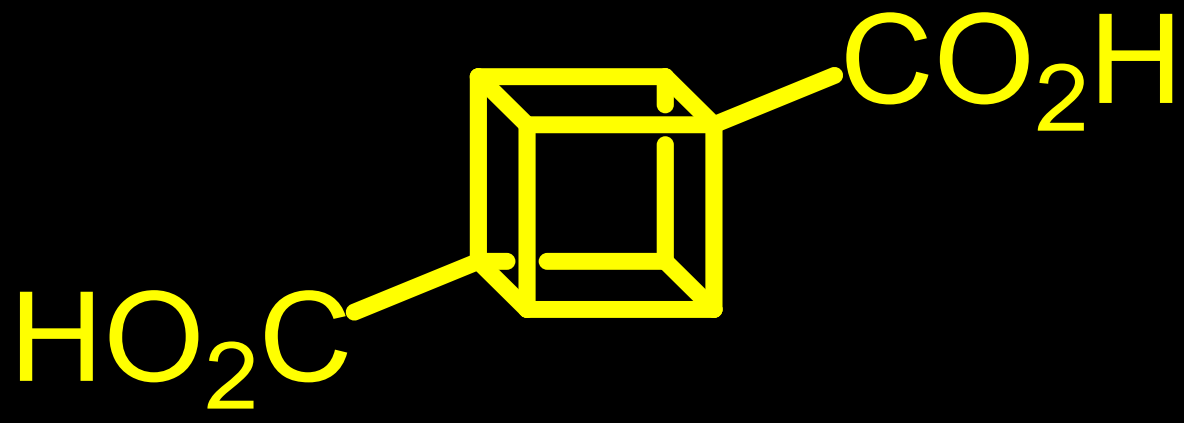
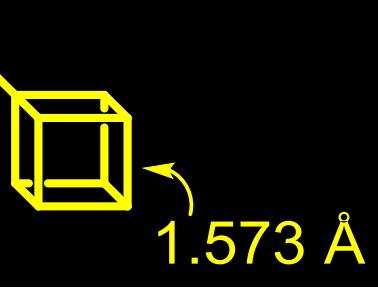



6-30-2015

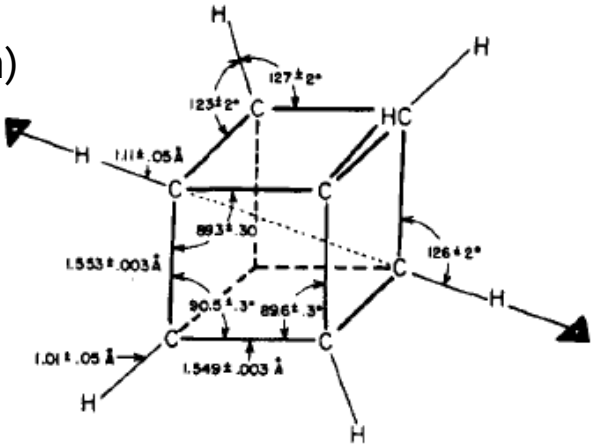
Jeremy Henle

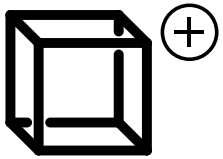
# Cubanes: A symphony of high-energy intermediates

# Cubanes…

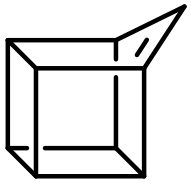



- C8H8 ("Acetylenic") – Cubane
  - Single 1H resonance at 4.04 ppm (13C: 47.3ppm)
  - Density: 1.29 g/cm3 (most dense hydrocarbon)
  - C-H bond angle of 125° (s-character: 31%)
- Have led to the "most unlikely" cation



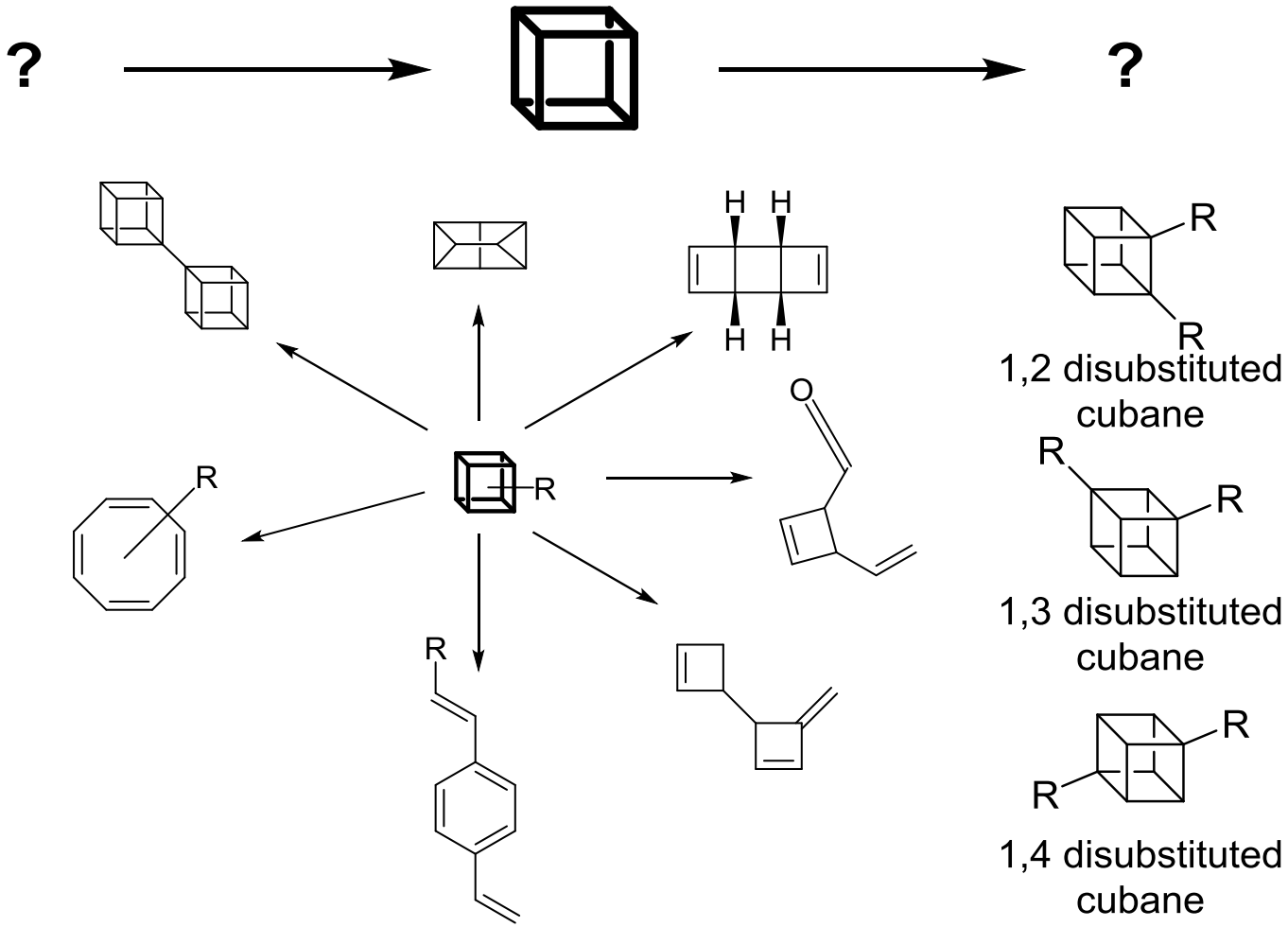


- Thought to form one of the most twisted alkenes (actually, two of the most twisted alkenes!



Hedberg, Eaton, et al., *J. Chem. Am. Soc.*, **1991**,*113*,1514

# Cubanes
# No handles, no problem

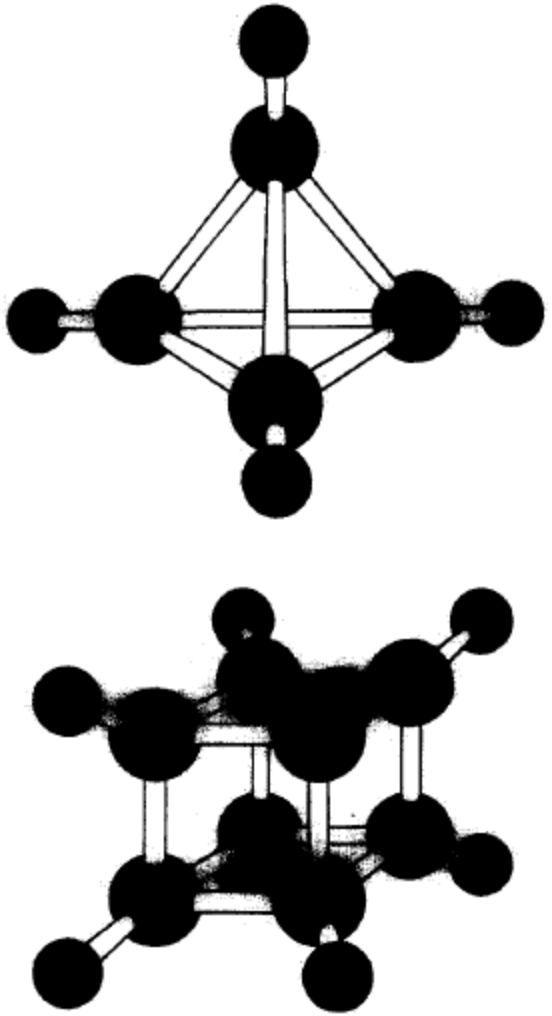


# Outline

- Synthesis of the Cubane nucleus
  - Hydrocarbon skeleton
  - Notable properties
- Modes of Reactivity of Cubanes
  - Moriarty Reaction
  - Reactions of diiodocubanes
  - "The Most Unlikely Cation"
- Breaking Cubane – Rearrangements and Fragmentations
- Applications
  - Explosives

