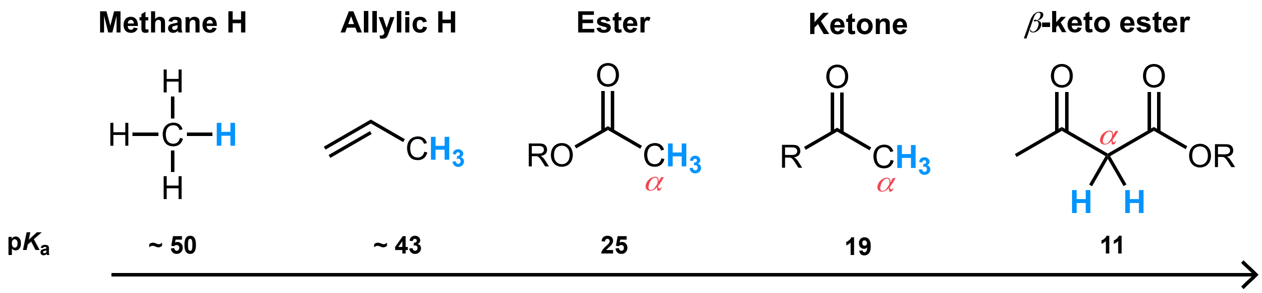
Reactions α- to Carbonyls

This Core Concept Sheet describes the general reactivity of enols and enolates as nucleophiles in a variety of α-**substitution, addition/condensation, and acyl substitution reactions.**

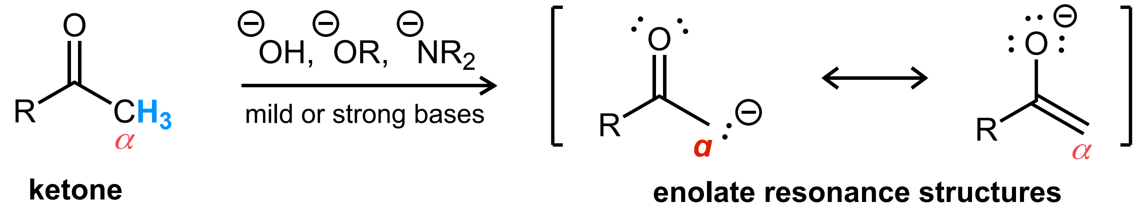
Unlike most C—H bonds, the C—H bonds α to a carbonyl are acidic.



acidity of H increases

[stability of conjugate base increases]

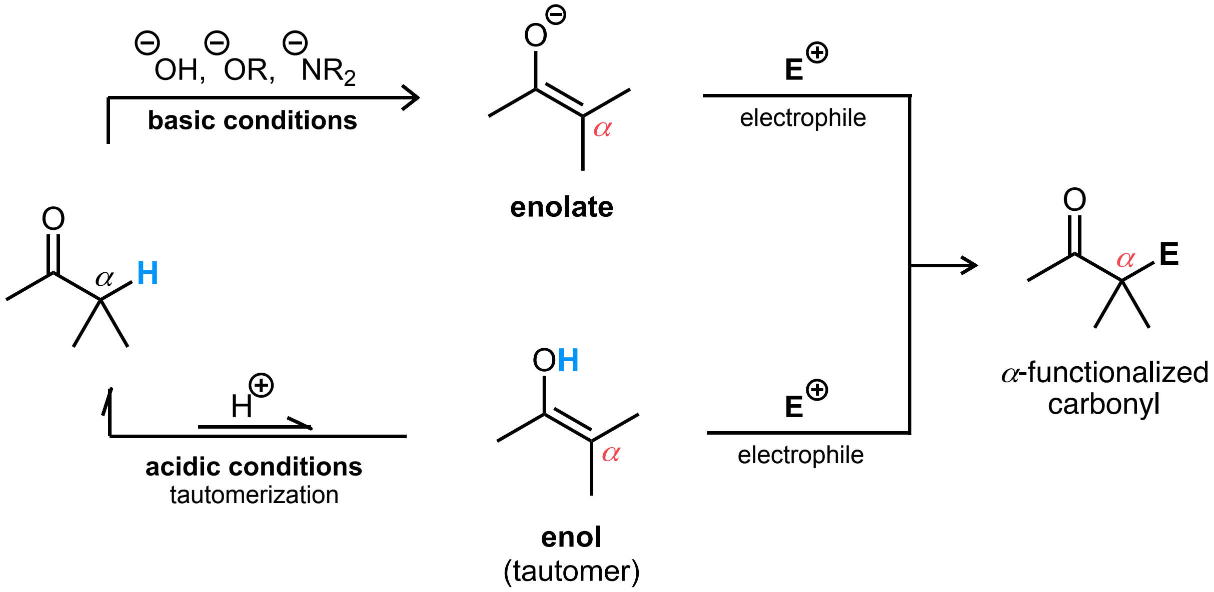
Therefore, such carbonyls with α-CH bonds can be depronated to form **enolates**.



