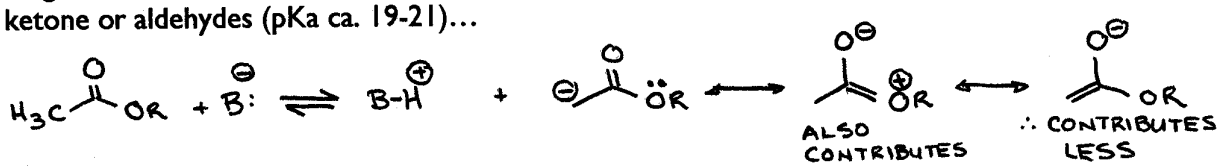
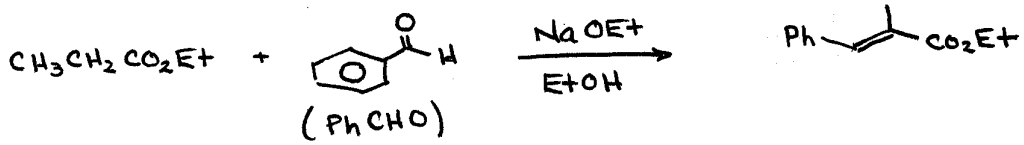
Finally, we've ignored esters. Esters can act as the acidic carbonyl source in aldol condensations, as long as one condition is met. As we've seen before that esters (pKa ca. 24-25) are less acidic than ketone or aldehydes (pKa ca. 19-21)...

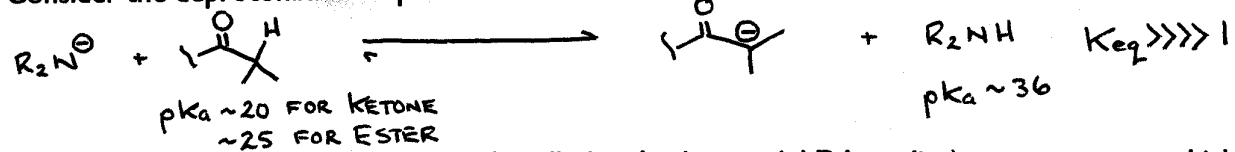


.....and as a result of this, only when the aldehyde or ketone partner is not acidic (i.e., benzaldehyde) does the aldol between the two work well (under these thermodynamic conditions). (Note: A different reaction occurs if there are acidic H's on the aldehyde or ketone. We'll look at that reaction shortly).

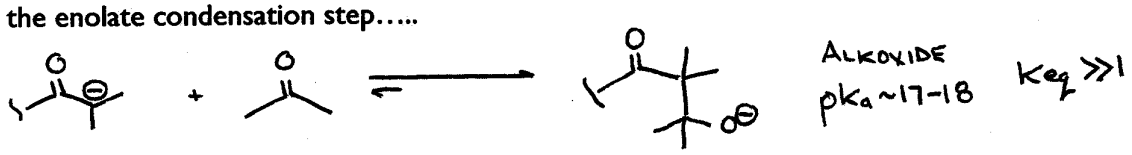


Kinetic Aldol Condensation

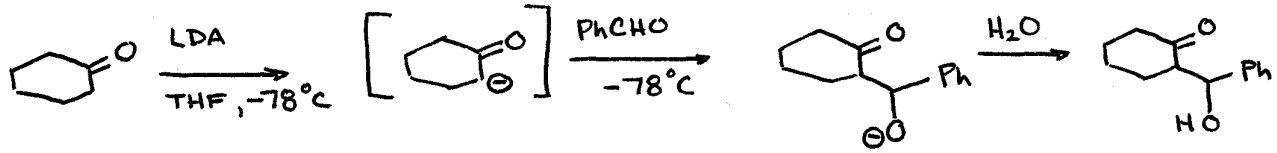
The aldol condensation we've looked at this point is sometimes called the thermodynamic or equilibrating aldol condensation. It is also possible to do the entire aldol under kinetic conditions. This kinetic aldol condensation has slightly different considerations, and a slightly different product. Consider the deprotonation step of the aldol...



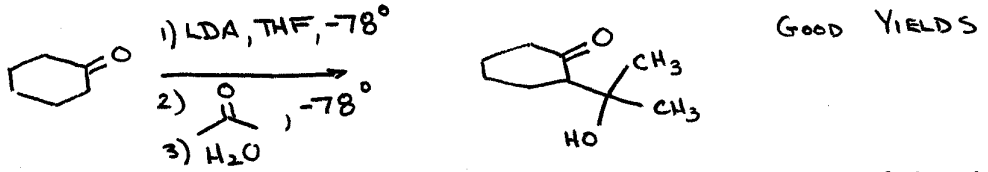
If you have a very strong base here (recall that I advocated LDA earlier), you get a very high concentration of enolate (essentially 100%) here, because this equilibrium is so far to the right. In the enolate condensation step.....



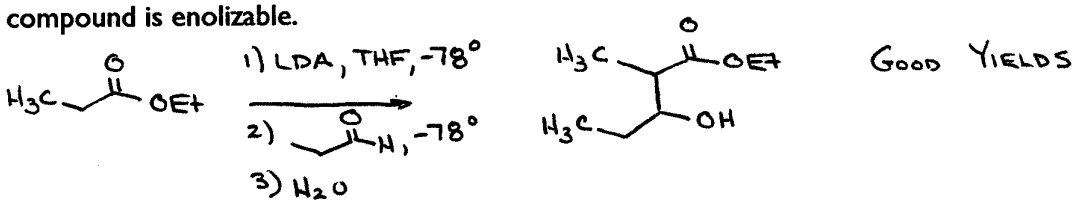
The equilibrium constant is also very far to the right. Just using the pKa's to measure this is a bit of an oversimplification, as there are other factors (sterics, relative strengths of the bond formed versus those broken), but K_{eqm} is >> 1. Given these facts, if you use an aprotic solvent (THF, Et_2O) and keep the temperature low (-78 °C is common), then the reverse reactions are slowed down so much that it is negligible and the entire reaction is kinetically controlled. At this point, the reaction is poured into water and the alkoxide is protonated to finish the reaction. In the kinetic aldol, the reaction stops at the alcohol; the elimination step does not occur. So an example of a kinetic aldol condensation is.....



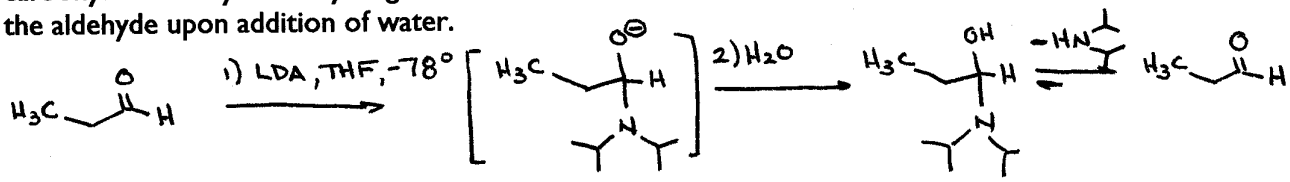
The fact that you are generating a stoichiometric amount of enolate gives you a considerable amount of flexibility in kinetic aldol condensations. Crossed aldols are now possible and quite regularly performed.....



Also, esters are quite regularly used as the enolate sources, even if the electrophilic carbonyl compound is enolizable.



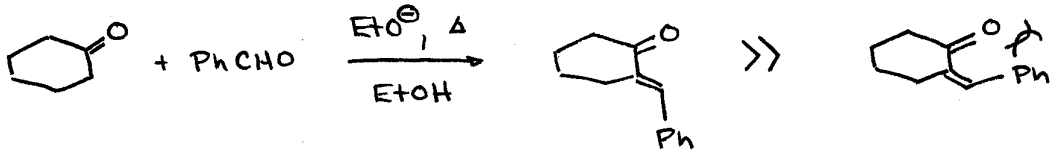
One shortcoming, however, is that aldehydes can't normally be used as the enolate source. The problem here is that the base, LDA (which is normally not very nucleophilic), attacks the aldehyde carbonyl too easily. What you get is a transient alkoxide of an N,O-acetal, which falls back apart to the aldehyde upon addition of water.



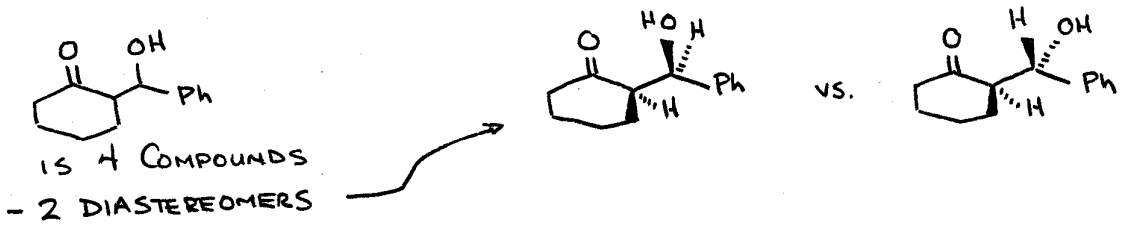
There is a way of getting around this problem; we'll look at it later.

Stereochemistry of aldol condensations

We have ignored the stereochemistry of aldol condensations to this point, but it must be addressed. Consider the base catalyzed aldol condensation between diethyl ketone (3-pentanone) and benzaldehyde. There are really two possible product isomers, which differ in their double bond stereochemistry. The product you obtained here is dictated by steric effects; although it's really a transition state phenomenon for the elimination step, it almost always work out that the thermodynamically more stable product isomer is formed.



In the kinetic aldol condensation between these same two reagents, there is a more complicated scenario. What you would obtain is really 4 compounds. We have two possible diastereomers, and each of the diastereomers can be one of two enantiomers. Since there are no reagents here which are chiral, we'll ignore the question of enantiomers here (although this is an interesting topic for a more advanced course) and focus on the two diastereomers.

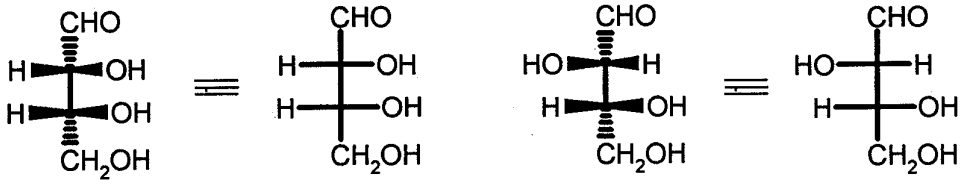


This brings up a question which has been glossed over in previous courses; what do you call these diastereomers?

A PRIMER ON DIASTEREOMER NOMENCLATURE

When there are two chiral centres in a molecule, there are two different relationships possible between them. These two compounds are diastereomers, with different (but often similar) physical properties. It is quite correct to use the Cahn-Ingold-Prelog system to define each centre as R or S. It is not used all that often, however, when defining the relationship of the two (or more) centres.

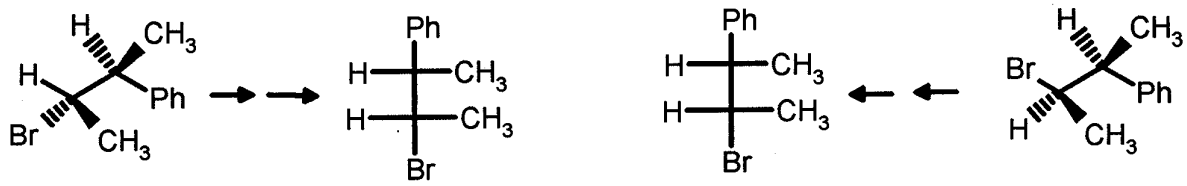
Historically, the way to define this stereochemical relationship was based on carbohydrate



D-erythrose D-threose

chemistry, and in particular, erythrose and threose. the following are the Fischer projections of these two molecules.

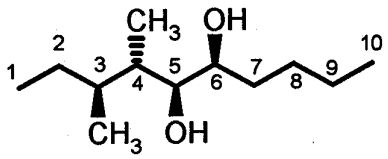
If one puts the two different substituents at the ends of the projection, you'll notice that the OH's are on the same side in erythrose, and the H's are on the same side too. in threose, however, the OH's are on opposite sides, as are the H's. From these two sugars, then, have come the terms *erythro* and *threo*. Consider now applying this to a non-carbohydrate, 2-bromo-3-phenylbutane. These are converted into the Fischer projections with the unlike substituents (i.e., Br and Ph) at the ends.



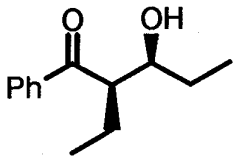
erythro threo

Unfortunately, *erythro* and *threo* as terms tend to fall apart when more than one substituent at each chiral centre is different. The problem is then defining the most different substituents to put at the ends of the Fischer projection, and the most similar ones to put on the sides, so that you can decide whether they're on the same or opposite sides. This decision can be quite subjective.

Masamune[1] has introduced a way to get around this. He has decided to abandon *erythro* and *threo* altogether, and to use ***syn*** and ***anti***. To do this, one draws the molecule in question in an extended, zig-zag conformation with the main chain horizontal and in the plane of the page. The substituents are then either out toward the viewer or back into the page.

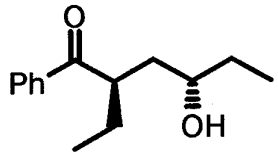


If the substituents are both out toward the viewer (or both back into the page), the stereochemical relationship is called syn. If one is in and the other is out, however, it is called anti. So for above, the relationships are 3,4-anti; 4,5-anti; 5,6-syn. This is particularly good for aldol stereochemistry, where the carbonyl is normally considered part of the main chain.



is therefore *syn*

As an aside, it is not necessary to have the chiral centres adjacent to assign a name. For example...



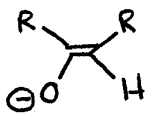
would be anti. One just keeps the chain going zig-zag.

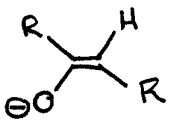
The syn/anti terminology is not without its problems too, and there are alternative ways proposed for describing diastereomeric relationships (including at least one better one, in my opinion)[2]. Nevertheless, the *syn/anti* formalism is the one that has gained international acceptance and wide usage.

References

1. Masamune, S.; Ali, Sk. I.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557.
2. (a)Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.
(b)Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654.

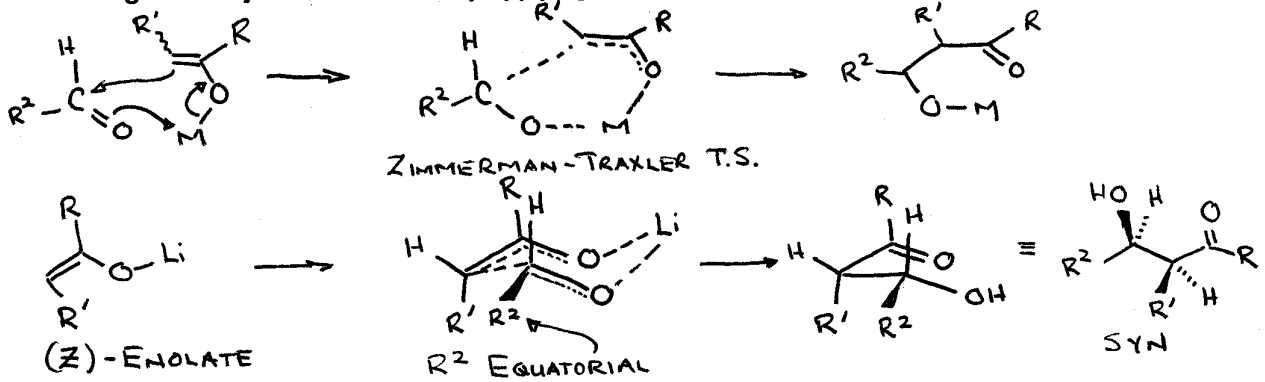
Now that diastereomer nomenclature has been addressed, the question of the preferred diastereomer can be discussed. Important here is the realization that in enolates, the resonance form with the "-" charge on the oxygen atom is the much 'better' resonance form, and that the metal counterion (usually lithium) is associated with that oxygen atom. As a result, enolates have two isomers forms possible, the ***Z*** and ***E*** isomers.



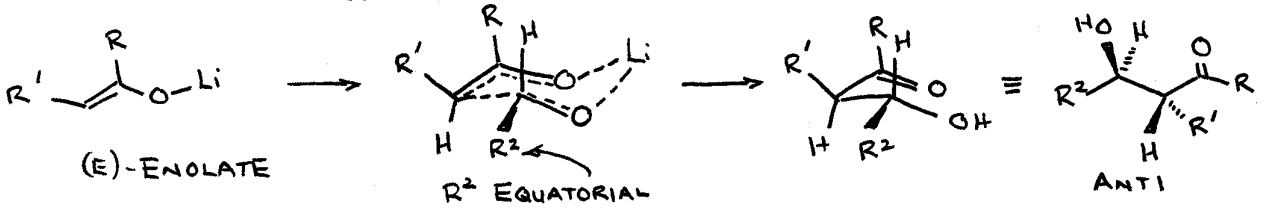


This piece of information is combined with a second important hypothesis, that the aldol condensation goes through a 6-membered, cyclic transition state (called the Zimmerman-Traxler transition state). The best way to approximate this transition state is to use cyclohexane as a model,

and to apply the conformational analysis known for six-membered rings to this transition state. As a result, it has been proposed that where possible, equatorial substituents will be preferred to axial ones, so that 1,3-diaxial interactions can be avoided. For the Z enolate of a typical case, one therefore gets the ***syn*** diastereomer by applying the Zimmerman -Traxler T.S.



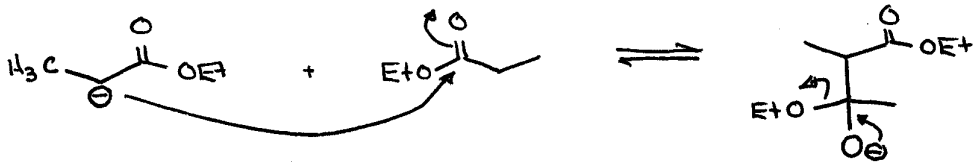
For the E enolate of a typical enolate, one gets the ***anti*** diastereomer by the same rationale.



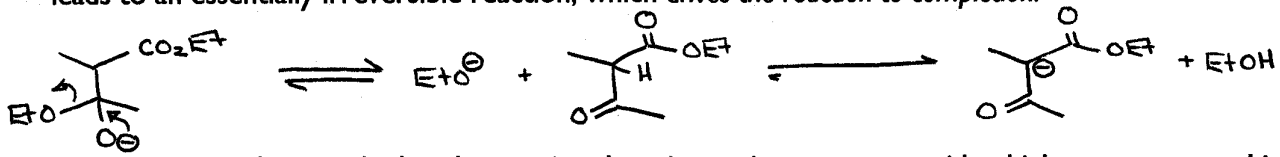
These are idealized cases, and in practice the selectivities are not always high (usually better for Z-enolates), but this basic approach seems to hold. The following case is demonstrative; note that how to prepare Z- or E- enolates selectively is beyond the scope of this course.

Claisen Condensation

Recall before, it was mentioned that esters can be enolate sources in aldol condensations only in selected cases. The reason for this is that the ester carbonyl can also be the electrophilic centre in condensation reactions, although it is somewhat <u>less</u> reactive than aldehydes or ketones in this respect. In any event, if an ester is subjected to base, the following will happen.



This intermediate loses its negative charge in a different way. This step produces a base (EtO^-) and a much more acidic compound (doubly activated), so that a deprotonation of this very acidic proton leads to an essentially irreversible reaction, which *drives the reaction to completion.*



The reaction is then worked up by pouring the mixture into aqueous acid, which reprotonates this site. I have arbitrarily chosen this aqueous as being only slightly acidic, because something further