

Hy Vu

# Organic Chemistry II

Lecture Notes

*Prof: Dr. Pavelka, et al.*



McGill



# **McGill Organic Chemistry II**

## **Lectures (CHEM 222)**

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# Foreword

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**Prerequisites:** General Biology I + II, adequate knowledge of general and organic chemistry.

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Chapter 1 will cover a brief revision of organic chemistry 1 (functional groups and hydrocarbons) and an introduction into IR spectroscopy which is a spectroscopy technique using infrared radiation.

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## 1.1 A brief Revision of Organic Chemistry I

**Definition 1.1.** **Organic Compounds** are compounds that contains at least 1 carbon-hydrogen or carbon-carbon bond.

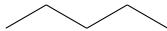
Because of this definition, there is a large amount of possible combination however, we still classified them into 3 groups: hydrocarbon, single and multiple bond functional group

### 1.1.1 Hydrocarbons

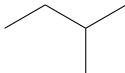
**Definition 1.2.** **Hydrocarbons** are any organic compounds with only C and H atoms covalently bond together.

We can further classifies these compounds according to the type of bond it possesses and also its structure

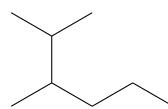
**Example 1.1.1.** We call hydrocarbons with only single bonds between the carbon, **Alkanes**. The C atoms for alkanes are  $sp^3$ -hybridized and would form a tetrahedral bond configuration.



pentane



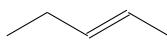
2-methylbutane



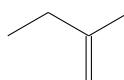
2,3-dimethylpentane

**Naming:** main strand would have suffix *-ane* while minor "daughter" strands would have suffix *-yl*

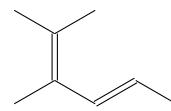
**Example 1.1.2.** We call hydrocarbons with at least 1 double bonds between the carbon, **Alkenes**. The C atoms for alkenes are  $sp^2$ -hybridized and would form a trigonal bond configuration.



1-methylbutene



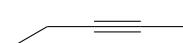
2-pentene



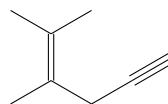
2,3-methyl-2,4-hexadiene

**Naming:** main chain would have suffix *-ene*; if 2 or more double bond exist add *di-*, *tri-* etc. prefix and indicate each of its position.

**Example 1.1.3.** We call hydrocarbons with at least 1 triple bonds between the carbons, **Alkynes**. The C atoms for alkynes are  $sp$ -hybridized and would form a linear bond configuration.



1-methylbutene



2,3-methylhexa-1-en-5-yne

**Naming:** main chain would have suffix *-yne*; if 2 or more double bond exist add *di-*, *tri-* etc. prefix and indicate each of its position.

**Remark 1.1.** When assign locant number, we prioritize double bond over triple and triple over single.

**Example 1.1.4.** We call hydrocarbons that forms ring (close loop) conformation **Cyclic Hydrocarbons** which can be cycloalkanes, cycloalkenes. When these cyclic hydrocarbons follows the *Huckel's rule*, we call them **Aromatic Hydrocarbons**.



cyclohexane



cyclohexene

benzene  
(aromatic)

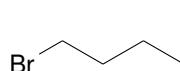
**Naming:** The ring would have prefix *cyclo-* added.

## 1.1.2 Single and Multiple Bond Functional Group

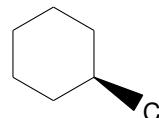
**Definition 1.3.** A **Functional Group** is a group of atom with distinctive chemical properties. While an **R Group** (R) is an abbreviation of any group of carbon or hydrogen atom attached to a molecule.

We begin with the so call "single bond functional group" which can be thought of as a functional group with maximum 1 single bond or even only 1 atom.

**Example 1.1.5.** A single bond functional group made from halogen (X) binding to an R group is called a **Alkyl Halide**.



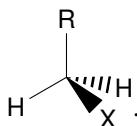
1-bromobutane



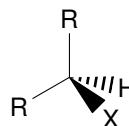
Chlorohexane

**Naming:** Prefix of *halo-* is added according to the atom will be added in alphabetical order e.g.

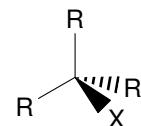
Additionally, alkyl halides are further classified according to the amount of R group attached to the C atom bearing the halide



1° Alkyl Halide

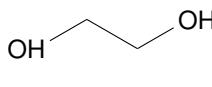


2° Alkyl Halide

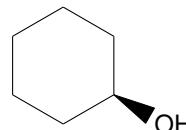


3° Alkyl Halide

**Example 1.1.6.** A single bond functional group made from an OH binding to an R group is called an **Alcohol**.



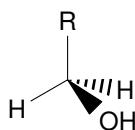
ethylene glycol



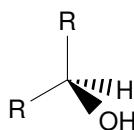
Phenol

**Naming:** Suffix of *-ol* or simply addition of *hydroxyl*.

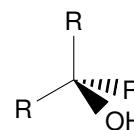
Like alkyl halides, alcohols are further classified according to the amount of R group attached to the C atom bearing the alcohol.



1° Alcohol

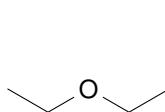
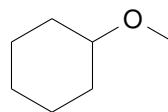


2° Alcohol



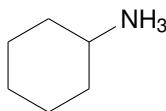
3° Alcohol

**Example 1.1.7.** A single bond functional group made from an O atom binding to 2 R group is called an **Ether**.

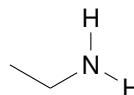
symmetrical  
ethersasymmetrical  
ethers

**Naming:** Suffix of *-oxy* or simply addition of *-ether* suffix.

**Example 1.1.8.** A single bond functional group made from an N atom binding to a/many R group is called an **Amine**.

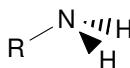


Aniline

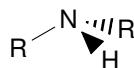


Ethylamine

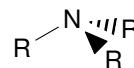
**Naming:** Addition of *-amine* suffix. Like alkyl halides, amines are further classified according to the amount of R group attached to the C atom bearing the amine.



1° Amine



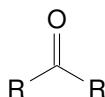
2° Amine



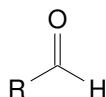
3° Amine

As for the multiple bond functional group, it is made up with many bonds of more than 1 atom. We will briefly go through the list.

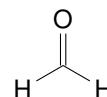
**Example 1.1.9.** Functional group consists of a CO bond to 2 R groups is called **Ketone**; if 1 of the R group is replaced with H atom, we call it an **Aldehyde**



Ketone

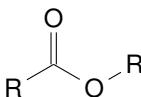


Aldehyde

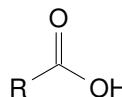


Formaldehyde

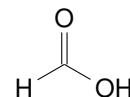
**Example 1.1.10.** Functional group consists of a *COO* bond to 2 R groups is called **Ester**; if the R group on the O atom is replaced by an H atom, we call it an **Carboxylic Acid**.



Ester

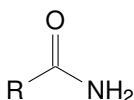


Carboxylic acid

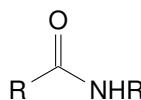


Formic Acid

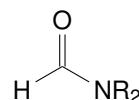
**Example 1.1.11.** Functional group consists of a *CNO* bond to 3 R groups is called **Amide**. An amide can be substituted or unsubstituted.



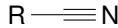
Unsubstituted Amide



Substituted Amide



**Example 1.1.12.** Functional group consists of a *CN* bond to 1 R groups is called **Nitrile**.



Nitrile

### 1.1.3 Saturation

**Definition 1.4.** **Saturation** of a molecule or compounds refers to the maximum amount of Hydrogen atom it can have.

Alkanes with formula  $C_nH_{2n+2}$  sets the standard saturated state for a certain amount of carbon found in an atom e.g. If a molecule was to have 6 carbon then maximum it should have 14 H atom. This standard will become unsaturated if structure like  $\pi$ -bond and ring was to occur. For alkanes or saturated molecules, it has a **degree/unit of unsaturation of 0** while

for 1  $\pi$ -bond or 1 ring it would count as 1 unit of unsaturation e.g. hexane has a unit of saturation of 0 but cyclohexane would have a saturation unit of 1. This unit is additive and can accumulate.

Not only  $\pi$ -bond and ring but other atoms too: O atom would be ignored; for every N atom, we subtract 1 H atom (i.e. add 1 unit of unsat.); and for every X atom, we add 1 H atom (i.e. subtract 1 unit of unsat.) The following are some common unsaturation of different compound we've seen above.

	Alkanes	Cycloalkanes	Alkenes	Cycloalkenes	Alkynes
Example Structure					
Saturated Formula	$\text{C}_5\text{H}_{12}$	$\text{C}_5\text{H}_{12}$	$\text{C}_5\text{H}_{12}$	$\text{C}_5\text{H}_{12}$	$\text{C}_5\text{H}_{12}$
1 Functional Group Formula	n/a	$\text{C}_5\text{H}_{10}$	$\text{C}_5\text{H}_{10}$	$\text{C}_5\text{H}_8$	$\text{C}_5\text{H}_8$
Difference in # of hydrogens	0	2	2	4	
Units of Unsaturation	<b>0</b>	<b>1</b>	<b>1</b>	<b>2</b>	<b>2</b>

	Halides	Alcohols	Ethers	Amines
Example Structure				
Saturated Formula	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$
1 Functional Group Formula	$\text{C}_4\text{H}_9\text{Br}$	$\text{C}_4\text{H}_{10}\text{O}$	$\text{C}_4\text{H}_{10}\text{O}$	$\text{C}_4\text{H}_{11}\text{N}$
Comparison Formula	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$	$\text{C}_4\text{H}_{10}$
Difference in # of hydrogens	0	0	0	0
Units of Unsaturation	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

**Figure 1.1:** Unsaturation of Hydrocarbons and Functional Groups.

	Aldehydes/ Ketones	Acids/Esters	Amides	Nitriles
Example Structure				
Saturated Formula	C <sub>4</sub> H <sub>10</sub>			
1 Functional Group Formula	C <sub>4</sub> H <sub>8</sub> O	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	C <sub>4</sub> H <sub>9</sub> N	C <sub>4</sub> H <sub>7</sub> N
Comparison Formula	C <sub>4</sub> H <sub>8</sub>	C <sub>4</sub> H <sub>8</sub>	C <sub>4</sub> H <sub>8</sub>	C <sub>4</sub> H <sub>6</sub>
Difference in # of hydrogens	2	2	2	4
Units of Unsaturation	1	1	1	2

## 1.2 IR Spectroscopy

**Definition 1.5.** **Spectroscopy** is a study of the absorption and emission of light and other radiation of matter. **IR Spectroscopy** (IR spec) is a spectroscopy technique that uses infrared radiation (IR) to study molecules interactions.

When molecules is exposed to different electromagnetic radiation, it would react differently. In the case of IR, it would cause the molecule to vibrate. The typical process of IR spec follows by passing an infrared beam (wavelength range of  $\lambda = 780 - 1.0 \times 10^6 \text{ nm}$ ) through a sample. The sample would absorb the IR at specific frequencies which we can the detect the new light frequencies/intensity.

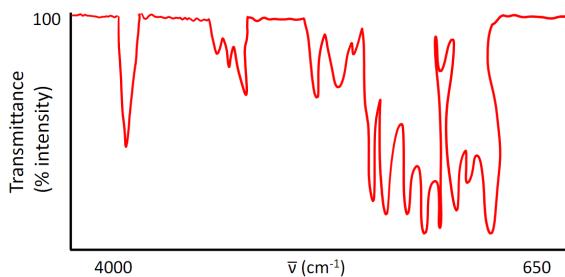
**Remark 1.2.** We typically measure the IR by a different "kind" of frequency which is the **wavenumber**  $\bar{v}$  calculated as

$$\bar{v} = \frac{1}{\lambda} \text{ (where } \lambda \text{ in cm)} \quad (1.1)$$

This also means that  $\bar{v}$  is measured in  $\text{cm}^{-1}$  and for IR, its range is  $10 - 12820.51 \text{ cm}^{-1}$ .

We plot the result from this absorption on a graph where the  $y$ -axis represents the percentage of transmission (with 100% being there's no absorption) while the  $x$ -axis represents the wavenumber range we would be measuring (typically we don't go to the entire IR spectrum but only a

small part of it that is  $650 - 4000\text{cm}^{-1}$ )

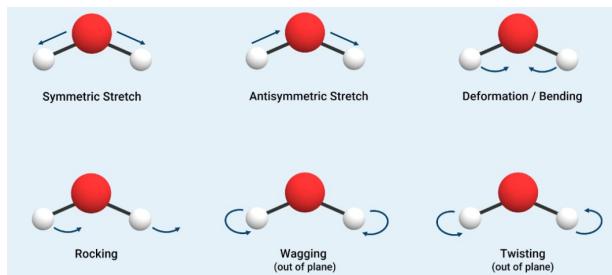


**Figure 1.2:** Brief illustration of IR spec.

### 1.2.1 Vibration

We said that IR spec measure cause the molecules to vibrate **but how do molecule vibrate?** Well...there are types of vibration at a bond (between 2 atoms) that is stretching and bending. We won't look much at bending bond but we would for stretching.

We can classify stretching vibration into 2 types **symmetric and asymmetric**. The name implies the meaning where symmetric stretch would have 2 bond apply the same stretch force of similar direction while asymmetric is the opposite.



**Figure 1.3:** Bending and stretching vibration from IR spectroscopy.

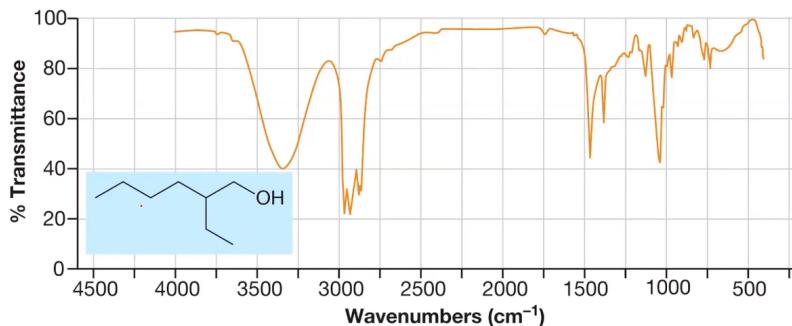
**Remark 1.3.** Molecules that is detectable or would react to IR if its vibration or movement result in a dipole moment change

**Definition 1.6.** **Dipole Moment** is the measurement of the negative and positive charge separation in a molecule.

Because of this, molecules or bonds that are symmetric would have no dipole moment change during vibration and thus is IR inactive while asymmetric would introduce dipole moment change and thus is IR active. The change of dipole due to IR would result in an electric wave which along the interference of the IR wave is called **IR absorption**.

The IR absorption intensity i.e. how strong the bond/molecule vibrate is dependent on **dipole moment strength and bond quantity**.

**Example 1.2.1.** IR spectroscopy of 2-ethylhexanol shows 2 distinctive valley or dip from frequency range of 3500 to 2500. The first dip would *OH* bond



**Figure 1.4:** IR spec of 2-ethylhexanol

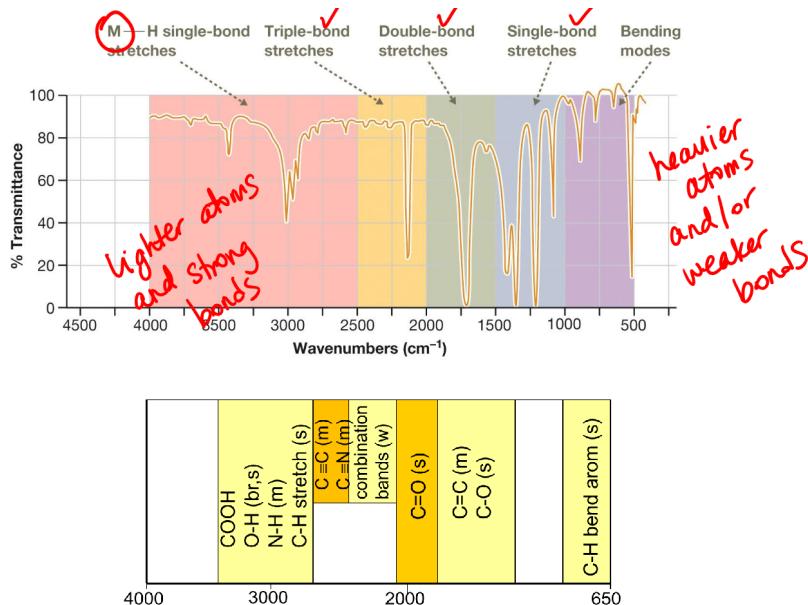
while in the second is that of *CH* bond. What you'd notice from the first dip is that it's a wide which is indicative of a very strong dipole moment (true since OH is very strong polar). In the second dip, it's much narrower but has a higher absorption (lower transmittance) indicating a smaller polar bond of *CH* but also a high amount of this bond (around 17 *CH* bond).

The IR absorption frequency  $\nu$  i.e. the frequency of IR that the molecules will absorb and produce vibration is dependent on **mass of the 2 atoms (connected by the bond)** and **bond strength**. You can think of the IR absorption frequency is proportional to a spring-mass system

$$\nu \propto \sqrt{\frac{K}{\mu}}$$

where  $K$  is the spring constant and  $\mu$  is some combination of 2 masses (more specifically  $\frac{m_1 m_2}{m_1 + m_2}$ ). For our purposes, we can think of  $K$  as the bond strength; that is, as we increase  $K$  the  $\nu$  would also increase. Similarly, if we increase the 2 atom's masses,  $\nu$  would decrease and vice versa.

*Unfortunately, the author do not have enough time to complete this section. So here's the brief summary of everything.*



Absorption Type	Functional Group	Frequency Range (cm <sup>-1</sup> )	Appearance
O—H stretch	Alcohol and phenol	3200-3600	Broad, strong
	Carboxylic acid	2500-3000	Very broad, strong
N—H stretch	Amine	3300-3500	Medium
	Amide	3350-3500	Medium
sp <sup>3</sup> C—H stretch	Alkane	2800-3000	Variable
sp <sup>2</sup> C—H stretch	Alkene	3000-3100	Weak
sp C—H stretch	Alkyne	~3300	Strong
sp <sup>2</sup> C=H stretch	Aldehyde	2720 and 2820	Strong
C≡N stretch	Nitrile	2210-2260	Medium
C≡C stretch	Alkyne	2100-2260	Variable
C=O stretch	Ketones/aldehydes	1680-1750	Strong
	Esters	1730-1750	Strong
	Carboxylic acid	1710-1780	Strong
	Amide	1630-1690	Strong
C=N stretch	Imine	1640-1690	Variable
C=C stretch	Alkene	1620-1680	Variable
	Aromatic	1450-1600	Variable
C—O stretch	Alcohol, ester, ether	1050-1150	Medium
sp <sup>2</sup> C—H aromatic bend	Monosubstituted	690-710 and 730-770	Strong
	Para-disubstituted	800-860	Strong
	Ortho-disubstituted	735-770	Strong
	Meta-disubstituted	680-725 and 750-810	Strong

# Nuclear Magnetic Resonance Spectroscopy

## Chapter

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Chapter 2 will cover core topic 1 and 2 which include nuclear magnetic resonance and mass spectroscopy and its uses for structure determination. Lectures will span on January 11<sup>th</sup>, 16<sup>th</sup> and 18<sup>th</sup>.

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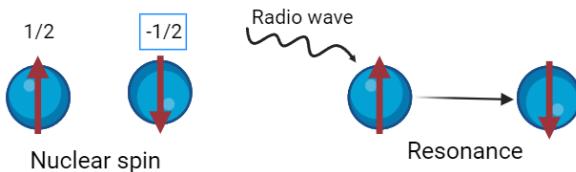
### 2.1 Theory of NMR Spectroscopy

**Definition 2.1.** **Nuclear magnetic Resonance (NMR) spectroscopy** is a spectroscopy technique which uses radio waves

From previous chapter with IR spectroscopy, we looked and analyzed sample with infrared radiation however in this chapter, we will do perform something similar but with a lower frequency that is *radio waves*. In NMR spec, we will be looking at a nuclei properties called a **nuclear spin**.

**Definition 2.2.** A **nuclear spin** is, for the sake of oversimplification, a magnetic property.

There exist 2 nuclear spin state that a nucleus can be in that is  $-1/2$  and  $1/2$  (no need to remember such number, just know that there are 2 states).

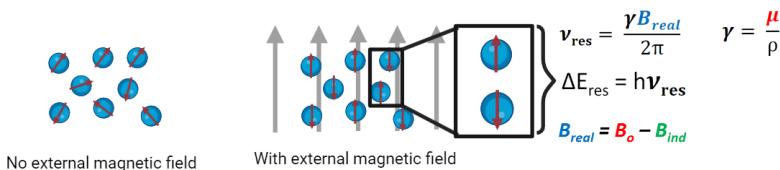


**Figure 2.1:** Nuclear spin and resonance.

**Definition 2.3.** A [nuclear] **resonance** which is the changing/flipping between nuclei's 2 spin states

**Remark 2.1.** This is not the same as electronic resonance which are structures whereby electron are moving around.

Fundamentally, when radio waves with enough energy (right frequency), it would hit the nuclei and flip its spin state. The NMR spec machine also create an external magnetic field encompassing the nuclei too. The reason for this is to align all of the nuclei's spin in a uniform manner or else they would be pointing in random direction.



**Figure 2.2:** Nuclei with and without external magnetic field.

When the spins are aligned, it would be aligned either **with or against** the direction of the external magnetic field and this allow us to measure the energy differences between them.

**Remark 2.2.** The energy differences  $\Delta E$  is dependent on several factors: strength of the external magnetic field (magnetic field where we create)  $B_o$ , nuclear magnet (inherit property of the element)  $\mu$  and electronic environment  $B_{ind}$ .

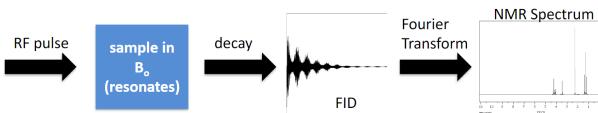
These factors are important as it gives a footprint of specific elements. In this course however, we will look at the NMR spec of Hydrogen 1 and Carbon 13 since they're considered **NMR active**.

### 2.1.1 Collecting NMR Spectrum

To collect the spectrum, we first fixed the external magnetic field at a fix value while varying the frequency of the radio wave ( $v$ ) that's being directed at the sample. Once the right frequency of radio wave is emitted in pulse, it will resonate sample in the field; after the pulse, the sample will return to its original state as well as emit energy.

Such energy will be captured and *Fourier transformed* into an NMR spectrum in frequency domain.

**Remark 2.3.** The frequency domain of NMR spectrum will carry the unit of ppm (unlike IR spec with wavenumber  $\text{cm}^{-1}$ ).



**Figure 2.3:** Brief outline of NMR spectrum obtaining.

As for the preparation of sample, we add in **deuterated NMR solvent**. We can think of this solvent as an invisible background to remove any  $^1H$  signals. Additionally, the solvent is only 99% deuterated since we need to observe also our solvent in the spectrum (differentiate it from the sample spectrum). The main NMR solvent that's used very often is **deuterated chloroform**.

Solvents	$\delta$ (ppm) of residual $^1H$
d3-acetonitrile	1.94
d6-acetone	2.05 (5)
d2-water	4.8
d4-methanol	4.87, 3.31 (5)
d2-dichloromethane	5.32 (3)
d6-benzene	7.16
<b>d-chloroform</b>	<b>7.26</b>
d6-DMSO	2.49 (5)

**Figure 2.4:** NMR deuterated solvent and their ppm of residual  $^1H$ .

**Remark 2.4.** Interestingly, the mechanism of the magnetic resonance imaging (MRI) machine is that of NMR spectroscopy. They coined the term MRI since it's more "patient friendly" than including the word "nuclear".

## 2.1.2 $^1H$ and $^{13}C$ NMR Spectroscopy

Finally, going back to the concept of NMR activity we said before when choosing which element we would be studying using NMR. The reason for  $^1H$  and  $^{13}C$  is because **they have a net nuclear spin which is dependent on the odd mass number**.

**Example 2.1.1.**  $^1H$  and  $^{13}C$ , with relative abundance of 99% and 1% respectively, has a nuclear spin of 1/2 and is thus NMR active. On the other hand,  $^{12}C$ , with relative abundance of 99%, has no nuclear spin and is thus NMR inactive.

### Features of NMR spec:

1. Number of signals (i.e. how many different nuclei)
2. Position of a signal (i.e. chemical environment of nucleus) [Chemical Shift]

3. Area under a signal (i.e. how many nuclei of a specific environment) [integration]
4. Splitting of a signal (i.e. how many neighbouring nuclei) [Multiplicity]

## 2.2 Chemical Shift

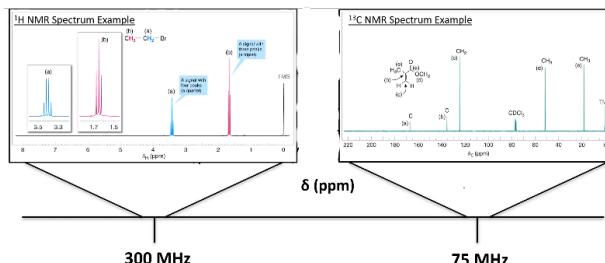
**Definition 2.4.** **Chemical shifts ( $\delta$ )** refers to the positions of signals along the  $x$ -axis of an NMR spectrum measured in ppm (part-per-million).

These chemical shifts represent the actual resonance frequency of a nucleus as well as their electronic environment.

**Remark 2.5.** It is important to note that we NEVER perform NMR of 2 elements together due to the differences in resonance frequency

**Example 2.2.1.** The standard external magnetic field we will be working with is always  $B_0 \approx 7.04\text{ T}$  (Tesla). Nevertheless, the frequency of the radiowave that will be used to resonate the nuclei (called **carrier frequency ( $v$ )**) would be different: for  $^1\text{H}$ ,  $v = 300\text{ MHz}$  ( $\gamma = 267.53\text{ rad/s/T}$ ); while for  $^{13}\text{C}$ ,  $v = 75\text{ MHz}$  ( $\gamma = 67.28\text{ rad/s/T}$ ) where

$$v = \frac{\gamma B_0}{2\pi} \quad (2.1)$$



**Figure 2.5:** NMR spec of  $^1\text{H}$  and  $^{13}\text{C}$  at 300 and 75MHz respectively.

We calculate chemical shift in ppm in order to standardize the process since it might possible that we change the magnetic field or the resonance frequency changes. Mathematically, it is given as

$$\delta = \frac{\nu_{\text{res}}(\text{nuclei}) - \nu_{\text{res}}(\text{TMS})}{\nu_{\text{carrier at } \mathbf{B}_o}}$$
 (2.2)

where  $\nu_{\text{res}}$  is the resonance frequency measured in Hz while  $\nu_{\text{carrier}}$  is the carrier frequency measured in MHz (hence part-per-million). N.B. we measure  $\delta$  in ppm with respect to TMS standard which we set to be 0 ppm.

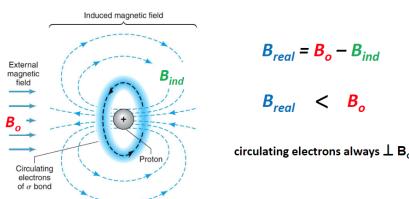
### 2.2.1 Electronic Effects

We've said that chemical shifts allow us to know about the electronic environment of a nucleus but **how?** Well...this is because when electrons move and they create their own magnetic field called **induced magnetic field  $\mathbf{B}_{\text{ind}}$** . This induced magnetic field would be parallel to the external magnetic field  $\mathbf{B}_o$  and depending on the types of electronics effect (2 types:  $\sigma$  or  $\pi$ ), it would either decrease or increase the net or **real magnetic field  $\mathbf{B}_{\text{real}}$**

$$\mathbf{B}_{\text{real}} = \mathbf{B}_o - \mathbf{B}_{\text{ind}}$$
 (2.3)

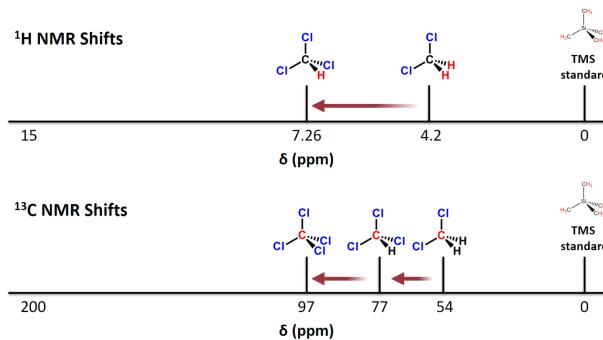
Because of the motion of electrons around a nucleus is  $\perp$  to  $\mathbf{B}_o$ ,  $\mathbf{B}_{\text{ind}}$  would be antiparallel to  $\mathbf{B}_o$  (parallel but opposing direction). This means that  $\mathbf{B}_{\text{real}}$  would decrease and this is called **shielding [effect]** N.B. the more  $e^-$  there are, the bigger the shielding effect. The opposing action where a reduced in  $e^-$  or decrease in  $\mathbf{B}_{\text{ind}}$  is called **deshielding [effect]**.

#### $\sigma$ Electronic Effects



The  $\sigma$  electronic effect deals with electrons in single bond. In such effect, nearby electronegative groups will deshield the nucleus by reducing  $e^-$  density of the  $\sigma$ -bond at the nucleus hence increases  $B_{\text{real}}$  and  $\nu_{\text{res}}$  and thus increases  $\delta$  also.

Figure 2.6:  $\sigma$ -electronic effect.

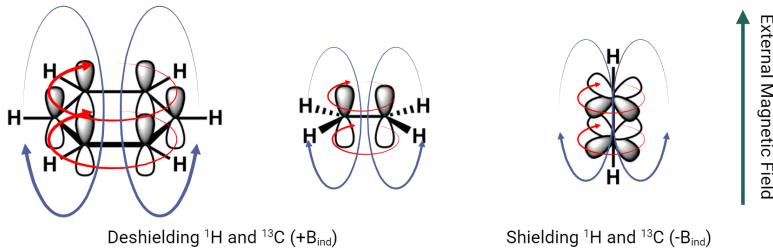


**Figure 2.7:** More deshielding (increase in resonance frequency) of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum as Hydrogen is replaced with a more electronegative element: Chlorine.

### $\pi$ Electronic Effects

On the other hand, the  $\pi$  electronic effect deals with electrons in double and triple bond. In such effect, the circulating electrons can either increase or decrease  $\mathbf{B}_{\text{real}}$  hence change the chemical shift depending on the geometry of the molecule.

