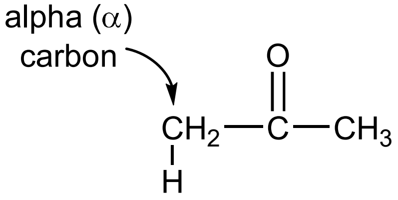
Organic Chemistry II, CHM 3150, Dr. Laurie S. Starkey, Cal Poly Pomona
Chapter 21 (Klein): Enols & Enolates, Part I

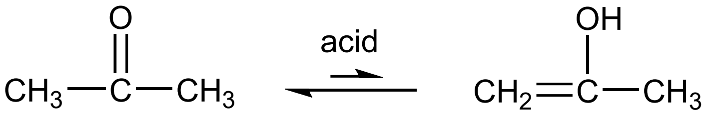
I. Review of the carbonyl, and keto-enol tautomerization (21.1)

The carbonyl



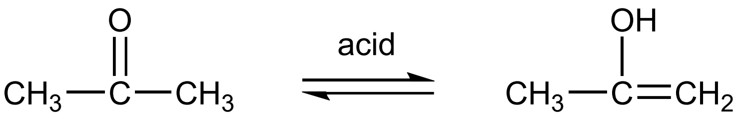
$CH_2(H)-C(=O)-CH_3$

Keto-enol tautomerization



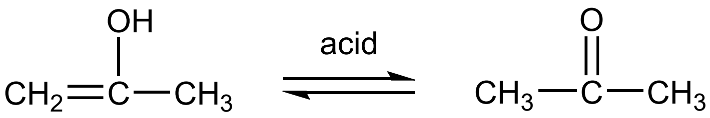
$CH_3-C(=O)-CH_3 \rightleftharpoons CH_2=C(OH)-CH_3$

Tautomerization Mechanism: Ketone → Enol (2 steps)



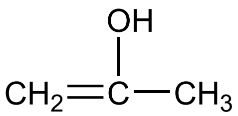
$CH_3-C(=O)-CH_3 \rightleftharpoons CH_3-C(OH)=CH_2$

Tautomerization Mechanism: Ketone → Enol (2 steps)
Reverse Tautomerization Reaction:



$CH_2=C(OH)-CH_3 \rightleftharpoons CH_3-C(=O)-CH_3$

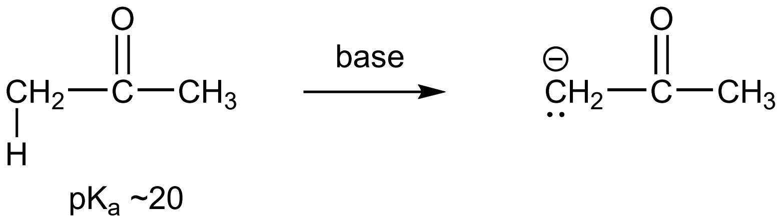
Tautomerization Mechanism: Enol → Ketone (2 steps)



$CH_2=C(OH)-CH_3$

Formation of Enolates

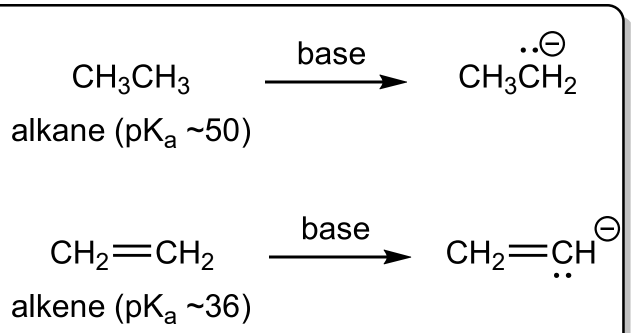
Why are a ketone's alpha protons acidic? Look at its conjugate base!

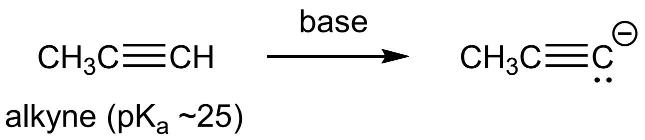


** acid-catalyzed mechanisms: **enol** is present*

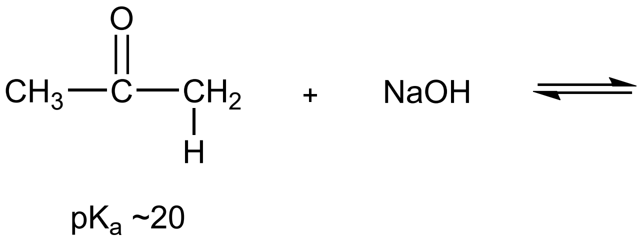
** base-catalyzed mechanisms: **enolate** is present*

Formation of Other Carbanions (review)

