

CHEM 125 – Freshman Organic Chemistry II – Spring 2015

Based on Lectures by Prof. Alanna Schepartz and Prof. Jonathan Ellman
and “Organic Chemistry 5th Edition” by Marc Loudon

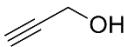
James Diao

Table of Contents

Chapter 14 – Alkynes	2
Chapter 15 – Dienes and Aromaticity	8
Chapter 16 – Benzene and Its Derivatives	17
Chapter 17 – Allylic and Benzylic Reactivity	23
Chapter 18 – Aryl and Vinylic Halides and Transition-Metal Catalysis.....	27
Chapter 19 – Aldehydes and Ketones: Carbonyl Addition.....	36
Chapter 20 – Carboxylic Acids	39
Chapter 21 – Carboxylic Acid Derivatives.....	41
Chapter 22 – Enols, Enolates, and α,β -Unsaturated Carbonyls	44
Chapter 23 – Amines	50
Chapter 24 – Carbohydrates	54
Chapter 25 – Aromatic Heterocycles.....	57
Chapter 26 – Amino Acids, Peptides, and Proteins	59

Chapter 14 – Alkynes

14.1 Nomenclature of Alkynes



- A. Common nomenclature: adding substituents to either side of a triple bond ex: ethylmethylacetylene
- B. Propargyl: triple-bond analog of the allyl group. Propargyl alcohol:

14.2 Structure and Bonding in Alkynes

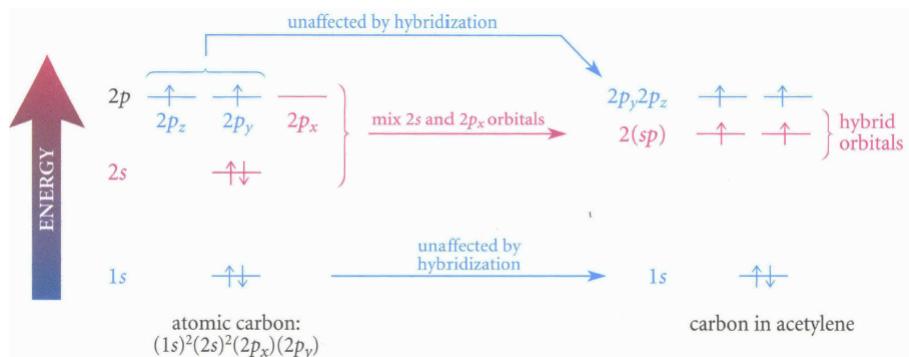
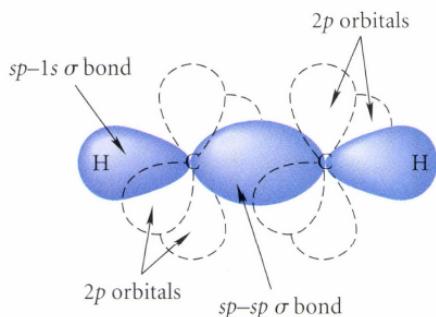
- A. 1 sigma bond (~88kcal/mol) and 2 pi bonds (~54kcal/mol)
- B. Alkynes have strong, short, linear C≡C bonds, with short, highly acidic C≡C—H bonds, and higher frequencies of IR absorption for all related bonds (because they're stronger).

Property	R—C≡C—H	R—C=C—H	R—C—C—H
Bond Angle	180° (linear)	120° (triangular)	109.5° (tetrahedral)
Bond Length (C to C)	1.20 Å	1.34 Å	1.54 Å
Bond Length (C to H)	1.06 Å	1.08 Å	1.11 Å
Bond Strength (C to C)	200 kcal/mol	150 kcal/mol	85 kcal/mol
IR Absorption (C to C)	~2200 cm ⁻¹	~1700 cm ⁻¹	~1000 cm ⁻¹
IR Absorption (C to H)	~3300 cm ⁻¹	~3100 cm ⁻¹	~2900 cm ⁻¹
Acidity	pKa = 25	pKa = 45	pKa > 55

C. Orbital Hybridization and Bonding

- a. 2x sp hybrids → 1 sigma bond.
- b. 2x unhybridized 2p orbitals → 2 pi bonds.

D. Rotatable because the ring-shaped cloud of electron density is cylindrically symmetrical.



E. Infrared Spectroscopy: C≡C stretch absorbs IR at a very high frequency, but only when asymmetric.

F. NMR: An applied field $B_0 \rightarrow$ e- circulation in the π -cylinder \rightarrow induced field (B_i) opposing B_0 .

- a. ^1H NMR: C≡C— ^1H 's experience a decreased chemical shift.
- b. ^{13}C NMR: All carbons associated with the triple bond R—C≡C—R experience a decreased chemical shift. Note that C≡C is still much stronger than C—C.

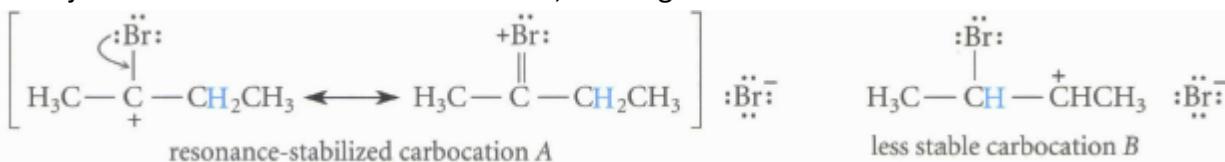
14.4 HX Addition to the Triple Bond

A. HBr Addition

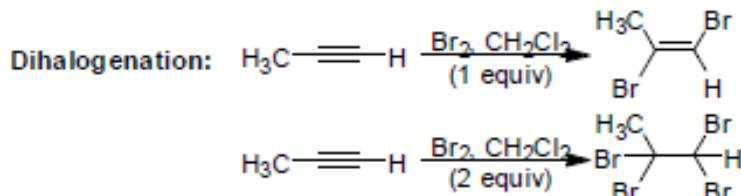
(1) Markovnikov addition (reversed by ROOR) \rightarrow substituted alkene (vicinal dibromides).

Note: The 1st Br exerts a rate-retarding, polar electron-withdrawing effect, which destabilizes BOTH DBCs (but the adjacent one more). Thus, the 2nd addition is much slower, requiring HBr (xs) + heat.

(2) Addition to the alkene. The carbocation reforms at the Br, which can resonance-stabilize the adjacent C+. The second Br attacks here, forming vicinal dibromides at the more substituted site.



B. Dihalogenation: same thing, but with Br₂.

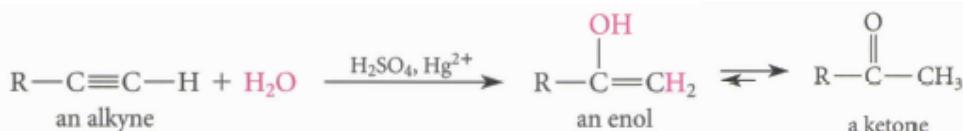


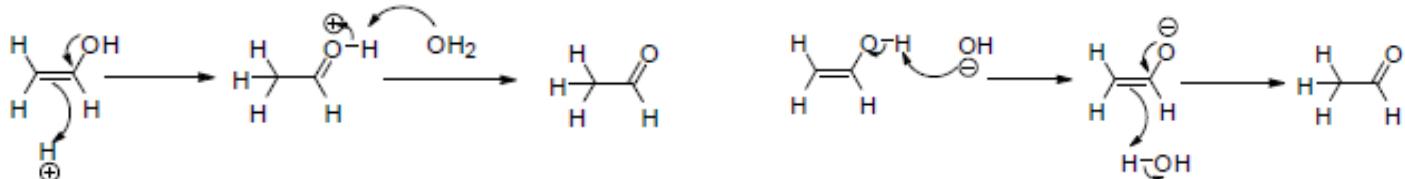
C. Difficult regioselective/stereoselective control for disubstituted alkynes (nonterminal).

