Skeleton Crew

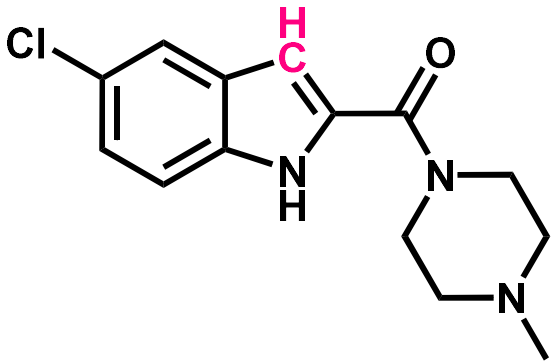
2024.12.7. Literature Seminar

D2 Kyohei Oga

Contents

Contents

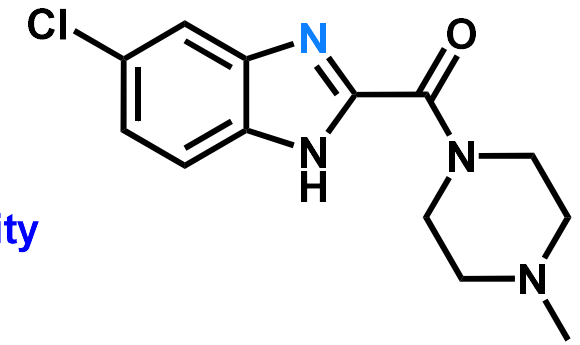
Effect of Atom Change in Medicinal Chemistry



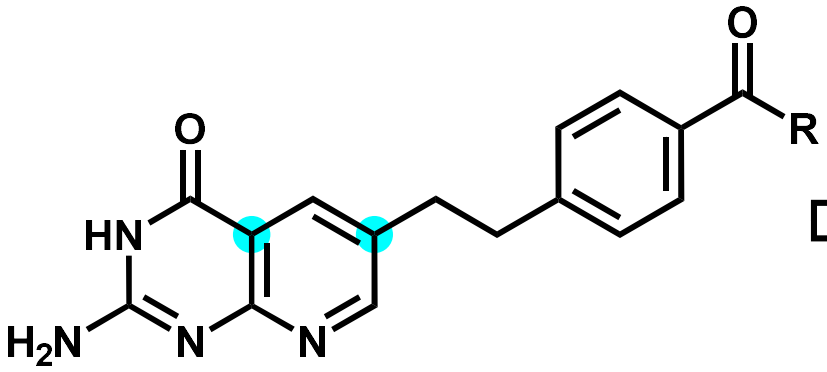
$t_{1/2}$ (HLM) = 28 min

CH → N

improving in vitro metabolic stability



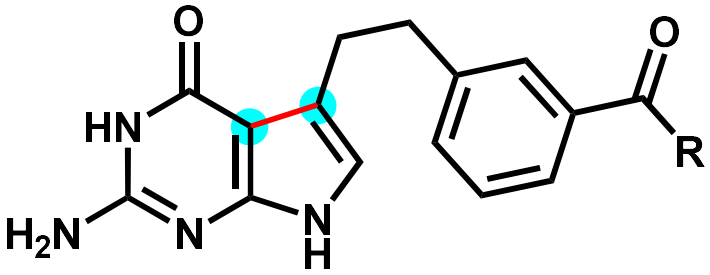
$t_{1/2}$ (HLM) = 100 min



5,10-dideazafolic acid
inactive

carbon deletion

improving activity

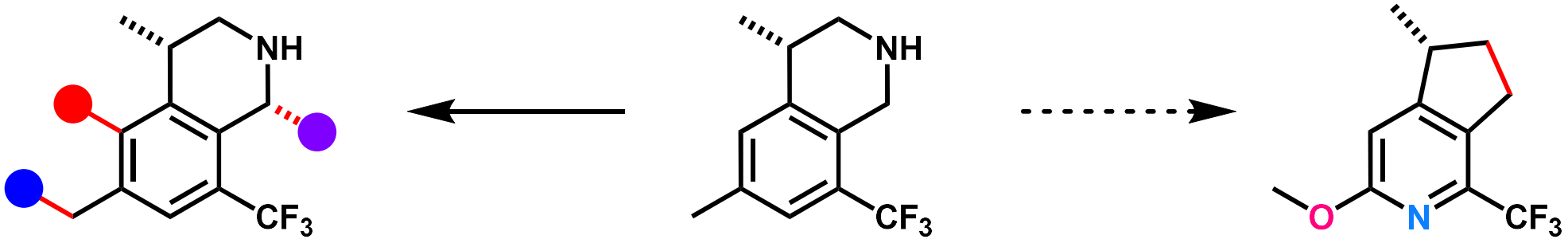


Pemetrexed (antifolate chemotherapy)
active

Medicinal chemist examine SAR by parallel synthesis → time, cost

1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

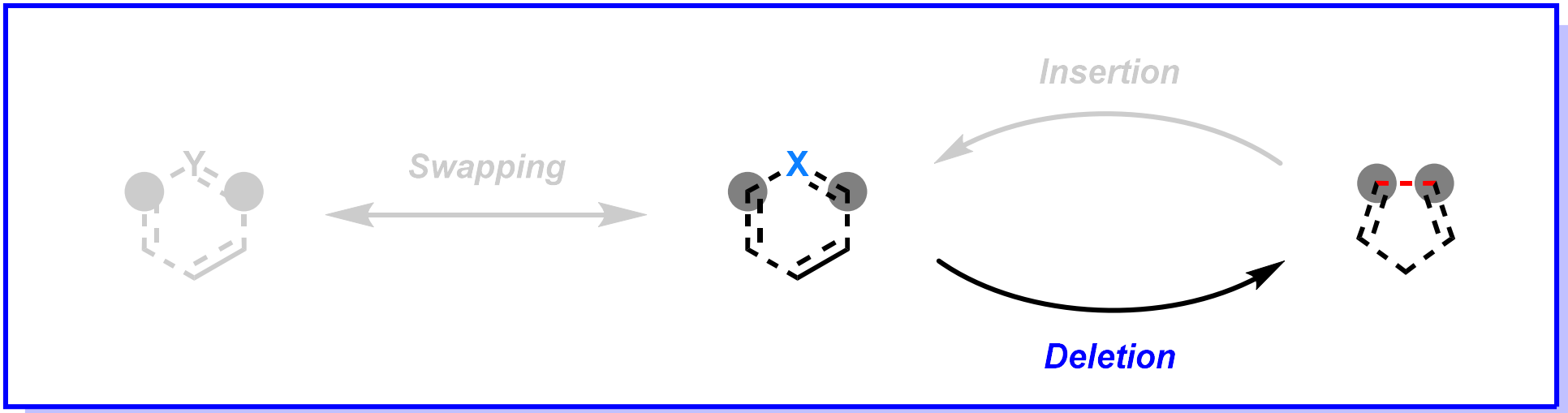
The Chemistry of Skeletal Editing



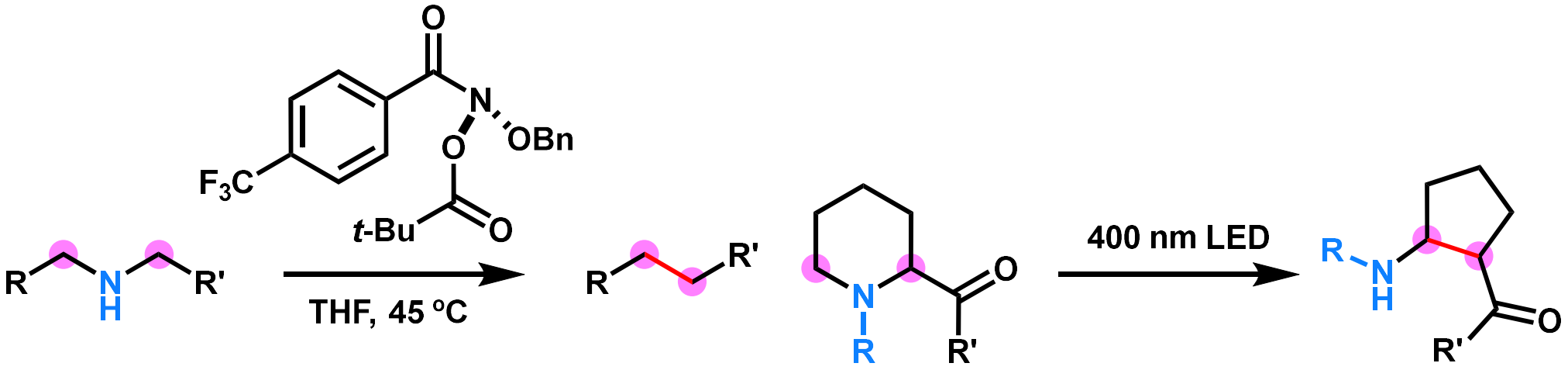
peripheral editing *original molecule* *skeletal editing*

1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Classification of Skeleton Editing / Deletion



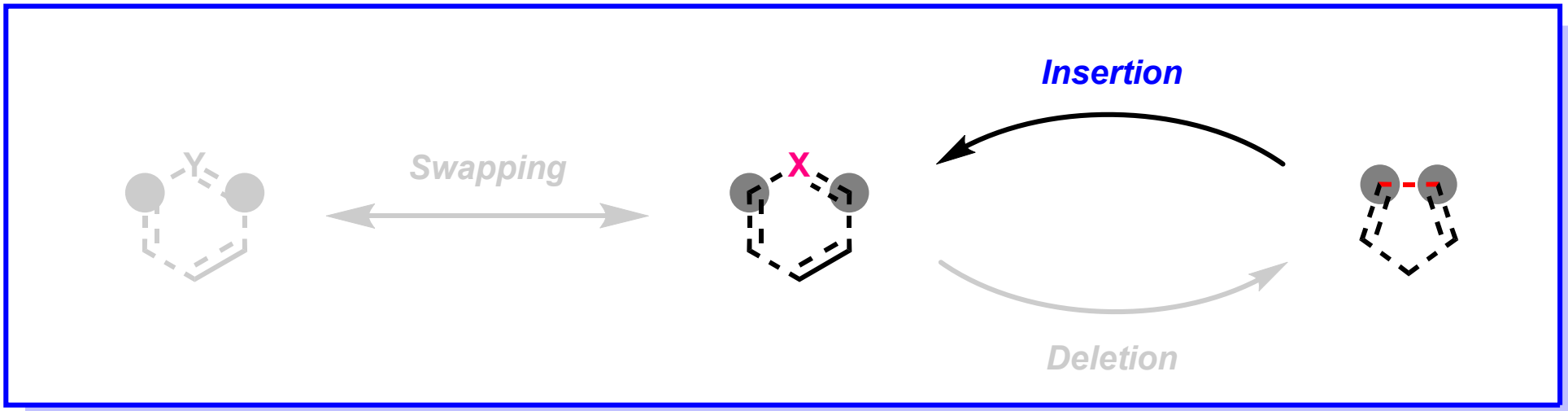
- **Nitrogen deletion**



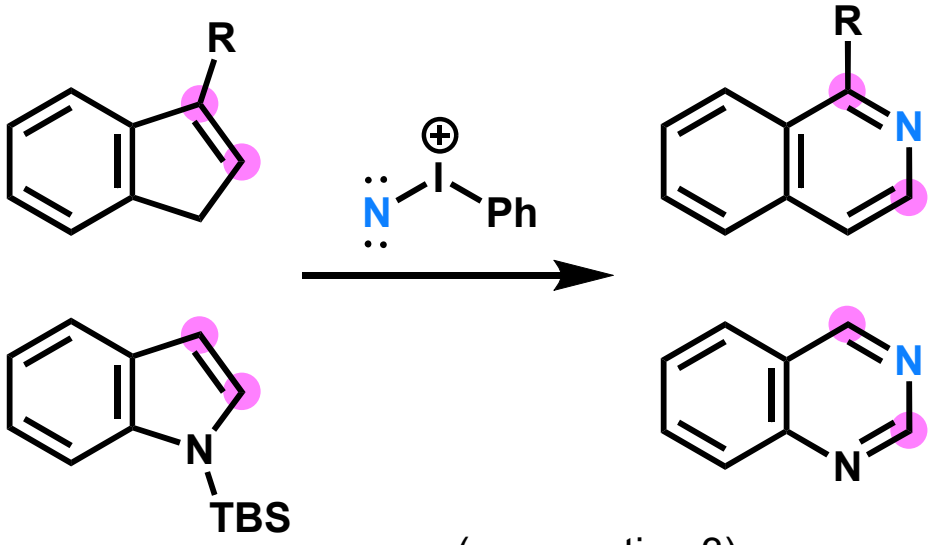
Levin, M. D. et al. *Nature* **2021**, *593*, 223.
(210529_LS_Junichi_Taguchi)

Sarpong, R. et al. *Science* **2021**, *373*, 1004.
(240406_LS_Shintaro_Fukaya)

Classification of Skeleton Editing / Insertion

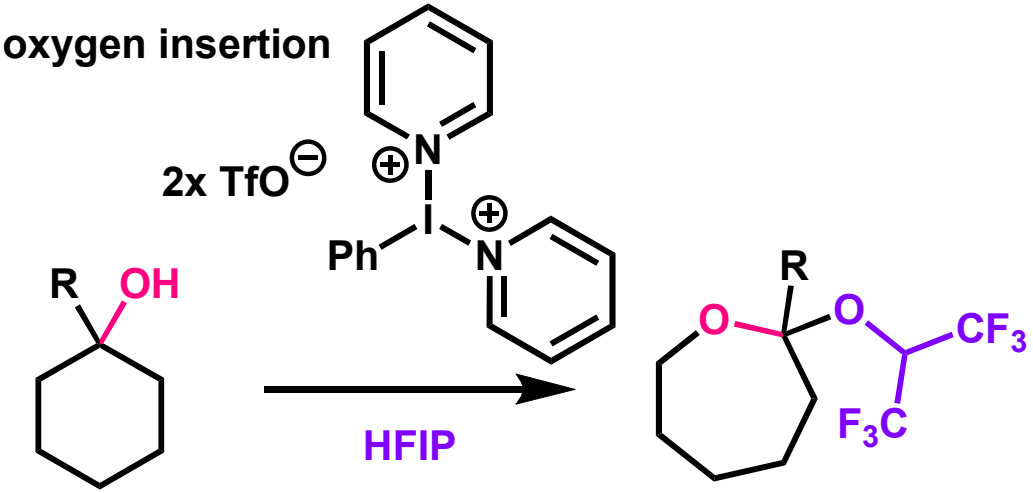


- **Nitrogen insertion**



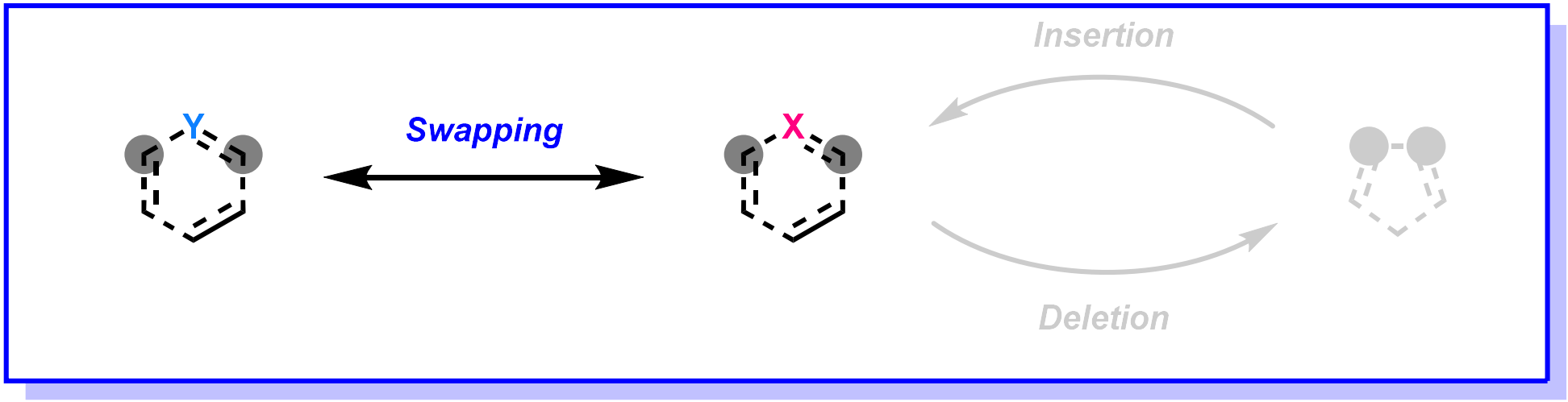
(see; section 3)

- **oxygen insertion**

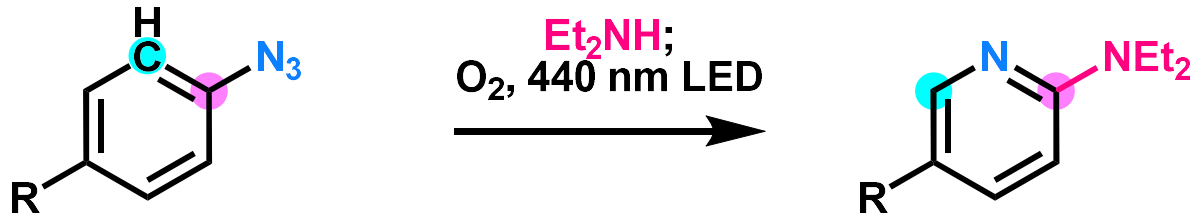


Wengryniuk. S. E. et al. *Org. Lett.* **2016**, *18*, 1896.

Classification of Skeleton Editing / Swapping

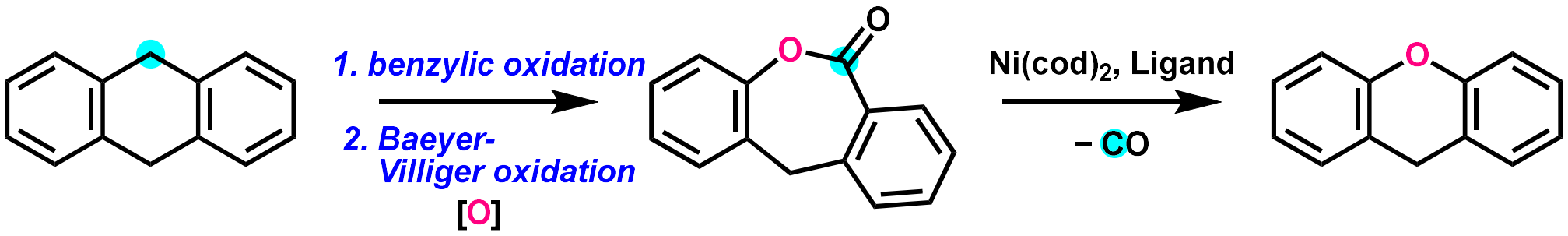


- carbon to nitrogen atom swapping



Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022,** *144*, 17797.
(230610_LS_Shuji_Toyama)

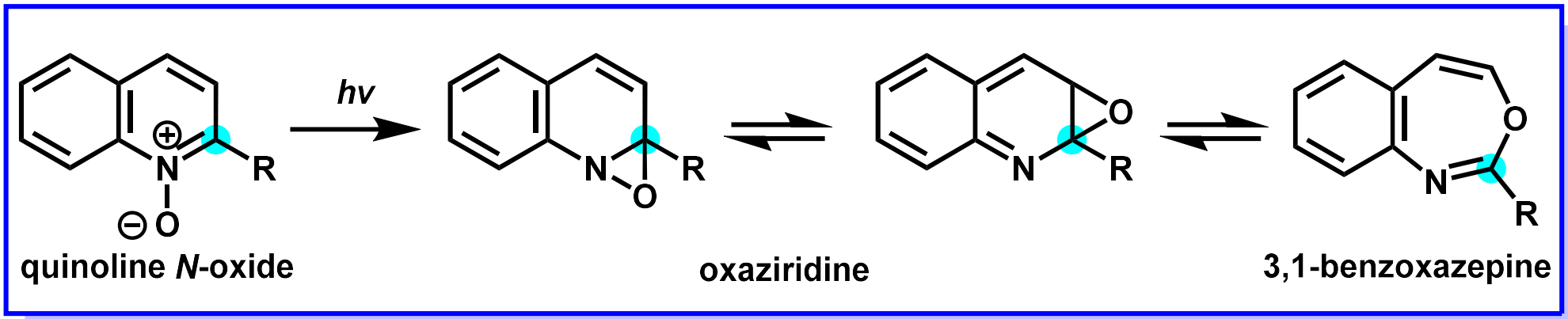
- carbon to oxygen atom swapping



Luu, Q. H.; Li, J. *Chem. Sic.* **2022,** *13*, 1095.

Contents

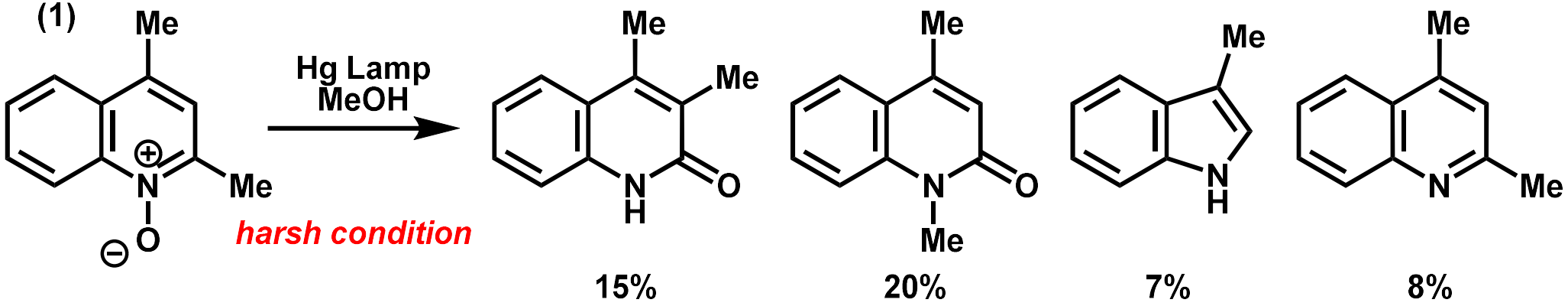
Classical N-Oxide Photochemistry



- **Prior art in quinoline-N-oxide photochemistry**

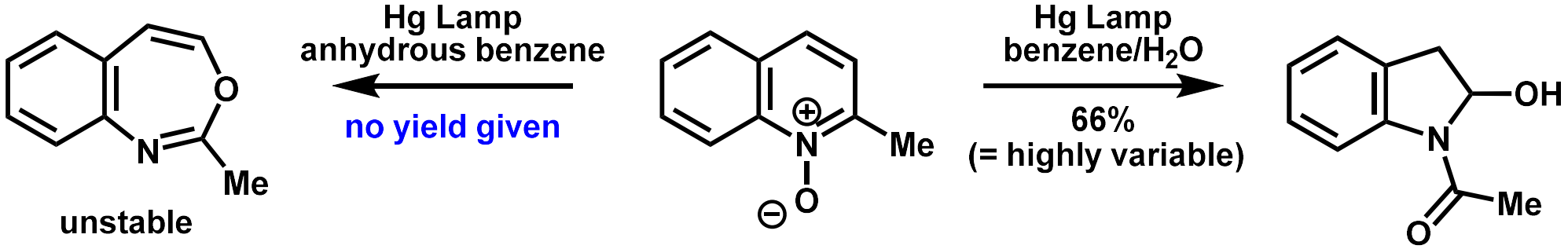
Albini, A.; Alpegiani, M. *Chem. Rev.* **1984**, *84*, 43.

(1)



Ishikawa, M.; Yamada, H.; Hotta, H.; Kaneko, C. *Chem. Pharm. Bull.* **1966**, *14*, 1102.

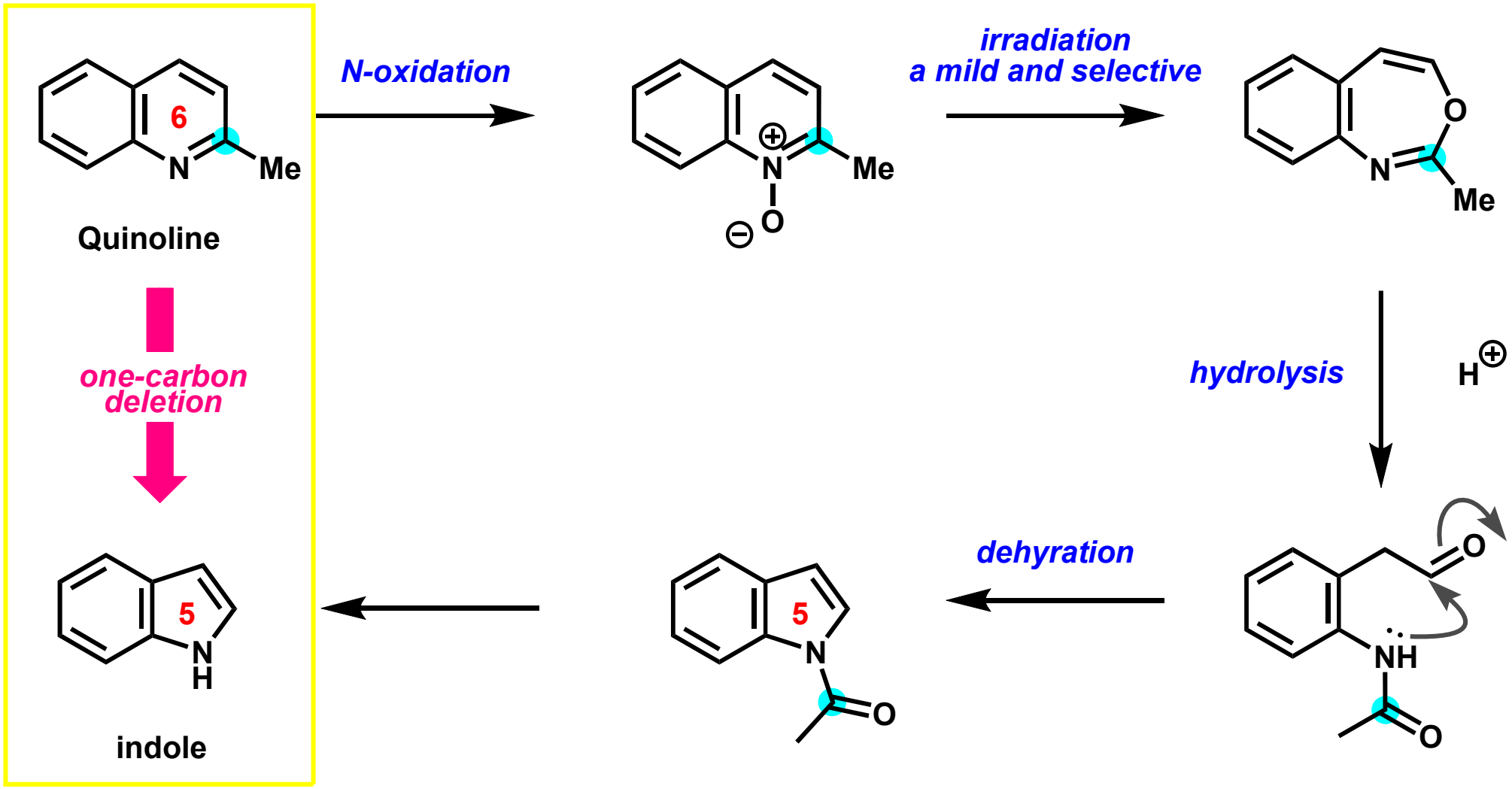
(2)



Kaneko, C. et al. *Tetrahedron Lett.* **1966**, *7*, 4701.

