

## I. Introduction

- A. (R)- and (S)-Carvone and Their Chemistry

**Not Covered:** This presentation only serves as an overview and sampling of some of the syntheses that have been completed with carvone as the starting material; thus, many great syntheses are not included for the sake of brevity.

## II. Exploiting the Enone Functionality

- A. The Diels Alder Reaction
  - i. (-)-Peribysin, Danishefsky, 2008
  - ii. Lairdinol A: Ward, 2008
- B. Radical Cyclization
  - i. Pavidolide B: Yang, 2017
- A. Enolate Chemistry
  - i. (+)-Shearilycine, Newhouse, 2023
  - ii. Crotophorbolone: Inoue, 2015
  - iii. Hapalindole Q: Baran, 2004
  - iv. (-)-Aristolochene: Pedro, 2006

## Helpful Supplemental Material:

*Natural Product Communications*, **2013**, 8, 7, 935-48.  
*Studies in Natural Products Chemistry*, **2007**, 39, 233-67.  
*Studies in Natural Products Chemistry*, **1995**, 16, 123-288.

Selected Syntheses That Are Not Covered:

Garg, *J. Am. Chem. Soc.*, **2011**, 133, 15797.  
 Fukuyama, *Org. Lett.*, **2011**, 13, 2068.  
 Trost, *J. Am. Chem. Soc.*, **1996**, 118, 233.  
 Shing, *Angew. Chem. Int. Ed.*, **2005**, 44, 7981.  
 Furstner, *J. Am. Chem. Soc.*, **2010**, 132, 11042.  
 Guang, *Angew. Chem. Int. Ed.*, **2019**, 58, 6659.  
 Shenvi, *J. Am. Chem. Soc.*, **2020**, 142, 11376.  
 Sarpong, *J. Am. Chem. Soc.*, **2015**, 137, 6327.  
 Sarpong, *J. Am. Chem. Soc.*, **2020**, 142, 15536.  
 Sarpong, *Acc. Chem. Res.*, **2022**, 55, 746.  
 Evans, *J. Am. Chem. Soc.*, **2017**, 139, 6046.  
 Sarpong, *J. Am. Chem. Soc.*, **2017**, 139, 11349.  
 Byrd, *J. Org. Chem.*, **1976**, 41, 16, 2773.  
 Sarpong, *J. Am. Chem. Soc.*, **2018**, 140, 9810.  
 Pan, *Angew. Chem. Int. Ed.*, **2006**, 45, 3651.  
 Giner, *J. Org. Chem.*, **2002**, 67, 4659.  
 Kirsch, *Angew. Chem. Int. Ed.*, **2007**, 46, 2310.

## III. Isopropenyl Group Modification

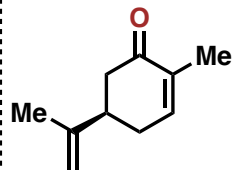
- A. Epoxidation and Coupling
  - i. Phomactin K: Sarpong, 2020
- B. Hydroboration
  - i. Briarellin E and F: Overman, 2002
- A. Halogenation
  - i. Himalensine A: Qiu, 2015

## IV. Cyclohexene Ring Fragmentation

- A. Favorskii Rearrangement
  - i. Nortrilobolide: Ley, 2003
- B. Oxidative Cleavage
  - i. (+)-Mikanokryptin: Maimone, 2019
  - ii. (+)-Omphadiol A: Romo, 2011
  - iii. (-)-Scabrolide: Stoltz, 2020

# Why Carvone? A Versatile Chiral Synthons In Total Synthesis

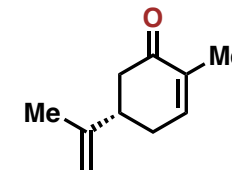
*(R)-(-)-carvone*



\$0.30/g  
First isolated in 1891  
50-60% content of  
spearmint oil



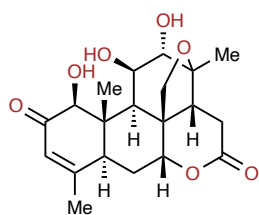
*(S)-(+)-carvone*



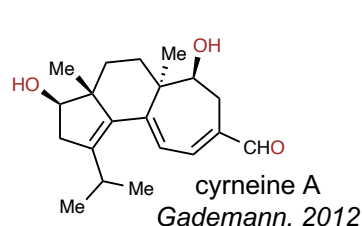
\$3.62/g  
First isolated in 1841  
Found in caraway and  
dill seeds



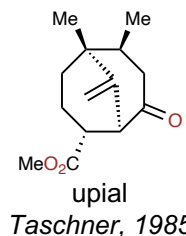
“The carvones constitute the most often used monoterpenoid starting materials in natural product synthesis.”



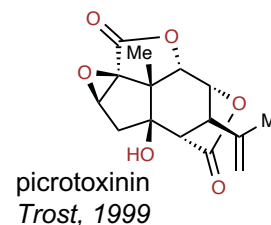
samaderine Y  
Shing, 2005



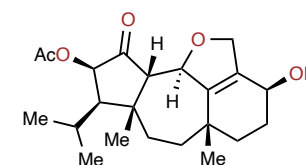
cyrneine A  
Gademann, 2012



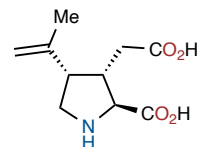
upial  
Taschner, 1985



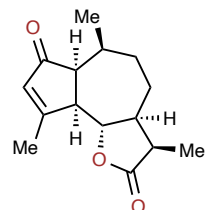
picrotoxinin  
Trost, 1999



guanacastepene  
Sorensen, 2006



kainic acid  
Fukuyama, 2011



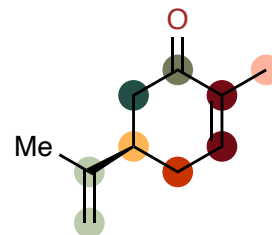
cladantholide  
Fukuyama, 2011

alkylation/acylation

reduction  
epoxidation  
dihydroxylation  
ozonolysis  
halogenation

chiral auxiliary

1,2 addition  
homologation

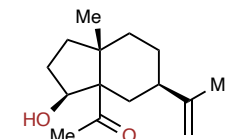


deprotonation  
oxidation

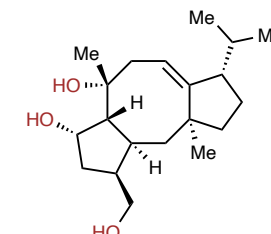
allylic oxidation

cycloaddition  
radical cyclization  
epoxidation  
reduction  
reductive alkylation