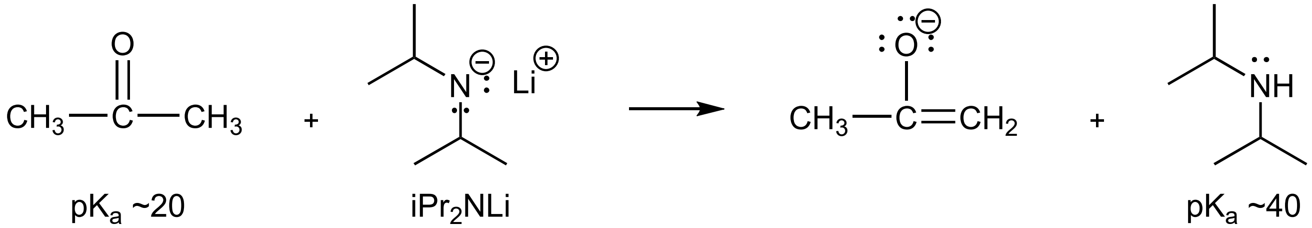




Formation of an Enolate: Choice of Base



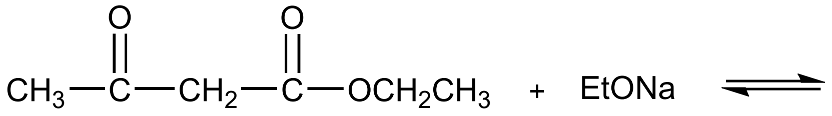
* To completely deprotonate, need a much stronger base!



Lithium Diisopropyl Amide (LDA) is ideal

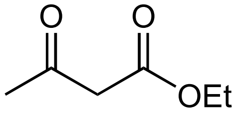
try SkillBuilder 21.1

* To make an enolate, a weaker base is okay for an "active" methylene

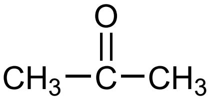
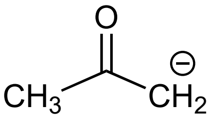
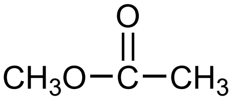
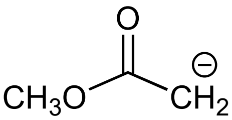
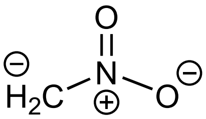
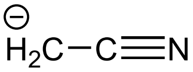


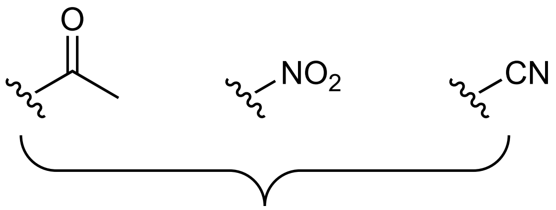
$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OCH_2CH_3 \quad + \quad EtONa \rightleftharpoons$$

Question: why use NaOEt instead of NaOH?



Other Acidic "alpha" Protons

pK_a		conjugate base
~20	 $CH_3-\overset{\overset{O}{\|}}{C}-CH_3$	
~25	 $CH_3O-\overset{\overset{O}{\|}}{C}-CH_3$	
~10	CH_3NO_2	
~25	CH_3CN	 $\overset{\ominus}{H_2C}-C\equiv N$



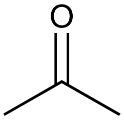
all are electron-withdrawing groups (EWG) that can stabilize an adjacent negative charge by resonance

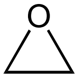
Question: why is an ester less acidic than a ketone?

How are enolates used?

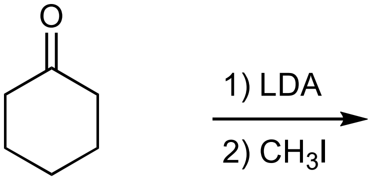
- enolates are carbanions
- carbanions are great **nucleophiles** (Nu:, electron-rich)

Possible **electrophiles** (E^+, electron-poor): R—X X—X

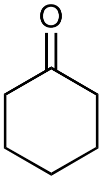




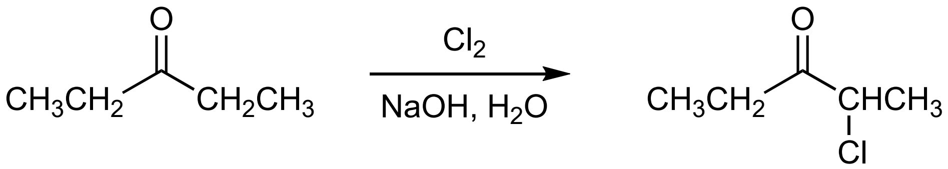
α-Alkylation of Enolates (21.5)



- S_N2 requires unhindered E^+/RX (methyl or primary), or E2 happens
- Enolate is a nucleophile at **carbon**
- "C-alkylation" is preferrod over "O-alkylation"
- Mechanism using the preferred resonance form looks like this:



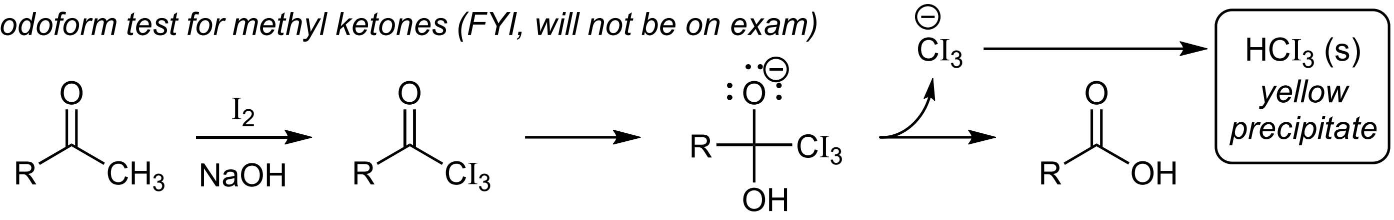
α-Halogenation of Ketones (21.2) (basic conditions)



