

Highly Enantioselective 6 π Photoelectrocyclizations Engineered by Hydrogen Bonding

Julien Lee Heberling
Shenvi Lab
Department of Chemistry
Scripps Research
10 February 2024

Introduction

J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JACS

Article

Highly Enantioselective 6π Photoelectrocyclizations Engineered by Hydrogen Bonding

Wesley B. Swords,[†] Hanna Lee,[†] Yerin Park, Franco Llamas, Kazimer L. Skubi, Jiyong Park, Ilia A. Guzei, Mu-Hyun Baik,^{*} and Tehshik P. Yoon^{*}

Cite This: *J. Am. Chem. Soc.* 2023, 145, 27045–27053

Read Online

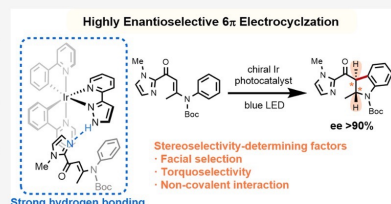
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: Photochemical electrocyclization reactions are valued for both their ability to produce structurally complex molecules and their central role in elucidating fundamental mechanistic principles of photochemistry. We present herein a highly enantioselective 6π photoelectrocyclization catalyzed by a chiral Ir(III) photosensitizer. This transformation was successfully realized by engineering a strong hydrogen-bonding interaction between a pyrazole moiety on the substrate and a basic imidazolyl ketone on the substrate. To shed light on the origin of stereoinduction, we conducted a comprehensive investigation combining experimental and computational mechanistic studies. Results from density functional theory calculations underscore the crucial role played by the prochirality and the torquoselectivity in the electrocyclization process as well as the steric demand in the subsequent [1,4]-H shift step. Our findings not only offer valuable guidance for developing chiral photocatalysts but also serve as a significant reference for achieving high levels of enantioselectivity in the 6π photoelectrocyclization reaction.



Mu-Hyun “Mookie” Baik

- Vordiplom (BS), Heinrich-Heine Universität Düsseldorf (1991-1995)
- PhD, UNC Chapel Hill (Cynthia K. Schauer) (1995-2000)
- Postdoc, Columbia (Richard A. Friesner)

- Faculty at KAIST since 2015
- Former faculty at Indiana University, 2003-2015

- Computational chemistry, focusing on the mechanism of organometallic catalysts
- Seeks to predict new catalysts



Tehshik Yoon

- AB, Harvard (David A. Evans) (1992-1996)
- MS, CalTech (Erick M. Carreira) (1996-1998)
- PhD, CalTech / UC Berkeley (David W.C. MacMillan) (2000-2002; 1998-2000)
- Postdoc, Harvard (Eric N. Jacobsen) (2002-2005)

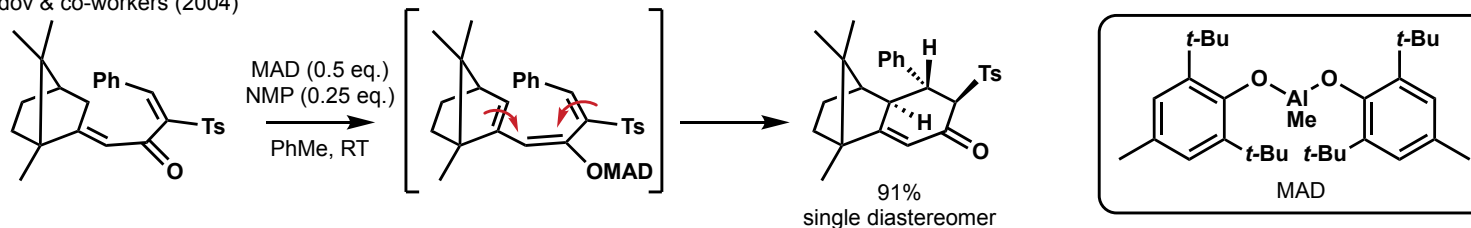
- Faculty at UW Madison since 2005

- Methodology-driven, specializing in the controlled synthesis of complex molecules via photochemistry

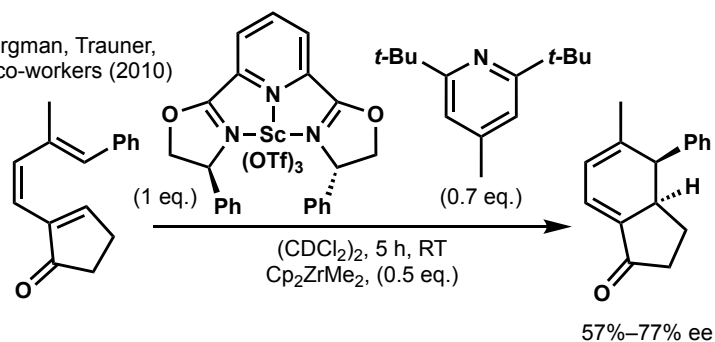
Context

Thermal: 6π disrotatory

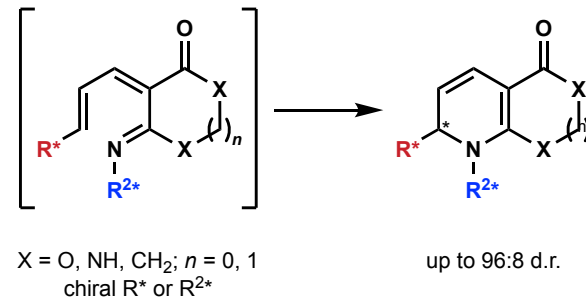
Magomedov & co-workers (2004)



