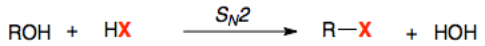
Synthesis Study Guide - Feynman Liang
CHEM231 - Spring 2012
Amherst College

I Substitution

- S_n2 - single step, 100% inversion, **1° electrophile** (else E2 dominates), **DMSO or acetone** solvent (polar aprotic)
- S_n1 - rate determined by carbocation formation, shifts possible, racemic product, **3° electrophile** (E1 will always be present), **H_2O or compatible (will not generate other products) ROH** solvent (polar protic)
- Good nucleophile (sterically unhindered, basic)
- Good leaving group (strong conj. acid)

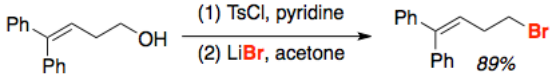
Making alkyl halides (R-X)

- **Alcohol using acid** from R-OH_2^+, protonation followed by halide substitution of H_2O^+:

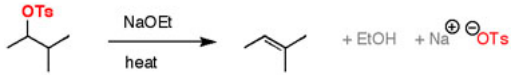


  - S_N1 unless 1° . S_N2 competes with elimination (unhindered substrate and good Nu to favor substitution)

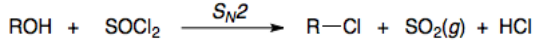
- **Alcohol using TsCl**, tosylate (OTs) L-group instead of OH_2^+:



  - Two-step process (1. convert, 2. substitute)
  - Could have also eliminated OTs after step 1 in E2 (Saytzeff's rule)

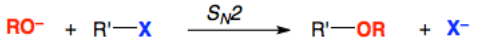


- **Alcohol using $SOCl_2$**:



  - One-step process, hydroxyl attacks S and SO_2 + Cl^- is displaced by Cl^- nucleophilic substitution
  - Pyridine should be used to neutralize HCl
  - Will also convert all COOH to COCl

Williamson ether synthesis (R-O-R')



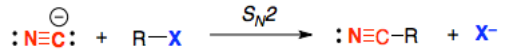
- S_N2, inversion of configuration
- Alkoxide (RO^-) formed by ROH + NaH (Na^+ ^-OR)
- Electrophile must be 1° , E2 predominates 2° and 3°
- Intramolecular forms cyclic ethers, bridged rings, epoxides, etc.
- Unlike acid Cl or Fisher esterification, does not require carbonyl group

Alkylation of amines (R_x-NH_x)

- S_N2, inversion
- Possible deprotonation of amide product by NH_3 $\rightarrow NH_4^+$ may result in multiple alkylations
- 1° substrate required (or else E2 predominates)

Other nucleophiles for C-C bond making

- **Cyanide ($^-$CN)**::



  - Moderate base/good Nu, favors S_N2
  - Can hydrolyze -CN to COOH

- **Acetylide anion ($^-$:C≡CR)**:

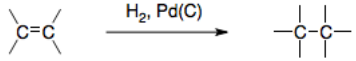
  - Anion generated from deprotonation (pKa≈25), $(Na^+)^-NH2$ is good base for this
  - Strong Nu, S_N2

- **Any decent nucleophile** (organometals, metal hyrdides, enolate-based (doubly-α-C))

II Alkene addition

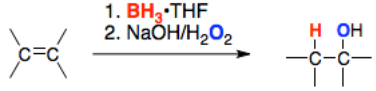
- Formed by **eliminaton**:
  - Alcohol dehydration: R-R-OH + H_3O^+ + $\triangle$ $\rightarrow$ R=R + 2 H_2O (reversed using strong base)
  - **E2** occurs between anti-periplanar H and L, favored over S_N2 with strong base, steric hindrance, higher temp
  - **E1** has unselective stereochemistry, always accompanies S_N1
  - Regiochemistry follows **Saytzeff's rule**: product favors more highly substituted alkene b/c hyperconjugation of transition state
- General Rules for Addition:
  - Markovnikov's rule: positively charged adding reagant (usually H^+) attaches to alkene to create more stable carbocation intermediate (to less substituted C so the carbocation has + charge on higher substituted C)
  - Dimerize/polymerize: the carbocation formed can be attacked by the nucleophilic π-bond
  - Br_2 and Cl_2 form trans-dihalides (through halonium ion). Halonium can also be attacked by other Nu (**Note:** Nu will attack carbon with more positive charge, which is usually more substituted one b/c hyperconjugation stabilized)