Buchardt, O. et al. *Acta Chem. Scand.* **1966**, *20*, 262.

Levin's Working Hypothesis



1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Prof. Mark D. Levin

-2012 B.S. @University of Rochester
(Prof. Alison J. Frontier)
-2017 Pd.D. @University of California, Berkeley
(Prof. F. Dean Toste)
-2019 Postdoctoral Fellow @ Havard University
(Prof. Eric N. Jacobsen)
-2022 Assistant Professor @University of Chicago
2022- Assosiate Professor @University of Chicago

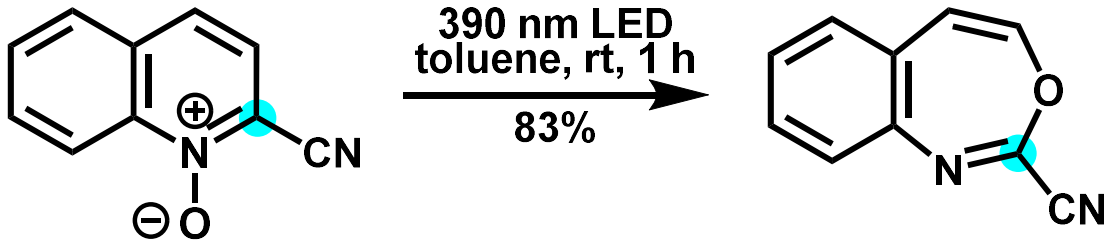
Research area:

- **Development of Synthetic Methods, Reagents**
- **Single-Atom Skeletal Editing**
- **Method for Isotope Labeling and Radiosynthesis**

https://levingroup.uchicago.edu/

Optimization of Light Sources

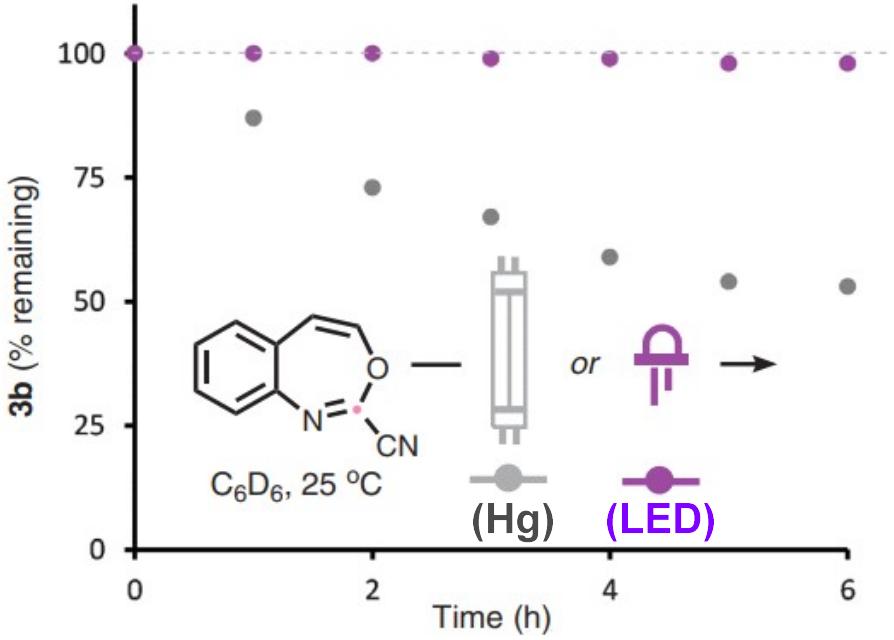
a) Synthesis of 1b



1b

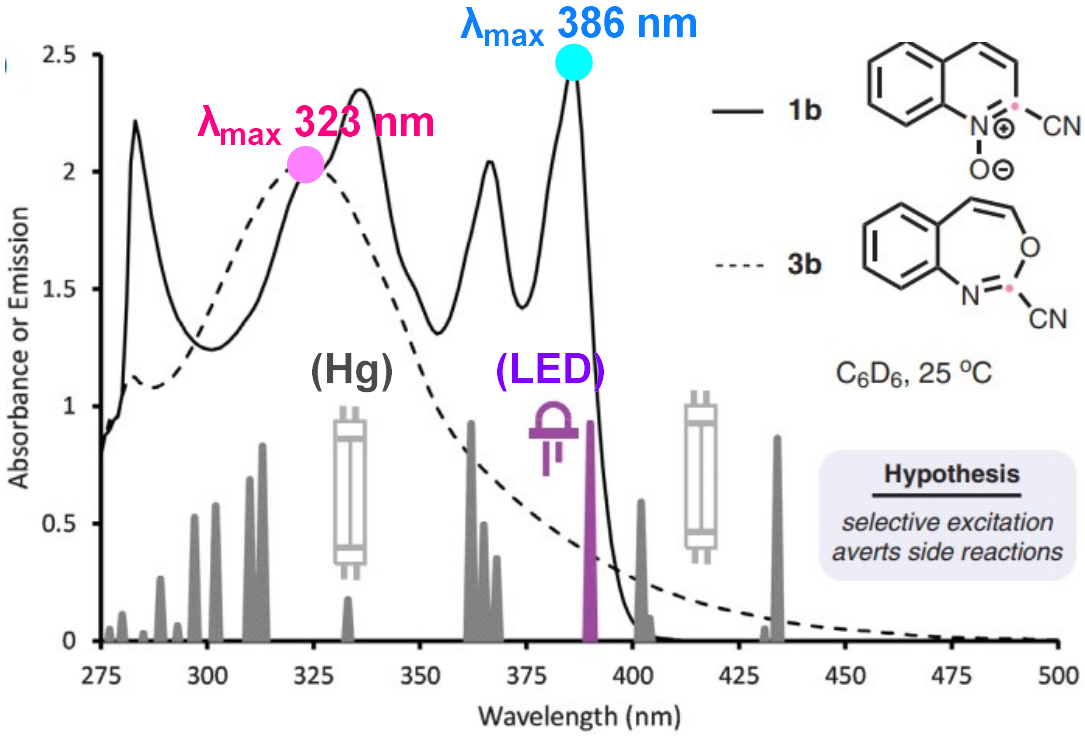
3b (isolable)

b) Photostability Test of 3b



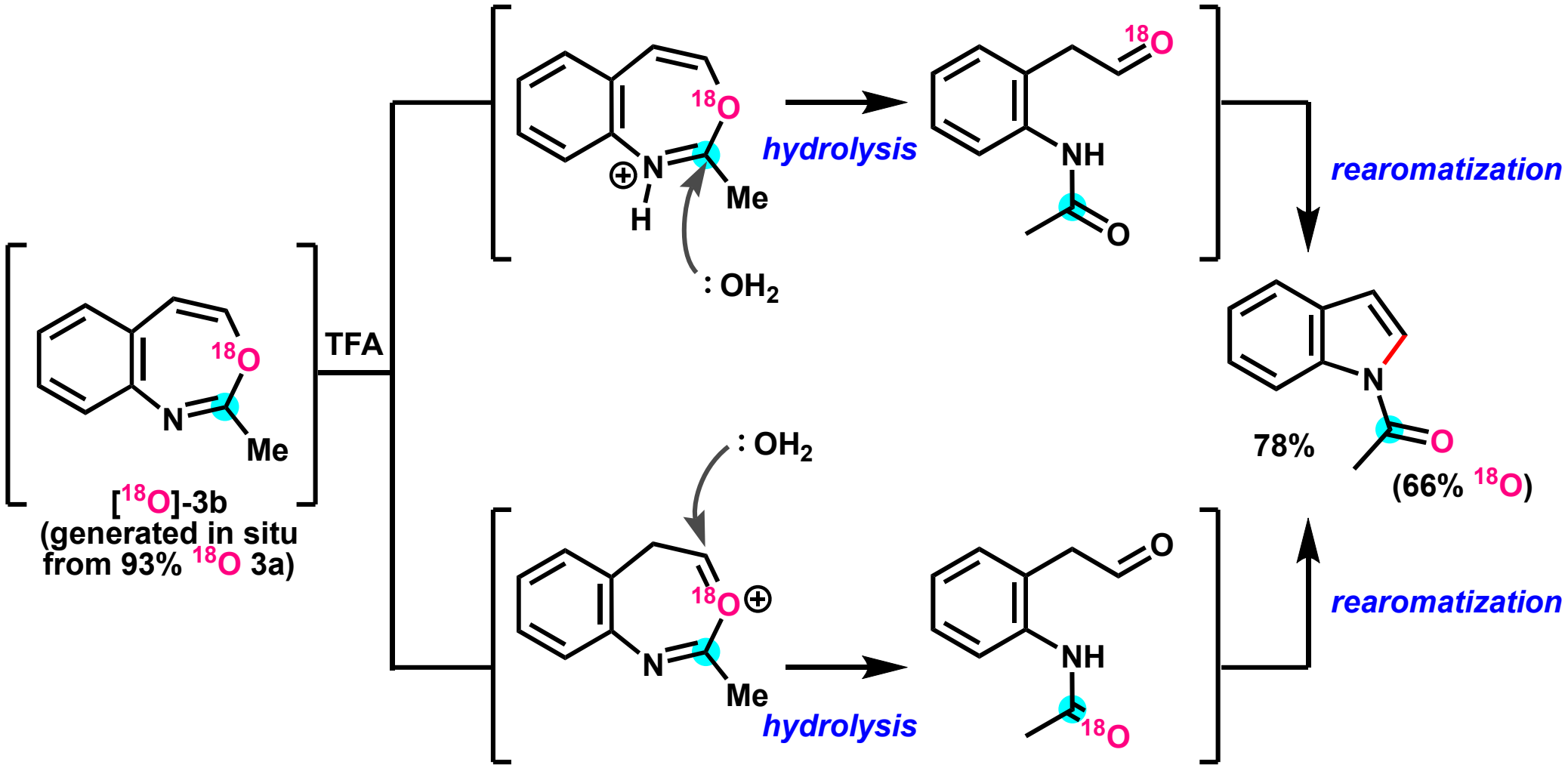
the mercury lamp promotes photodegradation of benzoxazepine

c) Ultraviolet-visible absorption of 1b and 3b



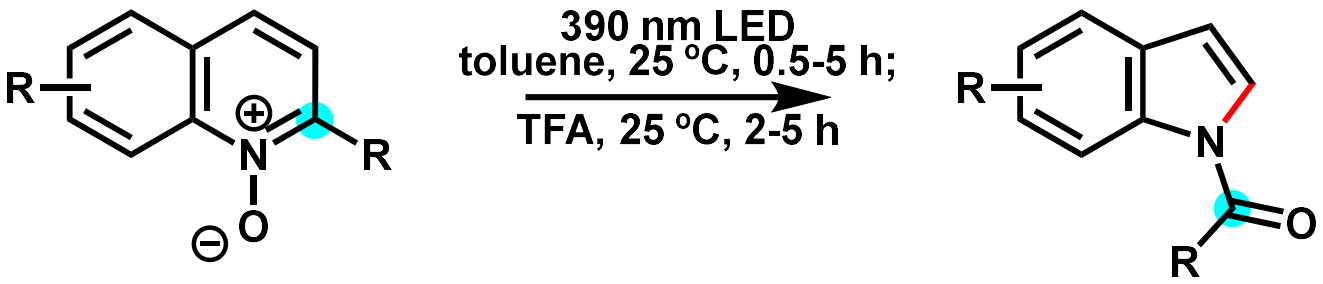
1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

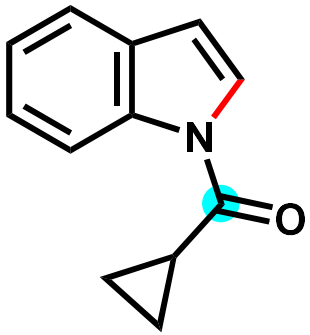
Mechanistic Study (^{18}O-Labeling Study)



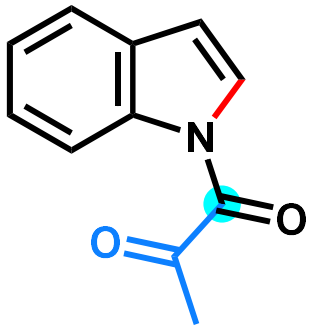
1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Substrate Scope

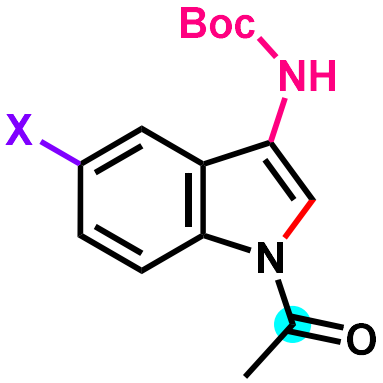




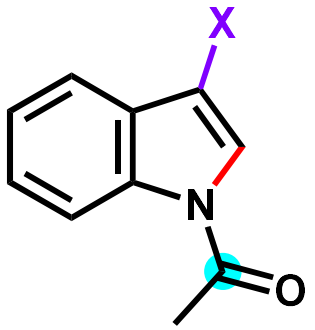
57%



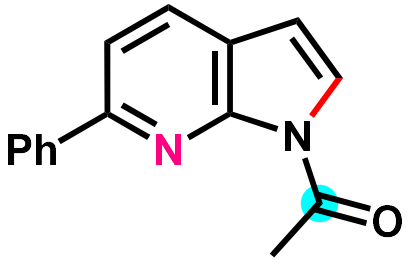
52%
[Hg Lamp: 10%]



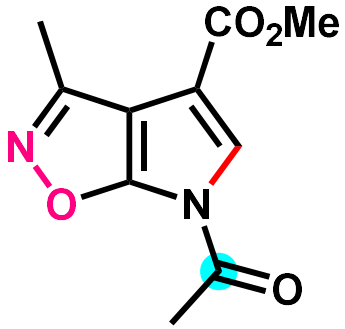
X = H, 83% [Hg Lamp: 0%]
X = Br, 67% [Hg Lamp: 0%]



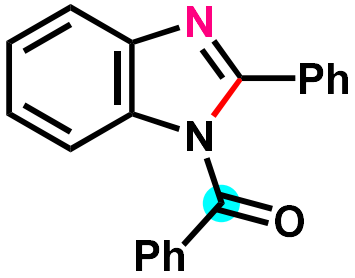
X = SO_2Me, 53% [Hg Lamp: 0%]
X = Cl, 64% [Hg Lamp: 13%]



71%



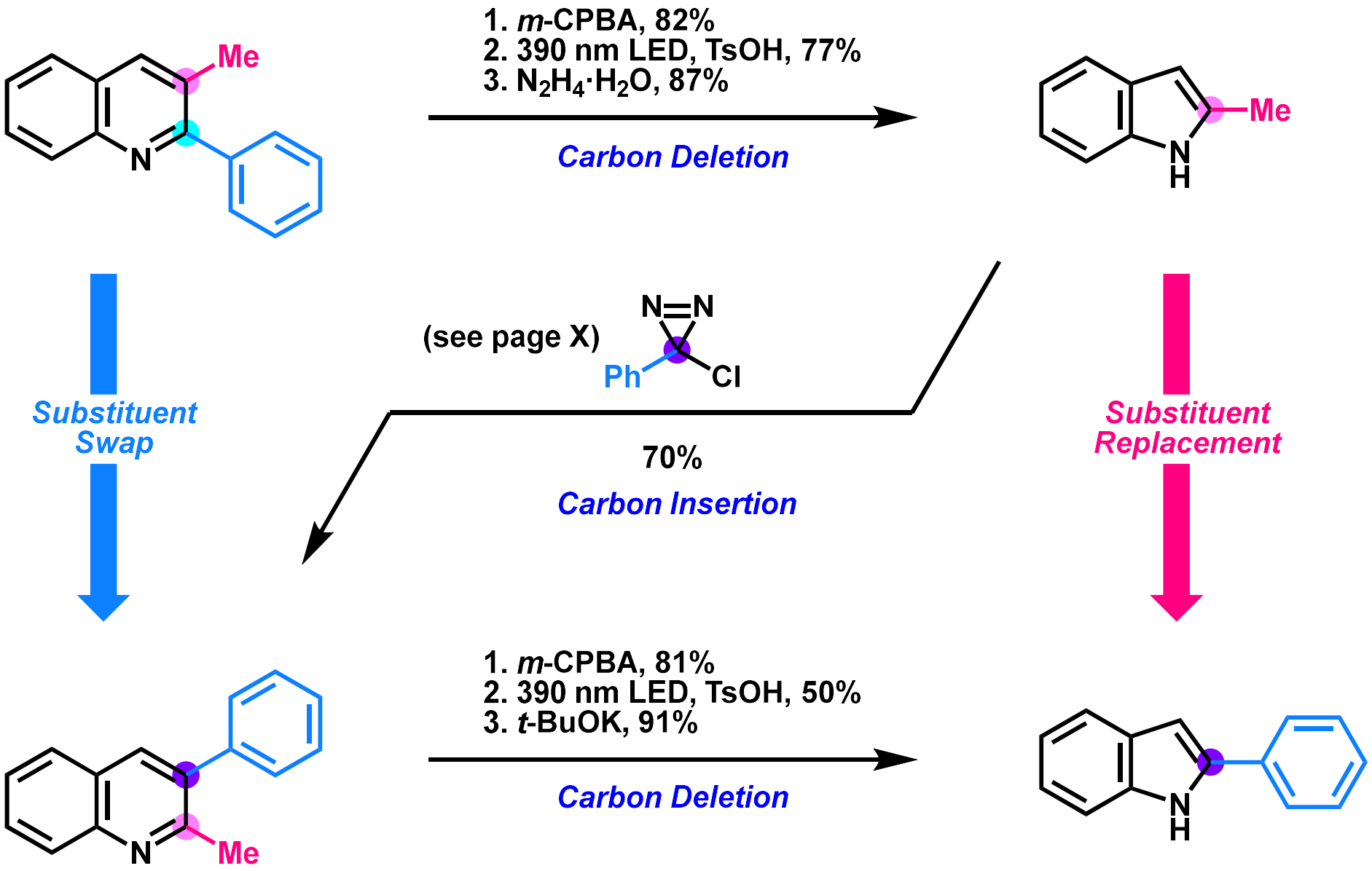
27%
[Hg Lamp: 3%]



29%

1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Application for Scaffold Hopping Strategies

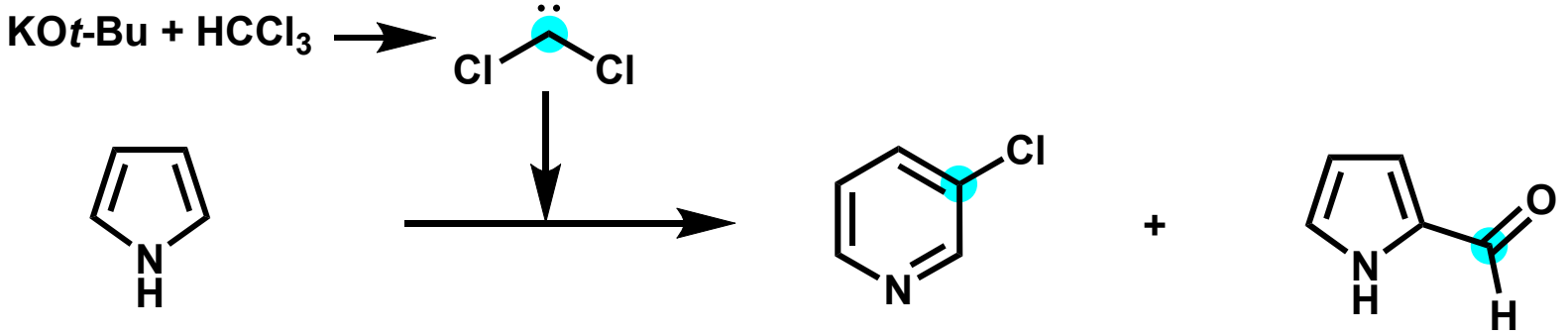


1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Contents

Carbon Insertion by Levin's Group

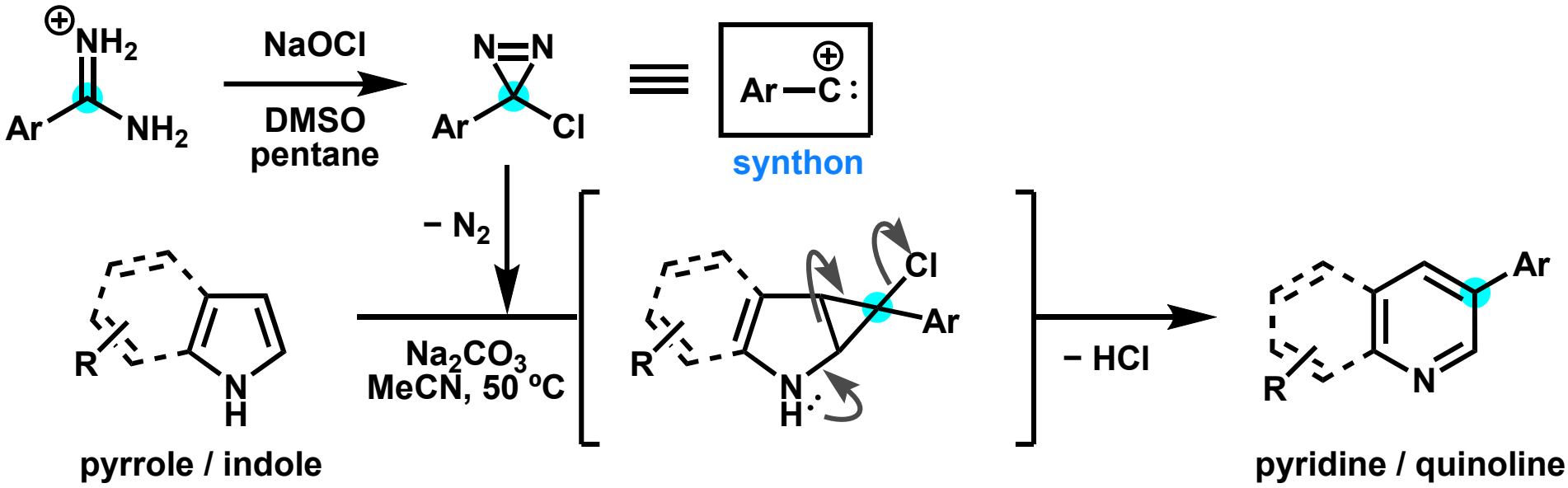
- **The classical Ciamician-Dennstedt Rearrangement (1981)**



Reimer-Tiemann Formylation

Ciamician, G. L.; Dennstedt, M. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1153.

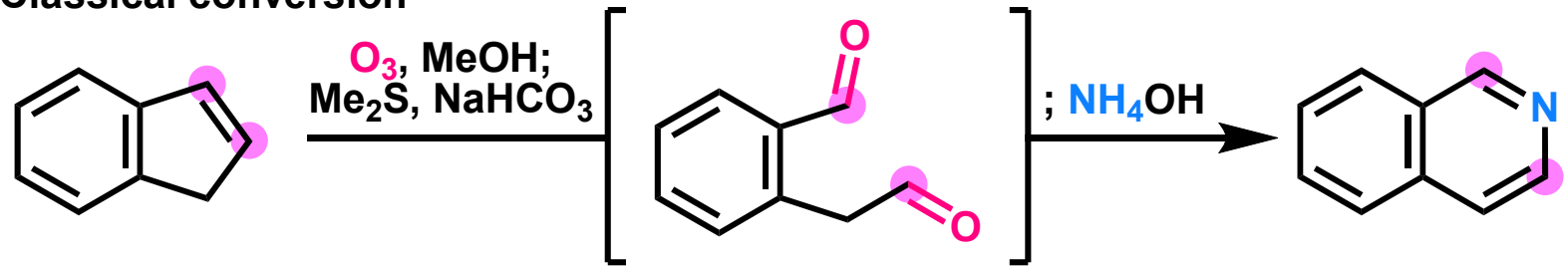
- **Carbon atom Insertion into pyrroles and Indoles (2021)**



Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Examples of Nitrogen Insertion

- **Classical conversion**

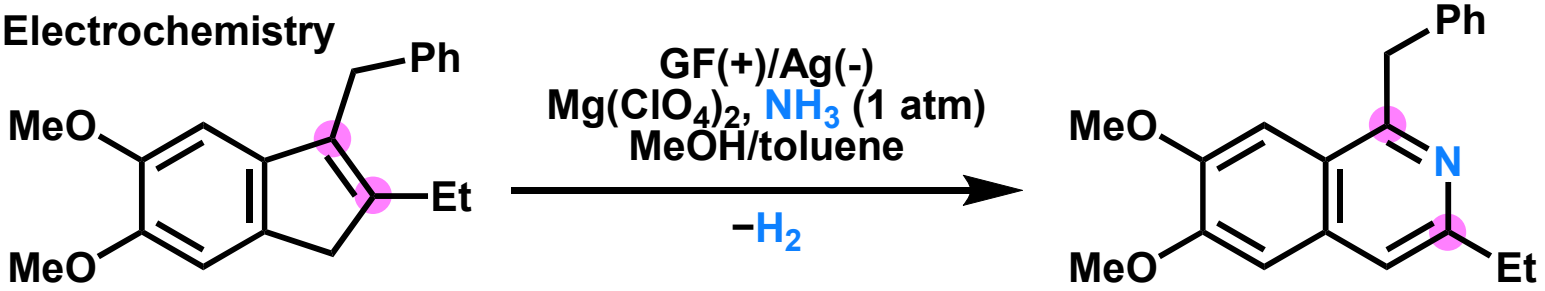


harsh oxidising conditions

Miller, R. B.; Frincke, J. M.; *J. Org. Chem*. **1980**, *45*, 5312.

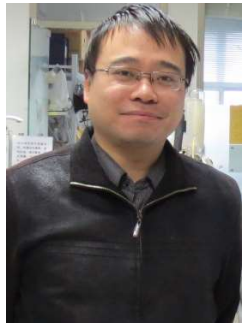
Prof. Bryan Miller

- **Electrochemistry**



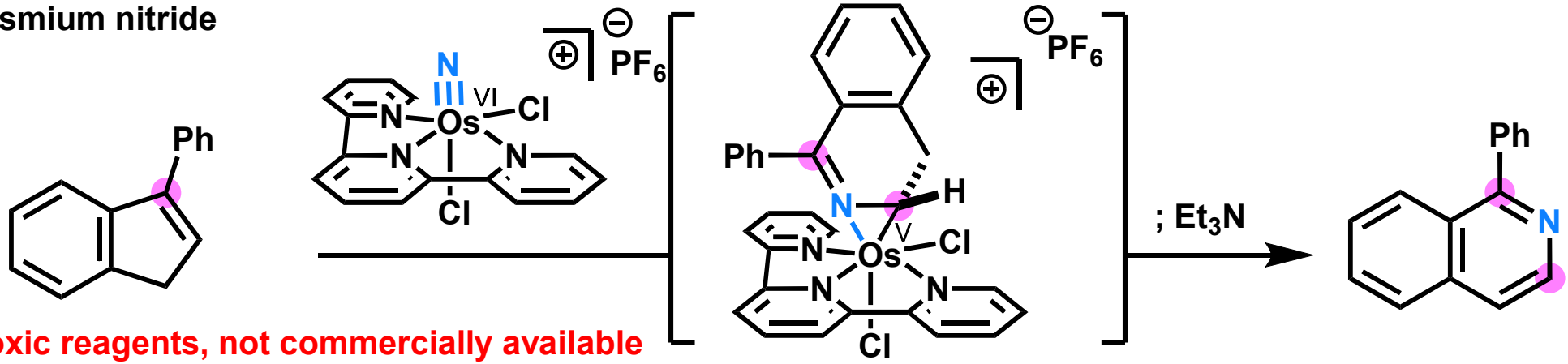
NH_3 gas, only activated and substituted indenes

Liu, S.; Cheng, X. *Nat. Chem*. **2022**, *13*, 425.



