Deracemization and Related Processes

Kevin Wu
13 January 2019
Yu Group

Asymmetric Catalysis – Known Strategies

- Selective reaction with a prochiral, planar precursor is a common strategy in asymmetric catalysis:

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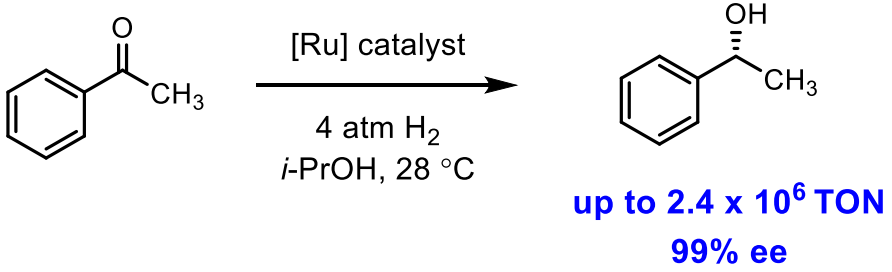

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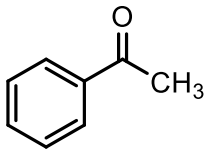
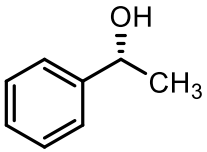


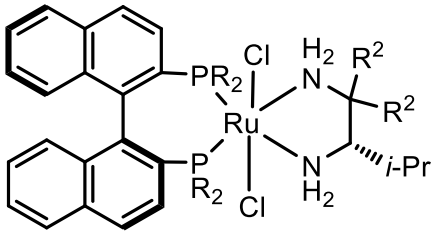
[Ru] catalyst

4 atm H_2
i-PrOH, 28 °C



up to 2.4 x 10^6 TON

99% ee



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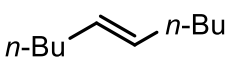
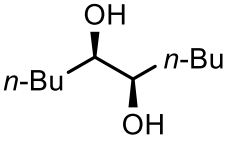


AD-mix-β

t-BuOH, H_2O, 0 °C



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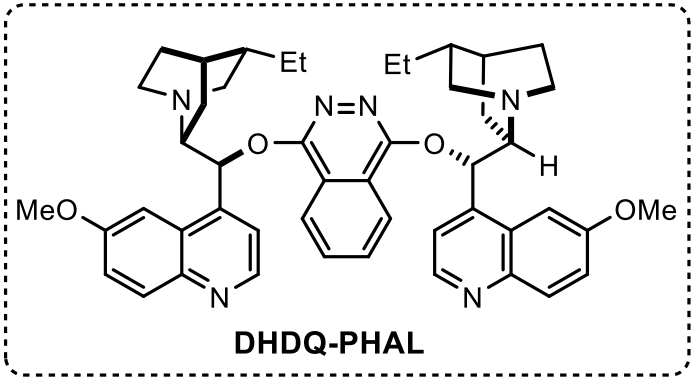

DHDQ-PHAL

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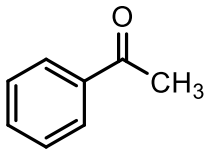

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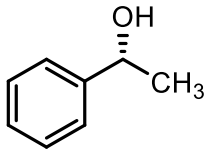

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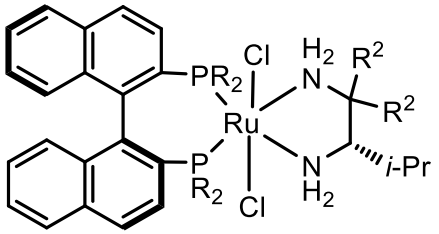

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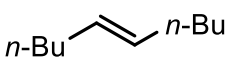

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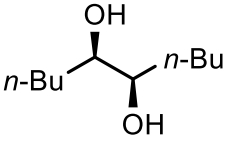

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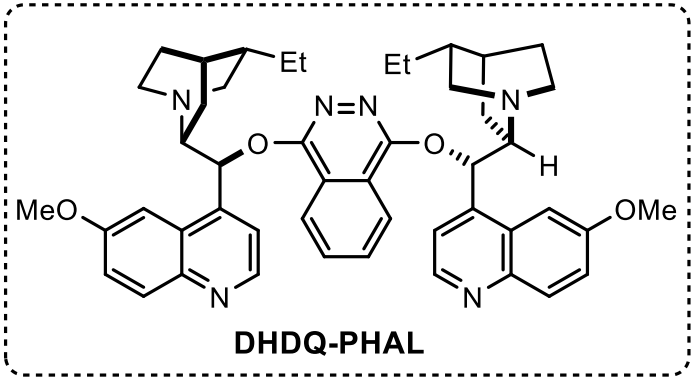

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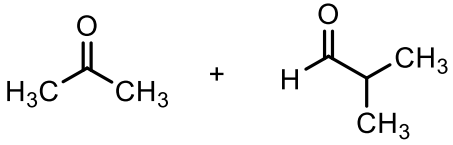
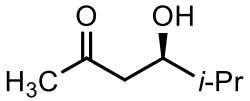


(S)-Proline

DMSO, rt



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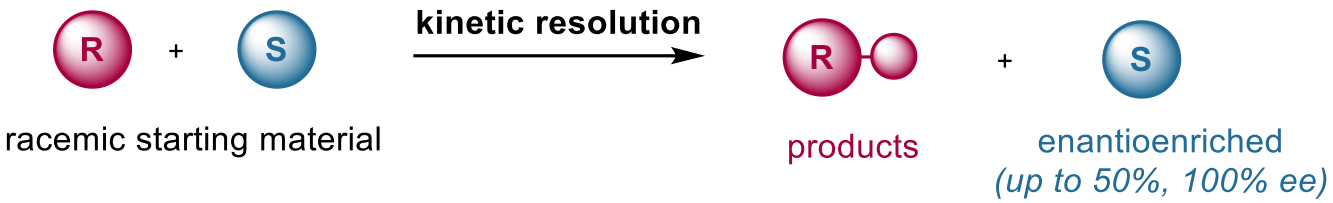

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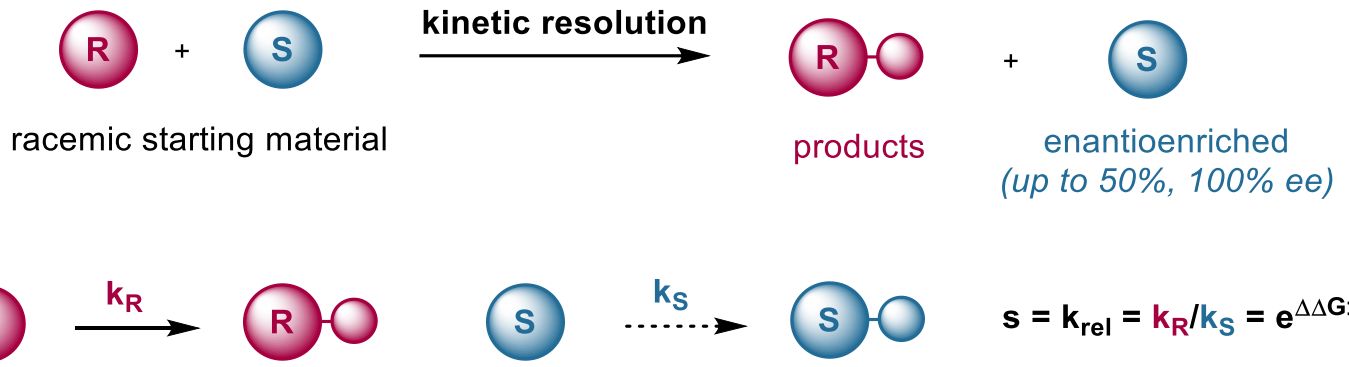

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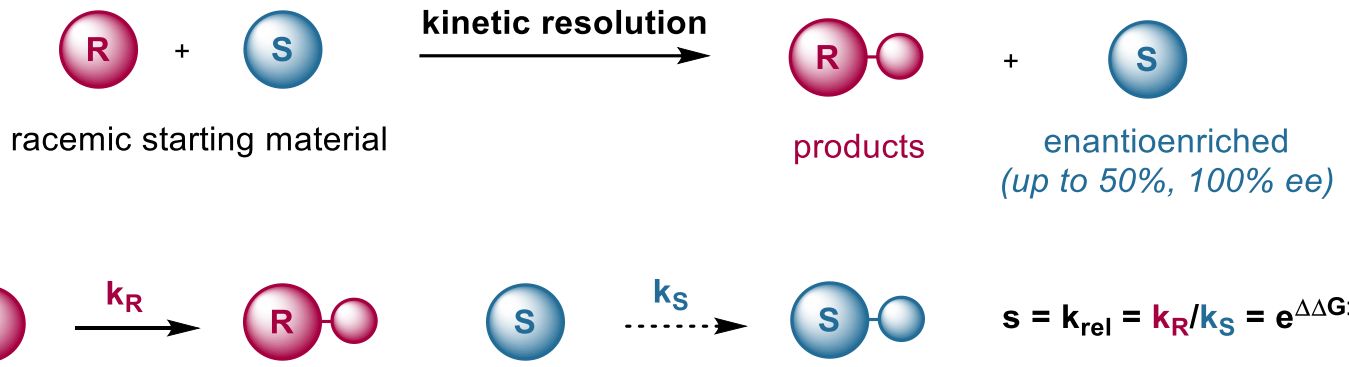

s (k_{rel})	$\Delta\Delta G^{‡}$ (kcal/mol)	Conversion (%) to achieve SM at: 90% ee	98% ee	>99% ee
1.5	**0.24**	**99.9**	**99.99**	**>99.999**
2	**0.41**	**97.2**	**99.5**	**>99.7**
5	**0.95**	**74.8**	**84.0**	**>86.6**
10	**1.35**	**62.1**	**69.7**	**>72.1**
100	**2.72**	**48.9**	**51.8**	**>52.4**
500	**3.66**	**47.7**	**50.0**	**>50.3**

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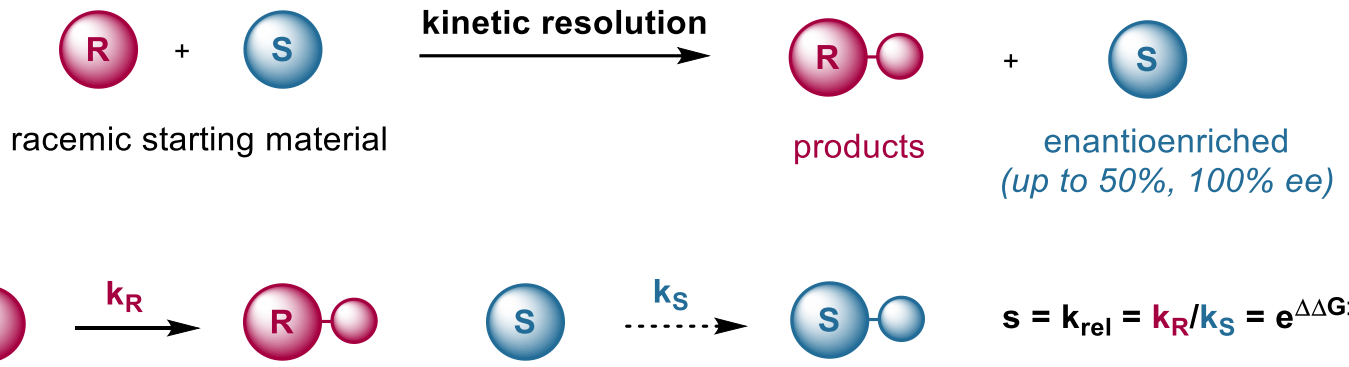

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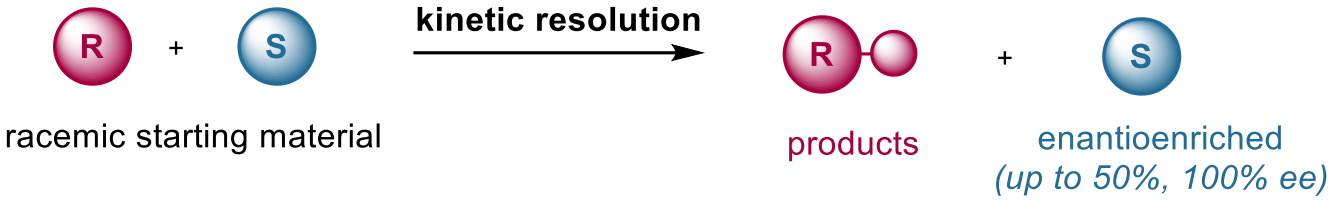

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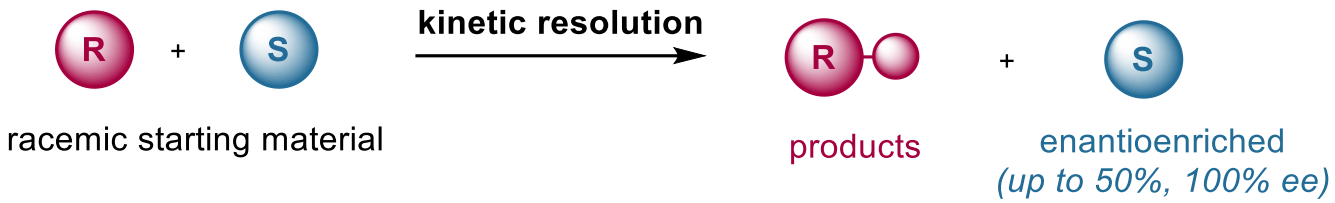

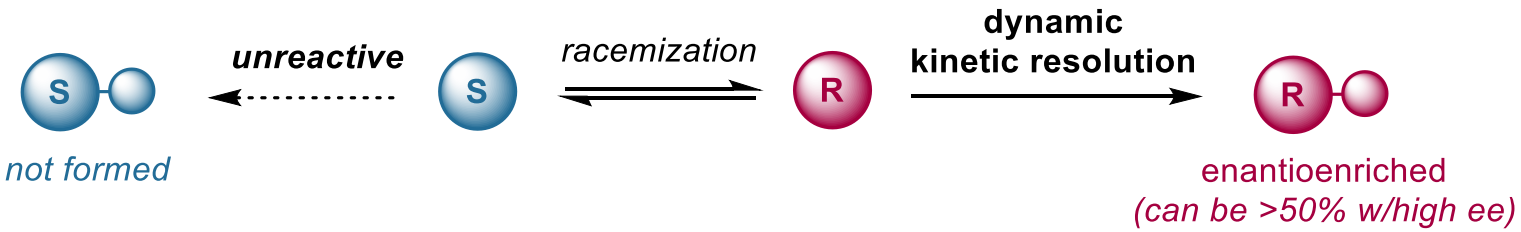

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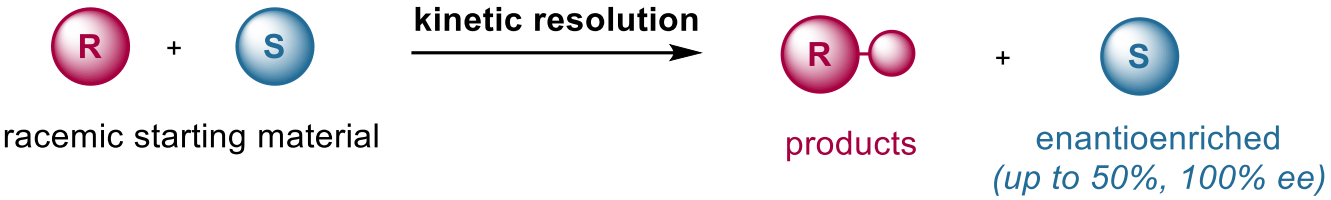

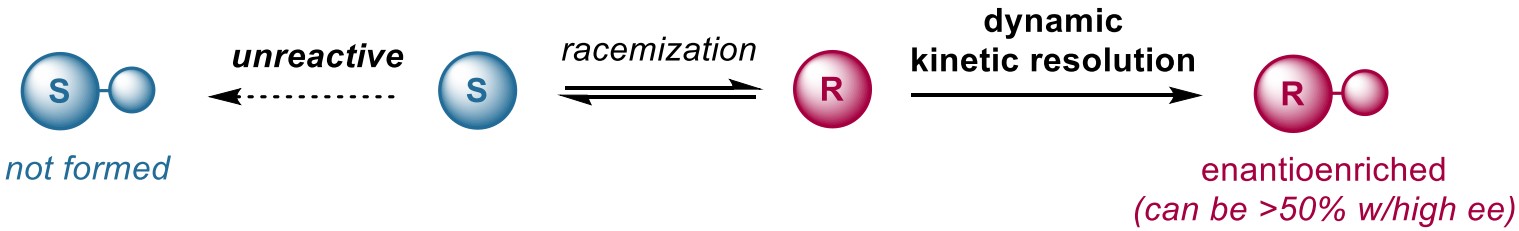

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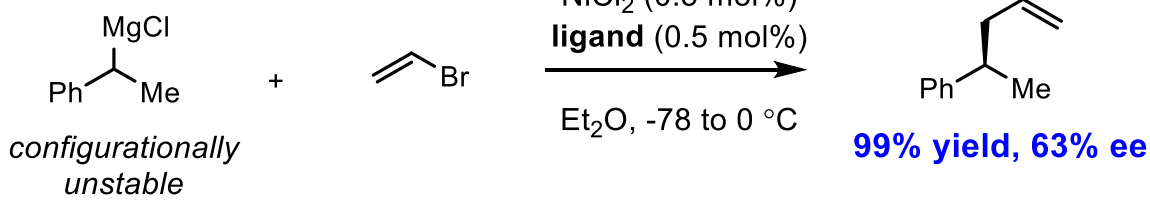

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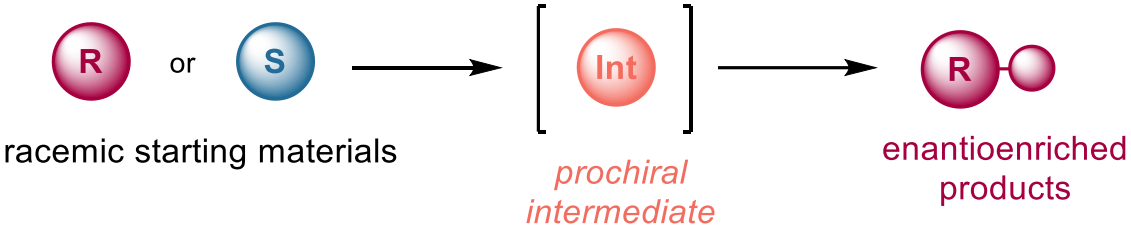

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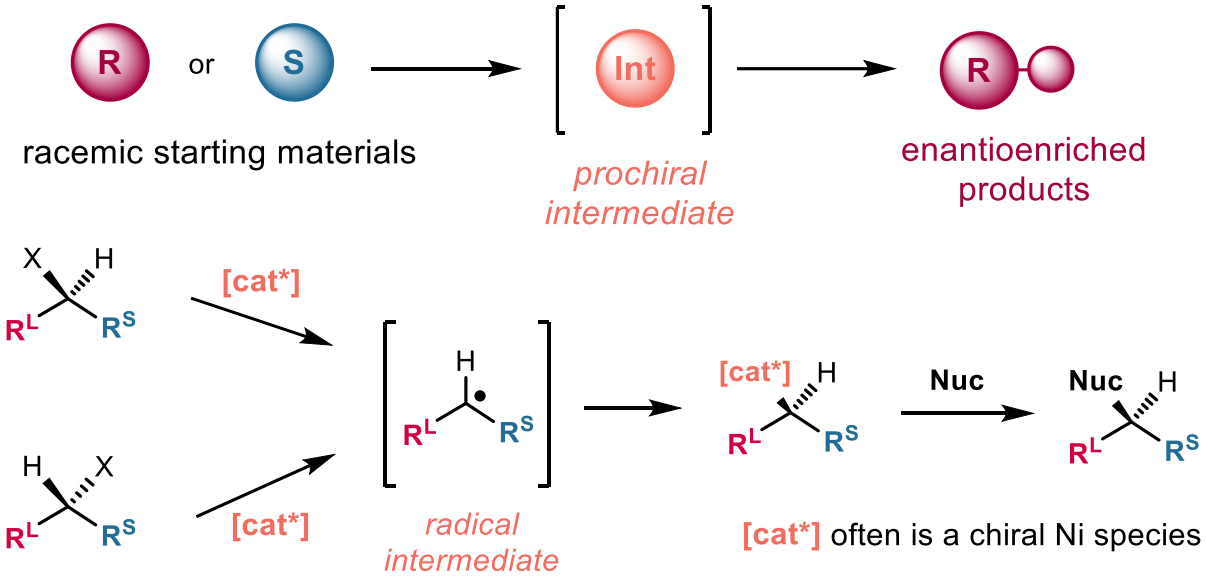

