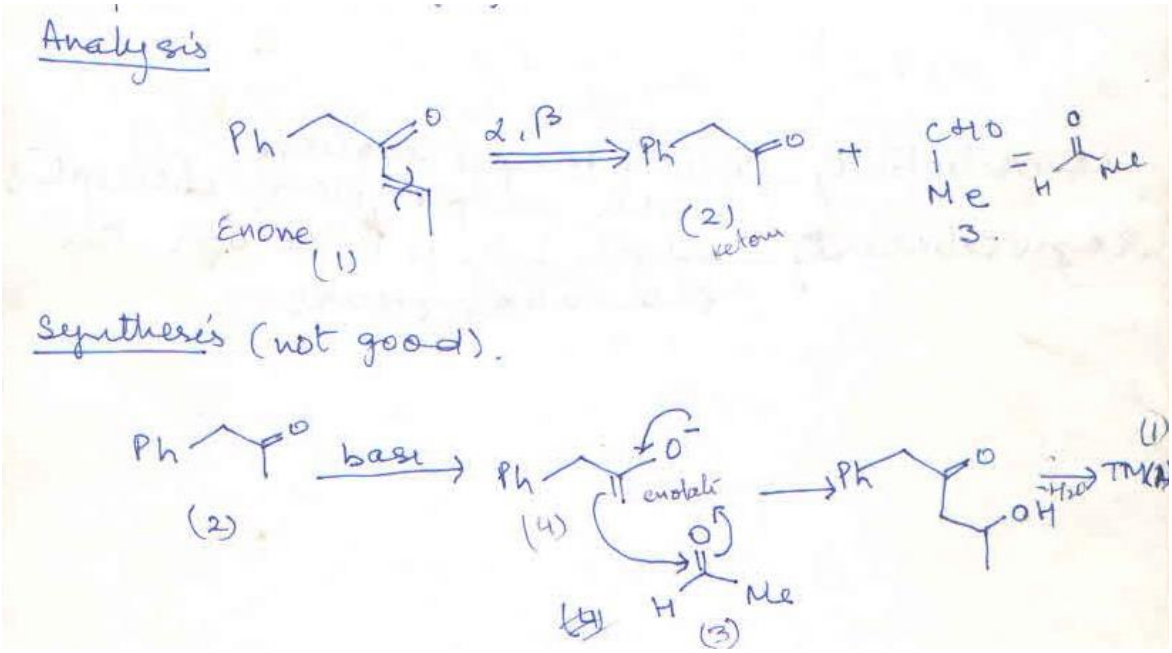
DISCONNECTION APPROACH

CONTROL IN CARBONYL CONDENSATION

The reaction on carbonyl chemistry is so important that it is worth while learning some methods to control both types of selectivity- chemoselectivity and regioselectivity.

All the chief difficulties crop up in the synthesis of enone (I)