Prof. Xu Cheng

- **Osmium nitride**



toxic reagents, not commercially available

Kelly, P. Q.; Filatov, A. S.; Levine, M. D. *Angew. Chem. Int. Ed.* **2022.** *61*, e202213041

Prof. Bill Morandi

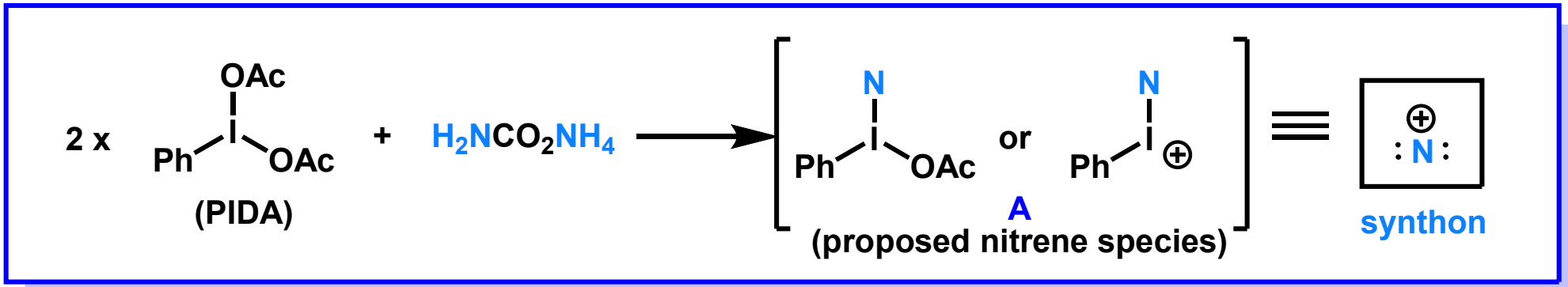
-2006 B.S. @ETH Zurich
-2012 Pd.D. @ETH Zurich (Prof. Erick M. Carreira)
-2014 Postdoctoral Fellow @California Institute of Technology (Prof. Robert H. Grubbs)
-2018 Group Leader @Max-Planck-Institute fur Kohlenforschung
-2022 Professor @ETH Zurich
2022- Full Professor @ETH Zurich

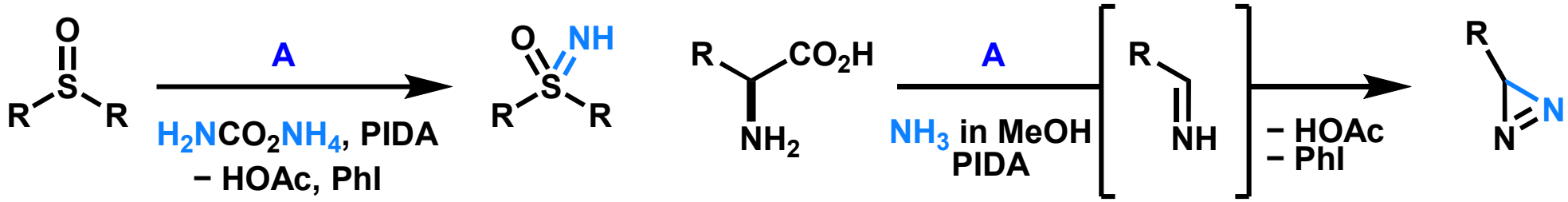
Research area:

- **Catalysis (Shuttle Catalysis, Metathesis Reactions, Amination, Alkene/Alkyne Functionalization)**
- **Molecular Editing**
- **Organometallic and Mechanistic Studies**

https://morandi.ethz.ch/

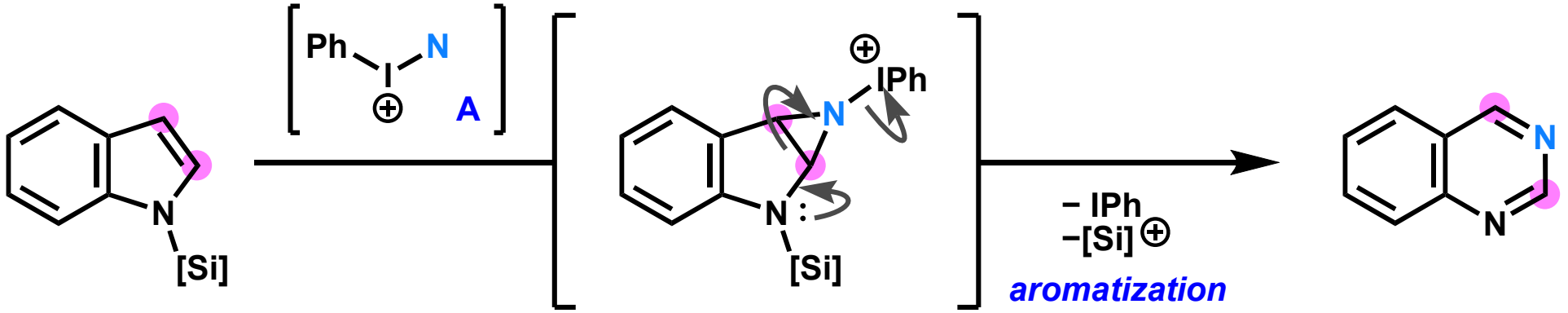
Morandi's Working Hypothesis





Bull, J. A. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 7203. Glaxhet, T. et al. *J. Am. Chem. Soc.* **2019**, *141*, 13689.

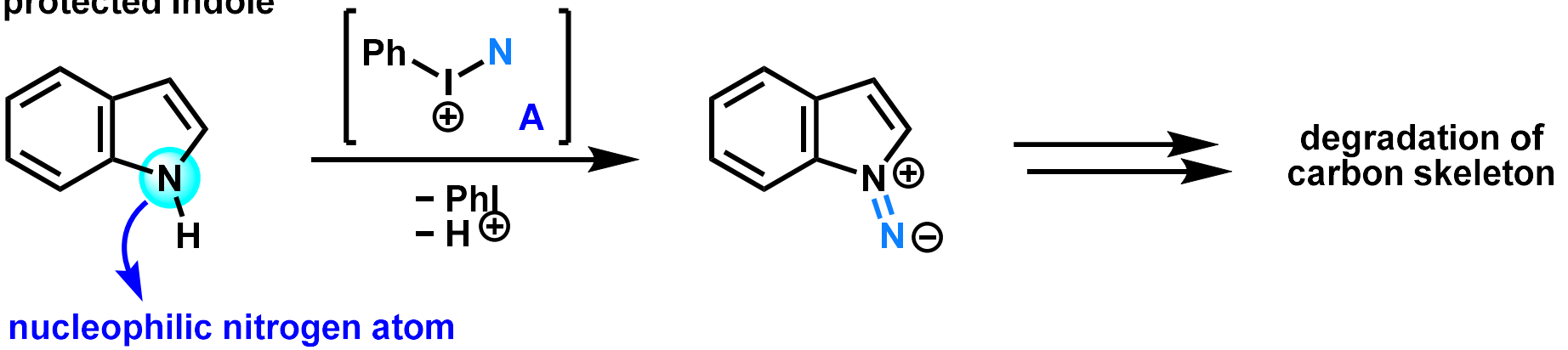
- **Morandi's mechanistic design**



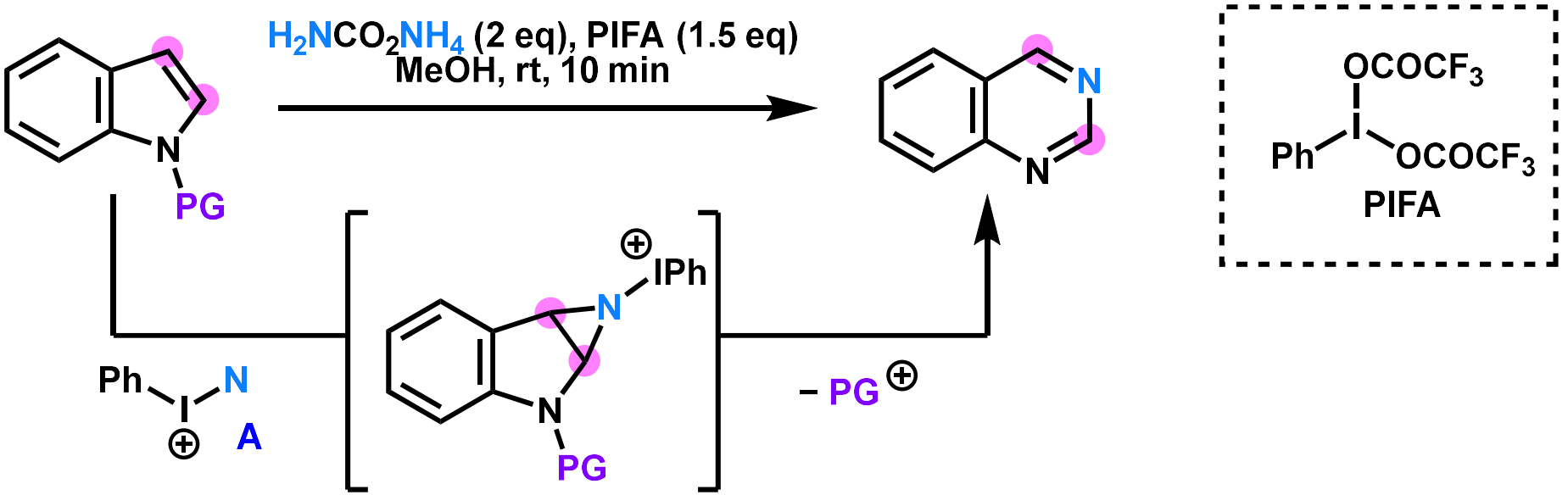
1) Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P. Morandi, B. *Science*. **2022**, *377*, 1104.

Investigation of Protecting Group Effect

- Unprotected Indole



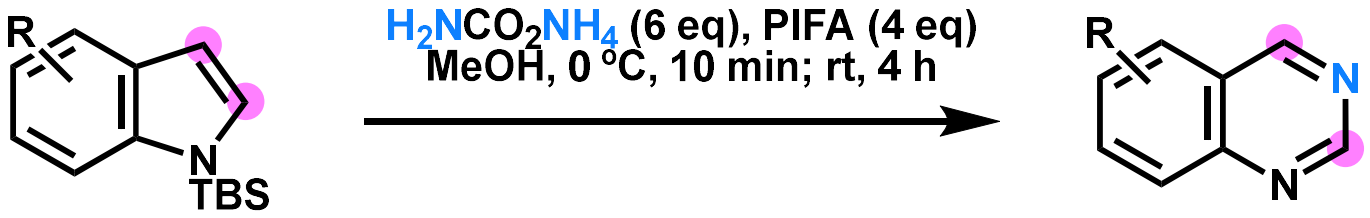
- Protecting group effect

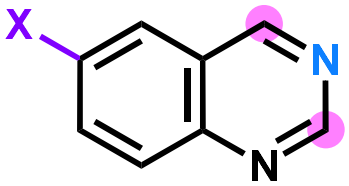


PG =	H	TBS	TBDPS	TIPS	CO_2t-Bu	CO_2Me	Me
GC yield	1%	47%	9%	27%	4%	2%	0%

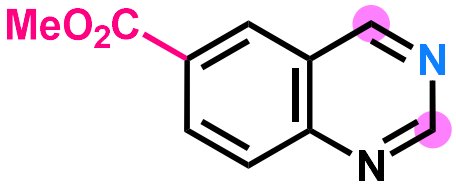
1) Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P. Morandi, B. *Science*. **2022**, *377*, 1104.

Substrate Scope (1)

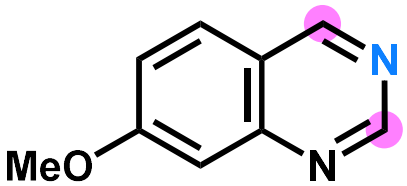




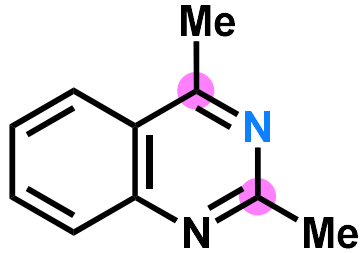
X = I, 74%
X = Br, 83%



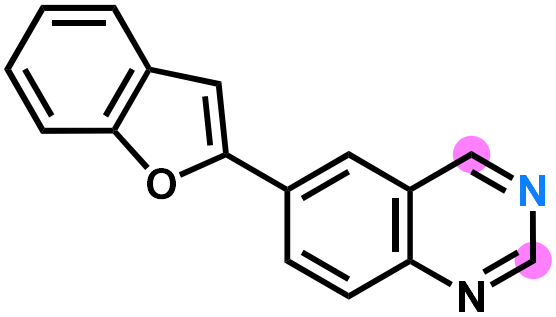
66%



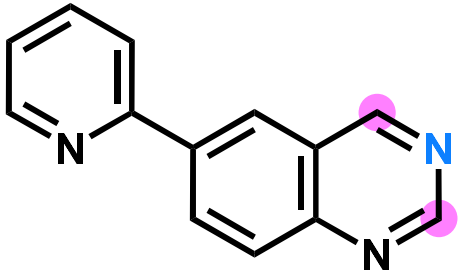
57%



66%



30%



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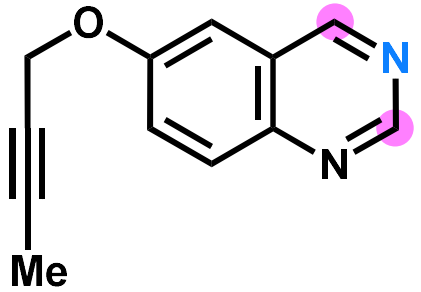
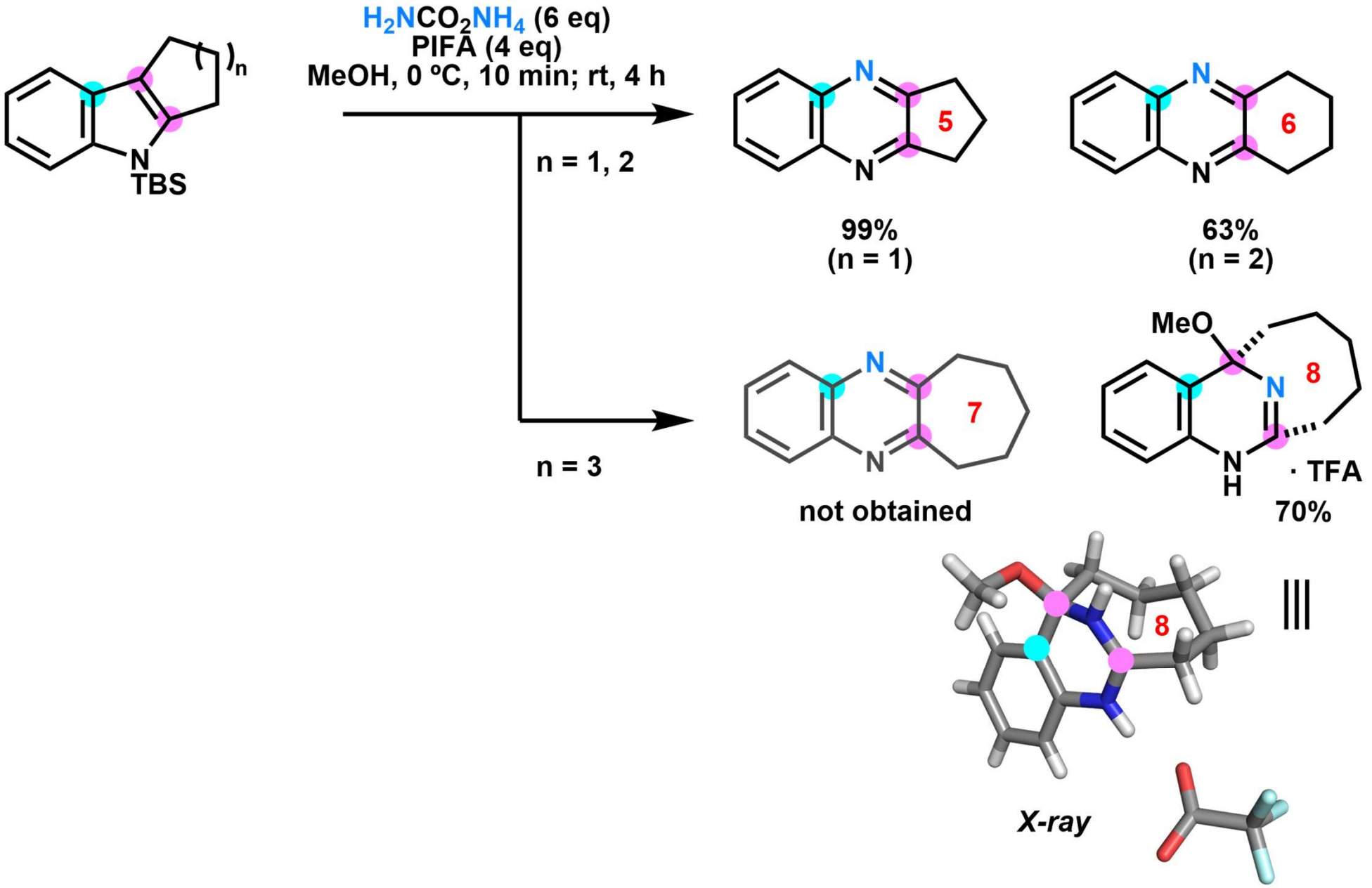


72%

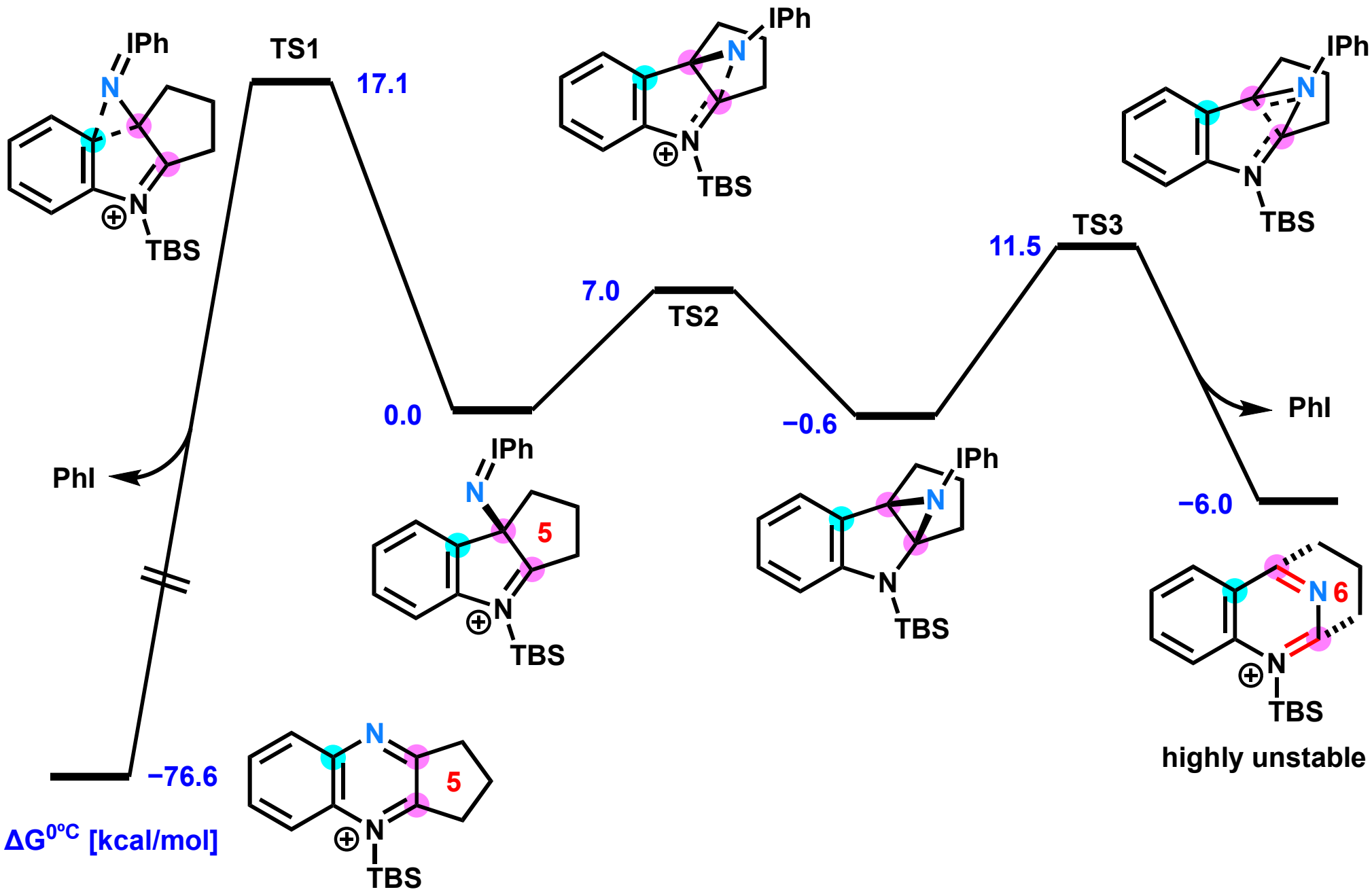
1) Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P. Morandi, B. *Science*. **2022**, *377*, 1104.

Substrate Scope (2)



1) Maier, W. F.; Schleyer, P von R. *J. Am. Chem. Soc*. **1981**, *103*, 1981.
2) Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P. Morandi, B. *Science*. **2022**, *377*, 1104.

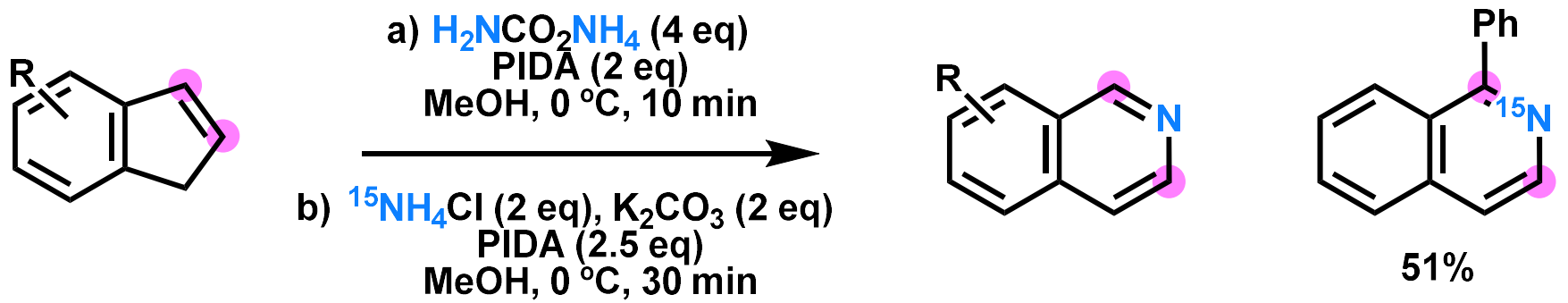
DFT Calculation for the Regioselectivity



1) Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P. Morandi, B. *Science*. **2022**, *377*, 1104.

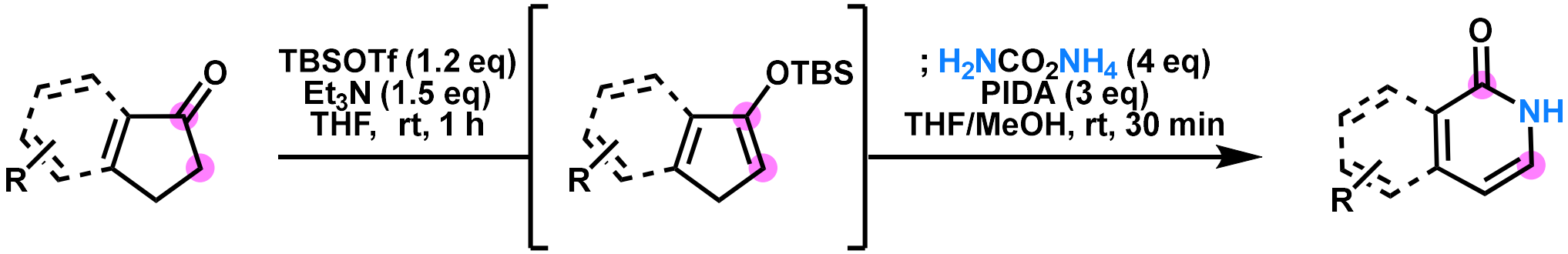
Application for Synthesis of Isoquinolines and Pyridones

- **Indenes to isoquinolines**



Finkelstein, P.; Reisenbauer, J. C.; Botlik, B. B.; Green, O.; Florin, A.; Morandi, B. *Chem. Sci.* **2023**, *14*, 2954.

- **Cyclopentenones to pyridones**



Botlik, B. B.; Weber, M.; Ruepp, F.; Kawanaka, K.; Finkelstein, P.; Morandi, B. *Angew. Chem. Int. Ed.* **2024.** *63*, e202408230.

