Asymmetric Catalysis for Fine Chemicals Synthesis

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Multi-faceted View on the Mechanism of a Photochemical Deracemization Reaction

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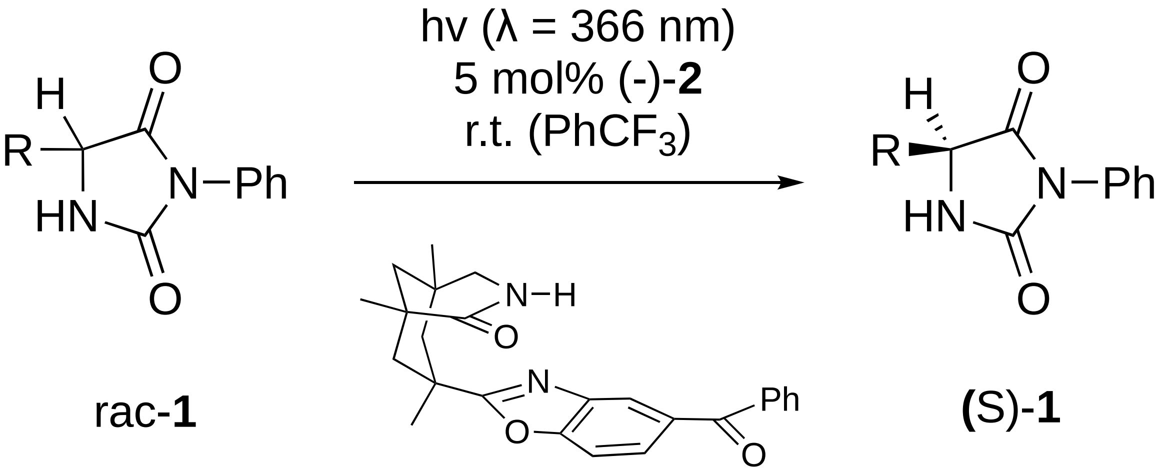
Introduction: Reaction and Reactivity

Photochemical Deracemization



rac-**1**

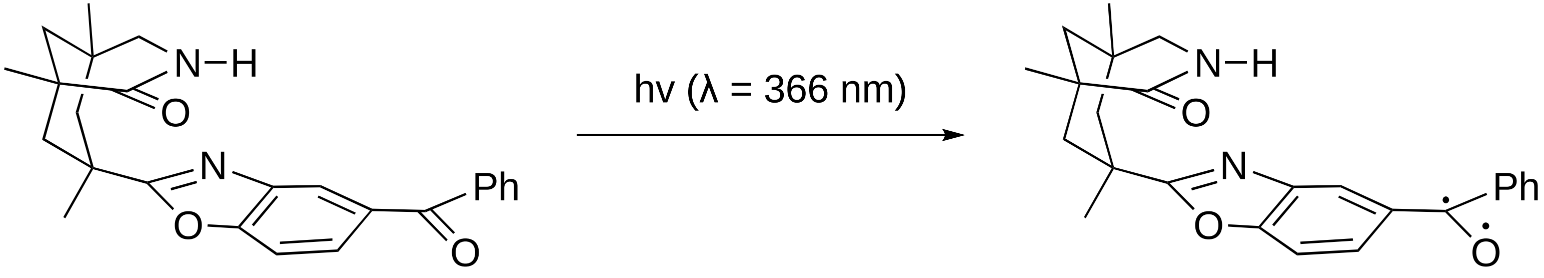
(S)-**1**

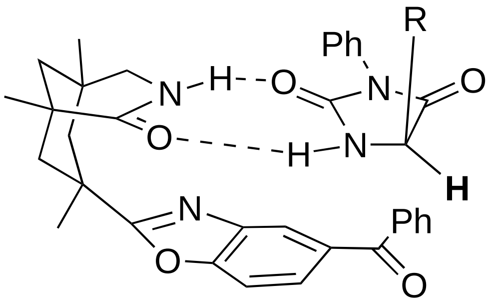
(-)-**2**

- The reaction is a **photochemical deracemization**.
- **«Electrophile»:** ketone of the benzophenone (-)-**2** in the triplet (n → π*) state
- «**Nucleophile»:** Hydrogen atom on the C5 carbon of the hydantoin
- **Bond formation**: Hydrogen abstraction by the catalyst, followed by Hydrogen Atom Transfer (HAT) to the substrate
- **Catalyst**: benzophenone (-)-**2**

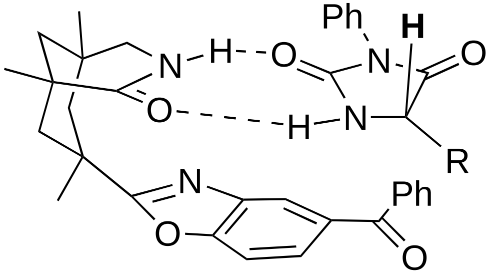
De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. Electrophilicity and Nucleophilicity Index for Radicals. *Org. Lett.* **2007**, *9* (14), 2721–2724.

Principle of Activation





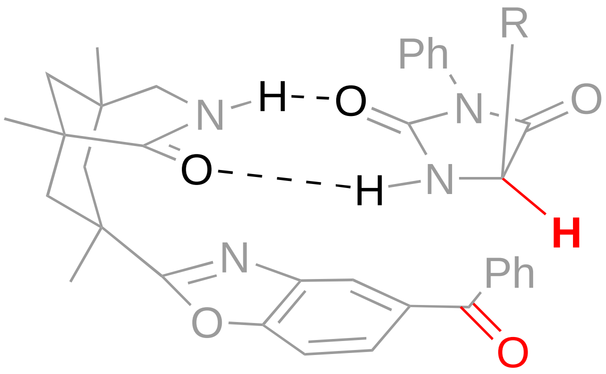
(-)-**2** · (R)-**1**



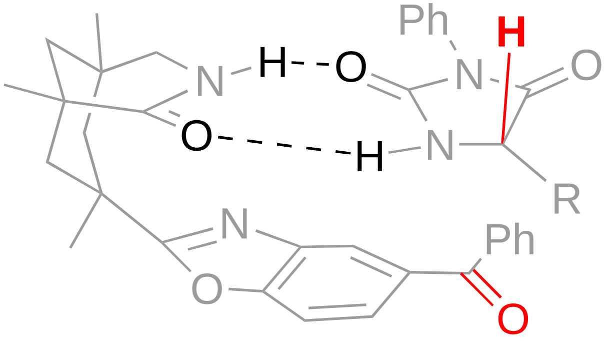
(-)-**2** · (S)-**1**

- **Conformational activation** by double hydrogen bonding
- **Activation of catalyst** by photoexcitation with 366 nm light to the triplet state (n → π*)
- **Stereoinduction** by hydrogen bonding of the substrate and the catalyst → selective hydrogen abstraction by the catalyst

