

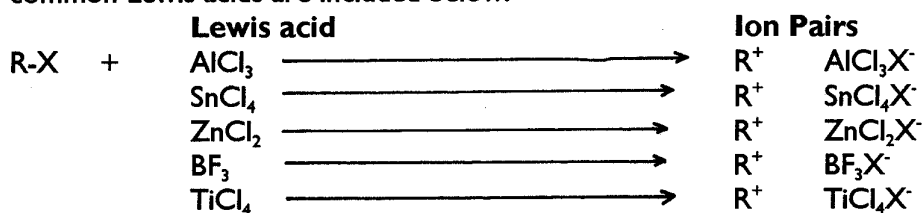
## Acid Induced (Catalyzed) Reactions

We have, so far, been focussing on reactions of  $C^- + C^{\delta+}$ . It's reasonable to assume that a possible alternative to this is for a reaction of  $C^{\delta-} + C^+$  to occur, giving carbon-carbon bond formation. These are the sorts of reactions we'll be looking at in this section.

### Generation of $C^+$

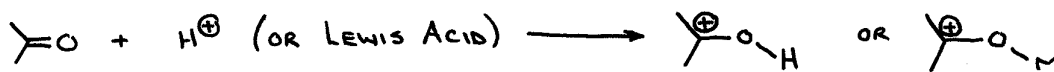
There are several ways of doing this, and some oversimplification is involved. The most common ways are, however...

- a) The addition of a Lewis acid to an organic substrate bearing a leaving group. Several of the common Lewis acids are included below.

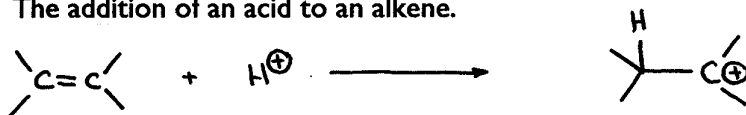


Whether discrete ion pairs are formed or not usually depends on the nature of the R group (remember cation stability is  $3^\circ > 2^\circ > 1^\circ$ ). In any event, they usually react as if they are ion pairs.

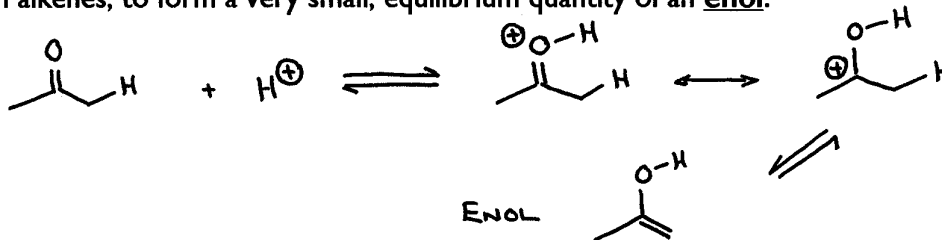
- b) The reaction of a protic or Lewis acid and a carbonyl compound



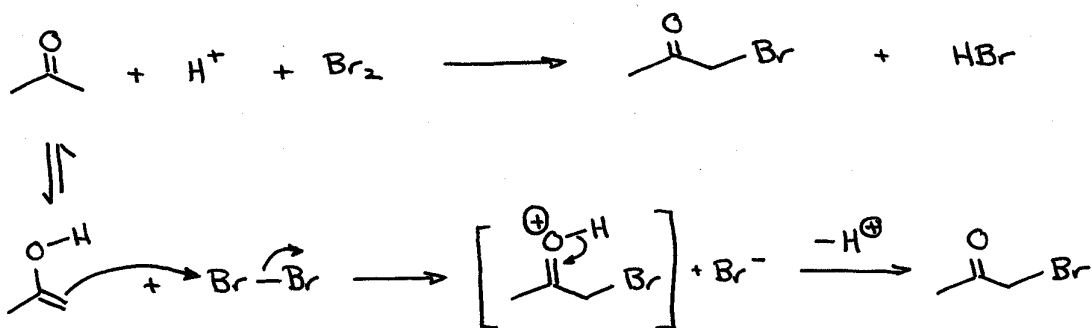
- c) The addition of an acid to an alkene.



Most of the important types of reaction we'll look at here belong to class 'b' of the above. An aldehyde or ketone with at least one hydrogen in the  $\alpha$ -position react in a very predictable way with alkenes, to form a very small, equilibrium quantity of an enol.

