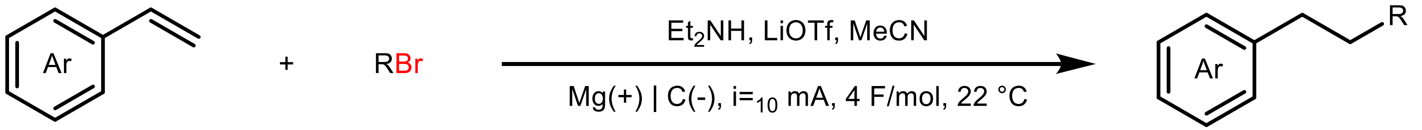
Content

Different photoenzymatic modes for enantioselective hydrofunctionalization

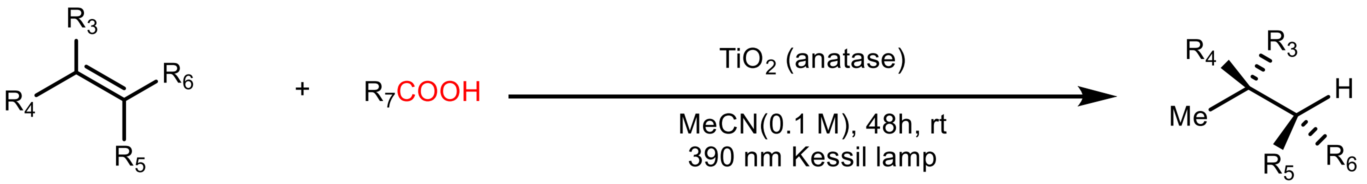


Zhao, H. M. et al. *Nature*, **2020**, *584*, 69-74
Zhao, H. M. et al. *Nat. Catal.* **2022**, *5*, 586-593