**Example 2.2.2.** For a triple bond, the  $\pi$  electrons would create a shielding effect since the direction of  $\mathbf{B}_{\text{ind}}$  is opposing to  $\mathbf{B}_o$ .



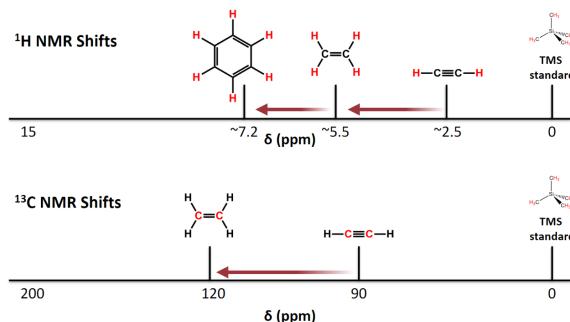
**Figure 2.8:** Deshielding of aromatic ring and double bond; and shielding of triple bond electrons. Red arrow represents electron motion while blue arrows represent  $\mathbf{B}_{\text{ind}}$ .

Meanwhile, for an aromatic ring such as benzene and double bonds, they would also have the same opposing  $\mathbf{B}_{\text{ind}}$  but there's no atom thus create no difference; however there are atoms in the surrounding where  $\mathbf{B}_{\text{ind}}$  is

with  $\mathbf{B}_o$  thus create a deshielding effect.

With these new understandings we can update the previous  $\mathbf{B}_{\text{real}}$  equation (2.3) to

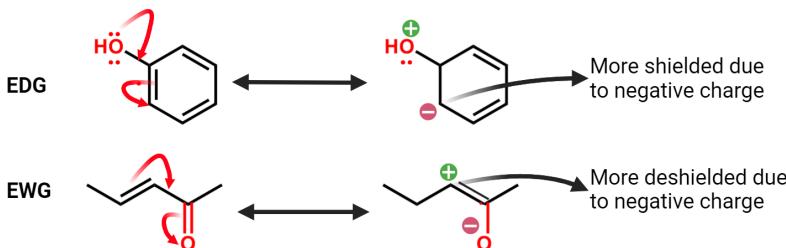
$$\mathbf{B}_{\text{real}} = \mathbf{B}_o - \mathbf{B}_{\text{ind}(\sigma)} \pm \mathbf{B}_{\text{ind}(\pi)} \quad (2.4)$$



**Figure 2.9:** More deshielding (increase in resonance frequency) of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum as triple is changed to double then benzene.

## 2.2.2 Electronic Resonances

We're just going to briefly go through resonance structure and chemical shift (come back to this idea later). In general, an atom/group that can give away their electrons in a molecule's resonance structure is called **resonance electron donating group (EDG)** while those that can take electrons is called **resonance electron withdrawing group (EWG)**.



**Figure 2.10:** EDG and EWG resonances and their effects on chemical shift.

### 2.2.3 Summary of NMR Chemical Shift Table

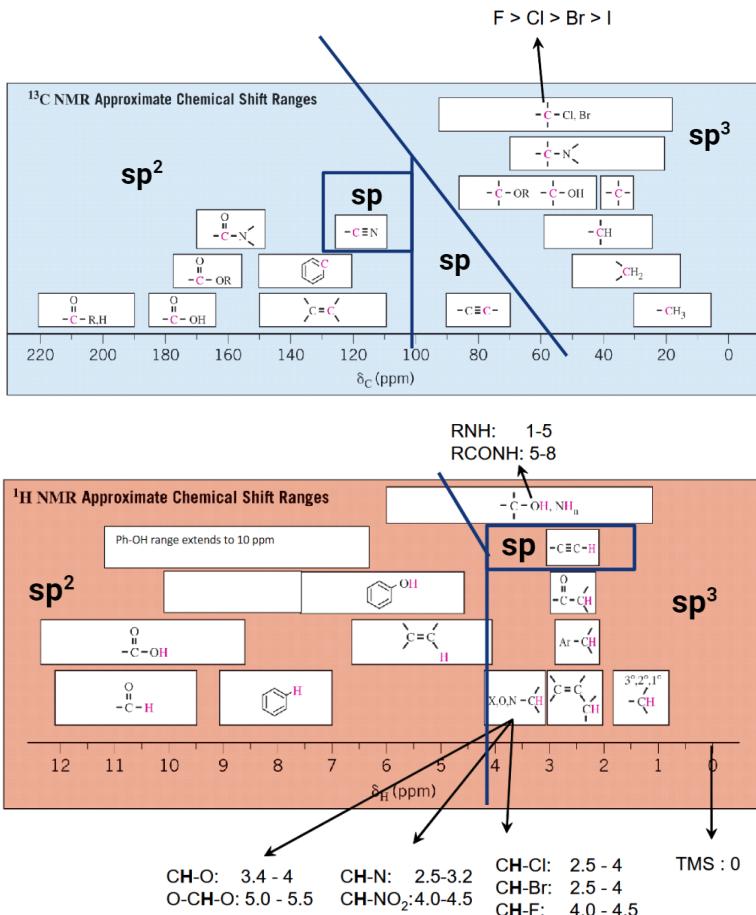


Figure 2.11: Table of  $^1\text{H}$  and  $^{13}\text{C}$  NMR.

## 2.3 $^{13}\text{C}$ NMR Spectral Analysis

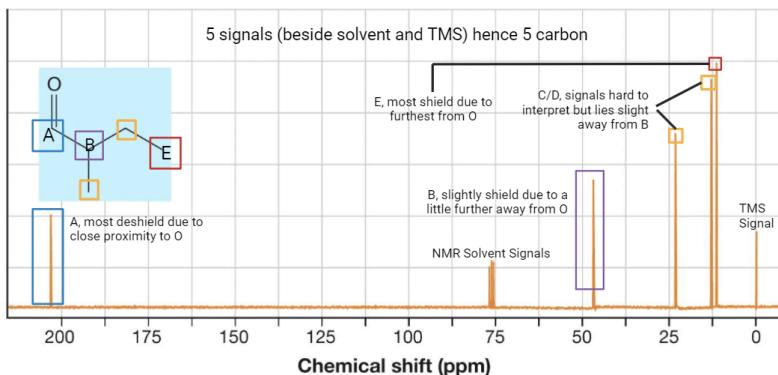
We'll go through a  $^{13}\text{C}$  NMR spectral analysis. First we need to remember how to calculate the units of unsaturation (look back at chapter 1) given as

the following formula

$$\text{Unit of unsat} = 1 + \frac{2n_1C - n_2H - n_3X + n_4N}{2} \quad (2.5)$$

where  $n_1, \dots, n_4$  are amount of each specified atoms. From the NMR spectrum, we can also determine the number of different carbon environment and brings all the information together to form a structure.

**Example 2.3.1.** The following is a simple NMR analysis of a compound.



## 2.4 Integration and Splitting

As the name implied **integration** of an  $^1H$  NMR signal is the area under curve of that signal. The signal integration value is **proportional to the amount of hydrogen at that signal**.

**Remark 2.6.** *The amount of signal does not equal the amount of hydrogen however it's the amount of hydrogen grouping.*

This number from the integration would be scaled accordingly to get a whole number that is the amount of hydrogen. An important thing to remember is that **splitting effect does not change the integration value**. When there's splitting on the  $^1H$  NMR, we simply integrate over the entire splitting grouping.

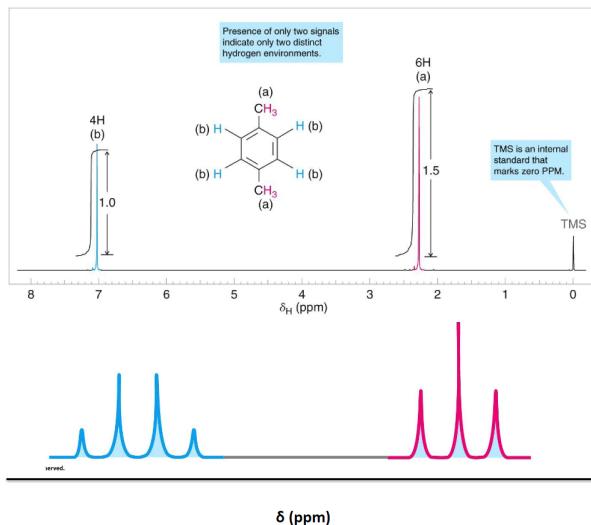


Figure 2.12:  $^1H$  NMR signal integration and splitting integration.

### 2.4.1 Splitting and Multiplicity

**Definition 2.5.** **Multiplicity** refers to the amount peak that an  $^1H$  signal split into.

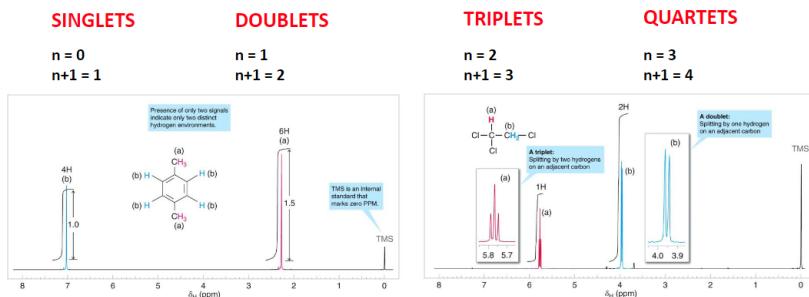


Figure 2.13: Multiplicity pattern

The splitting of signals is caused by **neighbouring nonequivalent hydrogen**. By neighbouring we mean hydrogen that are located next to the hydrogen of which we're taking the signal from. By nonequivalent we mean

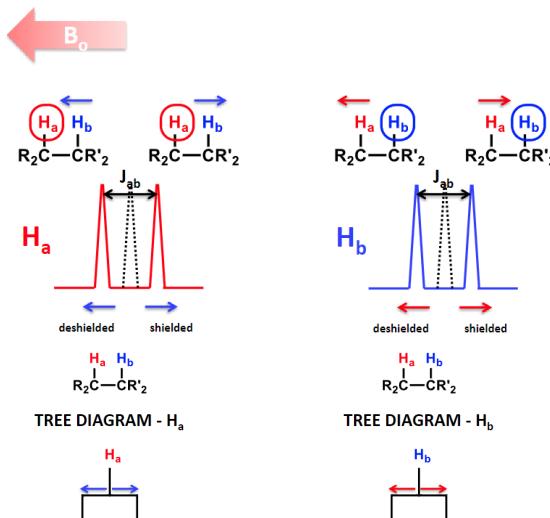
hydrogen that are not located on that same carbon as the hydrogen of which we're taking the signal i.e. hydrogen(s) that are located on carbon attached to the carbon that bear the hydrogen we're taking the signal.

These multiplicities are predictable as they follow the  $n + 1$  rule where  $n$  is the amount of neighbouring nonequivalent hydrogen. The simplest pattern is the *singlet* where there's  $n = 0$  hence multiplicity would be 1. Doublet would have  $n = 1$  hence multiplicity is 2 (2 peaks) and etc.

### Spin-Spin Coupling

The reason that the effect happens is due to the **spin-spin coupling effect**. To simplify, the signal of 1 hydrogen is affected by magnetism of the adjacent hydrogen nucleus which can either be with or against the magnetic field. This would then either deshield or shield the chemical shift hence creates splits pattern. This spin-spin coupling effect is quantified by the **coupling constant** (will be discussed next lecture).

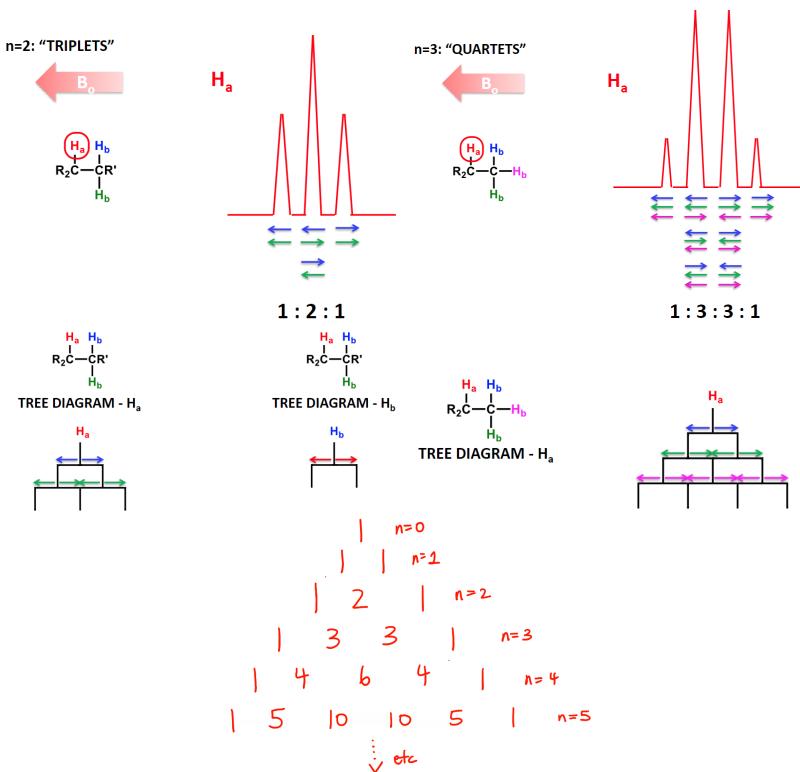
$n=1$ : "DOUBLETS"



**Figure 2.14:** Doublet pattern caused by 1 adjacent hydrogen shield and deshield the chemical shift lead to 2 peak split. A common way to represent this is through the tree diagram where each branch represent a possible spin alignment (for doublet it's 1 with or 1 against).

We can do this for triplet and quartet also and what we realize from the

pattern of their ratio combination (see Figure 2.15), it has a similarity to that of Pascal's triangle



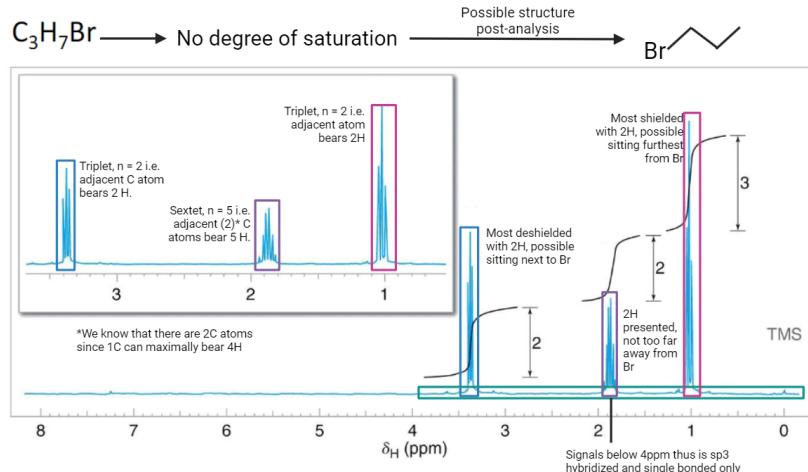
**Figure 2.15:** Triplet and quartet NMR signal and their tree diagram. The ratio simply represents the amount of each spin alignment combination of the nonequivalent hydrogen e.g. for 1:2:1, 1 means only 1 combination where both nonequivalent hydrogens align with the external field etc. The ratio pattern is similar of Pascal's triangle

## 2.5 $^1H$ NMR Spectral Analysis

Now that we're fully equipped, we'll look at  $^1H$  NMR spectral analysis. To do so, we first determine the degree of unsaturation, then determine the number of hydrogen environments, analyse the chemical shift, integration

and multiplicity. Finally, we can put together all of what we know and get the structure.

**Example 2.5.1.** The following is the  $^1H$  NMR spectral of  $C_3H_7Br$  to determine its structure.



**Remark 2.7.** We want to note that when certain groups are symmetric, for both NMR, **2 signals will merge into a bigger one!**

This lecture is a continuation of NMR spec where we will be looking at more advanced method and determination of a molecular structure.

## 2.6 Advanced $^1H$ Equivalency

The reason  $^1H$  NMR is hard because you tend to have multiple Hs on a carbon and as you will see later on, not all of H on the same carbon would be equivalent. A simple way to check equivalency is as follow

1. Draw all the hydrogen bond.
2. Check the bond rotation (e.g. 3H on an  $sp^3$  carbon are equivalent since they're related by rotation hence will appear as 1 signal).
3. Check symmetry (e.g. Hs are symmetric on benzene ring hence are equivalent and will appear as 1 signal.)

In this section, we will look at more complicated hydrogen location where there's a **chirality center** (a center atom with 4 groups bond in a way that it has a non-superimposable image), a ring and a terminal alkenes.

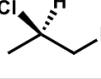
### 2.6.1 Replacement Test

To check if hydrogen in the above mentioned structures, we perform the replacement test which is as follow

1. Locate hydrogens that you want to check for equivalency
2. Replace 1 hydrogen with a random group (e.g. D or X) while keeping the other hydrogen. After replacement, observe its structure.
3. Replace the other hydrogen with a random group while keeping the previous hydrogen. After replacement observe its structure.
4. Compare these structure if they're **identical, enantiomers, diastereomers or completely different** then a number of signal will be associated with each stuctures.

After replacement, if the 2 structure are identical and we assign them as **homotopic** which has 1 signal. Similarly, if there were enantiomers, their assignment is **enantiotopic** which as 1 signals.

On the other hand, if after replacement and 2 structures are either diastereomers or different, their assignments are either **diastereotopic** or **heterotopic**, and both will have 2 signals.

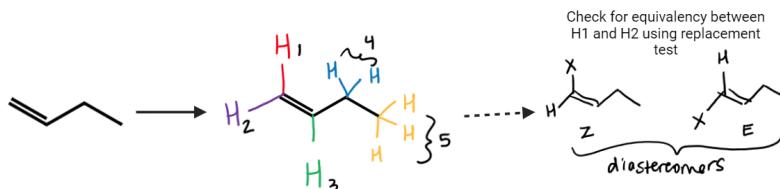
Example	Replacement 1	Replacement 2	Comparison	Assignment	Number of signals
			Identical	Homotopic	1
			Enantiomers	Enantiotopic	1
			Diastereomers	Diastereotopic	2
			Different	Heterotopic	2

**Figure 2.16:** Table of hydrogen equivalency using replacement test. The red star "\*" is for chirality center.

**Example 2.6.1.** How many different  $^1H$  signal would you be able to observe for the following compound:

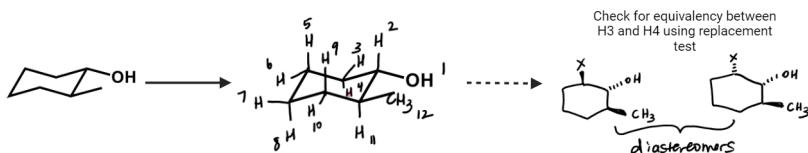


**Solution:** In the first compound, we would have 5 signals.



Starting from the carbon-4 side, we observe 3 hydrogen (yellow) that are equivalent by rotation hence 1 signal. On C-3 we observe (blue) the 2 Hs are also equivalent. On C-2 there's 1 hydrogen (green) which is evidently 1 signals. For C-1, 2 hydrogens (purple and red) at an alkenes terminals which after using replacement turns out to have diastereotopic assignment, hence 2 different signals.

In the second compound, we would have 12 signals. To begin with, all of the Hs in the ring make 1 signal since the replacement test between Hs at 1 carbon yield a diastereotopic relationship hence each carbon where 2 hydrogens are would give 2 signals. The ring has 5 carbon attached with 2 hydrogens hence 10 signals; the other 2 signals comes from the methyl group hydrogen and the hydroxyl group hydrogen.



## 2.7 Coupling Constants

Equivalency is important as it allows us to analyze more about the splitting pattern however 1 other things that can change splitting pattern is the **coupling constant (J)**.

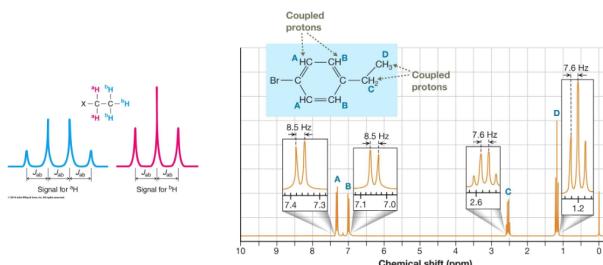
**Definition 2.6.** A **reciprocity** denotes the phenomenon between 2 neighbouring hydrogens where the effect of 1 hydrogen onto the other is equal in magnitude as the opposite effect.

We can measure reciprocity using the coupling constant i.e. the line spacing the multiplet (splitting pattern) of signal of 1 hydrogen is the same as the other H's signal.

Typically, coupling constant (J value) is measured in Hz instead of ppm and is given as the following equation

$$\frac{\text{line spacing in ppm}}{1\text{ppm}} = \frac{J \text{ value}}{300\text{Hz}} \quad (2.6)$$

The coupling constant is measured in Hz because we need to find a way to standardize the reciprocity e.g. if we were to increase the magnetic field

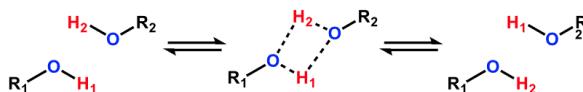


**Figure 2.17:** Reciprocity and coupling constant.

for a better resolution in the NMR spec, not much would change but the line spacing in ppm will increase which would change coupling constant if we measure it in ppm i.e. **J value is independent of field strength.**

### 2.7.1 OH and NH signals

1 thing you would notice that we don't see the OH and NH's hydrogen signal on  $^1H$  MNR spec, **why is that?** Well...because their signals are typically broad with a singlet pattern. The broad and non-splitting (singlet) is due to the hydrogen bonding and fast exchange of H between 2 OH or NH.



**Figure 2.18:** OH hydrogen bonding and fast exchange

### 2.7.2 J Value Variations

The main reason that J-value varies is due to non-equivalency between hydrogens however there are other contributing factors as well.

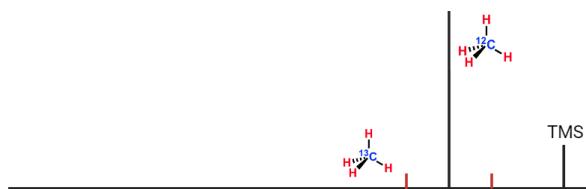
First is the **nuclei involved**. What we mean by that is the nuclei involved in the spin-spin coupling effect. Normally, we look at this in the case of  $^1H - ^1H$  couple but if we change the coupling nuclei, J value also changes. This is because **J value is proportional to the nuclei magnetic strength**

$$J_{AX} \propto \mu_A \mu_X \quad (2.7)$$

where  $A$  and  $X$  are 2 different nuclei. This is apparent when we look at  $J$  value of  $^1H - ^{13}C$  coupling that is  $^1J_{^{1H}-^{13}C} = 210\text{Hz}$ , or even with deuterium  $^1J_{^{2H}-^{13}C} = 32\text{Hz}$  and of course with  $^{12}C$ , there's no spin hence  $^1J_{^{1H}-^{12}C} = 0\text{Hz}$ .

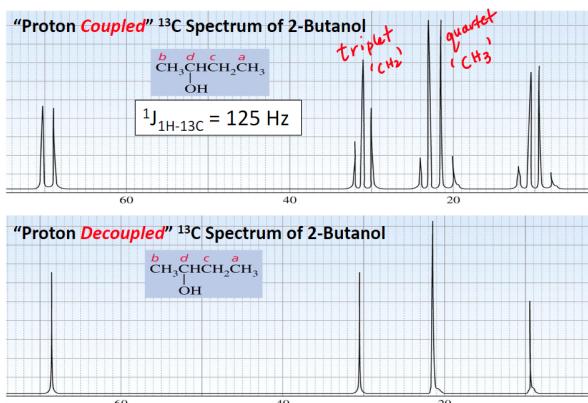
**Remark 2.8.** We don't usually see  $^1H - ^{13}C$  in  $^1H$  NMR spec because only 1% of carbon is  $^{13}C$  but when it's there we call those  $^{13}C$  **satellite peaks**.

We can spot these  $^{13}C$  when looking at the NMR of methane with strong signal and high sensitivity. The large spike represent hydrogen bounded to the  $^{12}C$  while the other are a doublet signal with  $J = 125\text{Hz}$  are Hs of  $^{13}C$ .



**Figure 2.19:** Signals of  $^{13}C$ 's hydrogen spot of methane forming an doublet signal

Talking about  $^{13}C$ , we want to take a look back into  $^{13}C$  NMR spec and ask **why are there no splitting signal (multiplicity) in it?** Well...This is due to 2 things: 1,  $^{13}C - ^{13}C$  splitting does not occur due to low abundances. 2,  $^1H - ^{13}C$  splitting pattern are often removed via **proton decoupling**.



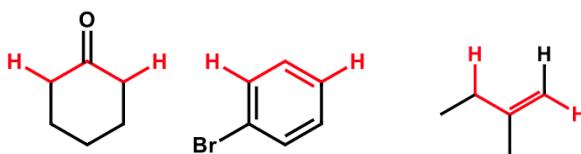
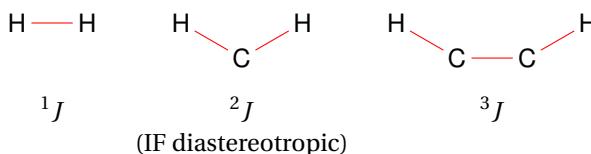
**Figure 2.20:** 2-butanol  $^{13}C$  NMR spectrum with and without proton decoupling.

If there was no proton decoupling, then the amount of splitting signals corresponds to the amount of hydrogen minus 1 ( $n-1$ ) i.e. a doublet means there's 1 H at that carbon. Now, the reason we do proton decoupling is to simplify the signal or else for complex molecules it would be hard to interpret. Additionally, proton decoupling allow us to obtain the  $^{13}\text{C}$  signals better.

The next reason for J-variation is **neighbours' distance**, that is the amount of bond between 2 neighbours (hydrogens for this examples). The amount can vary from 1 single bond all the way to 4 single bonds and what we realize is that **J-value will decrease as the distance increase**, that is

$$^1J \gg ^2J \& ^3J > ^4J$$

We mostly talk about  $^3J$  since it's the separation between 2 hydrogen with 3 bond i.e 1 bond from H to C then C to C then C to H. For  $^2J$ , it's exclusively observed in diastereotopic hydrogens; and for  $^4J$ , it's rarely observed and only in cases like rigid "W" conformation of benzenes or allylic hydrogens.

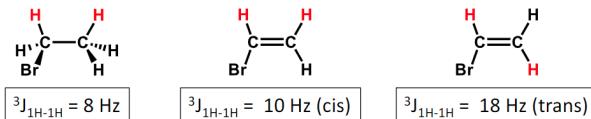


**Figure 2.21:** Rare case of  $^4J$

Next J-value variation is due to **hybridization of attached carbon**. The J-value increases as the hybridization pattern of attached carbon goes from  $sp^3$  to  $sp$  (rarely see).

$$sp^3 < sp^2 < sp$$

Remember as well, for  $sp^2$ , there are 2 possible arrangement, either *cis* or *trans* and the *trans* arrangement is always higher. Nevertheless majority of cases we'll see is  $sp^3$ .



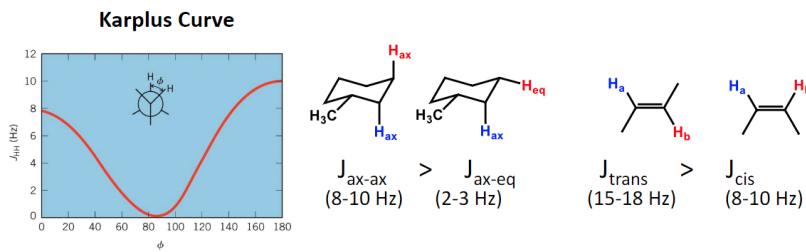
**Figure 2.22:** J value and attached carbon hybridization

Next factor of variation is **nearby electronegative elements**. When there's more EWG (see definition in lecture 1) the J value will increase

$$\text{EWG} \uparrow > \text{EWG} \downarrow$$

**Example 2.7.1.** Looking at methane and trichloromethane (chloroform) we can see an obvious difference in J value with chloroform being 210Hz while methane is 125Hz. The reason for this due to the presence of 3 electronegative chlorine in chloroform.

Finally, the last factor that lead to J-value variation is **neighbours' dihedral angle  $\phi$** . Starting  $\phi = 0$ , we have a certain amount of J-value and as it increases all the way to  $\phi = 90$ , the J-value drops to 0. Then from  $\phi = 90$  to  $\phi = 180$ , J-value will reach its maximal level (hence *trans* arrangement has a higher J-value than *cis*).

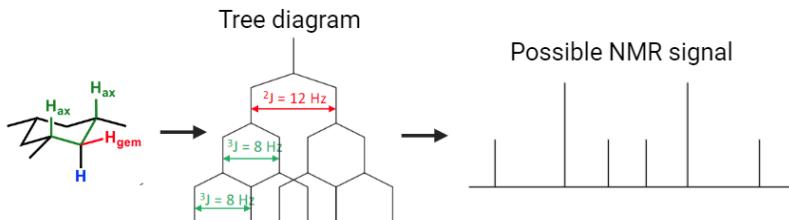


**Figure 2.23:** J-value varies according to dihedral angle.

## 2.8 Complex Splitting Patterns

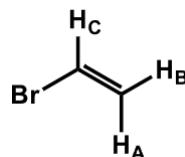
Knowing that coupling constants are not equal, we also realized that the splitting pattern will vary and lead to complex splitting pattern. This complexity can be due to splitting pattern of multiple types of  $^1H$ s

**Example 2.8.1.** The splitting pattern of the blue H (see below) is dictated first by its diastereotopic hydrogen with a coupling constant of  $^2J = 12\text{Hz}$ , then the signal split further due to its non-equivalent neighbour 3 bond away with  $^3J = 8\text{Hz}$ . Knowing this, we can construct a tree diagram and comes up with a possible signal presentation. This pattern is also called

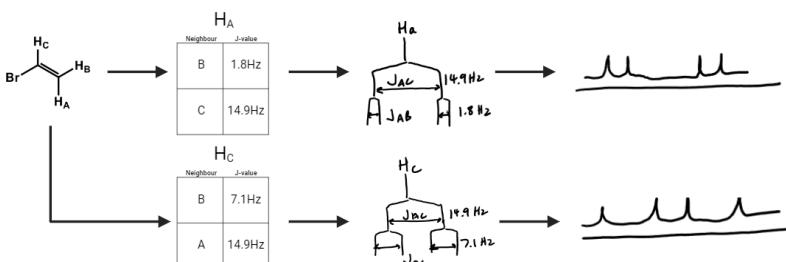


doublet of a triplet; it has a triplet since there's 2 non-equivalent neighbour while it's a double since it has 1 diastereotopic equivalent hydrogen.

