# Alkene Radical Cation

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**College of Chemistry and Molecular Engineering**
**March 19th 2022**

# Outline

- **Introduction**
- **Nucleophilic Addition**
  - Development
  - Regioselectivity: attempt to rationalize
- **Cycloaddition**
  - [2+2]
  - [4+2]
- **Bond Cleavage**
- **Summary**
- **Acknowledgement**

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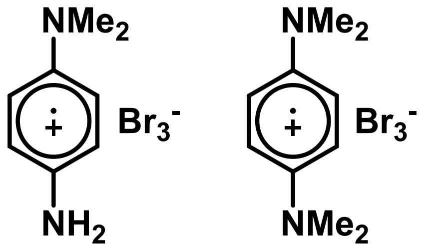
# Selected Milestones of Radical Cation

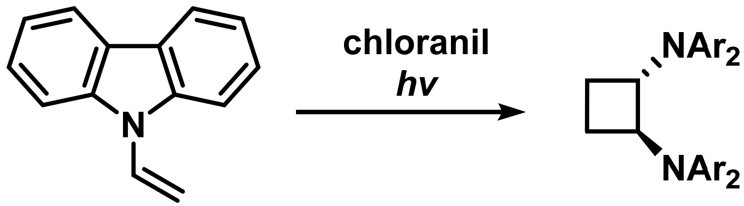
Stable cation radical salts were first isolated
**1879**

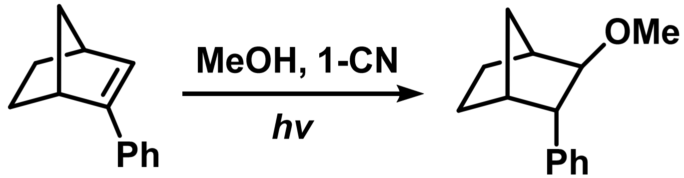



**Wurster's Salts**

Weitz coined the term 'cation radical'
**1926**

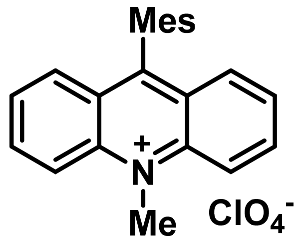
**1964**
Dimerization of NVC was disclosed by Ellinger




Arnold discovered nucleophilic attack on alkene cation radical
**1975**

**2012**
Nicewicz used acridinium as photocatalyst



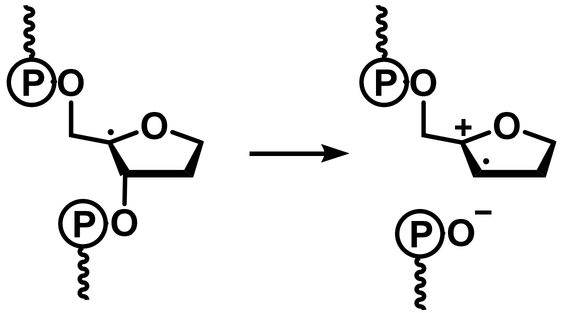
# Generation

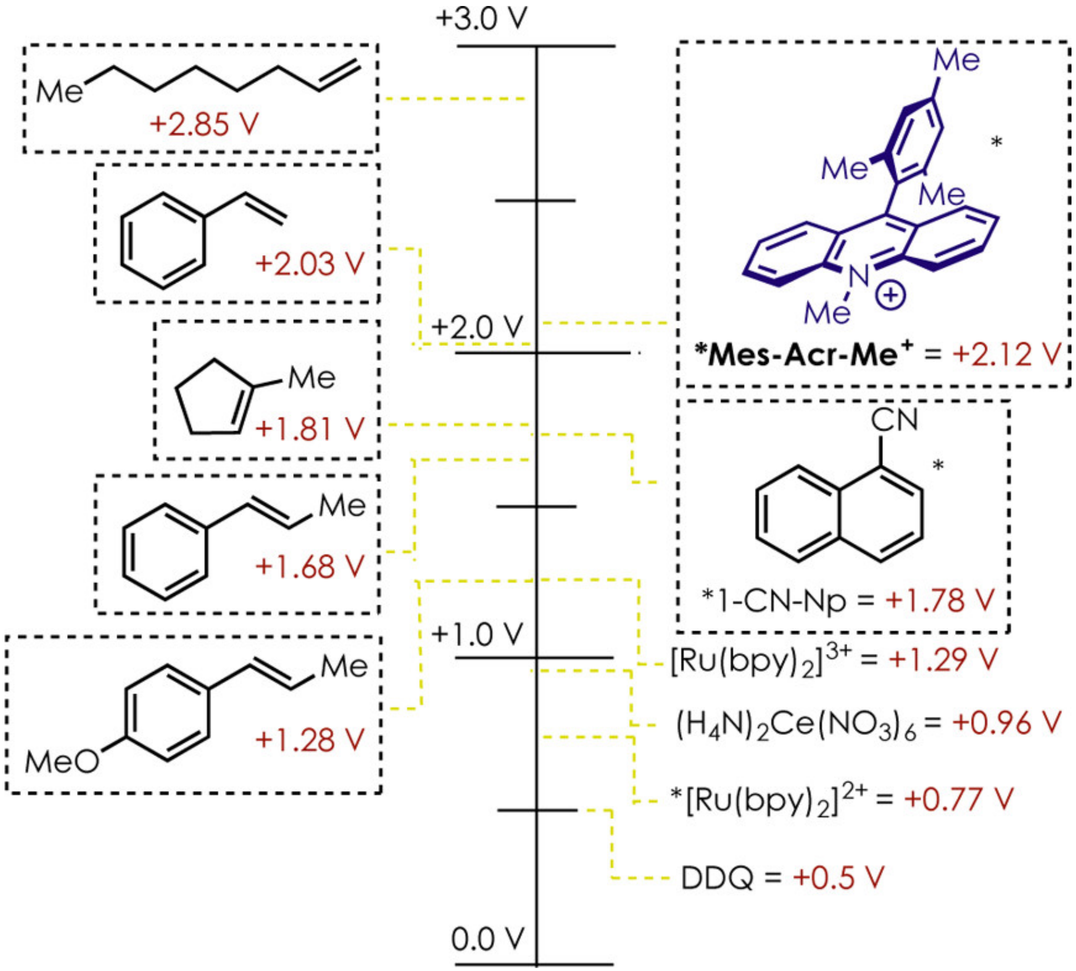
- Chemical Oxidation
- PET

$$\text{Sens} \xrightarrow{h\nu} [\text{Sens}]^* \xrightarrow{\text{S}} \text{S}^{\bullet+} + [\text{Sens}]^{\bullet-}$$

$$\text{D} + \text{A} \rightleftharpoons [\text{D,A}] \overset{h\nu}{\rightleftharpoons} [\text{D}^{\bullet+}, \text{A}^{\bullet-}]$$

- Anodic Oxidation
- Radiolytic Oxidation
- Spin-center Shift

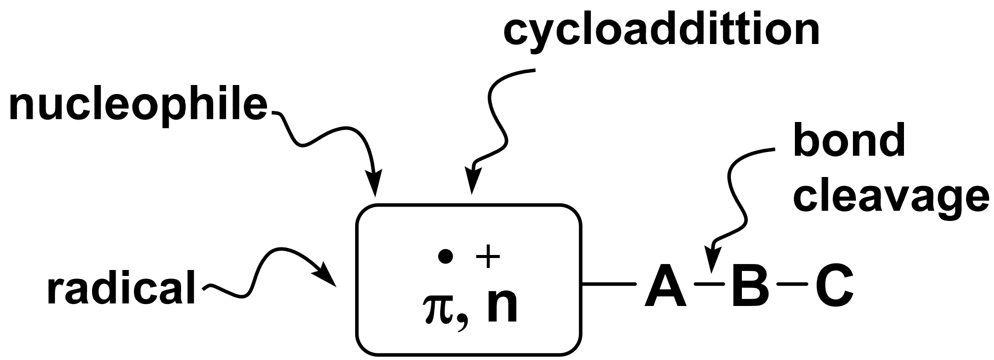





Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997.

Giese, B. *et al*. *Angew. Chem., Int. Ed*. **1993**, *32*, 1742.

# General Reactivity




Schmittel, M.; Burghart, A. *Angew*. *Chem*., *Int*. *Ed*. **1997**, *36*, 2550.

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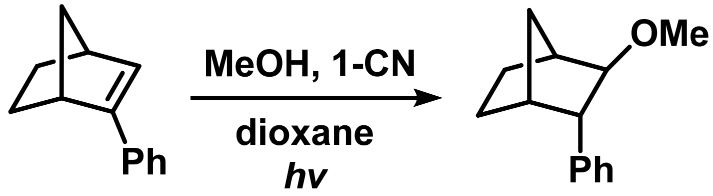
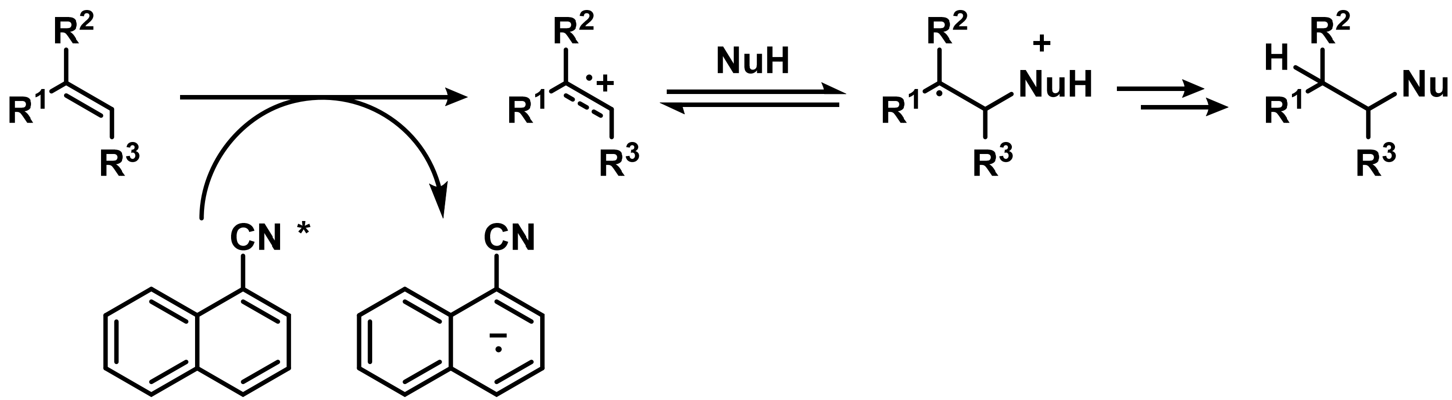
# *Anti*-Markovnikov Selectivity

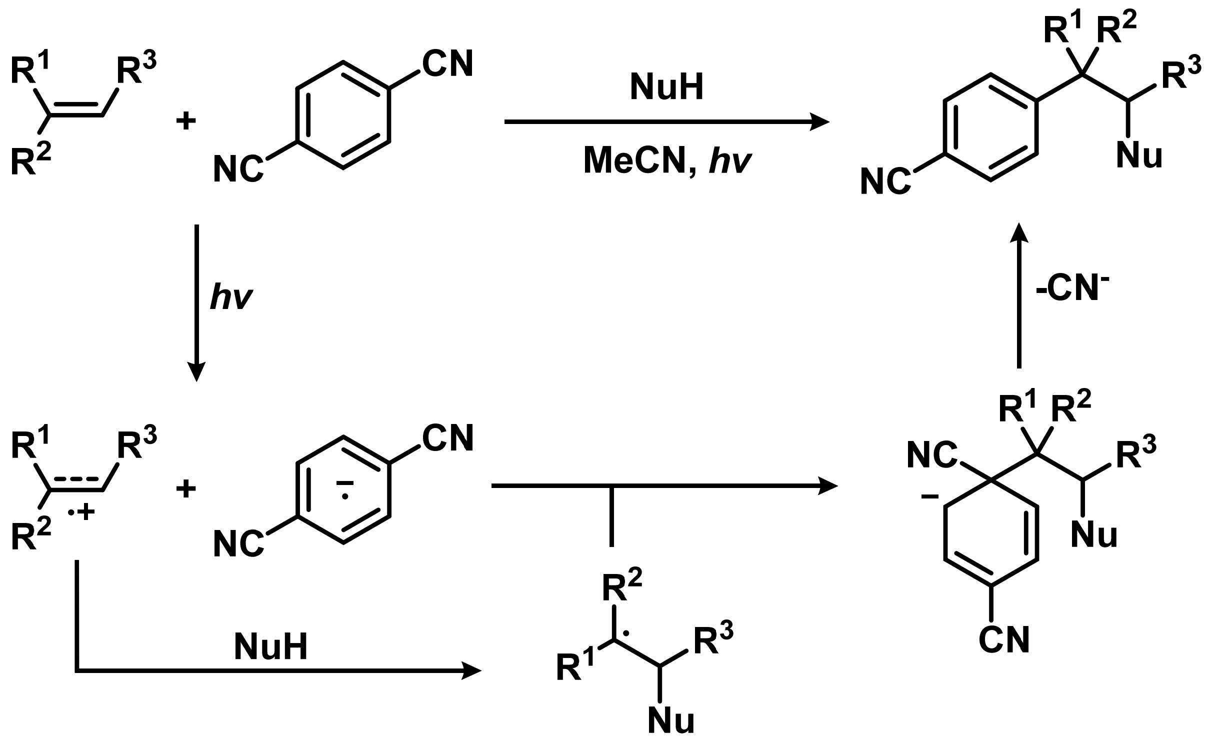



Shigemitsu, Y.; Arnold, D. R. *J. Chem. Soc., Chem. Comm.* **1975**, 407.

