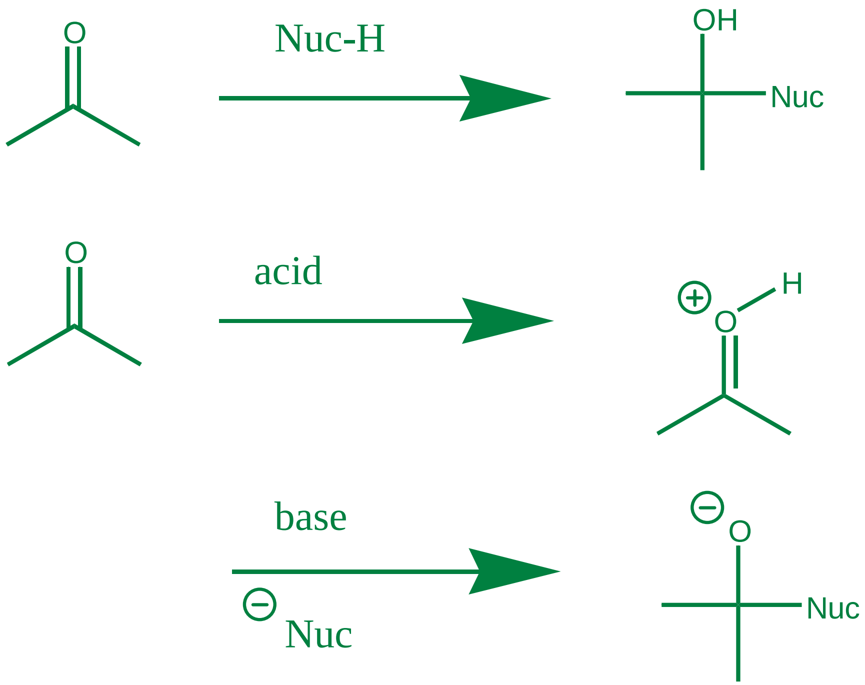
Enols, enolates, aldol

- Problems
  - 16.23, 16.25, 16.26, 16,27, 16,28, 16.31, 16.33, 16.35
  - 17.20, 17.23, 17.25, 17.26, 17.27, 17.28, 17.29, 17.32, 17.34, 17.36, 17.39, 17.43
  - 18.23, 18.25, 18.31, 18.32, 18.35, 18.37, 18.39

Recap



if Nuc is strong base - not reversible

if Nuc is weak base, may reverse, Drive to

completion by condensation

Strong bases

- Grignard
- Hydrides
- Alkynyl anions

- Additional – no need for acid or base catalysis (reagents all strongly basic)

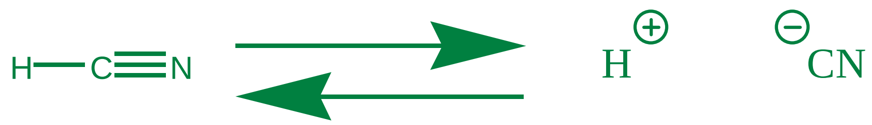
Weaker bases

- Water – hydration
- Alcohols – hemiacetal, reversible, acid catalysis leads to loss of water, acetal isolated if water removed (protecting group)
- Primary amines – imines if water removed
- Secondary amines – enamines if water removed

This chapter

- Less basic sources of nucleophilic carbon
- Formation of C-C bonds but some chance of reversibility
- Strategies for control of reversibility
- Use in synthesis
- Related reactions

