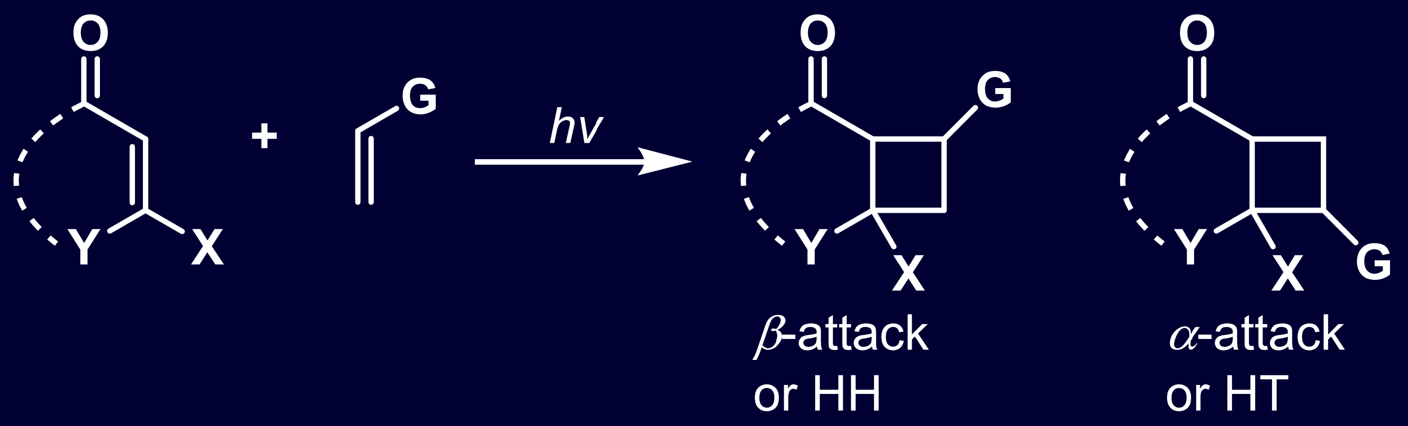


[2+2] Photocycloaddtion of α, β-Enones to Alkenes

Mechanism and Selectivity

Jingyao Bai
CCME, Peking University

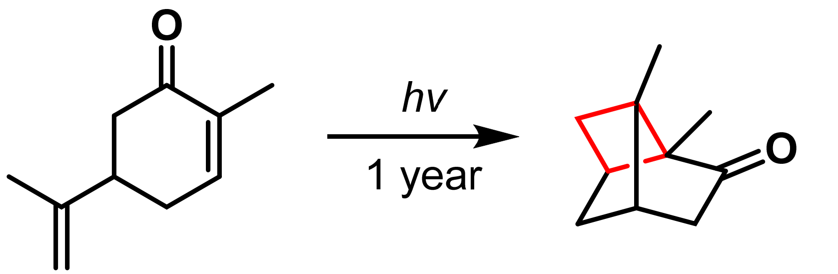
2022.02.26

Outline

- Introduction
  - History
  - Corey-de Mayo exciplex mechanism
- Mechanistic Studies
  - Excitation and excited states of enone
  - Formation of 1,4-diradical
  - Fates of singlet diradical
  - ISC of triplet diradical
- Selectivity
  - Regiochemistry
  - Stereochemistry
- Summary

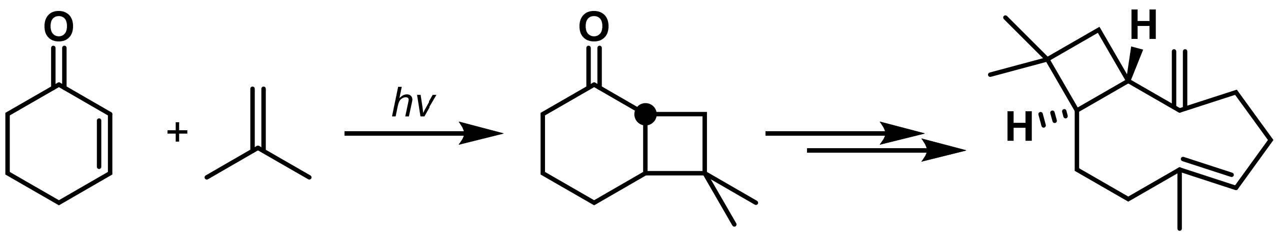
Introduction

➢ First reported by Ciamician in 1908

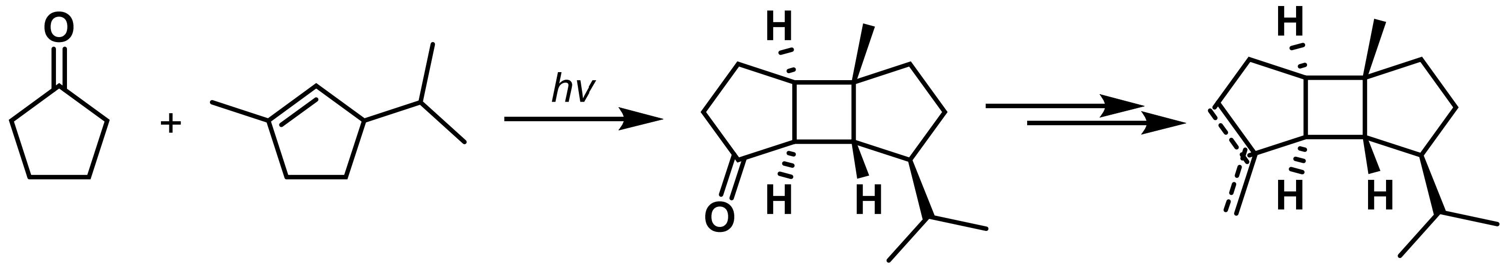


carvone　　　carvone camphor

➢ Mid-20th century: Use in total synthesis of natural products



β-caryophyllene, Corey 1964

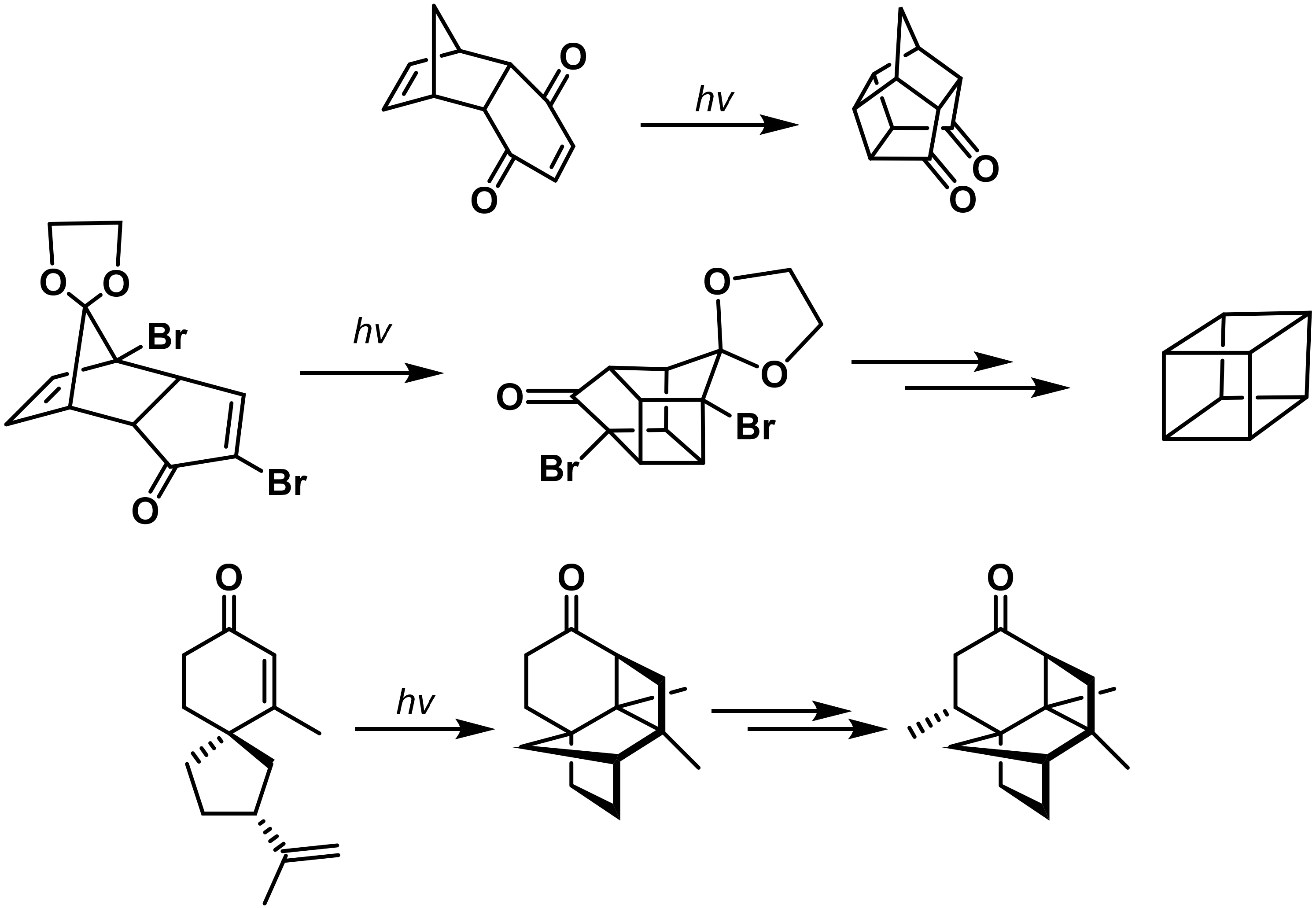


Bourbonene, White 1968

Corey, E. J. et al. *J. Am. Chem. Soc.* **1964**, *86*, 485.
White, J. D. et al. *J. Am. Chem. Soc.* **1968**, *90*, 6171.
Ciamician, G. et al. *Berichte der Deutschen Chemischen Gesellschaft* **1908,** 41, 1928.

Introduction

- Formation of strained structures

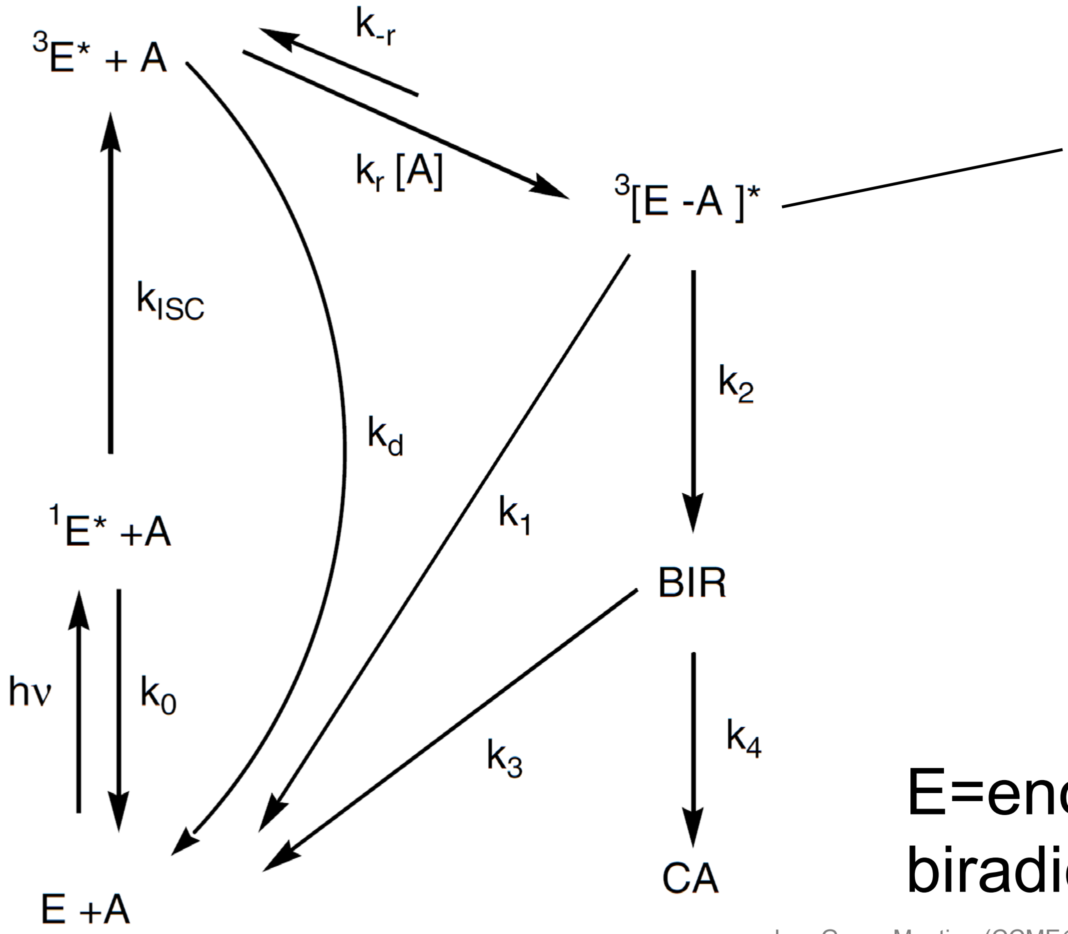


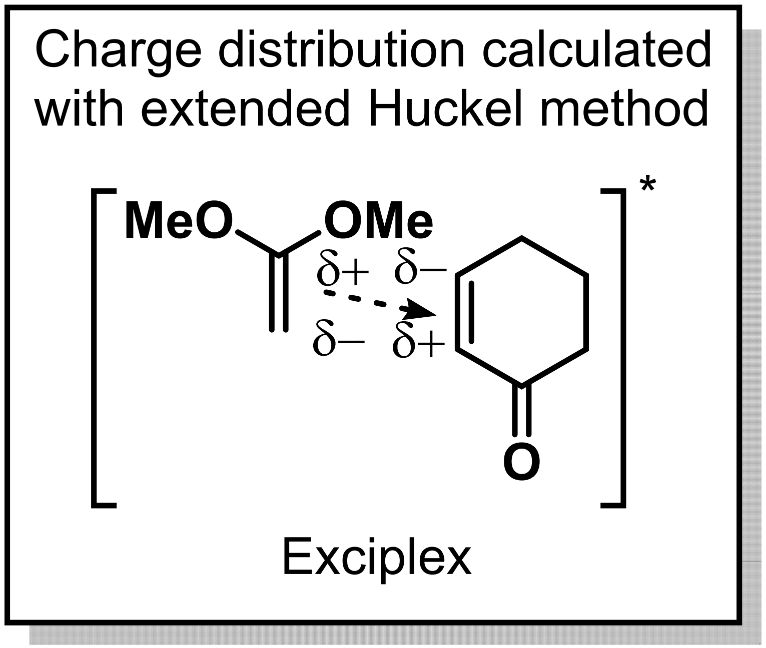
Cookson, R. C. et al. *J. Chem. Ind.* **1958**, 1003.
Eaton, P. E. et al. *J. Am. Chem. Soc.* **1964**, 86, 3157.
Srikrishna, A. et al. *Tetrahedron Lett.* **2005**, *46, 7373.*

Introduction

➢Corey-de Mayo “exciplex” mechanism, 1977

- First widely accepted mechanism for [2+2] photocycloaddition of enone and alkene





E=enone, A=alkene, BIR=1,4-biradical, CA =cycloadducts

Loutfy, R. O. et al. *J. Am. Chem. Soc.* **1977,** *99*, 3559.

