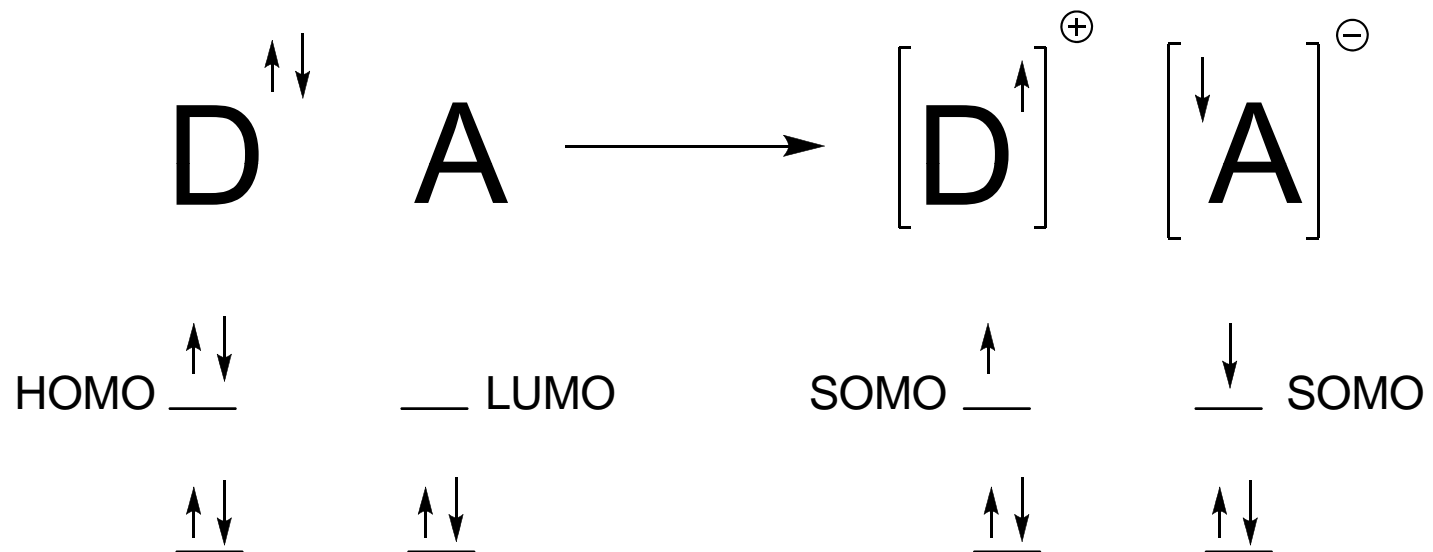


# Electron Transfer Catalyzed Cycloadditions Promoted by Radical Cation Salts

Colin Hughes  
February 1<sup>st</sup>  
2008

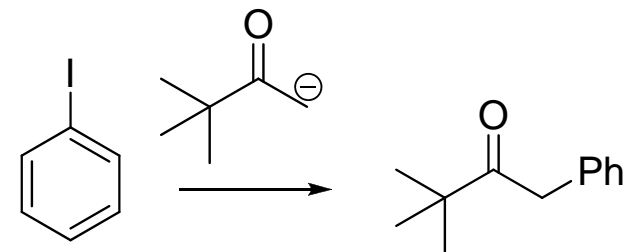
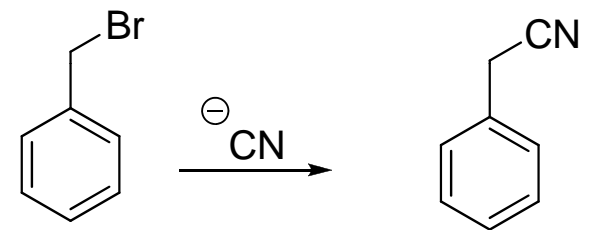
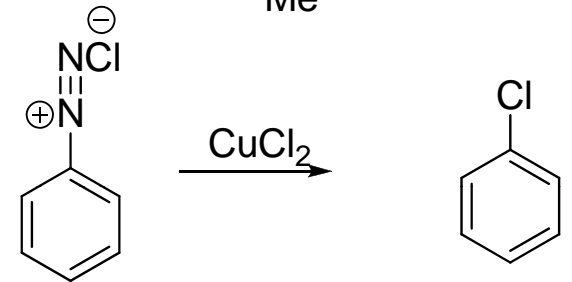
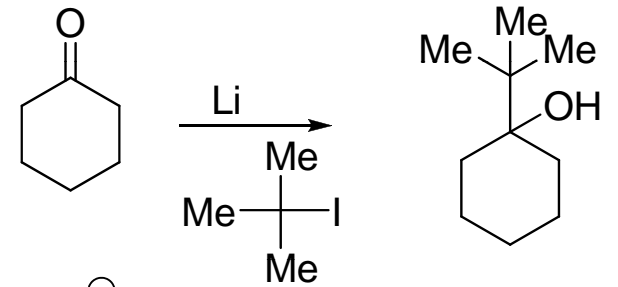
# Electron Transfer

- Electron Transfer - Transfer of an electron from one molecular entity to another, or between two localized sites in the same molecular entity



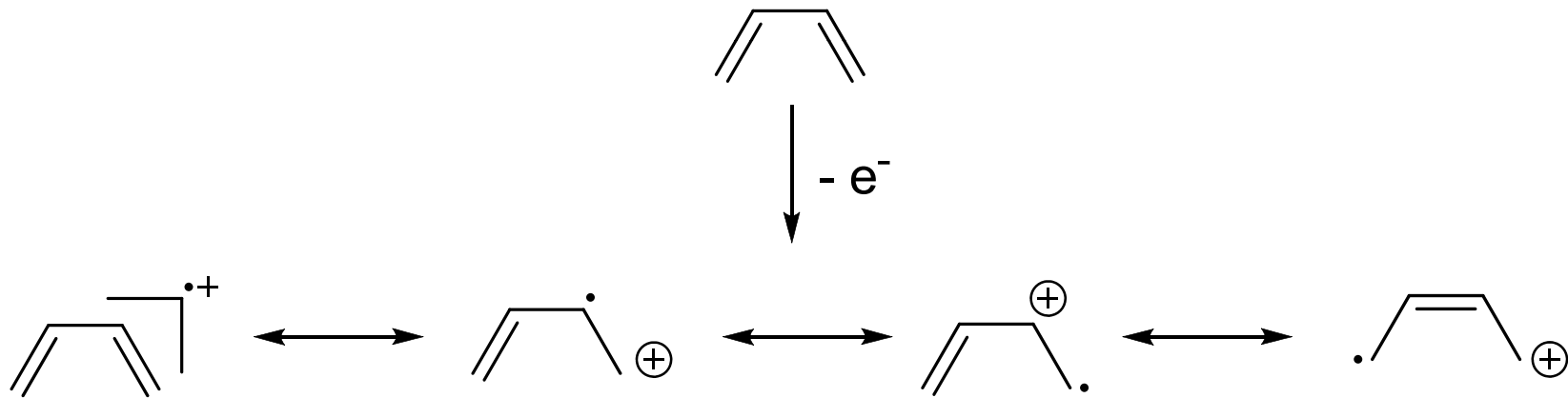
# Examples of ET Reactions

- Formation of Grignard reagents
- Barbier coupling
- Sandmeyer reaction
- Birch reduction
- $S_N2$
- $S_{RN}1$



# Radical Cations

- Are electron deficient
- Very acidic
- Formed by removing an electron from a compound (usually from a pi system)

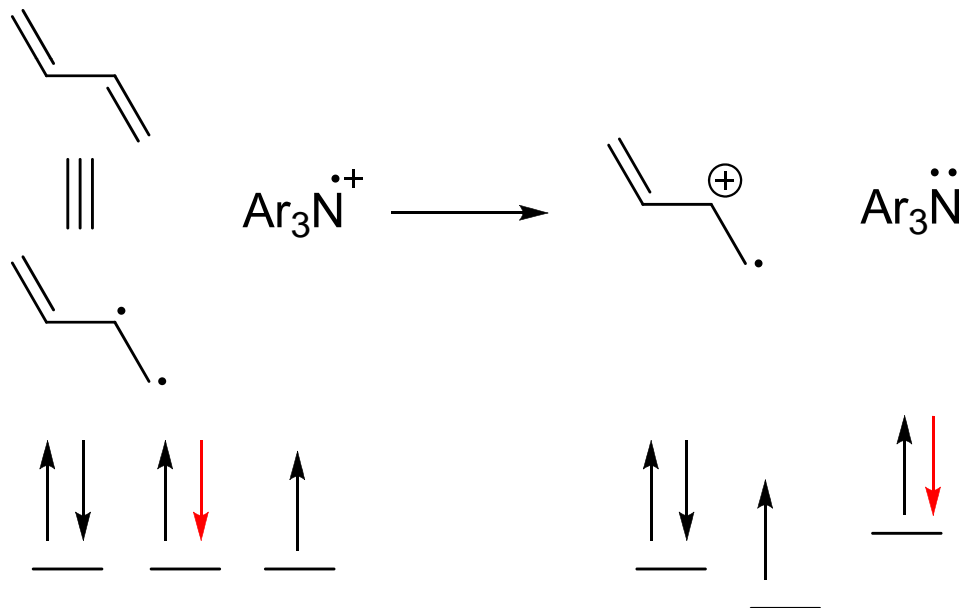
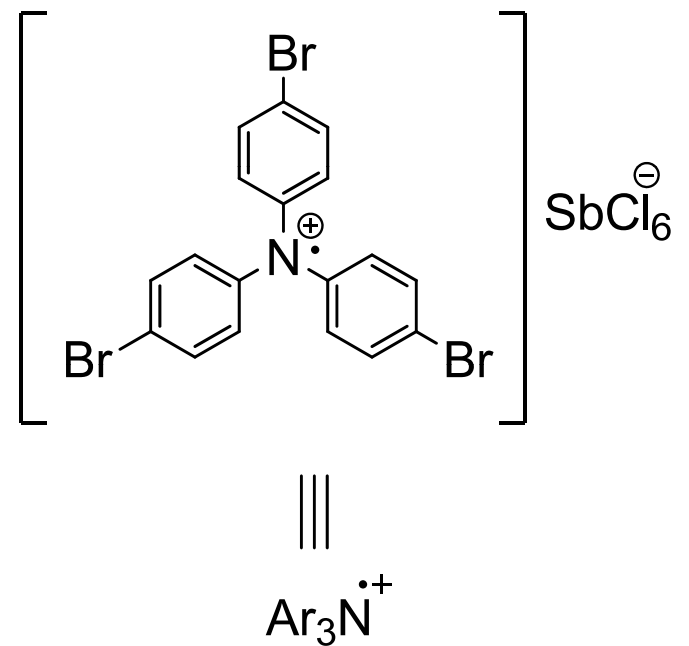


# Promotion of an Organic Radical Cation

- Electrochemically (anode)
- PET – Photoinduced Electron Transfer
- With metals i.e.  $\text{Fe}^{3+}$   $\text{Ce}^{4+}$   $\text{Cu}^{2+}$
- Radical cation salts

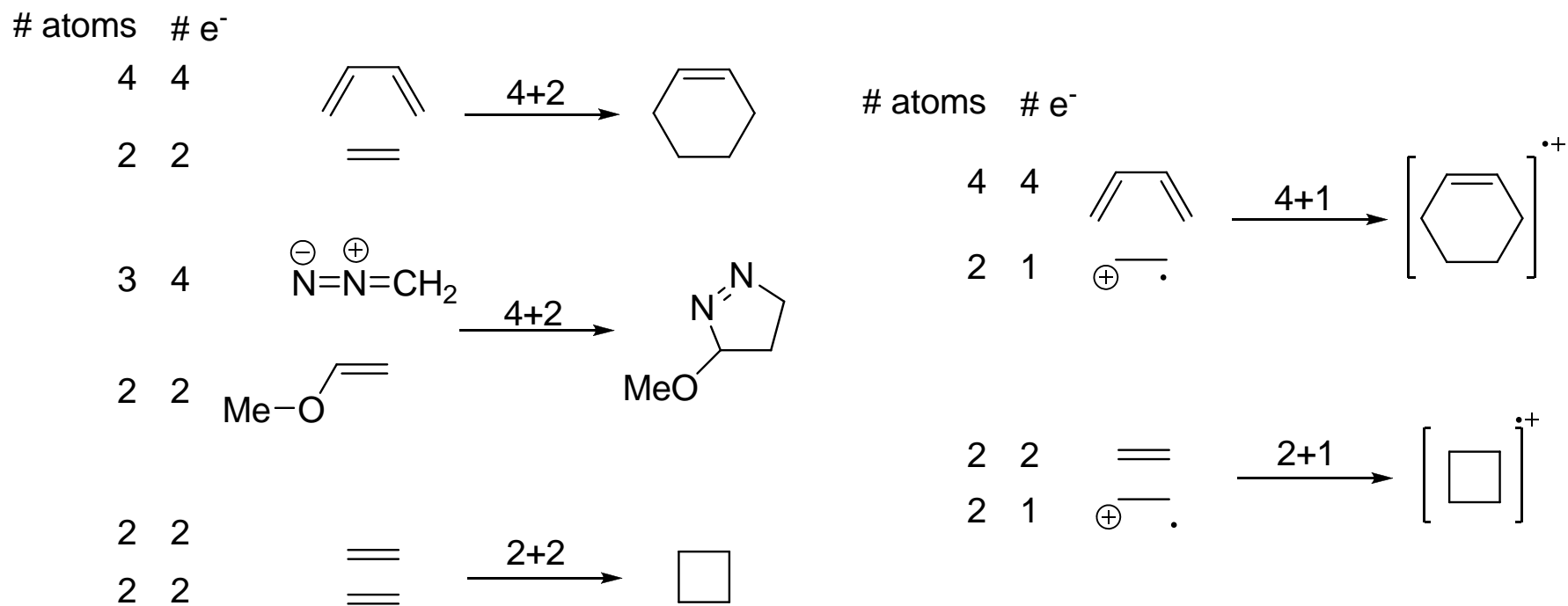
# Radical Cation Salt

- Tris(p-bromophenyl)aminium hexachloroantimonate (aka magic blue, aminium salt)
- 25 \$/gram from Aldrich
- Acts as an oxidizer



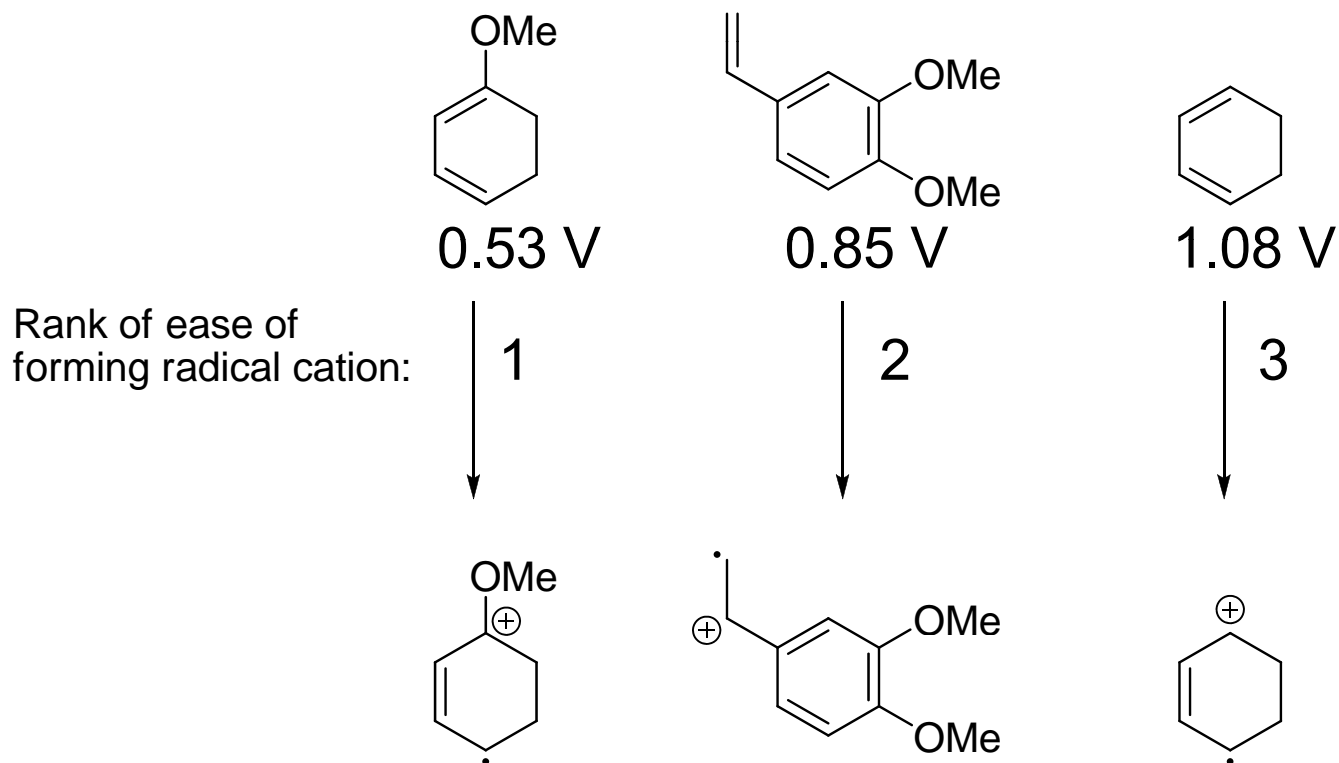
# m+n Terminology

- In [m+n], m and n are the number of electrons contributed by each reacting partner - NOT the number of atoms



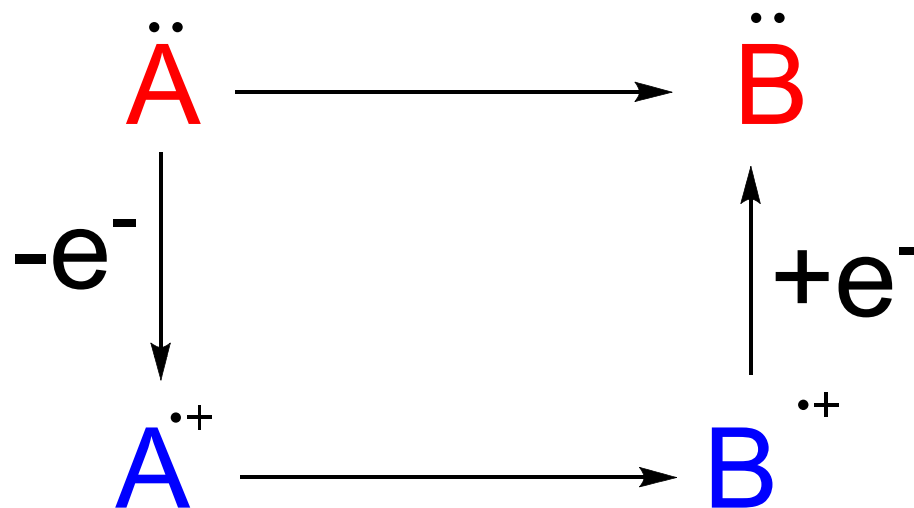
# Redox Potential

- The lower the redox potential, the easier to oxidize to a radical cation



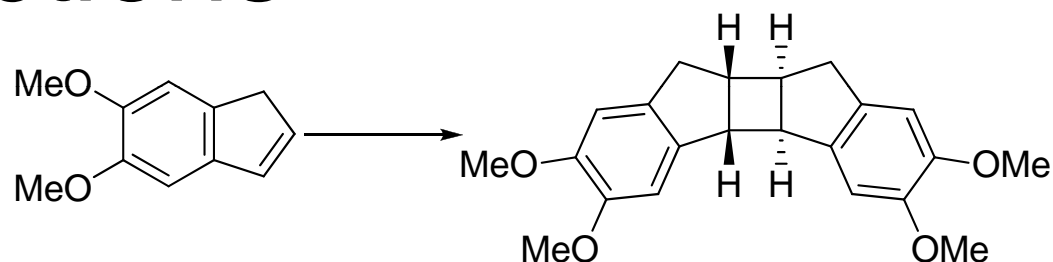
# Electron Transfer Catalysis (ETC)

- Involves reactions where the initial and final states are at the same oxidation level, and the intervening steps take place at an oxidation level one step above (or below)

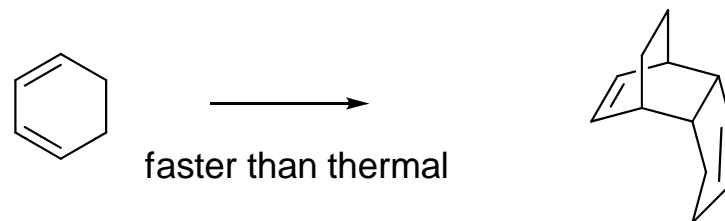


# Applications to Ring-Forming Reactions

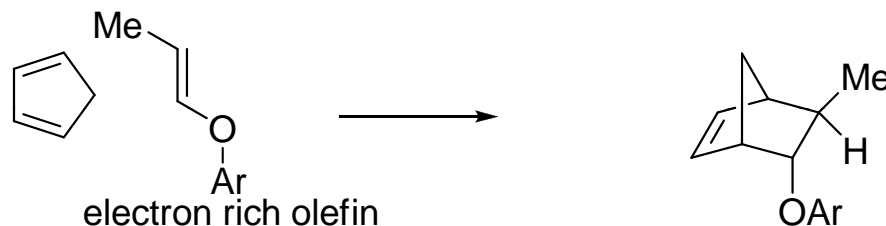
ETC cycloadditions all believed to have activation barriers of 1-5 kcal/mol, often 10-60 kcal/mol lower than corresponding neutral cycloadditions



