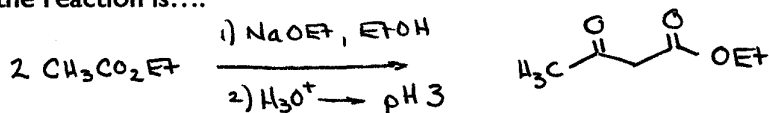happens if the reaction is made too acidic. The product is a β-**keto ester**, a class of very useful compounds. In any event, a β-keto ester is the fingerprint for this reaction type. Overall, therefore, the reaction is....

$$2 \; CH_3CO_2Et \quad \xrightarrow[\text{2) } H_3O^+ \longrightarrow \text{ pH 3}]{\text{1) } NaOEt, \; EtOH} \quad H_3C \overset{O}{\overset{\|}{C}} \diagdown \overset{O}{\overset{\|}{C}} \diagdown OEt$$
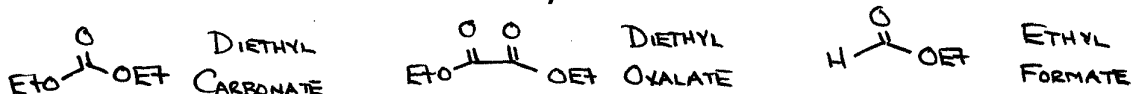
This reaction is called the **Claisen condensation**. (Note, there is also a reaction called a Claisen rearrangement, which is a very different reaction.)

One of the minor but worthwhile points to note is that the nature of the base and the nature of the esters involved are normally matched in the Claisen condensation (i.e., EtO⁻ with ethyl esters, MeO⁻ with methyl esters, etc.). The reason for this is that if the base can cause transesterification if the wrong alkoxide is employed. The exception to this is t-butoxide ((H₃C)₃C-O⁻); the base is bulky enough that it is not very nucleophilic. As a result, t-butoxide can be used with a wide variety of esters in Claisen condensation.

Claisen condensations between ketones and esters can be done. In these reaction, the ketone is acidic (and ultimately nucleophilic) component, and the ester is the electrophilic component. A stronger base is normally employed here (i.e., NaH, NaNH₂), but this is a minor point.
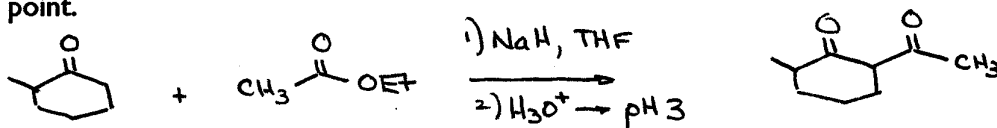
Note: The following compounds are useful electrophiles in Claisen condensations. Try the reaction of each of these with the anion of cyclohexanone.


NOTE: NO ACIDIC H'S

The Claisen condensation is a good example of something encountered many times in carbonyl chemistry; that many types of reactions with different names are really aldol-type reactions with a different electrophilic centre, or a different way of losing the "-" charge. For example....

