Pinacol-Type Rearrangement: Aptitude and Selectivity of Migration

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September 18th 2021

Outline

- **Introduction**
- **General Selectivity of Migration**
  General Mechanism
  Electronic Migration Aptitude
  Other Factors Influence Migration Aptitude
- **Migration Aptitude in Six-Membered Rings**
- **Summary**
- **Acknowledgement**

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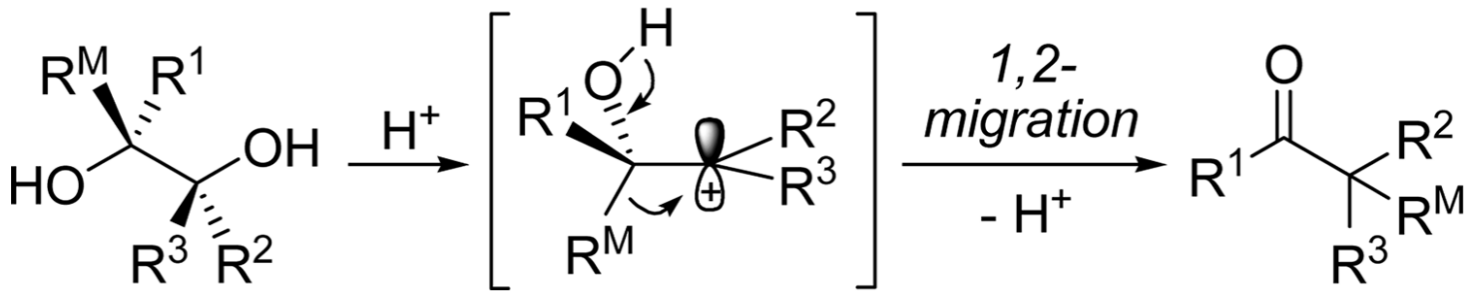
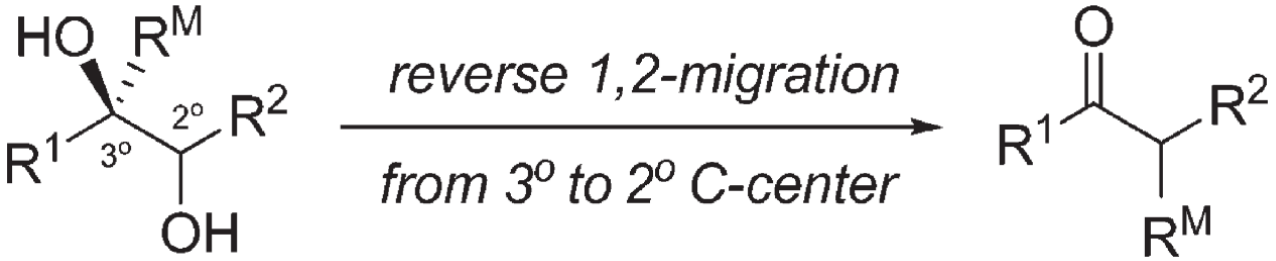
Introduction

- Pinacol rearrangement: acid-catalyzed transformation of 1,2-diols to ketones or aldehydes by 1,2-migration of a C-C or C-H bond



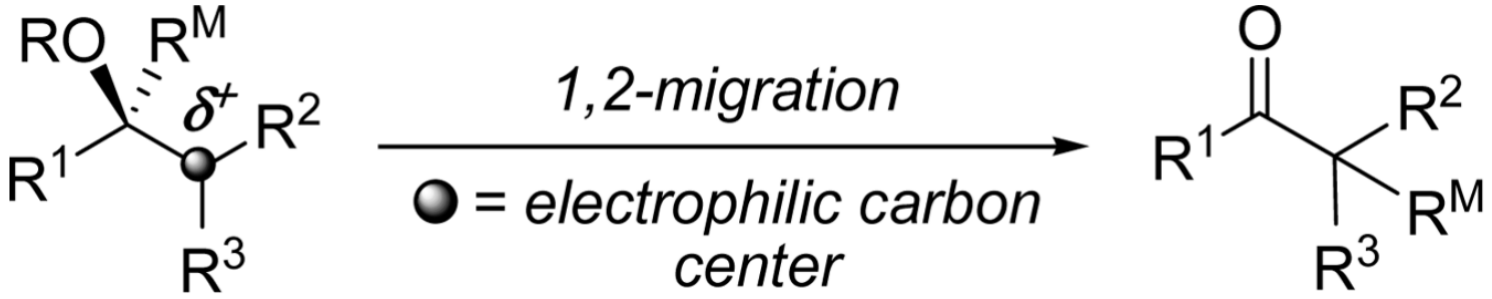
- Original semipinacol rearrangement: reverse migration



Chem. Rev. **2011**, *111*, 7523–7556.

Introduction

- General description of the pinacol-type rearrangement: *Mechanistically, all such processes share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2- migration of a C-C or C-H bond to terminate the process, generating a carbonyl group.*



Chem. Rev. **2011**, *111*, 7523–7556.

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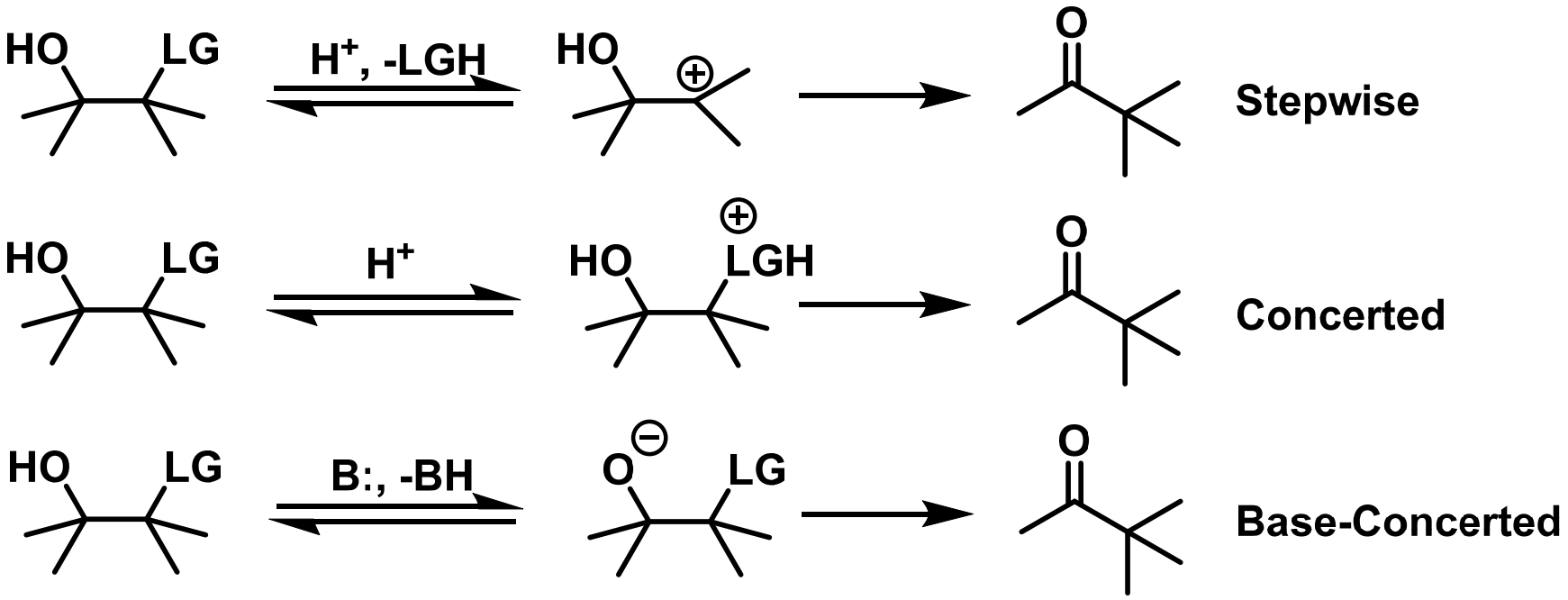
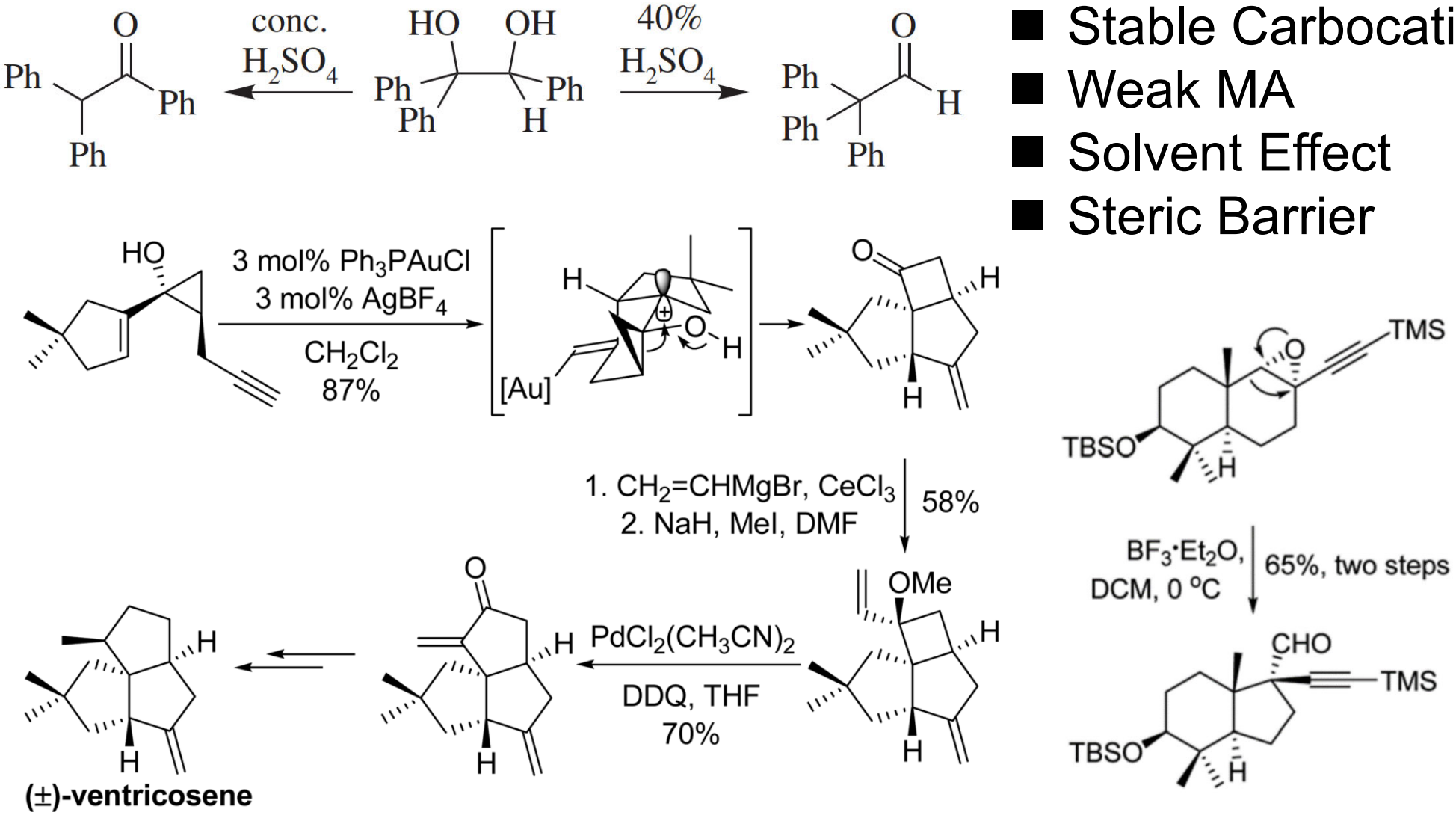
General Mechanism



- Types of Mechanism?
- Stereospecificity: Better Orbital Overlap
- Migration Aptitude (MA)?