Hydrogenation



- H_2 gas and metal catalyst (Pd/C), rxn on surface of metal

Hydroboration/oxidation

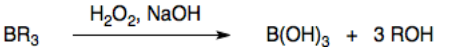


- Two-step anti-Markovnikov syn-addition of water across double bond with no rearrangements

1. Hydroboration:

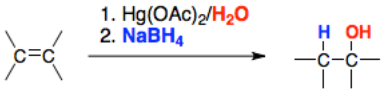
   - Concerted (single step, no rearrangements of carbocation possible)
   - Regioselective: BH_2 adds to less substituted end (Markovnikov's rule)
   - Syn-addition (H and BH_2 on same face of alkene) consistent w/ concerted
   - Product R-BH_2 reacts 3x more until trialkylborane (BR_3) is formed

2. Oxidation of alkylboranewith peroxide:



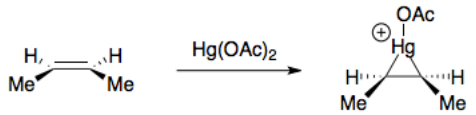
   - BR_3 attacked by $^-$OOH to form $B(OR)_3$, which is then substituted by $^-$OH
   - **Stereochemistry of carbon with BH2 is retained**

Oxymercuration/reduction



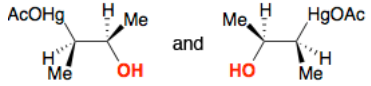
- Three-step Markovnikov anti-addition of water across double bond with no rearrangements
- Preferred way (vs acid catalyzed) to hydrate alkene

1. Oxymercuration:



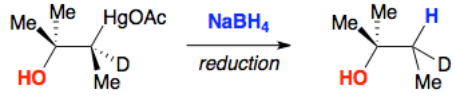
   - Mercurinium prevents rearrangements, can form on both faces of alkene

2. Opening of mercurinium ion:



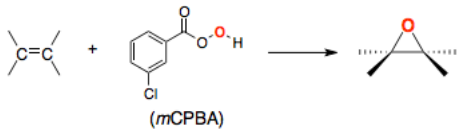
   - If not symmetric, $^-$OH adds to more substituted end (b/c more + charge, think halonium attack)

3. Reduction:

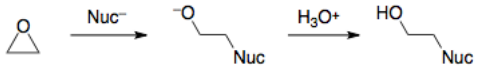


   - Stereochemistry of reduction is random

Alkene epoxidation (alkene → epoxide → 1-hydroxy,2-substituted)



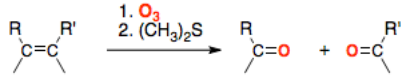
- Single-step formation of epoxide (3-membered ring with O), stereochemistry preserved
- Epoxides can be opened by Nu to give alcohol:



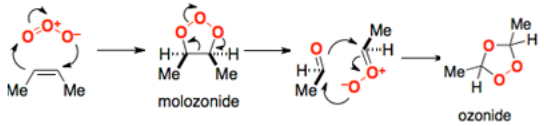
  - Under non-acidic, Nu attacks less-hindered carbon (think S_N2) with inversion
  - Examples of possible Nu: NC^-, HS^-, I^-, $RC{\equiv}C^-$, HO^-, RO^-, Br^-, $N_3{}^-$, NH_3, organometals, metal hydrides

Ozonolysis (alkene → two carbonyls)

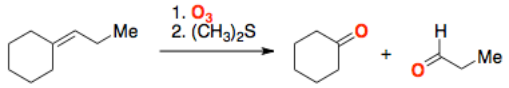
- Ozone cleavage of alkene to generate two separate carbonyls:



- Alkene → Molozonide (unstable) → Ozonide:



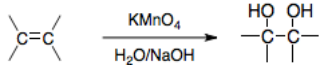
- Reduction of Ozonide (commonly Me_2S) yields two carbonyls:



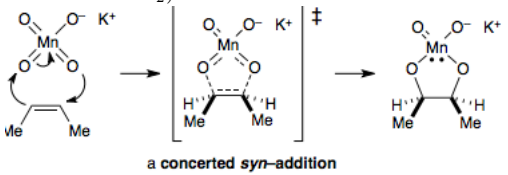
- Note: reaction can also be intermolecular, resulting in only one dicarbonyl product

Dihydroxylation (alkene → 1,2-diol)