Darzens' Condensation

A Darzens' condensation (sometimes called a Darzens' glycidic ester condensation) uses α-halocarbonyl compounds, most particularly ethyl chloroacetate. The chloro function here is quite critical, as it is a -I group, so it increases the acidity of the α-protons to a point where they are at least as acidic as a ketone. So in the presence of a base (usually t-butoxide) and an aldehyde or ketone......
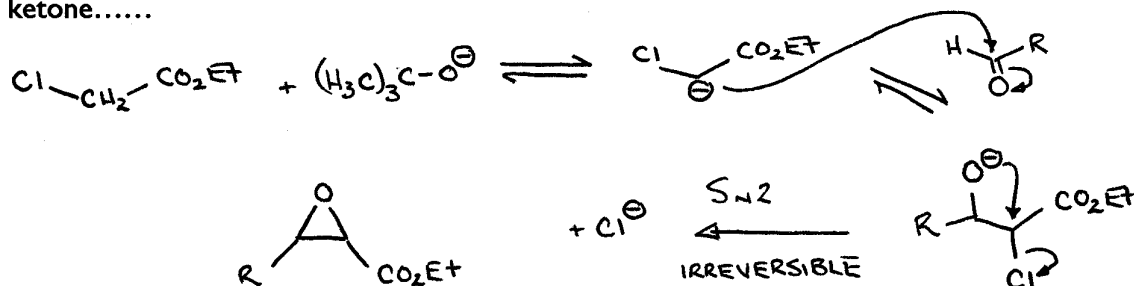
The key here is that the S_N2 ring closure step is irreversible. This new ring is called an epoxide (or oxirane), but when it is attached next to an ester, it has been called a glycidic ester. These glycidic esters are particularly useful because they cleave in a very interesting way.....
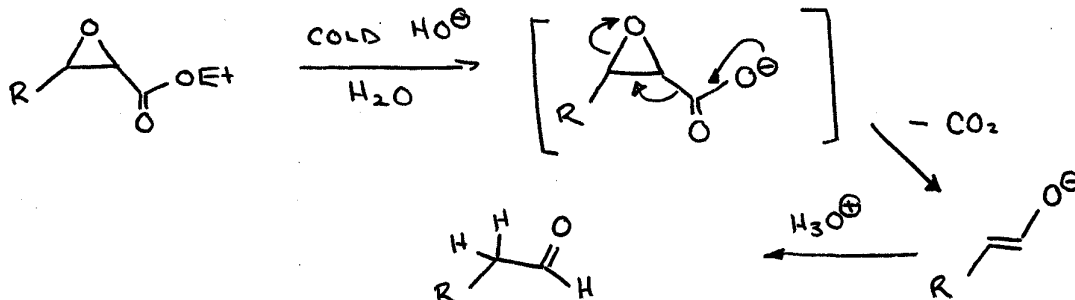
Overall, this transformation is R-CHO to R-CH$_2$-CHO; in other words, this adds one carbon to an aldehyde (or ketone). This is quite useful.

Stobbe Condensation

The Stobbe condensation is little more than an aldol type condensation where the acidic component is diethyl succinate. Once again, the second ester makes the α-protons to either ester somewhat more acidic. Due to the presence of that second ester, something slightly different also occurs with the negative charge.
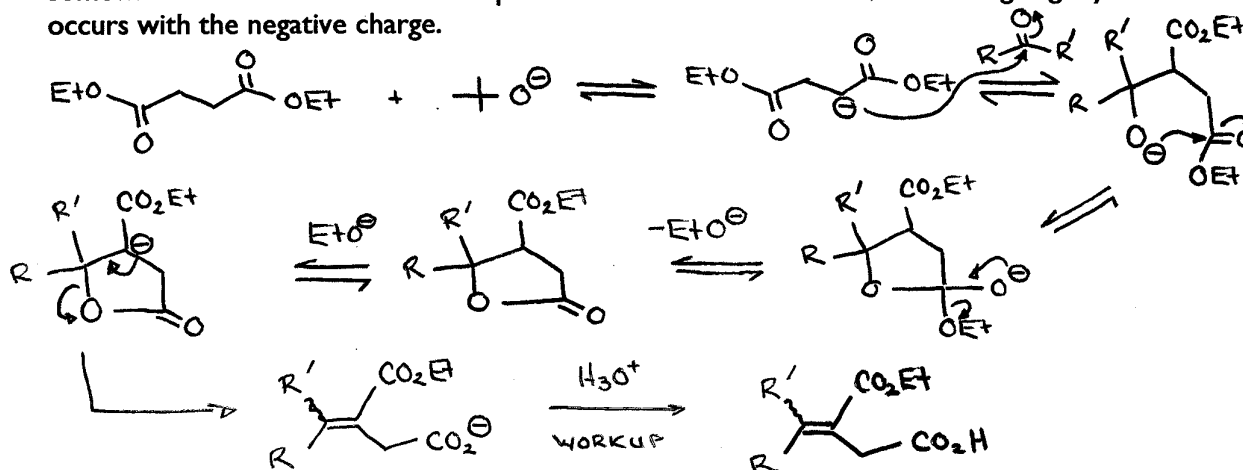

This works because it is particularly facile to form 5- and 6- membered rings. This is due to the fact that   i) 5- and 6- membered rings have little or no ring strain, and
               ii) the kinetics for forming 5- and 6- membered rings are very good

Intramolecular Reactions

So far, all the reactions between anions and carbonyl type functional groups have been between two molecules. If the two reacting moieties are in the same molecule these reactions still can go very well (in fact better in the right cases). For **reversible** reactions like the ones we have been looking at (mostly) so far, this works only (ok, that's an exaggeration...let's say by far the best) for 5- and 6- membered rings.

