Synthesis In Brief - Feynman Liang
CHEM231 - Spring 2012
Amherst College

I Designing Syntheses

Consider the target's:

- Molecular size/density
- Number of stereocenters
- Elements present
- Functional groups present
- Chemical reactivity

Synthesis Considerations

- Must be selective to be useful (protecting groups, solvent choice)
- Other functional groups on the molecule
- Be aware of limitations of proposed transformations

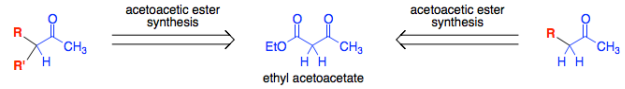
Retrosynthesis

Basically disconnect groups one by one and work backwards from target to start.

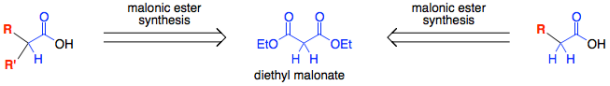
II Common reaction patterns

Carbonyl patterns

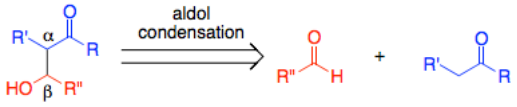
- Methyl ketones with alkyl groups attached to α-carbon



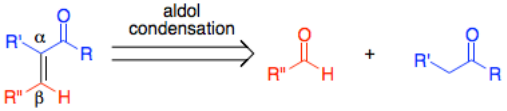
- Carboxylic acid with alkyl groups attached to α-carbon



- β-hydroxy carbonyl

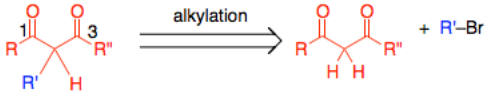


- α,β-unsaturated aldehyde/ketone: E1cb (removal of α-proton followed by elimination of β-hydroxy with - charge)

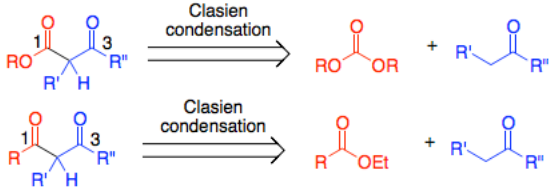


Dicarbonyl patterns

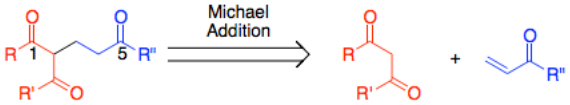
- 1,3-dicarbonyl



- 1,3-β-ketoester

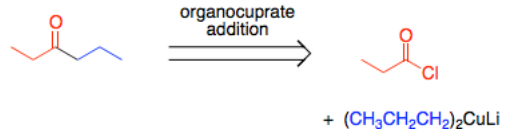


- 1,5-dicarbonyl

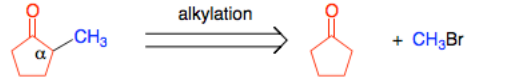


Enolate patterns

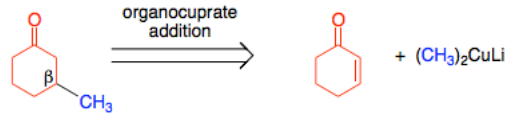
- Non-methyl ketone



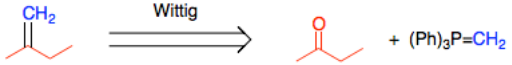
- Non-methyl ketone (branching at α)



- Non-methyl ketone (branching at β)

