Photochirogenesis using photosensitizers

Literature Seminar

2019/6/29

Takahiro Watanabe

Contents

1. **Introduction**

2. **Catalytic deracemization of chiral allenes**
(Bach et al. *Nature* **2018**, *564*, 240.)

3. **Enantioselective formation of 3-cyclopropylquinolones**
(Bach et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.)

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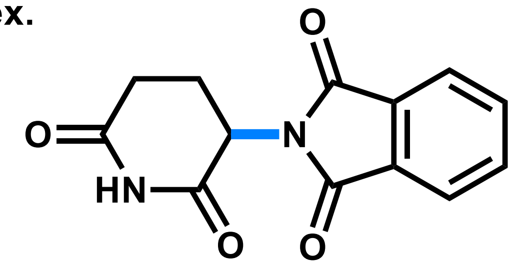
(Bach et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.)

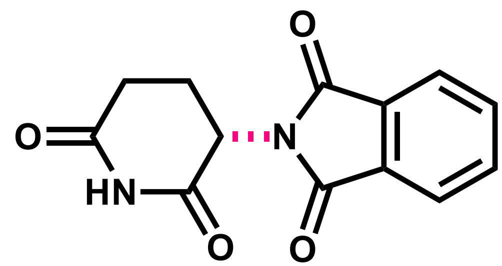
Importance of enantiomerically pure chiral compounds

Biological activity is different in both enantiomers:

ex.



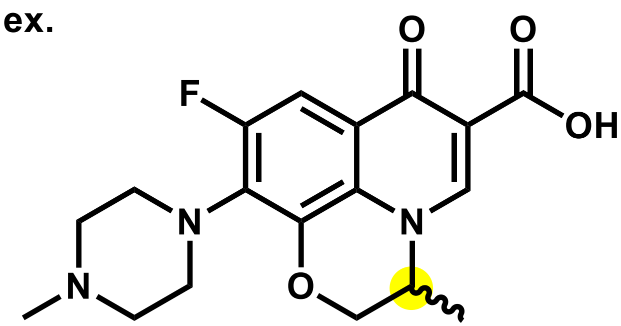
(*S*) - thalidomide
-> Hypnotic effect



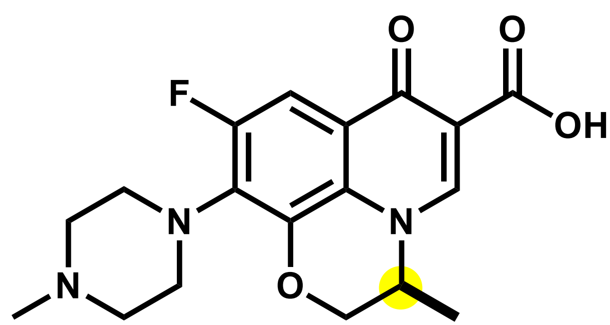
(*R*) - thalidomide
-> Teratogenicity

Intensity of medicinal activity is different between enantiomers:

ex.



Ofloxacin (racemic)



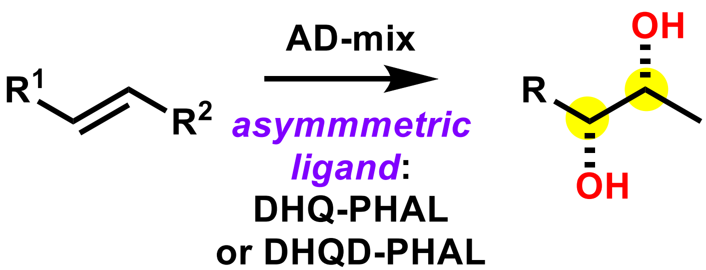
Levofloxacin (contains only (*S*) enantiomer)
-> (S) has 10~20 times stronger effect than (R)

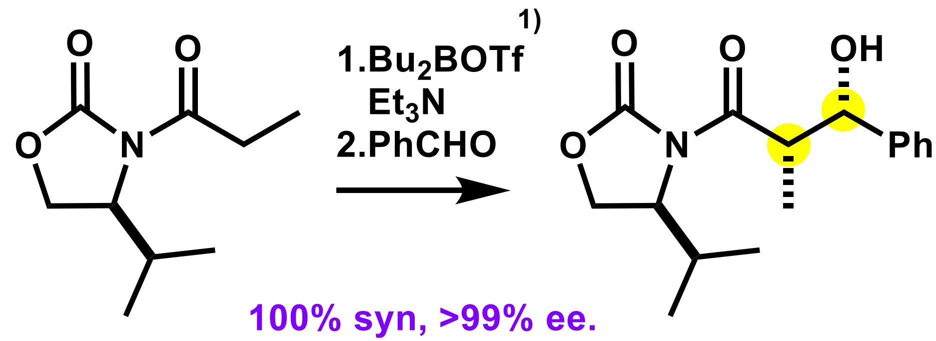
-> Enantioselective synthesis is needed for social demand and assists the development of organic synthesis.

The way to obtain enantioenriched compounds

1. Starting from optically active compounds (ex. chiral pool)

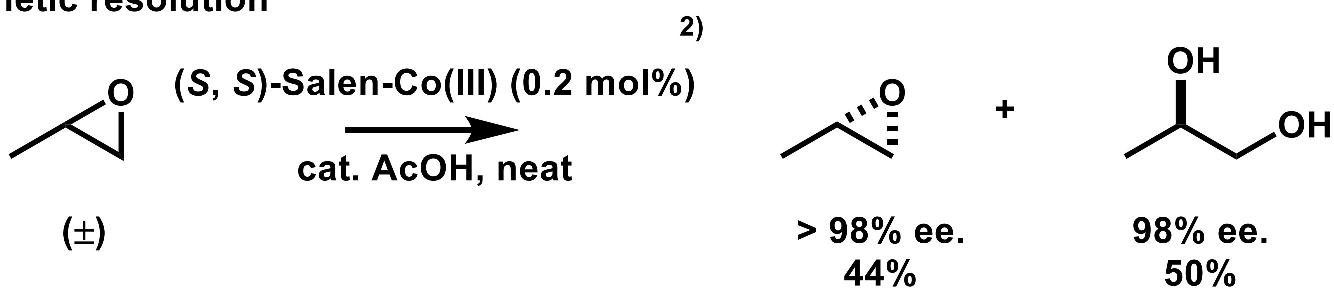
2. Using asymmetric reagent / catalyst





3. Resolution

- kinetic resolution



- dynamic kinetic resolution

- These methods are applied to substrates in ground state.

1) Evans et al. *Pure Appl. Chem.* **1981**, *53*, 1109. 2) Jacobsen et al. *Science* **1997**, *277*, 936.

Photochirogenesis

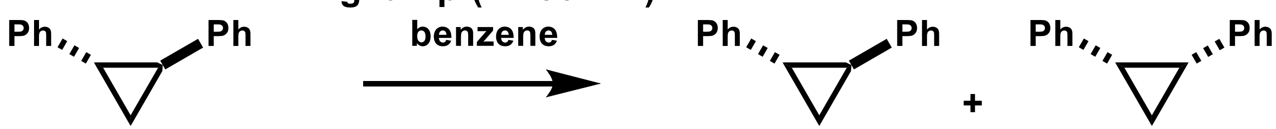
"Photochirogensis" = Photo + chiro + genesis

-> photochemical induction of molecular chirality
or new stereogenic centers

previous LS:
"Absolute Asymmetric Photoreaction"
170304_LS_Masanori NAGATOMO

First study in 1965 [1]:

sens* (12 mol%)
Hg lamp (> 250 nm)
benzene

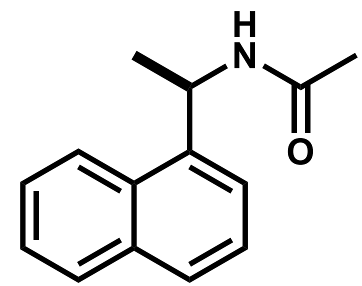


racemic

trans:cis = 49 : 51

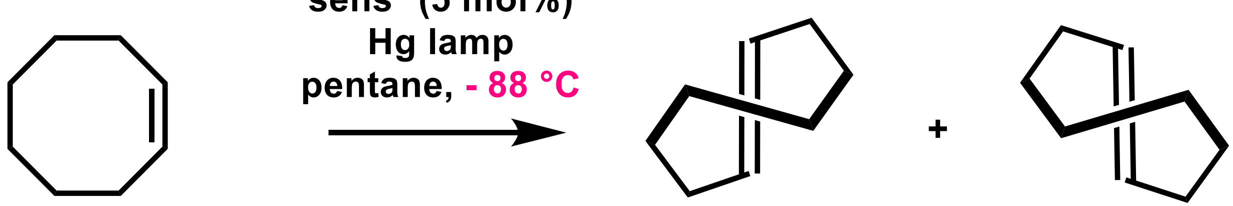
6.5% ee

sens* =



Enantiodifferentiating of cyclooctene [2]

sens* (5 mol%)
Hg lamp
pentane, - 88 °C



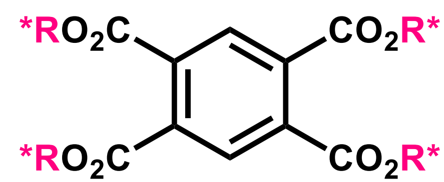
cis-cyclooctene

+ 41% ee
(12% conversion)
temperature dependent

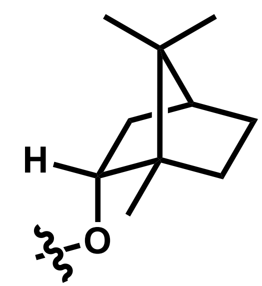
S-(+)-trans

R-(-)-trans

sens* =



-OR* =

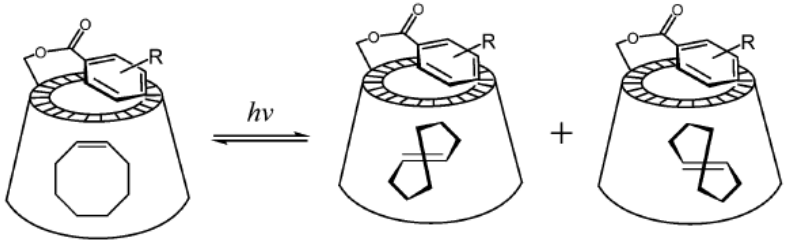


((-) - bornyl)

1) Hammond et al. *J. Am. Chem. Soc.* **1965**, *87*, 3256. 2) Inoue et al. *Nature* **1989**, *341*, 225.