**Example 2.8.2.** For vinyl bromide (bromoethylene), we've labelled the following hydrogens as  $H_A$ ,  $H_B$  and  $H_C$ . Determine the equivalency relationship between  $H_A$  and  $H_B$ . After, draw a tree diagram for the signal of  $H_A$  and  $H_C$



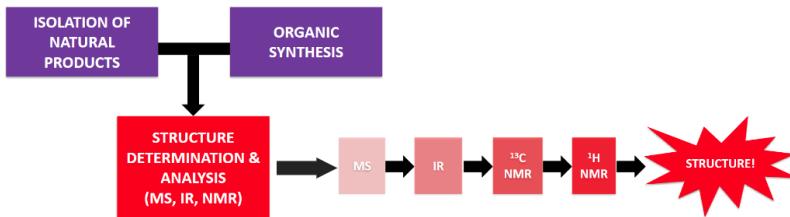
**Solution:** We can tell right-away that  $H_A$  and  $H_B$ 's relationship is a diastereotopic one. As for the tree diagram and signal, we will get it as follow



In both case, it's the signal is called *doublet of doublets*.

## 2.9 Structure Determination

With all of our knowledge of MS, IR and NMR spectroscopy; we can combine those technique together to fully solve problems involving structure determination.



**Figure 2.24:** Structure determination process' steps.

Typically, organic synthesized or isolated natural products will go under the process of structure determination to figure out what it is. This process first go through MS spectroscopy that allows us to the molecular weight and even formula of the chemical. Then IR spec would be useful to see all of the polar functional group (if there are any). Finally,  $^{13}\text{C}$  and  $^1\text{H}$  NMR spec would allow us to see the final picture of the amount, arrangement, and chemical environments of carbons and hydrogen respectively.

Chapter 3 will cover core topic 3 and 4 which include aromaticity and aromatic reaction. Lectures will span from January 23<sup>th</sup> to February 1<sup>st</sup>

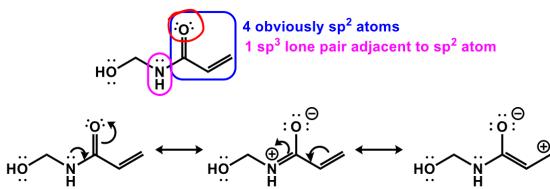
## 3.1 Revision Slides on Allylic and Conjugated System

The following will be a quick revision from CHEM 212 of all about conjugated system slides.

Not sure if a molecule has resonance structures? Follow the steps below.

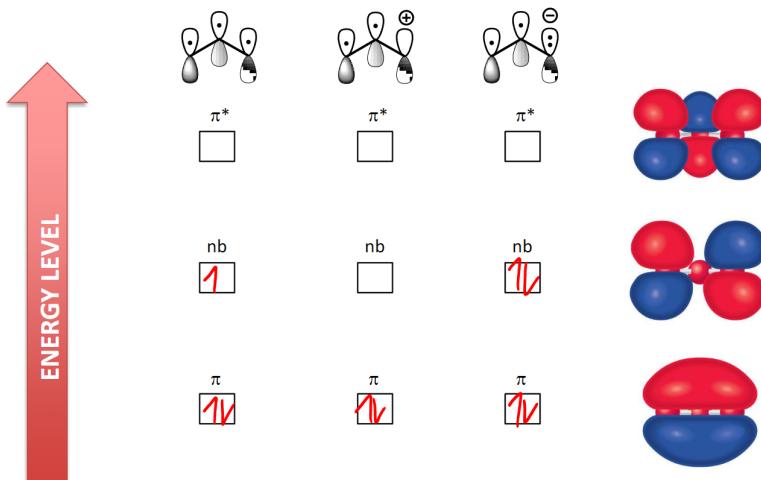
- Identify any obviously  $sp^2$  atoms (i.e. atoms involved in double bonds).
- Identify any lone pairs, cations, and/or anions (after you have labeled all formal charges and added all missing lone pairs).
- If a lone pair with four electron groups ( $sp^3$ ) is beside an obviously  $sp^2$  atom, it will be involved in resonance and take on  $sp^2$  hybridization (i.e. the lone pair will reside in a p orbital and be delocalized as part of a conjugated  $\pi$ -system).
- If there are **more than 3 consecutive  $sp^2$  atoms**, there is resonance.

\*Where to start your arrows?  
Electron movement starts at the HIGHEST electron density location (usually a lone pair on an initially assigned  $sp^3$  atom, otherwise a double bond)  
Lone pairs on obvious  $sp^2$  atoms generally do not participate in resonance



- $sp^3$  N lone pair donates towards C=O  $\pi$  bond, since O is electronegative
- $\pi$  bond breaks and electrons move onto oxygen as new lone pair

MO diagram or molecular orbital diagram is a way to describe energy of electrons in a conjugated system. Below is MO of an allylic system as we can see, it has 3 electron orbital and we characterize them through energy i.e. the lowest energy level is  $\pi$  and then the highest is  $\pi^*$ .



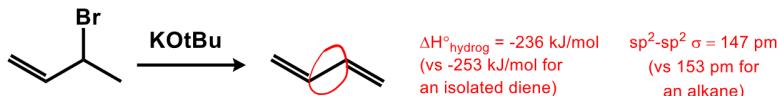
\* Orbital overlap less and less efficient as you go up in energy \*  
(introduce a new nodal plane with each step to higher energy)

## 3.2 Conjugated diene and benzene

We will now begin the lecture by looking at the conjugated system of diene (2 double bond lying close to each other) and benzene.

**Definition 3.1.** A **conjugated system** is a system of connected *p*-orbitals with delocalized electrons in a molecule, which in general lowers the overall energy of the molecule and increases stability.

### 3.2.1 Diene



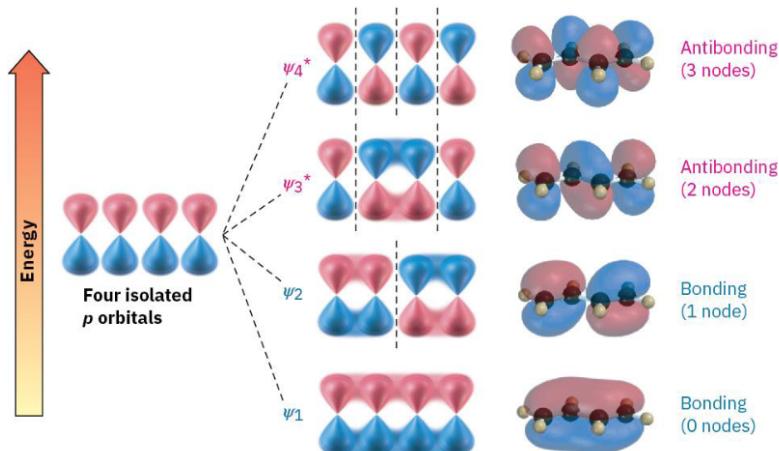
**Figure 3.1:** Bonding of diene.

An observation of diene shows that it has a lower heat of hydrogenation ( $\Delta H^\circ_{\text{hydrog.}} = -253$ ) than typical alkane. Not only that, its bonding length ( $\sigma$  bond) between 2  $sp^2$  are shorter (147pm) than that of alkane's  $sp^3$  (153pm).

**What's going on?** Well...It all comes down to the fact that there's an increased of orbitals overlap in its system.

Looking at its 4  $p$ -orbitals, we can see that at the lowest energy, we have all 4 merged together.

**Remark 3.1.** As orbital merge less, energy level increase because you're introducing new nodal plane to the structure every step to higher energy.

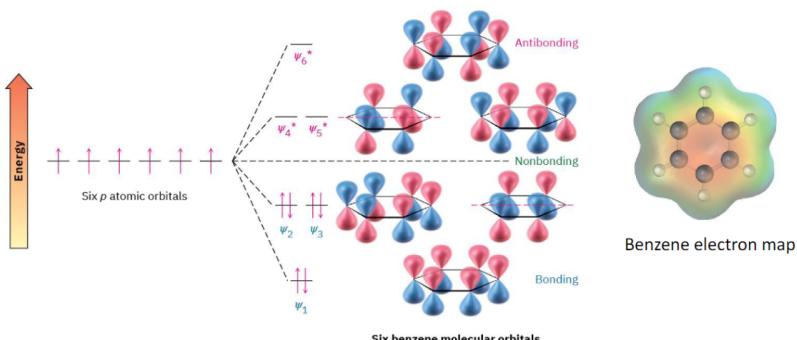


**Figure 3.2:** Different  $p$ -orbitals merging and energy level.

### 3.2.2 Benzene

**Benzene** was first isolated by Michael Faraday in 1825 and first synthesized by Eilhardt Mitscherlich in 1834, well before the structure was even elucidated! In 1929, Kathleen Lonsdale proved that benzene was flat using X-ray crystallography. We now know that this conjugated behaviour also exists in benzene, but it is even more pronounced.

What really stood out and interesting for us is that the bonding length is consistent all around the ring. Furthermore, we can look at its  $p$ -orbital energy level and realized that all of it is merged together forming a sort of electron cloud covering 2 surface of the benzene.



**Figure 3.3:** p-orbitals of benzene.

Interestingly, due to only knowing the chemical formula of  $C_6H_6$ , lots of different structure was proposed due to the peculiar chemical properties that benzene had.

### 3.2.3 Reactivity of Diene and Benzene

From what we've said above, it won't be much of a surprise that benzenes behave differently from other alkenes.

#### Diene Reactivity

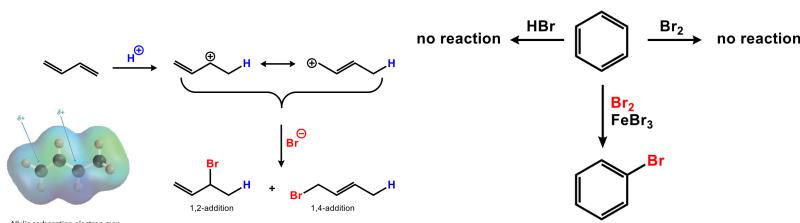
We first look at diene e.g. Butadiene does undergo standard alkene addition reactions, such as HBr addition, but there is an additional complication. Due to its conjugated system, it has a **conjugate addition, or 1,4-addition products.** (we will see why and how more on core topic 10).

#### Benzene Reactivity

Benzene does not undergo standard alkene addition reactions, such as  $HBr$  (hydrobromination) or  $Br_2$  addition (bromination). Under Lewis acid catalyst conditions, like  $FeBr_3$ , reaction will occur with  $Br_2$ , but **it is an electrophilic substitution process rather than electrophilic addition.**

**Maybe it has something to do with the cyclic structure of benzene?**

Well...to test this out, we get another molecule that has the same ring structure and conjugated  $\pi$ -system as benzene. In this case, we use **cyclooctate-**



**Figure 3.4:** Butadiene reaction yielding different the normal expected product along with its conjugated addition product (left). Meanwhile, benzene does not react with addition at all unless there's lewis acid catalyst, even then the reaction is not addition (right)

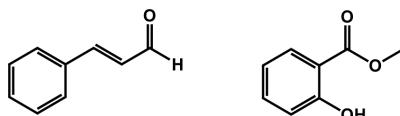
**traene** and found that **does not behave like benzene i.e. it can still undergo electrophilic addition like typical alkenes.** So **what's going on with benzene?** Well...it all comes down to a nature of benzene delocalized  $\pi$ -system



**Figure 3.5:** cyclooctatetraene hydrobromination and bromination addition.

### 3.3 Aromaticity

Gradually chemists realized that a great number of other substances were chemically related to benzene. In 1855, August Wilhelm von Hofmann used the term “*aromatic*” for the first time to describe the property those substances had in common.



**Figure 3.6:** Cinnamaldehyde and methyl salicylate has similar reactivity as benzene and thus is called begin aromatic. Interestingly, they also have smell.

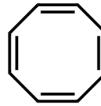
**Remark 3.2.** *Aromatic in this case does not necessarily means it has an aroma (although it usually does) but rather it's the chemical property.*

Now, the definition of "similar reactivity to benzene" is still somewhat ambiguous therefore we need a more rigorous definition of what aromaticity means. In 1931, Erich Huckel came up with the **Huckel's rule** which is a set of criteria that a molecule must meet in order to be called aromatic.

### Huckel's Rule:

1. Compound must monocyclic (1 ring) or is ring themselves.
2. Compound must be planar (continuous p-orbital array) and all atom (beside H) is  $sp^2$  hybridized.
3. The amount of  $\pi$  electron must follow  $4n+2$  rule (where  $n = 0, 1, 2, \dots$ )

From Huckel's rule, chemists also generalized it for other kind of cyclic  $\pi$ -system such as anti-aromatic and non-aromatic.

Aromatic	Anti-Aromatic	Non-Aromatic
Monocyclic, planar array of p-orbitals with " $4n+2$ " $\pi$ -electrons	Monocyclic, planar array of p-orbitals with " $4n$ " $\pi$ -electrons	Monocyclic, <b>non-planar</b> array of p-orbitals with any number of $\pi$ -electrons
<b>EXTRA STABILIZATION FOR <math>\pi</math>-SYSTEM</b>	<b>EXTRA DE-STABILIZATION FOR <math>\pi</math>-SYSTEM</b>	NO EXTRA STABILIZATION OR DE-STABILIZATION
Ex. Benzene 6 $\pi$ -electrons 	Ex. Cyclooctatetraene 8 $\pi$ -electrons 	Ex. Cycloheptatriene 6 $\pi$ -electrons (non-planar) 

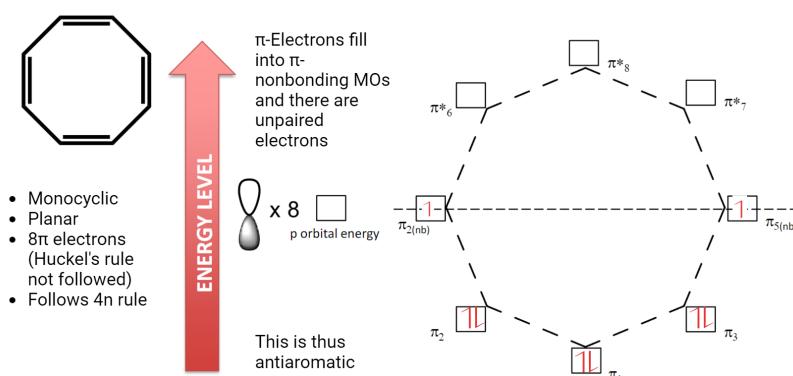
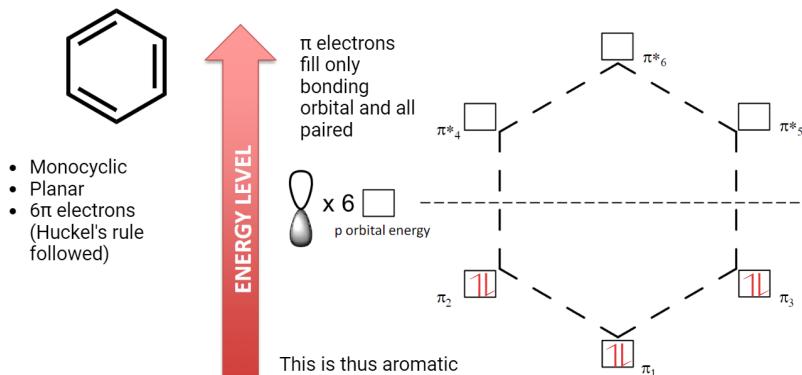
### 3.3.1 MO Diagram for Huckel's Rule

Now, another way to determine whether a molecule is aromatic or not can be seen through its MO diagram. In this instance, we use the so-called

### orbital polygon method (Frost circle)

Basically it has a circle that is inscribed with a **polygon with one vertex pointing down**; the vertices represent energy levels with the appropriate energies of the cyclic  $\pi$ -system. Vertices below the halfway mark of the circle are considered bonding orbitals  $\pi$ , and vertices above the halfway mark are considered antibonding orbitals  $\pi^*$ . If vertices are exactly in the middle (as they are for 4- and 8- membered rings) they represent non-bonding orbitals.

To be classified as aromatic using orbital polygon method, **all of its  $\pi$  electron must be in the bonding orbitals and paired up**. Let's look at some example.

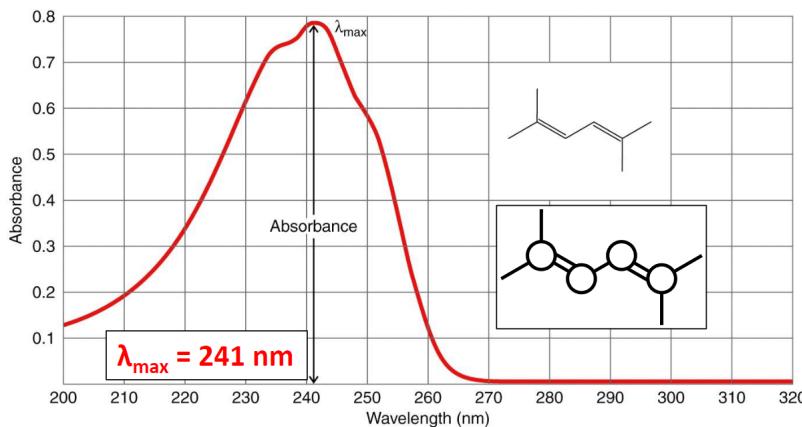


Aromatic system is important for us as some major biochemical molecule in your body (e.g. DNA) are aromatics. Nevertheless, this also poses a risk since there are toxic aromatic compounds that can come and disrupt the typical function of these our own molecules.

## 3.4 UV-Visible Spectroscopy

**Definition 3.2.** **UV-Vis spectroscopy** is a spectroscopy method that analyse with UV and visible wavelength.

UV-vis spec is important to determine the structure and conjugation of a molecule. It basically measure the amount of light absorbed by a sample at each wavelength (within the UV-VIS region of the electromagnetic spectrum). Below we can see the UV-vis spec of butadiene where it has a high absorbance at around 241nm.



**Figure 3.7:** UV-vis spec of butadiene.

**So what's going on here?** Well...to understand this, we need to know about the HOMO and LUMO gap. We can first look at the orbitals of butadiene and realized that it has 4 different p-orbitals with different energy, 2 of which is occupied at the lower energy level. The **HOMO** is the highest occupied molecular orbital while the **LUMO** is the lowest unoccupied molecular orbitals.

What happens during UV-vis spec is that light is shone onto the molecule and lead to absorption at a specific wavelength. During absorption, the electron from HOMO will be excited and jump up to LUMO. **The HOMO-LUMO energy gap is the basis behind the absorption wavelength of the molecule since energy is defined as**

$$E = \frac{hc}{\lambda} \quad (3.1)$$

where  $\lambda$  is the wavelength. So with this definition, we would know that the higher the HOMO-LUMO energy gap, the lower its absorption wavelength would be. **How can HOMO-LUMO gap changes?** Well...it can change base on the conjugation of the system. **As the molecule becomes more and more conjugated, its HOMO-LUMO energy gap decreases, therefore increases its absorption wavelength.**

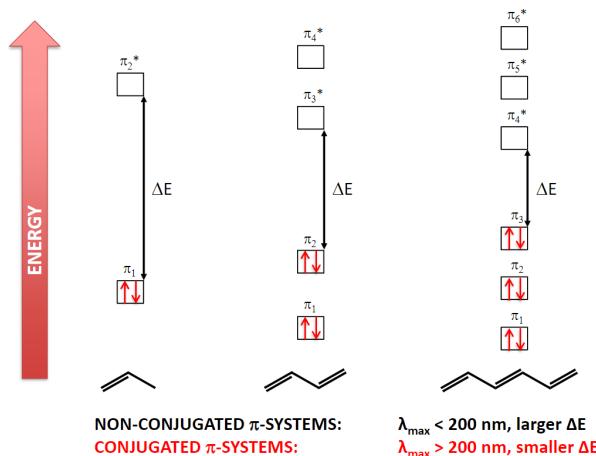
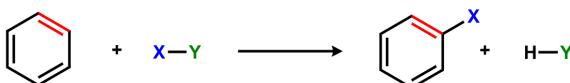


Figure 3.8: HOMO-LUMO gap variation with conjugation

For certain conjugated system, they have small enough energy gap for visible wavelength (400-700nm) to cause excitation. This ultimately will give the compound colour unlike higher energy gap where compound would have no colour.

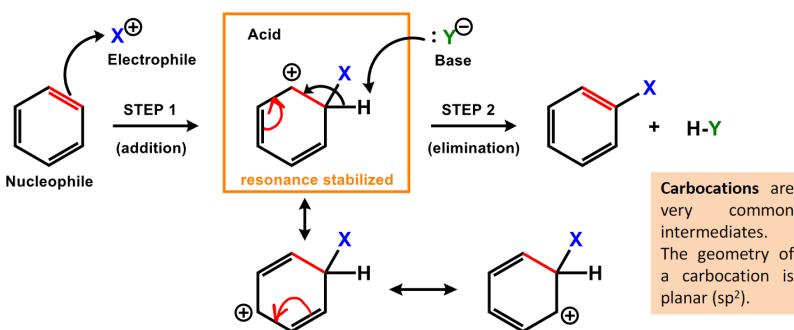
## 3.5 Electrophilic Aromatic Substitution

Instead of undergoing addition reaction like alkenes, benzenes undergo substitution reactions, called **electrophilic aromatic substitutions (EArs)**. In a substitution reaction a functional group or atom is replaced by another. The benzene p-bonds remain intact in EArs products, while a hydrogen is replaced by an electrophilic group.



**Figure 3.9:** EArs reaction where X is the electrophile (wants  $e^-$ ) while Y is the nucleophile (donates  $e^-$ ) which is also the leaving.

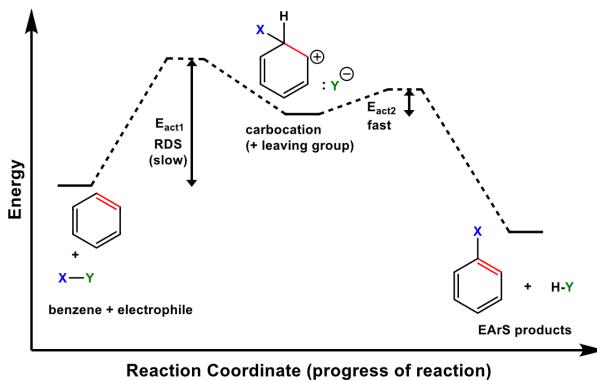
**Mechanism:** In the presence of an electrophile (X), the benzene will act as a nucleophile and attack it forming a new  $\sigma$ -bond (mechanism step 1), leading to the formation of a carbocation intermediate, just like in alkene additions. Then, rather than attack on the carbocation by the nucleophile (Y), the nucleophile (Y) acts as a base, deprotonating the  $sp^3$ C-H bond (E1 reaction), leading to the reformation of the aromatic ring (mechanism step 2).



**Figure 3.10:** EArs mechanism

EArs reactions are usually exothermic as the newly formed  $\sigma$ -bonds are more stable (higher dissociation energy) than the ones that were broken. We can visualize the energy changes during a reaction using a reaction coordinate diagram. The reaction coordinate diagram below describes

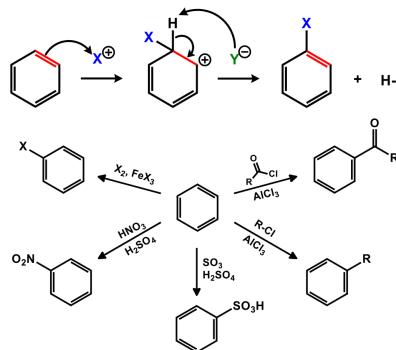
changes for a generalized EArS reaction.



**Figure 3.11:** EArS reaction coordinate.

We begin at a certain energy level for benzene then we reach the rate-determining step (RDS) that is the slowest where benzene and the electrophile reacts with each other and form the carbocation subsequently. Now, the free up nucleophile will come and pull out the hydrogen in the last step of elimination. At the end, we will get our product with a lower energy than initial i.e. there was energy released (e.g. as heat).

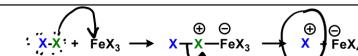
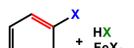
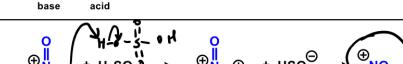
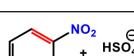
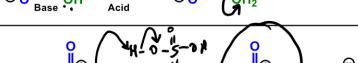
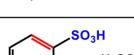
Benzene is in fact a good nucleophile however, due to its stability, it requires an even stronger electrophile to make a reaction.



**Figure 3.12:** General EArS reaction (top) and different EArS reactions (bottom).

### 3.5.1 Non-Carbon Electrophiles

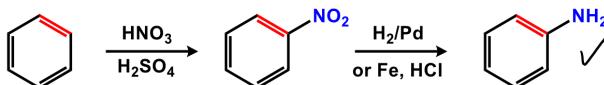
Here are the EArS reaction with electrophiles that does not involve carbons

	Conditions	"  Electrophile ("X+") Formation"	Products
Halogenation	$X_2$ , $FeX_3$		
Nitration	$HNO_3$ , $H_2SO_4$		
Sulfonation	$SO_3$ , $H_2SO_4$ ("fuming sulfuric acid")		

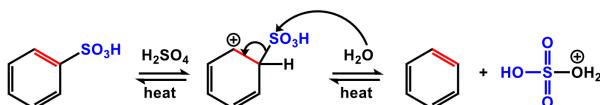
In general, you have an acid that will change the base (either by donating H or break it off in Lewis acid), which form the strong electrophiles to then attack benzene and form the desired product.

#### Post-EArS Modification

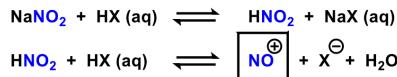
The 2 interesting reactions above that we'll look at is nitration and sulfonation. The reason is that: after completing nitration, you can perform a hydrogenation step to change the **nitrobenzene** (benzene- $-NO_2$ ) into **aniline** (benzene- $-NH_2$ ) i.e. forming an amine group from a nitro group.



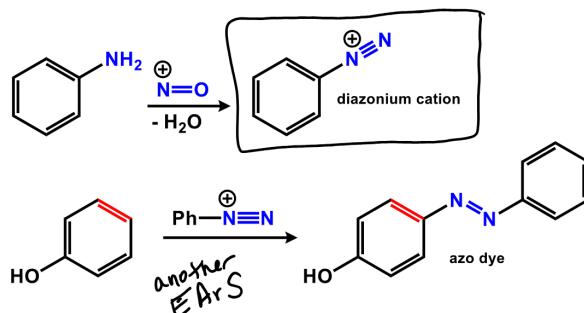
For sulfonation, it is interesting because you can reverse the chemical process i.e. you can desulfonate the sulfonation product (from benzene-sulfonic acid back to benzene). To do so, we only have to heat it up along with  $H_2SO_4$



Another reaction after this is called **Azo dye** which is commonly used in food dye. First, we need to prepare the isolated nitro group  $\text{NO}_2^+$ . This can be done by mixing sodium nitrite with a hydrogen halide (halogen acid,  $\text{HX}$ ) to form **nitrous acid**. This nitrous acid can react with more  $\text{HX}$  to break into the nitro group.



Now, using the same method as before, we will form the aniline (or more generally aryl amine), which we would use to react with the nitro group forming **diazonium cation**. This diazonium cation can then be reacted with **phenol** (benzene-OH) forming the azo dye.

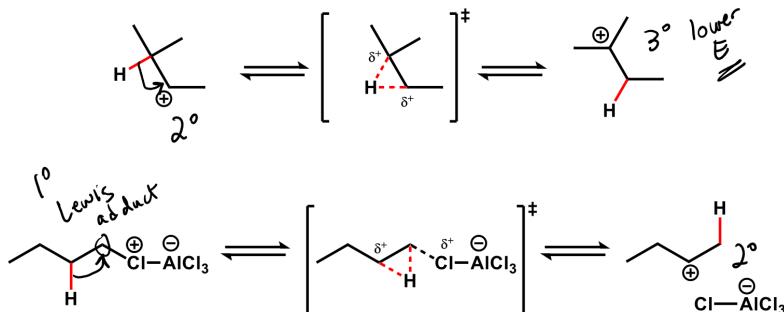


### 3.5.2 Carbon Electrophiles

The reaction of adding an R-group of carbon into benzene was proposed and developed by Charles Friedel and James Crafts. Because of this, the 2 reaction are name after them: **Friedel-Crafts alkylation** and **acylation**.

	Conditions	Electrophile ("X <sup>+</sup> ") Formation	Products
Friedel-Crafts Alkylation*	$\text{R-Cl}, \text{AlCl}_3$	<p>The mechanism shows <math>\text{R-Cl}</math> reacting with <math>\text{AlCl}_3</math>. <math>\text{Cl}^-</math> acts as a Lewis base, attacking the Lewis acid <math>\text{AlCl}_3</math> to form a <math>\text{Cl}^- \text{AlCl}_3</math> Lewis adduct. This then dissociates to form a carbocation (<math>\text{R}^+</math>) and <math>\text{AlCl}_4^-</math>. A note indicates "carbocation rearrangements!"</p>	$\text{C}_6\text{H}_5\text{R} + \text{HCl} + \text{AlCl}_3$
Friedel-Crafts Acylation	$\text{RCOCl}, \text{AlCl}_3$	<p>The mechanism shows <math>\text{RCOCl}</math> reacting with <math>\text{AlCl}_3</math>. <math>\text{Cl}^-</math> acts as a Lewis base, attacking the Lewis acid <math>\text{AlCl}_3</math> to form a <math>\text{Cl}^- \text{AlCl}_3</math> Lewis adduct. This then dissociates to form an acylium ion (<math>\text{RCO}^+</math>) and <math>\text{AlCl}_4^-</math>. A note indicates "(no rearrangements!)"</p>	$\text{C}_6\text{H}_5\text{COR} + \text{HCl} + \text{AlCl}_3$

1 thing we must pay attention about alkylation is that depending on the location of the halogen on the R-group, there could be a possible **carbocation rearrangement** event. Essentially, a carbocation always favours having the positive charge in a  $3^{\circ}$  position than in  $2^{\circ}$  than in  $1^{\circ}$ . What will happen is that hydrogen of carbon adjacent to the unfavoured cation will be there thus the cation center is moved to another the donor carbon.

