Photo-mediated Ring Contraction of Azacycle

2024.4.6. Literature Seminar

M2 Shintaro Fukaya

Contents

Contents

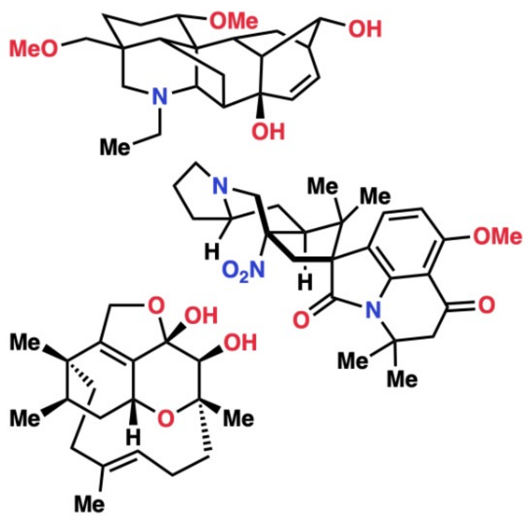
Introduction of Prof. R. Sarpong

Prof. Richmond Sarpong

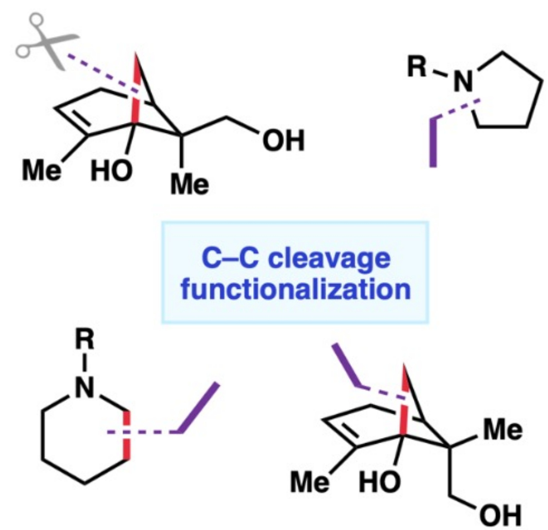
1995: B.S. @ Macalester College (Prof. R. C. Hoye)
2001: Ph.D. @ Princeton University (Prof. M. F. Semmelhack)
2000-2004: Postdoc @ California Institute of Technology (Prof. B. M. Stolzs)
2004-2010: Assistant professor @ University of California, Berkeley
2010-2014: Associate professor @ University of California, Berkeley
2014-: Professor @ University of California, Berkeley

Research topics:

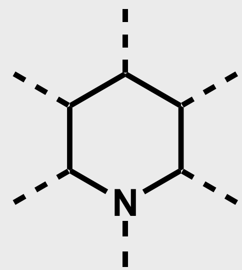
Natural products total synthesis



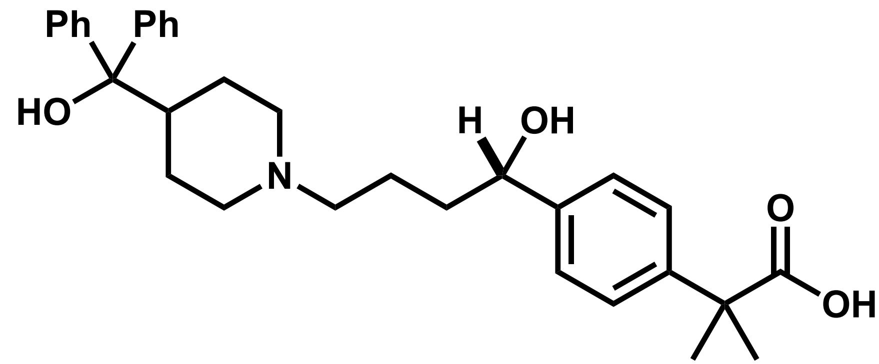
Carbon-carbon cleavage methodology



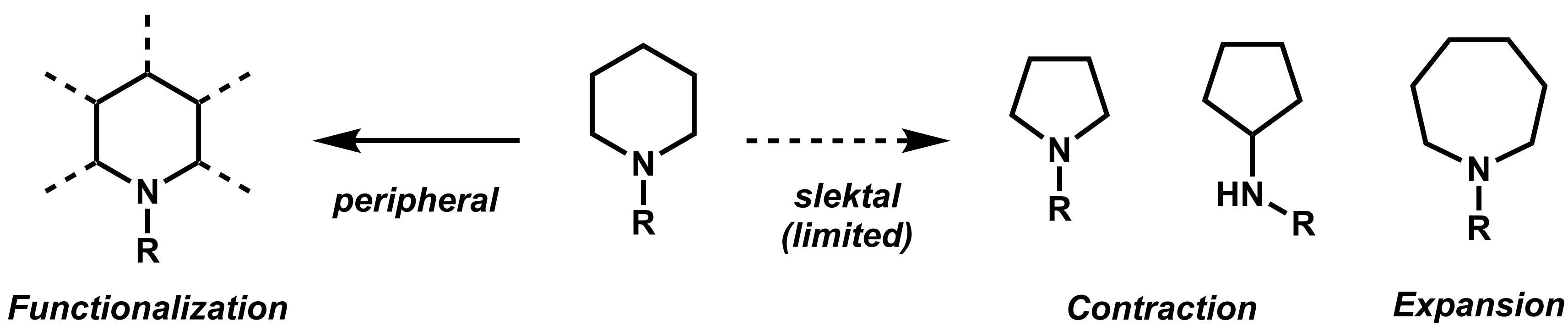
Piperidine



piperidine scaffold
a lot of pharmaceutical and agrochemical compound libraries

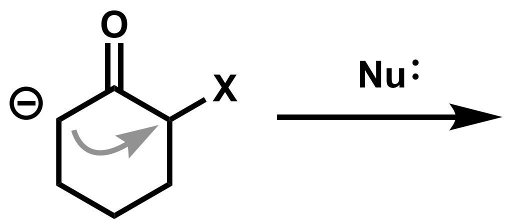


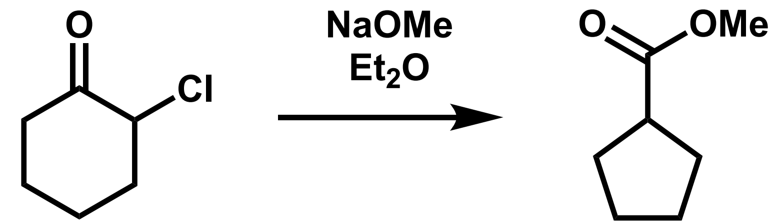
Fexofenadine (anti-histamine)



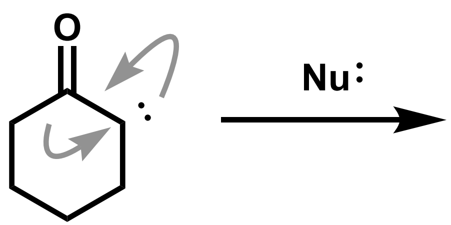
Ring Contractions

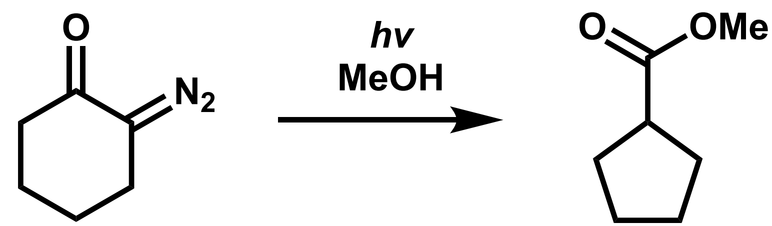
- Anionic



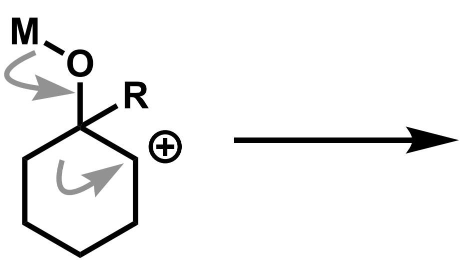


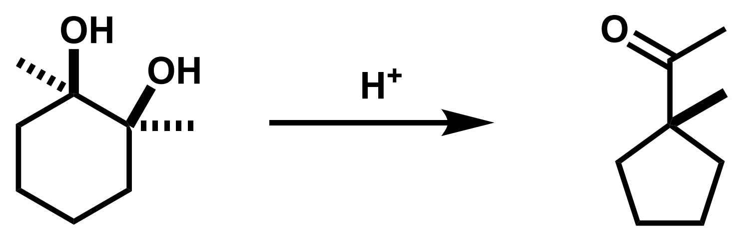
- Carbenoid





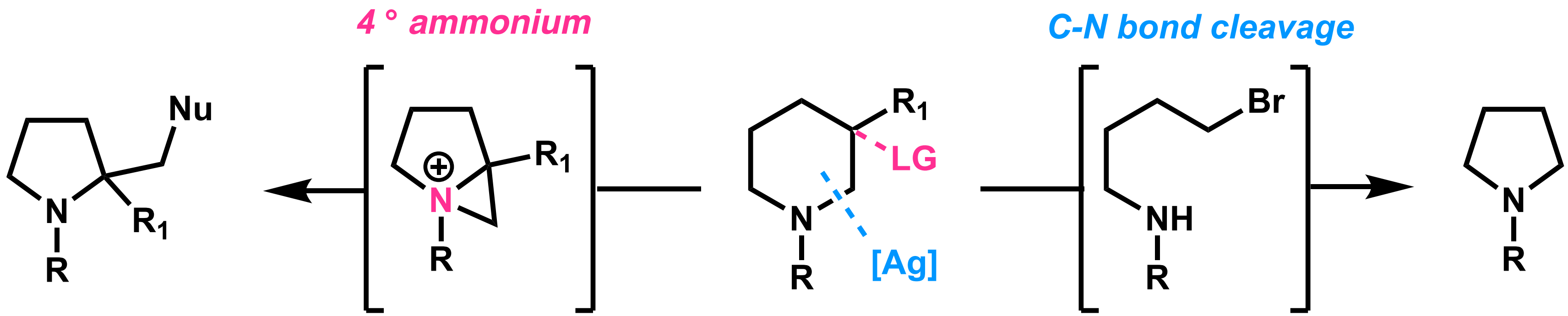
- Cationic



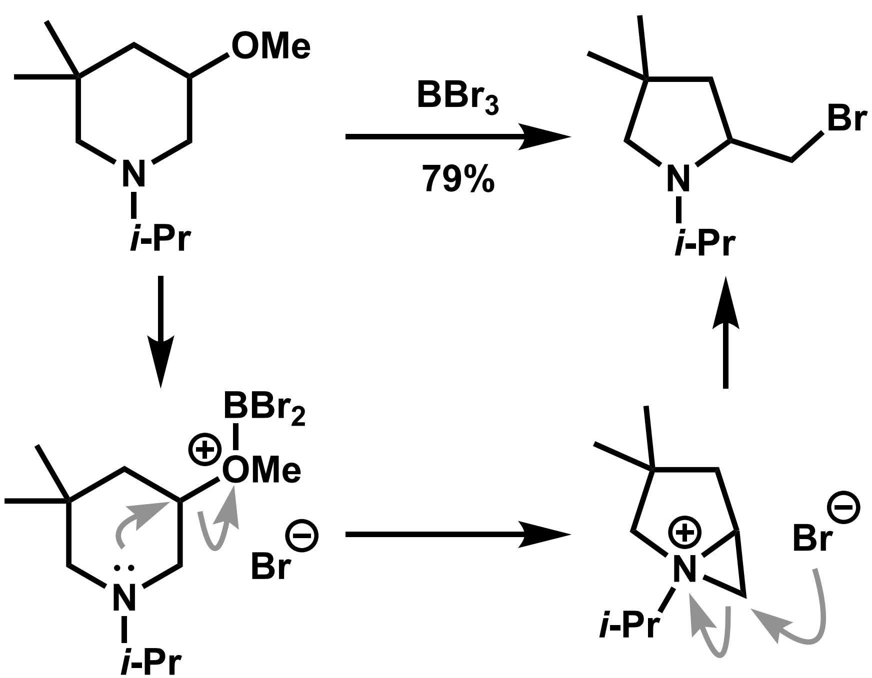


1) Goheen, D. W.: Vaughan, W. R. *Org. Synth.* **1959**, *39*, 37.
2) Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, *45*, 5278.
3) Pavlik, C.; Morton, M. D.; Smith, M. B. *Synlett* **2011**, 2191.

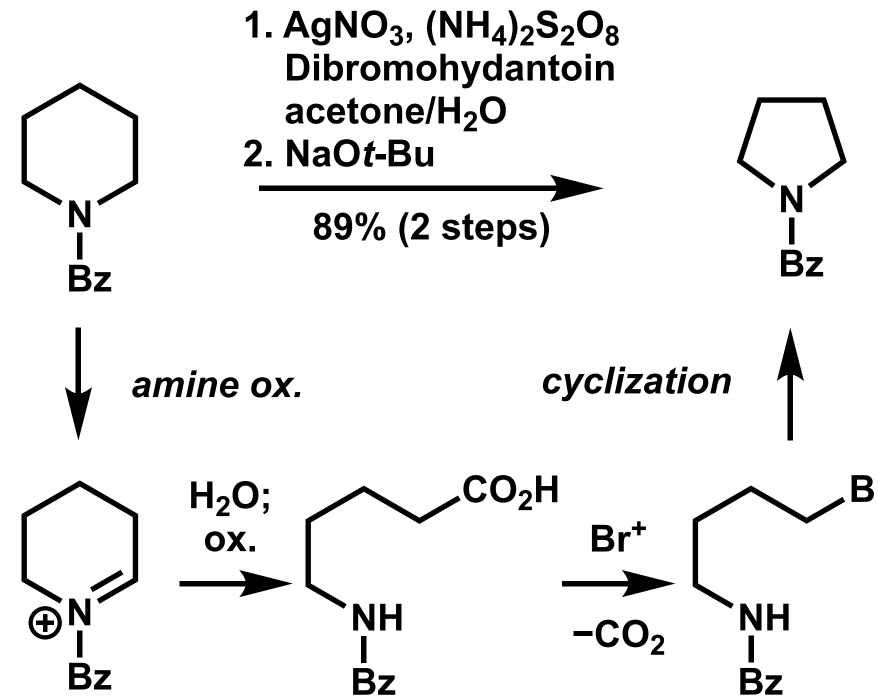
Piperidine-to-Pyrrolidine Scaffold Conversion



- *Knight, D. W. (2000)*



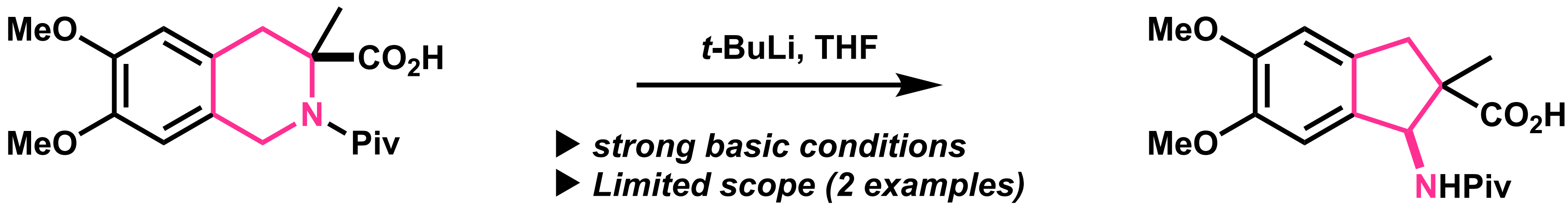
- *Sarpong. R. (2018)*



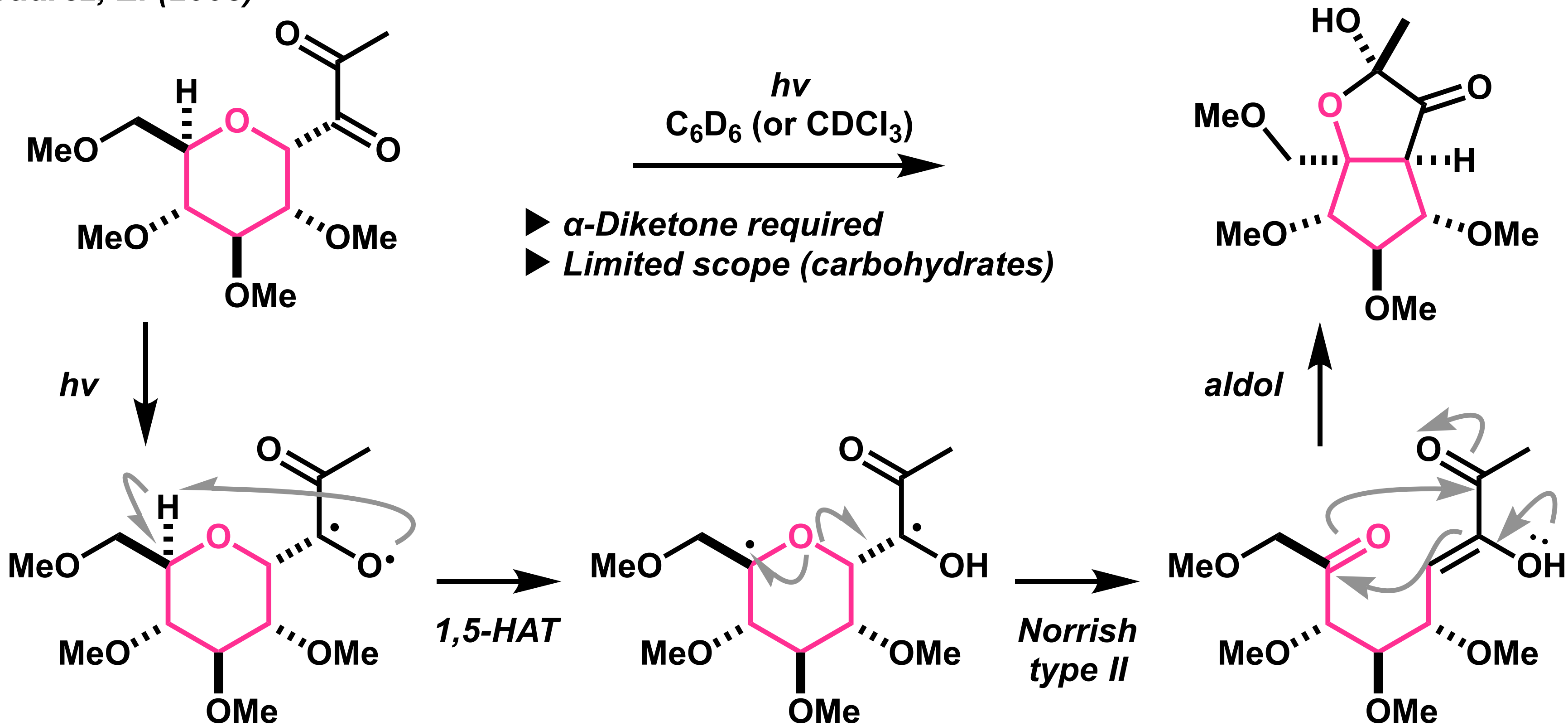
1) Tehrani, K. A.; Syngel, K. V.; Boelens, M.; Contreras, J.; Kimpe, N. D.; Knight, D. W. *Tetrahedron Lett.* **2000**, *41*, 2507. 2) Roque, J. B.; Kuroda, Y.; Gottemann, L. T.; Sarpong, R. *Nature* **2018**, *564*, 244.