Non-enzymatic radical hydroalkylation

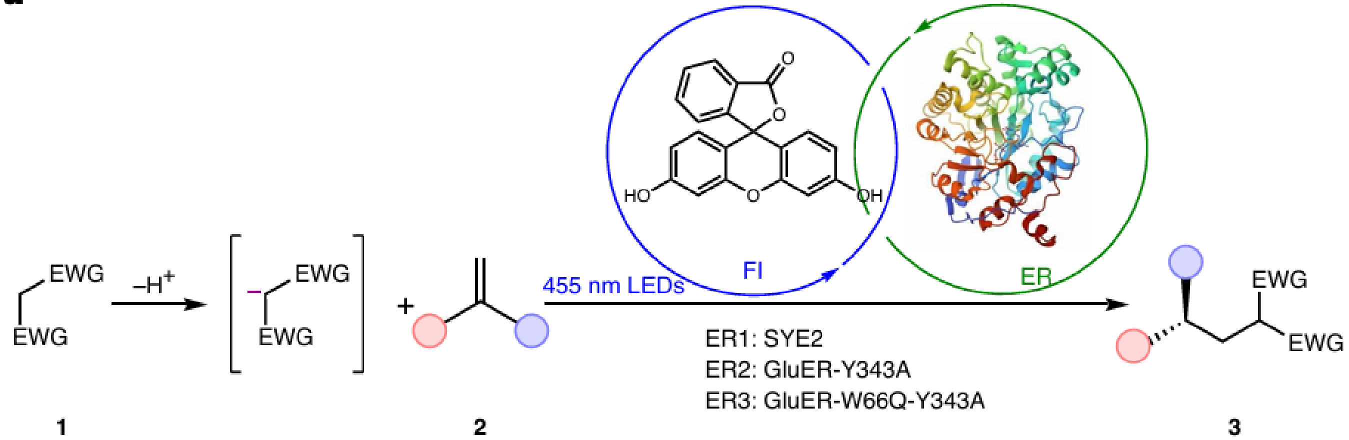


Necessitating presynthesis and atom economy



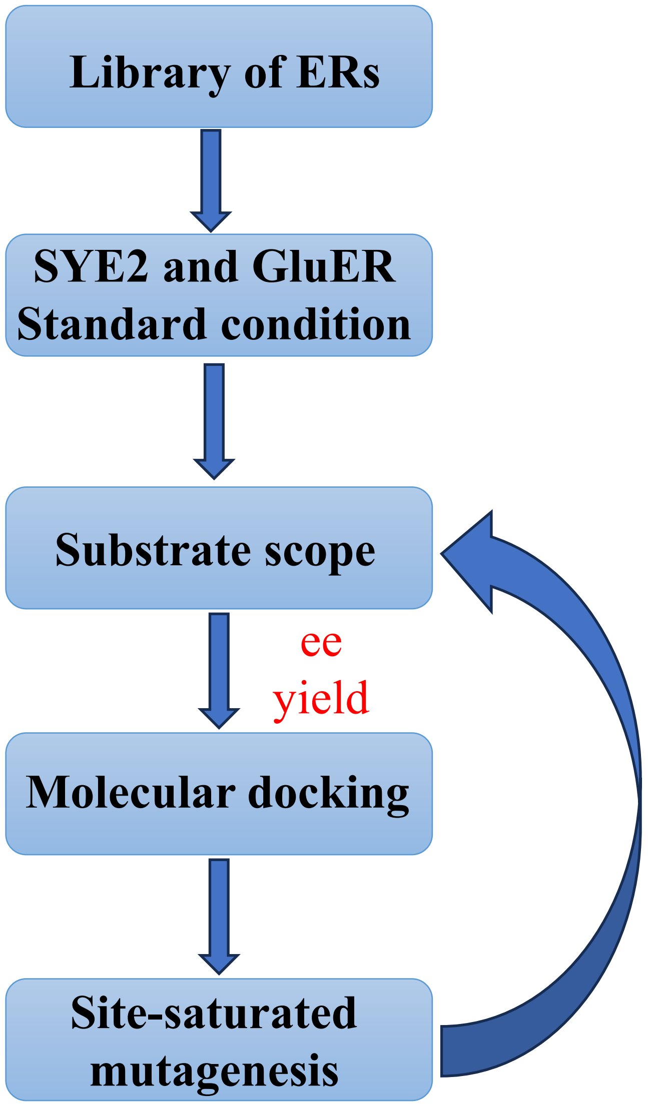
Photoenzymatic catalysis

