# Frontiers in Chemical Synthesis:

# Data-Driven Tools in Asymmetric Catalysis


Lara Lavrencic

PhD student at LSCI


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École
polytechnique
fédérale
de Lausanne

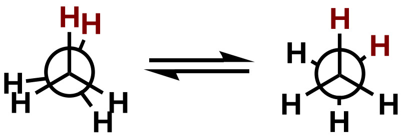
# Presentation Outline

1. Introduction
2. Origin of LFERs in Physical-Organic Chemistry
3. Early Examples of LFERs in Asymmetric Catalysis
4. MLR in Asymmetric Catalysis:
   - for Ligand Optimization
   - for Scope Expansion
5. Statistical Modelling for Reaction Prediction
6. Conclusions and Outlook

# Enantioselectivity Prediction in Asymmetric Catalysis

"Since achieving 95% *ee* only involves energy differences of about 2 kcal/mol, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that [...] one can predict what kind of ligand structures will be effective". - W. Knowles

***cca*. 2.9 kcal/mol**



| ***ee* in %** | **$\Delta\Delta G^{\ddagger}$ in kcal/mol** |
|---|---|
| 20 | 0.22 |
| 60 | 0.81 |
| 90 | 1.72 |
| 99 | 2.73 |
| 99 | 1.80 |

at -78 ℃

**Motivation behind non-empirical tools:**

- quantitative guidelines
- better pattern recognition
- faster broader applicability

**Transition-state based optimization:**

- QM
- Q2MM

**Data-driven optimization:**

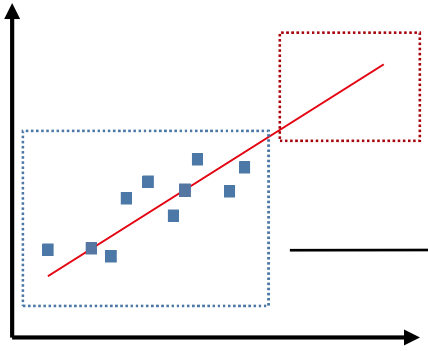
- **LFER**
- **MLR**
- PLR
- machine learning

M. S. Sigman, *Nature Chem*. **4**, 366–374 (2012); Brethomé, A., 2019, A Physical-Organic Approach to Asymmetric Catalysis: Design and Synthesis of Chiral Ligands using Multivariate Modelling, PhD thesis, University of Oxford, Oxford.

# LFERs in Asymmetric Catalysis

**Catalyst / substrate properties:**
- **steric parameters**
- **electronic parameters**

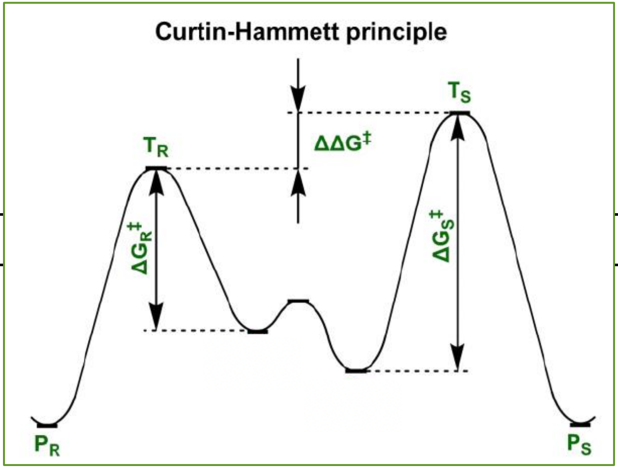
**Corresponding reaction outcome:**
- ***ee***
- **yield, regioselectivity …**



**Prediction of new catalysts**

**Mechanistic elucidation**

$$\Delta G^{\ddagger} = -RT\ \ln(kre_l)$$




$$ee = \frac{|R - S|}{R + S}$$

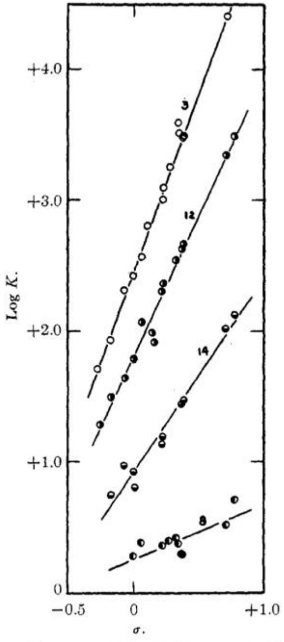
$$ee = \frac{1 - e^{\frac{-\Delta\Delta G^{\ddagger}}{RT}}}{e^{\frac{-\Delta\Delta G^{\ddagger}}{RT}} + 1}$$

M. S. Sigman, *Nature Chem*. **4**, 366–374 (2012); Brethomé, A., 2019, A Physical-Organic Approach to Asymmetric Catalysis: Design and Synthesis of Chiral Ligands using Multivariate Modelling, PhD thesis, University of Oxford, Oxford.

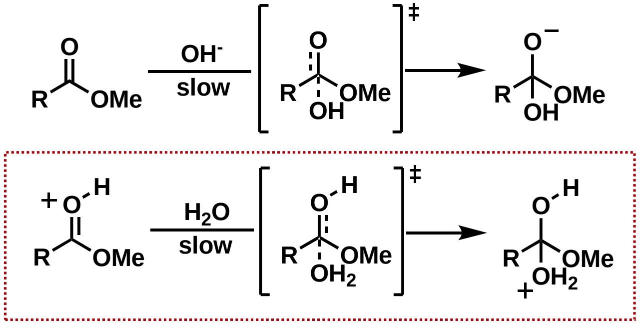
# LFERs: Hammett, Taft, Charton, …

## L. P. Hammett

$$\log\left(\frac{k}{k_H}\right) = \rho\left(pK_{a(H)} - pK_a\right) = \rho \cdot \sigma$$




## R.W. Taft, Jr.




$$\log\left(\frac{k}{k_{CH_3}}\right) = \rho^* \cdot \sigma^* + \delta \cdot E_S$$

## M. Charton

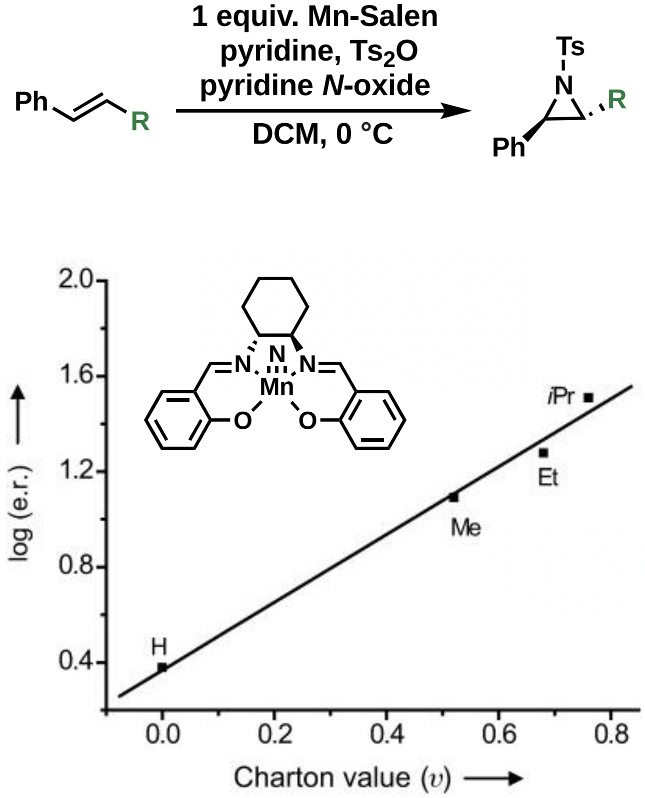
$$\log\left(\frac{k}{k_0}\right) = \psi \cdot \upsilon$$

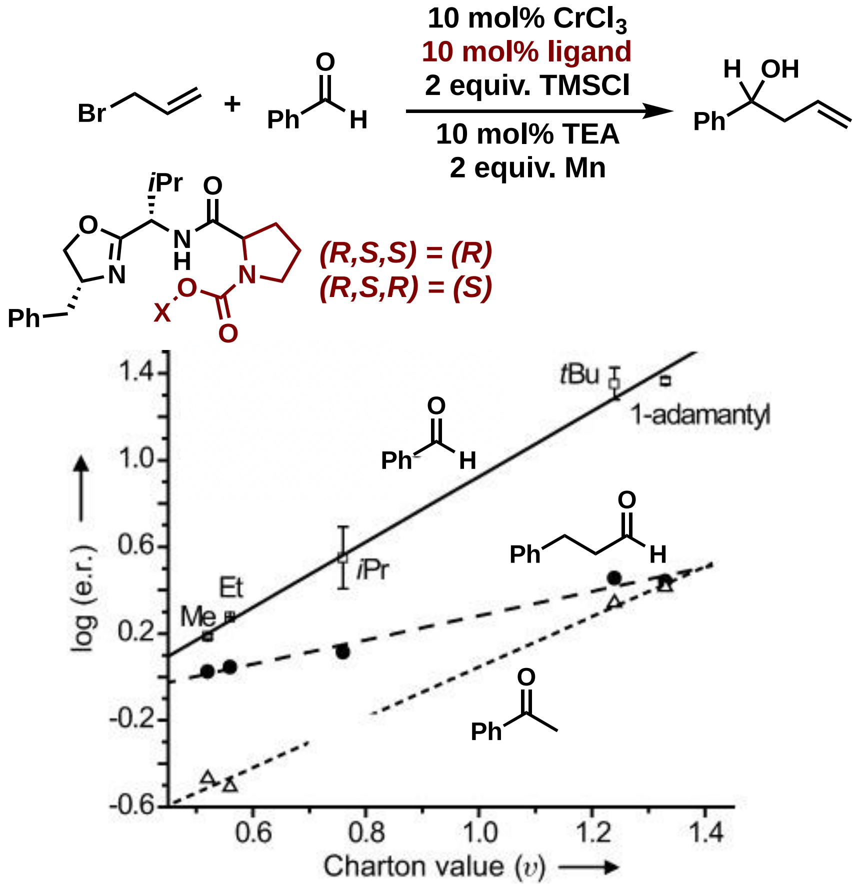
**Adjusted $E_S$ value**

| -R | - $E_S$ | $\upsilon$ |
|---|---|---|
| H | - 1.24 | 0 |
| Me | 0 | 0.52 |
| *t*Bu | 1.54 | 1.24 |
| Bn | 0.38 | 0.7 |
| $CEt_3$ | - | 2.38 |

- L. P. Hammett, *J. Am. Chem. Soc.* **59**, 96–103 (1937); M. Charton, *J. Am. Chem. Soc.* **91**, 615–618 (1969), M. S. Sigman, *Nature Chem*. **4**, 366–374 (2012).

# LFERs in Asymmetric Catalysis

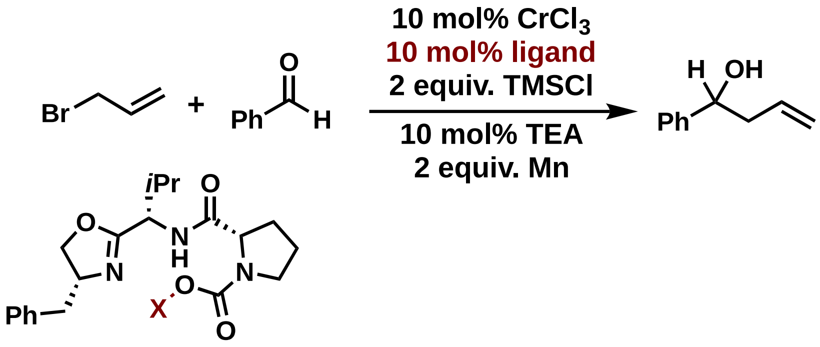


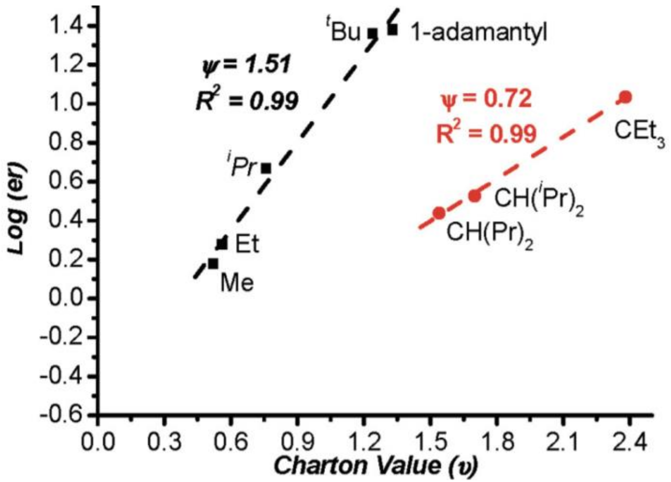



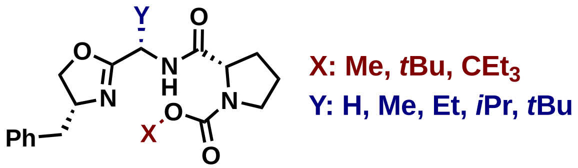

M. S. Sigman, *Angew. Chem.* **120**, 783–786 (2008); J. J. Miller, *J. Org. Chem.* **74**, 7633–7643 (2009).

# Breaks in Linearity

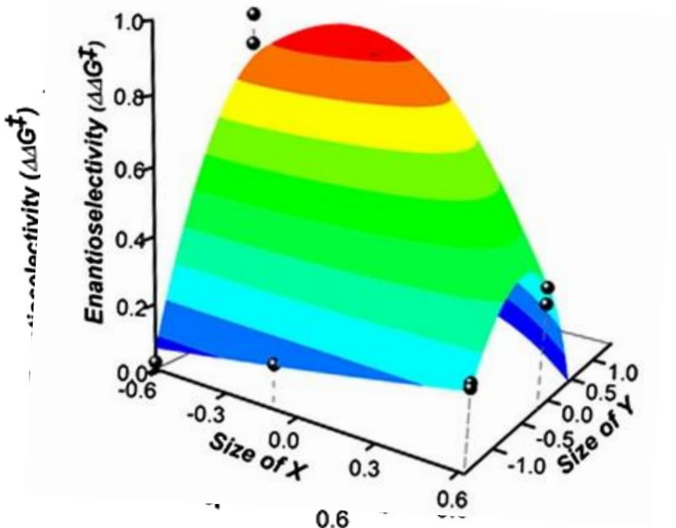




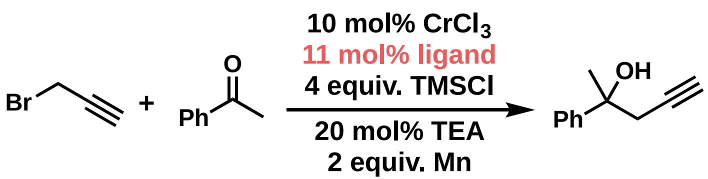

$$\Delta\Delta G^{\ddagger} = z0 + aX + bY + cX^2 + dY^2 + fXY + gX^3 + hY^3 + iXY^2 + jYX^2$$

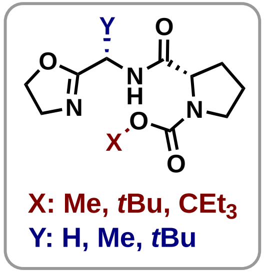


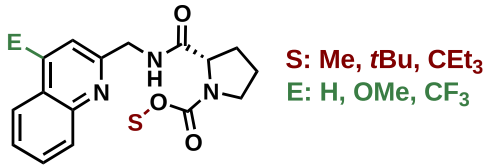

$$\Delta\Delta G^{\ddagger} = 0.895 - 0.489X - 0.813X^2 - 0.361Y^2 - 0.422YX - 0.571YX^2$$

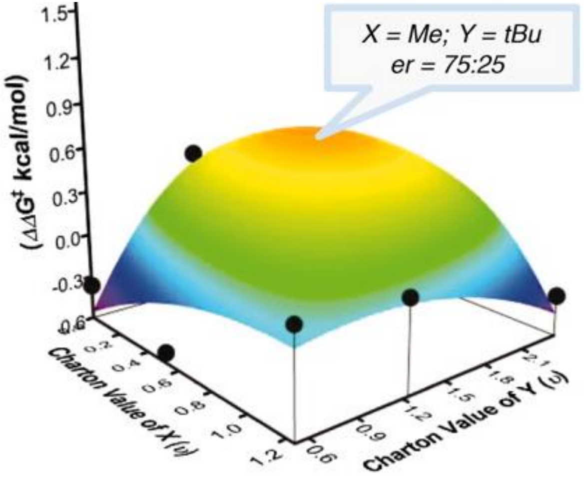
M. S. Sigman, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 2179–2183 (2011); M. S. Sigman, *Science*. **333**, 1875–1878 (2011).

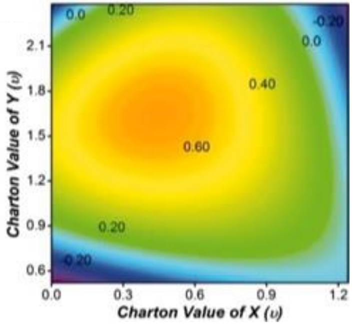
# Application in Ligand Optimization

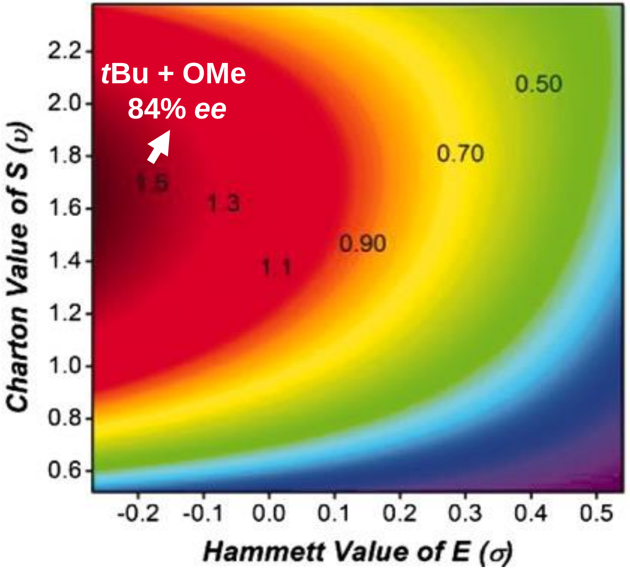


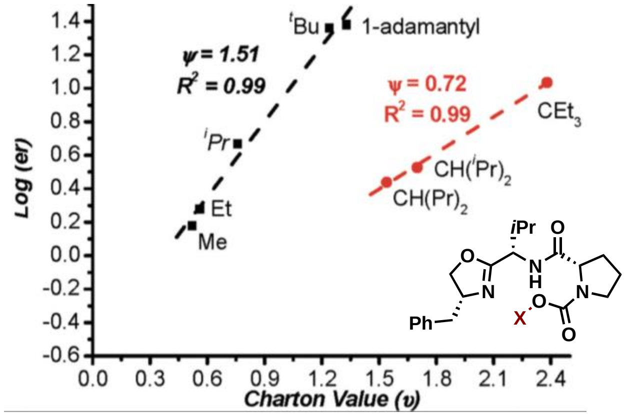



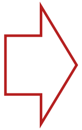



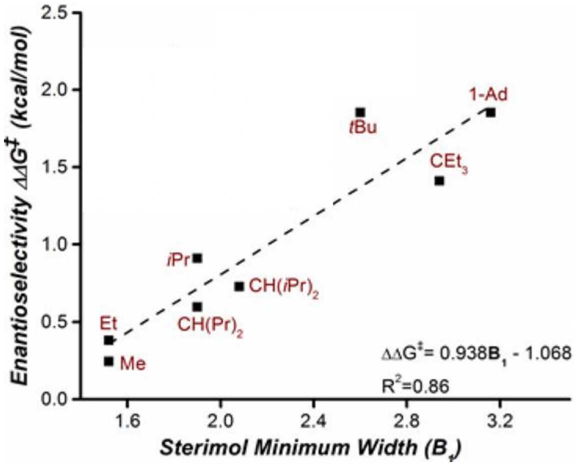

$$\Delta\Delta G^{\ddagger} = -1.2 + 1.22\,E + 2.84\,S - 0.85\,S^2 - 3.79\,ES + 1.25\,ES^2$$

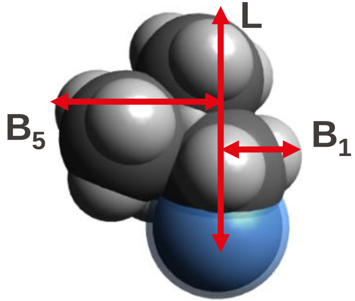
M. S. Sigman, *Science*. **333**, 1875–1878 (2011); A. Milo, *Acc. Chem. Res.* **49**, 1292–1301 (2016).

# Just a Descriptor Problem?

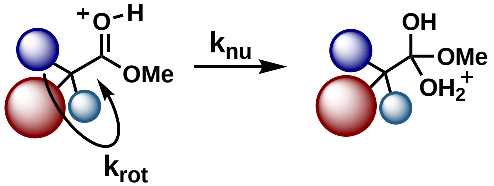


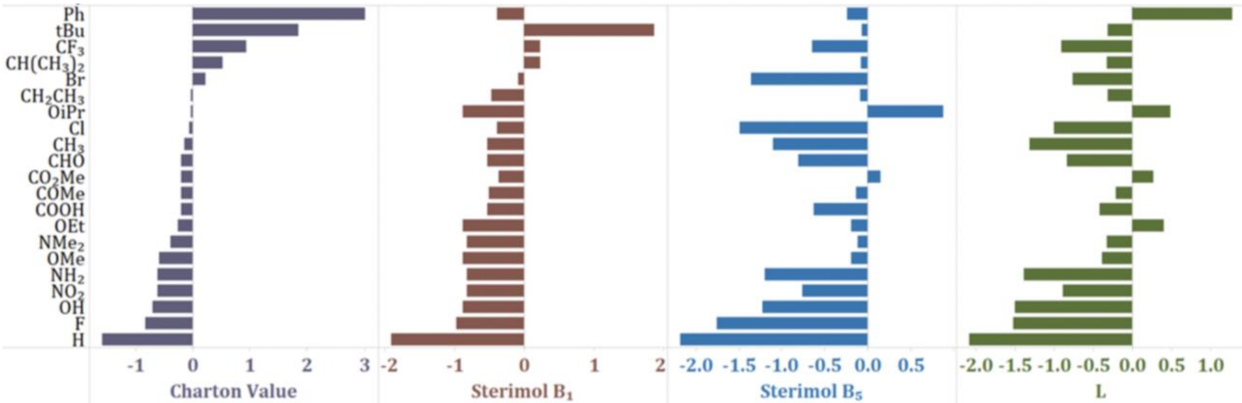





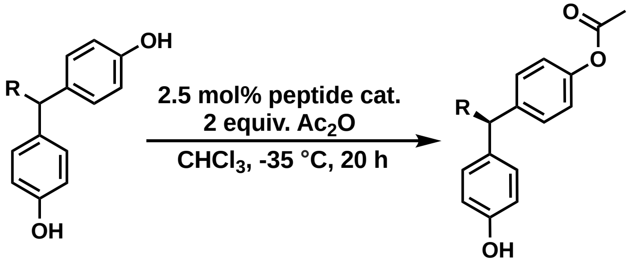

-$CH_2$-*t*Bu group



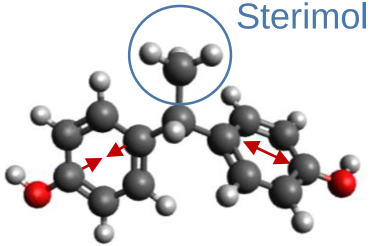




A. Milo, *Acc. Chem. Res.* **49**, 1292–1301 (2016); M. S. Sigman, *Nature Chem*. **4**, 366–374 (2012).

# Other Computationally-Derived Descriptors

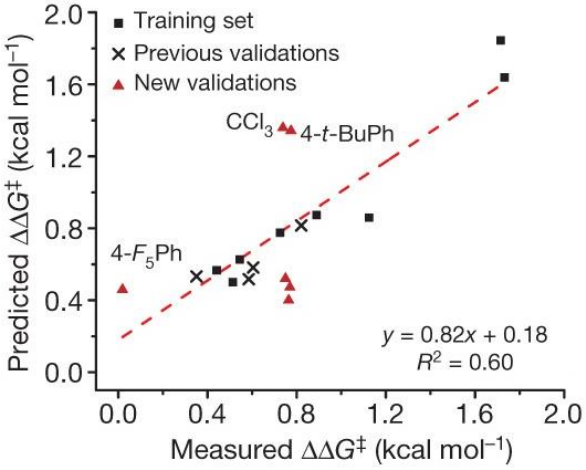


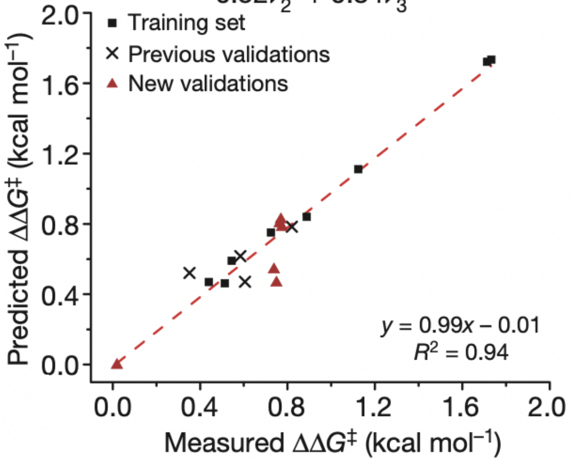

Sterimol



$\nu_1$ + another 5 stretches

$$\Delta\Delta G^{\ddagger} = -0.05 + 0.42B_1 - 0.51\nu_1 - 0.52\nu_2 + 0.34\nu_3$$

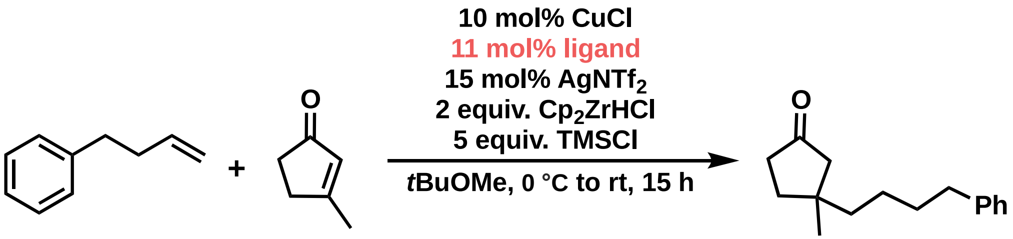


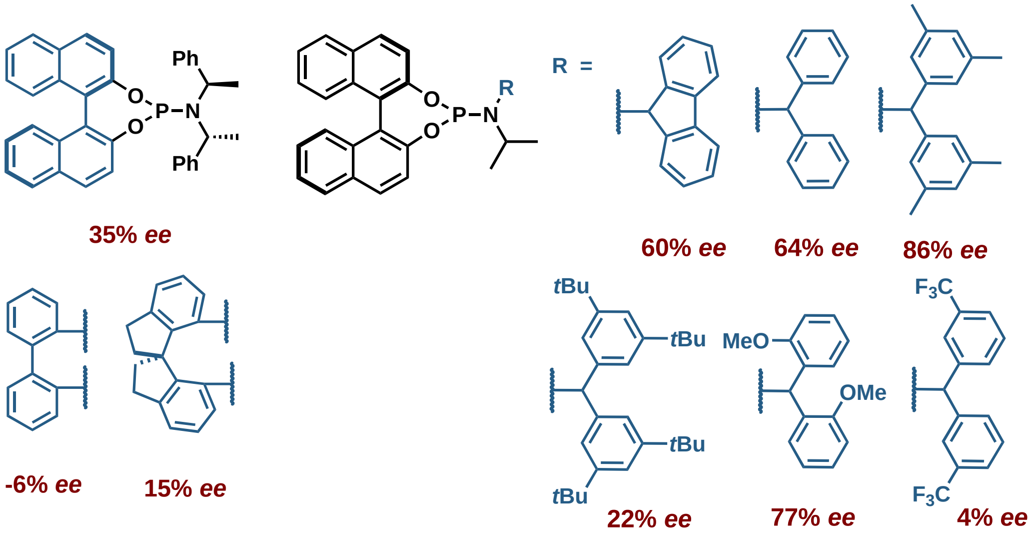




- **HOMO and LUMO energies**
- **NBO charges**
- **cone angle measurements**
- **bond lengths**
- **polarizabilities**
- **NMR shifts**
- **…**

- M. S. Sigman, *Nature*. **507**, 210–214 (2014).

# MLR in Ligand Optimization: Example 1



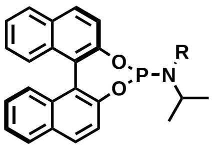




MLR to elucidate QSSR and further inform ligand design

S. P. Fletcher, *Chem. Sci.* **9**, 2628–2632 (2018).

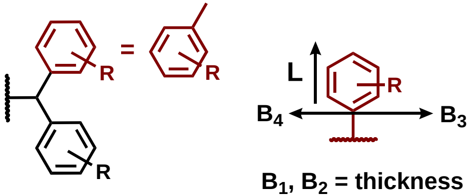
# Model Construction

1. Select a ligand type
2. Explore the ligand space
3. Identify a lead




4. Synthesise testing set:
   5 x n + 5
   size > 4 x descriptors

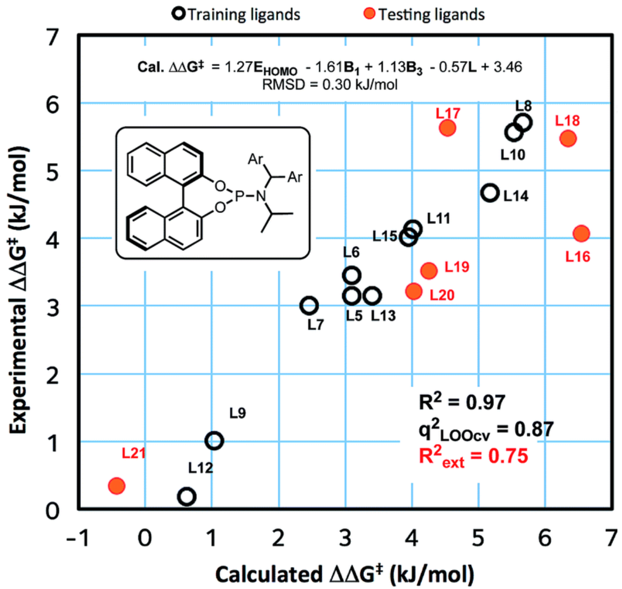
5. Generate descriptors
   - build 3D structures
   - generate conformers
   - optimize conformers (QM)
   - calculate descriptors

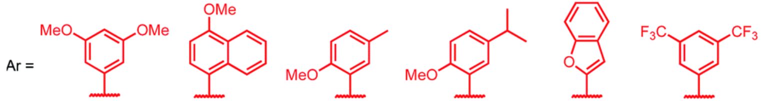



$B_1$, $B_2$ = thickness

6. Model contruction

7. Model validation




| L16 | L17 | L18 | L19 | L20 | L21 |
|---|---|---|---|---|---|
| 54%, 72% *ee* | 32%, 85% *ee* | 28%, 84% *ee* | 26%, 66% *ee* | 77%, 61% *ee* | 33%, 8% *ee* |

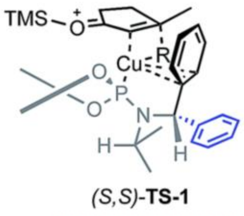
8. *In silico* predictions
9. 2$^{nd}$ ligand set

S. P. Fletcher, *Chem. Sci.* **9**, 2628–2632 (2018).

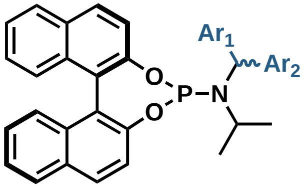
# Model Construction

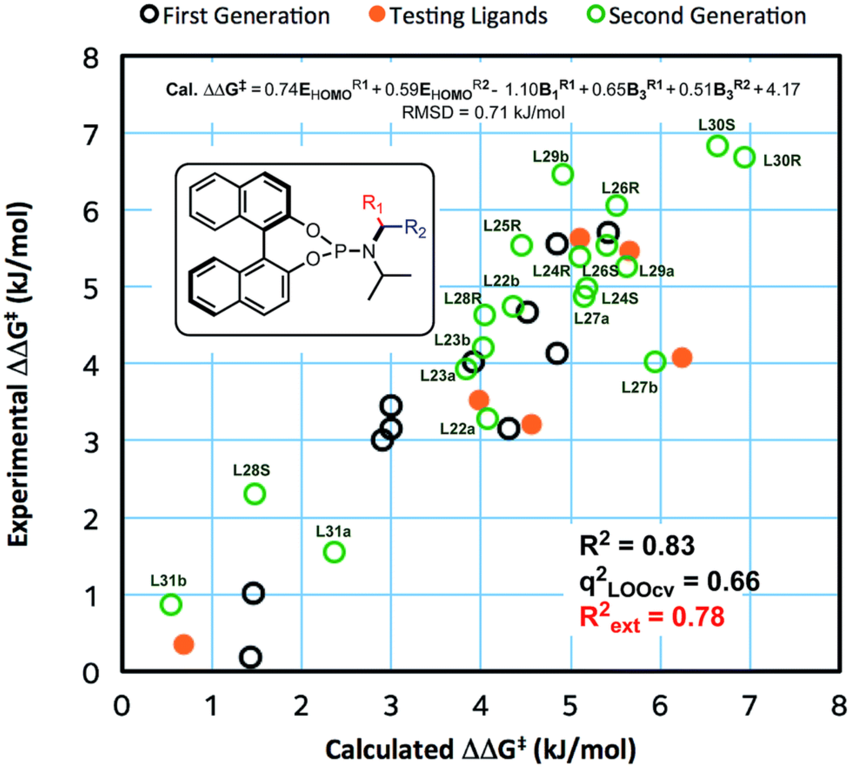


$$\Delta\Delta G^{\ddagger} = 1.27\ \mathrm{EHOMO} - 1.61\ B_1 + 1.13\ B_3 - 0.57\ L + 3.46$$



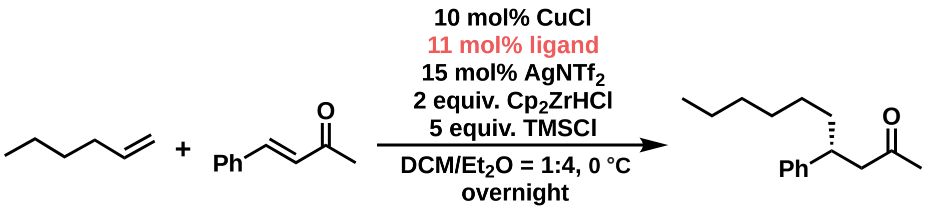

A set of new non-symmetrical ligands was added:

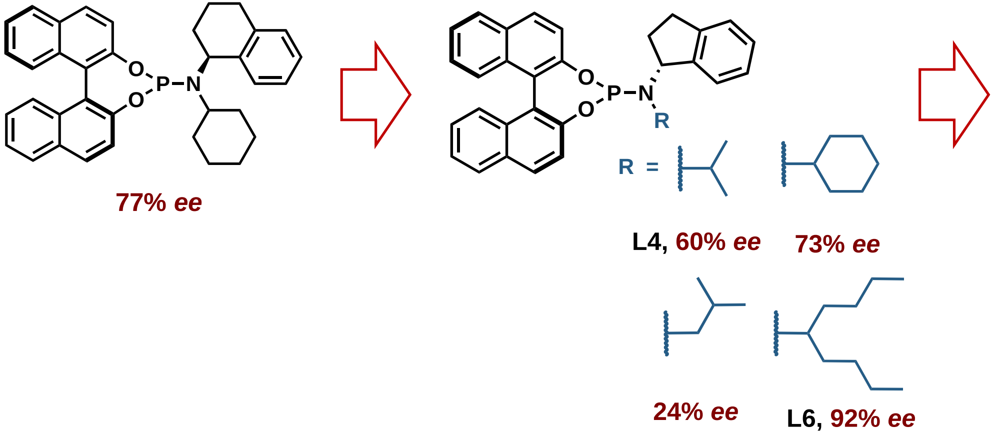


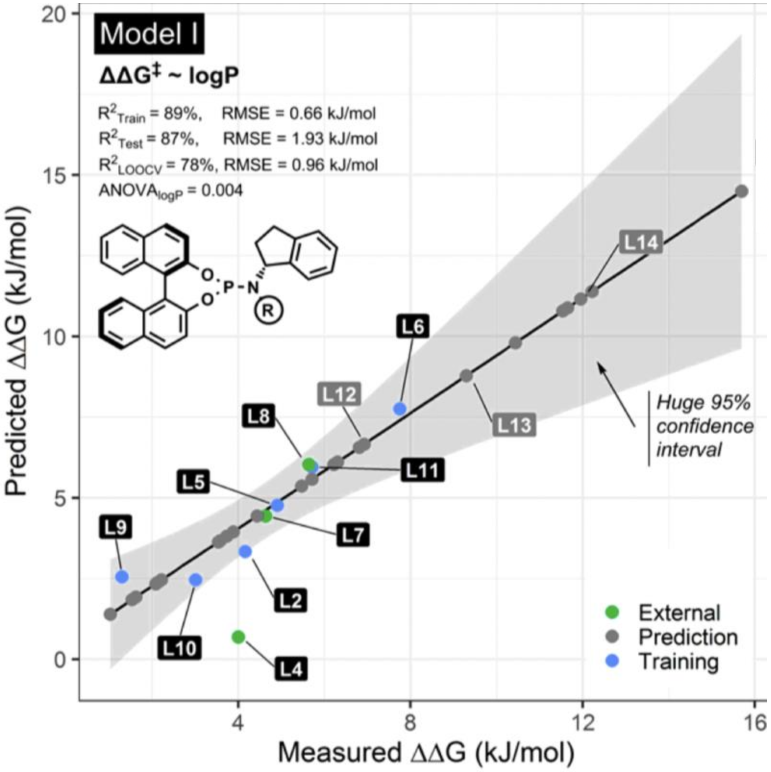




S. P. Fletcher, *Chem. Sci.* **9**, 2628–2632 (2018).

# MLR in Ligand Optimization: Example 2

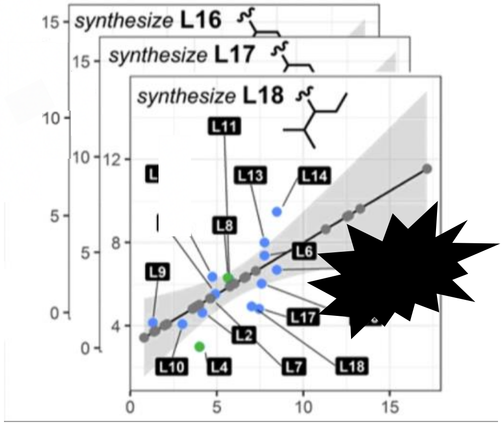


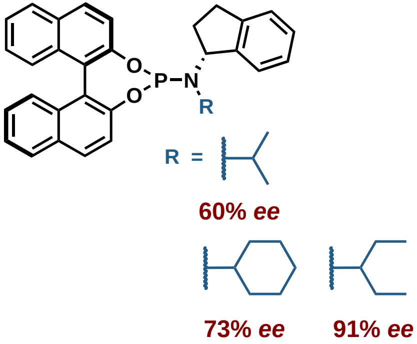



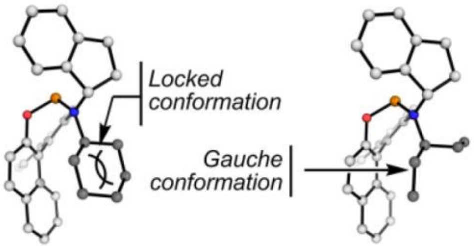




■ S. P. Fletcher, *ACS Catal.* **9**, 7179–7187 (2019).

# Model Breaks - New Model?

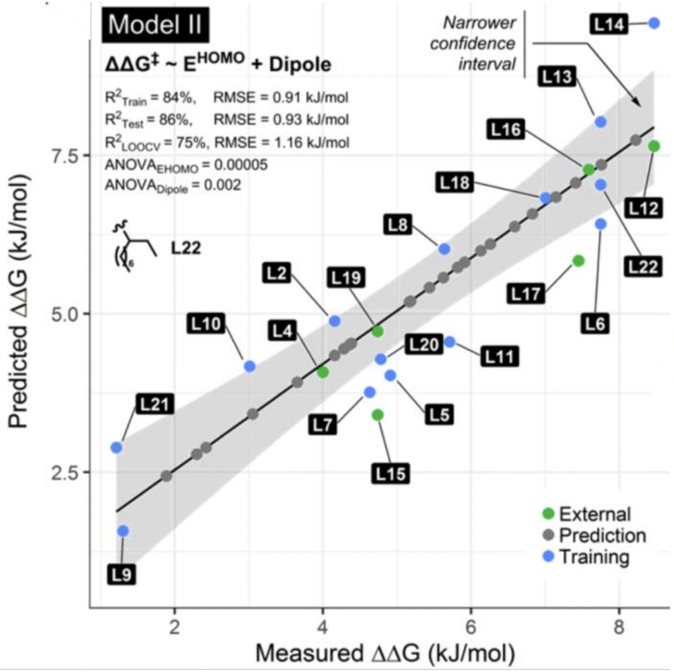


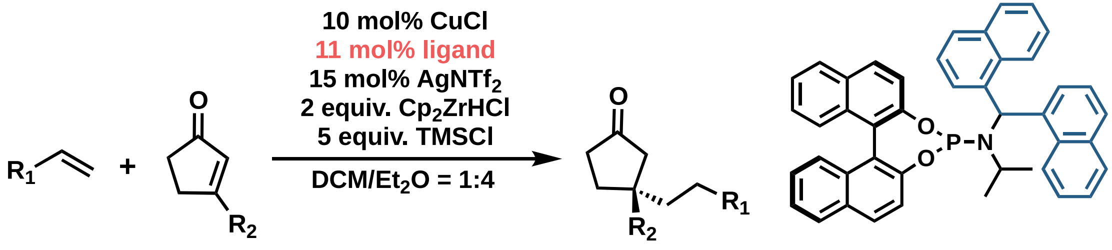

1. Generate conformers
2. Geometry optimization
3. Compute Sterimol parameters
4. Weigh parameters

$$\frac{N_i}{N_T} = \frac{e^{-\frac{E_i}{kT}}}{\sum_j e^{-\frac{E_j}{kT}}}$$




S. P. Fletcher, *ACS Catal.* **9**, 7179–7187 (2019).

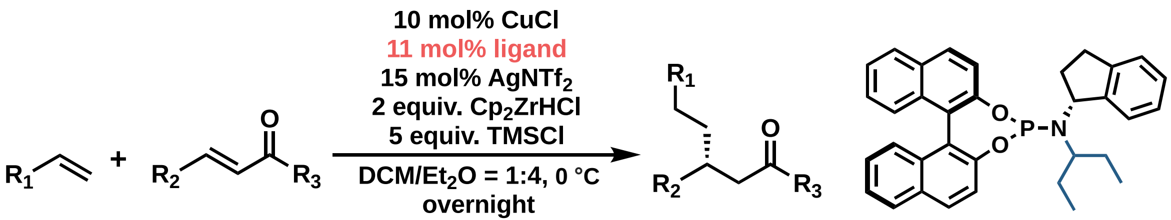
# Gains and Shortcomings




**90-84% *ee***

- >34 ligands evaluated before MLR
- $1^{st}$ ligand set = 21 ligands
- final ligand included in this $1^{st}$ set
- $2^{nd}$ ligand set = 40 ligands

- prior knowledge about TS



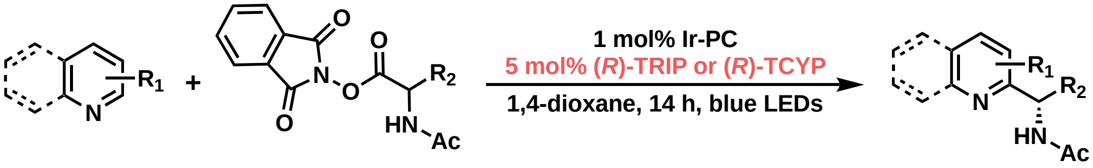

**76-95% *ee***

- 16 ligands evaluated before MLR
- 9 ligands included in Model I
- 22 ligands predicted with Model I
- 24 ligands predicted with Model II

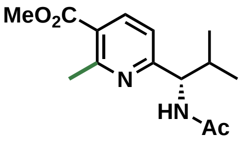
- difficult substituents to model
- more focused synthetic efforts

S. P. Fletcher, *Chem. Sci.* **9**, 2628–2632 (2018); S. P. Fletcher, *ACS Catal.* **9**, 7179–7187 (2019).

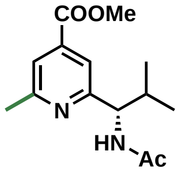
# MLC for Predicting Scope Expansion



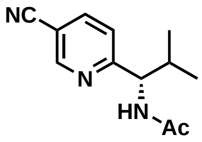

R. J. Phipps, *Science*. **360**, 419–422 (2018)



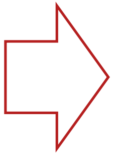

90% *ee*
with Me: 92% *ee*

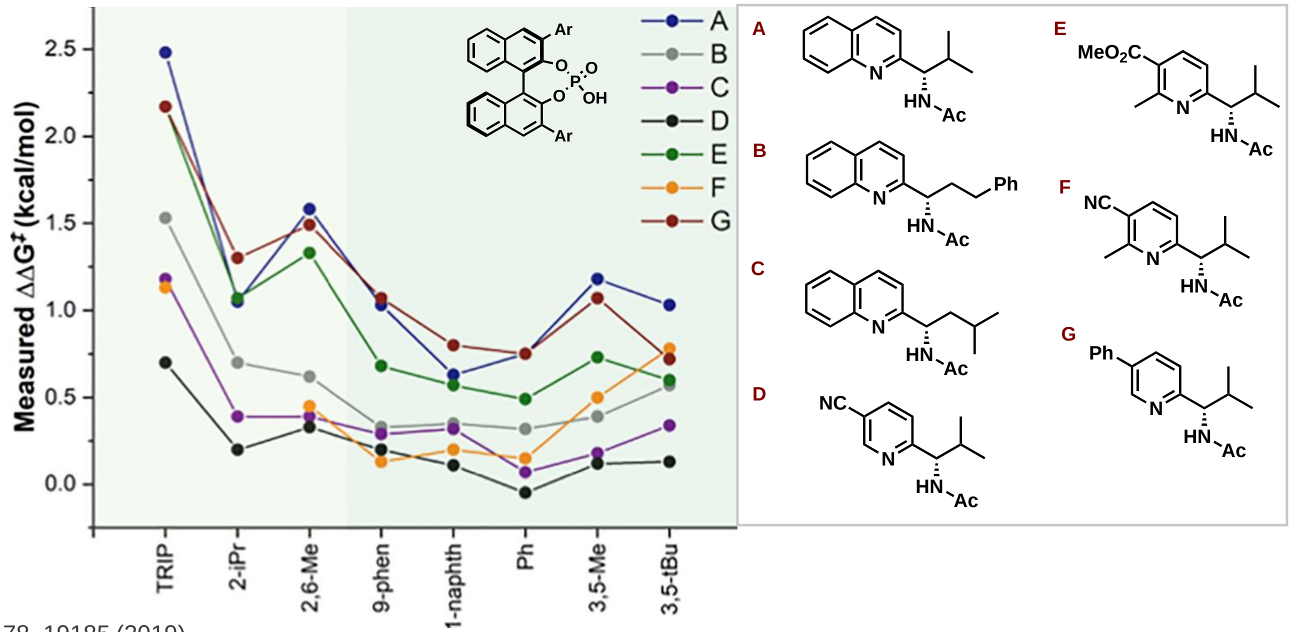



39% *ee*
with Me: 87% *ee*




61% *ee*

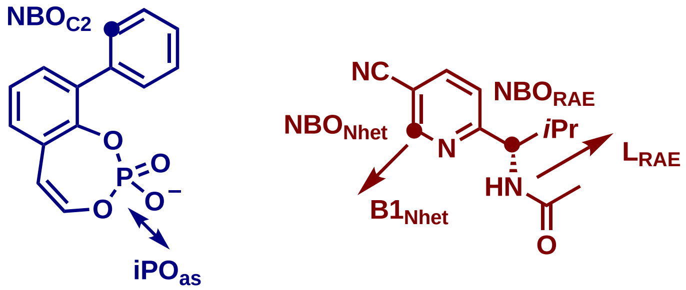





R. J. Phipps, *J. Am. Chem. Soc.* **141**, 19178–19185 (2019).

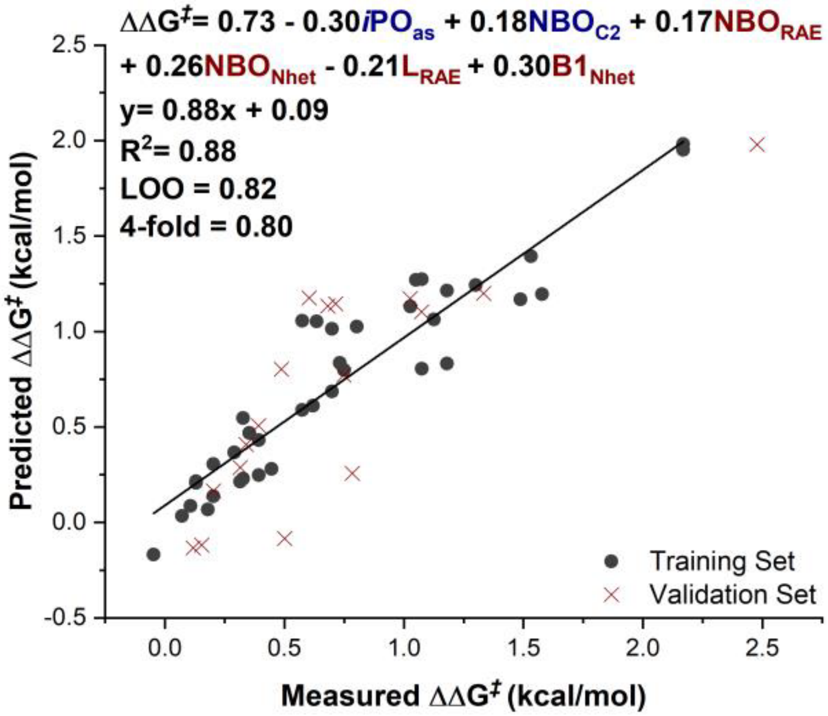
# Model Development






31 parameters

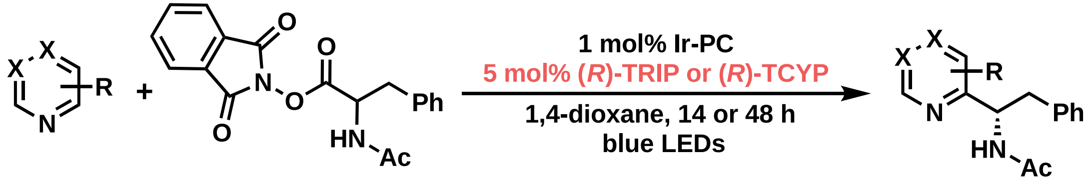
36 parameters

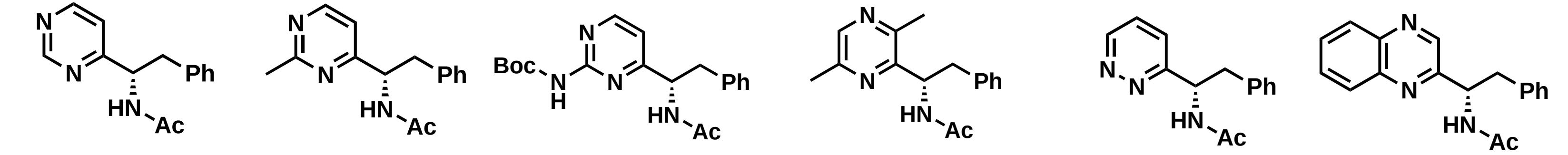



R. J. Phipps, *J. Am. Chem. Soc.* **141**, 19178–19185 (2019).

# Extrapolation to New Substrates






| | | | | | |
|---|---|---|---|---|---|
| 88% *ee* | 94% *ee* | 55% *ee* | 91% *ee* | NR | NR |
| predicted 89% *ee* | predicted 95% *ee* | predicted 97% *ee* | predicted 87% *ee* | | |

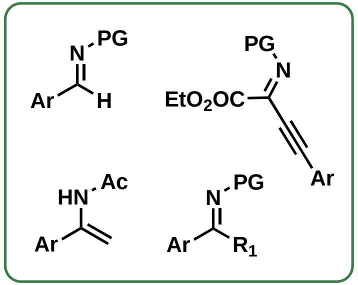
$$\Delta\Delta G^{\ddagger} = 0.73 - 0.30\, iPO_{as} + 0.18\, NBO_{C2} + 0.17\, NBO_{RAE} + 0.26\, NBO_{Nhet} - 0.21\, L_{RAE} + 0.30\, B1_{Nhet}$$

R. J. Phipps, *J. Am. Chem. Soc.* **141**, 19178–19185 (2019).

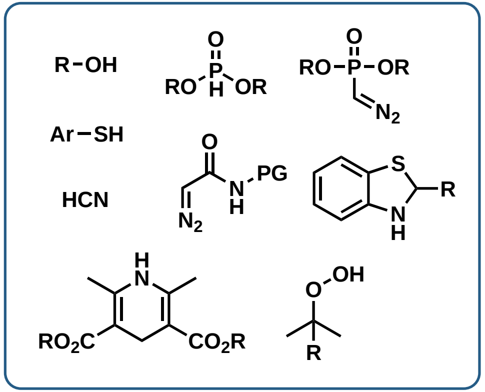
# Upscaling: Data-Mining for Reaction Prediction



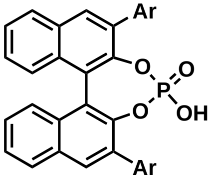
**367 reactions from 17 references:**




360 iminium structures

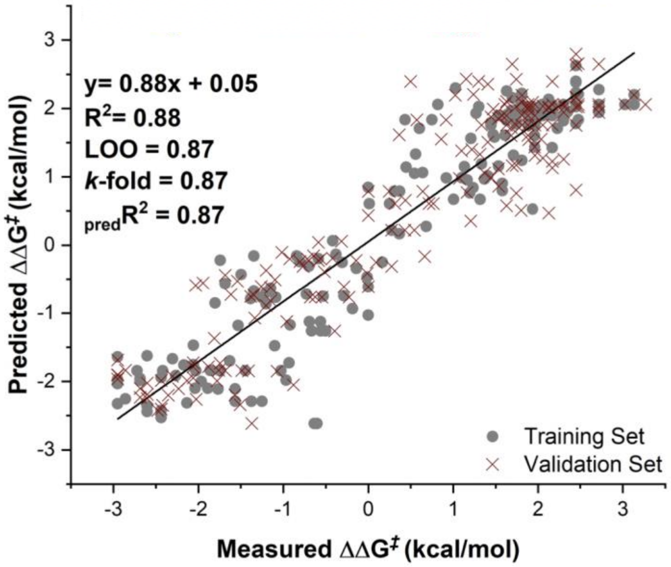



54 different Nu




18 different Ar groups

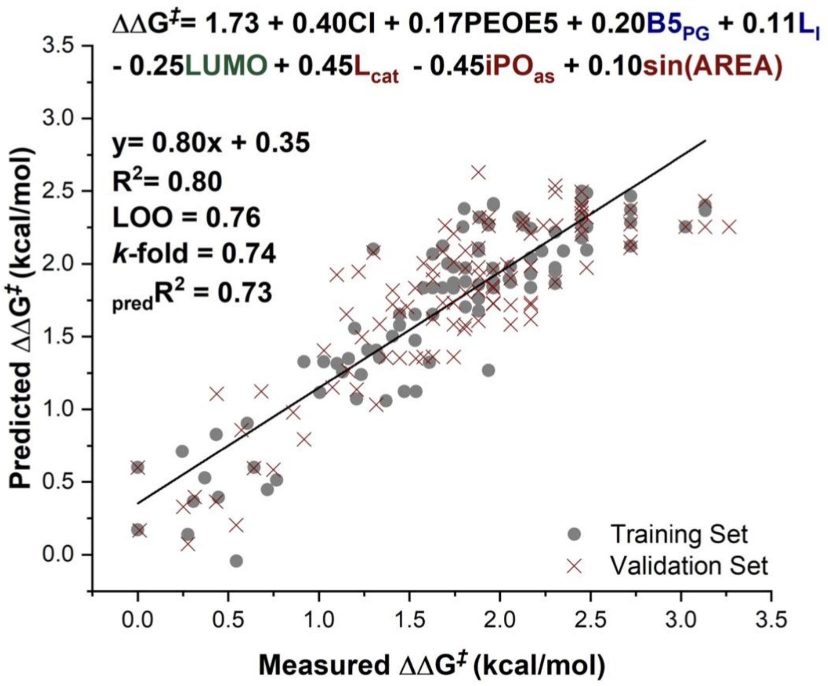
**12 different solvents**
- topological indices
- HOMO, LUMO
- AlogP …

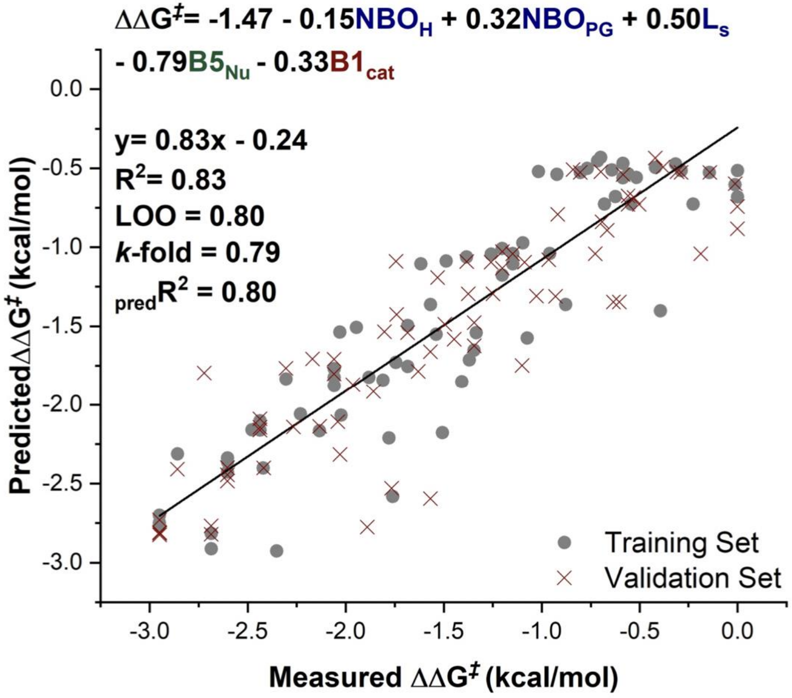



$$\Delta\Delta G^{\ddagger} = 0.42 + 0.29\ \text{sol} - 0.9\ \text{NBO}_{N} - 0.75\ \text{NBO}_{C} + 0.33\ L_{s} + 0.63\ \text{HXCNu} + 0.2\ L_{cat}$$

M. S. Sigman, *Nature*. **571**, 343–348 (2019).

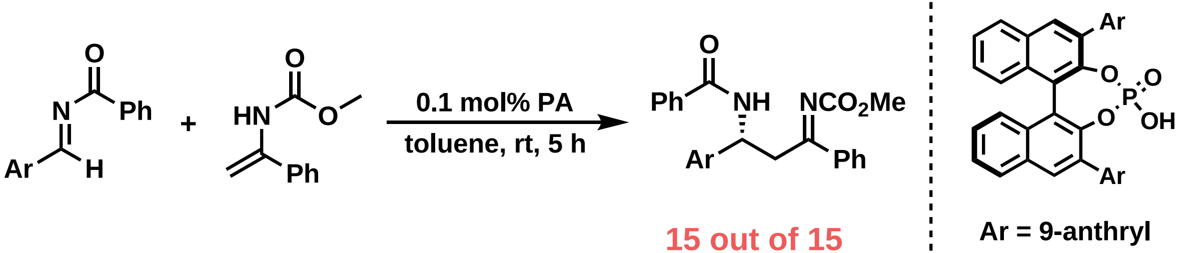
# *E* and *Z* Model Development



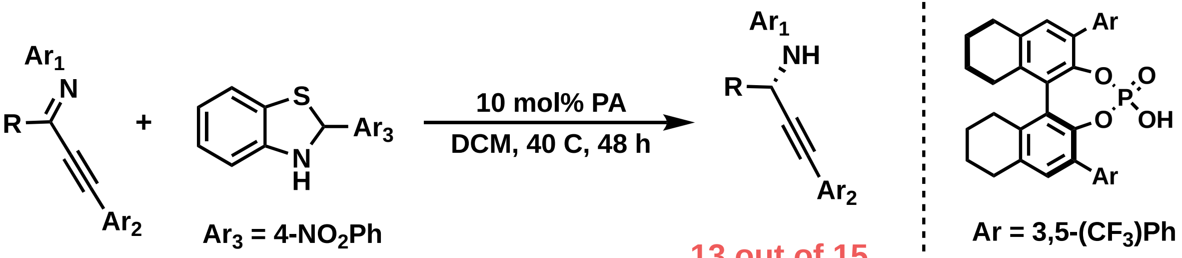




- M. S. Sigman, *Nature*. **571**, 343–348 (2019).

# Out-of-Sample Reaction Predictions




15 out of 15
within 5% *ee*




13 out of 15
within 2% *ee*

- M. S. Sigman, *Nature*. **571**, 343–348 (2019).

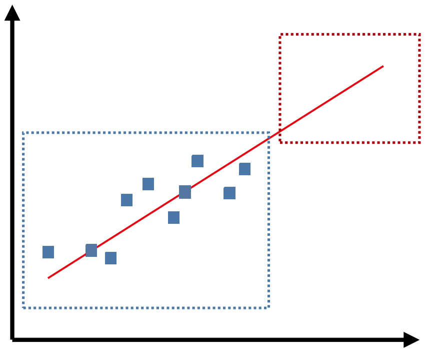
# Conclusions and Outlook

- Statistical modelling for ligand optimization still requires a fairly large ligand library before MLR analysis

- Better initial exploration of chemical space often needed to avoid problems later on

- Combination of statistical modelling with transitions state analysis to further inform catalyst design

- A change in perspective: “negative” results just as valuable as “positive”



EPFL

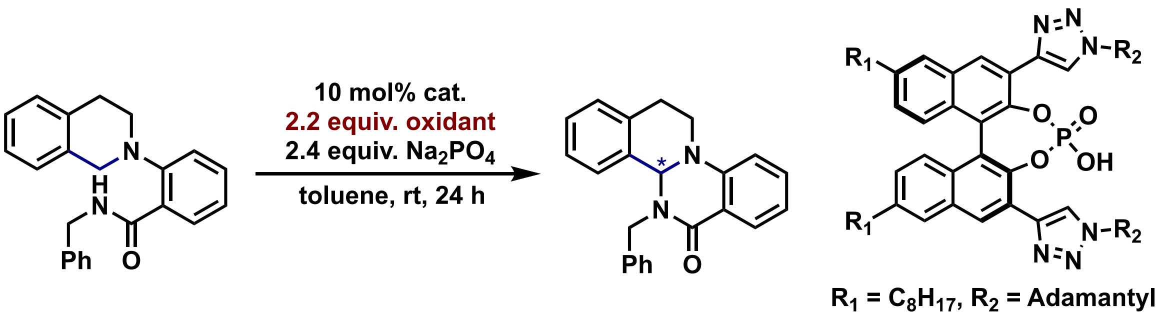

90
Th
THORIUM
232.04
11
Na
SODIUM
22.990
19
K
POTASSIUM
39.098
39
Y
YTTRIUM
88.906
8
O
OXYGEN
15.999
92
U
URANIUM
238.03

!

# Question 1:

a) What experiment type could establish whether chiral PA is already involved in the oxidation step?

b) Is this also the enantiodetermining step?




| Catalyst | KIE | %ee |
|---|---|---|
| (*S*)-cat | 3.42 | 81 |
| (*R*)-cat | 1.08 | -81 |

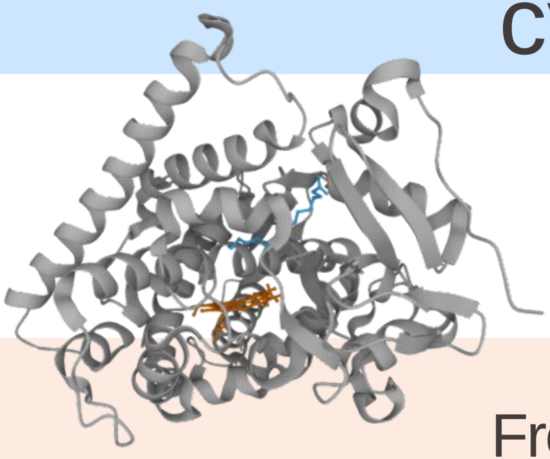
M. S. Sigman, *Science*. **347**, 737–743 (2015).

# Question 2:

a) Why are highly collinear parameters a problem in MLR?
How can you still efficiently model highly collinear data?

b) Why can the inclusion of cross-parameter terms be important (a + b + ab)?

# Engineered hemoproteins for asymmetric cyclopropanation



Elija Grinhagena

Frontiers in Chemical Synthesis II

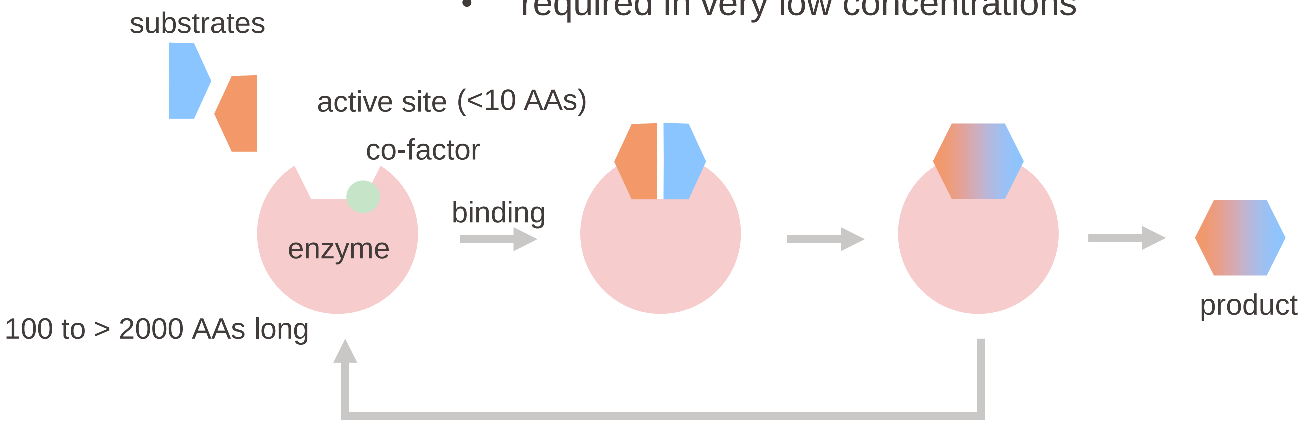
Stereoselective Synthesis

16.5.2022.

# Enzymes: nature`s catalysts

Enzymes: **catalysts** of biochemical reactions in living organisms

- speed up reactions
- not consumed
- required in very low concentrations




Specificity to:

- one type of substrates
- group specificity
- absolute specificity

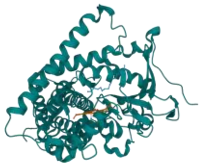
P. K. Robinson *Essays Biochem.* **2015**, *59*, 1–41.

# Enzymes: nature`s catalysts

Efficiency described by turnover number (TON) or (TTN)

number of substrate molecules that can be converted to product by a single enzyme molecule per unit time (usually per minute or per second)

Example:

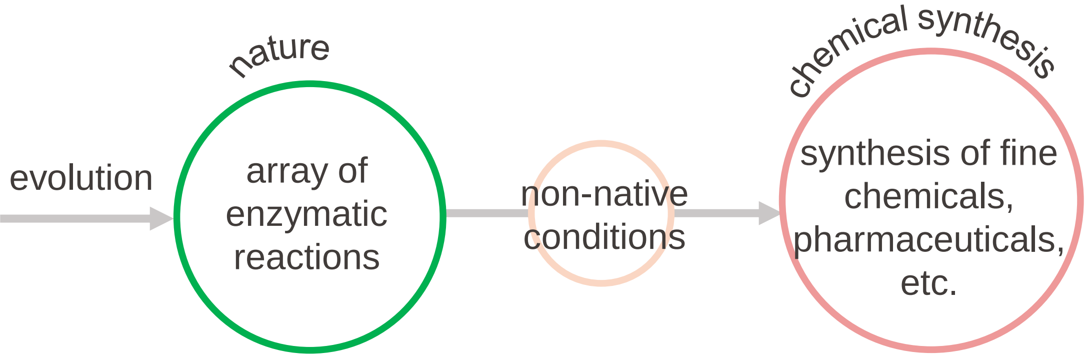


$$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} HCO_3^-$$

**TON = 600 000**

- P. K. Robinson *Essays Biochem.* **2015**, *59*, 1–41.

# Expanding enzyme catalysis

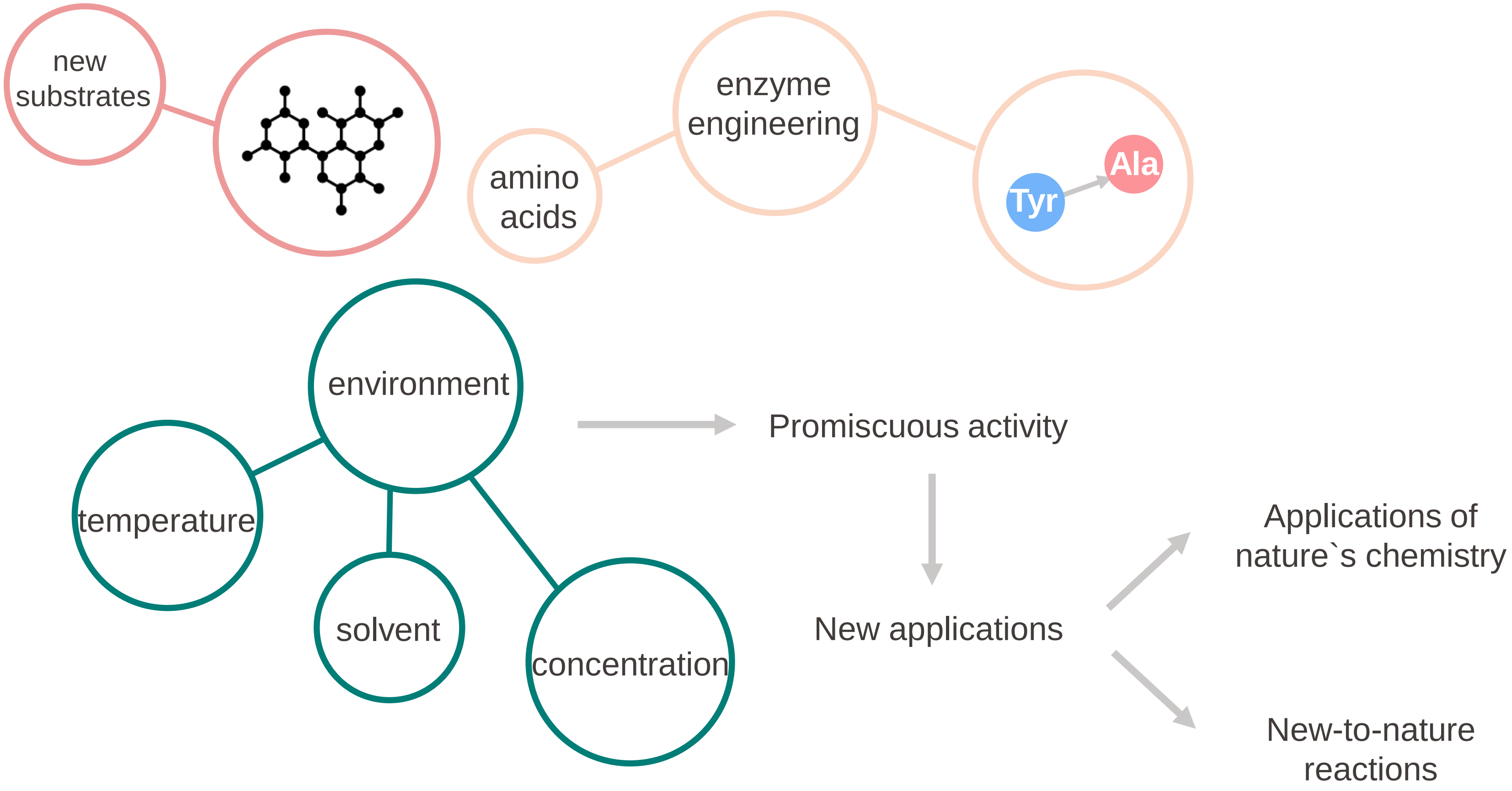



Can provided with:

- Efficiency
- Chemo- and steroselectivity
- Sustainability

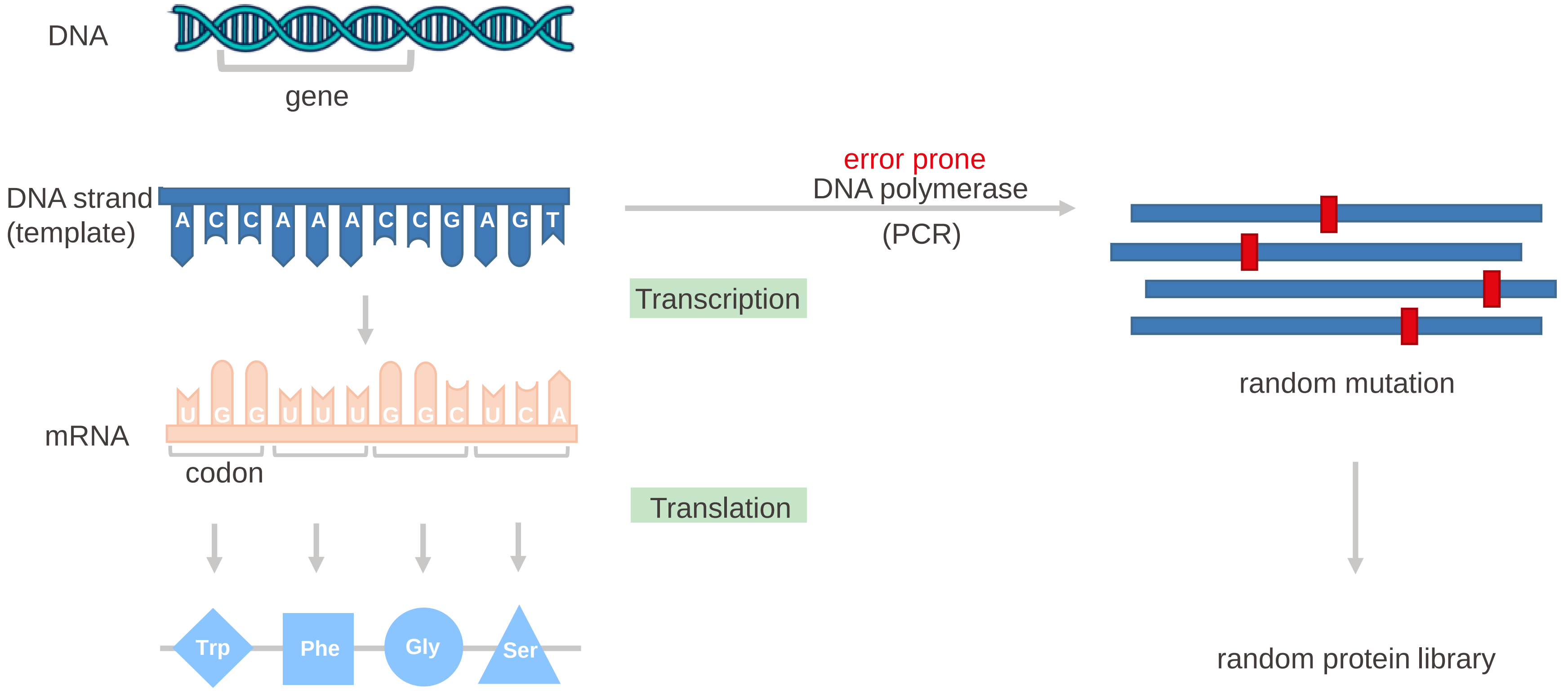
▪ K. Chen and F. H. Arnold *Nat. Catal.* **2020**, *3*, 203-213.

# Expanding enzyme catalysis

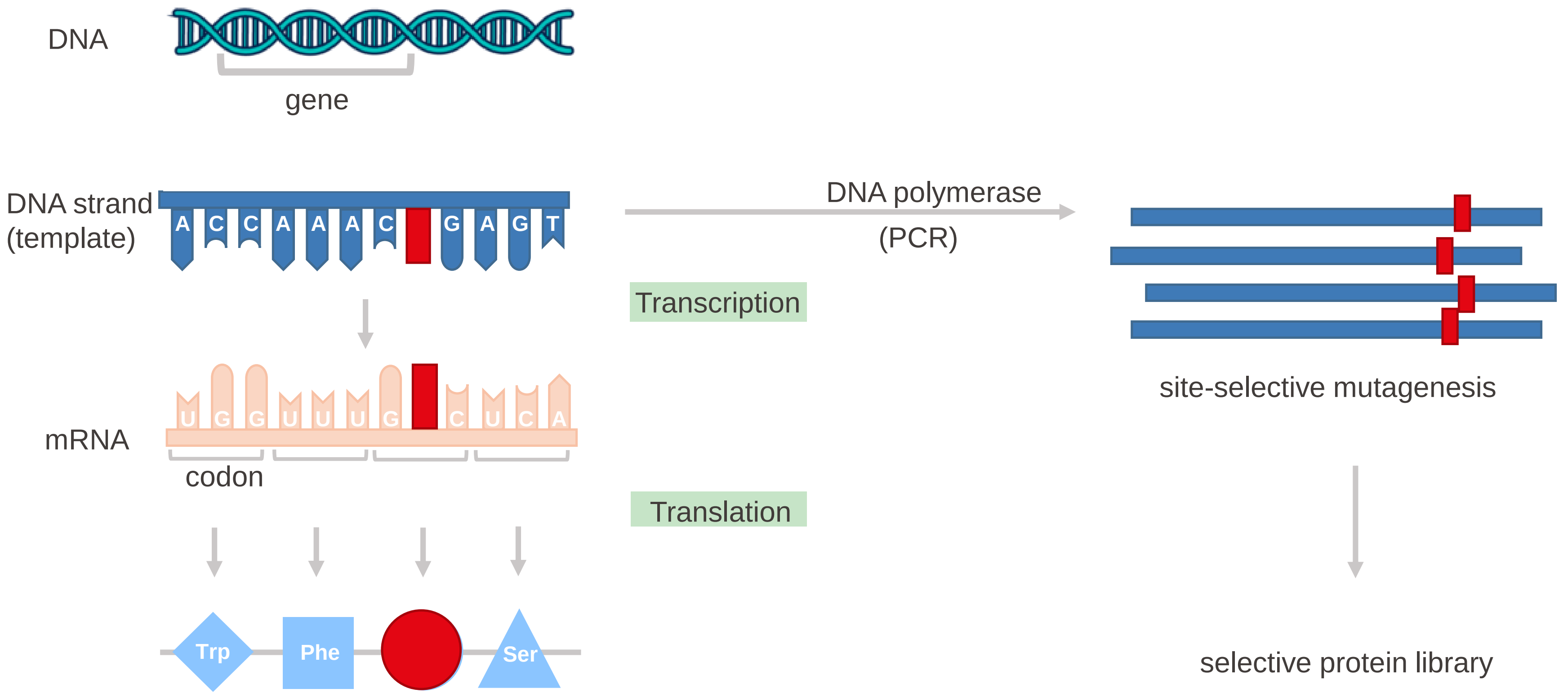



- Current Opinion in Green and Sustainable Chemistry **2017**, *7*, 23–30.

