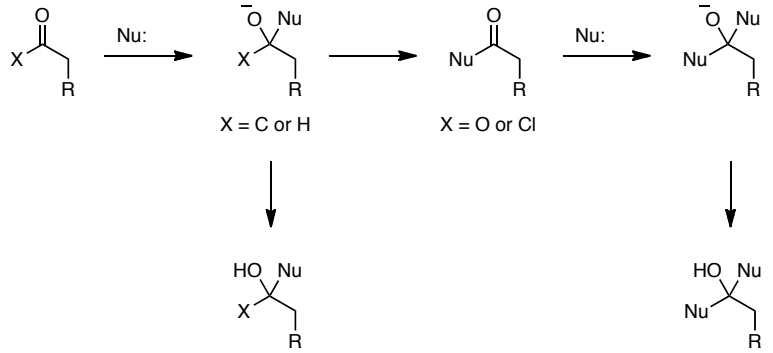
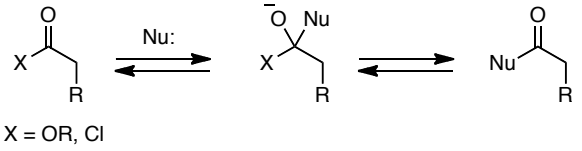
CHEM 234: Organic Chemistry II – Reaction Sheets

Nucleophilic addition at carbonyl groups: Grignards and reducing agents



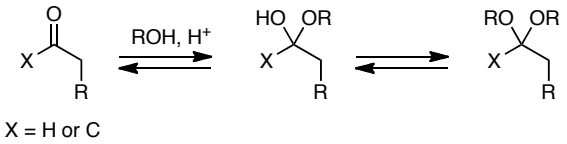
Nucleophilic addition at carbonyl groups: oxygen and nitrogen nucleophiles: acyl exchange

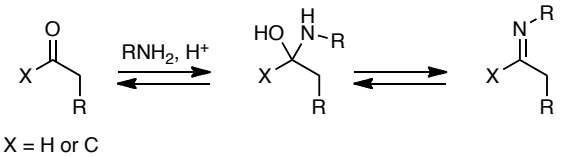


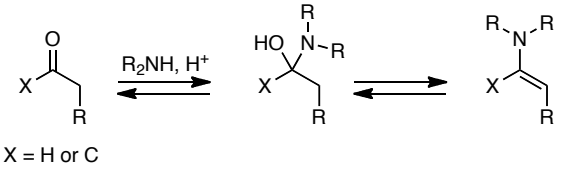
For X = OR, reactions are generally reversible with Nu = OR' and can occur under acidic or basic conditions.

If Nu = HO^-, reaction is generally irreversible due to deprotonation of the product acid.

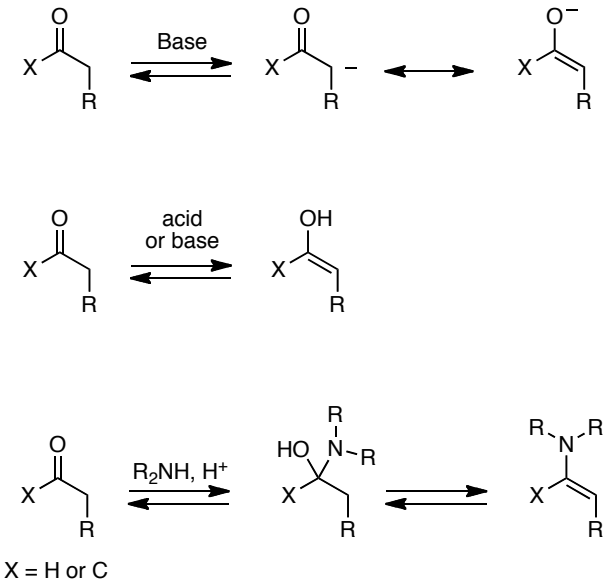
Nucleophilic addition at carbonyl groups: Oxygen and nitrogen nucleophiles



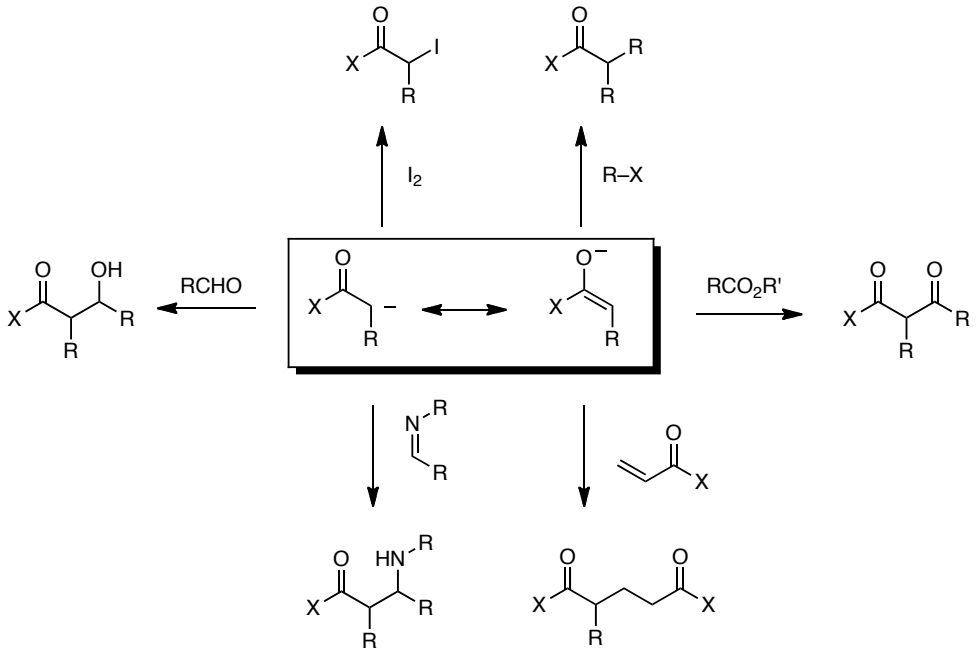




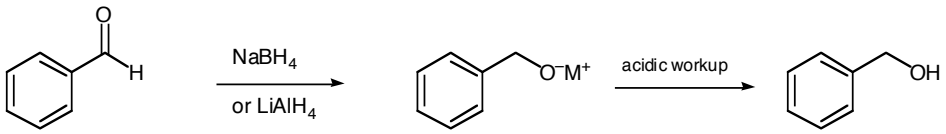
Enol and enolate formation

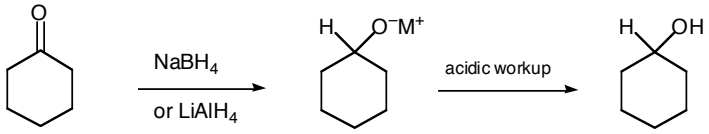


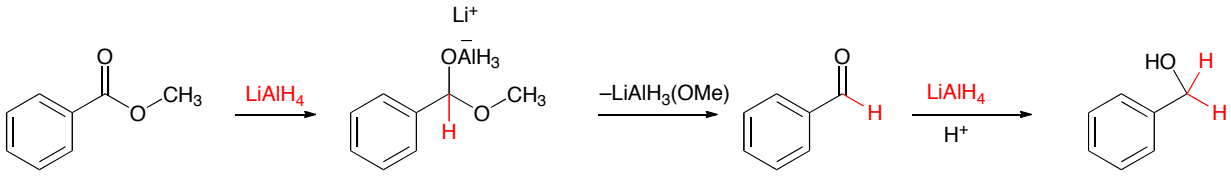
General reactions of enolates



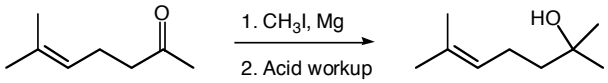
Reductions of aldehydes and ketones.