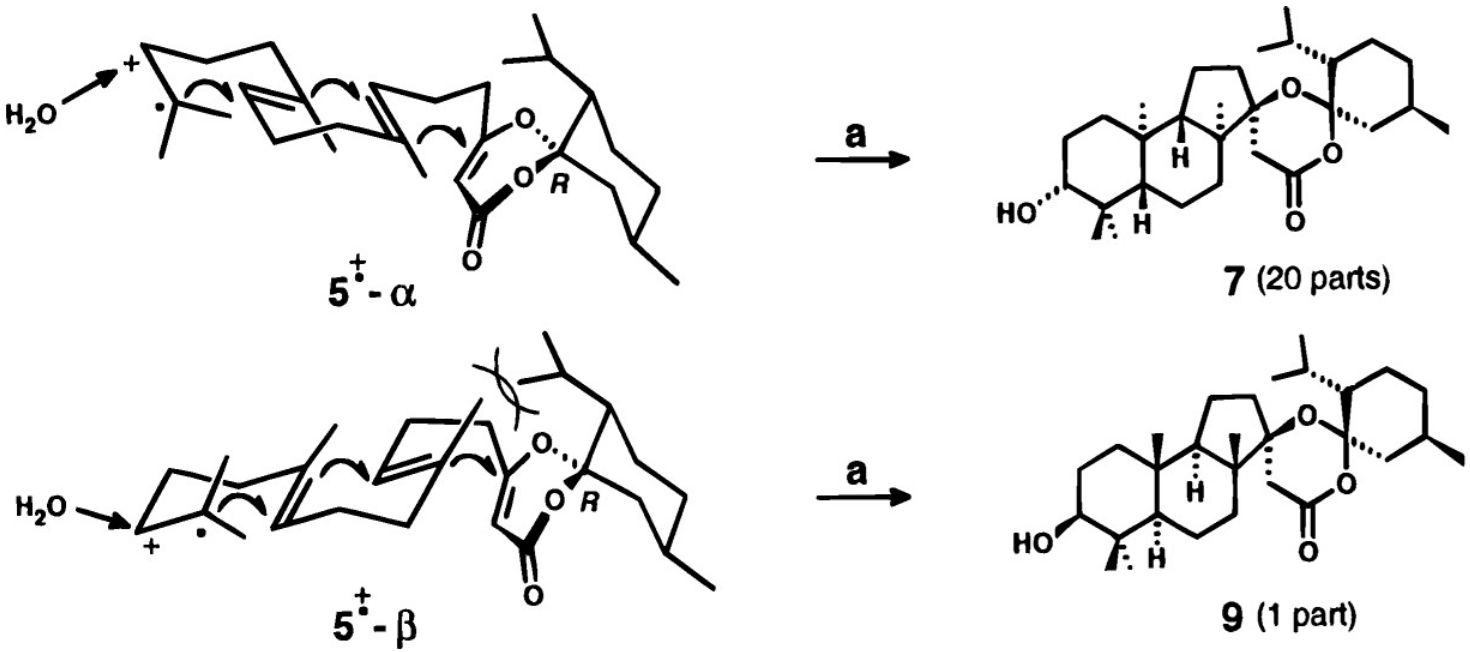
# Photo-NOCAS Reaction

The photochemical nucleophile-olefin combination, aromatic substitution reaction




Mangion, D.; Arnold, D. R. *Acc. Chem. Res.* **2002**, *35*, 297.

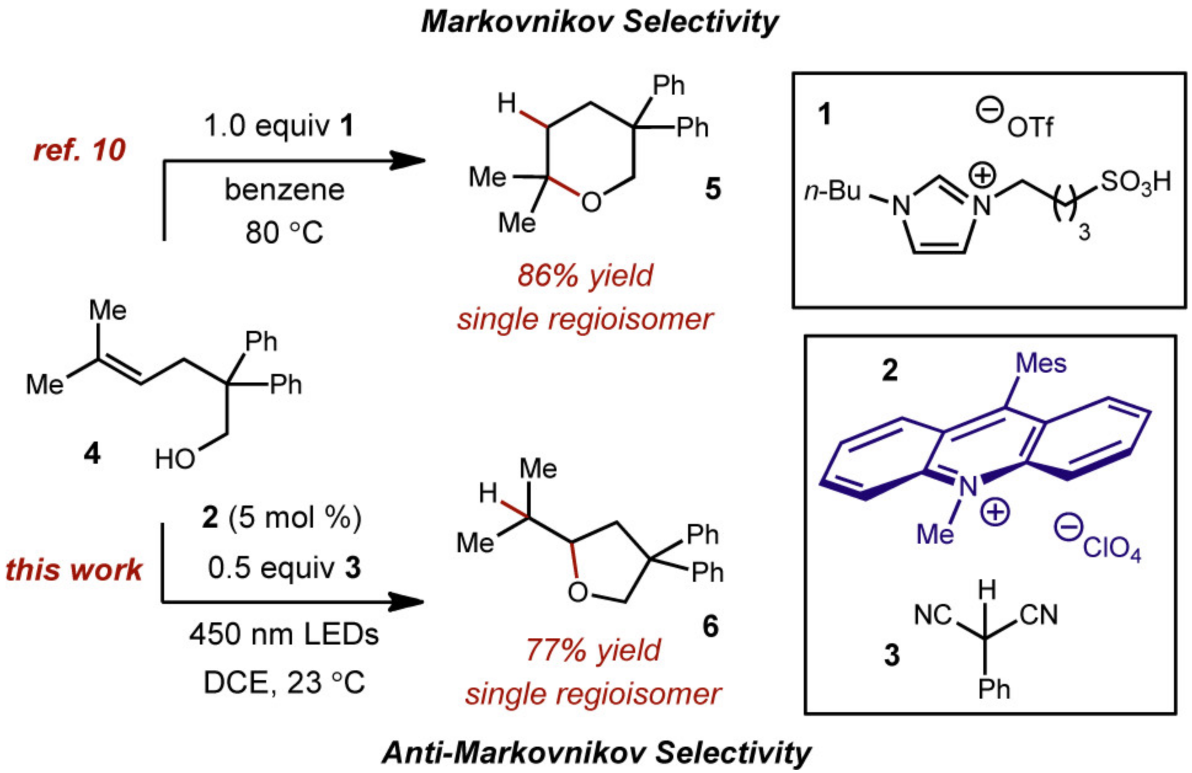
# Radical Cascade Initiator



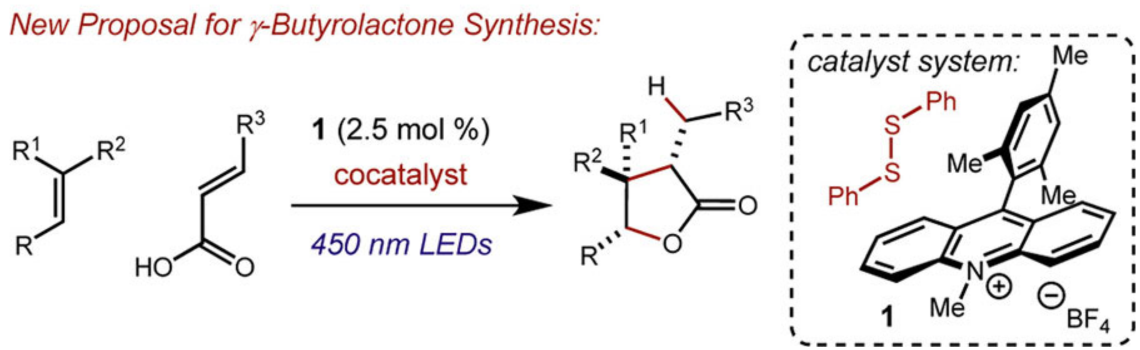

(a) biphenyl, 1,4-dicyano-2,3,5,6-tetramethylbenzene, *hv* (300 nm), MeCN/H2O 10:1

Demuth, M.; Heinemann, C. *J. Am. Chem. Soc.* **1997**, *119*, 1129.

# Hydrofunctionalization & Cyclization

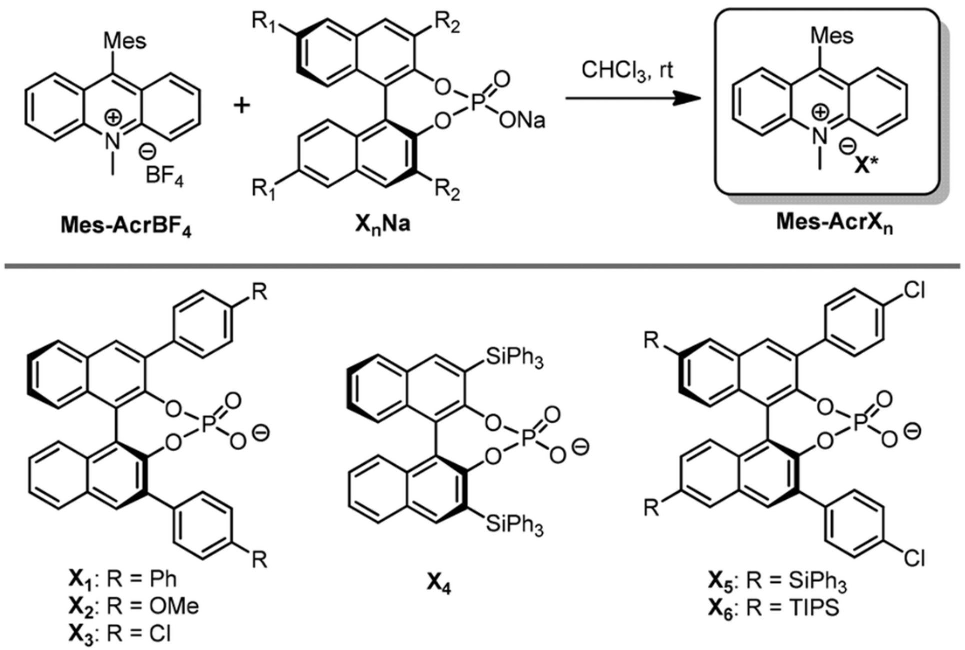


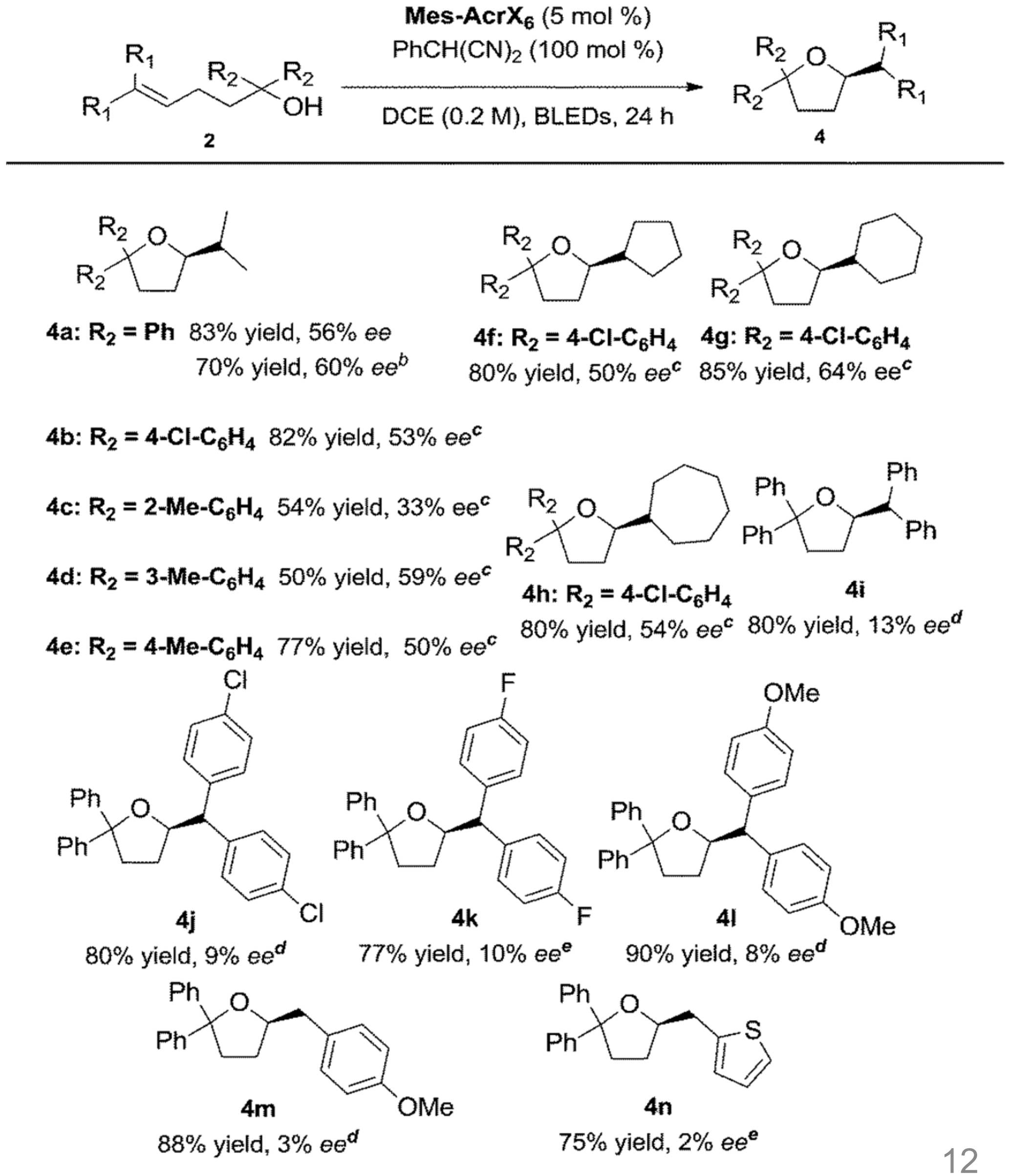

Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577.




Zeller, M. A.; Reiner, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810.

# Asymmetric Hydroetherification

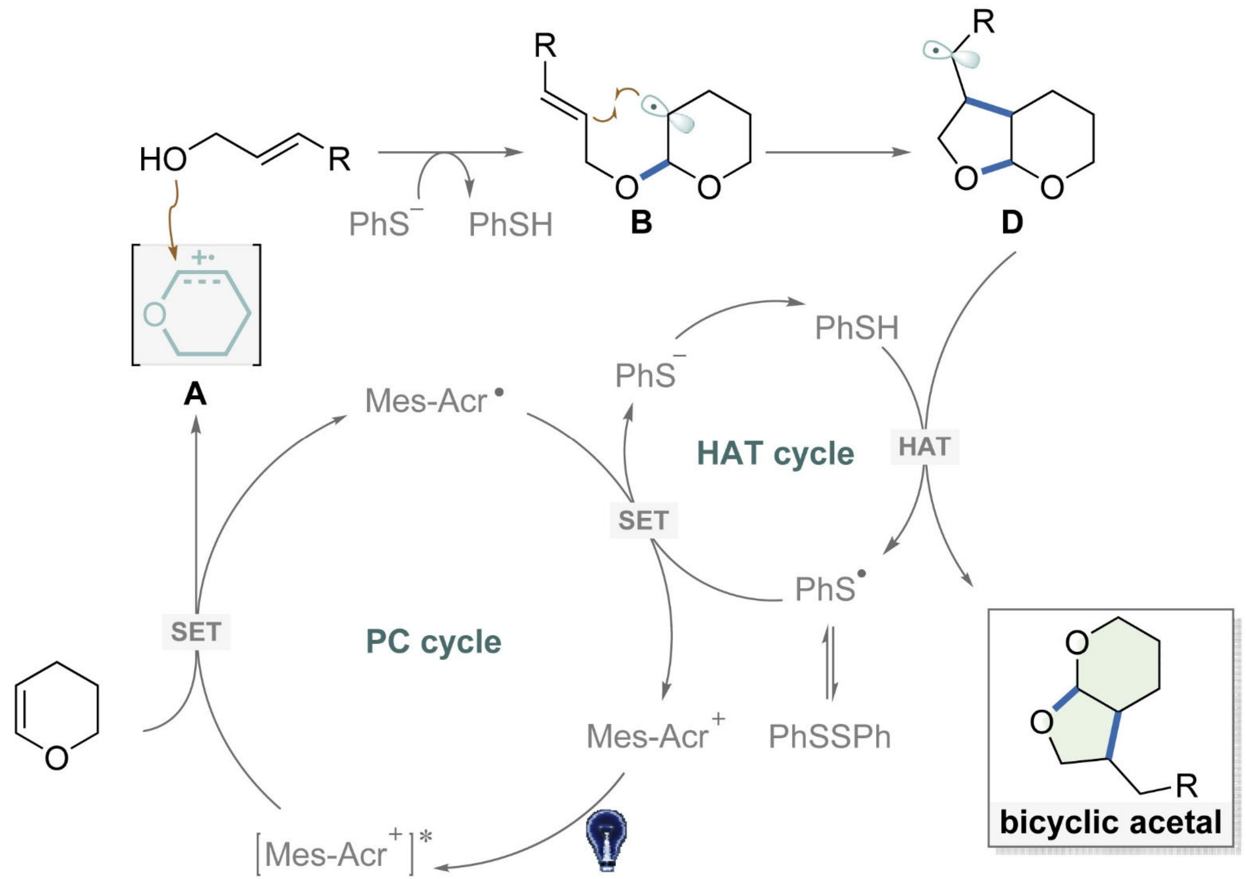



Yang, Z.; Li, H.; Li, S.; Zhang, M.; Luo, S.
*Org. Chem. Front.* **2017**, *4*, 1037.