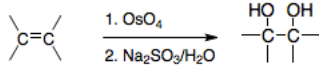
- Alkene oxidation to 1,2-diol using $KMnO_4$ or OsO_4



- Concerted first step forms unstable intermediate (followed by removal of MnO_2)

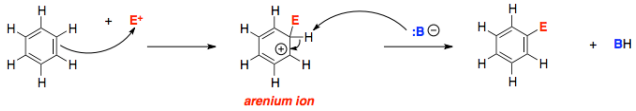


- OsO_4 is similar. Intermed can be isolated but generally transformed to diol with sodium sulfite:

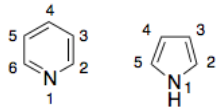


- Use OsO_4 if you do not want to oxidize aromatic alkyls to COOH

III EAS

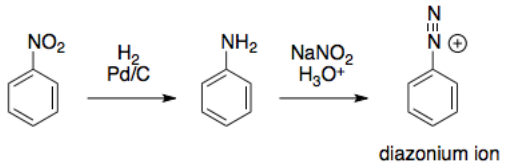


- Res. stabilized arenium intermed, substitution trumps addition b/c deprotonation restores aromaticity
- To determine rate and directing effects of substituents, compare stability (res, hyperconj, induct) of possible arenium intermed (Hammond Postulate)
- In general, EDG = o/p activating and EWG = m deactivating (**exception**: halogens are o/p deactivating due to induct ¿ res,)
- Not limited to just benzene, EAS also possible on:

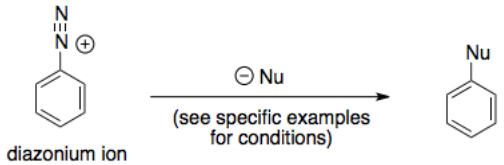


Diazonium ion (R-NO_2 → R-NH_2 → R-$N^+{\equiv}N$)

- Nitro (NO_2, meta directing) can be reduced to amino (NH_2, o/p directing)

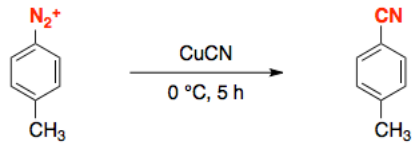


- **Careful!** H_2 with Pd/C *will also hydrolyze alkenes*
- Amine (R-NH_2) can be converted to diazonium ion (R-$N^+{\equiv}N$), which can be further substituted through S_N1:



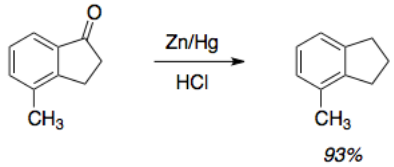
Reactions from diazonium (R-$N^+{\equiv}N$ → R-X)

- **Sandmeyer reaction**: Cuprous salt substitution of diazonium ion (see summary for reactants):



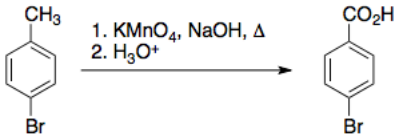
- Can also treat diazonium with KI to form R-I
- Can also hydrolize with H_3O^+ to form R-OH

Clemmensen reduction of acyl to alkyl



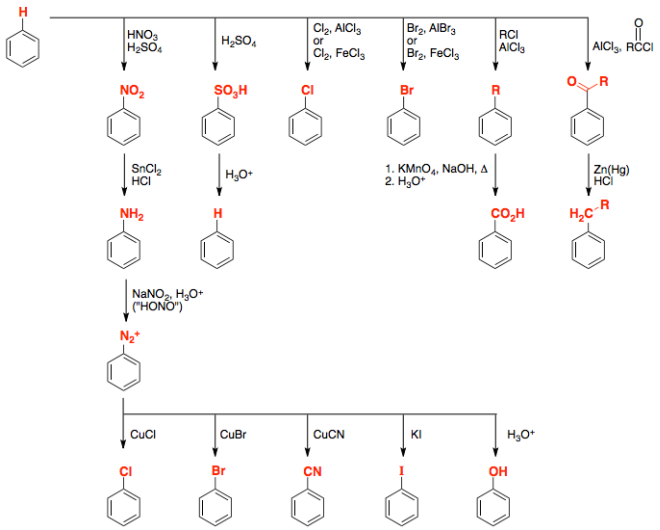
- Requires strongly acidic conditions. Allows for EAS alkylation using acyl groups (which won't undergo carbocation shifts and can be reduced to alkyl) and many other pathways.

