

Tapio Nevalainen
Drug synthesis II
2012

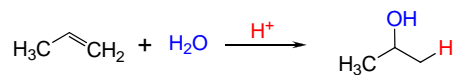
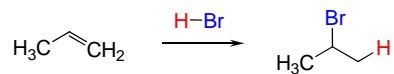
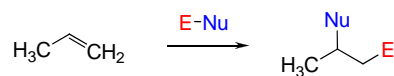
A Summary of Useful Reactions



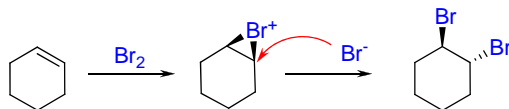
UNIVERSITY OF
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Reactions of alkenes

Electrophilic Addition

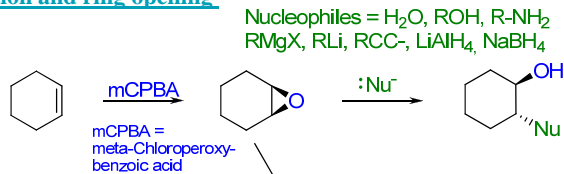


Halogenation

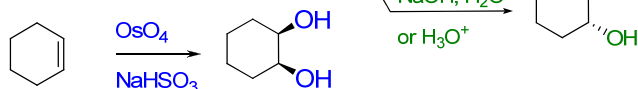


Reactions of alkenes

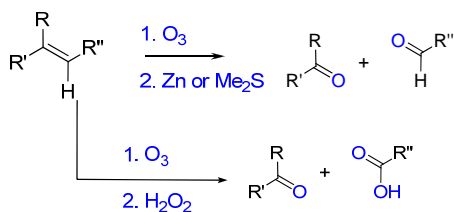
Epoxidation and ring opening



Hydroxylation

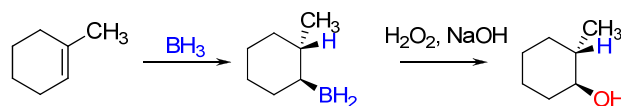


Ozonolysis

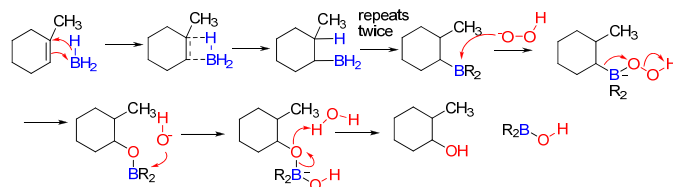


Reactions of alkenes

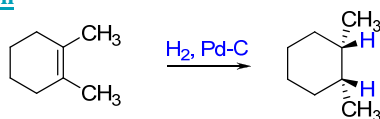
Hydroboration



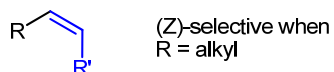
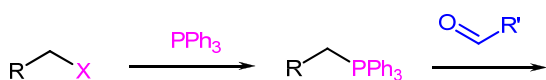
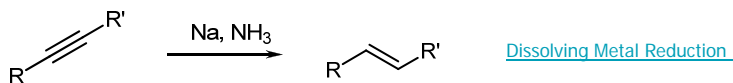
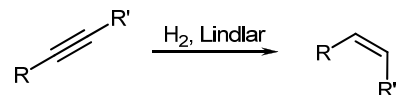
Mechanism



Hydrogenation



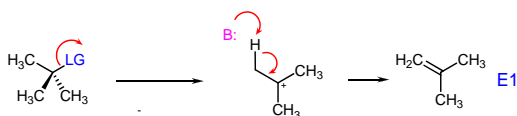
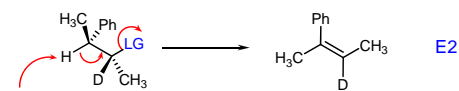
Formation of alkenes



[Wittig reaction](#)

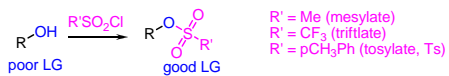


Formation of alkenes

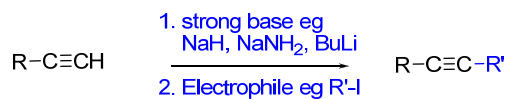
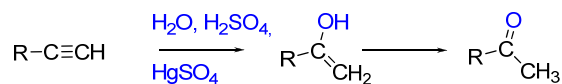


LG = Leaving group:

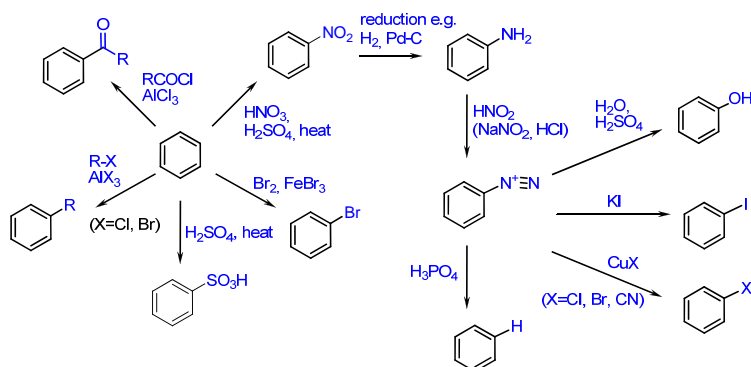
$\text{CF}_3\text{SO}_2\text{O} > \text{Ts} > \text{CH}_3\text{SO}_2\text{O} > \text{H}_2\text{O}, \text{I}^- > \text{Br}^- > \text{Cl}^-$