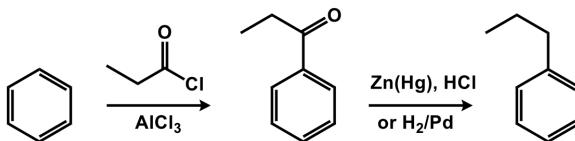


**Figure 3.13:** carbocation rearrangement

so does that mean that if we want an R-group at a certain position, we won't get it possibly due to rearrangement? Well...yes, but no worry, there are ways to go around thi.

### Aryl Alkyl Ketone Reduction Method

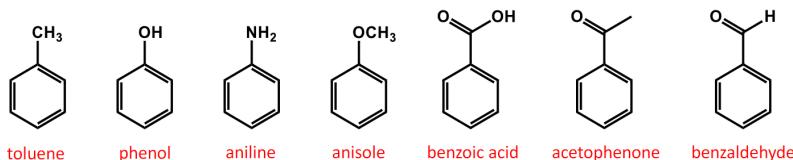
Supposed you want to add a linear alkyl group, let's say propyl, into your benzene. The usual way to do this is via Friedel-Crafts alkylation. This is problematic because the desired product we want is the minor product because there was a rearrangement event. To combat this, we first do Friedel-Crafts acylation then perform **Clemmensen reduction** on it to remove the = O. (will be discussed on Core Topic 6)



## 3.6 Substituent Effects on EArS

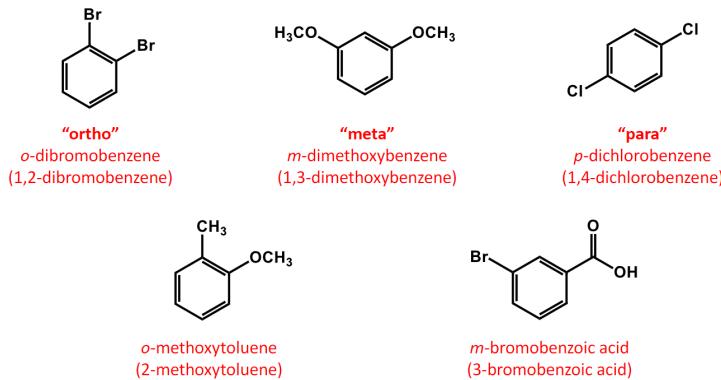
We will now move on to see how substituents position on benzene has any effects on its EArS reactivity. Before that, we'll have a little revision on the position substitution position and naming

### 3.6.1 Substitution Position and Naming Revision



**Figure 3.14:** Common benzene derivatives.

There are 3 possible substitution position: ortho (is abbreviated as o), meta (m) and para (p).



**Figure 3.15:** Ortho, meta and para substitution position.

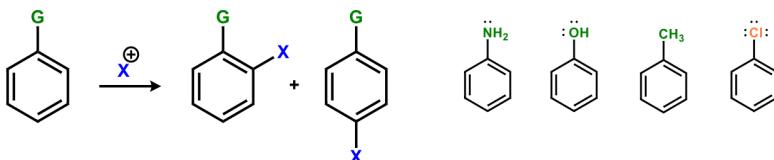
We can now begin to look at the effects.

We've dealt with EArS on benzene alone, but what if the benzene has a substitution on it? Would it change the how the reaction proceed? Well...not much that it would change the reaction itself however, we must take into

account the position and the nature of the substitution in order to have a good prediction on the regioselectivity of EArS reaction. This is because attaching an electrophile after EArS in the ortho position won't be same chemically as the para nor the meta position and v.v.

### 3.6.2 Directing Effects

In general, a substituent, depending on its structure, can either be an **electron donating group (EDG)** or **electron withdrawing group (EWG)**. EDG are ortho/para directors i.e. EArS would result in electrophile bonding at o/p position relative to the EDG/.



**Figure 3.16:** O/p director and some examples of them

**Remark 3.3.** Although halogens are weak EWG, they're still considered as o/p director.

EWG are primarily meta directors i.e. EArS would result in electrophile bonding at m position relative to the EDG.



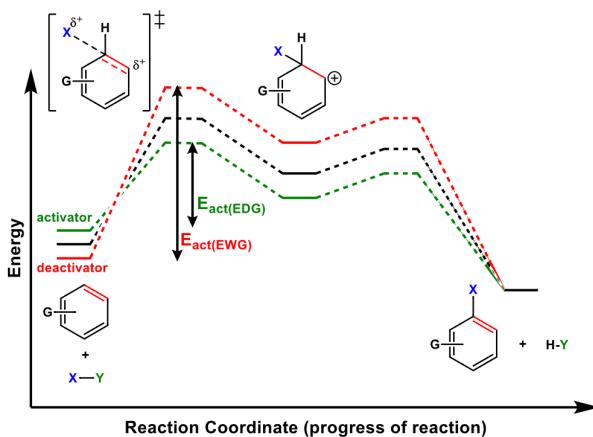
**Figure 3.17:** m director and some examples of them

### 3.6.3 Rate Effects

Benzene substituents can also have an impact on the EArS rate of reaction. Donating groups (EDG) will increase reaction rate, while withdrawing groups (EWG) will decrease reaction rate, as compared to benzene. For this reason, EDG are called **activators** and EWG are called **deactivators** in EArS

reactions.

Activators can increase nucleophilicity which means it will stabilize the transition state thus lower intermediate energy i.e. reaction goes faster. Deactivator would do the complete opposite, which means reaction goes slower.



**Figure 3.18:** Rate effect from activator and deactivator coordinate diagram.

### 3.6.4 Ortho/Para Directors

Majority of EDG o/p director would be alkyl and hydroxyl group and they're the strongest as well as formamide group (methyl+amide). As you can see, they make almost exclusively o/p position in EArS reaction.

Ortho/Para-Directing Substituents				Meta-Directing Substituents				Substituent	Relative Rate	Type of Group	
Substituent	O	M	P	O+P	Substituent	O	M	P	O+P		
—OH	50	0	50	100	—NO <sub>2</sub>	7	91	2	9	—NH <sub>2</sub>	N/A*
—NHCOCH <sub>3</sub>	19	2	79	98	—N(CH <sub>3</sub> ) <sub>3</sub>	2	87	11	13	—OH	1000
—CH <sub>3</sub>	63	3	34	97	—CO <sub>2</sub> H	22	76	2	24	—CH <sub>3</sub>	25
—F	13	1	86	99	—CN	17	81	2	19	—H (benzene)	1 (reference)
—Cl	35	1	64	99	—CO <sub>2</sub> Et	28	66	6	34	—I	0.18
—Br	43	1	56	99	—COCH <sub>3</sub>	26	72	2	28	—Cl	0.033
										—CO <sub>2</sub> Et	0.0037
										—NO <sub>2</sub>	6 × 10 <sup>-6</sup>
										—N(CH <sub>3</sub> ) <sub>3</sub>	1.2 × 10 <sup>-4</sup>

We can look at the coordinate diagram and see that the activation en-

ergy to produce o/p position is much lower than that of m by these groups hence the reaction is much faster. Additionally, we can also look at the resonance structure of the intermediate product.

Substitution Position	Contributing Resonance Structures	extra res str.
ORTHO		
META		enhances str.
PARA		

As you can see the o/p position has much more resonance structure thus allow better stabilization than m. Essentially, the adjacent lone pairs on OH donates its electron density through **resonance effect**.

Substitution Position	Contributing Resonance Structures
ORTHO	
META	
PARA	

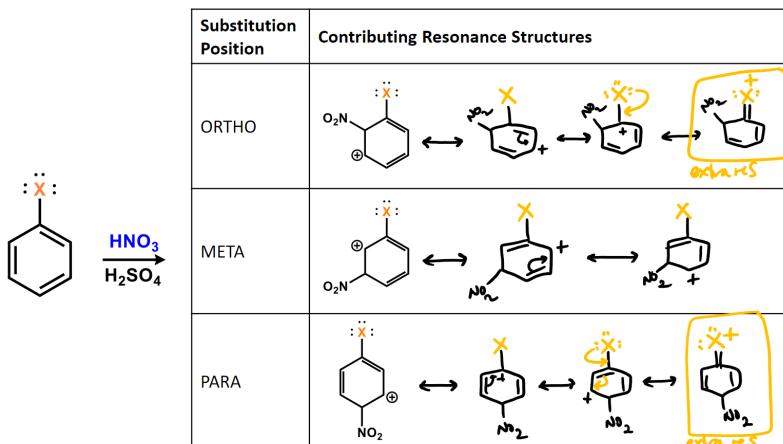
For alkyl group, they may not have more resonance structure in o/p than m however in o/p they have a carbocation center that can stabilize

the intermediate. This means the alkyl group donates its electron density through **inductive effect**.

Inductive effect are generally weaker than resonance effect which is why hydroxyl group is a strongly activating while alkyl group is a weakly activating o/p director. We also said that halogen, although an EWG, is also an o/p director.

Ortho/Para-Directing Substituents					Meta-Directing Substituents					Substituent	Relative Rate	Type of Group
Substituent	O	M	P	O+P	Substituent	O	M	P	O+P			
—OH	50	0	50	100	—NO <sub>2</sub>	7	91	2	9	—NH <sub>2</sub>	N/A*	Strongly activating
—NHCOCH <sub>3</sub>	19	2	79	98	—N(CH <sub>3</sub> ) <sub>3</sub>	2	87	11	13	—OH	1000	Strongly activating
—CH <sub>3</sub>	63	3	34	97	—CO <sub>2</sub> H	22	76	2	24	—CH <sub>3</sub>	25	Weakly activating
—F	13	1	86	99	—CN	17	81	2	19	—H (benzene)	1 (reference)	—
—Cl	35	1	64	99	—CO <sub>2</sub> Et	28	66	6	34	—I	0.18	Weakly deactivating
—Br	43	1	56	99	—COCH <sub>3</sub>	26	72	2	28	—Cl	0.033	Weakly deactivating

We can also look at its resonance structure like others



Here the halide, we can see that halide remove instead of donate the electron density through inductive effect. We can thus conclude that halides are weakly deactivating o/p director.

### 3.6.5 Meta Directors

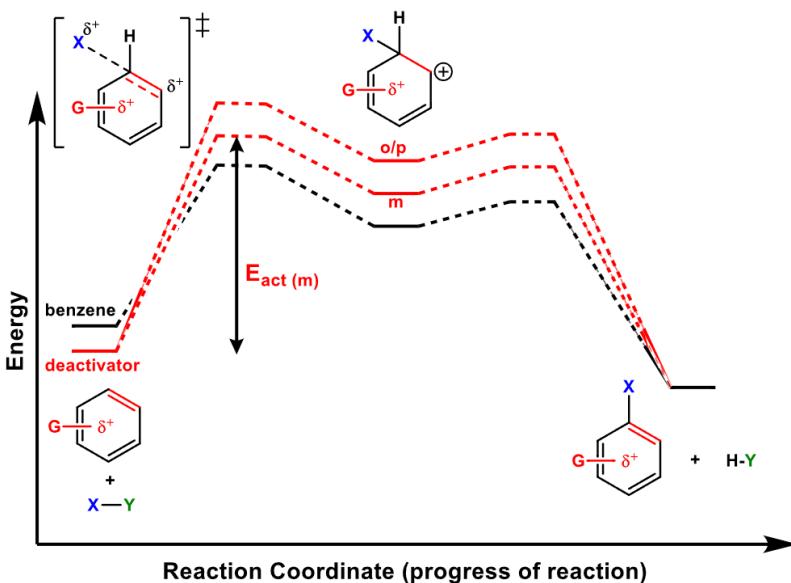
Some known meta directors are: nitro group, trimethylamine, carboxyl, cyanide, acetoxy and ketone.

Ortho/Para-Directing Substituents				Meta-Directing Substituents				Substituent	Relative Rate	Type of Group	
Substituent	O	M	P	O+P	Substituent	O	M	P	O+P		
—OH	50	0	50	100	—NO <sub>2</sub>	7	91	2	9	—NH <sub>2</sub>	N/A*
—NHCOC <sub>3</sub>	19	2	79	98	—N(CH <sub>3</sub> ) <sub>3</sub>	2	87	11	13	—OH	1000
—CH <sub>3</sub>	63	3	34	97	—CO <sub>2</sub> H	22	76	2	24	—CH <sub>3</sub>	25
—F	13	1	86	99	—CN	17	81	2	19	—H (benzene)	1 (reference)
—Cl	35	1	64	99	—CO <sub>2</sub> Et	28	66	6	34	—I	0.18
—Br	43	1	56	99	—COCH <sub>3</sub>	26	72	2	28	—Cl	0.033

Substituent	Relative Rate	Type of Group
—CO <sub>2</sub> Et	0.0037	Moderately deactivating
—NO <sub>2</sub>	$6 \times 10^{-6}$	Strongly deactivating
—N(CH <sub>3</sub> ) <sub>3</sub>	$1.2 \times 10^{-6}$	Strongly deactivating

For its coordinate diagram, we see the opposite effect where meta intermediate now is much more stable than o/p hence its reaction is faster.



We can also look at its resonance structure

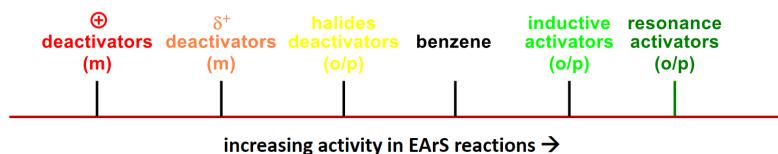
Here, we can see that all of them have the same amount of resonance structure with o/p position sometimes forming the carbocation at the EWG.

Substitution Position	Contributing Resonance Structures
ORTHO	
META	
PARA	

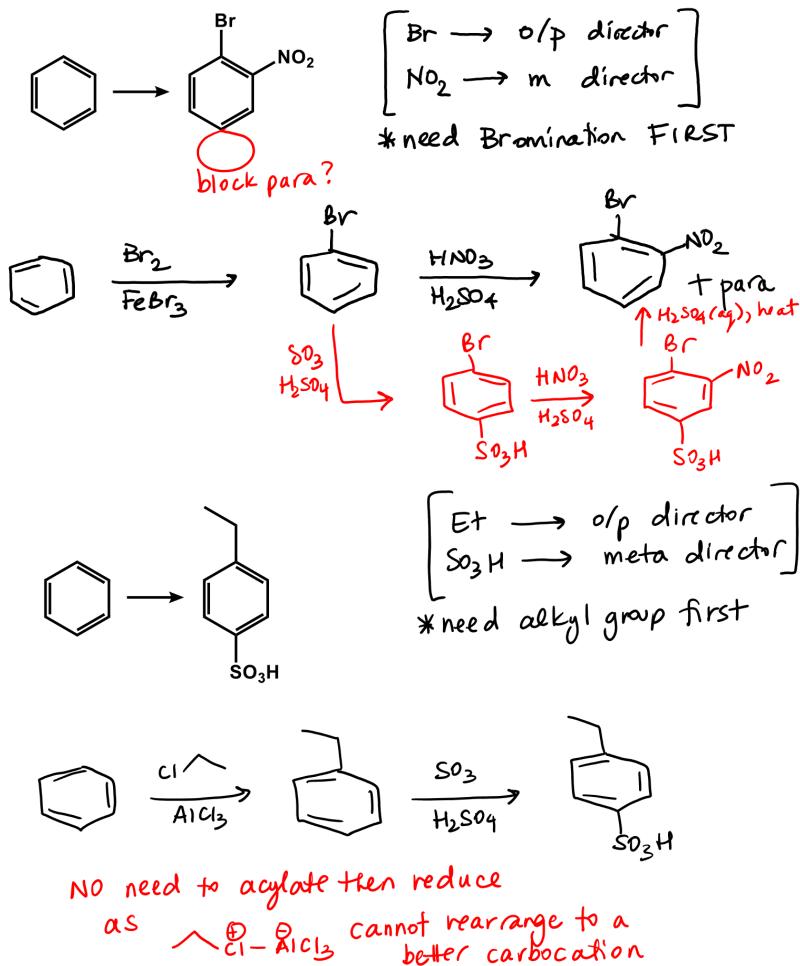
**wait...didn't we say carbocation is stable?** Well...yes but that's in the context of EDG, but here it is EWG so by having carbocation adjacent to it will worsen the stability. This is because EWG remove electron density via inductive effect (for nitro group).

Putting all of that together, we get the following summary of substituents, directors and its reactivity relative to benzene.

	Inductive effects	Resonance effects
o/p directors	<b>Activators (EDG)</b> <ul style="list-style-type: none"> <li>- weaker (no resonance)</li> <li>- alkyl groups</li> <li>- halides are weakly deactivating</li> </ul>	<b>Activators (EDG)</b> <ul style="list-style-type: none"> <li>- stronger (resonance)</li> <li>- adjacent lone pairs (N, O)</li> </ul>
m directors	<b>Deactivators (EWG)</b> <ul style="list-style-type: none"> <li>- cannot accept resonance electrons</li> <li>- adjacent + or <math>\delta+</math> (ex. <math>^+NR_3</math>, <math>CX_3</math>)</li> </ul>	<b>Deactivators (EWG)</b> <ul style="list-style-type: none"> <li>- can accept resonance electrons</li> <li>- adjacent + or <math>\delta+</math> (ex. <math>NO_2</math>, <math>C=O</math>, <math>C\equiv N</math>)</li> </ul>



Here are some example practice whether to do a certain reaction before others depending on the substitution.

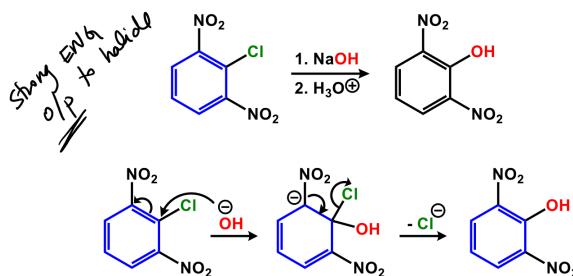


### 3.7 Other Benzene Reaction

We will briefly go through some benzene reactions. We first begin with

### 3.7.1 Nucleophilic Aromatic Substitution

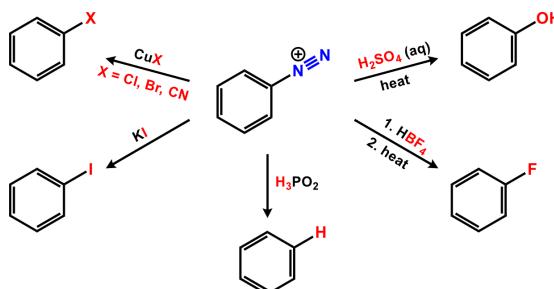
Aryl halides that have o/p EWG substituents can undergo nucleophilic aromatic substitution (SNAr). Neither SN1 nor SN2 are favoured with aryl halides: aryl carbocations are too high in energy for SN1 and aryl halides are sterically blocked by the p-system for the backside approach of SN2. Instead, an addition-elimination type reaction occurs (we will see more addition-elimination reactions in Topic 7).



**Figure 3.19:** Nucleophilic aromatic substitution of Cl to OH.

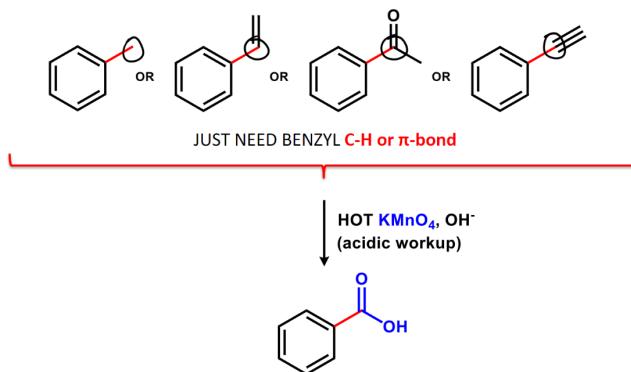
### 3.7.2 Other Diazonium Reaction

You can have aryl diazonium react under various condition to have different substitution.



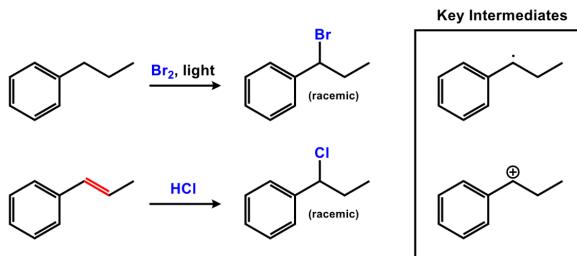
### 3.7.3 Side Chain Oxidation

Potassium permanganate is strong and can react with any C-H from a benzyl group to yield carboxyl group.



**Figure 3.20:** Side chain oxidation from various benzyl.

We can also have other side chain reaction such as radical addition and hydrohalogenation.



**Figure 3.21:** Side chain addition from CHEM 212

Chapter 4 will cover core topic 5 which include Synthesis of Carbonyls, Carboxylic Acids and Redection reaction and etc. Lectures will span from February 2<sup>nd</sup> and February 22<sup>nd</sup>

## 4.1 Properties of Carbonyls and Carboxylic Acid

Before getting into the synthesis of these 2 functional group, we will look at some of its properties. We shall begin with carbonyls

### 4.1.1 Carbonyls

Carbonyls is a general group that has  $C = O$  thus it is divided into **ketones** and **aldehyde functional group**, and they have the following properties.

	Structure	Condensed Form	Geometry	Examples
Ketones		RCOR'	sp <sup>2</sup> , planar	
Aldehydes		RCHO	sp <sup>2</sup> , planar	

Both aldehyde and ketone cannot form hydrogen bond amongst themselves however they can form that with alcohol or water. Normally, the interaction they have with each other are simply dipole-dipole interaction since they're a very polar molecule. Because they're very polar, **they tend to have higher boiling point and water solubility than most hydrocarbons.** However, these boiling point and water solubility cannot surpass that of alcohol since they can have H-bond amongst themselves.

### 4.1.2 Carboxylic Acid

**Carboxylic acid** refers to the function group -COOH.

	Structure	Condensed Form	Geometry	Examples
Carboxylic Acids		$\text{RCO}_2\text{H}$	$\text{sp}^2$ , planar	

Unlike carbonyls, carboxylic acid has strong H-bond amongst themselves as well as other polar-hydrogen carrying molecules. Like carbonyls, they tend to have much highest boiling point and solubility than most hydrocarbons but is still less than that of alcohol.

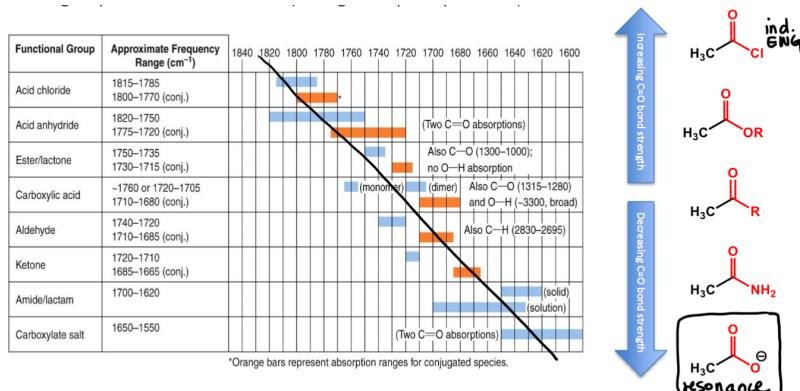
Here we can see some **carboxylic acid derivatives**, which are functional groups  $-RCO$  that has similar properties to carboxylic acid themselves.

	Structure	Condensed Form	Geometry	Examples
Anhydrides and Acid Chlorides		$\text{RCO}$	$\text{sp}^2$ , planar	
Esters and Amides		$\text{RCO}_2\text{R}$ and $\text{RCO NR}_2$ ( $\text{R} = \text{alkyl or H for amides}$ )	$\text{sp}^2$ , planar	
Nitriles		$\text{RCN}$	$\text{sp}$ , linear	

### 4.1.3 IR Spectra of Carbonyls and COOH

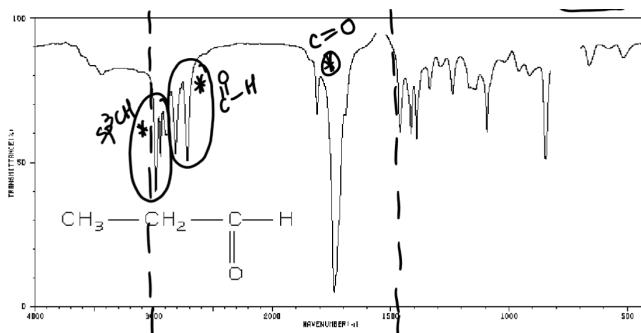
The main thing that carbonyls and COOH acid (+derivatives) share is the existence of a  $C = O$  stretch at around  $1590 - 1820\text{cm}^{-1}$ . The signal will appear on the IR as an intense and sharp band. This intensity is caused by the strong dipole moment that  $C = O$  has.

The table below shows different functional group bearing  $C = O$  and their frequency on the IR spec. What we realized is that there's a linear trend of decreasing in absorption frequency as you move down. Upon the analysis of the structure, we realized that starting from the top we have a strong inductive EWG that strengthen the  $C = O$  bond. However, as we move down, the EWG is replaced by and EDG which allow  $C = O$  to have resonance and thus weaken it hence lowering its absorption.



### IR Spec: Aldehyde

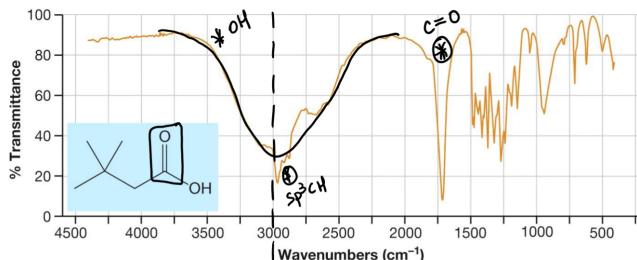
Aldehyde tends to have an  $sp^3$  C-H stretch at around 2720 and 2820  $\text{cm}^{-1}$  while its  $C = O$  stretch is 1680–1750  $\text{cm}^{-1}$  on the IR spec. The CH stretch is usually strong, sharp and similar thing can be said about the  $C = O$  stretch.



**Figure 4.1:** IR spec of aldehyde.

### IR Spec: COOH

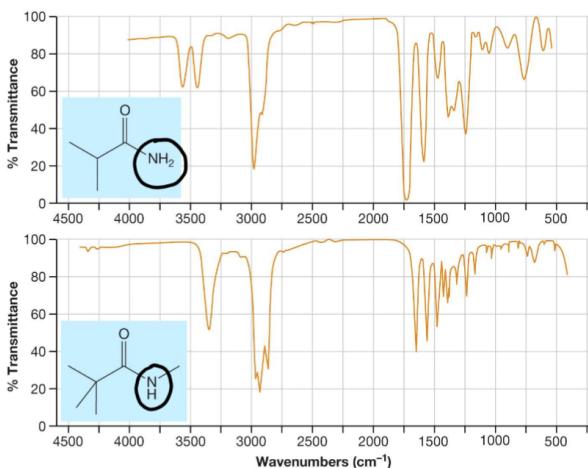
Carboxylic acid (COOH) tends to have very broad O-H stretch, 2500-3000 cm<sup>-1</sup> and C = O stretch, 1710-1780 cm<sup>-1</sup>. The OH is very broad due to H-bonding while C = O is very intense and sharp.



**Figure 4.2:** IR spec of COOH.

### IR Spec: Amines and amides

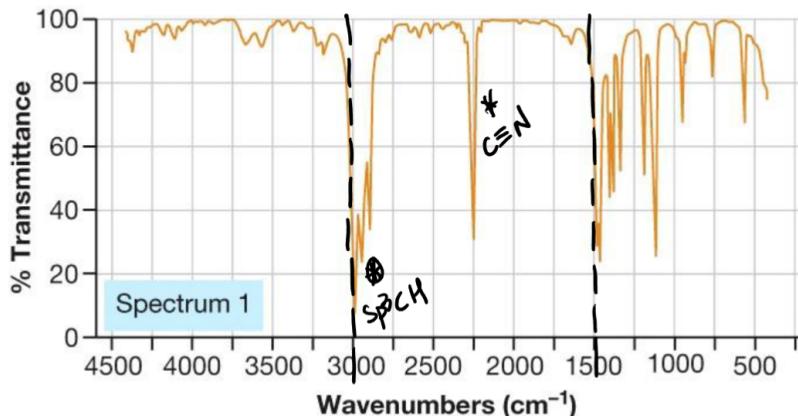
Amines and amides has N-H stretches, 3300-3500cm<sup>-1</sup> that are moderately intense and broad. The main difference between amines and amides is that for a  $RNH_2$ ' NH band, it is 2 signal while for  $R_2NH$ 's it is 1 signal.



**Figure 4.3:** IR spec of amines and amides.

### IR Spec: Nitriles

Nitriles have only  $C \sim N$  stretch, 2210-2260  $\text{cm}^{-1}$  that are moderate strong sharp bands due to large dipole moment.



**Figure 4.4:** Nitriles IR Spec.

#### 4.1.4 Naming of Carbonyls and Carboxylic Acid

For aldehyde group naming, we add in the suffix **-al** or **-aldehyde** e.g. ethanal or acetaldehyde.

For ketone group naming, we add in the suffix **-one** or **-ketone** e.g. dimethyl ketone or propanone.

For carboxylic acid naming, we add in suffix **-oic acid** or **oate** e.g. methanoic acid, sodium methanoate.

For acid chloride naming, we add in suffix **-oyl chloride** e.g. ethanoyl chloride. For anhydrides naming, we add *anhydride*.

For amide naming, we add in suffix **-amide** e.g. benzamide, ethanamide

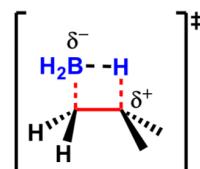
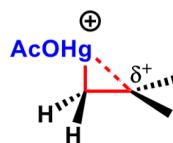
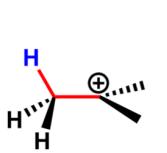
## 4.2 Synthesis of Alcohols

Here's a brief review on synthesizing alcohols.

### 4.2.1 Synthesizing Alcohol from Alkenes

Method	Key Features	Reaction Scheme
H <sub>2</sub> O Addition	<ul style="list-style-type: none"> <li>Markovnikov</li> <li>Scrambling of stereochem</li> <li>carbocation</li> </ul>	
Oxymercuration-Demercuration	<ul style="list-style-type: none"> <li>Markovnikov</li> <li>Scrambling of stereochem</li> <li>NO carbocation (mercuronium)</li> </ul>	
Hydroboration-Oxidation	<ul style="list-style-type: none"> <li>Anti-Markovnikov</li> <li>Syn addition</li> <li>Diastereoselective</li> <li>NO carbocation (concerted addn)</li> </ul>	

Here are 3 possible intermediate from the above conditions.