# Enol Ether: Markovnikov Selectivity

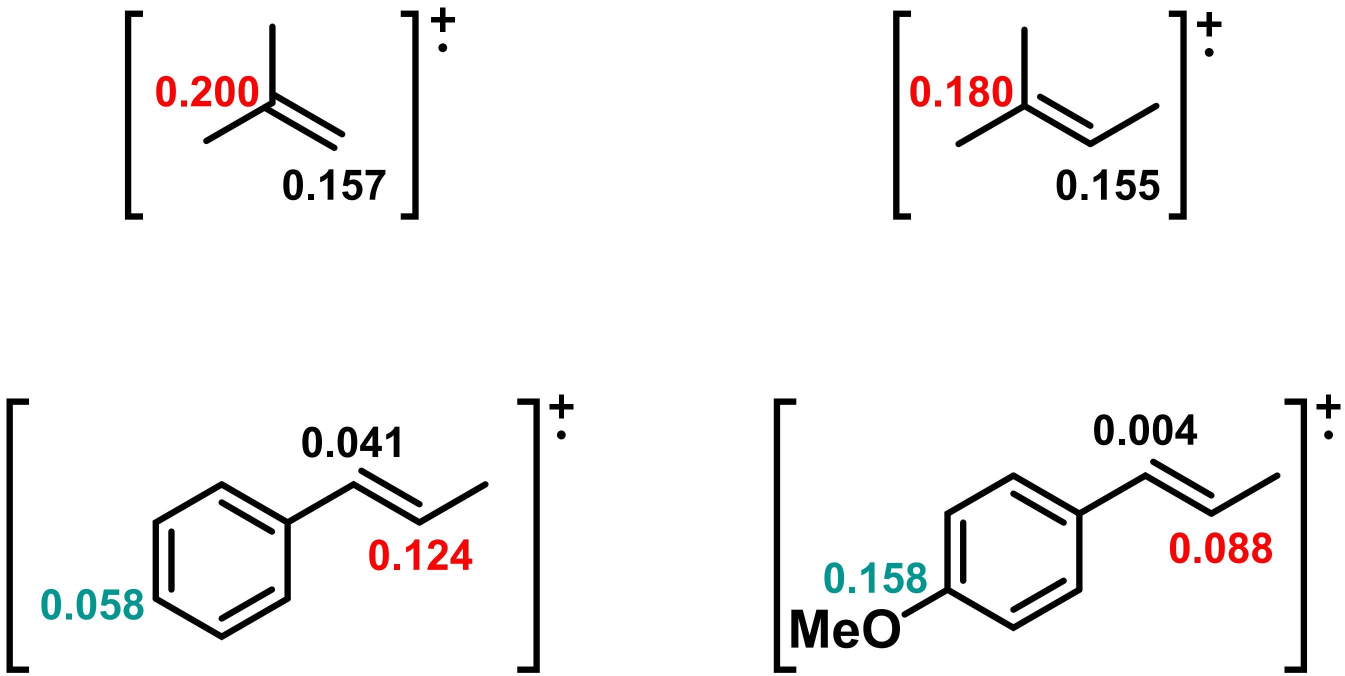
However, when enol ethers act as reactant, Markovnikov adducts predominate.




Wu, F.; Wang, L.; Ji, L.; Zou, G.; Shen, H.; Nicewicz, D. A.; Chen, J.; Huang, Y. *iScience.* **2020**, 101395.

# Selectivity: Electrostatic Control?

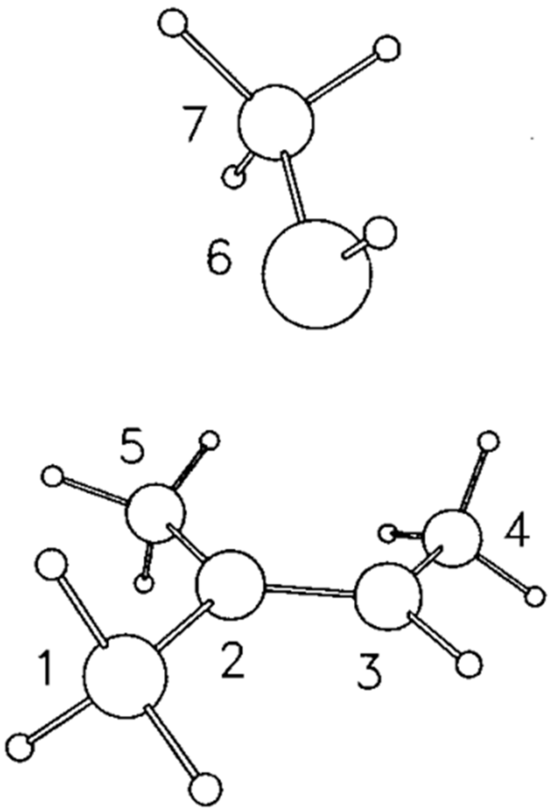
Atomic charge on carbon atoms does not correlate with the selectivity well.



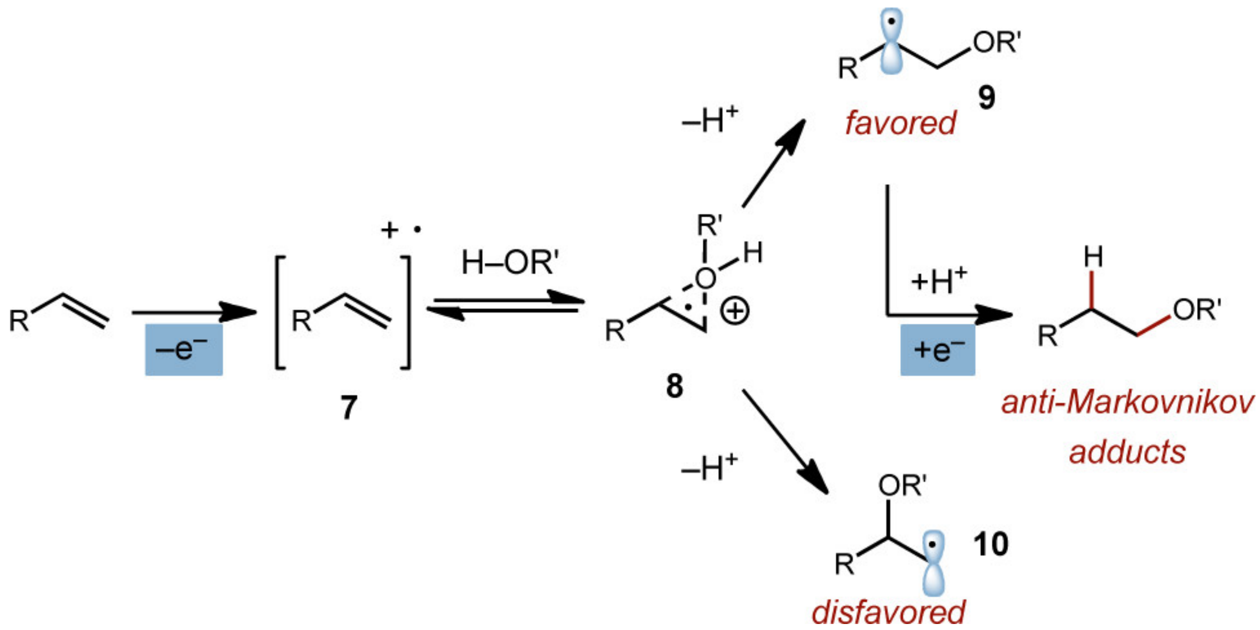

M06-2X-D3/def2-SVP/PCM(DCM)
Hirshfield charge at M06-2X level

# 3-Membered Intermediate

Arnold first proposed a 3-membered intermediate based on his calculation in 1996 .




Arnold, D. R.; Chan, M. S. W.; McManus, K. A. *Can. J. Chem.* **1996**, *74*, 2143.




"It is likely that the observed anti-Markovnikov selectivity results from the rupture of the weaker of the two C−X bonds, giving rise to the more stable radical intermediate."

Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577.

# 3-Membered Intermediate

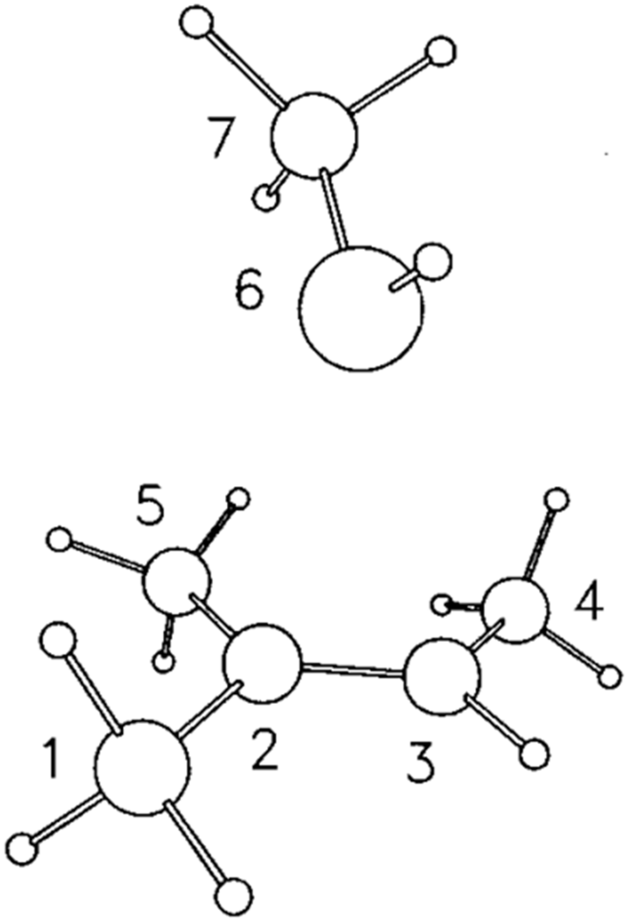


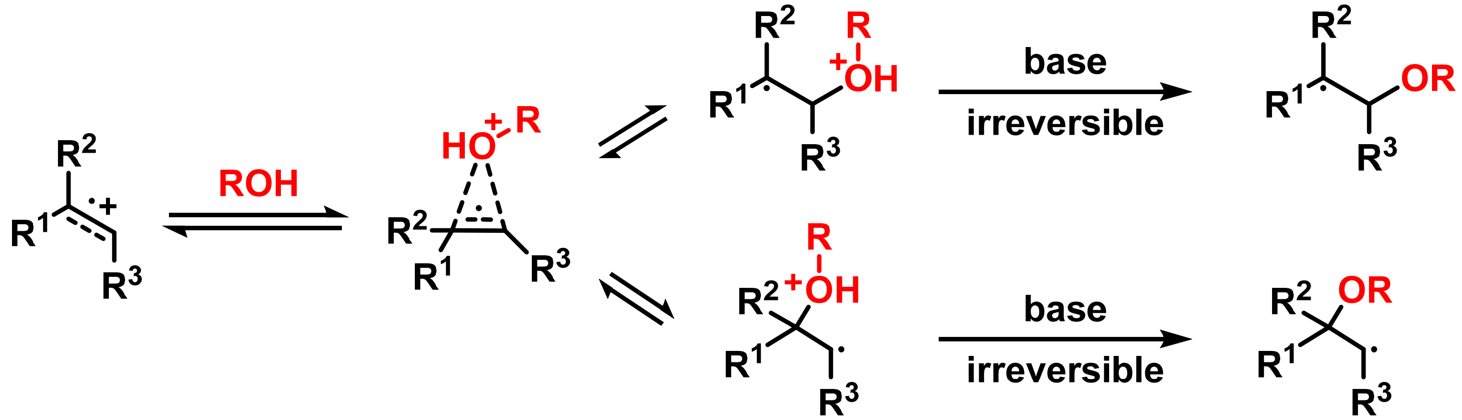

**Table 11.** (*a*) Optimized (UHF/6-31G*) structure for the 2-methyl-2-butene–methanol bridged radical cation (**6c**$^{+\bullet}$).

| Bond length (Å) | | Bond angle (deg) | | Dihedral angle (deg) | |
|---|---|---|---|---|---|
| C1—C2 | 1.488 | C1C2C3 | 120.2 | C1C2C3C4 | 179.0 |
| C2—C3 | 1.411 | C1C2C5 | 118.0 | C3C2O6C7 | 118.6 |
| C2—C5 | 1.489 | C2C3C4 | 126.2 | C2C3O6C7 | −89.0 |
| C3—C4 | 1.486 | C3C2C5 | 121.8 | | |
| C2—O6 | 2.806 | C3C2O6 | 81.7 | | |
| C3—O6 | 2.954 | C2O6C7 | 150.7 | | |
| O6—C7 | 1.418 | | | | |

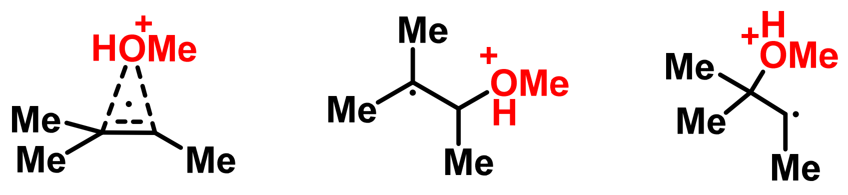
The distance between the O atom and C atom is actually too long for significant orbital interaction.


Arnold, D. R.; Chan, M. S. W.; McManus, K. A. *Can. J. Chem.* **1996**, *74*, 2143.

# Equilibrium?




Unfortunately, the relative stability of the 2 distonic radical ions does not match the regioselectivity as well.

