Some Arrow-Pushing Guidelines (Section 1.14)

1. Arrows follow electron movement.

2. Some rules for the appearance of arrows
    *   The arrow must begin from the electron source. There are two sources:
        a. An atom (which must have a lone pair to give)
        b. A bond pair (an old bond that breaks)
    *   An arrow must always point directly to an atom, because when electrons move, they always go to some new atom.

3. Ignore any Spectator Atoms. Any metal atom is always a "spectator"
    *   When you have a metal spectator atom, realize that the non-metal next to it must have negative charge

4. Draw all H's on any Atom Whose Bonding Changes

5. Draw all lone-pairs on any Atom whose bonding changes

6. **KEY ON BOND CHANGES**.   Any two-electron bond that changes (either made or broken) must have an arrow to illustrate:
    *   where it came from (new bond made) or
    *   an arrow showing where it goes to (old bond broken)

7. **Watch for Formal Charges and Changes in Formal Charge**
    *   If an atom's charge gets more positive Þ it's donating/losing an electron pair Þ arrow must emanate from that atom or one of it's associated bonds.   There are two "more positive" transactions:
        *   When an anion becomes neutral. In this case, an arrow will emanate from the atom. The atom has donated a lone pair which becomes a bond pair.
        *   When a neutral atom becomes cationic. In this case, the atom will be losing a bond pair, so the arrow should emanate from the bond rather than from the atom.

    *   If an atom's charge gets more negative Þ it's accepting an electron pair Þ an arrow must point to that atom. Ordinarily the arrow will have started from a bond and will point to the atom.

8. **When bonds change, but Formal Charge Doesn't Change, A "Substitution" is Involved**
    *   Often an atom gives up an old bond and replaces it with a new bond. This is "substitution".
    *   In this case, there will be an incoming arrow pointing directly at the atom (to illustrate formation of the new bond), and an outgoing arrow emanating from the old bond that breaks

4.16 Reactive Intermediates: Stability Patterns

- Shortlived, unstable, highly reactive intermediates
- Normally lack normal bonding

These are tremendously important:
1. They will be the **least stable intermediate** in any multistep mechanism
2. When formed, they are **products of the rate-determining step**
3. **Factors that stabilize them will speed up reaction rates**

Thus it is very important to know their stability patterns!

| Class	Structure	Stability Pattern		
Carbocations	$-\overset{\mid}{\underset{\mid}{C}}\oplus$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbon Radicals	$-\overset{\mid}{\underset{\mid}{C}}\cdot$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbanions	$-\overset{\mid}{\underset{\mid}{C}}:\ominus$	Allylic > alkenyl (vinyl, aryl) > methyl > 1º > 2º > 3º	Electron Rich	Nucleophilic/ Basic

Notes
1. Both carbocations and radicals have the same pattern. So you don't need to memorize them twice!
2. Carbanions are almost exactly the reverse, except that being allylic is ideal for both.
3. All benefit from resonance (allylic).
4. Cations and radicals both fall short of octet rule. As a result, they are both electron deficient. Carbanions, by contrast, are electron rich.
5. Alkyl substituents are electron donors. As a result, they are good for electron deficient cations and radicals (3º > 2º > 1º > methyl) but bad for carbanions.
6. Alkenyl (vinyl or aryl) carbons are inherently a bit electron poor. This is excellent for carbanions, but terrible for cations or radicals.

Stability/Reactivity/Selectivity Principles

1. **Reactant Stability/Reactivity**: The <u>more stable the reactant</u>, the <u>less reactive</u> it will be. In terms of rates, this means that the <u>more stable the reactant,</u> the slower it will react. (The concept here is that the more stable the reactant, the more content it is to stay as is, and the less motivated it is to react and change into something different)

   <u>**Key note:**</u> Often the "reactant" that's relevant in this context will not be the original reactant of the reaction, but will be the "reactant" involved in the rate determining step.
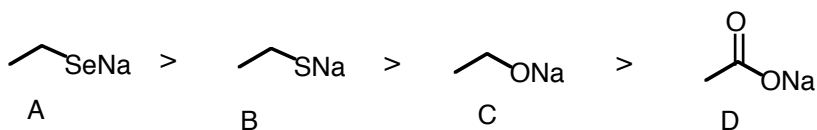
   - **Basicity**
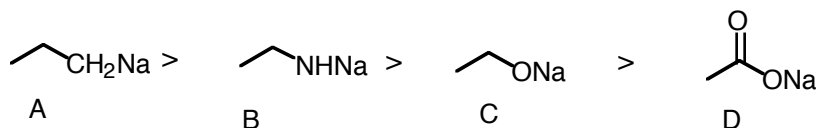
     CH_2Na > $NHNa$ > ONa >   (acetate) ONa

        A   B   C   D

     Why: As anion stability increases from A to D, the reactivity decreases

   - **Nucleophilicity**

     CH_2Na > $NHNa$ > ONa >   (acetate) ONa

        A   B   C   D

     Why: As anion stability increases from A to D, the reactivity decreases

   - **Nucleophilicity**

     $SeNa$ > SNa > ONa >   (acetate) ONa

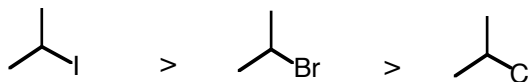   A   B   C   D
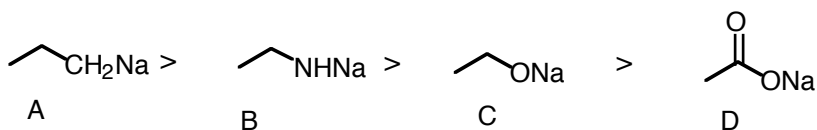
     Why: As anion stability increases from A to D, the reactivity decreases

   ---

   - **Reactivity toward alkanes via radical halogenation**

     $$F_2 \; > \; Cl_2 \; > \; Br_2 \; > \; I_2 \quad \text{because} \quad F\cdot \; > \; Cl\cdot \; > \; Br\cdot \; > \; I\cdot$$

     Why: Chlorine is more reactive the bromine because chlorine radical is less stable then bromine radical.

   - **Electrophilicity (Reactivity in S_N2, S_N1, E2, E1 Reactions)**

     (isopropyl)I   >   (isopropyl)Br   >   (isopropyl)Cl

     Why: As carbon-halogen bond stability increases, the reactivity decreases

2. **Product Stability/Reactivity**:   The <u>more stable the product</u>, the <u>more favorable its formation</u> will be.   In terms of rates, this means that the <u>more stable the product,</u> the faster the reaction. (The concept here is that the more stable the product, the more favorable it will be to make that product.)

Key note: Often the "product" that's relevant in this context will not be the final product of the reaction, but will be the "product" of the rate determining step.
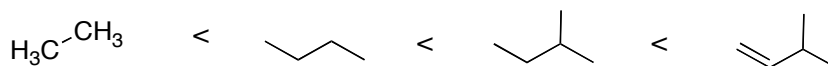
- Acidity

CH_3 < NH_2 < OH < $\underset{OH}{\overset{O}{\parallel}}$
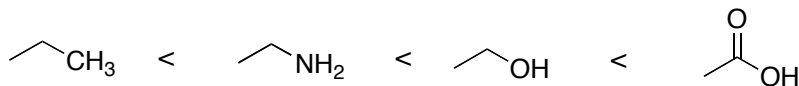
Why: Because as the stability of the anion products increases from A to D, the reactivity of the parent acids increase
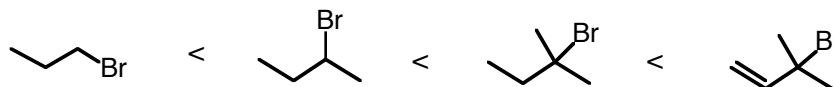
CH_2Na < $NHNa$ < ONa < $\underset{ONa}{\overset{O}{\parallel}}$

A   B   C   D
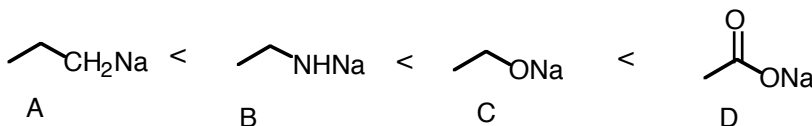
- **Reactivity of alkanes toward radical halogenation**

$H_3C\text{—}CH_3$ <   ⌁⌁   <   ⋏⋏   <   ⋎⋏
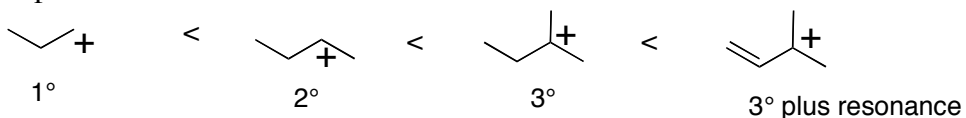
Why: Because as the stability of the radical produced during the rate-determining-step increases, the reactivity of the parent alkane increases

1°   <   2°   <   3°   <   3° plus resonance

- **S$_N$1, E1 Reactivity**

⌁Br   <   ⋏Br   <   ⋎Br   <   ⋎Br
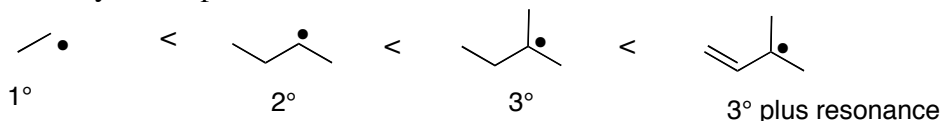
Why: Because as the stability of the cation produced in the rate-determining step increases, the reactivity of the parent halide increases as well

1°   <   2°   <   3°   <   3° plus resonance

3. **Transition-State Stability/Reactivity**:   The <u>more stable the transition state</u>, the <u>faster the reaction</u> will be. (The concept here is that the lower the transition state, the more easily it will be crossed.)

- **S$_N$2 Reactivity**
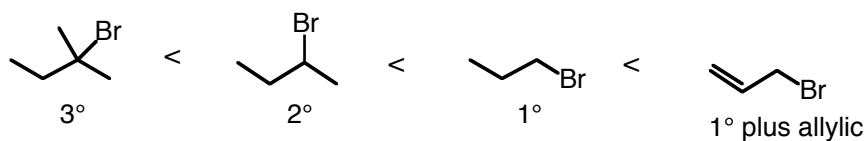
Why: The pattern reflects the relative stability of the transition states. In the case of 3° versus 2° versus 1°, the issue is steric congestion in the transition state. The transition states for the more highly substituted halides are destabilized. In the case of allylic halides, the transition state is stabilized for orbital reasons, not steric reasons.

Chem 350 Jasperse Ch. 6   Summary of Reaction Types, Ch. 4-6, Test 2

1. Radical Halogenation (Ch. 4)

resonance stabilized>3°>2°>1°>alkenyl
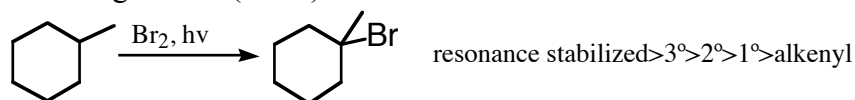
Recognition: X_2, hv
Predicting product: Identify which carbon could give the most stable radical, and substitute a Br for an H on that carbon.
Stereochemistry: Leads to racemic, due to achiral radical intermediate.
Mech: Radical. Be able to draw propagation steps.

slow step
+ H-Br
ready
to repeat
first step
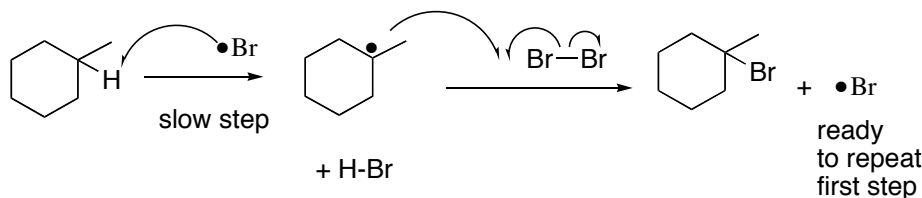
2. S_N2 Substitution

S_N2: 1°>2°>3°> alkenyl
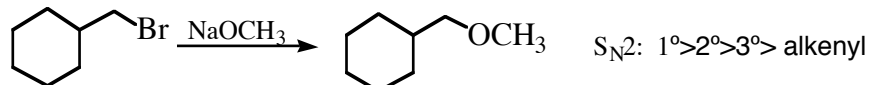
Any of a large variety of nuclophiles or electrophiles can work.
Recognition: A. Anionic Nucleophile, and
                            B. 1° or 2° alkyl halide
(3° alkyl halides fail, will give E2 upon treatment with Anionic Nucleophile/Base. For 2° alkyl halides, S_N2 is often accompanied by variable amounts of E2.)
Predicting product: Replace the halide with the anion nucleophile
Stereochemistry: Leads to Inversion of Configuration
Mech: Be able to draw completely. Only one concerted step!