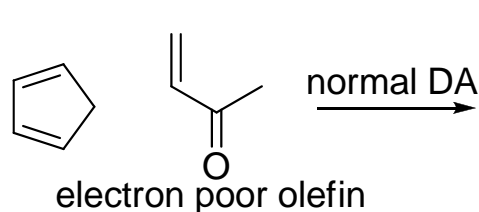
thermal reaction not known



faster than thermal



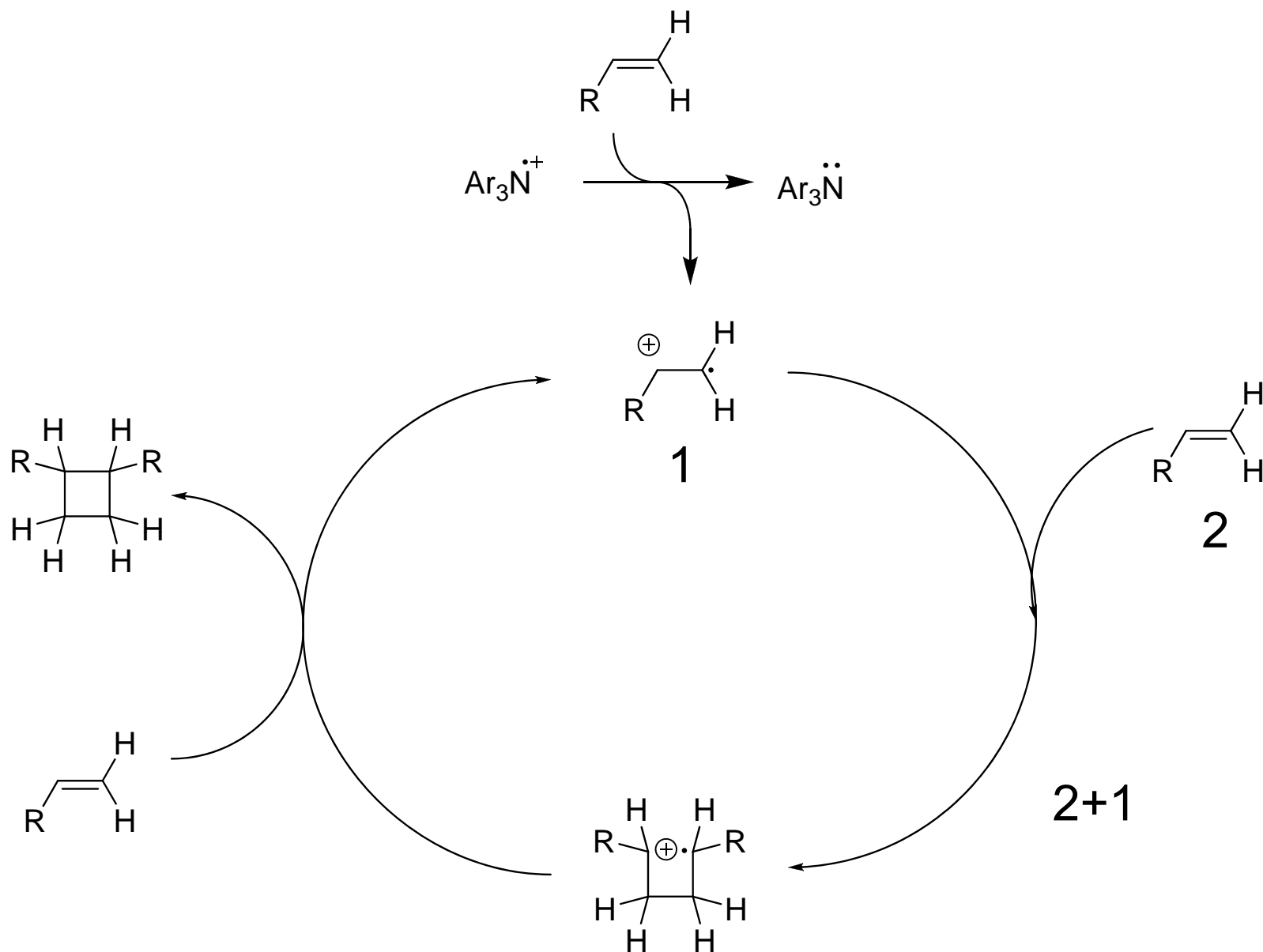
electron rich olefin



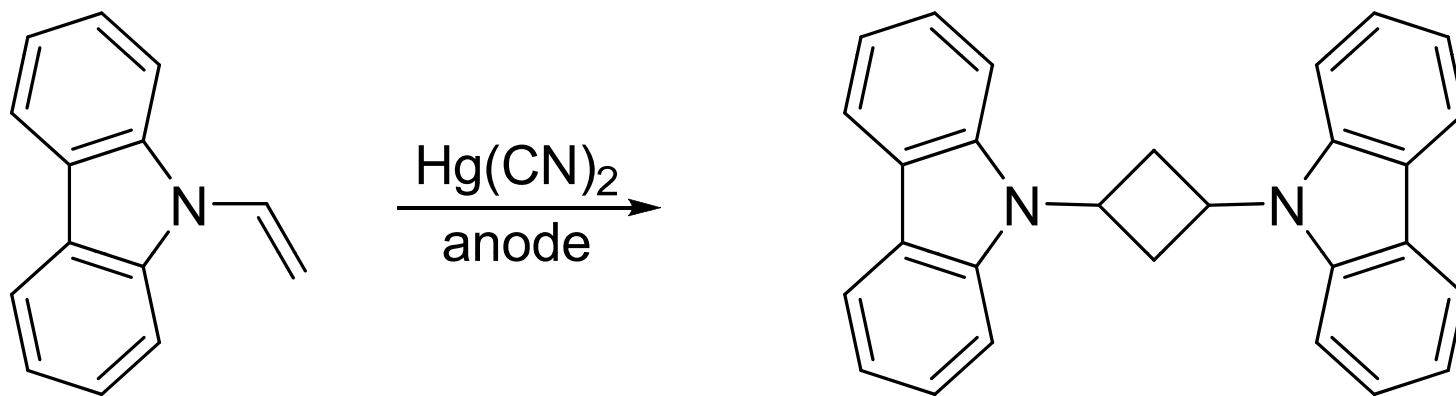
electron poor olefin

normal DA

# Cyclobutane Catalytic Cycle

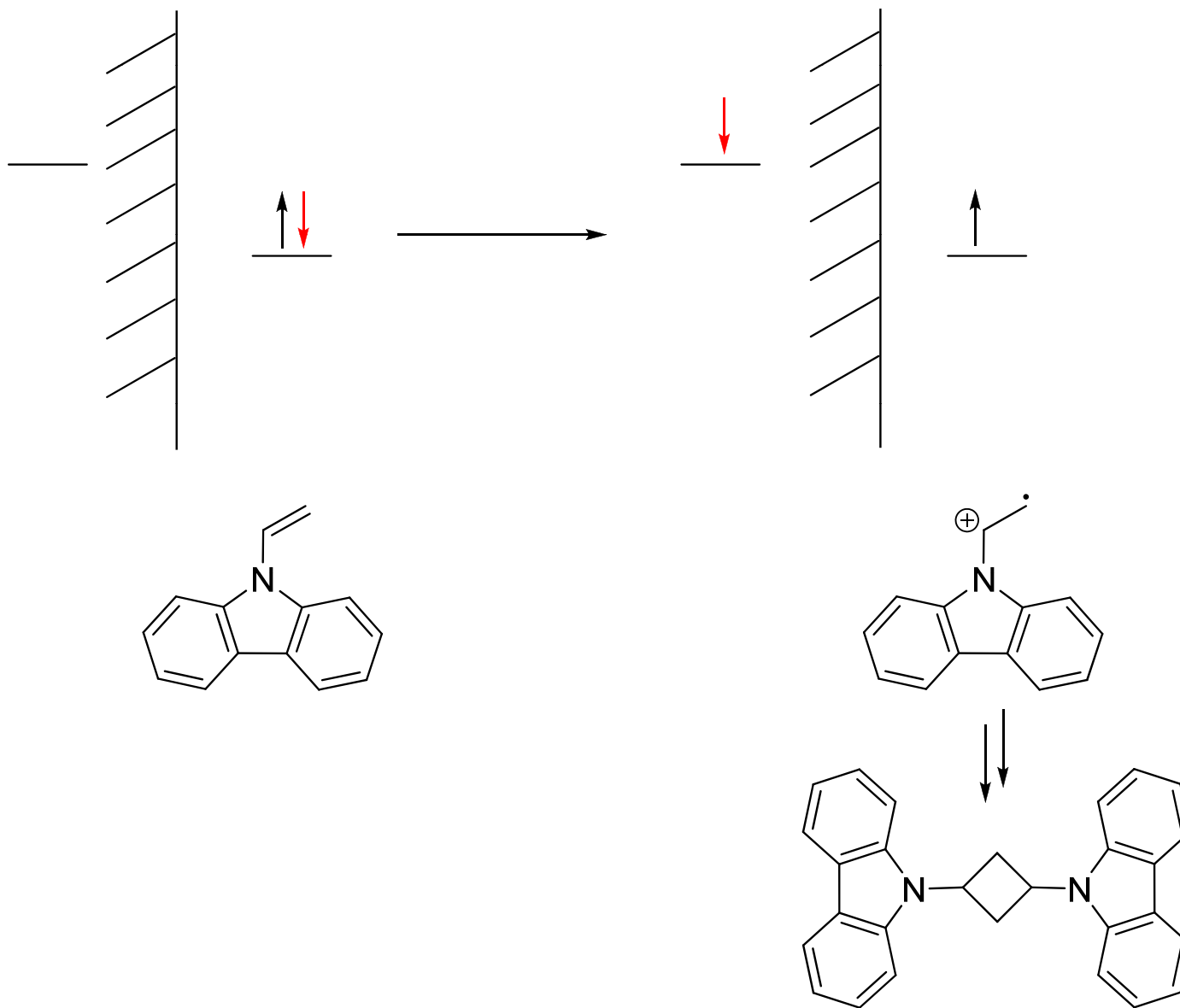


# An Accidental Discovery

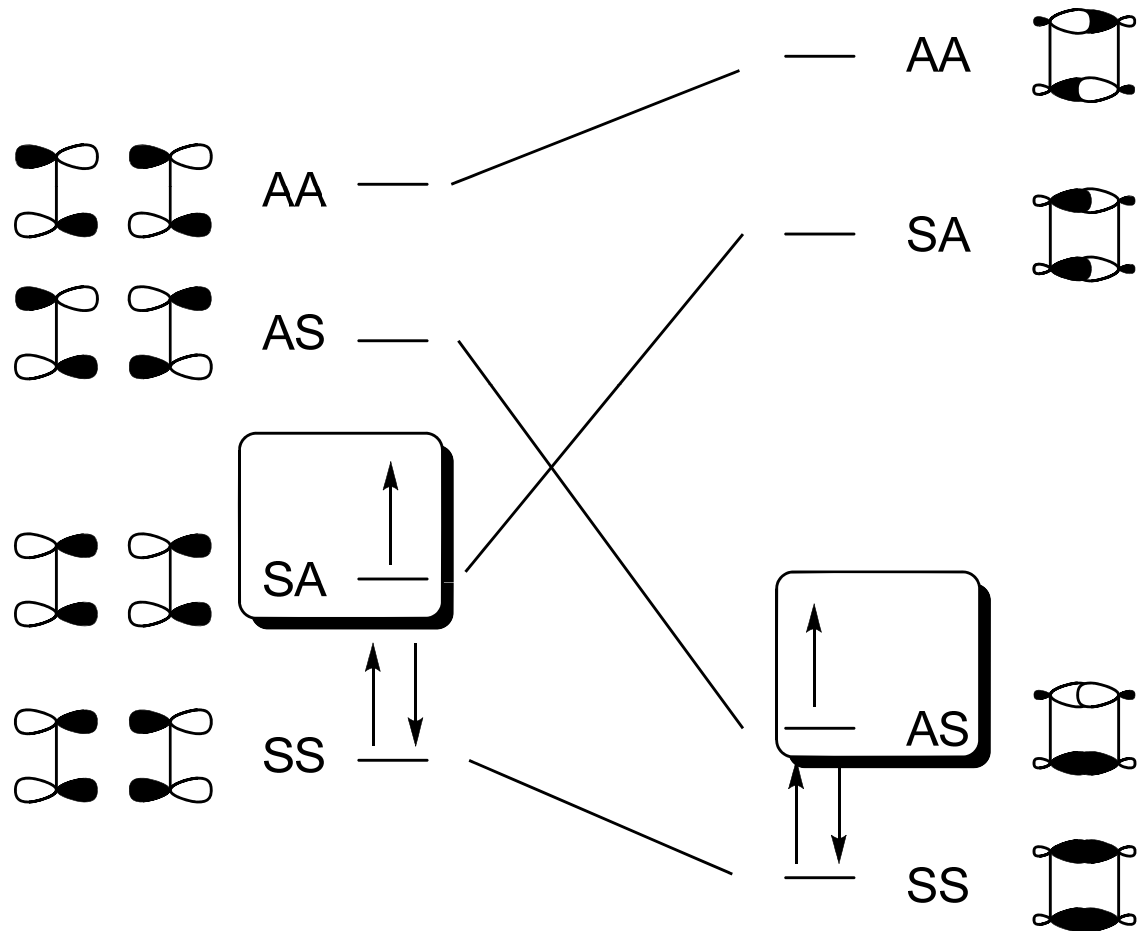
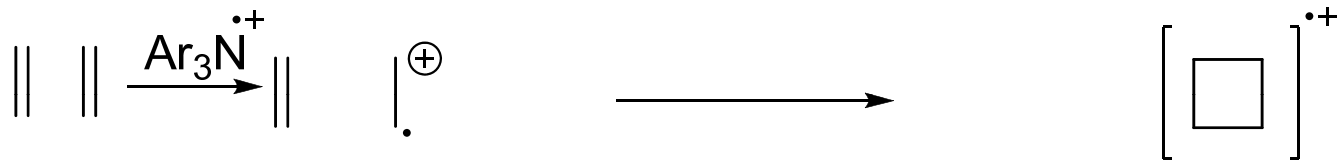


# MO picture

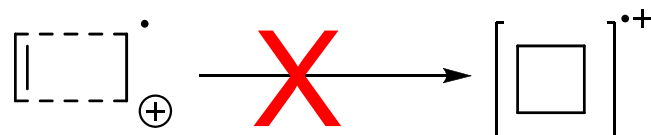
anode/oxidant



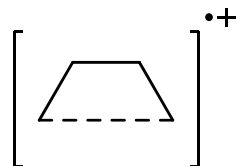
# Correlation diagram of 2+1



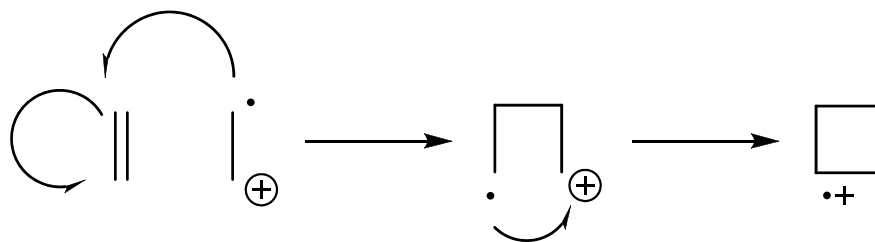
# Concerted or Stepwise Pathway



cannot be concerted and synchronous

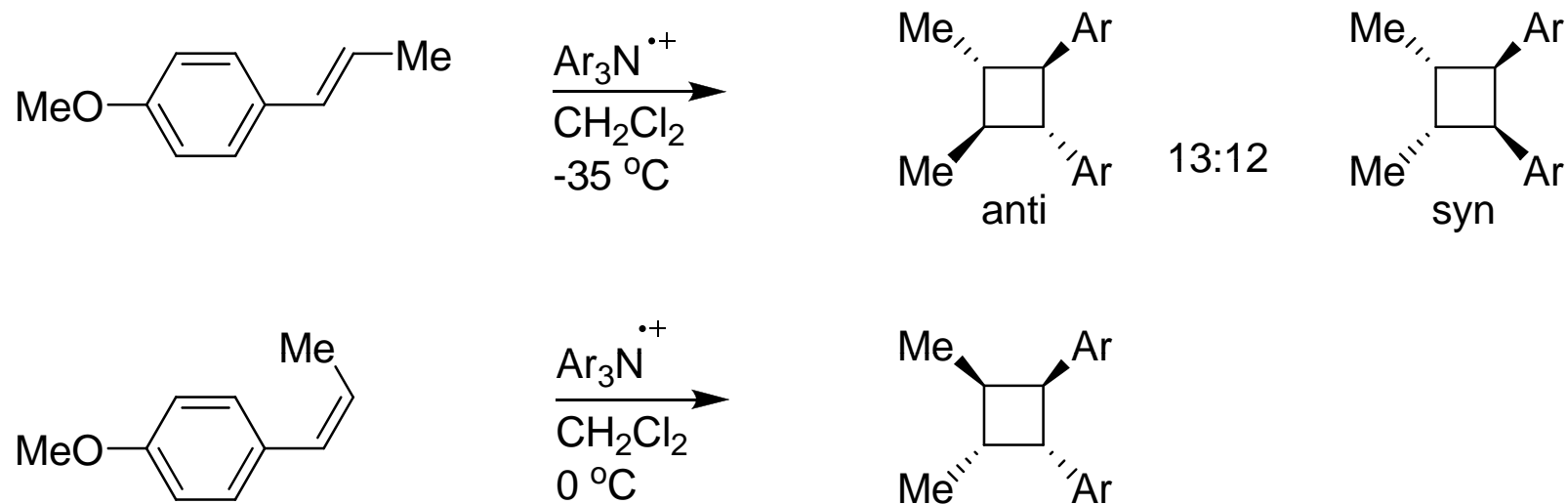


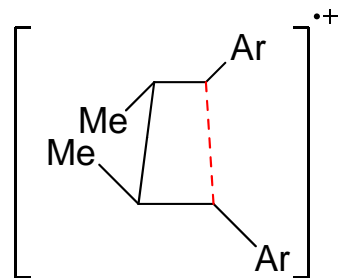
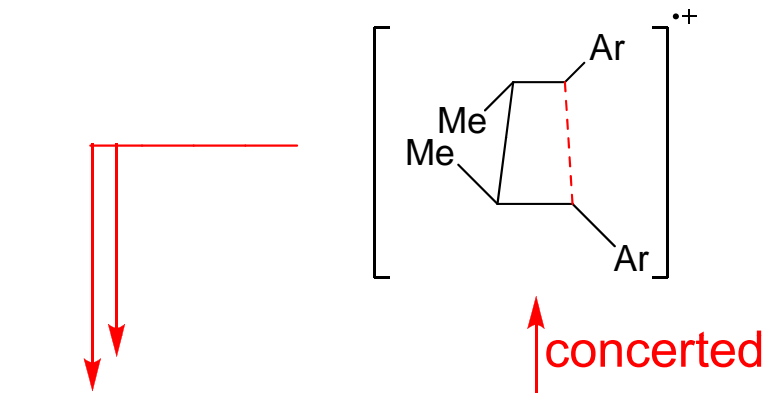
can be concerted, highly asynchronous  
stereospecific



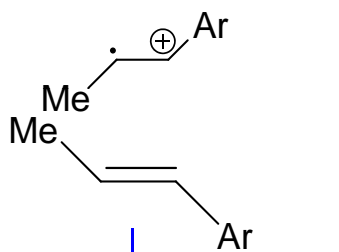
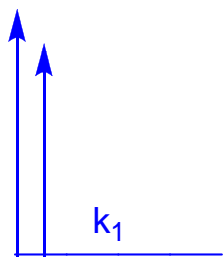
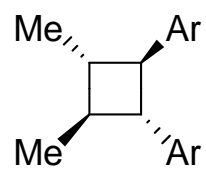
can be stepwise  
not stereospecific

# Stereospecific Cyclobutanation

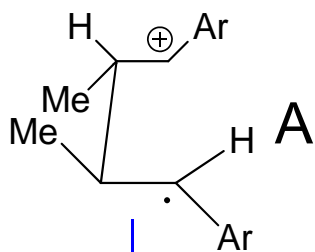




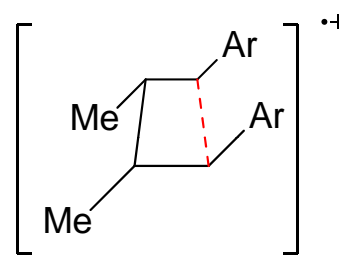
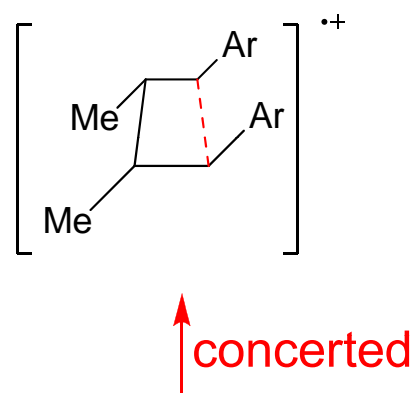
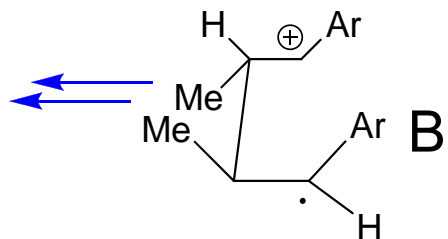
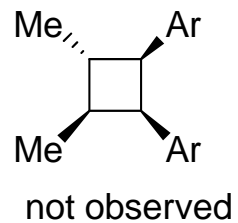
concerted



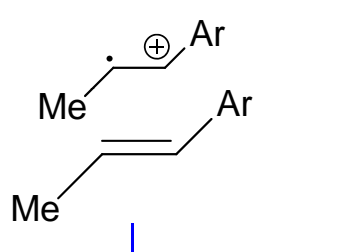
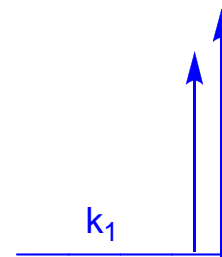
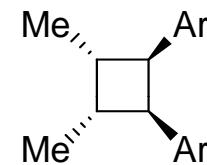
stepwise



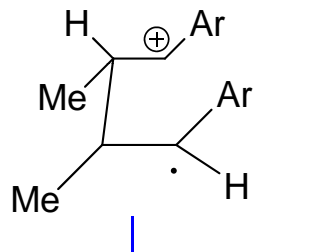
$k_2$  rotation



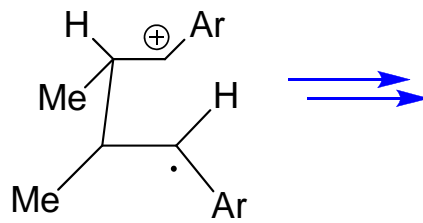
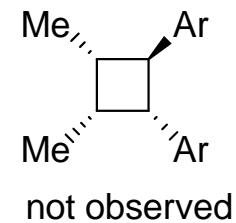
concerted



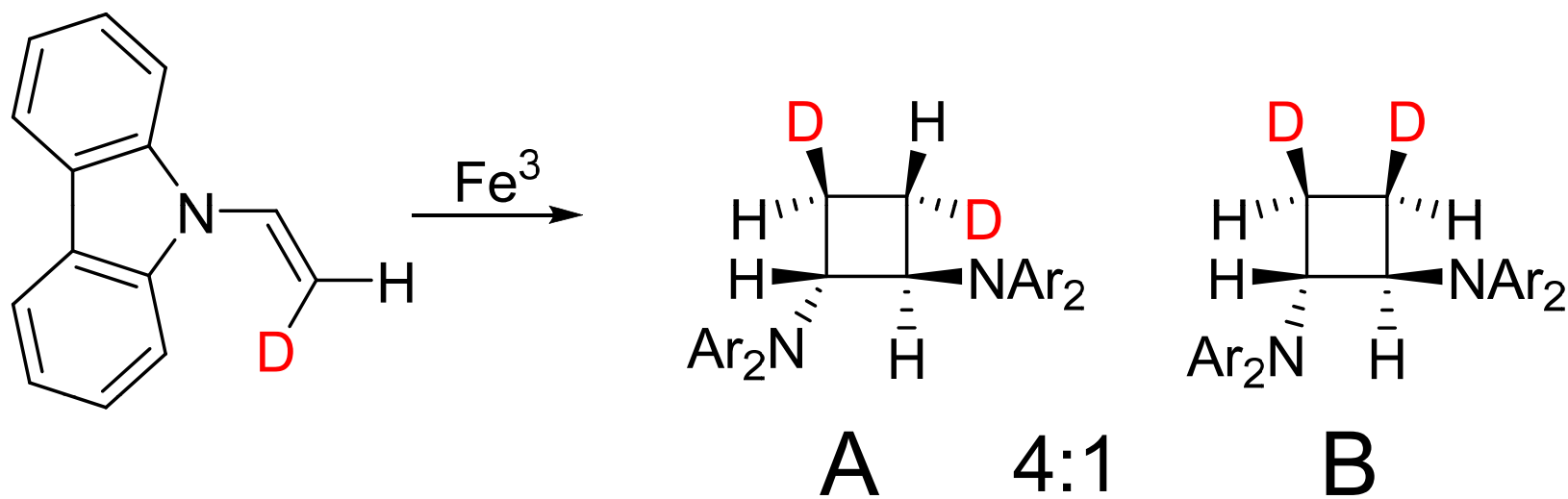
stepwise



$k_2$  rotation



# Stepwise Cyclobutanation

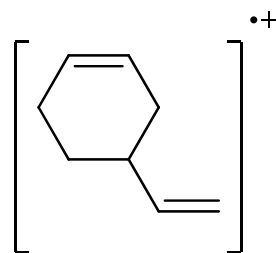
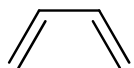
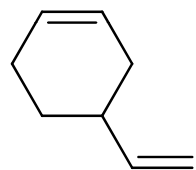
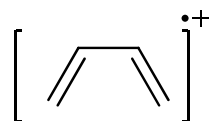
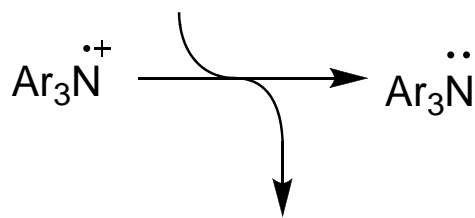
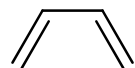