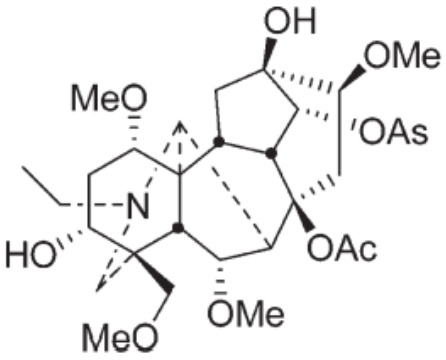
Stepwise: Stable or Be Forced



- Stable Carbocation
- Weak MA
- Solvent Effect
- Steric Barrier

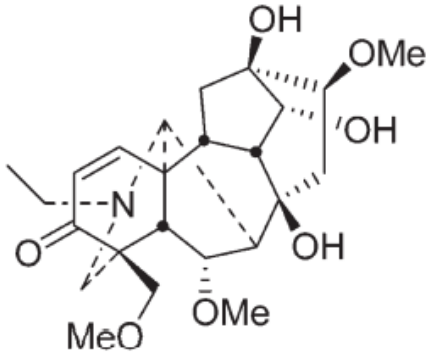
Org. Lett. **2008**, *10*, 4315; *J. Am. Chem. Soc.* **2020**, *142*, 8116.

Concerted: Normal Condition



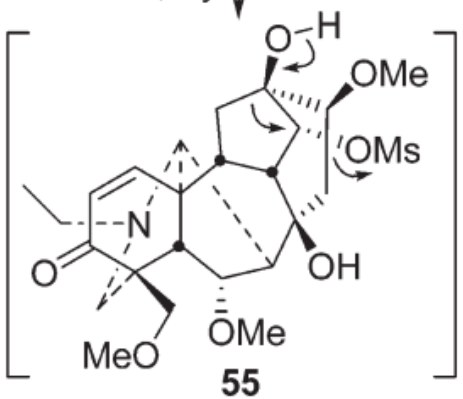
53 (As = COC_6H_4-*p*-OMe)

1. Jones oxidation
2. 5% NaOH, MeOH



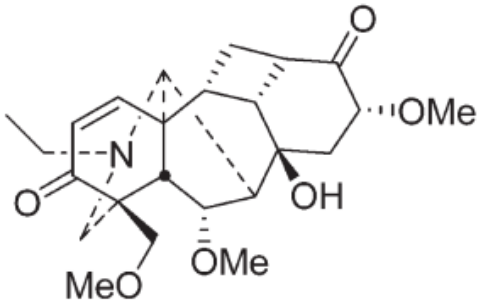
54

MsCl, Py



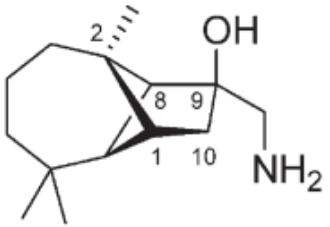
55

NaOH, DMF
reflux
4 steps 50%

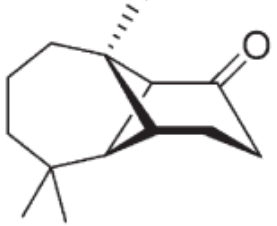


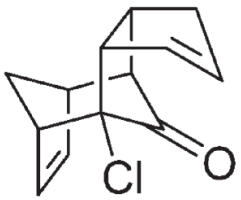
56

- Normal Pinacol
- Deamination
- Base-Concerted
- No Clear Boundary

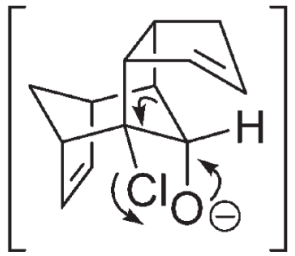


HNO_2 100%

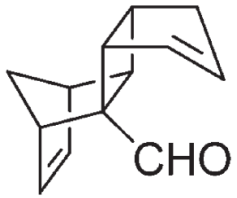




1. $LiAlH_4$, Et_2O
2. KH, THF

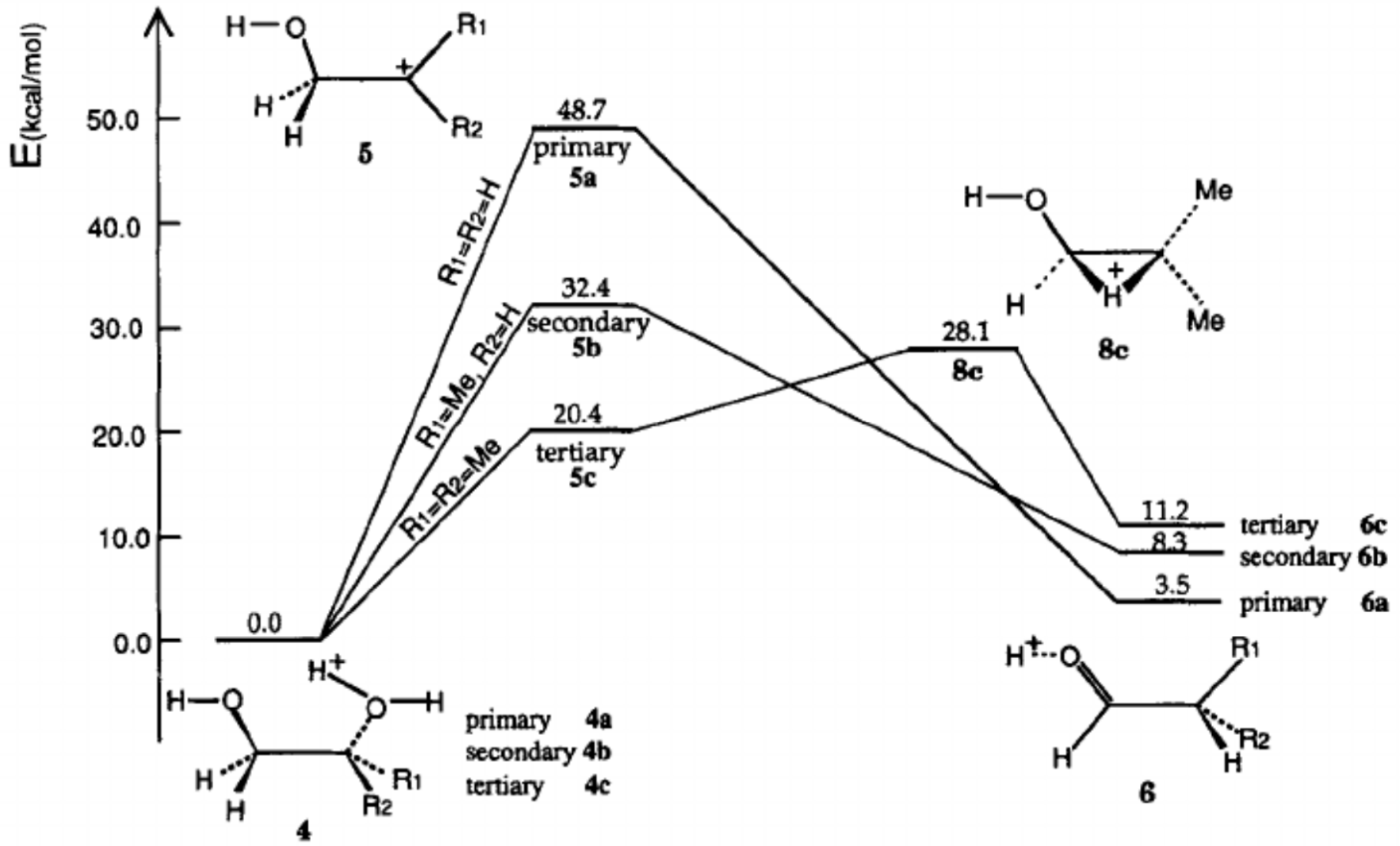


76%



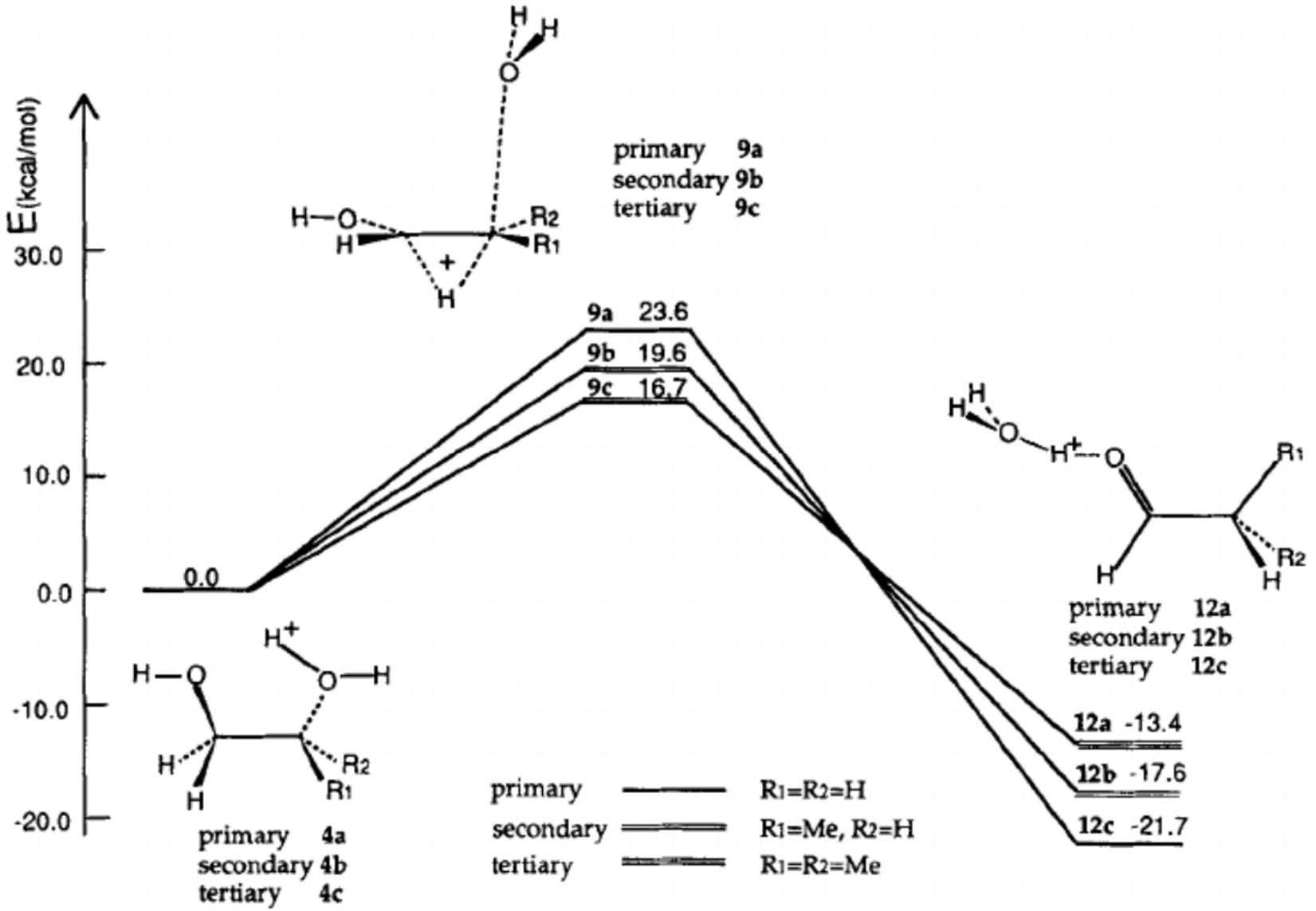
Tetrahedron **2001**, *57*, 4705; *Org. Lett.* **2003**, *5*, 59; *J. Am. Chem. Soc.* **1974**, *96*, 1917.