$+ Br^\ominus$ S_N2: 1°>2°>3°> alkenyl

3. E2 Reactions.

E2: 3°>2°>1°> alkenyl
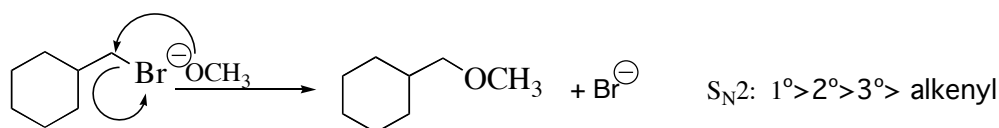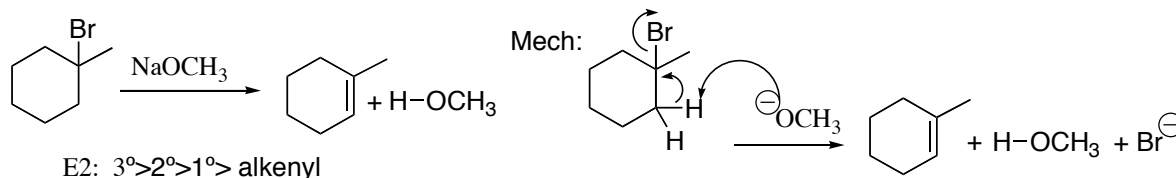
Recognition: A. Anionic Nucleophile/Base, and
                            B. 3° or 2° alkyl halide
(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, E2 is often accompanied by variable amounts of S_N2.)
Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)
Predicting product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.
Stereochemistry: Anti elimination. The hydrogen on the neighbor carbon must be trans/anti.
Mech: Concerted. Uses anion. Be able to draw completely. Only one concerted step!

4. S_N1 Reactions.
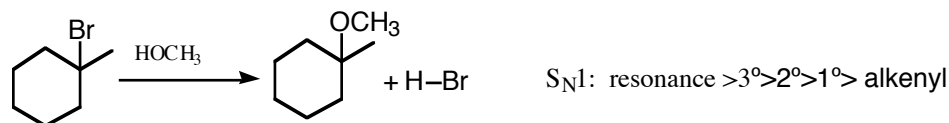
S_N1: resonance >3°>2°>1°> alkenyl
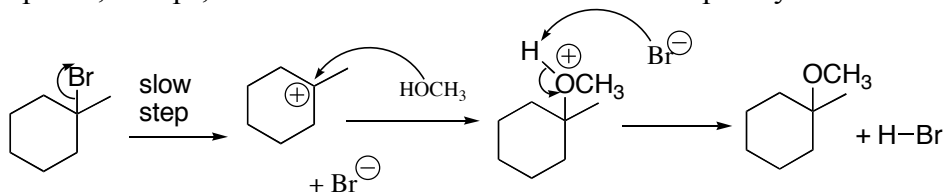
Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
                        B. 3° or 2° alkyl halide. (Controlled by cation stability).
(1° alkyl halides undergo S_N2 instead.   For 2° alkyl halides, S_N1 is often accompanied by variable amounts of E1.)
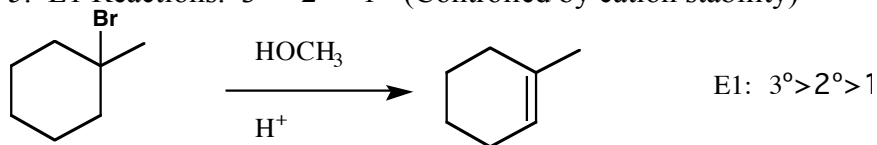**Predicting product:** Remove halide and replace it with the nucleophile (minus an H atom!)
Stereochemistry: Racemization. The achiral cation intermediate forgets any stereochem.
Mech: Stepwise, 3 steps, via carbocation. Be able to draw completely.

5. E1 Reactions. 3° > 2° > 1° (Controlled by cation stability)

E1: 3°>2°>1

Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
                        B. 3° or 2° alkyl halide. (Controlled by cation stability).
(For 2° alkyl halides, E1 is often accompanied by variable amounts of S_N1.)
Orientation: The most substituted alkene forms
Predicting the major product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.
Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .
Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.
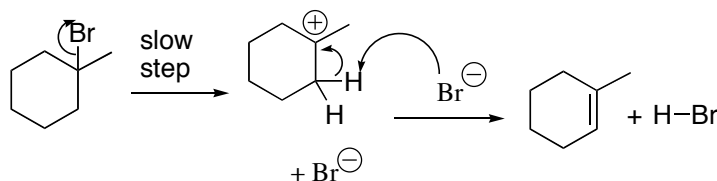
Sorting among S_N2, S_N1, E2, E1: How do I predict?
Step 1: **Check nucleophile/base**.
   • If **neutral**, then **S_N1/E1** → mixture of both
   • If **anionic**, then **S_N2/E2.**
Step 2: If **anionic**, and in the **S_N2/E2**, then **Check the substrate**.
            o 1° → **S_N2**
            o 2° → **S_N2/E2 mixture.**   Often more **S_N2**, but not reliable…
   o 3° → **E2**

6.16 Comparing S$_N$2 vs S$_N$1

		S$_N$1	S$_N$2
1	**Nucleophile**	**Neutral, weak**	**Anionic, strong**
2	**Substrate**	**3º R-X > 2º R-X**	**1º R-X > 2º R-X**
	Allylic effect…	Allylic Helps	Allylic helps
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry (on chiral, normally 2º R-X)	Racemization	Inversion
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never

6.21 Comparing E2 vs E1

		E1	E2
1	**Nucleophile/Base**	**Neutral, weak, acidic**	**Anionic, strong, basic**
2	Substrate	3º R-X > 2º R-X	3º RX > 2º RX > 1º RX
	Allylic effect…	Allylic Helps	Non-factor
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry	Non-selective	Trans requirement
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never
9	Orientation	Zaitsev's Rule: Prefer more substituted alkene	Zaitsev's Rule: Prefer more Substituted alkene (assuming trans requirement permits)

Comparing S$_N$2 vs S$_N$1 vs E2 vs E1: How Do I Predict Which Happens When?

Step 1: **Check nucleophile/base**.
- If **neutral**, then **S$_N$1/E1** → mixture of both
- If **anionic**, then **S$_N$2/E2.**

Step 2: If **anionic**, and in the **S$_N$2/E2** pool, then **Check the substrate**.
- 1º → **S$_N$2**
- 2º → **S$_N$2/E2 mixture.**   Often more **S$_N$2**, but not reliable…
- 3º → **E2**

Notes:

| 1º R-X	S$_N$2 only	No E2 or S$_N$1/E1 (cation too lousy for S$_N$1/E1; S$_N$2 too fast for E2 to compete)
3º R-X	E2 (anionic) or S$_N$1/E1 (neutral/acidic)	No S$_N$2 (sterics too lousy)
2º R-X	mixtures common	

Ch. 7 Structure and Synthesis of Alkenes

C. E-Z Nomenclature (7-5)
- Each carbon of an alkene has two attachments.
    1. Identify which of the two attachments on the left alkene carbon has higher priority.
    2. Then identify which attachment on the right alkene carbon has higher priority.
        - "Z" ("zusammen" = "together"): the priority attachments are cis
        - "E" ("entgegan = "opposite"): the priority attachments are trans
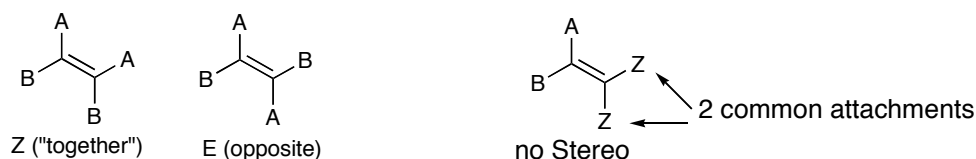
When does E/Z apply?
1. If either alkene carbon has two common attachments, than stereo doesn't apply
2. For tri- or tetrasubstituted alkenes (3 or 4 non-hydrogen attachments), E/Z must be used if there is stereochemistry
3. For di-substituted alkenes (one H on each alkene carbon), either E/Z or cis/trans designation can be used

7.7 Alkene Stability Pattern
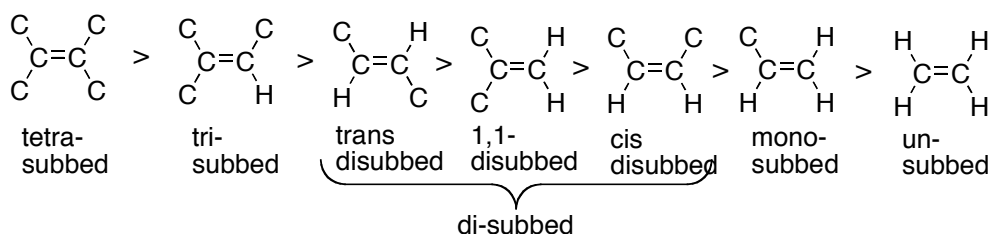
A. Increasing Substitution (# of non-hydrogens directly attached to alkene carbons) → Increased Stability
- Why? Electronic Reasons.
    o Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds. (One carbon doesn't really "get" as much of the other carbon's electron as is the case in a nice sigma bond).
    o Since alkyl groups are electron donors, they stabilize electron-deficient alkene carbons.
    o Analogous to why electron-donating alkyls give the $3° > 2° > 1°$ stability pattern for cations and radicals

B. Trans is more stable than cis for 1,2-disubstituted alkenes
- Why?
    o Steric Reasons

Reaction Mechanisms (see p. 310)

A. Recognizing/Classifying as Radical, Cationic, or Anionic

1. Radical
   ▪ initiation requires both energy (either hv or Δ) and a weak, breakable heteroatom-heteroatom bond
      o Cl-Cl, Br-Br, O-O (peroxide), N-Br, etc..

   > 2 Guides for That are Usually Reliable:
   > hv → radical mechanism
   > peroxides → radical mechanism

2. Anionic
   ▪ **a strong anion/base appears in the recipe**
   ▪ no strong acids should appear in the recipe
   ▪ mechanisms should involve anionic intermediates and reactants, not strongly cationic ones
      • (except for do-nothing spectators like metal cations)
   ▪ The first step in the mechanism will involve the strong anion/base that appears in the recipe

3. Cationic
   ▪ **a strong acid/electrophile appears in the recipe**
   ▪ no strong anion/base should appear in the recipe
   ▪ mechanisms should involve cationic intermediates and reactants, not strongly anionic ones
      • (except for do-nothing spectators like halide or hydrogen sulfate anions)
   ▪ The first step in the mechanism will involve the acid that appears in the recipe. The last step will often involve a deprotonation step. Often the main step occurs in between the proton-on and proton-off steps

B. Miscellaneous Mechanism Tips

   1. Keep track of hydrogens on reacting carbons
   2. **Each step in a mechanism must balance**
   3. The types of intermediates involved (cation, anion, or radical) should be consistent with the reaction classification above
      a. **If the reaction is cationic, don't show anionic intermediates**
      b. **If the reaction is anionic, don't show cationic intermediates**
   4. Usually conditions are ionic.
   5. **Use a reactive species, whether strong anion or an acid, to start the first step**
      a. **If acidic, first step will involve protonation of the organic**
      b. **If anionic, the first step will involve the anion attacking the organic.**
   6. While it isn't always easy to figure out what is a good mechanism, you should often be able to eliminate an unreasonable mechanism.