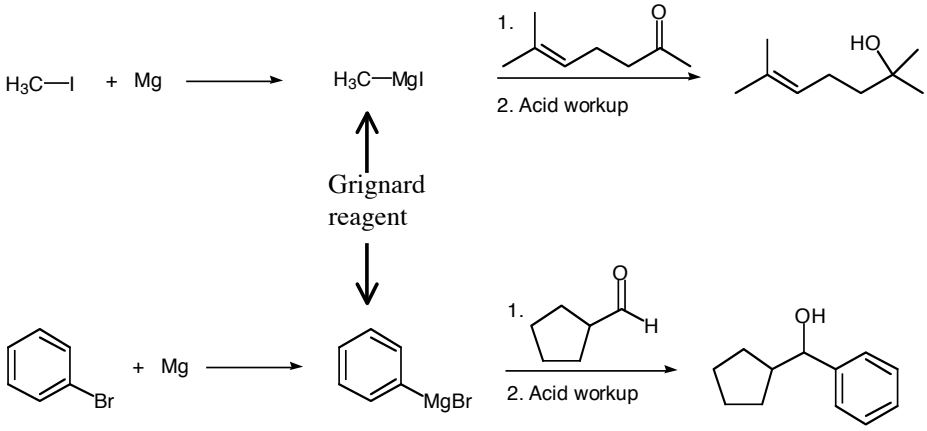




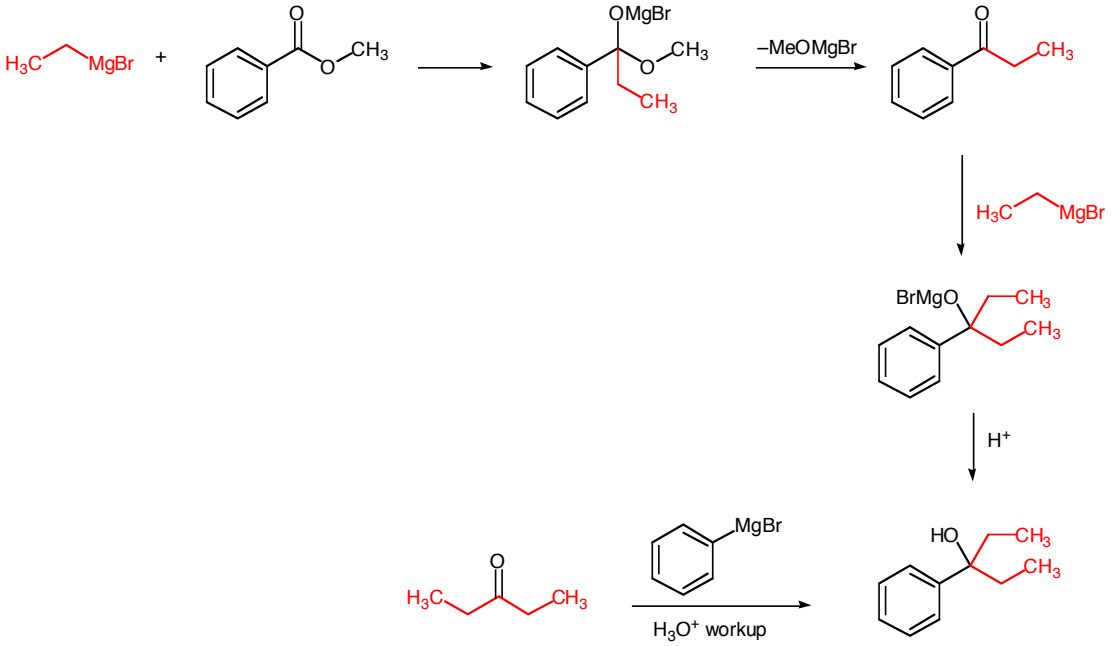
Barbier reaction (1899)



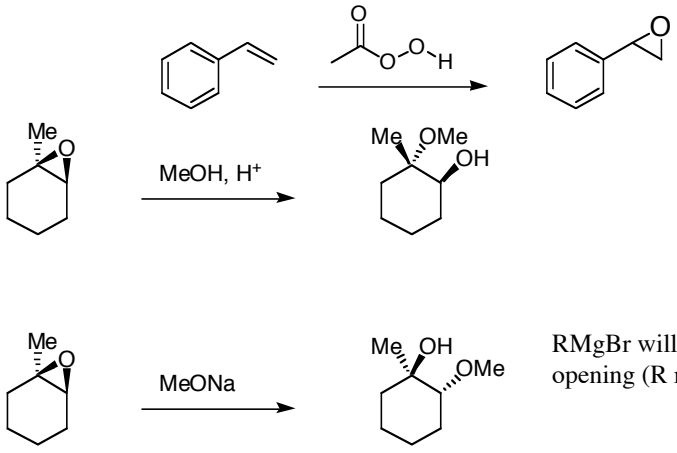
Grignard reaction (1900)



Grignard additions and reductions of esters.



Synthesis and reactions of epoxides:

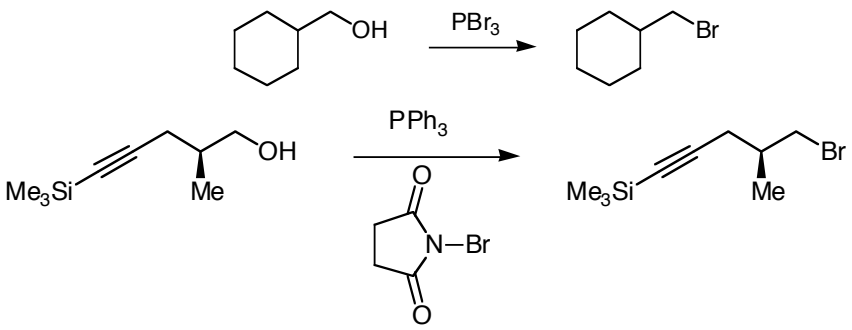


RMgBr will give similar opening (R replaces OMe)

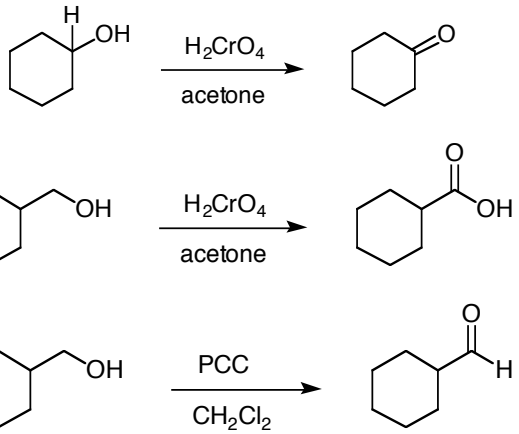
Formation of alkyl halides from alcohols

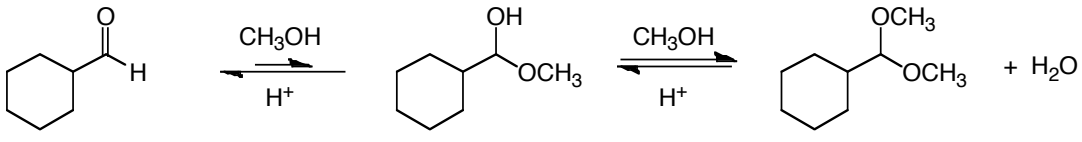
3° Alcohols - dry HBr or HCl

1° Alcohols - PBr_3 or $SOCl_2$



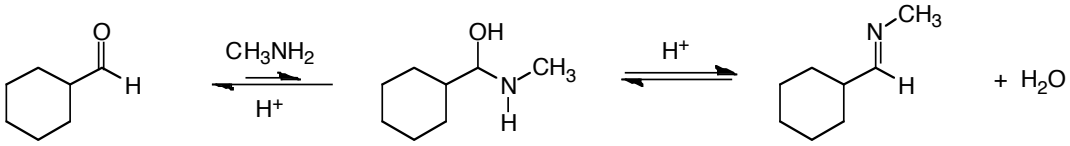
Oxidation of alcohols





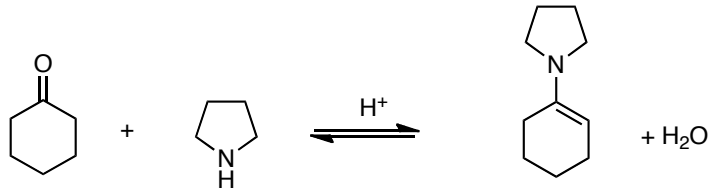
hemiacetal (unstable)

acetal (stable)



