Photocatalyzed Epimerization Using Imine

Literature Seminar
2025.4.5

D3 Yutaro Yamada

Contents

1. Introduction

2. Main paper

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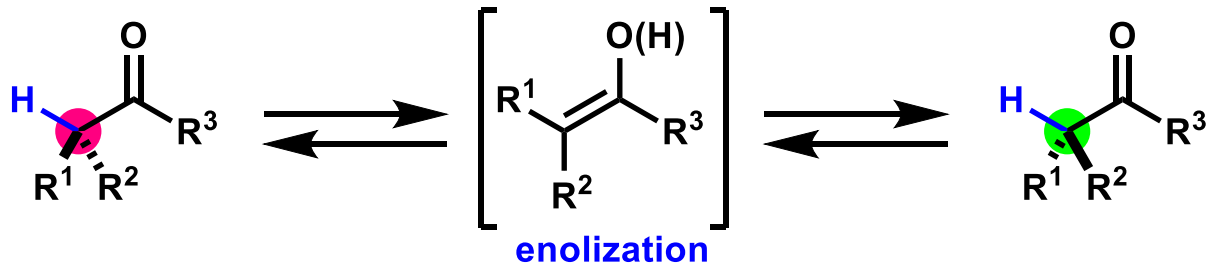
Article

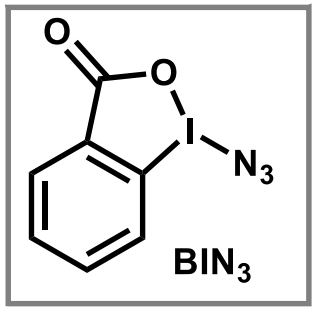
Photocatalyzed Epimerization of Quaternary Stereocenters

Licheng Wu, Baylee N. McIntyre, Supeng Wu, Ziqi Jiao, Carter B. Fox, Nathan D. Schley, and Alexander W. Schuppe*

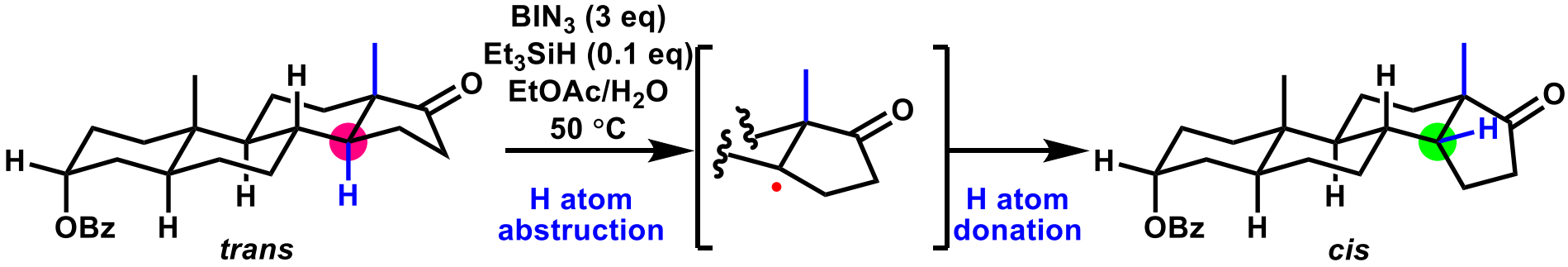
Epimerization of Tri-substituted Carbon *vs* Tetra-substituted Carbon

- Epimerization of tertiary carbon via acidic C-H bond





- Epimerization of tertiary carbon using radical[1)]



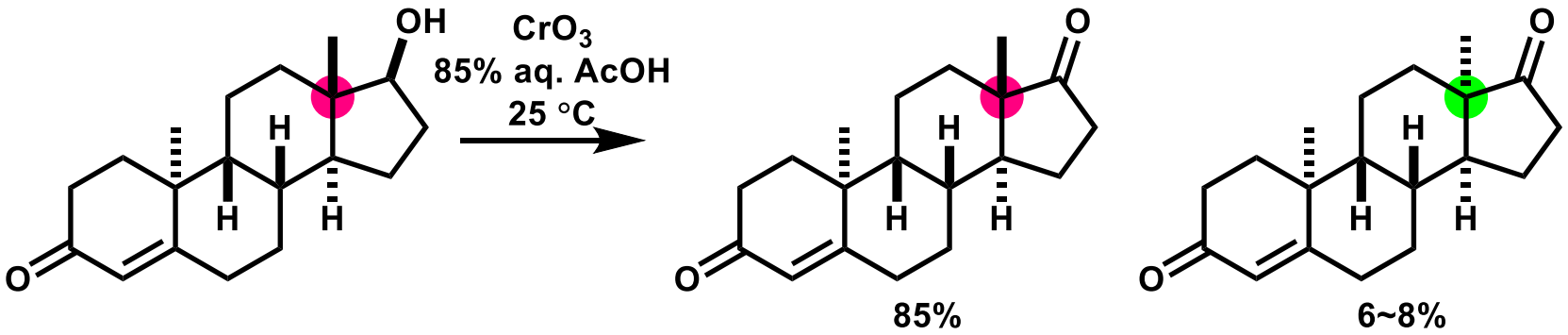
97% (*cis*:*trans* = 2.9:1)

- Challenges in the epimerization of a quaternary stereocenter
  - Cleavage of an inert C-C σ-bond (BDE: C-C 148 kcal/mol *v.s.* C-H 81 kcal/mol)
  - Reconstruction of the sterically conjested C-C σ-bond

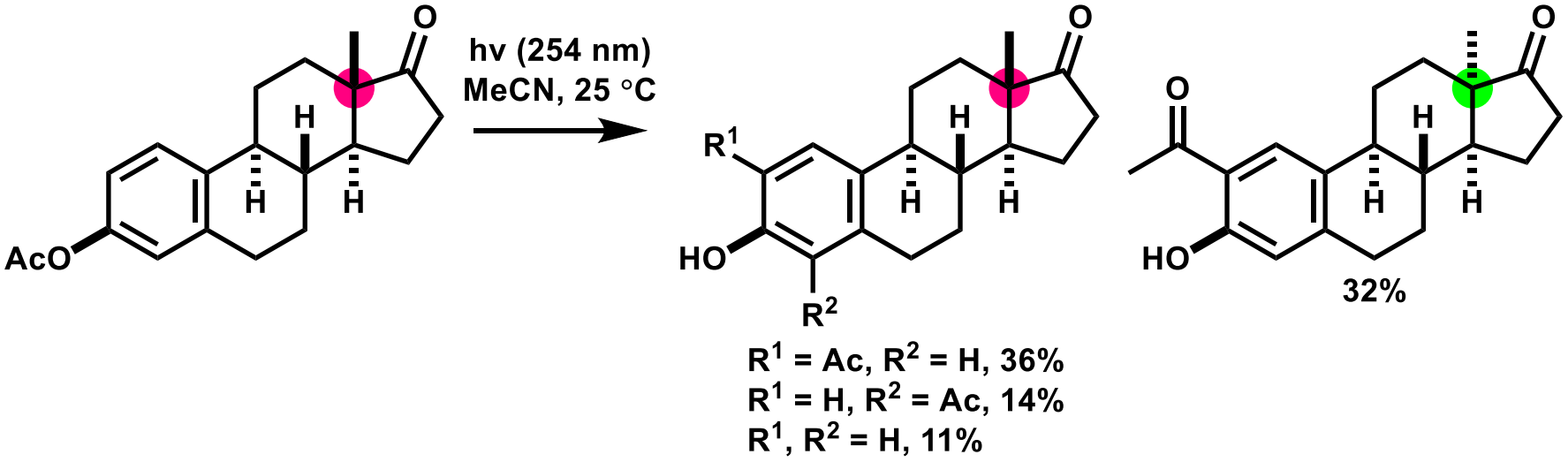
1) Wang, Y.; Hu, X.; Morales-Rivera, C. A.; Li, G. X.; Huang, X.; He, G.; Liu, P.; Chen, G., *J. Am. Chem. Soc.* **2018**, *140*, 9678.
2) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Epimerization of Quaternary Stereocenter

- Epimerization during oxidation[1]



- Photocatalyzed epimerization[2]

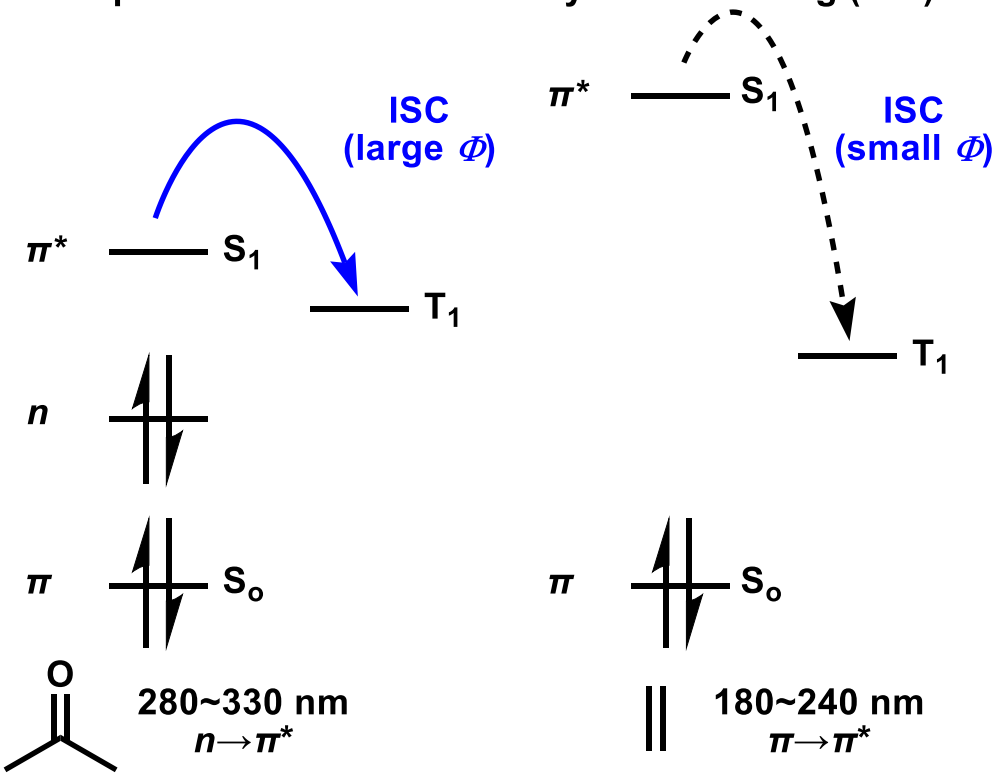


R^1 = Ac, R^2 = H, 36%
R^1 = H, R^2 = Ac, 14%
R^1, R^2 = H, 11%

1) Müller, M.; Kägi, D.; Fürst, A., *Tetrahedron* **1981**, *37,* 257. 2) Quindt, M. I.; Gola, G. F.; Ramirez, J. A.; Bonesi, S. M.; *J. Org. Chem.* **2019**, *84*, 7051.

Generation of Excited Triplet State

- Direct photoexcitation via intersystem crossing (ISC)



Feature of ketone

Triplet excitation could be induced by direct photoexcitation.

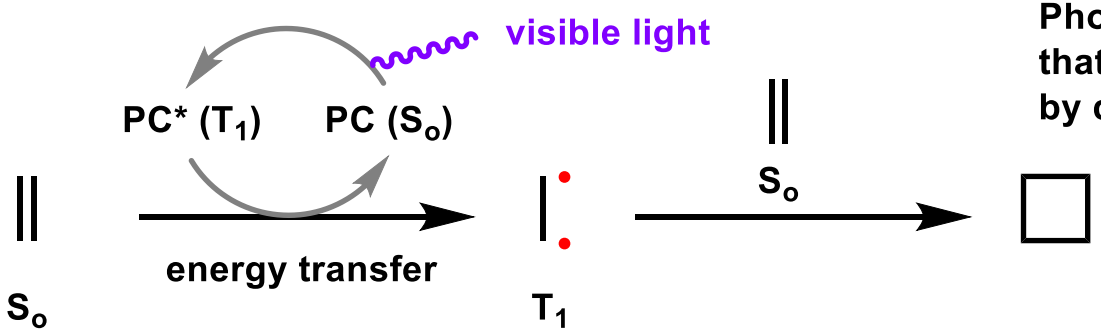
- small energy gap between π and π^* orbitals
- $n \rightarrow \pi^*$ transition
- efficient ISC (large Φ)

Feature of olefin

Triplet excitation induced by direct photoexcitation is difficult.

- large energy gap between π and π^* orbitals
- inefficient ISC (small Φ)

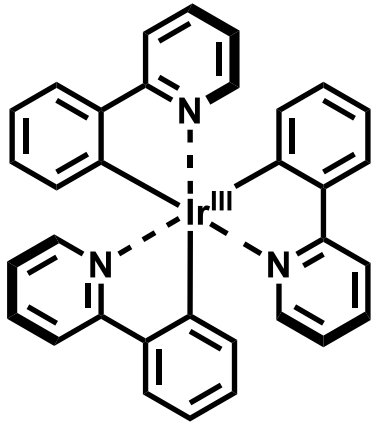
- Indirect excitation using photocatalyst



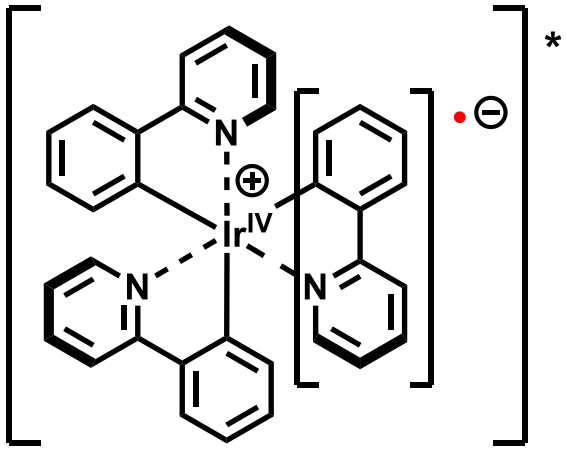
Photocatalyst could be applied to molecules that are difficult to excite to the triplet state by direct light irradiation.

