Photodecarbonylation of strained heterocycles: Synthetic applications, experimental insights, and computational models

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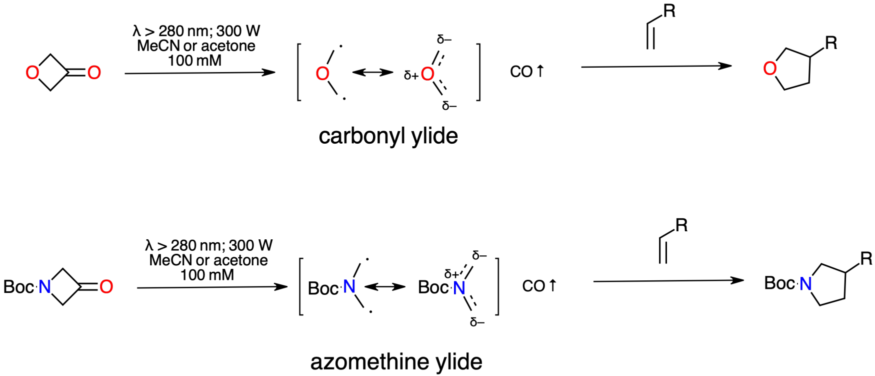
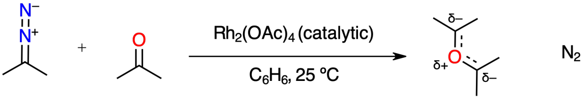
Indianapolis

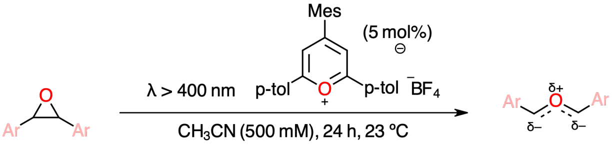
Access to the simplest ylides[1]



[1] Manvendra Singh et al. "Photochemical Decarbonylation of Oxetanone and Azetidinone: Spectroscopy, Computational Models, and Synthetic Applications". In: Angewandte Chemie International Edition 62.3 (2023), e202215856.

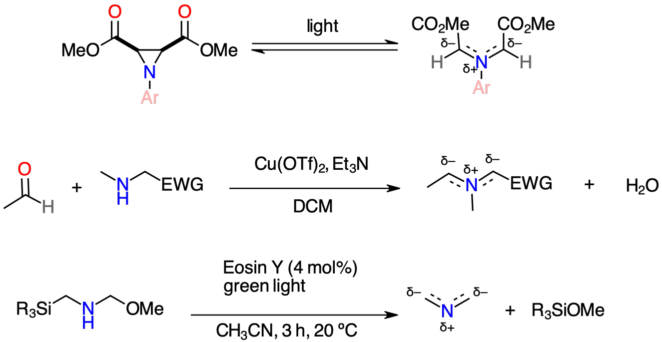
Methods of carbonyl ylide synthesis[2]





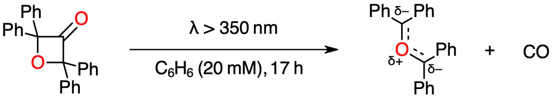
[2] Albert Padwa. "Generation and utilization of carbonyl ylides via the tandem cyclization-cycloaddition method". en. In: Accounts of Chemical Research 24.1 (Jan. 1991), pp. 22–28, Edwin Alfonzo, Felix Steven Alfonso, and Aaron B. Beeler. "Redesign of a Pyrylium Photoredox Catalyst and Its Application to the Generation of Carbonyl Ylides". In: Organic Letters 19.11 (June 2017), pp. 2989–2992.

Azomethine ylide synthesis[3]



[3] Rolf. Huisgen, Wolfgang. Scheer, and Helmut. Huber. "Stereospecific Conversion of *cis-trans* Isomeric Aziridines to Open-Chain Azomethine Ylides". In: Journal of the American Chemical Society 89.7 (Mar. 1967), pp. 1753–1755, Robert M. Williams et al. "Asymmetric [1,3]-dipolar cycloaddition reactions: synthesis of highly substituted proline derivatives". In: The Journal of Organic Chemistry 57.24 (Nov. 1992), pp. 6527–6532, Pat N. Confalone and Edward M. Huie. "The stabilized iminium ylide-olefin [3+2] cycloaddition reaction. Total synthesis of Sceletium alkaloid A4". In: Journal of the American Chemical Society 106.23 (Nov. 1984), pp. 7175–7178.