Stereoinduction and Selective H Abstraction



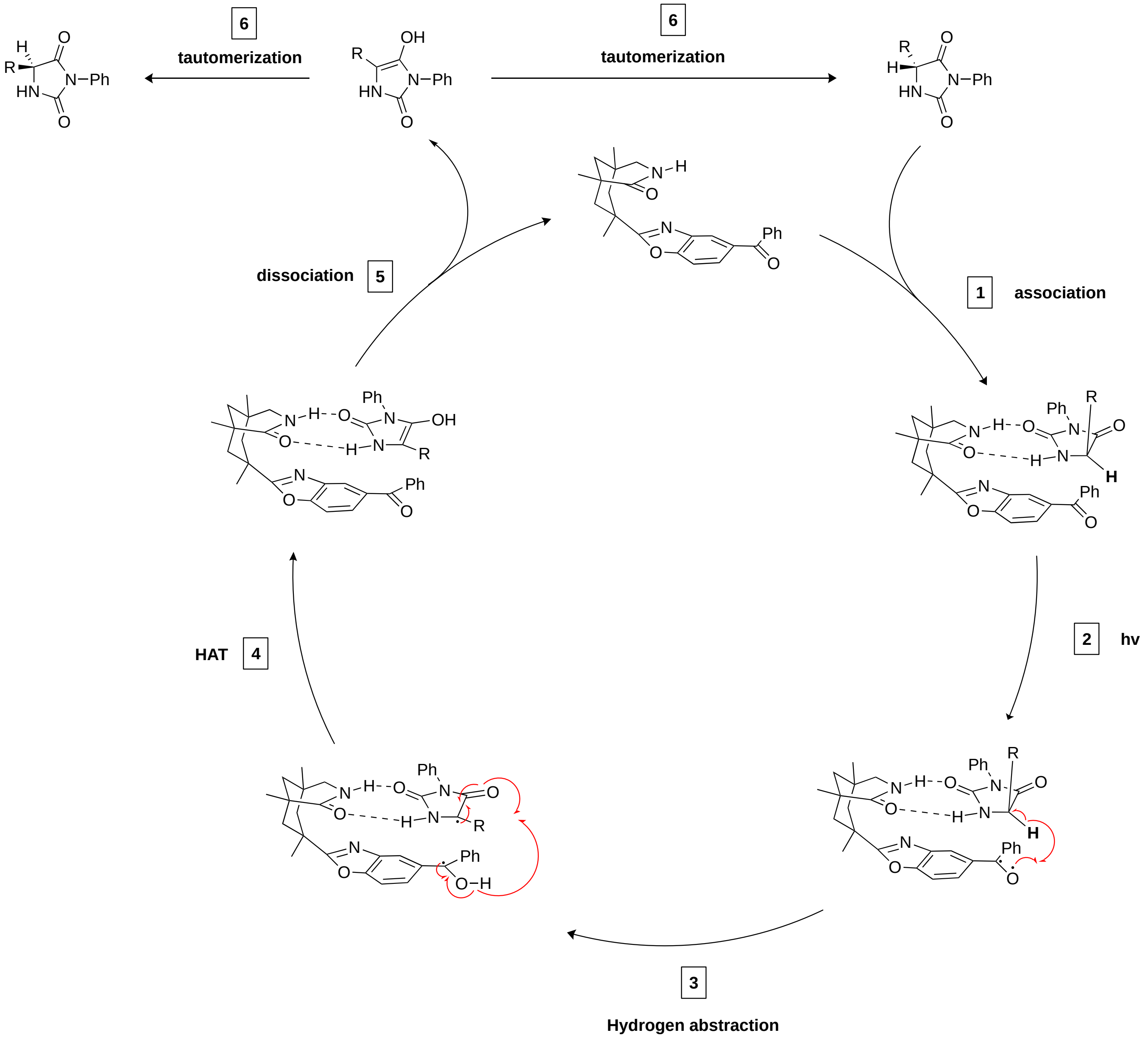
(-)-**2** · (R)-**1**



(-)-**2** · (S)-**1**

- **(-)-2 · (R)-1** complex has good superpositioning → **hydrogen abstraction**
- **(-)-2 · (S)-1** complex is not superpositioned well → **inactive**