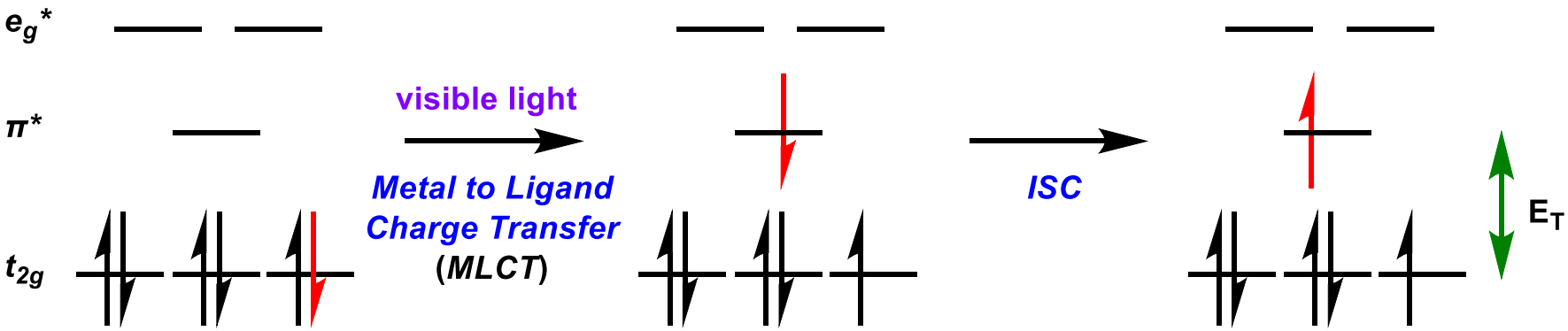
1) 230520_LS_Yuto_Hikone 2) 大学院講義 有機化学 I 第2版 P.249-253

Ir catalyst



fac-Ir(ppy)$_3$

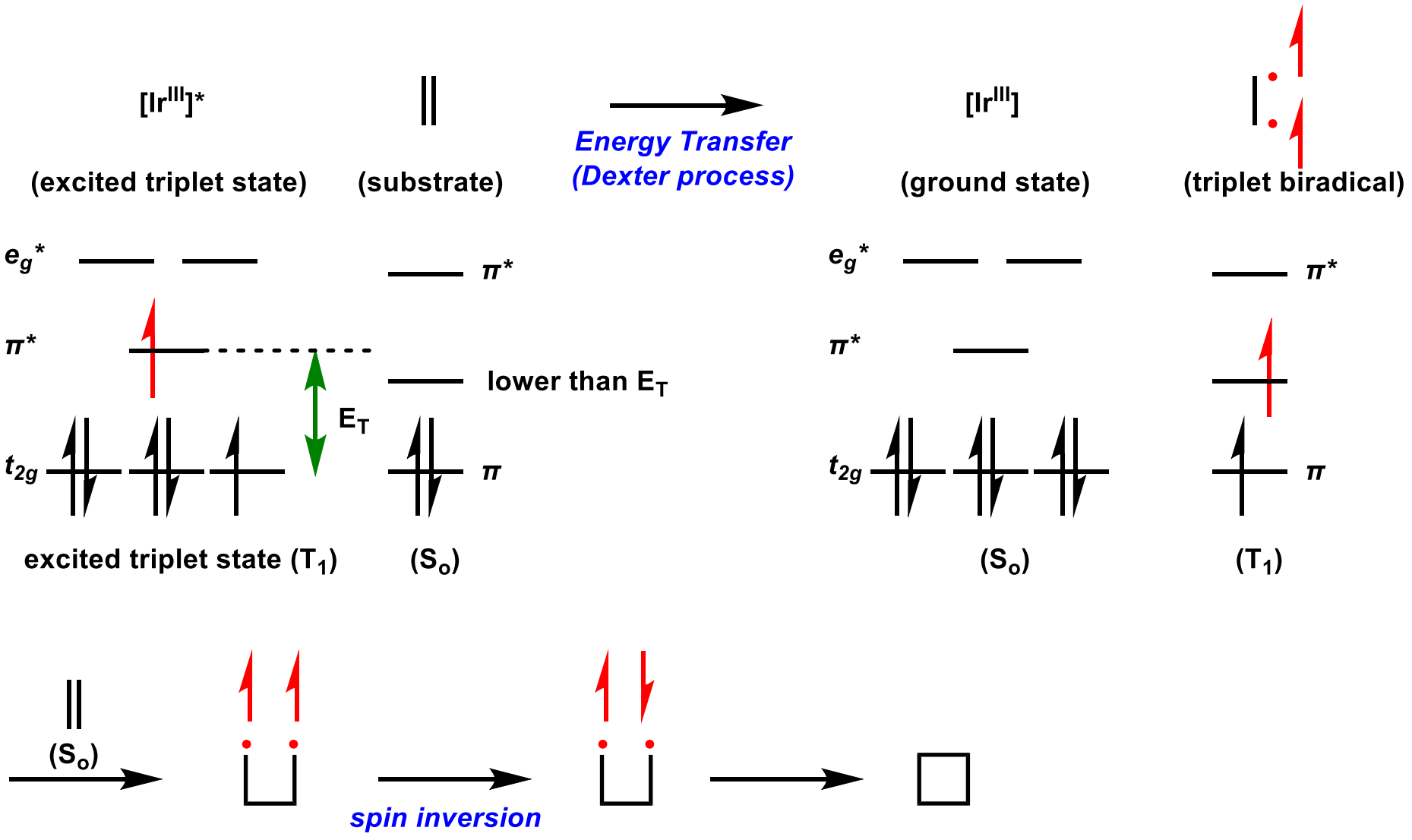




Iridium has a strong heavy atom effect, allowing rapid ISC from the singlet excited state (S_1) to the triplet excited state (T_1).

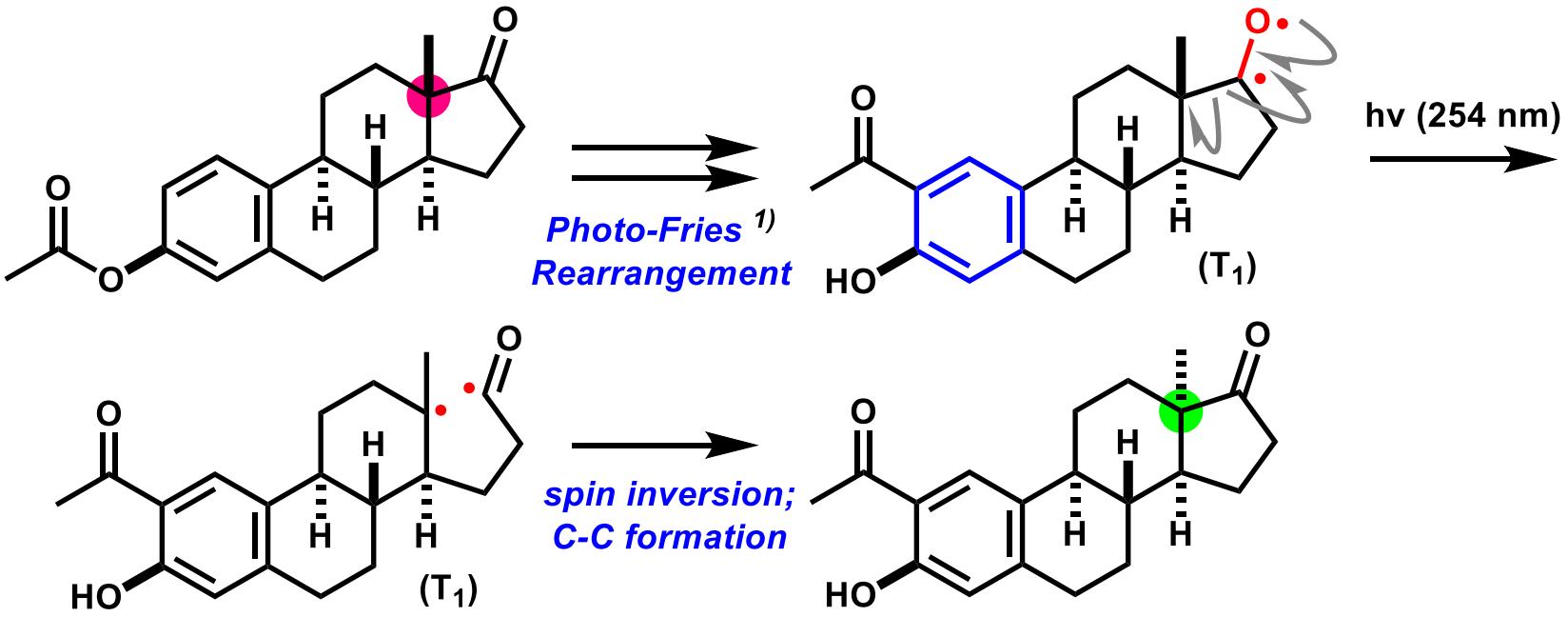
1) Chen, B. B.; Wang, S.; Jiang, S. W.; Yu, Z. G.; Wan, X. G.; Ding, H. F.; Wu, D. *New J. Phys.* **2015**, *17*, 013004.

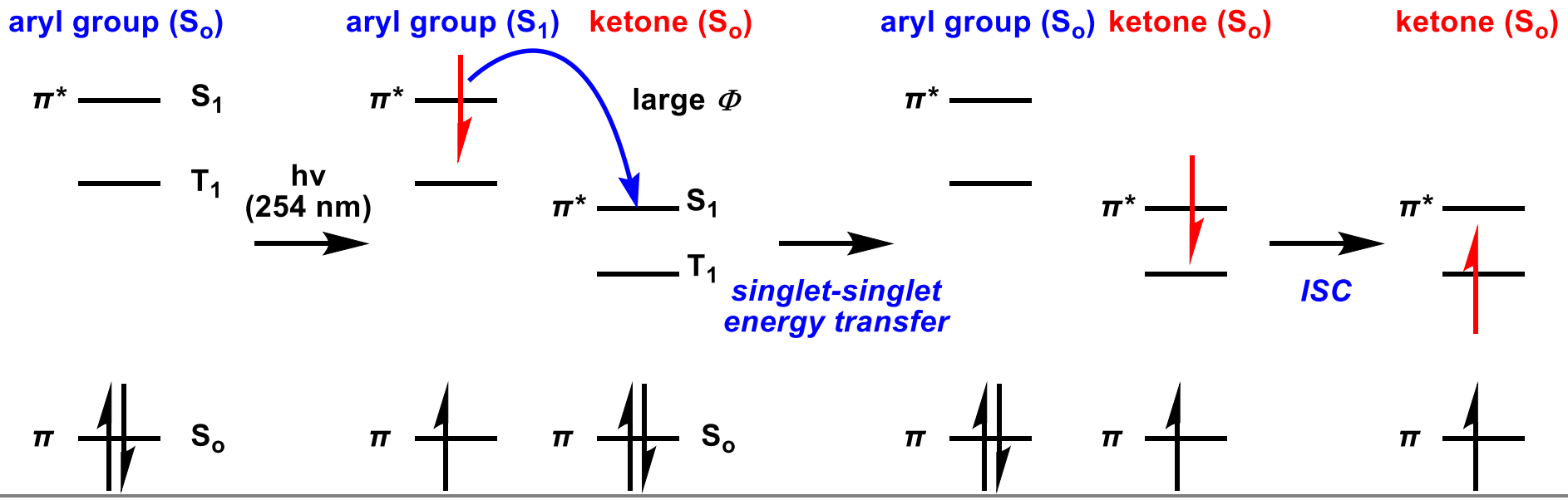
Energy Transfer



E_T, the energy gap between S_o and T_1, is important for photosensitization of substrates via energy transfer.

Proposed Reaction Mechanism of Epimerization





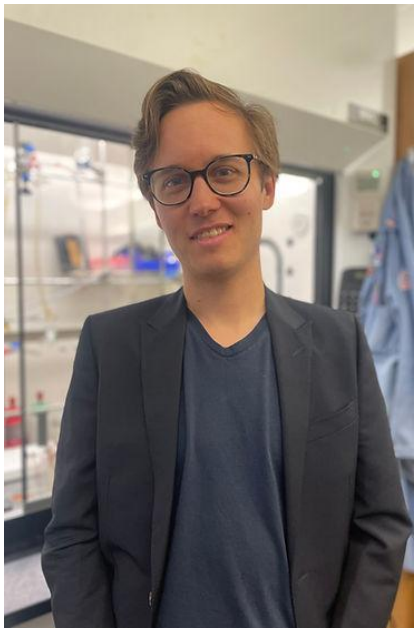
1) Appendix p.29 2) Quindt, M. I.; Gola, G. F.; Ramirez, J. A.; Bonesi, S. M.; *J. Org. Chem.* **2019**, *84*, 7051.

