<u>Organic Chemistry</u> is the study of carbon-containing molecules. This class has two points.

The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing molecules on the planet!!

You will learn how MRI scans work.

You will learn the basic principles of pharmaceutical science and how many drugs work.

You will learn about the special bond that holds carbohydrates such as glucose in six-membered rings, connects carbohydrate monomers together to make complex carbohydrate structures and is critical to DNA and RNA structure.

You will learn how soap is made from animal fat and how it works to keep us clean.

You will learn the important structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life.

You will learn how important antibiotics like penicillins work, including ones that make stable covalent bonds as part of their mode of action.

You will learn why carrots are orange and tomatoes are red.

You will learn the very cool reason that the DNA and RNA bases are entirely flat so they can stack in the double helix structure.

You will learn even more about why fentanyl is such a devastating part of the opioid problem and how Naloxone is an antidote for a fentanyl overdose.

You will learn even more details about why Magic Johnson is still alive, decades after contracting HIV, and how the same strategy is being used to fight COVID.

You will learn about the surprising chemical reason the Pfizer and Moderna mRNA vaccines elicit strong immune responses.

The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds, especially carbon-carbon bonds.

You will learn how carbon-metal bonds lead to new carbon-carbon bonds.

You will learn how most reactions of carbonyl compounds involve only the four common mechanistic elements operating in only a few common patterns.

You will learn how, by simply adding a catalytic amount of base like HO^- to aldehydes or ketones, you can make new carbon-carbon bonds, giving complicated and useful products.

You will learn a reaction that can convert vinegar and vodka into a common solvent.

You will learn why molecules with six-membered rings and alternating double bonds are stable.

You will learn a reaction that can turn model airplane glue into a powerful explosive.

Most important, you will develop powerful critical thinking skills:

1. You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.
2. You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.

The ability to rationally synthesize new molecules changed human destiny and drives the economies of the world by enabling:

1. The synthesis of new drugs to cure disease, dramatically increase human life span and improve everyone's quality of life.
2. The development of lubricants and components for virtually all machines.
3. The creation of new methods for integrated circuit production enabling faster computation.
4. The creation of new materials for millions of uses including 3d printing and biodegradable plastics.
5. The synthesis of new pigments for dyes, paints and cosmetics.
6. The synthesis of all synthetic clothing fibers.
7. The production of highly refined and cleaner burning fuels.
8. The creation of batteries to store energy, the most important element of the renewable energy solution.
9. …to name just a FEW applications.

***In other words, essentially everything that makes modern life so incredible*!**

Useful Definitions:

Mechanism – A scheme that illustrates all reaction intermediates, as well as the flow of electrons and movement of atoms during bond breaking and bond making processes. Remember that arrows are used only to indicate the movement of electrons. Movement of atoms is assumed, but not explicitly indicated, by the arrows.

Nucleophile – A molecule that contains an atom with a lone pair AND a full or partial negative charge.

Electrophile – A molecule that contains an atom with a full or partial positive charge AND can be attacked by a nucleophile without creating a non-viable species such as a pentavalent (five bonds) carbon.

Brønsted-Lowry Base – A molecule containing at least one atom with a lone pair that will accommodate binding to a proton during a proton transfer reaction.

Lewis Base – A molecule that can donate a lone pair in a bond-forming process.

Brønsted-Lowry Acid – A molecule that can donate a proton during a proton transfer reaction.

Lewis Acid – A molecule that can accept a lone pair in a bond-forming process.

Leaving group – A group that will be relatively stable when it departs, such as a small neutral species like H_2O or N_2, or a group such as a halide atom that departs as a relatively stable ion.

Stereochemistry – Refers to which of the possible stereoisomers predominate in a reaction. The details of the mechanism dictate whether a reaction will involve certain features such as *syn* addition, *anti* addition, require an antiperiplanar transition state geometry, involve stereochemical InVERSiON, etc.

Regiochemistry – Refers to which of the possible product constitutional isomers predominate in a reaction. The details of the mechanism dictate whether a reaction will predominately give products that are consistent with Markovinikov's rule, are exactly inconsistent with Markovnikov's rule (anti-Markovnikov), are consistent with Zaitsev's rule, give most reaction at the more substituted carbon, etc.

Key Recognition Element (KRE) – Characteristic functional groups in relation to a new carbon-carbon bond seen with many of the reactions encountered in second semester Organic Chemistry. Being able to identify the KRE's in product molecules for *each* reaction learned will greatly simplify the process of deciding which reactions to use in complex synthesis problems.

Intermediate – A species produced during a reaction mechanism that is less stable than the starting materials or products. It exists for a short time and knowing a key intermediate's structure can help predict stereochemistry and regiochemistry of a reaction (for example a carbocation intermediate or radical intermediate that predicts predominant products seen in many first semester reactions).

Transition State – A theoretical structure that represents the highest energy species encountered in moving between starting materials, intermediates or products during a reaction mechanism. Predicting the properties of a presumed transition state can sometime predict reaction stereochemistry or regiochemistry (for example an anti-periplanar transition state geometry required for an E2 reaction).

Mechanisms: The Basics

A) The Correct Use of Arrows to Indicate Electron Movement

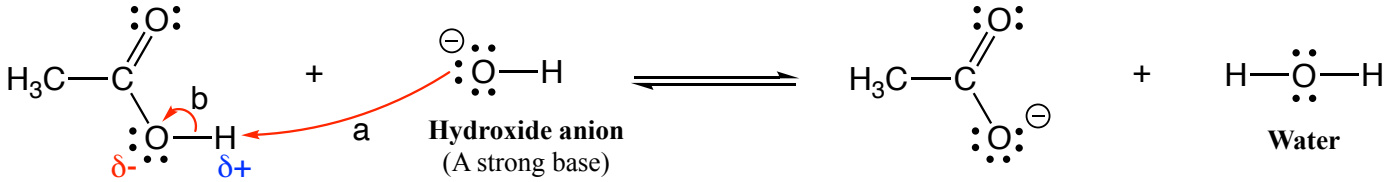
The ability to write an organic reaction mechanism properly is key to success in organic chemistry classes. Organic chemists use a technique called **arrow pushing** to depict the flow or movement of electrons during chemical reactions. Arrow pushing helps chemists keep track of the way in which electrons and their associated atoms redistribute as bonds are made and broken. The first essential rule to keep in mind is the following:

First rule: Arrows are used to indicate movement of *electrons*

A regular arrow (double-sided arrowhead) is used to indicate the movement of two electrons, while a line with a single-sided arrowhead (sometimes called a "fish hook arrow") is used for single electron movement involved with radical reactions.

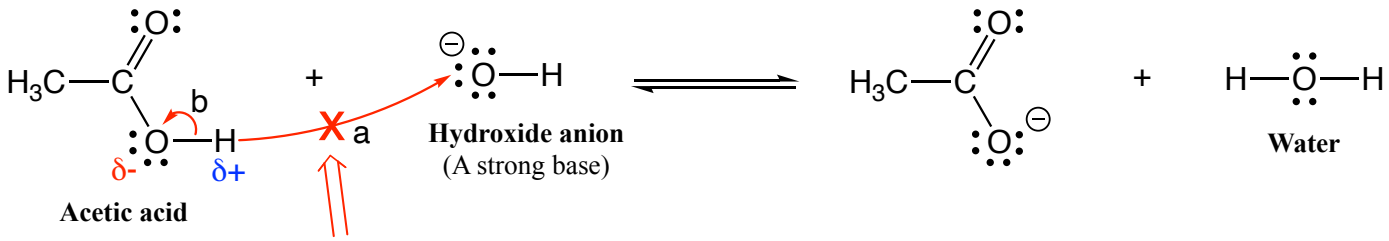
The great majority of reactions that will be discussed in this class involve movement of pairs of electrons, so they are represented by double-sided arrowheads.

Second Rule: Arrows are never used to indicate the movement of atoms directly. The arrows only show atom movement indirectly as a consequence of electron movement when covalent bonds are made and broken.



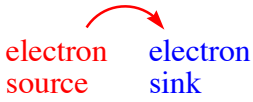
Correct use of arrows to indicate electron movement during reaction

A common mistake students can make is that they will erroneously write an arrow pointing *from* the H of the acetic acid *to* the O atom of the hydroxide anion (arrow a below). This is wrong, because such an arrow would be indicating the H *atom* movement directly, not *electron* movement!



Incorrect arrow because it is pointing in the wrong direction! Never use arrows to indicate atom movement directly

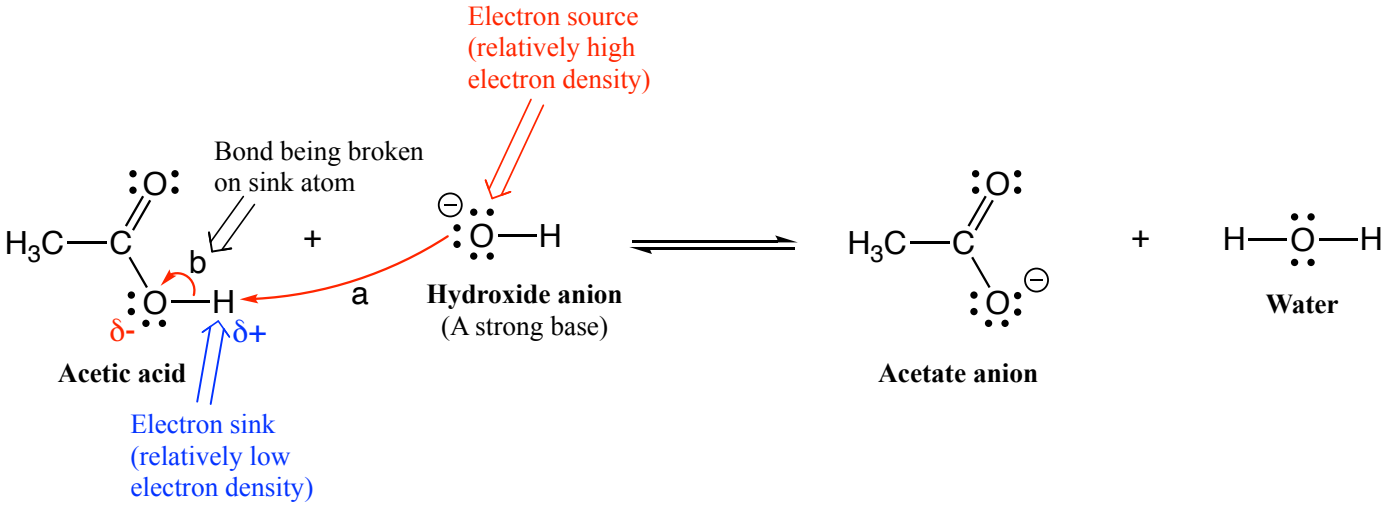
Third Rule: Arrows always start at an electron source and end at an electron sink.