Catalytic Cycle



6 tautomerization

6 tautomerization

1 association

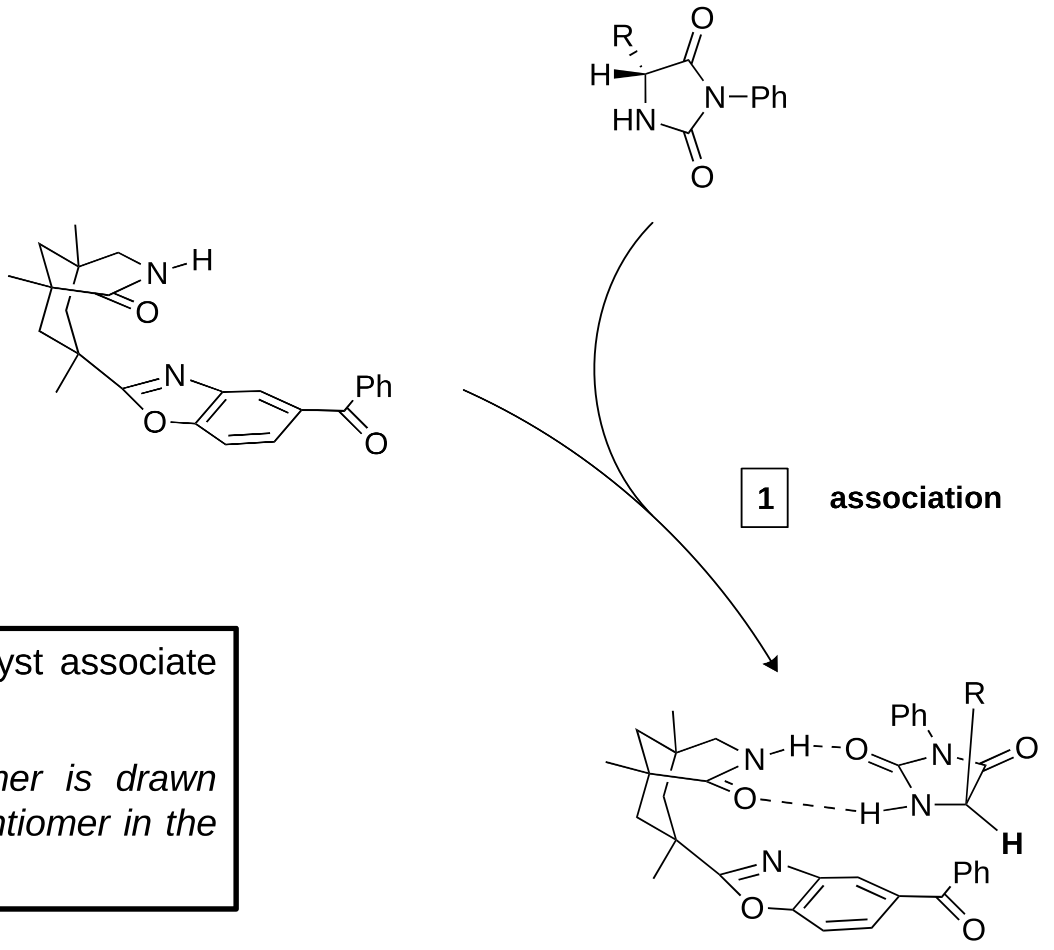
2 hv

3 Hydrogen abstraction

4 HAT

5 dissociation

Catalytic Cycle

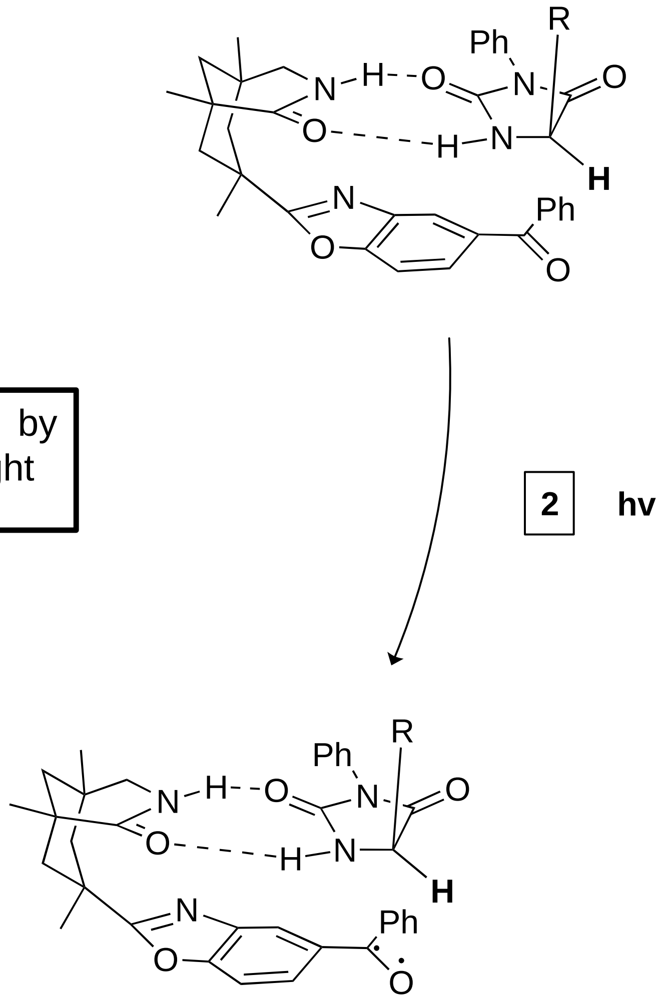


1 **association**

- The substrate and the catalyst associate by **hydrogen bonding**
- ***Note:*** *only the R enantiomer is drawn because it is the active enantiomer in the catalytic cycle*

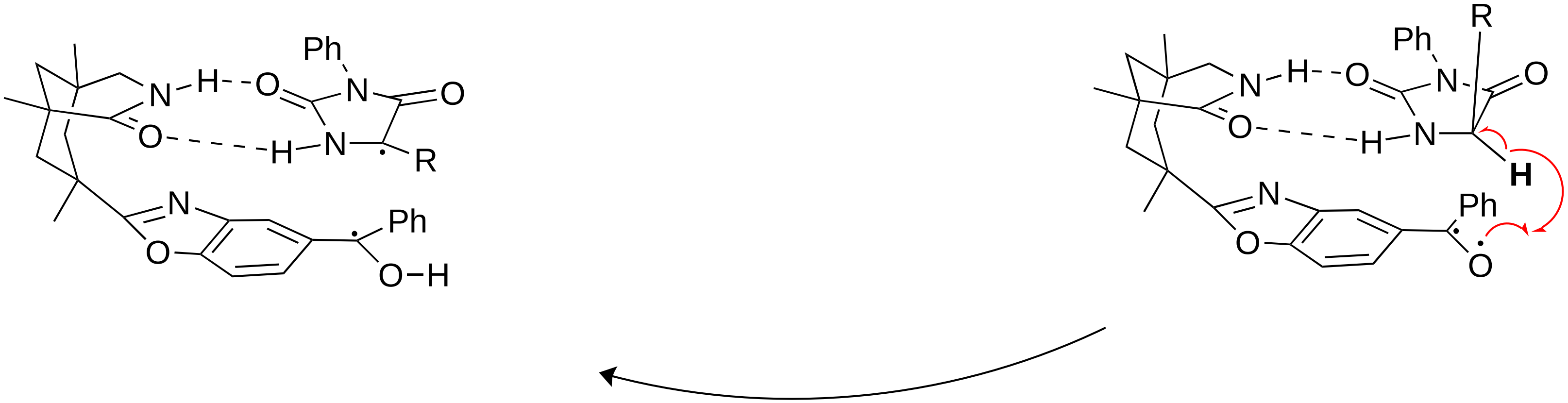
Catalytic Cycle

- The benzophenone catalyst is activated by **photoexcitation** (n → π*) with 366 nm light