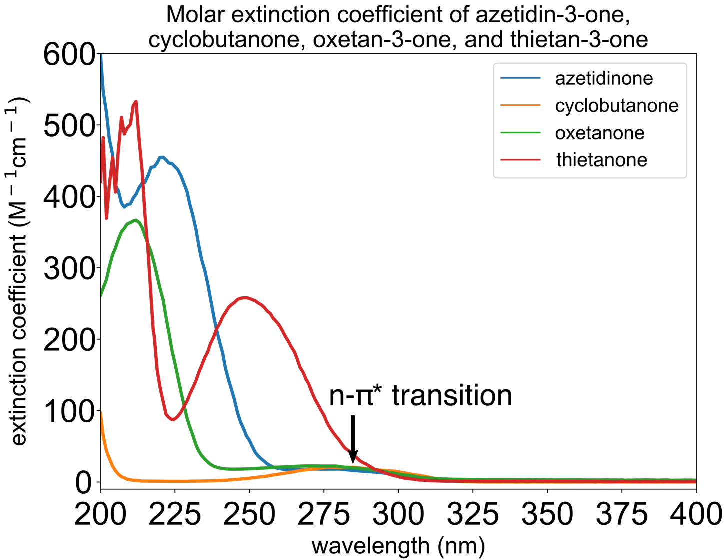
Griffin-Joullié observation[4]



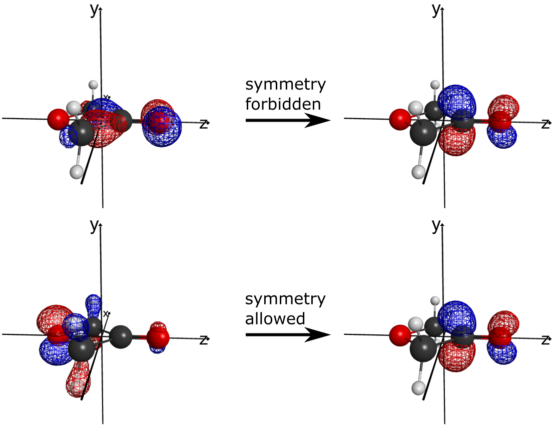
No synthetic application.

[4] J. P. Wasacz et al. "Photochemistry of 2,2,4,4-tetraphenyloxetan-3-one. Intermediates in the photofragmentation of aryl substituted oxiranes". en. In: The Journal of Organic Chemistry 41.3 (Feb. 1976), pp. 572–574.