conjugate addition



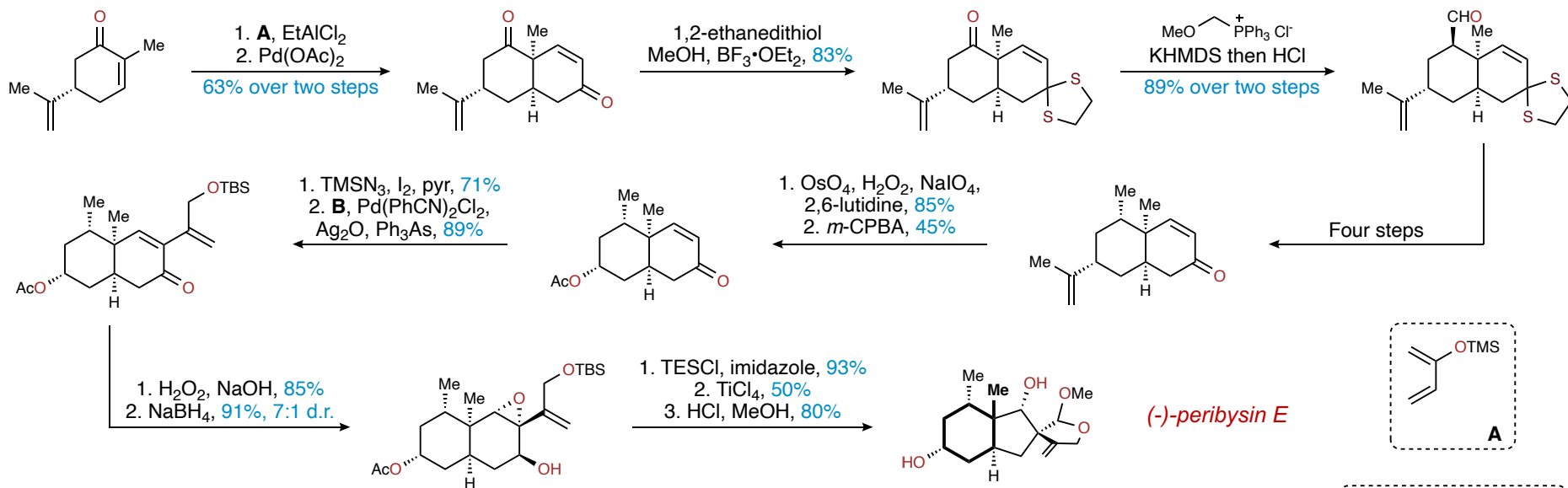
cyperolone  
Kirsch, 2012



cyclooctanin  
Kirsch, 2012

# Exploiting the Enone: The Diels Alder Reaction

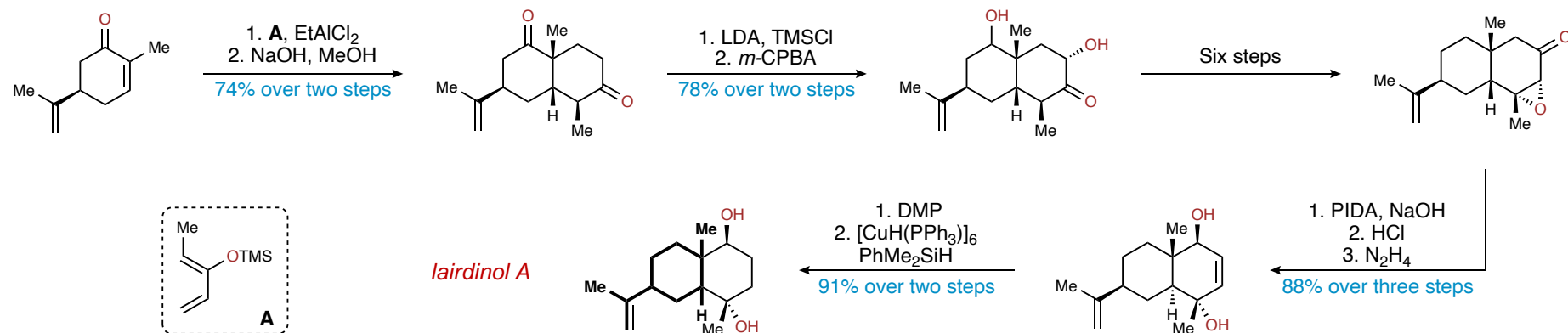
## 2008, Danishefsky: (-)-peribysin



**Key Reaction To Review:** Lewis Acid catalyzed Diels Alder reaction.

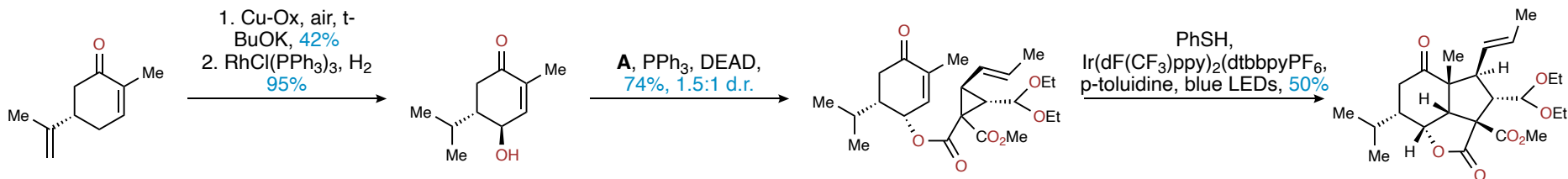
Stereoelectronic considerations: Reactions can take place with an endo or exo TS. The endo TS is kinetically favored (2° orbital effects) and the exo TS is thermodynamically favored (fewer steric interactions).