# Proposal of Cubane Nucelus

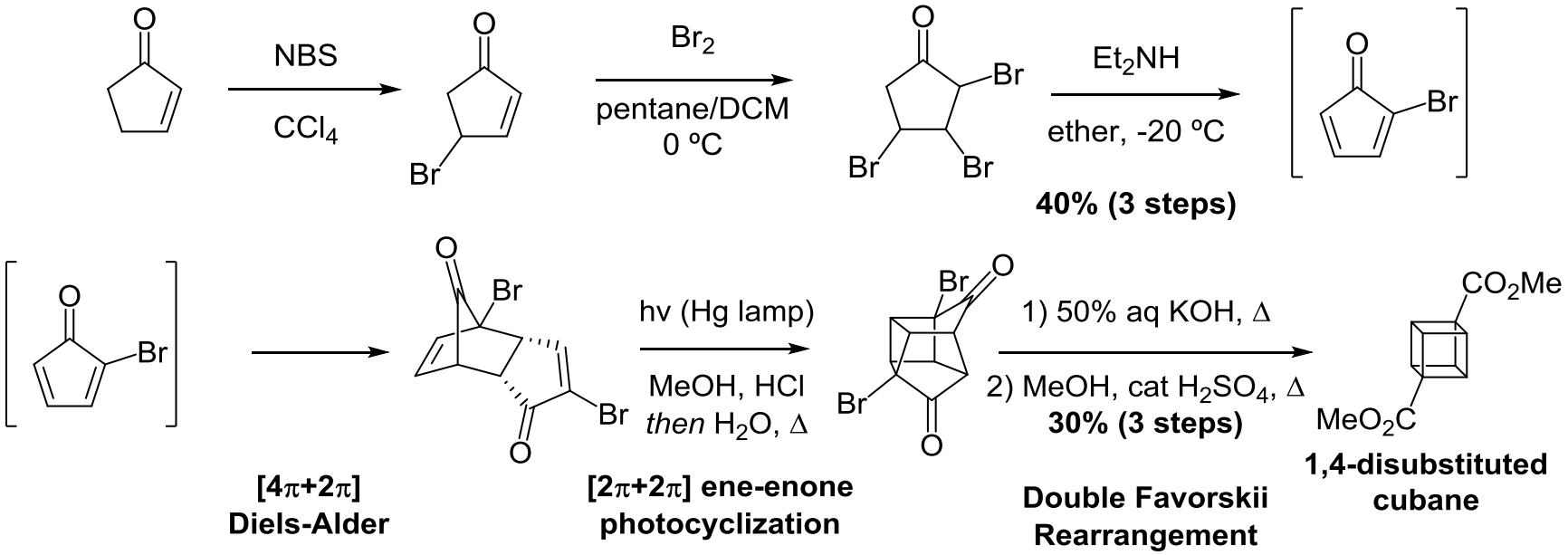
- 1953 – Weltner
  - Proposed "Acetylenic" strained hydrocarbons
  - Calculated strain energy of "tricyclooctane"
    - SE = 120-130 kcal/mol

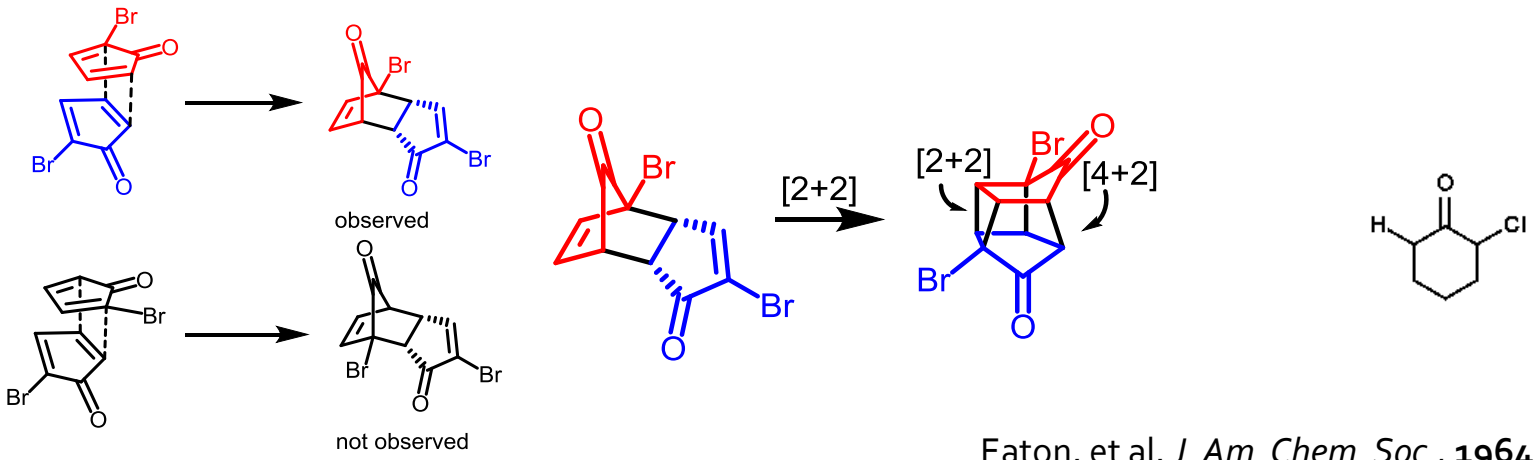


Weltner, *J. Am. Chem. Soc.*,**1953,** *75*, 4224.