$\pi^* \leftarrow n$ absorption

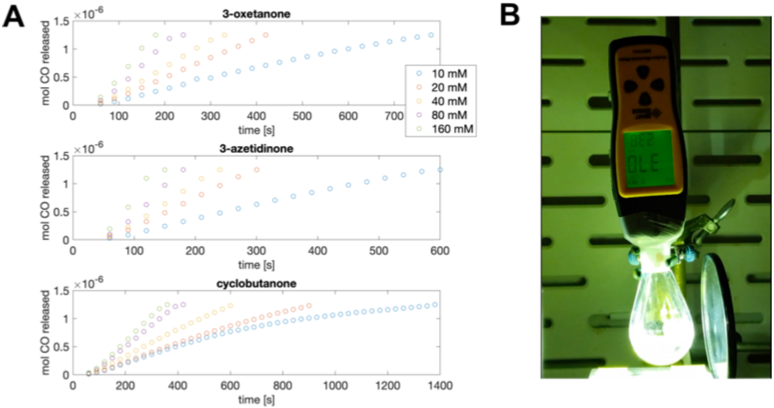


Symmetry controlled excitation

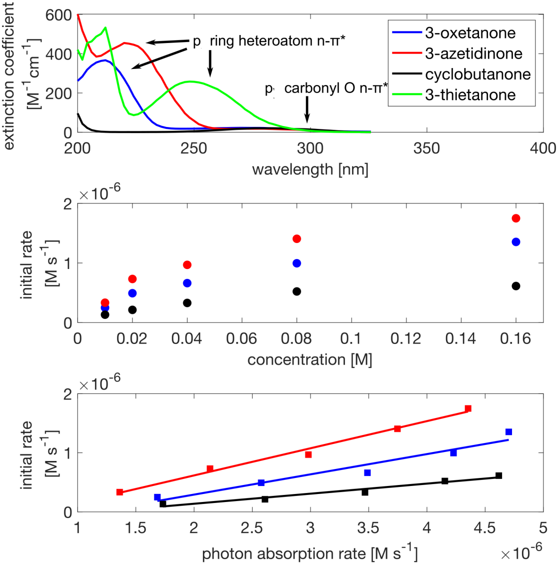


CO evolution

Convenient measure of reaction kinetics.

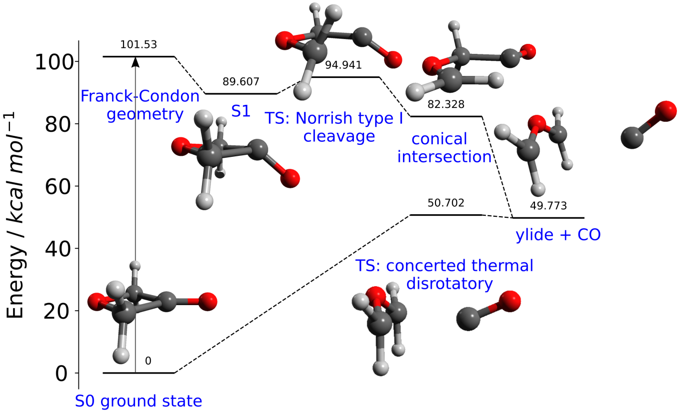


CO evolution



Model

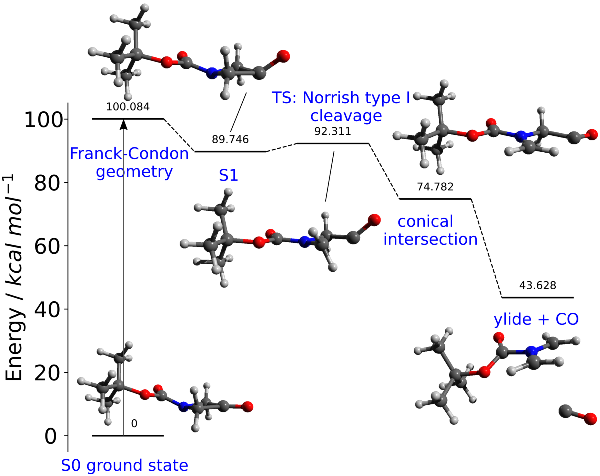
Carbonyl ylide formation



DFT for ground states B3LYP/6-311+G(2d,p)
TD-DFT for excited state energies; spin-flip for conical intersection