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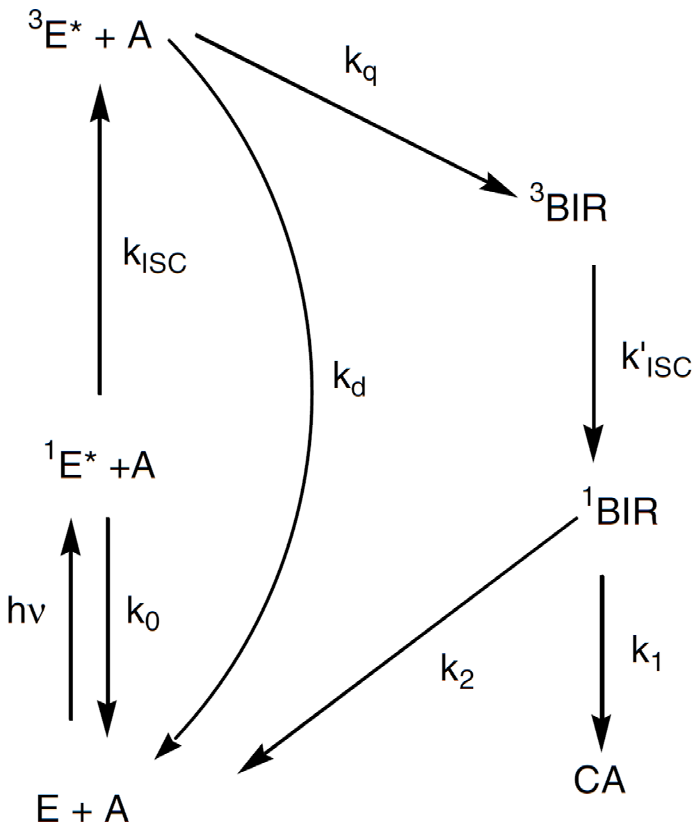
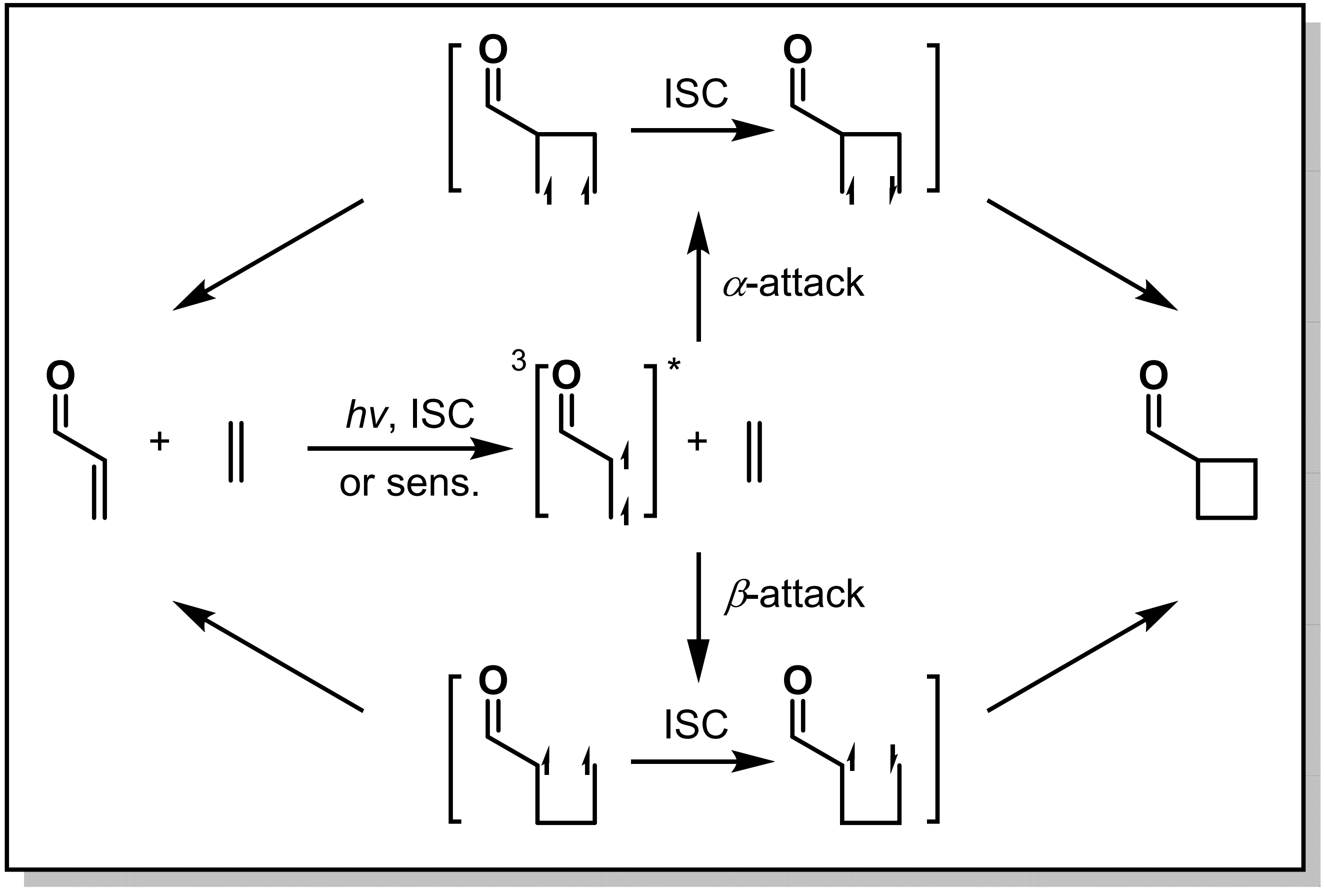
  - Stereochemistry
- Summary

Mechanistic Studies

➢The Bauslaugh–Schuster–Weedon Mechanism



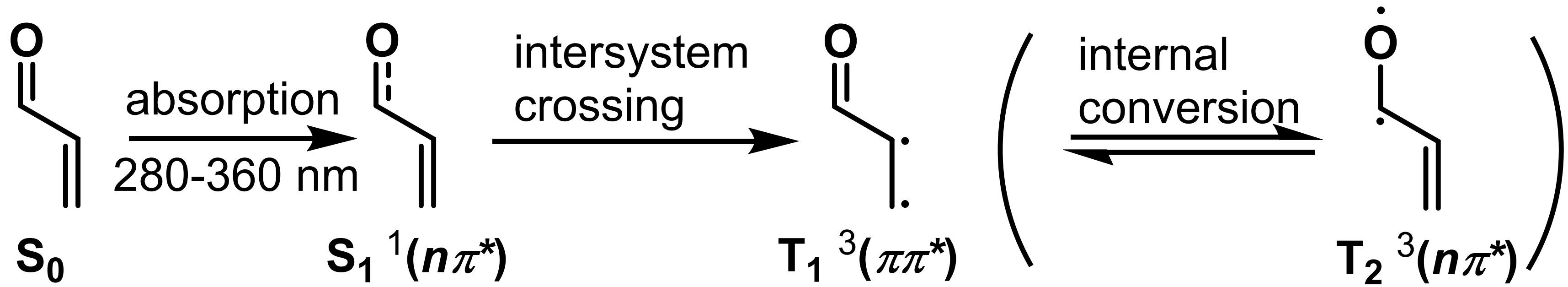


Schuster, D. I. et al. *Chem. Rev.* **1993**, *93*. 3.

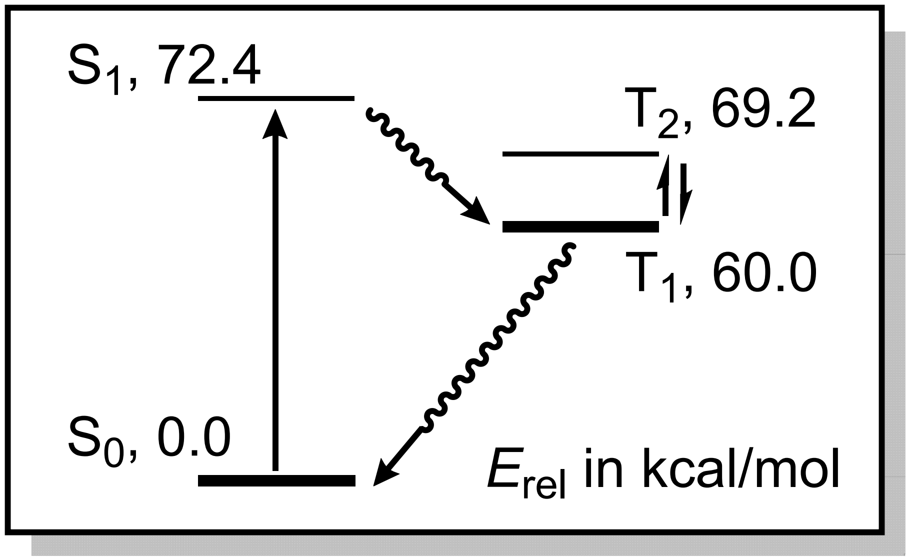
Mechanistic Studies

➢ Excitation of enone

- Quick intersystem crossing



- Calculated E_{rel} of acrolein

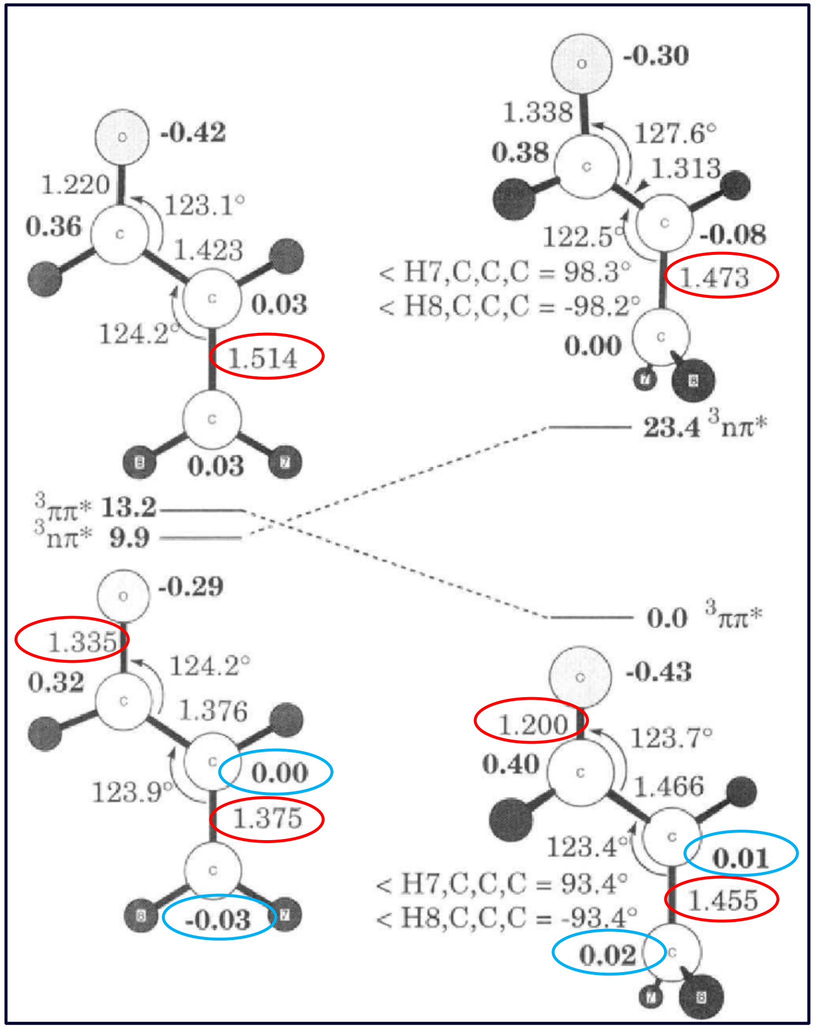


- One can also use a sensitizer to achieve T_1 directly

Wilsey, S. et al. *J. Am. Chem. Soc.* **2000**, *122*, 5866.

