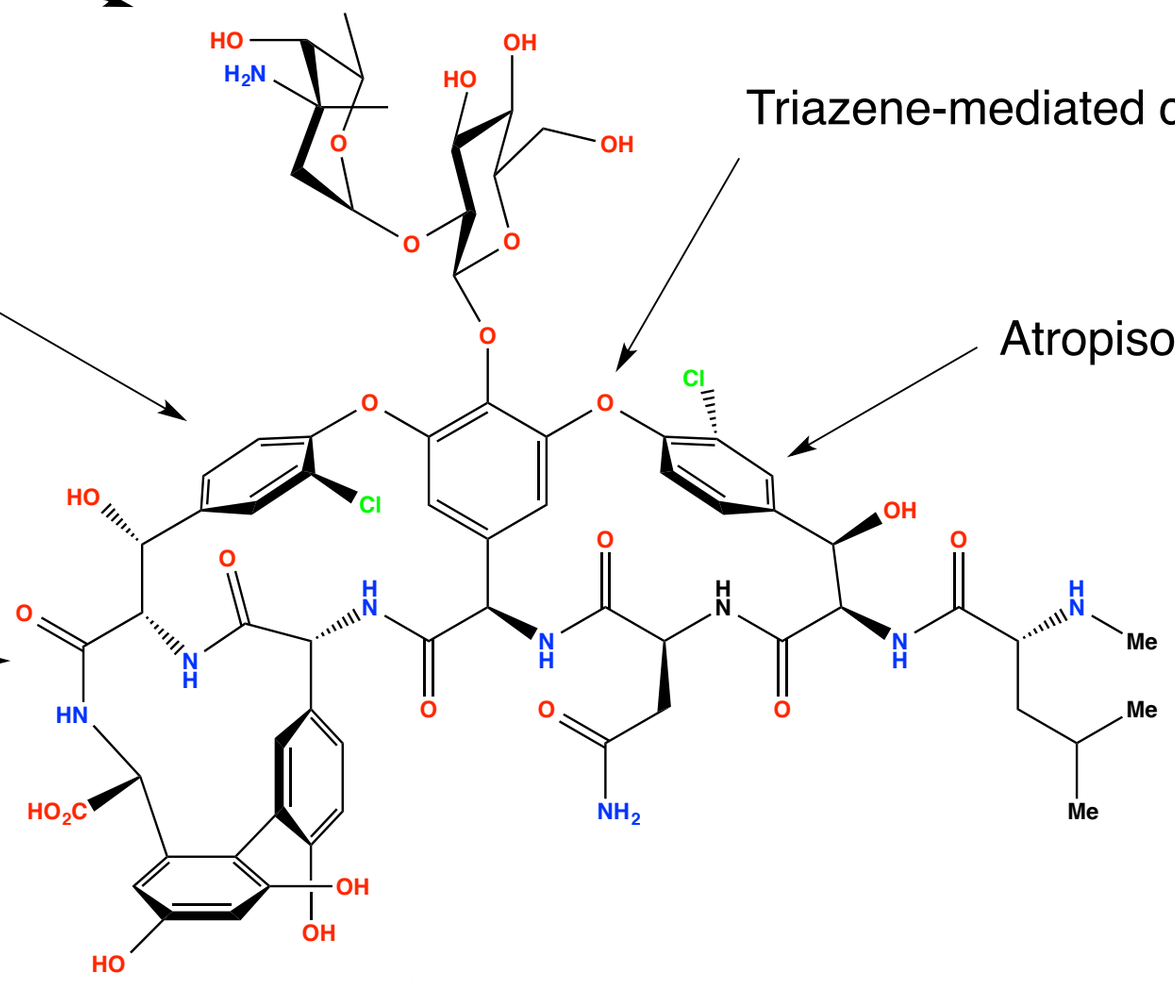
Sequential glycosidation
protecting groups matter!