Stereochemistry from alkyne to alkene.

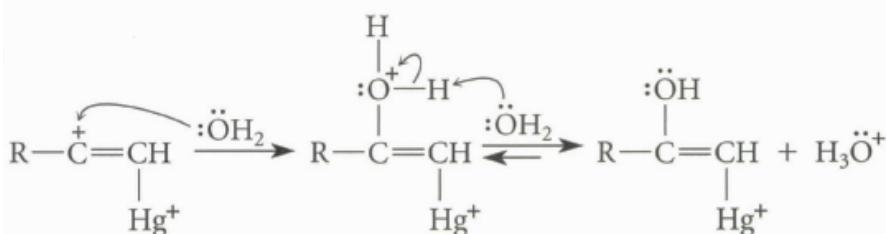
14.5 Conversion of Alkynes into Aldehydes and Ketones (highly versatile reaction)

A. Hydration of Alkynes (Terminal alkyne + H₂O + Hg²⁺ + H₂SO₄[dilute] → methylketone)
 (Hg²⁺ may come from HgSO₄)

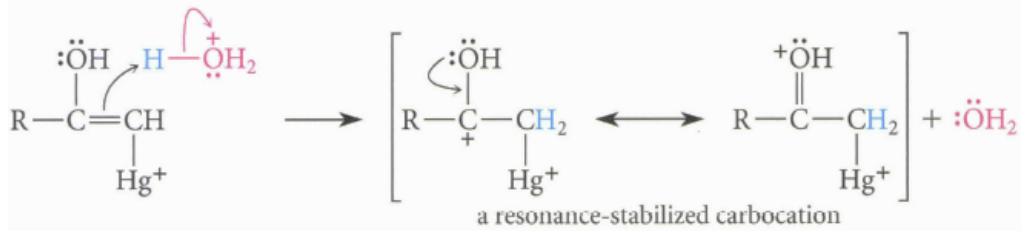




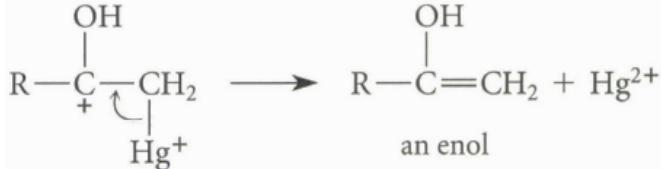
- d. STEP 1: H^{2+} acts as an electrophile with the pi electrons of the triple bond. C^+ forms at the more substituted DBC.
 - e. STEPS 2 and 3: Water attacks C^+ (most substituted site) to break the 3-membered ring.



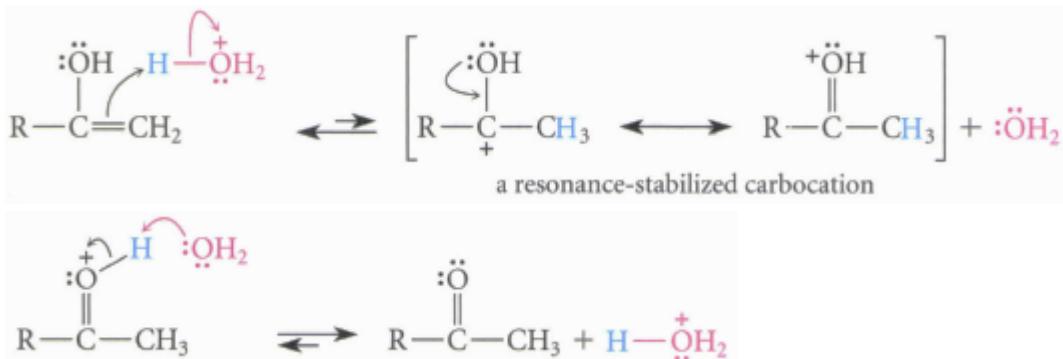
- f. STEP 4: Protonolysis: protonation of the double bond; —OH resonance-stabilizes C+ under hydration conditions. This makes the reducing agent NaBH_4 unnecessary.



- g. STEP 5: Dissociation of catalytic Hg^{2+} forms an enol and undergoes acid catalysis to ketone.



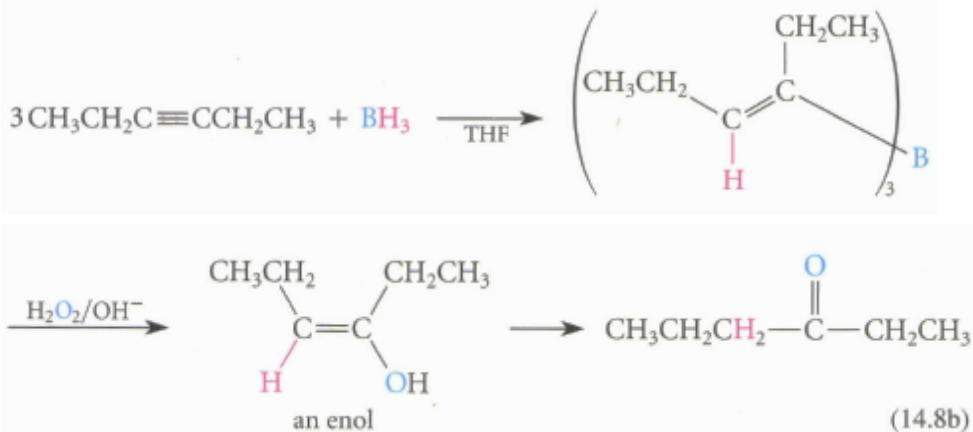
- h. STEPS 6, 7, and 8: Protonation of the double bond gives another resonance-stabilized C+



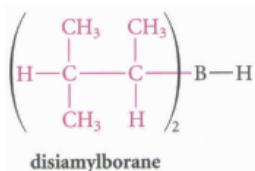
- i. Regiochemistry is predictable from 1-alkynes or symmetrical alkynes.

B. Hydroboration-Oxidation of Alkynes

- a. Disubstituted alkynes: analogous to alkenes; you get an enol \rightarrow carbonyl instead of alcohol.



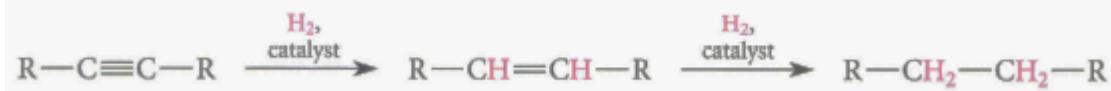
- b. Problem: terminal alkynes are less sterically hindered – may proceed beyond the enol.
c. Solution: use an organoborane with a lot of molecular shrubbery (highly branched), because more than 1 addition TO THE ALKENE results in terrible steric repulsions.



14.6 Reduction of Alkynes

A. Catalytic Hydrogenation of Alkynes

a. Alkynes \rightarrow cis-alkenes \rightarrow alkanes (syn-addition)



b. Catalyst poison: disrupts catalyst action

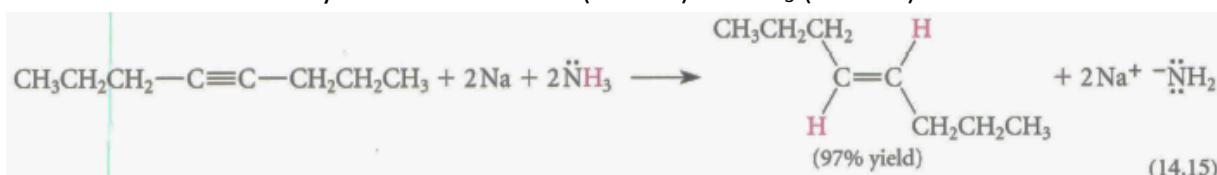
c. Pb^{2+} salts, pyridine, and amines selectively block the hydrogenation of alkenes, not alkynes.

