Photochemical and Photocatalytic Deracemization Reactions

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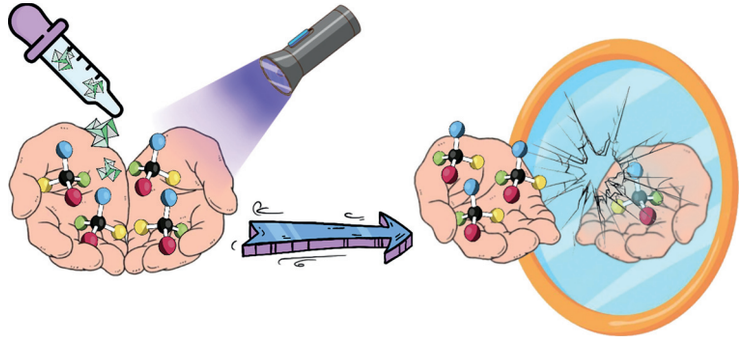

Received: 25.05.2024
Accepted after revision: 07.08.2024
Published online: 14.10.2024 (Version of Record)
DOI: 10.1055/s-0040-1720146; Art ID: SO-2024-05-0020-GR

Abstract Under photochemical conditions using an appropriate chiral catalyst, racemic mixtures of compounds can be converted into enantioenriched mixtures through distinguished pathways known as photochemical and photocatalytic deracemization reactions. In this graphical review, we highlight photochemical deracemization reactions that proceed in the presence of light as the key element along with a suitable chiral photocatalyst.

Key words photochemical deracemization, chiral compounds, enantioenrichment, photocatalyst, photoredox

The resolution of racemic mixtures into their constituent enantiomers is a very important area of research for chemists. The valuable applications and advanced properties of enantiomerically pure compounds in pharmaceuticals, catalysis, and materials, in comparison with their racemates, is one of the main reasons for this pursuit, leading chemists toward new pathways and reactions conditions, aiming to enhance the efficiency of deracemization reactions.

In this graphical review, we focus on photochemical deracemization reactions that occur using light as the critical element in the presence of suitable chiral photocatalysts. Due to the high-atom economy and efficient enantioenrichment of photocatalytic deracemization reactions in most cases, it has become a preferred technique among other methods for deracemization reactions.

Photons and chiral photocatalysts, as key components of these reactions, can make specific stereocenters of racemic compounds editable. This phenomenon occurs via the utilization of light to overcome thermodynamic constraints. Furthermore, the chiral photocatalyst cooperates with photons and facilitates the pathway for molecules to reach the excited state, which includes planar intermediates. The excited state plateau is also capable of inhibiting microscopic reversibility, which is a serious kinetic obstacle in deracemization reactions. In the next step, according to the particular mechanism of the reaction, the achiral intermediate can convert into both enantiomers, albeit the formation of one enantiomer is favorable over the other.

Considerable advancements have occurred in the field of photochemical and photocatalytic deracemization over the past few years. In this graphical review, we have attempted to compile these studies along with some early reports on photochemical deracemization, and organize the topic into logical classifications. We have thus classified these photochemical deracemization reactions into two major categories based on their different mechanisms: Energy-transfer-based (EnT) photocatalysis and photoredox catalysis. Consequently, each substrate is divided according to the photocatalyst applied.

In EnT-based photocatalysis, chiral photocatalysts can interact with each enantiomer in different ways to enable the stereoablative step that involves a prochiral intermediate, which is subsequently re-converted via an enantioselective transformation. Generally, the major enantiomer in the final enantiomeric mixture would be that which leads to steric hindrance with the chiral photocatalyst and results in a disfavored catalytic cycle, alongside a favored catalytic cycle which operates via the other enantiomer.

On the other hand, in photoredox catalysis, chiral organometallic complexes are mainly used, and the mechanism usually proceeds through different steps consisting of single-electron transfer (SET), hydrogen atom transfer (HAT) and enantioselective proton transfer (PT). It must be pointed out that in this mechanism each substrate can follow a specific and unique pathway based on its structural features. In some photoredox-based catalysis deracemization reactions, in addition to using the appropriate chiral photocatalyst, it may be necessary to use another additive.

Biographical Sketches

Seyed Parsa Hashemian was born in 2003 in Karaj, Iran. He is currently a B.Sc. student in chemistry at Kharazmi University, Tehran, Iran. His research focuses on photochemical deracemization reactions, a field he finds particularly interesting and intends to pursue further.

Seyed Mohammad Arabi Zanjani was born in 2002 in Tehran, Iran. Currently, he is an undergraduate student of chemistry at Kharazmi University, Tehran, Iran. In 2023, he joined the research group of Prof. Teimouri. His current research interests include multi-component reactions and photochemical reactions.

Tara Afshar Moghadam was born in 2002 in Tehran, Iran. At present, she is an undergraduate student of chemistry at Kharazmi University, Tehran, Iran. Her research interests encompass photochemical reactions and their pharmaceutical applications.

Mohammad Bagher Teimouri was born in 1975 and studied chemistry at Tabriz University, Iran. He subsequently completed his Ph.D. in 2004 with Prof. Ahmad Shaabani at Shahid Beheshti University. After being an assistant professor at the Iran Polymer and Petrochemical Institute, he moved to Kharazmi University as an associate professor, where he was promoted to full professor in 2022. His research focuses on the development of new multicomponent reactions (MCRs), especially on isocyanide-based and enaminone-based MCRs, MCRs in/on water, stereoselective transformations and the synthesis of novel functional dyes.