Hydrocyanation

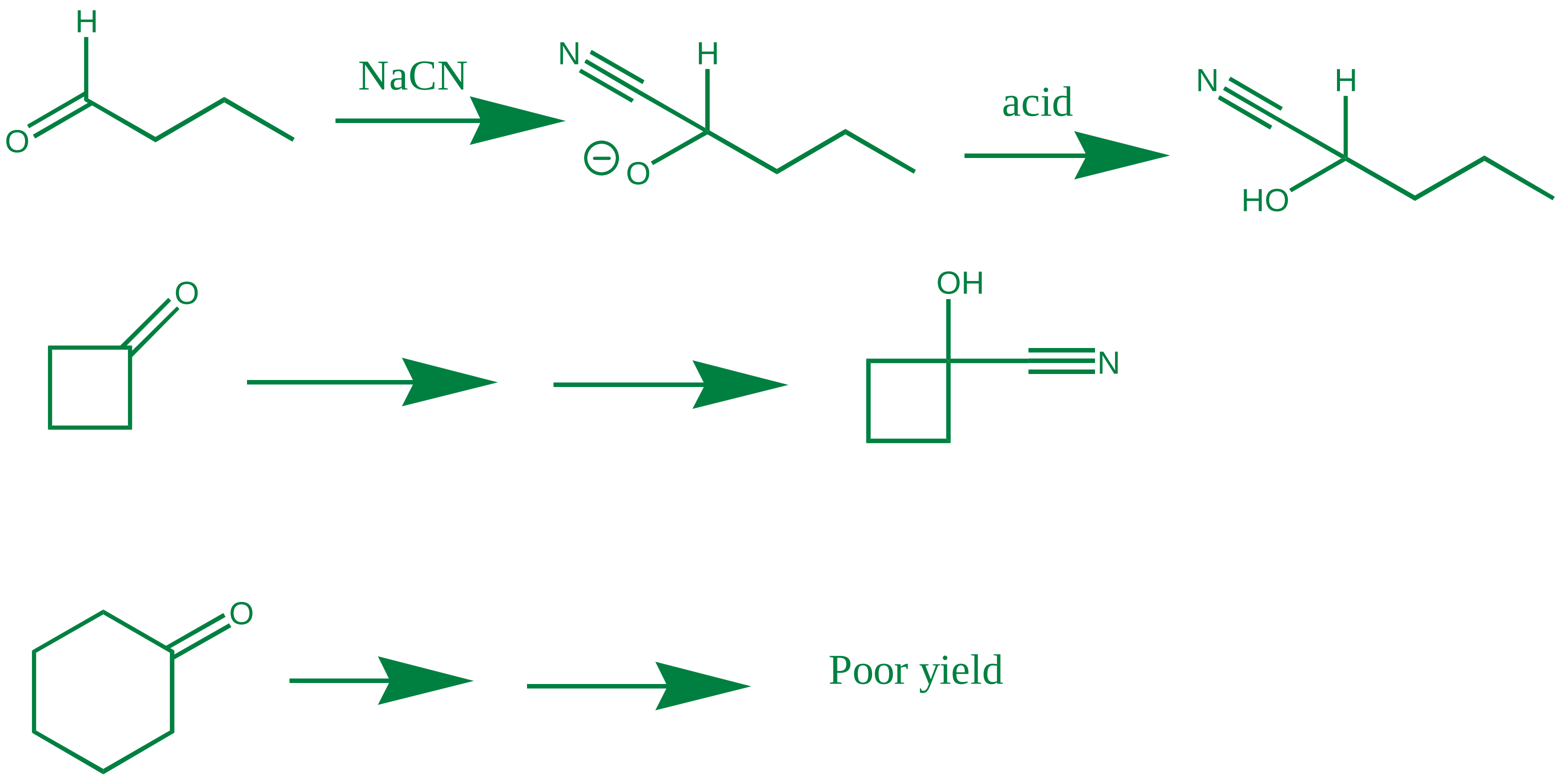


Weak Acid

Cyanide anion can be a nucleophile, but addition to C=O reversible

Can't use acid catalysis, toxic gas

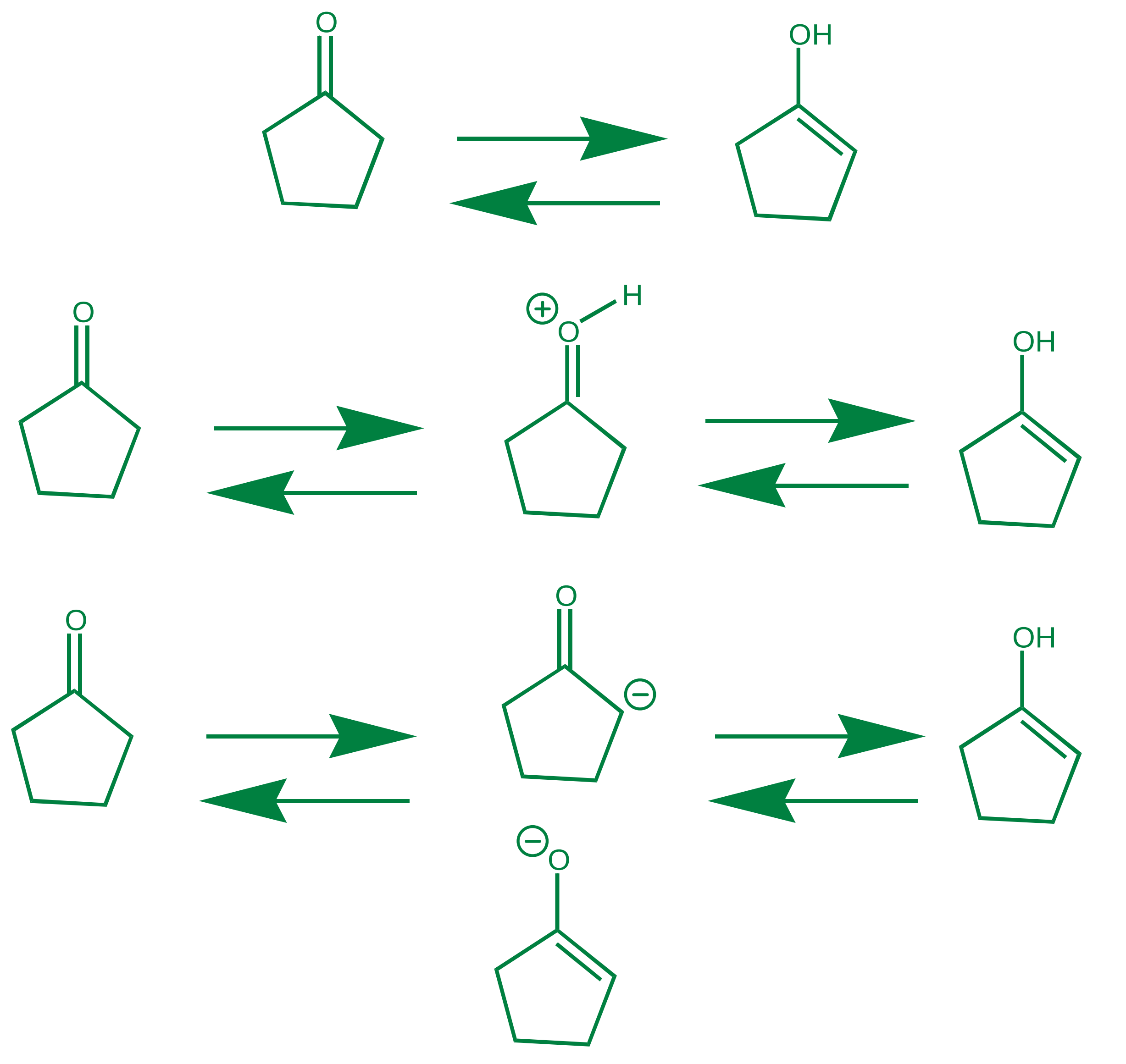
Reaction only favorable where steric effects make it favorable (recall hydration)


NaCN
acid
Poor yield

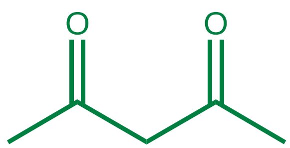
Carbonyl species

- We have seen as electrophile
- Also exists in a nucleophilic form
- These forms react with one another
  - Enol
  - Enolate anion
- Useful – adds much complexity
- Biomimetic

Enol Equilibrium



Electron withdrawing groups



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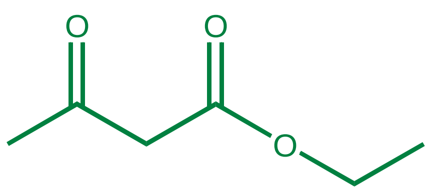
HCN 9.1



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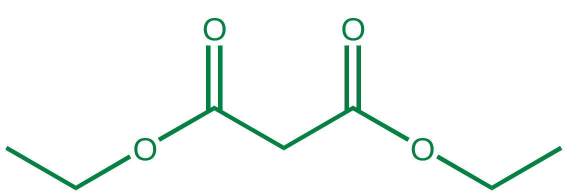

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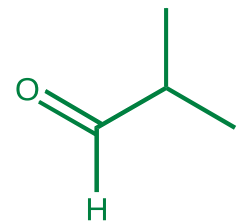
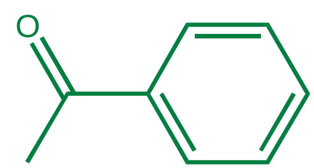
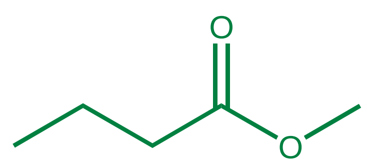


15.5



15.8



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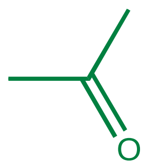
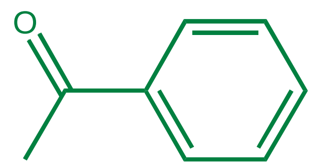
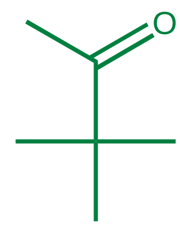
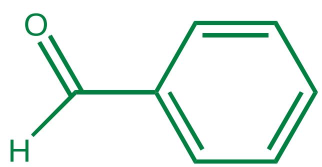
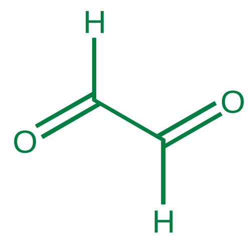
Acidic H is α hydrogen

