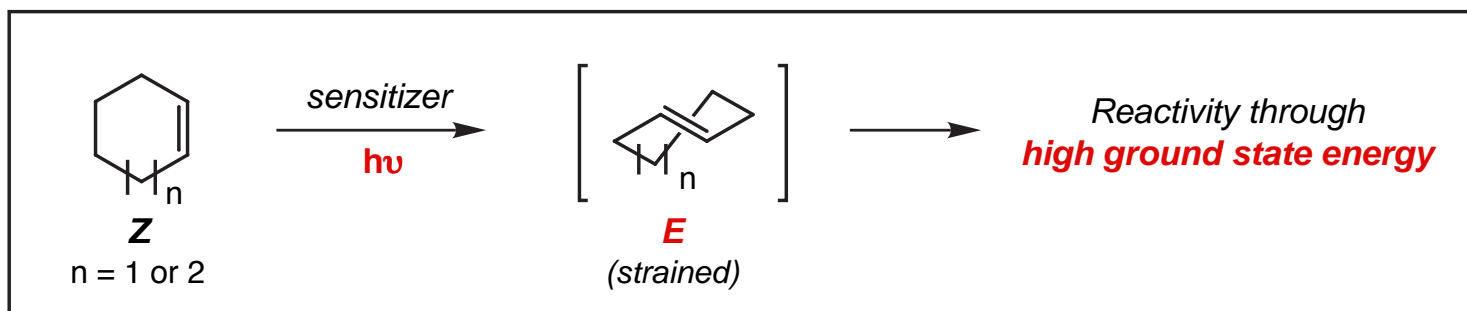


Generation and Reactivity of Strained *E*-Cycloalkenes



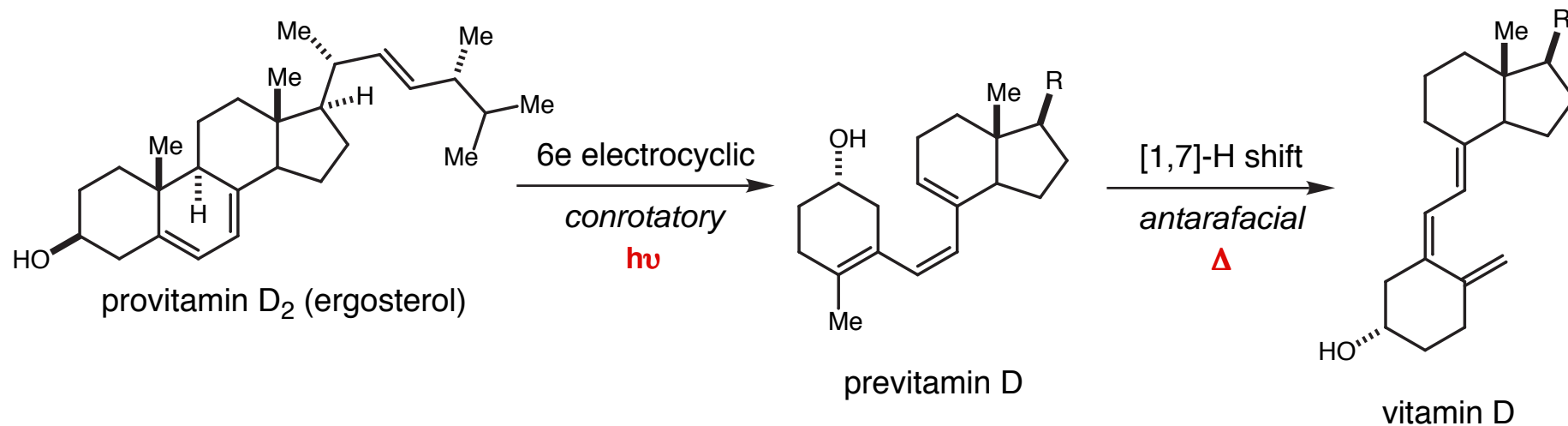
André Beauchemin

Evans Group Friday Seminars

January 16, 2004

Keywords: Photoisomerization, strain, photochemistry, high ground state energy, carbocations, isomerization

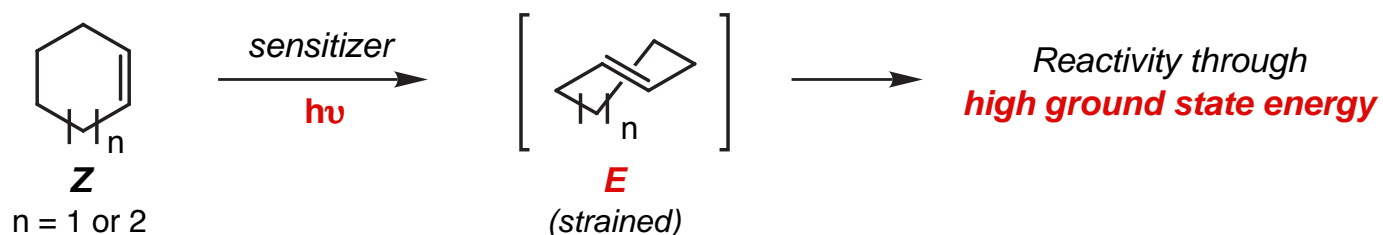
Industrial Applicability of Photochemistry: Synthesis of Vitamin D



- Ergosterol is produced by yeast which synthesize it in about 2.5% yield from simple sugars
- Vitamin D is a potent antirachitic
- Thanks to this synthetic approach, rachitis does not exist anymore in developed countries

Jacobs and Laarhoven in *CRC Handbook of Organic Photochemistry*, Horspool and Song, Eds, CRC Press: Boca Raton, 1995, Chap. 11.

The Chemistry of Strained *E*-Cycloalkenes



Miscellaneous about photoisomerization of cycloalkenes

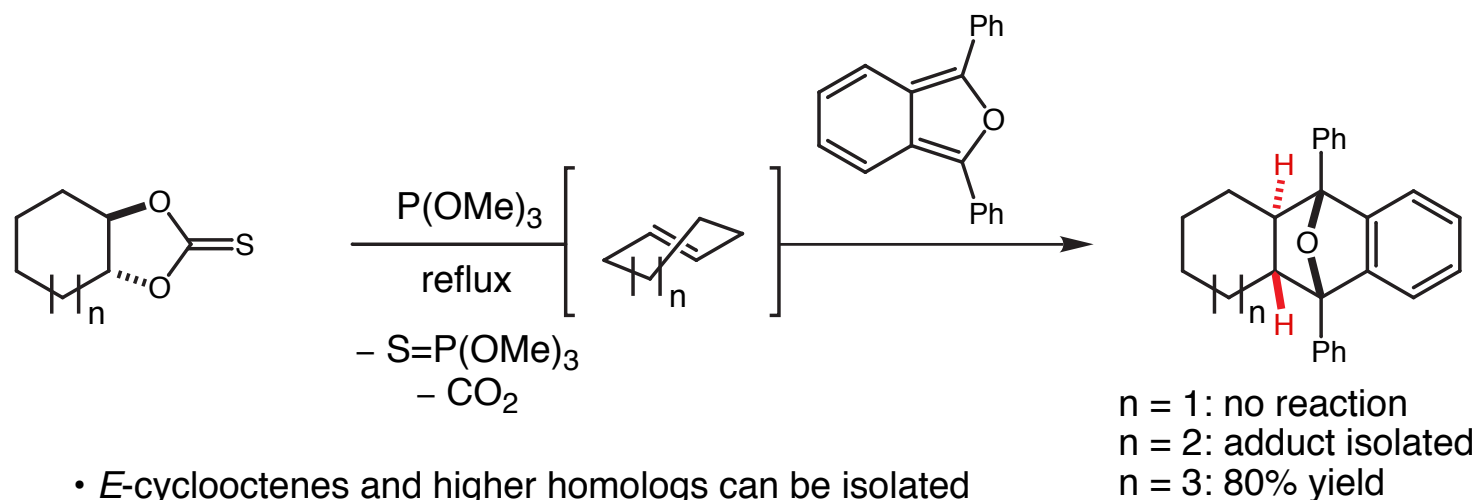
- The increase in ground state energy is ~ 33 and 27 kcal/mol for 6- and 7-membered *E*-cycloalkenes, respectively
- Photolysis of 5-membered cycloalkenes leads to generation of biradical species (*JACS* **1967**, 89, 3650)
- Increase in strain energy of *E*-cyclooctene is approx. 8 kcal/mol
- Isomerization can be affected in the singlet and triplet sensitization manifolds and is also possible in the absence of sensitizer
- *E*-1-phenylcyclohexene has been observed (*JACS* **1976**, 98, 4329)
- The activation energy for *trans-cis* isomerization is low and photoisomerization has to be conducted in the presence of the reagents

For reviews, see:

Marshall *Acc. Chem. Res.* **1969**, 2, 33; Marshall *Science* **1970**, 170, 137; Kropp *Mol. Photochem.* **1978**, 9, 39

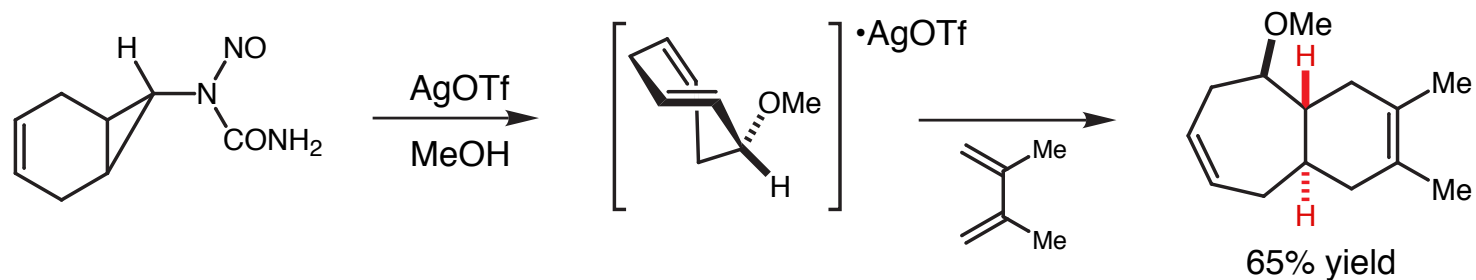
Strain elevates ground state energy in a variety of systems: Liebman and Greenberg *Chem. Rev.* **1976**, 76, 311

Non-Photochemical Approaches to *E*-Cycloalkenes



- *E*-cyclooctenes and higher homologs can be isolated

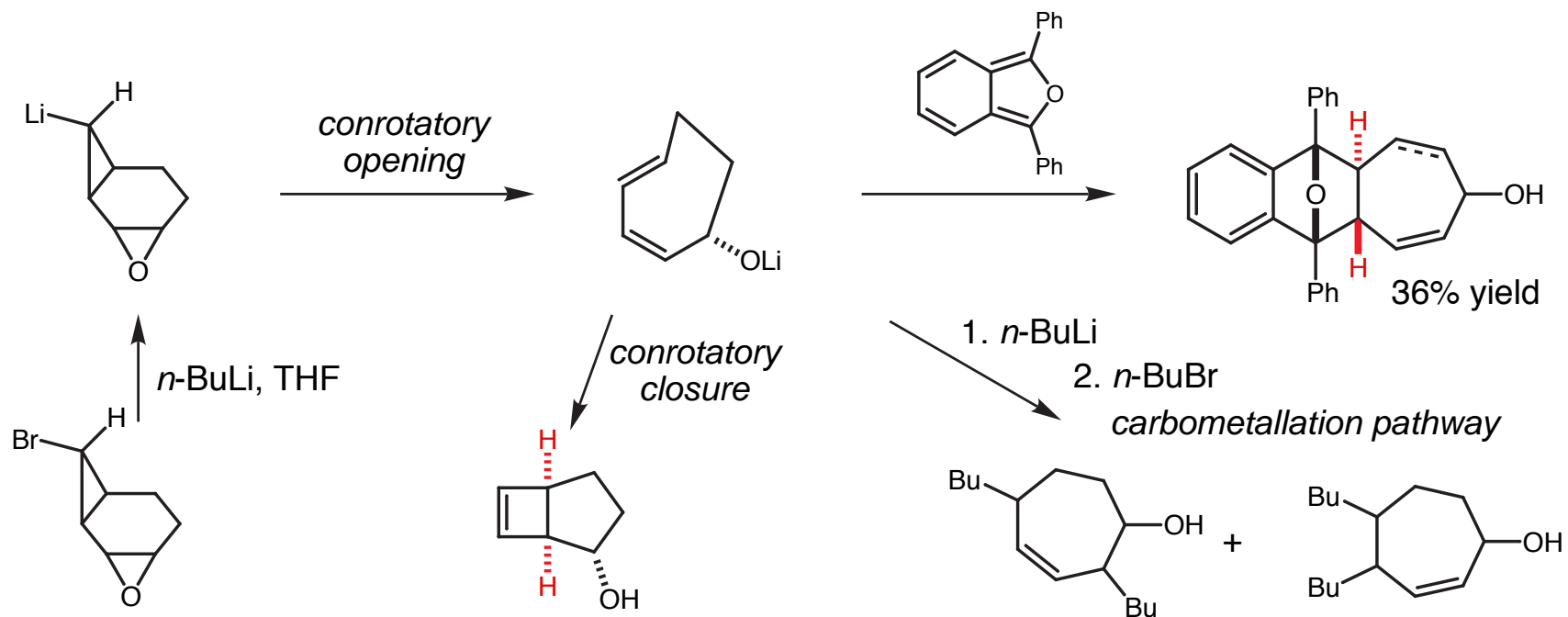
Corey et al. *JACS* **1965**, 87, 934



- AgOTf stabilizes the *E*-cycloheptadiene through complexation of the *E*-olefin
- *E*-cycloalkene does not react with MeOH!

