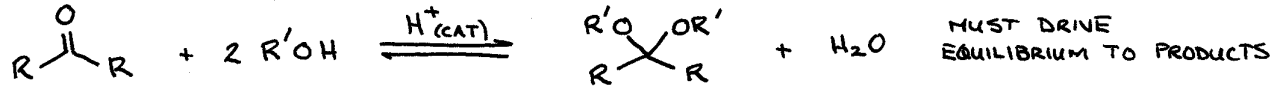
This works well due to the fact that 3° carbocations are relatively stable, so they hang around long enough for the enol silane to get to it. This would never occur by a base induced reaction, since S_N2 reactions on 3° alkyl halides "never" works. This type of acid induced alkylation also works well for other highly stabilized carbocations, such as allylic or benzylic ones.

Aside-Protecting Groups for Carbonyls

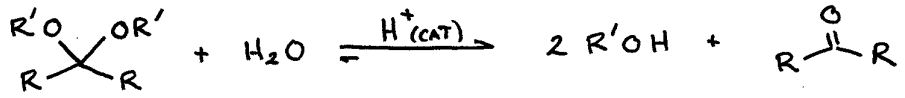
One important acid catalyzed reaction of ketones or aldehydes does not involve C-C bond formation. It is *protection* of that carbonyl.

To introduce the idea: If one has a ketone or aldehyde in a molecule, there are often situations where it's desired to add a reagent to that compound that normally reacts with that carbonyl....but in this case 'you' ***don't*** want it to react. What is normally done is to temporarily 'hide' the carbonyl as something that won't react with the other reagent, but can be easily converted back the original carbonyl when it is desired again. This is the idea behind **protecting groups**.

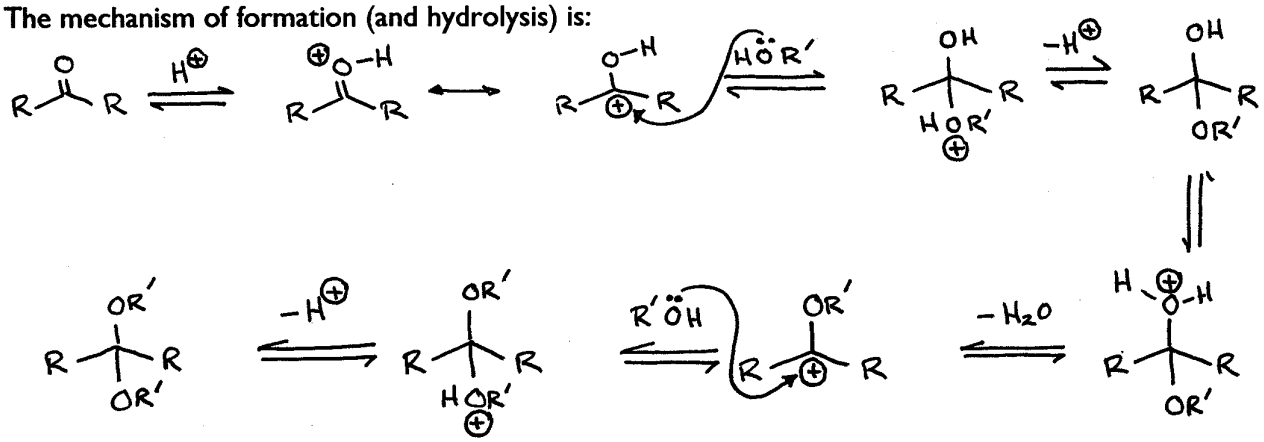
For ketones or aldehydes (but not esters), this is usually done by converting the carbonyl to an ***acetal*** (called *ketal* too, sometimes), but the acid catalyzed reaction with an alcohol. The usual alcohols are MeOH, EtOH, or one of two diols, $HO\text{-}CH_2\text{-}CH_2\text{-}OH$ or $HO\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OH$.



These acetals behave pretty much like the ethers that they are. In other words, they are inert to base induced proton abstraction, to most types of reduction, and are usually inert to nucleophiles. In fact, the only thing that causes easy reaction of these are acids (protic or Lewis). Therefore, when you want the ketone/aldehyde back, all you need to do is a catalytic amount of acid in water.



The mechanism of formation (and hydrolysis) is:



Note:

Here, H^+ is a true catalyst

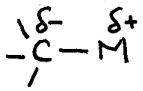
All the steps are reversible, so the entire reaction is reversible

The reaction is driven to the acetal by removing water is it is formed (either by a huge excess of alcohol, or by azeotropic removal with benzene).