Mechanistic Studies

➢ Triplet excited states of enone



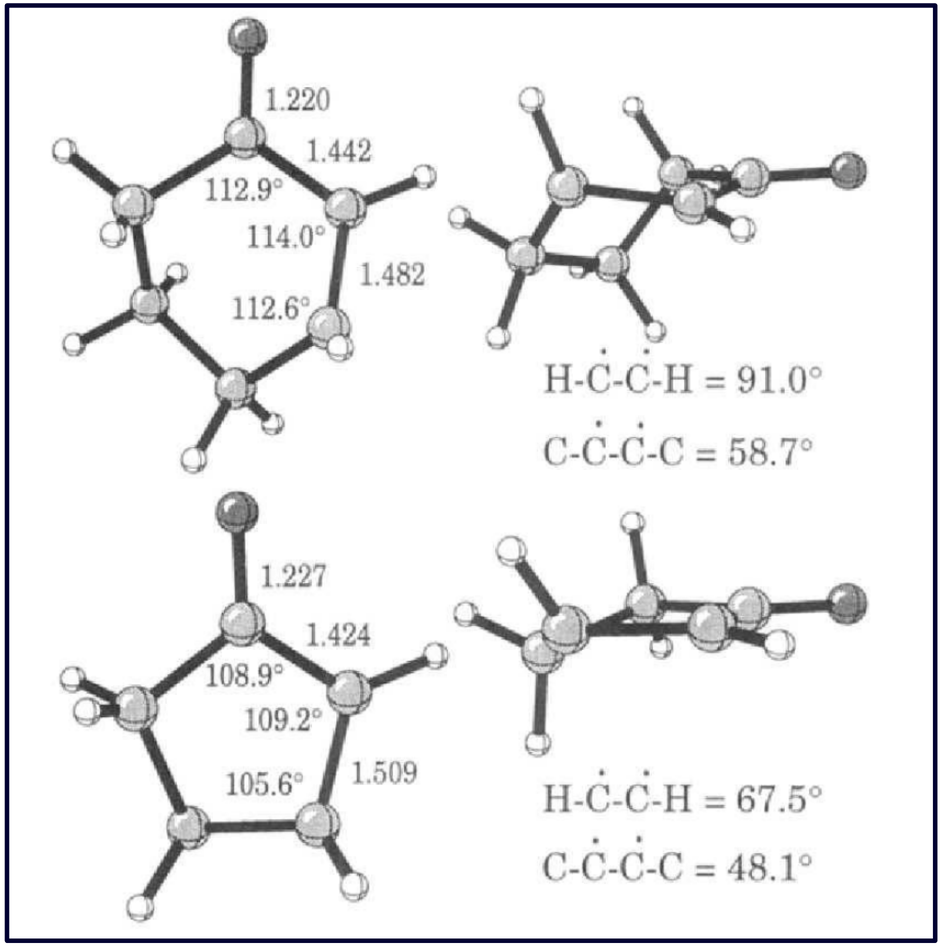
Acrolein, UMP4(SDTQ)/6-31G*

- $^3(n\pi^*)$ is more stable at planar (ground-state) geometry, but $^3(\pi\pi^*)$ is more stable globally
- $^3(\pi\pi^*)$ is **twisted** to make those unpaired electrons orthogonal
- PES crossing permits efficient internal conversion
- Planar $^3(n\pi^*)$ state has reversed polarity but $^3(\pi\pi^*)$ not (difference is small)

Broeker, J. L. et al. *J. Am. Chem. Soc.* **1995**, *117*, 1847.

Mechanistic Studies

➢ Excited states of cyclopentenone and cyclohexenone



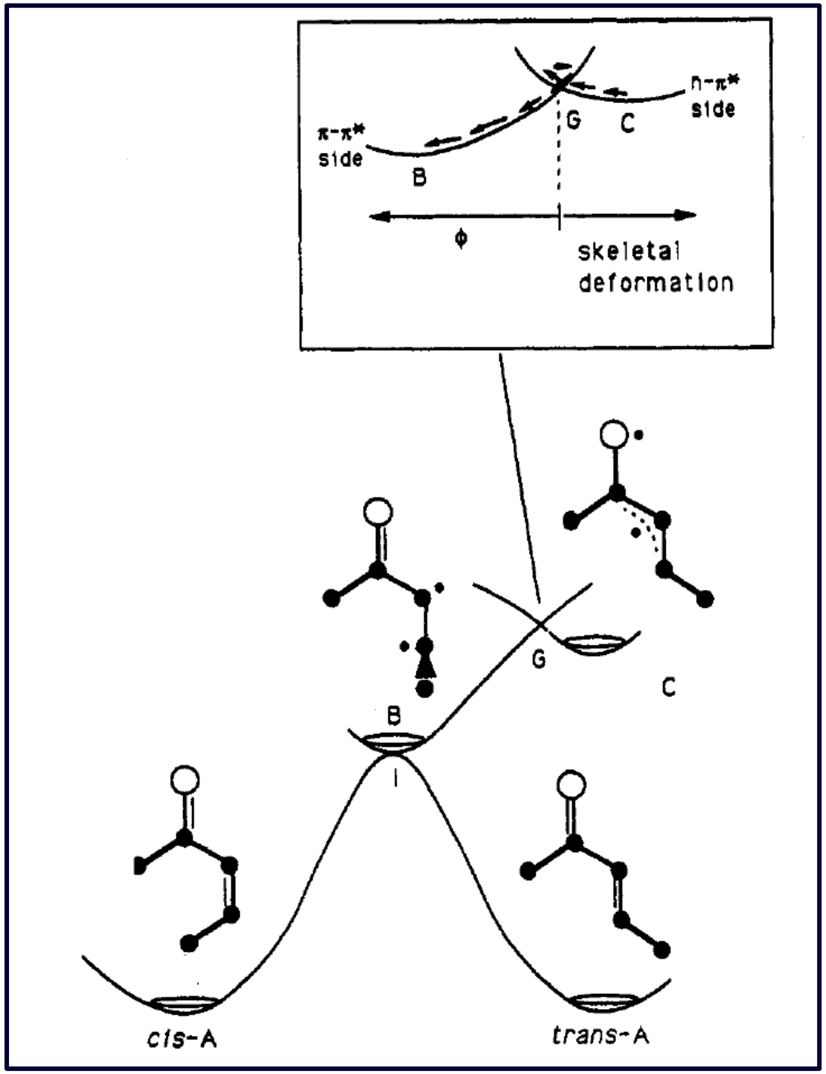
UHF/6-31G*

- $^3(\pi\pi^*)$ are 4.6 and 3.8 kcal/mol more stable than $^3(n\pi^*)$ states (9.9 in acrolein)
- *α*-C remains planar, while *β*-C pyrimidalize to avoid overlap of electrons

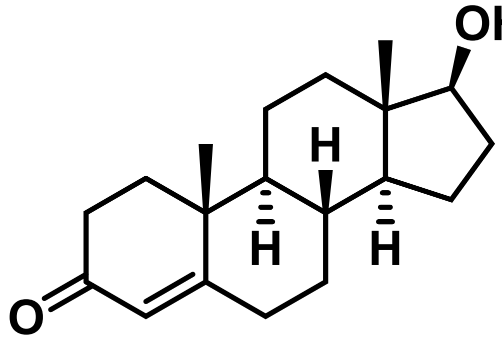
Broeker, J. L. et al. *J. Am. Chem. Soc.* **1995**, *117*, 1847.

Mechanistic Studies

➢ Lifetime study of triplet excited states



$\tau = 8$ ns $\tau = 30$ ns



$\tau = 440$ ns

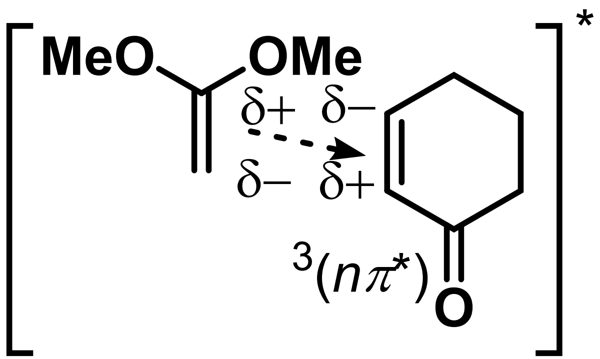
- Correlation between **flexibility** and lifetime matches $^3(\pi\pi^*)$

Schuster, D. I. et al. *J. Am. Chem. Soc.* **1991**, *113*, 6245.

Mechanistic Studies

➢ Formation of diradical with regiochemistry issues

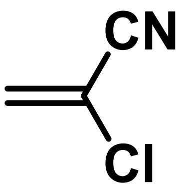
Charge distribution calculated with extended Huckel method



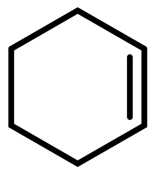
Exciplex

Diradical **Not** formed by intermediacy of exciplex

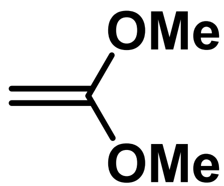
- $^3(\pi\pi^*)$ Does not have the required polarity
- Rate constant does not support alkene→enone charge transfer



1



2



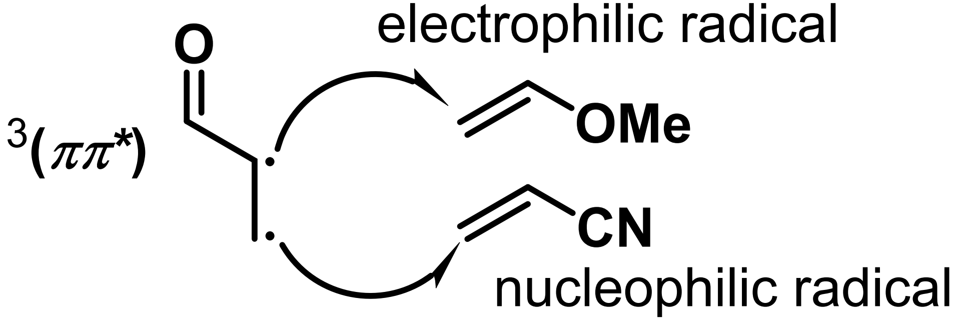
3

Alkene substrate	**^{3}enone* quenching rate k_q × 10^{-7} M·s^{-1}**
1	200
2	33
3	3

Schuster, D. I. et al. *J. Am. Chem. Soc.* **1988**, *110*, 8261.

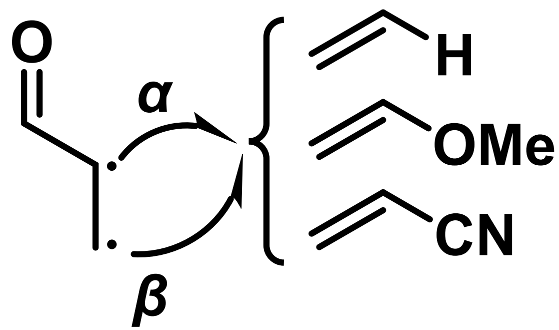
Mechanistic Studies

➢ Formation of diradical with **regioselectivity?**



- "Partially correct"

Alkene	$E^{\neq}_{TS}$ / kcal·mol^{-1}		
	α	*β*	*α - β*
-H	9.84	6.68	**3.16>0**
-OMe	6.48	5.58	**0.90>0**
-CN	9.14	4.96	**4.18>0**

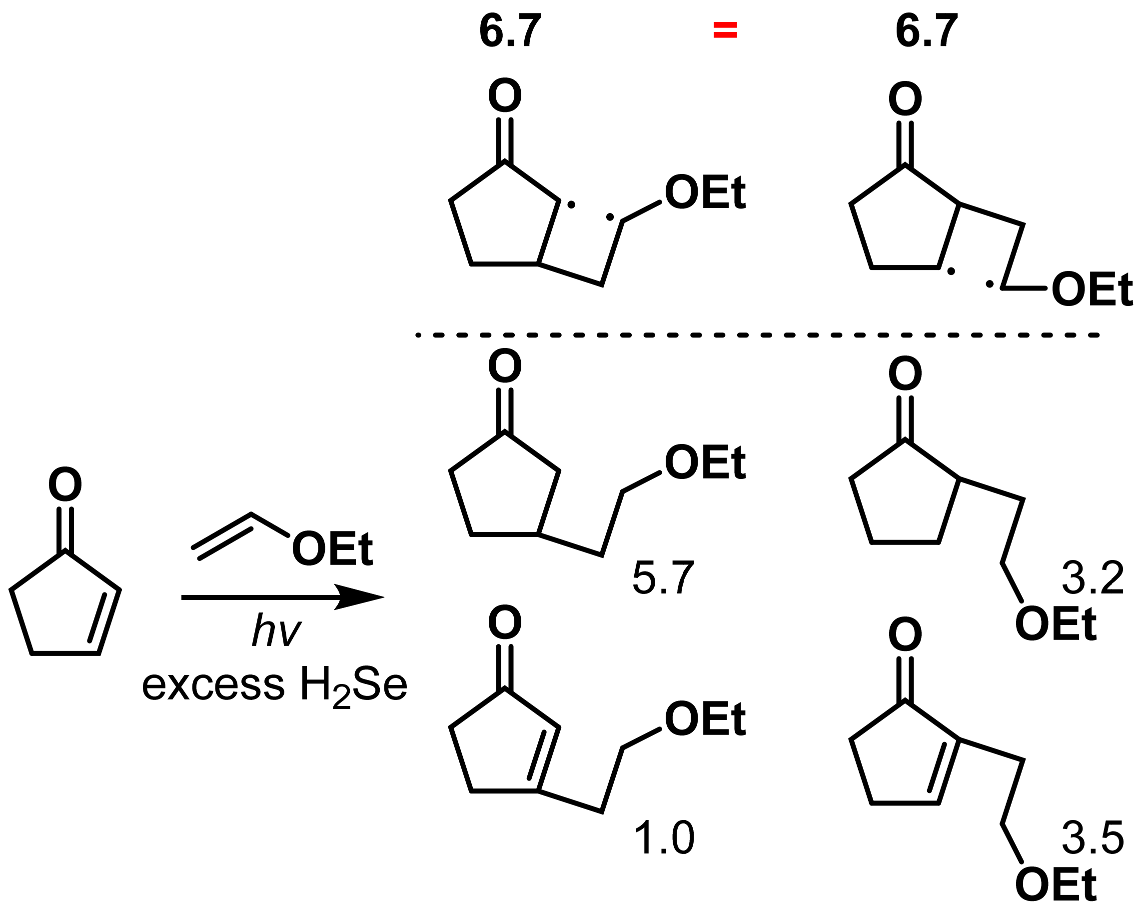


- There **exists** difference between EDG and EWG, but *α*-radical is **naturally** more stable

Jaque, P. et al. *J. Phys. Chem. A.* **2009,** *113,* 332.