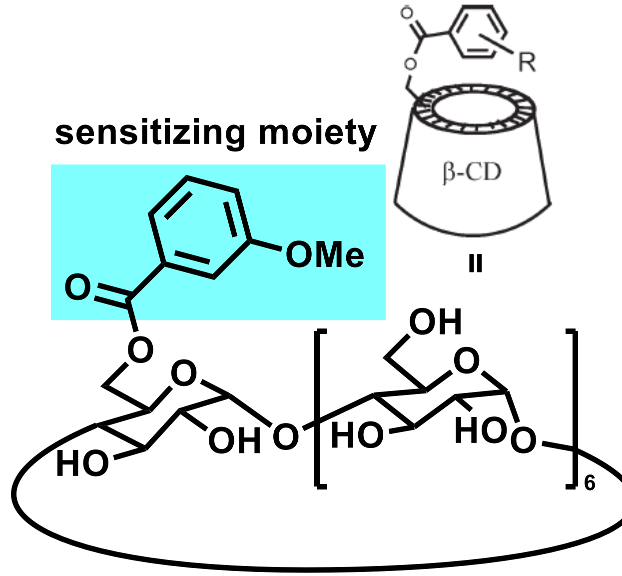
Supramolecular approaches

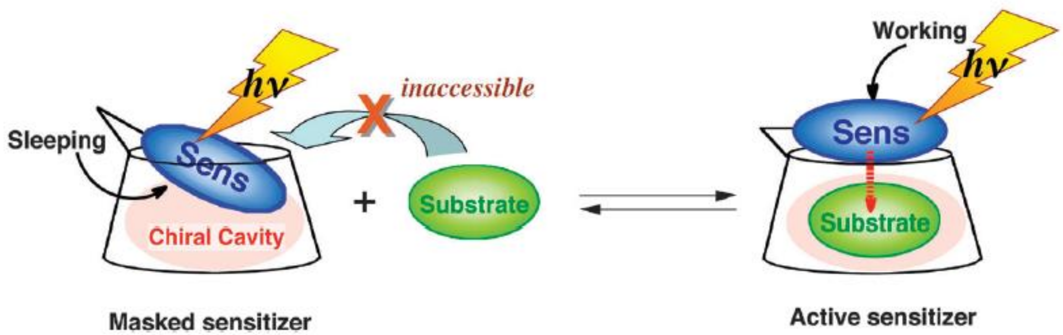
Use of β-cyclodextrin as a cavity [1]:



- 46% ee R-(-)-trans S-(+)-trans

MeOH/H_2O (10% MeOH), - 5 °C
cis/trans = 0.24



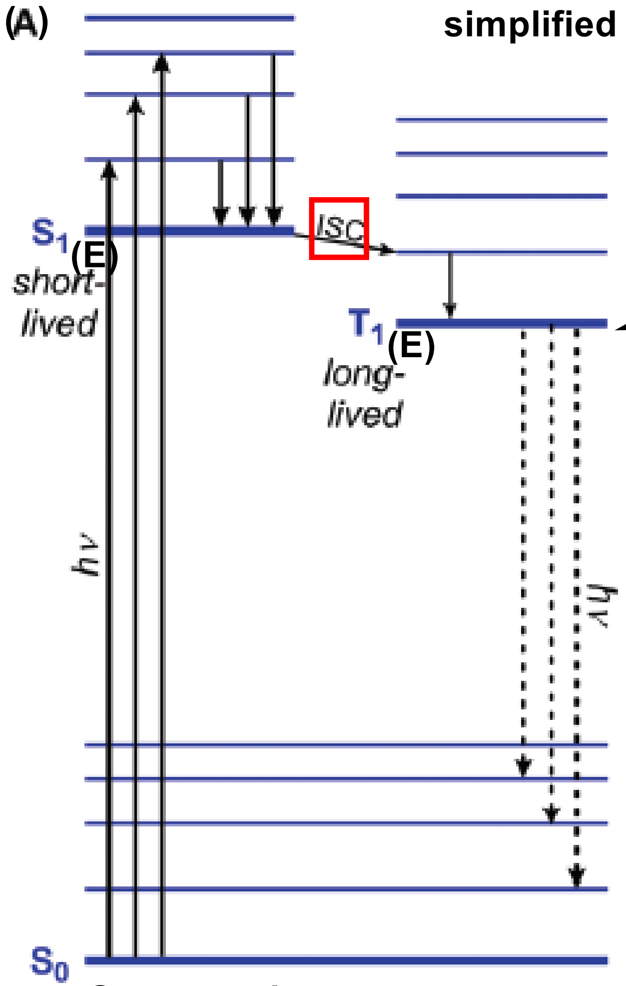


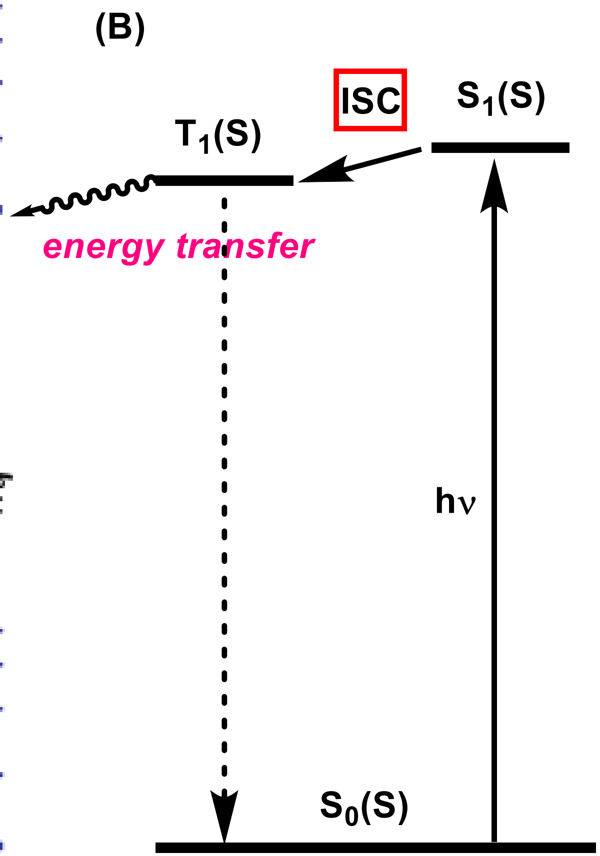
other supramolecular or biomolecular are also used. (ex. zeolite, bovin serum albumin)

1) Inoue et al. *Chem. Commun*. **2008**, 374.

Principle of sensitization

simplified Jablonski diagram





S_0: ground state
S_1: lowest excited singlet state
T_1: lowest excited triplet state
ISC: intersystem conversion
Φ: quantum yield

S_0(E): S_0 of substrate
S_0(S): S_0 of sensitizer
T_1(E): T_1 of substrate
T_1(S): T_1 of sensitizer

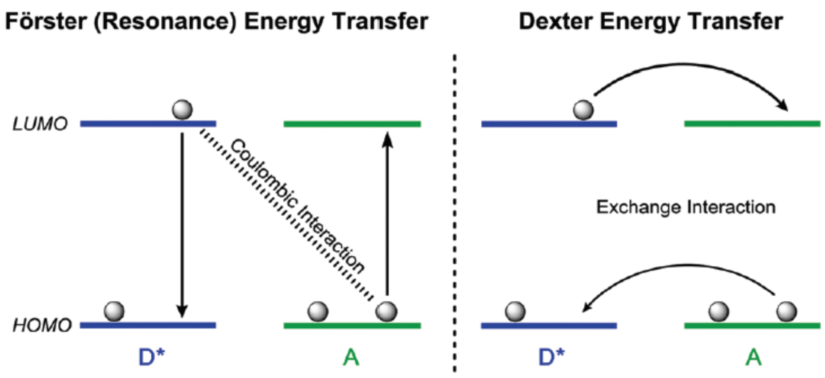
Triplet energy transfer can be shown as:
$S_0(E) + T_1(S) \rightarrow T_1(E) + S_0(S)$
(Spin multiplicity is maintained before and after energy transfer.)