Oxidation of alkyl to COOH



- Reverse of Clemmenson, basic rxn conditions, mechanism likely through benzylic

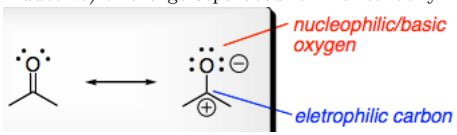
Summary of EAS



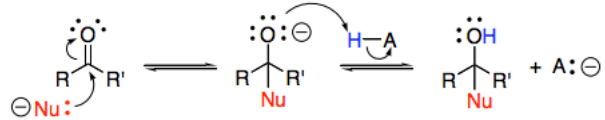
IV Carbonyl chemistry

Nucleophilic attack at carbonyl

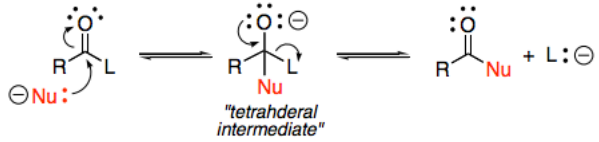
- To determine reactivity, look at stability (hyperconj, res, inductive) of charge separated form of carbonyl:



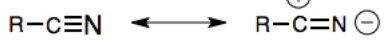
- Reactivity: Acid Cl > Aldehyde > Ketone > Ester > Amide
- Aldehydes and ketones undergo **addition** (because no L-group):



- Acid Cl, ester, amide, carboxylic acids undergo **substitution**:

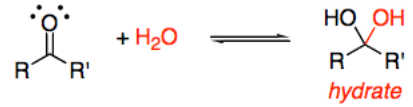


- Nitriles react similarly to carbonyl:

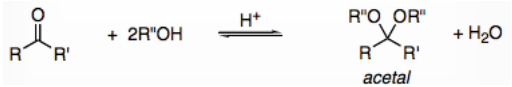


Addition reactions (ketones/aldehydes)

- **Hydration/dehydration**: carbonyl → 1,1-diol, acid or base catalyzed



- **Acetal formation**, carbonyl → acetal, acid catalyzed



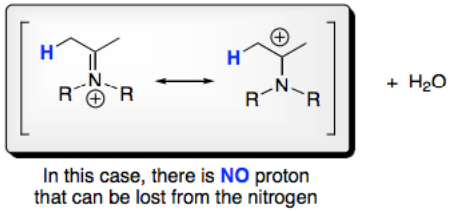
  - Hemiacetal intermed. unstable, only cyclic can be isolated
  - EQ driven towards acetal w/ excess alcohol or removing H_2O
  - Reverse is **acetal hydrolysis**, acid catalyzed
  - No rxn in basic conditions (can't eliminate from hemiacetal)

Addition w/ nitrogen nucleophile

- All drived forwards by removing H_2O, reverse is hydrolysis
- **Imine formation** from primary amine, netural conditions:

  - pH≥4 prevent protonation of amine to ammonium hydrolysis, pH≤6 to prevent deprotonation to unreactive carboxylate ion
  - **Reductive amination** can be achieved by reducing the resulting imine ($NaBH_4$):

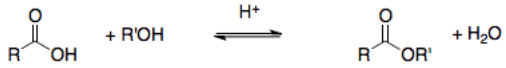
- **Enamine formation** from secondary amine (identical until last step):



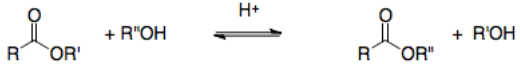
- **Tertiary amines are unreactive** b/c can't stabilize + charge

Substitution reactions (prefer acid Cl unless multiple COOH)

- **Fischer esterification**, RCO(OH) → RCO(OR')



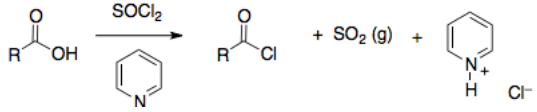
  - Acid catalyzed (K≈1), driven towards ester w/ excess RCOOH or R'OH or removing H_2O
  - No reaction in base (deprotonate to carboxylate)
  - Can also be done by attacking acid chloride with alcohol
  - Reverse is **ester hydrolysis** (RCO(OR') → RCO(OH)), acid catalyzed but base induced (deprotonate to carboxylate)
  - **Transesterification** (RCOOR' + R"OH → RCOOR" + R'OH):



