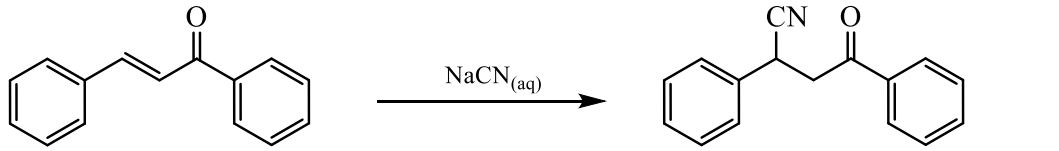
3:5) Nucleophilic addition:

Nucleophilic reagents doesn't attack simple alkenes, but in α,β-unsaturated carbonyl compounds the carbon – carbon double bond is polarized, thus nucleophilic reagents could be added to either carbon – carbon double bond or carbon – oxygen double bond.

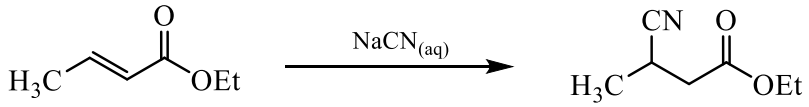
e.g.

1)



Benzalacetophenone — 3-Cyano-1,3-diphenyl-1-propanone

2)

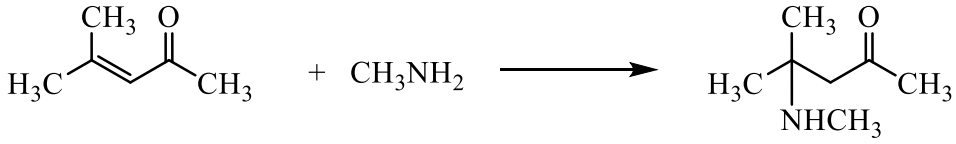


Ethyl crotonate — Ethyl-β-cyanobutyrate

Furthermore ammonia or certain derivatives of ammonia (amines, hydroxylamine, phenylhydrazine, --- etc.) added to these compounds to give β-amino carbonyl compounds.

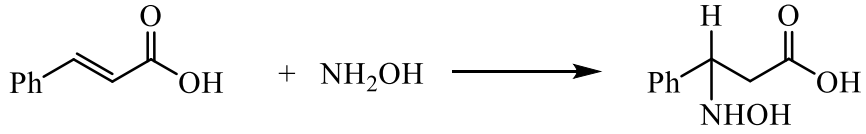
e.g.

1)



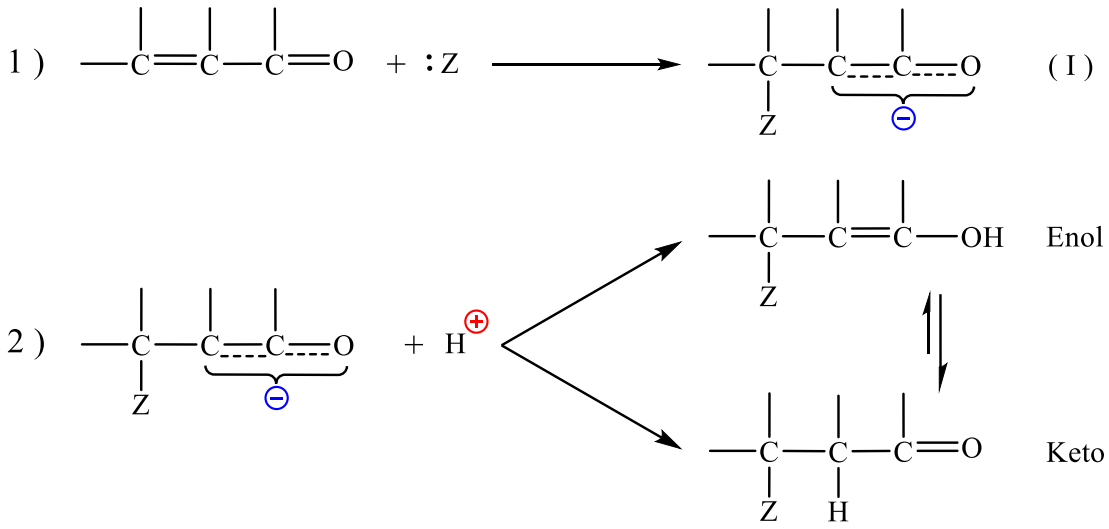
Mesityl oxide — Methylamine — 4-(N-methylamino)-4-methyl-2-pentanone

2)