Contents

1. Introduction

2. Main paper

Assistant Professor Alexander W. Schuppe

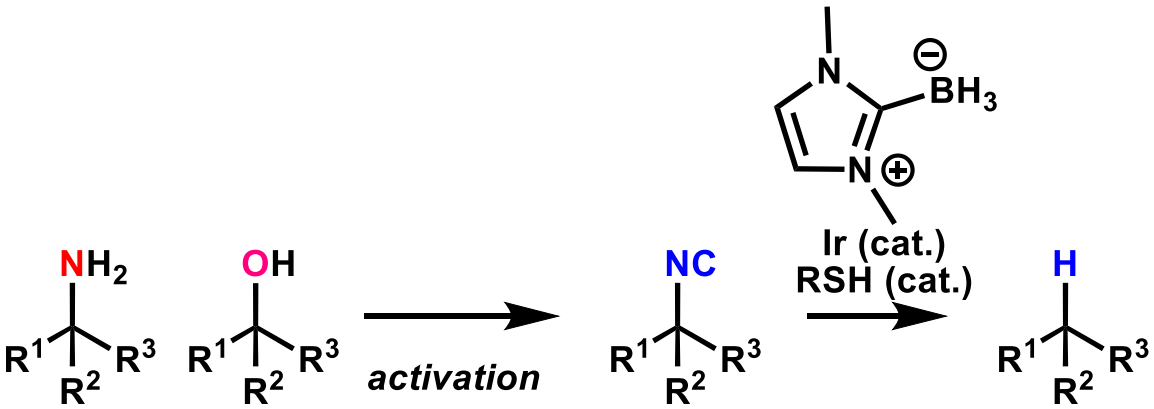


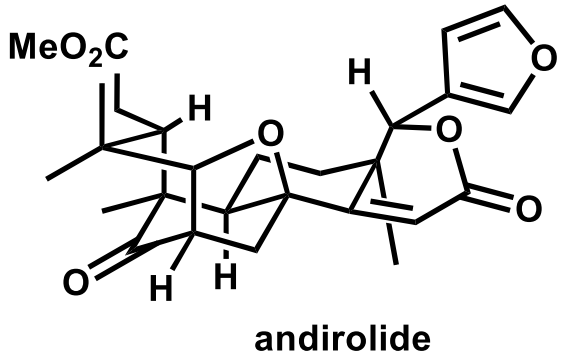
Career:

2009-2013 B.S. @ University of Texas at Austin (Prof. Dionicio Siegel)
2013-2018 Ph.D. @ Yale University (Prof. Timothy Newhouse)
2018-2022 Arnold O. Beckman Postdoctoral Fellow
@ Massachusetts Institute of Technology (Stephen Buchwald)
2022- Assistant Professor @ Vanderbilt University

Research interests:

1. Catalysis 2. Total synthesis of natural product
3. Biological evaluation

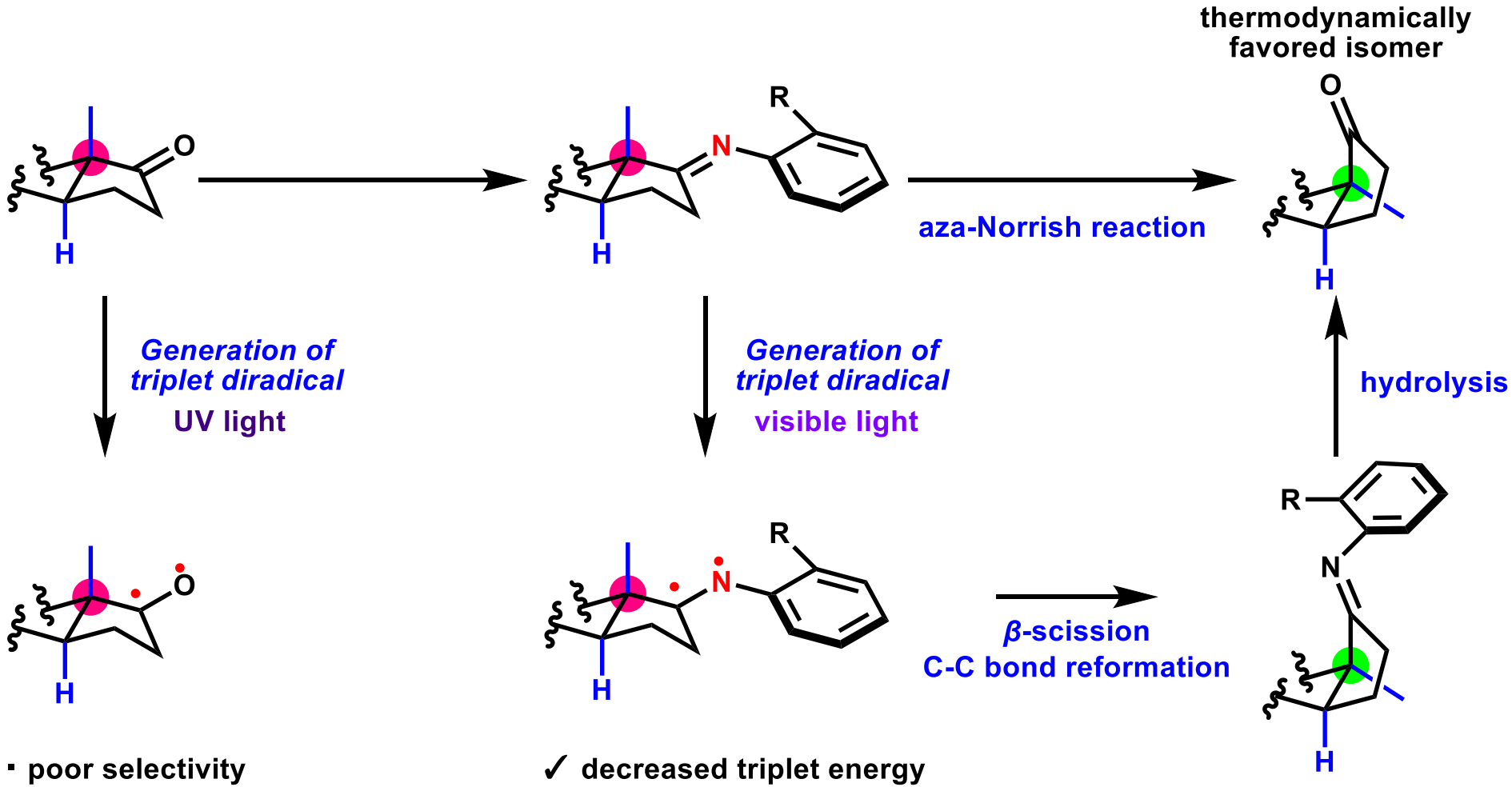




andirolide

1) https://www.schuppelab.com/research
2) *Angew. Chem. Int. Ed.* **2024**, *63*, e202409073

Author's Approach to Epimerization of Quaternary Stereocenter



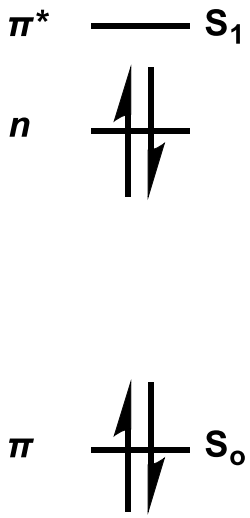
- poor selectivity
- inadequate functional group compatibility
- Generation of side-product via Hydrogen atom transfer (HAT)

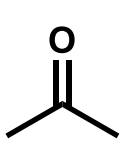
✓ decreased triplet energy relative to ketone
✓ stabilized *N*-centered radical
✓ catalytic generation of triplet-state

1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Photoexcitation of Carbonyl and Imine

carbonyl

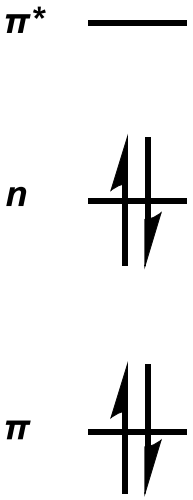


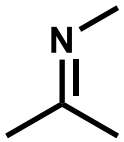


~190 nm
$\pi \rightarrow \pi^*$ (strong)

280~330 nm
$n \rightarrow \pi^*$ (weak)

alkyl imine

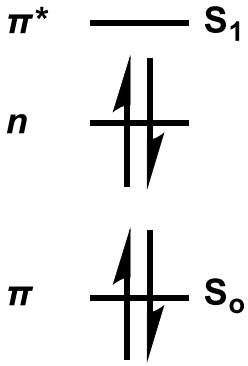


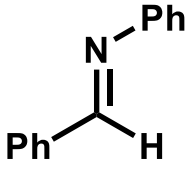


170~180 nm
$\pi \rightarrow \pi^*$ (strong)

230~260 nm
$n \rightarrow \pi^*$ (weak)

aryl imine





252 nm
$\pi \rightarrow \pi^*$ (strong)

315 nm
$n \rightarrow \pi^*$ (weak)

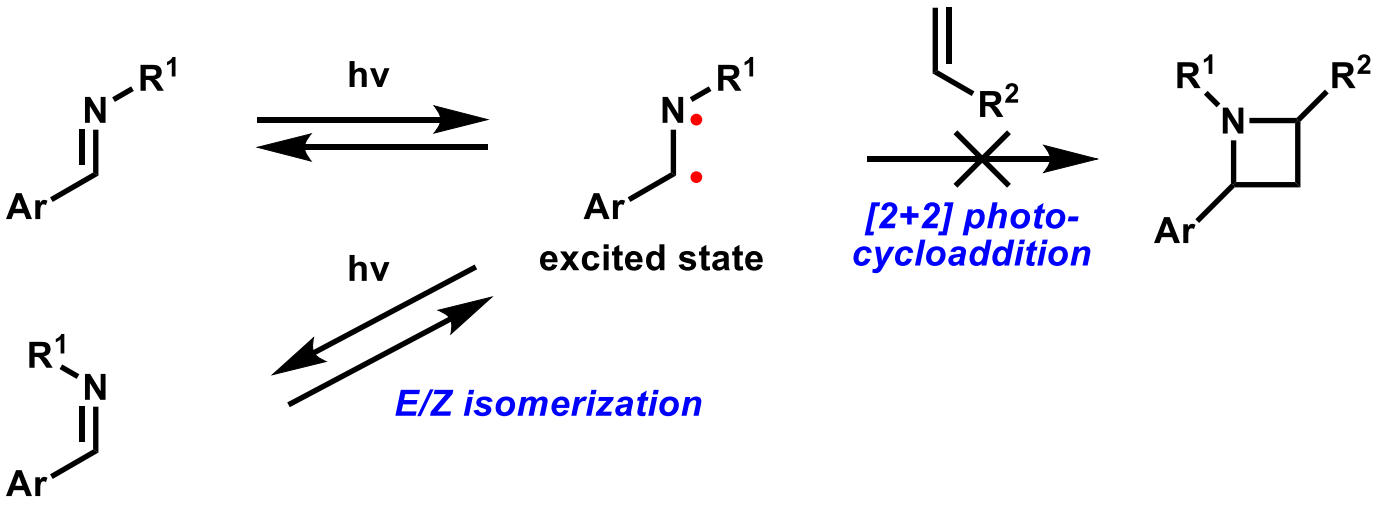
$n \rightarrow \pi^*$ transition (commonly used)

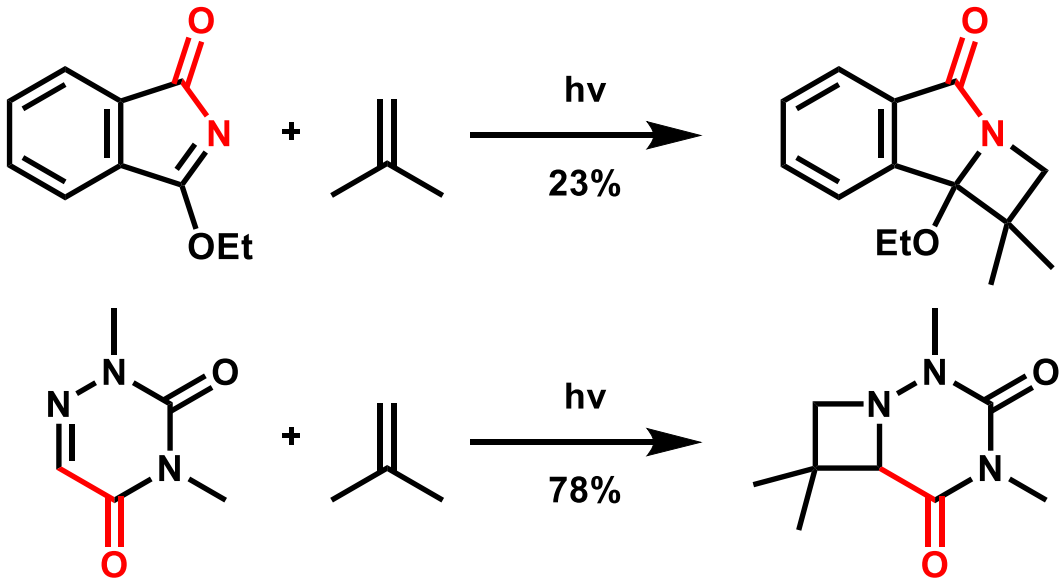
When the conjugated system is extended, the energy gap between the π and π^* orbitals becomes smaller, allowing excitation with longer-wavelength light.

1) Padwa, A.; *Chem. Rex.* **1977**, *77*, 37. 2) Pratt, A. C., *Chem. Soc. Rev.* **1977**, *6*, 63.