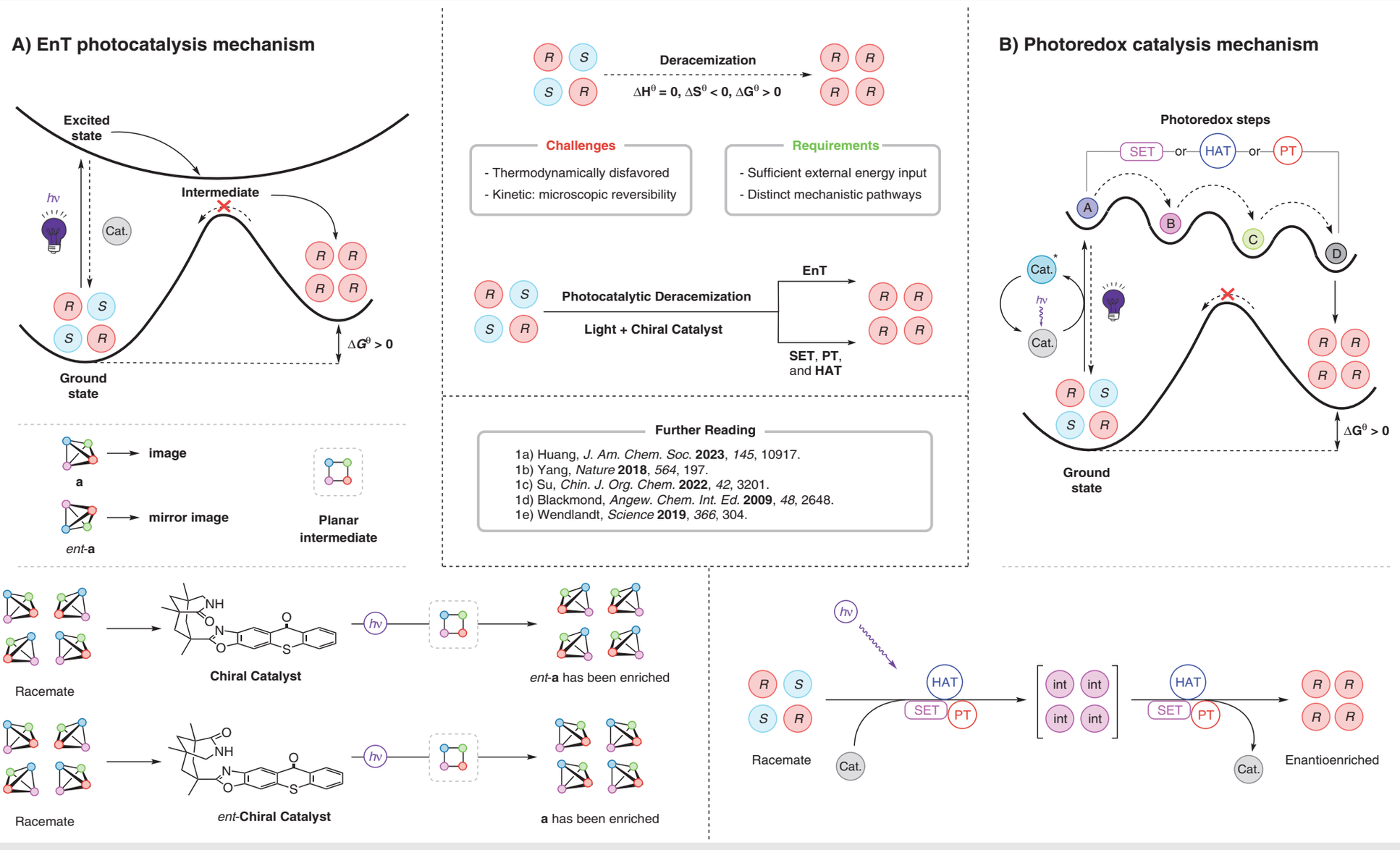

Figure 1 Overview of deracemization and distinct mechanisms for EnT catalytic and photoredox catalysis deracemization reactions[1a–e]

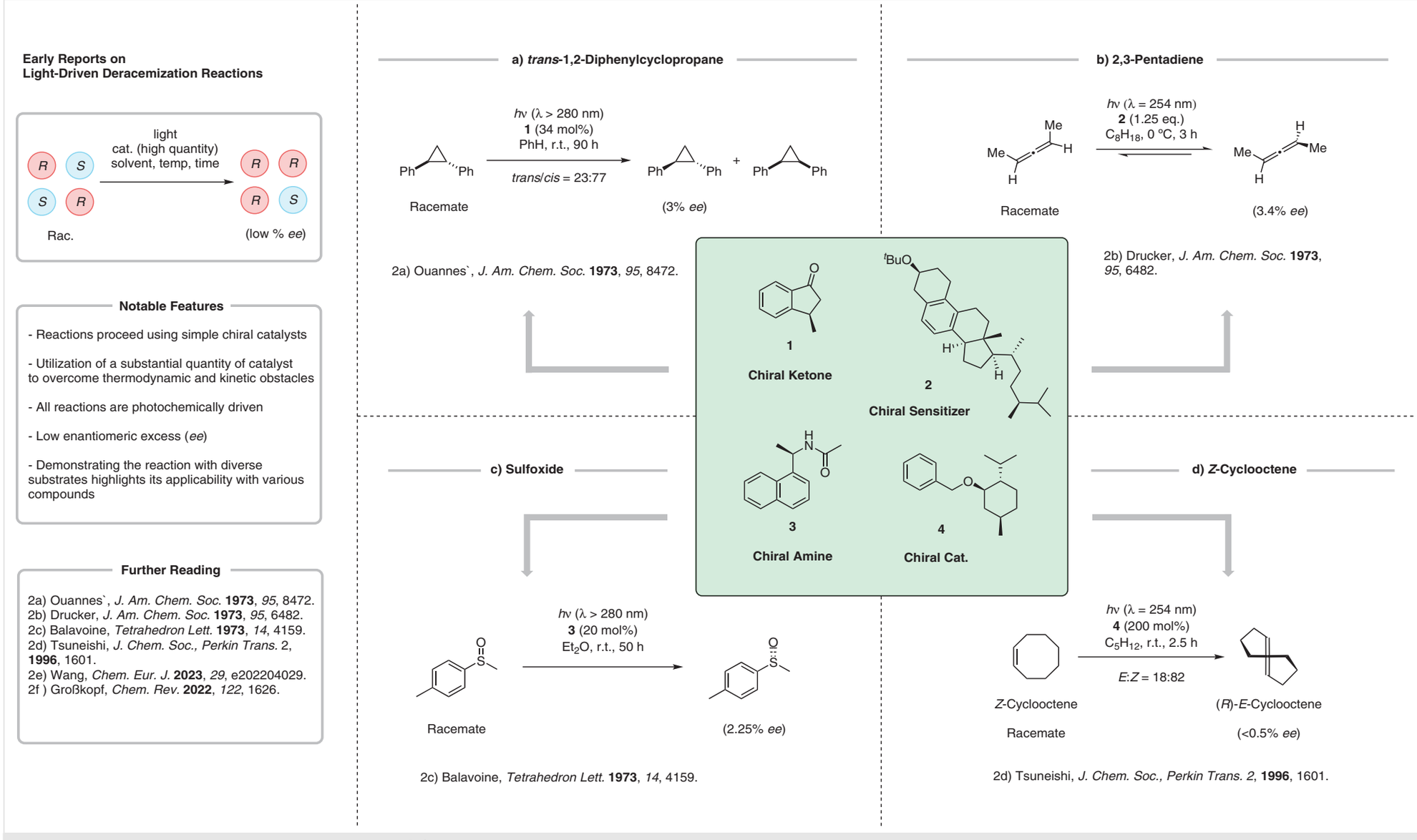

Figure 2 Early reports on photocatalytic deracemization reactions[2a–f]

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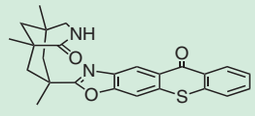
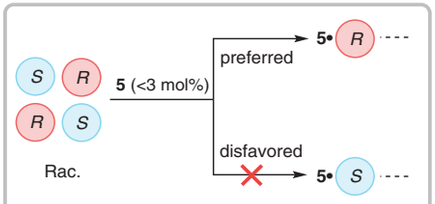
A) Energy-Transfer-Based (EnT) Photocatalytic Deracemization Reactions



5

Chiral Thioxanthone



Notable Features

- Allene lactam light-driven deracemization reactions proceed through a planar intermediate formed by C–C double bond cleavage

- The preferred cycle is always the one that avoids steric hindrance with catalyst **5**

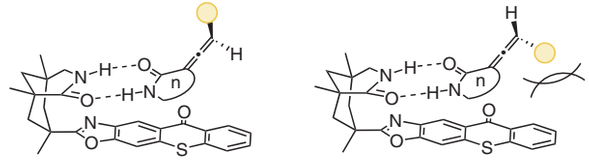
- The enriched enantiomer is always the one that does not prefer to form H-bonds with **5**

Further Reading

3a) Hölzl-Hobmeier, *Nature* **2018**, *564*, 240.
3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.
3d) Alonso, *Angew. Chem.* **2014**, *53*, 4368.
3e) Gotthardt, *Chem. Ber.* **1975**, *108*, 657.
3f) Shepard, *J. Am. Chem. Soc.* **1997**, *119*, 2597.
2e) Wang, *Chem. Eur. J.* **2023**, *29*, e202204029.

A.1) Allenes

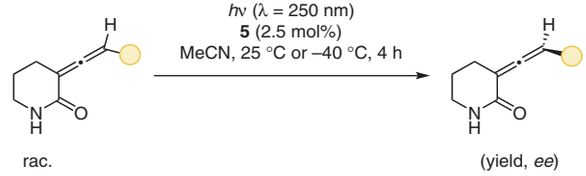
A.1.1) Allene Lactams



5•*ent*-A.1.1 **5•A.1.1**

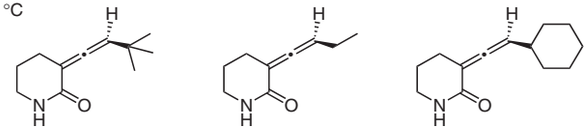
3a) Hölzl-Hobmeier, *Nature* **2018**, *564*, 240.
3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.