Catalytic Cycle

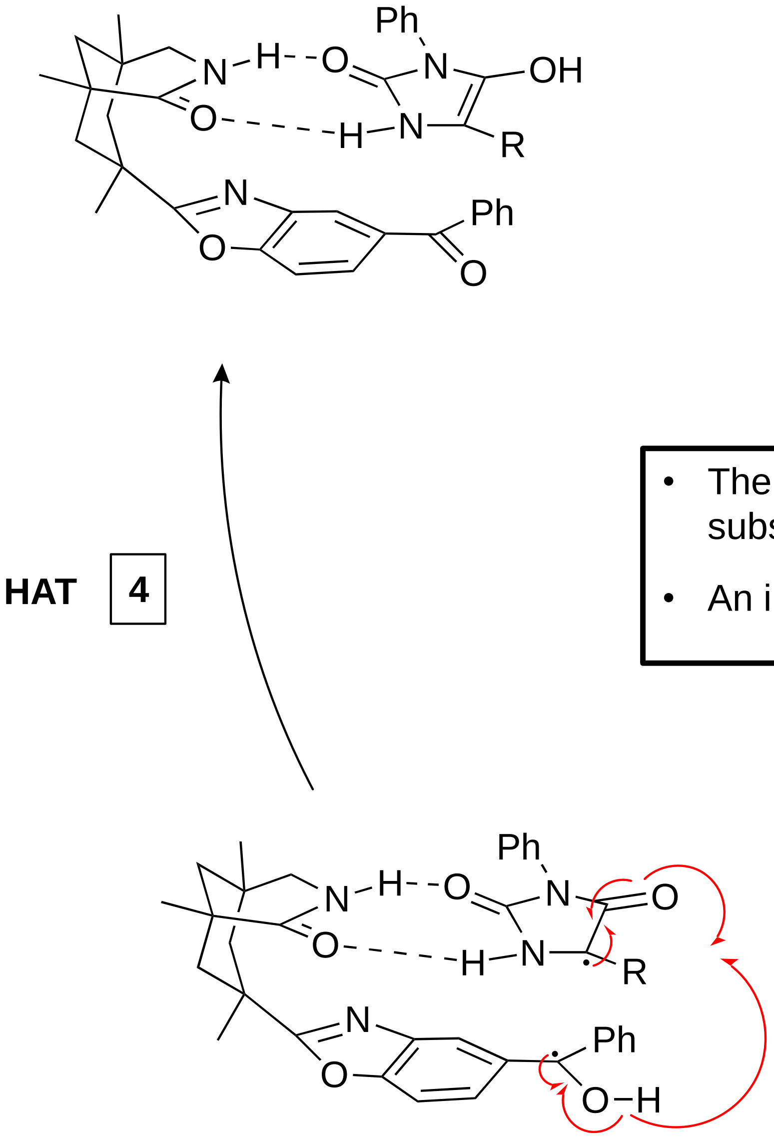
- The catalyst does a **hydrogen abstraction** with the hydrogen on the C5 atom of the hydantoin
- The carbon with the R group becomes sp^2 hybridized



3

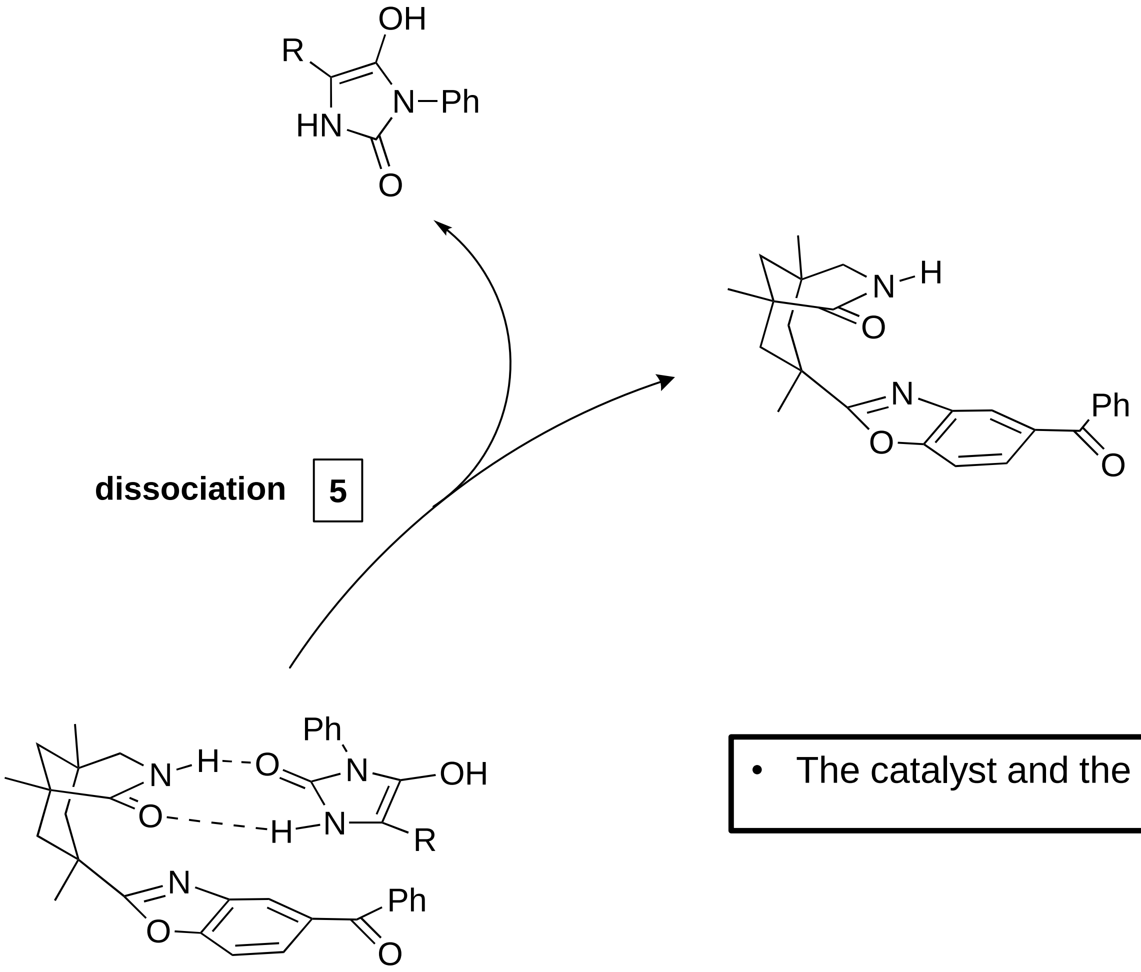
Hydrogen abstraction

Catalytic Cycle



- The catalyst does a **Hydrogen Atom Transfer** back to the substrate
- An imide enolate is formed