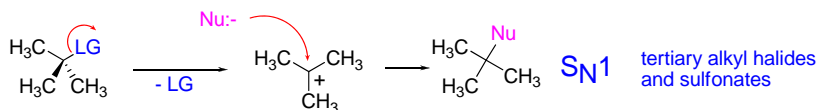
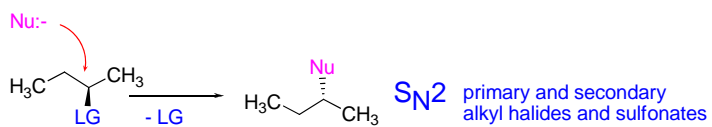
Alkynes



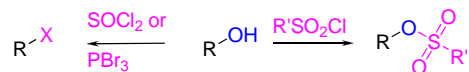
Aromatics



Nucleophilic Substitution Reactions

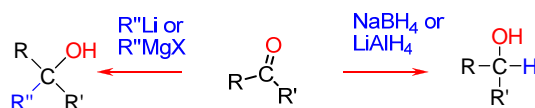
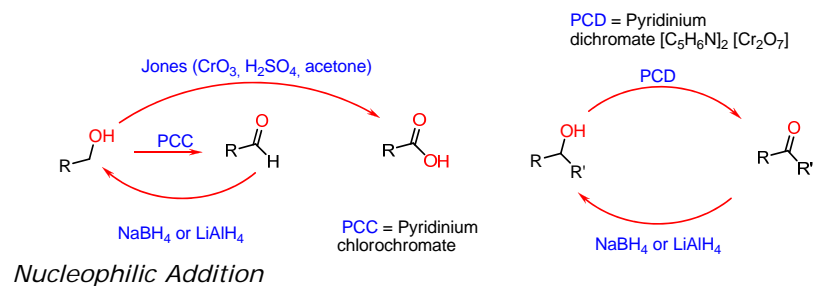


Alkyl halides and sulfonates are formed from the corresponding alcohols

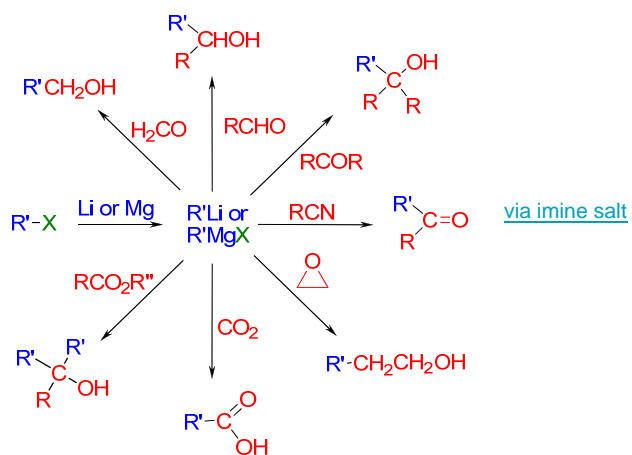


Chemistry of the Carbonyl Group

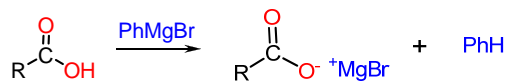
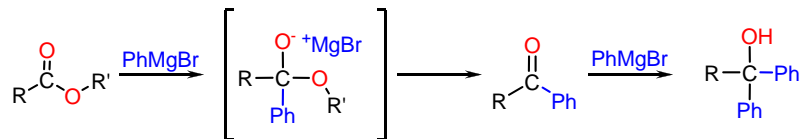
Oxidation and reduction