endo-to-exocyclic Heteroatom Transposition

- *Seebach, D. (1993)*



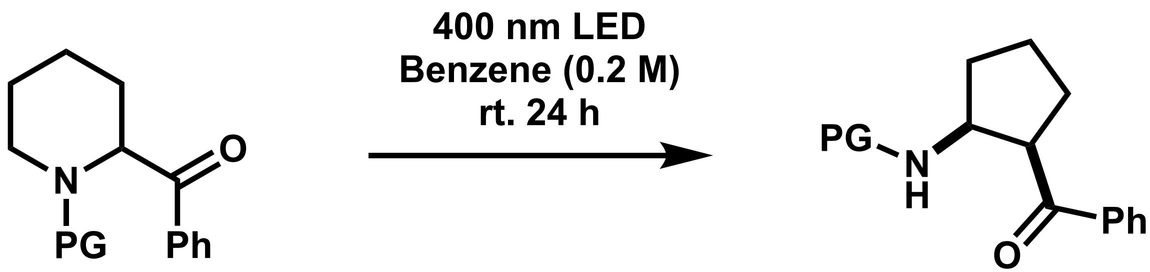
- *Suarez, E. (2008)*



1) Gees, T.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2640.
2) Alvarez-Dorta, D.; Leon, E. I.; Kennedy, A. R.; Riesco-Gagundo, C.; Suarez, E. *Angew. Chem.* **2008**, *120*, 9049.

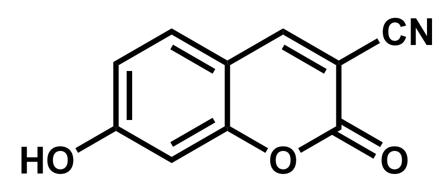
Contents

Optimization of the conditions



PG	*deviation*	*yield (%, d.r.)*
SO_2Ph	none	73% (20:1)
Bz	none	36% (17:1)
Boc	none	11% (20:1)
SO_2Ph	MeOH	53% (1.6:1)
SO_2Ph	MeCN	64% (7:1)
SO_2Ph	385 nm	17% (20:1)
SO_2Ph	450 nm	0%
SO_2Ph	0.05 M	84% (20:1)

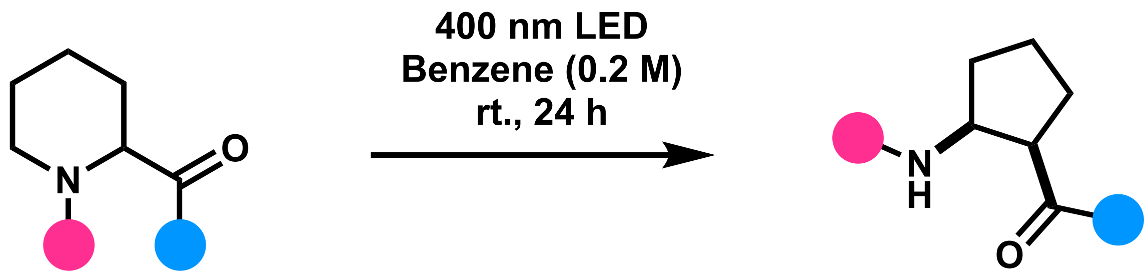
PG	*additive*	*ratio (product:SM)*
COBn	none	1:1.1
COBn	X	3.9:1

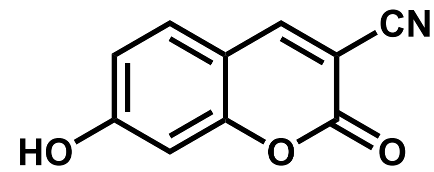


X

1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

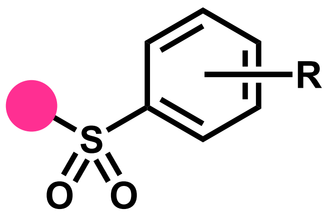
Scope 1: Substituents



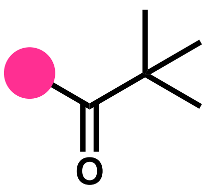


X

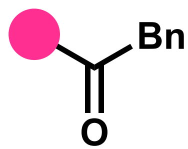
N Substitution **(= Ph, d.r.)**



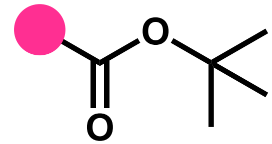
R = H	84% (20:1)	R = *p*-OMe	68% (8:1)
R = *p*-Me	79% (12:1)	R = *p*-Cl	59% (3.3:1)
R = *o*-Me	48% (19.1)	R = *p*-Ac	22% (5:2)



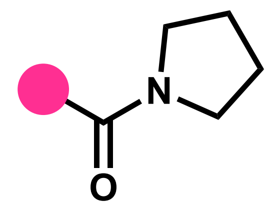
54% (14:1)*



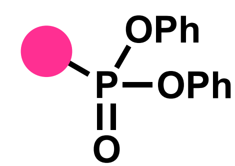
39% (20:1)*



22% (20:1)*



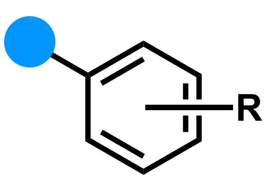
57% (19:1)*



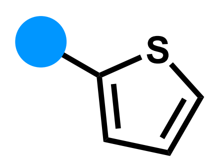
52% (19:1)*

* 30 mol% of X was added.

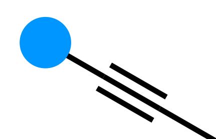
Aroyl Substitution **(= Ph, d.r.)**



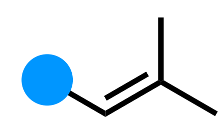
R = *p*-Me	63% (8.1:1)
R = *o*-Me	21% (2.1)
R = *p*-OMe	49% (13:1)
R = *p*-F	69% (9:1)
R = *p*-CF_3	33% (1.3:1)



56% (10:1)



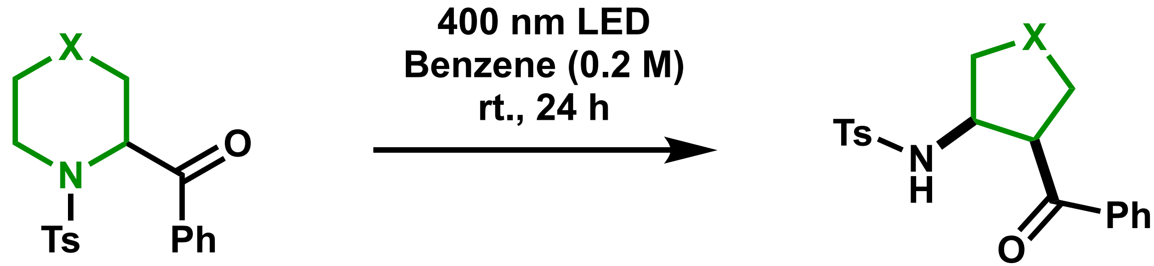
9% (3:1)

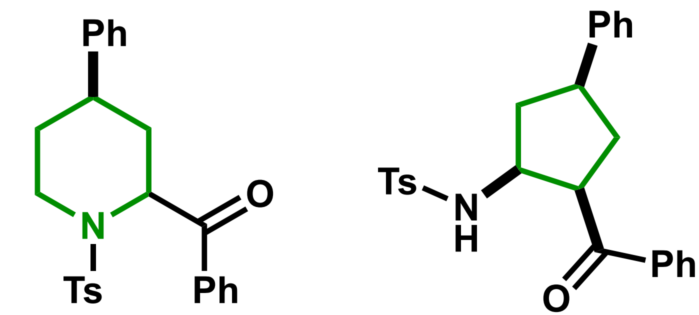


64% (6:1)

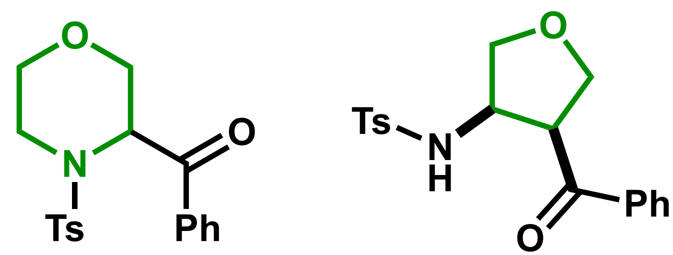
1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

Scope 2: Diverse Cores

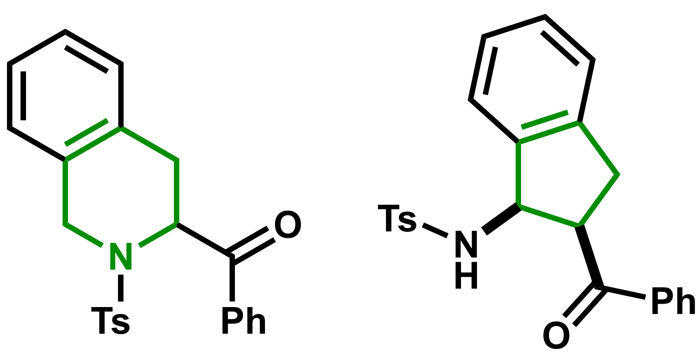




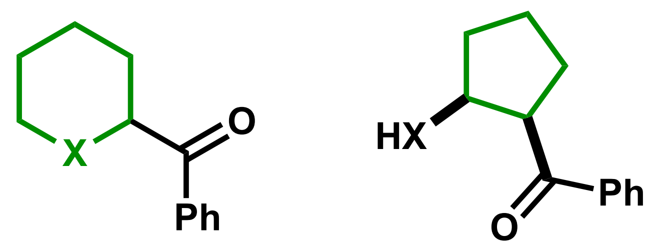
33% (10:1)



33% (10:1)



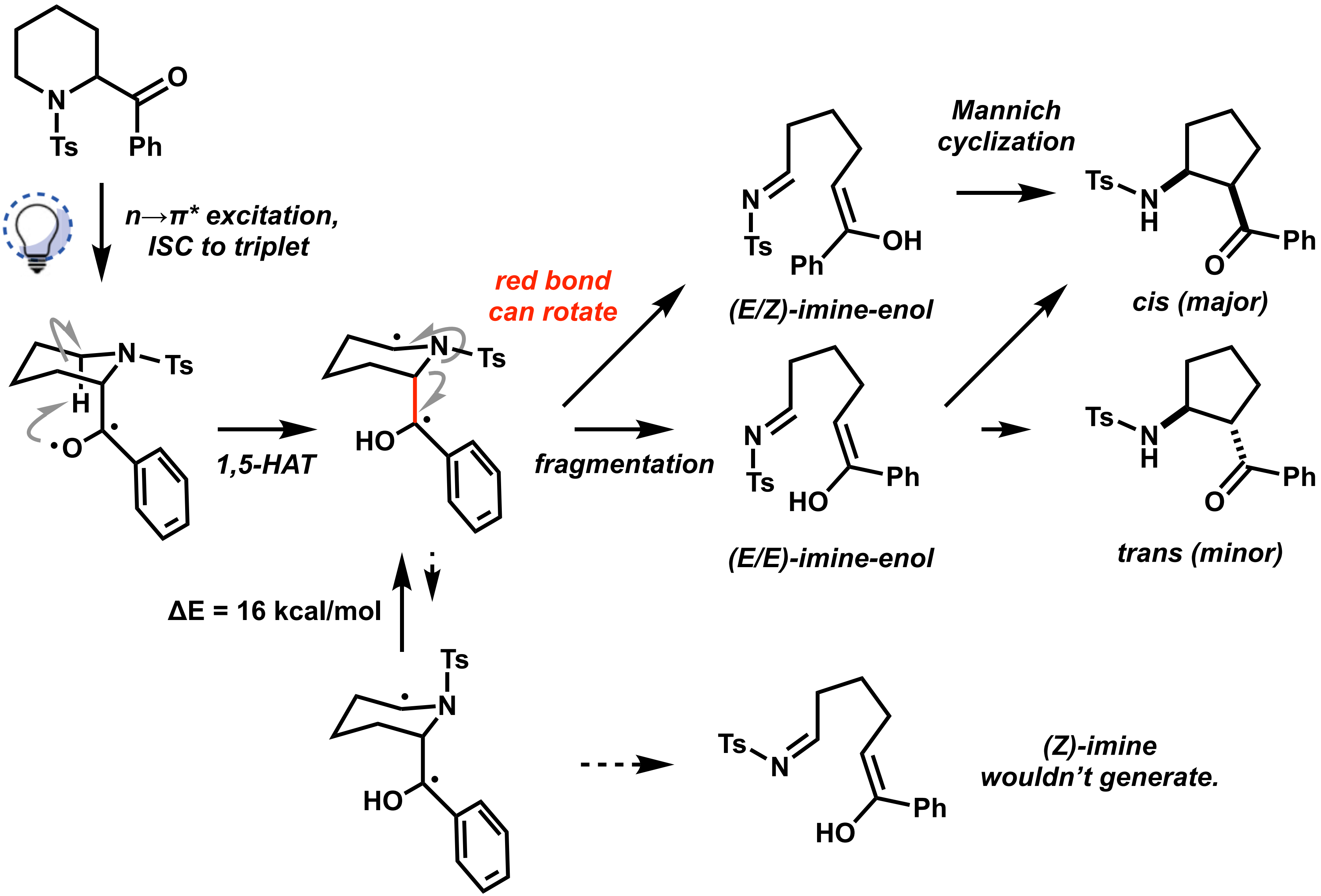
46% (2.4:1)



X = O: 75% (20:1)
X = S: 83% (20:1)