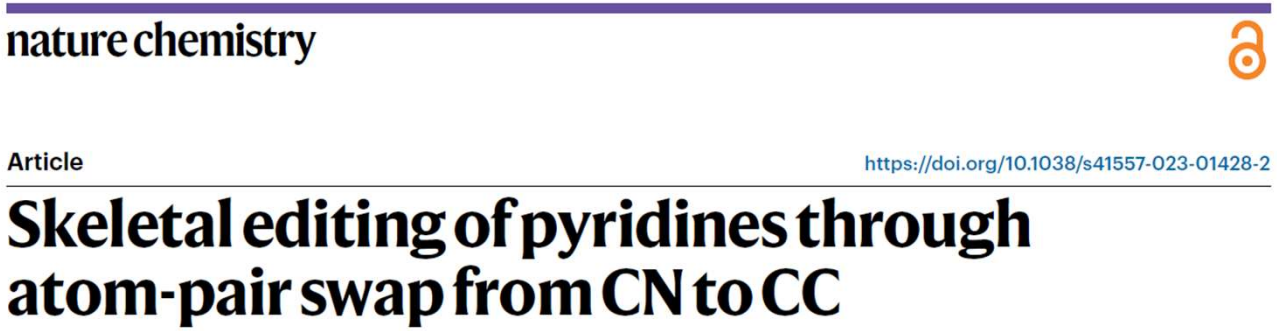
Contents

1. Introduction

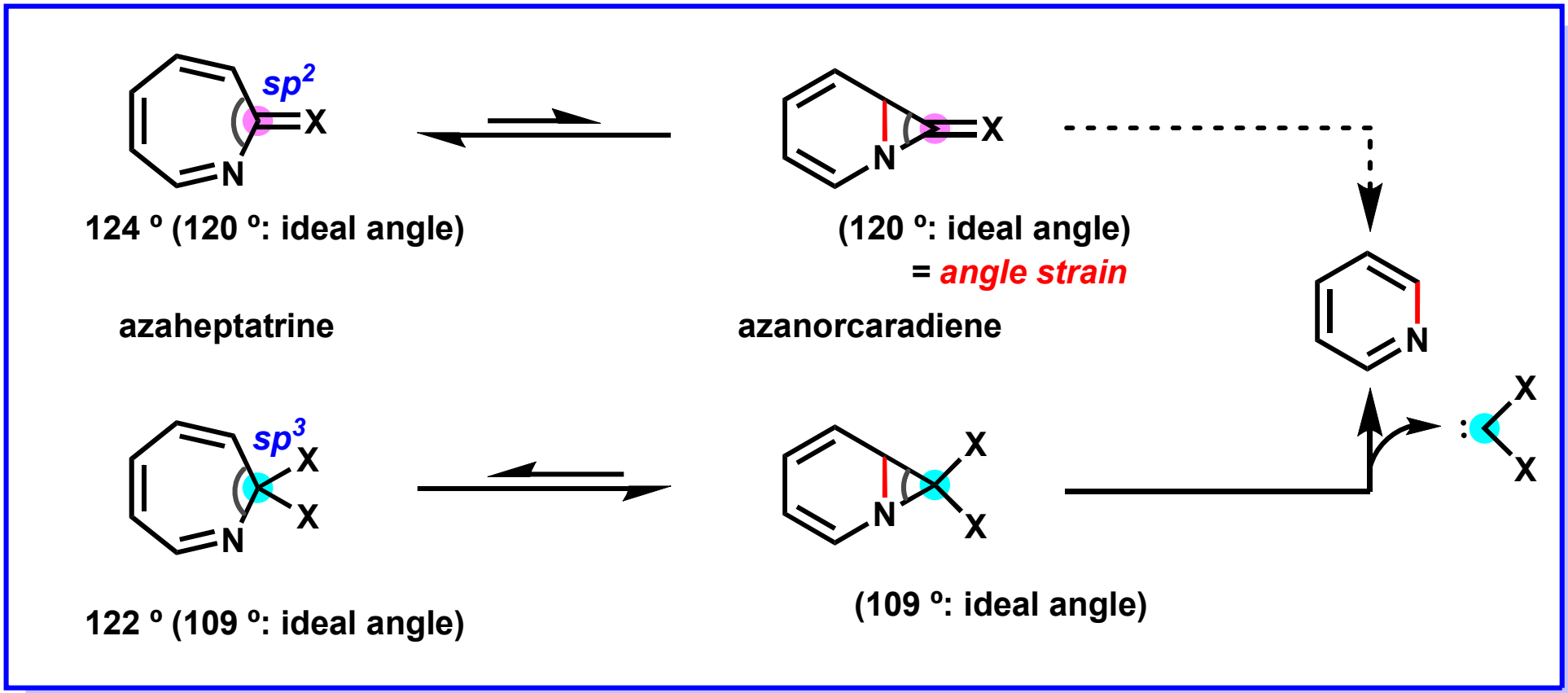
2. Deleting atoms

3. Inserting atoms

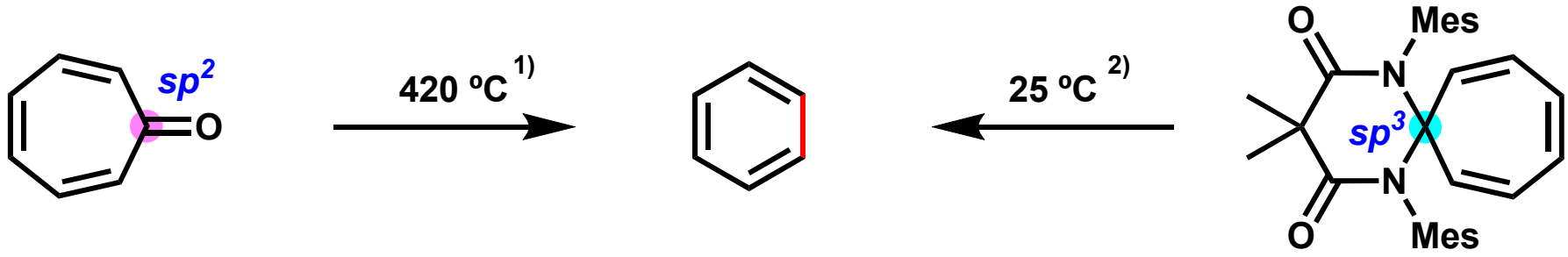
4. Swapping atoms (Studer group)



Design Concept of Levin and Burns group



- **Demonstrating hybriduzation effects in benzenoid systems**



1) Amano, A.; Mukai, T.; Nakazawa, K.; Okayama, K. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1671.
2) Perera, T. A.; Reinheimer, E. W.; Hudnall, T. W.; *J. Am. Chem. Soc*. **2017**, *139*, 14807.

Swapping Carbon to Nitrogen by Burn's group

Prof. Noah Burns

Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc*. **2022**, *144*, 17797. (see; 230610_LS_Shuji_Toyama)

Swapping Carbon to Nitrogen by Levin's group (1)

Prof. Mark Levin

Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

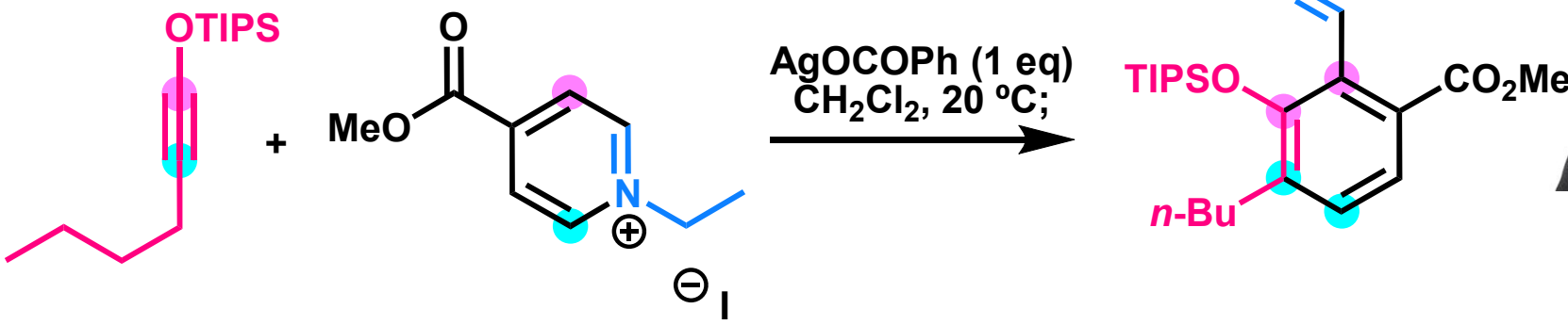
Swapping Carbon to Nitrogen by Levin's group (2)

Prof. Mark Levin

Woo, J.; Stein, C.; Christian, A. H.; Levin, M. D. *Nature* **2023**, *623*, 77.

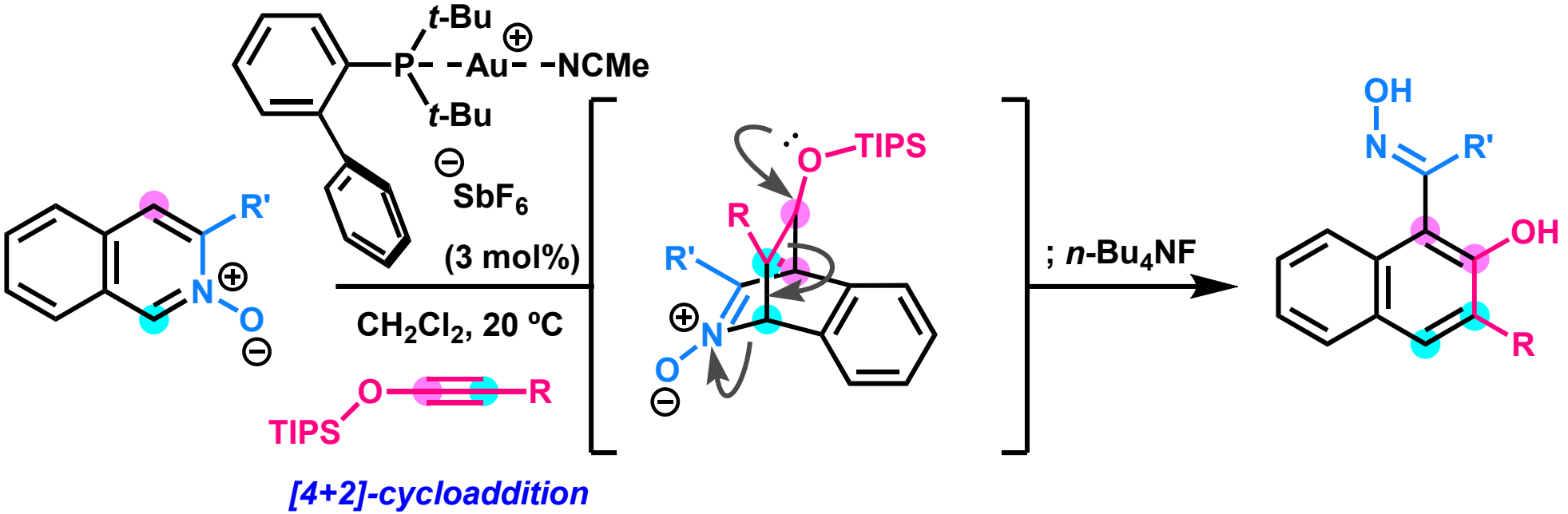
Swapping Nitrogen to Carbon by Kozmin's group

- CN (carbon-nitrogen) to CC (carbon-carbon) swapping



Prof. Sergey Kozmin

Carbrera-Pardo, J. R.; Chai, D.; Kozmin, S. A. *Adv. Synth. Catal.* **2013**, *355*, 2498.



Carbrera-Pardo, J. R.; Chai, D.; Liu, S.; Mrksich, M.; Kozmin, S. A. *Nature Chem.* **2013**, *5*, 423.

Prof. Armido Studer

-1991 B.S. @ETH Zurich (Prof. D. Seebach)
-1995 Pd.D. @ETH Zurich (Prof. D. Seebach)
-1996 Postdoctoral Fellow @University of Pittsburgh (Prof. D. P. Curran)
-2000 Independent Research @ETH Zurich
-2004 Associate Professor (C3) @Philipps-Universitat Marburg
-2009 Full Professor (C4) @WWU Munster
2009- Full Professor (W3) @WWU Munster

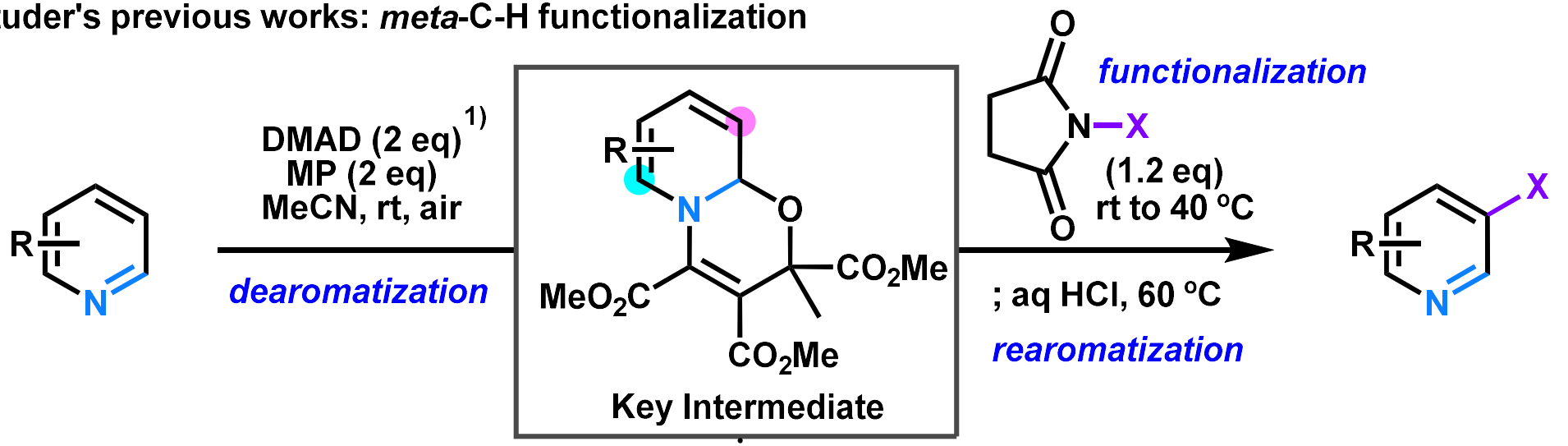
Research area:

- **Radical Chemistry in Organic Synthesis – Method Development**
- **Transition Metal Catalysis**
- **Nitroxide Mediated Controlling Radical Polymerization**

https://www.uni-muenster.de/Chemie.oc/studer/

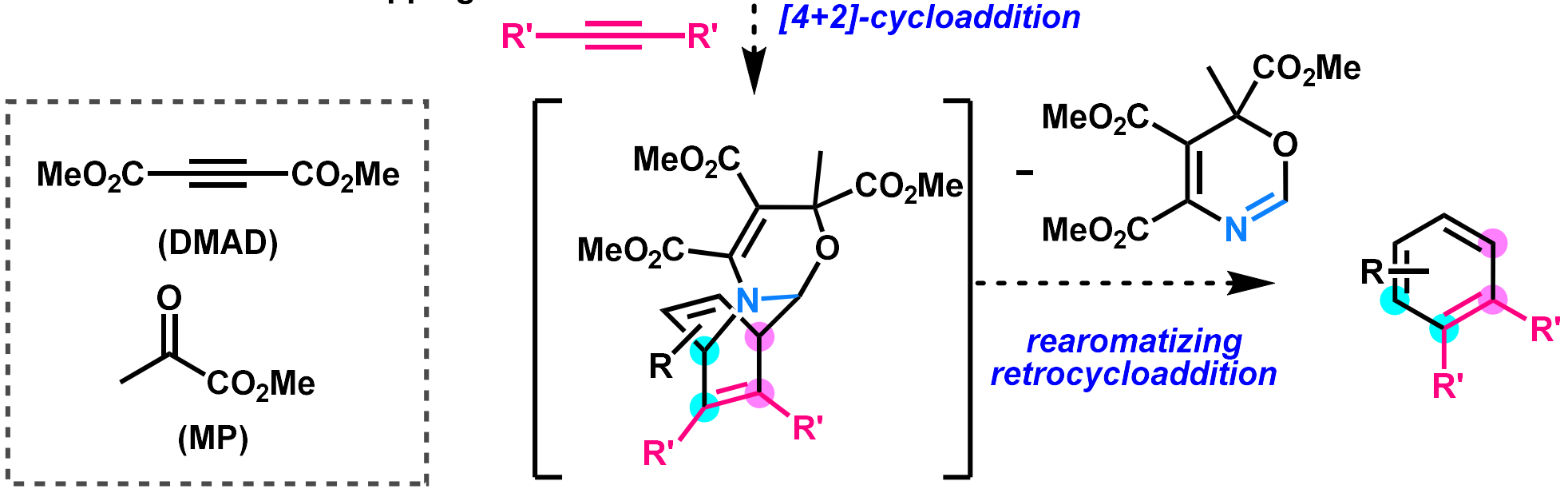
Studer's Working Hypothesis

- Studer's previous works: *meta*-C-H functionalization



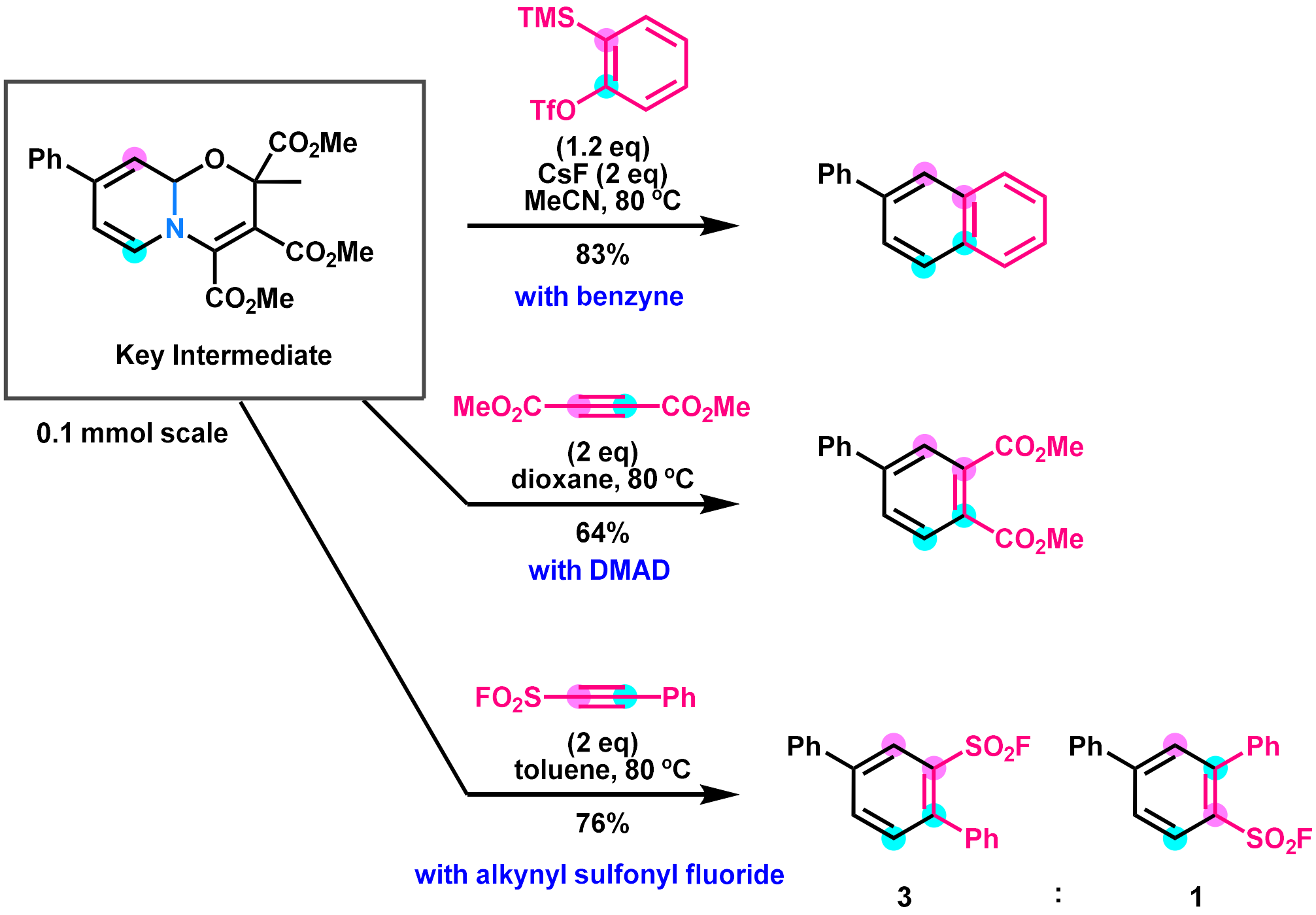
Cao, H.; Cheng, Q.; Studer, A. *Science* **2022**, *378*, 779.

- This time: CN to CC swapping 2)



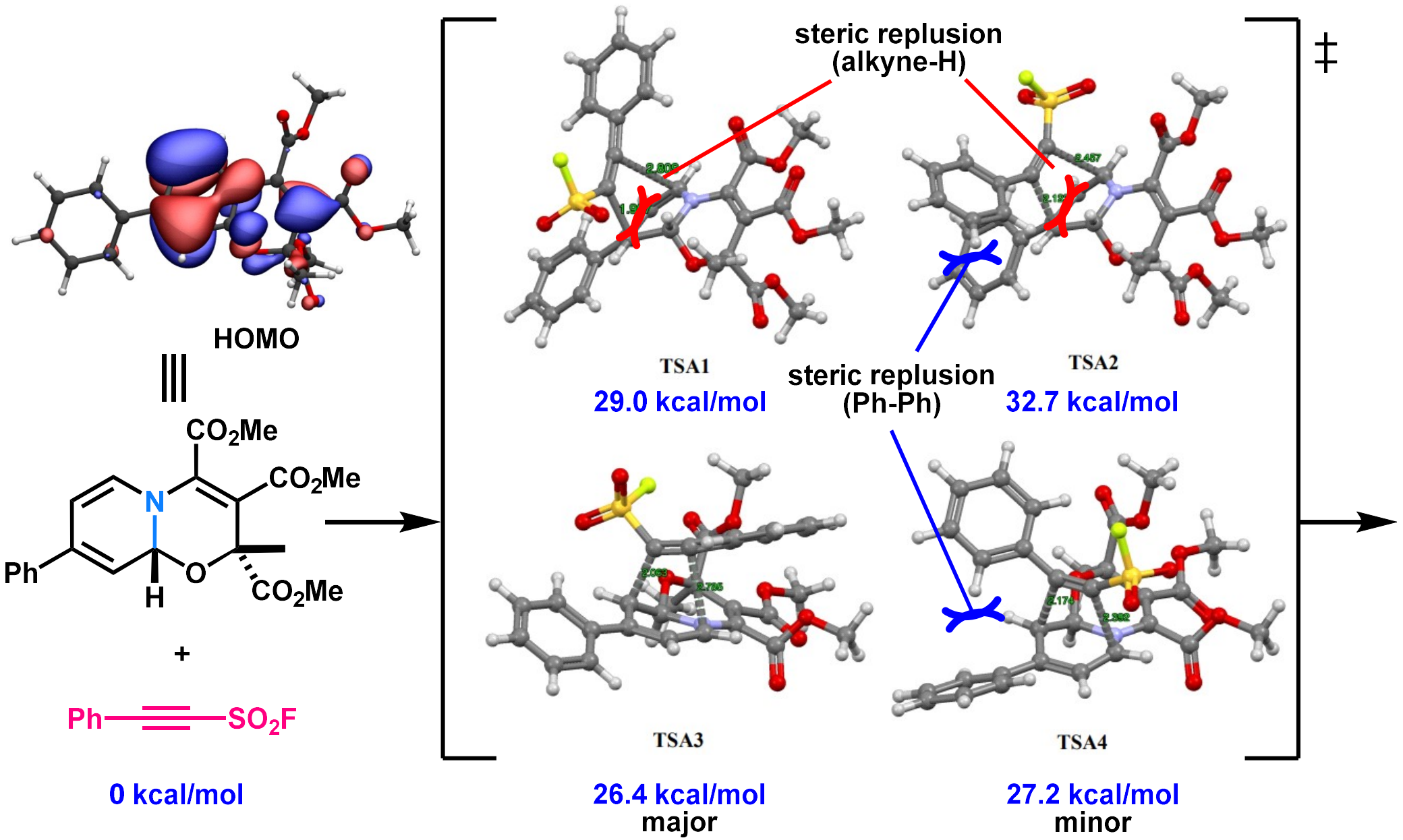
1) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094.
2) Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

Scope of Pyridine Skeletal Editing



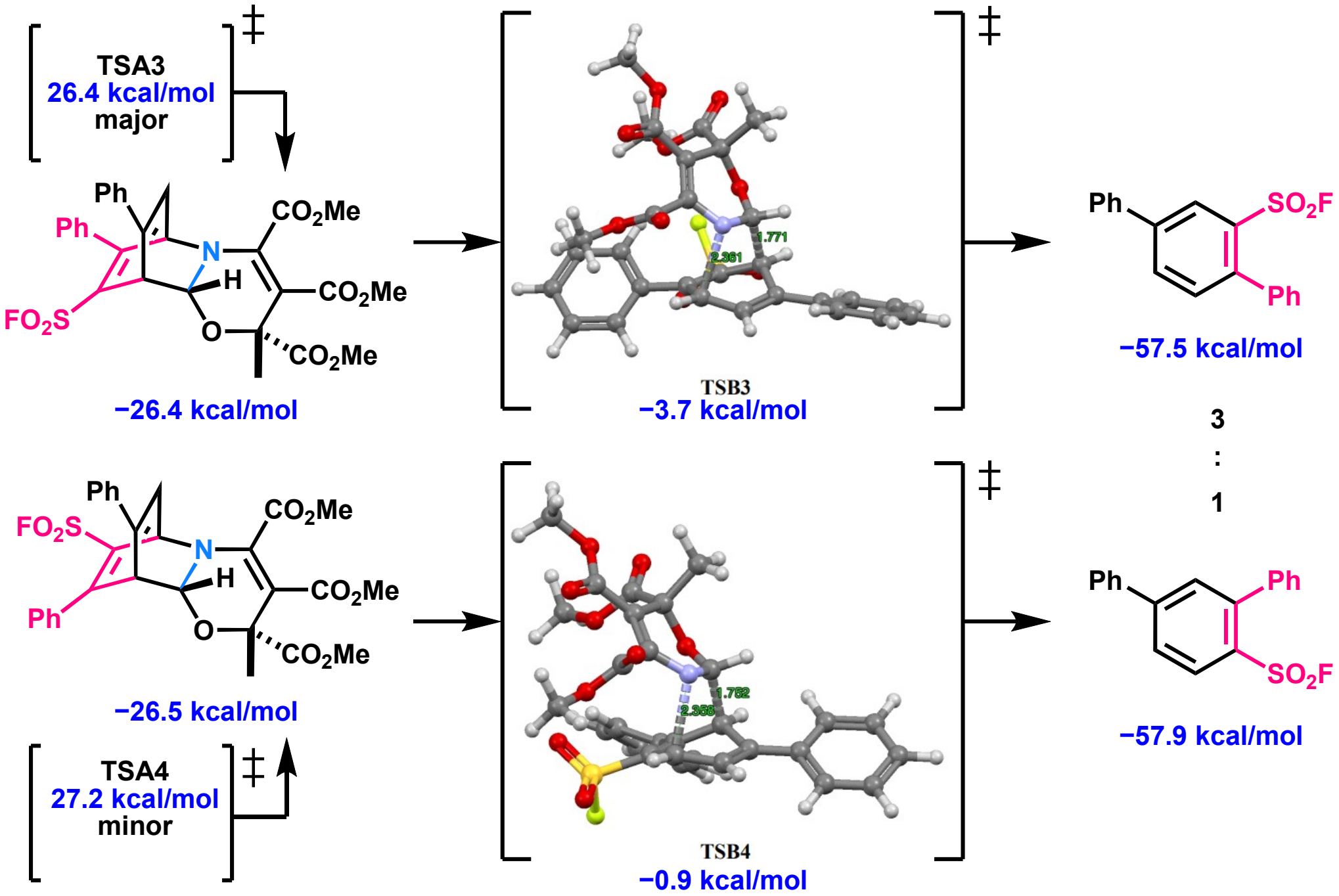
1) Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

Regioselectivity of [4+2] Cycloaddition (1)



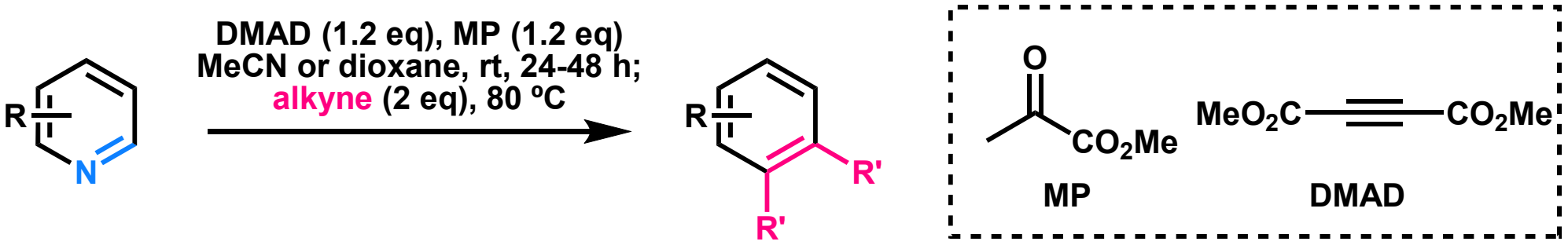
1) Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

