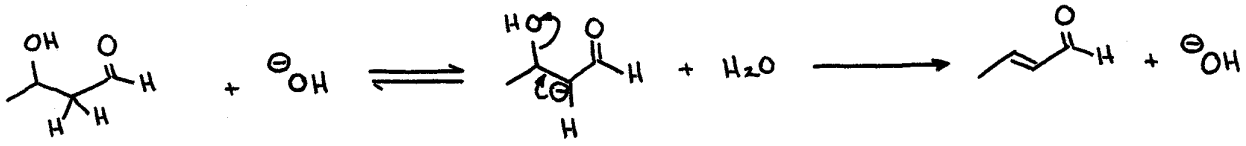
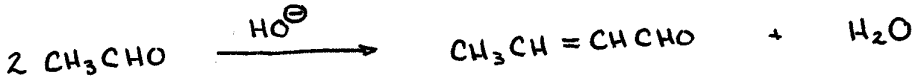
the aldol condensation by forcing an additional step, the base catalyzed elimination of water. For all intents and purposes, this step is <u>irreversible</u>.

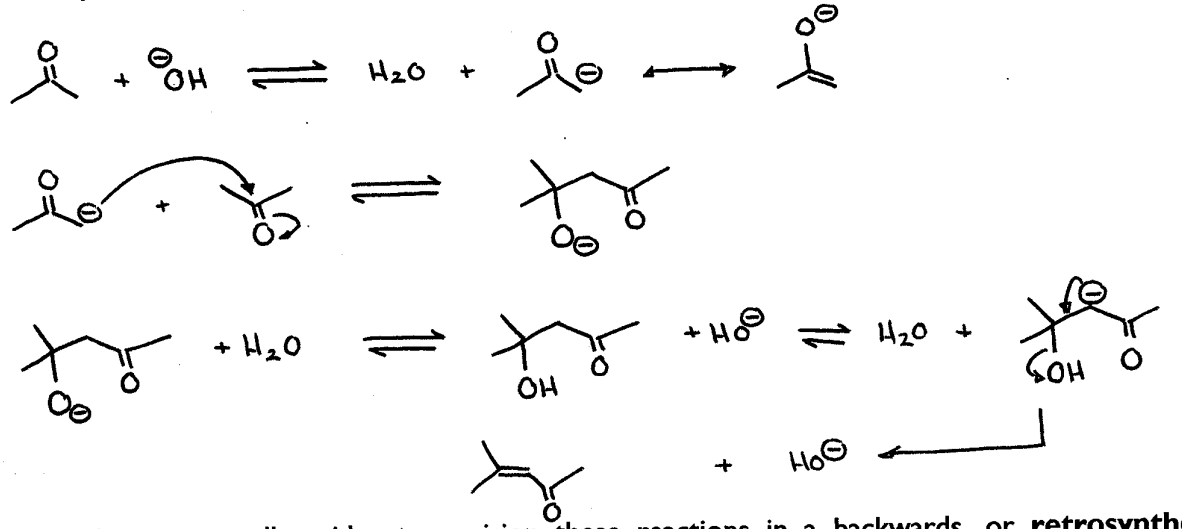


Now, the overall aldol condensation is



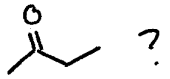
Besides, when the aldol reaction is run under its usual conditions (relatively weak bases, elevated temperatures), it is hard to avoid this elimination step anyway.

Many other carbonyl compounds will undergo this reaction , too. Consider the simplest ketone, acetone. As an aside, this is one of the cases that does not go anywhere near to completion, unless you force the water elimination step. Then the reaction is driven entirely to completion

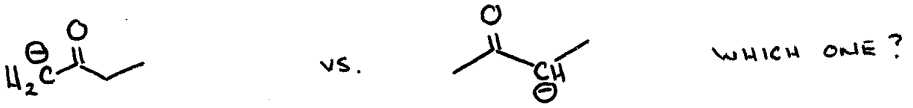


It is an excellent idea to envision these reactions in a backwards, or **retrosynthetic**, manner, so that when you see the appropriate functional in a synthetic target, you can immediately come up with the reaction to prepare it. For the thermodynamic aldol condensation....

So far we've looked at the simplest possible aldol condensations. How about if we try it on the following?



There are two possible anions



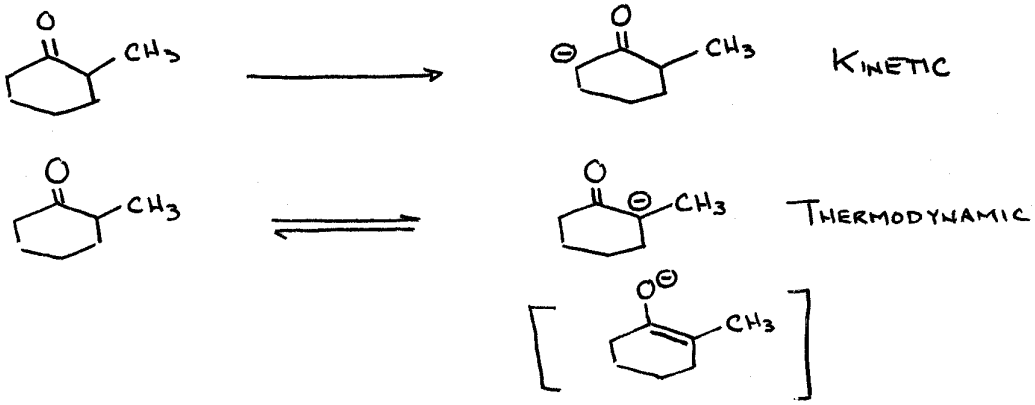
Which one we form depends on the conditions of enolate formation. Fortunately, it often (even usually) turns out that one anion is more stable, while the other is formed more rapidly.

If you can form an anion irreversibly, you will get the more rapidly formed enolate....this is step that is under **kinetic control.** In other words, the ratio of anions formed is dependent only on which one is formed faster, and *not* on their relative stability.

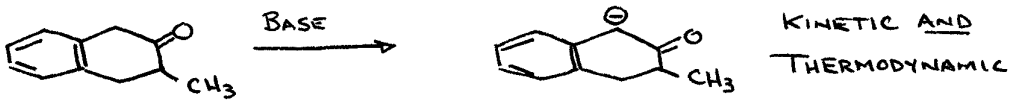
But...

If you form the enolate reversibly, the ratio of anions you obtain depends on their relative stability.....this is then **thermodynamic control.**

In general (there are, of course, some exceptions), the **kinetic** enolate is the **less substituted** of the two possible enolates. The **thermodynamic** enolate is in general the **more substituted** of the possible enolates. The reasons for this are as follows: a base which approaches the less substituted of the two sites α-to a ketone has less 'junk' (i.e., alkyl or other functional groups) to get by to abstract the proton there, so its approach is not slowed down (read faster). On the other hand enolates are really better described as the resonance forms with the negative charge on the oxygen and the C=C double bond. As you may recall from your first organic course, more substituted double bonds are stable, and the same therefore goes for enolates. So in the following case.....



Note that this is somewhat an oversimplification. In the following case, the same enolate is both kinetic and thermodynamic, due to the activating nature of the benzene ring.



So, then how do you pick conditions for the desired transformation? Consider...

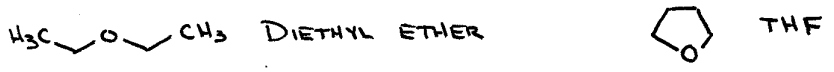
1) If the base you employ is *so* strong that the resultant Base-H^+ (conjugate acid) will not give up the H^+, you have an irreversible deprotonation, and therefore the kinetic enolate should be formed. Or..
2) If the Base-H^+ is removed from the system immediately (i.e., if it's a gas), the reverse H^+ transfer can't occur. You get the kinetic enolate here, too.

Some examples of these types of bases are...

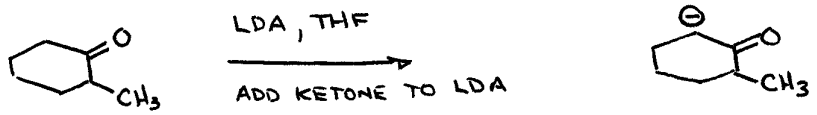
	NaH	*n*-BuLi	LDA
Criteria	1)? and 2)	1) and 2)?	1)
Base-H^+	$H_{2(g)}\uparrow$	butane (bp=0°C)	$HN(^iPr)_2$

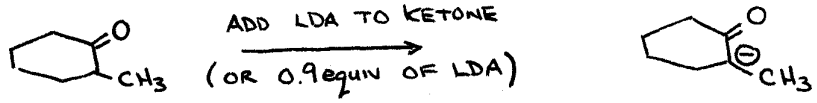
Of these three, NaH often reacts too slowly, so that it creates other problems, and *n*- BuLi is often too nucleophilic, so the base of choice here is really **LDA (lithium diisopropylamide).**

Notes: You still must be a bit careful how you use LDA as a kinetic base. First of all, any reactions must be performed in an aprotic solvent (no, OH's), since LDA will abstract them preferentially. This mistake would in fact give diisopropylamine and a lithium alkoxide (or LiOH) as products....these are each *thermodynamic* bases, so you'd really mess things up by doing this. The solvents that are recommended for use with LDA are polar but aprotic solvents; 95% of the time this ends up being either diethyl ether (Et_2O) or tetrahydrofuran (THF).



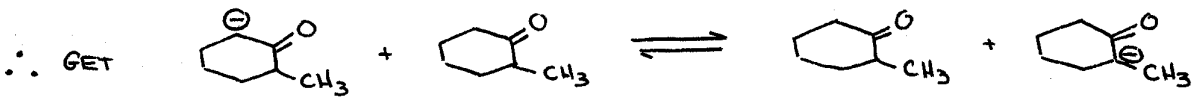
Secondly, you must be somewhat careful of how you employ a base like LDA. Consider the following set of reactions:



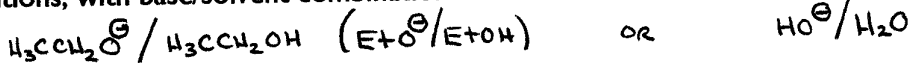


Why does the second of these deprotonations not go as planned? It is because the ketone itself is acidic , and after you added only some of the LDA, you will have the following species in solution....

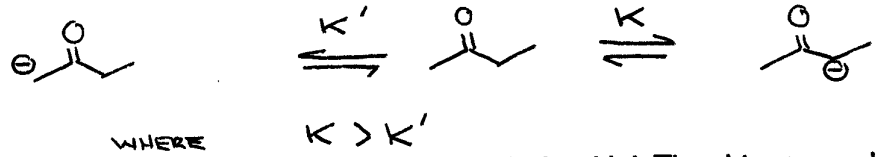
These have very close pKa's, so they will easily equilibrate among themselves. As a result, you get the thermodynamic result (the more substituted enolate).



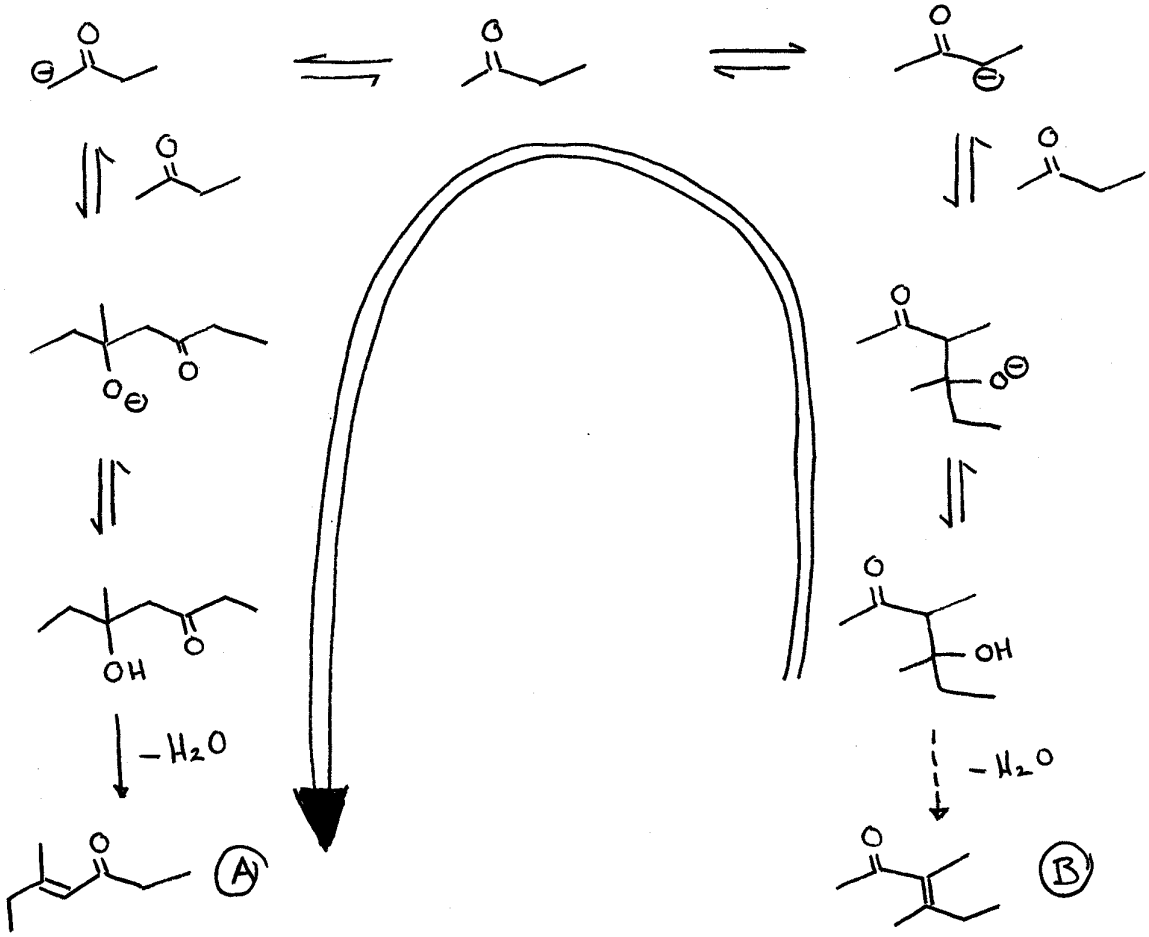
The aldol condensation, as we understand it to this point, is usually run under thermodynamic conditions, with base/solvent combinations such as...



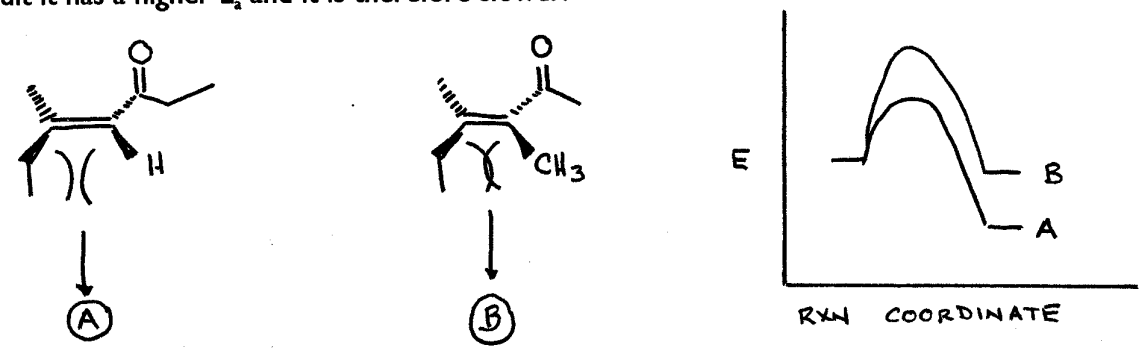
so, you expect the anion predominating in solution to be the *more* substituted one, but there will always be an equilibrium (small at any one time) concentration of the other one.



Now let's take this situation and follow it through the aldol. The ultimate product will surprise you.

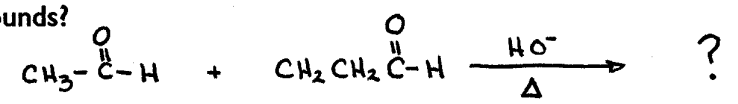


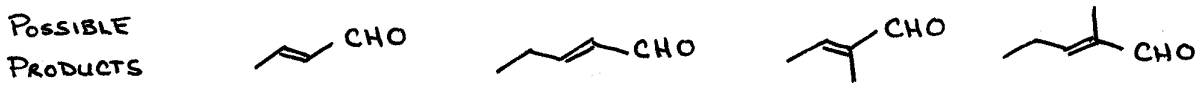
The reason for the observed result is that the last step for route **A** is much faster than the last step for route **B**. The transition state in the final irreversible, elimination step is more crowded; as a result it has a higher E_a and it is therefore slower.



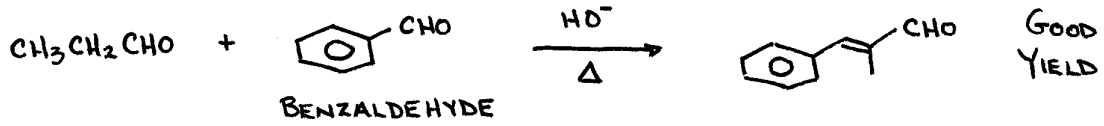
In general, the aldol condensation occurs predominantly at the least substituted side of unsymmetrical ketone.

Here's another slightly less straightforward case: what if an aldol between two different carbonyl compounds?

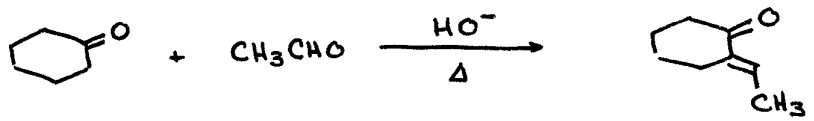




Here, there are two different possible enolates, and two potentially electrophilic centres. Thus there are four possible products. Unfortunately, you usually get all four. This is synthetically useless; in general these **crossed** or **mixed aldol** condensations are not useful *unless one of the components cannot form an anion.* An example of such a non-enolizable carbonyl compound is benzaldehyde (it has no acidic H's); this aldehyde can be used successfully in a crossed aldol.



A related question involves the aldol reaction between an aldehyde and a ketone (see below for an example). This looks bad, but in practice it works reasonably well. The product you get is the one that derives from the *anion of the ketone.*



The reason this works is similar two one we've seen before; the steric effects on the elimination step for the choice where the ketone would be acting as the electrophile make it just too slow to be competitive.