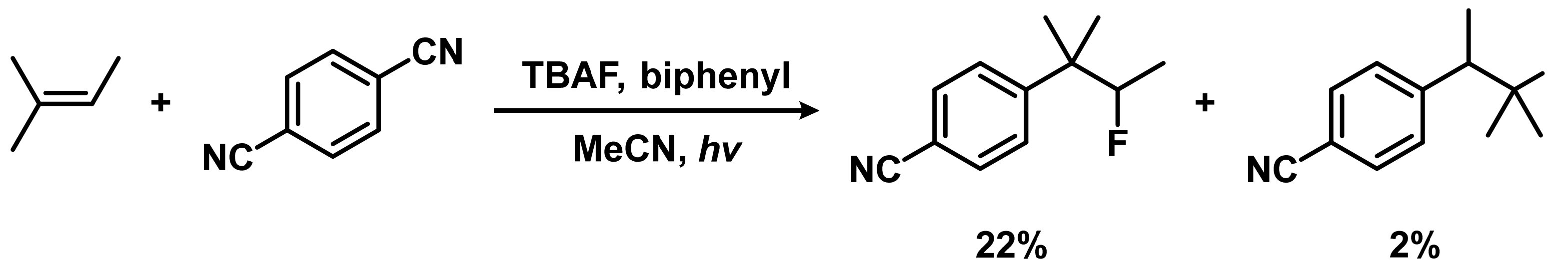


| | | | |
|---|---|---|---|
| $G_{rel}$ (kcal/mol) | 0 | 7.2 | 7.0 |

M06-2X-D3/def2-TZVP/PCM(DCM)//M06-2X-D3/def2-SVP/PCM(DCM)

# Fluoride Anion as Nucleophile

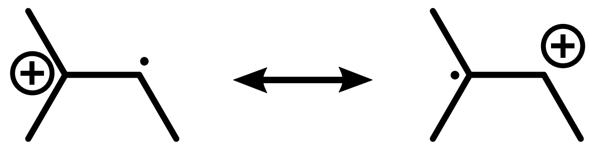
*Anti*-Markovnikov selectivity is still applicable when there is no such 3-membered intermediate.




Chan, M. S. W.; Arnold, D. R. *Can. J. Chem.* **1997**, *75*, 1810.

# Electrostatic Control

When the alkene cation radical is isolated, the ‘cation part’ needs more stabilization from hyperconjugation.



**Preferred**

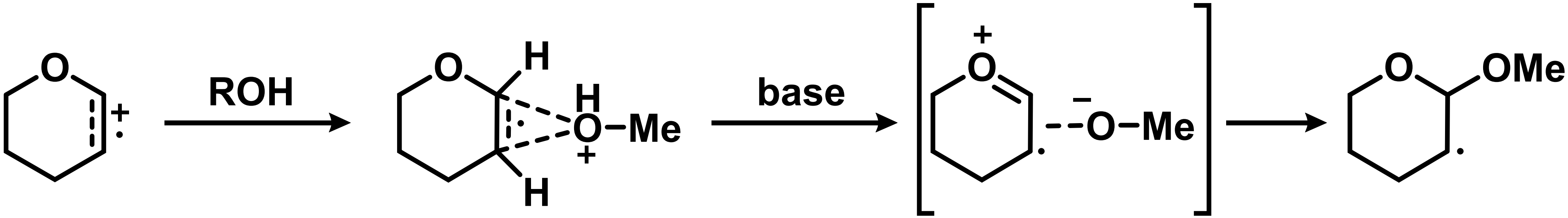
However, when the nucleophile is approaching, the positive charge on the alkene radical cation can be tremendously stabilized by the electrostatic attraction, so stabilizing radical is important in the TS.

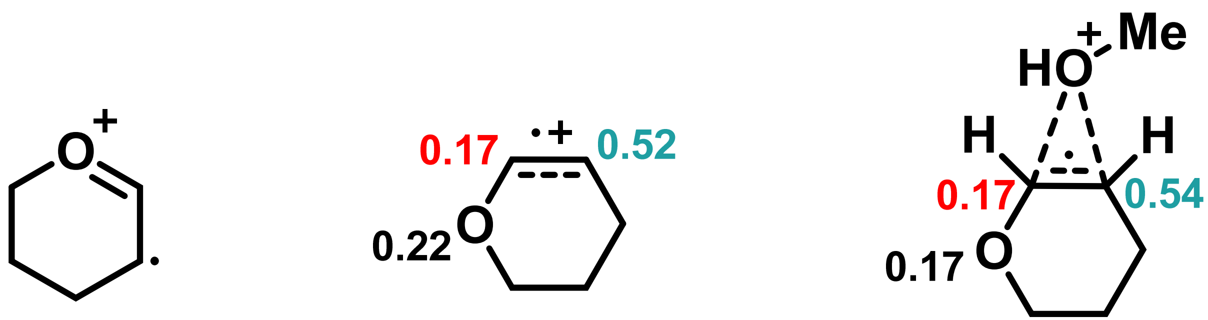

**Preferred**

Proposed by Mr. Y. Jiao


M06-2X-D3/def2-SVP/PCM(DCM)
Spin population at M06-2X level

# Enol Ether




M06-2X-D3/def2-SVP/PCM(DCM)
Spin population at M06-2X level

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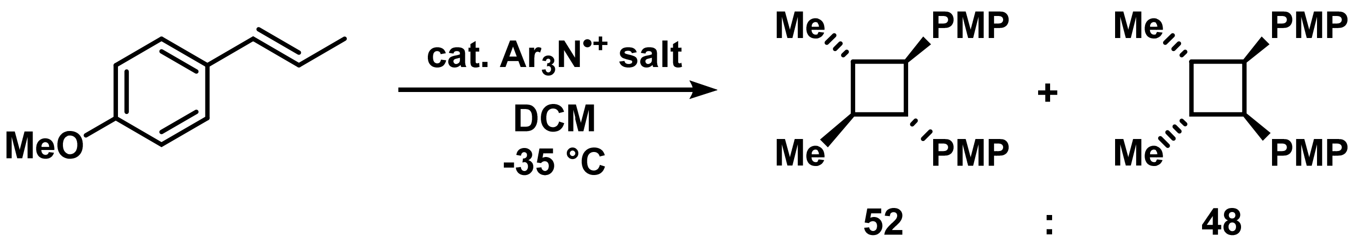
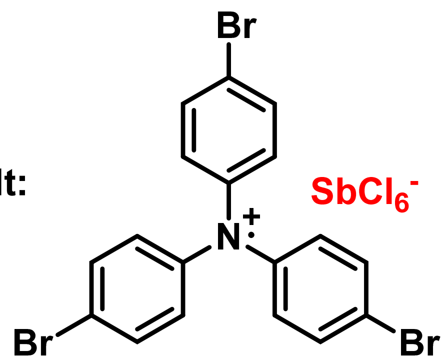
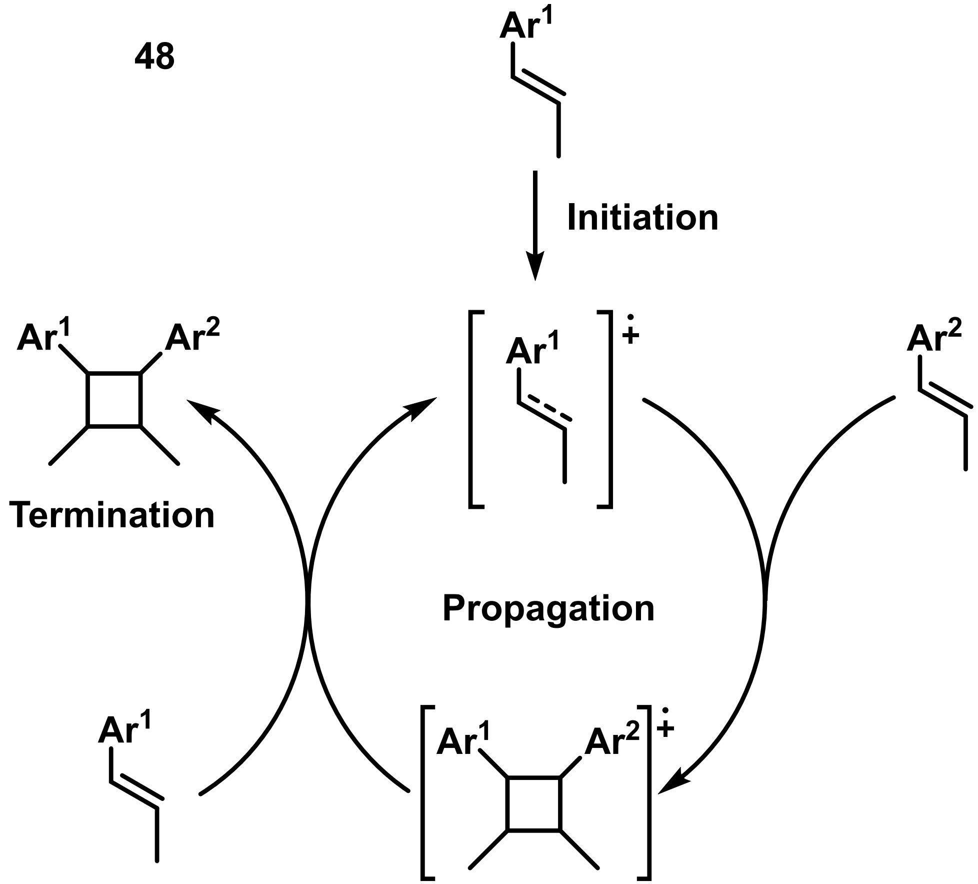
# Chain Reaction




Ar$_3$N$^{\bullet+}$ salt:




Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.* **1983**, *105*, 633.




**Experiment rate law:**

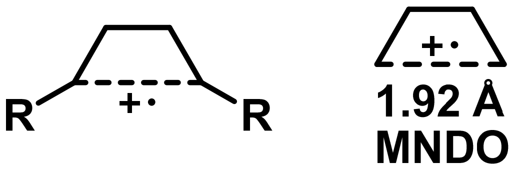
**rate = $k_{app}$[Ar$_3$N$^{\bullet+}$]$^{1/2}$[Alkene]$^{3/2}$**

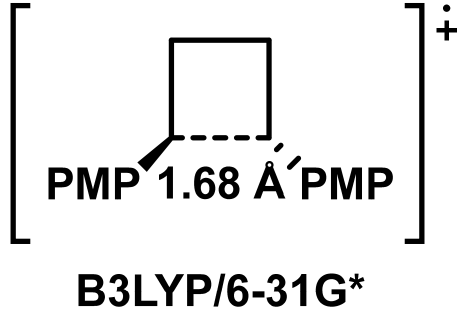
Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157.

Zhang, X.; Paton, R. S. *Chem. Sci.,* **2020**, *11*, 9309.

# Concerted or Stepwise?

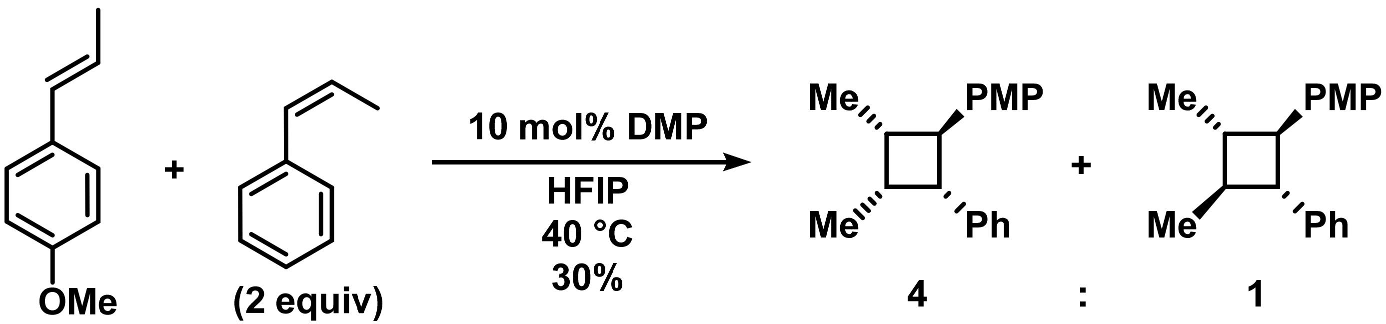
'Long-bond intermediate'




Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.* **1983**, *105*, 633.

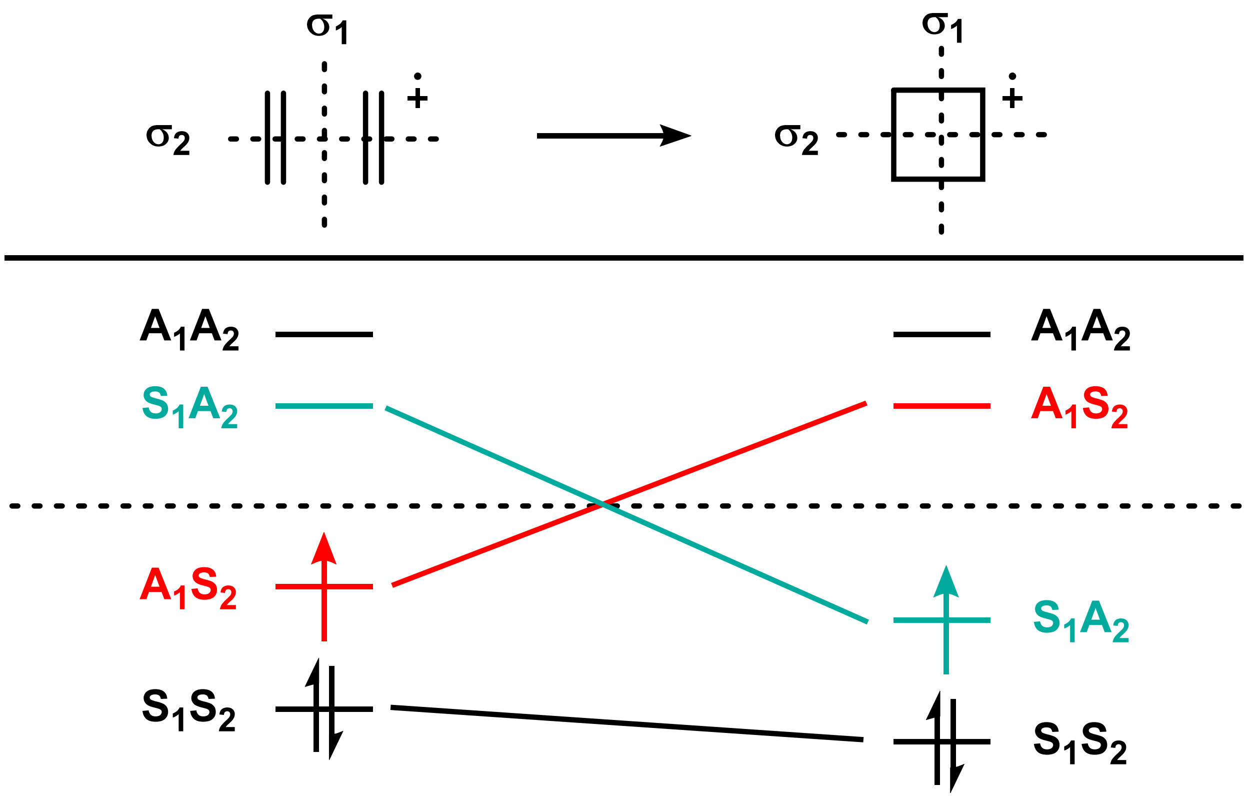
O'Nei, L. L.; Wiest, O. *J. Am. Chem. Soc.* **2006**, *71*, 8926.