Stepwise vs Concerted: Boundary?



J. Phys. Org. Chem. **1990**, *3*, 737.

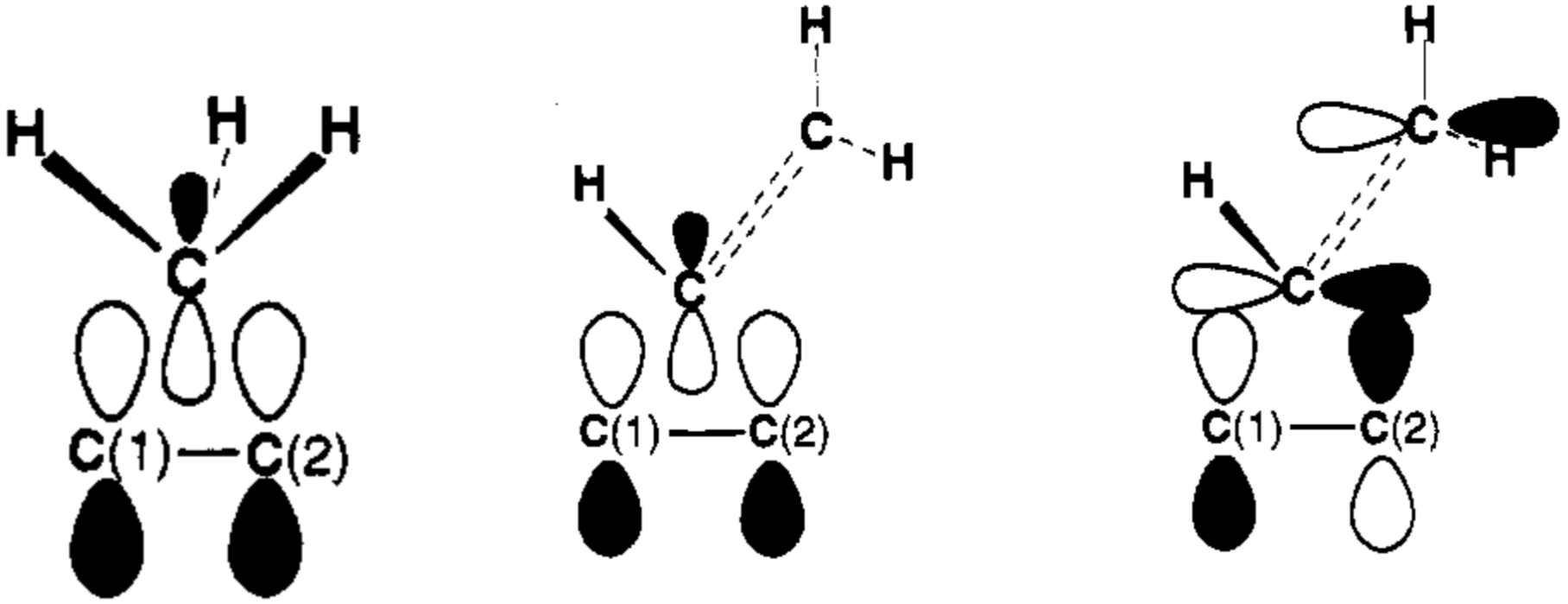
Stepwise vs Concerted: Boundary?



J. Phys. Org. Chem. **1990**, *3*, 737.

General Electronic MA: ERG-Prefer

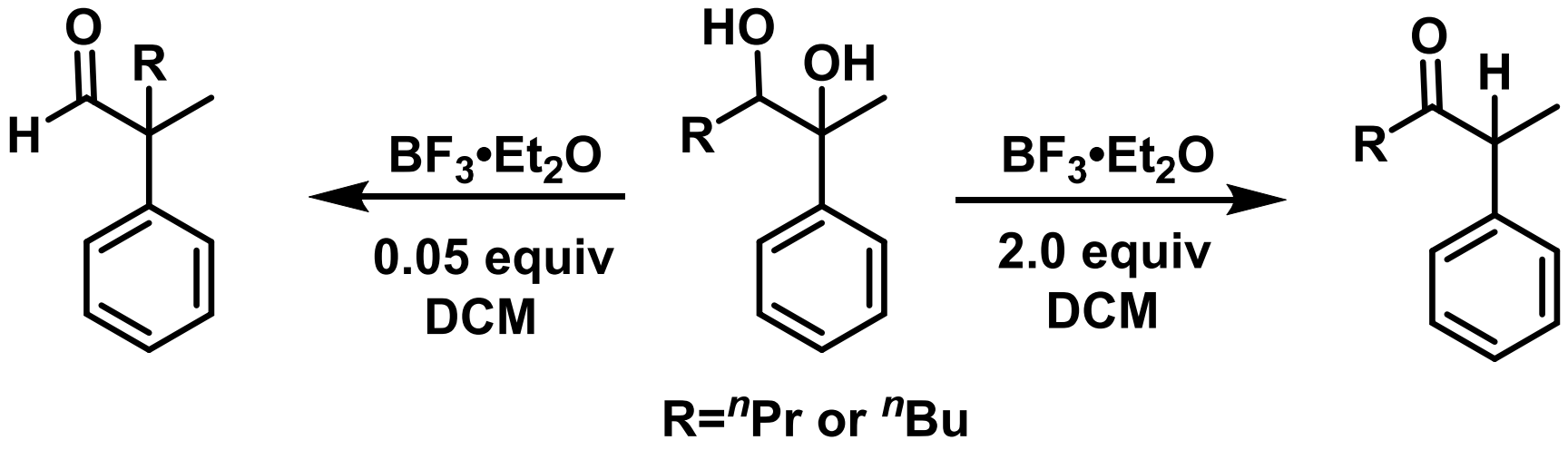
- Electron-deficient 3c-2e TS: aryl ~ vinyl (alkenyl) > t-Bu >> 2° alkyl > 1° alkyl



J. Am. Chem. Soc. **1993**, *115*, 9112.

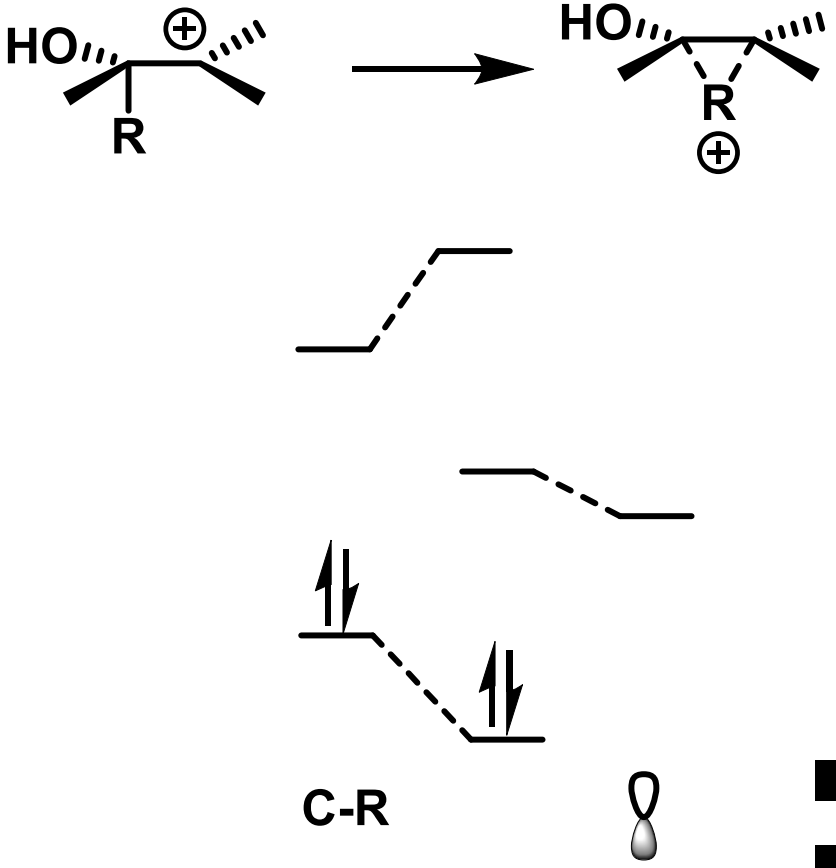
Electronic MA: Hydrogen?

- Electron Donating Ability (Hyperconjugation): H-C > C-C
- MA should be: aryl ~ vinyl (alkenyl) > H ~ t-Bu >> 2° alkyl > 1° alkyl
- Other factors?

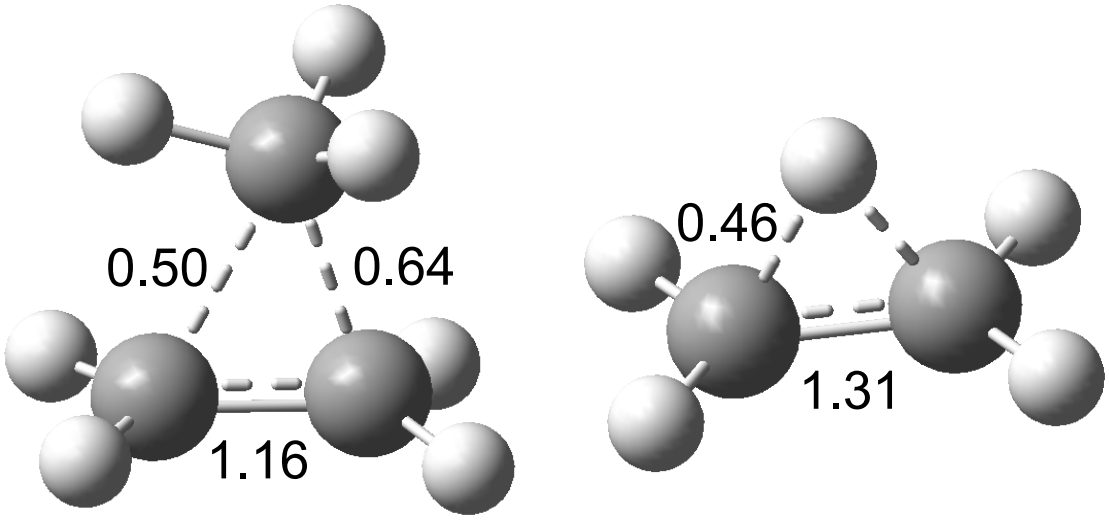


R=^{n}Pr or ^{n}Bu

Hyperconjugation ~ Migration?