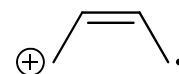
# Radical Cation Cyclobutanation

- Not concerted, synchronous
- Many examples are stepwise
- Others may be concerted, asynchronous
- No electron poor olefins known to undergo reaction

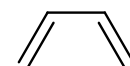
# Diels-Alder type reactions



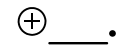
$3 e^-$



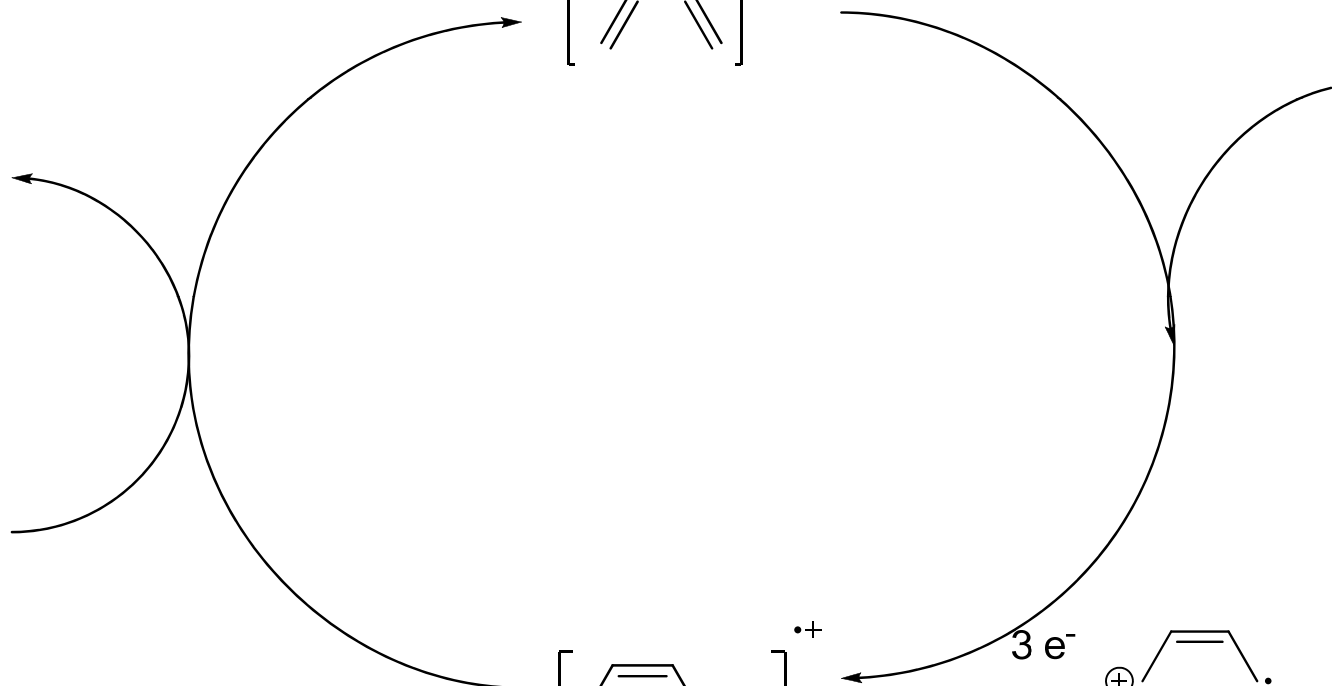
$2 e^-$



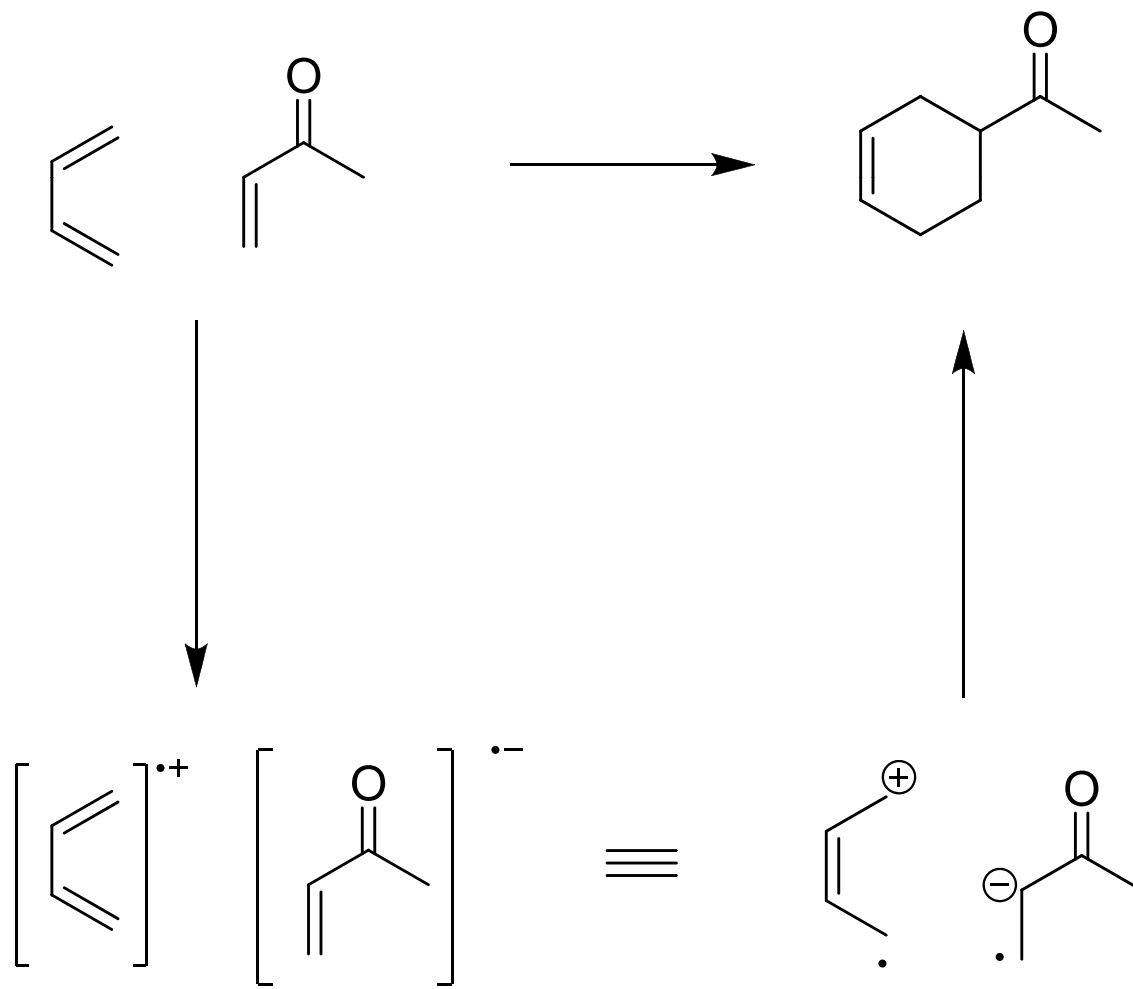
$4 e^-$



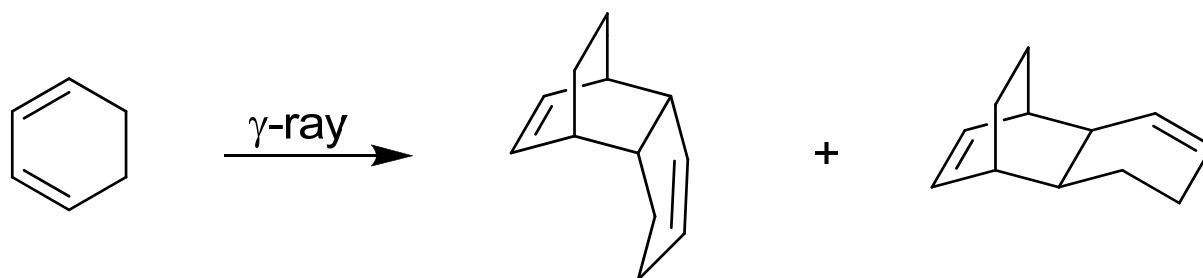
$1 e^-$



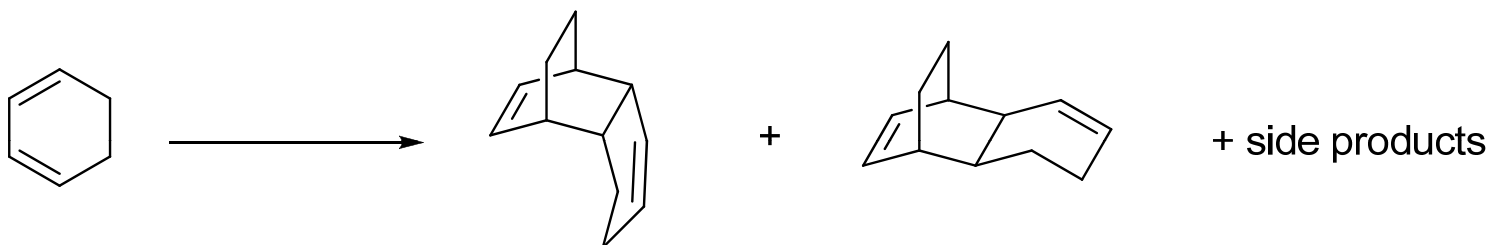
# An Early ET Diels-Alder Theory



# Another Accidental Discovery



# Comparison to Thermal



Temperature

200° C

0° C

Time

20 h

15 m

catalyst

none

$\text{Ar}_3\text{N}^+$

endo: exo

4:1

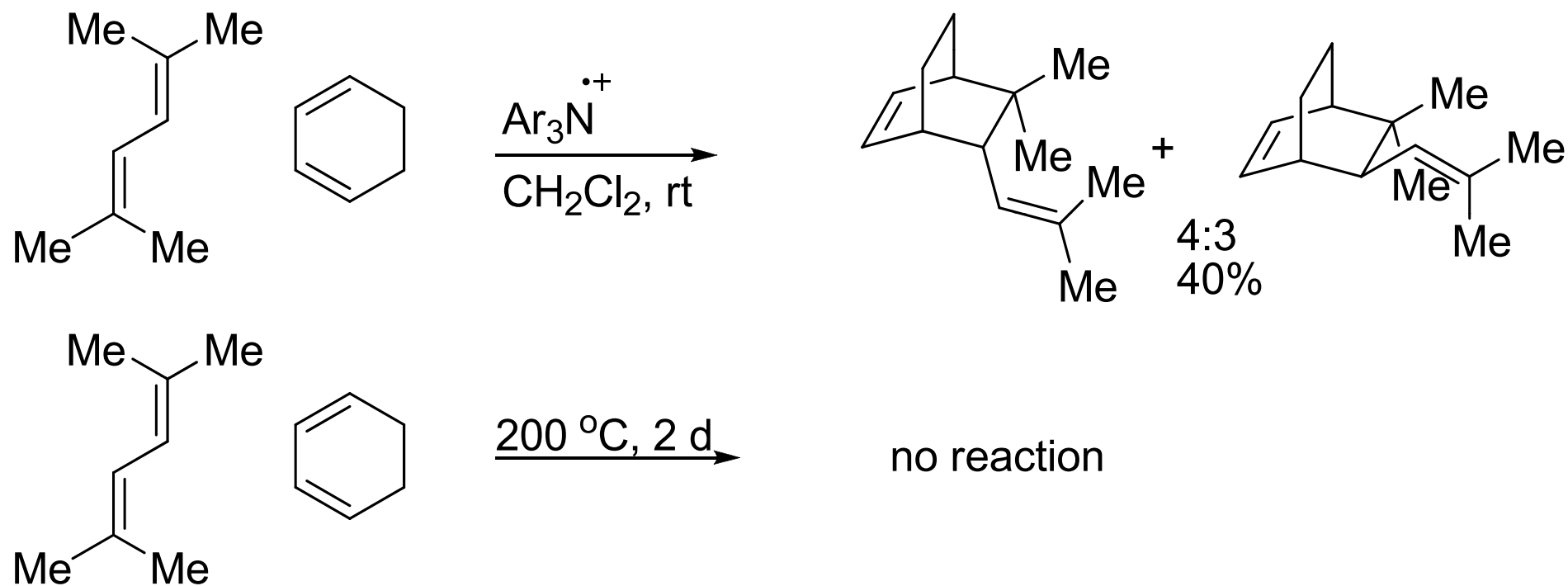
5:1

yield

30%

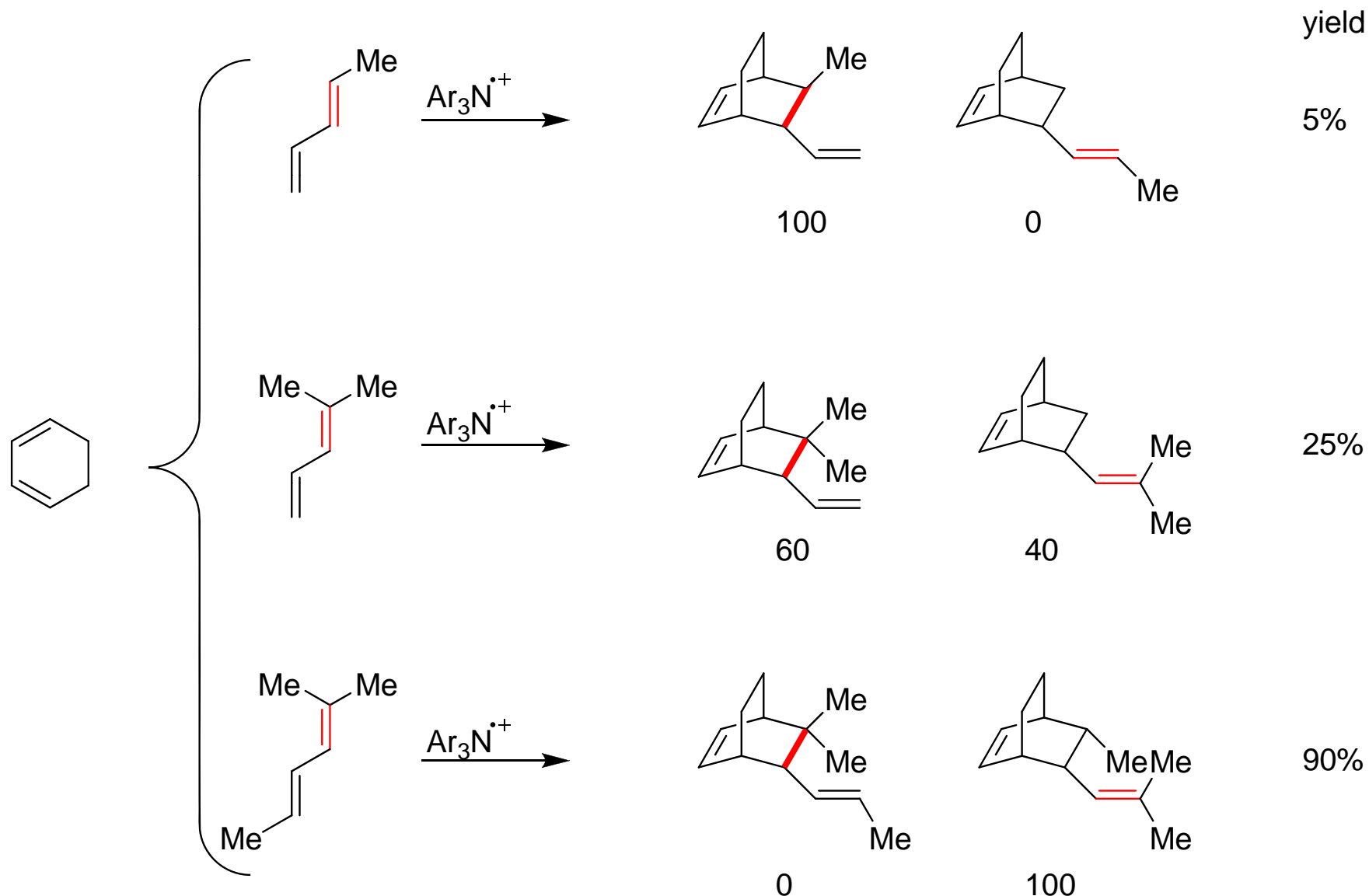
70%

# Sterically Encumbered Dieneophile

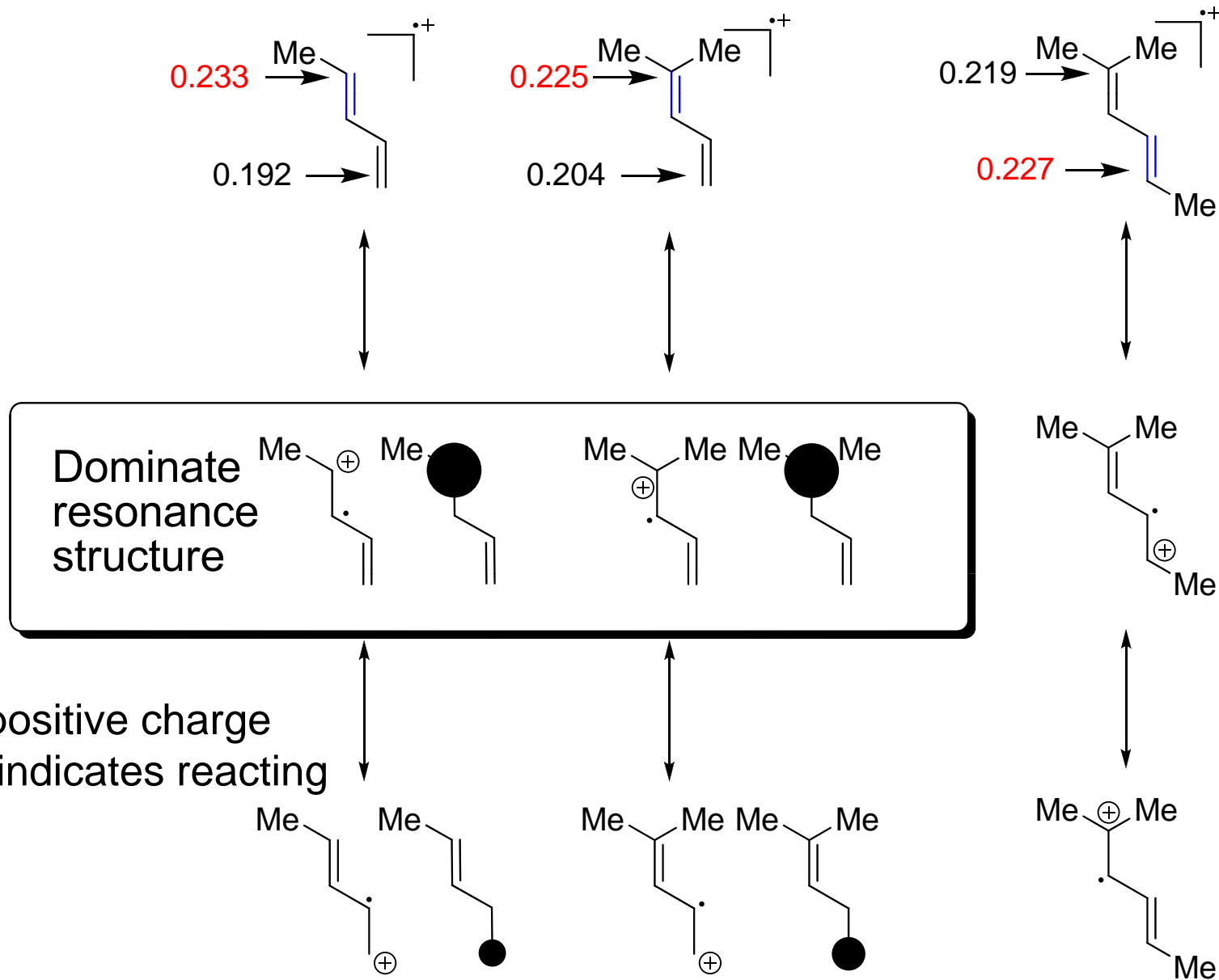


# Chemoselectivity

Why does the more substituted olefin participate in the Diels-Alder?



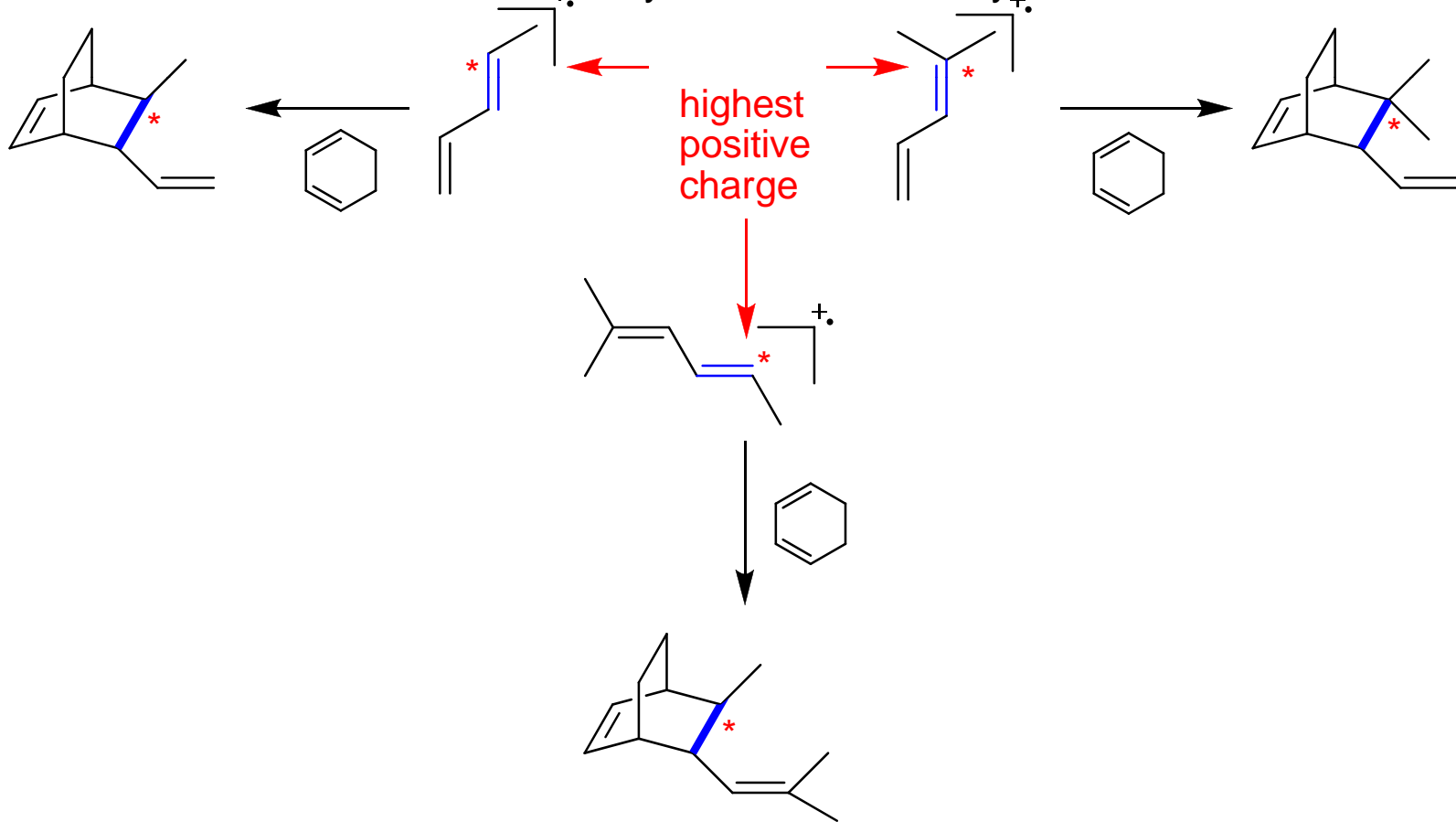
# Positive Charge Densities are Key



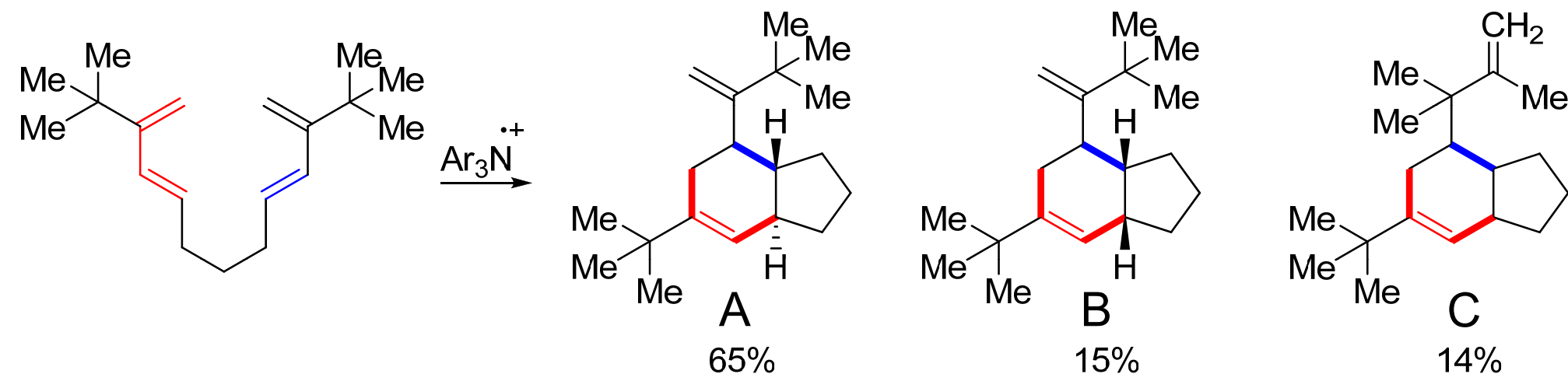
# Positive Charge Densities are Key

terminal alkyl groups bring positive charge to the carbon on which it is attached