Six-Membered Allene Lactams
n = 6



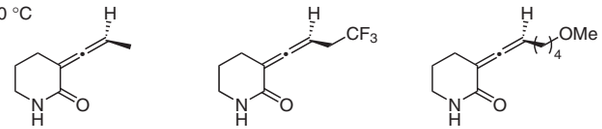
rac. (yield, *ee*)

T = 25 °C



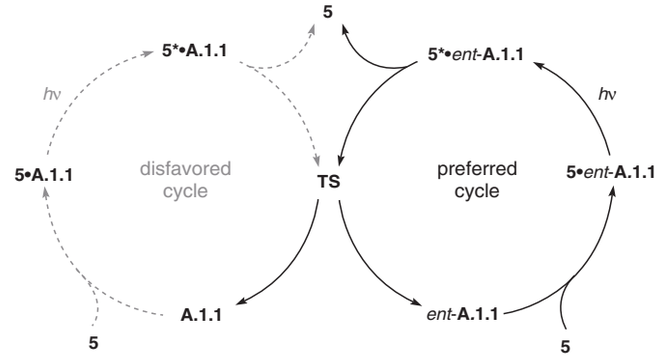
(89%, 96% *ee*) (quant., 93% *ee*) (76%, 94% *ee*)

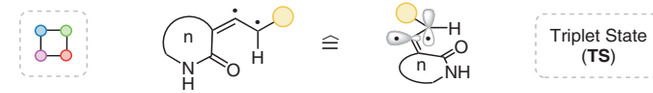
T = –40 °C

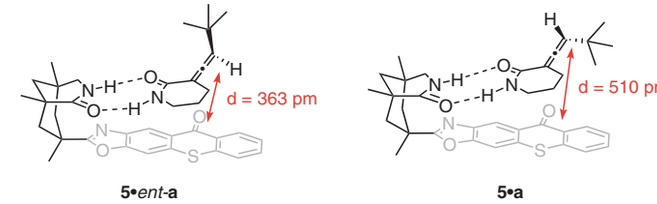


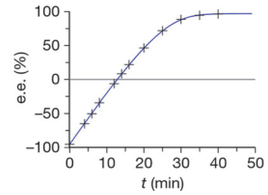
(56%, 90% *ee*) (92%, 89% *ee*) (94%, 94% *ee*)

3a) Hölzl-Hobmeier, *Nature* **2018**, *564*, 240.









(*ee*% - time) graph of the conversion of *ent*-**a** into **a**, with chiral thioxanthone **5**.

3a) Hölzl-Hobmeier, *Nature* **2018**, *564*, 240.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.

Figure 3 Light-driven deracemization reactions via energy-transfer-based photocatalysis[2e,3a–f]

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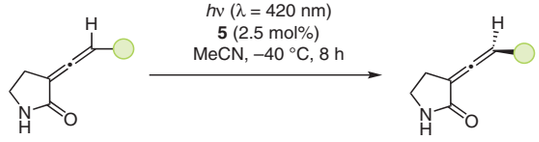
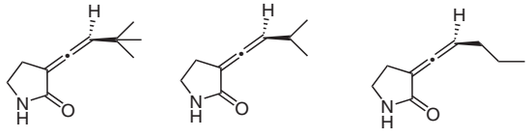
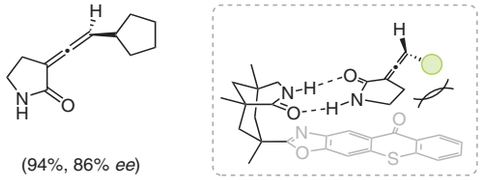
Five-Membered Allene Lactams
n = 5



rac. (yield, *ee*%)



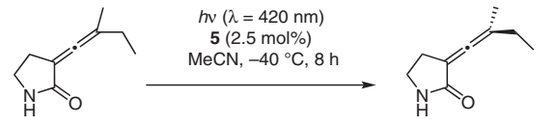
(92%, 98% *ee*) (96%, 96% *ee*) (80%, 89% *ee*)



(94%, 86% *ee*)

3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.

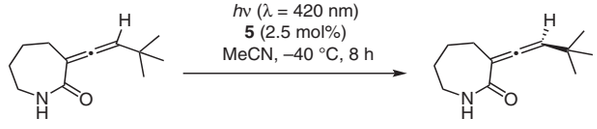
Five-Membered (Dialkyl-Substituted) Allene Lactams
n = 5



rac. (85%, 45% *ee*)

3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.

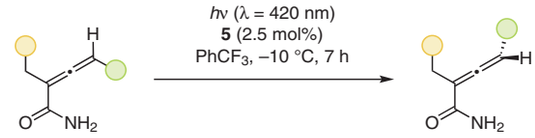
Seven-Membered Allene Lactams
n = 7



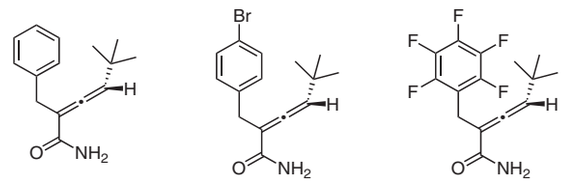
rac. (87%, 62% *ee*)

3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.

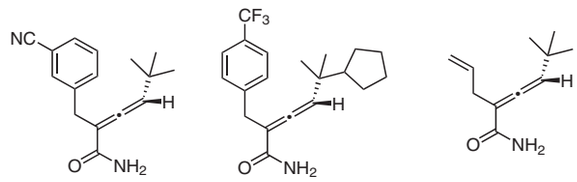
A.1.2) Allene Amides



rac. (yield, *ee*%)

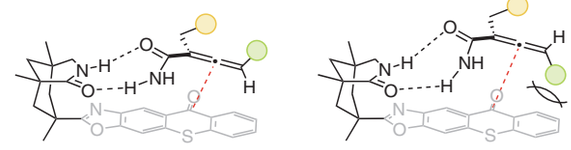


(91%, 85% *ee*) (84%, 86% *ee*) (quant., 91% *ee*)



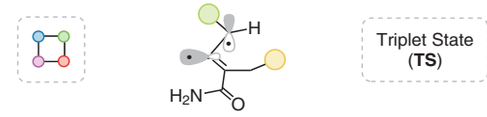
(74%, 88% *ee*) (quant., 93% *ee*) (87%, 76% *ee*)

4a) Plaza, *J. Am. Chem. Soc.* **2021**, *143*, 11209.

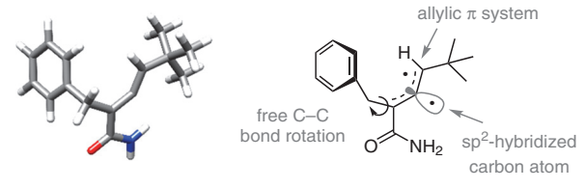


Faster Dexter-type energy transfer Slower Dexter-type energy transfer

2e) Wang, *Chem. Eur. J.* **2023**, *29*, e202204029.



3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.



