Lecture Notes
Chem 51C
S. King

Chapter 20 Introduction to Carbonyl Chemistry; Organometallic Reagents; Oxidation & Reduction

I. The Reactivity of Carbonyl Compounds

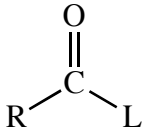
The carbonyl group is an extremely important functional group in organic chemistry, and it plays an important role in many biological processes.

The substituents attached to a carbonyl group strongly affect the reactivity of carbonyl compounds.

There are two major types of carbonyl compounds:

Type 1: The acyl group is attached to a group that does not have any lone pairs, and cannot act as a leaving group.

Type 2: The acyl group is attached to a group **L:** which has a lone pair, and is either a good leaving group, or can be protonated to make it a good leaving group.



L = $-Cl$, $-NH_2$, $-NR_2$, $-OR$, $-OH$, $-OCR$ (with O double-bonded)

A. Both Type 1 & Type 2 carbonyl compounds are electrophilic

The carbonyl carbon, with a partial (+) charge is quite electrophilic.

∴ Nucleophilic attack at the carbonyl carbon is often seen:

Type 2 compounds contain a group that is either a good leaving group or may be converted to a good leaving group by protonation:

∴ Following Addition, Elimination of **L** occurs

This gives a product where **L** has been replaced by **Nu.**

Overall Reaction:

With Type 2 compounds, the result is ***nucleophilic acyl substitution***

Example:

We have already seen substitution ***via*** Addition/Elimination twice in Chapter 9!

First time:

Second time:

✳ *Atoms that are not sp^3-hybrized undergo substitution via addition/elimination.*

Type 1 compounds, on the other hand, ***do not*** contain a group that is either a good leaving group or may be converted to a good leaving group by protonation, so only addition can occur (there is no L: to eliminate!)

Example:

With Type 1 compounds, the result is an ***addition reaction***.

B. Both Type 1 & Type 2 carbonyl compounds are weakly basic at the carbonyl oxygen and are protonated by strong acids.

NOTE: Protonation of carbonyl compounds *greatly enhances the electrophilicity of the carbonyl carbon*.

✳ *Acid catalysis is often used to enhance the electrophilicity of the carbonyl carbon so that it is more easily attacked by weak nucleophiles*.

IMPORTANT POINT:

✳ Protonation occurs on the carbonyl oxygen, ***not*** the carboxylate oxygen. ***Why?***

Compare:

C. Both Type 1 & Type 2 carbonyl compounds are acidic

The hydrogen atoms on the α-carbon of ***some*** Type 1 & Type 2 compounds are acidic. Deprotonation gives rise to resonance stabilized enolate anions.

The reactivity of the various Type 1 & Type 2 carbonyl compounds varies, depending upon the identity of the group bonded to the carbonyl.

Acid Chlorides & Anhydrides:

Carboxylic Acids, Esters, and Amides:

& Aldehydes are more reactive than Ketones.

Q. ***How can we explain this?***

A. The relative reactivities depend on the relative stability of each acyl derivative.

☛ *The least stable will be the most reactive*.

The stability is dependent on the concentration of positive charge on the carbonyl carbon, which is dependent on a combination of *inductive* and *resonance* effects.

Inductive effects (α-bonds):

As **L** becomes more electronegative, the charge on the carbonyl carbon becomes more positive (electron density is pulled away from **C**).

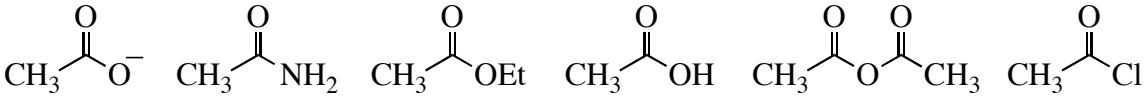
Resonance effects (π-bonds):

As the p orbital overlap of the lone pairs on **L** becomes greater, the charge on the carbonyl carbon becomes less positive (more delocalization of + charge).

The extent of resonance stabilization of an acyl derivative depends on how well the lone pair on **L** can donate its electrons. *This correlates with basicity*.