Carbanions From Non-Acidic Compounds

It is not necessary to make carbanions ($R_3C^{\ominus}$) by a proton abstraction of carbonyls , i.e.

- organometallic compounds possess this type of reactivity, too

i.e. 

(for metals less electronegative than C)

The most common metals for this purpose are **Mg**, **Li**, and **Cu**^{I}, although several others see some use

Common Preparation of organometallic reagents

1) Oxidative addition

R-Br + Mg ⟶ RMgBr

or

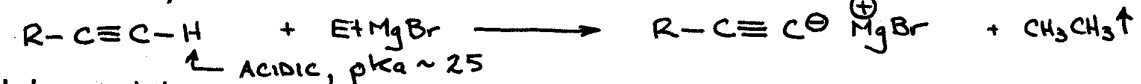
R-Br + 2 Li ⟶ RLi + LiBr

2) Abstraction

R-H + R'-M ⟶ R-M + R'-H

when R-H is more acidic than R'-H

i.e., with terminal alkynes



General characteristics

These compounds are strong bases, and so they react with OH's, O_2, and CO_2. As a result, they are normally prepared in either diethyl ether (Et_2O) or THF *in situ* (meaning they are not isolated).

These reagents are, for the most part, soluble in these reagents, and there is much discussion whether it is better to consider them as polar covalent or ionic. Generally, though, the more towards ionic the organometallic is, the more reactive it is...

i.e., reactivity RLi > RMgBr > RCu, R_2Cd

Some examples

Grignard Reaction - surely at least something of a review

These reagents (RMgX, where X = Br, I, or Cl), are almost always prepared by stirring the R-X with Mg metal (I'll use Mg° for this) in dry Et_2O or THF, under N_2 atmosphere.

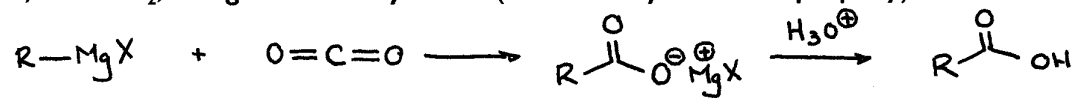
The formation can be a bit sluggish, so often an initiator such as I_2 helps start this reaction.

If water or an alcohol is present, the Grignard reagent is rapidly killed off

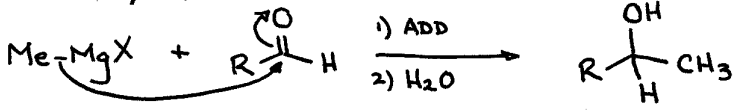
R-MgX + H_2O ⟶ R-H + Mg(OH)X

Grignard reagents are generally reactive to all sorts of carbonyl compounds, and the more reactive organic halides (i.e., allylic or benzylic ones). It usually doesn't react very well with simple alkyl halides.

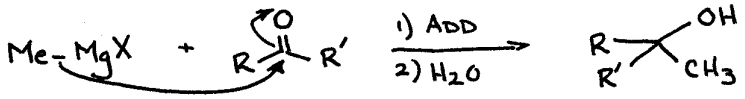
So, with CO_2, one gets a carboxylic acid (or a carboxylate, more properly)



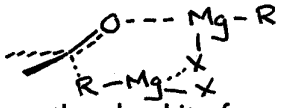
With aldehydes, a 2° alcohol is formed.



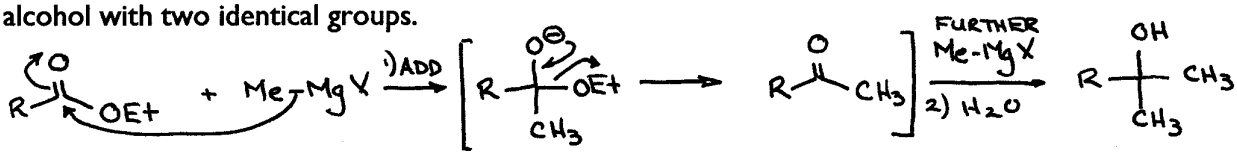
With ketones, a 3° alcohol is formed.



The reaction with these carbonyls is aided by the fact that the Mg centre is Lewis acidic, and so coordination of the carbonyl oxygen to the Mg atom enhances the reactivity of the carbonyl.