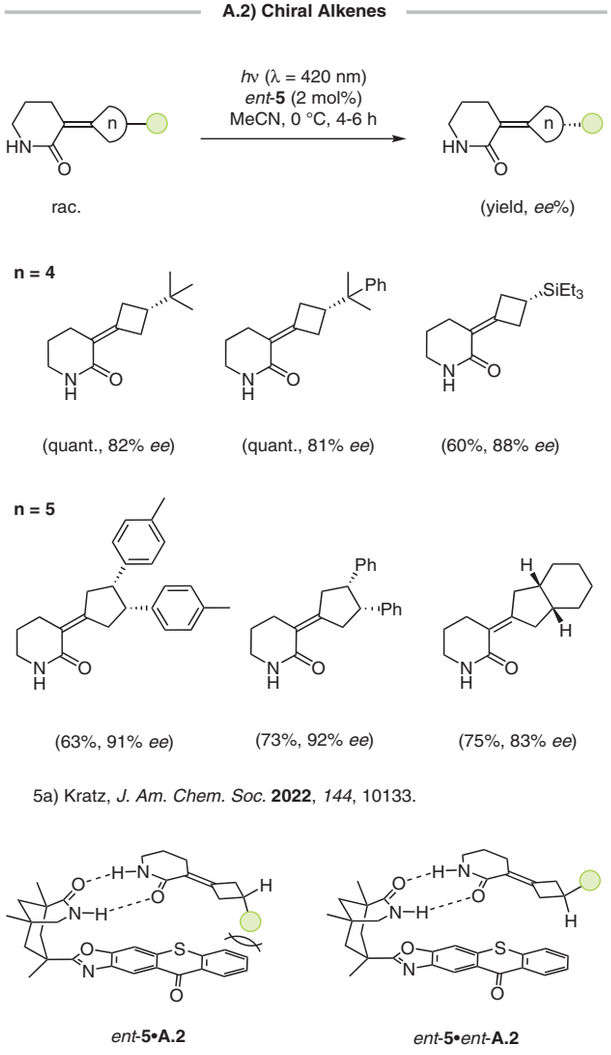
DFT calculated structure

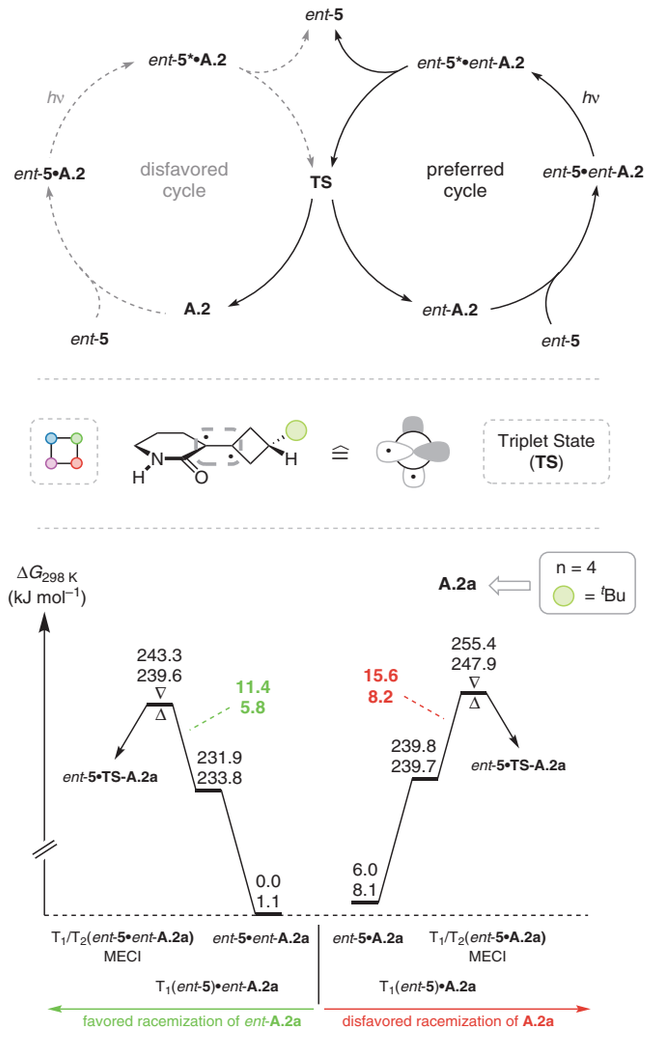
4a) Plaza, *J. Am. Chem. Soc.* **2021**, *143*, 11209.

Further Reading

4a) Plaza, *J. Am. Chem. Soc.* **2021**, *143*, 11209.
4b) Burg, *J. Org. Chem.* **2019**, *84*, 8815.
4c) Fackler, *J. Am. Chem. Soc.* **2012**, *134*, 12869.
4d) Ye, *Org. Chem. Front.* **2014**, *1*, 1210.
4e) Yu, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074.
3b) Plaza, *Angew. Chem. Int. Ed.* **2020**, *59*, 12785.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.
2e) Wang, *Chem. Eur. J.* **2023**, *29*, e202204029.

Figure 4 Allene lactam photochemical deracemization in the presence of a chiral thioxanthone catalyst[2e,3b,c,4a–e]





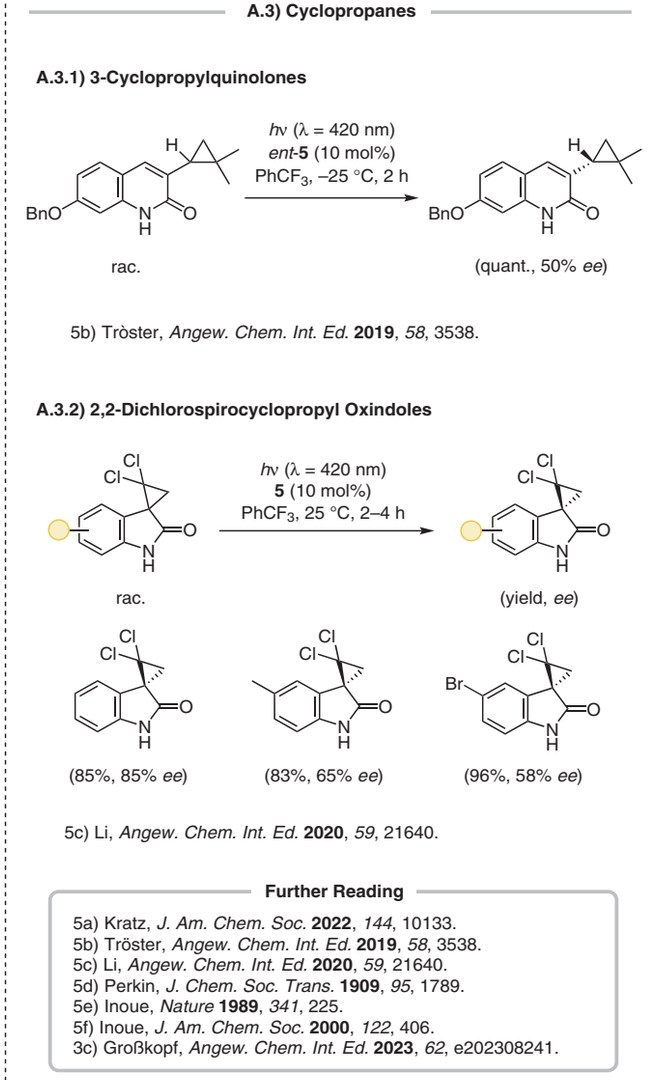


Figure 5 Mechanism and results of the photochemical deracemization of chiral alkenes and cyclopropanes[3c,5a–f]

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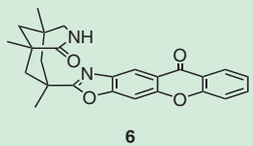
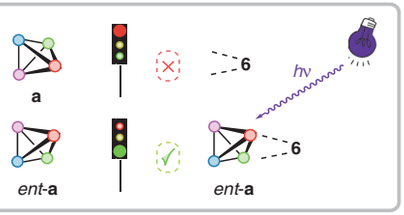


6

Chiral Xanthone



Notable Features

- Chiral sulfoxide groups exist in various drugs such as dexlansoprazole and esomeprazole, therefore deracemization of this functional group has significant importance

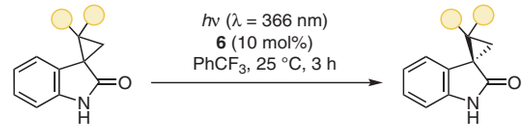
- Photocatalytic deracemization of sulfoxides does not result in a remarkable and practical enantiomeric excess (*ee*) as demonstrated

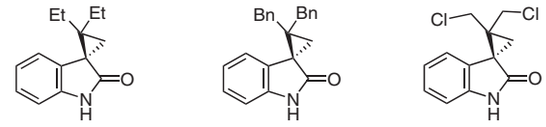
- It remains an open question whether the triplet state undergoes racemization via α-cleavage or through direct inversion

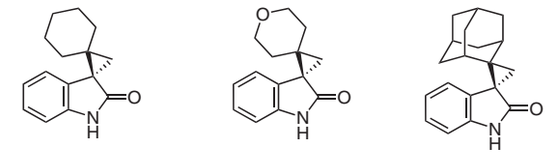
Further Reading

4b) Burg, *J. Org. Chem.* **2019**, *84*, 8815.
6a) Wimberger, *Synthesis* **2019**, *51*, 4417.
6b) Legros, *Adv. Synth. Catal.* **2005**, *347*, 19.
6c) Tozawa, *J. Org. Chem.* **2023**, *88*, 6955.
6d) Aurisicchio, *Org. Lett.* **2007**, *9*, 1939.
6e) Vos, *J. Am. Chem. Soc.* **2002**, *124*, 2544.
5c) Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 21640.
2e) Wang, *Chem. Eur. J.* **2023**, *29*, e202204029.