# Enzyme evolution: synthesis

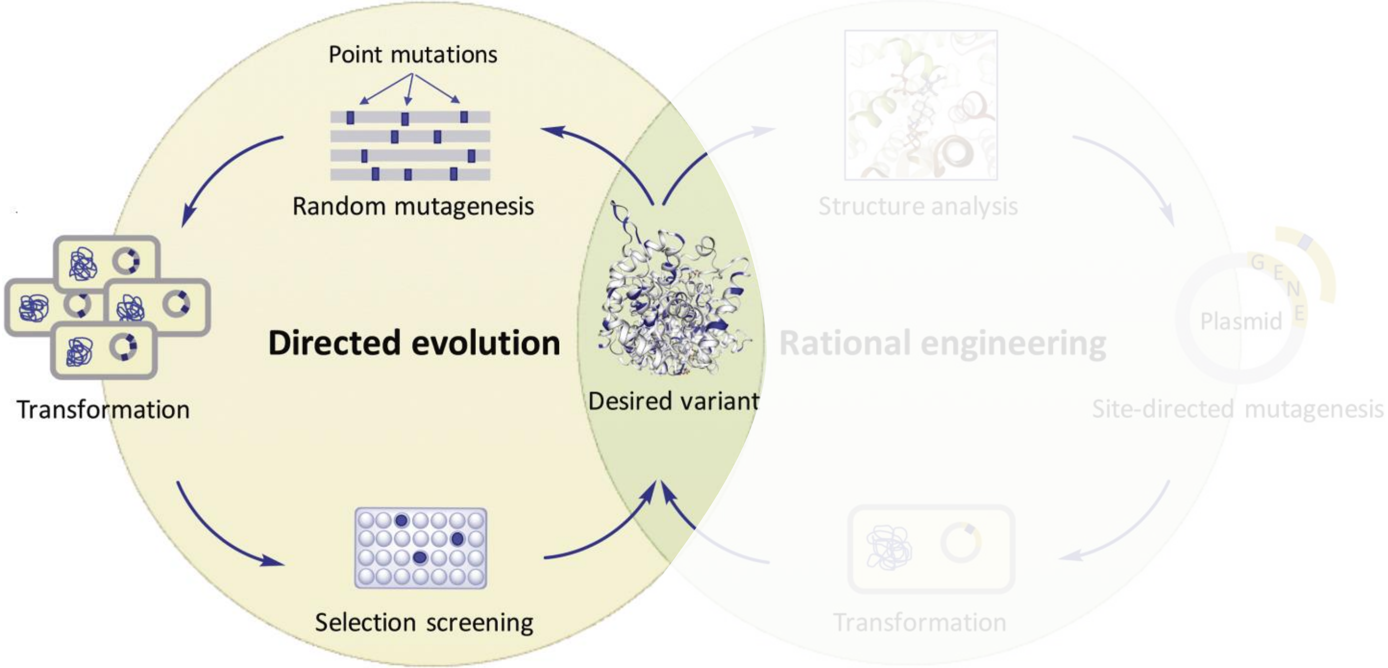


# Enzyme evolution: synthesis



# Enzyme evolution





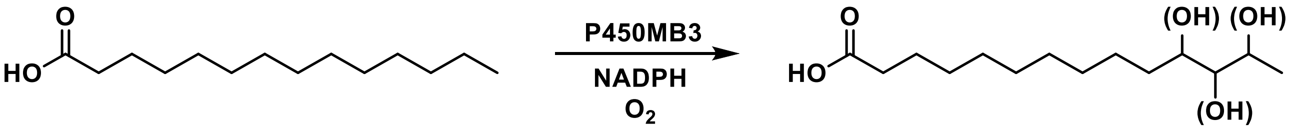

- Image: G. Daletos, G. Stephanopoulos *Metab. Eng. Commun.* **2020**, *11*, e00129.

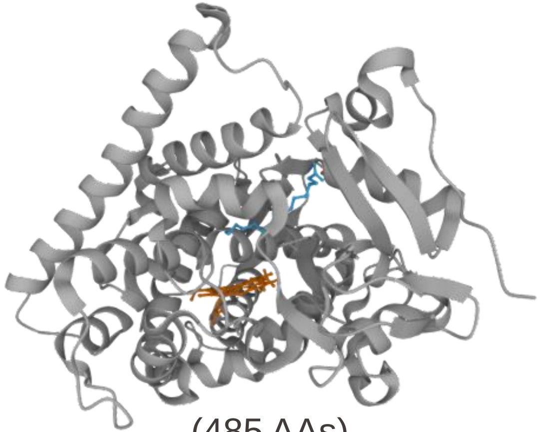
# Enzymes for new chemistry

- Broadly available
- Evolvable
- Variable parts
- Known mechanism

→ Cytochromes P450

**P450BM3 (Bacillus megaterium)**

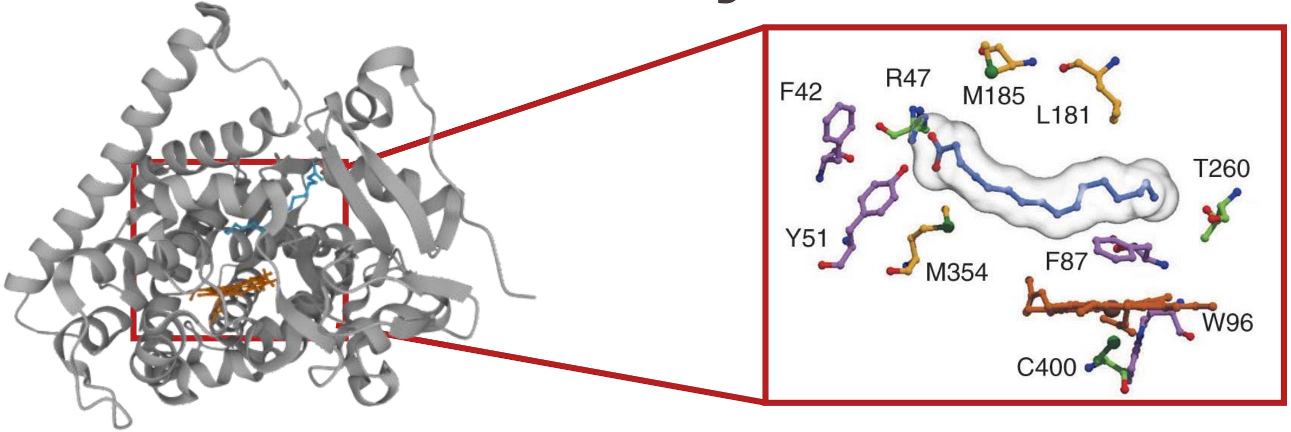


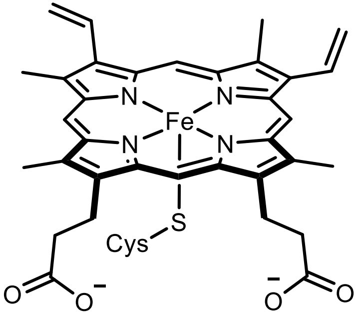



(485 AAs)

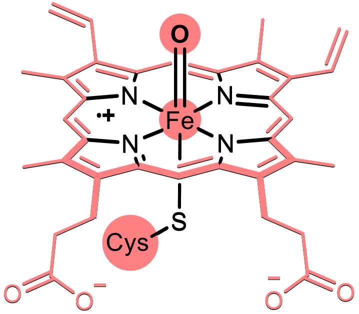
- Y. Yang and F. H. Arnold *Acc. Chem. Res.* **2021**, *54*, 1209−1225

# P450BM3 enzyme



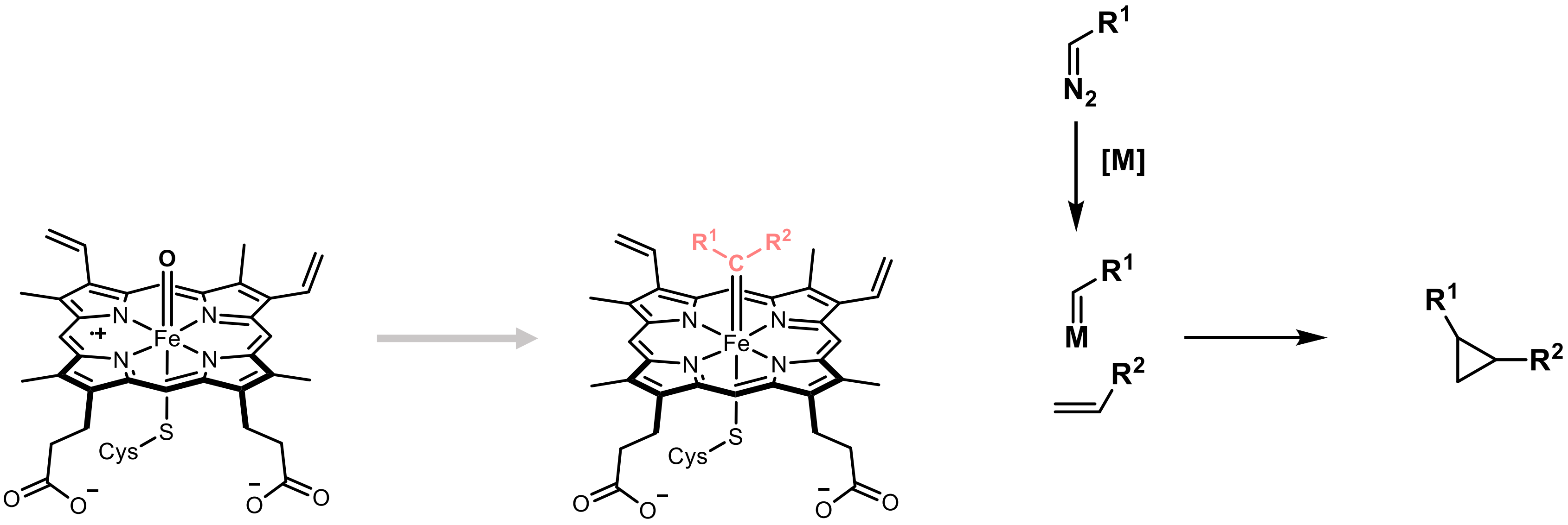




Heme cofactor




Fe (IV) oxo

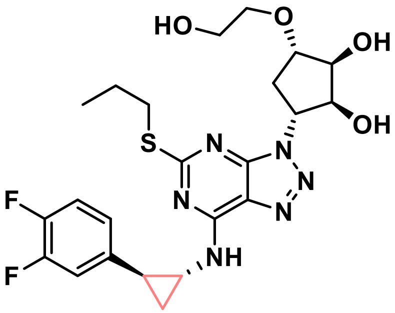
# P450 for new-to-nature chemistry



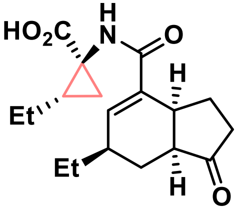

P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold, *Science* **2013**, *339*, 307–310.

# Cyclopropanes: widely used

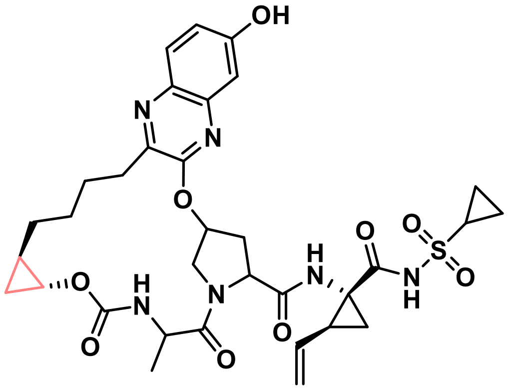




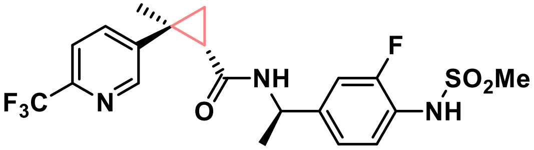
ticagrelor



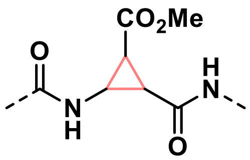
(+)-cotonatine
phytotoxin



**grazoprevir**
hepatitis C treatment

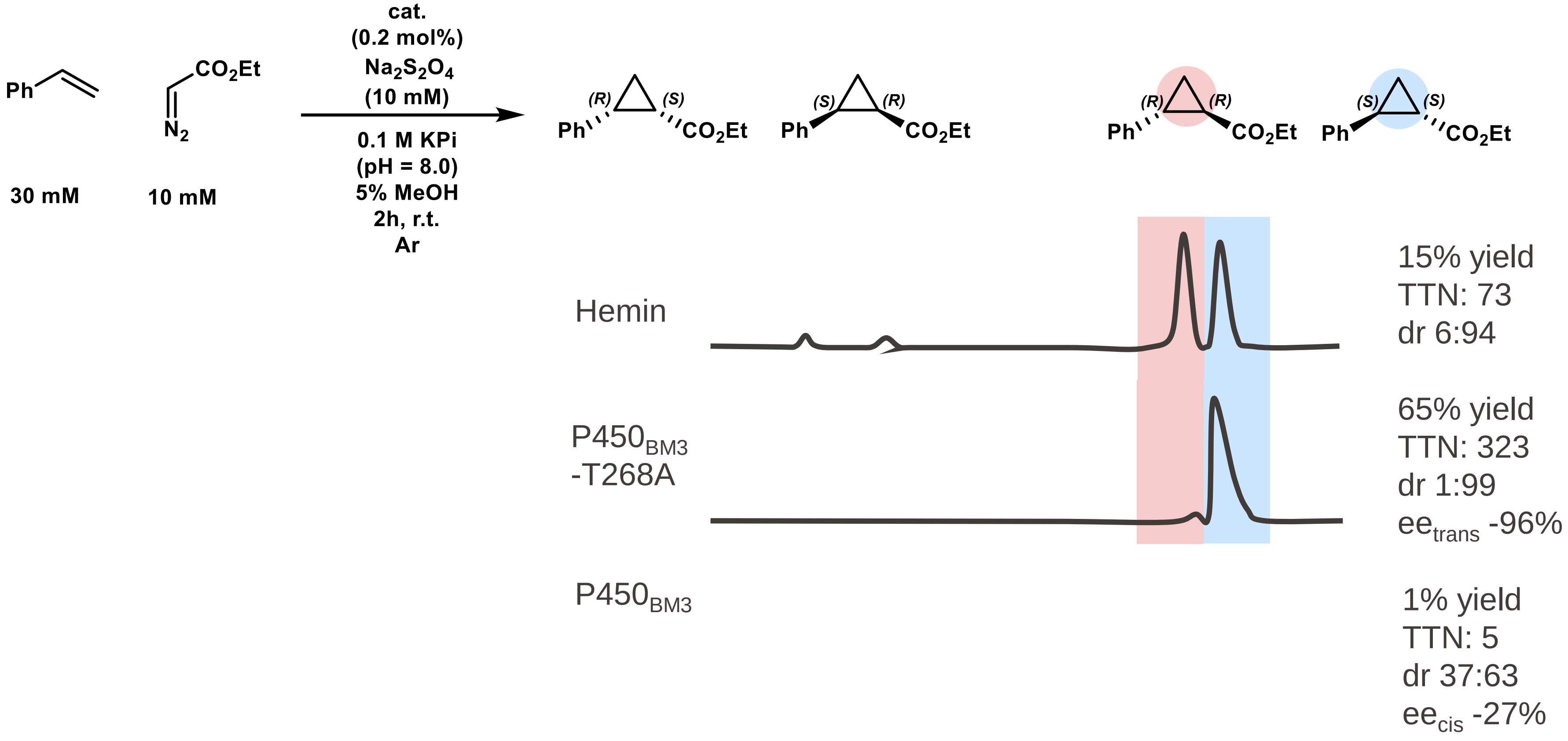


TRPV1 inhibitor



synthetic peptides

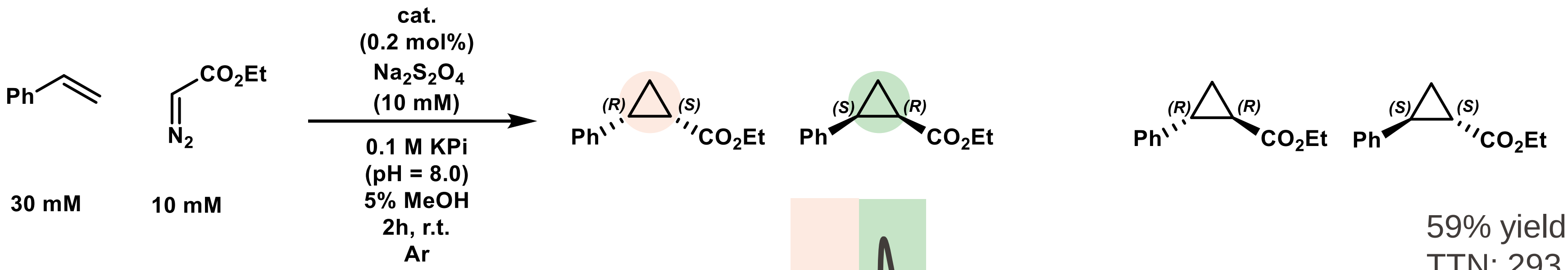
# First enzymatic olefin cyclopropanation




- P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold, *Science* **2013**, *339*, 307–310.

# Cis selectivity



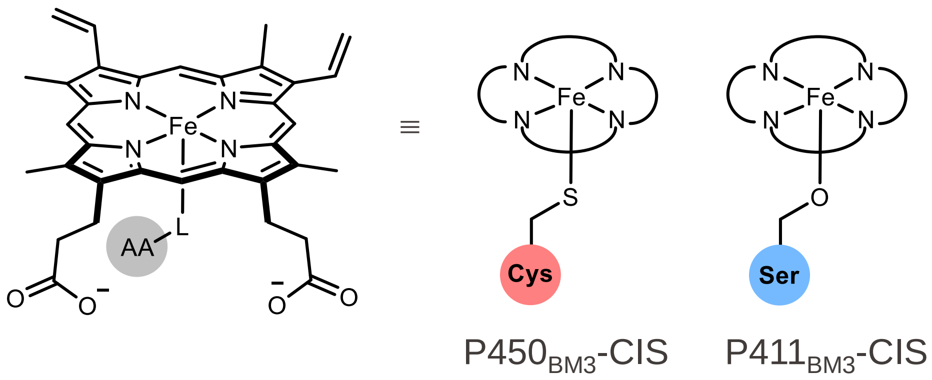



BM3-CIS-T438S
(14 mutations
from $P450_{BM3}$)

59% yield
TTN: 293
dr 92:8
$ee_{cis}$ -97%
$ee_{trans}$ -66%

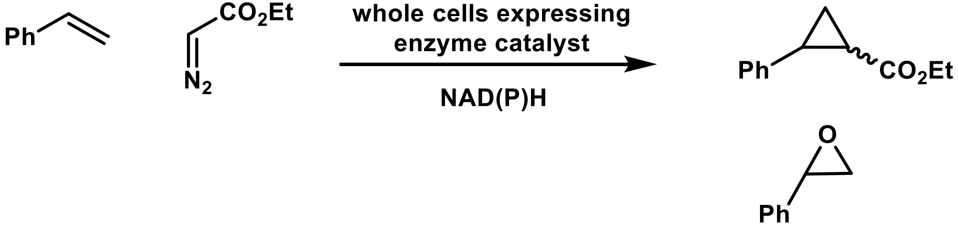
- P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold, *Science* **2013**, *339*, 307–310.

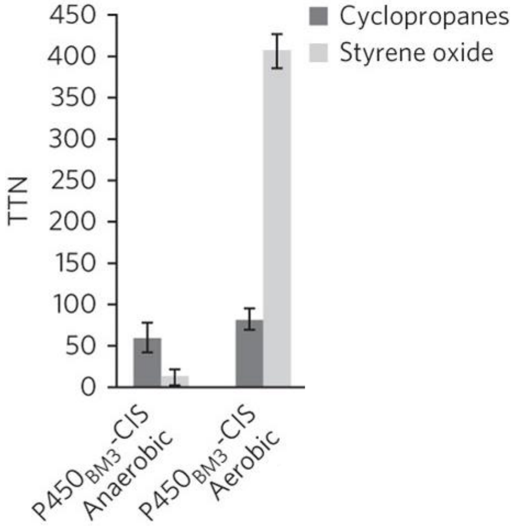
# Tuning the reactivity




→ whole cell catalysis → efficiency and scalability

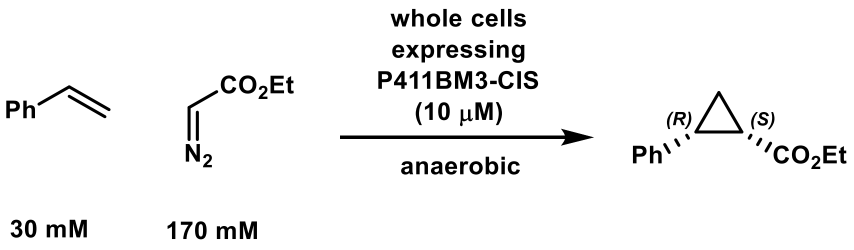
Challenges: oxygenation and use of native reducing agent




- P. S. Coelho, Z. J. Wang, M. E. Ener, S. A. Baril, A. Kannan, F. H. Arnold, E. M. Brustad, *Nat. Chem. Biol.* **2013**, *9*, 485–487.

# Cyclopropanation *in vivo*

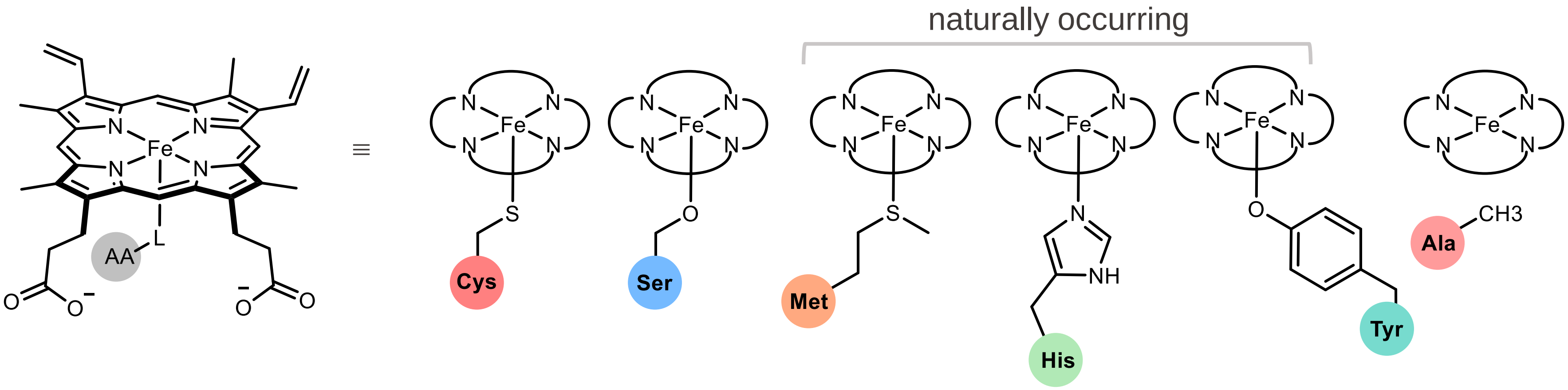


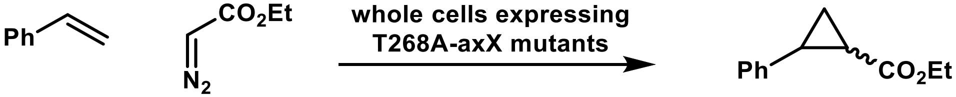

72% yield
TTN: 67 800
dr 90:10
$ee_{cis}$ 99%

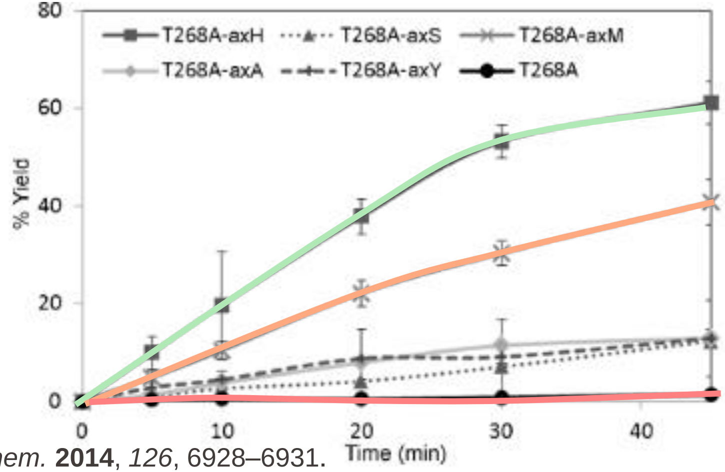
Scalable to make gram quantities: ($ee_{cis}$ 99%) (27 g/L), 78% yield, 48 800 TTN)

- P. S. Coelho, Z. J. Wang, M. E. Ener, S. A. Baril, A. Kannan, F. H. Arnold, E. M. Brustad, *Nat. Chem. Biol.* **2013**, *9*, 485–487.

# Further tuning the reactivity

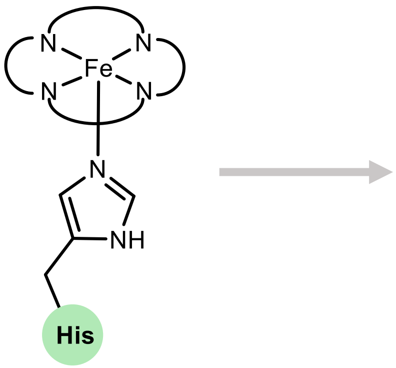


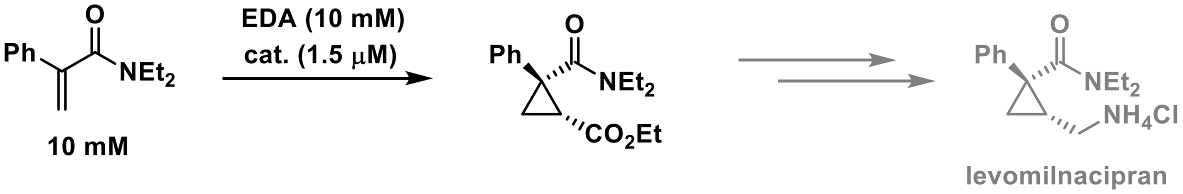




- Z. J. Wang, H. Renata, N. E. Peck, C. C. Farwell, P. S. Coelho, F. H. Arnold, *Angew. Chem.* **2014**, *126*, 6928–6931.

# Electron-deficient olefins




electron-deficient olefins

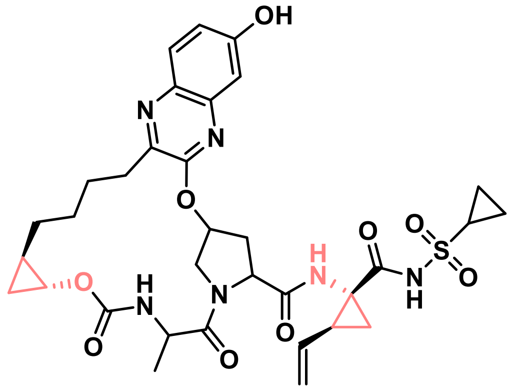



| | |
|---|---|
| T268A-axH | 81% yield, 6:94 dr, 42% ee |
| T268A-axH<br>-L437W-V78M-L181 | >90% yield, 2:98 dr, 92% ee<br>(anaerobic and aerobic) |

- Z. J. Wang, H. Renata, N. E. Peck, C. C. Farwell, P. S. Coelho, F. H. Arnold, *Angew. Chem.* **2014**, *126*, 6928–6931.

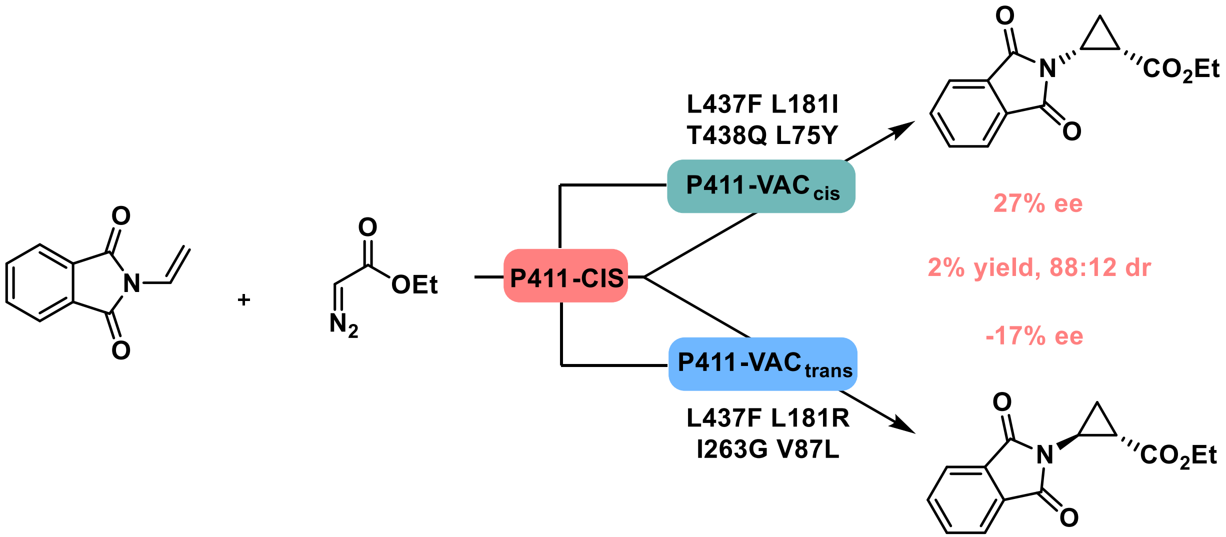
# Heteroatom-Substitutes Cyclopropanes

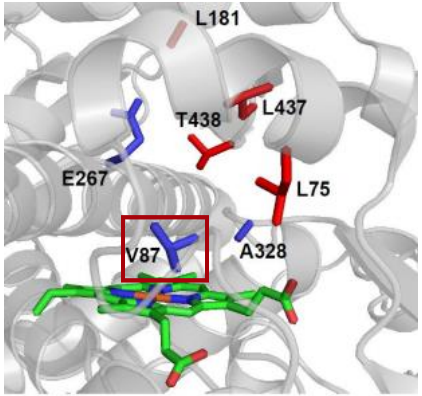

X= O, N, S




**grazoprevir**
hepatitis C treatment

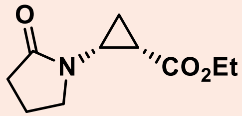
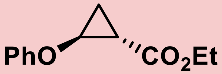
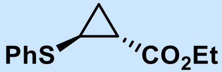
# Heteroatom-Substitutes Cyclopropanes




- O. F. Brandenberg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu, F. H. Arnold, *ACS Catal.* **2018**, *8*, 2629–2634.

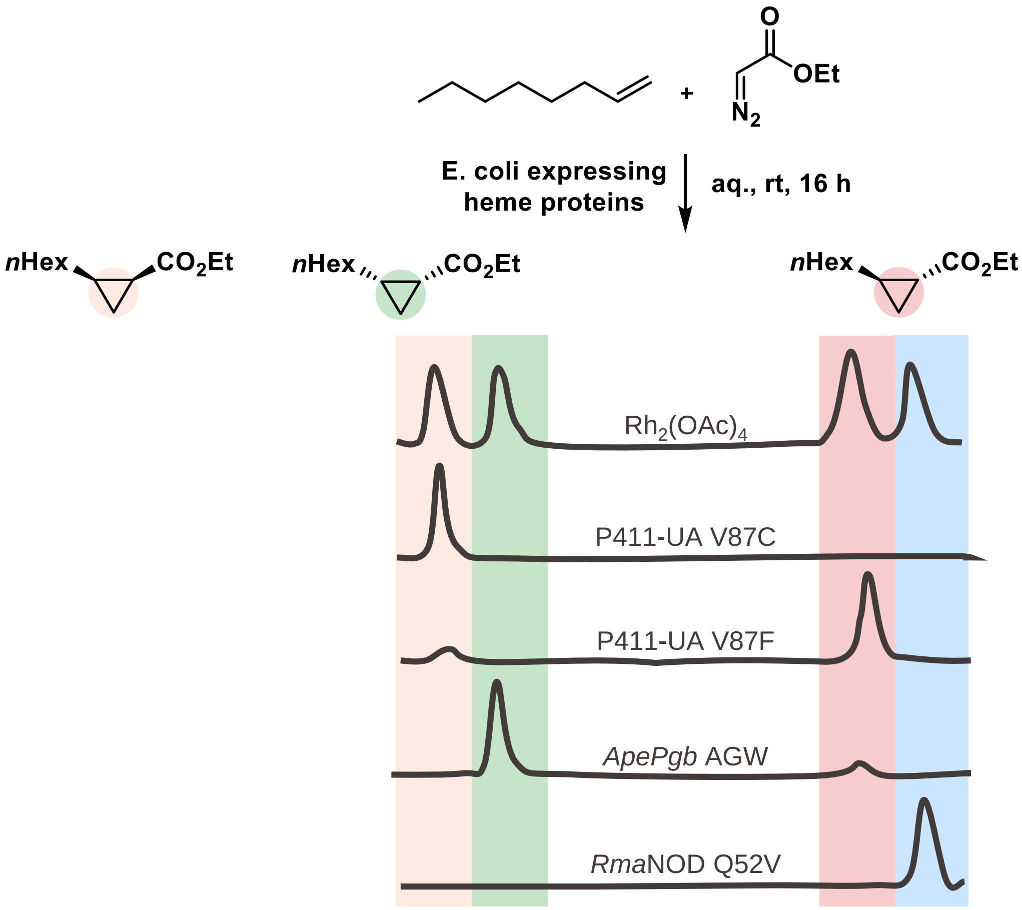
# Heteroatom-Substitutes Cyclopropanes

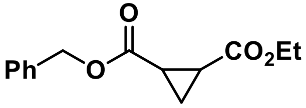
| Product | Catalyst | Yield | dr | ee | TTN |
|---|---|---|---|---|---|
|  | P411-VAC$_{cis}$ V87T | 59 | 97:3 | 74 (4 with P411-VAC$_{cis}$) | 2000 |
|  | P411-VAC$_{cis}$ V87T | 66 | 72:28 | 87 | 2200 |
|  | P411-VAC$_{cis}$ V87I | 74 | 2:98 | 94 | 2800 |
|  | P411-VAC$_{cis}$ A328N | 43 | 84:16 | 90 | 1400 |
|  | P411-VAC$_{cis}$ V87F | 58 | 13:87 | 84 | 1700 |

- O. F. Brandenberg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu, F. H. Arnold, *ACS Catal.* **2018**, *8*, 2629–2634.

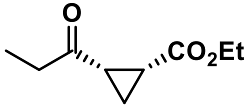
# Unactivated alkenes





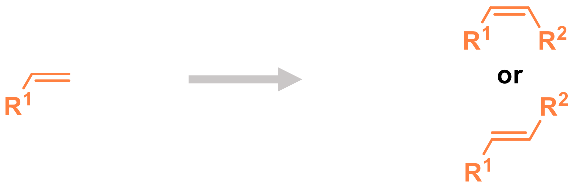

all enantiomers (>96% ee)

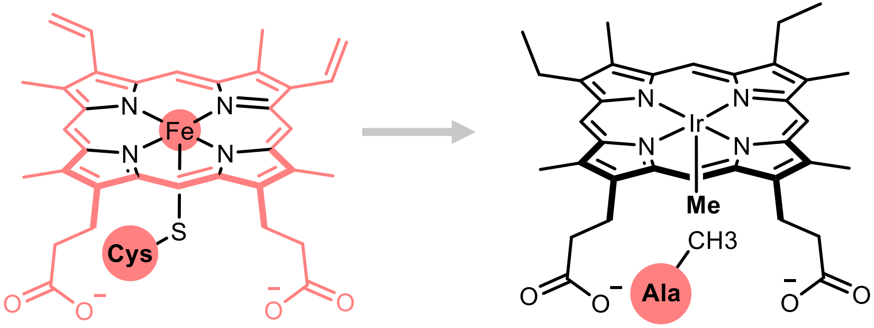



97% ee

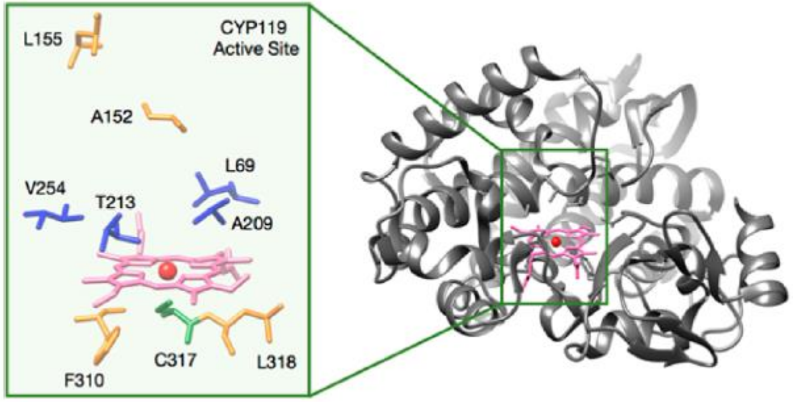
- A. M. Knight, S. B. J. Kan, R. D. Lewis, O. F. Brandenberg, K. Chen, F. H. Arnold, *ACS Cent. Sci.* **2018**, *4*, 372–377.

# Internal alkenes using Ir




Ir(Me)MPIX

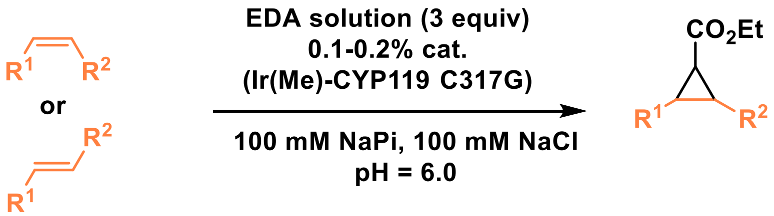


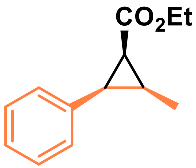

C317G

CYP119

- H. M. Key, P. Dydio, Z. Liu, J. Y. E. Rha, A. Nazarenko, V. Seyedkazemi, D. S. Clark, J. F. Hartwig, *ACS Cent. Sci.* **2017**, *3*, 302–308.

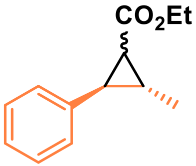
# Internal alkenes using Ir




(both enantomers)

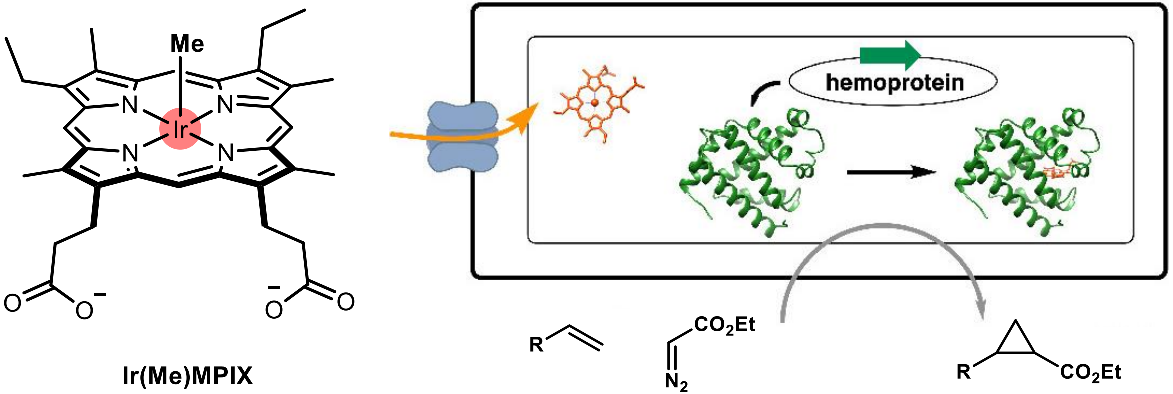
| additional mutations | |
|---|---|
| V254A | 54% (36:1 dr, 99% ee, 286 TON) |
| L69F, T213V | 45% (171:1 dr, -88% ee, 270 TON) |




| additional mutations | |
|---|---|
| V254L, T213G, A152V | 31% (30:1 dr, 90% ee, 310 TON) |

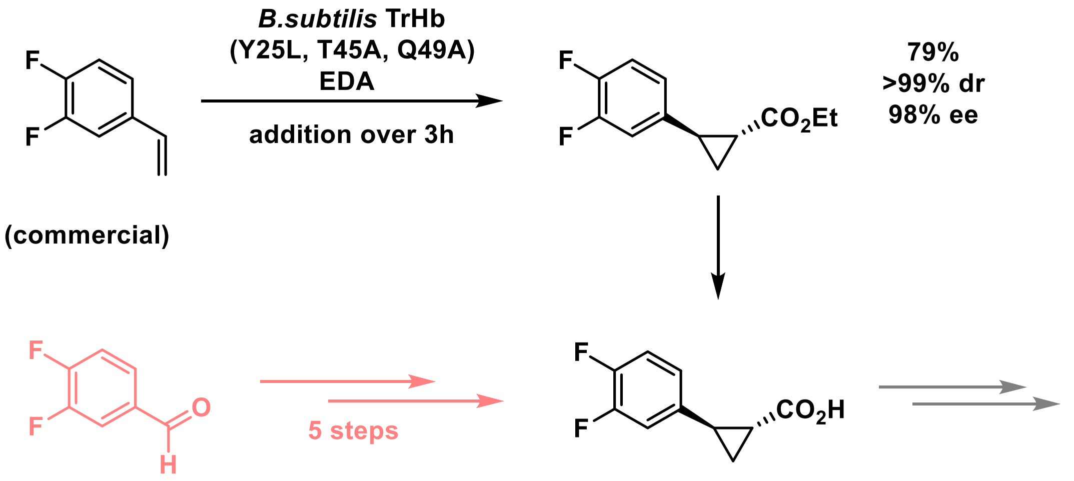
- H. M. Key, P. Dydio, Z. Liu, J. Y. E. Rha, A. Nazarenko, V. Seyedkazemi, D. S. Clark, J. F. Hartwig, *ACS Cent. Sci.* **2017**, *3*, 302–308.

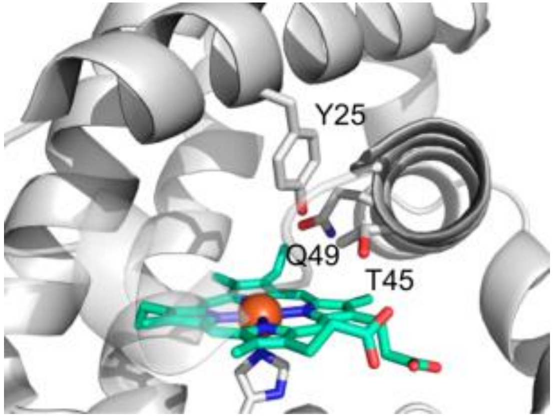
# Internal alkenes using Ir




- Z. Liu, J. Huang, Y. Gu, D. S. Clark, A. Mukhopadhyay, J. D. Keasling, J. F. Hartwig, *J. Am. Chem. Soc.* **2022**, *144*, 883–890.

# Synthesis of drug intermediates

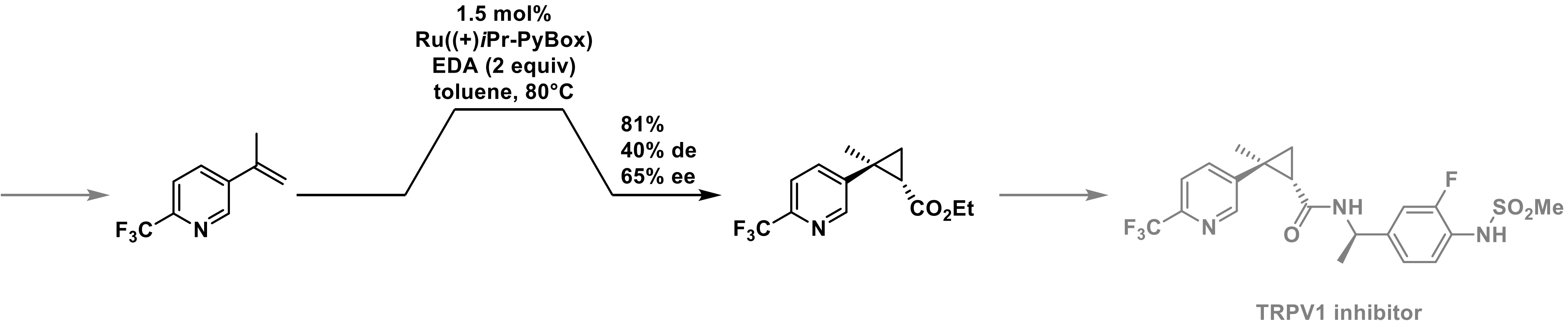



K. E. Hernandez, H. Renata, R. D. Lewis, S. B. J. Kan, C. Zhang, J. Forte, D. Rozzell, J. A. McIntosh, F. H. Arnold, *ACS Catal.* **2016**, *6*, 7810–7813.
P. Bajaj, G. Sreenilayam, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, *55*, 16110–16114.

# Synthesis of drug intermediates

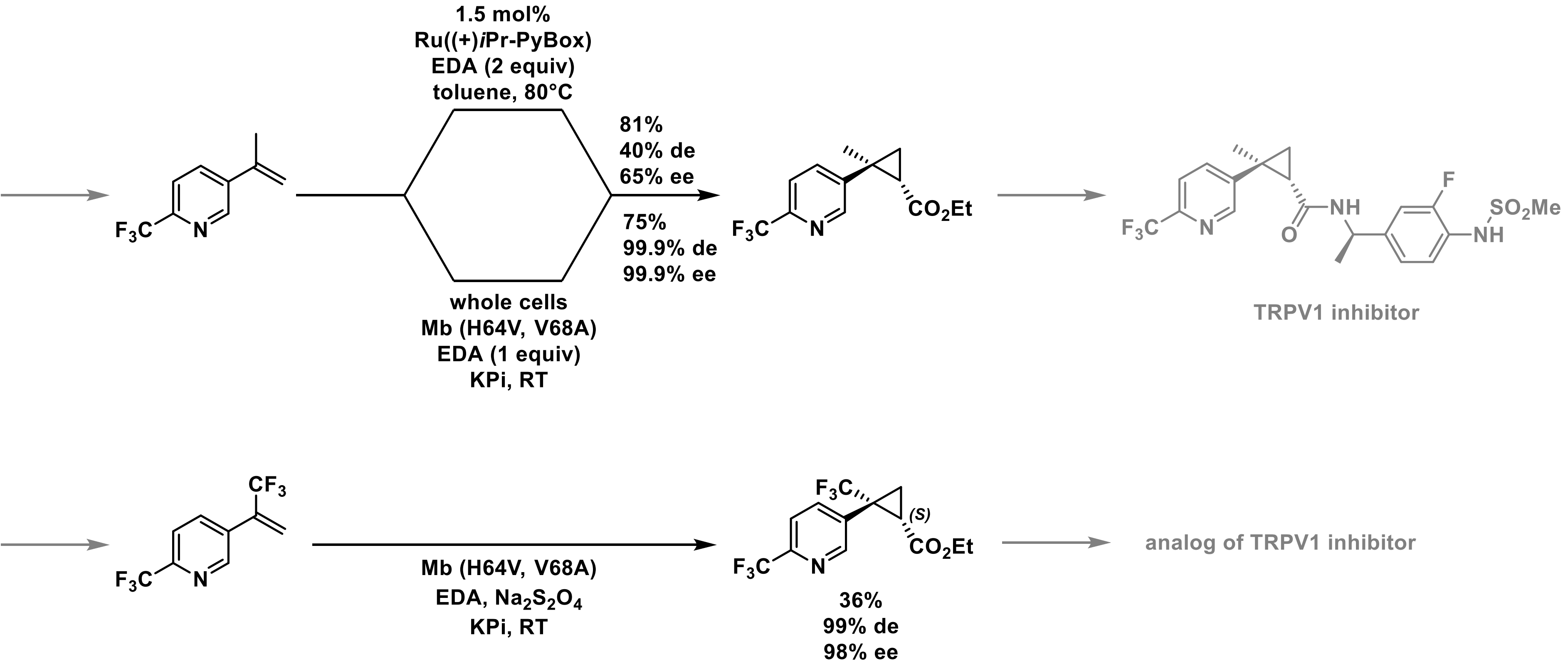






- P. Bajaj, G. Sreenilayam, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, *55*, 16110–16114.
  D. M. Carminati, J. Decaens, S. Couve-Bonnaire, P. Jubault, R. Fasan, *Angew. Chemie* **2021**, *133*, 7148–7152.

# Synthesis of drug intermediates

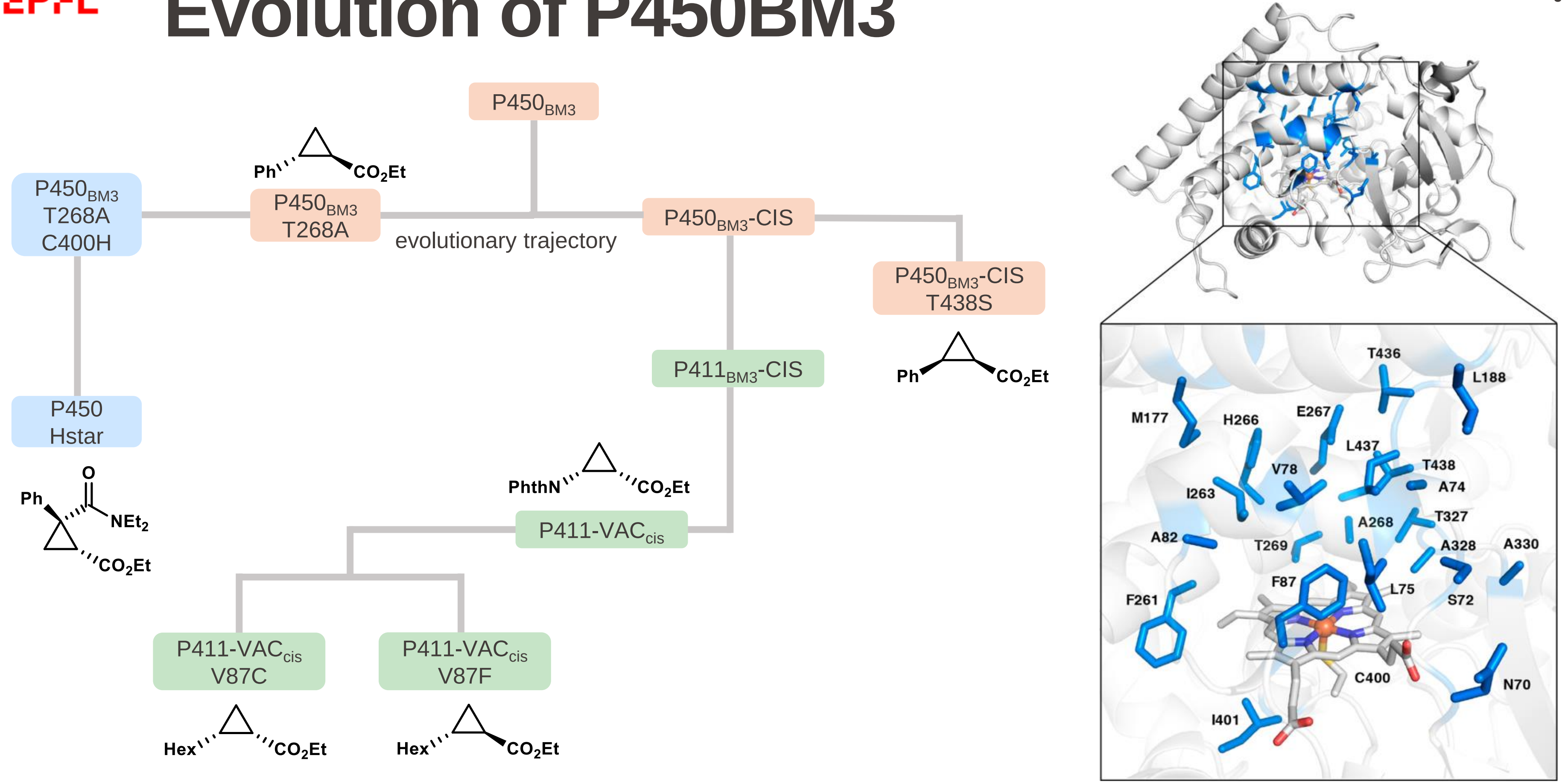



- P. Bajaj, G. Sreenilayam, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, *55*, 16110–16114.
D. M. Carminati, J. Decaens, S. Couve-Bonnaire, P. Jubault, R. Fasan, *Angew. Chemie* **2021**, *133*, 7148–7152.

# Advantages and disadvantages of enzyme catalysis

| Advantages | Disadvantages |
| --- | --- |
| Environmentally friendly | |
| Highly selective | Very limited scope |
| Highly evolvable | More difficult to obtain the other enantiomer |
| | Catalysts not commercially available |
| | Unfamiliar technics and knowledge |

# Evolution of P450BM3



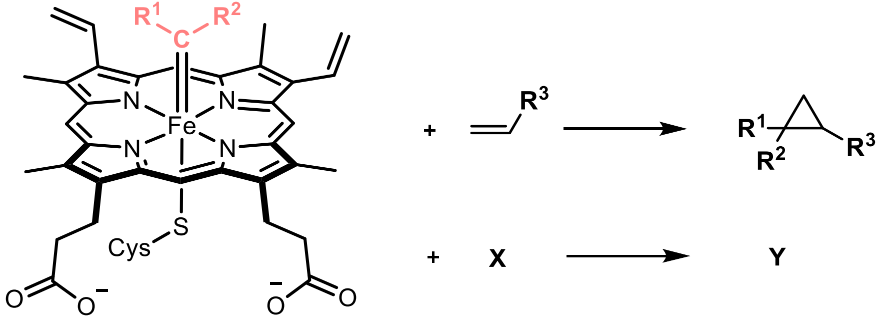

- Y. Yang, F. H. Arnold, *Acc. Chem. Res.* **2021**, *54*, 1209–1225.

# Thank you for your attention!

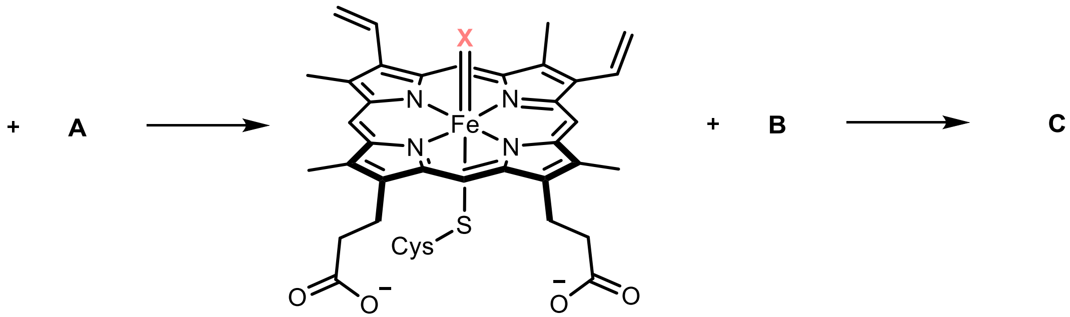
# Question 1: suggest other reactivity



1) Suggest other products



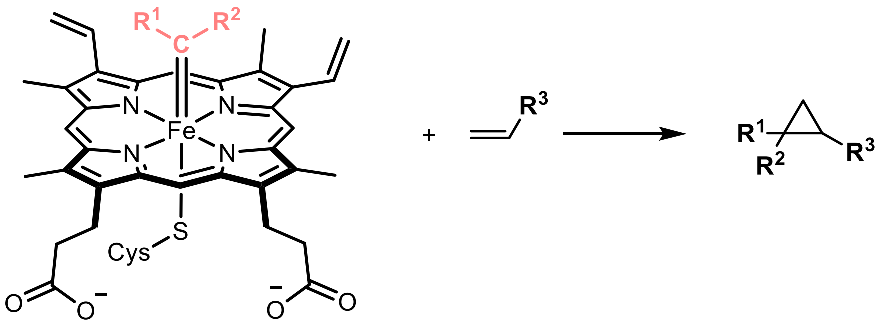

2) Suggest other reactive intermediate



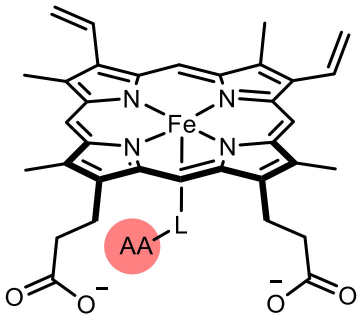
# Question 2: mechanism



1) Suggest mechanism and the role of the reducing agent




2) Suggest the why the change of axial ligand allowed for *in vivo* application?



# Asymmetric Catalysis for $CO_2$ fixation

**Tin Nguyen**

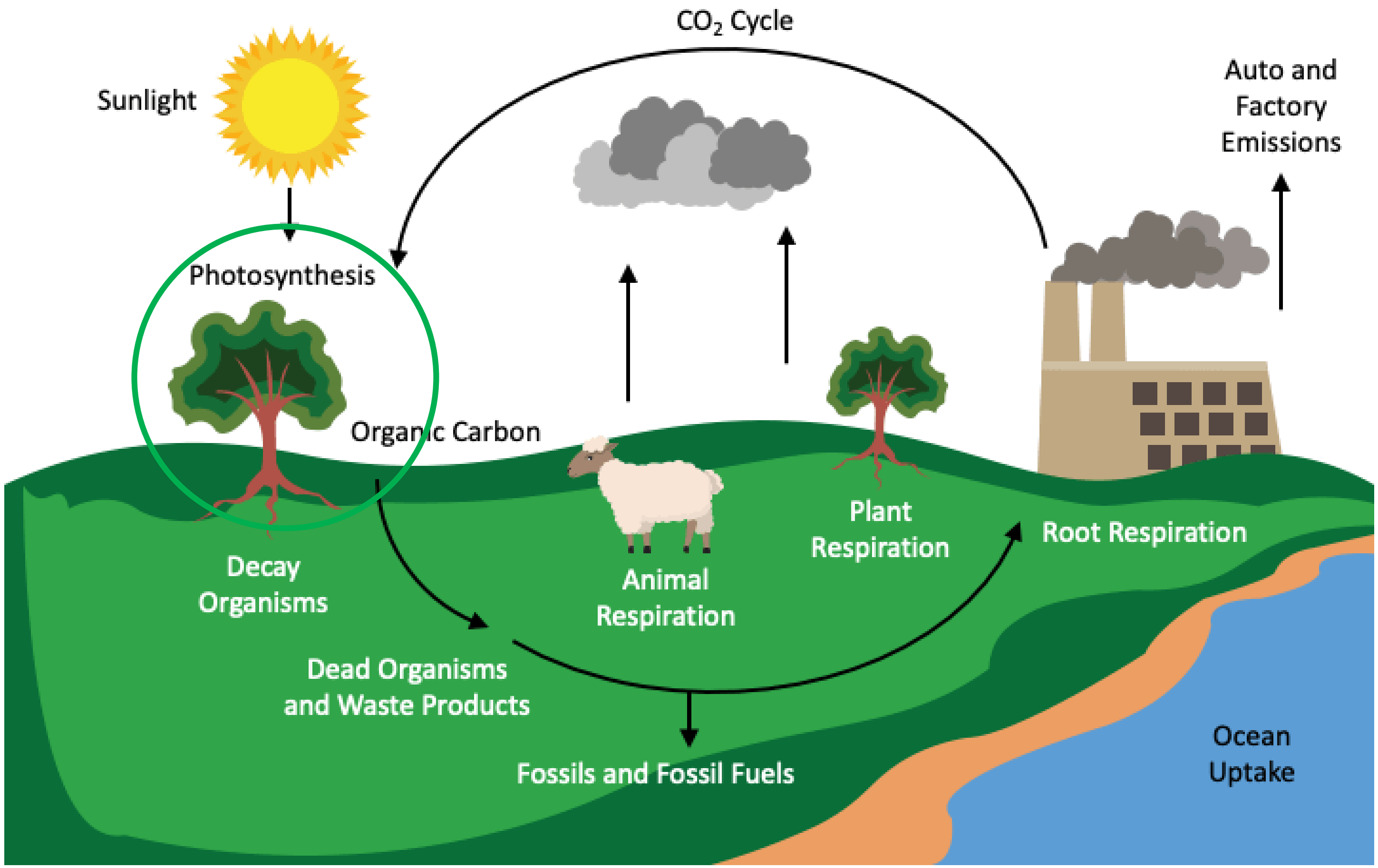
**Laboratory of Catalysis and Organic Synthesis**
***École Polytechnique Fédérale de Lausanne***

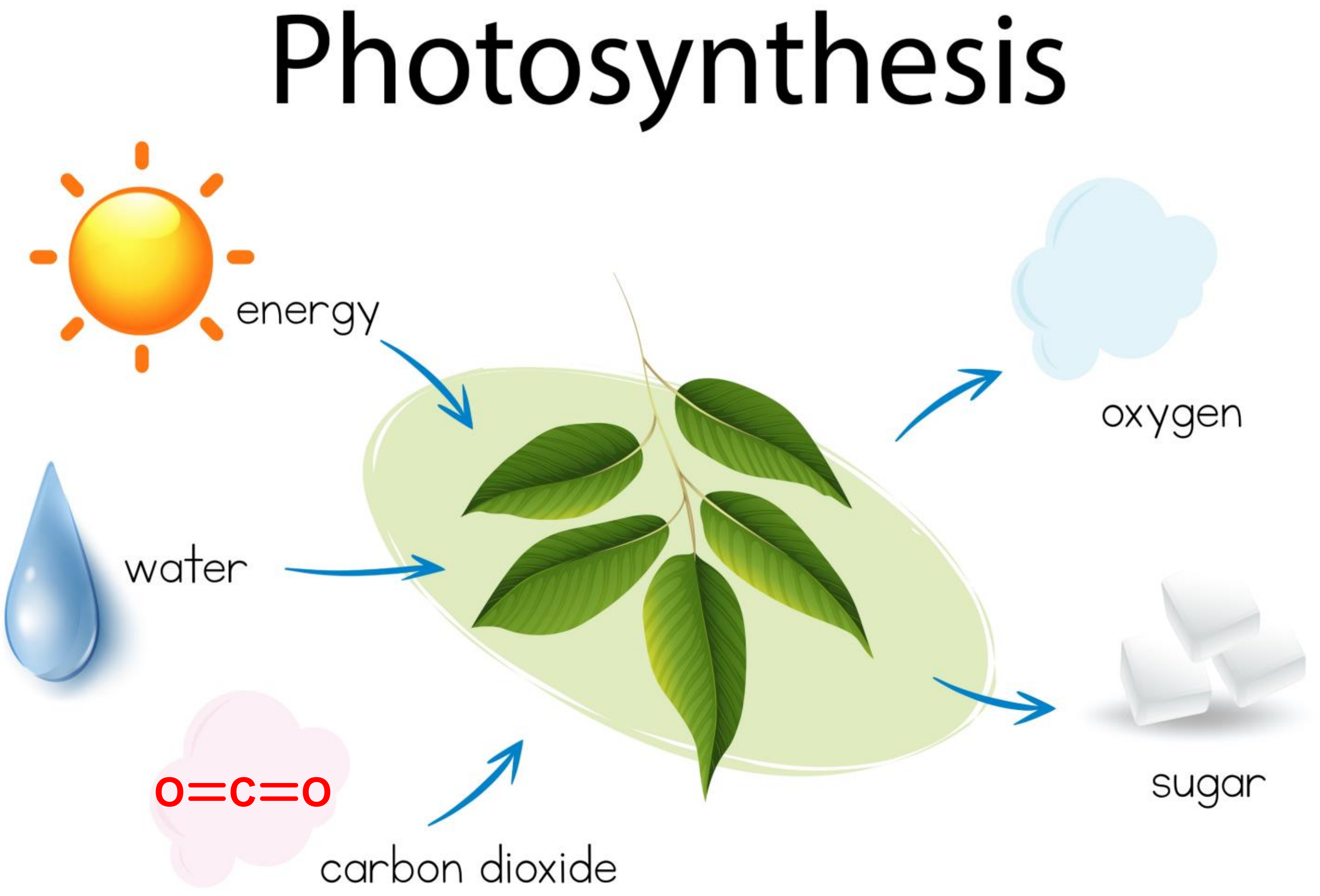
**Frontiers in Organic Synthesis. Part III Stereochemistry**
**16.05.2022**

EPFL

**CARBON CYCLE**

**Human activity alone generates ~33 billion metric tons of $CO_2$ per year**

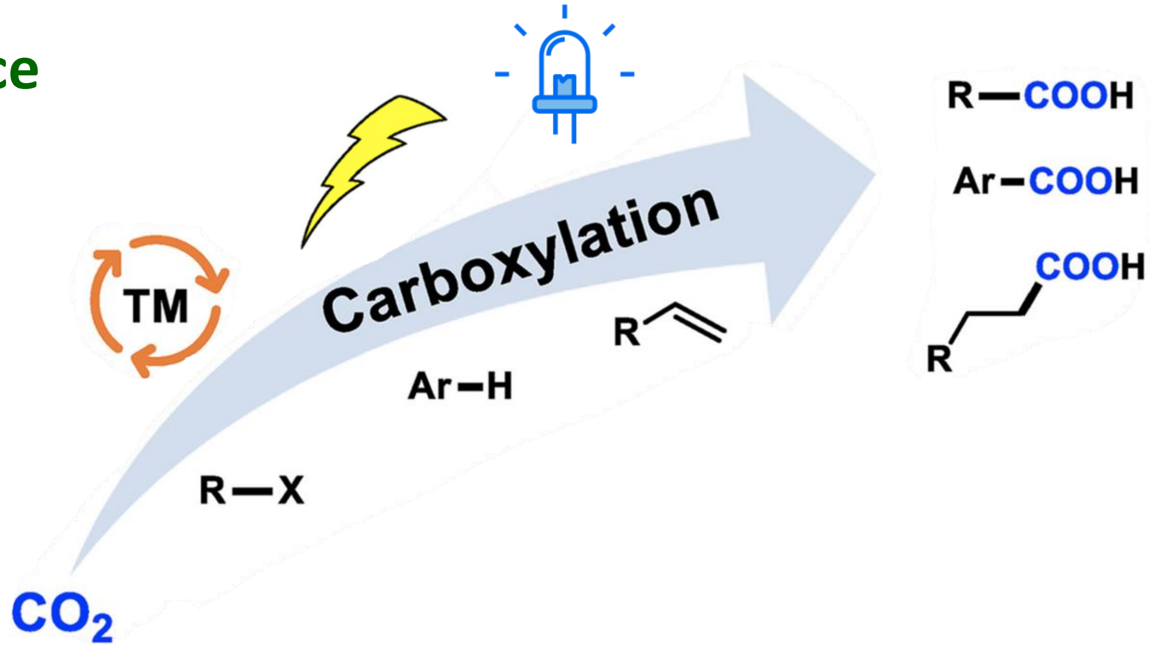


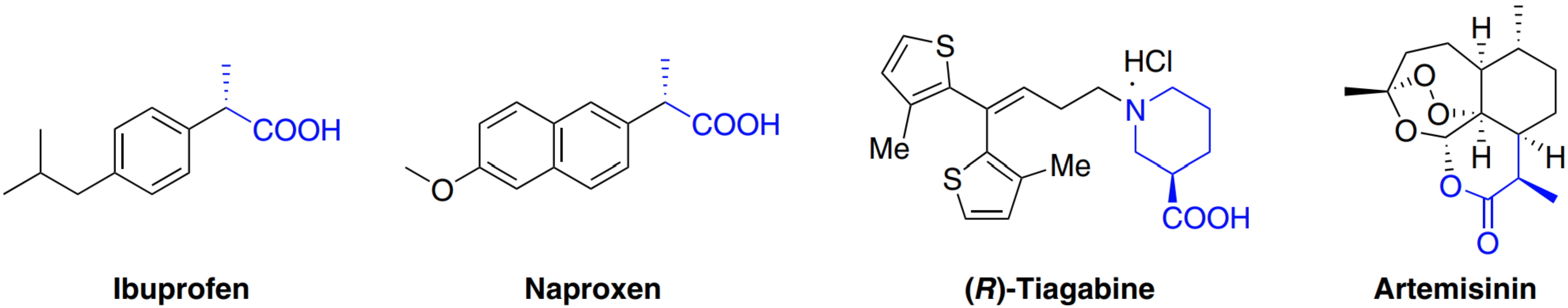

Photosynthesis
energy
water
O=C=O
carbon dioxide
oxygen
sugar

# Introduction

$O=C=O$

- An ideal C1 source
- High abundance
- Low cost
- Nontoxicity
- Renewability

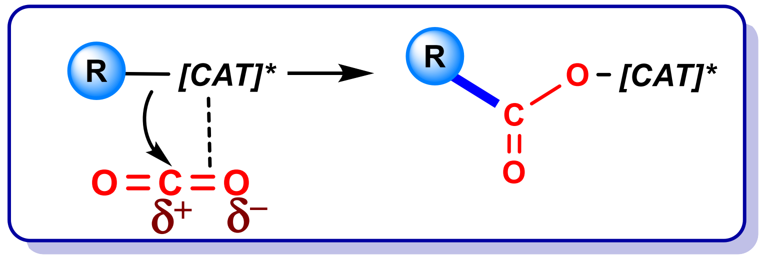


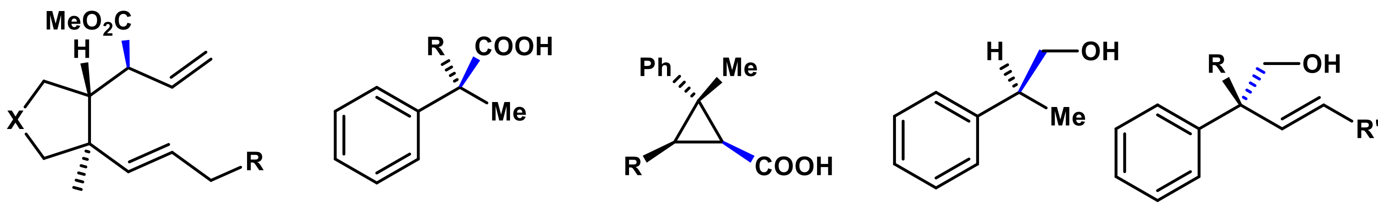




1.*Nature communications* 11, no. 1 (2020): 1-10,
2.*Current Opinion in Green and Sustainable Chemistry* 32 (2021): 100525

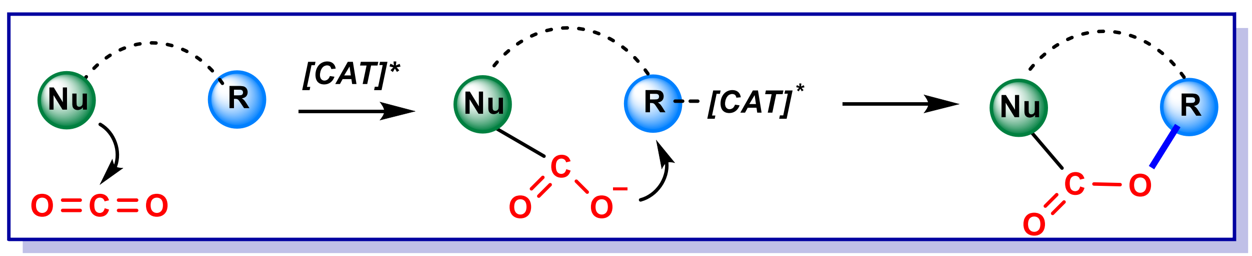
# Introduction

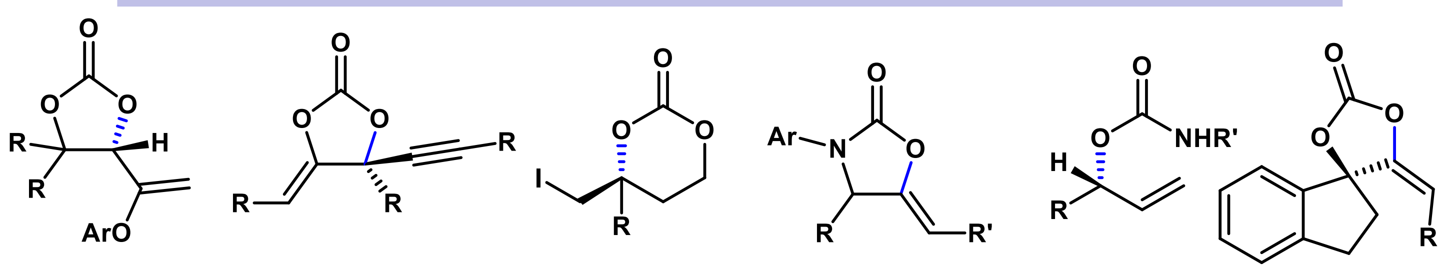
## C-C bond formation




## C-O bond formation



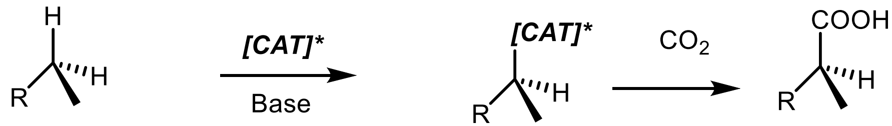




1. *Chinese Journal of Organic Chemistry* 40, no. 8 (2020): 2208-2220,
2. *ACS catalysis* 7, no. 10 (2017): 7231-7244

# Outline

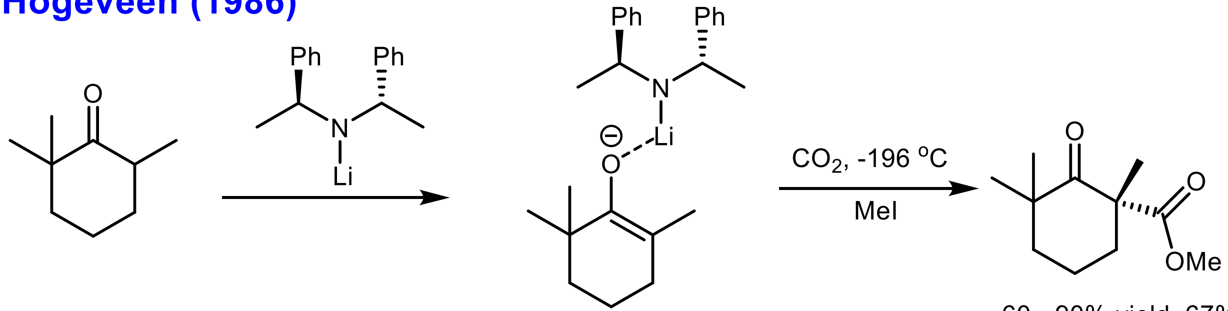
- Introduction
- **C-C bond formation**
- C-O bond formation
- Conclusion and outlook
- Questions

# Enantioselective deprotonation



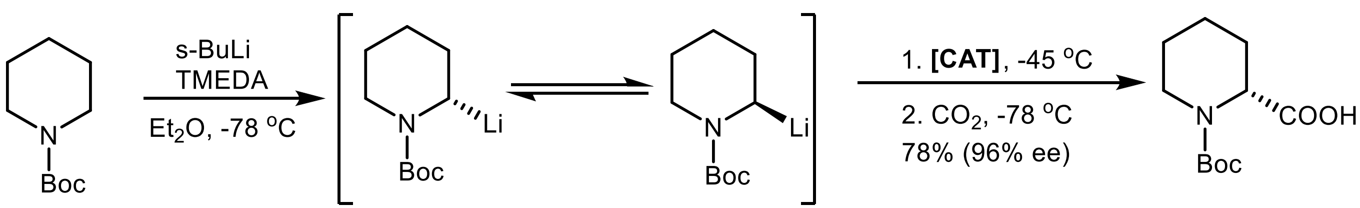

***Enantioselective deprotonation***

## Hogeveen (1986)

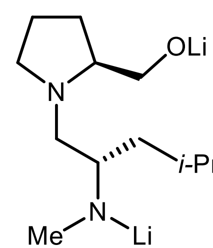



60 - 90% yield, 67% *ee*

## Gawley (2010)

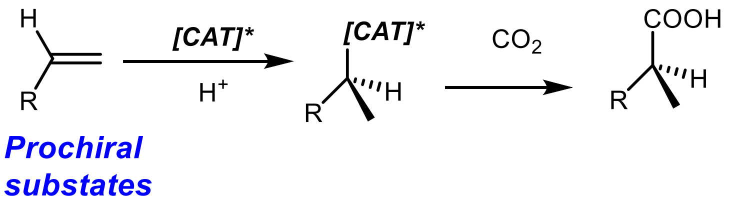



**[CAT]**

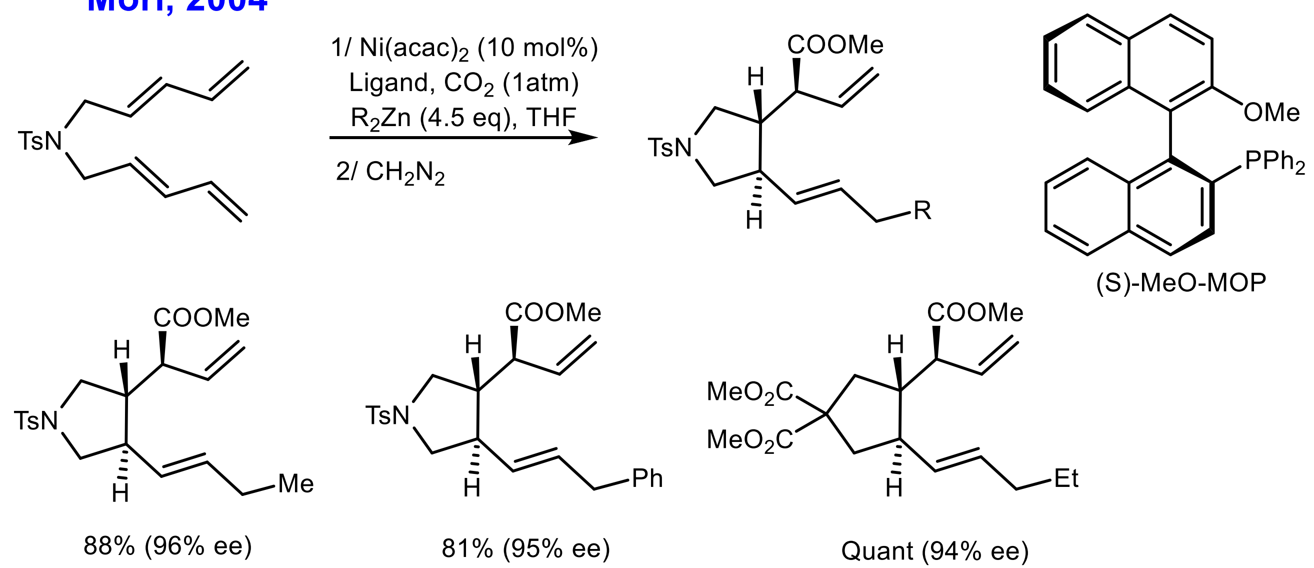



1. *Tetrahedron letters* 27, no. 24 (1986): 2767-2770.
2. *J. Am. Chem. Soc.* 2010, 132, 35, 12216–12217

# Enantioselective deprotonation

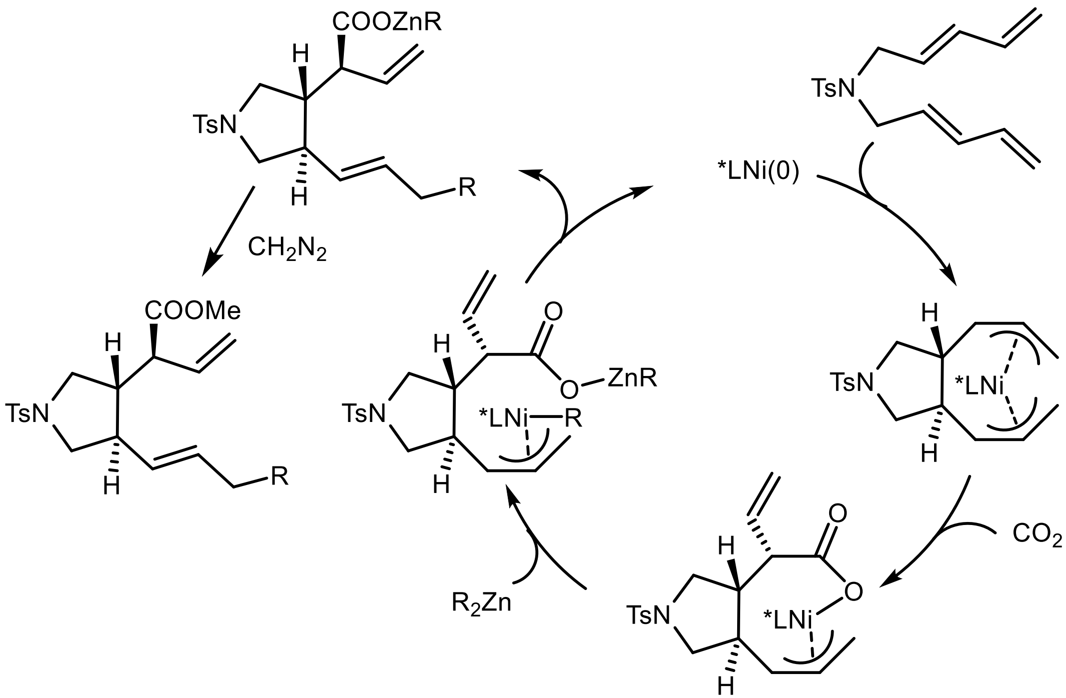


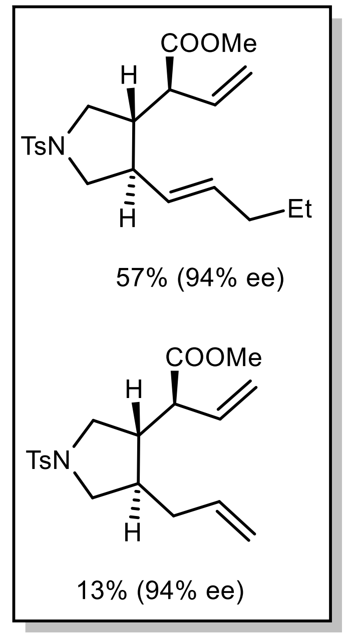

## Mori, 2004




*ACS catalysis* 7, no. 10 (2017): 7231-7244
J. Am. Chem. Soc. 2004, 126, 5956

# Carboxylation of unsaturated substrates by Mori

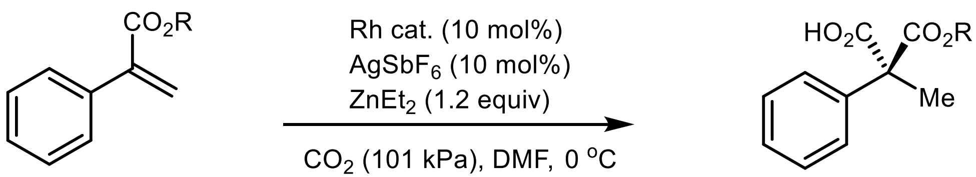


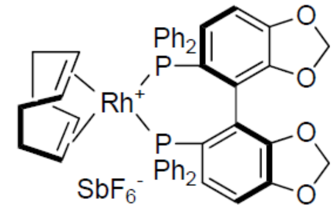






1. J. Am. Chem. Soc. 2002, 124, 10008
2. J. Am. Chem. Soc. 2004, 126, 5956

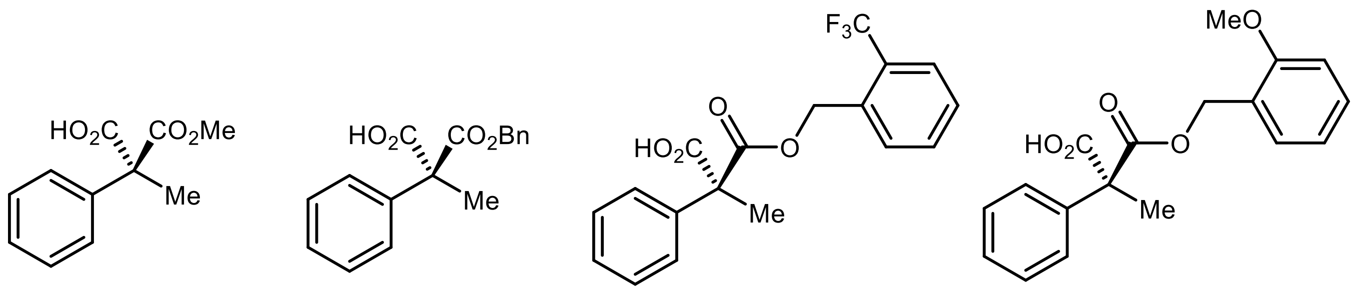
# Hydro - carboxylation of unsaturated substrates by Mikami



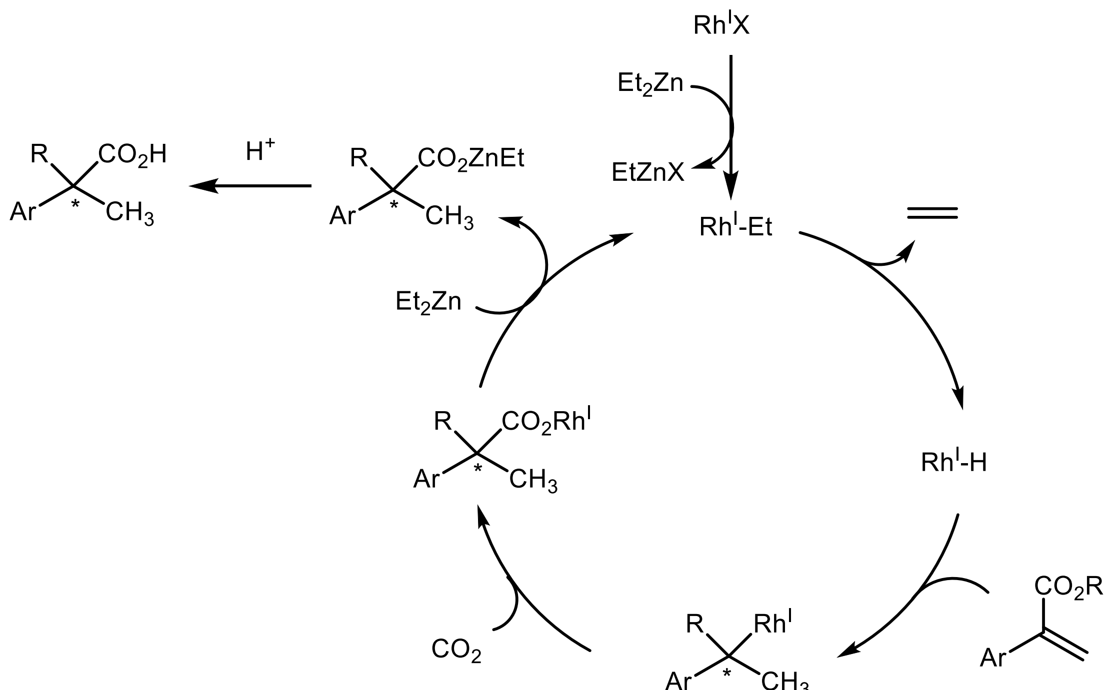



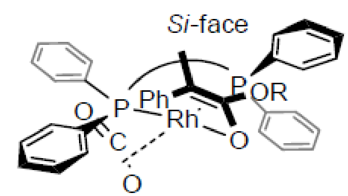

Rh cat.