Mechanistic Studies

- Formation of diradical with **little or none** regioselectivity
  - Evidence: radical trapping experiment

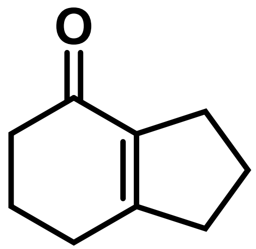


- Cyclization is 100% **suppressed** by H_2Se
- H_2Se can either fully reduce the diradical or catalyze its dispropor-tionation
- The formation of *α*- and *β*- diradicals is **not selective** in this case

Hastings, D. J. et al. *J. Am. Chem. Soc.* **1991**, *113*, 8525.

Mechanistic Studies

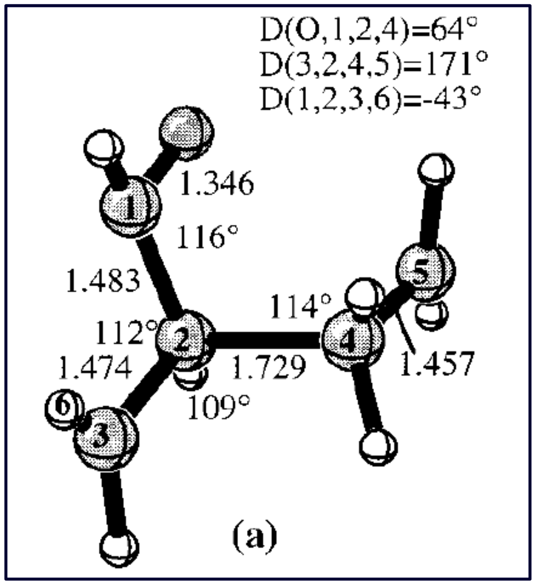
- Formation of diradical by $^3(n\pi^*)$ enone
  - Relative enegy of $^3(n\pi^*)$ and $^3(\pi\pi^*)$ could turn around in **rigid** enones

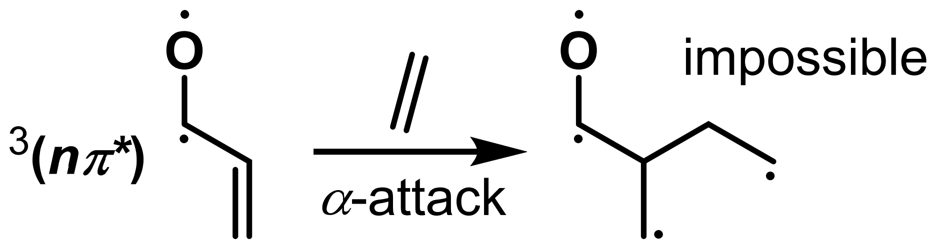


Minima on $^3(n\pi^*)$ and $^3(\pi\pi^*)$ PES are close

J. Am. Chem. Soc. **1992**, *114*, 7029-7034

  - $^3(n\pi^*)$ enone only undergoes ***β*-attack** (form HH adduct)





- *β*-attack only 3 kcal/mol higher than $^3(\pi\pi^*)$

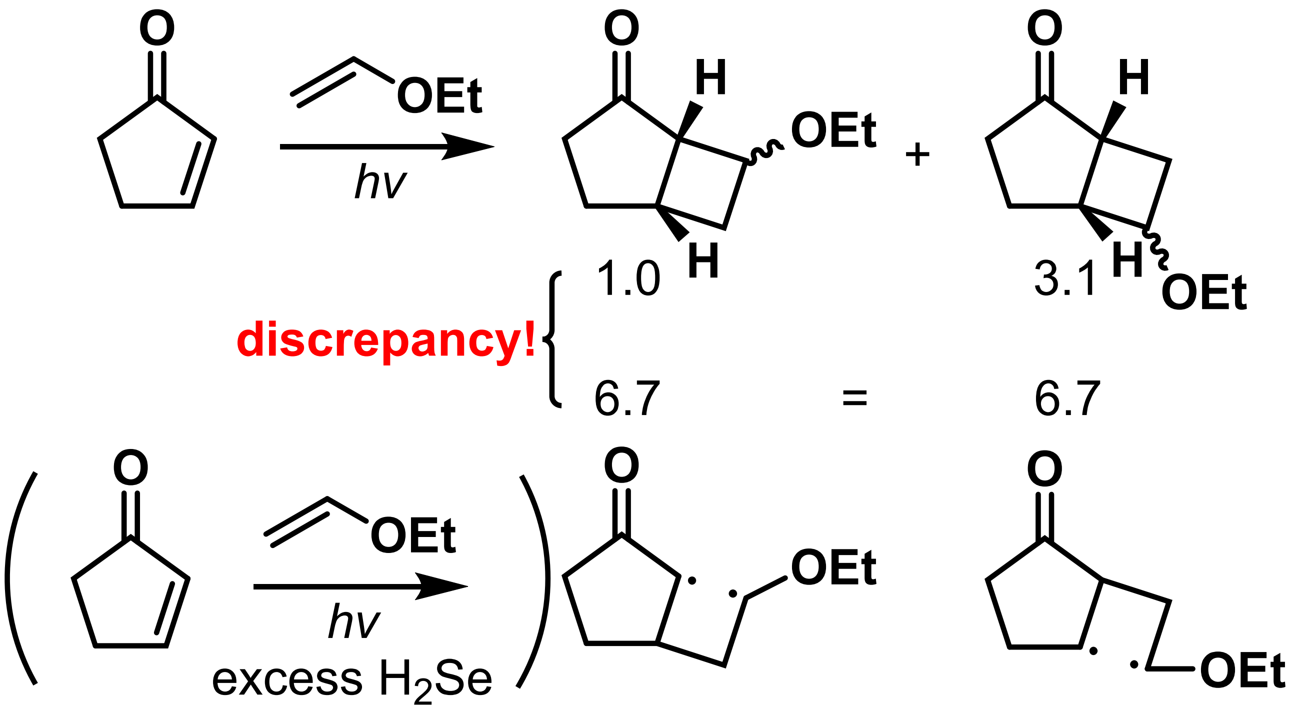
In case of *α*-attack：

- Very late TS (typical new bond in TS ~2.2Å)
- Long C-O and C-C bond in enone

Wilsey, S. et al. *J. Am. Chem. Soc.* **2000**, *122*, 5866.

Mechanistic Studies

- Intersystem crossing of ^{3}diradical to ^{1}diradical
- Fates of ^{1}diradicals: Ring closure or dissociation



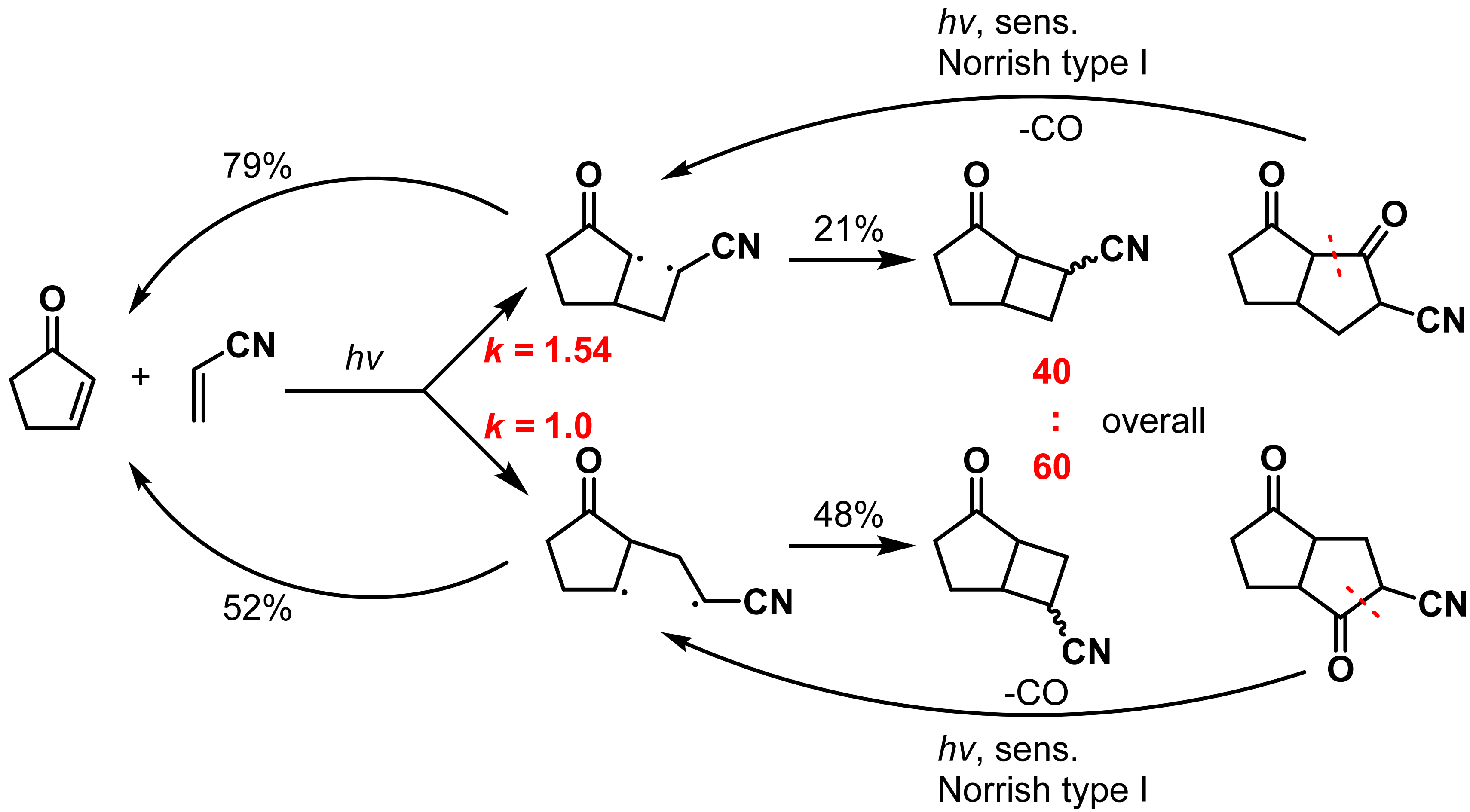
- Different **fates** of HH- and HT-diradicals lead to this selectivity

This example again!

Hastings, D. J. et al. *J. Am. Chem. Soc.* **1991**, *113*, 8525.

Mechanistic Studies

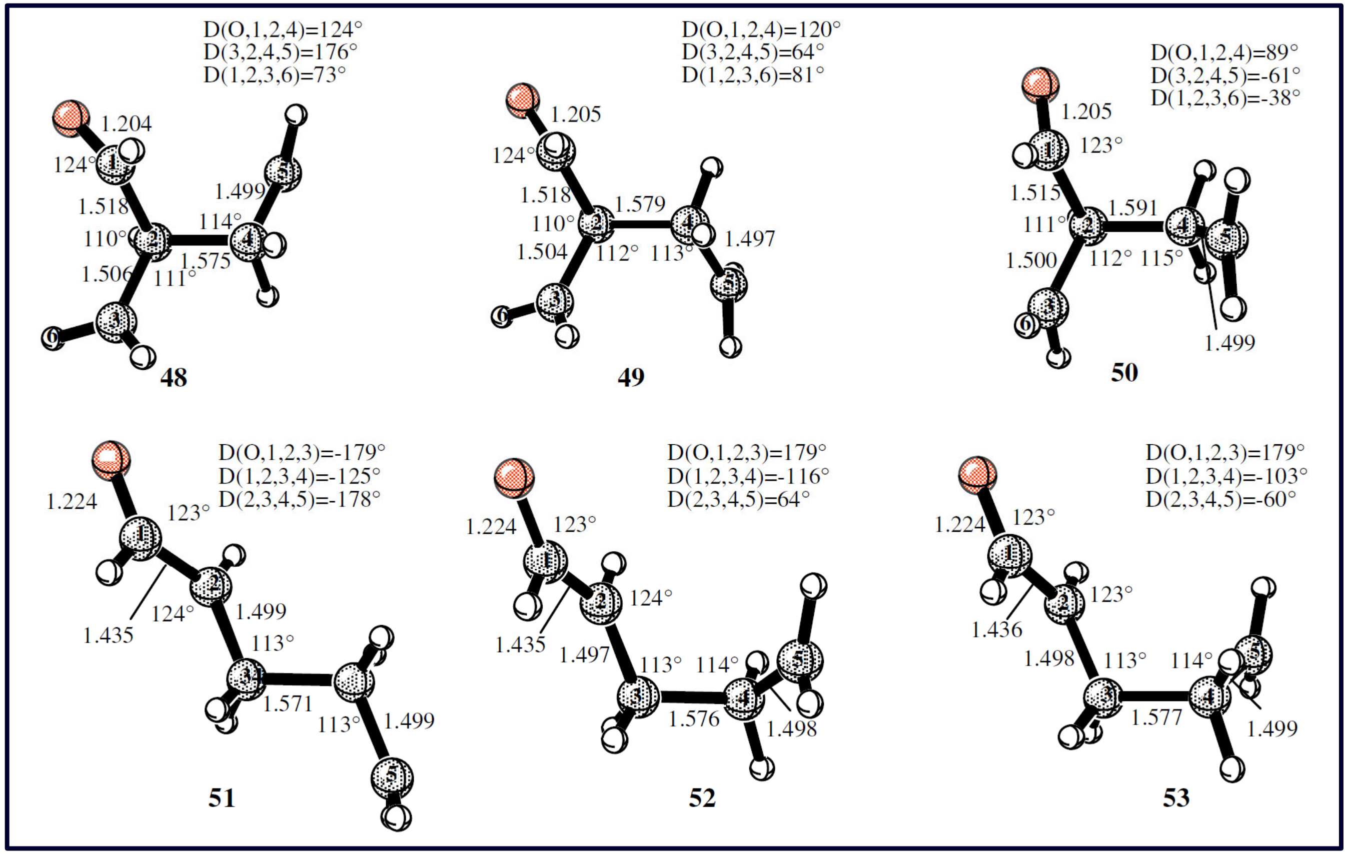
- Fates of [1]diradicals: Ring closure or dissociation
  - Could even **reverse** the preference of diradical forming

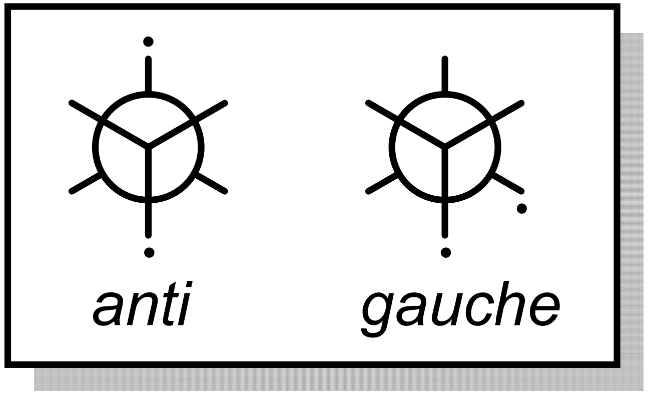


Krug, P. et al. *Tetrahedron Lett.* **1993,** *34*, 7221.