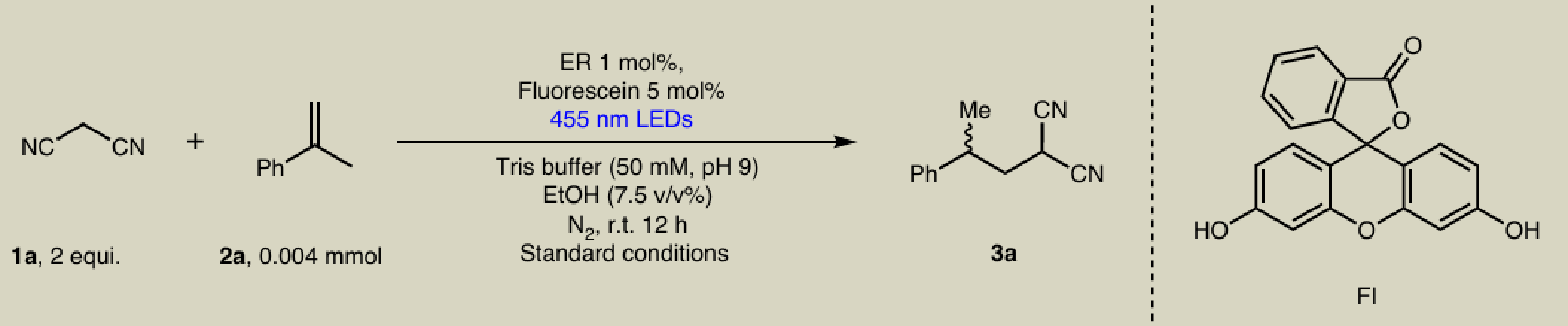
a

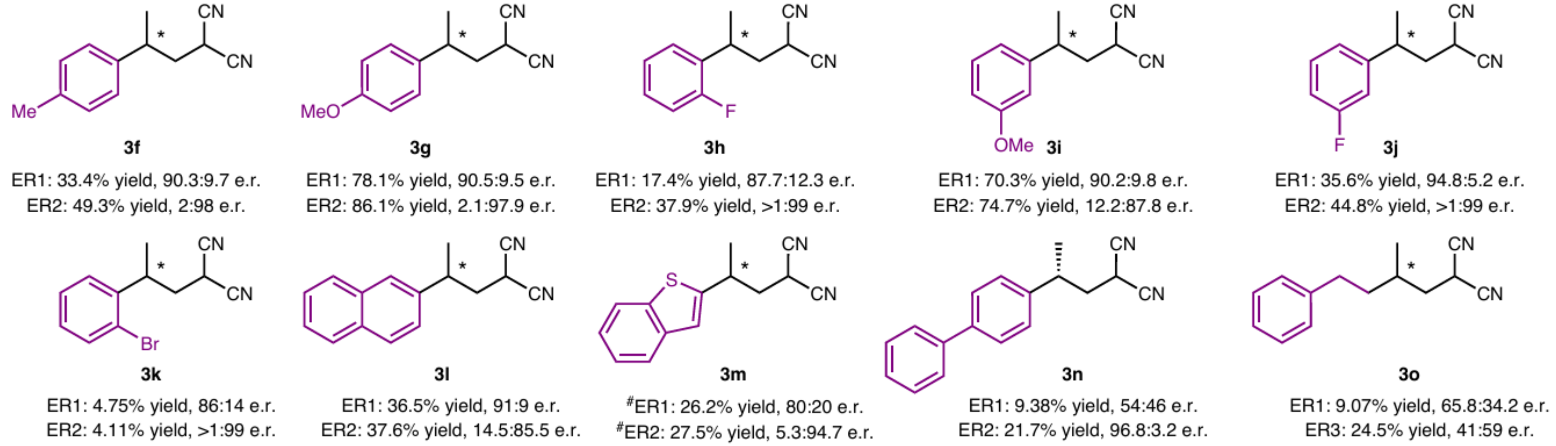


Lin, S. et al. *J. Am. Chem. Soc.* **2020,** *142*, 20661−20670
Nocera, D. G. et al. *J. Am. Chem. Soc.* **2020,** *142*, 17913−17918