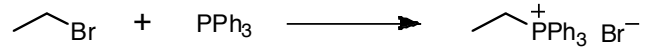
hemiaminal

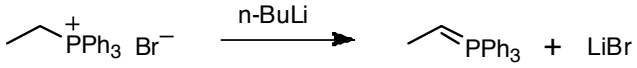
An imine

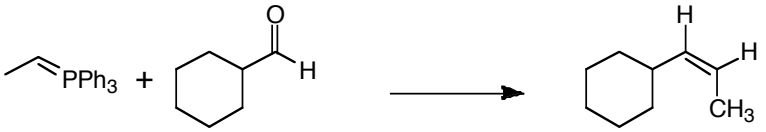


An enamine

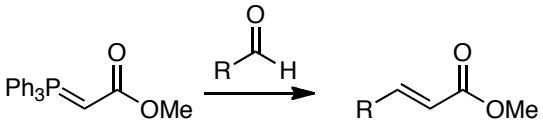
The Wittig reaction





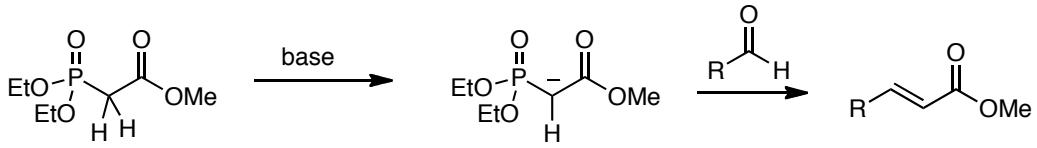


unstablized ylides give cis

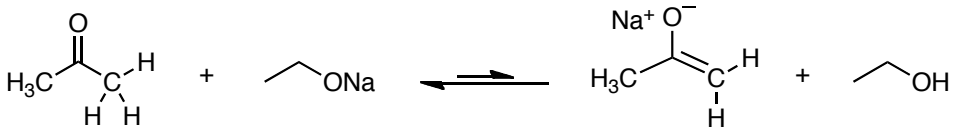


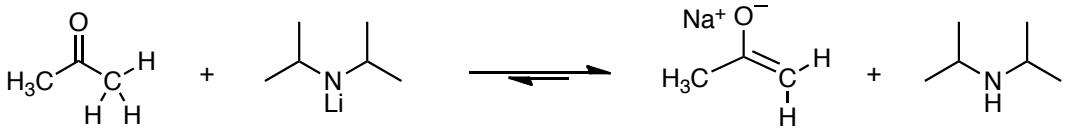
stabilized ylides give trans

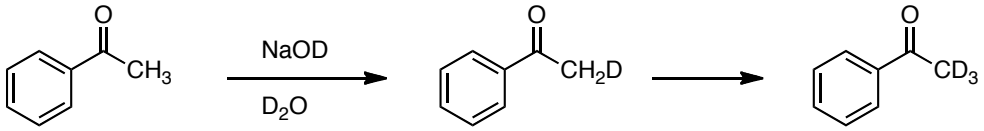
Horner-Wadsworth-Emmons reaction: A Wittig variant



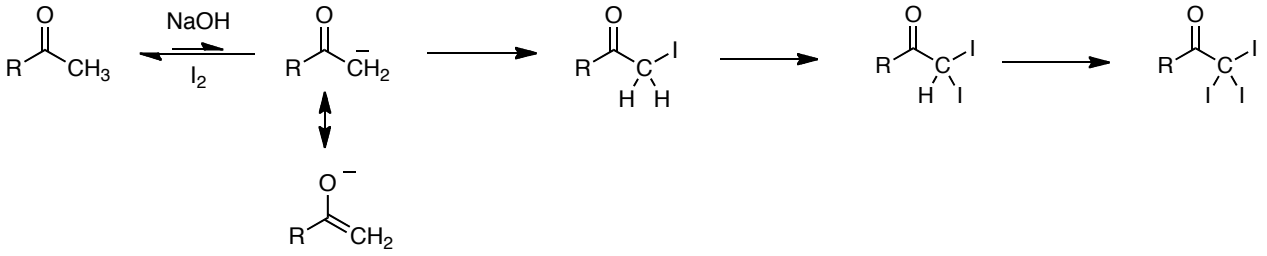
To generate enolates, use strong base.

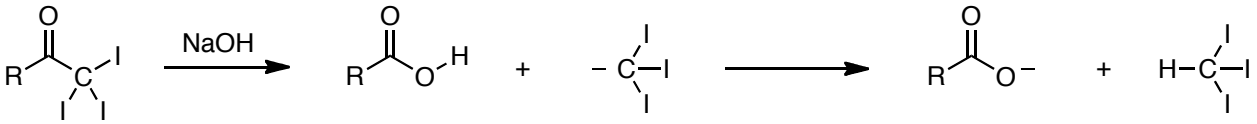




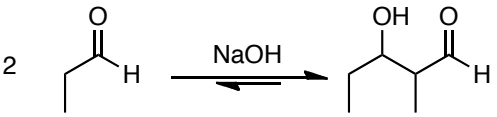


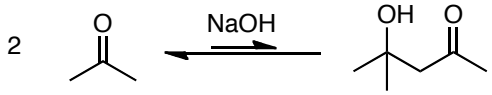
The Haloform Reaction





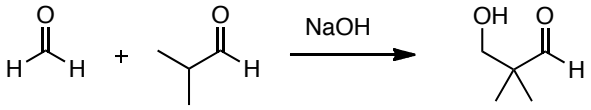
The Aldol Reaction

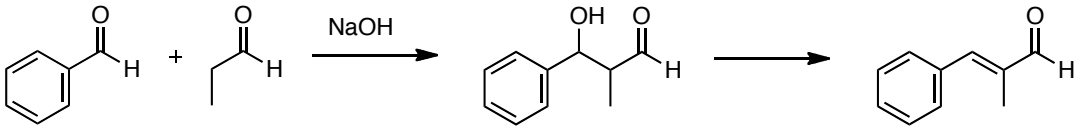




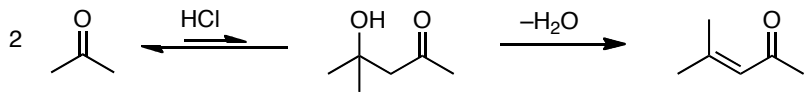
Crossed aldol reactions.