Jendralla *ACIEE* **1980**, 19, 1032; *JCS Chem. Commun.* **1984**, 887

Non-Photochemical Approaches to *E*-Cycloalkenes (continued)



Coates and Last *JACS* **1983**, *105*, 7322

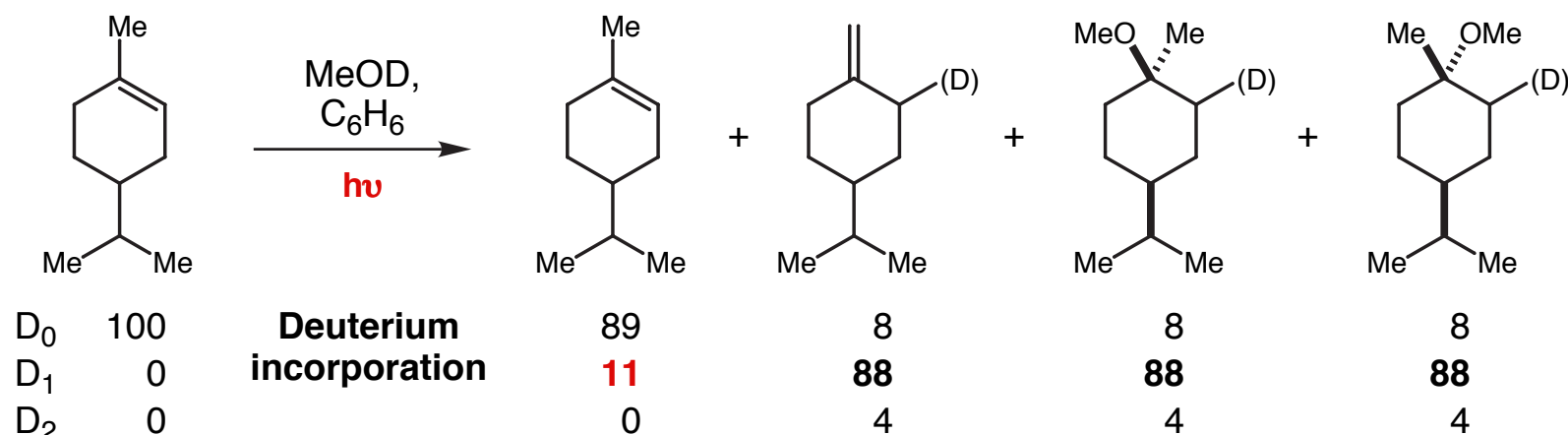
- Some successful, specific, non-photochemical approaches to 7-membered *E*-cycloalkenes
 - No successful (non-photochemical) approaches to 6-membered *E*-cycloalkenes have been reported.
- For attempts, see: Dervan and Jones *JOC* **1979**, *44*, 2116; Jendralla *Chem. Ber.* **1980**, *113*, 3585

⇒ Given the high ground state energy 6- and 7-membered *E*-cycloalkenes, photoisomerization appears to be the optimal route to these strained intermediates

Photoisomerization of Cycloalkenes: Background

- Most of the examples reported by Kropp and Marshall utilized a triplet sensitization manifold
Initial report: Kropp *JACS* **1966**, 88, 4091; Marshall and Carroll *JACS* **1966**, 88, 4092
- Increase in ground state energy (*E*-cycloalkene) allows olefin protonation by weak acids such as MeOH

Deuterium labelling experiments: Kropp and Krauss *JACS* **1967**, 89, 5199



reaction is reversible

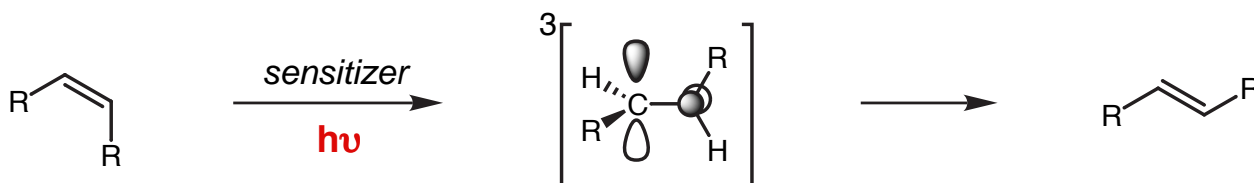
Product distribution

| | | | | |
|------------------|----|----|----|----|
| in MeOH | 5 | 36 | 16 | 27 |
| added morpholine | 41 | 21 | 16 | 23 |
| 0.006M NaOAc | 51 | 19 | 12 | 16 |

- Three** possible pathways:
- Trans-cis isomerization (forms starting material from *E*-cycloalkene)
 - Double bond isomerization (via E1 pathways)
 - Ether formation (from carbocation)

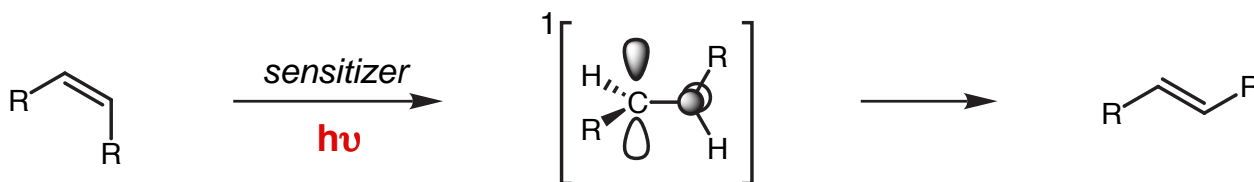
Photoisomerization of Alkenes: Direct vs. Sensitized Approaches

Triplet manifold



For a discussion, see: Kropp *Mol. Photochem.* **1978**, 9, 39

Singlet manifold



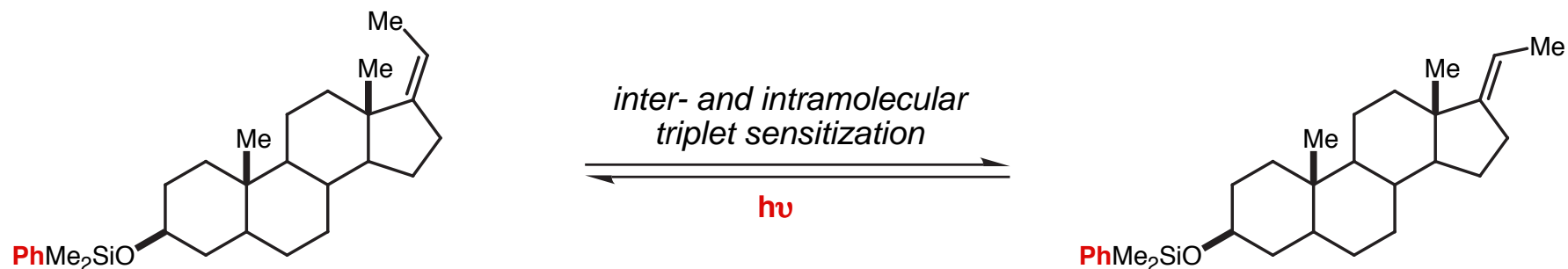
For a discussion, see: Jayathirtha Rao in *Organic Molecular Photochemistry*, Ramamurthy and Schanze, Eds, Marcel Dekker, 1999, Chap. 4

Direct irradiation

- The alkene behavior on direct irradiation arises from singlet excited states
- More side reactions possible

For a discussion, see: Kropp in *CRC Handbook of Organic Photochemistry and Photobiology*, Horspool and Song, Eds, CRC Press, 1995, Chap. 4

Steroids as Molecular Photonic Wires: Intramolecular Triplet Sensitization



Photonic wires: bonds between acceptor and reacting site

Antenna: group that absorbs incident radiation

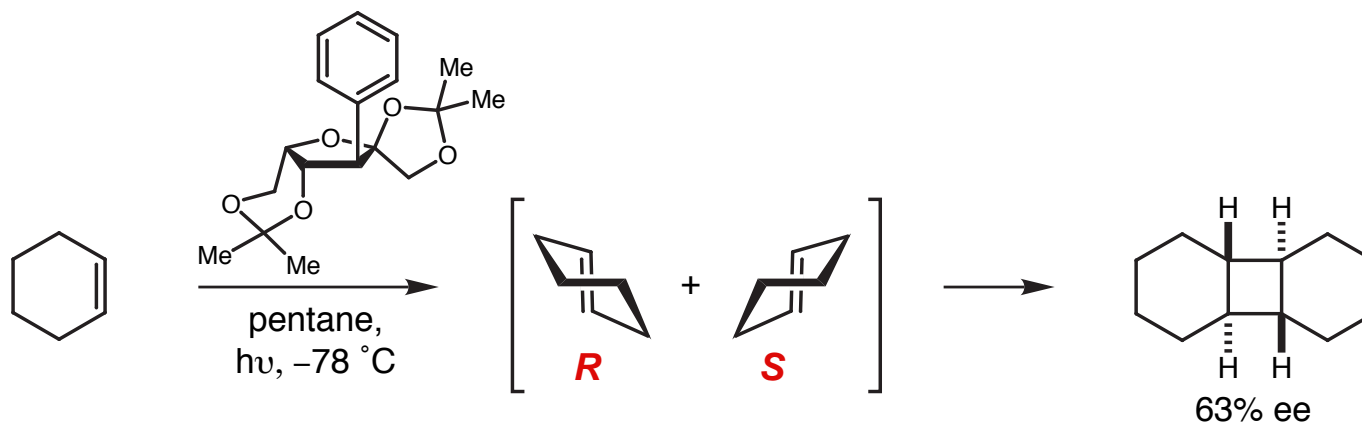
Gates and relays: groups that impede or facilitate energy migration

Acceptor: site of chemical reaction

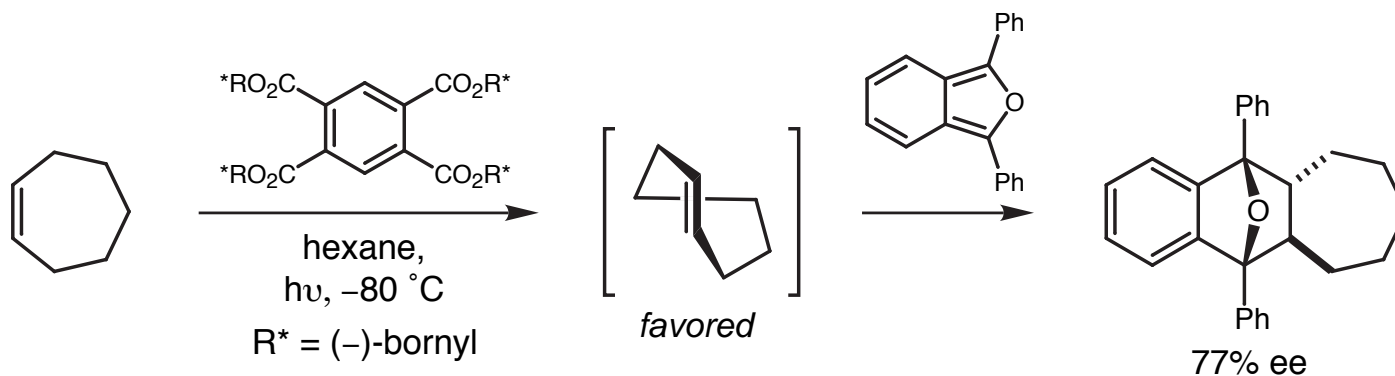
- Triplet-triplet excited state energy transfer (TTET) occurs both inter- and intramolecularly
- Using external quenchers allowed rate constants and quantum efficiencies to be determined (intra and inter)
- The 11 Å "antenna-acceptor" distance and $k_{\text{intra}} = 1.7 \times 10^6 \text{ s}^{-1}$ suggest that excitation energy is transmitted through the σ -bond framework

Timberlake and Morrison *JACS* **1999**, 121, 3618

Enantioselective Generation of *E*-Cycloalkenes



Inoue *et al.* *JCS Perkin 2* **2000**, 737

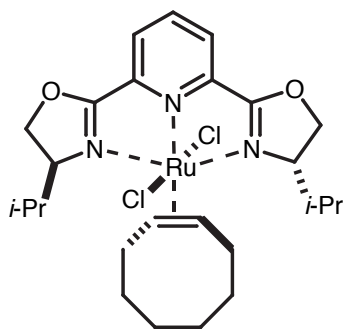
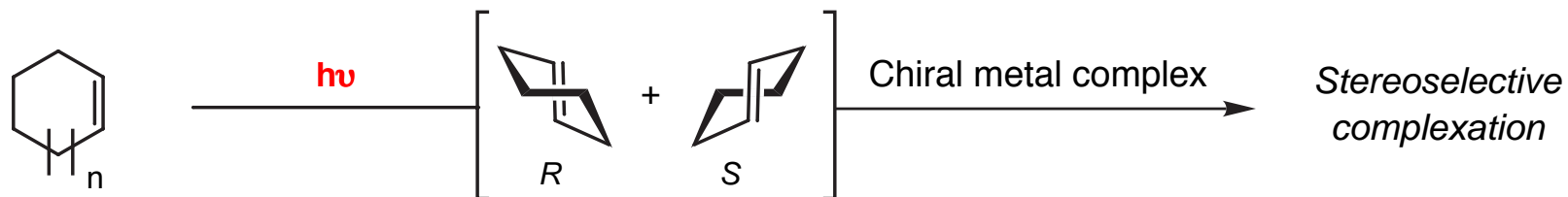


Hoffmann and Inoue *JACS* **1999**, 121, 10702

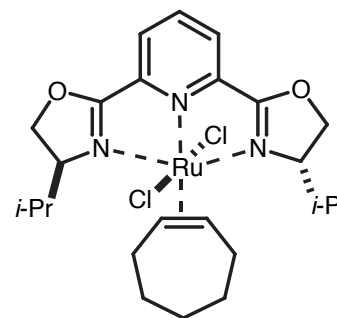
For the enantioselective generation of *E*-cyclooctene, see: Inoue *et al.* *JACS* **1998**, 120, 10687

- These enantioselective methods involve singlet sensitization: Inoue *et al.* *Pure Appl. Chem.* **2001**, 73, 475
- Enantioselectivity highly dependant on temperature and applied pressure: enantioselectivity can be reversed!

E-Cycloalkene Metal Complexes



one diastereoisomer
(X-ray)



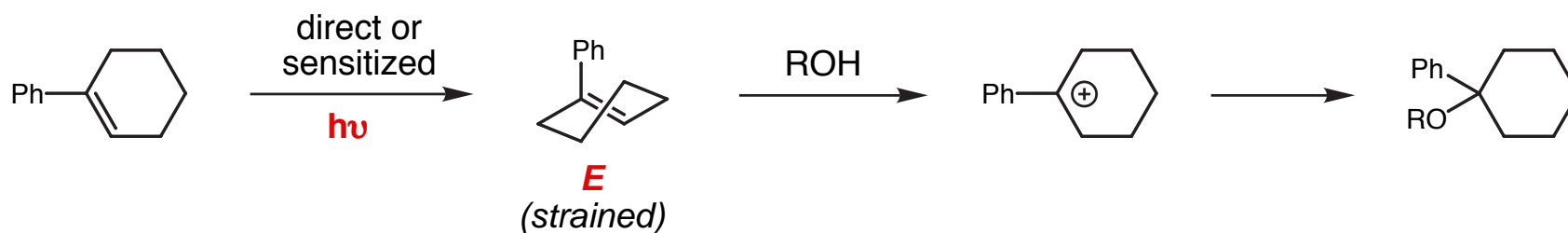
1:1 diastereomeric mixture
of *E*-cycloheptenes complexes

Nishiyama, H.; Naitoh, T.; Motoyama, Y.; Aoki, K. *Chem. Eur. J.* **1999**, *5*, 3509

For precedence on reactions in the presence of metal salts, see (CuOTf): Kochi *et al.* *JACS* **1974**, *96*, 1145

- *E*-cycloalkenes are better ligands than *Z*-cycloalkenes
- This approach could provide an enantioselective approach to products deriving from *E*-cycloalkenes

Direct Observation of Intermediates



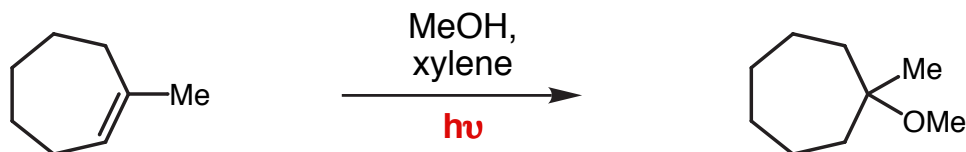
- Both the cationic and *E*-cycloalkene intermediates have been observed by **laser flash photolysis**
- Performing the reaction in hexafluoroisopropanol (HFIP) - CH_2Cl_2 : *E*-cycloalkene is observed if low HFIP content, cation not observed (solvent not sufficiently polar to separate the ion pair)
- Reaction in HFIP: cation is observed

McClelland *et al.* *JACS* **1993**, 115, 5050

For an earlier report on direct observation of *E*-cycloalkene, see: Jussot-Dubien *et al.* *JACS* **1976**, 98, 4329

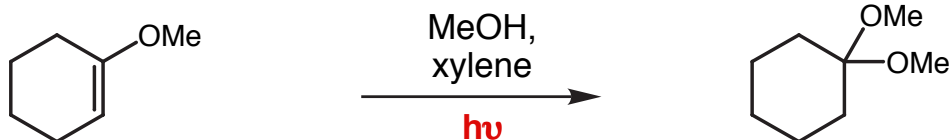
Reactivity of *E*-Cycloalkenes: Ether and Acetal Formation