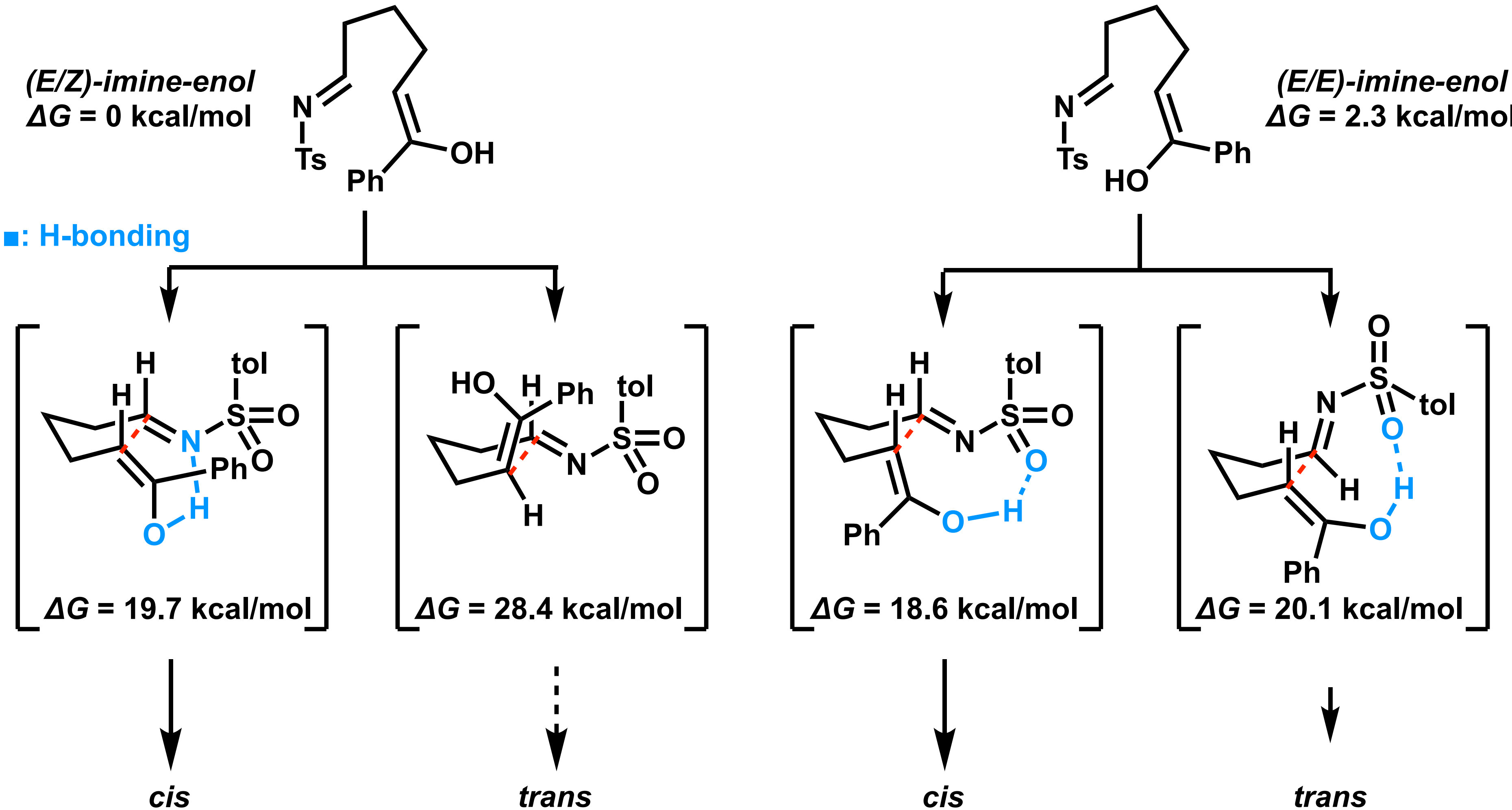
1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

Proposed Mechanism



1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

Diastereoselectivity

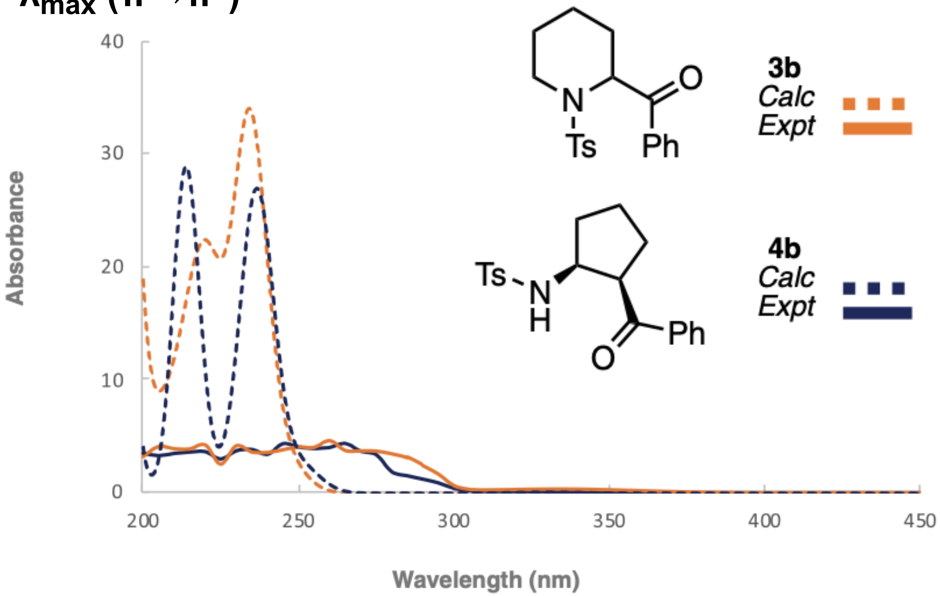


Calculations were performed at the M06-2X/6-31+G level.**

1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

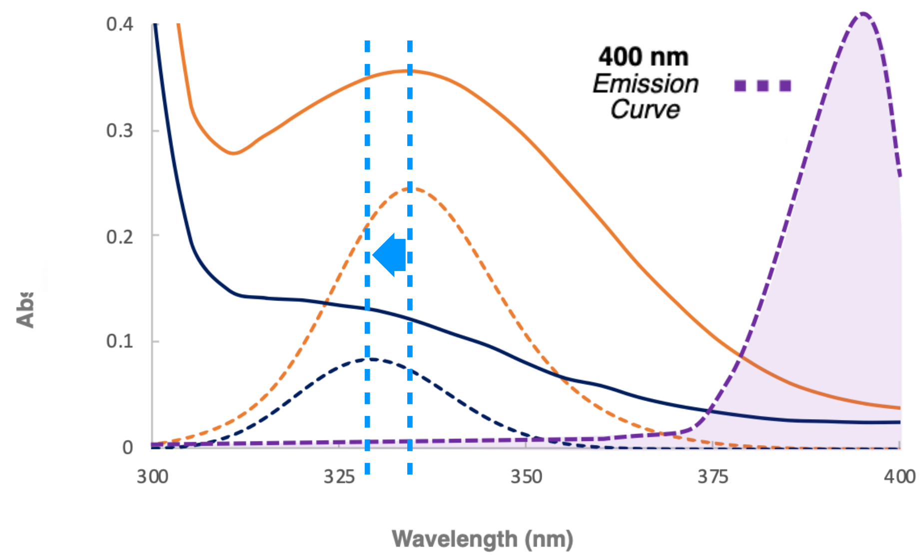
Photo-reactivity and remained problems

λ_{max} (π→π*)



subtle difference

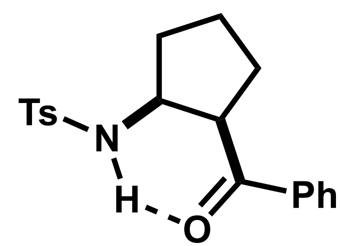
λ_{max} (n→π*)



hypsochromic (blue) shift

Remained problems:

- ▶ limited to substrates
- ▶ Preparation of substrates
- ▶ Relatively modest yields and diastereoselectivities
- ▶ 400 nm LED doesn't match for the reactivity.
  (The substrates absorb weakly at 400 nm (λ_{max} (n→π*) = 340 nm))



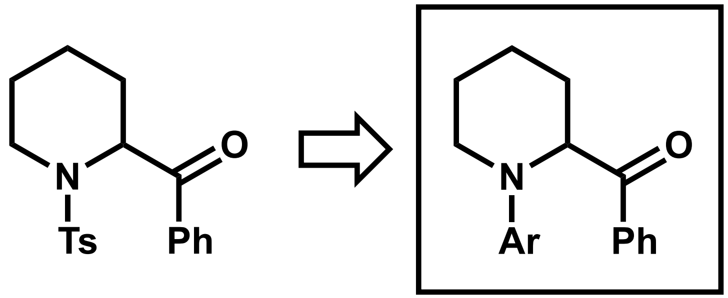
intramolecular H-bonding

O electron density ↓
required energy for n→π* ↑
stability for 400 nm ↑

1) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science* **2021**, *373*, 1004.

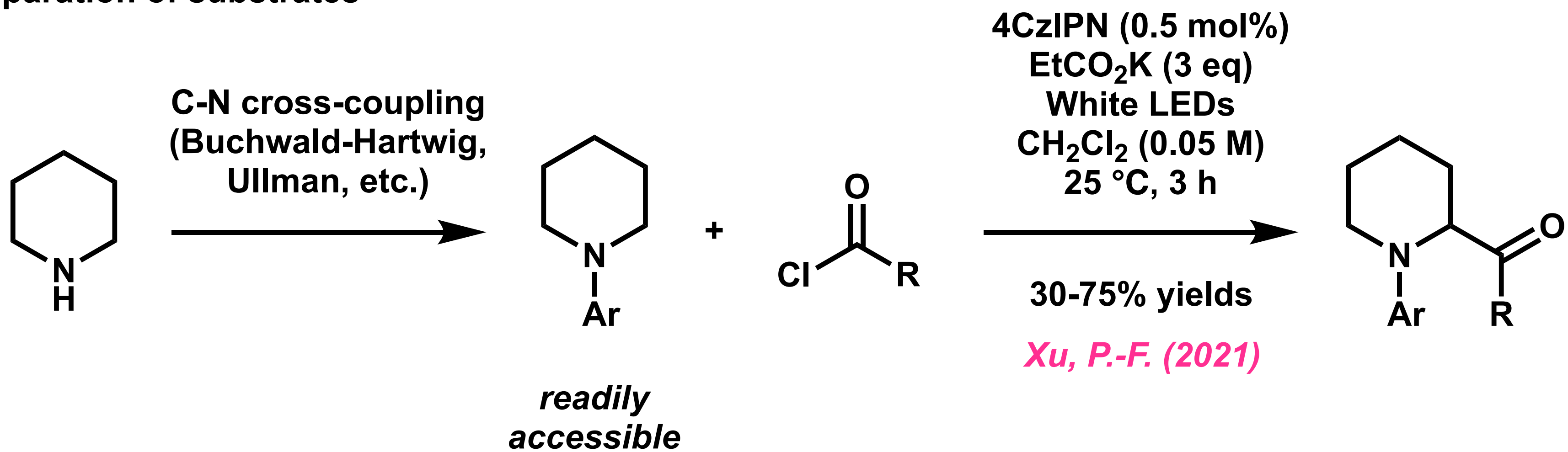
Contents

Working Hypothesis



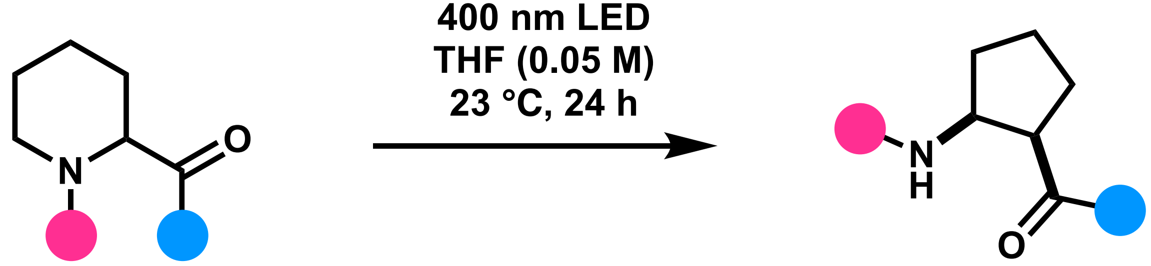
N: electron richer
→ intramolecular H-bonding interactions ↑
→ diastereoselectivity and photostability ↑

- Preparation of substrates

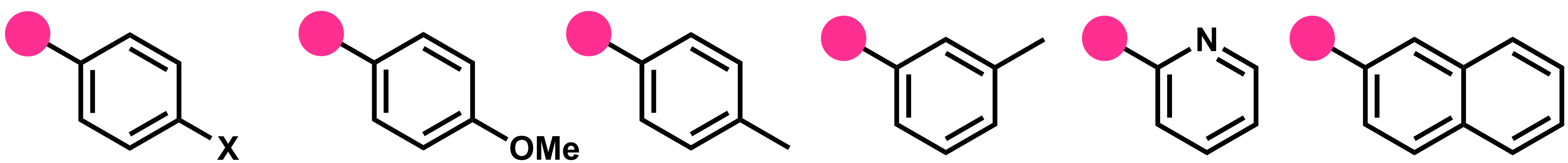


1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.
2) Xu, G.-Q.; Xiao, T.-F.; Feng, G.-X.; Liu, C.; Zhang, B.; Xu, P.-F. *Org. Lett.* **2021**, *23*, 2846.

Optimized Condition and Scope 1: Substituents



N-Ar Substitution **(= Ph, 20:1 d.r.)**



X = H: 94% X = Cl: 94%
X = F: 83% X = Br: 98%

90%

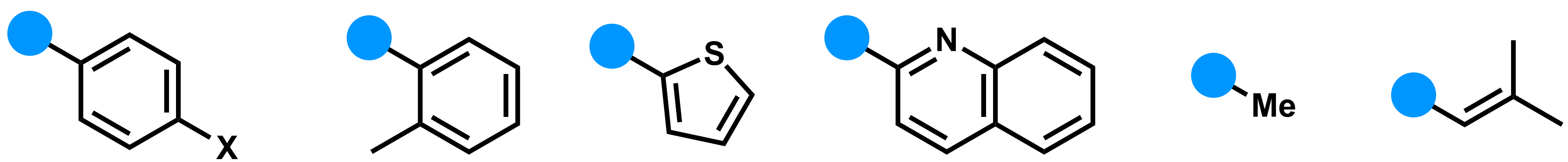
71%

89%

79%

54%

Aroyl Substitution **(= Ph)**



X = Me: 86% (20:1)
X = OMe: 97% (20:1)
X = Cl: 80% (20:1)

76% (20:1)

91% (20:1)

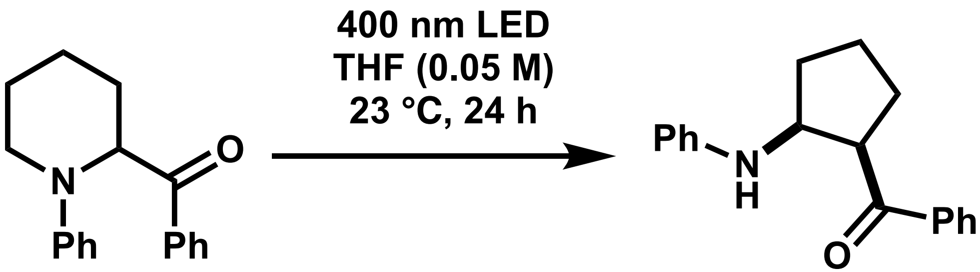
45% (1.3:1)

44% (20:1)

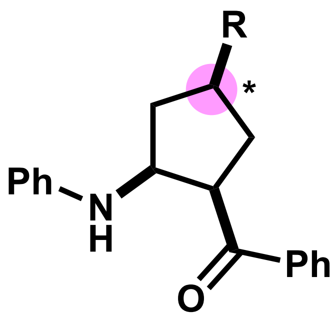
62% (20:1)

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Scope 2: Others

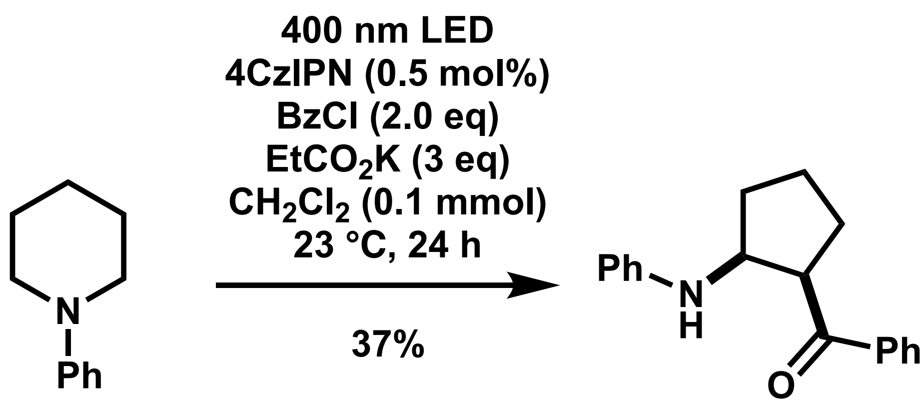


Backbone Substitutions

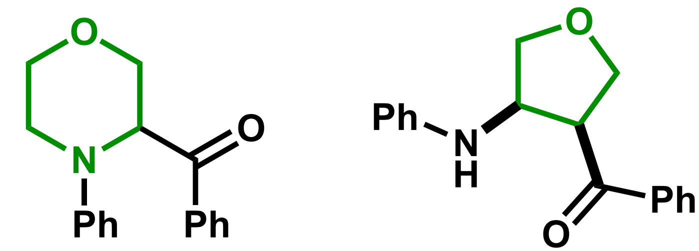


R = CO_2Me: 98% (2:1*)
R = Me: 89% (3.5:1*)
R = Ph: 83% (10:1*)

