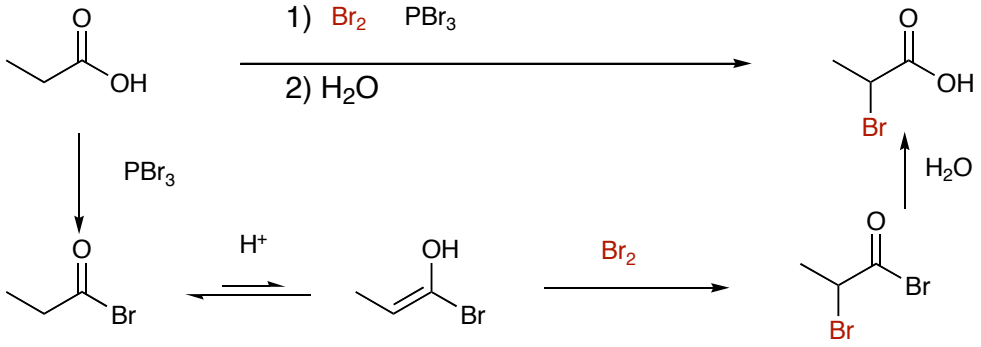
Chapter 22 - Carboxylic Alpha-Substitution Reactions

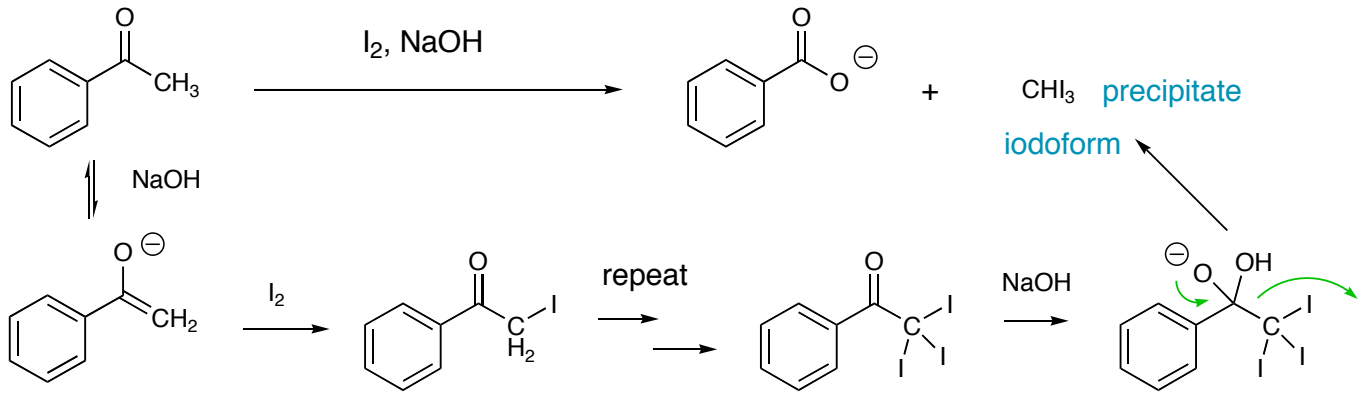
Alpha Halogenation

The alpha halogenation works well for aldehydes and ketones, but it does not work with carboxylic acids. That is because it is difficult to enolize a carboxylic acid (the proton on the acid oxygen comes off easier than the proton on the alpha carbon). Using PBr_3 with Br_2, an intermediate acid bromide is formed which undergoes enolization and bromination. The acid bromide is subsequently hydrolyzed to give the acid back. This is the Hell-Volhard-Zelinskii reaction.