B. Palladium (Pd/C): operates the same way it did with alkenes; unpoisoned.

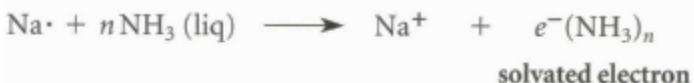
C. Lindlar catalyst: Pd/ CaCO_3 catalyst washed with $\text{Pb}(\text{OAc})_2$. SOLID-phase catalyst: Hs add to the same face to give the cis-alkene; poisoned.

D. Reduction of Alkynes with Sodium in Liquid Ammonia

a. Net reaction: Alkyne + 2 Alkali metal (usu Na) + 2 NH_3 (solvent) \rightarrow trans-alkene.

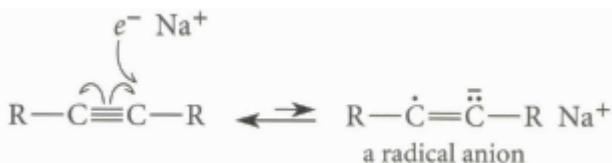


b. STEP 1: Electrons from the alkali are complexed with ammonia.



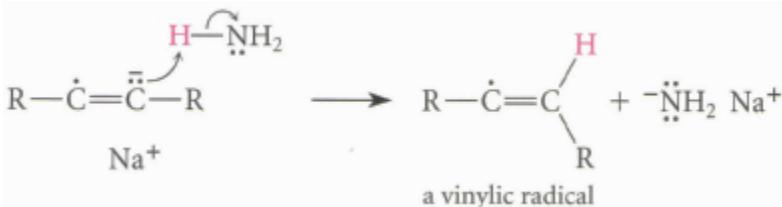
c. STEP 2: The solvated electron acts as a free radical, adding to $\text{C}\equiv\text{C}$ to give a radical anion.

OR: the e^- attacks one TBC and a pi bond jumps to the other TBC.

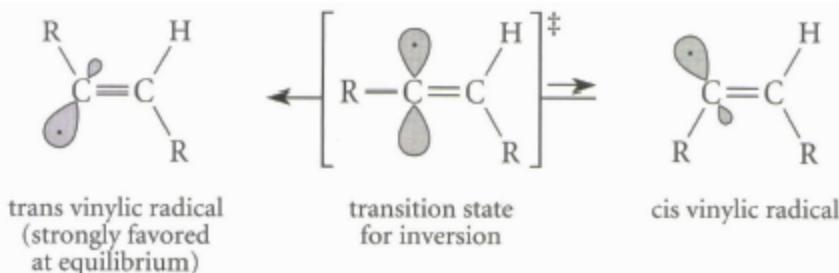


d. STEP 3: The strongly basic radical anion deprotonates ammonia to give a vinylic radical.

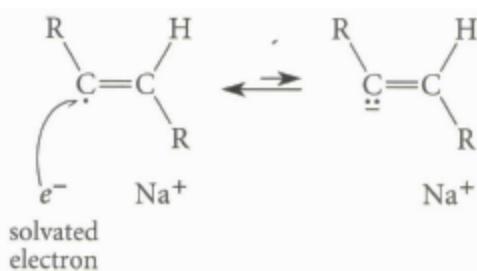
Destruction of the reactive radical anion is highly favorable.



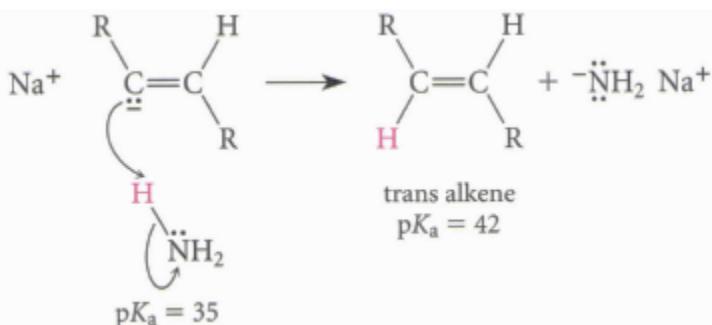
e. The vinylic radical rapidly inverts, but trans is much more sterically stable.



f. STEP 4: The vinylic radical accepts a solvated electron to form an anion. This is the product-determining step. The rate constants of reactions with cis/trans are ~equal, but there's just much more trans vinyl radical, which produces much more trans alkene.



g. STEP 5: The resulting highly basic carbanion abstracts H from NH₃ to form a trans-alkene, which is inert to solvated electrons.



h. This process does not work well on 1-alkynes, which are usually reduced by catalytic hydrogenation instead.

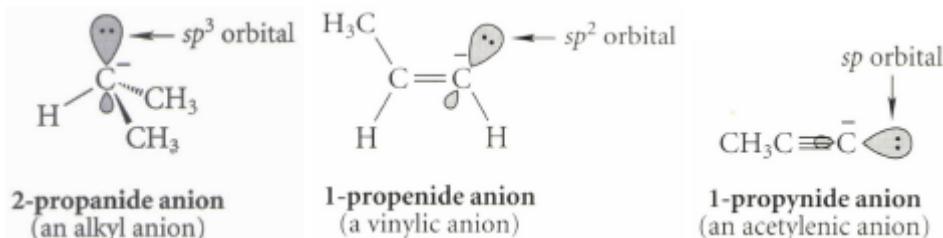
14.7 Acidity of 1-Alkynes

A. Nomenclature

- Alkyl anion: deprotonated conjugate base of an alkane (e- pair in an sp³ orbital).
- Vinylic anion: deprotonated conjugate base of an alkene (e- pair in an sp² orbital).
- Acetylenic anion: deprotonated conjugate base of an alkyne (e- pair in an sp orbital).

B. More s-character is more stable because the electron density is closer to the nucleus.

C. Aqueous workup: adding water to a dry solvent for a desired reaction.



D. Carbanions are super basic, and alkynes are the most acidic aliphatic hydrocarbons.

- Sodium hydride (Na⁺-H) can deprotonate a terminal alkyne. This is very useful because H₂ gas leaves the system – there's no equilibrium.
- Sodium amide (sodamide) [Na⁺-NH₂] dissolved in liquid ammonia. This delivers the highly basic amide ion (pKa ~35) which can easily deprotonate acetylenic protons.



E. Acetylenic Grignard reagents ($\text{R}-\text{C}\equiv\text{C}-\text{MgBr}$)

- It is difficult to make AGR via $\text{R}-\text{C}\equiv\text{C}-\text{Br} + \text{Mg}$.
- Instead, react 1-alkyne and another Grignard reagent.



- Transmetallation: a reaction where a metal is transferred from one carbon to another (essentially a Bronsted acid-base reaction).

F. Accounting for Relative Acidity

- Bond strength: $\text{C}\equiv\text{C}-\text{H} > \text{C}=\text{C}-\text{H} > \text{C}-\text{C}-\text{H}$; this implies that alkynes are least acidic.
- Electronegativity: $\text{sp} > \text{sp}^2 > \text{sp}^3$; this effect vastly outweighs bond strength.