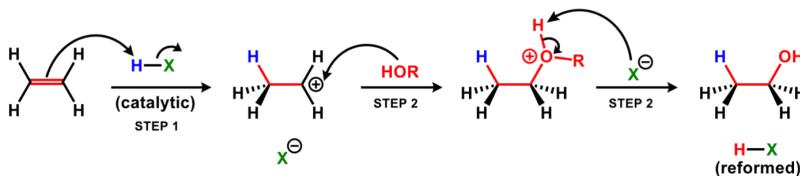


Addition of H<sub>2</sub>O/H<sup>+</sup>  
H<sub>2</sub>O with HX cat.  
Markovnikov Product  
not stereoselective  
**CARBOCATION REARRANGEMENT**

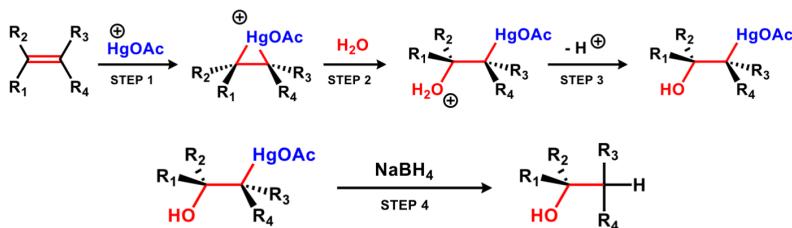
Oxymerc-Demercuration  
1. Hg(OAc)<sub>2</sub>, H<sub>2</sub>O; 2. NaBH<sub>4</sub>  
Markovnikov Product  
not stereoselective  
**MERCURIUM**  
**NO REARRANGEMENTS**

Hydroboration-oxidation  
1. BH<sub>3</sub>; 2. H<sub>2</sub>O<sub>2</sub>, NaOH  
ANTI Markovnikov  
syn addition (stereoselective)  
**CYCLIC TRANSITION STATE**  
**NO REARRANGEMENTS**

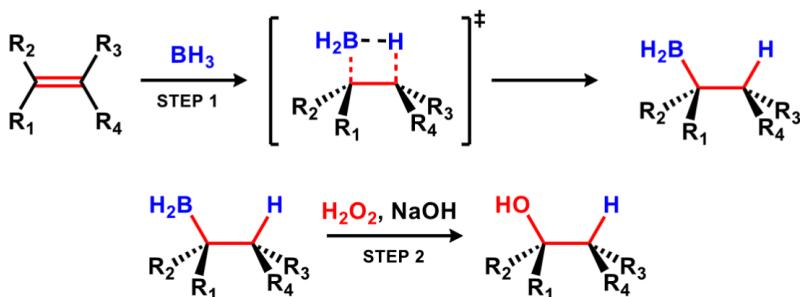
### Mechanism for Water Addition



### Mechanism of Oxymercuration-Demercuration



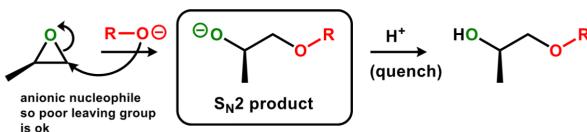
### Mechanism of Hydroboration-Oxidation



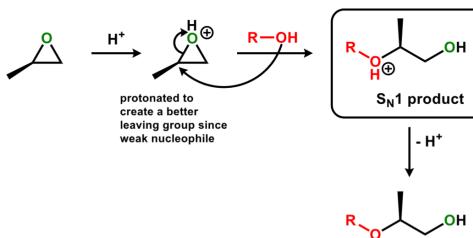
## 4.2.2 Synthesizing Alcohol From Ethers

Method	Key Features	Reaction Scheme
Strong acid (HA) with linear ethers	<ul style="list-style-type: none"> <li>• Acidic/aqueous/high temp</li> <li>• Ether to alcohol</li> <li>• S<sub>N</sub>1 or S<sub>N</sub>2</li> </ul>	$\text{R}-\text{O}-\text{R} + \text{H}_2\text{O} \xrightarrow[\text{(non nucleophilic A}^\ominus\text{)}]{\text{strong HA, heat}} \text{R}-\text{OH} + \text{R}-\text{OH}$
Acidic reagents with epoxides	<ul style="list-style-type: none"> <li>• Acidic/aqueous</li> <li>• Epoxide to opened chain</li> <li>• S<sub>N</sub>1-like</li> </ul>	
Basic reagents with epoxides	<ul style="list-style-type: none"> <li>• Basic/aqueous or not</li> <li>• Epoxide to opened chain</li> <li>• S<sub>N</sub>2-like</li> </ul>	

### Mechanism of S<sub>N</sub>2 Basic Epoxide Opening



### Mechanism of S<sub>N</sub>1 Acidic Epoxide Opening



## 4.3 Oxidation

**Oxidation** is when we add an oxygen or remove a hydrogen from the molecule while **reduction** is the opposite. We tend to have the definition of oxidation is the process of removing electrons which is coupled to reduction where that electron is donated to another molecule. Such definition is also correct but in our context, it's best to use the above.

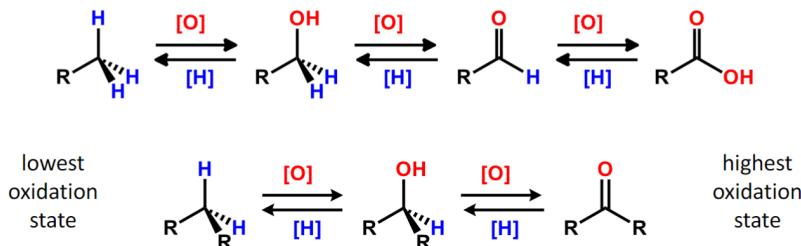


Figure 4.5: Oxidation and reduction illustration.

### 4.3.1 Alkene/Alkyne Oxidation

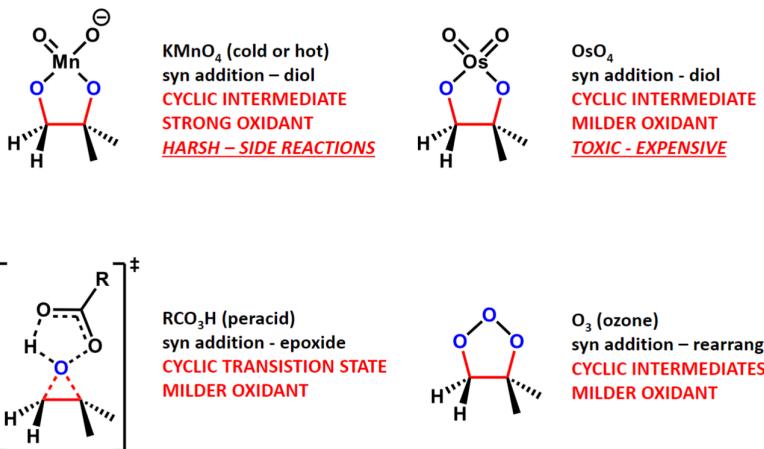
We will now look at reaction involving oxidizing alkene and alkynes.

Method	Key Features	Reaction Scheme
Ozonolysis (with reductive work-up)	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Alkene to ketone or aldehyde (depending on alkene substituents)</li> </ul>	
Alkyne Hydration	<ul style="list-style-type: none"> <li>Acidic/aqueous</li> <li>Alkyne to ketone</li> <li>Markovnikov addition</li> <li>Keto-enol tautomerization</li> </ul>	
Friedel-Crafts Acylation	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Benzene to acylated benzene</li> </ul>	

Method	Key Features	Reaction Scheme
Ozonolysis (with oxidative work-up)	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Alkene or alkyne to carboxylic acid (needs C-H on alkene)</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{R} \\   \\ \text{H}-\text{C}=\text{C}-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \\ \text{or} \\ \text{R}-\text{C}\equiv\text{C}-\text{R} \end{array} \xrightarrow[2. \text{H}_2\text{O}_2 \text{ (to oxidize)}]{1. \text{O}_3 \text{ in } \text{CH}_2\text{Cl}_2, \text{ COLD!}} \begin{array}{c} \text{R} \\   \\ \text{HO}-\text{C}=\text{O} \\   \\ \text{R} \end{array} + \begin{array}{c} \text{O}=\text{C}(\text{OH})-\text{O} \\   \\ \text{R} \end{array}</math> </p>
KMnO <sub>4</sub> Oxidative Cleavage	<ul style="list-style-type: none"> <li>Basic/aqueous</li> <li>Alkene or alkyne to carboxylic acid (needs C-H on alkene)</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{R} \\   \\ \text{H}-\text{C}=\text{C}-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \\ \text{or} \\ \text{R}-\text{C}\equiv\text{C}-\text{R} \end{array} \xrightarrow[2. \text{H}_3\text{O}^+ \text{ (to protonate)}]{1. \text{KMnO}_4, \text{NaOH, HOT!}} \begin{array}{c} \text{R} \\   \\ \text{HO}-\text{C}=\text{O} \\   \\ \text{R} \end{array} + \begin{array}{c} \text{O}=\text{C}(\text{OH})-\text{O} \\   \\ \text{R} \end{array}</math> </p>
Benzyl KMnO <sub>4</sub> Oxidation	<ul style="list-style-type: none"> <li>Basic/aqueous</li> <li>Benzyl compound to benzoic acid (needs sp<sup>3</sup> C-H or π-bond in benzyl position)</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2-\text{C}\equiv\text{C}-\text{R} \end{array} \xrightarrow[2. \text{H}_3\text{O}^+ \text{ (to protonate)}]{1. \text{KMnO}_4, \text{NaOH, HOT!}} \begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2-\text{C}(=\text{O})-\text{OH} \end{array}</math> </p>

Method	Key Features	Reaction Scheme
OsO <sub>4</sub> Oxidative Addition	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Alkene to diol</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{R} \\   \\ \text{H}-\text{C}=\text{C}-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \end{array} \xrightarrow[2. \text{NaHSO}_3 \text{ (aq)}]{1. \text{OsO}_4} \begin{array}{c} \text{HO} \\   \\ \text{R}-\text{C}(\text{OH})-\text{C}(\text{OH})-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \end{array}</math> </p>
KMnO <sub>4</sub> Oxidative Addition	<ul style="list-style-type: none"> <li>Basic/aqueous</li> <li>Alkene to diol</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{R} \\   \\ \text{H}-\text{C}=\text{C}-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \end{array} \xrightarrow[2. \text{H}_3\text{O}^+ \text{ (to protonate)}]{1. \text{KMnO}_4, \text{NaOH (aq), COLD!}} \begin{array}{c} \text{HO} \\   \\ \text{R}-\text{C}(\text{OH})-\text{C}(\text{OH})-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \end{array}</math> </p>
Epoxidation	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Alkene to epoxide</li> </ul>	<p style="text-align: center;"> <math>\begin{array}{c} \text{R} \\   \\ \text{H}-\text{C}=\text{C}-\text{R} \\   \quad   \\ \text{H} \quad \text{H} \end{array} \xrightarrow{\text{RCO}_3\text{H, COLD!}} \begin{array}{c} \text{O} \\    \\ \text{R}-\text{C}(\text{H})-\text{C}(\text{H})-\text{R} \end{array}</math> </p>

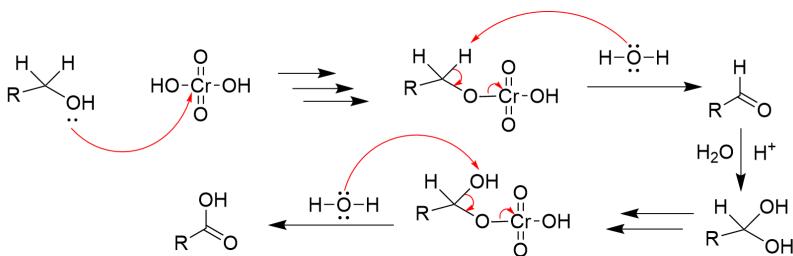
Some of the intermediate we can find from above reaction are



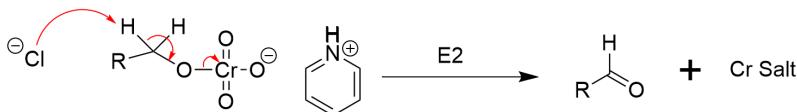
### 4.3.2 Alcohol Oxidation

Method	Key Features	Reaction Scheme
KMnO <sub>4</sub>	<ul style="list-style-type: none"> <li>Basic/aqueous</li> <li>Primary alcohol to carboxylic acid (Oxidize as many steps as possible)</li> </ul>	$\text{R}'\text{H} \xrightarrow[2. \text{H}_3\text{O}^+ \text{ (to protonate)}]{1. \text{KMnO}_4, \text{NaOH (aq)}}$ $\text{R}'\text{C}(=\text{O})\text{OH} + \text{Mn}^{2+}$ salts $\text{R}'\text{OH} \xrightarrow[2. \text{H}_3\text{O}^+ \text{ (to protonate)}]{1. \text{KMnO}_4, \text{NaOH (aq)}}$ $\text{R}'\text{C}(=\text{O})\text{R}' + \text{Mn}^{2+}$ salts
H <sub>2</sub> CrO <sub>4</sub>	<ul style="list-style-type: none"> <li>Acidic/aqueous</li> <li>Primary alcohol to carboxylic acid (Oxidize as many steps as possible)</li> </ul>	$\text{R}'\text{H} \xrightarrow[\text{H}_2\text{O}]{\text{H}_2\text{CrO}_4}$ $\text{R}'\text{C}(=\text{O})\text{OH} + \text{Cr}^{2+}$ salts $\text{R}'\text{OH} \xrightarrow[\text{H}_2\text{O}]{\text{H}_2\text{CrO}_4}$ $\text{R}'\text{C}(=\text{O})\text{R}' + \text{Cr}^{2+}$ salts
PCC or Swern Conditions	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Primary alcohol to aldehyde (Oxidizes alcohol ONLY ONE STEP)</li> </ul>	$\text{R}'\text{H} \xrightarrow{\substack{\text{PCC (in aprotic solvent)} \\ \text{or} \\ 1. (\text{COCl})_2, \text{DMSO, COLD} \\ 2. \text{Et}_3\text{N (base)}}}$ $\text{R}'\text{C}(=\text{O})\text{H}$ $\text{R}'\text{OH} \xrightarrow{\substack{\text{PCC (in aprotic solvent)} \\ \text{or} \\ 1. (\text{COCl})_2, \text{DMSO, COLD} \\ 2. \text{Et}_3\text{N (base)}}}$ $\text{R}'\text{C}(=\text{O})\text{R}'$

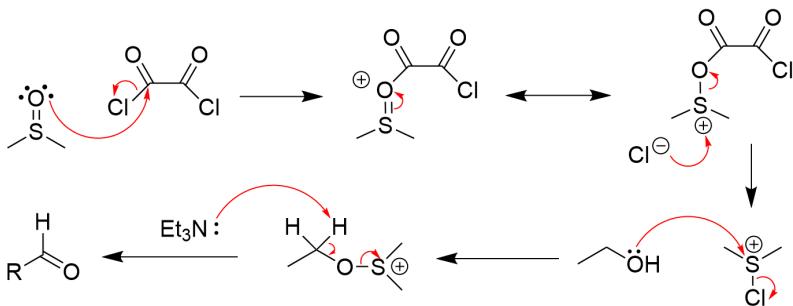
### Mechanism of $\text{H}_2\text{CrO}_4$



### Mechanism of PCC



### Mechanism of Swern Conditions



## 4.4 Other Synthesis Method

There are also other ways that can lead to the synthesis of carbonyls

### 4.4.1 Hydrolysis Reaction

Method	Key Features	Reaction Scheme
Acid Chloride or Anhydride Hydrolysis	<ul style="list-style-type: none"> <li>Neutral <math>\text{H}_2\text{O}</math></li> <li>Acid chloride or anhydride to carboxylic acid</li> <li>More in Topic 7</li> </ul>	
Ester, Amide, or Nitrile Hydrolysis	<ul style="list-style-type: none"> <li>Acidic or Basic/aqueous</li> <li>Ester or amide or nitrile to carboxylic acid</li> <li>More in Topic 7</li> </ul>	
Imine Hydrolysis	<ul style="list-style-type: none"> <li>Acidic/aqueous</li> <li>Imine to carbonyl</li> <li>More in Topic 6</li> </ul>	

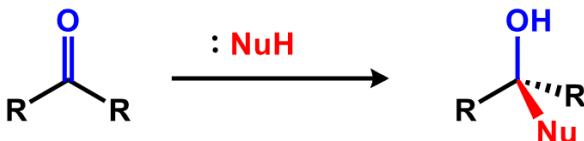
### 4.4.2 Acid Derivative Reduction

Method	Key Features	Reaction Scheme
LiAlH(OtBu) <sub>3</sub> Reduction	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Acid derivative to aldehyde</li> <li>More in Topic 7</li> </ul>	
DIBAL-H Reduction	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Acid derivative to aldehyde</li> <li>More in Topic 7</li> </ul>	
Grignard Reagents	<ul style="list-style-type: none"> <li>Aprotic conditions</li> <li>Nitrile to ketone, via imine</li> <li><math>\text{CO}_2</math> to carboxylic acid</li> <li>More in Topics 6, 7</li> </ul>	

Chapter 5 will cover core topic 6 and 7 which include addition and elimination of carbonyl groups. Lectures will span from February 23<sup>rd</sup> and February 22<sup>nd</sup>

## 5.1 Nucleophylic Addition to Carbonyls

So first, we will look at aldehydes and ketones as electrophiles where its carbon can be added with a nucleophile. In general, instead of undergoing electrophilic addition reaction like alkenes, carbonyls will undergo reactions called **nucleophilic additions ( $A_NCO$ )**. The carbonyl is the electrophile and a nucleophile is added as the reagent, to the  $\delta^+$  carbon centre. This generates a new, racemic (if applicable), tetrahedral carbon center.



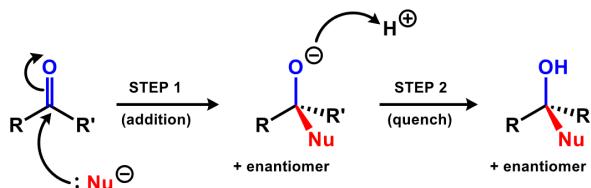
**Figure 5.1:** Illustration of nucleophilic addition to carbonyl where blue represents the nucleophile and red represents the electrophile.

When it comes to carbonyl group, we can divide it into either aldehyde or ketones which can have different reactivity. Aldehyde has only 1 R group thus only 1 EDG making it more reactive as an electrophile. On the other hand, ketones have 2 R group thus having 2 EDG making it less reactive as an electrophile.

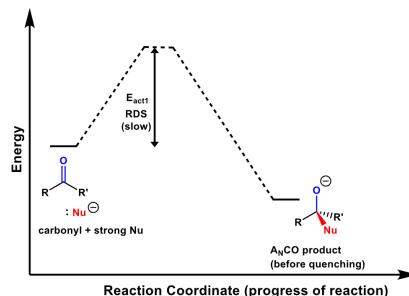
### 5.1.1 Strong Nucleophilic Reactions

The typical strong nucleophilic reaction has the following mechanism. When there's a strong anionic nucleophile ( $Nu^-$ ) present, the carbonyl will act

as an electrophile and form a new bond (mechanism step 1), leading to the formation of a tetrahedral oxyanion intermediate, as the C-O  $\pi$ -bond breaks. The anion is then neutralized with a source of acid: "quenched" (mechanism step 2). Strong nucleophiles is then added irreversibly to carbonyls



If we look at its reaction coordinate diagram, we can see that Strong nucleophile  $\text{A}_N\text{CO}$  reactions are usually exothermic as the newly formed  $\sigma$ -bonds are more stable (higher dissociation energy) than the ones that were broken.



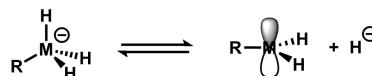
In summary of strong  $\text{A}_N\text{CO}$  reaction, you have the Nu attacking from "either side" (left/right, top/bottom) of the C=O. Due to this "either side"-attack, the final product could result in a racemic mixture, given that the center carbon is a stereocenter. Lastly, this addition is mostly irreversible since the energy barrier to do a reverse reaction is too large.

When it comes to strong  $\text{A}_N\text{CO}$  reaction, we can divided into 3 according to the reagent that it uses: Reducing, Grignard and Wittig reagents. Something to keep in mind about these reagents is that they're not only good nucleophiles, they're also good bases.

Method	Key Features	General Reaction Scheme
Reducing Agents	<ul style="list-style-type: none"> <li>Basic/mostly aprotic</li> <li>Addition of H<sup>-</sup></li> <li>New C-H bonds</li> <li>Reduction to alcohols</li> </ul>	
Grignard Reagents	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Addition of R<sup>-</sup></li> <li>New C-C bonds</li> <li>Substituted alcohols</li> </ul>	
Wittig Reactions	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Addition of ylide</li> <li>New C=C bonds</li> <li>Conversion to alkene</li> </ul>	

## Reducing Reagents

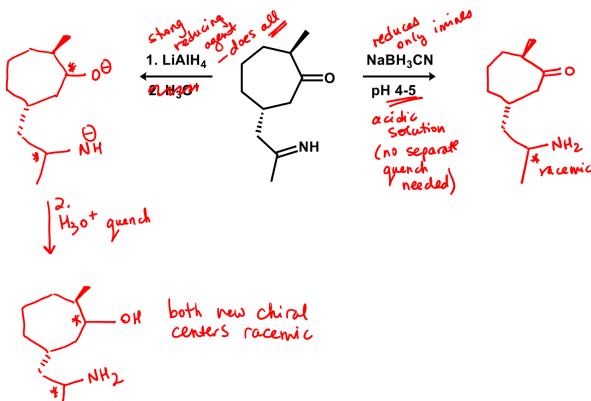
Carbonyl reducing agents are generally anionic salts, of which we will look at 3 in the following. With LiAlH<sub>4</sub> reagents, it's the most reactive with water and can reduce C=O and C=N bond by adding its hydrogen. NaBH<sub>4</sub> is similar but is less reactive and NaBH<sub>3</sub>CN is the same but can only reduce C=N bond. In fact, NaBH<sub>3</sub>CN is the least reactive out of the 3 and need to be used in mildly acidic environment or else they'll react with the carbonyls instead of only the imines.



Reducing Agent	Key Features	Example Reaction Scheme
LiAlH <sub>4</sub>	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Reactive to water</li> <li>Al-H bonds</li> <li>Reduction of C=O, C=N</li> </ul>	
NaBH <sub>4</sub>	<ul style="list-style-type: none"> <li>Basic/protic ok</li> <li>Less reactive to water</li> <li>B-H bonds</li> <li>Reduction of C=O, C=N</li> </ul>	
NaBH <sub>3</sub> CN	<ul style="list-style-type: none"> <li>Weakly acidic</li> <li>Least reactive to water</li> <li>B-H bonds</li> <li>Reduction of C=N</li> </ul>	

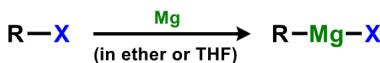
Figure 5.2: Carbonyl reducing agents summary.

**Example 5.1.1.** From the given compound, we can see that adding  $\text{LiAlH}_4$  will reduce both  $\text{C}=\text{O}$  and  $\text{C}=\text{N}$  while that with  $\text{NaBH}_3\text{CN}$  will reduce only  $\text{C}=\text{N}$



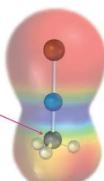
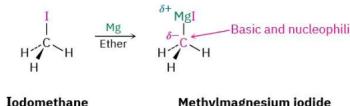
## Grignard Reagents

**Grignard reagents** are organometallic compounds, which contain a **carbon-metal bond**. The degree of polarization (ionic character) and basicity changes depending on the metal. Grignard reagents are typically made using magnesium. All organometallic compounds are poisonous and soluble in low polarity organic solvents. They are very reactive to water because they are basic and strong nucleophiles! Grignard reagents behave like carbanions.



$\text{R} =$

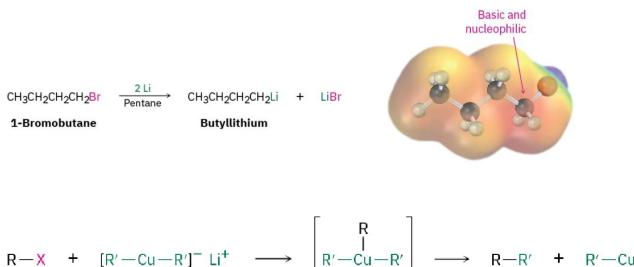
alkyl ( $1^\circ$ ,  $2^\circ$ ,  $3^\circ$ ),  
alkenyl, or  
alkynyl



**Figure 5.3:** Grignard reagent synthesis.

The synthesis of Grignard reagents is fairly simple. The starting material is any alkyl halide (an R group attached to a halogen) reacting with a

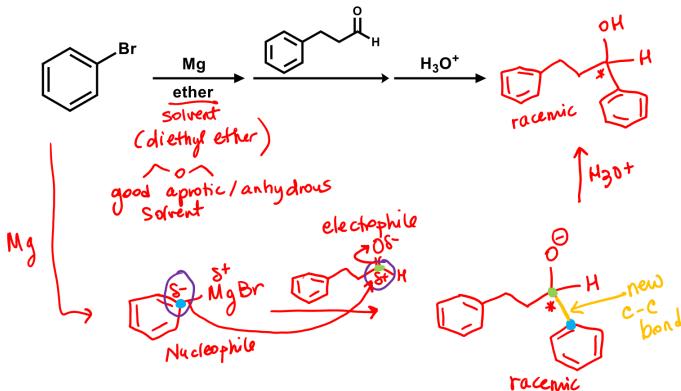
metal (such as Mg) in ether or THF. Several other carbanion type reagents can be made from halides, such as **alkyllithium reagents (RLi)** and **Gilman reagents (LiR<sub>2</sub>Cu)**. These can also be used to make new carbon-carbon bonds, by coupling them with other halides (alkyl, alkenyl, or aryl).



**Figure 5.4:** alkyllithium and gilman reagent

Unlike the reducing agent, the Grignard reagent will insert its R group onto the  $\delta^+$  carbon of the compound.

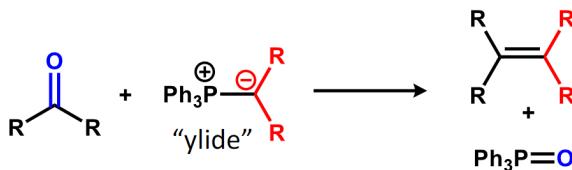
**Example 5.1.2.** We can use bromobenzene to generate phenylmagnesium bromide which is a Grignard reagent to react with 2-phenylpropanal which insert the phenyl group at the C=O.



## Wittig Reagents

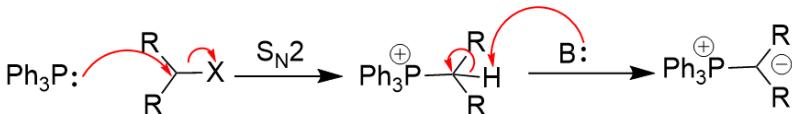
In a Wittiger reaction, we will perform the typical carbonyl addition (follows the same mechanism described previously) but we also have an addi-

tional step of getting an alkene. The nucleophile used to make this possible is called **ylide** which is something that has a  $C^\ominus$  that's beside a  $P^\oplus$  (not necessarily be phosphorus but we will look at only phosphorus in this course). One thing you should know is that **ylides cannot be added to acid derivatives.**



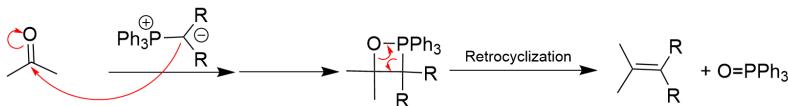
**Figure 5.5:** Wittig reaction.

To begin the Wittig reaction, we first need to form the ylides. To do so, a triphenylphosphorus will perform an  $S_N2$  attack on an alkyl halide. Then we need to deprotonate the CH that is  $\alpha$  to the  $\text{PPh}_3$  using a base.



**Remark 5.1.** Alkyl halide limited to  $\text{Me}$ ,  $1^\circ$ ,  $2^\circ$  (need at least 1 C-H to deprotonate).

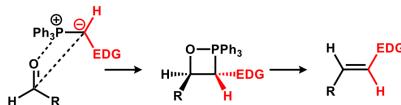
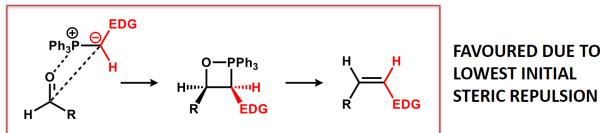
After synthesizing the Ylide, we will perform a strong  $\text{A}_N\text{CO}$  ylide addition which will form an intermediate 4-membered ring. This intermediate can **retrocyclize** into 2 part, 1 of which is the alkene.



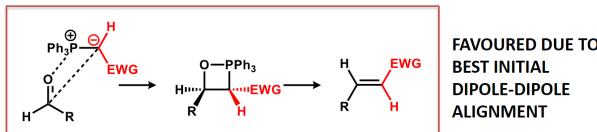
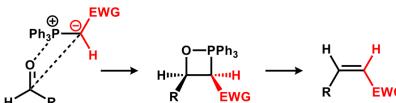
Notice that we generate an alkene, this also means that there are 2 possible configuration that it can take if there were to be only 1 R group: *cis* (*Z*) or *trans* (*E*). This configuration is dictated by the stability of the ylides.

For an unstabilized ylides, you have high reactive and low stabilized carbanion due to its R group being an EDG. This ylide will generate a *cis/Z*

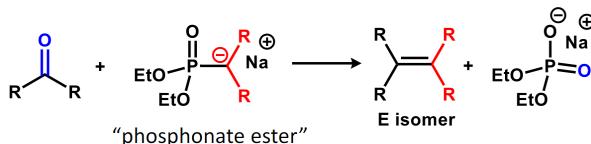
configuration on the alkene because of the lower steric repulsion in the initial  $S_N2$  attack to the ketone/aldehyde.



For a stabilized ylide, you have low reactive and stabilized carbanion thanks to EDG as R group. They can add to aldehyde only to generate trans/E configurated alkene which is due to initial favour of dipole-dipole moment.