- Most of the examples reported by Kropp and Marshall utilized a triplet sensitization manifold
- Increase in ground state energy (*E*-cycloalkene) allows olefin protonation by weak acids such as MeOH



62% yield

Kropp and Krauss *JACS* **1967**, 89, 5199



60% yield

Kropp and Krauss *JACS* **1967**, 89, 5199

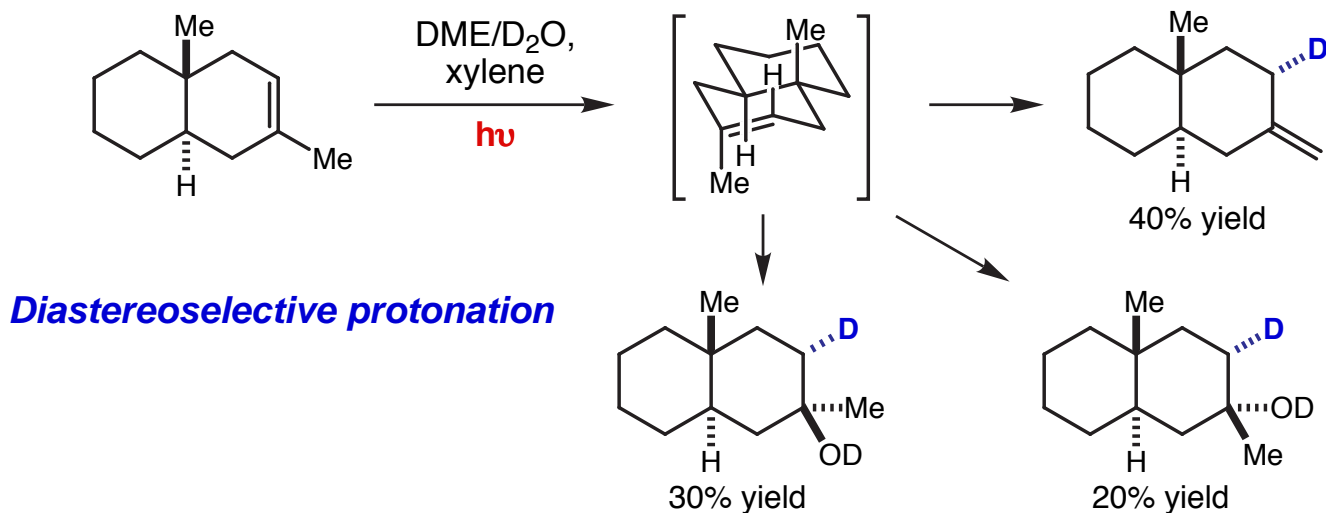
- Most of the original substrates were trisubstituted cycloalkenes. For *unsubstituted* cycloalkenes, **cyclodimerization** competes with ether formation: Kropp *JACS* **1967**, 89, 3650

"Acyclic, exocyclic and larger ring cyclic olefins, which are capable of readily forming both an orthogonal triplet and a relatively unstrained trans isomer, show no tendency to undergo either isomerization or reduction"

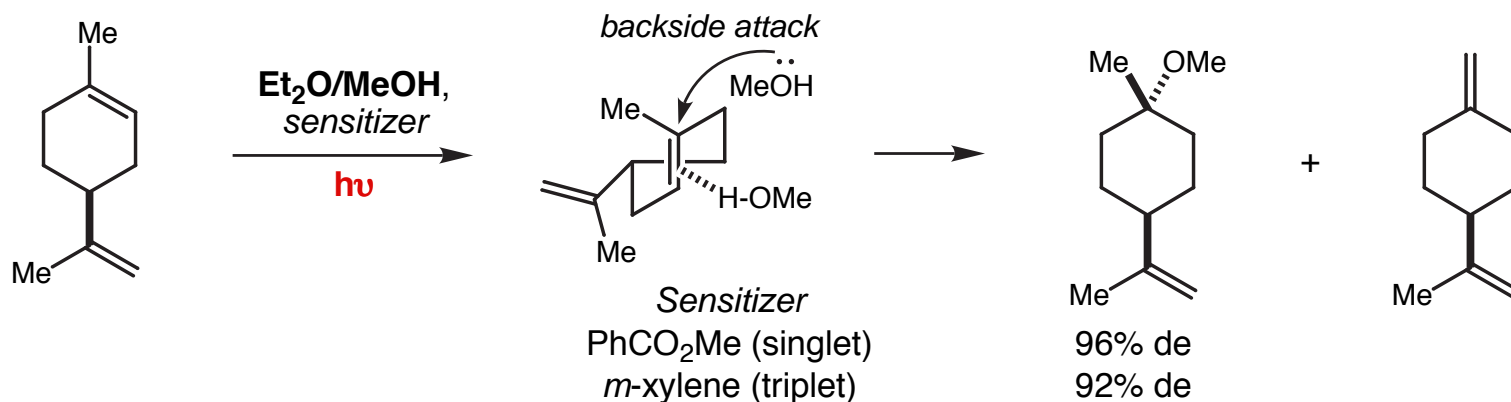
Kropp and Krauss *JACS* **1967**, 89, 5199 **However:**

"Under similar conditions acyclic and exocyclic alkenes undergo cis-trans isomerization, where structurally observable, but do not undergo any detectable protonation" Kropp *Mol. Photochem.* **1978**, 9, 39

Reactivity of *E*-Cycloalkenes: Diastereoselective Ether Formation



Marshall and Wurth *JACS* **1967**, 89, 6788

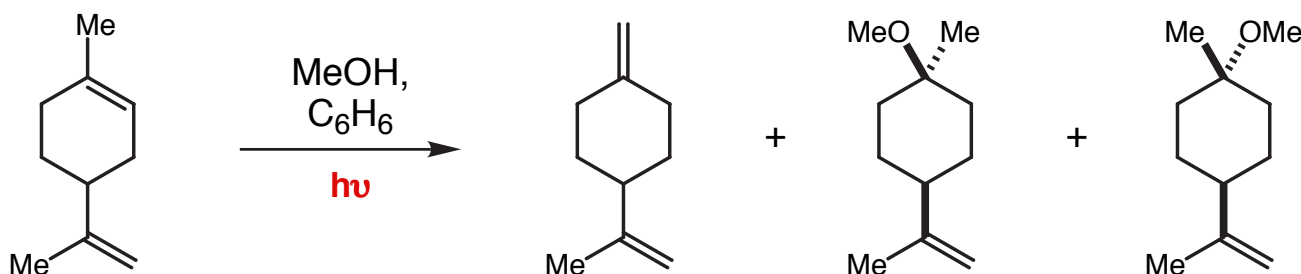


- Very high diastereoselectivity but low yields (ca. 10% of each product)

Inoue *et al. JOC* **2002**, 67, 5718

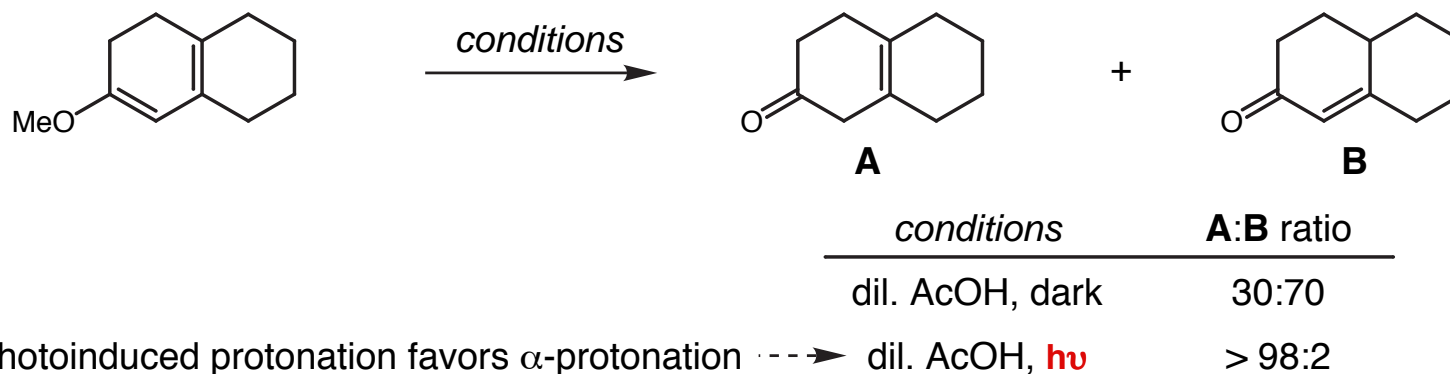
Photoinduced vs. Thermal Protonation

- Selective protonation of cyclic alkenes in the presence of acyclic olefins



Initial report: Kropp *JACS* **1966**, 88, 4091; Marshall and Carroll *JACS* **1966**, 88, 4092

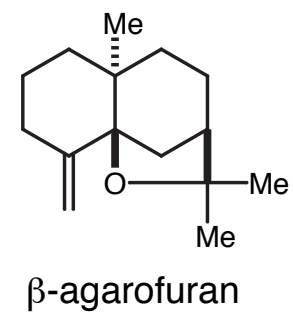
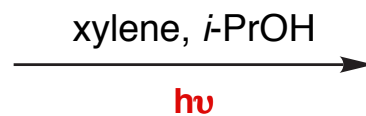
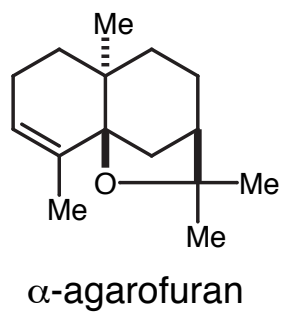
- Protonation regioselectivity can change in conjugated systems



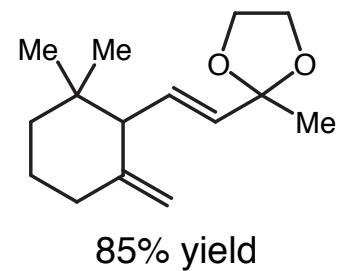
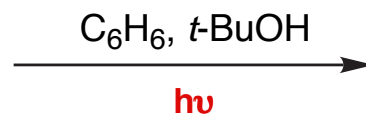
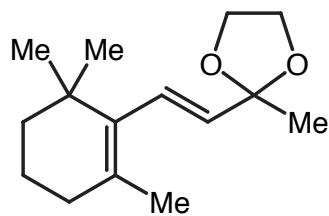
Rogers *et al.* *TL* **1967**, 1113

- Also, photoprotonation results in **complete addition** of H₂O or ROH to a cycloalkene: acid-catalyzed addition is reversible!

Photoinduced, Contra-Thermodynamic, Isomerization

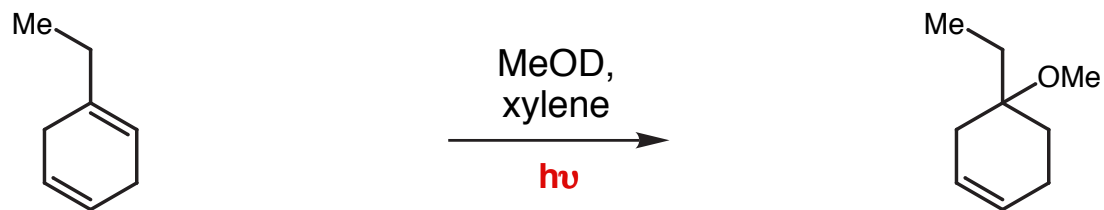


Marshall and Pike *JOC* **1968**, 33, 435

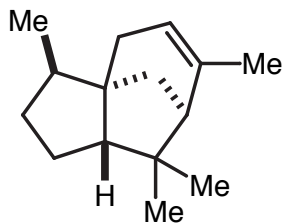


Evans *et al.* Unpublished results, 1972

Chemoselectivity in the Photoprotonation Reaction



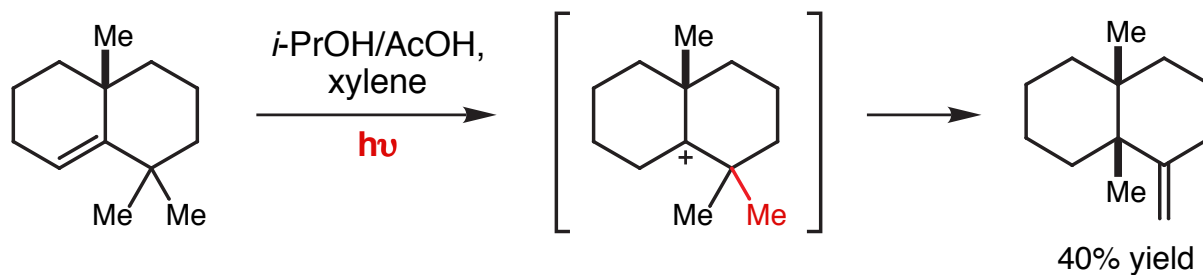
Selective formation of the tertiary ether



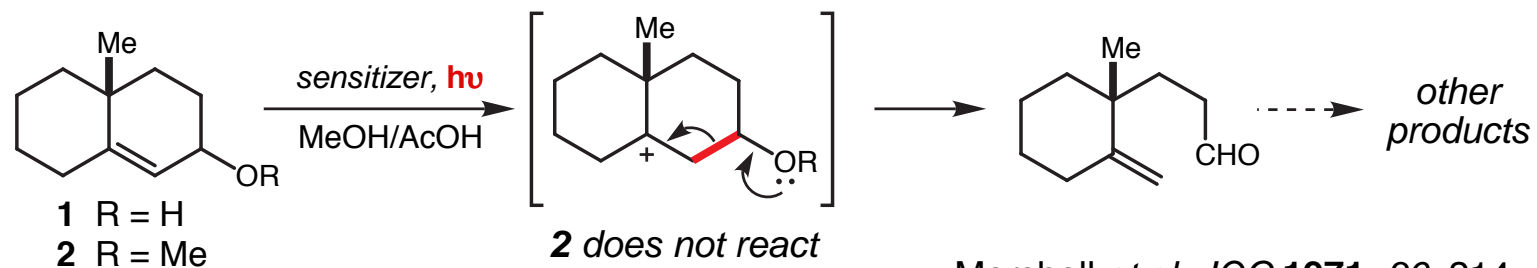
Strain can preclude the formation of the *E*-cycloalkene in 6-membered cycles as shown in the attempted photoprotonation of cedrene

Kropp *JACS* **1966**, 88, 4091

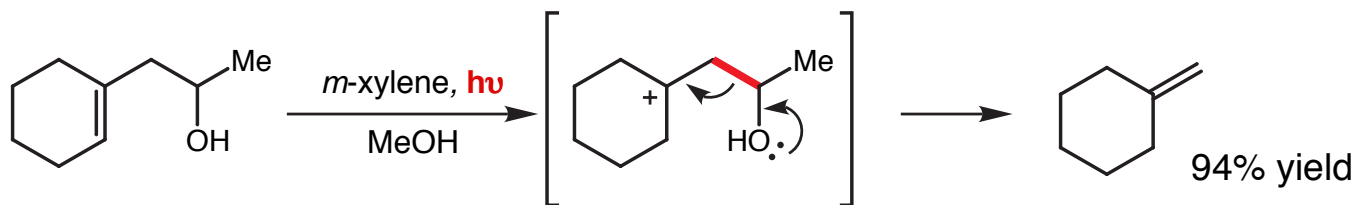
Mild Carbocationic Skeletal Rearrangements-1