G. Acetylenic Anions as Nucleophiles: Acetylenic anions are very strong bases, even stronger than alkoxides. They undergo $\text{S}_{\text{N}}2$ reactions with good leaving groups (halogens, epoxides), and terminal alkynes can be used to prepare disubstituted alkynes.



[PROBLEMS 14.18 – 14.22]

14.8 Organic Synthesis Using Alkynes [study problems]

- Alkynes add to carbenes the same way as they add to alkenes. This leads to a 3-membered ring on a double-bond.
- Retrosynthetic analysis: tool for synthesis. instead of trying to find processes from $A \rightarrow B$, you also consider pathways from $B \rightarrow A$. Generate a map of pathways on both sides, and look for overlap. This also helps identify the optimal series of steps necessary to prepare a desired target molecule from materials that can be readily purchased/obtained.

14.9 Pheromones [study problems]

- Pheromones: natural substances used for communication or signaling.
- Can be used for trapping without insecticides.

14.10 Occurrence and Use of Alkynes

- Naturally occurring alkynes are relatively rare. Typically synthesized from other compounds.
- $\text{CaO} + 3\text{C}$ (coke: carbon from coal) \rightarrow heat $\rightarrow \text{CaC}_2 (\text{Ca}^{2+} : \text{C}\equiv\text{C}^-) + \text{CO}$
 CaC_2 anion is a strong Bronsted base: reacts with water to yield the alkyne hydrocarbon and CaO .
- Thermal cracking (decomposition) of ethylene \rightarrow heat \rightarrow acetylene and H_2
- Acetylene is used as a chemical feedstock to create a lot of other materials.

Chapter 15 – Dienes and Aromaticity

15.1 Dienes, Resonance, and Aromaticity

C. Definitions

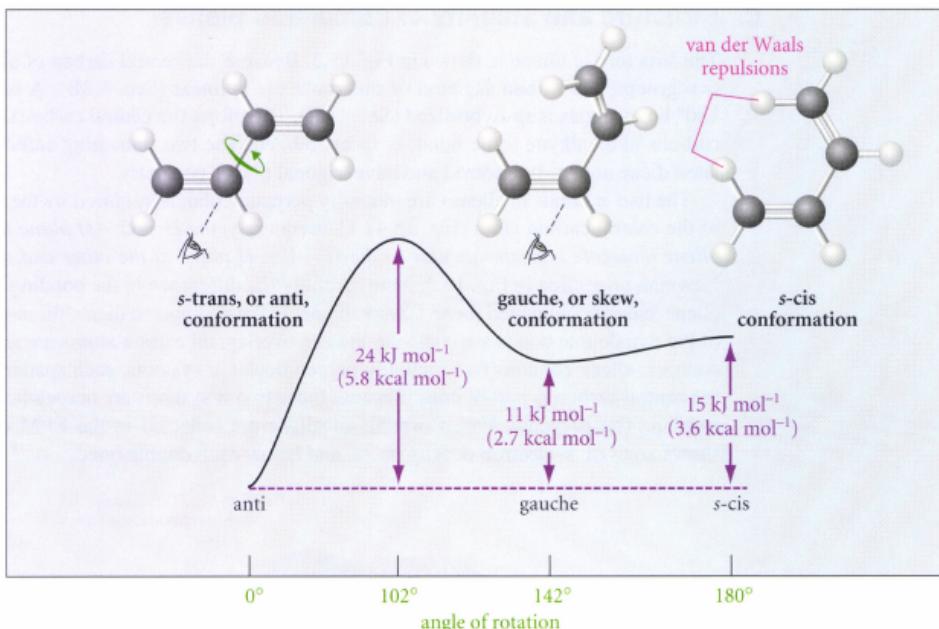
- Dienes: contain two C=C bonds; also: trienes, tetraenes, etc.
- Conjugated double bonds/dienes: C=C–C=C
- Cumulenes: contains C=C=C, e.g., propadiene

D. Conjugation Stabilizes Dienes

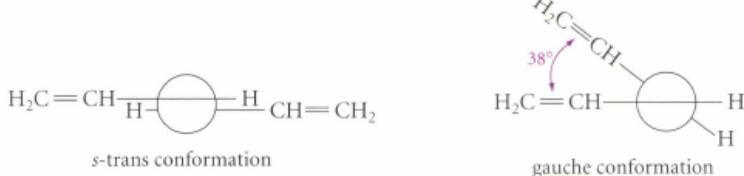
- Major reason: Pi bonds from 2p orbitals can occur BETWEEN alkenes (delocalized e⁻).
- Minor reason: sp^x–sp^y differences (sp²–sp² + sp³–sp³ more stable than 2x sp²–sp³)
- Delocalization energy (resonance energy): energetic advantage of conjugation.

E. Structure of Conjugated Dienes

- Conjugated dienes undergo rapid internal rotation about the single bond.
However, only planar forms predominate. Single bond is shorter/stronger than usual.



b.

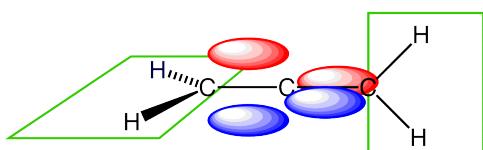
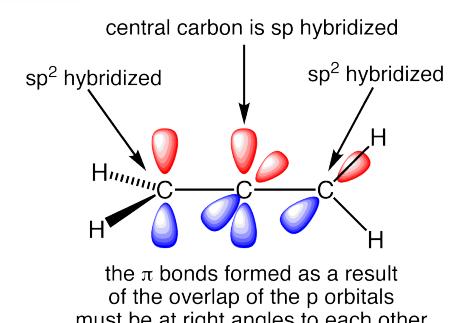


Gauche conformation loses some overlap, making it less stable than s-trans.

- The s-cis conformation is coplanar, but really bad van der Waals repulsions.

F. Structure and Stability of Cumulated Dienes (C=C=C)

- The sp hybridization of the central C makes the two pi bonds mutually perpendicular, which prevents overlap.
- Allenes are less stable than other isomeric dienes.

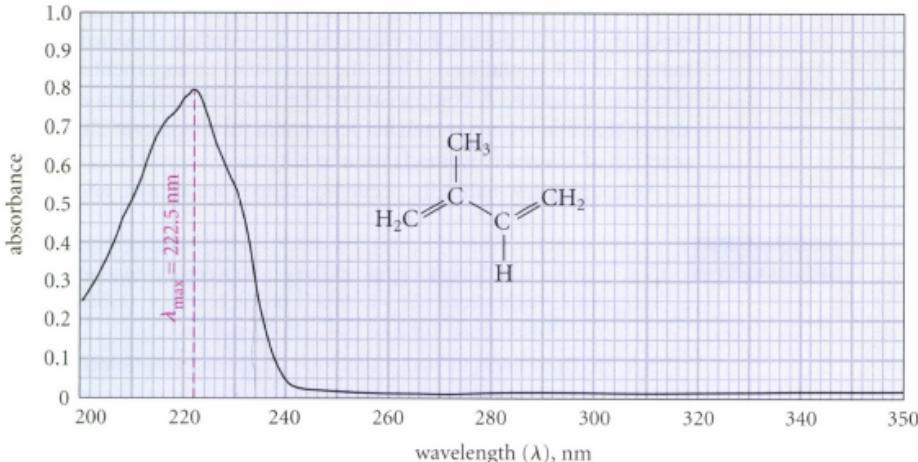


not only are the two π bonds perpendicular,
but the two methylene groups are too

15.2 Ultraviolet-Visible Spectroscopy

A. The UV-Vis spectrum

- UV light is absorbed by pi electrons and (sometimes) by unshared electron pairs.
- Pi electrons + UV may undergo $\pi \rightarrow \pi^*$ transition to a higher-energy antibonding orbital.
- Absorbance v. wavelength. $A = \log(I_0/I) = \epsilon c$ (molar absorptivity/extinction coefficient) (path length-cm)(concentration)



B. UV-Vis of Conjugated Alkenes

- In conjugated dienes, UV-vis absorption boosts a pi electron from the HOMO to the LUMO.
 - HOMO: highest occupied molecular orbital
 - LUMO: lowest unoccupied molecular orbital
- The HOMO-LUMO energy gap determines the wavelength of absorption. More conjugated double-bonds means more delocalized electrons, resulting in a smaller energy gap.
- Some compounds have so many double bonds that their $\lambda(\text{max})$ is in the visible spectrum e.g., β -carotene absorbs blue-green and looks red-orange.