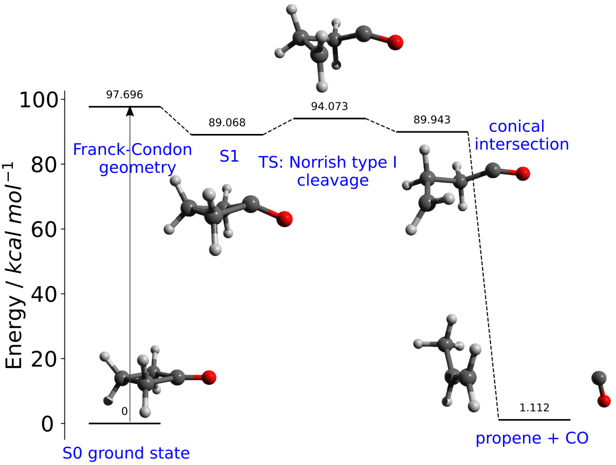
Model

Azomethine ylide formation

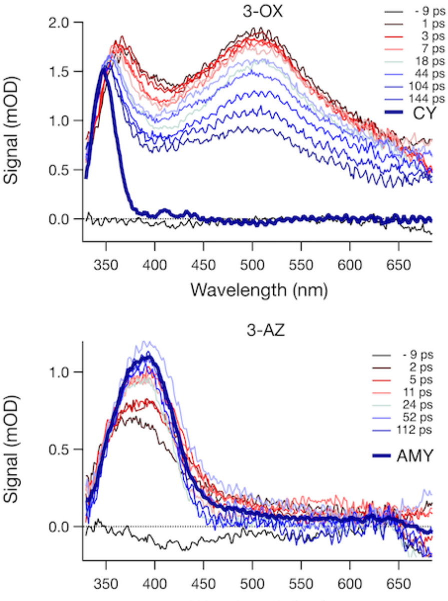


Model

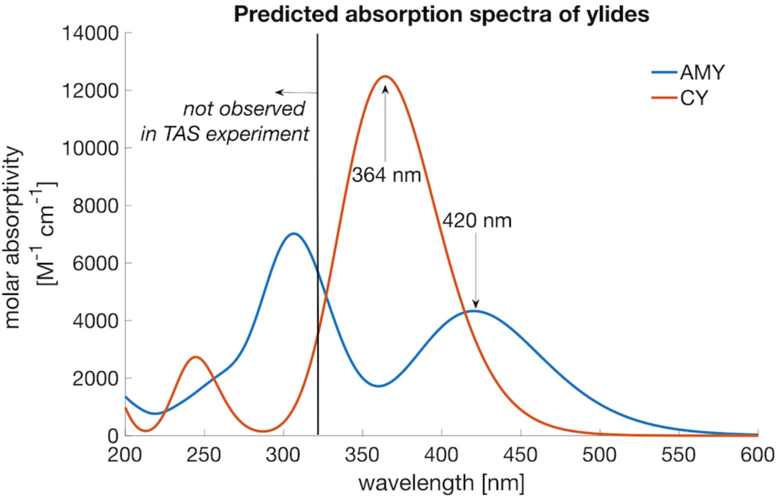
Cyclobutanone opening



Transient absorption spectroscopy

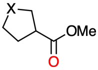


Transient absorption spectroscopy

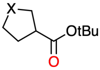


Scope

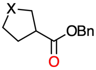
acrylates



X = O, 35%
X = NBoc, 75%
X = NTs, 80%

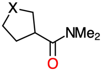


X = O, 28%
X = NBoc, 42%

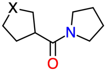


X = O, 33%
X = NBoc, 56%

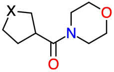
acrylamides



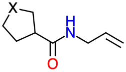
X = O, 47% (54%)*
X = NBoc, 67 %



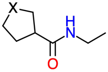
X = O, 54% (70%)*
X = NBoc, 67 %



X = NBoc, 56%

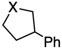


X = O, 25%
X = NBoc, 49%

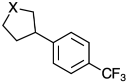


X = O, 68%
X = NBoc, 71%

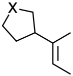
styrenes



X = O, 30% (51%)#
X = NBoc, 35 %

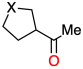


X = NBoc, 42%



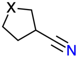
X = O, 32%
X = NBoc, 44%

vinyl ketones



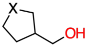
X = O, 20% (60%)#
X = NBoc, 24%

acrylonitriles

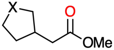


X = O, 40%
X = NBoc, 71%

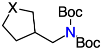
non-conjugated olefins



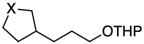
X = O, 48%



X = O, 30%



X = O, 32%

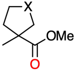


X = O, 61%

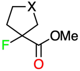
Scope

disubstituted olefins

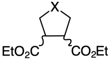
X = O, 48%
X = NBoc, 76%



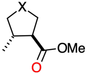
X = O, 48% (51%)*
X = NBoc, 75%



X = O, 40%
X = NBoc, 64%

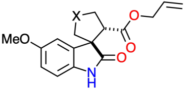


X = O, 53%
(trans:cis = 1:3)
X = NBoc, 75%
(trans:cis = 1:1)