Triazene-mediated coupling efficient

1 : 1 mixture of
Atropisomers

Atropisomers can be equilibrated

Macrolactamization
efficient



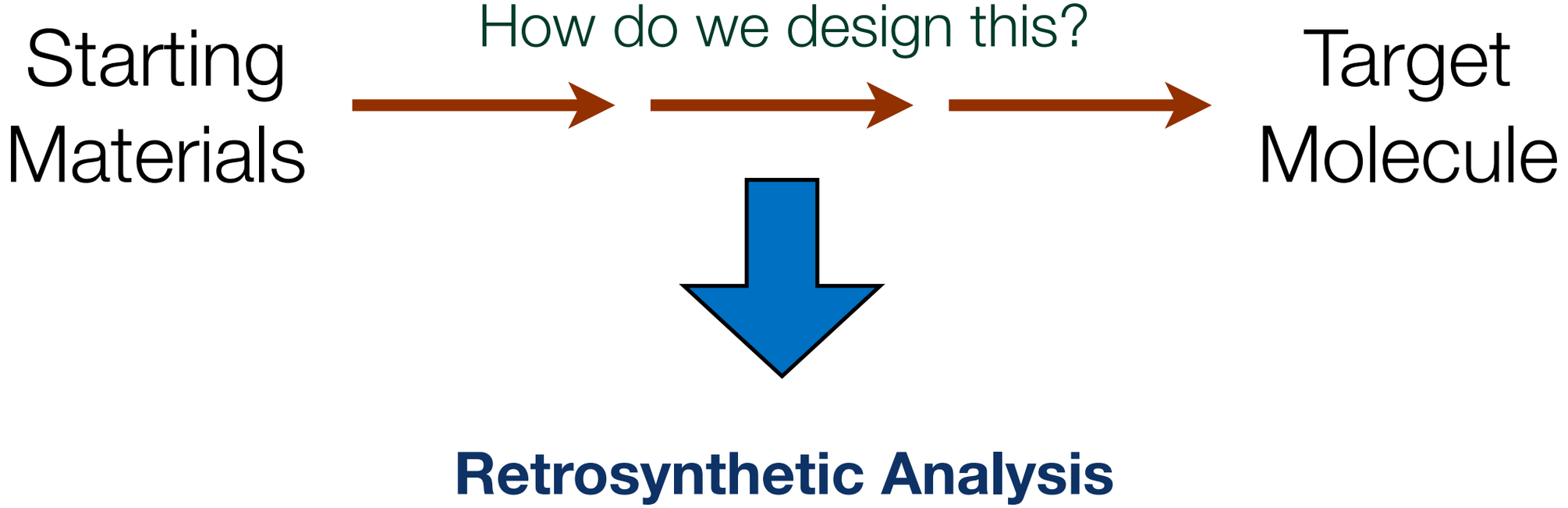
Asymmetric Suzuki sets atropisomer

745 Organic Synthesis

Spring 2015

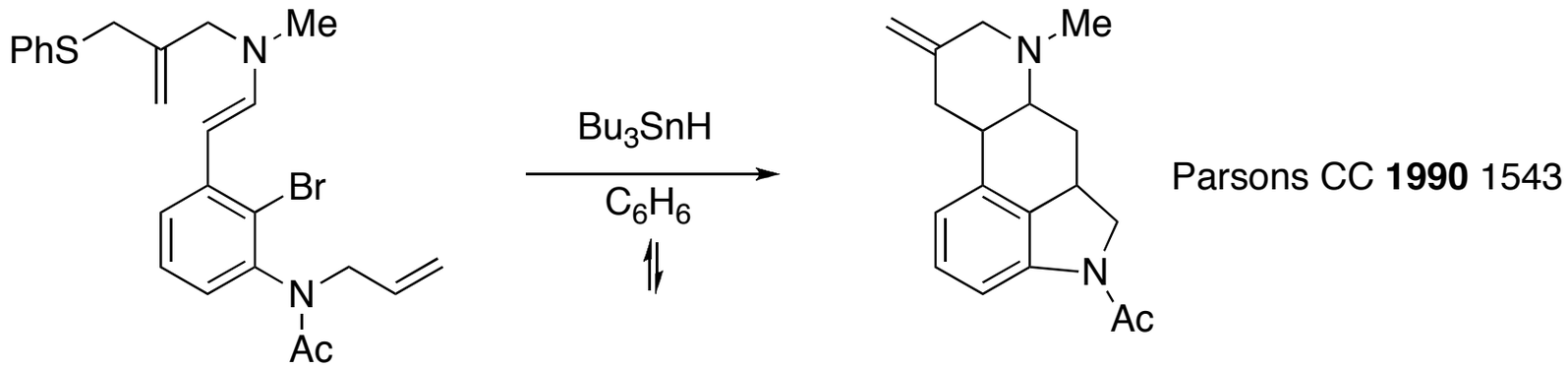
Organic Synthesis

- the preparation of complex molecules from commercially available starting materials via a multistep sequence of transformations
  - C-C bonds, oxidation/reduction, FG changes, protect/deprotect



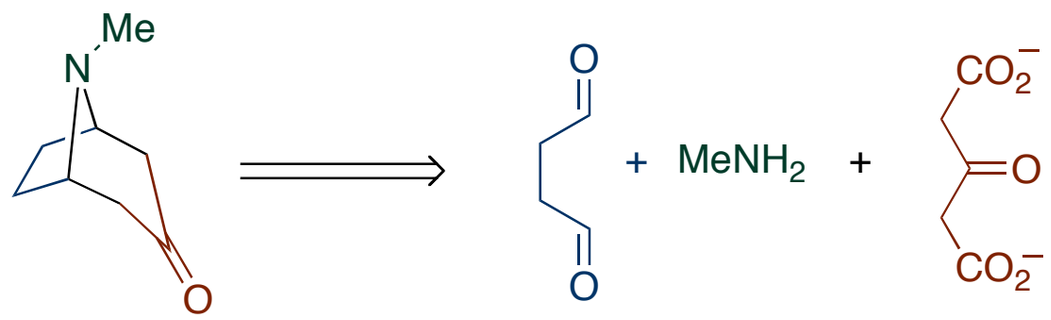
Synthetic Strategy

- ideal synthesis would be 1 step and 100% yield
- concise, high yield, convergent, ease of purification, atom economy
- build as much complexity in a single operation as possible



Parsons CC **1990** 1543

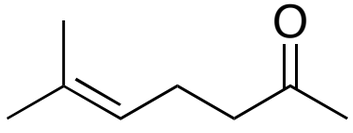
- make use of symmetry



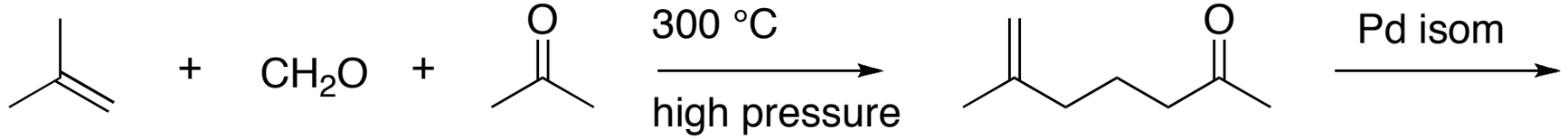
Robinson JCS **1917** 762

Knowledge of reliable reactions

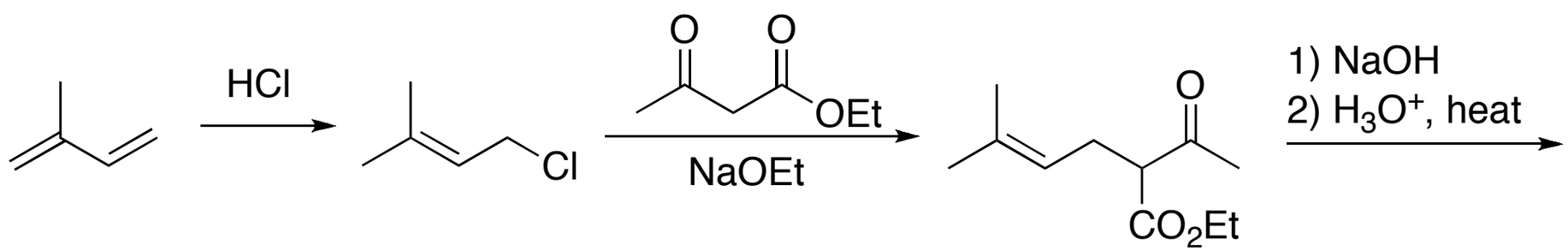
- knowing reactions help us to design better, higher yielding syntheses



made by the ton industrially for vitamin A, flavorings, perfumes

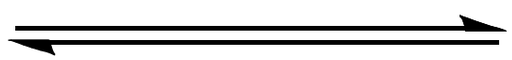
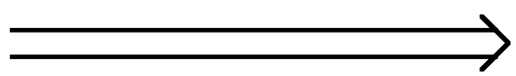


in the lab



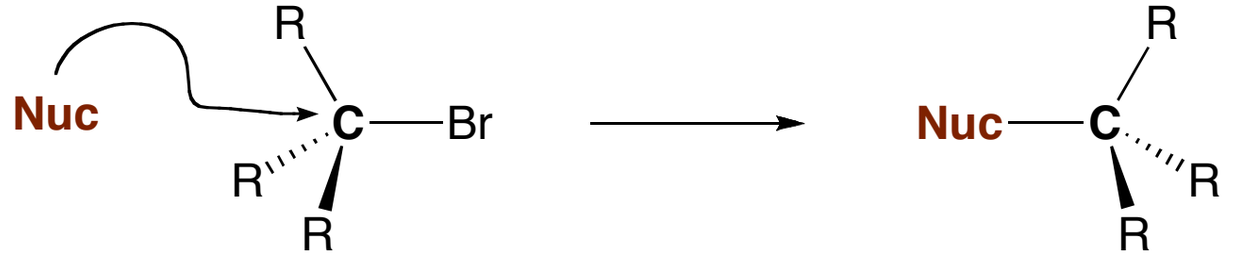
Chemical Reactions

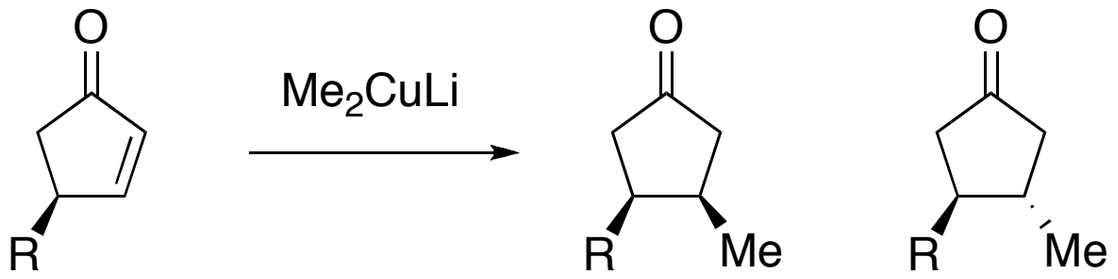
- a movement of electrons - most reactions are polar reaction
  - Nucleophile and Electrophile