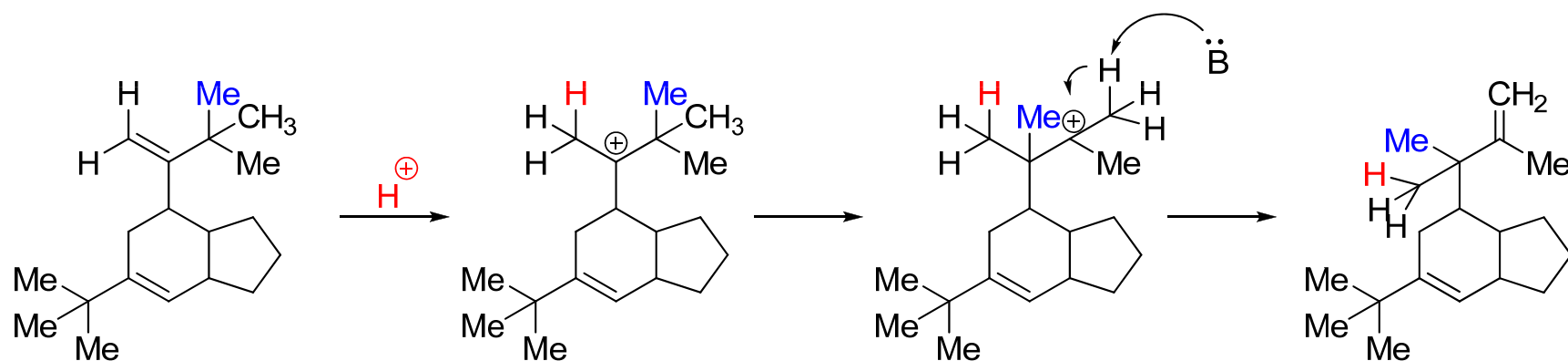
EXCEPTION: bis alkylated and mono alkylated termini



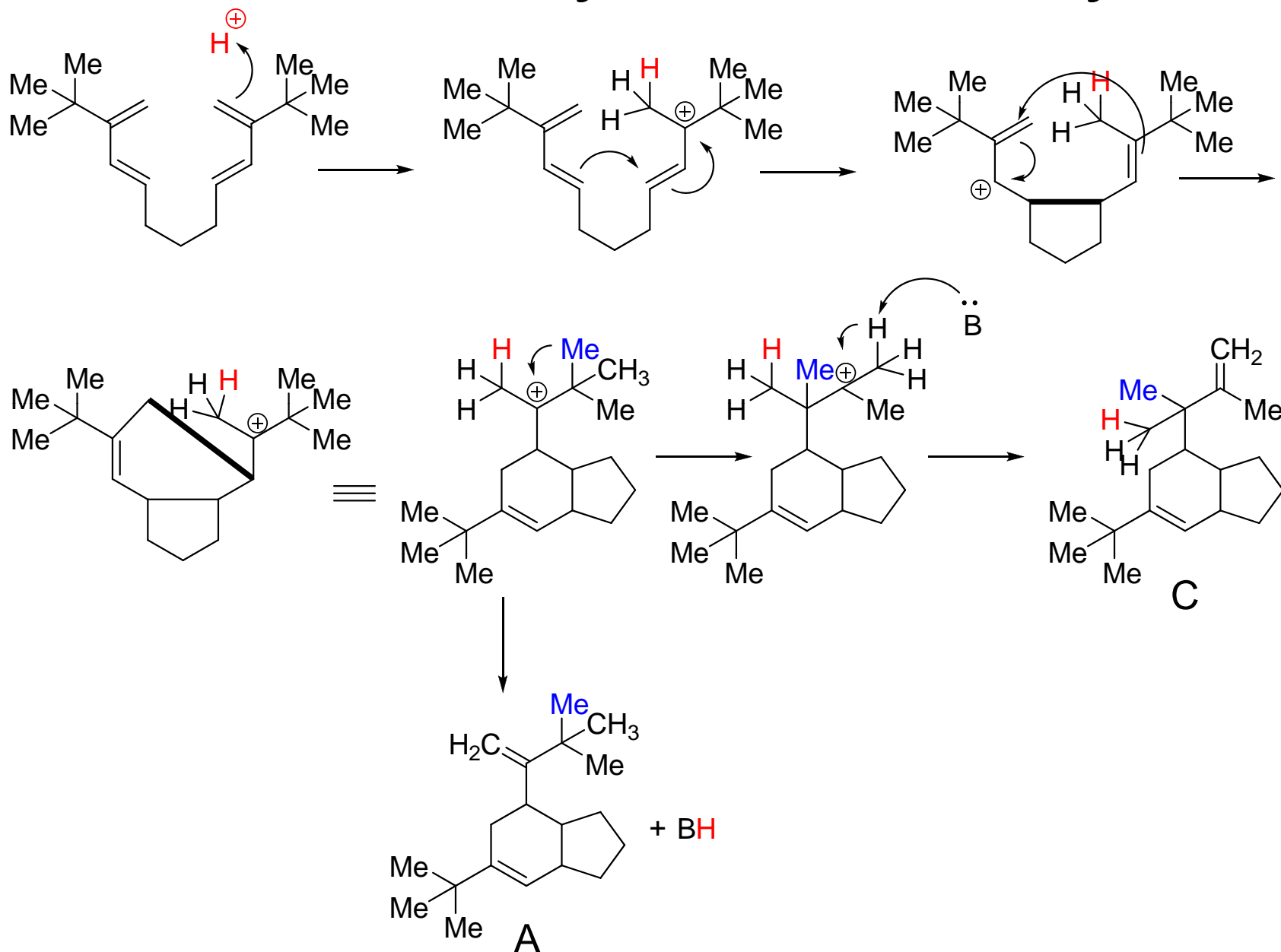
# Radical Cation, or Acid Catalyzed?



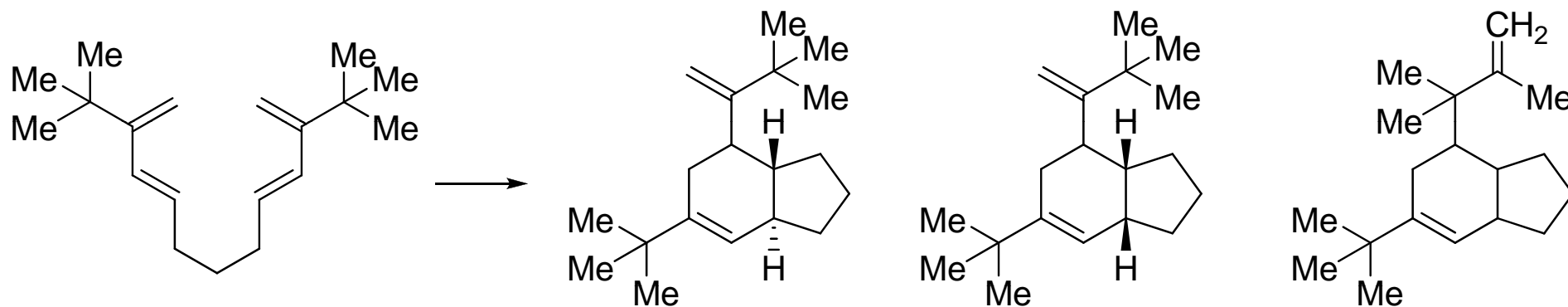
If acid is present, is the reaction acid catalyzed?



# Acid Catalyzed Pathway

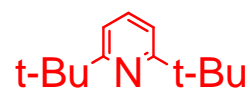


# Proof of Acid Catalysis



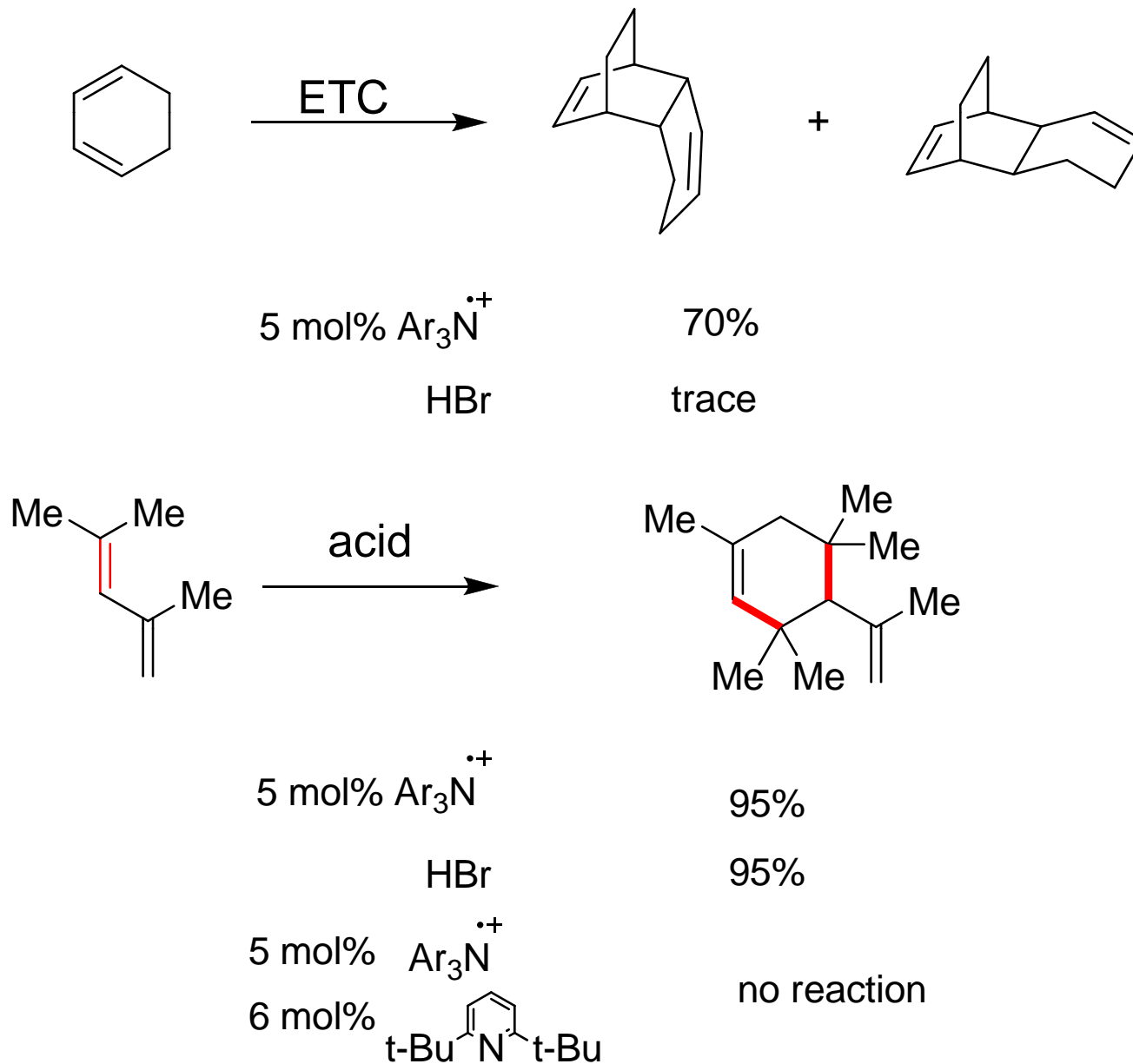
$\text{Ar}_3\text{N}^{\bullet+}$	64%	15%	14%
$\text{CF}_3\text{SO}_3\text{H}$	65%	23%	3%
$\text{Ar}_3\text{N}^{\bullet+}$	0%	0%	0%

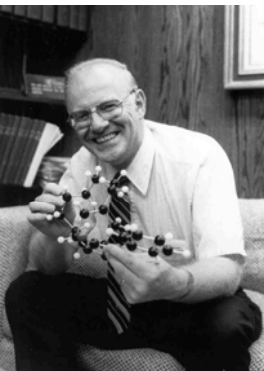
added to  
quench acid  
(does not affect  
ET)



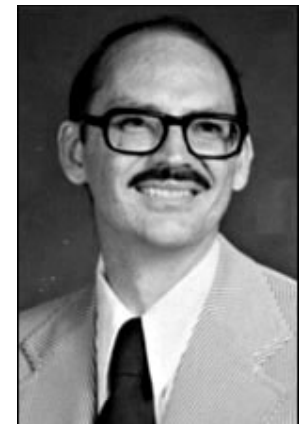
Are other radical cation salt Diels-Alder products actually just acid catalyzed?  
Do ETC reactions even exist?

# Gassman Revisits Bauld's Results

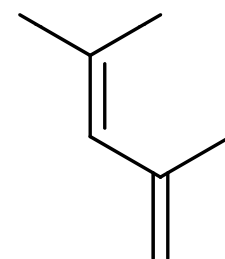




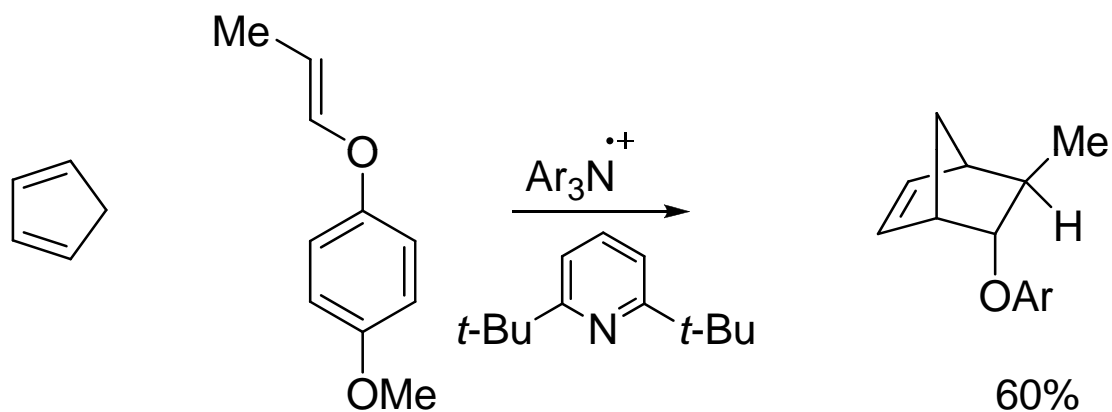
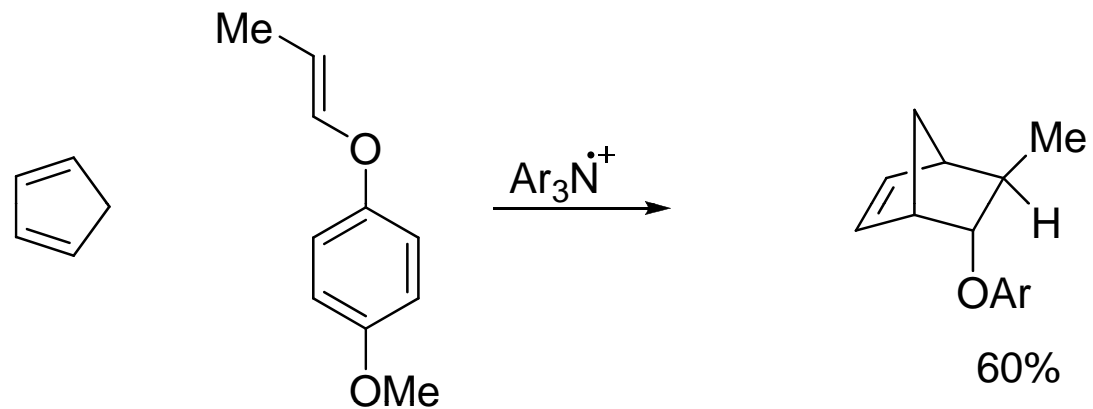
# Bauld's response



- Bauld redid every experiment, adding hindered base to quench any acid
- For every instance except for one, base did little to hinder the reaction, meaning a radical cation Diels-Alder type mechanism was operating
- The only acid catalyzed reaction happened to be chosen by Gassman
- Suggested that in the future, all experiments with radical cation salts should be run in presence of base as a control