Mechanistic Studies

- Fates of [1]diradicals: Ring closure or dissociation
  - Conformations of singlet diradical





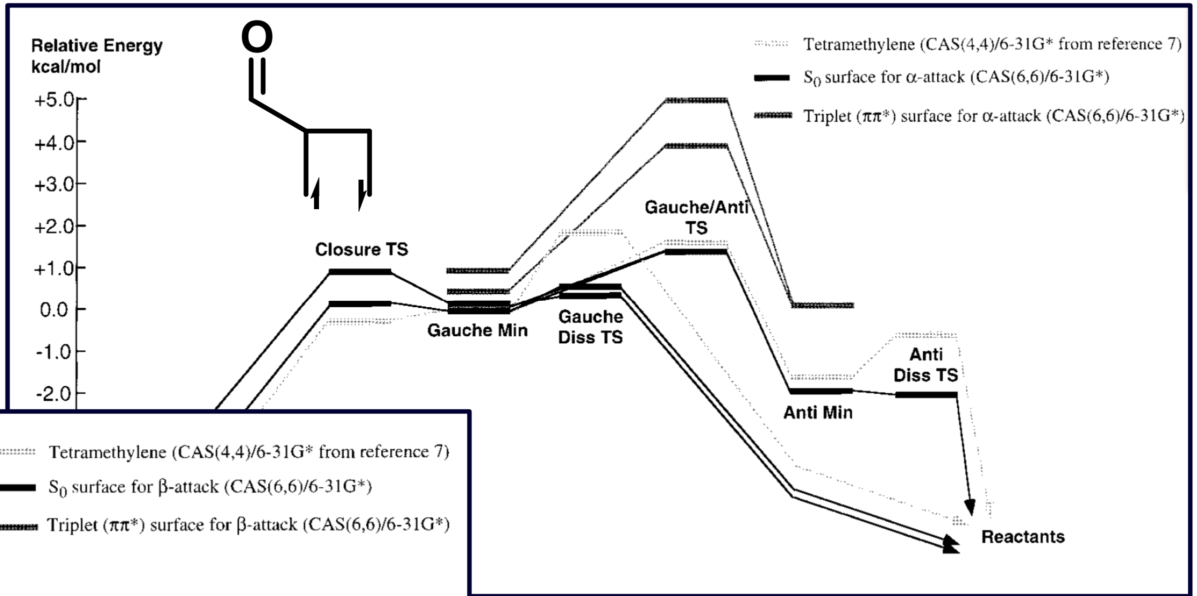
- 1 *anti* and 2 *gauche* for both *α*- and *β*- attack

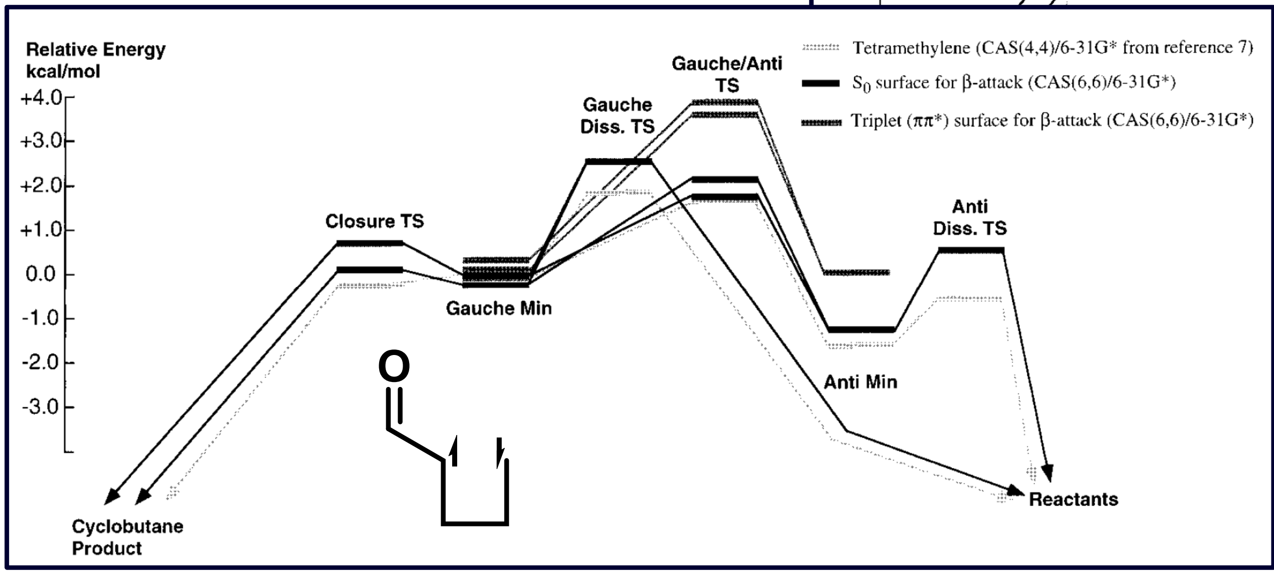
CASSCF(6,6)/6-31G*

Wilsey, S. et al. *J. Am. Chem. Soc.* **2000**, *122*, 5866.

Mechanistic Studies

- Fates of [1]diradicals: Ring closure or dissociation
  - PES of singlet diradical
  - *anti*→dissociate
  - *gauche*→mainly cyclize





- *anti-gauche* **can't reach** its equilibrium

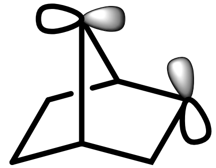
Wilsey, S. et al. *J. Am. Chem. Soc.* 2000, **122**, 5866.

Mechanistic Studies

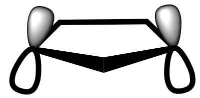
- Back to ISC of ^{3}diradical

Mechanisms of ISC:
- Electron-nuclear hyperfine coupling (HFC)
- Spin-lattice relaxation (SLR)
- **Spin-orbital coupling (SOC)**

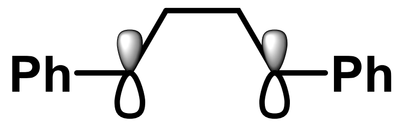
Rate of $^{3\rightarrow 1}$SOC proportional to:
(Salem & Roland, 1972)
- Orbital **perpendicularity**
- **Distance** between spin centers
- **Ionic character** of resulting singlet



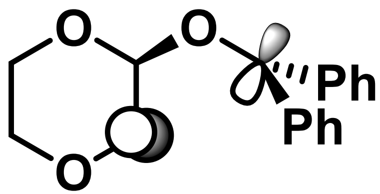
τ<0.1 ns, perpendicular and close



τ~100 ns, parallel but close



τ~190 ns, flexible

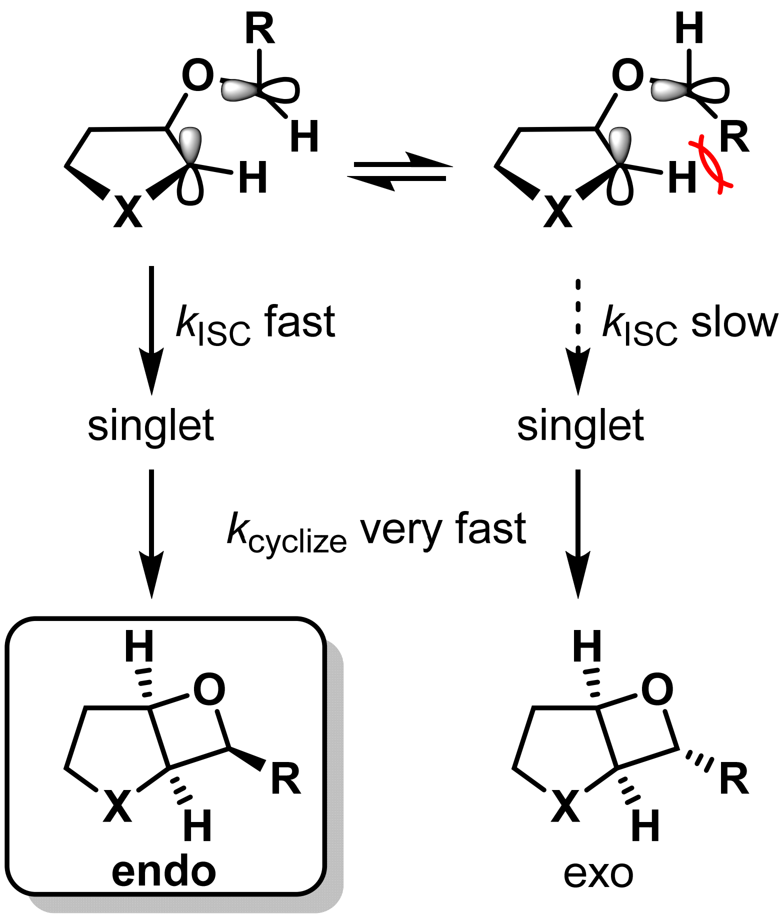


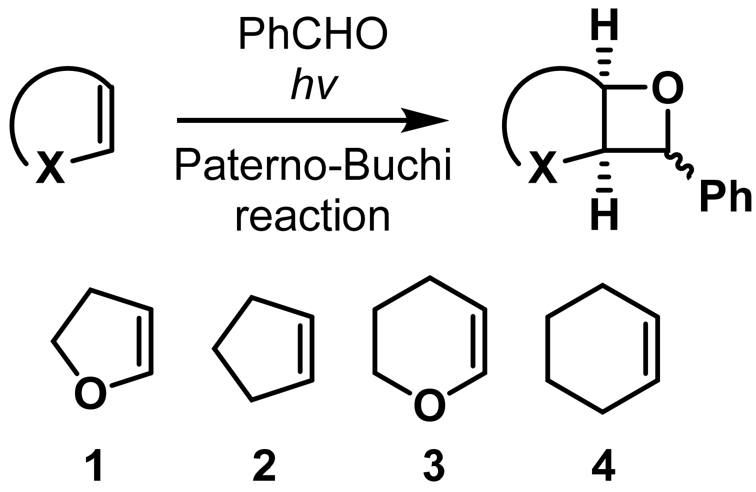
τ~1.6 ns, flexible and polar

Carlacci, L. et al. *J. Am. Chem. Soc.* **1987**, *109*, 5323.
Griesbeck, A. G. et al. *Acc. Chem. Res.* **1994**, *27*, 70.

Mechanistic Studies

- Back to ISC of ^{3}diradical
  - "Conformational memory effect"



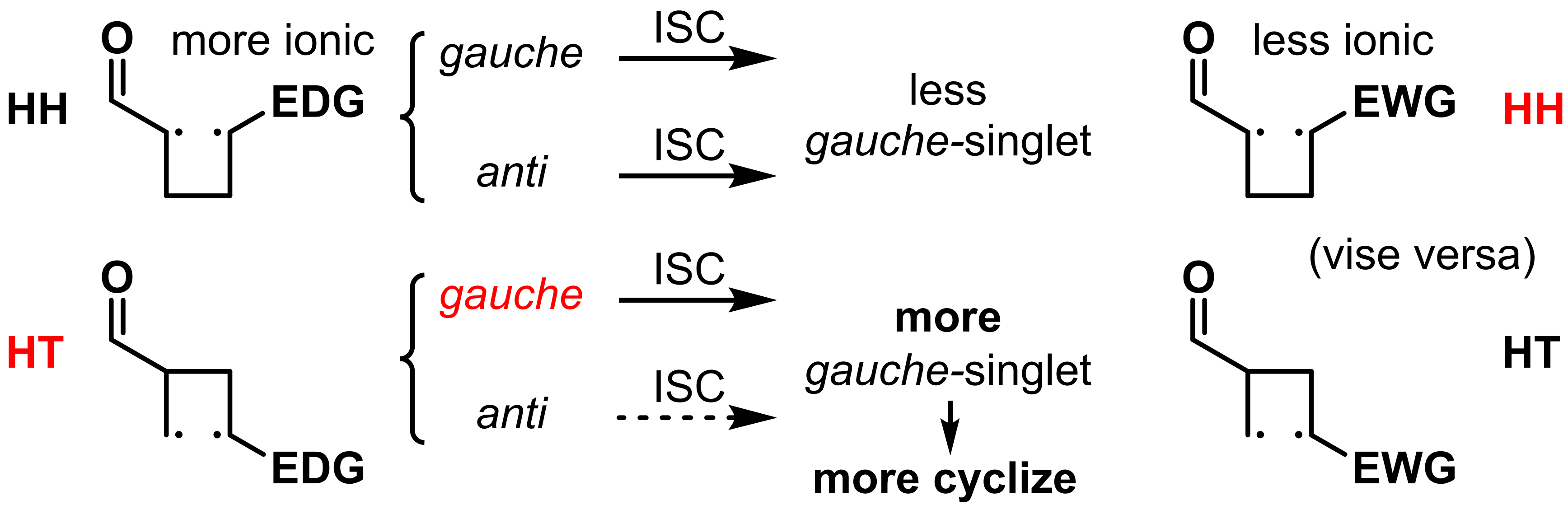


Enone	Yield%	Endo : Exo
1	98	**88**:12
2	55	**61**:39
3	45	**80**:20
4	34	**90**:10

Griesbeck, A. G. et al. *Acc. Chem. Res.* **1994**, *27*, 70.