Colomer, I.; Barcelos, R. C.; Donohoe, T. J. *Angew. Chem., Int. Ed*. **2016**, *55*, 4748.

# Correlation Diagram: Forbidden

**Orbital correlation diagrams of the radical cation [2+2] reaction**

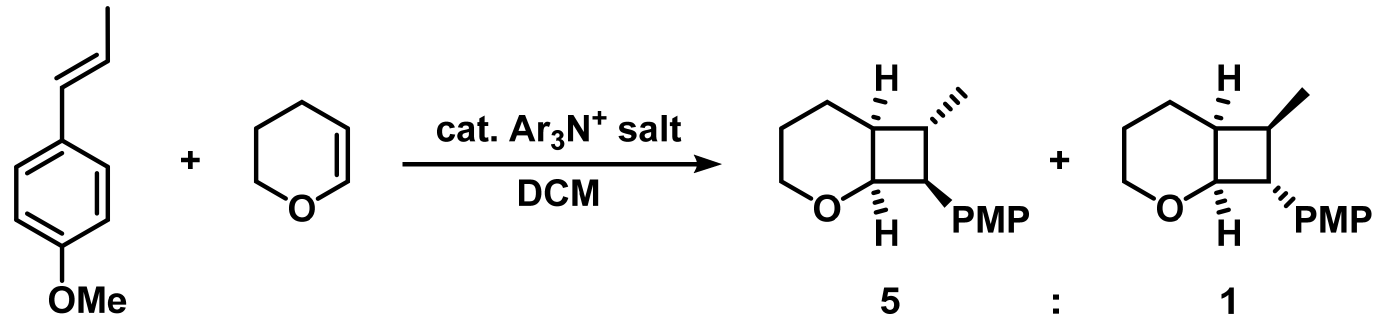



**"Forbidden"**

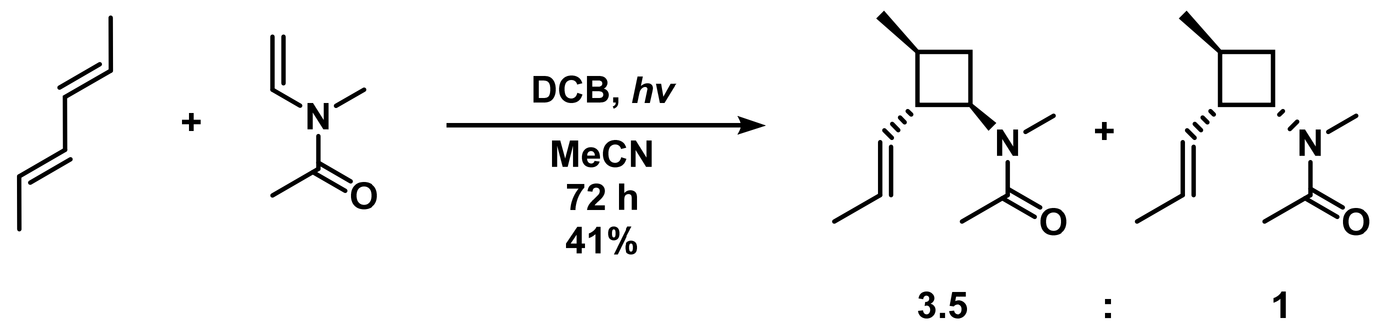
Bauld, N. L. *Tetrahedron.* **1989**, *45*, 5307.

# Regioselectivity: Head to Head

Head-to-head combination



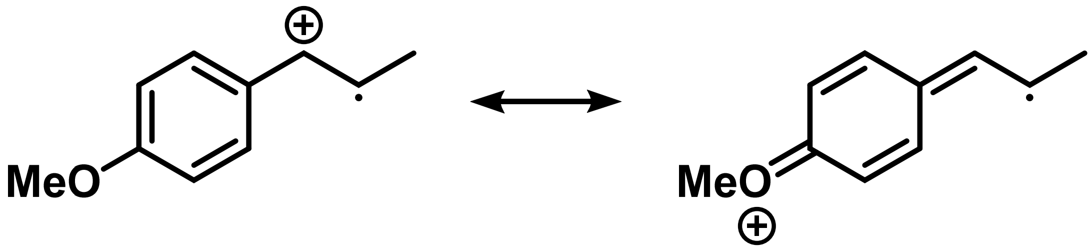

Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.* **1983**, *105*, 633.

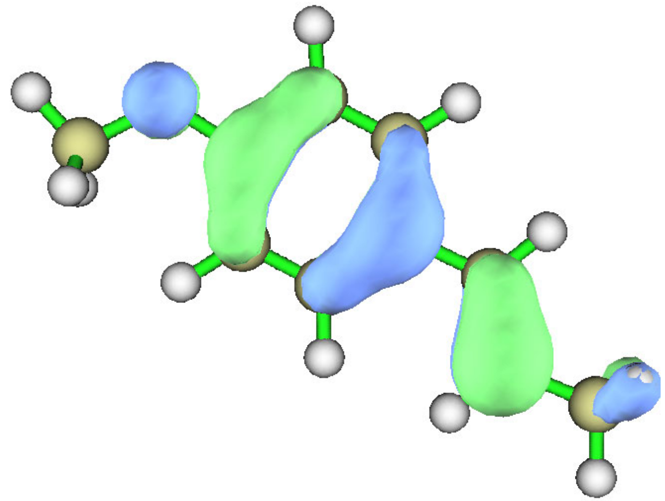



Bauld, N. L.; Harirchian, B.; Reynolds, D. W.; White, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 8111.

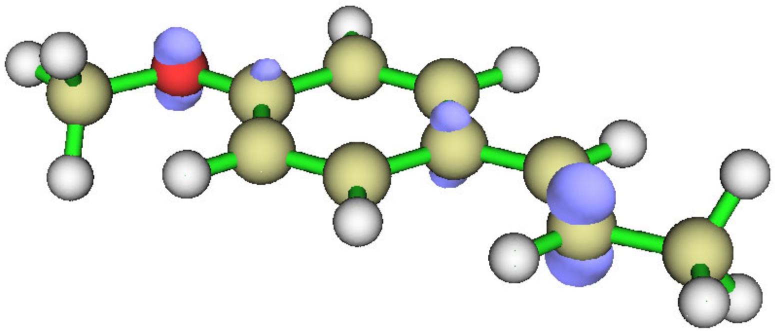
# Regioselectivity: Orbital Control

The radical is predominantly located on the β-carbon.

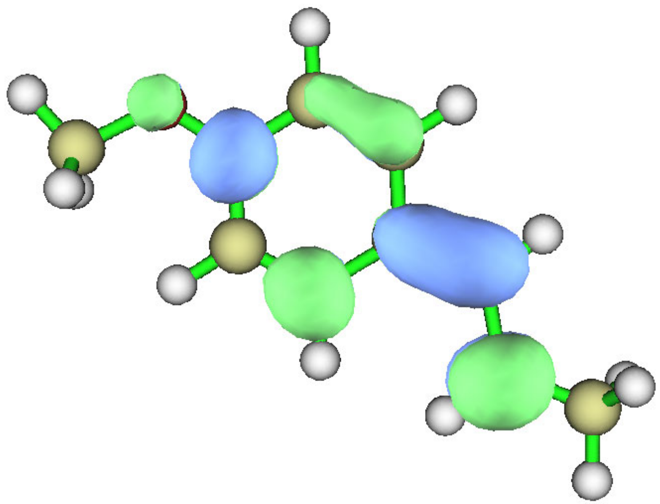


α-HOMO of anethole radical cation

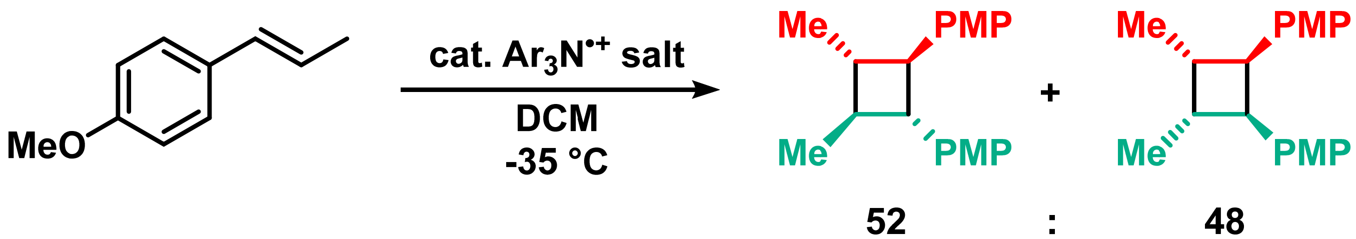


M06-2X-D3/def2-SVP/PCM(DCM)
Spin density isosurface at M06-2X level

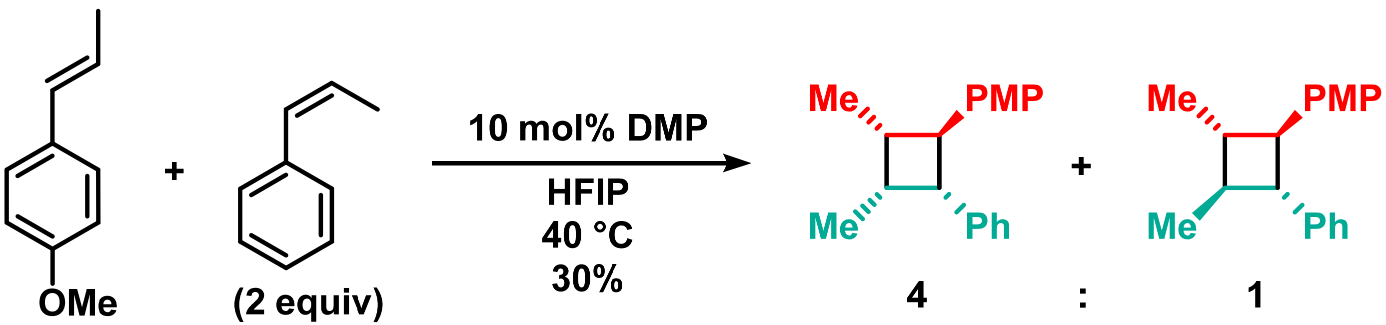


α-LUMO of anethole radical cation

# Isomerization

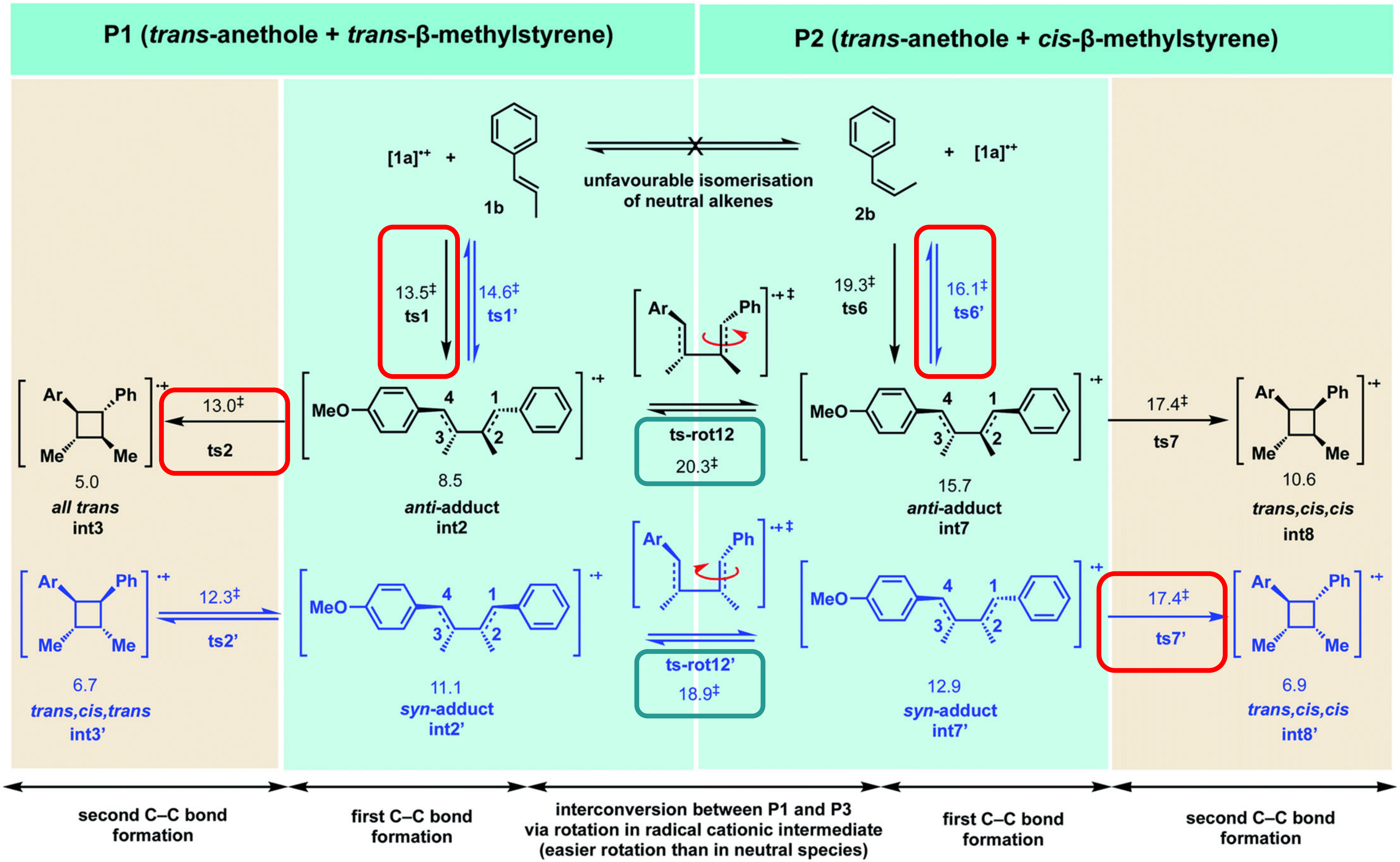



Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.* **1983**, *105*, 633.




Colomer, I.; Barcelos, R. C.; Donohoe, T. J. *Angew. Chem., Int. Ed*. **2016**, *55*, 4748.