# First Synthesis of Cubane Nucelus

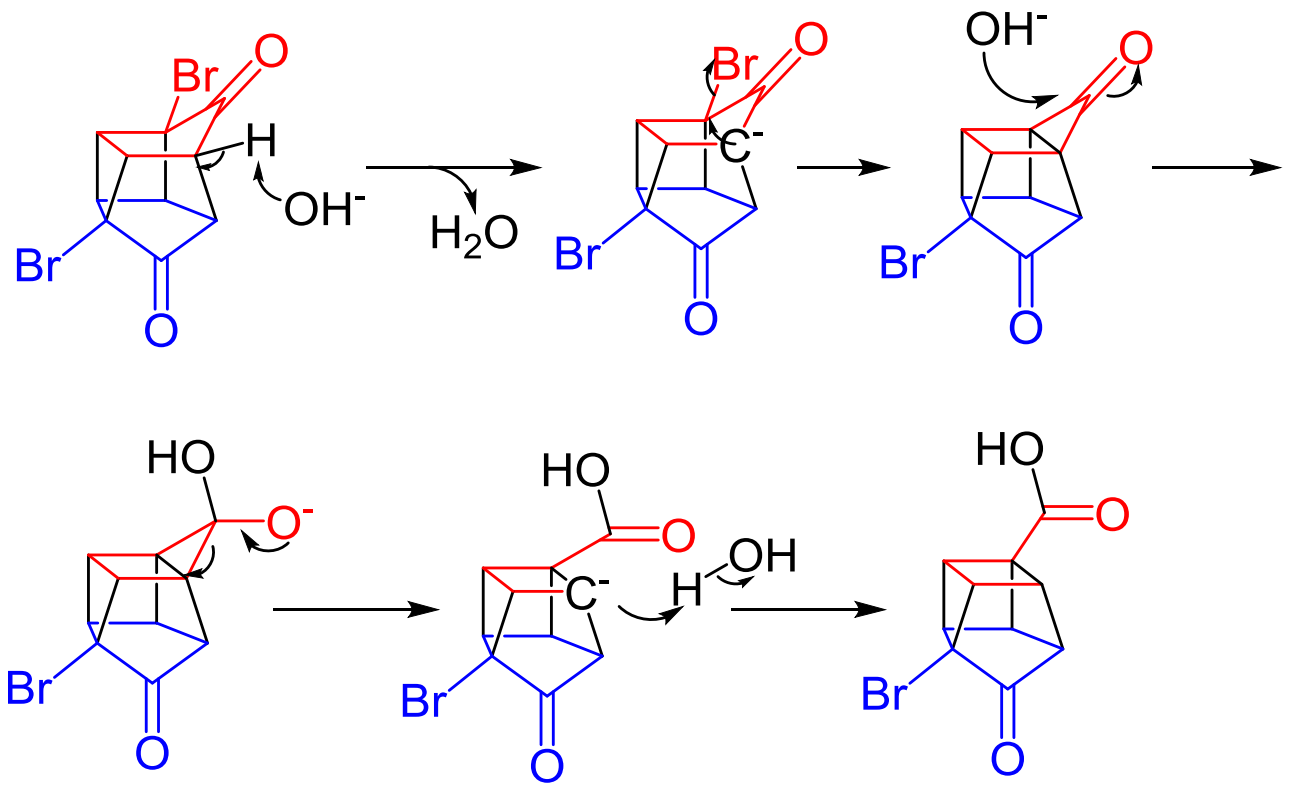
## 1964



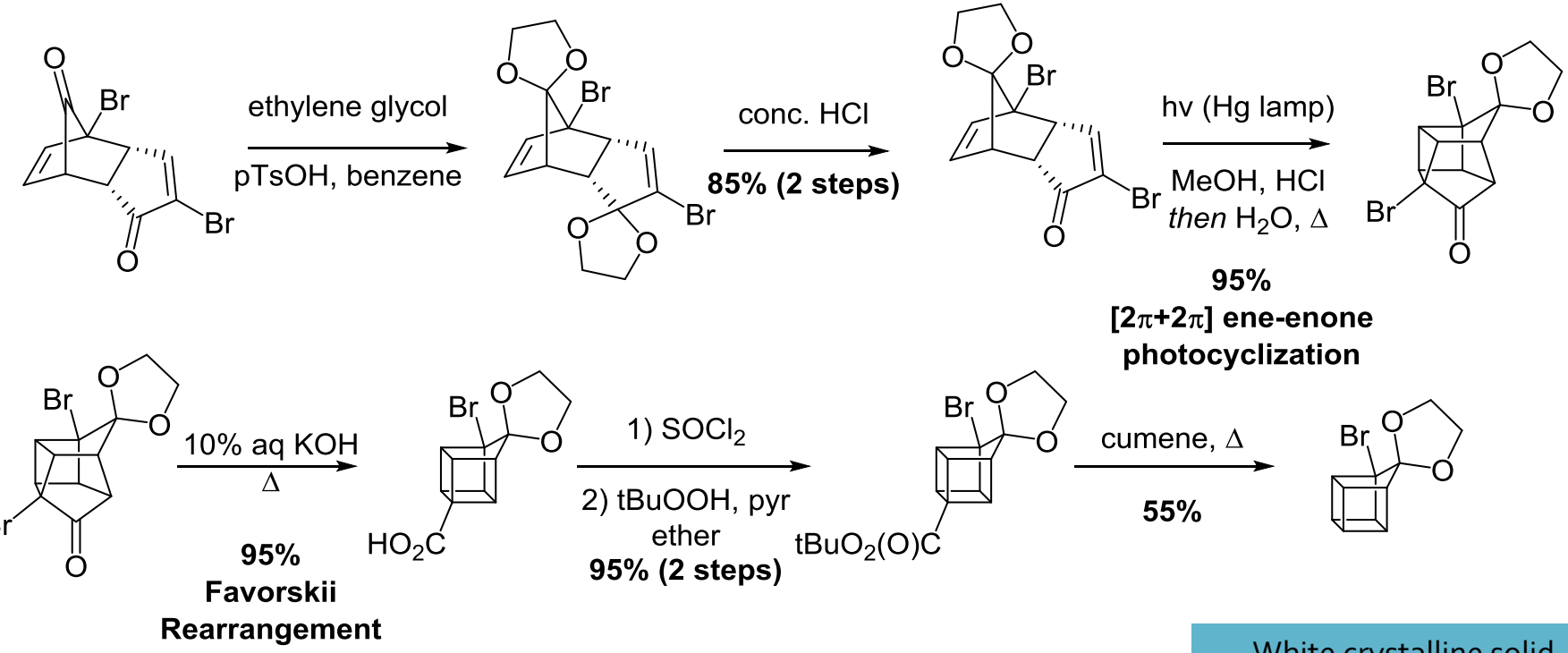




Eaton, et al, *J. Am. Chem. Soc.*, **1964**, *86*,962.

# Favorskii Rearrangement



# Finding Cubane

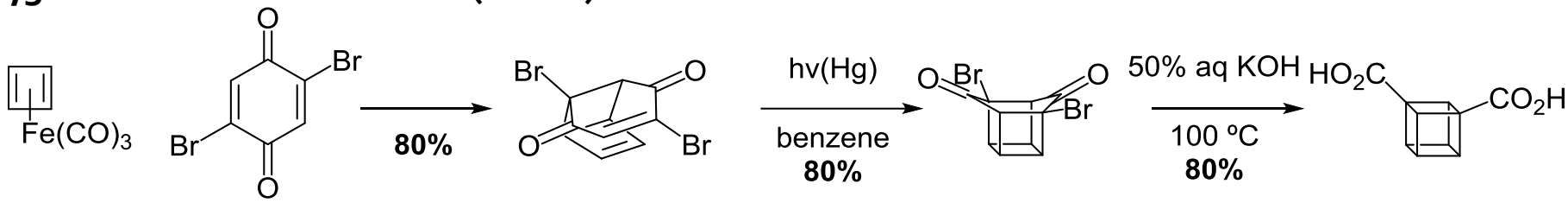



White crystalline solid
Forms as rhomboid crystals!

Eaton, et al., *J. Am. Chem. Soc.*, **1964**, *86*, 3157

# Short(er) Routes to Cubane Skeletons

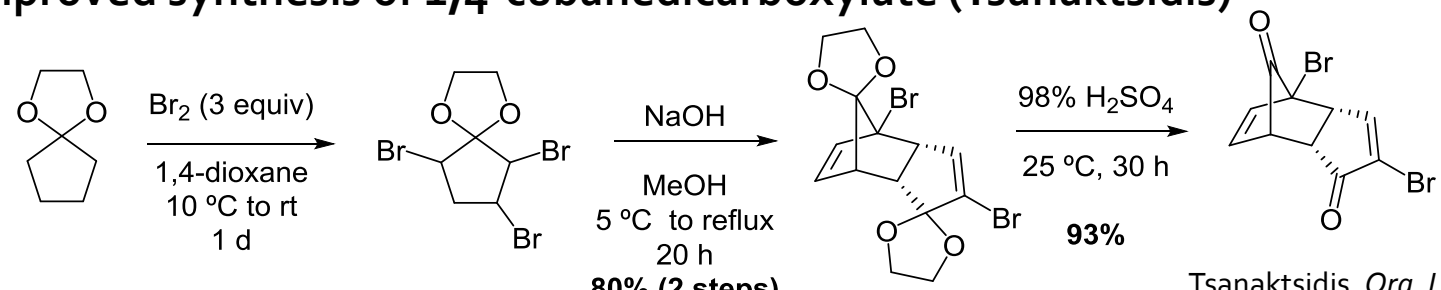
## 1,3-Disubstituted Cubanes (Pettit)



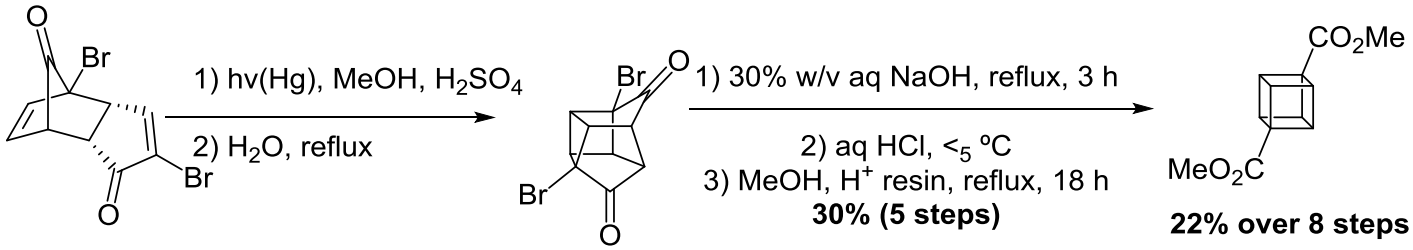

Limited by need for cyclobutadiene iron tricarbonyl

Pettit, *J. Am. Chem. Soc.* **1966**,*88*,1328

## Improved synthesis of 1,4-cubanedicarboxylate (Tsanaktsidis)



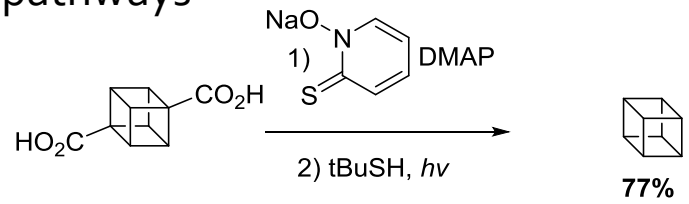

Tsanaktsidis, *Org. Lett.* **2013**, *17*, 1503.
Tsanaktsidis, *J. Aust. J. Chem.* **1997**, *50*, 189.




Scaled to at least 10 g scale

# Summary on Synthesis of Nucelus

- Generally, per-substituted cubanes are synthesized from non-cubane starting materials
- Most synthetically useful cubanes arise from functionalization of 1-cubanecarboxylate or other substituted cubane-*n*-carboxylates.
  - 1,4-cubanedicarboxylate being the most common
  - Can be synthesized on 10 g scale reliably (or purchased)
  - Main optimization in synthesis of cubylcarboxylates involve novel deoxygenation pathways




- Most traditional functional group manipulations are tolerated by the cubane structure, but can still lead to non-traditional products


Tsanaktsidis, *J. Aust. J. Chem.*, **1986**,*39*, 2061.
Tsanaktsidis, *J. Org. Chem.*, **2013**, *78*, 6677.
Tsanaktsidis, *J. Org. Lett*. **2011**, *13*, 1944.

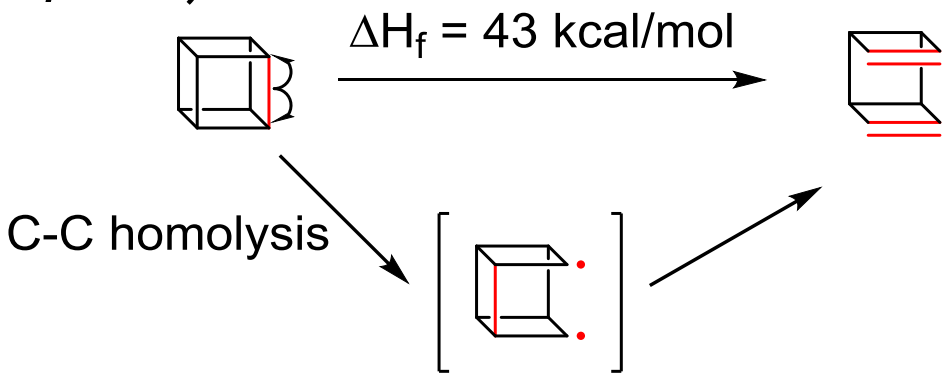
# Unusual Properties of Cubanes

- Kinetic stability vs Thermodynamic Instability
  - Thermodynamically unstable ($\Delta H_f$ = 144 kcal/mol)
  - Highly strained (SE = 161.5 kcal/mol)
  - Kinetically persistent
    - Unreactive to air, water, and temperatures up to ~230 °C
- 90° C-C-C bond angles give C-H bond large amounts of s-character
  - 31-32% vs 25% s-character in typical $sp^3$ C-H
  - Kinetic acidity about 63,000x greater than cyclohexane
- Substituents greatly effect the kinetic reactivity of cubane

Agapito, Santos, et al., *J. Phys. Chem. A.* **2015**,*119*, 2998.

# Origins of Kinetic Stability

- Large barrier to ring opening
  - No symmetry allowed pathways for concerted two-bond ring opening of cubane
  - Limited relief of strain (from 161.5 kcal/mol to ~90 kcal/mol)

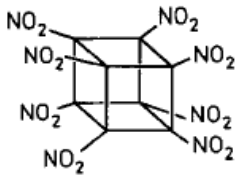



Anderson, S. L, et al, *J. Phys. Chem. A.*, **2003**, *107*, 1162.
Walsh, R., et al, *J. Chem. Soc. Chem. Commun.* **1985**, 964.