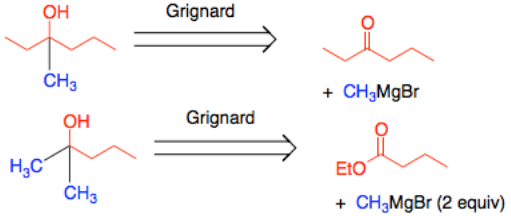


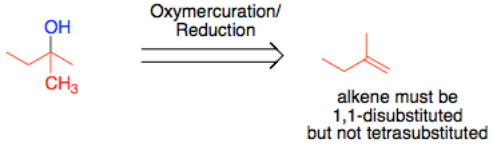
Unconjugated alkenes



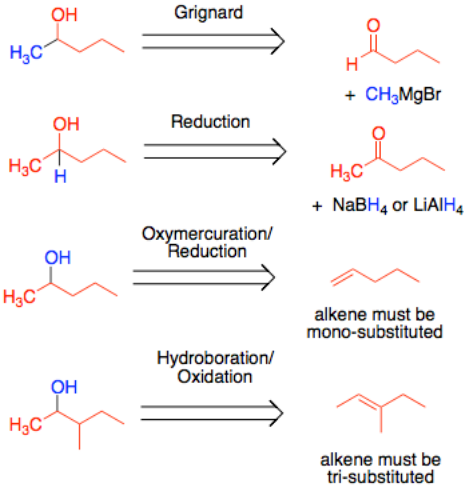
Alcohol patterns

- Tertiary alcohol

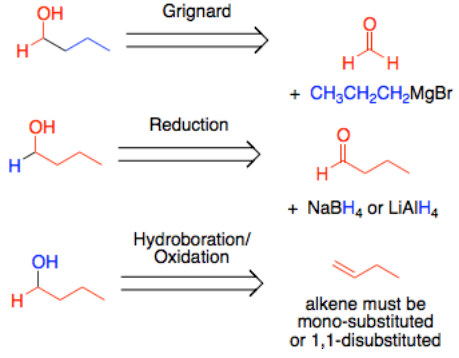




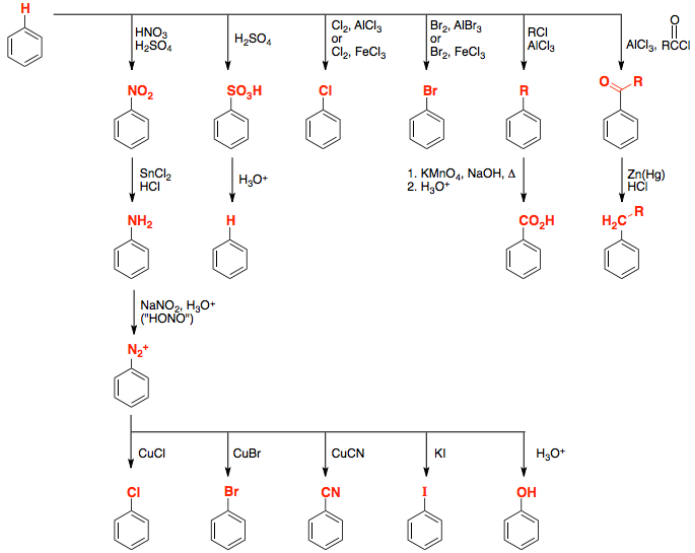
- Secondary alcohol



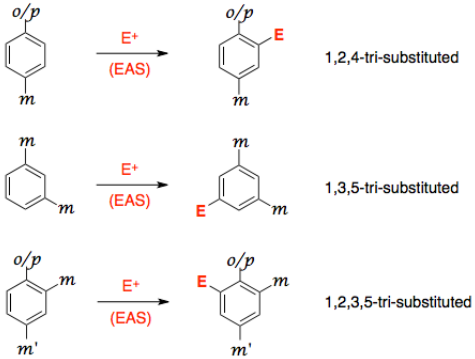
- Primary alcohol



EAS



- **EAS Rules:**
  - Can stop each EAS after one reaction
  - Only o/p di-substituted isomers can be seperates (no tri/tetra separation)
  - Proceed only through **privileged systems**: substituents symmetric or all direct to same positions
  - No Friedel Crafts alkyl/acylation (alkyl and acyl halide rxn through carbocation/acylium intermediate) if R-NO_2 present (too deactivating)
  - No Friedel Crafts alkylation (alkyl halide rxn through carbocation) if carbocation rearrangements are possible
  - EAS privileged systems (use for retro and fw):



- Strategies:
  - **Sulfonation/sulfonation is reversible**, can block 5 position of 1,2,3-trisub
  - NO_2 directs m, reduction (and Sandmeyer) converts to o/p director NH_2 (or from Sandmeyer: OH, Cl, Br, I)
  - Alkyl directs o/p, converted to acyl via **$KMnO_4$ oxidation**
  - Acyl directs m, can be converted to corresponding alkyl via **Clemmenson reduction**

III Ground Rules for Synthesis

- Any inorganic starting materials
- Any organometallic reagent (RMgX or R_2CuLi) where R=
  a) Allyl group
  b) Phenyl ring
  c) Saturated alkyl chain with $\leq$4 carbons
- Organic reagents:
  a) Any saturated alcohol, aldehyde, ketone, carboxylic acid, alkyl halide with $\leq$4 carbons
  b) Any ylide with $\leq$4 carbons (phenyls in PPh_3 don't count)
  c) Any ester which acid component contains $\leq$4 carbons (don't count ester's carbons)
- ONLY ONE functional group per molecule. ex. no Michael acceptors b/c contains both alkene and carbonyl
- Allowed reagents:

Ethyl acetoacetate	Acetoacetic ester synthesis
Diethyl malonate	Malonic ester synthesis
1,2-ethanediol	Carbonyl protecting group
Diethyl carbonate	Diol protecting group
Diethyl oxalate	1,2-dicarboxylic ester, used for polymer
Bromobenzene	Ph-Br, aromatic substitution target
Benzaldehyde	Ph-COH, aromatic aldehyde
Benzoic acid	Ph-COOH, aromatic carboxylic acid
Allyl bromide	C=C-C-Br, starting alkene
Benzyl bromide	Ph-CH2-Br, starting aromatic
Cyclohexanone	Hexane=O, ketone
Cyclopentanone	Pentane=O, ketone
Tosyl Chloride	Convert alcohols $\rightarrow$ R-OTs $\rightarrow$ R-X
Pyridine	Weak base/proton sink
mCPBA	Epoxidation
Dimethyl sulfide	Reducing agent for ozonolysis
Mercuric acetate	Oxymercuration
Benzene	Starting EAS
Toluene	Starting EAS