We want to obtain T_1(E) and sensitizers are effective when
1) Φ of ISC of sensitizer is high.
2) Φ of ISC of substrate is low.

Ideally, energy-level distribution is
$T_1(E) < T_1(S) < S_1(S) < S_1(E)$

Glorius et al. *Chem. Soc. Rev.* **2018**, *47*, 7190.

Energy transfer



(1) $S(S_1) + E(S_0) \rightarrow S(S_0) + E(S_1)$ - singlet energy transfer
(2) $S(T_1) + E(S_0) \rightarrow S(S_0) + E(T_1)$ - triplet energy transfer
(3) $S(T_1) + E(S_0) \rightarrow S(S_0) + E(S_1)$
(4) $S(S_1) + E(S_0) \rightarrow S(S_0) + E(T_1)$

Förster's theory- dipole-dipole interaction
Spin has to be allowed transition in both S and E. → (1) obey the theory, but (2) don't.

Dexter's theory- exchane energy transfer
Sum of spin multiplicity has to be conserved. → (2) obey the theory.

$$k_{\mathrm{EnT}} = K \cdot J \cdot e^{-\frac{2R_{\mathrm{DA}}}{L}}$$

k **decreases exponentially as R_{DA} increases.**
→ Control of R_{DA} is important for efficient triplet sensitization.

k_{EnT} : rate constant for Dexter's energy transfer
***K*: a parameter for specific orbital interaction between donor and acceptor**
***J*: spectral overlap between donor emission and acceptor absorption**
***L*: Bohr radius**

Glorius et al. *Chem. Soc. Rev.* **2018**, *47*, 7190.

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Thorsten Bach

1989-1991 Dr. rer. nat. (Kekule Fellowship) (Univ. Marburg, M.T. Reetz)

1991-1992 Postdoctoral Research (NATO Fellowship) (Harvard Univ., D.A.Evans)

1992-1996 Independent Research (Habilitation) (Univ. Munster)

1997-2000 Professor (Universitat Marburg)

since 2000 Professor (TU Munich)

Research Interests:

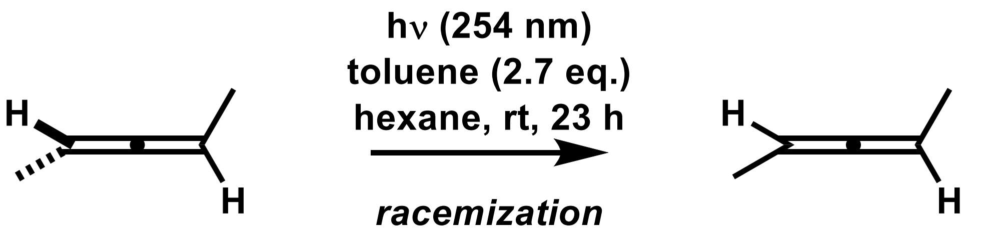
1. Natural Product Synthesis

2. Development of Catalytic Methods (ex. direct C-C bond formation by C-H activation reactions)

3. Photochemistry (Today's Topic)

allene

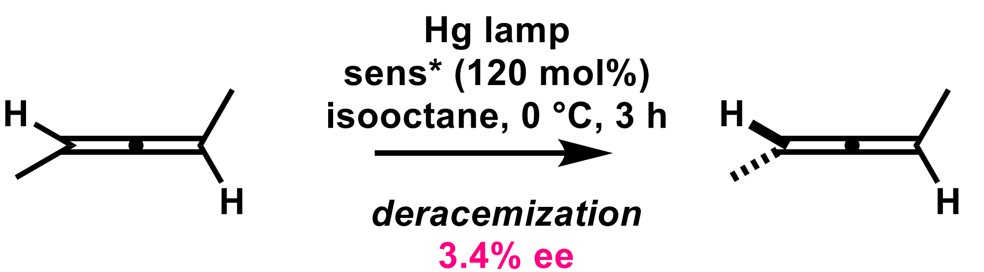
Known to undergo a configuration switch upon triplet-sensitized exitation[1]:



(+)-2,3-pentadione — **racemic**

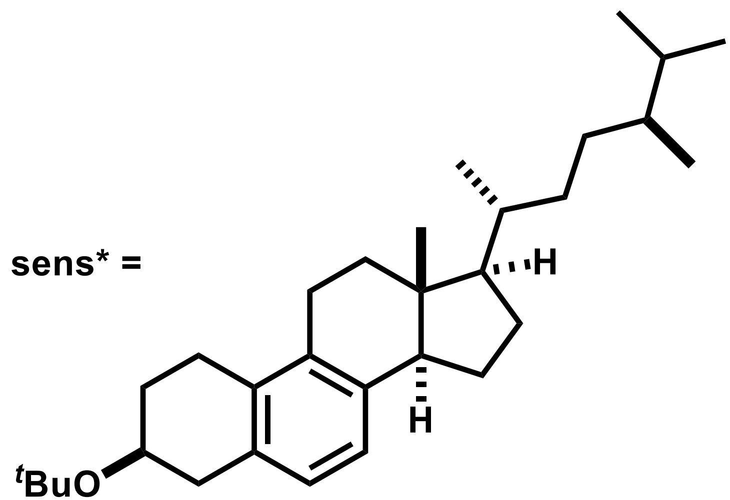
$[\alpha]_D^{25} = 16.3$ — $[\alpha]_D^{25} = 0.78$

Previous study [2]:



racemic — **(+)-2,3-pentadione**

sens* =



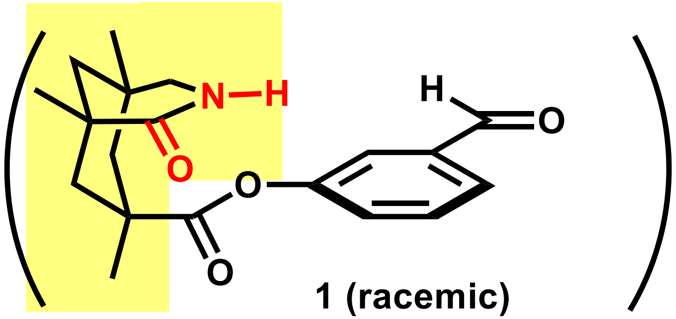
dihydroneoergosterol derivative

Allene isomerization occurs via an achiral planar triplet intermediate.[3]

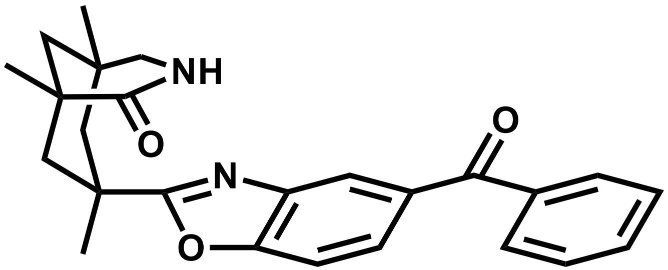
1) Morrison et al. *J. Chem. Soc. D* **1971**, 679. 2) Weiss et al. *J. Am. Chem. Soc.* **1973**, *95*, 6482.
3) Schmittel et al. *J. Org. Chem.* **2009**, *74*, 5850.

Thioxanthone sensitizer

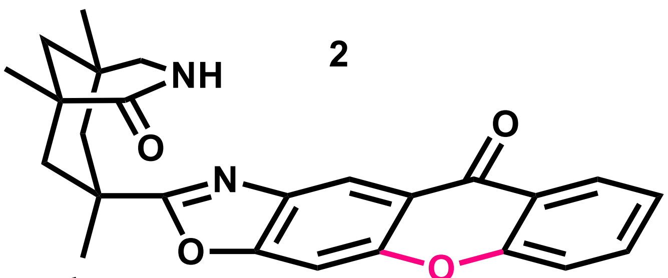
Time Flows



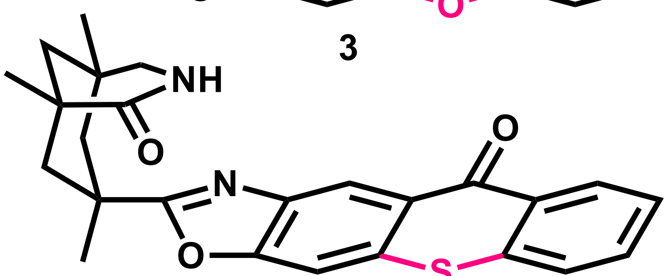
1 (racemic)



2



3



4

1,5,7-trimethy-3-azabicyclo[3.3.1]nonen-2-one skeleton was found to be efficient chiral template.[1)]

-> Hydrogen bonding with the substrate

Benzophenone catalyst 2:
worked well as a catalyst for enantioselective PET reactions[2)] but less suitable for triplet sensitizaion (rigid oxazole unit is introduced for stereocontrolling);

photoexcited benzophenone is not completely planar.
-> Dissociation of the substrate?