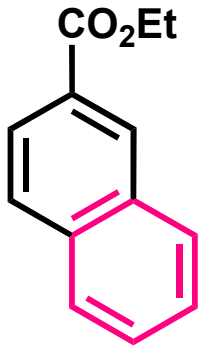
Regioselectivity of [4+2] Cycloaddition (2)



1) Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

Substrate Scope





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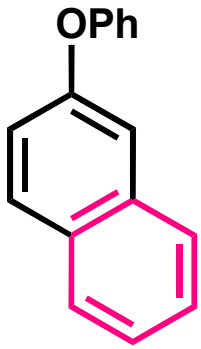

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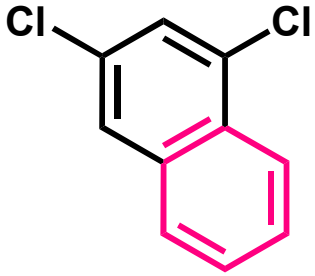

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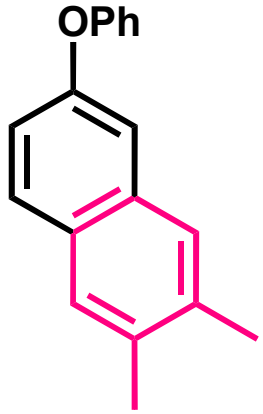

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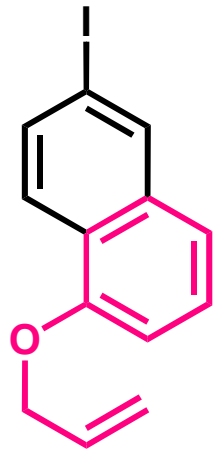
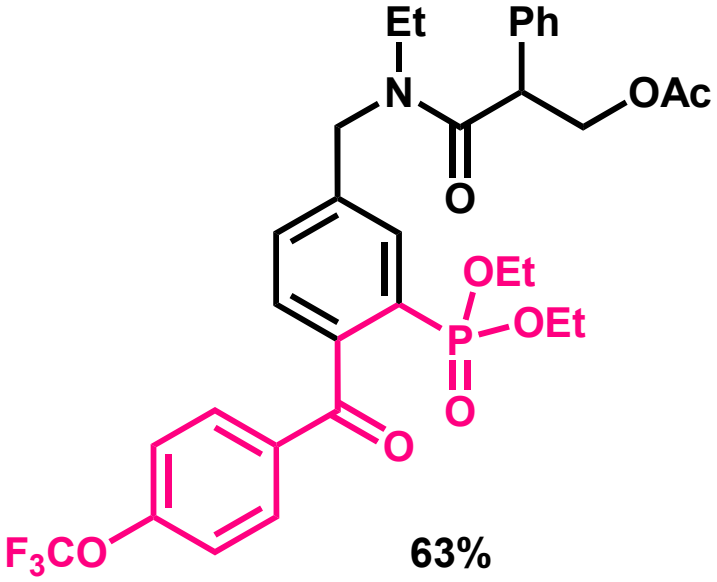


51%



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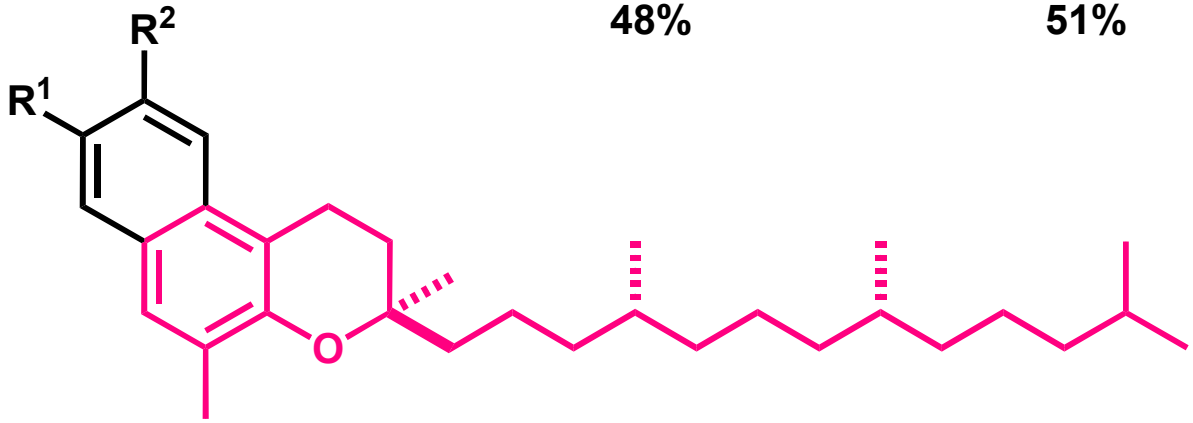
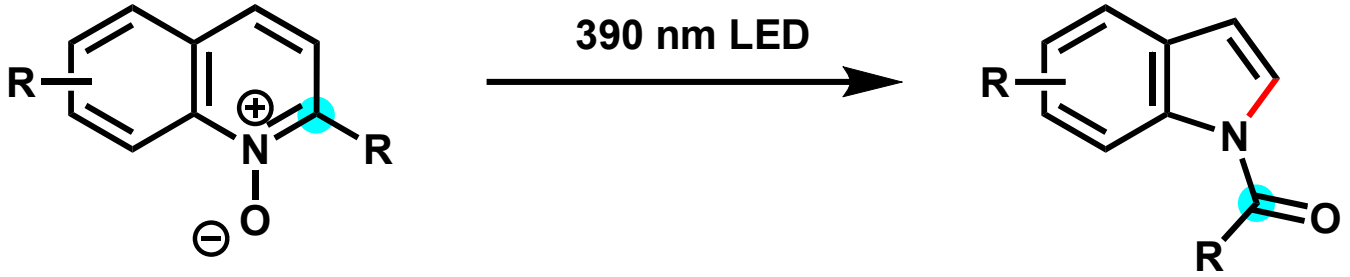


51% (A:B = 1.8:1)
A (R^1=Ph, R^2=H), B (R^1=H, R^2=Ph),

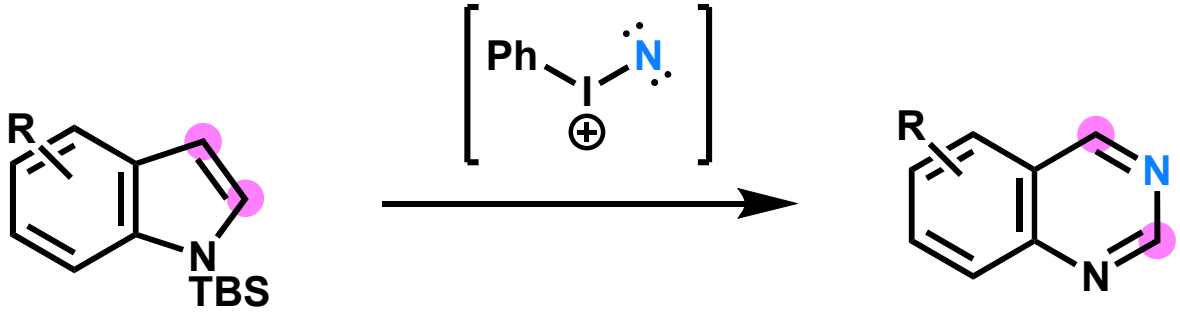
1) Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

Summary

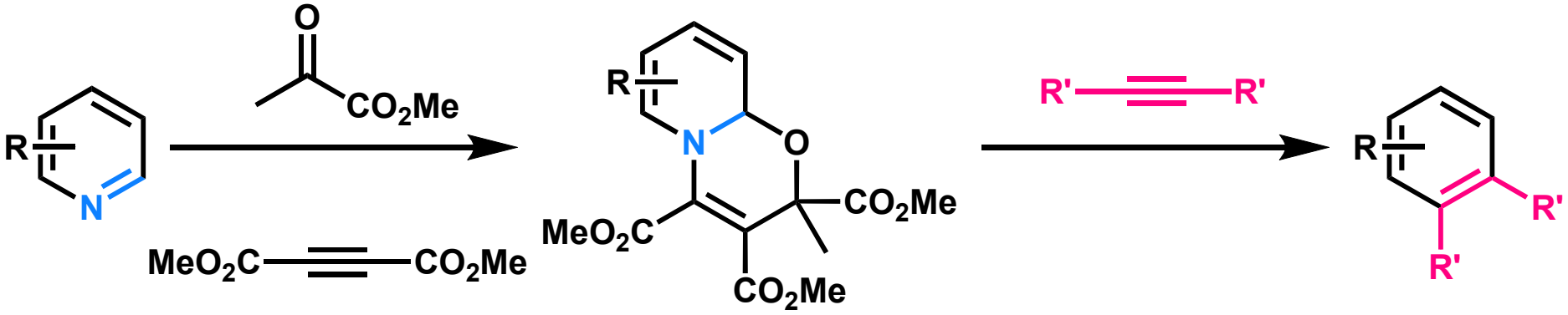
- Deletion (Levin group: 2022)



- Insertion (Morandi group: 2022)



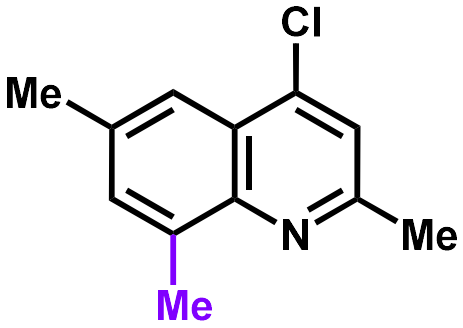
- Swapping (Studer group: 2023)



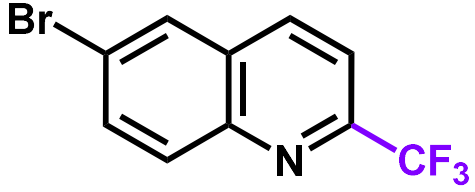
Appendix

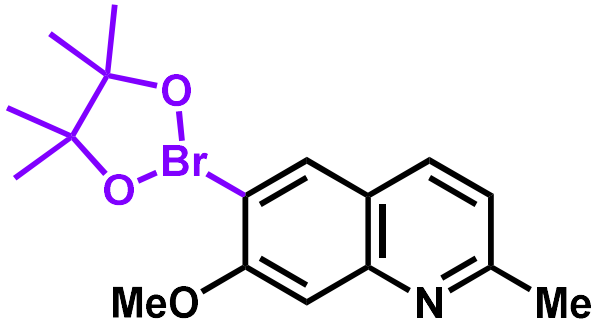
Appx. Section 2 / Limitations

1. *N*-oxidation limitations



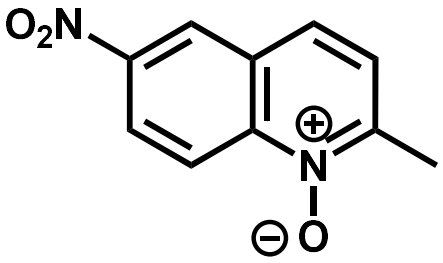
no reactivity



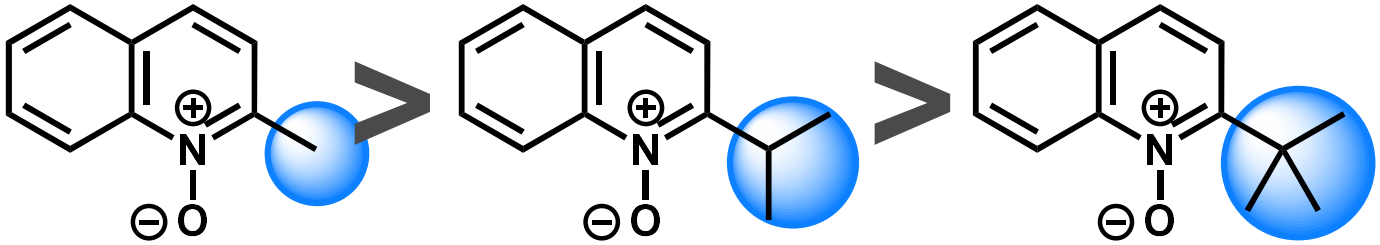


Bpin functional group did not tolerate *m*-CPBA oxidation condtion

2. Photolysis limitations



only deoxygenated product



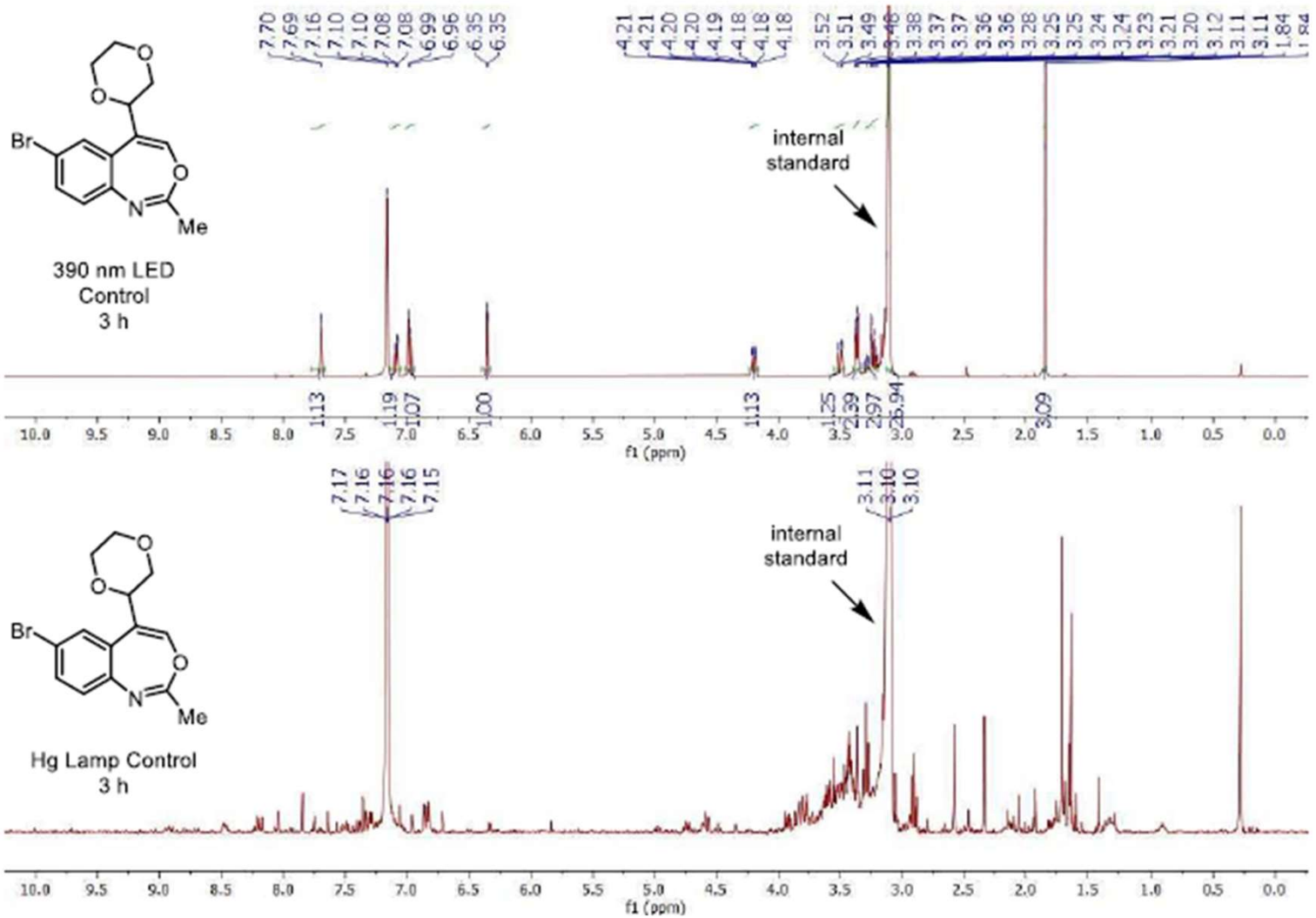
83%

50%

30% NMR yield

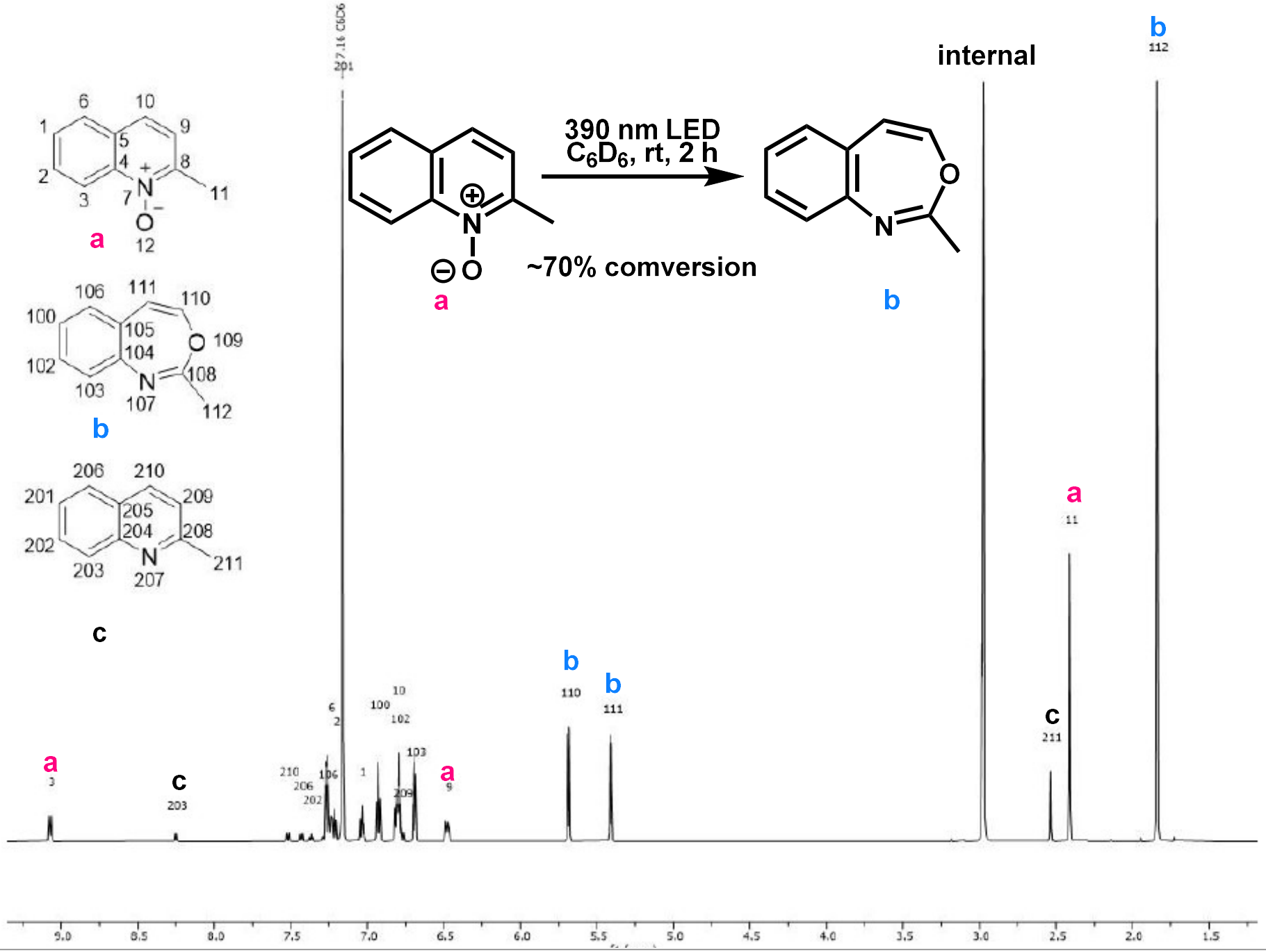
1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Representative Crude NMR of LED and Hg Lamp



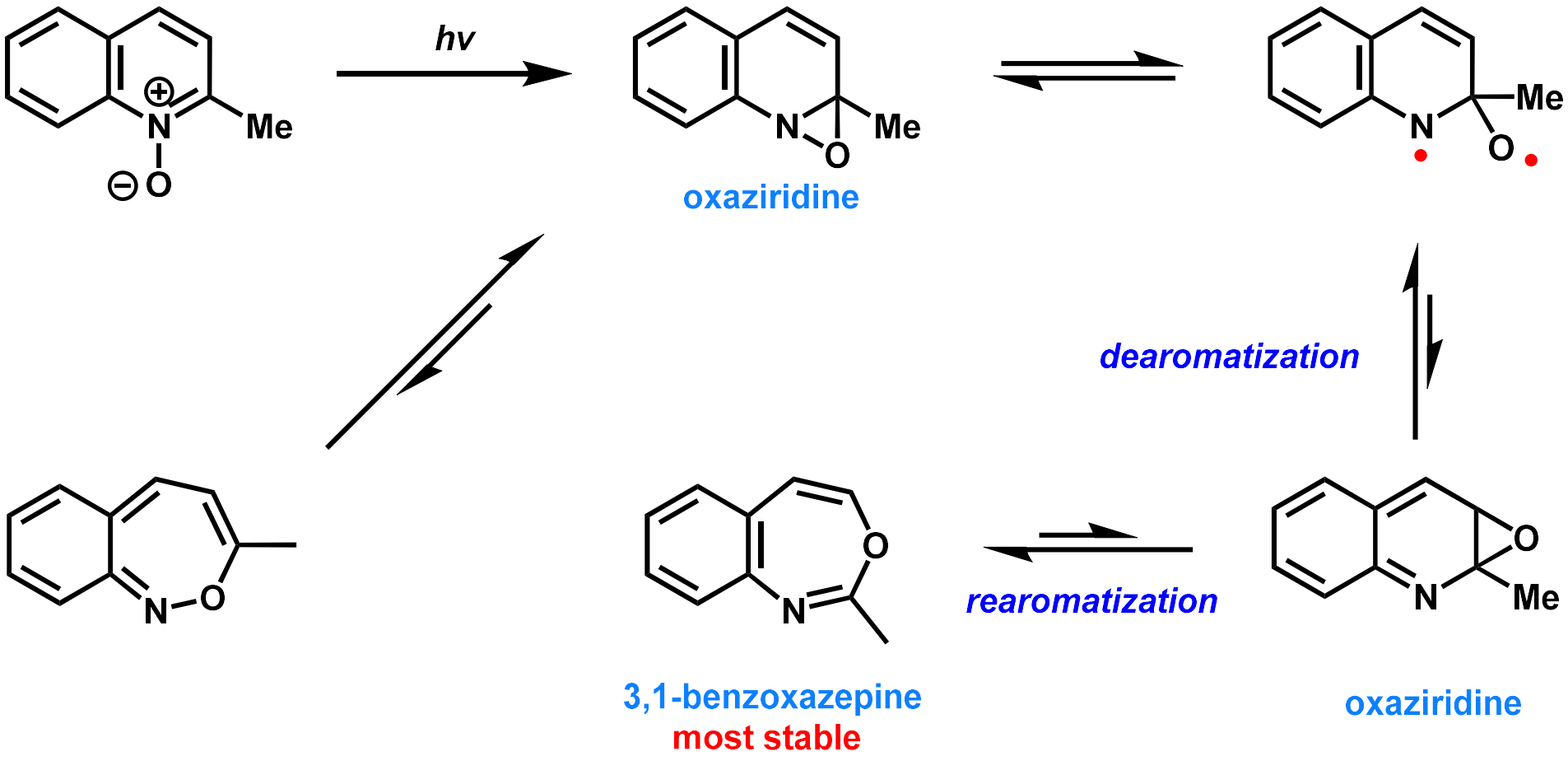
1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Monitoring the Reaction of Quinaldine N-Oxide



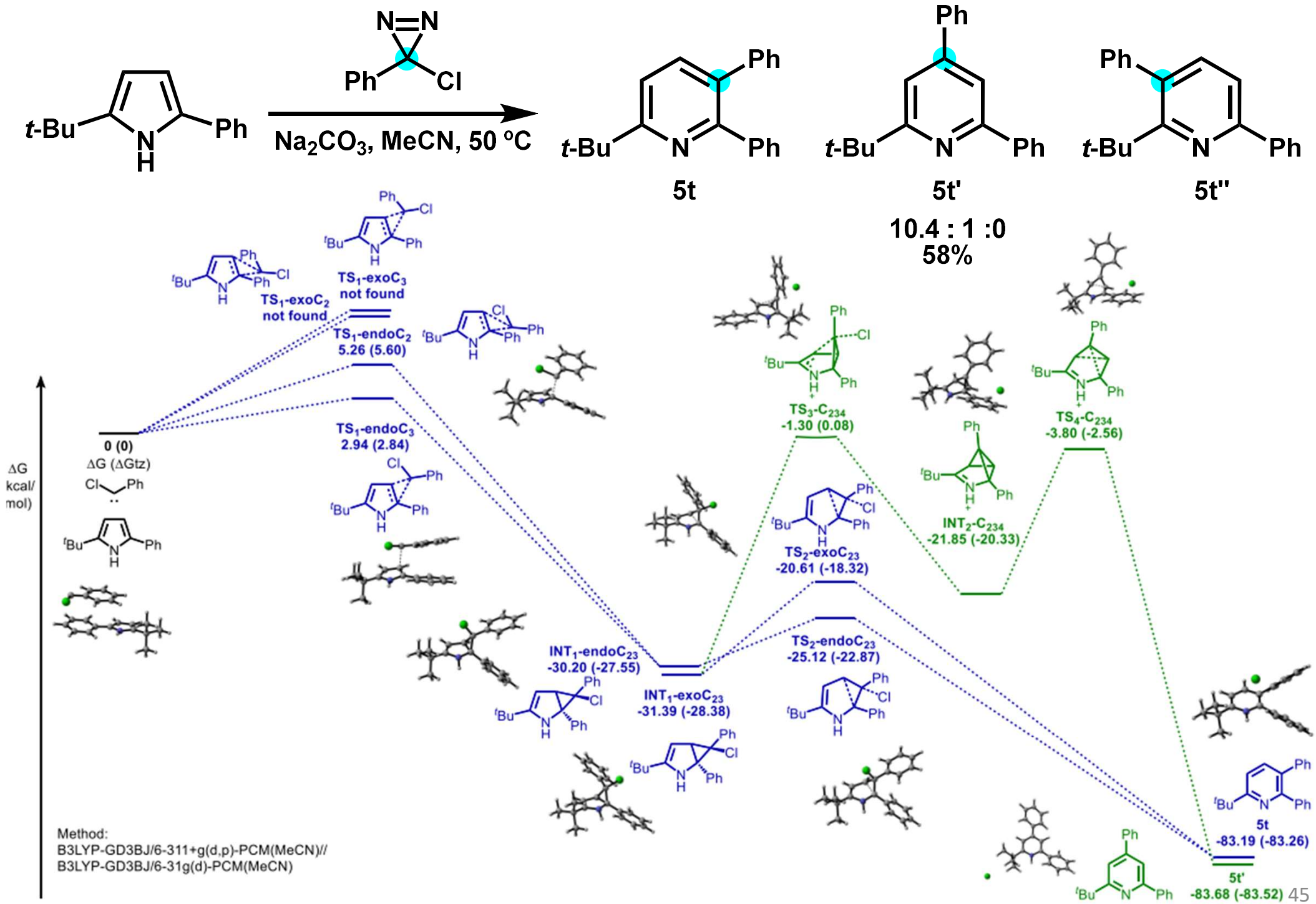
1) Woo, J.; Christian, A. H.; Burgess, S. A.; Jiang, Y.; Mansoor, U. F.; Levin, M. D. *Science*. **2022**, *376*, 527.