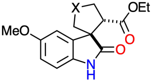


X = O, 44%
X = NBoc, 79%

trisubstituted olefins

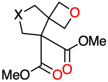


X = O, 21%

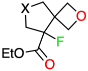


X = O, 34%

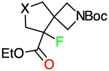
tetrasubstituted olefins



X = O, 42%
X = NBoc, 57%

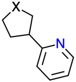


X = O, 38% (49%)*
X = NBoc, 54% (61%)*

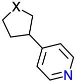


X = O, 65%
X = NBoc, 60%
(45%)*

heterocyclic olefins

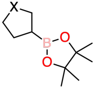


X = O, 20%
X = NBoc, 41%

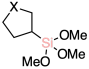


X = O, 20%
X = NH, 41%

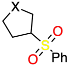
vinyl heteroatoms



X = O, 50% (71%)*
X = Nboc, 66%

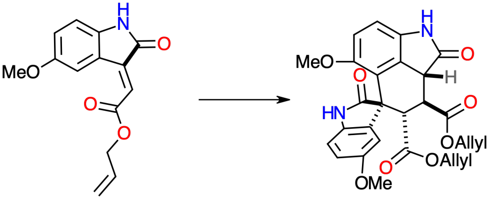


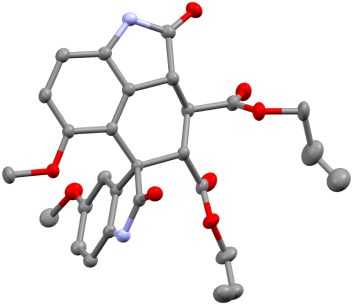
X = O, 44%
X = Nboc, 47%



X = O, 58%
X = Nboc, 72%

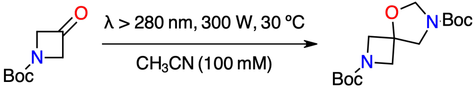
Dimer



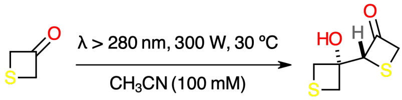


CCDC: 2193412

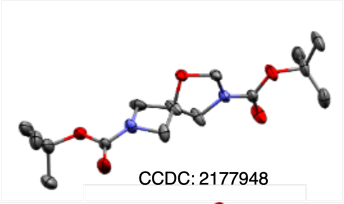
Homo-coupling

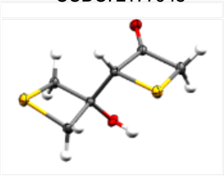


69%



40%

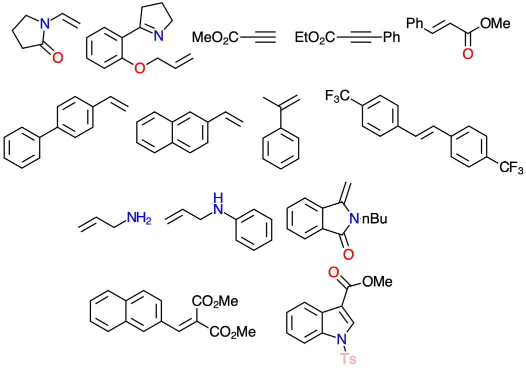




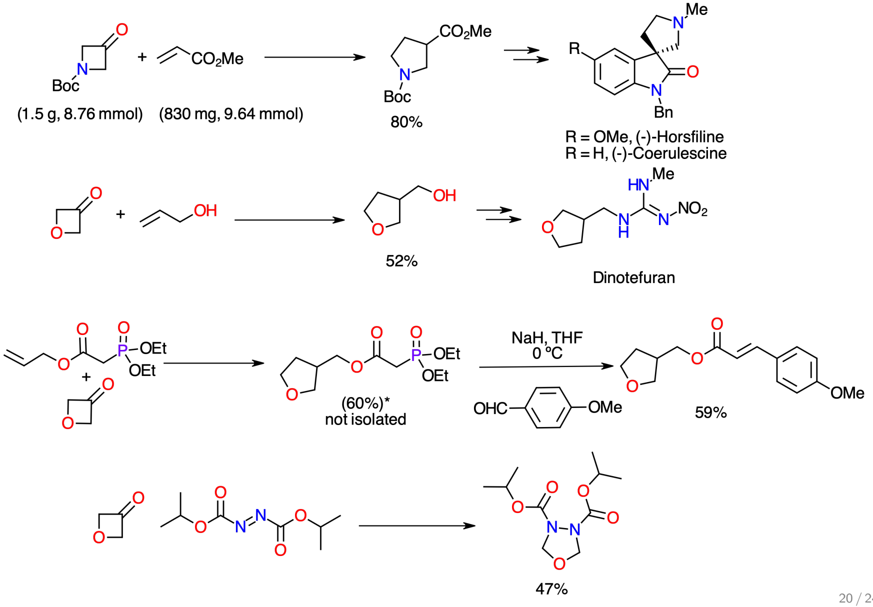
CCDC: 2179526

Anti-scope

Substrates that did not give the expected products.

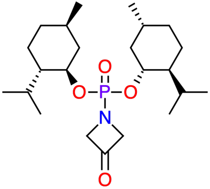


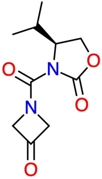
Use

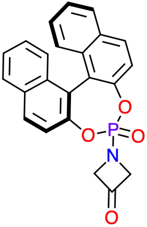

(1.5 g, 8.76 mmol)
(830 mg, 9.64 mmol)
80%
R = OMe, (-)-Horsfiline