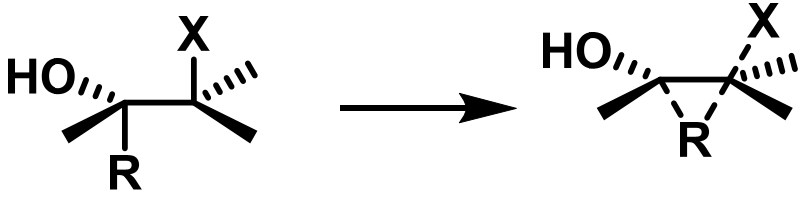
- Meyer Bond Order Analysis:



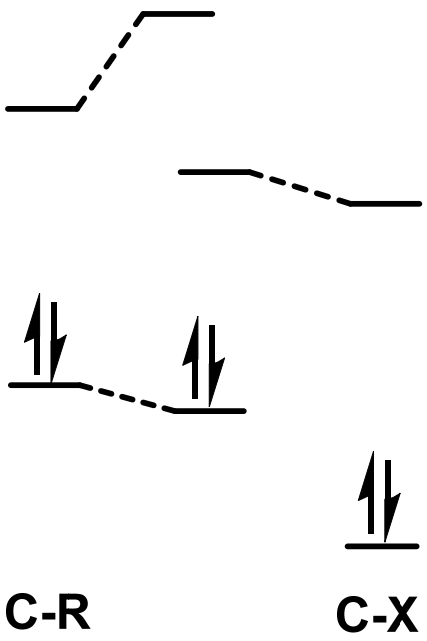
B3LYP/def2tzvp

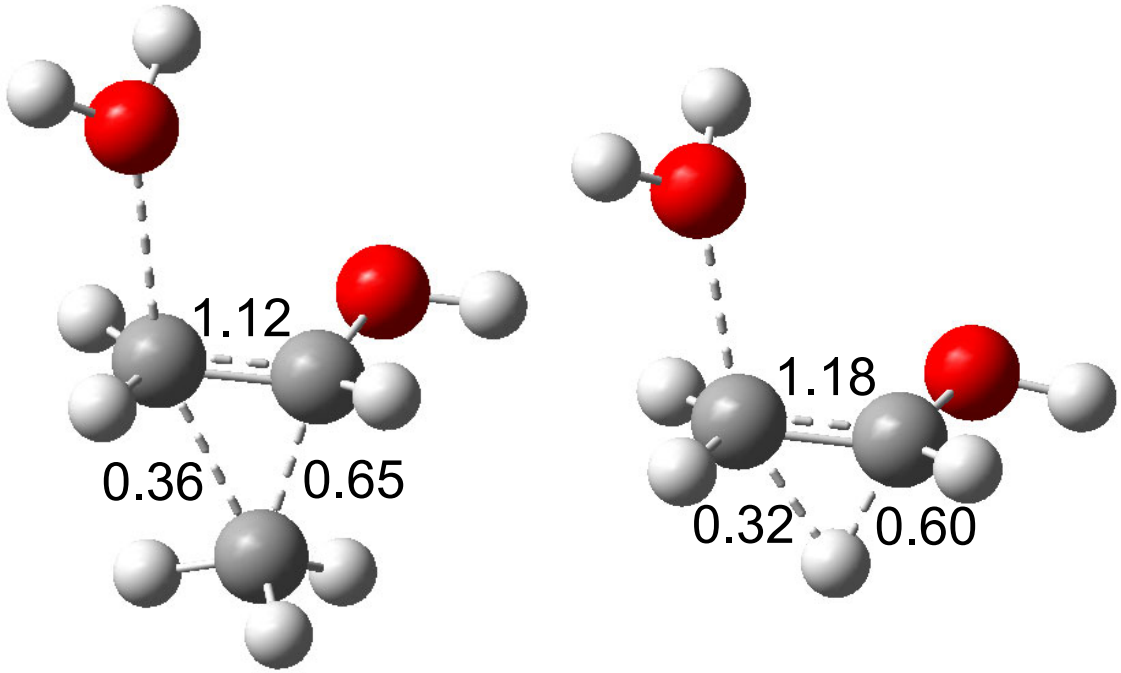
- Alkene-Complex; No Energy Barrier
- Energy Proximity: H-shift
- Alkene Stability: H-shift

Concerted: Energy Gap Increase



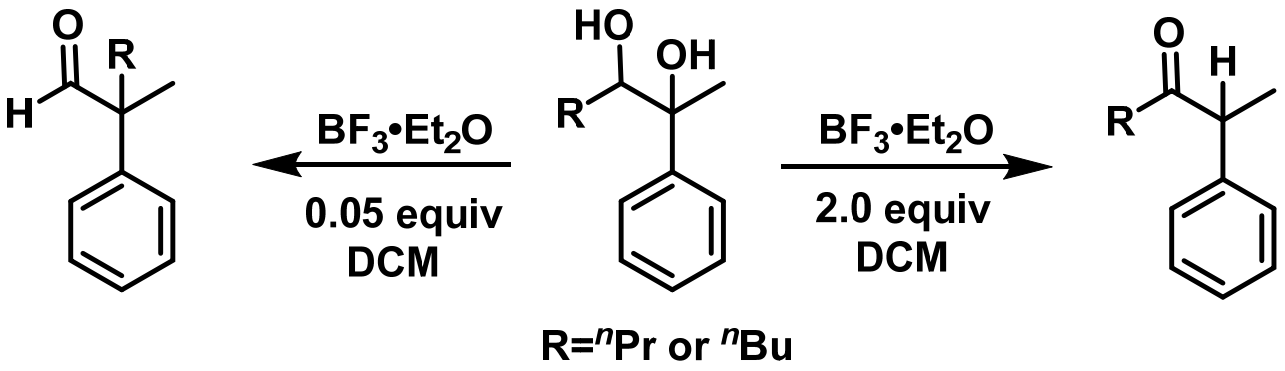
- Advantages of Alkyl?
- EP or Overlap: Wax and Wane
- Overlap: Coefficient and Dispersion





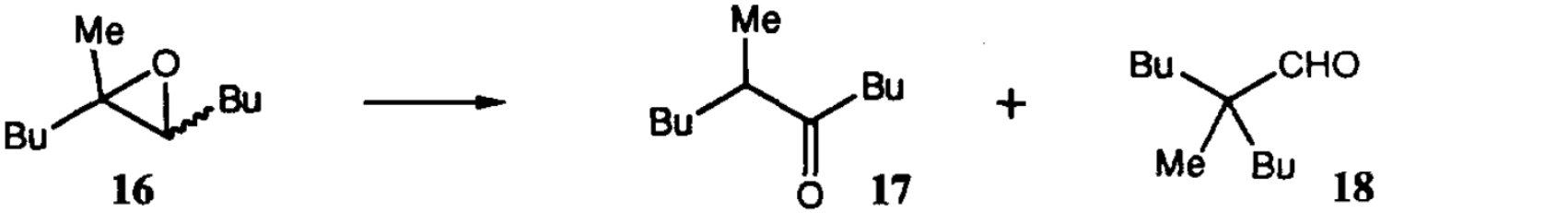
B3LYP/def2tzvp

Concerted: Make Allyl First?



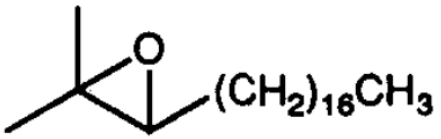
- Leaving Group
- Hydroxy Group
- Solvent
- Normal Concerted

  MA: Me < H < Alkyl



MABR	CH_2Cl_2	-20, 1	75	0 : 100
$BF_3{\cdot}OEt_2$	benzene	25, 2	77	70 : 30
SbF_5	toluene	-78, 2	86	82 : 18

Other Factors: Steric Effect



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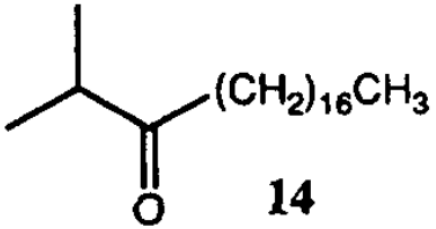

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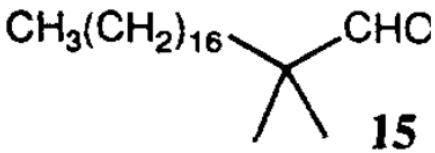
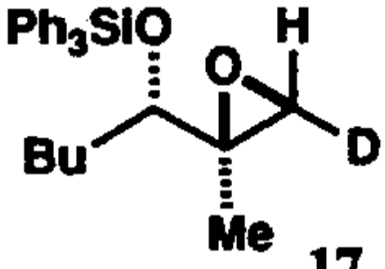


15

MABR	CH_2Cl_2	-20, 1	99	0 : 100
$BF_3{\cdot}OEt_2$	benzene	25, 1	73	75 : 25
$SnCl_4$	toluene	-78, 2	15	83 : 17
SbF_5	toluene	-78, 3	47	83 : 17