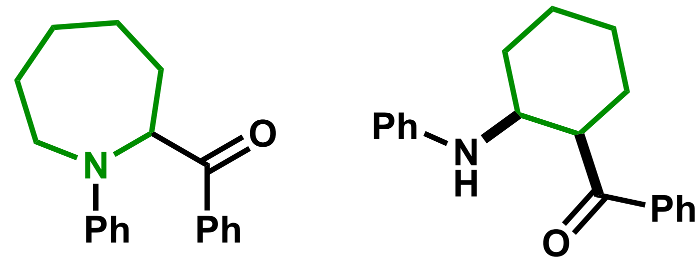
One-pot Aroylation & Ring Contraction



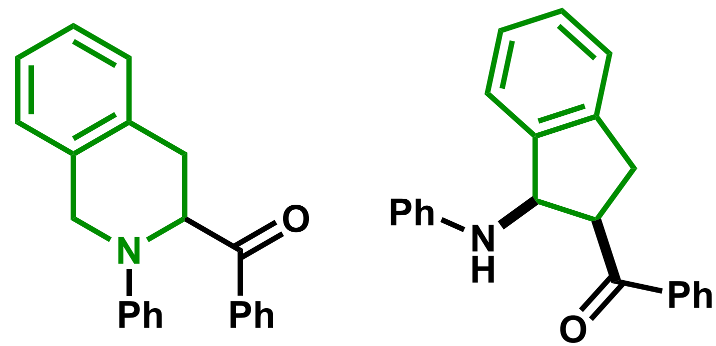
Diverse Cores



84% (20:1)
for *N*-Ts: 66% (3:1)



38% (1.5:1)
for *N*-Ts: 0%



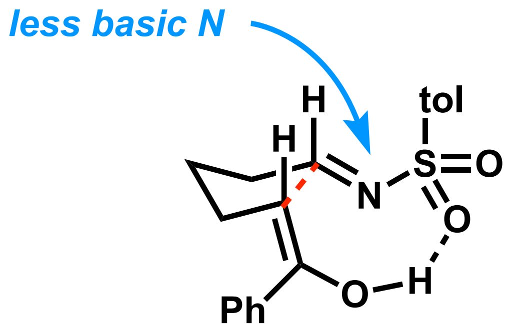
62% (20:1)
for *N*-Ts: 46% (2.4:1)

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

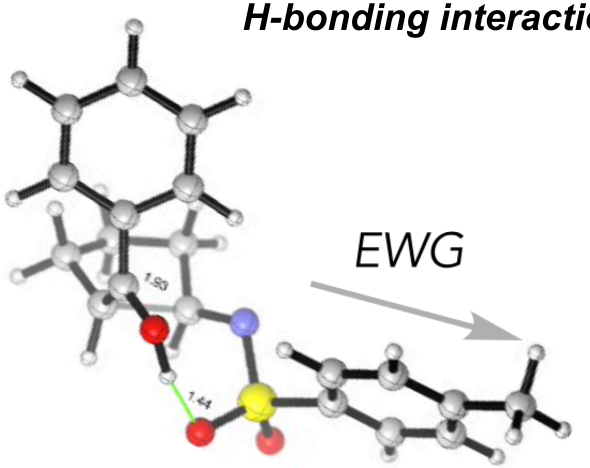
cis-Selectivity

- Lowest energy TS

N-Ts

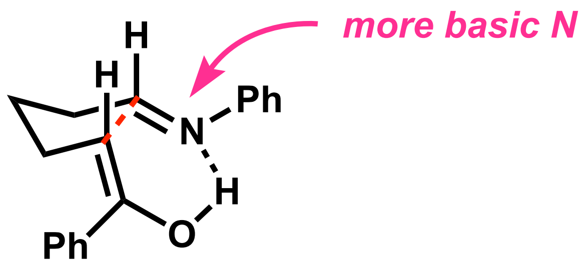


8-membered ring
H-bonding interaction



DFT

N-Ph



6-membered ring
H-bonding interaction

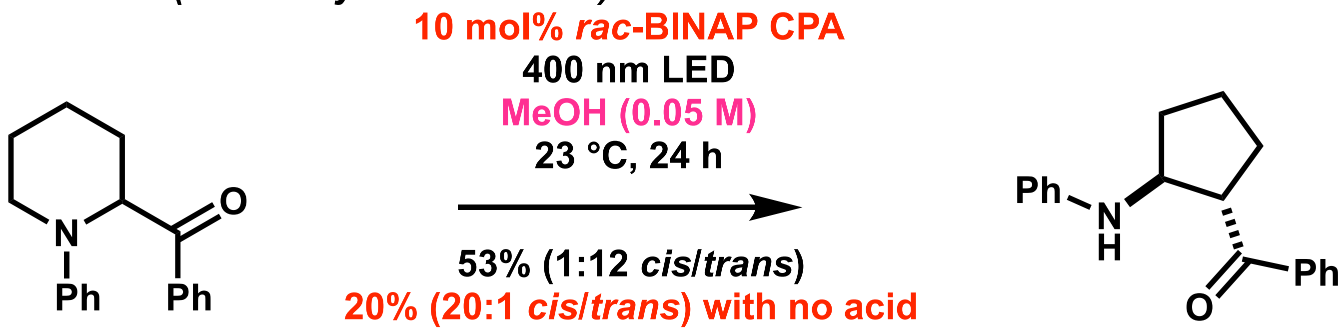
▶ **easier to take this TS geometry**
▶ **more tightly organaize this TS**

▶ **amplify the energy gap between *cis* and *trans* TS**
▶ **faster the desired Mannich reaction**

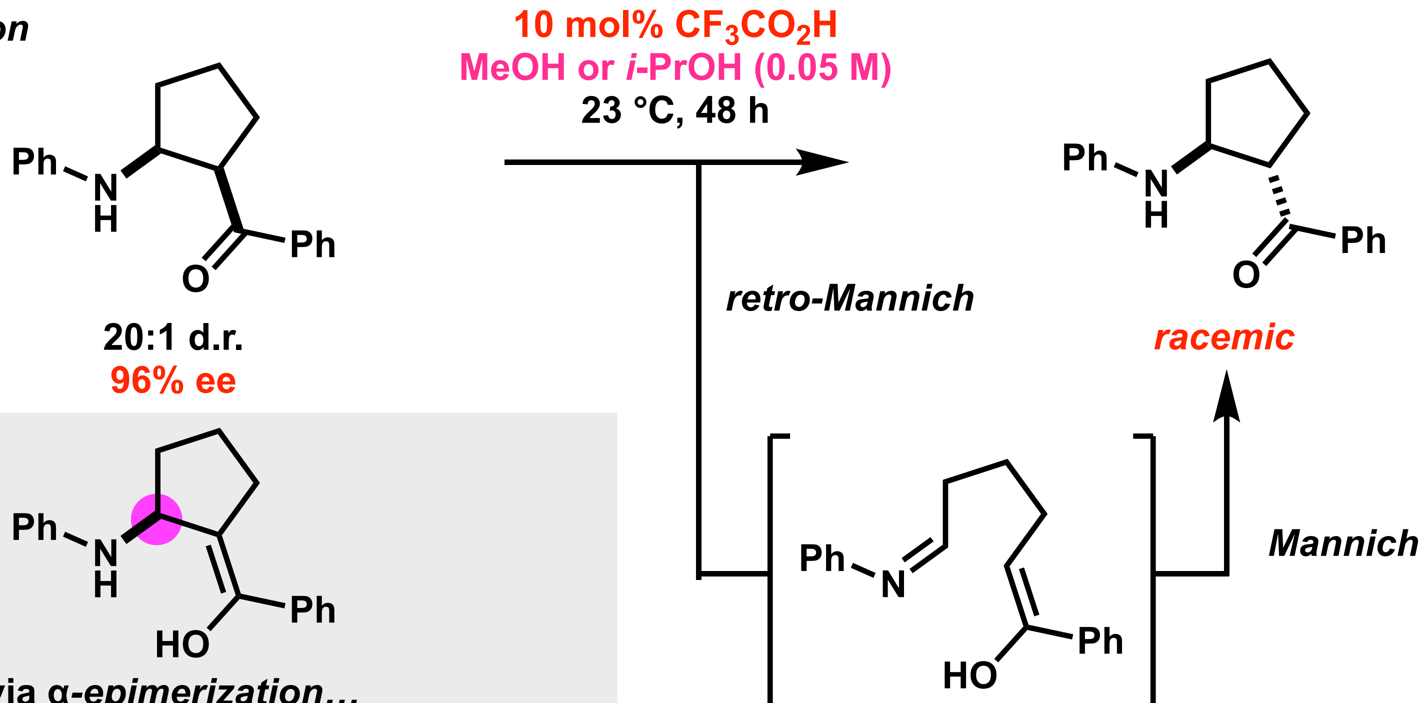
1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Control of Diastereoselectivity

- *Trans selective reaction (thermodynamic control)*



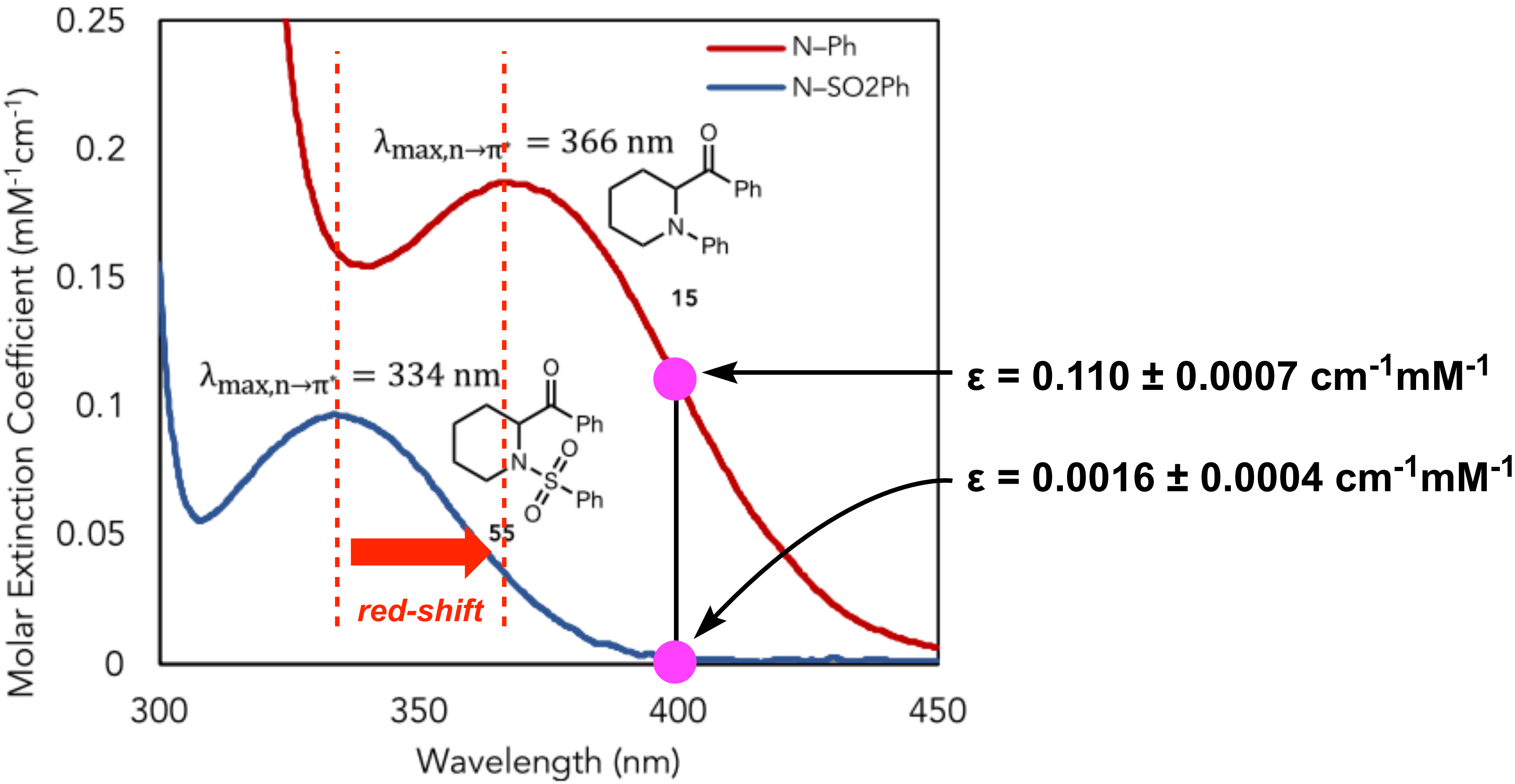
- *Epimerization*



via α-*epimerization…*
highlighted stereocenter would be retained and enantioenriched product would be obtained

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

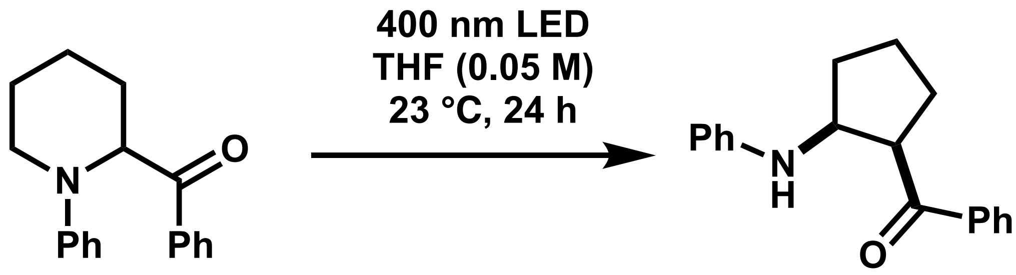
Improvement of the photo-reactivity

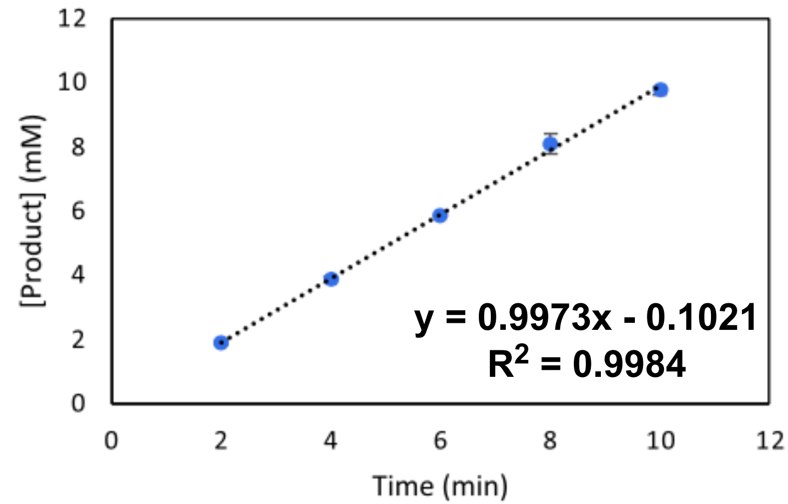


⇨ **N-Ph substrate absorbs over 67 times more strongly than $N\text{-}SO_2Ph$ substrate at 400 nm!**

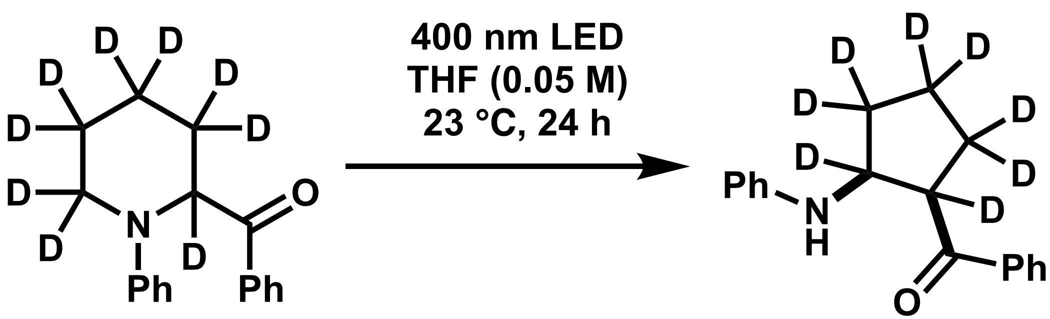
1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

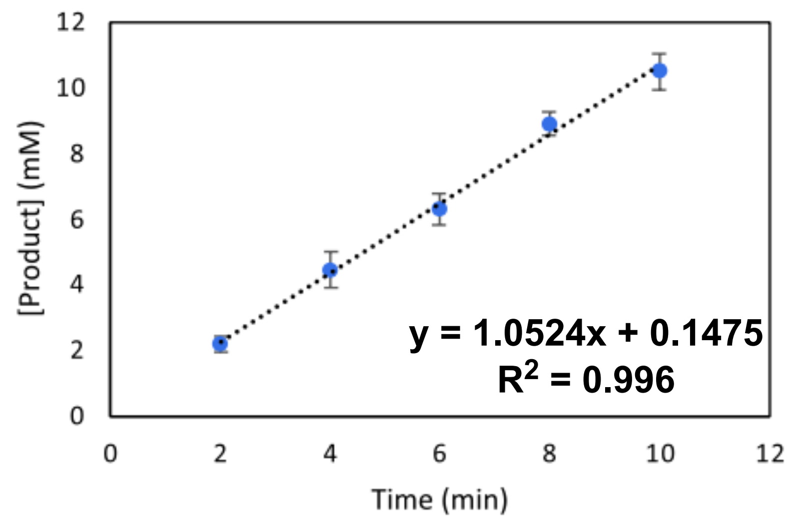
Mechanistic study: Kinetic Isotope Effect (KIE)