Mechanistic Studies

- Back to ISC of ³diradical
  - Different conformation has different ISC probability:



  - And influence the conformation distribution of ¹diradicals

☞ISC capability

Spin-donicity/eV	EDG = OMe	EWG = CN
HH	**-0.23**	-0.72
HT	-0.47	**-0.66**

Jaque, P. et al. *J. Phys. Chem. A.* **2009,** *113,* 332.

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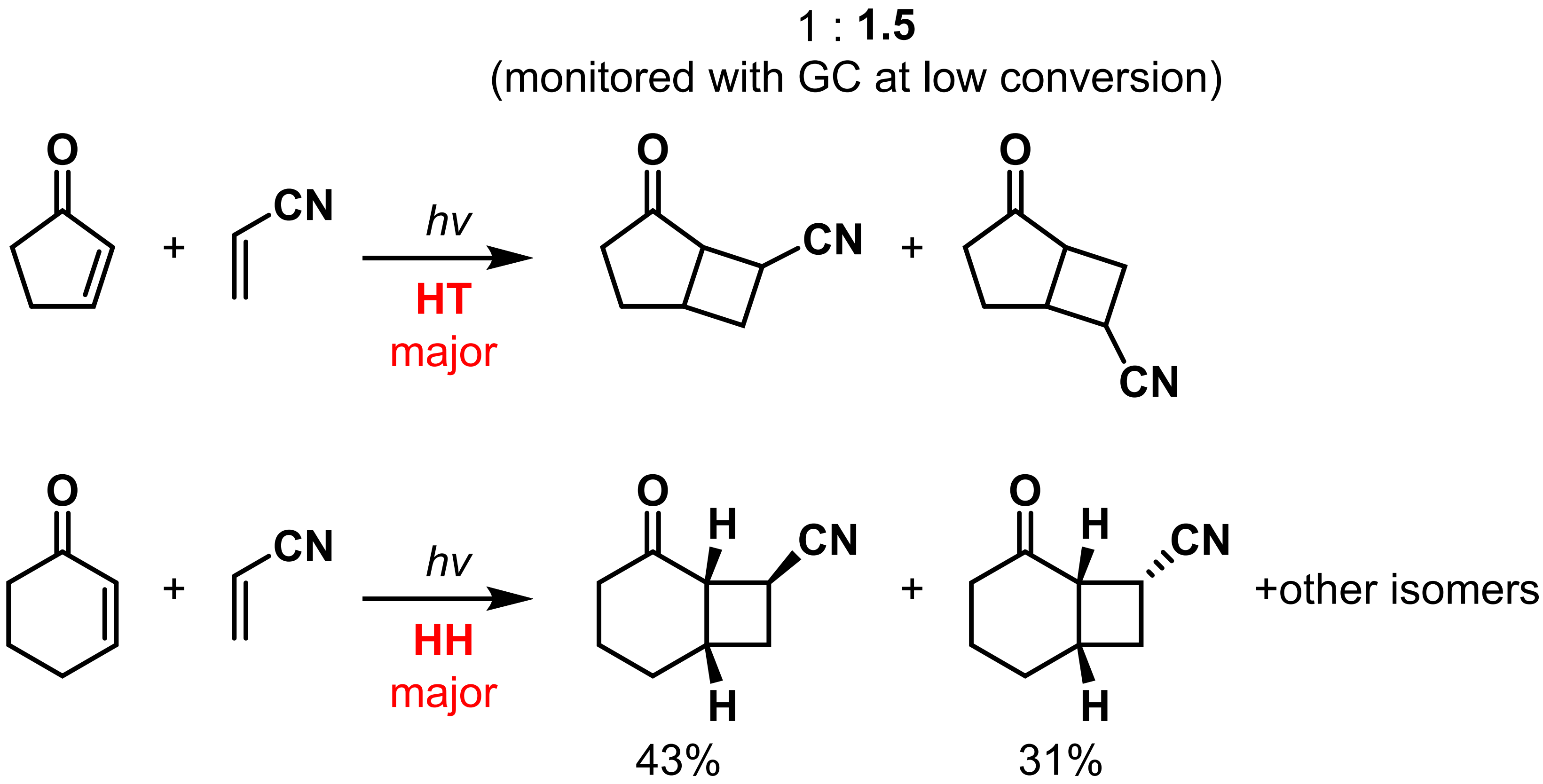
Regiochemistry

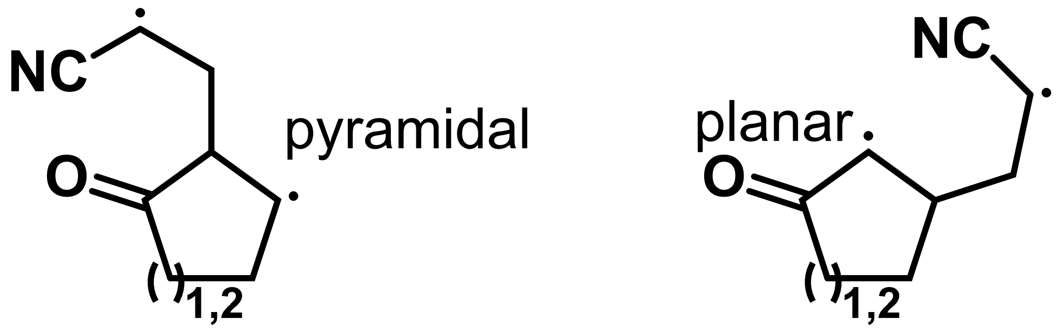
➢Reversed outcome of cyclopentenone and cyclohexanone



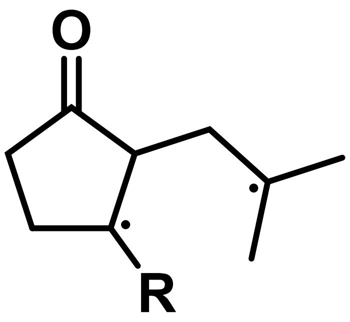
Krug, P. et al. *Tetrahedron Lett.* **1993,** *34*, 7221.
Meyer, L. et al. *Can. J. Chem.* **2003,** *81*, 417.

Regiochemistry

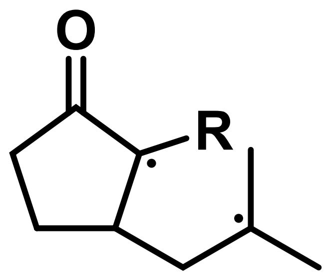
➢ Regioselectivity vs. ring size



- Planar radical makes dissociation easier, while pyramidal radical makes it harder.
- Formation of double bond is more favorable in 5-membered-rings, while losing a sp^2 atom is easier in 6.



R=H~R=Me



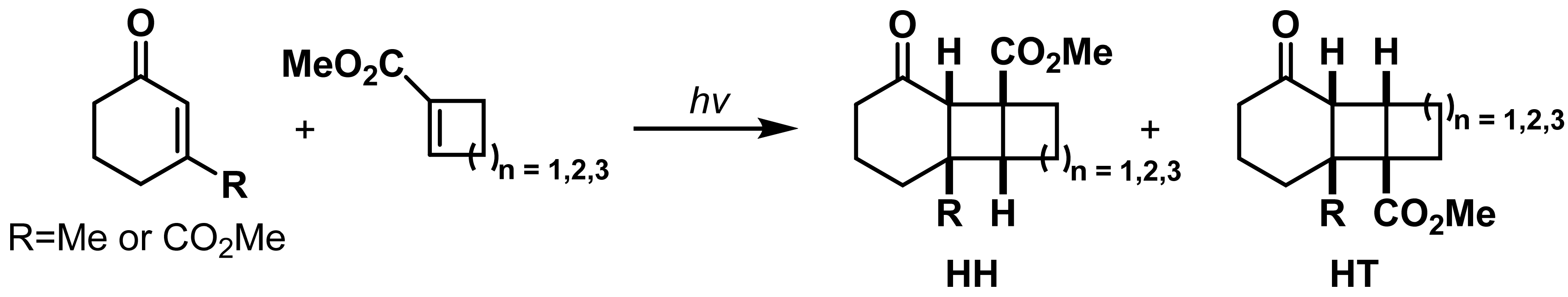
almost all dissociate when R=Me

- Me- on pyramidal center is less bulky

Andrew, D. et al. *J. Am. Chem. Soc.* **1995**, 117, 5647.

Regiochemistry

- Reversed outcome with different cyclo-unsaturated esters

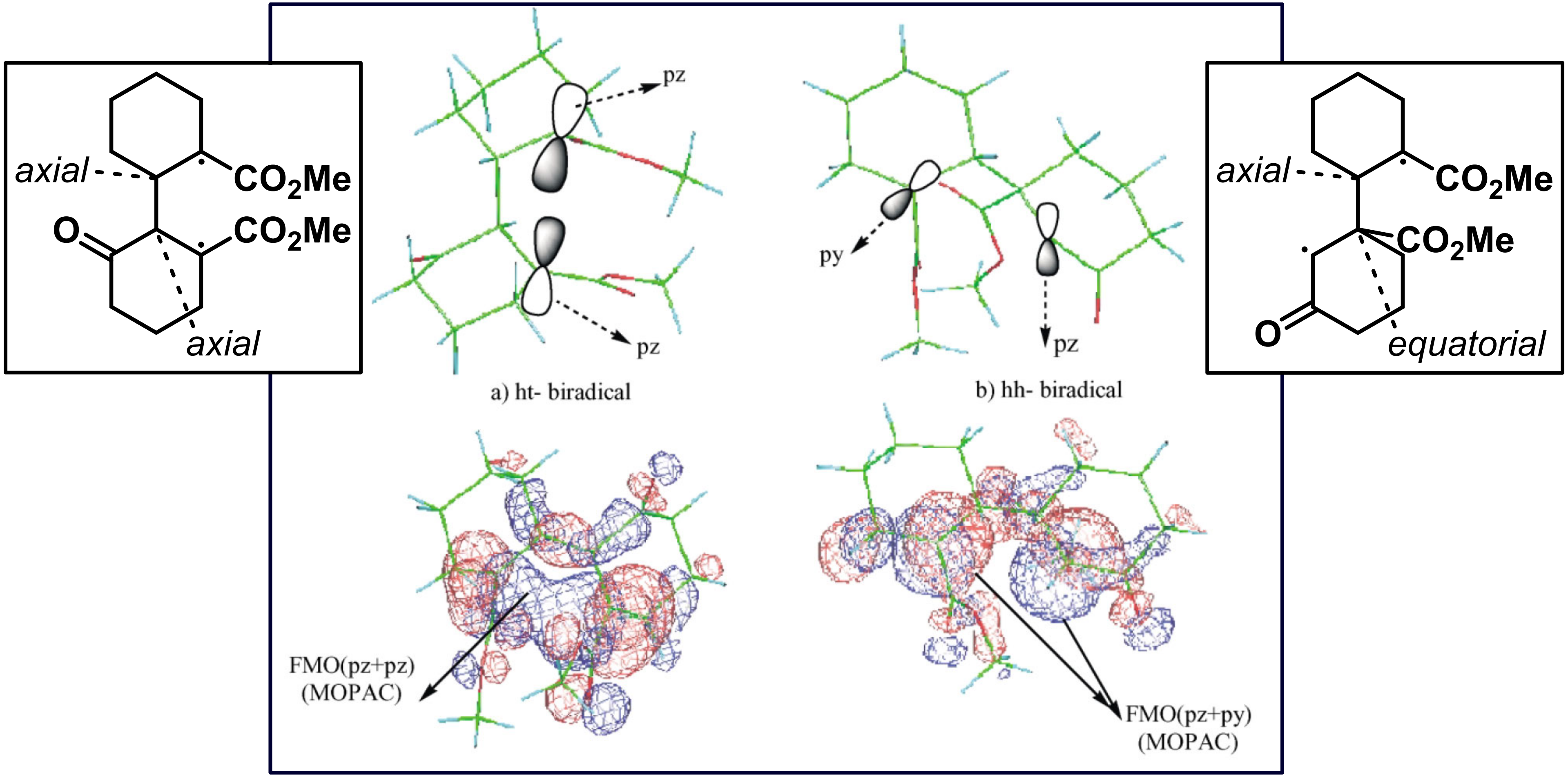


n =	R = Me		R = CO_2Me	
	HH	HT	HH	HT
1	>95%	<5%	>95%	<5%
2	50%	50%	60%	40%
3	11%	89%	<5%	>95%

Lee, M. et al. *Tetrahedron Lett*. **1990**, *31*, 4689.