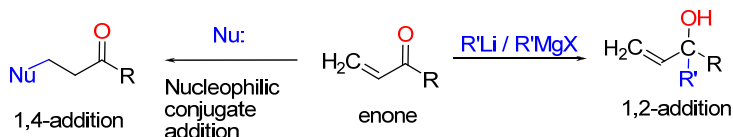
Overview of Organometallic Reactions



Chemistry of the Carbonyl Group

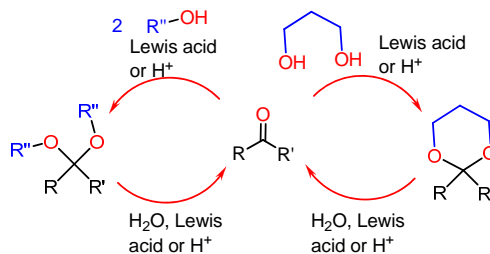


α,β -Unsaturated Carbonyl Compounds

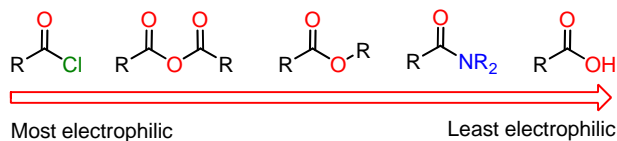


Chemistry of the Carbonyl Group

- *Acetals*

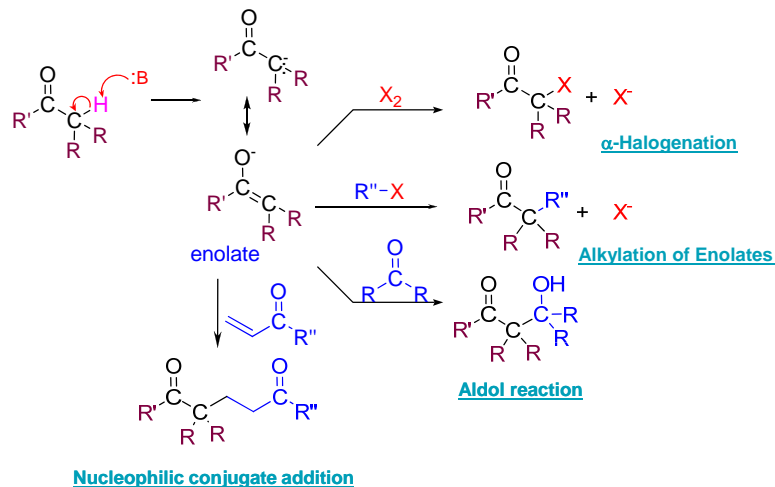


- *Carboxylic Acid Derivatives*



Chemistry of the Carbonyl Group

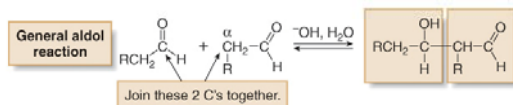
Enolate reactions



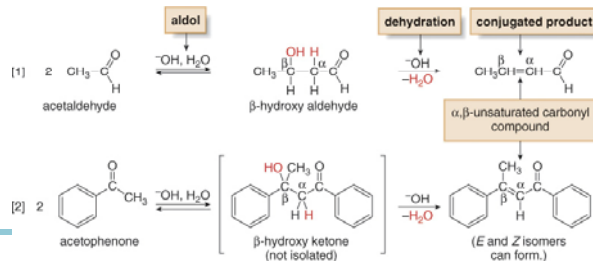
Carbonyl Condensation Reactions

• The aldol reaction

- the α carbon of one carbonyl component becomes bonded to the carbonyl carbon of the other component.



- Under the basic reaction conditions, the aldol product loses H_2O to form an α,β -unsaturated carbonyl compound



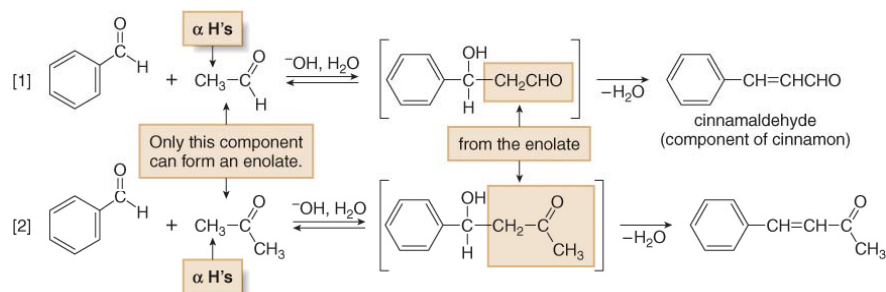
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Carbonyl Condensation Reactions

• Crossed Aldol Reactions

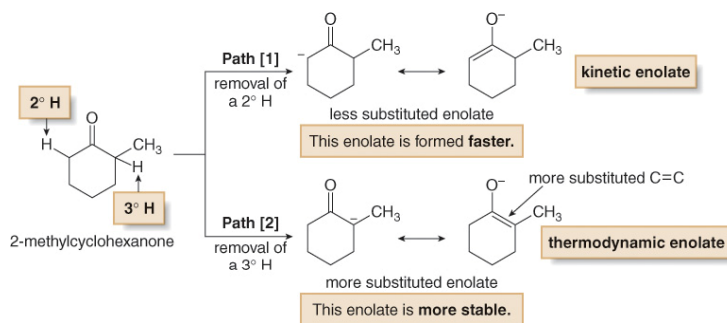
– Crossed aldols are synthetically useful in two different situations:

1. When only one carbonyl component has α hydrogens—such cases often lead to the formation of only one product.



Chemistry of the Carbonyl Group: Regioselective formation of enolates from ketones

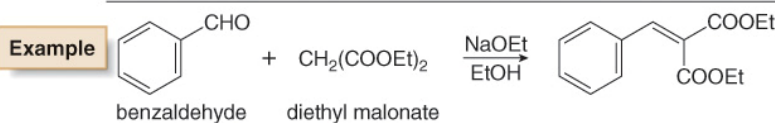
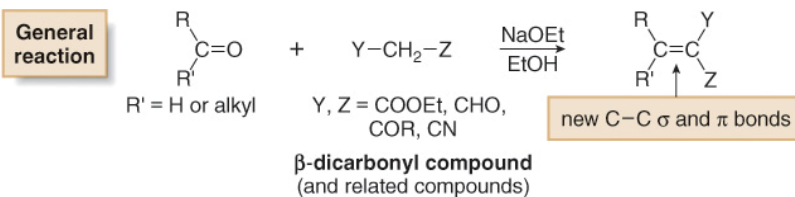
- When an unsymmetrical carbonyl compound like 2-methylcyclohexanone is treated with base, two enolates are possible.