A.3.3) 2,2-Dialkyl-Substituted Spirocyclopropyl Oxindoles



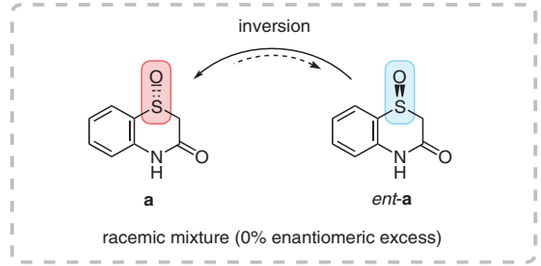


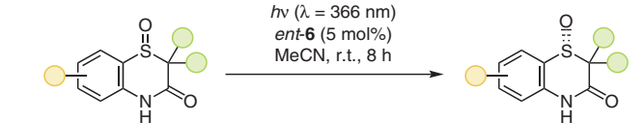


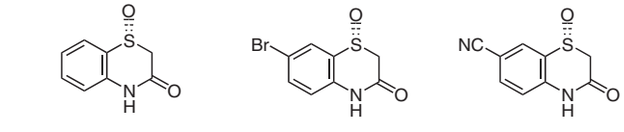
[a] The reaction was performed at –25 °C.

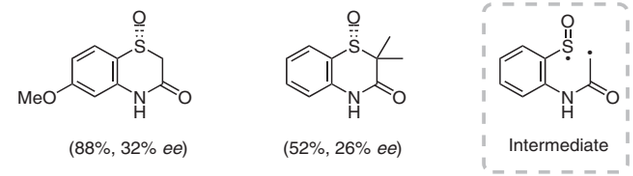
5c) Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 21640.
4b) Burg, *J. Org. Chem.* **2019**, *84*, 8815.

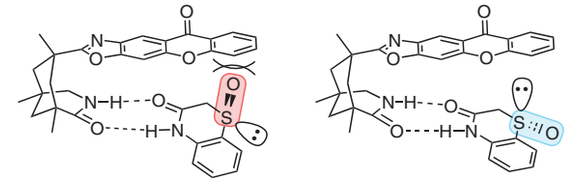
A.4) Sulfoxides



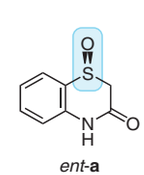


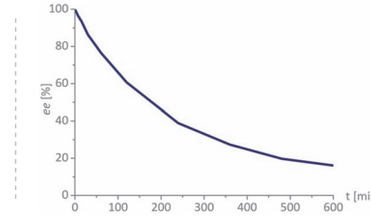






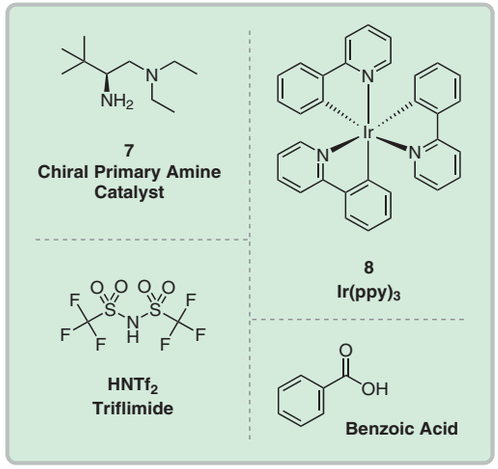
6a) Wimberger, *Synthesis* **2019**, *51*, 4417.





Time profile for the racemization of *ent*-**a** in the presence of **6** and λ = 366 nm

Figure 6 EnT-based photocatalytic deracemization of cyclopropanes and sulfoxides using a chiral xanthone catalyst[2e,4b,5c,6a–e]



Notable Features

- Isomerization of (*E*)-**A.5 in**to (*Z*)-**A.5** occurs through a diradical intermediate, under photocatalytic conditions using **8** as the catalyst

- **Benzoic acid** and **$HNTf_2$** are additives which facilitate the photochemical deracemization reaction

- In section **c,** some important synthetic applications of **A.5** in pharmaceutical usages are shown

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7a) Huang, *Science* **2022**, *375*, 869.
7b) Fu, *Org. Biomol. Chem.* **2018**, *16*, 510.
7c) Hofbeck, *Inorg. Chem.* **2010**, *49*, 9290.
7d) Mukherjee, *Chem. Rev.* **2007**, *107*, 5471.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.