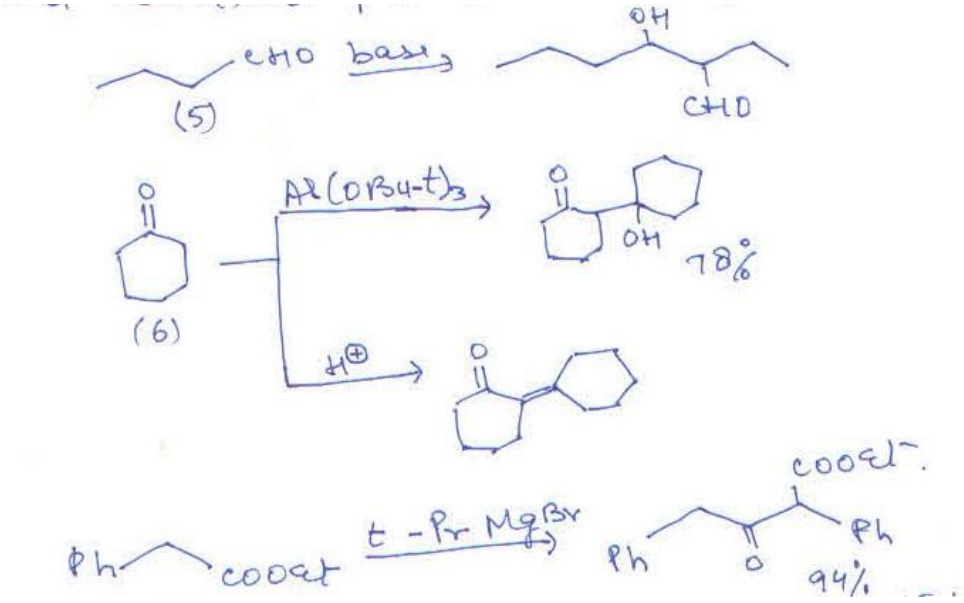


The analysis is very simple but when we come to the synthesis it is not as simple. We want ketone (2)to enolise, but why should'nt aldehyde (3) enolise too. We want (2) on the methyl side to give (4) but benzyl side might be preferred. We want the enolate (4) to attack the aldehyde but might it not also attack another molecule of (2).

For an unambiguous condensation , there must be no doubt as to which compound enolises, which compound act as an electrofile (chemoselectivity) nor any doubt about on which side of the C=O group the enolisation occurs (regioselectivity).The following are some methods to control both types of selectivity.

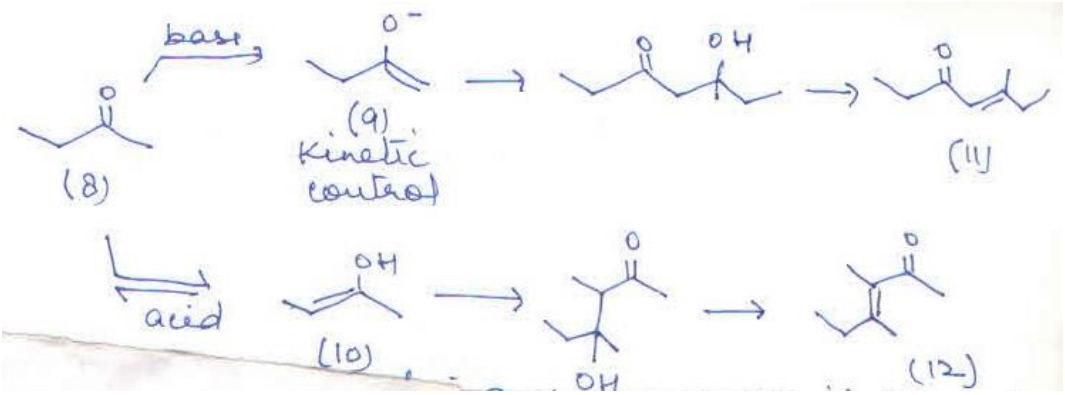
Self Condensation

The problem of chemoselectivity can be avoided if the two compounds are the same. The following aldehyde (5) , symmetrical ketone (6) and an ester (7) all provide unambiguous egs.



. (7)

Unsymmetrical ketones retain the question of regioselectivity in enolisation. Some selectivity can be achieved by varying the conditions. In base kinetic control ensures that the more acidic proton , usually on the less substituted carbon atom is removed eg.(8) gives (9). In acid rapid equilibration between ketone and enol means that the more stable enol , usually the more heavily substituted enol is formed eg.(10). Hence different products (11) and (12) are formed in basic and acidic conditions from ketone (8)

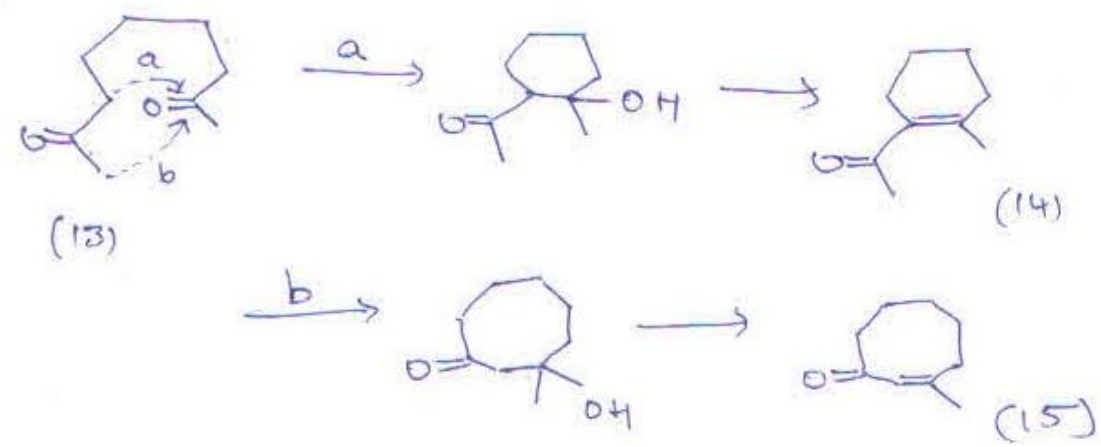


Experiment is needed in any caseto see if this method of control is adequate. Range of compound available from self condensation is limited and methods for controlling cross condensation are necessary..