- Path 1 occurs faster because it results in removal of the less hindered 2° H. Path 2 results in formation of the more stable enolate. This enolate predominates at equilibrium.

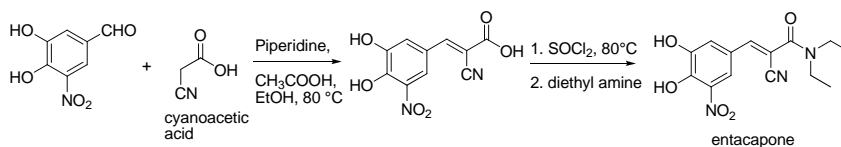
Carbonyl Condensation Reactions: Crossed Aldol Reactions

- 2. When one carbonyl component has especially acidic α hydrogens, these hydrogens are more readily removed than the other α H atoms. As a result, the β -dicarbonyl compound always becomes the enolate component of the aldol reaction.



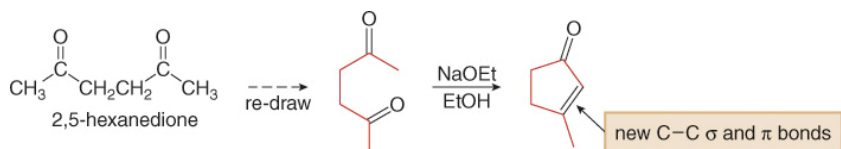
Carbonyl Condensation Reactions: Crossed Aldol Reactions

- Entacapone, a catechol-O-methyl transferase (COMT) inhibitor for the treatment of Parkinson's disease, is prepared by crossed aldol reaction (Knoevenagel condensation).

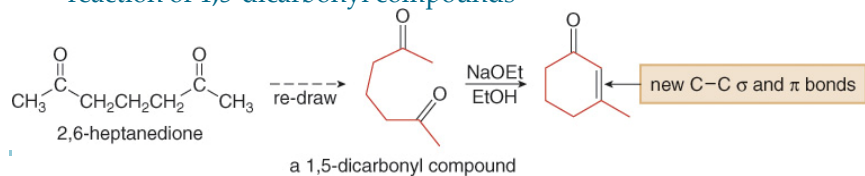


Carbonyl Condensation Reactions: Intramolecular Aldol Reactions

- 2,5-hexanedione forms a five-membered ring.

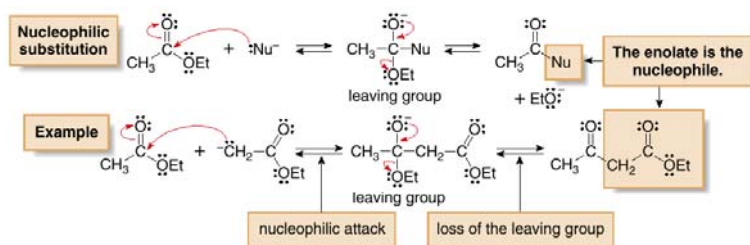


- Six-membered rings can be formed from the intramolecular aldol reaction of 1,5-dicarbonyl compounds



Carbonyl Condensation Reactions: The Claisen Reaction

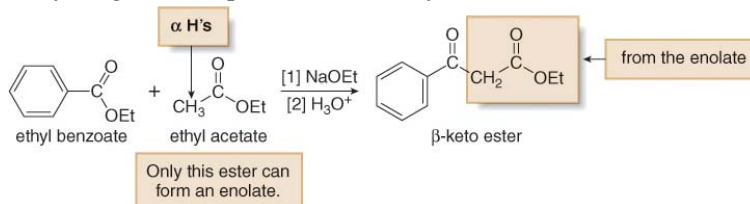
- A Claisen reaction is a nucleophilic substitution in which an enolate is the nucleophile



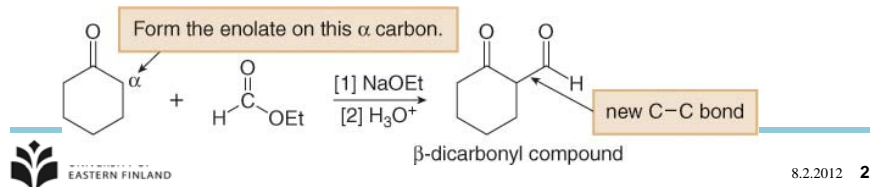
- Esters react by nucleophilic substitution. In a Claisen reaction, an enolate is the nucleophile that adds to the carbonyl group.

Carbonyl Condensation Reactions: The Crossed Claisen and Related Reactions

- A Claisen reaction between two different esters when only one has α hydrogens, one product is usually formed.