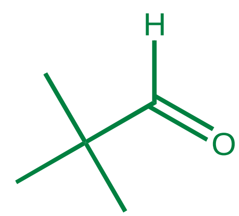




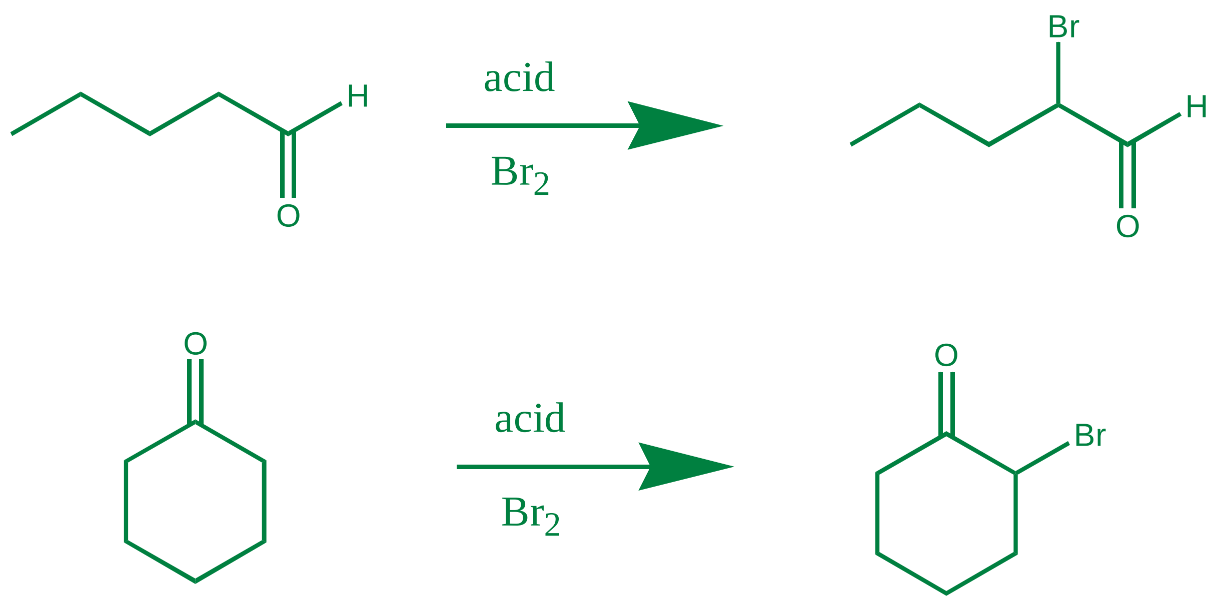




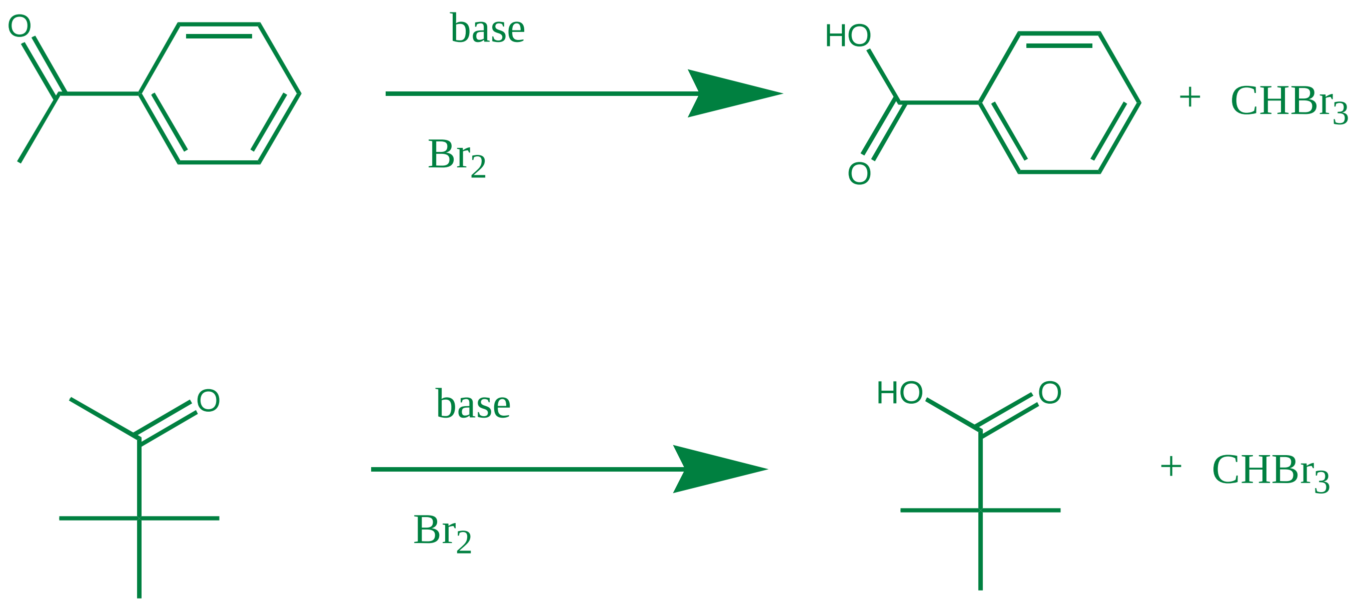




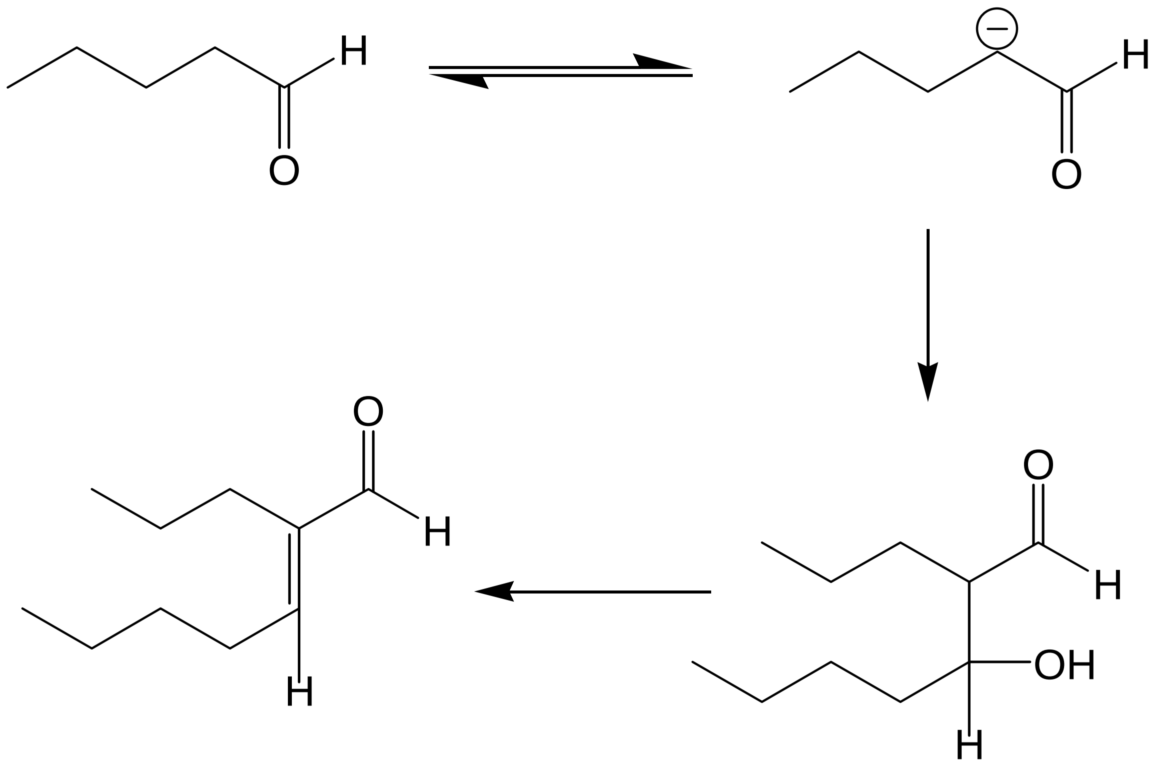
α halogenation of carbonyls



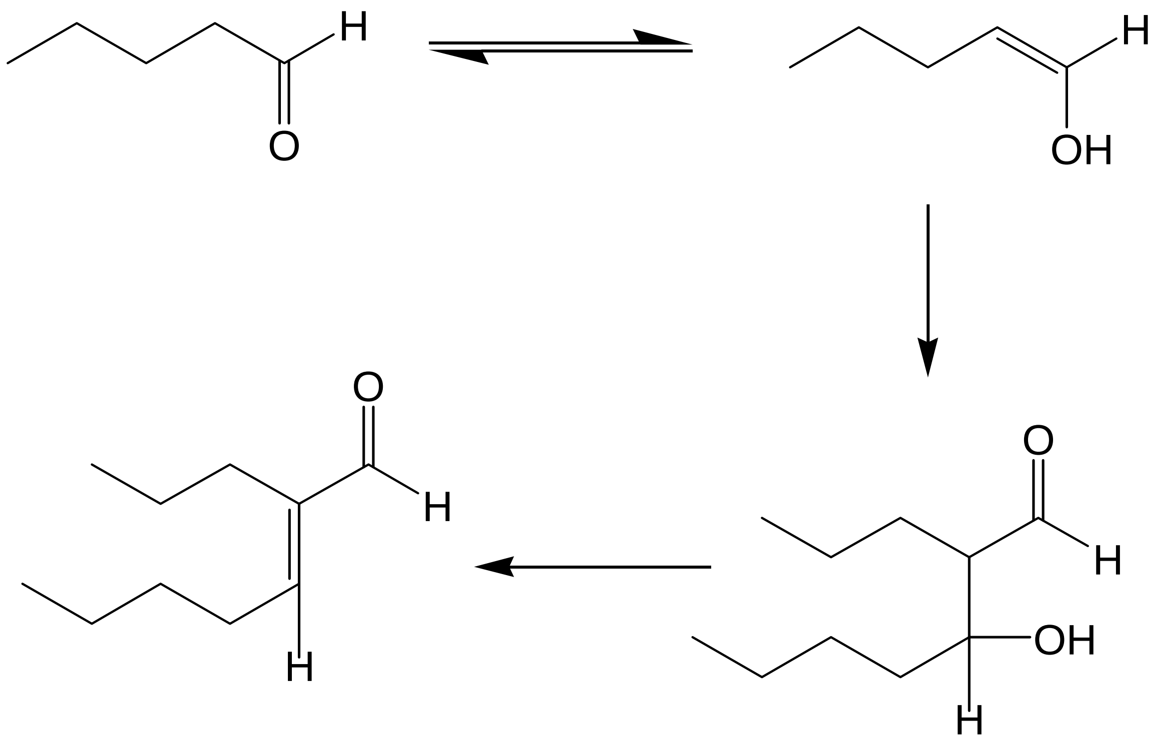