Enolates and enols are nucleophiles that can react with a variety of electrophiles!

Under basic conditions, we can deprotonate the alpha C—H to form **enolates.**

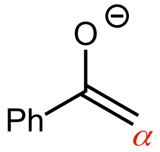
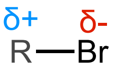
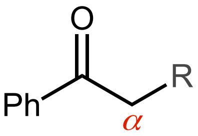
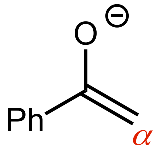
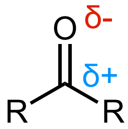
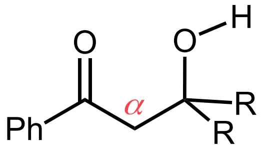
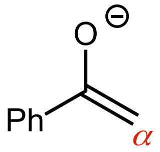
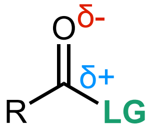
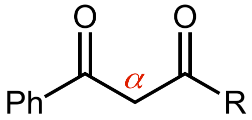
Under acidic conditions, enolizable **carbonyls can tautomerize to form enols**.



Variations in The Electrophile

You will commonly see enolates and enols reacting with **alkyl halides, ketones/aldehydes,** and **carboxylic acid derivatives.**

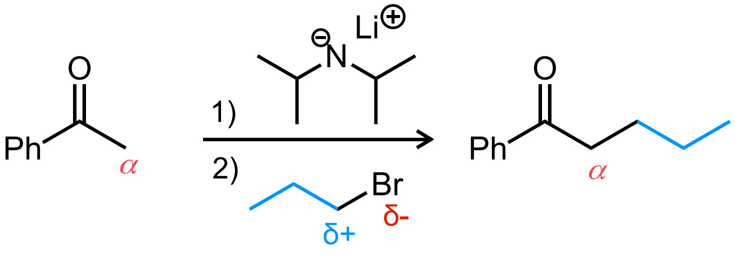
Different reactions (α-substitution, -addition, -acyl substitution) are observed depending on the type of electrophile used.

Enolate nucleophile	Electrophile	Reaction →	Product
	 **Alkyl halides**	**α-substitution**	
	 **Ketones** or **aldehydes**	**α-addition**	
	 **Carboxylic acid derivatives**	**α-acyl substitution**	

α-Substitution Reactions

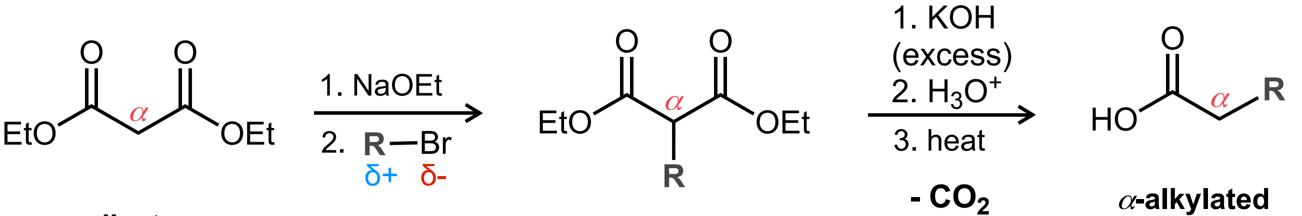
α-Alkylation

One of the most common α substitution reactions is the α-alkylation of carbonyls using 1) LDA and 2) an alkyl halide.



Decarboxylation in Alkylated Diesters

After the alkylation of a 1,3-diester, we can hydrolyze the ester to the acid, which can be decarboxylated using heat to afford a functionalized molecule containing only one carbonyl.