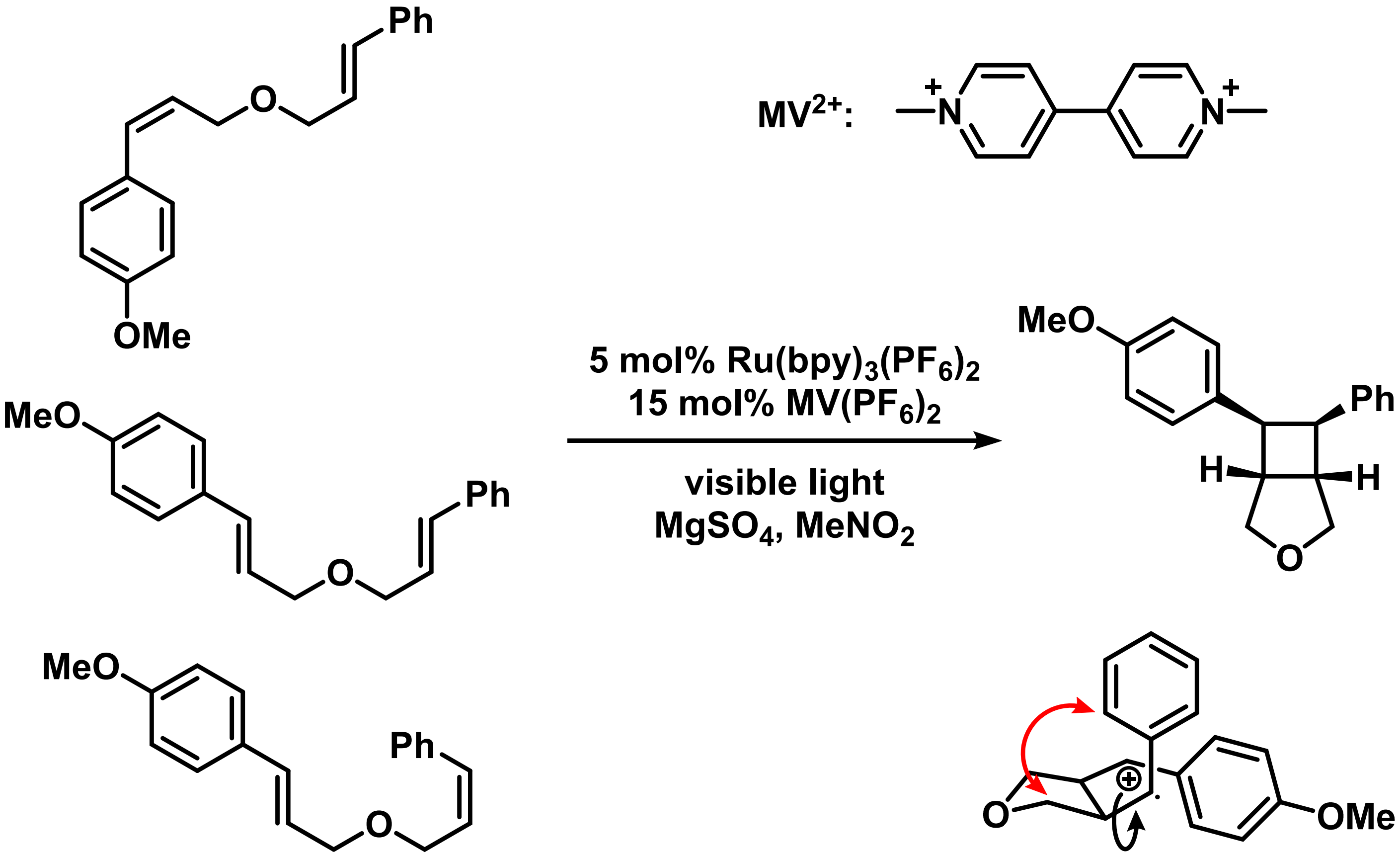
# Isomerization: Too Subtle!




Zhang, X.; Paton, R. S. *Chem. Sci.*, **2020**, *11*, 9309.

# Intramolecular: Stereoconvergent

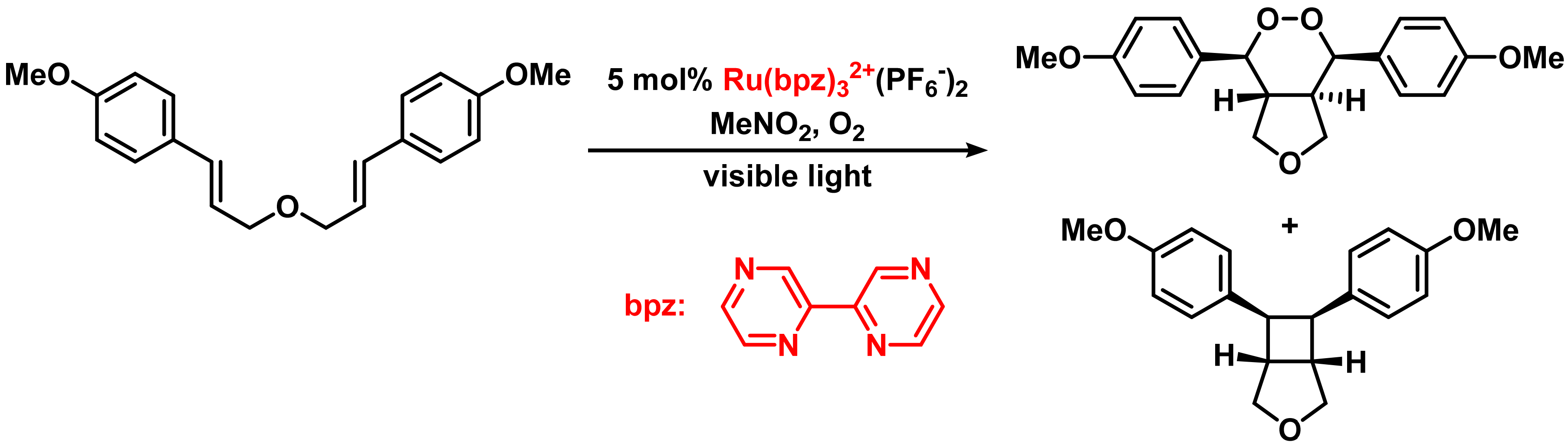
Bond rotation faster than the ring closure.

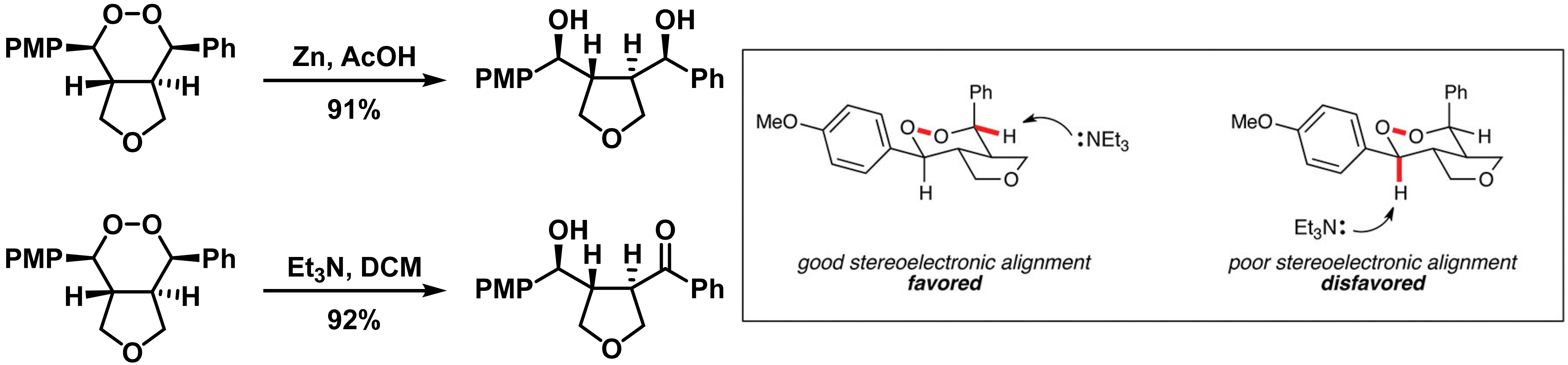



Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572.

# Trapping the *Anti*-Radical Cation

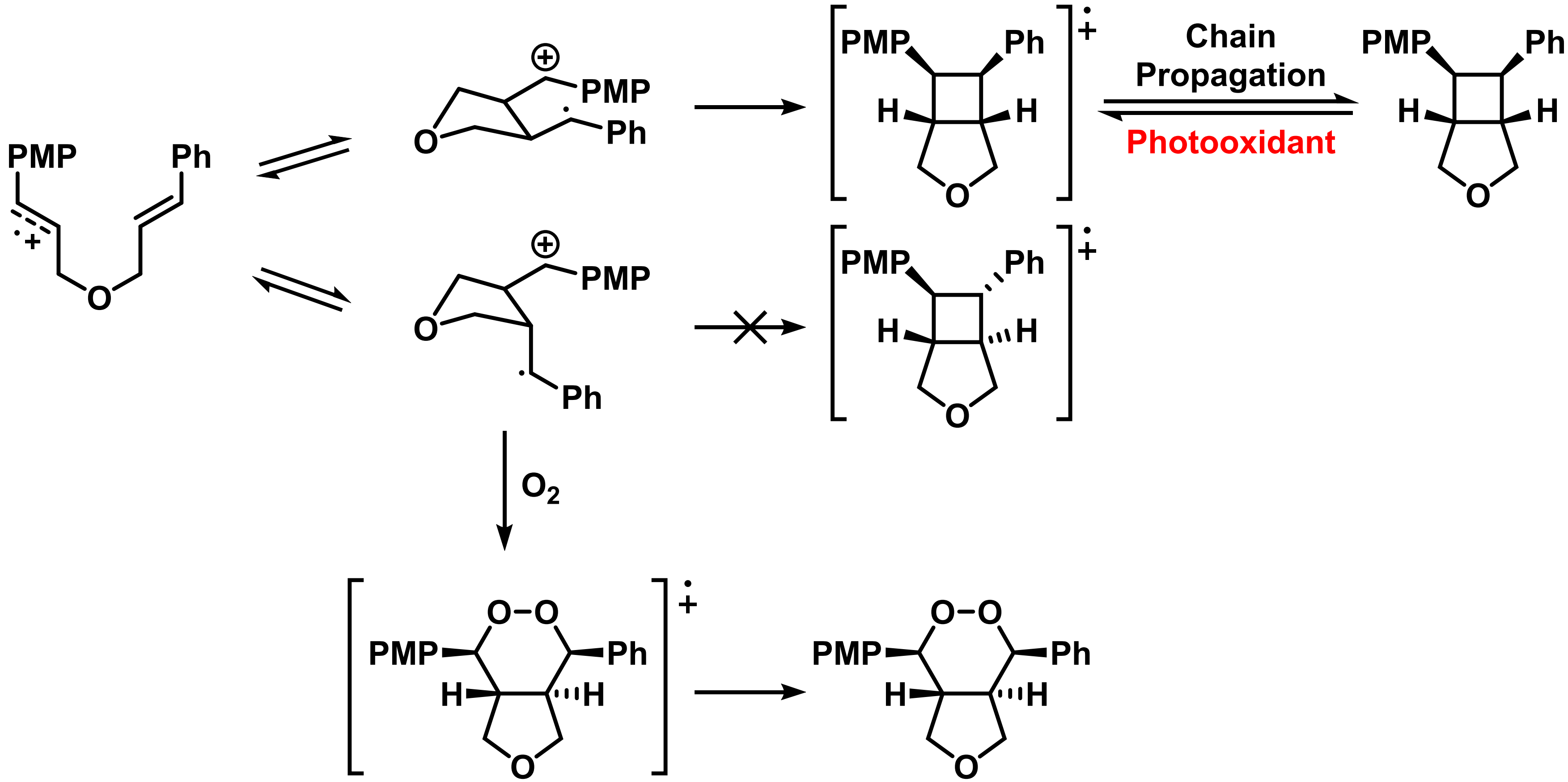
After adding $O_2$, the [2+2+2] product has a trans 6/5 system.



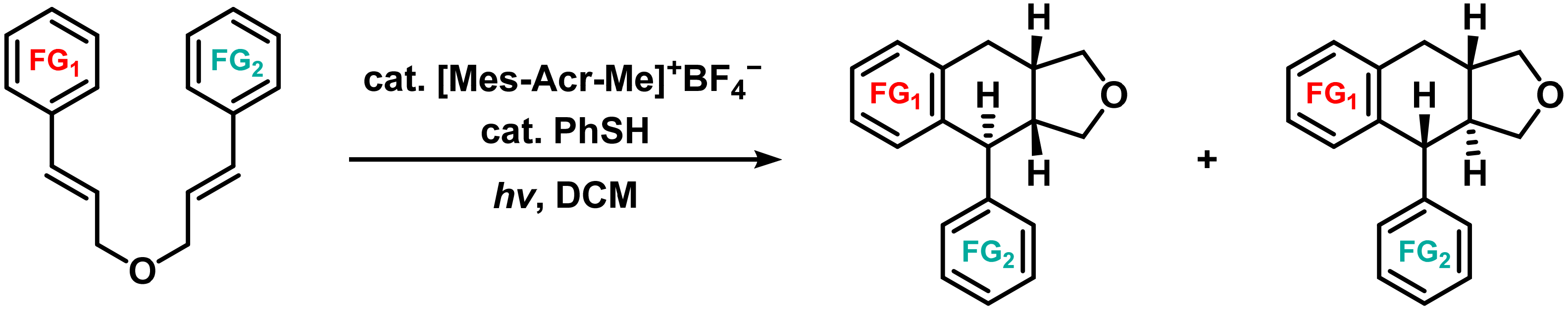



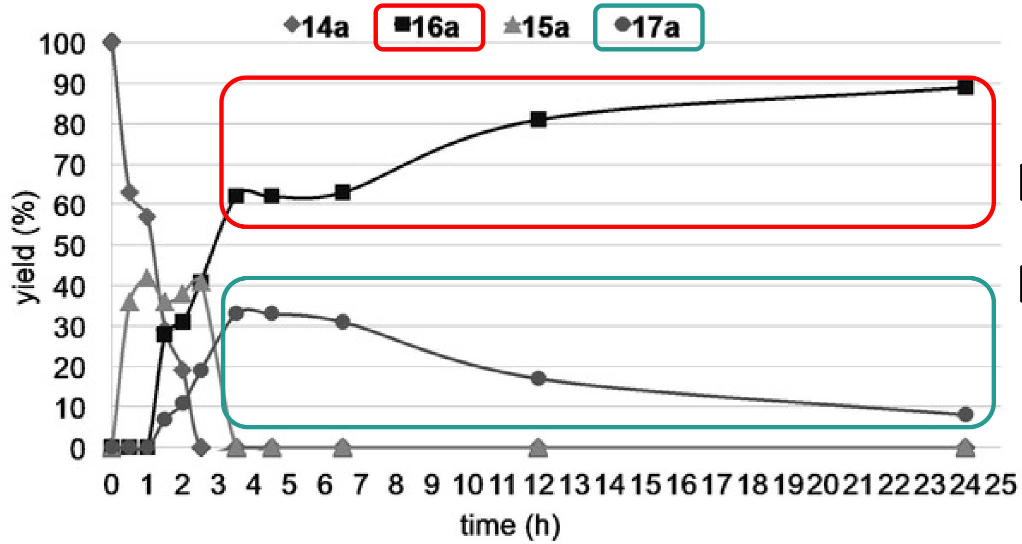

Parrish, J. D.; Ischay, M. A.; Lu, Z.; Guo, S.; Peters, N. R.; Yoon, T. P. *Org. Lett.* **2012**, *14*, 1640.