Haloform test – methyl ketones



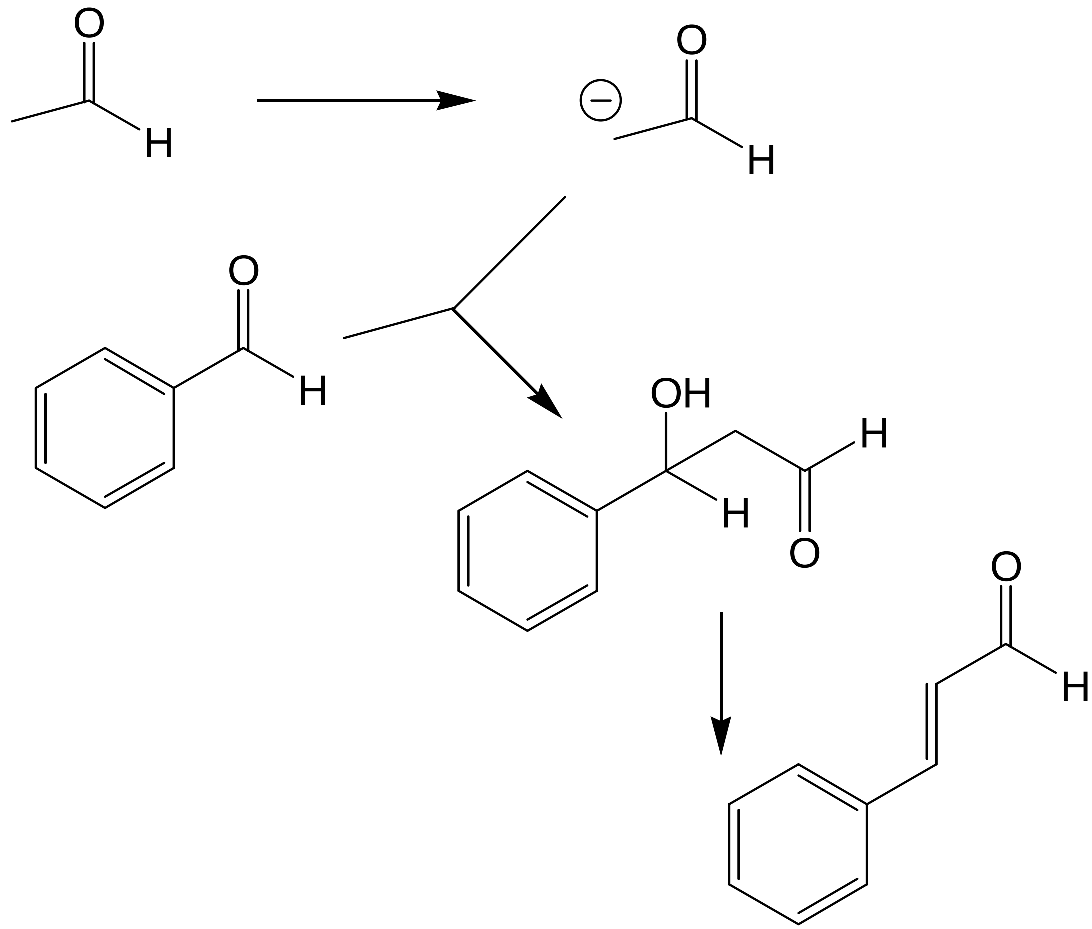
Aldol reaction – base catalyzed



Aldol Reaction – acid catalyzed

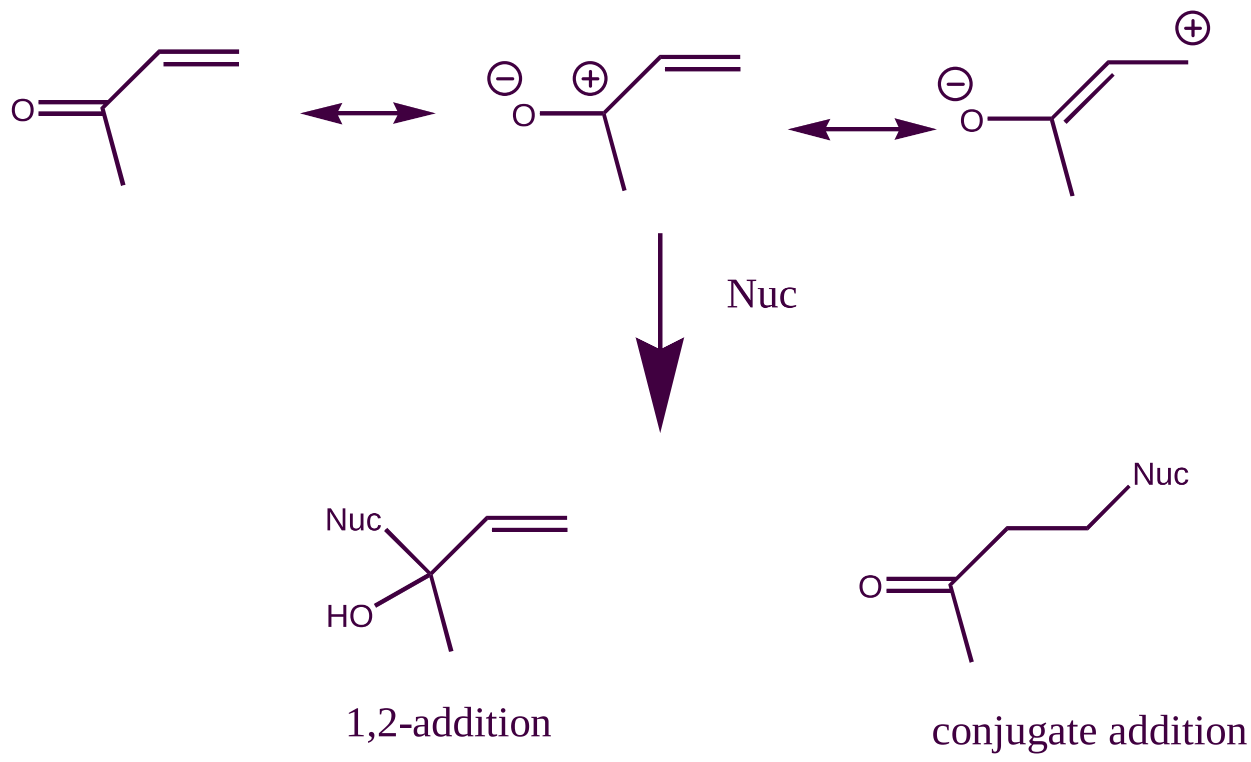


Mixed Aldol reaction



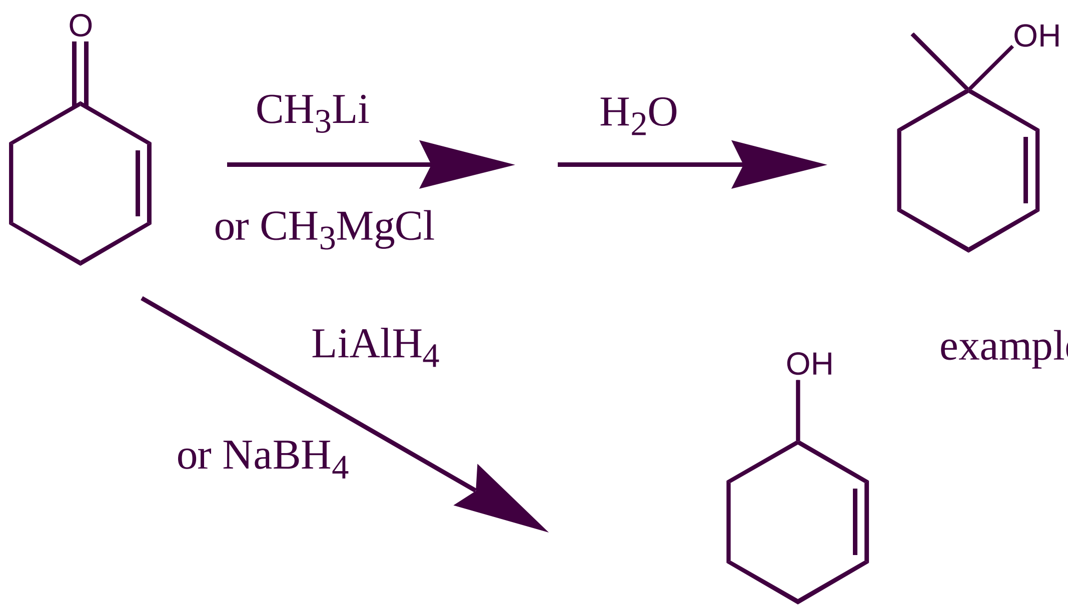
Consider α,β-unsaturated C=O

- Alkene now electron-poor, can react with nucleophiles
- Thus two sites for nucleophilic attack
- Called 1,2 and 1,4 (or conjugate addition)
- 1,2 addition is kinetic
- Conjugate addition is thermodynamic
- Cuprates also do conjugate addition