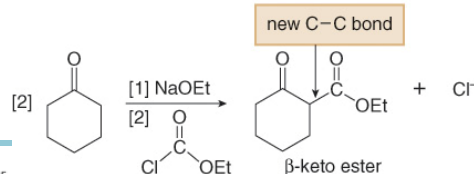
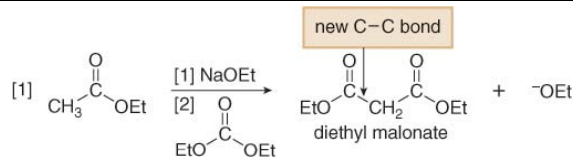
- A Claisen reaction between a ketone and an ester—the enolate is formed from the ketone and the ester has no α hydrogens



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Carbonyl Condensation Reactions: The Crossed Claisen and Related Reactions

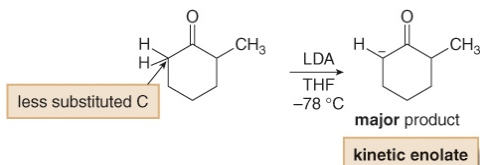
- β -Dicarbonyl compounds are also prepared by reacting an enolate with ethyl chloroformate or diethyl carbonate



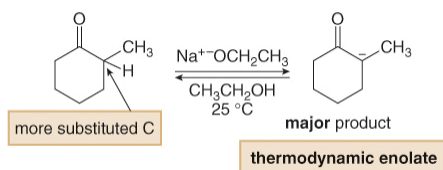
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Chemistry of the Carbonyl Group: Regioselective formation of enolates from ketones

- A kinetic enolate is favored by a strong nonnucleophilic base like LDA, polar aprotic solvent and low temperature (-78°C).



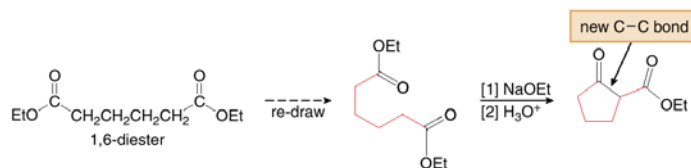
- A thermodynamic enolate is favored by a strong base (NaOEt, t-BuOK) in a protic solvent (EtOH) and room temperature (25°C).



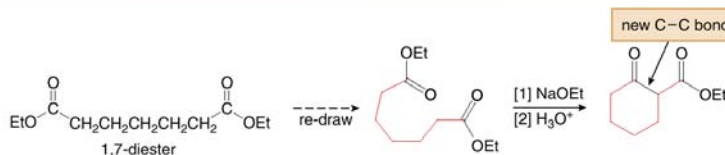
Carbonyl Condensation Reactions: The Crossed Claisen and Related Reactions

- An intramolecular Claisen reaction is called a Dieckmann reaction. Two types of diesters give good yields of cyclic products.

- 1,6-Diesters yield five-membered rings by the Dieckmann reaction.

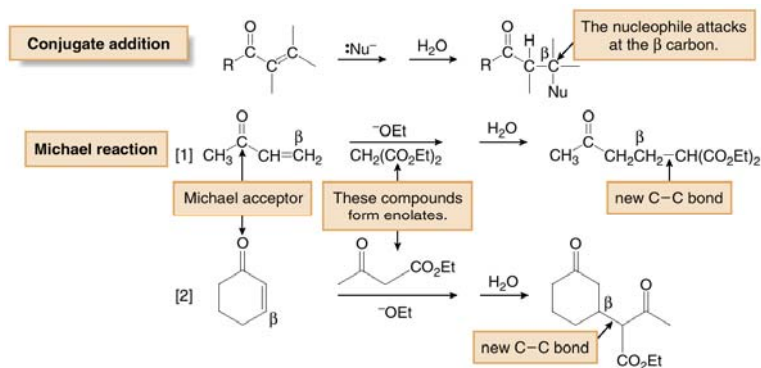


- 1,7-Diesters yield six-membered rings by the Dieckmann reaction.



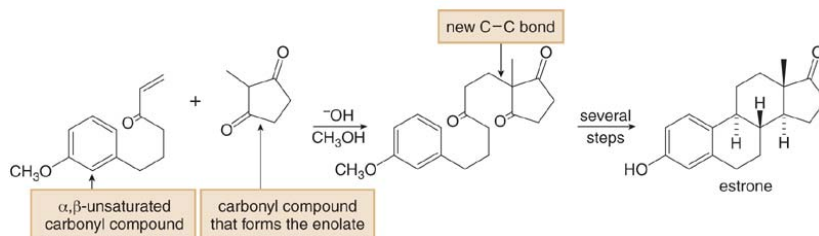
Carbonyl Condensation Reactions: The Michael Reaction

- The **Michael reaction** involves the conjugate addition (1,4-addition) of an enolate to the β -carbon of the α,β -unsaturated carbonyl compound.