Chapter 7 Reactions and Mechanisms, Review

E2
On
R-X,
Normal
Base

Br → NaOCH$_3$ (Normal base) → + H−OCH$_3$

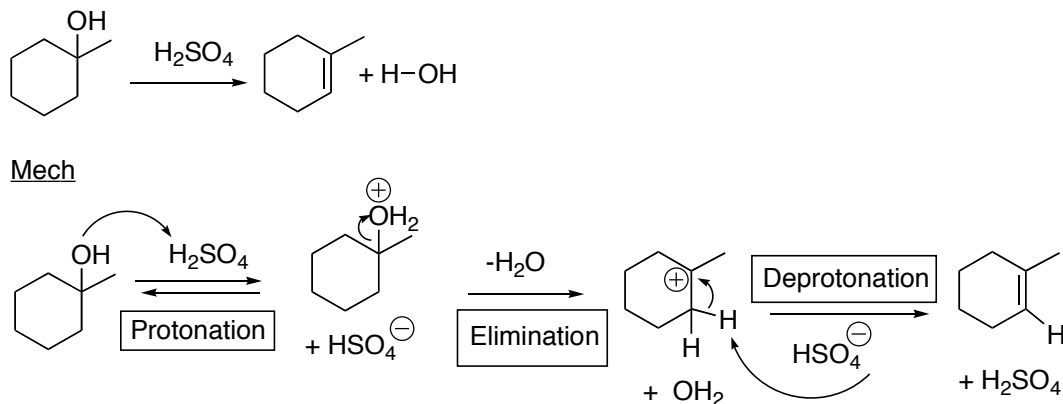Mech: (mechanism diagram) → + H−OCH$_3$ + Br$^{\ominus}$
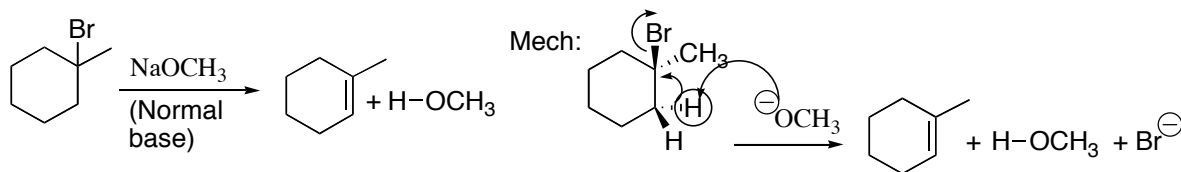
Notes
1. Trans hydrogen required for E2
2. Zaytsev elimination with normal bases
3. For 3° R-X, E2 only. But with 2° R-X, S$_N$2 competes (and usually prevails)
4. Lots of "normal base" anions.

E2,
On
R-X, Bulky
Base

Br → NEt$_3$ or KOC(CH$_3$)$_3$ (Bulky bases) →

Mech: (mechanism diagram) → + Et$_3$NH$^{\oplus}$ Br$^{\ominus}$
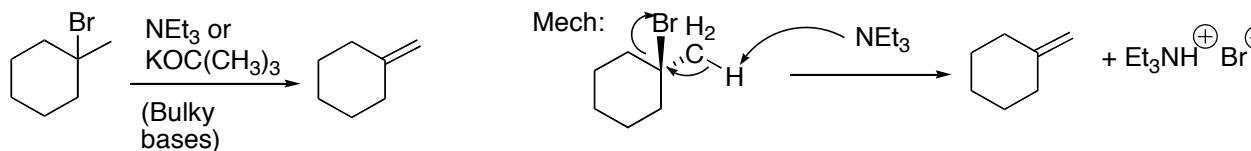
Notes:
1. Hoffman elimination with Bulky Bases
2. E2 dominates over S$_N$2 for not only 3° R-X but also 2° R-X
3. Memorize NEt$_3$ and KOC(CH$_3$)$_3$ as bulky bases.
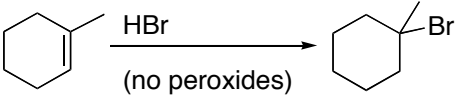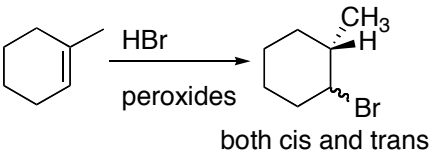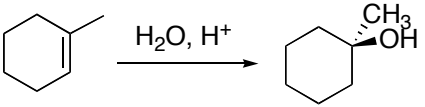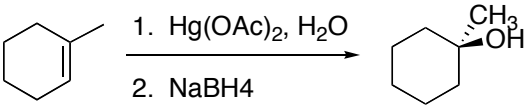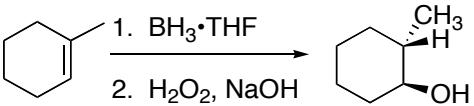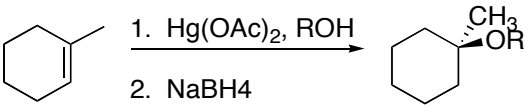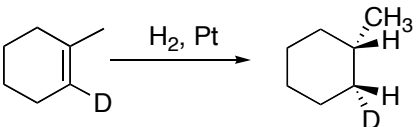
Acid-
Catalyzed
E1-
Elimination
Of
Alcohols

OH → H$_2$SO$_4$ → + H−OH

Mech

OH → H$_2$SO$_4$ / Protonation → $\overset{\oplus}{O}H_2$ + HSO$_4^{\ominus}$ → -H$_2$O / Elimination → (cation) + OH$_2$ → Deprotonation / HSO$_4^{\ominus}$ → + H$_2$SO$_4$

Notes:
1. Zaytsev elimination
2. Cationic intermediate means 3° > 2° > 1°
3. 3-Step mechanism

Summary of Alkene Reactions, Ch. 8.
Memorize Reaction, Orientation where Appropriate, Stereochemistry where Appropriate, and Mechanism where Appropriate.

-all are drawn using 1-methylcyclohexene as a prototype alkene, because both orientation and stereochemistry effects are readily apparent.

		Orientation	Stereo	Mechanism
1	HBr (no peroxides)	Markovnikov	None	**Be able to draw completely**
2	HBr peroxides both cis and trans	Anti-Markovnikov	**Nonselective. Both cis and trans**	**Be able to draw propagation steps.**
3	H_2O, H^+	Markovnikov	None	**Be able to draw completely**
4	1. $Hg(OAc)_2$, H_2O 2. $NaBH4$	Markovnikov	None	Not responsible
5	1. $BH_3 \cdot THF$ 2. H_2O_2, NaOH	Anti-Markovnikov	**Cis**	Not responsible
6	1. $Hg(OAc)_2$, ROH 2. $NaBH4$	Markovnikov	None	Not responsible
7	H_2, Pt	None	**Cis**	Not responsible

	Orientation	Stereo	Mechanism
8 Br₂ (or Cl₂) → CH₃, Br, H, Br	None	**Trans**	**Be able to draw completely**
9 Br₂, H₂O (or Cl₂) → CH₃, OH, H, Br	Markovnikov	**Trans**	**Be able to draw completely**
10 PhCO₃H → CH₃, O, H	None	**Cis**	Not responsible
11 CH₃CO₃H / H₂O → CH₃, OH, H, OH	None	**Trans**	**Be able to draw acid-catalyzed epoxide hydrolysis**
12 OsO₄, H₂O₂ → CH₃, OH, OH, H	None	**Cis**	Not responsible
13 1. O₃ 2. Me₂S → (ketone + aldehyde)	None	None	Not responsible
14 KMnO4 → (ketone + carboxylic acid)	None	None	Not responsible

Note: H-bearing alkene carbon ends up as aldehyde.

H-bearing alkene carbon ends as carboxylic acid

Summary of Mechanisms, Ch. 7 + 8.
Alkene Synthesis and Reactions.

1

HBr

(no peroxides)

Protonate

Cation
Capture

+ Br⁻
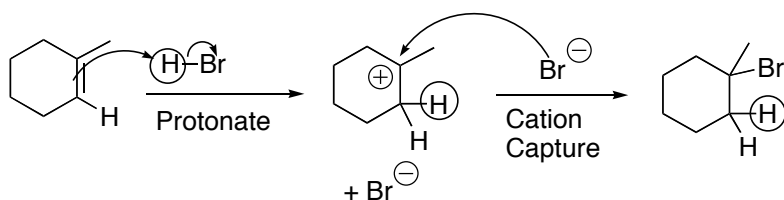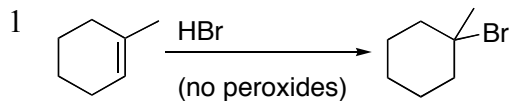
Note: For unsymmetrical alkenes,
protonation occurs at the <u>less</u>
substituted alkene carbon so that
the <u>more</u> stable cation forms
(3° > 2° > 1°), in keeping with the
product stability-reactivity principle

CH$_3$ CH$_3$

vs.

3°   2°

2

HBr

peroxides

both cis and trans

• Br

Brominate

H−Br

Hydrogen
Transfer

+ • Br
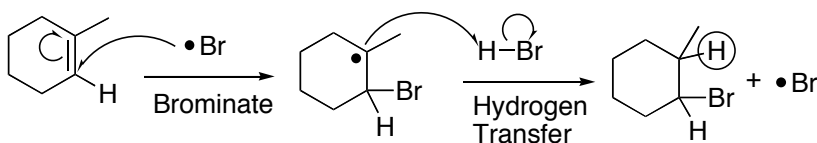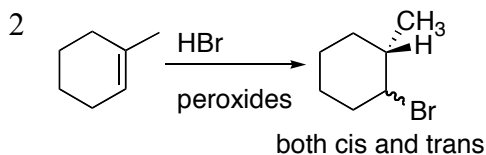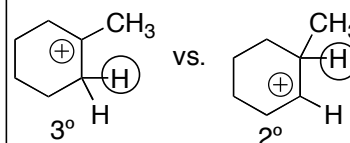
Note 1: For unsymmetrical alkenes,
bromination occurs at the <u>less</u>
substituted alkene carbon so that
the <u>more</u> stable radical forms
(3° > 2° > 1°), in keeping with the
product stability-reactivity principle

CH$_3$ CH$_3$

vs.