# "Cubane Renaissance"

- 1964-1980
  - Cubane considered a laboratory curiosity
- Early 1980s
  - Exceptionally high density of cubane realized as potential energy source for explosives and propellants
- Demand for substituted cubanes led to revival in cubane research

dard.[15] It is sufficient to comment here that detonation of




4

octanitrocubane would lead to an awesome amount of very hot gas [Eq. (a)].

$$C_8(NO_2)_8 \longrightarrow 8\,CO_2 + 4\,N_2 \qquad \text{(a)}$$

Eaton, P. *Angew. Chemie. Int. Ed.*, **1992**, *31*,1421

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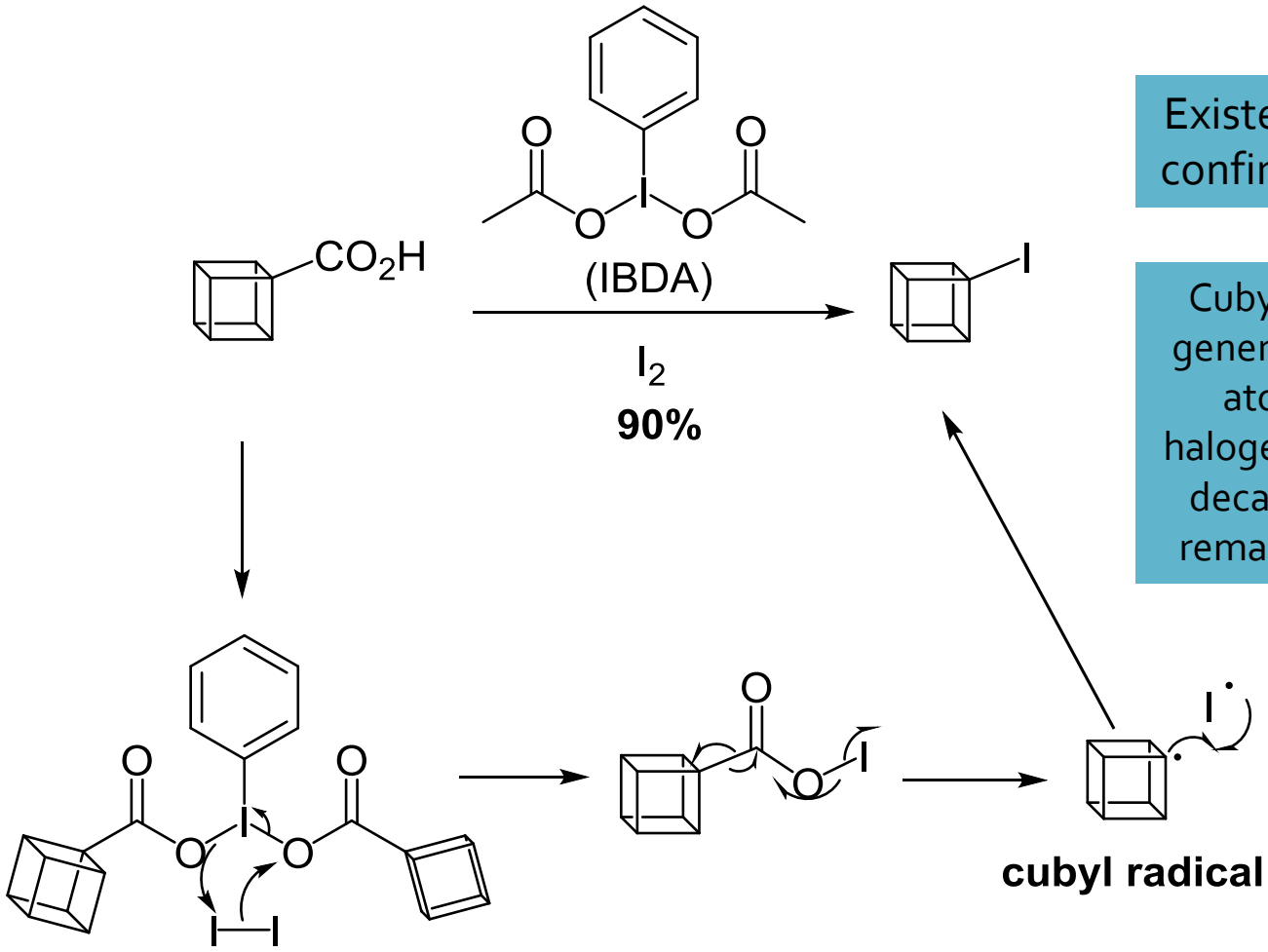
# Moriarty Reaction – Cubyl Radical




Existence of cubyl radical confirmed by EPR studies

Cubyl radicals can also be generated through direct H atom abstraction and halogen abstraction, though decarboxylative methods remain the most common.

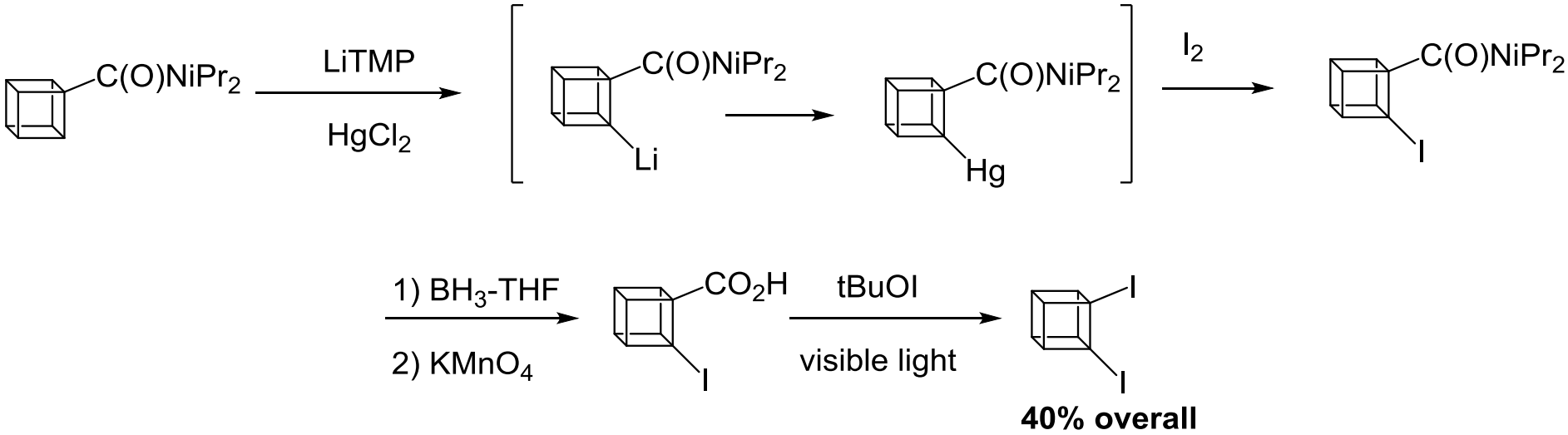

Moriarty, et al. *J. Chem. Soc., J. Chem. Commun.* **1987,** 675.
Eaton, et al. *J. Am. Chem. Soc.* **1988,***110,* 876.

# Diiodocubanes – Radical Precursors

- 1,2-diiodocubanes
  - cubene intermediates
- 1,4-diiodocubanes
  - 1,4-diyl intermediate

# Synthesis of 1,2-diiodocubanes

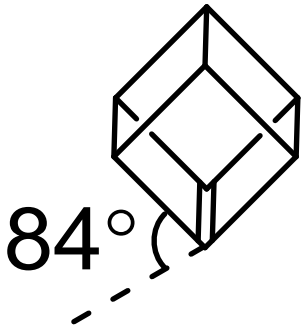
1,2-diiodocubane *via* ortho-lithation/transmetallation strategy



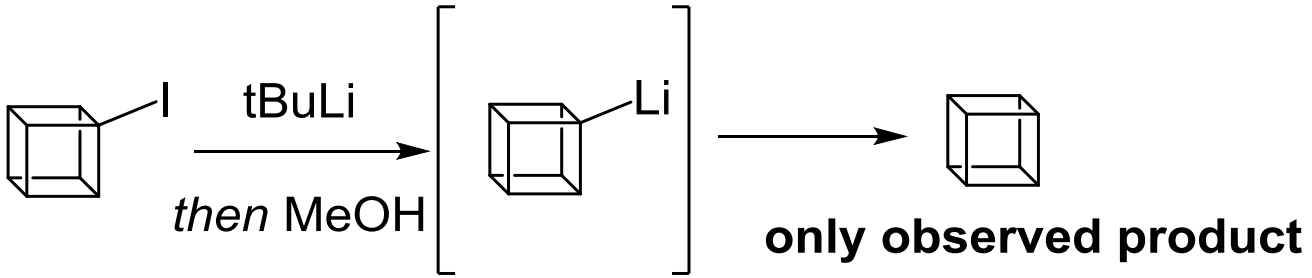

1,4-diiodocubanes can be synthesized directly from 1,4-cubanedicarboxylic acids via the Moriarty reaction.

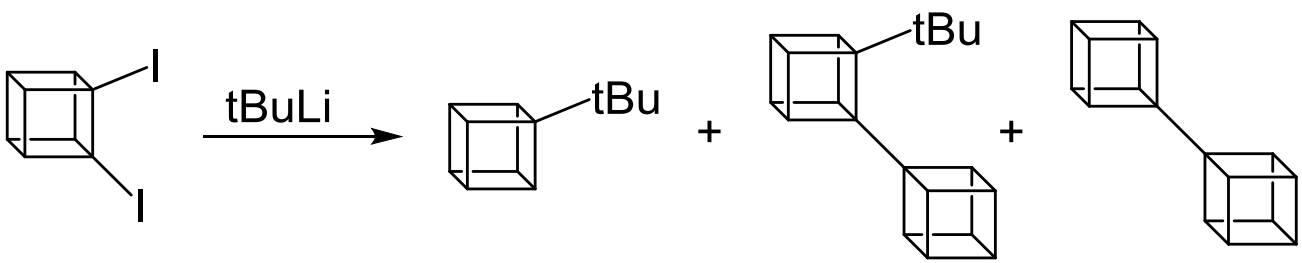
Eaton, et al. *J. Am. Chem. Soc.* **1988**,*110*, 876.