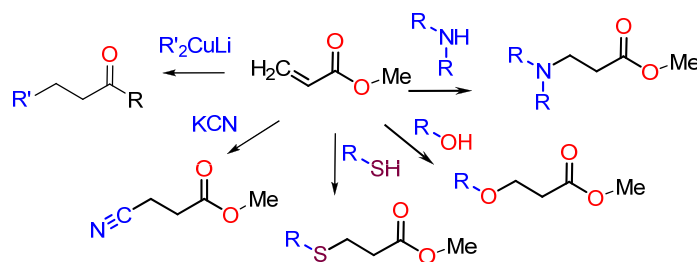
Carbonyl Condensation Reactions: The Michael Reaction

- Michael reaction that was a key step in the synthesis of estrone, a female sex hormone



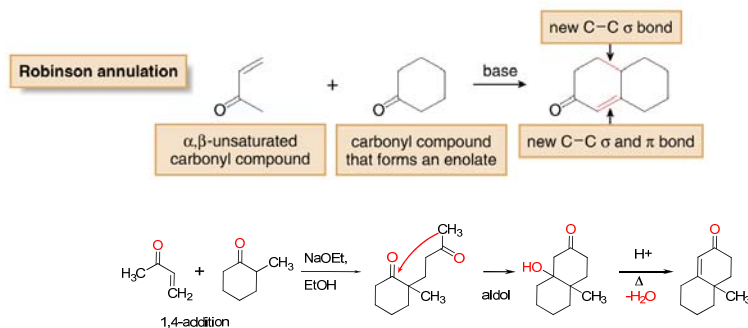
Carbonyl Condensation Reactions: Nucleophilic Conjugate Addition Reactions

- α,β -Unsaturated carbonyl compounds can potentially react with nucleophiles (amines, thiols, alcohols, cyanide ions, organocopper reagents R_2CuLi , and enolates) at the end of the conjugated system:



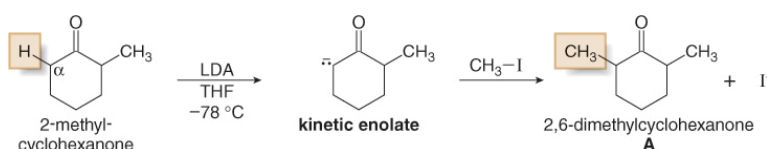
Carbonyl Condensation Reactions: The Robinson Annulation

- The **Robinson annulation** is a ring-forming reaction that combines a Michael reaction with an intramolecular aldol reaction.



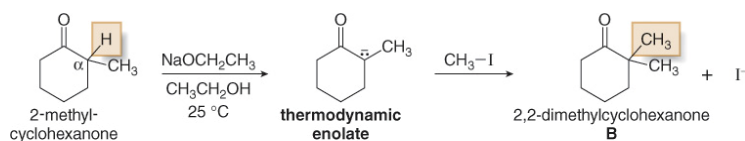
Chemistry of the Carbonyl Group: Regioselective formation of enolates from ketones

- An unsymmetrical ketone can be regioselectively alkylated to yield one major product.
- Treatment of 2-methylcyclohexanone with LDA in THF solution at -78°C gives the less substituted kinetic enolate, which then reacts with CH_3I to form A.

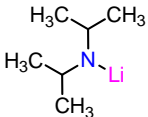
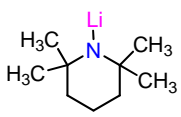



Chemistry of the Carbonyl Group: Regioselective formation of enolates from ketones

- Treatment of 2-methylcyclohexanone with $\text{NaOCH}_2\text{CH}_3$ in $\text{CH}_3\text{CH}_2\text{OH}$ solution at room temperature forms the more substituted thermodynamic enolate, which then reacts with CH_3I to form B.

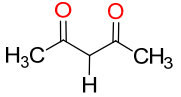
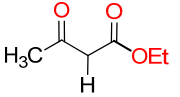
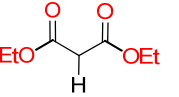
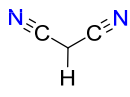
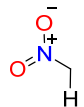
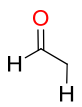
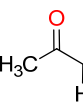
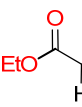
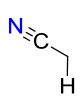
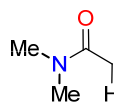


Common bases for preparing enolates

OH^-	$\text{CH}_3\text{CH}_2\text{O}^-$	$(\text{CH}_3)_3\text{C}^-$	Na^+H^-
Hydroxide pKa (HB ⁺) 15.7	Ethoxide pKa (HB ⁺) 16	t-Butoxide pKa (HB ⁺) 18	Sodium hydride pKa (HB ⁺) 35
			
lithium diisopropylamide LDA pKa (HB ⁺) 36	lithium tetramethylpiperidine LTMP pKa (HB ⁺) 37	lithium hexamethyldisilazide LHMDS pKa (HB ⁺) 30	



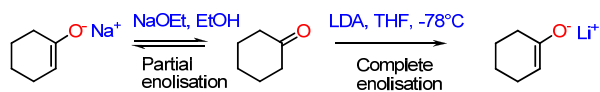
Some important pKa values of carbonyl-containing molecules, nitro compounds and nitriles

			
9.0	11.0	12.7	11.2
			
10	17	20	24.5
			
	25	30	

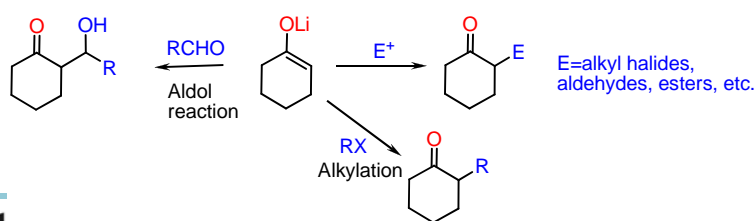


Enol equivalents : lithium enolates

- In the presence of a very strong base such as lithium diisopropyl amide (LDA), stable enolates can be formed