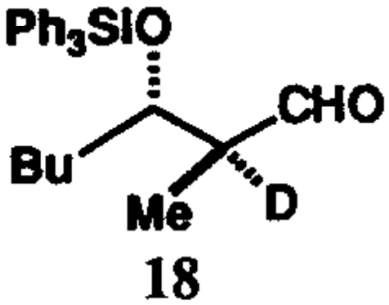


17

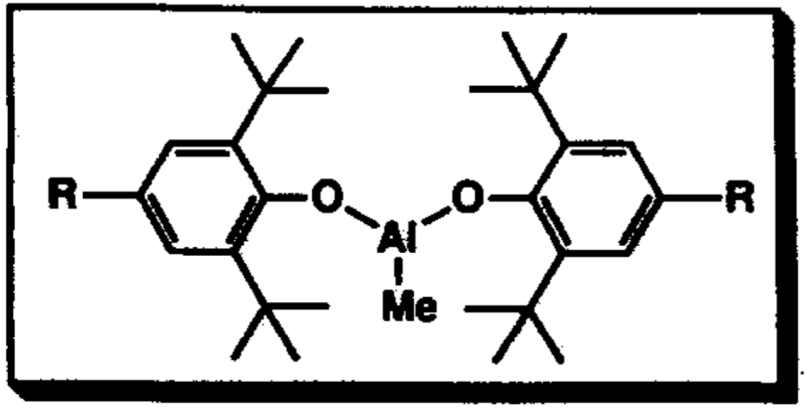
MABR

CH_2Cl_2

85%



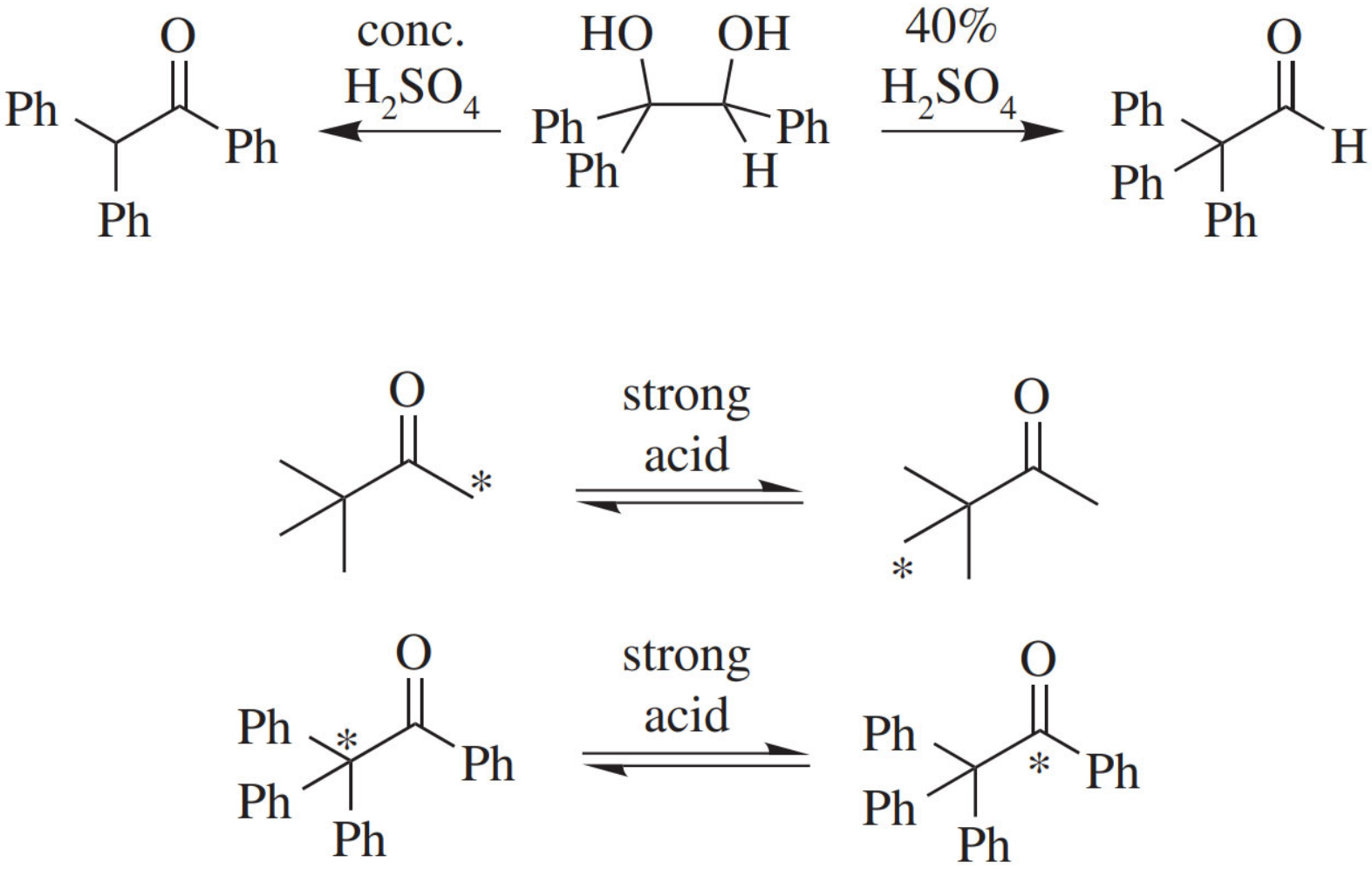
18



R = Me : MAD
R = Br : MABR

Tetrahedron **1994**, *12*, 3663; *Tetrahedron* **1992**, *16*, 3303.

Other Factors: Thermodynamic



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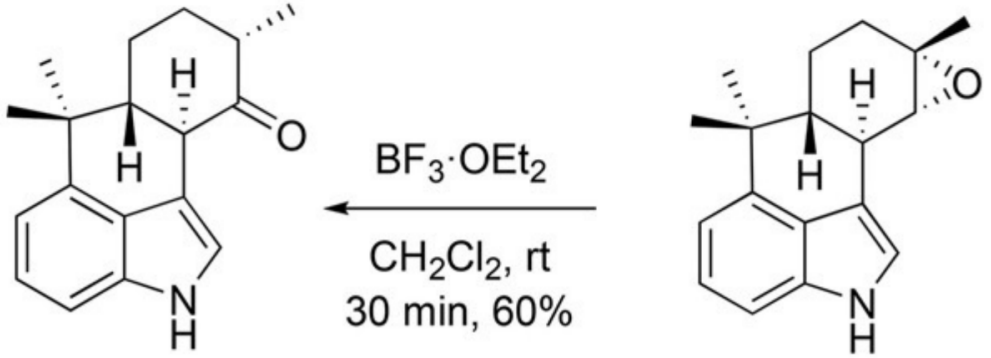
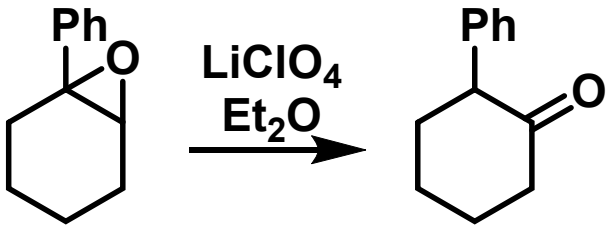
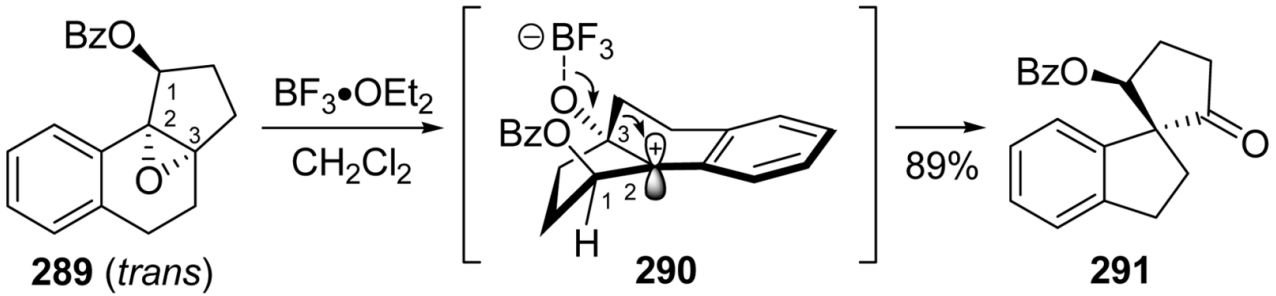
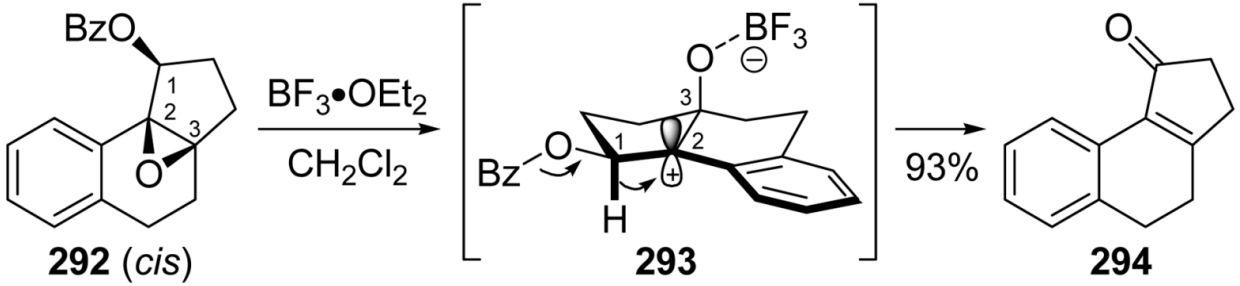
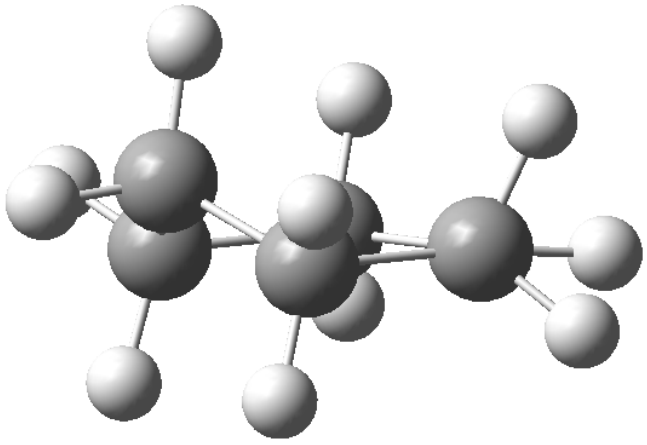
Six-Membered Rings: Axial First