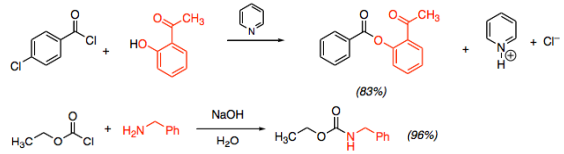
- **Amide hydrolysis** substitutes amide (-NH2) with (-OH):

  - Acid (NH_2R reacts with acid to form NH_4^+) and base (NHR reacts with COOH to form carboxylate) induced
  - Can also be done with NH3 nucleophile and acid Cl

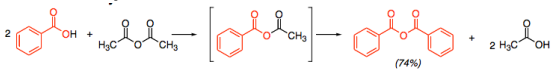
- **Activating COOH → acid Cl with $SOCl_2$** converts COOH to most reactive acid Cl:



  - Pyridine (proton sink) prevents excess HCl
  - Acid Cl can be substituted to any other carboxylic acid derivative (**add weak base to neutralize**), superior way to form esters and amides

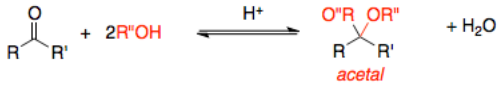


- **Activating COOH → anhydride** by reacting with acid Cl or another anhydride:

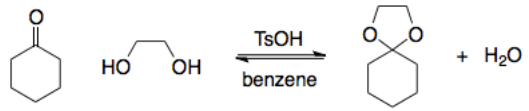


  - Anhydrides react similarly to acid Cl except eliminates a carboxylic acid

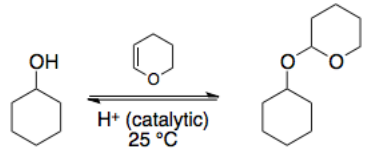
Acetals: carbonyl "protecting" groups



- Formed via addition of alcohol to carbonyl
- Acid catalyzed, driven towards acetal by removal of water water. Reversible (hydrolyze with excess water and acid)
- **Stable in basic conditions, unstable in acidic**. Allows reversible conversion of carbonyl to diester, removing electrophilicity
- Examples
  - Protecting carbonyl:



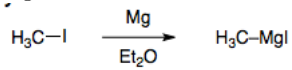
  - Protecting alcohol/di-alcohol:



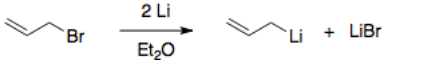
  - First acid catalyzed acetal formation (H^3O^+ w/ protecting group), do reaction, then acid catalyzed hydrolysis in excess water
  - 1,2-ethanediol protects carbonyl:
  - Diethyl carbonate protects diol:

Preparation of organometallic reagents (using R-X)

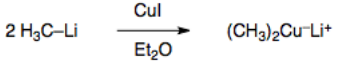
- X = halide (Mg, I)
- Reagents are very basic (reacts like R^- b/c metal is electron-donating) and reactive (must be DRY)
- These nucleophiles are very strong and can participate in all the previous substitution/addition reactions
- **Grignard reagents (R-MgX):** Mg metal with alkyl halide, Mg inserted in between halide and carbon



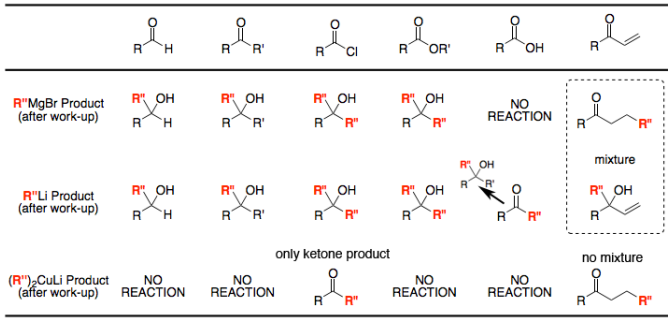
- **Organolithium reagents (R-Li)**: Li + R-X



- **Organocuprate reagents (R_2)-CuLi**: First make R-Li, then react with Cu-X twice