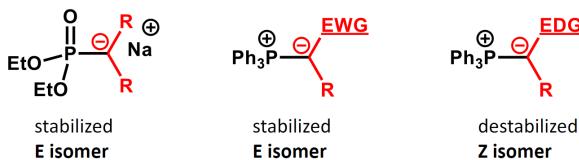


Another reaction that's similar to Wittig which also create the alkene from a carbonyl is the **Horner-Wadsworth-Emmons Reaction** that utilize a phosphonate ester. With the phosphonate ester, the built-in double bonds act like EWGs which will always lead to E-alkene out come.



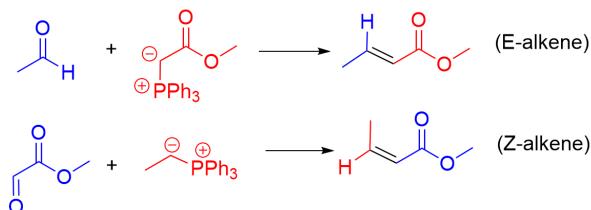
**Figure 5.6:** Horner Wadsworth Emmons reaction.

So we can summarize the product of Wittig reactions and similar reaction as the followings.



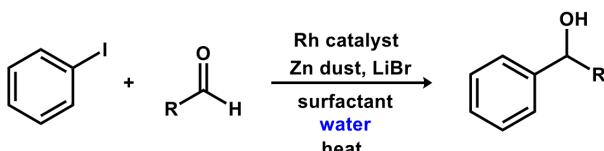
Phosphonate ester will generate E-alkene all the time along with stabilized ylides (bearing EWG). On the other hand, destabilized ylides (breaking EDG) will generate Z-alkene.

**Example 5.1.3.** The following 2 E/Z isomers can be synthesized by using different ylides.



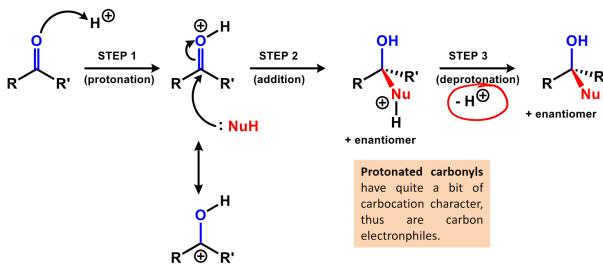
Strong nucleophiles are good however they're too good as a bases and nucleophile. This also means that if the structure has a electrophilic or acidic region, it will be problematic i.e. the limitation of strong nucleophiles are acidic and electrophilic groups. Some acidic groups include: **alcohols, amines, carboxylic acids and terminal alkynes;** and some electrophilic groups include: **epoxides, alkyl halides and other carbonyls.**

Interestingly, our professor at McGill Prof. CJ Li was able to perform an aqueous Grignard reaction under "abnormal" conditions such as carrying out the reaction with water.

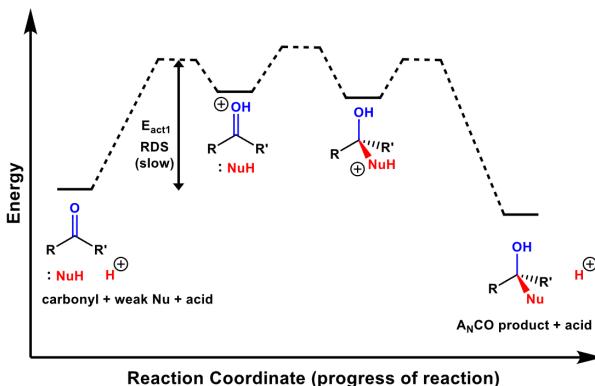


## 5.1.2 Weak Nucleophilic Reactions

Now we will look at weak nucleophilic reactions. In the presence of a weak, neutral nucleophile ( $\text{NuH}$ ), the carbonyl must first be protonated to react (mechanism step 1). After protonation, it will act as an electrophile and form a new bond (mechanism step 2) leading to the formation of a tetrahedral alcohol, as the C-O  $\pi$ -bond breaks. The alcohol can then do various things depending on the exact conditions. Weak nucleophiles generally add reversibly to carbonyls.



If we look at its reaction coordinate diagram, we can see that weak nucleophile  $\text{A}_N\text{CO}$  reactions are exothermic as the newly formed  $\sigma$ -bonds are more stable (higher dissociation energy) than the ones that were broken. What's different from strong nucleophile is that it has lots of small bump up in energy i.e. small variation in energy and is reversible.



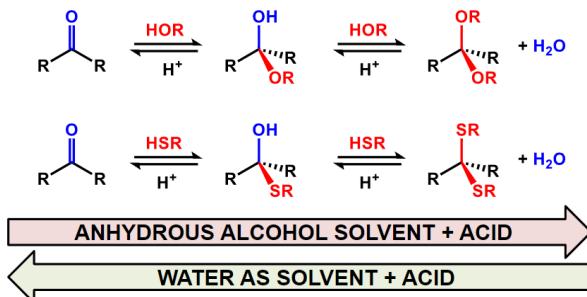
In summary of weak  $\text{A}_N\text{CO}$  reaction, you have the Nu attacking from "either side" (left/right, top/bottom) of the C=O. Due to this "either side"-attack, the final product could result in a racemic mixture, given that the

center carbon is a stereocenter. Lastly, this addition is possibly reversible since the energy barrier to do a reverse reaction is moderate.

The following is the summary of possible reactions with weak nucleophiles.

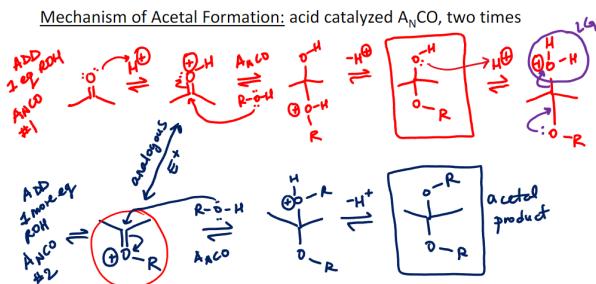
Method	Key Features	Reaction Scheme
Water or Alcohol addition	<ul style="list-style-type: none"> <li>• Acidic/protic</li> <li>• Addition of HOR</li> <li>• New C-O bonds</li> <li>• Hydrates and acetals</li> </ul>	
Thiol Addition	<ul style="list-style-type: none"> <li>• Acidic</li> <li>• Addition of HSR</li> <li>• New C-S bonds</li> <li>• Thioacetals</li> </ul>	
Amine or HCN Addition	<ul style="list-style-type: none"> <li>• Acidic</li> <li>• Addition of RNH2 or HCN</li> <li>• New C-N or C-C bonds</li> <li>• Imines or nitriles</li> </ul>	

### Water/Alcohol and Thiol Addition



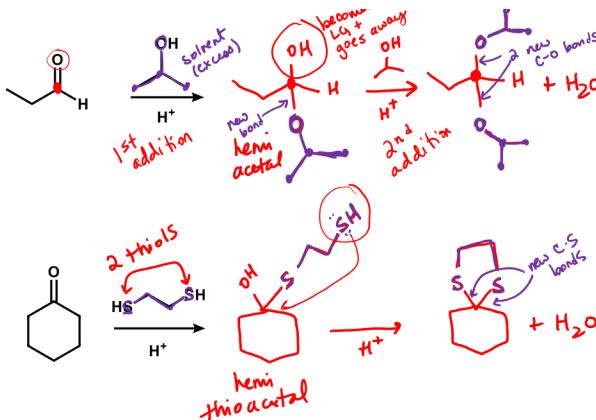
With alcohol and thiol as reagent, it will act as weak nucleophile and its equilibrium is controlled. Unlike the strong nucleophile, acidic conditions are needed. First, reaction between carbonyl and alcohol will lead to the generation of *hemiacetal* where there's an insertion of an OR group on the C=O. Even so, this hemiacetal is unstable and will have its OH remove for

an OR forming an **acetal**. Thiols follows a similar mechanism however the final product will be called **thioacetal**.



Most hemiacetals are unstable unless they're cyclic. 1 of the more familiar case is glucose which is a hemiacetal. The acetal is less stable in acidic as compared to basic and neutral conditions which we will see later, make a great protecting group and is removable.

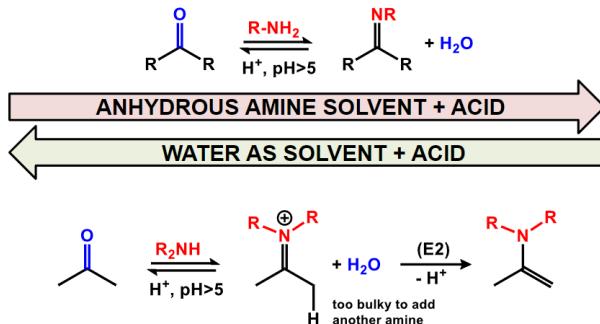
**Example 5.1.4.** We can perform alcohol and thiol addition in the following reaction.



### Amine/HCN Addition

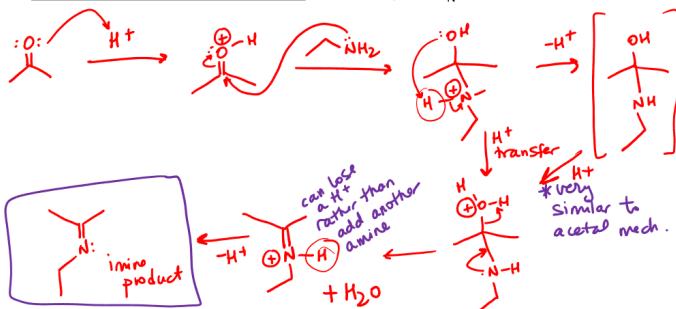
With amine/HCN addition, we need to be cautious with the acidic environment as it cannot be too acidic or we'll protonate the nitrogen (amine is a bit basic). The addition of amines to carbonyls is a reversible process.

When we add primary amines to the reaction, it will replace C=O with C=N which is an *imine*; and similarly if we add secondary amines, it will form an *enamine*.



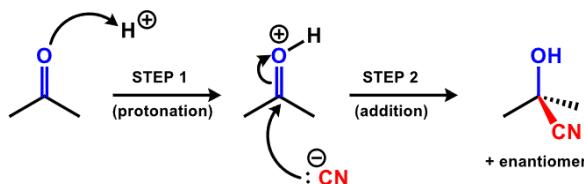
The mechanism of amine addition is as follows. First to form an imine, we need to protonate the carbonyl's oxygen forming the OH. Then the N from the primary amine will attack the C of the carbonyl and the π-bond of the C=O will break. The OH will now protonate using the attached amine's H. The OH<sup>-</sup> complex will break off as water while the N forms a new π-bond with the C. Finally, N is deprotonated another time by losing it or addition of another amine, and this form the imine product.

Mechanism of Imine Formation: acid catalyzed A<sub>N</sub>CO, eliminate water

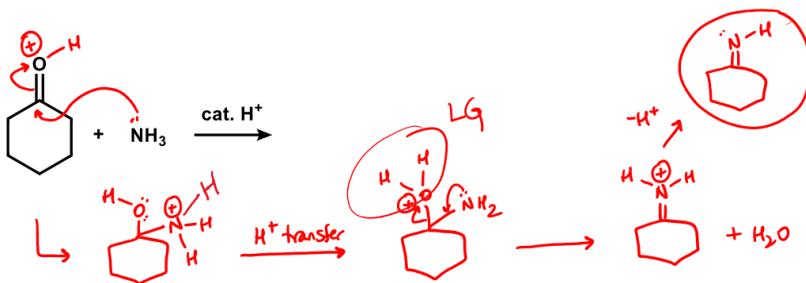


When it comes to the imine products, you can get a mixture of E and Z isomers. We're not going talk about how to make only the E or Z isomers like Wittig reaction. As for the R group on the amine, there are many types but we'll look at only a few like alcohol (OH), hydrazine (NH<sub>2</sub>NH<sub>2</sub>) and etc.

The mechanism of HCN addition is fairly similar but not as complicated. First, C=O is protonated; then, CN attach the center carbon which also lead to  $\pi$ -bond breakage between C=O and lead to the formation of the CN products called **cyanohydrins** (+ its enantiomer given that the carbon is chiral).



**Example 5.1.5.** The following is a guided practice of HCN addition.



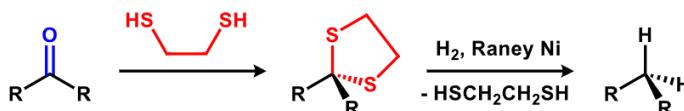
### 5.1.3 Protecting Groups and Synthesis

Sometimes, during the process of synthesis, we might encounter substrates that are poor for reduction, Grignard and even Wittig reaction, **why is that the case?** Well...a very likely scenario is that they have another site along their structure that compete with the site we want to synthesize when in contact with these reagent i.e. reagent might attack these sites as well lead to formation of undesirable products. To solve this, we use a so called **protecting group** which, as the name implied, protect these sites/functional groups from the attack of the reagent. One thing to note about them is that they have can be inserted onto the functional group but also can be removed once reactions is completed.

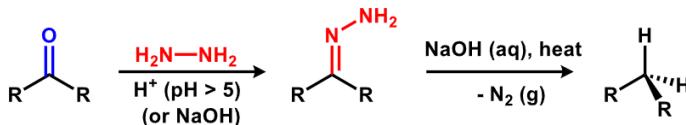
The following table shows 3 common method of alcohol protecting groups include: tBu ether, silyl ether and acetal.

Method	Key Features	Reaction Scheme
tBu Ether	<ul style="list-style-type: none"> <li>Reversible tert-butyl ether formation</li> <li>Alkene addition of ROH in acid (protect)</li> <li>Acidic ether cleavage (deprotect)</li> </ul>	
Silyl Ether	<ul style="list-style-type: none"> <li>Reversible silyl ether formation</li> <li>SN2 substitution of Si-Cl with alcohol (protect)</li> <li>SN2 substitution of Si-O with fluoride (deprotect)</li> </ul>	
Acetal (stable to basic conditions)	<ul style="list-style-type: none"> <li>Reversible acetal formation</li> <li>Acidic alcohol addition (protect)</li> <li>Aqueous acid acetal hydrolysis (deprotect)</li> </ul>	

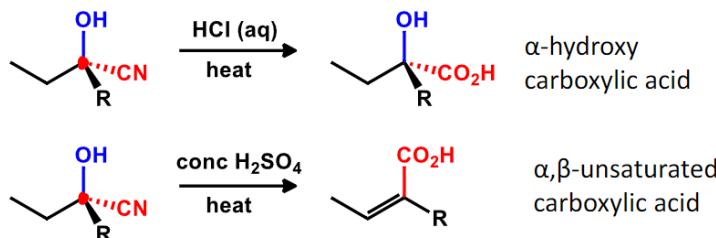
Lastly, before ending today's topic, we will go over some new way to reduce C=O down to alkane, and in fact, they work for any kind of carbonyl at any position. The first is through thiol addition which will form a thioacetal product. We can take this product and reduce it with **Raney Ni** (nickel) and  $H_2$ . This entire process is called **desulfurization**.



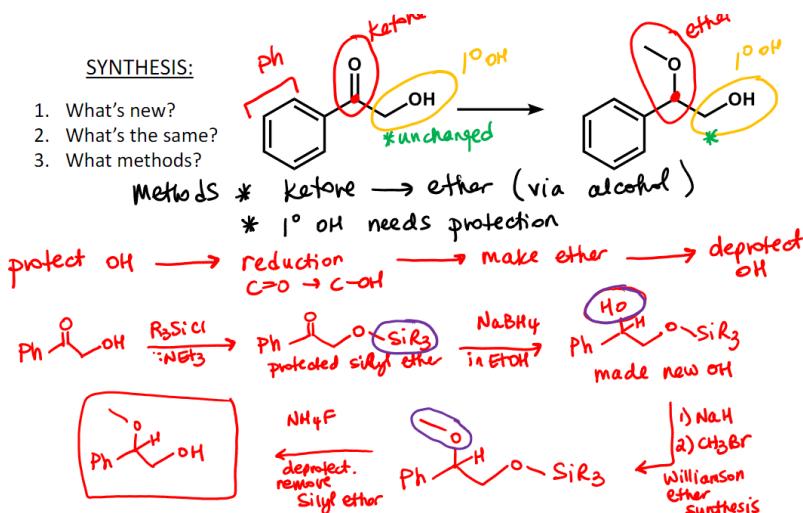
Another way to do this is through **Wolff-Kishner reduction** where a hydrazine is added under basic condition to form imine, and then the N will be eliminated under heating in basic conditions.

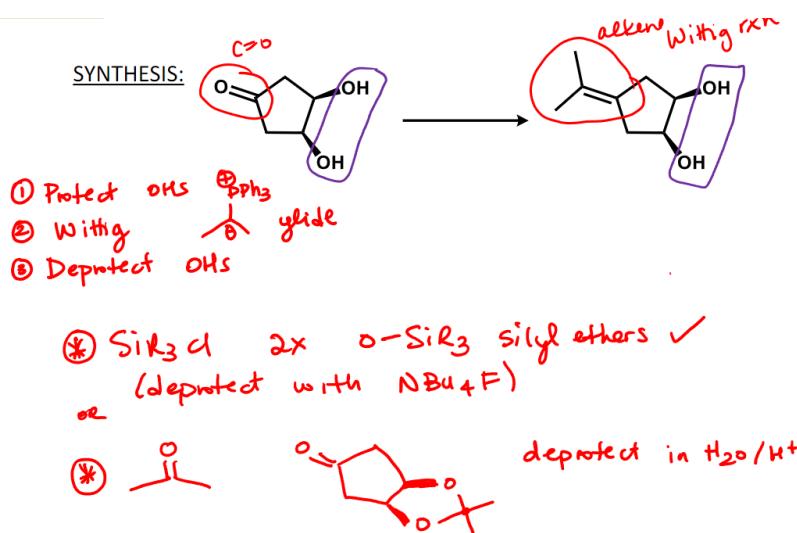


Here's another synthesis that we will touch on next in topics 7 which is **nitril hydrolysis** where we can make very interesting (position-wise) carboxylic acid function groups.



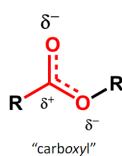
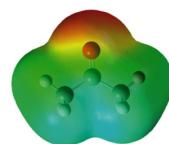
**Example 5.1.6.** Here are some guided practice on synthesis





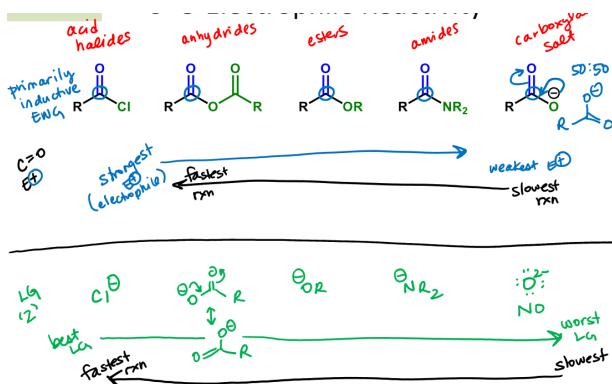
## 5.2 Nucleophilic Additions-Elim. to Acid Derivatives

In this topic 7, we will have a similar theme as the topic 7 which include nucleophilic addition to a carbonyl structure. The main difference in this topic is that the addition and elimination is performed on acid derivatives.



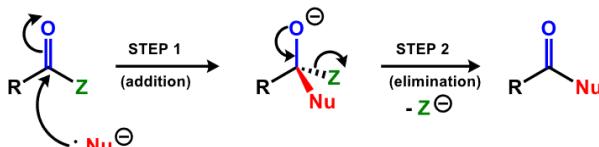
So first off, it's not surprising that acid derivatives are electrophilic and its carbon and can be added with many types of nucleophiles. The main difference we can see between the carbonyl and acid derivatives is that **acid derivatives are less electrophilic thus require stronger nucleophilic conditions.** (see above illustration)

Interestingly, even within the various types of acid derivatives, their electrophile activities can vary. This reactivity differs according to the different leaving group e.g. acid halides have the strongest electrophilic activity thus yield the fastest reaction while that of carboxylate salt is weakest hence yield the slowest reaction.



### 5.2.1 Strong Nucleophilic Addition-Elimination Reaction

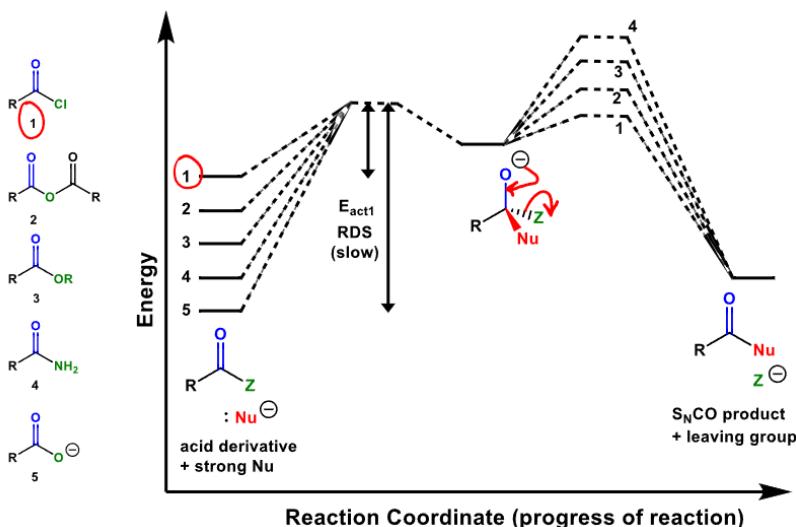
Instead of undergoing nucleophilic additions like carbonyls, acid derivatives undergo reactions called **nucleophilic addition-eliminations ( $S_NCO$ )**. The C=O is still the electrophile and a nucleophile is added as the reagent, to the  $\delta+$  carbon centre, but acid derivatives have leaving groups (Z) and undergo a further step.



Basically, in the presence of a strong, anionic nucleophile ( $Nu^-$ ), the

acid derivative C=O will act as an electrophile and form a new bond (mechanism step 1), leading to the formation of a **tetrahedral oxyanion** intermediate, as the C–O  $\pi$ -bond breaks. If a leaving group is present, the oxyanion can reform the C=O double bond and the leaving group is removed. Strong nucleophiles add irreversibly to carbonyls.

Like the reaction coordinate diagram of  $A_NCO$  reactions, those of strong nucleophile  $S_NCO$  are usually exothermic and its newly formed  $\sigma$ -bond are more stable than those that were broken. We can see this energy difference with different leaving group with halide that the highest initial energy potential meaning that it takes less time to get to activation level to start the reaction i.e. it's the fastest reaction (carboxylate salt is the slowest for the same but opposing reasons).



So to summarize  $S_NCO$  reaction, it will happen under anionic/basic condition. During the reaction, it will form a tetrahedral intermediate (breaking C=O) but also the elimination of a leaving group (reforming C=O). This reaction is irreversible since the energy for a reverse reaction is too large.

Like what we've done with aldehydes and ketones, we can perform an  $A_NCO$  reaction using Grignard and reducing agent but also a new reaction that is basic hydrolysis and alcoholysis.

Method	Key Features	General Reaction Scheme
Reducing Agents	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Addition of H<sup>-</sup></li> <li>Reduction to alcohols, amines, or aldehydes (depending on reagent/acid derivative)</li> </ul>	<p>Reaction scheme for reduction by <math>\text{Sn}_2^+</math> and <math>\text{NaBH}_4</math>:</p> $\text{R}-\text{C}(=\text{O})\text{Z} \xrightarrow{\text{Sn}_2^+, \text{NaBH}_4} \text{R}-\text{C}(\text{OH})\text{H} \xrightarrow{\text{NaBH}_4} \text{R}-\text{CH}_2\text{OH}$
Grignard Reagents	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Addition of R<sup>-</sup></li> <li>Substituted alcohols (or ketone if nitrile)</li> </ul>	<p>Reaction scheme for reduction by <math>\text{R}-\text{MgBr}</math>:</p> $\text{R}-\text{C}(=\text{O})\text{Z} \xrightarrow{\text{R}-\text{MgBr}} \text{R}-\text{C}(\text{OH})\text{R} \xrightarrow{\text{NaBH}_4} \text{R}-\text{CH}_2\text{OH}$
Basic Hydrolysis/ Alcoholysis	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Addition of OH<sup>-</sup>/OR<sup>-</sup></li> <li>Carboxylic acid or ester (depending on reagent)</li> </ul>	<p>Reaction scheme for basic hydrolysis:</p> $\text{R}-\text{C}(=\text{O})\text{Z} \xrightarrow{\text{RO}^-} \text{R}-\text{C}(\text{OH})\text{Z} \xrightarrow{\text{NaBH}_4} \text{R}-\text{CH}_2\text{OH}$

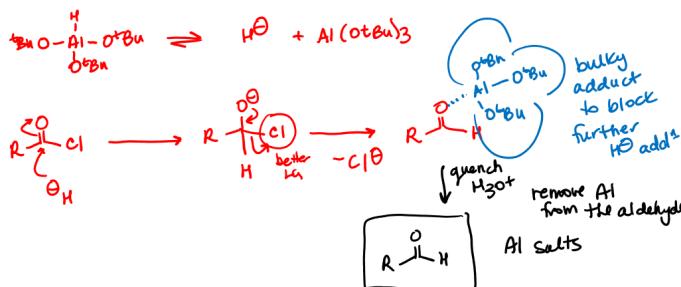
## Reducing Reagents

Similarly, reducing reagents include  $\text{LiAlH}_4$ ,  $\text{NaBH}_4$  and boro-hydride. With  $\text{LiAlH}_4$ , you would have the first reduction down to aldehyde but then it will continue to reduce down to alcohol; if it was a nitril or amide, it will reduce all the way down to amines. For  $\text{NaBH}_4$ , it is a little less reactive than  $\text{LiAlH}_4$  which means it doesn't react with most acid derivatives and mostly to acid halides. Like before, reduction will be completed all the way down to alcohol, but if you were to only want reduction down to aldehyde only (from acide chlorides and esters), we can use another last reagent that is  $\text{LiAlH}(\text{OtBu})_3$  or DIBAL-H.

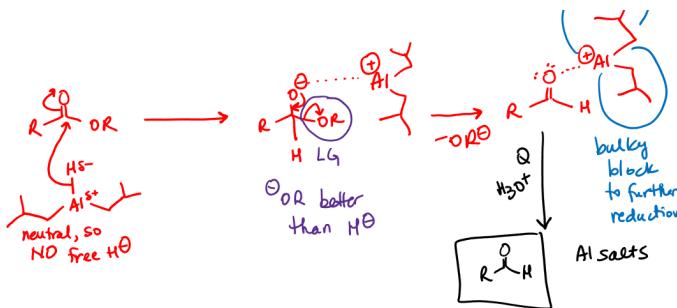
Reducing Agent	Key Features	Example Reaction Scheme
$\text{LiAlH}_4$	<ul style="list-style-type: none"> <li>Basic/aprotic</li> <li>Al-H bonds</li> <li>Multiple additions</li> <li>Reduction of all derivatives as far as possible</li> </ul>	<p>Reaction schemes for <math>\text{LiAlH}_4</math>:</p> $\begin{aligned} \text{R}-\text{C}(=\text{O})\text{Z} &\xrightarrow[2. \text{H}_3\text{O}^+ (\text{quench})]{1. \text{LiAlH}_4} \text{R}-\text{CH}_2\text{OH} \\ \text{R}-\text{C}(=\text{N})\text{NH}_2 \text{ or } \text{R}-\text{CN} &\xrightarrow[2. \text{H}_3\text{O}^+ (\text{quench})]{1. \text{LiAlH}_4} \text{R}-\text{CH}_2\text{NH}_2 \end{aligned}$
$\text{NaBH}_4$	<ul style="list-style-type: none"> <li>Basic/protic ok</li> <li>B-H bonds</li> <li>Multiple additions</li> <li>Reduction of acid chlorides</li> </ul>	<p>Reaction scheme for <math>\text{NaBH}_4</math>:</p> $\text{R}-\text{Cl} \xrightarrow[2. \text{H}_3\text{O}^+ (\text{quench})]{1. \text{NaBH}_4 \text{ in EtOH}} \text{R}-\text{CH}_2\text{OH}$
$\text{LiAlH}(\text{OtBu})_3$ or DIBAL-H	<ul style="list-style-type: none"> <li>Basic/aprotic &amp; COLD</li> <li>Al-H bonds, hindered</li> <li>Reduction of acid chlorides and esters to aldehydes</li> </ul>	<p>Reaction scheme for <math>\text{LiAlH}(\text{OtBu})_3</math> or DIBAL-H:</p> $\text{R}-\text{C}(=\text{O})\text{Z} \xrightarrow[2. \text{H}_3\text{O}^+ (\text{quench})]{1. \text{LiAlH}(\text{OtBu})_3 \text{ or DIBAL-H}} \text{R}-\text{CH}_2\text{OH}$

We can look at some of the mechanism beside the first 2 which we've already covered in topic 6. First is the  $\text{LiAlH}(\text{OtBu})_3$  deprotonation creat-

ing a anionic hydrogen and an  $\text{Al}(\text{OtBu})_3$  complex. This anionic proton will attack the C=O of the acid halide breaking the  $\pi$ -bond. The negative charge will come back down from the O reforming the broken  $\pi$ -bond while breaking the bond with the halide. The oxygen of the C=O can interact with the  $\text{Al}(\text{OtBu})_3$  complex which has a bulky adduct to block any further addition of anionic H. We can quench this step to remove any Al from the formed aldehyde.

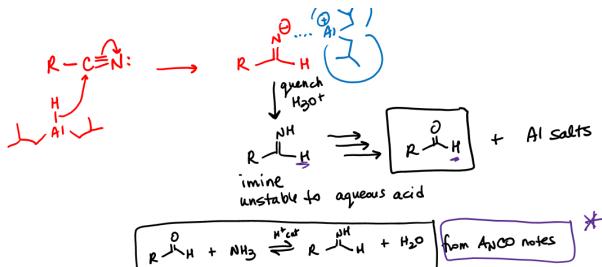


The mechanism of  $\text{S}_{\text{N}}\text{CO}$  with DIBAL-H (similar structure to  $\text{Al}(\text{OtBu})_3$  but with only 2 butyl) begins with its H attacking the C=O and breaking the  $\pi$ -bond. The  $\pi$ -bond reformed when H is added and the leaving group dissociate. No more reduction can be done as the oxygen is interacting with the Al with its bulky adduct. Finally, we quench the entire apparatus which lead to Al salts formation and our aldehyde product.