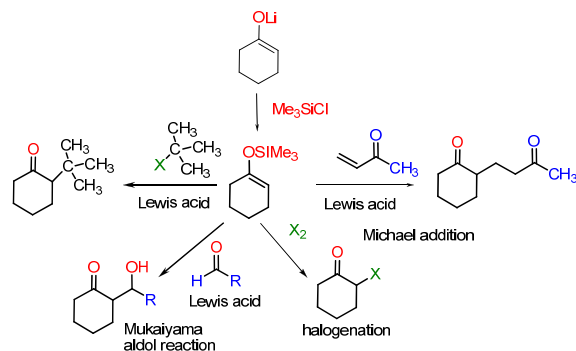


- The lithium enolate is stable at low temperature (-78 °C) but reactive enough to be useful.
- Lithium enolates are the most commonly used stable enolate equivalents in chemistry



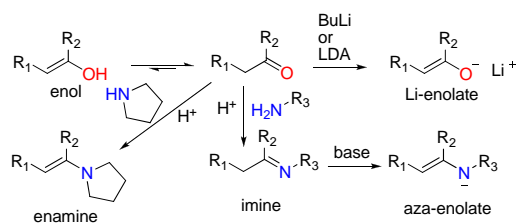
Enol equivalents: silyl enol ethers

- Silyl enol ethers are more stable, but less reactive, than lithium enolates.
- They are made by treating an enolate with a silicon electrophile.

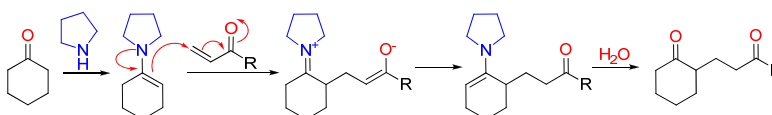


Enol equivalents

- The problem of self-condensation of carbonyl compounds can be avoided by using specific enol equivalents (lithium enolates, enamines, silyl enol ethers, aza-enolates).

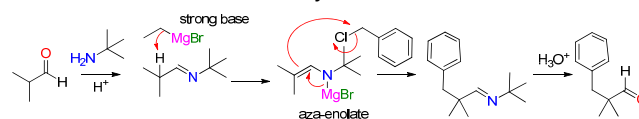


- Use of enamines as enol equivalents (Stork enamine alkylation)

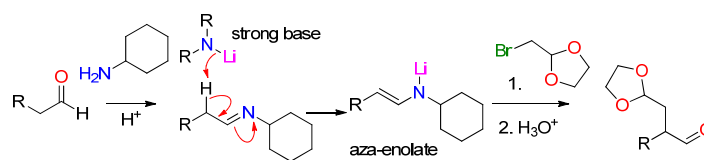


Enol equivalents: aza-enolates

- The aza-enolates can be alkylated



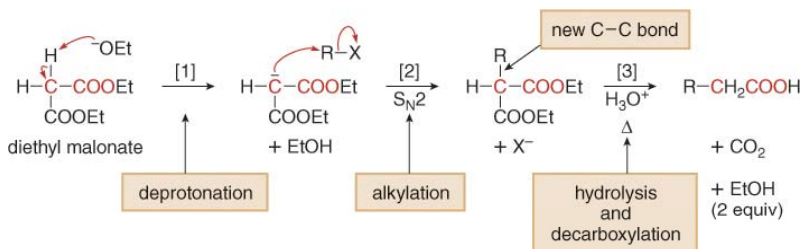
- Mono-protected dialdehydes can be made using aza-enolates



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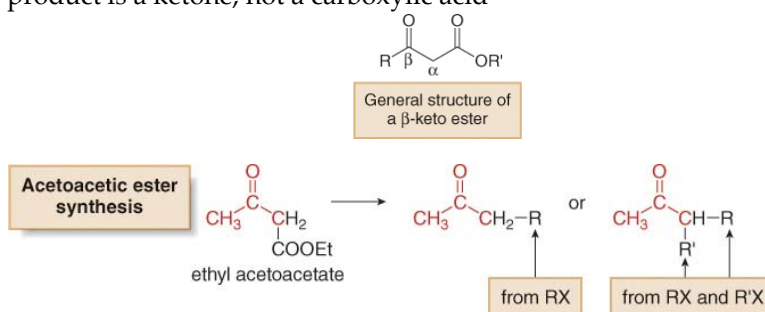
Reactions of Enolates – Malonic Ester Synthesis

- The malonic ester synthesis converts diethyl malonate to a carboxylic acid in three steps.