Intramolecular reaction.

Although one molecule is involved in these reactions, the chemoselectivity and regioselectivity problems may still arise, but since these carbonyl condensations are reversible, a route leading to a stable five or six membered ring is thermodynamically preferred. Intramolecular reactions are therefore easier to control than the bimolecular equivalent. Cyclisation of symmetrical diketone (13) could occur in two ways (a) and (b)

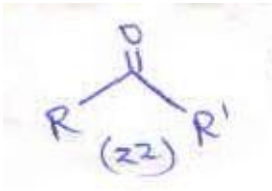
depending on which side of the ketoneenolise. In practice, in acid or base only route (a) is followed to give stable six membered (14) rather than less stable eight membered (15).



Discrimination against a small ring (3 or 4 membered) is usually effective.

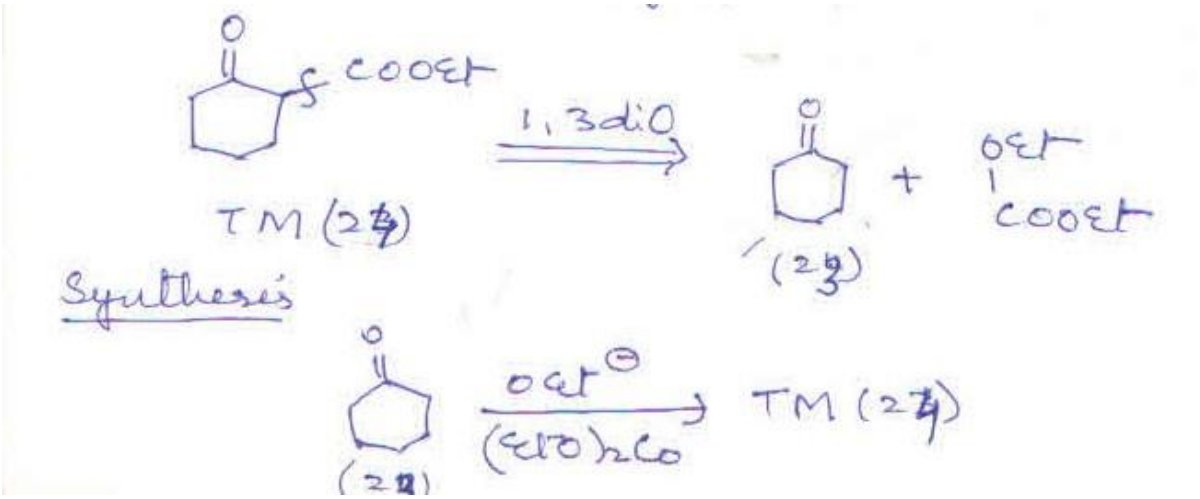
Cross condensation I: use of compounds which cannot enolise.

If a compound cannot enolise, it can react only as the electrophilic component in the condensation eg. (22) in which neither substituent has any α-proton.