**(S)-Segphos**

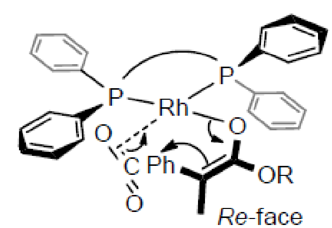



59% (60% ee) 41% (50% ee) 64% (60% ee) 37% (60% ee)



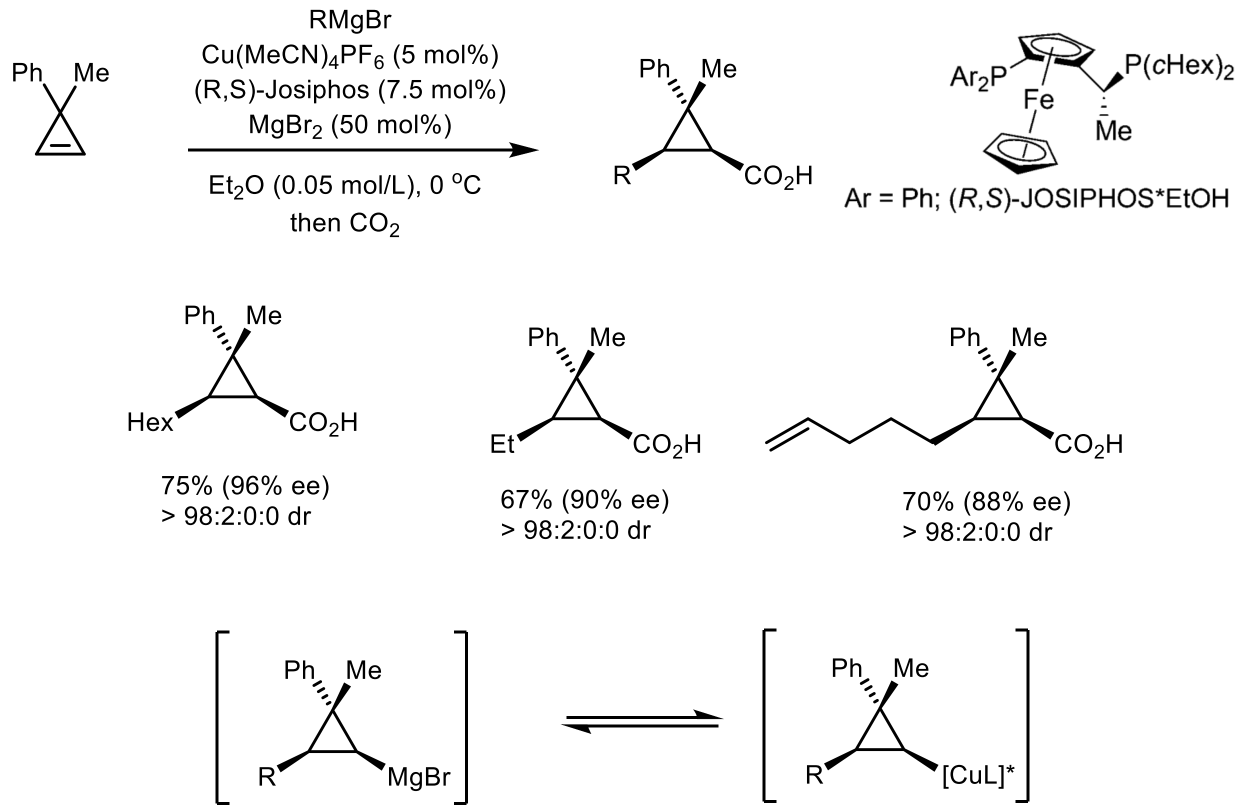

*disfavored*




***Favored***

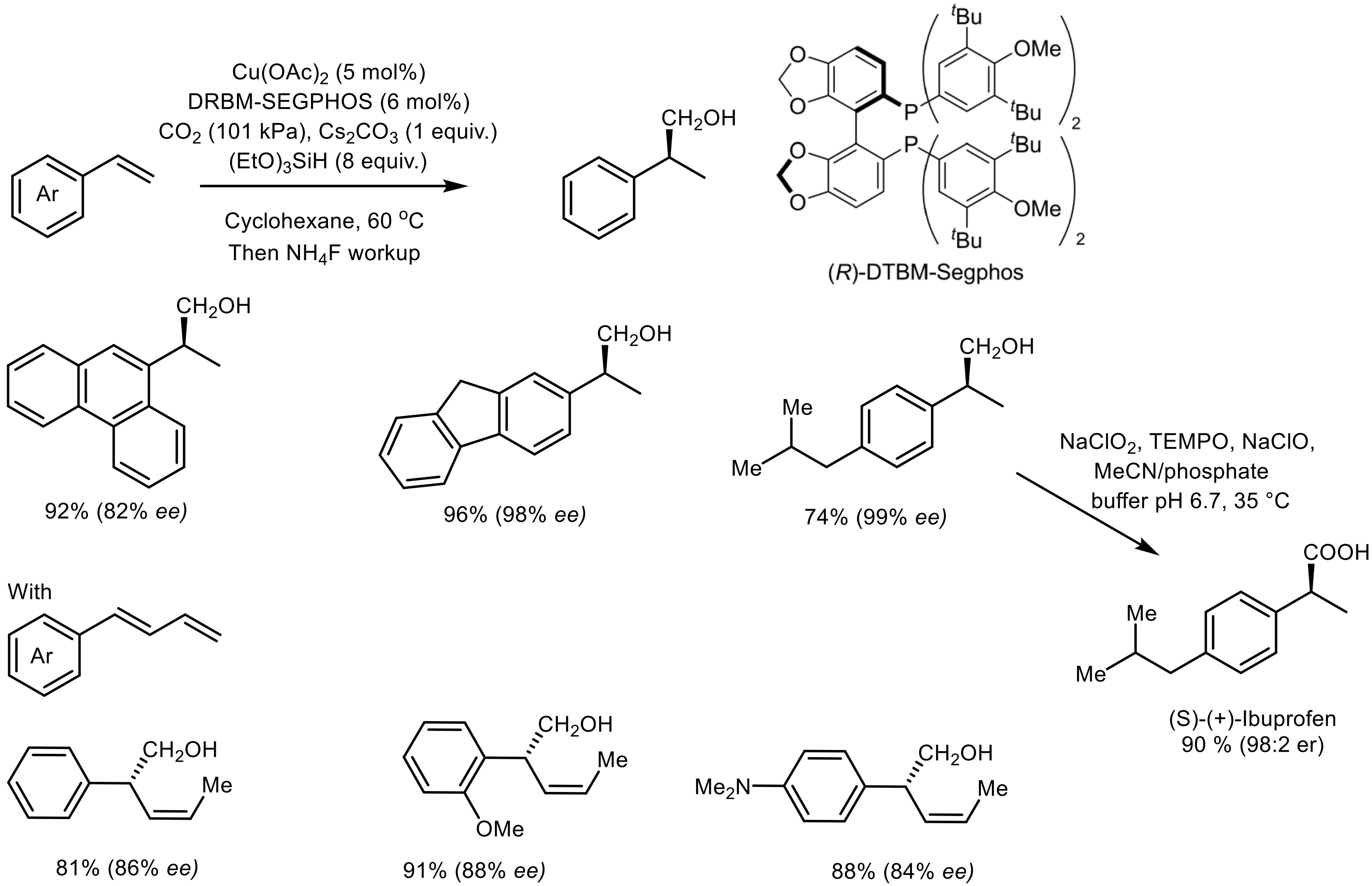
1. Angew. Chem., Int. Ed. **2017**, 56, 6783.

# Carboxylation of cyclopropene by Marek



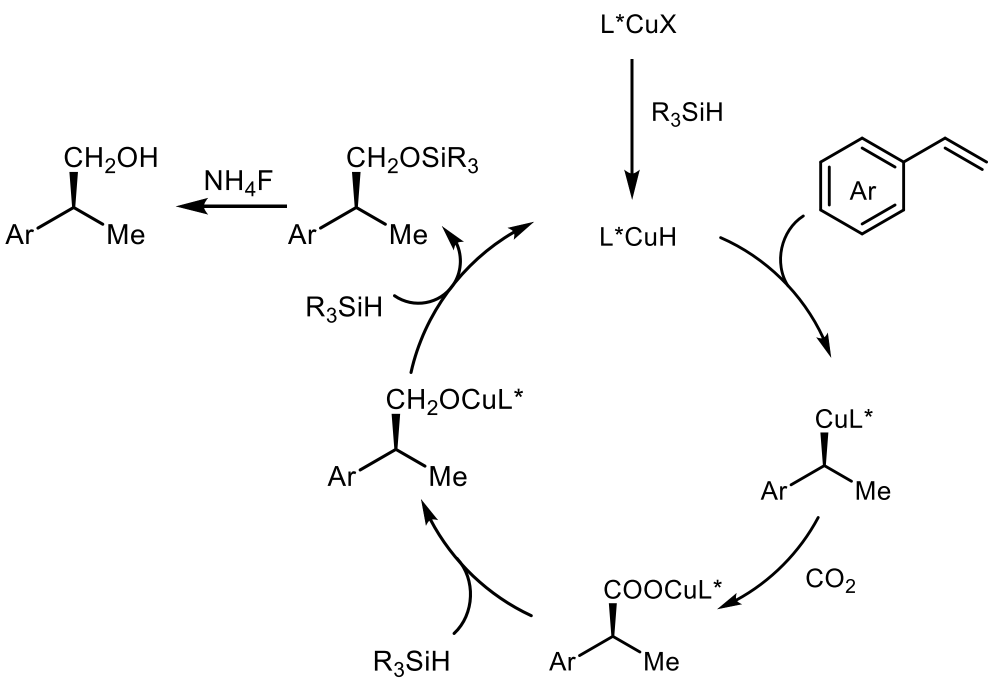

1. Angew. Chem., Int. Ed. 2017, 56, 6783.

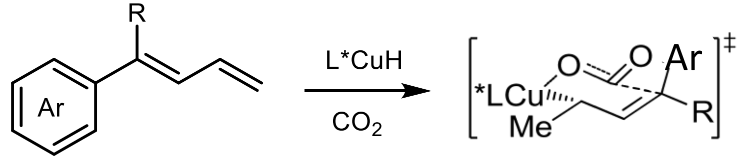
# Carboxylation of unsaturated substrates by Yu




1. J. Am. Chem. Soc. 2017, 139, 17011.

# Carboxylation of unsaturated substrates by Yu



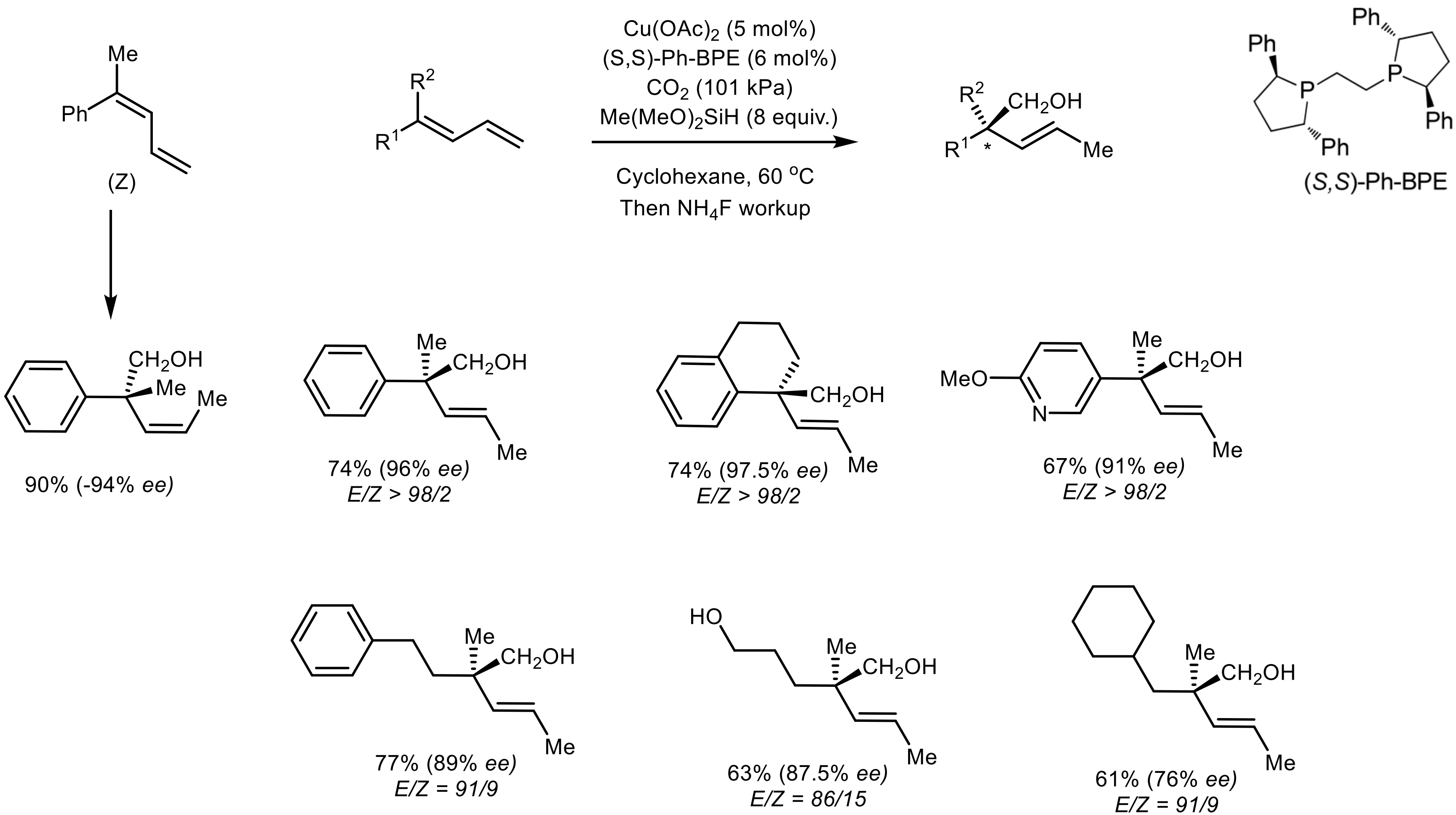




R = H



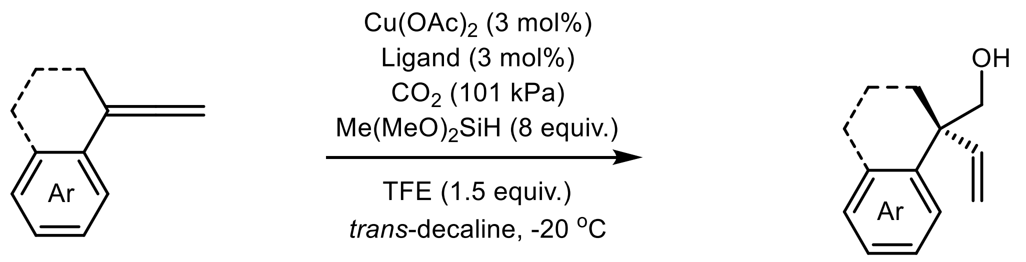

1. J. Am. Chem. Soc. 2017, 139, 17011.
2. J. Am. Chem. Soc. 2019, 141, 18825

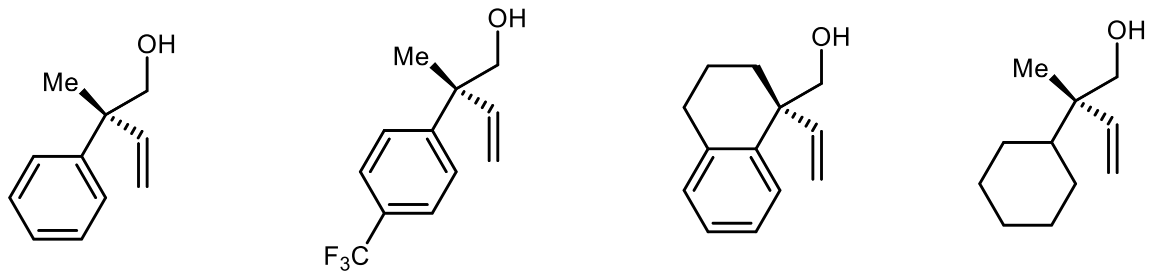
# Carboxylation of unsaturated substrates by Yu



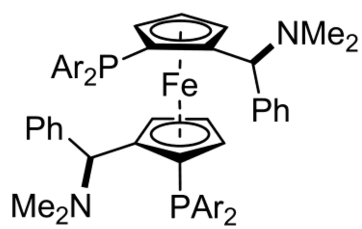

1. J. Am. Chem. Soc. 2019, 141, 18825

# Hydroxymethylation of 1,1-disubstituted allenes by Ding




88% (90% *ee*) 85% (84% *ee*) 81% (90% *ee*) 93% (66% *ee*)

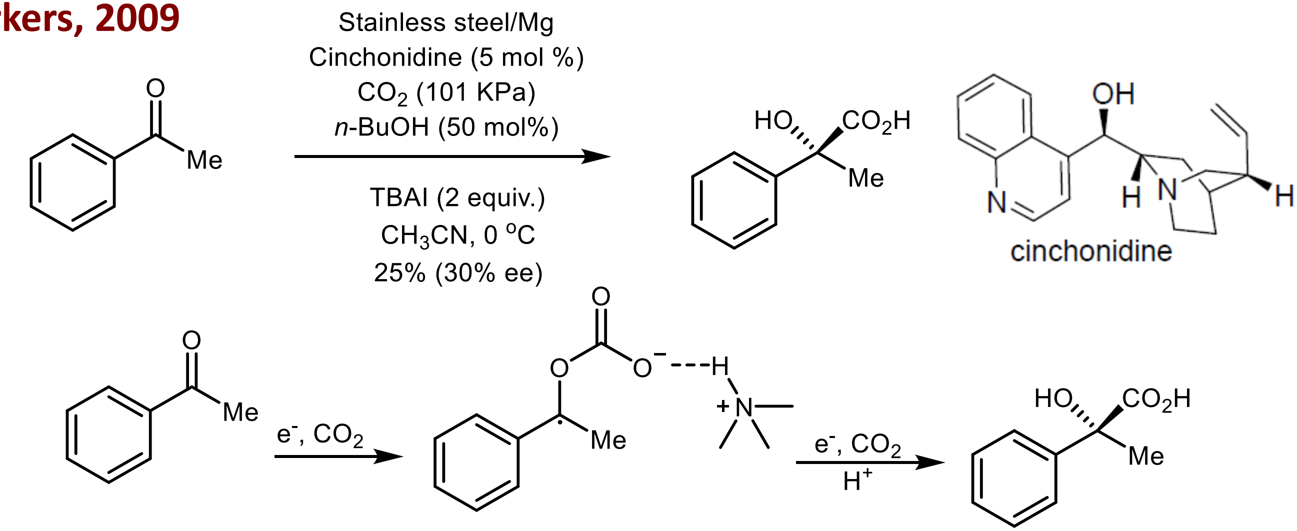



**Mandyphos ligand**

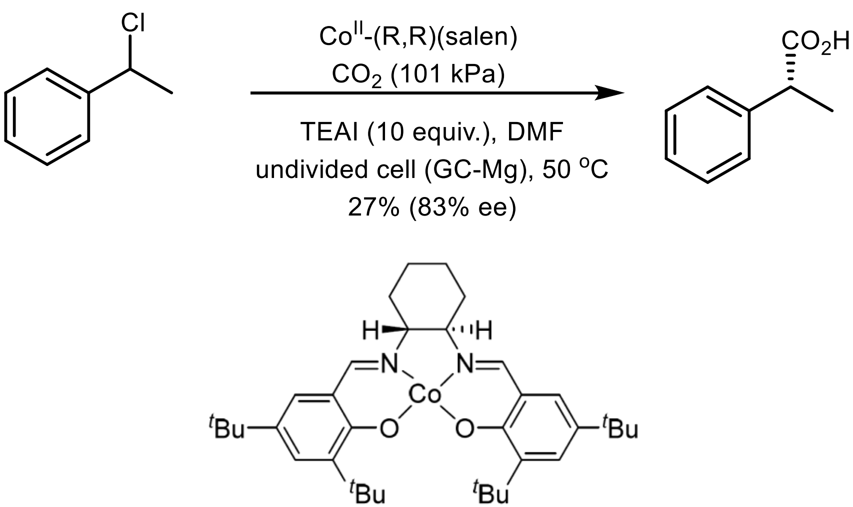
1. Chem.-Eur. J. 2019, 25, 13874

# Enantioselective electrochemical carboxylation

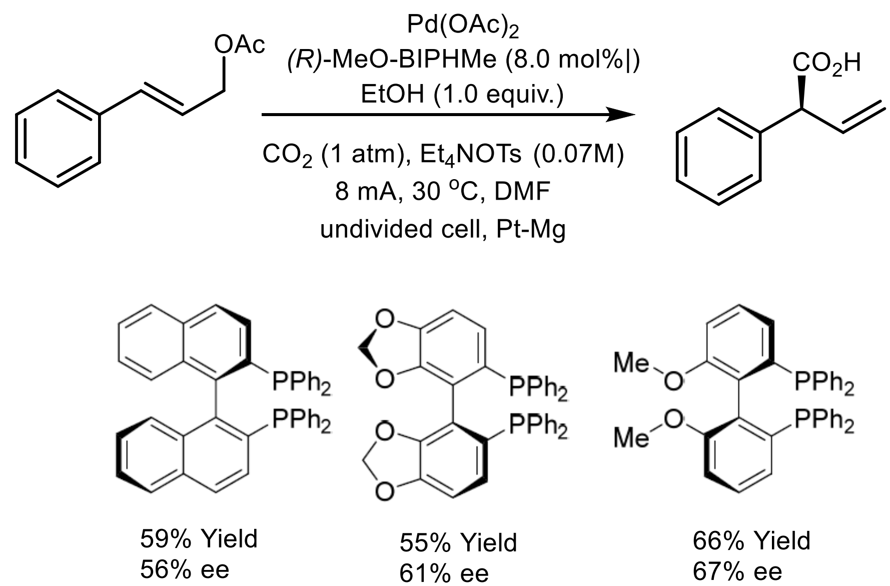
## Lu and co-workers, 2009




## Wang, Lu and co-workers, 2014




## Mei and co-worker, 2018



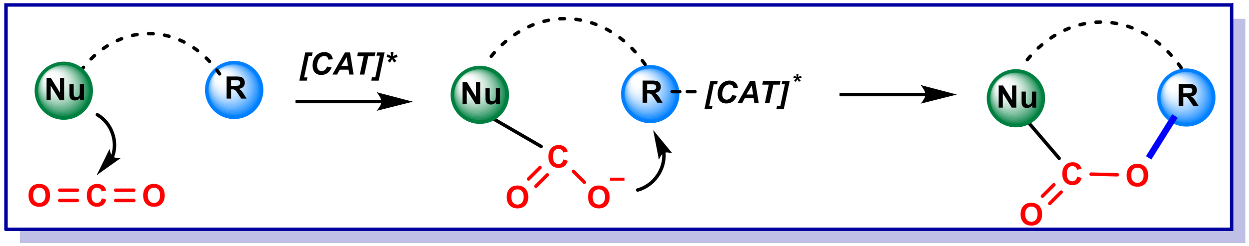


1. Electroanal. Chem. 2009, 630, 35. 2. Electrochim. Acta 2014, 116, 475. 3. Electrochem. Commun. 2014, 42, 55 . 4. Org. Chem. Front. 2018, 5, 2244.

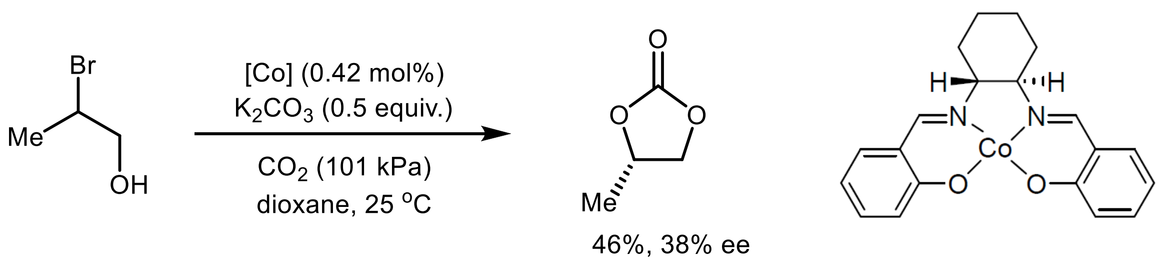
# Outline

- Introduction
- C-C bond formation
- **C-O bond formation**
- Conclusion and outlook
- Questions

# C-O bond formation

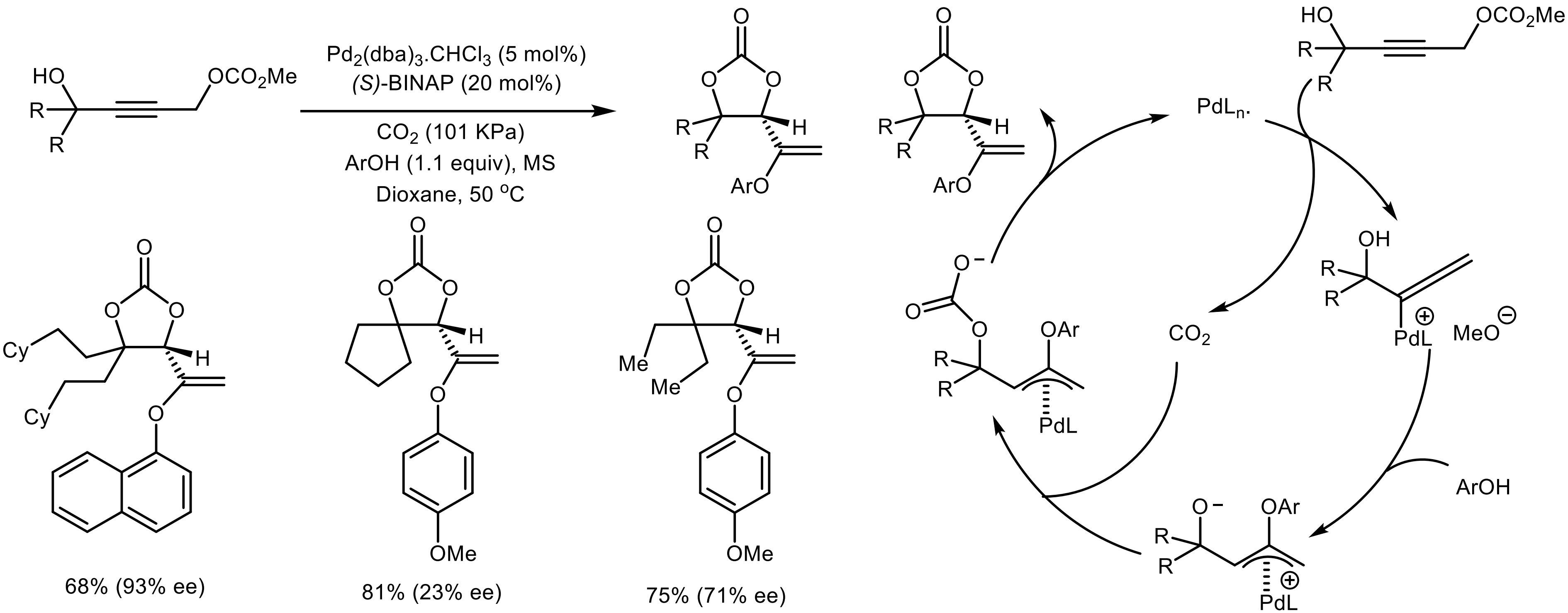


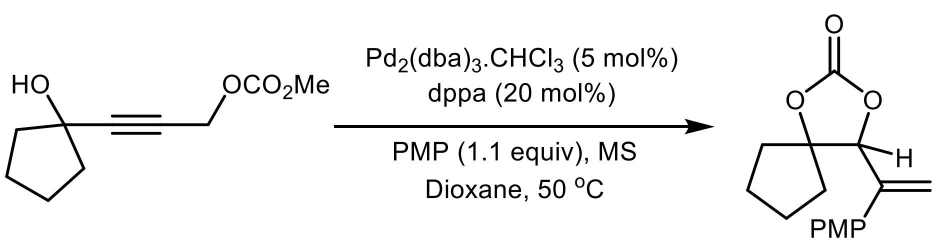

## 1987, Takeichi and co-workers




1. Chem. Lett. 1987, 1137.
2. Chem. Sci. 2012, 3, 2094–2102

# Asymmetric $CO_2$ elimination-fixation of propargylic carbonates

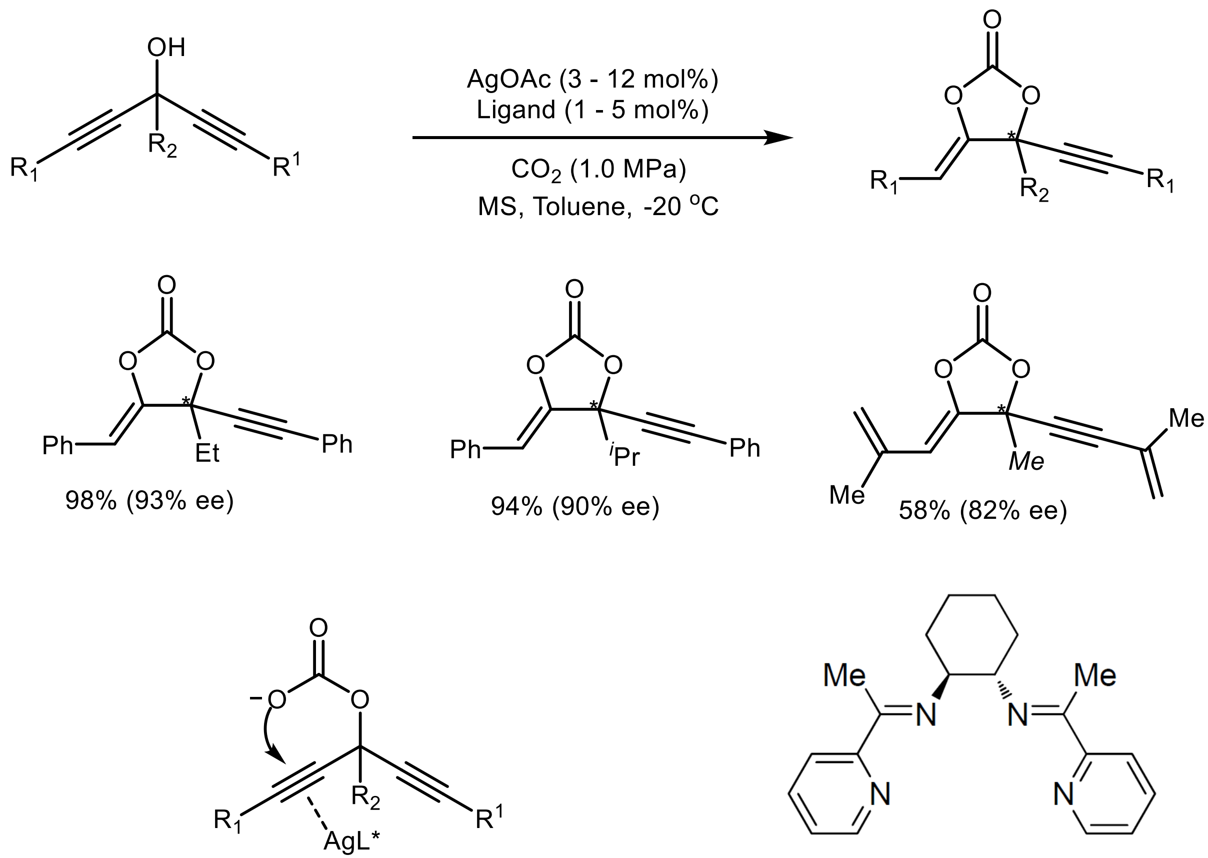



Under argon : 85%
$CO_2$ atmosphere: 96%
Bubbling Ar: 21%

1. J. Am. Chem. Soc. 2003, 125, 4874

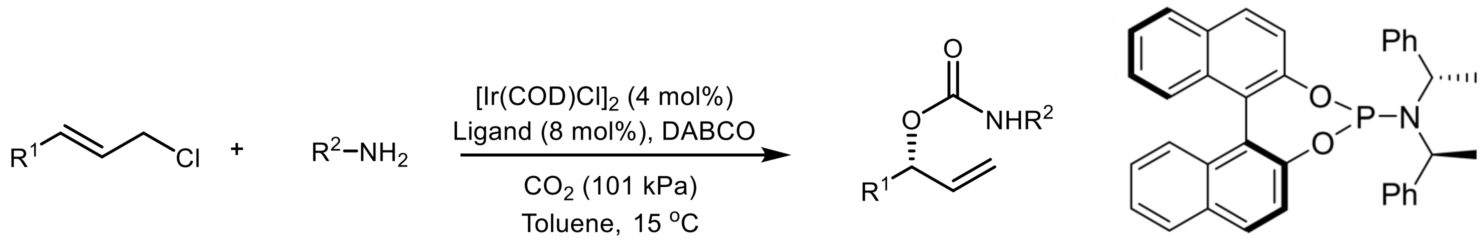
# Asymmetric $CO_2$ fixation with propargyl alcohols by Yamada

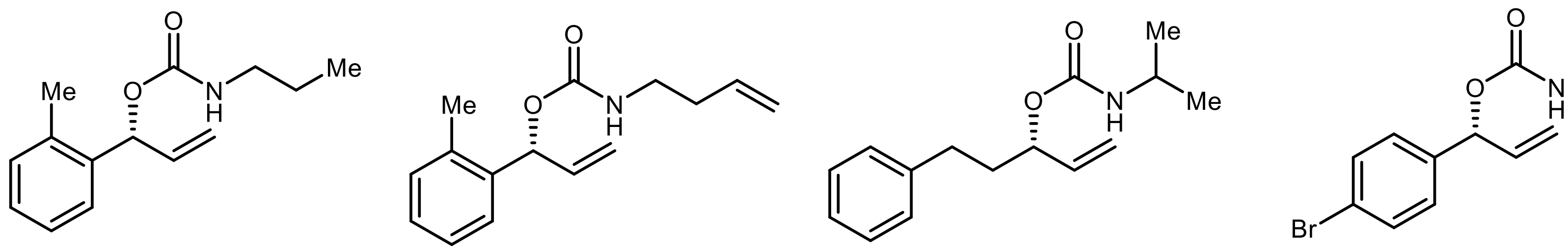



**Chiral Schiff base Ligand**

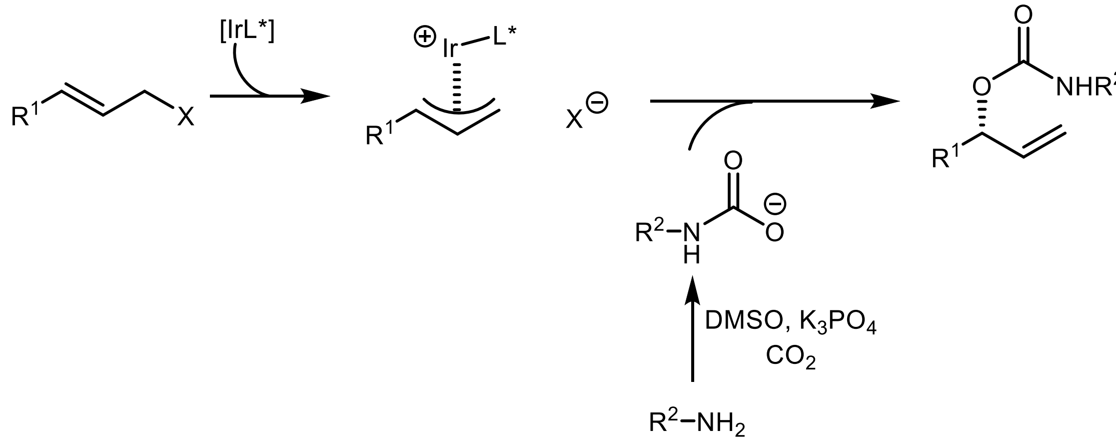
1. J. Am. Chem. Soc. 2010, 132, 4072.

# Ir-catalyzed asymmetric allylation



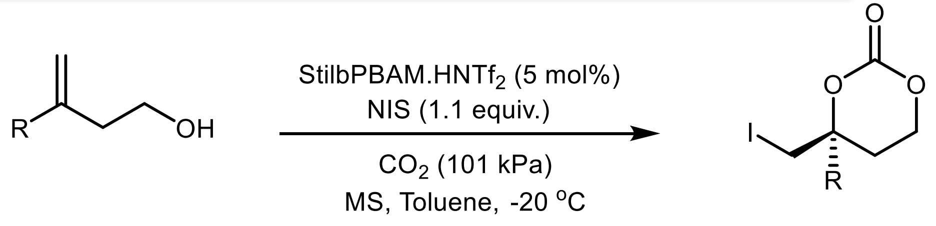



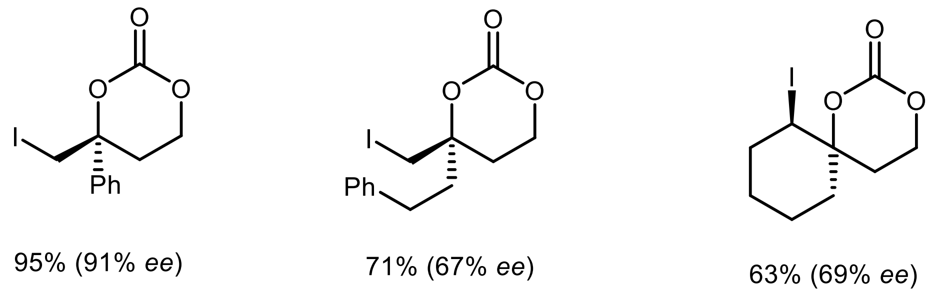

74% (84% *ee*)   50% (93% *ee*)   41% (38% *ee*)   35% (68% *ee*)

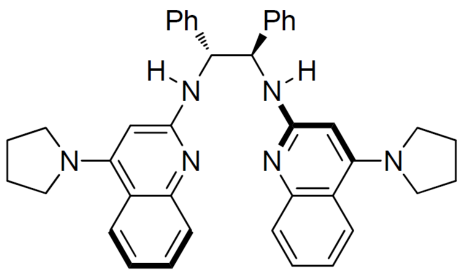



1. Chem.-Eur. J. 2014, 20, 7216.
2. Chem. Commun. 2014, 50, 4455

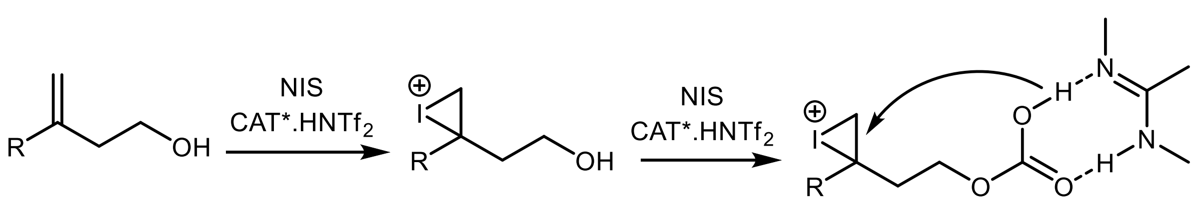
# Organocatalysis of asymmetric $CO_2$ fixation by Johnston



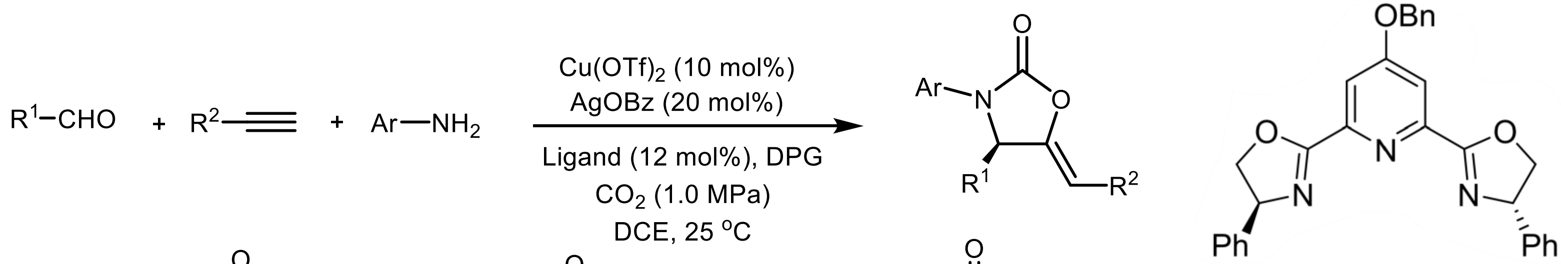



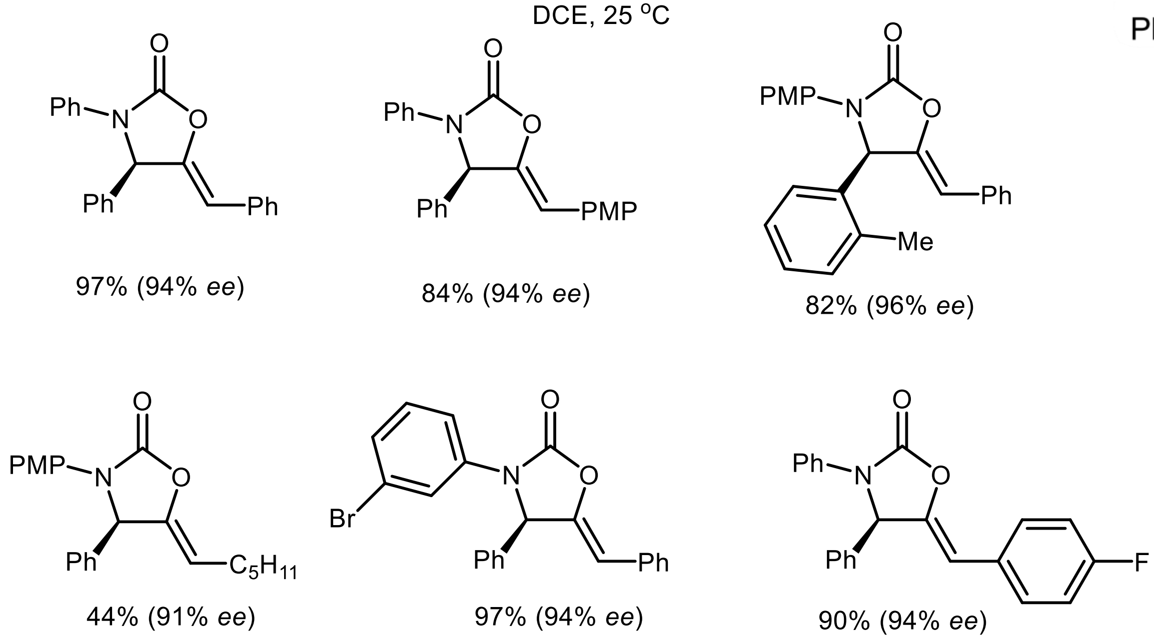

**Bifunctional catalyst**

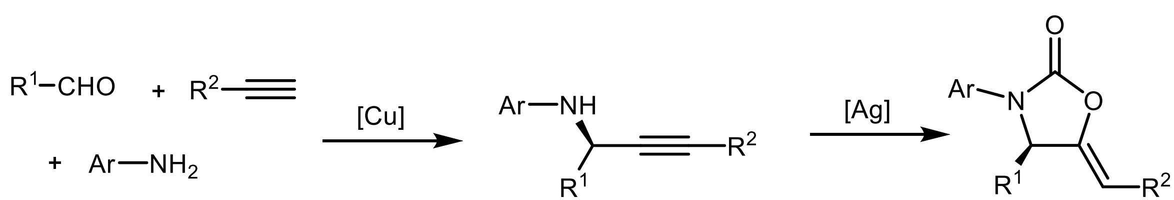



1. J. Am. Chem. Soc. 2015, 137, 7302

# Cu/Ag cocatalyzed tandem asymmetric carboxylation

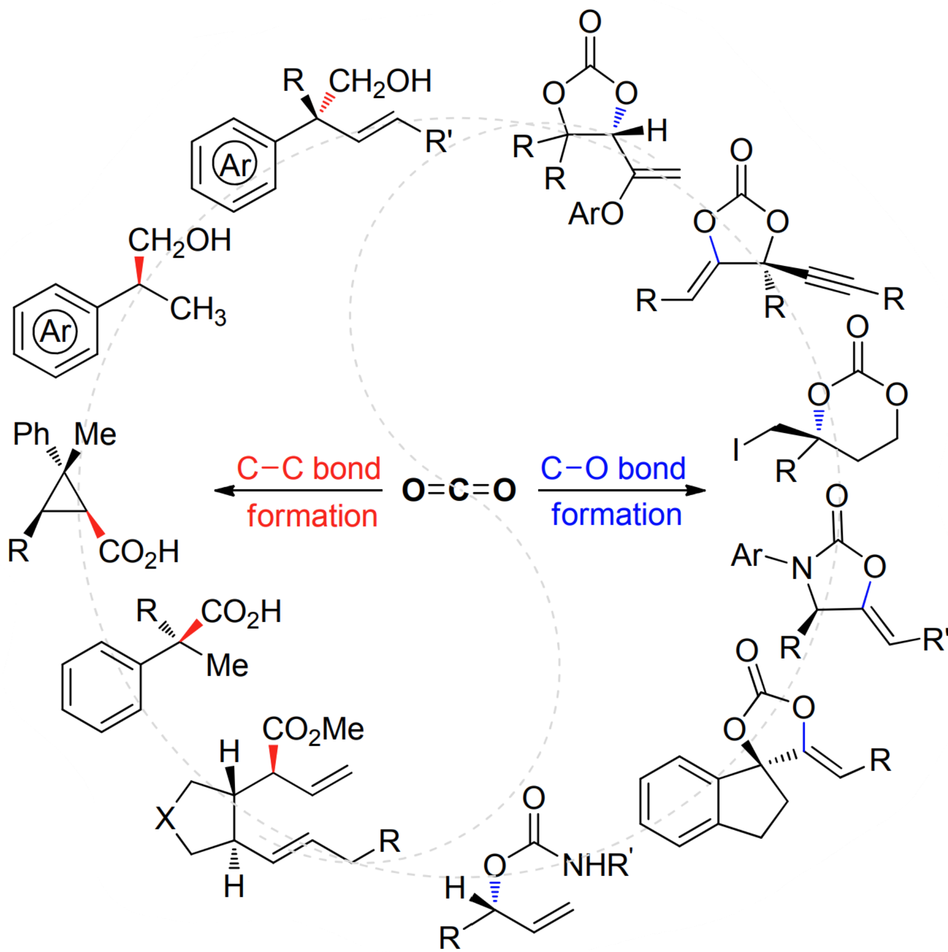



1. Chem. Commun. 2019, 55, 14303.

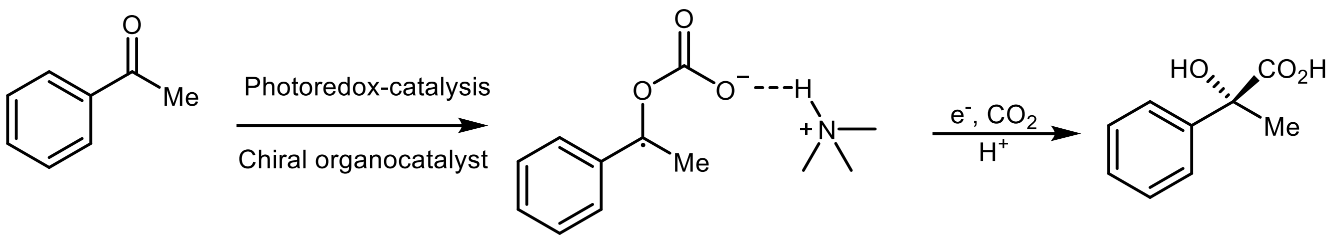
# Conclusions

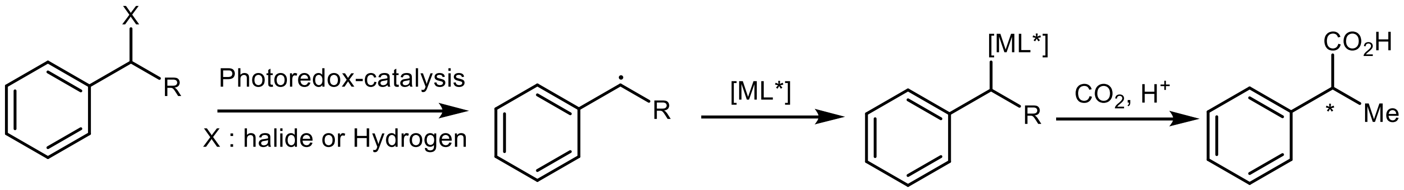


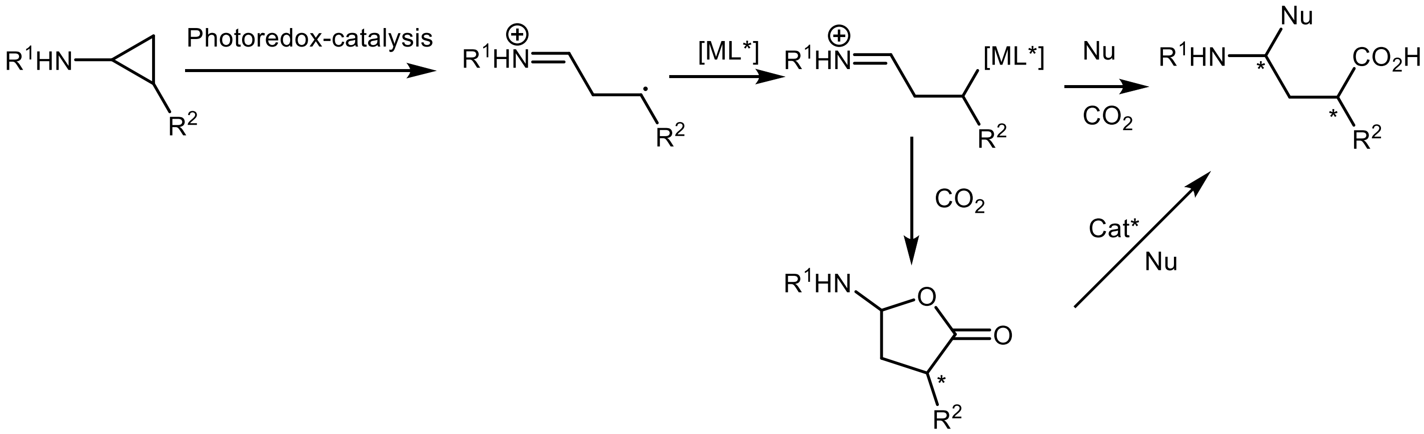


1. *Chinese Journal of Organic Chemistry* 40, no. 8 (2020): 2208-2220,
2. *ACS catalysis* 7, no. 10 (2017): 7231-7244

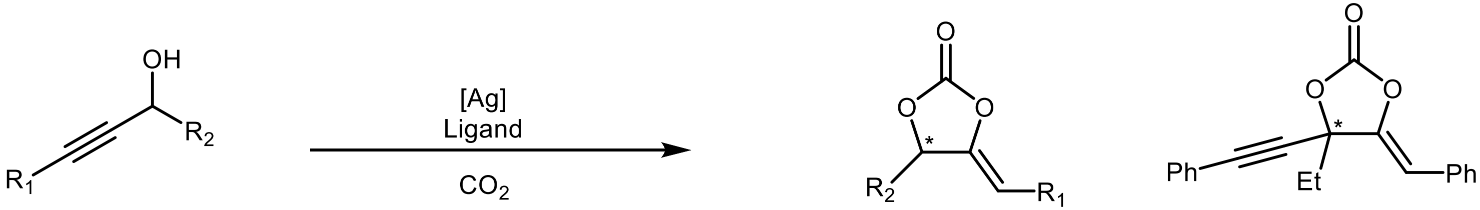
# Merging photoredox and asymmetric catalysis for carboxylation



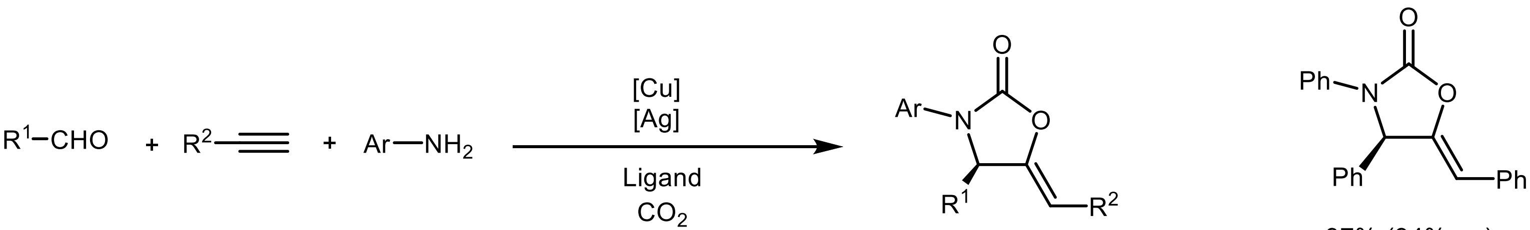



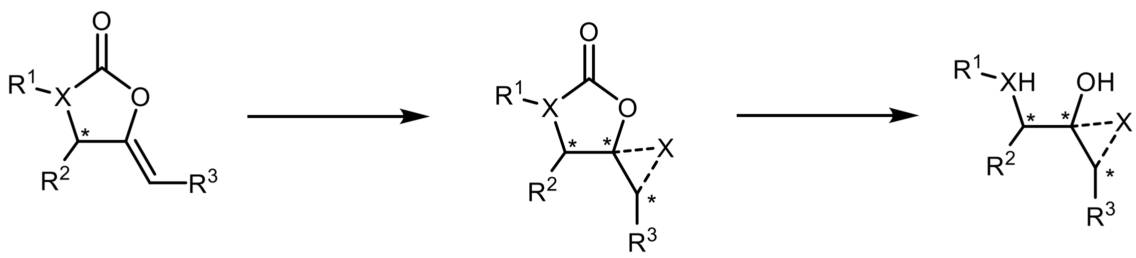
# Perspectives – application for tether chemistry




J. Am. Chem. Soc. 2010, 132, 4072.



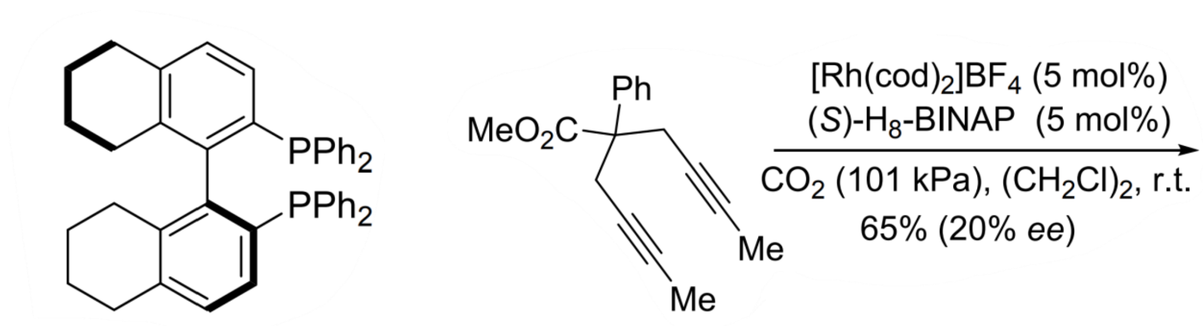

Chem. Commun. 2019, 55, 14303.

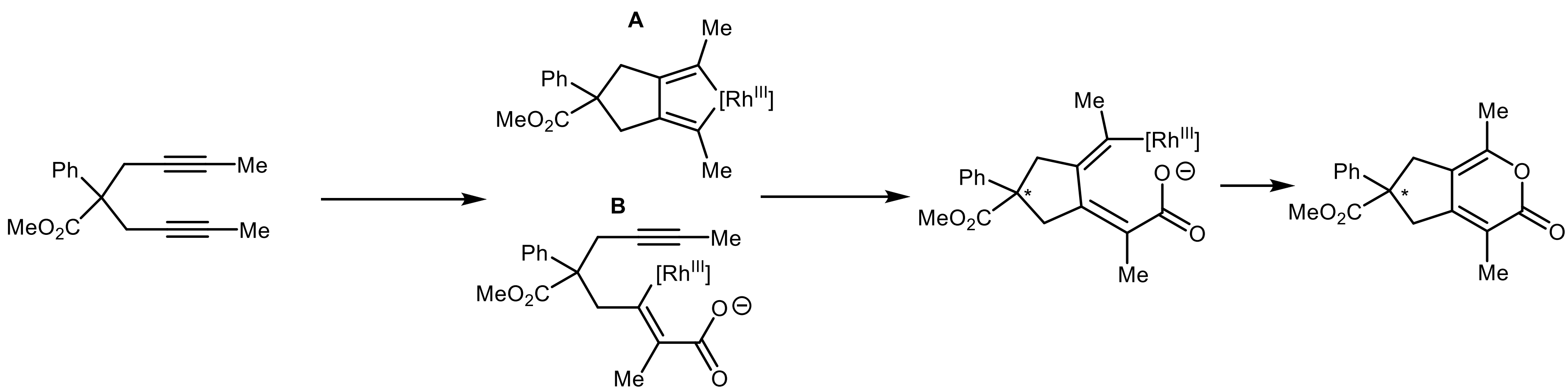


# Outline

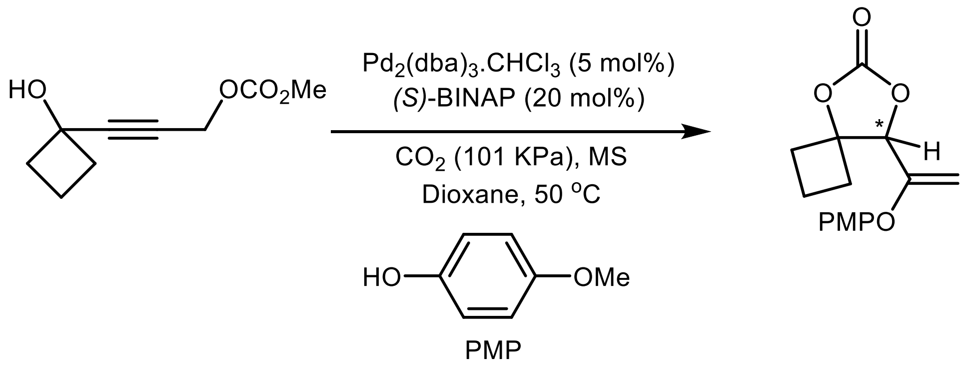
- Introduction
- C-C bond formation
- C-O bond formation
- Conclusion and outlook
- **Questions**

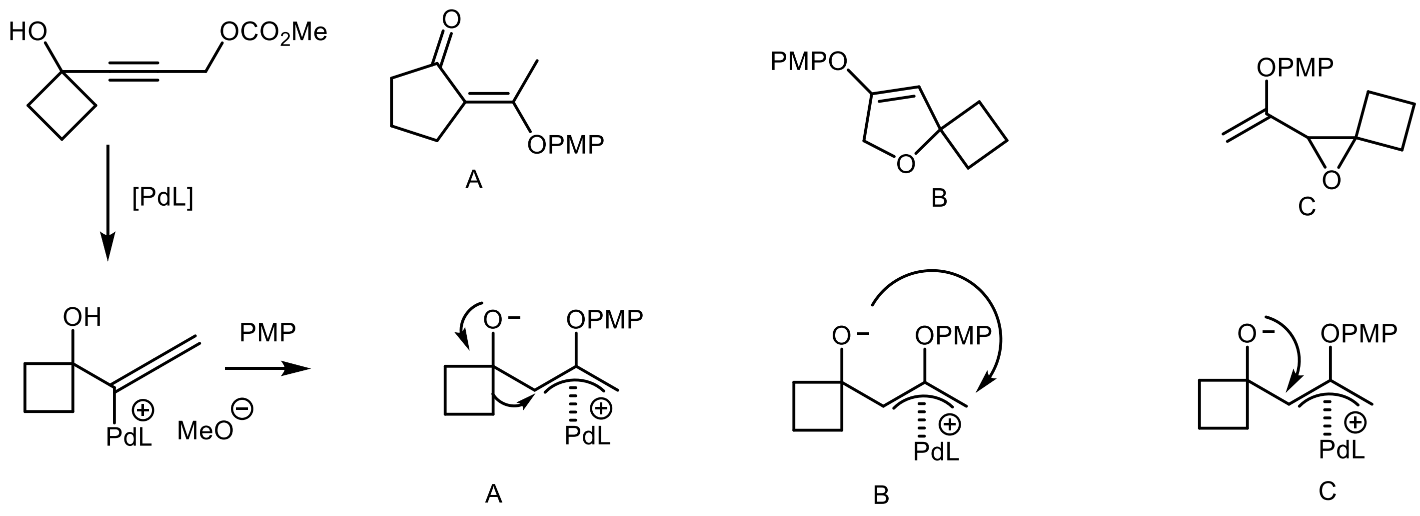
# Question 1 : Suggest the product and propose mechanism



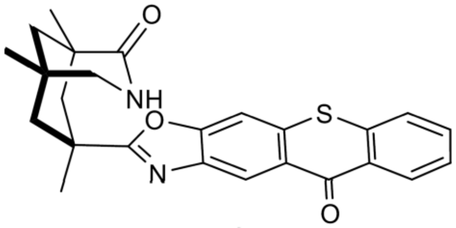



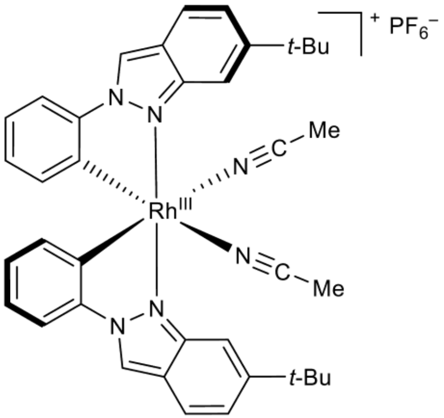
# Question 2: Propose mechanism for the formation of by-products

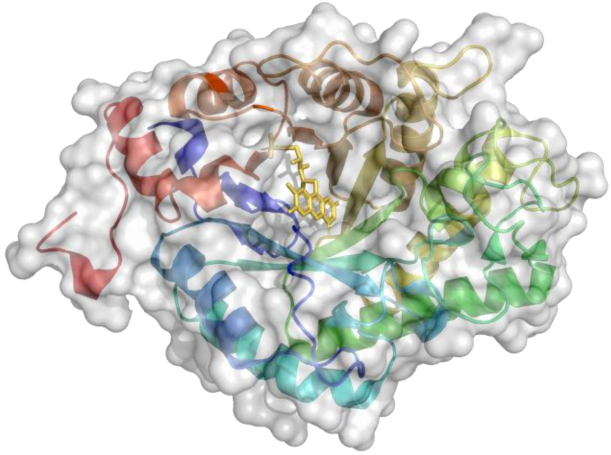


# THANK YOU



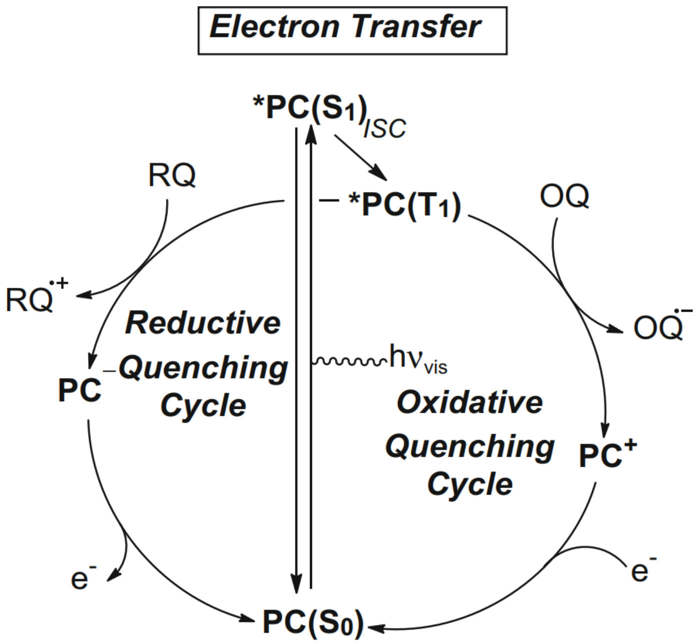
# Asymmetric induction based on chiral photocatalyst

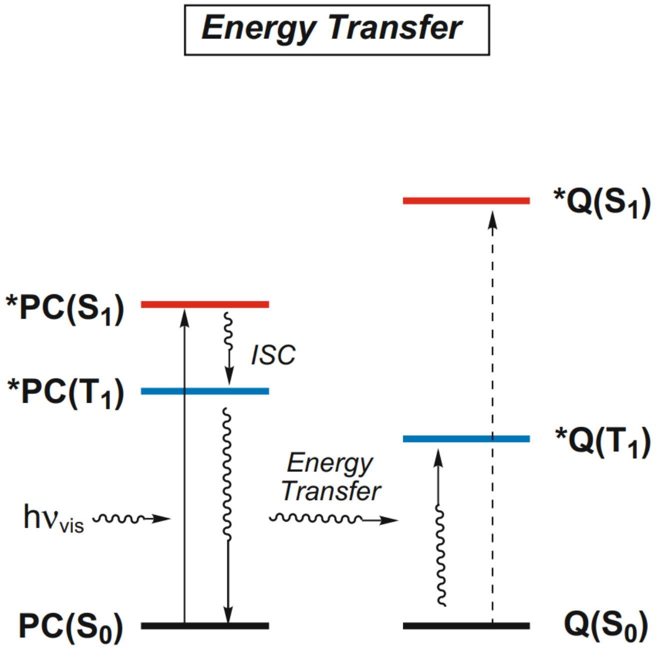
Weijin Wang

Advisor: Prof. Xile Hu

May 16, 2022

# Photocatalysis

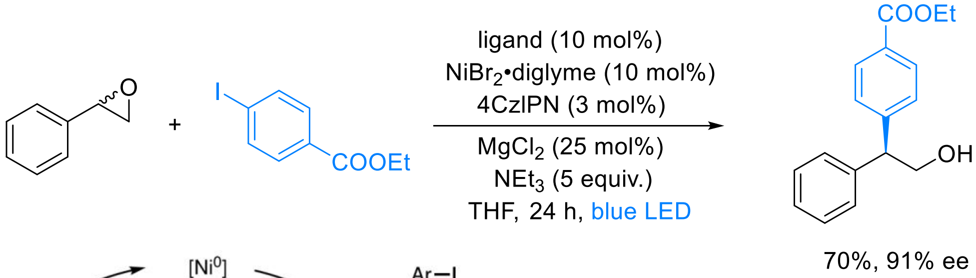


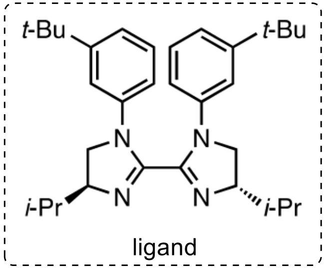



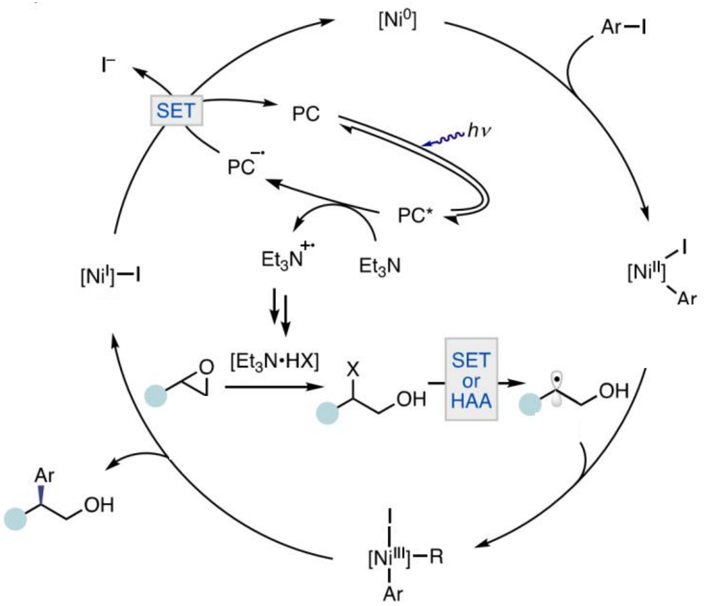

**PC** photocatalyst
**Q** quencher (e.g. substrate),
**RQ** reductive quencher
**OQ** oxidative quencher

**ISC** intersystem crossing
**$S_0$** singlet ground state
**T1** first triplet excited state
**$S_1$** first singlet excited state

# Related content: merging photoredox and transition metal



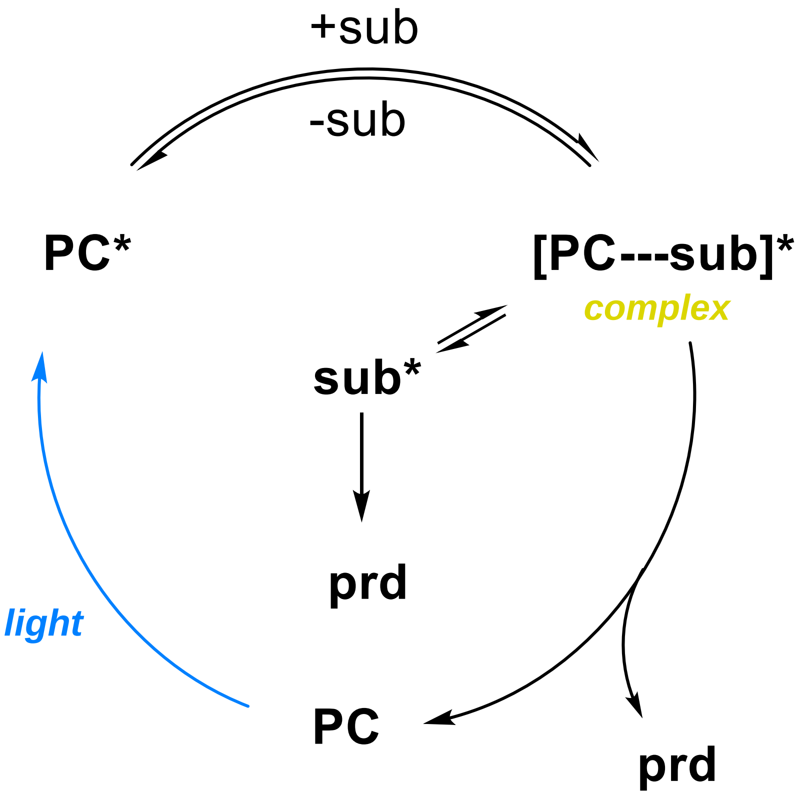




- Achiral PC
- Inherent catalytic cycle of [Ni], [Co], [Cu]
- *Redox process*

For a review: Twilton, J., Le, C., Zhang, P. *et al. Nat. Rev. Chem*. **2017**, *1*, 0052.
Lau, S. H.; Borden, M. A.; Steiman, T. J.; Parasram, M.; Wang, L. S.; Doyle, A. G. *J. Am. Chem. Soc.* **2021**, *143*, 15873-15881.

