XU LAB
Innovation through Catalysis

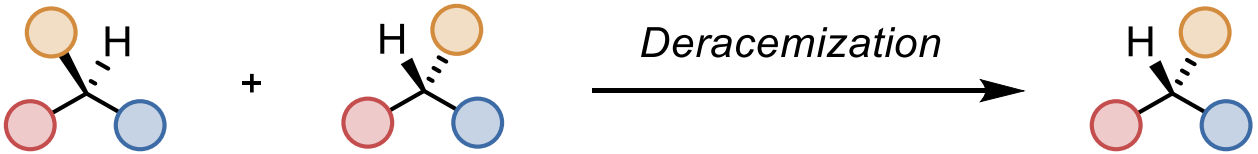
北京大学
PEKING UNIVERSITY

XU GROUP
Department of Chemistry, Peking University

Selected Weekly Literature Presentations

Disclaimer:
These slides contain personal interpretations and may include errors or subjective views.

Deracemization reaction in organic synthesis



Reporter: Ken Chen (陈垦)
Supervisor: Yan Xu (许言)
2023.03.17

Content

- Introduction of cyclic deracemization
- Deracemization by chemical methods
- Enzyme catalyzed deracemization
- Light-enpowered deracemization

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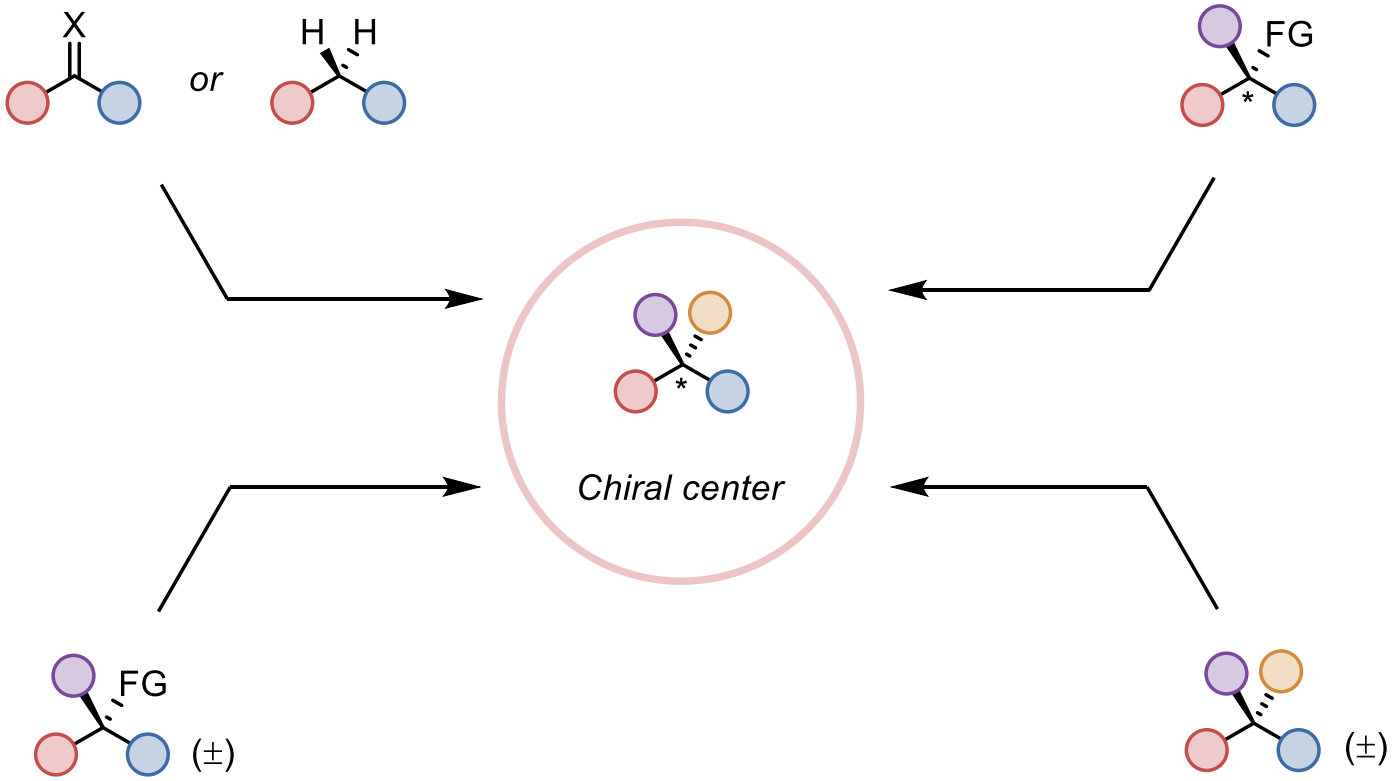
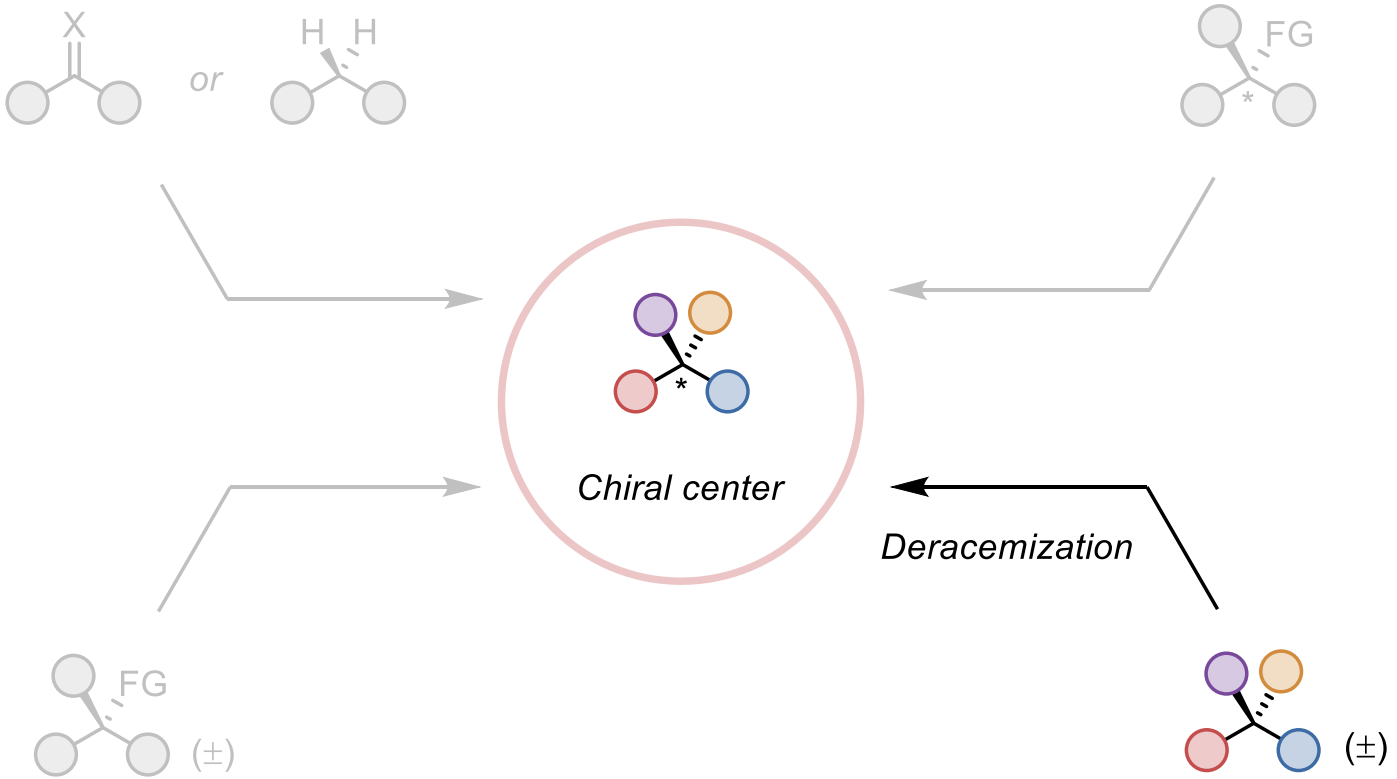
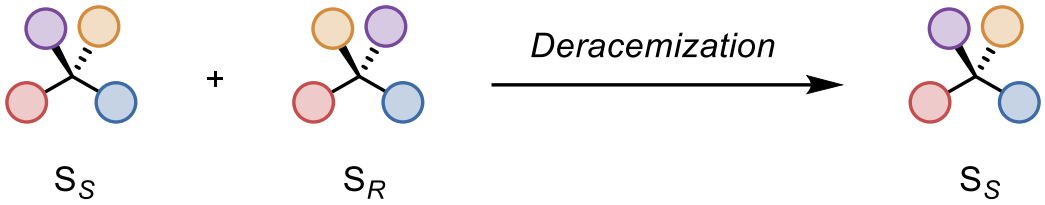
Forming a chiral center

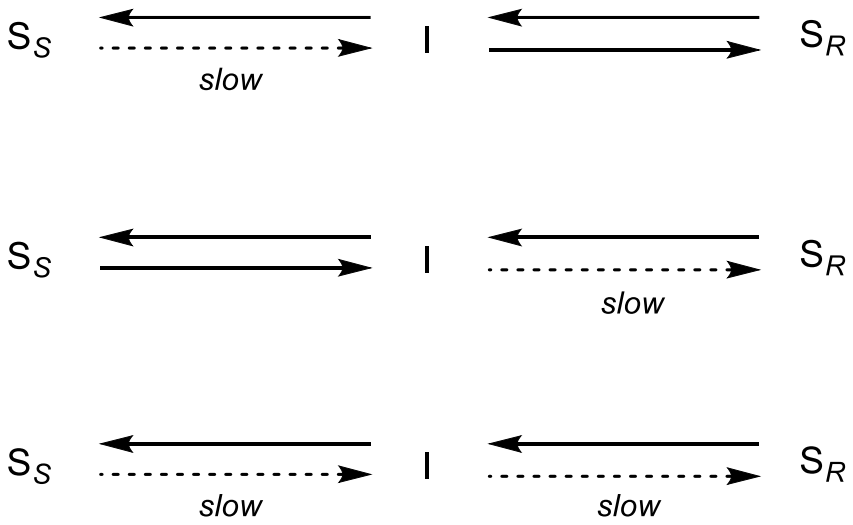


Deracemization



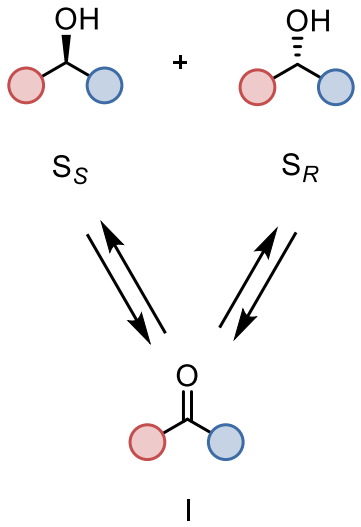
Deracemization modes





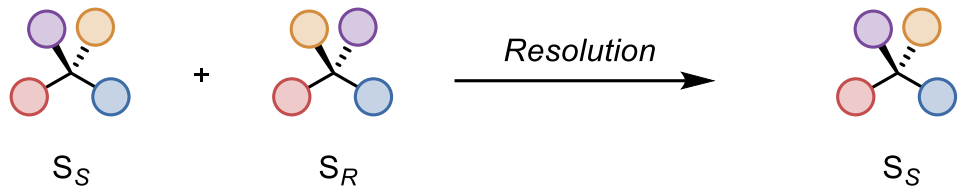
- *Find an intermediate*
- *Construct two converse processes*

For example:

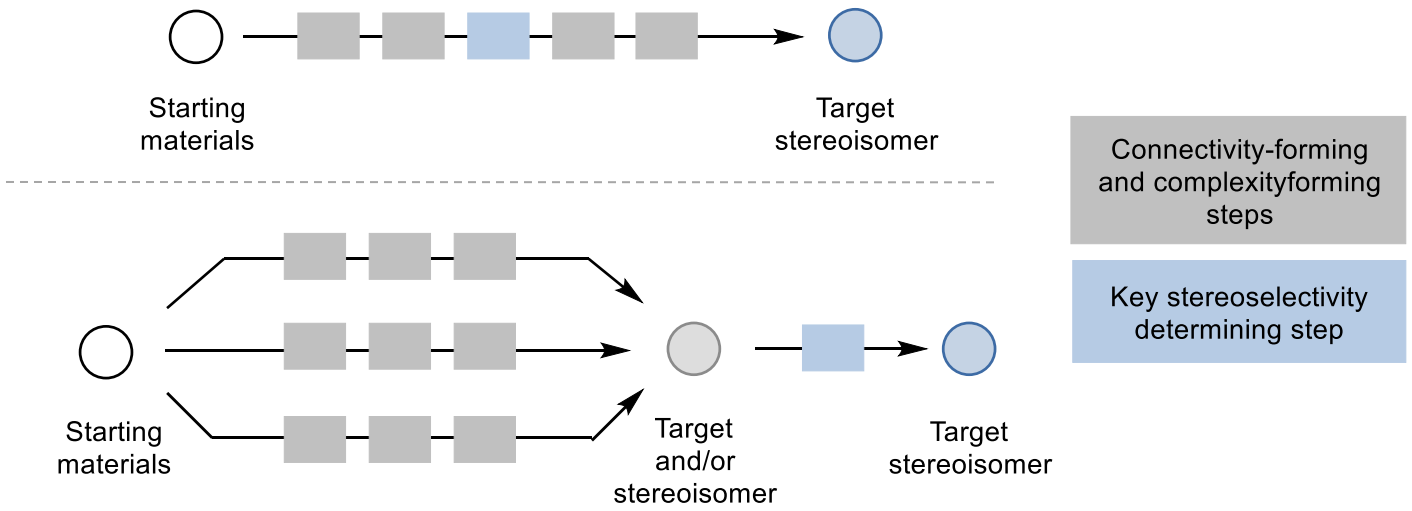


Advantages of deracemization

- *100% theoretical yield*

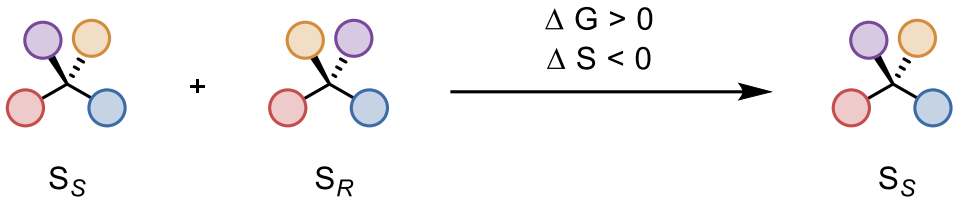


- *Stereochemical editing at late stage*



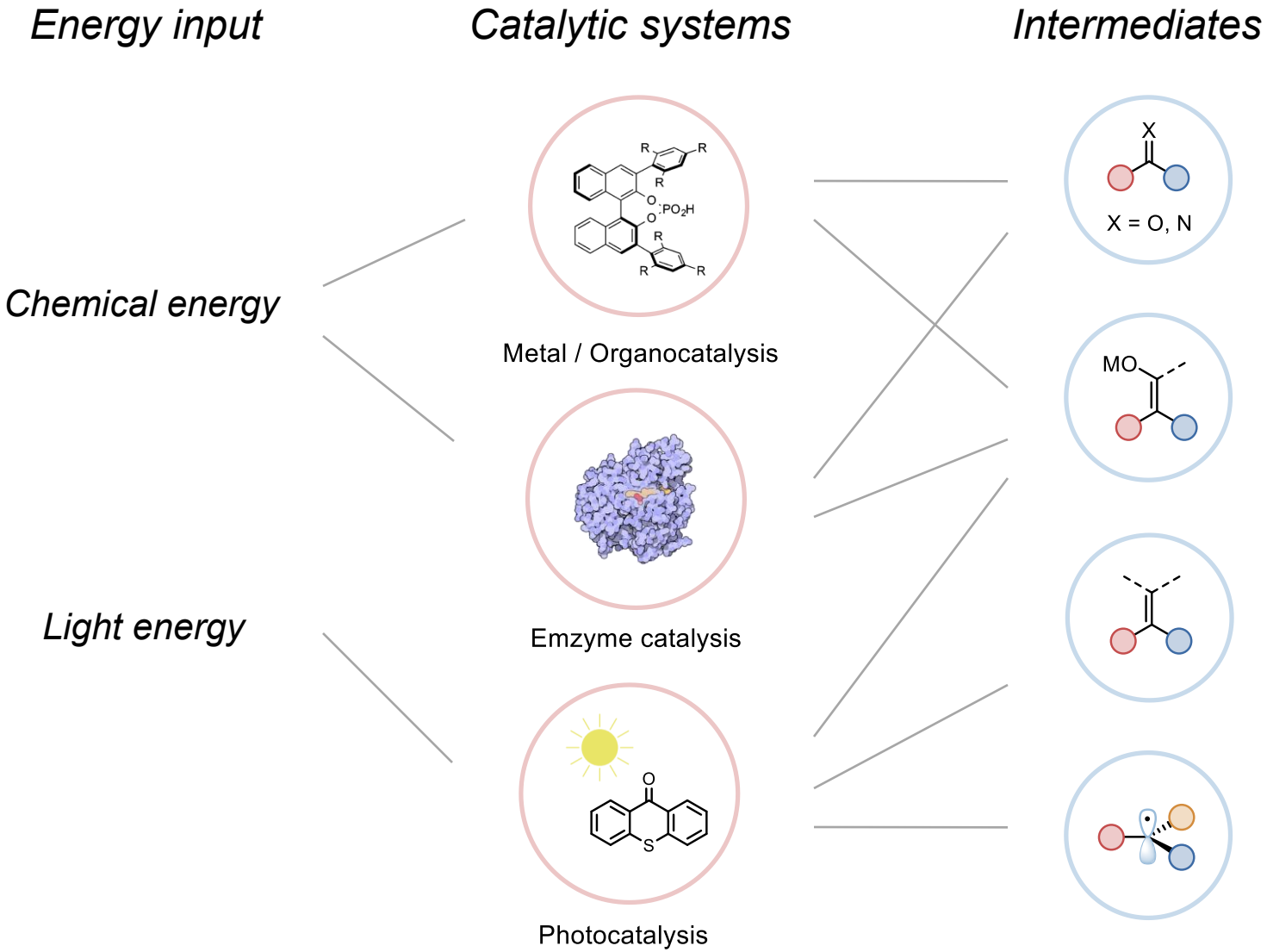
Challenges of deracemization

- *Require energy input*



- *'Two processes in one pot'*

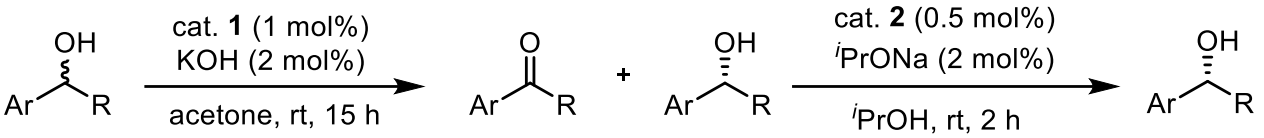
Deracemization

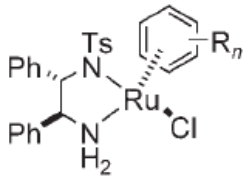


Content

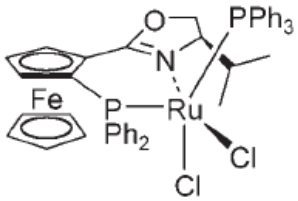
- Introduction of cyclic deracemization
- Deracemization by chemical methods
- Enzyme catalyzed deracemization
- Light-enpowered deracemization

Deracemization of alcohol in two steps





cat. **1**, [RuCl{(*S*,*S*)-tsdpen}(η^6-mesitylene)]

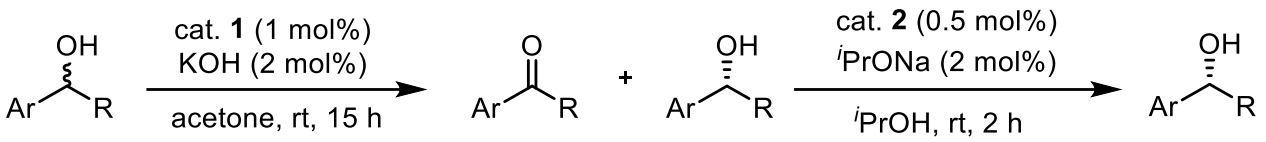


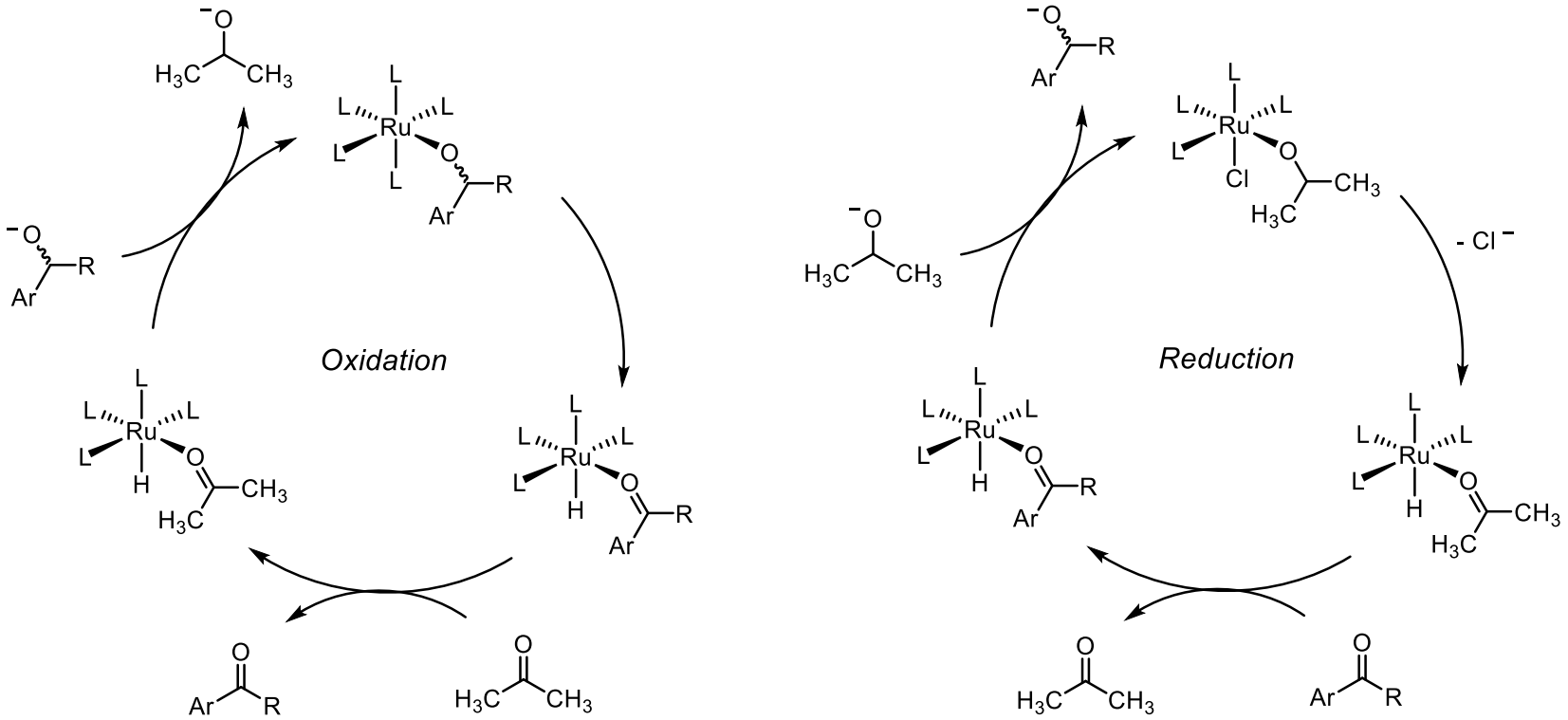
cat. **2**, [$RuCl_2(PPh_3)$(ip-FOXAP)]

Entry	Ar	R	Recovery of **3** [%][b]	*ee* of **3** [%][c,d]
1	Ph	Me	90 (**3a**)	94 (*R*)
2	4-MeC_6H_4	Me	92 (**3b**)	92 (*R*)
3	4-FC_6H_4	Me	82 (**3c**)	90 (*R*)
4	4-ClC_6H_4	Me	99 (**3d**)	89 (*R*)
5	4-BrC_6H_4	Me	99 (**3e**)	92 (*R*)
6[e]	4-PhC_6H_4	Me	99 (**3f**)	93 (*R*)
7[f]	3-MeC_6H_4	Me	81 (**3g**)	91 (*R*)
8	2-MeC_6H_4	Me	93 (**3h**)	2 (*R*)
9[e]	Ph	Et	88 (**3i**)	95 (*R*)
10	Ph	Et	>95 (**3i**)	88 (*R*)
11[e]	Ph	*n*Pr	85 (**3j**)	90 (*R*)
12	Ph	*n*Pr	96 (**3j**)	81 (*R*)
13[e]	Ph	*n*Bu	86 (**3k**)	94 (*R*)
14	Ph	*n*Bu	>95 (**3k**)	85 (*R*)

Nishibayashi, Y. *et al. Chem. − Asian J.* **2007**, *2*, 393−396.