Optimization of reaction conditions

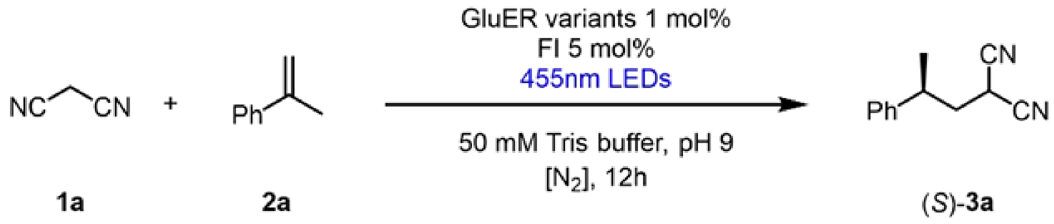


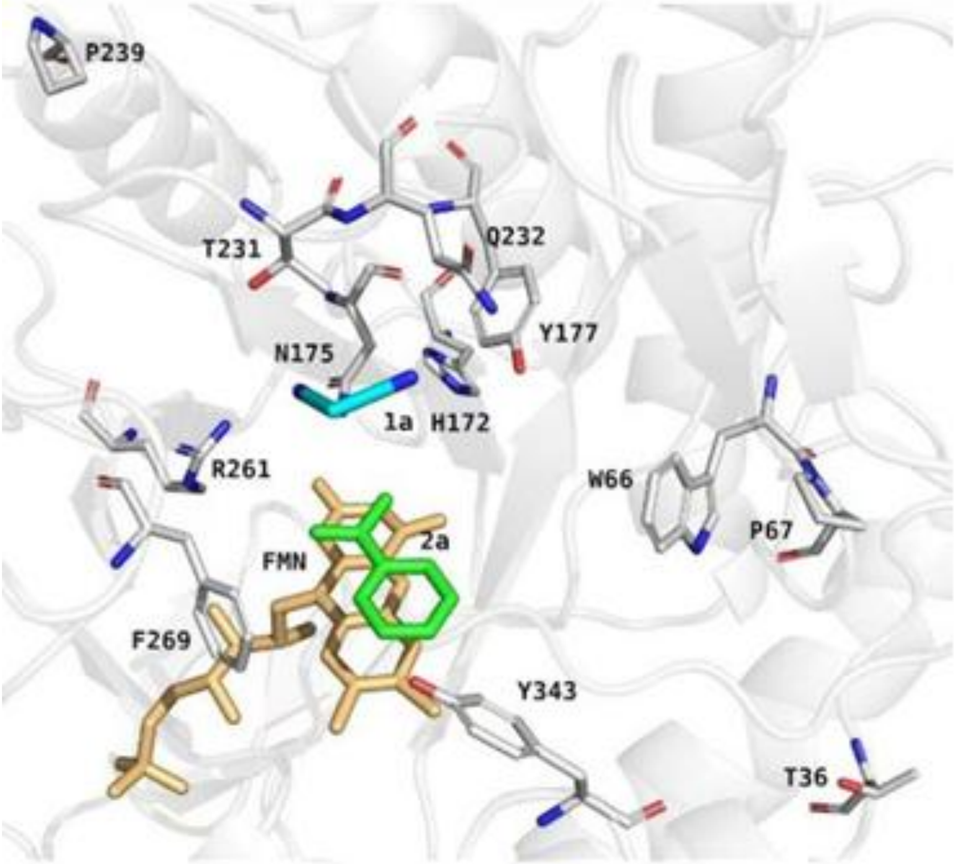




Factor: FI, pH, co-factor regeneration, dark, air, enzyme

Molecular docking of GluER's crystal structure with 1a and 2a





FMN (yellow)
substrates 2a (green)
substrates 1a (cyan and blue)
11 key active-site residues (grey)