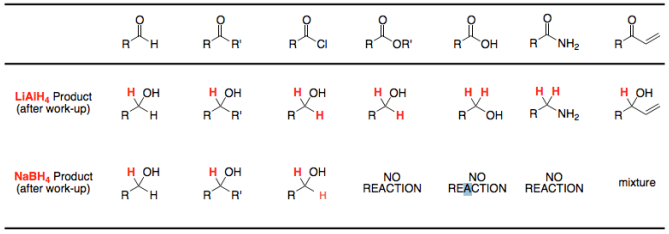


Reactions with organometallic reagents (carbonyl → alcohol/ketone)

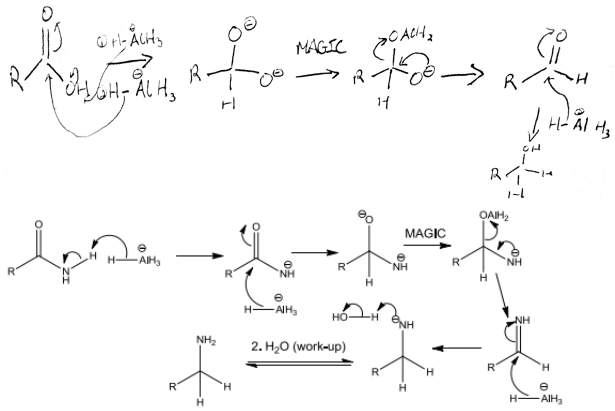


- Electron-donating metal gives electrons to alkyl (forming R-C^-H_2) which acts as nucleophile
- Carboxylic-acid derivatives (have L-group) are substituted, aldehyde/ketone are reduced
- **Summary**: Use organocuprate to make 1,4-addition on Michael acceptor and converting acid chlorides to ketone. All else should use organolithium
- Don't forget acidic aqueous workup to protonate R-O^- to alcohol

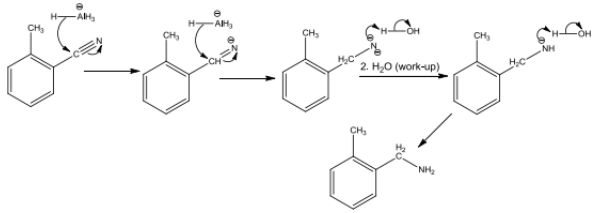
Metal hydride addition (carbonyl → alcohol/amide)



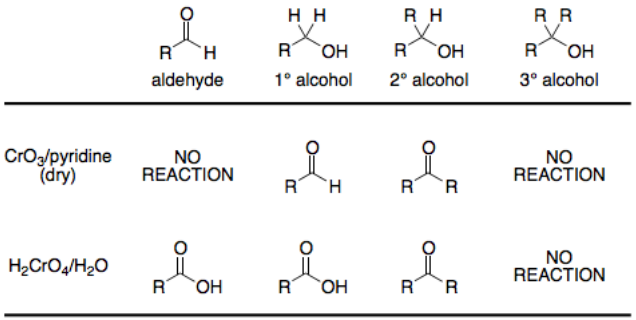
- **Summary**: ALWAYS use $LiAlH_4$
- Electron-donating metal allows hydride (H^-) to act as nucleophile
- The Al metal is "magical":



- Nitriles can be hydrolyzed twice:



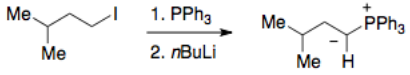
Chromium oxidants (alcohol → carbonyl)



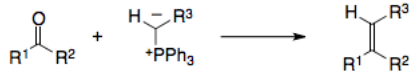
- **Summary**: Use $H_2Cr_2O_4/H_2O$ fol all except making aldehyde from 1° alcohol
- Difference is due to hydration in aqueous conditions, thus any Cr oxidation rxn w/ aqueous conditions will react similar to H_2CrO_4/H_2O
- Reaction begins with carbonyl oxygen attacking CrO_3 to form chomate ester intermed, $HCrO_3^-$ is eliminated in E2 by any base

Wittig reaction (carbonyl → alkene)

- Wittig reagent ("ylide") prepared from alkyl halide via phosphonium ion formation and deprotonanion w/ strong base



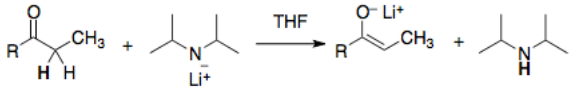
- Converts aldehydes and ketones into alkenes by replacing carbonyl double bond



- Reaction proceeds through 4-membered ring ("ylide" carbon attacks carbonyl)