Let's take a molecule with two ketone functions, and look at the possibility of performing an intramolecular aldol condensation (of the base catalyzed type).
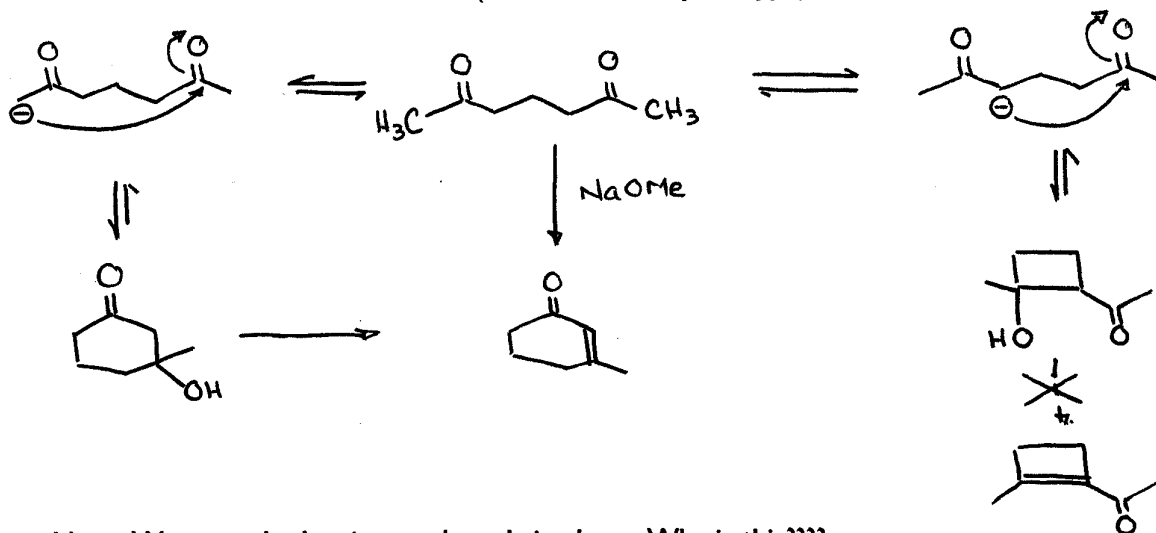
Note: We get only the six membered ring here. Why is this????

In 4- membered rings, the C-C-C bond angles must average 90°. On the other hand, the 'natural' bond angles for sp^3 hybridized carbons is 109.5°, and for sp^2 hybridized carbons it's 120°. This discrepancy results in angle strain (which costs energy). In 5- and 6- membered rings, the angles are all quite near 109°.

Now, let's look at another case with one more carbon in the chain, so the competition is between a 5- and a 7- membered ring.
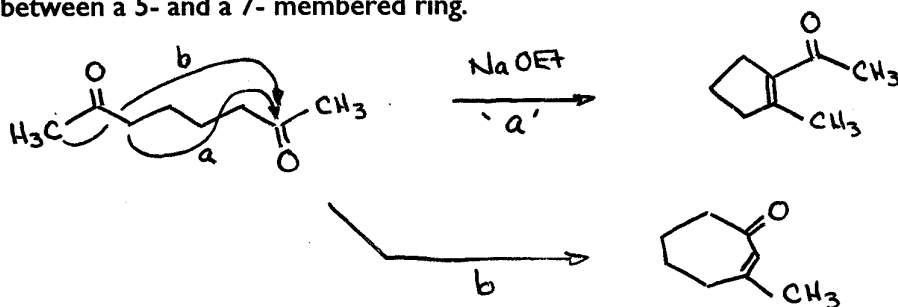
Note; We get only the five membered ring. The reason here has to do with the kinetics of the ring closing step; basically, in the seven membered ring cases, the two ends 'can't find each other'. This actually manifests itself in the entropy term ($\Delta S^{\neq}$), making it too negative in the seven membered case, so that the $\Delta G^{\neq}$ ($=\Delta H^{\neq} - T\Delta S^{\neq}$,)is less favourable. To give an idea for an unrelated reaction, here are some relative rates of ring closing reactions; as you can see 5- and 6- are best, followed by 4- (see March, p. 212). The 5-/7- ring closing rate ratios are about 1.5×10^4.