# 1,2-Diiodocubane: Cubene precursor



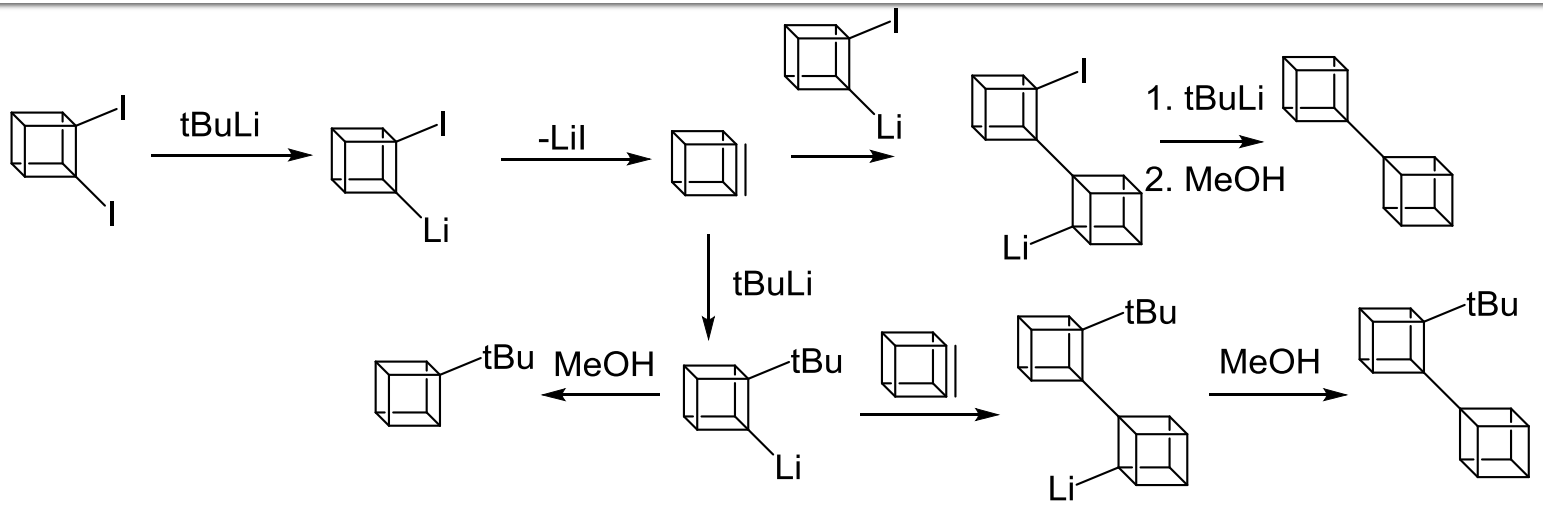

Calculated pyramidalization angle makes forming cubene incredibly unlikely



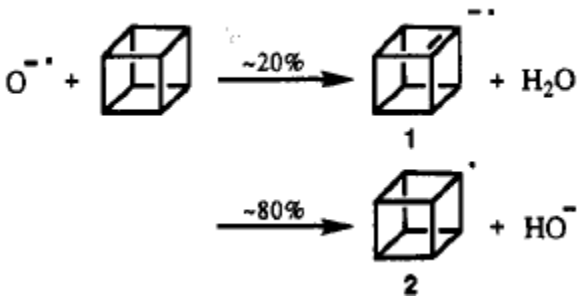




Borden, et al., *J. Am. Chem. Soc.* **1988**, *110*, 4710.
Eaton, et al. *J. Am. Chem. Soc.* **1988**, *110*, 876.

# Invoking Cubene




Cubene observed in "home built" FT-ion cyclotron resonance MS

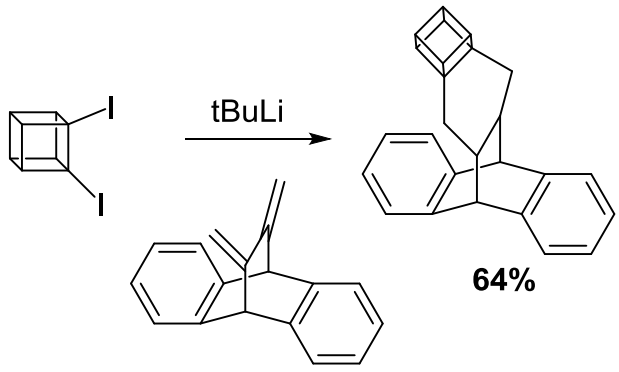



Other calculated values

$\Delta H_{hydro}$ = 88 kcal/mol

SE = 225 kcal/mol

Olefin SE = 61 kcal/mol

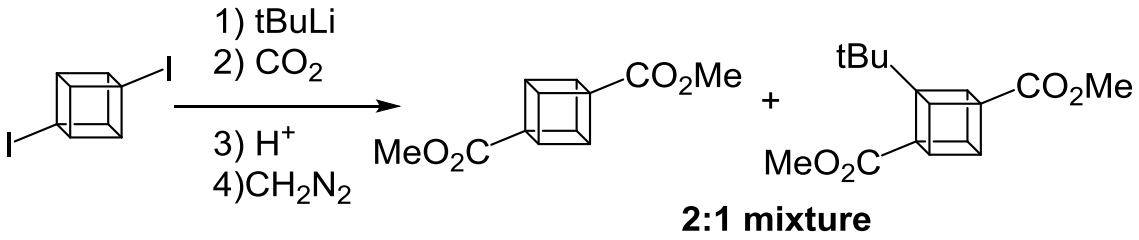



Eaton, Kass, et al., *J. Am. Chem. Soc.* **1997,** *119,* 237.

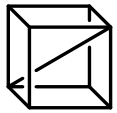
Eaton, et al. *J. Am. Chem. Soc.* **1988,***110,* 876.

# 1,4-diiodocubane

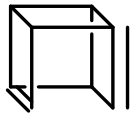
## Cubylane: Can a bond be formed?



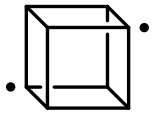

## Proposed Intermediates



**cubylane [2.2.2] propellane**



**diene**

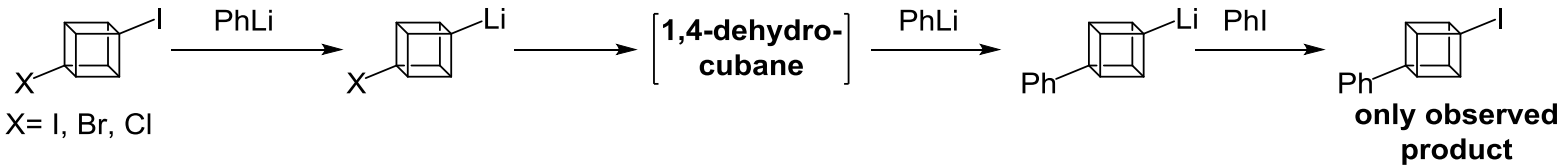


**diyl**

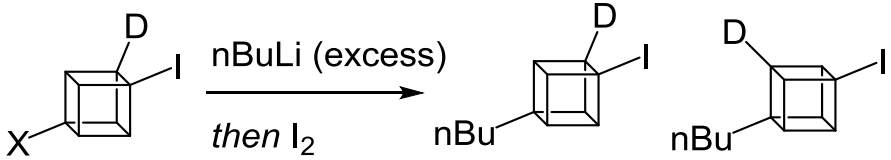

Eaton, Tsanaktsidis, *J. Am. Chem. Soc.* **1990**, *112*, 876.
Michl, *J. Am. Chem. Soc.* **1990**, *112*, 873.
Eaton, *J. Am. Chem. Soc.*, **1995**, *60*, 966.

# Intermediate Determination

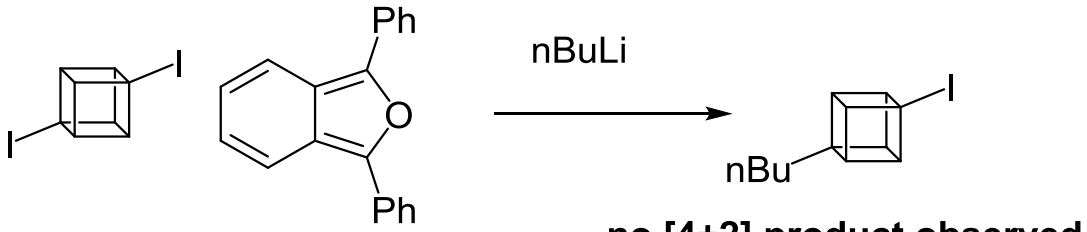
## Indications of a common intermediate/initial exchange with iodine




## Deuterium labeling supports "symmetrical" intermediate




## No Diels-Alder product resulting from diene intermediate observed

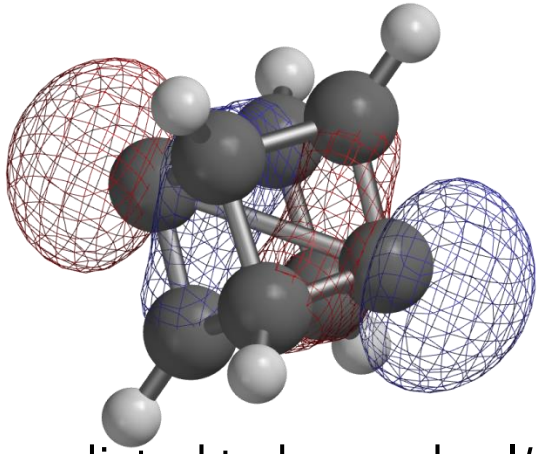




Eaton, Tsanaktsidis, *J. Am. Chem. Soc.* **1990**, *112*, 876.
Michl, *J. Am. Chem. Soc.* **1990**, *112*, 873.
Eaton, *J. Am. Chem. Soc.*, **1995**, *60*, 966.