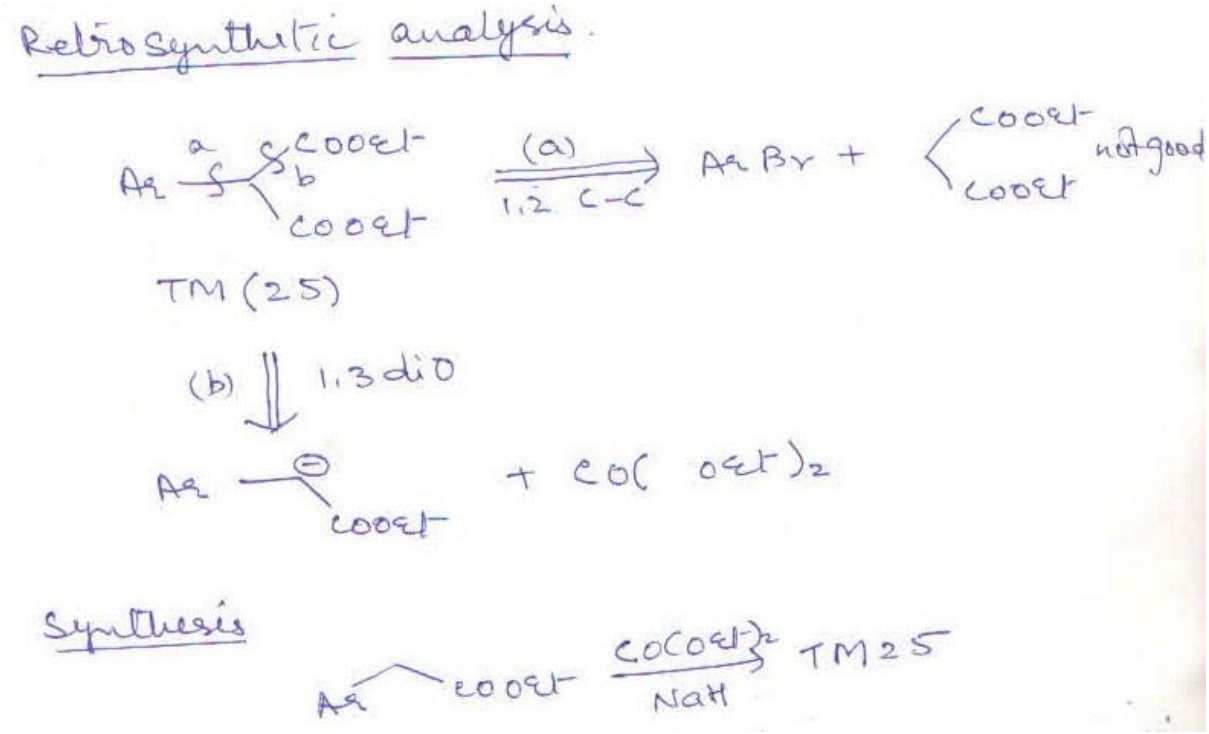


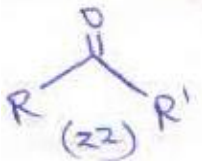
Eg. R,R′=H,OEt, Cl, Ar, t-Alkyl, COOEt

One useful case is the introduction of activating group COOEt in such compounds as (24).The disconnection requires a carbonic acid ester $CO(OEt)_2$ (diethyl carbonate)



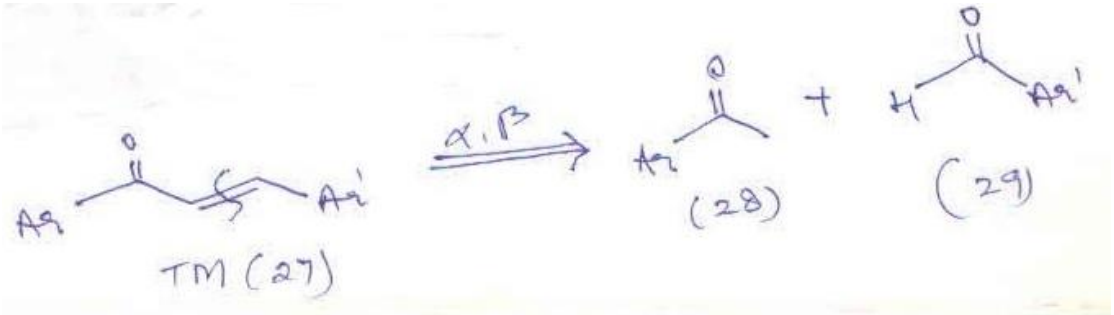
Aryl substituted malonates (25) are made in way, as the aiternative disconnection (a) requires the unreliable SN^2 reaction at an aryl halide.

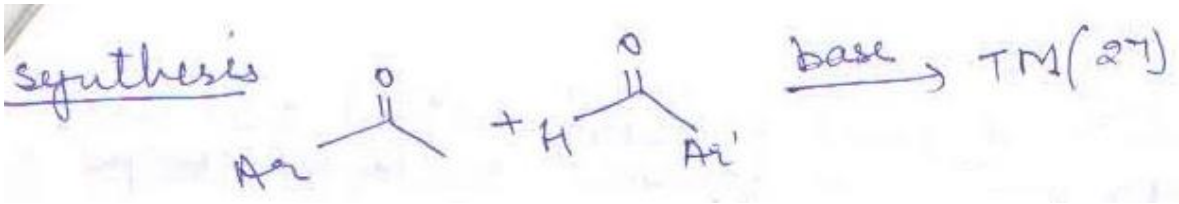




Although , the electrophiles cannot enolise, their reaction partners may also be electrophilic and may self condense . Thus the electrophilic components eg. (22) must be more electrophilic than the enol component.