Direct Photoexcitation of Imine

- [2+2] photocycloaddition between C=N and C=C bond

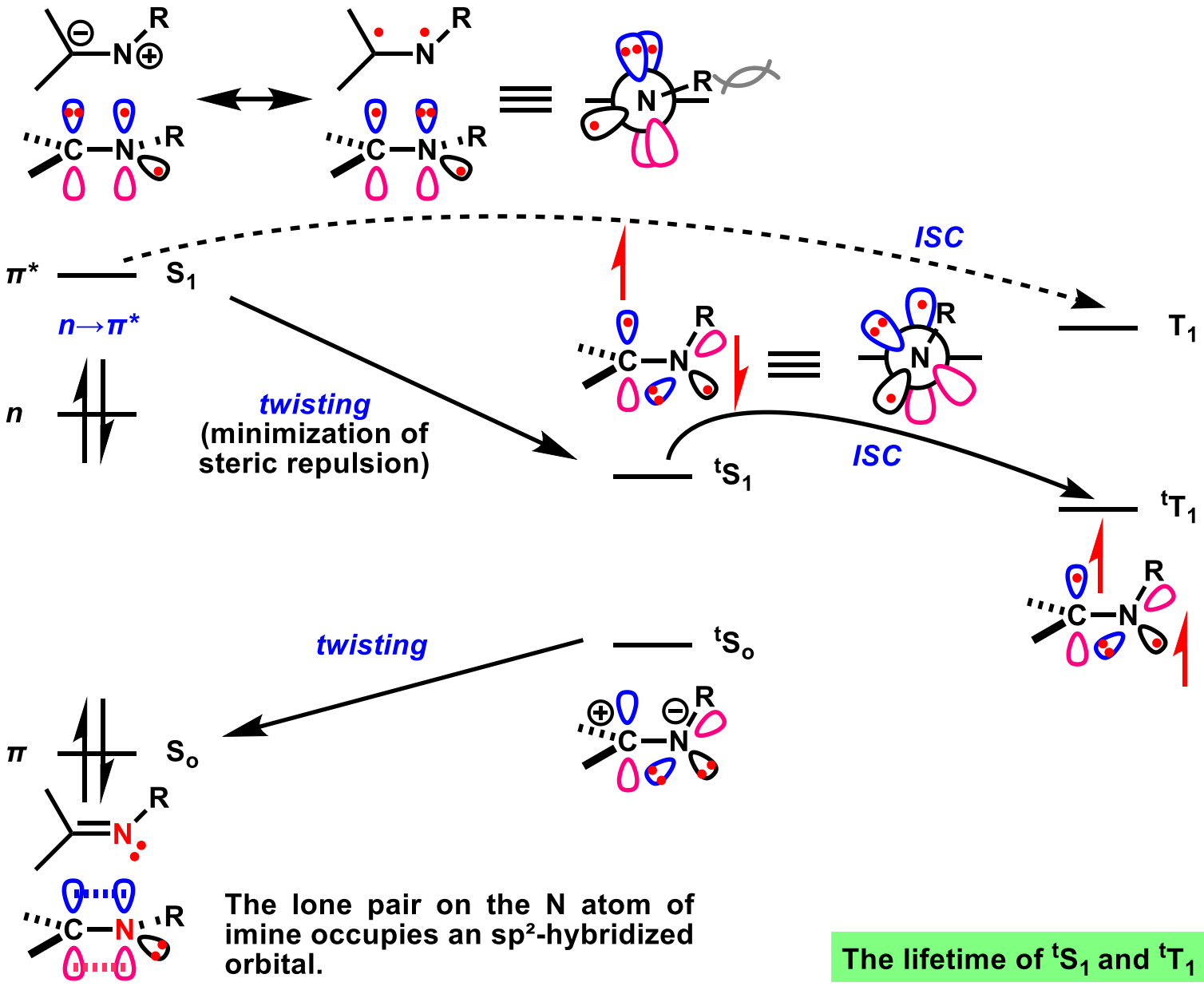




Thus, [2+2] photocycloaddition between C=N and C=C bonds has been accomplished only for cyclic C=N bond with electron-withdrawing group (EWG).

1) Swenton, J. S.; Hyatt, J. A., *J. Am. Chem. Soc.* **1974**, *96,* 4879. 2) Howard, K. A.; Koch, T. H., *J. Am. Chem. Soc.* **1975**, *97*, 7288.

Rational Explanation

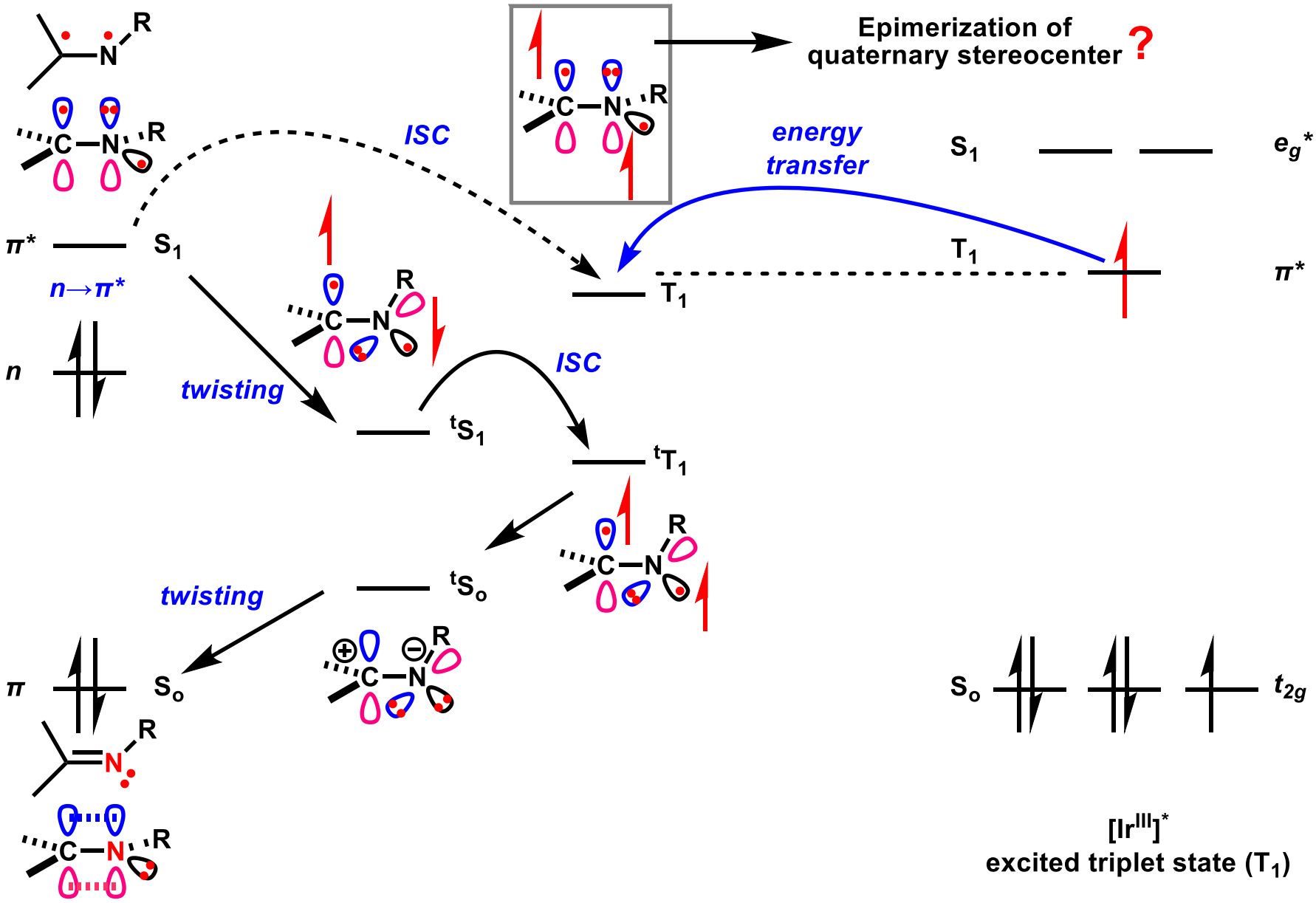


The lone pair on the N atom of imine occupies an sp²-hybridized orbital.

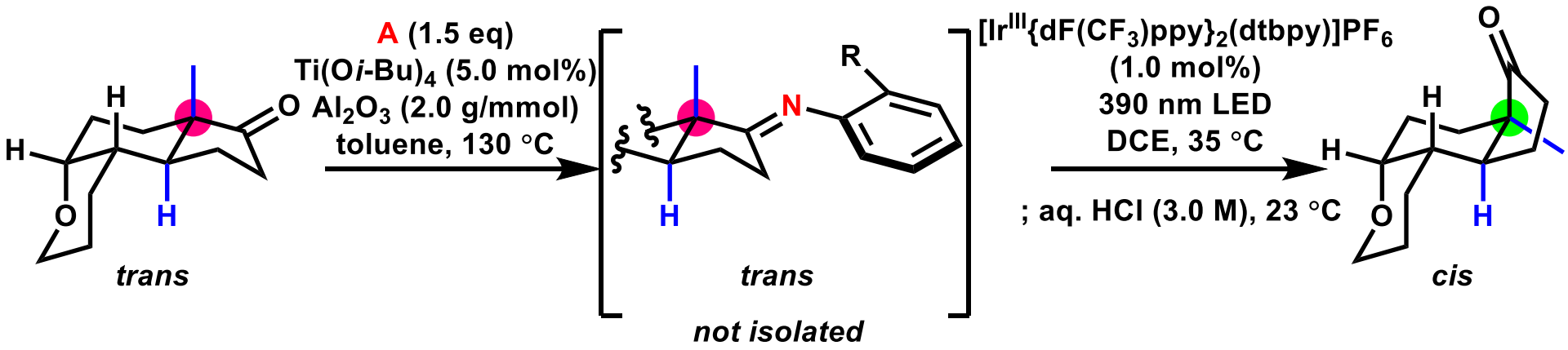
The lifetime of $^tS_1$ and $^tT_1$ is very short.

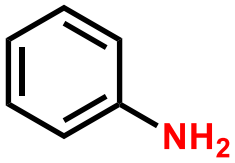
1) Uraguchi, D.; Tsuchiya, Y.; Ohtani, T.; Enomoto, T.; Masaoka, S.; Yokogawa, D.; Ooi, T., *Angew. Chem. Int. Ed.* **2020**, *59*, 3665.

Reaction Design

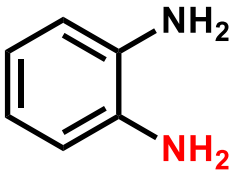


Optimization (aniline structure)

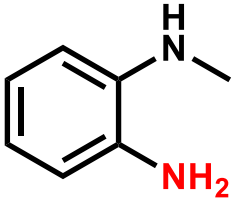




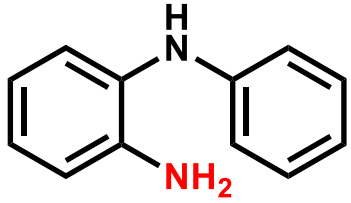
trans: 45%
cis: 0%



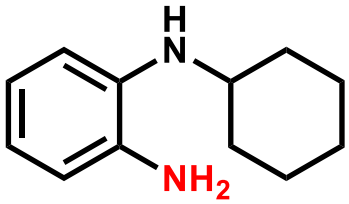
trans: 16%
cis: 0%



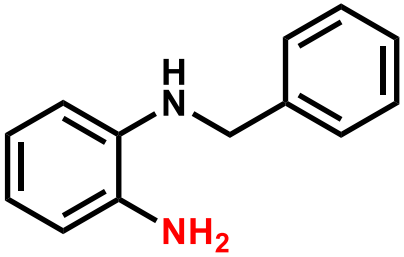
trans: 0%
cis: 29%



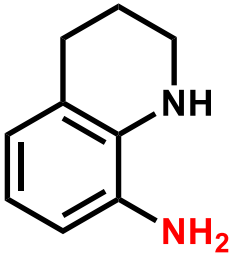
trans: 0%
cis: 37%



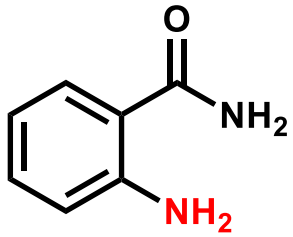
trans: 45%
cis: 0%



trans: 0%
cis: 0%



trans: 0%
cis: 71%

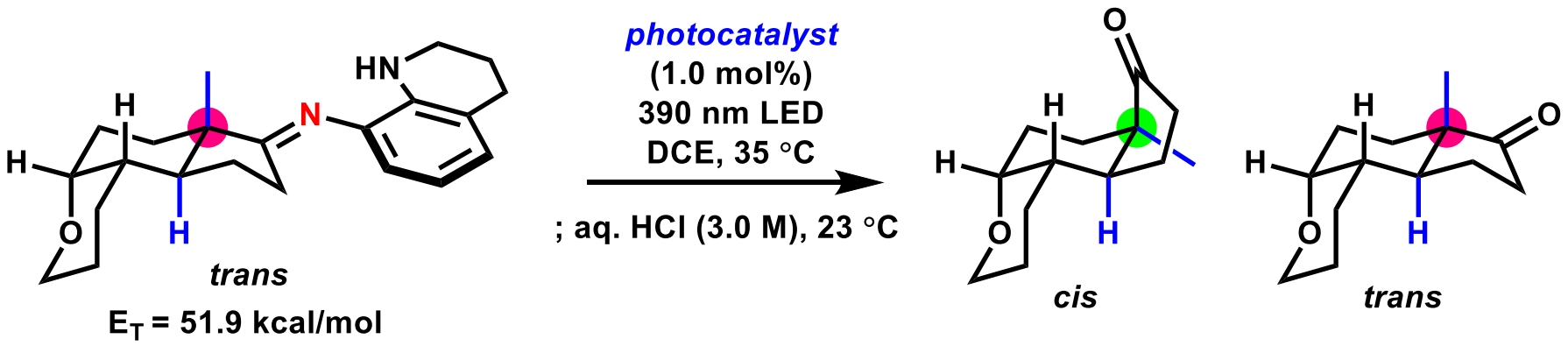


trans: 21% a)
cis: 0%

a) Condensation: iodine (5.0 mol%), DMF, 90 °C

1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Optimization (photocatalyst)