KIE = k_H / k_D = 0.95 ± 0.04
(small 2° inverse KIE)

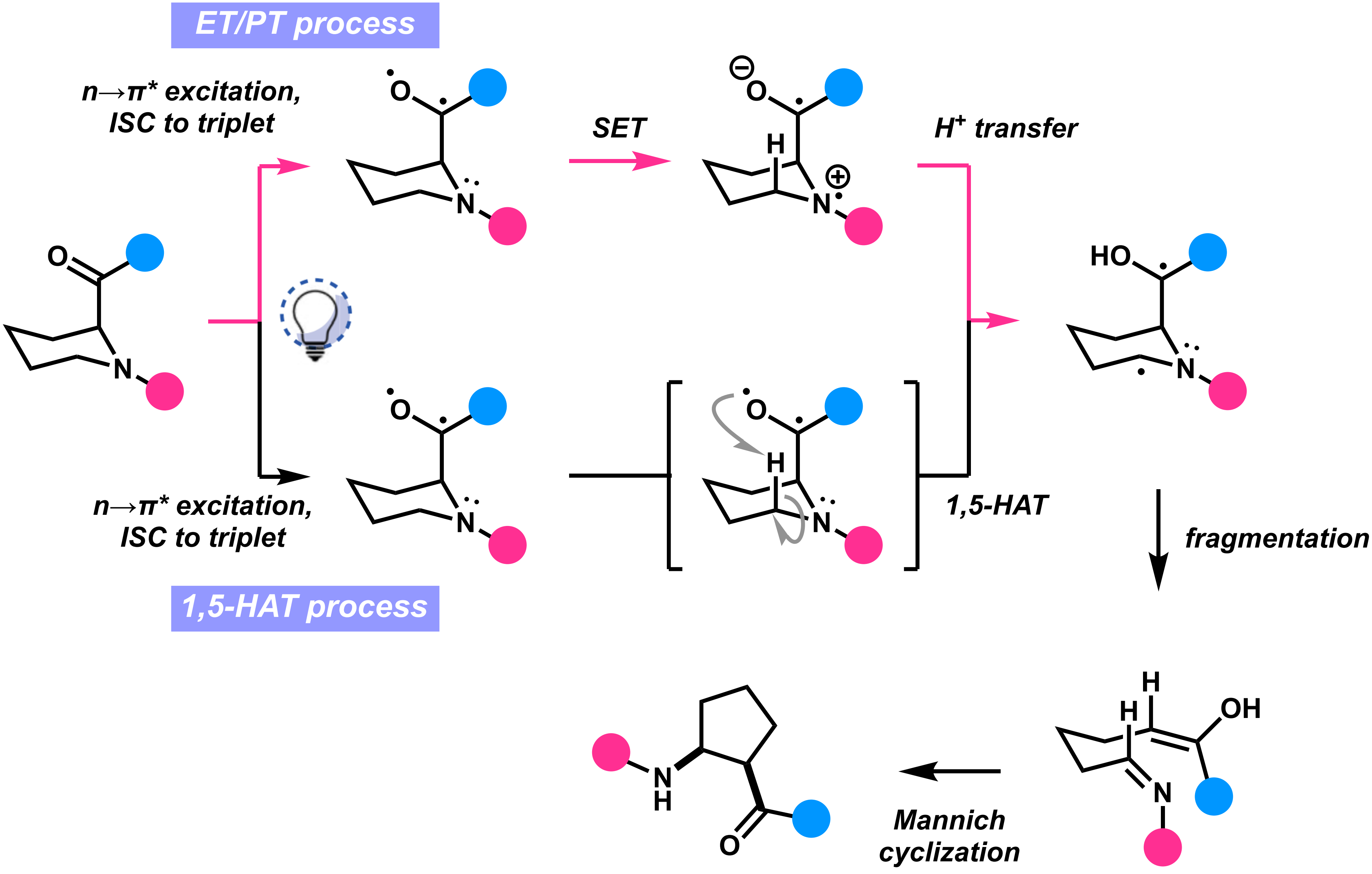




If the reaction involves C-H/D bond cleavage (HAT),
KIE should be larger than 1 (1°).

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

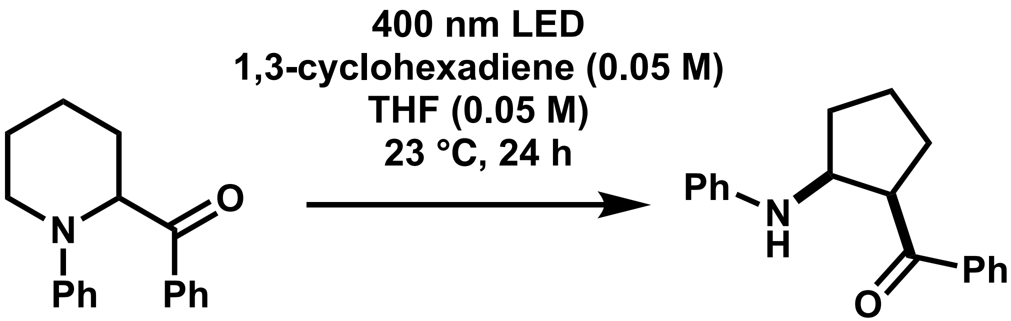
Revised Mechanism: ET/PT process

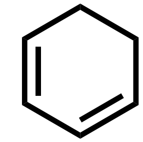


1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Mechanistic study: Triplet Quenching

- Triplet quenching with 1,3-Cyclohexadiene

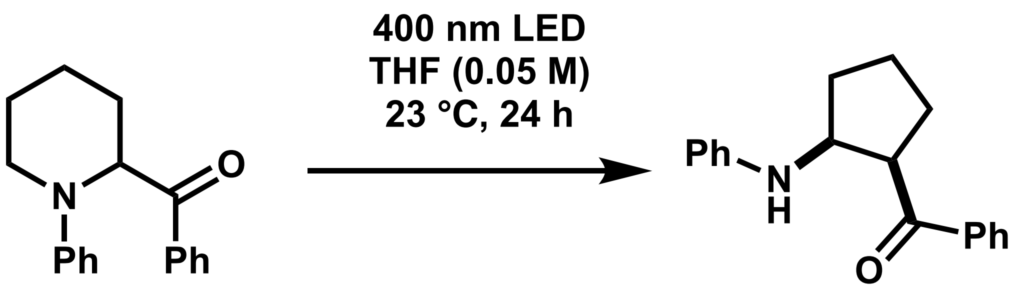




1,3-cyclohexadiene as a triplet quencher (E_T = 54 kcal/mol)

k(quenched) / k(unquenched) = 0.97 ± 0.05 → No significant triplet quenching

- O_2 is a highly efficient triplet quencher.

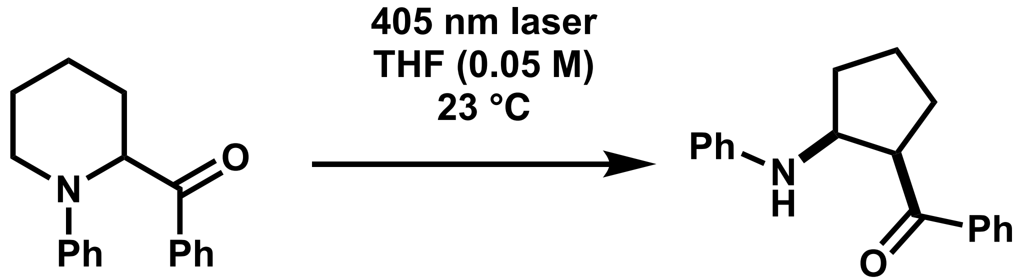


air-free	**94% (20:1 d.r.)**	**only 10-15% drop in yield**
open to air	**80% (20:1 d.r.)**	

Excited triplet state reacts or relaxes before encountering a quencher molecule. (faster than diffusion)

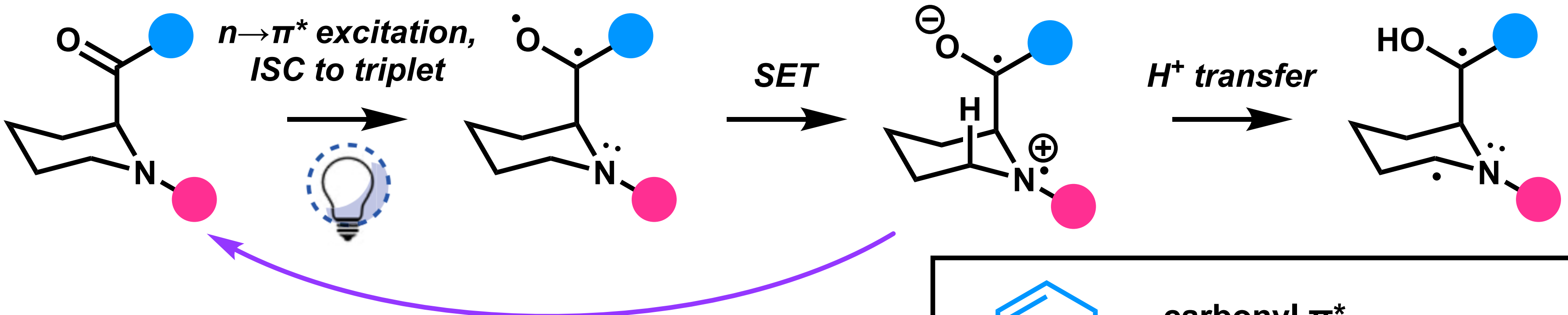
1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Mechanistic study: Quantum Yield (φ)



quantum yield (φ) = $\frac{\text{number of events}}{\text{number of photons absorbed}}$ = **0.022 ± 0.002**

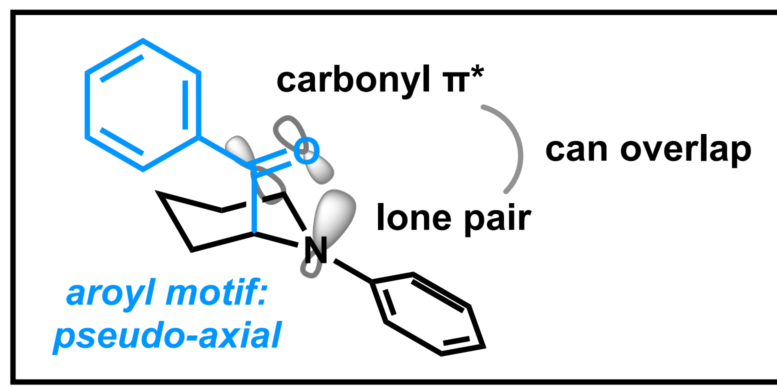
- ▶ φ << 1 : no radical chain processes
- ▶ φ < 0.15: indicates unproductive back-electron transfer



back electron transfer

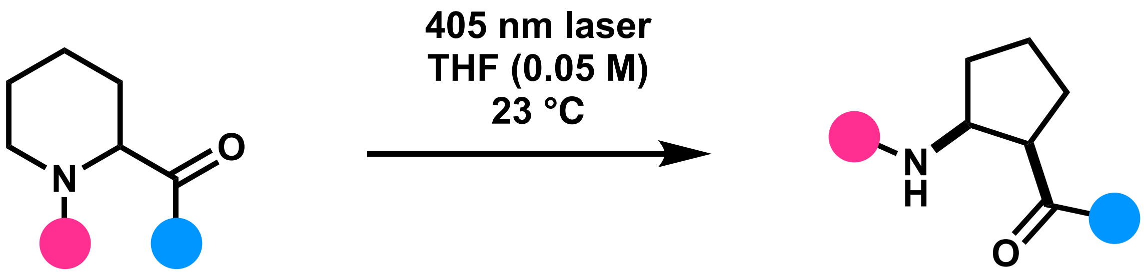
↓

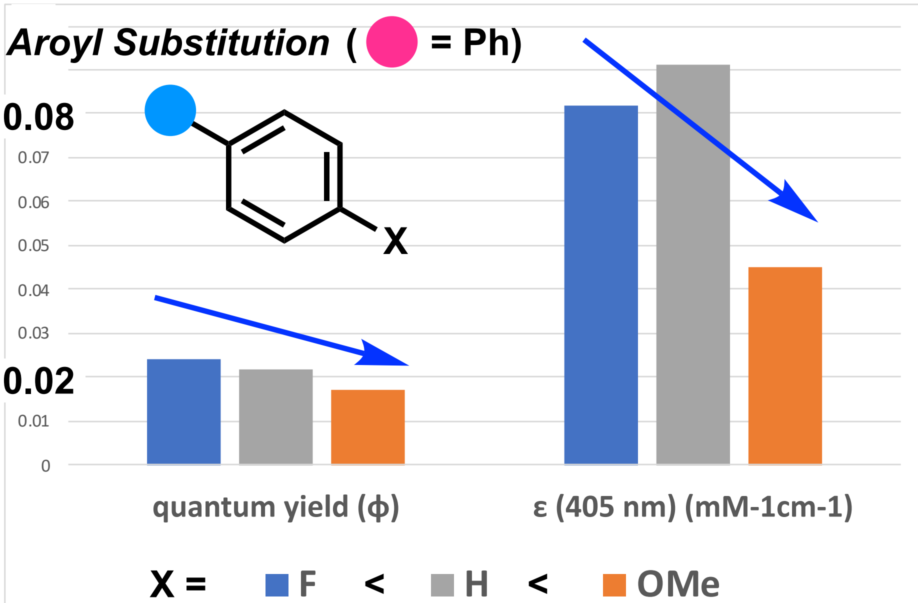
quantum yield should be lowered

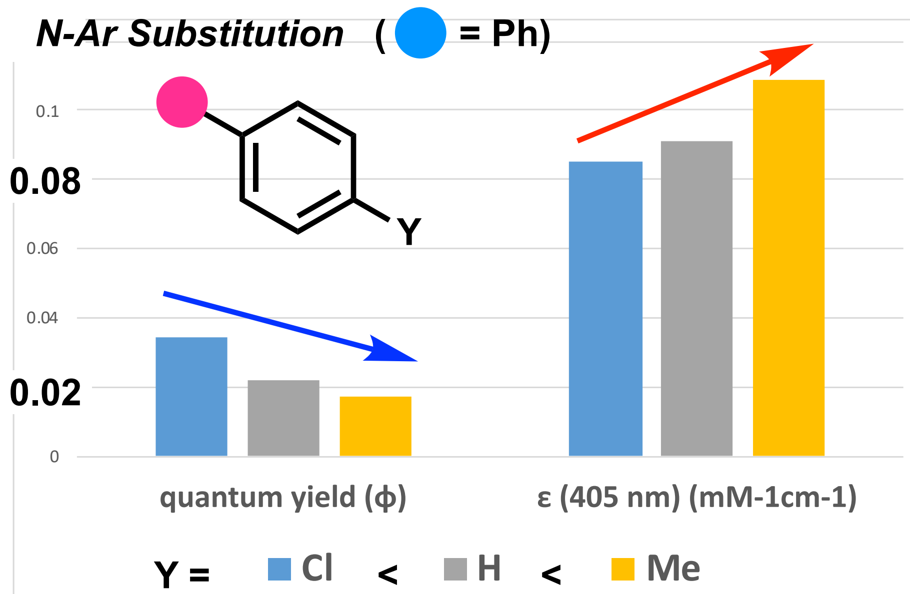


1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Mechanistic study: Photo-reactivity







electron-donating ability

electron-donating ability

electron richness of aryl ketones ↑

⇩

photo-reduction efficiency ↓

electron richness of N lone pair ↑

⇩

ET/PT process ↑

the efficiency of back-electron transfer ↑

ET/PT process can rationalize these trends!