- Arrow Notation 
  - Reaction Arrows 
  - Equilibrium Arrows 
  - Resonance Arrows 
  - Mechanistic Arrows 
  - Retrosynthetic Arrows 

Chemical Reactivity and Selectivity

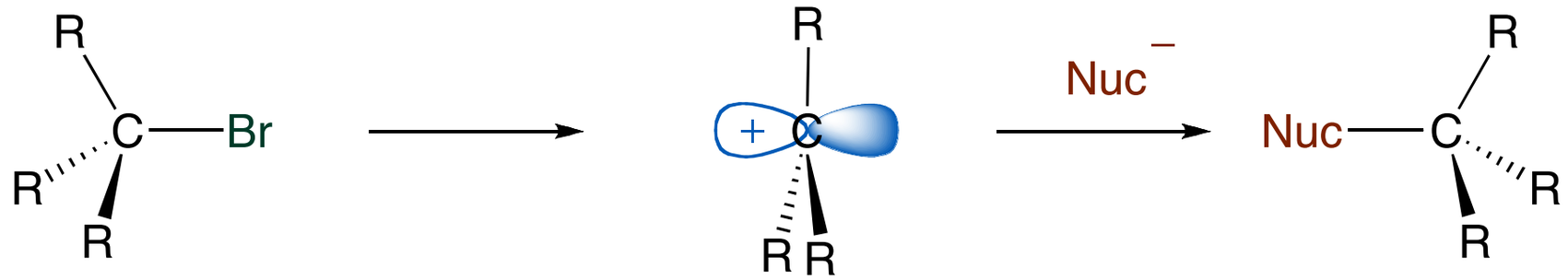
- Sterics affects both the reactivity and the selectivity (regio- and stereo-)

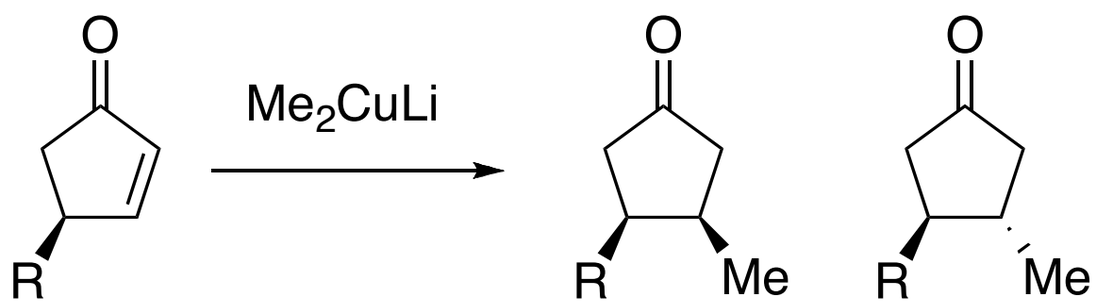


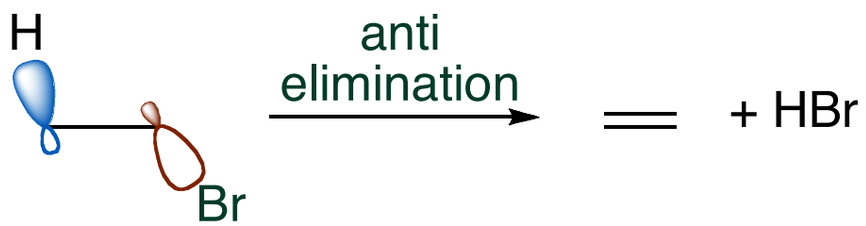


Chemical Reactivity and Selectivity

- Electronics affects both reactivity and selectivity (regio- and stereo-)
  - Inductive effects - through bond polarization
  - Field effects - through space polarization
  - Stereoelectronics - geometrical constraints placed upon ground and transition states by orbital overlap considerations

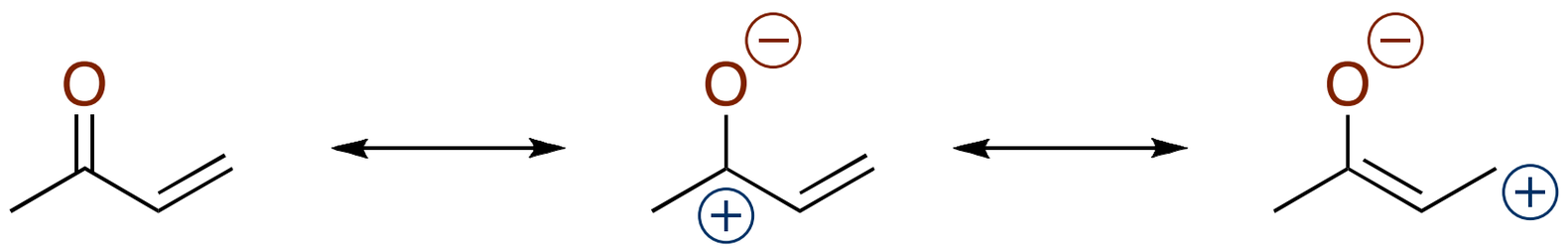






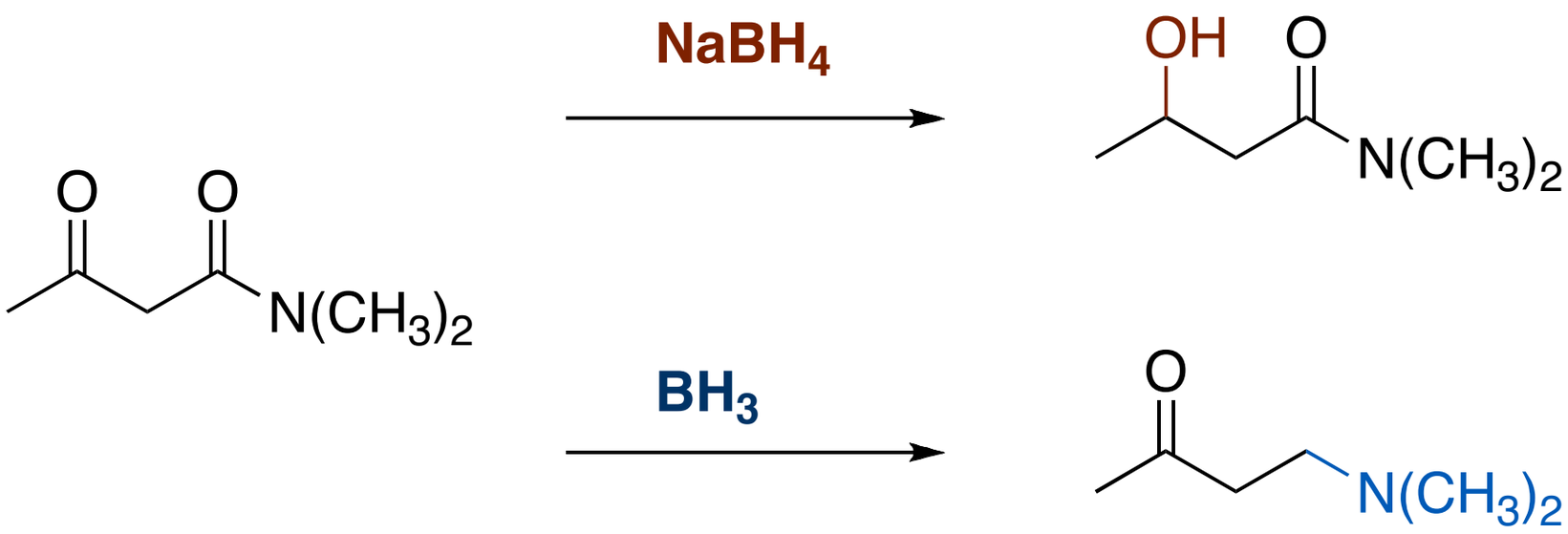
Inductive and Resonance Effects

- Where are electrons and where do they want to go?