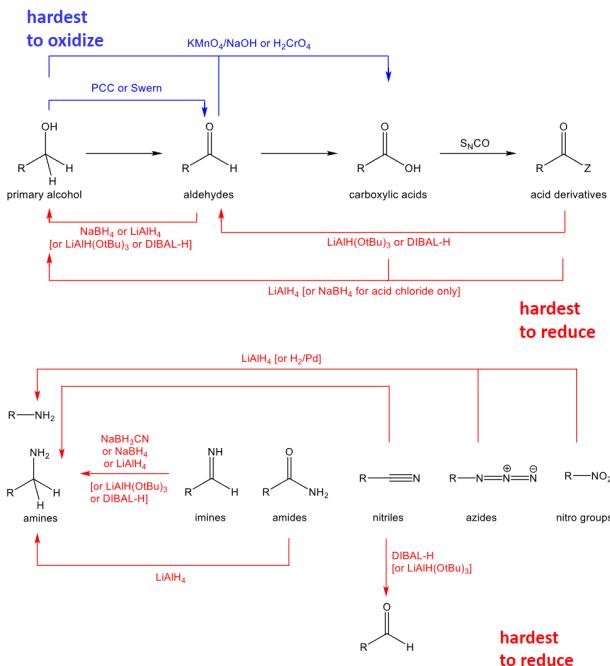


Last is the mechanism of DIBAL-H and nitrile. First, we have the same proton attack on C which break the triple bond into double bond with the nitrogen forming an imine. The reduction step ends here as there's an interaction between the N and the Al with its bulky adduct. We can remove the Al by quenching thus forming Al salt. The imine can be converted into

aldehyde under aqueous acidic condition which we've discussed in topics 6.



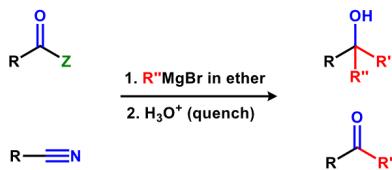
The followings are summary of redox reaction of oxygen and nitrogen compounds that we've done so far.



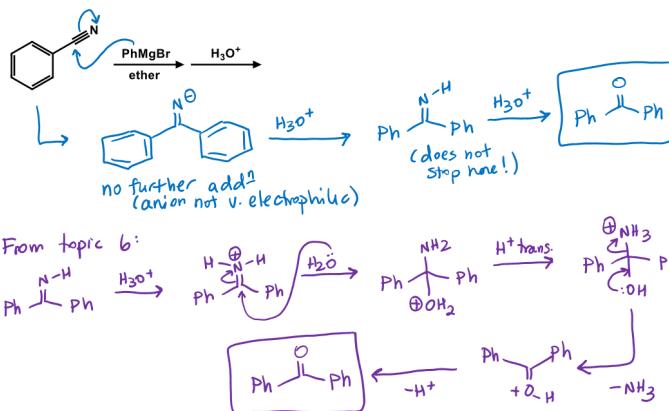
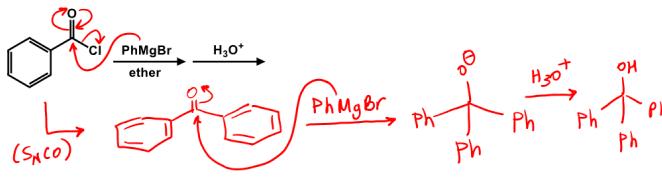
### Grignard Reagents

Like reducing reagents, Grignard reagents' addition are very hard to control and stop i.e. the reagent will add its R group as many time as possible.

When it's added to carboxylic acids, it will create  $3^\circ$  alcohol with the addition of 2 new R group from the Grignard reagent. Addition to the nitrile will lead to creation of ketone with the addition of 1 new R group from the Grignard reagent.



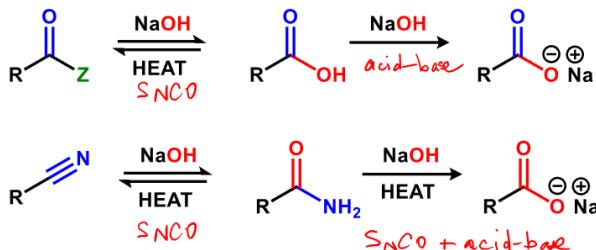
**Example 5.2.1.** Here are some guided practice



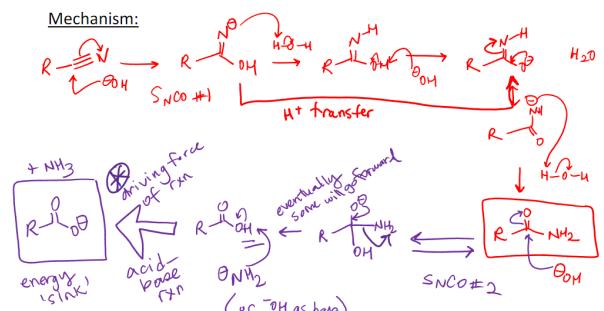
### Basic Hydrolysis/Alcoholysis

The last strong nucleophile condition is basic hydrolysis or alcoholysis which we're dealing with an  $\text{O}^-$  nucleophile (from a hydroxide or alkoxide anionic

reagents) and if it was  $\text{OH}^-$ , the product would yield carboxylic acid. In the following illustration, we can see the acid derivative is treated with  $\text{NaOH}$  where  $\text{OH}^-$  is the nucleophile which generates carboxylic acid. Because it's fairly acidic and we're in basic condition, we will have a deprotonation step at the end to reach the carboxylate salt. Similarly with nitrile, it will form amide and then continue with a longer mechanism under basic condition to reach the carboxylate salt.



The mechanism of basic nitrile hydrolysis is more complicated than acid derivatives so we will look into it more. First, the  $\text{OH}^-$  from the  $\text{NaOH}$  will attack the nitrile's carbon and the triple bond breaks into a double bond where N now has a negative charge. The  $\text{N}^\ominus$  will be protonated by water while another  $\text{OH}^-$  group deprotonates the attached OH group on the carbon. The deprotonated O will now form a  $\pi$ -bond with the carbon while  $\text{C}=\text{N}$   $\pi$ -bond is broken. The  $\text{N}^\ominus$  is now protonated again by water forming the first intermediate that is the amide. Now, another  $\text{OH}^-$  group will attack the  $\text{C}=\text{O}$  while its  $\pi$ -bond is broken. After the new OH is attached, O will reform its  $\pi$ -bond with the carbon while the amide leaves. Lastly, amide will come back and deprotonate the OH which finally forms the carboxylate salt and  $\text{NH}_3$ .

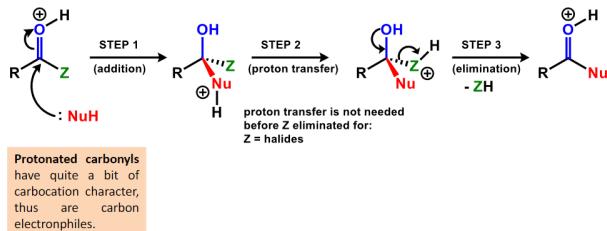


**Remark 5.2.** Carboxylate salt us the least reactive of all the acid derivatives and they're kind of the "sink" for all acid derivatives.

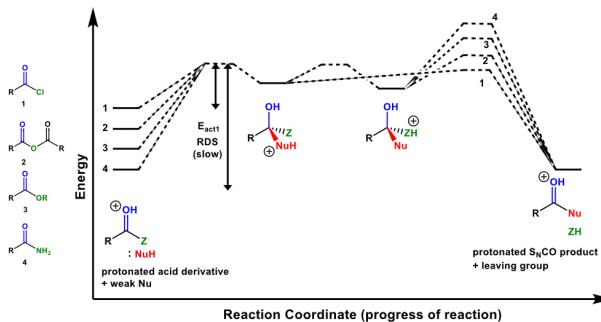
Ester hydrolysis is the original way that we used to make soap! So now, we will change gear and turn to the weak nucleophiles

### 5.2.2 Weak Nucleophilic Addition-Elimination Reactions

In the presence of a weak, neutral nucleophile ( $\text{NuH}$ ), the acid derivative must first be protonated to react. After protonation, it will act as an electrophile and form a new bond (mechanism step 1) leading to the formation of a tetrahedral alcohol, as the  $\text{C}=\text{O}$   $\pi$ -bond breaks. After a proton transfer (mechanism step 2), the  $\text{C}=\text{O}$  is reformed with elimination of the  $\text{ZH}$  leaving group. Weak nucleophiles generally add reversibly to carbonyls.



We can see that the reaction coordinate diagram has similar looks as that with strong nucleophiles but a little more complicated. Nevertheless, all you need to conclude is that acide halides have the fastest reaction in both steps.



To summarize  $\text{S}_{\text{N}}\text{CO}$  reaction with weak nucleophile, under neutral/acidic condition, nucleophile is added to the  $\text{C}=\text{O}$  (break  $\pi$ -bond) forming the

tetrahedral intermediate. Then, there will be an elimination of the leaving group while C=O reform (form  $\pi$ -bond). This reaction is a reversible addition since the barrier for a reverse is moderate.

We have 3 different reagent to used as weak nucleophile in this case: water, alcohol and amine which will correspond to their reactions of neutral/acidic hydrolysis, alcoholysis and aminolysis. Under hydrolysis, you will convert acid derivative into carboxylic acid; under alcoholysis, acid derivative turns into ester; and under aminolysis, it turns into amide.

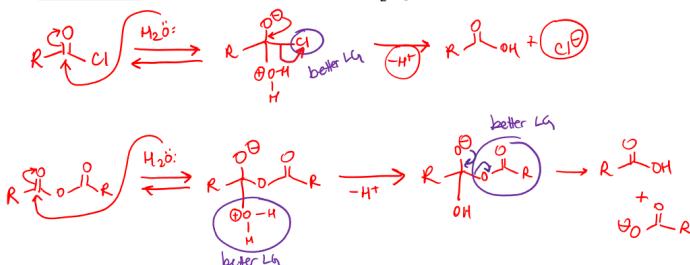
Method	Key Features	Reaction Scheme
Neutral or Acidic Hydrolysis	<ul style="list-style-type: none"> <li>• Acidic or neutral</li> <li>• Addition of <math>H_2O</math></li> <li>• New C-O bond</li> <li>• Carboxylic acids</li> </ul>	
Neutral or Acidic Alcoholysis	<ul style="list-style-type: none"> <li>• Acidic or neutral</li> <li>• Addition of HOR</li> <li>• New C-O bonds</li> <li>• Esters</li> </ul>	
Neutral or Acidic Aminolysis	<ul style="list-style-type: none"> <li>• Acidic or neutral</li> <li>• Addition of RNH2</li> <li>• New C-N bonds</li> <li>• Amides</li> </ul>	

### Neutral/Acidic Hydrolysis

With acidic hydrolysis, you will turn acid halides and anhydrides irreversibly to carboxylic acids but it's much faster than the hydrolysis of ester which is reversible.

The mechanism of acidic hydrolysis of amide and esters are straightforward so we won't be looking into it. We will look at that of acid chlorides and anhydrides in neutral condition (neutral is slightly different because we're not deprotonating the C=O first). First, water will attack the C=O and break its  $\pi$ -bond. Then,  $\pi$ -bond reform while the leaving group is eliminated. In the case of acid halide, the leaving group is the halide which is eliminated directly. Then  $\pi$ -bond is reformed and we get the product. In the case of anhydrides, the leaving group that's favoured initially is the  $H_2O^\oplus$ ; but after its deprotonation, the better leaving group is the ester. In the end,  $\pi$ -bond is reformed like usual but now we got a yield of either carboxylic acid and carboxylate salt.

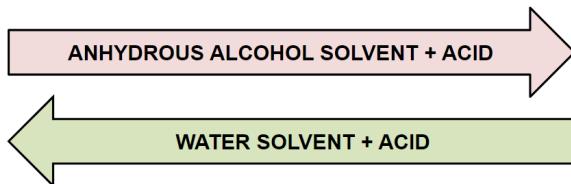
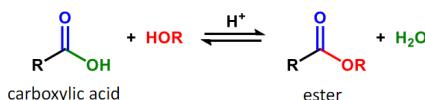
Mechanism: (not reversible,  $\text{Cl}^-$  and  $\text{RCO}_2^-$  good LG)



Interestingly, a lot of hydrolysis occurs in our body all the time for different types of functional groups e.g. acetylcholine hydrolysis using **acetal-cholinesterase** as the catalyst and it is reversible. In previous topics, we also discuss about nitrile hydrolysis where we form carboxylic acids from these cyanohydrin compounds. Because they fall under hydrolysis, their mechanism is similar to the above hydrolysis.

### Neutral/acidic Alcoholsysis

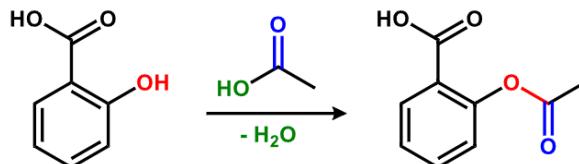
So now, instead of breaking bonds with water, we want to break it with alcohol which would give us ester product at the end. Alcohol is a weak nucleophile, controlled via equilibrium and needed to be in acidic condition to perform the addition. It can add to acid halides and anhydrides irreversibly while to other acid derivatives reversible to form ester. It cannot add to amides nor nitriles because they're not reactive enough.



If you're looking at the conversion from carboxylic acid to ester, it's called **Fischer esterification**. To perform Fischer esterification, you need

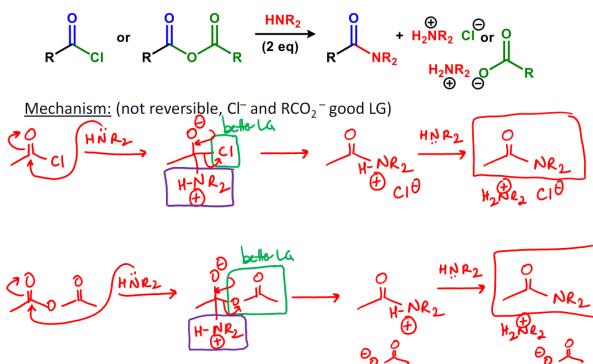
an absence of water to start making ester because you have higher concentration of carboxylic acids and anhydrous alcohol solvent. If you were to have lots of water present, the reverse reaction generating carboxylic acid is favoured. So basically, it's the same but opposite mechanism as acidic hydrolysis.

Fischer esterification is important to generate ester for different pharmaceutical purposes such as making aspirin, morphine and etc.



### Aminolysis

Lastly, we have amine as our nucleophile. In aminolysis, it's under equilibrium controlled and required neutral condition to perform the addition. It can add to acid halides, anhydrides and ester irreversibly to form amides. On the other hand, it can add to carboxylic acid but require a **carboiimide (DCC)** to avoid acid-base side reactions.



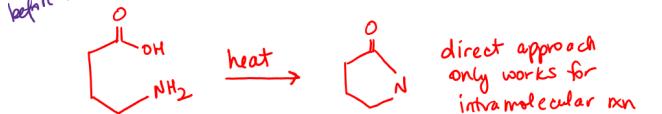
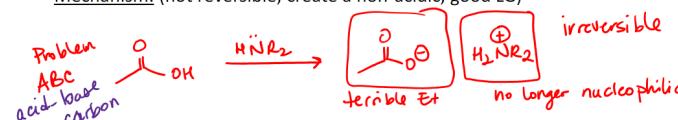
**Mechanism of Action (Acid Chlorides & Anhydrides Aminolysis):**

First, amine attack the C=O and break its  $\pi$ -bond. The  $\pi$ -bond reforms while the halide (from acid halide) or the ester (from anhydrides) will be eliminated. Finally, another amine reagent can come and deprotonate the attached nitrogen forming the amide product.

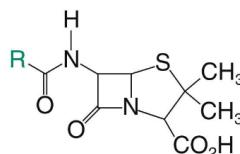
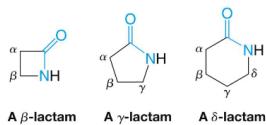
As for the carboxylic acid, we would encounter the so called "**ABC problem**" which is simply an unwanted acid-base reaction. If we were to react carboxylic acid with amine normally, all we will get is a proton exchange and at the end we will get a horrible carboxylate salt and a non-nucleophilic amine. The reason ABC happened is because it's much faster than the reaction at the carbon. To bypass this ABC, we add a compound called DCC which will form our desired product. We can in fact go further with our illustration by heating the product to directly form a ring (cyclic amides).



Mechanism: (not reversible, create a non-acidic, good LG)



These cyclic amides are called **lactams** and they're very common biological functional group. In fact, one of these lactams can be found in penicillin that can shut down bacteria. Bacterial has enzymes within its cell wall that can attack penicillin and become inactivated.



Penicillins

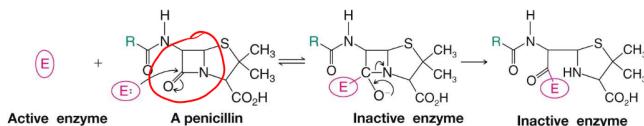
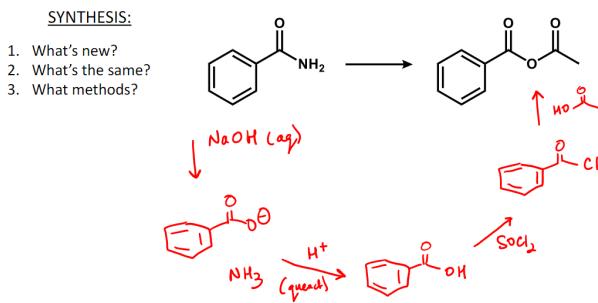
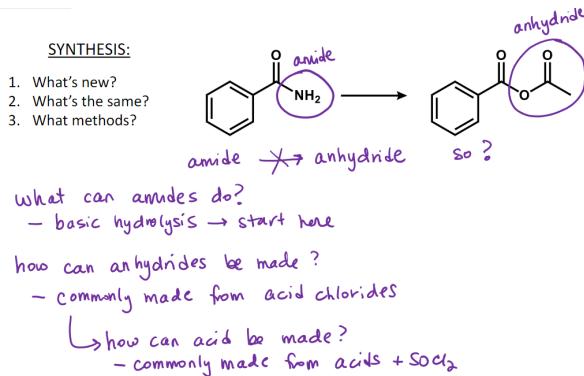


Figure 5.7: Action of penicillin on bacterial enzymes.

### 5.2.3 Synthesis

**Example 5.2.2.** The following are some guided practice



# 6

# Reactions with Enols and Enolates

## Chapter

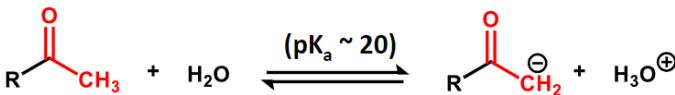
Core Topic 8 (Mar 13<sup>th</sup>, 2024)

This final chapter 6 will cover core topic 8, 9 and 10 which is the continuation of carbonyl but as a nucleophiles. Lectures will span from March 13<sup>th</sup> and March 28<sup>th</sup>

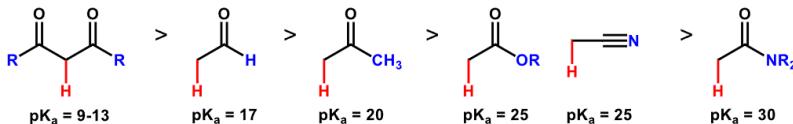
### 6.1 Enols and Enolates

Like we've said above, this is a continuation of carbonyl chemistry but we are looking into using carbonyls as nucleophiles at the  $\alpha$  carbon (position beside the carbonyl carbon). This nucleophilic activity of carbonyl is mediated by enols/enolates.

To understand this, we need to come back to some of our foundational understand about acid-base chemistry as well as EWG. Basically, we will be considering the carbonyls to be the EWG while the adjacent CH as an acid. Generally, CH are not very acidic but because they resides near this C=O EWG, their acidity increases e.g. alkane CH has pKa of 50 while C=O's CH is around 20 only. But not only that the C=O is an EWG, it's also a resonance withdrawing group where which provide extra stability by having  $O^-$  characteristic instead of  $C^-$  when CH donates H.



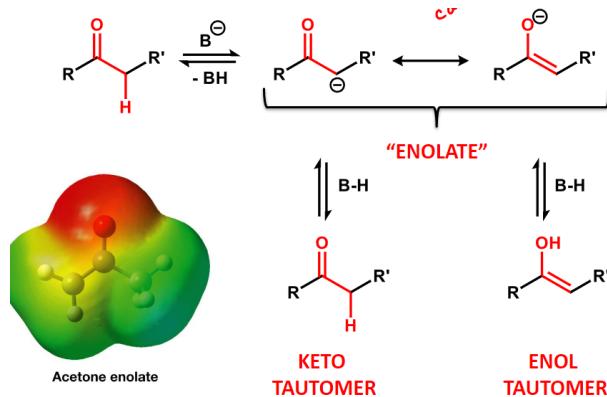
We can see below different types of compounds and its associated pKa range from 9-30. We can see a trend that follow where an increase in EDG behaviour adjacent to the C=O EWG can destabilize the conjugate base. On the other hand, we see this  $\beta$ -keto type compound with 2 carbonyls which is indicative of extra resonance structure for anion stabilizes conjugate base.



### 6.1.1 Keto-Enol Tautomers

**Definition 6.1.** **Enolate** is the conjugate base/anion forms of the  $\alpha$ -carbon (including the C=O) after it's deprotonated.

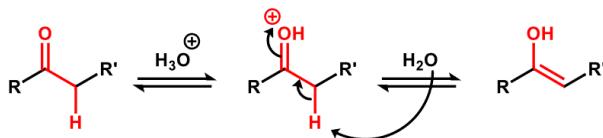
This anion has 2 equivalent structure due to the resonance provided by the C=O EWG: 1 is where the O is the anion and the other is where the C is the anion. When we re-protonate the enolate with the  $\text{C}^-$ , the product is called **keto tautomer**; meanwhile, re-protonation of the  $\text{O}^-$  enolate will yield **enol tautomer**. Nevertheless, it must be noted that the  $\text{O}^-$  are more favoured thus enole tautomer is more likely to form post-protonation.



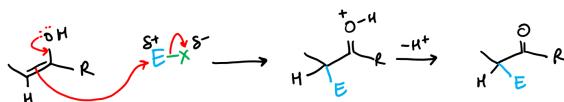
From what we've said above, we can see that **tautomers** are just constitutional isomers which can be interconverted by a process called **tautomerization**. If  $\text{O}^-$  structure was favoured in enolate then **neutral keto tautomer are usually favoured than others**. The main difference between Keto and enol tautomer is the bonding: keto has C=O while enol has C=C, keto has C-H while enole has O-H.

Under acidic conditions, protonated keto carbonyls are in equilibrium with their enol forms. This tautomerization, called **acid-catalyzed tautomerization**, occurs via an E2 elimination reaction. Water removes the

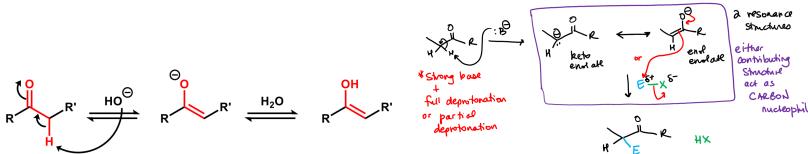
C-H proton, which allows the C-H bond electrons to be used to form the new C=C  $\pi$ -bond and break the C=O  $\pi$ -bond.



In such condition, you can have enols acting as nucleophiles and perform the typical  $S_N2$  substitution with an alkyl halide or dihalide and this reaction is reversible. Basically, you have the alkene attacking the substituent group and attaching it onto the  $\alpha$  carbon.



Under basic conditions, keto carbonyls are in equilibrium with their enolate forms. This tautomerization, called **base-catalyzed tautomerization**, also occurs via an E2 style elimination reaction. Hydroxide anion removes the C-H proton, which allows the C-H bond electrons to be used to form the new C=C  $\pi$ -bond and break the C=O  $\pi$ -bond.

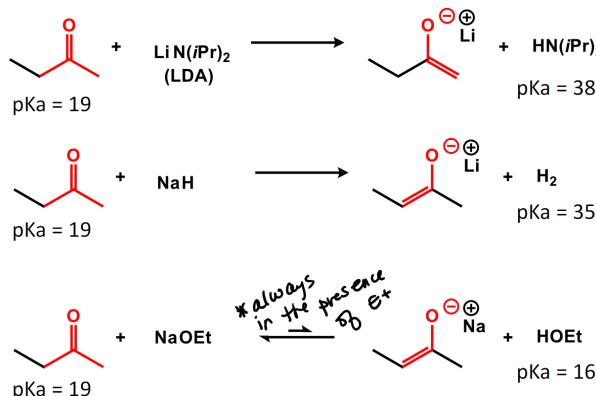


When treated with a strong base, it will lead formation of an enolate (keto and enol switching back and forth) and in the presence of an electrophile, enolate will act as a strong nucleophile. this reaction is irreversible.

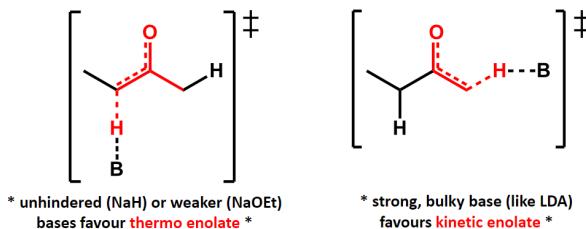
### What if there's 2 different $\alpha$ -hydrogen?

Well...in this instance, it's mainly ketone that we're going to have issues with since aldehyde there's only 1  $\alpha$ -hydrogen. For 2 different  $\alpha$ -CH, position of the alkene made will be dependent on the type of base used. If we were

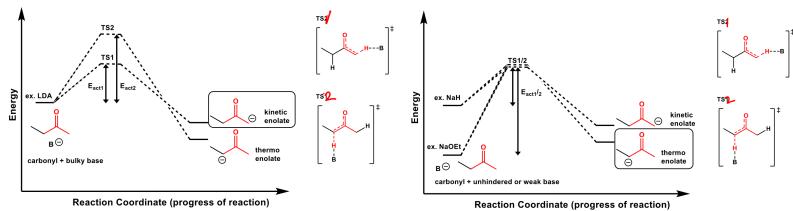
to use strong bulky base like **LDA**, it will favour the  $\alpha$ -H that's the least hindered. For smaller and weaker bases respectively like NaH and NaOEt, it prefers the more substituted H. Additionally, because this is acid-base-like reaction, everything is in equilibrium and its position is dependent on the strength of the base e.g. weaker the base, the less the product will form.



With this, we can classify enolate according to the base we treat it with. When we treat it with a bulky base, the enolate formed is called **kinetic enolate** where it's the least substituted alkene and has lower transition state energy. On the other hand, when treated with smaller bases, it will form the **thermodynamic enolate** where it's the most substituted alkene with the higher transition state energy.



We can see this difference by look at their reaction coordinate diagram. Bulky bases prefer to deprotonate the least hindered hydrogen during the rate determining step due to less steric hindrance. Because of steric hindrance, there will be a significant difference in activation barrier between the two processes.



Unhindered or weaker bases prefer to deprotonate the more substituted (i.e. more hindered) hydrogen during the rate determining step due lower product energy. There is little difference in activation barrier between the two processes.

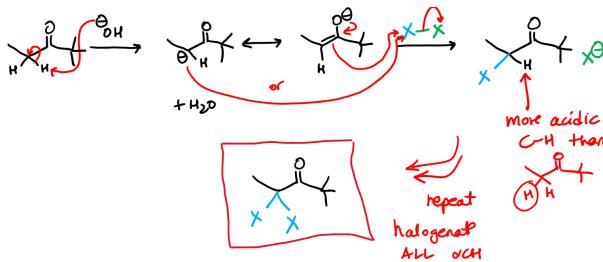
We will now look at some more details on reactions that use enols and enolates as nucleophiles.

Method	Key Features	General Reaction Scheme
Halogenation	<ul style="list-style-type: none"> <li>Basic or acidic</li> <li>Enolate or enol Nu (<math>S_N2</math>)</li> <li><math>X_2</math> electrophile</li> </ul>	$\text{CH}_3\text{CH}(\text{H})\text{CO}_2^- + \text{X}_2 \xrightarrow{\text{acid or base}} \text{CH}_3\text{CH}(\text{X})\text{CO}_2^- + \text{HX}$
Simple Alkylation	<ul style="list-style-type: none"> <li>Basic</li> <li>Enolate Nu (<math>S_N2</math>)</li> <li>R-X electrophile</li> </ul>	$\text{CH}_3\text{CH}(\text{H})\text{CO}_2^- \xrightarrow[-\text{HN}(i\text{Pr})_2]{\text{LDA}} \text{CH}_3\text{CH}(\text{Li}^+)\text{CO}_2^- \xrightarrow{-\text{LiBr}} \text{CH}_3\text{CH}(\text{R})\text{CO}_2^- + \text{LiBr}$
$\beta$ -Keto Ester Alkylation	<ul style="list-style-type: none"> <li>Basic</li> <li><math>\beta</math>-diketo enolate Nu (<math>S_N2</math>)</li> <li>R-X electrophile</li> <li>Hydrolyze, decarboxylate <math>\beta</math>-ester</li> </ul>	$\text{CH}_3\text{CH}(\text{H})\text{C}(=\text{O})\text{CO}_2^- \xrightarrow[4. \text{H}^+, \text{heat}]{1. \text{NaOEt}, 2. \text{CH}_3\text{Br}, 3. \text{NaOH (aq)}} \text{CH}_3\text{CH}(\text{R})\text{CO}_2^- + \text{HOCH}_2\text{CH}_3 + \text{CO}_2$

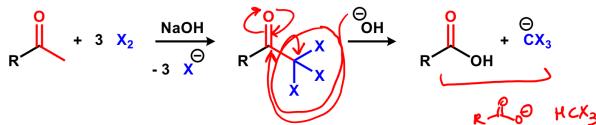
## 6.1.2 Halogenation

In basic halogenation, we first perform base catalyzed tautomerization on our ketone which generate the enolate. This enolate (either the carbanion or alkene) then attack the halogen and forming a bond with it. Interestingly, the  $\alpha$ -H that remains is now more acidic than the  $\alpha$ -CH that we started with which means that the tautomerization and halogen addition

happens again for it leading to complete addition of halogen at the  $\alpha$ -C.

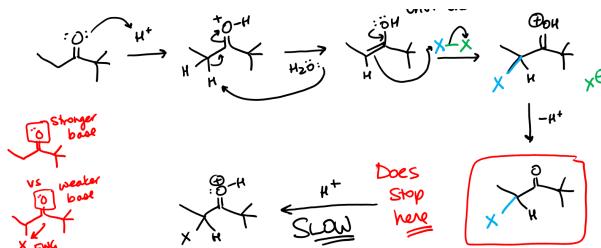


This basic tautomerization and halogen addition has its application in **haloform** reaction where we add 3 halogen on the  $\alpha$ -C which can then be gone through a  $\text{S}_{\text{N}}\text{CO}$  reaction to form carboxylic acid and haloform.