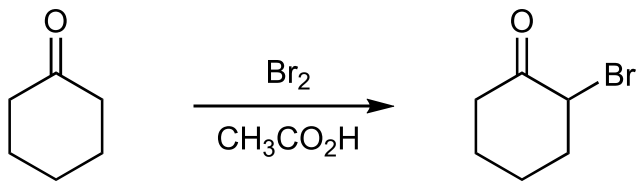
$$CH_3CH_2C(=O)CH_2CH_3 \xrightarrow[NaOH,\ H_2O]{Cl_2} CH_3CH_2C(=O)CHClCH_3$$

WARNING: product is more acidic than starting material, so multiple halogenations are possible/likely!

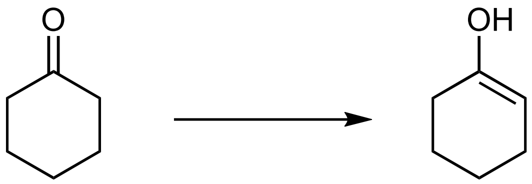
Iodoform test for methyl ketones (FYI, will not be on exam)



α-Halogenation of Ketones (acid-catalyzed - use enol, not enolate)

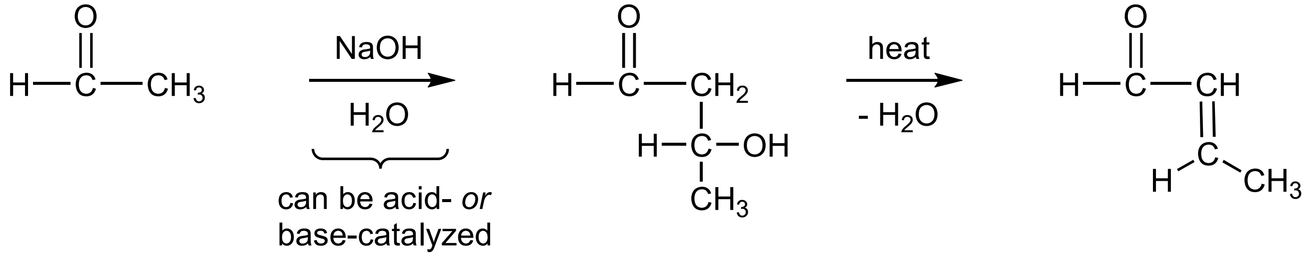


Mechanism: *first, make enol (2 steps)*

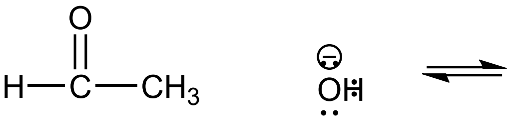


What other electrophiles/E$^+$, beside RX, X$_2$?

Aldol Condensation (21.3)



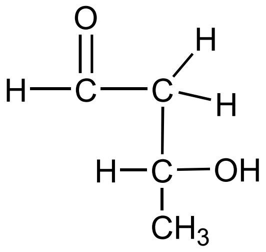
Mechanism: In base, so deprotonate first! Where?



* Aldol Reaction forms a new C-C bond between:

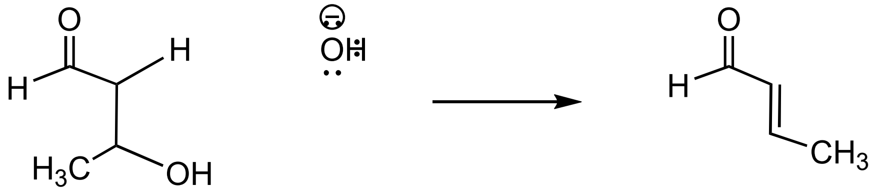
the α carbon of one ketone (Nu:) and the carbonyl carbon of another (E$^+$)

Aldol Condensation - Mechanism for loss of H_2O: 2 steps (β-elimination)

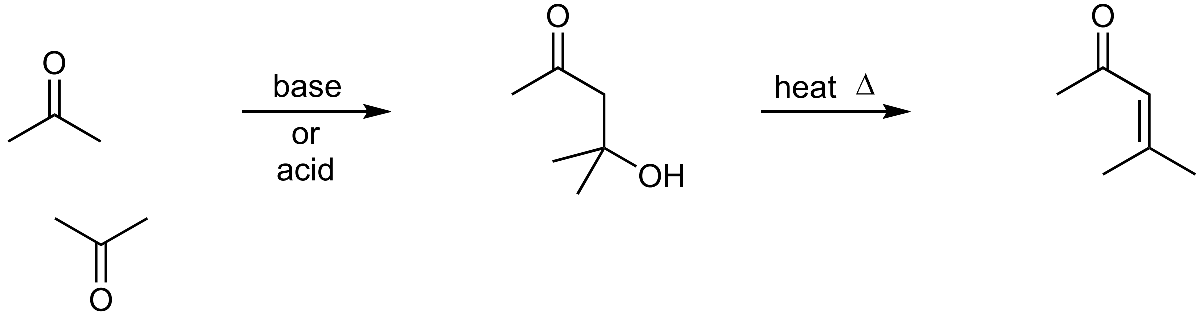


* HO^- is ok LG for collapse of CTI and for β-elimination mechanism

* **Loss of H_2O is not E2!** (HO^- is NOT a good LG for S_N2/E2)