Iodoform Reaction - test for methyl ketones

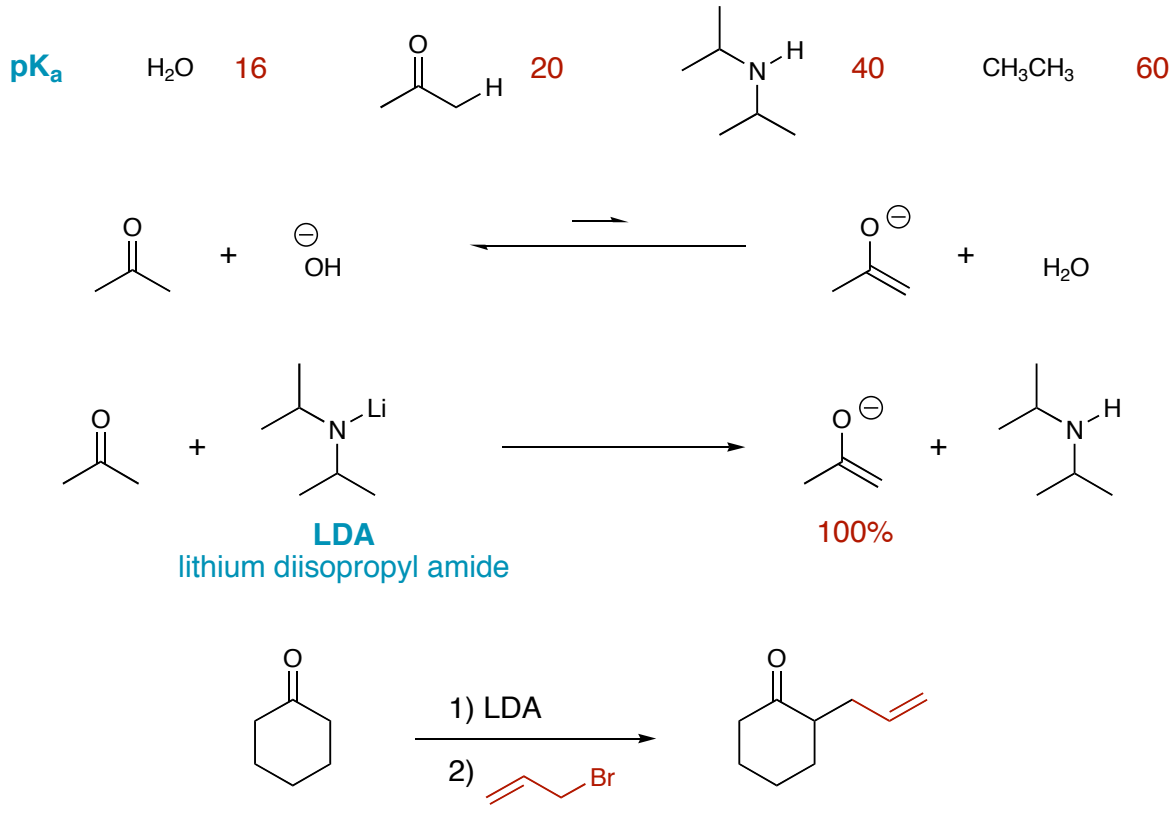
Alpha halogenation can be done with enolates as well as enols. One difference with base catalyzed conditions is that often more than one halogen adds. One can replace all the alpha hydrogens with halogens under basic conditions. A standard test for the presence of methyl ketones is to treat the compounds with iodine and sodium hydroxide. Once all three hydrogens are replaced with iodine, it is a pretty good leaving group and is substituted with the hydroxide like a typical nucleophilic acyl substitution reaction. The iodoform precipitates as a solid indicating the presence of the methyl ketone.



Ketone Enolates

Enols will only react with very reactive electrophiles like bromine. In order to do alpha substitution with less reactive electrophiles, like alkyl halides, you need to deprotonate with a

strong base to make an enolate. The hydrogen alpha to a ketone is less acidic than water, so hydroxide is not a strong enough base to completely form the enolate, though it will exist in a small amount in equilibrium with the ketone. To fully form an enolate, LDA is used as the base. It is a very strong base as well as a very bulky base, so there is no problem with the LDA adding to the carbonyl carbon.



1,3-Dicarbonyl Compounds

Having two carbonyls makes a proton on a carbon even more acidic than one. For example, acetone has a pK_a of 20 while the central carbon of 2,4-pentanedione has a pK_a of 9. Malonic esters are a little bit higher than the diketone, but still much more acidic than a ketone. Dicarbonyls can be alkylated readily with milder bases like NaOH in alcohol solvents. Overalkylation can be a problem as the product can also enolize and react with the alkyl halide.