Regiochemistry

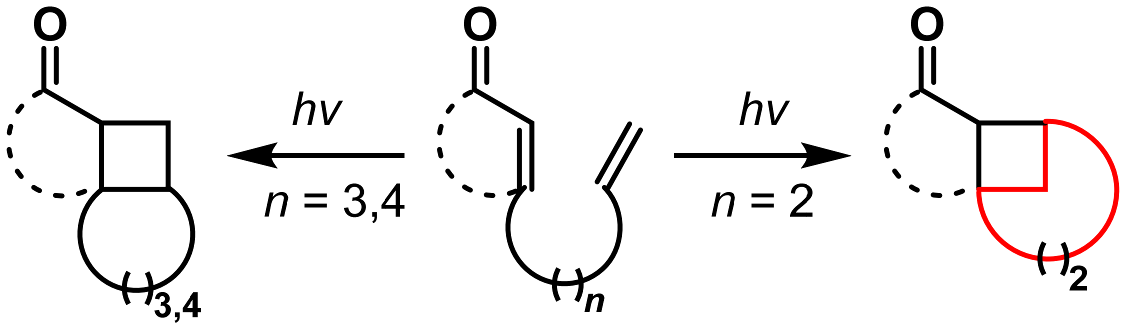
➢ Regioselectivity vs. ring size

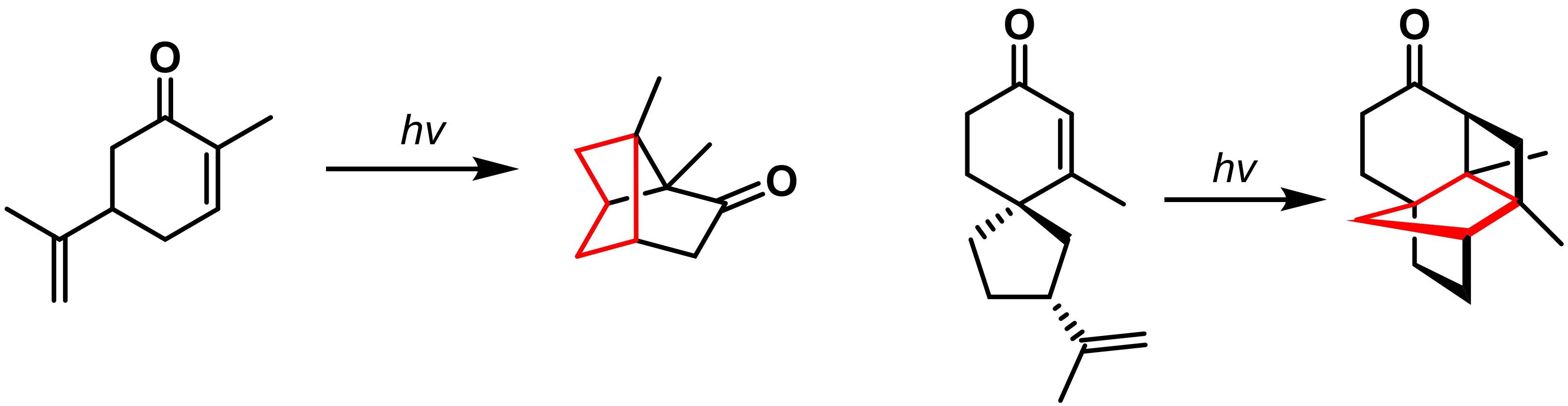


Omar, H. I. et al. *Tetrahedron Lett.* **2003**, *59*, 8099.

Regiochemistry: Intramolecular

- Intramolecular reactions: “Rule of five”
  - Form 5-membered-ring when possible



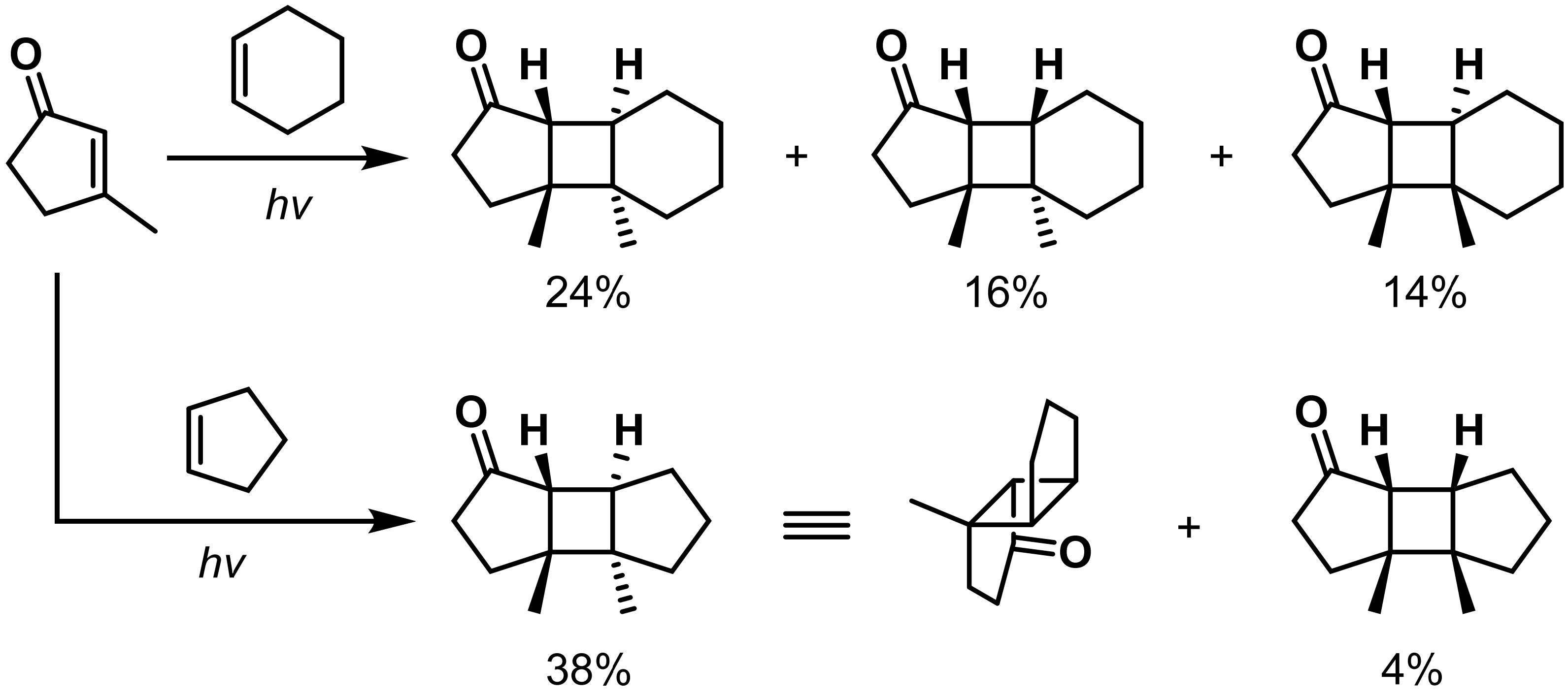


Poplata, S. et al. *Chem. Rev.* **2016**, *116*, 9748.
Srikrishna, A. et al. *Tetrahedron Lett.* **2005**, *46, 7373.*

Stereochemistry

➢Ring fusion of cyclic enones

- 3, 4, 5-membered rings are ***cis*-fused**



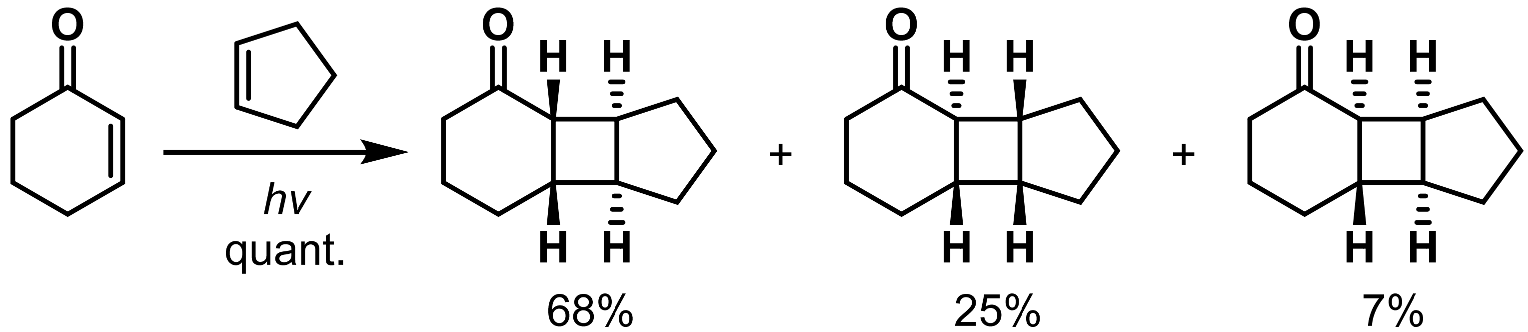
- Also notice the ***exo-*** diastereoselectivity

Grota, J. et al. *Synthesis* **2005**, *14*, 2321.

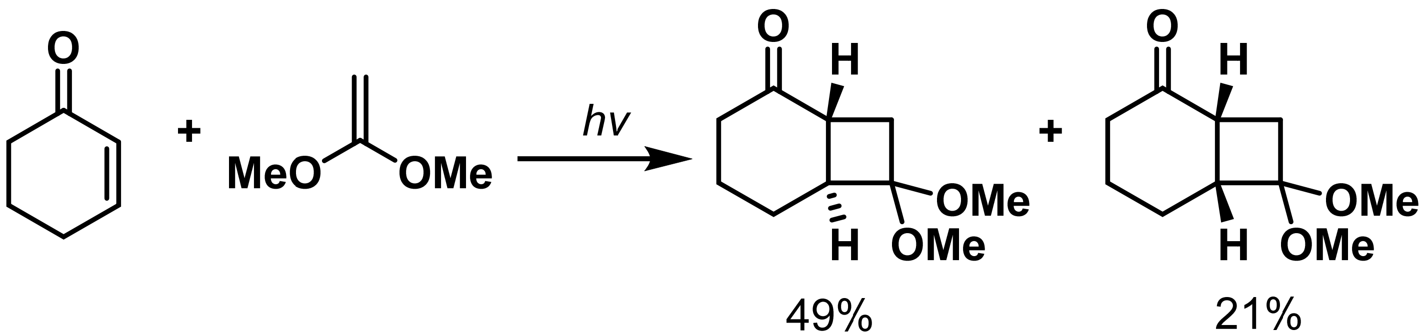
Stereochemistry

➢Ring fusion of cyclic enones

- 6-membered-ring can be ***cis*- and *trans*-** fused



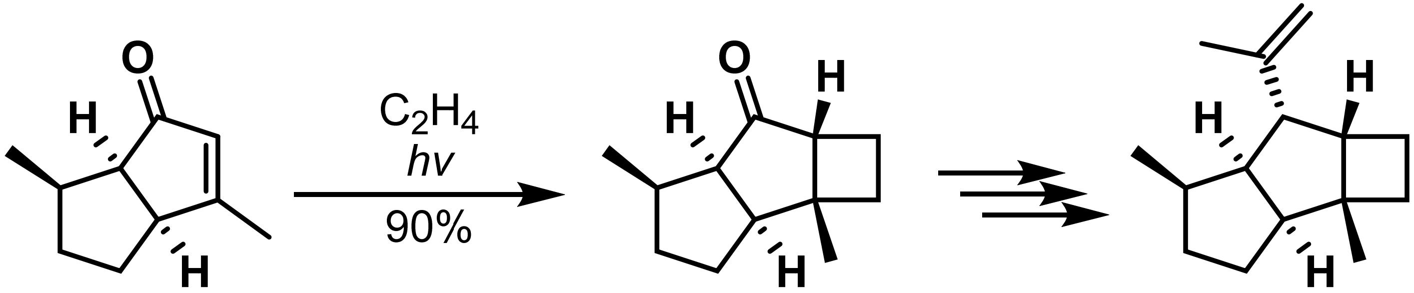
- Sometimes *trans*- becomes the major product



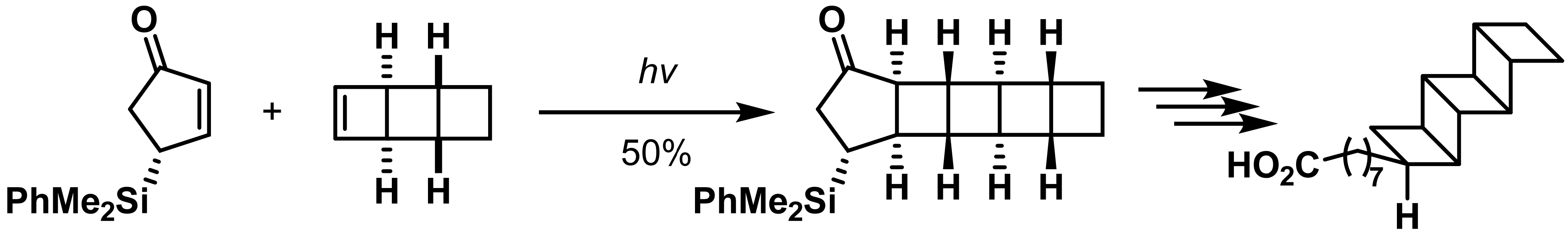
Corey, E. J. et al. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