Enolates

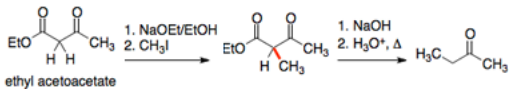
- Properties of enolates:
  - α-carbon of ketones/aldehydes have weakly acidic H (resonance with carbonyl), deprotonation generates enolate
  - Keto/enol forms equilibate, keto is lower energy and favored at neutral
  - Tautomerization to enol catalyzed by base or acid
- **Must use LDA** to forms enolate quantitatively and explicitly (prevent multiple alkylations):



LDA

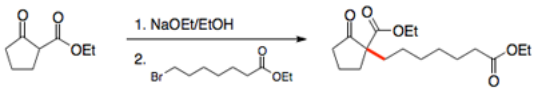
- Enolate can then act as nucleophile in substitution reactions with alkyl halides (α-hydrogen → α-substituted). However, this requires a strong base and can be avoided
- If possible, prefer the doubly-α enolates (only one possible enolate, less reactive base required)

Acetoacetic ester synthesis(doubly-α-proton → α-substituted carbonyl or β-ketoester)



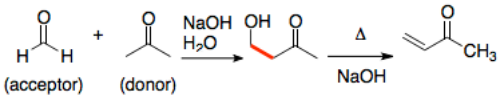
- β-ketoester stabilizes enolate and allows quantitative formation with mild bases ($^-$OEt/EtOH), enolate itself is also less reactive
- Synthetic equivalence - β-ketoester decarboxylation (note: requires β-carbonyl to COOH) generates same products as regular enolate attack
- Multiple alkylations before decarboxylation possible (as is stopping and extracting 1,3-dicarbonyl)

Malonic ester synthesis (doubly-α-proton $\rightarrow$ α-substituted carboxylic acid or β-ketoester)



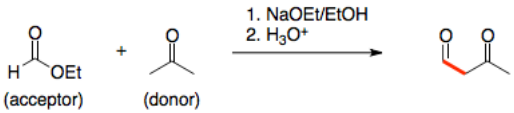
- Same as acetoacetic except during acidic workup one COOEt wil decarboxylate and **other will hydrolyze to carboxylic acid**
- Note: **any proton doubly-α to two anion stabilizing groups** can react similarly

Aldol condensation (aldehyde $\rightarrow$ β-hydroxy or α-β-unsaturated ketone)



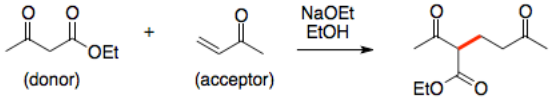
- Aldehyde acceptor, aldehyde/ketone (enolate) donor
- **Crossed Aldol:** acceptor is aldehyde w/ **no α-protons** and donor is **symmetrical** ketone or has protons on **only one α-carbon**
- Ketone acceptor possible **only in intramolecular ring forming** rxn
  - Last step of Robinson annulation
- Optional: β-hydroxyl group can be eliminated in E1cb reaction (1. Deprotonate 2. Eliminate $^-$OH L-group and form α-β-unsaturated carbonyl)
- Reversible, acid and base catalyzed

Claisen condensation (ketoester $\rightarrow$ 1,3-dicarbonyl)

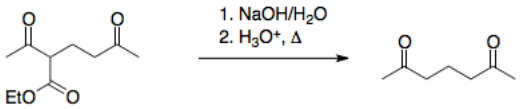


- Ester acceptor, ester/ketone (enolate) donor
- **Crossed Claisen Donor**: **symmetrical ketone with 2/3 protons on each α-C** or **unsymmetrical with 1 H on one α-C and 2/3 H on other**
- **Crossed Claisen Acceptor**: **ester w/ no α-C**
- Reversible, **β-ketoester must deprotonate to drive EQ**

Michael addition (α-β-unsaturated carbonyl $\rightarrow$ 1,5-dicarbonyl)



- Any good nucleophile (enolate, -CN, organometals, etc) attacks a Michael acceptor ($\alpha - \beta$-unsaturated carbonyl)
- Competes with normal carbonyl addition, increased by acid (protonated R=O$^+$H has res. struct. w/ + on β-carbon)
- Ketoester can be decarboxylated to give 1,5-dicarbonyl



Robinson Annulation

Forms bicyclic ring from cyclic enolate donor and Michael acceptor. Enolate adds in Michael addition, proton shifts form enolate on other side of Michael acceptor's carbonyl, enolate attacks in intramolecular aldol condensation.