E_T = 51.9 kcal/mol

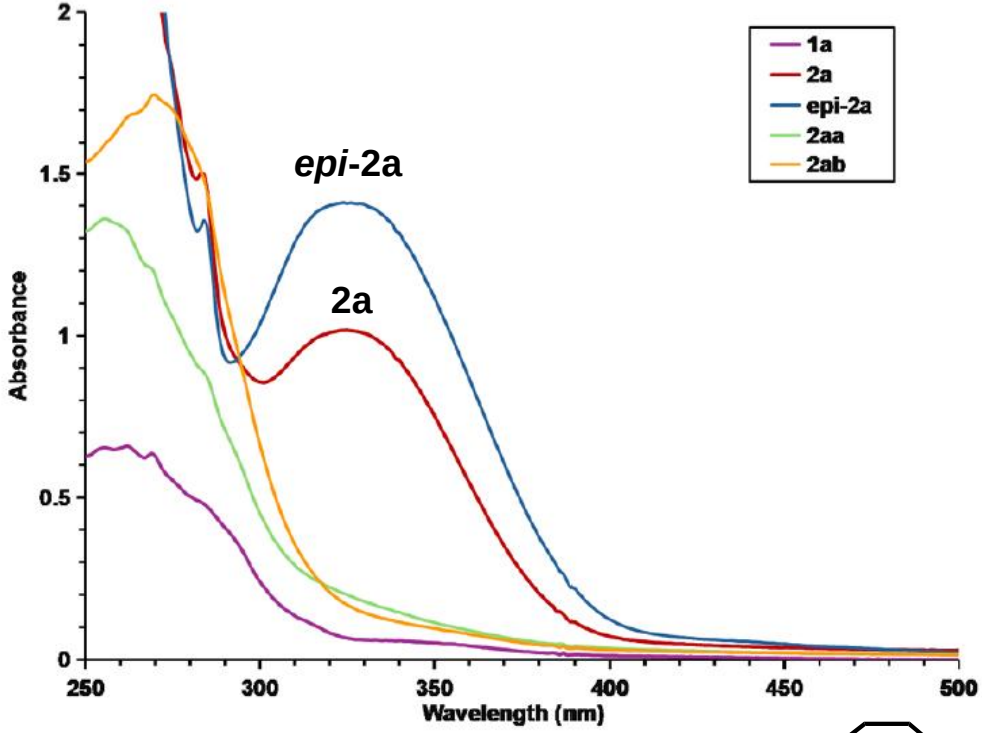
photocatalyst	E_T (kcal/mol)	yield (*cis*:*trans*)
$[Ir^{III}\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (1)	60.1	86% (>20:1)
fac-Ir(dFppy)$_3$ (2)	60.1	66% (3:1)
fac-Ir(ppy)$_3$ (3)	55.2	51% (1:1)
$[Ir^{III}(ppy)_2(dtbpy)]PF_6$ (4)	49.2	21% (1:2)
thioxanthen-9-one (5)	63.3	90% (10:1)
4-CzIPN (6)	58.3	<5% (n.d.)
no photocatalyst	-	89% (1:11)

The structure of photocatalysts was listed on Appendix.

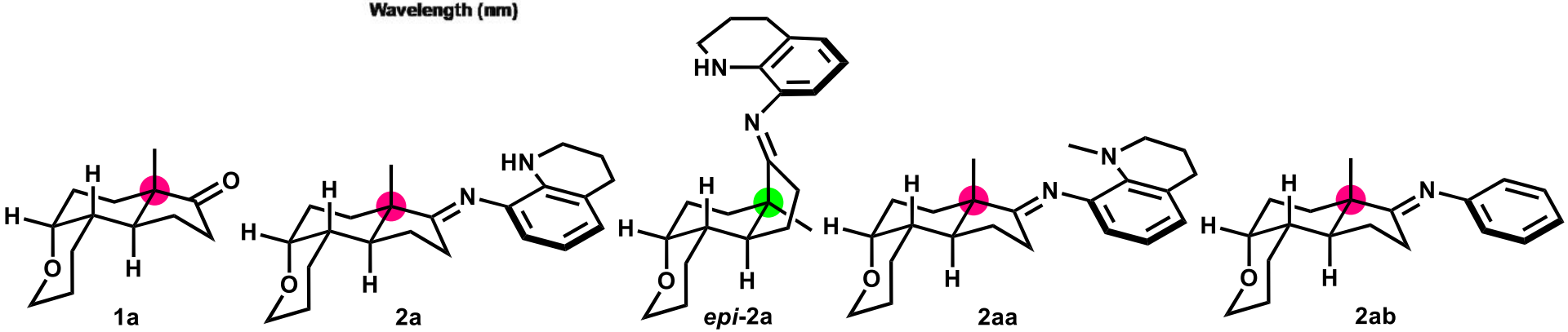
1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Mechanistic Investigation (1)

UV-Vis absorption spectra

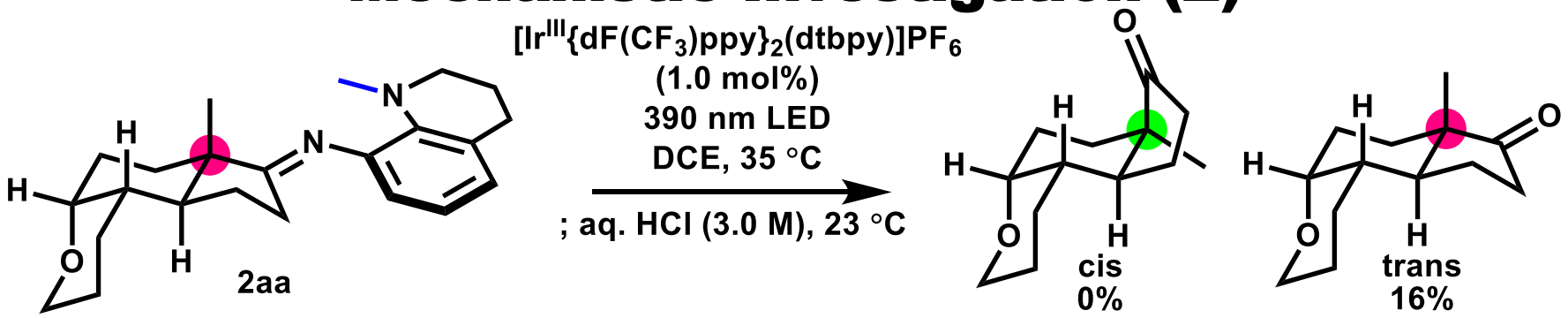


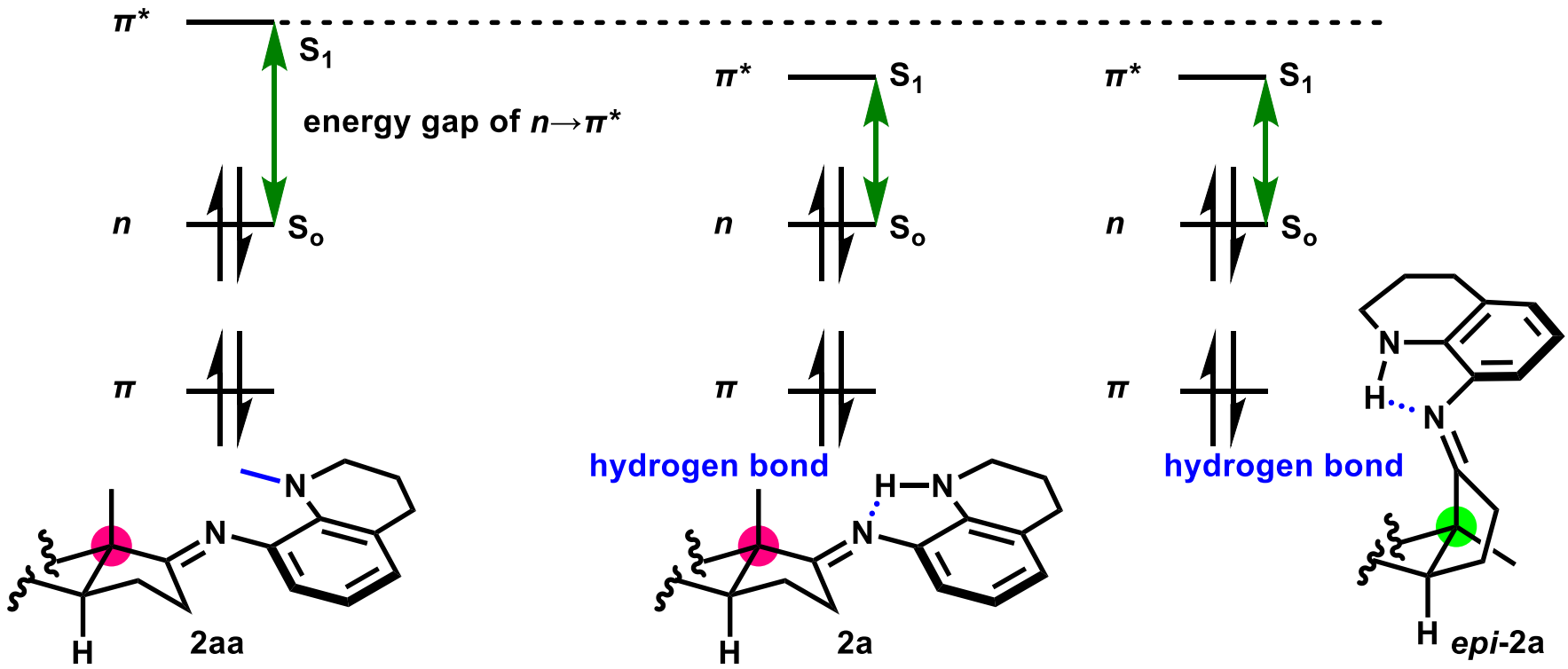
Bathochromic shift (red shift) for $n \rightarrow \pi^*$ transitions of 2a and *epi*-2a was observed.



1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Mechanistic Investigation (2)



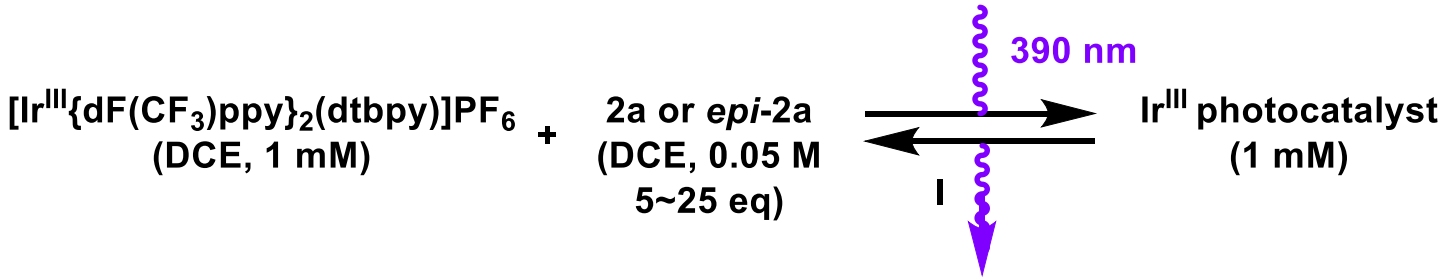


The π^* orbital was stabilized by hydrogen bond, leading to a longer absorption wavelength of $n \rightarrow \pi^*$ transitions.

1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Mechanistic Investigation (3)