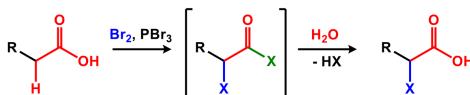
### What if we want to halogen only once?

Well...we simply does acid-catalyzed tautomerization follow by addition of halogen. After the doing so, the reaction should stop with 1 substituted halogen but theoretically, given a long period of time, 1 proton can come and protonate the  $\text{C=O}$ . The reason that it's so slow because addition of halogen, an EWG, causes the  $\text{C=O}$  base becoming weaker hence much slower to accept the hydrogen.

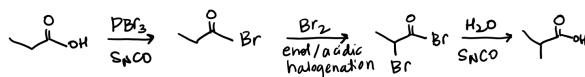


Now sometimes we need to perform tautomerization on carboxylic acid, which is hard because that's readily occur. A way to approach this is by

converted the carboxylic acid into an acid halide using phosphorus trihalide which will replace OH with halogen using  $S_NCO$  reaction. Then we can run this through acid catalyzed tautomerization and halogen addition. Lastly, to bring back the OH, we perform acidic catalyzed hydrolysis with water.

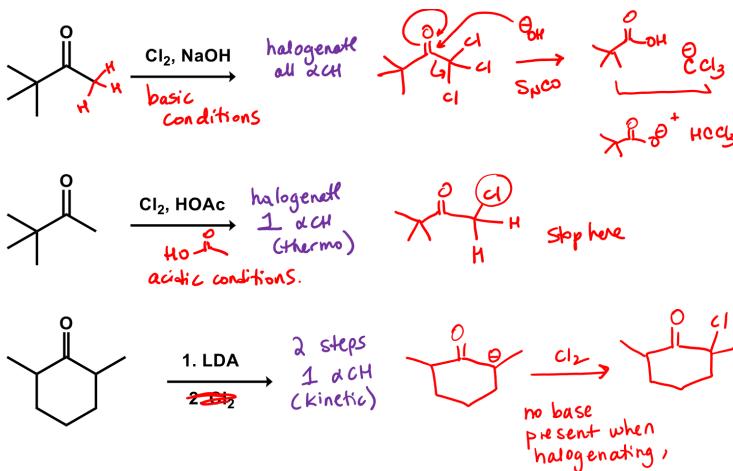


Mechanism: make acid halide,  $\alpha$ -halogenation,  $S_NCO$  hydrolysis



\*  $PBr_3$  is Lewis acid / acidic conditions

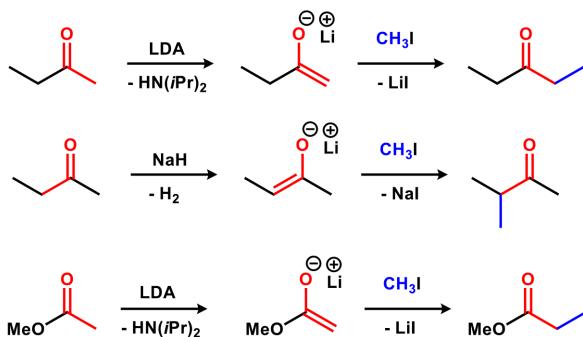
**Example 6.1.1.** Here are some guided practice



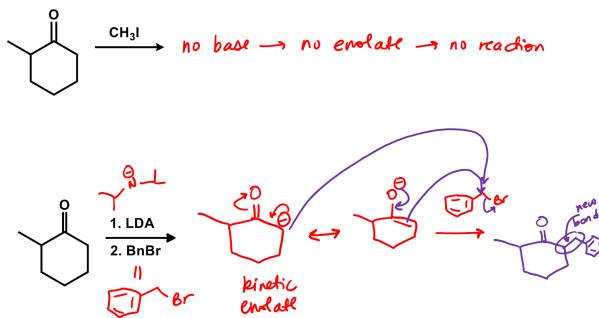
### 6.1.3 Alkylation

Enolates can be a very powerful tool for selective substitution. To perform alkylation, you first enolate the compound with a selective base (depending on whether you need a thermodynamics or kinetics product) then you perform  $S_N2$  reaction with the alkyl halide (the alkyl group you want to add

attached to a halogen). The following is the summary of possible alkylation with iodomethane when treated with different base.

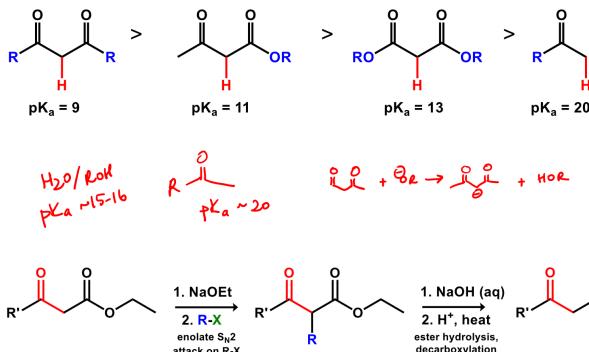


**Example 6.1.2.** Here are some guided practice



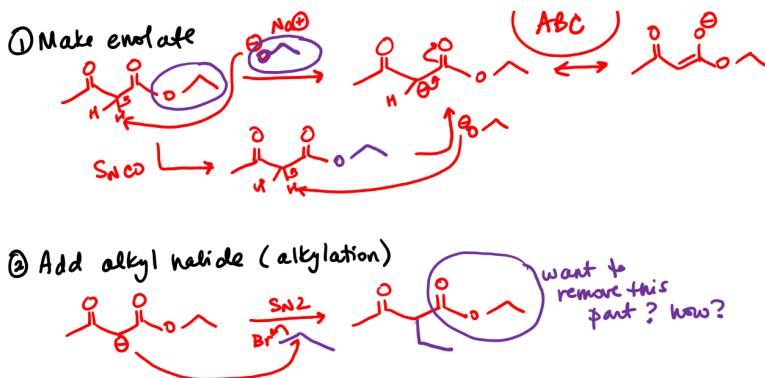
Now, as for alkylation of  $\beta$ -keto ester, you would have an easier time forming the enolate because of 2 withdrawing groups. At the end of the alkylation, it would yield a ketone connected to the alkyl group we need. The  $\beta$ -keto ester are part of a group of compound called the **active methylene compound** that all have an  $\alpha - CH_2$  connected to 2 EWGs and their pK<sub>a</sub>s are low (acidic). Because they're acidic, it's easier to deprotonate using water and other oxygen bases.

The most common of these active methylene we will be using to describe our synthesis is acetoacetic and malonic ester syntheses. In both base, you have 2 steps to follow: 1, insert the alkyl group on the  $\beta$ -ketoester; 2, remove the the other carbonyl group and replace with hydrogen.



### Alkylation Step

In this step, you'll first make the enolate and to do so, you'll be treating the compound with a oxygen base with the same *OR* group as the compound. The reason for this is that there could be a slow step of  $S_N\text{CO}$  reaction with the attack of the base group so it's best to match it. Although, not required, it's recommended to have the same *OR* group. After, the enolate will be alkylated with an alkyl halide like before

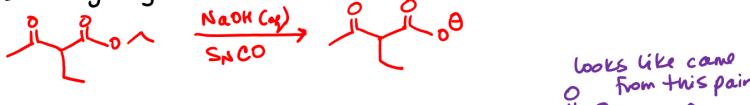


### Hydrolysis/Decarboxylation Step

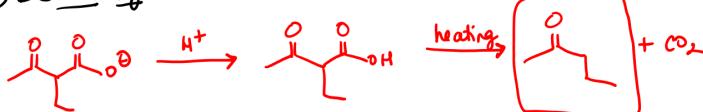
Now that you have the attached R group, you will need to remove the other group that you don't want. To do so, we first perform a  $S_N\text{CO}$  hydrolysis where there's a removal of R group on the OR. Then we will decarboxylate

it by first prodiving  $H^+$  for it to form carboxylic acid. The carboxylic acid group can then be removed by heat and leave as  $CO_2$

③ Basic hydrolysis



④ Decarboxylation ( $-CO_2$ )



Now when it comes to the removal of carboxylic acid group, it's possible for every compound however for compounds with just an R group attached to the carboxylic acid, the decarboxylation step is very slow. Decarboxylation by heat for  $\beta$ -ketoester is generally faster and occurs much more readily. To see this, we can compare the reaction coordinate diagram of these 2. What we found is that  $\beta$ -Keto acids can form a six-membered ring transition state (vs four-membered ring for regular carboxylic acids). This leads to a significantly lower energy barrier.

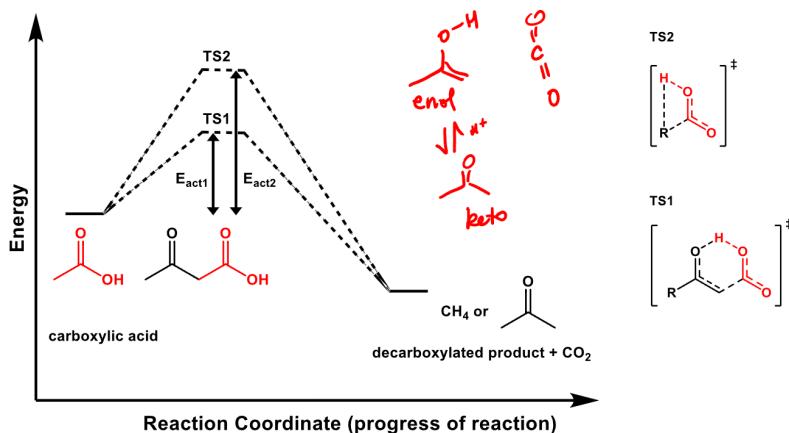
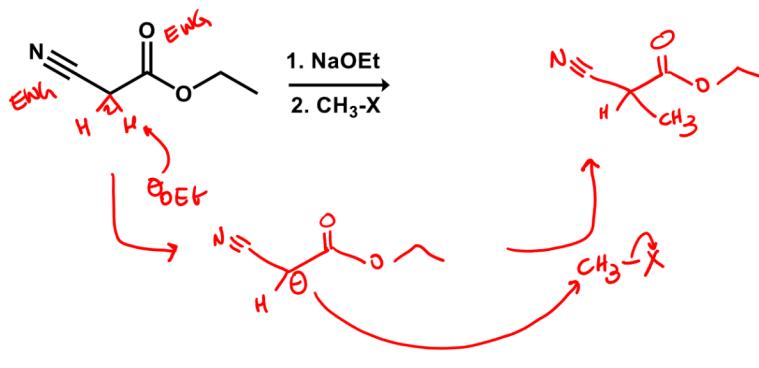
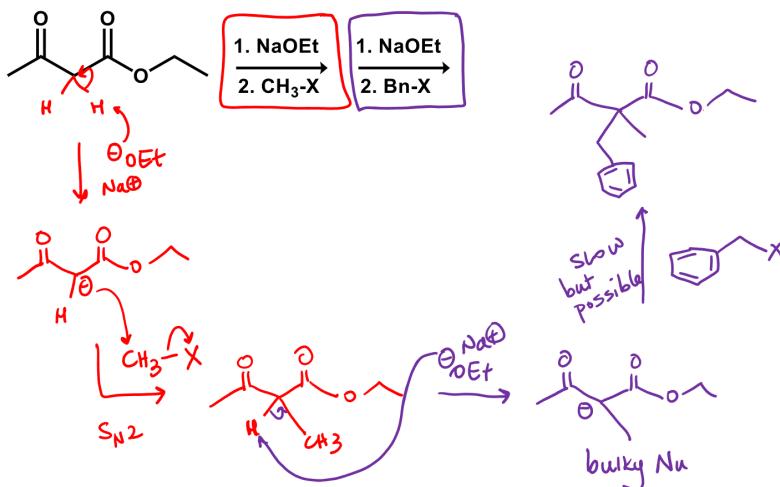


Figure 6.1: Reaction coordinate diagram of decarboxylation.

**Example 6.1.3.** So now, we can look at some guided practice.



End of Core Topic 8

## 6.2 Condensation Reactions

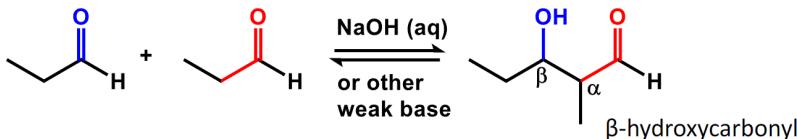
Now, with our new knowledge about enolates, we can combine it  $\text{A}_N\text{CO}$  and  $\text{S}_N\text{CO}$  reactions to form the **condensation reaction**.

There are 3 main classification to condensation reactions: **Aldol addition, Aldol and Claisen condensation.**

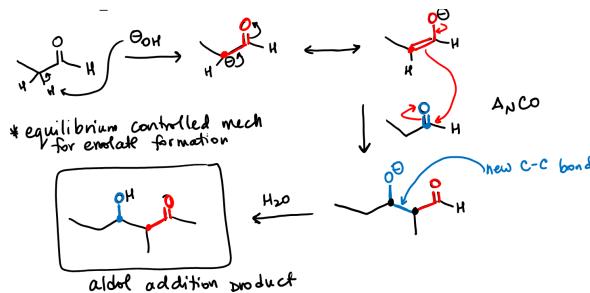
Method	Key Features	General Reaction Scheme
Aldol Addition	<ul style="list-style-type: none"> <li>• <b>Basic</b></li> <li>• Enolate Nu (<math>\text{A}_\text{N}\text{CO}</math>)</li> <li>• Carbonyl electrophile</li> </ul>	
Aldol Condensation	<ul style="list-style-type: none"> <li>• <b>Basic or acidic</b></li> <li>• Dehydration following Aldol Addition (E2 or E1cB)</li> </ul>	
Claisen Condensation	<ul style="list-style-type: none"> <li>• <b>Basic</b></li> <li>• Enolate Nu (<math>\text{S}_\text{N}\text{CO}</math>)</li> <li>• Ester electrophile</li> </ul>	

### 6.2.1 Aldol Addition and Condensations

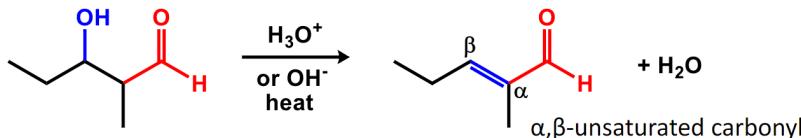
In an Aldol addition, you have the enolate as nucleophile while the carbonyl from another as electrophile. It mainly works for aldehyde and less for ketone because of steric hindrance and the electrophilic activity of ketone is also less. You can still have ketone aldol addition but with insignificant yield and slow.



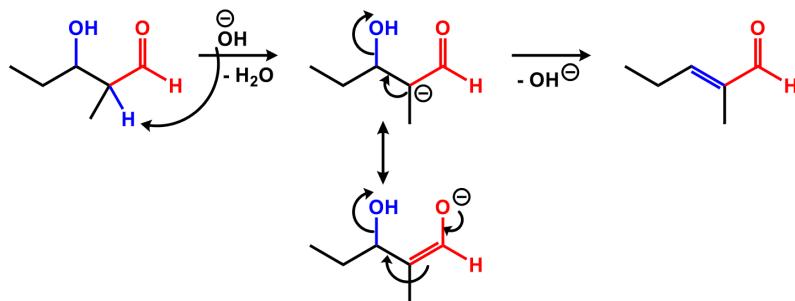
So first, you enolate your aldehyde using a weak base. Then this enolate will react with the aldehyde by using its alkene to attack the C=O and break its  $\pi$ -bond in an  $\text{A}_\text{N}\text{CO}$  reaction. This lead to the formation of new C-C bond between the enolate and carbonyl. The negative O will be re-protonated (if you need to add a quenching step, it's possible) forming the  $\beta$ -hydroxycarbonyl.



So, you can actually promote Aldol addition (supposedly in the case of ketone) by forming aldol condensation (dehydration) product which is a reversible reaction.

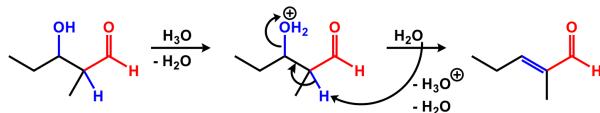


There are 2 ways you can approach this: acidic or basic. With the basic way, you make a basic enolate and it will self-rearrange into  $\alpha,\beta$ -unsaturated carbonyl.

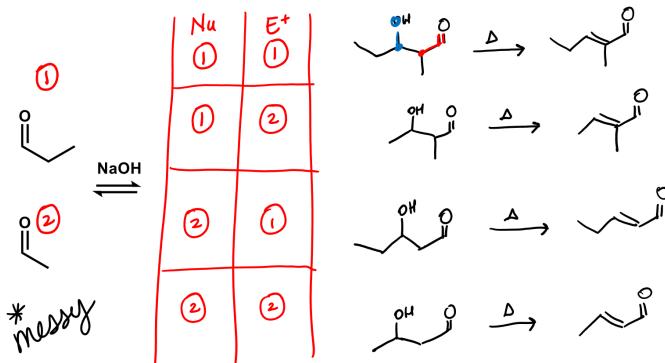


Acidic follows similar mechanism with slight modification in steps but also form the  $\alpha,\beta$ -unsaturated carbonyl.

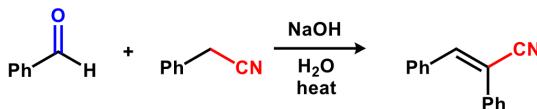
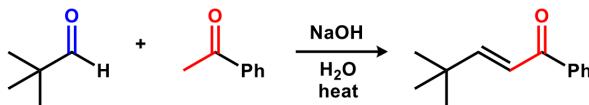
Now, theoretically, you could do a "crossed" aldol addition reaction i.e. performing aldol addition on 1 compound with another different com-



pound. Even so, the product we get will be a variation of different combination and is uncontrolled.

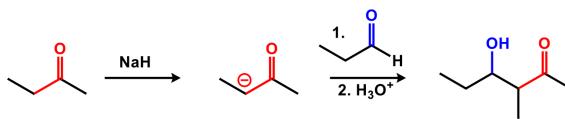
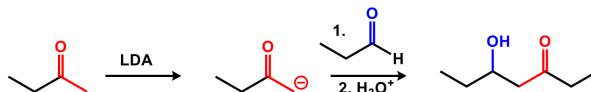


A way to do a "crossed" aldol more efficiently and selectively is by creating a reactants compounds with specific geometry or in a specific order; with this, you have 2 options: 1) addition between non-enolizable aldehyde and enolizable ketone



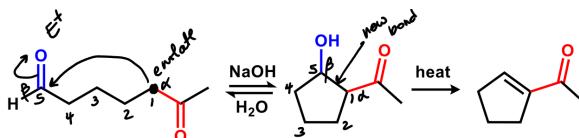
**Figure 6.2:** Enter Caption

or 2) addition between any carbonyl and quantitative enolate.

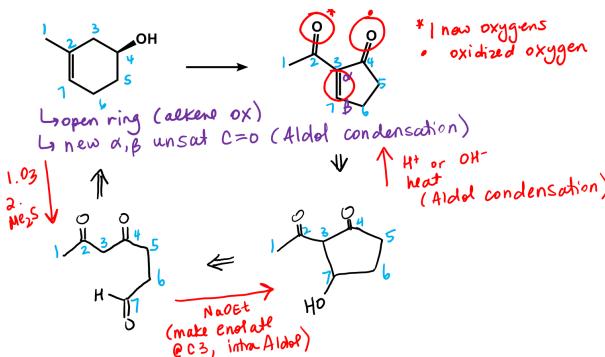


### Intramolecular Aldol

We can use aldol addition to form called **intramolecular aldol addition** and they tend to favour 5 & 6 membered ring. In order to form a ring we need to look at 2 factors that can come into play. First, we need to look at the  $\alpha - \text{CH}$  acidity which in this case is negligible since acidity between ketone and aldehyde is not too different. Second, we need to look at the electrophilicity of the C=O bond, in our case, ketone electrophilicity is much stronger than ketone so it will be the electrophile.

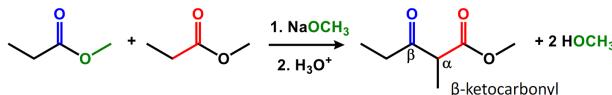


**Example 6.2.1.** Here's a guided practice for intramolecular aldol addition

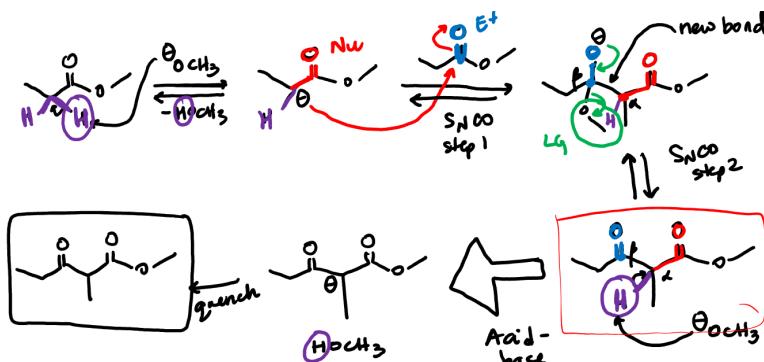


## 6.2.2 Claisen Condensation

Claisen condensation is a reaction used for adding ester or acid derivative ( $\text{C}=\text{O}$  attached to an OR group). In the reaction, 1 of them will be the enolate while the other will be the electrophile. To form the enolate, the ester must be treated with a base that has the same OR group as it. The reason for this was already said previously but basically there's a possibility that the base attack the OR group of ester in a  $\text{S}_{\text{N}}\text{CO}$  reaction. This process is called **trans-esterification**, so by having the same OR, transesterification is the same.

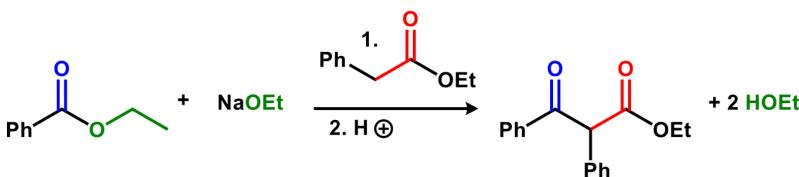
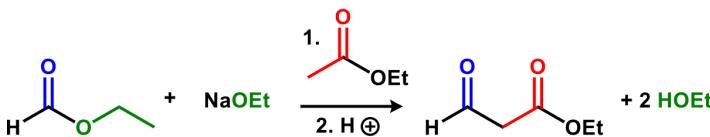


So Claisen condensation follows the same mechanism. First you form your enolate. The enolate then acts as a nucleophile and attack the ester C=O and break its  $\pi$ -bond. The different here is that you're going to have the OR as the leaving group when  $\text{O}^\ominus$  reform its  $\pi$ -bond. Ideally the reaction should stop here but because you still have the other H at the  $\beta$ -ketoester position, it will be acidic and thus be deprotonated very quickly by your previous base to form enolate again. Solve this, we simply add a quenching step to reprotonate the  $\beta$ -carbon.

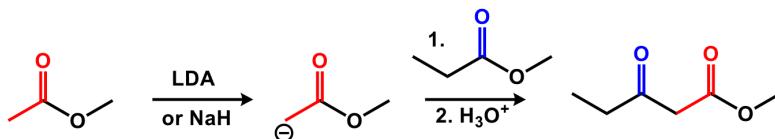


Similar to aldol, when you have a crossed aldol condensation, it will be problematic. To solve this, we have almost the same options as before. 1) reaction between non-enolizable ester and enolizable ester with at least 2  $\alpha$ -CH. But even this would generate its own complication which is why we

can do a the second option.

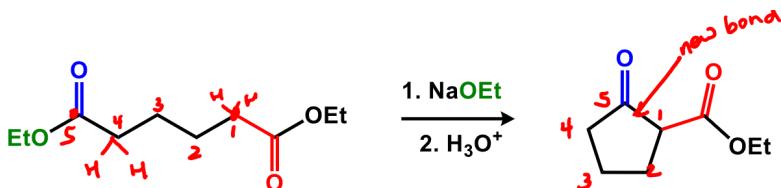


2) reaction between any ester with a quantitative ester enolate.

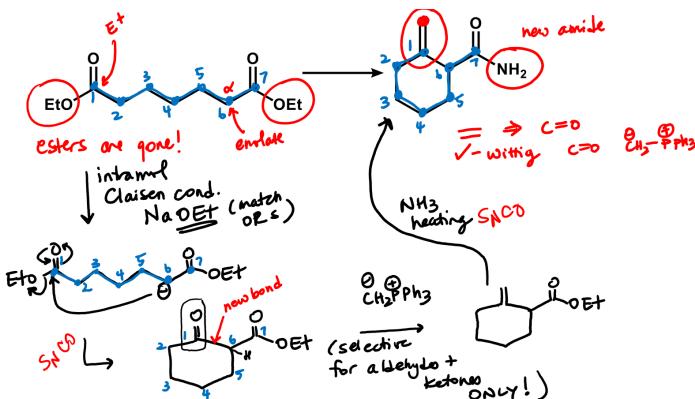


### Intramolecular Claisen Condensation

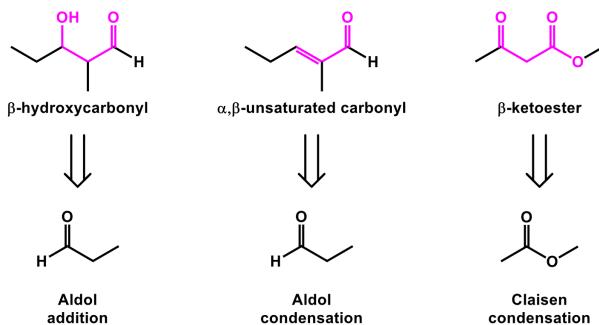
Like before, you can use claisen condensation to form a ring via **intramolecular Claisen condensation (Dieckman cyclization)**. Like before, we will have to check for the  $\alpha$ -CH acidity as well as electrophilicity to form know where to attack and form the ring.



**Example 6.2.2.** Here's a guided practice for intramolecular claisen condensation



We can summarize all of this reaction by the motifs that they will be synthesizing.

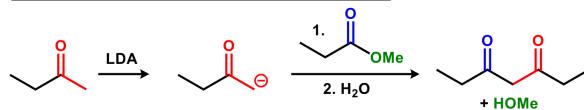
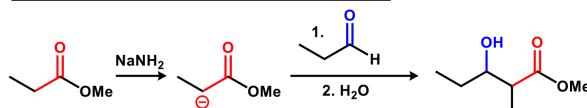


### 6.2.3 Aldol-Claisen Reactions

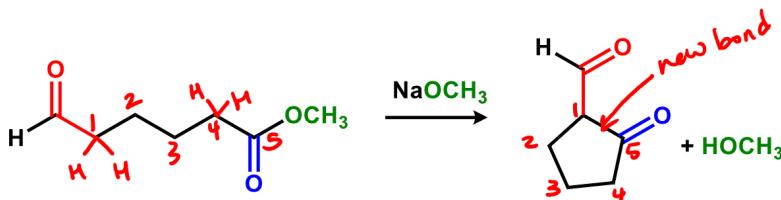
Now, you can even combine the aldol and claisen reaction together. This can be done by either combine quantitative ketone/aldehyde enolate with ester as electrophile or the opposite would also work.

#### Intramolecular Aldol-Claisen Reactions

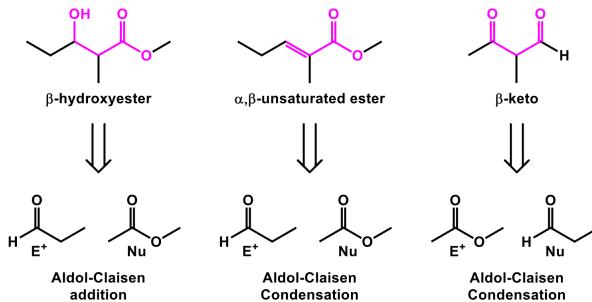
Similarly, you can form rings via reaction between aldehyde/ketone and ester group via intramolecular aldol-claisen reaction. Like before, you need to look at acidity and electrophilicity of the  $\alpha$ -CH. Because this is aldol-claisen reaction combined, the acidity of aldehyde/ketone will be different

Quantitative Ketone/Aldehyde Enolate, Ester E+Quantitative Ester Enolate, Ketone/Aldehyde E+

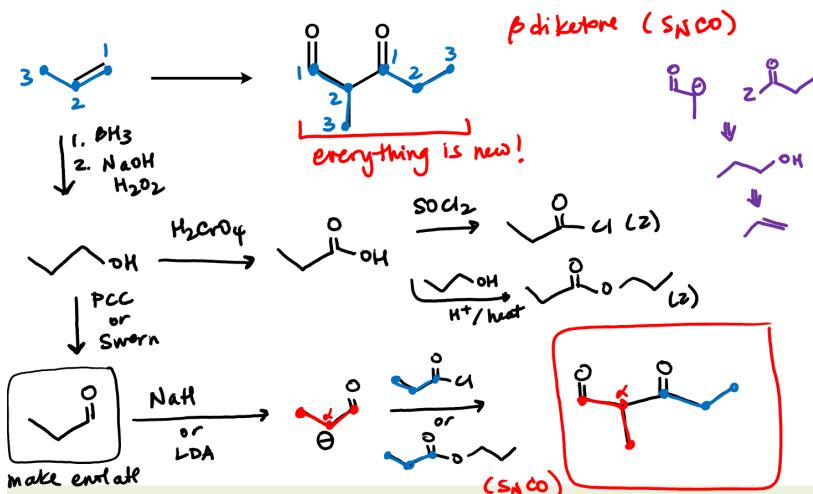
than the ester. In this case aldehyde/ketone has pKa of 18-20 while that of ester is 25. This means aldehyde/ketone are more acidic which makes them ideal to form enolate while the ester will act as the electrophile.



We can summarize the all the aldol-Claisen reactions as the following motif.



**Example 6.2.3.** Here's a guided practice for topic 9



Topic 10 was not included because the author did not have enough time. Nevertheless this last lecture includes conjugate carbonyl addition, Michael addition and Robinson annulation.

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**Note to Author:** Good luck on your final exam on April 15<sup>th</sup>, 2024!!! (Don't forget your dad's birthday :)))



Modern spectroscopic techniques for structure determination. The chemistry of alcohols, ethers, carbonyl compounds, and amines, with special attention to mechanistic aspects. Special topics.

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