An **electron source** is a bond or a lone pair of electrons. It is either a π bond or a lone pair on an atom of relatively high electron density in a molecule or ion, or a bond that must break during a reaction. An **electron sink** is an atom on a molecule or ion that can accept a new bond or lone pair of electrons.

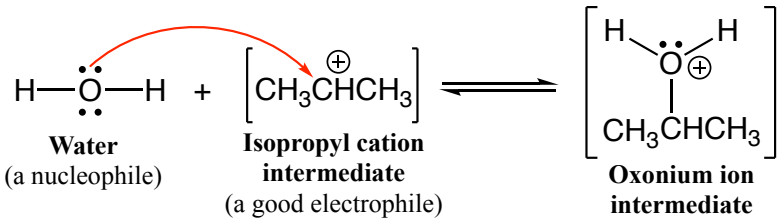
Fourth rule: Breaking a bond will occur to avoid overfilling valence (hypervalence) on an atom serving as an electron sink.

In these cases, the electron source for the arrow is the bond being broken, and the sink is an atom able to accommodate the electrons as a lone pair, generally an electronegative atom such as an O atom or a halogen. If an ion is created, that ion is often stabilized by resonance delocalization or other stabilizing interactions.

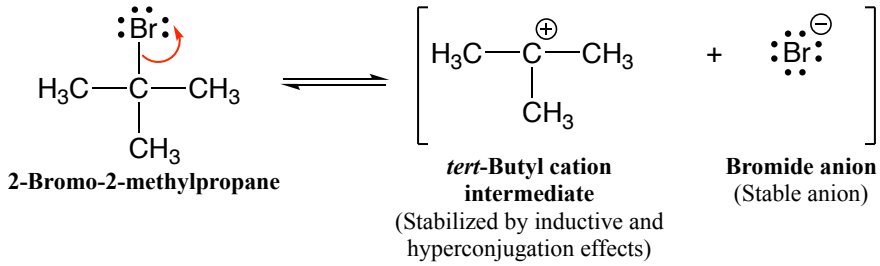


Polar Reaction Mechanisms: Polar reactions are most of what you will see in organic chemistry. There are only four different mechanistic elements that combine to make up the different steps of almost all the mechanisms you saw in CH320M/CH328M. Better yet, in CH320N the following four mechanistic elements are pretty much all you need to think about until we get to electrophilic aromatic substitution.

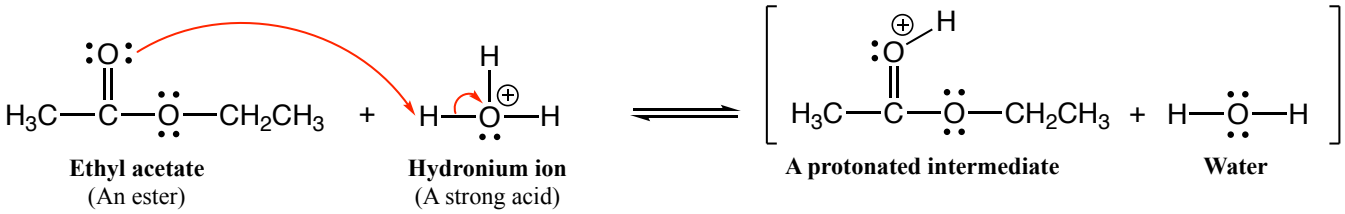
1. **Make a new bond between a nucleophile (source for an arrow) and an electrophile (sink for an arrow).** Use this element when there is a nucleophile present in the solution as well as an electrophile suitable for reaction to occur.



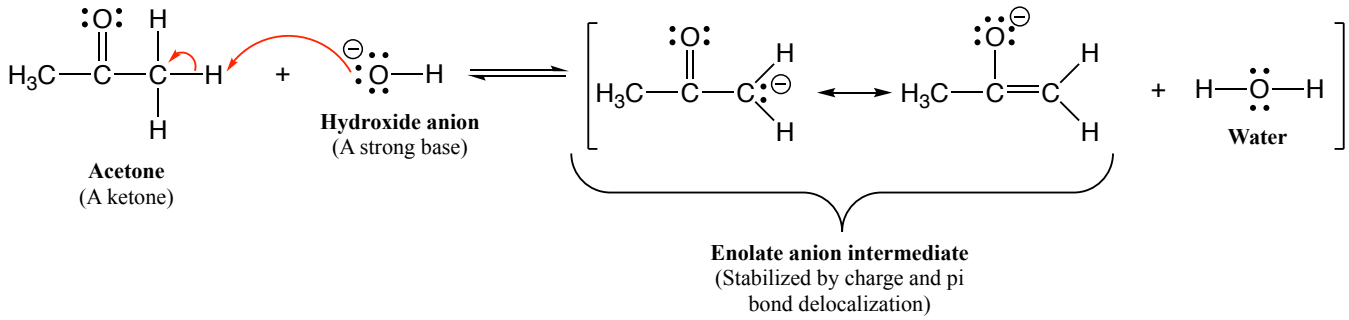
2. **Break a bond so that relatively stable molecules or ions are created** Use this element when there is no suitable nucleophile-electrophile or proton transfer reaction, but breaking a bond can create neutral molecules or relatively stable ions, or both.



3. **Add a proton** Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly basic functional group or there is a strong acid present.



4. **Take a proton away** Use this element when there is no suitable nucleophile-electrophile reaction, but the molecule has a strongly acidic proton or there is a strong base present.



The situation is even simpler than you might expect because 1 and 2 are the functional reverse of each other, as are 3 and 4.

Mechanism Summary

The following questions and mechanistic elements are described from the point of view of the carbon-containing reagent, written in the form of a flowchart.

Is there a strong acid present or is the carbon-containing reagent a strong base?

YES ⟹ **Add a proton**

NO ⇓

Is there a strong base present or is the carbon-containing reagent a strong acid?

YES ⟹ **Take a proton away**

NO ⇓

Are there a nucleophile and electrophile present?

YES ⟹ **Make a bond**

NO ⇓

Can a bond be broken to create stable molecules or ions?

YES ⟹ **Break a bond**

NO ⇓

Think about alternative mechanistic elements (radical reaction, S_N2, E2, etc.)