C. Other (Smaller) Influences

- Conformation: dienes locked into s-cis conformations have higher $\lambda(\text{max})$ values and lower extinction coefficients (more stable) ???
- Substituents: each alkyl group on a conjugated DBC adds $\sim 5 \text{ nm}$ to $\lambda(\text{max})$.

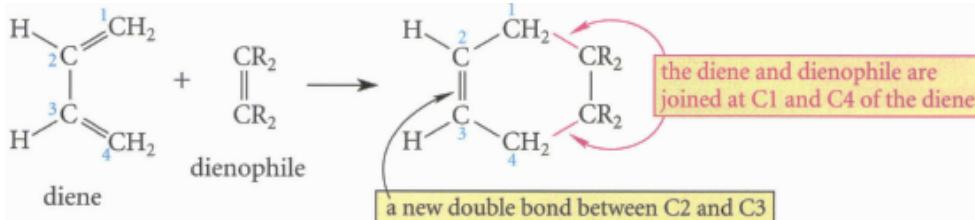


constrained by the ring to an **s-cis** conformation
 $\lambda_{\text{max}} = 256 \text{ nm}$ ($\epsilon = 8000$)

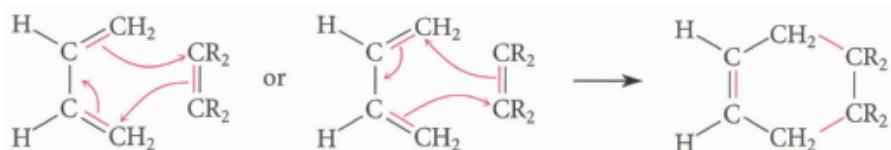
15.3 The Diels-Alder (D-A) Reaction: Reaction of Conjugated Dienes with Alkene Dienophiles

A. 1,4-addition (conjugate addition): addition occurring across the outer carbons of a diene.

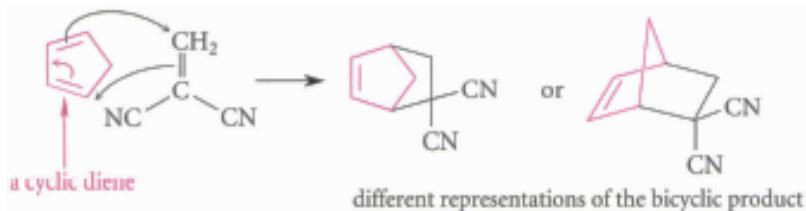
Conjugate addition results in carbon 2 forming a double bond with carbon 3.



B. Mechanism: concerted pericyclic reaction: cyclic electron flow.

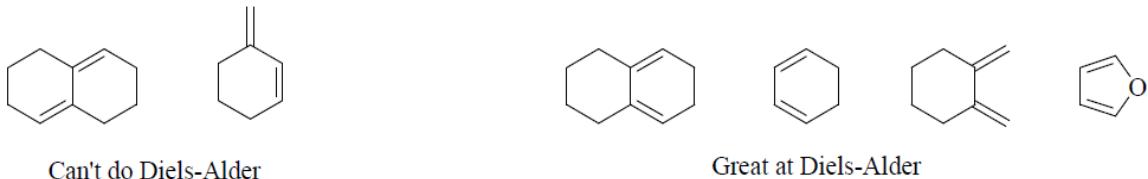


- C. D-A needs heat, pressure, or electron-withdrawing substituents like esters, aldehydes, carboxylic acids, nitriles ($-CN$), and sp^2 -hybridized carbons.
- D. Cycloaddition reaction: forms a ring. With a cyclic diene, D-A forms a *second* ring (bicyclic).

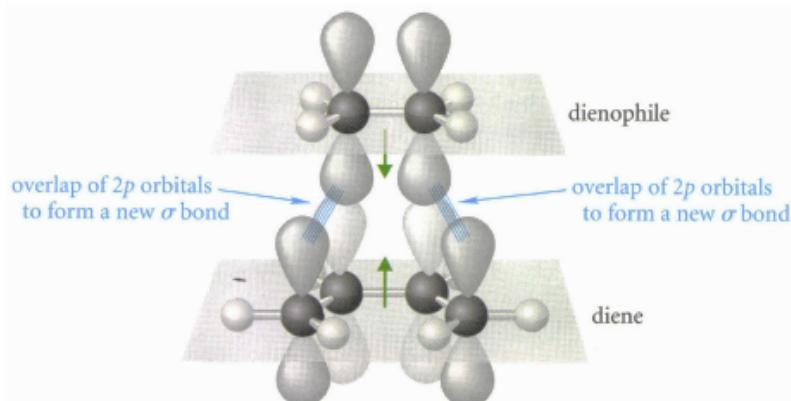


E. Effects of Diene Conformation

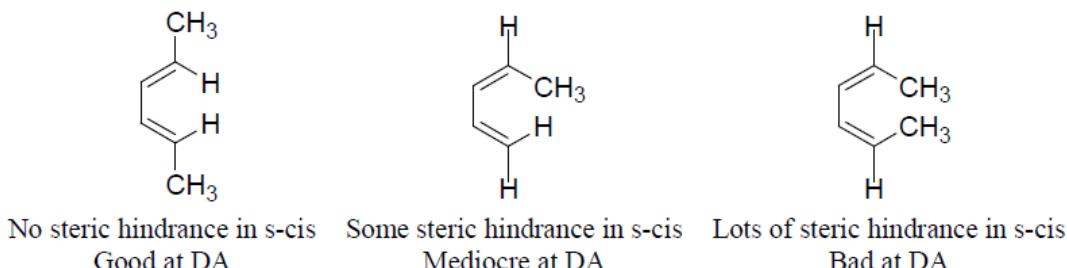
- Dienes locked into *s*-trans are unreactive in D-A reactions. The diene's single bond would become a trans bridgehead double-bond, in violation of Bredt's rule.
- Dienes locked into *s*-cis conformations are more reactive than noncyclic dienes.



- In the optimal transition state, the diene and the dienophile approach in parallel planes – this allows the 2p orbitals from both reagents to merge and form the new sigma bonds.

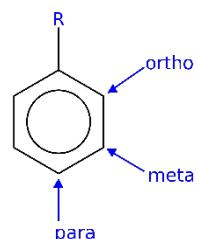


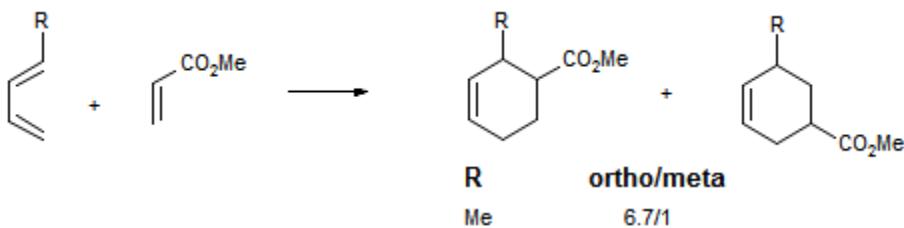
- Noncyclic dienes prefer *s*-trans, so [*cis* \rightarrow *trans*] is part of the energy barrier.
- The more steric repulsions in the *cis* conformation, the less reactive it is.