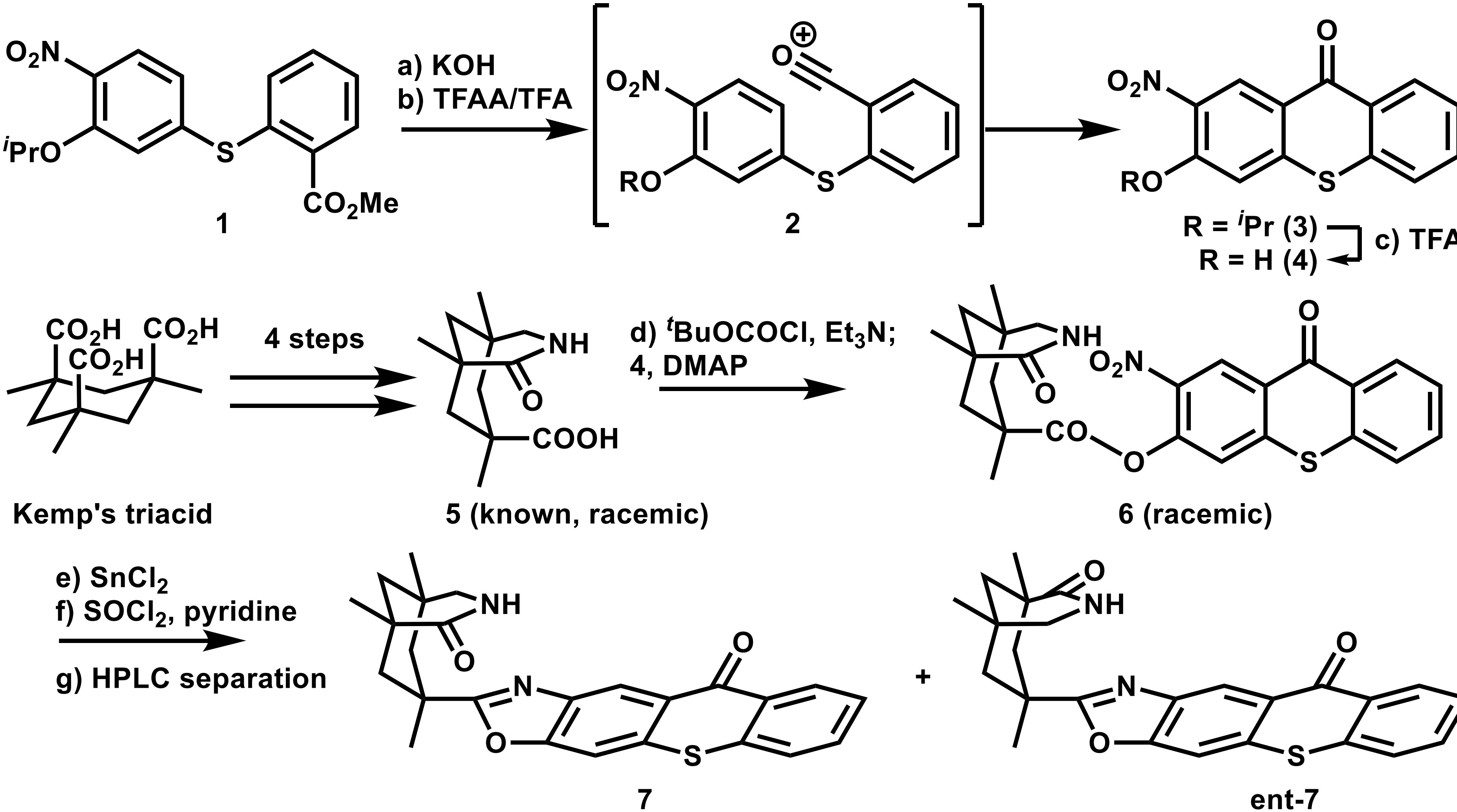
Xanthone catalyst 3: [3)]
Completely flat -> favor substrate binding
Triplet energy of parent compounds xanthone is highr than that of benzophenone (310kJ/mol vs. 287 kJ/mol)
-> Energic preference compared to 2

Thioxanthone catalyst 4: [4)]
bathochromic shift in UV/Vis spectra compared to 3
-> Less aggressive towards hydrogen abstraction than 3

Higher stability for irradiation than 3

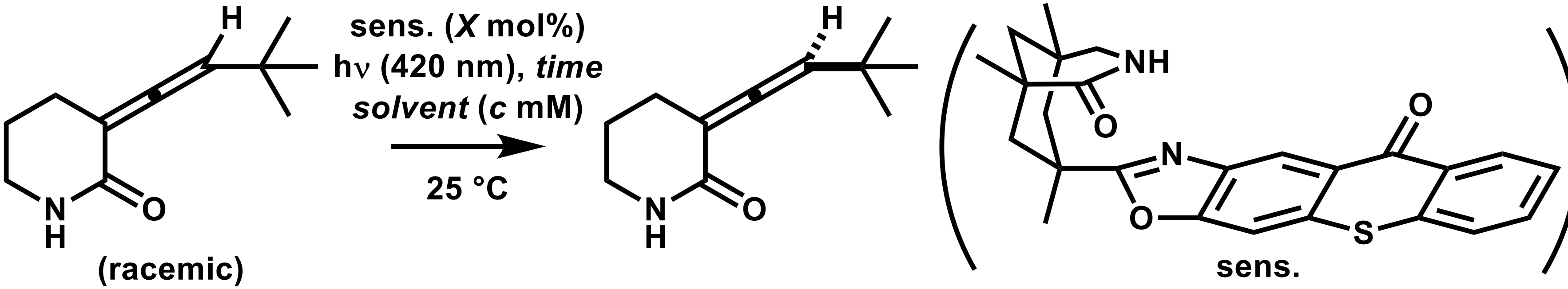
1) Bach et al. *J. Am. Chem. Soc.* **1999**, *121*, 10650. 2) Bach et al. *Nature* **2005**, *436*, 1139.
3) Bach et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 6640. 4) Bach et al. *Angew. Chem. Int. Ed.* **2014**, 53, 4368.

Synthesis of thioxanthone catalyst



Bach et al. *Angew. Chem. Int. Ed.* **2014**, 53, 4368.

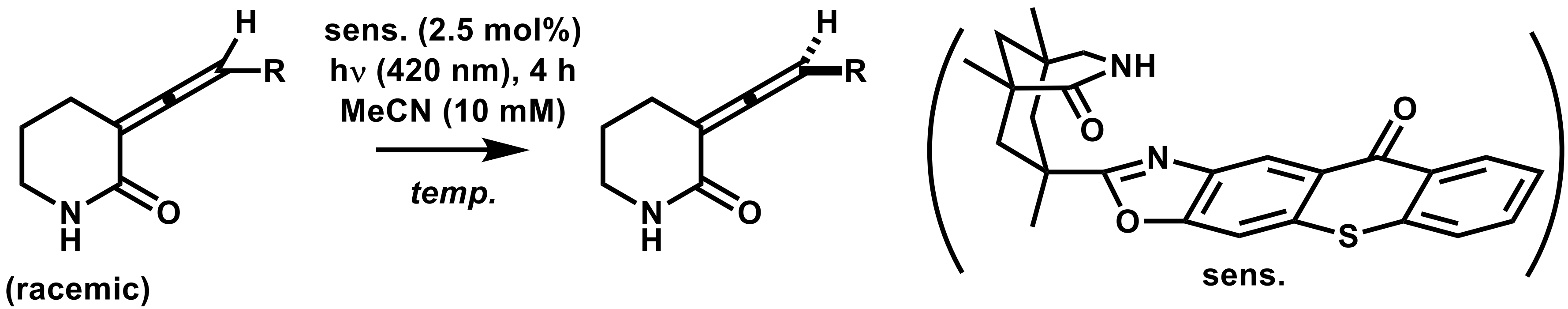
Optimization of conditions



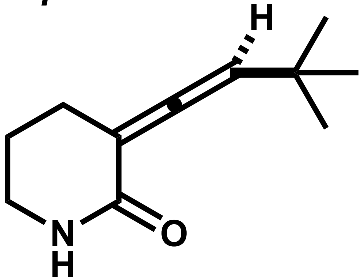
Entry	*c* (mM)	*solvent*	*X* (mol%)	*time* (h)	*ee* (%)
1	5.0	$PhCF_3$	5.0	0.25	72
2	5.0	$PhCF_3$	5.0	0.5	88
3	5.0	$PhCF_3$	5.0	1	94
4	5.0	$PhCF_3$	5.0	4	94
5	10.0	$PhCF_3$	2.5	4	95
6	10.0	PhH	2.5	4	97
7	10.0	MeCN	2.5	4	95
8	10.0	MeOH	2.5	4	10

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

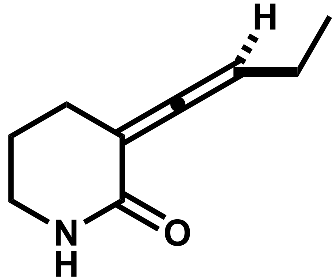
Substrate Scope



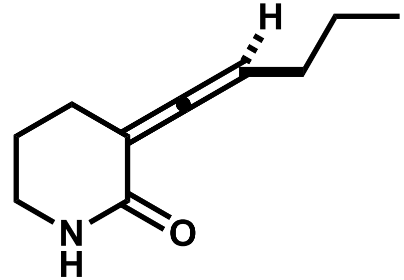
***temp*: 25 °C**



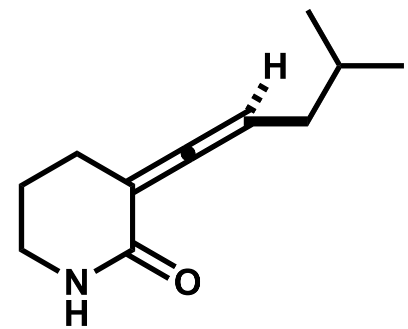
89% (96% ee.)