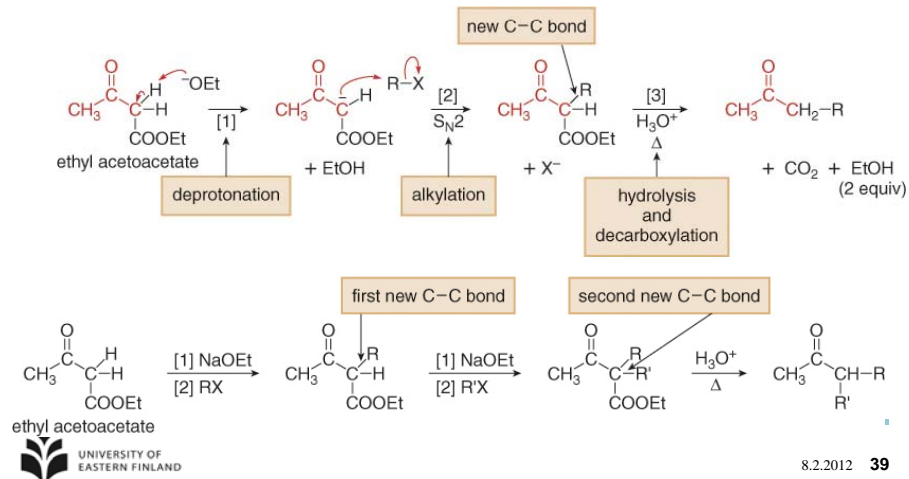
Reactions of Enolates – Acetoacetic Ester Synthesis

- The acetoacetic ester synthesis is a stepwise method for converting ethyl acetoacetate into a ketone having one or two alkyl groups on the α carbon. Because the starting material is a β-ketoester, the final product is a ketone, not a carboxylic acid



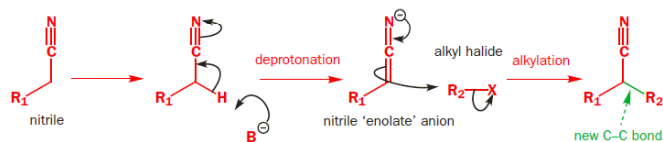
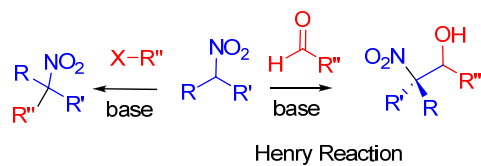
Reactions of Enolates—Acetoacetic Ester Synthesis

- The steps in acetoacetic ester synthesis are exactly the same as those in the malonic ester synthesis.



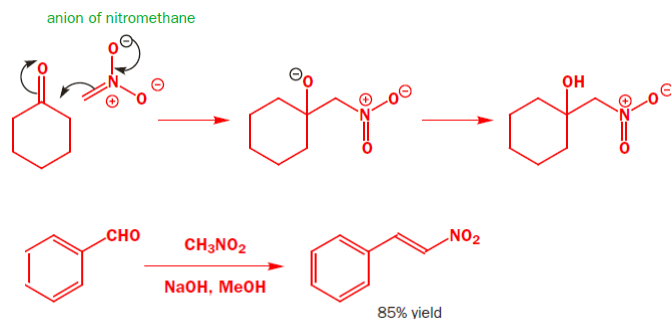
Nitriles and nitroalkanes are enolizable

- Nitriles and nitroalkanes can be alkylated and can undergo aldol-like condensations



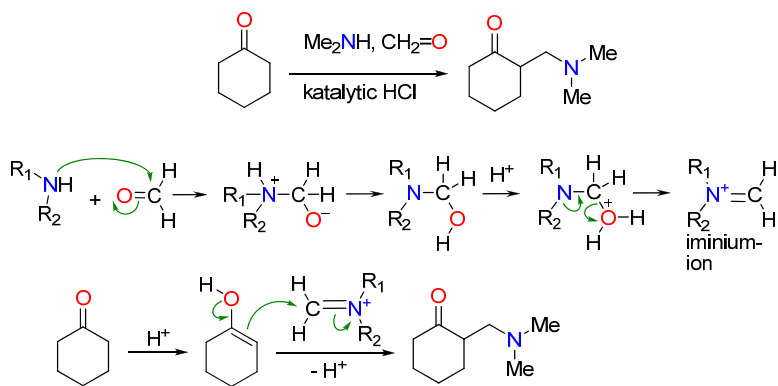
Nitriles and nitroalkanes are enolizable

- Nitroalkanes are enolized to nitronates and react well with aldehydes and ketones.



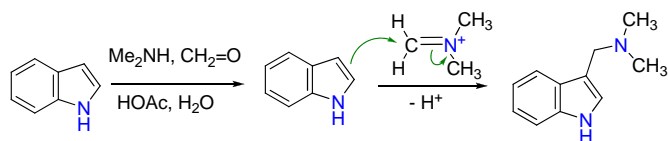
The Mannich reaction

- Amino alkylation of an acidic proton with formaldehyde and amine. The product is known as a Mannich base

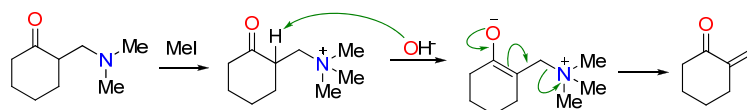


The Mannich reaction

- Electron-rich heterocycles such like indoles and pyrroles form Mannich bases



- The Mannich products can be converted to enones (vinyl ketones) by alkylation with MeI and then treat the ammonium salt with base.



The Mannich reaction

- In the original synthetic route of fluoxetine (4) starts with Mannich reaction of acetophenone (7) to yield the aminoketone 8.