From GluER to GluER-Y343A and GluER-W66Q-Y343A

Proposed catalytic cycle

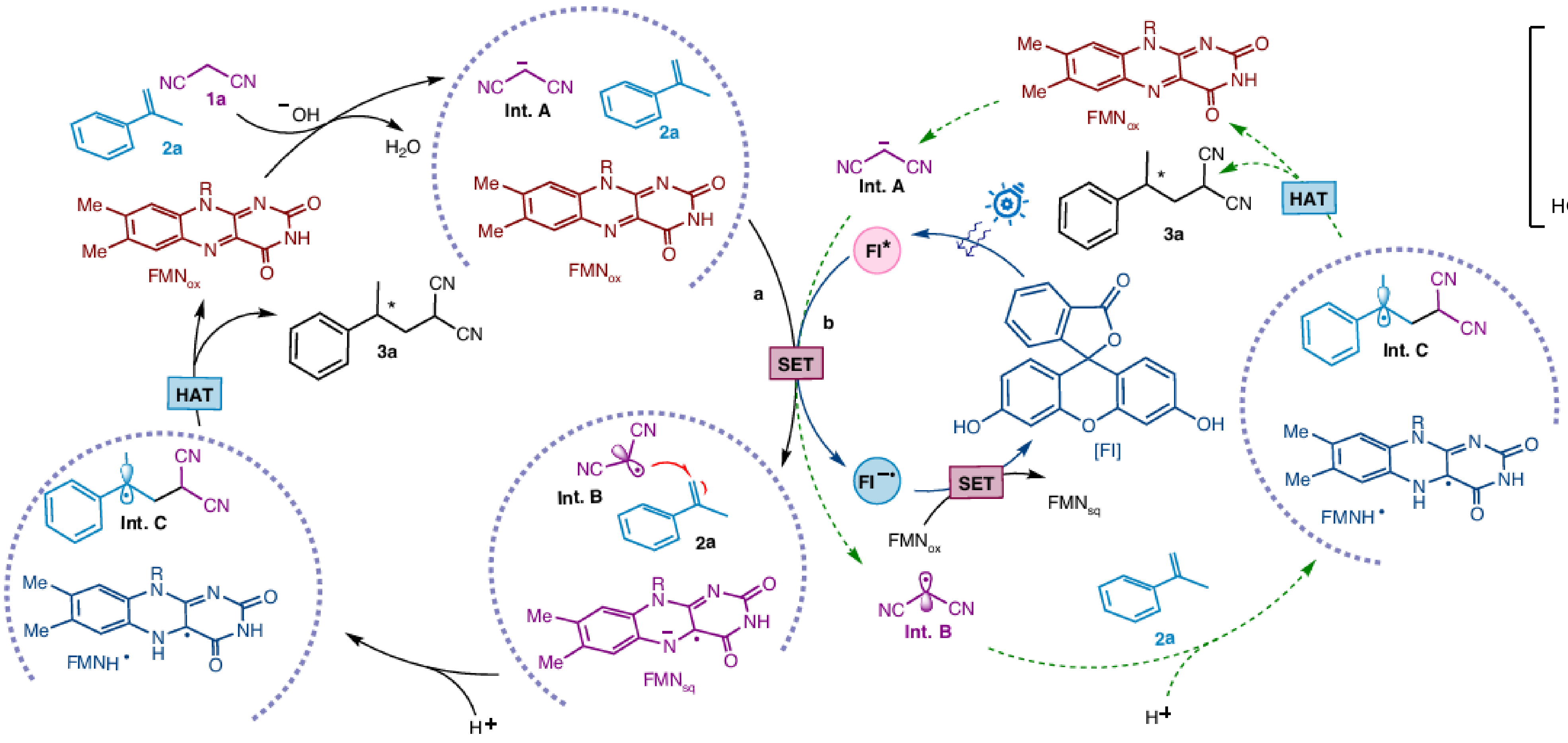
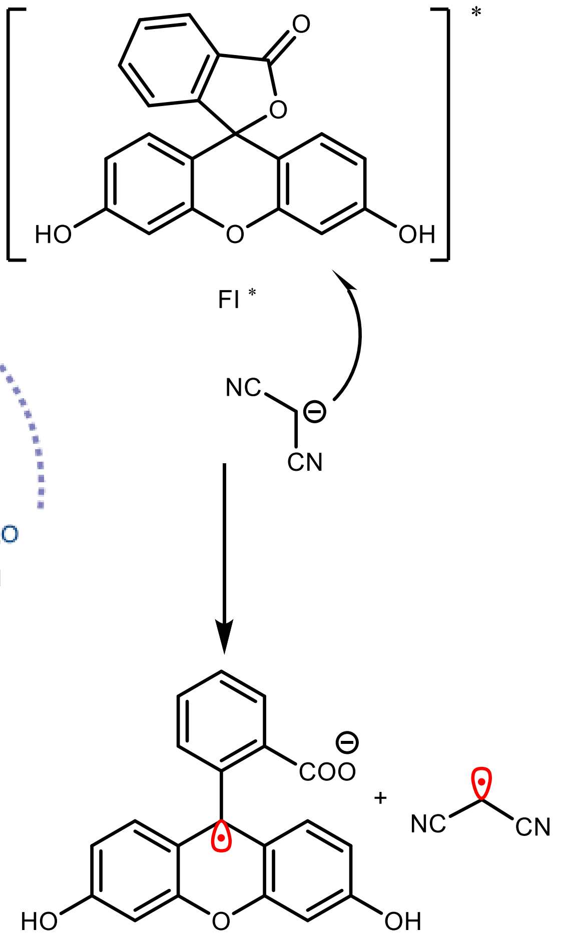
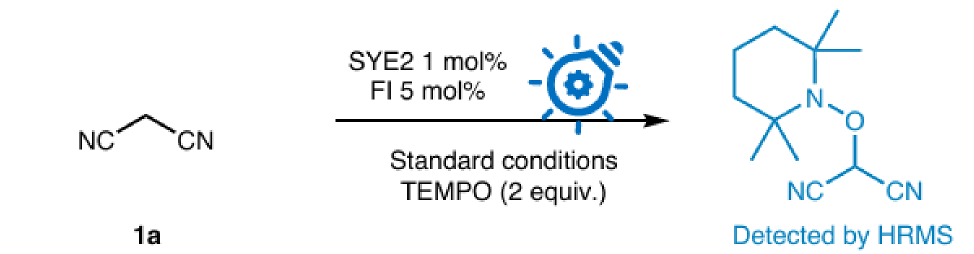
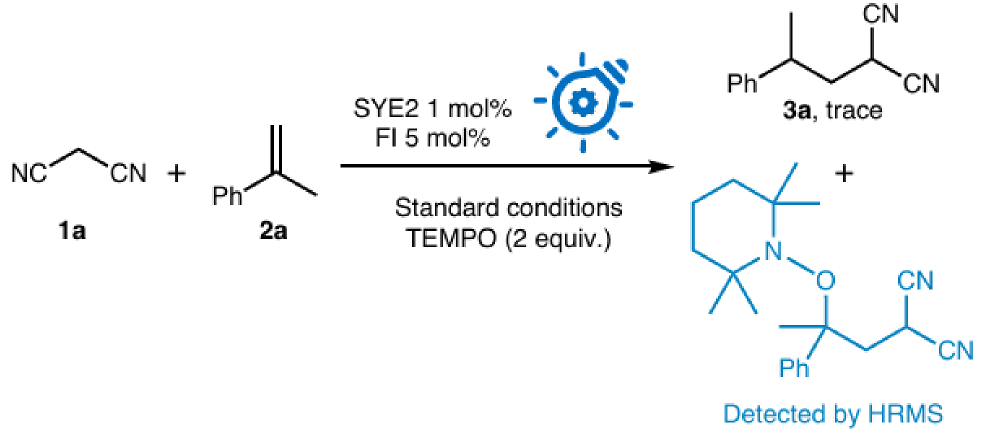