Reaction Mechanism of 3,1-Benzoxazepine

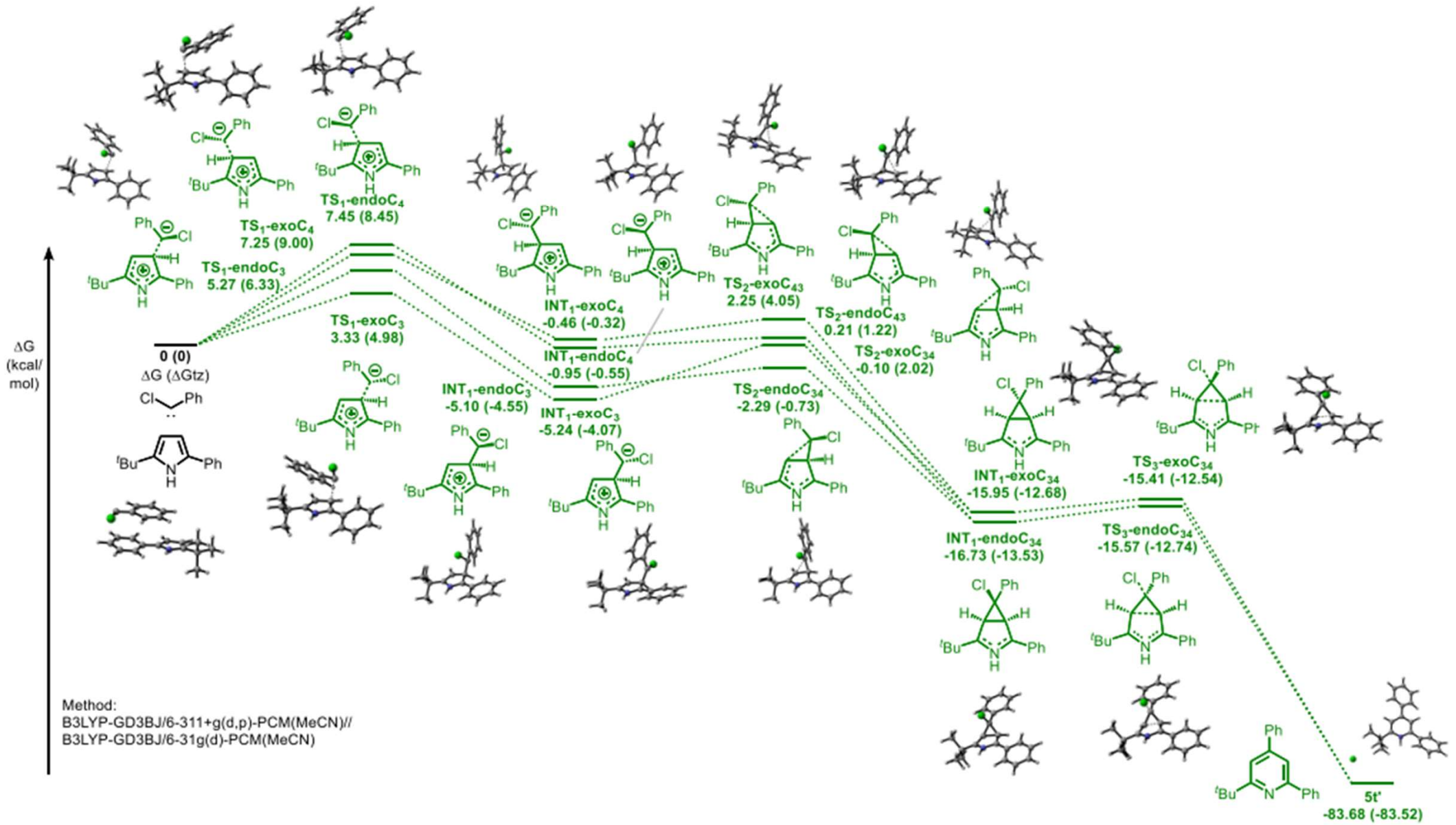


1) Albini, A.; Alpegiani, M. *Chem. Rev*. **1984**, *84*, 43.
2) Spence, G. G.; Taylor, E. C.; Buchardt, O. *Chem. Rev*. **1970**, *70*, 231.

Appx. Section 3 / Proposed Mechanism of Carbene Insertion

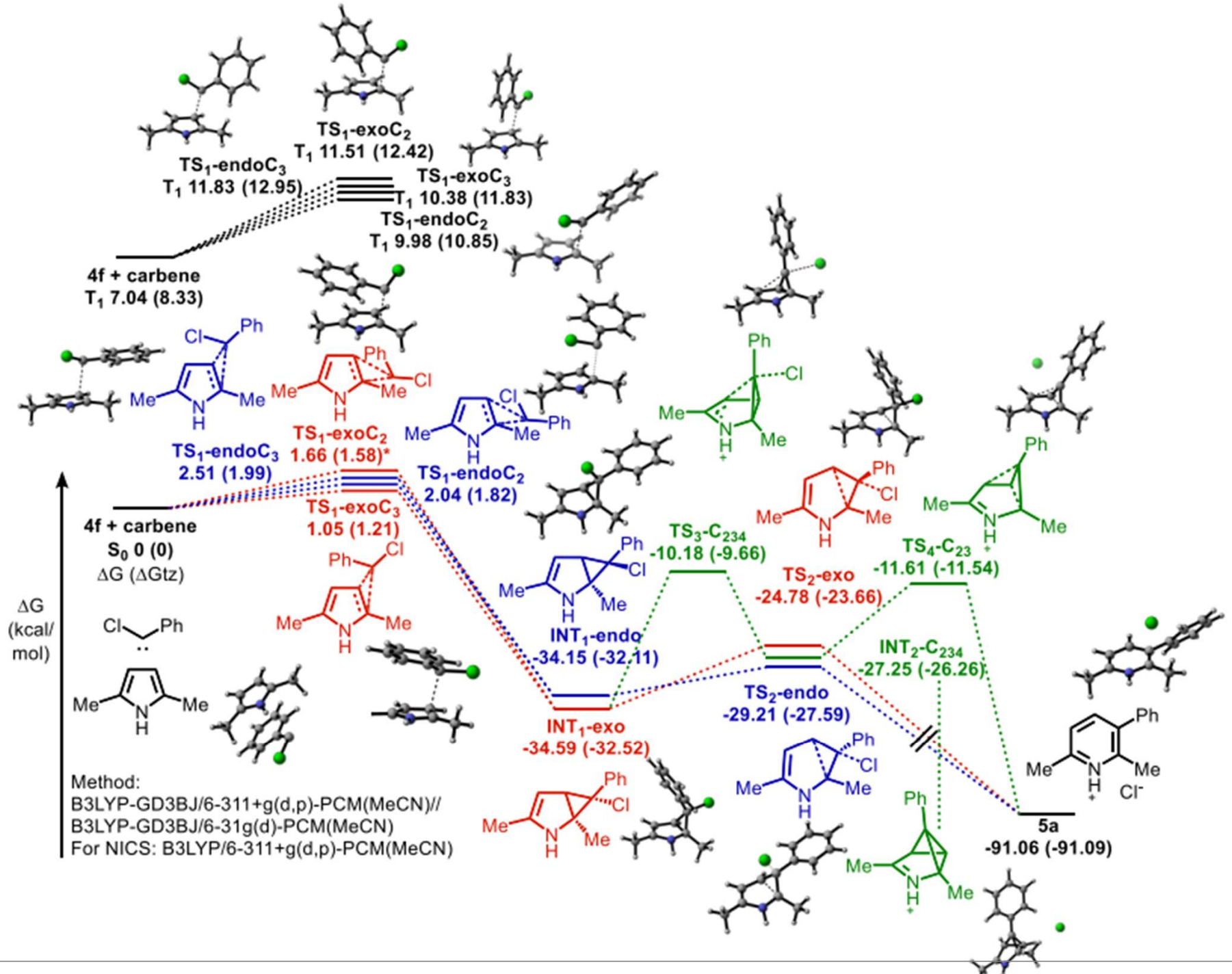


Other Pathway to Compound 5t”



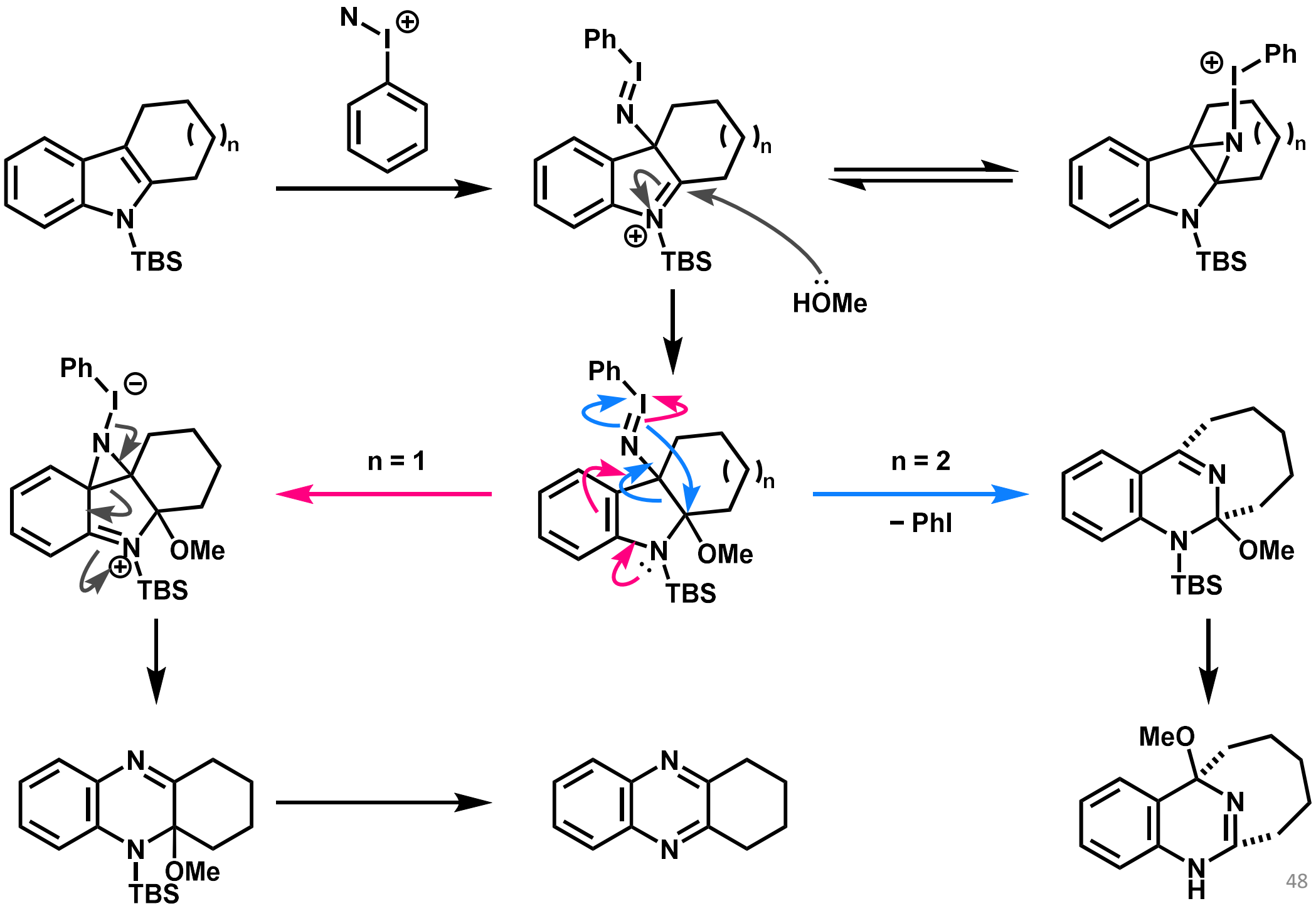
Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Reaction Mechanism (Triplet Energies Pathway)

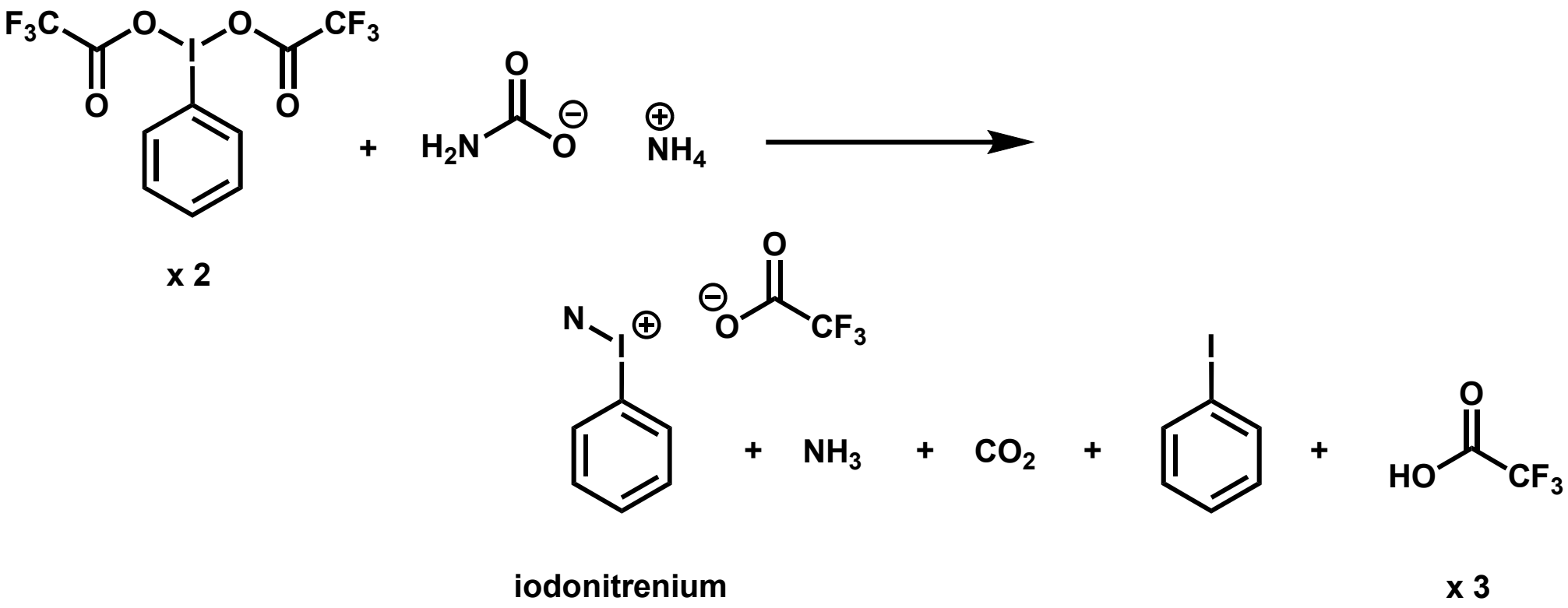


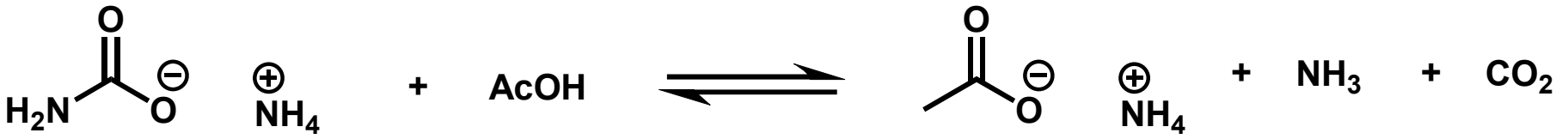
Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Another Reaction Mechanism (My Opinion)



Generation of Iodonitrenium



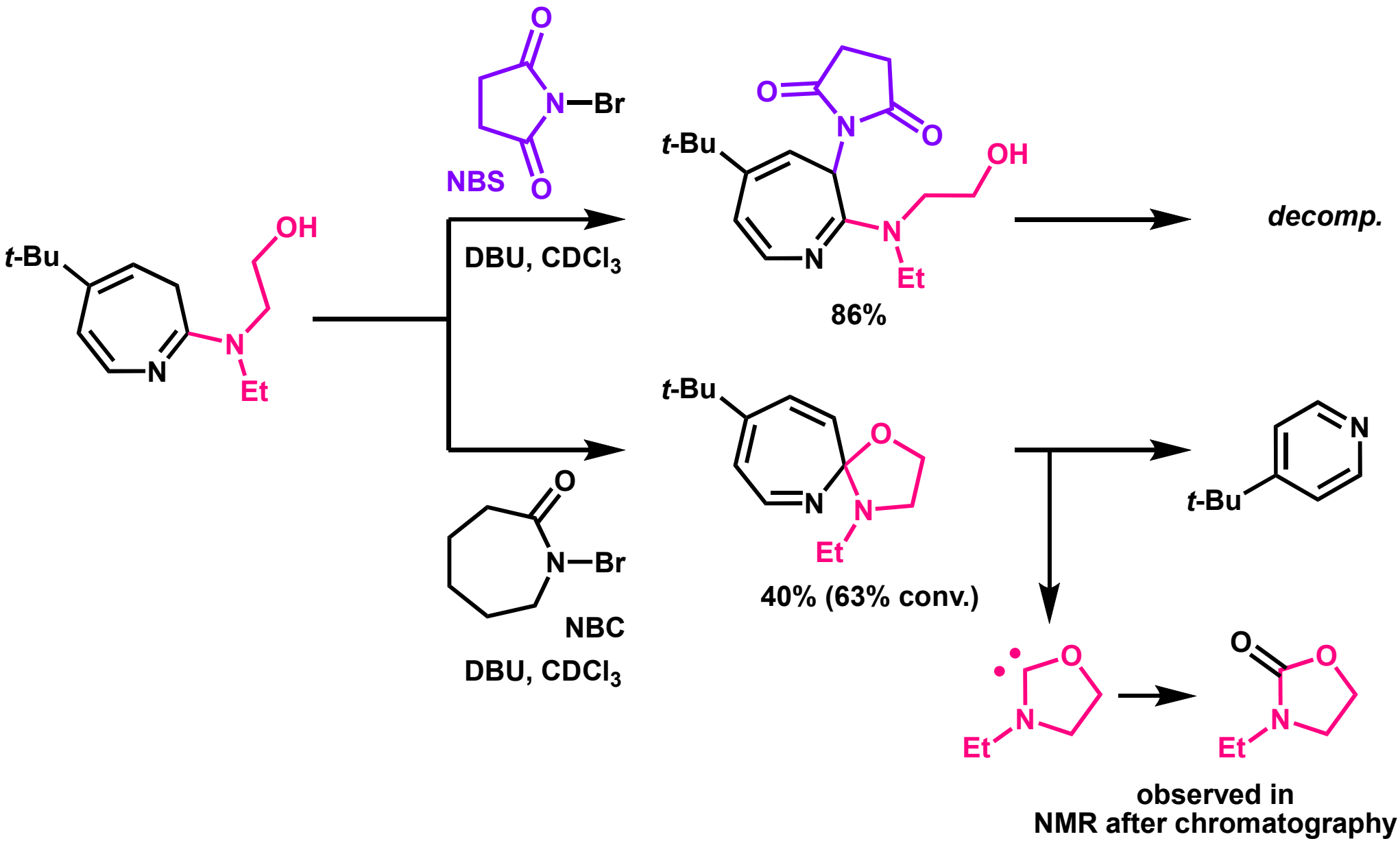


fast in MeOH

slow in toluene or MeCN

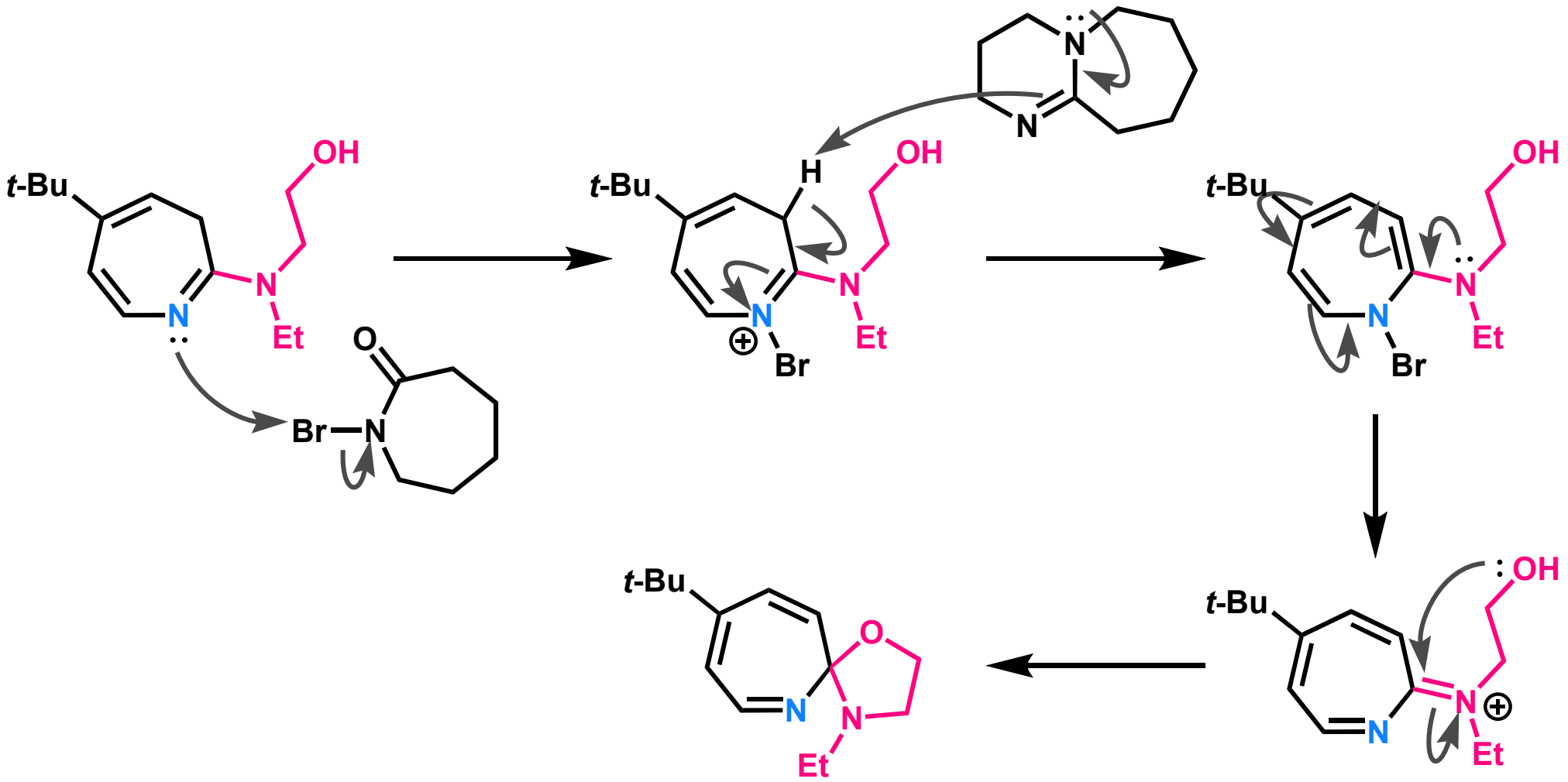
Zenzola, M.; Doran, R.; Degennaro, L.; Luisi, R.; Bull, J. A. *Angew. Chem. Int. Ed*. **2016**, *55*, 7203.