Chemoselectivity

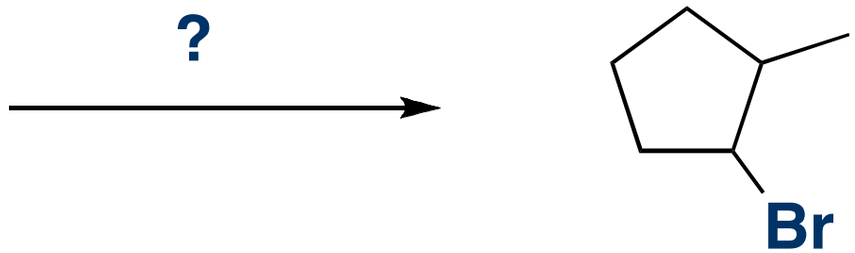
- selective reaction of one functional group over another



- why? What do we know about the functional group properties? What do we know about the reagent properties?

Regioselectivity

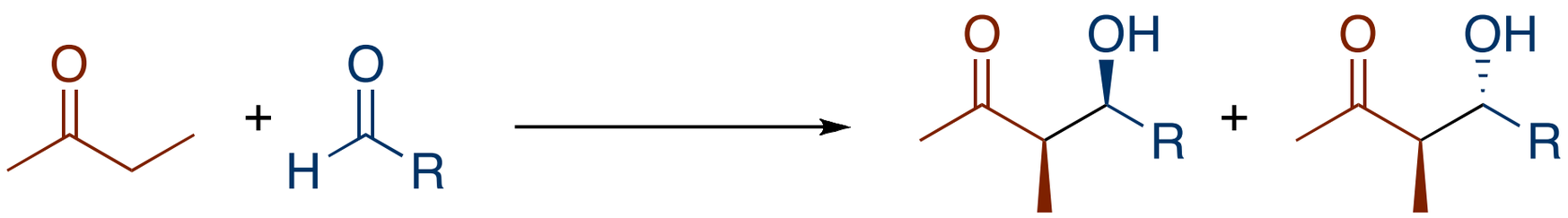
- selective reaction of one region of a functional group over another

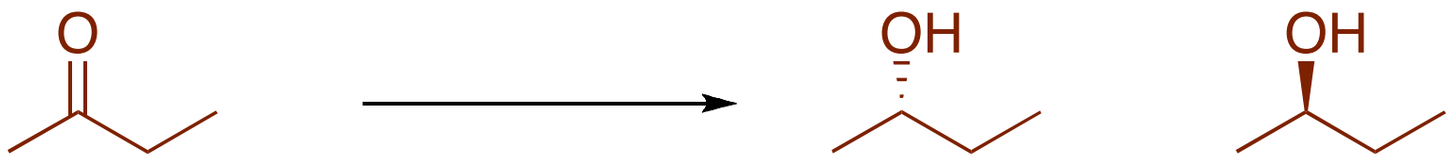


- how can you alter regioselectivity?
  - change the mechanism!

Stereoselectivity

- selective reaction to produce one possible stereoisomer over another





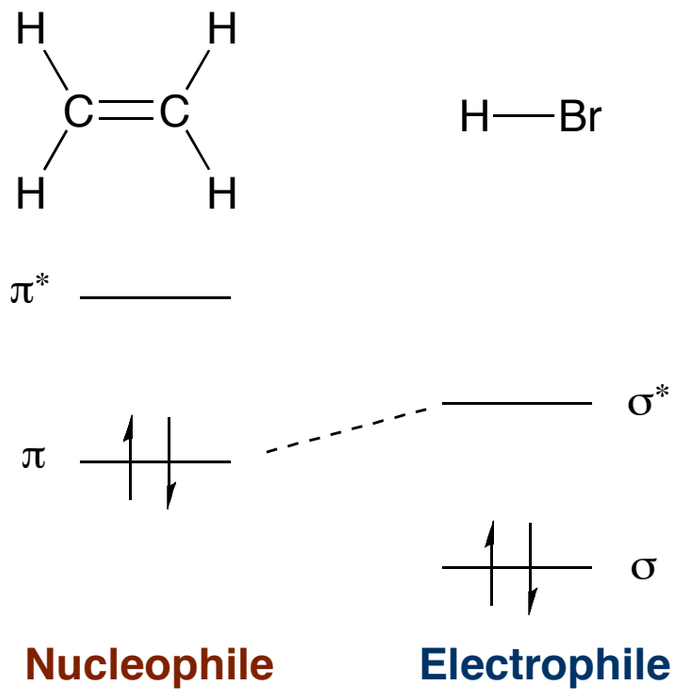
- diastereoselectivity, enantioselectivity

Tuesday, January 13, 15

Reactivity and Bonding - Frontier MO Theory

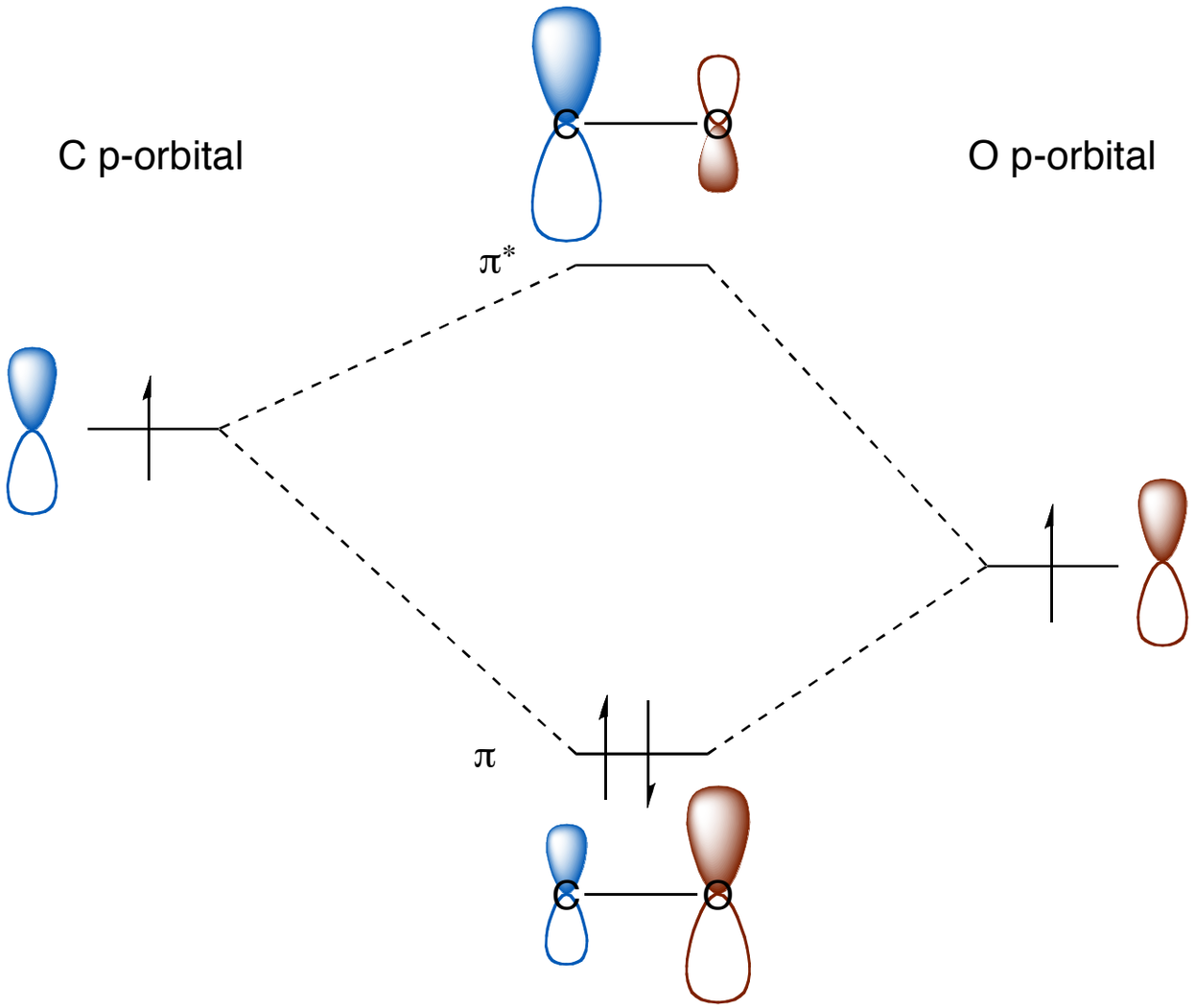
- Fukui Postulate
  - *during the course of chemical reactions, the interaction of the highest filled molecular orbital (HOMO) and the lowest unfilled molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition state.*

