CHEM 22000 (Organic Chemistry I) Notes

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Weeks

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Week 1

The Basics: Bonding and Molecular Structure

1.1 Course Information

9/28:

- No labs this week.
- Virtual lab: Watch a video and record data in your notebook; answer embedded quiz questions.
- Collaborative Learning in Organic Chemistry (CLOC).
  - 2hr Sunday or Monday.
  - Contact Dr. Britni Ratliff (ratliff@uchicago.edu).
  - Pass/Fail grading (based on attendance).
  - You work on problems related to the lecture content under the supervision of someone who's taken the class before.
  - You can opt-in/out on a quarter-by-quarter basis.
- Review syllabus: Download alternate textbooks, put exam dates in the calendar, add office hours to calendar.
- Develop an understanding of how structure affects reactivity — mechanistic principles.
- You don't have to memorize anything, but you have to remember everything.
  - Like learning a language.
    - Vocabulary, grammar (principles), apply to understand and predict.

1.2 Defining Organic Chemistry

- **Organic chemistry**: Traditionally, the chemistry of living organisms. Now, the chemistry of carbon compounds.
  - Carbon is of particular import because it can bond with itself, and it can form strong bonds with other elements (e.g., C, O, H, S, N, and P) as well.
  - Carbon is bound in simple molecules (such as CO_2 and CH_4), and highly complex ones (such as proteins, DNA, and RNA).
- Carbon compounds:

  - Natural: Sugars, fats, gasoline, hydrocarbons, hormones, natural drugs, peptides, rubber, silk, starch, cotton, etc.
  - Synthetic: Dyes, fragrances, soaps, drugs, medicines, plastics, materials, teflon, nylon, etc.
- OChem is a central science that feeds into fields such as biochemistry, molecular biology, molecular medicine, math/theory (e.g., buckyballs), engineering, and physics.

1.3 Gen Chem Review

- Today:
  1. Intro (done).
  2. Atomic structure and bonding (review from Gen Chem).
  3. Chemical bonds — octet rule.
  4. Writing Lewis structures.
  5. Formal charges.
- Atomic structure and bonding.
  - Atoms $\rightarrow$ elements $\rightarrow$ compounds.
  - Nucleus (protons and neutrons) surrounded by electrons.
  - This year, we'll concern ourselves with the main group elements.
  - Electron configuration:
    - Aufbau principle: Electrons fill orbitals from lowest energy to highest energy.
    - Pauli exclusion principle: 2 elections/orbital with opposite spin quantum numbers (must pair $+\frac{1}{2}$ with $-\frac{1}{2}$).
    - Hund's rule: Orbitals with equivalent energy get partially filled first before more electrons are added.
    - Example: $1s^2 2s^2 2p^6 3s^1$ is Na.
  - Valence electrons are key in this class.
- Noble gas configurations and the octet rule.
  - Lewis noticed that there is a special stability associated with a filled outer shell.
  - Thus, we generally have 8 electrons in the filled outer shell.
    - For example, $\mathrm{Cl} \xrightarrow{1\,e^-} \mathrm{Cl}^-$ and $\mathrm{Na} \xrightarrow[-1\,e^-]{} \mathrm{Na}^+$.
  - Chemical bonds form because they allow the atoms to achieve a filled octet.
  - Two kinds of bonding: Ionic and covalent.
    - Ionic: Not covered much this year. Lose or gain an electron (forming cations and anions, respectively) to for a filled outer shell. Usually involves a metal and a nonmetal.
    - Covalent: Covered a lot this year. Sharing electrons to satisfy the need for an octet.
    - The atoms involved dictate whether bonding will be ionic or covalent.
  - Electronegativity: The ability of an atom to attract its valence shell electrons.
    - Defined by Pauling, who let Li = 1.0 and F = 4.0.
    - This is a very important concept for understanding bonding and reactivity.
    - EN increases across and up on the periodic table: More protons and a shorter distance away from the nucleus both mean a greater pull on the electrons.
    - Mnemonic (highest to lowest electronegativity): F O Cl N Br I S C H P.

    - Non-polar covalent bonds form when $\Delta\text{EN} < 0.5$.
    - Polar covalent bonds form when $\Delta\text{EN} \approx 0.5 - 1.9$.
  - Exceptions to the octet rule: H wants $2\,e^-$. Be wants $4\,e^-$. B and Al want $6\,e^-$. Molecule has an odd number of electrons (e.g., NO with 11 electrons is stable).

- Lewis structures.
  - General rules/procedure (there are exceptions).
    1. Determine the total number of valence electrons for the molecule. Add electrons for negative charges; remove for positive charges.
    2. Draw a skeleton and join atoms with single bonds. Put the atom that likes to make the most bonds in the center.
    3. Deduct 2 electrons from the count in step 1 for each single bond. Fill outside atoms with lone pair electrons.
    4. The remaining electrons go on the central atom.
    5. If you have too few electrons for every atom to have an octet, use lone pair electrons to convert single bonds to double bonds. We can also use triple bonds.
  - CH_4 and NH_3 presented as worked examples.

9/30:

- Today:
    4. Lewis Structures.
    5. Formal charges.
    6. Isomers.
    7. Structural formulas.
    8. Resonance.
    9. Orbitals and bonding.

- Lewis structures:
  - H_2CO (formaldehyde) and CH_3COOH (acetic acid) presented as worked examples.

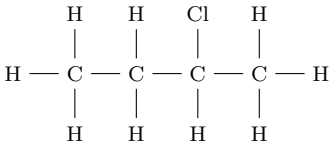
- Formal charge determination:
  - If the number of valence electrons does not equal the total number of electrons on an atom, then you will have a formal charge.
  - Rule:

$$\begin{aligned}\text{Formal Charge} &= \text{normal valence } e^- - \text{actual } e^- \\ &= \text{valence } e^- - \left(\text{nonbonding } e^- + \frac{1}{2}\text{bonding } e^-\right) \\ &= \text{valence } e^- - (\text{dots} + \text{lines})\end{aligned}$$

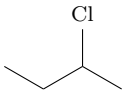
  - CH_3COO^- (acetate) has a formal charge of $6 - 7 = -1$ on its singly bonded oxygen.
  - $CH_3NH_3{}^+$ (methyl ammonium) has a formal charge of $5 - 4 = +1$ on its nitrogen.
  - Exceptions: Open shell Group III central atoms (e.g., B and Al).
    - BF_3 acts as a Lewis acid because it wants to grab $2\,e^-$ to form an octet.
    - It often acts in acid-base coupling reactions, grabbing a lone pair from an oxygen in an adjacent molecule and bonding through it.

1.4 OChem Basics

- Isomers:
  - Constitutional isomers: Same molecular formula but different bond connectivities.
  - Acetone vs. 3-propenol, yet both are C_3H_6O.
- Structural formulas:



(a) Dash structural formula.



(b) Bond line formula.

$CH_3CH_3CH_2ClCH_3$

(c) Condensed formula.

Figure 1.1: Structural formulas.

- **Dash structural formula**: A Lewis structure.
- **Bond line formula**: No C–H's, show a vertex for each carbon, show heteroatoms and heteroatom H's. *Also known as* **line-angle structure**, **zig-zag structure**.
- **Condensed formula**: All atoms written out with no bonds or lone pairs.
- **3D representation**: A dash structural/bond line formula with wedges and dashes.
- **Resonance**: When a molecule or an ion can be represented by 2 or more Lewis structures, i.e., two or more structures with the same skeleton connected by different electrons.
  - Resonance structures or resonance contributors.
  - The actual molecule is somewhere between the contributors.
  - $CO_3{}^{2-}$ presented as a worked example.
  - Guidelines:
    1. Only lone pairs or π electrons move (never move single bonds).
    2. No structure with greater than $8\,e^-$ on a 2nd row atom.
    3. The species with the maximum number of octets is the strongest contributor.
    4. Charge on suitable atoms (e.g., negative charge on the atom with the highest electronegativity).
  - Resonance stabilization comes from delocalization. When 2 or more resonance structures, the "real" structure is somewhere in between (the real is more stable than any contributor).
  - CH_3COO^- (acetate), $CH_2CHCH_2{}^+$, and $(CH_3)_2CO$ presented as worked examples.
  - You can also depict delocalization with a curving dashed bond and δ^-'s.

1.5 Bonding and Orbital Diagrams

10/5:
- Today:
  9. Orbital theory and bonding.
  10. Methane.
  11. Ethane.
  12. Ethylene.

13. Acetylene.
14. Comparison of sp^3, sp^2, sp orbitals.
15. VSEPR Model + Molecular Symmetry.

- Orbital theory and bonding:
  - Defines **atomic orbitals**.
  - Reviews s and p orbital shapes, positive and negative regions, and nodes.
  - Energy of orbitals diagram.
  - Phosphorous and sulfur can exceed the octet rule since they have d orbitals in which to stash extra electrons.
  - Filled with the Aufbau/Pauli Exclusion principles, and Hund's Rule.
  - Goes over bonding energy diagram.
  - Mathematically, we have a Linear Combination of Atomic Orbitals (or LCAO).
    - Electrons are represented as waves; thus, they have + and − phases.
    - Opposite phases are destructive; this forms σ^* orbitals.
    - Same phases are constructive; this forms σ orbitals.
  - Goes over MO diagrams.
- **Atomic orbital**: A space where electrons are likely to be found 95% of the time.
- **Degenerate** (orbitals): Two orbitals with the same energy.
- **Chemical bond**: A favorable interaction between 2 atoms, i.e., one that helps to fill the outer orbitals to achieve a noble gas configuration.
- Bonding in methane:

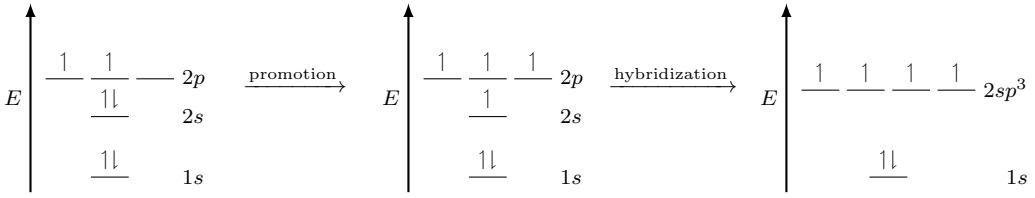


Figure 1.2: Bonding in methane.