Aldol Summary ***try SkillBuilders 21.2 & 21.3***



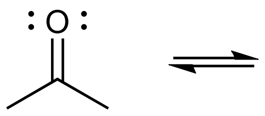
Nucleophile (Nu:) Electrophile (E^+)

Base-catalyzed mechanism
(neutral or ⊖ charges)

Acid-catalyzed mechanism
(neutral or ⊕ charges)

Acid-Catalyzed Aldol Mechanism

1st steps: make enol

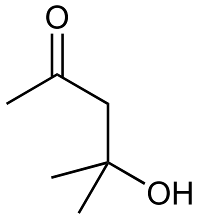


Loss of H_2O (β-Elimination Mech.)

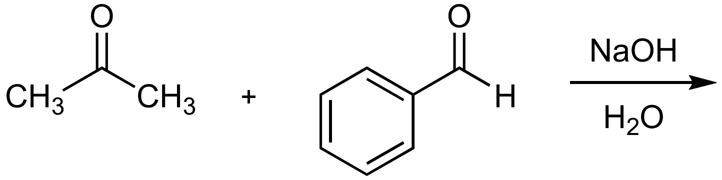
base mechanism

1. make enolate
2. eject beta LG

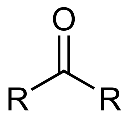
acid mechanism



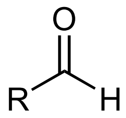
Crossed/Mixed Aldol - reasonable if only one compound has α H's



* Which is better E^+? Alkyl groups **donate** electron density,
so ketone is more electron-rich (aldehyde is the better E^+).

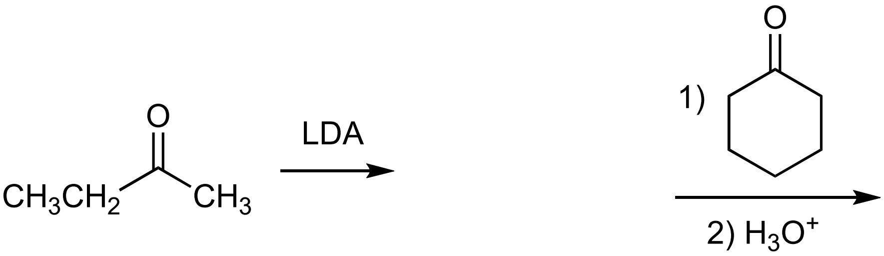


ketone

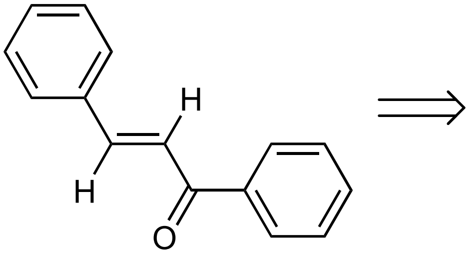


aldehyde

Crossed/Mixed Aldol - control using a stepwise process (with LDA)



Aldol Retrosynthesis - Predict the aldol starting materials

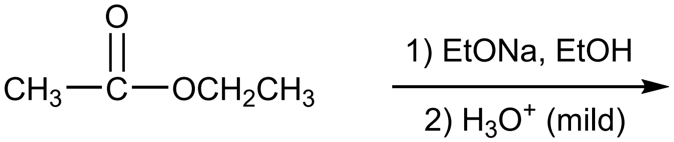


target molecule (TM)

try SkillBuilder 21.4

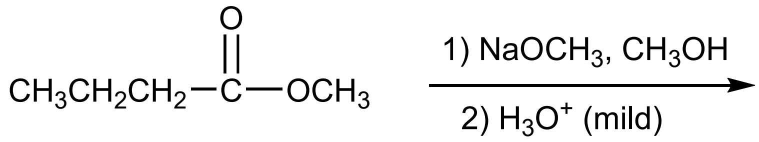
Claisen Condensation (21.4)

(like an aldol reaction, but with esters)

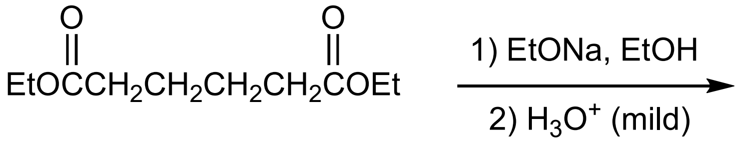


$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-OCH_2CH_3 \xrightarrow[\text{2) } H_3O^+ \text{ (mild)}]{\text{1) EtONa, EtOH}}$$

