



LITERATURE SEMINAR GAICH GROUP

Ring
Expansion
Reactions in
Organic
Synthesis

OVERVIEW

- Main Concepts
- One Atom Insertion
 - Carbon Insertion Reactions
 - Nitrogen Insertion Reactions
 - Oxygen Insertion Reactions
- Three-membered Ring as Building Element
- Four-membered Rings in Ring Enlargements
- Büchner Reaction

RING EXPANSION REACTIONS

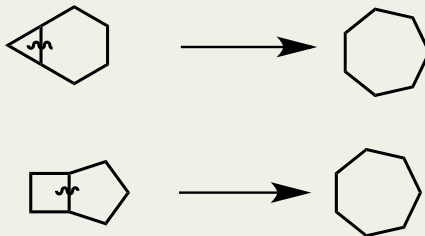
Main Concepts

Group X



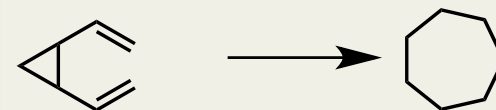
- X either possesses a charge (full or latent) or has carbene character
- Regioselective outcome is predictable through migration rules

Homo- or Heterolysis



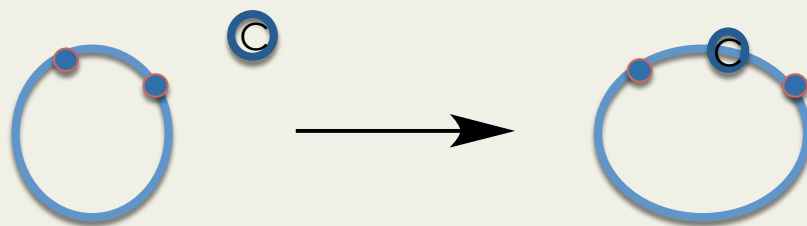
- Promoted by functional groups adorning the ring
- Strained ring must not be present in the starting material but it is a pivotal intermediate

Pericyclic reactions

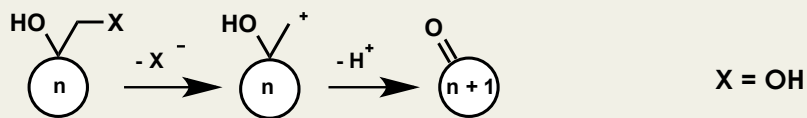


- Electrocyclic and sigmatropic reactions
- Woodward-Hoffmann rules

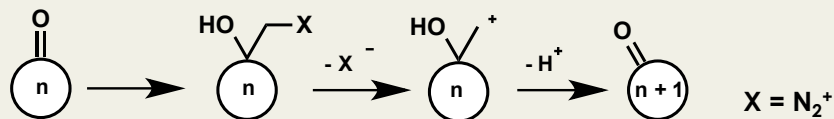
ONE ATOM INSERTION REACTIONS



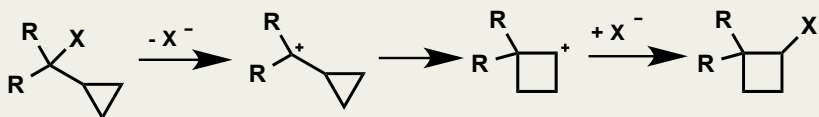
1. Pinacol Rearrangement



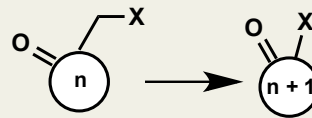
2. Tiffeneau-Demjanow Rearrangement



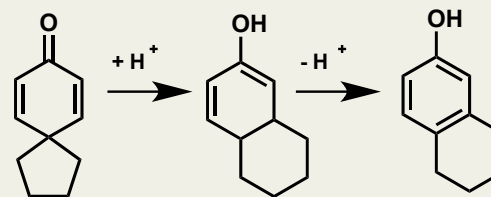
3. Wagner-Meerwein-Rearrangement



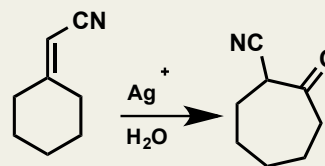
4. Side-Chain Incorporation



5. Dienone Phenol Rearrangement



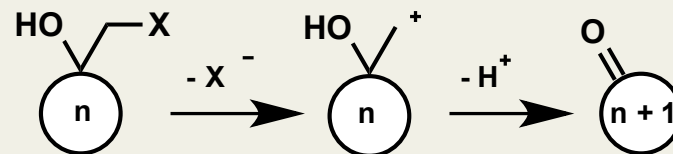
6. Wittig-Prevost Reaction



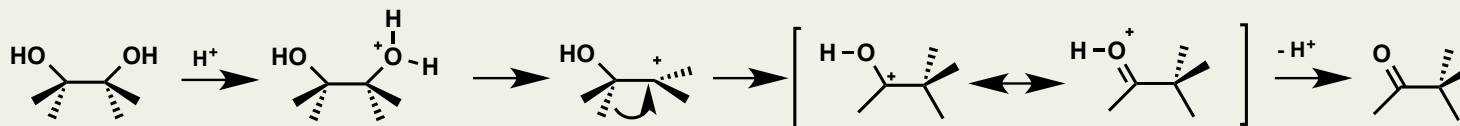
PINACOL REARRANGEMENT

FACTS

- First reported in 1860 by R. Fittig
- Acid-catalyzed rearrangement of vicinal diols to aldehydes/ketones
- Incorporation of a group X that will serve as a latent carbocation adjacent to a preexisting ring
- Any cyclic or acyclic vicinal diol can be applied
- Ring expansion rearrangements are strongly influenced by the ring-size
- **Migration Rule:** the substituent that is able to stabilize a positive charge tends to migrate preferentially

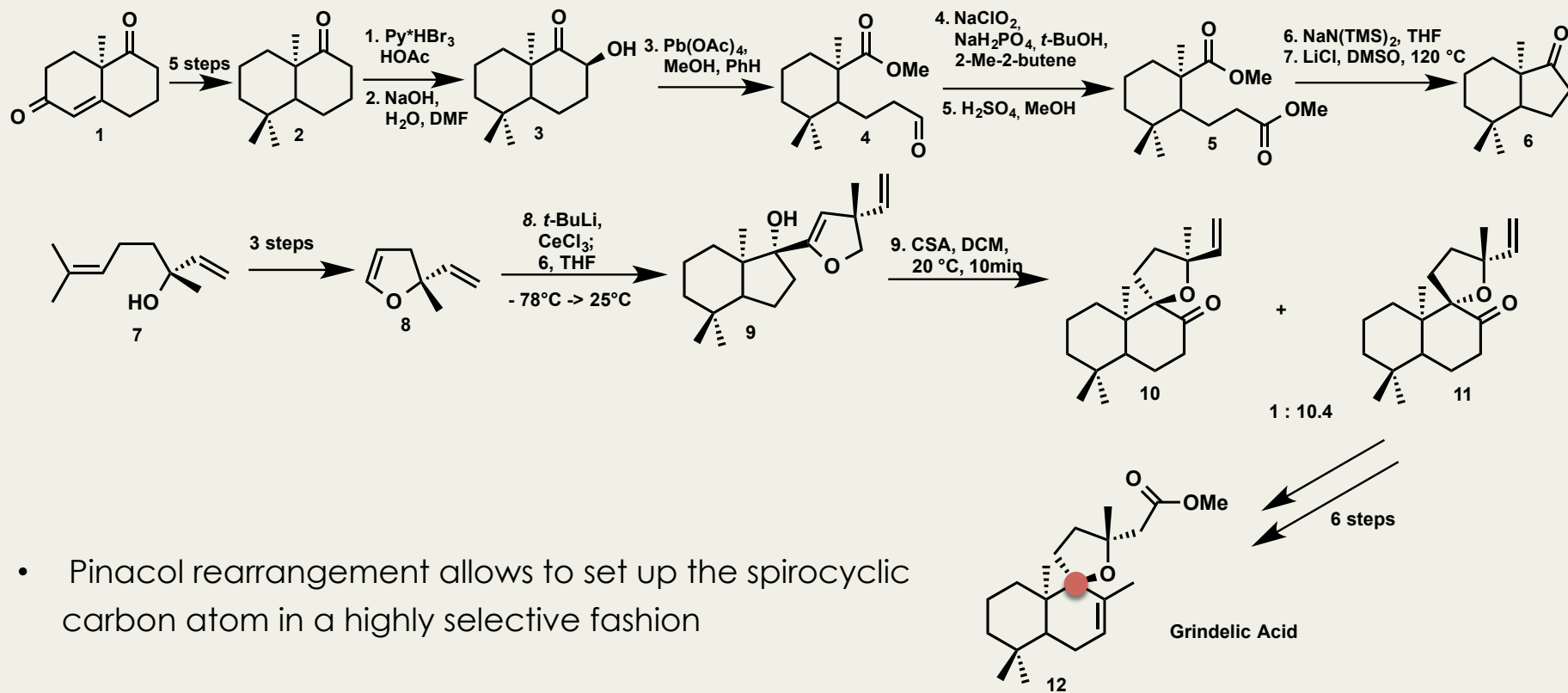


Mechanism:



PINACOL REACTION

Application in Total Synthesis - (+) Grindelic Acid by Leo A. Paquette (1995)

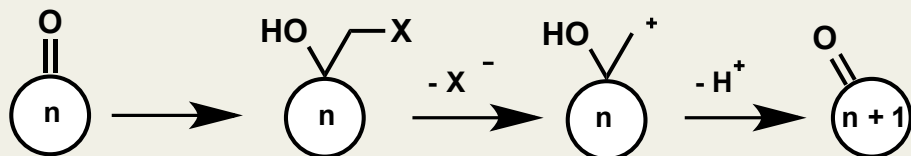


- Pinacol rearrangement allows to set up the spirocyclic carbon atom in a highly selective fashion

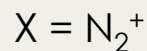
VARIATIONS OF THE PINACOL REARRANGEMENT

Semipinacol Rearrangement:

- Term first coined by M. Tiffeneau
- Use of 2-heterosubstituted alcohols
- Very mild conditions; almost exclusively utilized in complex molecule synthesis



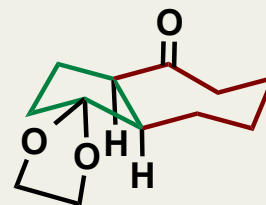
Tiffeneau-Demjanov Rearrangement



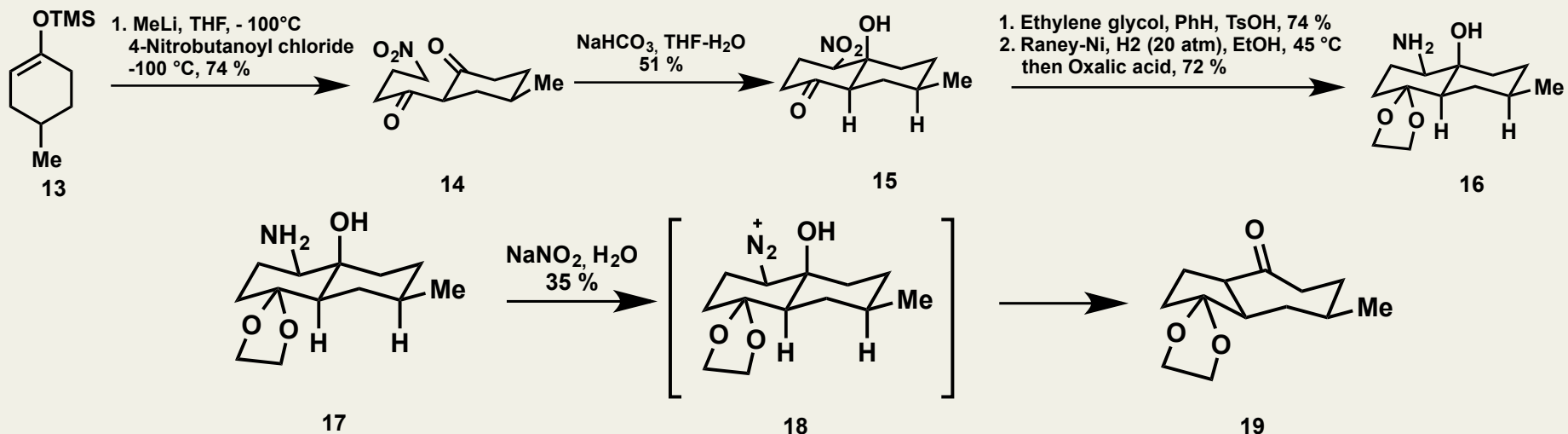
TIFFENEAU DEMJANOV REARRANGEMENT

Application in Total Synthesis – Echinopenes by G. Liang (2013)

- Methodology was first reported by Seebach:

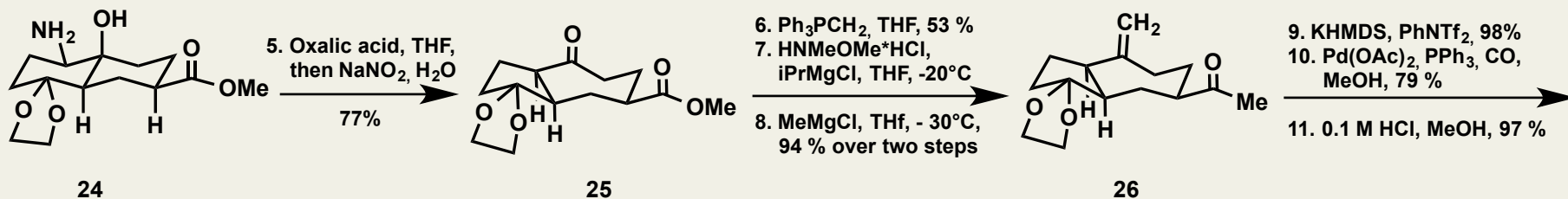
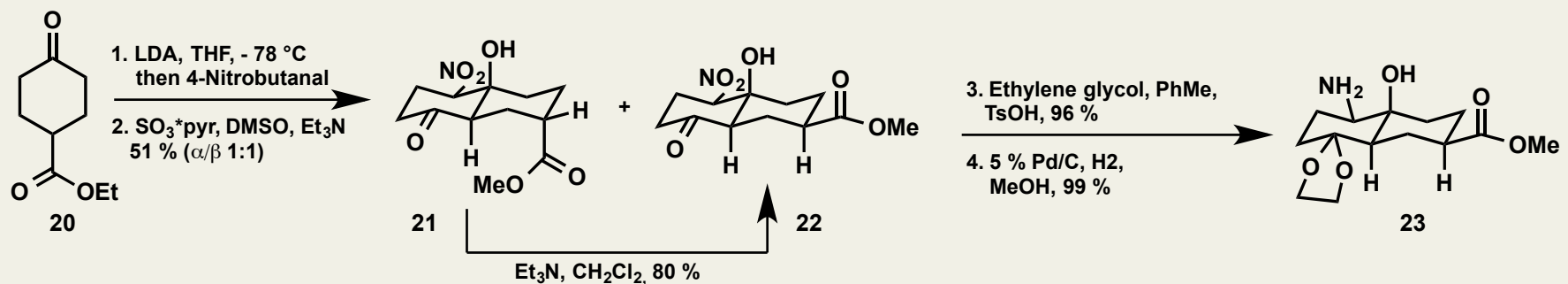


Cis-decalin system with
5/7-fused membered ring



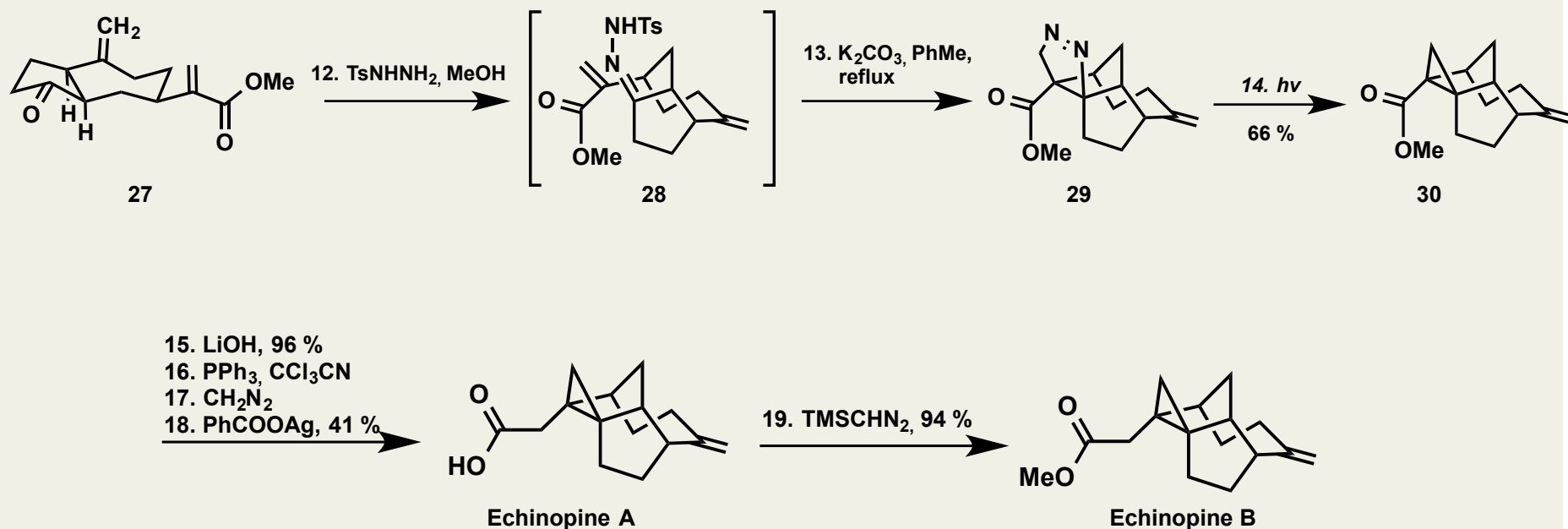
TIFFENEAU DEMJANOV REARRANGEMENT

Application in Total Synthesis – Echinopenes by G. Liang (2013)