  - Draws an orbital diagram for carbon.
  - Promotes an electron from $2s \to 2p_z$.
  - Hybridizes $2s, 2p_x, 2p_y, 2p_z$ into 4 degenerate sp^3 orbitals of weighted average energy, each containing only 1 electron.
  - Links each of these sp^3 electrons to the $1s$ electron in H_2, forming σ orbitals.
  - The new orbitals adopt a tetrahedral arrangement to be as far apart as possible.
- Bonding in ethane.
  - Two sp^3 electrons combine in a σ orbital; no electrons go into the σ^* MO.
- The structure of ethylene.
  - Side by side overlap of p orbitals forms a π bond.
  - The angle between the hydrogens in ethylene is slightly less than 120°.

  - The bond is slightly shorter than in ethane (greater s character plus an additional type of bond).
  - Features of the C=C double bond.
    - sp^2-hybridized carbons making 3σ and 1π bond.
    - A π bond is weaker than a σ bond, but still strong.
    - $\sigma_{sp^2-sp^2}$ is stronger than $\sigma_{sp^3-sp^3}$.
    - Restricted rotation (hard to twist C_2H_2 by 90°).
    - cis-trans isomerism as a result of restricted rotation.
    - The π bond acts like a Lewis base with some systems since the π electrons are held relatively weakly. In other words, the π-electrons are exposed.
  - Draws an MO diagram for the carbons.

- The structure of acetylene.
  - 2 π bonds, 1 σ bond.
  - Even greater strength, but not quite as much greater as the $\sigma_{sp^3-sp^3} \rightarrow \sigma_{sp^2-sp^2}$ difference.

1.6 VSEPR Theory

10/7:

- There's a special kind of electronegativity that relates to hybridization: An sp-hybridized carbon is more electronegative than an sp^3-hybridized carbon, for instance.
- VSEPR Model:
  - Electron pairs want to stay as far apart as possible in space.
  - Consider the bonding electrons (number of atoms bound) and nonbonding electrons.
  - Describe shape based on the position of nuclei.
- Constructs VSEPR table for linear, trigonal planar, tetrahedral, trigonal pyramidal, bent

Week 2

Families of Carbon Compounds / Acids and Bases

2.1 Families of Carbon Compounds

10/7:

- Hydrocarbons:
  - Alkanes (C_nH_{2n+2}) and cycloalkanes C_nH_{2n}.
  - Alkenes (C_nH_{2n}).
  - Alkynes (C_nH_{2n-2}).
- Aromatic:
  - Contains a benzene ring.
  - All bonds $\sim 140\,\text{Å}$.
  - All carbons sp^2.
  - Planar.
  - π electrons above and below the ring.
  - Special stabilization.
- Covers drawing dipoles.
- Polar and nonpolar molecules:
  - Dipole = distance × change between charges.
  - $\mu = r \times Q$
  - $1\,\text{D} = 3.336 \times 10^{-30}\,\text{C m}$.
  - Analyzes molecules by drawing a Lewis structure, drawing a dipole along each bond, and drawing and labeling a net dipole, if applicable.
  - Goes through a number of examples.
  - Acetonitrile is a strong polar solvent.
- **Functional group**: A common arrangement that determines shape, bonding physical and reactivity of organic compounds.
- Families of carbon compounds:
  - Hydrocarbons: Aliphatic, aromatic.
  - Methyl, ethyl, propyl, R = alkyl groups.

  - Phenyl: Ph- or ϕ-.
  - Benzyl: Ph$-CH_2$-, $C_6H_5CH_2$-, Bn-
  - Compounds with R$-$Z where Z is a heteroatom.
    - If Z is a halogen X, then the halogroup makes it an alkyl halide or haloalkane.
  - Alkenyl halide: X$-=$.
  - Aryl halide: Ph$-$X.
  - Alcohols or phenols: R$-$OH.
  - Ether: R$-$O$-$R$'$.
  - Amines: NH_2R, NHRR$'$, NRR$'$R$''$.
  - Thiols or mercathols: R$-$SH.
  - Carbonyl group: R$-$CO$-$R$'$.
  - Aldehyde: R$-$COH.
  - Ketone: R$-$CO$-$R$'$.
  - Carboxylic acid derivatives:
    - Acid: R$-$COOH.
    - Ester: R$-$COOR$'$.
    - Acid chloride: R$-$COCl.
    - Acid halide: R$-$COX.
    - Amide: R$-CONH_2$.
    - Acid anhydride: R$-$COOCO$-$R$'$.
  - Nitrile: R$-$C$\equiv$N.
  - Acrylonitrile: $=-$C$\equiv$N.

2.2 Discussion Section

- ACS in-text citations should be in superscripts as a list of number with no brackets or parentheses.
- Molecular formulas are C_2H_6O, not C_2H_5OH or CH_3CH_2OH.
- Make a table if you have a lot of data to put in (make it readable!).
- Distillation:
  - We need a boiling chip and stir bar inside the flask.
  - Vapor comes up from a round-bottomed flask, encounters a rubber stopper and gets diverted through a condenser instead.
  - Make use of countercurrent exchange and increase pressure by inflowing water in the gravitationally lower portion of the condenser.
  - Boiling chip is a coarse material with a lof of micropores inside.
  - The surface energy is reduced when the fluid is inside the micropores; within, it can more easily become a gas.
- As the mole fraction χ of a substance A increases...
- Raoult's law:
$$P_{\text{total}} = \frac{P_A\chi_A}{P_B\chi_B} = \frac{P_A\chi_A}{P_B(1-\chi_A)}$$
- Dalton's law: The total pressure is equal to the sum of the partial pressures.

2.3 Intermolecular Forces and IR Spectroscopy

10/12:

- Intermolecular forces and physical properties.
- **Boiling point**: The temperature at which the vapor pressure is equal to the pressure of the atmosphere above.
  - The stronger the intermolecular forces, the higher the boiling point.
  - The higher the molecular weight, the higher the boiling point.
- **Melting point**: The temperature at which the crystalline solid and liquid are in equilibrium.
  - The stronger the intermolecular forces, the higher the melting point.
  - The more symmetrical, the higher the melting point.
- Solubility.
- Intermolecular forces.
  - All electrostatic attractions related to bond polarity.
  - 3 types: Dipole-dipole forces, hydrogen bonding, and dispersion forces.
- **Dipoloe-dipole forces**: Attraction between opposite poles (1 kcal/mol to 3 kcal/mol).
- **Hydrogen bonding**: Dipole-dipole interaction between H-atoms bonded to O, N, F (2 kcal/mol to 10 kcal/mol).
- **Dispersion forces**: Weak (< 1 kcal/mol). Momentary distortion of the electron cloud (temporary dipole). Induces dipoles in surrounding molecules. *Also known as* **London forces**.
  - Depends on **relative polarizability**.
  - Dependes on the surface area of the molecule — more surface area means more distance electrons can spread apart.
- **Relative polarizability**: How far valence electrons are from the nucleus.
- Solubility:
  - For something to be soluble, you need to have favorable forces between them.
  - Ionic compounds are soluble in water, less soluble in polar solvents, and insoluble in nonpolar solvents.
  - Organic compounds: < 3 carbons is soluble, 4-5 carbons is borderline, ≥ 6 is insoluble. More soluble in organic solvents.
- Organic solvents:
  - CH_2Cl_2 — methylene chloride.
  - $HCCl_3$ — chloroform.
  - H_3CCOCH_3 — acetone.
  - Diethyl ether.
  - THF.
  - Cyclohexane.
- In TLC, the silica gel is very polar, so polar compounds will not move far up the plate. Nonpolar solvents will drag nonpolar compounds up pretty high.
- HOMO and LUMO get closer as conjugation increases.
- IR spectroscopy:

- The frequencies absorbed vary based on the type. Higher stretching frequencies for lighter atoms and stronger bonds.
- IR radiation causes transitions in vibrational modes of bonds.
- The stronger the bond and the lighter the atoms, the faster the vibration of the molecule and the higher the stretching frequency.
- The ΔE's are inherent characteristics of the bonds and nuclei.
- Bonds absorb light of characteristic energy, frequency, and wavelength.
- We usually report IR spectra in terms of the wavenumber $\bar{\nu}$.
- The frequencies absorbed can indicate bond types and functional groups in the molecule.
- Anything above 1500 (of wavenumber less than 1500) is called the **fingerprint region** — it may not tell you what a molecule is, but it will tell you if two molecules are the same.
- Sharp peaks at high wavenumbers are characteristic of N–H interactions.
- Make a line at $3000\,\mathrm{cm}^{-1}$. Things to the right of that indicate aliphatic C–H's. Things to the left indicate sp^2 C–H groups. Things more to the left indicate sp C–H groups.
- Not all bonds are visible — stretching bands must change the dipole. Thus, for example, the C=H stretch in trans-but-2-ene is not IR active, but the C=H stretch in cis-but-2-ene is IR active.
- If you want to substitute D for H, the peak formerly associated with the R–H bond will move lower.