Geminal
Dihaloalkanes

Vicinal
Tetrahaloalkanes

Alkynes

Aldehydes/Ketones

Vicinal
Dihaloalkanes

Vicinal
Diols

Alkenes

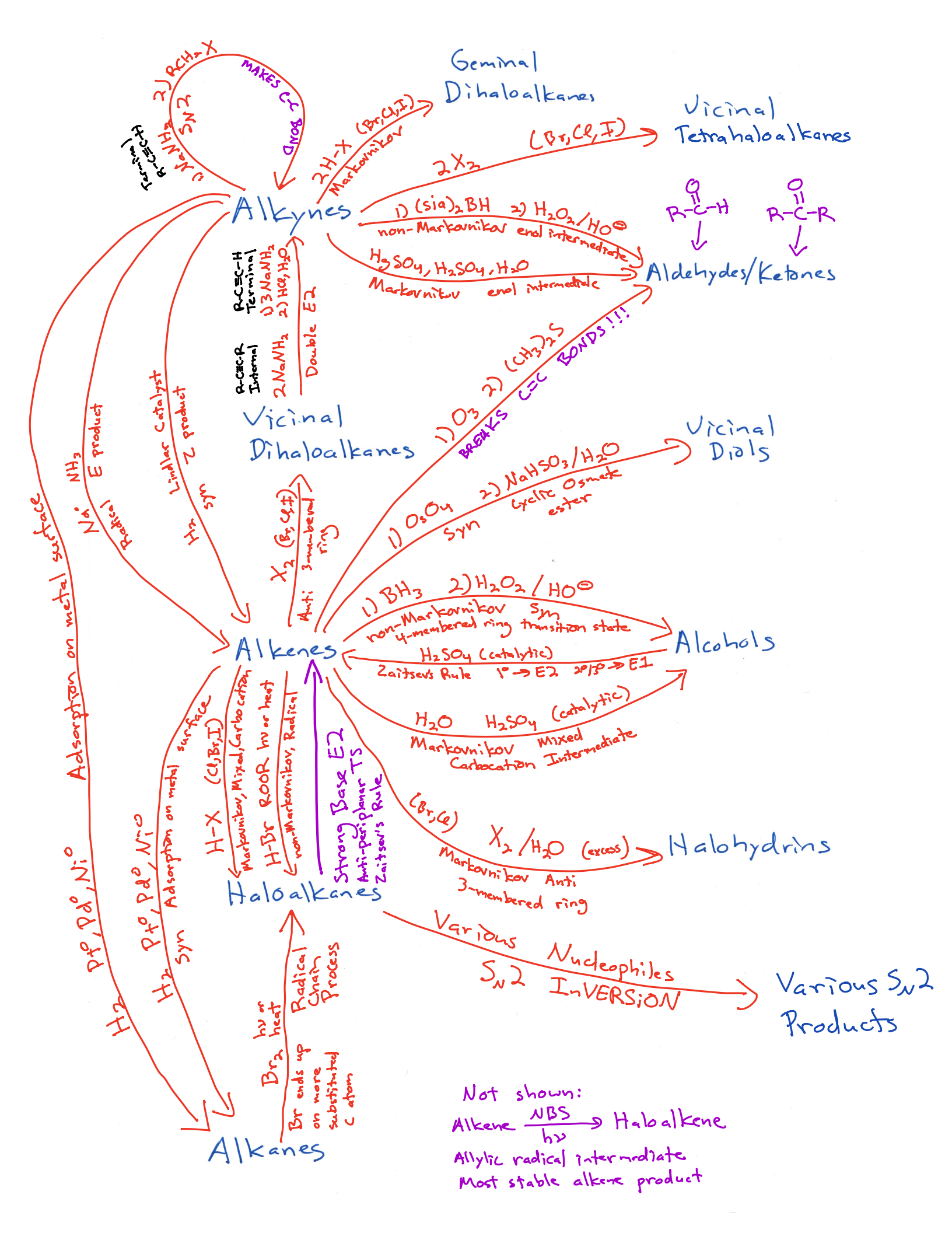
Alcohols

Halohydrins

Haloalkanes

Various S_N2
Products

Alkanes


Terminal RC≡CH
1) NaNH2
2) RCH2X
SN2
MAKES C-C
DOES
Geminal Dihaloalkanes
2 H-X (Br,Cl,I)
Markovnikov
Vicinal Tetrahaloalkanes
(Br, Cl, I)
2 X2
Alkynes
1) (sia)2BH 2) H2O2/HO⊖
non-Markovnikov enol intermediate
H2SO4, H2SO4, H2O
Markovnikov enol intermediate
Aldehydes/Ketones
R-C(=O)-H
R-C(=O)-R
R-C≡C-H Terminal
1) 3 NaNH2
2) H⊕, H2O
R-C≡C-R Internal
2 NaNH2
Double E2
Vicinal Dihaloalkanes
1) O3 2) (CH3)2S
BREAKS C=C BONDS!!!
1) OsO4
Syn
2) NaHSO3/H2O
cyclic Osmate ester
Vicinal Diols
X2 (Br, Cl, I)
Anti
3-membered ring
Adsorption on metal surface
Pt°, Pd°, Ni°
H2
Na° NH3
Radical
E product
Lindlar Catalyst
Z product
H2
syn
Alkenes
1) BH3 2) H2O2 / HO⊖
non-Markovnikov
4-membered ring transition state
Syn
Alcohols
H2SO4 (catalytic)
Zaitsev's Rule
1° → E2 2°/3° → E1
H2O H2SO4 (catalytic)
Markovnikov
Mixed Carbocation Intermediate
(Br, Cl)
X2 / H2O (excess)
Halohydrins
Markovnikov Anti
3-membered ring
H-X (Cl, Br, I)
Markovnikov, Mixed, Carbocation
H-Br ROOR hv or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2
INVERSION
Various SN2 Products
Pt°, Pd°, Ni°
H2
Adsorption on metal surface
syn
Br2
hv or heat
Radical Chain Process
Br ends up on more substituted C atom
Alkanes
Not shown:
Alkene NBS / hv → Haloalkene
Allylic radical intermediate
Most stable alkene product

Geminal Dihaloalkanes

Vicinal Tetrahaloalkanes

Alkynes (DFW)

Carboxylic Acids

Aldehydes, Ketones

Vicinal Diols

Vicinal or Geminal Dihaloalkanes (Waco)

Epoxides

Alkenes (Austin)

Alcohols

Halohydrins

Allylic Halides

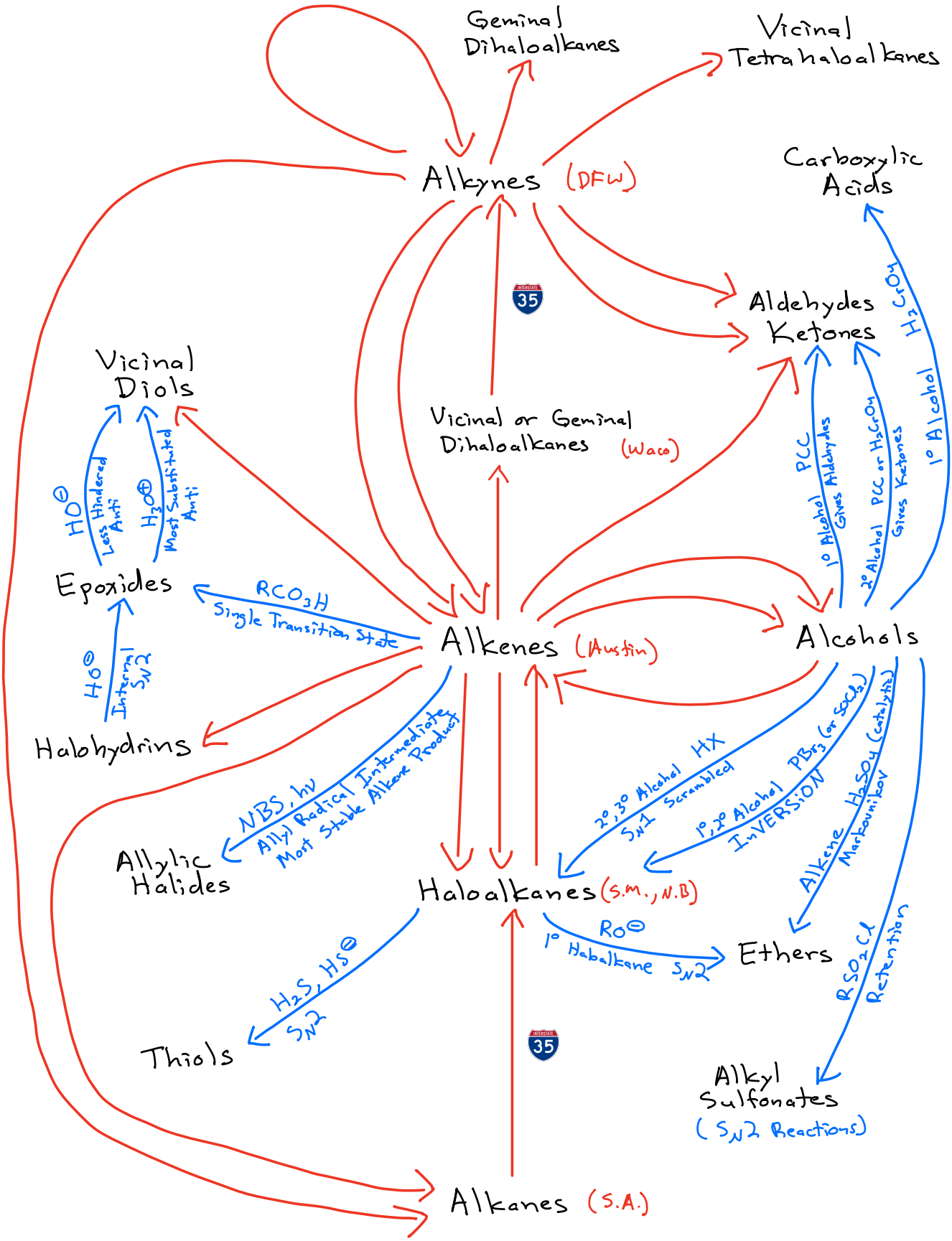
Haloalkanes (S.M., N.B)

Ethers

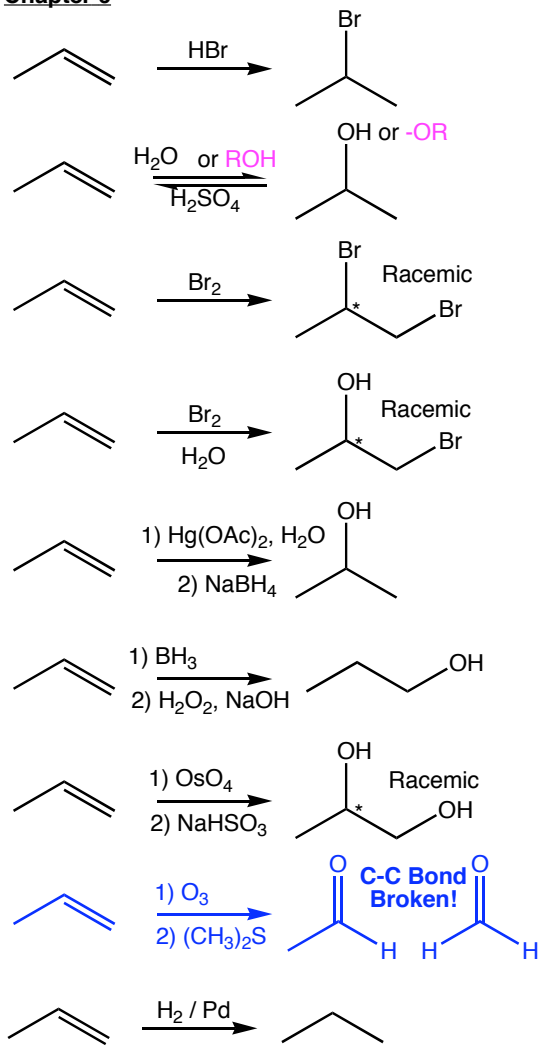
Throls

Alkyl Sulfonates

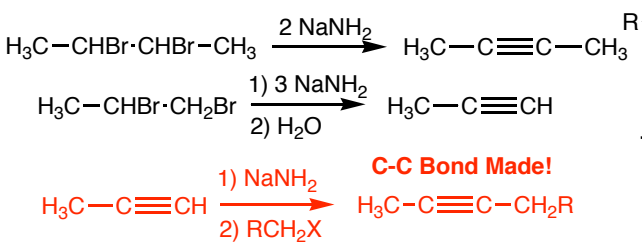
Alkanes (S.A.)

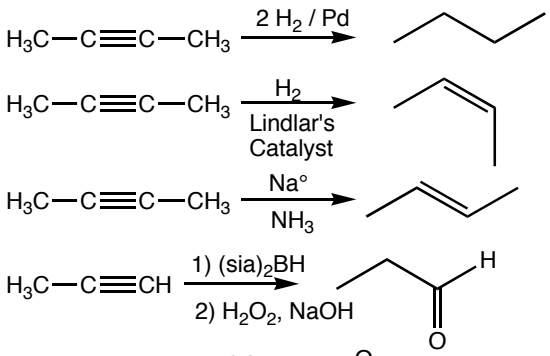

Geminal Dihaloalkanes
Vicinal Tetrahaloalkanes
Alkynes (DFW)
Carboxylic Acids
Aldehydes Ketones
Vicinal Diols
Vicinal or Geminal Dihaloalkanes (Waco)
Epoxides
Alkenes (Austin)
Alcohols
Halohydrins
Allylic Halides
Haloalkanes (S.M., N.B)
Ethers
Thiols
Alkyl Sulfonates (SN2 Reactions)
Alkanes (S.A.)
HO⊖ Less Hindered Anti
H3O⊕ Most Substituted Anti
H⊖ Internal SN2
RCO3H Single Transition State
PCC 1° Alcohol Gives Aldehydes
2° Alcohol PCC or H2CrO4 Gives Ketones
H2CrO4 1° Alcohol
NBS, hv Allyl Radical Intermediate Most Stable Alkene Product
3°,2° Alcohol HX SN1 Scrambled
1°,2° Alcohol PBr3 (or SOCl2) INVERSION
Alkene H2SO4 (catalytic) Markovnikov
RSO2Cl Retention
H2S, HS⊖ SN2
R⊖ 1° Haloalkane SN2