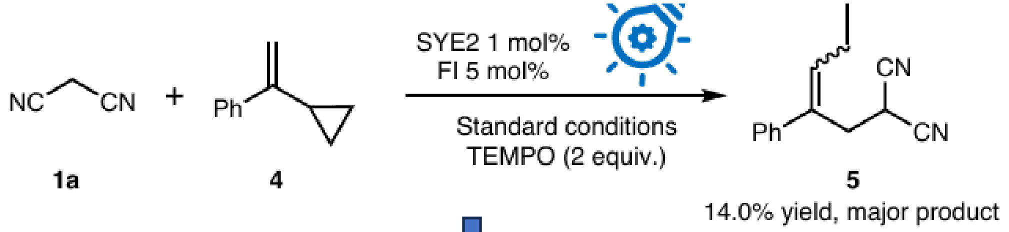
Fig. 3 | Proposed catalytic cycle. Path a (black cycle): SET oxidation of carbanions occurs within enzyme's active site (solid black curve). Path b (green cycle): SET oxidation of carbanions occurs outside the enzyme's active site, with the resulting prochiral radicals **Int. C** diffusing into the active site (dashed green curve).



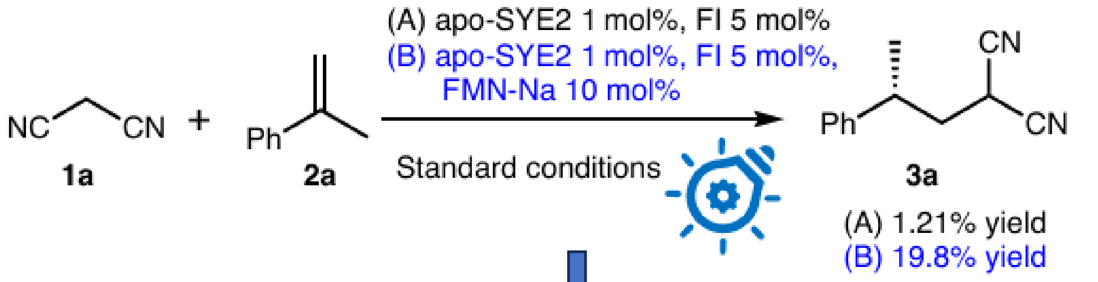
Mechanistic experiments



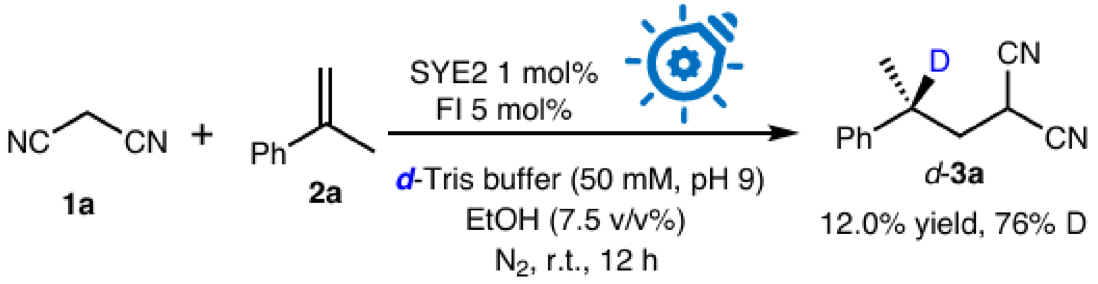




Radical intermediates



The catalytic cycle requires the cooperative action of ER_FMN and FI.



The hydrogen atoms in the HAT process mainly come from FMNH.