Bergman, Trauner,
& co-workers (2010)

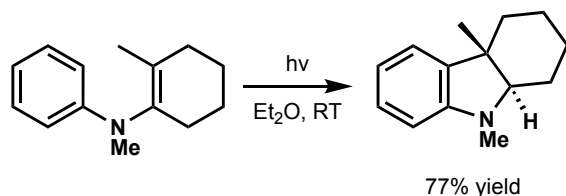


Hsung & co-workers (2008)

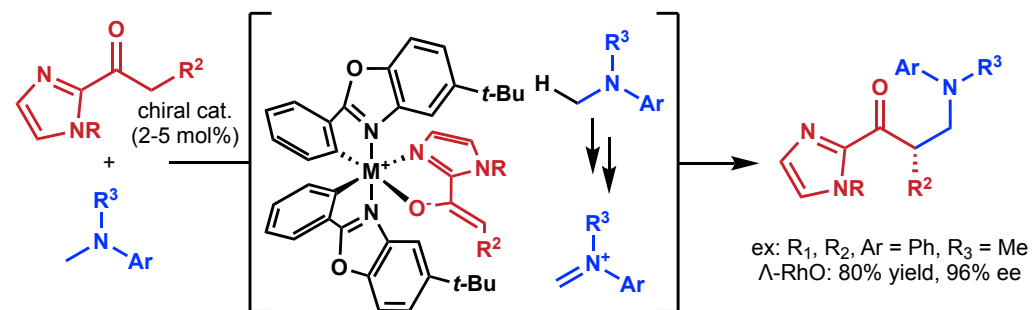


Photochemical

Chapman & co-workers (1968)



Gong, Meggers, & co-workers (2015)



Thompson, S.; Coyne, A. G.; Knipe, P. C.; Smith, M. D. *Chem. Soc. Rev.* **2011**, *40*, 4217

Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *Org. Lett.* **2004**, *6*, 3373

Bishop, L. M.; Roberson, R. E.; Bergman, R. G.; Trauner, D. *Synthesis* **2010**, 2233

Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *64*, 883

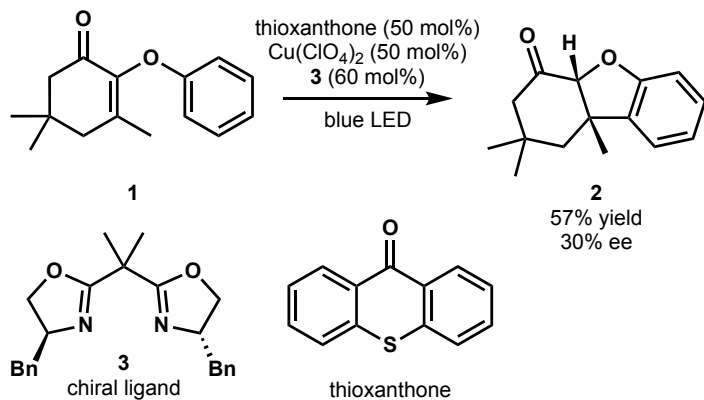
Chapman, O. L.; Eian, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5329

Huang, X.; Meggers, E. *Acc. Chem. Res.* **2019**, *52*, 833

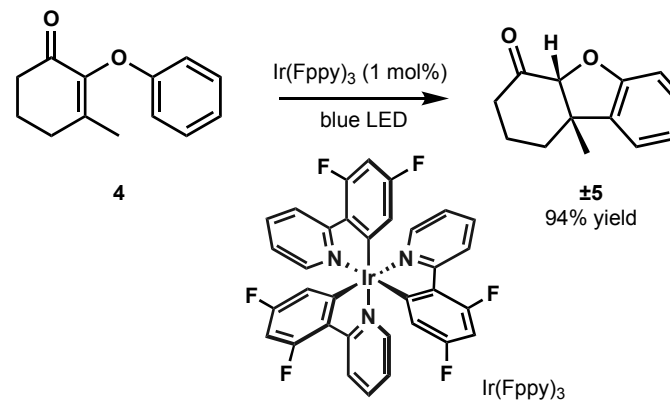
Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 13045