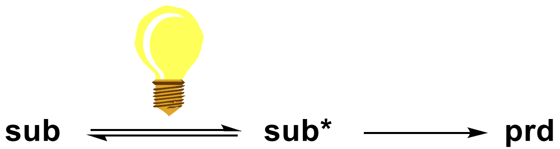
# Challenges with the design of chiral photocatalyst




- *Short-lived complex*

*Dissociation of complex faster than bond formation*

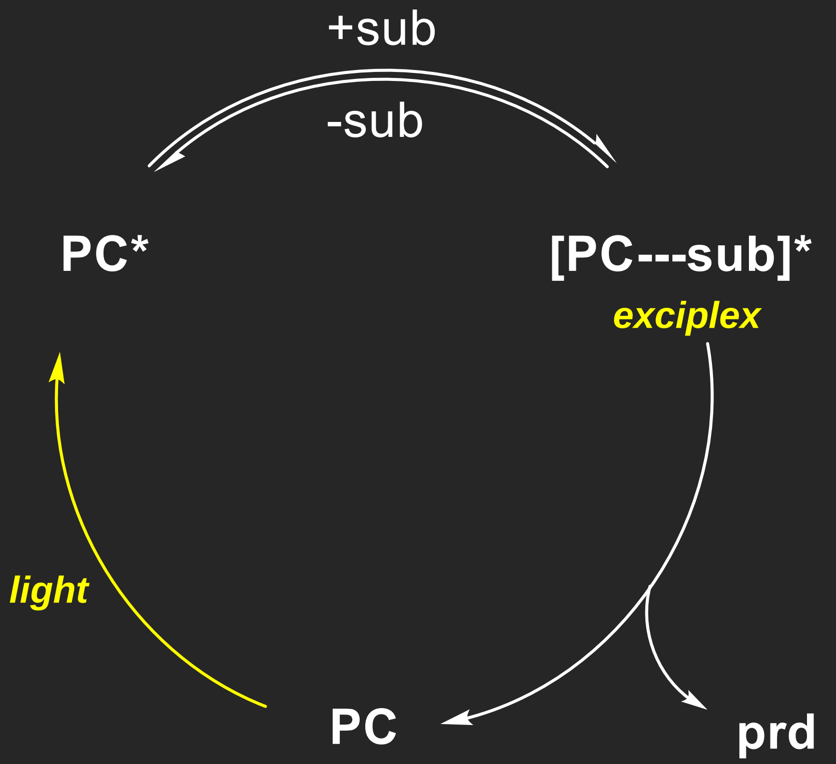
- *Competitive direct photoexcitation*




- Inoue, Y. *Chem. Rev.* **1992**, *92*, 741−770.

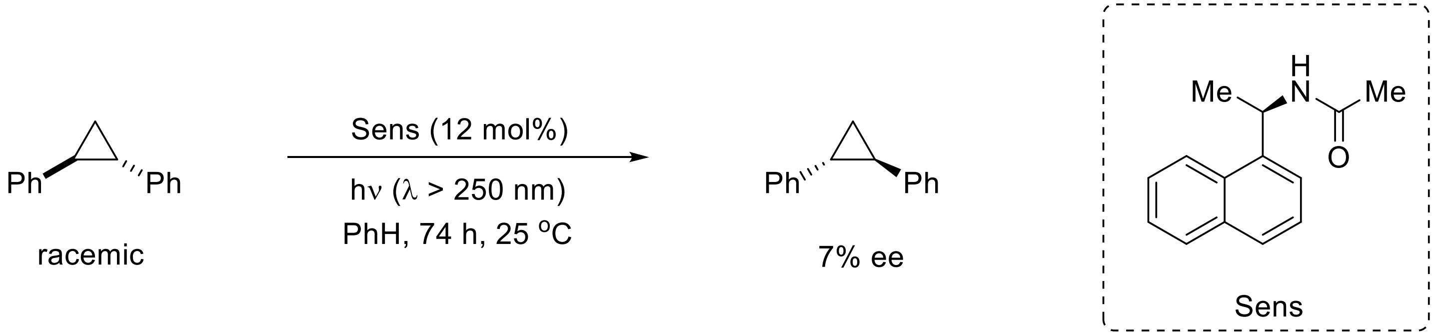
**Part 1:**

**Exciplex**

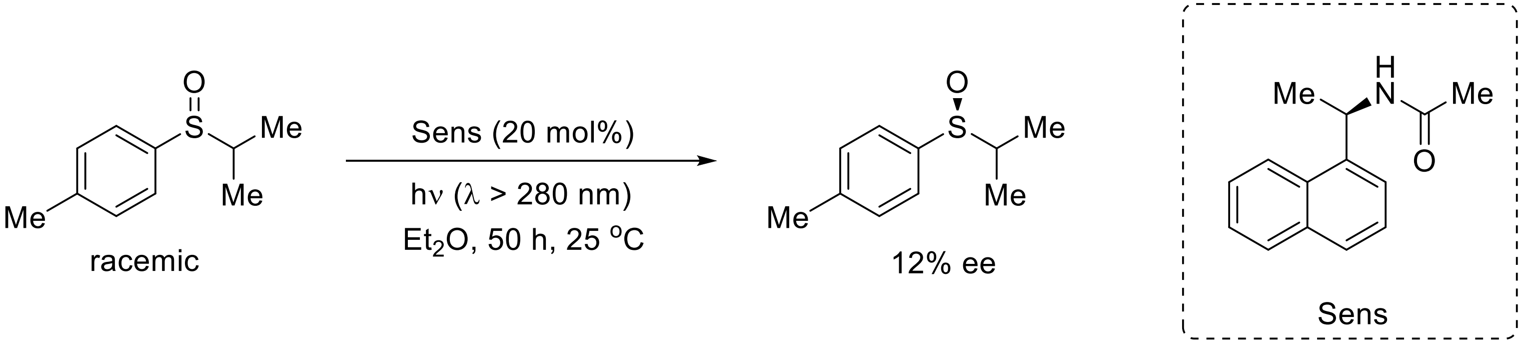


EPFL

## *Hammond : cyclopropane isomerization*

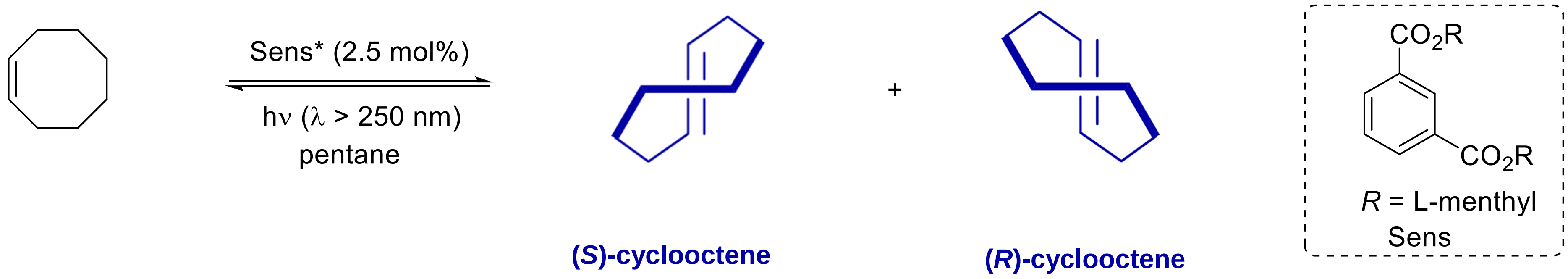



## *Kagan : sulfoxide deracemization*




- Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256−3257; Balavoine, G.; Jugé, S.; Kagan, H. B. *Tetrahedron Lett.* **1973**, *14*, 4159−4162.

# *Inoue : isomerization of achiral (Z)-cyclooctene*

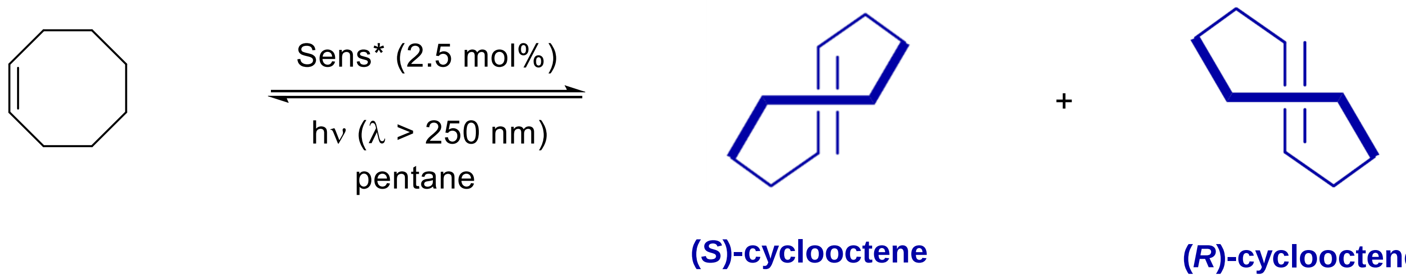



4% ee, conv. < 10 %

Prof. Yoshihisa Inoue
Department of Applied Chemistry
Osaka University

- Inoue, Y.; Kunitomi, Y.; Takamuku, S.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 1024– 1025.

# *Inoue : isomerization of achiral (Z)-cyclooctene*

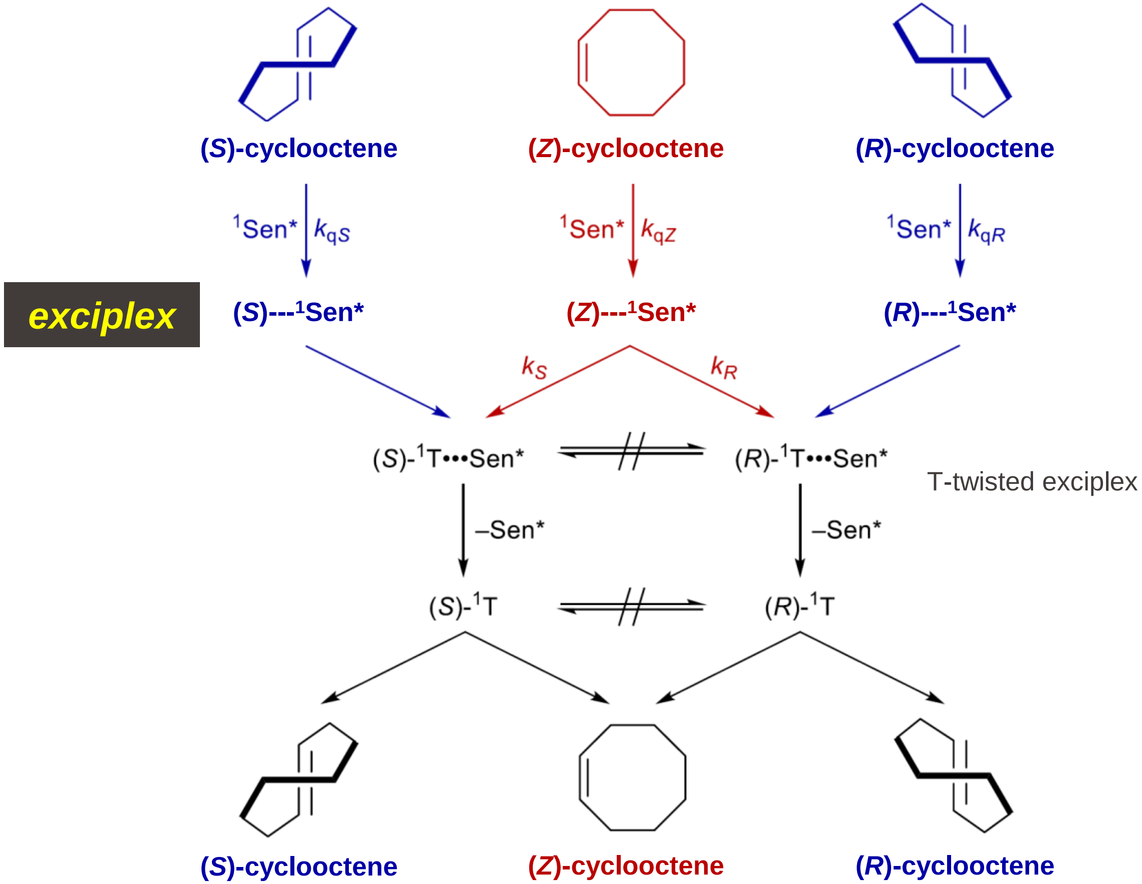



| Sensitizer | λ | E/Z | Triplet energy ($E_T$) |
|---|---|---|---|
| - | 185 nm | 0.96 | - |
| others | > 250 nm | 0.05 | > 72 kcal/mol |
| methyl benzoate | > 250 nm | 0.25 | 78.7 kcal/mol |

- *a twisted singlet state of cyclooctene as an intermediate （what else could be done?）*
- *how to define R/S here?*

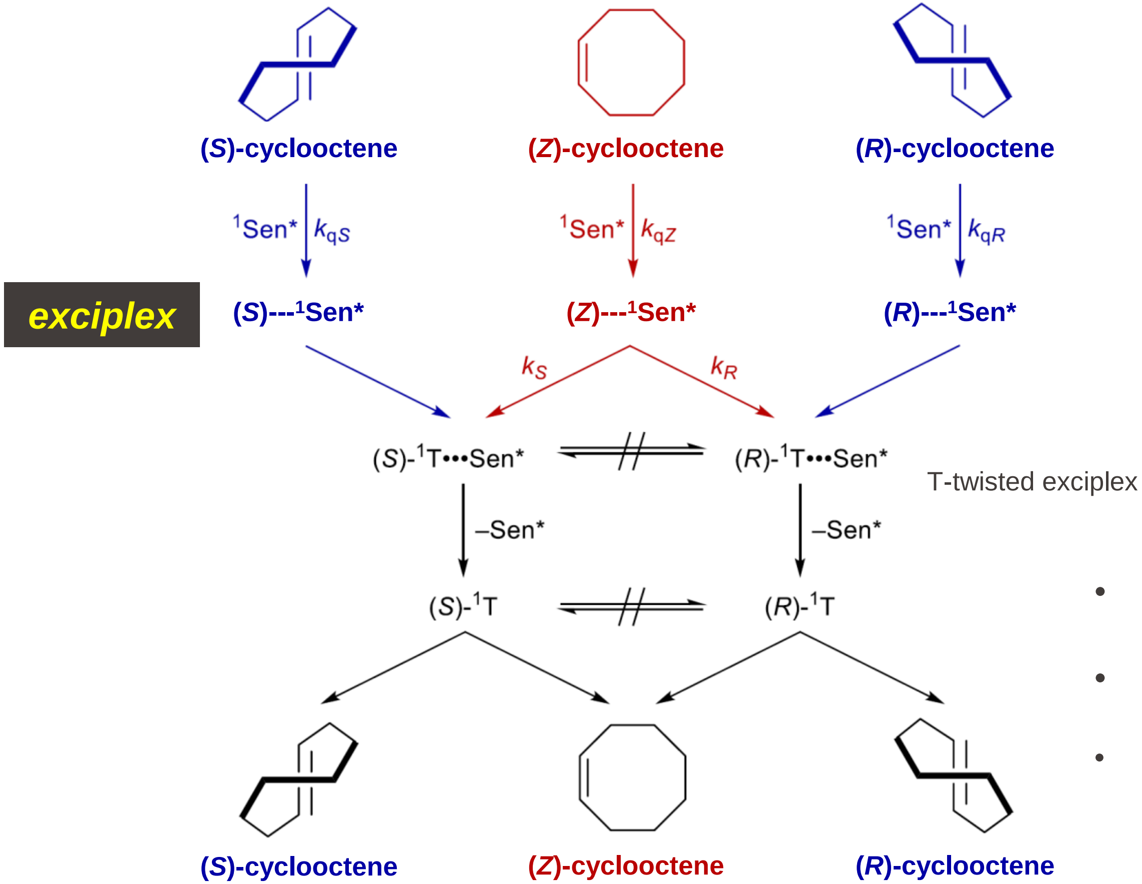

Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672– 1678.

# Inoue : isomerization of achiral (Z)-cyclooctene




- Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672– 1678.

# *Inoue : isomerization of achiral (Z)-cyclooctene*

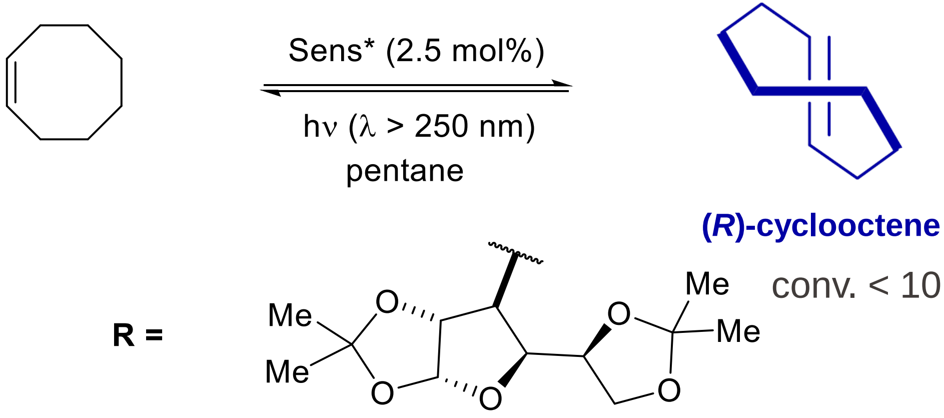



***Q1***

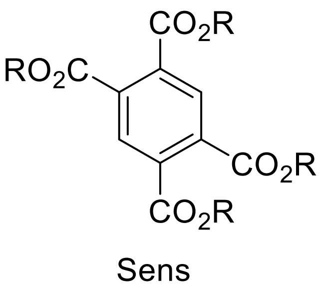
- *enantiodetermining step?*
- *sensitizer quenching ($k_{qS}$ vs $k_{qR}$)*
- *rotational relaxation ($k_S$ vs $k_R$)*

Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672– 1678.

# Inoue : isomerization of achiral (Z)-cyclooctene



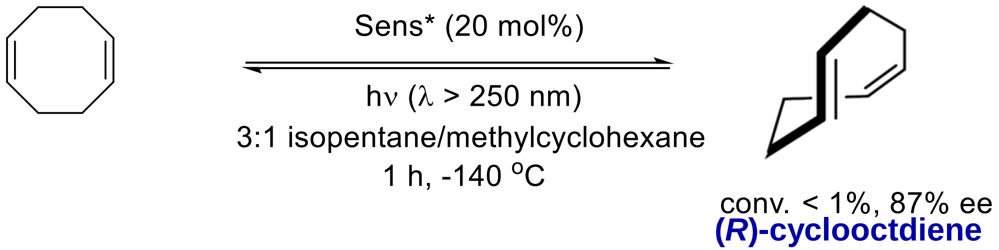

conv. < 10 %



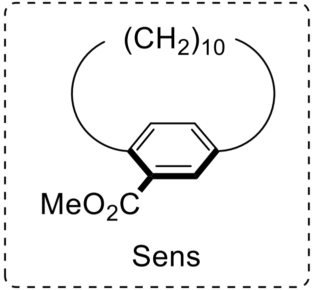

| Temperature | pentane | $Et_2O$ |
|---|---|---|
| 25 ºC | -5% ee | -5% ee |
| -40 ºC | -22% ee | 22% ee |
| -78 ºC | -40% ee | 50% ee |
| -100 ºC | - | 73% ee |

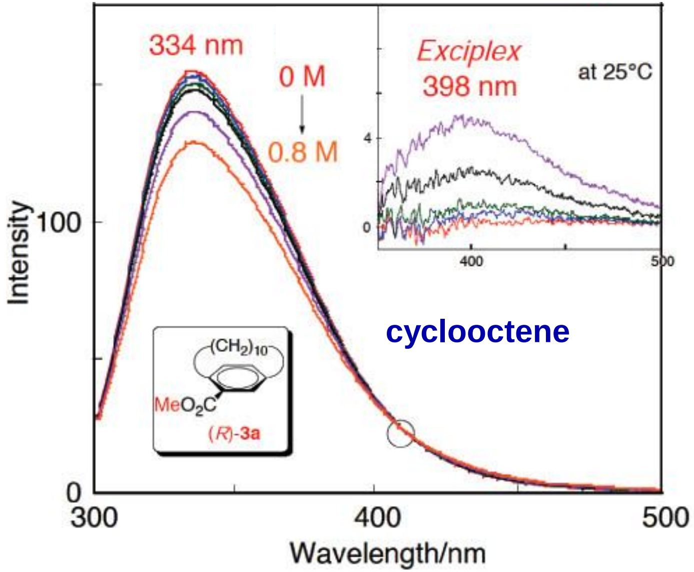

- Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406– 407

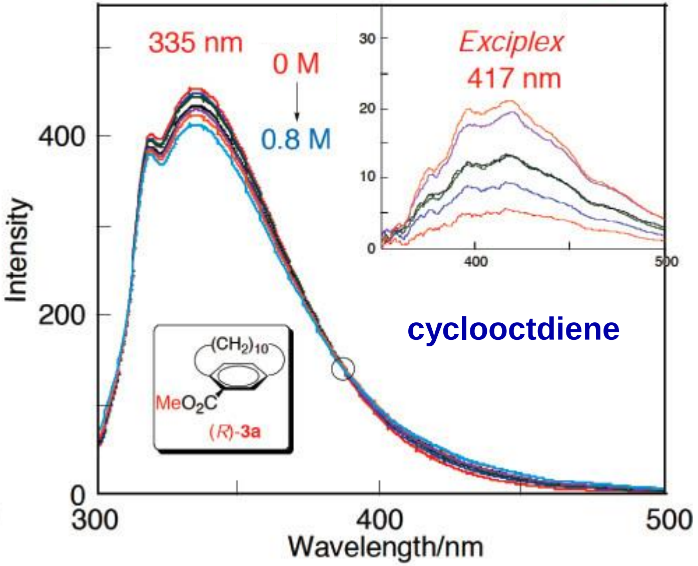
# Inoue : isomerization of achiral cyclooctdiene




paracyclophane

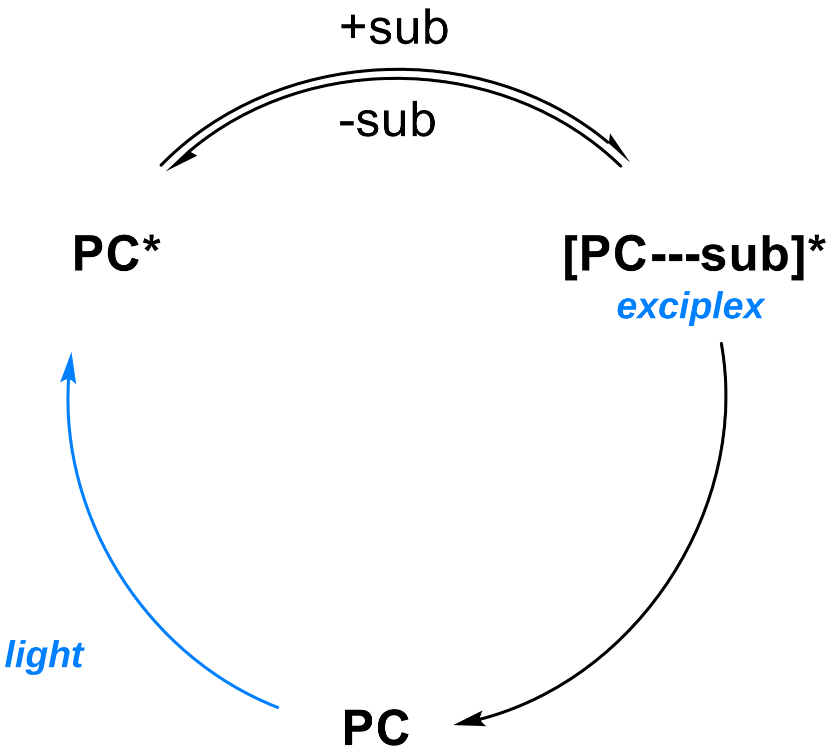



- Maeda, R.; Wada, T.; Mori, T.; Kono, S.; Kanomata, N.; Inoue, Y. *J. Am. Chem. Soc.* **2011**, *133*, 10379– 10381.

# Summary about exciplex



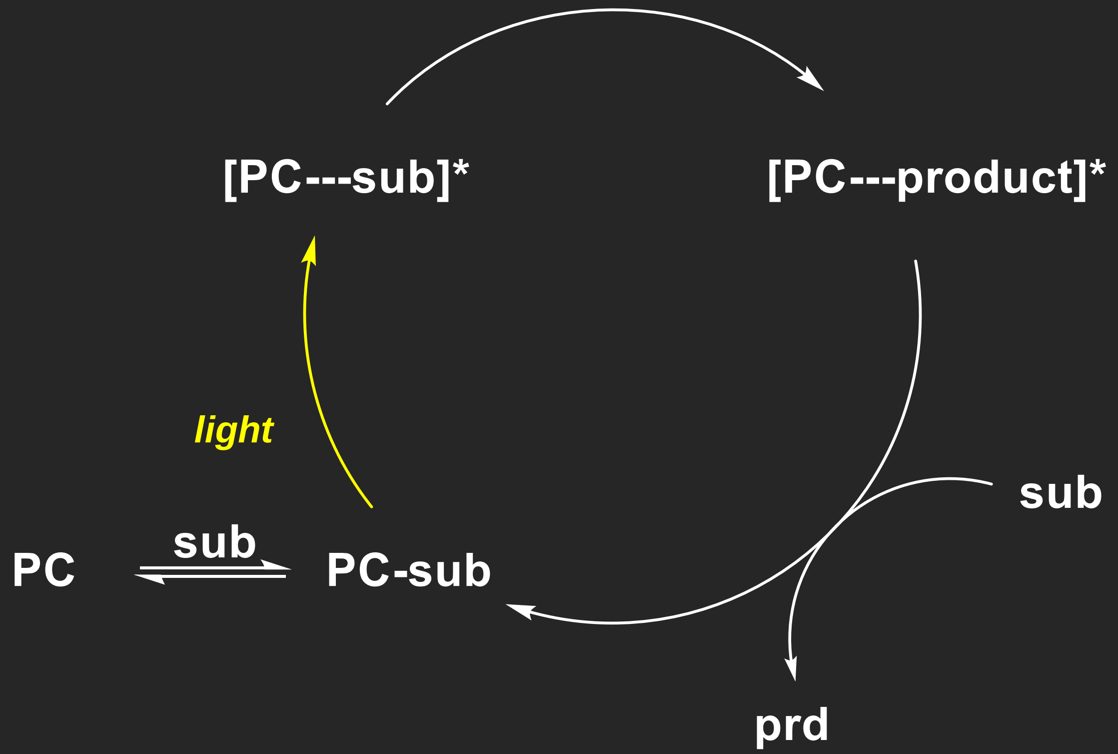

- *transient excited-state interaction*
- *reactivity vs selectivity*
- *limited scope : cycloaddition/isomerization*
- *lack of a structure type for optimization*

EPFL

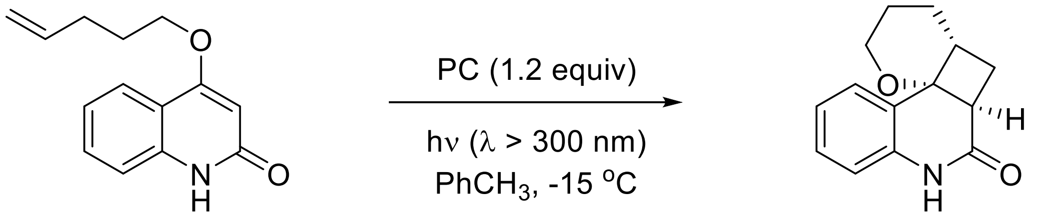


## Part 2:

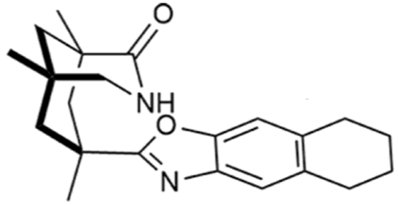
## Pre-association



# Bach : [2+2] cycloaddition promoted by **hydrogen bonding**




88% yield, 88% ee




PC

oxazaborolidine

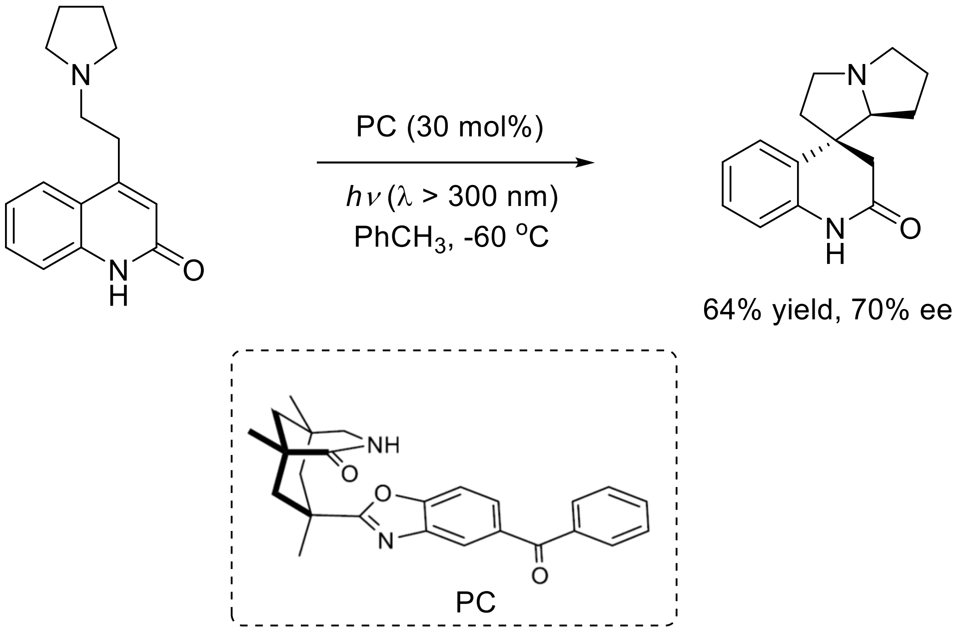
Prof. Thorsten Bach
Technical University Munich

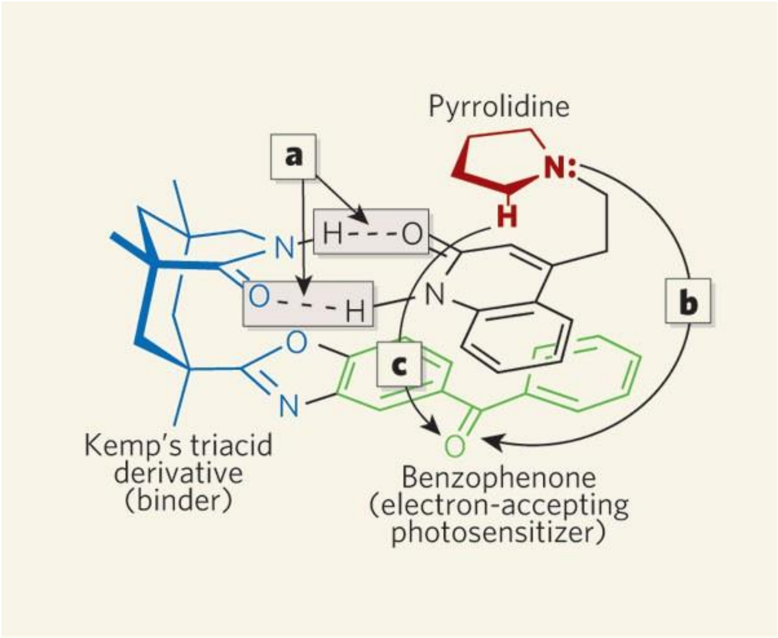
- *high yield and high ee!*
- *1.2 equiv. "PC" required*


For a recent review: Großkopf, J.; Kratz, T.; Rigotti, T.; Bach, *Chem. Rev.* **2022**, *122*, 1626-1653.

- Bach, T.; Bergmann, H.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2302 – 2304.

# Bach : radical cyclization promoted by **hydrogen bonding**

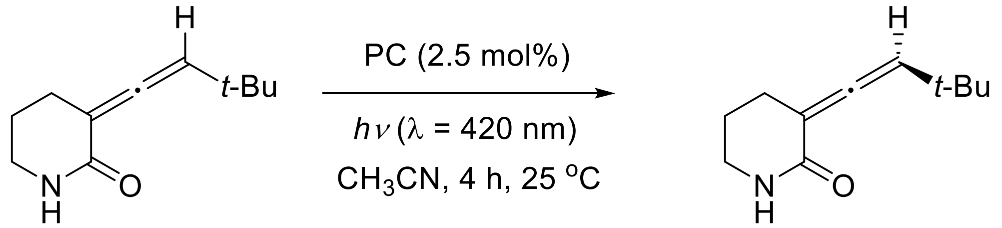



- *limitations: UV light, H-atom abstraction*

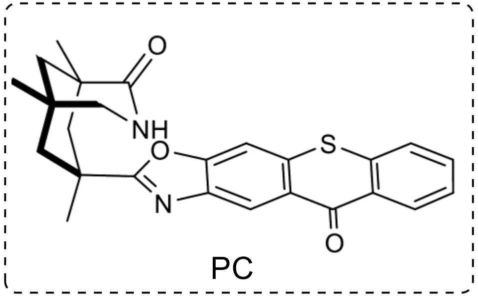

- Bauer, A.; Westkämper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139– 1140

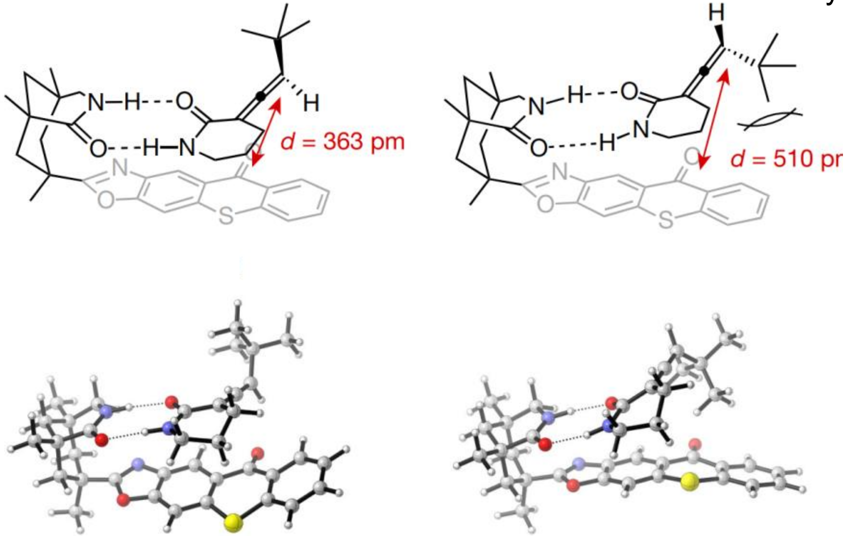
# Bach : deracemization of chiral allenes promoted by **hydrogen bonding**

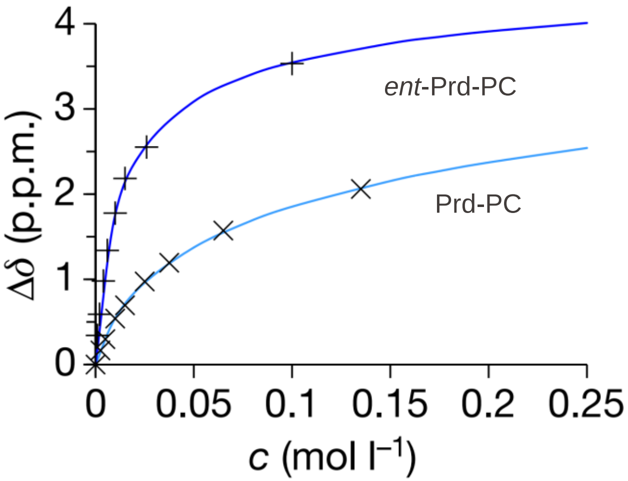



89% yield, 96% ee

thioxanthon



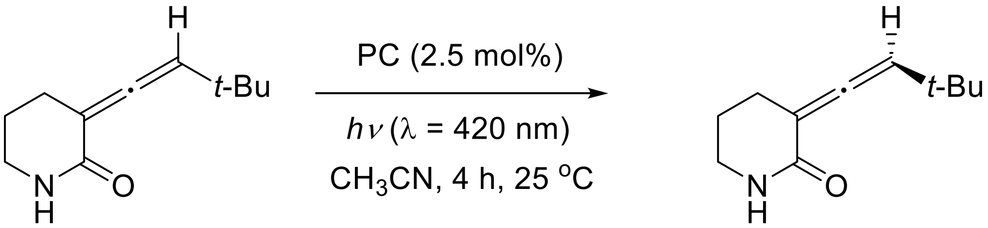



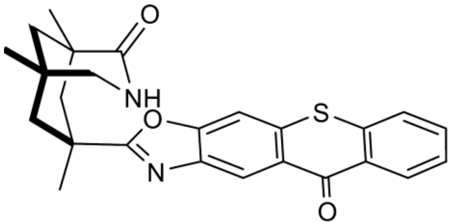

- *solves both limitations*

Hölzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. *Nature* **2018**, *564*, 240– 243

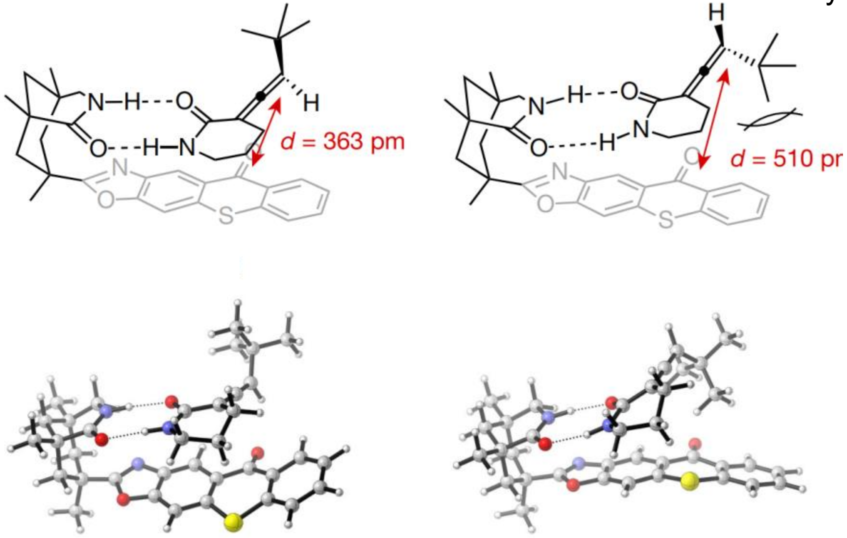
# Bach : deracemization of chiral allenes promoted by **hydrogen bonding**




89% yield, 96% ee




PC

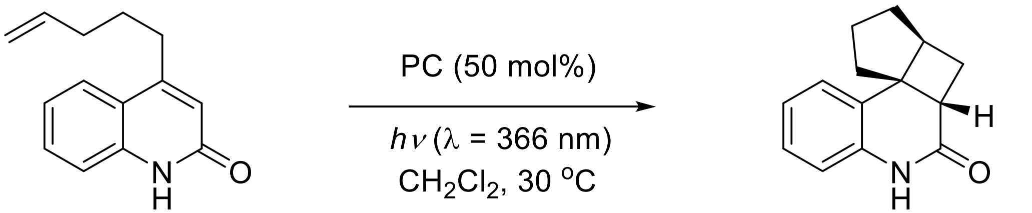



$$k_{dexter} \propto \frac{D_D^2 D_A^2}{R_{DA}^6}$$

- *solves both limitations*

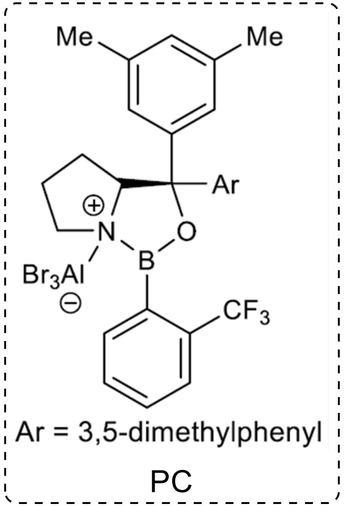

Hölzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. *Nature* **2018**, *564*, 240– 243

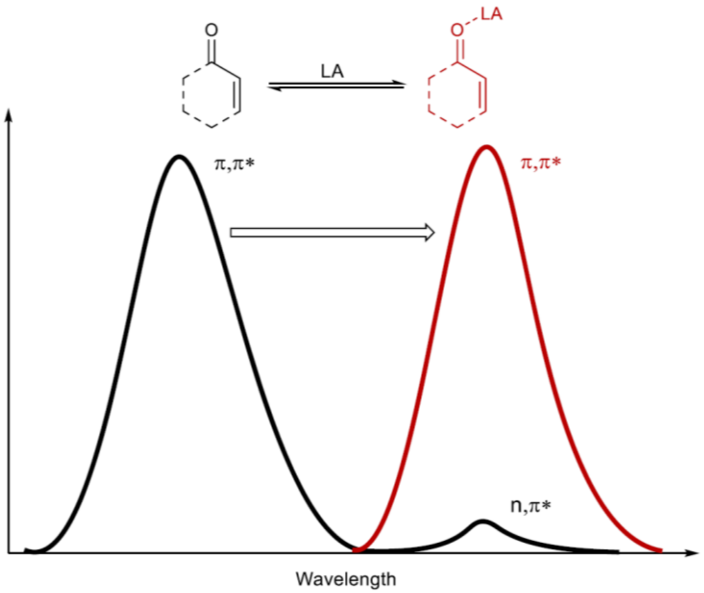
# Bach : [2+2] cycloaddition promoted by **Lewis acid catalysis**

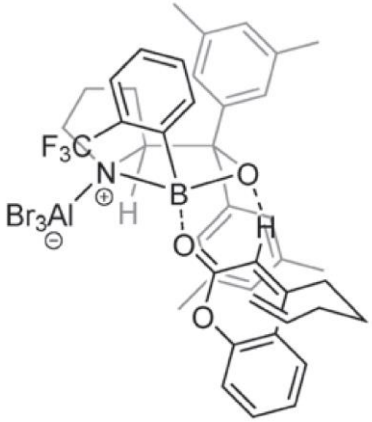



82% yield, 62% ee

w/o PC, 28% yield

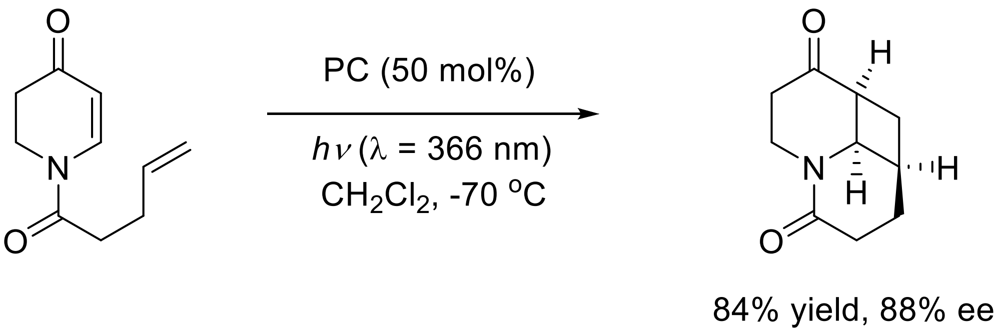


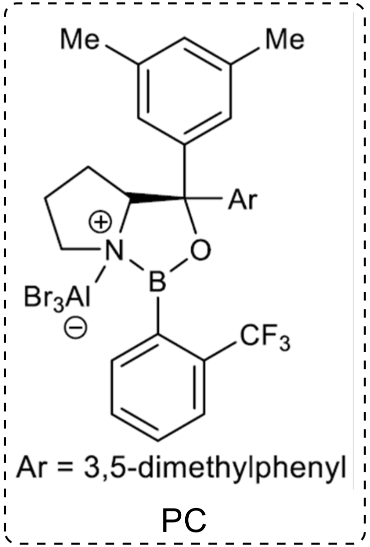



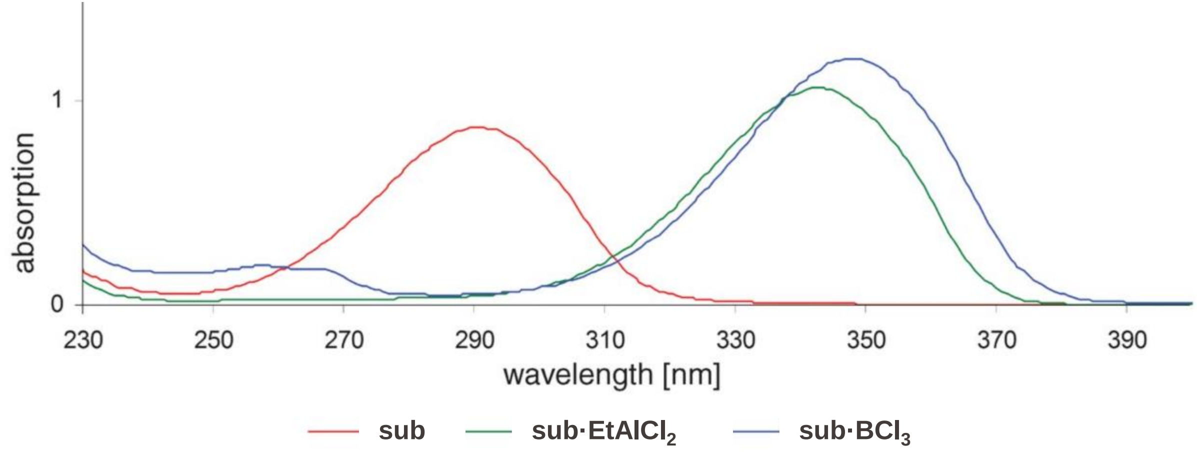



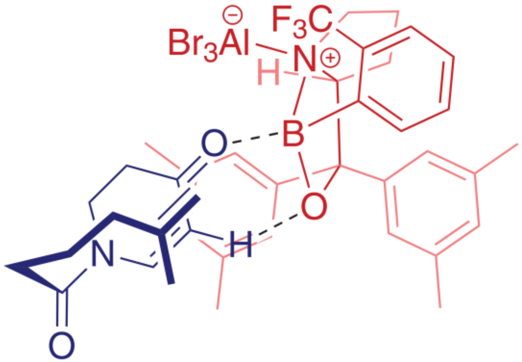

- Guo, H.; Herdtweck, E.; Bach, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7782– 7785.

# EPFL *Bach : [2+2] cycloaddition promoted by* ***Lewis acid catalysis***



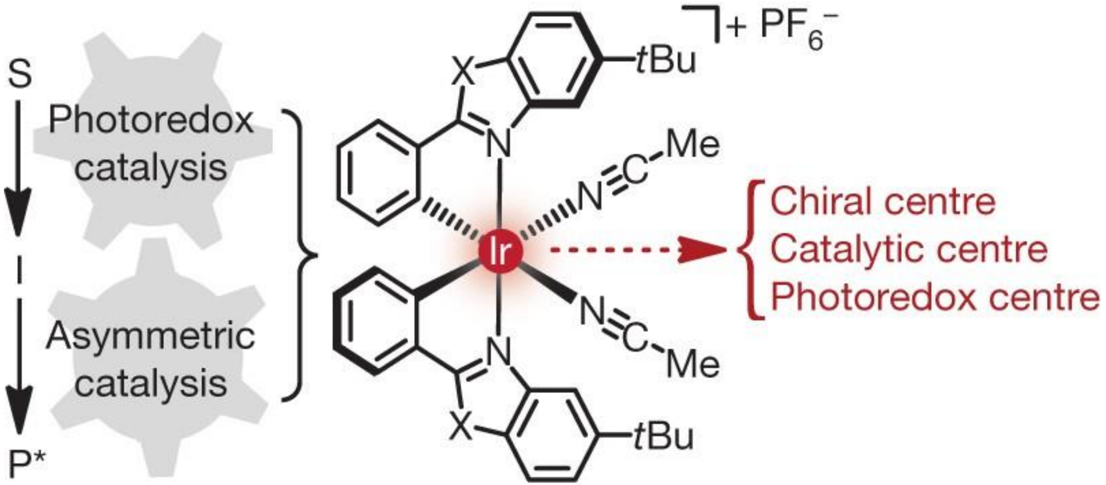




- *limitations: high loading of LA + uv light*

- Brimioulle, R.; Bach, T. *Science* **2013**, *342*, 840– 843.

# Meggers : chiral iridium/rhodium **Lewis acid photocatalyst**



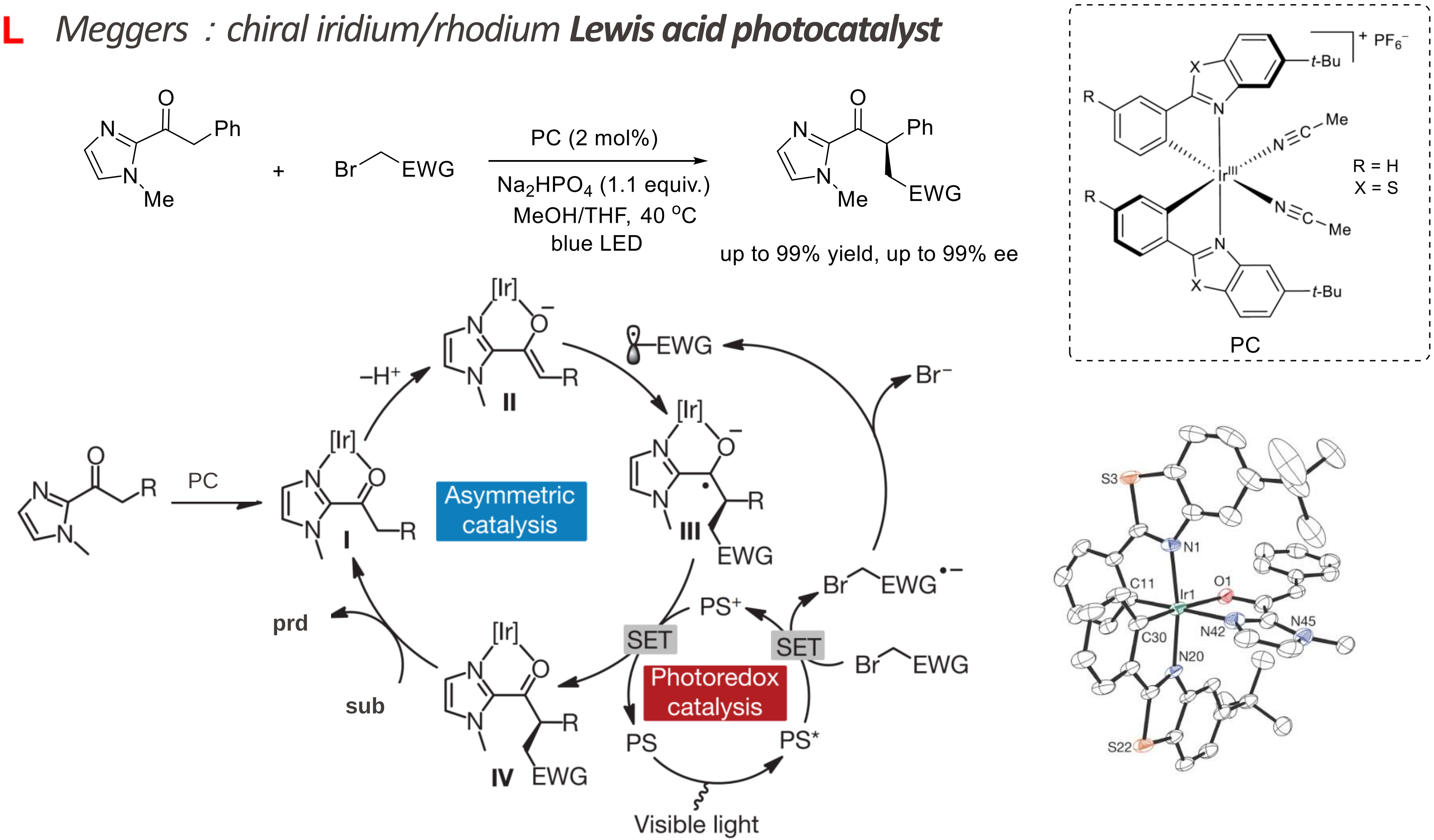

Λ-**Ir1** (X = O), Λ-**Ir2** (X = S)

Prof. Eric Leif Meggers
Philipps-Universität Marburg

For a review on chiral-at-metal iridium complex: *Acc. Chem. Res.* **2017**, *50*, 320– 330.

- Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100– 103.

# Meggers : chiral iridium/rhodium **Lewis acid photocatalyst**




- Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100– 103.

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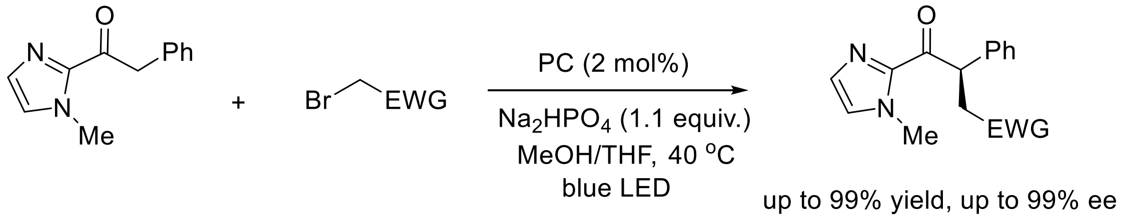
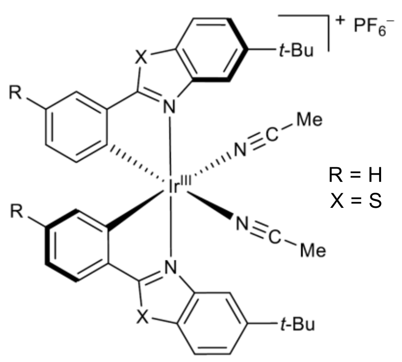
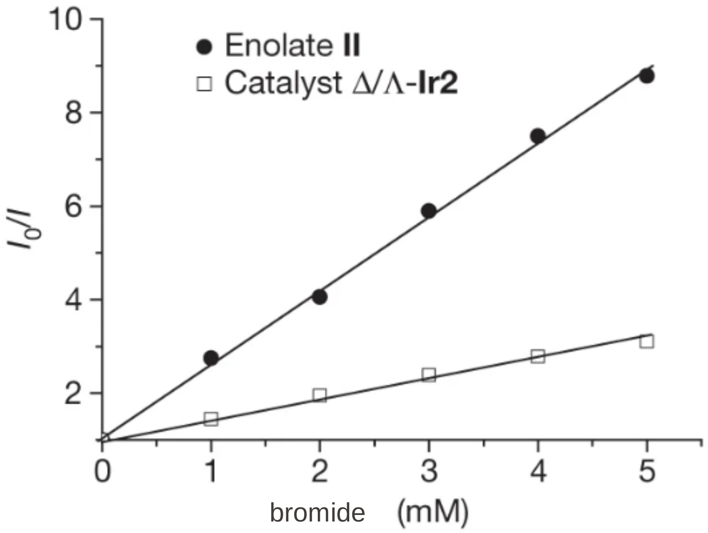



*Photosensitizer: PC or enolate?*

*Stern–Volmer plots*

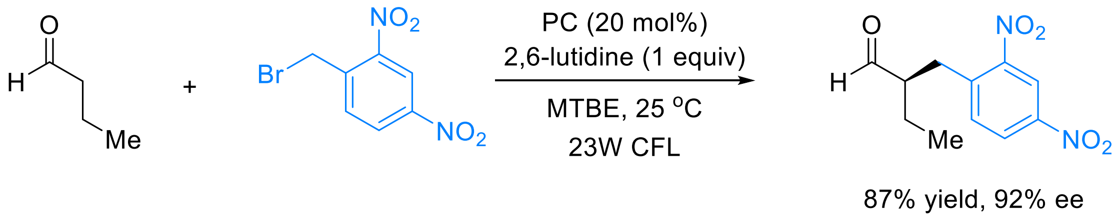


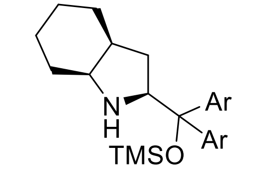

*cyclic voltammetry*

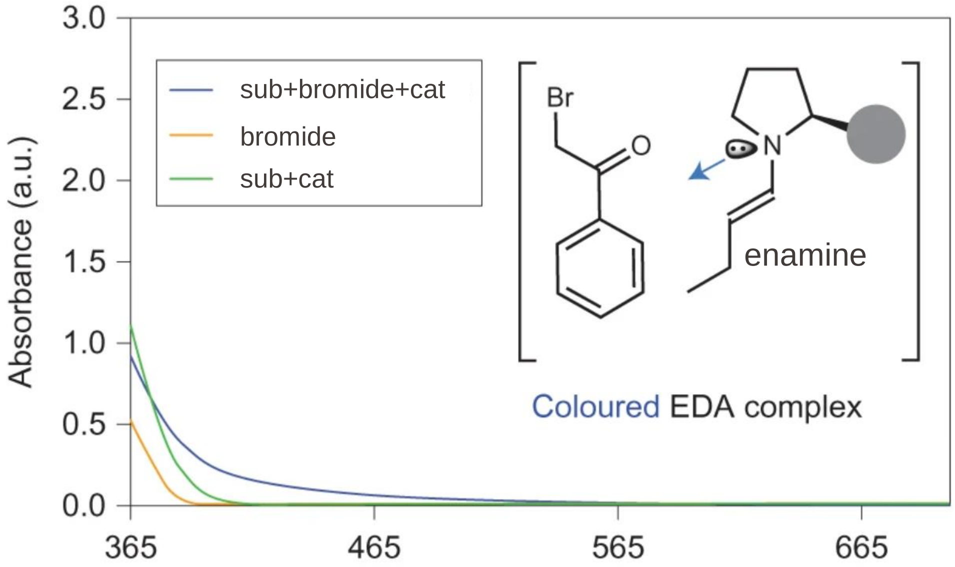
| Complex | $E_{1/2}$ ($PS^+/PS^*$) |
|---|---|
| PC | > -0.71 V |
| enolate | -1.74 V |


- Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100– 103.

# Melchiorre : α-alkylation of aldehyde via **EDA complex**



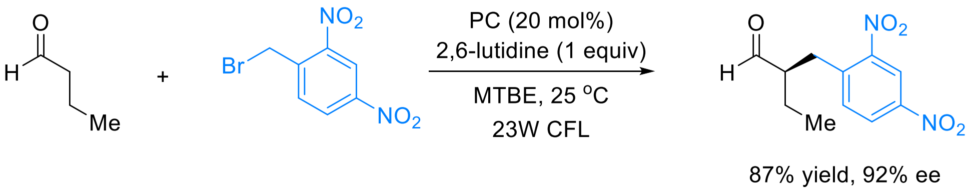



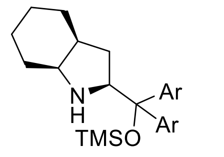

Prof. Dr. Paolo Melchiorre
Institute of Chemical Research of Catalonia (ICIQ)

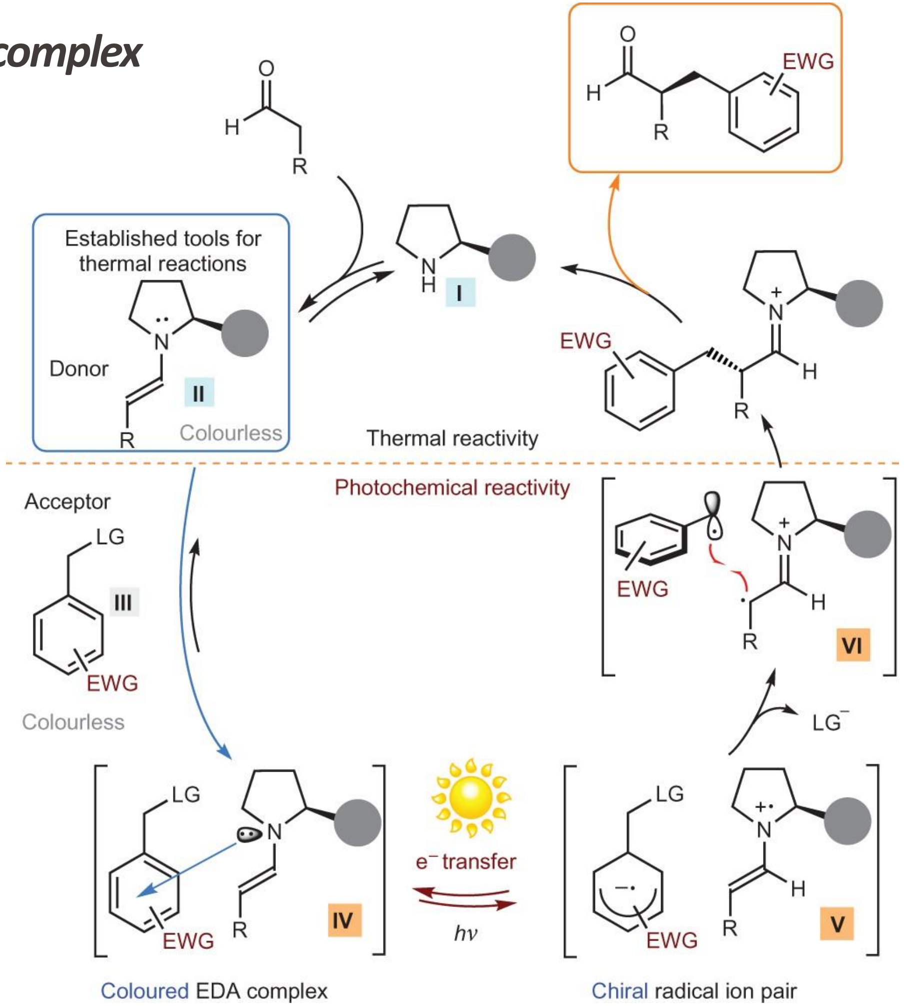
***Q2: how to tell the difference between exciplex and EDA complex?***

- Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750– 756

# Melchiorre : α-alkylation of aldehyde via **EDA complex**

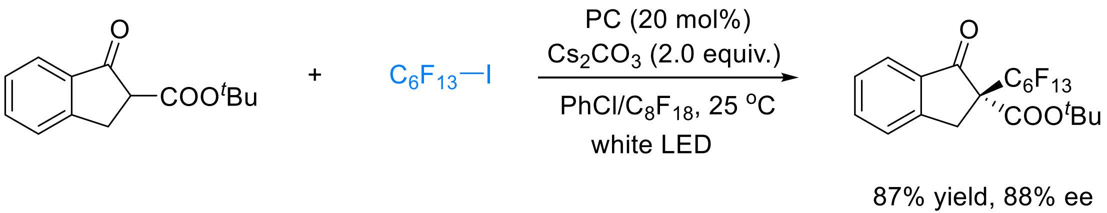


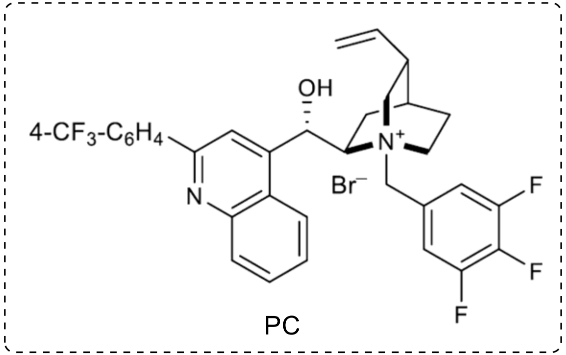



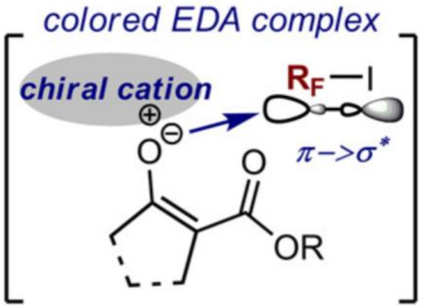



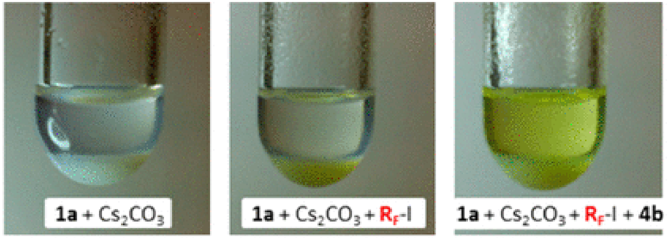

- Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750– 756

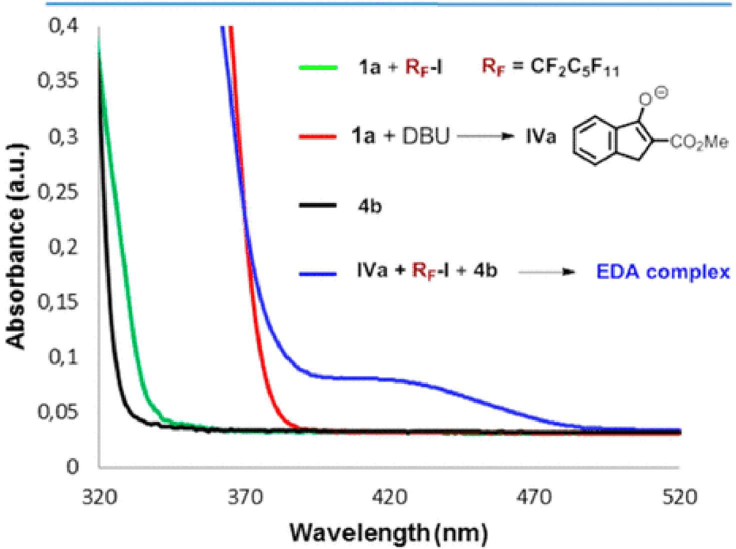
# Melchiorre : counter-ion phase transfer catalysis



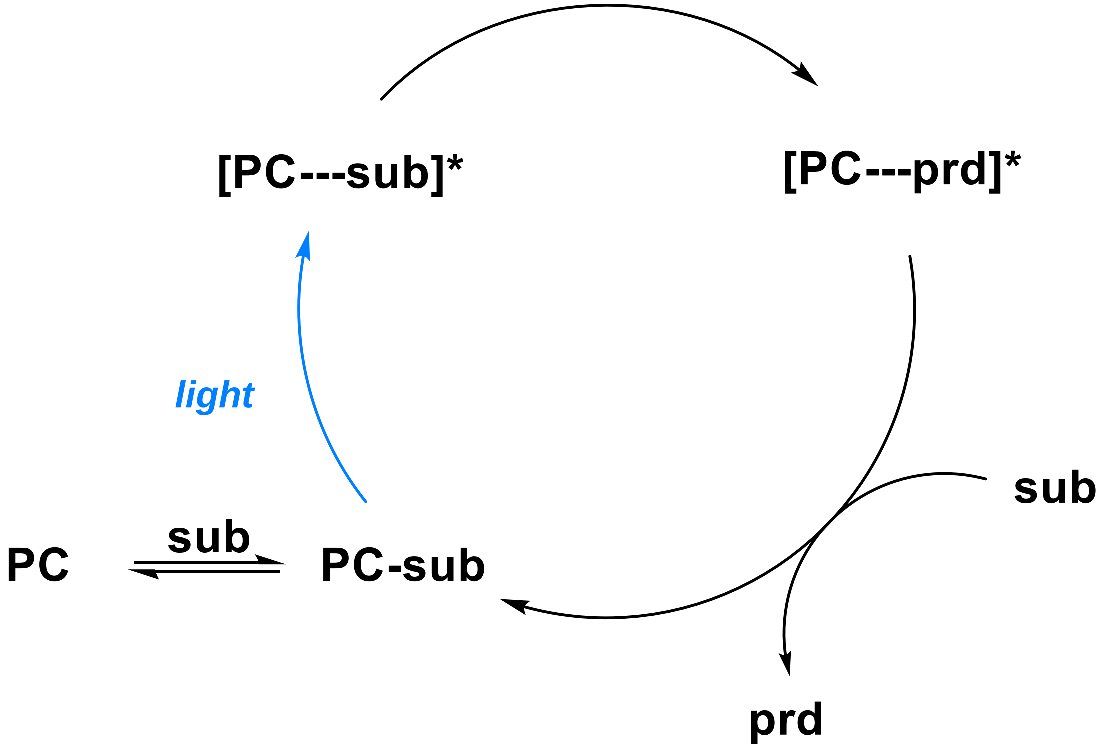




- *challenges: EDA+PTC+multicomponent*


*For a review on CAPT catalysis:* Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603– 614

- Woźniak, Ł.; Murphy, J. J.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 5678– 5681

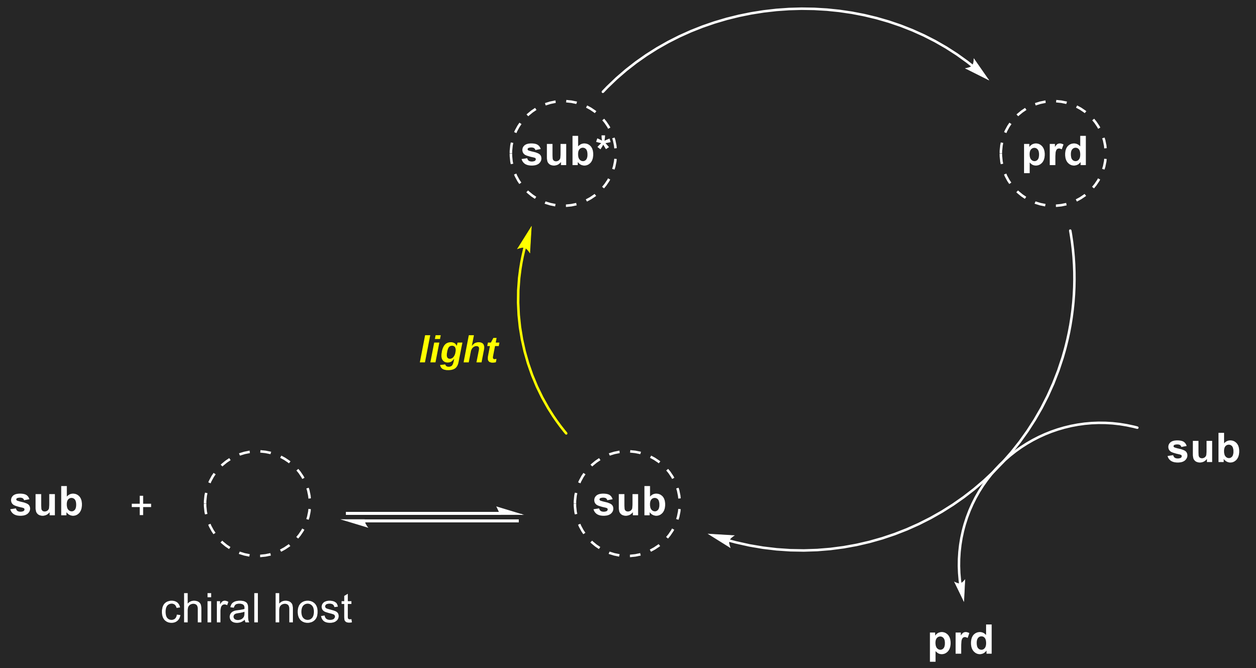
# Summary about pre-association



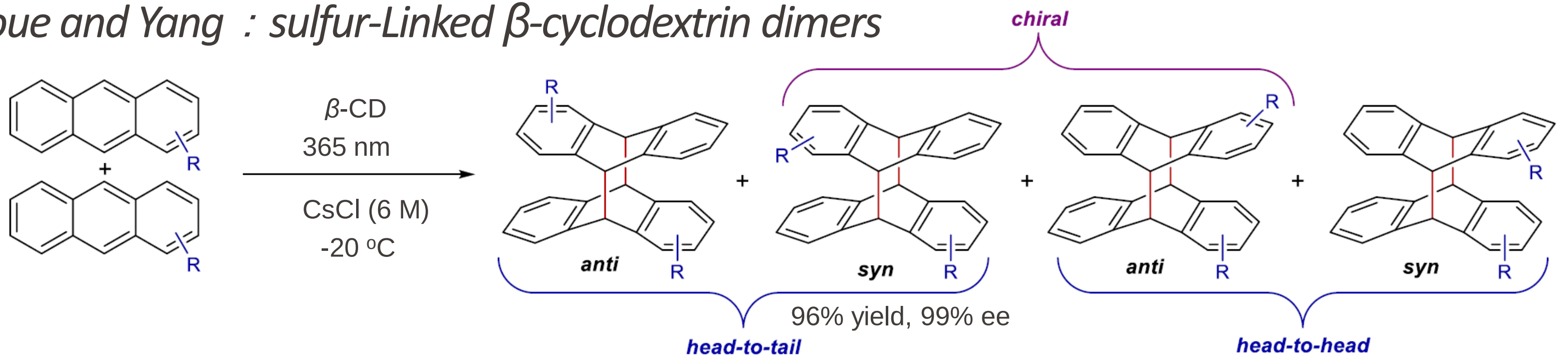

- *high yield and high ee*
- *bonding site required*
- *redox process possible*

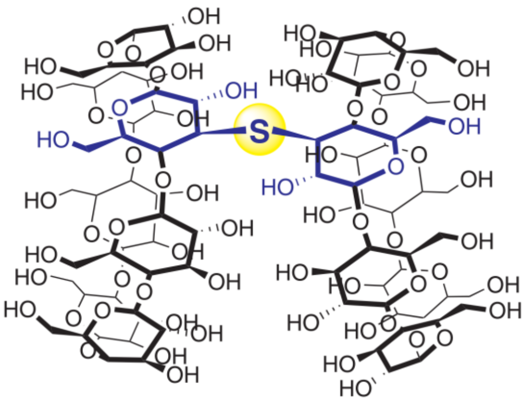
## Part 3:

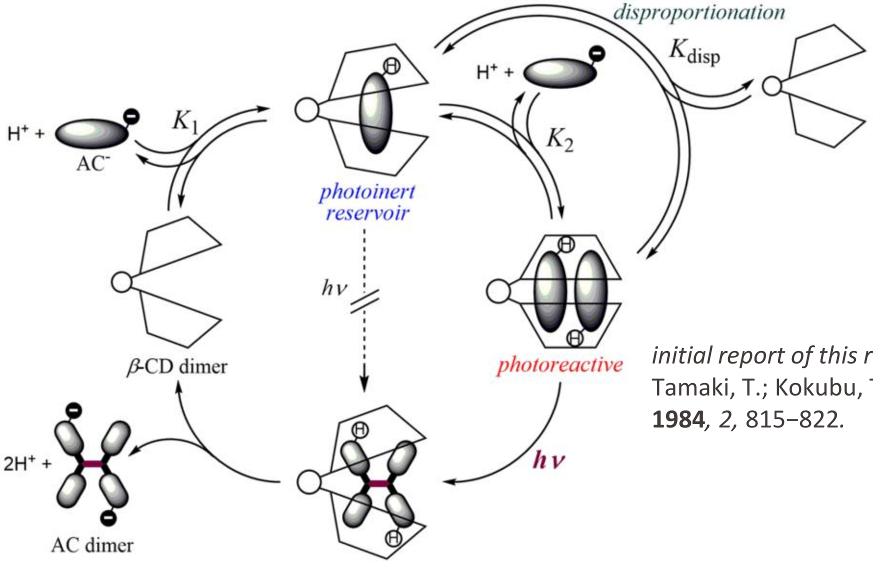
## Macromolecule Catalysis



# *Inoue and Yang : sulfur-Linked β-cyclodextrin dimers*



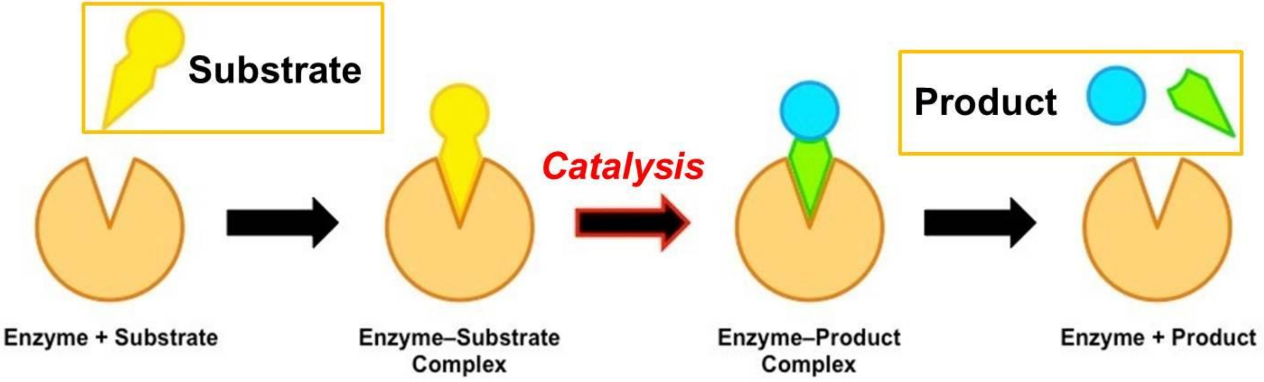




*initial report of this reaction:*
Tamaki, T.; Kokubu, T. *J. Inclusion Phenom.* **1984**, *2,* 815–822.

For a review on β-cyclodextrin catalysis: Ramamurthy, V.; Sivaguru, N. *Chem. Rev.* **2016**, *116*, 9914.