Stereochemistry

- Facial diastereoselectivity
  - Less-hindered ***exo*-**face



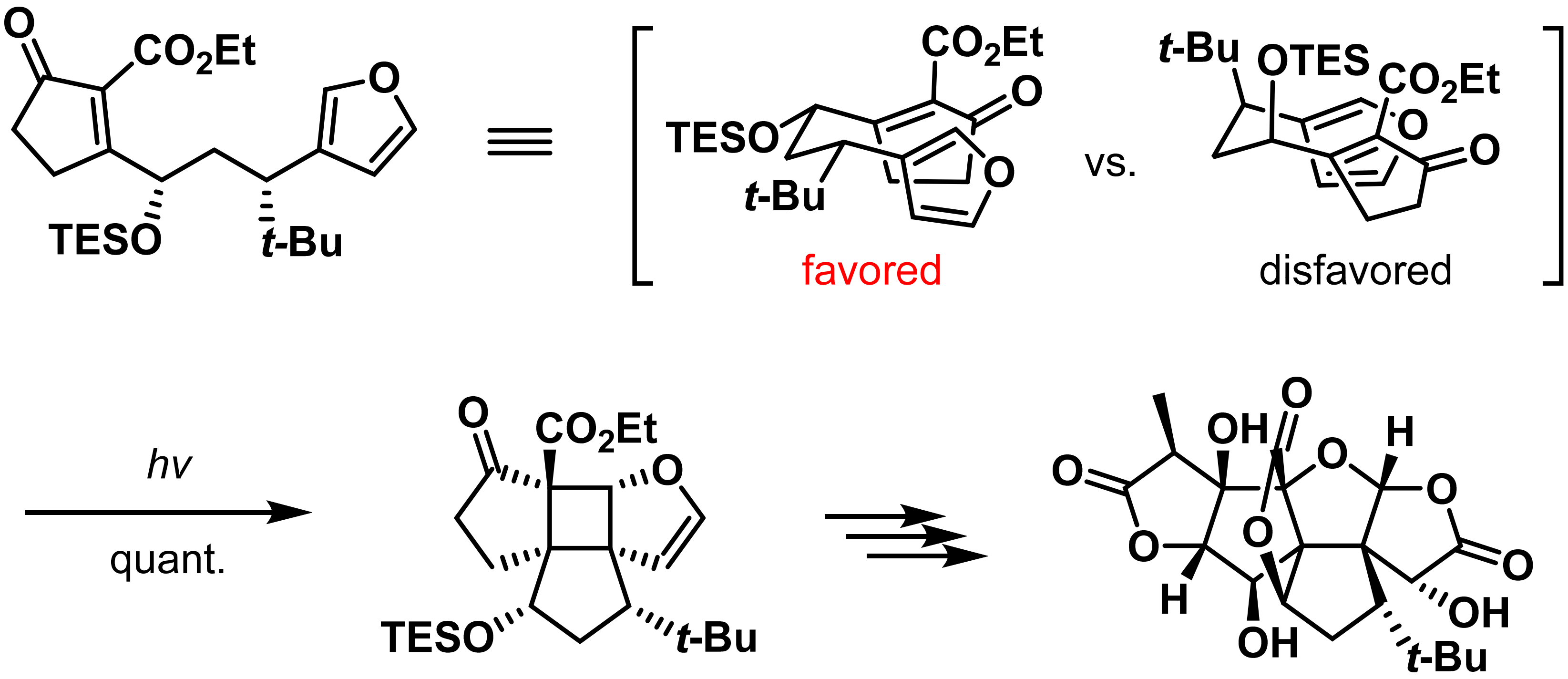
  - *Exo*-face for both components and *exo*-fusion



Piers, E. et al. *Synthesis* **2001**, *14*, 2138.
Mascitti, V. et al. *J. Am. Chem.Soc.* **2006**, *128*, 3118.

Stereochemistry

- Facial diastereoselectivity
  - Controlled by intramolecular tethering

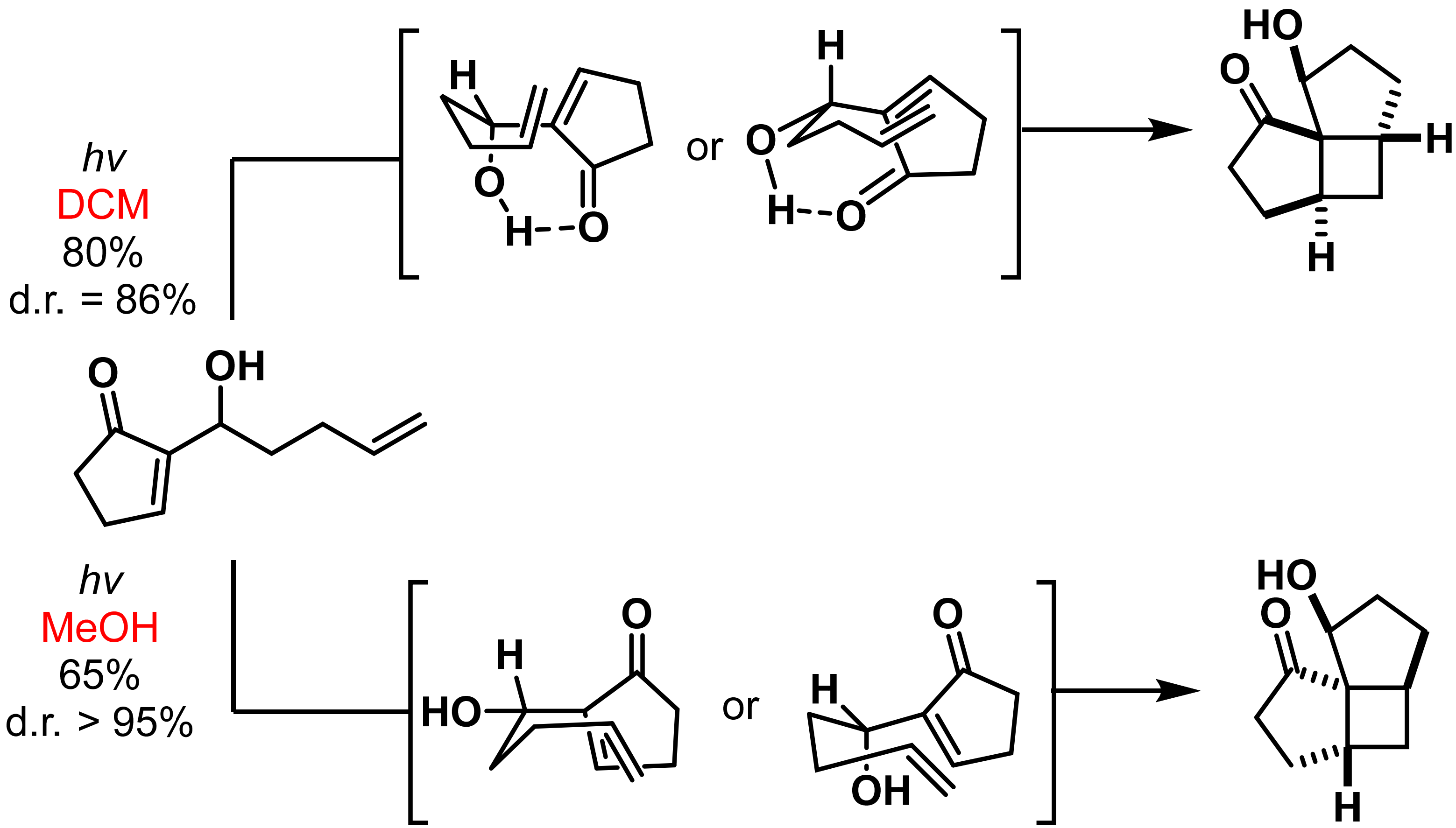


Crimmins, M. T. et al. *J. Am. Chem.Soc.* **2000**, *122*, 8453.

Stereochemistry

➢ Facial diastereoselectivity

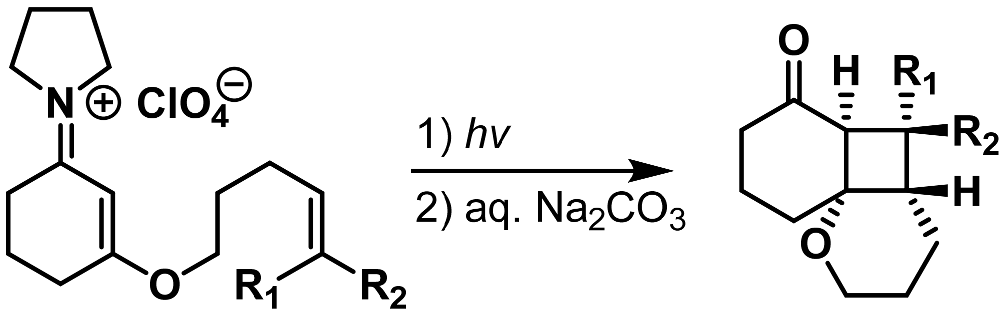
- Controlled by intramolecular tethering and **hydrogen-bonding**



Ng, S. M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 7315.

Stereochemistry

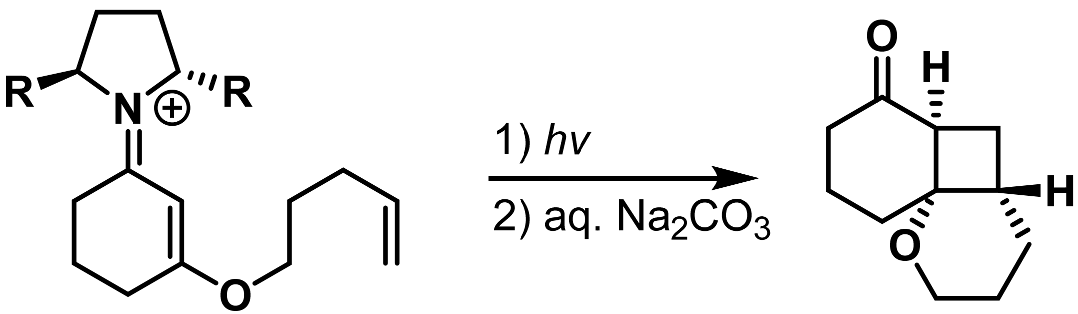
- Retention of alkene stereochemistry with iminium salt
  - **Concerted** cycloaddition



Only works well with electron-deficient alkenes

R_1 = CO_2Me, R_2 = H → **(R_1 = CO_2Me, R_2 = H)** 7 : 1 (R_1 = H, R_2 = CO_2Me)
R_1 = H, R_2 = CO_2Me → **(R_1 = H, R_2 = CO_2Me)** 100 :1 (R_1 = CO_2Me, R_2 = H)

  - Absolute stereochemical control

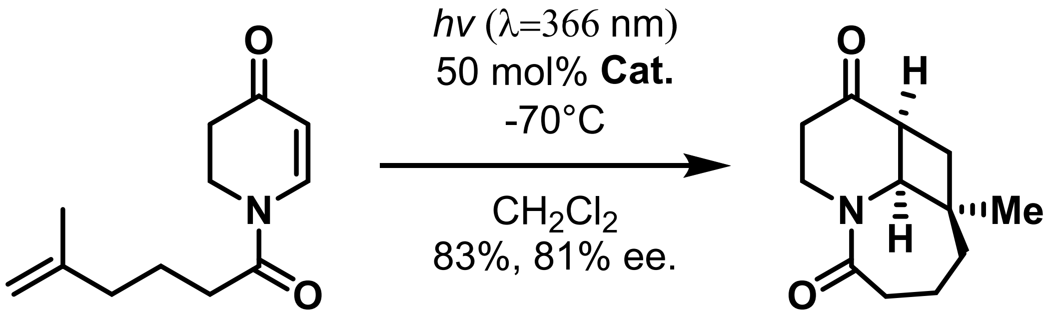


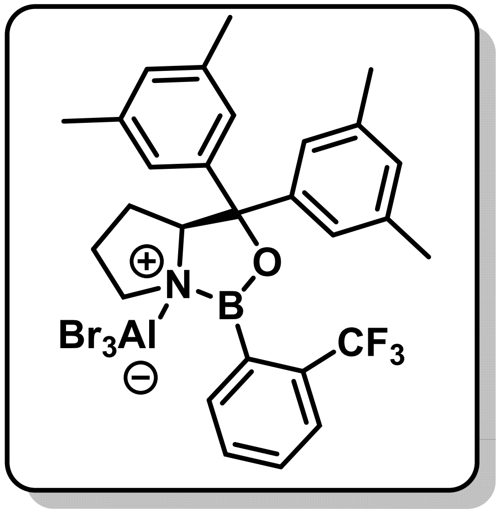
R = MOM, 61%, 82% ee.
R = Me, 31%, 37% ee.

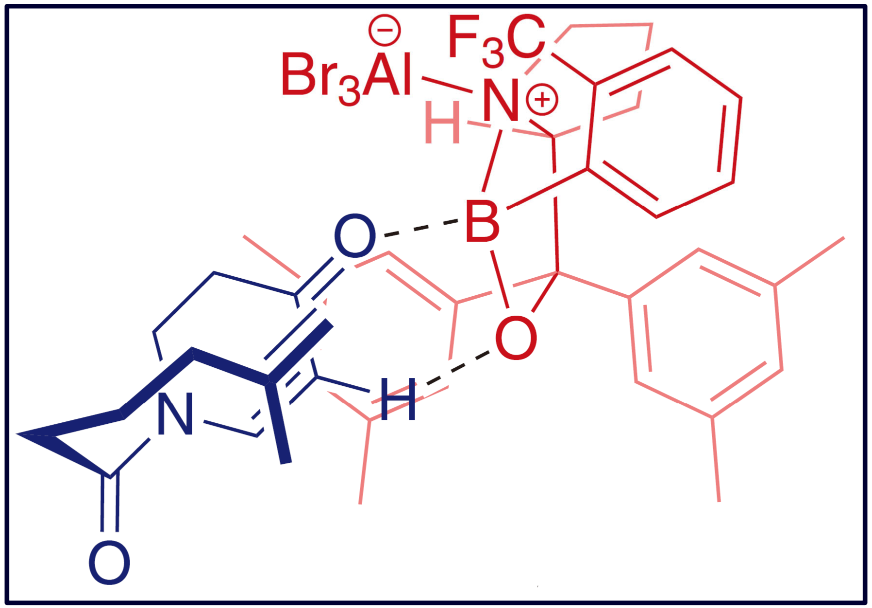
Cai, X. et al. *Tetrahedron Lett.* **2000**, *41*, 9445.
Chen, C. et al. *J. Am. Chem. Soc.* **2001**, *123*, 6433.

Stereochemistry

- Chiral catalysts (e.g., chiral lewis acid)







Brimioulle, R. et al. *Science* **2013,** *342*, 840.

Outline

- Introduction
  - History
  - Corey-de Mayo exciplex mechanism
- Mechanistic Studies
  - Excitation and excited states of enone
  - Formation of 1,4-diradical
  - Fates of singlet diradical
  - ISC of triplet diradical
- Selectivity
  - Regiochemistry
  - Stereochemistry
- Summary

Summary

- Mechanism
  - Exciplex not participated
  - $^1(n\pi^*)\rightarrow{}^3(\pi\pi^*)\rightarrow{}^3$biradical$\rightarrow{}^1$biradical$\rightarrow$cyclize/dissociate.
    (Bauslaugh–Schuster–Weedon Mechanism)
- Selectivity
  - Complicated regioselectivity. Governed by fate (cyclize or dissociate) of biradical
  - Stereoselectivity could be controlled by various methods