Closing of Br-$(CH_2)_n$-COO⁻ to the lactone at 50 °C

| Ring size	rate of lactone formation	Ring size	rate of lactone formation
3	21.7	6	1.7×10^4
4	5.4×10^3	7	97.3
5	1.5×10^6	8	1.00

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With esters, intramolecular reactions are also entirely possible. Once again, these work really well only for 5- and 6- membered ring forming. Oddly enough, these reactions have been given an entirely different name...they are called **Dieckmann condensations.**
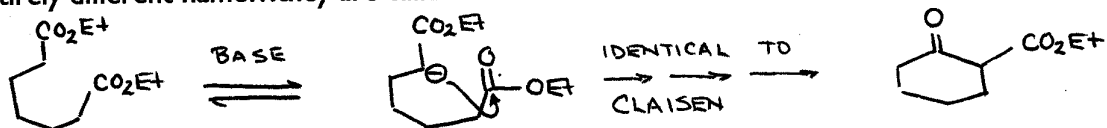
Consider the following possible aldol type condensation. Neither of these dehydrate to give the α,β-unsaturated ketone.


(A) SPIROBICYCLIC   NO!   (B) BRIDGED BICYCLIC
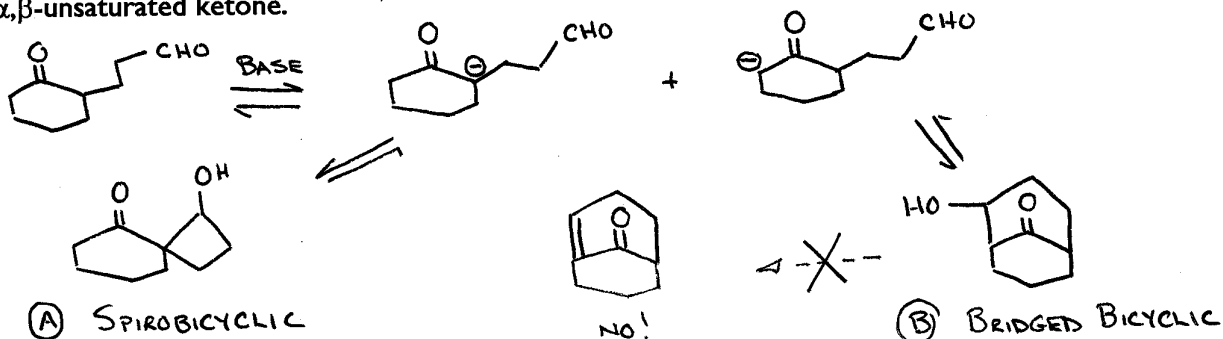
For route **A**, this doesn't dehydrate because there is no H atom α- to the carbonyl. For route **B**, there is an α- H, but the elimination is energetically prohibited. The double bond formed would be highly strained, as it is <u>very</u> difficult to get a bridgehead C=C when the largest ring is <10 membered in bridged bicyclic compounds(impossible when <8). This is a practical definition of **Bredt's Rule.**
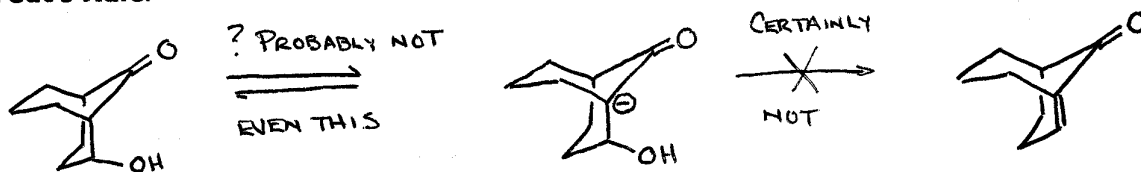
So to sum up for reversibility in aldol type reactions...unless a reaction sequence has an irreversible step, you can only get an equilibrium amount of product
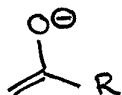Corollary: If two reactions are in competition, with one reversible, and one irreversible, you will <u>always</u> end up with the product from the irreversible one.
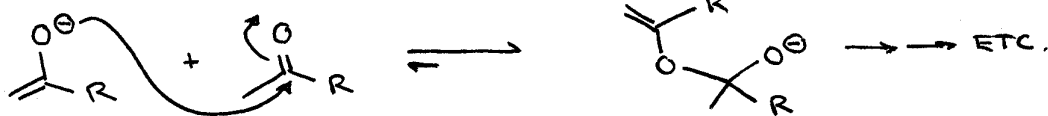For example...
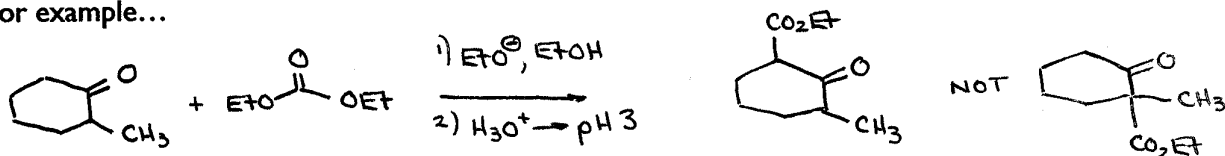
Ambident Nucleophilicity
    Recall that enolates have a structure that is better described by