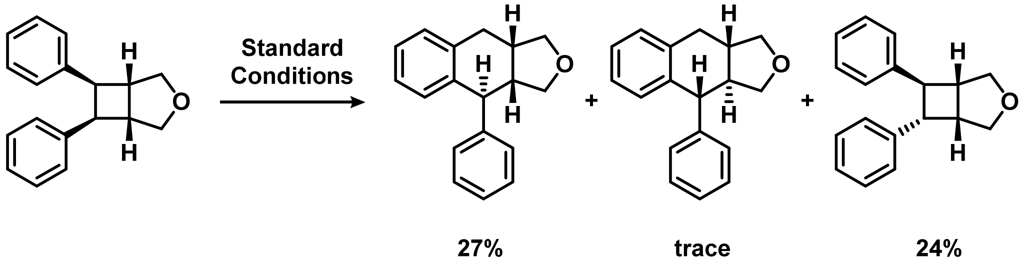
# Trapping the *Anti*-Radical Cation

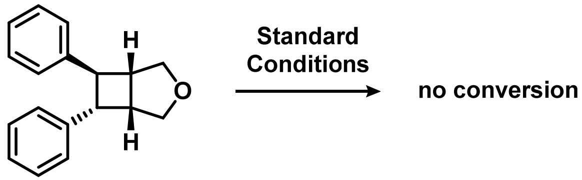


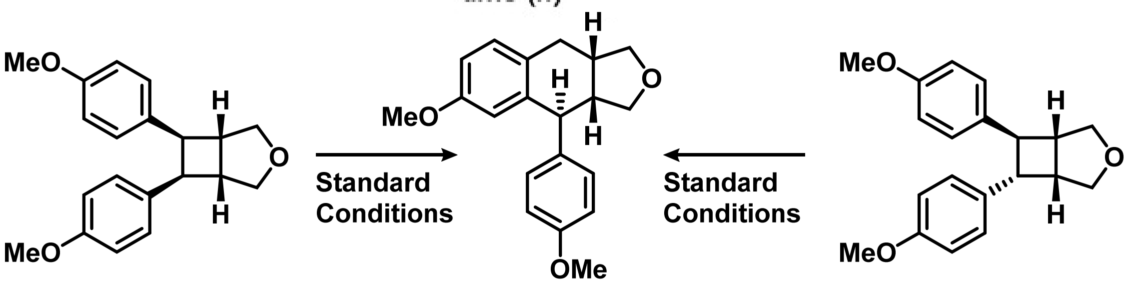
# Ring Expansion



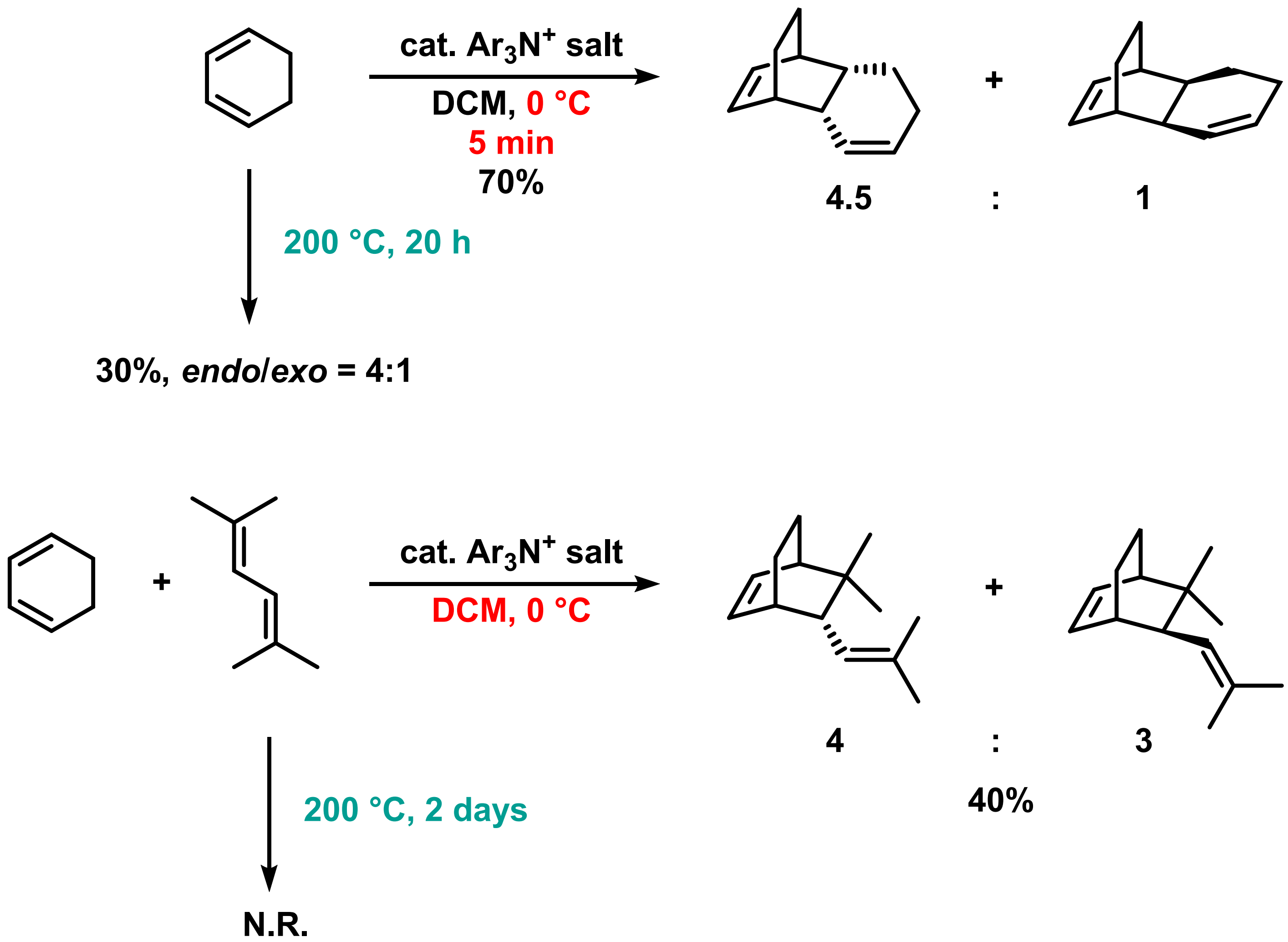




15a 16a 17a

Xiang, J.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2020**, *59*, 21995.

# D-A: Acceleration

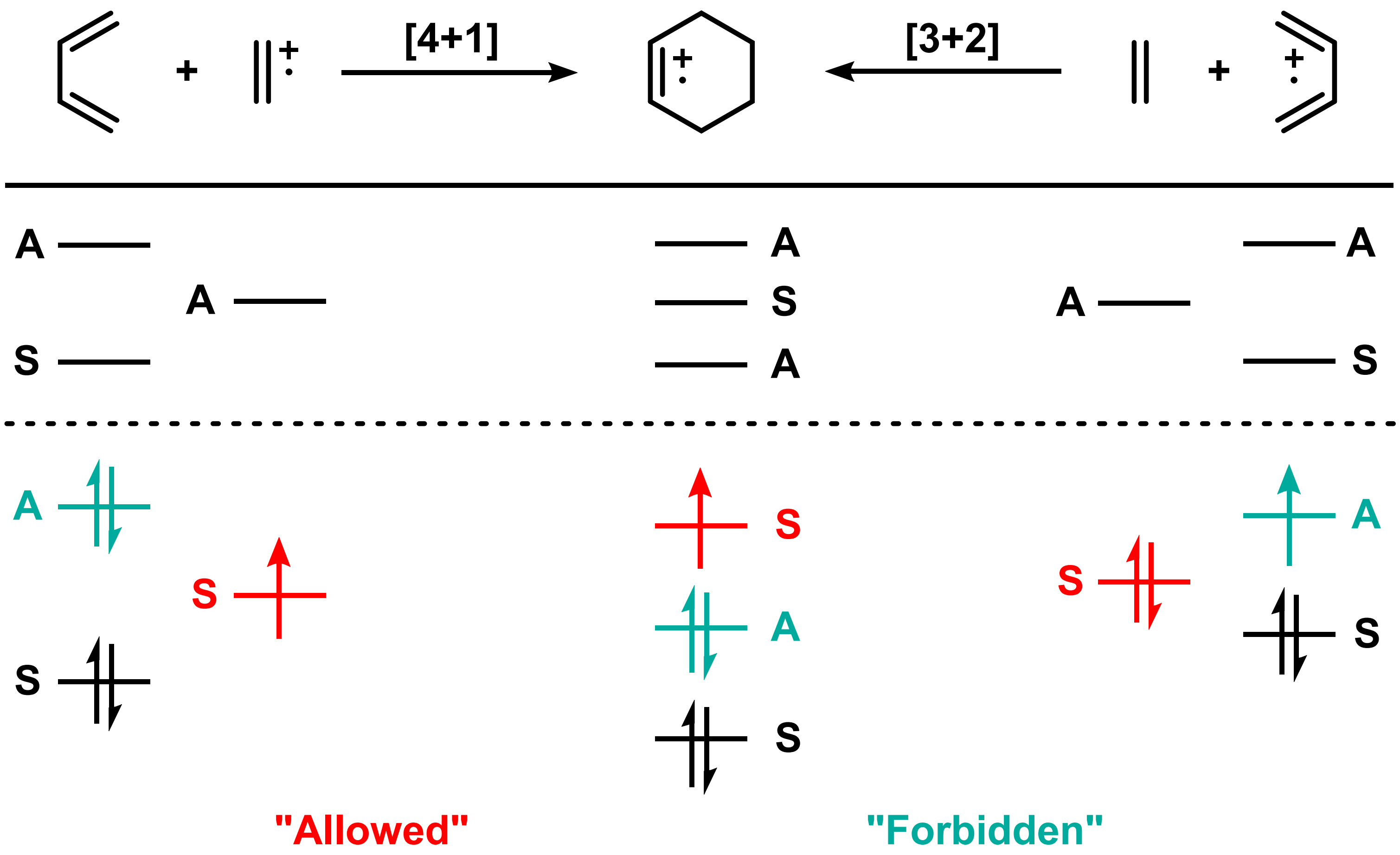





Bellville, D. J.; Wirth, D. W.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718.

# [4+1] or [3+2]?

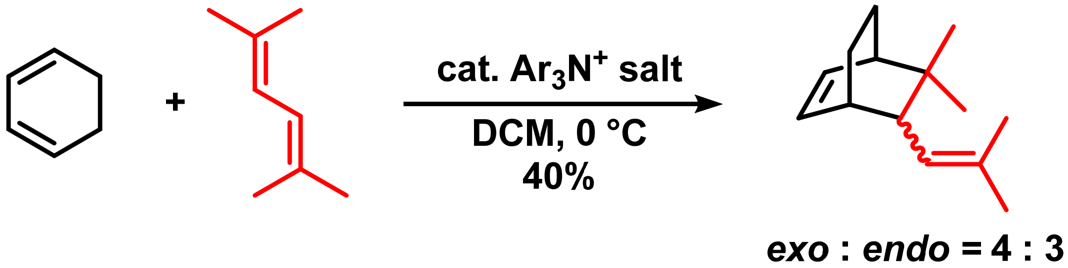
Orbital correlation diagrams of the radical cation D-A reaction



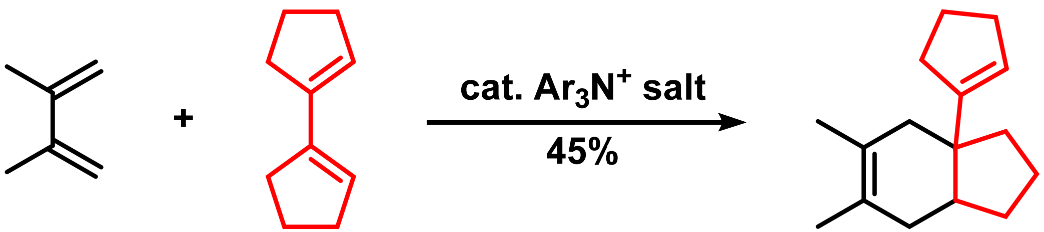

Bellville, D. J.; Bauld, N. L. *Tetrahedron.* **1986**, *42*, 6167.

# Role Selectivity

The diene that has lower oxidation potential act as dienophile.



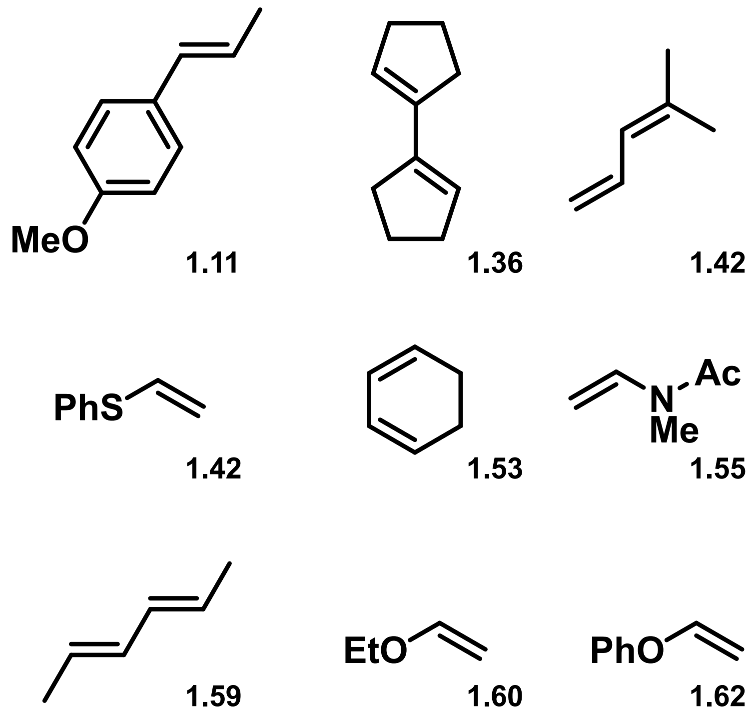

Bellville, D. J.; Wirth, D. W.; Bauld, N. L.
*J. Am. Chem. Soc.* **1981**, *103*, 718.