Remember periodic trends for base strength:

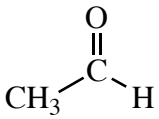
order of resonance stabilization:

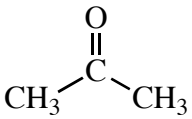


An acid chloride has the least resonance stabilization for two reasons:

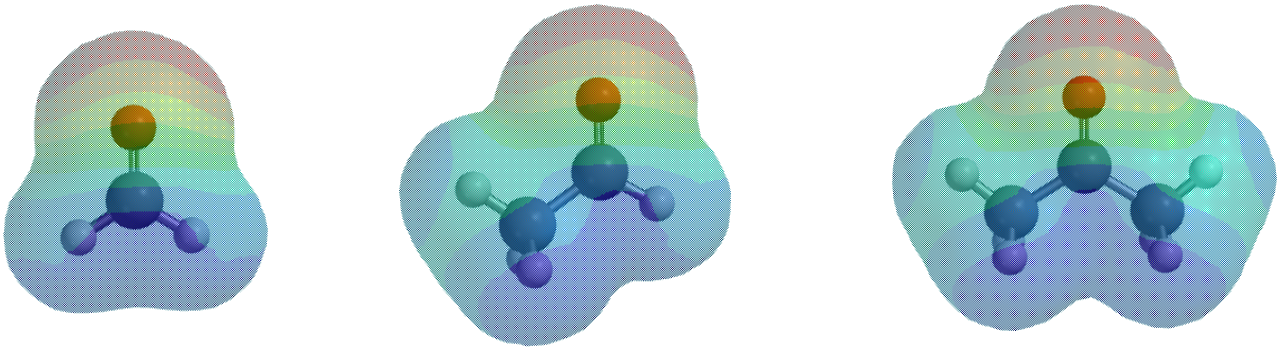
#1: Chloride ion is the weakest base (*it doesn't like to donate its electrons!*)
#2: There is poor 2p-3p overlap in the resonance structure with the double bond between carbon and chlorine. (poor overlap = poor resonance stabilization!)

Aldehydes and ketones do not have a group **L:** that can stabilize by resonance. A combination of **inductive** & **steric** effects can be used the explain the relative reactivity of aldehydes and ketones:

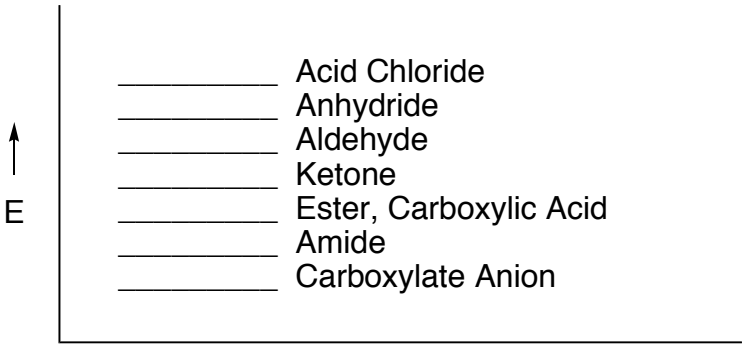




Compare the electrostatic potential maps of the various Type 1 *carbonyls:*



SUMMARIZING:



II. Irreversible Addition Reactions of Type 1 & Type 2 Carbonyls

When powerful nucleophiles add to Type 1 & Type 2 carbonyls, the reaction is irreversible.

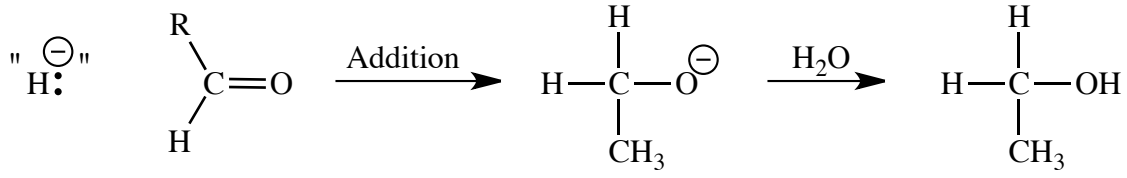
POWERFUL NUCLEOPHILES: Hydride Reagents, Organometallic reagents, Sodium alkynides

Type 1:

Type 2:

A. Addition of Hydride Reagents

Nucleophilic addition of hydride ion (**H–**) to the electrophilic carbon atom of the carbonyl group results in the reduction of the carbonyl group.



Addition of H_2 across double bond
(reduction!)