TIFFENEAU DEMJANOV REARRANGEMENT

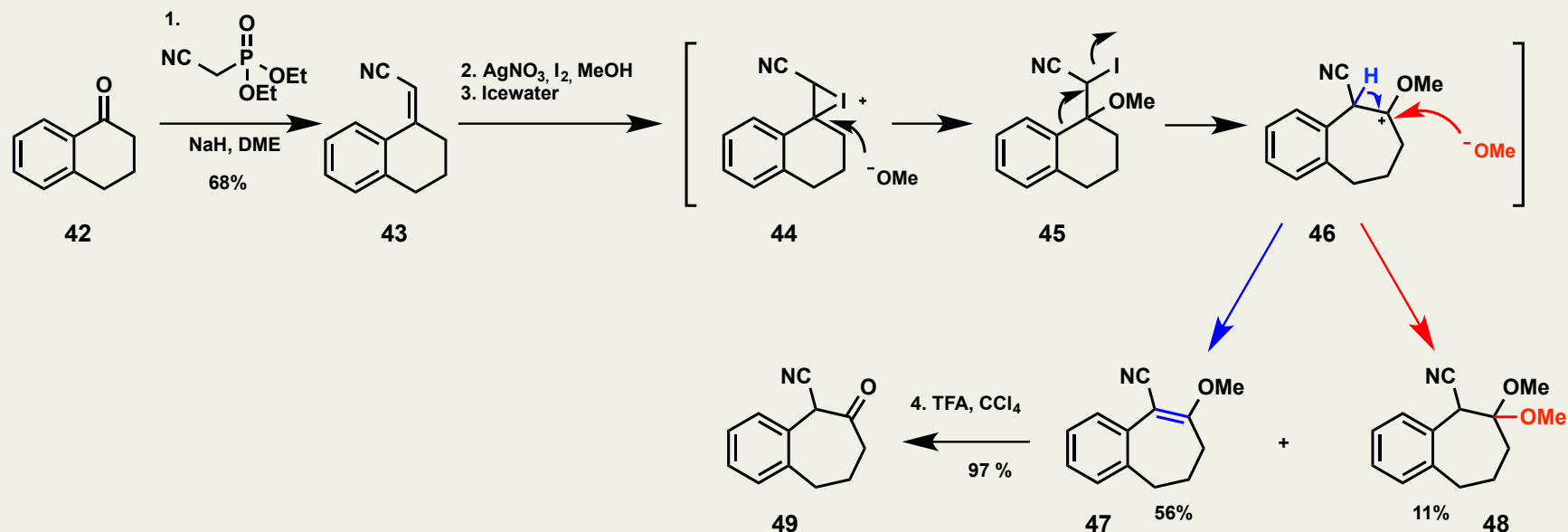
Application in Total Synthesis – Echinopenes by G. Liang (2013)



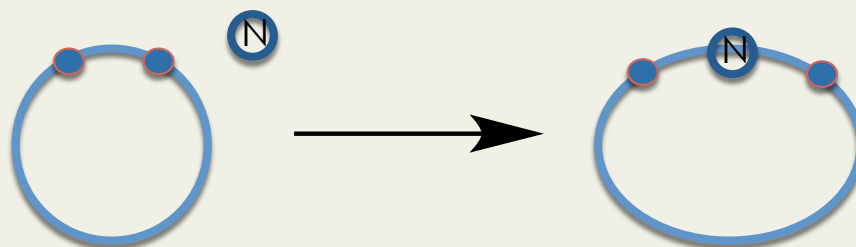
WITTIG PREVOST REACTION

- First reported in 1986, no application in total synthesis
- Treatment of the Wittig product under Prevost conditions resulted in ring expansion

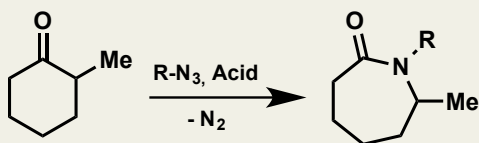
Mechanism:



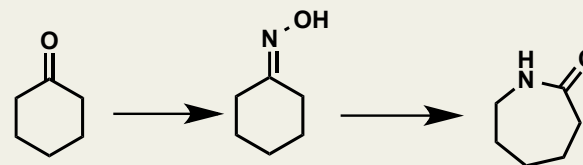
ONE ATOM INSERTION REACTIONS



Schmidt Reaction



Beckmann Rearrangement



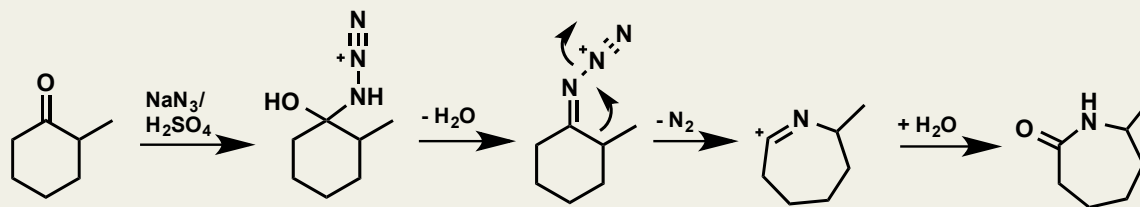
- Boyer reaction: intramolecular Schmidt reaction

SCHMIDT REACTION

FACTS

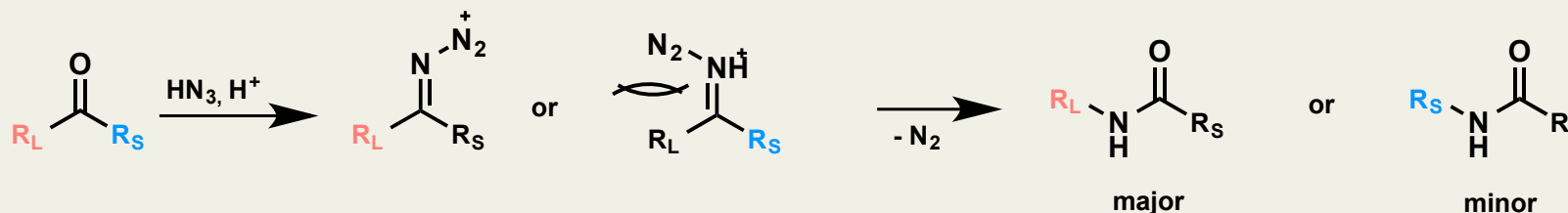
- First reported in 1923 by K. F. Schmidt
- Valuable method of inserting nitrogen adjacent to carbonyl groups

Mechanism:



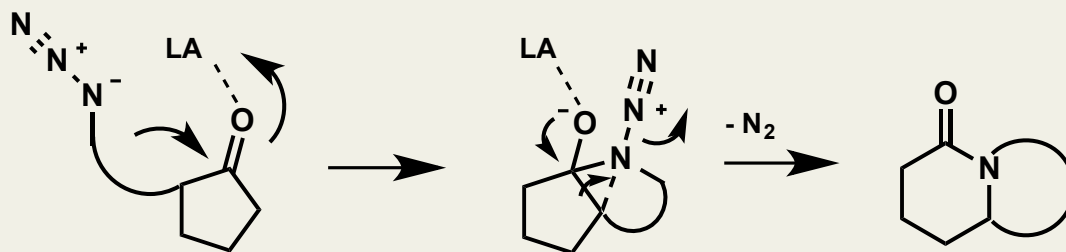
- **Migration rule:** the larger and the more electron donating substituent attached to the carbonyl will preferentially migrate