Appx. Section 4 / Optimization of Oxidant



Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

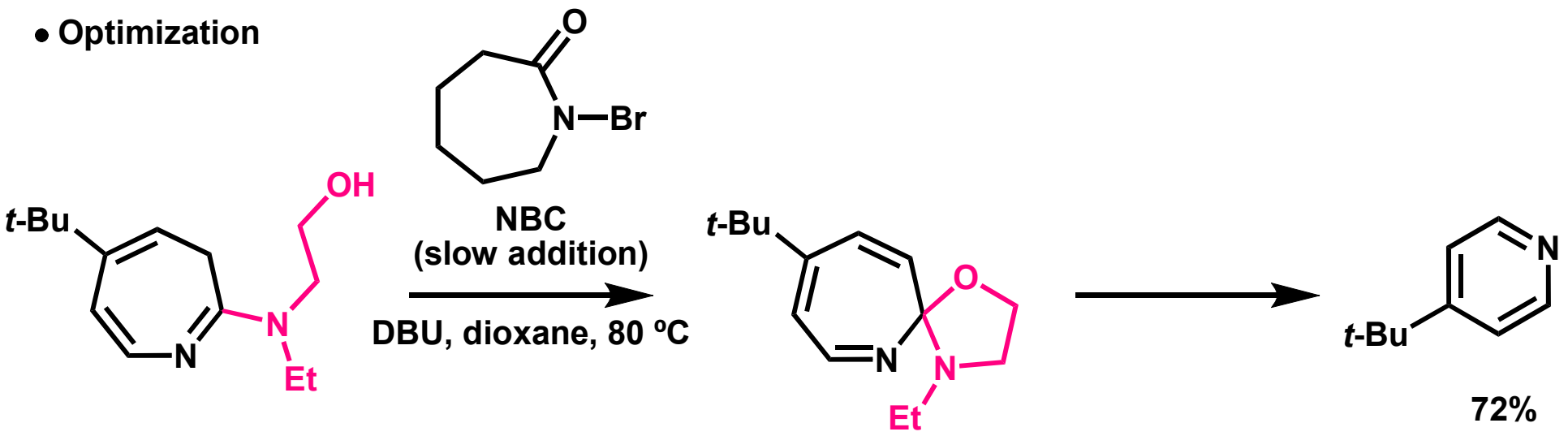
Reaction Mechanism



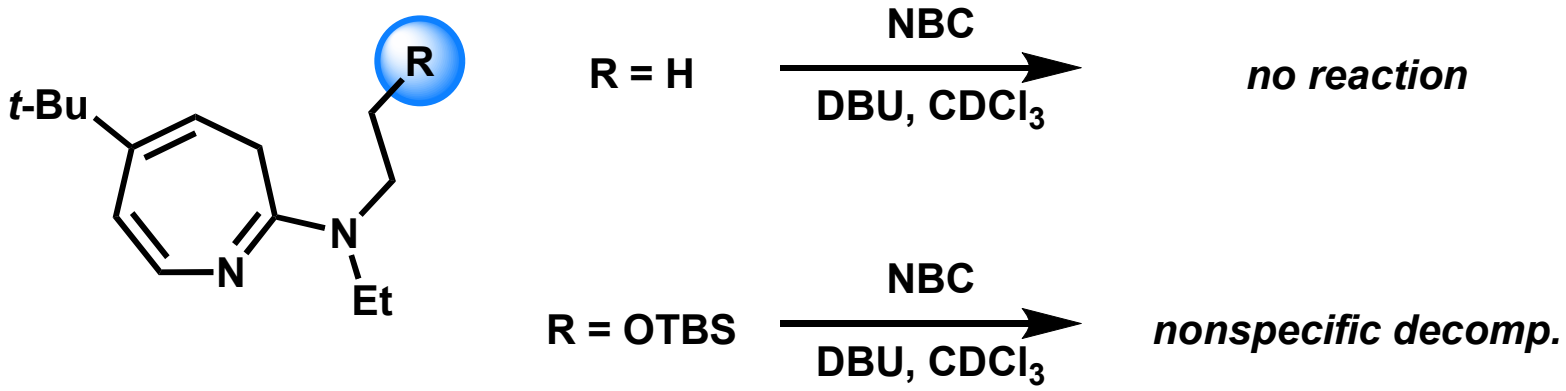
Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

Optimization and Control Experiment

- Optimization

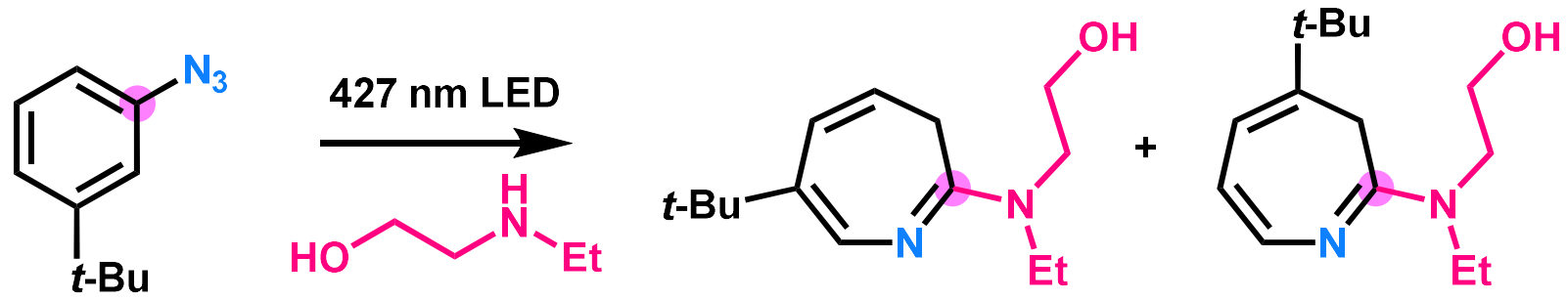


- Control experiment

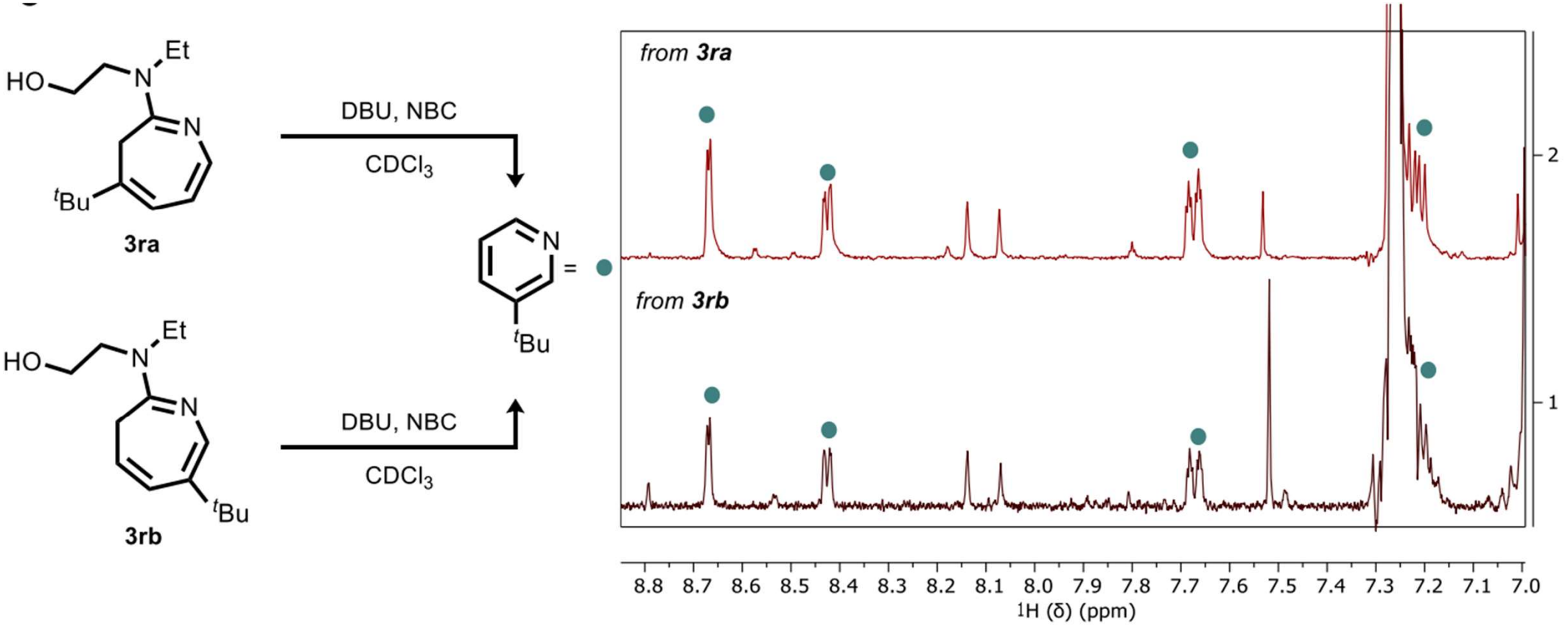


Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

Demonstration of Ipso Selectivity

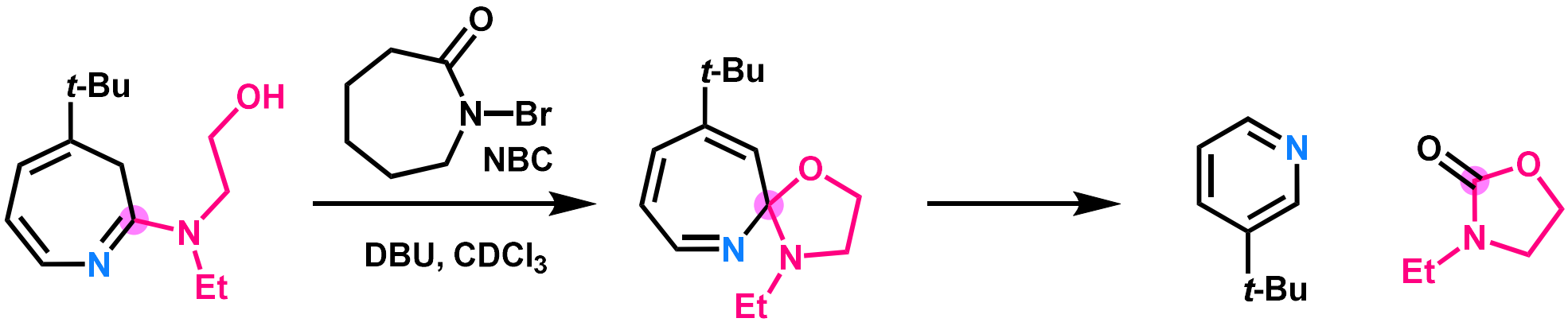


1 : 1 mixture

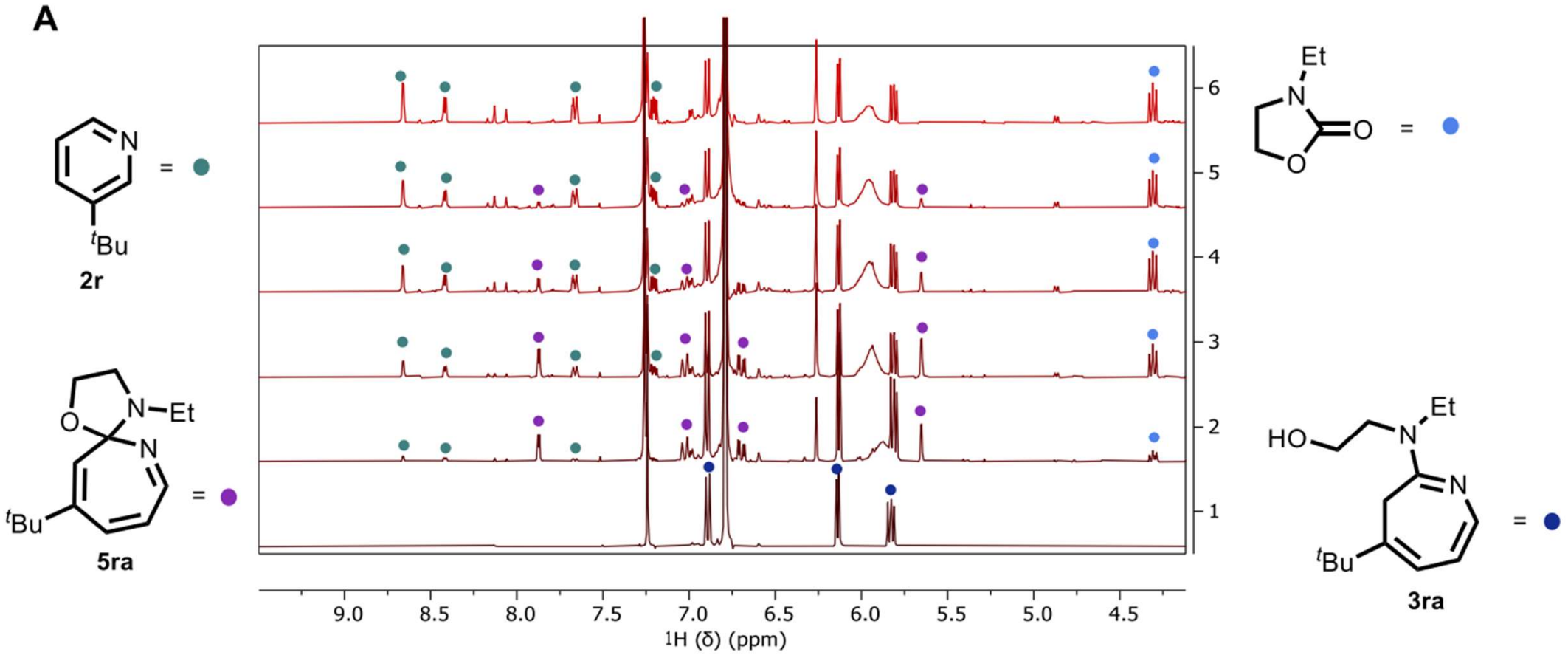


Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

Monitoring the Putative Spirocyclic intermediates

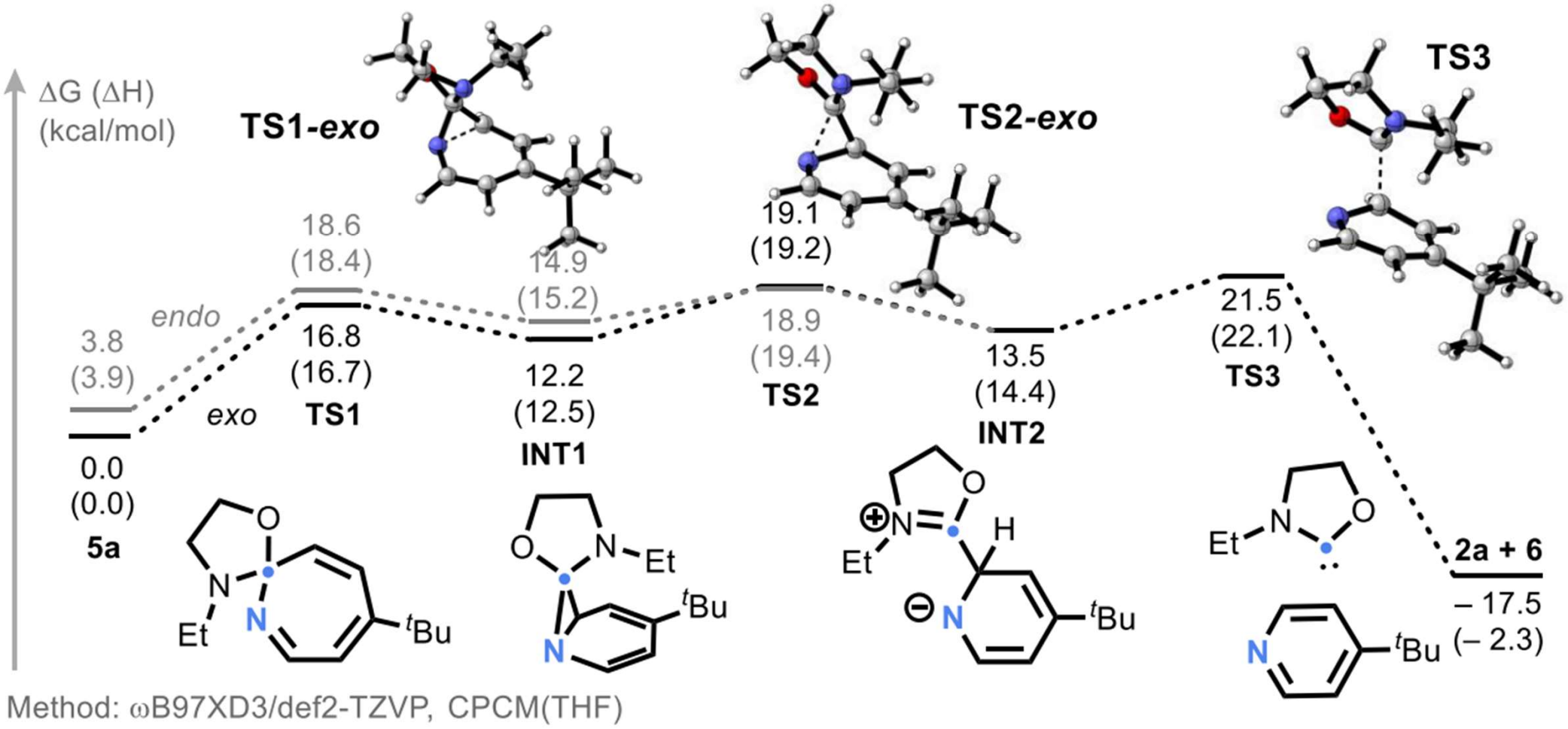


putative intermediate

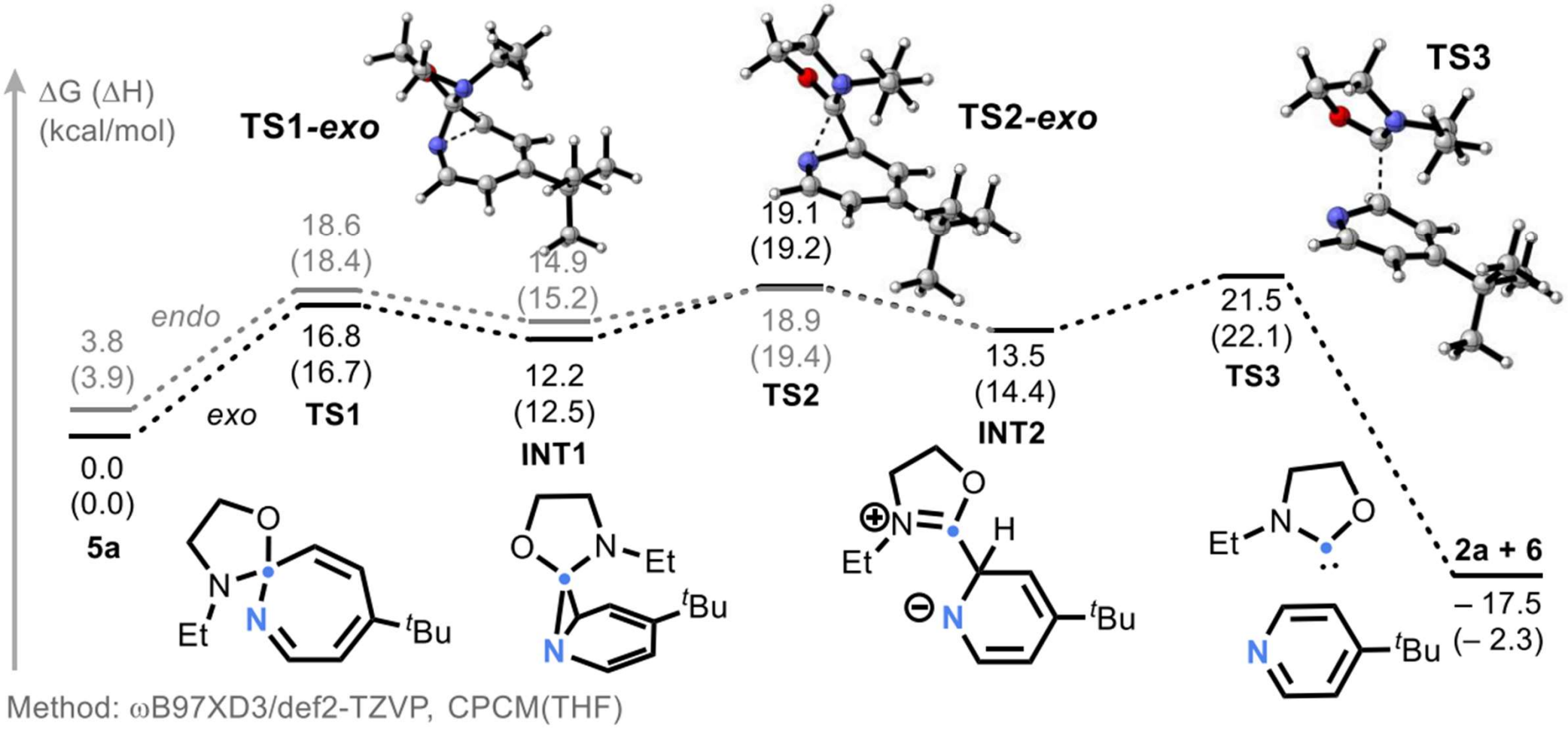


Pearson, T. J.; Shimazumi, R.; Driscoll, J. L.; Dherange, B. D.; Prak, D.; Levin, M. D. *Science* **2023**, *381*, 1474.

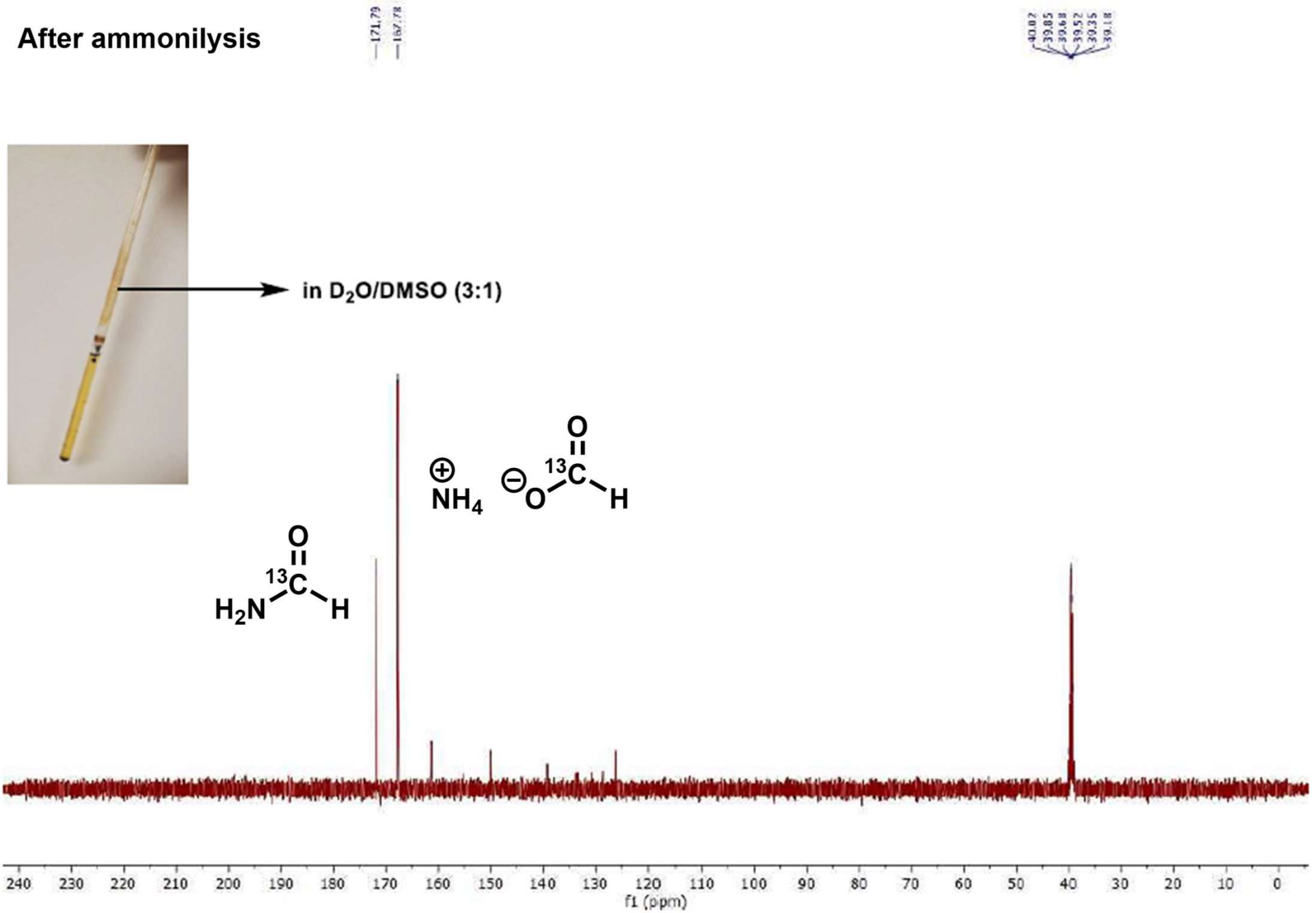
Computed Mechanism for Carbene Extrusion



Computed Mechanism for Carbene Extrusion

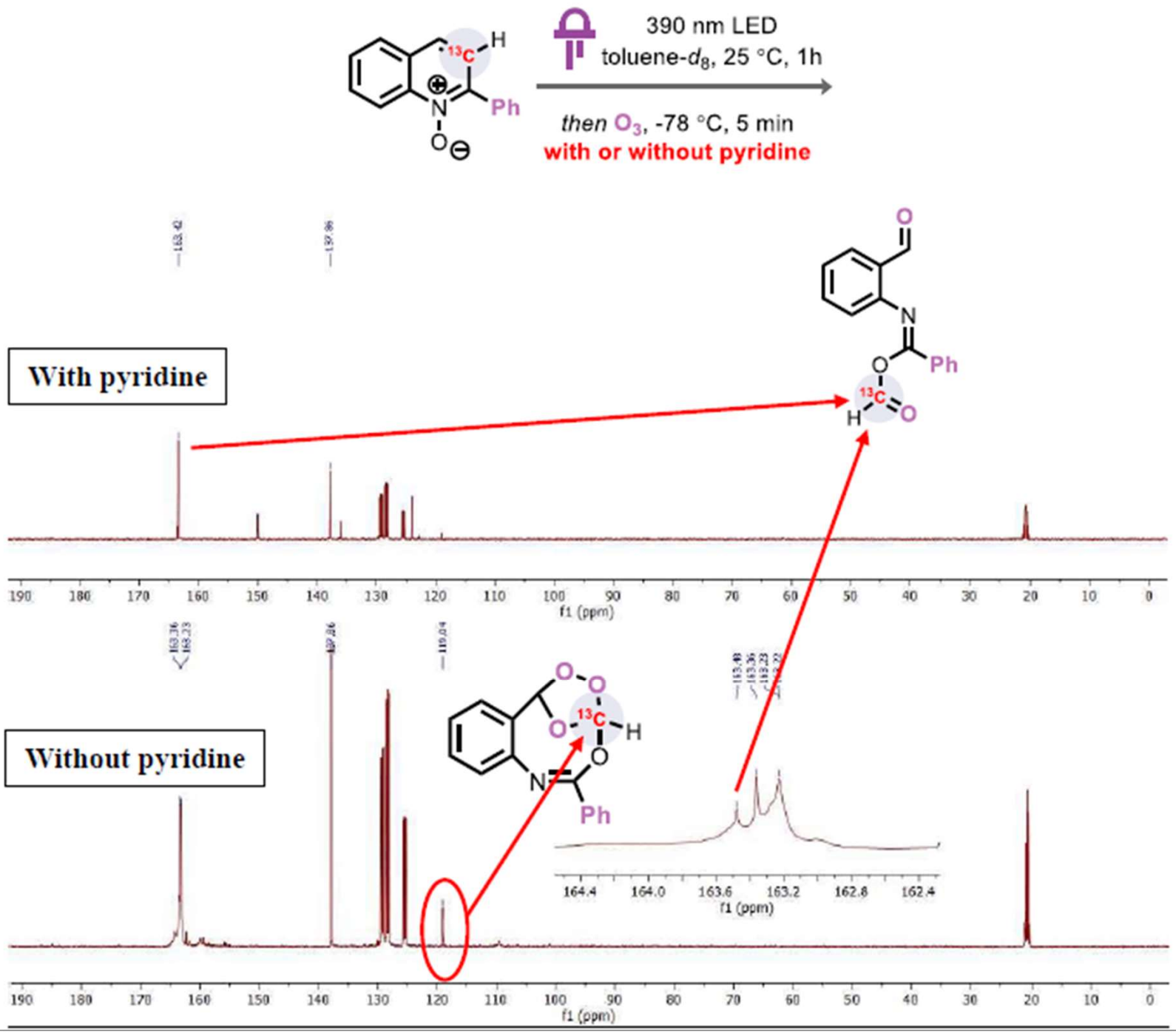


13C-NMR Shifts of Product Standards Measured in D_2O/DMSO (3:1)



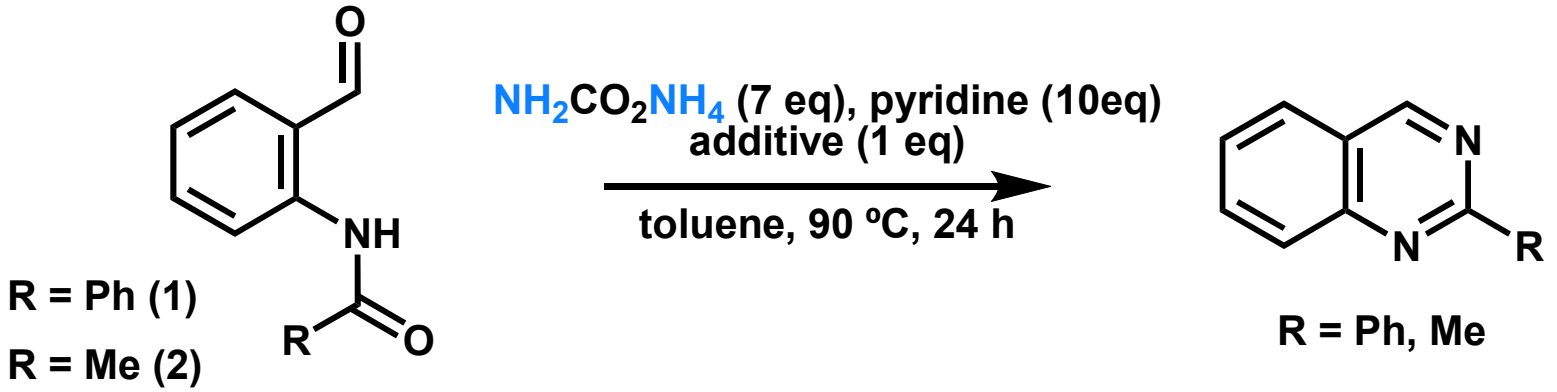
Woo, J.; Stein, C.; Christian, A. H.; Levin, M. D. *Nature* **2023**, *623*, 77.