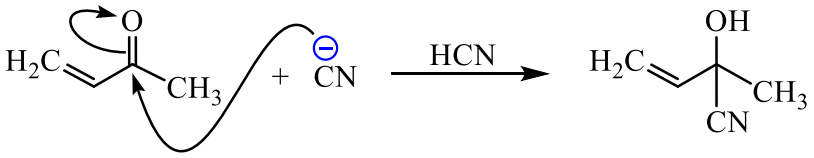
Cinnamic acid — Hydroxylamine — 3-(N-hydroxylamino)-3-phenyl propanoic acid

Mech.: these reactions are believed to take place as the following:



In the first step the nucleophilic reagent adds to the carbon – carbon double bond to give hybrid anion (I), which then accept in step two a hydrogen ion from the solvent to give the final product.
The hydrogen can add either to the α-carbon or to the oxygen, and this will give either the keto or the enol form of the product; in either case the same equilibirium mixture, chiefly keto, is finally obtained.
In the examples we have just seen, nucleophilic reagent (:Z), is either strongly basic anion, $:CN^-$, or a nuteral base like ammonia and its derivatives, $:NH_2$-G.
These are the same reagents which we have seen, add to the carbonyl group of simple aldehydes and ketones. (Indeed, nucleophilic reagents rearely add to the carbon – carbon double bond of α,β-unsaturated aldehydes, but rather to the highly reactive carbonyl group).

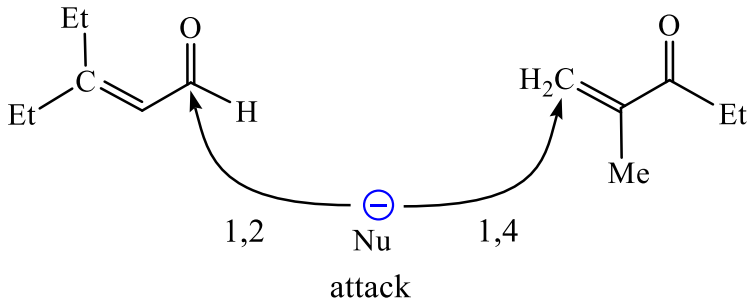
e.g.



Addition of a nucleophile to the carbonyl carbon is known as 1,2-addition, but the addition at the β- carbon is called 1,4- addition.

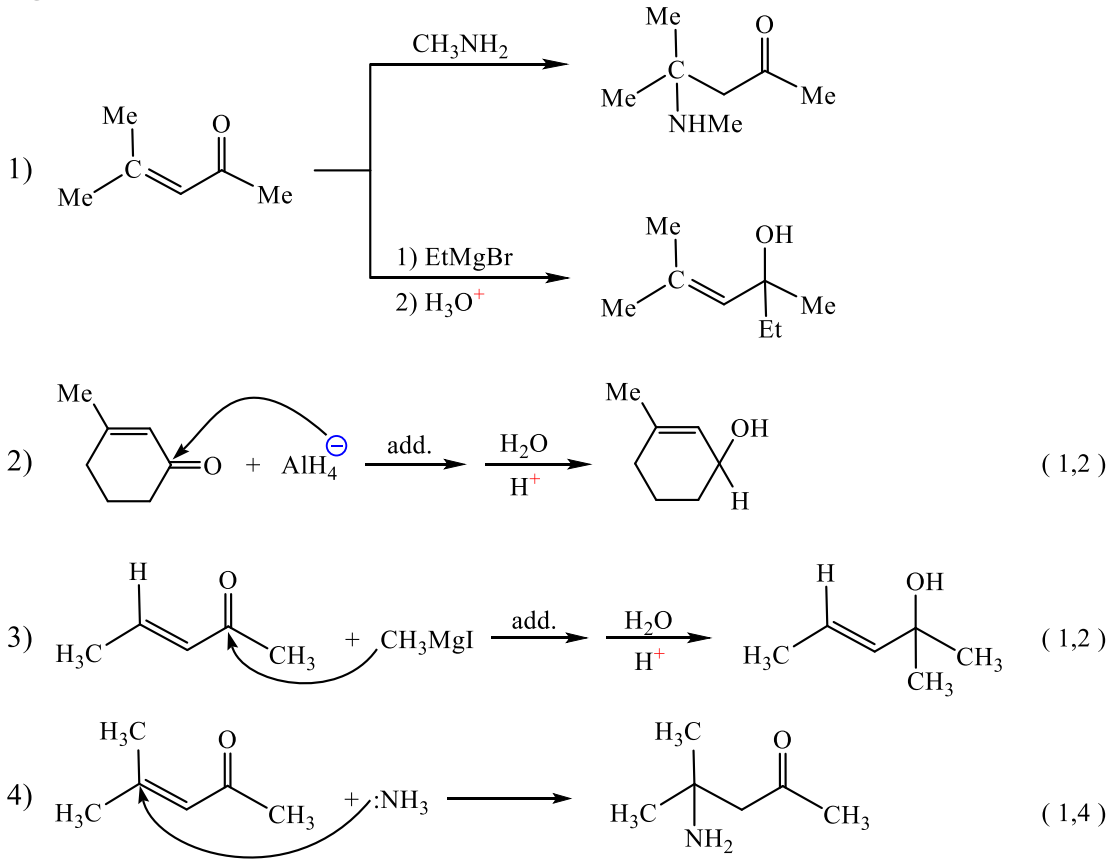
Addition type can be controlled by two factors:

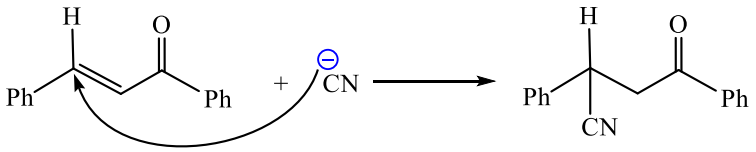
1- Steric hindrance:
Increasing steric hindrance at the carbonyl group will lead to the 1,4- addition product, while increasing steric hindrance at the β-position will lead to the 1,2- addition product.



2- Strength of nucleophile:
Strong nucleophiles such as organolithium and Grignard reagents tend to react at the carbonyl group yielding the 1,2-addition products. In contrast weaker nucleophiles such as amines and cyanide ion will react at the β- position yielding the 1,4-addition product.

e.g.

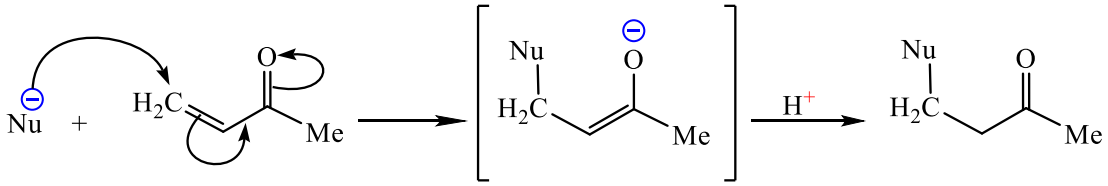


5) 

(1,4)

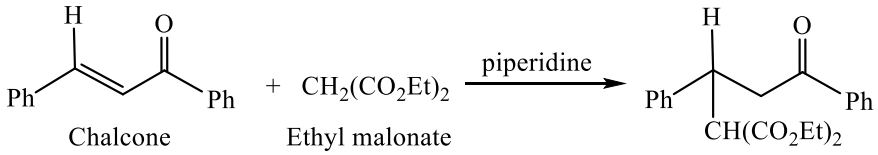
3:6) The Michael addition:

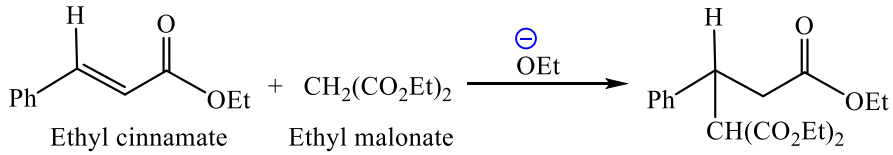
Previously we note that the carbon – carbon double bond that in conjugation with the carbonyl group can be a good reaction center for nucleophilic attack that afford the 1,4-addition reactions as the following:

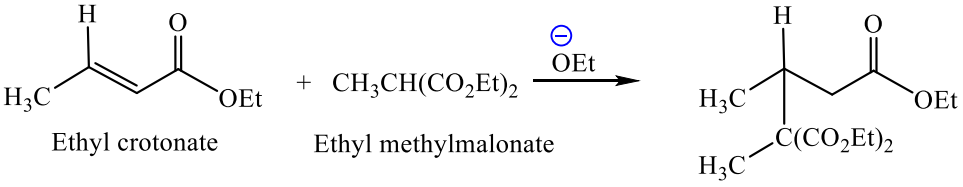


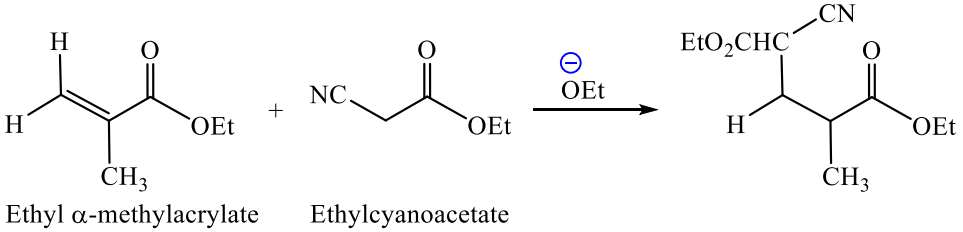
One of special importance in synthesis is the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds known as the Michael addition. This reaction results in the formation of carbon – carbon single bond.

e.g.