Fukui 1952



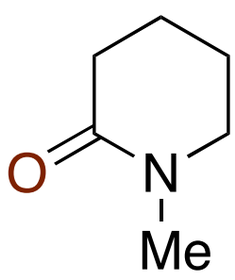
Orbital Coefficients

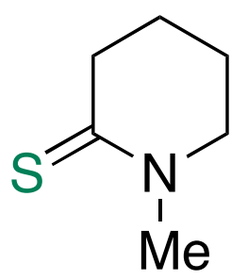
- Square of the orbital coefficients is a measure of electron population

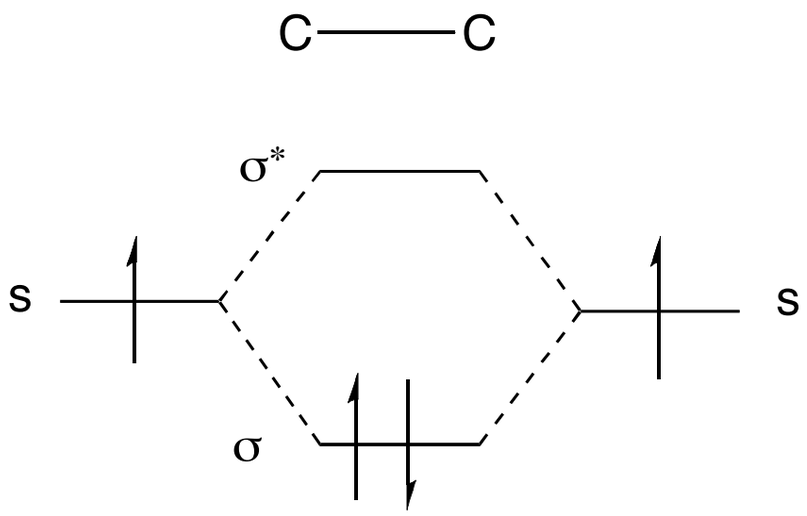


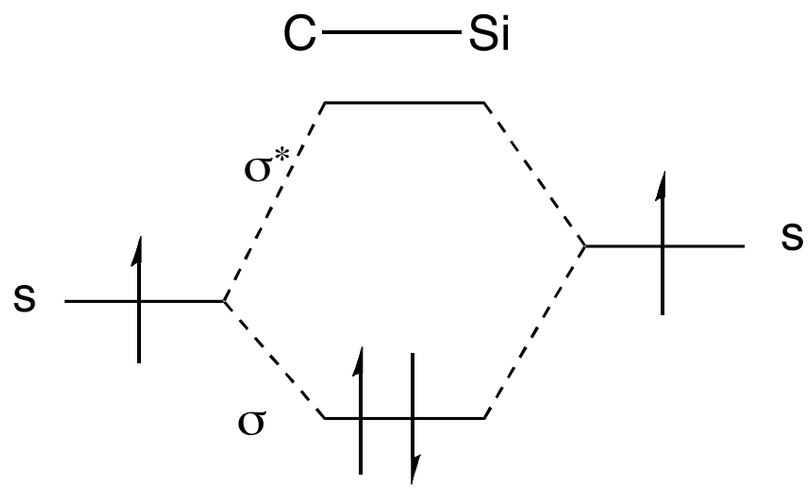
Orbital Overlap

- Orbitals of similar energy overlap to make stronger bonds
  - BDE C-C (88 kcal/mol), C-Si (70 kcal/mol)
  - BDE C=C (65 kcal/mol), C=Si (36 kcal/mol)
  - note - sigma bonds stronger than pi bonds