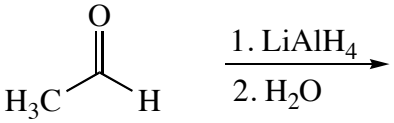
H^- source: Sodium borohydride ($NaBH_4$)
Lithium Aluminum hydride ($LiAlH_4$)
No NaH!!!

These two hydride sources have very different reactivity:

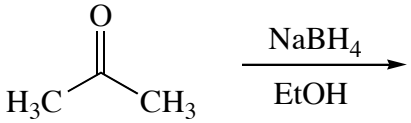
- $NaBH_4$ is much weaker than $LiAlH_4$ and reacts slowly with water.

- $LiAlH_4$ reacts violently with water (use dry solvents - quench carefully).

Typical reaction of Type 1 carbonyl:

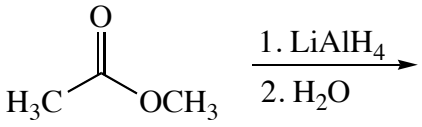


A similar reaction occurs with Type 1 carbonyls and $NaBH_4$:



- $NaBH_4$ only reacts with aldehydes and ketones.
- Reaction is typically run in an alcohol solvent, so a second protonation step is not needed.

Typical reaction of Type 2 carbonyl:

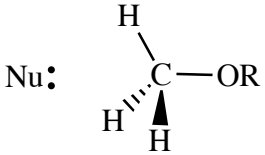


NOTE!!! Alkoxide ion is a leaving group in this reaction!

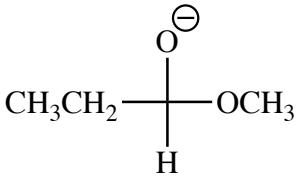
Q. ***How*** can an alkoxide act as a L.G???

A. The bond energy of a carbonyl group is so high (179 kcal/mole), that there is a powerful driving force for the expulsion of the alkoxide and the formation of a carbonyl group in this type of reaction.

In an S_N2 reaction:



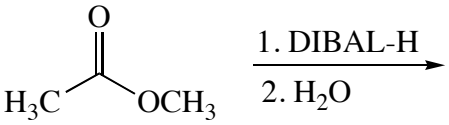
Compare with:



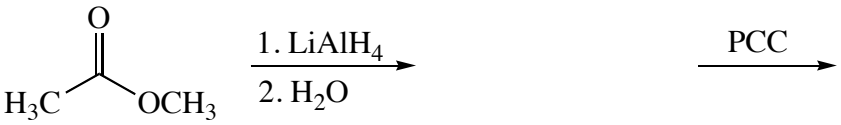
Another reaction where we've seen an alkoxide act as a L.G.:

IMPORTANT **points about hydride addition to carbonyls:**

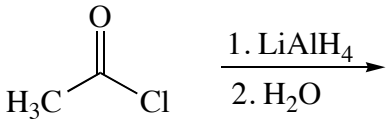
1. Remember, $NaBH_4$ is not powerful enough to add to Type 2 carbonyls.
2. $LiAlH_4$ adds twice to esters, even if only one equivalent is used. To stop at only *one* addition to an ester, use Diisobutylaluminim Hydride, $[(CH_3)_2CHCH_2]_2AlH$ (DIBAL-H). It is stronger than $NaBH_4$, but less reactive than $LiAlH_4$. It is used ***exclusively*** to reduce ***esters*** to ***aldehydes.***



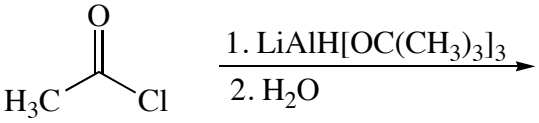
SIDE NOTE: An alternate way to convert esters into aldehydes is to use $LiAlH_4$ first to form an alcohol, and then oxidize with PCC:



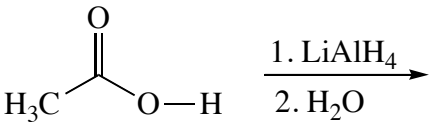
3. $LiAlH_4$ also adds twice to acid chlorides to give alcohols:



4. To stop at only *one* addition to the acid chloride, use Lithium tri-*tert*-butoxyaluminum hydride, $LiAlH[OC(CH_3)_3]_3$. It is used ***exclusively*** to reduce ***acid chlorides*** to ***aldehydes.***