COMMON ABSORPTIONS	
Aromatic C–C	Two peaks usually in the range of $1500\,\mathrm{cm}^{-1}$ to $1600\,\mathrm{cm}^{-1}$
C=C	$\sim 1650\,\mathrm{cm}^{-1}$
C=O	$\sim 1710\,\mathrm{cm}^{-1}$ (shifts to $\sim 1735\,\mathrm{cm}^{-1}$ for esters)
C≡C	$2100\,\mathrm{cm}^{-1}$ to $2300\,\mathrm{cm}^{-1}$
C≡N	$2100\,\mathrm{cm}^{-1}$ to $2300\,\mathrm{cm}^{-1}$
C–H (aldehyde)	Two peaks at $2170\,\mathrm{cm}^{-1}$ and $2810\,\mathrm{cm}^{-1}$
sp^3 C–H	Just to the right of $3000\,\mathrm{cm}^{-1}$
sp^2 C–H	Just to the left of $3000\,\mathrm{cm}^{-1}$
sp C–H	$\sim 3300\,\mathrm{cm}^{-1}$
N–H	$\sim 3300\,\mathrm{cm}^{-1}$ (one peak for –NH–, two peaks for $-NH_2$)
O–H (alcohol)	$\sim 3400\,\mathrm{cm}^{-1}$ (a broad, smooth peak)
O–H (acid)	$\sim 2500\,\mathrm{cm}^{-1}$ to $3500\,\mathrm{cm}^{-1}$ (a very broad, ugly [not smooth] peak)

Table 2.1: Common IR spectroscopy absorptions.

2.4 Acids and Bases

10/14:

- **Brønsted-Lowry acid**: A proton donor.
- **Brønsted-Lowry base**: A proton acceptor.
- General reaction:

$$H{-}A + H_2O \rightleftharpoons H_3O^+ + A^-$$

  - Does curved-arrow formalism for the above reaction.

- The reaction equilibrium is given by

$$K_{\text{eq}} = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}][\text{H}_2\text{O}]}$$
$$K_{\text{eq}}[\text{H}_2\text{O}] = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]}$$
$$K_{\text{a}} = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]}$$

- Note that $[\text{H}_2\text{O}] = 55.5\,\text{M}$.
- $\text{p}K_{\text{a}} = -\log K_{\text{a}}$ gives numbers that are easier to work with.
  - The larger the $\text{p}K_{\text{a}}$, the weaker the acid.
  - The smaller the $\text{p}K_{\text{a}}$, the stronger the acid.
- Gives $\text{p}K_{\text{a}}$'s and conjugate bases for the strong acids HI, HBr, HCl, H_2SO_4, and HNO_3.
  - Also for the weak acids $\text{CH}_3\text{CO}_2\text{H}$, HF,
- There is a relationship between acid strength and conjugate base strength.
  - The stronger the acid (lower $\text{p}K_{\text{a}}$), the weaker the conjugate base.
  - The weaker the acid (higher $\text{p}K_{\text{a}}$), the stronger the conjugate base.
- Almost any reaction can be thought of as an acid/base reaction using the Lewis definition.
- Acid-base reaction equilibria:

$$\text{H}{-}\text{A} + \text{B} \overset{\text{K}_{\text{eq}}}{\rightleftharpoons} \text{A}^- + \text{HB}$$

  - Let

$$K_{\text{a}_1} = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \qquad\qquad K_{\text{a}_2} = \frac{[\text{H}_3\text{O}^+][\text{B}^-]}{[\text{HB}]}$$

  - Then

$$K_{\text{eq}} = \frac{K_{\text{a}_1}}{K_{\text{a}_2}}$$
$$\log K_{\text{eq}} = \log K_{\text{a}_1} - \log K_{\text{a}_2}$$
$$= \text{p}K_{\text{a}_2} - \text{p}K_{\text{a}_1}$$
$$K_{\text{eq}} = 10^{\Delta \text{p}K_{\text{a}}}$$

    so for any acid-base reaction, the position of the equilibrium can be predicted from the relative $\text{p}K_{\text{a}}$'s.

- Factors influencing acidity:
  - Bond strength and size.
    - As bond strength decreases, acidity increases.
    - As size of the conjugate base increases, acidity increases (there is more area over which to delocalize the positive charge).
  - Electronegativity.
    - As electronegativity differences increase, acidity increases.
  - Hybridization.

    - *sp* orbitals are more acidic than sp^3, with sp^2 in between. This is because the electrons are held closer to the nucleus and are less easily given away.
  - Inductive effects.
    - Electronic effects transmitted through bonds.
    - Electron donating or electron withdrawing groups.
    - Stronger electron withdrawing groups create more acidic compounds (the conjugate base is more stable, and the proton more easily dissociates).
    - Falls off with distance.
    - Alkyl groups are electron donating.
  - Resonance effects.
    - Pulling a proton off of an alcohol leaves negative charge on the oxygen; pulling a proton off a carboxylic acid group leads to an anion that has resonance (and thus is more stable, so the the acid is stronger).
  - Solvation effects.
    - Charges that are more accessible (primary vs. tertiary) are more easily solvated and thus have more stable conjugate bases. Thus, an acid that has charges on its conjugate base that are more easily solvated is stronger.

2.5 Acids and Bases in Nonaqueous Solutions

10/21:

- The strongest base you can have in water is OH^-.
  - This is because strong bases (e.g., H_2N^-) give you

$$H_2N^- + H{-}OH \rightleftharpoons HO^- + NH_3$$

  - Since $pK_a(H_2O) = 16$ and $pK_a(NH_3) = 38$, $K_{eq} = 10^{38-16} = 10^{22}$.
- We need a solvent with less acidic protons, e.g., hexane, diethyl ketone.
  - $Li(CH_2)_3CH_3$, LDA (lithium diisopropylamide), NaH are all very strong bases.
- **Lewis acid**: Electron pair acceptor.
- **Lewis base**: Electron pair donor.
- $AlCl_3$ has an empty *p*-orbital with which it can accept electrons.

Week 3

Nomenclature and Conformations of Alkanes and Cycloalkanes

3.1 Conformers

10/21:

- **Conformational isomers**: Groups connected by single bonds undergo rotation resulting in different molecular conformations. *Also known as* **conformers**.
  - These are transient states.
- **Conformational analysis**: The process of understanding how the conformation relates to the energy of the molecule.
- Newman projections and the sawhorse model.
- Staggered to eclipsed ethane conformations: $\Delta E = 12\,\text{kJ/mol}$.
  - Rate $= 5 \times 10^{10}\,\text{Hz}$.
- **Torsional strain**: Repulsive interactions (steric hindrance) between the clouds of electrons of bonded groups.
- Goes through butane conformations.
  - **Gauche** vs. **anti** methyl groups.
- **Ring strain**: The combination of angle strain and torsional strain in a cycloalkane.
- Puckering of cyclobutane relieves some of the torsional strain.
- Puckering of cyclopentane relieves some torsional strain *and* angle strain.
- Cyclohexane has chair and boat conformations.
  - Goes through Newman projections for each.

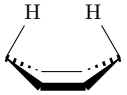


Figure 3.1: Flagpole interactions.

- **Flagpole interaction**: The interaction between the two hydrogens on opposite carbons in cyclohexane that bend toward each other.

- Axial and equatorial positions.
- In a ring flip, axial and equatorial hydrogens invert.
- When you have substituents on a ring, you have 1,3-diaxial interactions.

10/26:
- Covers disubstituted cyclohexanes and bicyclic/polycyclic alkanes.

Week 4

Stereochemistry

4.1 Intro to Chirality and Chiral Compounds

10/26:

- Today:
  1. Stereoisomers / chirality center.
  2. Chirality test.
  3. Keeping track of stereoisomers (R/S system).
  4. Physical properties of enantiomers.
  5. Molecules with multiple chirality centers.
  6. Fischer projections.
  7. Meso compounds.
  8. Chiral molecules with no chirality center.
- **Achiral** (object): An object such that it and its mirror image are identical.
- **Chiral** (object): An object such that it and its mirror are nonidentical (cannot be superimposed).
- Single enantiomer drugs is about a $100 billion industry.
  - Biological molecules are chiral.
- **Stereoisomers**: Same connectivity; different spatial arrangement of groups.
- **Enantiomers**: Non-super-imposable mirror images.
  - E.g., 2-butanol.
- **Diastereomers**: Stereoisomers that are not mirror images of each other.
  - E.g., cis and trans 2-butene.
- **Chirality center**: A tetrahedral carbon that is bonded to four different groups.
- Molecules with one chirality center are chiral and exist as a pair of enantiomers.
- Chirality test: Check for a **plane of symmetry**.
- **Plane of symmetry**: An imaginary plane that bisects the molecule such that the two halves are mirror images of each other.
- Lowest priority group away from you; clockwise 1,2,3 is R; counterclockwise is S.

- Enantiomers have the same boiling and melting point.
  - They are only different when interacting with other chiral substances.
  - They also rotate plane-polarized light different directions.
- **Racemic mixture**: An equimolar mixture of enantiomers.
- **Enantiomeric excess**: The following quantity. *Denoted by* **ee**. *Given by*

$$\frac{(\text{moles enantiomer 1}) - (\text{moles enantiomer 2})}{\text{total moles of both}}$$

  - $ee = 0$ for a racemic mixture; $ee = 100\%$ for an enantiomerically pure mixture.
- How many possible stereoisomers?
  - 2^n possible ones, where n is the number of chirality centers.