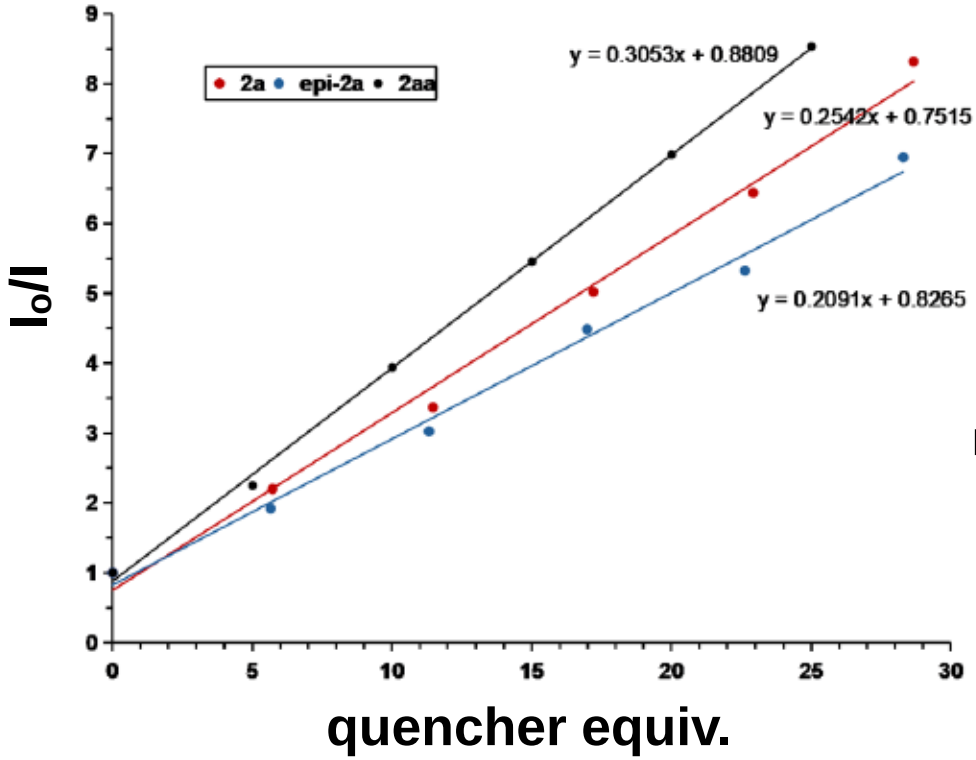
Stern-Volmer fluorescence quenching

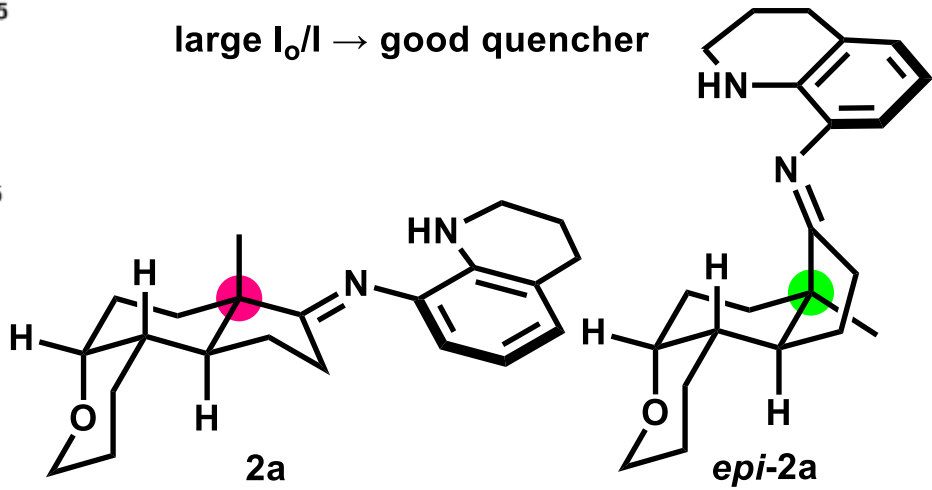


I_o: catalyst emission intensity in absence of quencher

I : catalyst emission intensity in presence of quencher

large I_o/I → good quencher

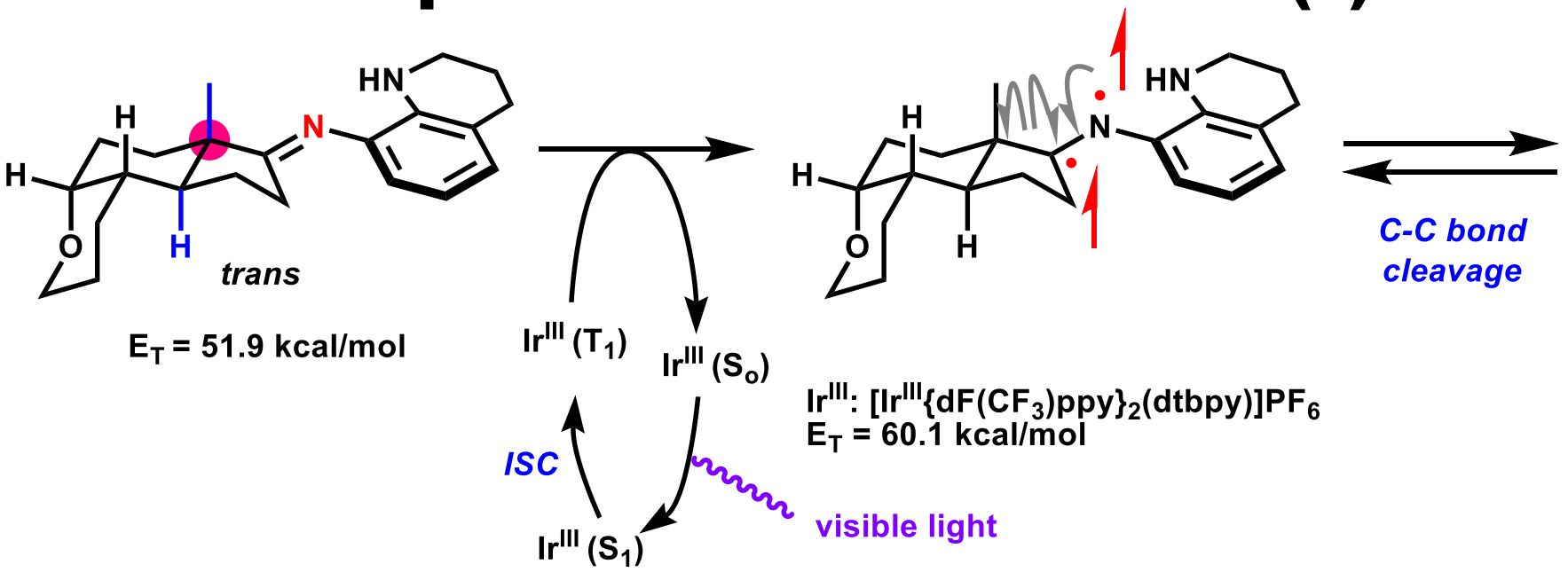


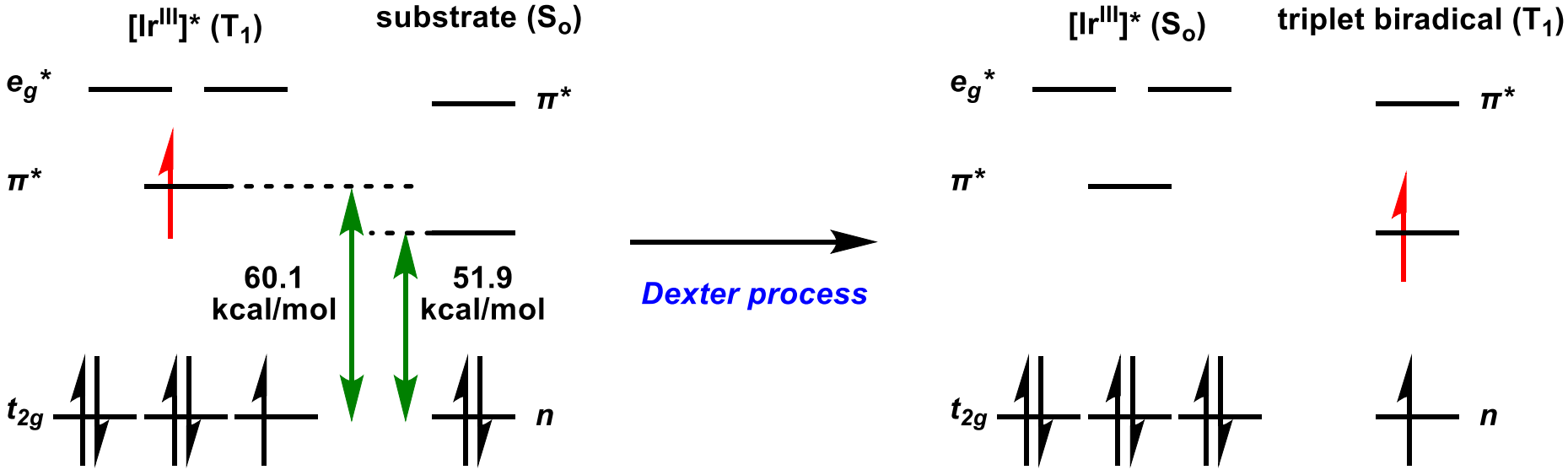


Both imines 2a and *epi*-2a were effective at quenching the excited photocatalyst.

1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

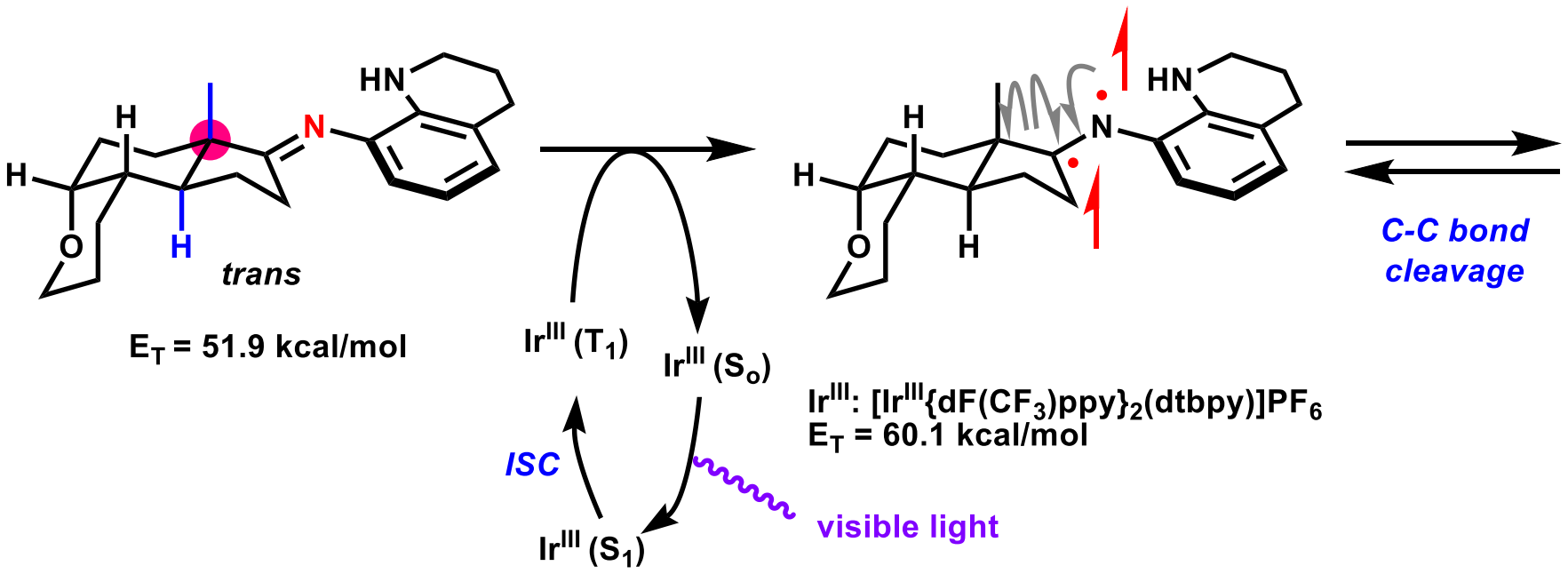
Proposed Reaction Mechanism (1)



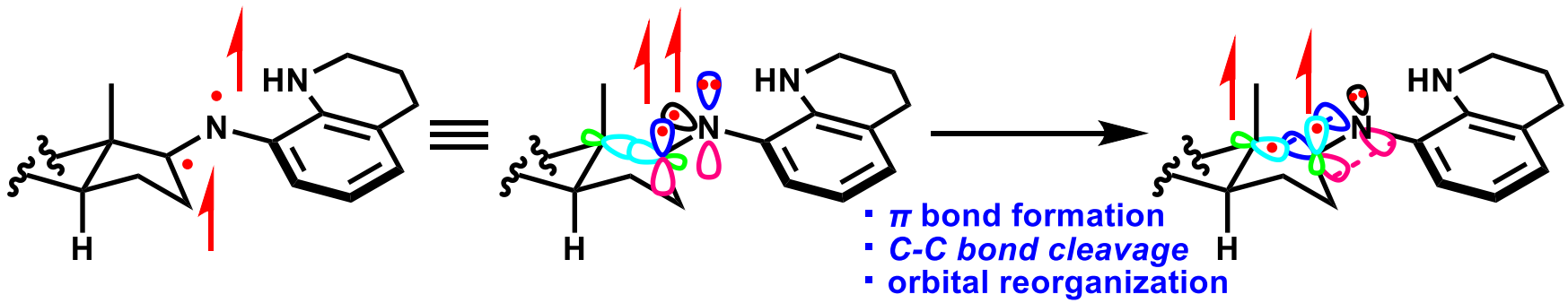


1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Proposed Reaction Mechanism (1)

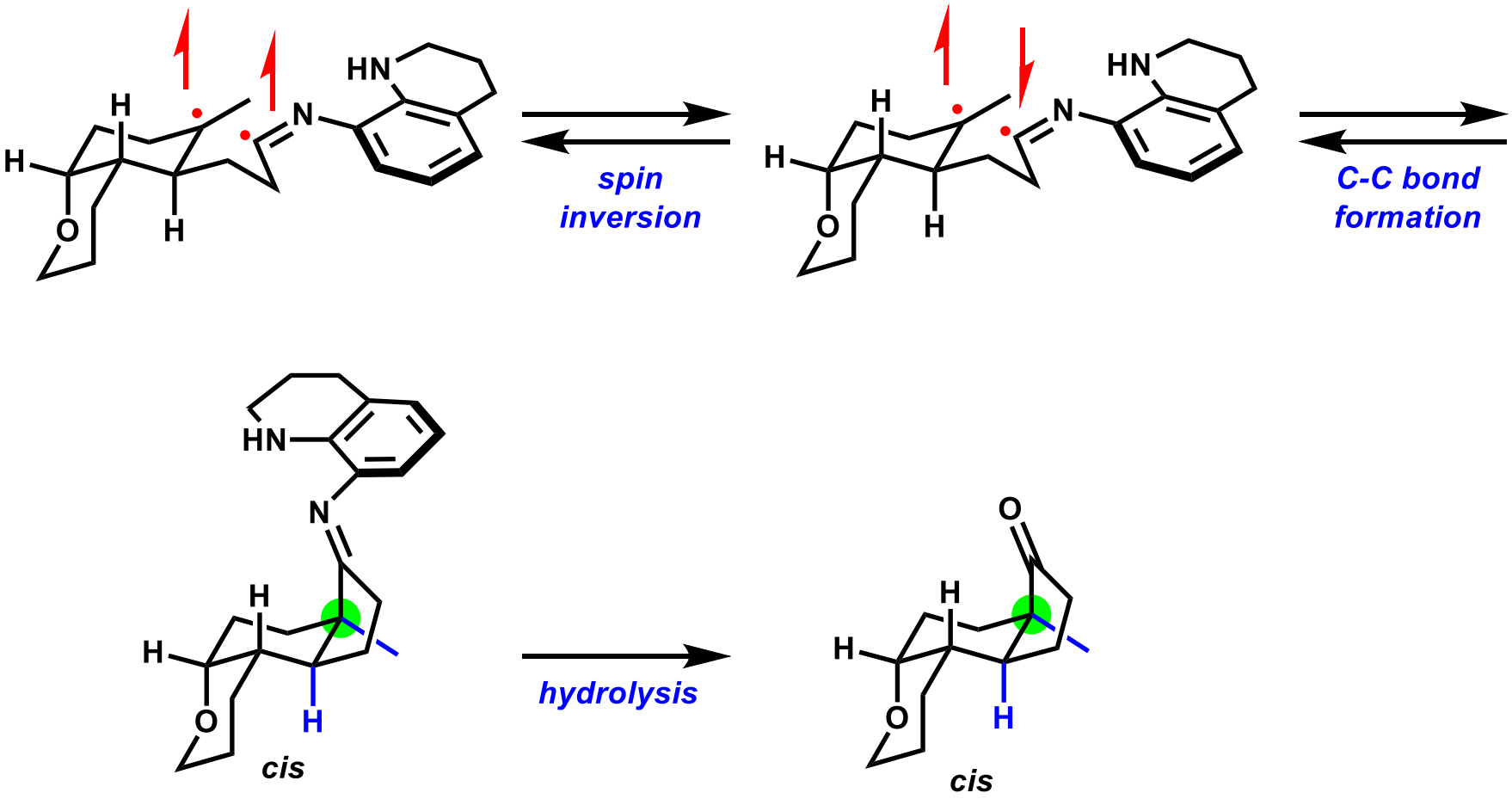


<Explanation from the molecular orbital perspective>



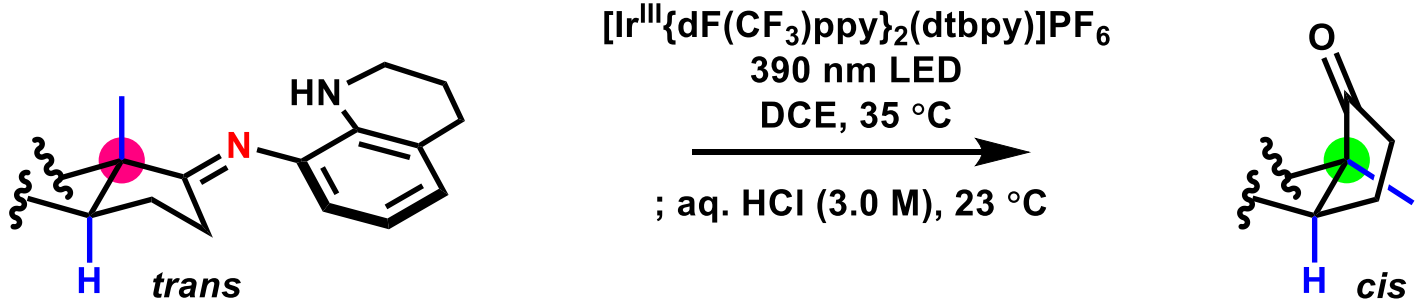
1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