5. $LiAlH_4$ reduces carboxylic acids to alcohols



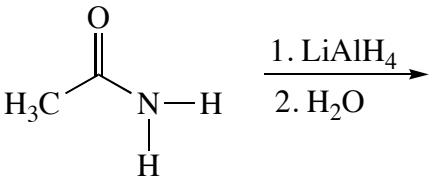
★★ **You can't directly convert a carboxylic acid into an aldehyde!**

Two alternatives:

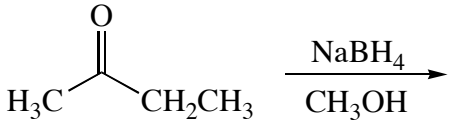
a. Reduce all the way down to an alcohol, then oxidize with PCC:

b. Convert to ester, then use DIBAL-H:

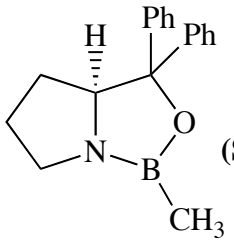
6. $LiAlH_4$ reduces amides to amines.



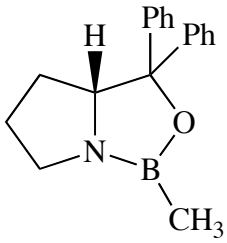
7. The stereochemistry of carbonyl reduction follows the same principles we have previously learned (*if achiral reagents react to form a new stereocenter, the result will be a racemic mixture*).



8. If a chiral reducing agent is used, enantioselective formation of a single enantiomer can occur. The CBS reagent, named for the **C**orey, **B**akshi, and **S**hibata, is one example:

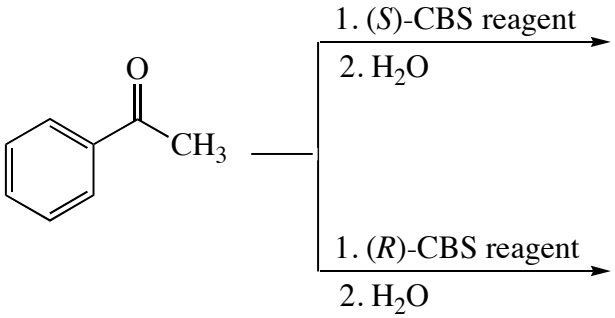


(S)-CBS reagent



(R)-CBS reagent

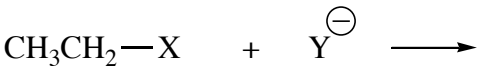
Example:



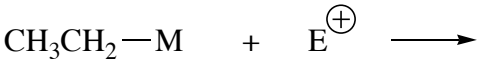
B. Addition of Carbon Nucleophiles: Organometallic Reagents

Organometallic Reagents – Background:

Alcohols, ethers, and alkyl halides all contain a carbon atom that is bonded to a more electronegative atom. The carbon atom, therefore, is electrophilic and reacts with nucleophiles.



If carbon is bonded to an atom that is less electronegative than itself, it will have a partial negative charge, and therefore be nucleophilic:



A carbon bonded to a metal is nucleophilic because most metals are less electronegative than carbon. An **organometallic compound** is a compound that contains a carbon-metal bond. We will look at three major types: organolithium, organomagnesium and organocopper reagents:

C—Li C—Mg C—Cu

- These are covalent C-metal bonds (to be ionic, the electronegativity difference must be ≥ ≈ 1.6)
- The reactivity of an organometallic compound towards an electrophile depends on the polarity of the carbon-metal bond.

Preparation of Organometallic Reagents:

Organolithium and organomagnesium (**Grignard**) Reagents are typically prepared by reaction of an alkyl halide with the corresponding metal.

ORGANOLITHIUM REAGENTS:

$$RX + 2\,Li \longrightarrow RLi + LiX$$

example:

GRIGNARD REAGENTS:

$$RX + Mg \xrightarrow[ether]{} RMgX$$

example:

Organocopper reagents (*AKA:* **cuprates** or **Gilman reagents**) are prepared from organolithium reagents by reaction with a Cu^+ salt (usually CuI)

Organocopper Reagents (Cuprates):

$$RX + 2\,Li \longrightarrow RLi + LiX \xrightarrow{CuI} R_2CuLi$$

example:

- A Grignard reagent is in the form R–Mg–X, where X= Br, Cl, or I. An organolithium reagent is in the form R–Li. An organocuprate reagent is in the form R_2CuLi
- Grignard and organolithium reagents react as if they were ***carbanions***! They are *not* true carbanions because they have **covalent** carbon-metal bonds. However we can think about them conceptually as carbanions.