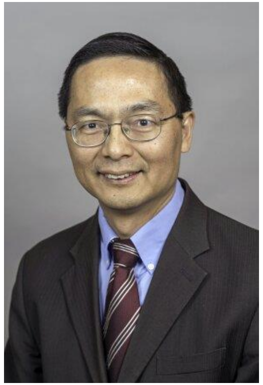
- Ji, J.; Wu, W.; Liang, W.; Cheng, G.; Matsushita, R.; Yan, Z.; Wei, X.; Rao, M.; Yuan, D. Q.; Fukuhara, G. *et. al. J. Am. Chem. Soc.* **2019**, *141*, 9225– 9238

# Photoenzymatic catalysis




- *Specific*
- *Green: loading of catalyst, production of proteins, reaction in water…*
- *Developed engineering methods*

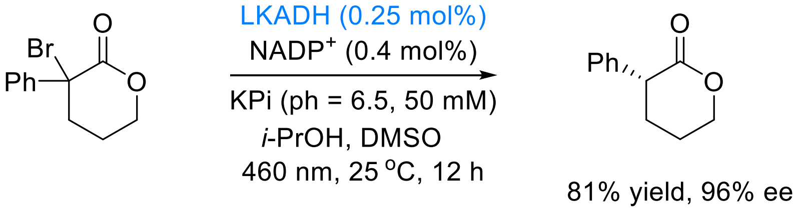
Prof. Todd Hyster
Cornell University

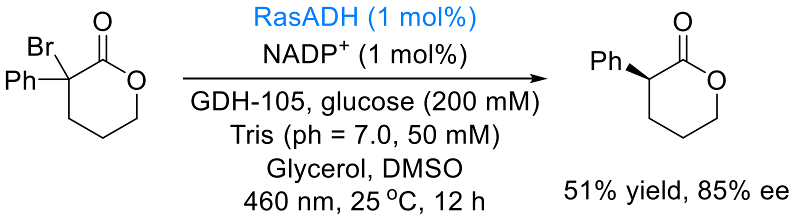


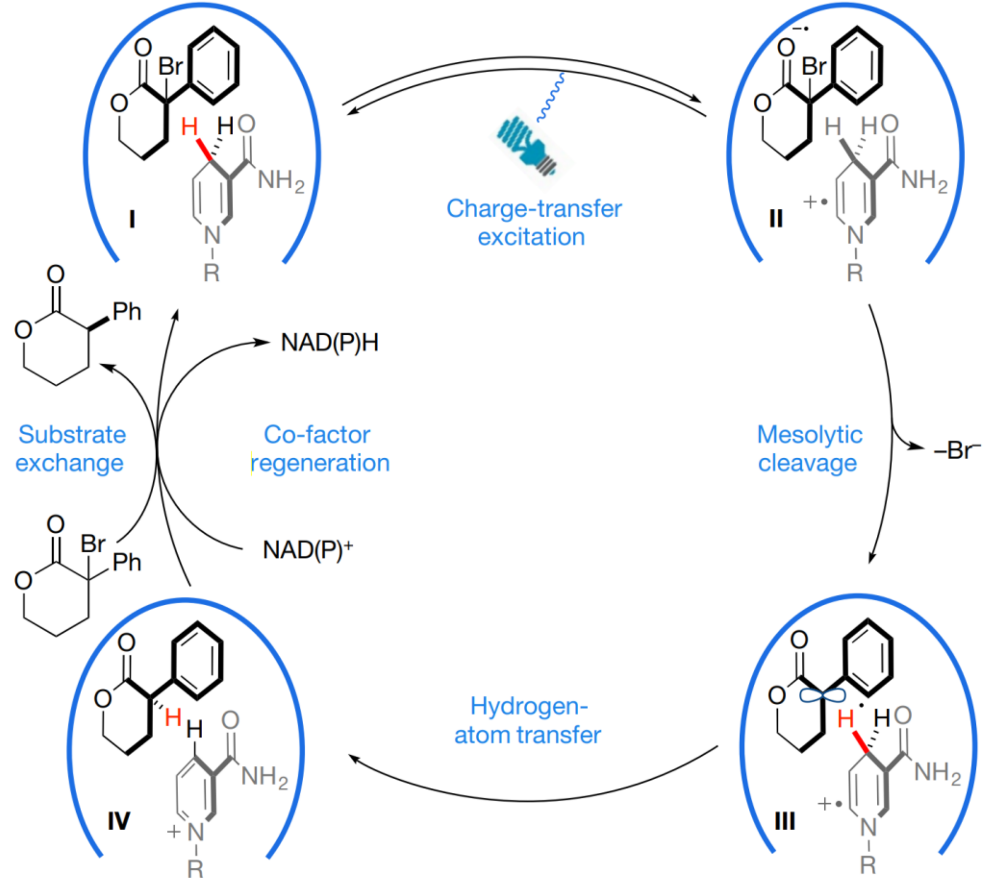
Prof. Huimin Zhao
University of Illinois at Urbana-Champaign

- For a recent review: Miller, D.C., Athavale, S.V. & Arnold, F.H. *Nat. Synth.* **2022**, *1*, 18–23.

# Hyster : photoenzymatic debromination with KREDs



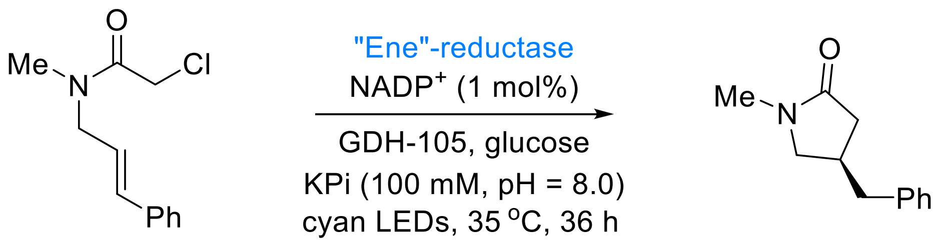




- *functions of NADP+ here: photocatalyst*

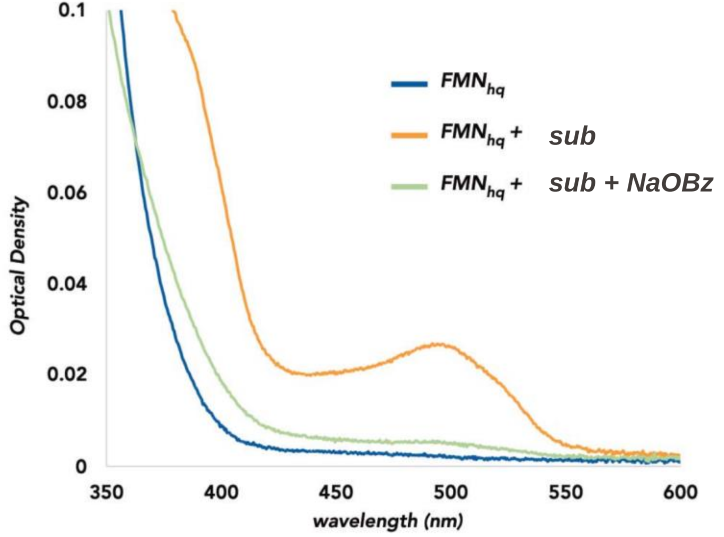

- Emmanuel, M. A.; Greenberg, N. R.; Oblinsky, D. G.; Hyster, T. K. *Nature* **2016**, *540*, 414– 417

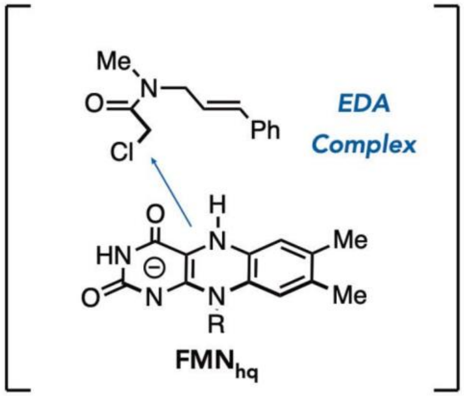
# *Hyster : photoenzymatic radical cyclization with EREDs*




"Ene"-reductase = Glu T36A (0.42 mol%), 91% yield, 88% ee

"Ene"-reductase = OYE1 (1 mol%), 34% yield, -38% ee



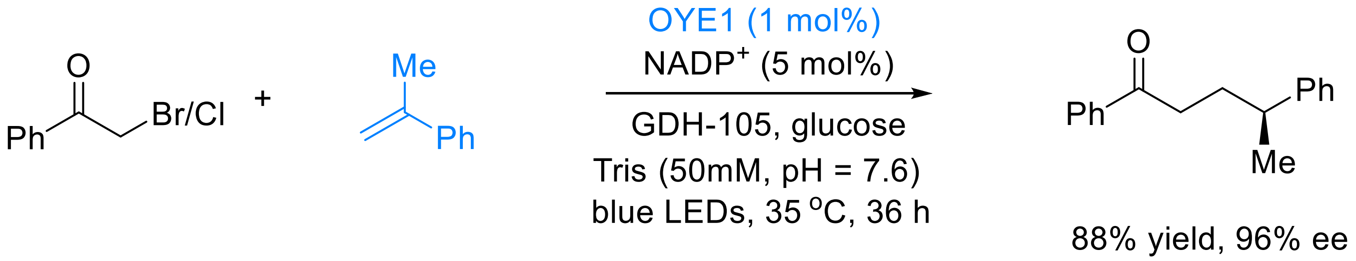



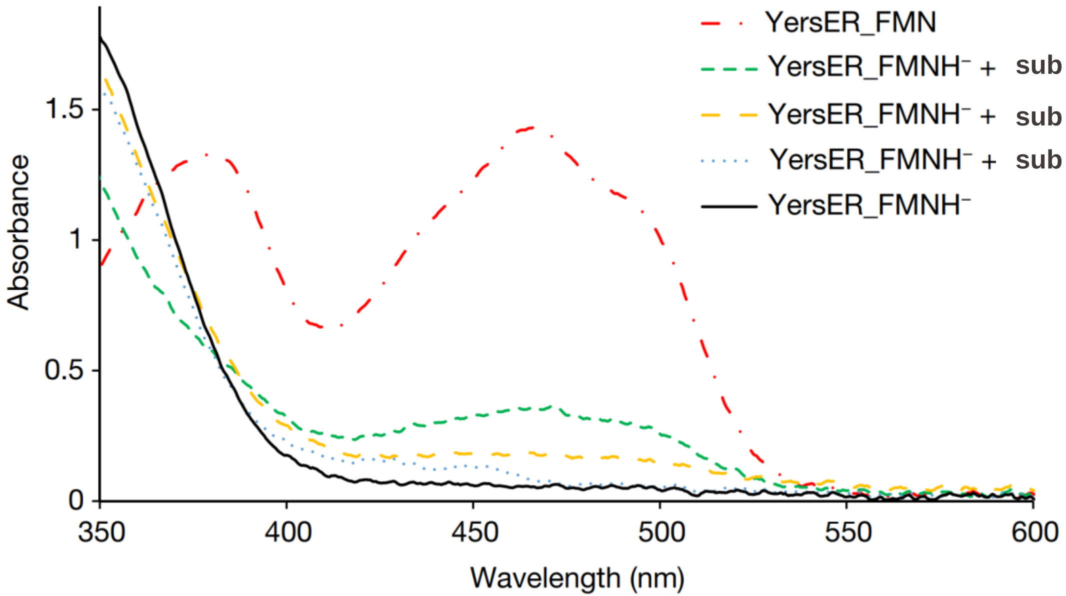

- **Photoexcitation of an EDA complex directly promotes electron transfer**

- *functions of NADP+ here: cofactor regeneration*


- Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblinsky, D. G.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B. A.; Scholes, G. D.; Hyster, T. K. *Science* **2019**, *364*, 1166– 1169

# *Zhao : photoenzymatic intermolecular radical addition*

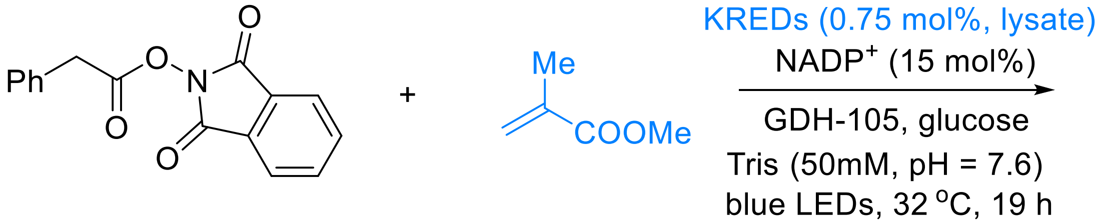



- *a natural enzyme in this case*

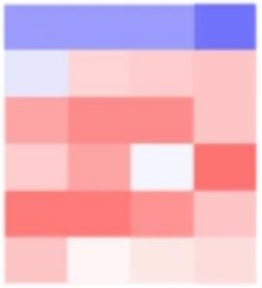
Huang, X.; Wang, B.; Wang, Y.; Jiang, G.; Feng, J.; Zhao, H. *Nature* **2020**, *584*, 69– 74

# Zhao : photoenzymatic intermolecular radical addition




75% yield, 89% ee

Screening of 24 KREDs



Parent: P2-D12

Sites: M206, M205, A202, L199, L195, P190, T152, I144, S143, S96

Mutated to A (or G), L (or I), F

Parent: P2-D12_M206F (K1)

Sites: M205, A202, L199,P190, I144

- *engineered enzyme in this case*

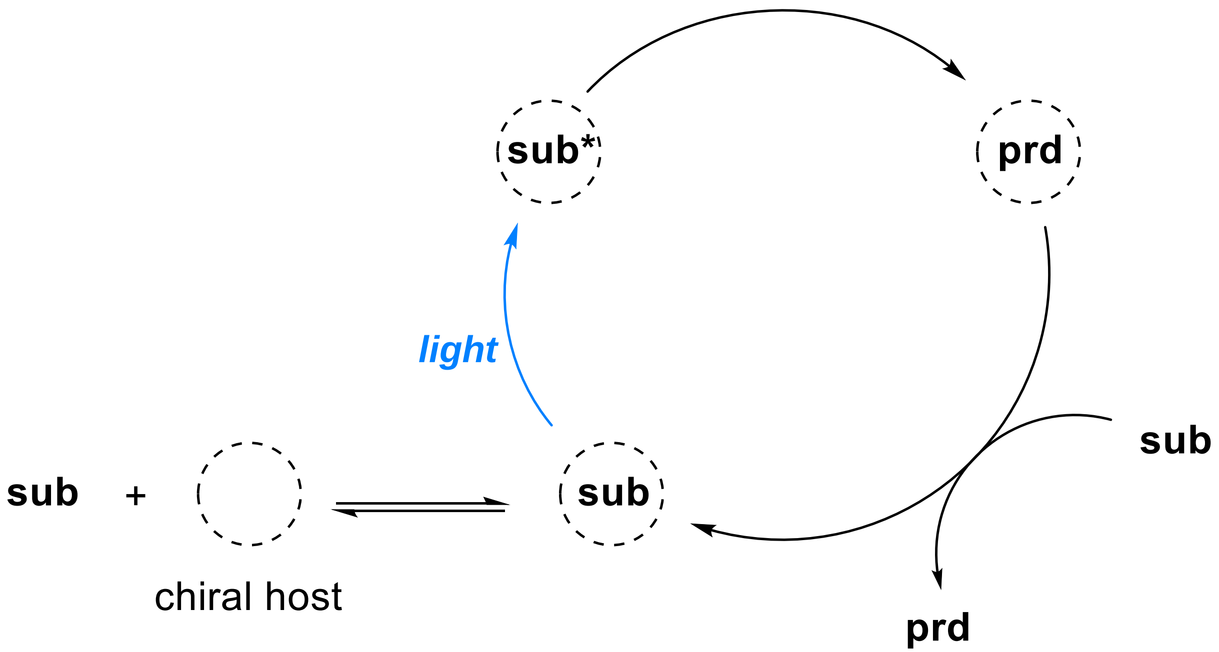
Parents:
P2-D12_M206F/L199A (K2)
P2-D12_M206F/L199F
P2-D12_M206F/M205A

Sites: 190/199/202/205

Four variants (ER > 96:4) for screening of conditions

SC[a] and optimal variant P2-D12_M206F/L199A/M205F (K3)

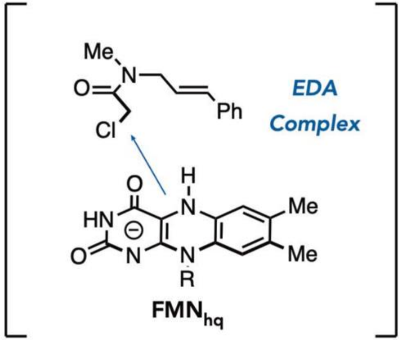
Huang, X., Feng, J., Cui, J. et al. *Nat. Catal.* **2022**, 10.1038/s41929-022-00777-4




- *except for enzymes, other approaches are underdeveloped*
- *substrate-related limitations*
- *innate flavin/NAD(P)H acticity*
- *lack of mechanistic understanding*

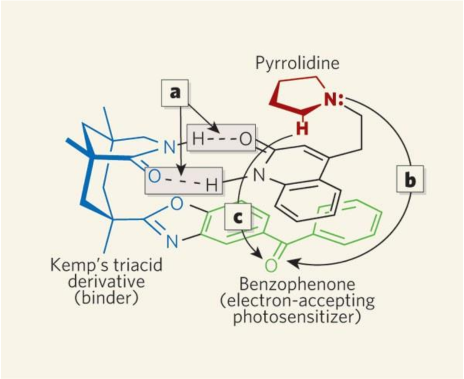
# Summary

- *a rapid increase in the pace of chiral photocatalysts*
- exciplex: usually low conversion and low ee
- pre-association is usually needed

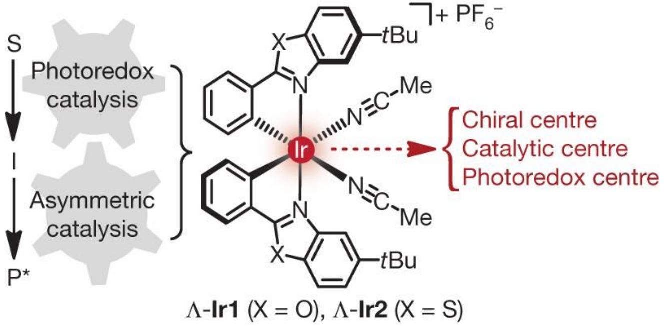



EDA complex

enzymes




hydrogen bonding




Lewis acid

# Outlook

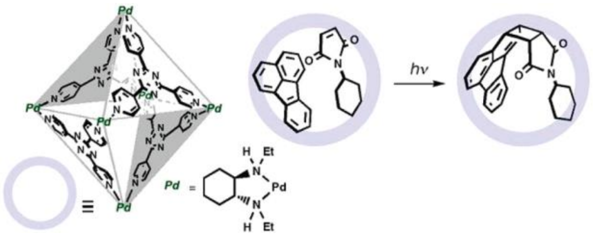
- *preassociation sets the substrate within the chiral environment*

⬇

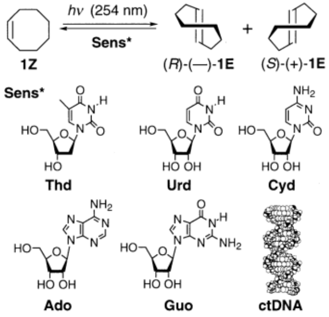
- *rigid and well-defined interaction*
- *"general" catalyst?*

⬇

- *macromolecular cage, MOF, COF, more substrate promiscuous enzymes, DNA catalysis?*

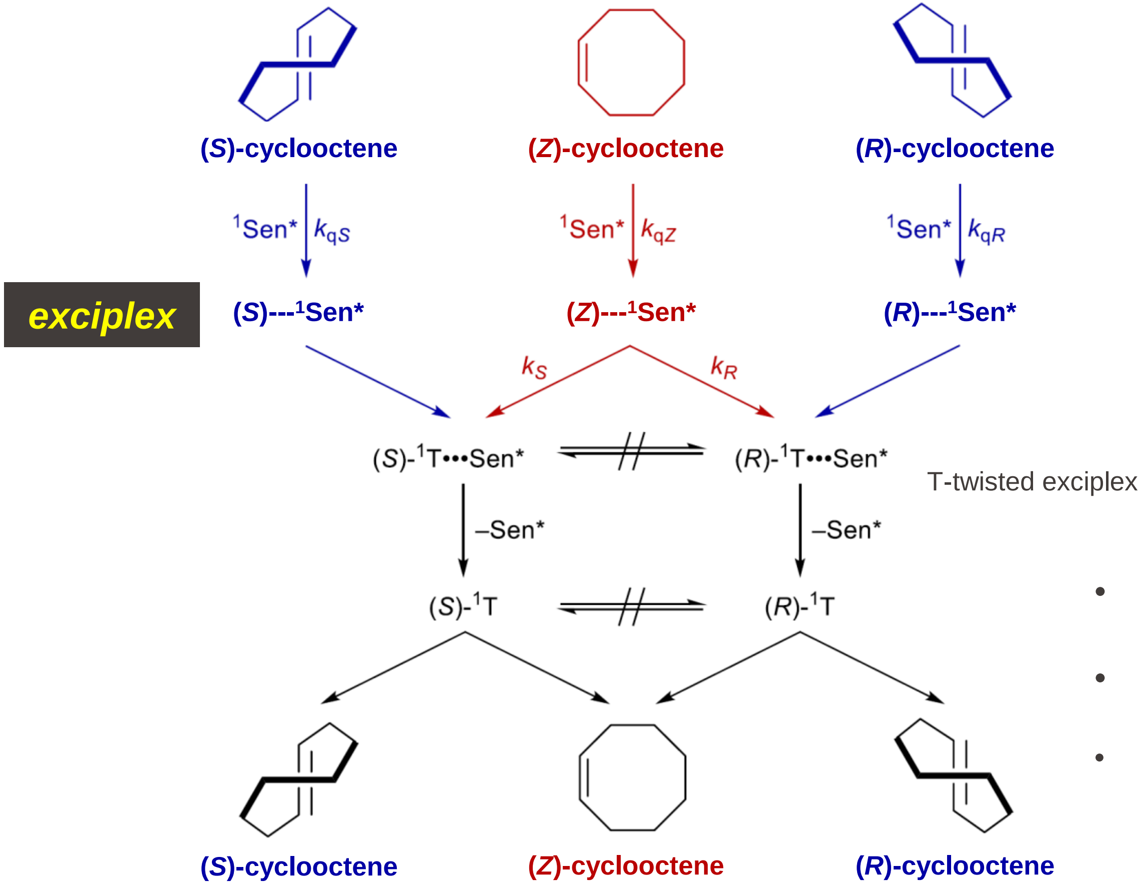



Nishioka, Y.; Yamaguchi, T.; Kawano, M.; Fujita, M. *J. Am. Chem. Soc.* **2008**, *130*, 8160– 8161




Wada, T.; Sugahara, N.; Kawano, M.; Inoue, Y. *Chem. Lett.* **2000**, *29*, 1174– 1175

# *Inoue : isomerization of achiral (Z)-cyclooctene*

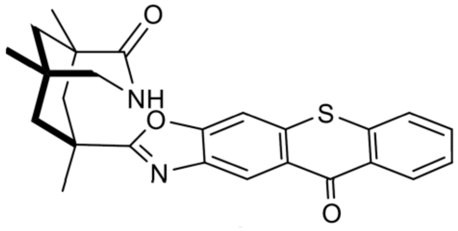


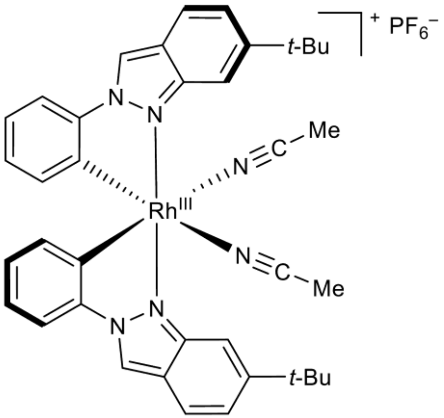

***Q1***

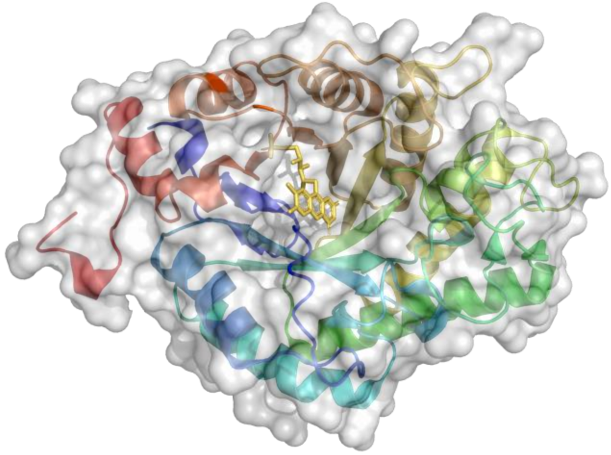
- *enantiodetermining step?*
- *sensitizer quenching ($k_{qS}$ vs $k_{qR}$)*
- *rotational relaxation ($k_S$ vs $k_R$)*


- Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672– 1678.

EPFL



# Thank you for your attention!

Weijin Wang

Advisor: Prof. Xile Hu

May 16, 2022

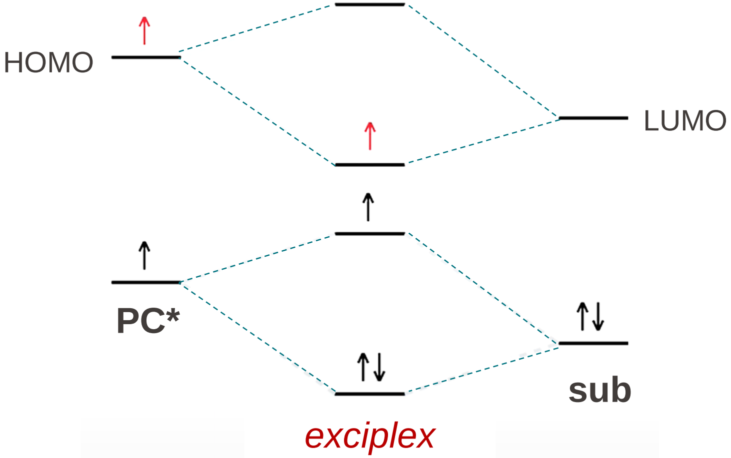
# *Q2: how to tell the difference between exciplex and EDA complex?*

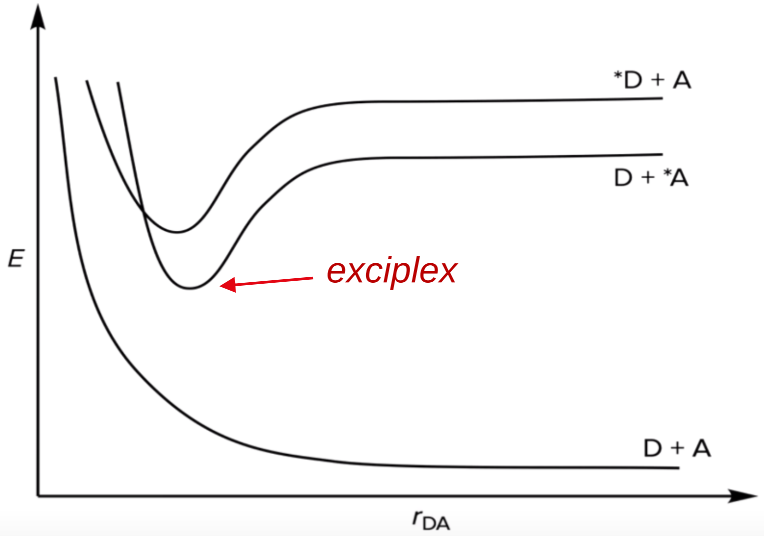
# Exciplex

$$PC + sub \xrightarrow{h\nu} PC^{*} + sub \rightleftharpoons [PC\text{-----}sub]^{*}$$

*exciplex*

- *held together by charge-transfer interactions in the excited state*

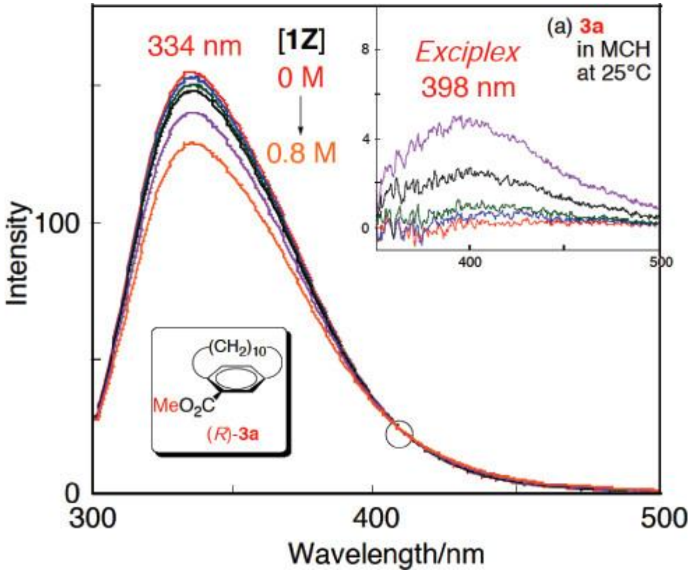


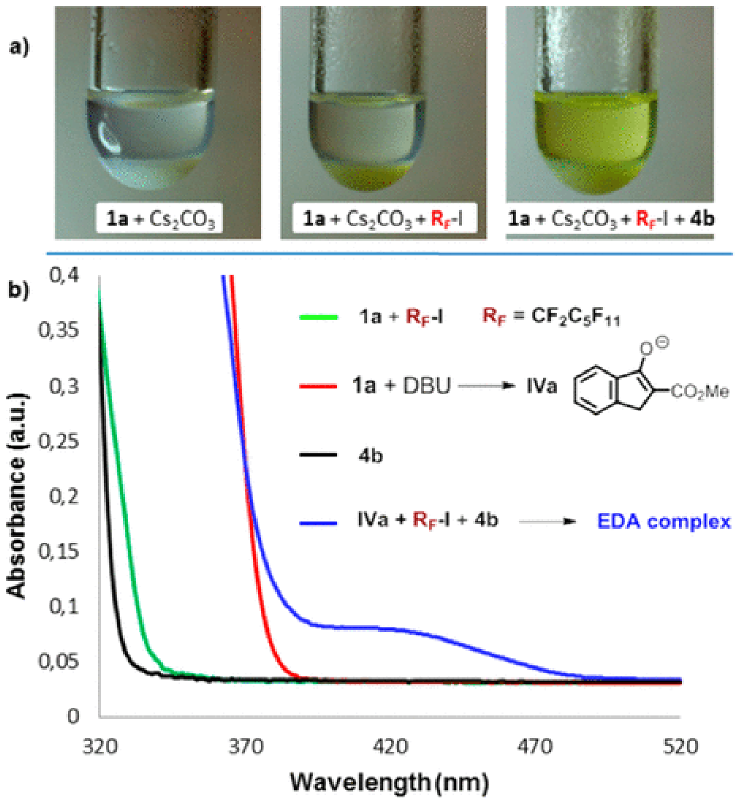




- Inoue, Y. *Chem. Rev.* **1992**, *92*, 741−770.

# Q2: how to tell the difference between exciplex and EDA complex?

By definition:
EDA complex: stable in ground state
Exciplex: stable in excited state only




- *Angew. Chem. Int. Ed.*, **2015**, *54*, 1485

# Stern–Volmer relationship

From Wikipedia, the free encyclopedia

The **Stern–Volmer relationship**, named after Otto Stern and Max Volmer,[1] allows the kinetics of a photophysical *intermolecular* deactivation process to be explored.

Processes such as fluorescence and phosphorescence are examples of *intramolecular* deactivation (Quenching (fluorescence)) processes. An *intermolecular* deactivation is where the presence of another chemical species can accelerate the decay rate of a chemical in its excited state. In general, this process can be represented by a simple equation:

$$\mathrm{A}^* + \mathrm{Q} \rightarrow \mathrm{A} + \mathrm{Q}$$

or

$$\mathrm{A}^* + \mathrm{Q} \rightarrow \mathrm{A} + \mathrm{Q}^*$$

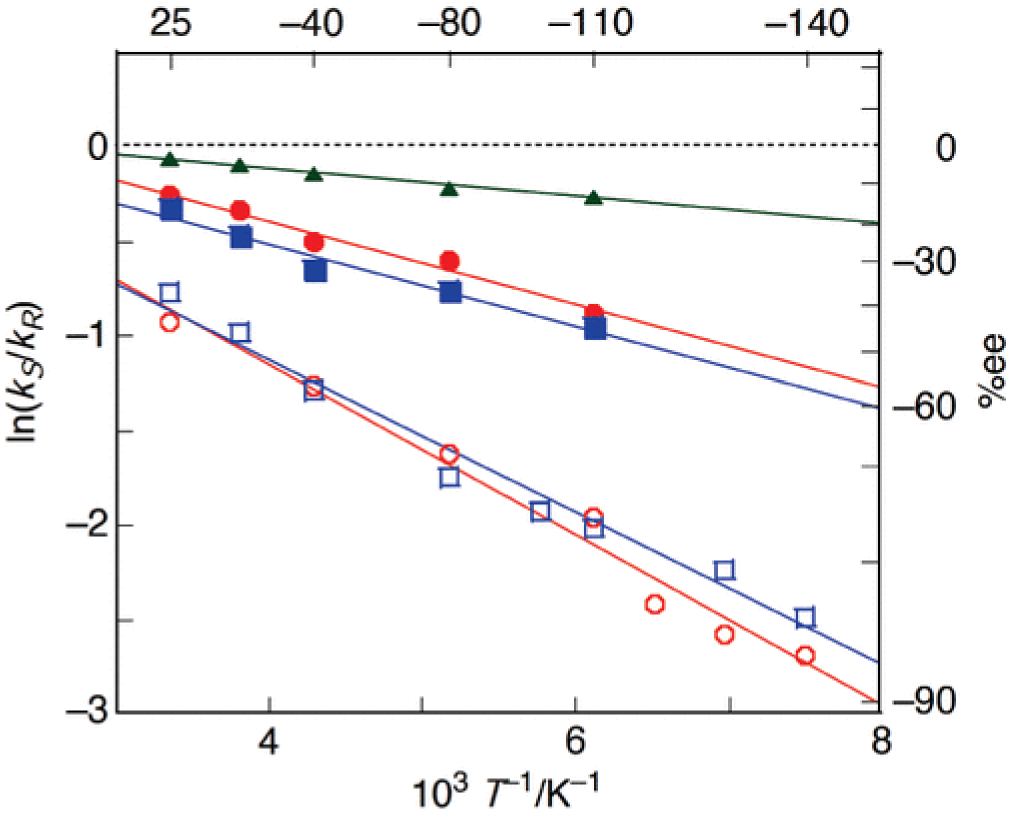
where A is one chemical species, Q is another (known as a quencher) and * designates an excited state.

The kinetics of this process follows the Stern–Volmer relationship:

$$\frac{I_f^0}{I_f} = 1 + k_q \tau_0 \cdot [\mathrm{Q}]$$

Where $I_f^0$ is the intensity, or rate of fluorescence, without a quencher, $I_f$ is the intensity, or rate of fluorescence, with a quencher, $k_q$ is the quencher rate coefficient, $\tau_0$ is the lifetime of the emissive excited state of A without a quencher present, and $[\mathrm{Q}]$ is the concentration of the quencher.[2]

$$\Delta\Delta G^{\ddagger}_{S-R} = \ln\left(\frac{k_S}{k_R}\right) = \ln(\text{e.r.}) = -\frac{\Delta\Delta H^{\ddagger}_{S-R}}{RT} + \frac{\Delta\Delta S^{\ddagger}_{S-R}}{R}$$

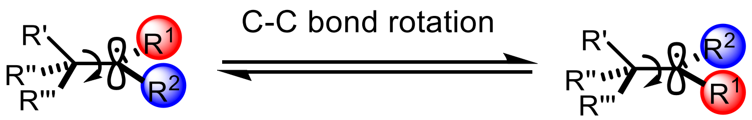


# Asymmetric Transformations with Radicals: Merging Amino- and Photoredoxcatalysis

Frontiers in Chemical Synthesis III:
Stereochemistry

*Johannes Klett*

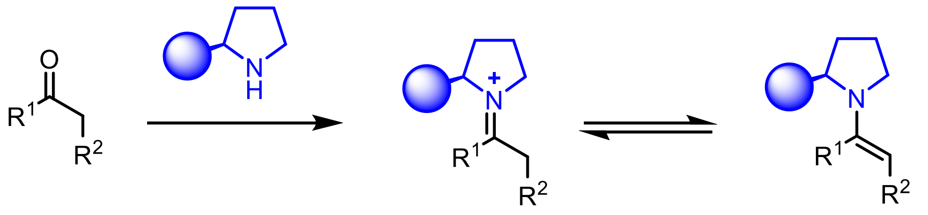
- Radicals




- Often involves problematic reagents (stannanes, AIBN, etc.)
- Reactive species
- Mild conditions
- Good functional group tolerance

*Chem. Ber.* **1985**, *118*, 1058; *Toxicology* **1989**, *55*, 253; *J. Organomet. Chem.* **2013**, *724*, 129; *Chem. Rev.* **2022**, *122*, 5842-5976.

# Aminocatalysis in Radical Chemistry

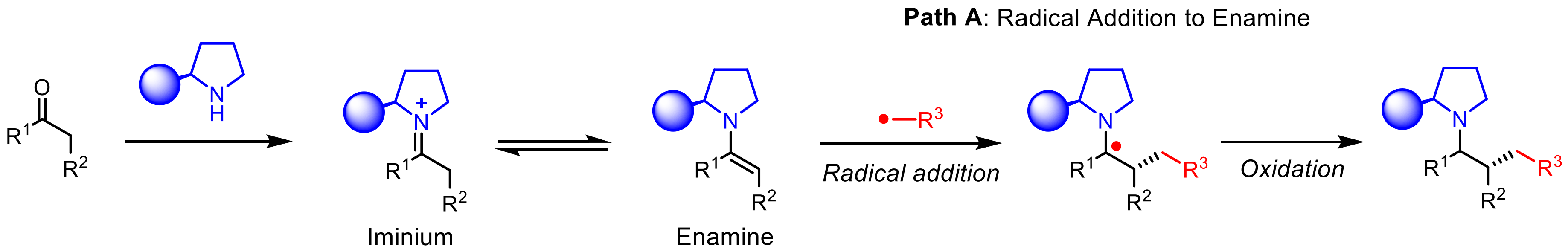



Iminium

Enamine

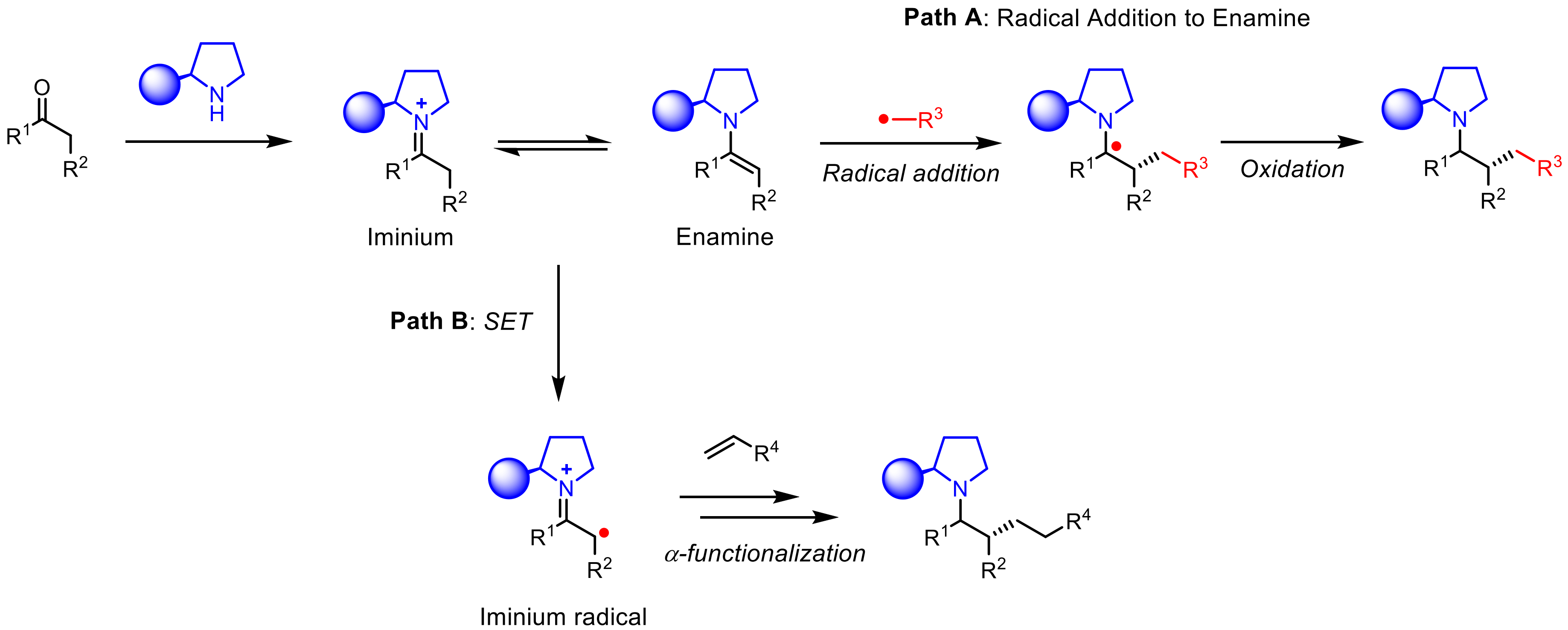
*ACS Catal*. **2018**, *8*, 5466-5484; *Chem. Rev.* **2022**, *122*, 5842-5976.

# Aminocatalysis in Radical Chemistry




ACS Catal. **2018**, *8*, 5466-5484; *Chem. Rev.* **2022**, *122*, 5842-5976.

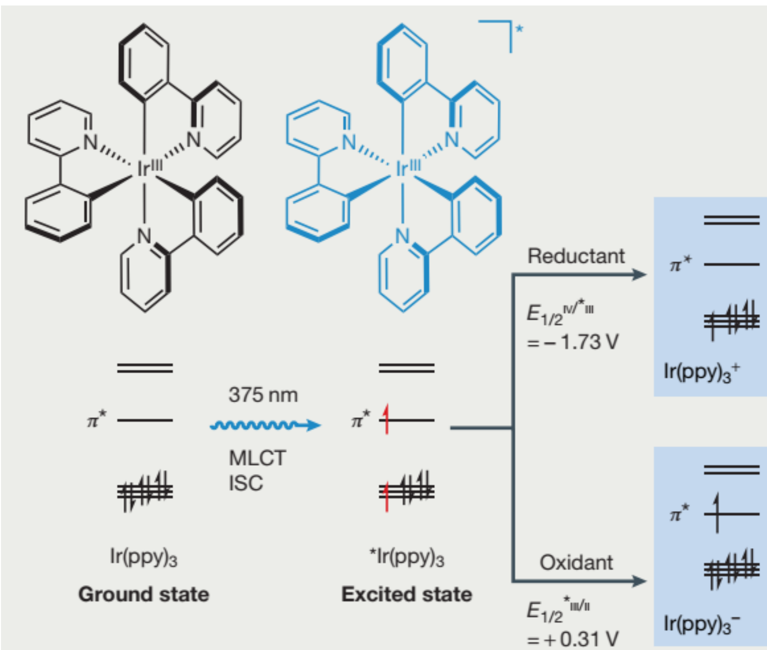
# Aminocatalysis in Radical Chemistry

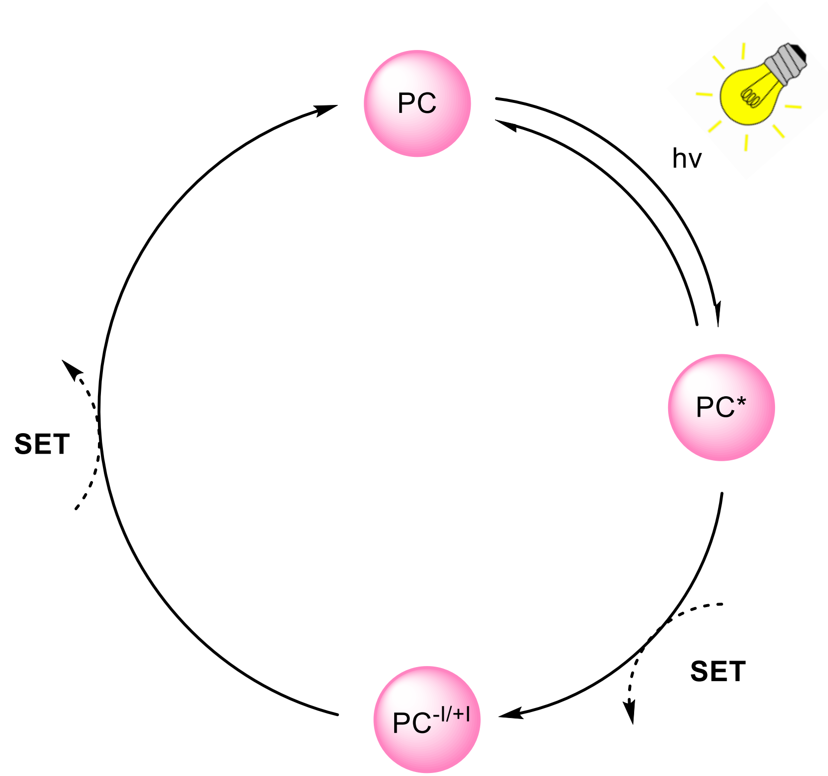



*ACS Catal*. **2018**, *8*, 5466-5484; *Chem. Rev.* **2022**, *122*, 5842-5976.

# Photoredoxcatalysis

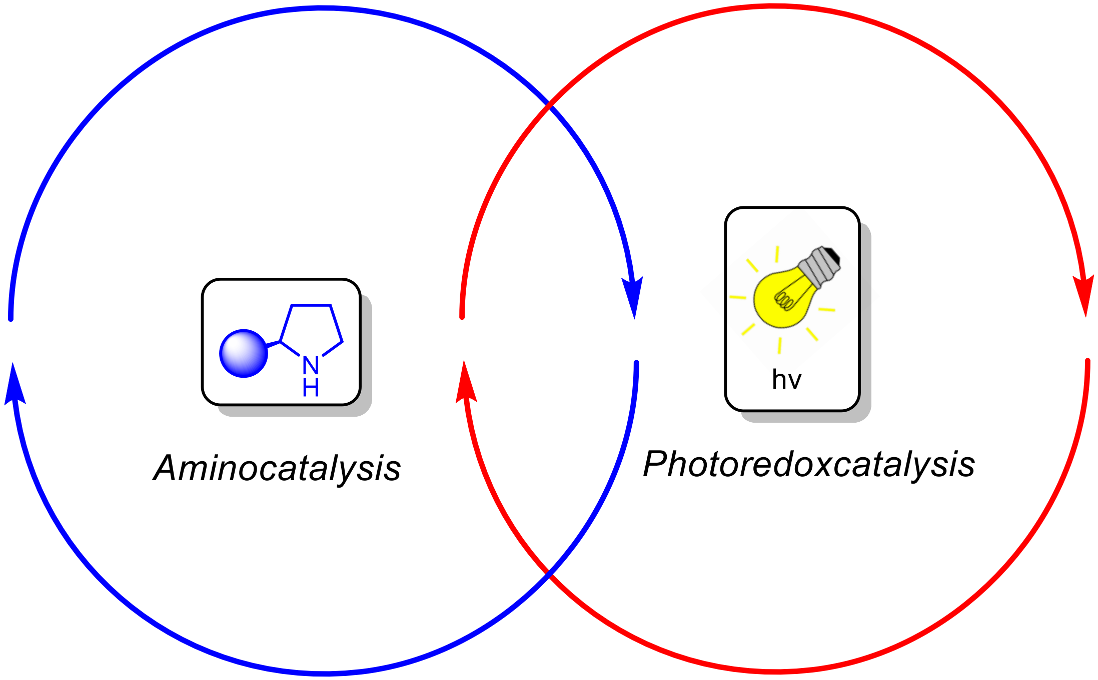
- Advantages: very mild conditions, no stochiometric reductants, high functional group tolerance



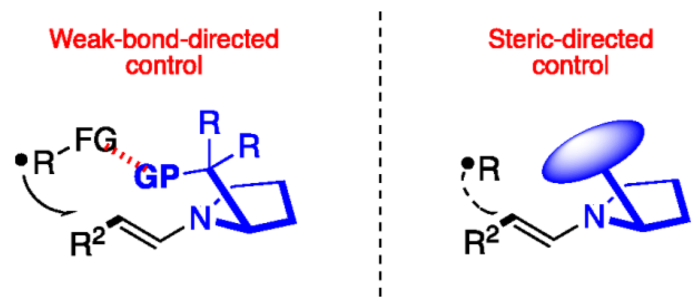




*Nat Rev Chem* **1,** 0052 (**2017**) (DOI: 10.1038/s41570-017-0052)

# Combine!

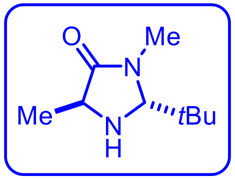



- ✓ No stoichiometric reductants
- ✓ Selective SET
- ✓ Covalent bound to substrate
- ✓ Chiral amine catalyst: enantioinduction

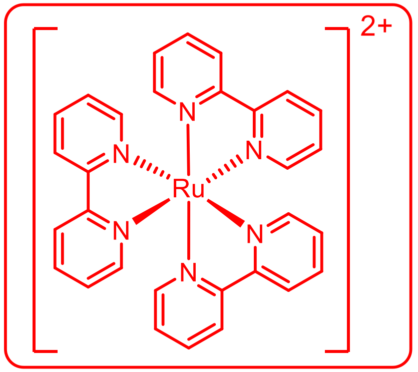



*Chem. Rev.* **2022**, *122*, 5842-5976.

# Detailed Catalytic Cycles



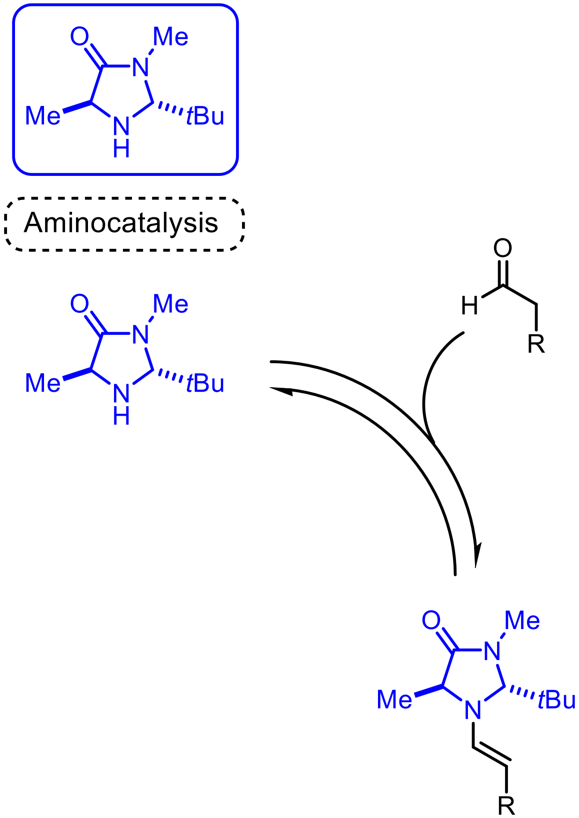

Aminocatalysis

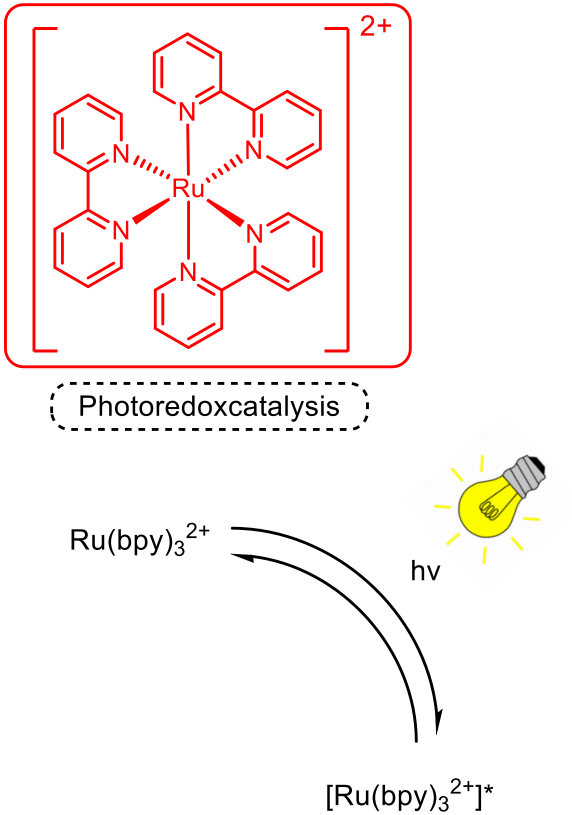



Photoredoxcatalysis

McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

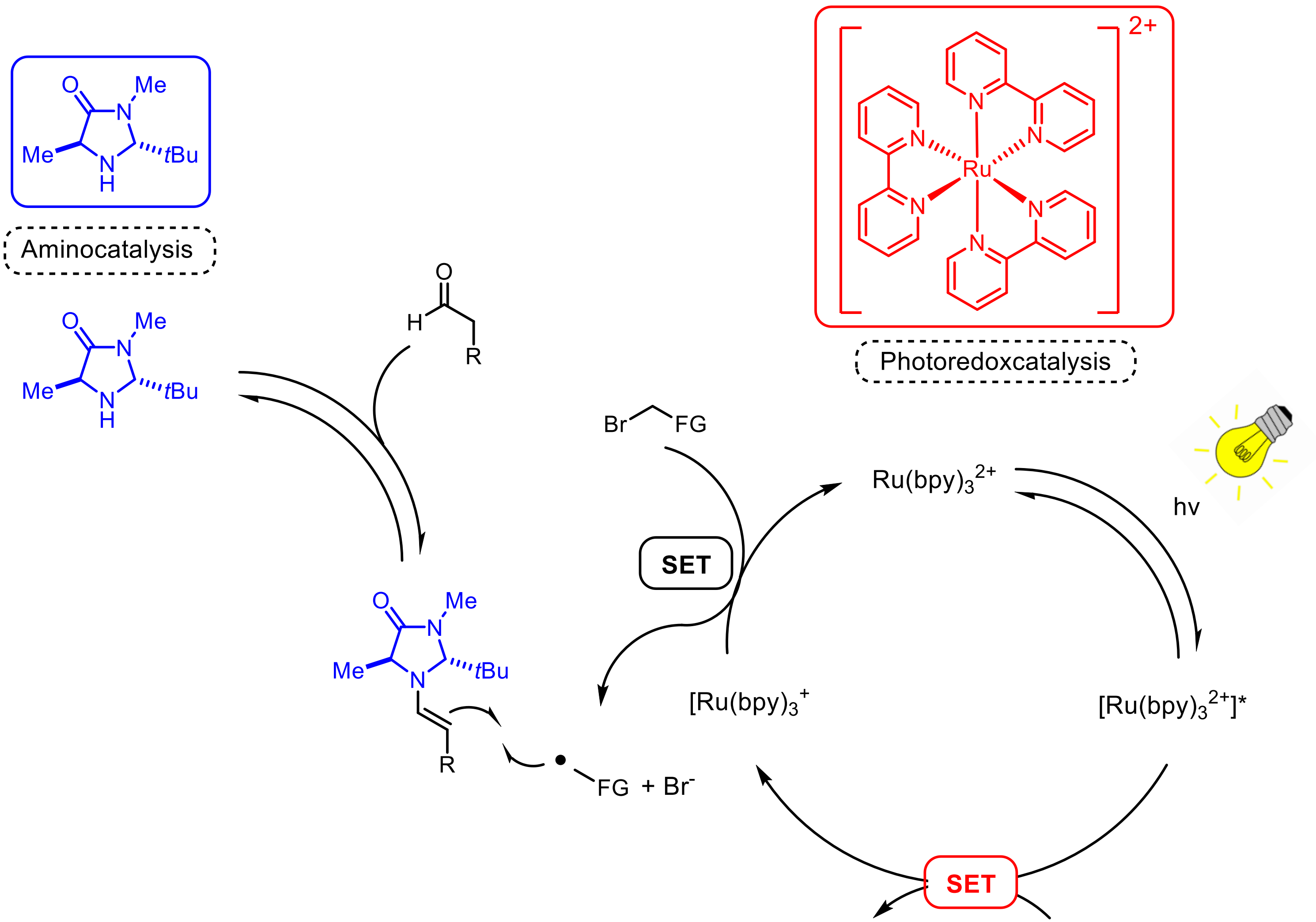
# Detailed Catalytic Cycles



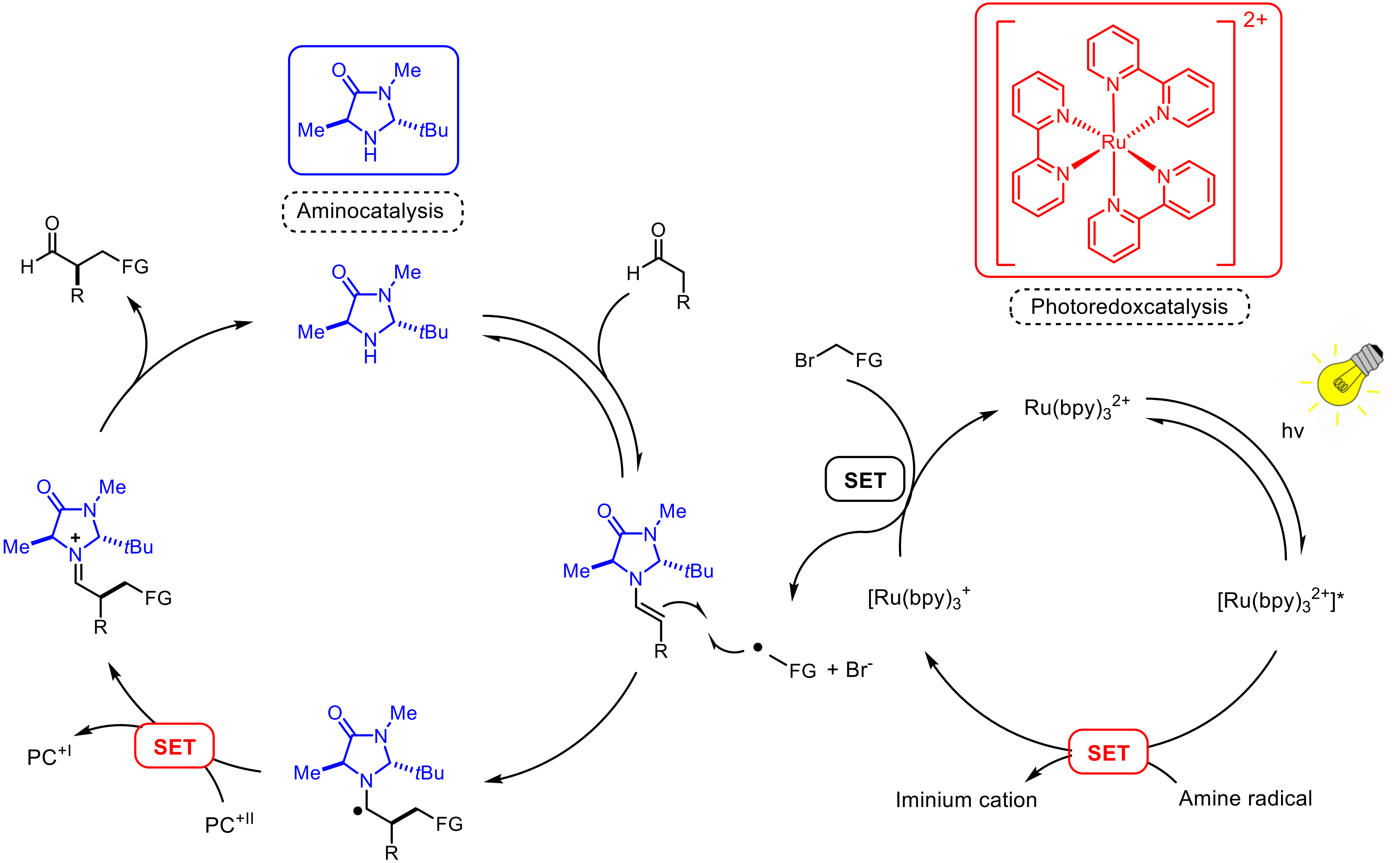

McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

# Detailed Catalytic Cycles



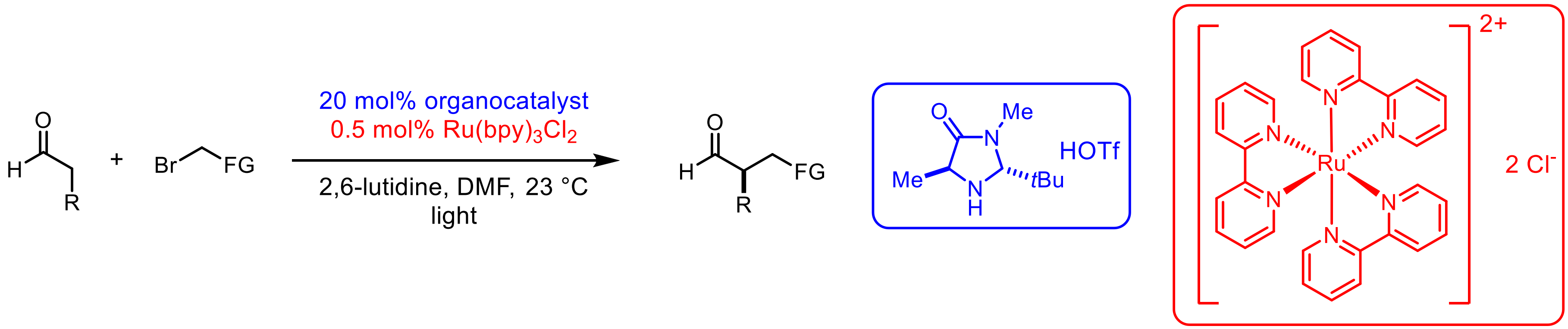

McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

# Detailed Catalytic Cycles



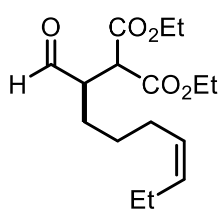

McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

# α-Alkylation of Aldehydes

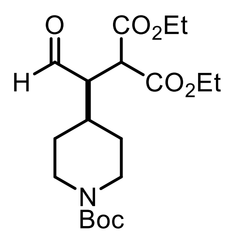



**2008**

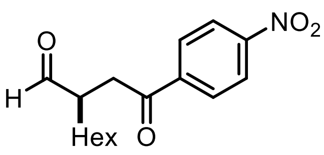
12 examples
up to 93 % yield
up to 99 % *ee*



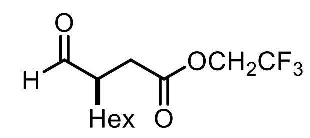

86 % yield
90 % *ee*




66 % yield
91 % *ee*



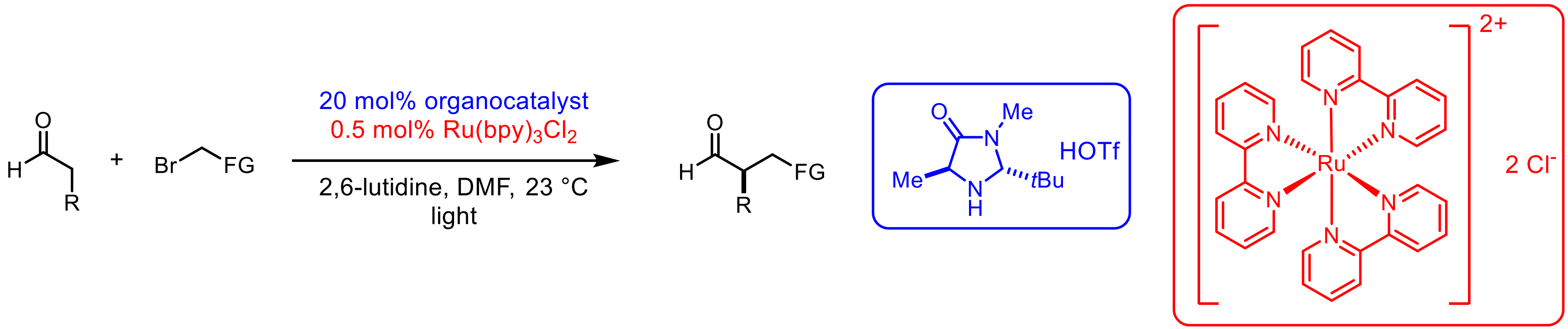

84 % yield
95 % *ee*




80 % yield
92 % *ee*

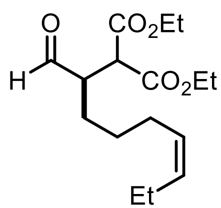
McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

# α-Alkylation of Aldehydes

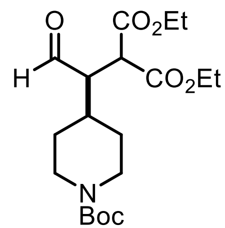



**2008**

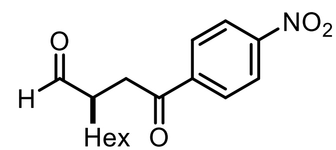
12 examples
up to 93 % yield
up to 99 % *ee*



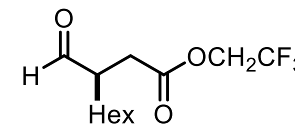
86 % yield
90 % *ee*



66 % yield
91 % *ee*



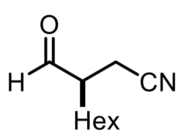
84 % yield
95 % *ee*



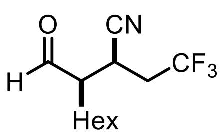
80 % yield
92 % *ee*

**2015**

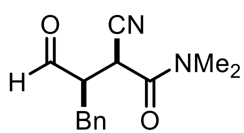
18 examples
up to 95 % yield
up to 98 % *ee*



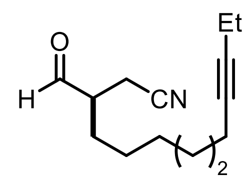
95 % yield
95 % *ee*



85 % yield
95 % *ee*



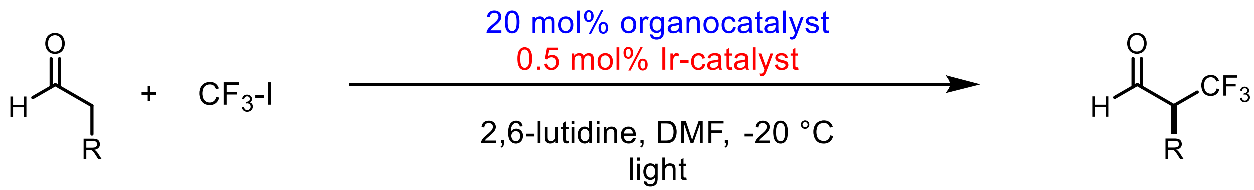
78 % yield
93 % *ee*



68 % yield
91 % *ee*

McMillan *et al. Science* **2008**, *322*, 77-80; McMillan *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 9668-9672.

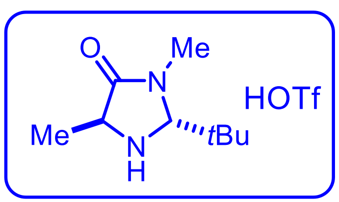
# α-Trifluoromethylation of Aldehydes

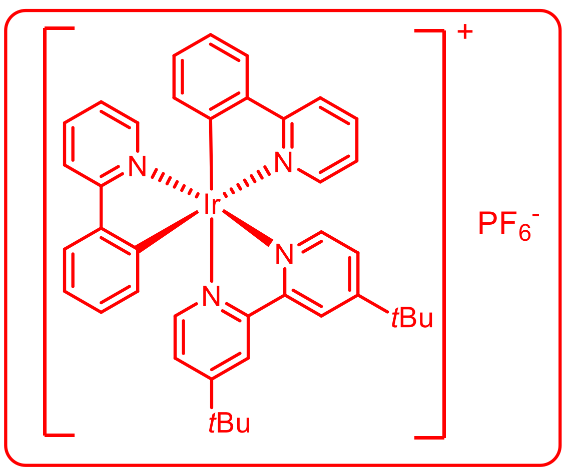


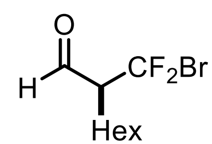

*α-trifluoromethylation*

**2009**

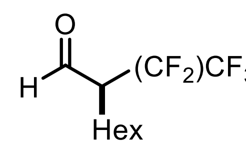
18 examples
up to 89 % yield
up to 99 % *ee*



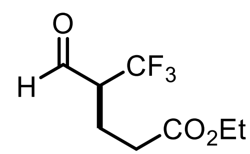



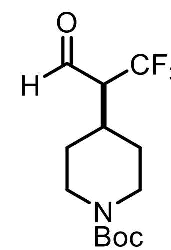

68 % yield
99 % *ee*




67 % yield
96 % *ee*



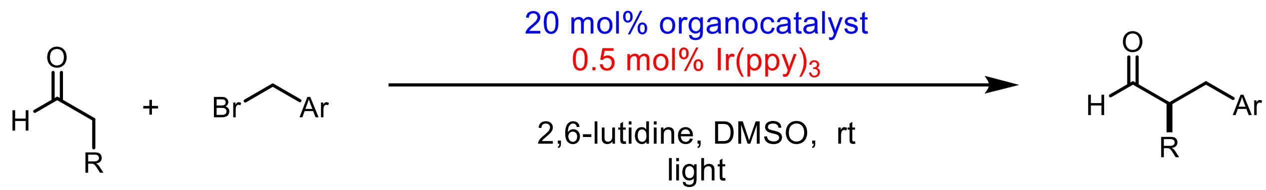

86 % yield
97 % *ee*




70 % yield
99 % *ee*

McMillan *et al. J. Am. Chem. Soc.* **2009**, *131*, 10875-10877

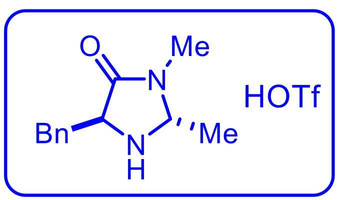
# α-Benzylation of Aldehydes

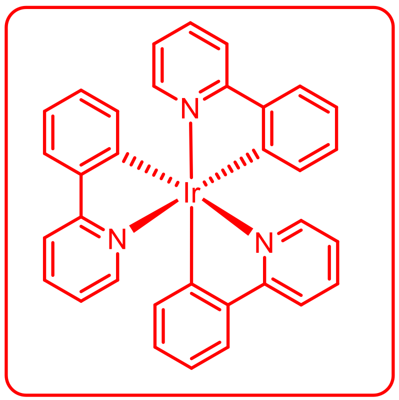


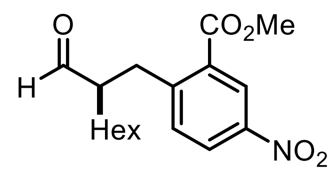

*α-benzylation*

**2010**

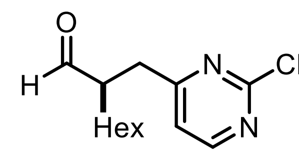
16 examples
up to 94 % yield
up to 97 % *ee*



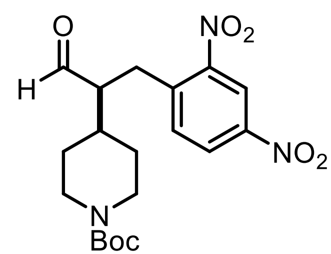



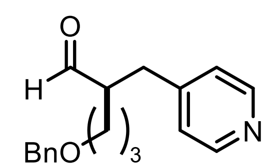

76 % yield
93 % *ee*




78 % yield
87 % *ee*



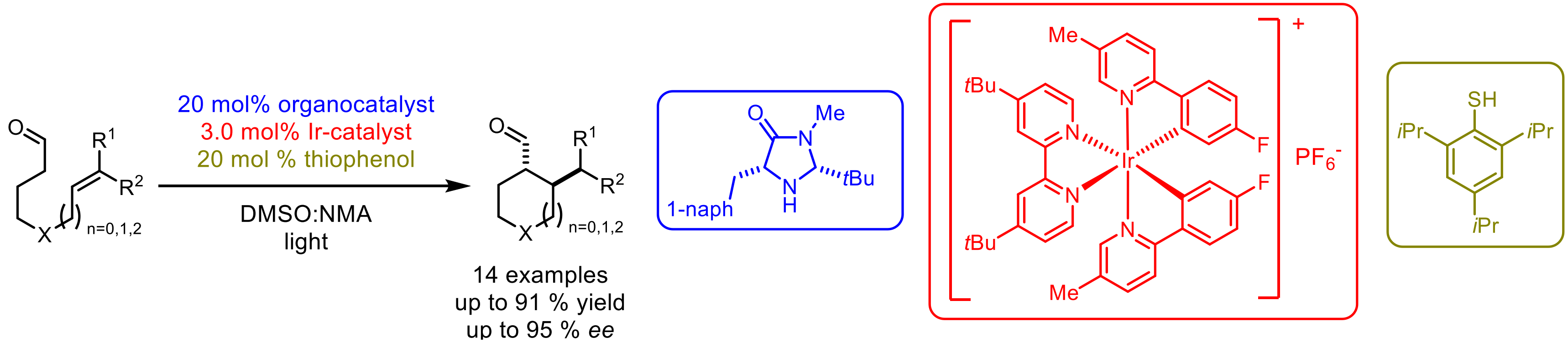

75 % yield
90 % *ee*




75 % yield
90 % *ee*

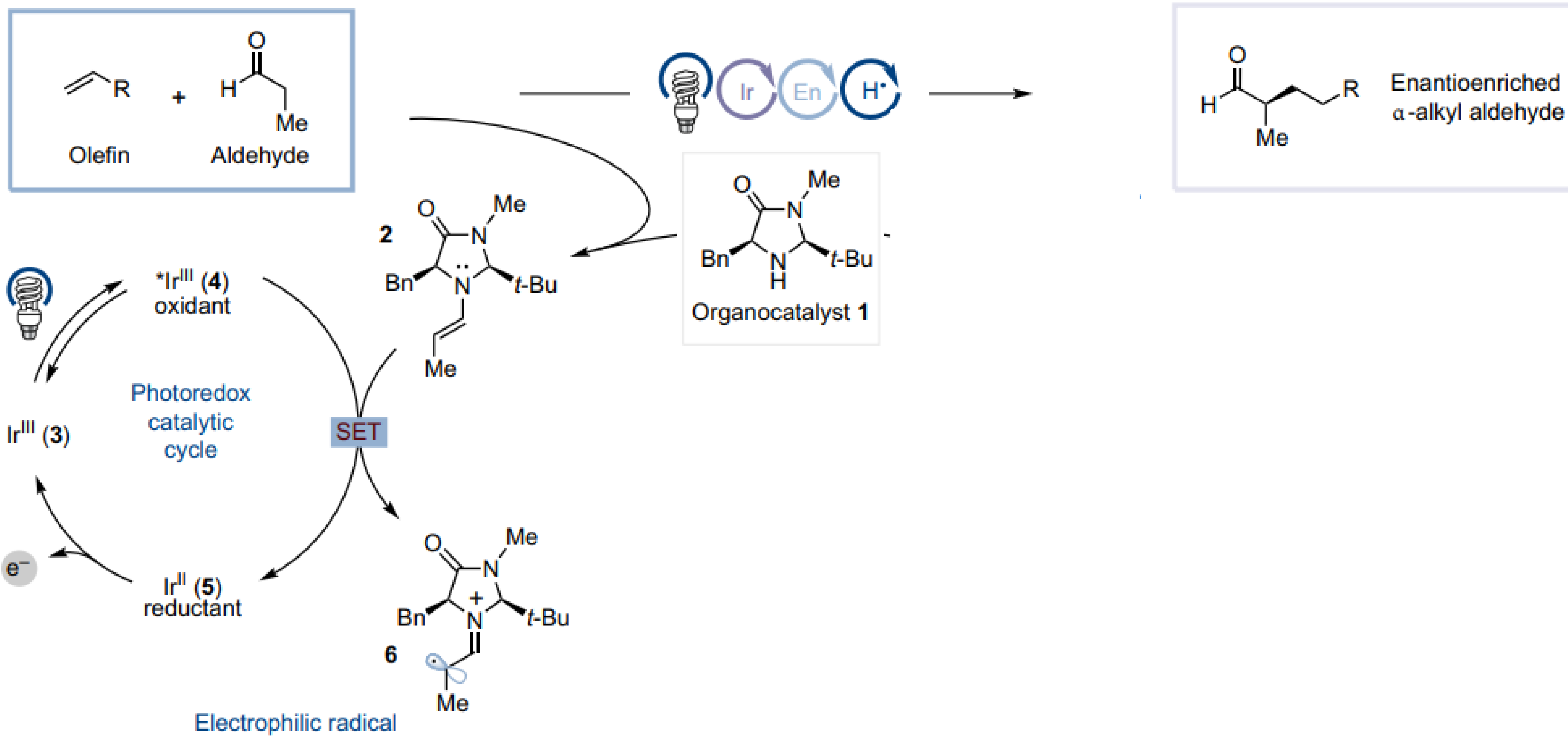
McMillan *et al. J. Am. Chem. Soc.* **2010**, *132*, 13600-13603.

# Triple Catalysis: Enamine Radicals



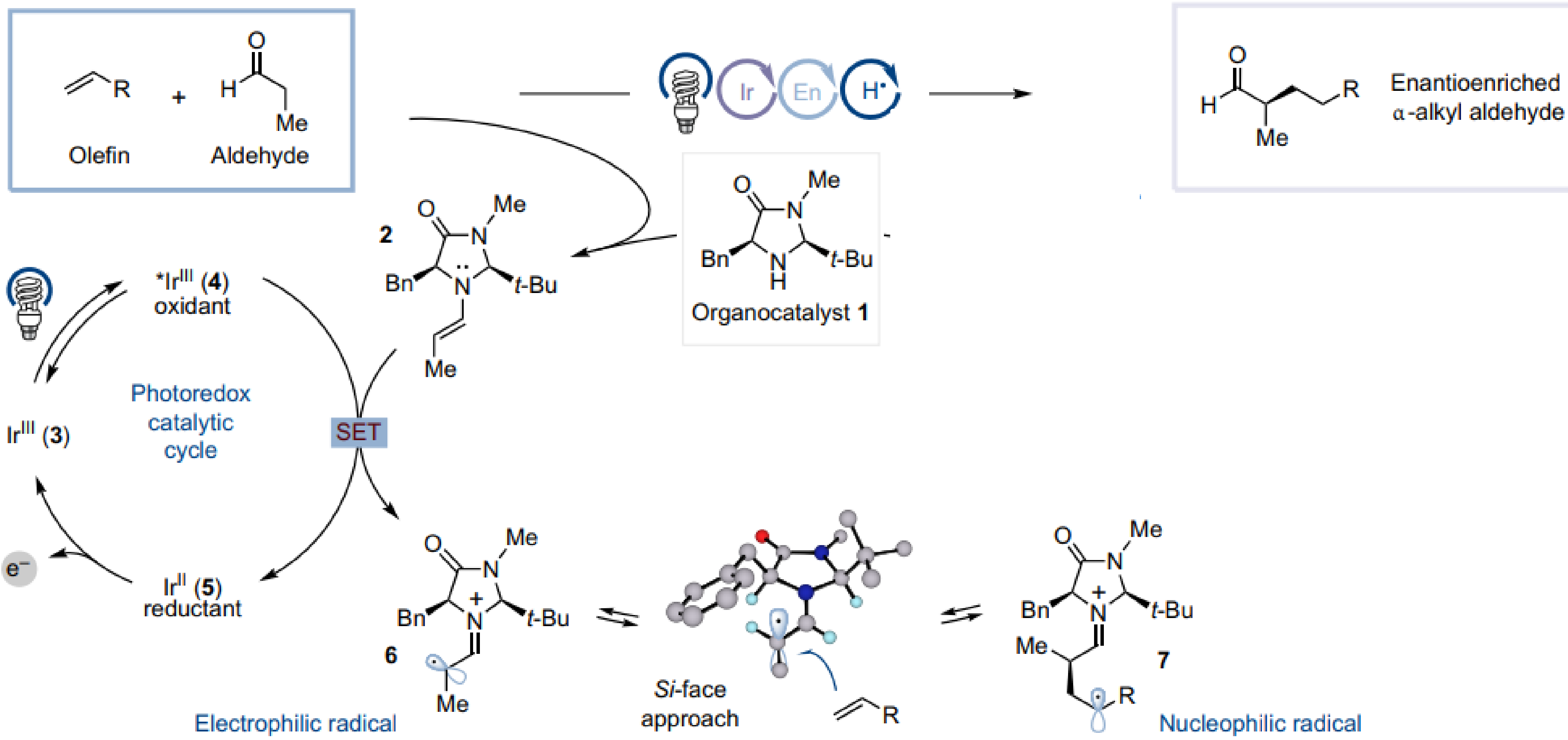

McMillan *et al. Nat. Chem.* **2017**, *9*, 1073-1077.