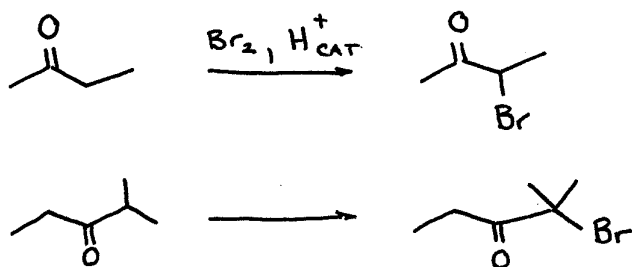


In most of the acid catalyzed reactions of aldehydes or ketones, the enol (even though it's present in only a small concentration at any one time) is the nucleophilic species participating. Perhaps the simplest of these reactions is **halogenation** of the ketone/aldehyde; i.e.,



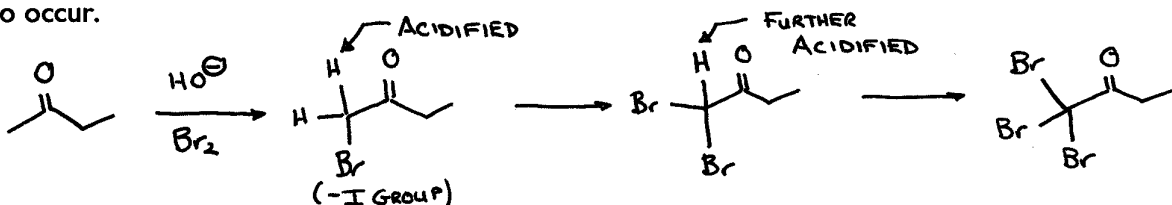
The enolization is the slow step of this reaction, so one can actually use this reaction to measure the rate of enolization of the carbonyl. Another consequence of this fact is that the halogenation (usually bromination) occurs selectively where the enol was predominantly formed.

-under acid catalyzed conditions, this is normally the most substituted enol. Therefore,

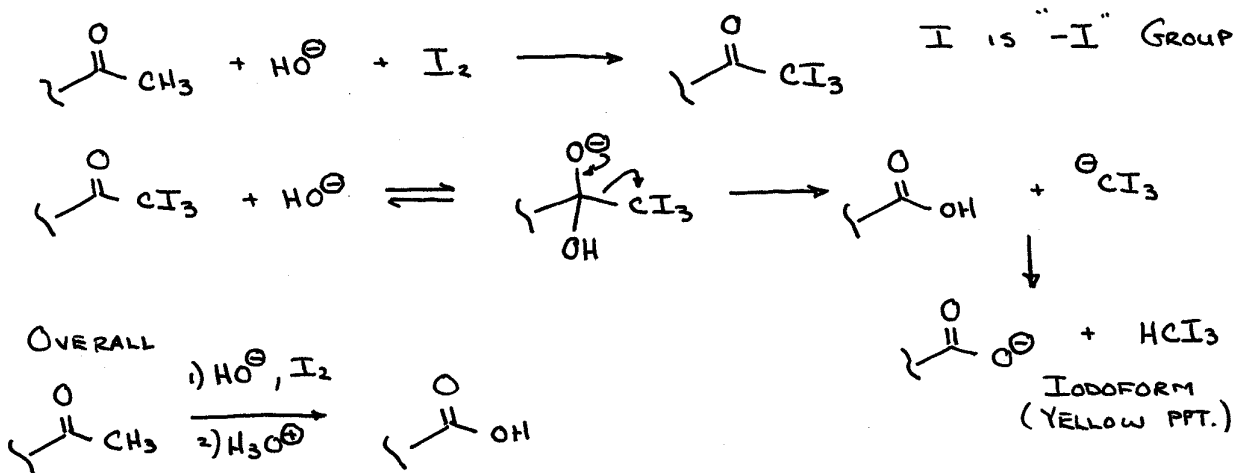


Fortunately, introduction of a second Br is normally slower than the first one, so it is easy to get the monosubstituted product almost exclusively.