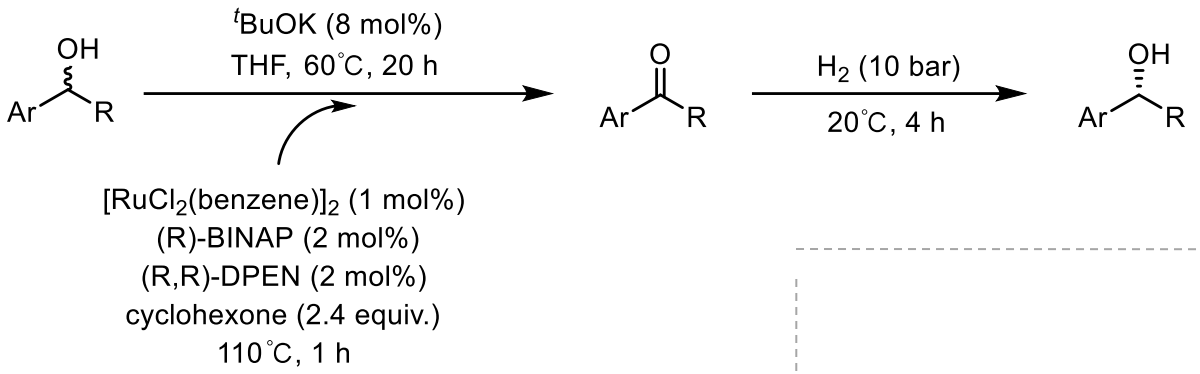
Deracemization of alcohol in two steps



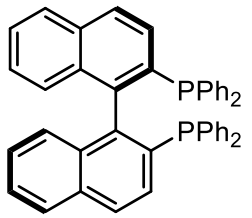


Nishibayashi, Y. *et al. Chem. − Asian J.* **2007**, *2*, 393−396.

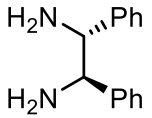
Deracemization of alcohol in two steps



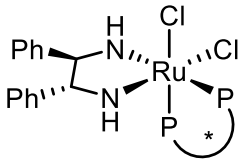
Alcohol	Ar	R	Yield[a] (%)	ee (%)
4	C_6H_5	C_2H_5	87	83
5[b]	C_6H_5	C_3H_7	82	87
6	C_6H_5	C_4H_9	92	86
7	2-Naphthyl	C_5H_{11}	95	82
8	*m*-MeC_6H_4	C_5H_{11}	97	90
9	*p*-$MeOC_6H_4$	CH_3	89	79
10	*p*-$MeOC_6H_4$	C_5H_{11}	94	88
11	*m*-ClC_6H_4	C_5H_{11}	26	57
12	*p*-$Me_2NC_6H_4$	C_5H_{11}	96	92



(*R*)-BINAP



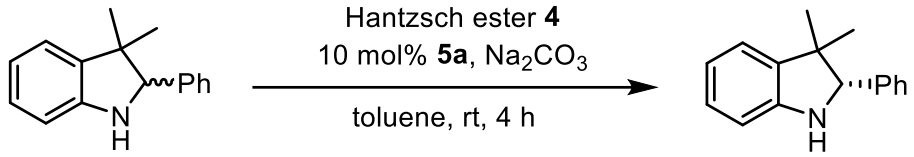
(*R,R*)-DPEN

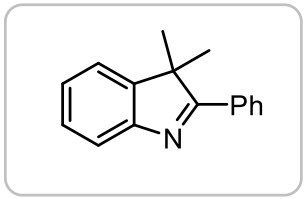


$RuCl_2$[(*R*)-BINAP][(*R,R*)-DPEN]

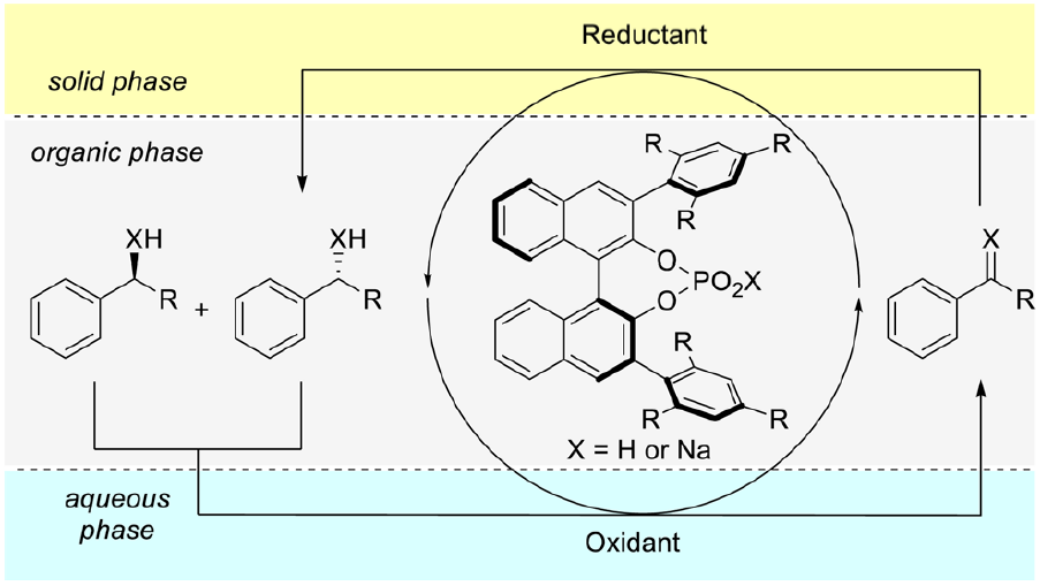
Williams, J. M. J. *et al. Chem. Commun*. **2007**, 2608−2609.

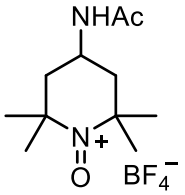
Deracemization of 3H-Indolines in one pot



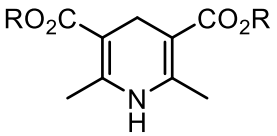


Intermediate

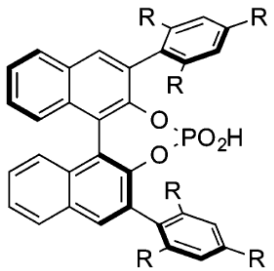




oxopiperidinium **3**



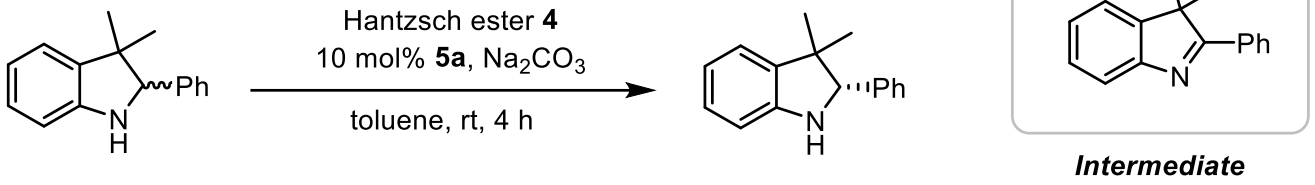
Hantzsch ester **4**
R = 2,6-Cl_2Bn



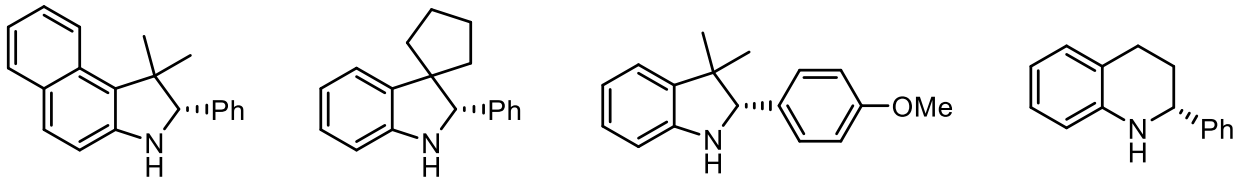
5a
R = Cy

Toste, F. D. *et al. J. Am. Chem. Soc*. **2013**, *135*, 14090−14093.

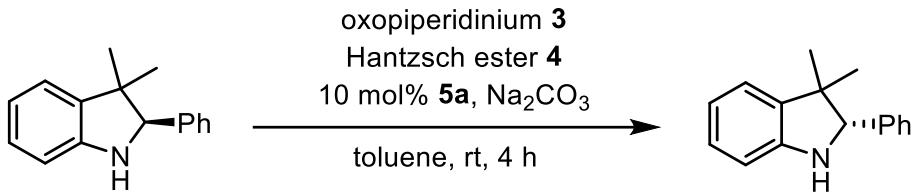
Deracemization of 3H-Indolines in one pot



Intermediate

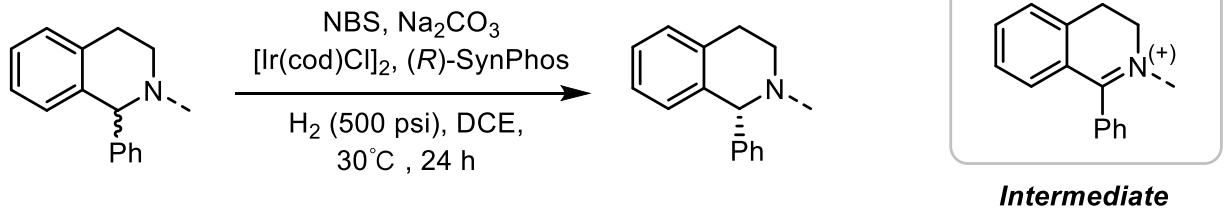


92%, 93% ee | 89%, 93% ee | 82%, 88% ee | 95%, 92% ee

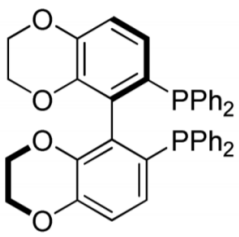


Toste, F. D. *et al. J. Am. Chem. Soc*. **2013**, *135*, 14090−14093.

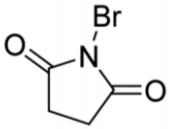
Deracemization of tetrahydroisoquinoline



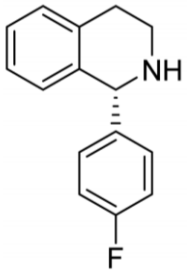
Intermediate



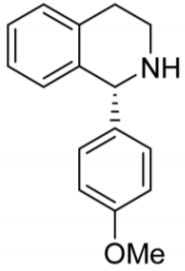
(*R*)-SynPhos



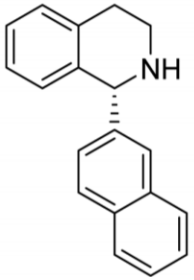
NBS



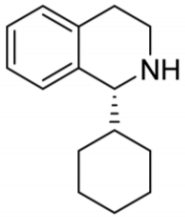
90%, 98% ee



91%, 88% ee



94%, 98% ee

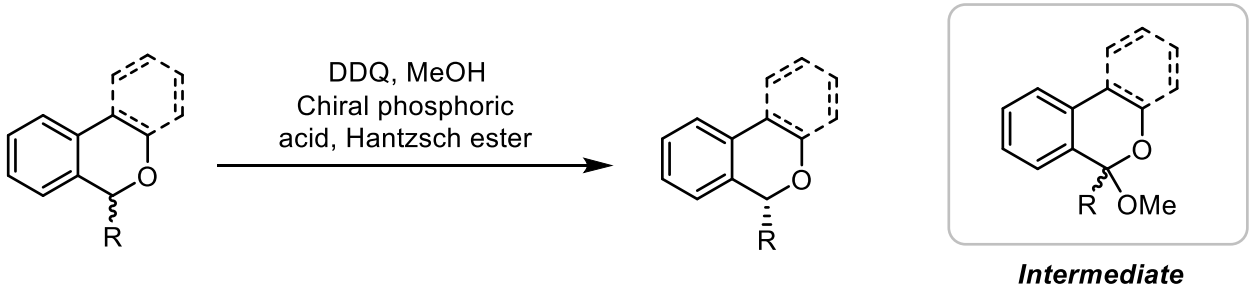


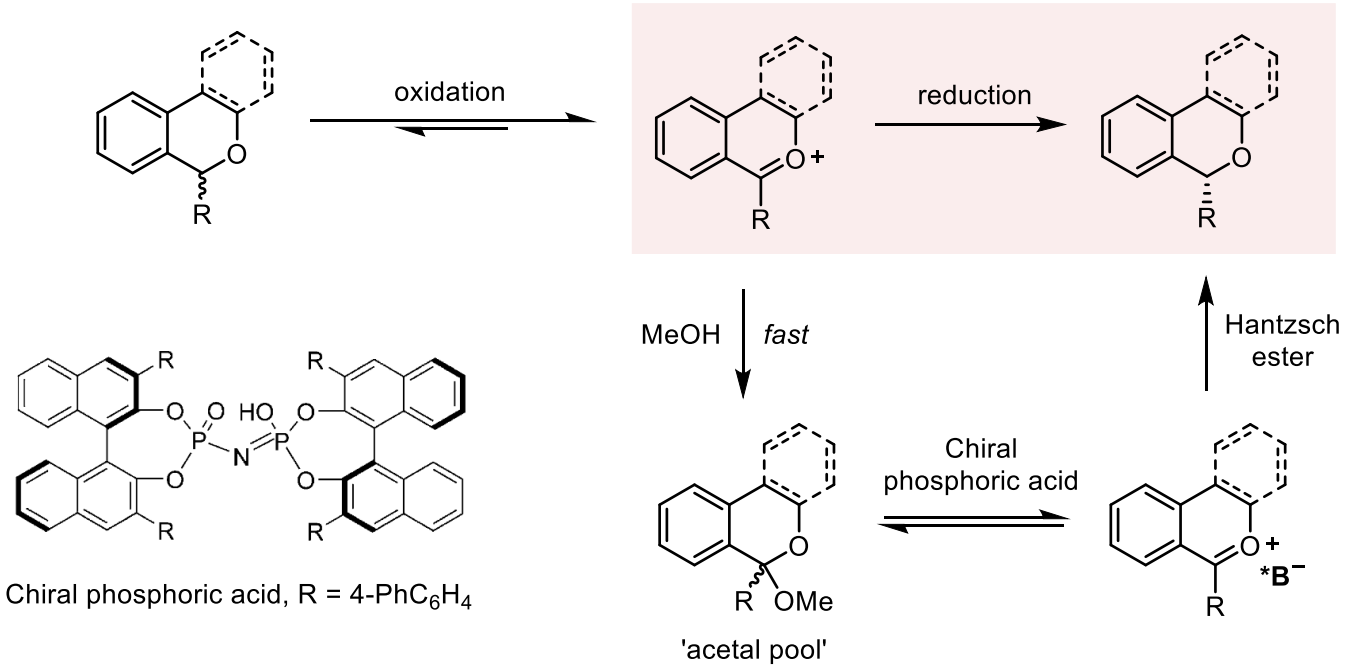
87%, 92% ee

88%, 95% ee

Zhou, Y. -G. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10496−10499.