So why is the following not possible?

Actually, you can do this, but this reaction is also reversible, and the product of reaction at the α- C is the thermodynamic one. We'll discuss more later about O- versus C- alkylation/acylation of enolates.

Alkylation

The electrophile in reactions of enolates does not have to be a carbonyl (C=O). One can also get reaction when then the $C^{\delta+}$ is due to a C-X bond (X= halogen, pseudohalogen).

There are several important notes about this reaction.

i)   This reaction is <u>irreversible</u>, in contrast to many of the steps of the aldol type reactions.

ii)   The mechanism is almost always S_N2. This means that for R-X, the relative reaction rates are R = methyl > 1° > 2° >> 3° (3° R-X usually give gives elimination)
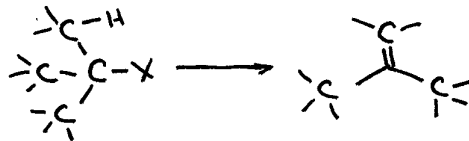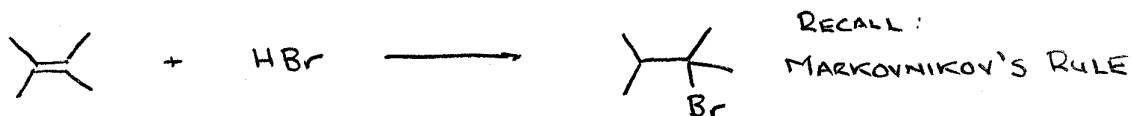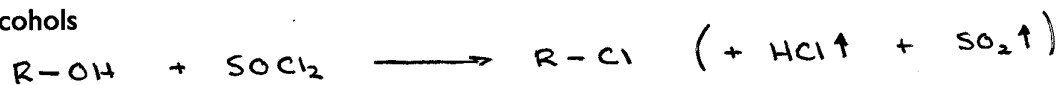
iii)   in reactivity X = I > Br > Cl >> F
        Taking into account R-X availability and stability, X = Br is usually the best compromise

iv)   vinyl and aryl halides are normally unreactive

Preparation of halides
From alcohols

$$R-OH \ + \ SOCl_2 \longrightarrow R-Cl \quad (+ \ HCl\uparrow \ + \ SO_2\uparrow)$$

$$R-OH \ + \ PBr_3 \longrightarrow R-Br \quad (+ \ P(OH)_3)$$

RECALL :
MARKOVNIKOV'S RULE

Sulphonate esters- behave like halides, but aren't actually halides. Compare these to carboxylic esters.

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