## 2008, Ward: lairdinol A

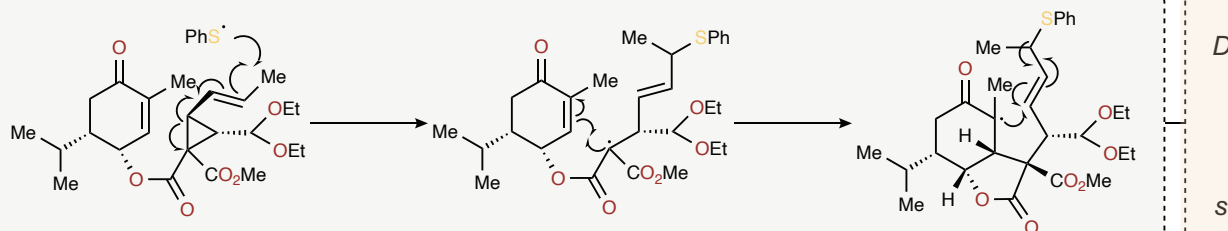


# Exploiting the Enone: Radical Cyclization

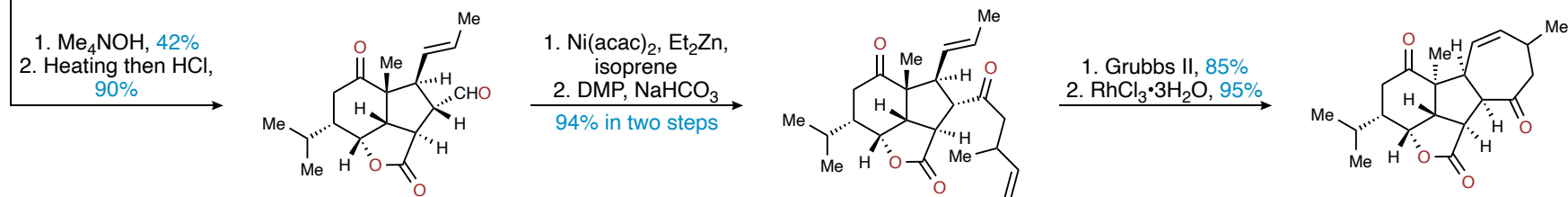
## 2017, Yang: pavidolide B



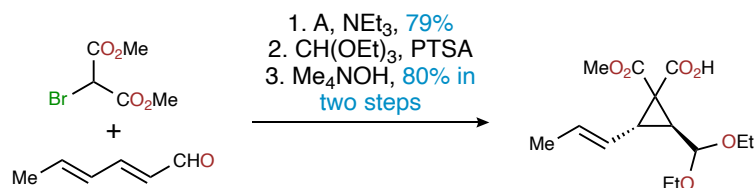
### Mechanism For the Radical Cyclization



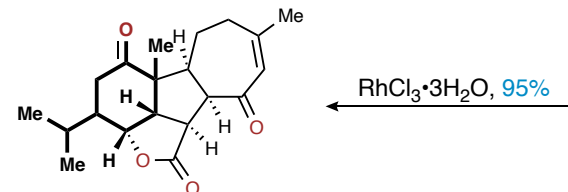
**Key Reaction To Review:** Radical cyclizations  
 Driving force: Ring strain release and the formation of stabilized radical  
 Radical stability: EDGs and EWGs both stabilize radicals. **Captodative effect** – the presence of an EDG and EWG for any one radical has a greater stabilizing effect than the presence of two EDGs or two EWGs.



### Synthesis of the Vinyl Cyclopropane A

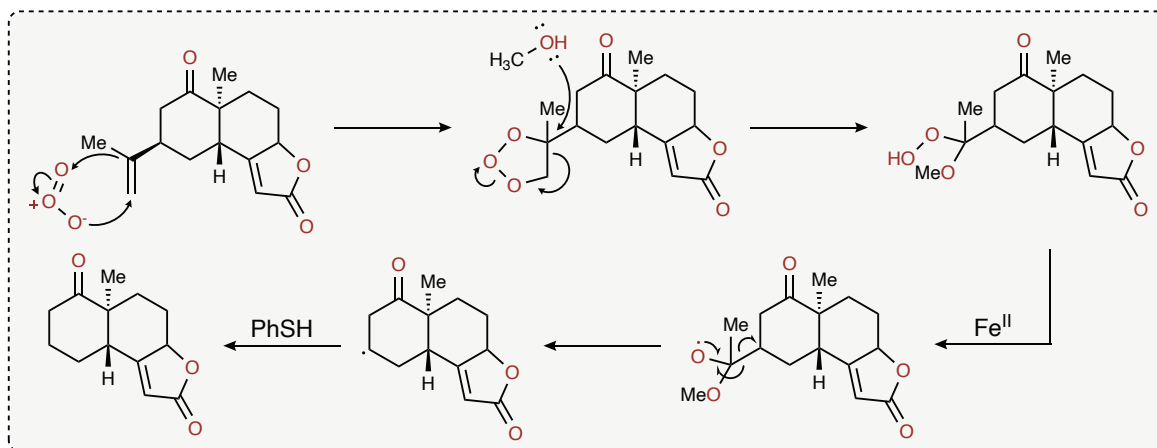
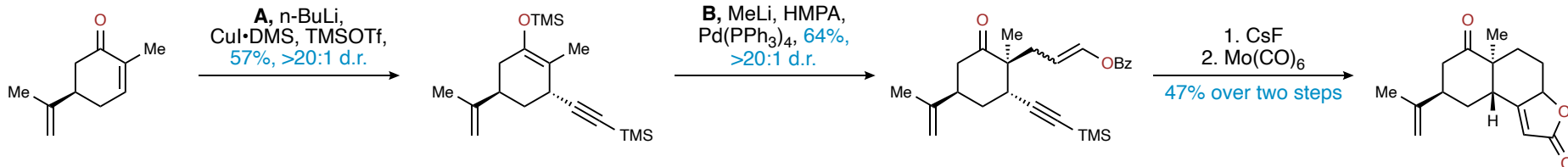