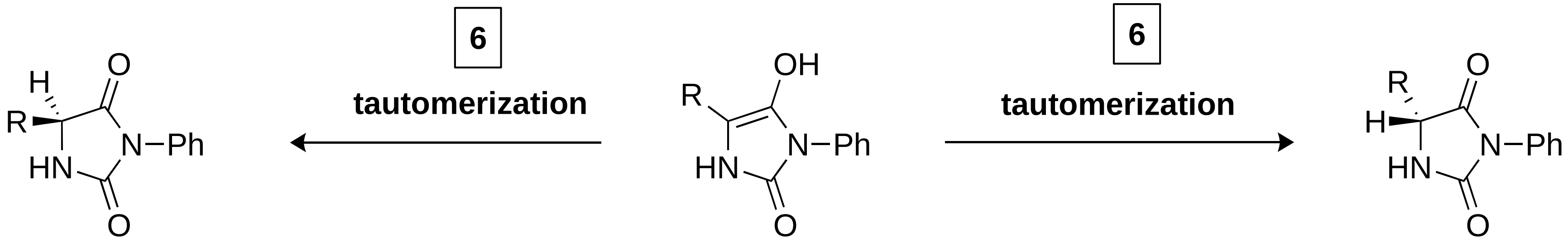
Catalytic Cycle



dissociation **5**

- The catalyst and the substrate **dissociate**

Catalytic Cycle



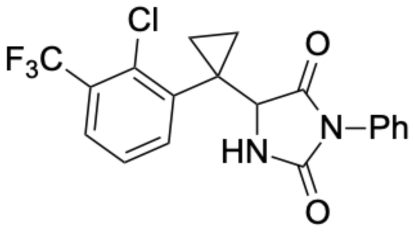
(S)-**1**

(R)-**1**

- The substrate **tautomerizes** to both the S and the R enantiomers
- The **R enantiomer** goes back into the catalytic cycle
- The S enantiomer is inactive → **enrichment of the S enantiomer** by the catalytic cycle

Control experiments and side products

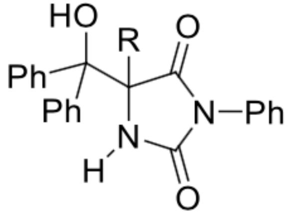
Control experiment



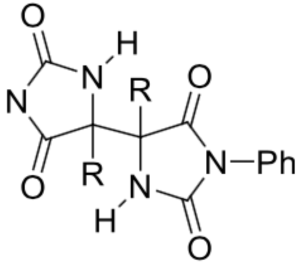
1a

(+)-**2**: (R)-**1a** in 87% yield 94% ee
(-)-**2**: (S)-**1a** in 86% yield 94% ee

Side products



4c (R = ^{i}Pr)

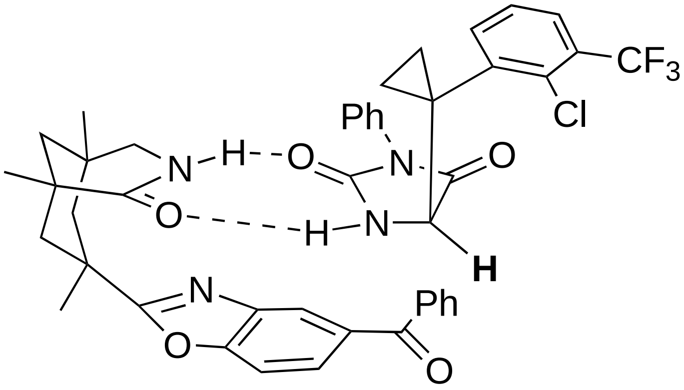


5c (R = ^{i}Pr)

Observed using **BP** as catalyst

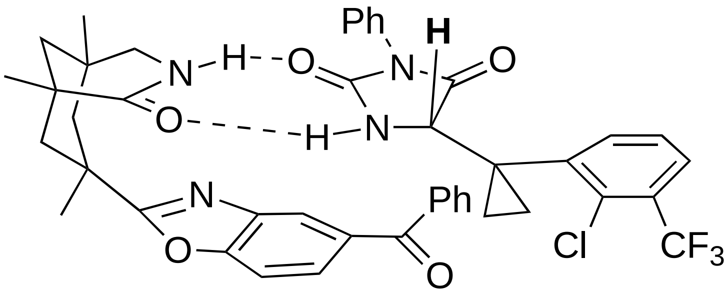
- The other catalyst enantiomer leads to the **opposite** configuration
- Radical-radical recombination products observed with BP. The reaction goes through hydantoin **radical intermediates**.

Formation of Complexes by NMR Titration



(-)-**2** · (R)-**1a**

K_a = 89 ± 11 L·mol^{-1}



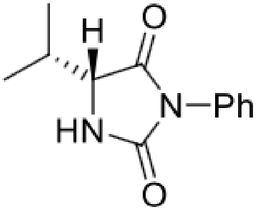
(-)-**2** · (S)-**1a**

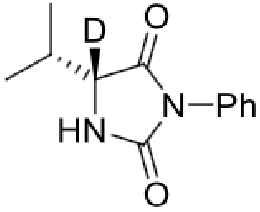
K_a = 56 ± 10 L·mol^{-1}

- Association via **2 hydrogen bonds**
- The (-)-**2**·(S)-**1a** less favored due to **sterics** (benzoyl group and bulky hydantoin substituent)
- H atom at sterogenic center of (-)-**2**·(R)-**1a** close to carbonyl of benzophenone → good for intramolecular HAT

KIE effect and H/D crossover

KIE effect


(*R*)-**1c**

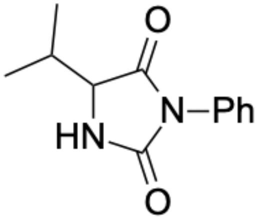

(*R*)-**1c**-d_1

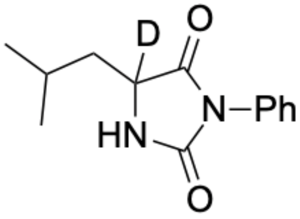
Separate kinetics: $k_H/k_D = 1.4$

Competition kinetics: $k_H/k_D = 1.8$

QCC calculation: $k_H/k_D = 1.9$

H/D crossover


1c


1d-d_1

(+)-**2** cat.:

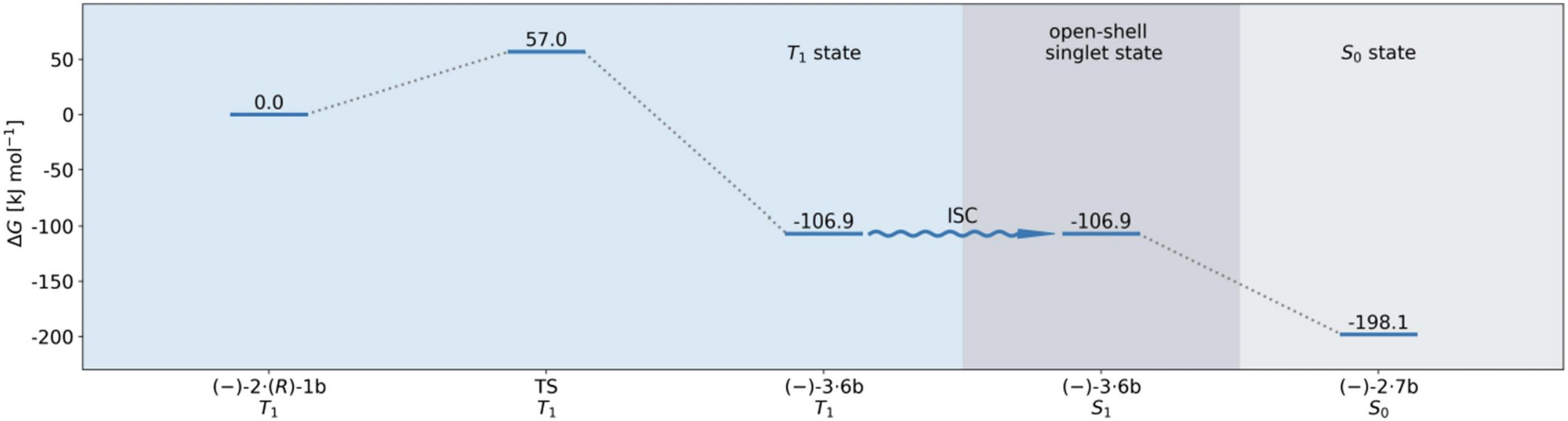
(S)-**1**: 50% of H/D crossover

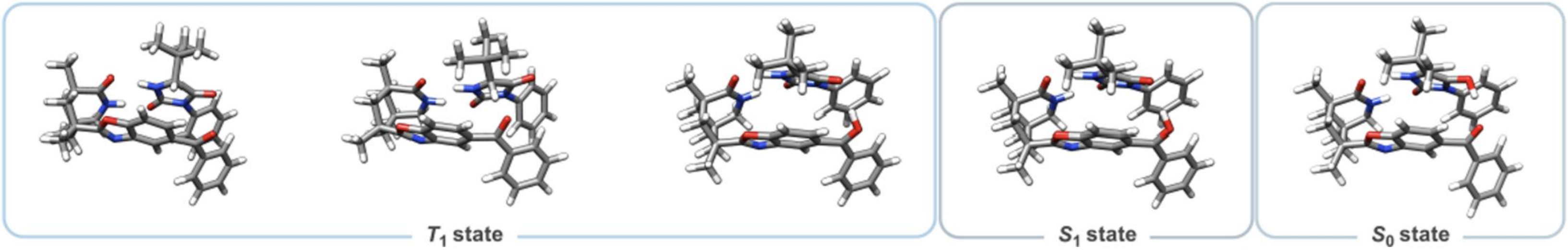
Racemic: 25% of H/D crossover

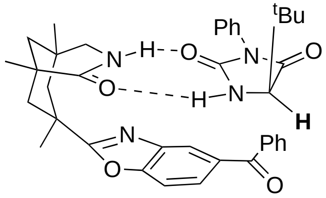
(R)-**1**: No H/D crossover

- Light **KIE** observed and confirmed by QCC: HAT is rate-determining step
- KIE allowed the identification of the transition state's conformation
- H/D crossover is observed to be 50% of the converted starting material → Proton exchange occurs in a bimolecular fashion through **tautomerization**.