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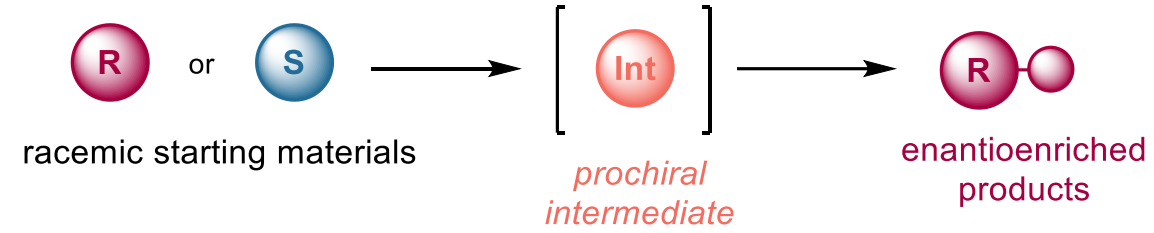

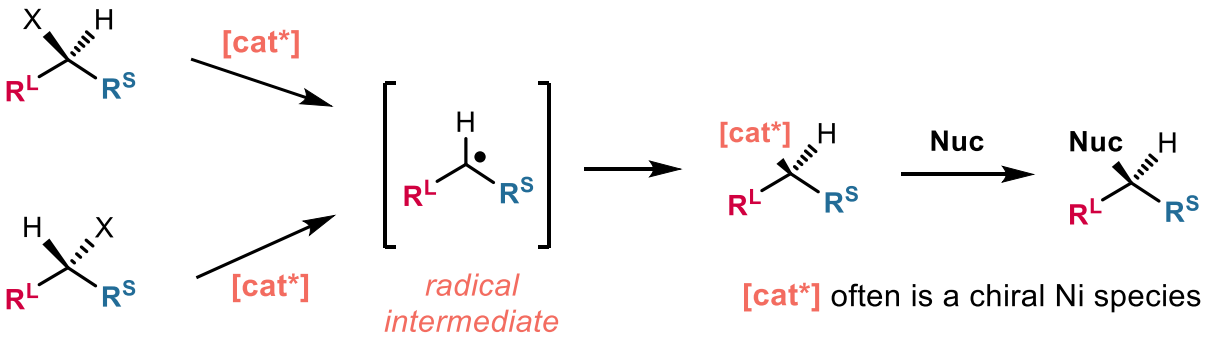

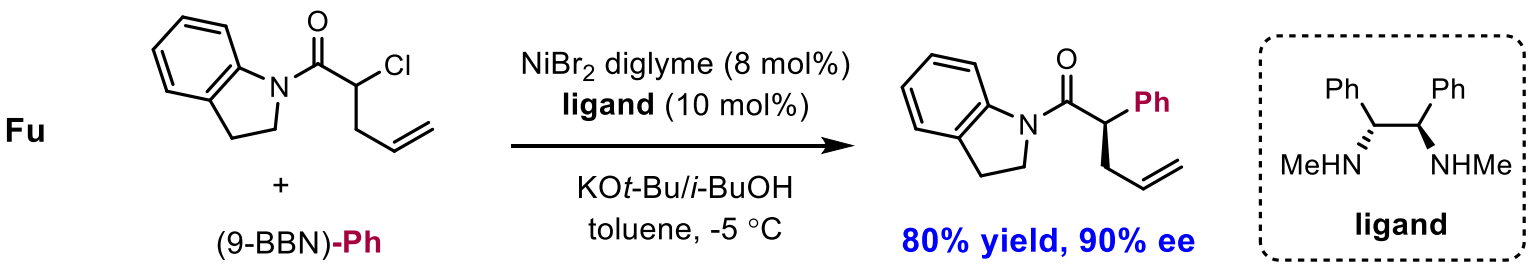

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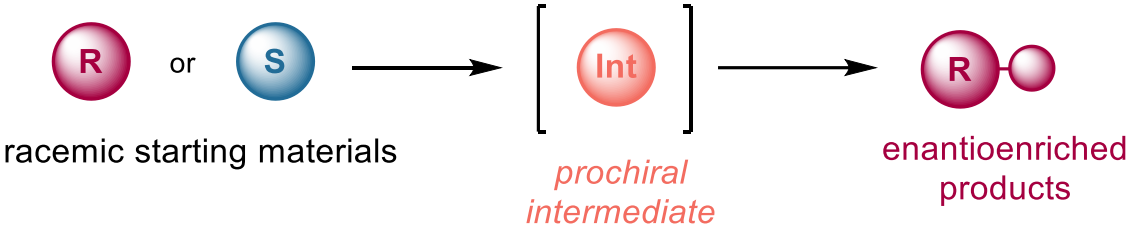

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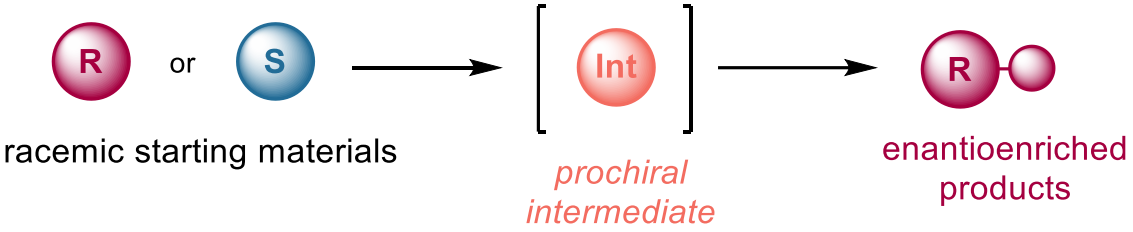

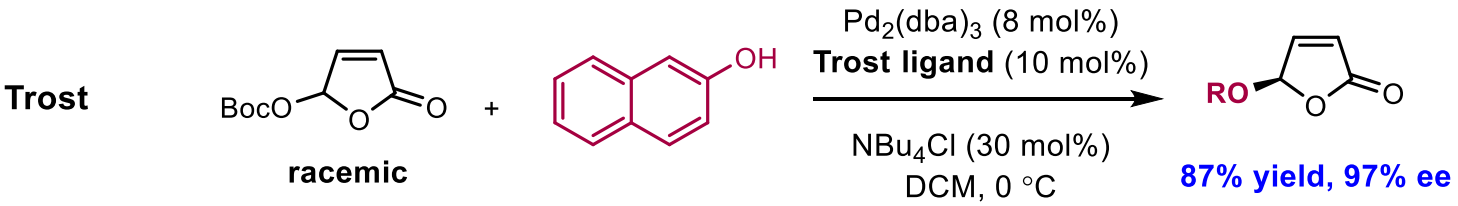

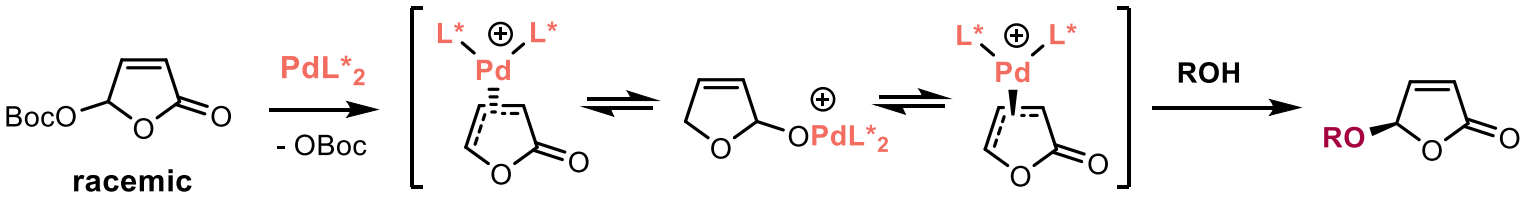

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$\Delta G = \Delta H - T\Delta S$

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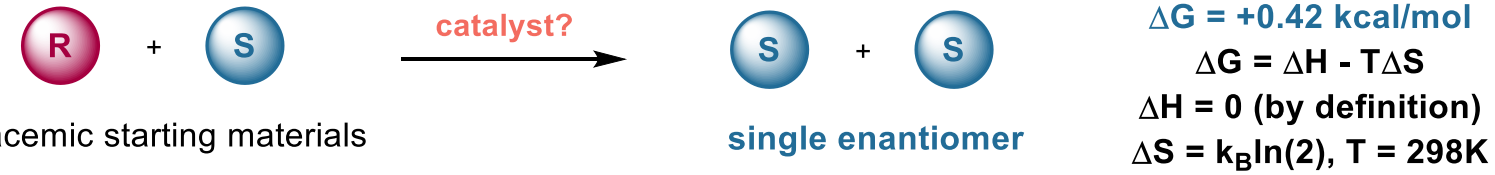

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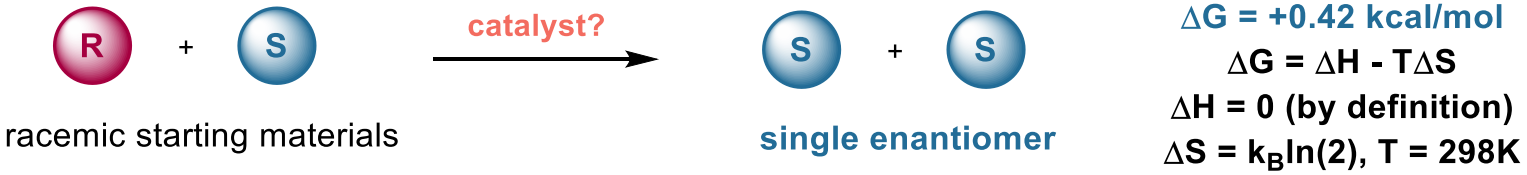

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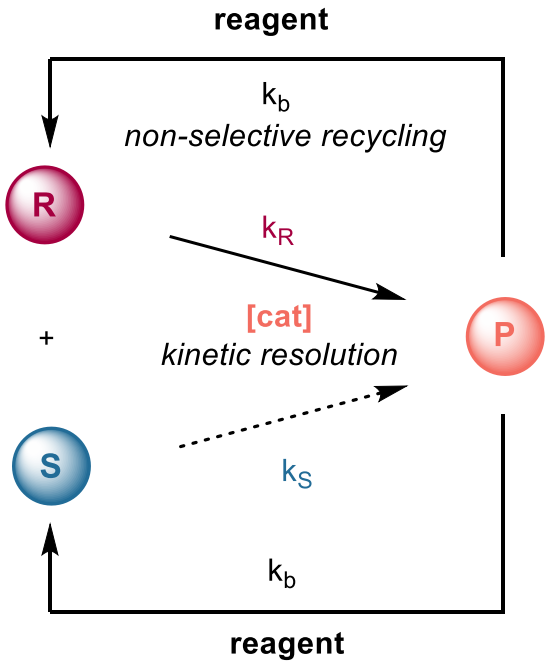

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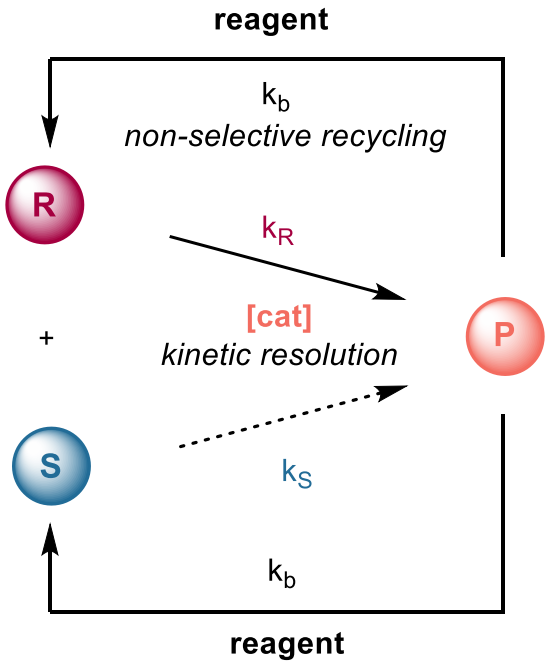

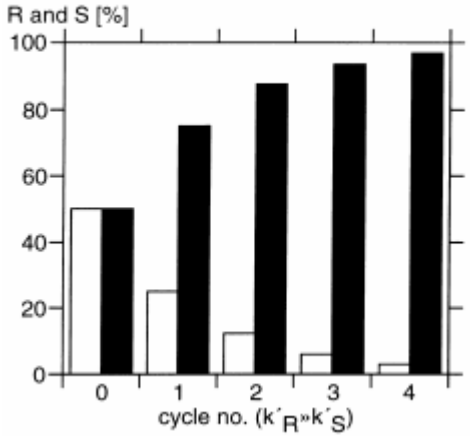

Repeated cycling leads to the accumulation of *(S)*

Kroutil, W.; Faber, K. *Tetrahedron: Asymmetry* **1998**, *9,* 2901.

Deracemization Concepts

- Deracemization is inherently endothermic due to the decrease in entropy required:

racemic starting materials

single enantiomer

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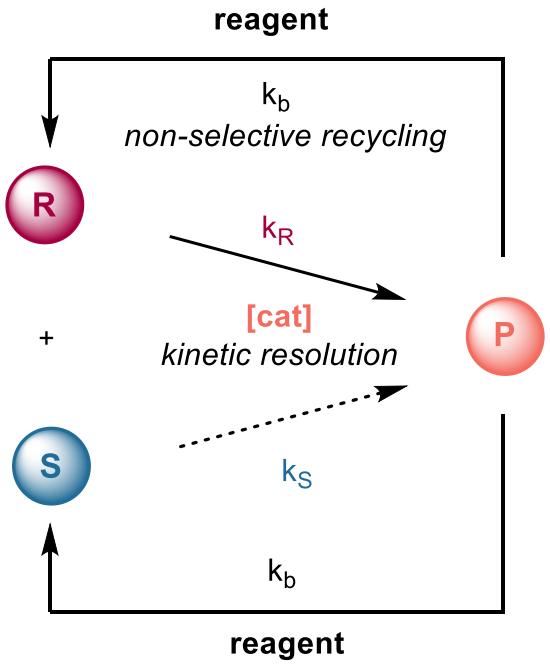

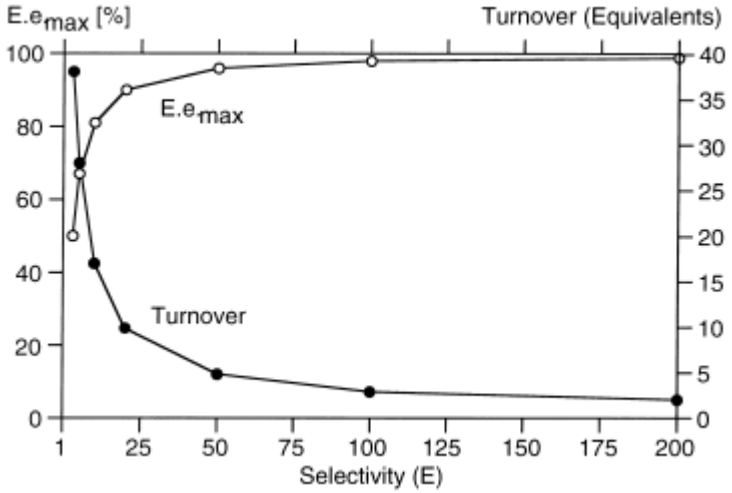

Selectivity Factor E = k_R/k_S

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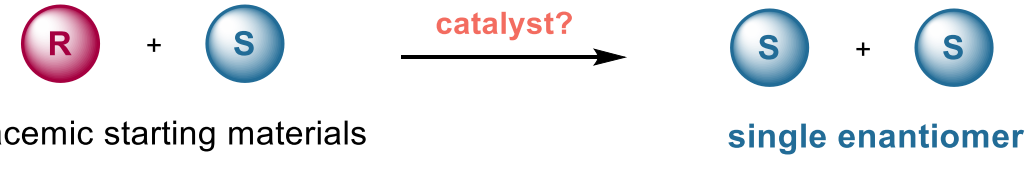

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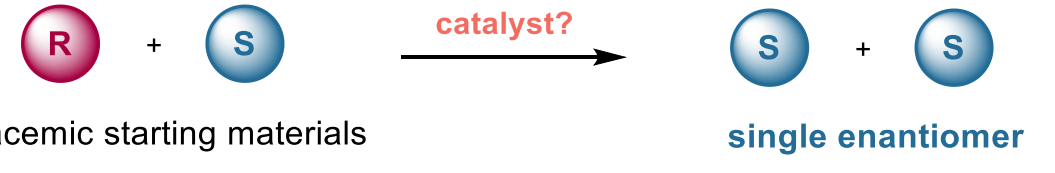

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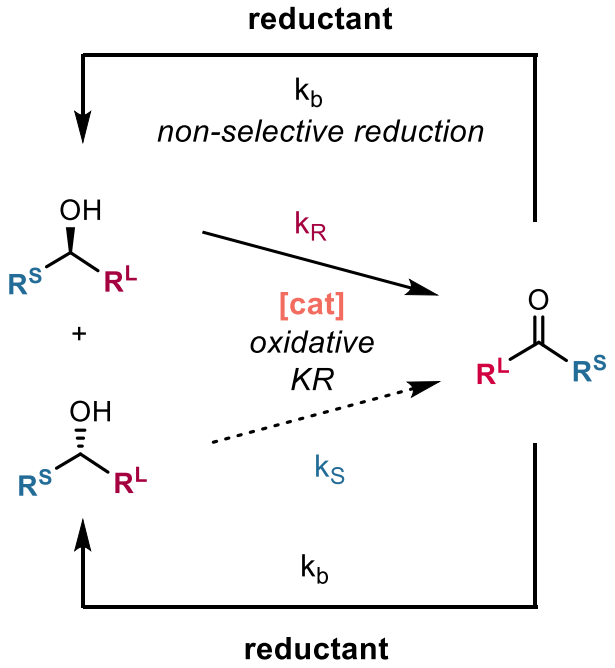

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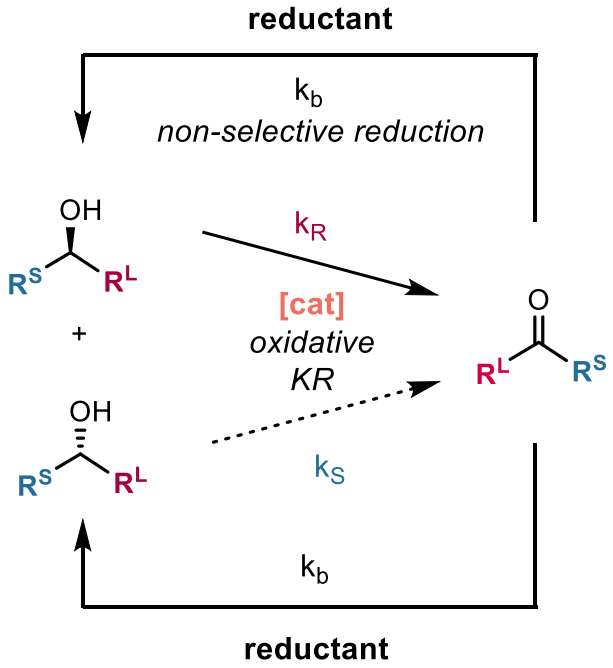