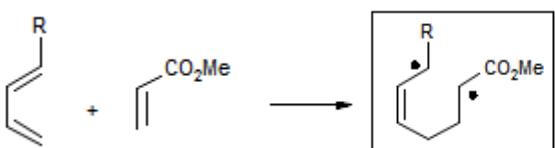
F. Regioselectivity of the Diels-Alder Reaction

- Naming Conventions: with an R group on a ring, ortho is immediately adjacent (1 away), meta is 2 away, and para is directly across (3 away).
- Ortho products are preferred. An electron-withdrawing group makes its adjacent carbon electron-deficient. An electron-donating alkyl group makes its adjacent carbon more electron-rich. A direct interaction here is better.





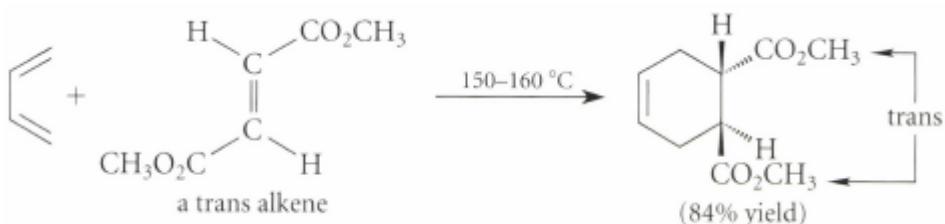
- c. This may also be because the “radicals” in the transition state are stabilized by the two substituents when they’re at both ends of the final bond being formed.



- d. Para products are preferred over meta products; less important than the ortho rule.

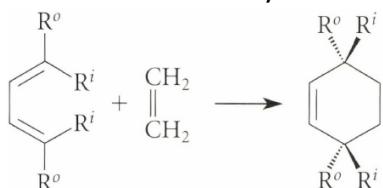
G. Stereochemistry of the Diels-Alder Reaction

- a. Dieneophile stereochemistry is retained.



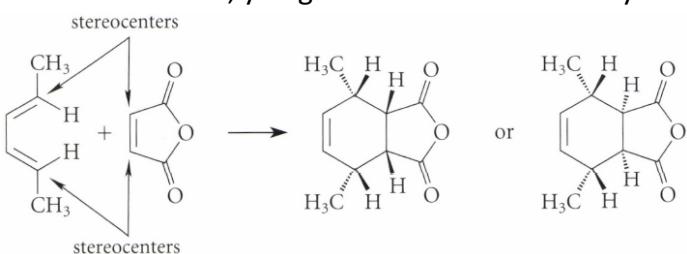
- i. RACEMIC product: both starting materials are achiral.

- b. Diene stereochemistry is retained.

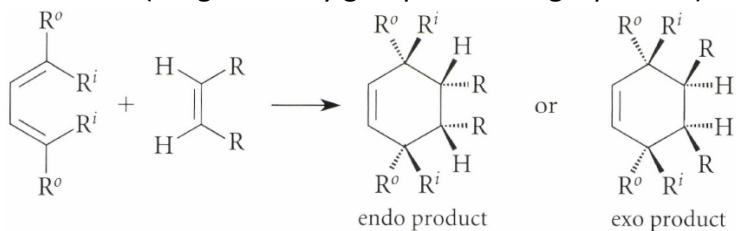


- i. Inner and outer substituents react in characteristic ways. Inner ones forced up; outer ones forced down, or vice versa.

- ii. When BOTH the terminal carbons of the diene AND the carbons of the dienophile are stereocenters, you get two diastereomeric syn-addition products.

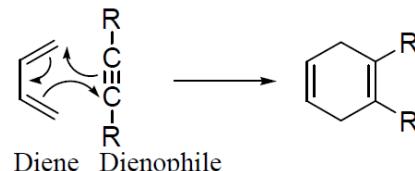
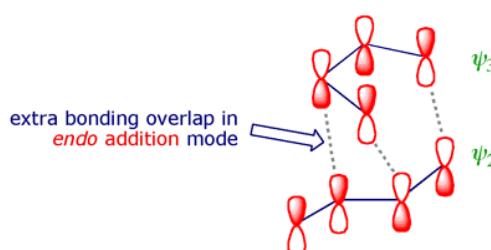


H. Endo Rule (R signifies any group containing a pi-bond)



- a. Endo product: when R is cis to R°; Exo product: when R is cis to R¹

- b. The endo products form more rapidly because secondary orbital interactions between the pi systems help stabilize the transition state of the endo product.



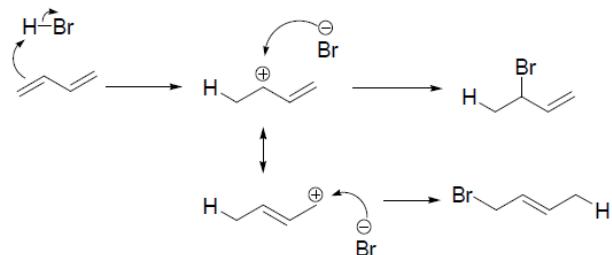
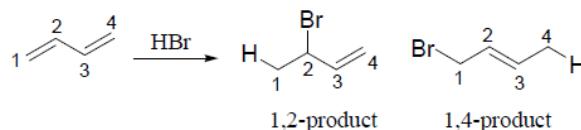
- I. Alkynes as the Dienophile: forms a cyclohexane diene.

15.4 Addition of Hydrogen Halides to Conjugated Dienes

A. 1,2- and 1,4- Additions with HX

- a. Major product: 1,2-addition – X^- adds at the adjacent carbon.

- b. Minor product: 1,4-addition – X^- adds at the other side of the molecule.



- c. Mechanism:

- (1) C+ forms at the inner DBC, where it is allylic and can be resonance-stabilized.
- (2) Br attacks at the allyl C+ in the dominant resonance structure.
- (3) Another HBr equivalent *may* react.

- d. Reaction Rate:

- i. Rate-determining step: protonation of the double-bond.
- ii. Product-determining step: addition of X^- to one of the partial C+'s
- iii. 1,4-product: more stable due to more substituted alkene (thermodynamic product)
- iv. 1,2-product: X^- is more likely to attack the closer 2-carbon (kinetic product)

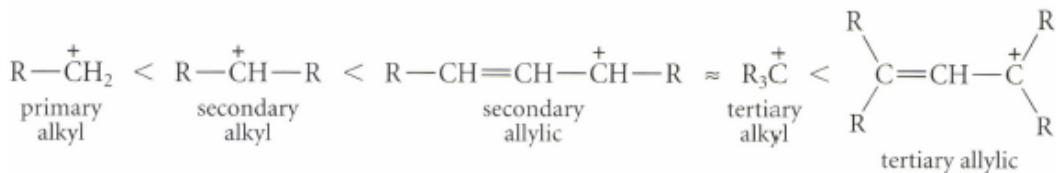
B. Allylic Carbocations: Resonance and Stability

- a. Allylic carbocation: C+ adjacent to a double-bond.

- i. Allylic: adjacent to a DBC.
- ii. Vinyl: attached to a DBC.

iii. The allylic/vinylic group can be hydrogen, bromine, carbocation, radical, etc.