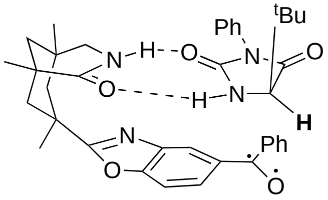
Quantum Chemical Calculations – HAT

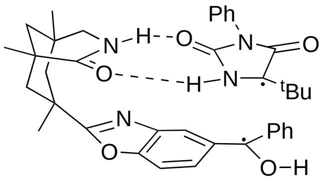




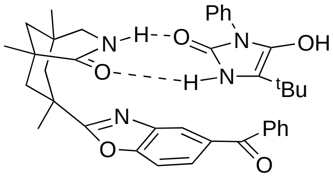


(-)-**2** · (R)-**1b**



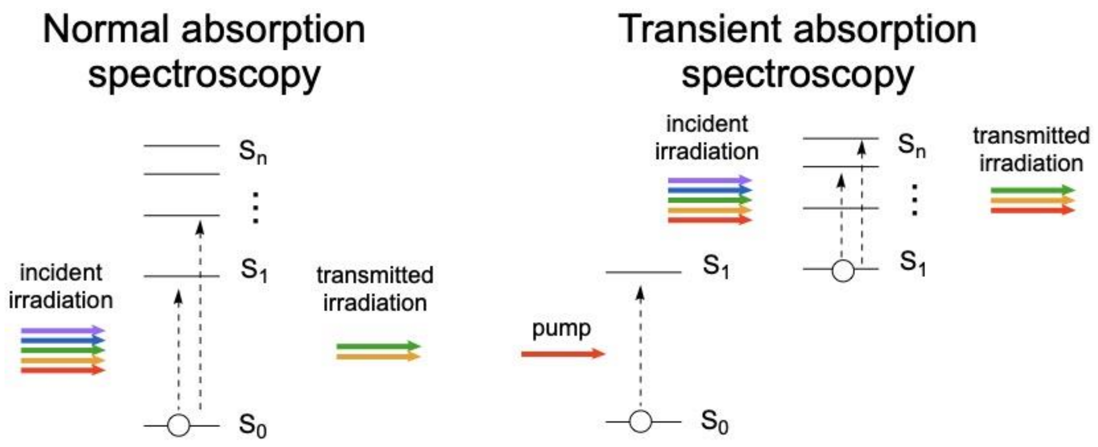


(-)-**3** · **6b**



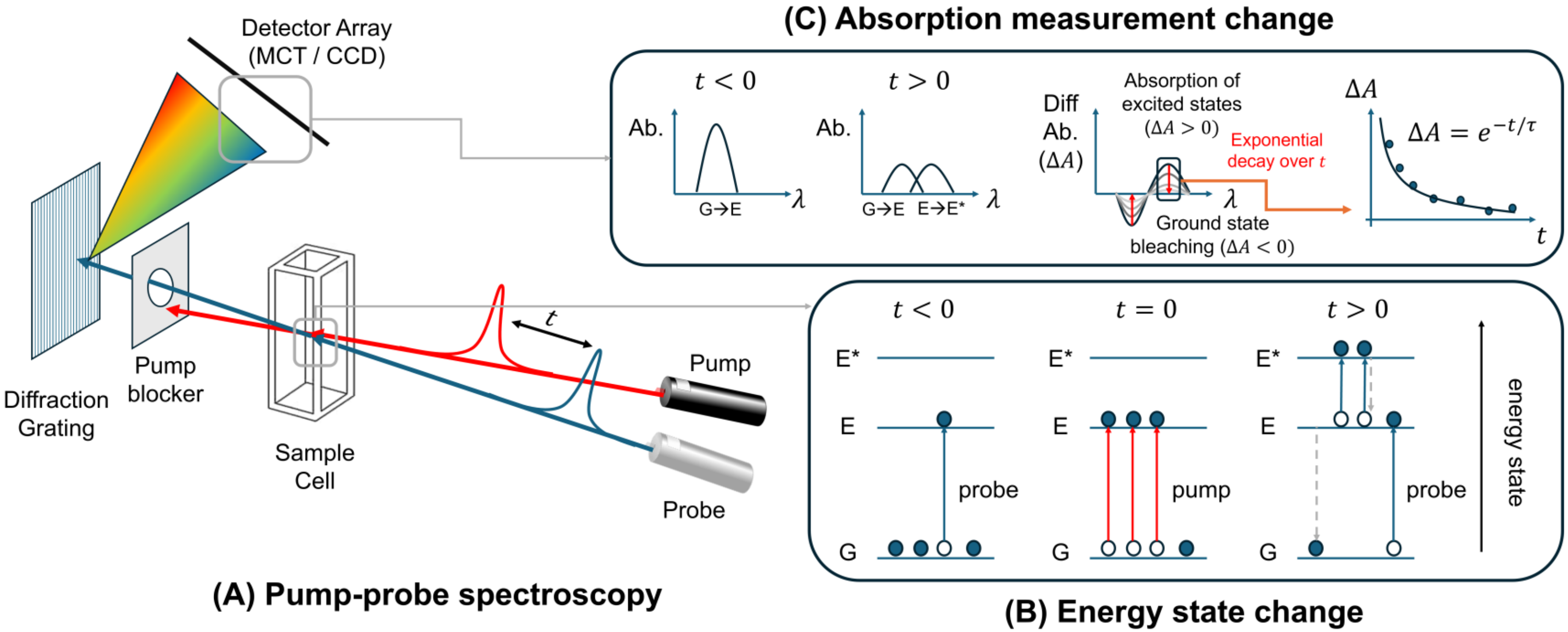
(-)-**2** · **7b**

Transient Absorption Spectroscopy – Introduction


Normal absorption spectroscopy

Transient absorption spectroscopy

Study of excited states

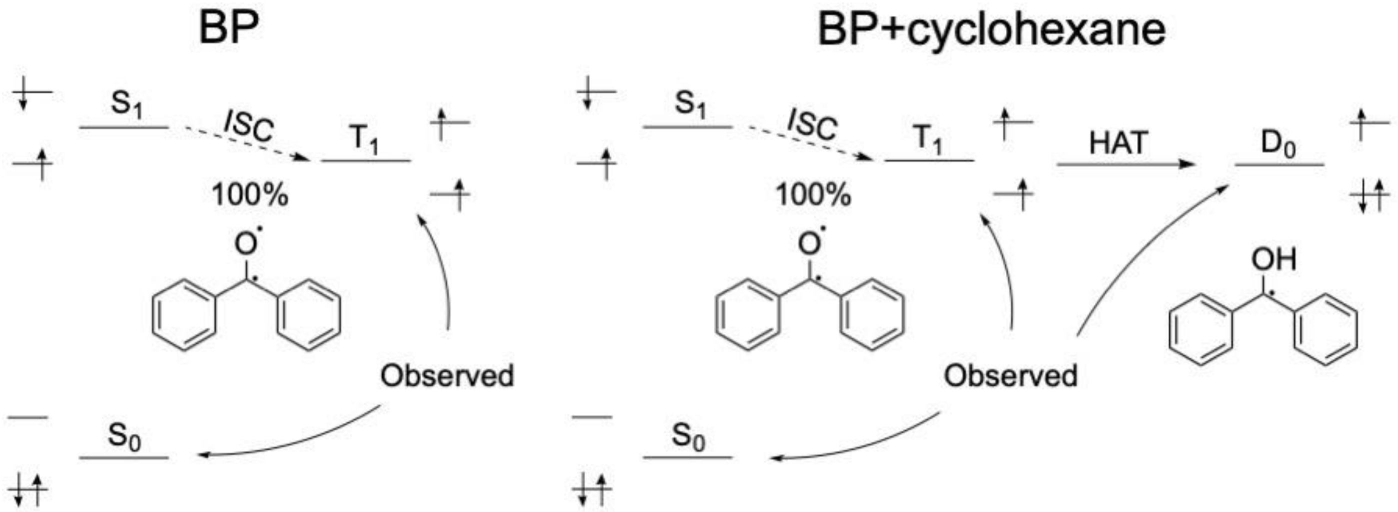

(C) Absorption measurement change

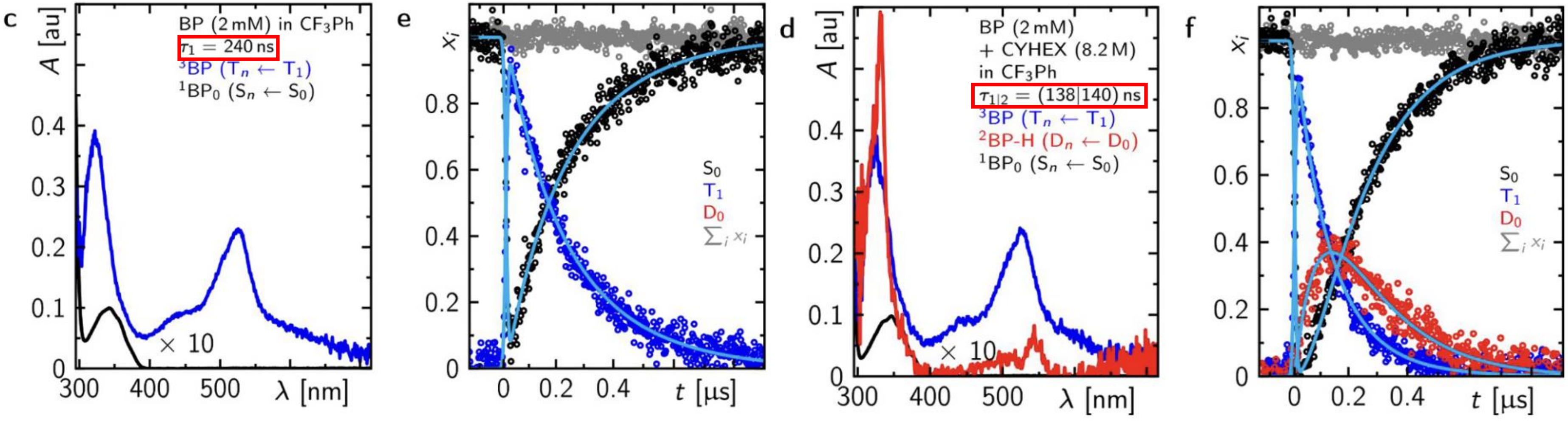
(A) Pump-probe spectroscopy

(B) Energy state change

https://juhyeonkim95.github.io/project-pages/transient_absorption_spectroscopy/

Transient Absorption Spectroscopy – Benzophenone





- Acceleration of decay and observation of the BP ketyl radical with cyclohexane

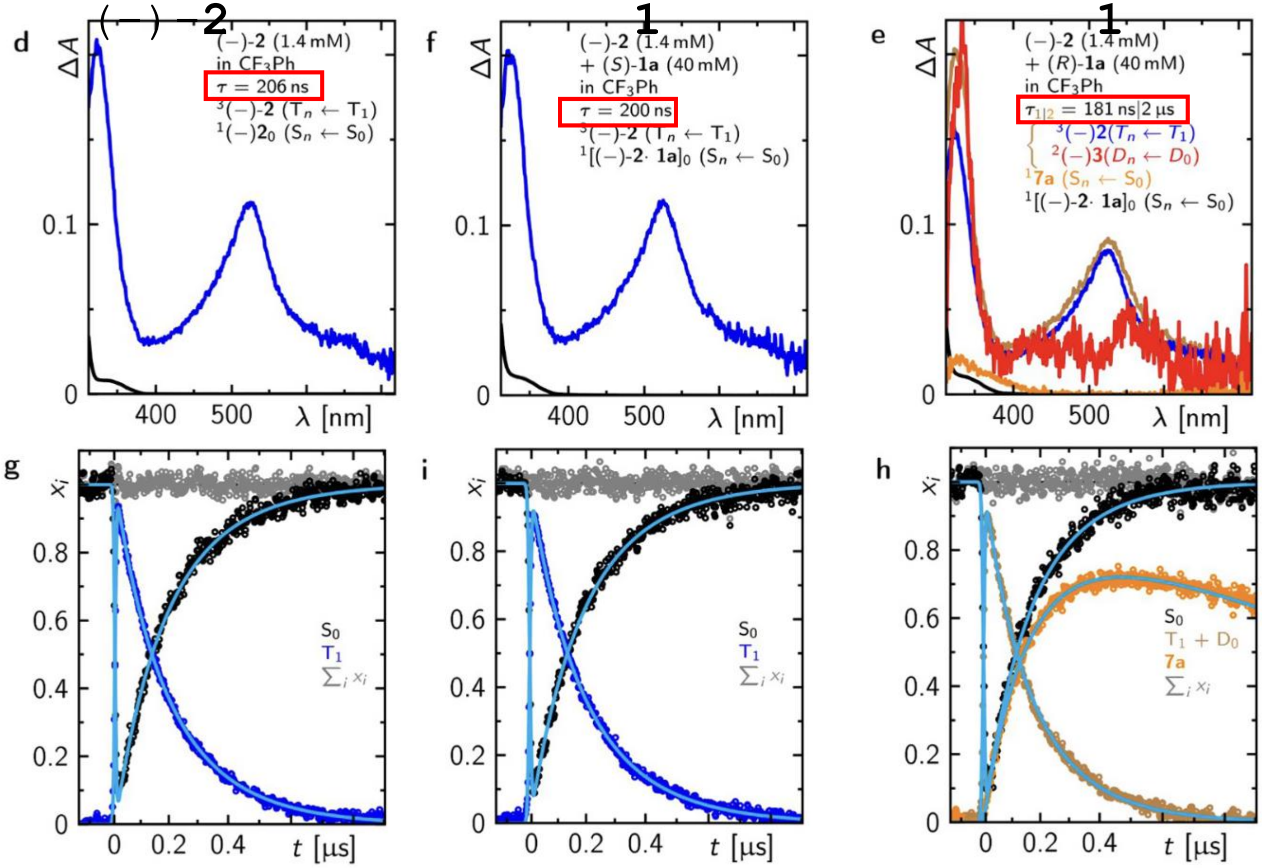
Transient Absorption Spectroscopy – Intermediates

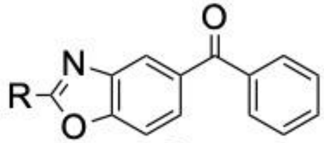
Only cat. (−)−**2**

(−)−**2**+(S)−**1**

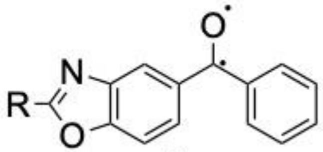
(−)−**2**+(R)−**1**

Observed

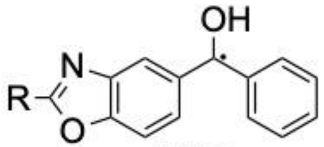




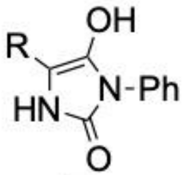
^{0}(-)**2**



^{3}(-)**2**



^{2}(-)**3**



7

- Only enantiomer R undergoes HAT with the catalyst, with a quantum yield of 12%
- Formation of **3** is then followed by quick ISC and back-HAT to form enol **7**