100% (93% ee.)

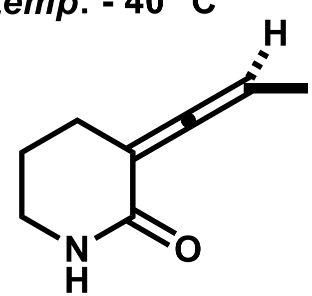


84% (92% ee.)

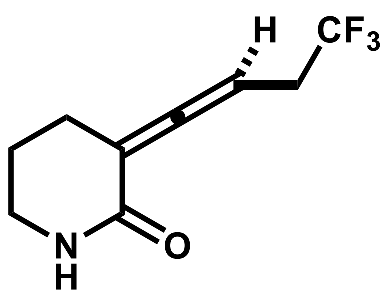


98% (91% ee.)

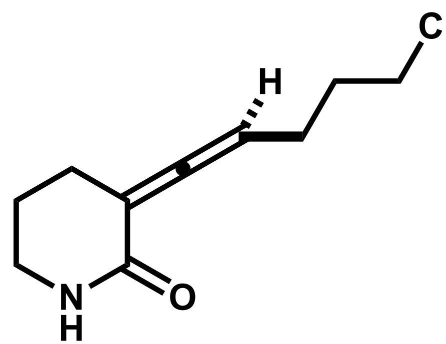
***temp*: - 40 °C**



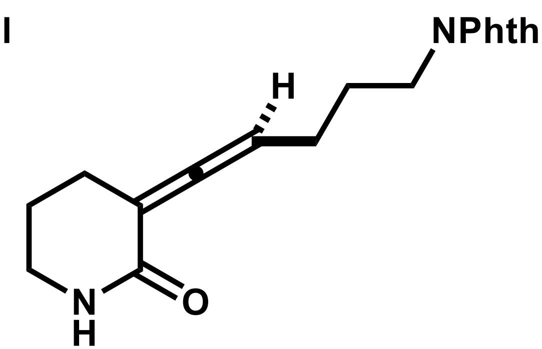
56% (90% ee.)



92% (89% ee.)



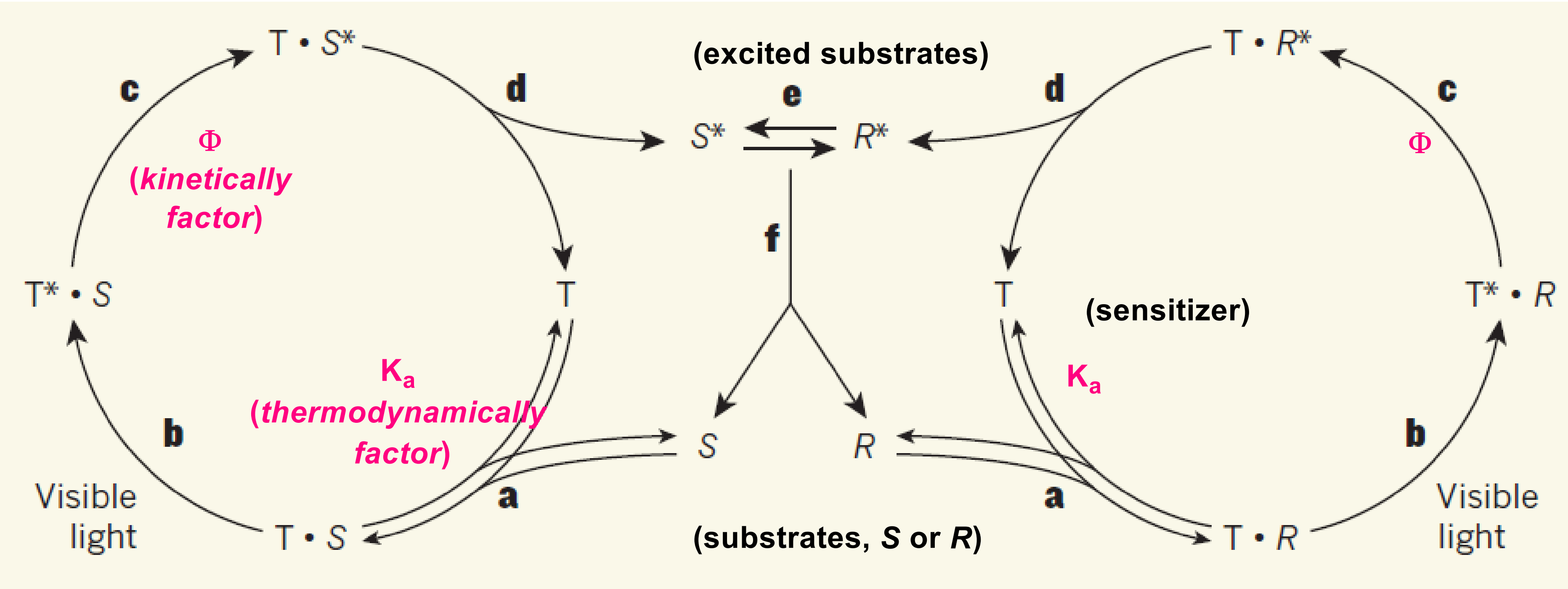
87% (92% ee.)



72% (90% ee.)

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

Plausible mechanism for light-activated deracemization



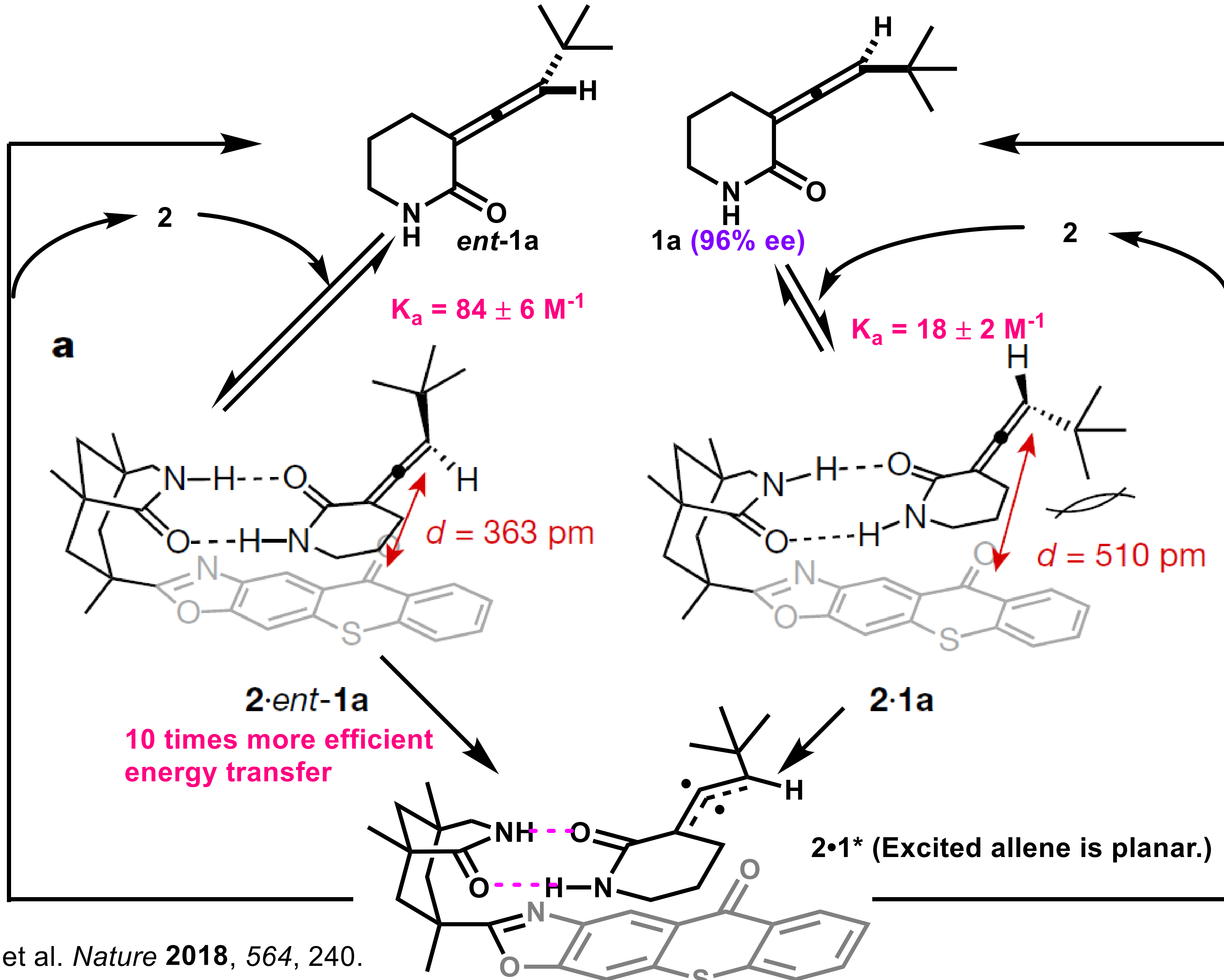
Ka: association constant
Φ: quantum yield

a. Formtion of complex
b. Excitation of T and generation of triplet state
c. Energy transfer
d. Releasing excited S* or R*
e. Interconversion in excited states
f. Relaxation to ground state

→ The difference of Ka and Φ between both enantiomers generates ee.