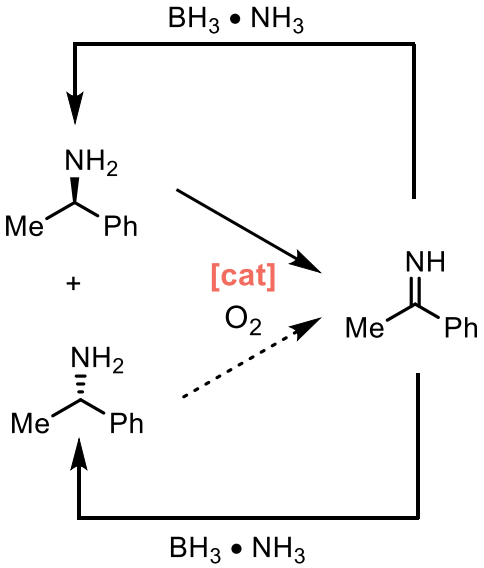

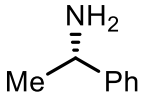

after 24 h of cycling
77% yield, 93% ee

[cat] = Type-II monoamine oxidases

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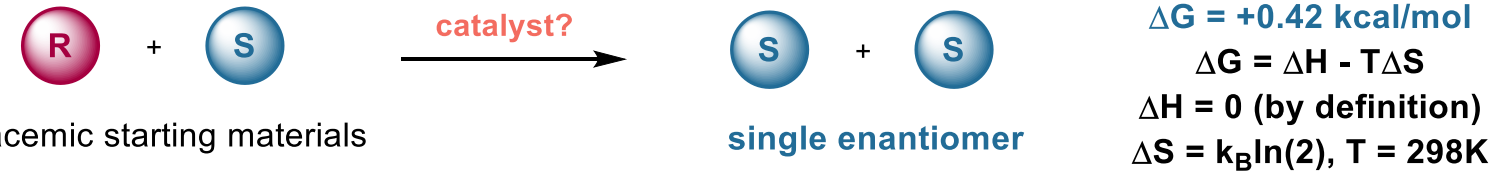

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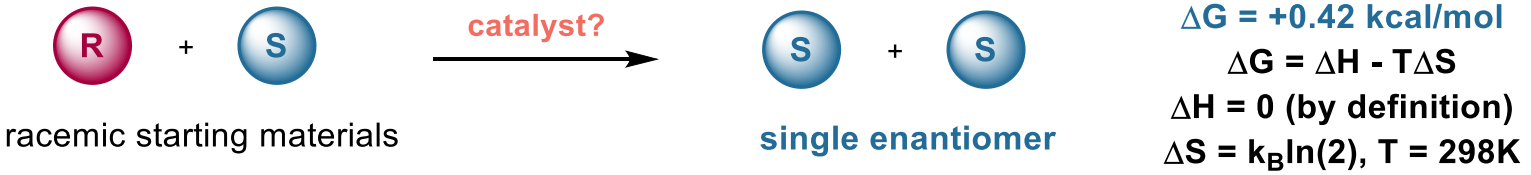

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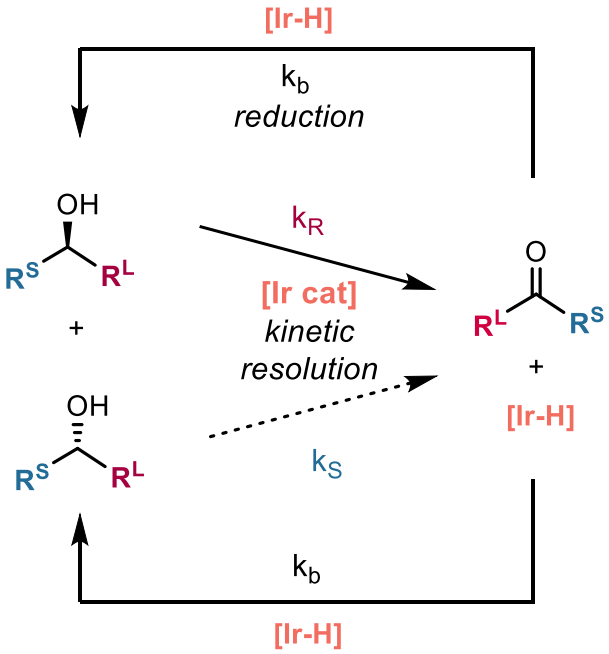

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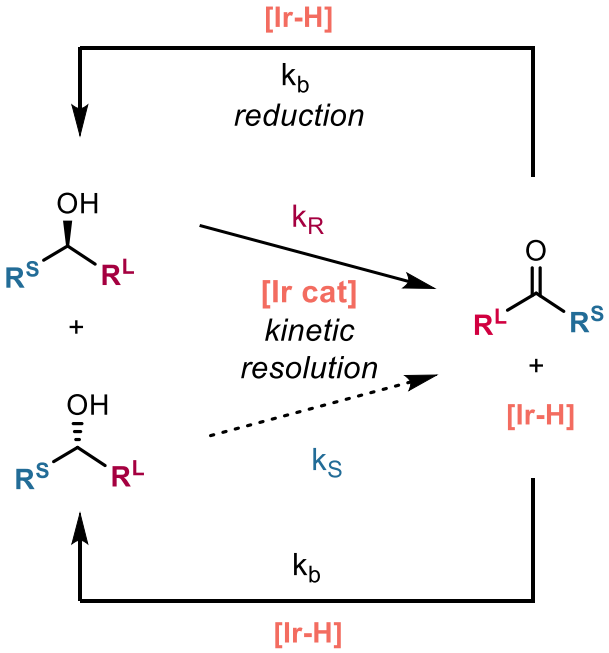

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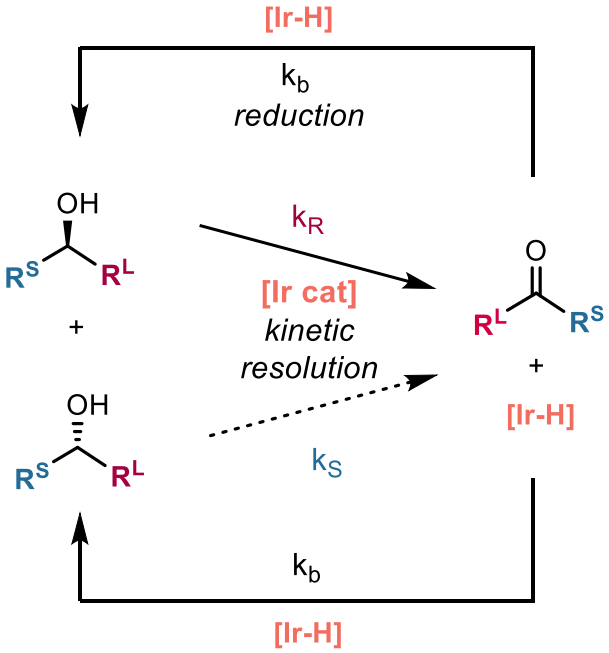

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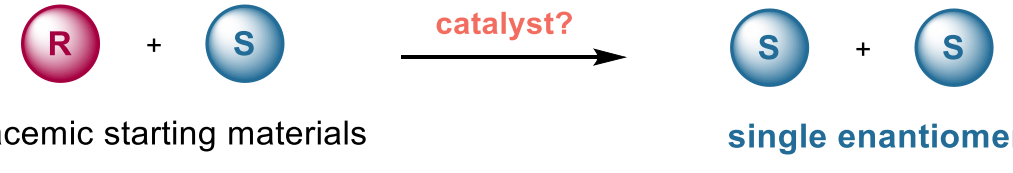

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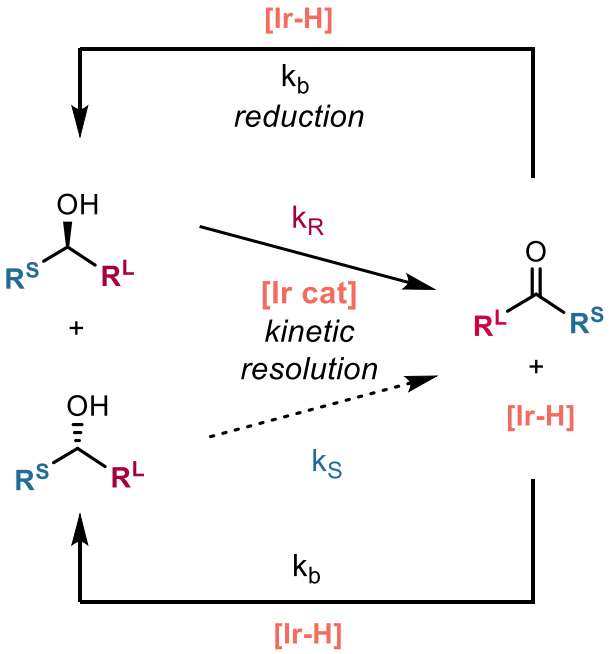

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- Yet these proposals remained common
- To understand why such proposals are infeasible, the **principle of microscopic reversibility** must be considered

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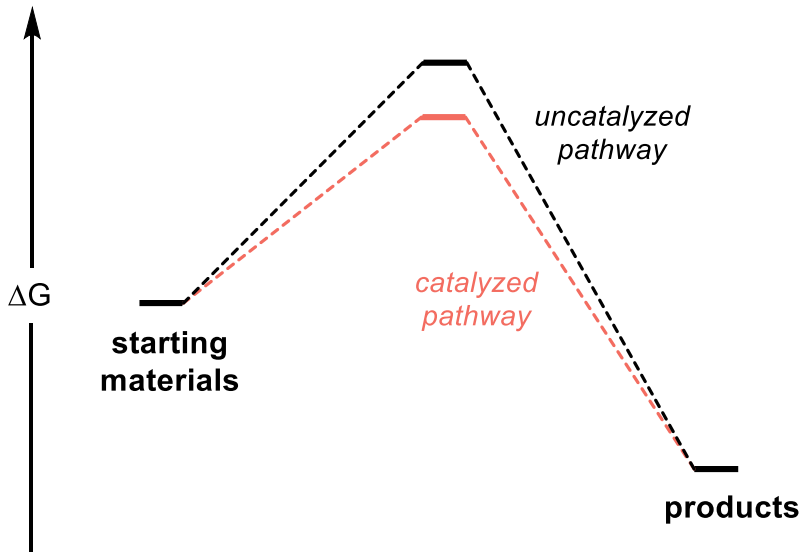

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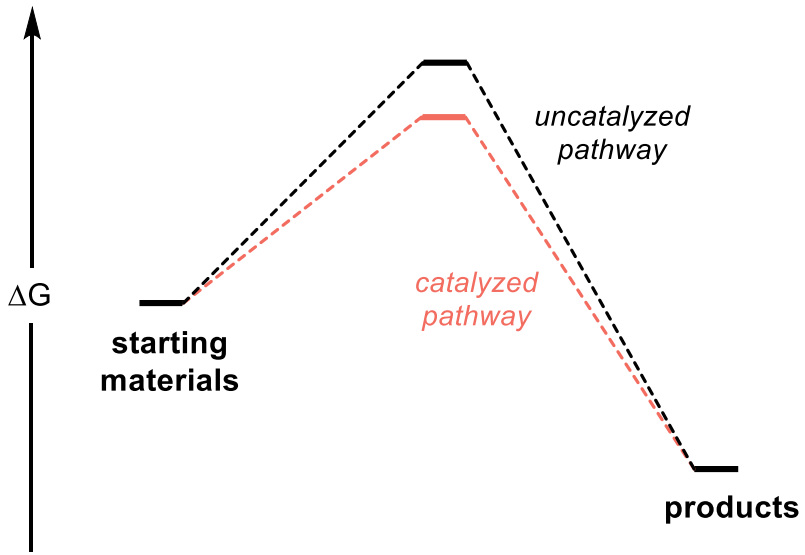

The lowest path backward must always be identical to the lowest path forward

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Deracemization: Applying the Principle of Microscopic Reversibility

- When considered from this perspective, the issue with closed system recycling is clear:

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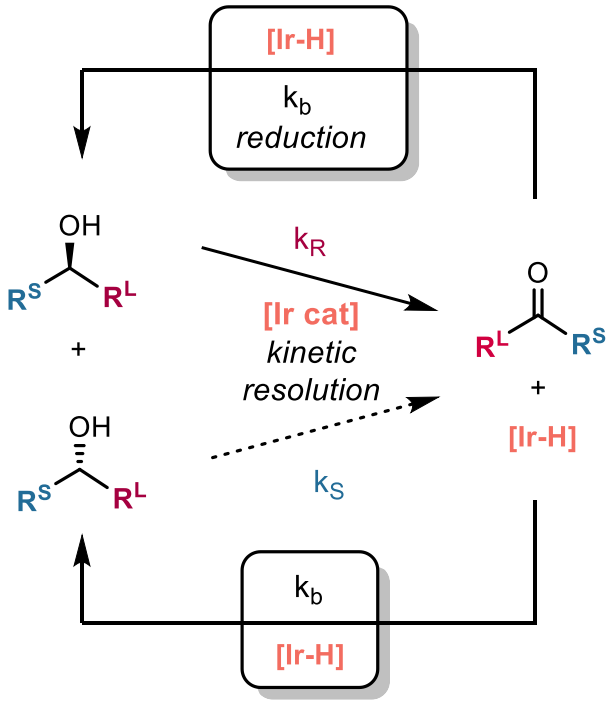

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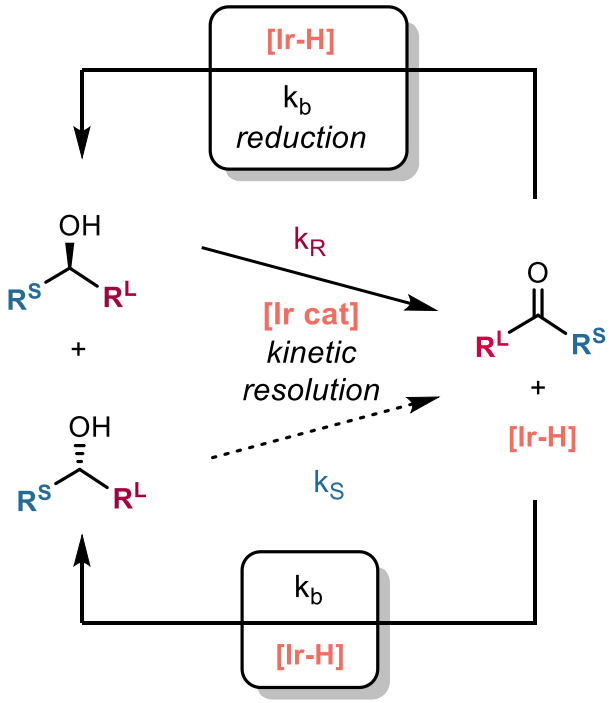

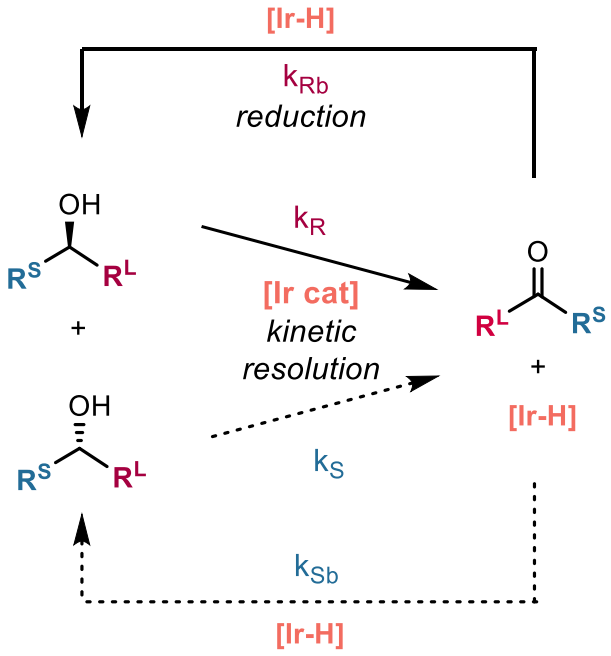

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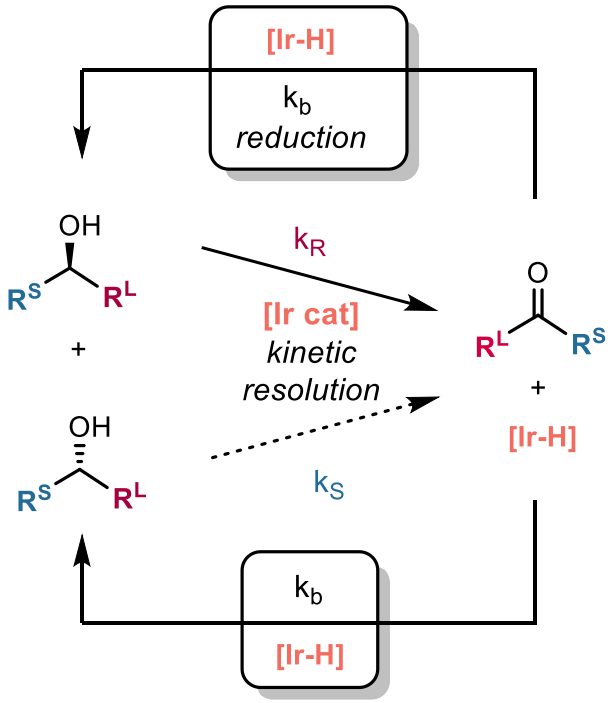

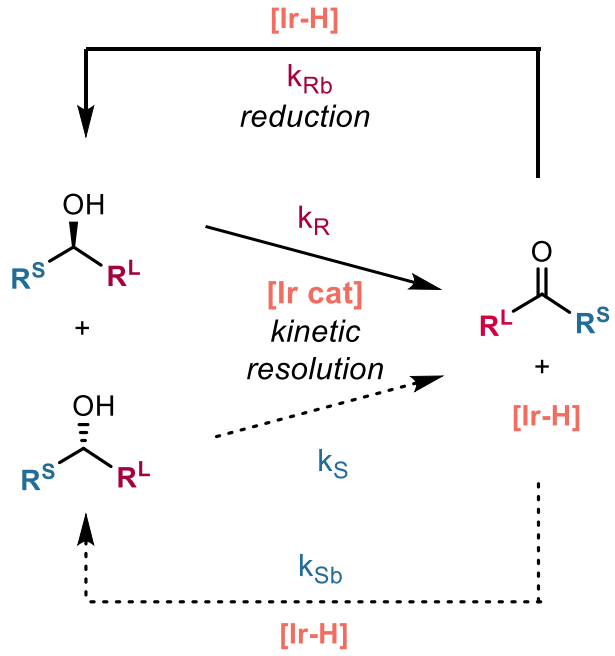

- "Attempts to recycle a catalytic reaction back by its uncatalyzed route clearly breaks the rules"

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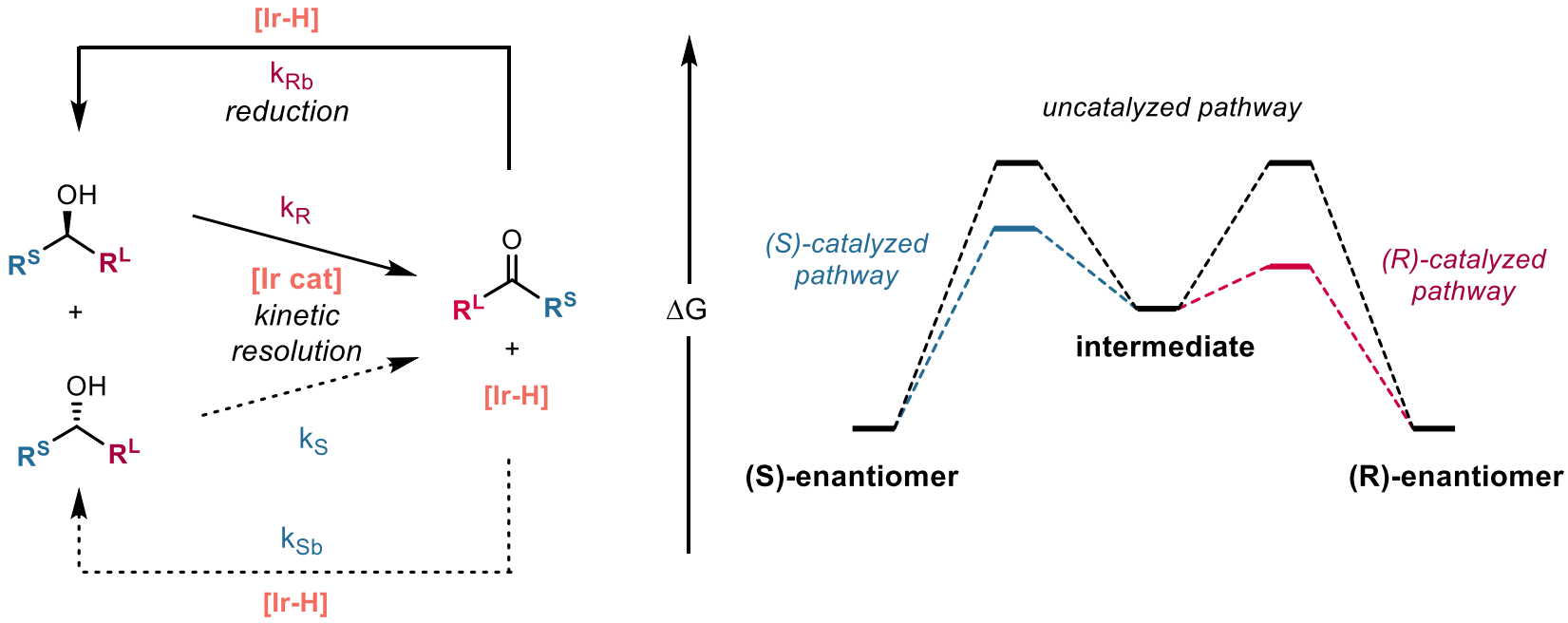