3°   2°
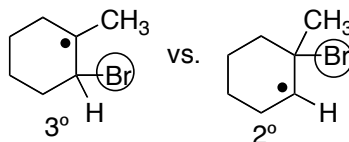
Note 2: Hydrogenation of
the radical comes from either
face, thus cis/trans
mixture results

top

cis

bottom

trans

3

H$_2$O, H⁺

H⁺

Protonate

OH$_2$

Cation
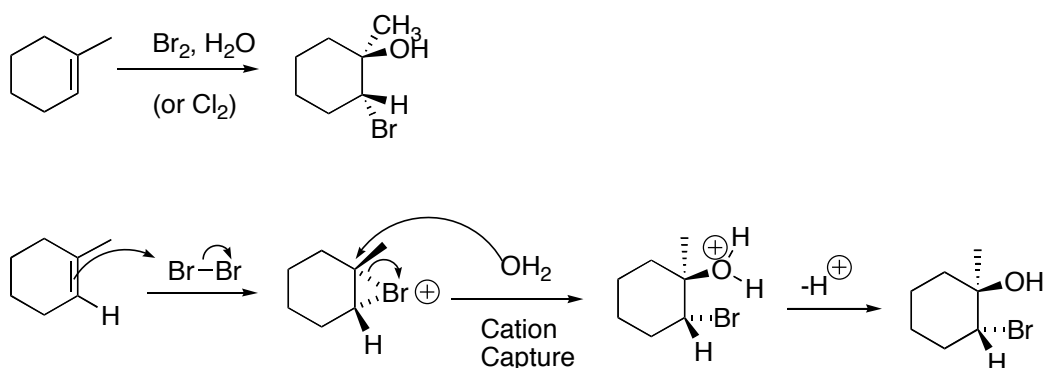Capture

-H⁺
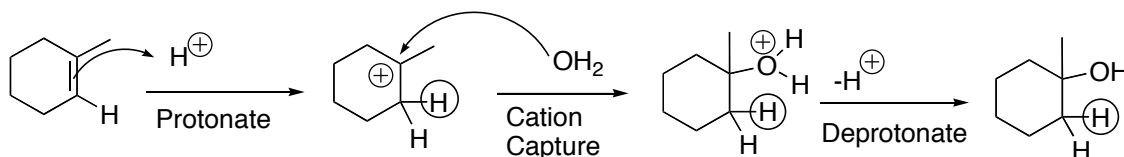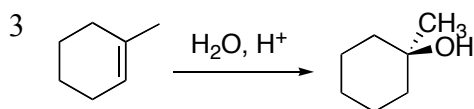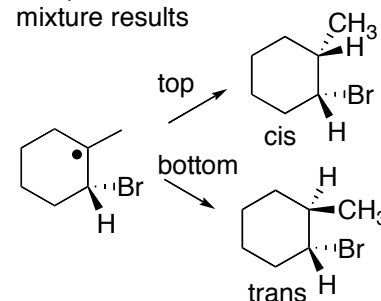
Deprotonate

Note: For unsymmetrical alkenes, protonation again occurs at the <u>less</u> substituted end of the
alkene, in order to produce the <u>more</u> stable radical intermediate (3° > 2° > 1°)

8
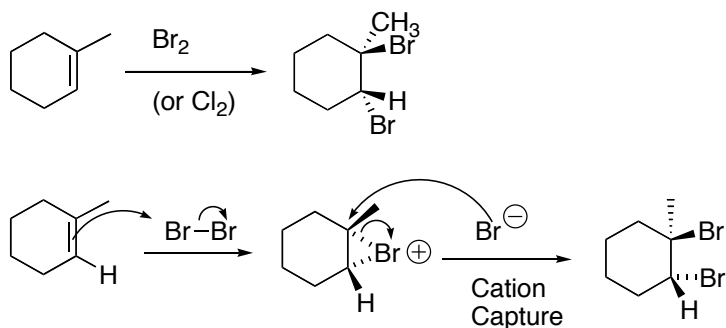
3 Notes
1. Cation intermediate is cyclic bromonium (or chloronium) ion
2. The nucleophile captures the bromonium ion via backside attack
-this leads to the trans stereochemistry
3. The nucleophile attacks the bromonium ion at the *more* substituted carbon

9

4 Notes
1. Cation intermediate is cyclic bromonium (or chloronium) ion

2. The nucleophile captures the bromonium ion via backside attack (ala SN2)
-this leads to the trans stereochemistry

3. The nucleophile attacks the bromonium ion at the *more* substituted carbon
-this explains the orientation (Markovnikov)
a. There is more + charge at the more substituted carbon
b. The Br-C bond to the more substituted carbon is a lot weaker
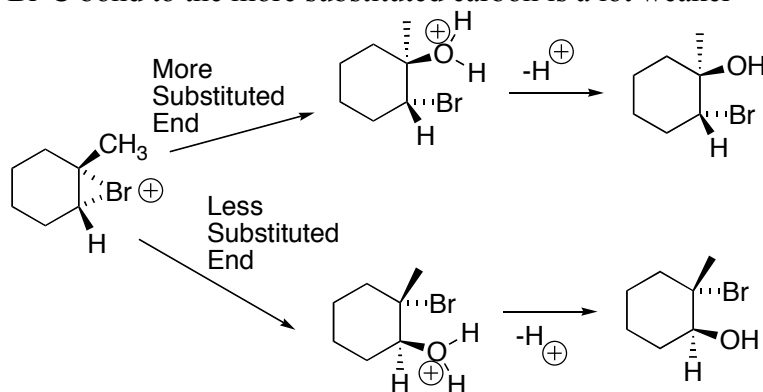
4. Alcohols can function in the same way that water does, resulting in an ether OR rather than alcohol OH.

Ch. 15 Conjugated Systems

The General Stabilization Effect of Conjugation (Section 15.1, 2, 3, 8, 9)

		Conjugated (more stable)	Isolated (less stable)	Notes:
1	Cations			
2	Radicals			
3	Anions			
4	Dienes			
5	Ethers	sp^2, not sp^3!!	sp^3	An N or O next to a double bond becomes sp^2. An isolated N or O is sp^3
6	Amines	sp^2	sp^3	
7	Esters	sp^2	sp^3	
8	Amides	sp^2	sp^3	Very special, chapter 23, all of biochemistry, proteins, enzymes, etc.
9	Oxyanions (Carboxylates)	sp^2	sp^3	Very special, chapter 21
10	Carbanions (Enolates)	sp^2	sp^3	Very special, chapter 22
11	Aromatics			Very special, chapters 16 + 17

Conjugation: Anything that is or can be sp^2 hybridized is stabilized when next to π bonds.
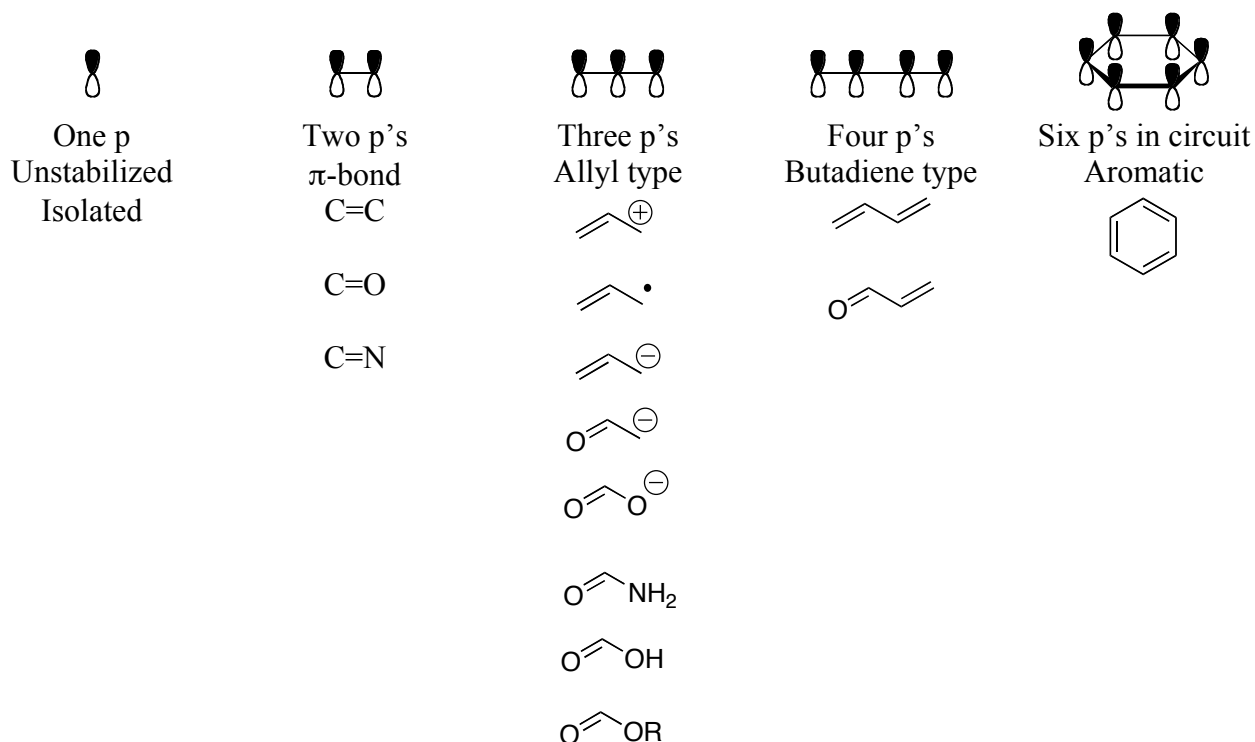- oxygens, nitrogens, cations, radicals, and anions

---

Notes:
1. Any atom that can be sp^2 will be sp^2 when next to a double bond
2. "Conjugation" is when sp^2 centers are joined in an uninterrupted series of 3 or more, such that an uninterrupted series of p-orbitals is possible
3. Any sp^2 center has one p orbital

<u>Impact of Conjugation</u>
4. **Stability:** Conjugation is **stabilizing** because of p-orbital overlap (Sections 15.2, 4, 7)
   • Note: In the allyl family, **resonance = conjugation**

One p	Two p's	Three p's	Four p's	Six p's in circuit
Unstabilized	π-bond	Allyl type	Butadiene type	Aromatic
Isolated	C=C			
	C=O			
	C=N			

5. **Reactivity:** Conjugation-induced stability impacts **reactivity** (Sections 15.4-7)
    • If the **product** of a rate-determining step is stabilized, the reaction rate will go **faster** (product stability-reactivity principle)
        o Common when allylic cations, radicals, or carbanions are involved
    • If the **reactant** in the rate-determining step is stabilized, the reaction rate will go **slower** (reactant stability-reactivity principle)
        o Why aromatics are so much less reactive
        o Why ester, amide, and acid carbonyls are less electrophilic than aldehydes or ketones

6. **Molecular shape** (Sections 15.3, 8, 9)
    • The p-orbitals must be aligned in parallel for max overlap and max stability
    • The sp^2 centers must be coplanar
        All four sp^2 carbons must be flat for the p's to align
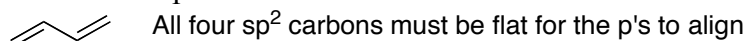
7. **Bond Length:** Bonds that look like singles but are actually between conjugated sp^2 centers are **shorter** than ordinary single bonds

1.54 A normal single   1.33 A normal double   1.48 A = Shortened and Strengthened conjugated single   Shortened and Strengthened   Shortened and Strengthened   Shortened and Strengthened
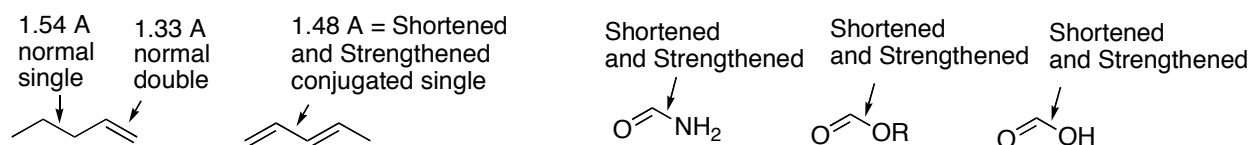
    • In amides, esters, and acids, the bond between the carbonyl and the heteroatom is shortened

8. **Bond Strength:** Bonds that look like singles but are actually between conjugated sp^2 centers are **stronger** than ordinary single bonds

9. **Bond Rotation Barrier:** Bonds that look like singles but are actually between conjugated have much larger rotation barriers than ordinary single bonds
   - Because in the process of rotating, the p-overlap and its associated stability would be temporarily lost

10. **Hybridization:** Conjugated sp^2 atoms have both sp^2 and p orbitals. You should always be able to classify the hybridization of **lone pairs on nitrogen and oxygen**.
    - **Isolated** oxygens or nitrogens: sp^3 atom hybridization, sp^3 lone-pair hybridization, and tetrahedral, 109º bond angles
    - **Conjugated nitrogens**: sp^2 atom hybridization, **p lone-pair hybridization (needed for conjugation**), and 120º bond angles
    - **Conjugated oxygens**: sp^2 atom hybridization, **one p lone-pair hybridization** (needed for conjugation), **one sp^2 lone-pair**, and 120º bond angles

15.2 Diene Stability and the Stability of other Acyclic Systems with 2 Elements of Unsaturation

Stability Factors for Simple Dienes:
1. Isolated versus Conjugated: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.