Practical when one component contains no α-hydrogens

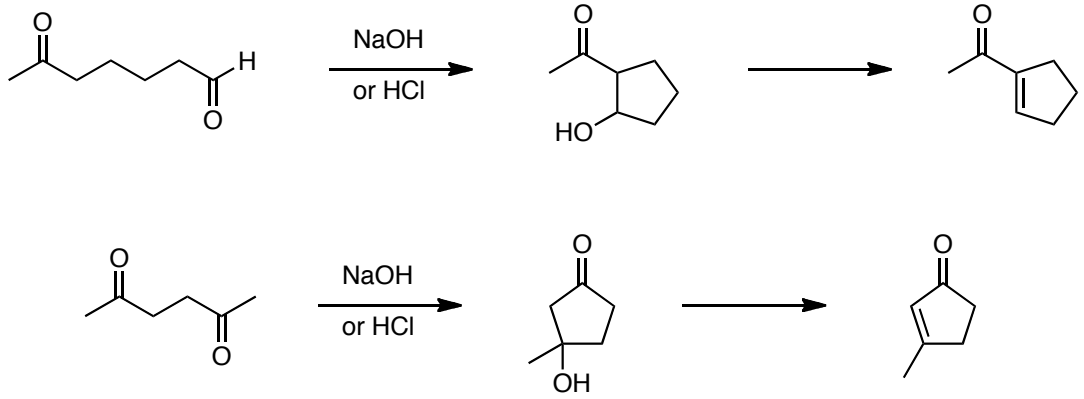




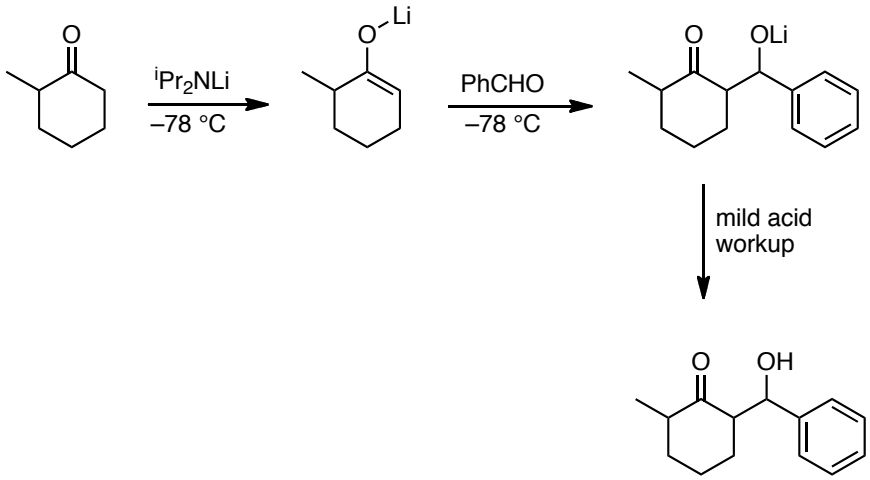
Dehydration is also very common in acid catalyzed aldol reactions.



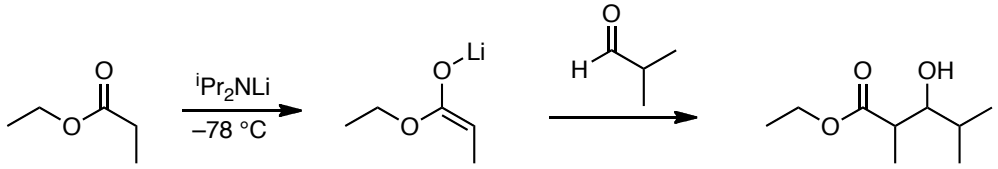
Intramolecular aldol: cyclizations to form rings.



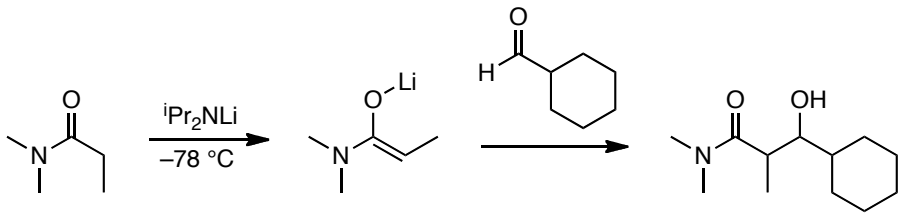
The use of strong base is advantageous for "directed" aldol reactions



Strong base is also useful for generating enolates of esters and amides.

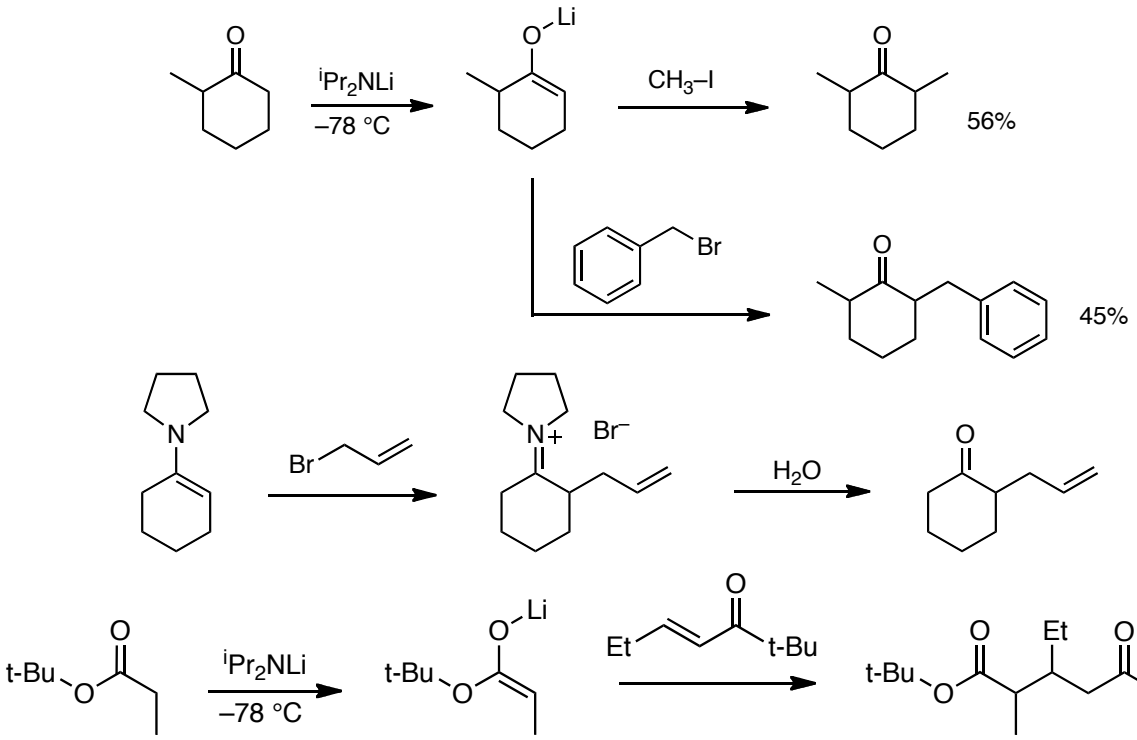


pKa ~ 24-25

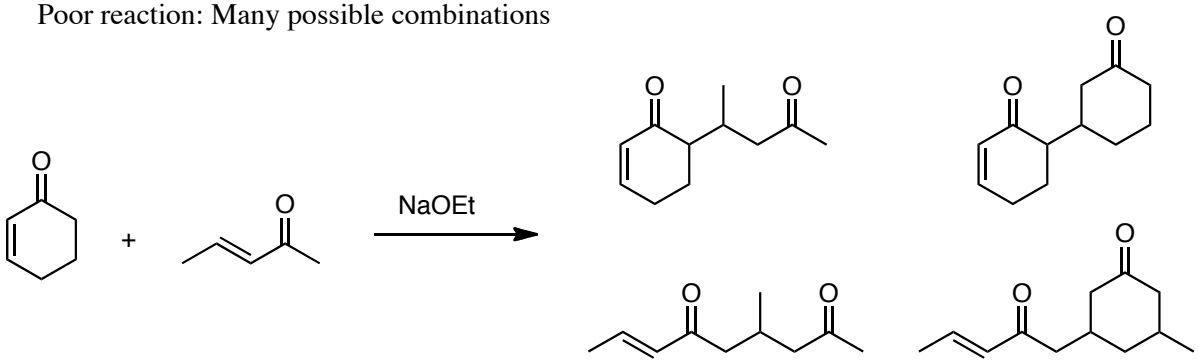


pKa ~ 27-28

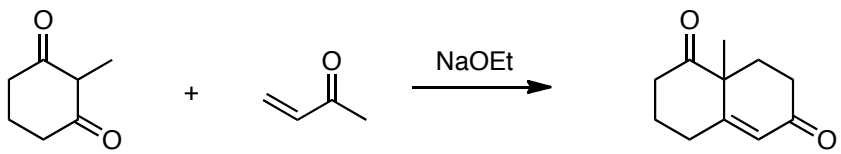
Additional uses of lithium enolates: alkylation