O
O
O
Nuc
Nuc
HO
Nuc
O
1,2-addition
conjugate addition

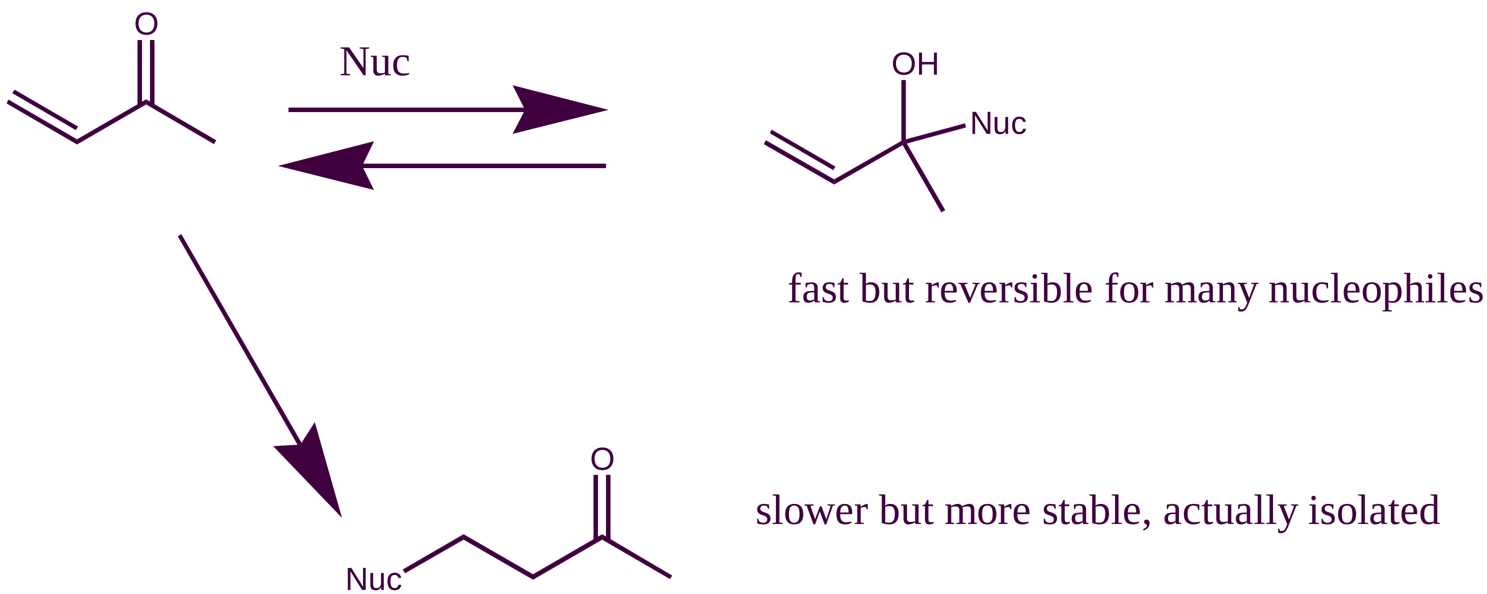
Irreversible Additions



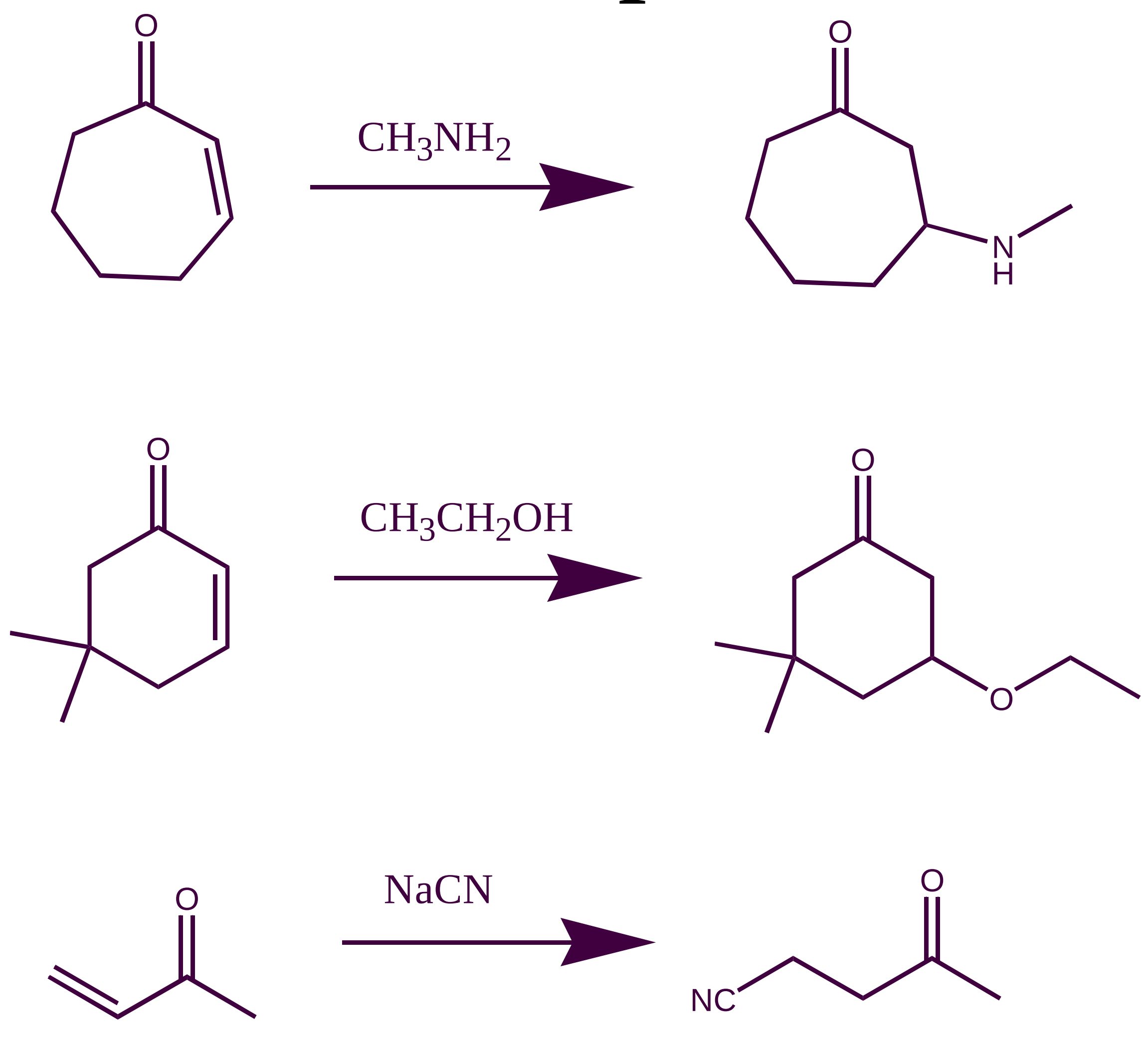
examples of kinetic reaction, 1,2-addition

Conjugate Additions

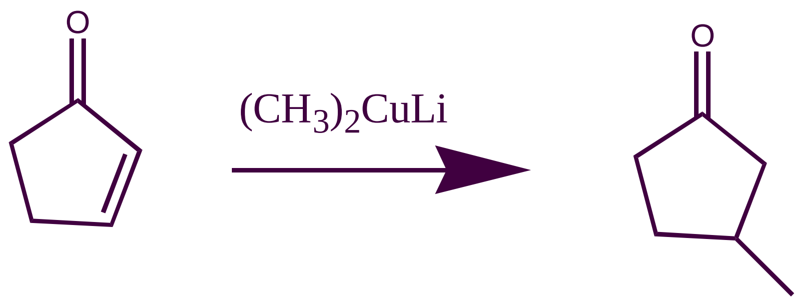
- Reversible nucleophiles
- Cuprates
- Enolate anions – Michael Addition
- Robinson Annellation reaction