Ring expansion reactions: migrating substituent is antiperiplanar to the azido group

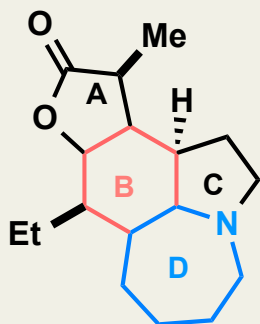


BOYER REACTION/INTRAMOLECULAR SCHMIDT REACTION

- In 1955: Boyer reported the first intramolecular reaction between enones and azides that gave the Schmidt-product:



Application in Total Synthesis – Stenine by J. Aube (2008)



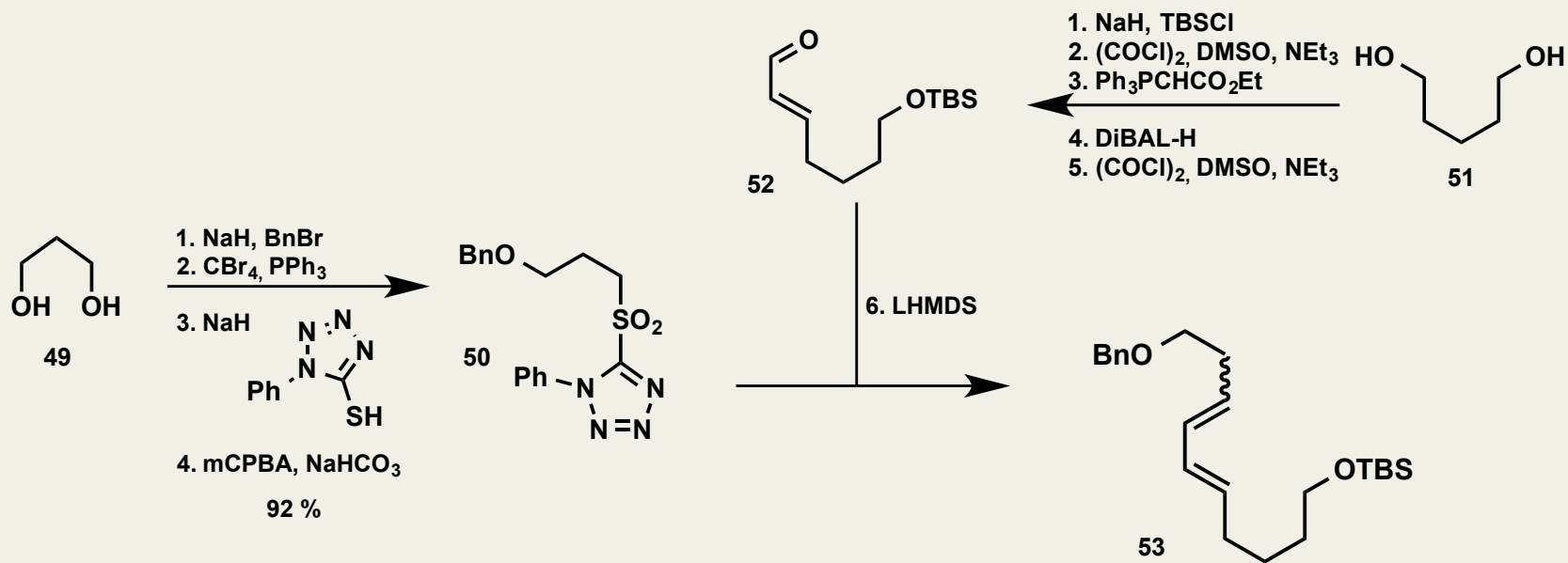
stenine

- Challenge: construction of the B ring
- Intramolecular Schmidt reaction will set up ring D in a Diels-Alder cyclization cascade

J. H. Boyer, J. Hamer *J. Am. Chem. Soc.* **1955**, 77, 951.
J. Aube, G. L. Milligan *J. Am. Chem. Soc.* **1991**, 113, 8965–8966.
J. Aube *J. Am. Chem. Soc.* **2008**, 130, 6018–6024.

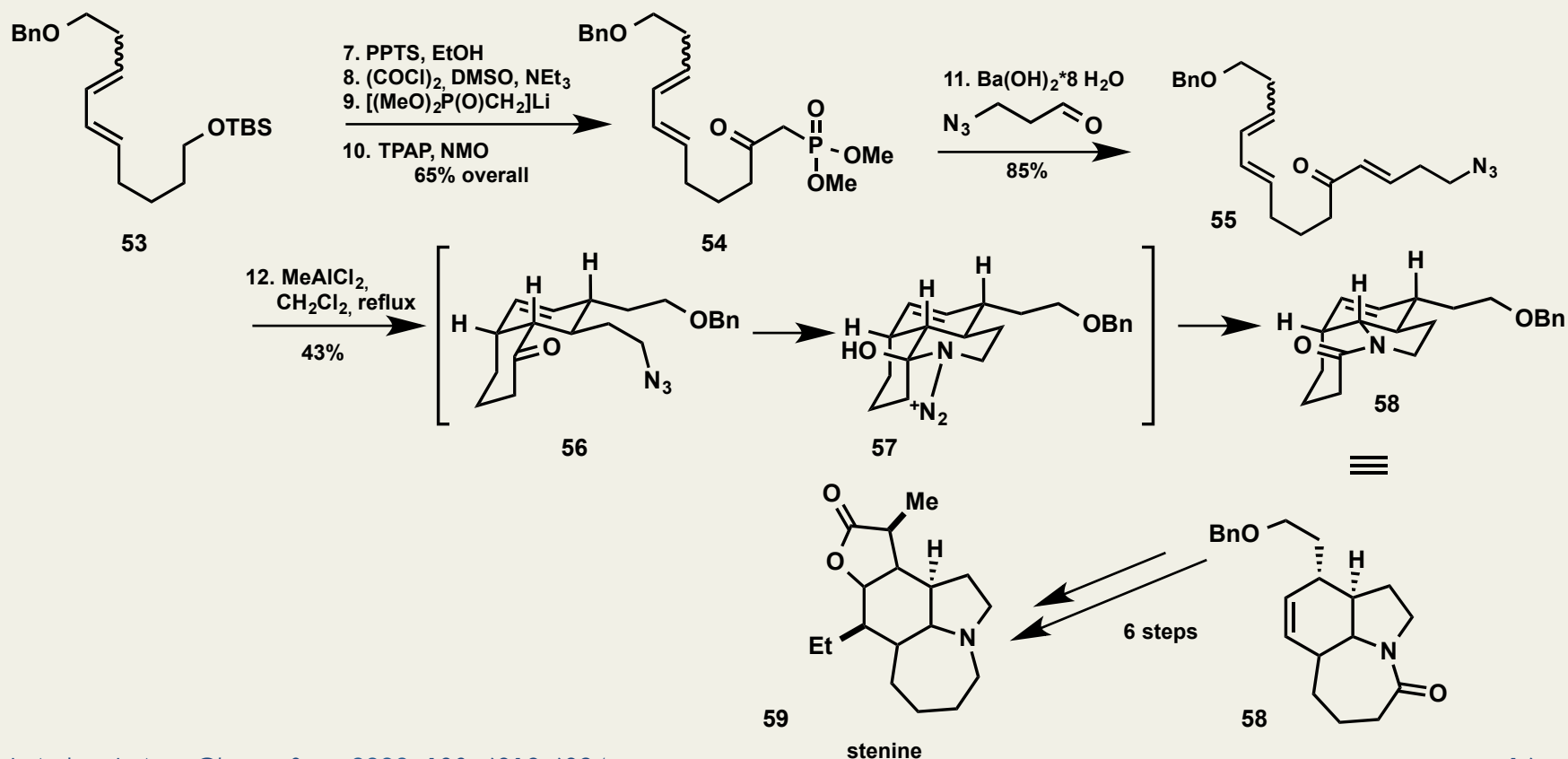
BOYER REACTION/INTRAMOLECULAR SCHMIDT REACTION

Application in Total Synthesis – Stenine by J. Aube (2008)