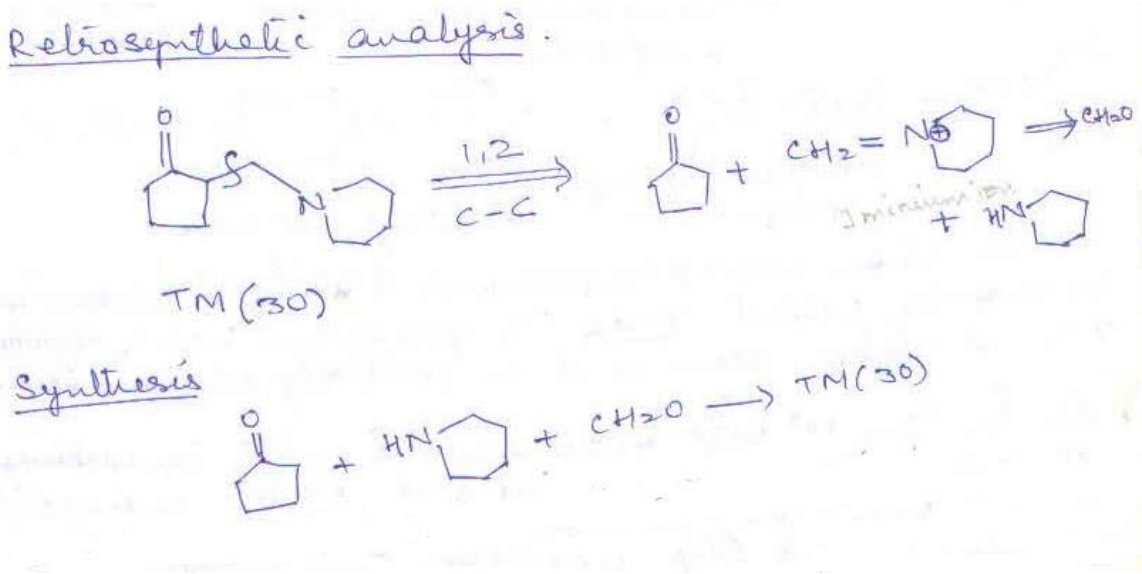
Eg. Chalcone (27) may be synthesized by the obvious route from (28) and (29) as only (28) can enolise and aldehyde (29) is more electrophilic than ketone (28).





Formaldehyde : The Mannich reaction

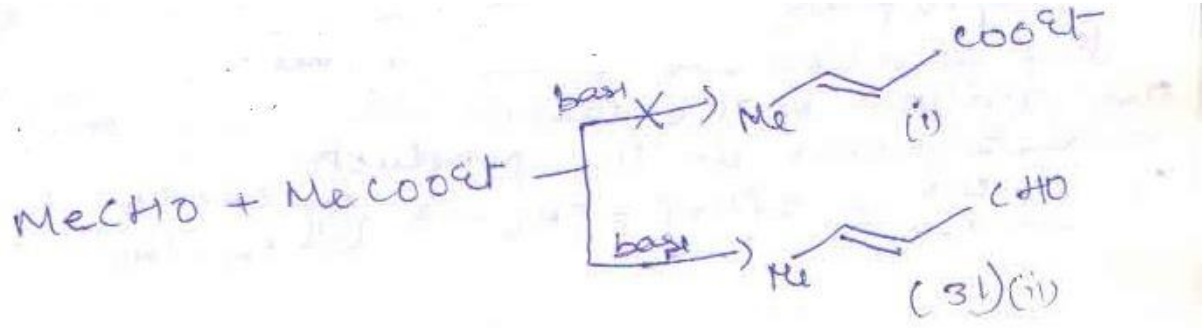
Let us plan a synthesis of Mannich base (30) involving the Mannich reaction.