(-)-pavidolide B

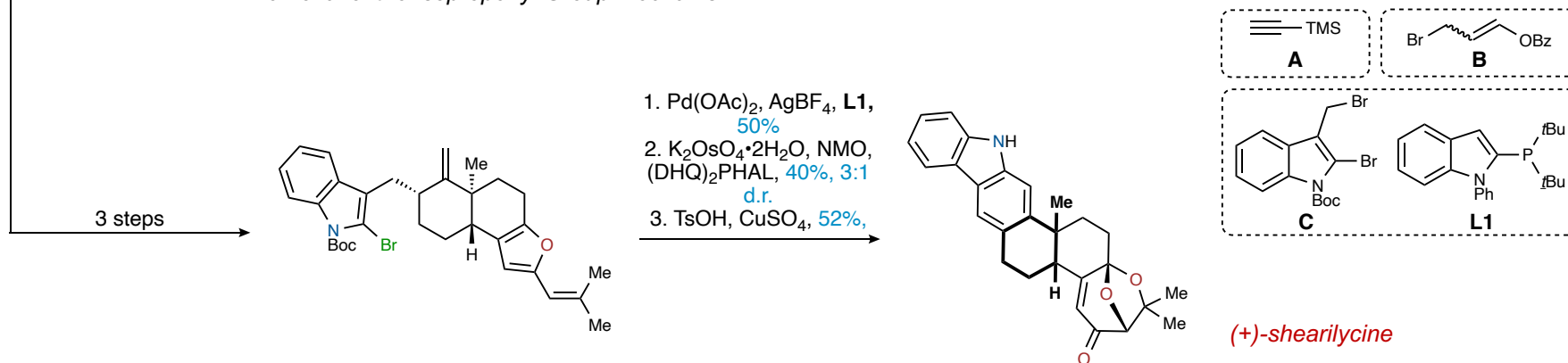


# Exploiting the Enone: Enolate Chemistry

2023, Newhouse



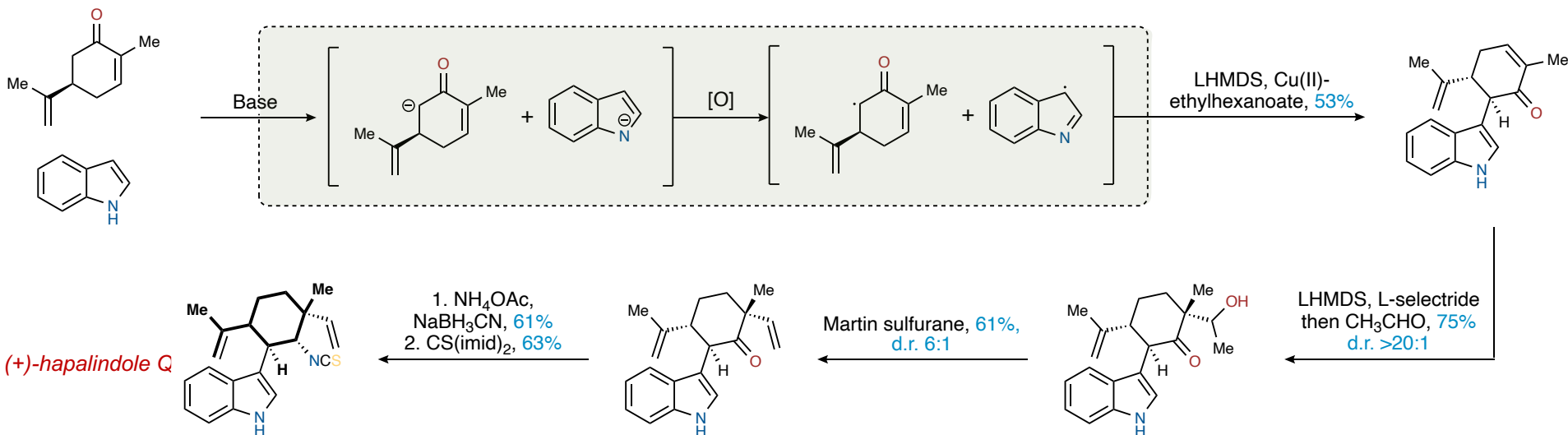
Removal of the Isopropenyl Group Mechanism