Previous Photocatalytic Electrocyclizations

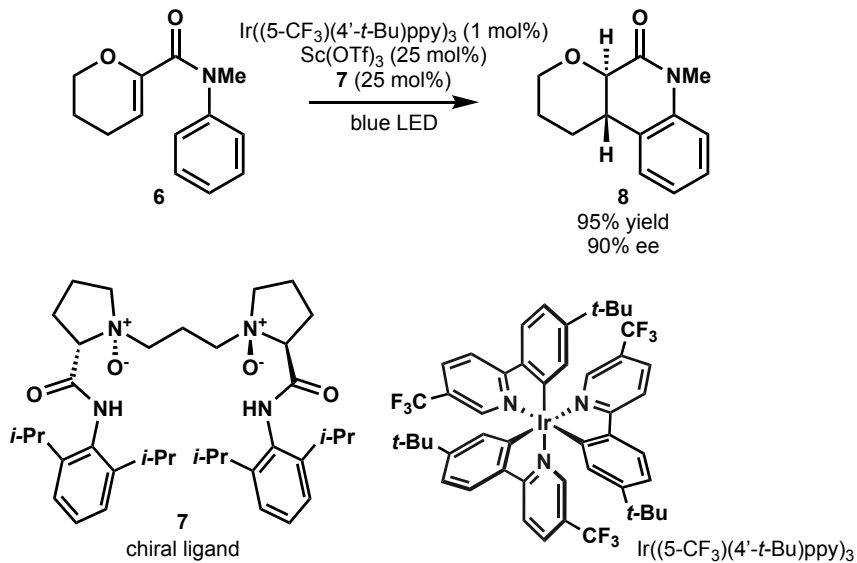
Bach & co-workers (2017)



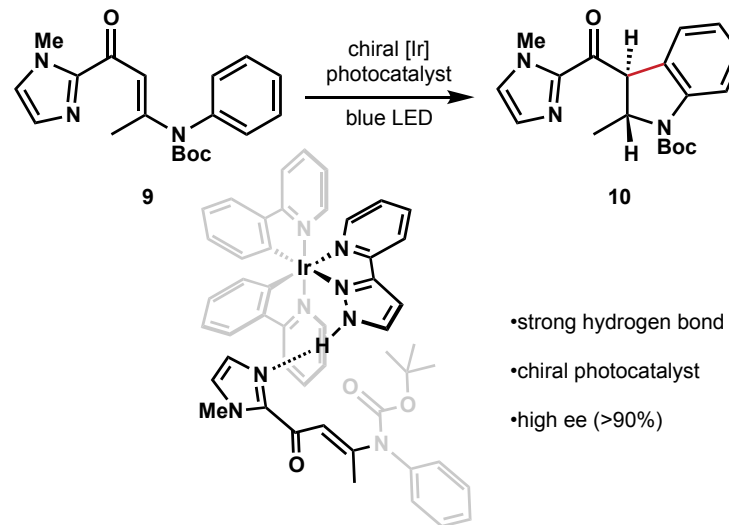
Paton, Smith, & co-workers (2017)



Paton, Smith, & co-workers (2022)

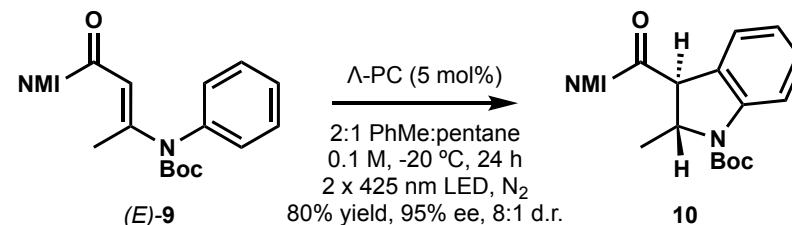


Baik, Yoon, & co-workers (2023)



Reaction Optimization

entry	modification	yield	d.r.	ee
1	PhMe	57%	6:1	87%
2	CH ₂ Cl ₂	29%	3:1	87%
3	MeCN	17%	3:1	53%
4	20 °C	60%	8:1	73%
5	-40 °C	58%	5:1	96%
6	1 mol% Λ -PC	39%	5:1	74%
7	0.01 M	55%	7:1	82%
8	in air	<5%	–	–
9	dark	0%	–	–
10	no Λ -PC	0%	–	–
11	(Z)- 9	84%	8:1	91%
13	11 instead of 9	0%	–	–
14	12 instead of 9	0%	–	–
15	13 instead of 9	0%	–	–



- Λ -PC serves both as a photosensitizer and as a chiral ligand to enhance enantioselectivity

- Presence of a **carbamate** (with Boc or Fmoc) is required for the reaction to work

- The PC can only transfer the energy to the substrate with a carbamate

- Cyclized product from tertiary amine **12** decomposes

- Triplet energies based on calculations:

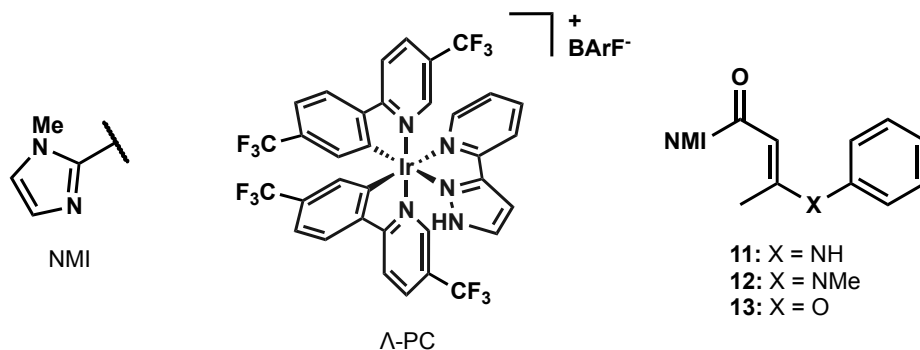
- carbamate: 50.9 kcal·mol⁻¹

- secondary amine: 53.4 kcal·mol⁻¹

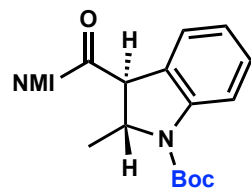
- ether: 54.0 kcal·mol⁻¹

- Presence of the **imidazole** (NMI) allows for hydrogen bonding between Λ -PC and the substrate

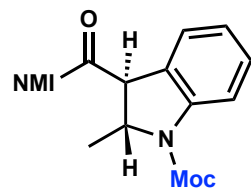
- Binding of the substrate to the photocatalyst post energy transfer promotes the enantioselectivity



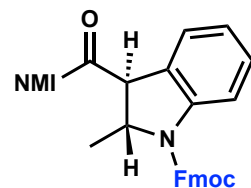
Substrate Scope



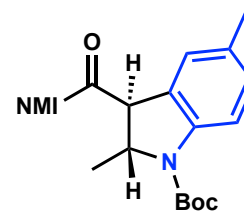
10
71% yield
93% ee, 8:1 d.r.



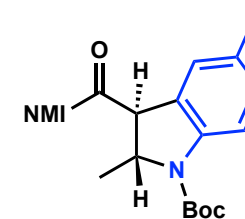
14
48% yield
82% ee, 3:1 d.r.



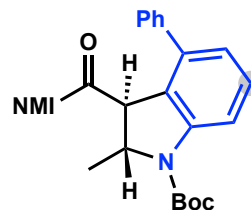
15
62% yield
93% ee, 10:1 d.r.



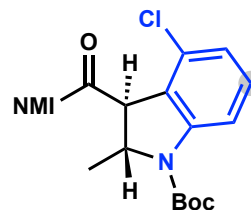
16
49% yield
89% ee, 5:1 d.r.



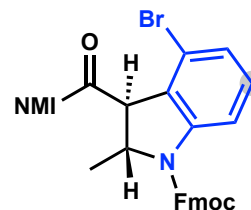
17
9% yield
74% ee, 9:1 d.r.



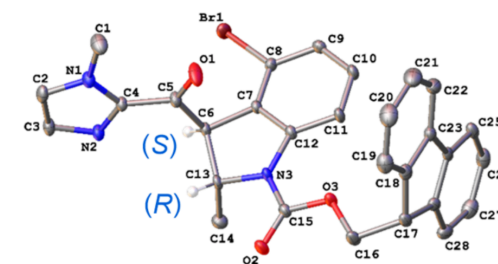
18
89% yield
96% ee, 1.1:1 r.r., 5:1 d.r.



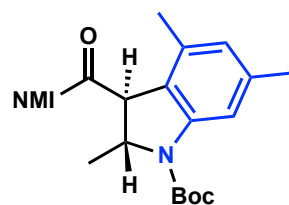
19
55% yield
96% ee, 2.5:1 r.r., 8:1 d.r.



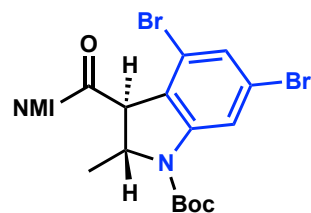
20
81% yield
97% ee, 2:1 r.r., >10:1 d.r.



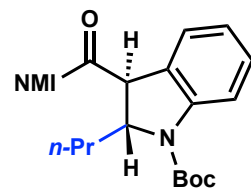
20 (x-ray)



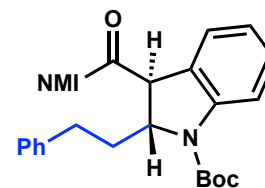
21
76% yield
93% ee, 1.1:1 d.r.



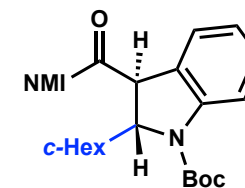
22
71% yield
96% ee, 10:1 d.r.



23
56% yield
94% ee, 12:1 d.r.

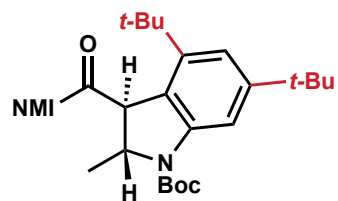


24
82% yield
93% ee, 10:1 d.r.