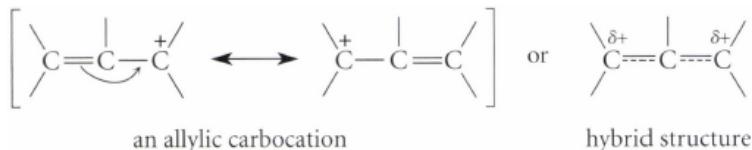
- b. Allylic stability: being adjacent to a double-bond is worth about +1 alkyl group.



- c. This is due to resonance stabilization of allylic charges.



- d. NBMO (nonbonding molecular orbital): MO with the same energy as an isolated 2p orbital.
 π_2 is an NBMO: energy halfway between bonding and antibonding.
 - e. The allyl cation has both electrons in the delocalized MO with no nodes. This is represented by a hybrid resonance structure.



C. Kinetic and Thermodynamic Control

- a. Kinetically controlled
 - i. Low temperature
 - ii. Reaction products do NOT go to equilibrium under reaction conditions
 - iii. Relative proportions set by relative rates of formation and transition-state energy.
 - iv. Either the less stable OR the more stable product could predominate.
 - b. Thermodynamically controlled:
 - i. High temperature
 - ii. Reaction products DO go to equilibrium under reaction conditions
 - iii. Relative proportions set by thermodynamic stability.
 - iv. The more stable product will ALWAYS predominate.

15.5 Diene Polymers

A. Free-Radical Polymerization



- a. This radical adds to another butadiene, and repetition yields the final polymer.



- b. A small amount of 1,2-addition may also occur, and both cis and trans double-bonds are present. (1,4-addition polymer)

- B. Copolymer; produced by the simultaneous polymerization of more than one monomer.

- C. 1,3-butadiene can be copolymerized with styrene (PhCH=CH_2) in a 3:1 ratio to give styrene-butadiene rubber (SBR) used in tires.

15.6 Resonance

A. Drawing Resonance Structures

- a. Resonance shows the delocalization of electrons, NOT atoms.
 - b. Involves electron-pushing in pi-bonds, cations/anions, unshared e- pairs, or radicals.
 - c. Place within brackets and use \longleftrightarrow notation.
 - d. More resonance forms \rightarrow more stable molecule

B. Relative Importance of Resonance Contributors

- a. Identical structures are equally good.
 - b. Incomplete octets are bad.
 - c. Following electronegativity is good.
 - d. Impossible/highly-strained geometry is bad (esp with double-bonds).

15.7 Introduction to Aromatic Compounds

A. Benzene and COT

- a. Benzene is stable and unreactive – inert to X_2 addition, hydroboration, hydration, ozonolysis.
- b. 1,3,5,7-cyclooctatetraene (COT) is tub-shaped, and as reactive as 4 separate ethenes.
Its double-bonds are fixed, because the tub-shape doesn't allow overlap of pi systems.
No resonance: its double-bonds are shorter than its single-bonds.



B. Structure of Benzene

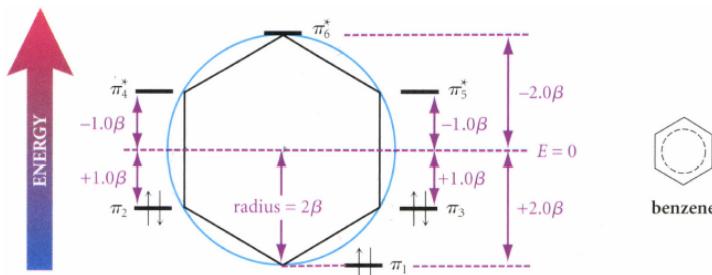
- a. Four 1.5 bonds – midway between sp^2 - sp^2 single-bonds and double-bonds.
- b. Planar: all the 2p orbitals can overlap to provide additional bonding MOs.

C. Stability of Benzene

- a. Benzene's ΔH_f is 13.8 kJ/mol CH. COT's ΔH_f is 37.3 kJ/mol CH.
- b. Thus, benzene is 141 kJ/mol more stable than a hypothetical 6-carbon conjugated triene with the stability of COT. This is called the empirical resonance energy.

D. Aromaticity and the Hückel $4n + 2$ Rule

- a. Aromatic structures: (1) are planar, (2) contain a ring, with (3) $4n + 2$ pi electrons, where (4) every atom in the ring has a p-orbital that can participate in the pi system - from pi bonds, lone pairs (-), empty orbitals (+), or radicals.
- b. Frost circle:
 - i. Inscribe your cyclic structure with j sides within a circle of radius 2β , vertex-up.
 - ii. Place an MO energy level at each vertex. j vertices $\rightarrow j$ MOs.
 - iii. The lowest energy level is at the lowest vertex (2β). The energies of other levels are determined by their respective vertical positions.
 - iv. Add the pi electrons to energy levels, following the Aufbau, Hund, and Pauli.



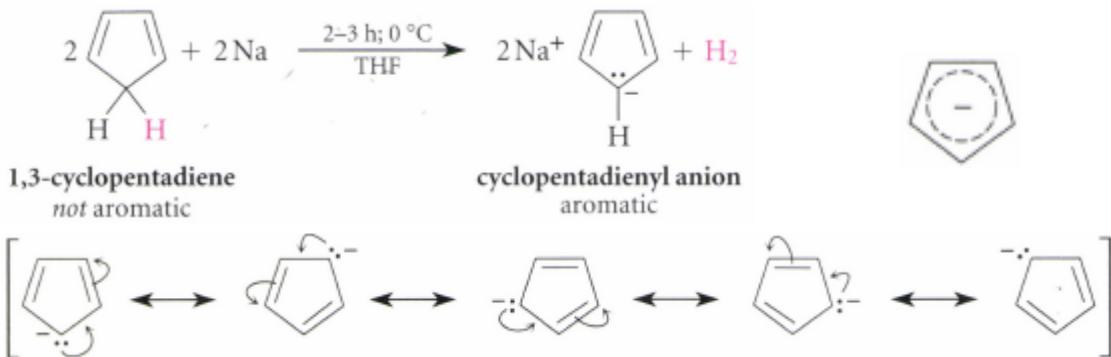
- c. $4n + 2$ is exactly the number of electrons required to fill the bonding MOs. More electrons would go into antibonding orbitals, and fewer electrons would reduce the resonance energy.
Ex: Benzene has 6 pi e- for 3 bonding MOs. A planar cyclic conjugated hydrocarbon has 10 pi e- for 5 bonding MOs.
- d. β is the energy of a single pi-electron in an isolated ethylene bonding MO.
 $j^*\beta$ = pi-electron energy of the equivalent number of isolated, noncyclic pi-systems.
- e. Cyclic conjugated molecules have a super low energy bonding MO that noncyclics lack.

E. Aromatic Heterocycles

- a. Heterocycle: ring containing a non-carbon vertex.
- b. Vinylic electrons are NOT counted as pi electrons. They reside in an sp^2 orbital like -H.
- c. Allylic electrons ARE counted as pi electrons when they can overlap with parallel p-orbitals. This adds two pi electrons to the $4n + 2$ count.

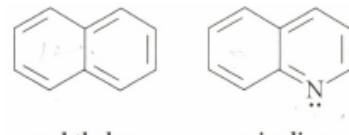
F. Aromatic Ions

- a. Adjusting the number of pi electrons via ionization may confer aromaticity.