Week 5

Stereochemistry / Reactions of Alkenes

5.1 Stereochemistry Nomenclature and Intro to Alkenes

10/28:

- Last time:
  - Chapter 4 (di-substituted cyclohexanes, bicyclic/polycyclic rings).
  - Chapter 5 (stereochemistry, stereoisomers/chirality center, chirality tests [plane/center symmetry], R/S system [nomenclature; a very important survival skill for this class], physical properties of enantiomers, achiral environment: same; chiral environment: different, rotate plane polarized light [left (-) levorotatory, right (+) dextrorotatory, racemic (±) mixture], $[\alpha]_D^{2t}$ specific rotation, enantiometric excess, Fischer projections [less important]).
- Intro to Guangbin Dong.
- The textbook is only a guide — follow the lecture. Also, if you see discrepancies either with the book or with Piccirilli, bring them up.
- Capital E is energy and lowercase e is electrons in this class.
- Reading assignment: Chapter 5.12, 5.14, 4.5 (review), 4.17, 7.1-7.4.
- Nongraded homework: 6.39, 5.40, 5.46, 5.48, 7.1, 7.17, 7.18, 30a-d.
- Multiple stereocenters.
- Worked example: Naming (2S,3R)-2-chloro-3-iodobutane.
  - $n = 2$ stereocenters yields at most $2^n = 2^2 = 4$ stereoisomers.
  - Draws all enantiomers.
- **Diastereomers**: Have at least 2 stereocenters, same formula, same connectivity, but different orientation in space and are not mirror images of each other.
  - Special case: cis/trans isomerism.
- Compounds with 2 stereocenters don't always have 4 stereoisomers.
- Example: Tartaric acid, for which the (2S,3R) compound is superimposable on the (2R,3S) compound. This stereoisomer is a **meso** isomer and not a chiral molecule (there exists a plane of symmetry).
  - Thus, a molecule can be achiral even if it has a chiral center!

- **Meso** (compound): A compound with chiral stereocenters and an internal plane of symmetry.
  - The following compound (two conformers shown) is also meso because the Conformer 2 has the desired plane of symmetry.

(a) Conformer 1. (b) Conformer 2.

Figure 5.1: Meso compounds.

- Alkenes:
  - One of the most important functional groups.
  - Basic industry materials: polyethylene and polypropylene.
  - Biological systems: Fatty acids, vitamins (Vitamin A), drugs/natural products, important building block in other FGs.
- Alkenes have a π bond — $2s$, $2p_x$, and $2p_y$ get hybridized into sp^2 orbitals, and $2p_z$ forms the π bond.
  - The π bond leads to the enforced coplanar geometry of the alkanes.
  - The bond energy of a C=C bond is significantly greater than that of a C−C bond.
- Alkene cis/trans isomerism.
  - Trans is more stable b/c of steric hindrance.
  - E/Z system.

Week 6

Reactions of Alkenes

6.1 Alkene Nomenclature and Reactions

11/2:

- Alkene nomenclature.
- Degree of unsaturation, aka hydrogen deficiency.
  - Indicate the sum of the number of rings and π bonds in a molecule simply by examining the formula.
  - Recall for hydrogens and other heteroatoms (e.g., oxygen, nitrogen, halogens, etc.).
- Reactions of alkenes:
  - Important because an understanding of reactions enables us to do syntheses.
  - There are three components in a chemical reaction: The reactants, products, and conditions.
    - We should be able to predict any one of these from the other two.
    - We should also be able to draw the reaction mechanism.
- **Reaction mechanism**: A stepwise description of what happened in the reaction.
  - This involves arrow pushing.
- Know Table 6.1 from the textbook.
- **Hydrohalogenation**: Addition of H−X across a C=C double bond.

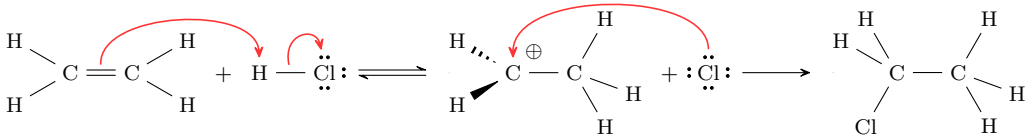


Figure 6.1: Hydrohalogenation mechanism.

  - We add the H to one of the alkene carbons and the X to the other.
  - Since H−X likes electrons, it is the **electrophile**.
  - If a carbocation is formed, you have an **electrophilic addition reaction**.
  - For unsymmetric alkenes, we add the X to the more substituted position since a carbocation will form there during the mechanism and be stabilized by **hyperconjugation**.
    - This is Markovnikov addition.

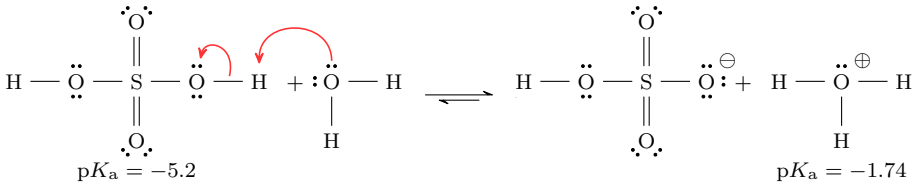
- **Hyperconjugation**: Adjacent C–H bonding electrons donate electron density into vacant p orbitals (of C^+), thus stabilizing the carbocation.
  - Thus, alkyl groups are considered electron-donating groups because they delocalize positive charges through inductive effects.

11/4:

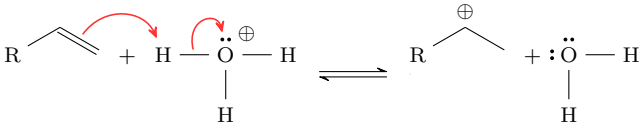
- **Markovnikov addition**: The side of the alkene with more H's gets the H.
- Energy diagram of hydrohalogenation.
  - Energy of the product is lower than the energy of the reactants (this is an exergonic reaction).
  - Energy of the intermediate is higher than either reactants or products.
  - The first transition state is higher energy than the second.
  - The first activation energy is significantly greater than the second (thus, the first step is slow).
  - Driving force: Thermodynamics — more stable product. This makes sense since we're breaking one π bond and one σ bond and forming two σ bonds, and σ bonds are stronger than π bonds.
- Introduces methyl/hydride 1,2-shifts to form a more stable, more substituted carbocations.
  - Is there enough of a driving force to go from a primary to a secondary carbocation, or a secondary to a tertiary carbocation, or is it just a primary to a tertiary carbocation?
- Acid-catalyzed hydration.
- General form:

$$\mathrm{R{-}{=}{+}\,H_2O \xrightarrow{H_2SO_4} R{-}({-}OH){-}}$$

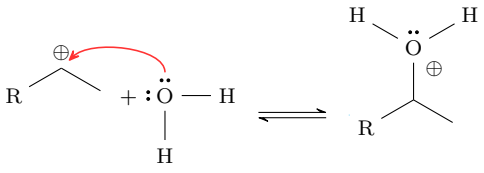
- Mechanism:



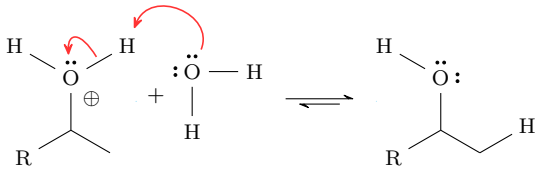
(a) Acid dissociation.



(b) First step.



(c) Second step.



(d) Third step.

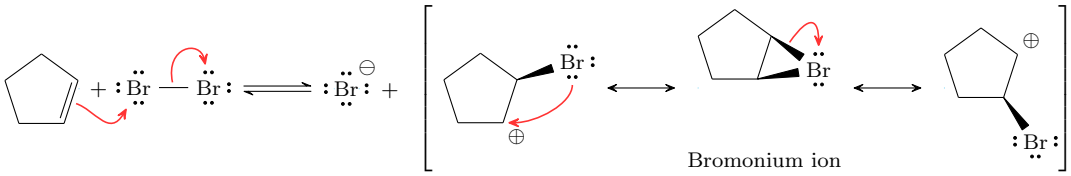
Figure 6.2: Acid-catalyzed hydration mechanism.

  - Thus, the hydronium ion is a catalyst.
  - Same regioselectivity — this is Markovnikov addition.
  - Same possibility for 1,2-shifts.
  - Racemic mixture of product since the carbocation is sp^2 planar and water has equal probability of attacking both faces.

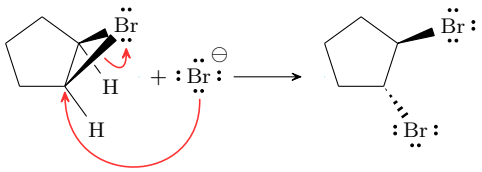
- Replacing H_2O with ROH: Just replace OH in the product with OR.
  - This is a way to make ethers.
- Addition of X_2 to alkenes (typically Br_2 or Cl_2).
- General form:

$$= + X_2 \xrightarrow{CCl_4} X---X$$

  - Generates the trans-product only, if there is a choice.
  - Thus, the reaction does not proceed through a carbocation mechanism.
- Consider Br_2 first.
  - Each bromine is very electronegative.
  - Thus, the bond is weak since both atoms are fighting for electrons.
  - Think about Br_2 as Br^+Br^-.
  - Thus, Br_2 is a very good electrophile.
- Mechanism:



(a) First step.



(b) Second step.

Figure 6.3: Halogenation mechanism.