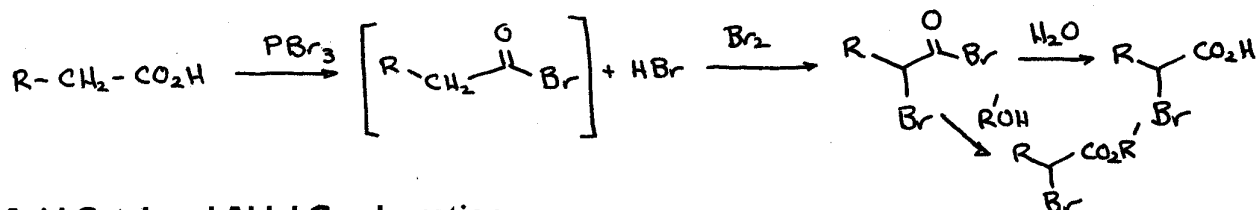
This is quite different than the situation where one tries to halogenate under base catalyzed conditions, since the less substituted side is halogenated most rapidly, and perhalogenation tends to occur.



This perhalogenation under base catalyzed conditions actually has one major synthetic use. This is called the **iodoform reaction**, (March 2-44) and occurs with methyl ketones. It occurs because an iodine is a -I group (inductively electron withdrawing), and  $\text{CI}_3$  is a good leaving group.

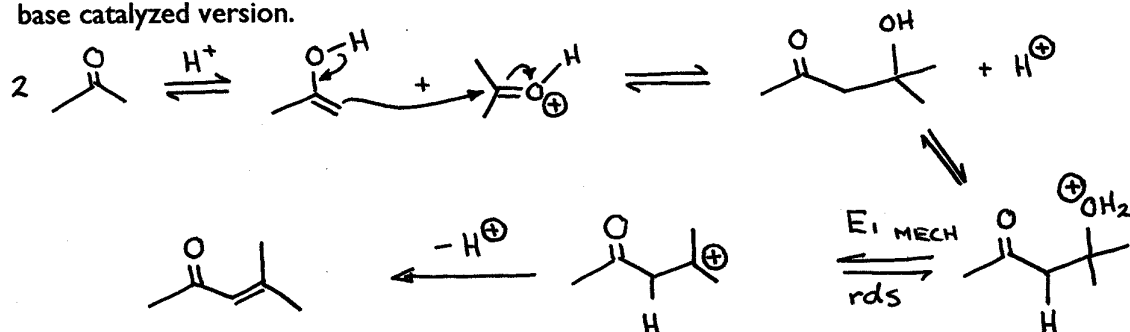


Halogenation of esters is not so easily done, as esters have such a tiny enol concentration that it's essentially zero. Instead, the reaction is done on the acid (which also has a negligible enol content) with  $\text{Br}_2$  and  $\text{PBr}_3$ . This converts the acid into the acid bromide (which has a substantial enol content), which then  $\alpha$ -halogenates by an acid catalyzed mechanism. Addition of water (or an alcohol) at the end of the reaction gives the  $\alpha$ -halogenated acid (or ester). This is called a **Hell-Volhard-Zelinskii reaction (March 2-5)**. We'll see a use for these compounds later on.

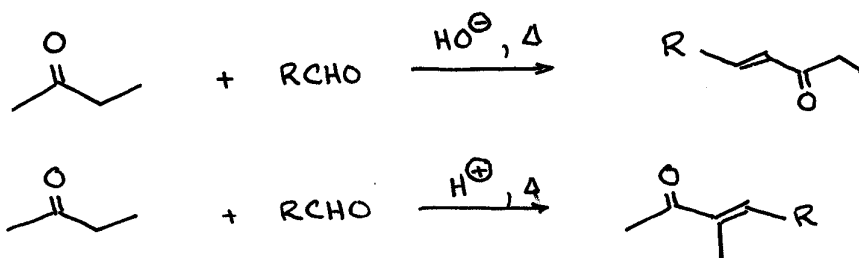


### Acid Catalyzed Aldol Condensation

Aldol condensations can also be acid catalyzed. The mechanism must be different than the base catalyzed version.



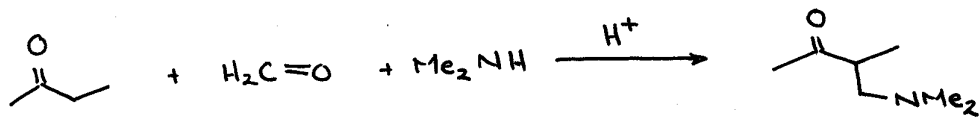
Although this transformation can and does work, its yield is normally inferior to the base catalyzed version. As a result, acid catalyzed aldol aren't normally used, except in specific cases. One of these cases is where one wants the aldol to occur on the *more* substituted side of an unsymmetrical ketone, i.e.