Chapter 6

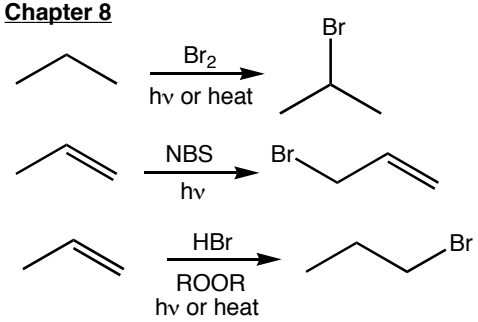


Chapter 7

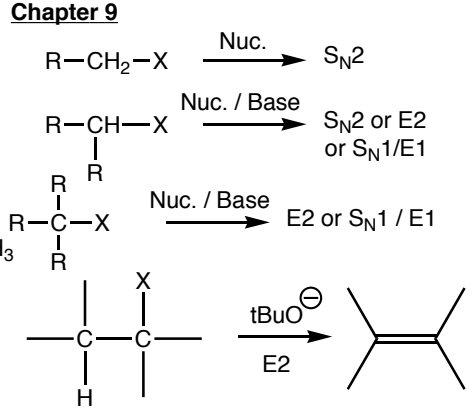




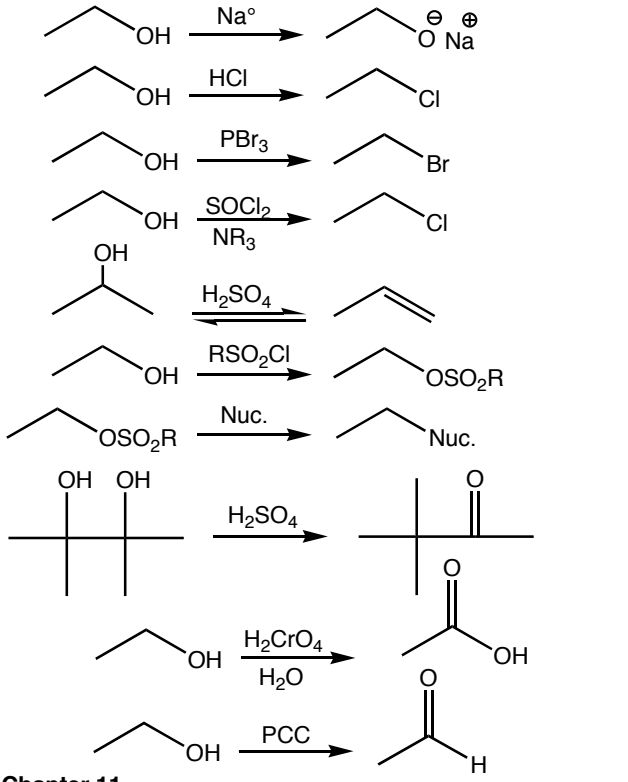
Chapter 8



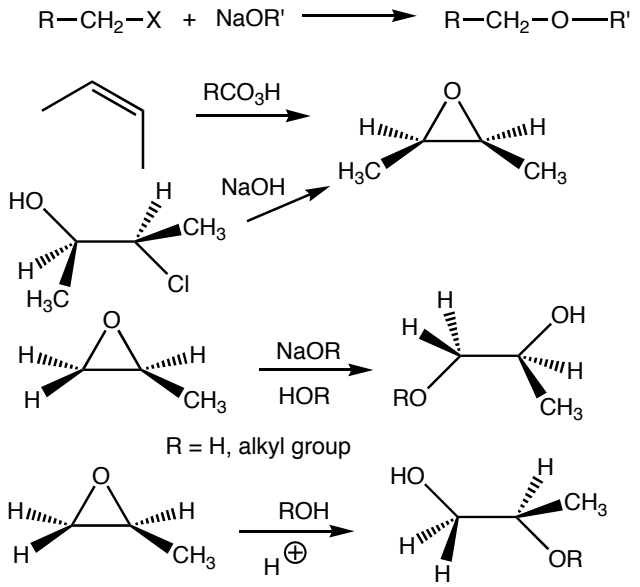
Chapter 9



Chapter 10

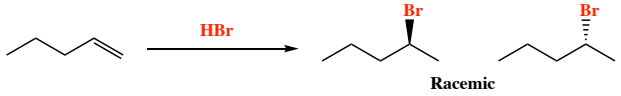


Chapter 11

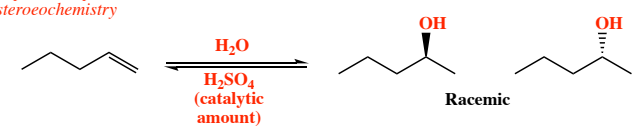


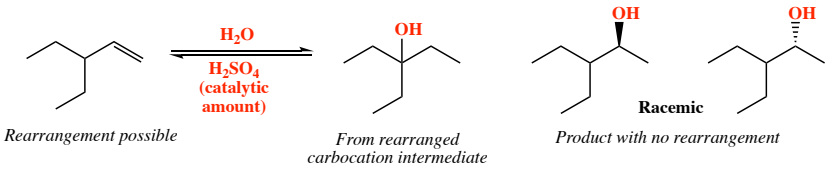
Chapter 6

1) Reaction of Alkenes with HX to Give Haloalkanes
Mechanism Keys: **Carbocation intermediate (rearrangement possible), add the proton to make the more stable carbocation when there is a difference** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**
Replace the pi bond with bonds to X on the more substituted carbon and H on the less substituted carbon with mixed stereochemistry

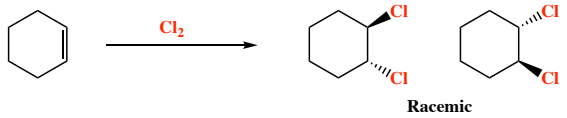


2) Acid-Catalyzed Hydration of Alkenes to Give Alcohols
Mechanism Keys: **Carbocation intermediate (rearrangement possible) add the proton to make the more stable carbocation when there is a difference** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**
Replace the pi bond with bonds to OH on the more substituted carbon and H on the less substituted carbon with mixed steroeochemistry

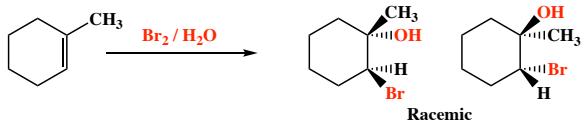




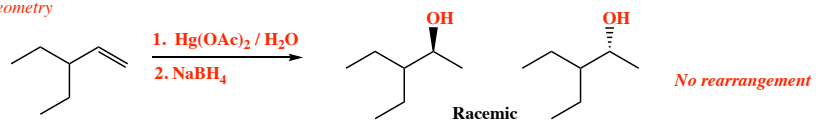
3) Halogenation of Alkenes to Give Vicinal Dihaloalkanes
Mechanism Keys: **Three-membered ring halonium ion intermediate** Regiochemistry: **N/A** Stereochemistry: **Anti**
Replace the pi bond with bonds to X with anti stereochemistry only



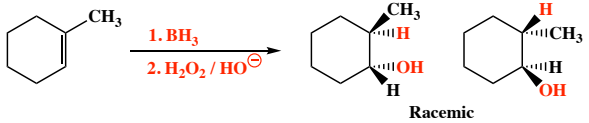
4) Hydrohalogenation of Alkenes to Give Halohydrins
Mechanism Keys: **Three-membered ring halonium ion intermediate, water will attack the more highly substituted carbon because that has more positive charge** Regiochemistry: **Markovnikov** Stereochemistry: **Anti**
Replace the pi bond with bonds to OH on the more substituted carbon and X on the less substituted carbon with anti stereochemistry only



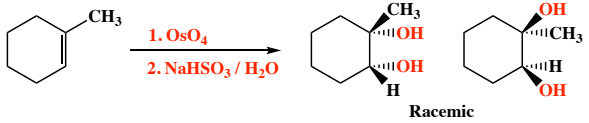
5) Oxymercuration-Reduction of Alkenes to Give Alcohols
Mechanism Keys: **Does not rearrange, the OH ends up on the more highly substituted carbon** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**
Replace the pi bond with bonds to OH on the more substituted carbon and H on the less substituted carbon with mixed geometry



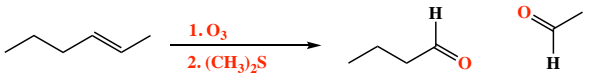
6) Hydroboration-Oxidation of Alkenes to Give Alcohols
Mechanism Keys: **Four-membered ring transition state as H and B atoms add simultaneously to same face of pi bond, the H atom goes on the more substituted carbon atom** Regiochemistry: **non-Markovnikov** Stereochemistry: **Syn**
Replace the pi bond with bonds to H on the more substituted carbon and OH on the less substituted carbon with syn geometry only



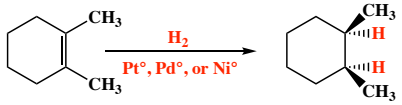
7) Geminal Dihydroxykation of Alkenes to Give Vicinal Diols (the Ozzy Osbourne reaction)
Mechanism Keys: **Cyclic osmate ester intermediate makes it so both OH groups are added to the same face of the double bond** Regiochemistry: **N/A** Stereochemistry: **Syn**
Replace the pi bond with bonds to OH with syn geometry only



8) Ozonolysis of Alkenes to Give Aldehydes and Ketones
Mechanism Keys: **Malozonide that then rearranges into an ozonide intermediate, explaining why the carbon-carbon bond is broken** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace the carbon-carbon double bond with two double bonds to an O atom (C=O) while BREAKING THE C=C!

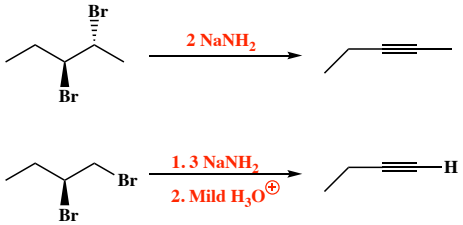


9) Hydrogenation of an Alkene to Give Alkanes
Mechanism Keys: **Alkene and H_2 adsorb on metal surface, then new bonds form to both carbon atoms essentially simultaneously so the H atoms add to the same face** Regiochemistry: **N/A** Stereochemistry: **syn**
Replace the pi bond with bonds to H with syn geometry only

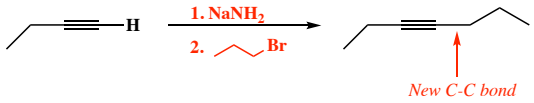


Chapter 7

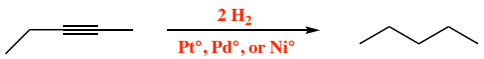
10) Reaction of Vicinal Dihalides with Base to Give Alkynes
Mechanism Keys: **Double E2 reaction. For terminal alkynes, 3 equivalents of base are needed because the terminal H atom is also removed and must be replaced in mild acid** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace the bonds to X with two pi bonds to give an alkyne



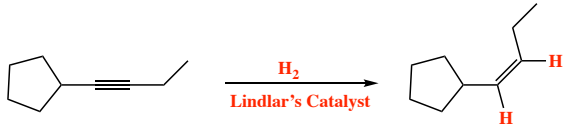
11) Reaction of Terminal Alkynes with Base then a Primary Haloalkane to Give an Alkyne with a New C-C Bond
Mechanism Keys: **S_N2 reaction. Haloalkane must be primary to avoid E2.** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace the terminal C-H bond with a new C-C bond to the carbon that had the C-X bond.



