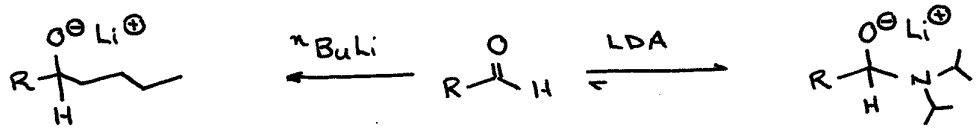
This works much better for reactive R-X such as allylic or benzylic halides, but is does not work so well with alkyl halides

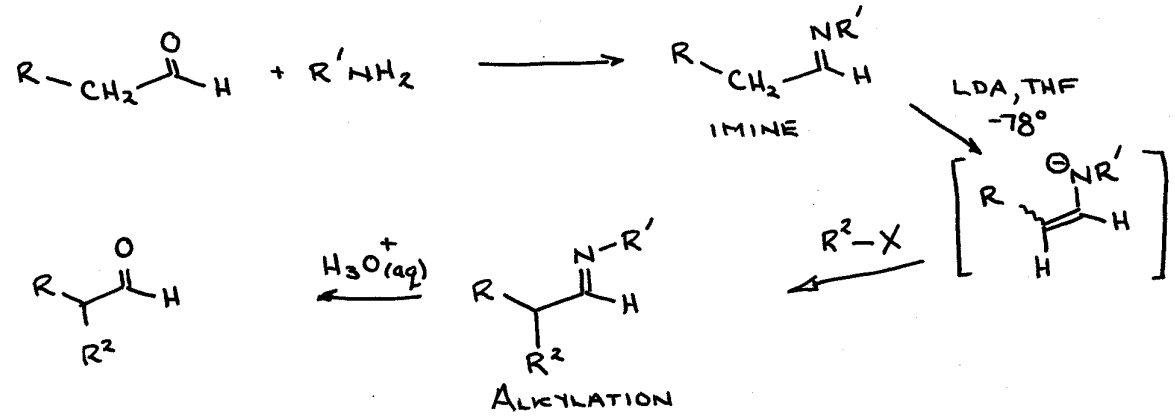
It also works with acid chlorides (to give acylation).

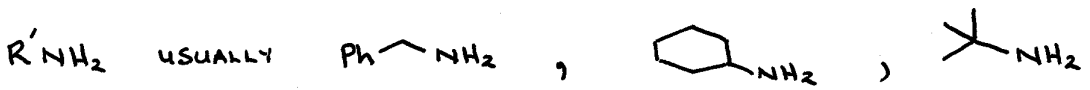
Imines (*see March 0-95, 6-14, 6-2*)

Enamines, aside from being rather limited with respect to suitable electrophiles, generally don't work as enolate equivalents for aldehydes, primarily because N-alkylation tends to occur in these cases. Aldehyde alkylation, in fact is a problem in most cases, since strong bases such as LDA and *n*-BuLi tend to attack the aldehyde carbonyl, rather than deprotonate them.



A very practical solution to this problem is to convert the aldehyde to an imine. This is a simple conversion, and the imines are reasonably stable as long as the R group on nitrogen is fairly large (benzyl, cyclohexyl, *tert*-butyl, etc.). The imine function is *less* susceptible to nucleophilic attack, and the α-protons are still fairly acidic. As a result, a base such as LDA can deprotonate these sites quite easily, and alkylation of these anions (they are often called *azaenolates*) occurs readily. The imine function can then be hydrolyzed back to the aldehyde by aqueous acid. The overall result is α-alkylation of the aldehyde.

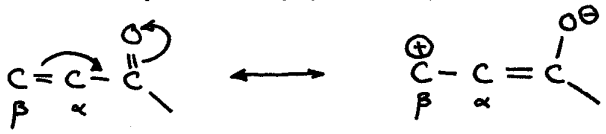




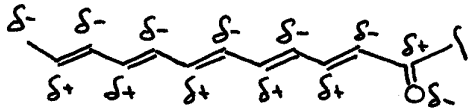
Note: Many other C=N function groups, such as hydrazones and oxime ethers, also can be alkylated similarly.

Conjugate Additions (Michael Reaction) *(March 5-17)*

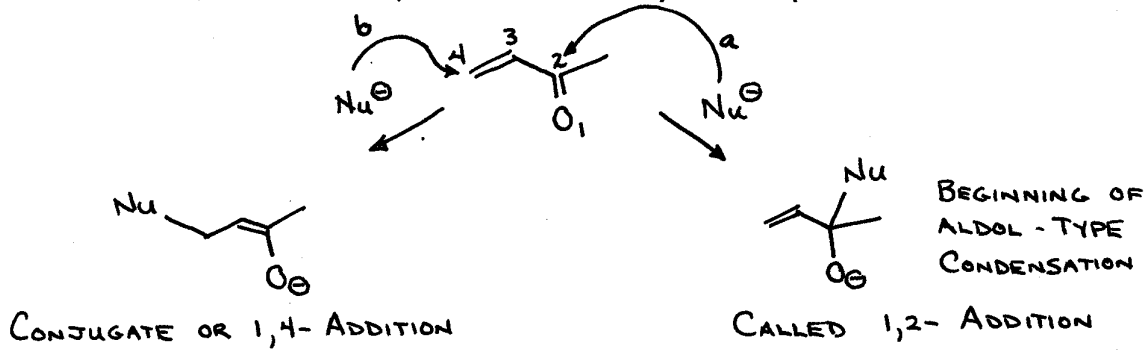
So far, the electrophilic (δ^+ C) centres we have looked at for C-C bond formation have been restricted to carbonyl functions (C=O) and alkyl halides/pseudohalides (C-X). Consider, however, an α,β-unsaturated carbonyl {C=C-C(O)} and its possible resonance forms.



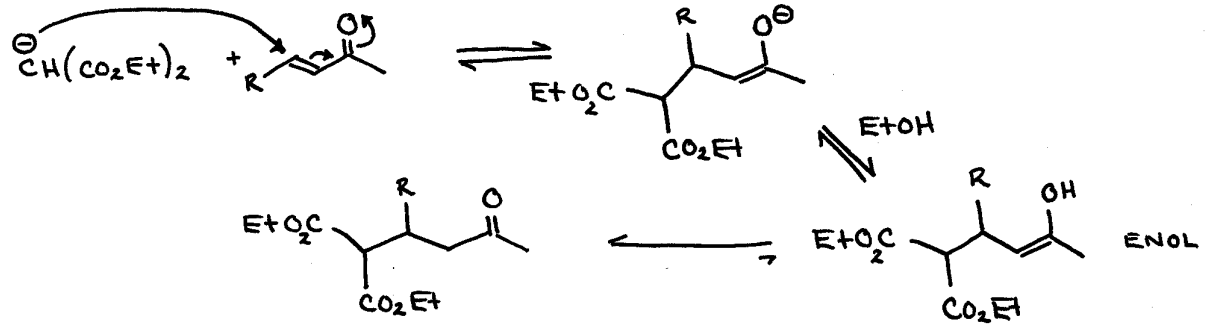
Clearly, if you believe this, the β-carbon atoms in systems of this type should be electrophilic, and this is certainly the case. In fact, if one has a carbonyl compound with even highly extended conjugation, every alternate carbon is either δ^+ or δ^-.



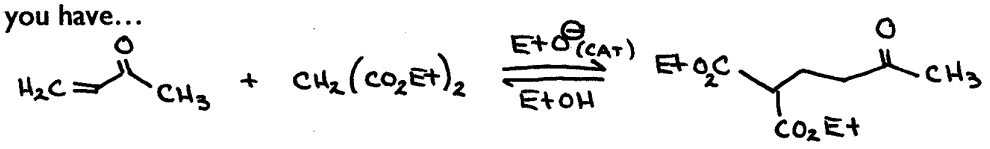
Therefore, attack on an α,β-unsaturated carbonyl has two possibilities....



If this latter, 1,4-mode of addition is followed, and the nucleophile is an enolate, the reaction is called a **Michael reaction** (or Michael addition). The prototypical Michael reaction is...



Note here that all the steps of this reaction, and therefore the total reaction, is reversible. Overall you have...

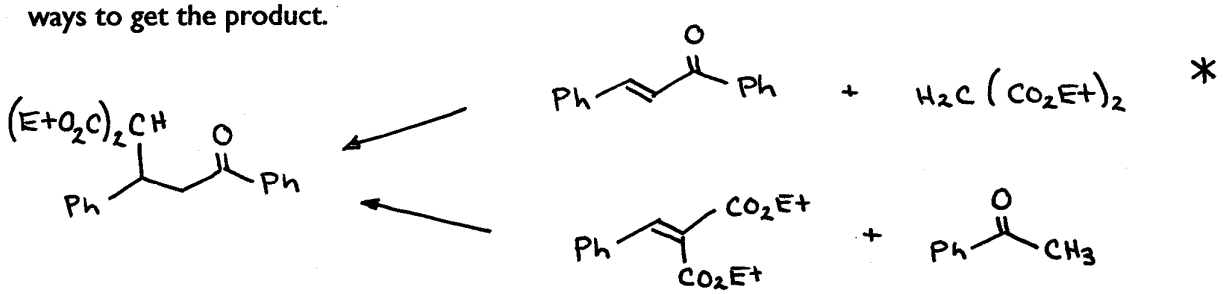


Since the Michael reaction is reversible, and the aldol condensations (after loss of H_2O) is irreversible, and since the Michael and aldol are always in potential competition in these systems, you must chose reaction conditions carefully to get what you want.

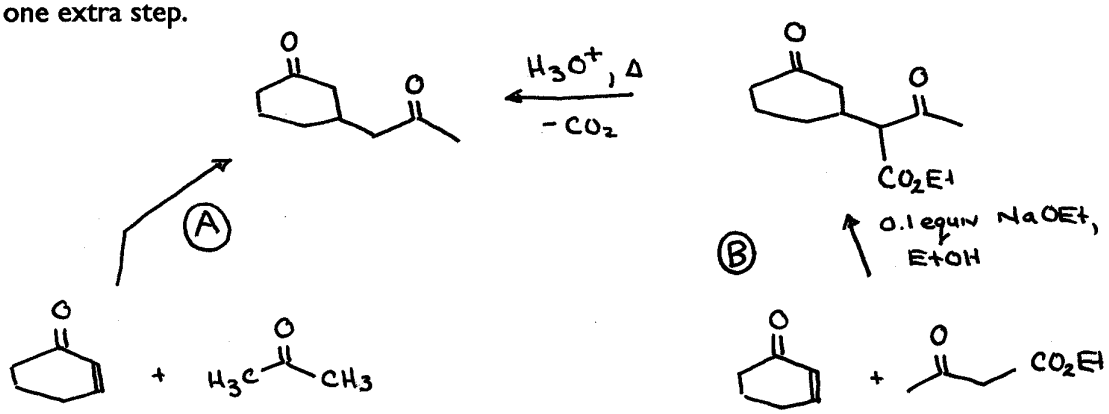
If the reaction is run in a way that forces the elimination of water (i.e., excess base, reaction at reflux), you'll always get the aldol product. (This version is called the Knoevenagel reaction)

To get the Michael product, it is best to use a catalytic amount of base, and ambient temperatures.

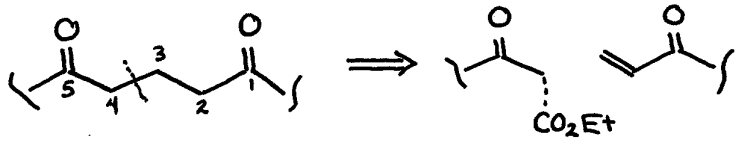
Furthermore, if one considers the Michael reaction products, there are always two possible ways to get the product.



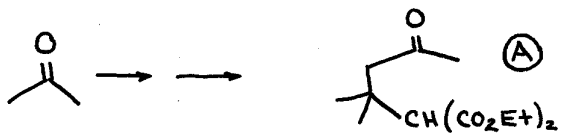
The best route of the two is the one that employs the **most acidic** compound for the original carbanion source. The corollary of this is that the Michael reaction works best for **doubly activated anions** (i.e. malonic esters, β-keto esters). So if you consider the following possible routes to the indicated target compound, route **B** is usually better than route **A**, even though there is one extra step.



Notes: Since we wish to think retrosynthetically, the fingerprint for a Michael reaction is a 1,5-dicarbonyl.

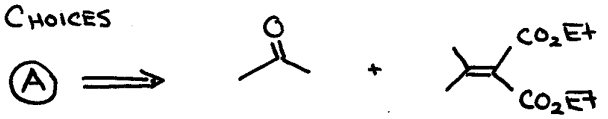


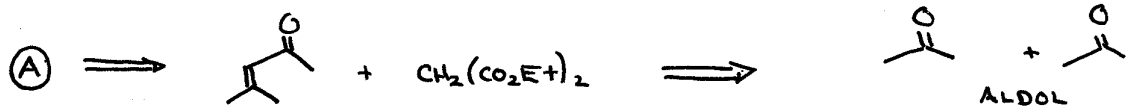
Also note, that the aldol reaction produces an α,β-unsaturated carbonyl, and the Michael reaction uses it. Therefore, there are many, many cases where these two reactions are used in tandem in a synthetic route. Consider the following examples…

1) 

START BY LOOKING AT PRODUCT
1,5- DICARBONYL ∴ MICHAEL RXN

CHOICES

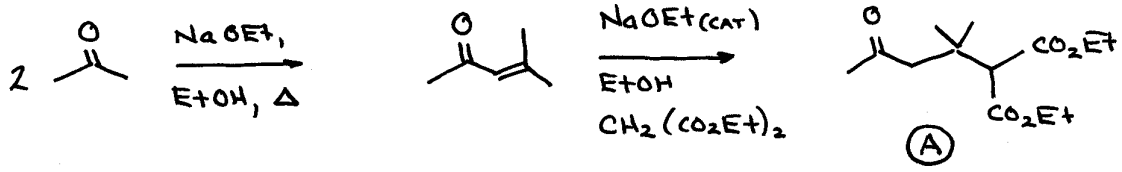


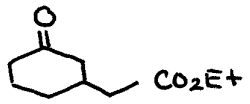


ALDOL

THIS LOOKS BETTER

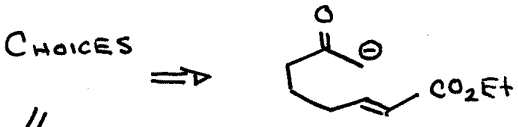
THEREFORE :



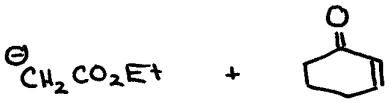
2) 

AGAIN, MICHEAL

CHOICES

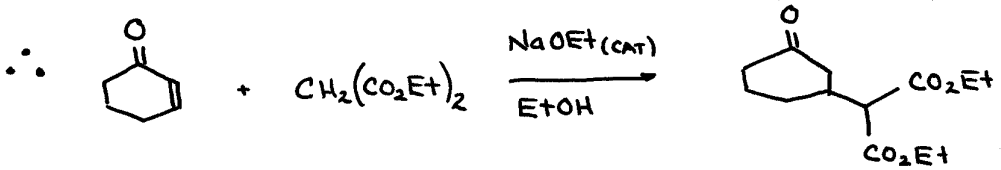


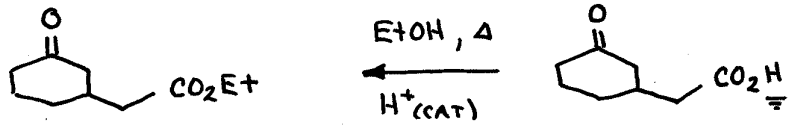
NOT VERY GOOD
- NOT MUCH SIMPLIFICATION

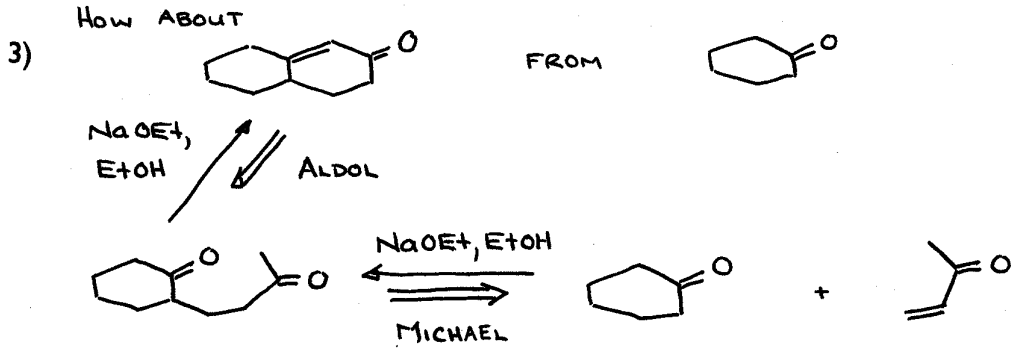


NOT GREAT, BUT ....

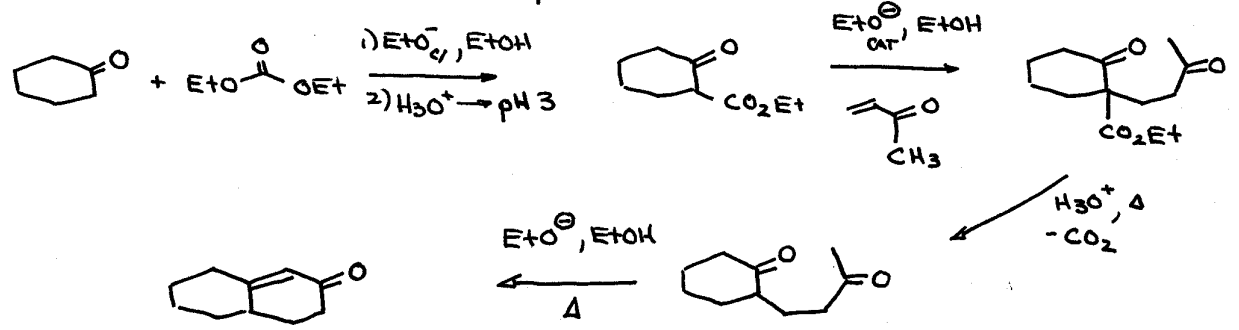
USE $^{\ominus}CH(CO_2Et)_2$ INSTEAD OF $^{\ominus}CH_2CO_2Et$

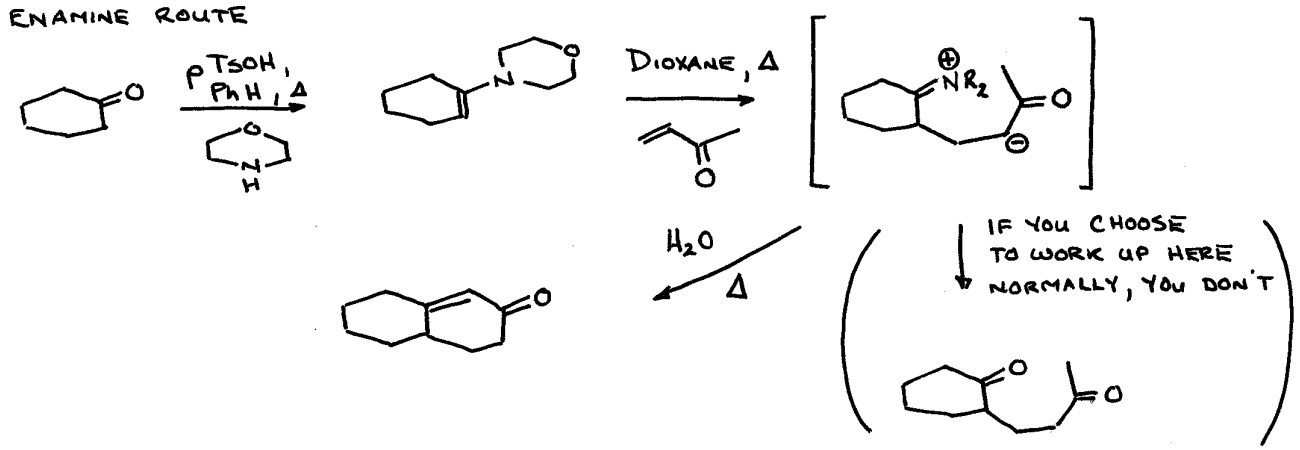






This tandem use of a Michael reaction, followed by an aldol condensation, to fuse a cyclohexanone ring system on to an existing unit is a well known strategy, and is called the **Robinson Ring Annulation** (or Annellation). As drawn, the reaction does work, but yields are low. Alternatives which gives better yields involves using the β-keto ester as an intermediate, or to use an enamine to do the Michael reaction portion.





This will suffice for now for base induced C-C bond forming reactions. We have overly focussed on carbonyl compounds; other sources as C^- exist, such as nitro compounds (see the *Henry reaction*), terminal alkynes, or cyanide ion. You may wish to try some of these in reactions with, say aldehyde electrophiles, and see what you get.