Marshall and Hochstetler *JACS* **1969**, *91*, 648

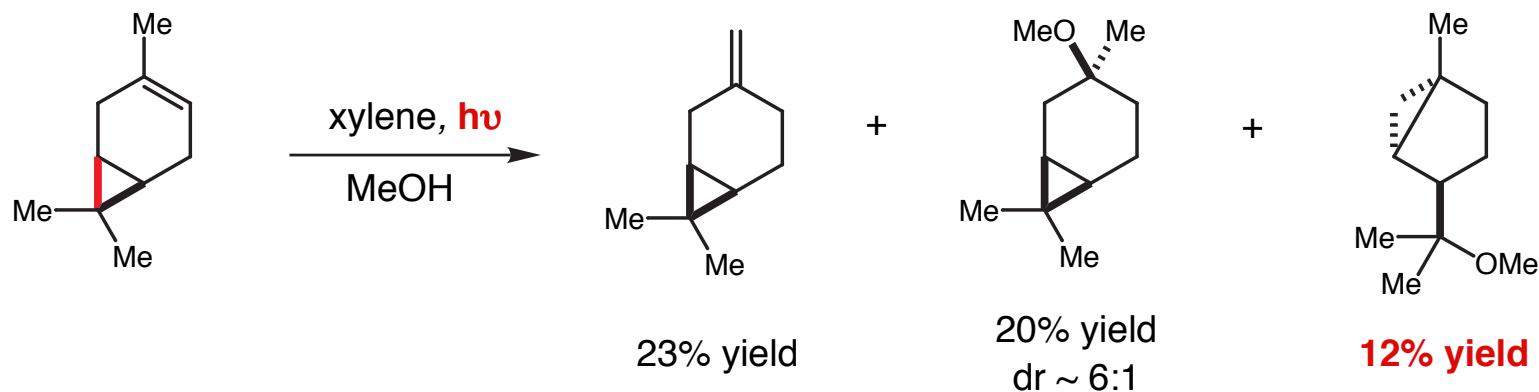


Marshall *et al.* *JOC* **1971**, *36*, 214



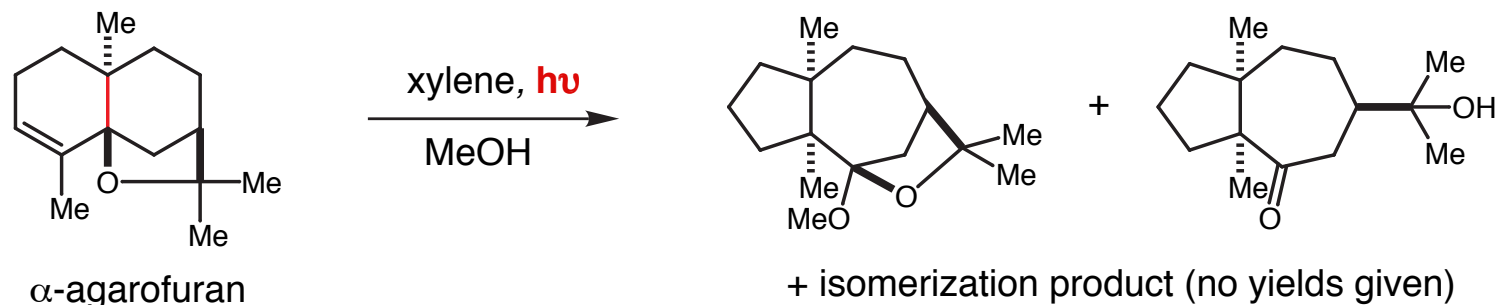
Kropp *et al.* *JACS* **1969**, *91*, 7466

Mild Carbocationic Skeletal Rearrangements-2

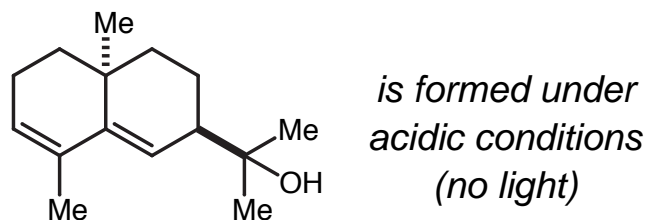


Kropp *JACS* **1966**, 88, 4091

• Wagner-Meerwein Rearrangement

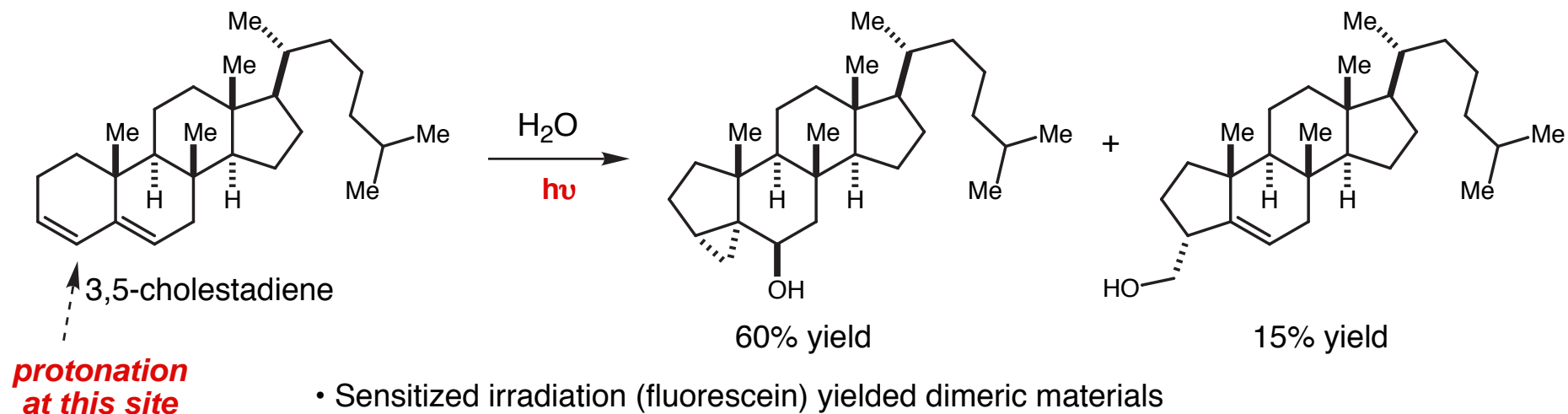


If reaction is performed in *i*-PrOH, only isomerization occurs: Marshall and Pike *JOC* **1968**, 33, 435

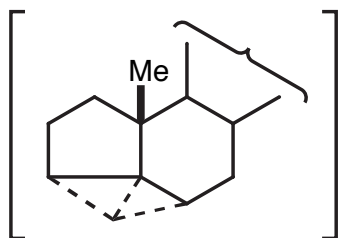


Thomas and Ozainne *Helv. Chim. Acta* **1976**, 59, 1243

Mild Carbocationic Skeletal Rearrangements-3

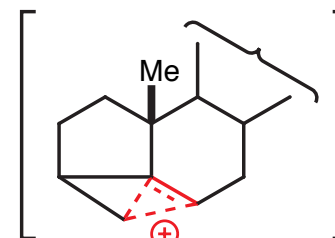


- Sensitized irradiation (fluorescein) yielded dimeric materials
- Irradiation in pentane led to a "valence isomeric hydrocarbon"



Dauben's proposal

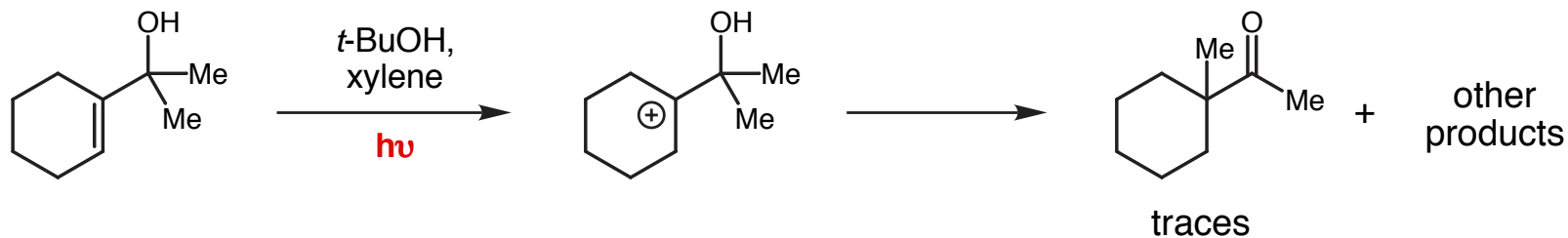
Dauben *Pure Appl. Chem.* **1964**, 9, 539



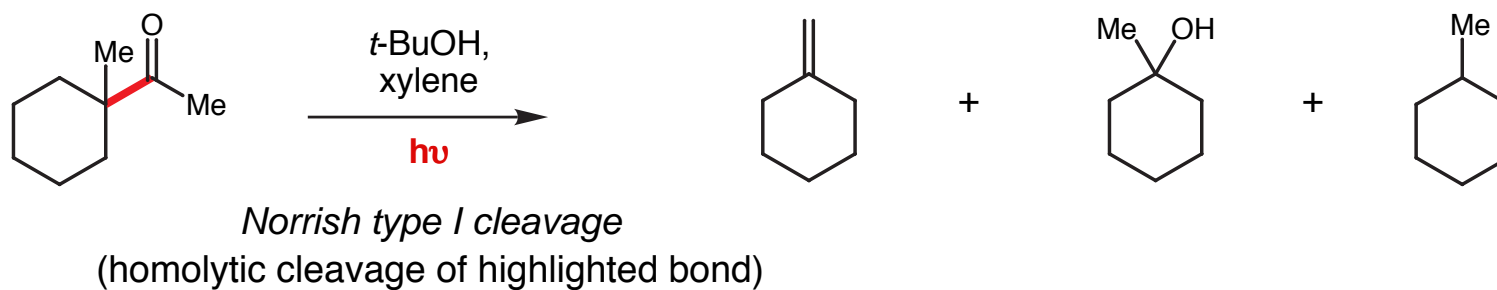
Alternative proposal: **non-classical carbocation** formed from *E*-cycloalkene

- Isomerization and etherification products (from *E*-cycloalkene) also observed in similar systems
 Proposed *E*-cycloalkene as intermediate: Kropp *JACS* **1967**, 89, 5199

Attempted Pinacol-Type Rearrangement



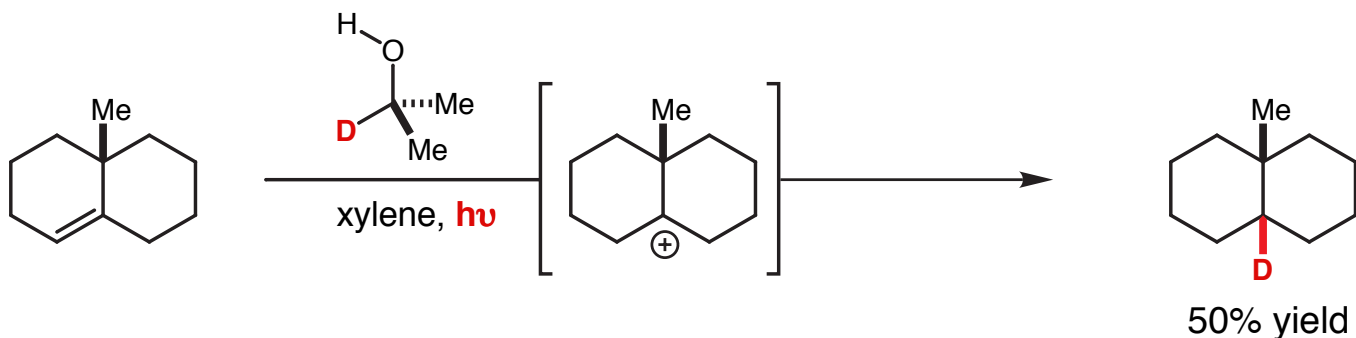
However,



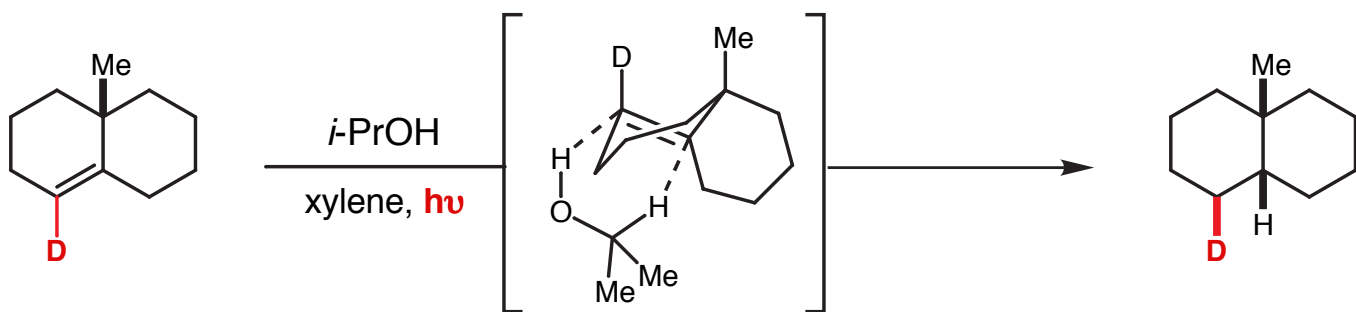
- Norrish type I cleavage problem led to "abandonment of this line of investigation"

Marshall and Greene *Tetrahedron* **1969**, 25, 4183

Reduction of *E*-Cycloalkenes Using Isopropanol



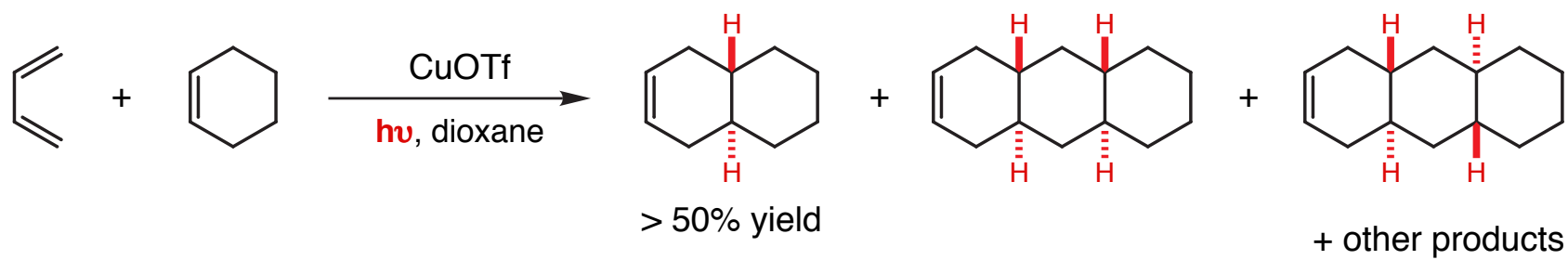
- Isopropyl ethers (10% yield) and Paterno-Buchi adducts from acetone (40% yield) are also formed



- Concerted or ionic pathway?