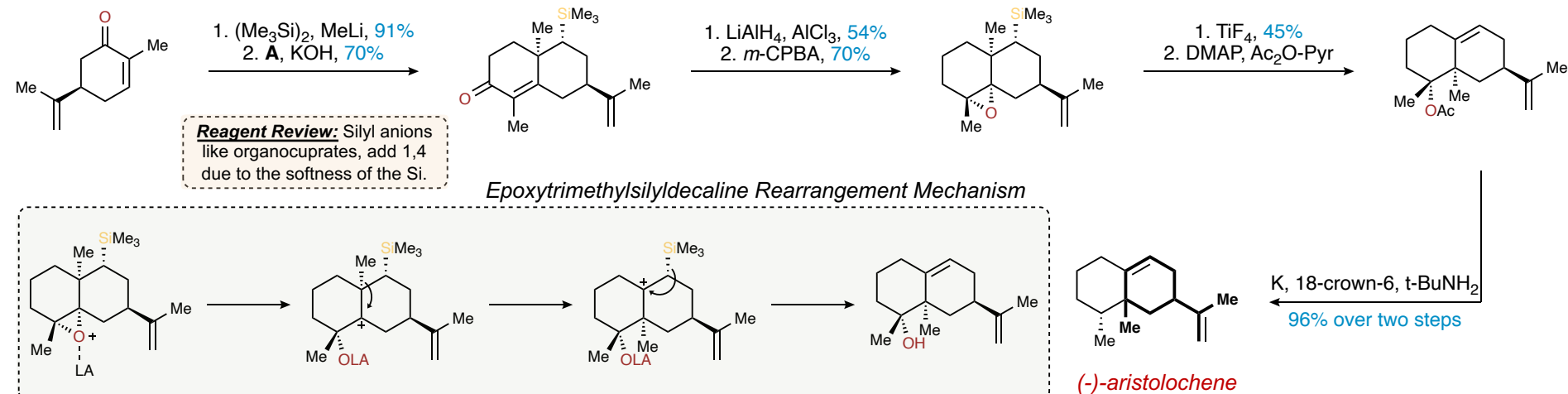


# Exploiting the Enone: Enolate Chemistry

## 2004, Baran: hapalindole Q



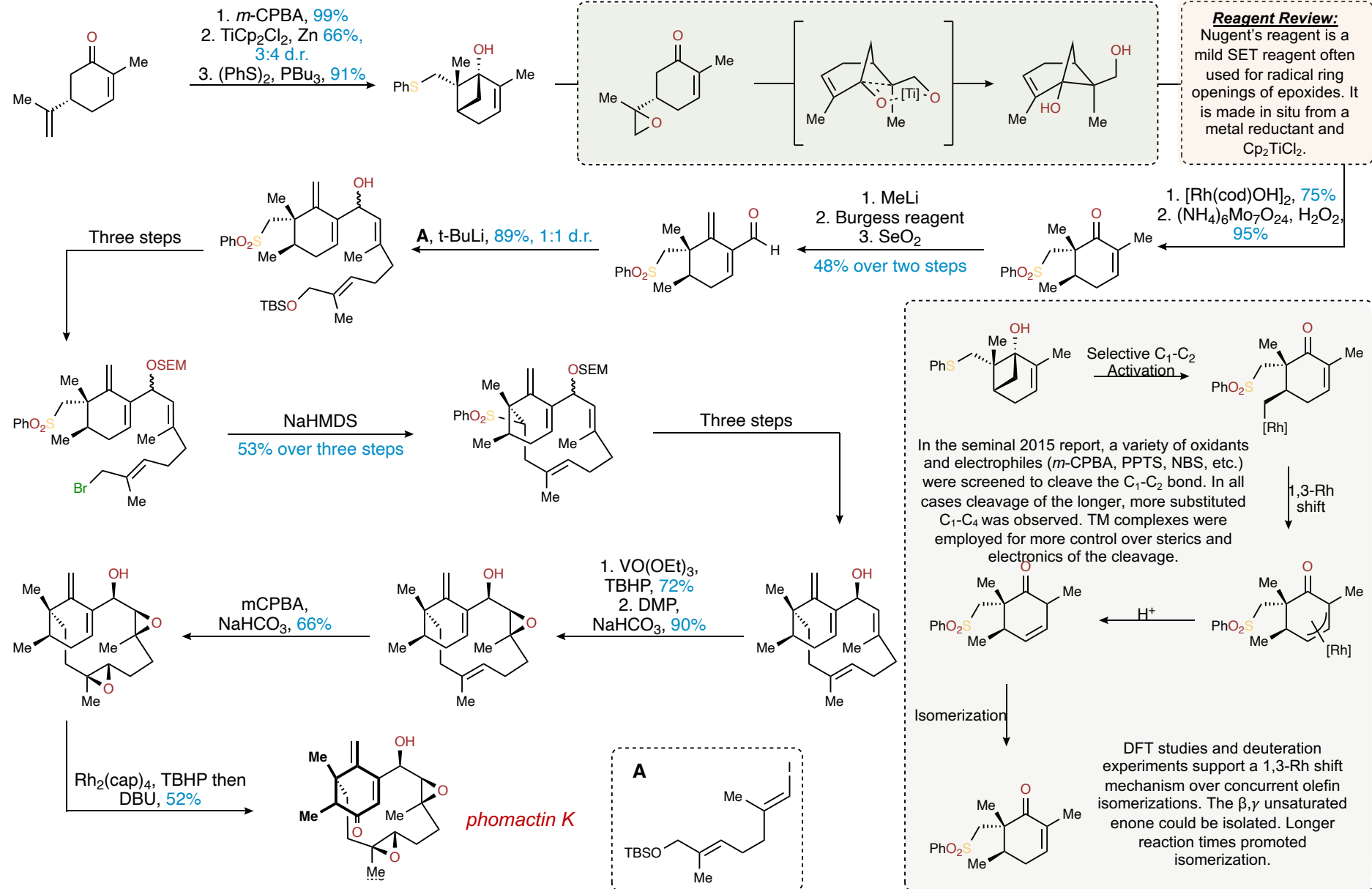
## 2006, Pedro: (-)-aristolochene



**Key Reaction Review:** The presence of the TMS groups stabilizes the carbocation that forms as the methyl migrates. This stabilizing effect is described by the **beta silicon effect** which states the presence of a Si group helps stabilize carbocations that form on the beta carbon. The C-Si sigma orbital overlaps with the antibonding orbital of the leaving group, donating electron density, which lengthens and weakens the C-LG bond. (The Hosomi-Sakurai reaction, among others, is an example from 534 where this effect applies. Different transformation, same stabilization.)