BOYER REACTION/INTRAMOLECULAR SCHMIDT REACTION

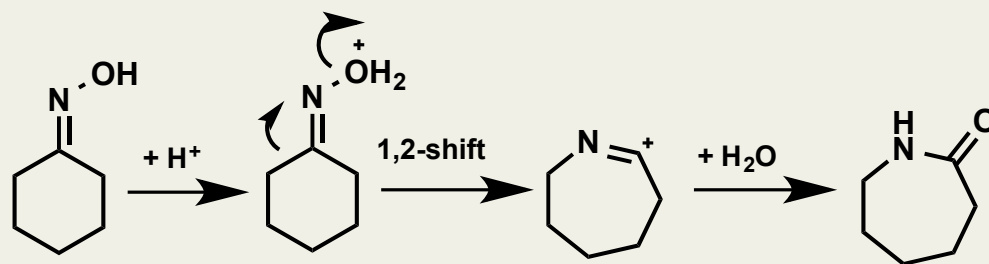
Application in Total Synthesis – Stenine by J. Aube (2008)



BECKMANN REARRANGEMENT

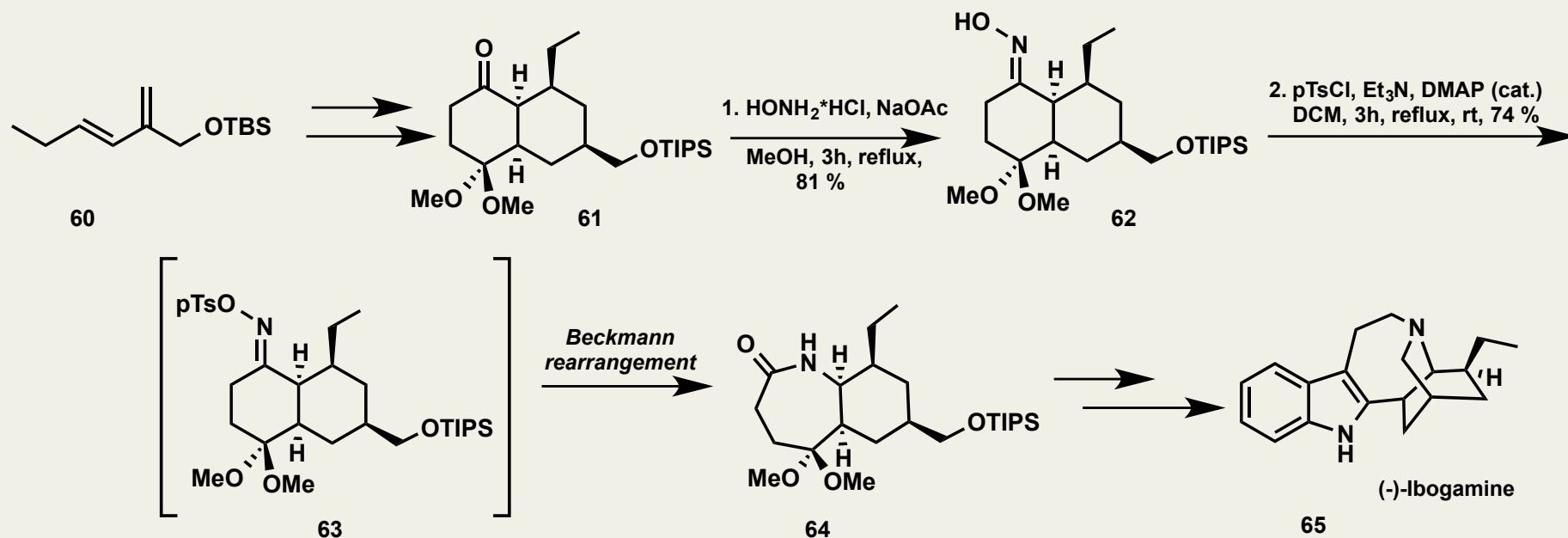
- Conversion of oximes into amides in acidic medium
- Requires high temperature, large amounts of strong Brönstedt acids, non-catalytic
- Stereochemical outcome: R group anti to the leaving group on the nitrogen will migrate

Mechanism:

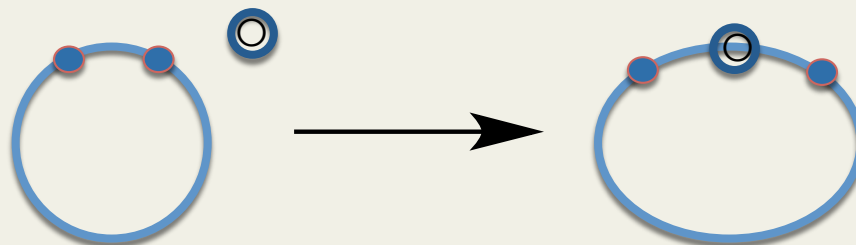


BECKMANN REARRANGEMENT

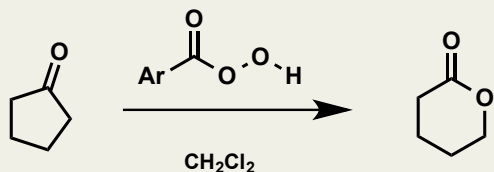
Application in Total Synthesis – Ibogamine by J. D. White (2000)



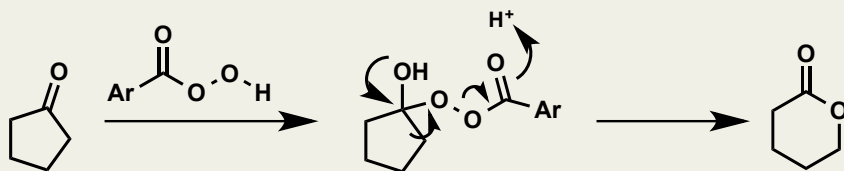
ONE ATOM INSERTION REACTIONS



Baeyer-Villiger Reaction

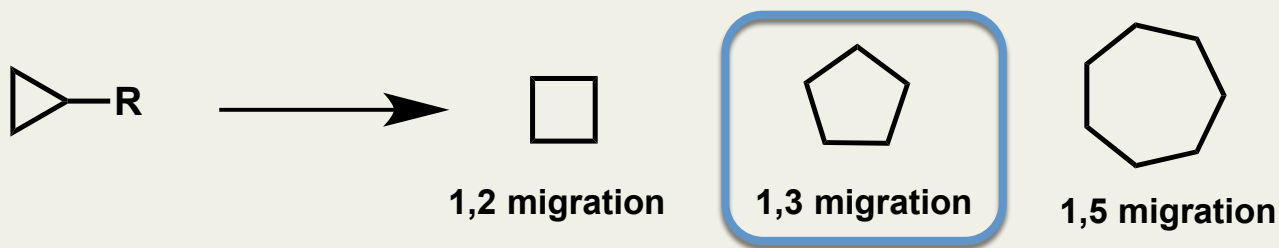


- Discovered in 1899 by A. Baeyer and V. Villiger
- **Migration rule:** tert. alkyl > sec. alkyl > aryl > prim. alkyl > methyl

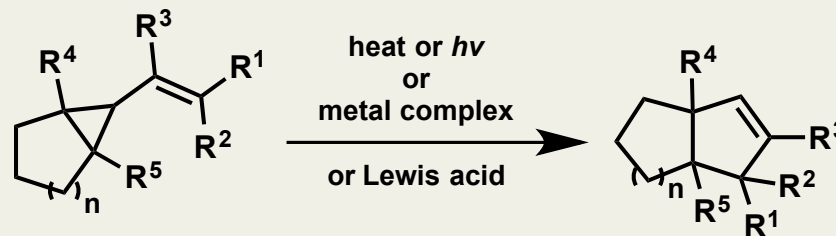


THE THREE-MEMBERED RING

Building elements for ring enlargements reactions due to their ring strain



Vinylcyclopropane-cyclopentene rearrangement

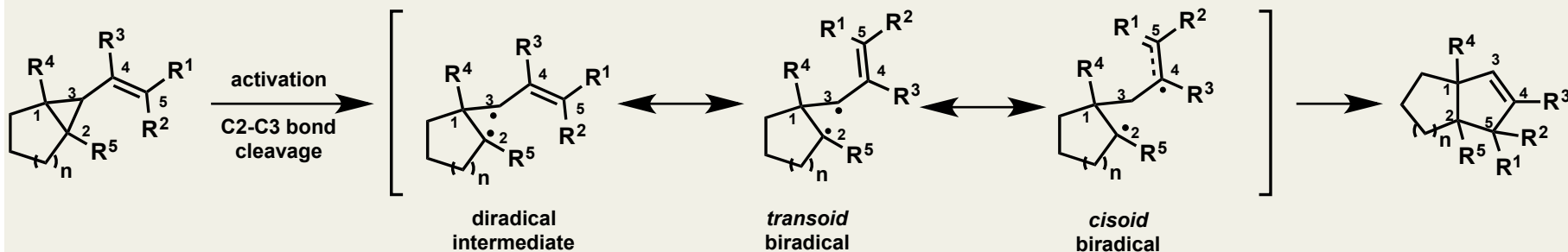


VINYLCYCLOPROPANE- CYCLOPENTENE REARRANGEMENT

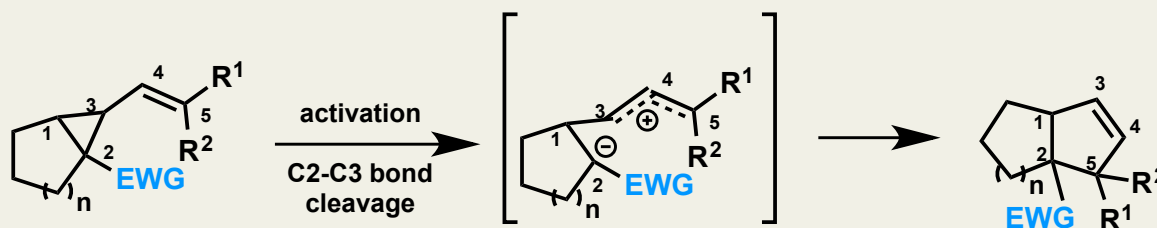
Mechanism:

- Two major pathways for cyclic vinylcyclopropanes are possible

1) Cyclopentene formation via biradical intermediates:

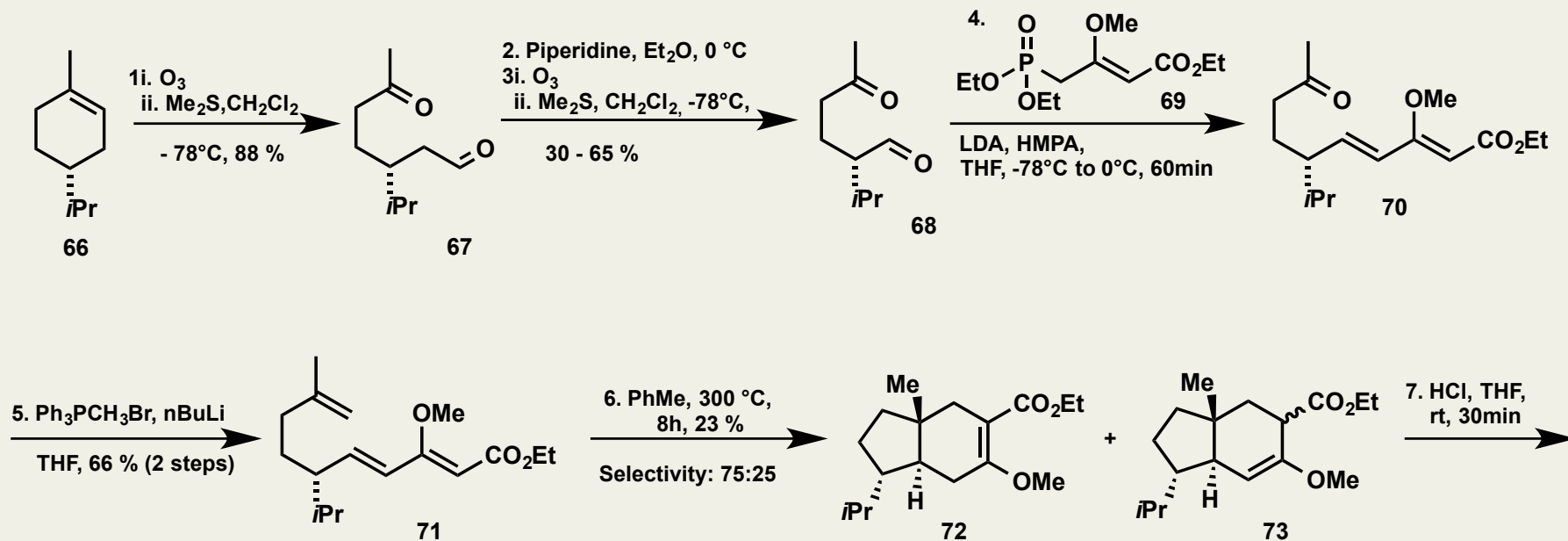


2) Cyclopentene formation via dipolar intermediates:



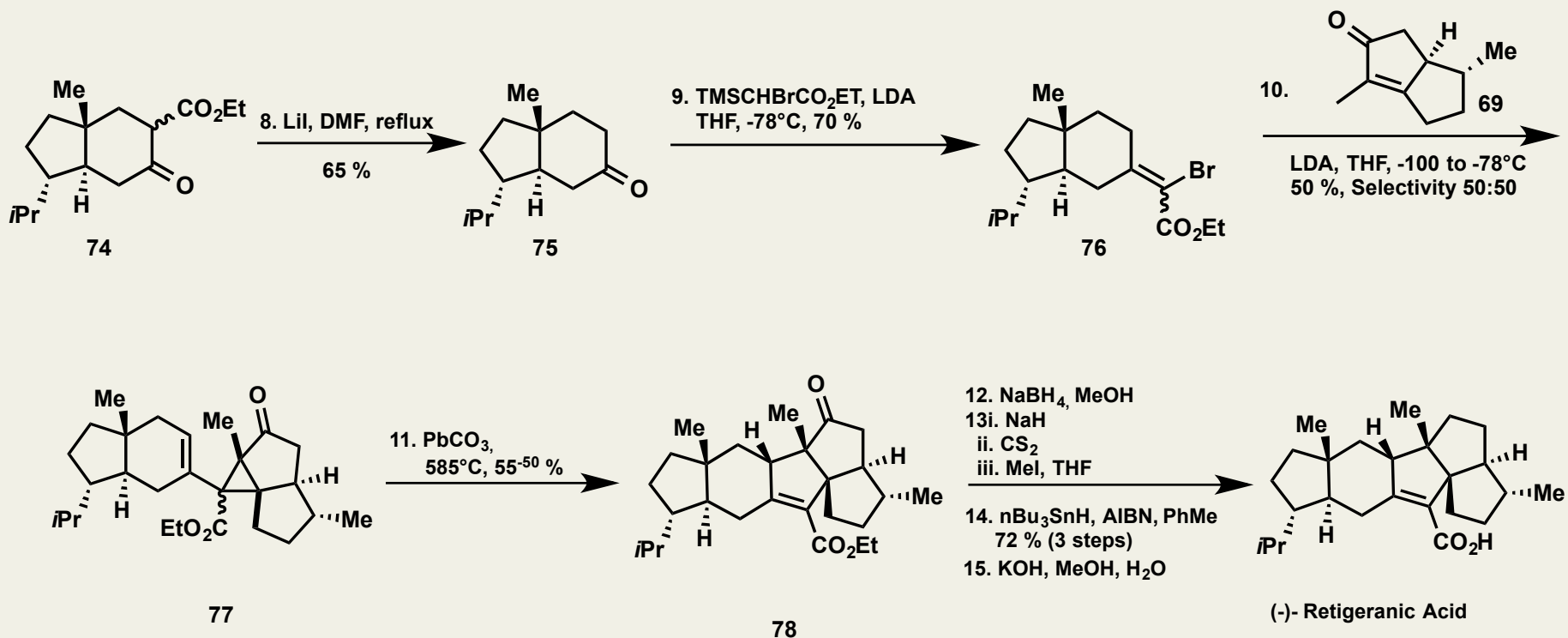
VINYLCYCLOPROPANE- CYCLOPENTENE REARRANGEMENT

Application in Total Synthesis – (-) Retigeranic Acid by T. Hudlicky (1988)



VINYLCYCLOPROPANE-CYCLOPENTENE REARRANGEMENT

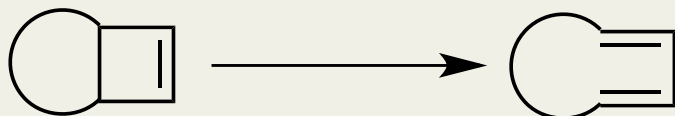
Application in Total Synthesis – (-) Retigeranic Acid by T. Hudlicky (1988)



FOUR-MEMBERED RING

Ring expansion of four-membered rings or via four-membered ring intermediates

- Cyclobutane derivatives: easily accessible by a number of reliable preparative methods
- Selective cleavage of a cyclobutane bond is facile due to the inherent ring strain
- Ring expansion with four-membered ring systems:



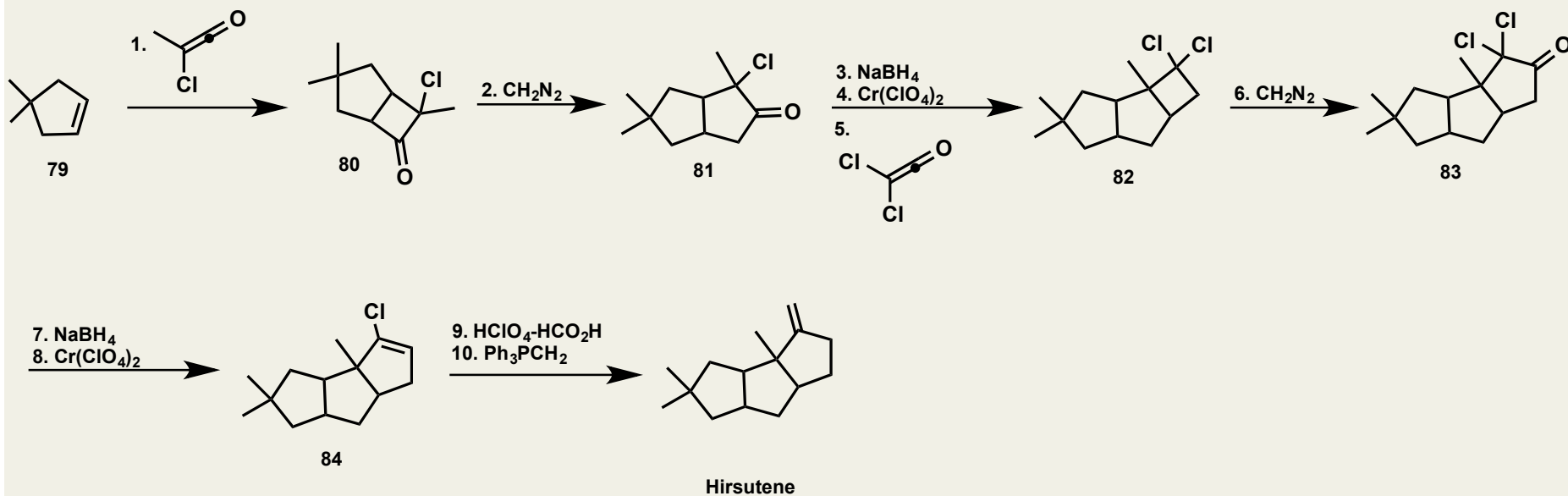
- Wolff rearrangement
- Photocyclic reactions
- Lewis Acid-catalyzed
- Electrocyclic reactions
- Cationic rearrangements
- Acid-catalyzed
- Transition metal catalysis

FOUR-MEMBERED RING

Examples in Total Synthesis

1. Wolff rearrangement

Synthesis of Hirsutene by A. E. Greene (1980)

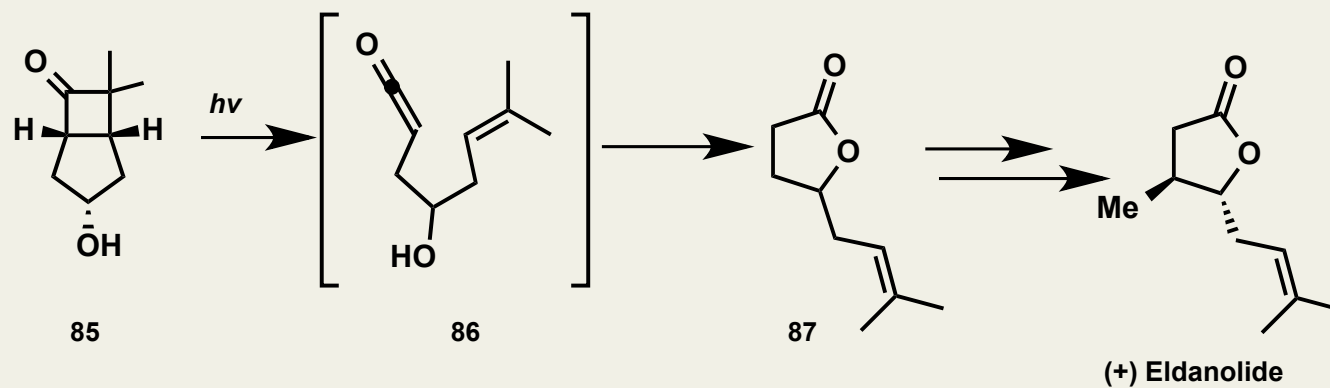


FOUR-MEMBERED RING

Examples in Total Synthesis

2. Photochemical reaction

Synthesis of Eldanolide by Butt and Winders (1980)

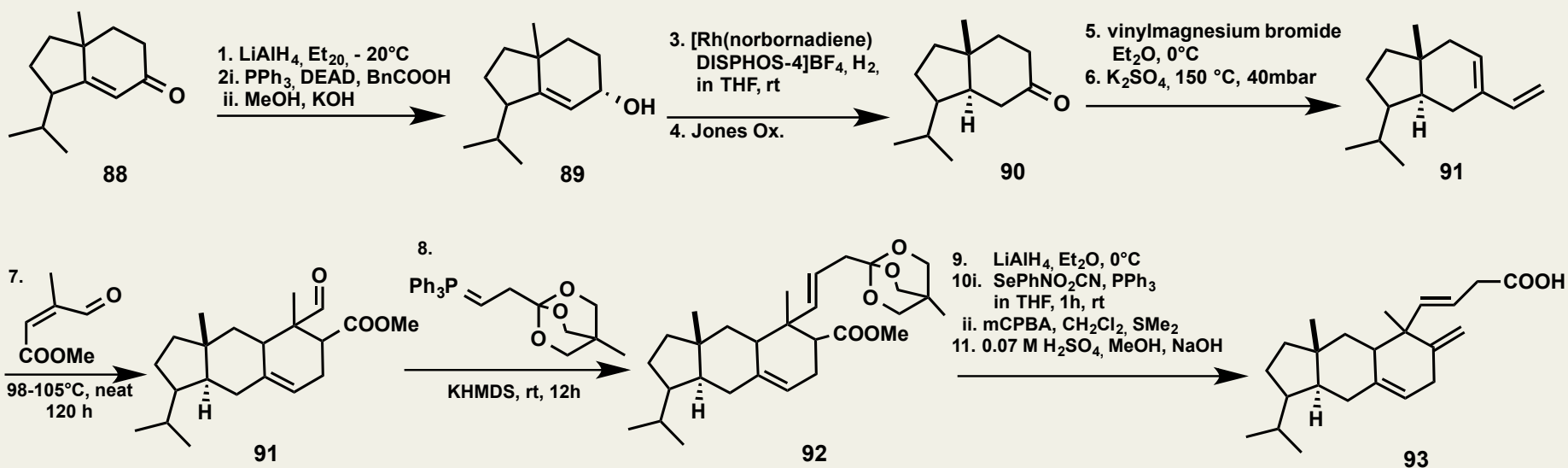


FOUR-MEMBERED RING

Examples in Total Synthesis

3. Lewis acid catalysis

Synthesis of Retigeranic Acid by E. J. Corey (1987)

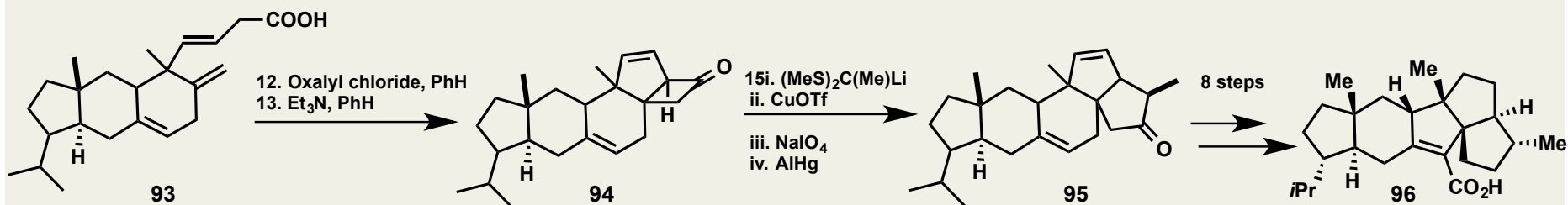


FOUR-MEMBERED RING

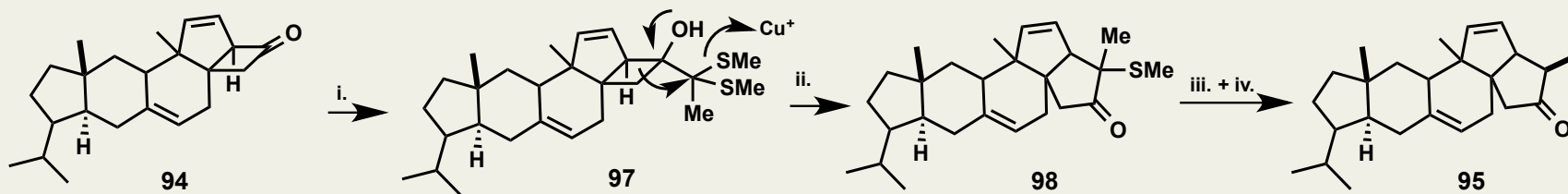
Examples in Total Synthesis

3. Lewis acid catalysis

Synthesis of Retigeranic Acid by E. J. Corey (1987)