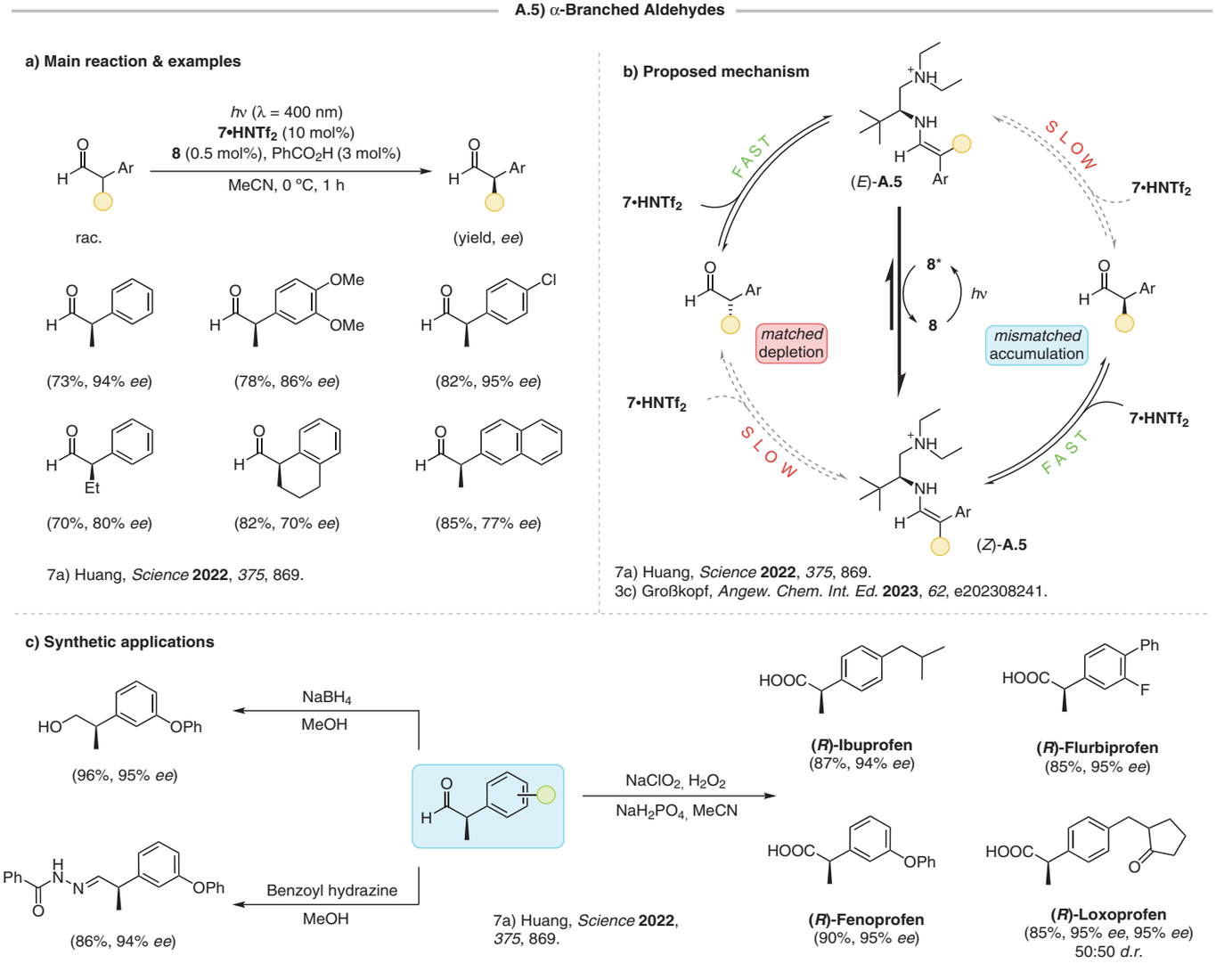

Figure 7 EnT-based photocatalytic deracemization of α-arylated aldehydes using a chiral primary amine and a chiral iridium complex as catalysts[3c,7a–d]

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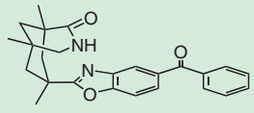
B) Photocatalytic Deracemization Reactions By Photoredox Catalysis



9

Chiral Benzophenone

rac. (high *ee*)

Notable Features

- Photochemical deracemization using a chiral benzophenone catalyst usually passes through two steps of **HAT** and one **tautomerization** step

- It is crucial to know that the benzophenone catalyst exists as two enantiomers: **9**, which is the **(+)**-enantiomer, and *ent*-**9**, the **(–)**-enantiomer

- It is essential to consider that each enantiomer of the catalyst can result indifferent enantioenrichment of a substrate

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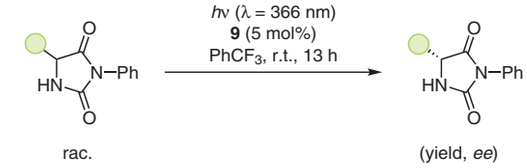
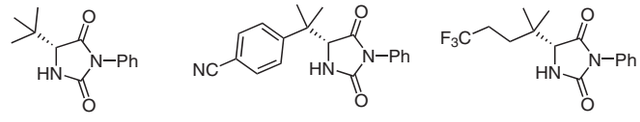
8a) Großkopf, *J. Am. Chem. Soc.* **2021**, *143*, 21241.
8b) Kutta, *J. Am. Chem. Soc.* **2023**, *145*, 2354.
8c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202305274.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.

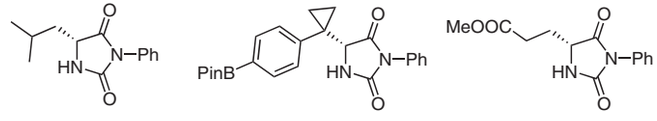
B.1) Hydantoins



rac. (yield, *ee*)



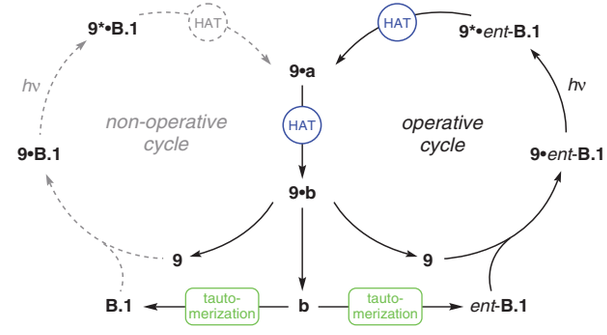
(quant., 95% *ee*) (77%, 94% *ee*) (88%, 92% *ee*)



(86%, 93% *ee*) (quant., 95% *ee*) (84%, 81% *ee*)

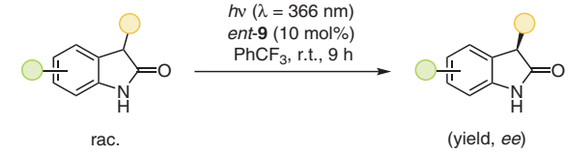
[Pin = pinacolate]

Proposed mechanism

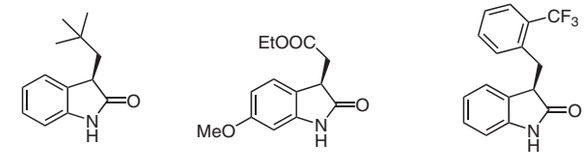


8a) Großkopf, *J. Am. Chem. Soc.* **2021**, *143*, 21241.
8b) Kutta, *J. Am. Chem. Soc.* **2023**, *145*, 2354.

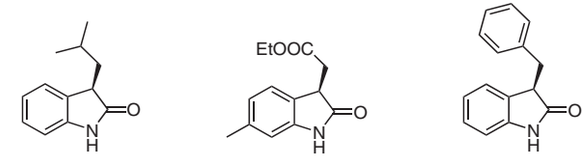
B.2) 3-Substituted Oxindoles



rac. (yield, *ee*)

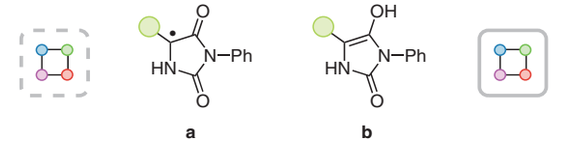


(88%, 91% *ee*) (90%, 83% *ee*) (89%, 93% *ee*)



(99%, 90% *ee*) (94%, 80% *ee*) (91%, 90% *ee*)

8c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202305274.