# Isopropenyl Group Modification: Epoxidation and Coupling

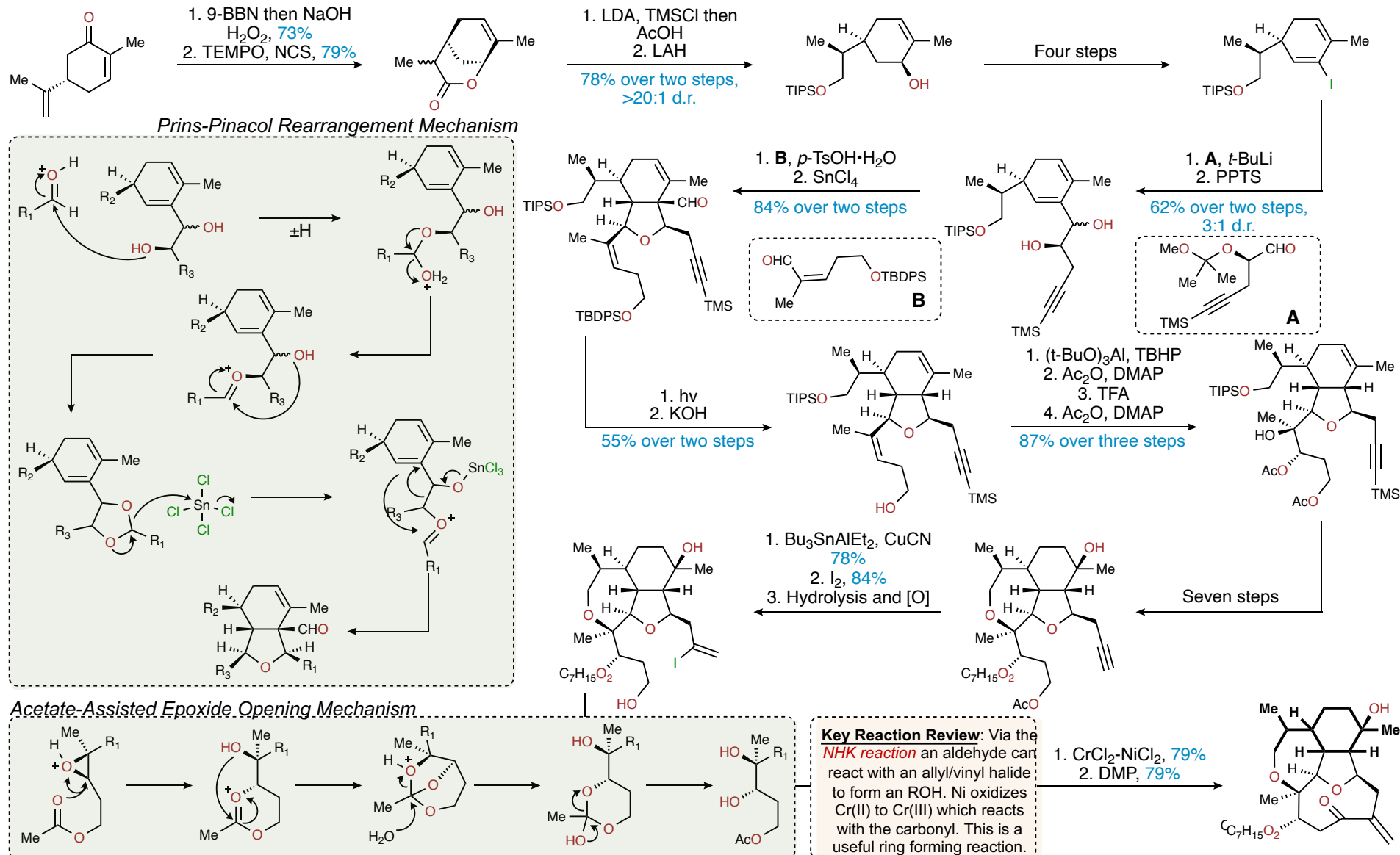
## 2020, Sarpong: phomactin K





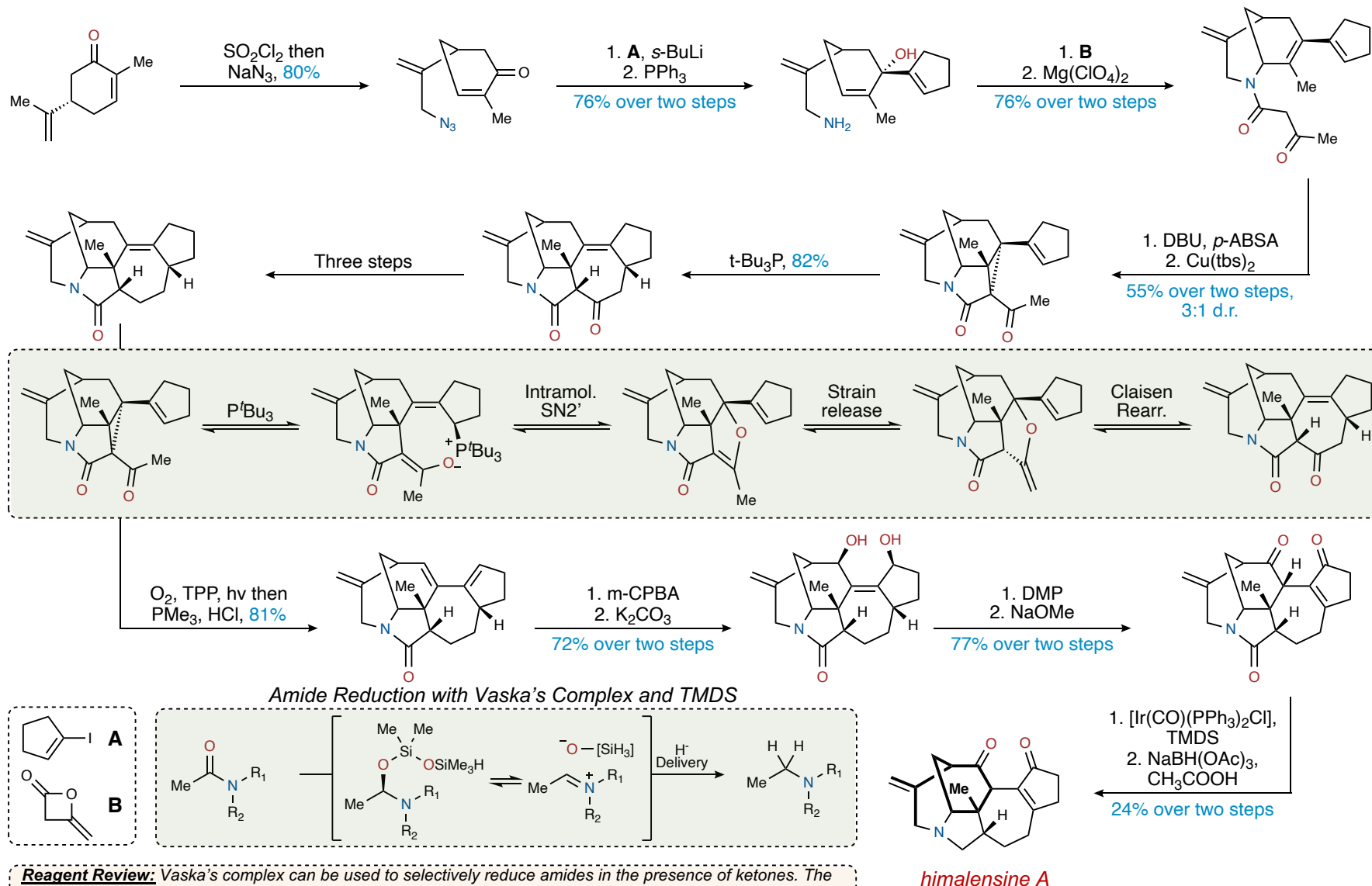
# Isopropenyl Group Modification: Hydroboration

## 2002, Overman: briarellin E and F



# Isopropenyl Group Modification: Halogenation

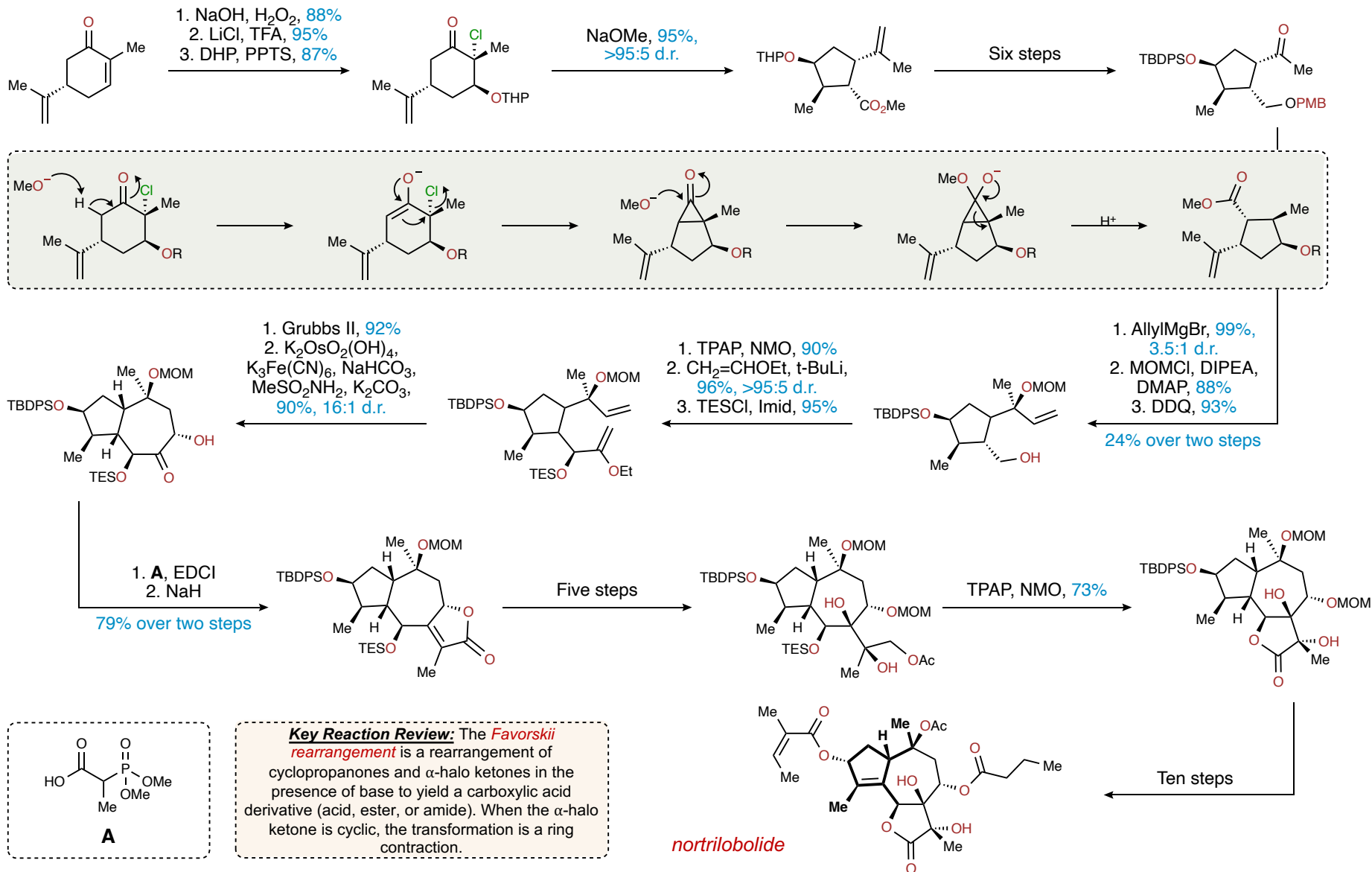
## 2021, Qiu: *himalensine A*



**Reagent Review:** Vaska's complex can be used to selectively reduce amides in the presence of ketones. The intermediate imine can also be intercepted with other nucleophiles than a hydride.