O
Nuc
OH
Nuc
fast but reversible for many nucleophiles
O
slower but more stable, actually isolated
Nuc

Examples



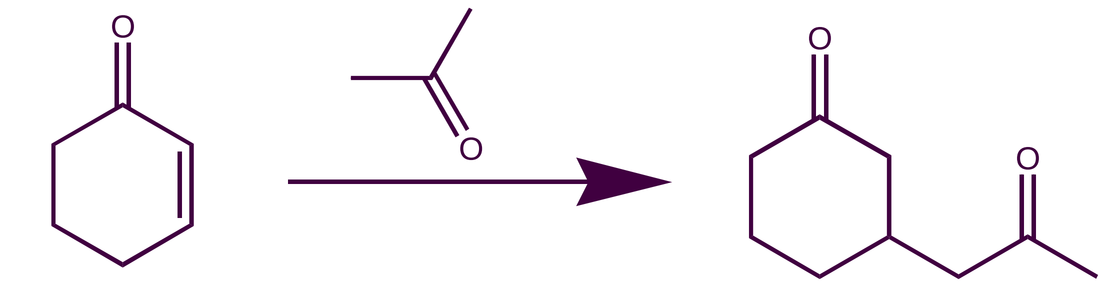
Cuprates

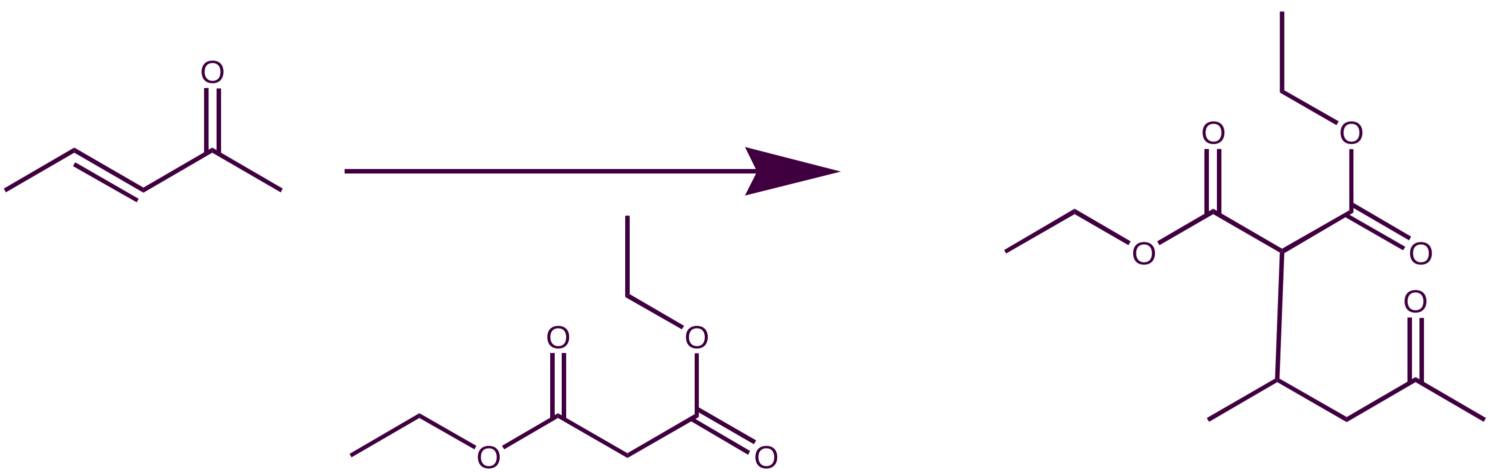


mechanism complex

example above - prostaglandin synthesis

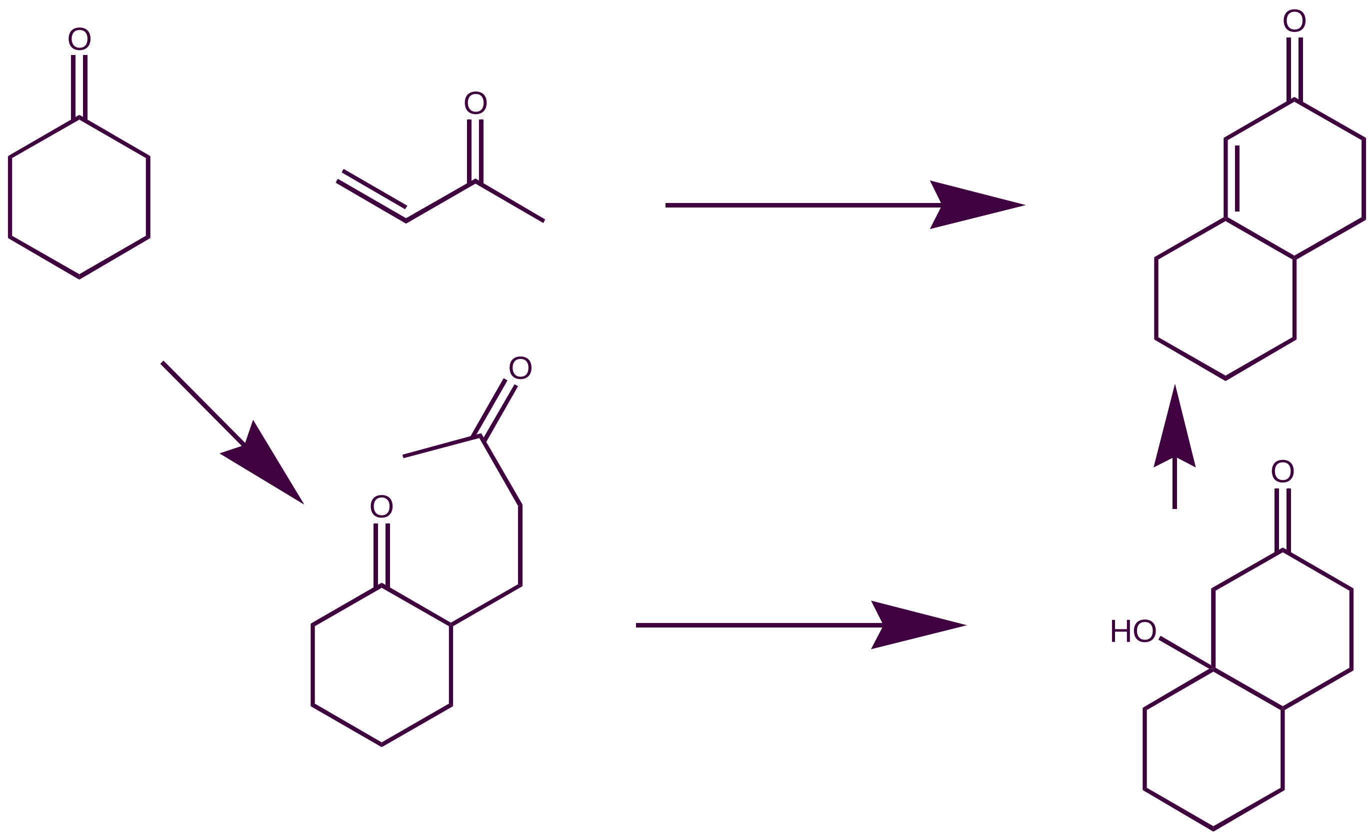
Enolates – Michael Addition

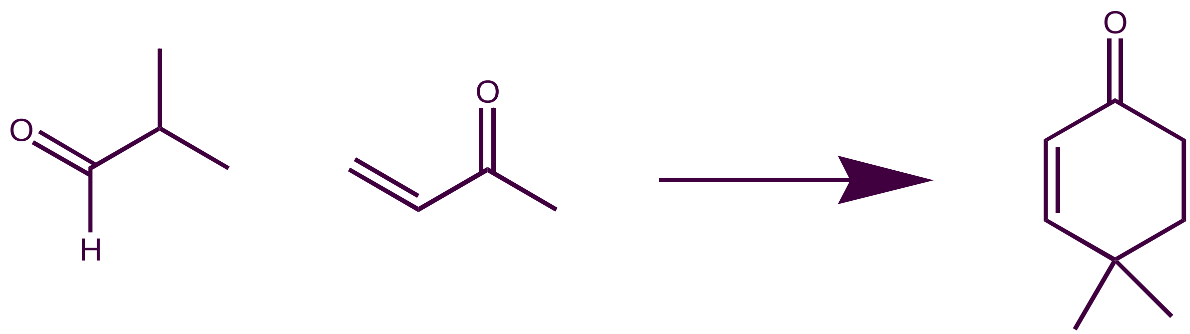




Robinson Annelation

- Alternative method to form six member rings
- Michael addition followed by aldol condensation
- Often used in steroid syntheses – alternative to Diels-Alder