Critical Analysis: Novelty

Strong points

- Extensive analysis and study of the reaction mechanism
- Use of Transient Absorption Spectroscopy to observe excited state species.
- Use of Quantum Chemical Calculations for HAT mechanism studies
- The reaction only needs the chiral photocatalyst

Weak points

- Deracemization is a well known concept
- Catalytic system already discovered (*Nature* 564, 240–243 (2018))

Critical Analysis: Practicability

Strong points

- Mild conditions (room temperature, only light)
- Organocatalyst
- No strong UV light needed

Weak points

- Need specific wavelength of light (366 nm)
- Applicable specifically on hyndatoin moieties
- Complex catalytic scaffold

Critical Analysis: Sustainability

Strong points

- Metal-free catalyst
- Mild conditions (room temp)
- Atom economy (absence of side products)
- Reuse of unwanted enantiomers (waste recycling)

Weak points

- Irradiation for 13 hours
- Undesirable solvent (trifluorotoluene classified «yellow»)
- 5 mol% catalytic loading

Questions

Question 1

Why are deracemization reactions inherently challenging?

Question 2

Why is one of the two enantiomers not able to under Hydrogen Atom Transfer?

Question 3

When using benzophenone as catalyst, radical-radical C-C coupling side products are observed, but not with the chiral catalyst: why?