Compare with sodium acetylide:

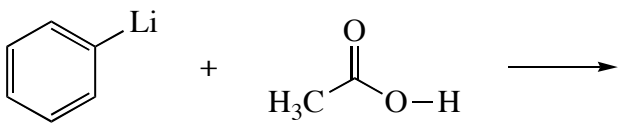
$CH_3C{\equiv}CNa$

Reaction of Organometallic Reagents:

1. **Organometallic reagents are *powerful* bases and react rapidly with protons in an acid-base reaction.**

Examples:

$$CH_3CH_2{-}MgBr + H{-}OH \longrightarrow$$



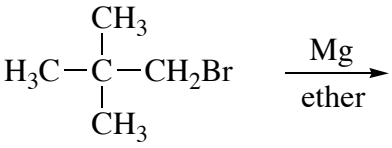
✶ This rapid reaction with water or any protic acid means that Grignard reagents, organolithium reagents, & cuprates ***cannot*** be prepared from compounds that contain acidic groups:

ACIDIC GROUPS THAT INTERFERE WITH GRIGNARD FORMATION:

$-OH$, $-NH_2$, $-NHR$, $-SH$, $-CO_2H$, $-C\equiv CH$

Example of a failed synthesis:

✶ This rapid reaction with water or any protic acid can be used synthetically to turn an alkyl halide into a hydrocarbon, or to convert an alkyl halide into a labeled hydrocarbon.



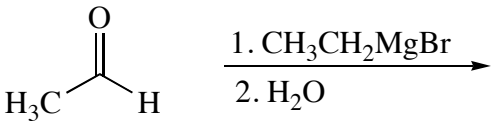
2. Organometallic reagents are powerful nucleophiles.

Organometallic reagents are very important in organic chemistry. They can react with epoxides to form alcohols. The result is an extension of the carbon chain by two carbons!

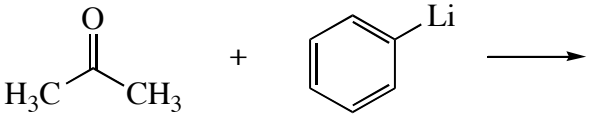
Longer extensions can be made by using substituted epoxides:

BY FAR, **the most important use of organometallic reagents is their reaction with carbonyl compounds:**

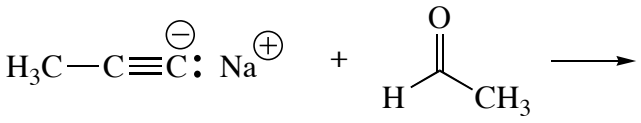
Typical reaction with a Type 1 carbonyl:



- Organolithium reagents also add in a similar way to aldehydes and ketones. They are even ***more reactive*** than Grignard reagents.



- Sodium acetylide reagents also add to ketones and aldehydes.

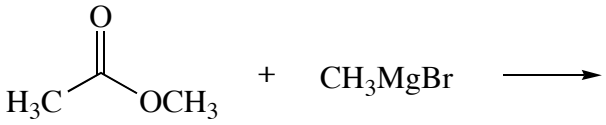


- All of these reagents react with aldehydes and ketones to form new C–C bonds. Carbon-carbon bond forming reactions are very important in organic synthesis!

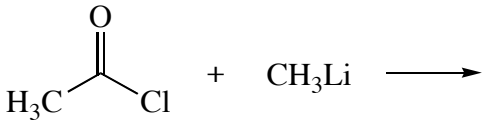
Typical reaction with a Type 2 carbonyl:

Grignard reagents, organolithium reagents, and sodium alkynides can also add to many carboxylic acid derivatives. The reaction is different, however, since carboxylic acid derivatives contain a group **L:** that can act as a leaving group.

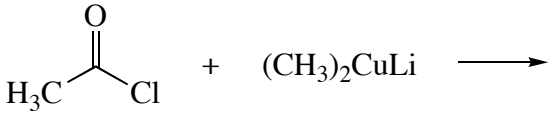
Example 1:



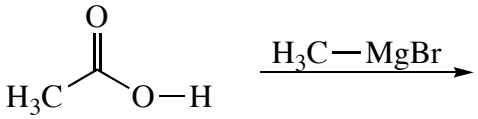
Example 2:



- Grignards will also add twice to acid chlorides because they are too reactive. Cuprates, which are the least reactive organometallic reagents will add only once.