  - Note that in the first step, the bromonium ion will be the major contributing structure because it satisfies the octet rule and it's symmetrical. This is why we show only it in the second step.

  - In the second step, because of the steric hindrance of the bromonium ion, the bromide ion engages in a "special attack" from the back side, resulting in the trans geometry. Note that it can attack either carbon, not just the one shown in Figure 6.3b.

- When we use chlorine, the reaction proceeds through a chloronium ion.
- Trapping the bromonium or chloronium ion.
  - These ions can be trapped by H_2O, leading to a bromo/chloro-alcohol.
    - This reaction is both regiospecific and stereospecific.
    - It proceeds through a mechanism that is the natural cross between the halogenation and acid-catalyzed hydration mechanism.
- Take-home message: The more substituted carbon has more cationic character, so it tends to be attacked more by the nucleophile.
- Oxymercuration.
- General form:

$$\mathrm{R{-}{=}} \xrightarrow[\text{2. } \mathrm{NaBH_4}]{\text{1. } \mathrm{Hg(OAc)_2},\, \mathrm{H_2O}} \mathrm{R{-}(-OH){-}}$$

  - $NaBH_4$ is a very good hydrogen source.
  - The mechanism proceeds through a mercurinium ion that is trapped by water, and the resulting mercury acetate ligand is replaced with a hydride ligand by $NaBH_4$.
  - No possibility for hydride/methyl shifts.

Week 7

Reactions of Alkynes

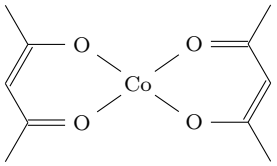
7.1 Methods of Hydration

11/9:

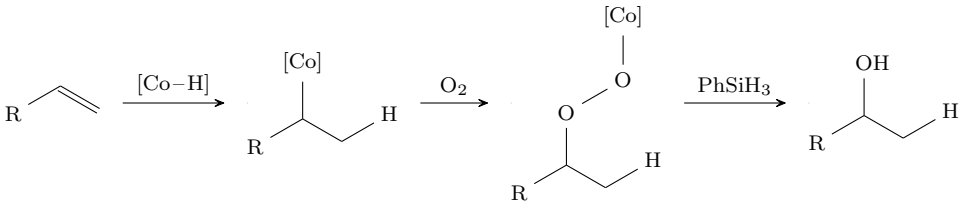
- Mukaiyama Hydration.
  - A "greener" method.
- General form.

$$\mathrm{R{-}{=}} \xrightarrow[\mathrm{PhSiH_3}]{\mathrm{Co(acac)_2,\,O_2}} \mathrm{R{-}(-OH){-}}$$

- Mechanism:



(a) Cobalt catalyst.



(b) Mechanism.

Figure 7.1: Mukaiyama hydration mechanism.

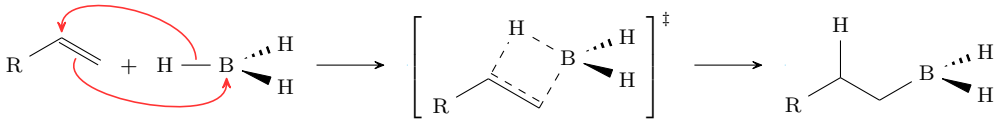
  - Note that $Co(acac)_2$ is a catalyst.
- Hydroboration/oxidation of alkene.
  - Nobel Prize (1979).
  - Discovered by a UChicago undergrad, H. C. Brown.
- General form.

$$\mathrm{R{-}{=}} \xrightarrow[\mathrm{2.\,H_2O_2,\,NaOH}]{\mathrm{1.\,BH_3}} \mathrm{R{-}{-}{-}OH}$$

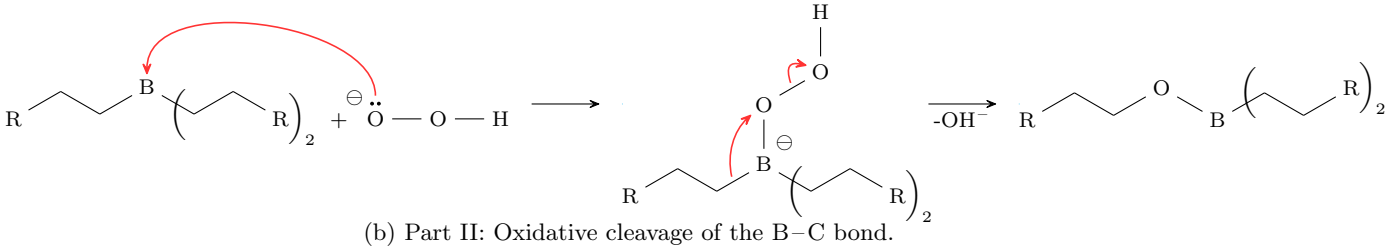
  - Regioselective (anti-Markovnikov).

- Stereospecific (H and OH add cis).
- Covers BH_3 with its empty p orbital that makes it a good Lewis acid and dimerizes to B_2H_6 with its "3C-2e" bond in the gas phase.

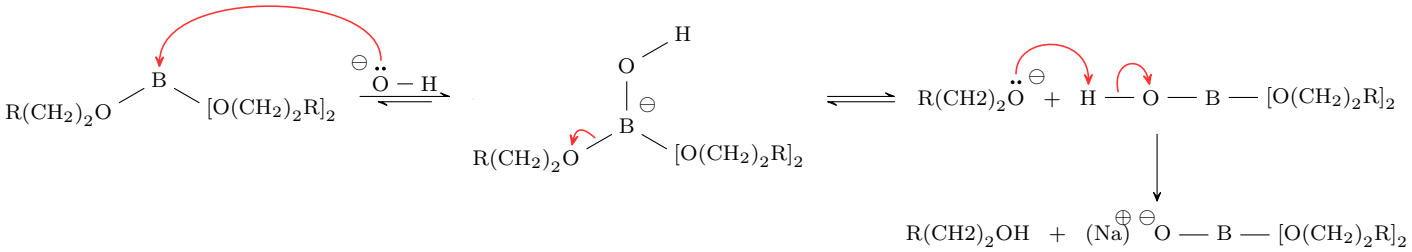
- Mechanism:



(a) Part I.



(b) Part II: Oxidative cleavage of the B−C bond.



(c) Part III: Hydrolysis of boric acid ester.

Figure 7.2: Hydroboration mechanism.

- The step in Part I is a concerted step (this is key for cis addition).
- BH_3 adds the way it does in part I (with the H put on the more substituted carbon) due to sterics (bulky group attaches to the less bulky side) and electronics (the π-bonding electrons of the alkene connecting to the boron first will create a partial positive charge, and it is more stable to have that partial positive on the more substituted position).
- The alkene does not attack an H on BH_3 because said H's are not acidic (it is the boron that is electron deficient).
- Each part repeats an additional two times with the product of the n^{th} run the reactant of the $(n+1)^{\text{th}}$ run to create the reactant of the next part.
- In part II, mixing H_2O_2 with OH^- yields a deprotonated peroxide (O_2H^-).
- The final product of part II is the boric acid ester.
- Part III has a borate salt as a final byproduct.
- The mechanism implies that the hydrogen added comes from BH_3, and the oxygen added (as part of the hydroxide) comes from H_2O_2.

- If we add to an alkene borane, and then a strong acid and heat, we end up hydrogenating it.

- Summary of alcohol synthesis:
  - If you want Markovnikov addition, use...

    - Acid-catalyzed hydration.
    - Oxymercuration/reduction.
    - Mukaiyama hydration.
  - If you want anti-Markovnikov addition, use...
    - Hydroboration.

- Ozonolysis of alkenes.
  - An **oxidation** reaction (adding oxygen or removing hydrogen).
  - Treat an alkene with ozone and dimethyl sulfide to cleave the C=C bond and add oxygen onto each carbon, forming carbonyls (and associated groups).
  - Note that if we consider the resonance structures of ozone, we will find that charger separation is unavoidable, i.e., that the molecule must have a plus and a minus charge somewhere. This makes it very reactive.

- Mechanism.

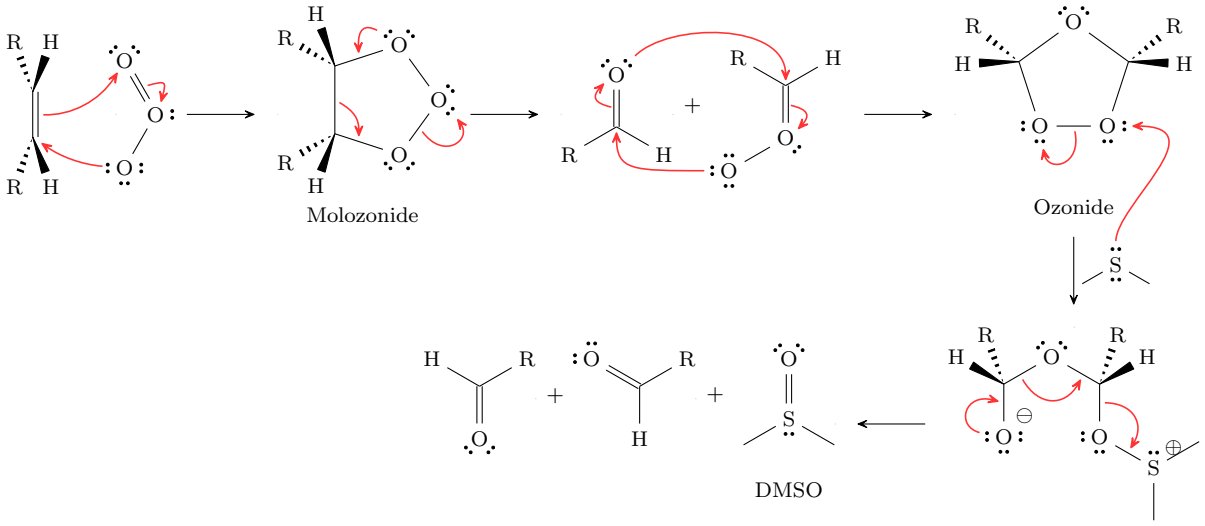


Figure 7.3: Ozonolysis of alkenes.