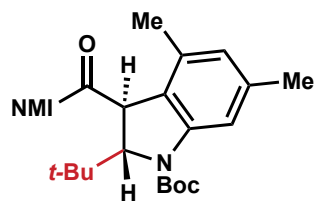


24
82% yield
93% ee, 10:1 d.r.

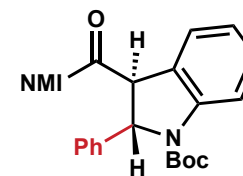
Incompatible Substrates



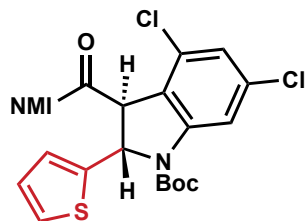
10% yield
(80% r.s.m.)



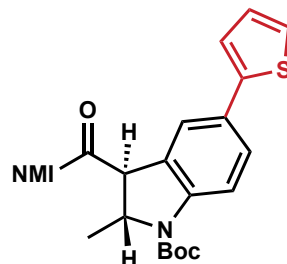
0% yield
(90% r.s.m.)



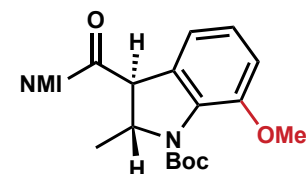
5% yield
(85% r.s.m.)



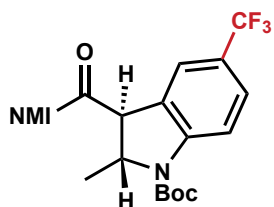
4% yield
(92% r.s.m.)



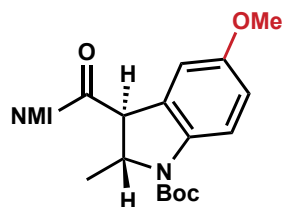
21% yield
64% ee, (56% r.s.m.)



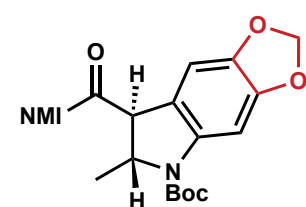
0% yield
(89% r.s.m.)



16% yield
23% ee, (72% r.s.m.)

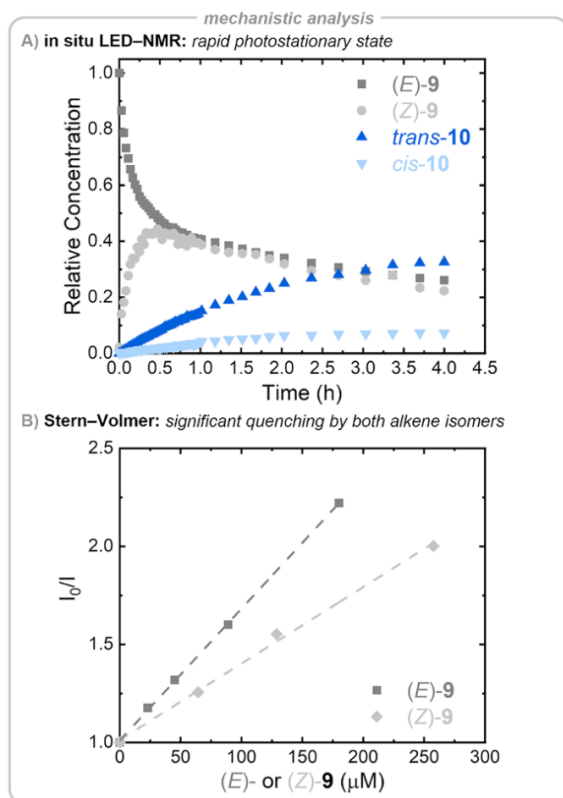


33% yield
50% ee, (30% r.s.m.)



35% yield
55% ee, (8% r.s.m.)

Mechanistic Inquiry

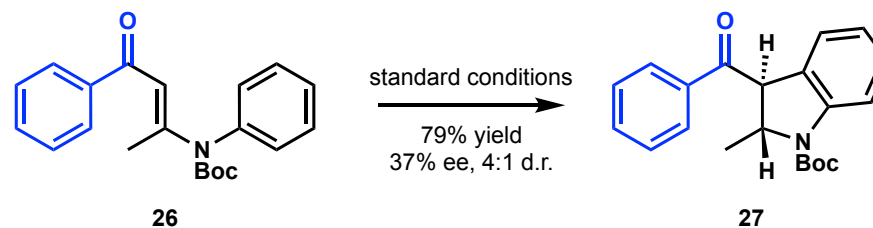


A) Reaction profile monitoring the concentrations of (*E*) & (*Z*) olefin starting materials, as well as *cis* & *trans* products