Content

Author

Yajie Wang

2021-present Westlake University **Tenure-Track Assistant Professor**

2018-2021 University of Illinois at Urbana-Champaign

Postdoctoral Fellow Advisor: **Huimin Zhao**

2012-2018 University of Illinois at Urbana-Champaign **Ph. D.**

Advisor: **Huimin Zhao**

2008-2012 Nanyang Technological University **B.S.**

Todd K. Hyster

2015-present Princeton University

2021-2023 Cornell University

2013-2015 California Institute of Technology

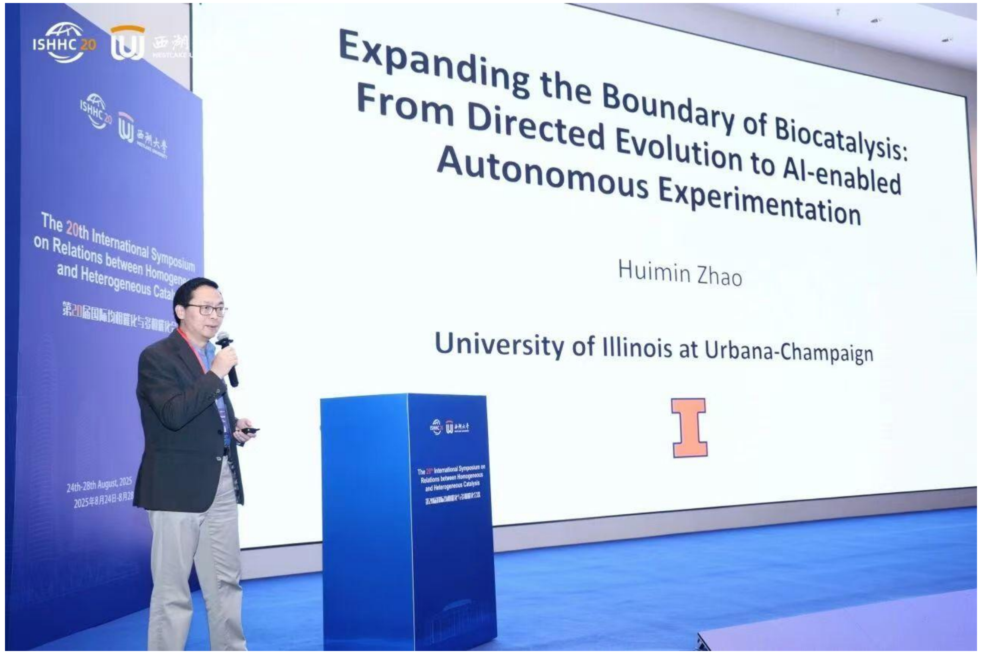
Postdoctoral Fellow Advisor: **Frances Arnold**

2008-2013 Colorado State University

Ph. D. Advisor: Tomislav Rovis

2004-2008 University of Minnesota **B.S.**

Some groups of focusing on photoenzymatic catalysis



Huimin Zhao

2000-present University of Illinois at Urbana-Champaign

1998-2000 Dow Chemical Company

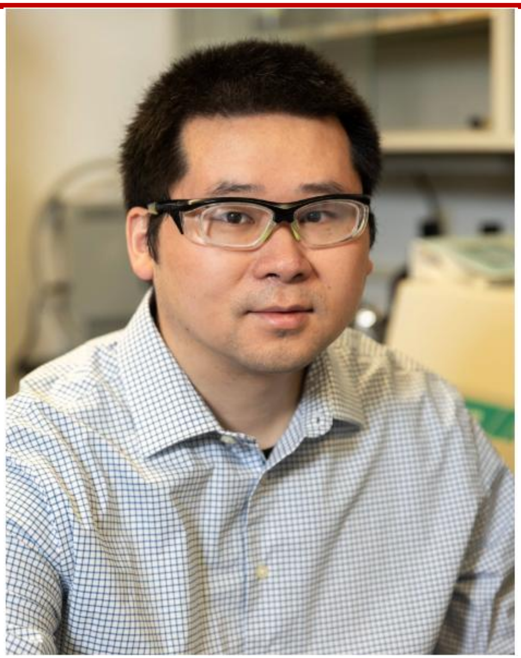
1992-1998 California Institute of Technology **Ph. D.**

Advisor: **Frances Arnold**

1988-1992 University of Science and Technology of China **B.S.**

算法模型 EZSpecitificity，CLEAN

“设计-实验-学习”