  - The first step of the reaction is a concerted $3+2$ addition.
  - The ozonide intermediate is more stable than the molozonide owing to its symmetry.
  - Motivation for the last intermediate to split is eliminating charge separation.

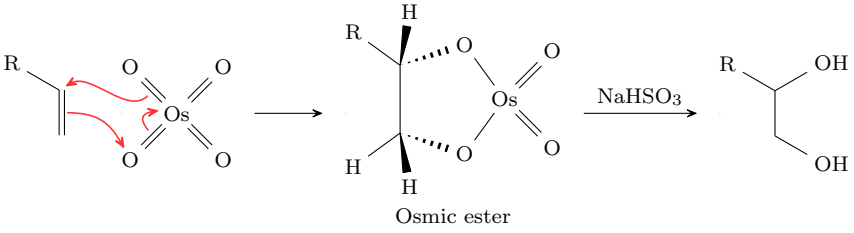
- Dihydroxylation of alkene (creation of a 1,2-diol).

- General form.

$$\mathrm{R{-}{=}} \xrightarrow[2.\ \mathrm{NaHSO_3}]{1.\ \mathrm{OsO_4}} \mathrm{R{-}(-OH){-}{-}OH}$$

  - Stereospecific (cis).
    - Compare to bromination, which gives the trans-product (the difference is for mechanistic reasons).
  - The product is a 1,2-diol, or a vicinal diol.

- Mechanism.



Osmic ester

Figure 7.4: Dihydroxylation.

  - The first step is concerted, once again.
  - Osmium gets reduced in the first step (oxidation number goes from +8 to +6).
  - In the second step, sodium bisulfite cleaves the two osmium oxygen bonds in a very complex process.
- Problems: OsO_4 is very expensive and very toxic.
- Solutions:
- UpJohn process (1976).
  - The same as dihydroxylation but with only 1% OsO_4 and NMO (N-methylmorpholine oxide) and H_2O added second instead of $NaHSO_3$.
- Sharpless asymmetric dihydroxylation.
  - Nobel prize (2001).
  - Gives high ee for each product.
  - Conditions are catalytic potassium osmium salt ($K_2OsO_2(OH)_4$), potassium carbonate (K_2CO_3), and potassium iron cyanate ($K_3Fe(CN)_6$).
- Alkene dihydrogenation.

11/13:
- General form:

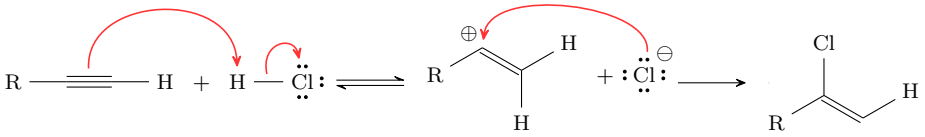
$$\text{R}{-}{=} \xrightarrow[\text{cat}\cdot\text{Pt}]{\text{H}_2} \text{R}{-}{-}$$

  - A reduction reaction.
  - The catalyst can be Pd, Ru, Rh, Ir, etc.
  - This reaction happens on the solid surface of a metal catalyst.
  - Most of the time, this is cis-addition (as we can determine with deuterium labeling).

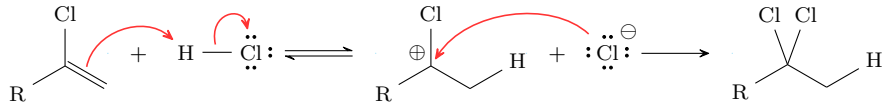
7.2 Alkynes

- Review of bonding.
  - Consider acetylene, or ethyne (H−C≡C−H).
    - Bond angle 180°.
    - Linear
    - *sp* hybridization.
    - Orbital diagram (similar to homework 1.7b).
  - Driving force: Break weaker π bonds.

- IUPAC nomenclature.
  - If there is a stereocenter, we need (R/S). If there is cis/trans, we need that, too.
  - Same rules as for alkenes except with "-yne."
  - No Z/E for alkyne.
  - Alkenes have higher priority than alkynes, e.g., we have but-1-ene-3-yne, not but-1-yne-3-ene.
  - Alkenes have higher priority than alkynes, have higher priority than halogens, e.g., we have 3-bromo-3-methyl-1-butyne.
- Acidity of terminal alkynes.
  - Recall that *sp* hydrogens are more acidic than sp^2 hydrogens, are more acidic than sp^3 hydrogens (more *s* character means that the charge on the conjugate base is held closer to the positive nucleus and thus stabilized better).
  - Indeed, R–C≡C–H is a reasonable Brønsted acid (it can react with a strong base).
    - For example, acetylene and sodium amide react to establish an acid-base equilibrium to the right.
  - Take home message: Strong bases can remove hydrogen from terminal alkynes to give $R–C{\equiv}C^-$.
  - Two more strong bases (that can fully remove a hydrogen from a terminal alkyne): NaH (sodium hydride) and LDA (lithium diisopropylamide).
  - NaOH cannot remove a hydrogen from a terminal alkyne.
- Reactions of alkynes.
  - Tip: Learn alkyne reactions simply by making an analogy to an alkene reaction.
- Hydrohalogenation.



(a) One equivalent HBr.



(b) Another equivalent HBr.

Figure 7.5: Hydrohalogenation mechanism (alkynes).

  - Two equivalents of HBr yields a **geminal dichloride**.
  - Still Markovnikov addition.
  - If we wanted to form a viscinal (or 1,2-) dichloride, we would use chlorination, but if we want to form the geminal chloride, we must start with an alkyne.
- Halogenation.
  - Similarly, one equivalent yields a trans alkene.
  - Two equivalents yield a tetrahalo alkyne.

- Acid-catalyzed hydration.

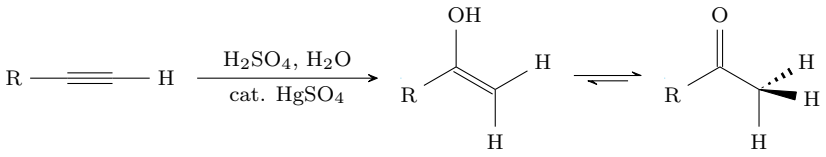
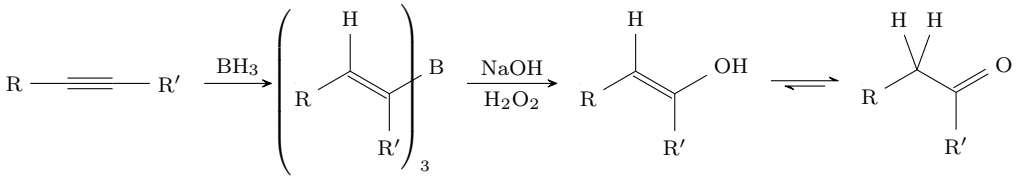


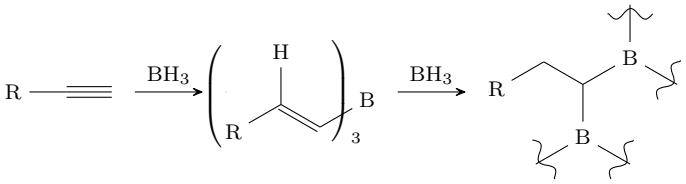
Figure 7.6: Hydration mechanism (alkynes).

  - For an alkyne, we need a more forcing condition. In particular, we will add catalytic $HgSO_4$.
  - After running once, we will form an enol.
    - Enols are unstable and undergo enol-keto tautomerizations, forming a ketone.
    - If we are asked to draw the products of this reaction, draw *only* the ketone.
    - The tautomerization favors the ketone for thermodynamic reasons: The ketone is more stable (by about $15\,\mathrm{kcal\,mol^{-1}}$), and the O–H and C–H bonds have similar BDEs.
  - This is Markovnikov.
  - A good method for ketone synthesis: Alkyne to ketone.
  - We do not need to know the mechanism because the introduction of the mercury catalyst goes beyond this class.
  - Know, however, that alkyne hydration requires a more forcing condition because alkynes' hybridization leads to tighter holding of electrons relative to alkenes. Thus, we say that alkenes are more electron rich.
  - There are some alternative greener methods, but we will not cover them.

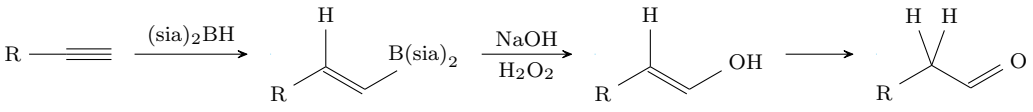
- Hydroboration.



(a) Alkyne hydroboration.



(b) Over hydroboration.



(c) Solving over hydroboration.

Figure 7.7: Hydroboration mechanism (alkynes).

  - Three equivalent of the reactant go through at once to form three equivalents of the product.
  - The product results from typical hydroboration cis-addition followed by the keto-enol tautomerization.