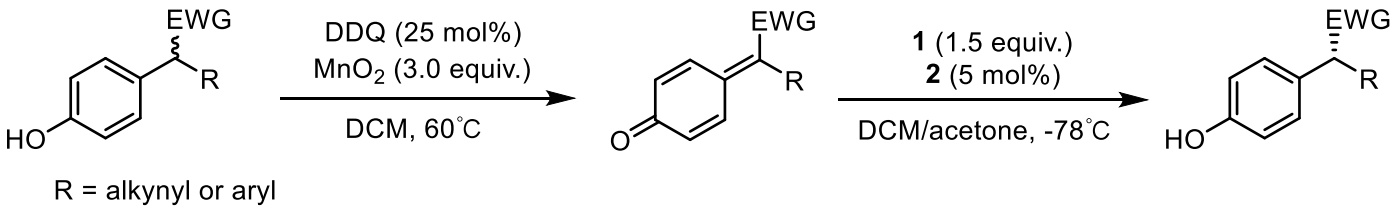
Deracemization of cyclic benzylic ethers



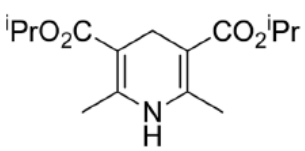


Liu, L. *et al. Angew. Chem. Int. Ed*. **2017**, *56*, 5116−5120.

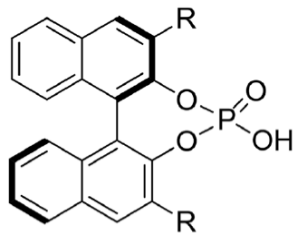
Deracemization via semiquinone intermediate



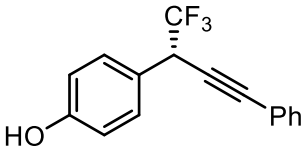
R = alkynyl or aryl



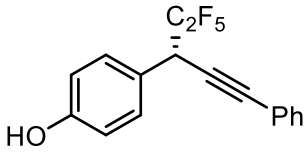
1



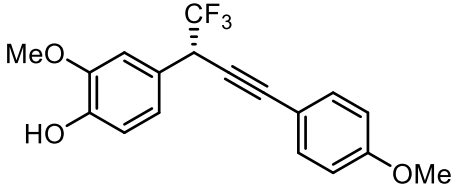
2, R = 2,4,6-$Cy_3C_6H_2$



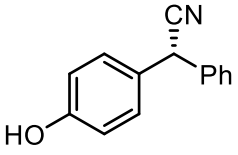
83%, 95% ee



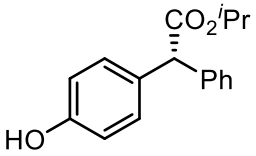
80%, 97% ee



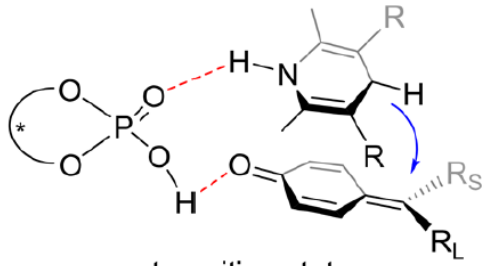
77%, 83% ee



90%, 99% ee



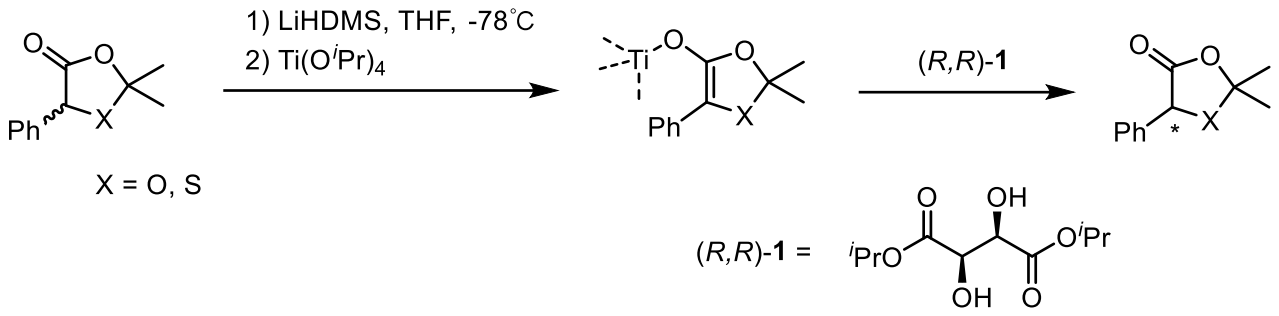
80%, 81% ee



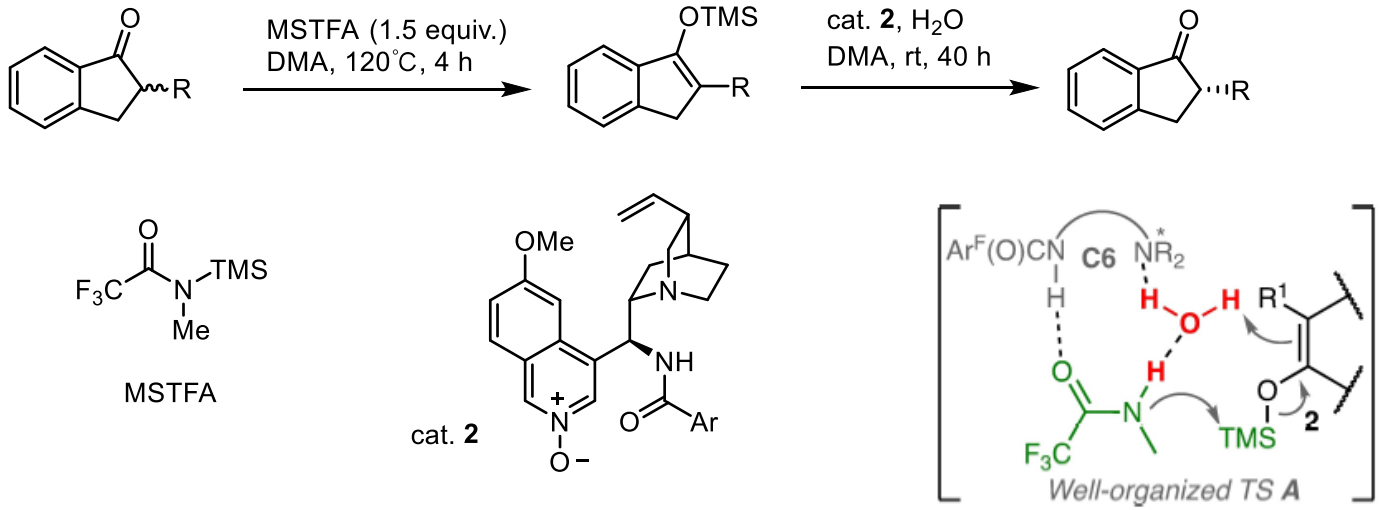
transition state

Liu, L. *et al. ACS Catal.* **2020**, *10,* 7785−7791.

Deracemization by acid and base reaction



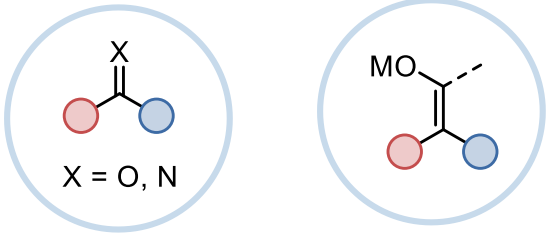
Hünig, S. *et al. Chem. Ber.* **1994**, *127*, 1981–1988.



Oudeyer, S. *et al. Adv. Synth. Catal.* **2022**, *364*, 3794–3799.

Summary

- Chemical method
  - Common intermediate



  - Common process
    - Redox
    - Proton transfer

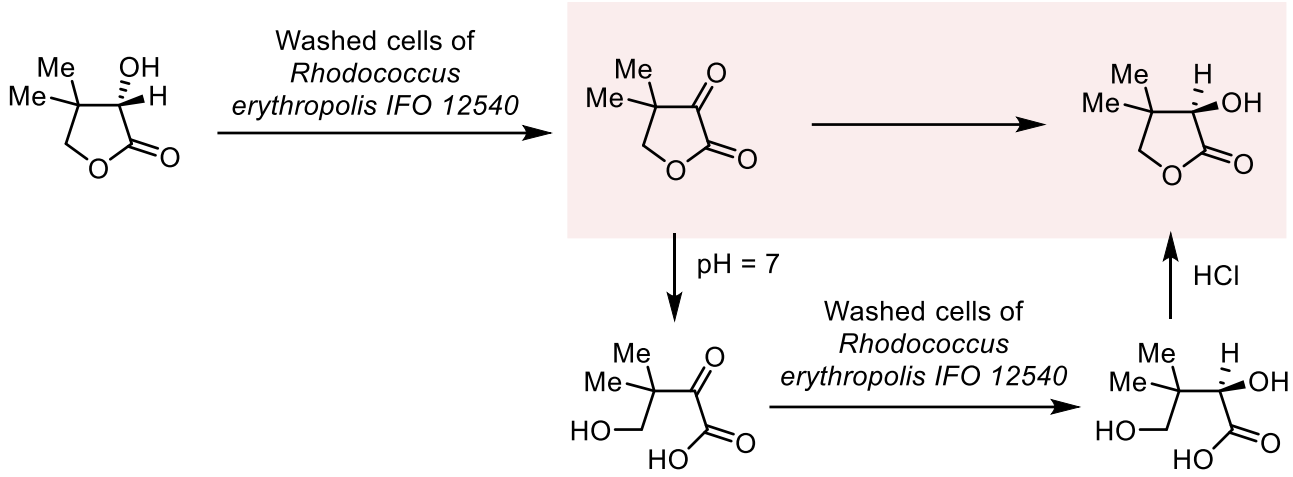
- Energy input
  - Chemical energy
- Stereocontrol
  - Chiral ligands
  - CPA
- Two converse processes need to be compatible in one pot

Content

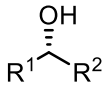
- Introduction of cyclic deracemization
- Deracemization by chemical methods
- Enzyme catalyzed deracemization
- Light-enpowered deracemization

Deracemization by washed cell

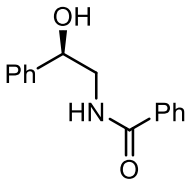
- *First work:*



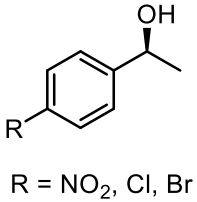
- *Examples (using washed cells):*



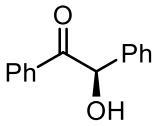
Sphingomonas paucimobilis



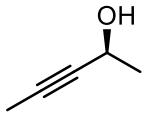
Cunninghamella echinulata



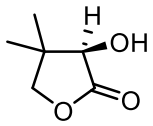
Aspergillus terreus CCT 3320 and CCT 4083