Marshall and Hochstetler *JCS Chem. Commun.* **1968**, 296

CuOTf-Mediated Diels–Alder Reactions of *E*-cyclohexene



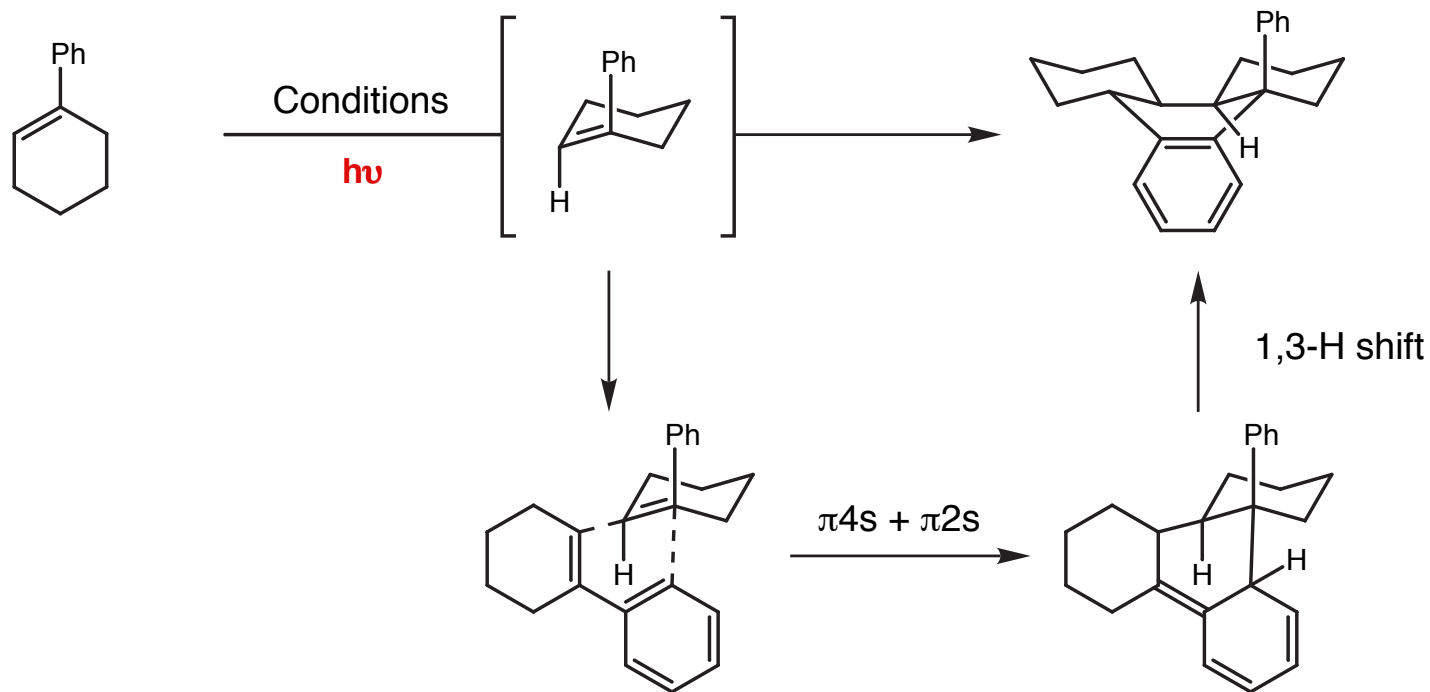
- *AgOTf* (decomp), Cu^0 and $\text{Cu}(\text{OTf})_2$ do not catalyze the reaction
- Reaction goes even if butadiene is a triplet quencher!
- Other products are arising from decomposition of *E*-cycloalkene•*CuOTf*

Roles of *CuOTf*:

- Sensitizer
- Stabilize *E*-cycloalkene formed
- Might mediate the cycloaddition reaction

Evers and Mackor *TL* **1978**, 2317; 2321

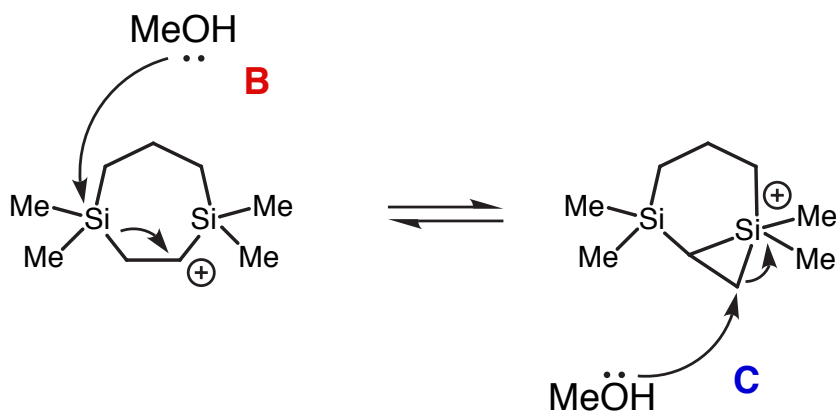
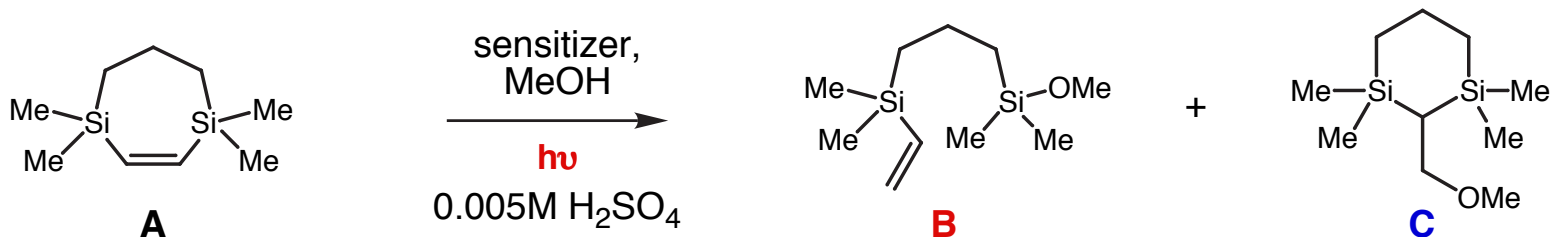
Unusual Diels–Alder Reaction of *E*-Phenylcyclohexene



| Conditions | Yield |
|---------------------------------------------|-------|
| MeOH, $-75\text{ }^{\circ}\text{C}$ | 24% |
| acetophenone, $-75\text{ }^{\circ}\text{C}$ | 16% |

Dauben et al. *JACS* **1979**, *101*, 1901; 6383

A *E*-Heterocycloalkene With 2 Silicon Groups

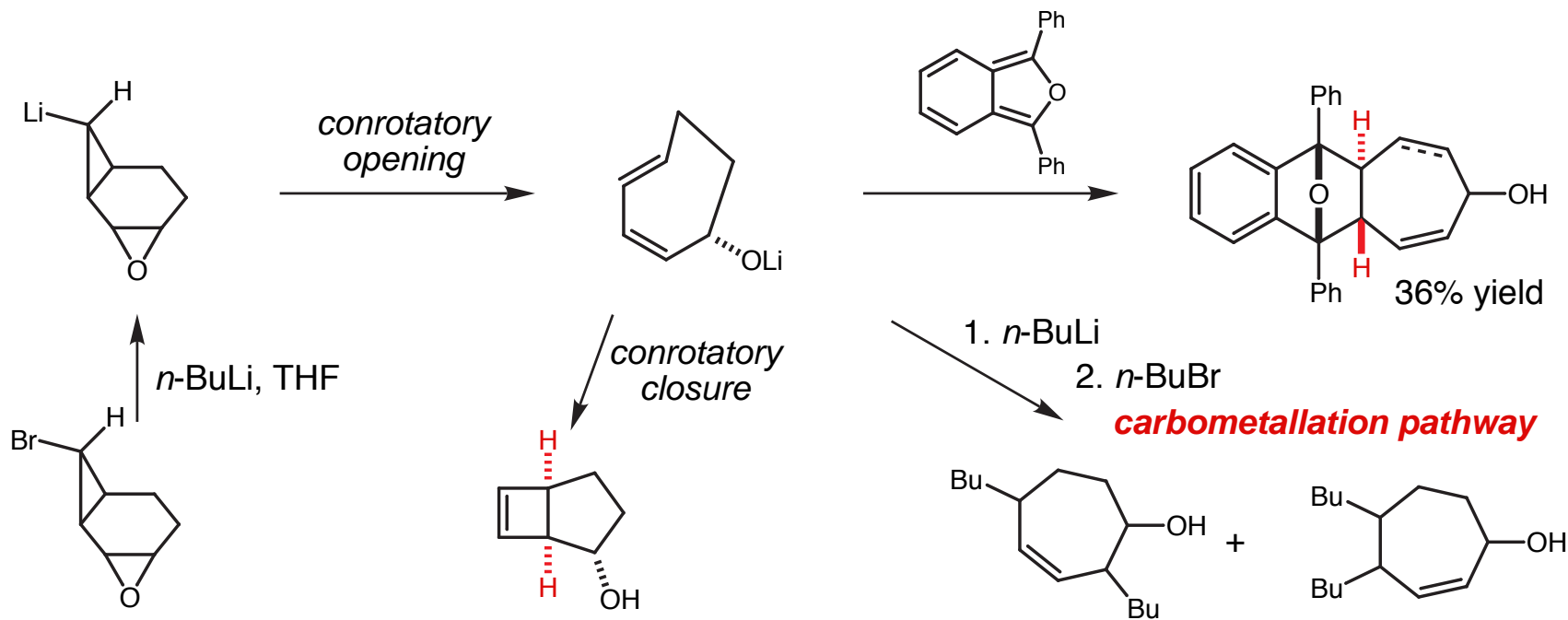


| sensitizer | A:B:C |
|----------------------|----------|
| none | 36:54:11 |
| PhCO ₂ Me | 53:44:9 |
| <i>p</i> -xylene | 30:47:13 |

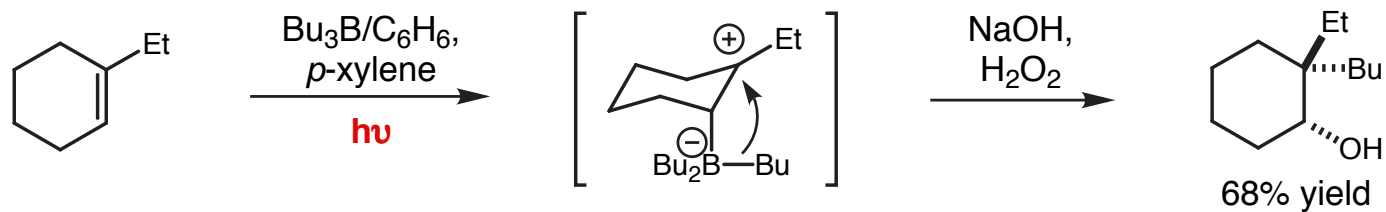
- Further evidence for a *E*-cycloalkene intermediate was obtained from low temperature trapping experiments: [2+2] and [4+2] adducts with *trans* ring junction were isolated

Steinmetz *et al.* *JACS* **1990**, *112*, 6601

Reactivity of *E*-Cycloalkenes: Carbometallation



Coates and Last *JACS* **1983**, *105*, 7322



Miyamoto *et al. Tetrahedron* **1973**, *29*, 2365

Overview of Reactivity Reported for *E*-cycloalkenes

E-cycloalkenes

- Contra-thermodynamic isomerization
- Protonation
 - Chemoselective
 - Diastereoselective
- Carbometallation (boron, RLi)
- Ene reaction
- [2+2] cycloaddition
- [4+2] cycloaddition (metal-controlled)
- [4+2] cycloaddition (unusual)
- Reduction using isopropanol

Carbocationic rearrangements documented

- Pinacol-type
- Wagner-Meerwein rearrangement
- Fragmentation reactions
- Rearr. possibly involving non-classical carbocations
- Hypervalent silicon-based rearrangement

E-cycloalkenones

- Isomerization
- Protonation/conjugate addition
- [2+2] cycloaddition
- [4+2] cycloaddition (metal-controlled)
- Nazarov cyclizations

Carbocationic rearrangements documented

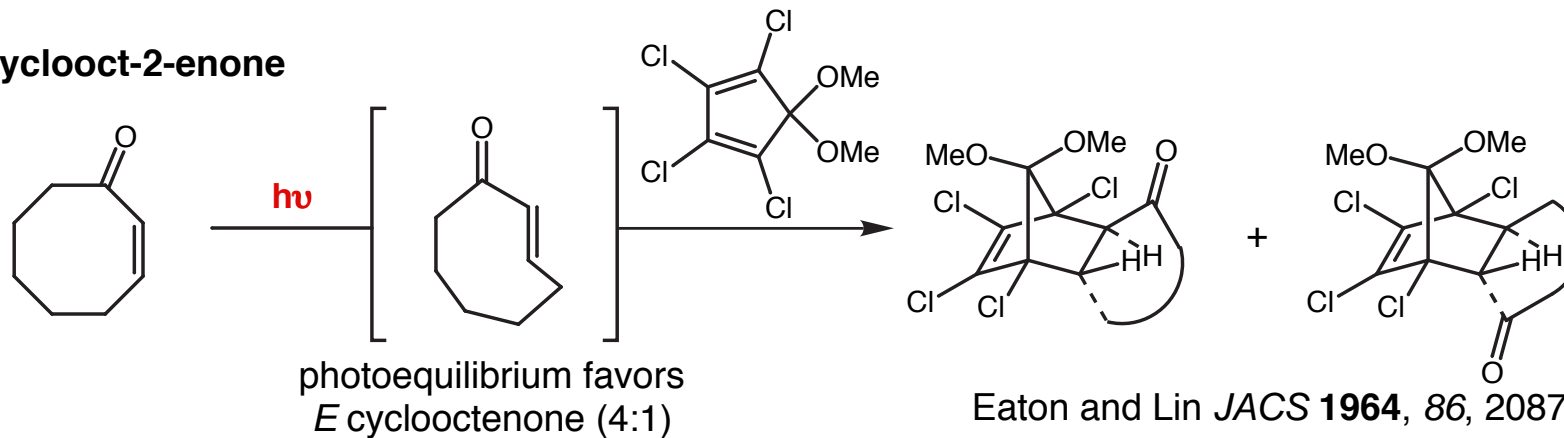
- Wagner-Meerwein rearrangements

Proposal that *E*-cycloalkene intermediate is involved in various **enone photolysis reactions**:

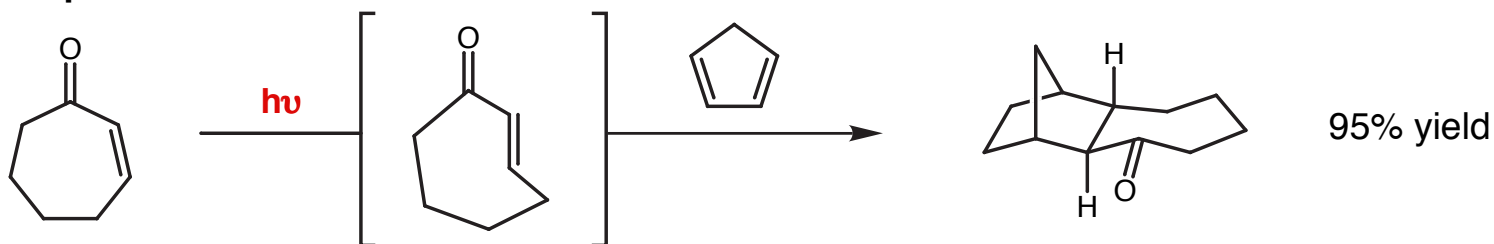
Kropp *JACS* **1967**, 89, 5199

Reactivity of *E*-Cycloalkenones: Initial Reports

trans Cyclooct-2-enone

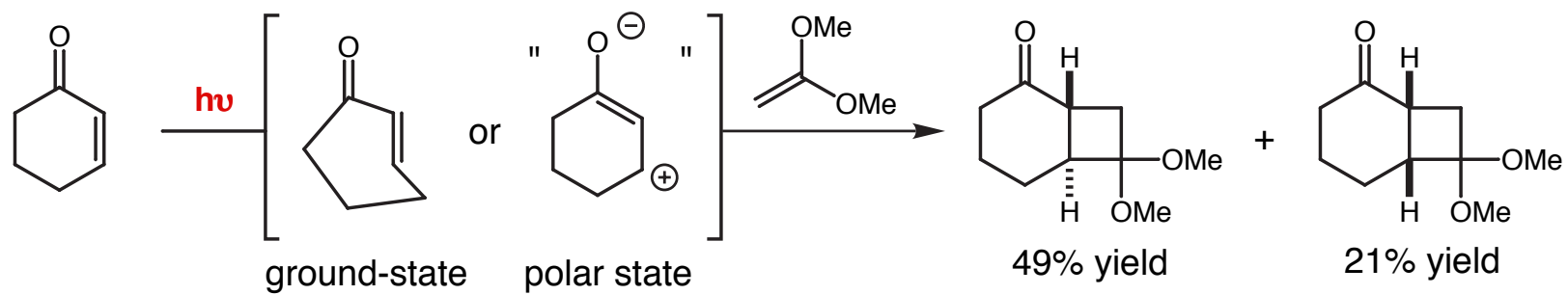


trans Cyclohept-2-enone



Corey, Tada, LaMahieu and Libit *JACS* **1965**, 87, 2051;
See also: Eaton and Lin *JACS* **1965**, 87, 2052

trans Cyclohex-2-enone?