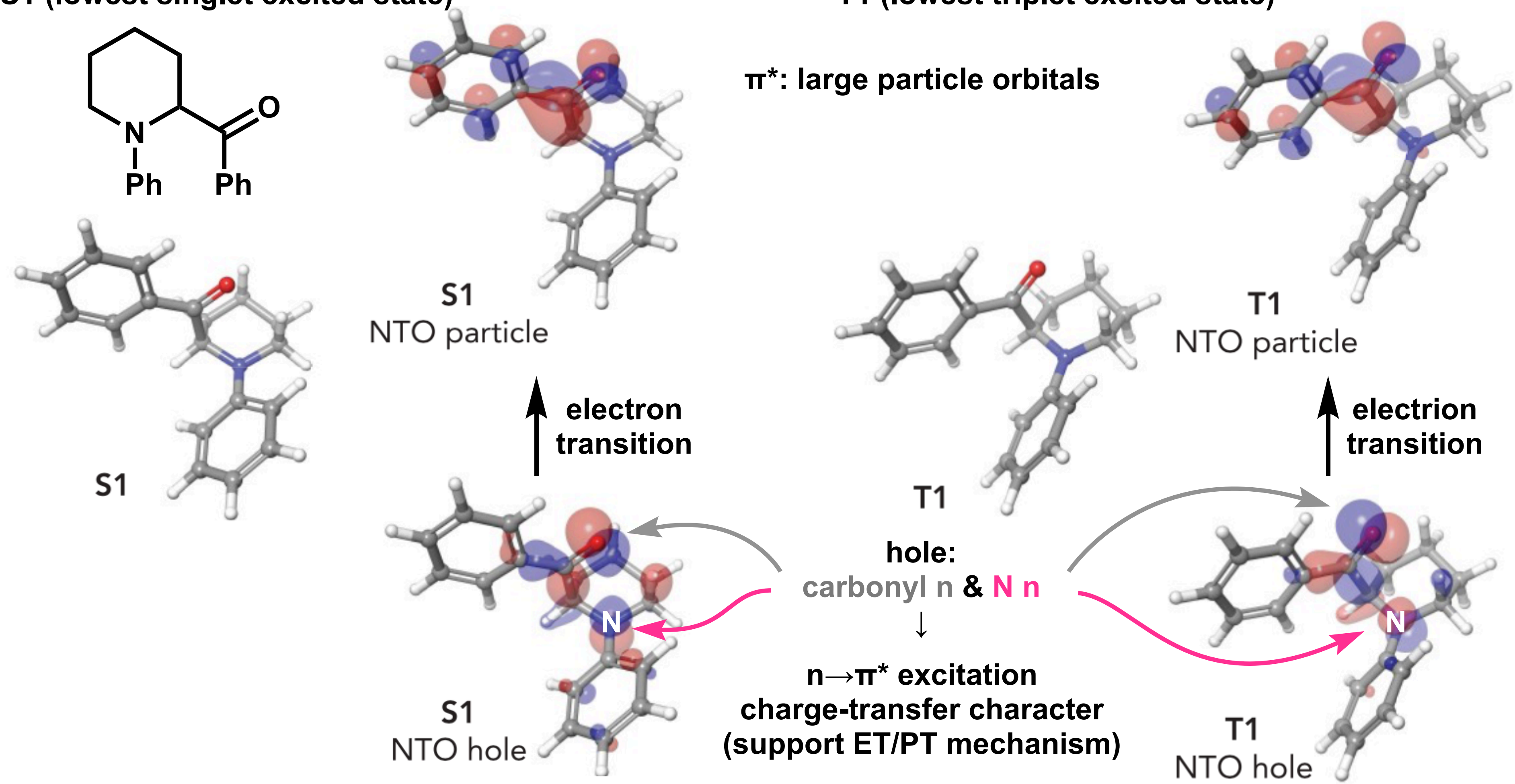
1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Computational analysis: NTO (1)

What is NTO (natural transition orbital) ?

describe the character of a given excited state by hole and particle pairs that constitute electron transition.
NTO hole: where an electron is promoted from
NTO particle: where an electron is promoted to

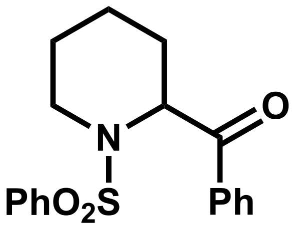
S1 (lowest singlet excited state) **T1 (lowest triplet excited state)**



1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

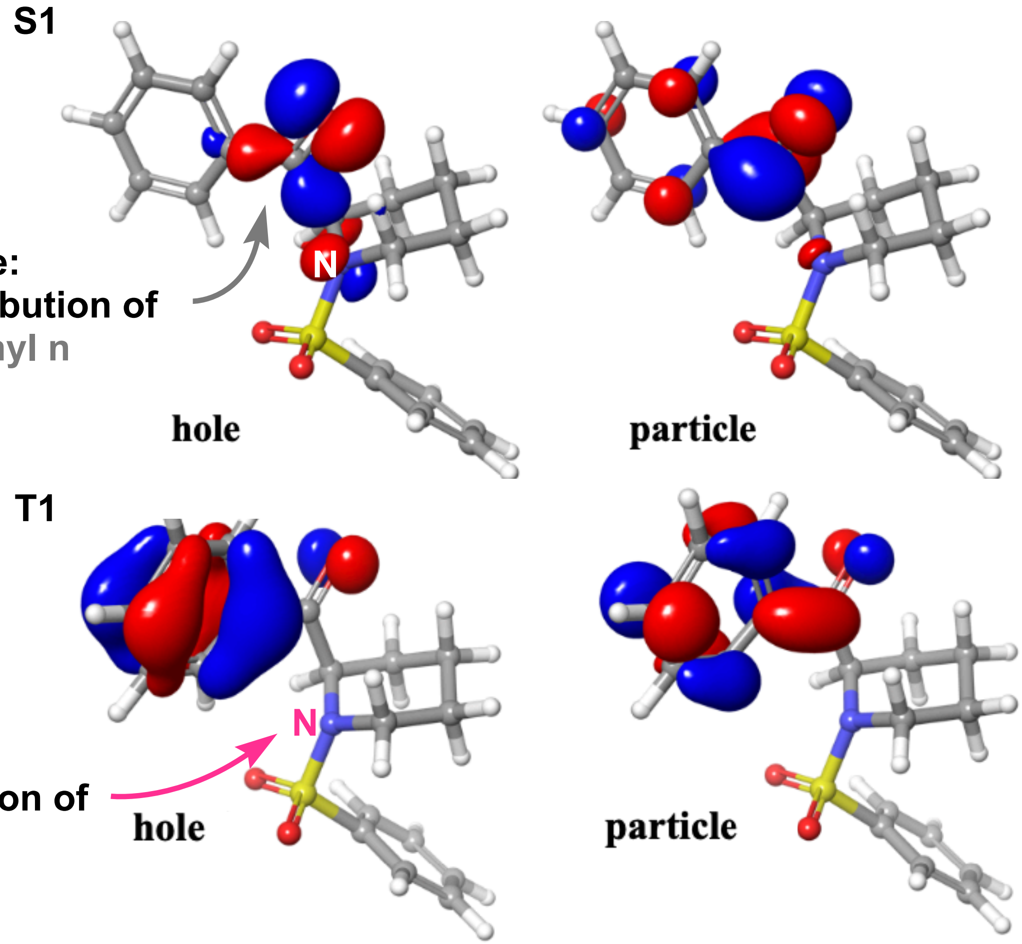
Computational analysis: NTO (2)

<u>In the case of *N*-SO_2Ph…</u>



low electron density of N

weak
charge-transfer
character



hole:
large contribution of
carbonyl n

no contribution of
N n

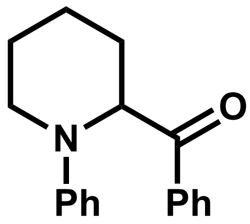
<u>Authors' hypothesis:</u>
There is likely a spectrum between ET/PT and HAT mechanisms for the photomediated ring contraction.

low — electron density of N — high

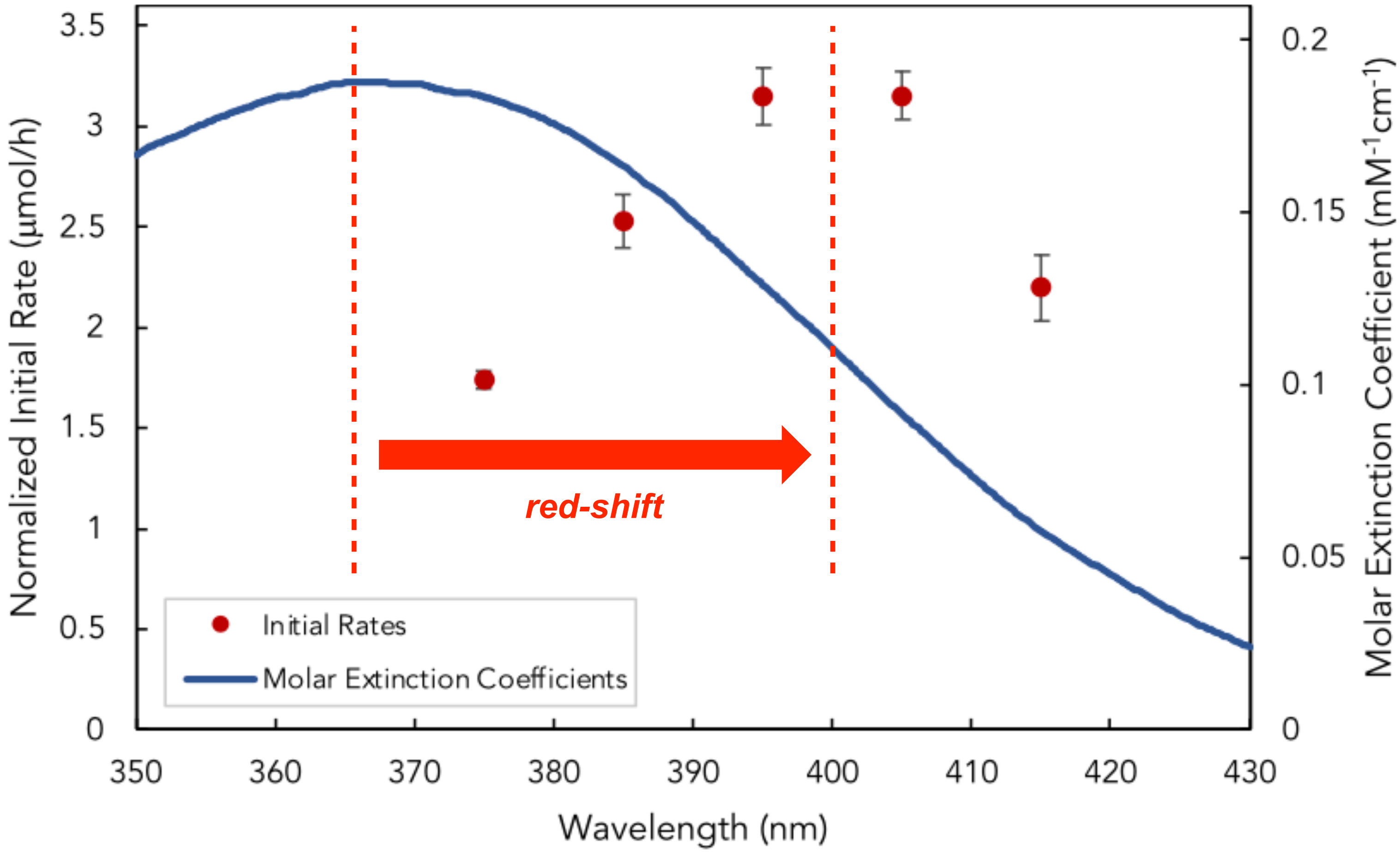
1,5-HAT ⟷ ET/PT

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Wavelength dependent reactivity



(in THF)

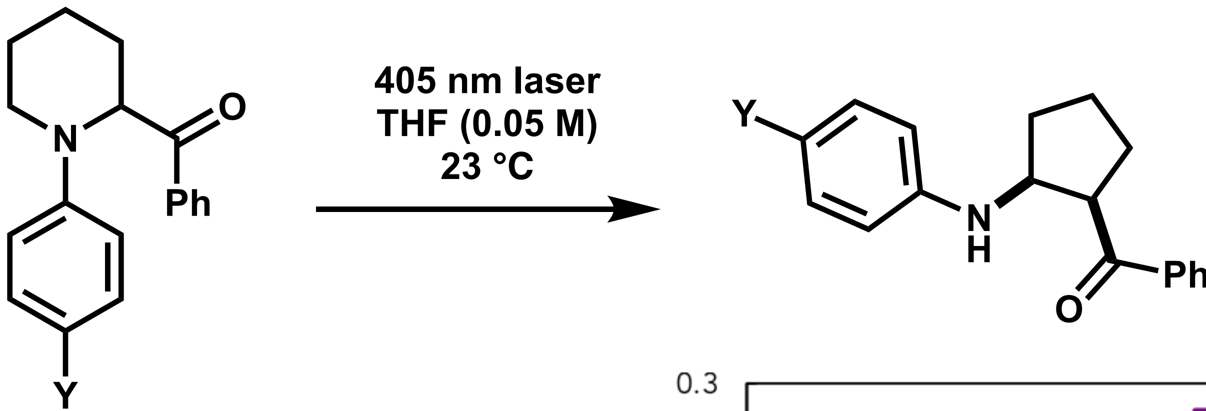


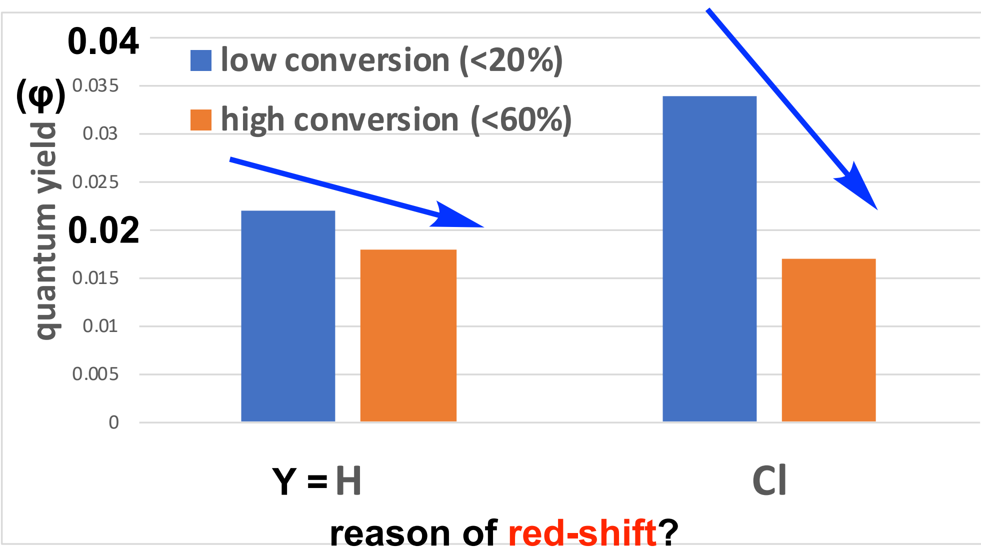
⇨ **In order to achieve the best reactivity, it seems suitable to irradiate substrates at the wavelength of maximum absorbance (λ_{max}).**

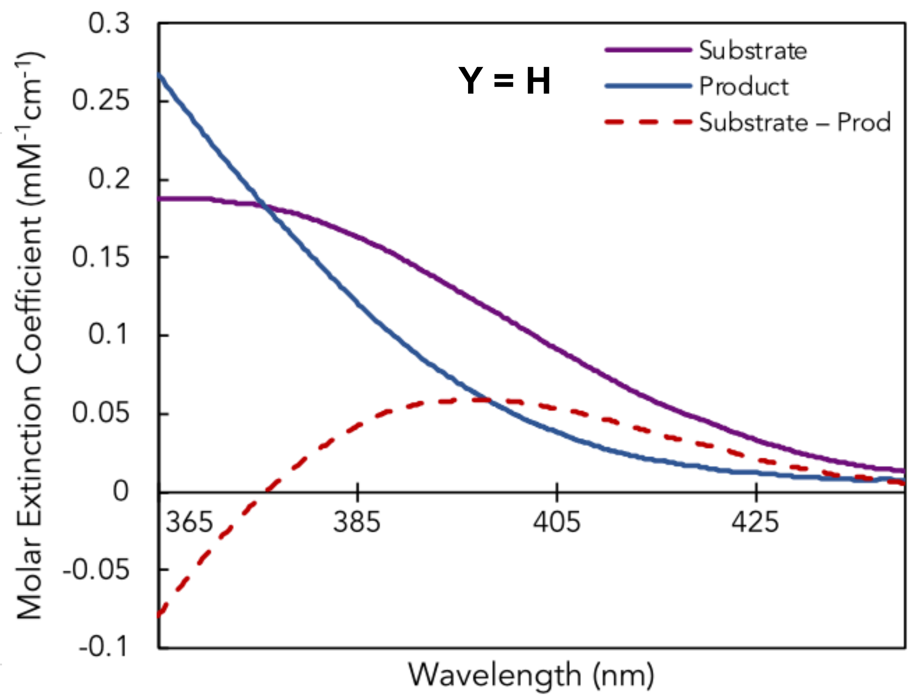
<u>**However, the most efficient irradiation wavelength was red-shifted in this case…**</u>

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Possible Reasons of Red-Shift (1)