# Triple Catalysis: Enamine Radicals



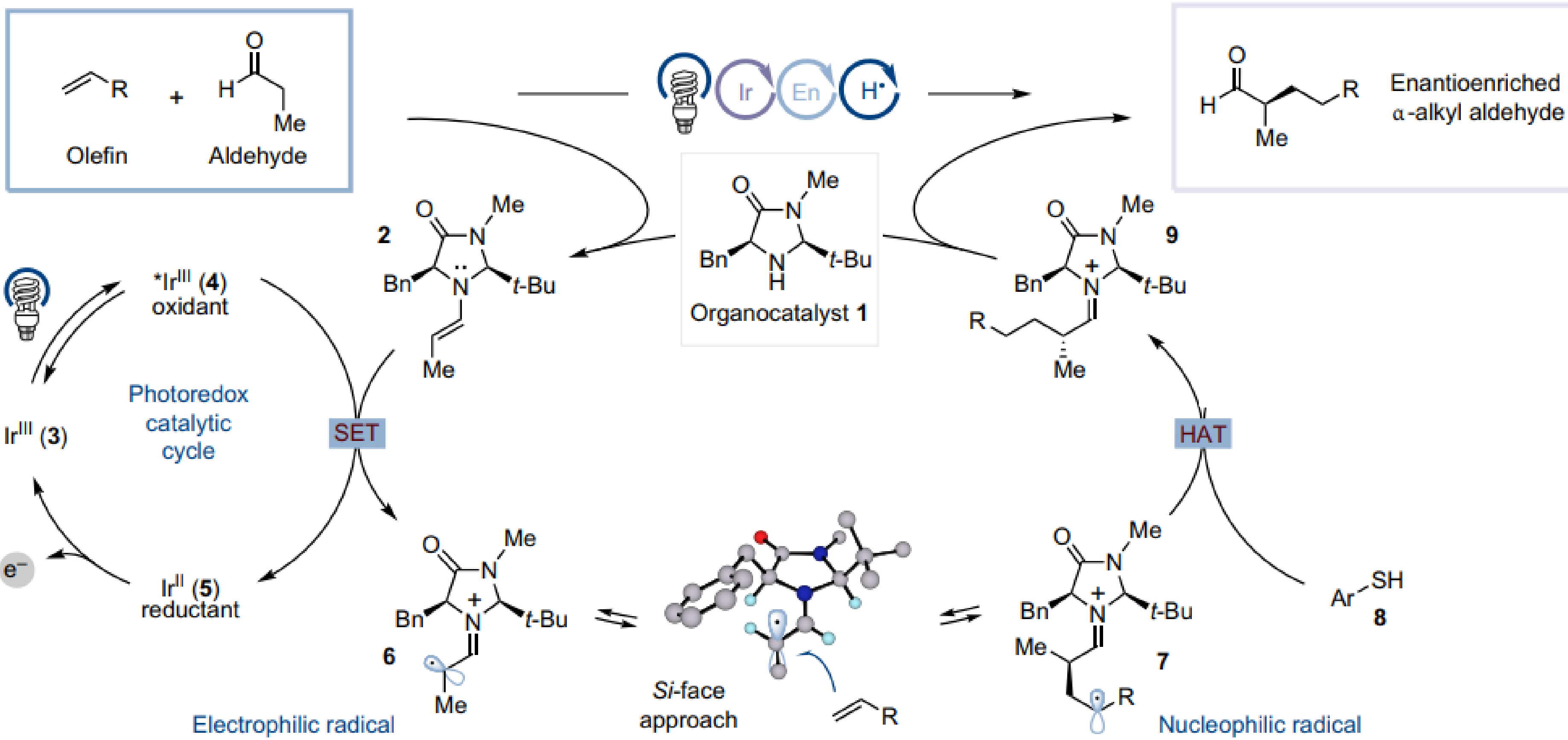

McMillan *et al. Nat. Chem.* **2017**, *9*, 1073-1077.

# Triple Catalysis: Enamine Radicals



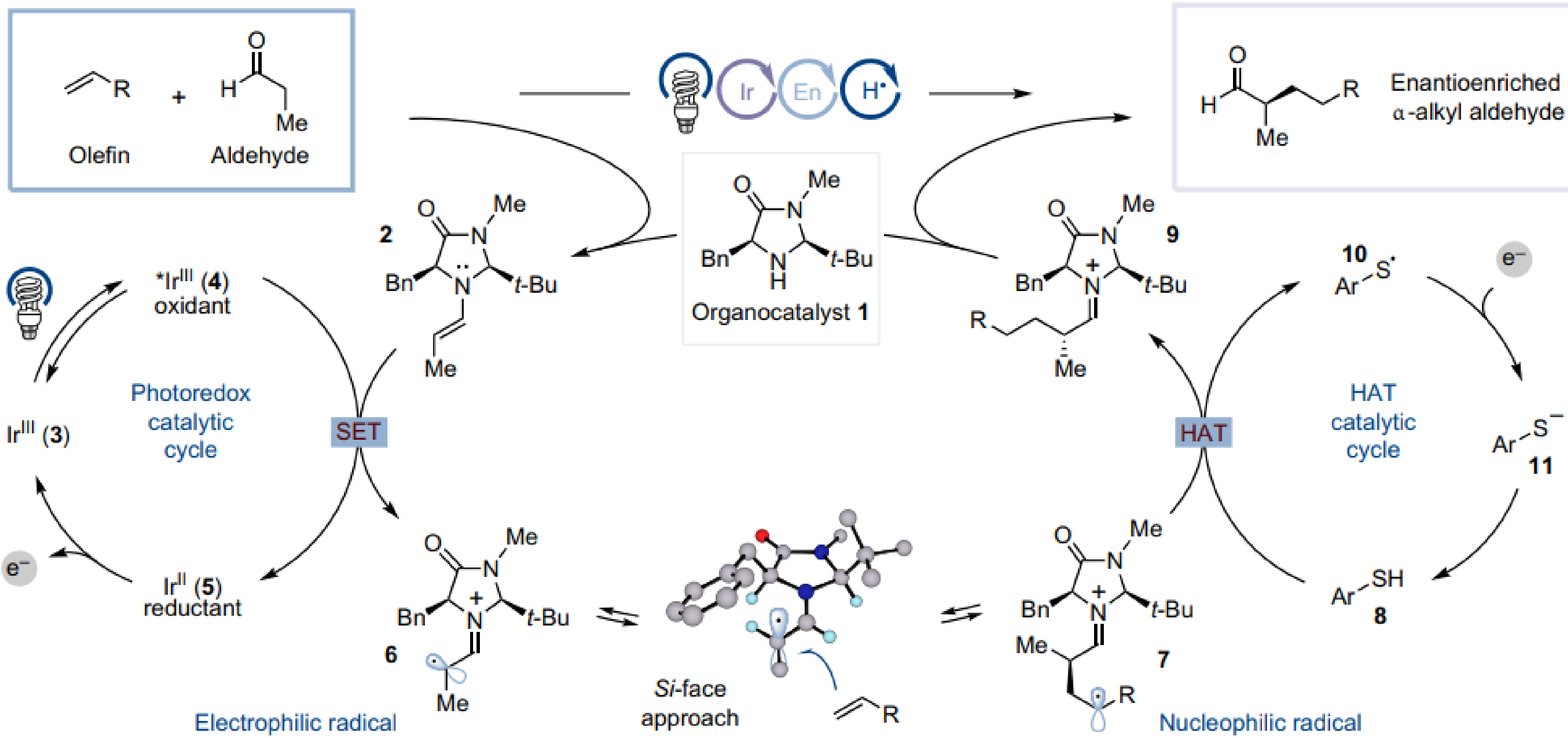

McMillan *et al. Nat. Chem.* **2017**, *9*, 1073-1077.

# Triple Catalysis: Enamine Radicals



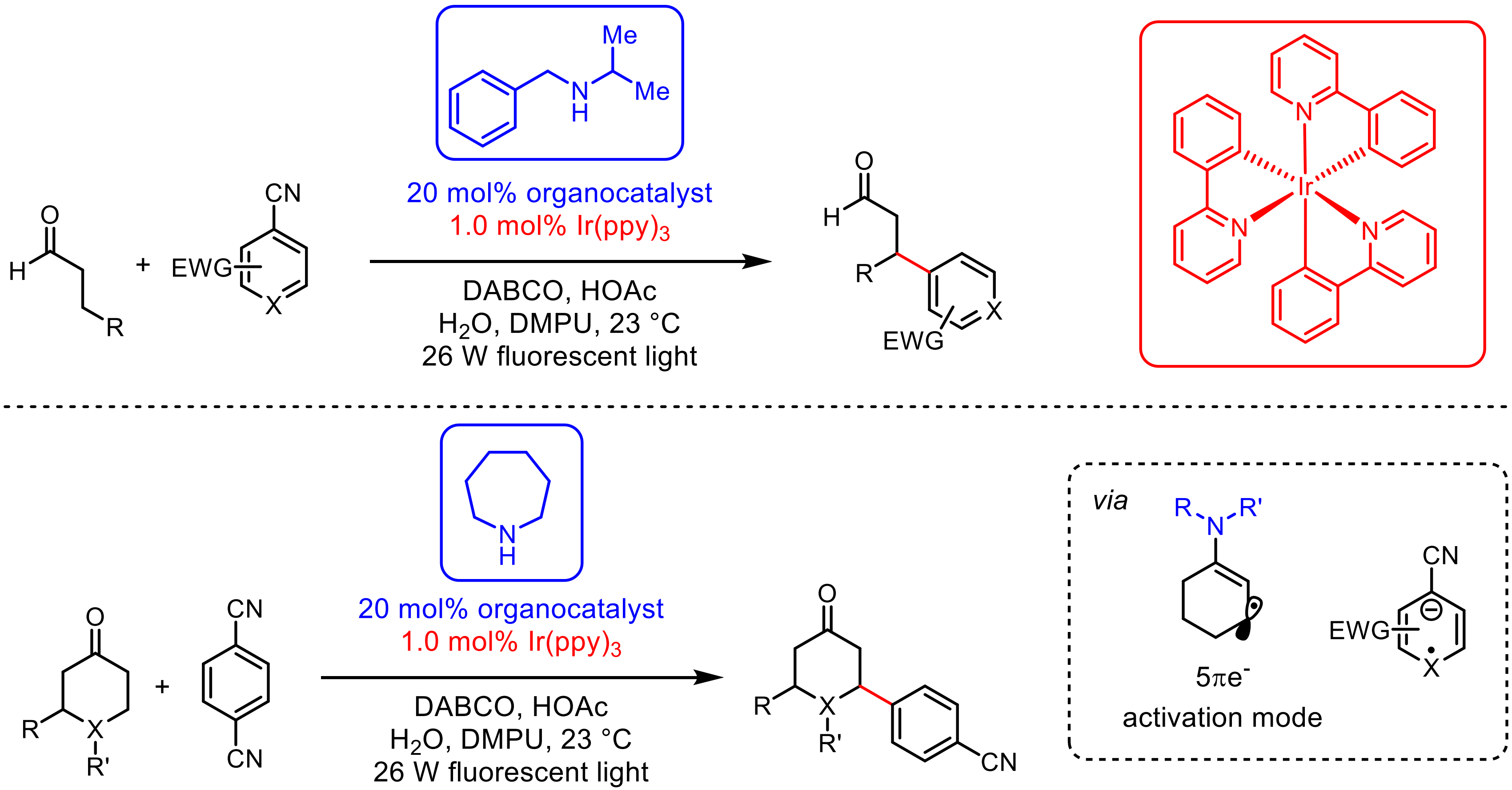

McMillan *et al. Nat. Chem.* **2017**, *9*, 1073-1077.

# Triple Catalysis: Enamine Radicals



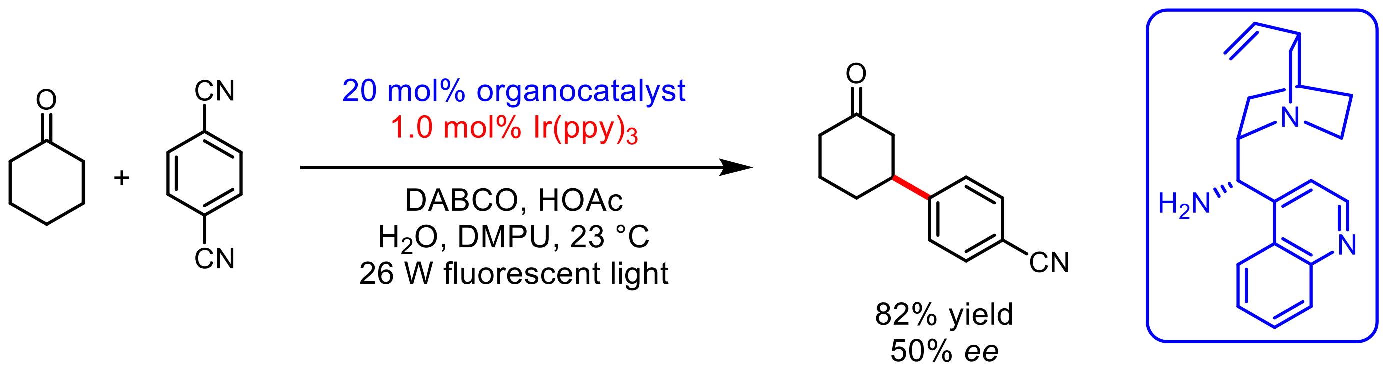

McMillan *et al. Nat. Chem.* **2017**, *9*, 1073-1077.

# *β*-Functionalization



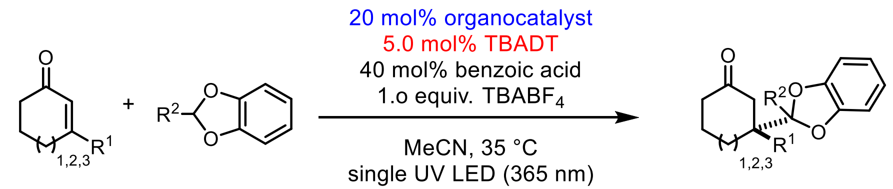

Dong *et al.* *Tetrahedron Lett.* **2014**, *55*, 5869-5889; McMillan *et al.* *Science* **2013**, *339*, 1593-1596.

# *β*-Functionalization



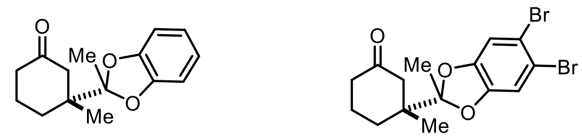

McMillan *et al.* *Science* **2013**, *339*, 1593-1596.

# β-Functionalization



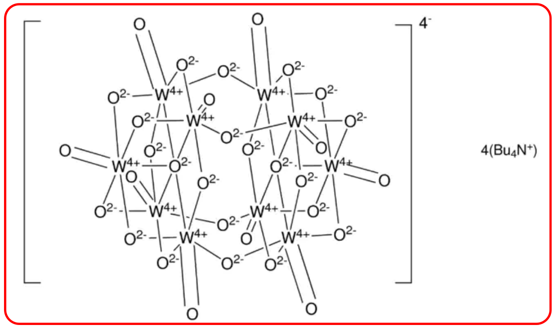

10 examples
up to 99% yield
up to 98% *ee*

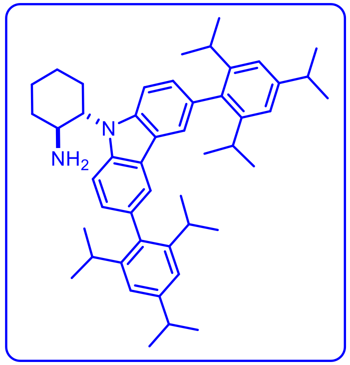
*via* HAT and SET

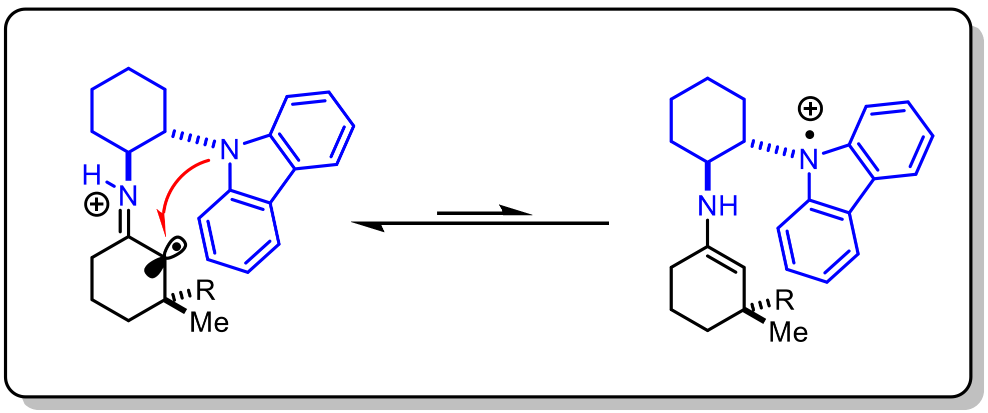



69% yield
97% *ee*

49% yield
91% *ee*

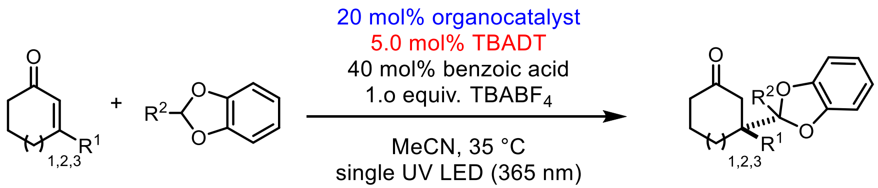


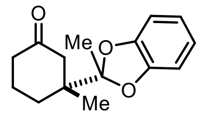

Melchiorre *et al. Nature* **2016**, *532*, 218-222.

# β-Functionalization

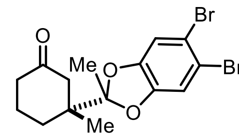



10 examples
up to 99% yield
up to 98% *ee*

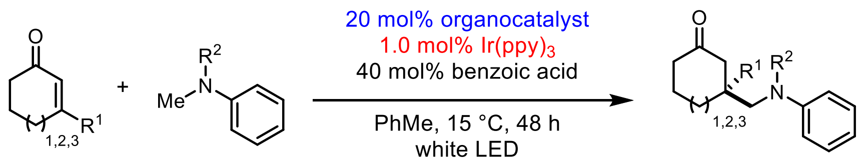
*via* HAT and SET




69% yield
97% *ee*

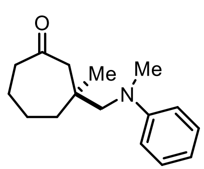



49% yield
91% *ee*

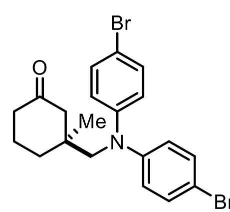



11 examples
up to 92% yield
up to 90% *ee*

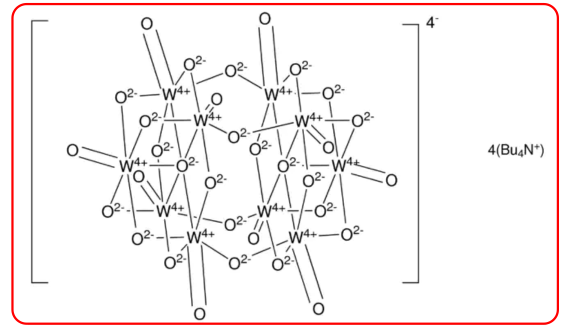
*via* double SET

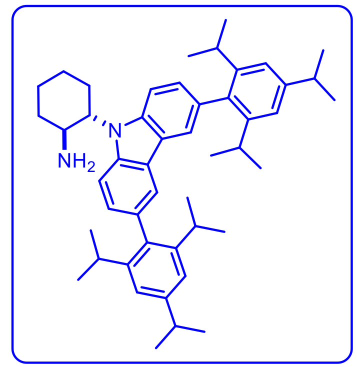


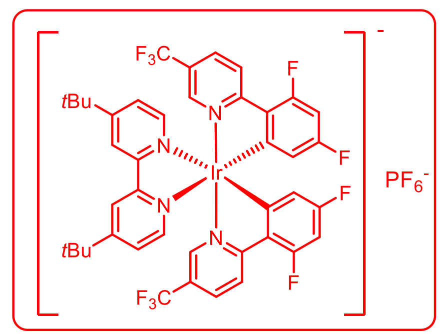

92% yield
88% *ee*




52% yield
80% *ee*

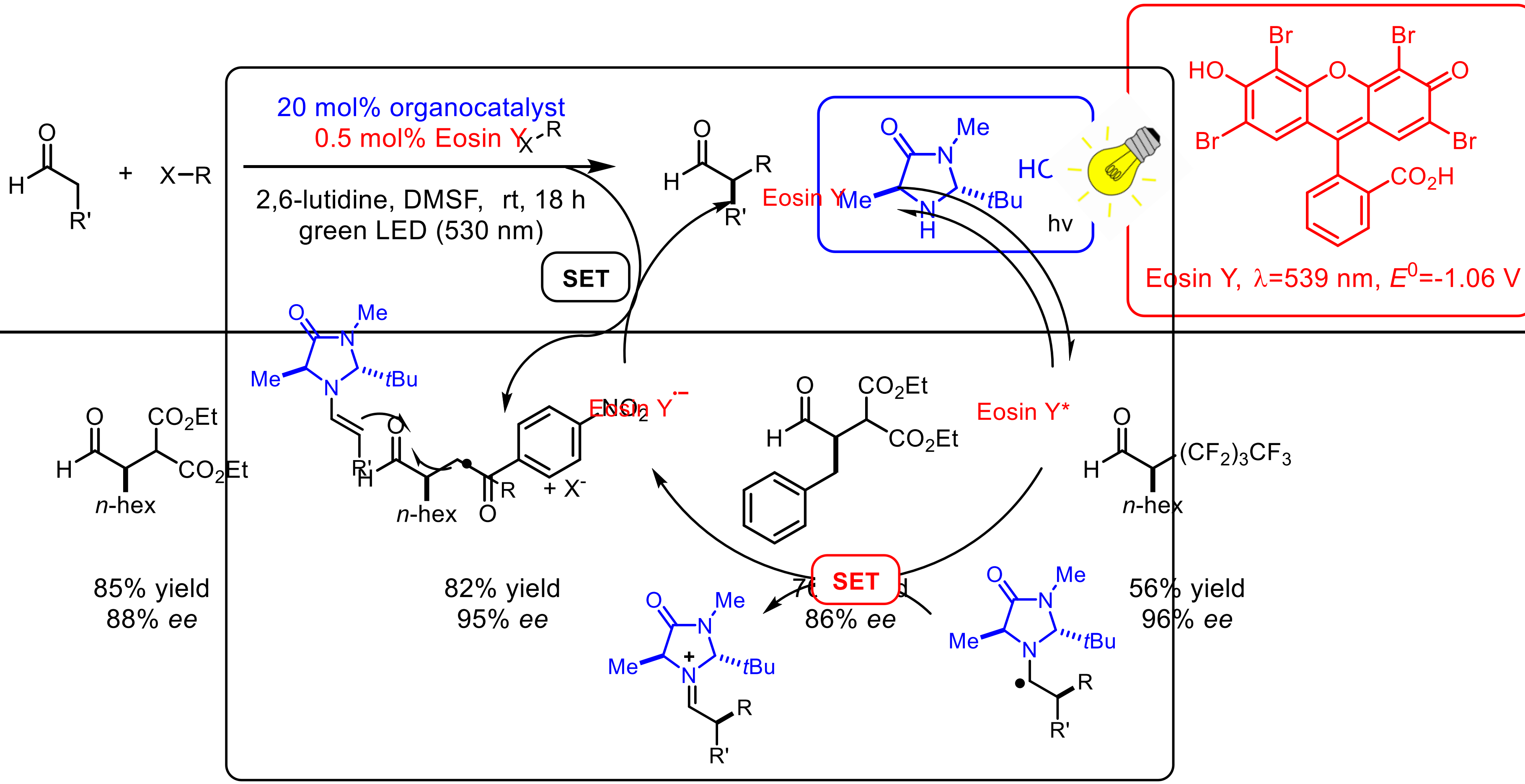


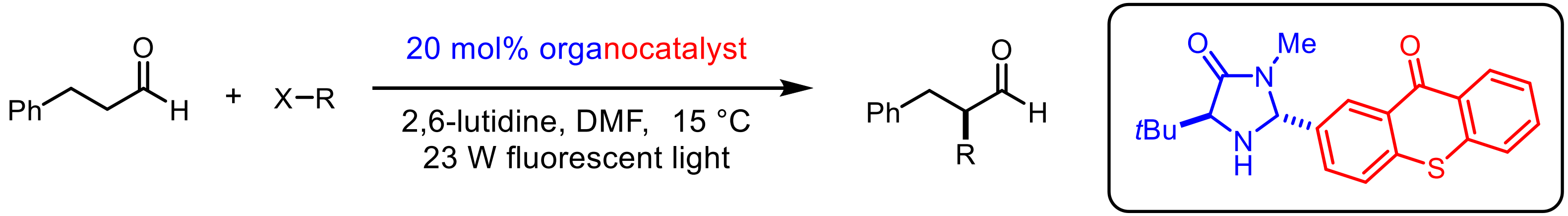

Melchiorre *et al.* *Nature* **2016**, *532*, 218-222.

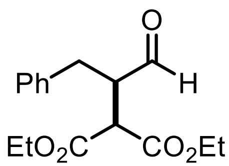
# Metal-free Approach: Organic Dyes



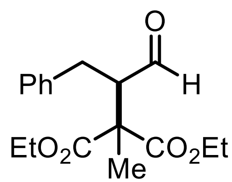

König *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 951-954; Singh *et al. RSC Adv.* **2017**, **7**, 31377-31392; Bach *et al. Chem. Soc. Rev.* **2018**, *47*, 278-290.

# One for All: a Chiral Amine Dye

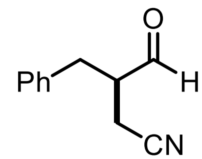


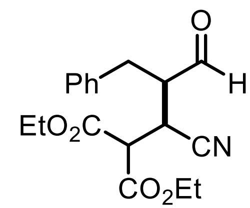
99% yield
98% *ee*



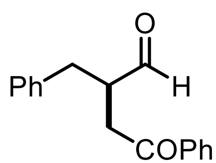
98% yield
97% *ee*



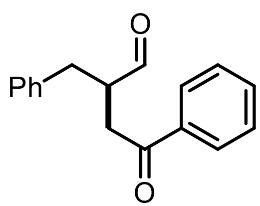
82% yield
97% *ee*



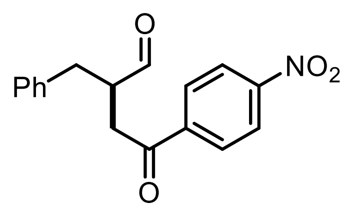
92% yield
99% *ee*



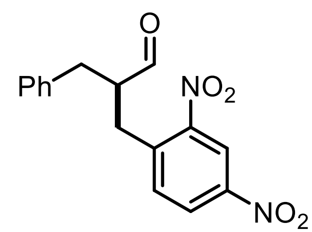
79% yield
90% *ee*



85% yield
95% *ee*



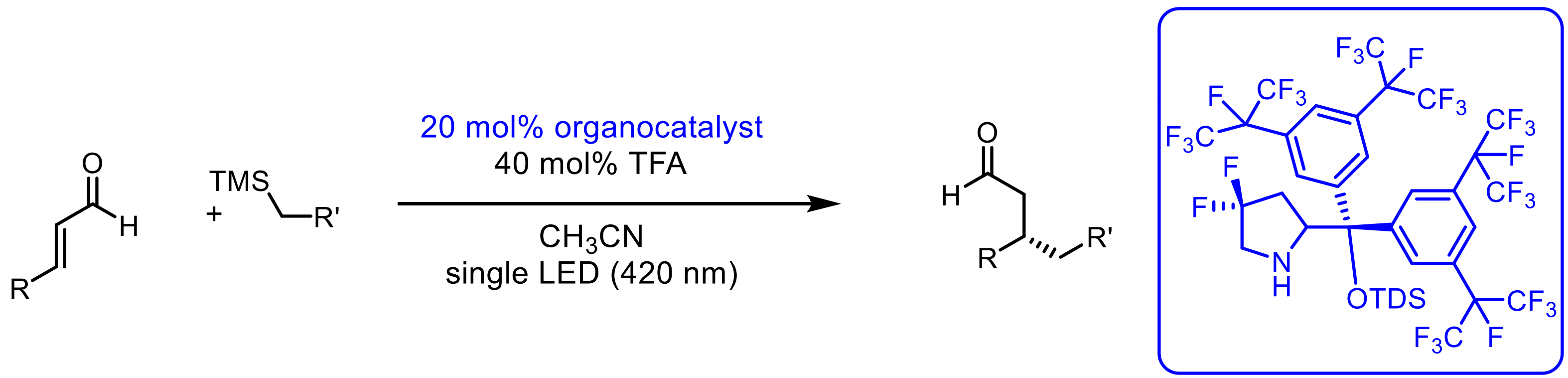
73% yield
84% *ee*



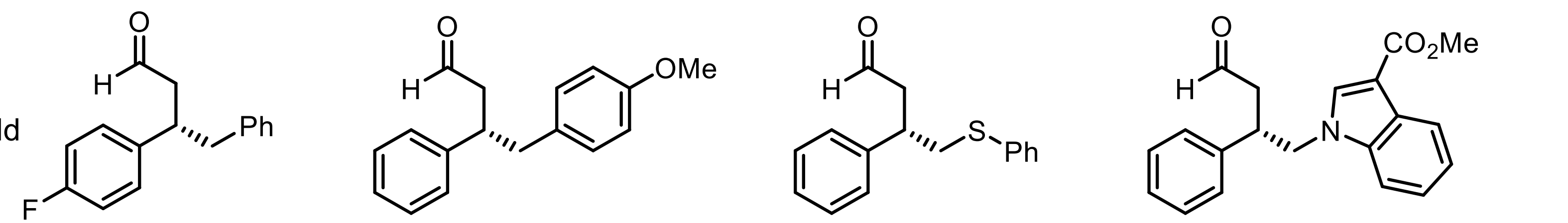
61% yield
97% *ee*

Alemán *et al. ACS Catal.* **2018**, *8*, 5928-5940.

# *β*-Functionalization of Enals



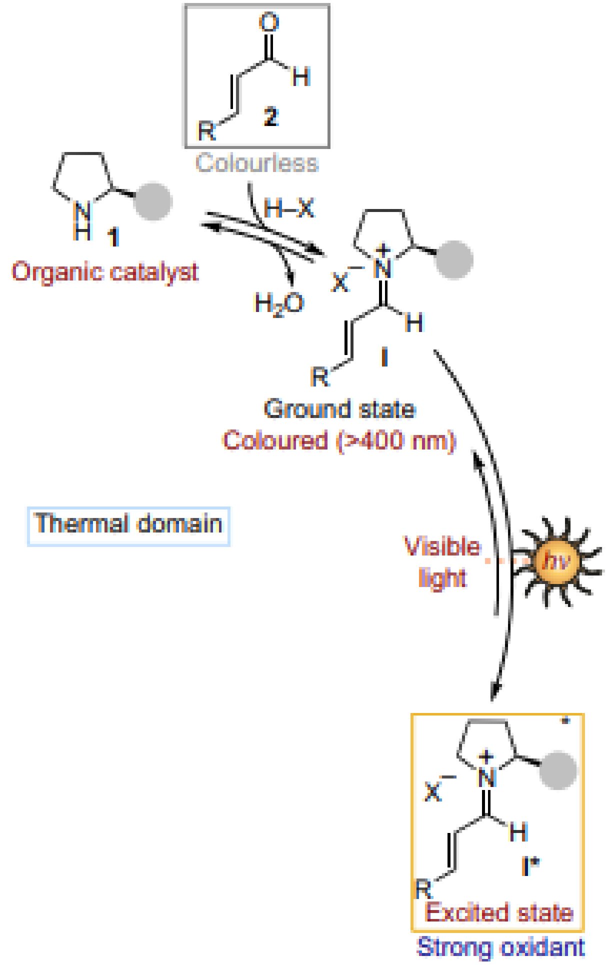

27 examples
up to 88% yield
up to 94% *ee*




76% yield, 85% *ee* | 77% yield, 92% *ee* | 73% yield, 90% *ee* | 64% yield, 92% *ee*

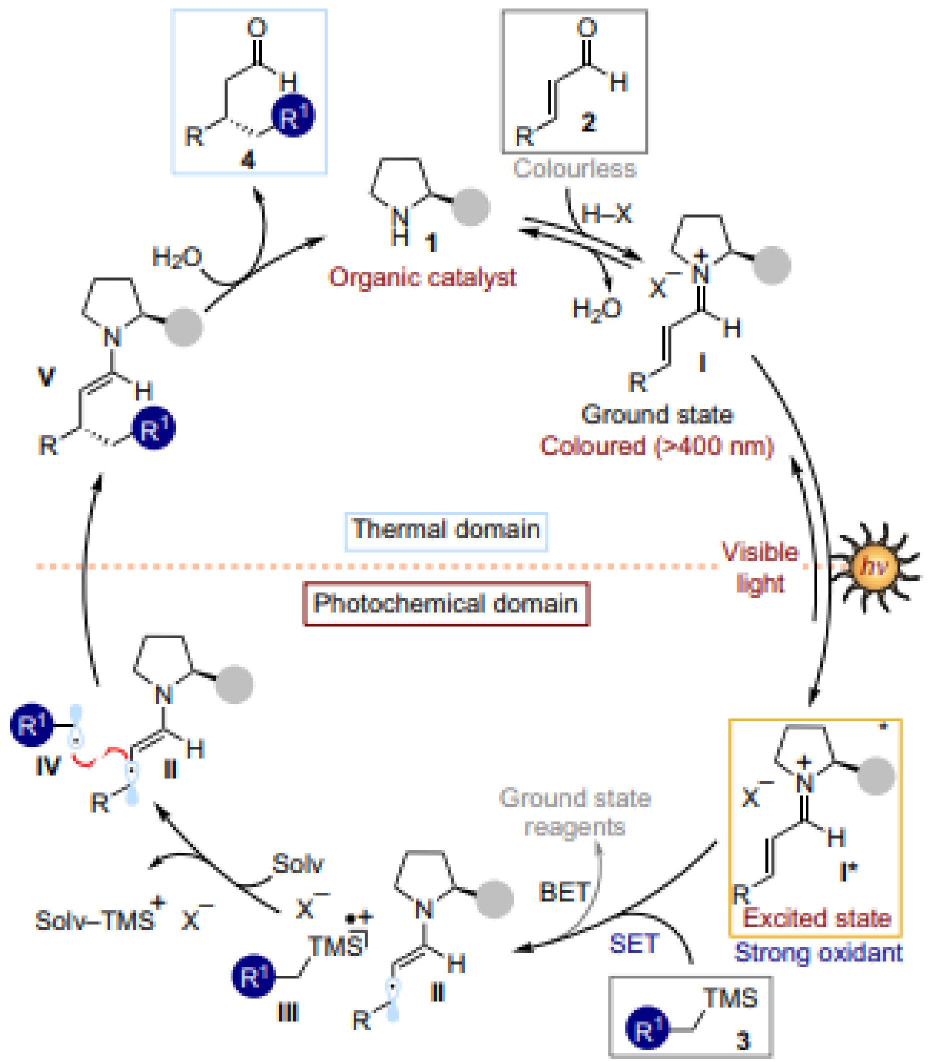
Melchiorre *et al.* Nat. Chem. **2017**, 9, 868-873.

# *β*-Functionalization of Enals



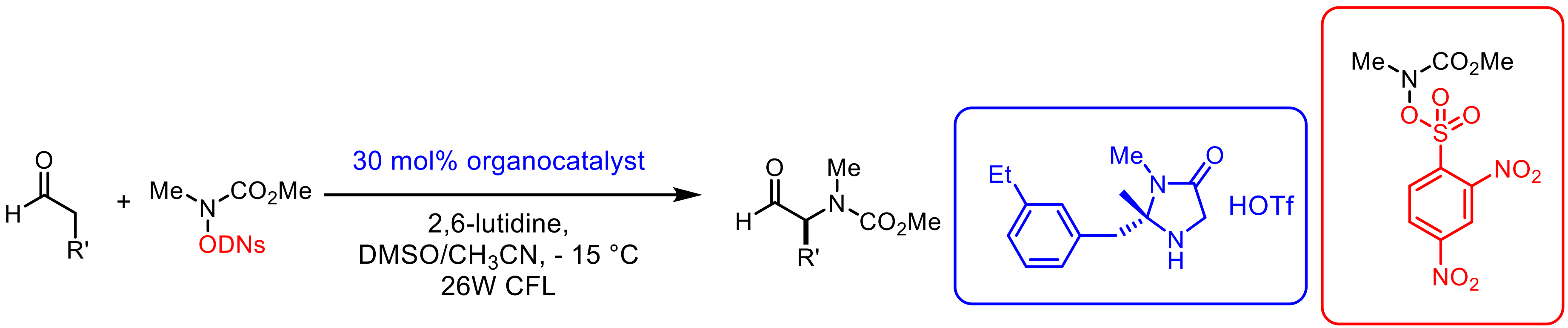

Melchiorre *et al.* Nat. Chem. **2017**, 9, 868-873.

# *β*-Functionalization of Enals

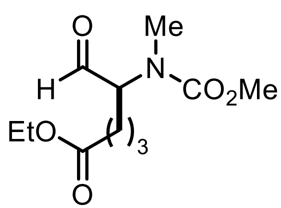



Melchiorre *et al.* Nat. Chem. **2017**, 9, 868-873.

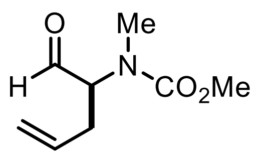
# α-Amination of Aldehydes



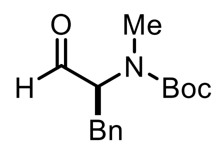

16 examples
up to 79% yield
up to 94% ee



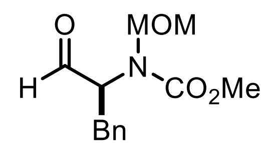

71% yield
90% *ee*




76% yield
90% *ee*



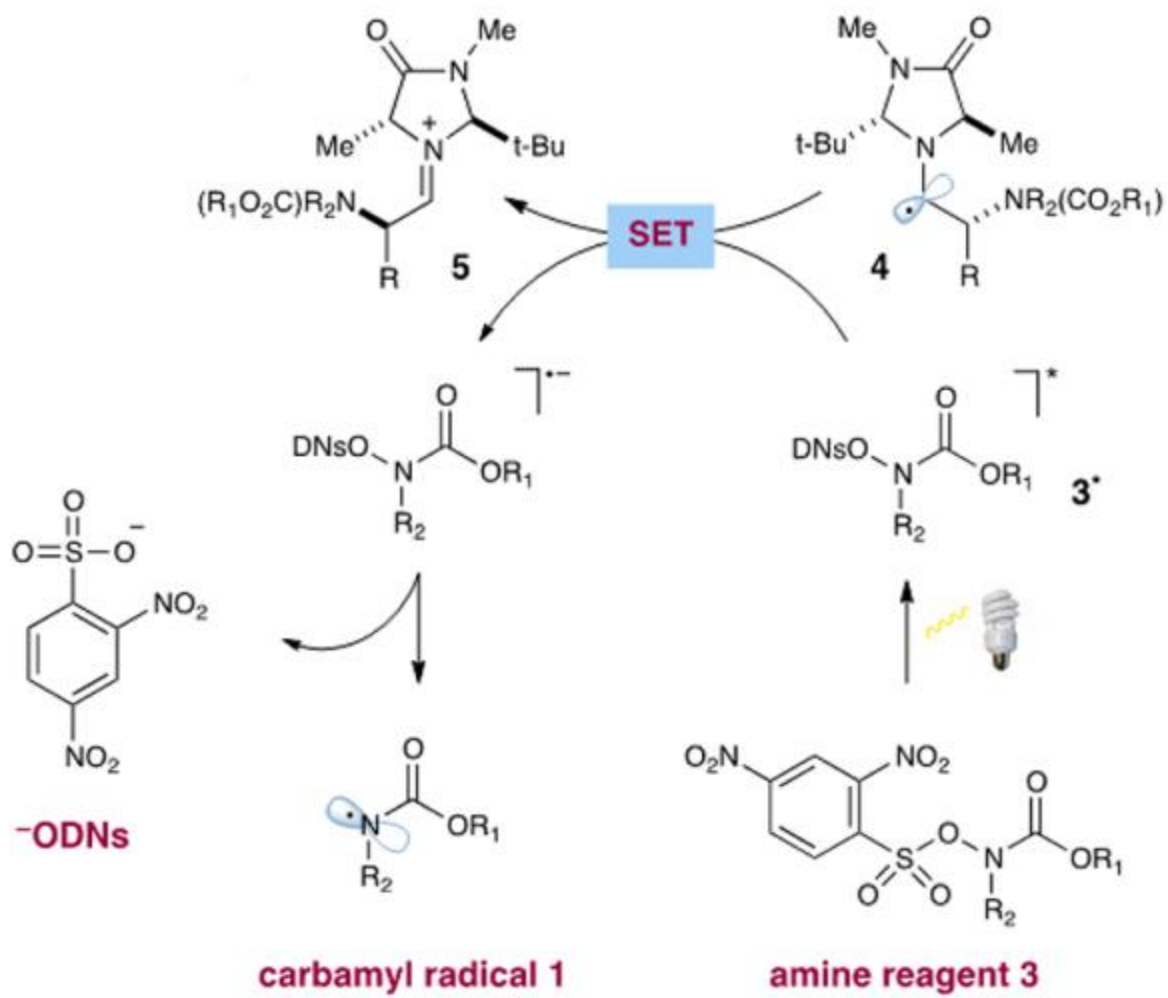

71% yield
89% *ee*




74% yield
94% *ee*

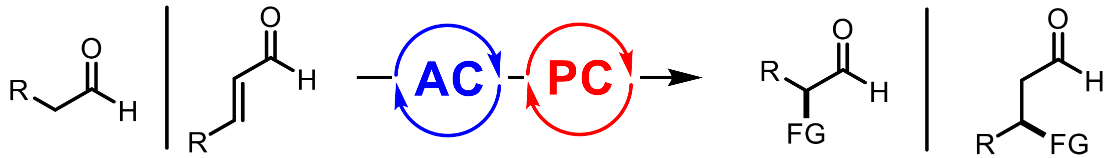
McMillan *et al. J. Am. Chem. Soc.* **2013**, *135*, 11521-11524.

# α-Amination of Aldehydes




McMillan *et al. J. Am. Chem. Soc.* **2013**, *135*, 11521-11524.

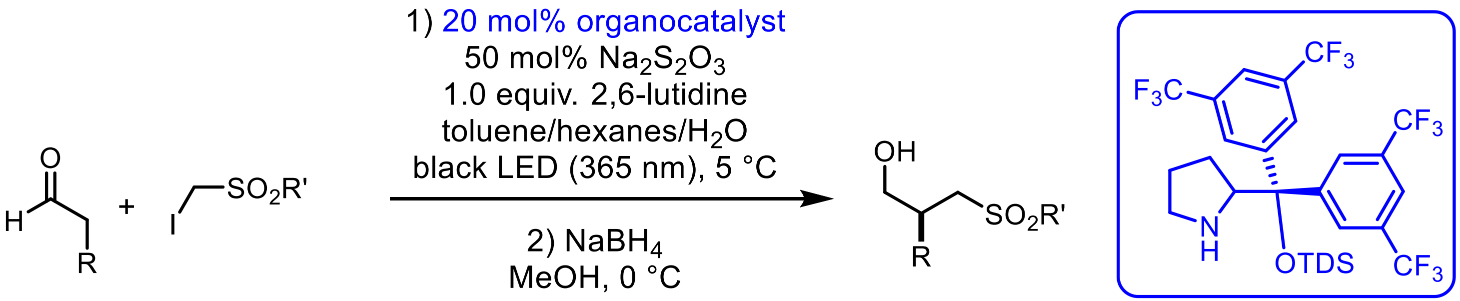
# Conclusion



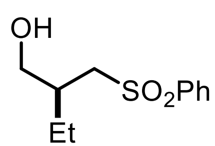

- ✓ synthetically usefull tool
- ✓ broad application
- ✓ high in yield and selectivities
- ✓ complies with green chemistry prinicpcles
- ✓ bright future to be expected

# Thank you for your attention!

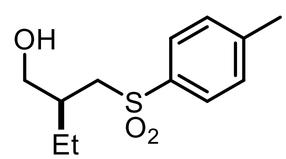
## *α*-Methylation and -benzylation of Aldehydes *via* excited Enamines: Role of $Na_2S_2O_3$?




12 examples
up to 95% yield
up to 87% *ee*

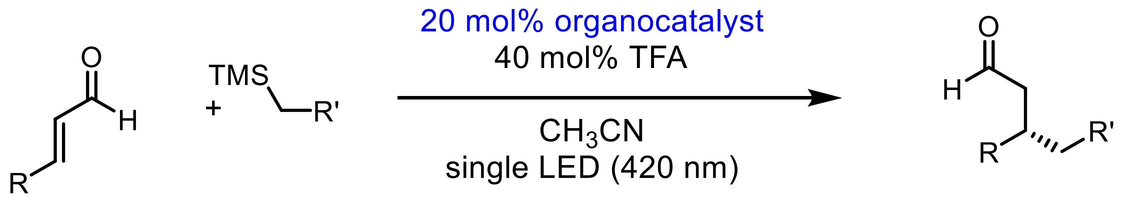


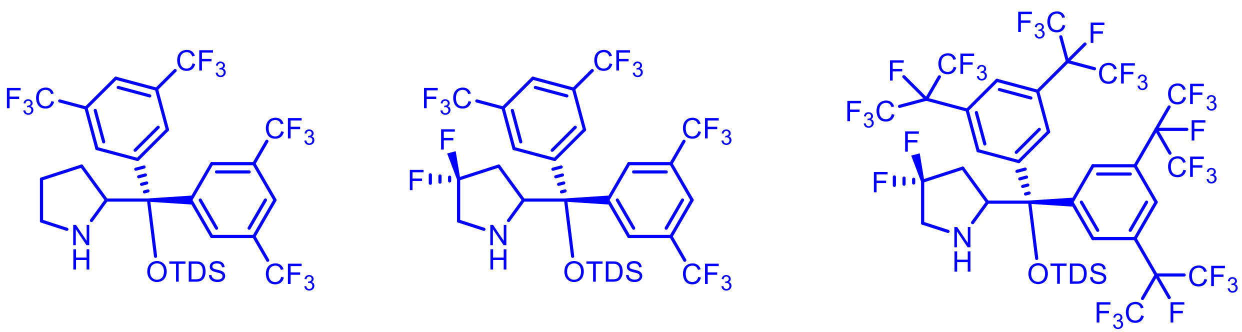

94% yield
82% *ee*



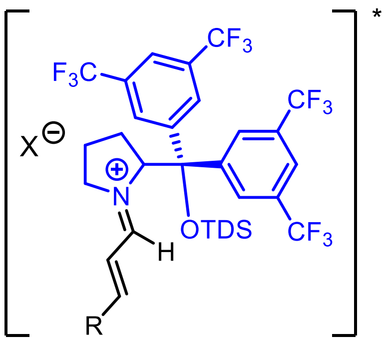

95% yield
80% *ee*

## Catalyst optimization: How to rationalize the improved reaction outcomes?



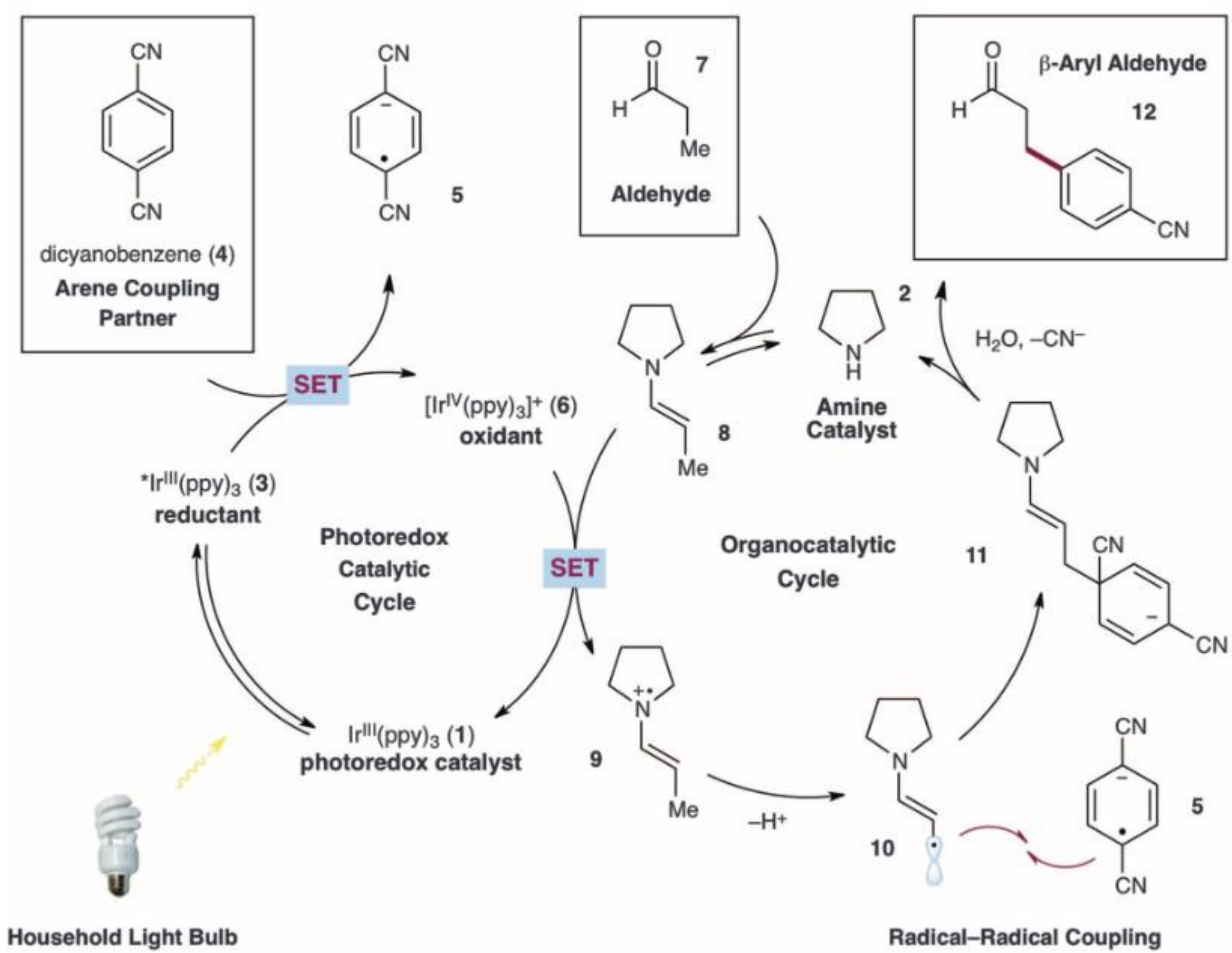

| | | |
|---|---|---|
| $E_{ox}$= +1.57 V | $E_{ox}$= +2.20 V | $E_{ox}$= +2.40 V |
| 28% yield<br>76% *ee* | 83% yield<br>85% *ee* | 87% yield<br>88% *ee* |




$E_{red}^{*}$(**Im*/Im·⁻**)= +2.30 V

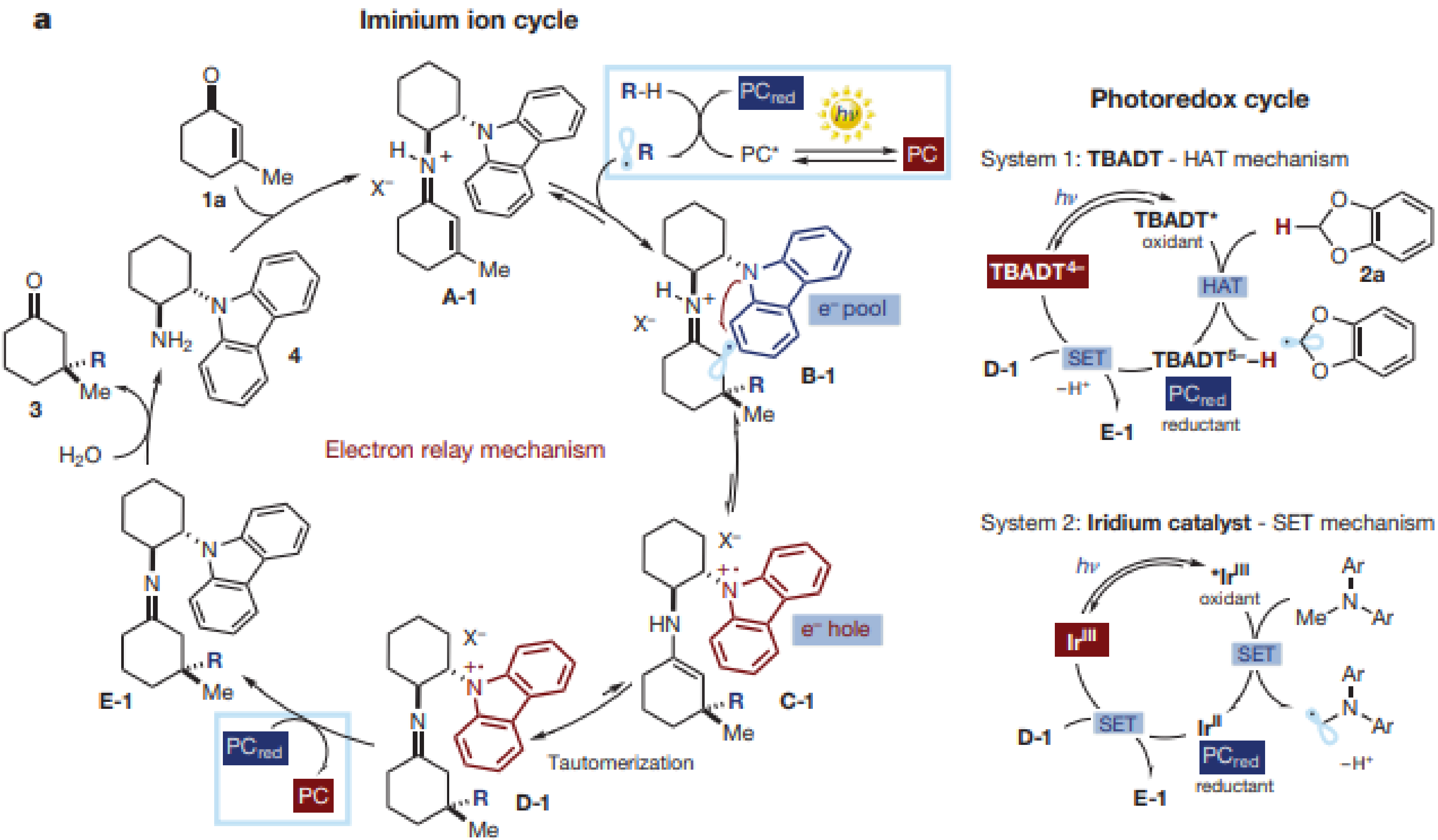
Melchiorre *et al.* Nat. Chem. **2017**, 9, 868-873.

# β-Functionalization



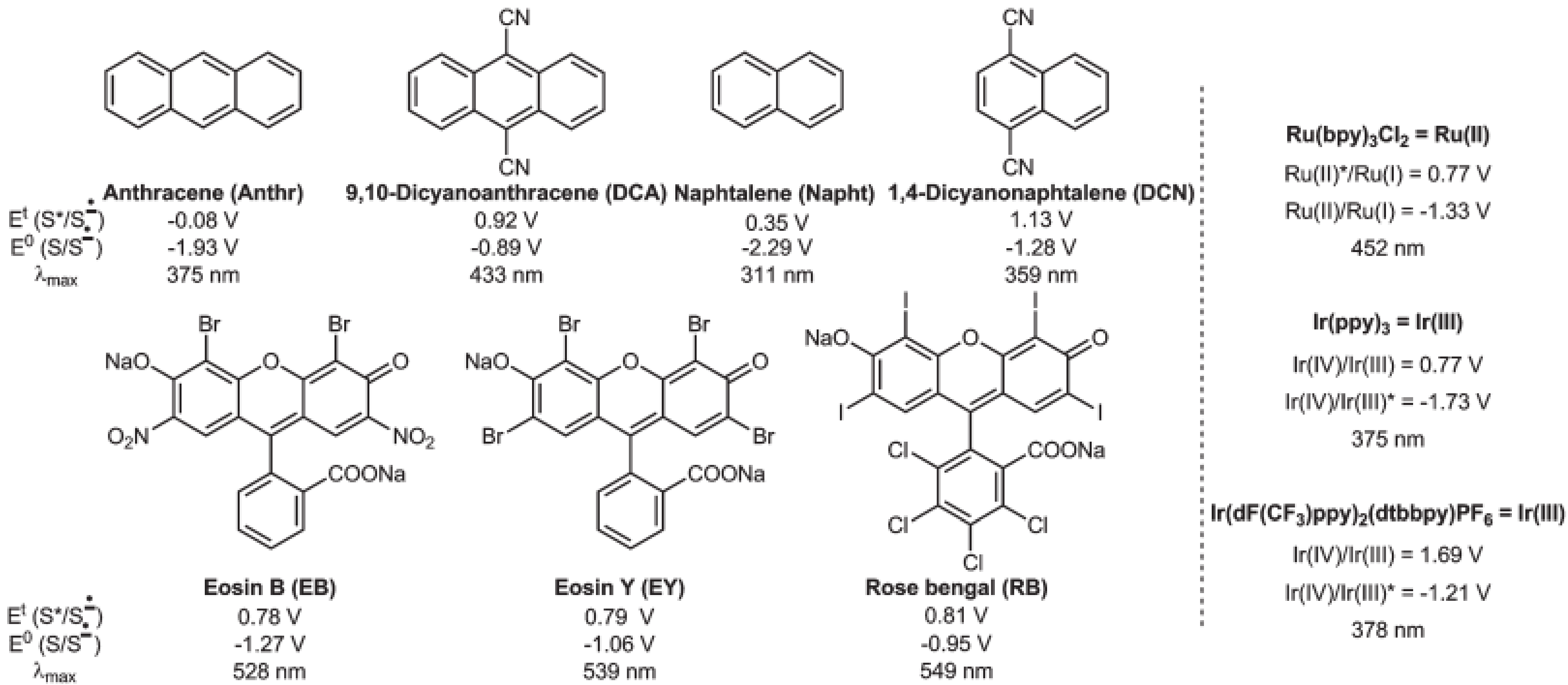

McMillan *et al. Science* **2013**, *339*, 1593-1596.

# β-Functionalization



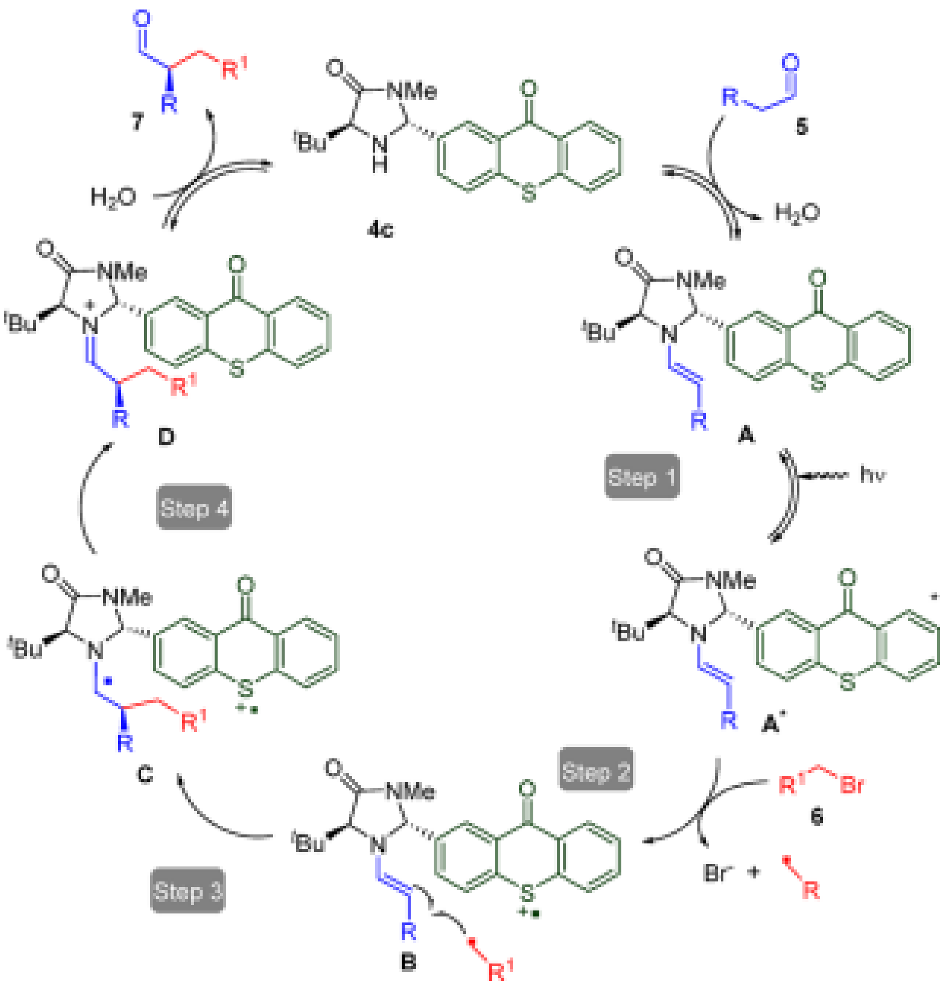

Melchiorre *et al. Nature* **2016**, *532*, 218-222.

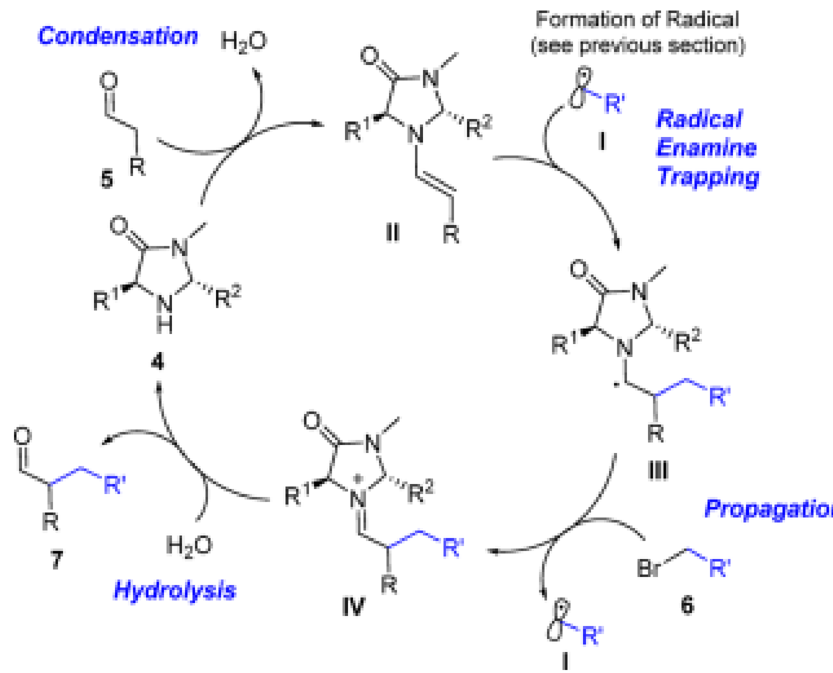
# Dyes/Metals: Redox Potentials




Ferroud *et al*. *Green Chem.* **2012**, *14*, 1293-1297.

# One for All: a chiral Amine Dye




Alemán *et al. ACS Catal.* **2018**, *8*, 5928-5940.

# Stereogenic-at-Metal complexes: Structure, synthesis and applications in asymmetric catalysis

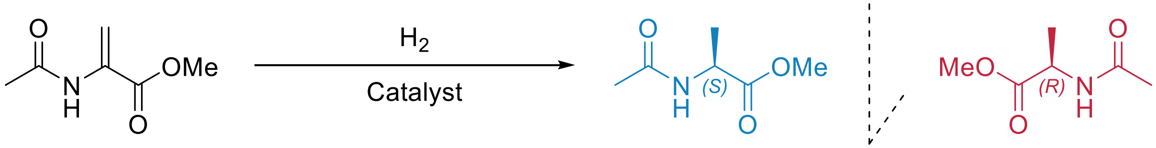
**Pierre Palamini**

**Frontiers in Chemical Synthesis: Stereochemistry**

Ecole Polytechnique Fédérale de Lausanne
Laboratory of Catalysis and Organic Synthesis (LCSO)

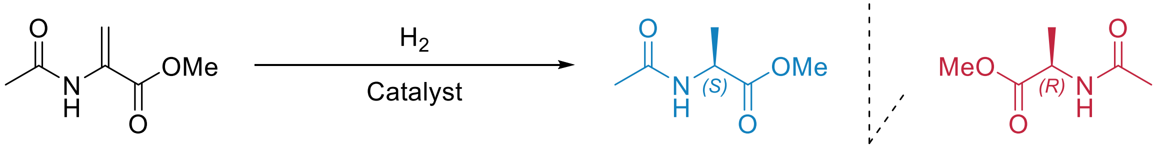
16.05.2022

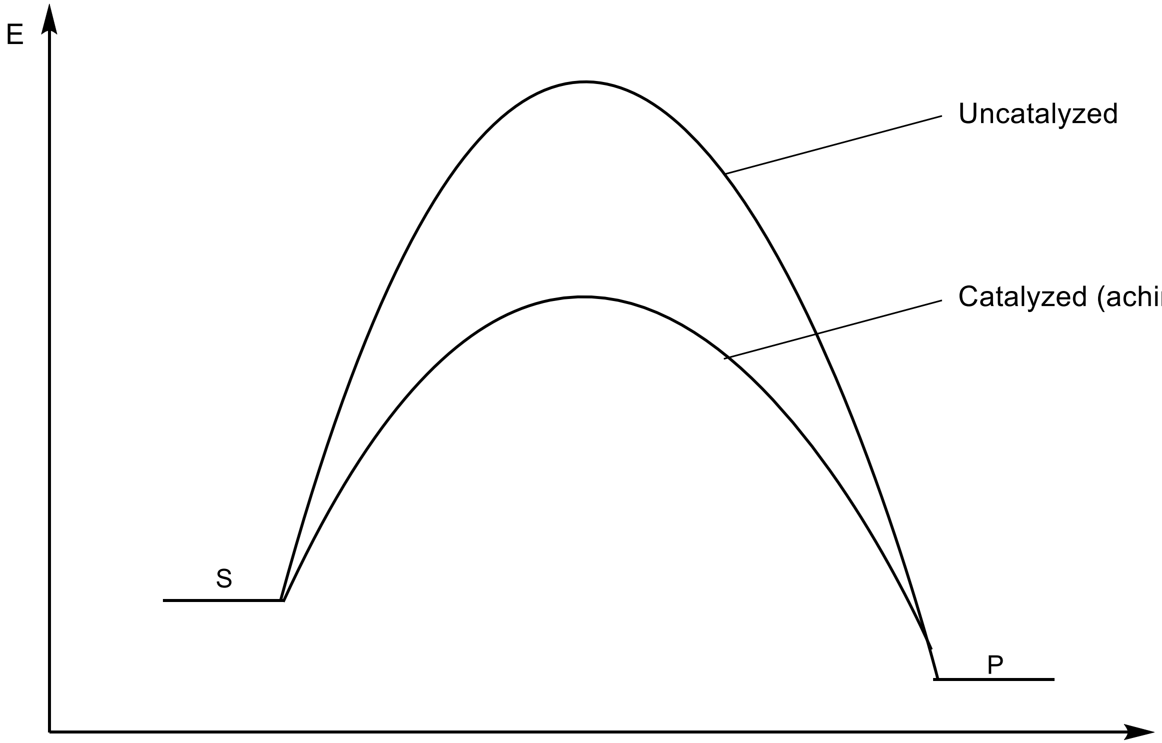
# How to achieve high enantioselectivity?




Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science.* **2013**, *342* (6162), 1076–1080.
https://www.uni-marburg.de/en/fb15/researchgroups/meggers-research-group/research

# How to achieve high enantioselectivity?





Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science.* **2013**, *342* (6162), 1076–1080.
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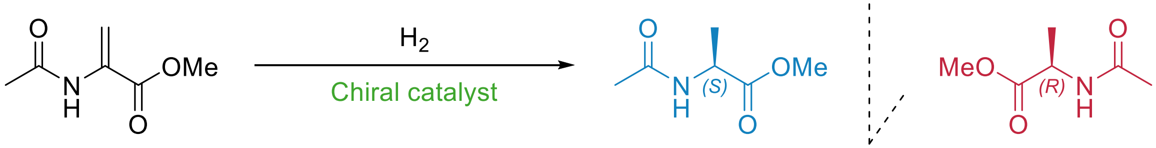
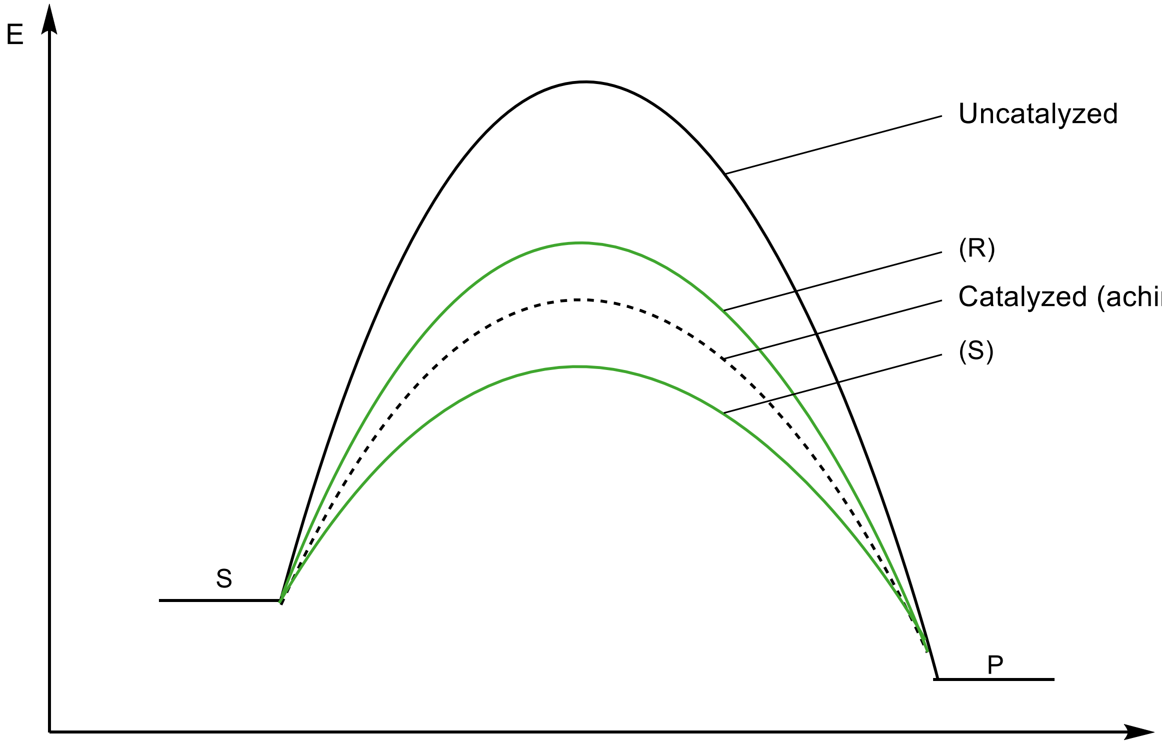
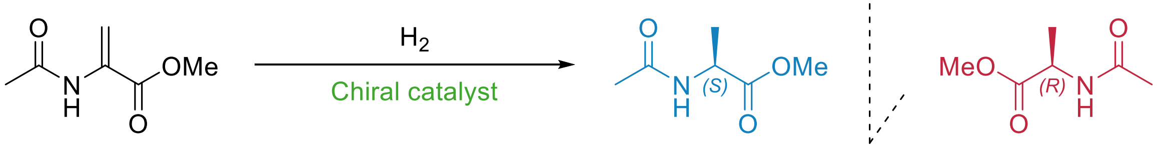
# How to achieve high enantioselectivity?

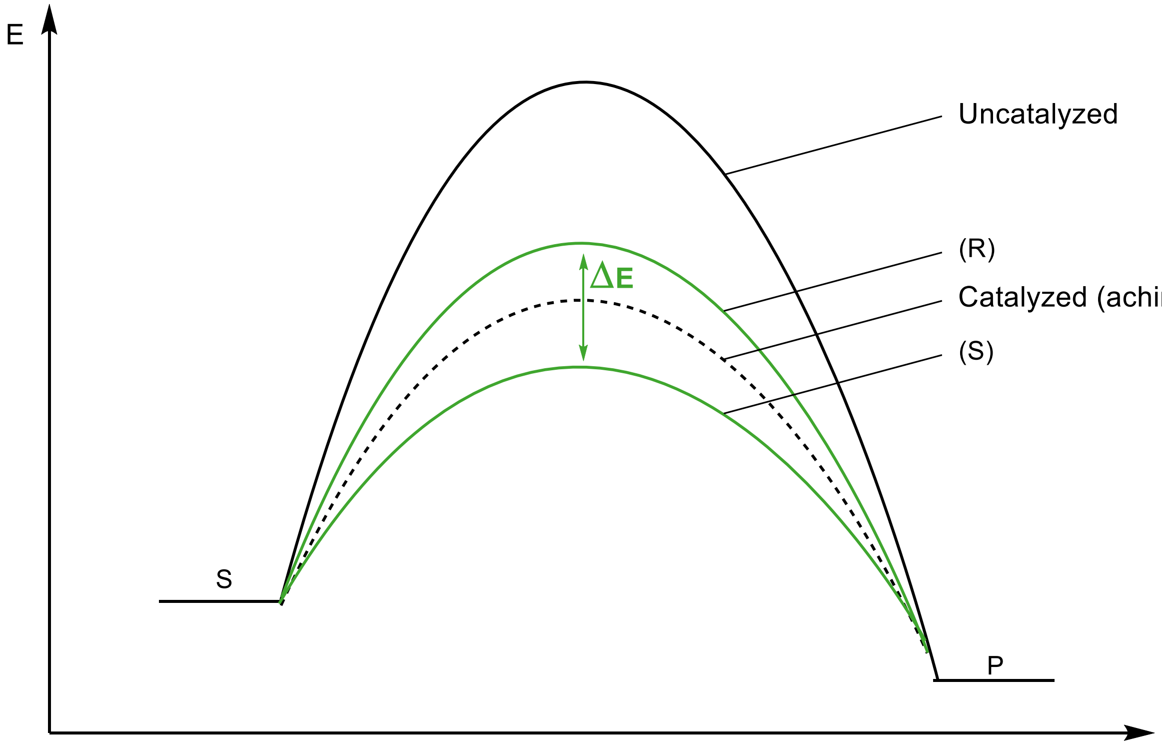



Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science.* **2013**, *342* (6162), 1076–1080.
https://www.uni-marburg.de/en/fb15/researchgroups/meggers-research-group/research

# How to achieve high enantioselectivity?

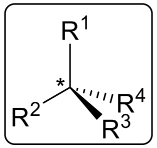



With good design, ΔE is sufficient enough to get only one enantiomer !


Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science.* **2013**, *342* (6162), 1076–1080.
https://www.uni-marburg.de/en/fb15/researchgroups/meggers-research-group/research

# How to obtain chirality?

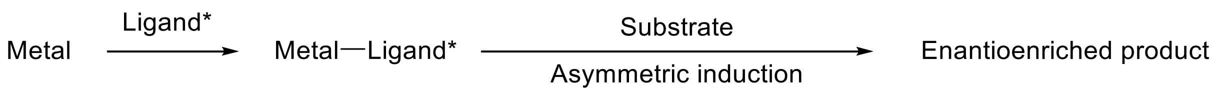


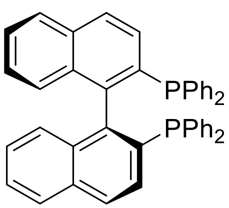

Agudo, R.; Roiban, G.-D.; Reetz, M. T. *J. Am. Chem. Soc.* **2013**, *135* (5), 1665–1668.
List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122* (10), 2395–2396.
Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; Rezende, D. C.; Alves Nogueira Diaz, M. *Chirality* **2019**, *31* (10), 776–812.

# How to obtain chirality?

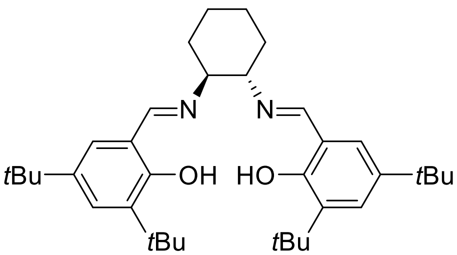
## Metal-catalysis

- ➢ Chirality established *via* chiral ligands

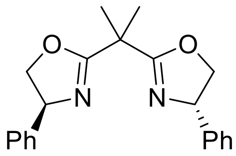



(S)-BINAP




Salen

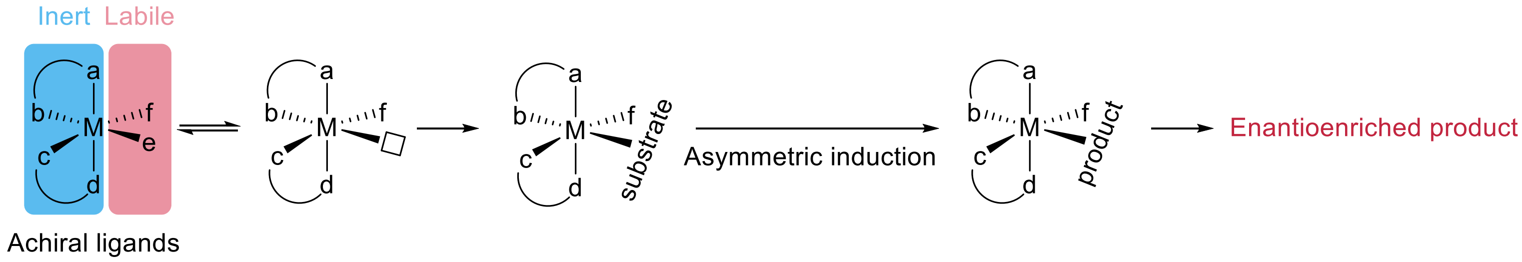


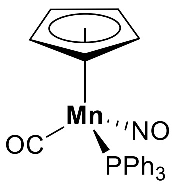

Bisoxazoline

Stradiotto, M.; Lundgren, R. J. *Ligand Design in Metal Chemistry*; Stradiotto, M., Lundgren, R. J., Eds.; John Wiley & Sons, Ltd: Chichester, UK, 2016.

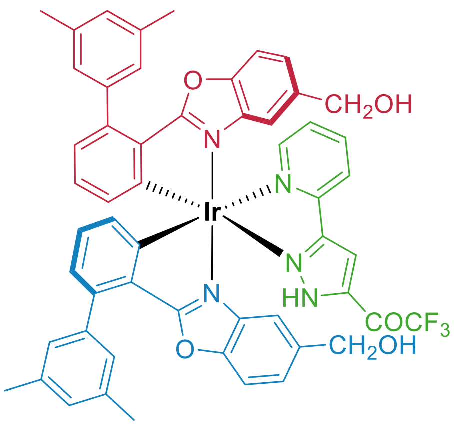
## Metal-catalysis

- Chirality located on the metal center

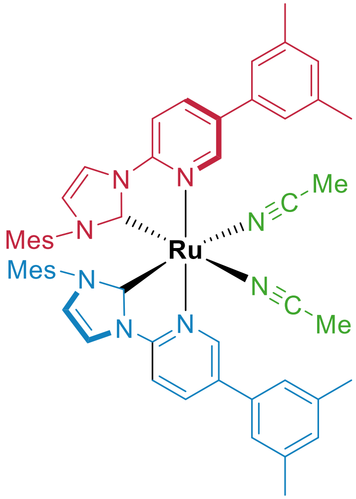



**Mn1**




**Λ-Ir1**

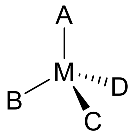



**Λ-Ru1**

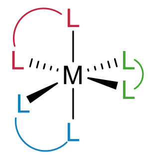
H. Brunner, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 382–383.
Chen, L. A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135* (29), 10598–10601.
Ye, C.-X.; Shen, X.; Chen, S.; Meggers, E. *Nat. Chem.* **2022**, *14* (5), 566–573.