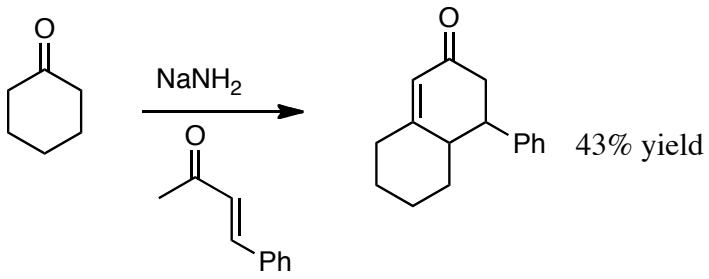
Poor reaction: Many possible combinations

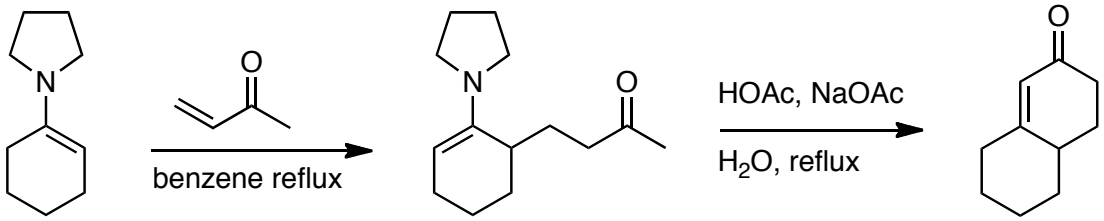


Robinson Annulation

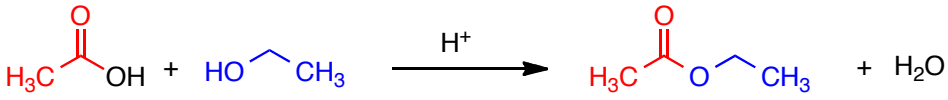


65% yield

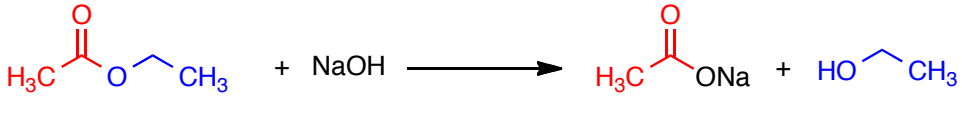


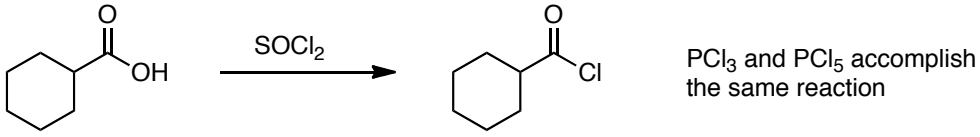


Synthesis of esters from alcohols and carboxylic acids: esterification

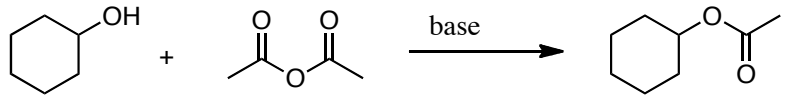


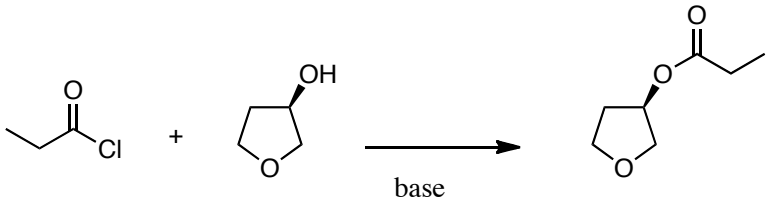
Saponification: <u>irreversible</u> hydrolysis of an ester



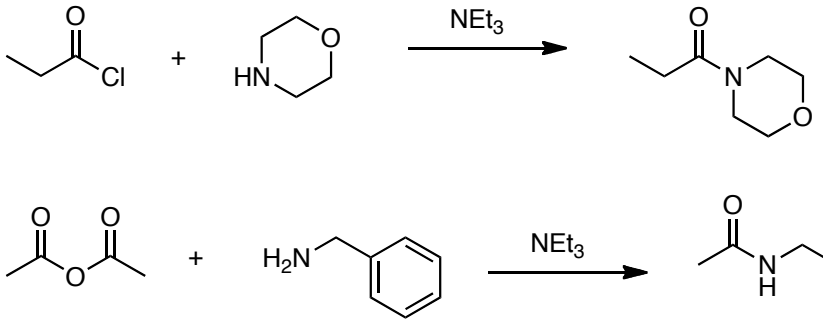


Acid chlorides and anhydrides react with alcohols to form esters.

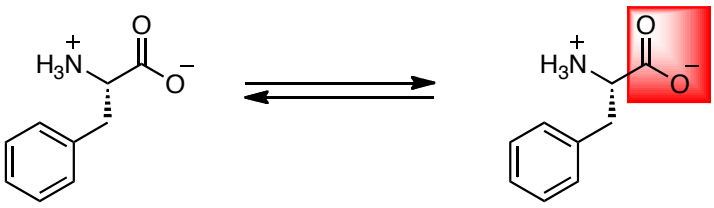


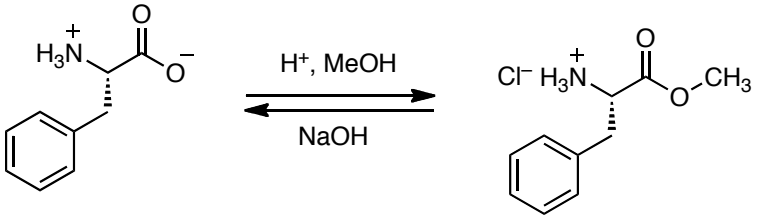


Amines react easily with acid chlorides and anhydrides to form amides. Catalysts are not generally needed.