Reynold Dissertation at the University of Texas Austin 1988

**Half-Wave Oxidation Potentials**
**($Ag/Ag^+$ vs. SCE, MeCN, Irreversible)**

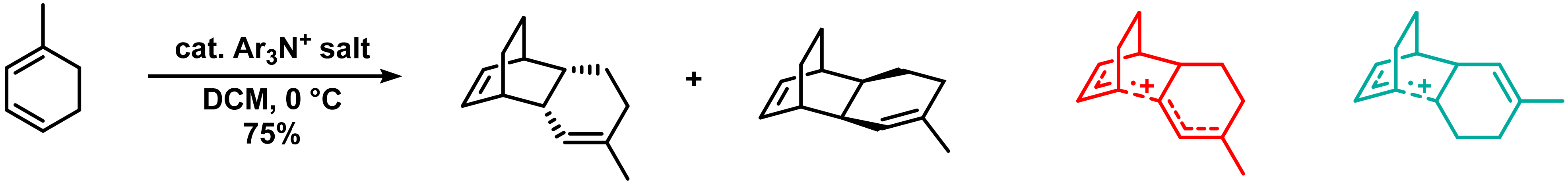
**Compound** **Potential**




Su, S. Baran Group Meeting 10/03/2007
https://www.scripps.edu/baran/images/grpmtgpdf/Sushun_Sept_07.pdf

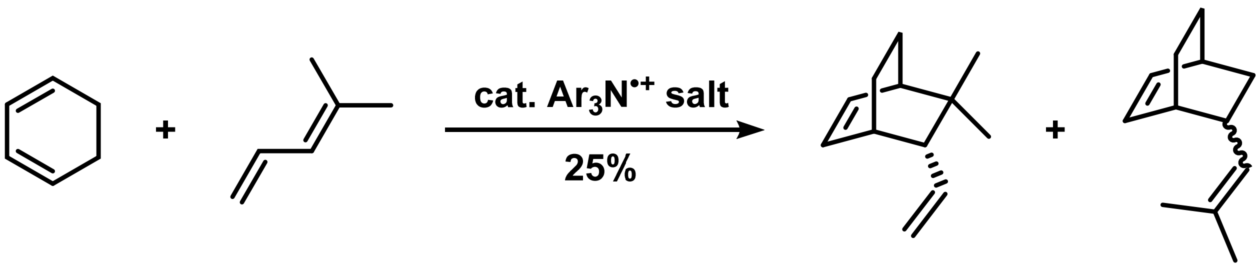
# Regioselectivity

Maximum stabilization of the bisallylic transition state




2 : 1 favored disfavored

However, terminal double bonds tend not to react.(electrostatic factor?)

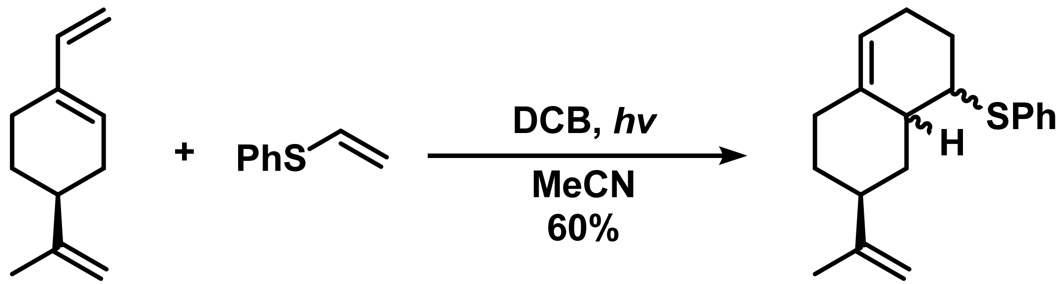



3 : 2

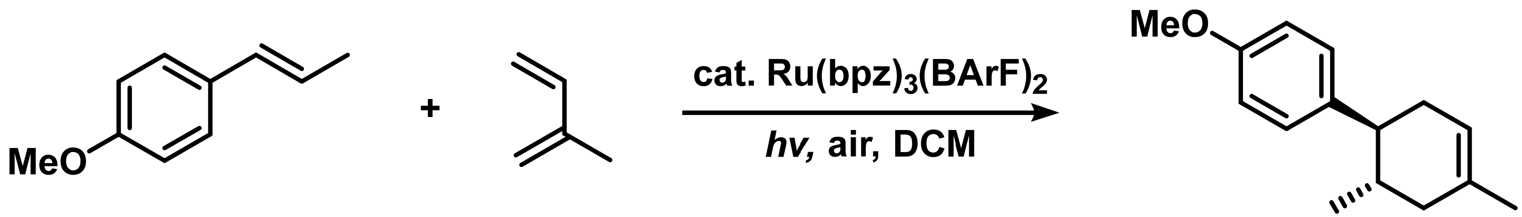
Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 2665.

# D-A vs. Cyclobutane

[4+1] favors over [2+1]




Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 2665.

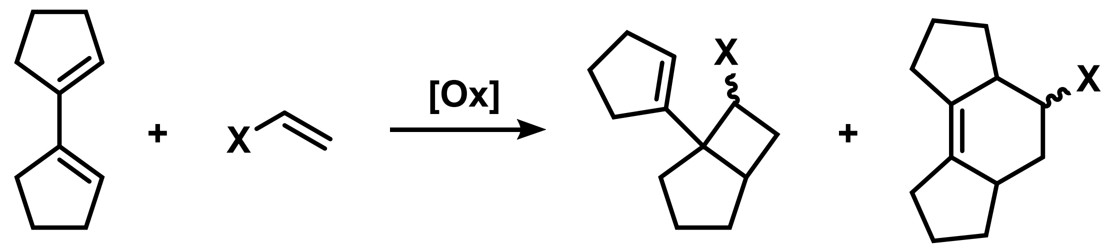



Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350.

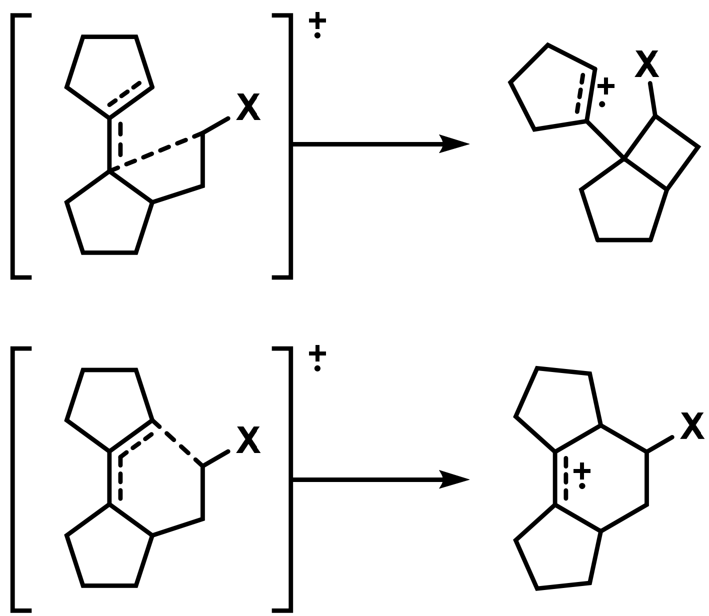
# D-A vs. Cyclobutane

Since [3+2] is stepwise too, there's a competition between D-A and cyclobutane.

Acyclic dienes usually prefer cyclobutane due to the favorable *s-trans* configuration.




| | | | |
|---|---|---|---|
| X= | NAcMe | 100 | 0 |
| | OEt | 98 | 2 |
| | $OCH_2CH_2Cl$ | 97 | 3 |
| | OPh | 82 | 18 |
| | SPh | 69 | 31 |
| | Ph | 0 | 100 |

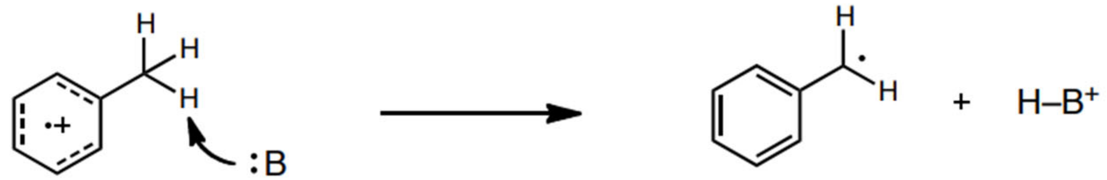



Bauld, N. L. *et al. Acc. Chem. Res.* **1987**, *20*, 371.

# Outline

- **Introduction**
- **Nucleophilic Addition**
  - Development
  - Regioselectivity: attempt to rationalize
- **Cycloaddition**
  - [2+2]
  - [4+2]
- **Bond Cleavage**
- **Summary**
- **Acknowledgement**

# α-Bond Cleavage

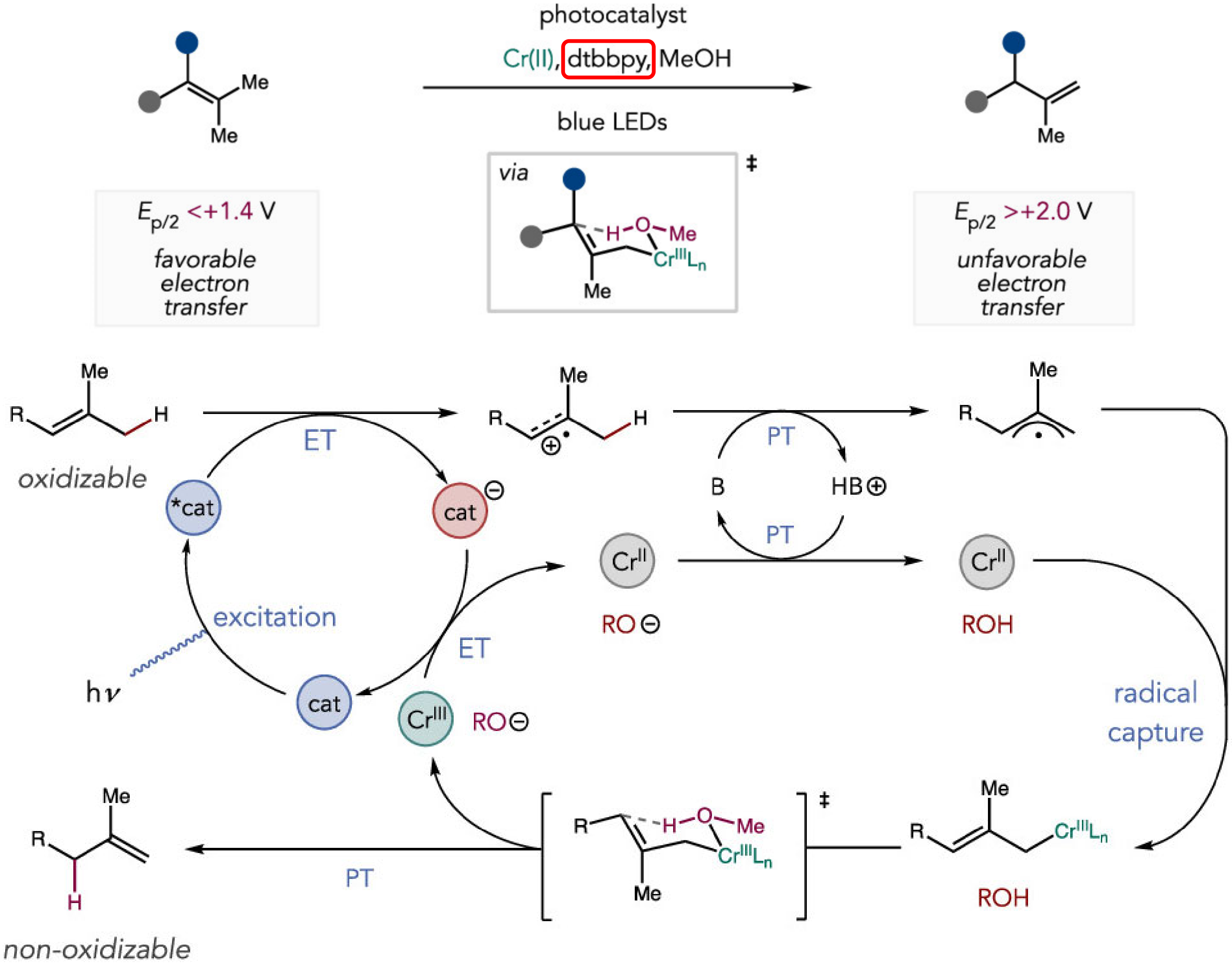



| R-H | pKa (π-RH·+) | pKa (π-RH) | reference |
|---|---|---|---|
| PhC**H₂**CN | –32 | 21.9 | a |
| PHC**H₂**SO2Ph | –25 | 23.4 | b |
| $Ph_2C$**$H_2$** | –25 | 32.2 | c |
| PhC**$H_3$** | –20 | 43 | c |
| indene (**3-H**) | –18 | 20.1 | d |
| Cp**H** | –17 | 18.0 | c,e |
| fluorene (**9-H**) | –17 | 22.6 | f |
| $C_5Me_5$**H** | –6.5 | 26.1 | e |


a) Bordwell et al. *J. Phys. Org. Chem.* **1988**, *1*, 209. b) Bordwell et al. *J. Phys. Org. Chem.***1988**, *1*, 225. c) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1989**, *111*, 1792. d) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1992**, *114*, 10173. e) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1988**, *110*, 2872. f) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 2867.

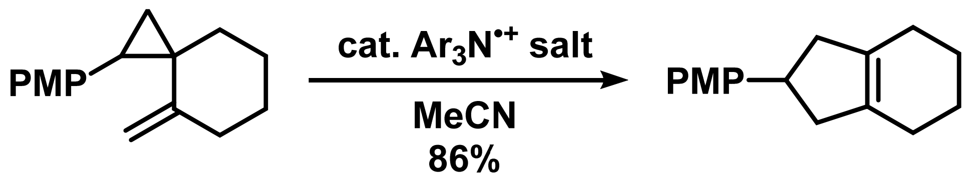

Casarez, Z. Macmillan Group Meeting 4/27/2011
https://macmillan.princeton.edu/wp-content/uploads/ADC_Radical-Cations.pdf

# Generation of Allylic Radical

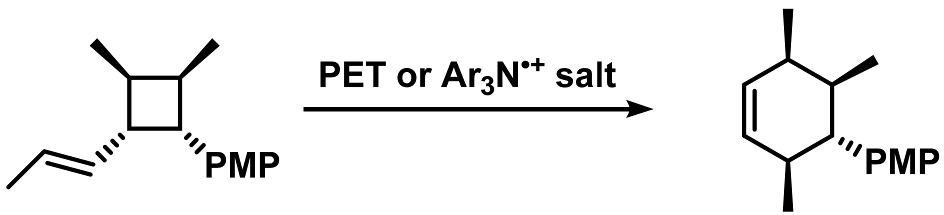



Zhao, K.; Knowles, R. R. *J. Am. Chem. Soc.* **2022**, *144*, 137.

# Catical Sigmatropic Shifts




Dinnocenzo, J. P.; Conlon, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 2324.




Reynolds, D. W.; Bauld, N. L. *Tetrahedron.* **1986**, *42*, 6189.

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- **Summary**
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# Summary

**Nucleophilic addition:**

Electrostatic control

Cascade and difunctionalization

Asymmetric

**Cycloaddition:**

Mostly stepwise

Oxidant matters

**Umpolung**