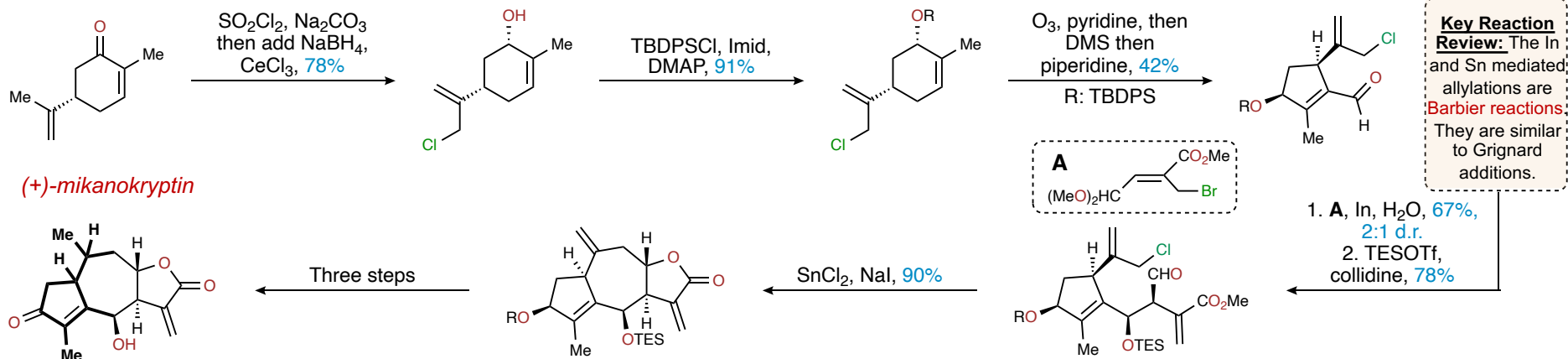
# Cyclohexene Ring Fragmentation: Favorskii Rearrangement