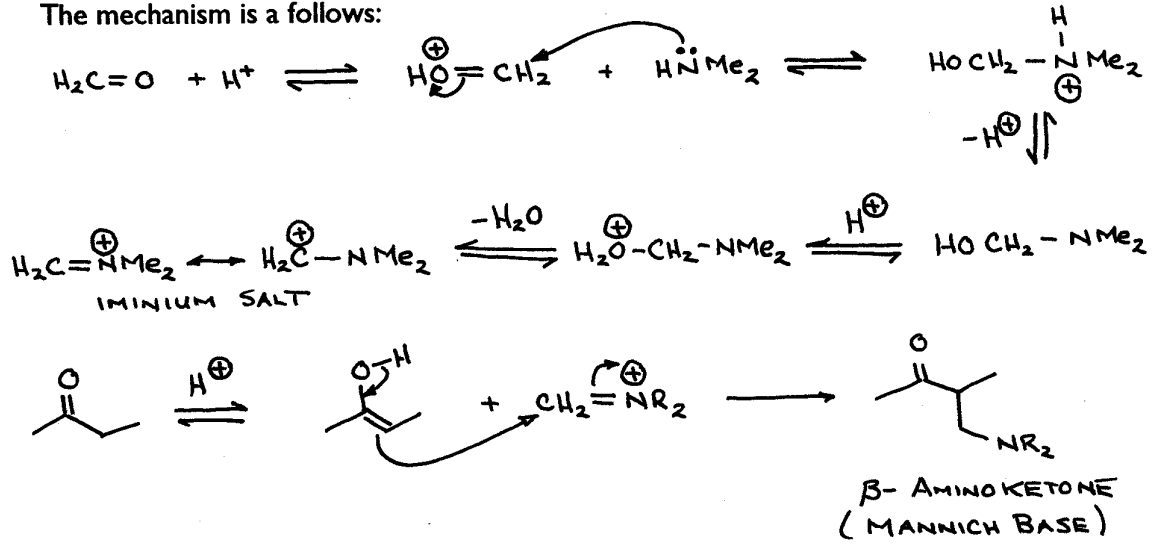
-the regiochemistry is reversed in acid catalyzed aldols

### Mannich Reaction

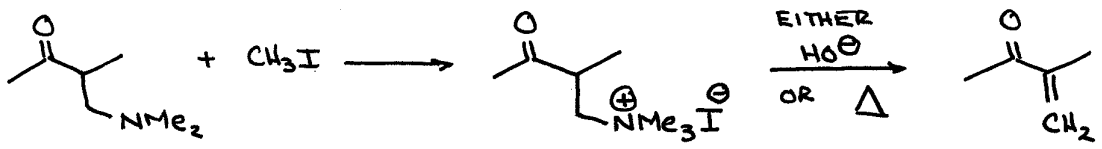
A still more common modification of an acid catalyzed aldol is a **Mannich reaction**. This is a very useful reaction, which employs an aldehyde (usually formaldehyde,  $\text{H}_2\text{C}=\text{O}$ ) + a 2° amine + a ketone.



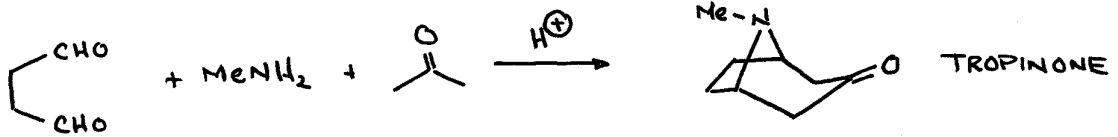
The mechanism is as follows:



The synthetic applications are often as a precursor to an α,β-unsaturated ketone.