15.4 Stability of Allylic/Benzylic (Conjugated) Cations
Stability Factors for Cations:
1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
   - Conjugation/allylic is more important than the substitution pattern of an isolated cation (i.e. 1º allylic > 3º isolated)

Allylic Cations, Resonance, Charge Delocalization, and Allylic Symmetry/Asymmetry
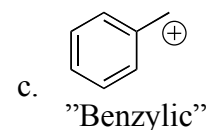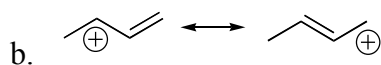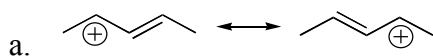
1. Two resonance structures each (at least)
2. Charge is delocalized, shared
3. Allylic cations can be symmetric or asymmetric
4. When an allylic cation is asymmetric, it's helpful to evaluate which form would make a larger contribution to the actual hybrid
   - Cation substitution is more important than alkene substitution

Impact of Allylic Cation Resonance on Reactivity and Product Formation

1. **Rates**: Resonance/conjugation stability enhances rates when cation formation is rate-determining
2. **Product Distribution:** Product mixtures often result if an allylic cation is asymmetric.
   - The two different resonance structures can lead to different products.
   - When two isomeric products can form from an allylic cation, consider two things:
     1. Which product is more stable?
        - This will impact "product stability control" = "thermodynamic control" = "equilibrium control"
        - To assess product stability, focus on the alkene substitution
     2. Which resonance form of the cation would have made a larger contribution?
        - This will often favor "kinetic control", in which a product which may not ultimately be the most stable forms preferentially
3. **Position of Cation Formation**: When a conjugated diene is protonated, consider which site of protonation would give the best allylic cation.

Sections 15.5,6 **1,2 vs. 1,4 Addition to Conjugated Dienes: "Kinetic" vs. "Thermodynamic" Control**
Note: "Thermodynamic Control" = "Product-Stability Control" = "Equilibrium Control"
- This is when **the most stable** of two possible **products** predominates. Either of two factors can cause this:
  - **Transition State:** The most stable product is formed fastest via the most stable transition state (normally true, but not always)
  - **Equilibrium**: Even if the most stable product is not formed fastest, if the two products can equilibrate, then **equilibrium** will favor the most stable product
Kinetic Control: If **the less stable** of two possible products predominates.
- This will always require that for some reason the less stable product forms via a better transition state (transition-state stability/reactivity principle). Common factors:
  - Charge distribution in an allylic cation or radical. The position of charge in the major resonance contributor may lead to one product, even though it may not give the most stable product.
  - Proximity of reactants. In an H-X addition to a diene, often the halide anion is closer to one end of the allylic cation than the other, resulting in "1,2 addition" over "1,4 addition".
  - Steric factors. With a bulky E2 base, for example, the transition state leading to what would be the more stable Zaytsev alkene has steric problems, so it gives the Hoffman alkene instead.

15.7 Allylic/Benzylic Radicals
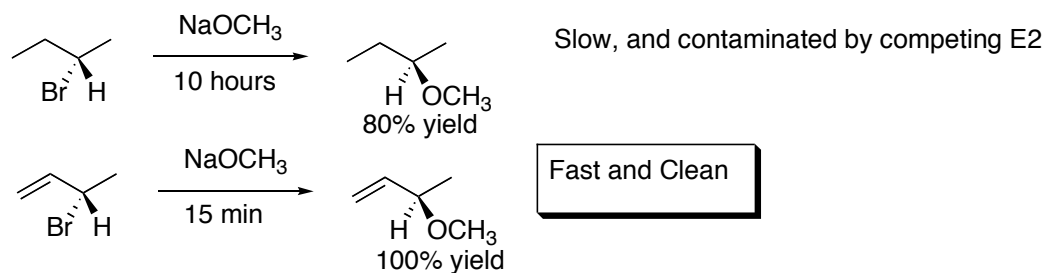Stability Factors for Radicals:
1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
   - Conjugation/allylic is more important than the substitution pattern of an isolated cation

Impact of Radical Resonance on Reactivity and Product Formation
1. **Rates**:
2. **Product Distribution:** Product mixtures often result if an allylic radical is asymmetric.
3. **Position of Radical Formation**

Section 15.10   S$_N$2 on Allylic, Benzylic Systems Are Really Fast
Ex.

NaOCH$_3$

10 hours

Br H

H OCH$_3$
80% yield

Slow, and contaminated by competing E2

NaOCH$_3$
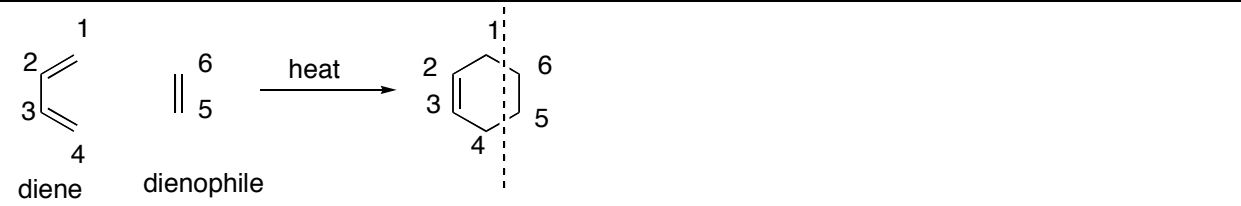
15 min

Br H

H OCH$_3$
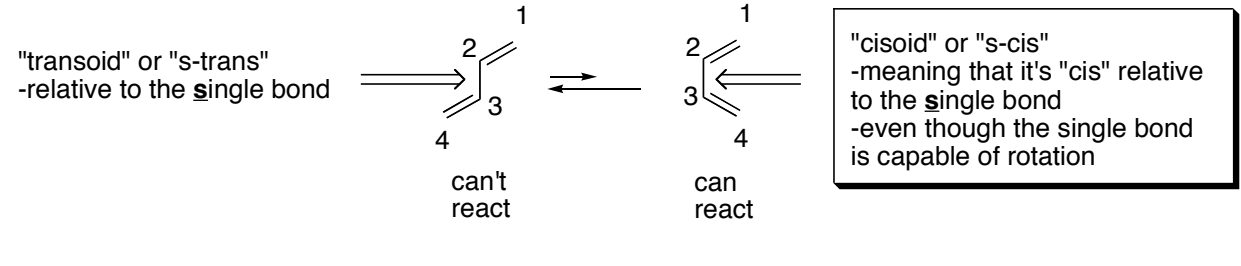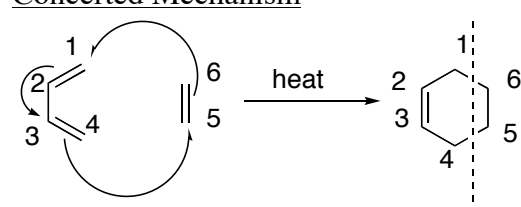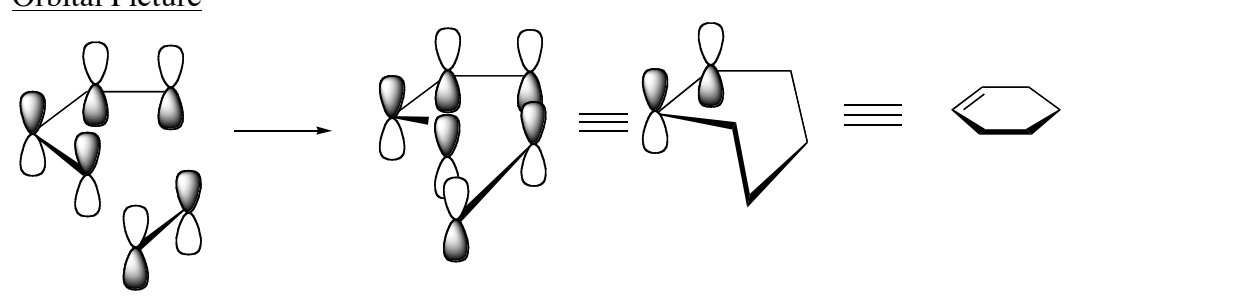100% yield

Fast and Clean

Why? Because the backside-attack transition-state is stabilized by conjugation!
(Transition state-stability-reactivity principle).

Br H

Br

H$_3$CO   H

H OCH$_3$
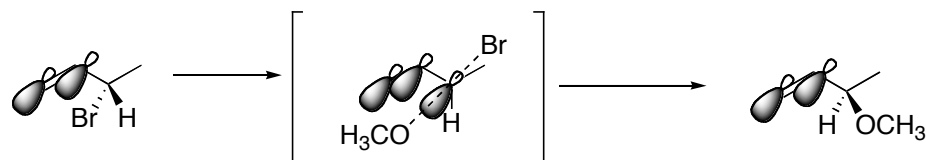
1. Neither the product nor the reactant has conjugation, so it's hard to see why conjugation should apply
2. However, in the 5-coordinate T-state the reactive carbon is sp^2 hybridized
▪ the nucleophile and the electrophile are essentially on opposite ends of a temporary p-orbital.
3. That transient sp^2 hybridization in the transition-state is stabilized by π-overlap with the adjacent p-bond.
4. This stabilization of the transition-state lowers the activation barrier and greatly accelerates reaction

Section 15.11   The Diels-Alder Reaction. The Reaction of Conjugated Dienes (Dienes) with Electron-Poor Alkenes (Dienophiles) to make Cyclohexenes.

Quick Overview Summary

1.	 diene dienophile heat →
2.	s-cis diene conformational requirement: The diene must be locked or be able to single-bond rotate it's way into the "s-cis" conformation in order to react "transoid" or "s-trans" -relative to the **s**ingle bond can't react can react "cisoid" or "s-cis" -meaning that it's "cis" relative to the **s**ingle bond -even though the single bond is capable of rotation

3.	Rate Factors
	1. Dienophile
	   ▪ activated by electron withdrawing groups ("W" or "EWG") for electronic reasons
	2. Diene:
	   ▪ Deactivated by substituents that make it harder or less stable to exist in the s-cis conformation. This is true when a diene alkene has a Z-substituent.
	   ▪ Steric factors equal, activated somewhat by electron donating groups ("D" or "EDG")

4.	Concerted Mechanism heat → All bond making and breaking happens at once: *3 π-bonds break *2 σ-bonds and 1π-bond form The diene is really the "nucleophile" (HOMO) The dienophile is really the "electrophile" (LUMO)
5.	Orbital Picture

6.	Product Prediction Highlights
	   ▪ Try to match up the 4 diene and 2 dienophile carbons with the product
	      o The product double bond will be between C2 and C3 of the diene
	   ▪ Substituents are spectators
	   ▪ 1,4/1,2 Rule: when asymmetric dienes react with asymmetric dienophiles
	      o Match δ- end of nucleophilic diene with δ+ end of electrophilic dienophile
	   ▪ For disubstituted dienophiles:
	      o cis-substituents end up cis, and trans-substituents end up trans

A. The General Diels-Alder Reaction
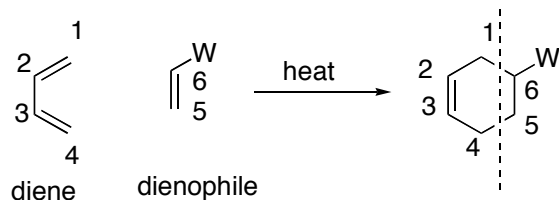
diene   dienophile

1. **Electronics**: The diene HOMO reacts with the dienophile LUMO
   - Effectively the diene is the nucleophile and the dienophile functions as the electrophile
2. The **dienophile** usually **needs an electron-withdrawing attachment** ("W") (at least one)
   - This makes the dienophile more electrophilic
   - Electron Withdrawing Groups to Memorize:

   - Keys:
     - The atom that is connected to the alkene has $\delta+$ charge
     - Anything with a double-bond to a heteroatom tends to have this
       - $C=O, C\equiv N, N=O, S=O$

B. Predicting Products When the Diene or the Dienophile (or both) is Symmetric
   1. Always make a cyclohexene 6-ring product
   2. Number the diene from 1-4, and identify those four carbons in the product ring.
   3. A double bond in the product will always exist between carbons 2 and 3.
   4. Any substituents on the diene or dienophile are spectators: they will be attached to the same carbons at the end.
   - Beware of cyclic dienes
   - Beware of dienes that are drawn in their zigzag s-trans form, but could react following rotation into an s-cis form

C. Stereochemistry: For Cis- or Trans- **Disubstituted Dienophiles**
- Both carbons of a disubstituted dienophile usually turn into stereocenters.
1. **Cis in → cis out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene
2. **Trans in → trans out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene
- **Note**: this is for the **dienophile only**. The diene alkenes may also have substitution such that one or both diene double bonds are cis or trans, but the "cis-in-cis-out" guideline does not apply to the diene.