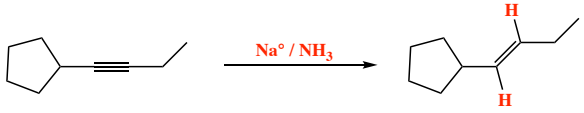
12) Hydrogenation of Alkynes to Give Alkanes
Mechanism Keys: **Alkyne and H_2 adsorb on metal surface, then new bonds form to both carbon atoms essentially simultaneously. Happens twice and cannot be stopped because alkenes produced as intermediates react faster than alkynes**
Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace the two pi bonds with four bonds to H atoms



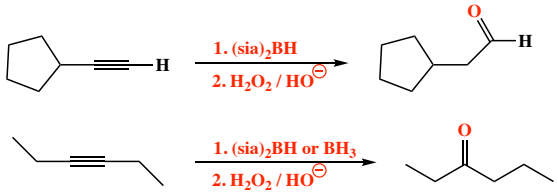
13) Reduction of Alkynes with H_2 and Lindlar's Catalyst to Give *Z* Alkenes
Mechanism Keys: **Alkene and H_2 adsorb on metal surface, then new bonds form to both carbon atoms essentially simultaneously. Pb and quinoline poison the catalyst so the reaction stops at a *Z* alken** Regiochemistry: **N/A**
Stereochemistry: **Syn**
Replace one pi bond of an alkyne with bonds to H atoms to give only a Z product



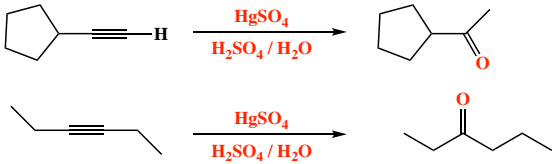
14) Reduction of Alkynes with Na° and NH_3 to Give *E* Alkenes
Mechanism Keys: **Radical mechanism, two one-electron transfers from Na°, followed by adding two protons from NH_3, the more stable *trans* alkene (less steric strain) predominates.** Regiochemistry: **N/A** Stereochemistry: **Anti**
Replace one pi bond of an alkyne with bonds to H atoms to give only an E product



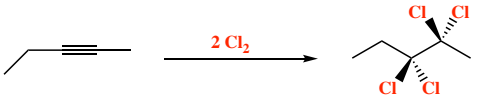
15) Hydroboration-Oxidation of Terminal Alkynes to Give Aldehydes (Using the "Antler" Reagent)
Mechanism Keys: **Four-membered ring transition state as H and B atoms add to same face of pi bond, enol intermediate followed by enol-keto tauatomerization, "antlers" ensure regiochemical control so that H adds to more substituted carbon.**
Regiochemistry: **non-Markovnikov** Stereochemistry: **N/A**
Replace the two pi bonds of a terminal alkyne with double bonds to an O atom to give an aldehyde. When the alkyne is not terminal, a ketone is the product.



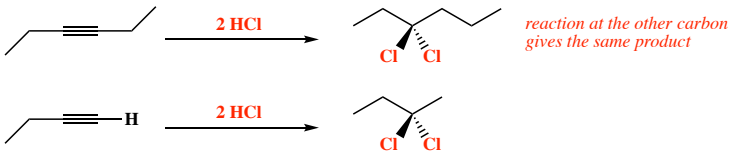
16) Oxymercuration-Reduction of Alkynes to Ketones
Mechanism Keys: **Enol intermediate followed by enol-keto tauatomerization. O atom ends up bonded to more stubstituted carbon** Regiochemistry: **Markovnikov** Stereochemistry: **Mixed**
Replace the two pi bonds of an alkyne with double bonds to an O atom to give a ketone. When the alkyne is terminal the internal carbon ends up as the C=O



17) Reaction of Alkynes with X_2 to Give Tetrahaloalkanes
Mechanism Keys: **X_2 reacts with both pi bonds** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace both pi bonds with 2 bonds to X atoms for each carbon atom.



18) Reaction of Alkynes with HX to Give Geminal Dihaloalkanes
Mechanism Keys: **HX reacts with both pi bonds, and both X atoms always end up on the same carbon atom, which is the internal carbon of terminal alkynes** Regiochemistry: **Markovnikov** Stereochemistry: **N/A**
Replace both pi bonds on one carbon with 2 bonds to X atoms, and the other carbon with 2 bonds to H. For terminal alkynes, the internal carbon gets the two bonds to X and the terminal carbon gets the two bonds to H

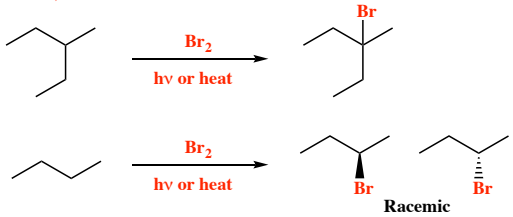


Chapter 8

19) Free Radical Halogenation of Alkanes to Give Haloalkanes

Mechanism Keys: **Free radical chain process, initiation when Br_2 is exposed to light (hν) or heat to give Br radicals that abstracts an H atom on the most substituted carbon during the propagation step** Regiochemistry: **Br ends up on most stubstituted C atom** Stereochemistry: **N/A**

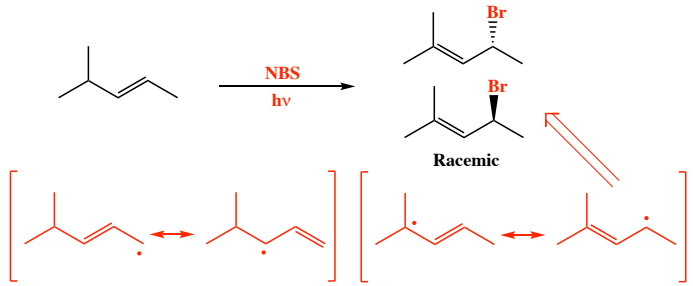
On the most substituted carbon with an H atom, replace one C-H bond with a C-Br bond. Use Br_2 because it is more selective than Cl_2 (Hammonds postulate: The Br_2 reaction has an endothermic first step so the transition state has more radical character).



20) Allylic Halogenation of Alkenes to Give Haloalkenes

Mechanism Keys: **Free radical chain process, initiation when NBS is exposed to light (hν) to give Br radicals that abstracts an H atom on the carbon adjacent to the C=C to create allylic radical intermediates that add a Br atom to make the most stable product (most highly substituted alkene)** Regiochemistry: **Br ends up on the carbon adjacent to the most stable possible alkene product** Stereochemistry: **N/A**

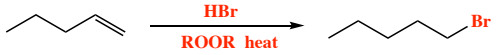
Analyze both of the contributing structures for both allyl radicals that are possible, consider adding a Br atom to the location of each carbon radical on each contributing structure, analyze each of these possible products and choose the most stable alkene (most substituted alkene) as the predominant product



21) Reaction of Alkenes with HBr in the Presence of H_2O_2 and Heat to Give Haloalkanes

Mechanism Keys: **Radical mechanism initiated by peroxide and hν or heat, product comes from most stable radical**
Regiochemistry: **non-Markovnikov** Stereochemistry: **Mixed**

Replace the pi bond with bonds to Br on the less substituted carbon and H on the more substituted carbon with mixed geometry

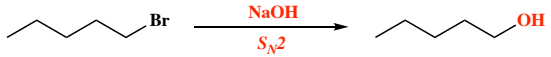


Chapter 9

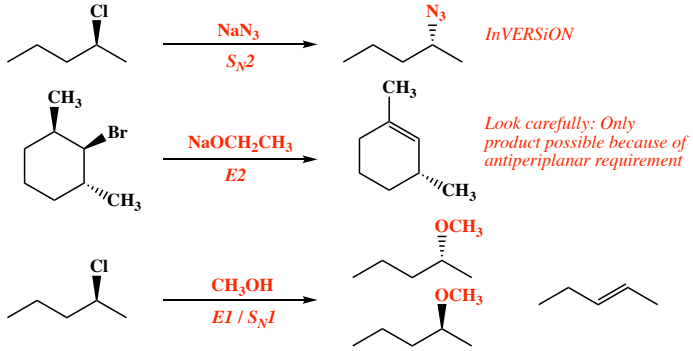
22) Substitution vs. Elimination of Haloakanes to Give Various Substitution Products and Alkenes From Elimination

S_N2: Nucleophile attacks backside of carbon-leaving group bond as the leaving group departs
Regiochemistry: **N/A** Stereochemistry: **InVERSiON**
E2: Base removes H atom on carbon adjacent to leaving group as the leaving group departs. The H atom being removed and the leaving group must be in an antiperiplanar geometry for reaction to take place
Regiochemistry: **Zaitsev product (most highly substituted alkene)** Stereochemistry: **determined by antiperiplanar transition state requirement**
S_N1: Leaving group departs to give carbocation intermediate then nucleophile binds to carbocation
Regiochemistry: **N/A** Stereochemistry: **Scrambled (not quite racemic)**
E1: Leaving group departs to give carbocation intermediate that loses a proton on an adjacent carbon to give an alkene
Regiochemistry: **Zaitsev product (most highly substituted alkene)** Stereochemistry: **N/A**

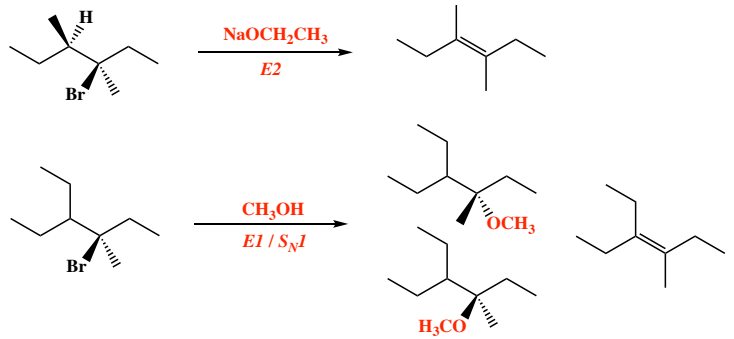
Primary haloalkane - S_N2 only (except when KOtBu is the base)