B) Stern-Volmer plot, showing quenching of Λ -PC via both (*E*) & (*Z*) olefins

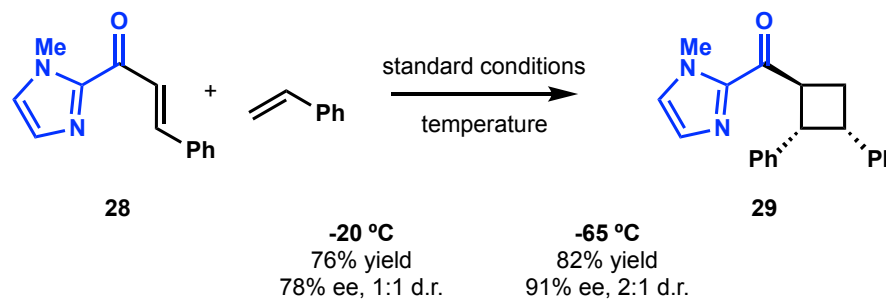
- likely through energy transfer (oxidation & reduction potentials of Λ -PC are too low to perform either redox process)

Testing the reaction without NMI



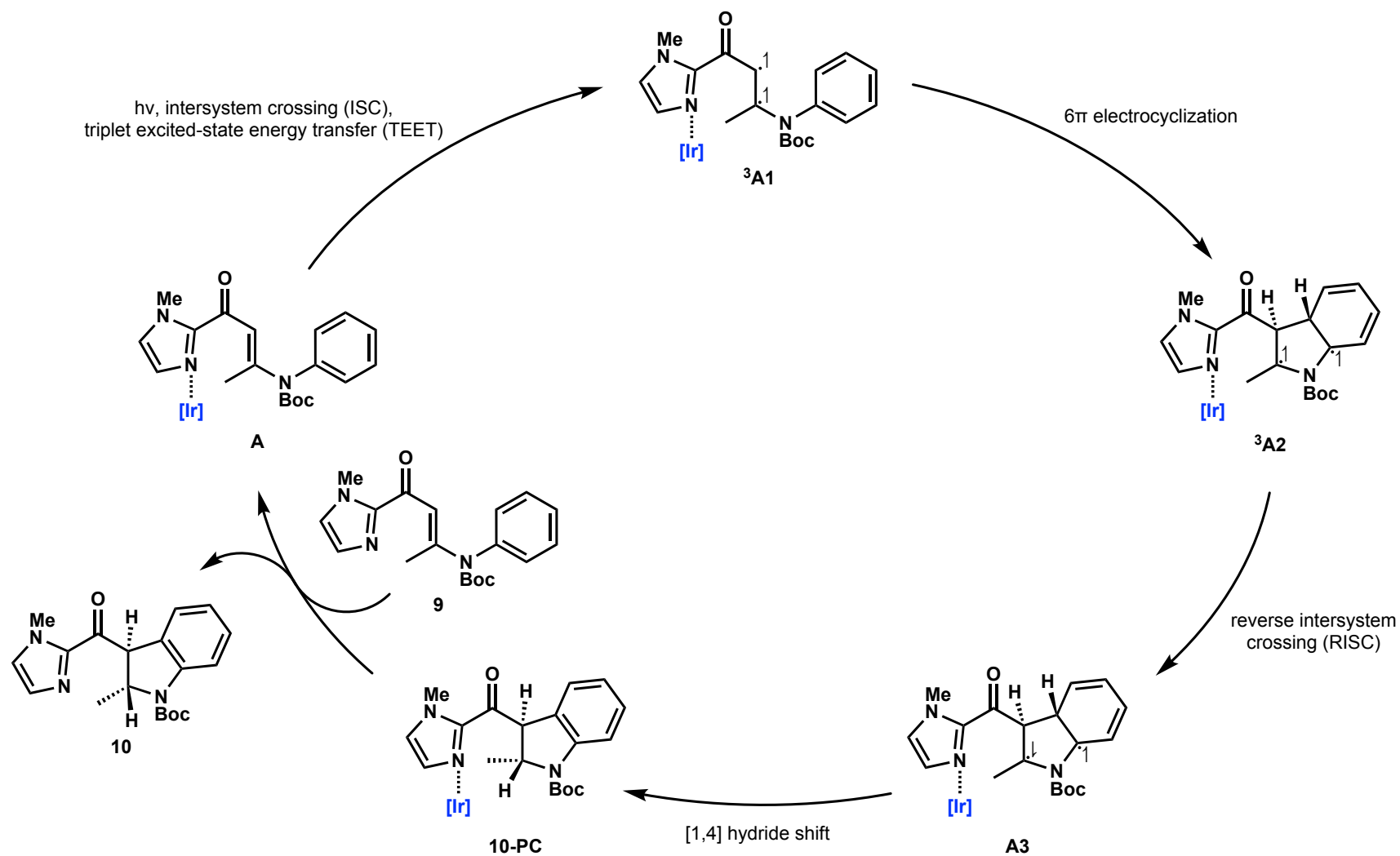
- In the absence of NMI, reduced hydrogen bonding interaction between substrate and Λ -PC results in lower ee