- The R′ group in the normal hydroboration prevents boron from adding to the alkene again via steric hindrance.
- We can solve over hydroboration by using $(sia)_2B-H$ instead of BH_3, which only works one molecule at a time and is too bulky for over hydroboration.
  - The sia ligand is sec-isoamyl (5 carbons, prong at the end, bonds through the second carbon along the tail).
  - The full name of $(sia)_2BH$ is di-sec-iso-amylborane.

- Three ways to make ketones:
  1. Ozonolysis of alkenes.
  2. Acid-catalyzed hydration of alkynes.
  3. Hydroboration of alkynes.

- Reduction (hydrogenation).
  - The reaction is hard to stop at the alkene if we use catalytic platinum and hydrogen.
  - To stop at the alkene stage, we can use a Lindlar catalyst (has some Pd, $CaCO_3$, and PbO).
    - A **poisoned catalyst** that does not have the same reactivity as platinum. It can bind with the alkyne, but not the alkene.
  - Alternatively, we can use Ni_2Br.
  - We can get the trans product with a special condition called dissolving metal reduction.

$$R-\equiv-R' \xrightarrow[2\,NH_3]{2\,Na} \textit{trans}\text{-}R-=-R' + 2\,NaNH_2$$

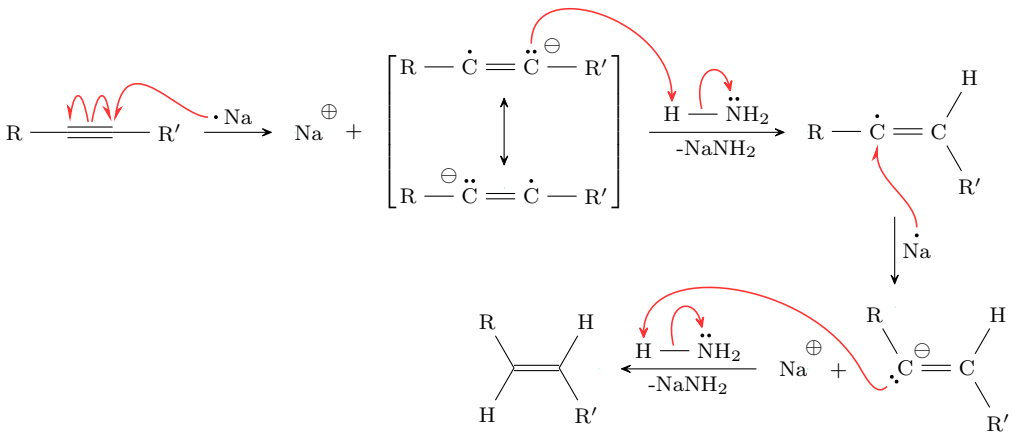


Figure 7.8: Monohydrogenation of an alkyne.

- Dissolve two equivalents of sodium in NH_3.
- Stereospecific (trans).
- Sodium is very electropositive, a single electron donor. On the other hand, the alkyne is electron poor.
- We favor the trans intermediate for steric reasons.

Week 8

Nucleophilic Substitutions

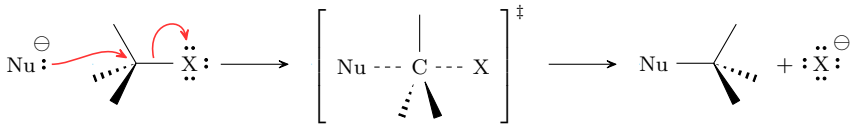
8.1 Nucleophilic Substitutions

11/18:

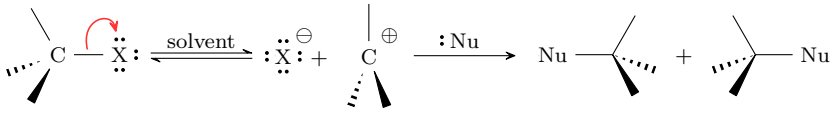
- Philosophy of learning mechanisms (the most difficult and important part of organic chemistry to understand):
  - The origin is the structure, which determines the reactivity of the reagent, which determines the mechanism.
- In this chapter, we consider **haloalkanes** or **alkyl halides**.
  - Alkyl halides have polar bonds.
  - The electropositive carbon center is key for attracting electrons from nucleophiles or other things.
- Nucleophilic substitution.
- General form.

$$\mathrm{Nu^- + R{-}X \longrightarrow Nu{-}R + X^-}$$

  - The nucleophile ($\mathrm{Nu^-}$) attacks the electrophile ($\mathrm{R{-}X}$), generating the product ($\mathrm{Nu{-}R}$) and leaving group or LG ($\mathrm{X^-}$).
  - Motivation: Stability — $\mathrm{X^-}$ is more stable than $\mathrm{Nu^-}$.
  - We can use this to perform a wide variety of coupling reactions (coupling R to $\mathrm{Nu^-}$) given a good leaving group.
    - For example, generating methanol from hydroxide and bromomethane.
- Mechanisms.



(a) S_N2.



(b) S_N1.

Figure 8.1: Nucleophilic substitution mechanisms.

- **S_N2**: Bimolecular nucleophilic substitution. *Also known as* **backside attack**.
  - Bimolecular refers to the number of reactants in the rate-determining step.
  - Compare to the opening of the bromonium ion (see Figure 6.3b).
  - The backside attack breaks the carbon-halogen bond by pumping electrons into the large lobe of the σ^* antibonding orbital on the back side of the carbon.
  - Mechanism type.
    - Concerted, as per the energy diagram.
  - Rate law.
    $$r = R[\mathrm{Nu}^-][\mathrm{RX}]$$
    - First-order dependence on both the nucleophile and alkyl halide.
  - Stereochemistry.
    - Flips.
    - Stereoinversion (as opposed to stereoretention).
- **S_N1**: Unimolecular nucleophilic substitution.
  - Unimolecular refers to the number of reactants in the rate-determining step.
  - Initiated by a **sloppy electrophile**.
  - Since it still take a lot of energy to break the C–X bond, the first step is the RDS.
  - Gives a racemic mixture of products since the nucleophile can attack the carbocation intermediate from either face.
  - Mechanism type.
    - Stepwise, as per the energy diagram.
  - Rate law.
    $$r = R[\mathrm{RX}]$$
    - Zeroeth-order dependence on the nucleophile; first-order dependence on the alkyl halide.
  - Stereochemistry.
    - Racemic.
- **Sloppy electrophile**: An electrophile that can undergo a self-ionization reaction.
- Key requirement: Predict whether a reaction proceeds through an S_N1 or S_N2 mechanism.
  - Experimentally, we can do...
    - Kinetic/rate law studies.
    - Stereochemical analyses.
  - For the exam, we need to be able to predict based off of the reactants and conditions.
- Choosing between the mechanisms.
- The general form has four variables/parameters.
  1. Structure of the nucleophile.
     - A good nucleophile has electron pairs that are "held loosely."
     - Trend:
       - Nucleophilicity of elements in the same period.

       $$\mathrm{F}^- < \mathrm{OH}^- < \mathrm{NH_2}^- < \mathrm{CH_3}^-$$

- Nucleophilicity of elements in the same group.

$$\mathrm{MeO^-} < \mathrm{MeS^-}$$
$$\mathrm{Me_2O^-} < \mathrm{Me_2S^-}$$
$$\mathrm{F^-} < \mathrm{Cl^-} < \mathrm{Br^-} < \mathrm{I^-}$$

- Nucleophilicity of the same element.

$$\mathrm{MeOH} < \mathrm{MeO^-}$$
$$\mathrm{H{-}OH} < \mathrm{H{-}O^-}$$

- Nucleophilicity of species with differently sized ligands.

$$\mathrm{Bu^{\mathit{t}}{-}O^-} < \mathrm{MeO^-}$$

– Basically, elements that are more positive, less electronegative, and larger (i.e., more basic) hold electron pairs more loosely. Sterically hindered bases are also less nucleophilic because they're too bulky to attack (linear nucleophiles are often the best).
– Take-home message: A good nucleophile favors S_N2.

2. Structure of the R group.
   – Tertiary alkyl halides.
     - Backside is blocked.
     - Carbocation is stable.
     - S_N1 is favored.
   – Primary alkyl halides.
     - Backside is wide open.
     - Carbocation is unstable.
     - S_N2 is favored.
   – For S_N2 reactions, sterics matter (affect the rate) a lot.
     - Neopentyl alkyl halides block S_N2 reactions.
   – Secondary alkyl halides.
     - Case-by-case analysis.
3. Leaving group.
   – Important for both S_N1 and S_N2 reactions.
   – Good leaving groups are stable, weak bases.

$$\mathrm{I^-} > \mathrm{Br^-} > \mathrm{Cl^-} > \mathrm{F^-}$$

   – These raise the reaction rate.

Week 9

Nucleophilic Substitutions and Elimination

9.1 Nucleophilic Substitutions (cont.)

11/30:

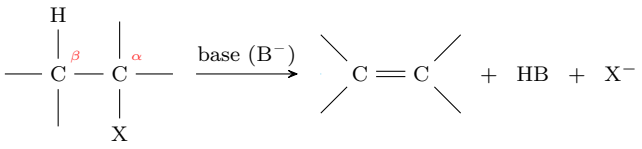
- Choosing between the mechanisms (cont.).

    4. Solvent.
        - Critical for borderline cases.
        - The solvent is important for dissolving things/providing an environment for the reaction.
        - There are two types of solvents: **protic** and **aprotic**.
        - We need to know all of the common solvents (a table will be uploaded).
        - Key difference between protic and aprotic solvents.
            - Protic solvents can do hydrogen bonding with anions (LGs), stabilizing them.
            - Aprotic solvents cannot do this.
        - Protic solvents can stabilize X^-, easing the self-ionization step in S_N1.
        - Protic solvents stabilize both the nucleophile and LG in S_N2.
            - With the nucleophile retarded, the rate of S_N2 goes down.
        - In an aprotic solvent, the nucleophile is even more reactive.
        - Take-home message: For secondary alkyl halides (the borderline cases), protic solvents promote S_N1 and aprotic solvents promote S_N2.