Yang, C.; Inoue, Y. *Nature*, **2018**, *564*, 197.

Generation of ee



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

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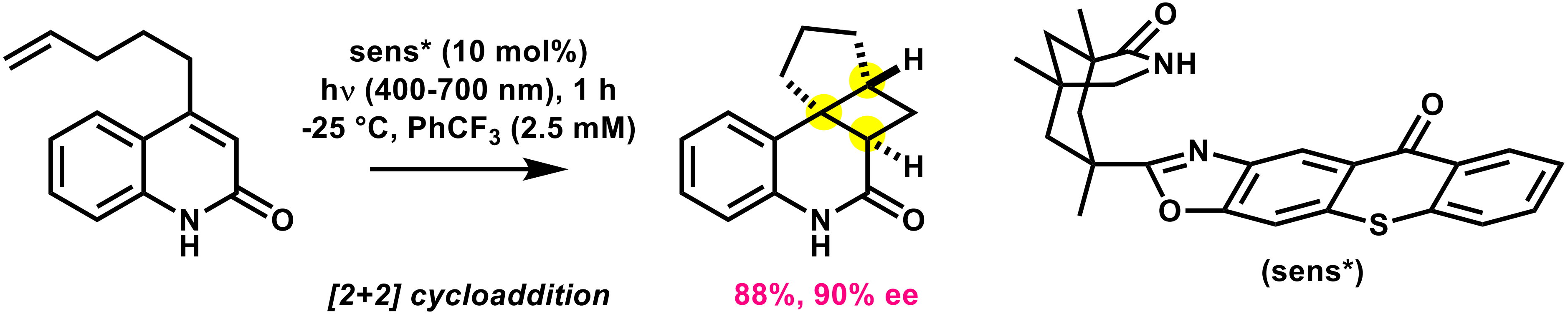
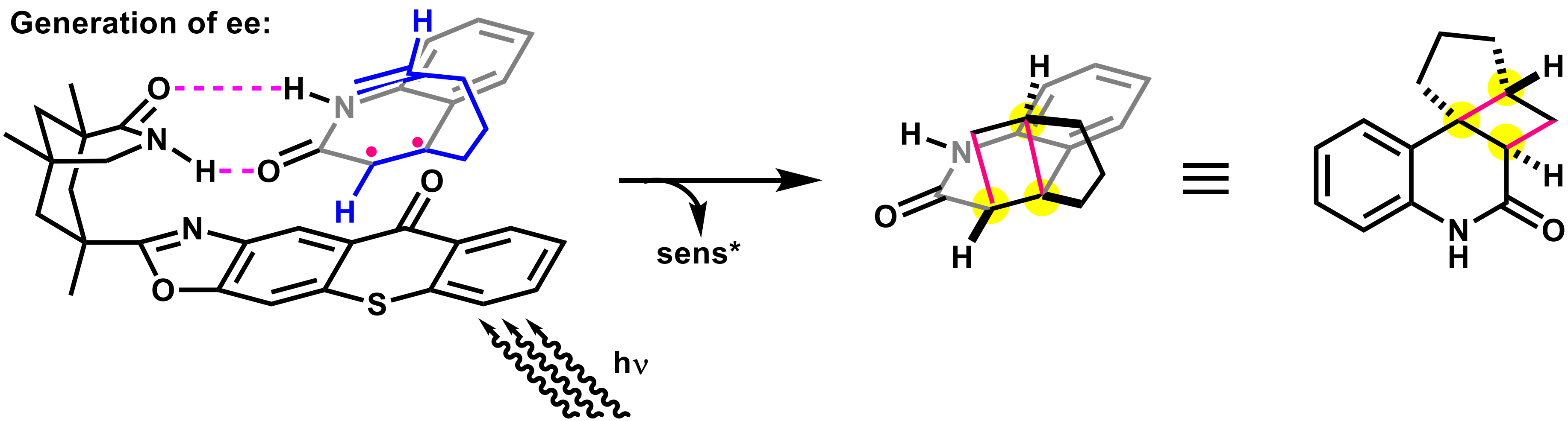
Background: intramolecular [2+2] photocycloaddition



Generation of ee:

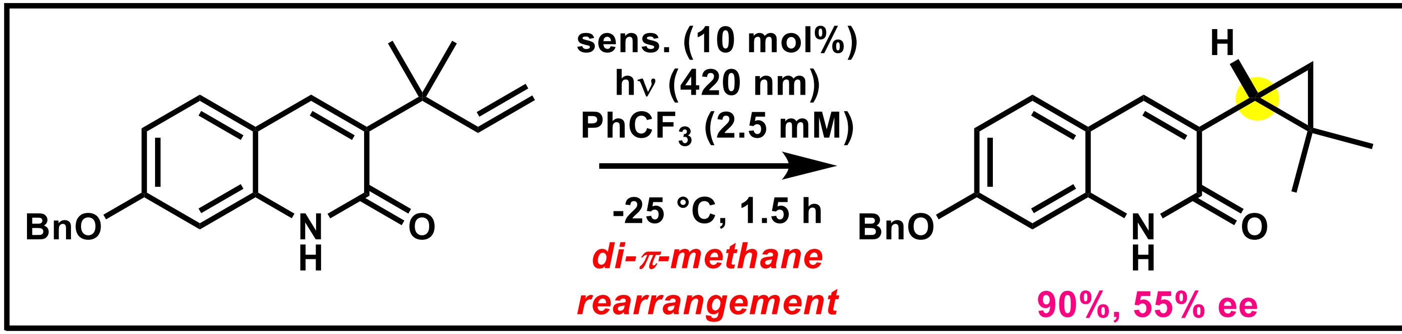


1. **Substrate is positioned as above;**
   Hydrogen bonding between the sensitizer and catalyst determines the position.

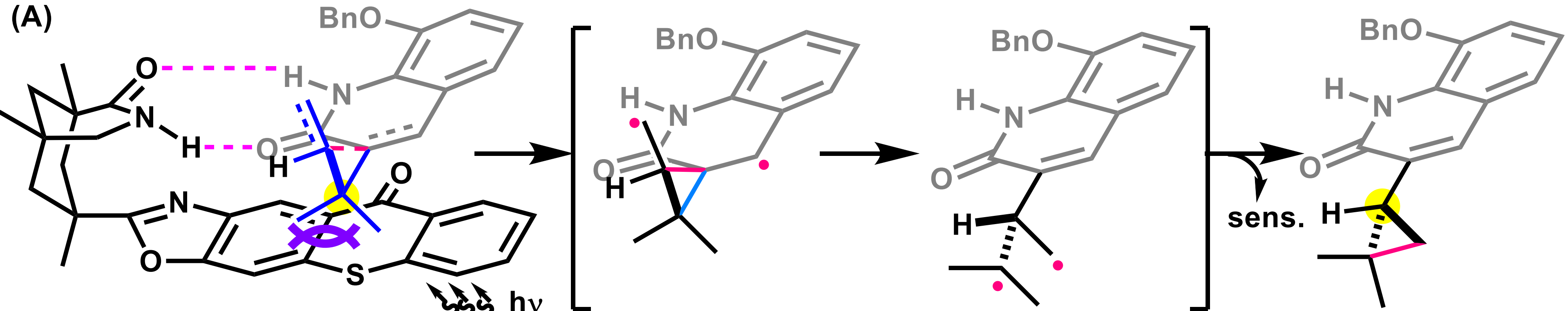
2. **Side chain approaches to avoid the sensitizer and [2+2] cycloaddition occurs.**

Bach et al. *Angew. Chem. Int. Ed*. **2014**, 53, 4368.

Absolute configuration is counterintuitive ?