Secondary haloalkane - S_N2 when nucleophile is not strong or very weak base
E2 when nucleophile is a strong base
E1/S_N1 when nucleophile is a very weak base

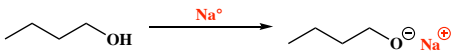


Tertiary haloalkane - S_N2 never
E2 when nucleophile is anything but a very weak base
E1/S_N1 when nucleophile is a very weak base

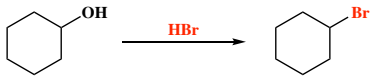


Chapter 10

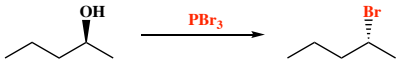
23) Reaction of Alcohols with Alkali Metals (Na°, Li°) to Give Alkoxides
Mechanism Keys: **Alkali metals react with alcohols to make alkoxides and H_2** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace the H atom of an OH group with a negative charge



24) Reaction of Alcohols with HX to Give Haloalkanes
Mechanism Keys: **Alcohols react with HX by protonating the OH group (thus creating a good leaving group), then the halide anion reacts via an S_N2 mechanism for primary alcohols and via an S_N1 mechanism for secondary/tertiary alcohols, to give a haloalkane** Regiochemistry: **N/A** Stereochemistry: **InVERSiON for S_N2 and scrambled for S_N1**
Replace the alcohol OH group with X. This reaction must be used with tertiary alcohols as PBr_3 and $SOCl_2$ only work with primary and secondary alcohols.

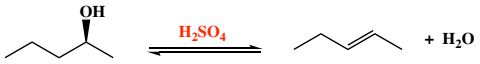


25) Reaction of Alcohols with PBr_3 to Give Bromoalkanes
Mechanism Keys: **Primary and secondary alcohols react with PBr_3 to give an intermediate with an O-P bond (thus creating a good leaving group), that reacts with bromide anion via an S_N2 mechanism to give a haloalkane**
Regiochemistry: **N/A** Stereochemistry: **InVERSiON**
Replace the alcohol OH group with Br with InVERSiON of any stereochemistry at the carbon that was bonded to the OH group of the original alcohol. Primary and secondary alcohols only because teertiary alcohols cannot react via S_N2.

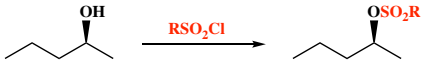


26) Reaction of Alcohols with $SOCl_2$ to Give Chloroalkanes
Mechanism Keys: **Primary and secondary alcohols react with $SOCl_2$ to give an intermediate with an O-S bond (thus creating a good leaving group), that reacts with chloride anion via an S_N2 mechanism to give a haloalkane**
Regiochemistry: **N/A** Stereochemistry: **InVERSiON**
Replace the alcohol OH group with Cl with InVERSiON of any stereochemistry at the carbon that was bonded to the OH group of the original alcohol. Primary and secondary alcohols only because teertiary alcohols cannot react via S_N2.

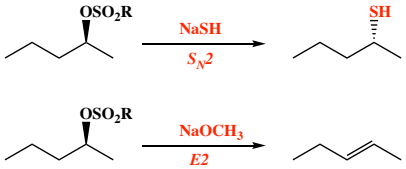
27) Reaction of Alcohols with Sulfuric Acid to Give Alkenes
Mechanism Keys: **Alcohols react with H_2SO_4 to give alkenes via a carbocation intermediate, in a mechanism that is the exact reverse of hydration of an alkene, this is a reversible equilibrium proces (*Le Chatlier*)** Regiochemistry: **Zaitsev**
Stereochemistry: **N/A**
Replace the alcohol OH group with a new pi bond chosen to make the Zaitsev product (most substituted alkene)



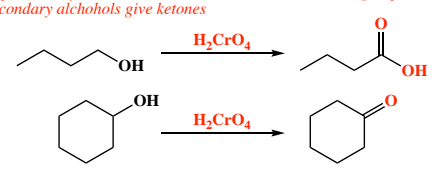
28) Reaction of Alcohols with Sulfonyl Chlorides to Give Sulfonyl Esters
Mechanism Keys: **Alcohols react as nucleophiles with sulfonyl chlorides to give sufonyl esters, a good leaving group**
Regiochemistry: **N/A** Stereochemistry: **Retention (not InVERSiON)**
Replace the alcohol OH group with a new sulfonyl ester, without changing the stereochemistry



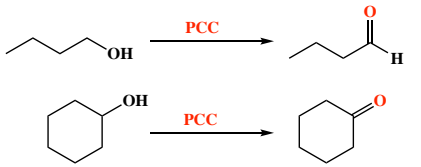
29) Reaction of Sulfonyl Esters with Nucleophiles to Give Various Substitution and Elimination Products
Mechanism Keys: **Sulfonyl esters react with nucleophiles and bases analogous to haloalkanes** Regiochemistry: **E2 and E1 give Zaitsev product alkene** Stereochemistry: **S_N2 gives InVERSiON, S_N1 scrambled, E2 gives product based on antiperiplanar transistion state**
Replace the sulfonyl ester with a nucleophile with InVERSiON or carry out an elimination to give the Zaitzev alkene (most substituted) based on the same rules used with haloalkanes



30) Reaction of Alcohols with Chromic Acid (Jones Reagent) to Give Carboxylic Acids and Ketones
Mechanism Keys: **The mechanism with primary alcohols involves a chromate ester intermediate then loss of an H atom on the carbon of the orginal alcohol to give an aldehyde, that adds water then reacts again. Secondary alchohols react once to give a ketone** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace every H atom on the carbon attached to the OH group with bonds to O atoms. Primary alcohols give carboxylic acids, secondary alchohols give ketones

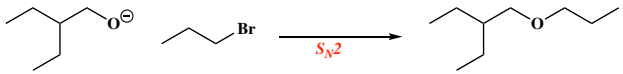


31) Reaction of Alcohols with PCC (Pyridinium Chlorochromate) to Give Aldehydes and Ketones
Mechanism Keys: **The mechanism with primary alcohols involves a chromate ester intermediate then loss of an H atom on the carbon of the orginal alcohol to give an aldehyde, and because there is no water it stops there. Secondary alchohols react once to give a ketone** Regiochemistry: **N/A** Stereochemistry: **N/A**
Replace an H atom on the carbon attached to the OH group with a pi bond to an O atom. Primary alcohols give aldehydes, secondary alchohols give ketones

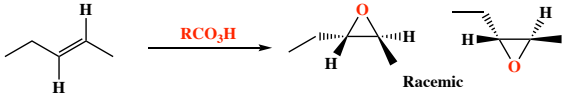


Chapter 10

32) Reaction of Alkoxides with Primary Haloalkanes to Give Ethers (Williamson Ether Synthesis)
Mechanism Keys: **Alkoxides and primary haloalkanes react via an S_N2 mechanism. The haloalkane must be primary to avoid E2.** Regiochemistry: **N/A** Stereochemistry: **N/A**
Choose the alkoxide and haloalkane so the haloalkane is primary

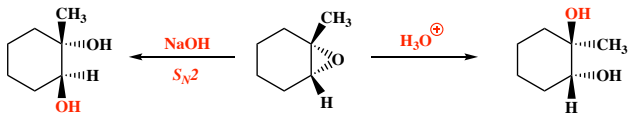


32) Reaction of Alkenes with Peracids to Give Epoxides
Mechanism Keys: **Alkenes react with peracids in a single concerted step to give the epoxide and a carboxylic acid**
Regiochemistry: **N/A** Stereochemistry: **N/A**
Create the epoxide from the alkene, making sure to keep the groups consistent (groups that are cis on the alkene stay cis in the epoxide) and add the O atom to both the top and bottom faces of the alkene

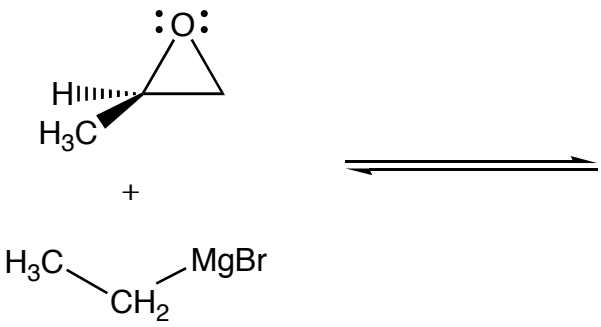


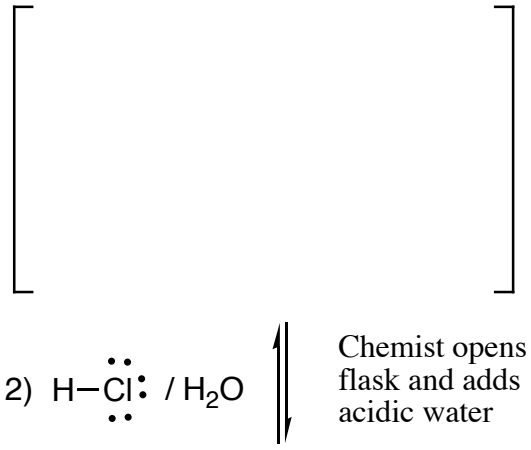
33) Reaction of Halohydrins with Base to Give Epoxides
Mechanism Keys: **Halohydrins react with base to deprotonate the OH group and give an alkoxide intermediate, which attacks the backside of the C-X bond in a single step to give the epoxide** Regiochemistry: **N/A** Stereochemistry: **N/A**
Create the epoxide from the halohydrin by lining up the OH group to be antiperiplanar to the X before making the new bond from O to the carbon of the orginal C-X bond

34) Reaction of Epoxides in Acid or Base to Give Vicinal Diols
Mechanism Keys: **Epoxides react with hydroxide from the backside of the C-O bond via an S_N2 mechanism at the less-hindered carbon, and in acid epoxides are protonated to give a positively-charged intermediate analogous to the halonium ion intermediate, so water attacks the more substituted carbon** Regiochemistry: **In base, OH adds to less-hindered carbon atom, in acid OH adds to the more substituted carbon atom** Stereochemistry: **Anti (backside attack on epoxide C-O bond)**
Create the vicinal dihalide by adding the OH from the less-hindered side in base and more hindered side in acid, inverting the chiral center at the carbon of the attack and retaining stereochemistry at the carbon that keeps the O atom of the original epoxide, always giving trans product in both cases