Yang Yang

2020-present University of California Santa Barbara

2018-2020 California Institute of Technology

Postdoctoral Fellow Advisor: **Frances Arnold**

2016-2018 University of California, Berkeley

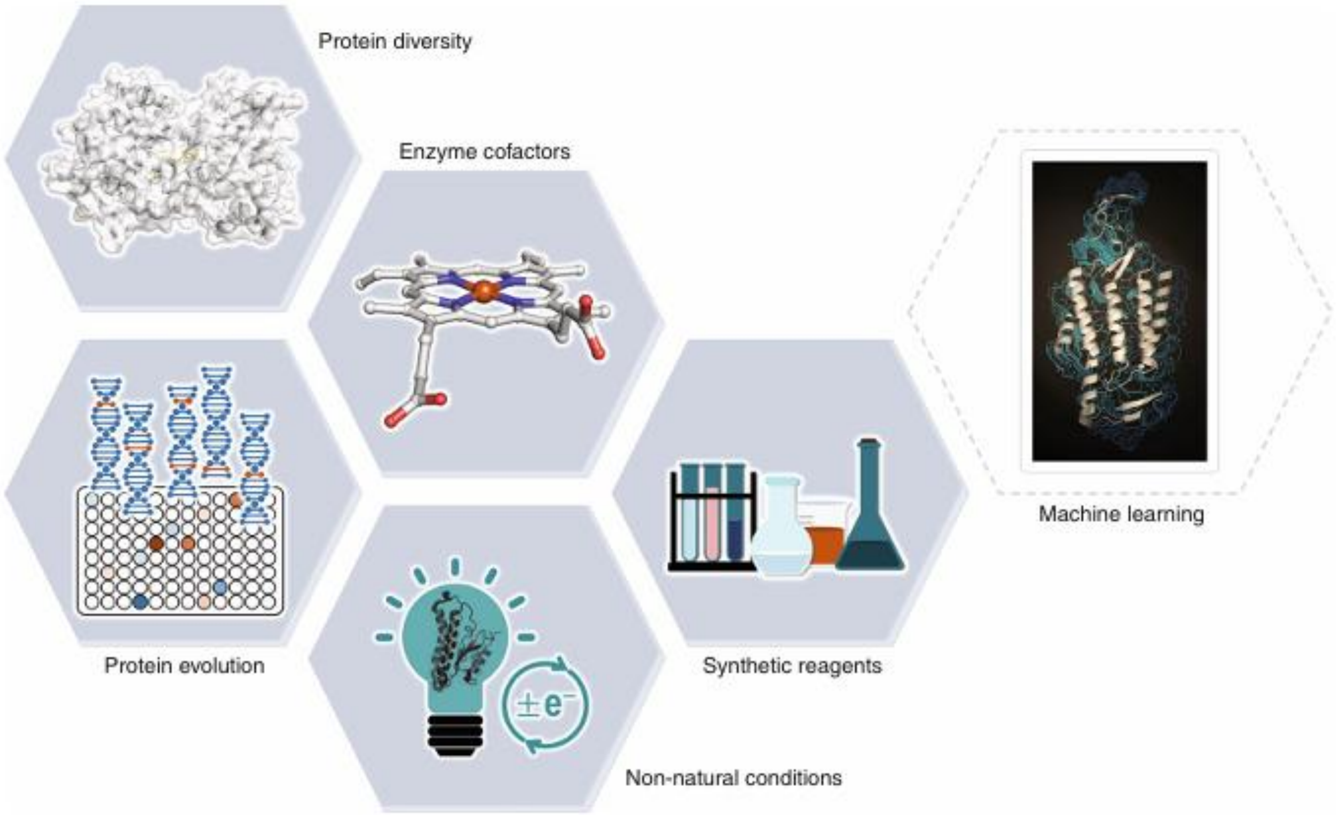
Postdoctoral Fellow Advisor: Jeffrey Long

2011-2016 Massachusetts Institute of Technology

Ph. D. Advisor: Stephen Buchwald

2007-2011 Peking University **B.S.** Advisor: Jianbo Wang

The limitation of photoenzymatic catalysis



1. The radical reactions in the enzyme cavity are restricted by many factors.
2. The reported naturally available photosensitive cofactors, such as NAD(P)H and types of FMN/FAD, are limited in variety.
3. For the vast majority of photolyase reactions, their turnover number (TON) is low and the substrate scale is low.
4. There are no standardized protocols, so it is difficult to reproduce the data.
5. Mechanism……

吴起 光酶催化混乱性反应的研究进展. **2024** , *5*, 997-1020

Arnold, F.H. et al. *Nat. Catal.* **2020**, *3*, 203-213

PEKING UNIVERSITY

敬请批评指正！