Claisen Condensation Examples



$$CH_3CH_2CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3 \xrightarrow[\text{2) } H_3O^+ \text{ (mild)}]{\text{1) } NaOCH_3\text{, } CH_3OH}$$

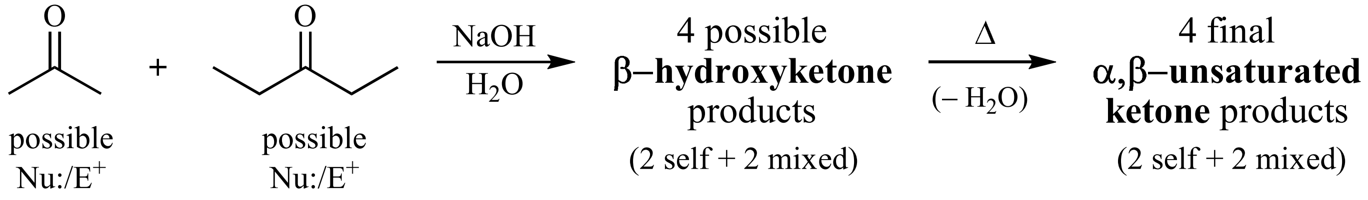


$$Et O\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}OEt \xrightarrow[\text{2) } H_3O^+ \text{ (mild)}]{\text{1) EtONa, EtOH}}$$

try problems 21.24 – 21.28

"Messy Aldol" Homework (Gradescope)

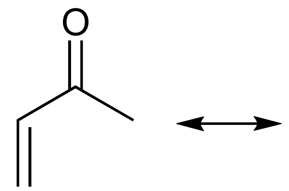
Before working on this homework, review Mechanisms 21.4, 21.6 and work on SkillBuilders 21.2, 21.3. Predict the possible aldol products for the following reaction (**provide 8 structures**). Choose one of the **mixed aldol final products** (α,β-unsaturated ketone) and show the complete base-catalyzed mechanism.

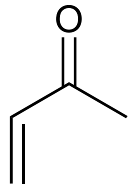


Conjugate Additions - Reactions of Enones (21.6)

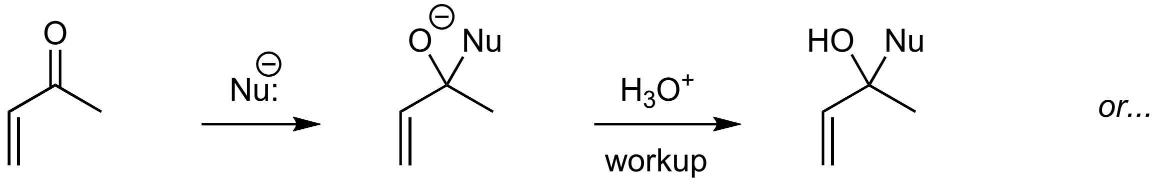
overall:

α,β-unsaturated carbonyls

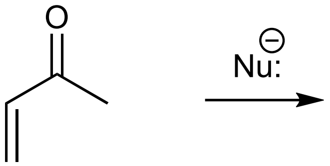




Nucleophiles can add to C=O carbon, called "**1,2-addition**" (Nu: = $LiAlH_4$, RMgX, RLi)

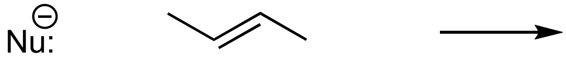


Nucleophiles can add to beta (β) carbon, called "**1,4-addition**" or "**conjugate addition**"
(preferred by enolates and cuprates, R_2CuLi)

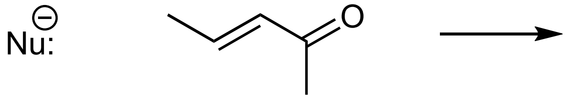


Question: Why can a nucleophile add to this alkene?

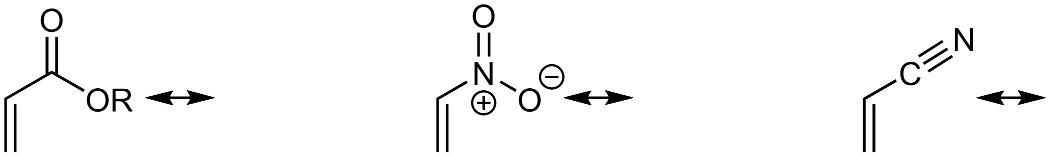
Typical alkene:

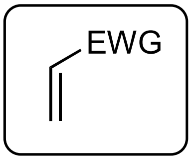


α,β-unsaturated
alkene:



Other *electrophilic* alkenes (called "Michael acceptors"):