D. Structural Factors for **Dienes**

1. s-cis (cisoid) diene conformational requirement (p 682): The diene must be locked "s-cis" or be able to single-bond rotate it's way into the "s-cis" (cisoid) conformation in order to react

"transoid" or "s-trans"
-relative to the **s**ingle bond

can't
react

can
react

"cisoid" or "s-cis"
-meaning that it's "cis" relative to the **s**ingle bond
-even though the single bond is capable of rotation
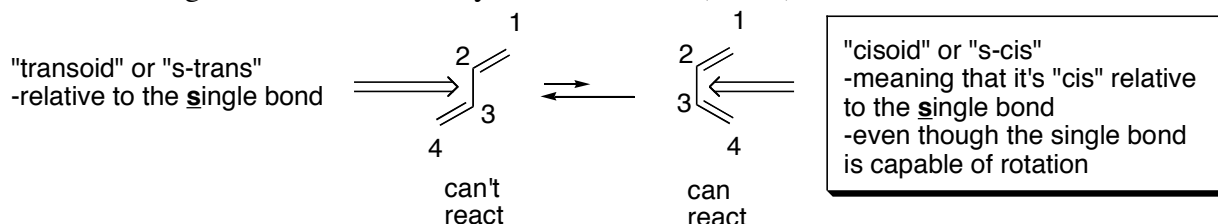
F. Predicting Products When **Both Diene and Dienophile are Asymmetric** (****) (15-11B)
If either component is symmetric, you don't have structural isomer issues.
- If both ends of diene are the same, it doesn't matter which adds to which end of dienophile
- If both ends of dienophile are the same, it doesn't matter which adds to which end of diene

If both components are asymmetric: two structural isomers are possible; one dominates.

****** A 1,2 or 1,4 relationship is always preferred over a 1,3 relationship, if possible   *****
- Although ortho/meta/para terms don't really correctly apply to cyclohexenes, many students remember this is an "**ortho/para preferred**" rule, to avoid number confusion

Ch. 16 Aromatic Compounds

16.1,2 Structure and Unique Properties of Benzene

C_6H_6

A   **B**   **C**

2 Resonance Structures
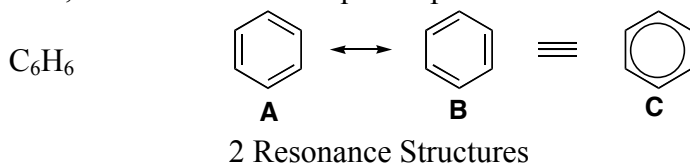
Notes on Pictures and Structural Features
1. All 6 carbons are sp^2, with one p orbital each
2. 120º angles, so all 6 carbons and each of their attached hydrogens are all co-planar.
3. Perfectly flat.
4. Perfect 120º angles, no angle strain whatsoever
5. Complete symmetry
6. Each C-C bond is equal in length and strength
7. Each C-C bond is longer than a normal double but shorter than a normal single bond

Normal Bond Lengths:	C-C: 1.54A	C=C: 1.34 A	Benzene CC: 1.39A

- "1.5" bonds, as we see from resonance.

1. Molecular Orbital for Benzene

Mix to Make
6 Molecular
Orbitals

Benzene: 6 p's

Antibonding

Nonbonding
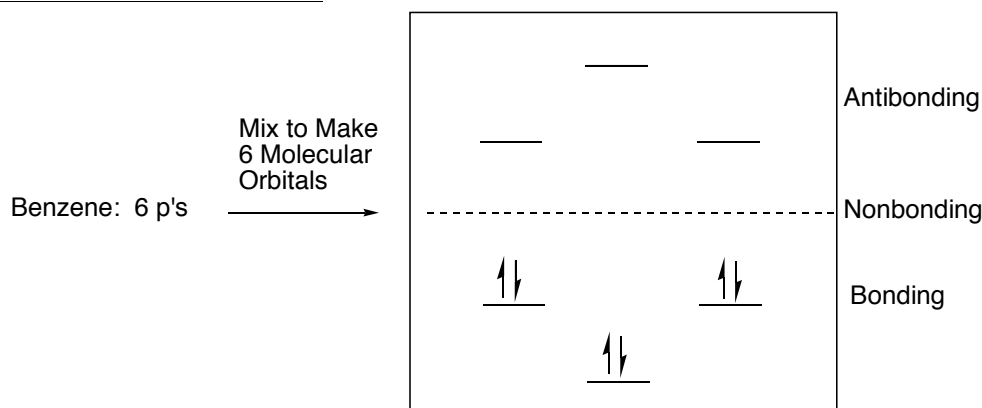
Bonding

- All and only the bonding molecular orbitals are completely filled. Special stability
- But how can you know what the molecular orbitals will look like for other rings?

Frost Diagram/Polygon Rule: For a **complete ring** of sp^2 **centers**,
1. Draw the ring/polygon with a vertex down, basically inside what would be a circle
2. Each apex represents a molecular orbital
3. A horizontal line through the middle of the ring provides the non-bonding reference point
4. Populate the MO's as needed depending on how many π-electrons are available

Molecular Orbital Rules for a cyclic π-system:
1. If all and only bonding molecular orbitals are occupied→ good ("aromatic")
2. If any nonbonding or antibonding MO's are occupied, or if any bonding MO's are not completely occupied → bad, poor stability ("antiaromatic")

- Below nonbonding line → bonding
- Above nonbonding line → antibonding
- On nonbonding line → nonbonding

16.5,6, 7 Aromatic, Antiaromatic, Nonaromatic. **Huckel's Rule**: For a **planar**, **continuous ring** of **p-orbitals**, (sp^2 all around):

- If the number of π-electrons = 2,6,10 etc. (4N + 2) → AROMATIC, STABILIZED
- If the number of π-electrons = 4,8,12 etc. (4N) → Anti-aromatic, destabilized

- Why: the 4N+2 rule always goes with favorable Frost diagrams: bonding and only bonding MO's are always filled.

- Generality: Huckel's Rule applies for cycles, bicycles, ionic compounds, and heterocycles.
a. Cycles (one-ring)   b. Polycycles (2 or more)   c. Ionic rings   d. Heterocycles

Keys to Recognizing Aromatic or Not:
1. Do you have an uninterrupted sp^2 ring?
2. Apply Huckel's Rule: Do you have 2,6,10 etc. π electrons?
3. Applying Huckel's Rule requires that you can accurately count your π-electrons. Be able to count:
   - Anions: contribute 2 π-electrons
   - Cations: contribute 0 π-electrons
   - Heteroatoms (O or N): can provide 2 π-electrons if it helps result in aromatic stability.

16.8 Aromatic Ions
3 common, important Aromatic Ions

15.2 Heterocyclic Aromatics. Memorize 3.
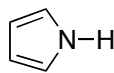
Pyridine   **Pyrrole**   **Furan**
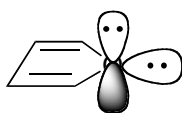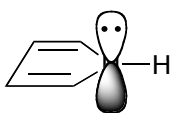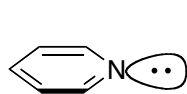
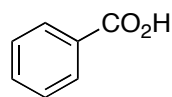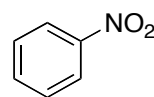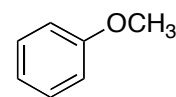Nitrogens: Atom hybridization, Lone-Pair hybridization, and Basicity
- Amine nitrogens are normally basic, but not when the N-lone pair is p-hybridized
- Rule: If a nitrogen lone pair is p (used in conjugation) → nonbasic
- Nitrogen lone-pair basicity: $sp^3 > sp^2 >>> p$

Situations	N-Atom	N-Lone Pair	N-Basicity
1. Isolated	sp^3	sp^3	Normal
2. Double Bonded	sp^2	sp^2	Normal (a little below, but not much)
3. Conjugated (not itself double bonded, but next to a double bond)	sp^2	p	Nonbasic

p-lone pairs are less basic because conjugation stability in the reactant is lost upon protonation.
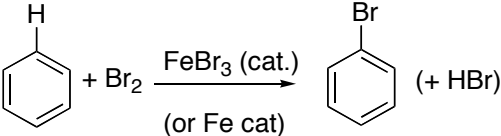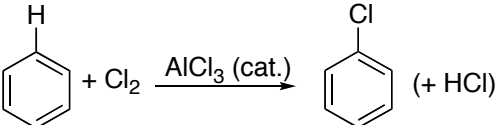
16.13 AROMATIC NOMENCLATURE

1. **Memorize** Special Names.
*   Six Special Monosubstituted Names You Must **Memorize**
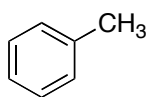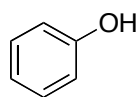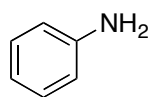
| **Toluene** | **Phenol** | **Aniline** | **Benzoic Acid** | **Nitrobenzene** | **Anisole** |

2. Mono-substituted benzenes, if not one of the special memory names: use "benzene" as core name

3. Di- or polysubstituted aromatics
    a. If one of the "special" memory names can be used, use that as the core name and number with the special substituent on carbon 1.
    b. Special Terms:
        *   "ortho" or o-   1,2 relationship
        *   "meta" or m-   1,3 relationship
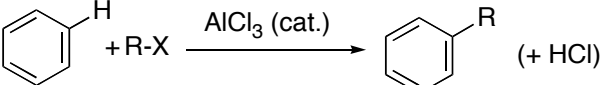   *   "para" or p-   1,4 relationship

5 Major Electrophilic Aromatic Substitution Reactions

	Activating/ Deactivating	Ortho/Para Or Meta Directing	Book

1 Benzene-H + Br_2 →[$FeBr_3$ (cat.) (or Fe cat)] Bromobenzene-Br (+ HBr)   Deactivating   Ortho/Para   17.2

Benzene-H + Cl_2 →[$AlCl_3$ (cat.)] Chlorobenzene-Cl (+ HCl)   Deactivating   Ortho/Para   17.2

The halides are unique in being deactivating but ortho/para directing. All other o/p-directors are activating, and all other deactivating groups are m-directors.   **Mech**
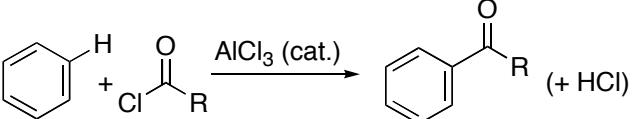
2 Benzene-H + HNO_3 →[H_2SO_4] Nitrobenzene-NO_2 (+ H_2O)   Deactivating   Meta   17.3

The product can be reduced to Ar-NH_2 by Fe/HCl or Sn/HCl. Nitration/Reduction provides an effective way to introduce an NH_2 group. Reduction converts m-directing NO_2 group into an o/p-directing NH_2 group.   **Mech required.**

3 Benzene-H + R-X →[$AlCl_3$ (cat.)] Benzene-R (+ HCl)   **Activating**   Ortho/para   17.10

a. Restricted to 3°, 2°, or ethyl halides. 1° halides suffer carbocation rearrangements.
b. Since product is more active than starting material, polyalkylation is often a serious problem.
c. Fails with strongly deactivated benzenes.

Mech required.