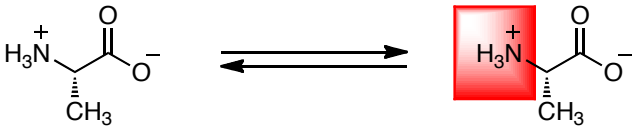


Acid blocking groups: esters

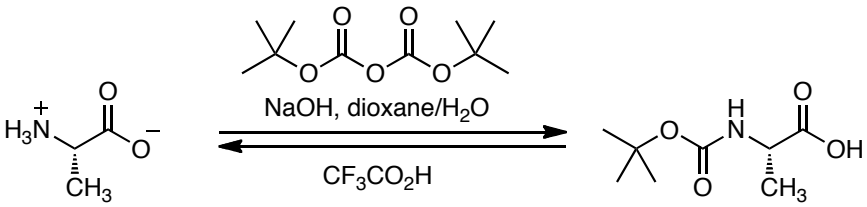




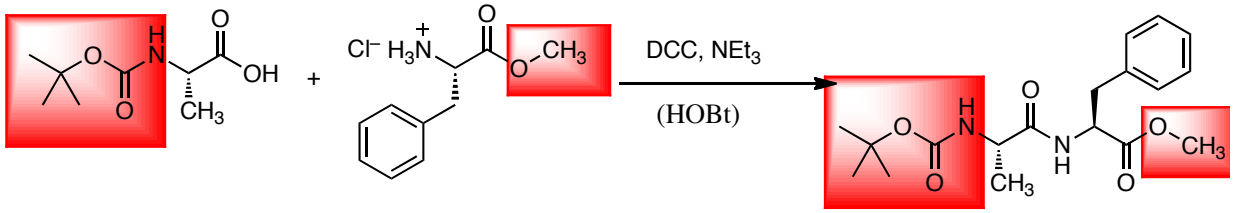
Amine blocking groups: carbamates



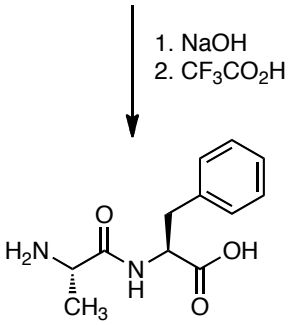
Most common example: the tert-butyloxycarbonyl group (Boc)



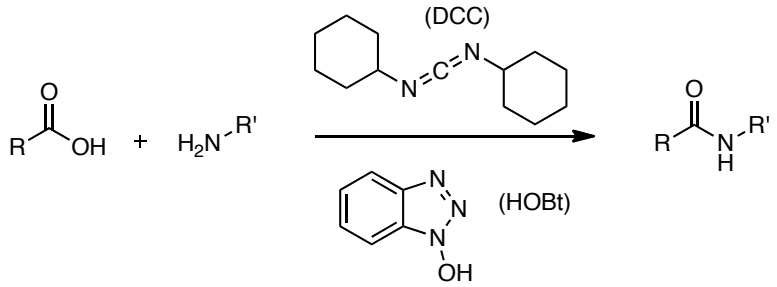
Dipeptide synthesis:



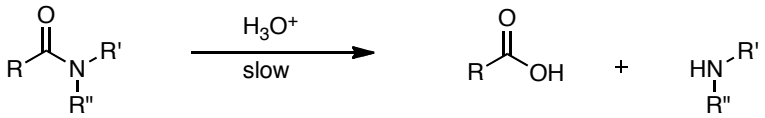
Although acid chloride or acid anhydrides might be used in theory, in practice they lead to some racemization of the acid component. We thus use DCC or other carbodimides, sometimes in combination with HOBt or other nucleophiles.



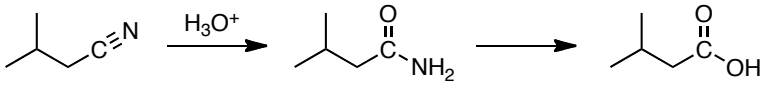
Dicyclohexylcarbodiimide (DCC) and N-hydroxybenzotriazole (HOBt) in amide formation.



Acid hydrolysis of amides is very slow. Common conditions 6 M HCl

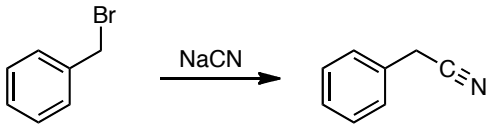


Hydrolysis of nitriles produces 1° amides or carboxylic acids.

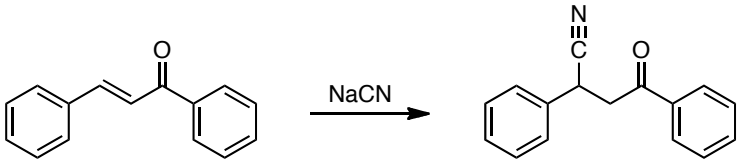


Nitriles are more conveniently prepared by nucleophilic reactions:

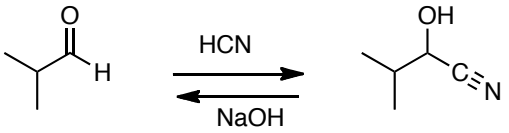
Halide displacement S_N2



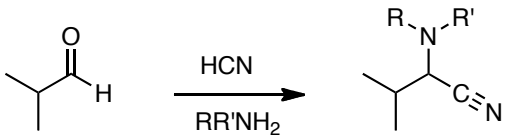
Conjugate addition



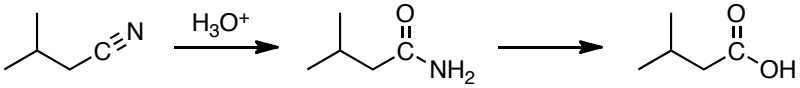
Formation of cyanohydrins



Formation of an α-aminonitrile

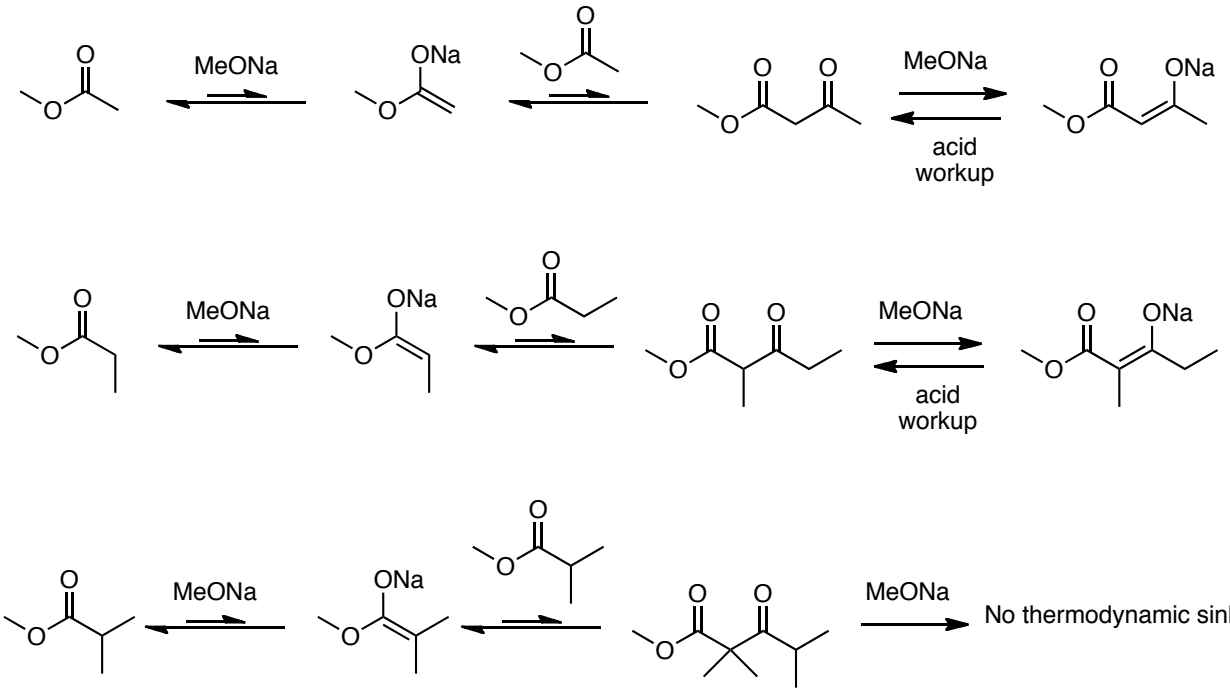


Hydrolysis of nitriles produces 1° amides or carboxylic acids.