1) 

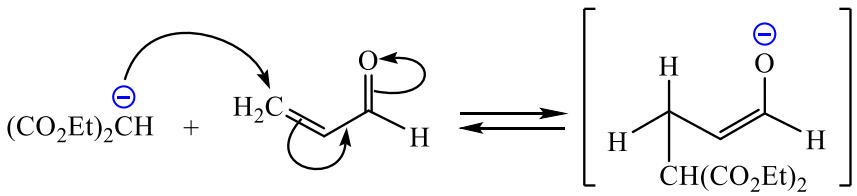
2) 

3) 

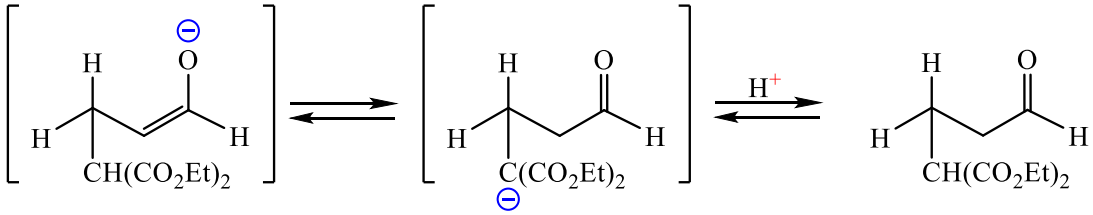
4) 

The intermediates are the simply the enolate ion that on protonation give the final 1,4-addition product.

e.g.

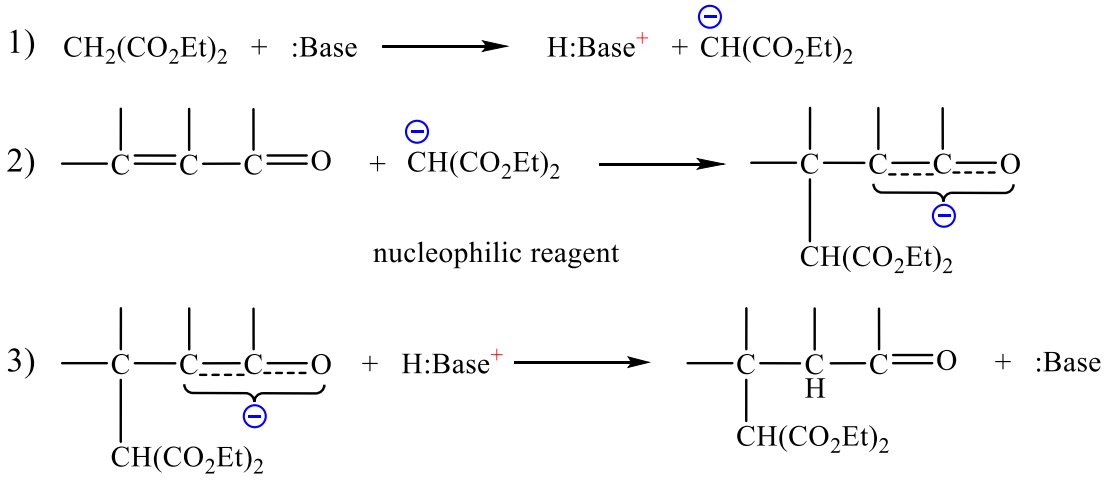


enolate



enolate more stable enolate

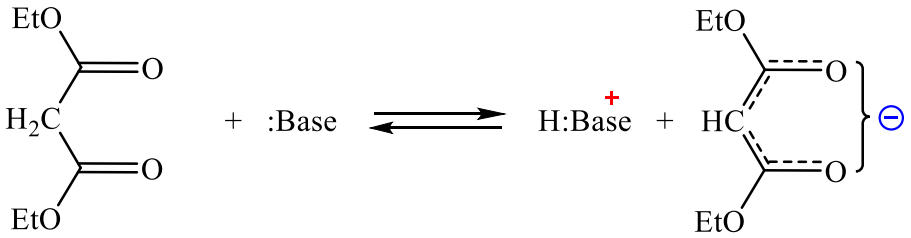
The Michael addition is believed to proceed by the following mechanism (shown for malonic ester):