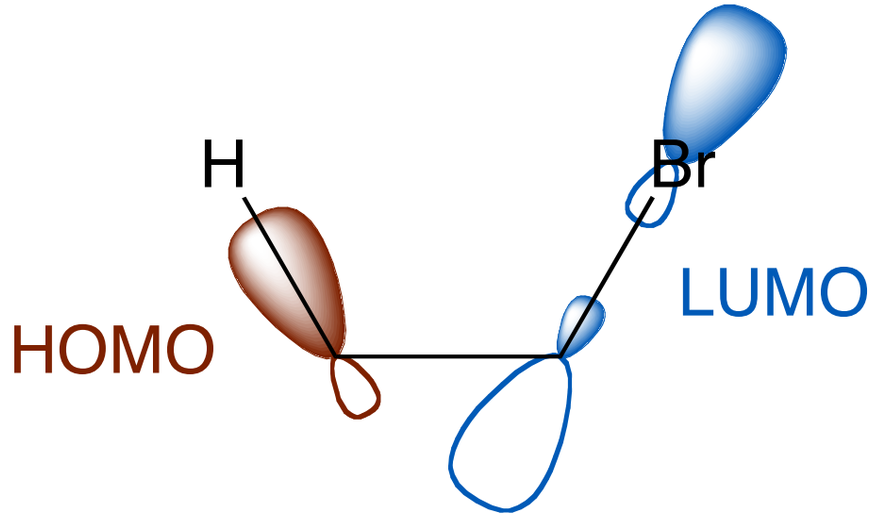




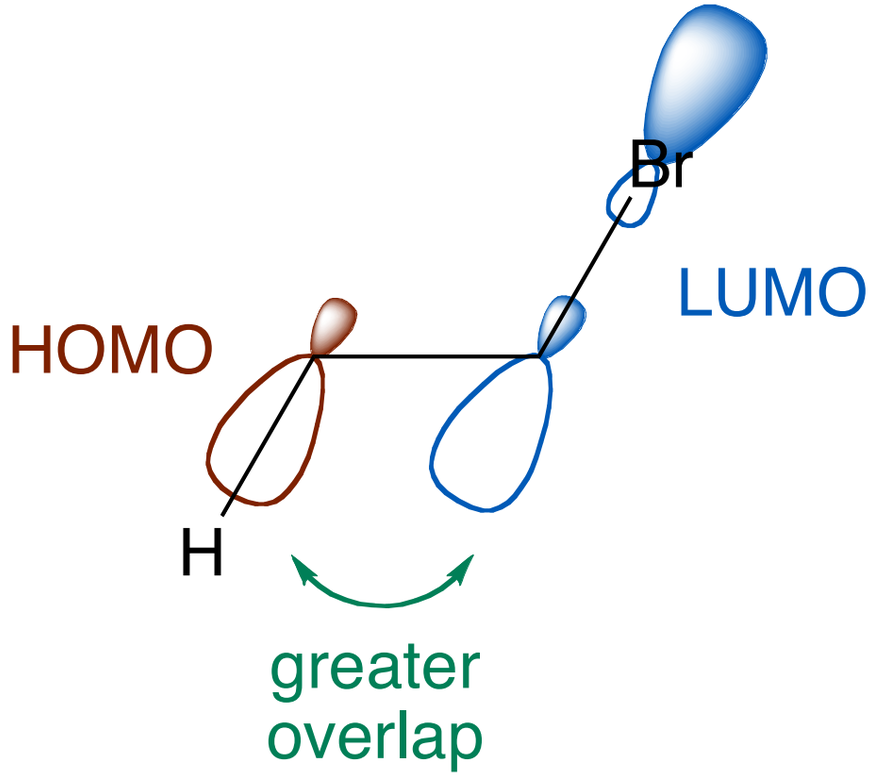
Orbital Overlap and Stereoelectronics

- Orbital overlap effects the transition state structure for reactions

syn
elimination

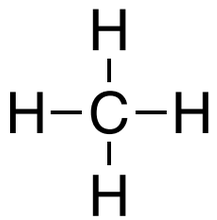


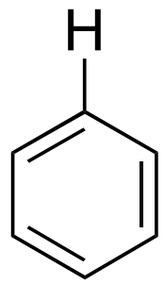
anti
elimination

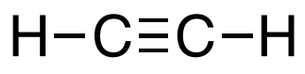


Hybridization

- electrons are more stable in s orbitals







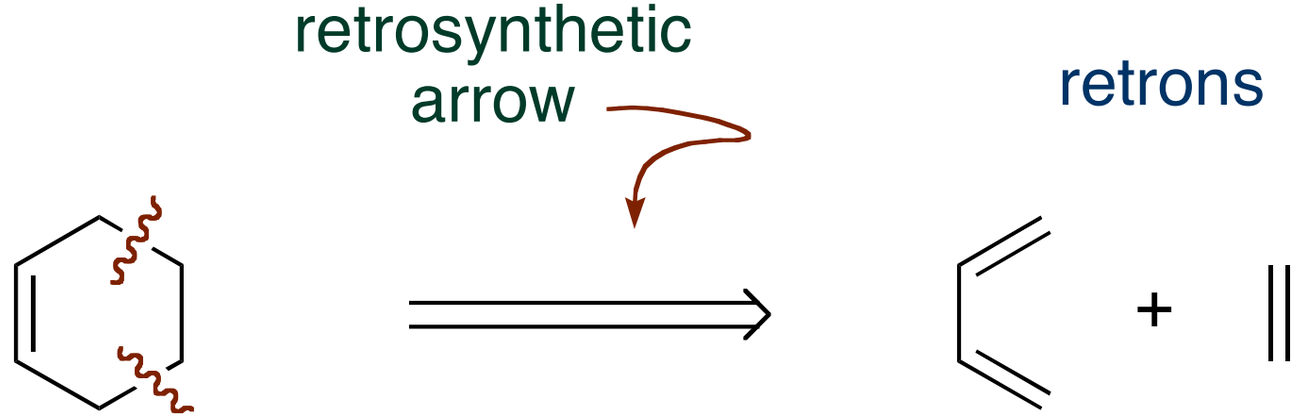
pK_a	48	43	24

Retrosynthetic Analysis

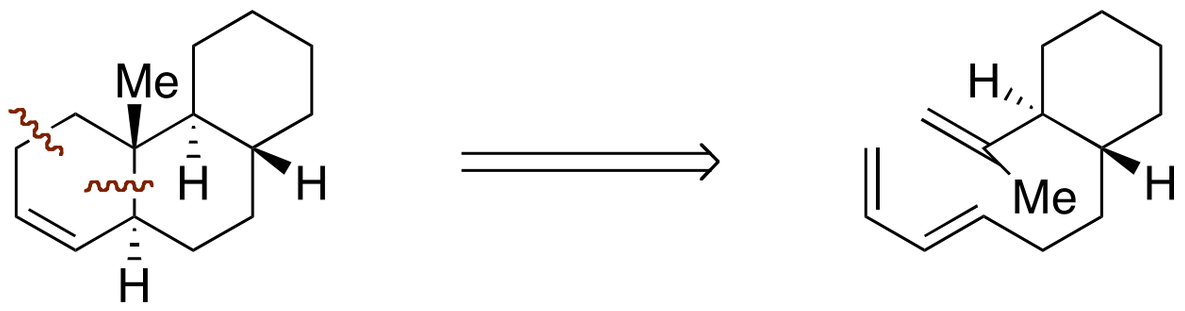
- a problem solving technique using a disconnection approach
  - Start with the target structure and think about the immediate precursor
  - Continue working backwards until you reach readily available starting materials
- Need to have insight into synthetic strategy
  - understanding of chemical bonding and conformation
  - repertoire of reactions (transformations)
  - knowledge of feasible reaction mechanism
  - understanding of selectivity

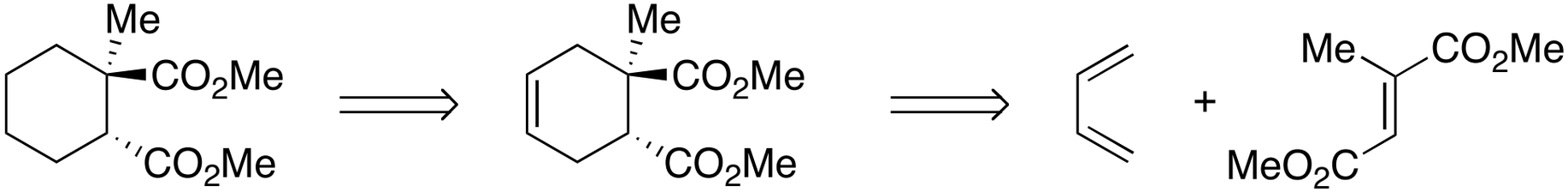
Retrosynthetic Analysis

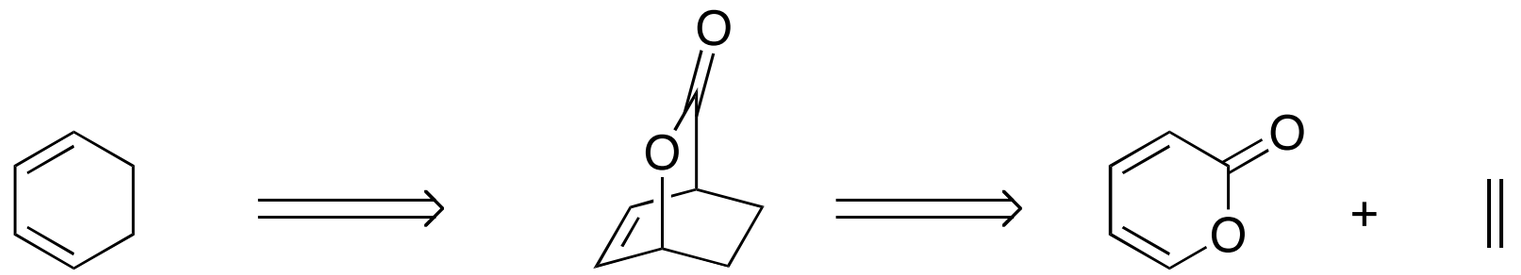
- recognize structural features and FG's in the target
- disconnect bonds by methods corresponding to known *reliable* reactions
- repeat