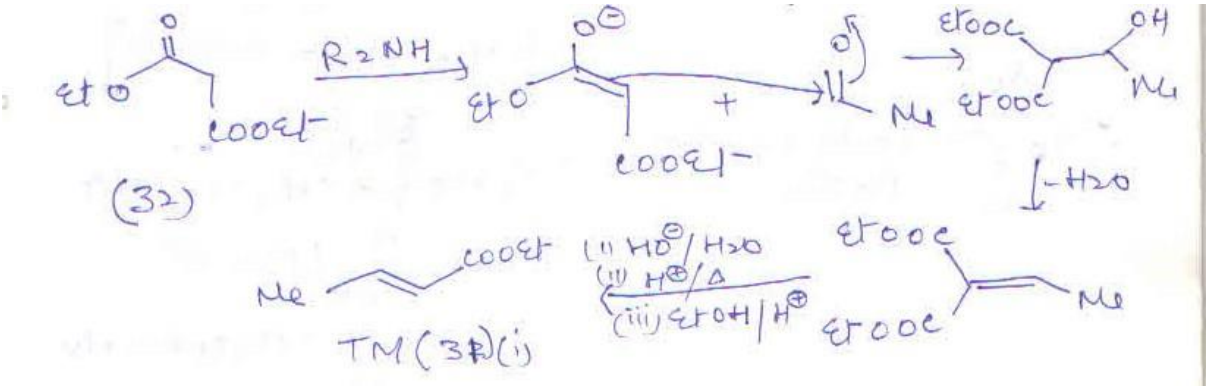
Cross Condensation II: Use of specific Enol Equivalent

Activating groups

The regioselective alkylation of ketone can be carried out by inyroducing an activating group usually COOEt, at the position we wish to be enolised. The same method can be used for carbonyl condensation . Condensation of the enol of an ester with an aldehyde as electrophile will not normally work as the aldehyde is more reactive in both senses and condenses with itself to give (31).



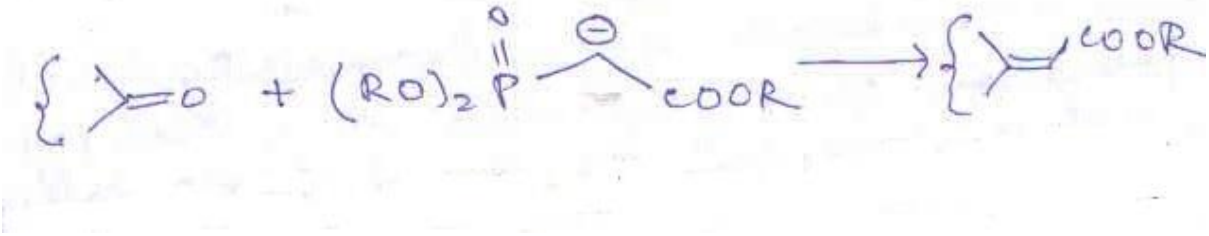
If the ester is replaced by malonate (32) the specific enol equivalent, the condensation works well. Malonate (32)enolises completely under the reaction conditions while the aldehyde is only slightly enolised and the most electrophilic carbonyl group id still the aldehyde. This is known as Knoevenagel reaction.



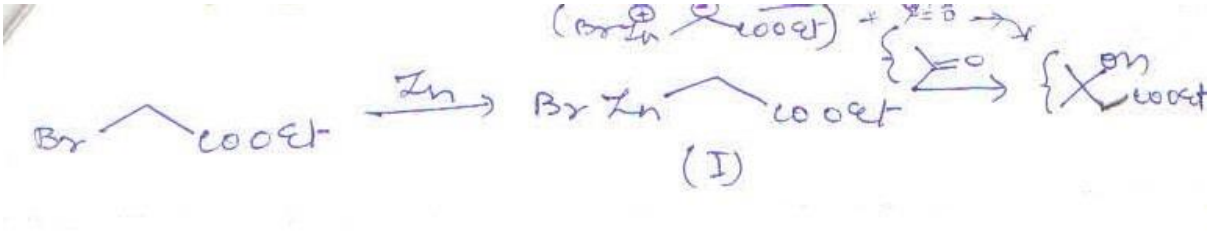
Any combination of two carbonyl group or similar anion-stabilising groups is suitable for this reaction.