# Computational Support for Diyl

- C1 and C4 HOMO calculated to be antibonding
  - If C1-C4 bond existed, it would be incredibly weak

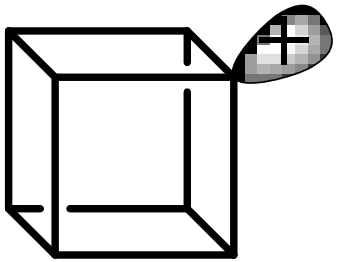


- Singlet biradical predicted to be ~10 kcal/mol more stable than triplet state
  - Stabilization of the singlet state thought to arise from "Moebius" type twisting of the orbitals

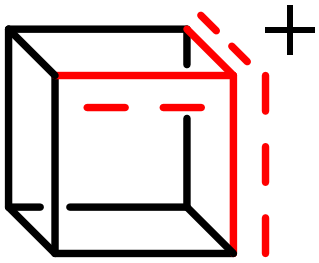
Michl, *J. Am. Chem. Soc.* **1990,** *112*, 873.

# Cubyl Cation

- "The Most Unlikely Cation"
  - Geometry of the cation carbon is far from flat
  - Exocyclic orbitals of cubane are s-rich
    - Loss of electron density is destabilizing
  - Hyperconjugative interactions require cubene-like intermediates



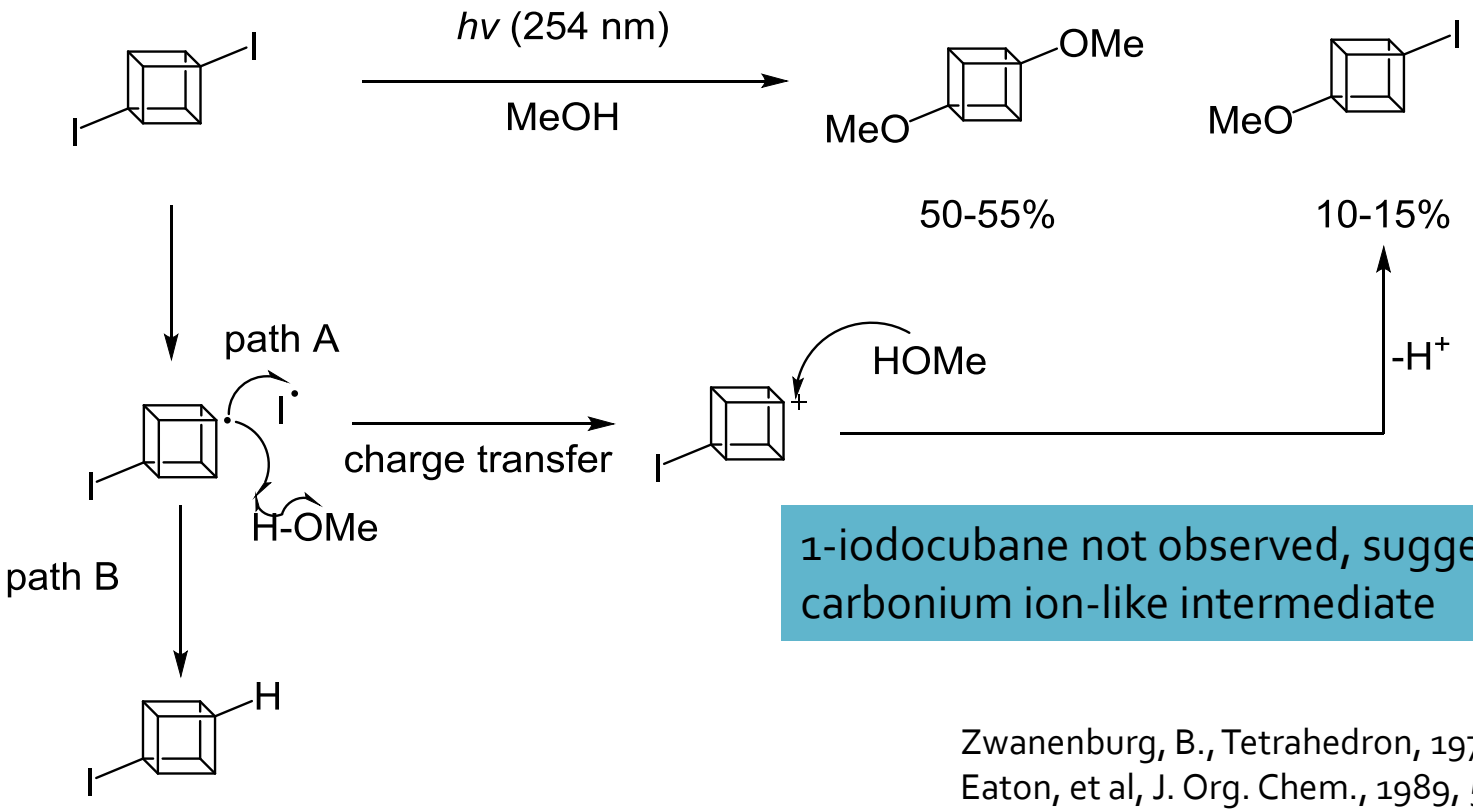
Calculated to be +20 kcal/mol
higher in energy than tBu cation
+5 kcal/mol w.r.t. 1-norbornyl cation



Eaton, P. *Angew. Chemie. Int. Ed.*, **1992,** *31*,1421

# Suspecting the Cubyl Cation

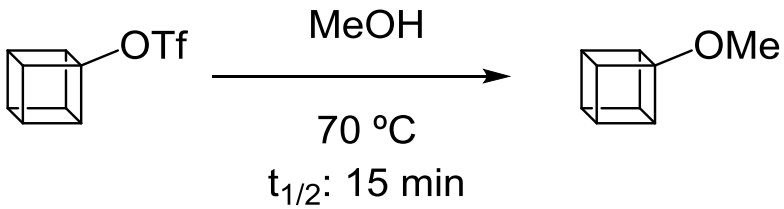
- Variety of cubane reactions that could proceed through cubyl cation




1-iodocubane not observed, suggesting carbonium ion-like intermediate

Zwanenburg, B., Tetrahedron, 1972, 28, 4131.
Eaton, et al, J. Org. Chem., 1989, 54, 722.

# Solvolyis of Cubyl Triflates



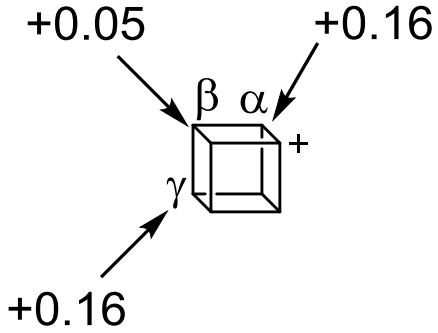

Solvolysis of tertiary tosylates in AcOH at 70 °C

| Tosylate | Experimental | calculated |
|---|---|---|
| *tert*-Butyl | 1 | 1 |
| 1-adamantyl | $10^{-3}$ | $10^{-4}$ |
| 1-bicyclo[2.2.2]octyl | $10^{-7}$ | $10^{-8}$ |
| 1-norbornyl | $10^{-13}$ | $10^{-14}$ |
| cubyl | $10^{-10}$ | $<10^{-25}$ |

Eaton, Zhou, J. Am. Chem. Soc., **1992**, *114*, 3118

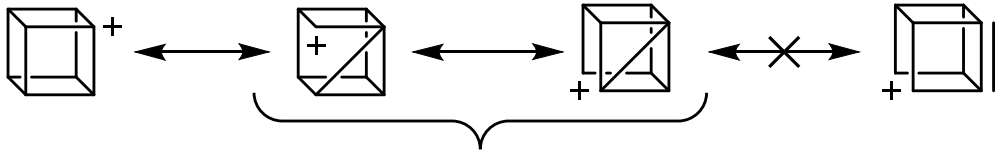
# Nature of the Cubyl Cation

- *p*-rich C-C bonds allow for delocalization of charge through the carbon skeleton

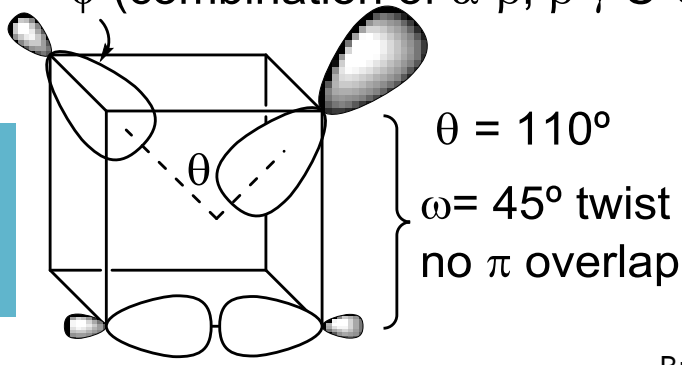



Also noted that there is very little C-H hyperconjugation

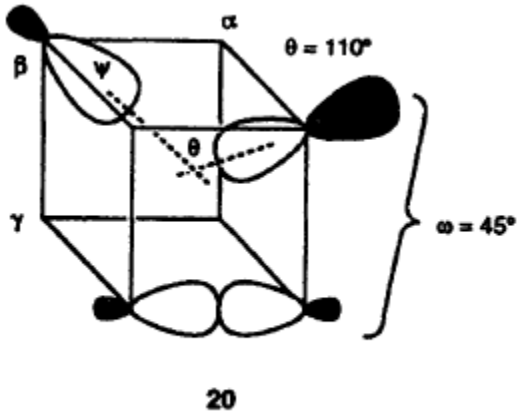
- Cubyl cation appears to behave like a non-classical cation



ψ (combination of α-β, β-γ C-C)




Less energy required to form cubyl cation over 1-norbornyl cation




20

Broden, et al., J. Am. Chem. Soc, 1990, 112, 3227.