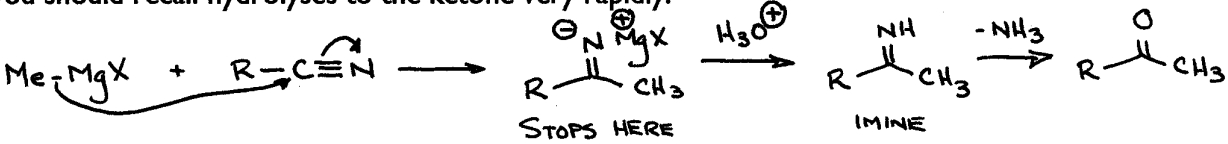
With esters, there's a bit of a surprise. The intermediate from the first attack falls apart to a ketone, which is more reactive than the starting ester, so the Grignard reagent adds again. The result is a 3° alcohol with two identical groups.



Note: All these reactions would be exactly the same (only a bit faster) with organolithium compounds (RLi).

This brings up a question. What would you react with an organometallic compound to get a ketone? There are several answers to this, and you should realize that there are more once we discuss oxidation of alcohols, but I'll give you two right now.

The first involves using a nitrile (cyanide) with the organometallic. Attack of the organometallic would give the anion of an imine, which is <u>less</u> readily attacked by organometallics, so the addition stops there. Addition of water (usually acidified) gives an unsubstituted imines, which you should recall hydrolyses to the ketone very rapidly.

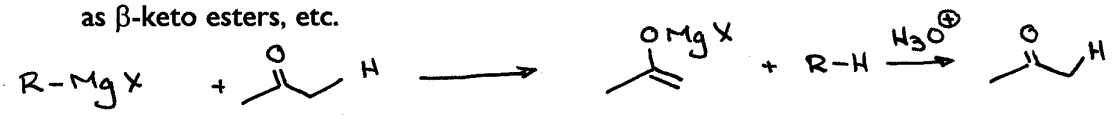


The second method, which is becoming the most popular, is to use a particular type of amide, commonly called a Weinreb amide, as the carbonyl substrate. These are useful because the methoxy group on N causes the tetrahedral intermediate from one attack of *one* molecule of organolithium *or* organomagnesium reagent to be stable (certainly at T's like -78 °C). As a result, upon addition of water an N,O acetal is formed immediately formed, which rapidly falls apart into a

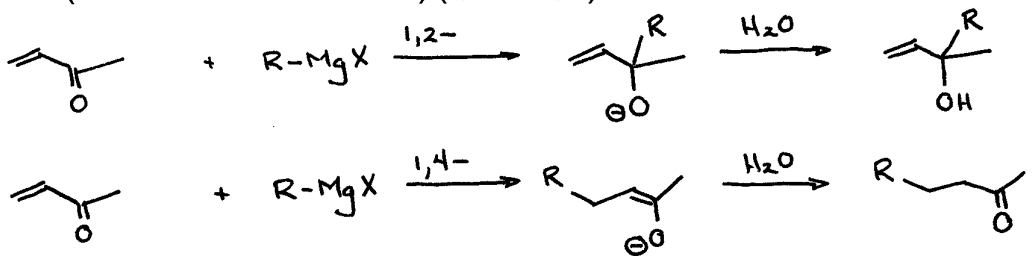
ketone. Weinreb amides are most often prepared from acid chlorides, by attack with N-methoxy, N-methylamine.

Limitations of Grignard reagents.

1) They tend to be rather sensitive to steric hindrance around the electrophilic site intended to undergo attack
2) If the ketone substrate is particularly acidic, the Grignard (or organolithium) with deprotonate rather than attack. This is particularly noticeable with compounds such as β-keto esters, etc.

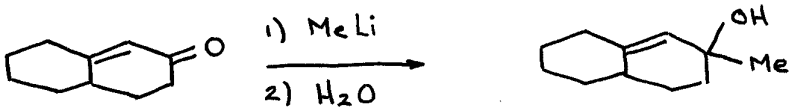


3) An α,β-unsaturated carbonyl compound can, once again, react in two potential ways ("aldol like" vs. "Michael like") (1,2- vs. 1,4-).