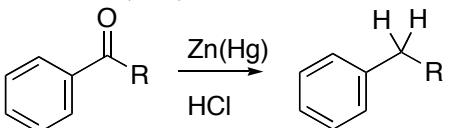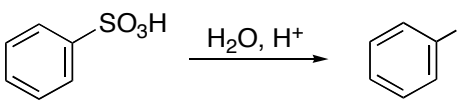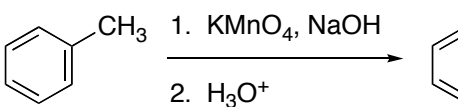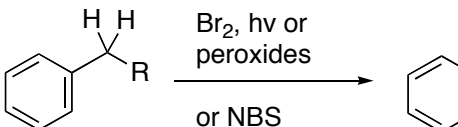**4** Benzene-H + (O=)C(Cl)(R) →[$AlCl_3$ (cat.)] Benzene-C(=O)R (+ HCl)   Deactivating   Meta   17.11
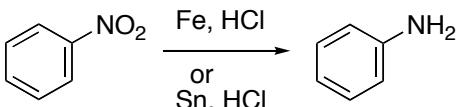
a. The product can be reduced to -CH_2R by Zn(Hg)/HCl.
b. The acylation-reduction sequence provides an effective way to introduce a 1° alkyl group.
c. Reduction converts meta-directing acyl group into an ortho/para-directing alkyl group.

Mech required.

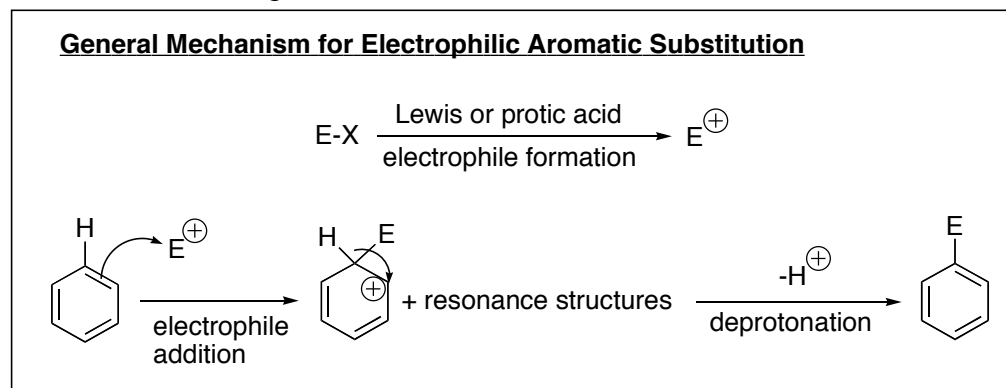**5** Benzene-H + SO_3 →[H_2SO_4] Benzene-SO_3H Deactivating   Meta   17.4

The sulfonyl group is a useful para-blocking group, since it can later be removed upon treatment with H_2O/H^+.   **No mech required.**

5 Major Aromatic Support Reactions

	Activating/ Deactivating	Ortho/Para Or Meta Directing	Book

6

NO_2 $\xrightarrow[\text{Sn, HCl}]{\text{Fe, HCl} \\ \text{or}}$ NH_2 — Activating — Ortho/Para — 19.21

- Reduction converts meta-director into an ortho-para director.
- Fe, Sn, or several other reducing metals can work.   No mech required.

7

$\overset{O}{\underset{R}{\|}}$ $\xrightarrow[\text{HCl}]{\text{Zn(Hg)}}$ $\overset{H\ H}{\underset{R}{}}$ — Activating — Ortho/Para — 17.12

- Clemmensen reduction converts meta-director into an ortho-para director.
- Acylation (#4) followed by Clemmensen Reduction (#7) is the standard method for introducing a 1° alkyl group. (Direct alkylation with a 1° alkyl halide, reaction #3, fails due to cation rearrangement problems…)
                                                             No mech required.

8

SO_3H $\xrightarrow{H_2O, H^+}$ H — ------ — ------ — 17.4

- The sulfonyl group is a useful and reversible para-blocking group, since it can be temporarily put on (reaction 5) but then can be removed later upon treatment with H_2O/H^+ (reaction 8).
- The sulfonation/other reaction/desulfonation sequence is crucial for clean ortho-substitution of an o/p director.
                                                             No mech required.

9

CH_3 $\xrightarrow[\text{2. } H_3O^+]{\text{1. } KMnO_4, NaOH}$ CO_2H — Deactivating — Meta — 17.14

- Oxidation converts ortho/para-director into a meta-director.
- Side alkyl chains longer than methyl can also be oxidized to benzoic acid in the same way, although more time and heat is required.
- For test purposes, just writing $KMnO_4$ will be OK. But the real reaction requires a basic solution for the $KMnO_4$ to work, so an acidic workup step is actually required to isolate the neutral carboxylic acid.
                                                             No mech required.

10

$\overset{H\ H}{\underset{R}{}}$ $\xrightarrow[\text{or NBS}]{\text{Br}_2, \text{hv or} \\ \text{peroxides}}$ $\overset{H\ Br}{\underset{R}{}}$ — ------ — ------ — 17.14

- Bromination occurs via free-radical mechanism.
- It is selective for substitution at the benzylic position because the benzylic radical intermediate is resonance-stabilized.
- Note: keep distinct $Br_2/FeBr_3$ from Br_2/peroxides!
- Product is subject to S_N2 substitutions (benzylic bromides are especially good, better than normal 2° bromides) and E2 eliminations with bulky bases.
- "NBS" is N-bromosuccinimide, which functions just like Br_2/peroxides, but is much more convenient and cleaner because it avoids competing reactions caused by lots of Br_2 and HBr.
                                                             Mech required.

Section 17.1 Electrophilic Aromatic Substitution

General Mechanism for Electrophilic Aromatic Substitution

$$E\text{-}X \xrightarrow[\text{electrophile formation}]{\text{Lewis or protic acid}} E^{\oplus}$$

Three Resonance Structures for Every Electrophilic Aromatic Substitution
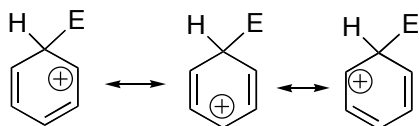
Additions to Substituted Benzenes. The Effect of Substituents on Reactivity Rates and the Position of Substitution. (17.4, 5, 6)

Three Issues
1. Activators versus Deactivators
2. Electron Donors versus Electron Withdrawing Groups
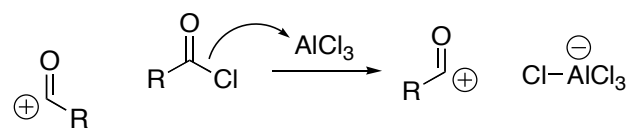3. Ortho-Para directors versus Meta Directors

Fact: The rate determining step is the cation addition step
▪ The transition state much resembles the carbocationic product of that step
▪ What's good for the cation is good for the reaction rate (product stability-reactivity principle)

Cation stabilizers = **electron donors** → good for cations → good for rates = **activators**
Cation destabilizers = **electron withdrawers** → bad for cations → bad for rates = **deactivators**

Formation of the Active Electrophiles

1. In each case, the cationic form of the thing that adds must be generated
2. The arrow pushing in the E+ generation always involves an arrow going from the cation precursor to the Lewis or Bronsted acid
3. For class, we will focus on sulfuric acid as Bronsted acid, and $AlCl_3$ or $FeBr_3$ as Lewis acids
   - But in an actual synthesis lab, other Bronsted or Lewis acids are available and may sometimes provide superior performance.
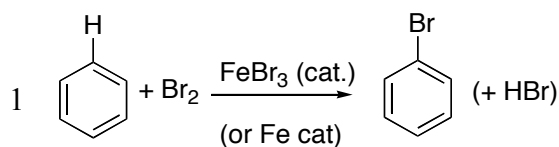
Cation Needed
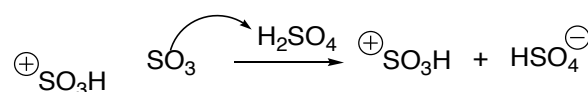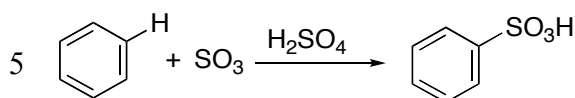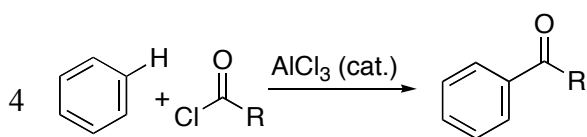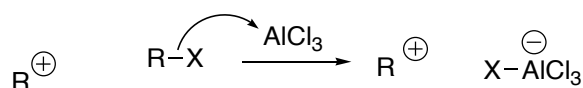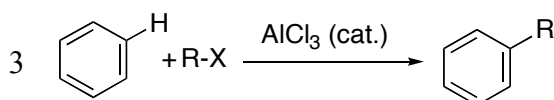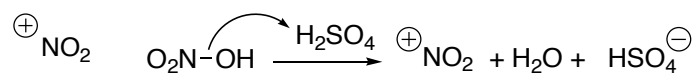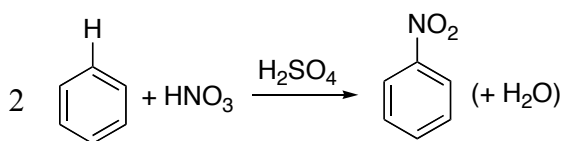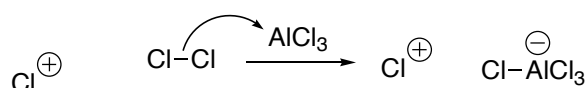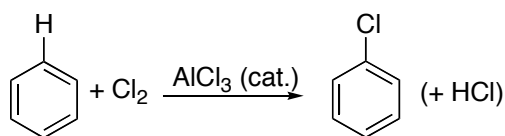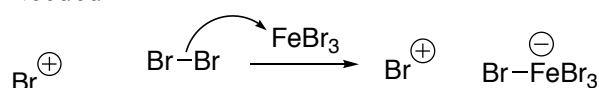
The Situation with an Electron **Donor**/Cation Stabilizer (Ortho-Para Director) (Section 17-6)

Ortho
Addition
Relative to a
Donor

Boxed form is especially good electronically.
Ortho addition often has some steric destabilization.

Meta
Addition
with a
Donor

None of the three resonance forms benefits from the electron donor.

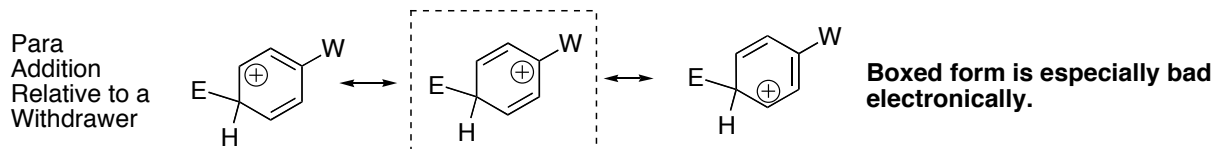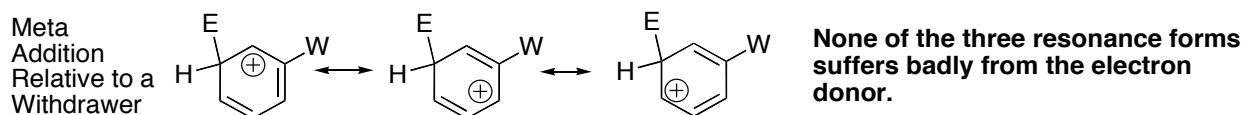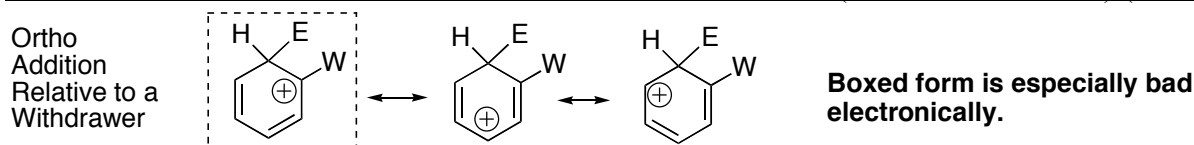Para
Addition
Relative to a
Donor