Performing [2+2] cycloaddition

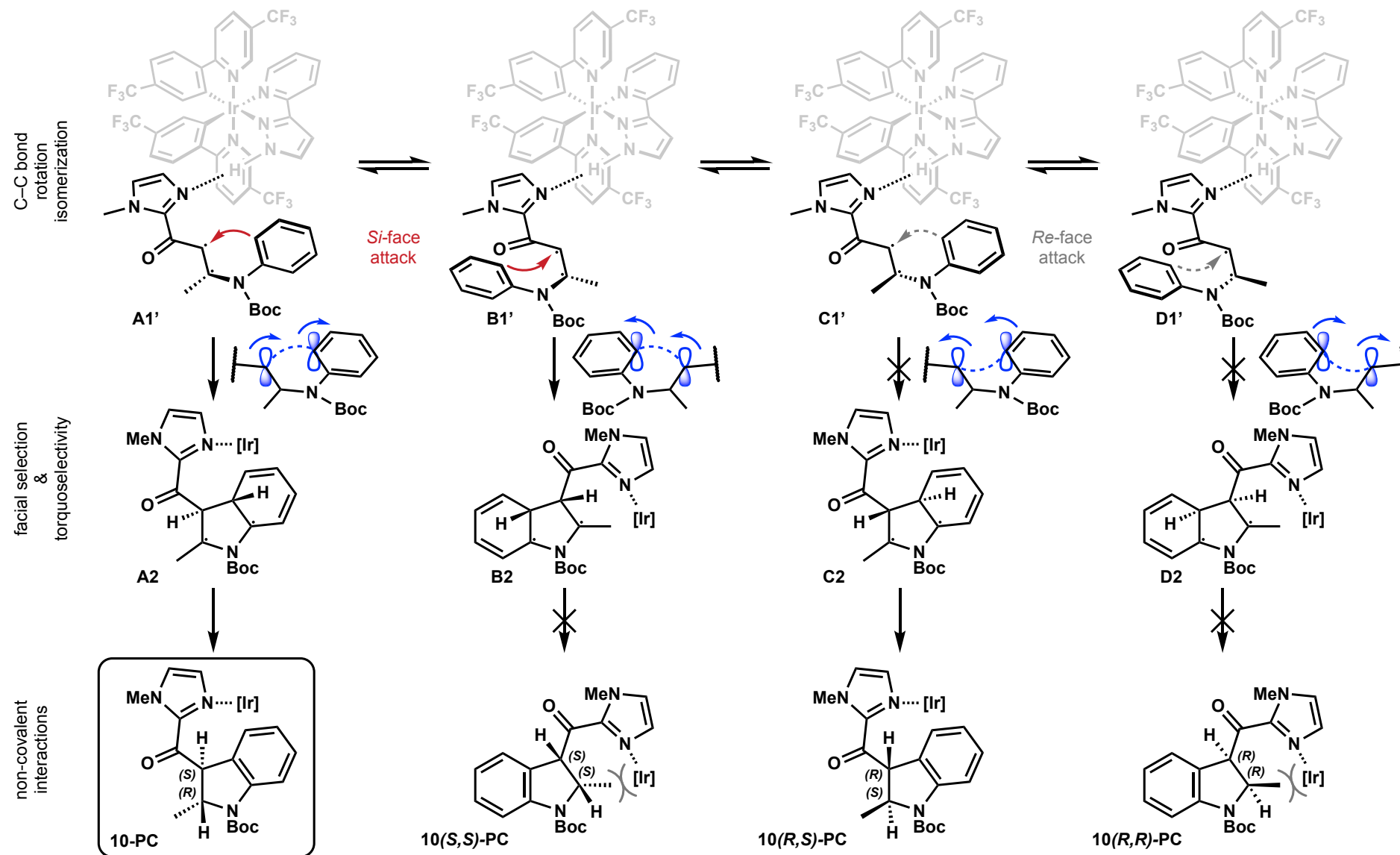


- The presence of NMI in enone **28** performs with relatively good ee (up to 91% ee at -65 °C) in the [2+2] cycloaddition