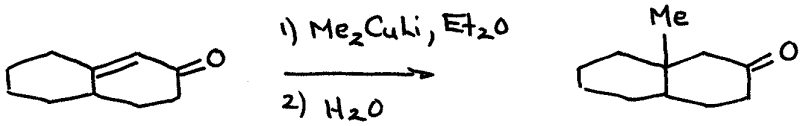


In the case of **Grignard reagents**, what happens is somewhat dependent upon the individual case, but one normally gets **more 1,2- addition** *unless* there are steric problems around the carbonyl.

If the organometallic "R-M" is **R-Li**, there is even a greater tendency to get **1,2-addition**

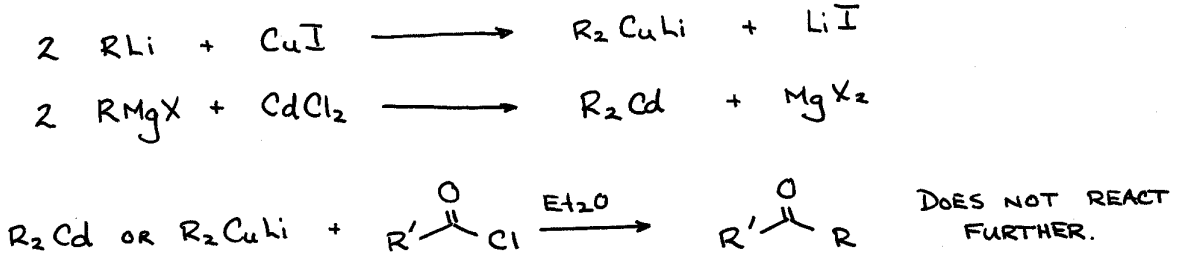


On the other hand, if one adds **Cu^{+1}** salts to either RMgX or RLi, **1,4-addition** is the normal path of reaction.
The actual organometallic reagent attacking is dependent upon the ration of reagents added here.
If the ratio of **Cu^{+1} : R-M** is **1 : 1**, the attacking reagent is **R-Cu**. These are called organocopper reagents.
If the ratio of **Cu^{+1} : R-M** is **1 : 2**, the attacking reagent is **R_2CuM** (or $[R_2Cu]^- M^+$). These are called **cuprates** (sometimes Gilman cuprates, especially for R_2CuLi). These are probably the most widely used of this type of reagent.
Even higher order cuprates (i.e., R_3CuLi_2) are known and are useful synthetic reagents, but a bit beyond this course's scope (see B. Lipshutz, UC Santa Barbara, if you're interested).

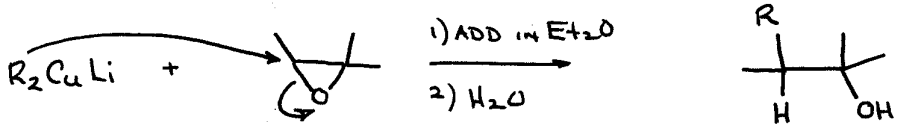


The reasons why these reagents prefer 1,4-addition is still under some discussion. Some people invoke a complex between the π-system of the alkene of the Cu atom, and others just make a HSAB argument (Li = hard acid, C=O hard E^+; Cu = softer acid, C=C softer E^+).

Cuprates do a few other useful things, as well. Since they don't add to ketone carbonyl carbons well at all, attack of a cuprate on an acid chloride gives nucleophilic attack which stops at the ketone stage. Organocadmium reagents also do this, but they have fallen out of favour, probably due to Cd's toxicity.



Cuprates are also very good at doing nucleophilic attack at epoxides (oxiranes), and although Grignards also do this, the cuprates are usually better. Epoxides are interesting compound since other ethers will not react well with 'common' organometallics. By virtue of being in a strained (3-membered) ring, epoxides are relatively reactive to nucleophiles. The reaction do most often occur by an S_N2 mechanism, which means that the least substituted C atom of the epoxide is the one attacked, and that attack occurs with inversion at the electrophilic carbon atom.



Reformatsky Reaction ***(March 6-30)***

Very little (any?) organozinc chemistry has been discussed in this course, but there is one particularly noteworthy reaction which does employ these reagents. α-Haloesters (X = Br usually) react with Zn metal, to give an oxidative addition, analogously to Mg. The organozinc reagents which result are sufficiently nucleophilic to attack aldehydes and ketones, but not (well maybe *very slowly*) with esters. After addition of water, β-hydroxy esters result. This is an irreversible reaction, which is an advantage over many of the aldol-type processes. It works very well in many cases. The name for this reaction is the **Reformatsky** (sometimes Reformatskii) **reaction.**