# Table of contents

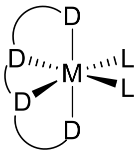
# Structure




**1**

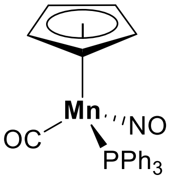



**2**

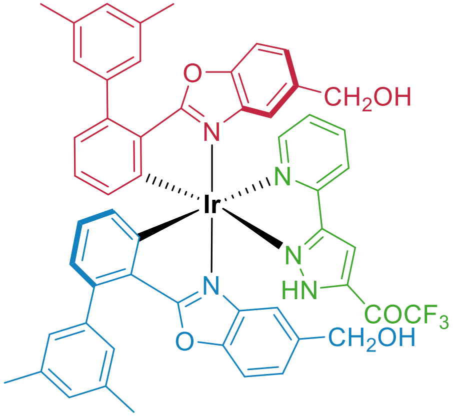



**3**

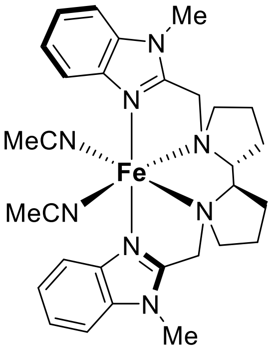
- Tetrahedral
- Octahedral
- Octahedral




**Mn1**
Brunner 1969



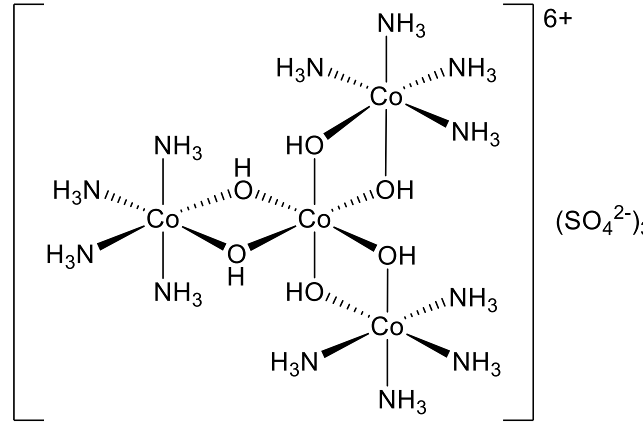

**Λ –Ir1**
Meggers 2013




**Δ-Fe1**
Meggers 2022

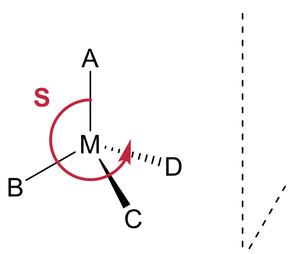
H. Brunner, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 382–383.
Chen, L. A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135* (29), 10598–10601.
Steinlandt, P. S.; Xie, X.; Ivlev, S.; Meggers, E. *ACS Catal.* **2021**, *11* (12), 7467–7476.

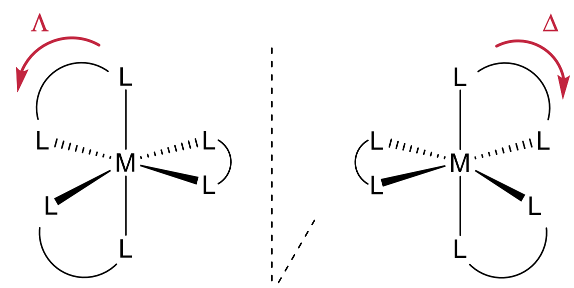
Alfred Werner and Arthur Hantzsch

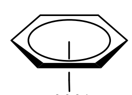
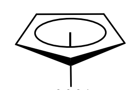



Hexol

- Nomenclature and vocabulary




Updated CIP rules  I > Br >  >  > Cl > P > O > N > $\eta^1$-C

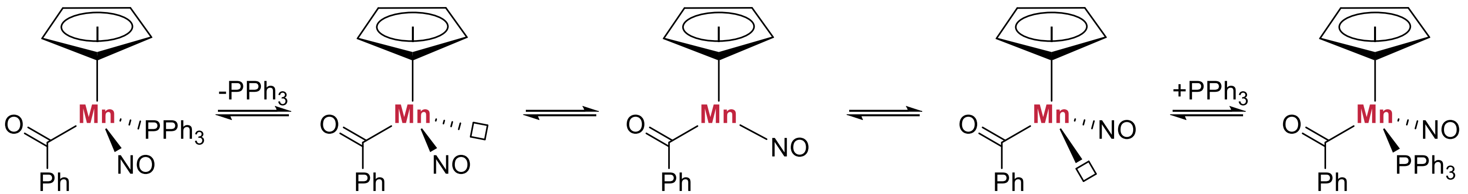
**Chiral-at-metal**: only the metal center is chiral

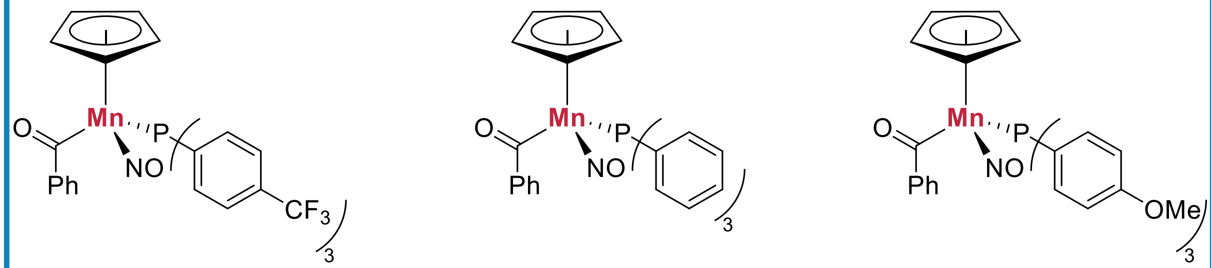
**Stereogenic-at-metal**: The metal center is chiral but other chiral center are present on the molecule

MOSS, G. P. Basic Terminology of Stereochemistry. *Pure Appl. Chem* **1996**, *68* (12), 2193–2222.
Bauer, E. B. *Chem. Soc. Rev.* **2012**, *41* (8), 3153.
https://www.nobelprize.org/prizes/chemistry/1913/werner/lecture/

# Challenges: racemization and epimerization

- Racemization



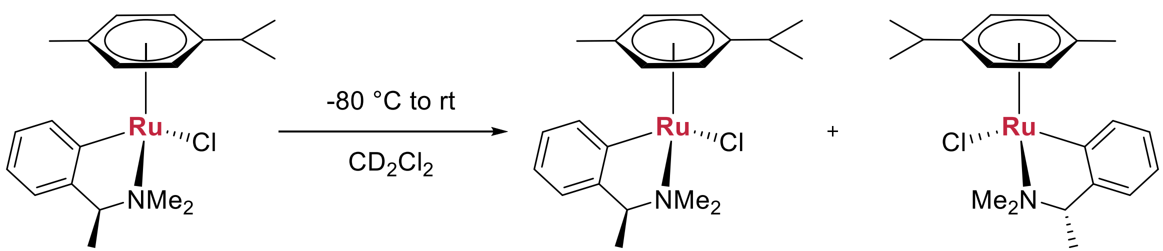




**(R)-Mn1**
$\tau_{1/2}$ = 5.9 min

**(R)-Mn2**
$\tau_{1/2}$ = 50 min

**(R)-Mn3**
$\tau_{1/2}$ = 337 min

- Epimerization




**($R_{Ru}$, $S_C$)-Ru1**
>99.9:0.1 er

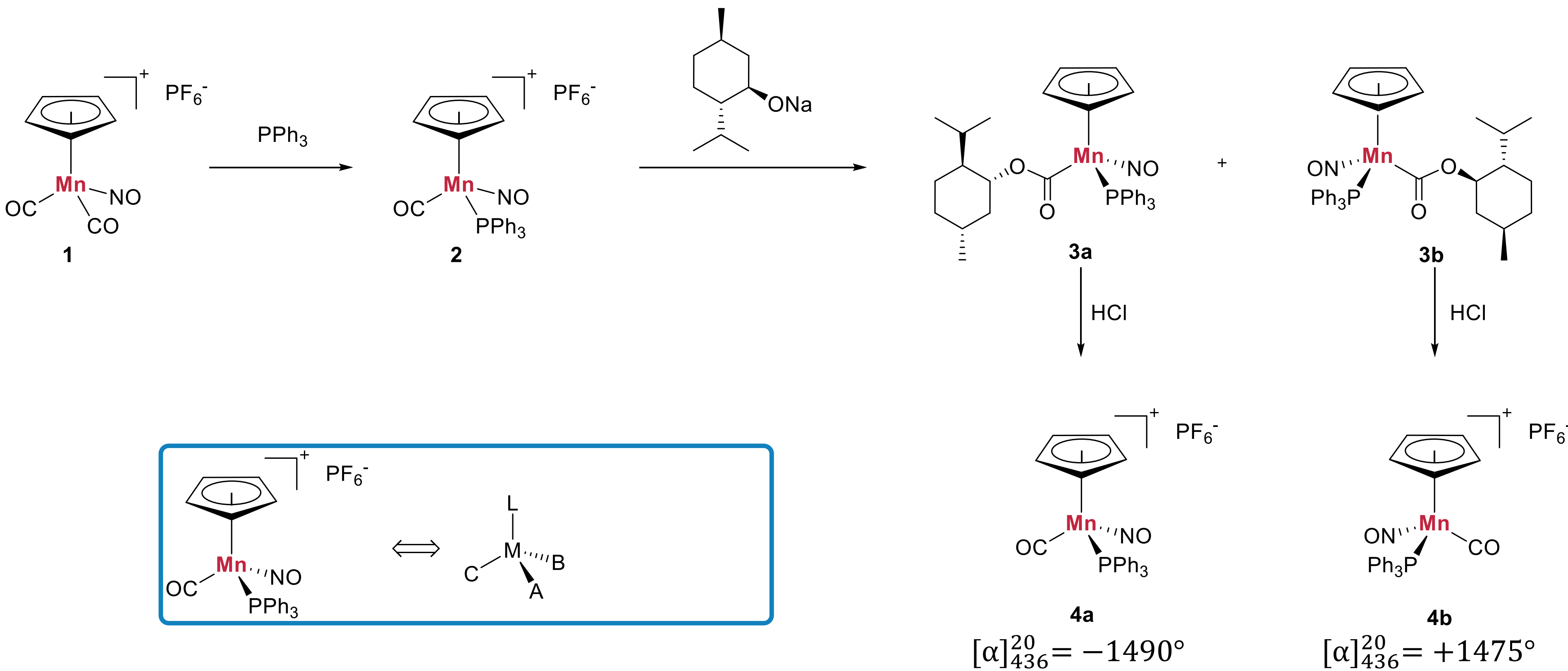
**($R_{Ru}$, $S_C$)-Ru1**
**87%**

**($S_{Ru}$, $S_C$)-Ru1**
**13%**

No change with time

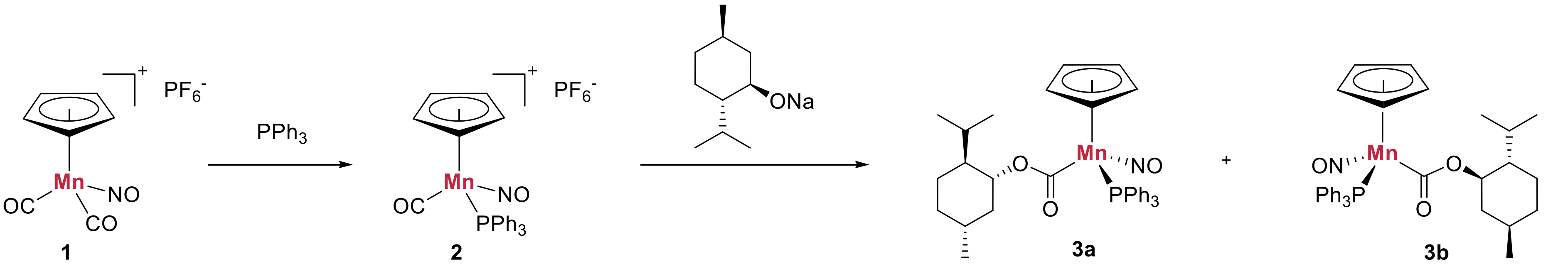
Brunner, H.; Langer, M. *J. Organomet. Chem.* **1975**, *87* (2), 223–240.
Brunner, H.; Zwack, T. *Organometallics.* **2000**, *19* (13), 2423–2426.

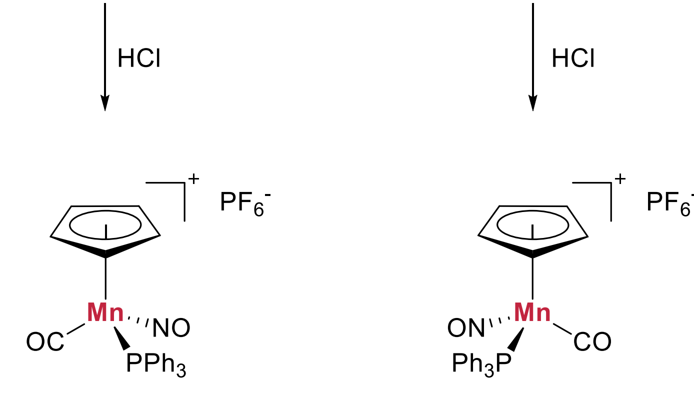
- First stereogenic-at-metal sandwich complex – Brunner **1969**



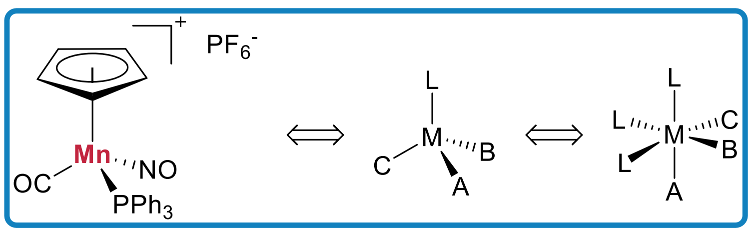

H. Brunner, *Z. Anorg. Allg. Chem.*, **1969**, *368*, 120–126.

- First stereogenic-at-metal sandwich complex – Brunner **1969**




$[\alpha]_{436}^{20} = -1490°$ $[\alpha]_{436}^{20} = +1475°$

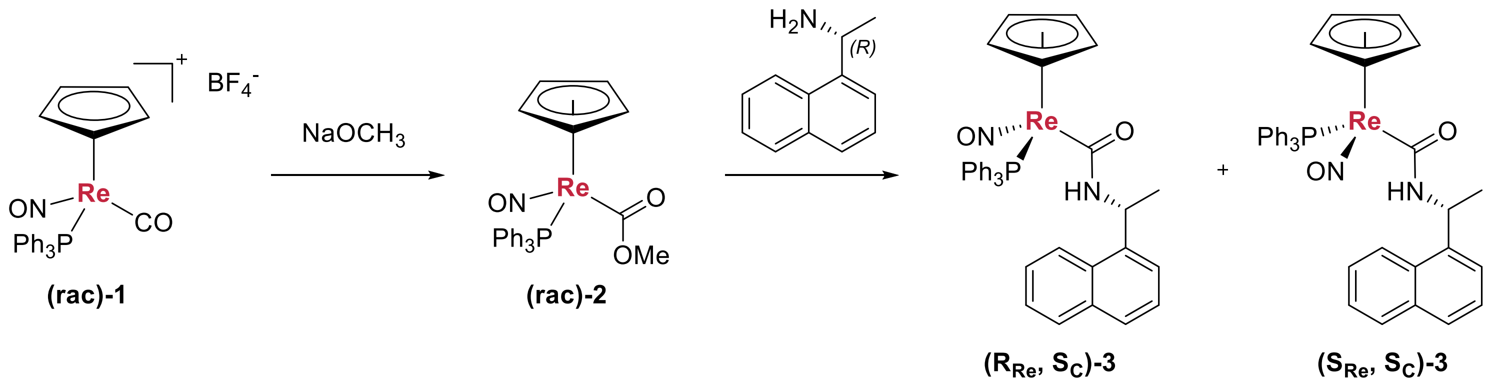


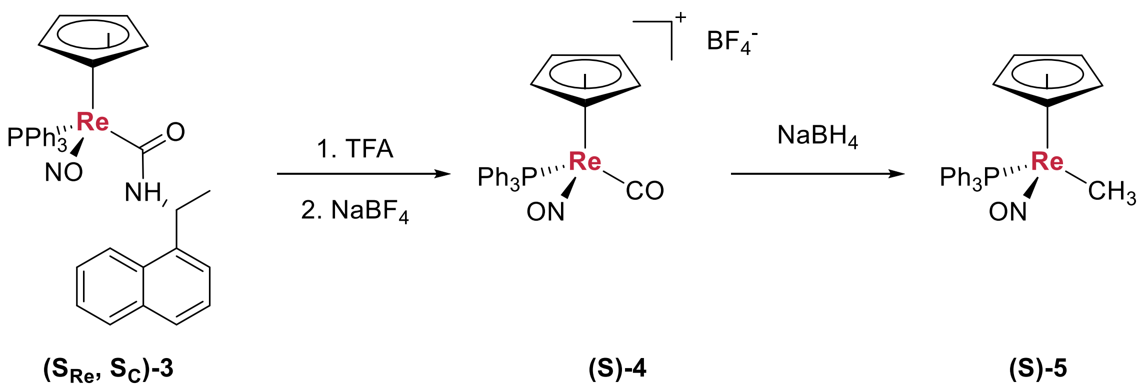

**A half sandwich complex can be viewed as an octahedral architecture with a fac-arrangement**

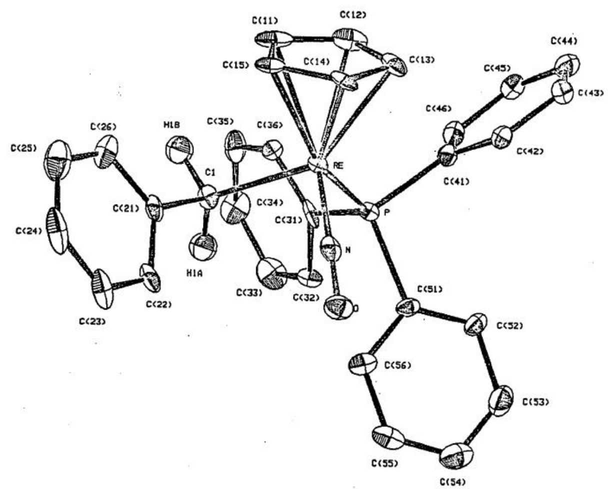
H. Brunner, *Z. Anorg. Allg. Chem.*, **1969**, *368*, 120–126.

# Pionnering works

- Gladysz - 1982

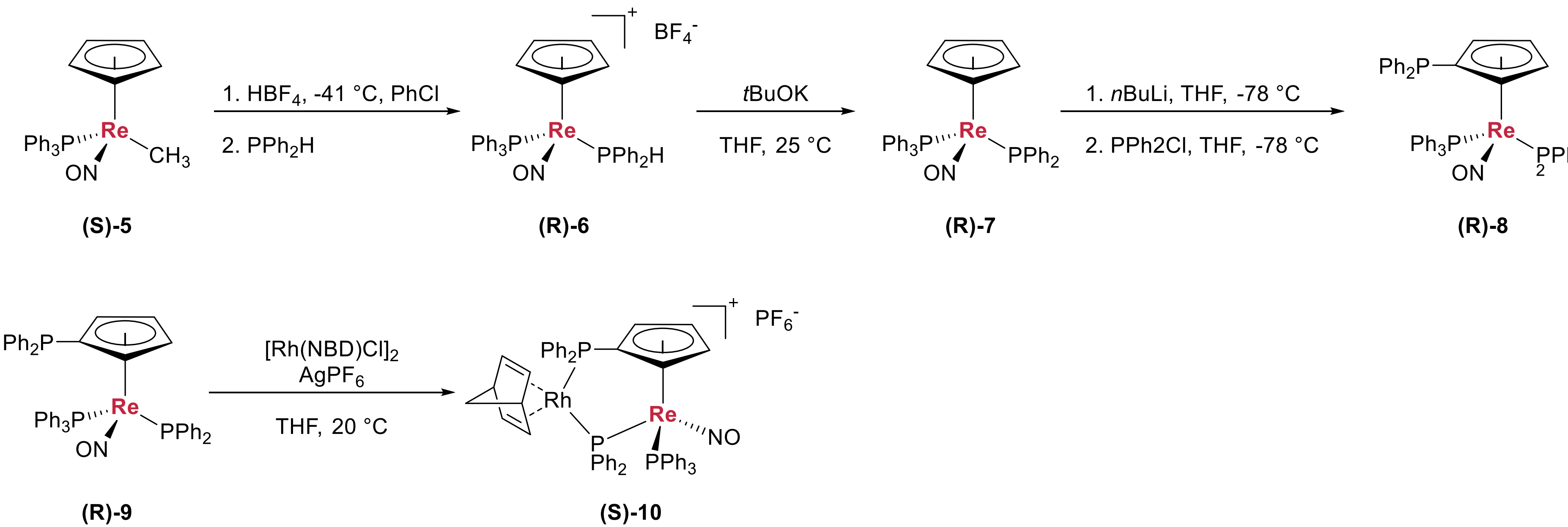


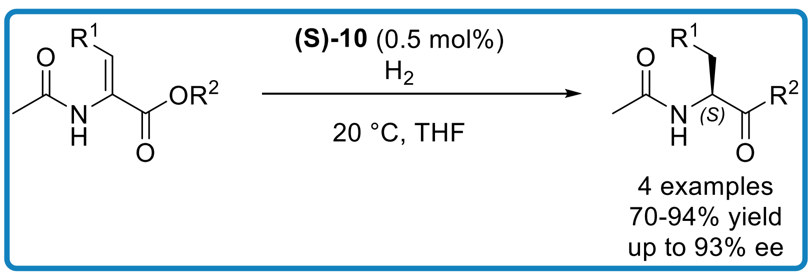



Merrifield, J. H.; Strouse, C. E.; Gladysz, J. A. *Organometallics.* **1982**, *1* (9), 1204–1211
Agbossou, F.; O'Connor, E. J.; Garner, C. M.; Quirós Méndez, N.; Fernández, J. M.; Patton, A. T.; Ramsden, J. A.; Gladysz, J. A. *Inorg. Synth.* **1992**, *29*, 211-225.

- Gladysz - 2001

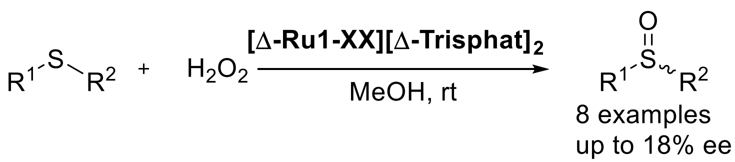


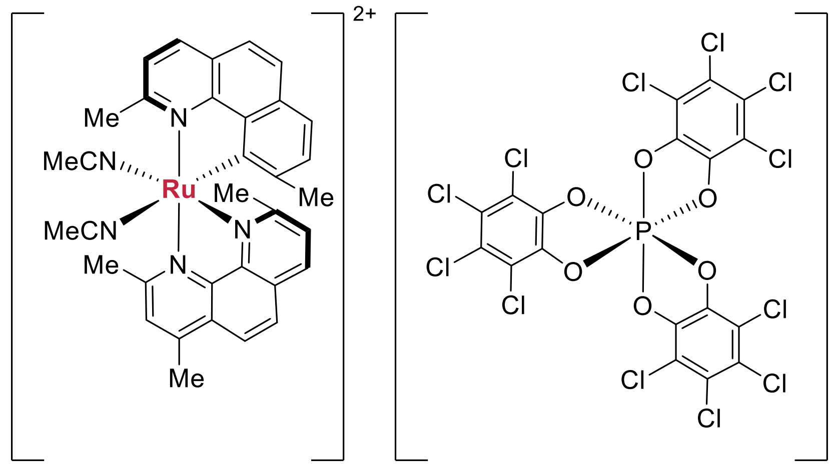




Kromm, K.; Zwick, B. D.; Meyer, O.; Hampel, F.; Gladysz, J. A. *Chem. Eur. J.* **2001**, *7* (9), 2015–2027.

# Pionnering works

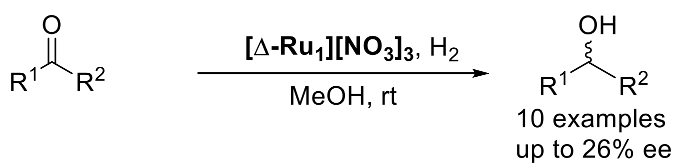
- Fontecave 2003

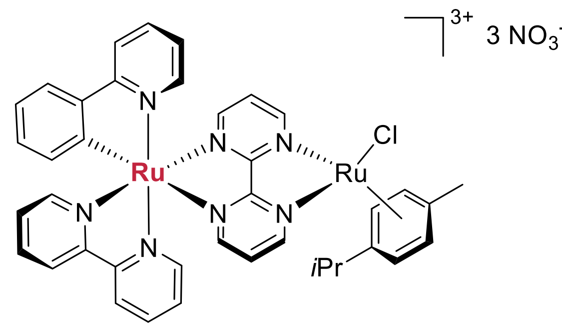



[Δ-Ru1][Δ-Trisphat]$_2$

- Fontecave 2007




[Δ-Ru$_1$][NO$_3$]$_3$

Chavarot, M.; Ménage, S.; Hamelin, O.; Charnay, F.; Pécaut, J.; Fontecave, M. *Inorg. Chem.* **2003**, *42* (16), 4810–4816
Hamelin, O.; Rimboud, M.; Pécaut, J.; Fontecave, M. *Inorg. Chem.* **2007**, *46* (13), 5354–5360. .

# Table of contents

1. Structure, properties and challenges
2. First syntheses and applications in asymmetric catalysis
3. **Key works and recent applications**
4. Conclusion

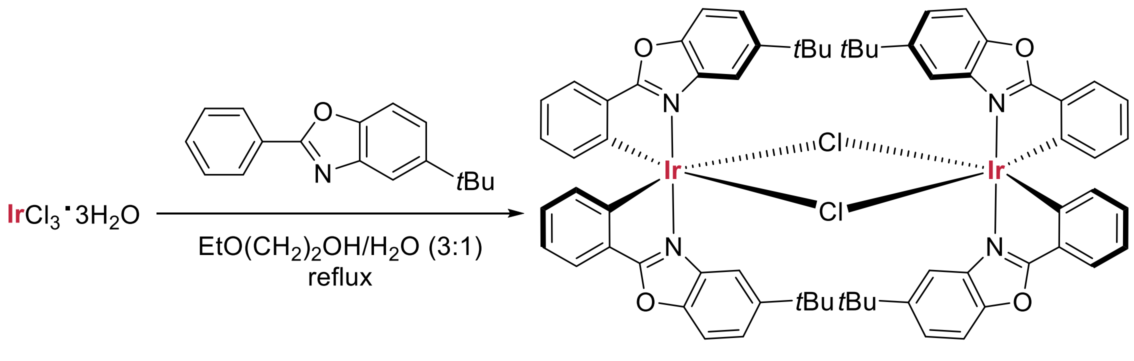
- Eric Meggers

  - 1995, Diploma in Chemistry (with honors), University of Bonn, Germany
  - 1999, Ph.D. in Organic Chemistry, University of Basel, Switzerland
  - 2002-2007, Assistant Professor, University of Pennsylvania, USA
  - Since 2007, Full Professor, Department of Chemistry, University of Marburg, Germany

Current main research topics:

- Chiral-at-metal catalyst design
- Sustainable catalysis with iron
- Stereocontrolled organic photochemistry
- Stereocontrolled electrochemistry
- Enantioselective nitrene chemistry

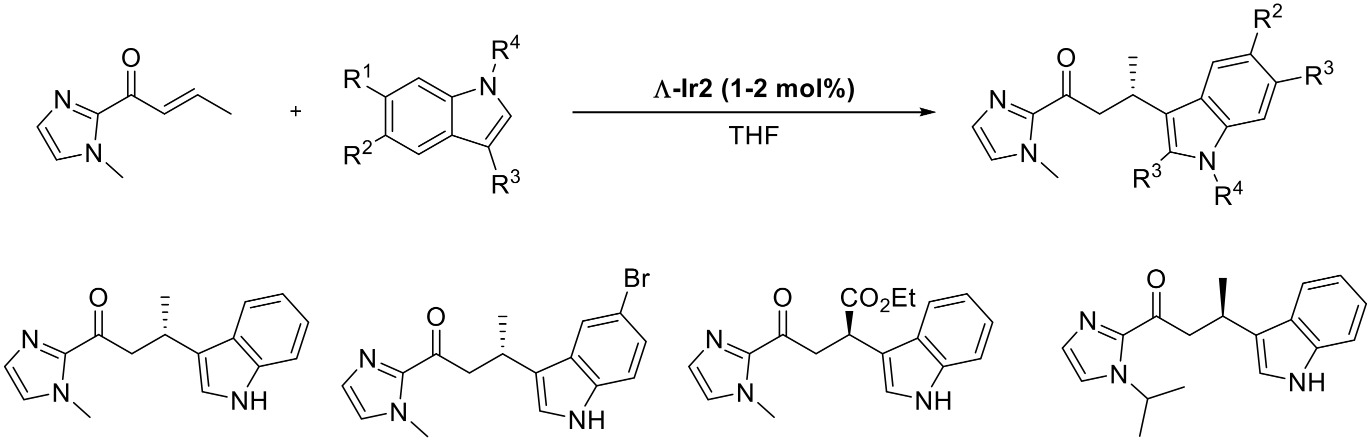
- Meggers - 2014



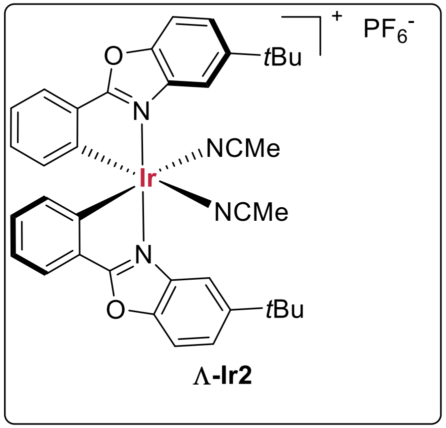

**rac-1**

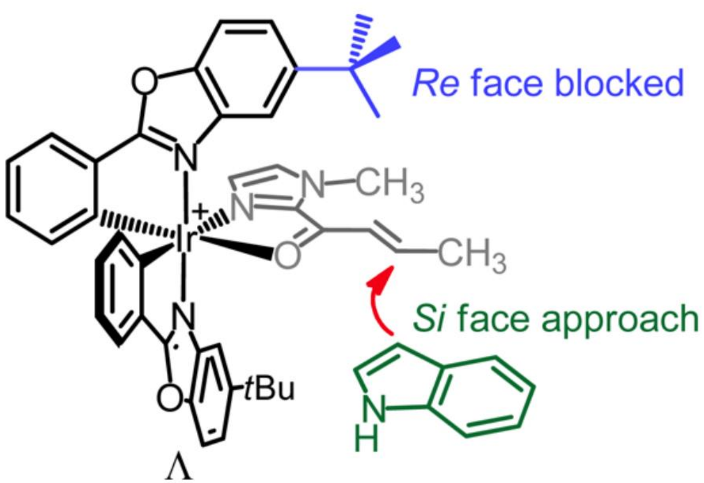
Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136* (8), 2990–2993.
Zhang, L.; Meggers, E. *Acc. Chem. Res.* **2017**, *50* (2), 320–330

➤ Meggers - 2014



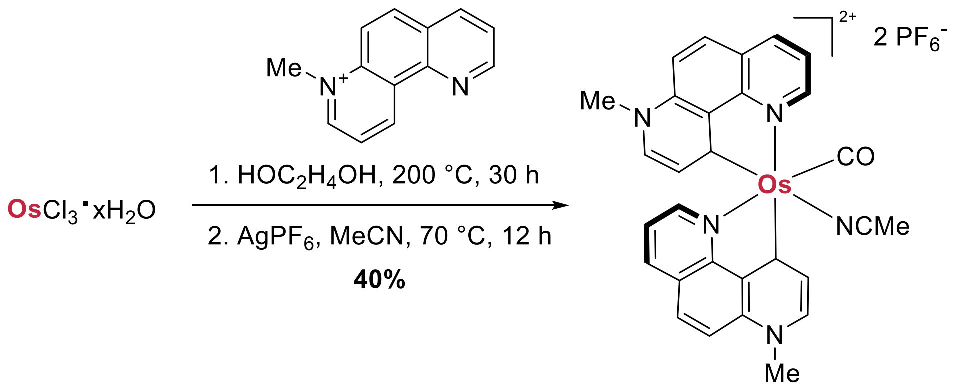

97%, 96% ee | 75%, 92% ee | 97%, 98% ee | 99%, 97% ee




Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136* (8), 2990–2993.

- Meggers - 2020

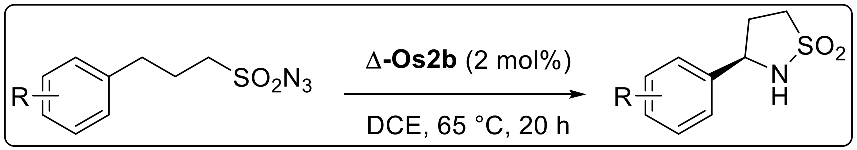


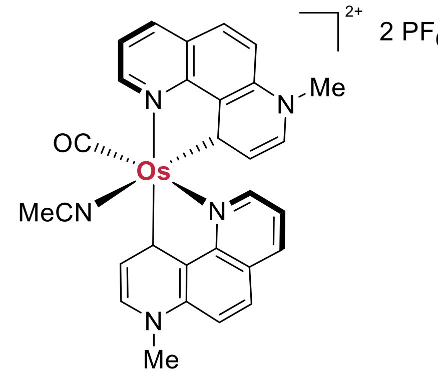

***rac*-1**

Wang, G.; Zhou, Z.; Shen, X.; Ivlev, S.; Meggers, E. *Chem. Commun.* **2020**, *56* (56), 7714–7717.

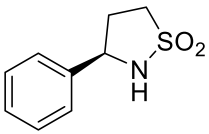
# Recent works – Stereogenic-at-Osmium

- Meggers 2020

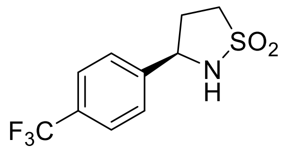


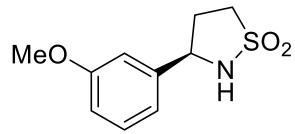

**Δ-Os2b**



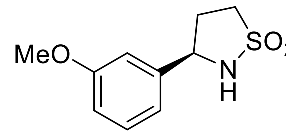
**96%, 86% ee**



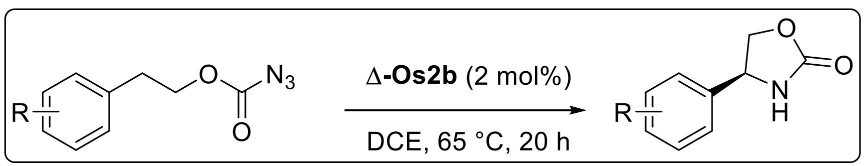

**95%, 82% ee**

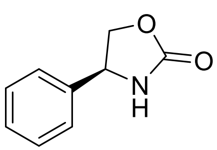



**97%, 76% ee**

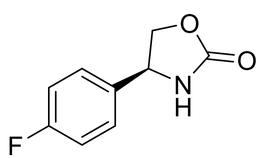



**99%, 80% ee**

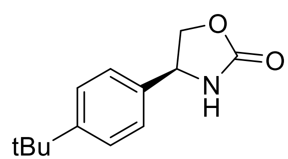


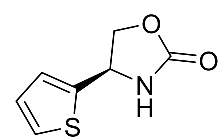
**86%, 78% ee**




**80%, 80% ee**




**85%, 86% ee**

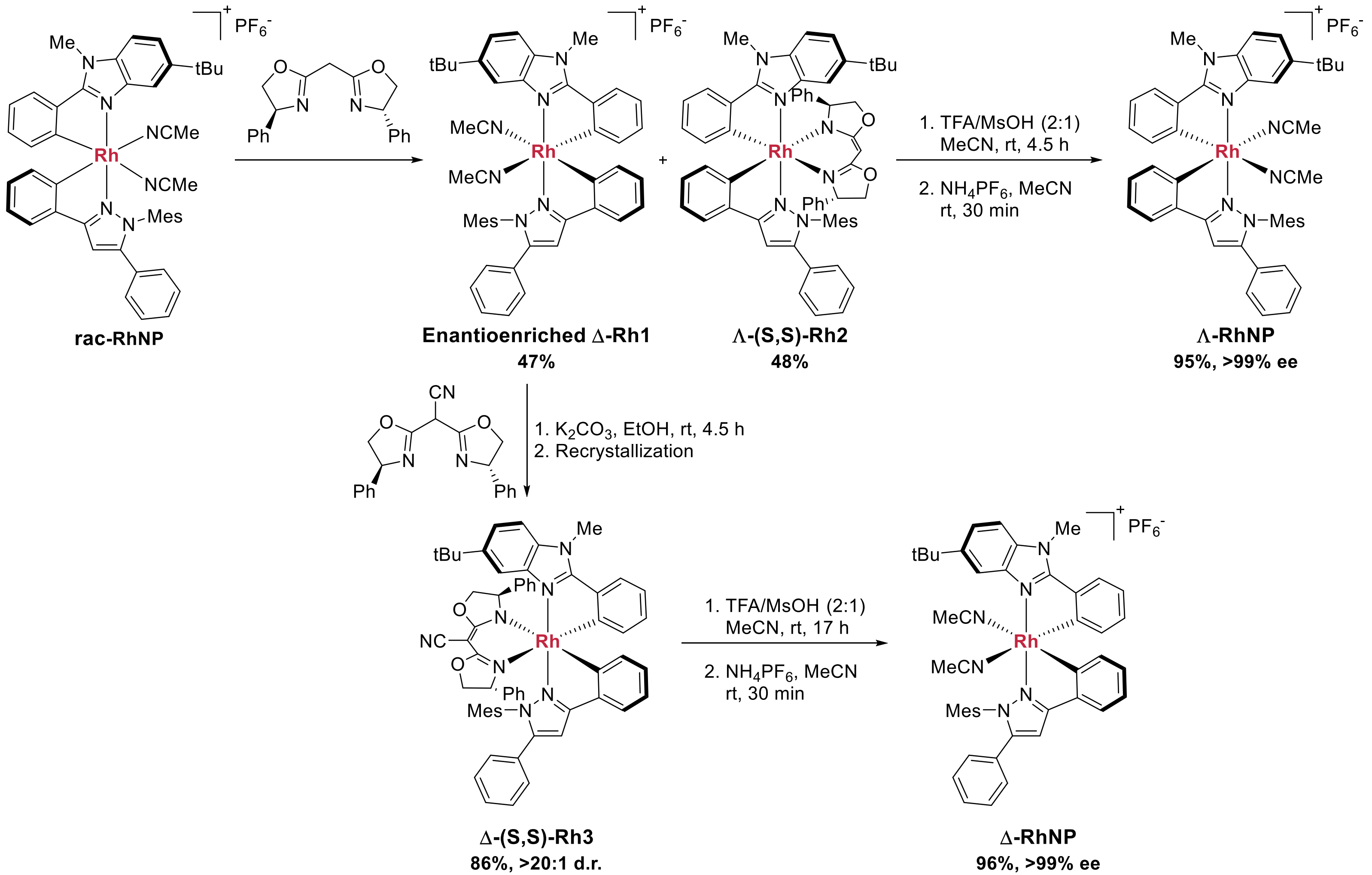



**90%, 86% ee**

Wang, G.; Zhou, Z.; Shen, X.; Ivlev, S.; Meggers, E. *Chem. Commun.* **2020**, *56* (56), 7714–7717.

# Recent works – Stereogenic-at-Rhodium

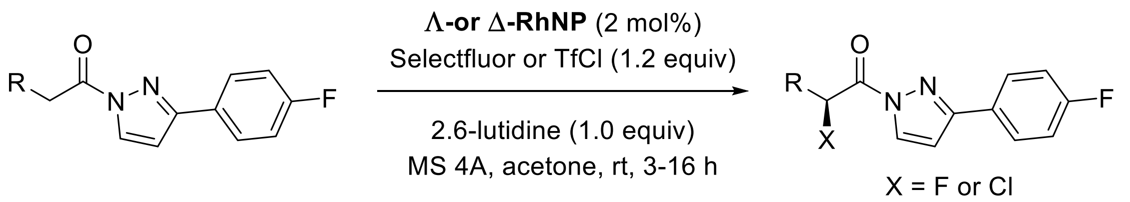
- Meggers - 2021
  - Synthesis of Chiral-At-Rhodium complex Δ-RhNP

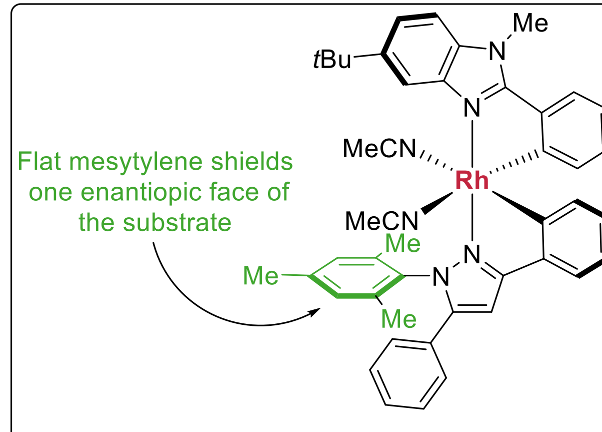



Grell, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. *ACS Catal.* **2021**, *11* (18), 11396–11406.

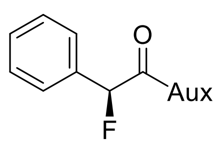
# Recent works – Stereogenic-at-Rhodium

- Meggers - 2021
  - α-Fluorination and α-Chlorination

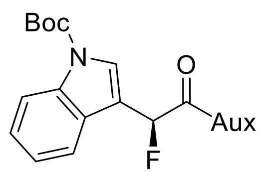


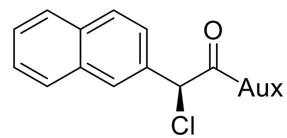

**Δ-RhNP**



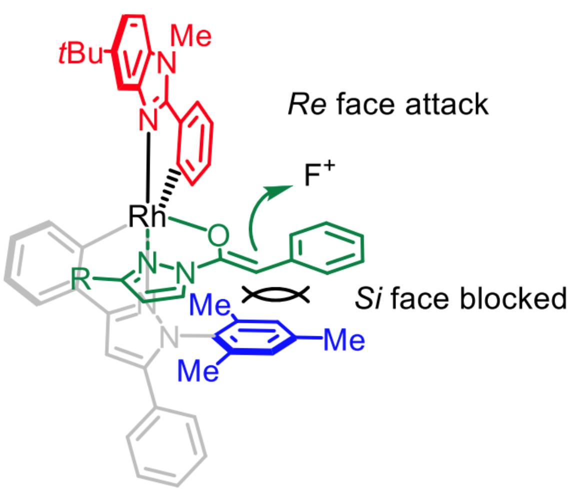
**99% yield, >99% ee**



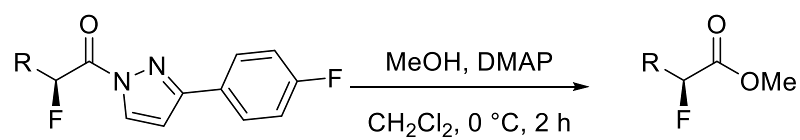
**87% yield, >99% ee**



**94% yield, 90% ee**



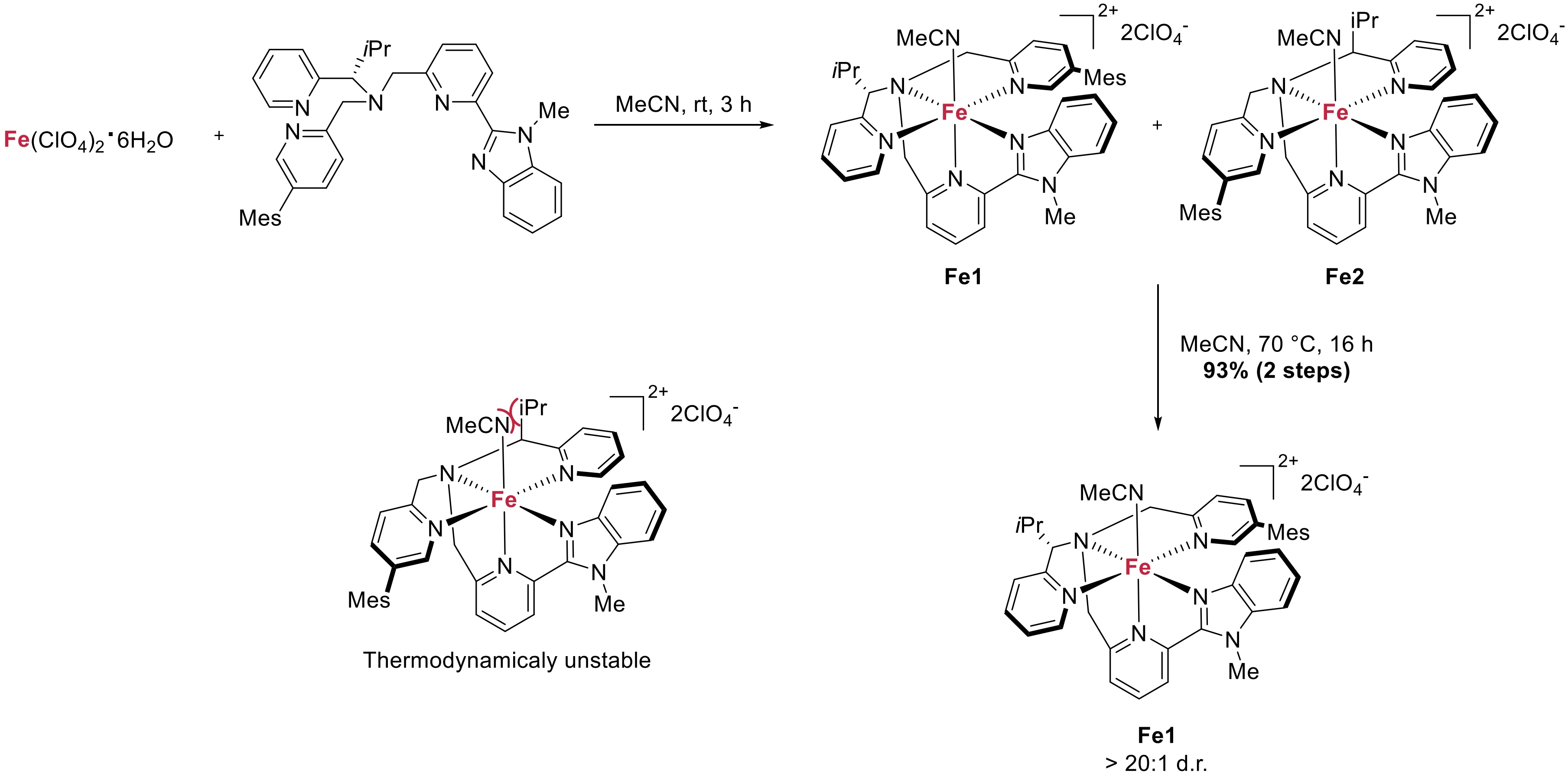

Λ




**1, >99% ee** **2, >99% ee**

Grell, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. *ACS Catal.* **2021**, *11* (18), 11396–11406.

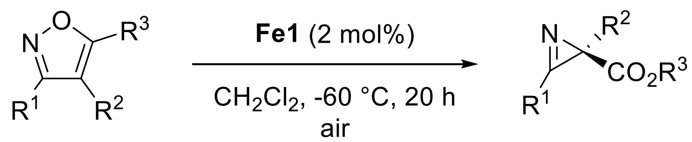
- Meggers - 2021

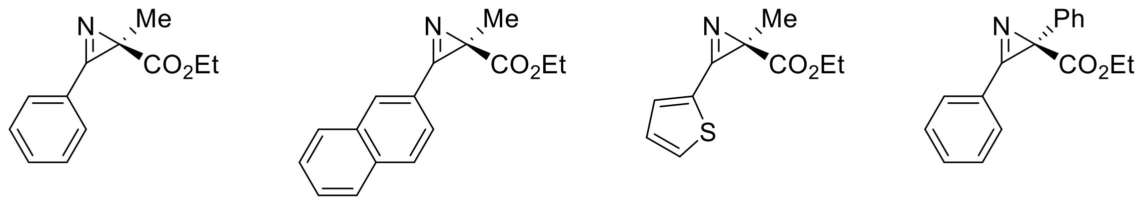



Steinlandt, P. S.; Xie, X.; Ivlev, S.; Meggers, E. *ACS Catal.* **2021**, *11* (12), 7467–7476.

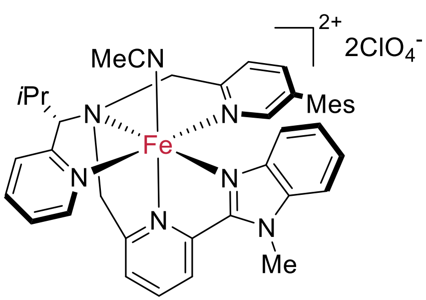
# Recent works – Stereogenic-at-Iron

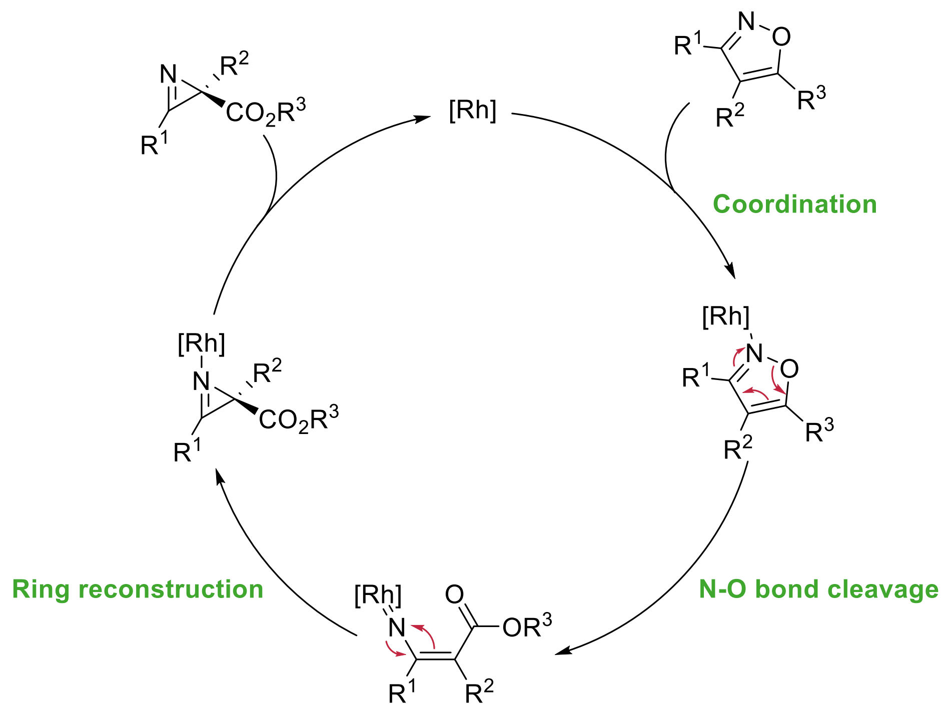
- Meggers - 2021




**98%, 89% ee** **97%, 82% ee** **65%, 74% ee** **98%, 93% ee**

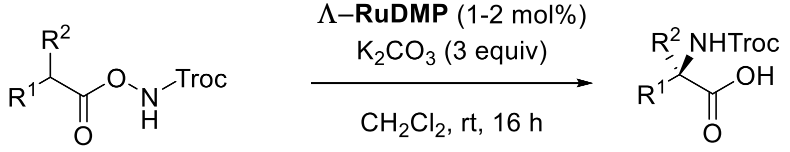


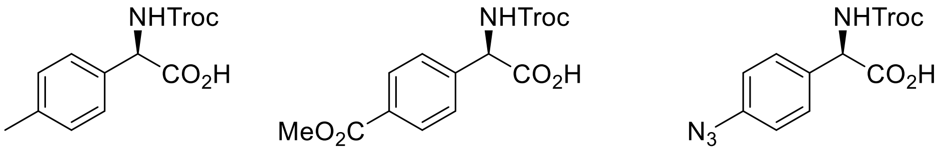




Steinlandt, P. S.; Xie, X.; Ivlev, S.; Meggers, E. *ACS Catal.* **2021**, *11* (12), 7467–7476.

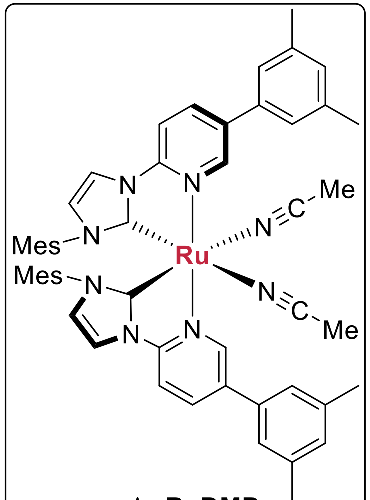
# Recent works – Stereogenic-at-Ruthenium

- Meggers - 2022

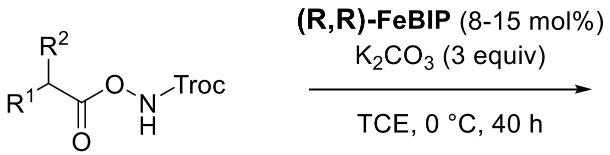


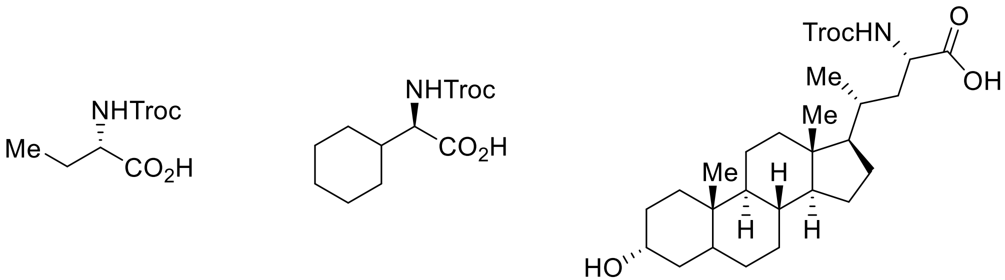




**86%, 97% ee** | **91%, 93% ee** | **95%, 97% ee**

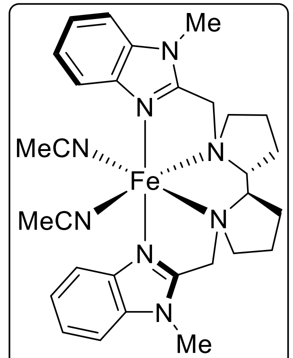



**Λ–RuDMP**




**62%, 91% ee** | **48%, 89% ee** | **77%, 23:1 d.r.**

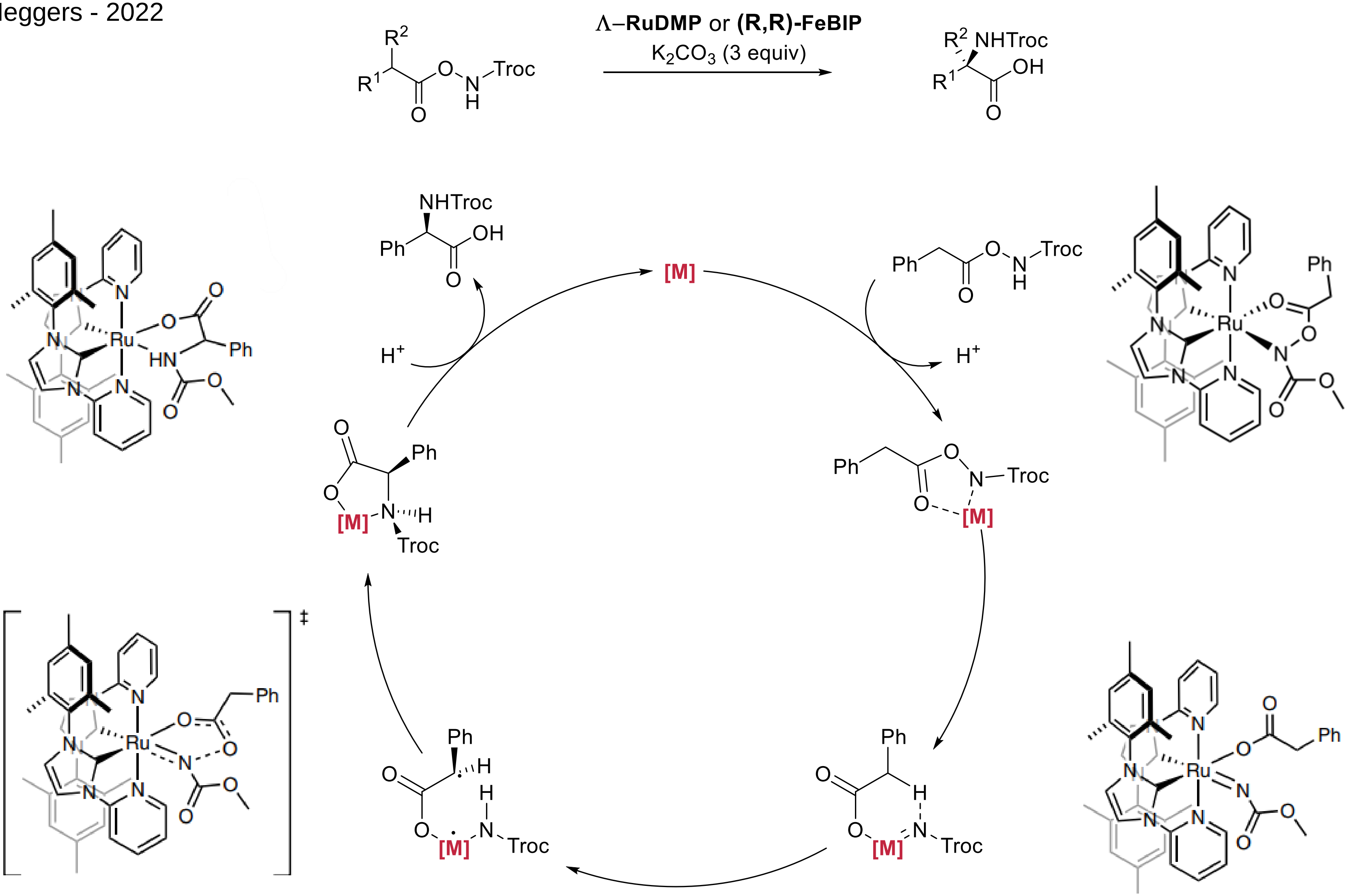



**(S,S)-FeBIP**

Ye, C.-X.; Shen, X.; Chen, S.; Meggers, E. *Nat. Chem.* **2022**, *14* (5), 566–573.

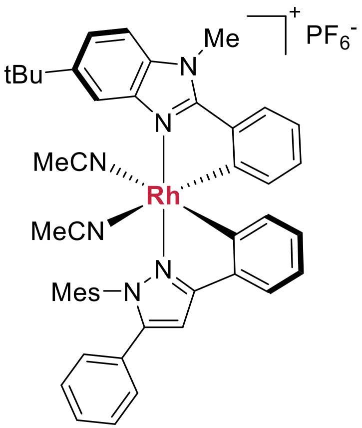
# Recent works – Stereogenic-at-Ruthenium

- Meggers - 2022

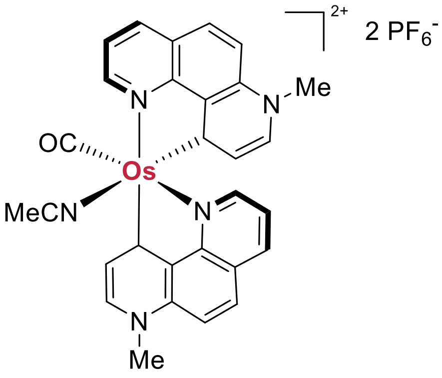



Ye, C.-X.; Shen, X.; Chen, S.; Meggers, E. *Nat. Chem.* **2022**, *14* (5), 566–573.

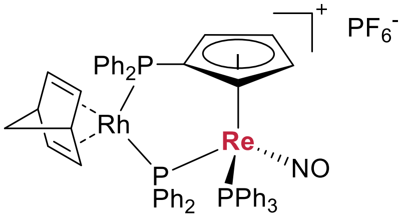
# Conclusion




Δ-RhNP



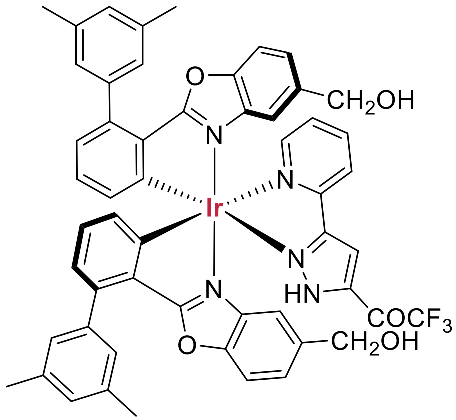

Δ-Os2b

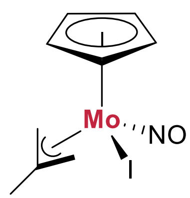


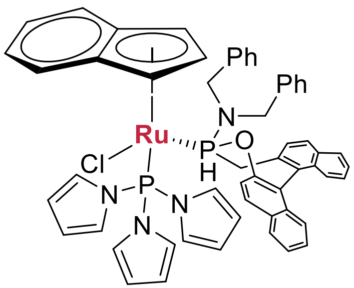

(S)-10

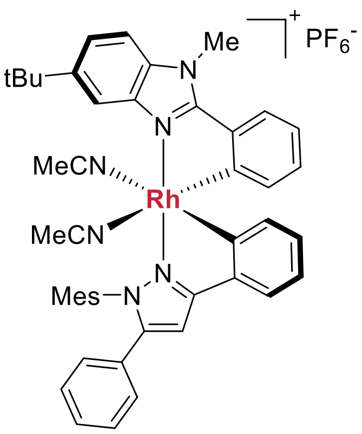
- No chiral ligand needed → only achiral ligands
- Various metal can be used, including earth-abundant iron
- Access to new enantioselective transformations with low catalyst loading

# Question 1



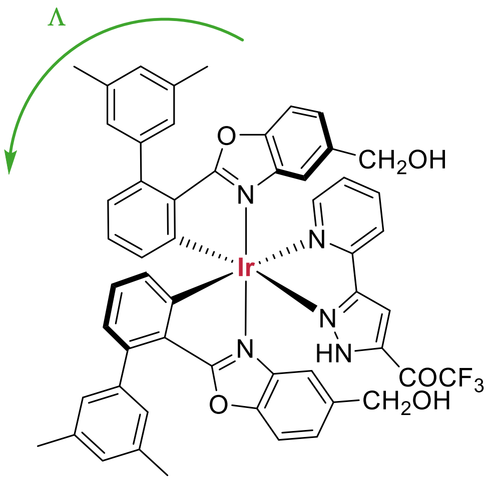



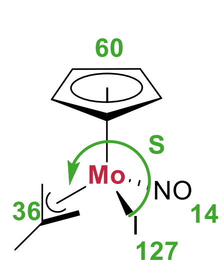

## What is the stereodescriptor of each complex ?

Chen, L. A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135* (29), 10598–10601.
Faller, J. W.; Nguyen, J. T.; Ellis, W.; Mazzieri, M. *Organometallics* **1993**, *12* (4), 1434–1438.
Costin, S.; Rath, N. P.; Bauer, E. B. *Inorg. Chem. Commun.* **2011**, *14* (3), 478–480.
Grell, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. *ACS Catal.* **2021**, *11* (18), 11396–11406.

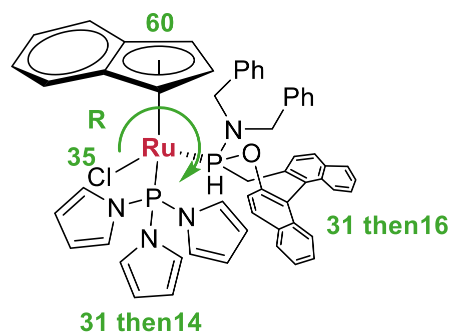
# Question 1



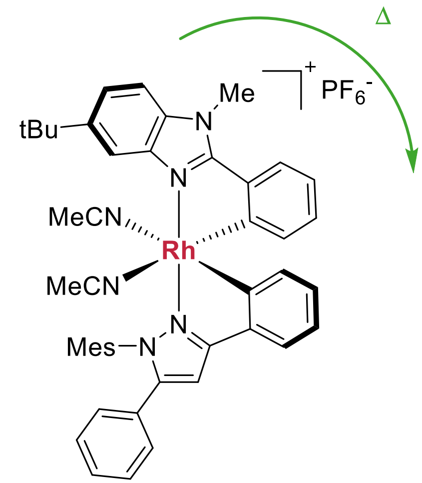

Λ




S



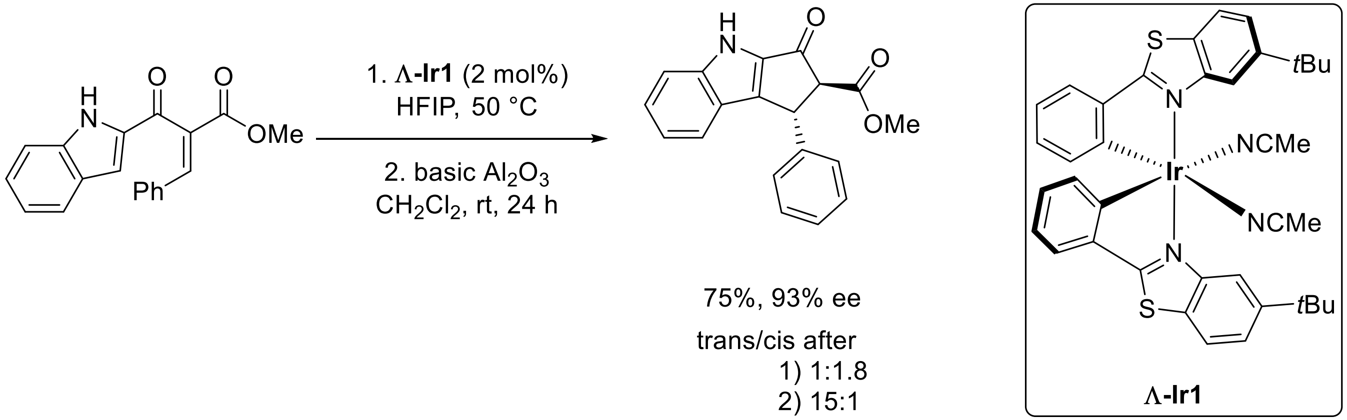

R




Δ

Chen, L. A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135* (29), 10598–10601.
Faller, J. W.; Nguyen, J. T.; Ellis, W.; Mazzieri, M. *Organometallics* **1993**, *12* (4), 1434–1438.
Costin, S.; Rath, N. P.; Bauer, E. B. *Inorg. Chem. Commun.* **2011**, *14* (3), 478–480.
Grell, Y.; Xie, X.; Ivlev, S. I.; Meggers, E. *ACS Catal.* **2021**, *11* (18), 11396–11406.

# Question 2

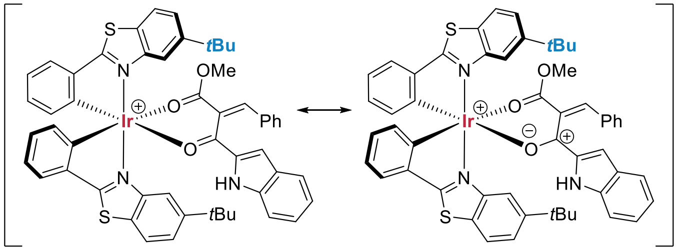



**What is the name and the mechanism of the reaction ?**

**Rationalize the stereochemistry observed**

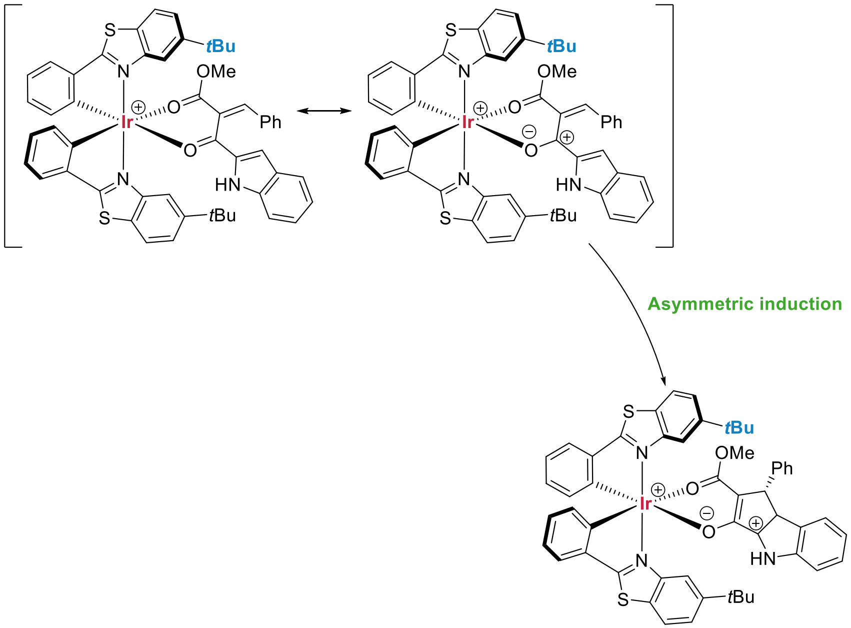
Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal.* **2018**, *360* (11), 2093–2100.

# Question 2



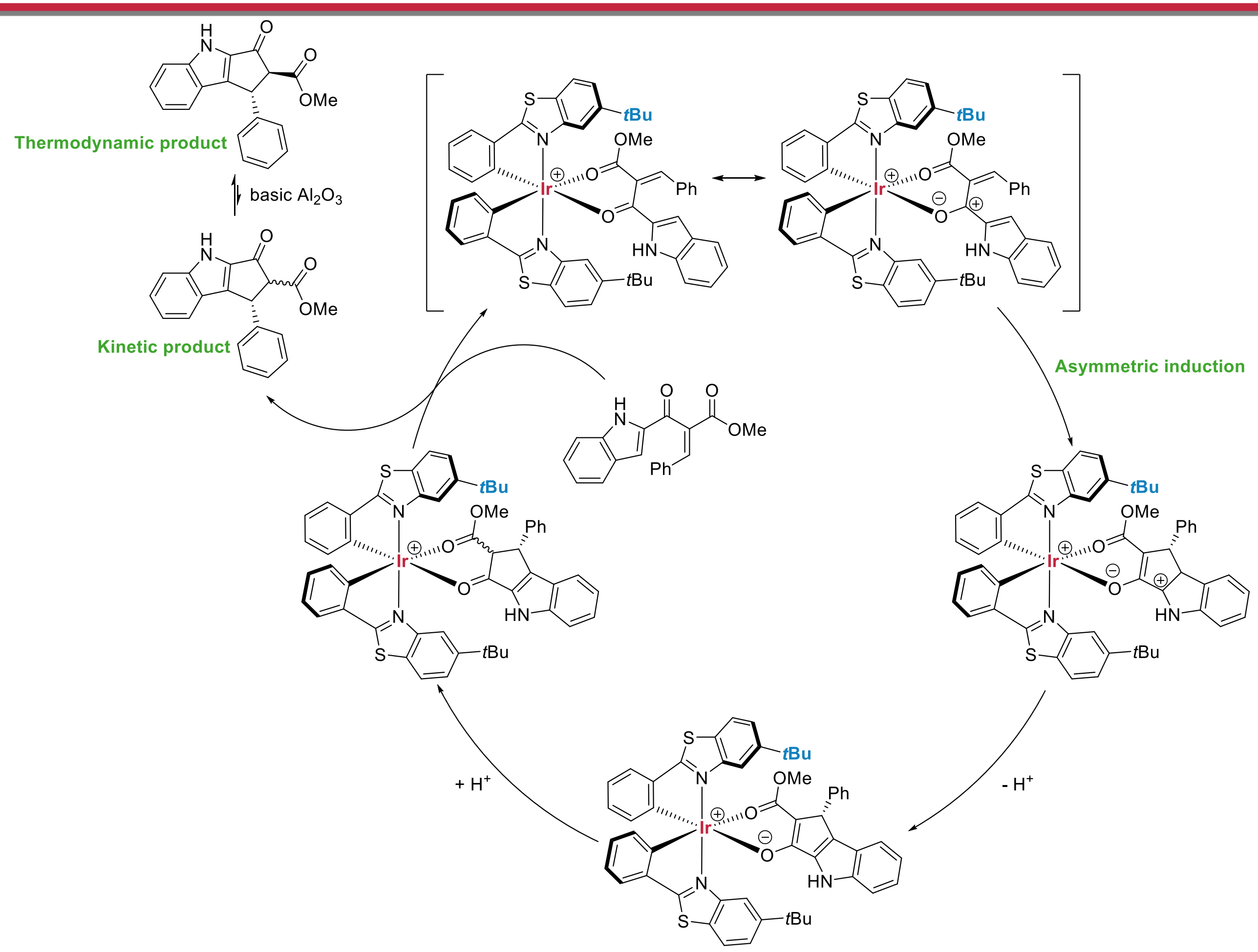

Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal.* **2018**, *360* (11), 2093–2100.

# Question 2



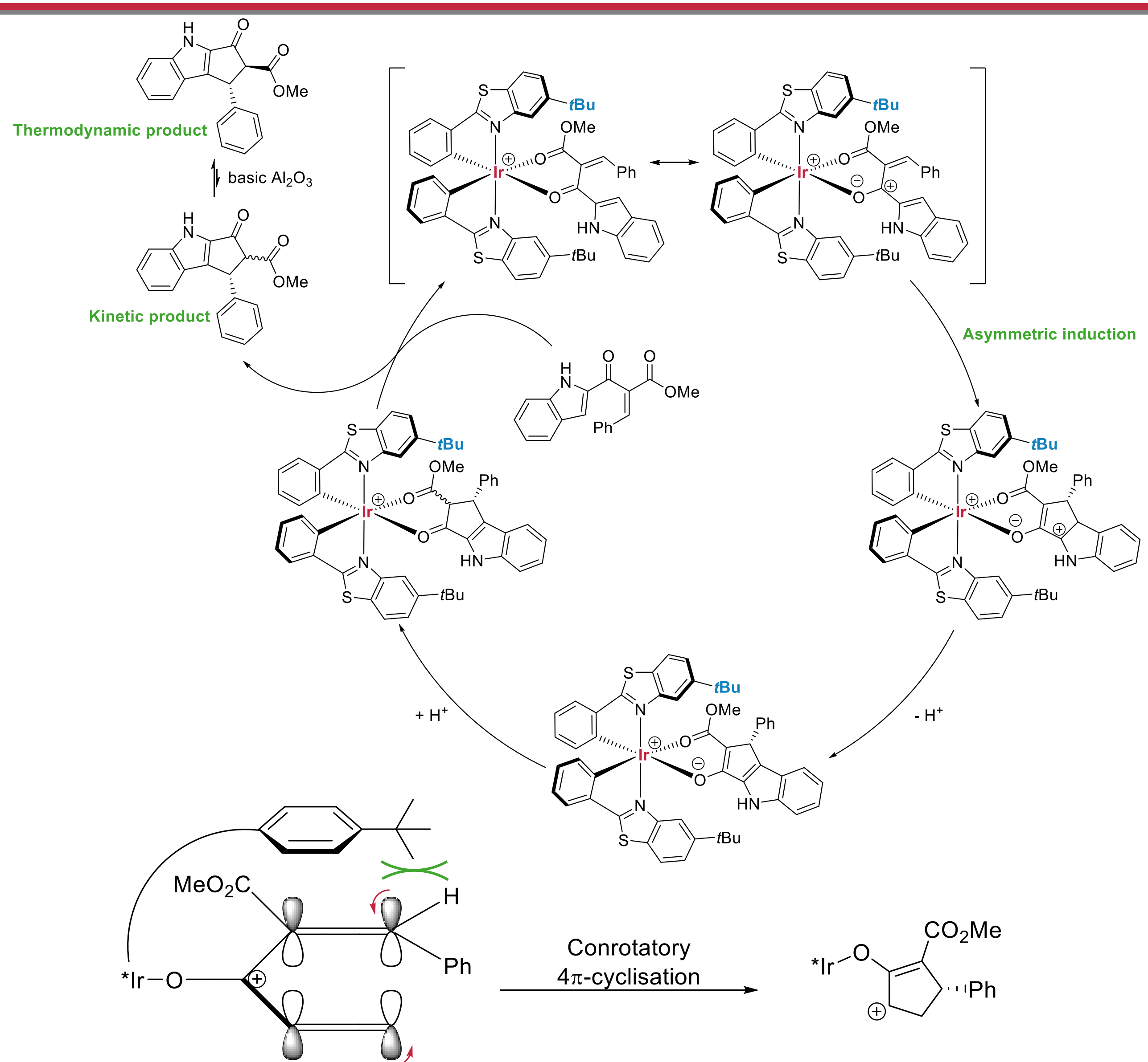

Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal.* **2018**, *360* (11), 2093–2100.

# Question 2




Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal.* **2018**, *360* (11), 2093–2100.

# Question 2




Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal.* **2018**, *360* (11), 2093–2100.