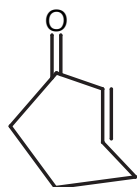


Corey, Bass, LeMahieu and Mitra *JACS* **1965**, 86, 5570

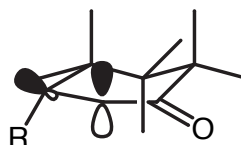
Nature of the Intermediate Involved in Photoreactions of Cyclohexenones

Does the addition of an additional trigonal carbon prevents the formation of *E*-cyclohexenones?

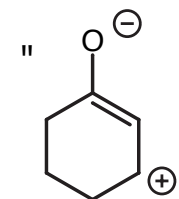
Hypotheses from the literature



E-cyclohexenone
estimated to ~60 kcal/mol
about ground state (Z)



proposed structure: Triplet
Triplet energy: 63 kcal/mol

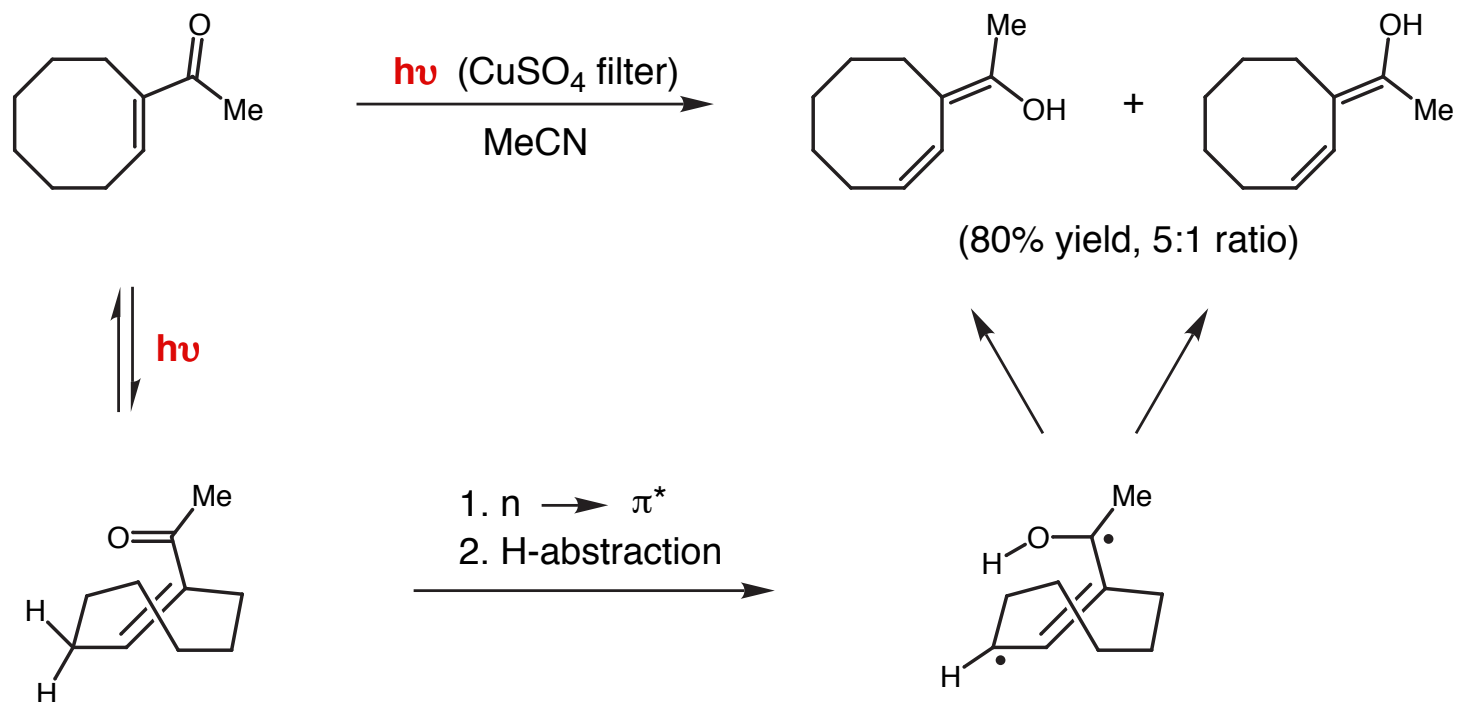


polar state

- The best evidence for a *E*-cyclohexenone derives from experimental results (stereochemistry of products in a variety of reactions)
- In contrast to 7 and 8-membered cycloalkenones and 6 to 8-membered cycloalkenes, *E*-cyclohexenones have not been observed directly

For a discussion, see: Schuster in *CRC Handbook of Organic Photochemistry and Photobiology*, Horspool and Song, Eds, CRC Press, 1995, Chap. 48.

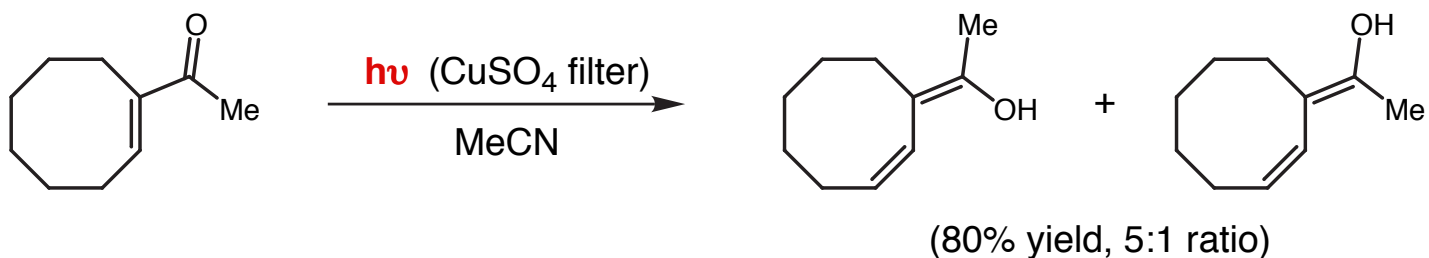
Photodeconjugation of Cyclic Enones



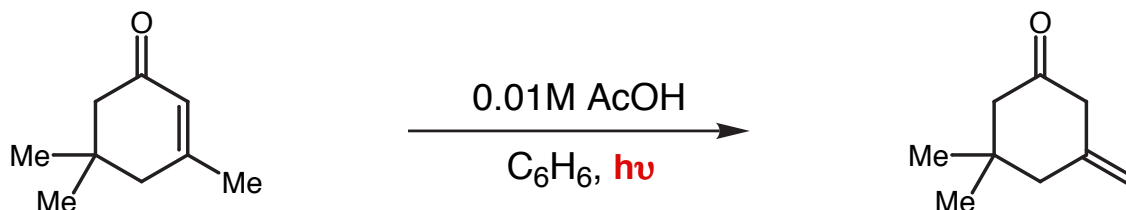
Acetic anhydride/pyridine at -20°C furnished the dienolacetates in 60% yield (5:1 ratio)

Noyori, Inoue, Katô *JACS* **1970**, *92*, 6699

Photodeconjugation of Cyclic Enones



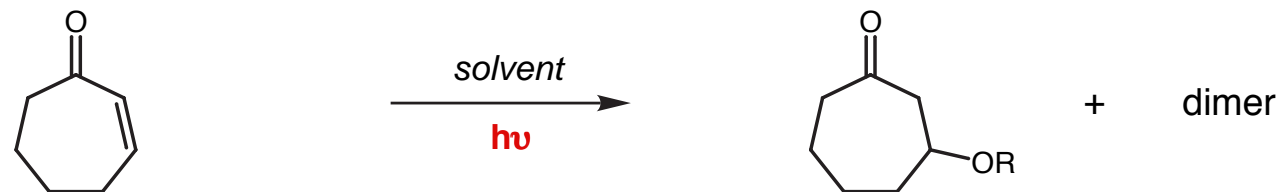
Noyori, Inoue, Katô *JACS* **1970**, *92*, 6699



- The authors invoke the formation of a ***E*-cyclohexenone**
- Tertiary ether is formed if MeOH is also present
- This paper **reconciles a number of conflicting reports** as they demonstrate that traces of acid are necessary for the photodeconjugation reaction to occur

Rudolph and Weedon *JACS* **1989**, *111*, 8756

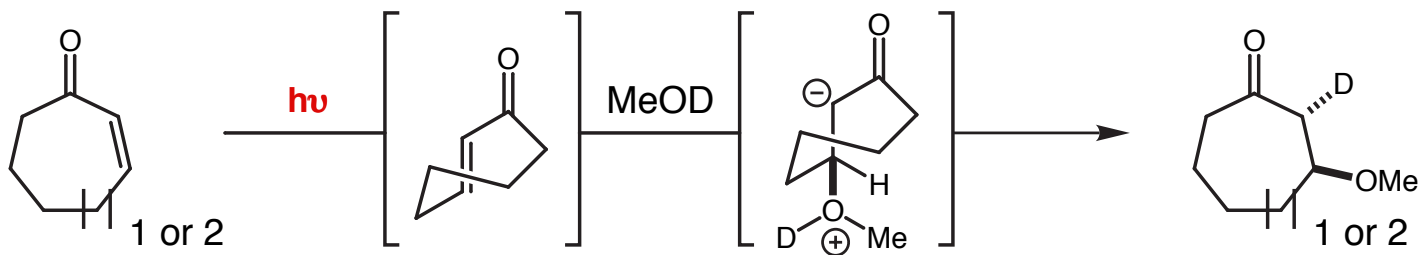
Reactivity of *E*-Cycloalkenones: Conjugate Additions to Enones



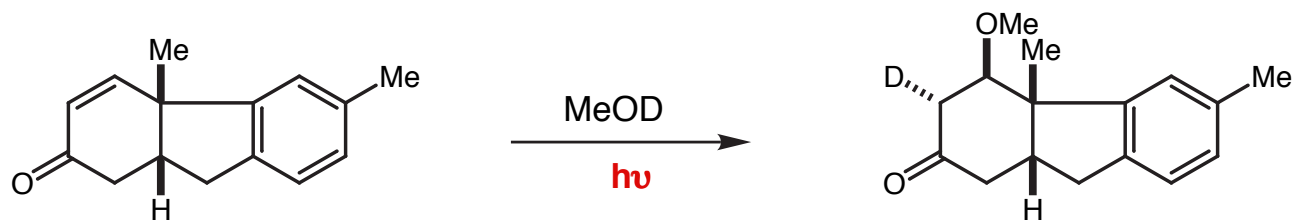
| | | |
|----------------|---|-----------|
| <i>solvent</i> | - | 88% yield |
| cyclohexane | - | 86% yield |
| MeOH | - | 3% yield |
| <i>t</i> -BuOH | - | 23% yield |
| AcOH | - | 31% yield |

Nozaki *et al.* *TL* **1968**, 9, 2025

Also efficient for 2-cyclooctenone: Noyori *et al.* *TL* **1968**, 9, 5443

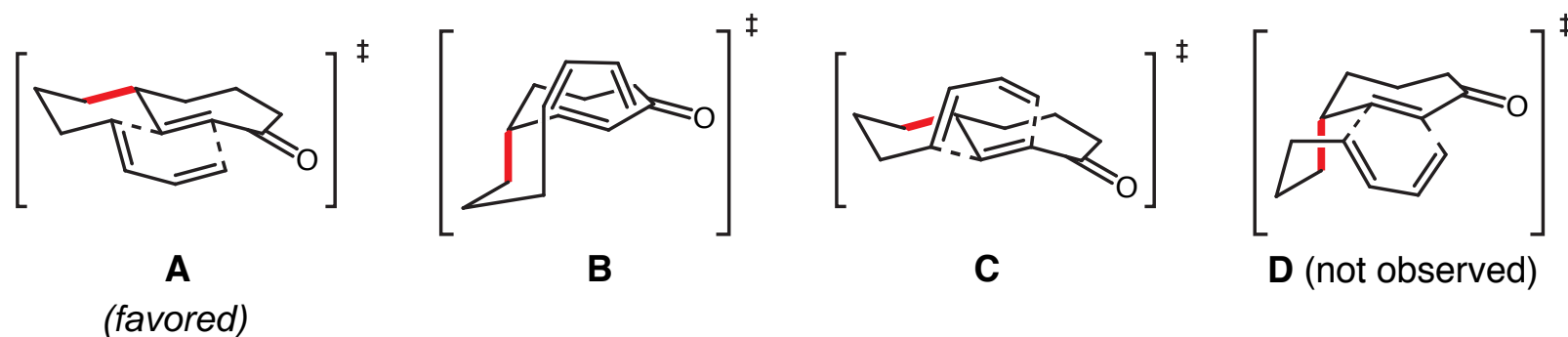
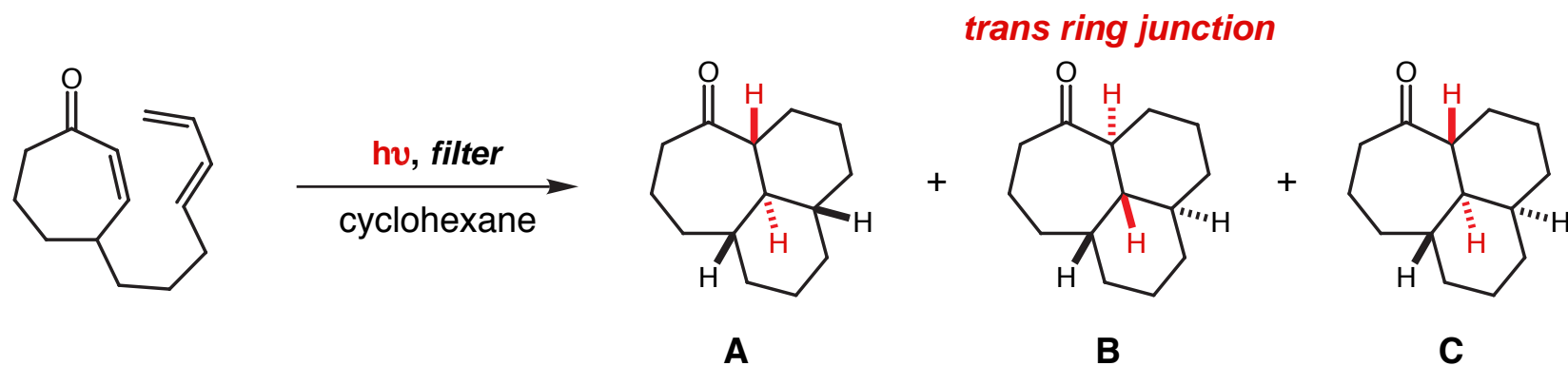