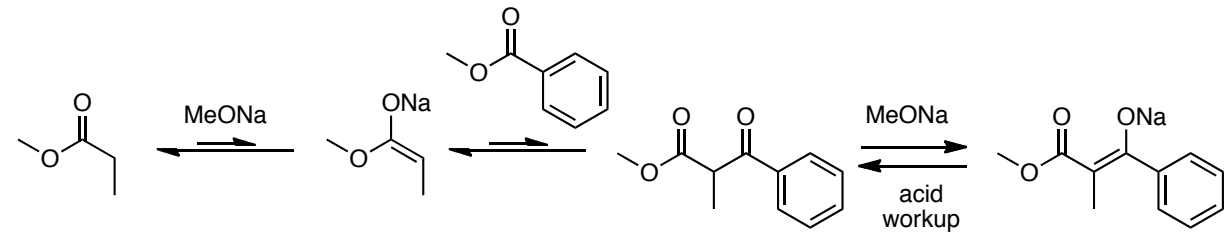


Claisen Condensation

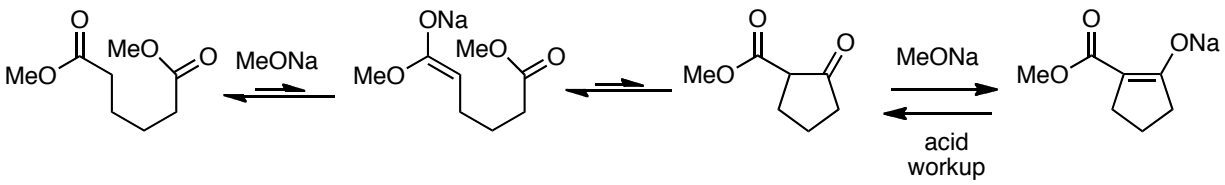
Esters are enolized by weaker bases. If we have a methyl ester, we use sodium methoxide so that transesterifcation is redundant.



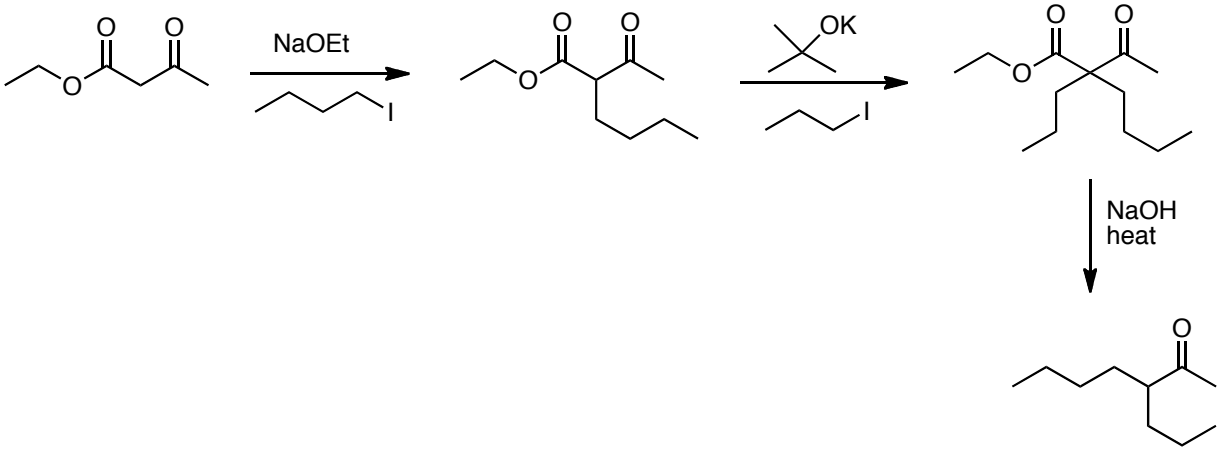
Crossed Claisen condensations are sometimes difficult to carry out. As with aldol, they work out well if one component has no α-hydrogens.

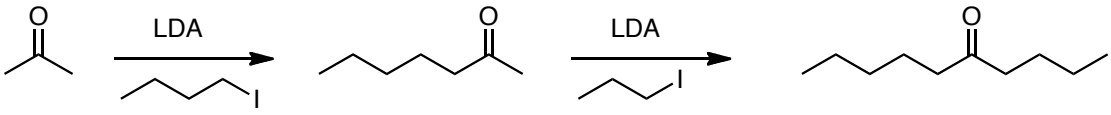


Intramolecular Claisen condensation: Dieckmann condensation

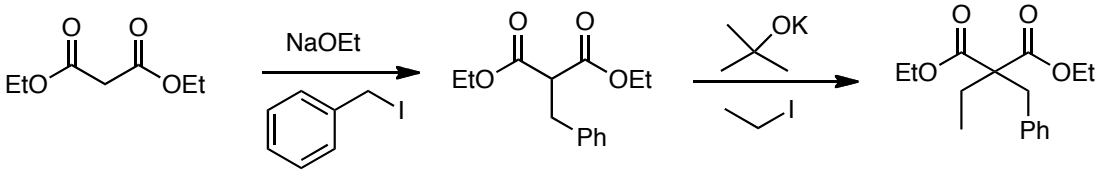


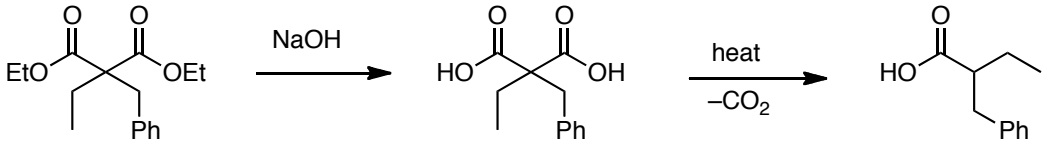
Comparison of simple ketone alkylation vs. acetoacetic ester method





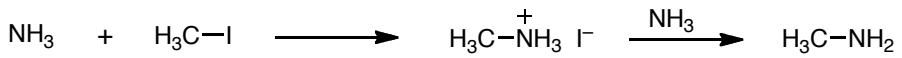
Malonic esters have similar chemistry to acetoacetates

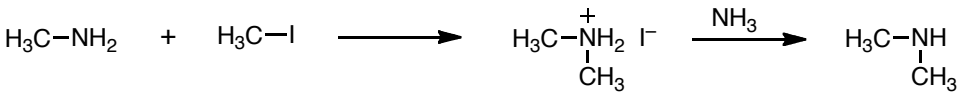


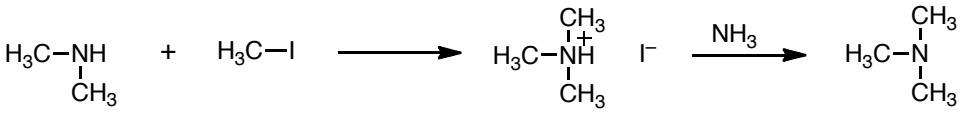


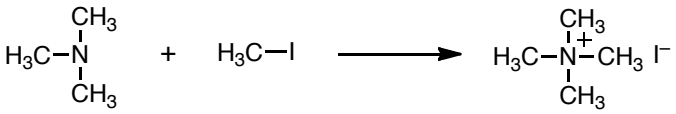
Synthesis of amines

Simple S_N2 displacement of alkyl halides



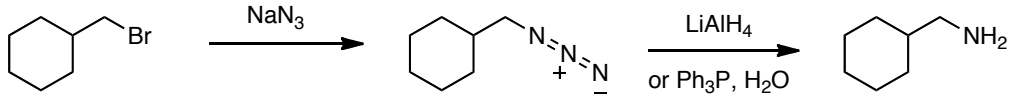




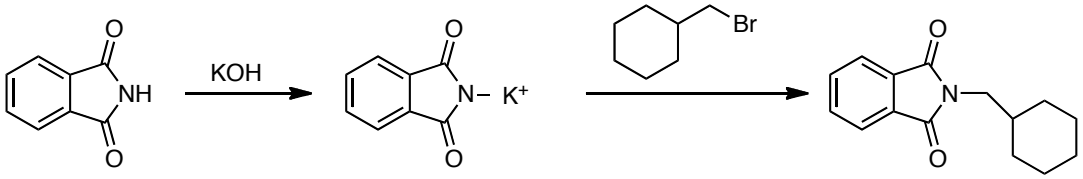


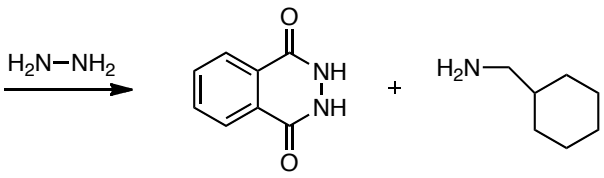
Synthesis of amines

Azide is a good replacement for ammonia in a simple SN2.