# Recent Advances in Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Center

Dina Boyarskaya

16th of May 2022

# Content

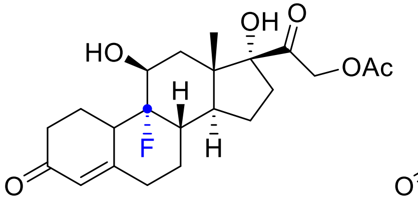
# Content - Precisions

1. Only enantioselective transformation
2. Only formation of quaternary carbon atoms
3. Only fluorination methods
4. Only electrophilic N-F fluorinating agents
5. Only achievements during the last 10 years will be discussed

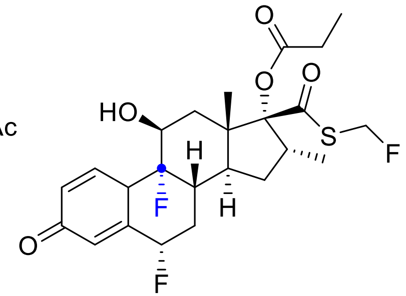
# Introduction – fluorine-containing compounds

New methods for preparation of fluorine-containing compounds are in extremely high demand in nearly every sector of chemical industry:

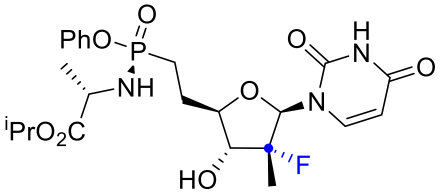
1. Solar cells industry;
2. Fluoro-containing markers for biological studies by NMR;
3. $^{19}F$ magnetic resonance imaging (MRI), a superior alternative to the current diagnostic procedures using harmful ionizing radiation;
4. Agrochemical industry - about half of newly developed pesticides contain some type of fluorination;
5. Pharmaceutical industry - fluorine is found in more than half of most-prescribed multibillion-dollar pharmaceuticals



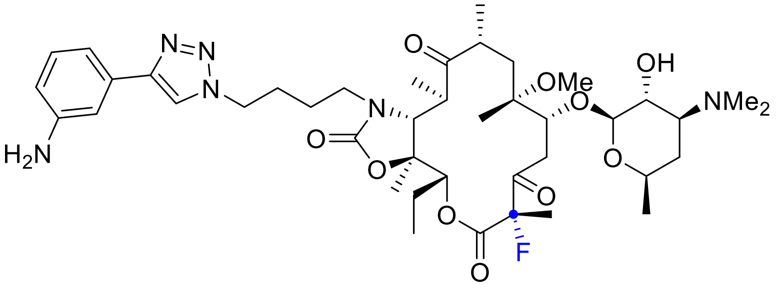
**Fludrocortisone**



**Fluticasone propionate**
treatment of asthma



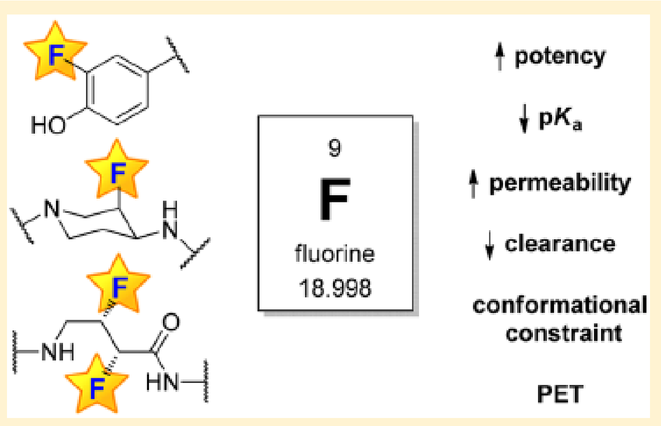
**Sofosbuvir**
HCV antiviral



**Solithromycin**
antibacterial

Due to the fact that F is slightly larger and hydrophobic than H, its extreme electronegativity and that F can be H-bond acceptor, introduction of C-F to replace C-H influence the properties of the drug and can lead to modification of :

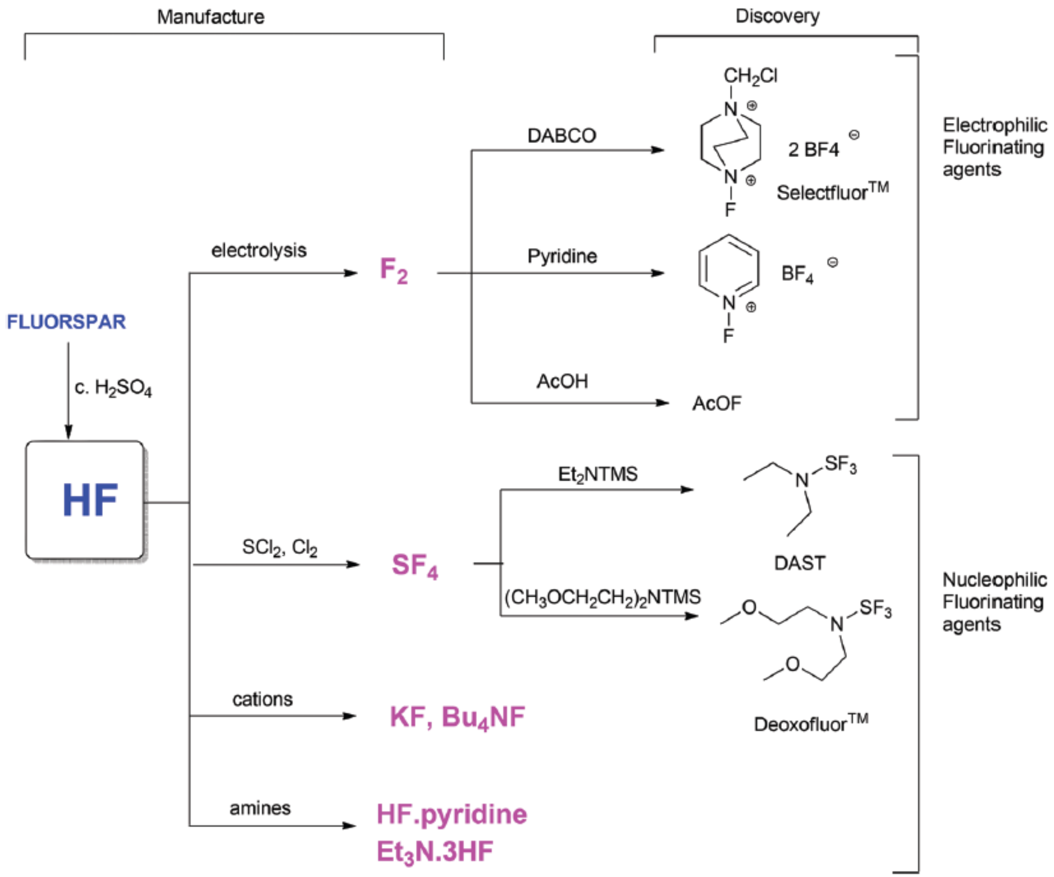
- Molecular conformation;
- Polarity;
- Acid-base properties;
- Electronic interactions based on gauche-anomeric effect.



# Introduction – fluorinating reagents

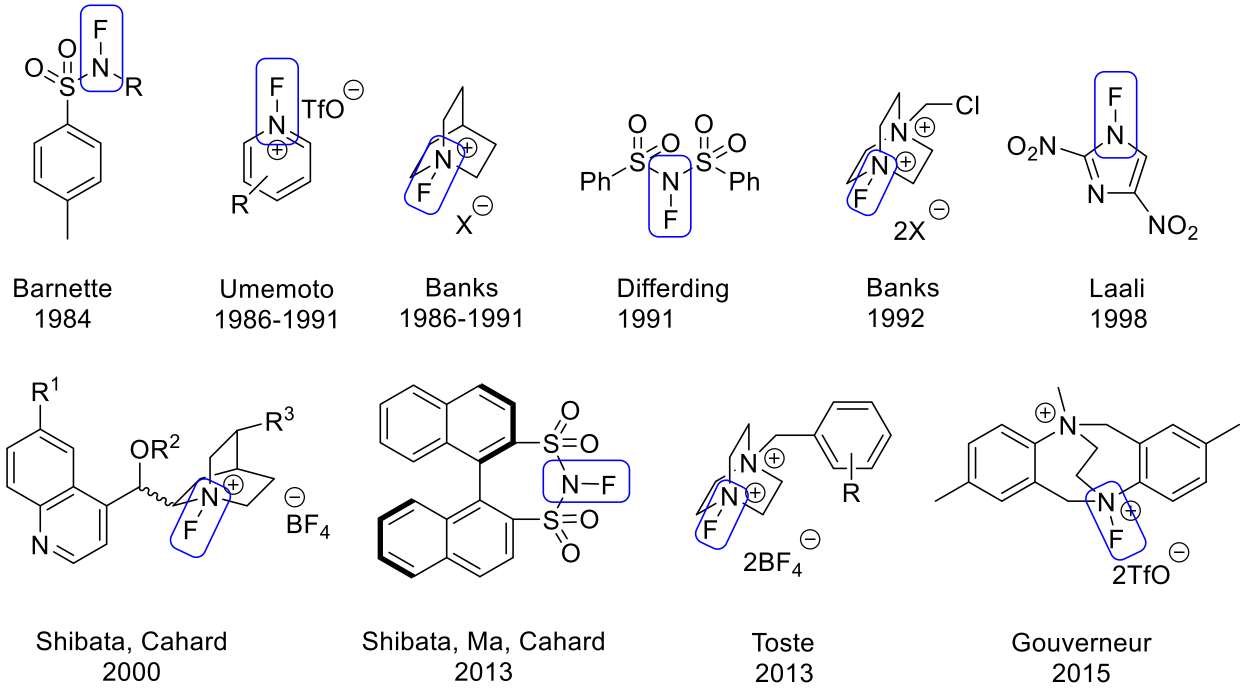
Three major factors prohibit chemical and biological evolution of fluorine:

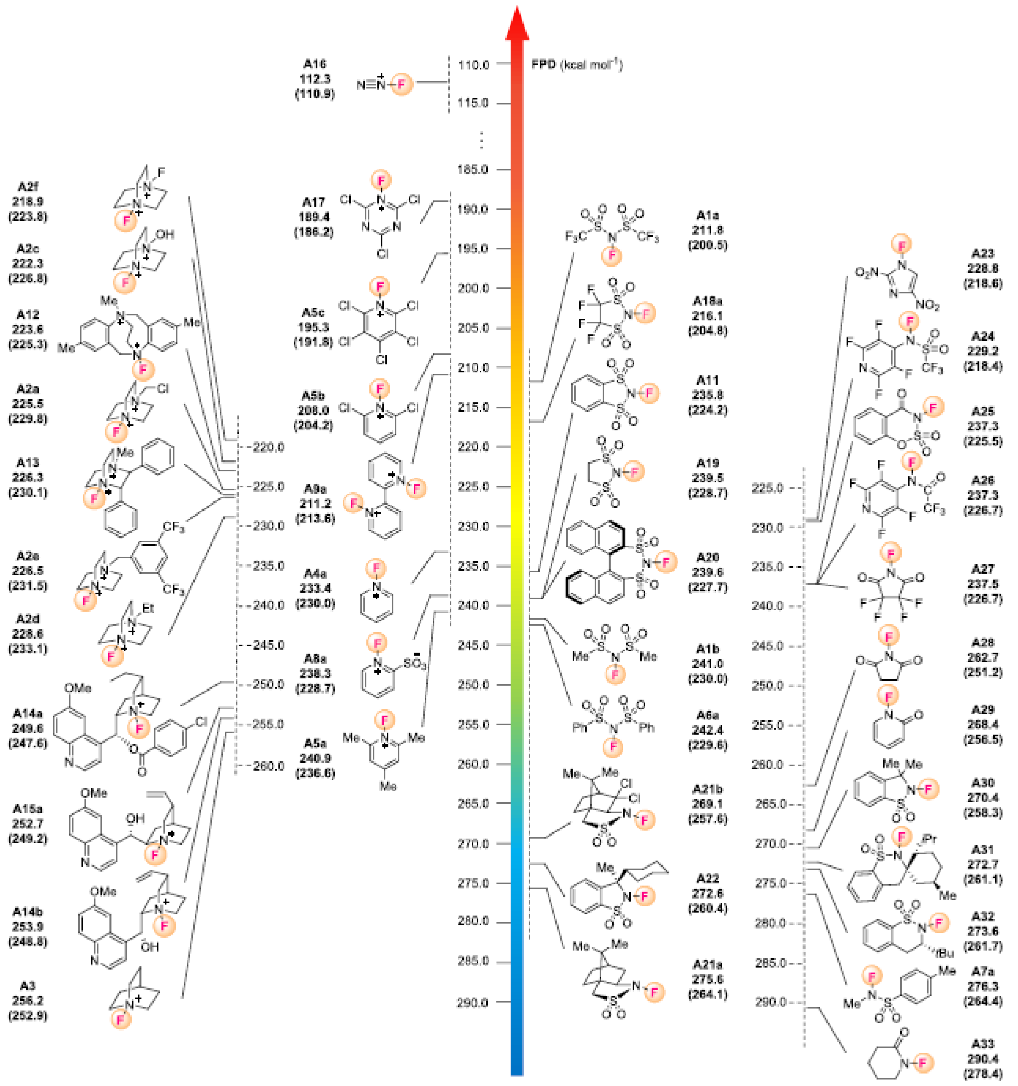
1. the three richest natural sources of fluorine, the minerals fluorospar ($CaF_2$), fluorapatite ($Ca_5(PO_4)_3F$), and cryolite ($Na_3AlF_6$) are water-insoluble;
2. high oxidation potential of fluorine (−3.06 V);
3. high hydration energy of fluorine (117 kcal/mol) renders fluoride a very poor nucleophile in an aqueous/biological environment.



# Introduction – Electrophilic N-F fluorinating reagents

## Shelf-stable electrophilic fluorinating reagents




In 2016, the first systematic quantum mechanical calculation of fluorinating strength of 130 electrophilic N−F reagents values was performed in two commonly used solvents ($CH_2Cl_2$ and CH3CN) based on FPD (**F**luorine **P**lus **D**etachment) energy.

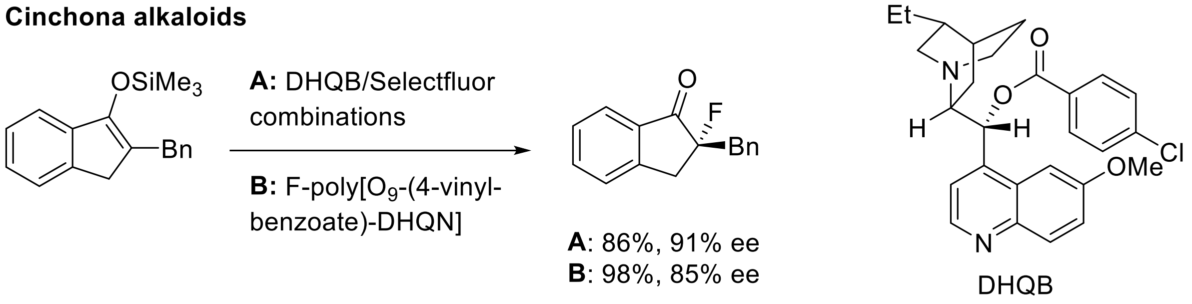
$$Y-F \xrightarrow[\text{FPD}]{\Delta H_{het}} Y^{-} + {}^{+}F$$

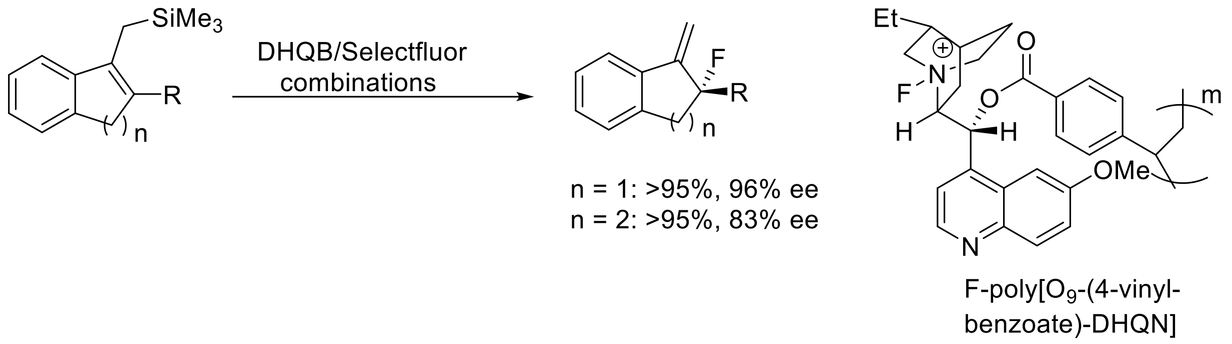
Cheng, J.P. *Acc. Chem. Res.* **2020**, *53*, 182−197, *J. Org. Chem.* **2016**, *81*, 4280−4289

# Achievements before 2011

## Stochiometric reactions

**Cinchona alkaloids**

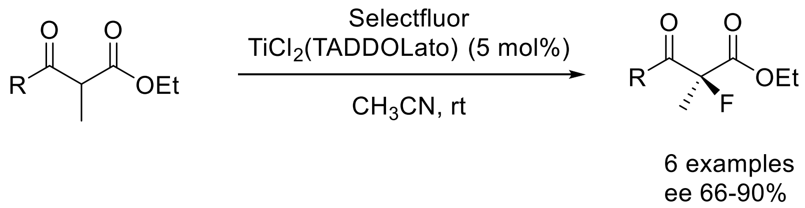


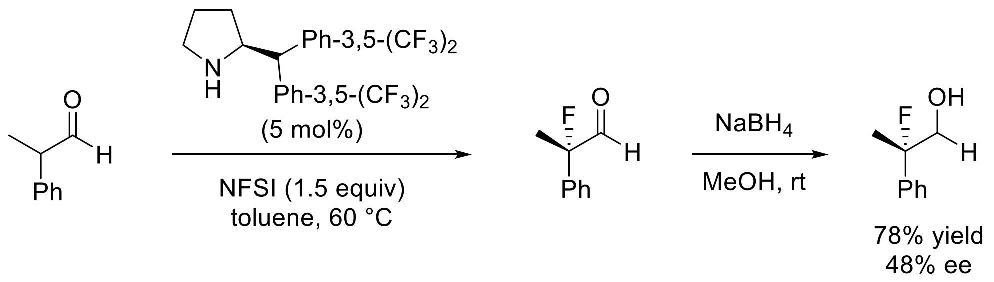

Many of the most effective published enantioselective fluorination protocols require formation of a **nucleophilic chiral enolate equivalent/activated starting materials**.
The **catalytic** generation of a chiral electrophile has proven quite challenging; usually a stoichiometric amount of chiral promoter is necessary to suppress the **racemic background reaction**

## Catalytic reactions (first approaches)

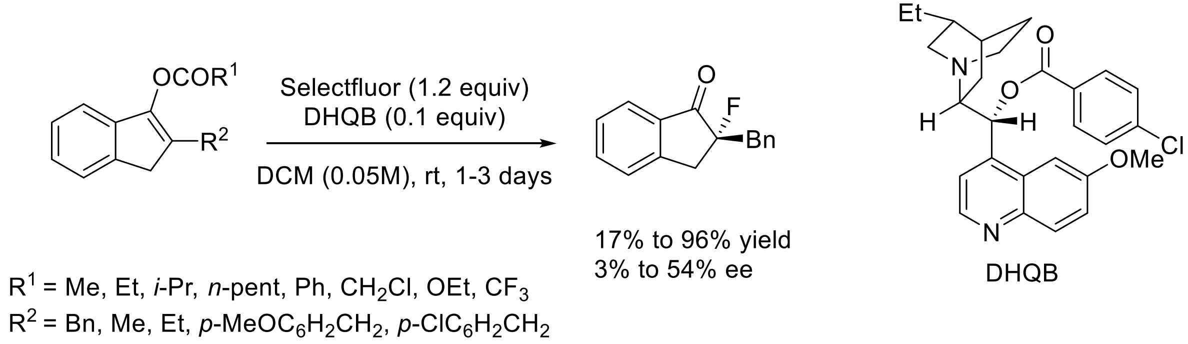
**Metal Catalysed**, Togni, 2000




**Enamine catalysis**, Jorgensen, 2005




**Tertiary amine catalysts**, Shibata, 2006

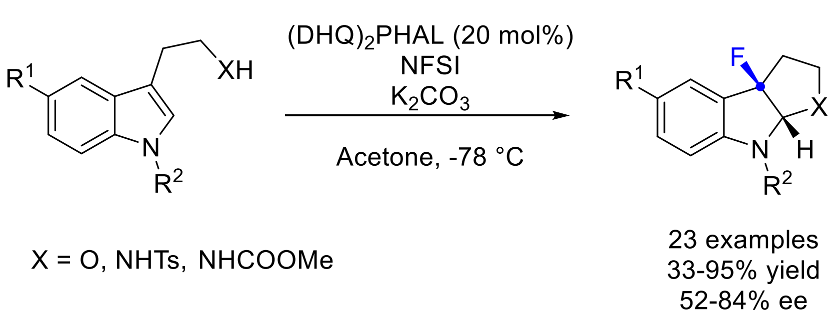


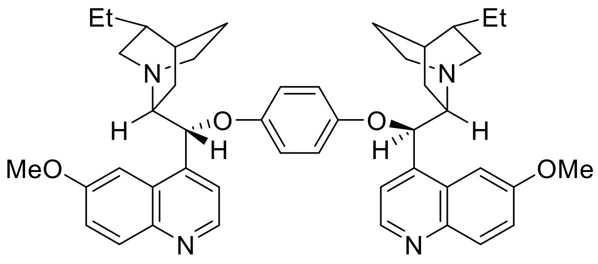

Shibata, N *JACS* **2000**, *122*, 10728−10729; Cahard, D. *Synlett* **2004**, 0856−0860; Gouverneur, V. *ACIE* **2003**, *42*, 3291−3294; Togni, A. *ACIE* **2000**, *39*, 4359-4362; Jorgensen, K.A. *ACIE*, **2005**, *44*, 3703-3706; Shibata, N. *J. Fluorine Chem.* **2006**, *127*, 548−551

# Content

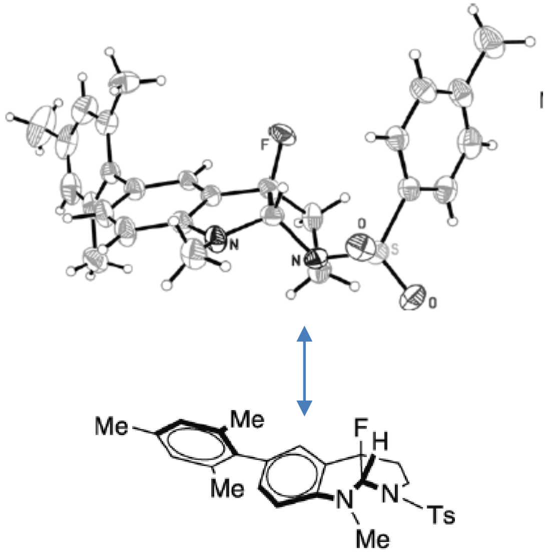
# Cinchona alkaloids

## 1. Fluorocyclization of indoles – 1st example of enantioselective fluorocyclization

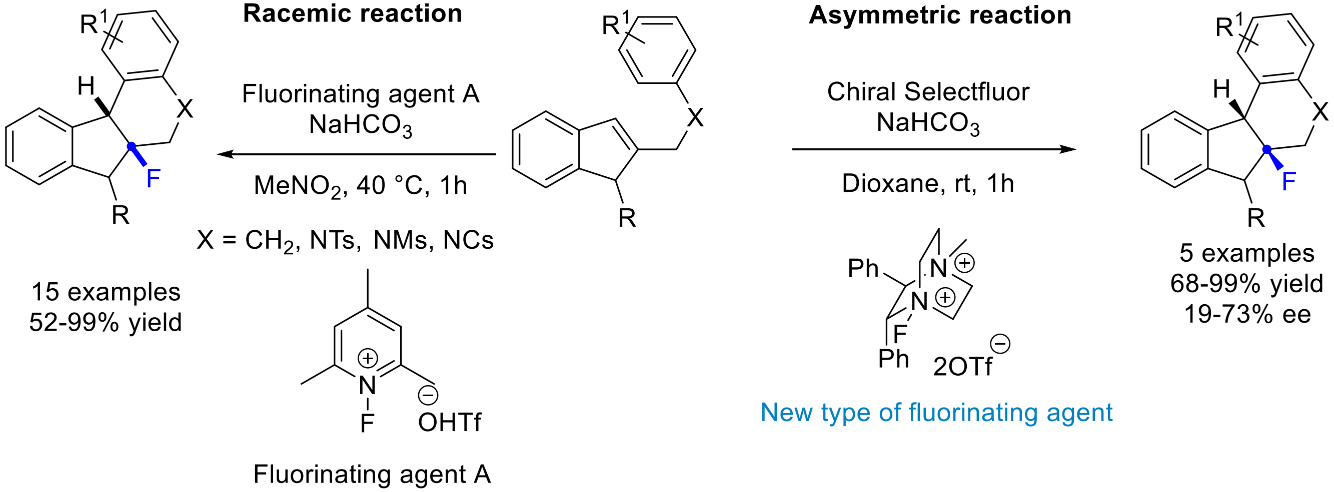



$(DHQ)_2PHAL$




## 2. Fluorocyclization of prochiral polyenes

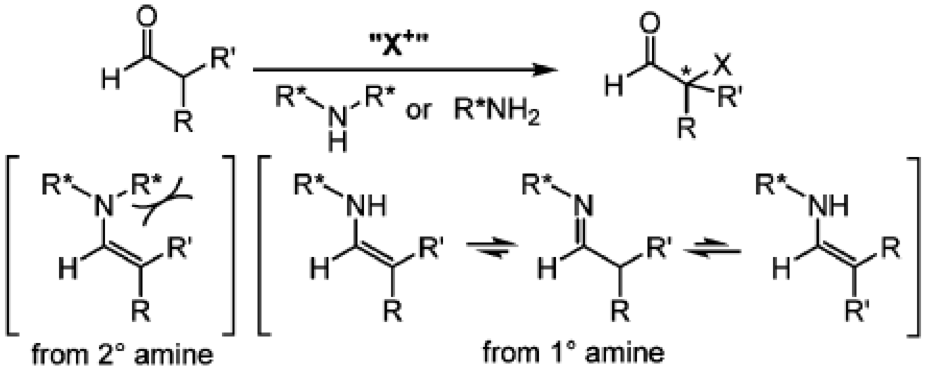



*Syn* – diastereoisomers – confirmed by NMR

Gouverneur, V. *ACIE.* **2011**, *50*, 8105-8109; *ACIE.* **2013**, *52*, 9796-9800

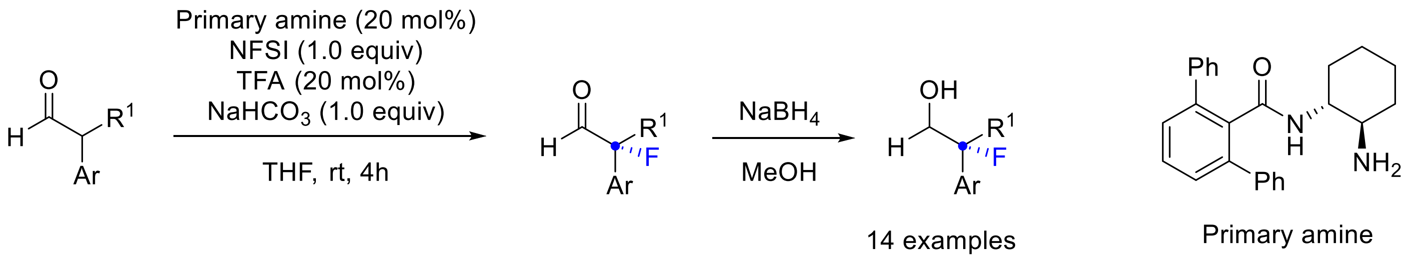
# Primary Amine Catalysis

## 1. α-Fluorinations of Branched Aldehydes




Secondary amines are ineffective catalysts due to the steric hindrance and primary amines suffers from the formation of E and Z isomers.

Jacobsen, 2015




Substituted arylpropionaldehyde derivatives undergo α-fluorination with consistent results. α,α- dialkyl branched aldehydes afforded products with significantly lower ee.

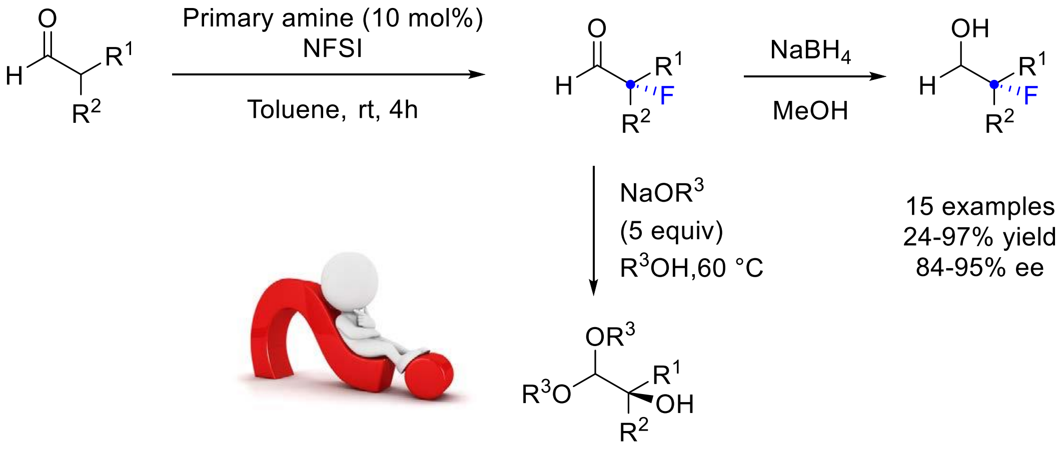

The stereochemical analysis raises the possibility that enantioselectivity is dictated primarily by the E/Z ratio of the enamine intermediates.

Jacobsen, E.N. *Org.Lett* **2015**, *17*, 2772-2775

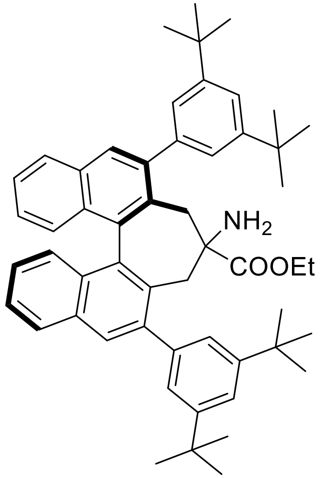
# Primary Amine Catalysis

## 2. α-Fluorinations of Branched Aldehydes

### Iwasa

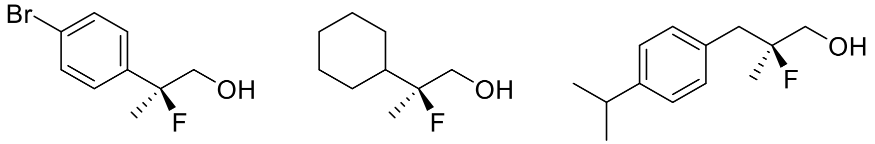



Stereospecific process




Primary amine

Various α-alkyl-α-aryl aldehydes were successfully fluorinated to afford the corresponding α-fluoroaldehydes in high yields with high ee. The reaction with α,α-dialkyl aldehydes yielded the products with worse results.




97% yield
92% ee

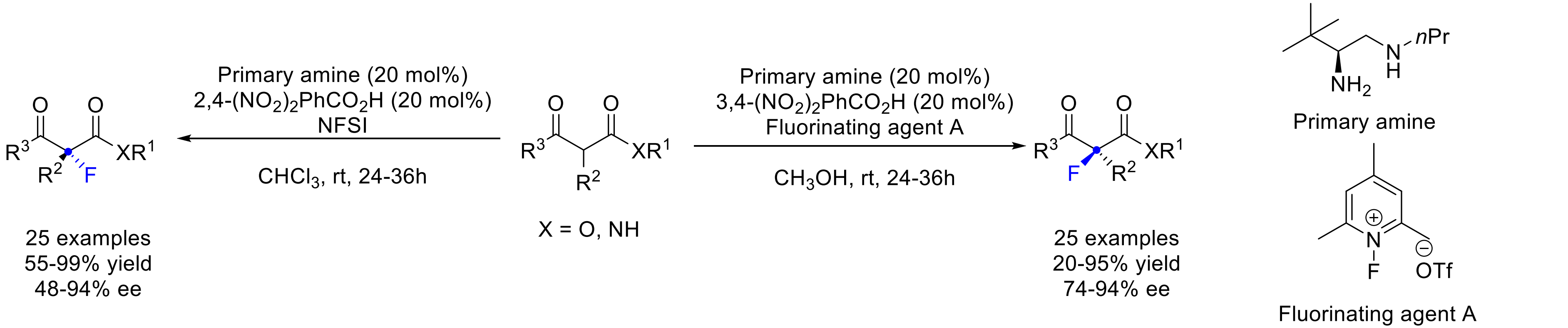
24% yield
83% ee

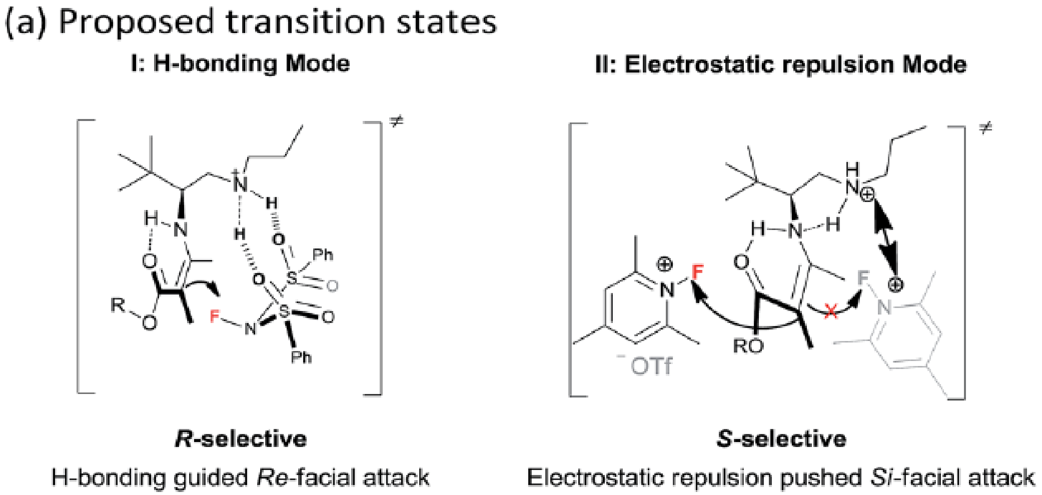
59% yield
14% ee

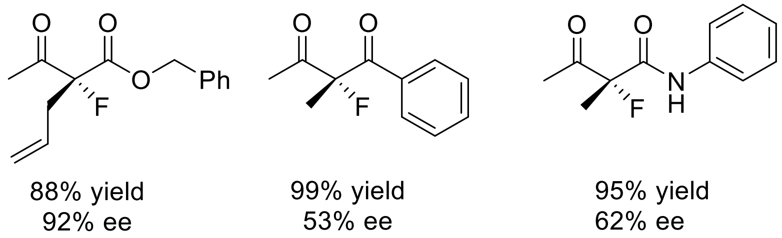
Iwasa, S. *Chem.Sci.* **2016**, *7*, 1388-1392

# Primary Amine Catalysis

## 3. α-Fluorinations of acyclic ketones




β-ketoesters – 18 examples, high yields and ee
1,3-dicarbonyls – 1 example, good reactivity, moderate ee
β-ketoamides – 7 examples, good yields and good to moderate ee

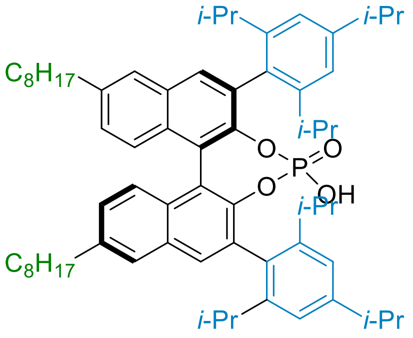
Luo, S. *Chem.Sci.* **2017**, *8*, 621-626

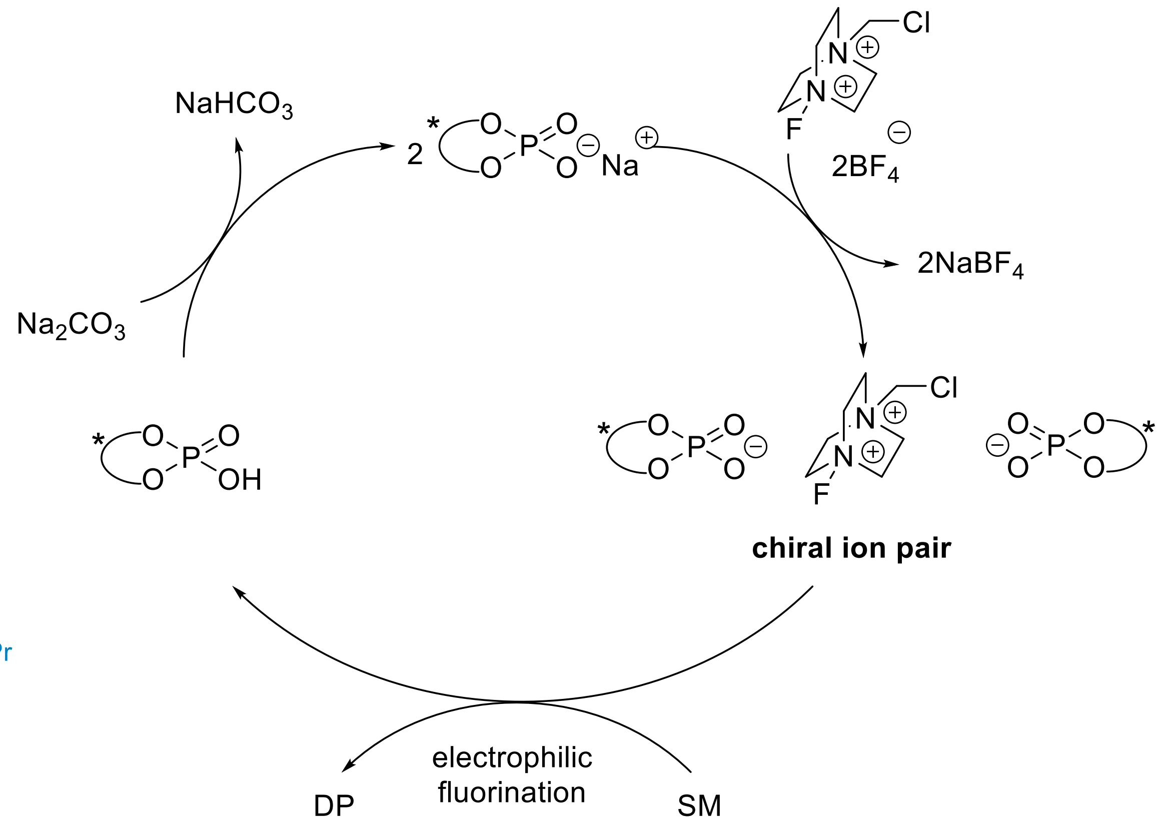
# Anionic Phase-Transfer Catalysis

The use of chiral cation salts as phase-transfer catalysts for anionic reagents has enabled a vast set of enantioselective transformations.

To overcome the problem of background reaction of electrophilic fluorinating agent and starting material – Toste decided to keep low the concentration of electrophilic fluorine in organic solution by applying anionic phase –transfer catalysis

1. Lipophilic backbone phase –transfer catalyst
2. Bulky, chiral phosphonic acid
3. Selectfluor is not soluble in nonpolar solvents

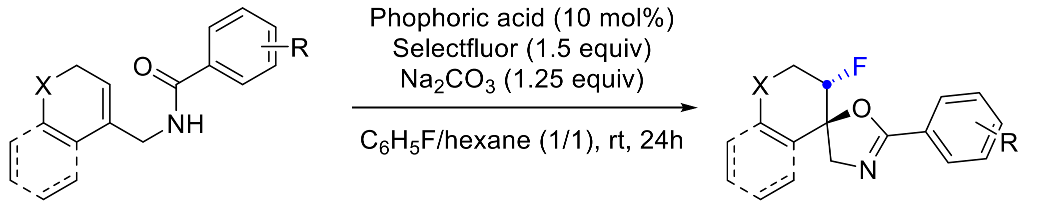


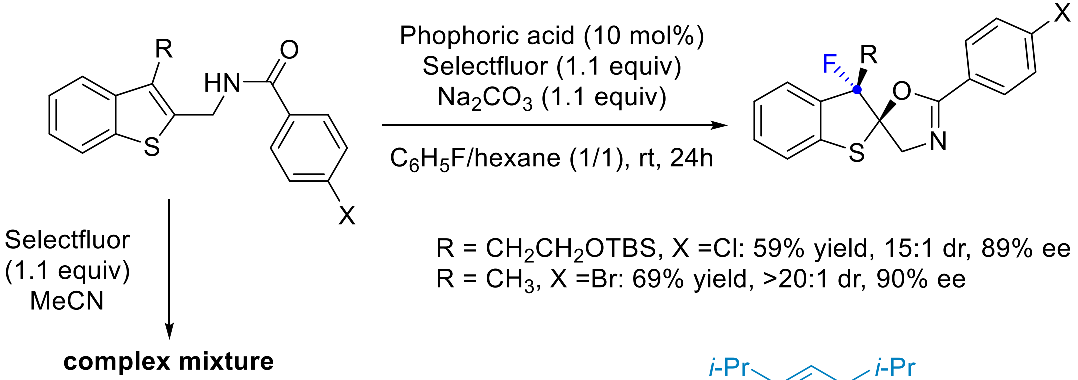

Toste, F.D. *Science* **2011**, *334*, 1681-1684

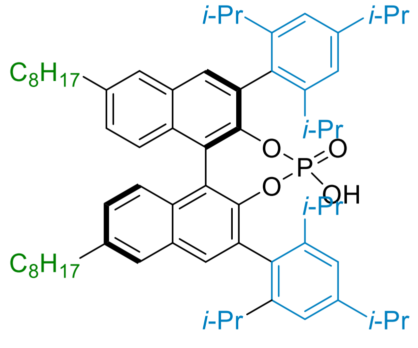
# Anionic Phase-Transfer Catalysis

## 1. Fluorocyclization of olefins

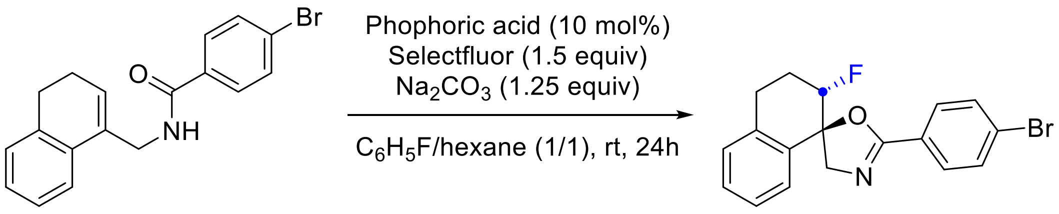


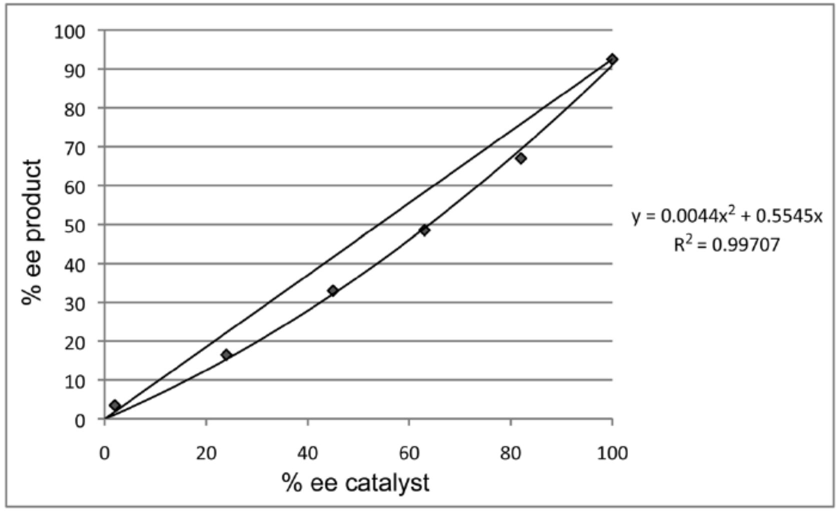

67-95% yield
>20:1 dr, 79-96% ee




**Phosphoric acid**




A nonlinear effect was observed, supporting a pathway in which both $BF_4$ anions are exchanged for chiral phosphates before the reaction with substrate.

Toste, F.D. *Science* **2011**, *334*, 1681-1684

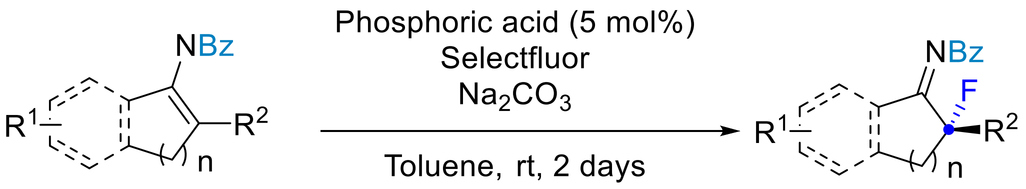
# Anionic Phase-Transfer Catalysis

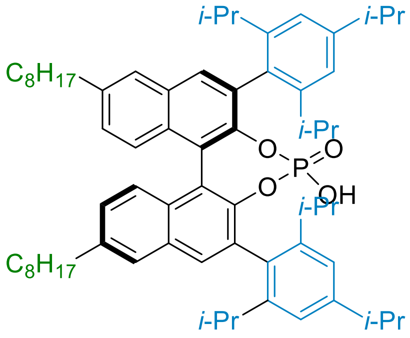
## 2. Fluorination of Enamides

Asymmetric synthesis of β-fluoroamine

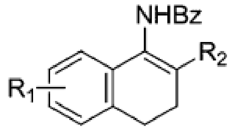
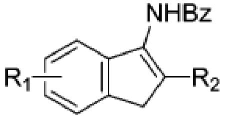
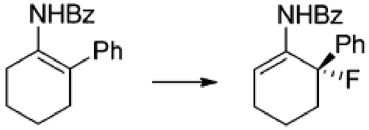
↗ Enantioselective fluorination of ketones and aldehydes

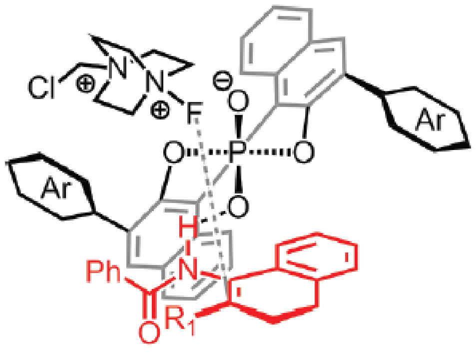
↘ Desymmetrization of fluoro-containing compounds



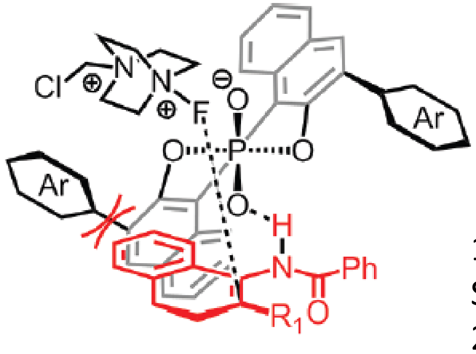




**Phosphoric acid**

| Entry | Substrate 1 | $R_1$ | $R_2$ | Product | % yield 2[a] | %ee 2[b,c] |
|---|---|---|---|---|---|---|
| 1 |  | H | Me | **2d** | 88 | 96 |
| 2[d] | | H | Allyl | **2e** | 80 | 96 |
| 3 | | H | Bn | **2f** | 92 | 99 |
| 4[e] | | 6-OMe | Me | **2g** | 94 | 92 |
| 5 |  | H | Me | **2h** | 66 | 96 |
| 6[d,f] | | H | Ph | **2i** | 79 | 90 |
| 7 | | H | Bn | **2j** | 84 | 98 |
| 8 | | 5-OMe | Bn | **2k** | 68 | 96 |
| 9[g] | | 5-F | Bn | **2l** | 75 | 94 |
| 10[d] | | 5-Cl | Bn | **2m** | 85 | 93 |
| 11 | | H | (3-OMe)Bn | **2n** | 83 | 98 |
| 12[h] |  | | | **2o** | 58 | 87 |




*favored*




*disfavored*

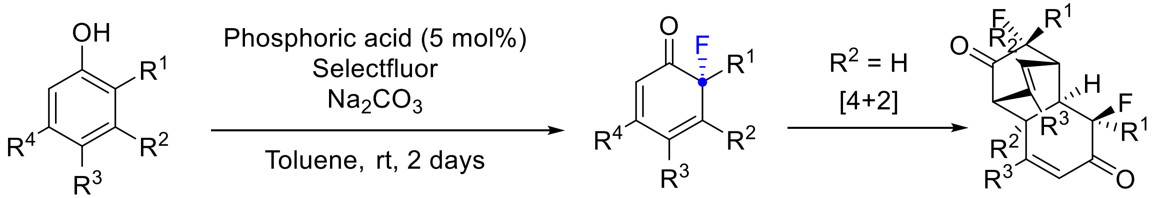
1. an ion pair with the Selectfluor reagent
2. activating the enamide through hydrogen bonding

Toste, F.D. *JACS* **2012**, *134*, 8376-8379

# Anionic Phase-Transfer Catalysis

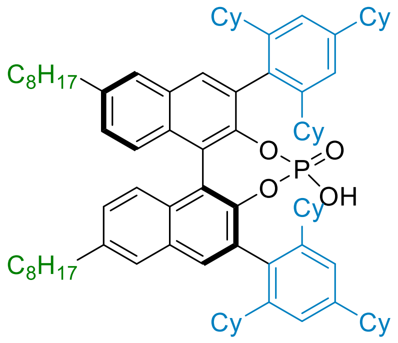
## 3. Dearomatization of phenols

Direct asymmetric dearomatization through discrimination between the enantiotopic faces of the arene

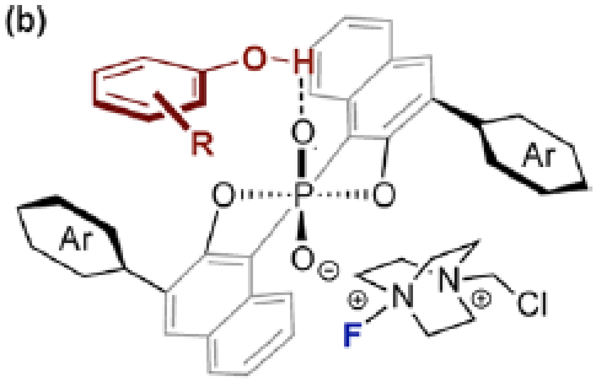



18 examples
28-81% yield
79-97% ee

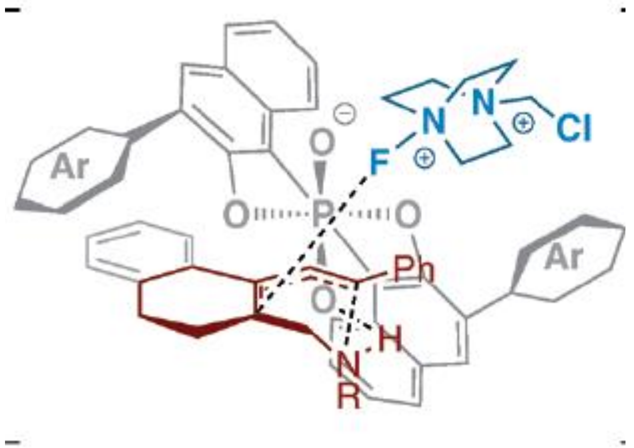
9 examples



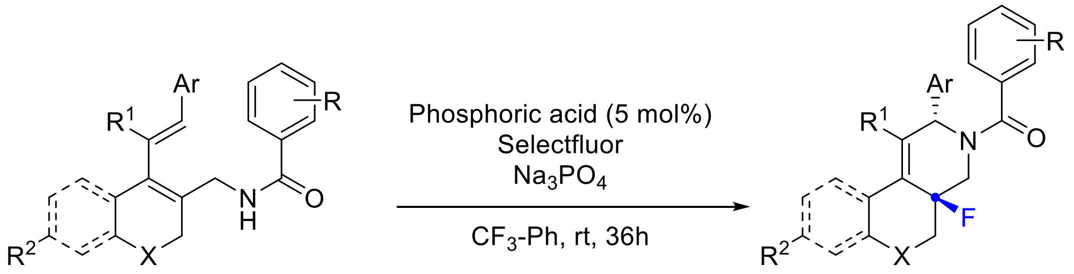

**Phosphoric acid**




Interaction of non-symmetrical phenol with catalyst may allow face-selective fluorinative dearomatization



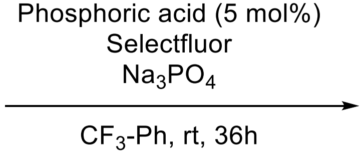

## 4. Fluoroamination: 1,4-Addition to Conjugated Dienes




**E**-isomer

65-97% yield
>5.5:1 dr
73-96% ee

**Z** - isomer



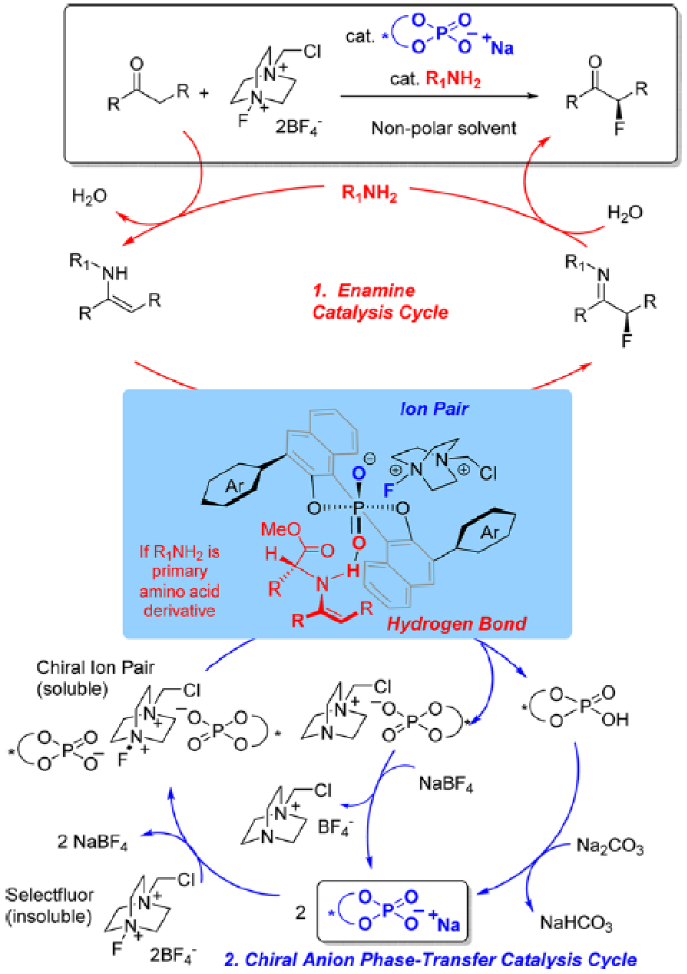

no reaction

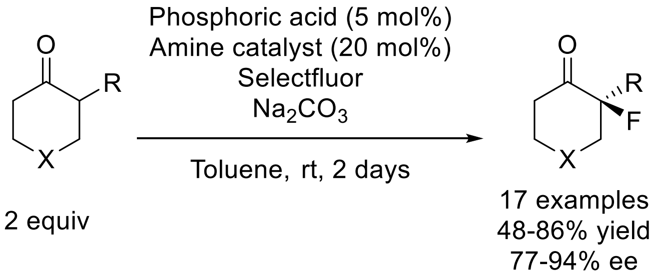
$A^{1,3}$-strain in TS

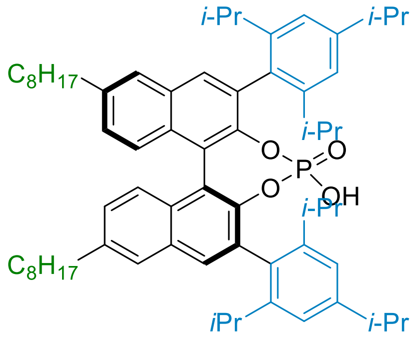
Toste, F.D. *JACS* **2013**, *135*, 1268-1271; *ACIE* **2013**, *52*, 7724-7727

# Anionic Phase-Transfer Catalysis

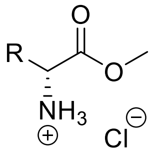
## 5. Fluorination of α-Branched Cyclohexanones Enabled by a Combination of Chiral Anion Phase-Transfer Catalysis and Enamine Catalysis



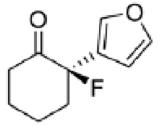



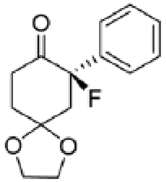
Phosphoric acid



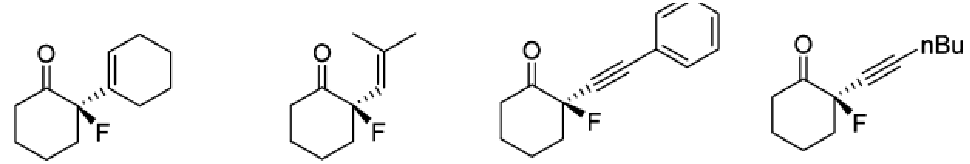
Amino acid catalyst



**2i**, with **A12**
31% (62%) yield,
89% ee



**2k**, with **A13**
32% (63%) yield,
92% ee



**2n**, with **A13**
26% (52%) yield,
86% ee

**2o**, with **A12**
35% (70%) yield,
85% ee

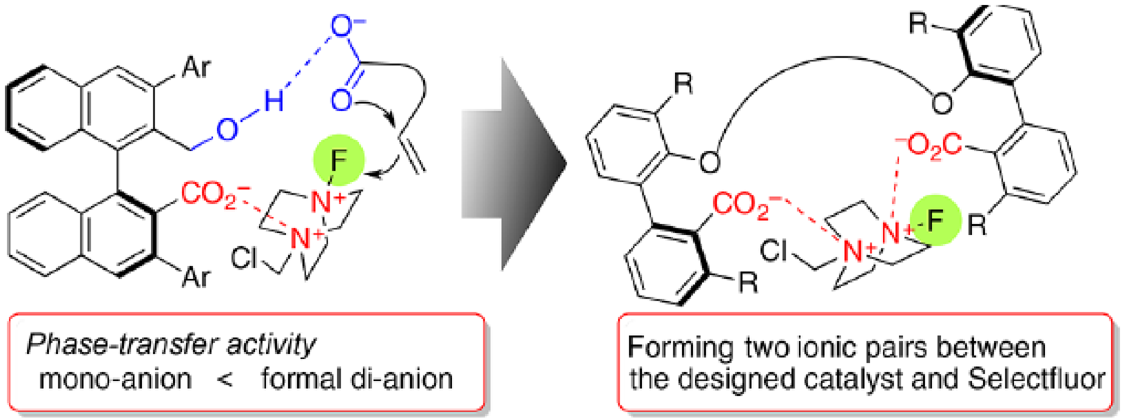
**2p**, with **A12**
43% (86%) yield,
78% ee

**2q**, with **A12**
39% (77%) yield,
77% ee

Toste, F.D. *JACS* **2014**, *136*, 5225-5228

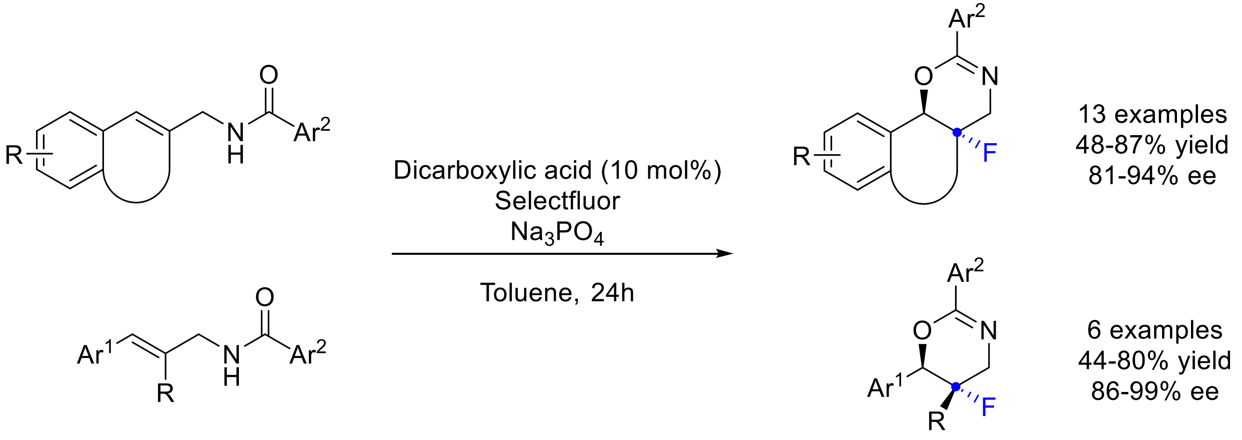
# Anionic Phase-Transfer Catalysis

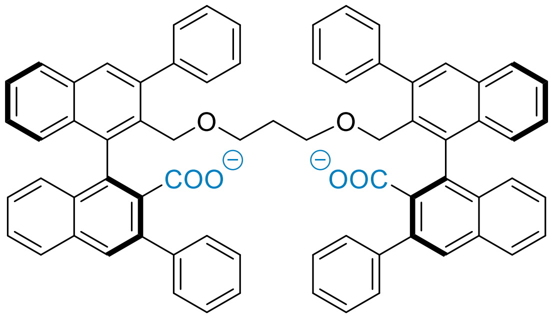
## 6. Fluocyclization with dicarboxylic chiral acids




The designed catalysts are conformationally flexible, but the two-point ionic pairing of the catalyst with Selectfluor would form a well-defined chiral environment.

Enantioselective fluorocyclization of allylic amides



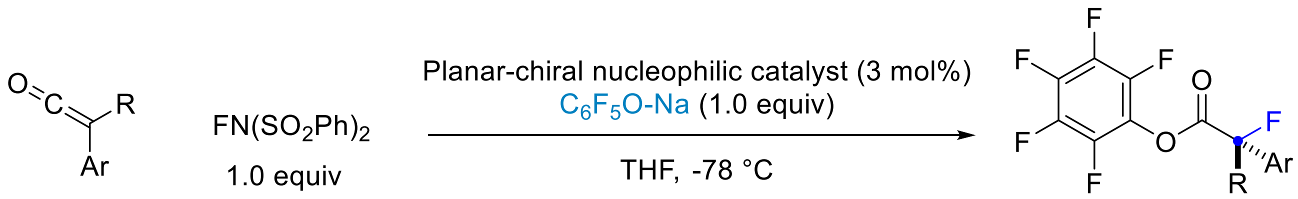



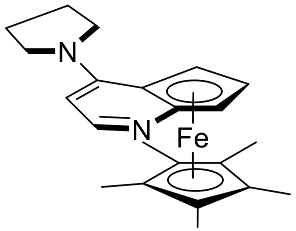

Dicarboxylic acid

Hamashima, Y. *JACS* **2018**, *140*, 2785-2788

# Planar-chiral nucleophilic catalysis

## 1. α-Fluorination of Ketenes



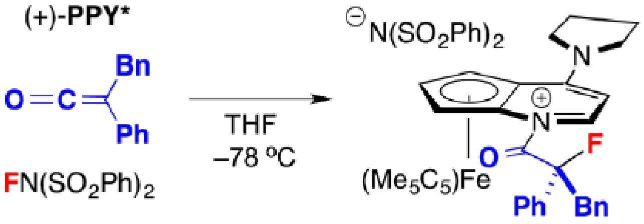




Planar-chiral nucleophilic catalyst
(-)-PPY

11 examples
86-98% yield
78-99% ee

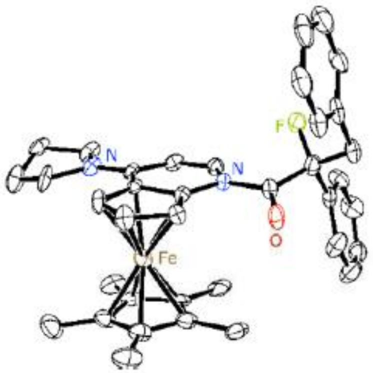
| entry | Ar | R | ee (%) | yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph | Et | 99 | 98 |
| 2 | Ph | Me | 98 | 92 |
| 3 | Ph | *i*-Bu | 95 | 95 |
| 4 | Ph | Bn | 78 | 96 |
| 5[c] | Ph | cyclopentyl | 80 | 84 |
| 6 | 4-ClC$_6$H$_4$ | Et | 97 | 86 |
| 7 | 4-MeC$_6$H$_4$ | Et | 97 | 92 |
| 8 | 4-(OMe)C$_6$H$_4$ | Et | 97 | 91 |
| 9 | 3-MeC$_6$H$_4$ | Et | 97 | 97 |
| 10 | 2-naphthyl | Et | 94 | 89 |
| 11 | 3-thiophenyl | *i*-Bu | 98 | 94 |

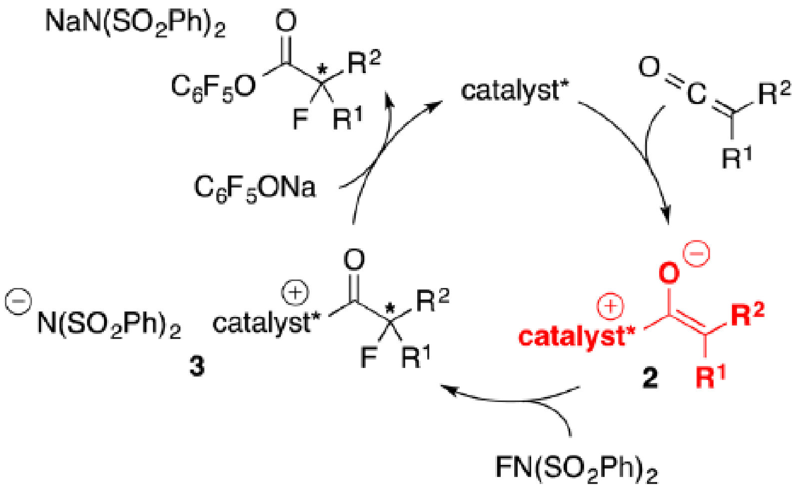
(+)-**PPY***




(+)-**5**
*95% yield*

*N*-acylated intermediate

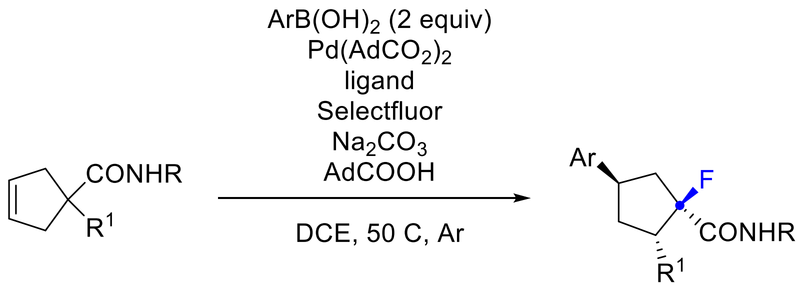




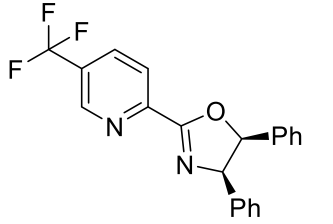

Fu, G.C. *JACS* **2014**, *136*, 8899-8902

# Transition-metal catalyzed transformations

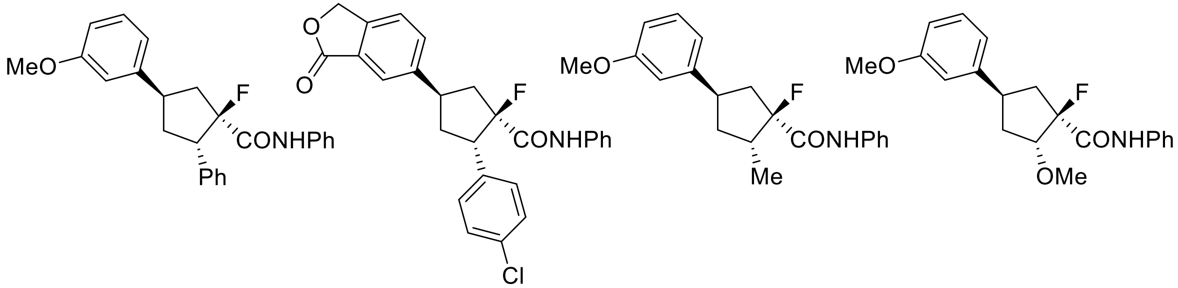
## 1. Dyotropic rearrengement with Pd(IV)



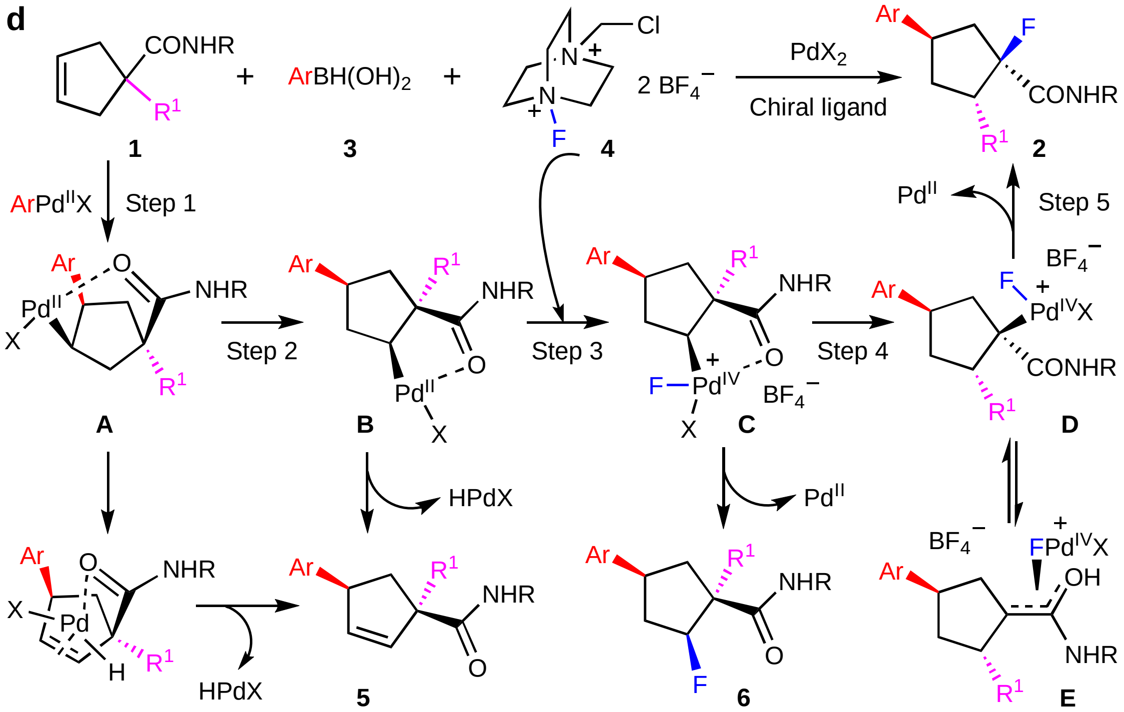

26 examples
27-72% yield
74-95% ee




Ligand




| 70% yield | 51% yield | 27% yield | 26% yield |
|---|---|---|---|
| 92% ee | 89% ee | 95% ee | 80% ee |

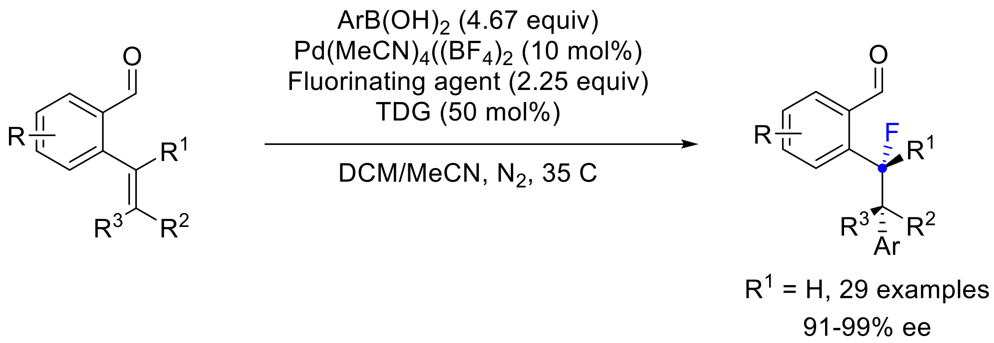


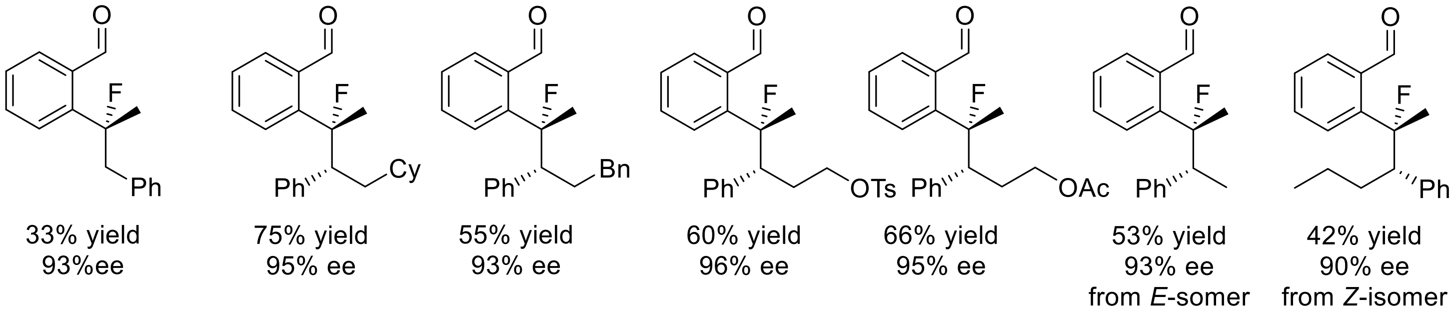

The whole catalytic process would create three stereocentres including one quaternary C–F bond from a prochiral substrate, the whole sequence would be diastereoselective if the initial carbopalladation be effectively directed.

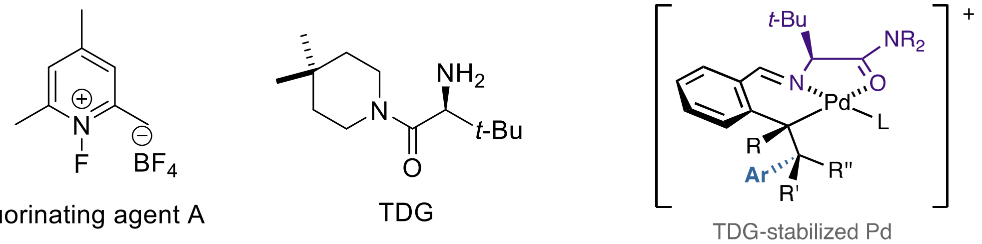
Zhu, J. *Nat.Chem.* **2021**, *13*, 671-676

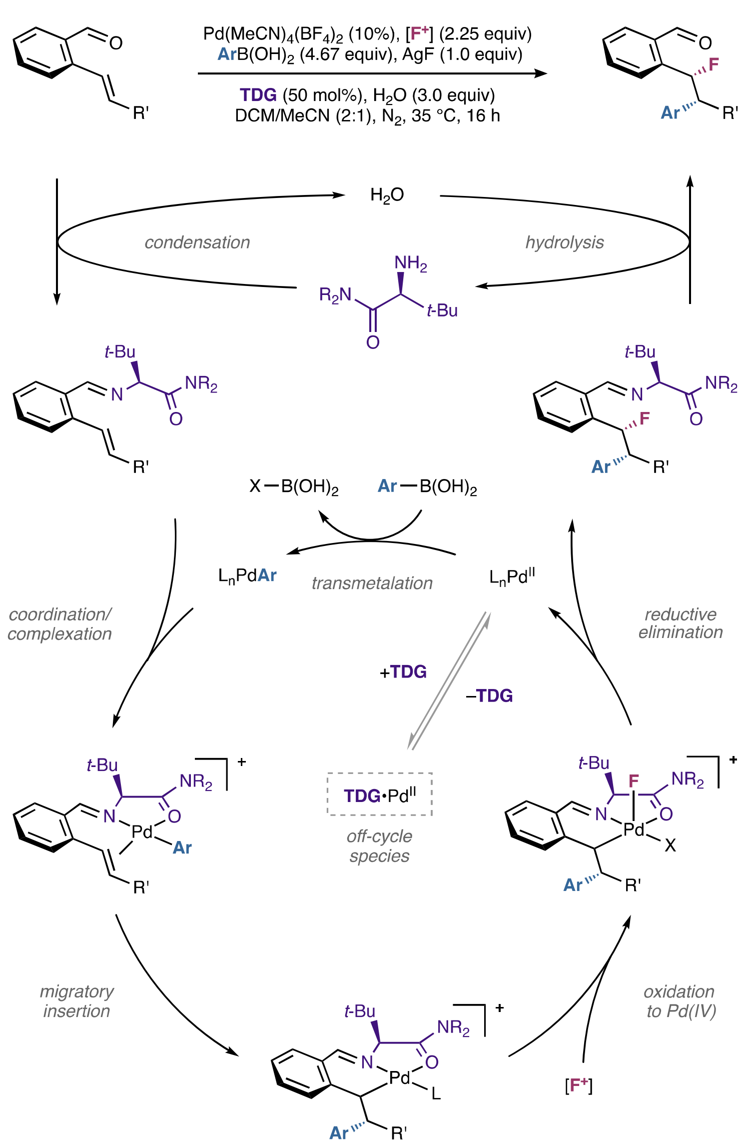
# Transition-metal catalyzed transformations

## 2. Transient directing group arylfluorination



# Conclusion

- Enantioselective formation of carbon-fluorine bond has become a field of great interest, due to the beneficial pharmarcokinetic properties that judiciously placed fluorine atoms can confer.

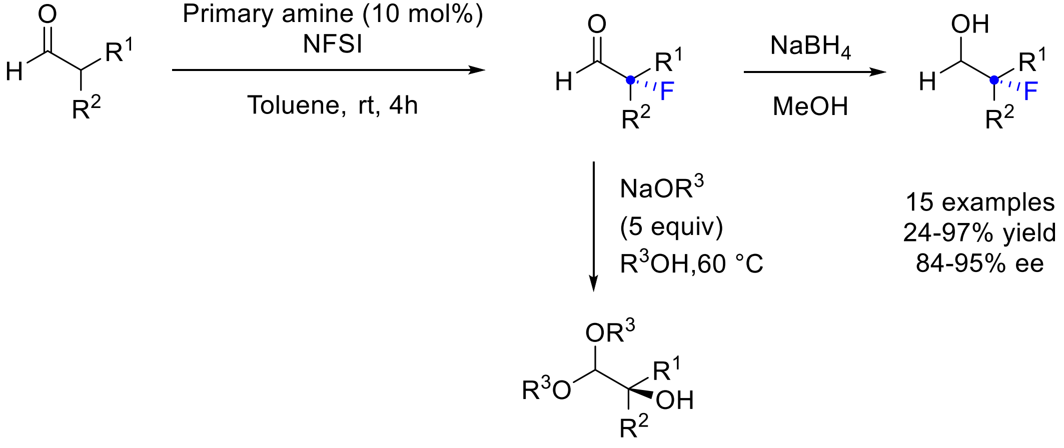
- Even though many methods have been discovered to perform such transformation with high enantioselectivity, still number catalytic transformations are still limited, especcialy in case of formation of quaternary center.

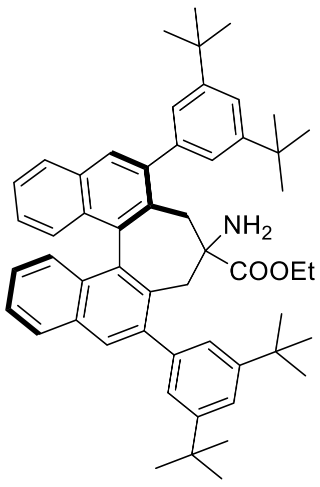
Thank you for your attention

# Primary Amine Catalysis

## 1. α-Fluorinations of Branched Aldehydes

Iwasa




Primary amine

Various α-alkyl-α-aryl aldehydes were successfully fluorinated to afford the corresponding α-fluoroaldehydes in high yields with high ee.

The reaction with α, α-dialkyl aldehydes yielded the products with worse results.