Hart and Dunkelblum *JACS* **1977**, 100, 644; *JACS* **1977**, 100, 5141



Dunkelblum, Hart and Jeffares *JOC* **1978**, 43, 3409

Reactivity of *E*-Cycloalkenes: Diels-Alder Reactions of Enones



| rxn temp | pyrex yield | uranium filter yield | A:B:C |
|----------|-------------|----------------------|--------|
| rt | 69% | 88% | 3:2:1 |
| -75 °C | 39% | 77% | 10:-:1 |

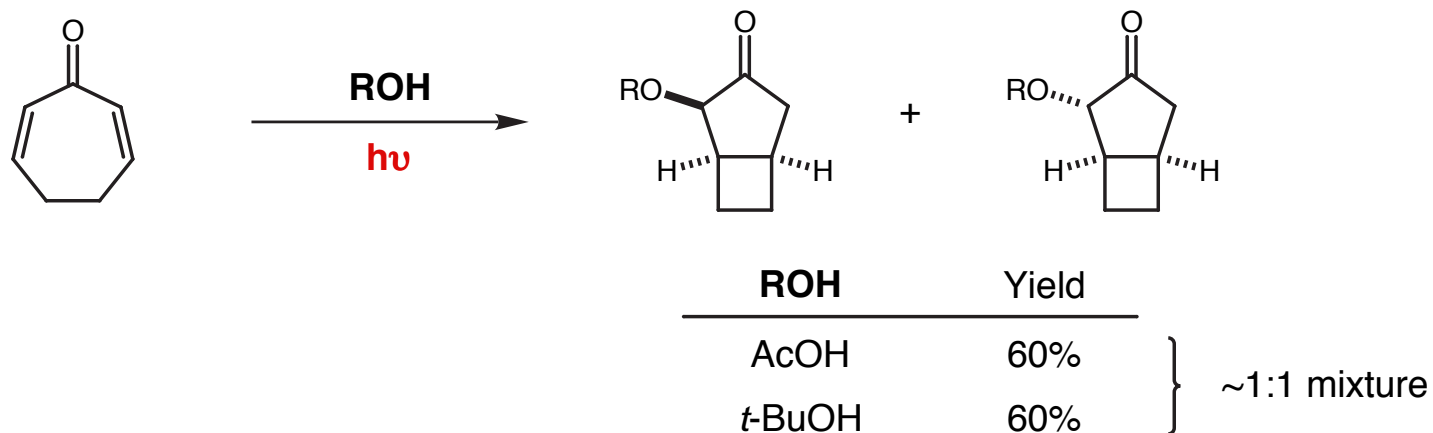
cut off ~285 nm cut off ~340 nm

- Use of an uranium glass filter avoids Norrish-type products unlikely

Dorr and Rawal *JACS* **1999**, 121, 10229

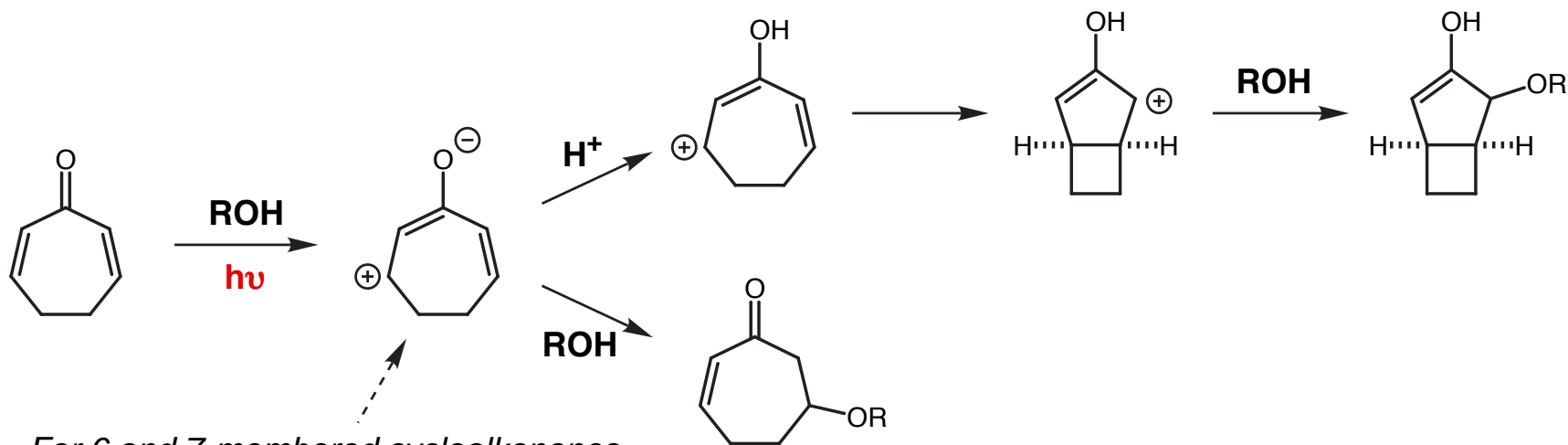
For intermolecular reaction, see: Corey, E. J. *et al.* *JACS* **1965**, 87, 2051; Eaton and Iin *JACS* **1965**, 87, 2052

Reactivity of *E*-Cycloalkenones: Nazarov Cyclizations



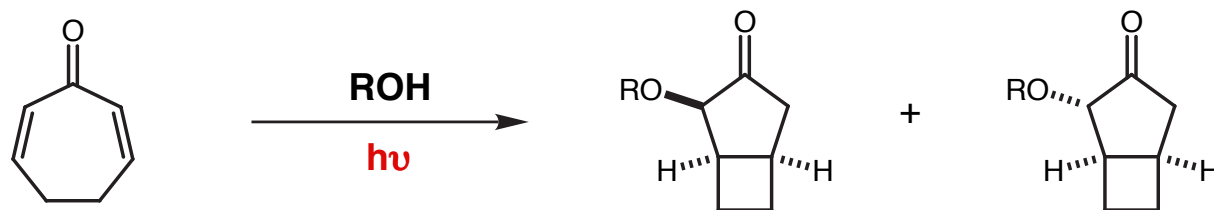
Upon irradiation in MeOH, a mixture of diastereomeric conjugate addition products was formed

Nozaki, Kurita and Noyori *TL* **1968**, 3635



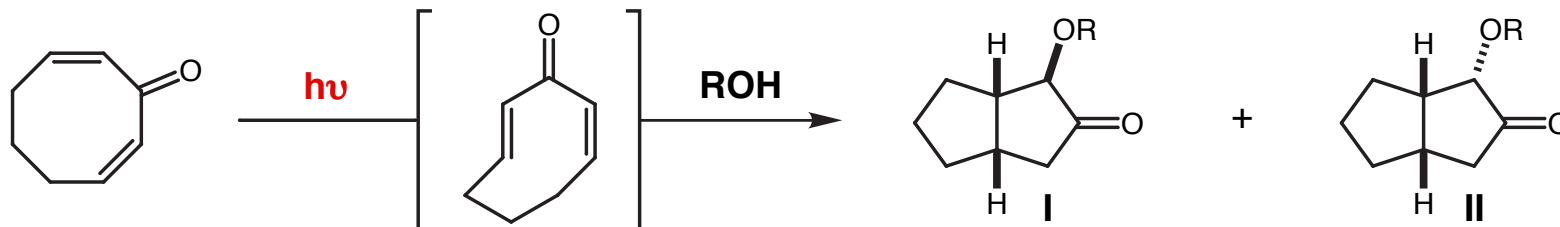
For 6 and 7-membered cycloalkenones, formation of this polar state is often invoked

Reactivity of *E*-Cycloalkenones: Nazarov Cyclizations



| ROH | Yield | } ~1:1 mixture |
|----------------|-------|----------------|
| AcOH | 60% | |
| <i>t</i> -BuOH | 60% | |

Nozaki, Kurita and Noyori *TL* **1968**, 3635

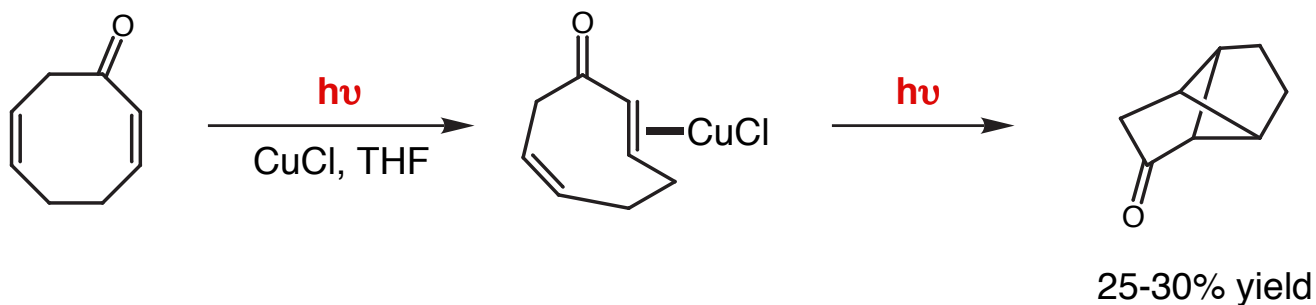


- O-Protonation of the *E*-cyclooctadienone: pentadienyl cation
- Thermal conrotatory ring closure accounts for the stereochemistry

| ROH | Yield | I:II |
|------|-------|------|
| AcOH | 70% | 4:1 |
| MeOH | 60% | 8:1 |

Noyori and Katô *TL* **1968**, 5075
 Crandall and Haseltine *JACS* **1968**, 90, 6251

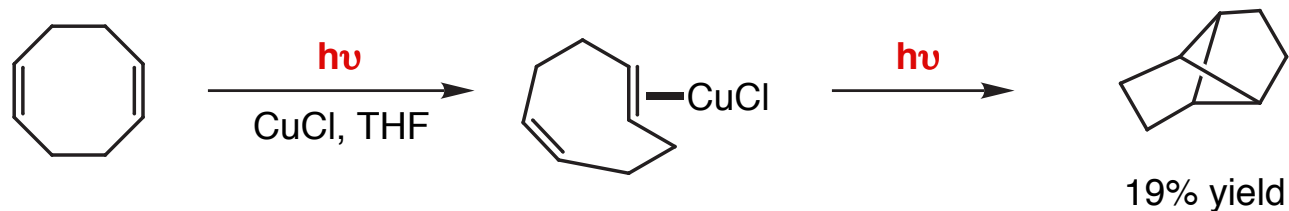
Reactivity of *E*-Cycloalkenones: [2+2] cycloaddition



Light is required for the 2+2 reaction to occur

Noyori *Chem. Comm.* **1970**, 1695

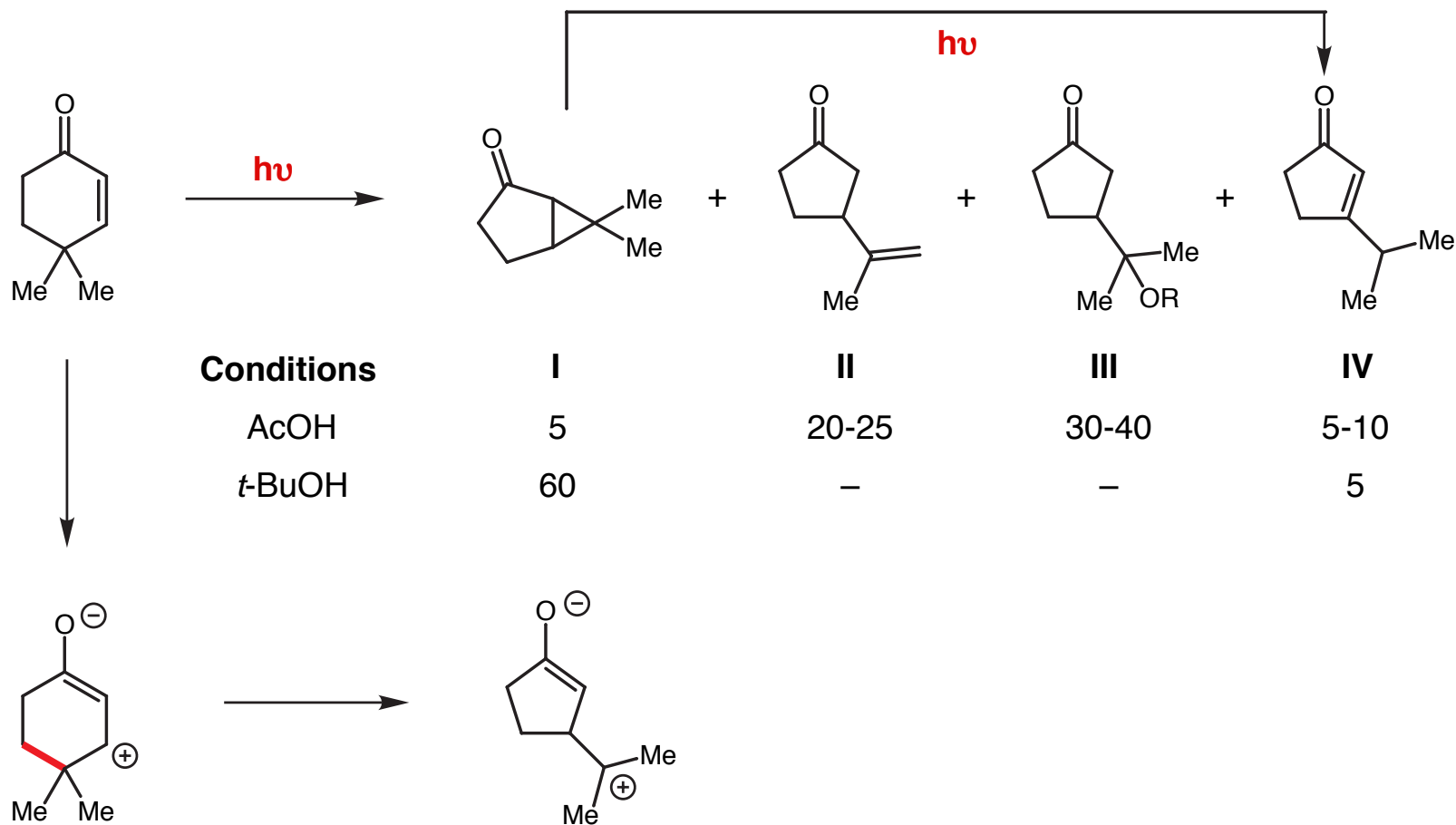
Precedence:



Srinivasan *JACS* **1964**, 86, 3318

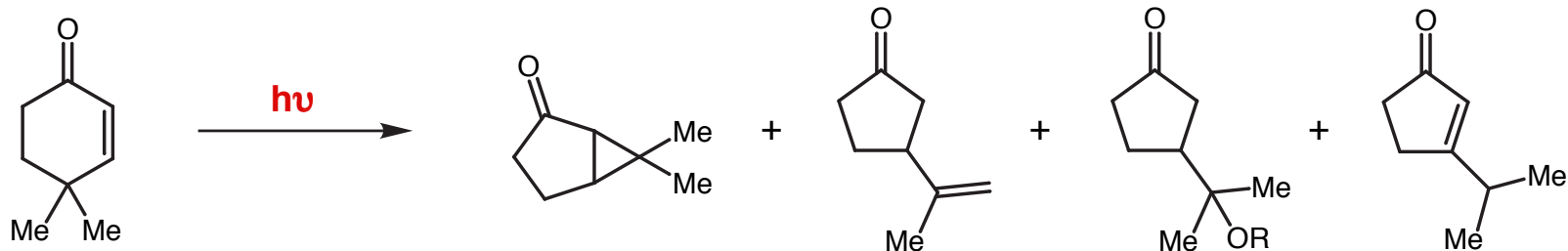
Whitesides, Goe and Cope *JACS* **1969**, 91, 2608