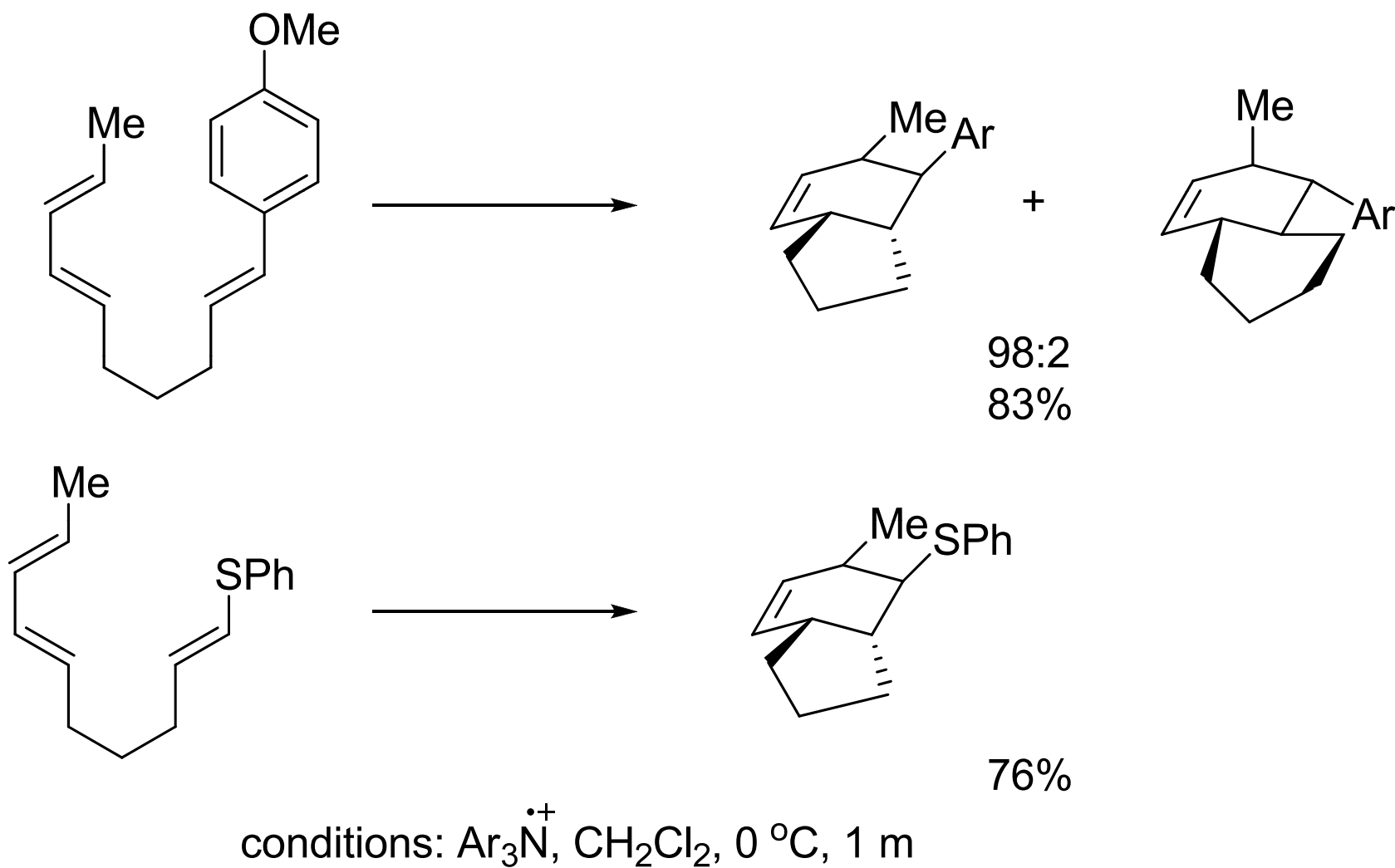


# An example

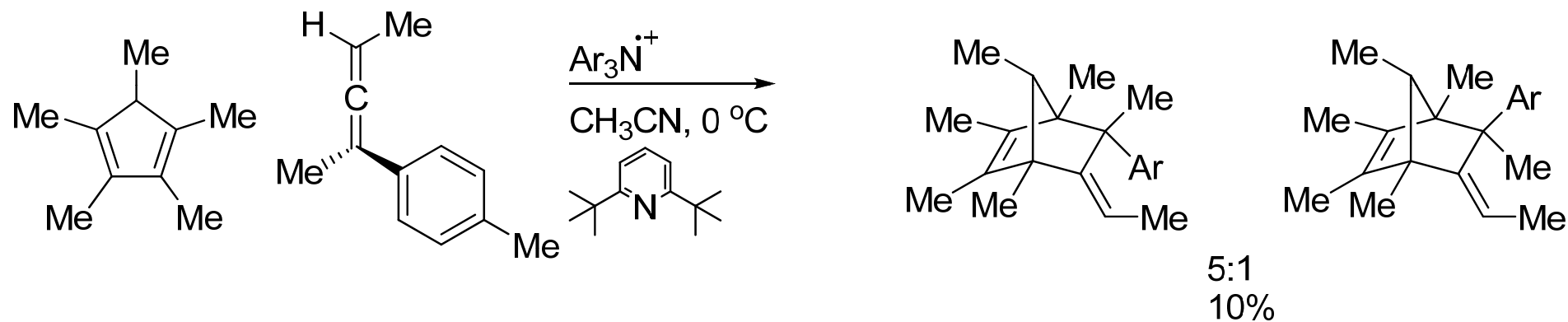


Identical yields, therefore, not acid catalyzed

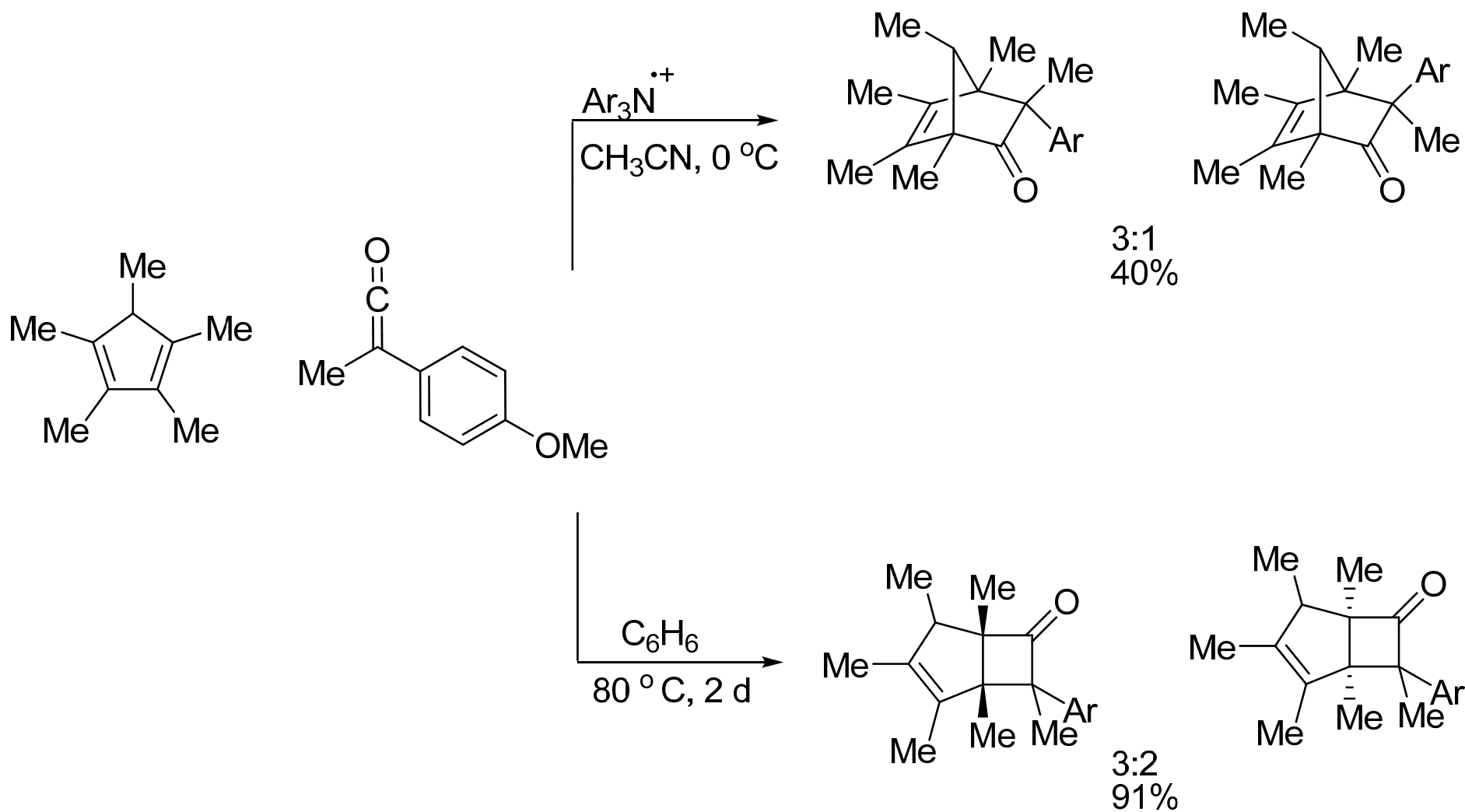
# Intramolecular ETC DA



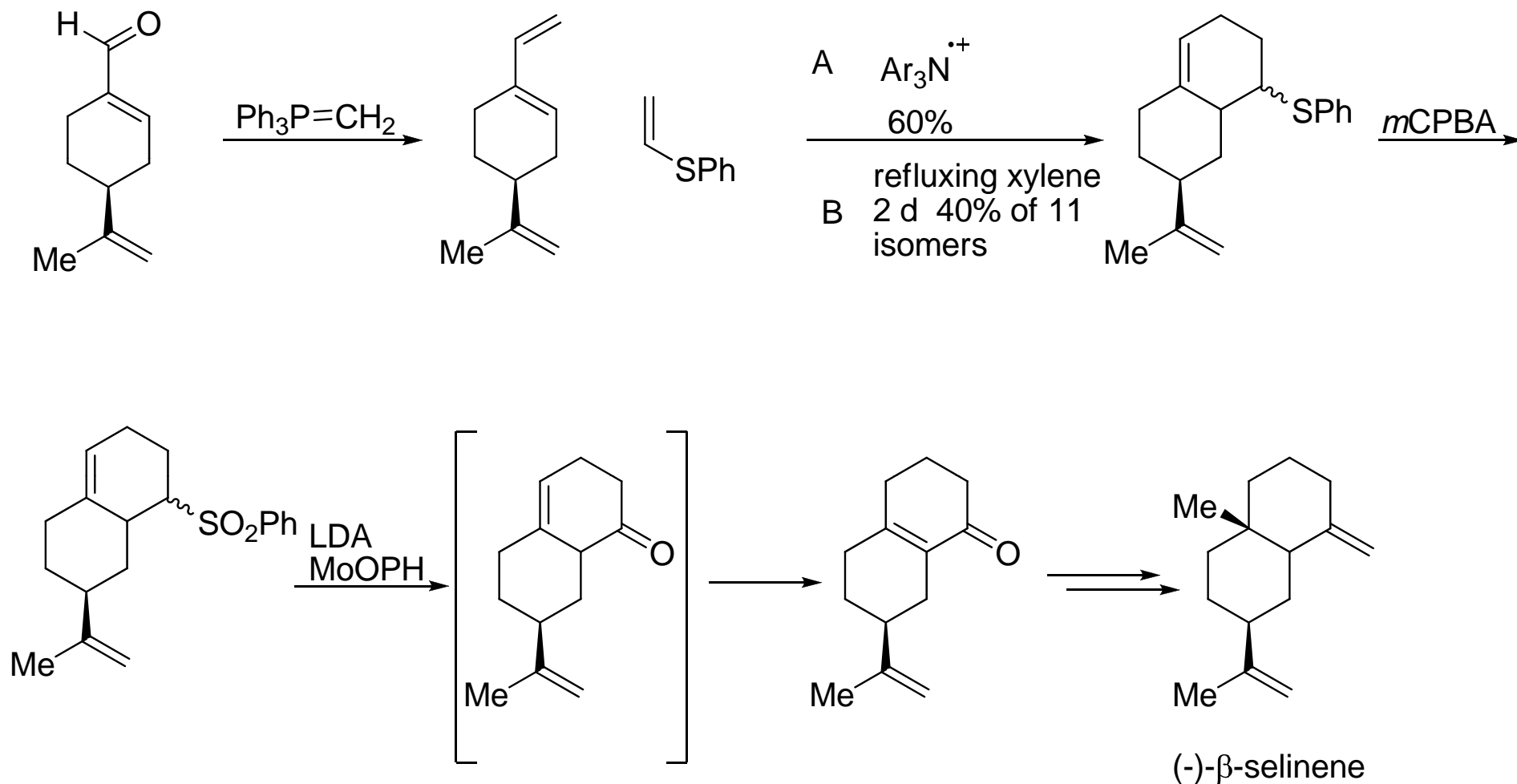
# Expanding the Scope to Allenes



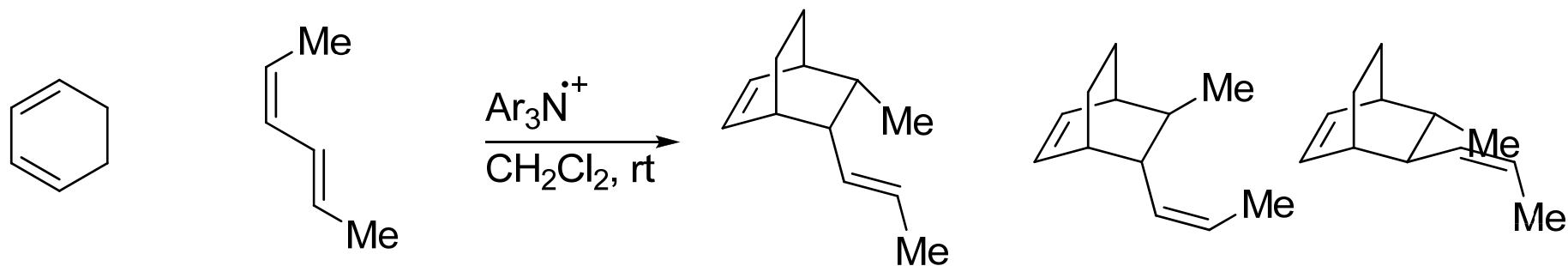
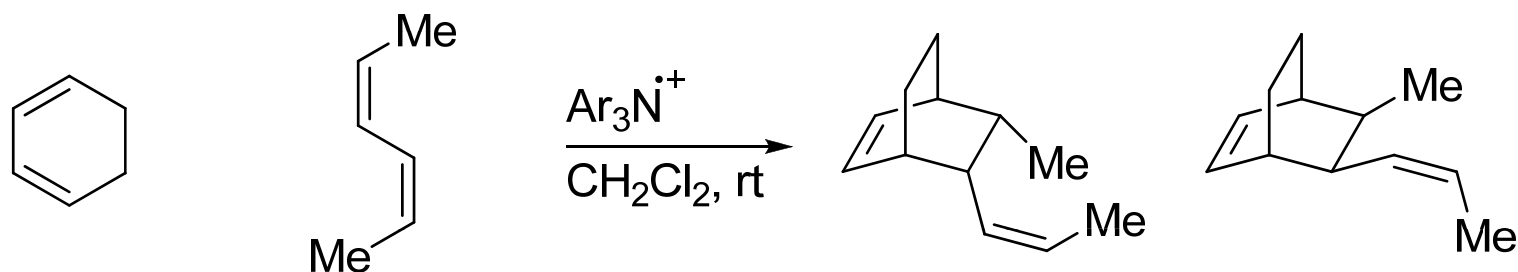
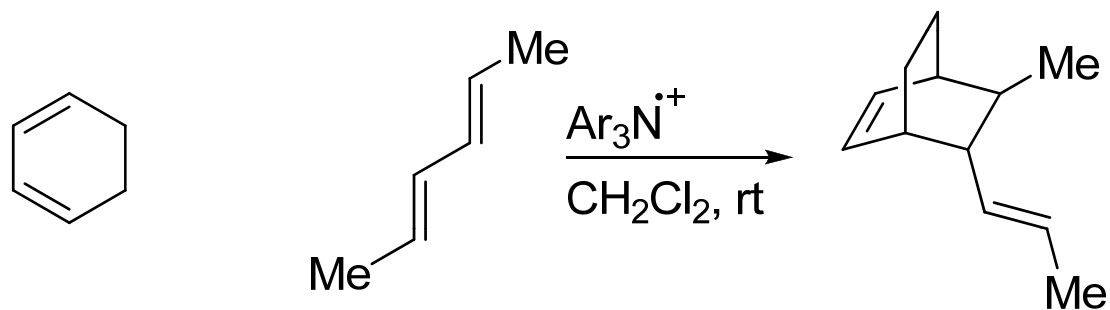
# Expanding the Scope to Ketenes



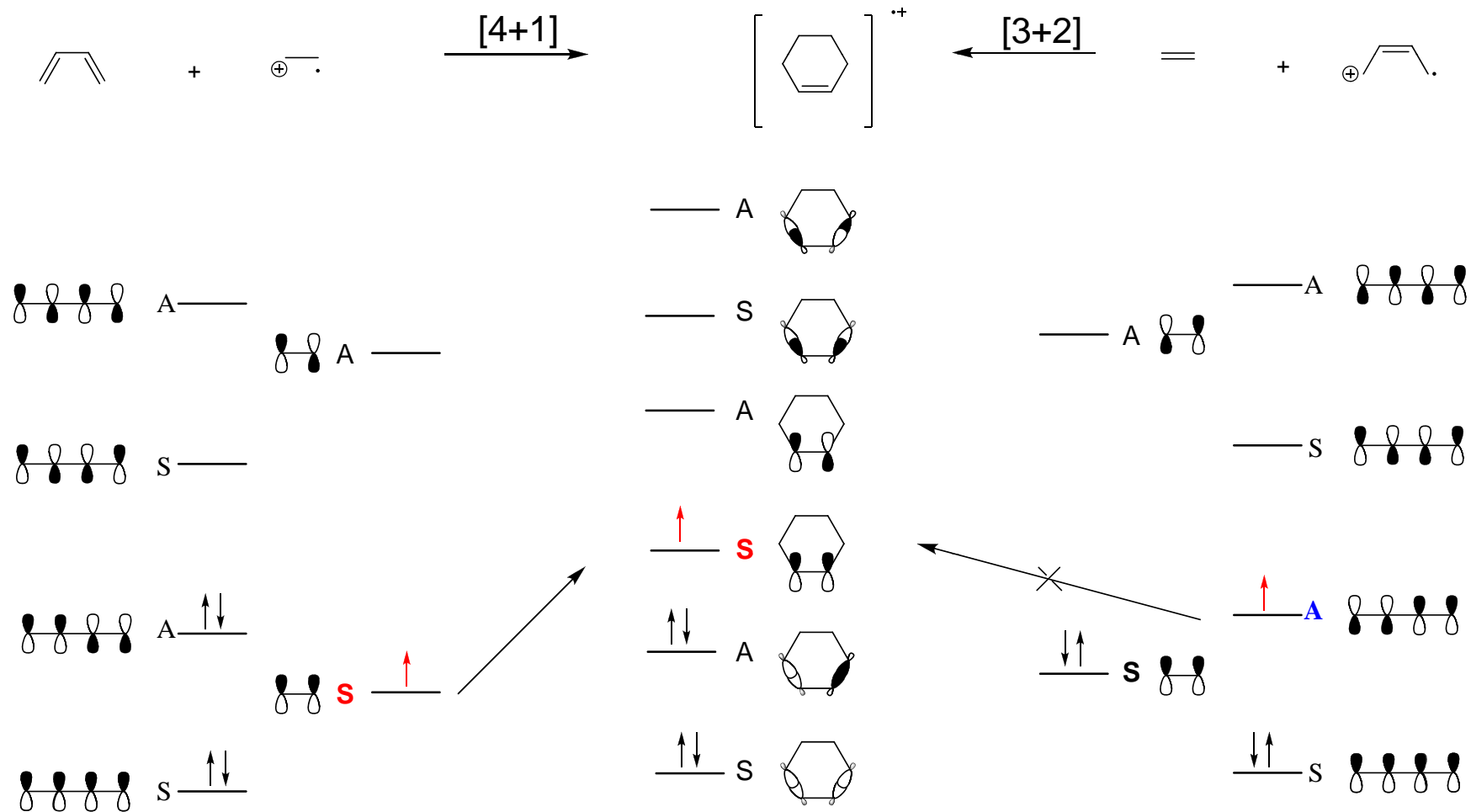
# Synthetic Utility - a Formal Synthesis



# Stereospecific ETC Diels-Alder

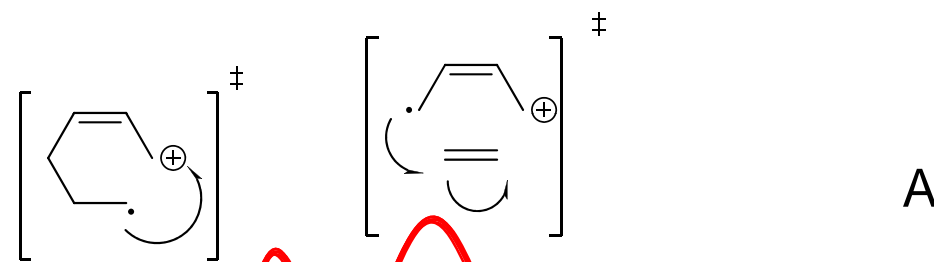


# Correlation diagram



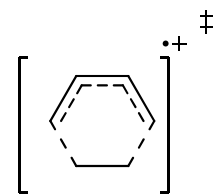
SOMOs have matched symmetry elements  
therefore 4+1 is a symmetry allowed reaction

SOMOs do not have matching symmetry elements  
therefore 3+2 is a symmetry forbidden reaction



Assumption:

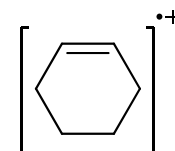
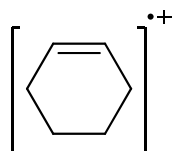
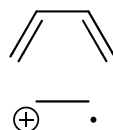
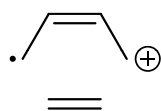
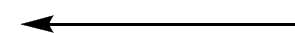
Allowed pericyclic pathways  
are lower in energy than  
corresponding stepwise paths



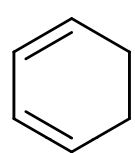
3+2 pathway



4+1 pathway

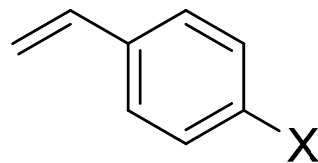


# First Suggestion of a 3+2

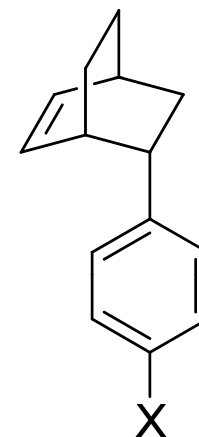


1.08 V

+

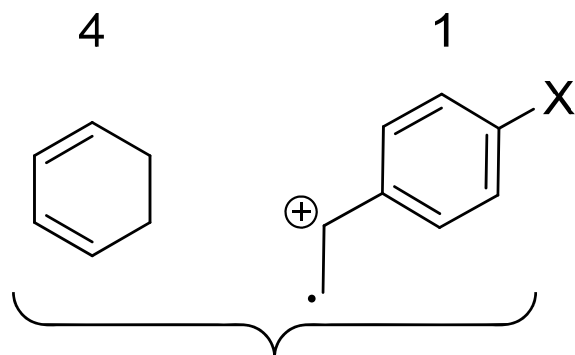


anode (0.9 V)