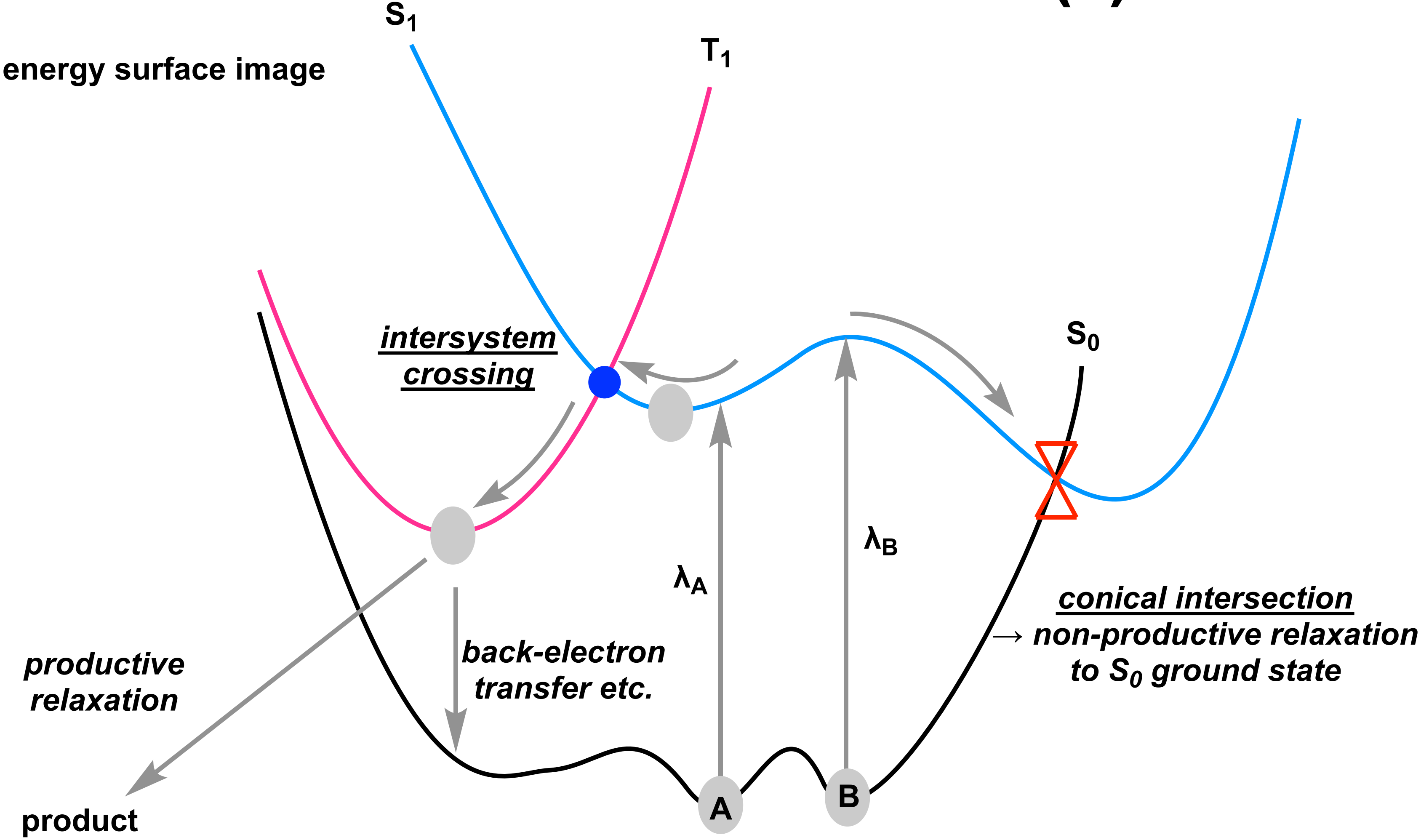
Inner Filter Effect:
The generated product absorbs and "filters out" light from reaching the remaining substrate.

maximum difference
→ around 400 nm
(One of the reason why 400 nm is optimal.)

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

Possible Reasons of Red-Shift (2)

potential energy surface image



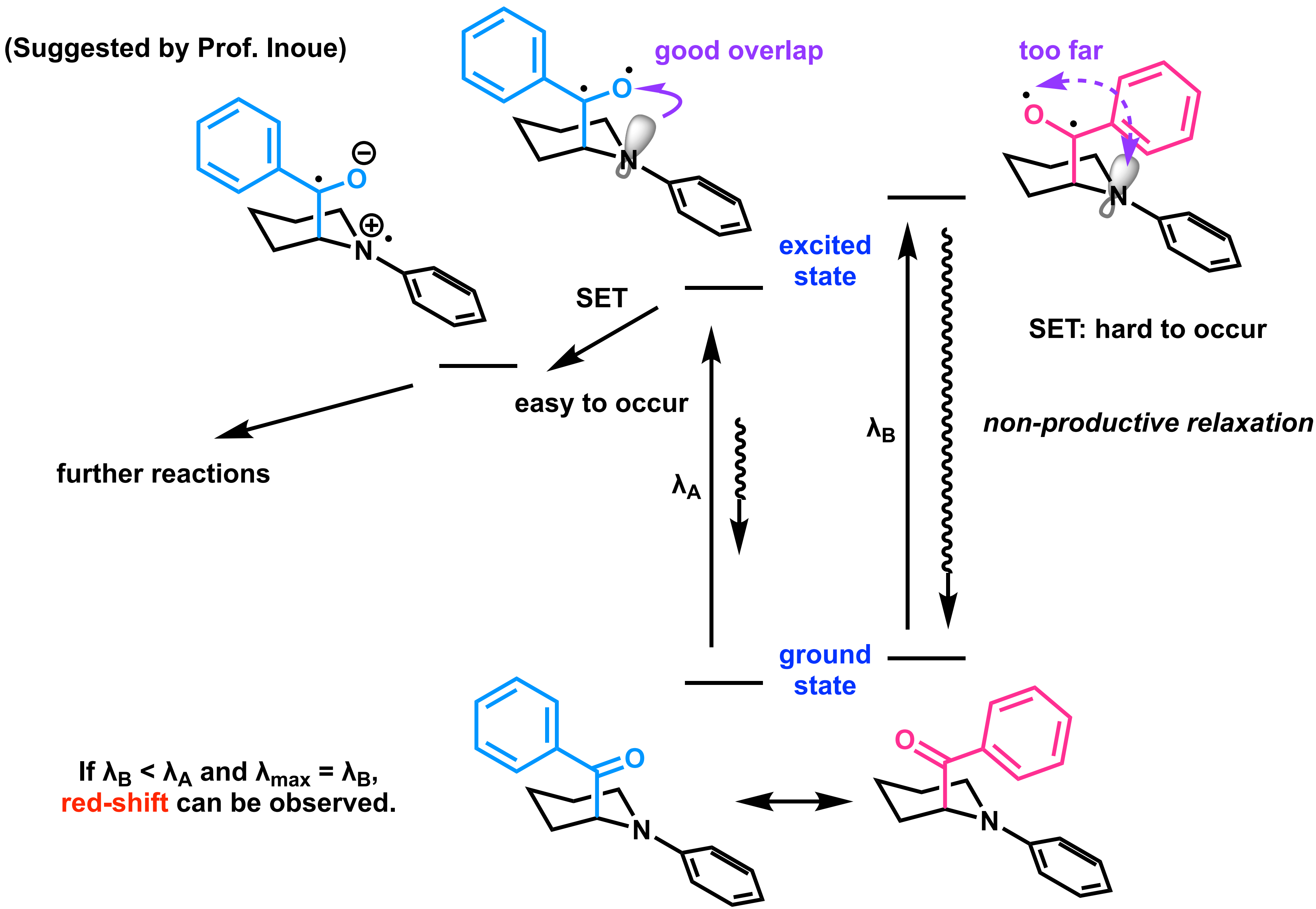
Substarte can some low-energy conformers in solution at room temperature.

- ▶ **excitation by λ_B nm: primarily relaxes through a non-productive relaxation pathway**
- ▶ **excitation by λ_A nm: primarily relaxes through a productive pathway**

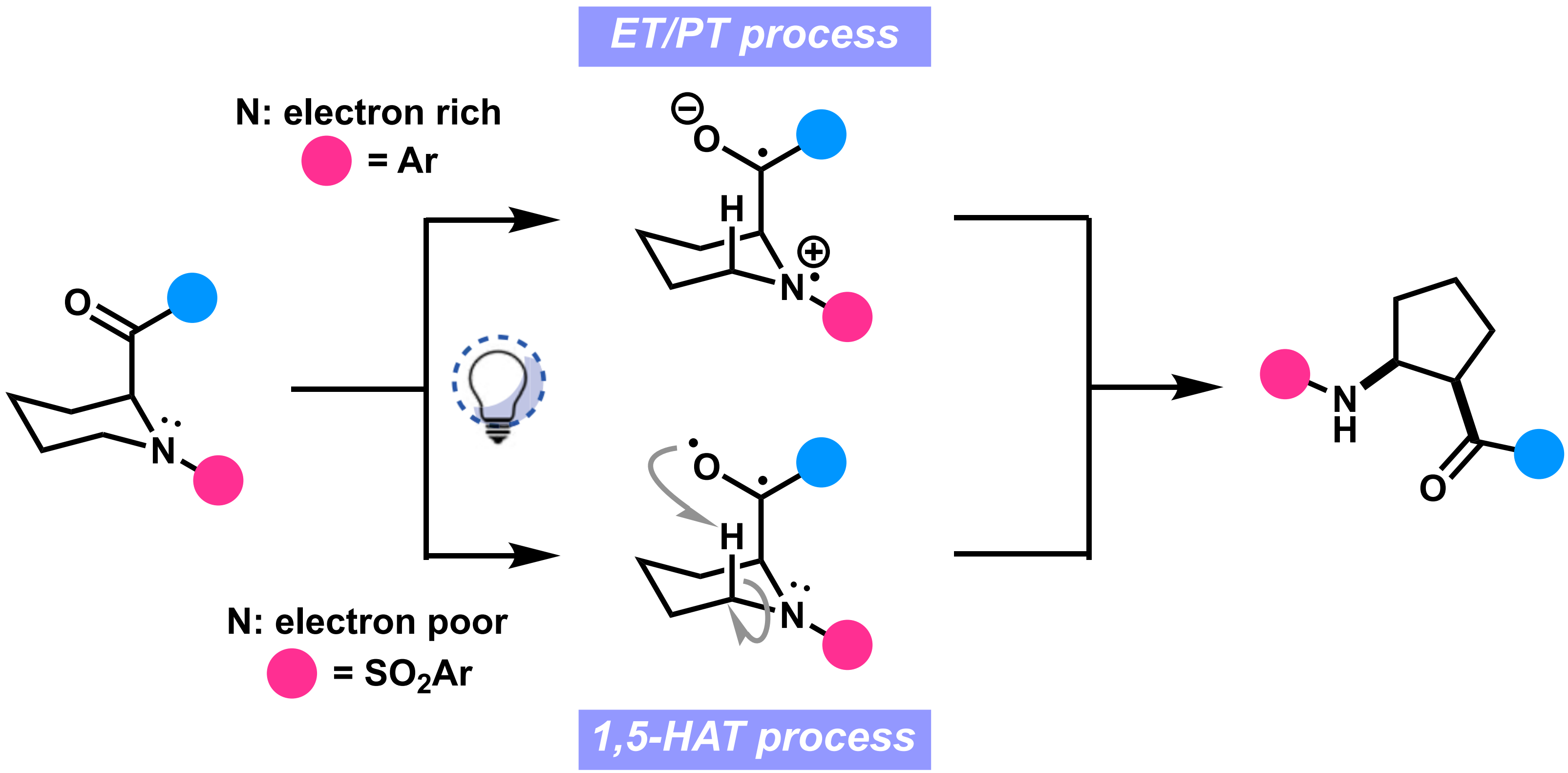
If $\lambda_B < \lambda_A$ and $\lambda_{max} = \lambda_B$, red-shift can be observed.

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

More Possible Reasons of Red-Shift (3)

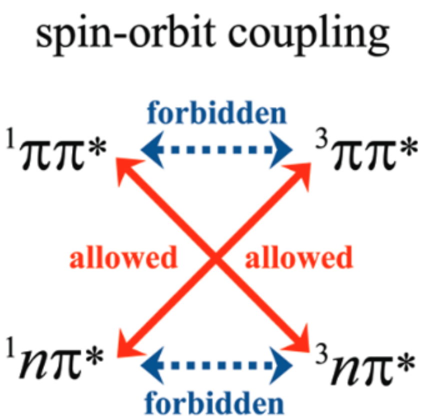


Summary

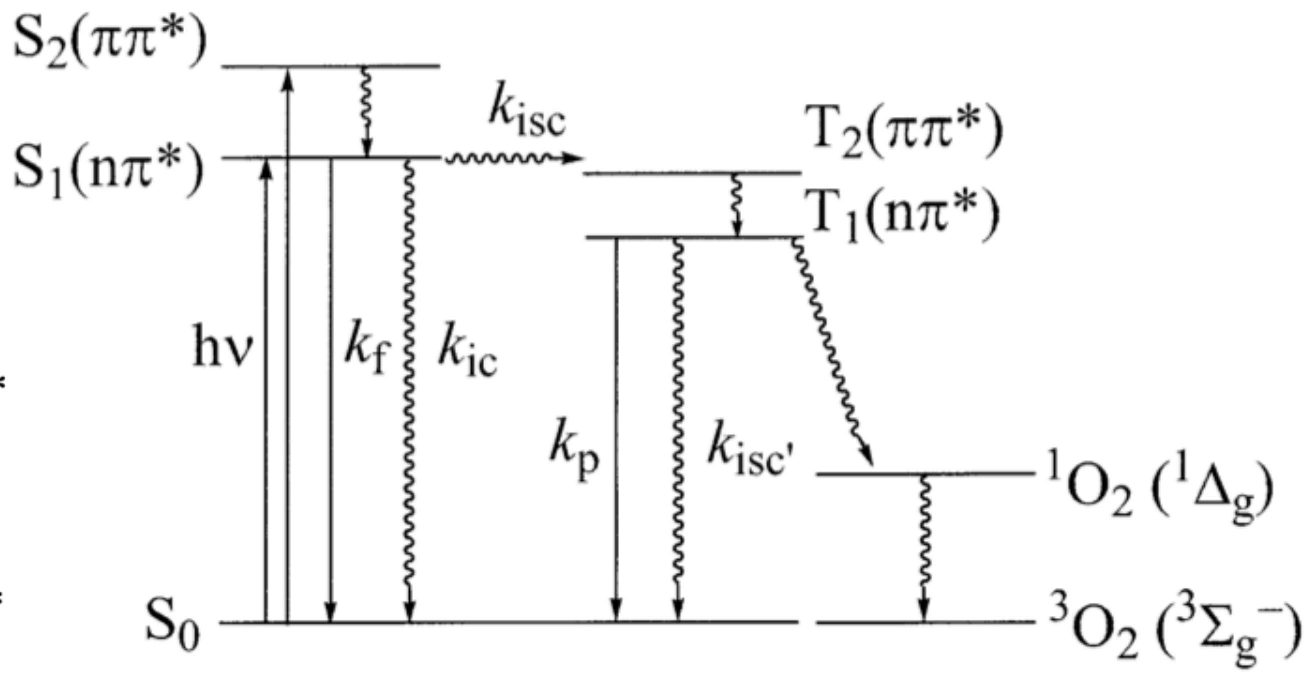

ET/PT process
N: electron rich
= Ar
O
H
N
N: electron poor
= SO2Ar
1,5-HAT process