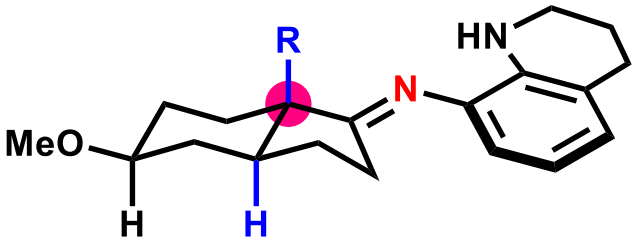
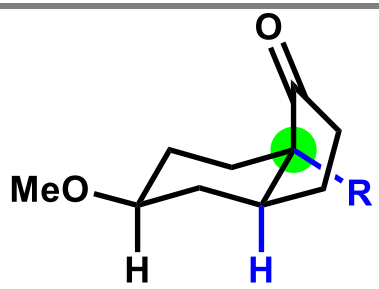
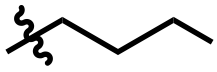
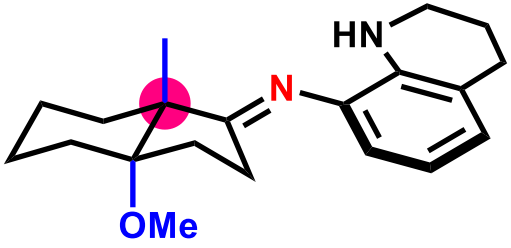
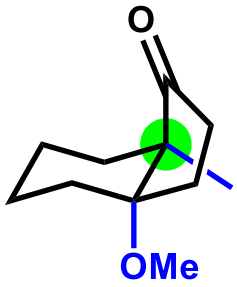
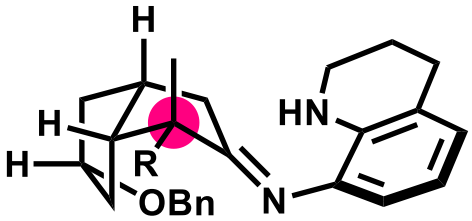
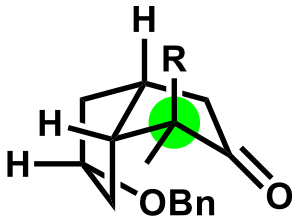
Proposed Reaction Mechanism (2)



1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

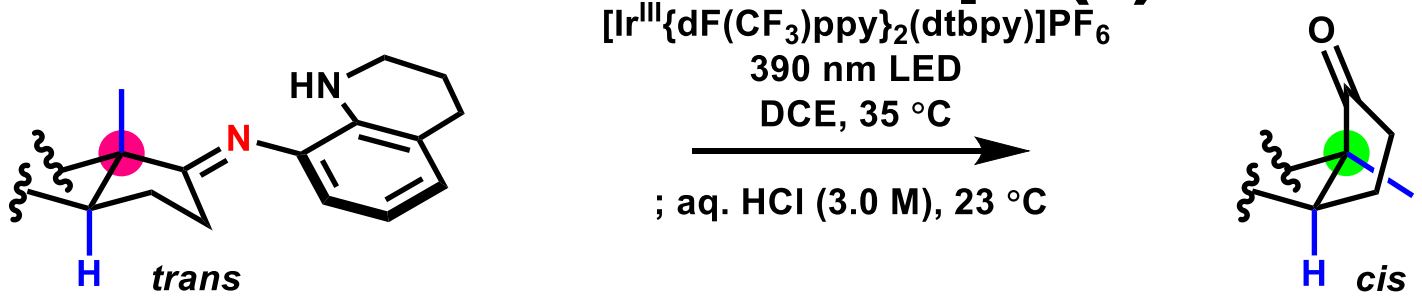
Substrate Scope (1)

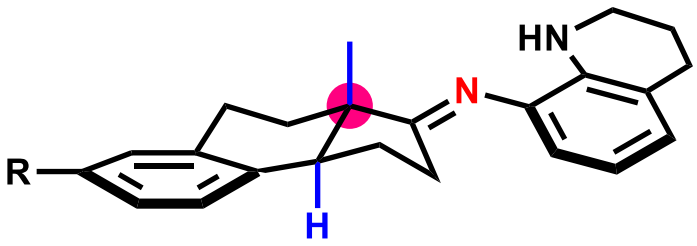
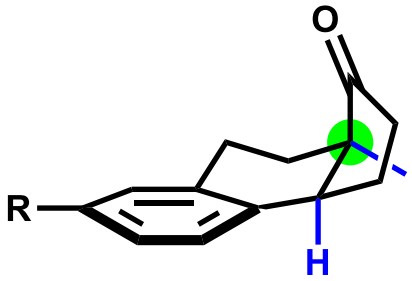
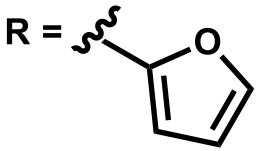
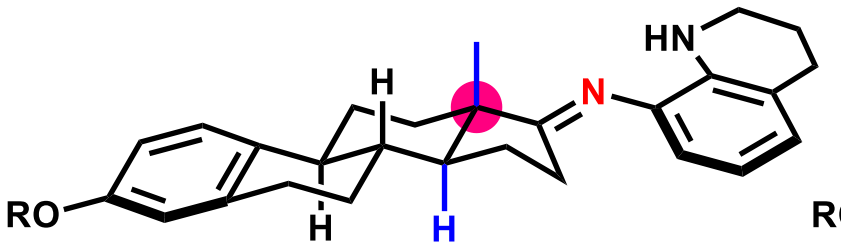
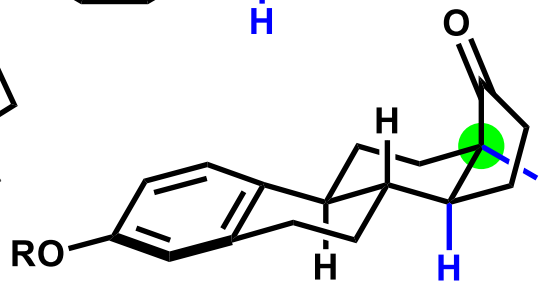
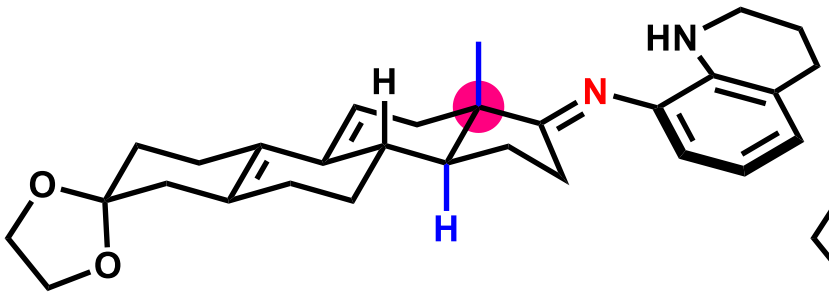
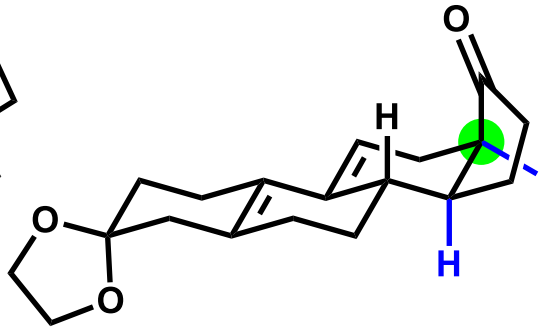


SM	Epimer	
		R = Me, 64% (*cis*:*trans* = >20:1) Et, 70% (*cis*:*trans* = >20:1)  (55% (*cis*:*trans* = >20:1)
		88% (*cis*:*trans* = >12:1)
		R = CH_2Ph, 71% (dr = 5:1) CH_2Cy, 57% (dr = 4:1)

1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

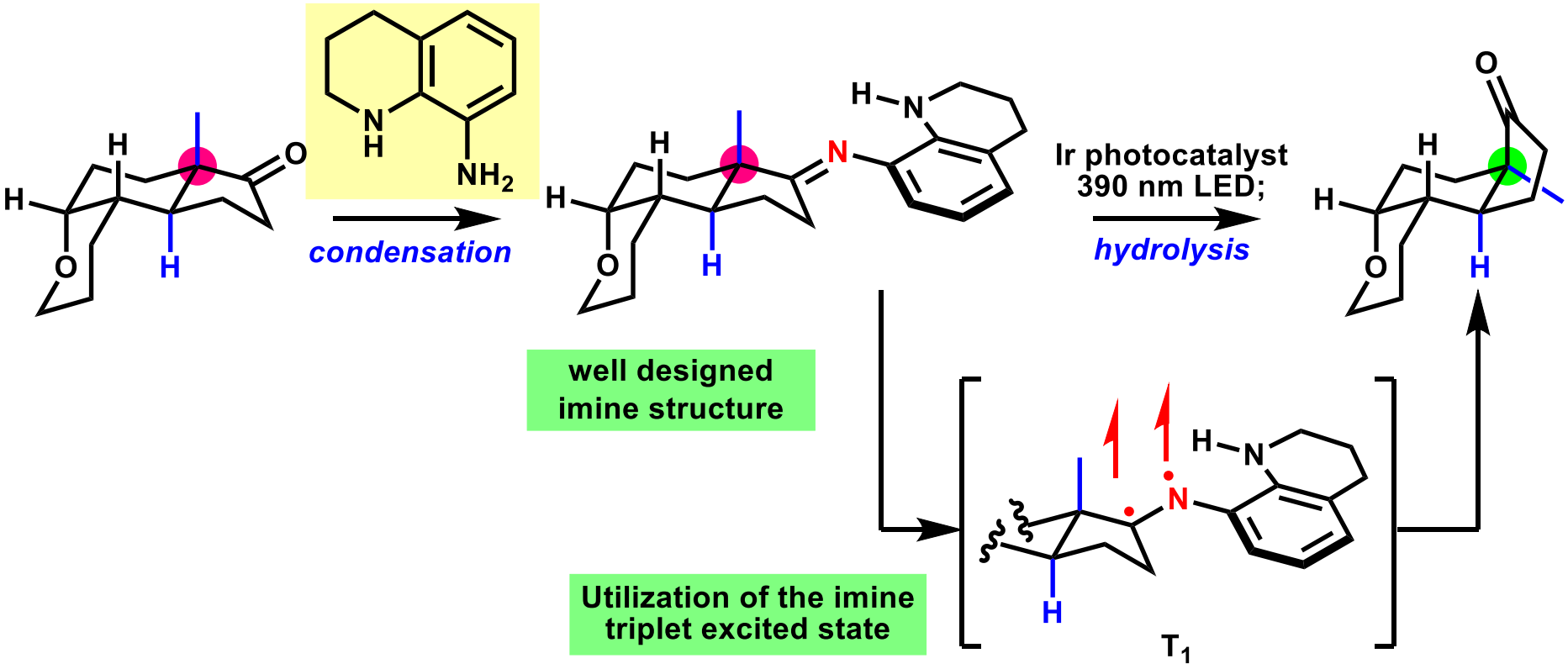
Substrate Scope (2)



SM	Epimer	
		 79% (*cis*:*trans* = >20:1) CN, 91% (*cis*:*trans* = >20:1)
		 77% (*cis*:*trans* = >20:1) Tf, 62% (*cis*:*trans* = >20:1)
		64% (*cis*:*trans* = 1:1)

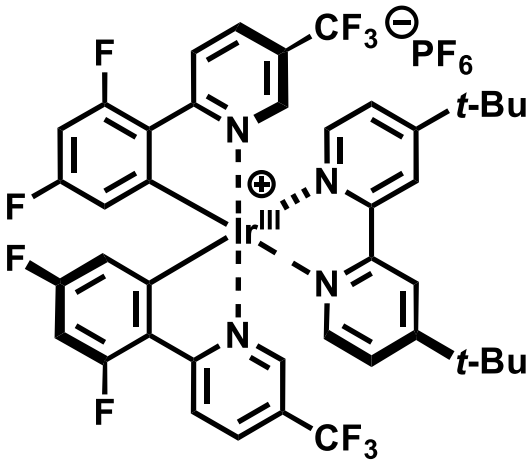
1) Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W., *J. Am. Chem. Soc.* **2025**, *147*, 11080.