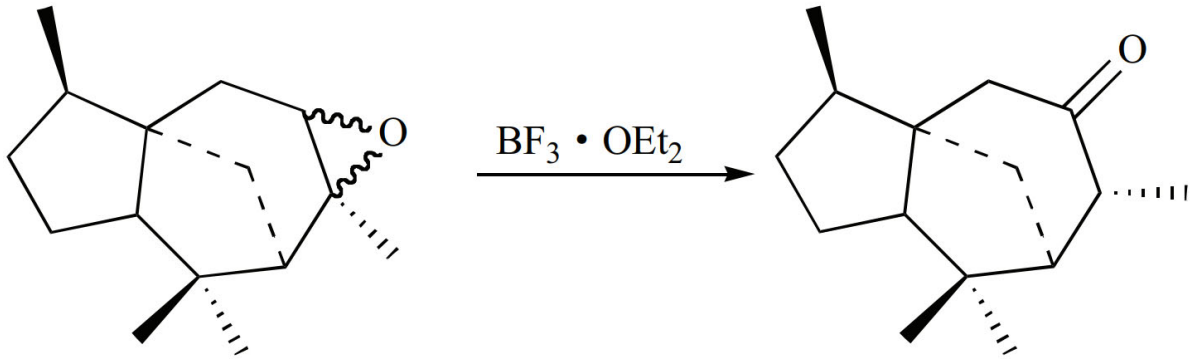


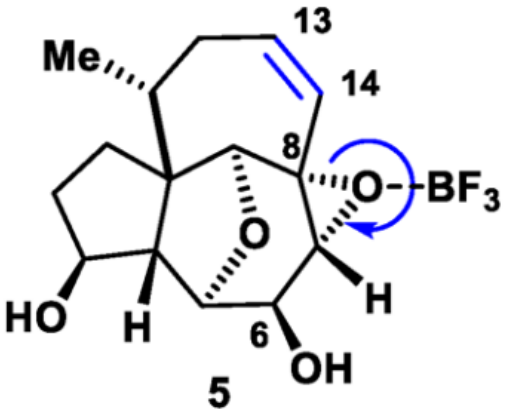




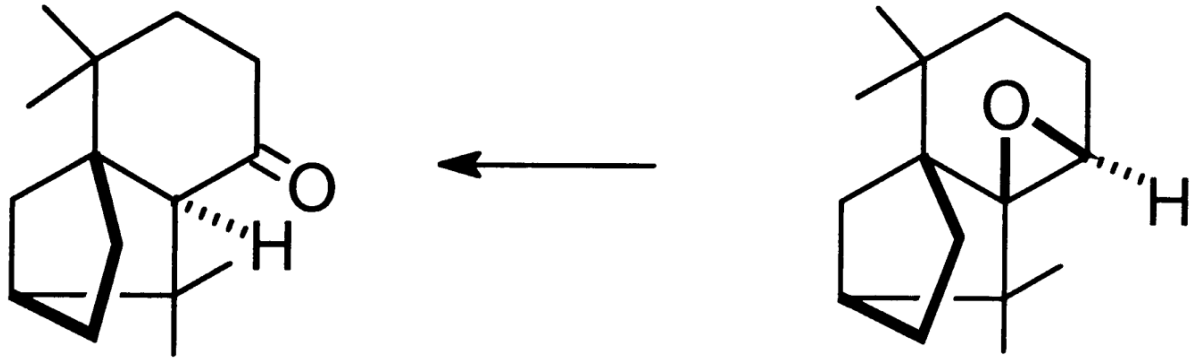
Chem. Eur. J. **2018**, *24*, 8980; *Angew. Chem., Int. Ed.* **1999**, *38*, 683; *J. Org. Chem.* **1996**, *61*, 1877.

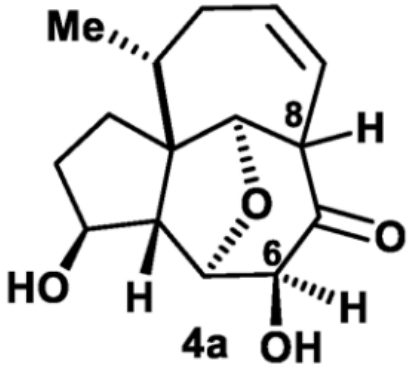
Rigidity Restriction: Bridged Ring





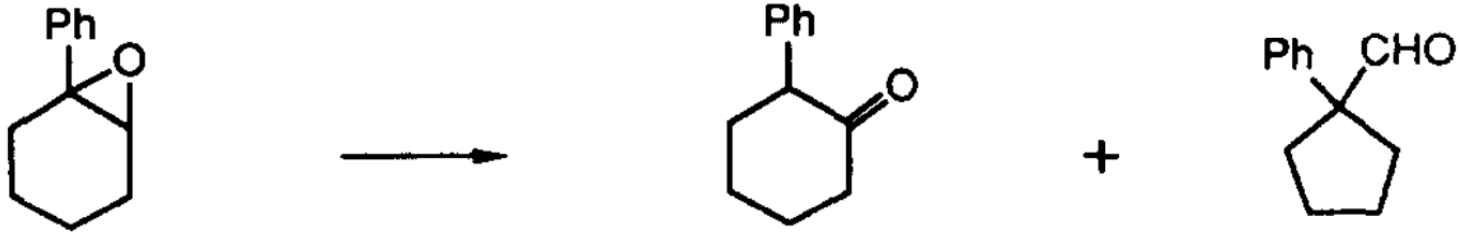
$BF_3 \cdot Et_2O$ | DCM, 25 °C, 60%





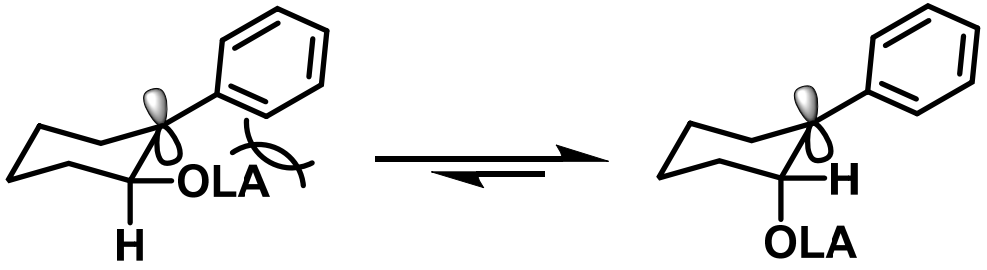
Letters in Organic Chemistry **2013**, *10*, 223; *Journal of Fluorine Chemistry* **2000**, *102*, 51; *Org. Lett.* **2017**, *19*, 2742.

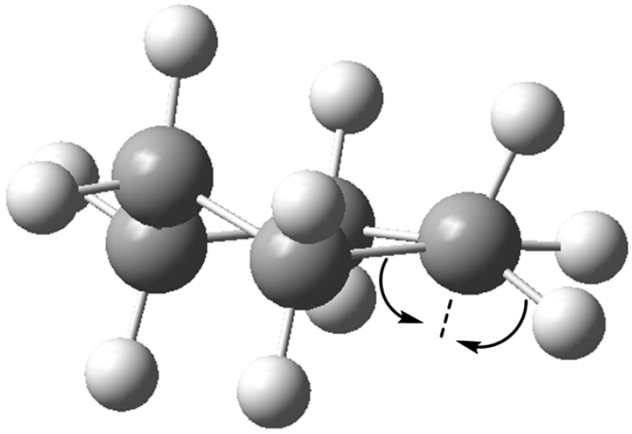
Both Equatorial: Twist or Stretch?



8 **9**

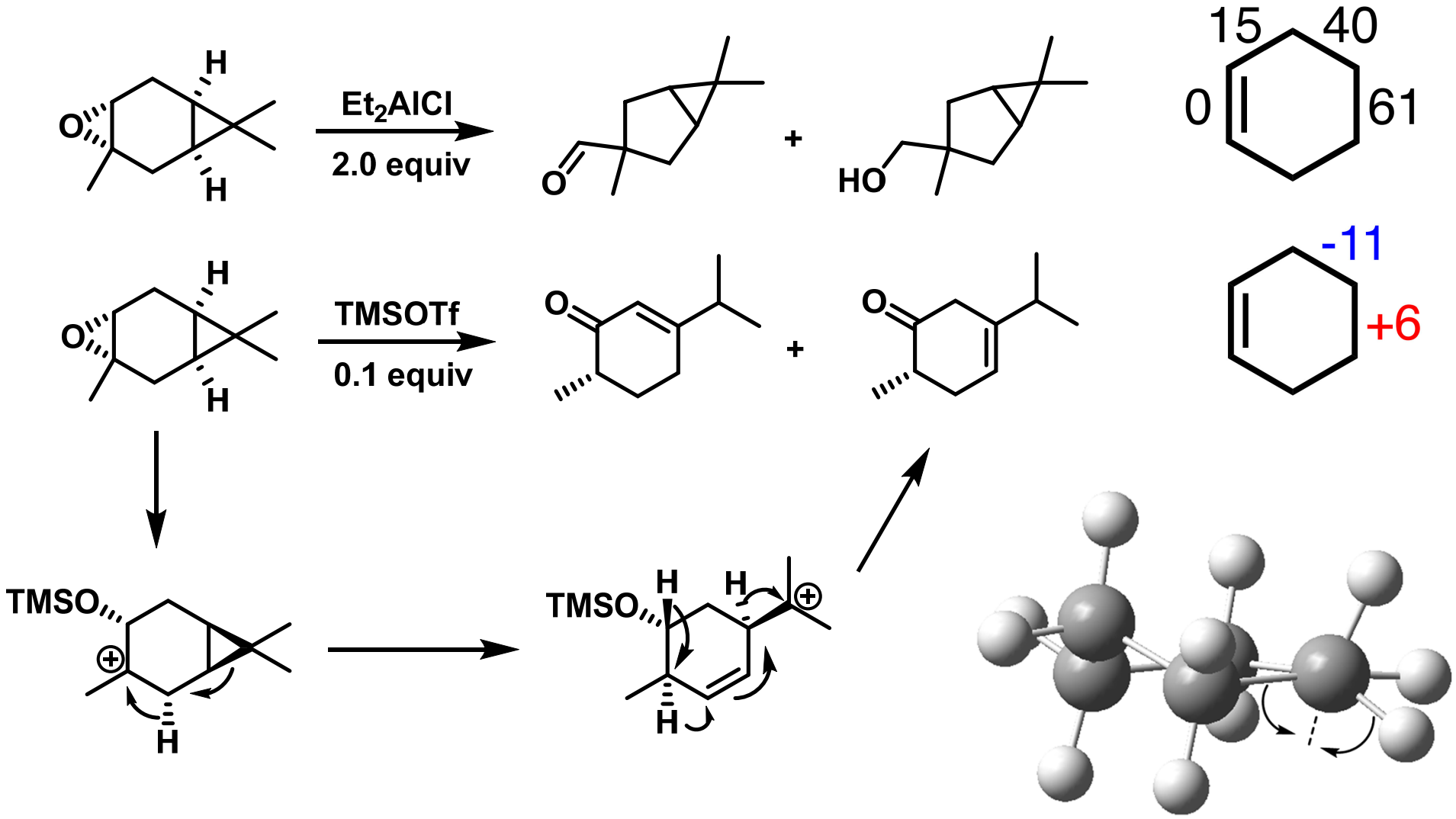
MABR	CH_2Cl_2	-78, 0.5	98	0 : 100
$BF_3{\cdot}OEt_2$	benzene	25, 1	72	0 : 100
$BF_3{\cdot}OEt_2$	hexane	0, 3	37	0 : 100
SbF_5	toluene	-78, 2	17	0 : 100





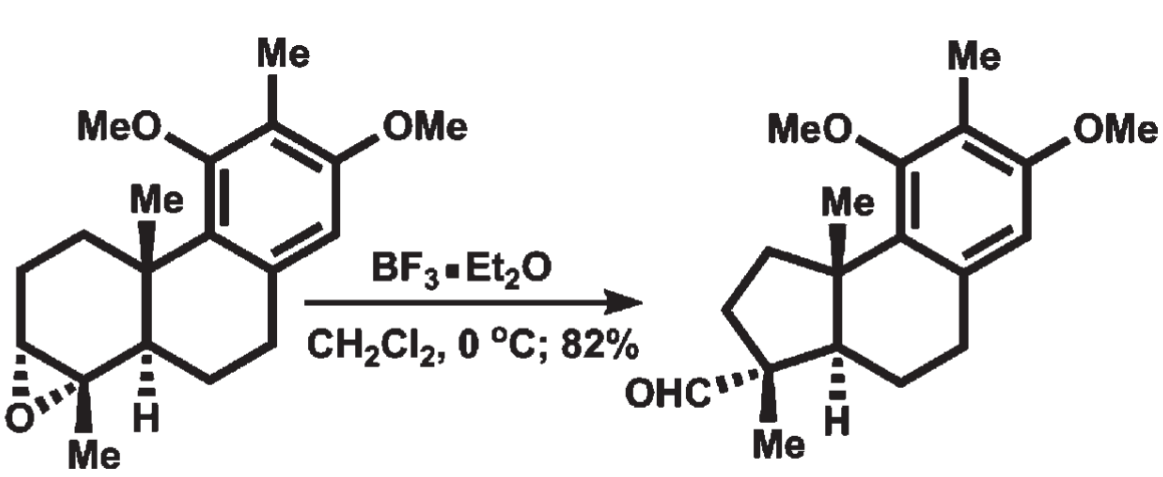
Tetrahedron **1994**, *12*, 3663.