Appendix

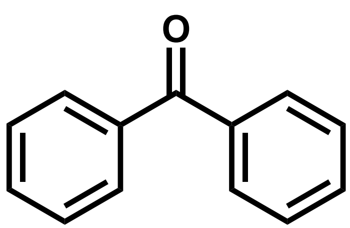
Intersystem Crossing of Benzophenone



El-Sayed rule



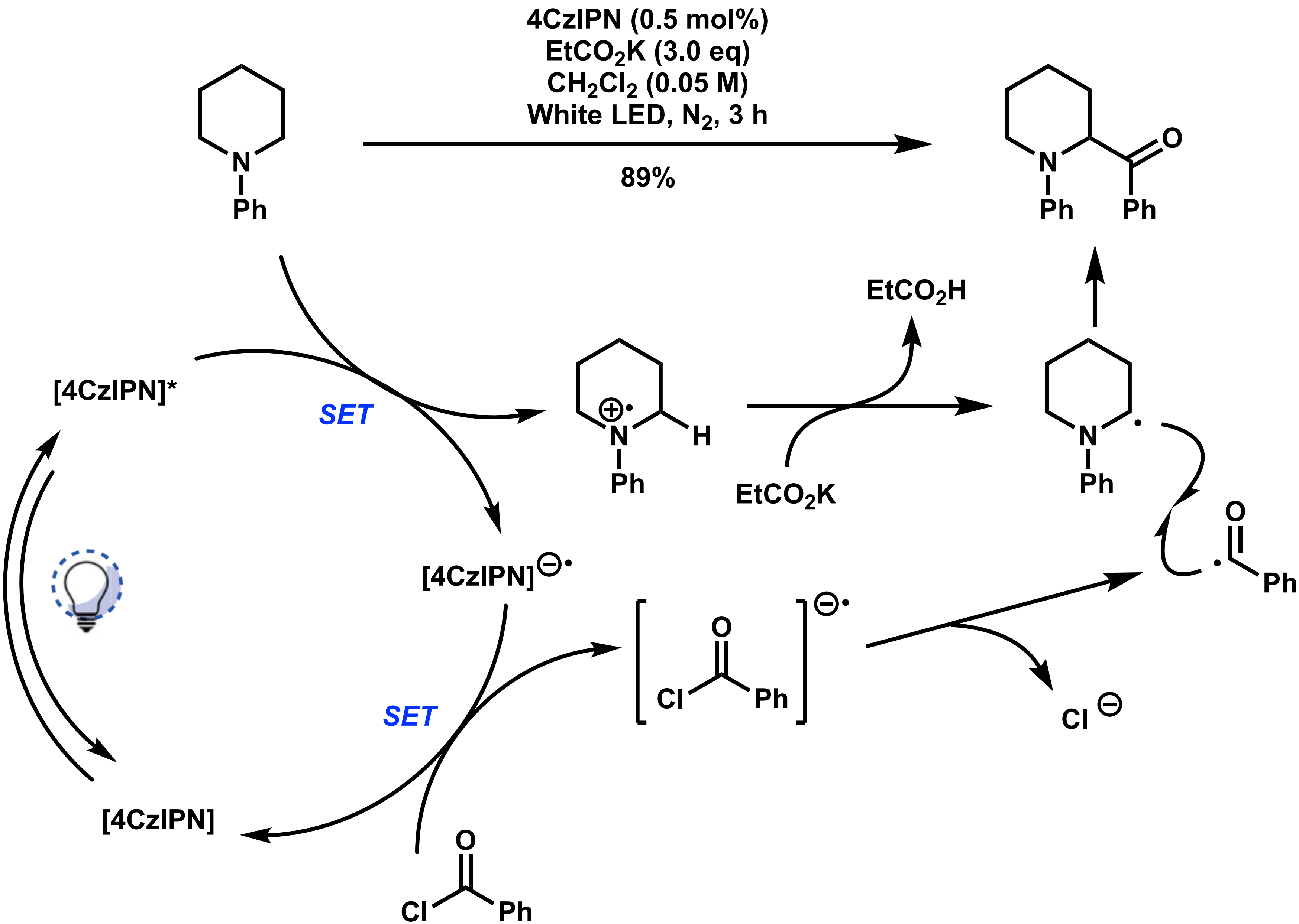
energy phase diagram of benzophenone



$S_1\ (n\pi^*)$ —**ISC**→ $T_2\ (\pi\pi^*)$ —**vibrational relaxation**→ $T_1\ (n\pi^*)$

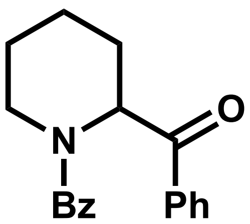
1) Baba, M. *J. Phys. Chem. A.* **2011**, *115*, 9514.

α-Aroylation

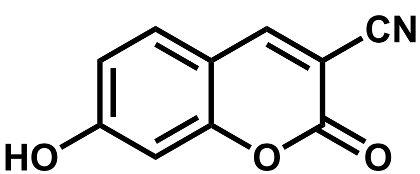


1) Xu, G.-Q.; Xiao, T.-F.; Feng, G.-X.; Liu, C.; Zhang, B.; Xu, P.-F. *Org. Lett.* **2021**, *23*, 2846.

Role of 3-cyanoumbelliferone



3



3-cyanoumbelliferone

form EDA complex

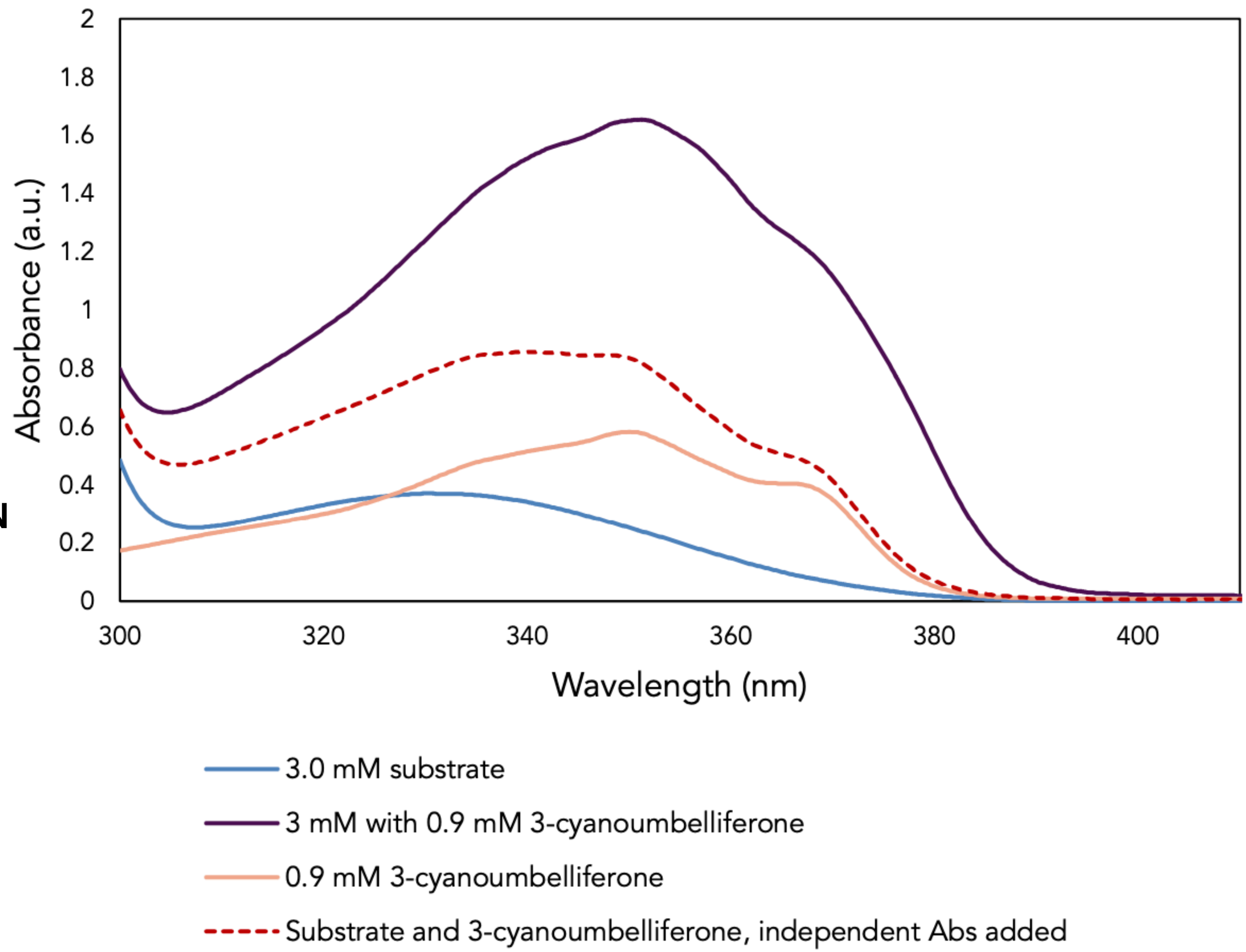
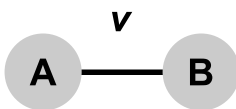


Figure S27. UV–Vis optical absorption spectra of *N*–benzoyl substrate **3** with and without 3-cyanoumbelliferone additive (30 mol%).

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.

KIE



$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}} \qquad \mu = \frac{m_A m_B}{m_A + m_B}$$

k: spring constant   μ: reduced mass

C-H bond: $\mu = 12 \times 1 / (12+1) \sim 0.92$

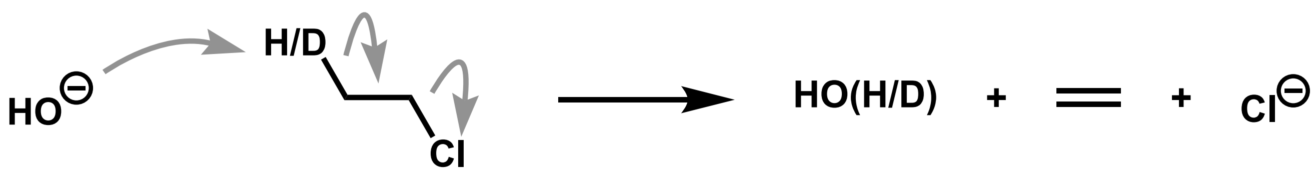
C-D bond: $\mu = 12 \times 2 / (12+2) \sim 1.71$

⇨ $v_{c\text{-}D} / v_{c\text{-}H} = 1 / \sqrt{2} \sim 0.71$

(orign of KIE)

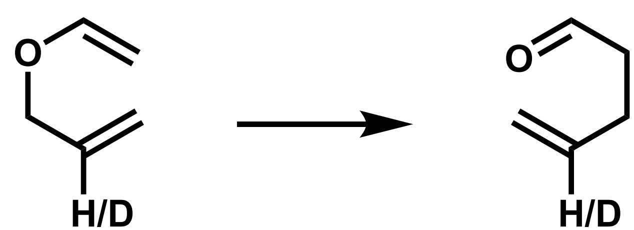
<u>primary (1 °) KIE</u>: A bond is broken or formed to the isotope in the rate-determining step.

ex. E2 elimination:

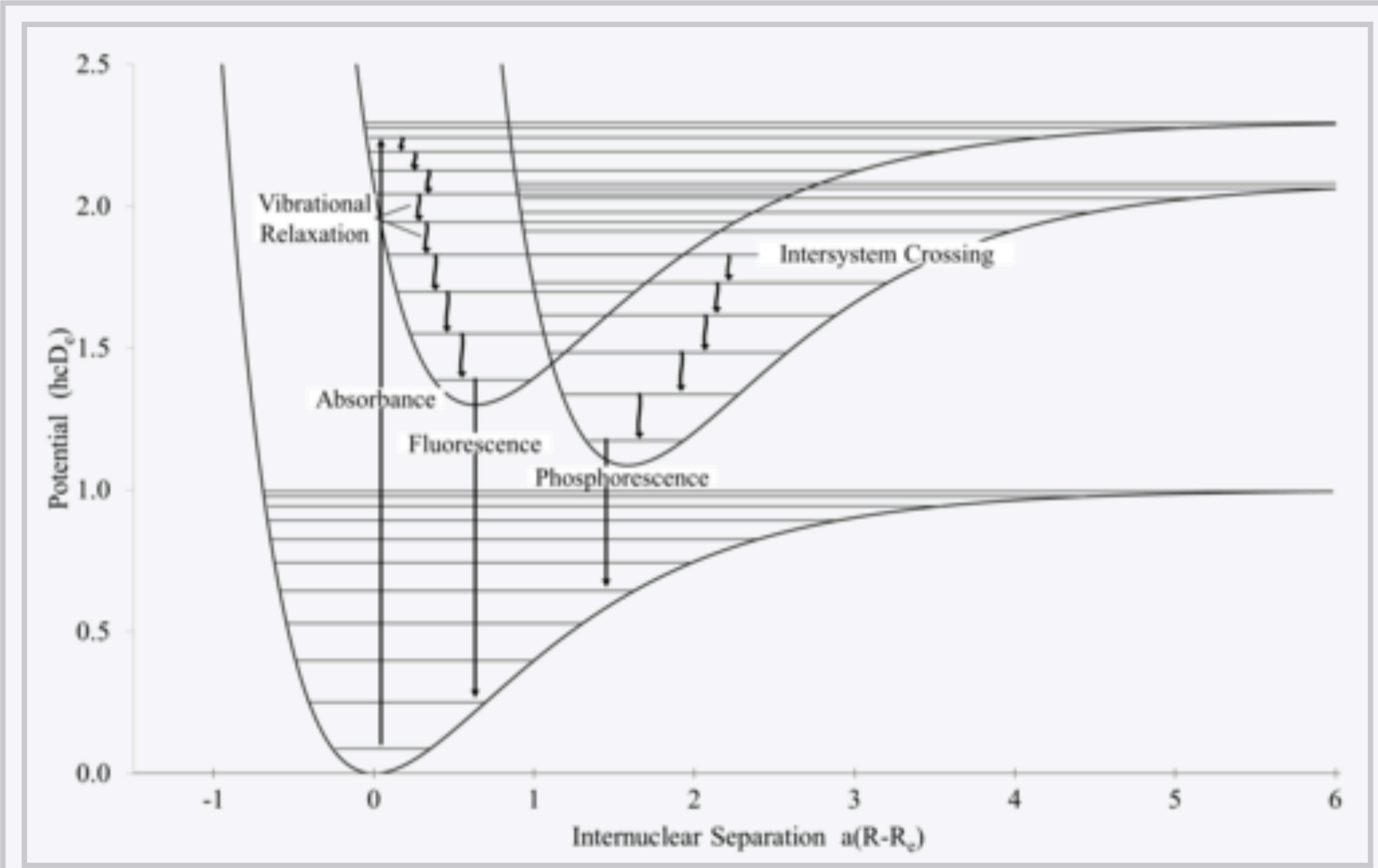


<u>secondary (2 °) KIE</u>: The isotole is not directly involved in the rate-determining step.

ex. Claisen rearrangement:



Interpretation of the 2° inverse KIE



$\nu_{c\text{-}D} / \nu_{c\text{-}H} = 1 / \sqrt{2} \sim 0.71$ ⇨ Rates of vibrational relaxation slow down due to deuteration.

Suppression of the vibrational relaxation can lead to high reactivity of SM-d9?
(→ 2° inverse KIE)

ESP-based atomic charges

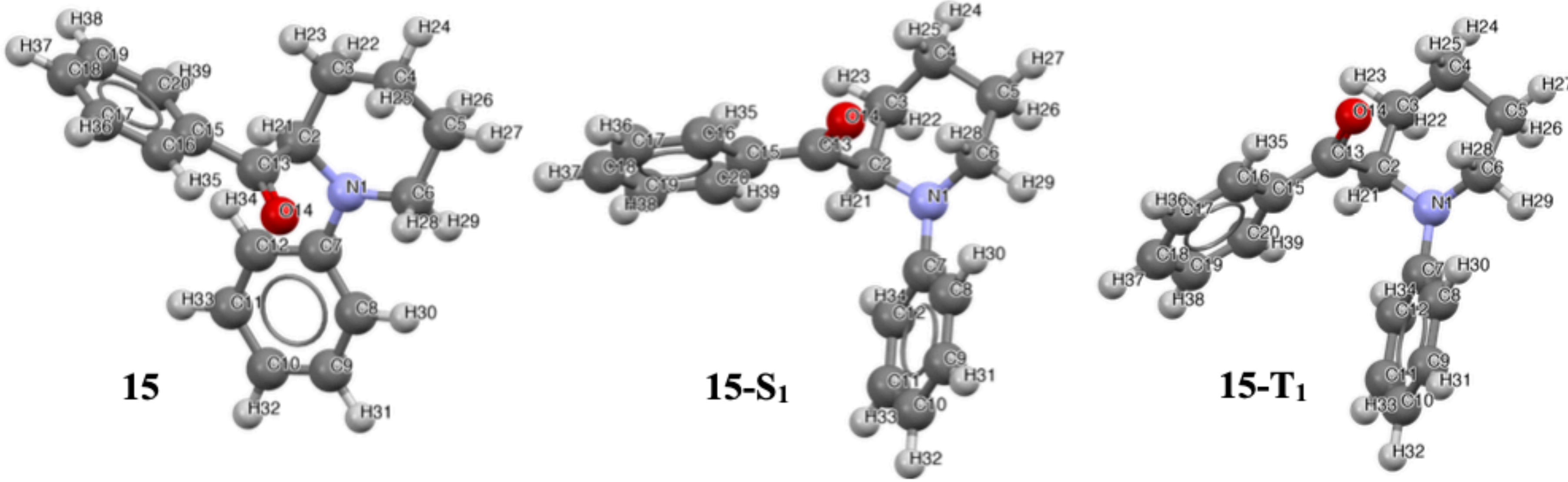
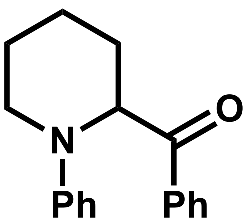


Figure S56. Atom numbering in **15**, **15-S$_1$**, and **15-T$_1$** rendered in Mercury[48].



15

Label	15-S_0	15-S_1	15-T_1	difference between S_0 and T_1
N1	−0.7012	−0.6466	−0.5746	+0.13
O14	−0.4525	−0.4507	−0.489	−0.04
H28	0.0116	0.0255	0.0376	+0.03

(H28: α-hydrogen)

indicates the increase of the charge transfer character

1) Kim, S. F.; Schwarz, H.; Jurczyk, J.; Nebgen, B. R.; Hendricks, H.; Park, H.; Radosevich, A.; Zuerch, M. W.; Harper, K.; Lux, M. C.; Yeung, C. S.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 5580.