diester

alkylated diester

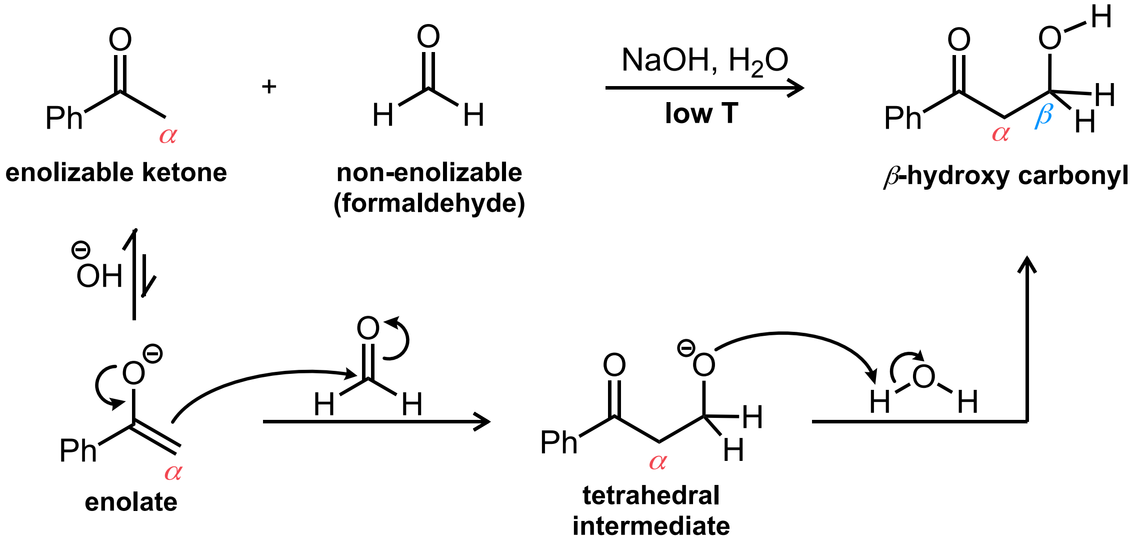
α-alkylated carboxylic acid

α-Addition Reactions

Aldol Addition

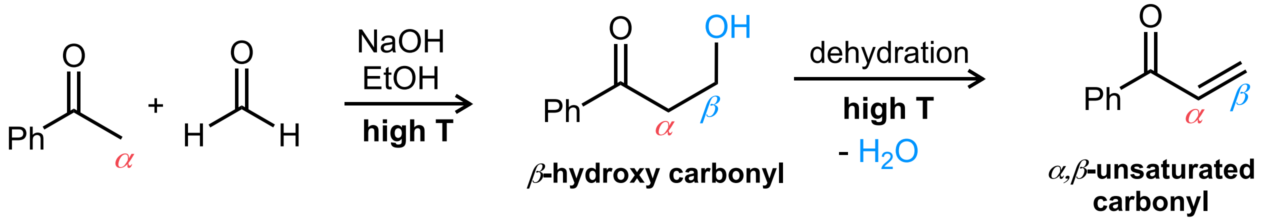
The reaction between an **enolate or enol nucleophile** with **a ketone/aldehyde electrophile** is known as the **Aldol addition reaction**.

The **product** of an **aldol addition** reaction is a **β-hydroxy carbonyl.**



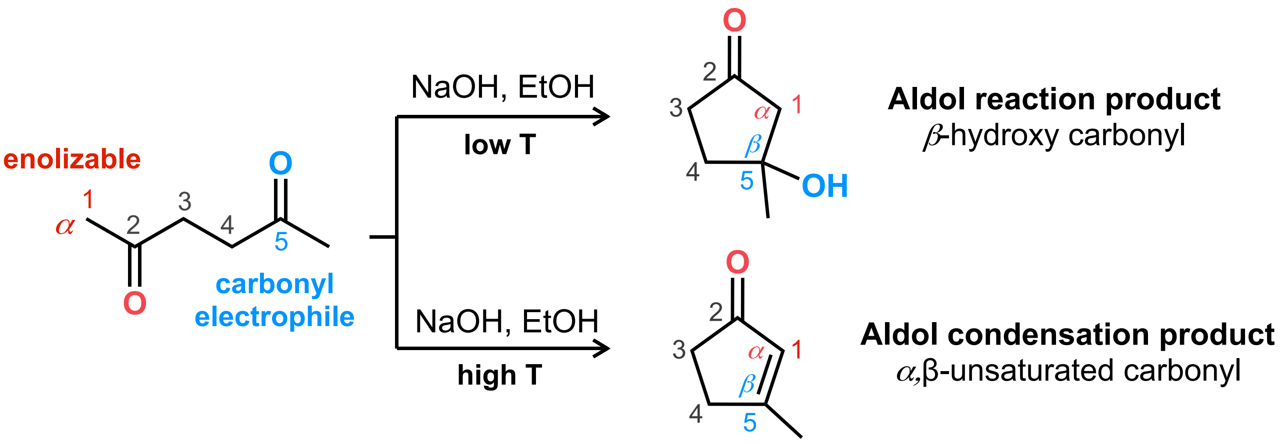
The Aldol Condensation

However, **adding heat to the reaction above** results in a dehydration reaction of the β-hydroxy carbonyl to yield an **α,β-unsaturated carbonyl (enone)**. The dehydration can be done under either acidic or basic conditions.



Intramolecular Aldol Addition and Aldol Condensation

When there are two ketones/aldehydes in the same molecule, an intramolecular reaction is possible by using one carbonyl as the enolate nucleophile and the second as a carbonyl electrophile. These intramolecular reactions work best for forming 5- and 6-membered rings.