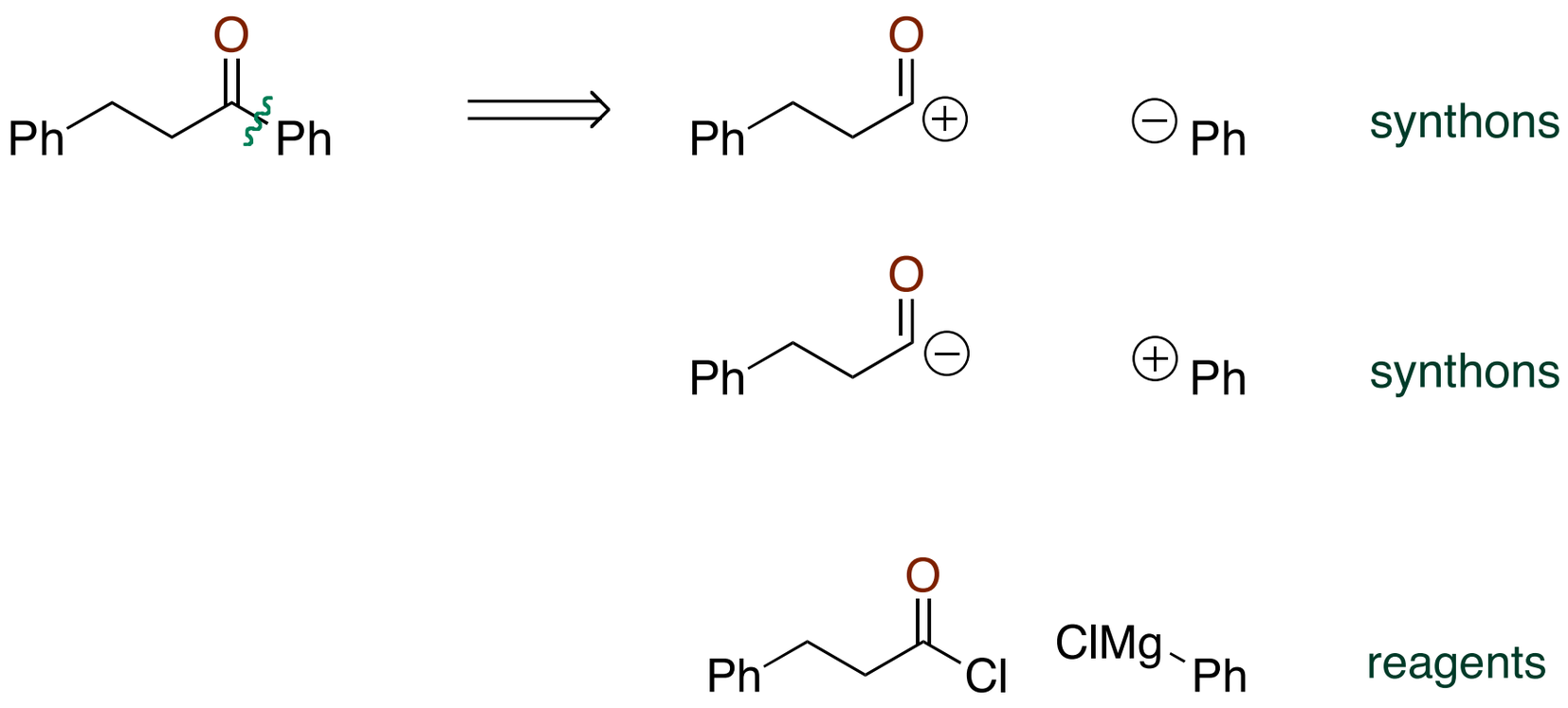
Diels-Alder Strategies



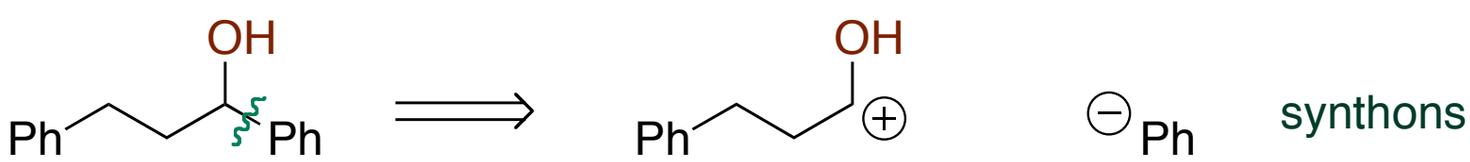


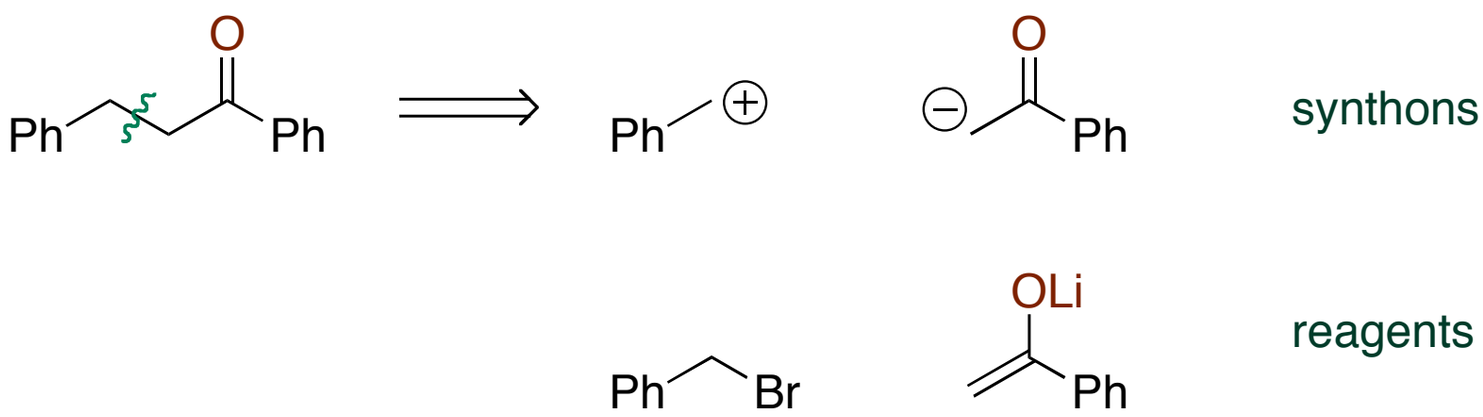


Retrosynthetic Strategy



Retrosynthetic Strategy

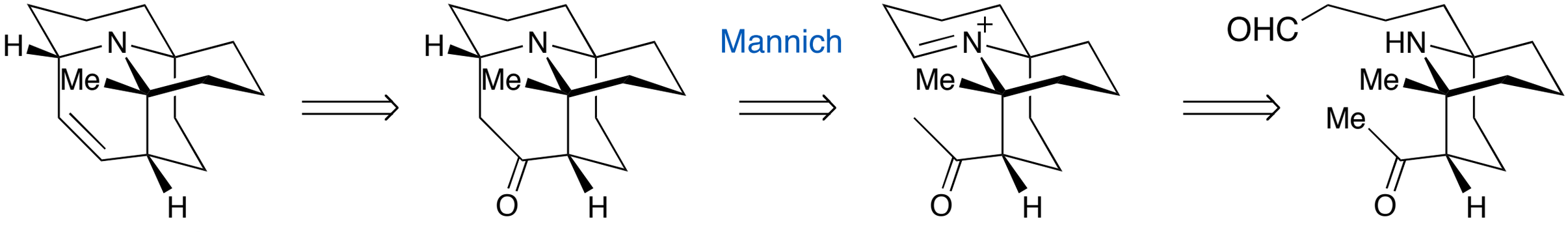




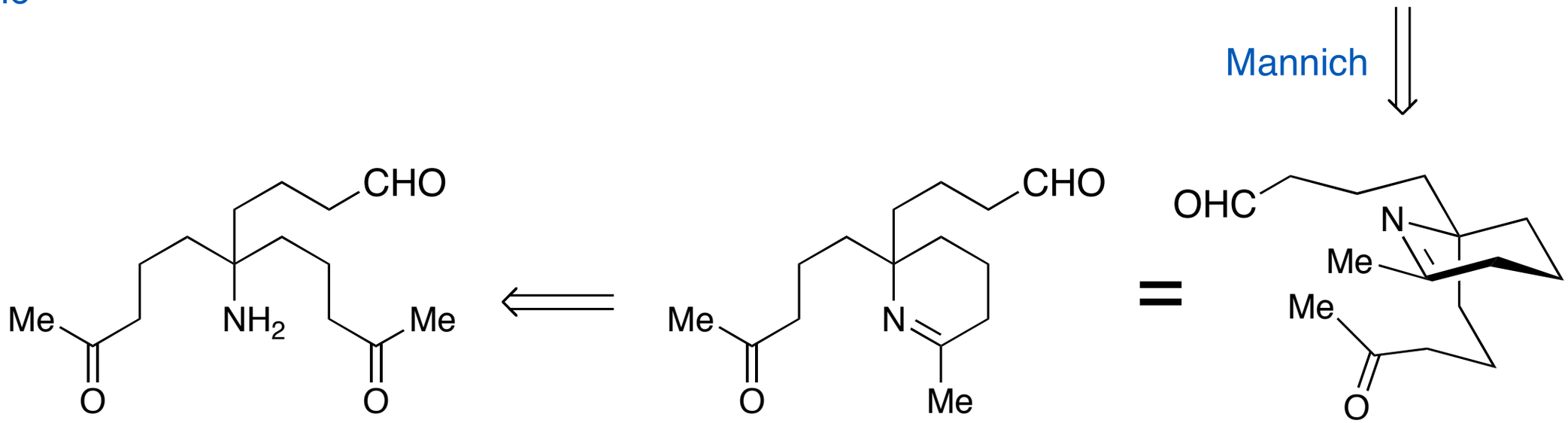
Retrosynthetic Analysis Strategies

- Functional Group Strategies
  - FG transformations can significantly alter complexity and reactivity
- Stereochemistry Strategies
  - use stereoselective and stereospecific reactions
- Structure-goal Strategies