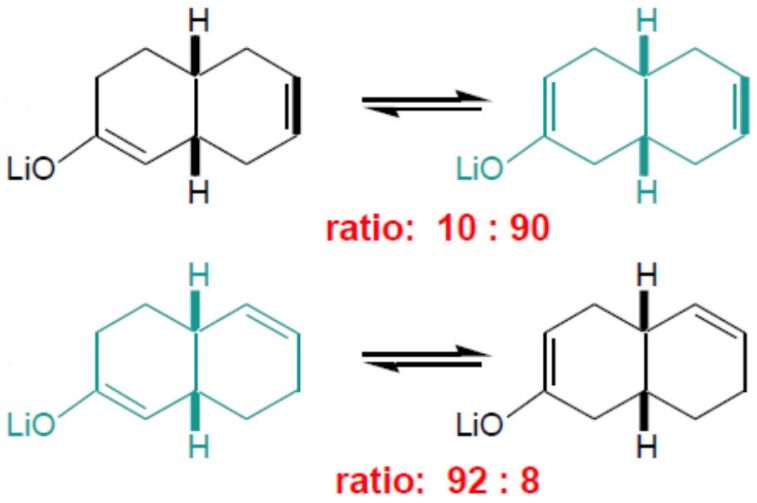
Twist or Stretch?

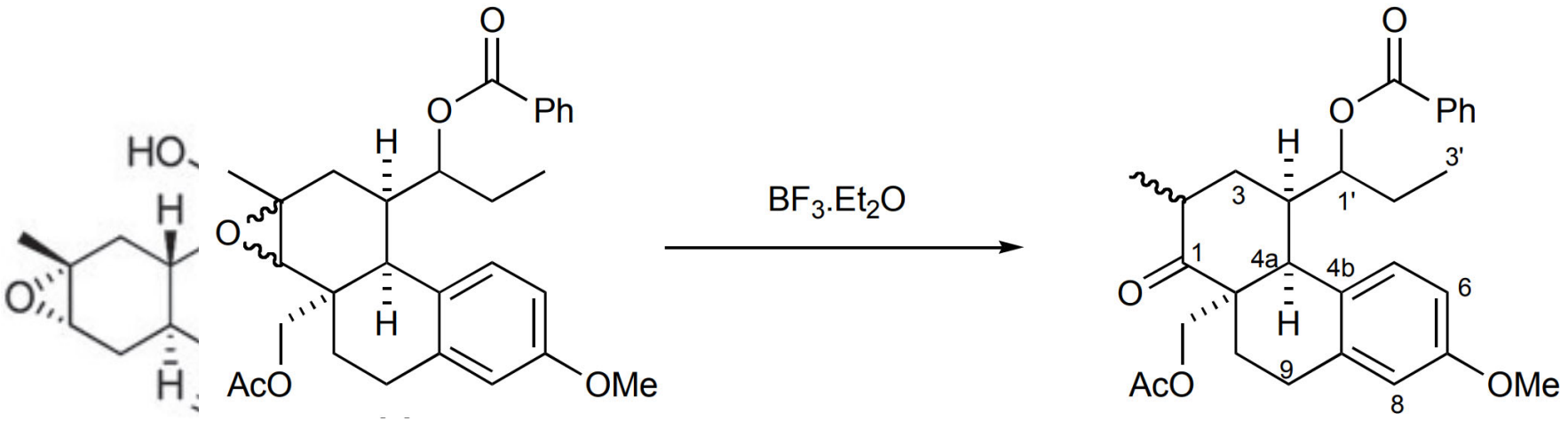


J. Org. Chem. **1995**, *60*, 465.

Both Equatorial: Condensed Ring

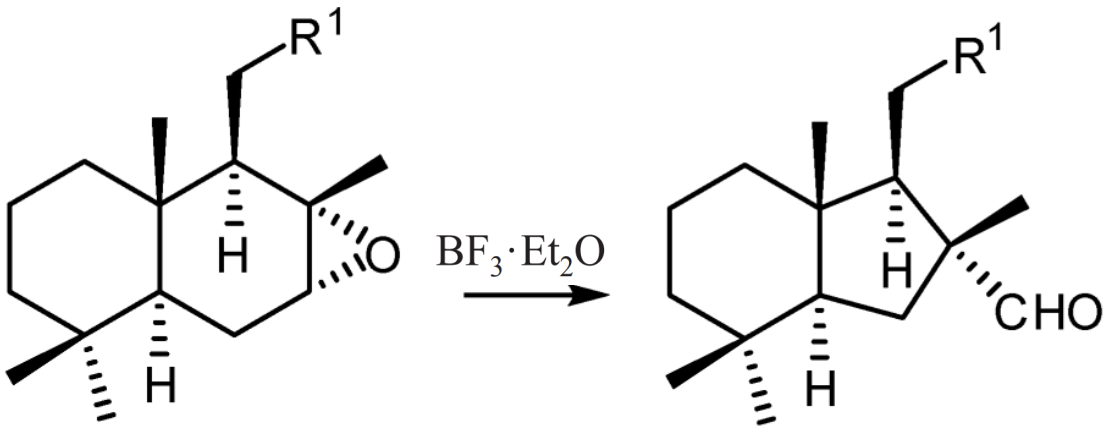


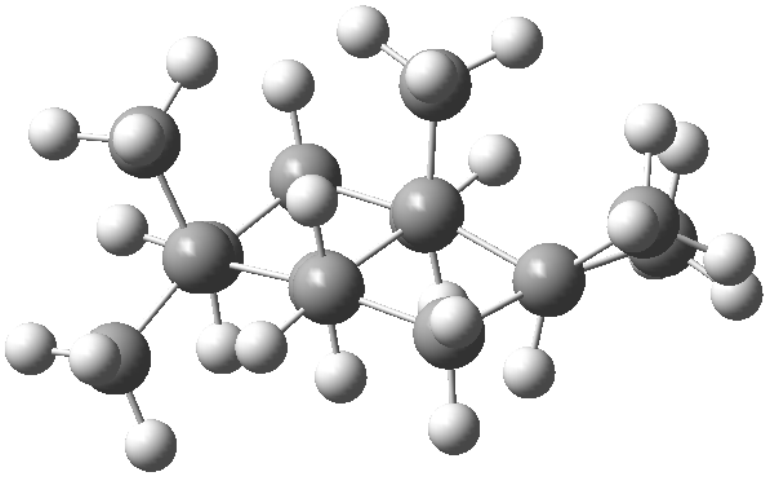


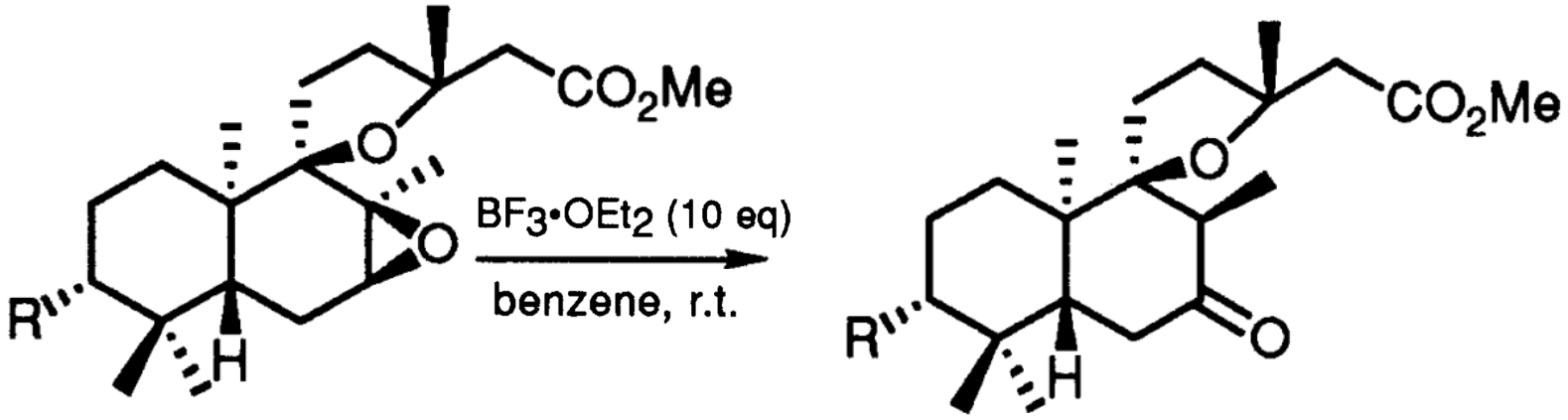


Org. Lett. **2011**, *21*, 5895; *Chem. Commun.* **2015**, *51*, 2871.