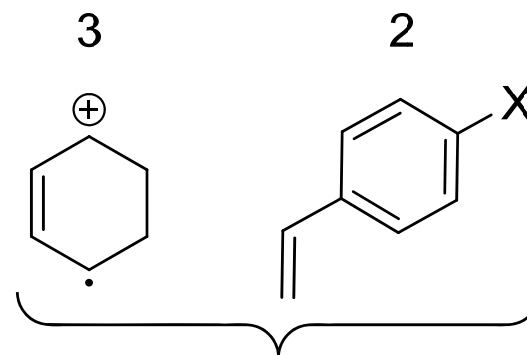


11-22%

X	potential (V)
NO <sub>2</sub>	1.8
Cl	1.49
H	1.45
CH <sub>3</sub>	1.35

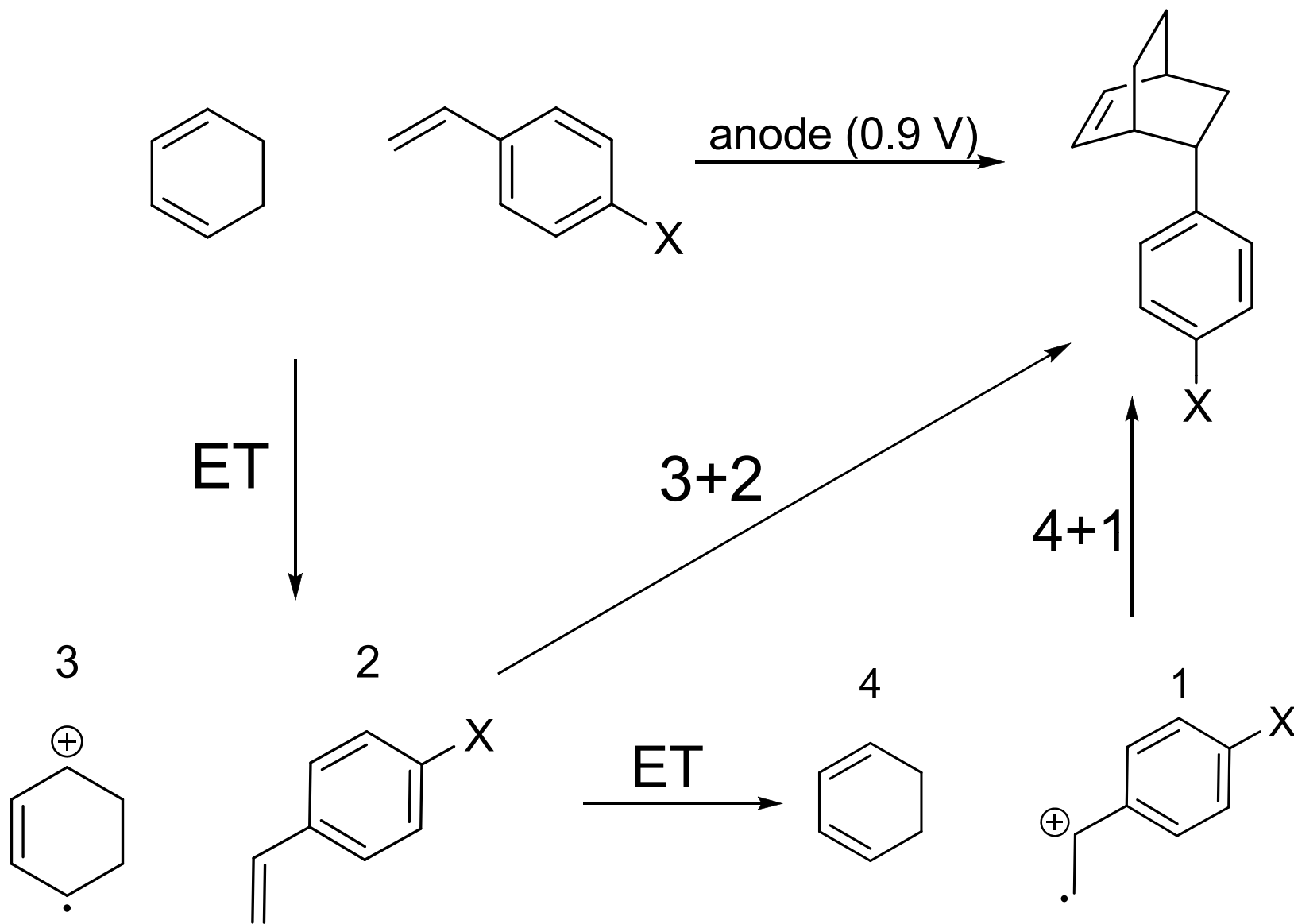


Bald's model

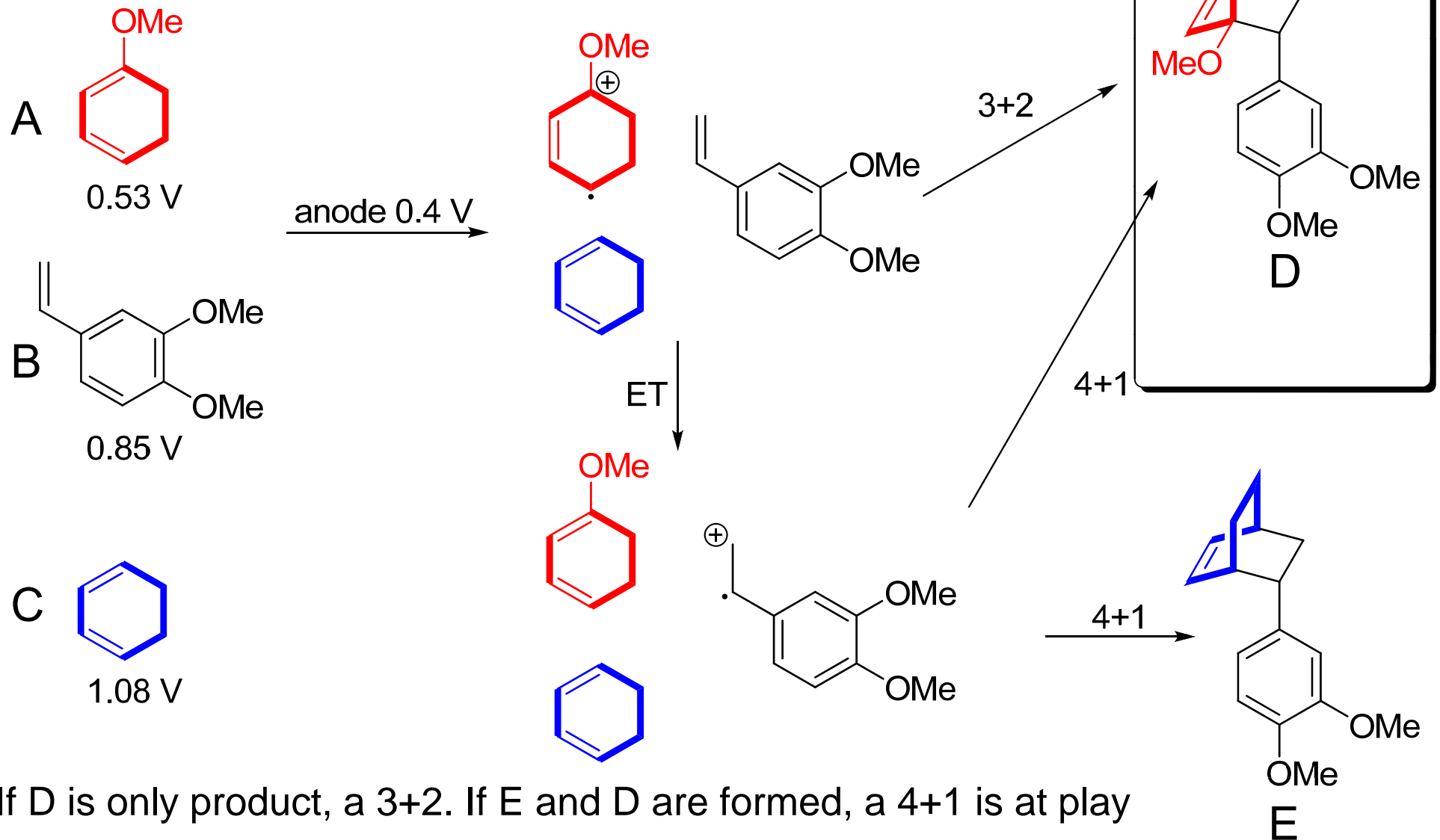


Steckhan's model

# Could it be Double Electron Transfer?

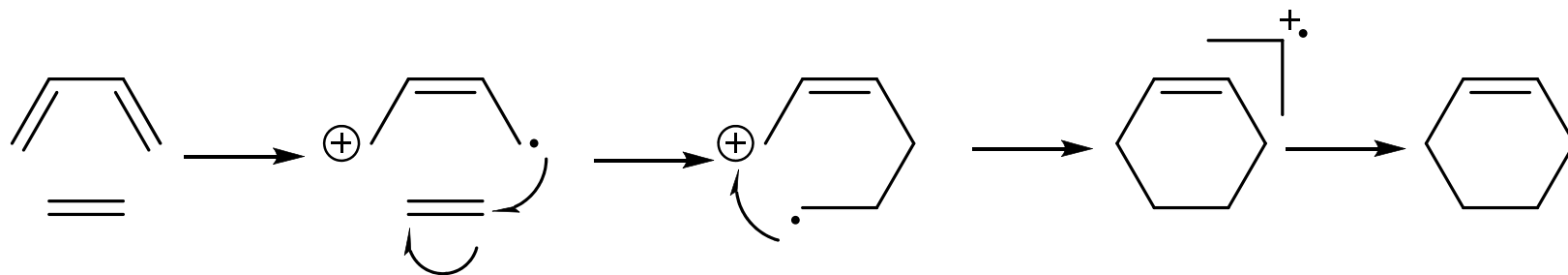


# Proof of 3+2

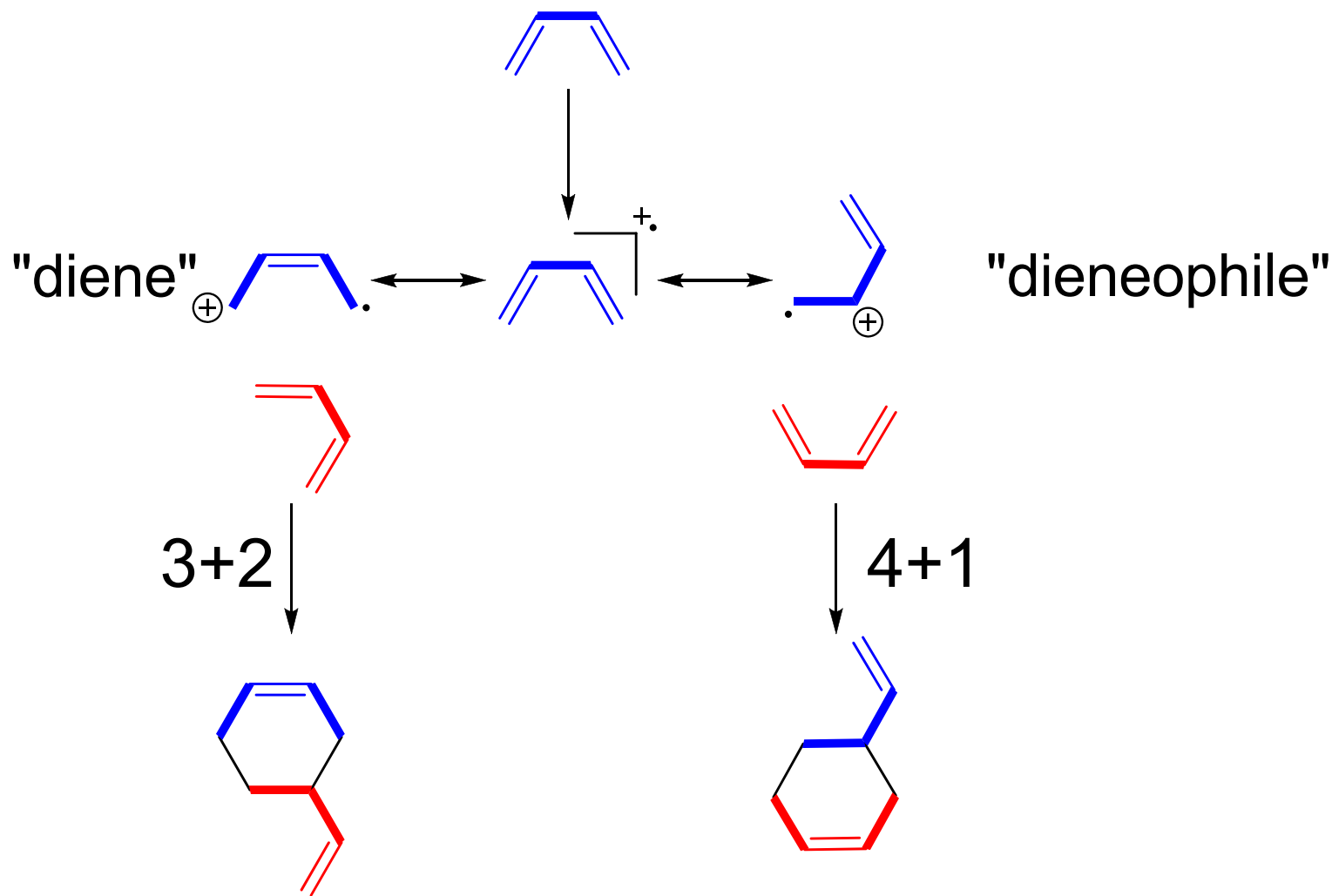


# Proof of 3+2

- It shouldn't have been a shock, seeing as how "forbidden" 2+1 reactions took place
- 3+2 is symmetry forbidden by Woodward-Hoffman rules, so cannot be concerted and synchronous
- Most likely is stepwise

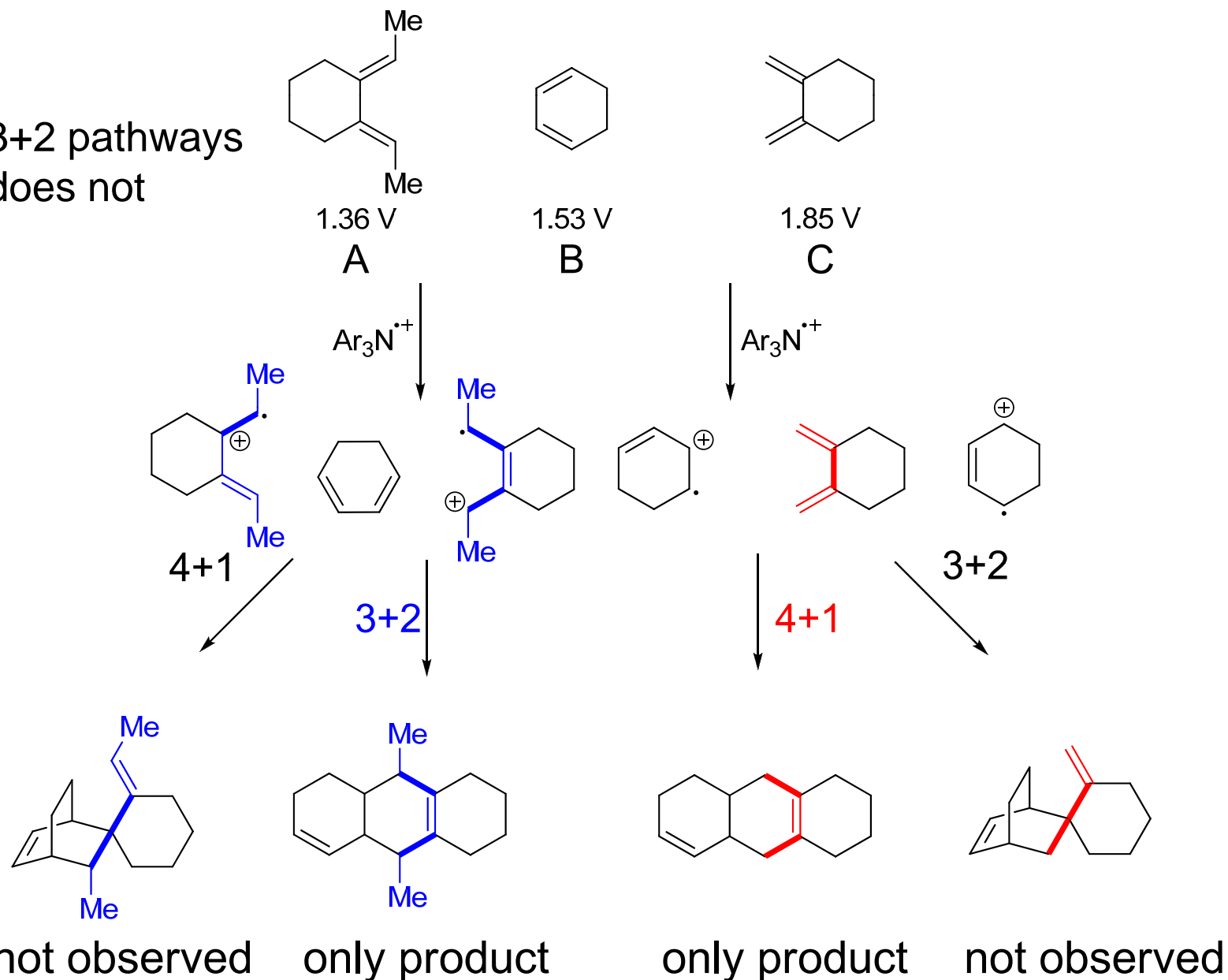


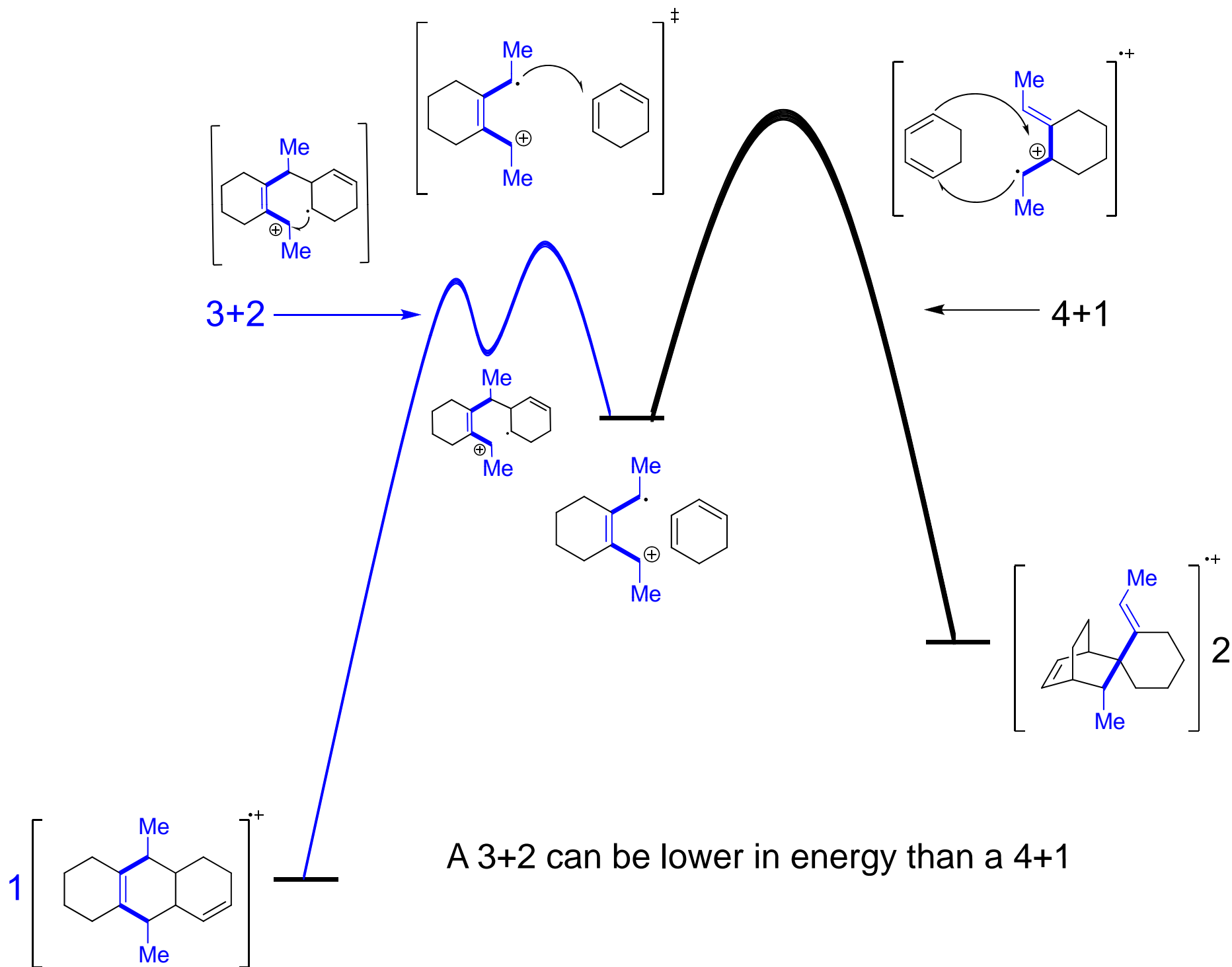
# Radical cation as diene or dieneophile?



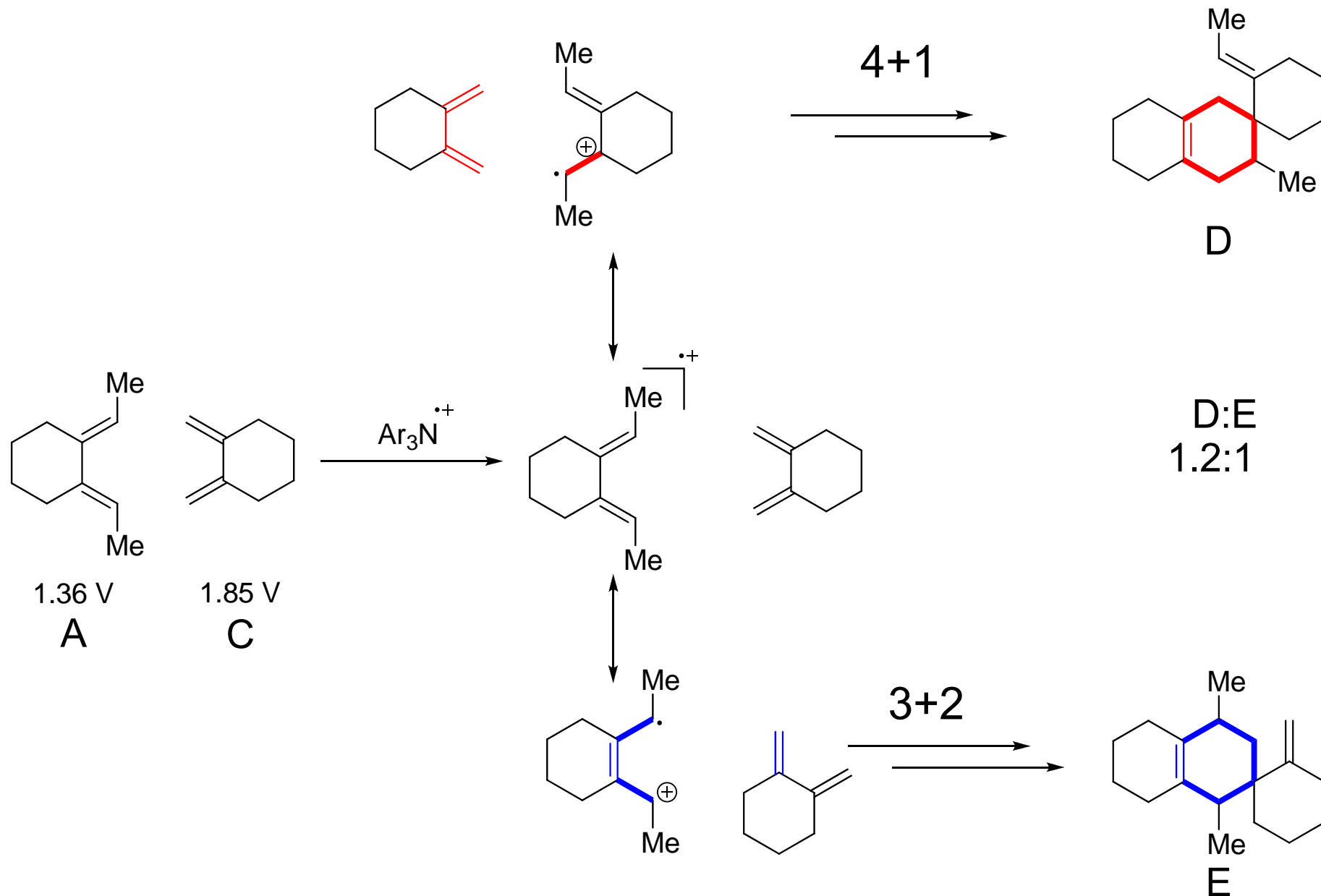
# Dissimilar 3+2 and 4+1 Adducts

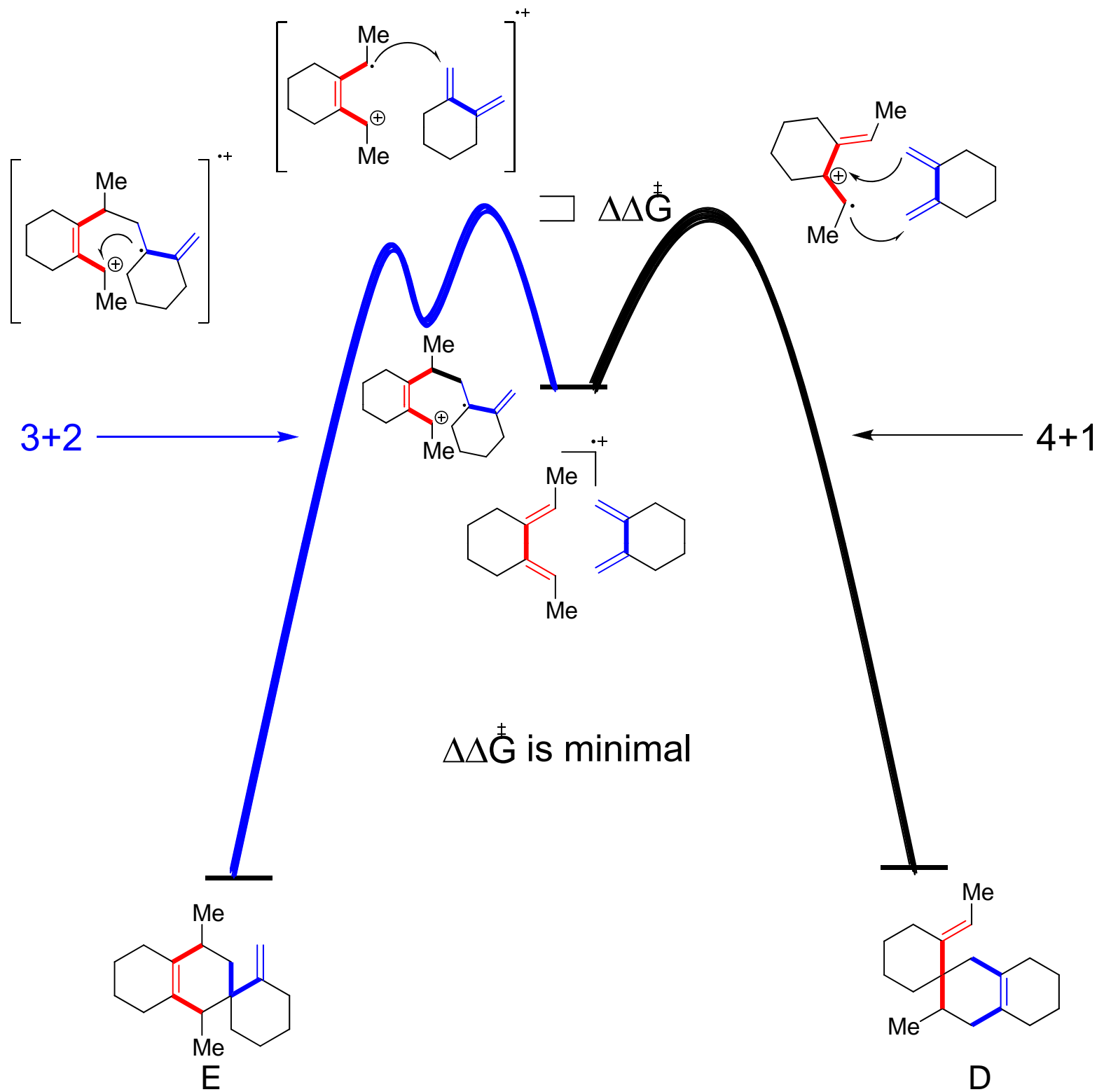
When both 4+1 and 3+2 pathways are possible, a 4+1 does not necessarily dominate



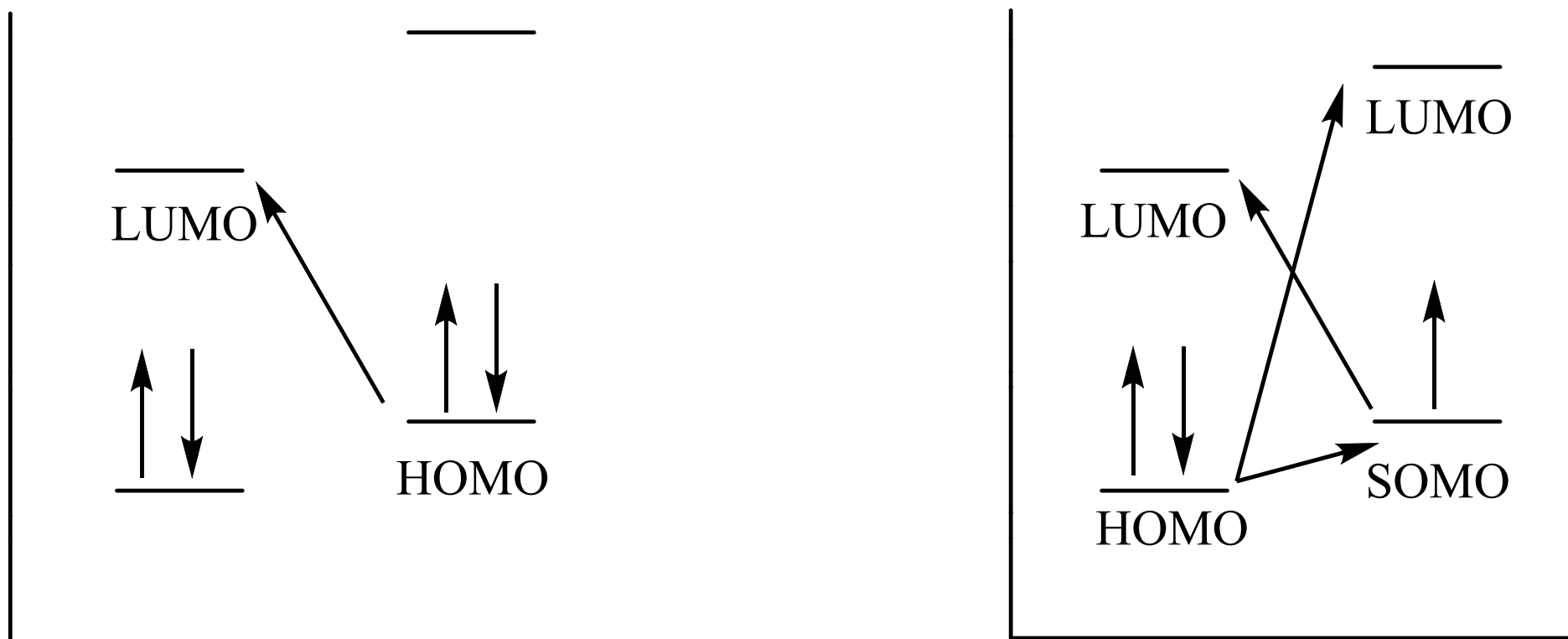


# Similar 4+1 and 3+2 Adducts





# Why Would a 3+2 Happen When a 4+1 Could?

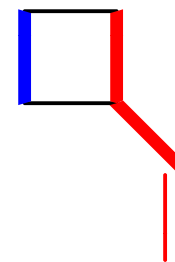
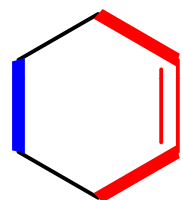