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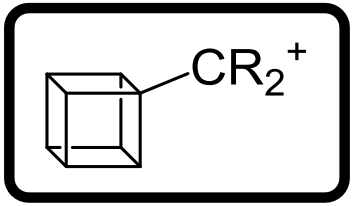
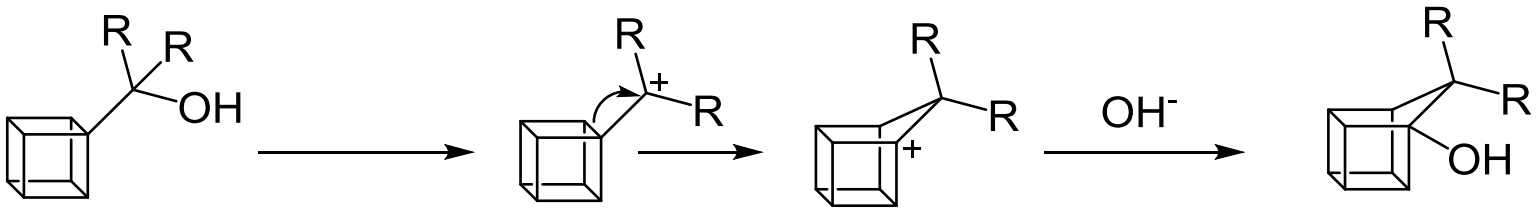
# Breaking Cubane

- The energetic bonds of cubane can lead to a large number of rearrangements
- Kinetic barrier generally prevents these thermodynamically favorable processes
- Two major types of cubane rearrangements
  - Substituent based
    - Changing groups on the cubane nucleus allows for additional reaction pathways
  - Metal/reagent based
    - Insertion/breaking bonds normally inaccessible due to symmetry rules

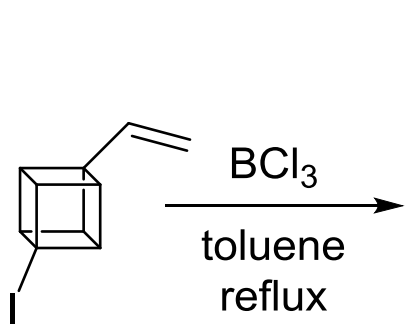
# Cubylcarbinyl Cations Group Problem

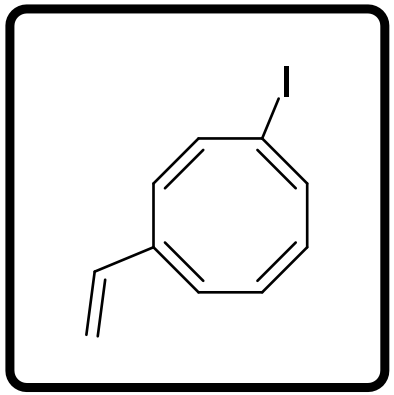



Tsanaktsidis, J. Org. Chem. **1997**, *62*, 5709.




**Propose mechanism for the formation of the distyrene from 4-vinyl-iodocubane**



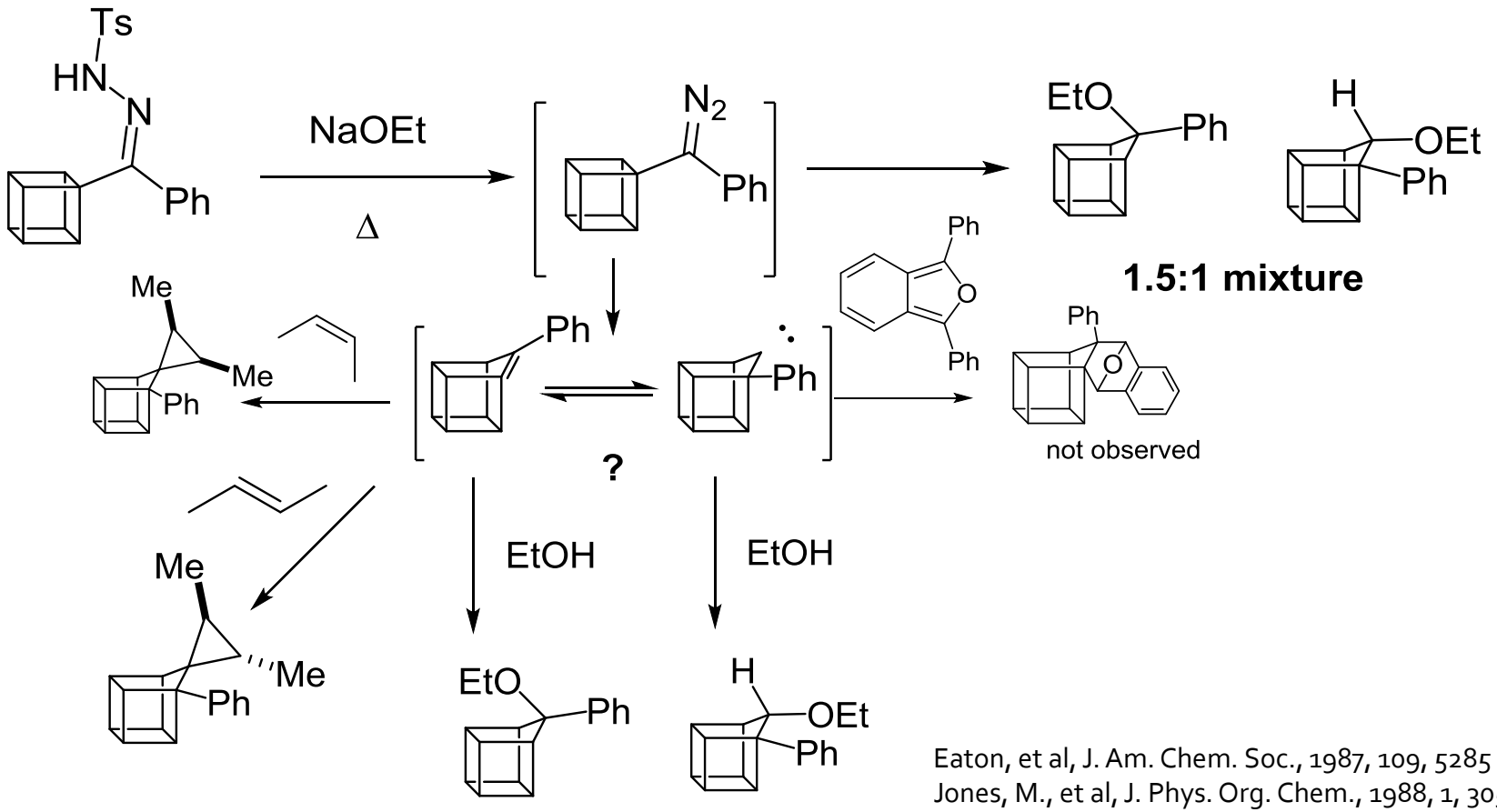




**proposed intermediate**

# Group Problem - Answer

# Homocubenes: Another pyramidalized olefin

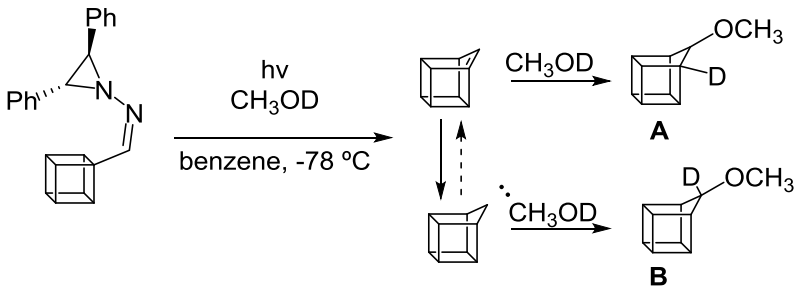
Reaction of cubylphenyldiazomethane gave unexpected products





Eaton, et al, J. Am. Chem. Soc., 1987, 109, 5285
Jones, M., et al, J. Phys. Org. Chem., 1988, 1, 305.
Halton, Lovett, et al, Tet. Lett., 1990, 31, 1313.
White, et al., J. Am. Chem. Soc., 1991, 113, 4981.

# Homocubene <-> Homocubyl carbene



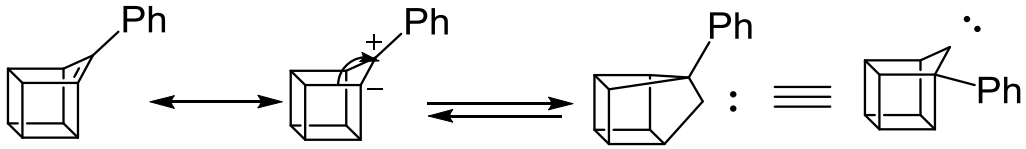

| % MeOD | Ratio A:B |
|---|---|
| 100 | 8:1 |
| 50 | 8:1 |
| 25 | 9:1 |
| 9 | 4:2 |
| 3 | 9:2 |
| 2 | 3:7 |
| 1 | 5:9 |

Increasing A as MeOD conc. increases suggests homocubene forms first, then converts to the carbene

Further experiments have determined that the equilibrium constant between carbene-olefin to be near unity