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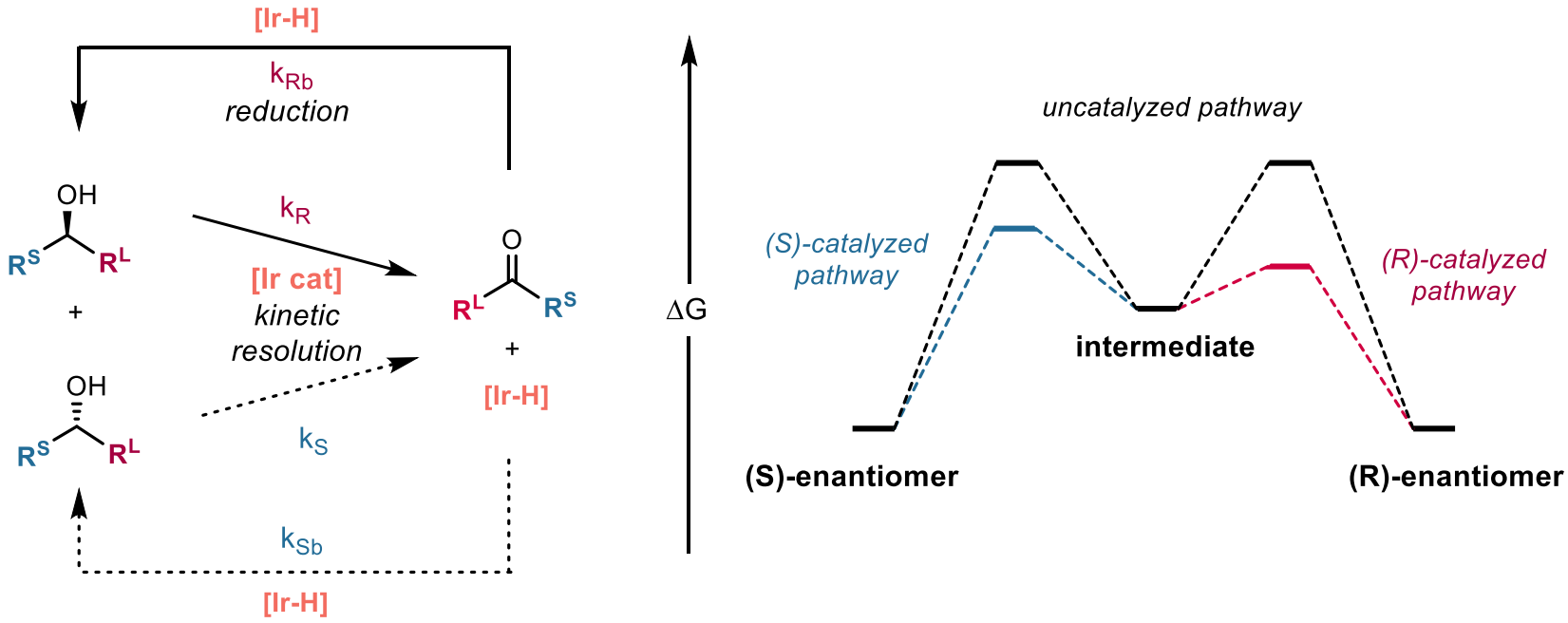

- The energetics that favor the catalytic conversion of the undesired (R)-enantiomer also will favor its re-formation from the intermediate (if k_R is large, then k_{Rb} must also be)
- The closed system will inexorably proceed towards equilibrium (racemization)

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Deracemization: Overcoming the Limitations of Closed Systems

- To overcome the limitation of a closed systems, a source of chemical or light energy is needed

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Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

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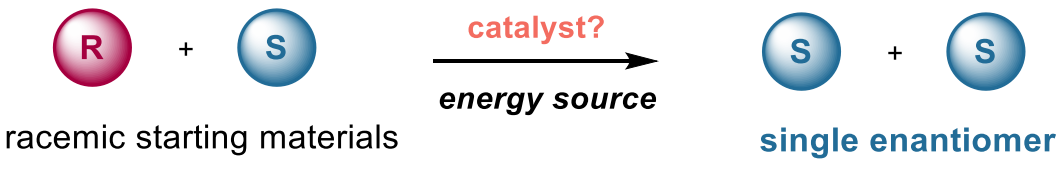

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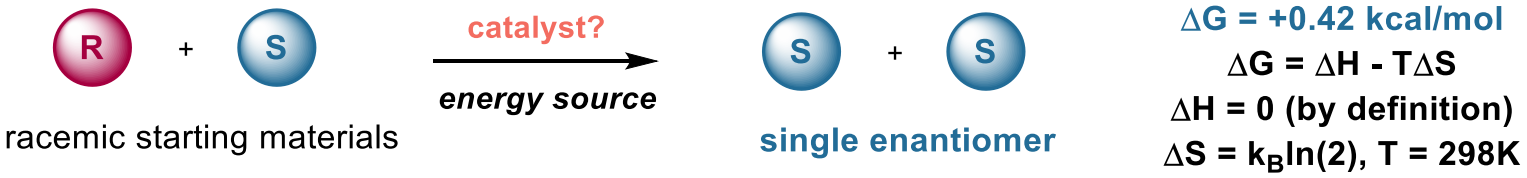

- The principle of microscopic reversibility prohibits a single catalytic step from deracemizing a reaction
- Two or more steps proceeding through distinct mechanisms are necessary
  - Chemical compatibility of reagents can be a challenge, especially in redox cycling
  - Temporal separation is one possible solution (stepwise reactions)
  - Photochemical methods would be ideal, but few candidate systems exist

Knowles, R. R.; et al. *Science* **2019**, *366*, 364.
Blackmond, D. G. *Angew. Chem. Int. Ed.* **2009**, *48,* 2648.

Deracemization: Phase Separation and Chemical Energy

- Catalytic enantioselective reduction of imines with chiral phosphoric acids is well known:

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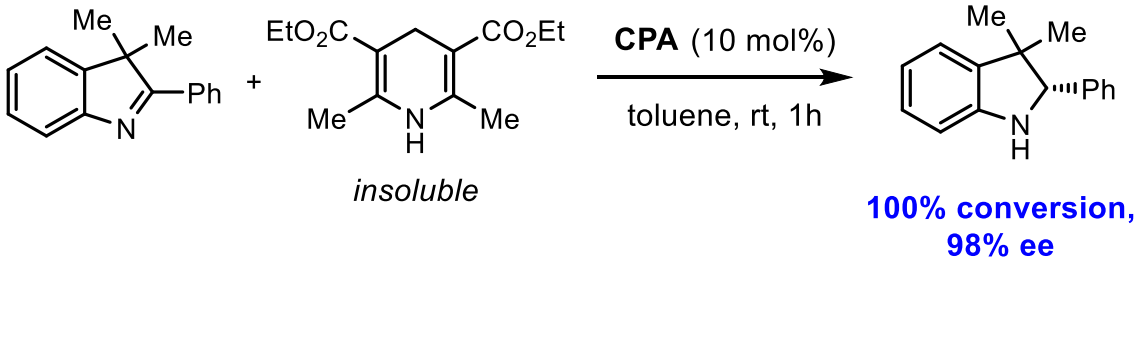

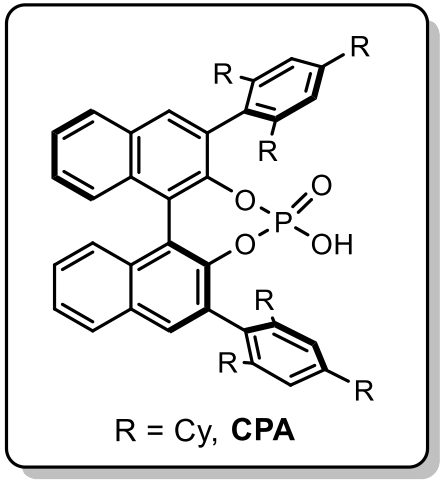

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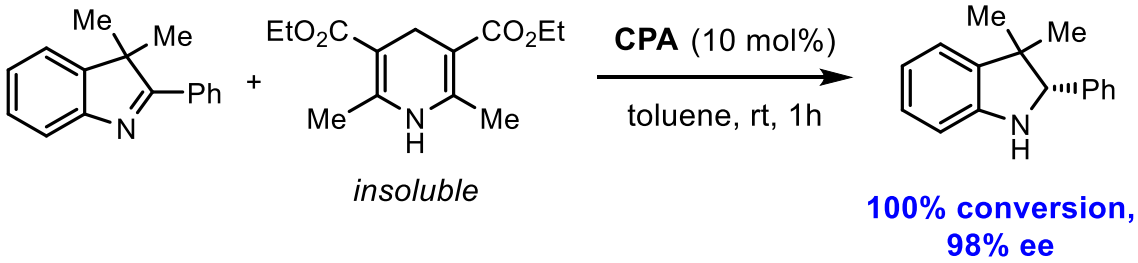
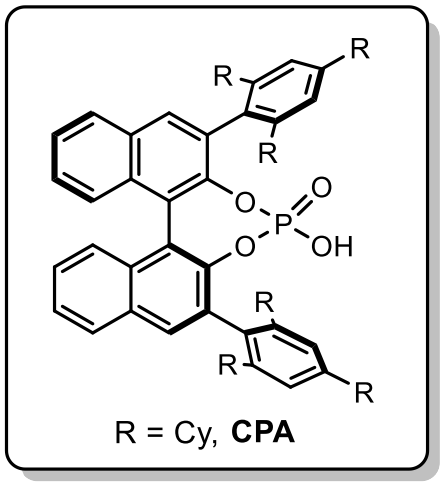
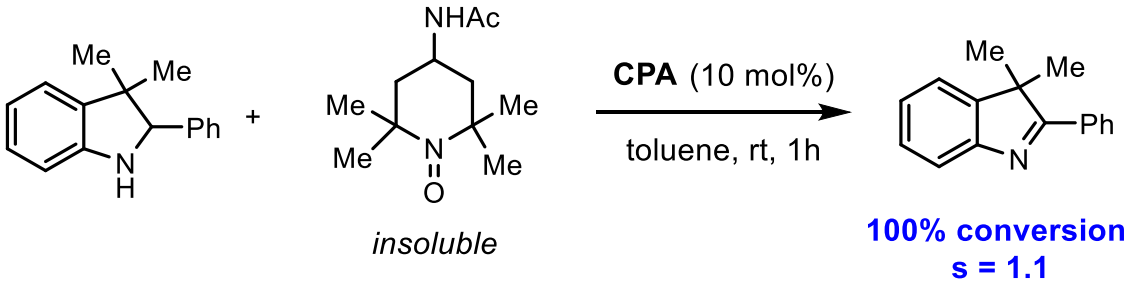




- The Toste group found CPAs can facilitate phase-transfer oxidation of indolines, with low selectivity



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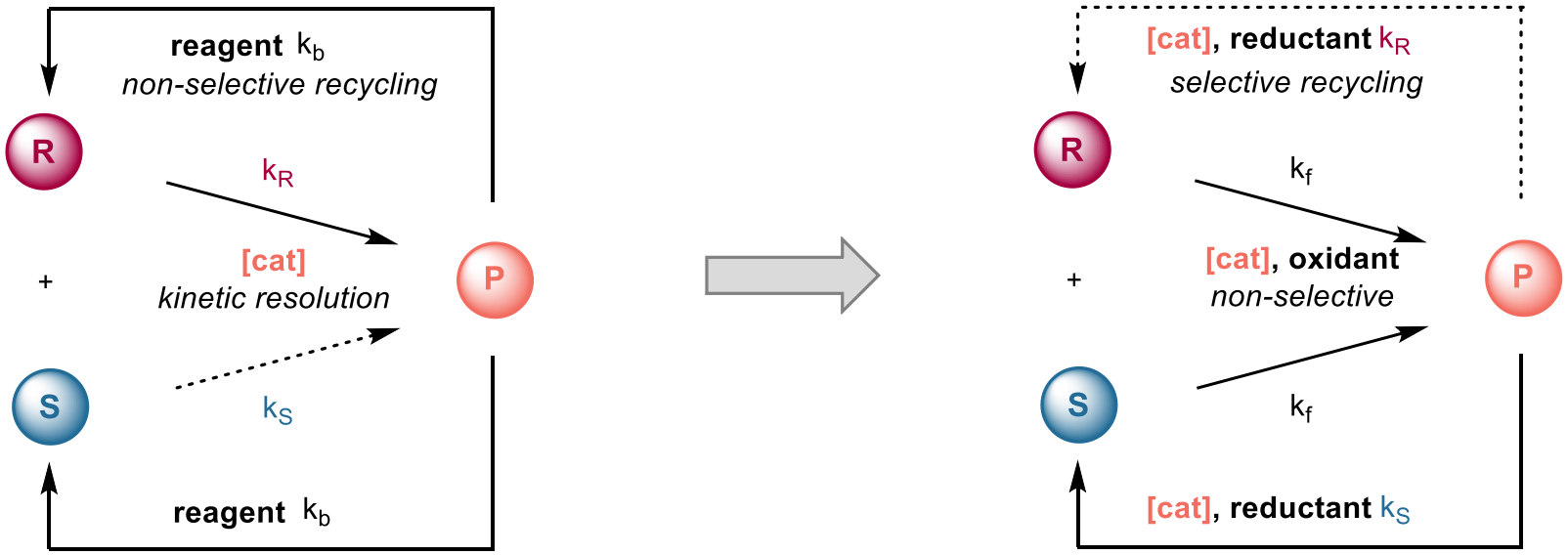

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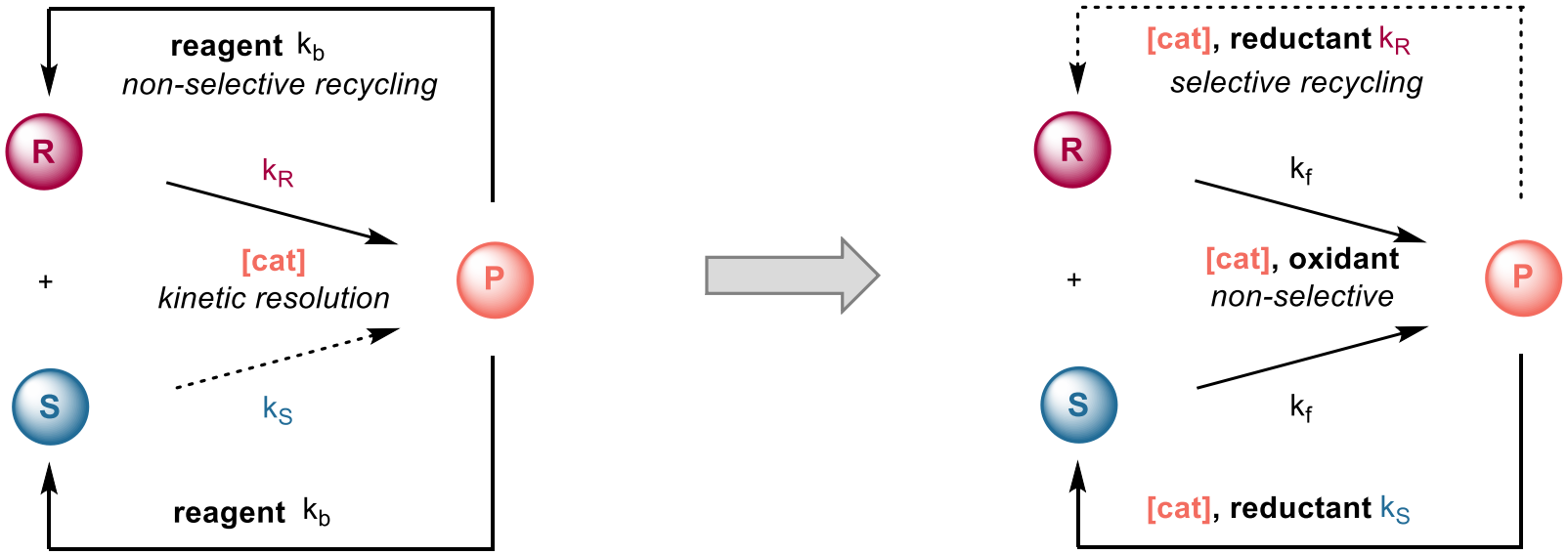
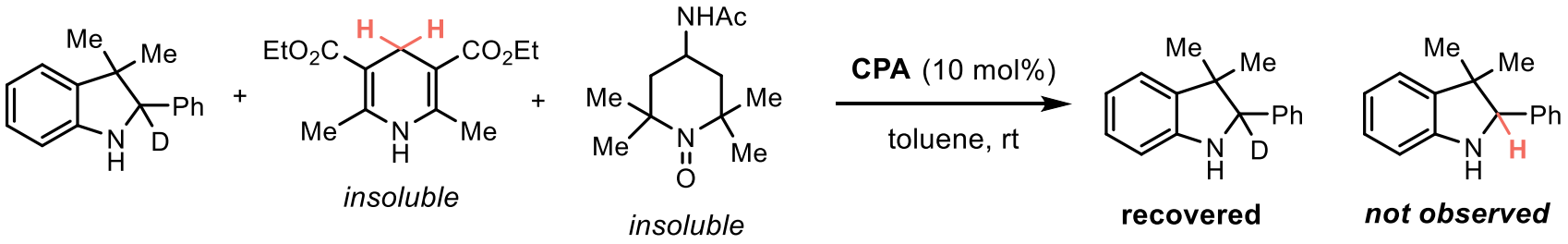


- However, no deuterium erosion (no reaction) was observed when the two cycles were combined:



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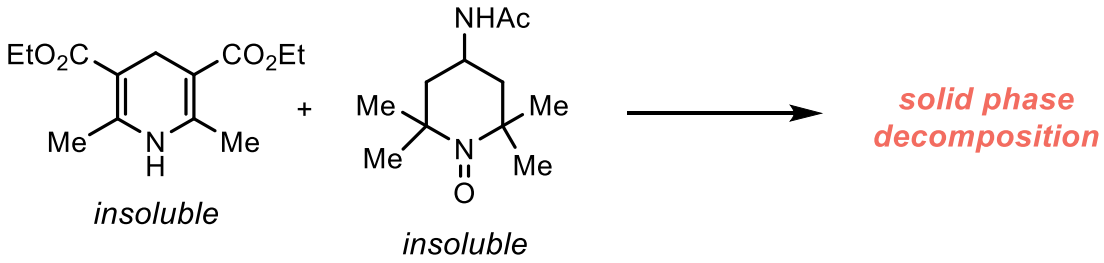