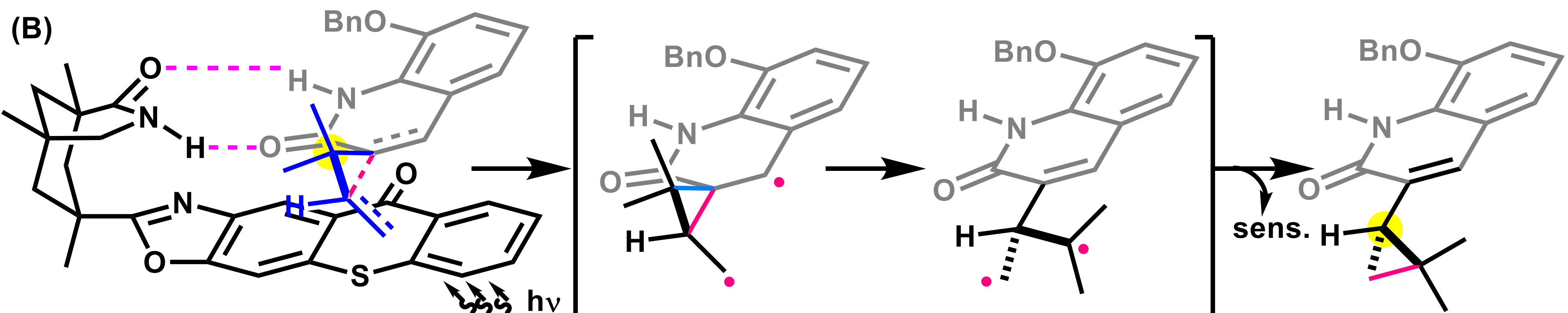
(A)



1 (major enantiomer)

**sensitizer is omitted for clarity.

(B)

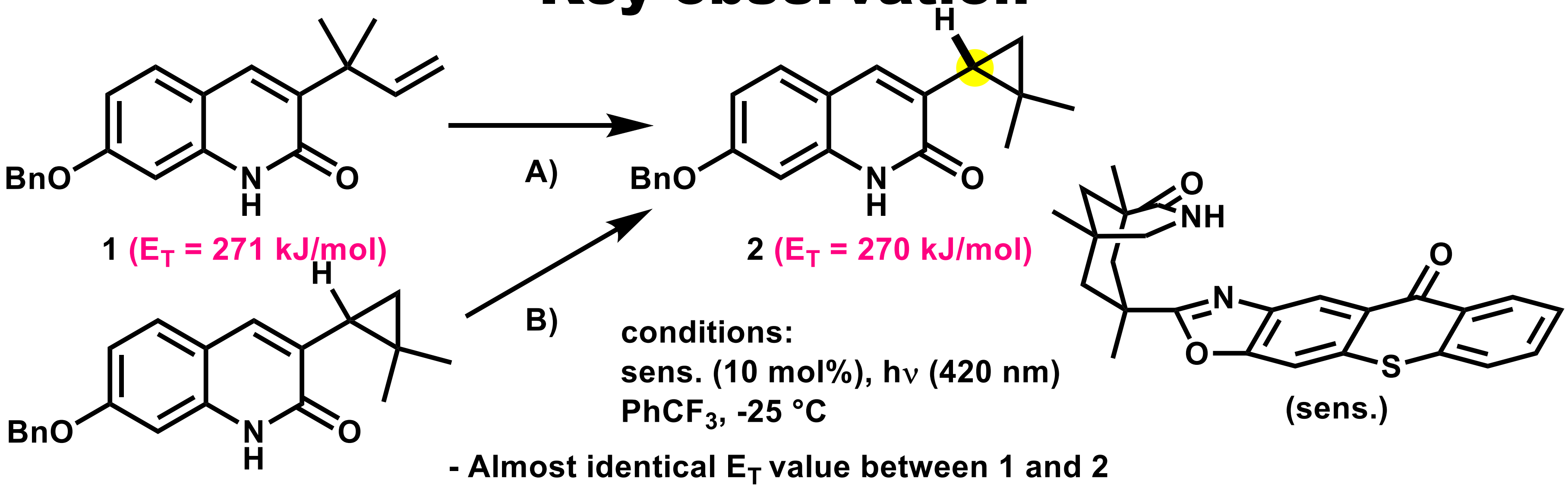


ent-1 (minor enantiomer)

Though steric repulsion between side chain and the sensitizer was larger in scheme (A), major enantiomer was 1.

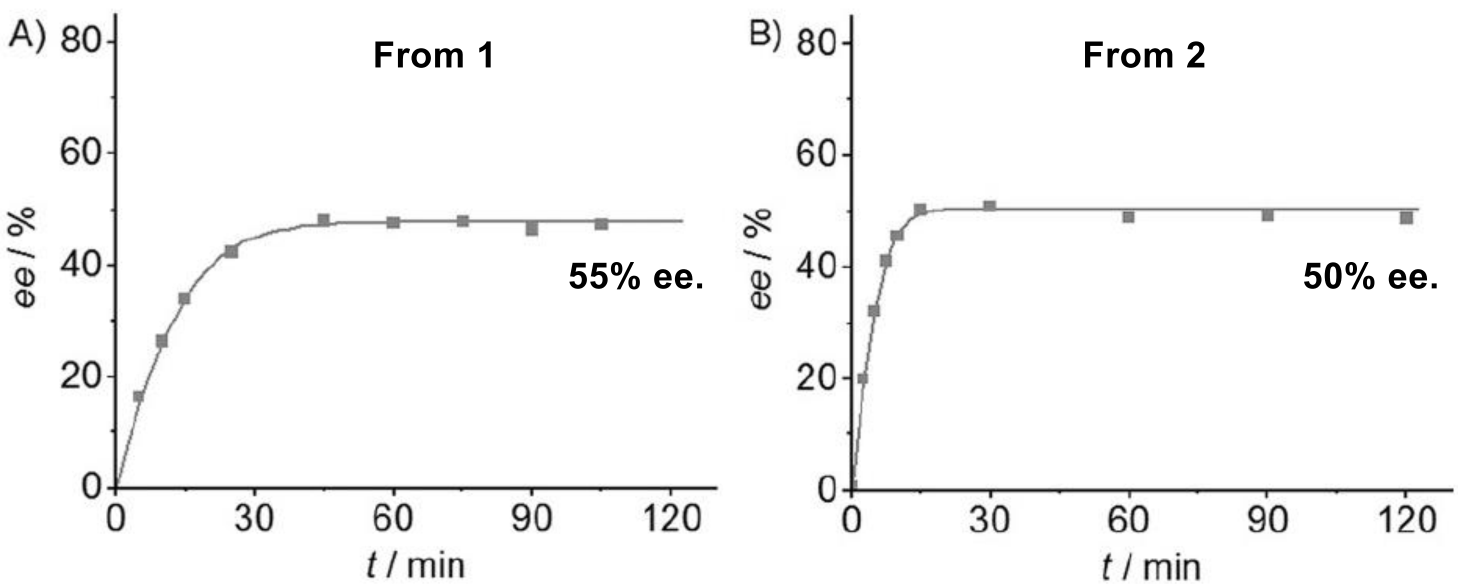
Bach et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.

Key observation



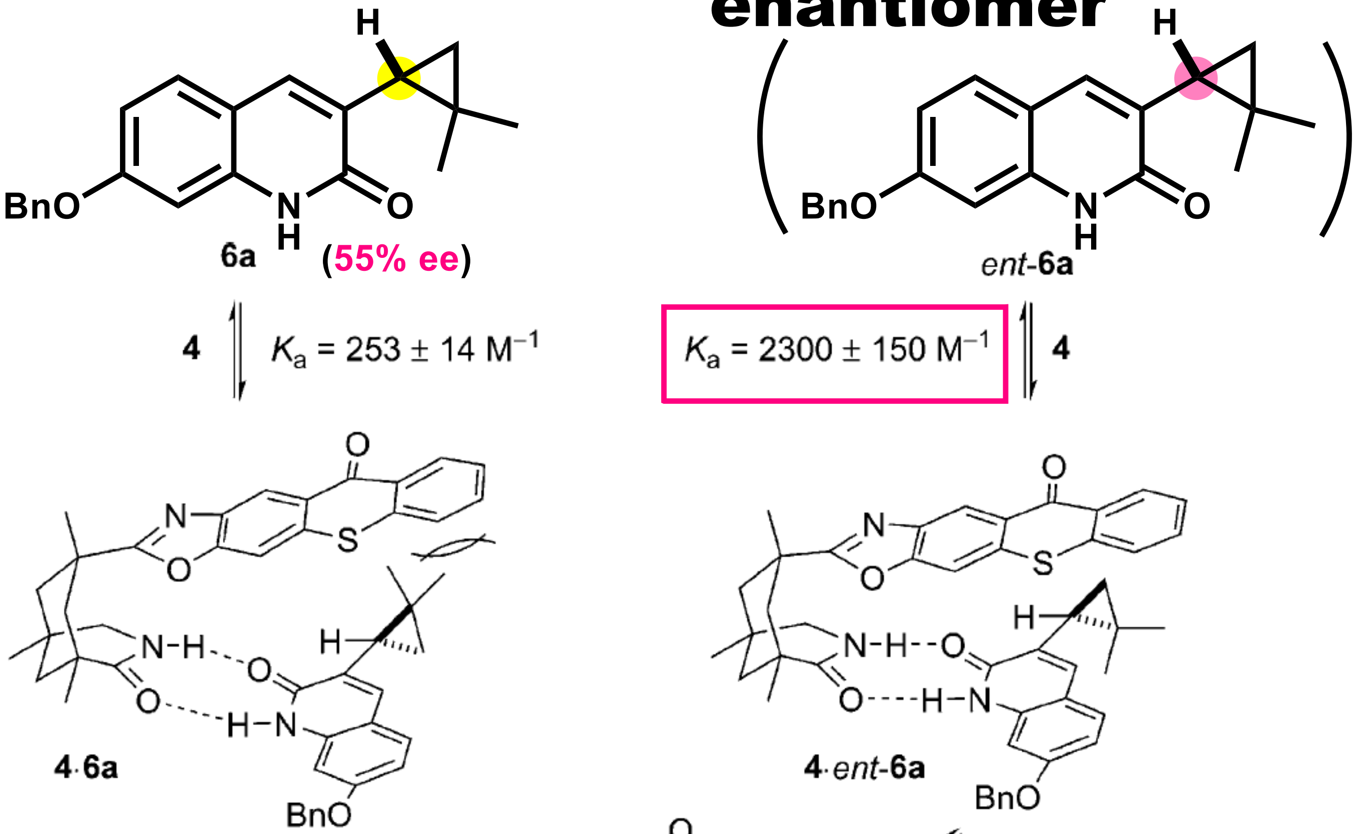
2 (racemic)