SOMO MO diagrams have increased complexity – simple symmetry analysis not necessarily correct

# 4+1 vs. 3+2

- 4+1
  - Can be concerted
  - Due to SOMO interactions, can be disfavored
  - Requires diene and dieneophile to be identical OR the dieneophile to have a lower redox potential
- 3+2
  - Stepwise

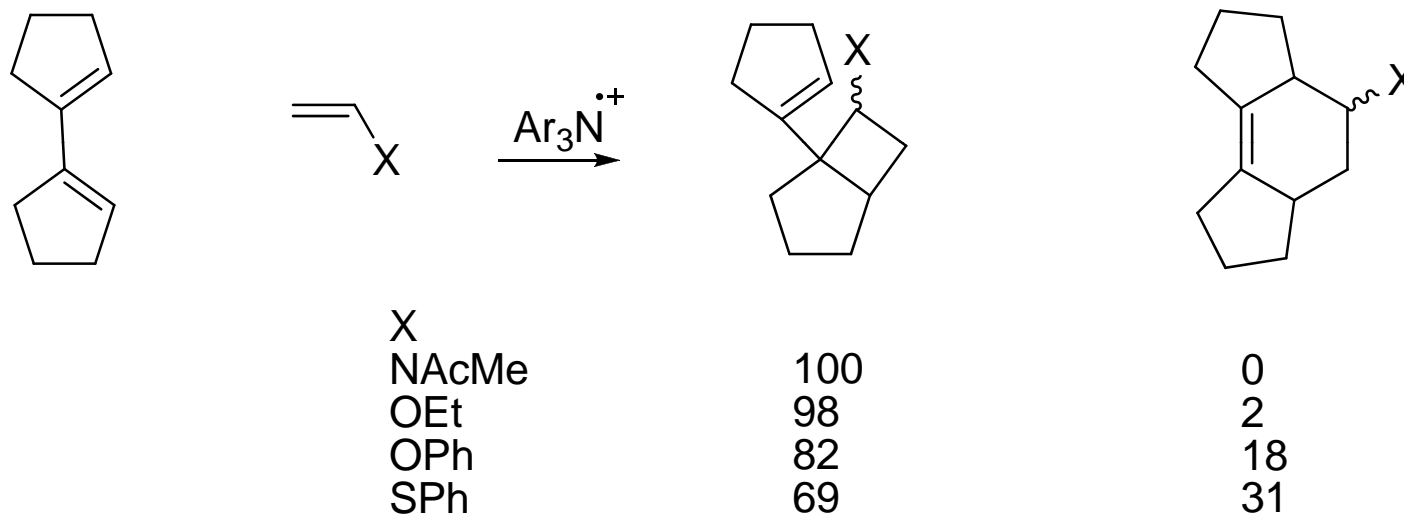
# When Diels-Alder and when cyclobutanation?



Diels-Alder

cyclobutanation

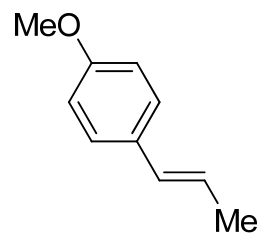
# Varying electron density on olefin



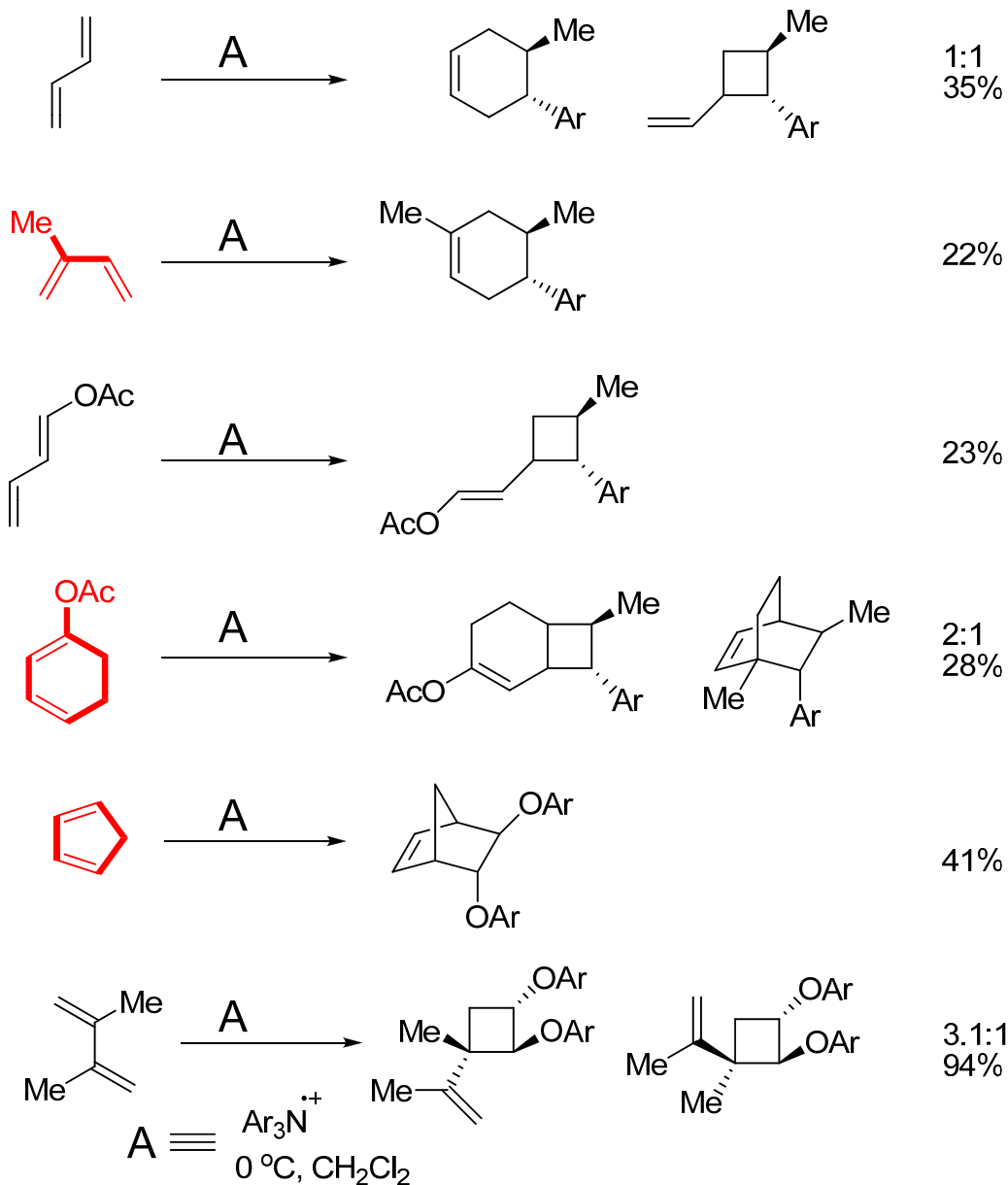
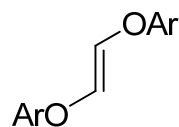
More electron rich olefins yield cyclobutane products

# Diene Conformation

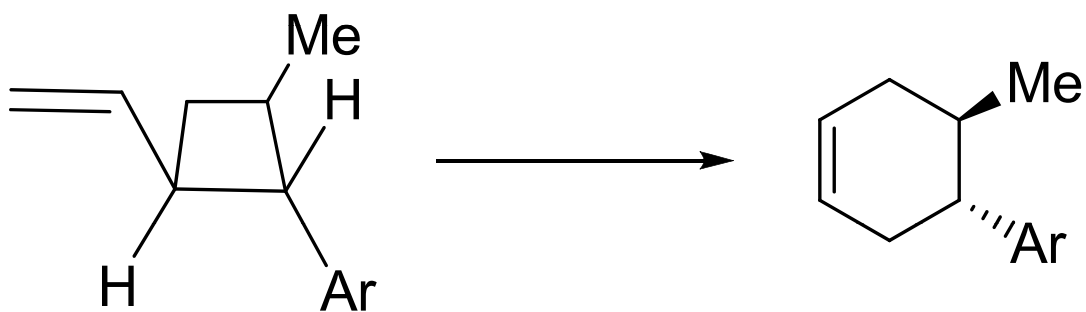
red olefins have high degree of *s-cis* character



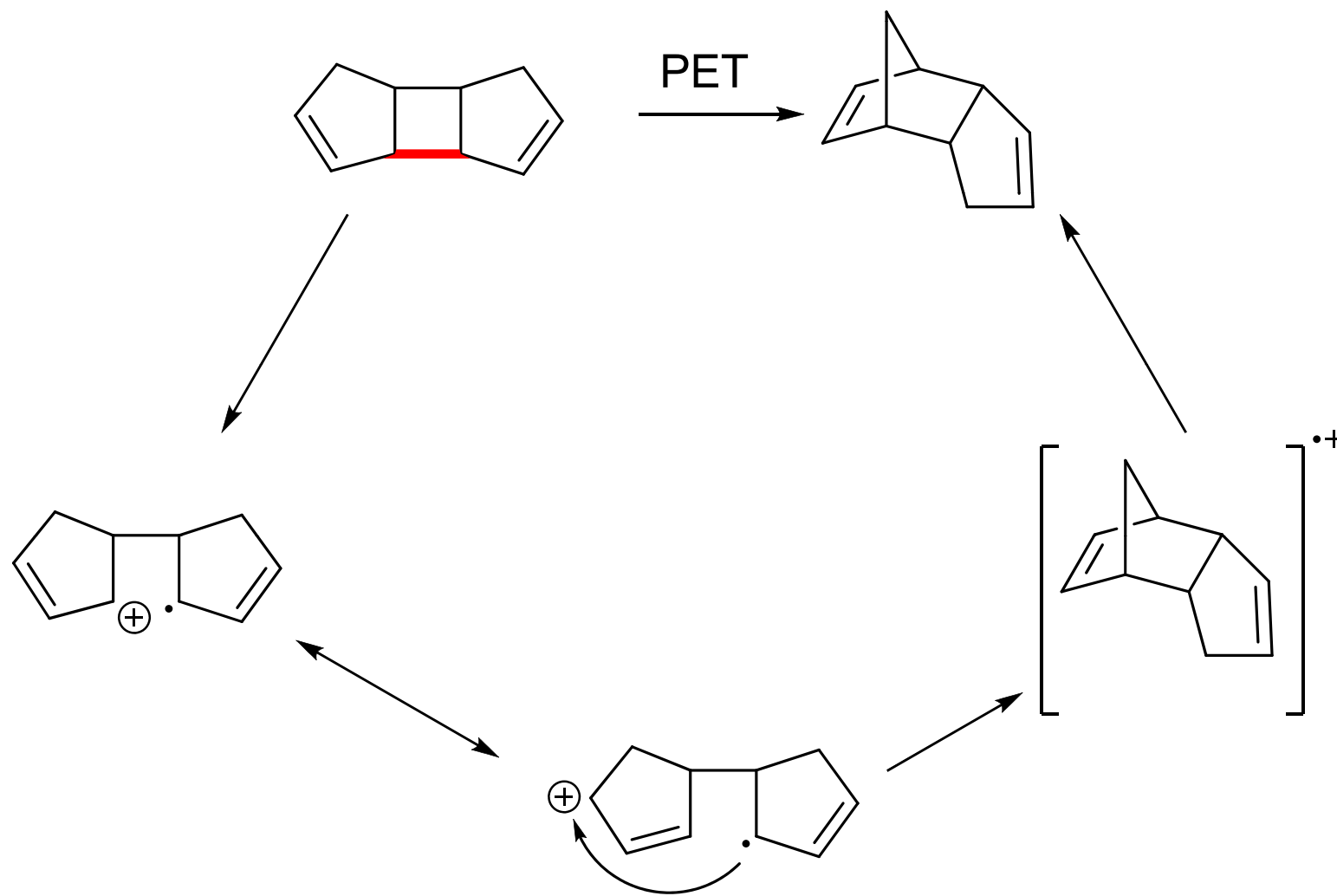
*s-cis* dienes favor Diels-Alder products



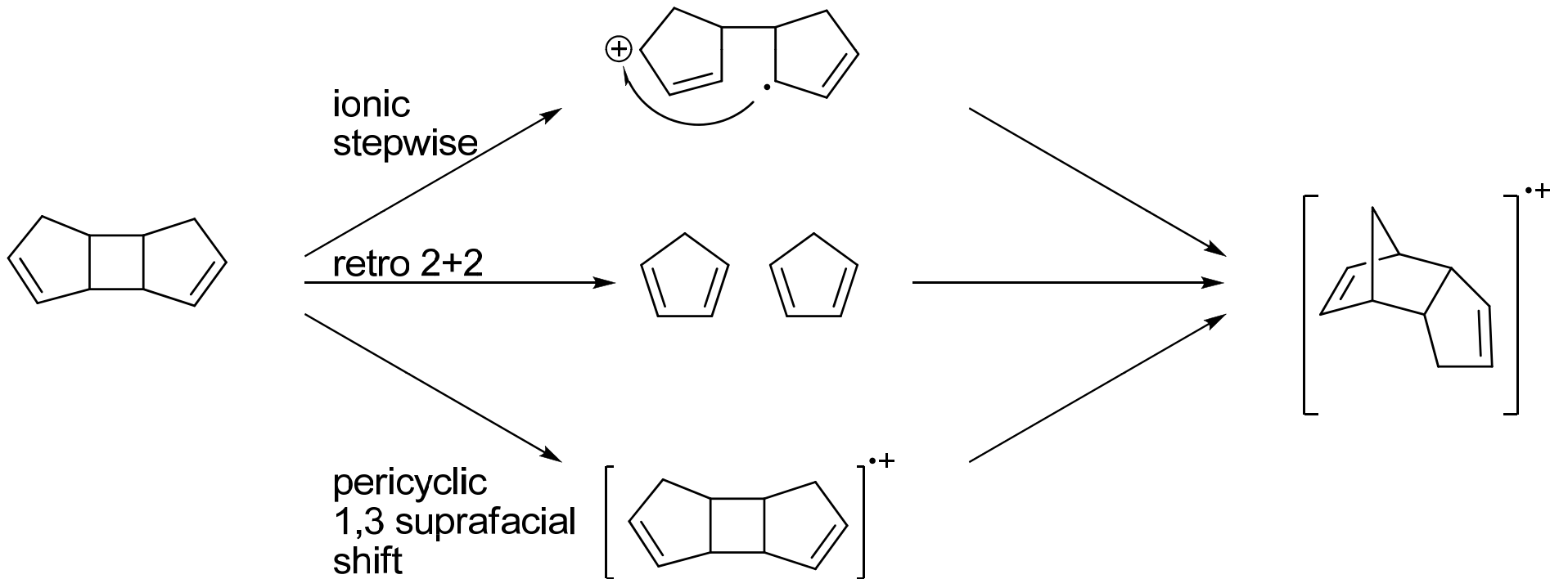
# Vinylcyclobutane (VCB) rearrangement



# PET Induced Vinylcyclobutane Rearrangement

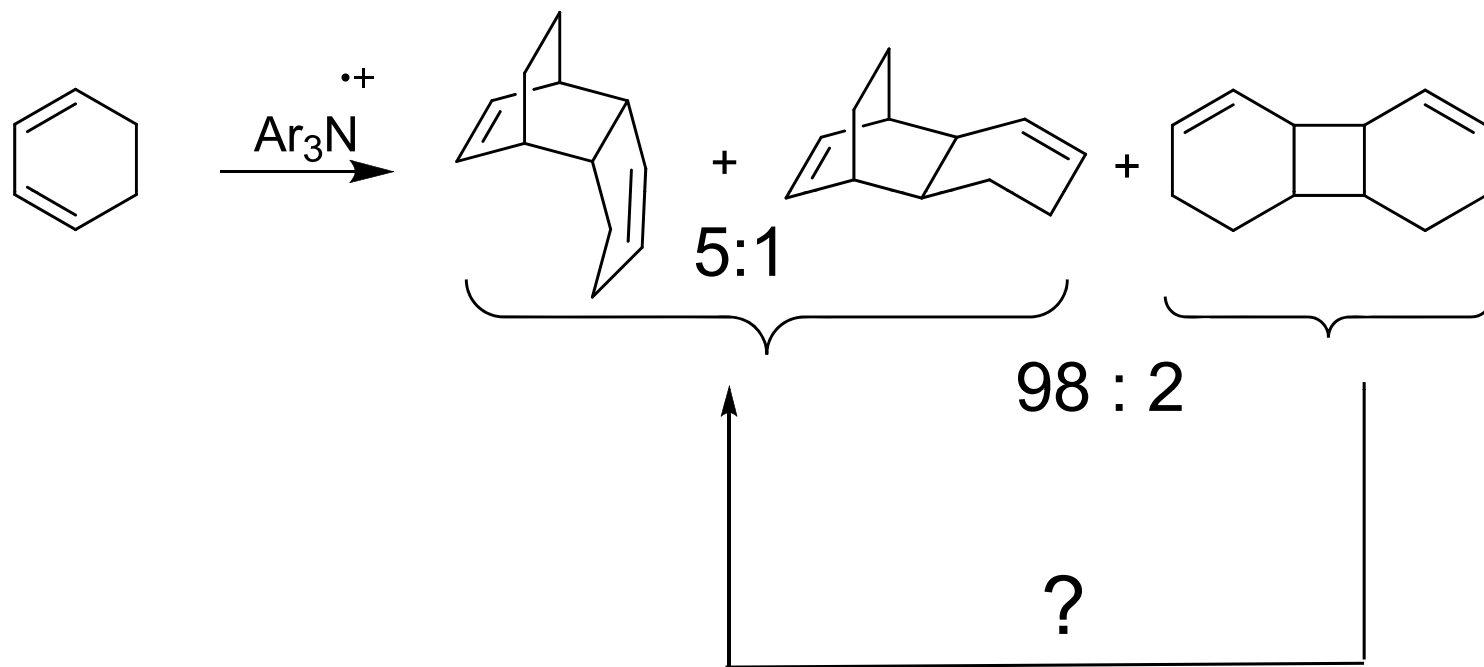


# Alternatives

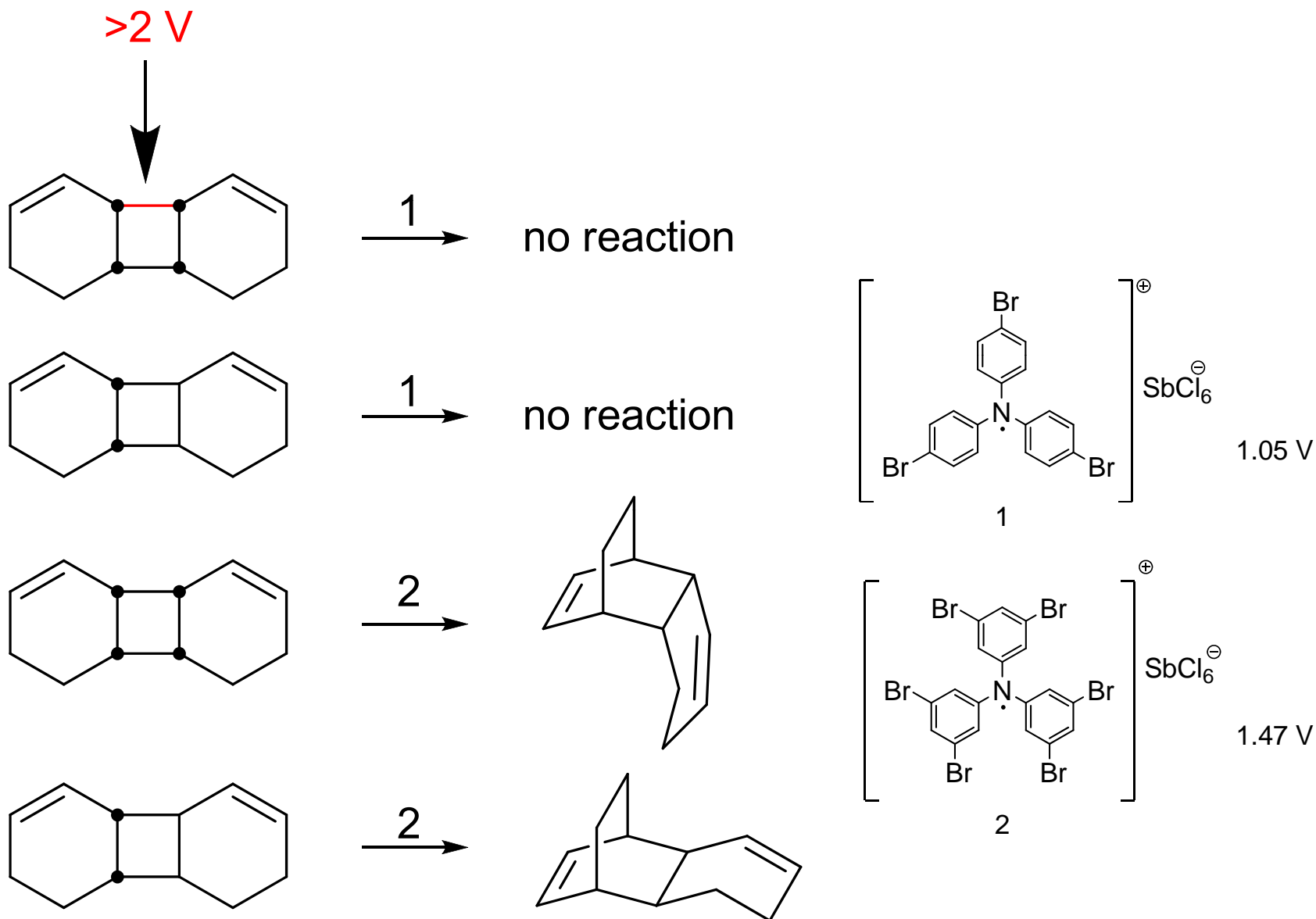




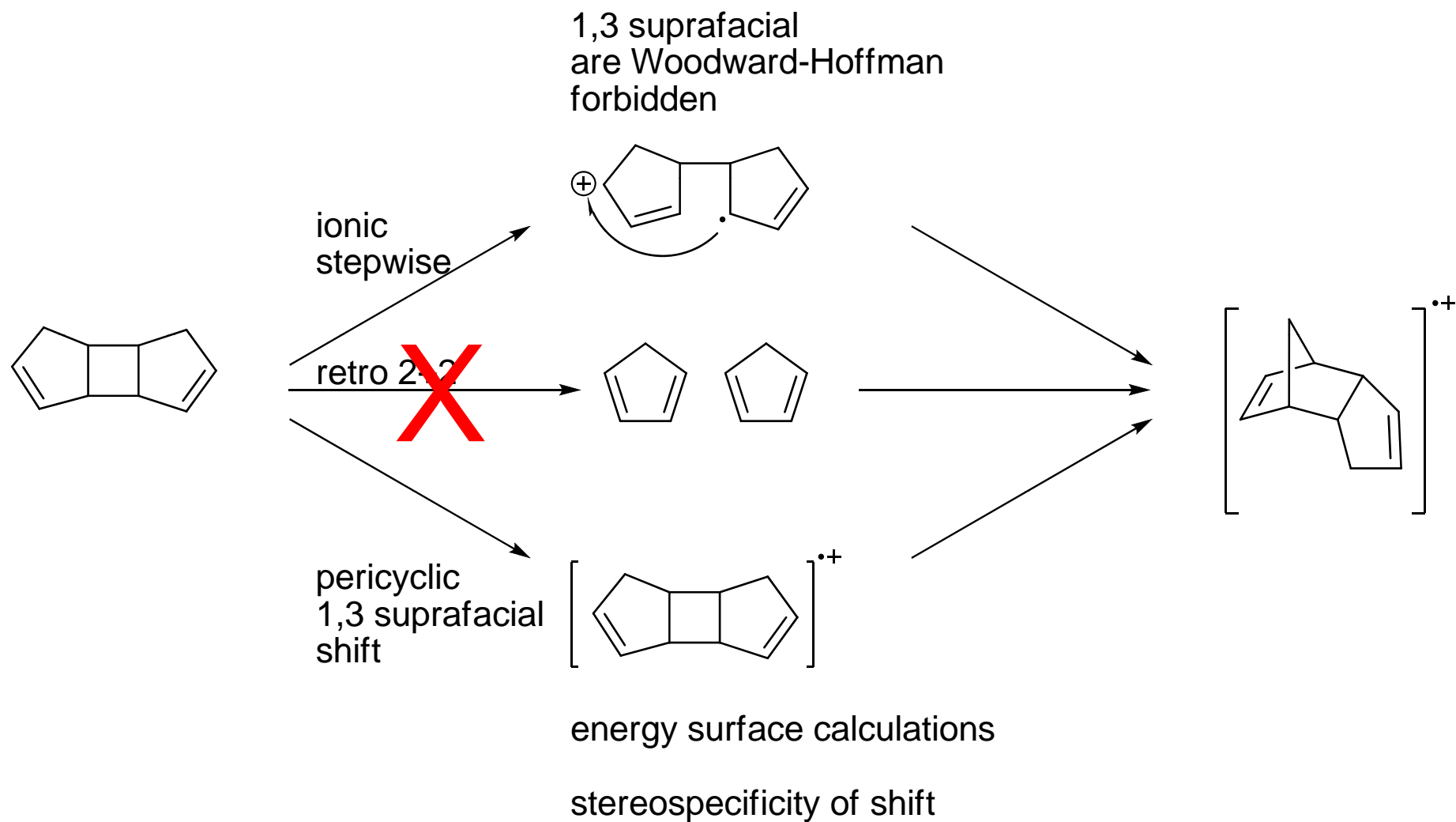
# Could all ETC Diels-Alder products be from VCB rearrangements?