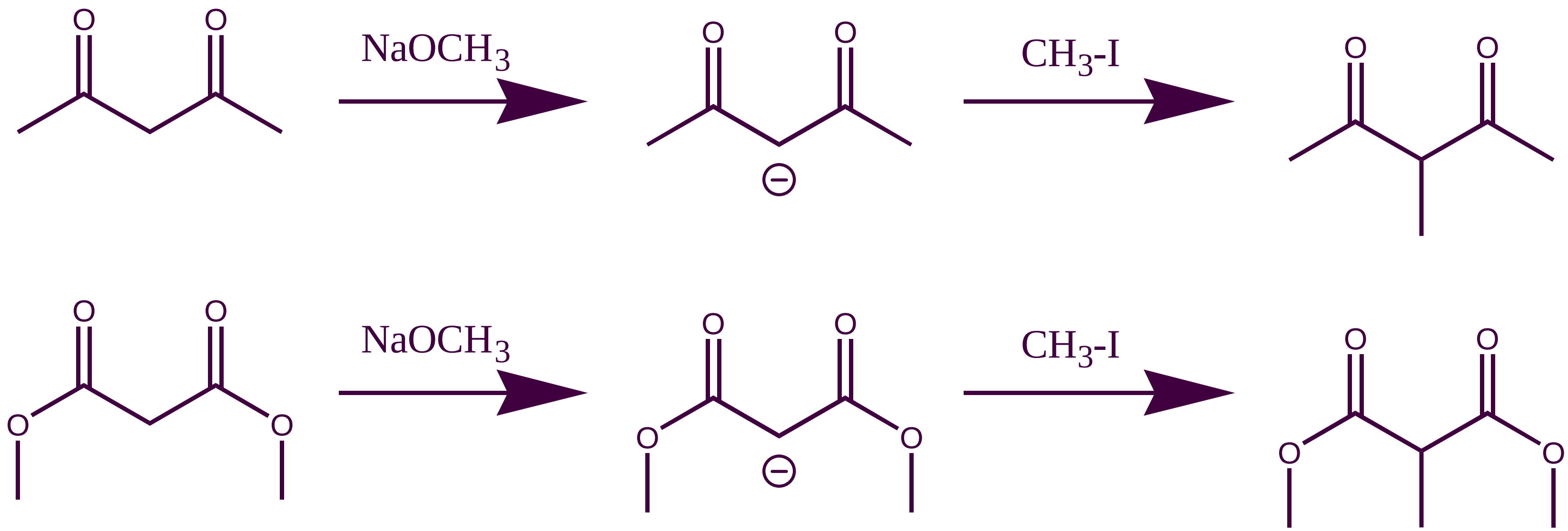

O
O
O
O
O
HO
O

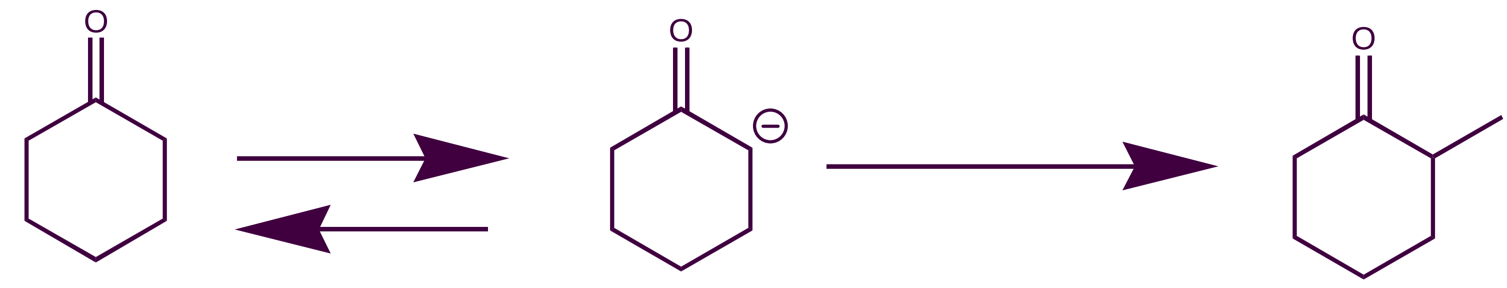


O
H
O
O

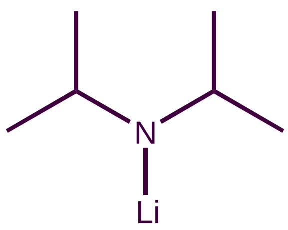
Alkylation of Enolates

- Use in Sn2 reactions to make C-C bonds
- Difficulty – competing aldol reaction
- Alkylation will only work where the enolate can be formed in absence of starting C=O
- Thus only useful for highly acidic enolates


O
O
NaOCH3
CH3-I
O
O
O
O
O
NaOCH3
CH3-I



need strong enough base to prevent reverse reaction, but will not add to C=O



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