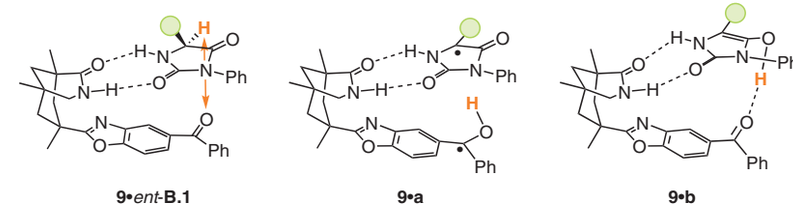
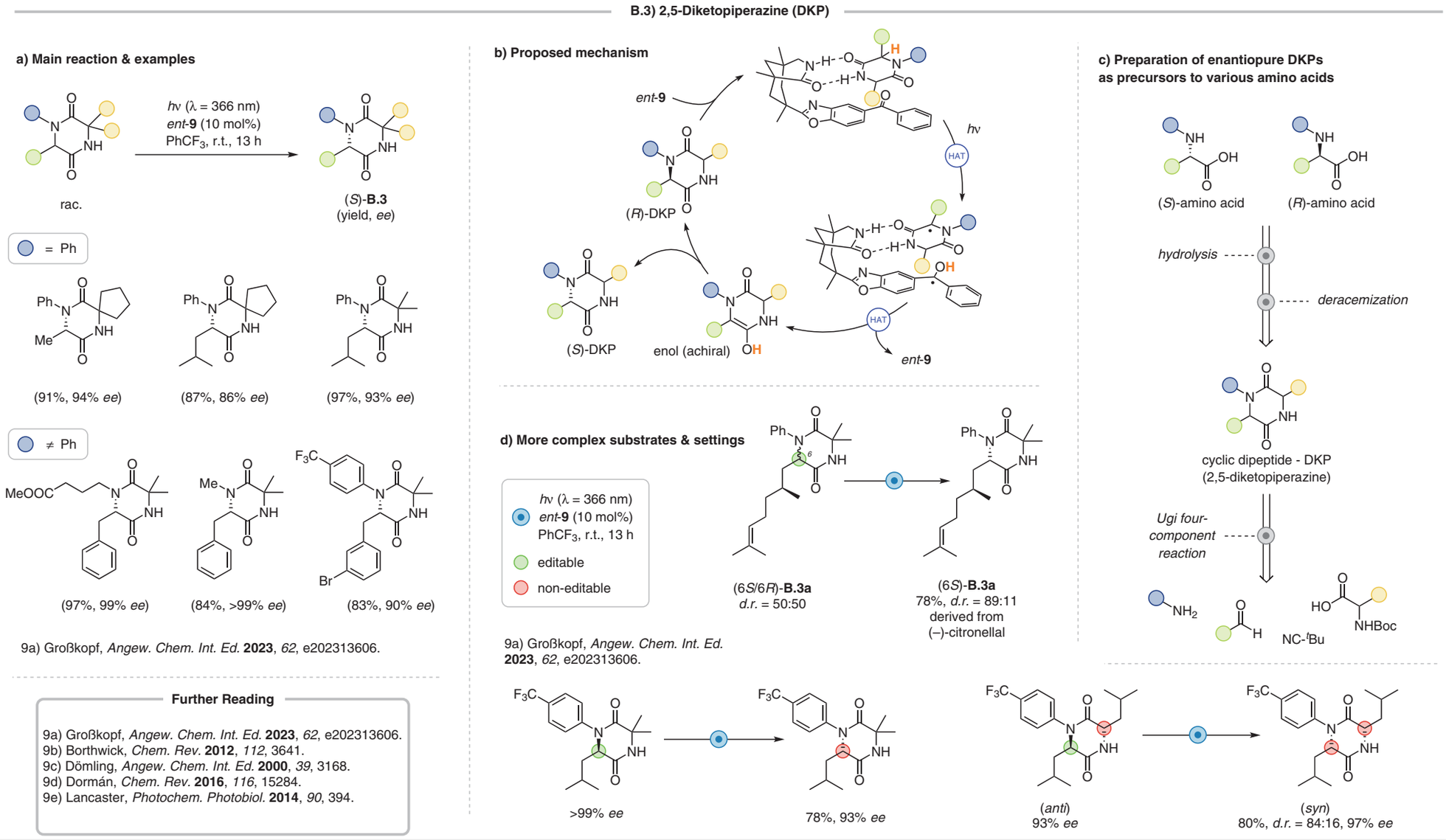


Figure 8 Photochemical deracemization reactions via photoredox catalysis in the presence of a chiral benzophenone[3c,8a–c]



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9a) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202313606.
9b) Borthwick, *Chem. Rev.* **2012**, *112*, 3641.
9c) Dömling, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
9d) Dormán, *Chem. Rev.* **2016**, *116*, 15284.
9e) Lancaster, *Photochem. Photobiol.* **2014**, *90*, 394.

Figure 9 Photoredox catalytic deracemization of amino acids and cyclic dipeptides in the presence of a chiral benzophenone catalyst[9a–e]

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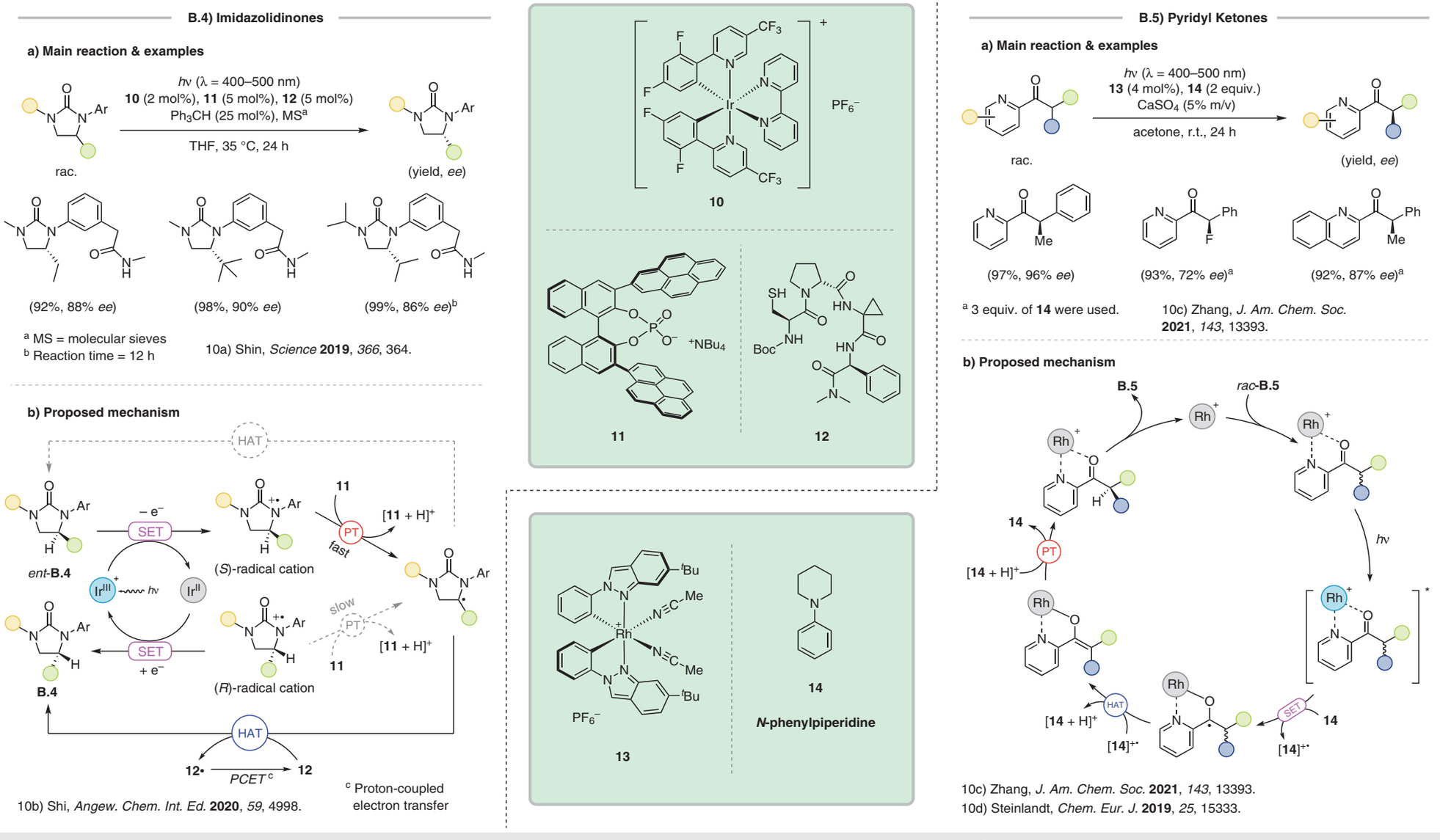

Figure 10 Deracemization of imidazolidinones and pyridylketones under photochemical conditions using chiral iridium and rhodium complexes, respectively[10a–d]

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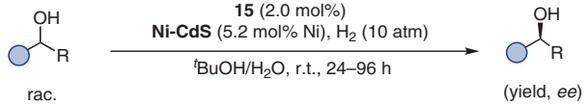
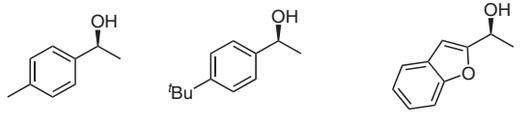
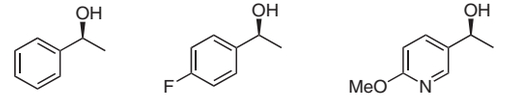
B.6) Secondary Alcohols

a) Main reaction & examples



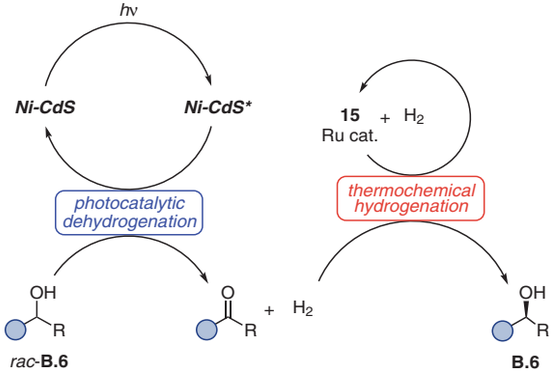




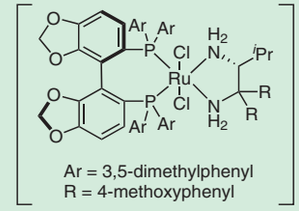
[a] Without external H_2 pressure

11a) Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 22833.

b) Proposed mechanism



11a) Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 22833.