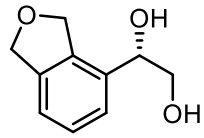
Rhizopus oryzae



Nocardia pseudosporangifera



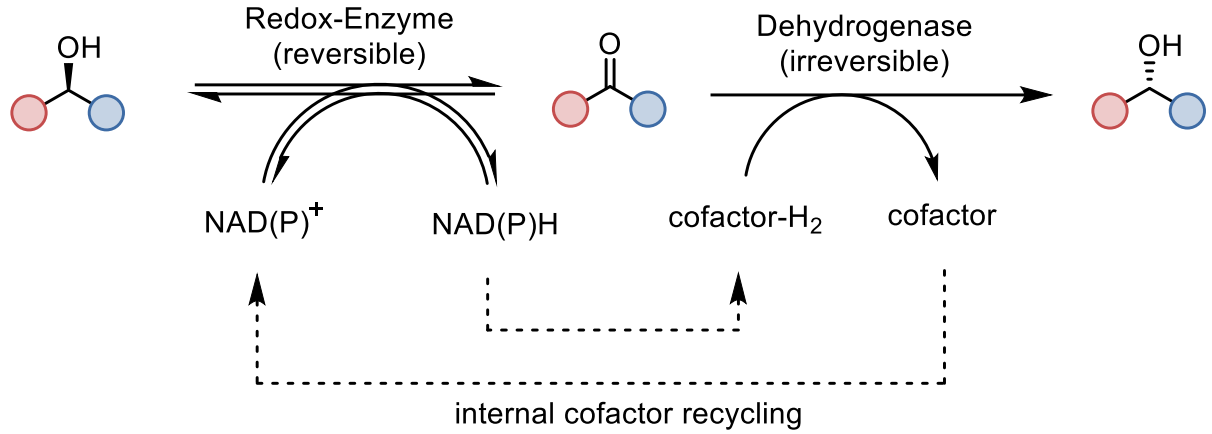
Rhodococcus erythropolis

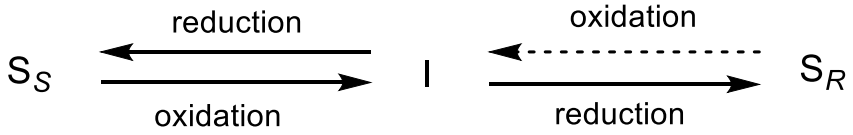


andida boidinii Pichia methanolicaHansenula polymorpha

Yamada, H. *et al. Appl. Environ. Microbiol*. **1987**, *53*, 519–522.
Kroutil, W *et al. Adv. Synth. Catal*. **2006**, *348*, 1789–1805.

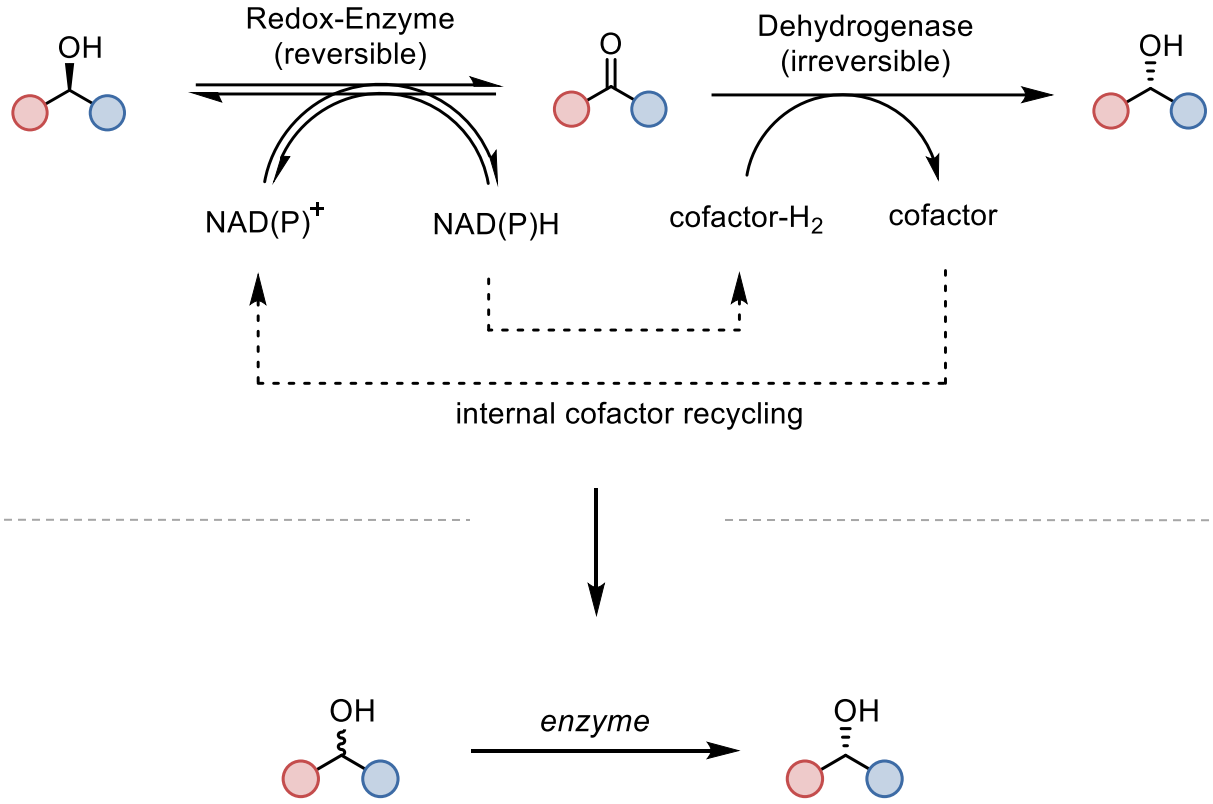
Catalytic mechanism of washed cell





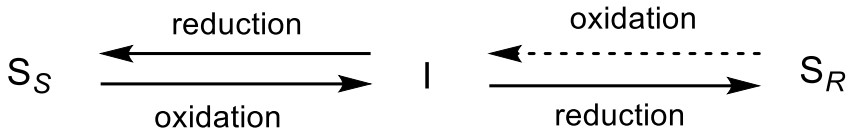
Kroutil, W *et al. Adv. Synth. Catal*. **2006**, *348*, 1789–1805.

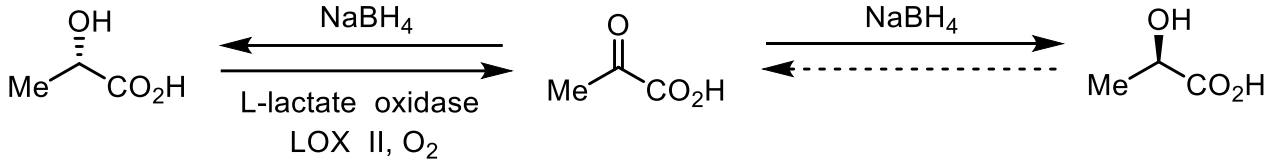
Catalytic mechanism of washed cell

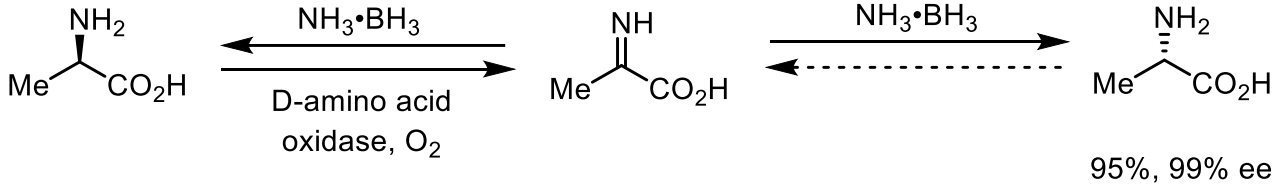


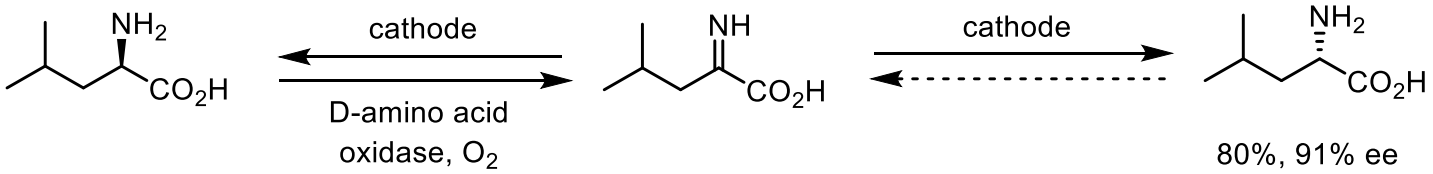
Kroutil, W. *et al. Adv. Synth. Catal*. **2006**, *348*, 1789–1805.

Deracemization by enzyme



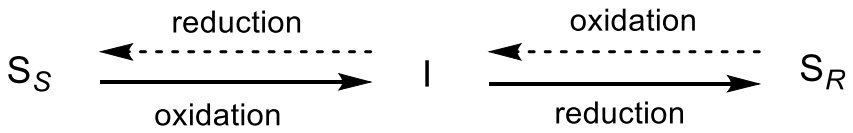


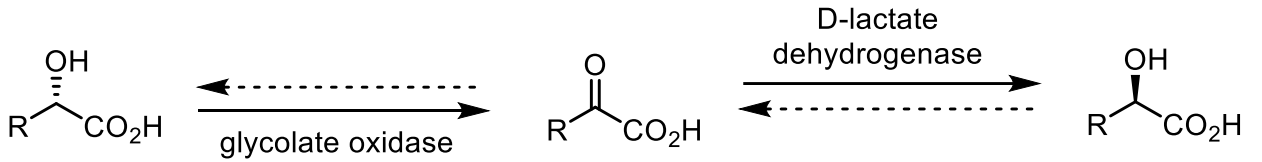




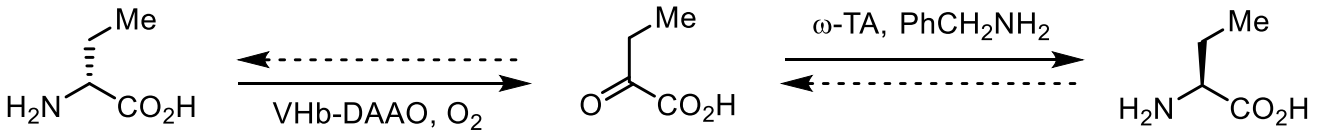
Soda, K. *et al. Biotechnol. Bioeng*. **2001**, *73*, 80–82.
Turner, N. J. *et al. Biochem. Soc. Trans*. **2006**, *34*, 287–290.
Lütz, S. *et al. Electrochim. Acta.* **2008**, *53*, 3175–3180.