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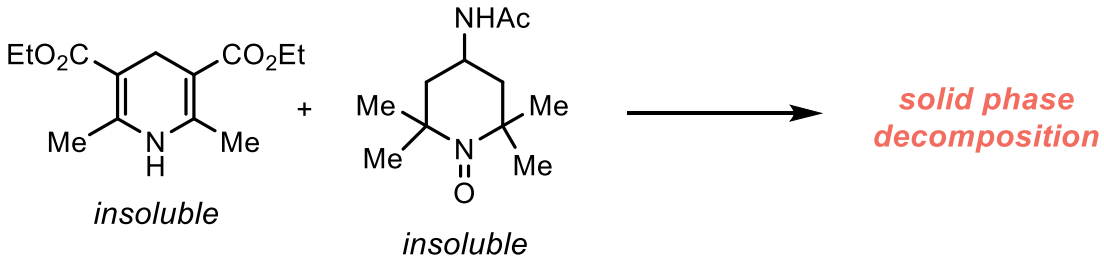
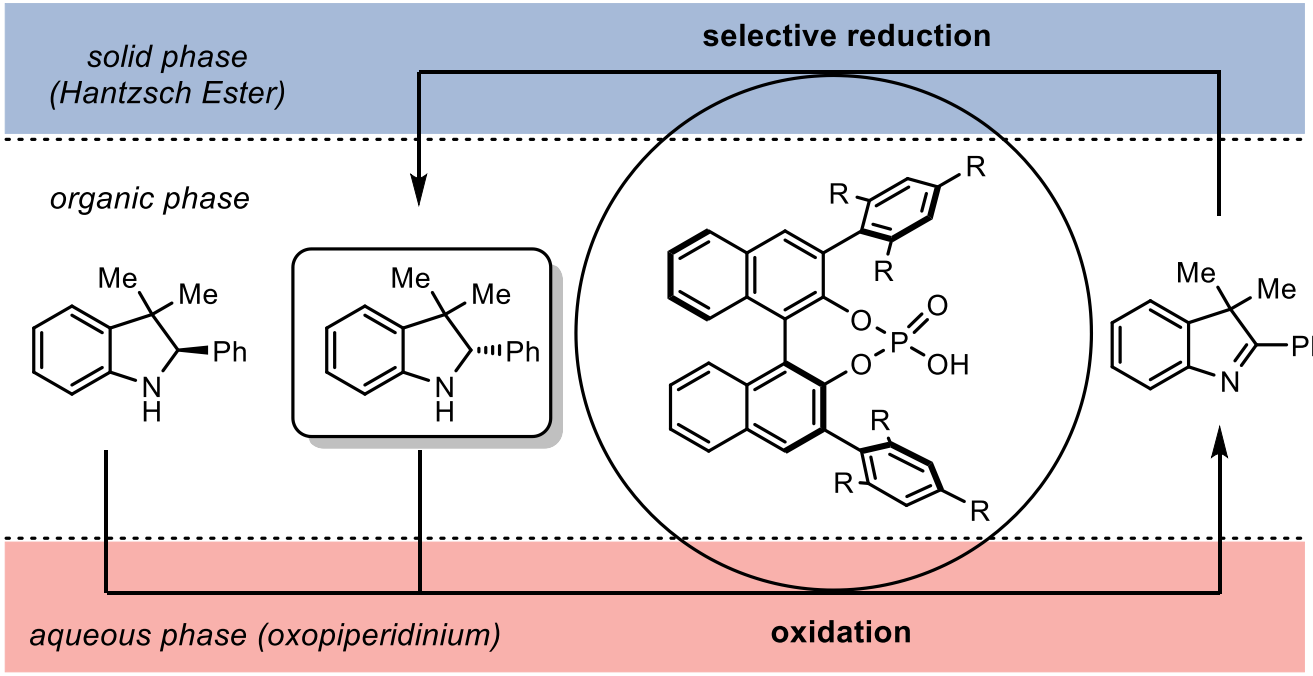


- Therefore, a three-phase strategy (solid, organic, and aqueous) was devised:



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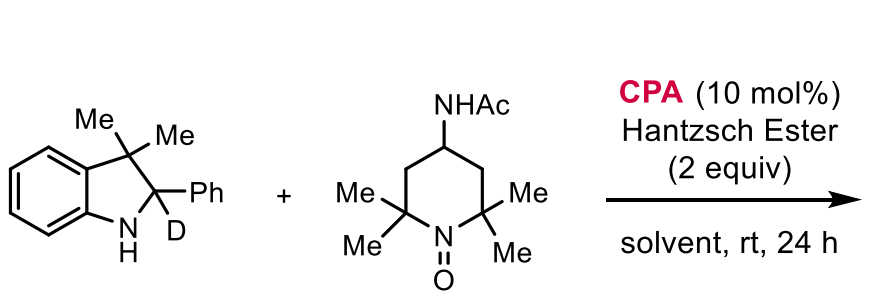
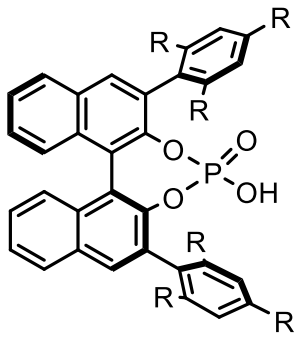


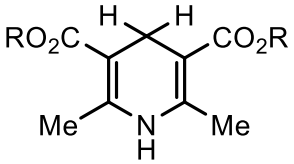
CPA (10 mol%)
Hantzsch Ester
(2 equiv)

solvent, rt, 24 h



CPA
Entry 1-7:
R = Cy
Entry 8:
R = *i*-Pr

entry	Hantzsch Ester	solvent	additive	H incorp (%)	ee
1	**1a**	**PhMe**	-	**0**	**0**
2	**1a**	**1:1 PhMe/H_2O**	-	**5**	**4**
3	**1a**	**9:1:10 Hex/Et_2O/H_2O**	-	**68**	**67**



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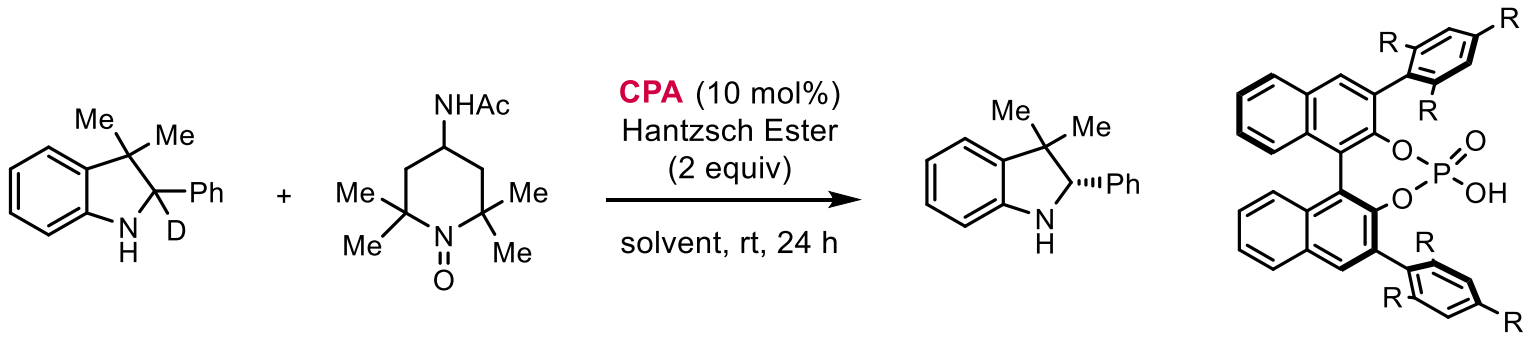

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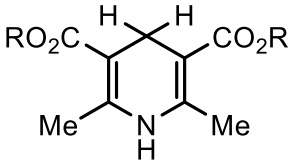
4	1a	9:1:10 Hex/Et_2O/H_2O	HCl	84	81
5	1b	9:1:10 Hex/Et_2O/H_2O	HCl	56	56



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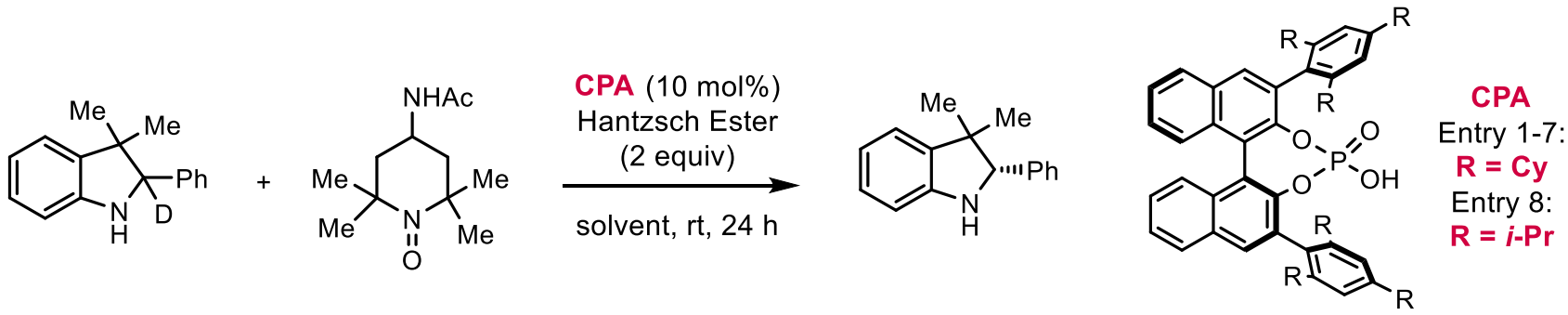

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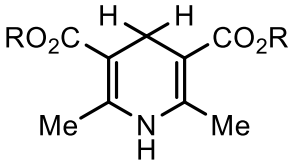
7	1d (1.5 eq)	9:1:10 Hex/Et_2O/H_2O	HCl	96	92



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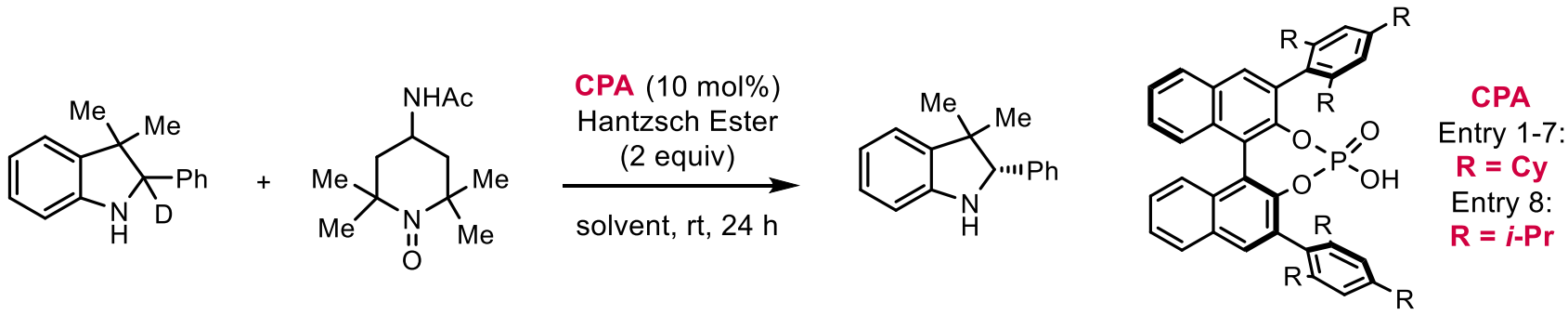

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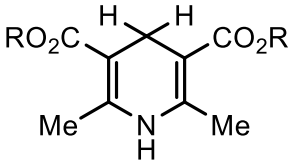

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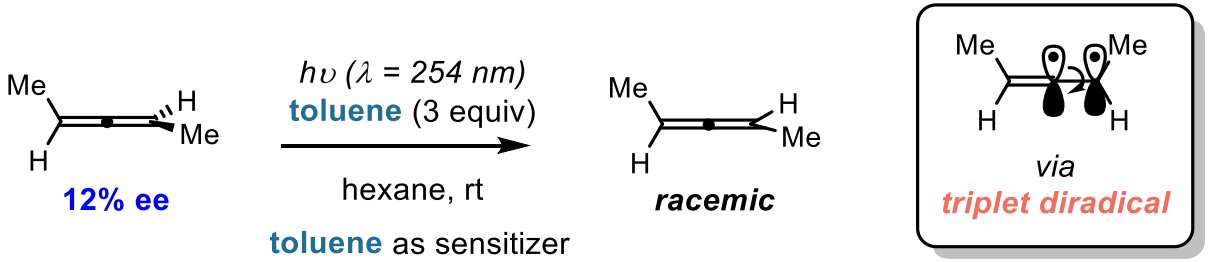

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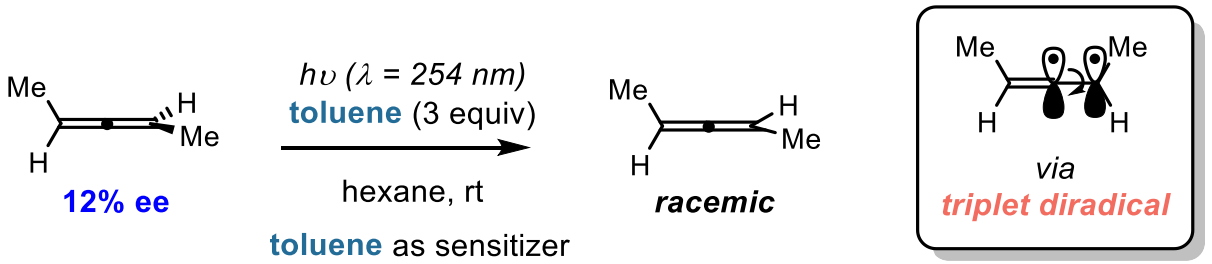

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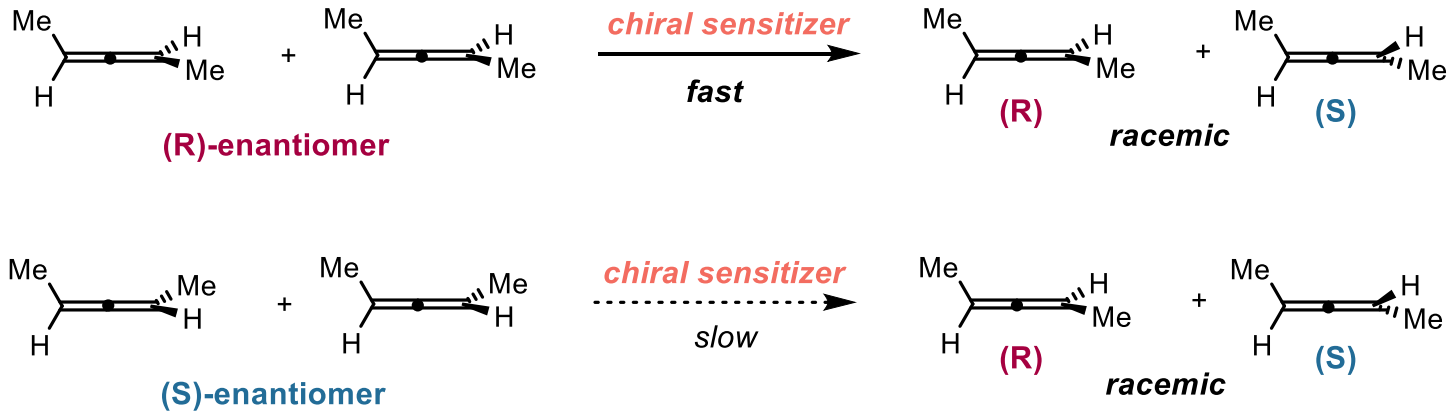

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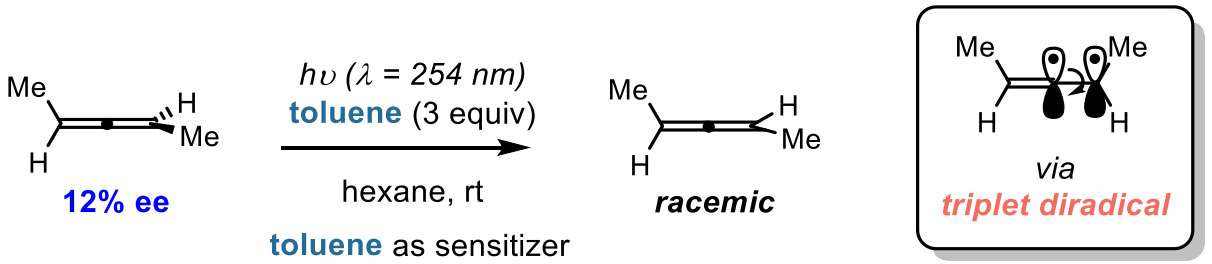

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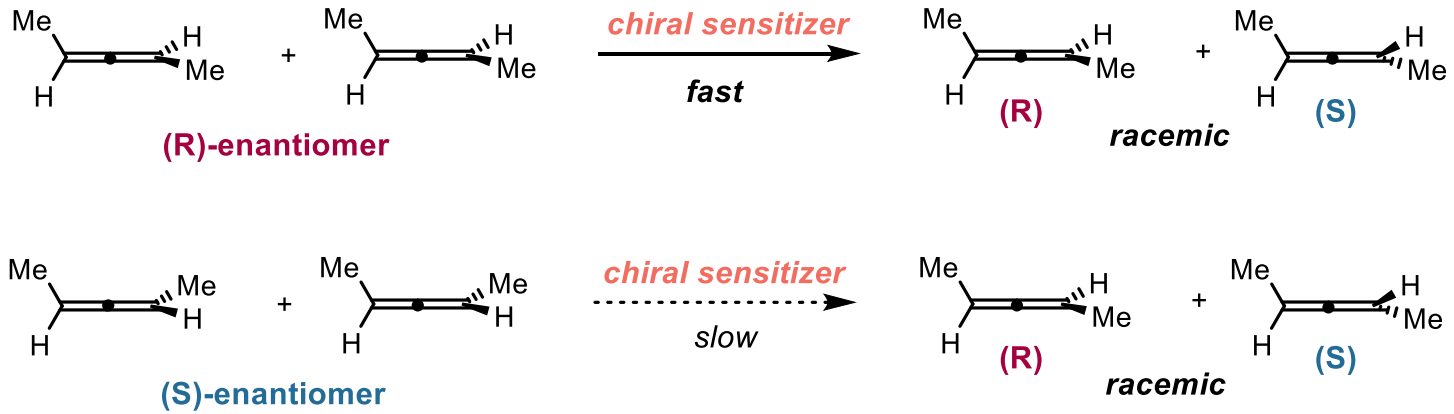

Continuous cycling of substrate will lead to accumulation of (S)

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Deracemization: Photochemical excitation of axially chiral molecules

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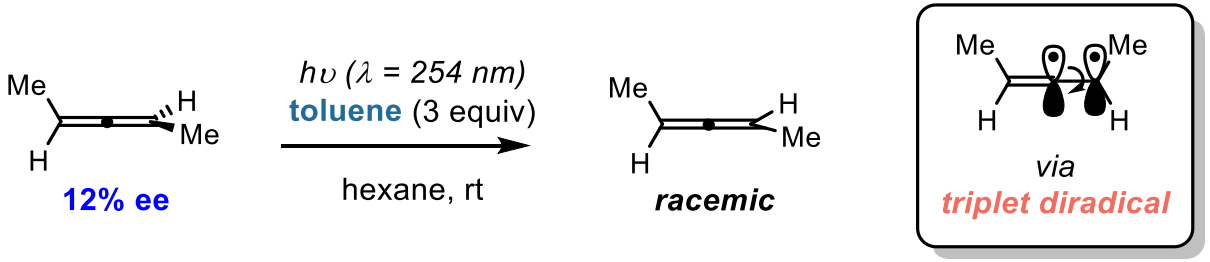

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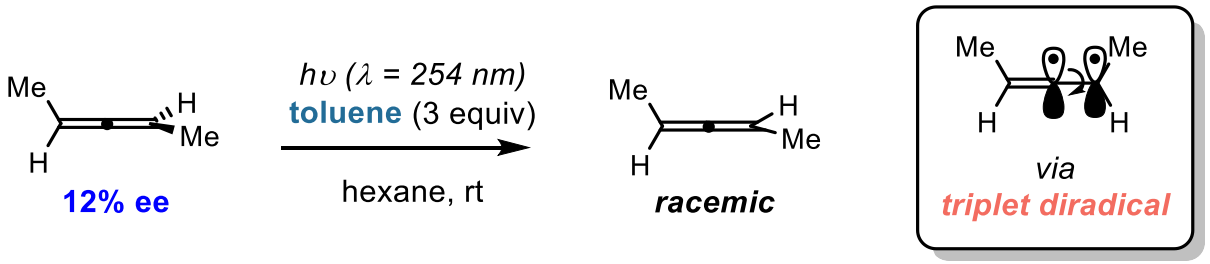
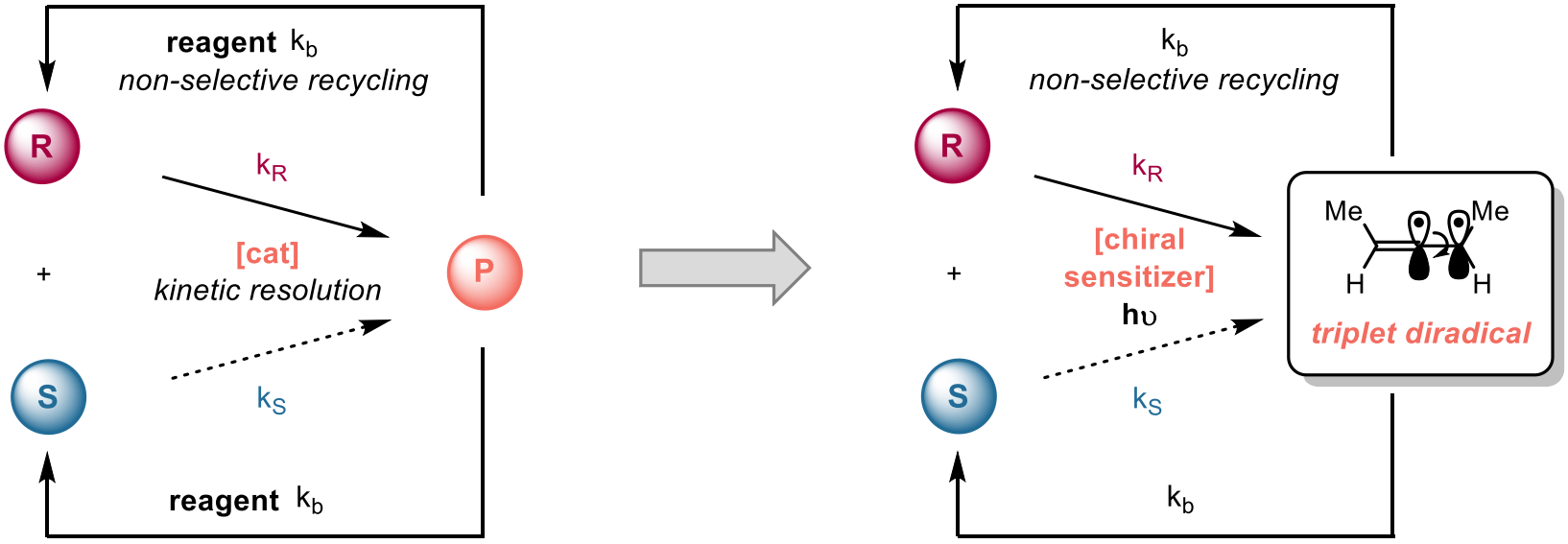