Boxed resonance form is especially benefitted electronically.
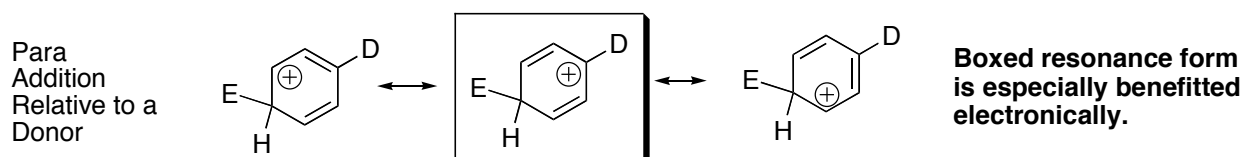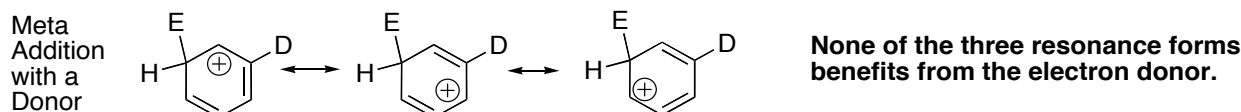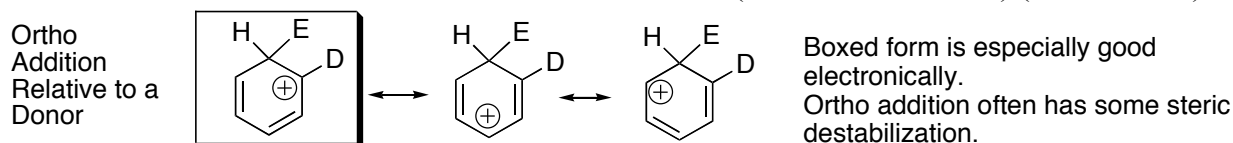
Summary: Electronic Factor: An electron donor (cation stabilizer) is especially beneficial electronically when the electrophile adds ortho or para relative to the donor.
   ▪ **Thus donors are ortho/para directors.**
Steric Factor: Ortho addition relative to the donor is always destabilized somewhat by steric interactions.   Thus, when addition para relative to the donor does not involve any steric interactions, (usually but not always the case), para addition is faster than ortho addition.

The Situation with an Electron **Withdrawer**/Cation Stabilizer (Ortho-Para Director) (12.13)

Ortho
Addition
Relative to a
Withdrawer

Boxed form is especially bad electronically.

Meta
Addition
Relative to a
Withdrawer

None of the three resonance forms suffers badly from the electron donor.

Para
Addition
Relative to a
Withdrawer

Boxed form is especially bad electronically.

Summary: An electron withdrawer (cation destabilizer) is especially harmful electronically when the electrophile adds ortho or para relative to the withdrawer. Thus withdrawers are meta directors. Not because meta is that good; it's just not as bad as ortho or para.
Note: Meta is still deactivated somewhat, it's just not as slow as ortho or para addition.

Seeing the Mechanism and Resonance Structures from Different Perspectives
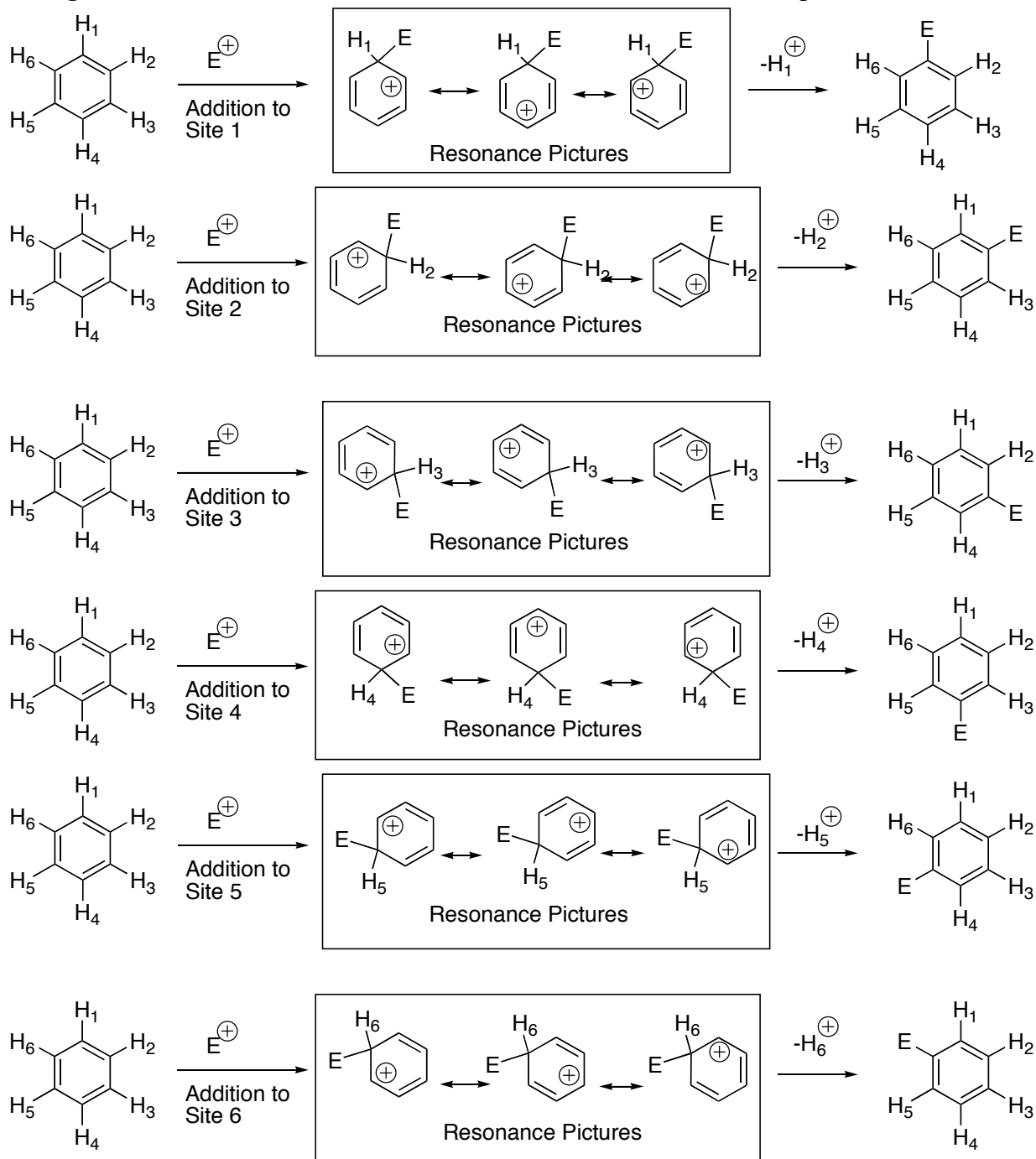
NOTES:
1. These focus on drawing the resonance structures and seeing how the positive charge is delocalized in the cation.
2. Notice that regardless of which position the electrophile adds to, the positive charge still ends up delocalized onto the positions ortho and para **relative to the site of addition**
3. Notice that the site of addition does <u>not</u> have positive charge
4. Notice that the hydrogen that is lost is from the same carbon where the electrophile adds, not from an ortho carbon

4 Classes of Substituents: Memorize! (Sections 17-6-8)

Donating?	Memorize the list	Activating/Deactivating	Directing Effect
	OH, OR, NH_2, NHR, NR_2	Strong Activators	Ortho/para directors
	R, Ar	Weak Activators	Ortho/para directors
	Cl, Br	Weak Deactivators	Ortho/para directors
	Carbonyl, NO_2, CN, SO_3H	Strong Deactivators	Meta directors

Note: Halogens are a special case that are ortho-para directors despite being deactivating
Otherwise, the following pattern is general:
▪ Activator = ortho-para director (and vice versa,with exception of halides)
▪ Meta director = deactivator (and vice versa,with exception of halides)

Rules for Additions to Disubstituted/Polysubstituted Aromatics (17.9)
1. Effects are additive if both direct to the same spot
2. If there is a conflict of interest, the more activating group controls the outcome
   ▪ You need to know the relative activating/deactivating strengths!
3. Steric considerations: if two substituents have a 1,3 (meta) relationship, addition in between
   (to give a 1,2,3 relationship) is prohibitively slow for steric reasons

---

Some Special "Combination" Sequences, to indirectly install NH_2 or CH_2R groups, or to install a new group ortho to an ortho-para director without competition from para-insteallation.

2-Step Route to Add NH_2:
1) HNO_3, H_2SO_4 (have NO_2 group, which is a meta director)
2) Fe, HCl (have NH_2 group, which is an ortho/para director)
   ▪ at nitro stage, Nitrogen is a meta director
   ▪ at amino stage, Nitrogen is an ortho-para director

2-Step Route to Add 1° Alkyl:
1) RCOCl, $AlCl_3$ (have COR group, which is a meta director)
2) Zn(Hg), HCl (have CH_2R group, which is an ortho/para director)
   ▪ at acyl stage, acyl carbon is a meta director
   ▪ at alkyl stage, alkyl is an ortho-para director

Sulfonylation/Reaction/Desulfonylation:
1. SO_3, H_2SO_4 (protect, or block the para position)
2. Whatever   (react, install at the ortho position)
3. H_2O, H_2SO_4 (deprotect, or unblock the para position)
   ▪ Ideal procedure for when you have an ortho/para director, but you want an electrophile to
     end up ortho rather than para

Problem: Activating or Deactivating Effect by a Newly Added Substituent. Polysubstitution vs. Clean Monosubstitution. A thought exercise.

At Halfway Point

What happens when the 2nd 50% of electrophile adds?
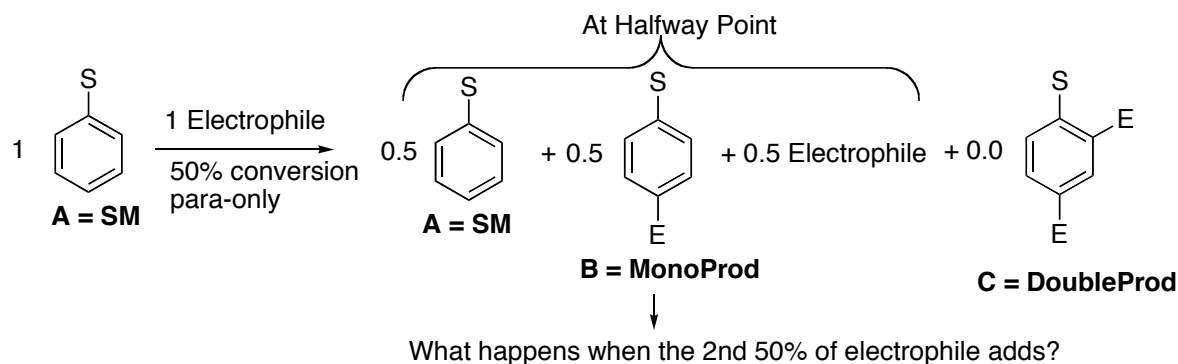
Case:	If: (hypothetically)	Activating/Deactivating Effect of Added Group "E"	Amount of A	Amount of B	Amount of C
1	Product "**B**" " is much **more** reactive than SM "**A**"	Activating	0.5 (50%)	0 (0%)	0.5 (50%)
2	Product "**B**" " is much **less** reactive than SM "**A**"	Deactivating	0 (0%)	1.0 (100%)	0 (0%)
3	Product "**B**" " is **equally reactive** to SM "**A**"	No Effect	0.25 (25%)	0.50 (50%)	0.25 (25%)

Synthetic Planning: To make multisubstituted aromatics, choose sequence with care!

If:	Make From:
Para Disubbed	An ortho-para director (a donor)
Meta Disubbed	A meta director (a strong, deactivating withdrawer)
Ortho Disubbed	An ortho-para director **and** para position blocked using the sulfonation/desulfonation trick