Mechanism:

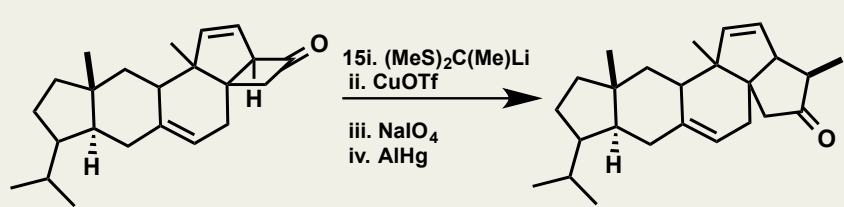


RETIGERANIC ACID

Introduction of the tricyclic fused-ring system

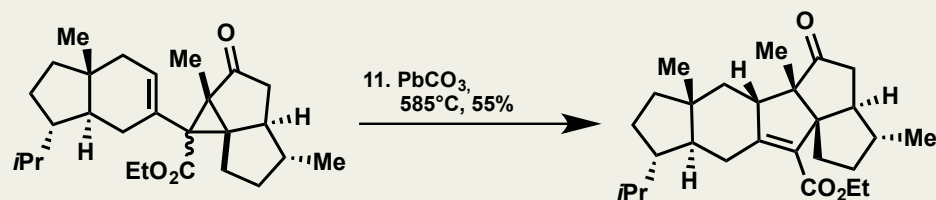
Corey (1987)

- Key step: Lewis acid mediated ring expansion reaction
- racemic
- 22 steps



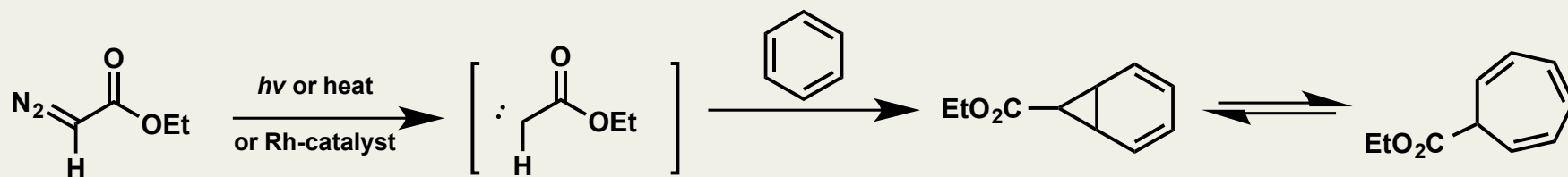
Hudlicky (1988)

- Key step: Vinylcyclopropane cyclopentene rearrangement
- enantioselective
- 14 steps



BÜCHNER REACTION

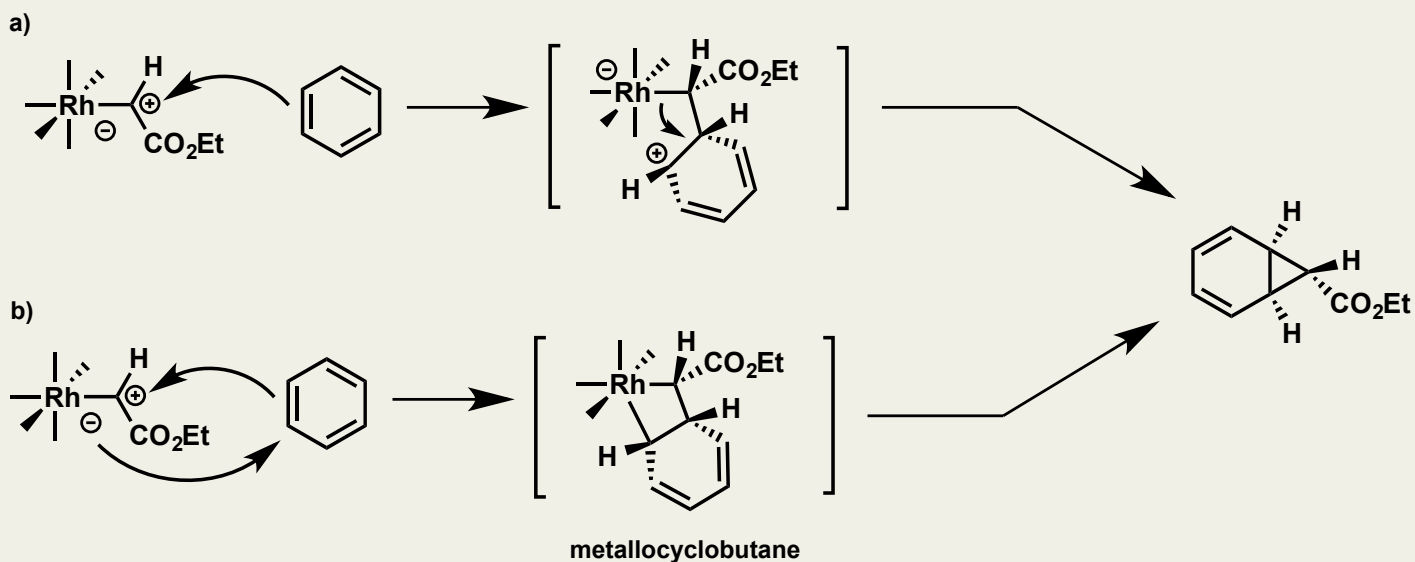
- First reported by Büchner and Curtius in 1885
- Thermal or photochemical reaction of ethyl diazoacetate with benzene and its homologs
- Convenient entry to seven-membered carbocycles both inter- and intramolecularly
- The amount of side products was significantly reduced by the use of transition metals catalysts especially Rhodium-based catalysts



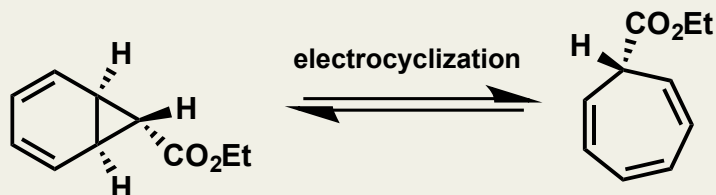
BÜCHNER REACTION

Mechanism:

1. Step:

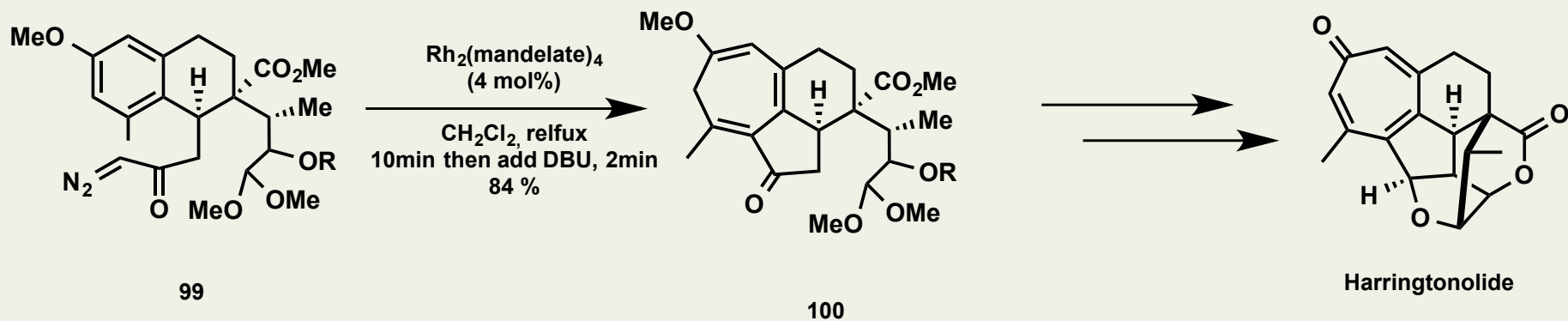


2. Step:



BÜCHNER REACTION

Application in Total Synthesis – (-) Harringtonolide by L. N. Mander (1998)



Thank you for your kind attention!

Questions?