- Light (the source of energy) and a chiral catalyst selectively form a high energy intermediate that non-selectively recycles to the racemic substrate:



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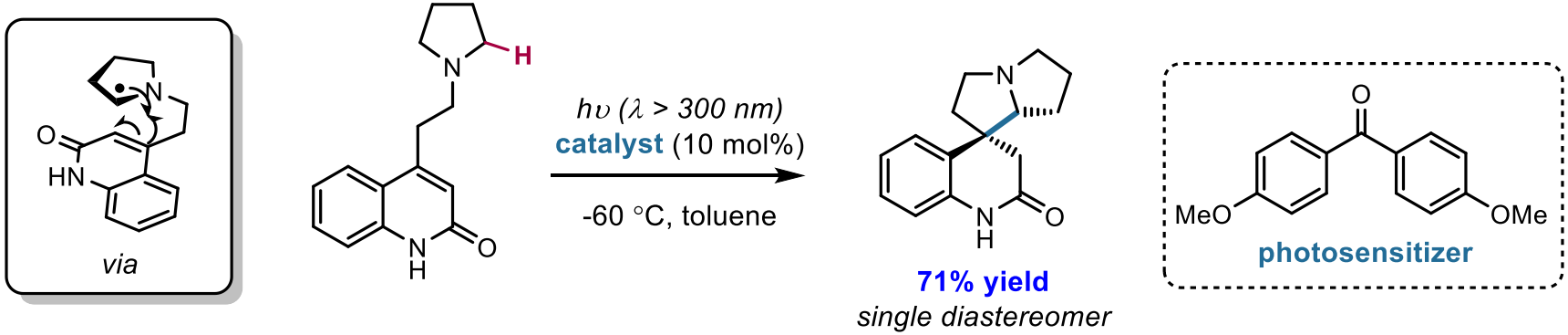

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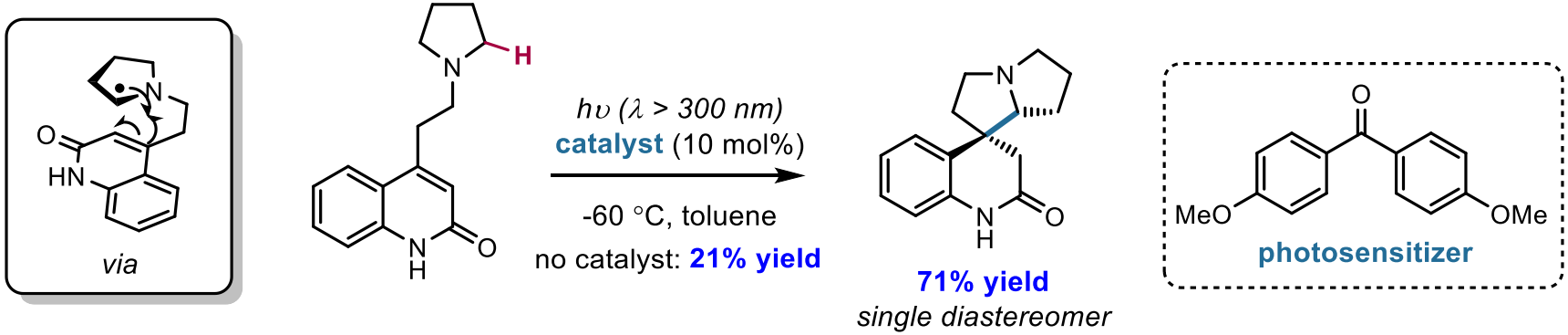

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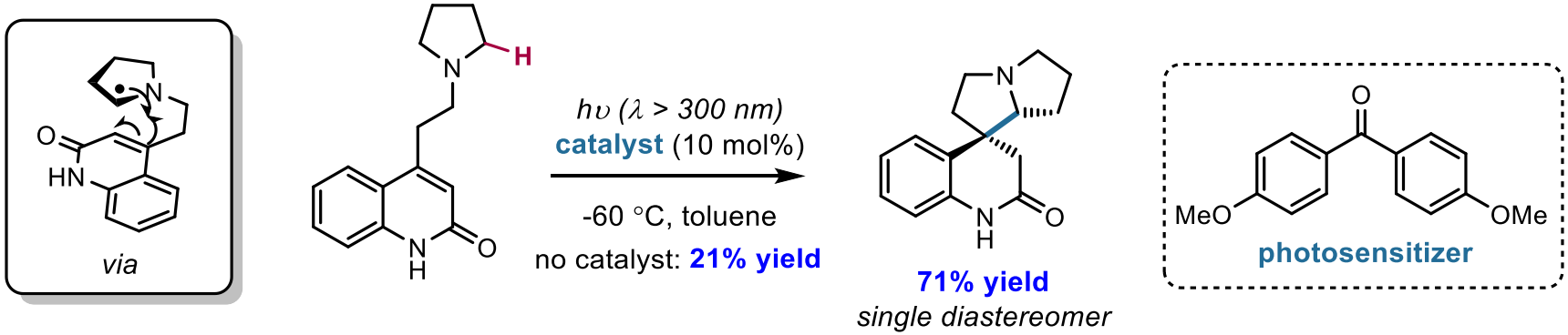

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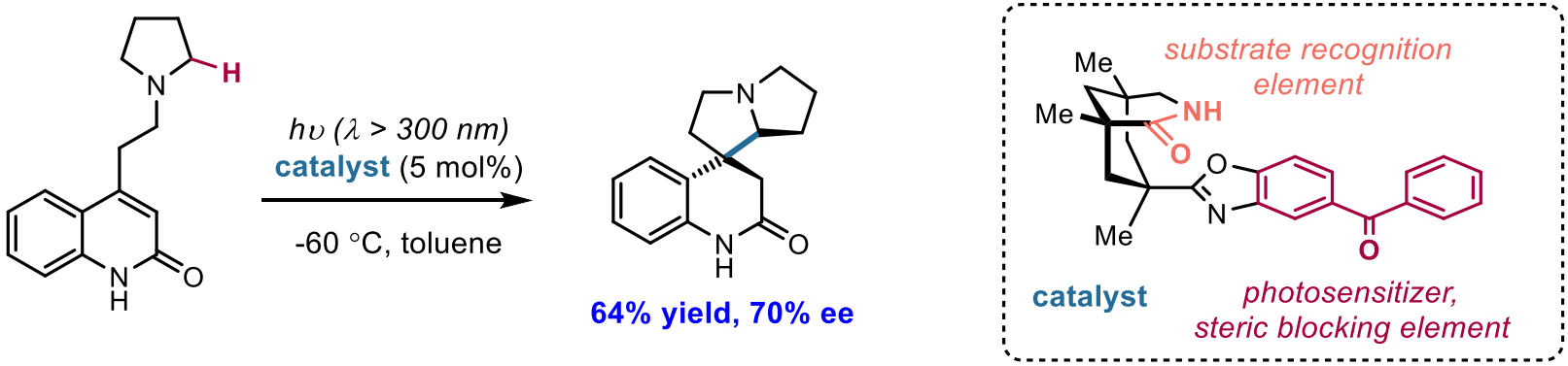

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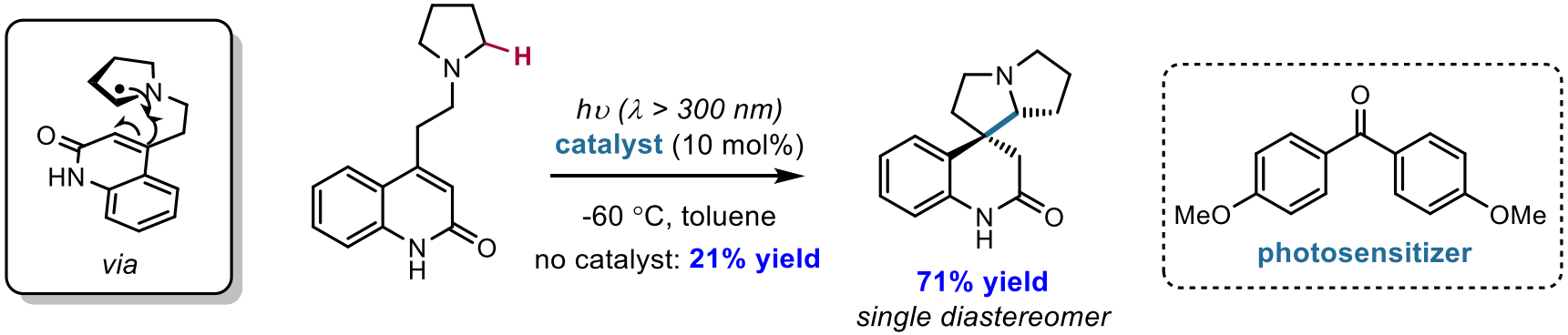

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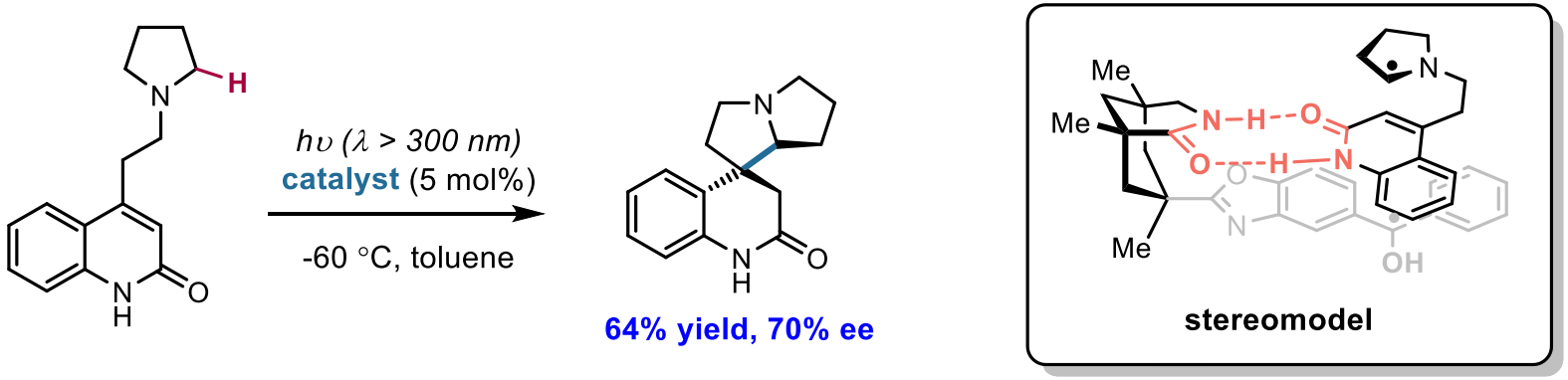

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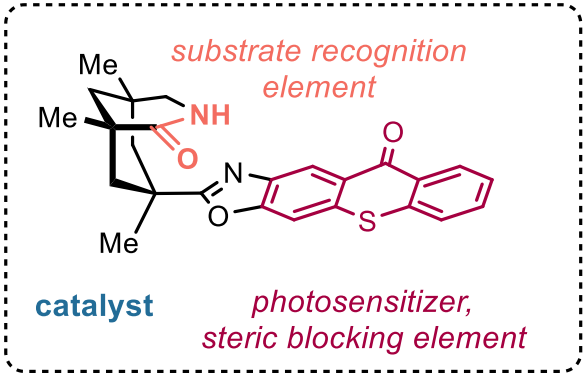

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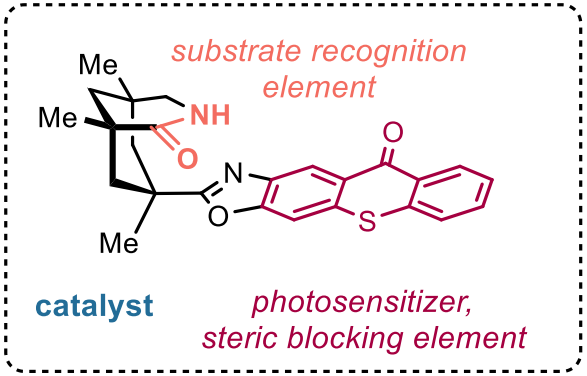

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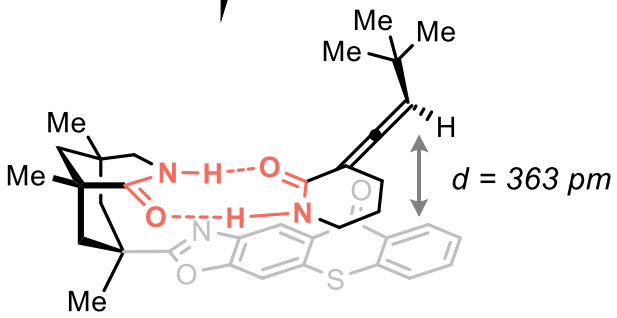
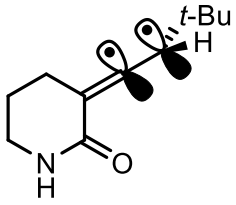
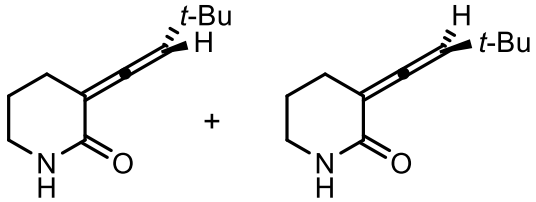


intramolecular energy transfer





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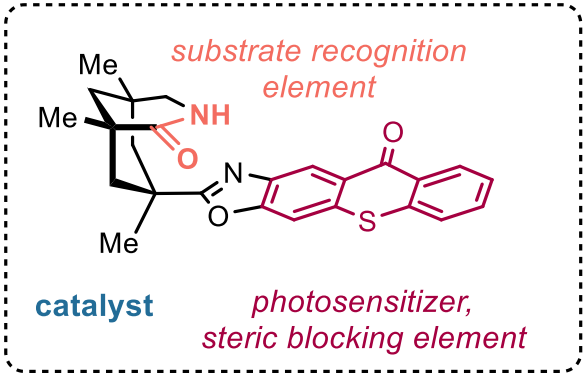
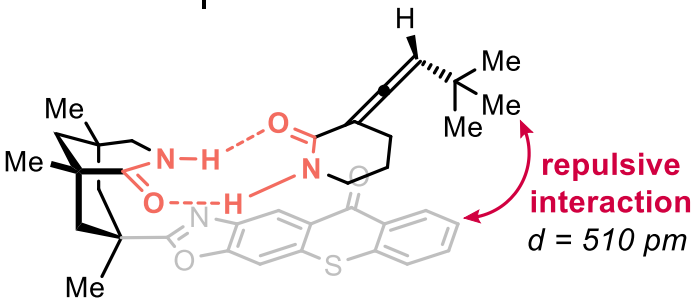
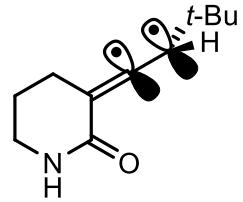




inefficient energy transfer

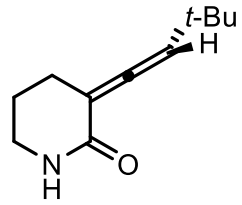


triplet diradical inaccessible

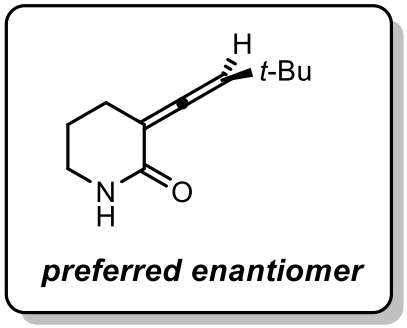
Bach, T.; et al. *Nature* **2018**, *564,* 240.

Allene Deracemization: Reaction Design and Implementation

- The concept of hydrogen-bonding chiral recognition could be used to selectively sensitize allenes

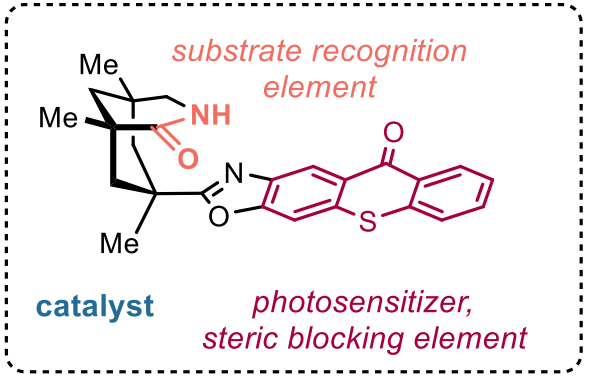


racemic mixture



preferred enantiomer

not reactive



Bach, T.; et al. *Nature* **2018**, *564,* 240.

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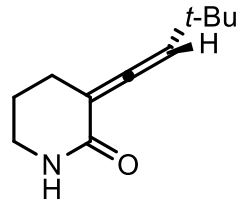

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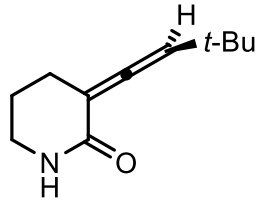

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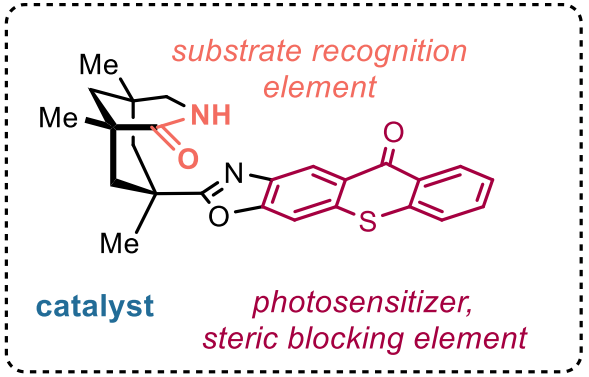
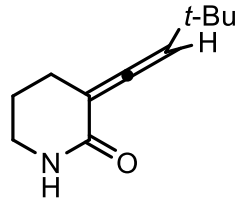


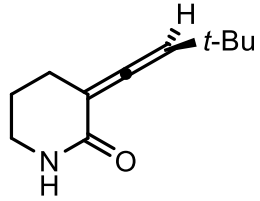
- Irradiating either enantiomer with catalyst results in rapid formation of the preferred enantiomer:



racemic mixture

λ = 420 nm
catalyst (2 mol%)

MeCN (10 mM), 4 h
T = 25 °C



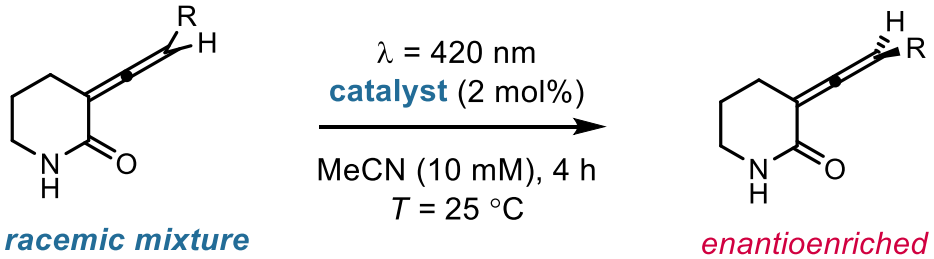
89% yield, 96% ee

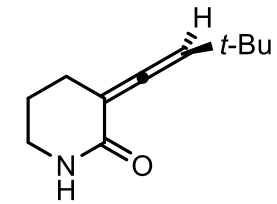
H-bonding is critical for high enantioselectivity
solvent = MeOH, **10% ee**

Bach, T.; et al. *Nature* **2018**, *564,* 240.