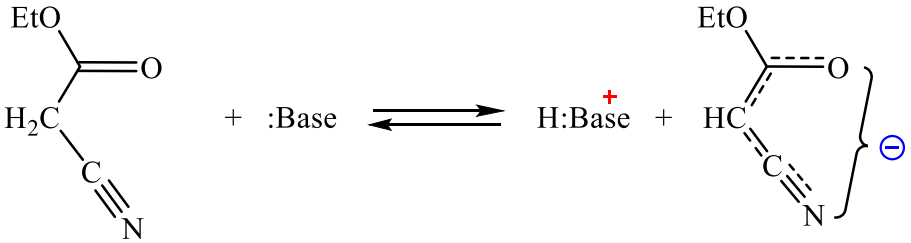
The first step involve abstraction of a hydrogen ion from malonic ester and thus generate a carbanion which act as nucleophilic reagent, then attack the conjugated system in the usual manner (step 2) to give the most stable enolate. The final step involves the addition of a proton to the enolate ion to give the final product.

Note:

1- *In place of ethylmalonate, compounds like ethyl cyanoacetate can be used.*
2- *The most stable enolate is due to the presence of two electron-withdrawing groups which can help accommodate the negative charge of the carbanion.*

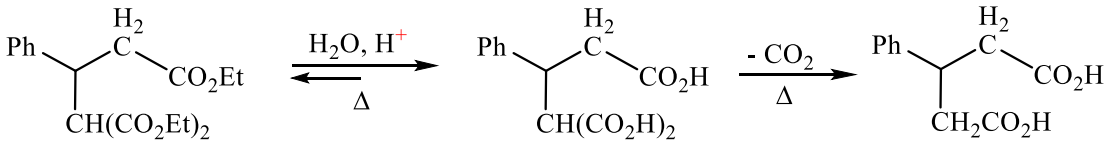


Ethyl malonate



Ethyl cyanoacetate

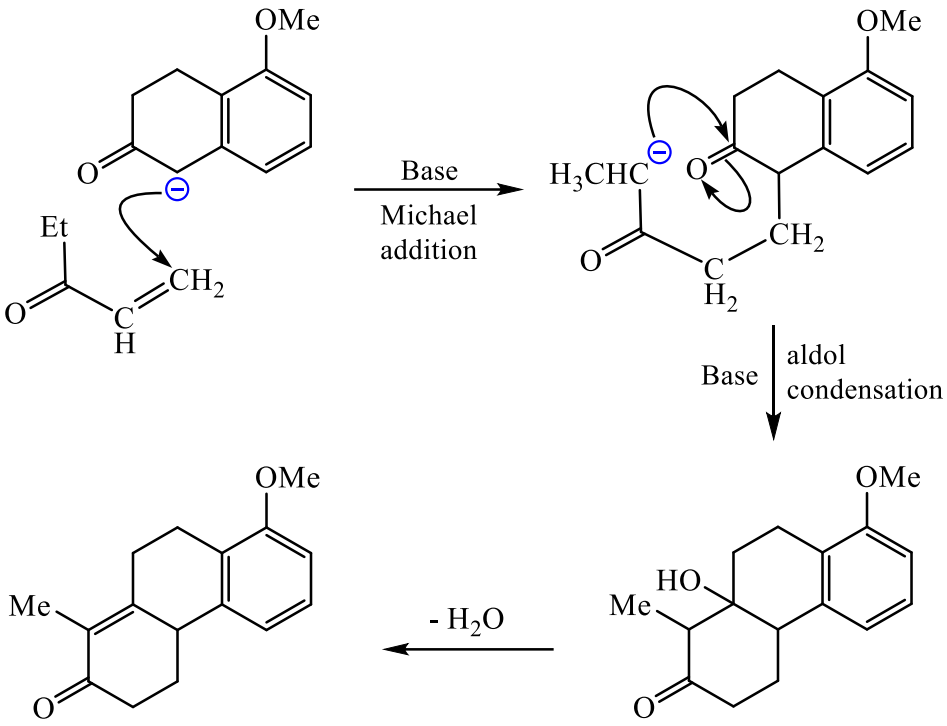
The Michael addition reaction is of great importance in organic synthesis, since if we examine the following reaction:



Tri ester | Tri caboxylic acid | Di carboxylic acid

Clearly we can see that the starting compound is a tri ester which on saponification and acidification will produce the tri carboxylic acid which can undergoes loss of carbon dioxide molecule to give the di carboxylic acid.

The Michael addition has been used beside other condensation reactions to synthesize important compounds like steroids.



The above reaction is consist of Michael addition and aldol condensation, the overall reaction is called Robinson annulation.