Wittig and Reformatsky reagents

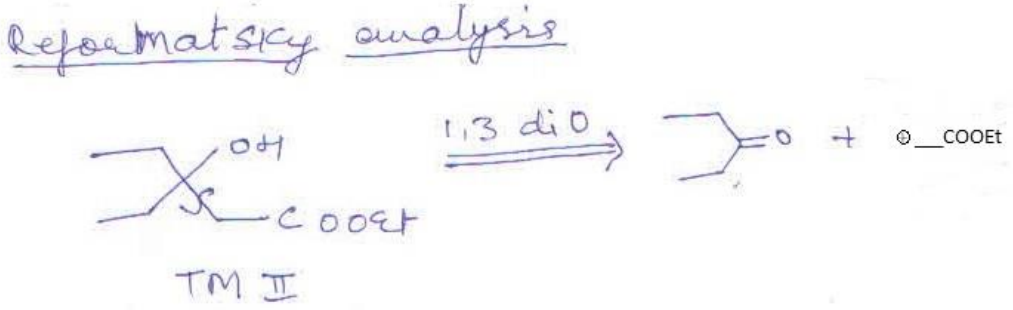
One series of specific enol equivalents is Wittig and Reformatsky reagents which may be used as :

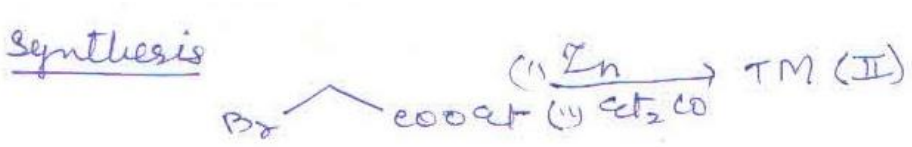


More useful alternatives for β-hydroxy compounds are organometallic reagents. Organozinc reagent (I) react with aldehyde and ketones (Reformatsky reaction) but not with esters so they can be made from α- halo esters.



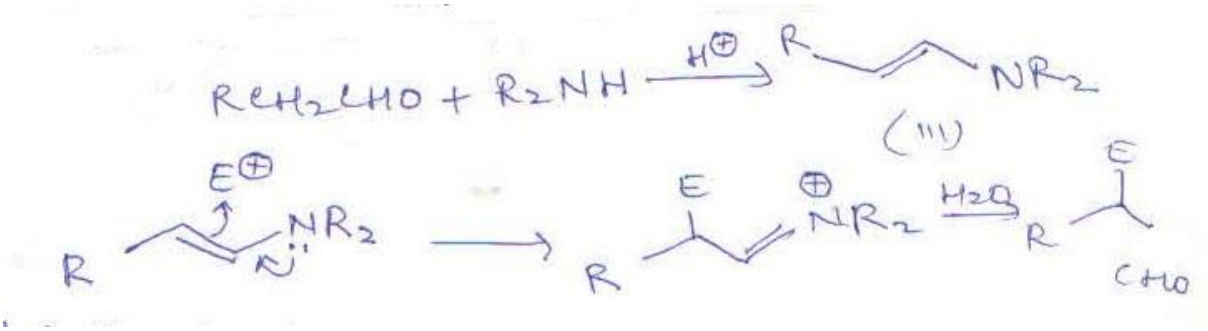
The synthesis of the alcohol (II) gives good yield by the Reformatsky reaction.