Photoinduced Skeletal Rearrangements of Enones



Chapman *et al.* *TL* **1963**, 2049

Photoinduced Skeletal Rearrangements of Enones



Conditions

AcOH

t-BuOH

I

5

60

II

20-25

—

III

30-40

—

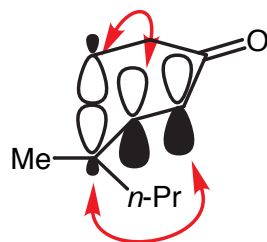
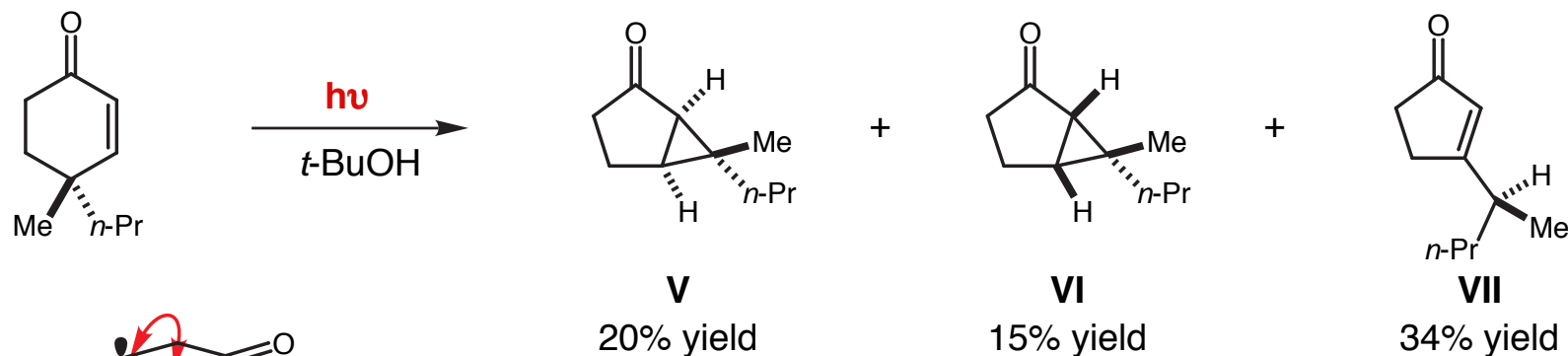
IV

5-10

5

Chapman *et al.* *TL* **1963**, 2049

Reaction is stereospecific

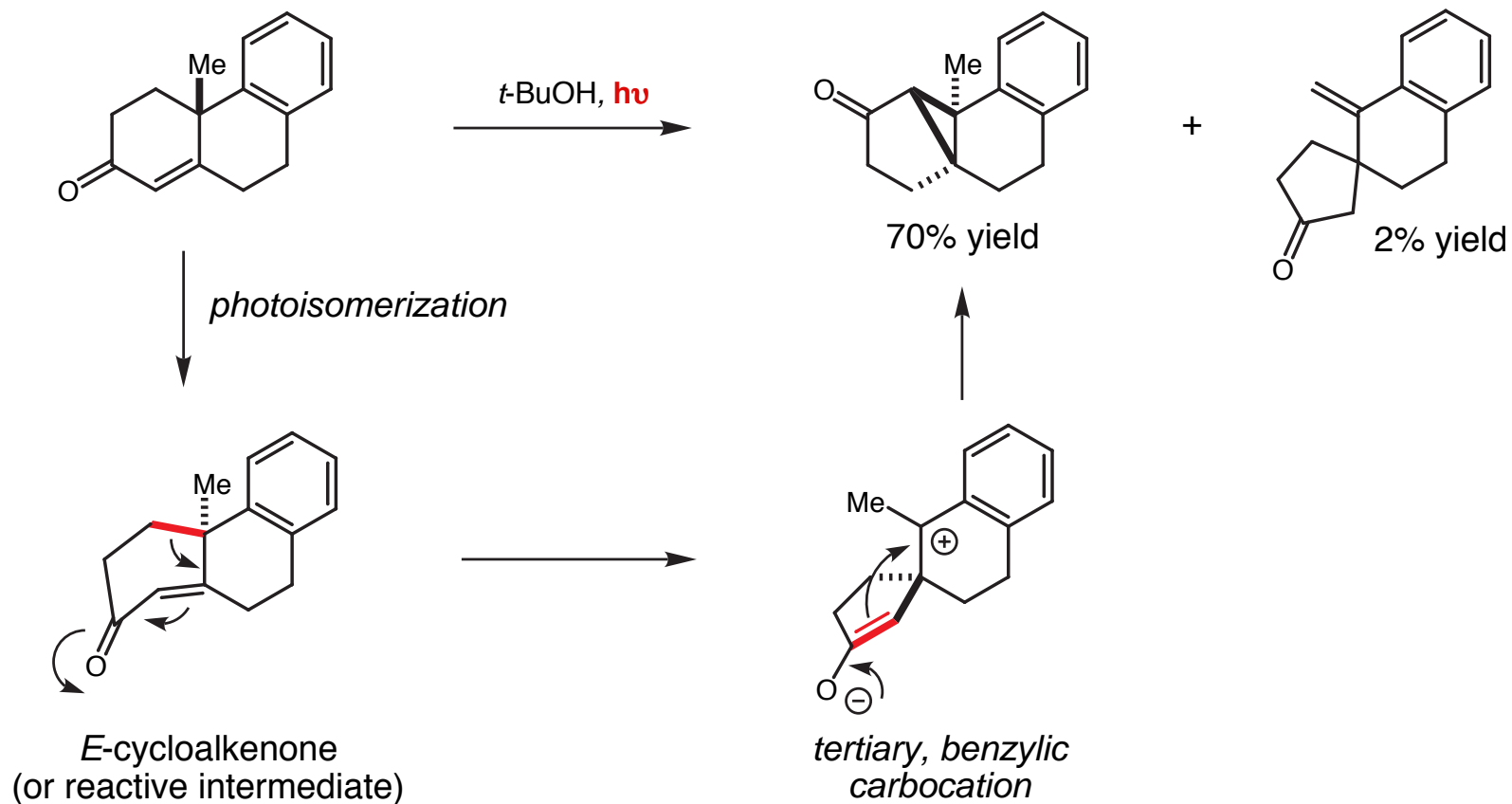


concerted $[\pi^2_a\sigma^2_a]$ cycloaddition

Schuster, Brown and Resnick *JACS* **1978**, 100, 4504

Photoinduced Skeletal Rearrangements of Enones

Lumiketone Rearrangement

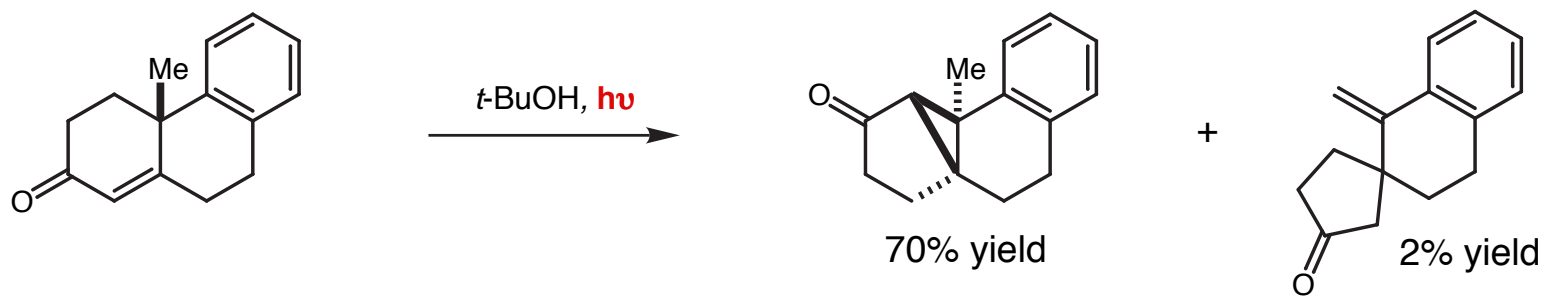


Reaction occurs with no detectable loss of optical purity

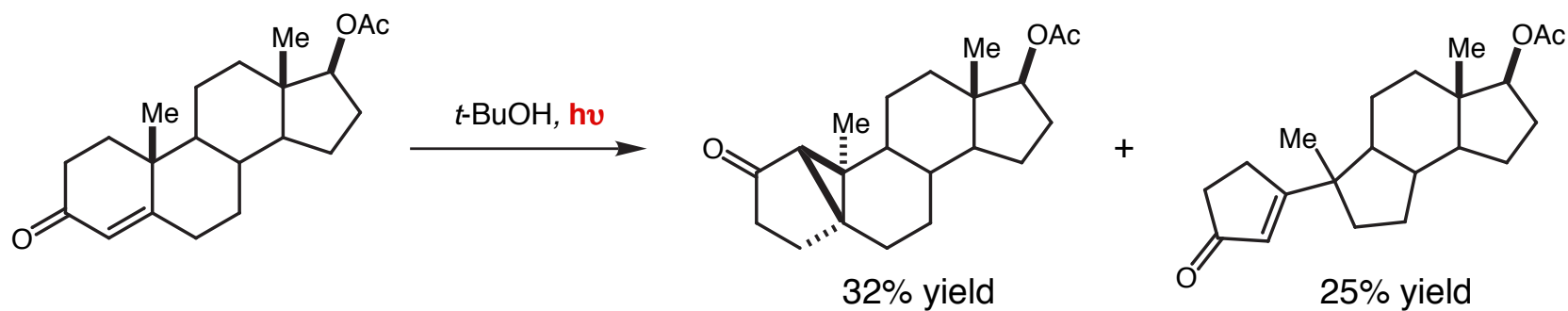
Chapman *JACS* **1966**, 88, 161

Proposed *E-cycloalkene* mechanism: Kropp *JACS* **1967**, 89, 5199

Photoinduced Skeletal Rearrangements of Enones

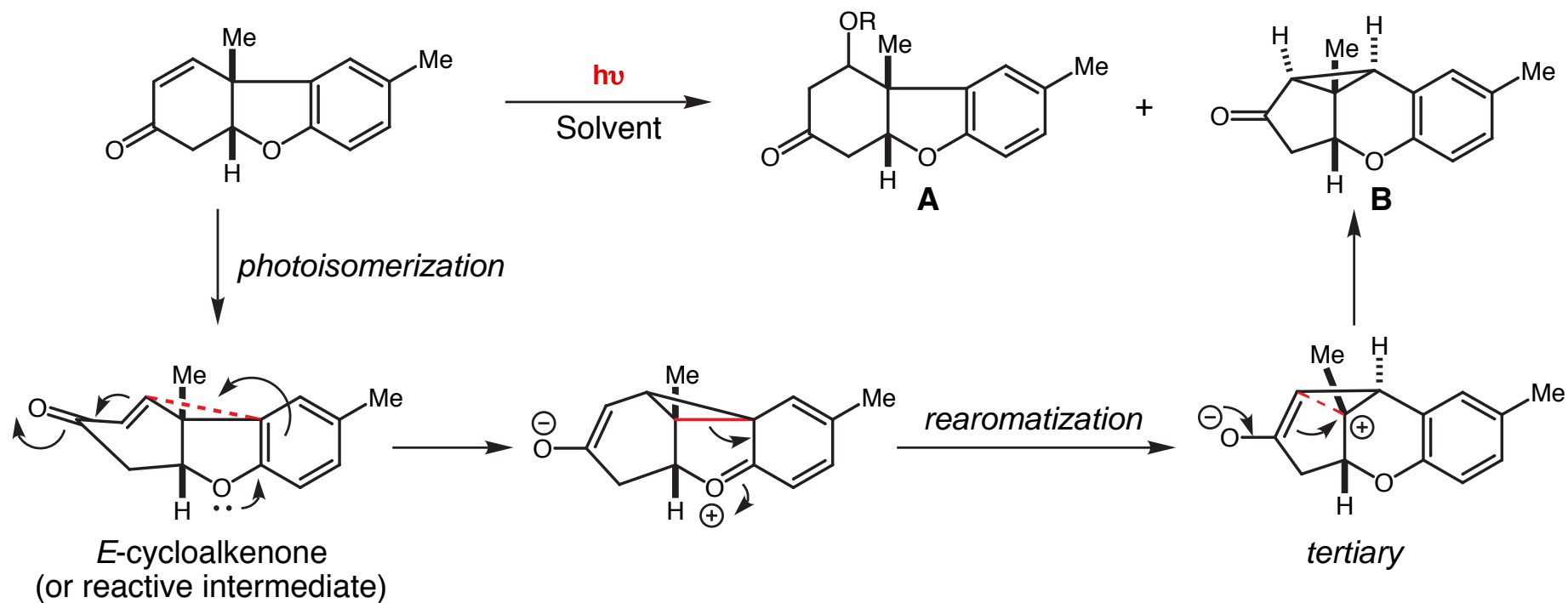


Chapman *JACS* **1966**, 88, 161



Chapman *et al. TL* **1963**, 2049

Photoinduced Skeletal Rearrangements of Enones

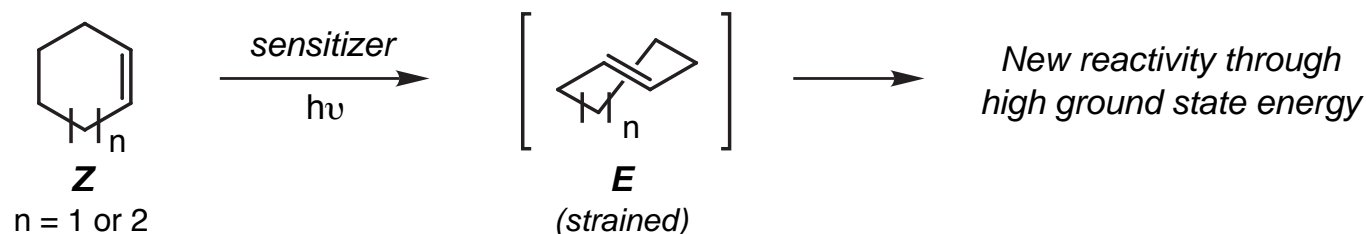


| Solvent | A | B |
|-----------------------------------|--------------------------|------------------|
| MeOH | 79% yield, 1:1 dr | ? |
| <i>i</i> -PrOH | 37% yield | 22% yield |
| <i>t</i> -BuOH | ? | 43% yield |
| C₆H₆ | - | 72% yield |

Matsuura and Ogura *JACS* **1966**, 88, 2602

Proposed *E*-cycloalkene mechanism: Kropp *JACS* **1967**, 89, 5199

Photoisomerization of Cycloalkenes: Summary



- A high ground state energy can be accessed in 6- and 7-membered cycloalkenes
 - Reaction occurs in singlet or triplet sensitization manifolds, can also occur in the absence of sensitizer
 - Various reactivity types have been documented
 - Synthetic utility of *E*-cycloalkenes remains to be established
 - Ionic reactions lead to formation of carbocations under very *mild* conditions
- Similar reactivity is also documented for cycloalkenones