  - focussing on an intermediate structural goal can narrow the retrosynthetic possibilities
- Transformation based Strategies
  - focussing on key transformations may help reduce complexity of a synthesis
- Topological Strategies
  - identify substructures and preserve ring structures as much as possible

Retrosynthetic Analysis Example - porantherine

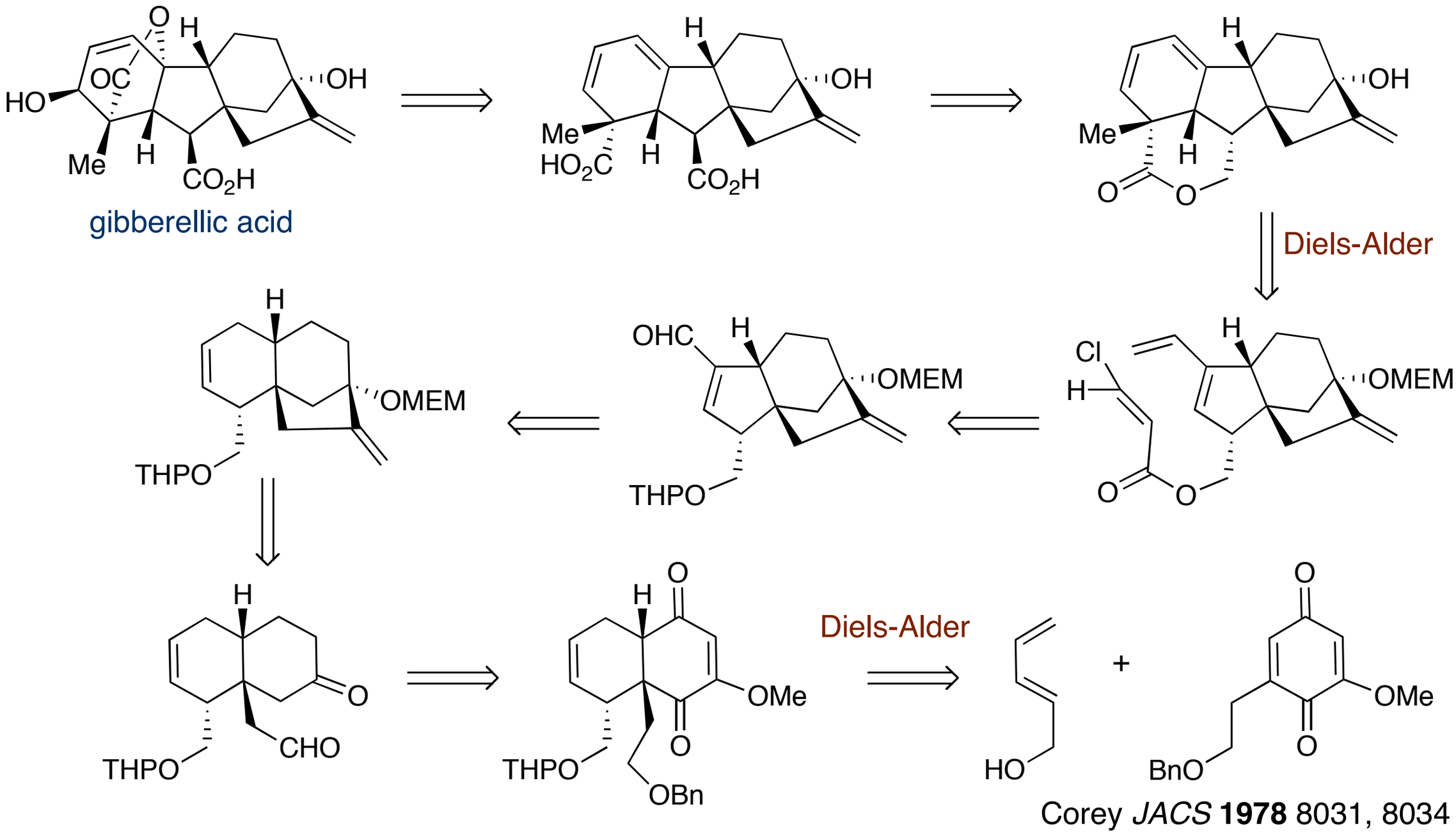


porantherine



Corey *JACS* **1974** 6516

Retrosynthetic Analysis Example - gibberellic acid



Corey *JACS* **1978** 8031, 8034