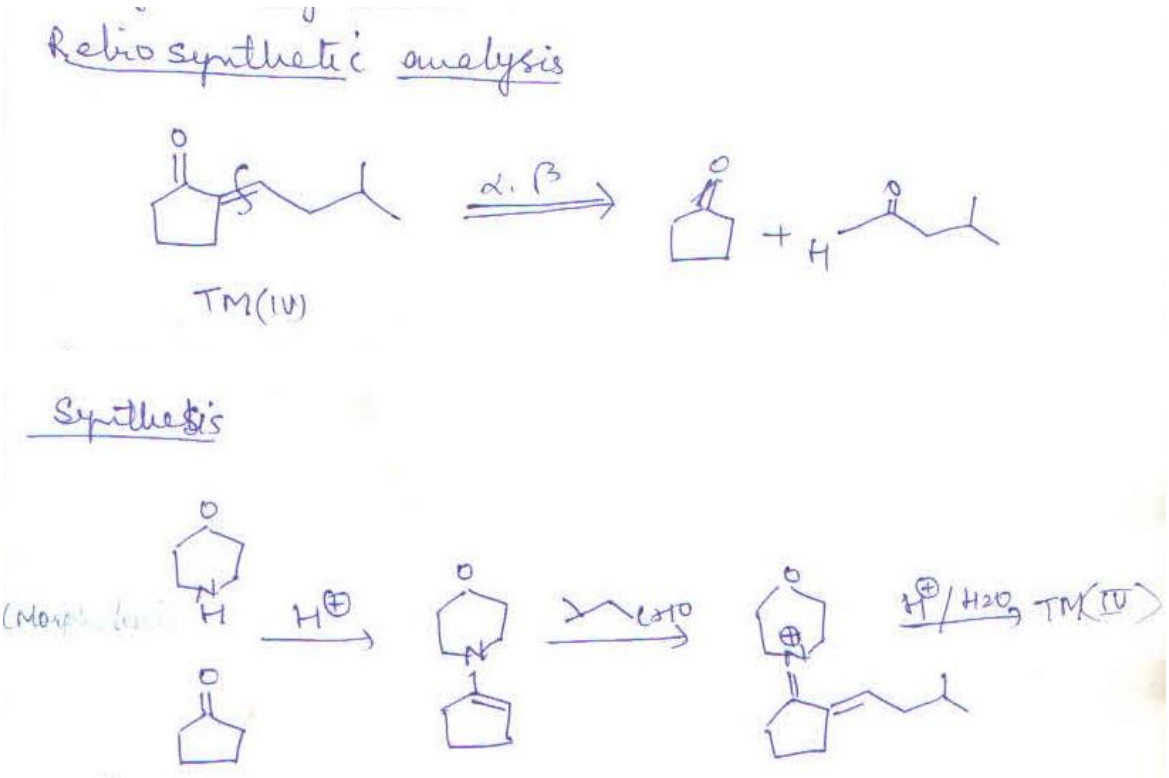


Enamines

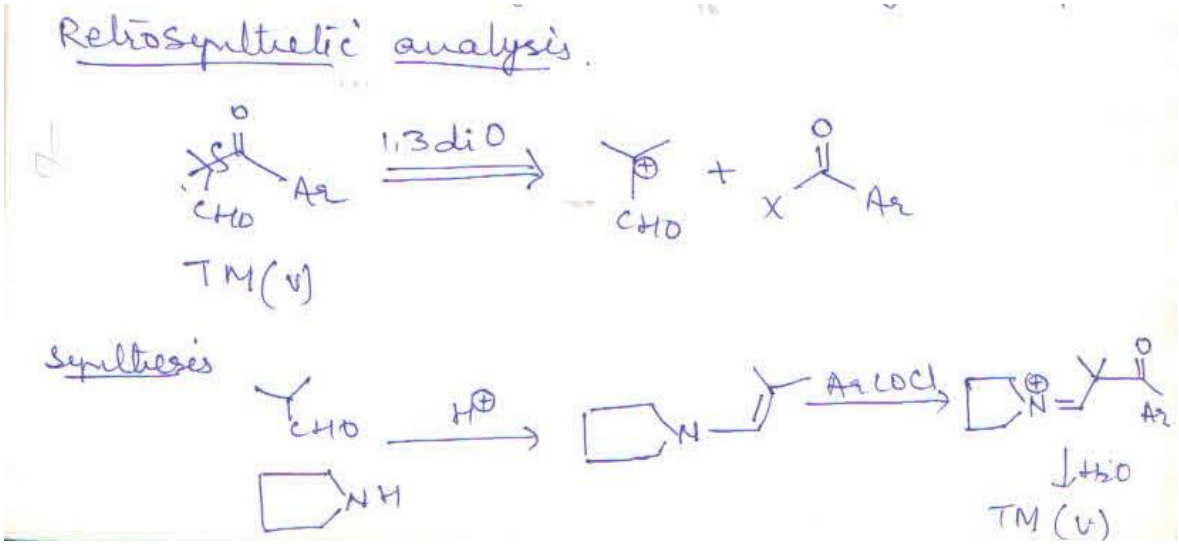
The best specific enol equivalents for aldehyde are enamines (III) and these are also very useful for ketones. They are easily made from the carbonyl compound and a secondary amine, are stable, isolable compounds and react in the same way as enols.



Retrosynthetic analysis of enone (IV) reveals a condensation between an aldehyde and the enol of less reactive ketone, easily achieved by first making the enamines of the ketone: the cyclic secondary amine, morphine is generally used.



Enamines can also be acylated hence used in the synthesis of 1,3 dicarbonyl compounds



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