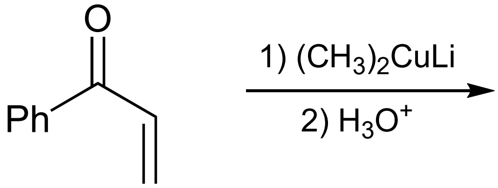




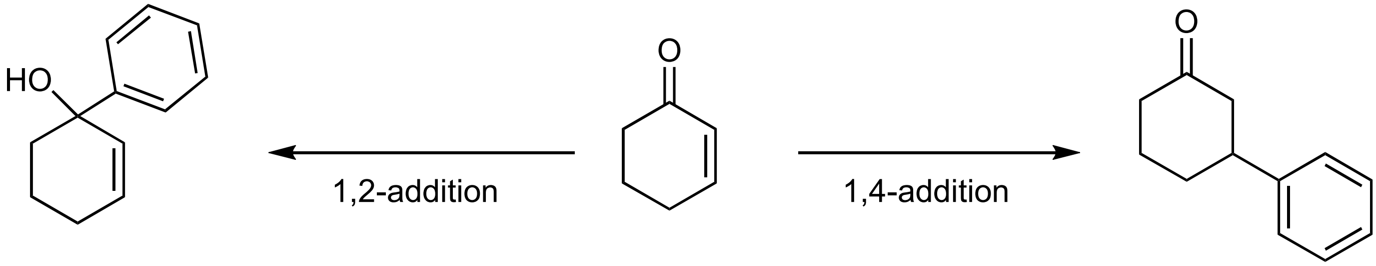
**** All electron-withdrawing groups (EWG) can stabilized the C^- intermediate by resonance ****

1,4-Addition of Cuprates (R_2CuLi)

R_2CuLi - an organometallic reagent that prefers conjugate addition (1,4-addition)



* Use organocuprates in synthesis



* Prepare organocuprate from organolithium

$CH_3Br \xrightarrow{Li} CH_3Li$

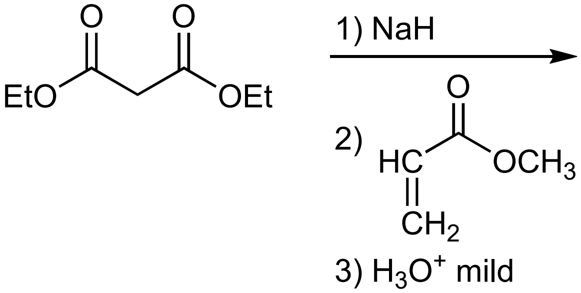
$2\ CH_3Li \xrightarrow{CuI} (CH_3)_2CuLi$

* Organocuprates also do "S_N2" with RX electrophile (not true for RMgX, RLi)

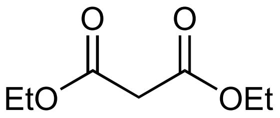
$R_2CuLi + R'X \longrightarrow R{-}R'$ (coupling reaction)

1,4-Addition of Enolates: Michael Reaction

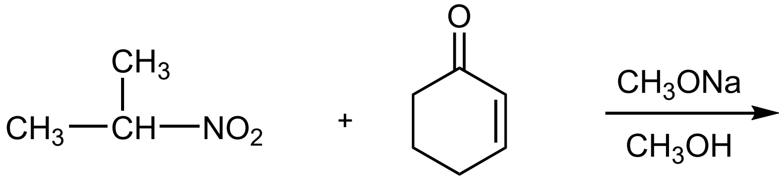
Nu: = enolate E$^+$ = enone



Michael Reaction Mechanism

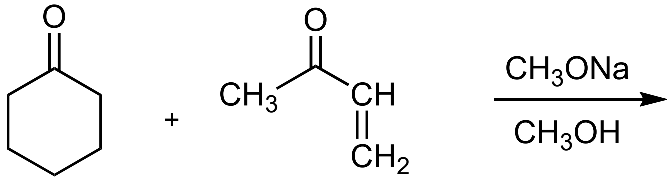


Michael Reaction example:

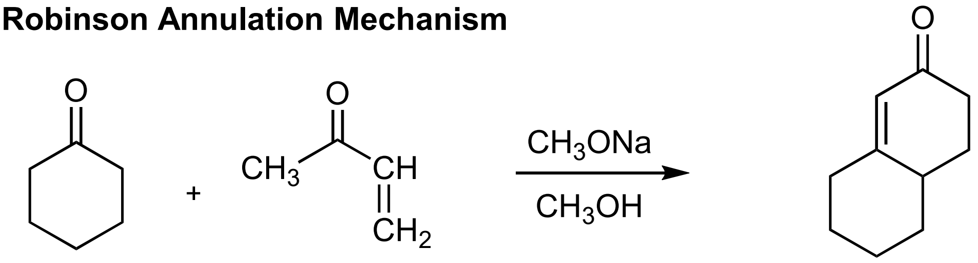


1,4-Addition of Enolates: Robinson Annulation

Michael reaction, followed by an intramolecular aldol



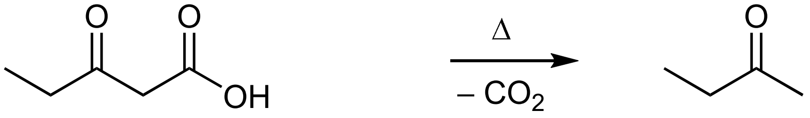
Robinson Annulation Mechanism



Try SkillBuilders 21.8 & 21.9

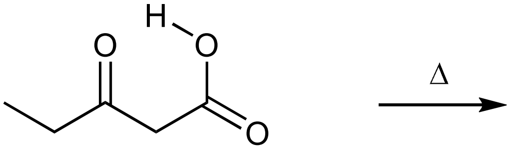
Advanced Synthesis Topics

Stabilized enolates and the decarboxylation reaction (21.5)