R = H, (-)-Coerulescine
52%
Dinotefuran
(60%)*
not isolated
NaH, THF
0 °C
59%
47%

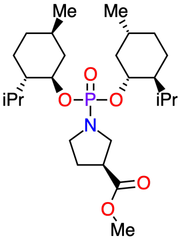
Chiral auxiliary

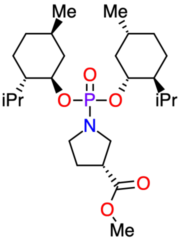
Diastereoselective β-proline synthesis.





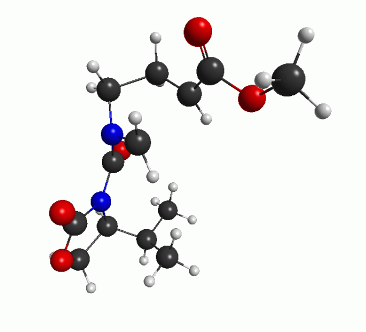


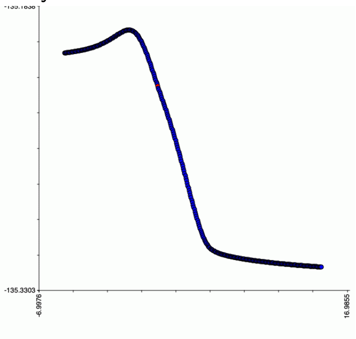




Can we achieve facial selectivity?

Early transition state.
About 7 kcal/mol activation energy from ylide.





Lab goals

- Experimentally access new chemical space through the "upside-down" world of photochemistry
- Leverage measurements and quantitative models to better understand and improve synthetic chemistry
- Connect structures of newly made molecules to their biological effects in complex living systems

Credits

Current group:

Manvendra Singh	Graduate student
Bryce Gaskins	Undergraduate student
Mauricio Bahena Garcia	Graduate student
Victor Fadare	Graduate student
Alhamza Hamza	PharmD student
Elizabeth Miller	Undergraduate student

Collaborators:
Elles lab KU (Transient absorption spectroscopy)

Funding:
Chemical Biology of Infectious Disease COBRE pilot project, General Research Fund (KU), KU Cancer Center pilot project, XSEDE/ACCESS NSF computational resource.

Former group members:
Zach Pearson (UG), Sri Kolluru (PDF), Pawan Dhote (PDF), Nathan Garza (Tech), Amar Kumar (GRA), Koki Takemoto (GRA), Matt McCurry (GRA), Vishva Shah (UG), Cybelle Arrey (PharmD), Ambrosee Wilkinson (UG).