Grignard Reagent Reacting with an Epoxide



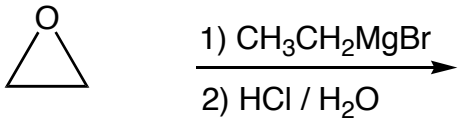


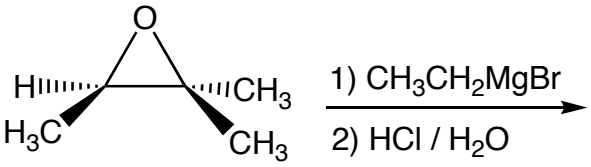
2) H–Cl: / H_2O

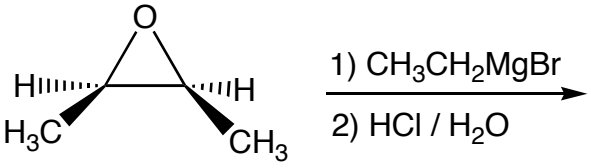
Chemist opens flask and adds acidic water

Key Recognition Element (KRE):

Products







In the classic ^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) experiment:

1. A sample of the molecule of interest is placed in solvent (the solvent has deuterium atoms in place of H atoms so the solvent molecules will not show up in the spectra.
2. The solution is put in a spinning tube in a very strong magnetic field.
3. The sample is exposed to radiofrequency irradiation and if it is of exactly the right frequency, energy is absorbed and spins flip from +1/2 to -1/2 spin states (the energy absorption/spin flipping process is called resonance).
4. The absorbed energy is plotted on the spectra as a function of wavelength, normalized by using the parts per million (ppm) scale.
5. ^{1}H nuclei in different functional groups come into resonance at different and characteristic values of ppm and adjacent ^{1}H nuclei split signals in predictable ways, allowing for chemical structures to be determined based on ^{1}H NMR spectra.

The old way to carry out an NMR experiment:

1. Scan wavelengths (ex. High to low wavelengths) of radiofrequency electromagnetic radiation.
2. Measure absorbance during the scan and plot the amount of energy absorbed versus wavelength using the normalized ppm scale.
3. This is NOT used any more.

What we did not tell you: After a nuclear spin is flipped back from +1/2 to -1/2, it will relax back to the +1/2 spin state and EMIT a photon of the same wavelength it absorbed in the first place.

How modern NMR works:

1. The sample is irradiated with all wavelengths simultaneously with a short blast. All of the ^{1}H spins are flipped at once.
2. The sample is monitored for emitted photons as the ^{1}H nuclear spins "relax" back to the +1/2 spin state.
3. The emitted photons are analyzed using a technique called Fourier Transform (FT) to extract frequency and intensity information.
4. The frequency and intensity information is plotted on the ppm scale.
5. This process is repeated hundreds or thousands of times with the same sample to dramatically improve signal-to-noise.

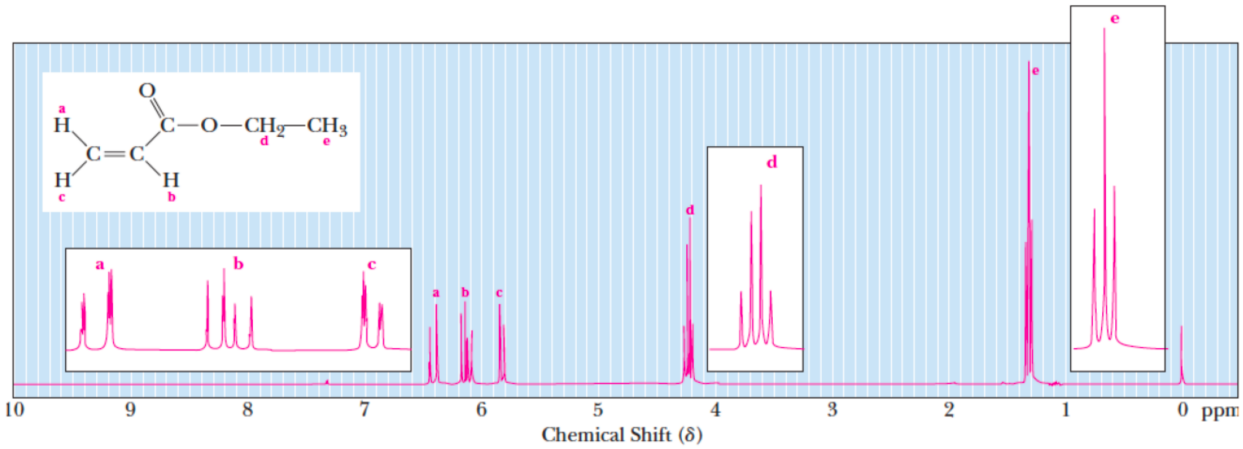


Figure 13.21
300 MHz ^{1}H-NMR spectrum of ethyl propenoate.

MRI – Nuclear Magnetic Resonance Imaging – Produces a 3-d image inside the body.

MRI is similar in approach, but complementary to, a CAT scan, which uses X-rays for imaging.

MRI is therefore safer than a CAT scan (no X-rays or other damaging radiation is used). Radiofrequency electromagnetic radiation does not cause DNA damage or any other kind of damage.

MRI primarily visualizes soft-tissue and especially cancer tumors while a CAT scan primarily visualizes bones or Calcium based dyes drunk to visualize the digestive tract.

MRI uses the same principles and NMR.

1) The patient is placed in a very strong magnetic field. Creating this very strong magnetic field is technically very demanding, explaining MRI machines are so expensive (~ 0.5 – 1.5 $ million)
2) The patient is irradiated with radiofrequency electromagnetic radiation.
3) The flipping (resonance) of ^{1}H nuclear spins is monitored – Actually emitted photons are measured using the FT method.
4) Magnetic field gradients are used to gain imaging information. The magnetic field gradients are rotated around a central point and measurements are taken at each angle around 360° to gain 2-dimensional information. This technique is called **tomography**.

The same three spots seen from different angles—

By analyzing all angles the locations and intensities can be calculated

The overall MRI imaging approach involves looking at each 2-dimensional slice.

Each slice is added to give a 3-dimensional stack (analogous to stacking DVD's or CD's).

Each slice is shaded to indicate differences in the amount of ^{1}H atoms in different areas/tissues.

Water and fat have the highest density of ^{1}H atoms, so these are primarily being monitored in an MRI image.

The popular medical diagnostic technique of magnetic resonance imaging (MRI) is based on the same principles as NMR, namely the flipping (i.e. resonance) of nuclear spins of H atoms by radio frequency irradiation when a patient is placed in a strong magnetic field. Magnetic field gradients are used to gain imaging information, and rotation of the gradient around the center of the object gives imaging in an entire plane (i.e. slice inside patient). In an MRI image, you are looking at individual slices that when stacked make up the three-dimensional image of relative amounts of H atoms, especially the H atoms from water and fat, in the different tissues [Memorize the preceding passage, as it will be worth 14 points on the next midterm. No I am not kidding, I just gave you 14 points right there.]


m- m...
he's about to say his first words
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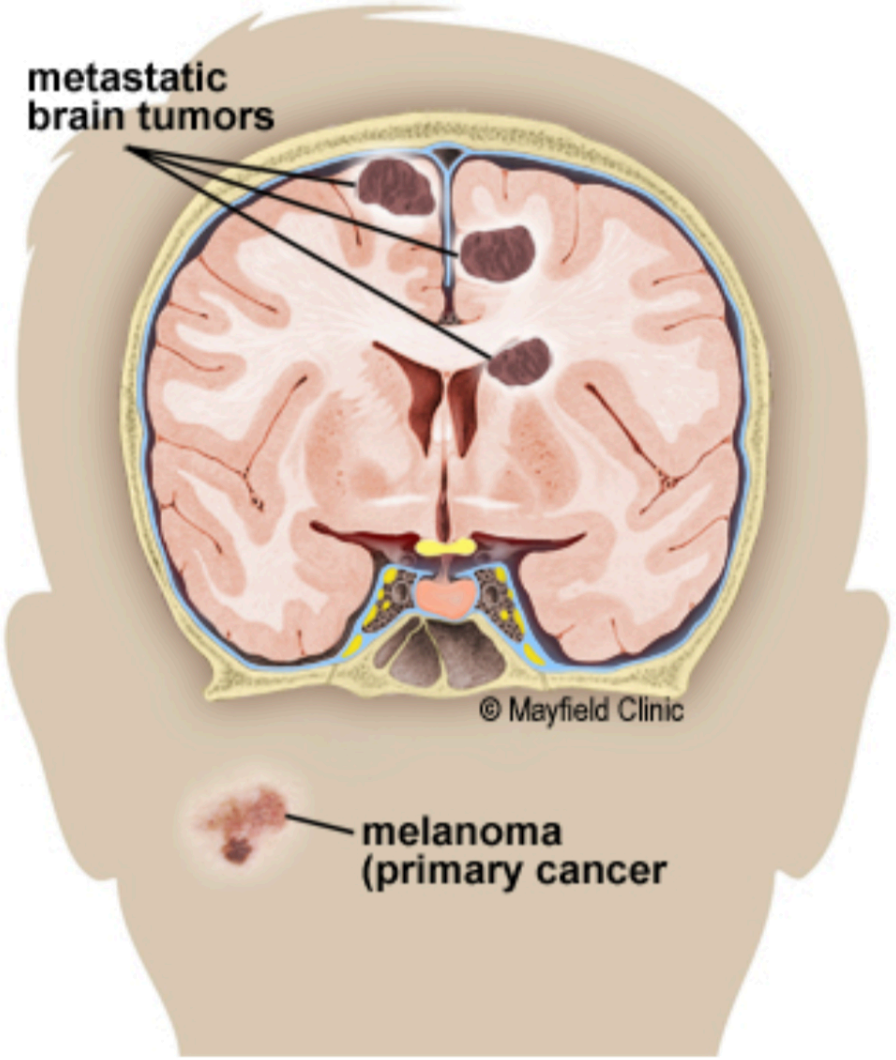