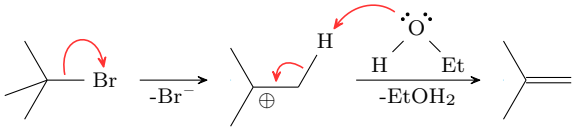
- **Protic** (solvent): A solvent with an acidic proton.
- **Aprotic** (solvent): A solvent without an acidic proton.
- If you see a nucleophilic substitution-type reaction with just one compound surrounding the arrow, assume it is both the nucleophile *and* the solvent.
- **Allylic** (carbocation): A carbocation on a carbon adjacent to an alkene.
    - Extra stable due to resonance stabilization.

9.2 β-Elimination

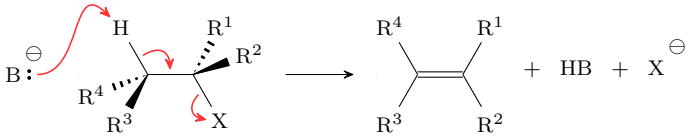
- β-elimination is a form of dehydrohalogenation.
- General form.



- Mechanisms.



(a) E1.



(b) E2.

Figure 9.1: Elimination mechanisms.

- **E1**: Unimolecular elimination.
  - Not a clean reaction — E1 and S_N1 often happen together.
  - They will not ask us to tell which pathway is more favored.
  - Features.
    1. Tertiary alkyl halides are favored (secondary sometimes).
    2. Protic solvents are needed.
    3. We need a weak base/poor nucleophile.
    4. Selectivity: Determined by the alkene stability; we favor forming the more stable alkene (as per **Zaitsev's Rule**).
  - E1 is not a useful reaction to prepare alkenes from alkyl halides since we get a mixture of products and there are selectivity issues.
- **Zaitsev's Rule**: More substituted alkenes are more stable.
  - For secondary carbons, cis < trans < geminal in terms of stability.
  - Since sp^2 is more electronegative than sp^3 and R is an EDG, more R groups can provide more electrons to stabilize the sp^2 carbons.
- **E2**: Bimolecular elimination.
  - Often very selective, and you can make it very selective.
    - The lack of a carbocation intermediate and the fact that it's a concerted mechanism both contribute to the higher yield.
  - In order to realize E2, the conformation *must* adopt **anti-periplanar geometry**.
    - E2 is a stereospecific reaction.
  - A bulky base (such as Bu^tO^-) is preferred since such a base reduces competition from S_N2.
- **Anti-periplanar geometry**: Two groups of importance are opposite each other and lie in the same plane.
  - Consider the H and X in Figure 9.1b.

- Example: Consider *cis*-1-chloro-2-isopropylcyclohexane in solution with MeONa and MeOH.
  - Only the more stable cyclohexane conformation (with Cl axial and Pr^i equatorial) has hydrogens anti to the chlorine.
  - Both of these hydrogens will undergo E2 elimination with the chlorine, and the trisubstituted product will be the major product (as per Zaitsev's rule).
  - However, if we use *t*-butoxide instead of methoxide, the disubstituted product would be the major product due to sterics.
- Example: Consider *trans*-1-chloro-2-isopropylcyclohexane in solution with MeONa and MeOH.
  - Since the less stable conformation is the reactive one, the reaction will still go, but it will be very slow.
- Take-home summary: For E2, the first priority is anti-periplanar, and then Zaitsev.

12/6:
- Deciding between S_N2 and E2 in secondary cases.
  - When you have a strong base, E2 is favored.
    - Examples: OH^-, MeO^-, EtO^-, Bu^tO^-.
  - When you have a good nucleophile that is not too basic, S_N2 is favored.
    - Examples: Br^-, I^-, RS^-, $N{\equiv}C^-$, $N_3{}^-$, PPh_3.
- Deciding between E2 and E1/S_N1.
  - For E2, the role of the base is critical — without a strong base, it will not take place.
  - For E1, the role of the base is not important; ionization is more important.
  - Since ionization is a very slow process, if there is competition between E2 and E1 and a strong base is present, E2 will usually win out because it's so much faster.
  - Primary alkyl halides lead to E2 only.
  - Secondary and tertiary alkyl halides lead to E2 in the presence of a strong base, and E1/S_N1 in the presence of a weak base/solvent.

9.3 Alkyl Halide Equivalents

- Other species that can behave with the above chemistry.
- Consider the following sulfonate ester.

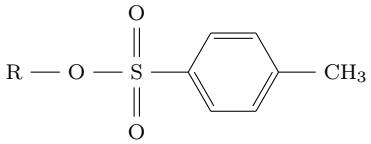


Figure 9.2: A sulfonate ester.

  - Often abbreviated OTs and called tosylate.
- This species is important because we can make it from alcohols with stereoretension.

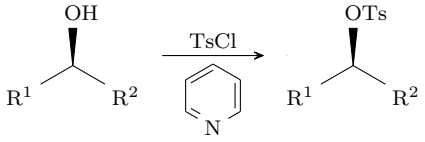


Figure 9.3: Making tosylate species.

  - The species below the arrow above is called pyridine and is often abbreviated Py.
  - The mechanism of the above reaction is not needed.

- You can then hit the product in Figure 9.3 with a nucleophile to perform S_N2.
- Note that like RX, ROTs can also undergo β-elimination (such as E2).

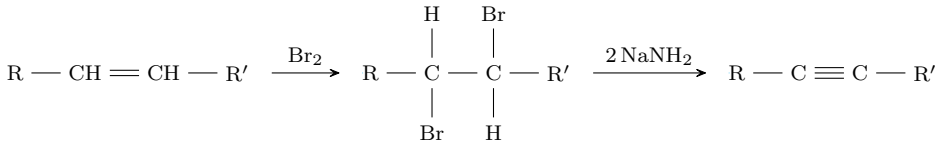
9.4 Alkyne Synthesis

- You can form alkynes from simpler alkynes, alkenes, and ketones (though we don't have to know the last one for this class).
- Alkylation of acetylides with RX via S_N2.

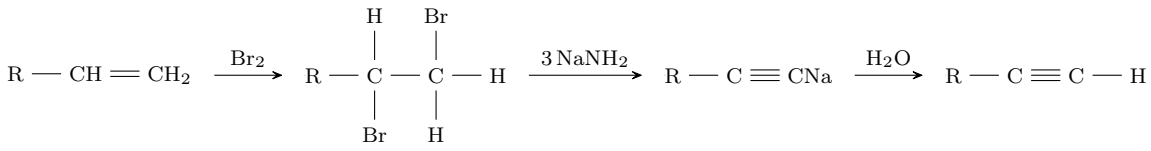
$$\mathrm{H{-}C{\equiv}C{-}H} \xrightarrow[\text{2. R{-}Br}]{\text{1. NaNH}_2} \mathrm{H{-}C{\equiv}C{-}R} \xrightarrow[\text{2. R'{-}Br}]{\text{1. NaNH}_2} \mathrm{R'{-}C{\equiv}C{-}R}$$

  - Start with an acetylide such as $\mathrm{NaC{\equiv}C{-}H}$.
  - React it with an alkyl bromide (RBr) in THF to attach it to that alkyl species at the former bromium site with inverted stereochemistry (yielding $\mathrm{RC{\equiv}C{-}H}$ and NaBr).
  - React the terminal alkyne species with a strong base (e.g., NaH, $NaNH_2$, LDA) to generate a species such as $\mathrm{NaC{\equiv}CR}$.
  - React this with another alkyl bromide ($\mathrm{R'Br}$) to yield the final $\mathrm{RC{\equiv}CR'}$ species.

- **Synthesis**: Making a large and more useful molecule from readily available small molecules.
  - Using alkynes is a very important approach to make carbon-carbon bonds.
- From alkenes.



(a) Internal alkene.



(b) Terminal alkene.

Figure 9.4: Synthesis of alkynes from alkenes.

  - The elimination mechanism for the two pairs of HBr in Figure 9.4a is different from E1 and E2, and we do not need to know it.
  - In Figure 9.4b, we need the third equivalent of base in the second step because once an alkyne species is formed, its acidic proton will react with any base in solution. Thus, if we used only two equivalents, some of the reactant would get converted all of the way to the $\mathrm{R{-}C{\equiv}CNa}$ species, and some would not get converted at all. Therefore, we push all of the reactant to be converted, and then work with the product, quenching with H_2O to get our final desired product.
  - Note that various byproducts are generated that are not shown (they are the predictable ones, though).
  - We can also use chloride here.

9.5 Multi-Step Synthesis

- These problems are the core of organic chemistry, using both our imagination and our knowledge to construct *a* right answer (there are often more than one).
- Tip: Think backwards!
  - Formally, "retro-synthetic analysis," as coined by E. J. Corey, a Nobel laureate at Harvard.
- Example: Construct cyclohexane-1,2-diol from cyclohexanol.

$$C_6H_{11}OH \xrightarrow{TsCl,\, Py} C_6H_{11}OTs \xrightarrow[-Bu^tOH,\, OTs^-]{Bu^tO^-} C_6H_{10} \xrightarrow[2.\, NaHSO_3]{1.\, OsO_4} C_6H_{10}(OH)_2$$

- More examples given.