Both Equatorial: Torsional Strain







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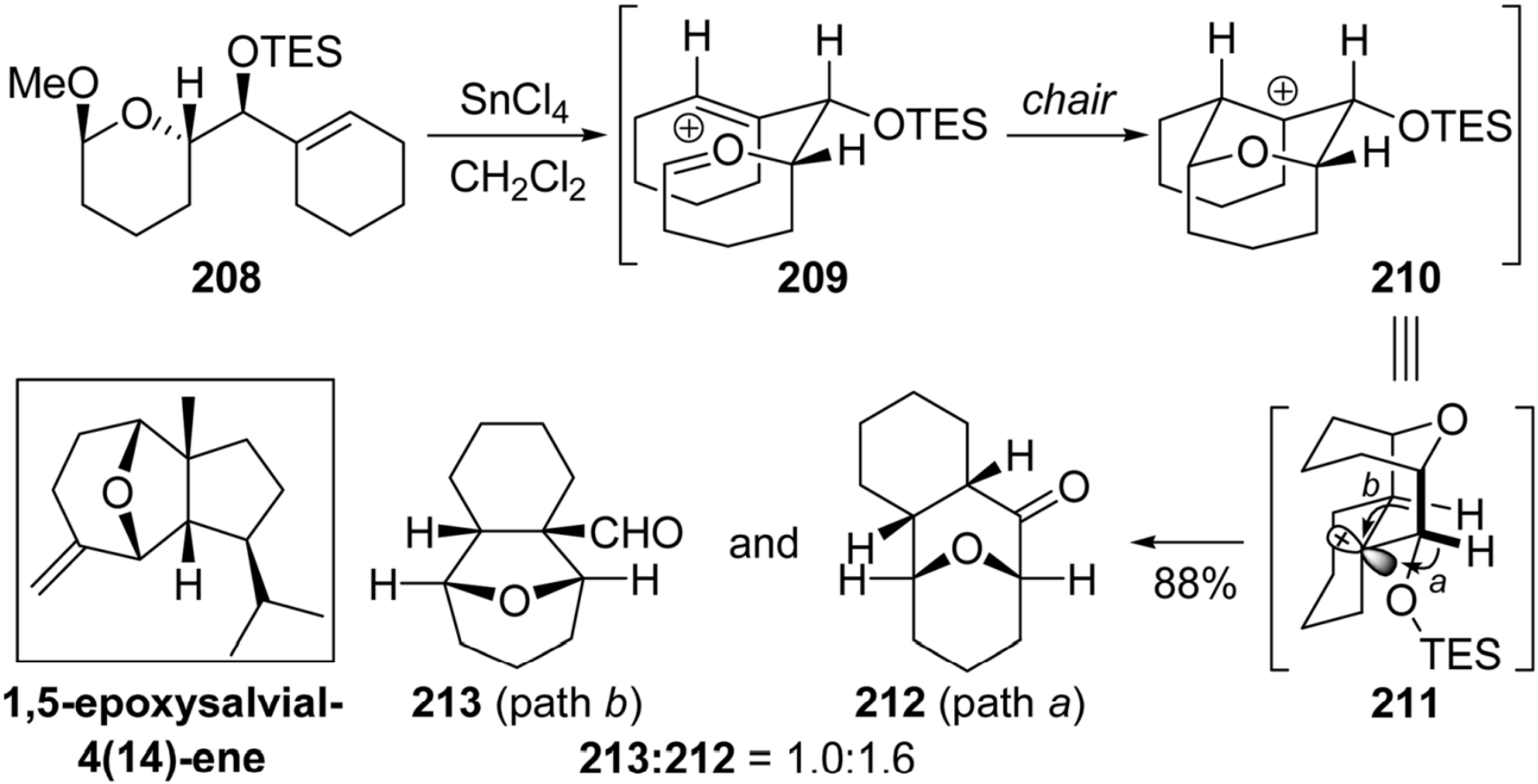
Conformation-Dependent Selectivity



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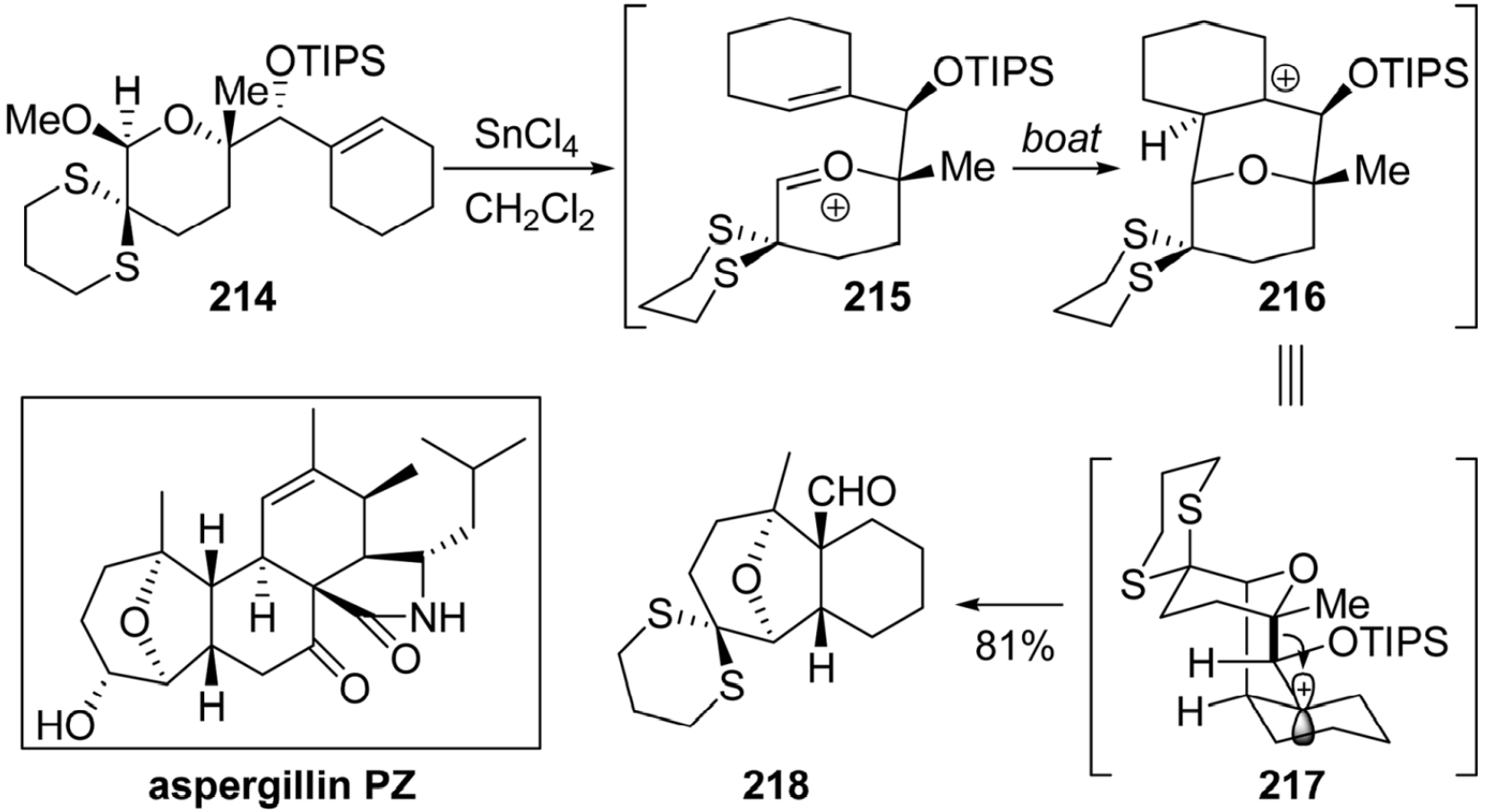
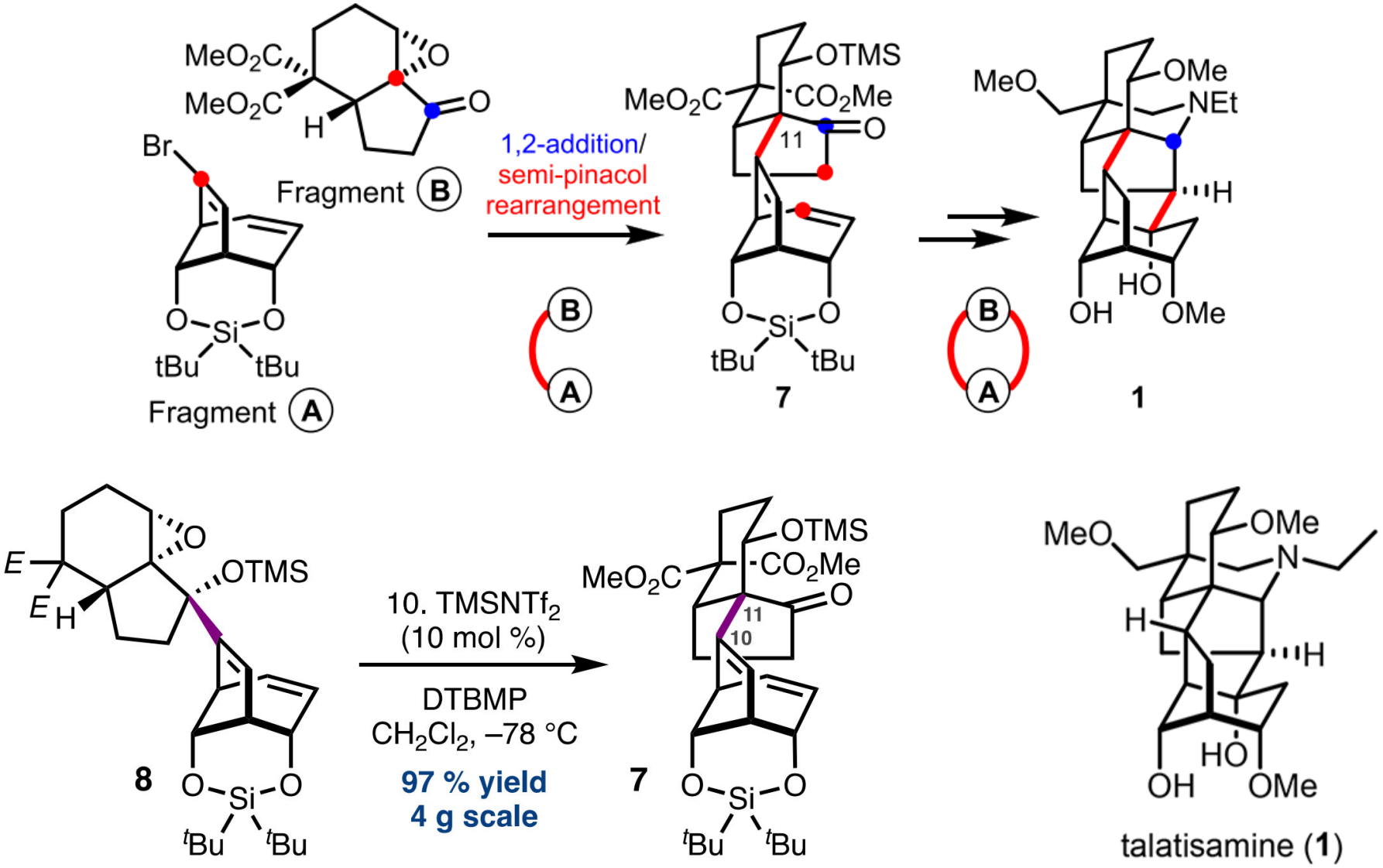
Conformation-Dependent Selectivity



J. Org. Lett. **2004**, *6*, 3853..

Talatisamine: Fragment Coupling



ACS Cent. Sci. **2021**, *7*, 1311.

Outline

- **Introduction**
- **General Selectivity of Migration**
  General Mechanism
  Electronic Migration Aptitude
  Other Factors Influence Migration Aptitude
- **Migration Aptitude in Six-Membered Rings**
- **Summary**
- **Acknowledgement**

Summary

- Mechanism: Stepwise and Concerted
- Migration Aptitude: Electronic and Steric
- Electronic MA: Better ERG and Better Overlap
- H vs Allyl: ERG vs Overlap in Different Mechanisms
- Six-Membered Rings: Factors are Complex, Subtle and Changeable
- Key: Be Perpendicular to Carbocation Easier
- Important Method of Skeleton Construction of Natural Products
- **Analyze Factors, Compare Differences and Adjust Strategies**