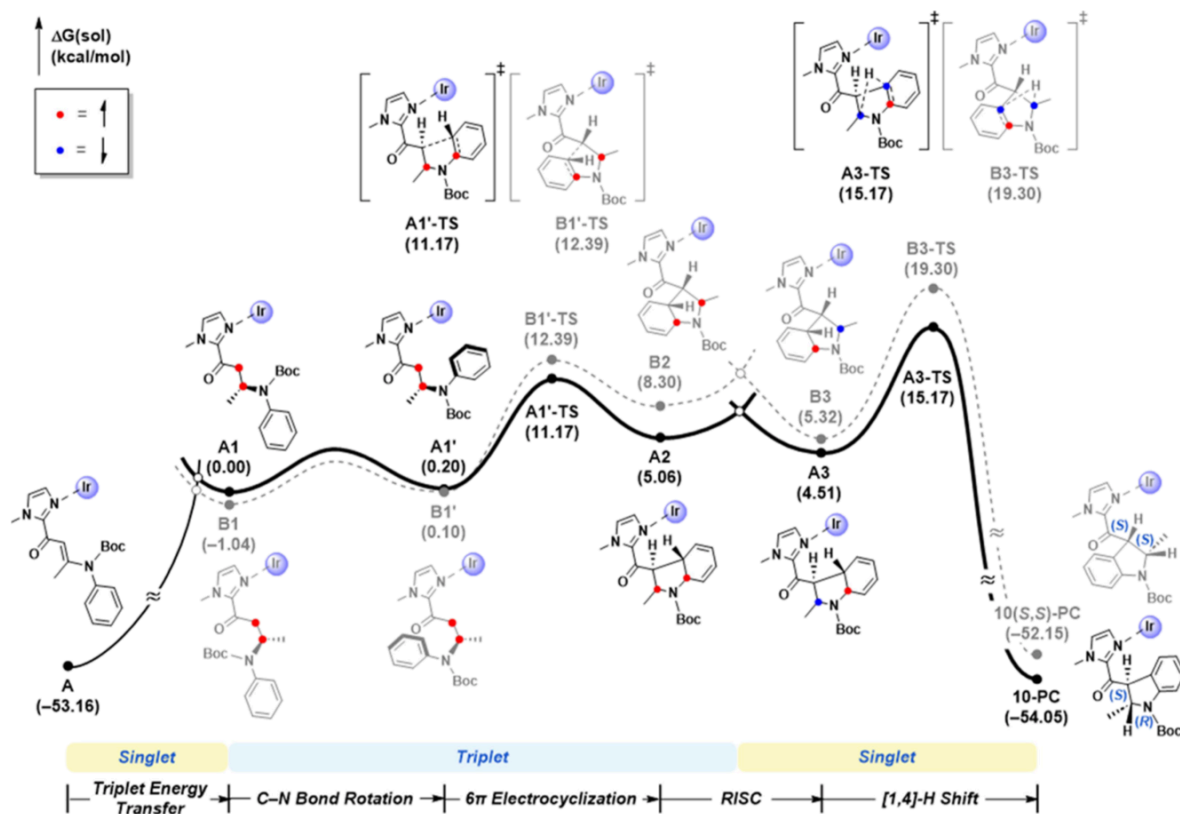
Proposed Mechanism



Stereodetermining Factors



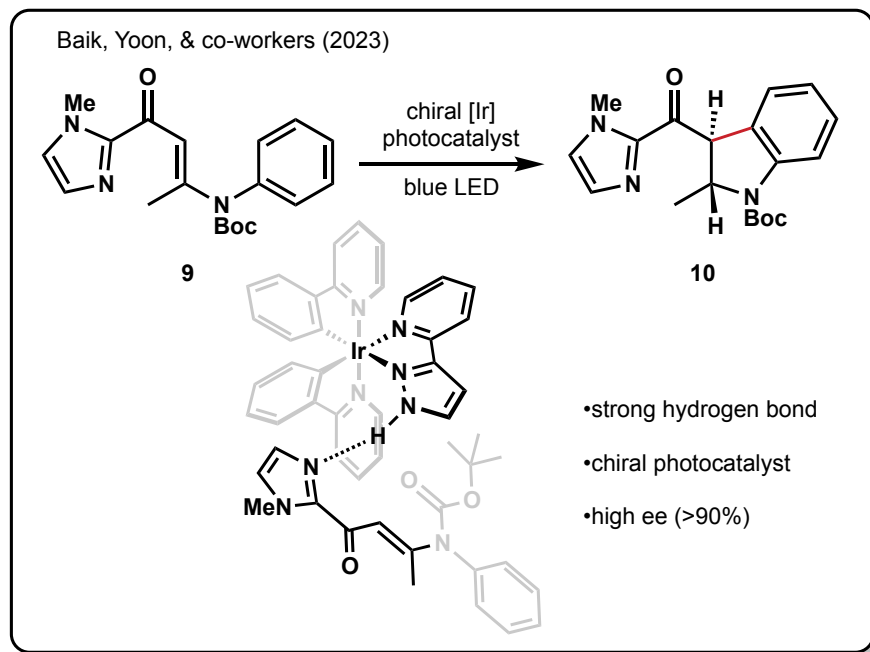
Computational Studies



•Viable encounter complexes A and B, with their respective free energies (kcal·mol⁻¹)

•6 π electrocyclization energy diagram, differentiating both profiles for the formation of (S,S) and (R,S) diastereomers

Concluding Remarks



- Effective method to access indoline scaffolds with high ee, and reasonable to high yield on a variety of substrates

- Photocatalyst serves two important purposes:

- Chiral ligand (effectuated through hydrogen bonding)
- Photosensitizer which performs an energy transfer to the substrate

- Considerations from this method:

- NMI (or potentially another strong H-bond donor) is required to achieve high ee
- Carbamate is required for the reaction to work (incompatible with secondary amine and ether, and tertiary amine decomposes)