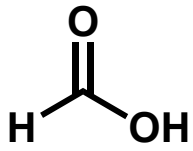
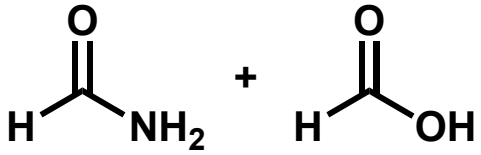
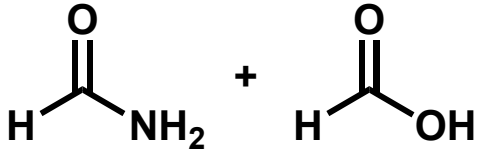
Oxidative Cleavage



Woo, J.; Stein, C.; Christian, A. H.; Levin, M. D. *Nature* **2023**, *623*, 77.

Control Experiment



substrate	additives	result
1 or 2	no additives	no reaction
1 or 2		trace quinazoline product
1	 (0.5 eq) + (0.5 eq)	17 % NMR yield (78% SM remaining)
2	 (0.5 eq) + (0.5 eq)	28 % NMR yield (55% SM remaining)

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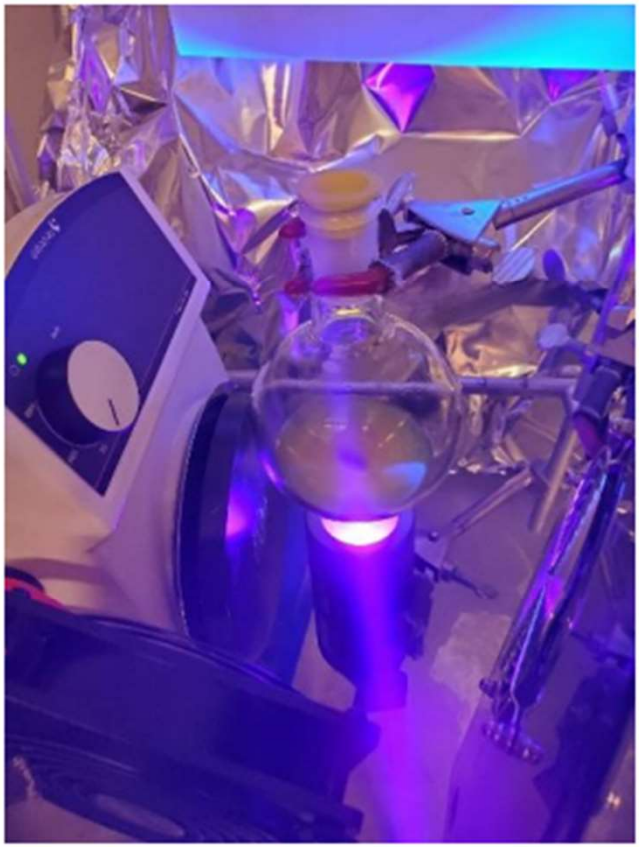
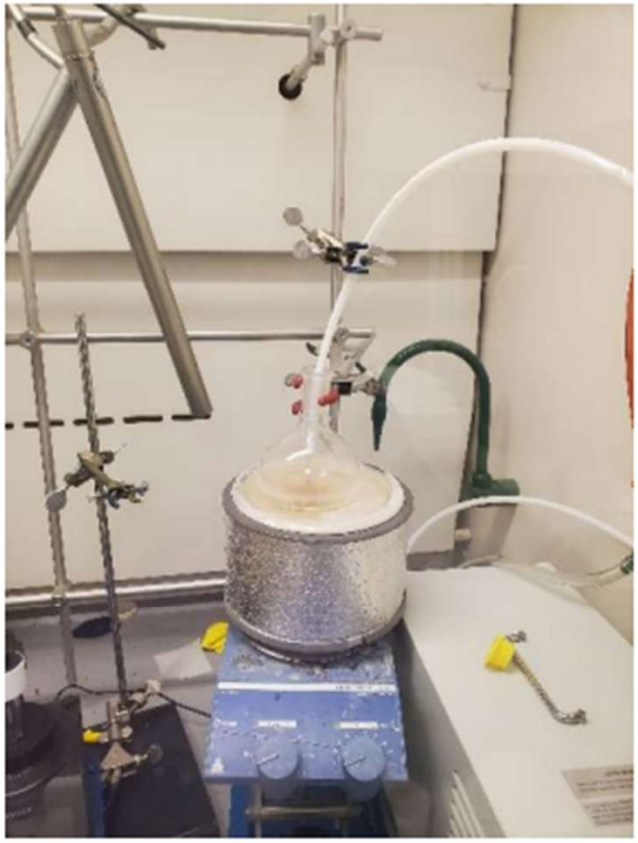
Gram-Scale Set Up (Levin Group)



1. gram-scale photolysis



2. Gram-scale ozonolysis

3. Gram-scale ammoniolysis

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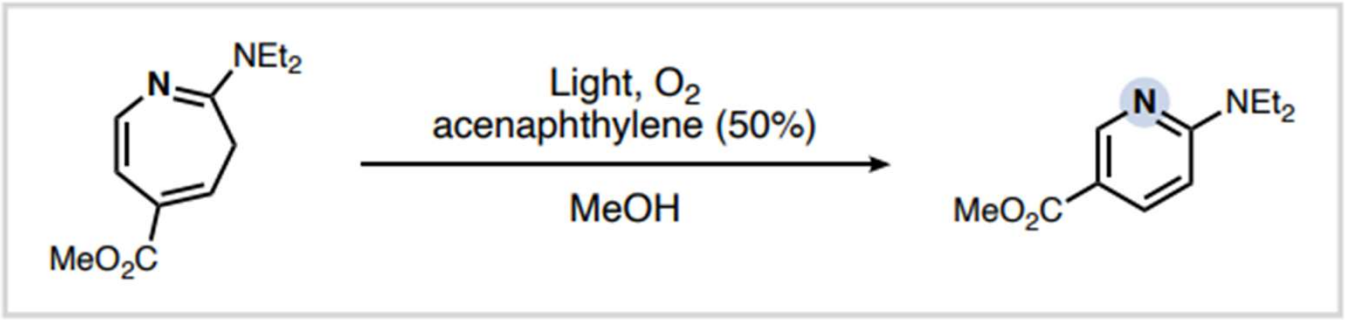
Optimization Of Light Sources

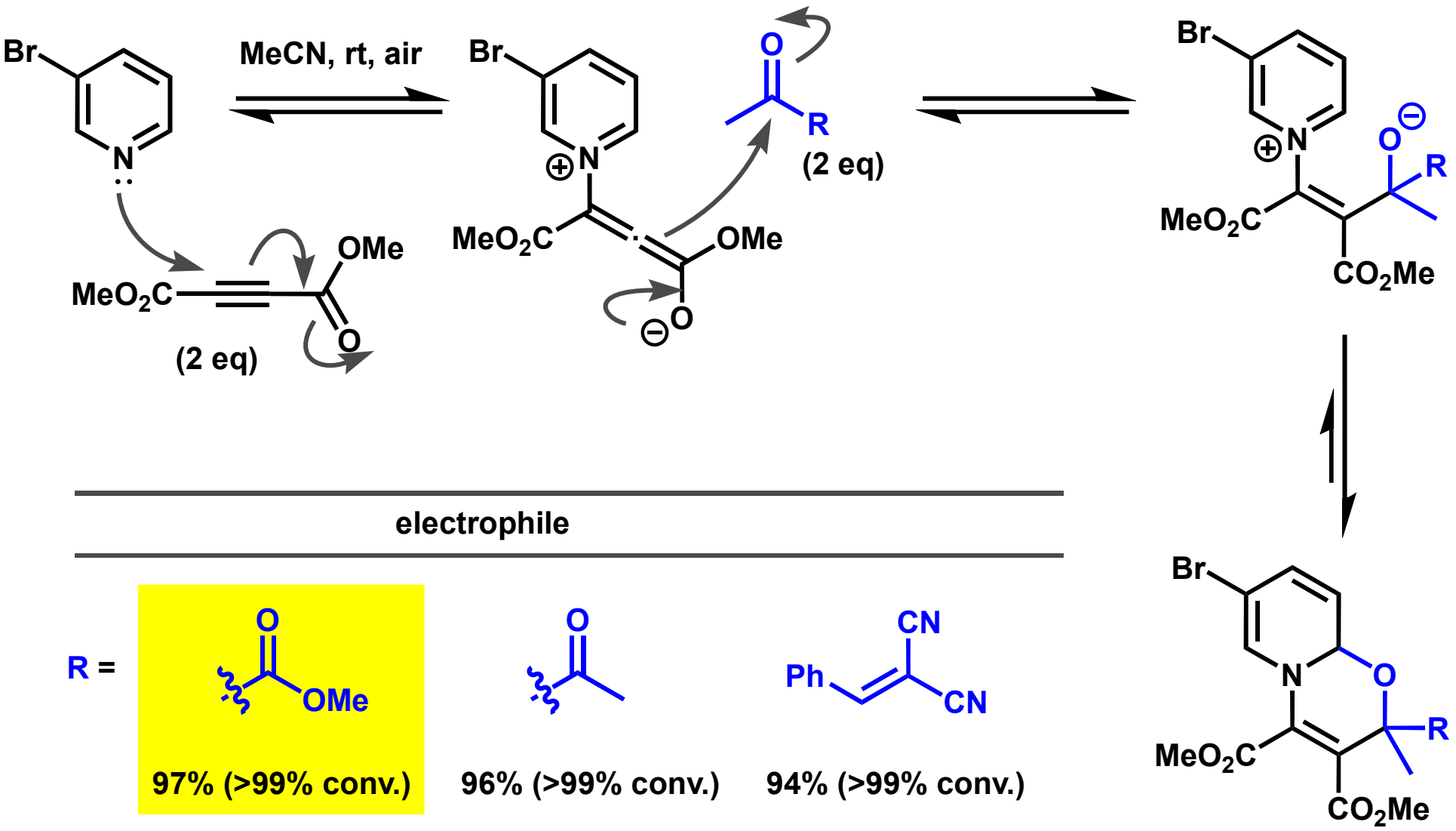
C. Variable light sources:



Entry	Light	Yield[a]
1	440 nm	53%
2	420 nm	12% (41% brsm)
3	350 nm	0% (41% rsm)

[a]determined using 1,4-dintrobenzene as an internal standard

Reaction Mechanism of Dearomatization



electrophile		
R =		
97% (>99% conv.)	96% (>99% conv.)	94% (>99% conv.)

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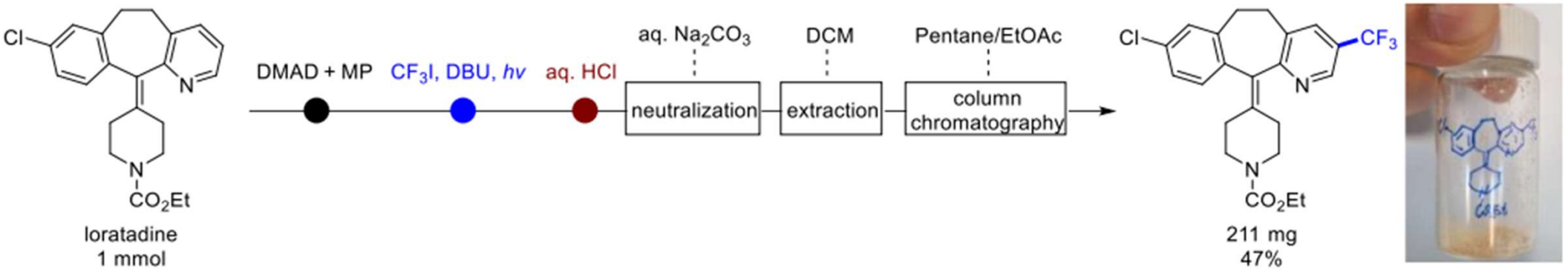
One-Pot Meta-Tfifluoromethylation of loratadine



a. dearomatization (0 h) | **b. dearomatization (12 h)** | **c. trifluoromethylation (0 h)** | **d. trifluoromethylation (24 h)** | **e. rearomatization (0 h)** | **f. rearomatization (24 h)**

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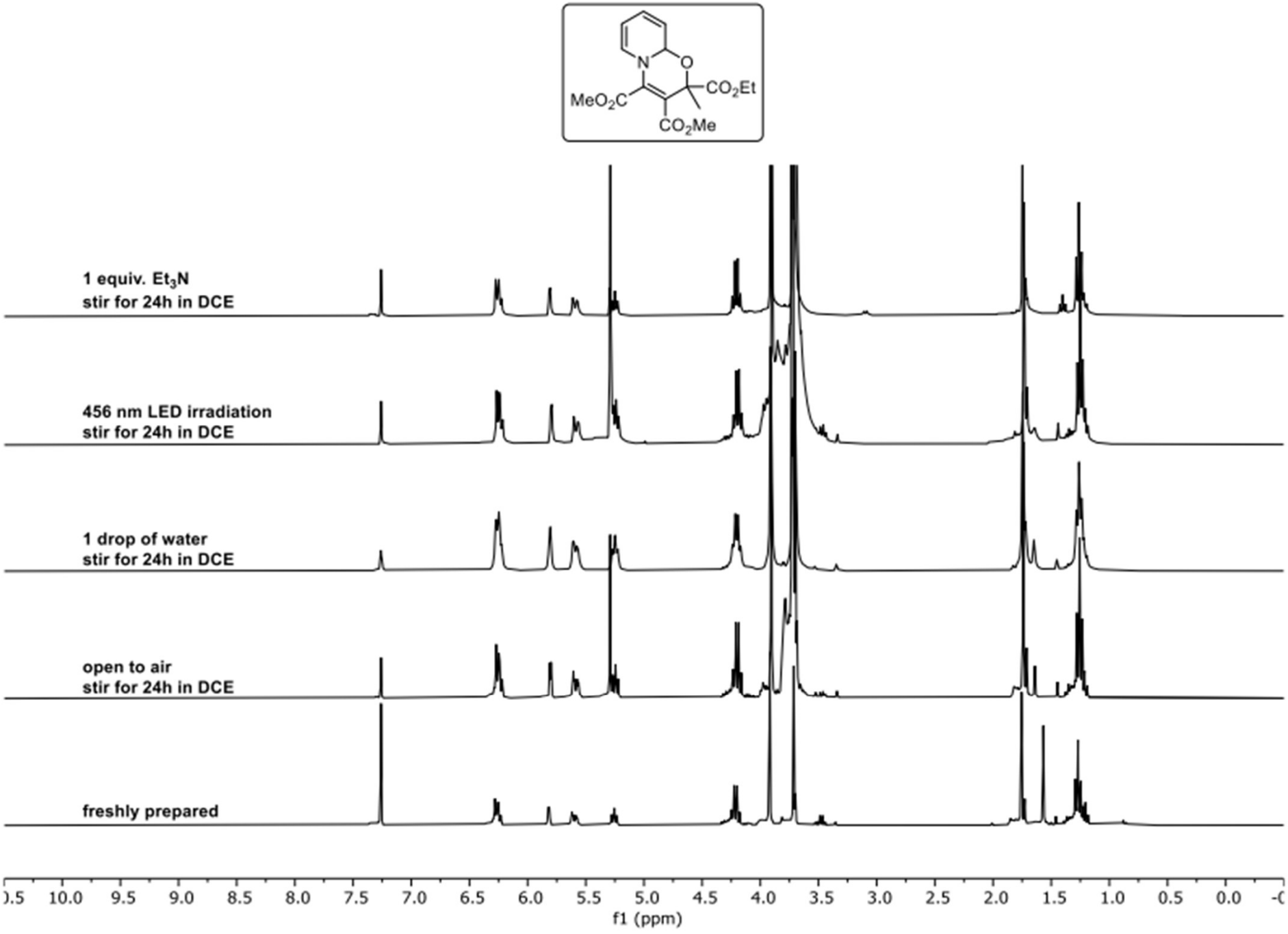
Stability of the Dearomatized Intermediates



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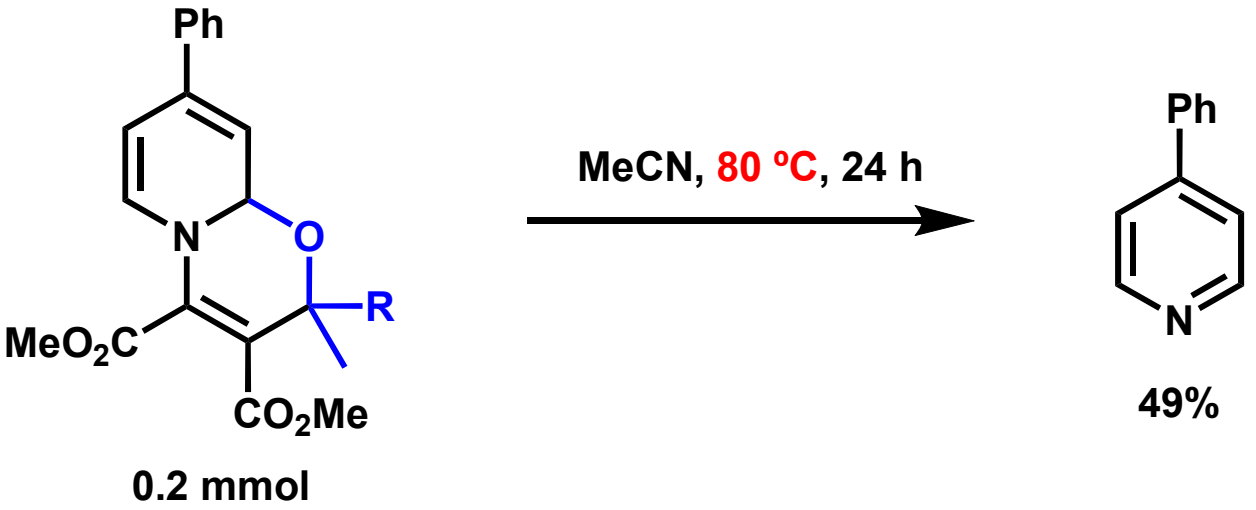
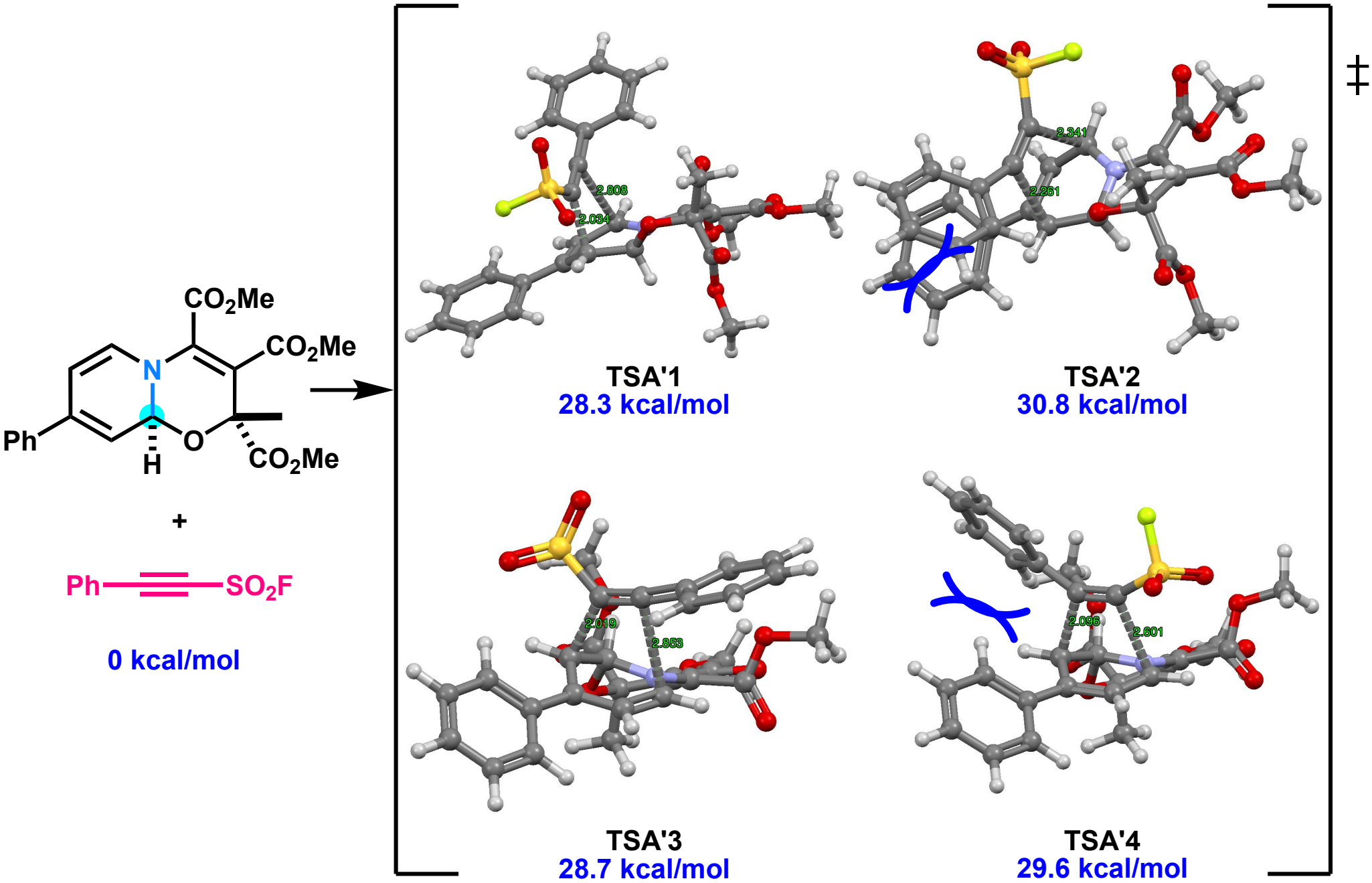
Control Experiment



Cheng, Q.; Bhattacharya, D.; Haring, M.; Cao, H.; Lichtenfeld, C.-M.; Studer, A. *Nat. Chem.* **2023**, 16, 741.

Selectivity of [4+2] Cycloaaddition (3)



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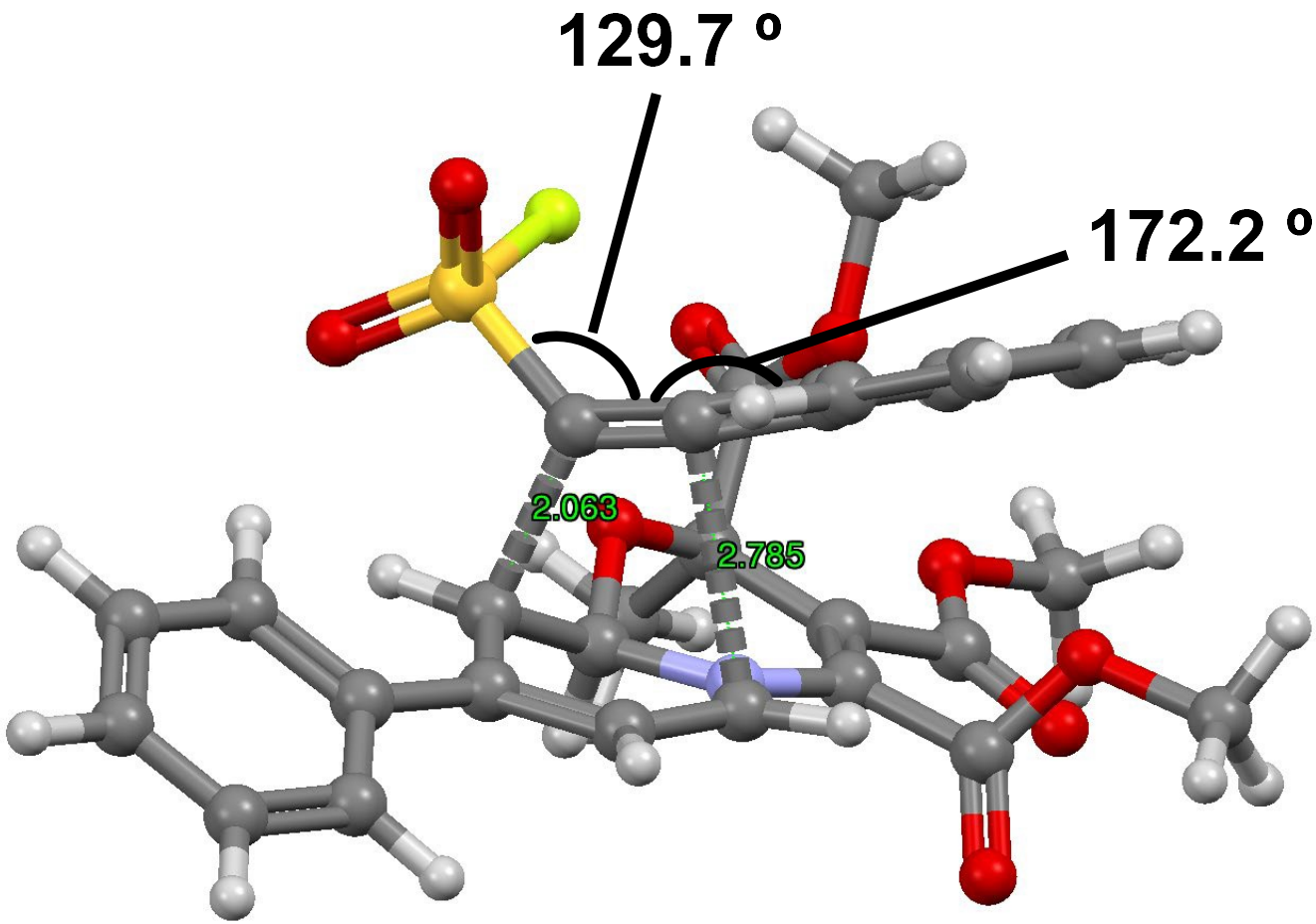
Bond Angles of the Triple Bond



TSA3

TS	ΔE_{def} (A/A')[a] [kcal/mol]	ΔE_{def} (D)[a] [kcal/mol]	ΔE_{int}(A/A'-D)[b] [kcal/mol]	$\Delta G^{RRHO}{}_{353}$[c] [kcal/mol]	$\Delta G^{solv}{}_{353}$[c] (1,4-dioxane) [kcal/mol]	**$\Delta G(353)_{solv}$[c] (1,4-dioxane) [kcal/mol]**
TSA1	14.15	12.32	-14.97	19.25	-1.78	28.97
TSA2	16.76	22.96	-23.53	19.45	-2.89	32.75
TSA3	12.36	13.33	-18.06	19.80	-0.98	26.44
TSA4	15.41	18.97	-25.12	19.05	-1.14	27.16

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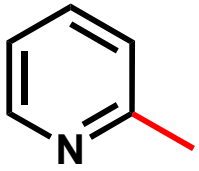
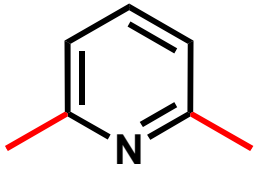
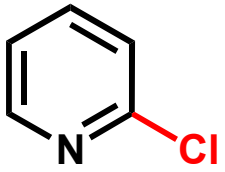
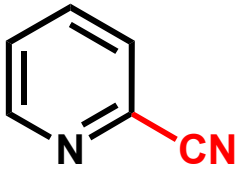
Unsuccessful Pyridines in the Initial Dearomatization Step

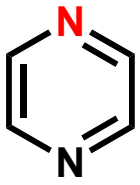


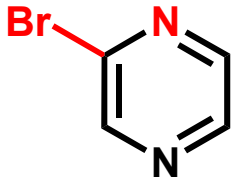


messy









no conversion

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