Summary

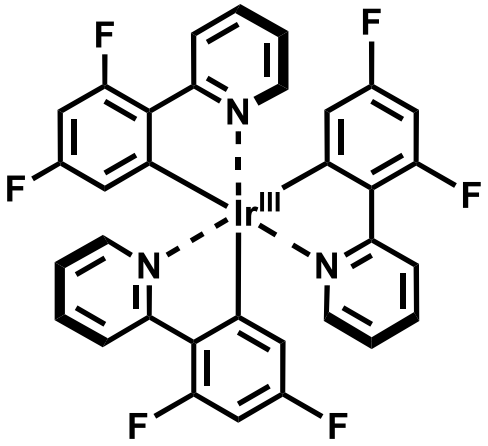

condensation
Ir photocatalyst
390 nm LED;
hydrolysis
well designed
imine structure
Utilization of the imine
triplet excited state
T1

Appendix

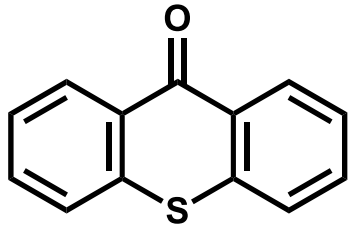
Structure of Photocatalyst



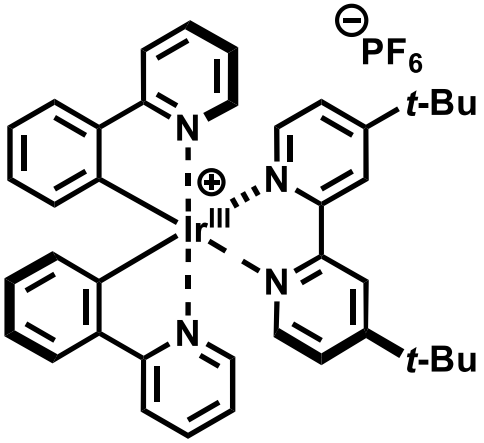
$[Ir^{III}\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (1)



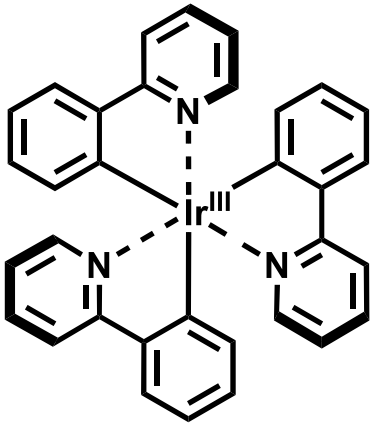
fac-$Ir(dFppy)_3$ (2)



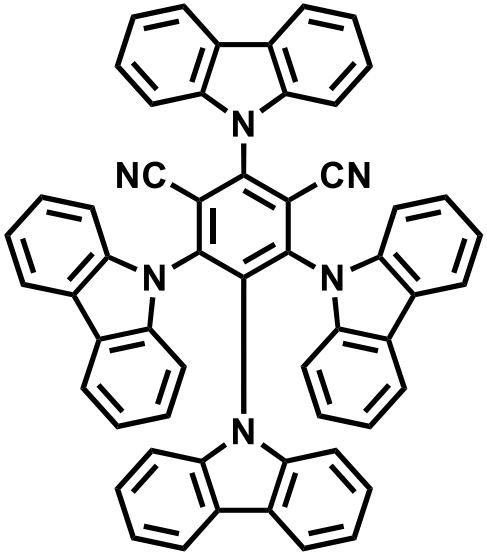
thioxanthen-9-one (5)



$[Ir^{III}(ppy)_2(dtbpy)]PF_6$ (4)



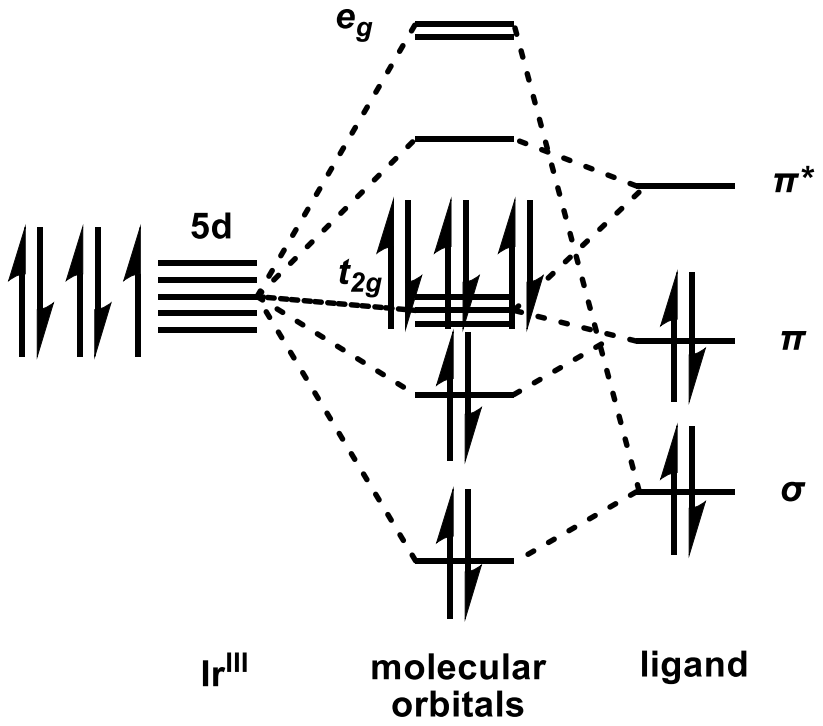
fac-$Ir(ppy)_3$ (3)

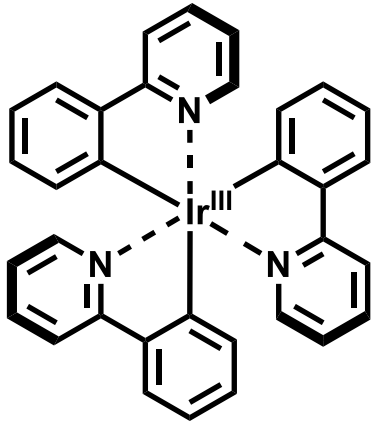


4-CzIPN (6)

Ir-ligand complex

Ir (group 9, period 6): $[Xe]4f^{14}5d^{7}6s^{2}$

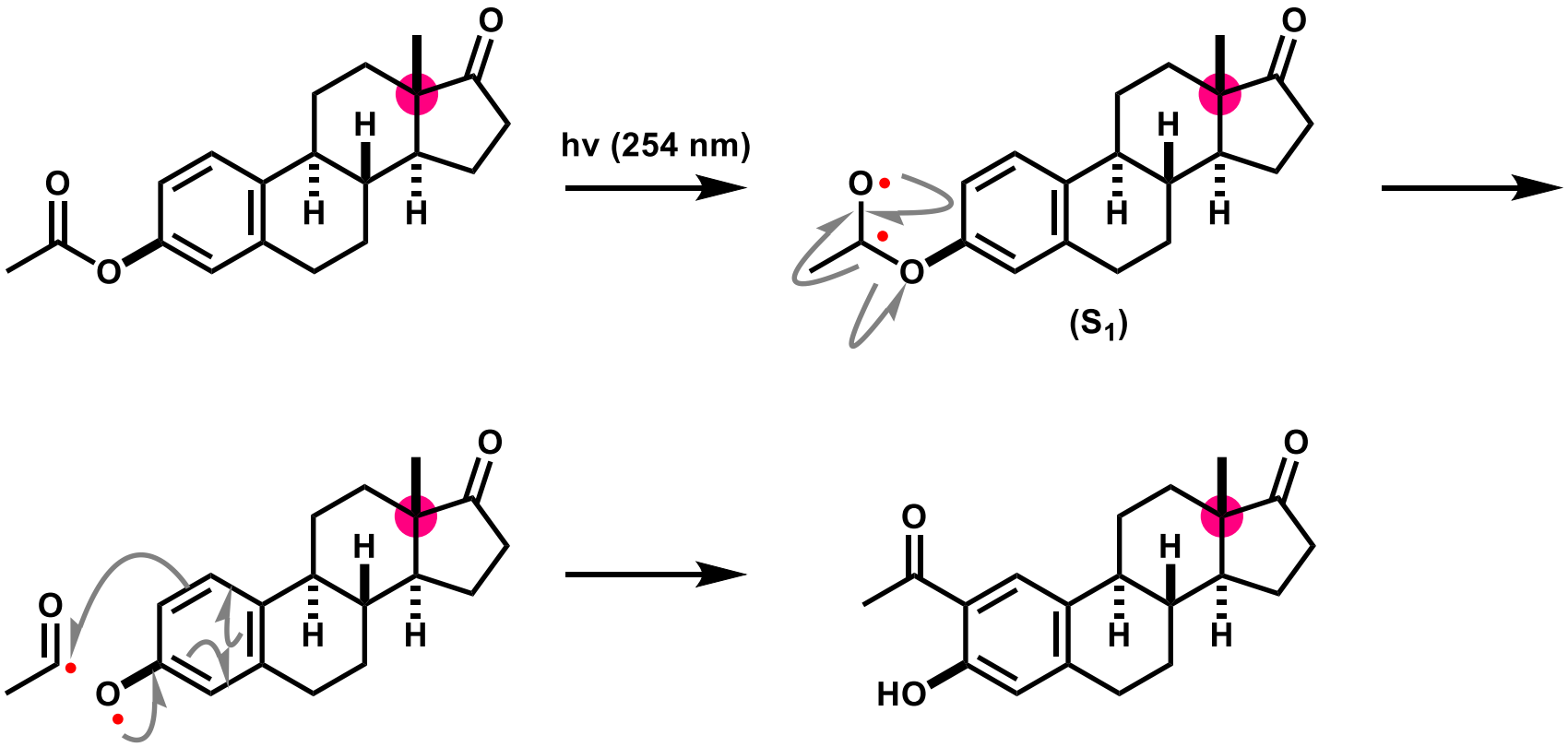




***fac*-Ir(ppy)$_3$**

1) Chen, B. B.; Wang, S.; Jiang, S. W.; Yu, Z. G.; Wan, X. G.; Ding, H. F.; Wu, D. *New J. Phys.* **2015**, *17*, 013004.

Photo-Fries Rearrangement



1) Quindt, M. I.; Gola, G. F.; Ramirez, J. A.; Bonesi, S. M.; *J. Org. Chem.* **2019**, *84*, 7051.

Emission Spectra with Protic Solvent

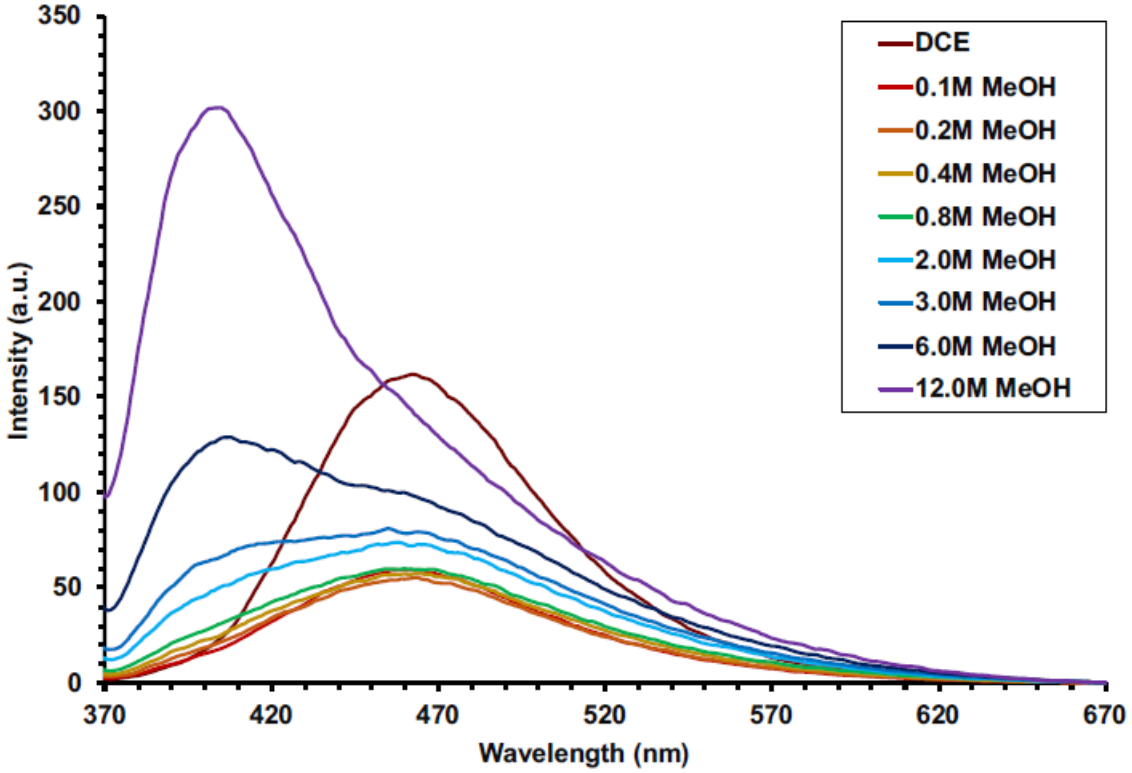
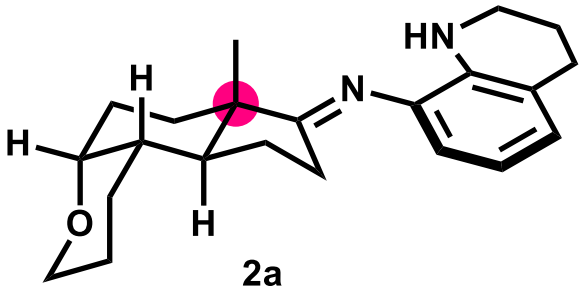


Figure SI-26. Emission spectra of **2a** with different MeOH concentrations in DCE.



2a

The presence of an intramolecular hydrogen bond, which can be perturbed by the addition of a protic solvent.