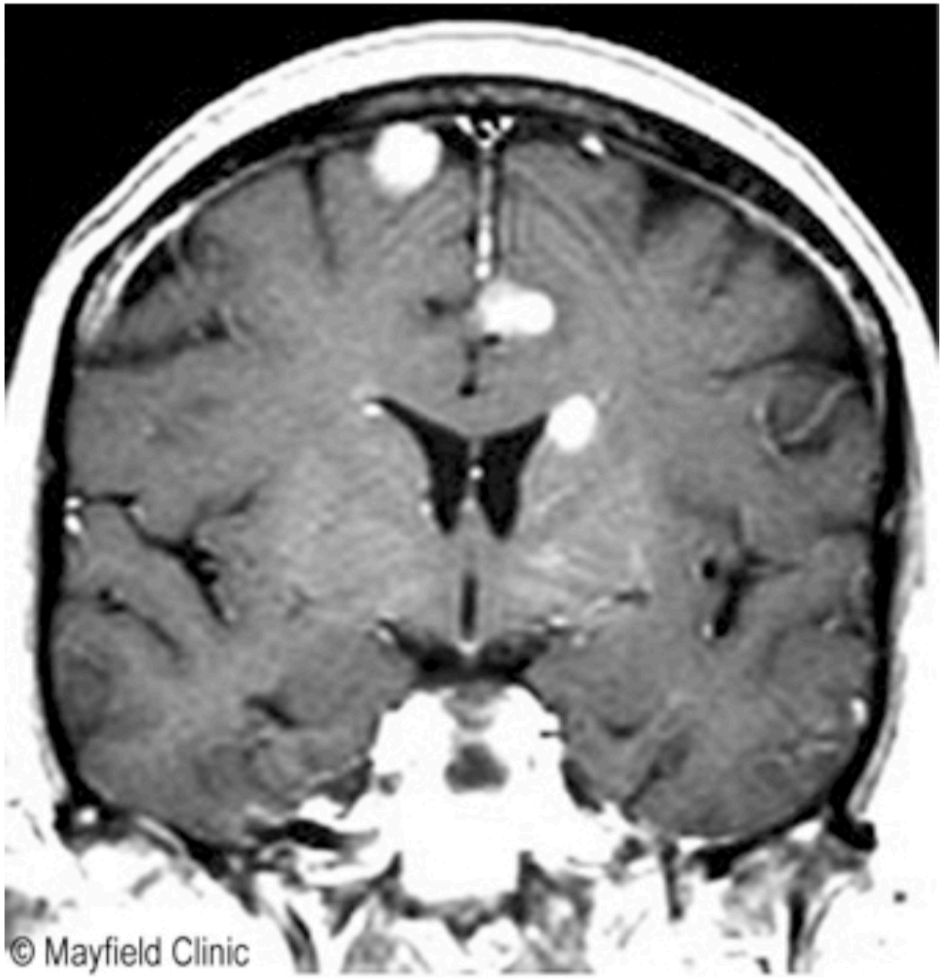
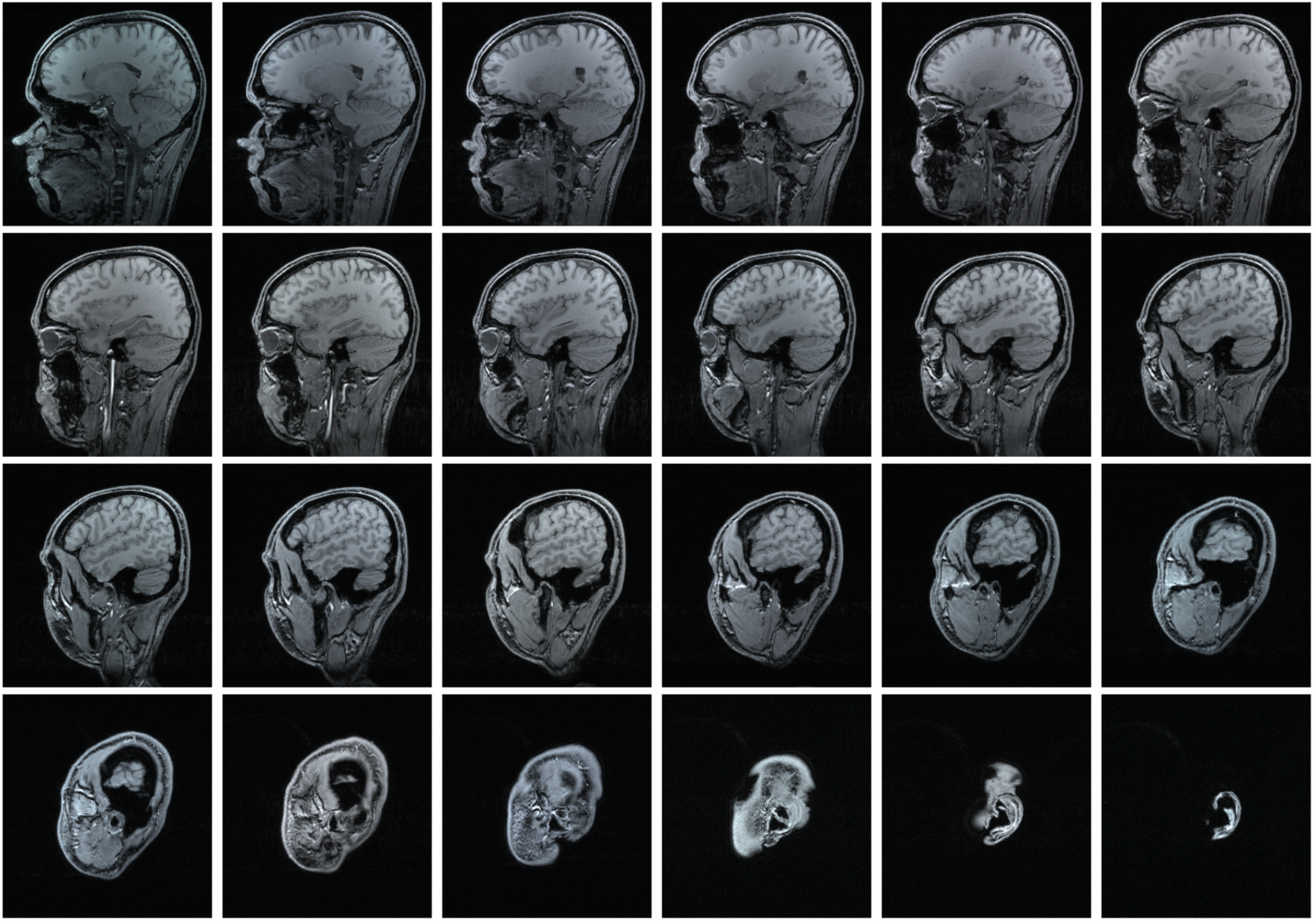


Figure 1. Illustration and MRI of multiple metastatic brain tumors that have spread from the melanoma skin cancer on the face.



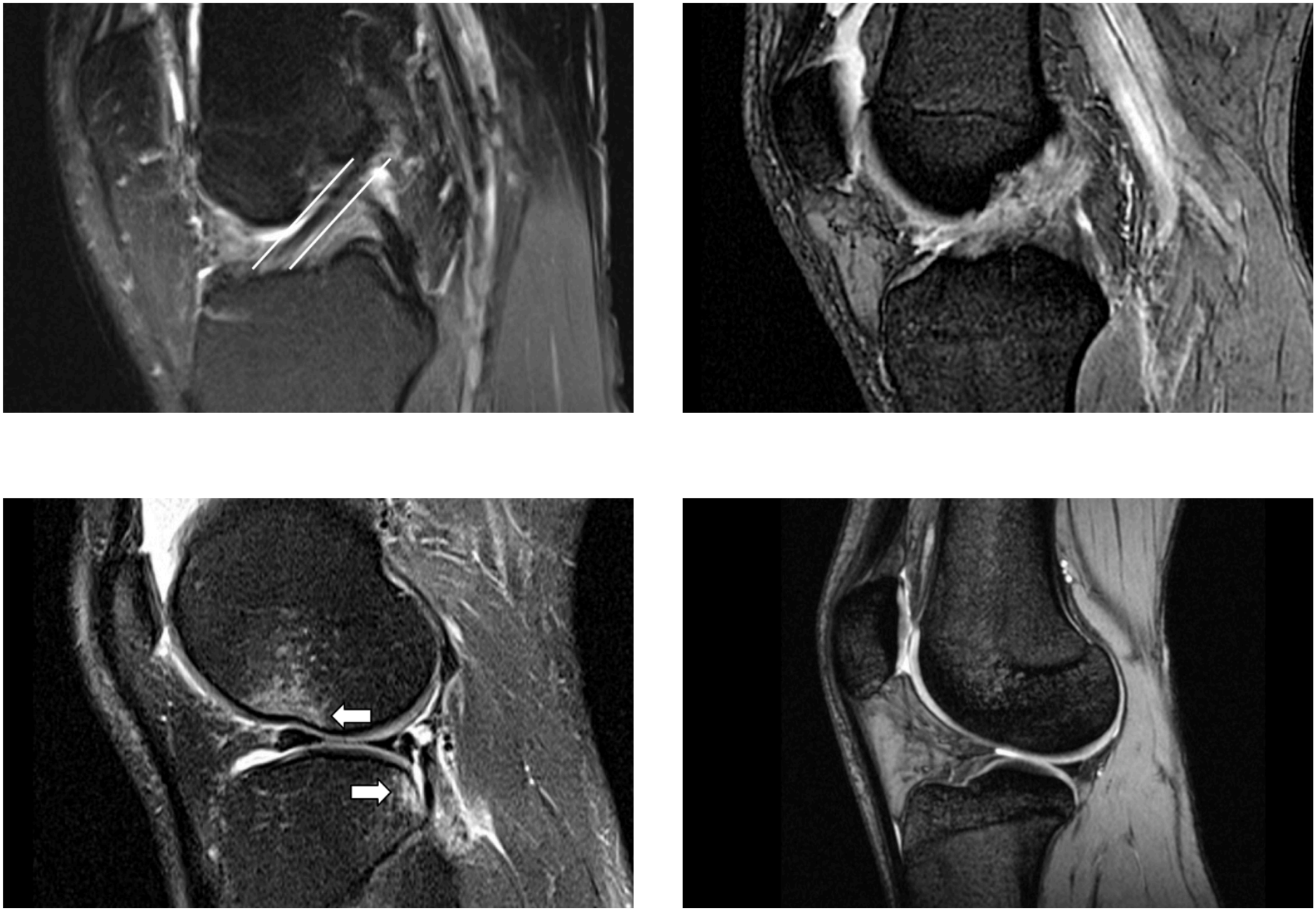


Image 13-16: MRI images of a normal ACL (between white lines), ruptured ACL (ligament not clearly visible), bone marrow oedema (white arrows) and anterior tibial translation.