15

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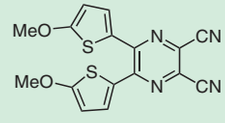
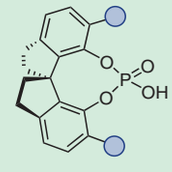
11a) Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 22833.
11b) Gu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211241.
11c) Lin, *Angew. Chem. Int. Ed.* **2017**, *56*, 13842.
11d) Yin, *J. Am. Chem. Soc.* **2020**, *142*, 19451.
11e) Kong, *J. Am. Chem. Soc.* **2021**, *143*, 4024.
3c) Großkopf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308241.



Dicyanopyrazine DPZ

16



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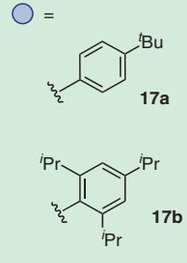
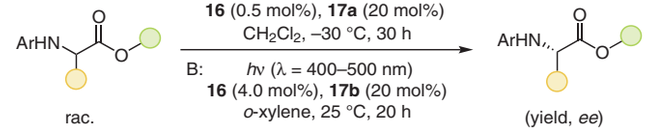
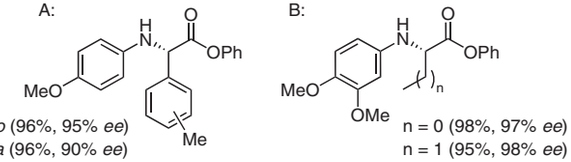


B.7) α-Amino Acid Esters

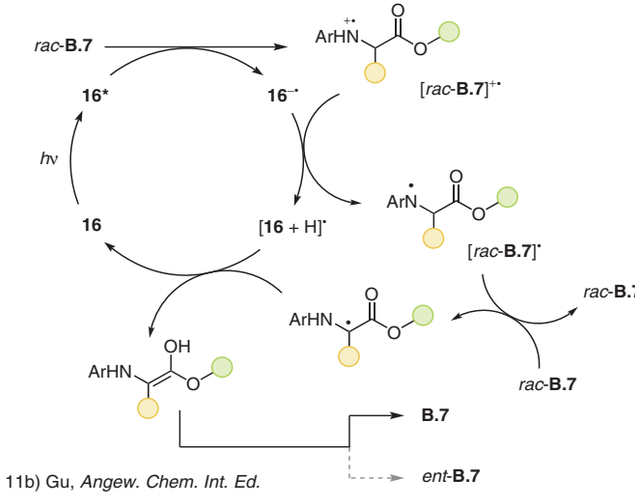
a) Main reaction & examples





11b) Gu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211241.

b) Proposed mechanism



11b) Gu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211241.

Figure 11 Photocatalytic deracemization reactions of secondary alcohols and α-amino acid esters via photoredox catalysis mechanisms[3c,11a–e]

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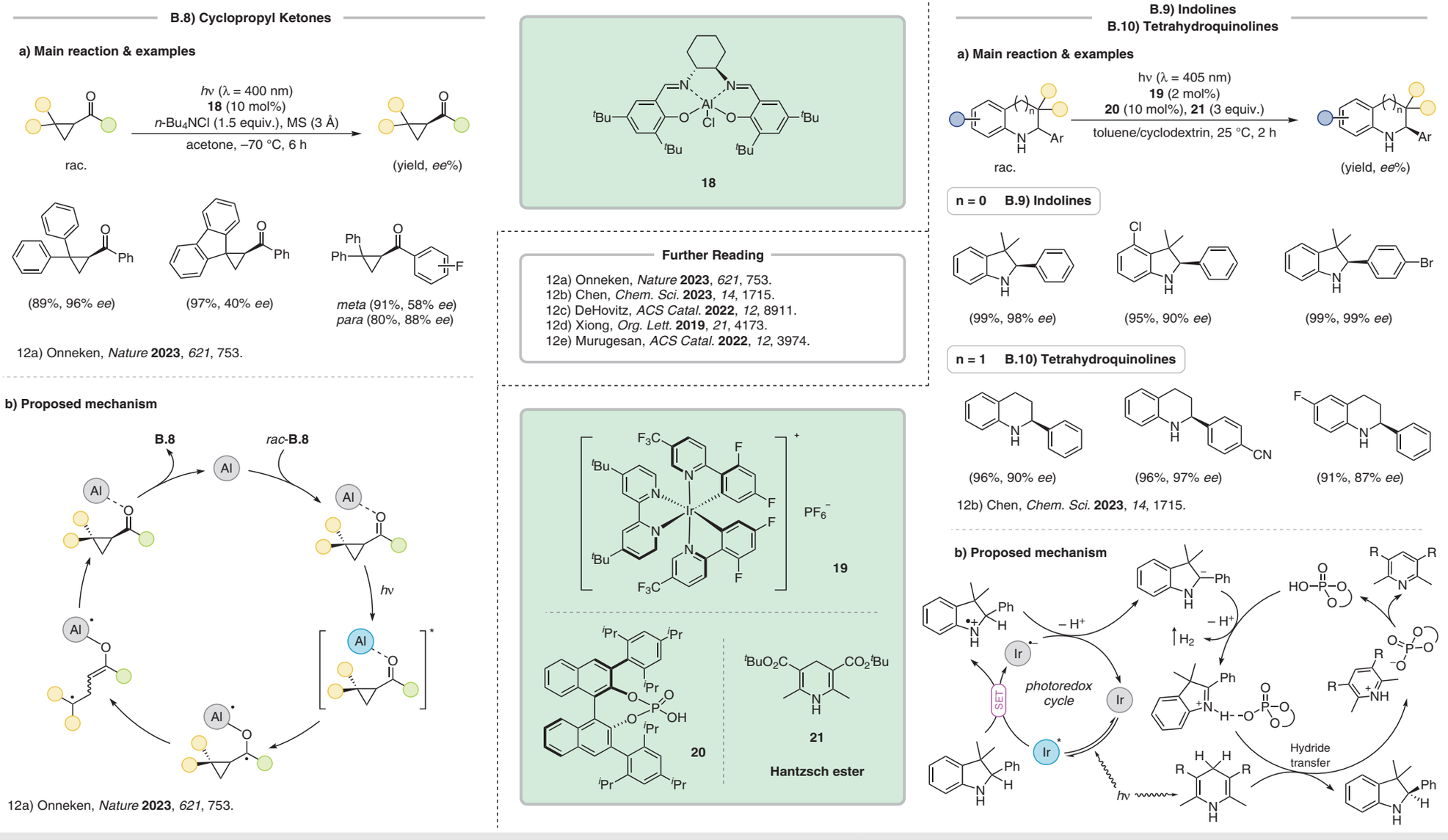

Figure 12 Photochemical deracemization of cyclopropyl ketones, indolines and tetrahydroquinolines via photoredox catalysis mechanisms[12a–e]

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Conflict of Interest

The authors declare no conflict of interest.

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