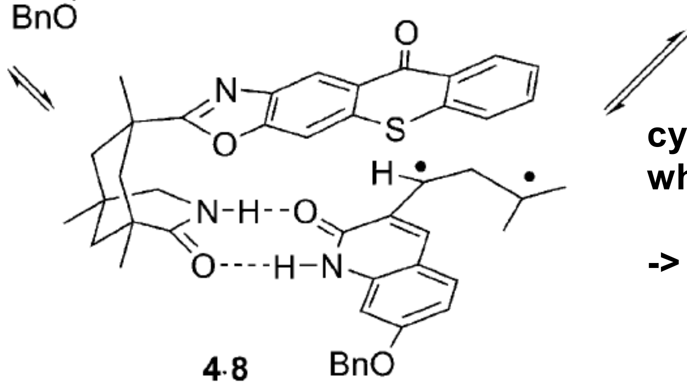
- Almost identical E_T value between 1 and 2
-> Both will be sestized.
- 2 is also generated from racemic 2. (below figure)



Bach et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.

Explanation of formation of preferred enantiomer



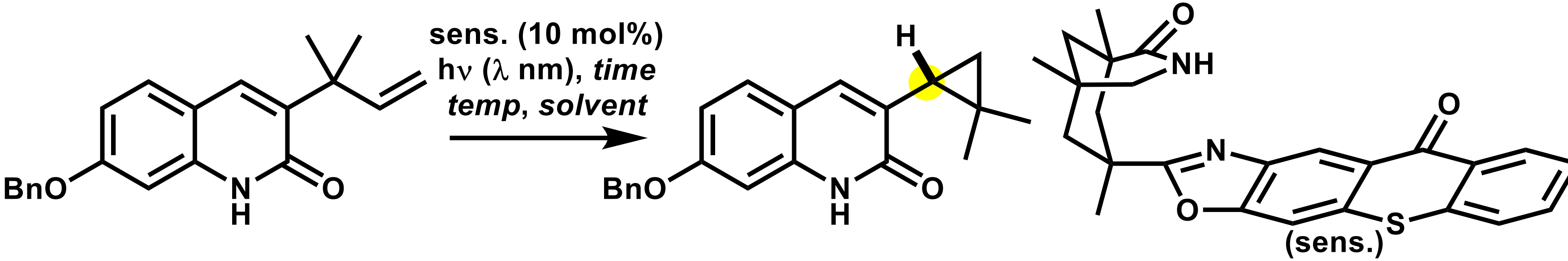


cyclopropane formation favors formation of *ent*-6a while sensitization favors formation of 6a.

-> 6a was given in moderate ee.

Bach et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3538.

Optimization of conditions



Entry	λ (nm)	sens.	*temp.* (C°)	*time* (h)	*solvent*	*yield* (%)	*ee* (%)
1	300	no	20	0.75	$PhCF_3$	90	-
2	350	no	20	0.75	$PhCF_3$	88	-
3	420	no	20	4	$PhCF_3$	-	-
4	420	yes	20	0.5	$PhCF_3$	85	33
5	420	yes	-25	1.5	$PhCF_3$	90	55
6	420	yes	-65	3	$PhCF_3$/HFX* = 1:2	91	55
7	420 (2 W LED)	yes	-25	3.5	$PhCF_3$	85	43
8	420	yes	-25	5	MeCN	33 (brsm)	3

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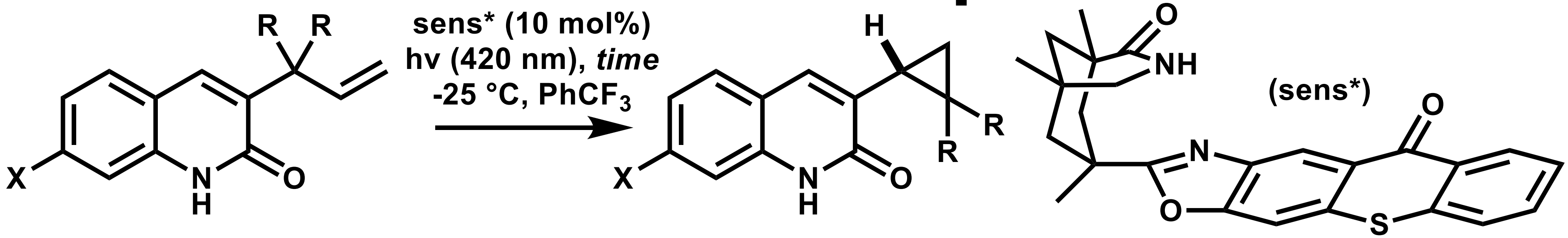
HFX* = hexafluoro-*meta*-xylene

Substrate scope



Entry	X	R, R	*time* (h)	*yield* (%)	*ee* (%)
1	BnO	Me, Me	1	91	55
2	MeO	Me, Me	1.5	96	53
3	MeO	$-(CH_2)_4-$	1	95	44
4	MeS	Me, Me	2	88	40
5	MeO_2S	Me, Me	1.5	94	32
6	TfO	Me, Me	1	91	47
7	H	Me, Me	1	88	45
8	Me	Me, Me	2	88	47
9	Ph	Me, Me	3	88	37

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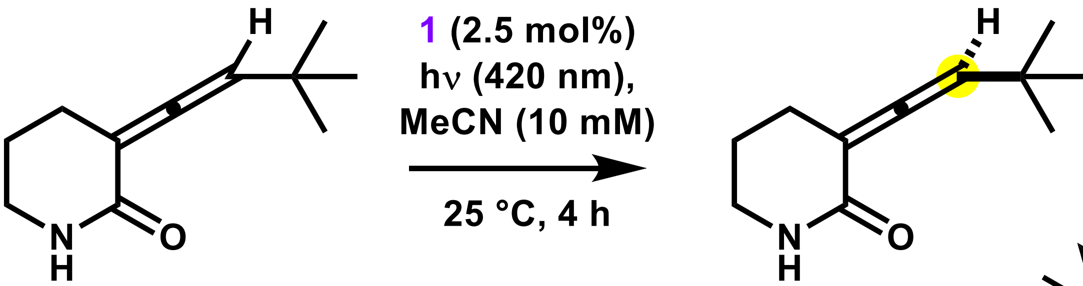
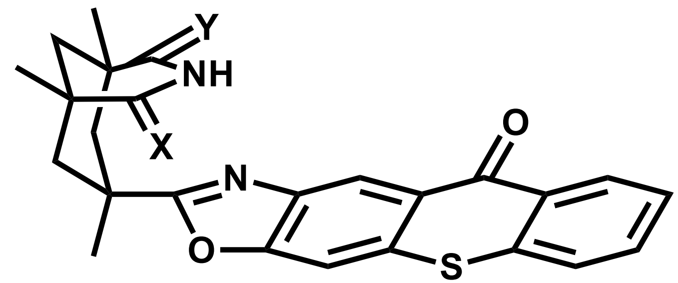
Summary

Photochirogenesis using thioxanthone sensitizers by Bach's group:

1. Deracemization of allene

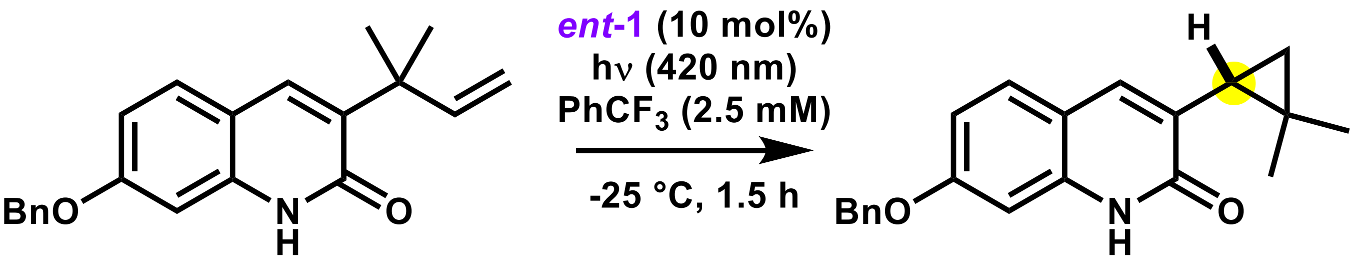


(racemic) *high yield and ee* 89%, 96% ee



thioxanthone sensitizer
1: X=O, Y=H_2
ent-1: X=H_2, Y=O

2. Enantioseletive di-π-methane rearrangement:



90%, 55% ee

Enantiodifferenciation is the result of a deracemization event.