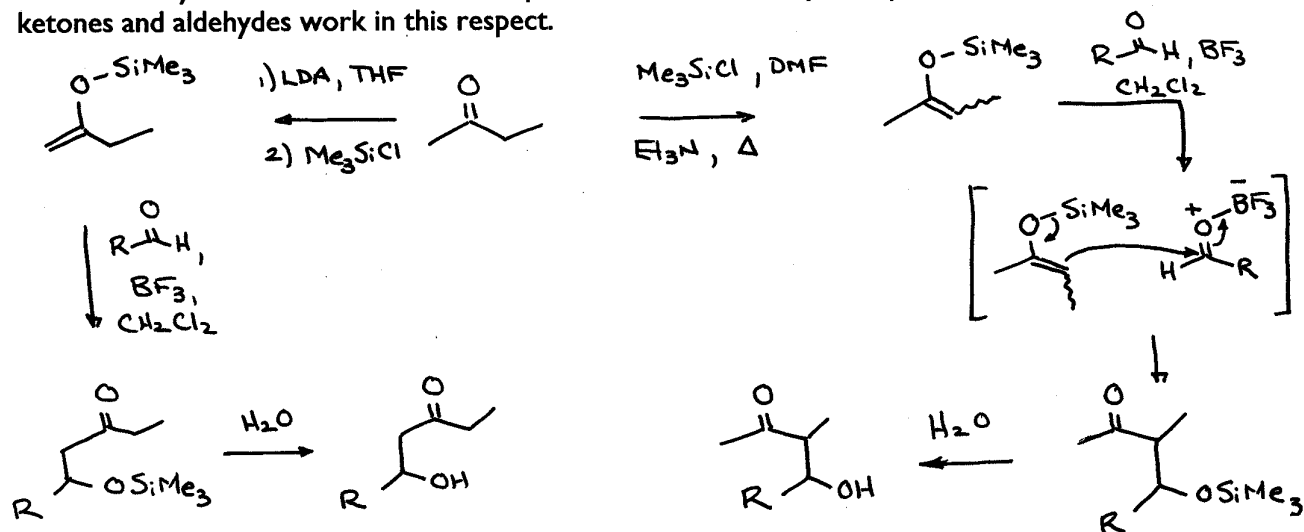
This looks like an aldol between a ketone and H<sub>2</sub>C=O; it is used because H<sub>2</sub>C=O usually polymerizes before it can enter into an aldol. The Mannich works very well, on the other hand. A double Mannich reaction was used in the original Robinson synthesis of tropinone. This also demonstrates that aldehydes other than formaldehyde can be used in Mannich reactions.



**(Lewis) Acid Induced Kinetic Aldol Condensations**

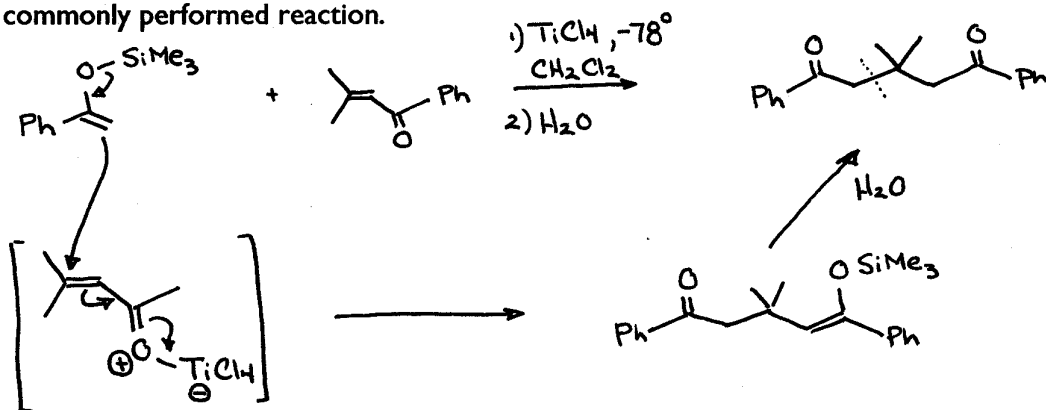
Based on a strict analogy with base induced kinetic aldol condensation (*directed aldol* is often used), what we would need for the kinetic acid induced aldol is some way of getting a *stoichiometric* amount (meaning 1 full equivalent, not a catalytic amount) of the nucleophilic partner. Since enols only form to an equilibrium (and very small amount), these are usually replaced by **enol silanes** (also called **silyl enol ethers**). These are readily available by base induced reaction of the ketones,

and one can get either regioisomer in most unsymmetrical ketones. Once these are in hand, they are sufficiently reactive to attack the complex between a carbonyl compound and a Lewis acid. Both ketones and aldehydes work in this respect.



### Lewis Acid Induced Michael Reactions

In  $\alpha,\beta$ -unsaturated ketones or aldehydes (with Lewis acids), an enol silane could be expected to attack in either a 1,2- mode (aldol type) or 1,4-type (Michael type) manner. Most often, 1,4-attack is observed, and as a result, Michael reactions between silyl enol ethers and enones is a commonly performed reaction.



### Tertiary Alkylation of Silyl Enol Ethers

One other reaction, which is unavailable to base induced reaction, is the reaction of silyl enol ethers to 3° alkyl halides, in the presence of Lewis acids.