What about carboxylic acids? Will they work in this reaction?



solution: Use CH_3Li instead

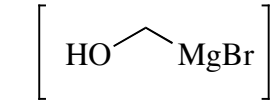
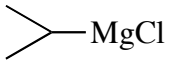
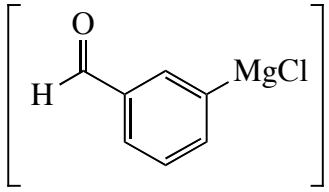
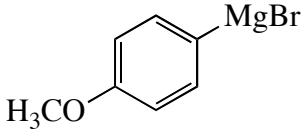
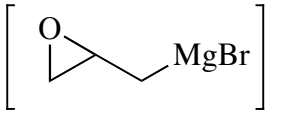
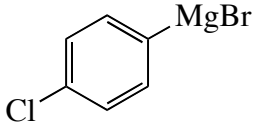
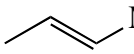
✣ **A clever reaction using Grignard reagents can actually be used to synthesize carboxylic acids:**

Summarizing **Grignard Reagents, Organolithium Reagents & Cuprates:**

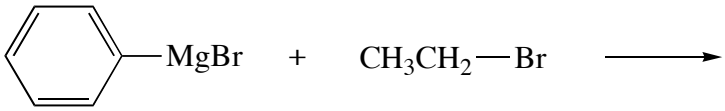
- **Grignard reagents & organolithium compounds** are extremely strong bases and powerful nucleophiles that add to Type 1 & Type 2 carbonyls and epoxides.
- Because they are strong bases, you can't make Grignard or organolithium reagents from compounds that contain acidic hydrogens. And since organocopper reagents are made from organolithium reagents, they also cannot be made from compounds that contain acidic hydrogens.

NO: $-OH$, $-NH_2$, $-NHR$, $-SH$, $-CO_2H$, $-C\equiv CH$

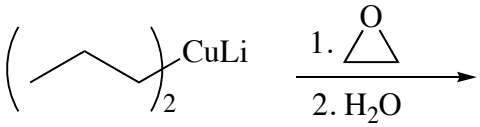
- Because Grignard reagents react with carbonyls and epoxides, that also means you can't make Grignard reagents from compounds that contain epoxides, and carbonyls! The same holds true for organothium reagents and cuprates!

Possible Grignard Reagents	Impossible Grignard Reagents
CH_3MgBr	
	
	
	
	
	

- ***Grignards & organolithium reagents DO NOT*** *react with alkyl halide in S_N2 reactions!*

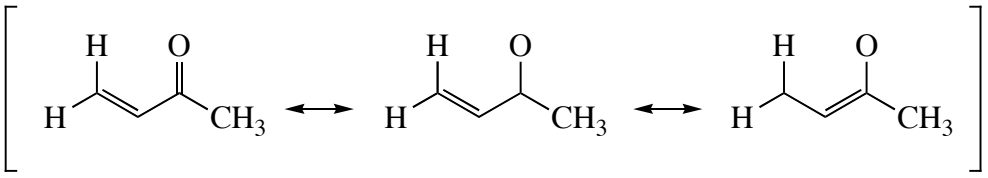


- **Cuprates** have their own unusual chemistry. They react with epoxides and acid chlorides, but they ***do not*** add to other Type 1 & Type 2 carbonyls. They also add to α, β- unsaturated carbonyl compounds in the β-position exclusively, as we'll see in the next section. Cuprates ***do*** react with alkyl halides to produce substitution products, but we will not be covering this reaction in 51C.

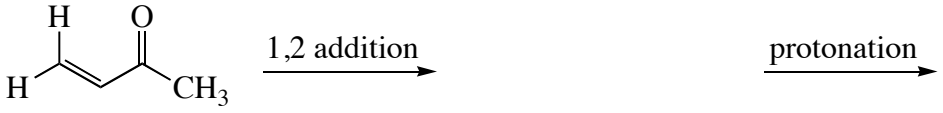


III. α, β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds have unusually reactive double bonds. The β-carbon atom is electrophilic because it shares the δ^+ charge of the carbonyl carbon through resonance.