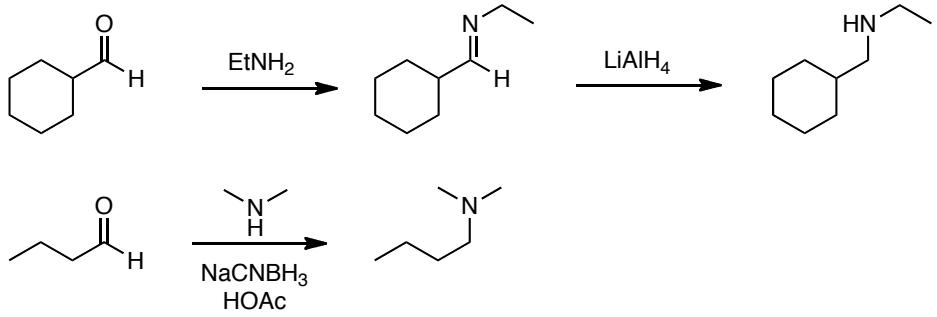


Gabriel synthesis: Phthalimide as an ammonia equivalent.

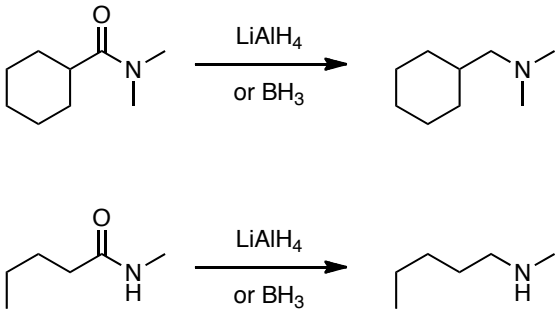




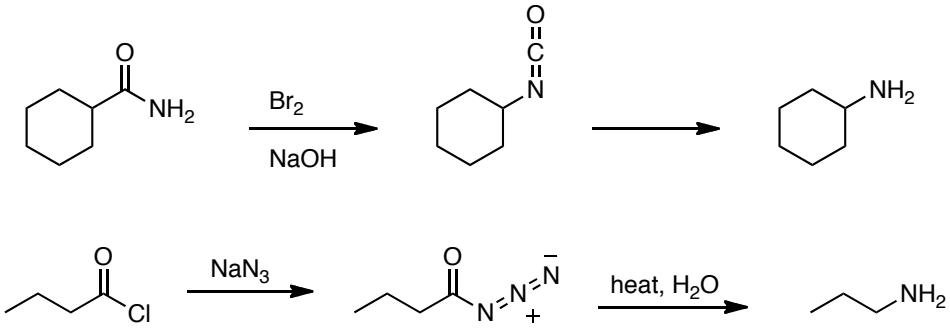
Reductive amination



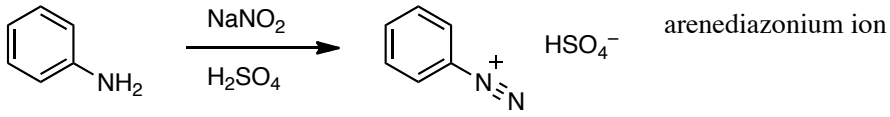
Reductions of nitriles and amides



Primary amines from amides via Hoffman and Curtuis rearrangement

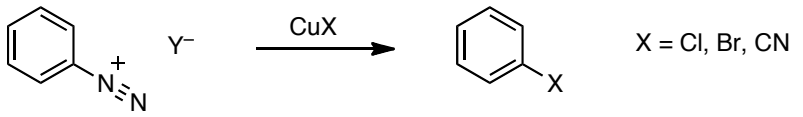


Diazotization

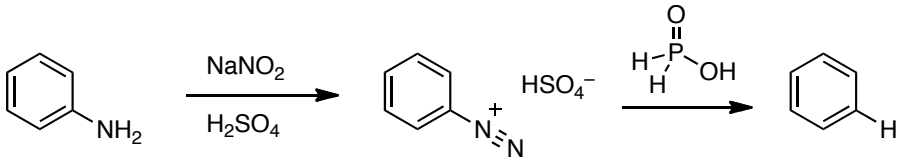


Arenediazonium ions are more stable (up to 5 °C) and are synthetically useful.

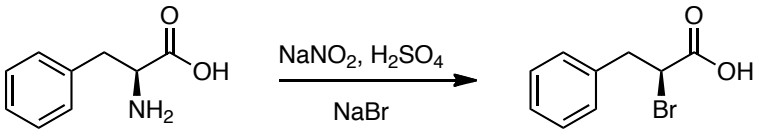
Sandmeyer reaction



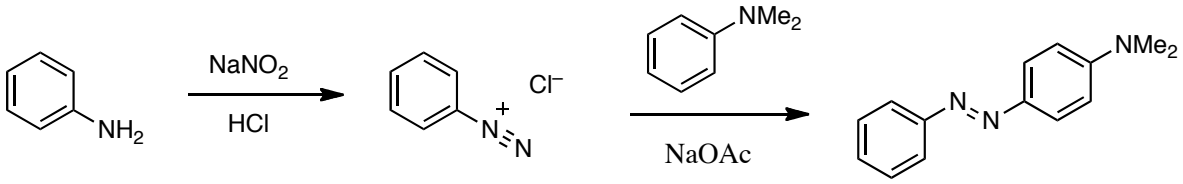
Also Cu_2O to get X = OH



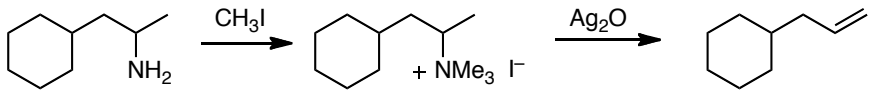
Alkyl diazonium ions mainly useful in amino acids.

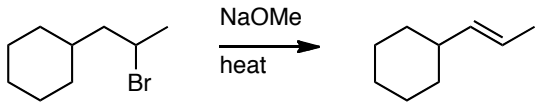


Azo compounds by diazo coupling.

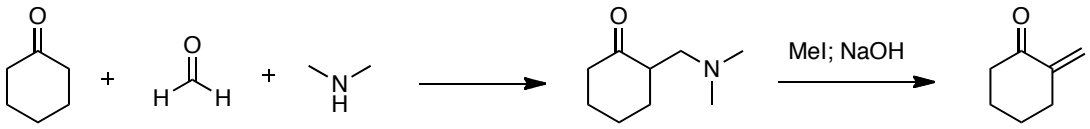


Hofmann elimination gives different regioselectivity compared to normal eliminations.





The Mannich reaction is a good way to install methylene groups adjacent to ketones.



In some cases, aryl halides <u>can</u> undergo displacement with nucleophiles.