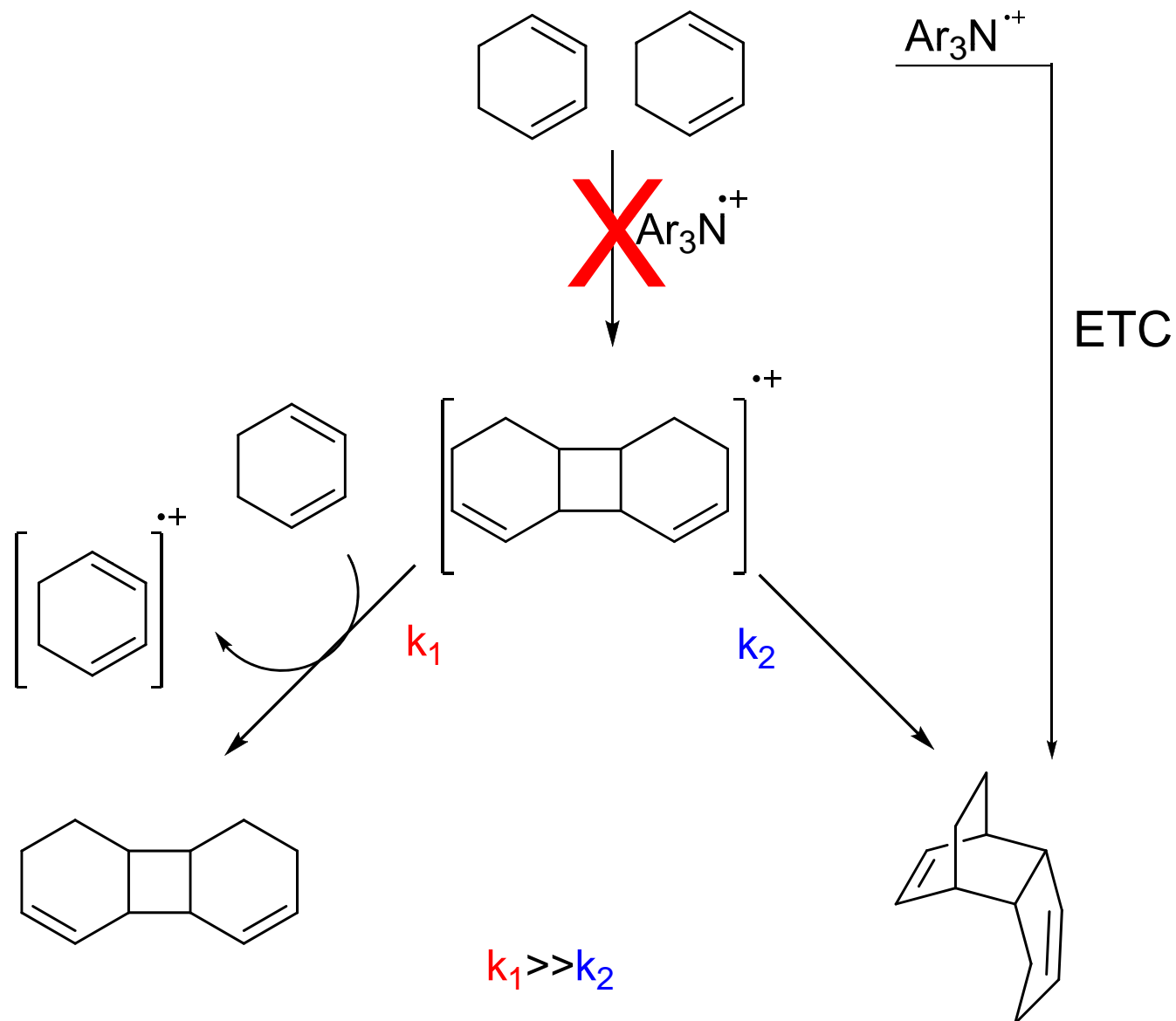
# Rearrangement is Stereospecific



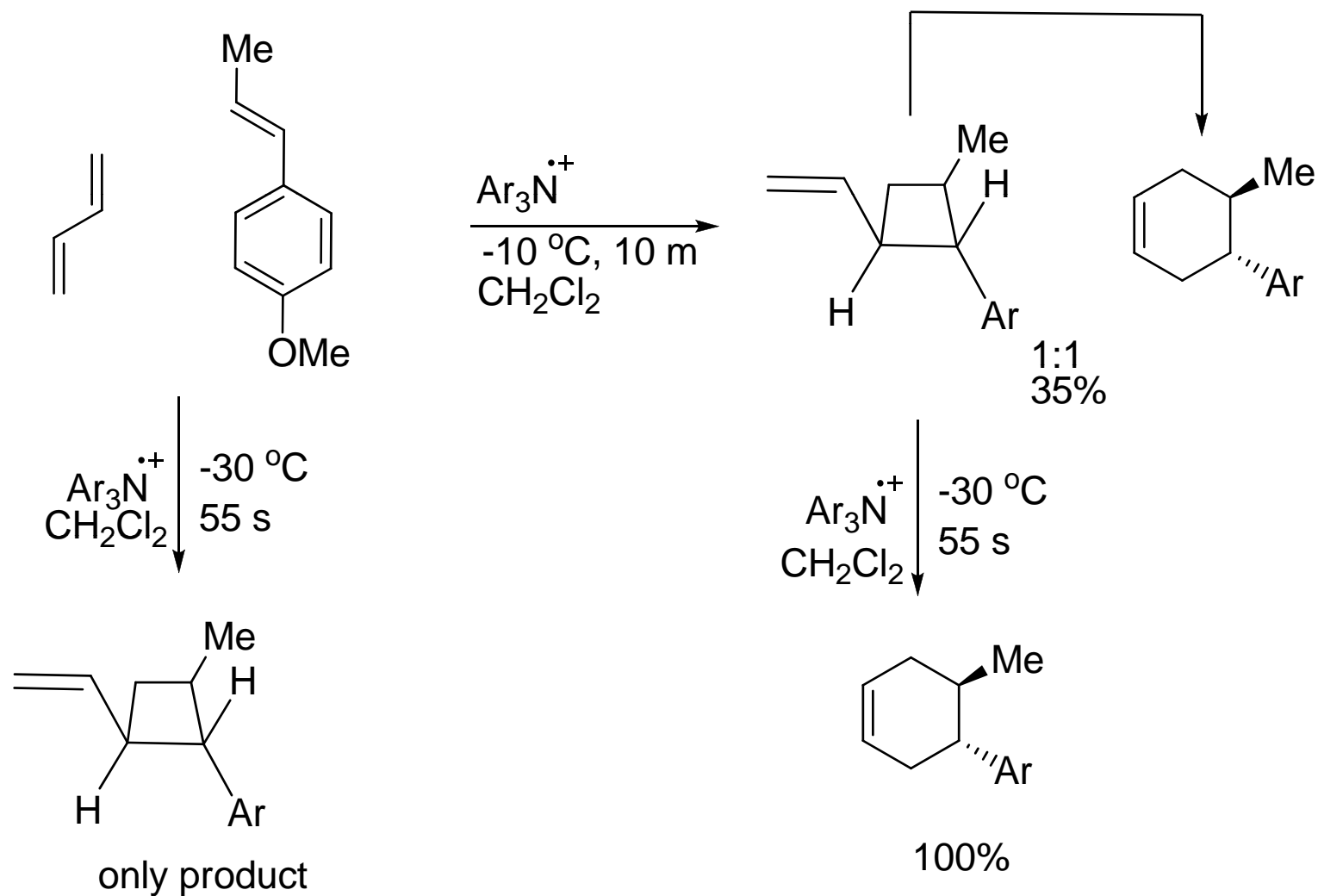
# Intramolecular Shift



# Quenching vs. Rearrangement

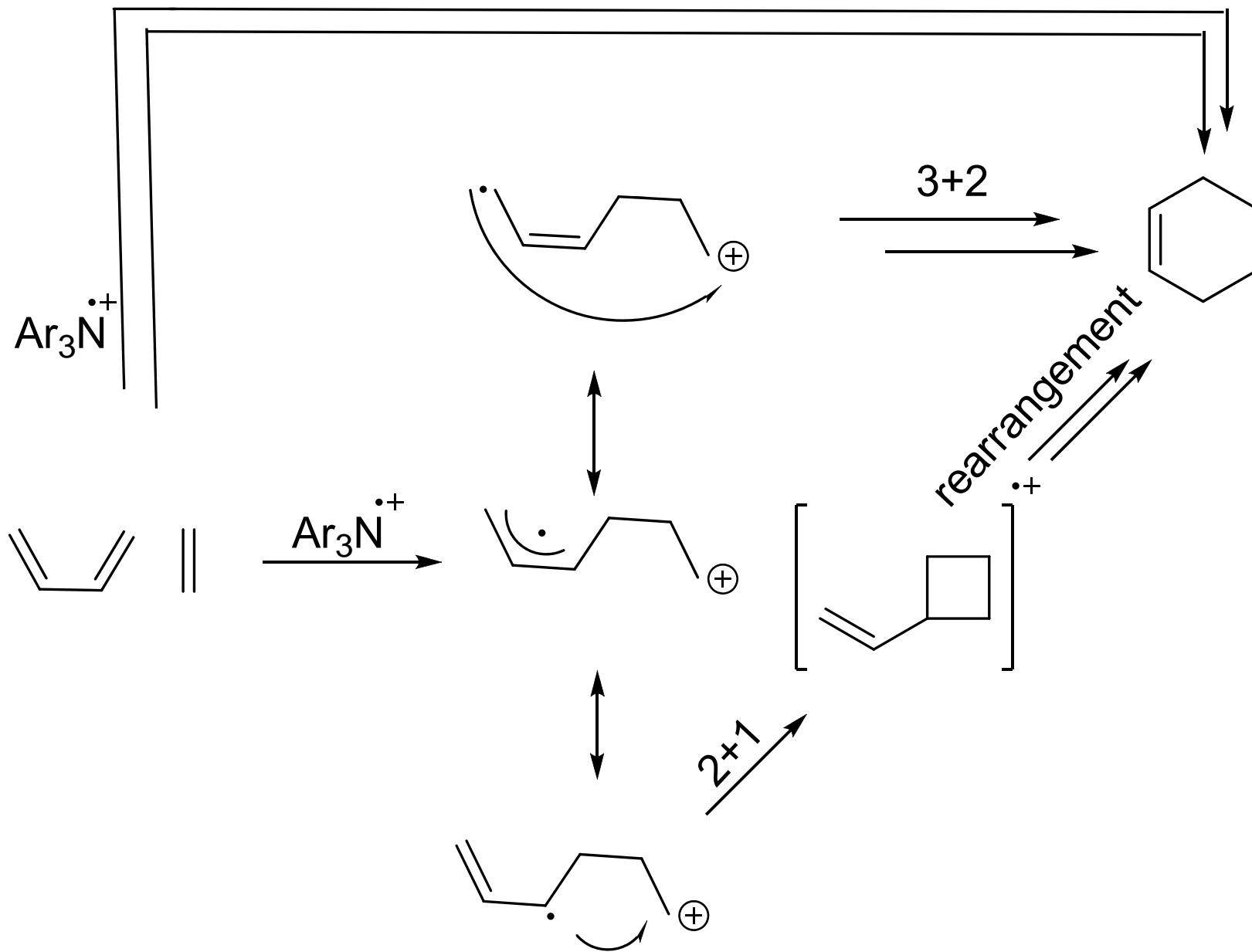


# VCB Rearrangement to DA Product

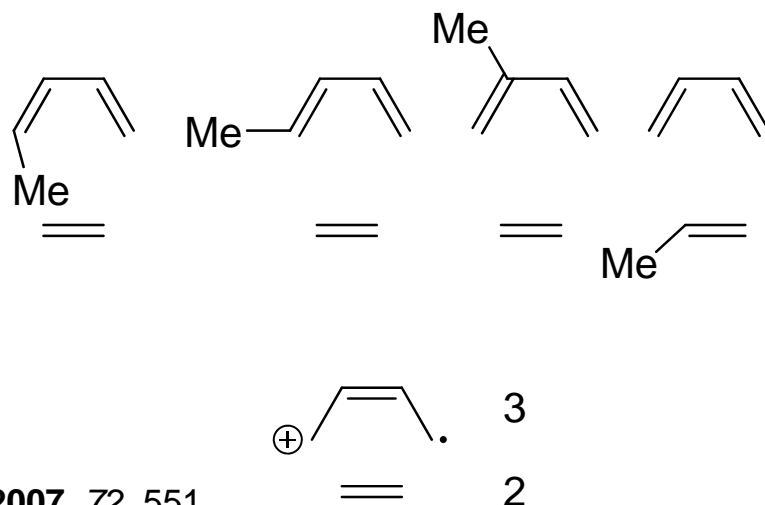
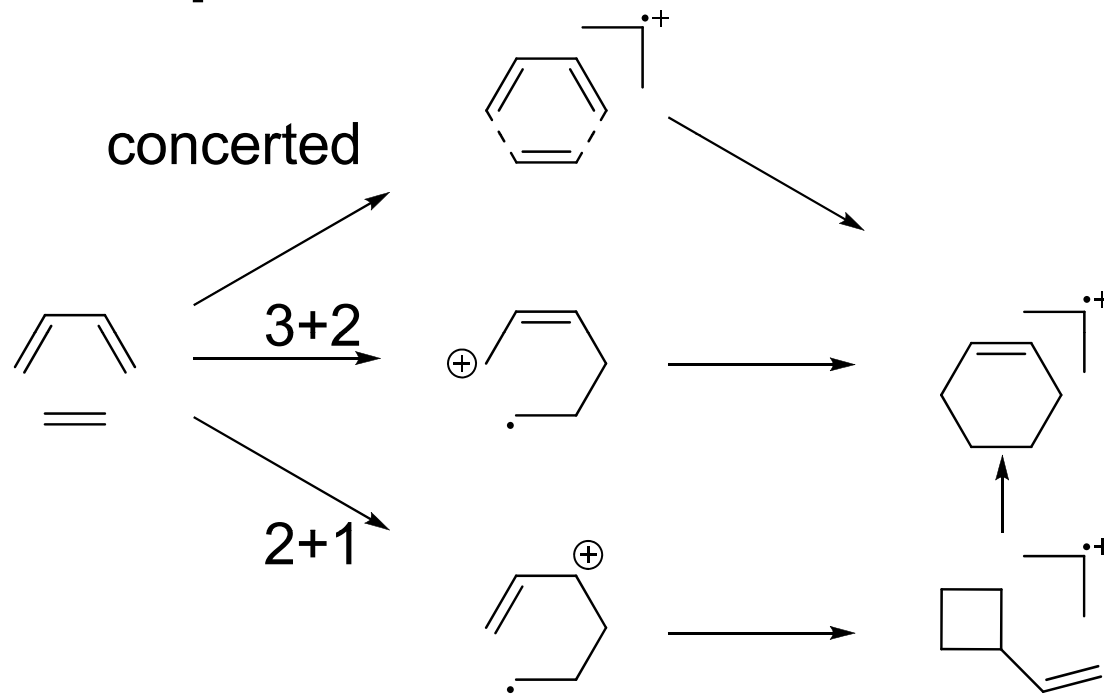


# Three Pathways

4+1



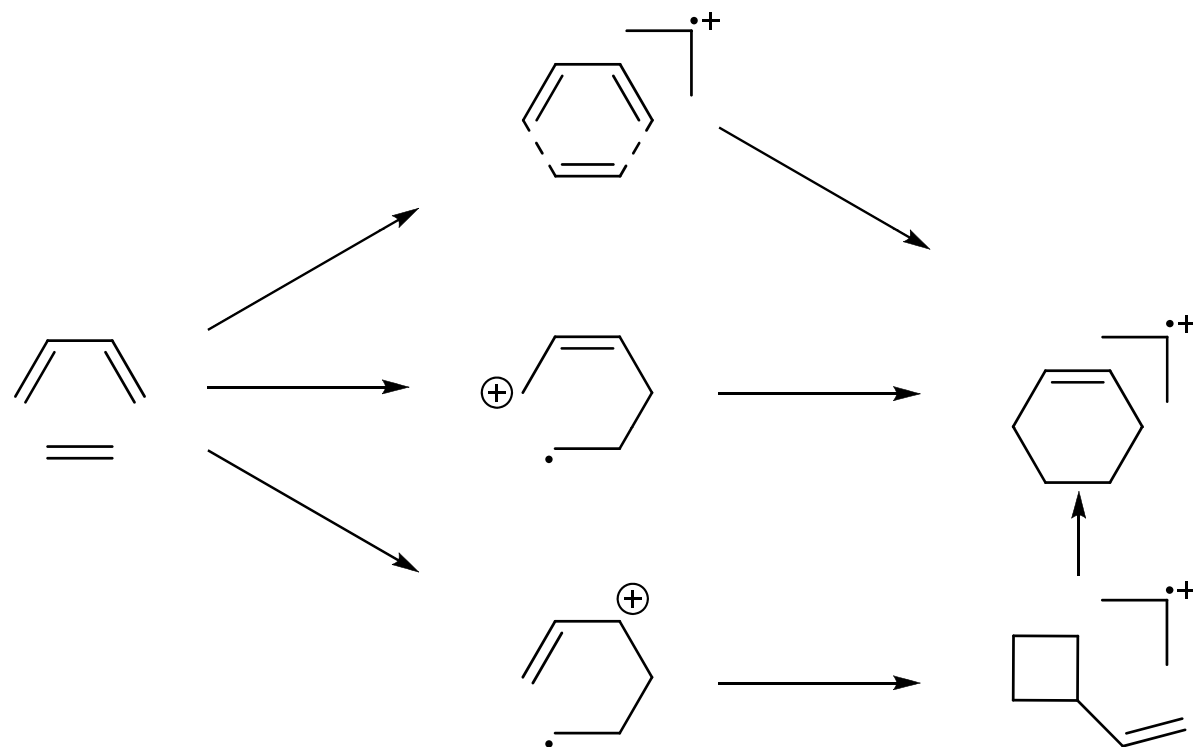
# Computational Chemistry



# DA Conclusions

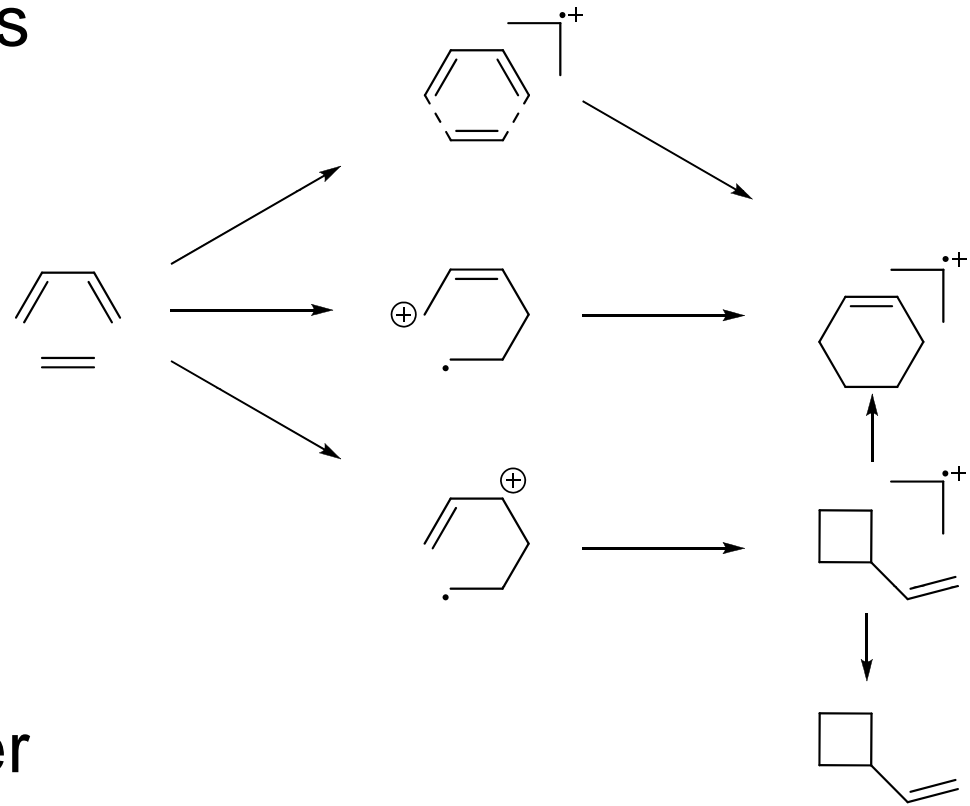
- Diels-Alder products can be formed through several pathways

- 4+1 concerted
- 3+2 stepwise
- Vinylcyclobutane rearrangement



# Overall Conclusions

- Formal 2+2 and 4+2 products can be made via ETC
- ETC cycloadditions allow access to Diels-Alder and Cyclobutane products under milder conditions
- Multiple pathways possible due to flat energy surface
- ETC cycloadditions are under explored by synthetic organic chemists



# Acknowledgements

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