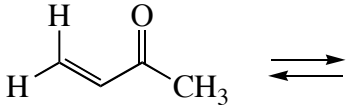


A nucleophile can attack an α,β-unsaturated carbonyl compound @ the carbonyl carbon itself. This is known as a **1,2 addition**.

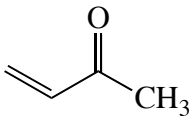


Or

A nucleophile can attack an α,β-unsaturated carbonyl compound at the β-position. This is known as a **1,4-addition** or a **conjugate addition**.



Conjugate Addition Competes With Addition to the Carbonyl!



* When nucleophiles that undergo irreversible carbonyl additions are used, the carbonyl addition product is observed.

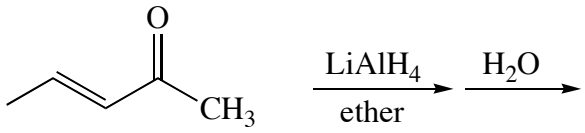
RMgX, RLi, $LiAlH_4$, $NaBH_4$, $RC{\equiv}C^{\ominus}$

* When nucleophiles that undergo reversible carbonyl additions are used, the conjugate addition product is observed.

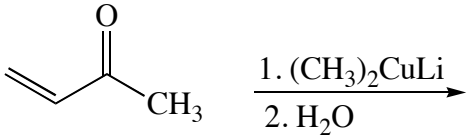
ROH, RNH_2, RSH, cuprates, $N{\equiv}C^{\ominus}$ + stabilized enolates

Examples:

1.



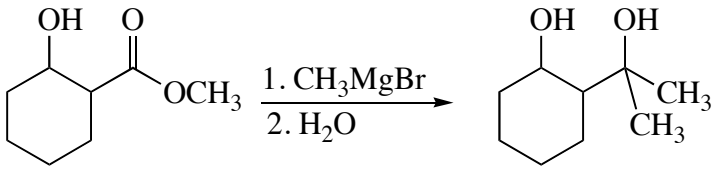
2.



IV. Protecting Groups in Synthesis

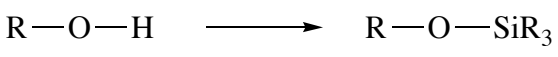
A protecting group converts a reactive functional group into a group inert to the conditions of a desired reaction. This is important in synthesis because molecules of biological interest often contain multiple functional groups that can cross-react.

Example: *Suppose you wanted do the following transformation:*

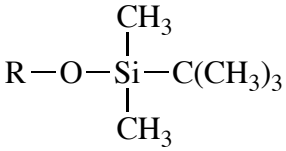


Problem: GRIGNARD WILL DEPROTONATE OH INSTEAD!

Solution: **Protect the alcohol.** A common alcohol protecting group is a silyl ether. A widely used version is the tert-butyl-dimethylsilyl ether:



Most common silyl ether: **TBDMS ether**



tert-butyl-dimethylsilyl ether

Synthesis:

- Trialkylsilyl ethers are stable from pH 2 – pH 12.
- Deprotect with strong acid or F^-. *Why F^-? The S-F bond is one of the strongest σ-bonds known.*

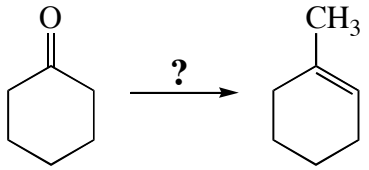
V. Designing Syntheses

We are rapidly building up an "arsenal" of organic reactions that we can use to transform one compound into another.

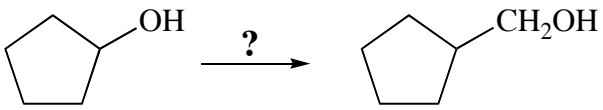
Synthetic Design: The ability to combine and transform simple molecules into new structures with the desired functional groups, is both a skill and an art. There may be many different approaches, each with its own advantages and disadvantages. And, more often than not, synthetic plans yield unexpected and surprising results in the lab, necessitating changes along the way in a multi-step synthetic strategy.

Restrosynthetic Analysis: A helpful tool for solving multi-step synthetic problems, this strategy involves working backwards from the product to the starting material. A retrosynthetic arrow is used to denote that this strategy is being used.

Example 1: Synthesize the following compound from the given starting material:



Example 2: Synthesize the following compound from the given starting material:



Example 3: Devise a synthesis of the following compound from compounds having four or fewer carbons.