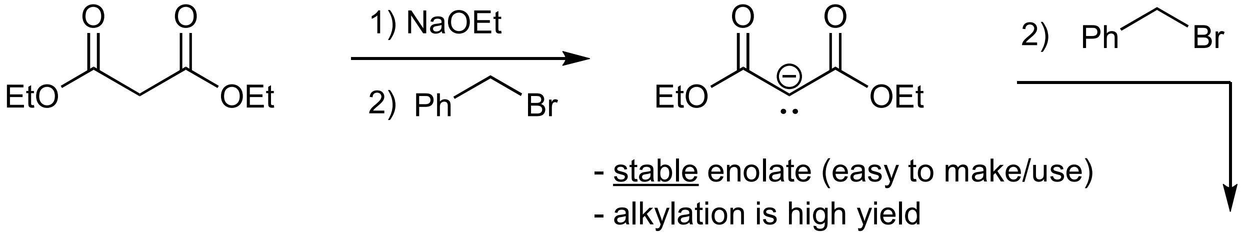
β-keto acids
lose CO_2 when heated

mechanism:
a *pericyclic* reaction



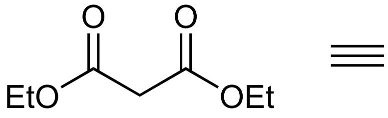
favorable 6-membered
transition state (T.S.)

Example:

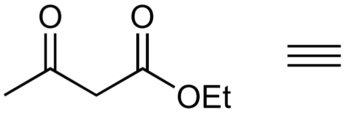


- <u>stable</u> enolate (easy to make/use)
- alkylation is high yield

Common Reagents

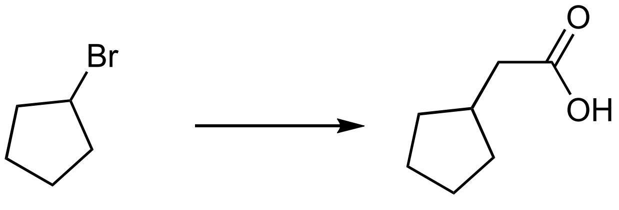


diethyl malonate



ethyl acetoacetate

Transform Example::



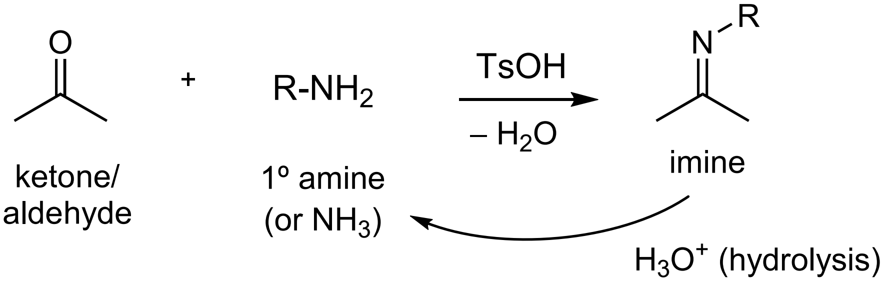
Try SkillBuilders 21.5 & 21.6

Additional Advanced Synthesis Topic (FYI*)

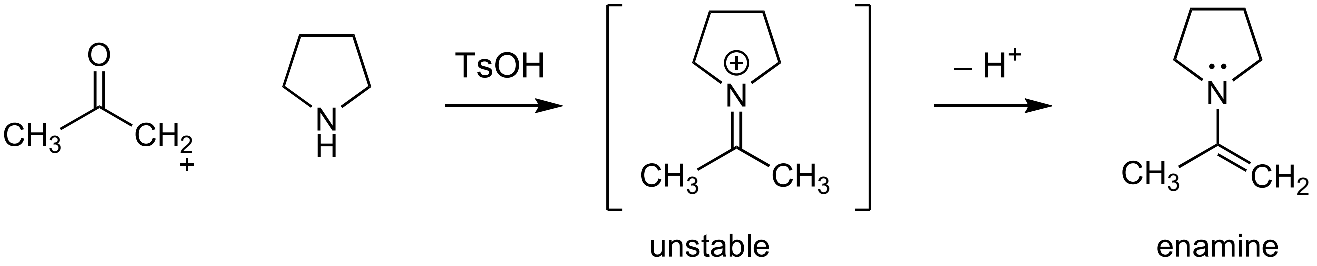
Synthetic Utility of Enamines (21.6) ***Will not be on the midterm/final**

Enamines - synthetic equivalents of enolate nucleophile

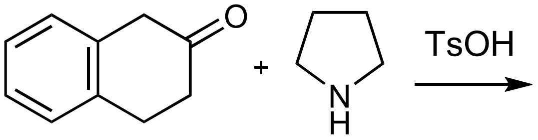
Recall:



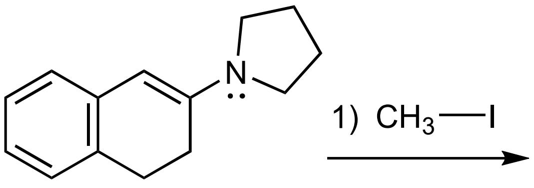
Reaction with ketone/aldehyde is different with 2° amine (R_2NH)



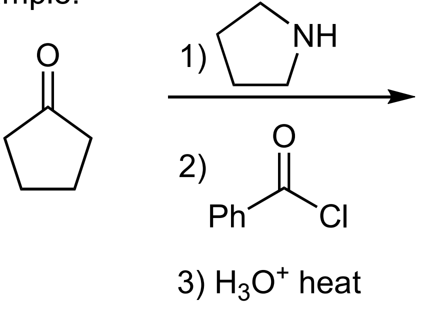
Example:



Use enamine as nucleophile (like an enolate!) *See SkillBuilder 21.7 (Stork Enamine Synthesis)*



Example:



Organic |Chemistry II CHM 3150, Dr. Laurie S. Starkey, Cal Poly Pomona
Chapter 21 Summary (Klein): Enols and Enolates

I. Review of the Carbonyl C=O (21.1)
- A) carbonyl: carbonyl carbon is electrophilic (E^+), α-hydrogens are acidic
- B) enol form is present in small amounts at equilibrium
  - i) keto-enol tautomerization mechanism (2-steps; protonation/deprotonation)
  - ii) enols make α-carbon of a carbonyl nucleophilic (Nu:)

II. Review of Stabilized Carbanions (Nu:)
- A) organometallics (RLi, RMgX, R_2CuLi, prepared from RX; 12.6)
- B) alkynyl (9-10), cyanide, Wittig reagent (19.10)
- C) resonance-stabilized (21.1) ***SkillBuilder 21.1***
  - i) enolate (α to a carbonyl electron-withdrawing group)
  - ii) α to nitro (NO_2) or cyano (CN) electron-withdrawing groups (EWG)
  - iii) active methylene (CH_2 α to 2 EWG's)

III. Formation and Reactions of Enols and Enolates
- A) bases that can be used to deprotonate α hydrogens (LDA, $NaNH_2$, NaH) (21.1)
- B) halogenation of the α carbon (base- and acid-catalyzed mechanisms) (21.2)
- C) reactions with RX electrophiles (alkylation) (21.5)
- D) selective alkylation of active methylenes (21.5)

IV. Aldol Reaction & Aldol Condensation (21.3) ***SkillBuilder 21.2, SkillBuilder 21.3***
- A) forms a new C–C bond between an α-C (Nu:) and a carbonyl C (E^+)
- B) addition of heat to lose H_2O (β-elimination, E1cB)
- C) acid- and base-catalyzed mechanisms
- D) mixed/crossed aldol reactions ***SkillBuilder 21.4***
- E) *Aldol skills/LOs: predict the product, draw mechanism (acid or base), retrosynthetic analysis of aldol product (β-hydroxy carbonyl or α,β-unsaturated carbonyl)*

V. Claisen Condensation (aldol reaction with esters) (21.4)
- A) forms β-keto esters with active methylene groups (the reaction's driving force)
- B) *Claisen skills/LOs: predict the product, draw mechanism, explain choice of base & need for acidic workup, retrosynthetic analysis of Claisen product (β-ketoester)*

VI. Enones: α,β-unsaturated carbonyls (21.6)
- A) definition of conjugated π bonds
- B) resonance stabilized with a δ^+ on carbonyl carbon <u>and</u> β carbon (both are E^+)
- C) 1,4-(conjugate) addition of Nu: (attack β carbon)
  - i) mechanism is via enolate intermediate
  - ii) possible for electrophilic alkenes (CH_2=CH–EWG)
- D) 1,4-(conjugate) addition of enolates
  - i) Michael reaction (enolate Nu: and enone E^+)
  - ii) enolate and enone equivalents (carbonyl-like EWG's: $-NO_2$ and -CN)
  - iii) Robinson annulation
    - a) ketone + MVK gives cyclohexenones
    - b) mechanism: Michael addition followed by aldol condensation
- E) FYI: Enamines (synthetic equivalent of enolates) *SkillBuilder 21.7*
  - i) ketone + 2° amine → enamine
  - ii) enamine + enone, then $H_3O^+ \rightarrow$ Michael reaction
  - iii) enamine + RX, then $H_3O^+ \rightarrow$ α-alkylated ketone

VII. Synthesis - disconnection approach to retrosynthetic analysis (21.7) ***SkillBuilder 21.8***
- A) Synthesis with active methylenes (21.5) ***SkillBuilder 21.5, SkillBuilder 21.6***
  - i) decarboxylation (– CO_2) of β-carbonyl acids
  - ii) use of malonic ester and acetoacetate ester as synthetic equivalents
- B) Alkylation of α and β positions ***SkillBuilder 21.9***

SKIP*: Haloform reaction and HVZ reaction (section 21.2)*
SKIP*: Stork Enamine Synthesis (SkillBuilder 21.7)*