## 2003, Ley: *nortrilobolide*

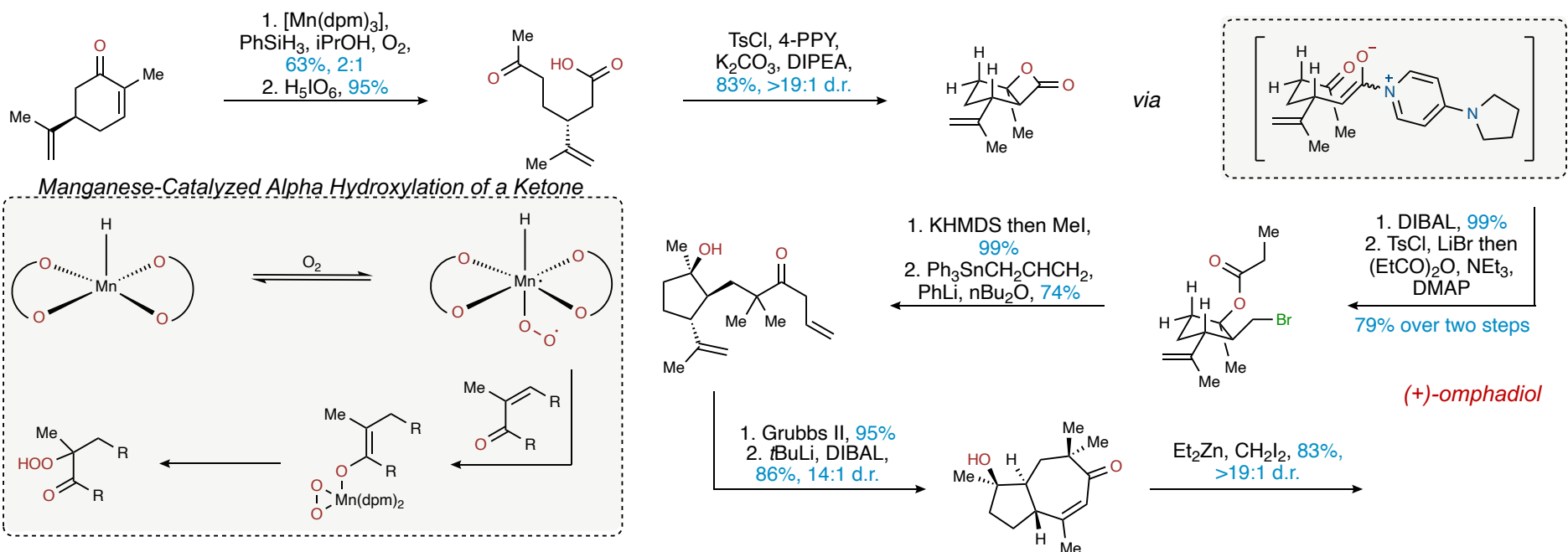


# Cyclohexene Ring Fragmentation: Oxidative Cleavage

## 2019, Maimone: (+)-mikanokryptin

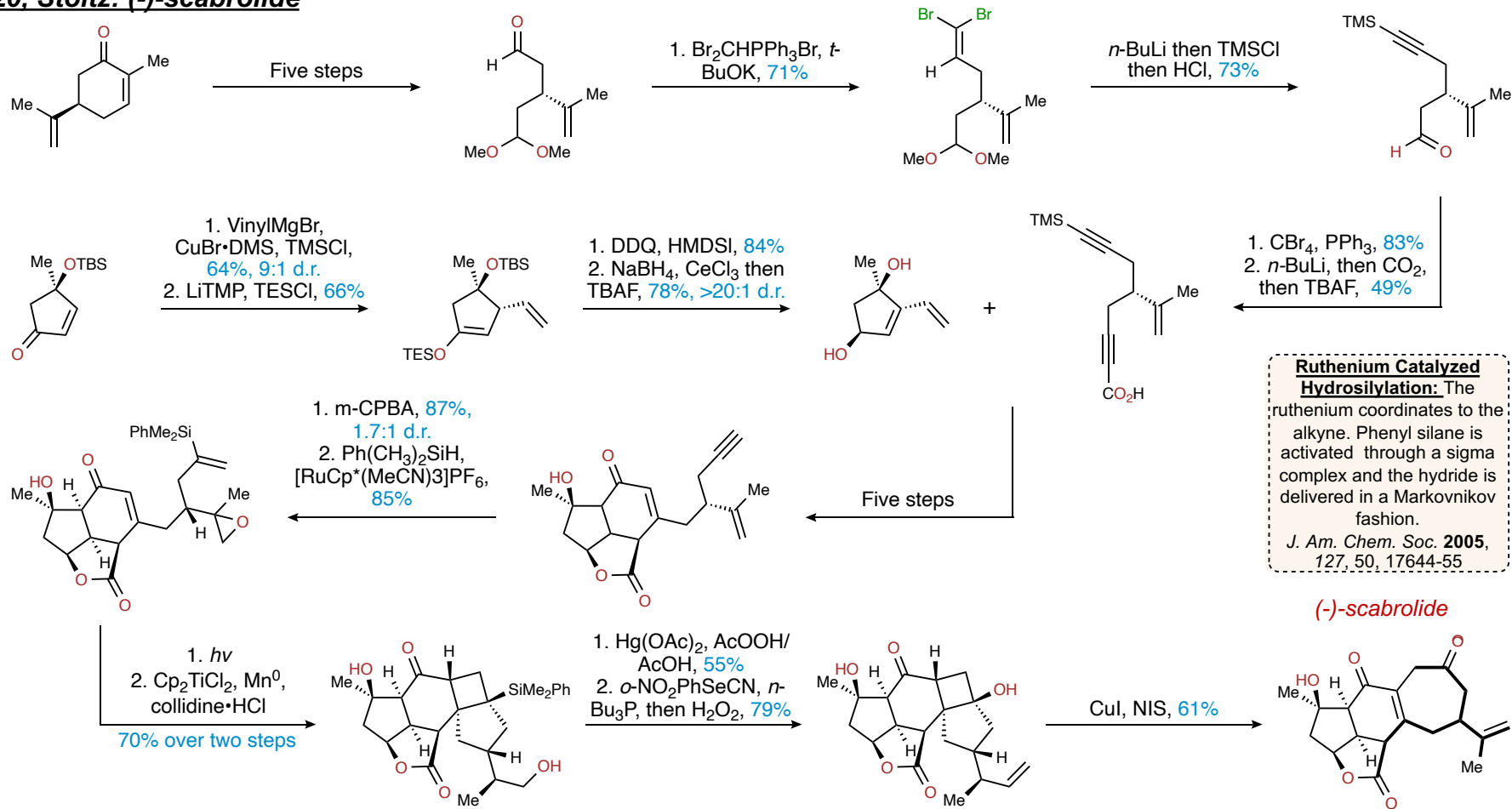


## 2011, Romo: (+)-omphadiol



# Cyclohexene Ring Fragmentation: Oxidative Cleavage

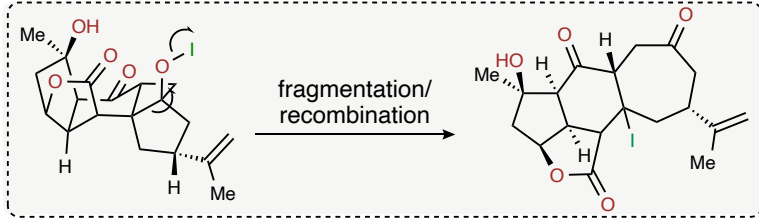
## 2020, Stoltz: (-)-scabrolide



**Ruthenium Catalyzed Hydrosilylation:** The ruthenium coordinates to the alkyne. Phenyl silane is activated through a sigma complex and the hydride is delivered in a Markovnikov fashion.  
*J. Am. Chem. Soc.* **2005**, 127, 50, 17644-55

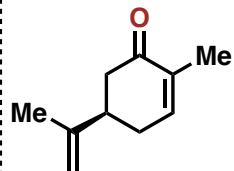
**Titanocene Mediated Epoxide Opening:** Titanocene is reduced to the active Ti(III) species via the metal reductant, manganese. The most stable carbon centered radical is formed upon epoxide opening and collidine is protonates the Ti-O bond.

**Tamao-Fleming Oxidation:** The Tamao-Fleming oxidation converts a C-Si bond to a C-O bond via the action of a peroxy acid or hydrogen peroxide. This reaction is often used for oxidations of fluorosilanes.



# Why Carvone? A Versatile Chiral Synthons In Total Synthesis

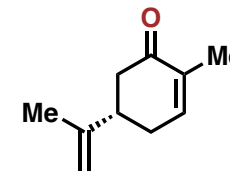
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\$0.30/g  
First isolated in 1891  
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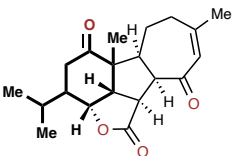


*(S)-(-)-carvone*

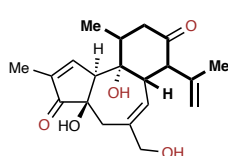


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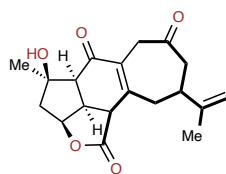
*"The carvones constitute the most often used monoterpenoid starting materials in natural product synthesis."*



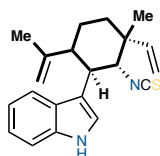
*(-)-pavidolide B*  
Yang, 2017



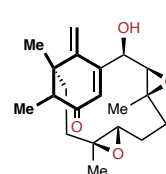
crotophorbolone  
Inoue, 2015



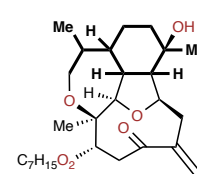
*(-)-scabrolide A*  
Stoltz, 2020



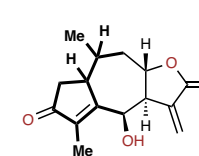
hapalinole Q  
Baran, 2004



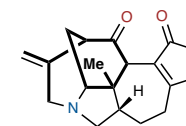
phomactin K  
Sarpong, 2020



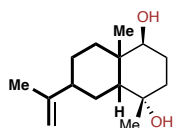
briarellin E and F  
Overman, 2002



*(+)-mikanokryptin*  
Maimone, 2019

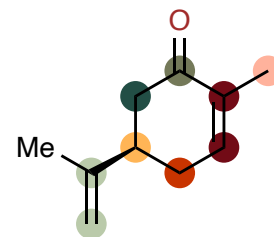


himalensine A  
Qiu, 2021

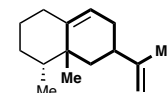


lairdinol  
Fukuyama, 2011

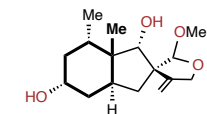
The carvones are a linchpin in total synthesis. Their inherent chirality and access to all carbons on the cyclohexene ring allow access to thousands of natural products while allowing for the rapid build up of complexity.



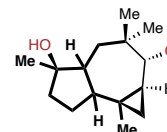
While 15 syntheses were detailed here, there are countless examples of the excellent use of the carvones in natural product synthesis and only a brief survey of distinct disconnections have been considered here.



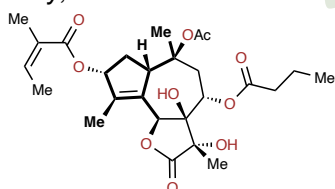
aristolochene  
Pedro, 2006



peribysin E  
Danishefsky, 2008



*(+)-omphadiol*  
Romo, 2011



nortrilobolide  
Ley, 2003

*(-)-shearilcine*  
Newhouse, 2023