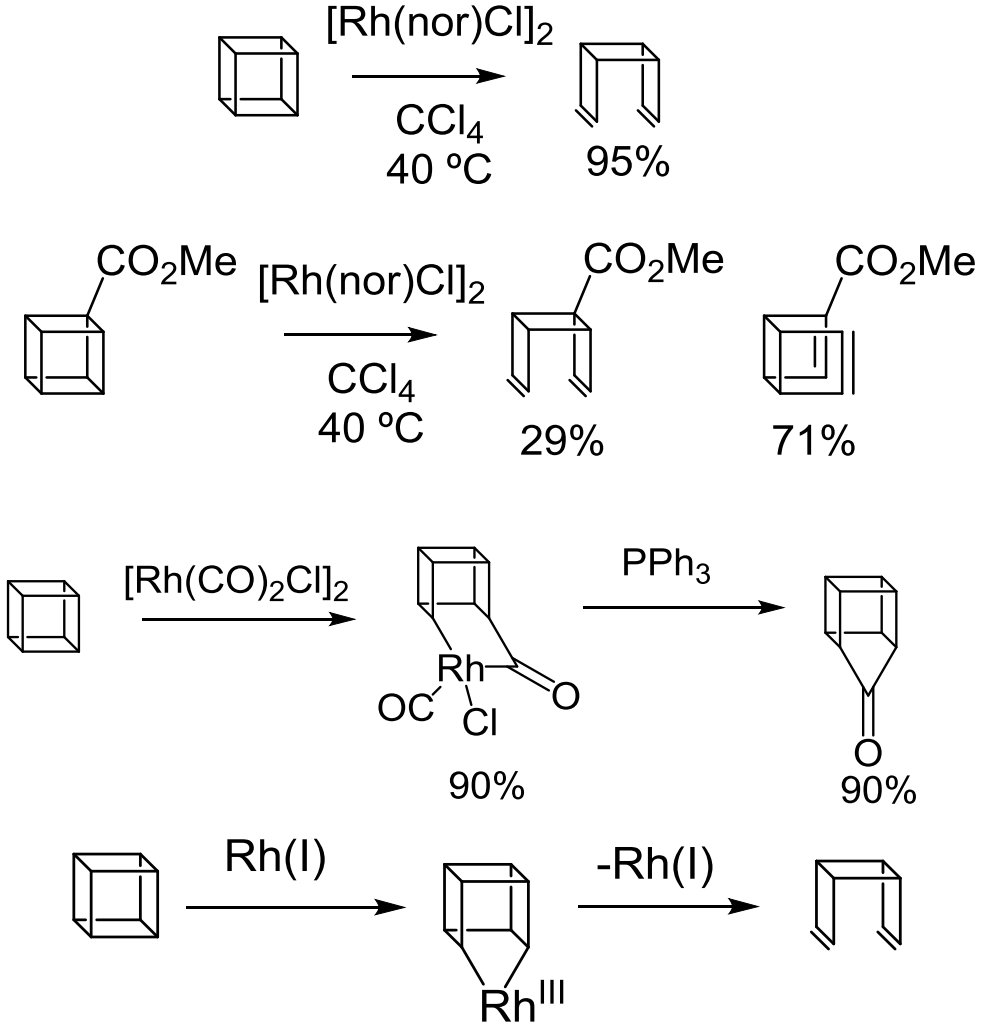
Eaton, et al, J. Am. Chem. Soc., 1987, 109, 5285
Jones, M., et al, J. Phys. Org. Chem., 1988, 1, 305.

13C labeling confirms skeletal rearrangement



# Transition Metal Rearrangements

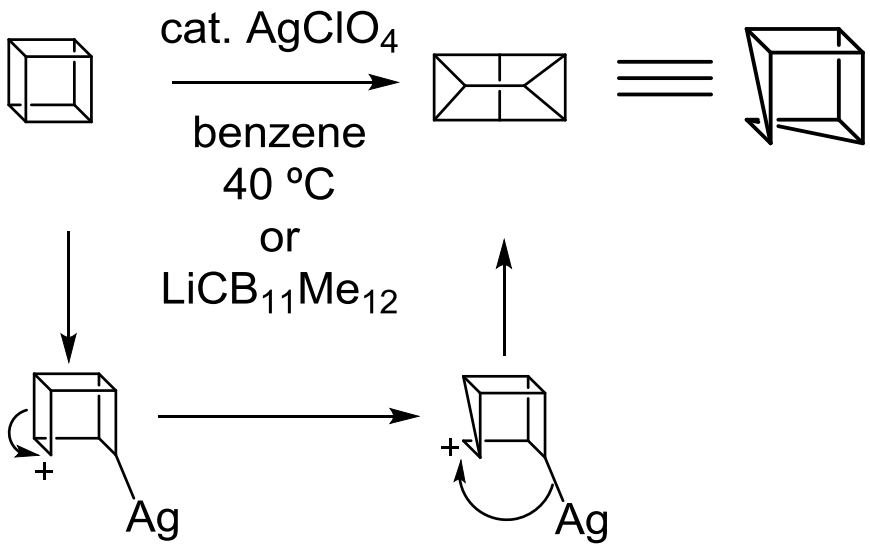
- Rh




Eaton, Halpern J. Am. Chem. Soc., 1970, 92, 3515

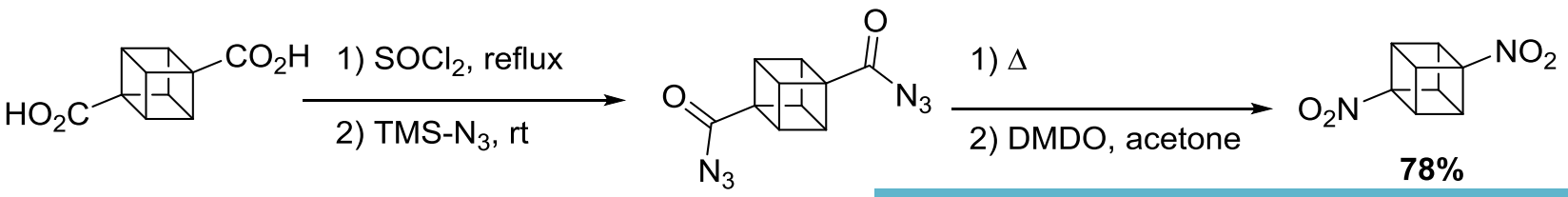
# Transition Metal Rearrangements

- Isomerization



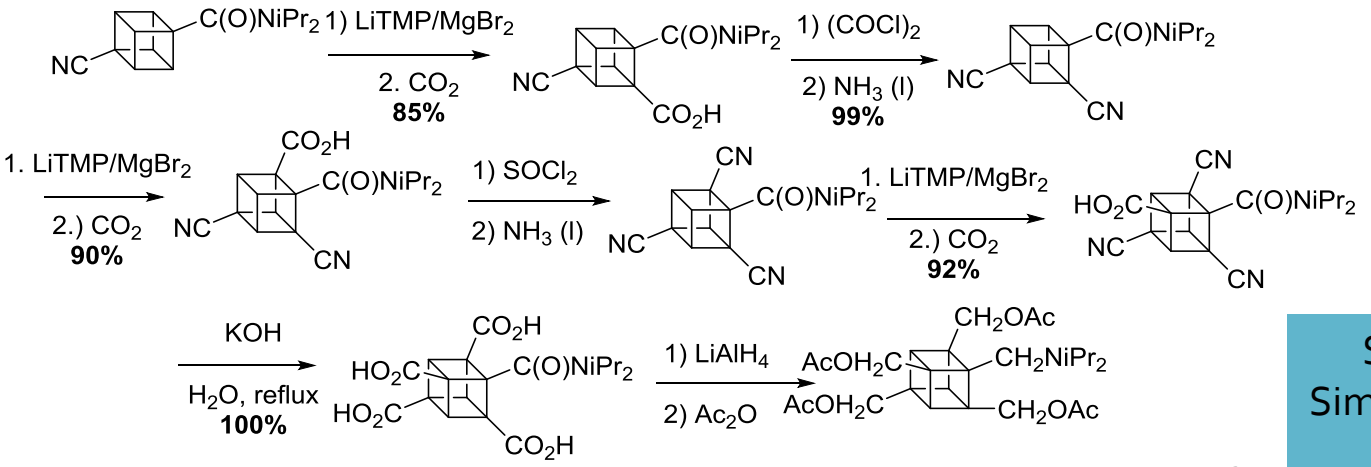

Eaton, Halpern J. Am. Chem. Soc., 1970, 92, 3515
Eaton, Michl, et al, Org. Lett., 2001, 3, 2375.

# In Search of Better Explosives: Synthesis of nitrocubanes




Eaton, et al., *J. Org. Chem.* **1988**, *53*, 5353.

Stable until compressed to 7 GPa, then decomposes explosively

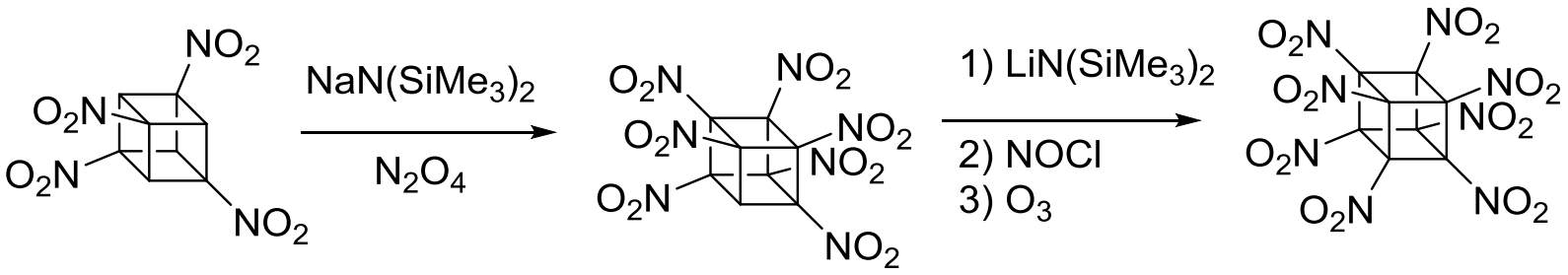



Stable to 230 degC
Similarly shock stable as 1,4-dinitrocubane

Eaton, J. Am. Chem. Soc., 1993, 115, 10195.

# Octanitrocubane

- Synthesis from tetranitrocubane (pKa ~ 20)




- Density of 1.979 g/cm$^3$
  - Too low to beat current explosives
- Synthesis not amenable to larger scale synthesis


Eaton, et al, ACIE, 2000, 39, 401
Eaton, et al, Propell. Explos. Pyrot. 2002, 27, 1.

# Summary

- Cubane synthesis is a testament to persistence and advancement in organic synthesis
- The strained nature of the cubane skeleton leads to a number of different reactivity patterns
- Most early research has focused on identifying high energy intermediates
- Current work is incorporating the cubane skeleton into materials and medicine.
  - Probes for oxidation mechanisms
  - Novel drugs