Allene Deracemization: Substrate Scope

- The concept of hydrogen-bonding chiral recognition could be used to selectively sensitize allenes

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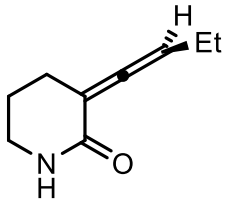
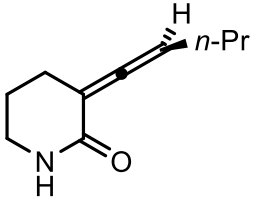
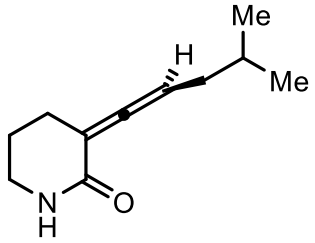
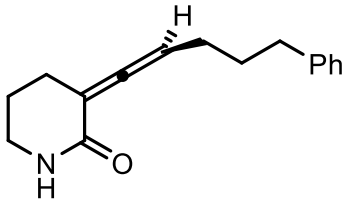
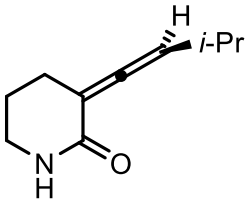
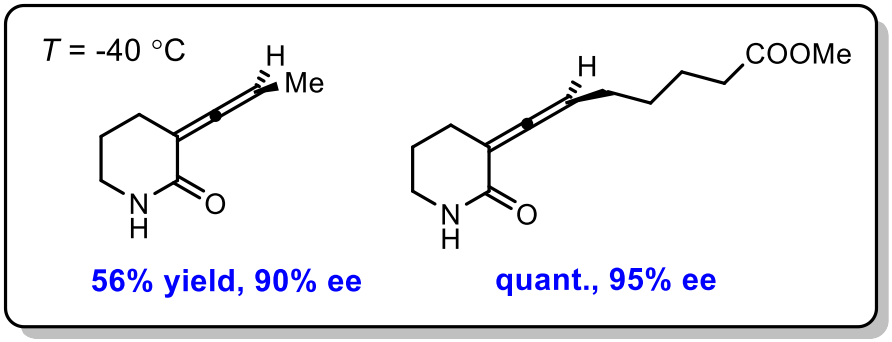

quant., 93% ee


84% yield, 92% ee


98% yield, 91% ee


52% yield, 89% ee


78% yield, 95% ee



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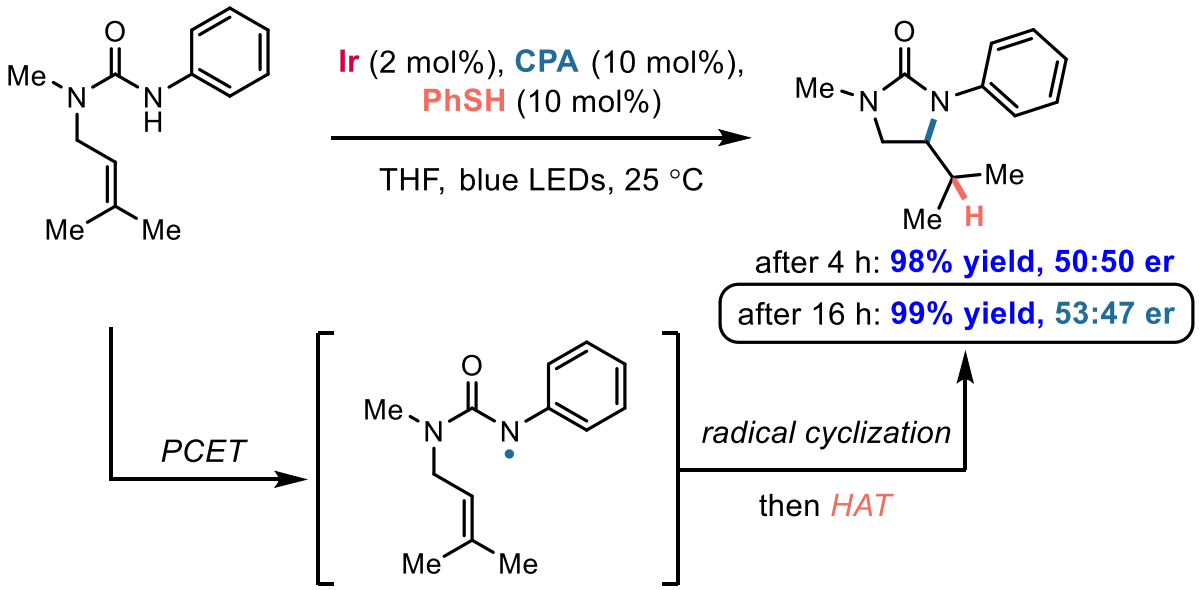
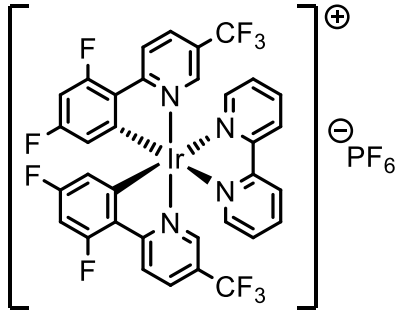
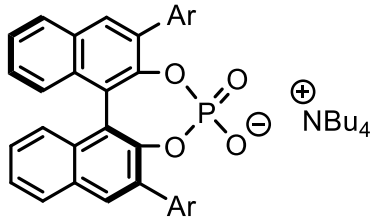
Deracemization of Ureas via Excited-State Electron Transfer

- Knowles observed unexpected product enantioenrichment under PCET hydroamination conditions





[Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ **(Ir)**



Chiral phosphate

Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137,* 13492.
Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

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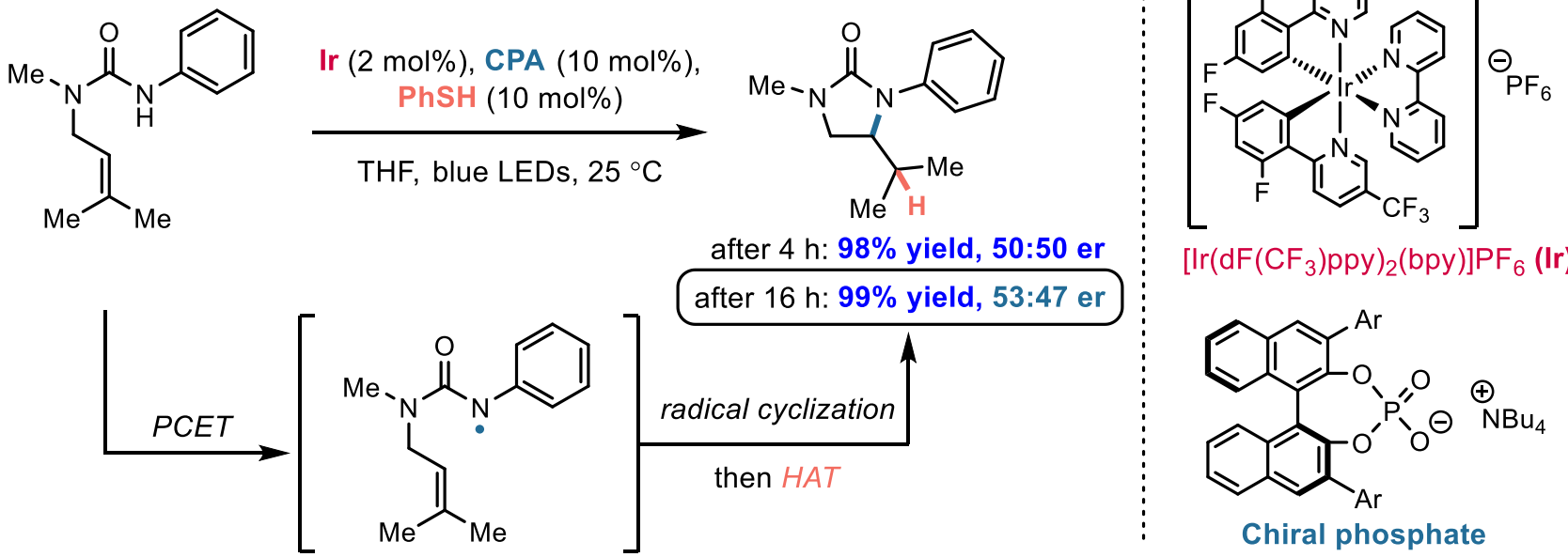

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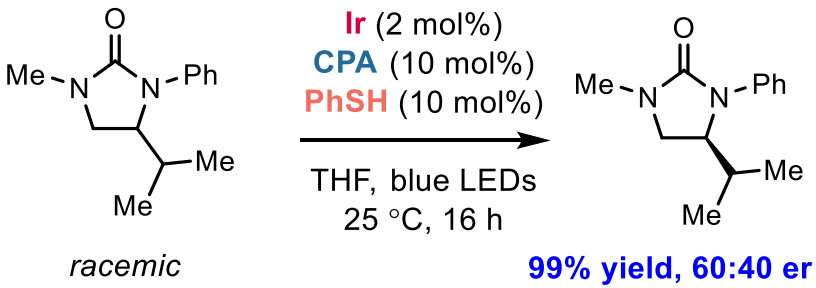
Deracemization of Ureas: Design Strategy

- The potential for a deracemization approach was then recognized:



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99% yield, 60:40 er

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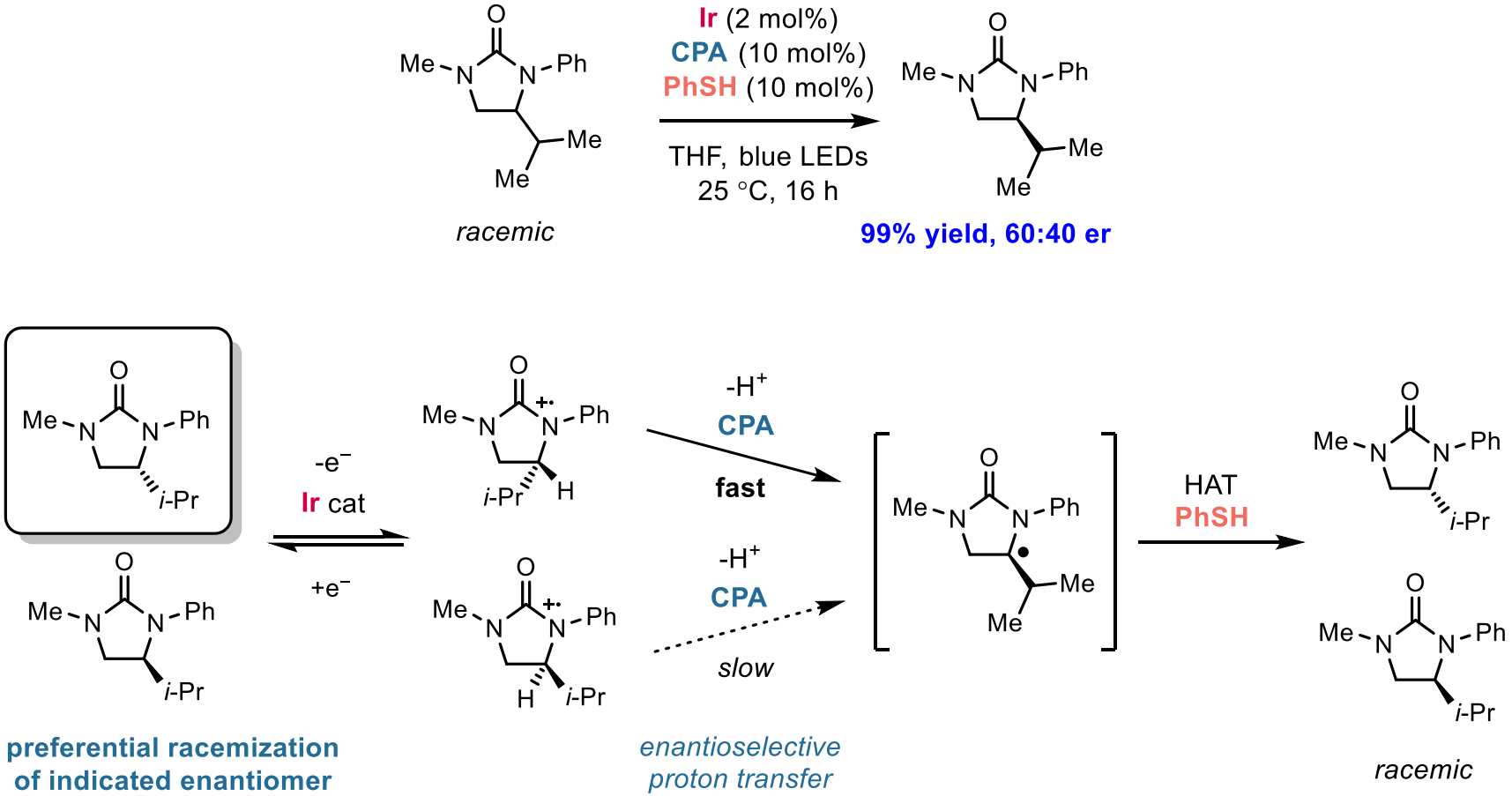
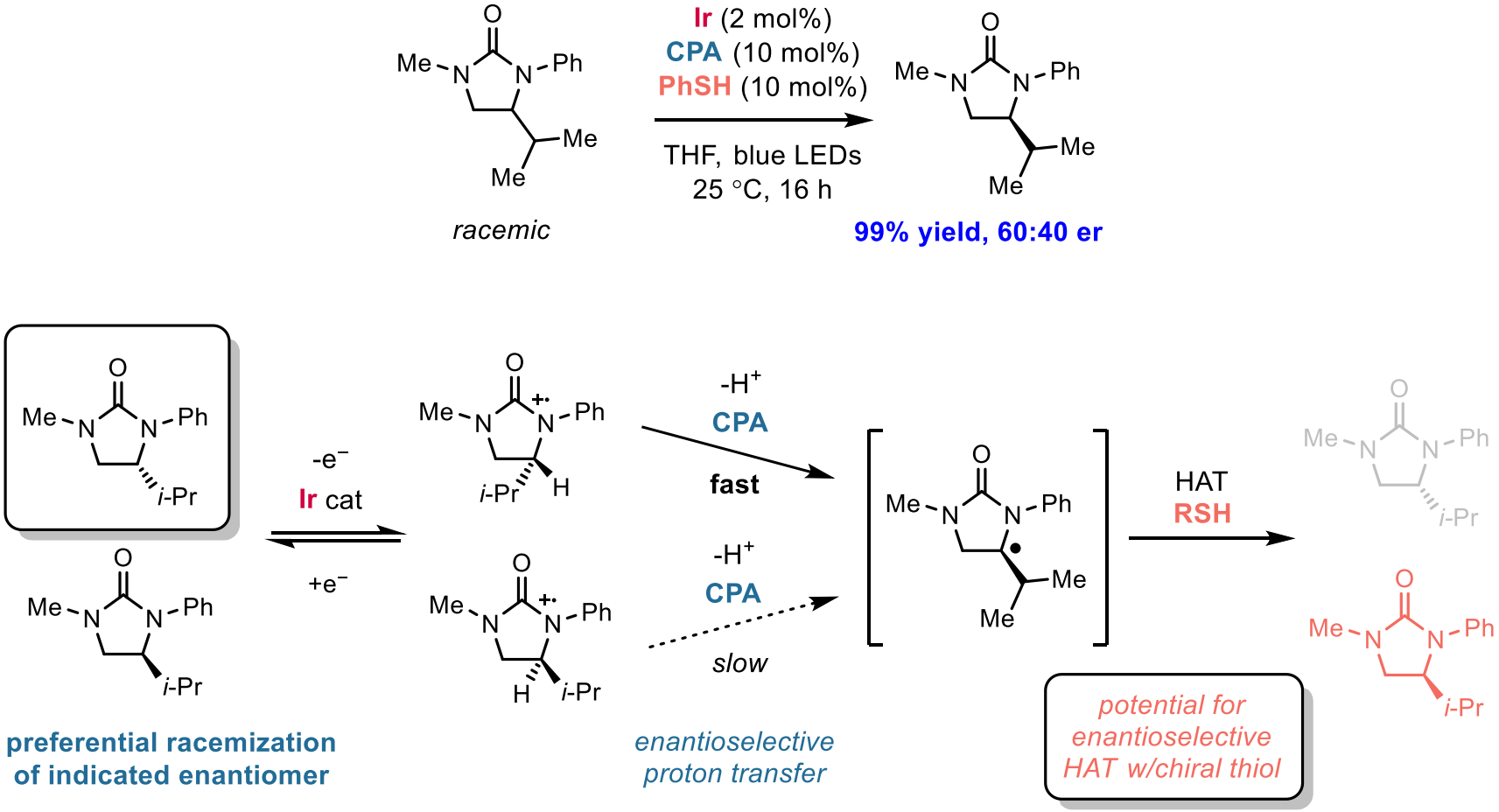


Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

Deracemization of Ureas: Design Strategy

- The potential for enantioselective HAT to regenerate the substrate was also recognized :



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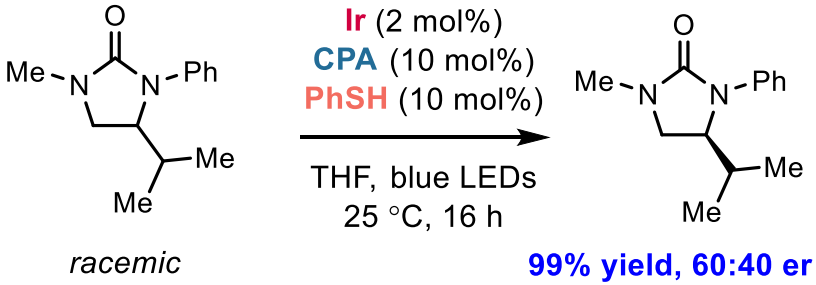