Deracemization by enzyme





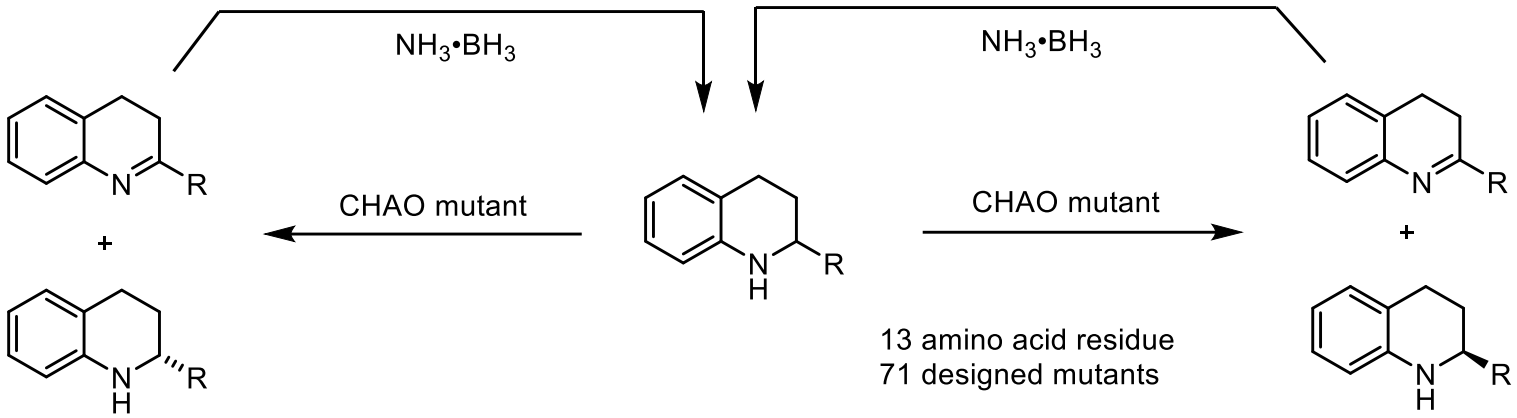
67% - 99% ee

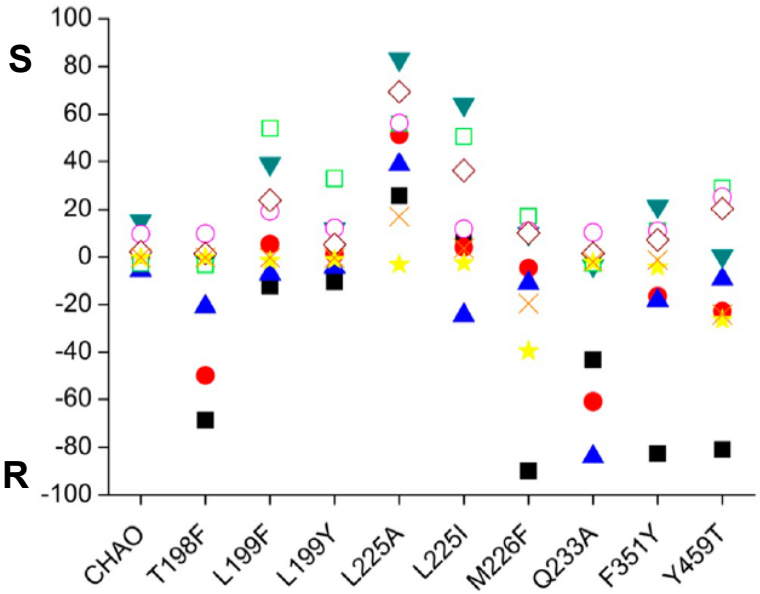


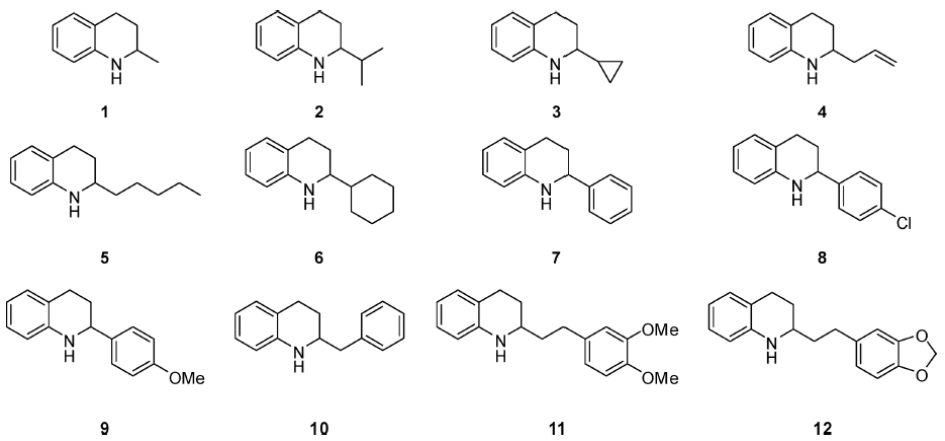
99% conversion,
>99% ee, 8 h

Schreier, P. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 351–355.
Patel, R. N. *et al. Org. Process Res. Dev*. **2011**, *2*, 241.

Optimized by mutants



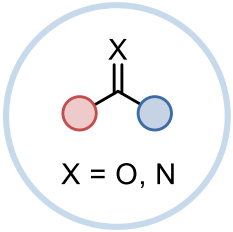




Zhu, D. *et al. ACS Catal.* **2018**, *8*, 1648−1652.

Summary

- Enzyme catalysis
  - Common intermediate



  - Common process
    - Redox

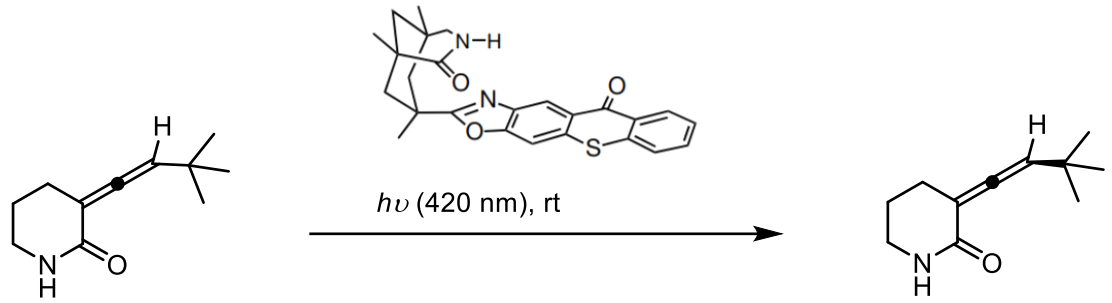
- Energy input
  - Chemical energy

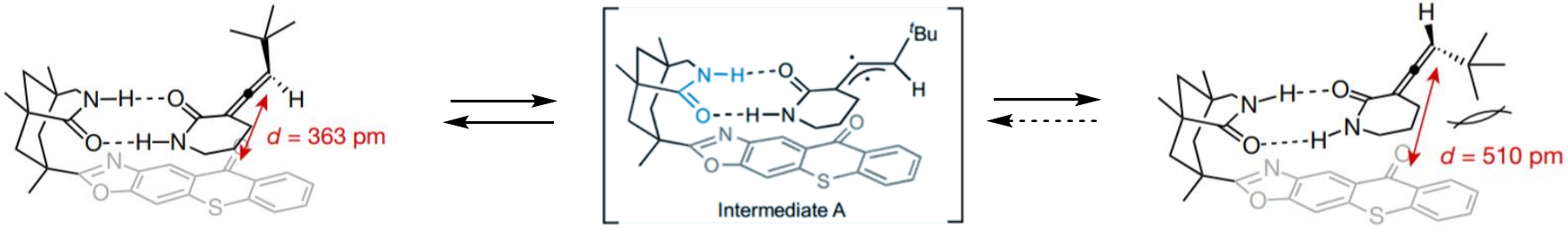
- Washed cell
- Natural enzyme
- Enzyme mutants

Content

- Introduction of cyclic deracemization
- Deracemization by chemical methods
- Enzyme catalyzed deracemization
- Light-enpowered deracemization

Deracemization of chiral allenes

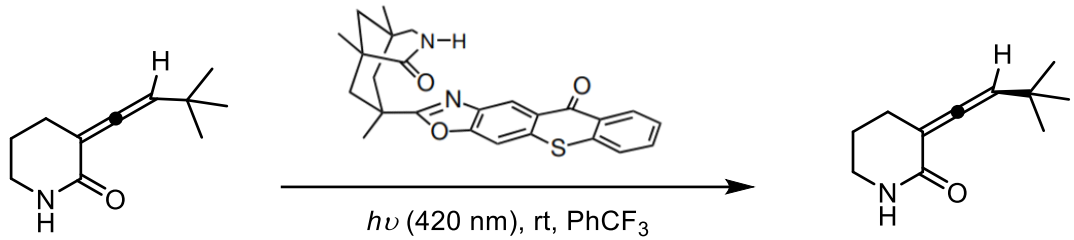


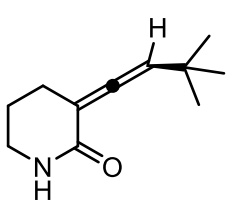


- Low association constants
- Low sensitization efficiencies

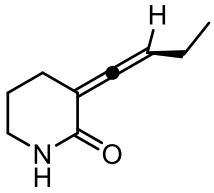
Bach, T. *et al. Nature* **2018**, *564*, 240–243.

Deracemization of chiral allenes

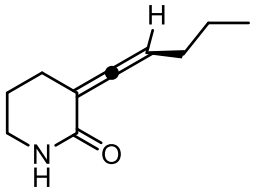




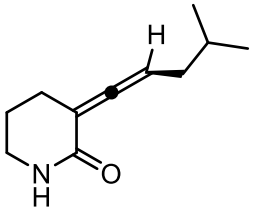
89%, 96% ee



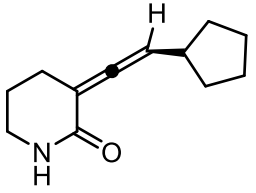
100%, 93% ee



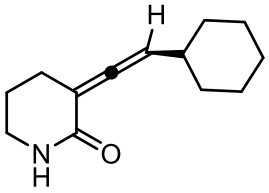
84%, 92% ee



98%, 91% ee

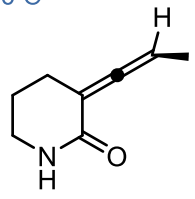


100%, 93% ee

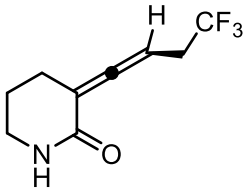


76%, 94% ee

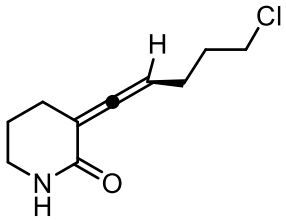
- 40°C



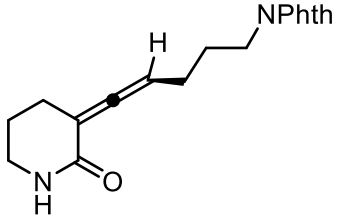
56%, 90% ee



92%, 86% ee



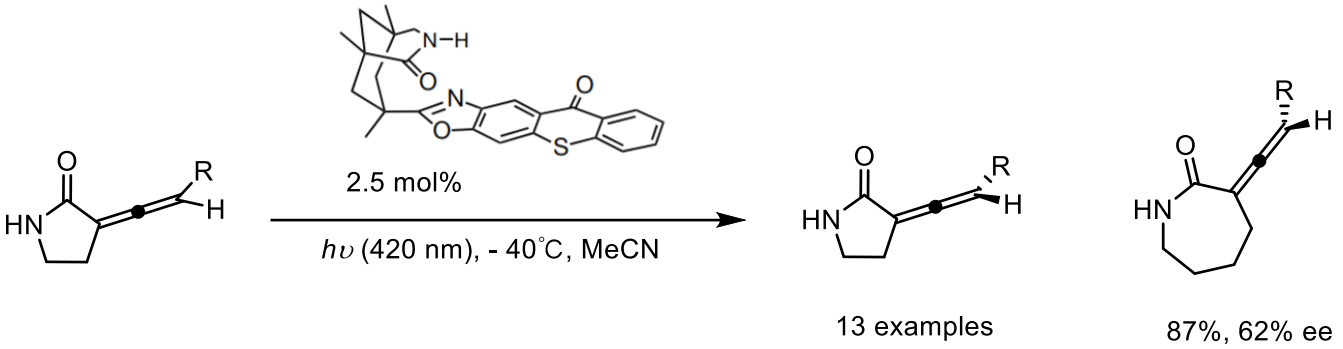
87%, 92% ee

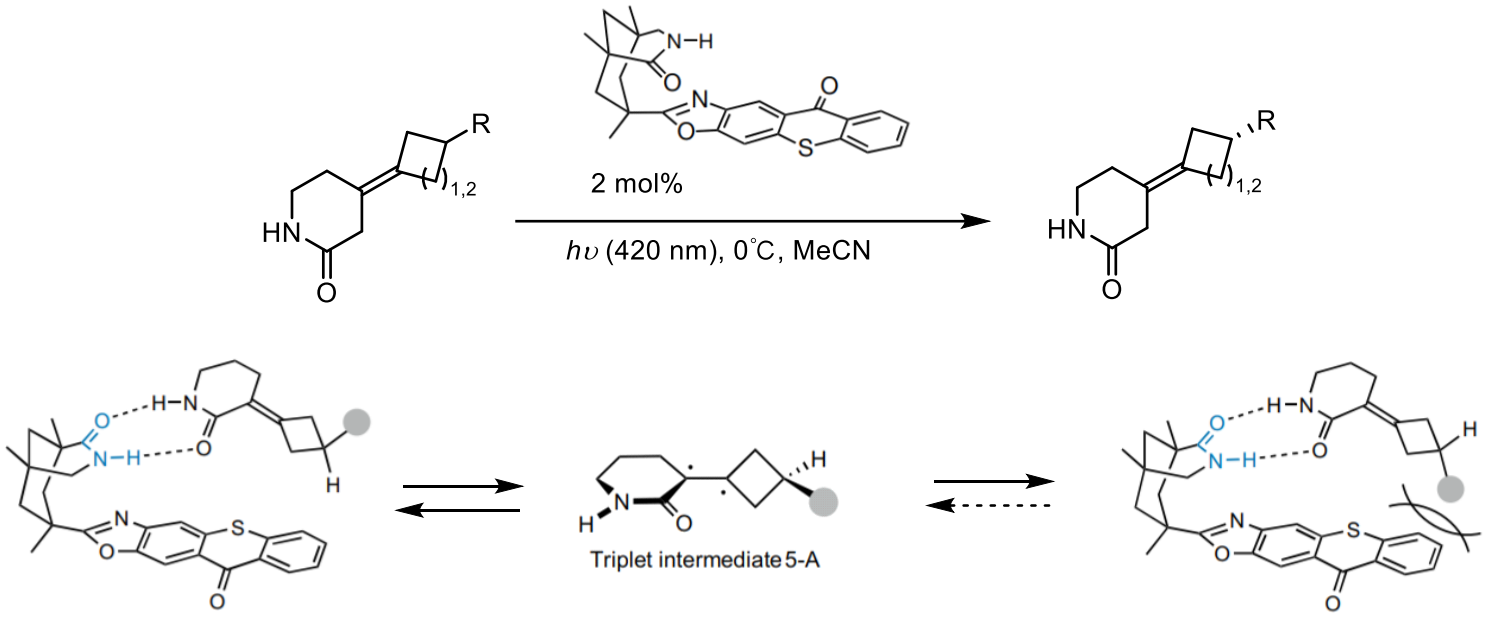


72%, 90% ee

Bach, T. *et al. Nature* **2018**, *564*, 240–243.

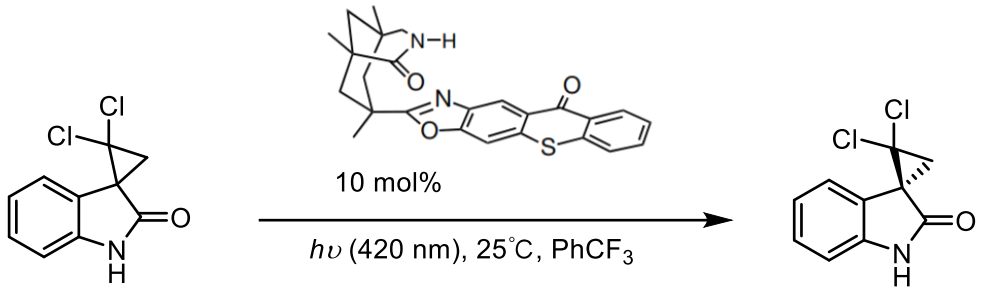
Deracemization of Chiral Alkenes

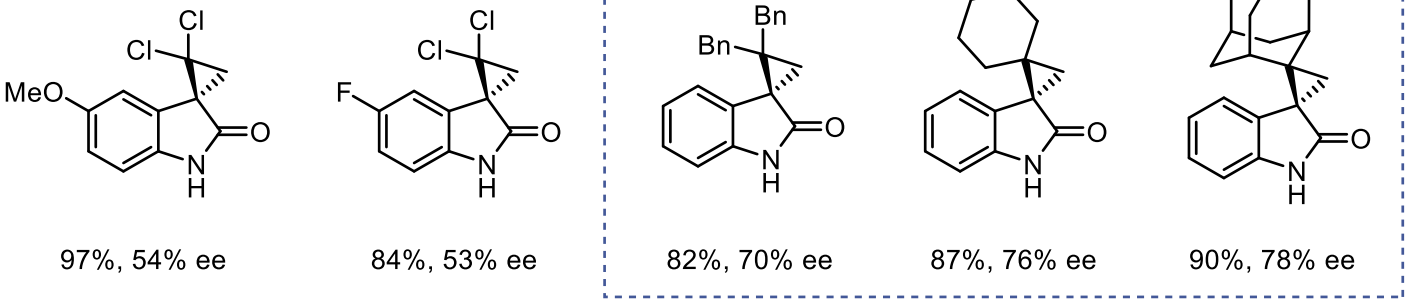


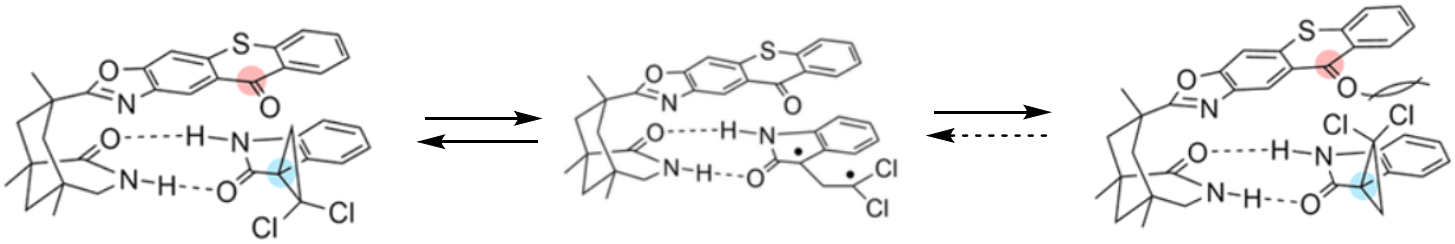


Bach, T. *et al. Angew. Chem. Int. Ed.* **2020**, *59*, 12785–12788.
Bach, T. *et al. J. Am. Chem. Soc.* **2022**, *144*, 10133–10138.

Deracemization of Spirocyclopropyl

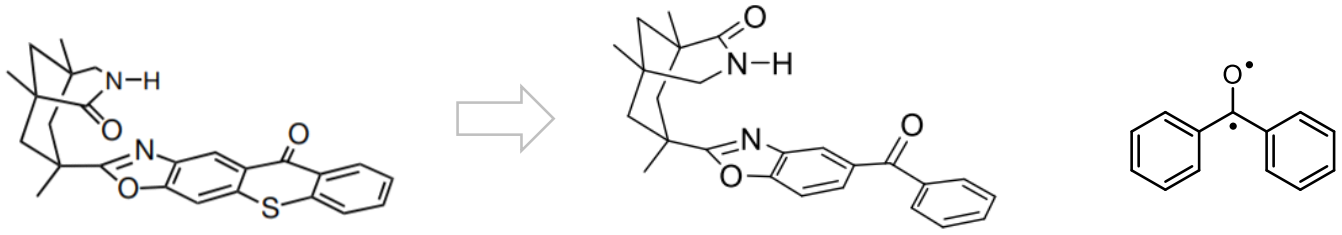






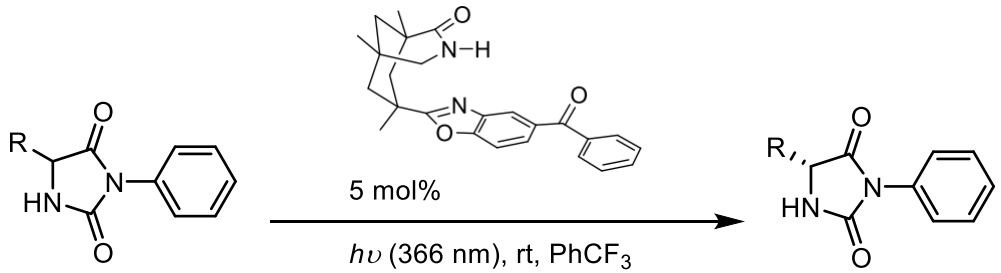
Bach, T. *et al. Angew. Chem. Int. Ed.* **2020**, *59*, 21640–21647.

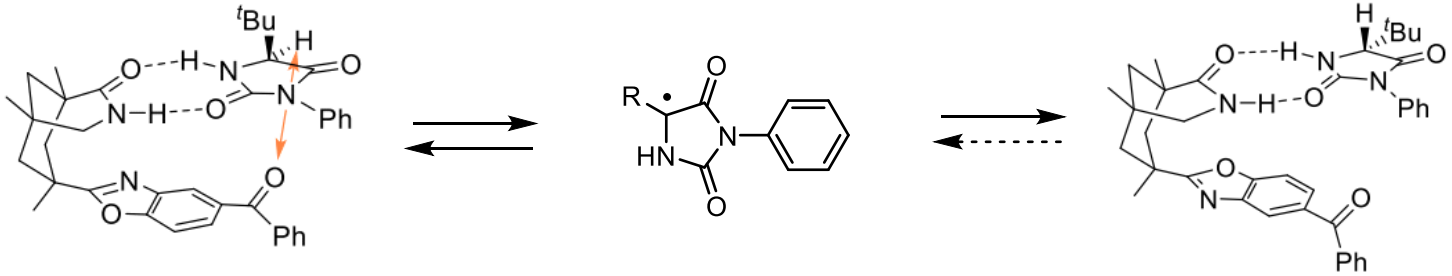
Deracemization at sp³-Hybridized Carbon



triplet sentisizer

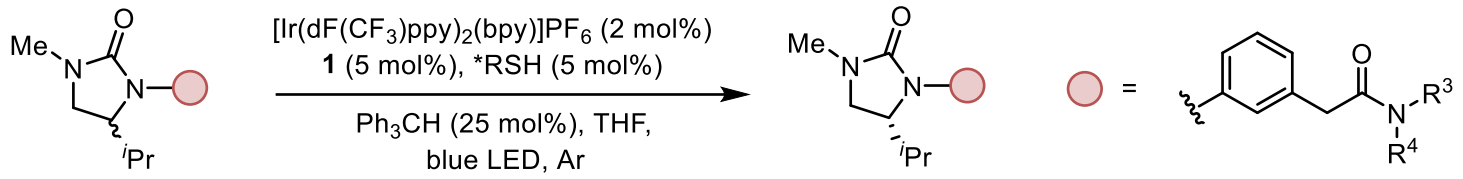
HAT reagent

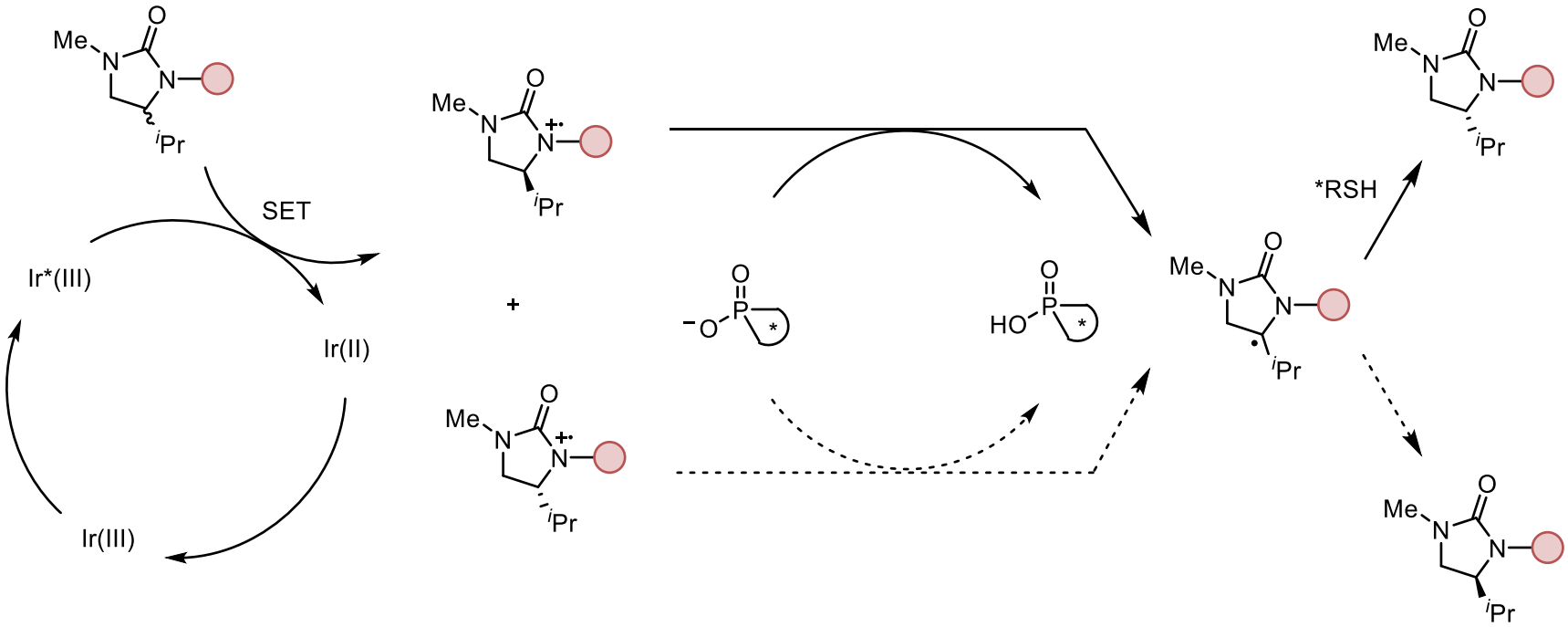




Bach, T. *et al. J. Am. Chem. Soc.* **2021**, *143*, 21241−21245.

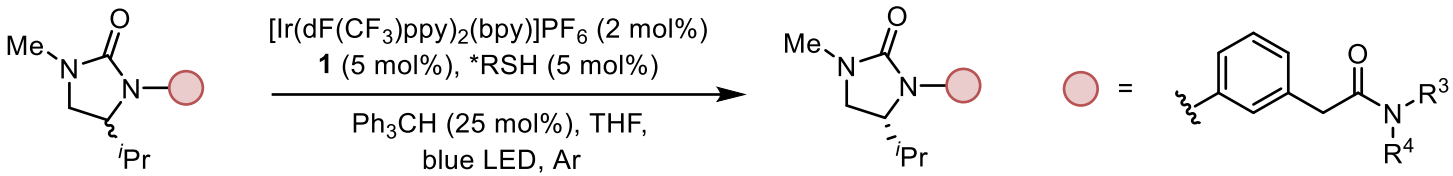
Deracemization at sp^3-Hybridized Carbon

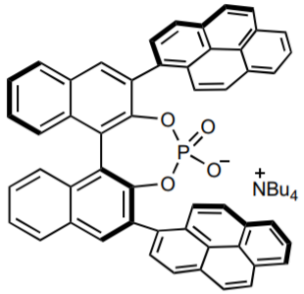




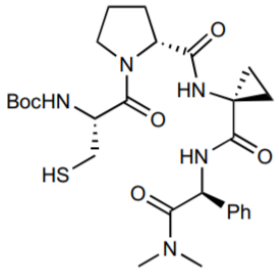
Knowles, R. R.; Miller, S. J. *et al. Science* **2019**, *366*, 364−369.

Deracemization at sp^3-Hybridized Carbon

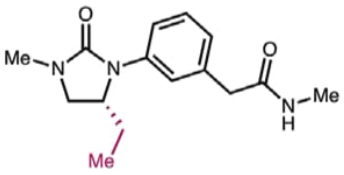




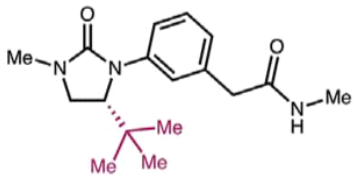
1



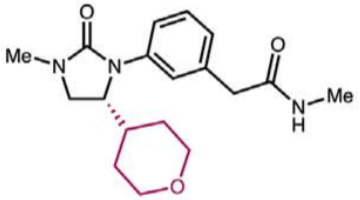
*RSH



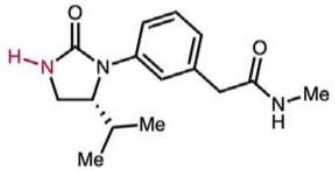
2b§ 92%, 94:6 er
(99%, 95:5 er)



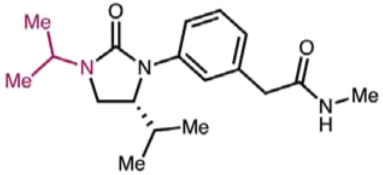
2c 98%, 95:5 er
(97%, 95:5 er)



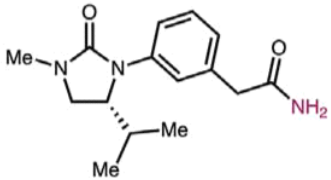
2e 96%, 94:6 er
(99%, 95:5 er)



2f§ 99%, 92:8 er
(96%, 94:6 er)



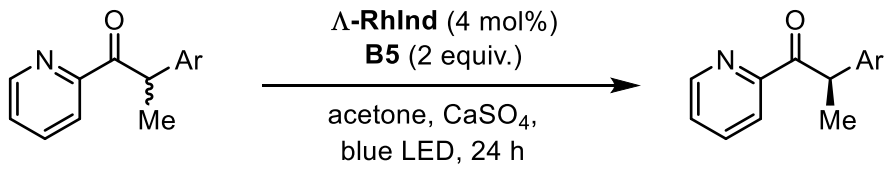
2h¶ 99%, 93:7 er
(99%, 93:7 er)

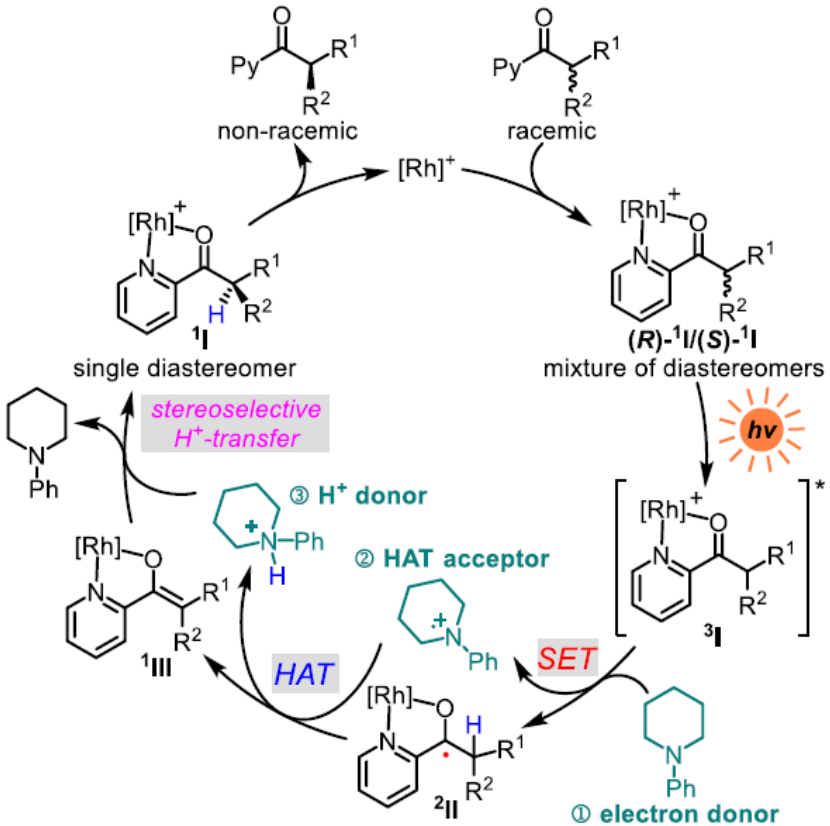


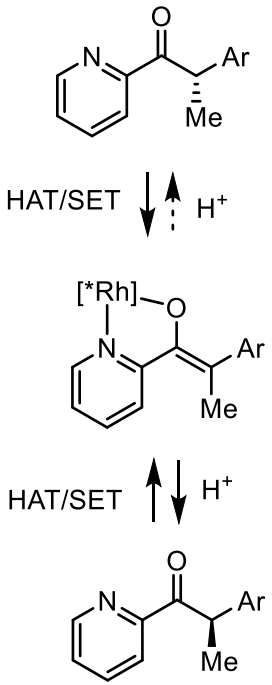
2i 96%, 93:7 er
(99%, 93:7 er)

Knowles, R. R.; Miller, S. J. *et al. Science* **2019**, *366*, 364−369.

α-Deracemization of Ketones

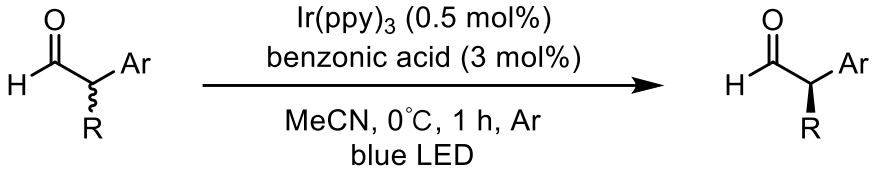


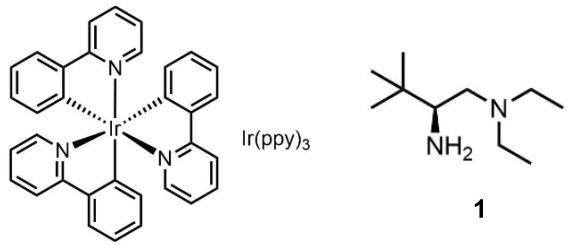


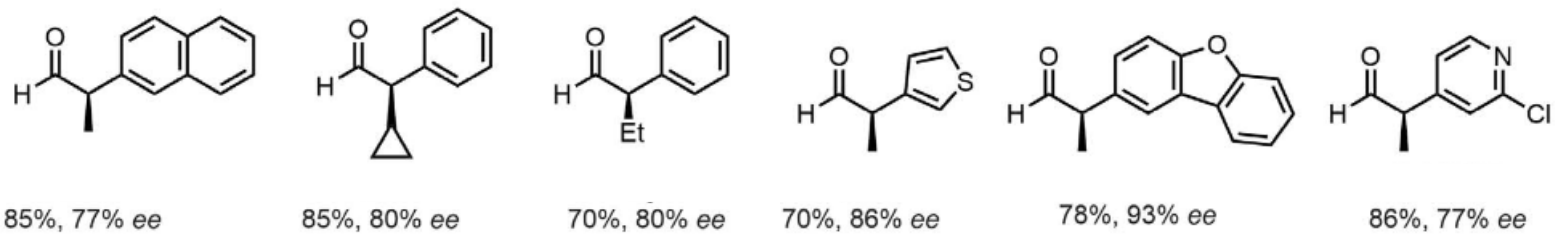


Meggers. E. *et al. J. Am. Chem. Soc.* **2021**, *143*, 13393−13400.

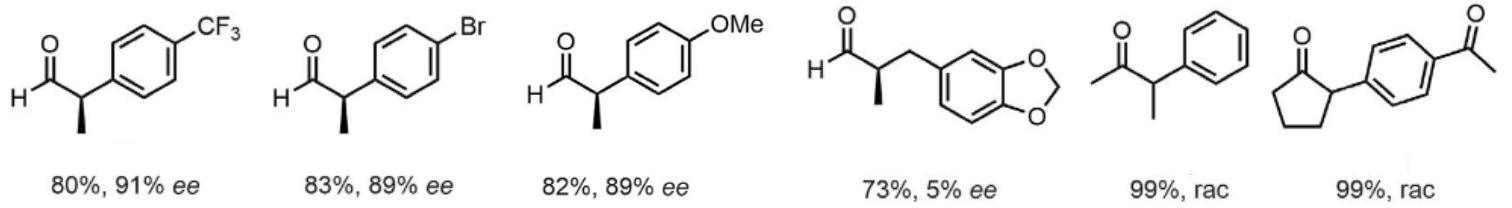
α-Deracemization of Ketones







unsuccessful substrates



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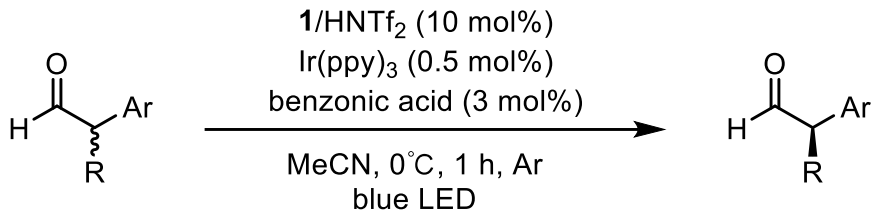
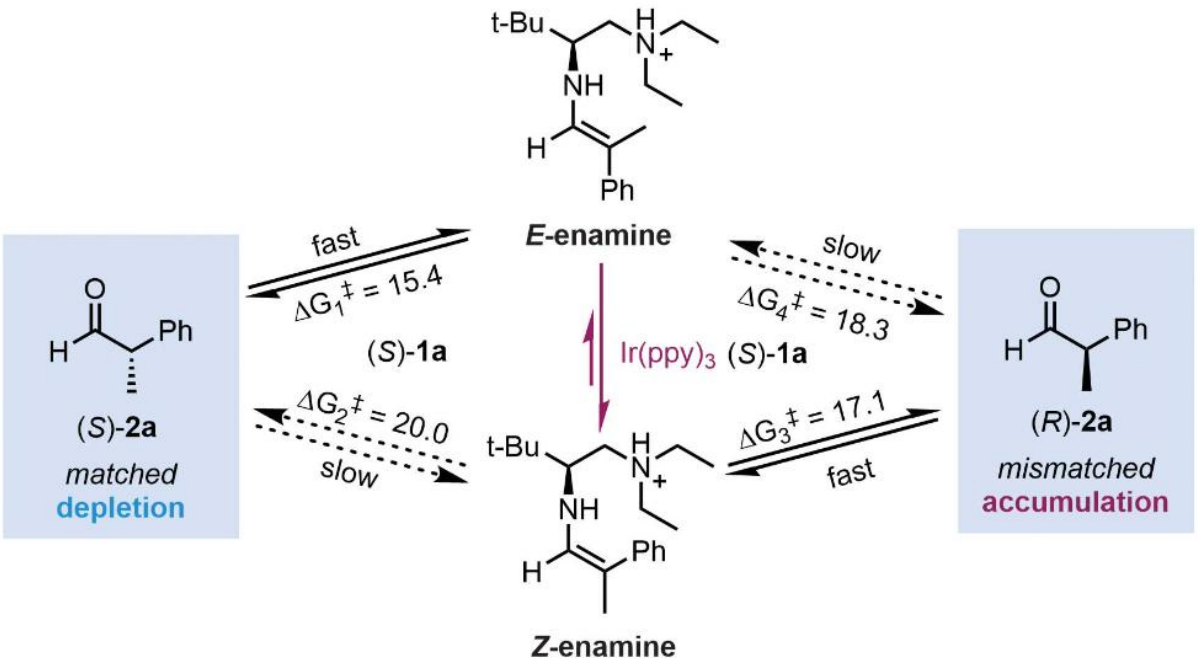
α-Deracemization of Ketones





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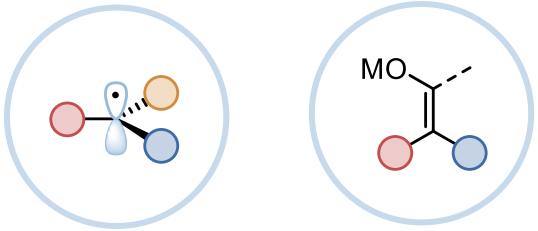
Summary

- Photocatalysis
  - Common intermediate



- Energy input
  - Light energy