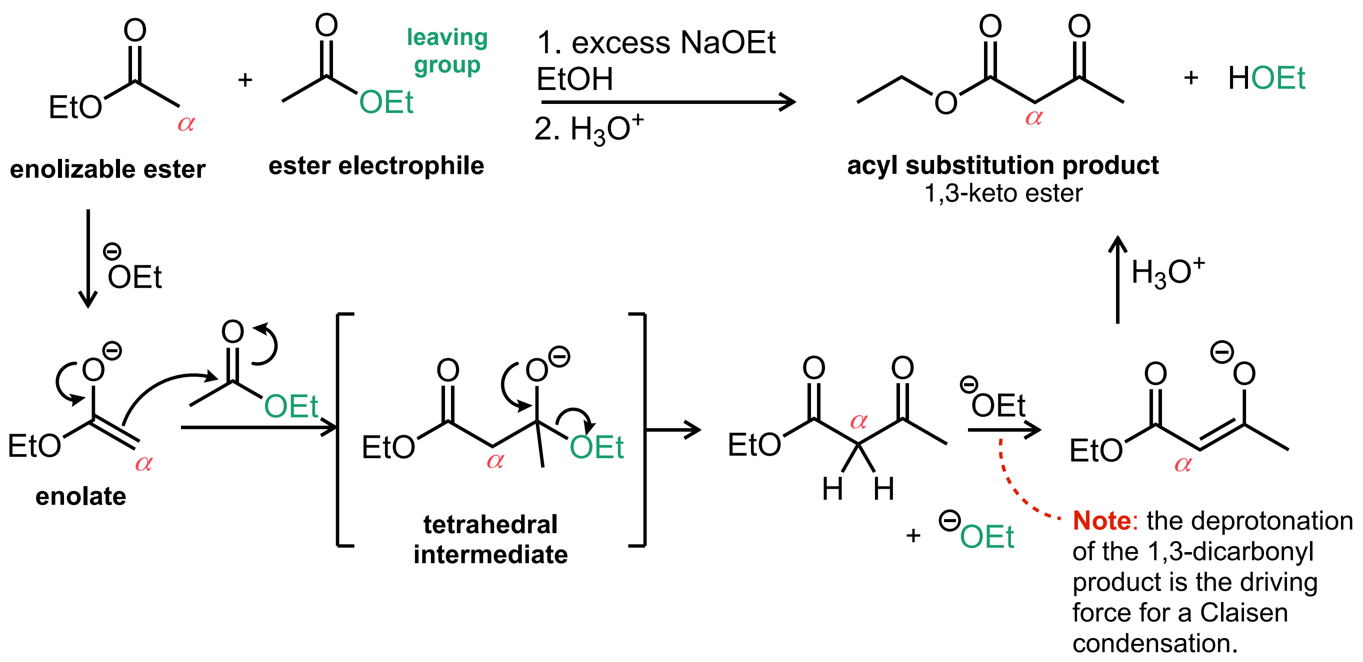


α-Acyl Substitution Reactions

The Claisen Condensation

The reaction of an **enolate nucleophile** with a **carboxylic acid derivative** results in an **acyl substitution** product rather than an addition product (as seen in the Aldol reaction). This is because the tetrahedral intermediate formed after addition can collapse to expel the leaving group and reform the C=O pi bond.

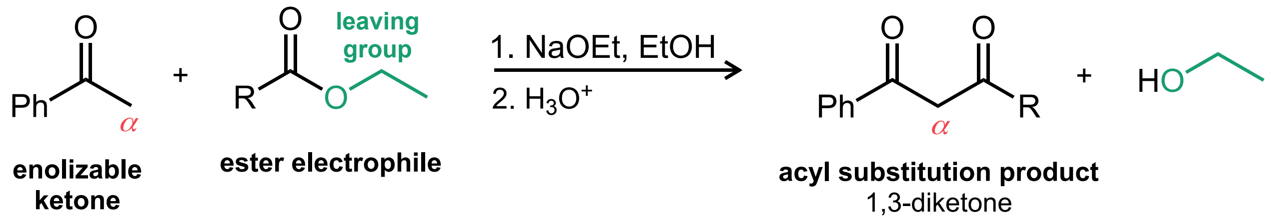
The product of a Claisen condensation **is a 1,3-dicarbonyl**.



Note: the deprotonation of the 1,3-dicarbonyl product is the driving force for a Claisen condensation.

Mixed Claisen

Utilizes two different carbonyls - one as the enolate, the other as the electrophile



Intramolecular Claisen Condensation (Dieckmann condensation)

As we saw in the aldol addition reactions, if a nucleophile (enolate) and electrophile (e.g. ester) are containing in the same molecule, an intramolecular acyl substitution reaction can occur. This is known as the Dieckmann condensation. These intramolecular reactions work best for forming 5- and 6-membered rings.