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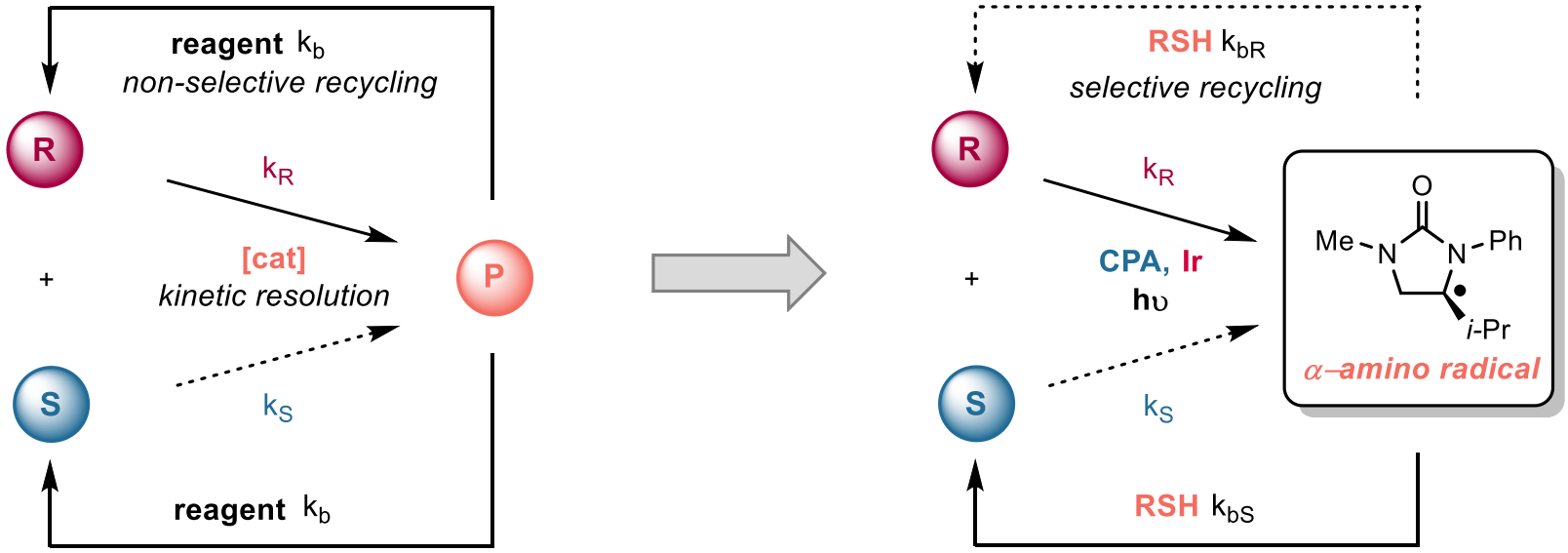
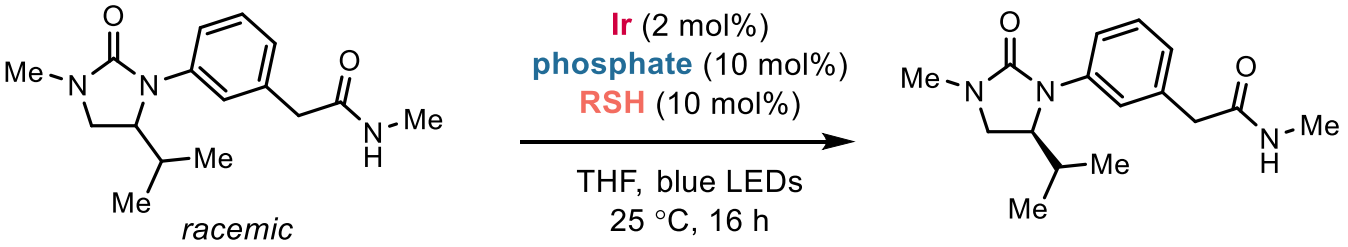


Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

Deracemization of Ureas: Catalyst Evaluation

- Use of a chiral phosphate and chiral thiol together gave the highest selectivity



entry	phosphate	thiol	additives	yield (%)	er
1	**CPA**	**PhSH**	-	**84**	**79:21**
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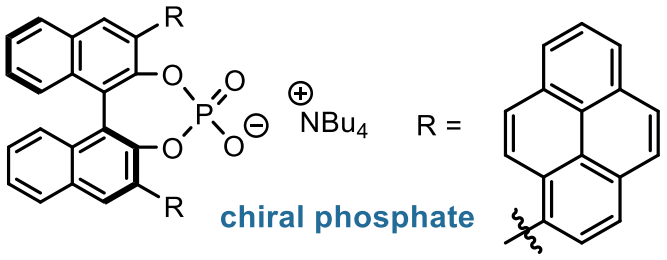

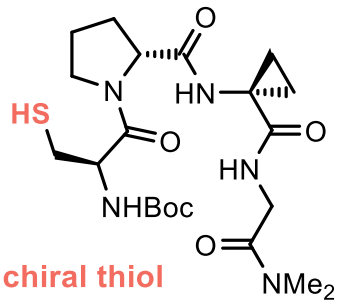

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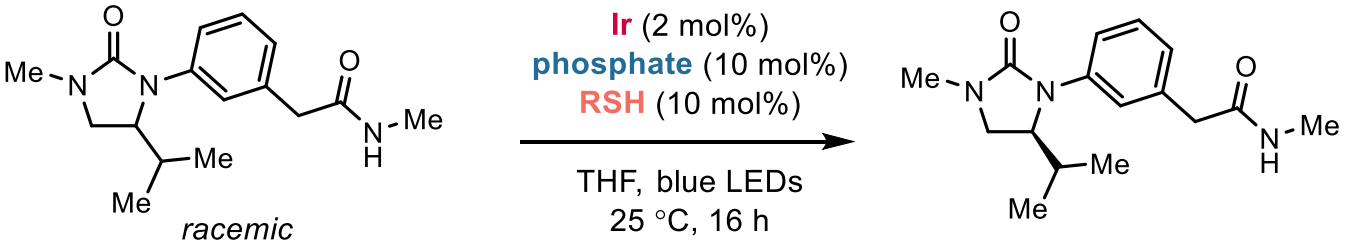

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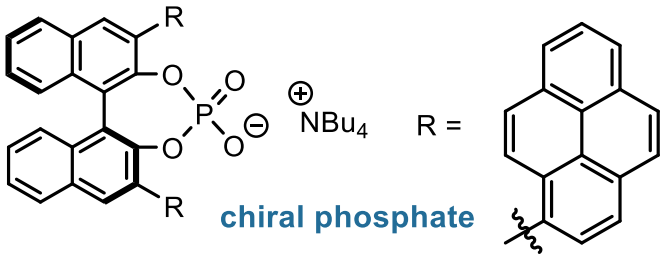
5	**CPA**	**chiral RSH**	MS, 25 mol% tol	**96**	**96:4**



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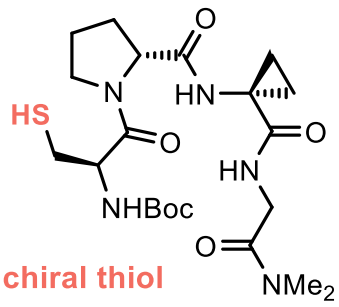

chiral thiol

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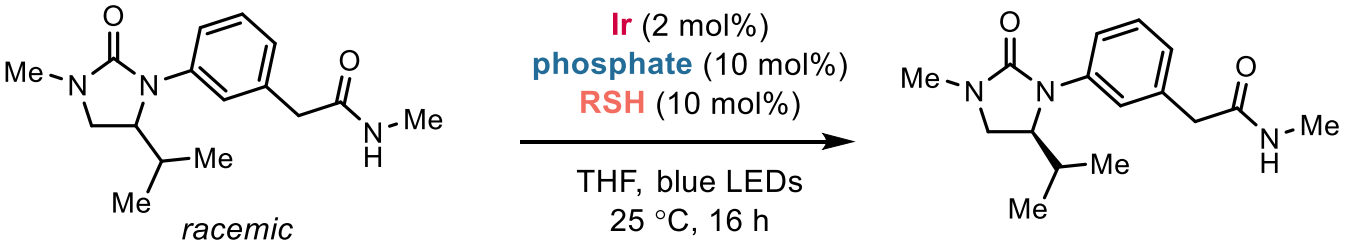

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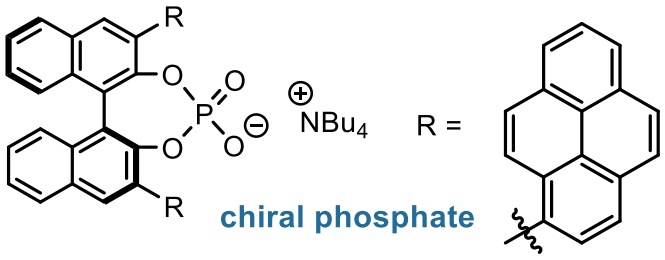
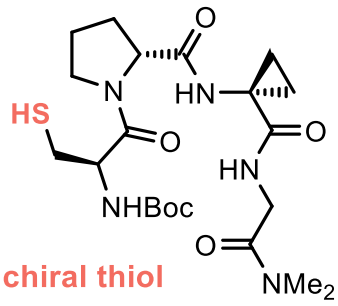
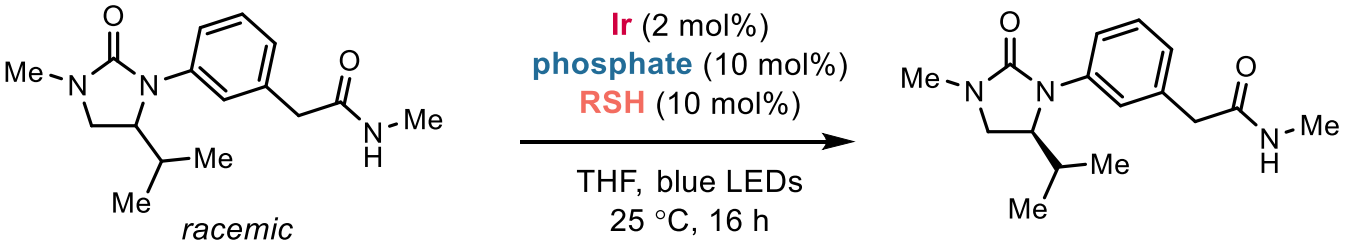


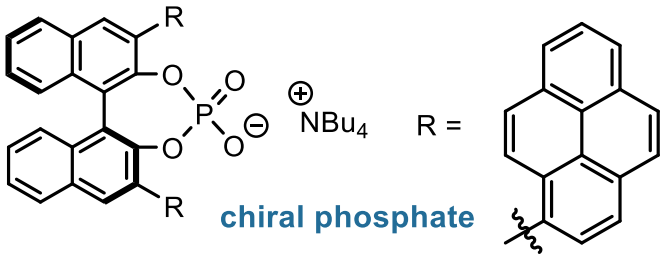


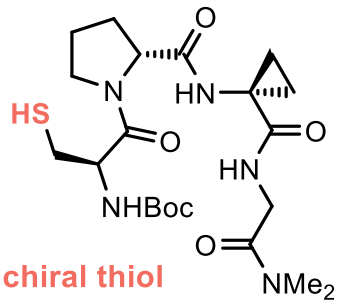
Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

Deracemization of Ureas: Stereoinversion

- This system was also capable of performing selective stereoinversion:







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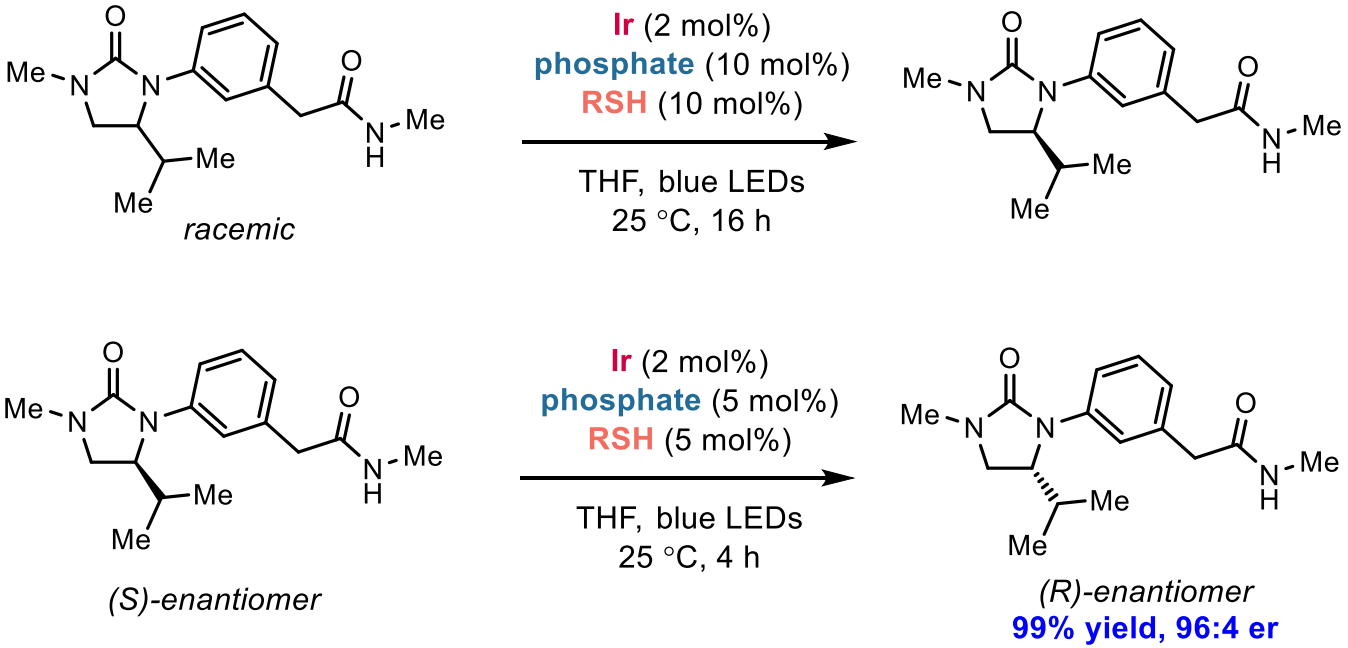

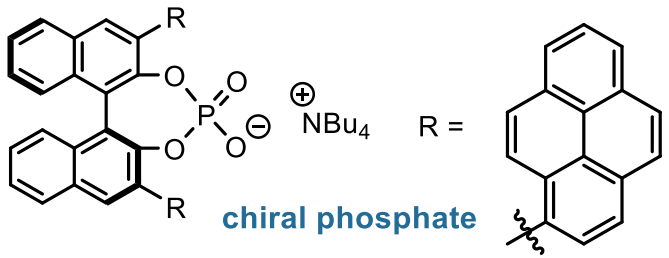

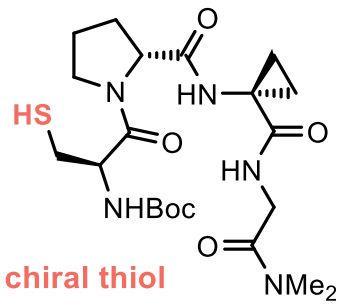

Knowles, R. R.; et al. *Science* **2019**, *366*, 364.

Conclusion

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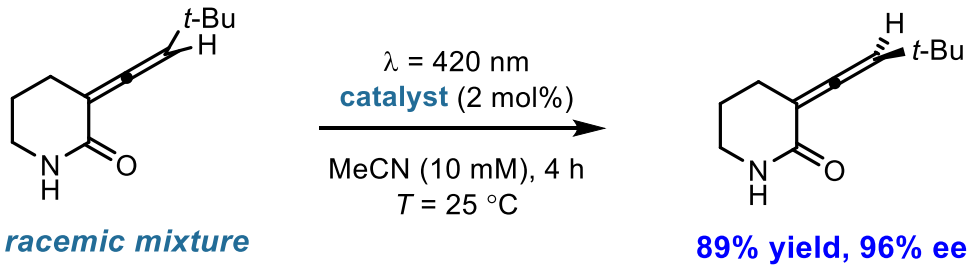

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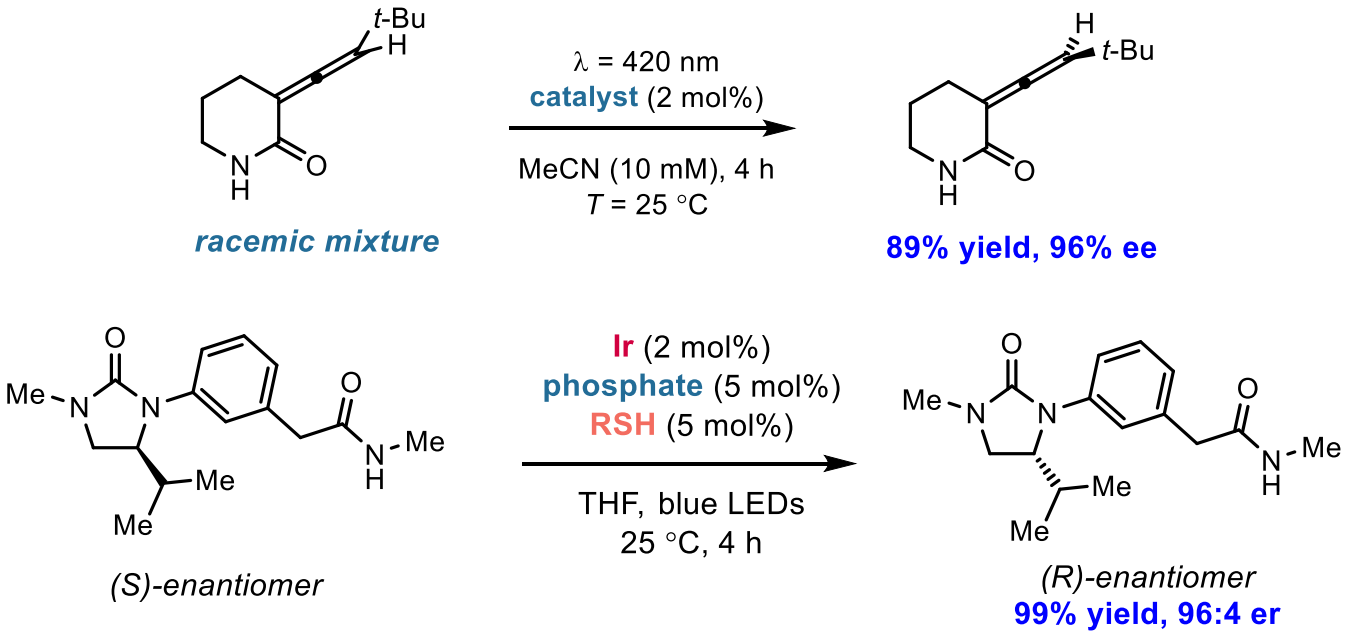

Conclusion

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- Light is a particularly promising energy source to drive selective formation of a single enantiomer
- Considerable limitations remain with regards to substrate scope and synthetic utility

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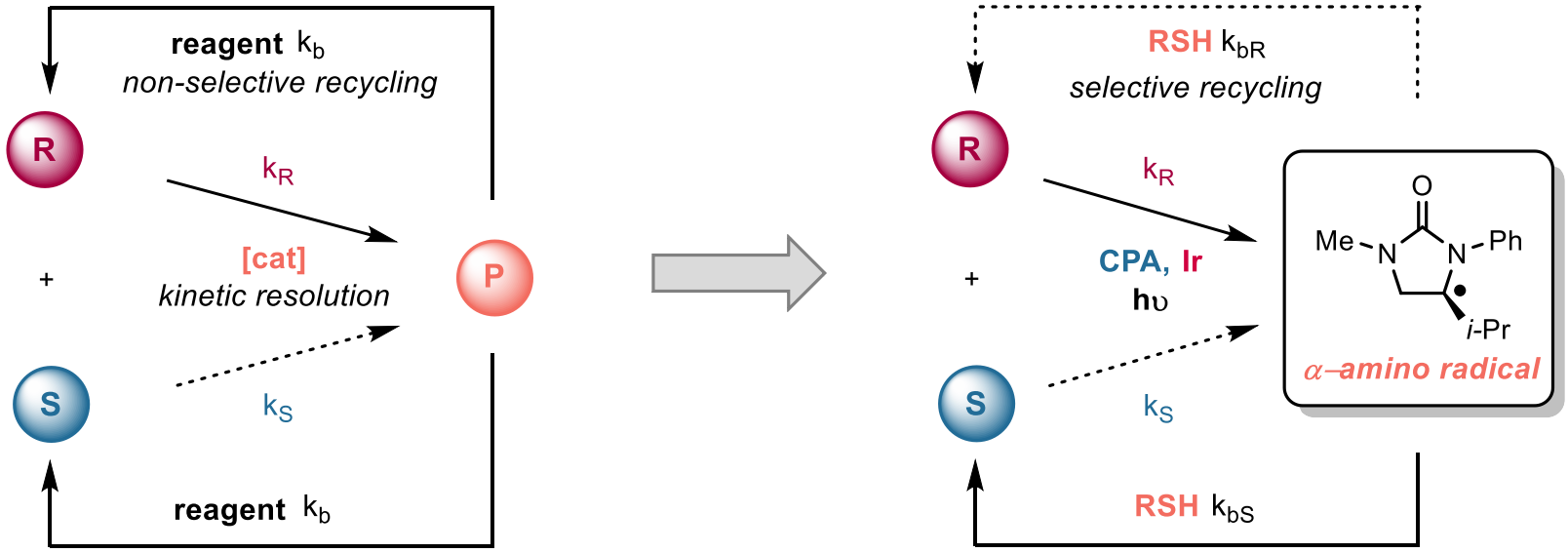
- Deracemization has recently seen increased activity as a field of asymmetric catalysis
- Light is a particularly promising energy source to drive selective formation of a single enantiomer
- Considerable limitations remain with regards to substrate scope and synthetic utility
- However, further study of system and catalyst design may result in more practical systems: