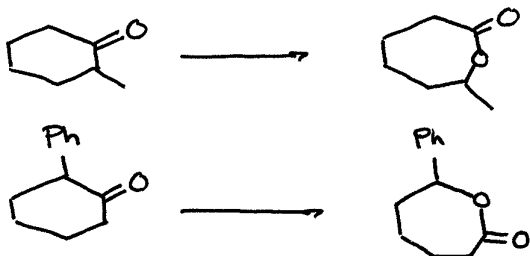
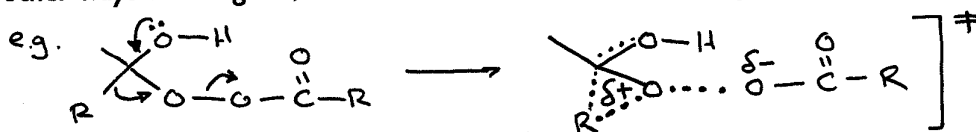


the R group (+I or +M group), the more it stabilizes this + charge, and the lower energy the TS for migration (aka faster). This means that the more substituted side migrates preferentially; amore exact order is 3° alkyl > 2° alkyl ≈ aryl > 1° alkyl > methyl. In aldehydes, the H atom is the one that normally migrates, so that a carboxylic acid normally results (of course, there are only about 100 other ways of doing this, so it's not the most common aldehyde oxidation reaction).

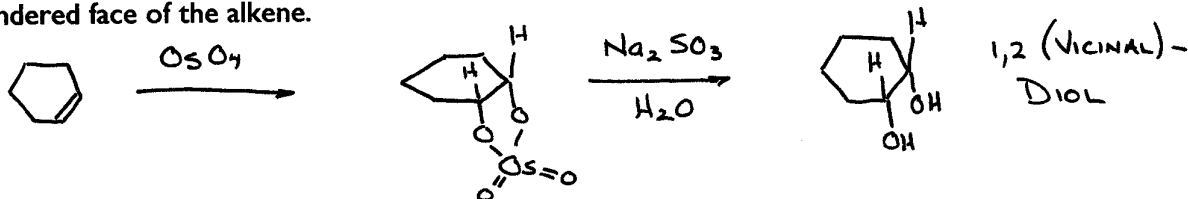


Stereochemistry: An interesting stereochemical point should be addressed here. Since the group that migrates uses the same orbital to bond to the C atom in the hemiacetal, the transition state, and when bonded to the O in the migrated product, the result is retention of configuration in the R group if there is a chiral centre at the migrating carbon.



Dihydroxylation of Alkenes (March 5-25)

OsO_4 (osmium tetroxide) also adds to $\text{C}=\text{C}$'s in a *cis* fashion. Instead of giving an epoxide, this results in formation of a vic (or 1,2-) diol (after workup). Addition here is from the less hindered face of the alkene.

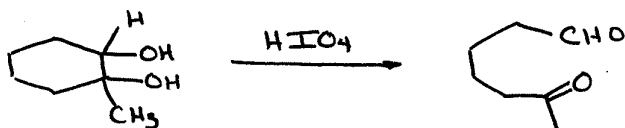
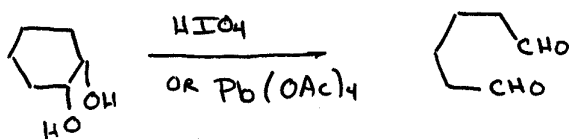


This is a useful alternative to the epoxidation/ring opening method of diol synthesis. That gave *trans* addition; this gives *cis*.

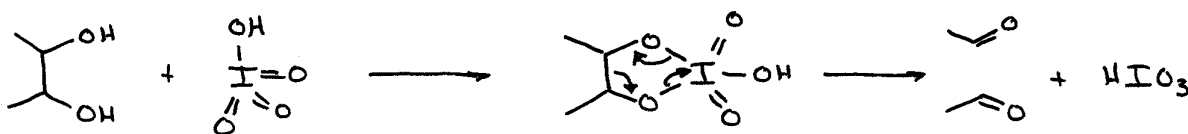
Note: This reaction can also be accomplished, less commonly, by using KMnO_4 , then HO^- .

Periodic Acid Oxidation (March 9-7)

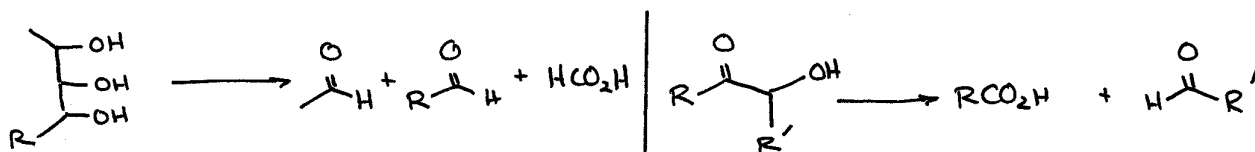
One important reaction of 1,2-diols (*vic*-diols) involves their oxidative cleavage to two carbonyl compounds (aldehydes or ketones, depending on the substituent). This is accomplished by addition of periodic acid (HIO_4) to the diol. $\text{Pb}(\text{OAc})_4$ also induces the identical transformation.



This reaction occurs by using the diol to form a cyclic periodic ester, and then concerted cleavage of the ester to reduce the I atom and to cleave the C-C bond between the two alcohols.



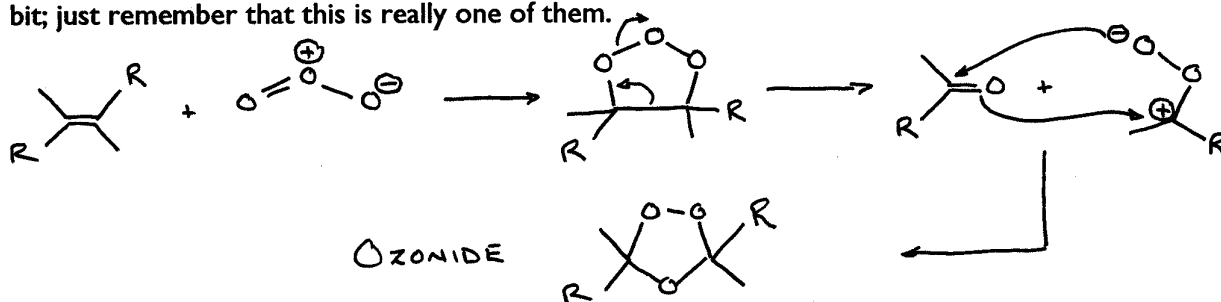
If one has a 1,2,3-triol, on the other hand, one gets two aldehydes/ketones, by the carbon bearing the central OH is oxidized up to HCOOH. Additionally, an α -hydroxy ketone (or aldehyde) gives an aldehyde/ketone (from the alcohol) and an acid (from the ketone/aldehyde).



This reaction is obvious that it's often used in tandem with the OsO_4 induced hydroxylation of alkenes. There is a way to do both of these processes in one step however, and that uses a highly electrophilic oxidant, ozone.

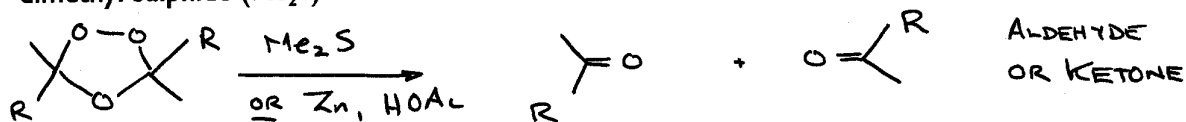
Ozonolysis (March 9-9)

As mentioned above, O_3 (ozone) is a very strong electrophile. It reacts with an alkene by way of a complex mechanism to give an ozonide. Note that the first step involves the concerted reaction of a 2π -electron system (the alkene) with a 4π -electron system (ozone, which is one of a class of compounds called 1,3-dipoles). We'll see how important $[4\pi + 2\pi]$ cycloadditions are in a bit; just remember that this is really one of them.

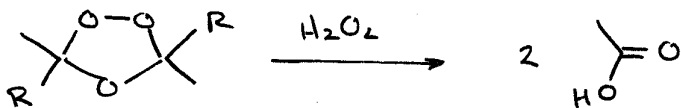


Ozonides are quite unstable (recall that O-O bonds are not that strong) and so they are almost never isolated. These ozonides are usually treated, before any isolation, with a reductant which cleaves the O-O bond. That would give what amounts to two hemi acetals, which hydrolyzed

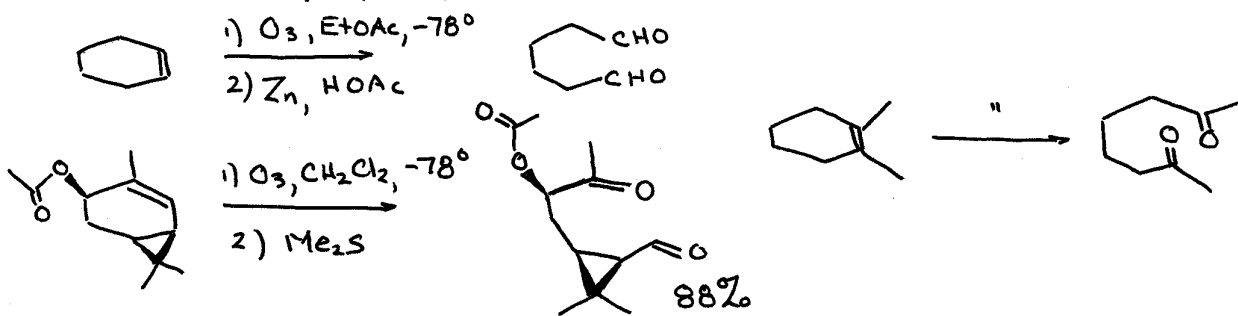
to an aldehyde or a ketone. The most common reductants for this purpose are either Zn/HOAc or dimethyl sulphide (Me₂S).



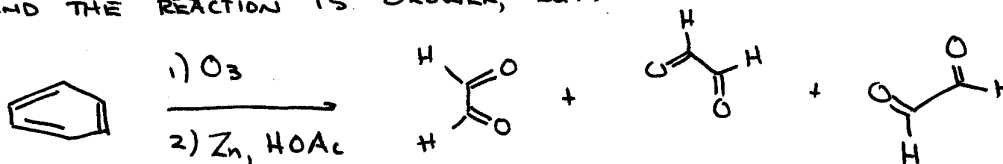
Less commonly, these ozonides can be worked up oxidatively, by H₂O₂ (most commonly), a peracid, or O₂, one can get a carboxylic acid, presuming one of the R groups shown was an H (otherwise one gets the ketone).



Notes: Ozone is very reactive. To prevent from oxidizing other functional groups, the reaction is normally conducted at low T (-78 °C), in an inert solvent (ethyl acetate, MeOH, CH₂Cl₂). Nevertheless, aldehyde (-CHO) and amine (R₂N-) functional groups are still oxidized.



AND THE REACTION IS SLOWER, BUT....

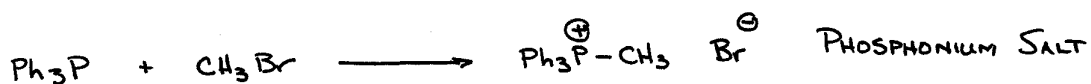


Other Reactions

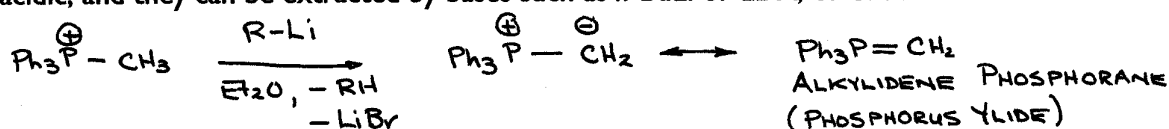
We're now going to look at a couple of other reactions which I have chosen to put separately from enolate chemistry, organometallic chemistry, or redox reactions, but which are extremely useful synthetically. This distinction is arbitrary, especially for the Wittig reaction and its variants.

Wittig Reaction (March 6-47)

The Wittig reaction involves the chemistry of phosphorus, which has a number of useful properties which stem from it being a second row element. First of phosphines are nucleophilic, much like amines, only more so. So if one adds the most commonly used phosphine, Ph₃P, in the presence of an alkyl halide, one rapidly forms a phosphonium salt. This works well for both methyl halide and *n*-alkyl halides.

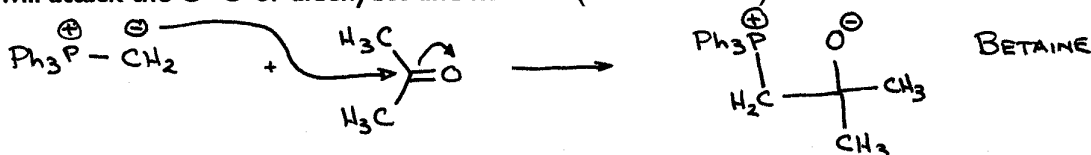


Due to the electronic nature of phosphorus (a highly polarizable P atom, and perhaps the availability of low lying d orbitals), the protons on the α -carbon of phosphonium salts are somewhat acidic, and they can be extracted by bases such as *n*-BuLi or LDA, or even NaH.

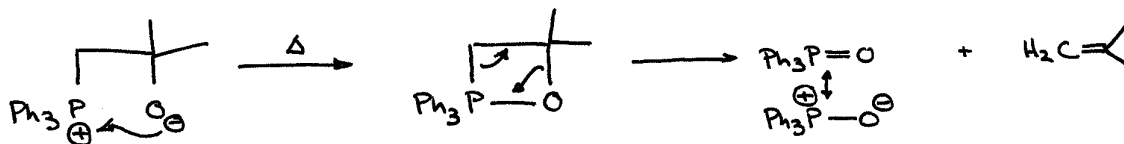


The following is a lie, but a very convenient one.....I'll give you the truth at the end.

Even though their overall charge is 0, these phosphorus ylides are nucleophilic enough that it will attack the C=O or aldehydes and ketones (but not esters).

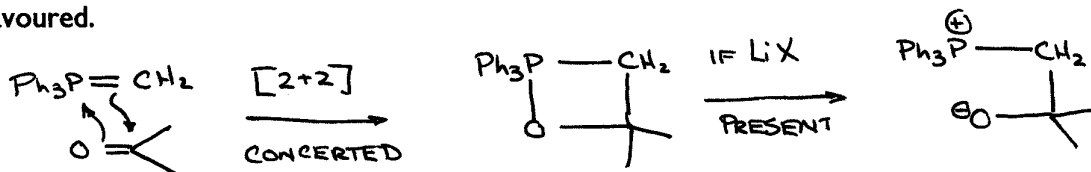


Upon heating, the betaines eliminate triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$), a stable white solid. More importantly, the organic remnant of this reaction is an alkene.

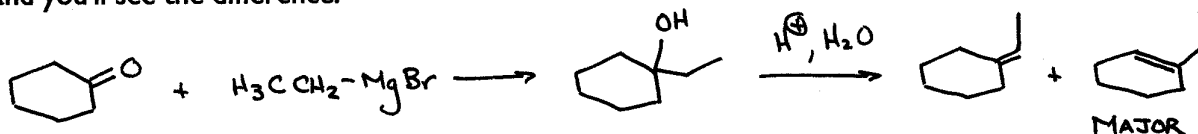


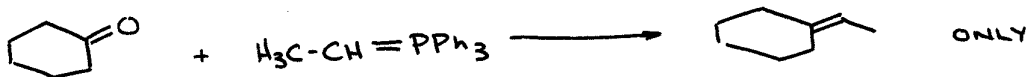
Overall, this constitutes the replacement of $\text{R}'_2\text{C}=\text{O}$ with a $\text{R}'_2\text{C}=\text{CR}_2$. This is the **Wittig** (pronounced *Vittig*) reaction.

Now for that lie. It's relatively recently been found that the initial step in the Wittig reaction is really a [2+2] cycloaddition between the phosphorus ylide and the carbonyl, to immediately give the 4 membered ring oxaphosphetane. In the presence of lithium salts (which is how the reaction is run conventionally), this falls apart into the betaine, so the rest of what I wrote down is true. If salts are rigorously excluded, the betaine is never seen. Nevertheless, alkenes do not normally react with phosphorus ylides; this is one reason why the ionic mechanism, though wrong, was initially favoured.

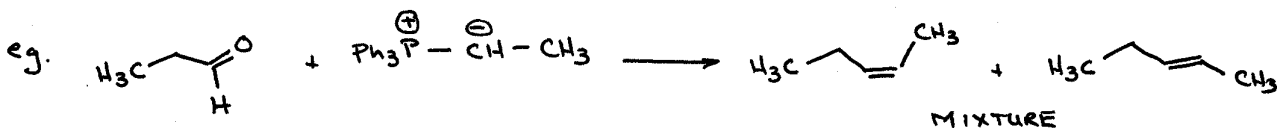


Use of the Wittig: The biggest advantage of the Wittig is that you always know exactly where the double bond is going to end up; it's where the C=O used to be in the S.M. Let's compare this to an attempt to do the analogous transformation by a Grignard addition/elimination sequence, and you'll see the difference.

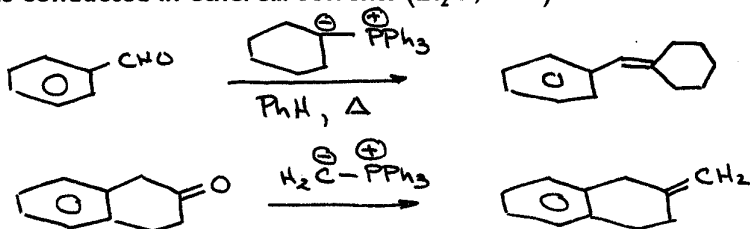




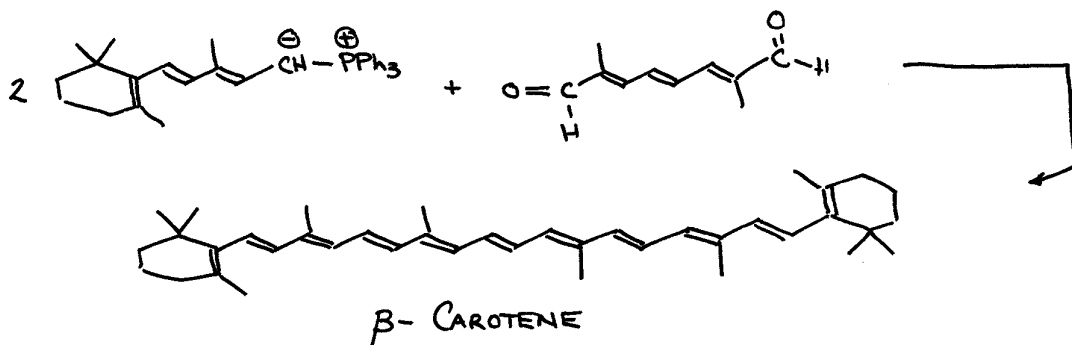
Stereochemistry-Unfortunately, the stereochemistry of the Wittig reaction is less sure. Most of the time, one gets a mixture of Z- and E- isomers. There is much work at trying to make Wittig reactions (or their modifications) stereoselective, but that is beyond this course's scope.



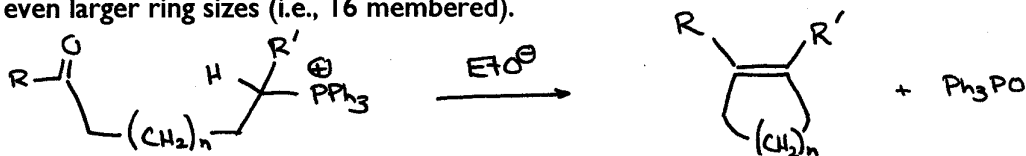
Experimental conditions: Most ylides react rapidly with water or O₂, and so the reaction is conducted in ethereal solvents (Et₂O, THF) or even benzene, under N₂.



NOTE: A GRIGNARD ROUTE WOULD GIVE NONE OF THIS COMPOUND



The Wittig reaction can also be done intramolecularly, to prepare rings of normal sizes or even larger ring sizes (i.e., 16 membered).



Many other functional group are tolerated pretty well, except for free OH's. The reactivity of Wittig reagents (the ylide) is as follows:

Aldehydes > ketones >>> esters, amides, acids (they are inert).

One very useful extension employs the ylide derived from chloromethyl methyl ether. This results in the synthesis of an aldehyde with one extra carbon (see the Darzens').