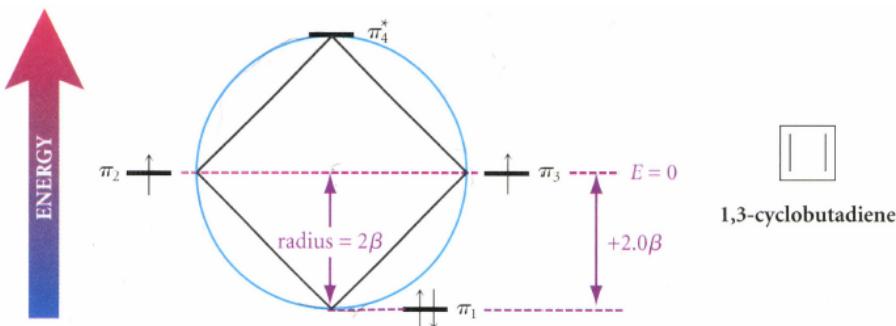
- b. The stability of the anion makes the conjugate-acid starting material 1,3-cyclopentadiene an unusually strong acid.

G. Aromatic Polycyclic Compounds: the Hückel $4n + 2$ rule only applies to single rings. No simple rules exist for fused-ring aromatics.



H. Antiaromatic Compounds

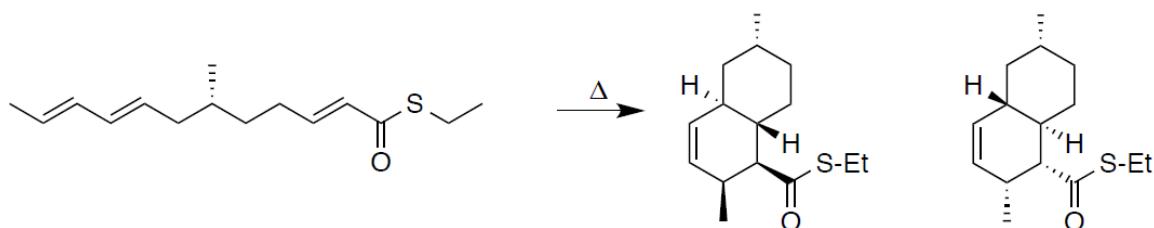
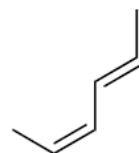
- a. Antiaromatic: planar, continuous rings of $4n$ pi-electrons – highly unstable.
b. Cyclobutadiene has two unpaired e-, making it a double free radical.



- c. The overlap of p-orbitals in π_2 and π_3 are destabilizing. Cyclobutadiene reduces overlap by lengthening single bonds and shortening double-bonds. This allows one MO to lie slightly lower energy, and be doubly occupied, but increases other strains.
d. Cyclobutadiene contains localized double-bonds.
e. COT (stop-sign diene) is NOT antiaromatic because tub-shape prevents antiaromatic overlap.

I. Homework Notes

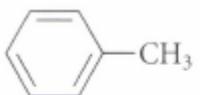
- a. When rotating s-trans dienes, be careful not to change to a diastereomeric conformation. The structure on the right has one in-group and one out-group.
b. Remember that a chiral compound undergoing a reaction that normally creates racemates may in fact create diastereomers. JUST DRAW THE RACEMIC STRUCTURE, BUT LEAVE THE ORIGINAL STEREOCENTER UNCHANGED.



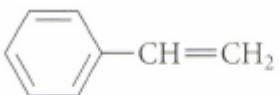
Chapter 16 – Benzene and Its Derivatives

16.1 Nomenclature of Benzene Derivatives

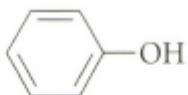
G. Common Nomenclature:



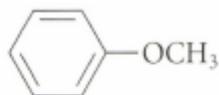
toluene



styrene



phenol



anisole

- a. Di-methylbenzenes are called *xylanes*, and methylphenols are called *cresols*.

H. Substituted Nomenclature

- a. Modern substitutive nomenclature: same as cyclohexane, but use “benzene” or “phenol”. If phenol is used, the –OH is always numbered “1”.
 - b. Old substituted nomenclature: ortho (1,2) – meta (1,3) – para (1,4)

I. Benzene as a Substituent: Aryl, Phenyl, Benzyl

16.2 Physical Properties of Benzene Derivatives

- A. Benzene and cyclohexane have high melting points due to symmetry. Substituted rings are asymmetrical and therefore lower. Para-disubstituted is higher than ortho/meta.
 - B. Aromatic compounds are more dense than aliphatic ones. Insoluble.

16.4 Electrophilic Aromatic Substitution Reactions

- A. Definition: an aromatic hydrogen is substituted by an electrophile (Lewis acid).

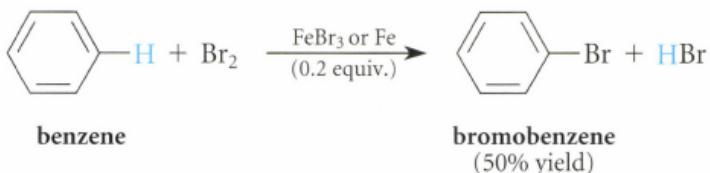


B. Steps of Electrophilic Aromatic Substitution

- a. Generation of an electrophile (complex of Br and FeBr_3)
 - b. Nucleophilic reaction of aromatic pi-electrons with the electrophile to form a resonance-stabilized carbocation intermediate.
 - c. Deprotonation of the intermediate to form the substituted aromatic.

C. Halogenation of Benzene

- a. Harsh conditions: benzene + liquid Br_2 solvent, FeBr_3 (cat) \rightarrow Bromobenzene
 Iron filings may also be used ($\text{Fe} + \text{Br}_2 \rightarrow \text{FeBr}_3$)



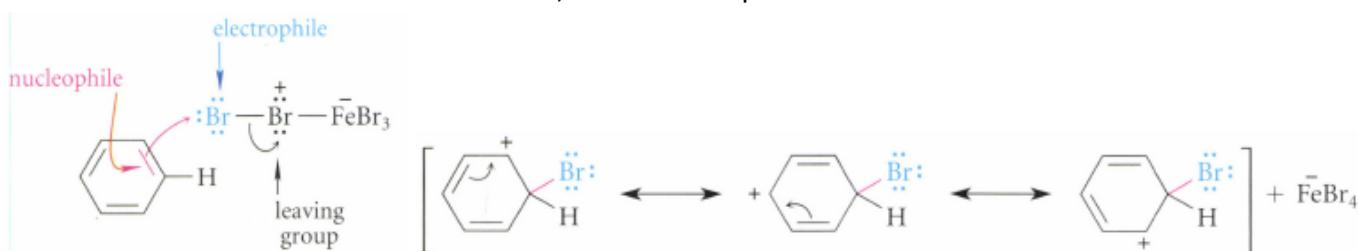
b. Mechanism

- i. Step (1): Electrophile generation: Br_2 complexes with catalytic Lewis acid FeBr_3 , forming a structure with Br^+ , a strong e- acceptor/leaving group. This makes the neutral Br a strong electrophile.

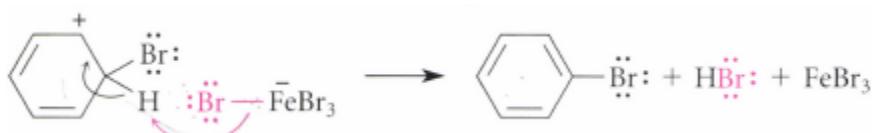


ii. Step (2): Attack of aromatic pi-electrons to form C+ intermediate.

The nucleophilic pi-electrons attack at the electrophilic Br. The resulting carbocation is resonance-stabilized, but still disrupts aromatic stabilization.



iii. Step (3): Deprotonation: Br (complexed to FeBr₃) removes the ring proton, restoring aromatic stability.

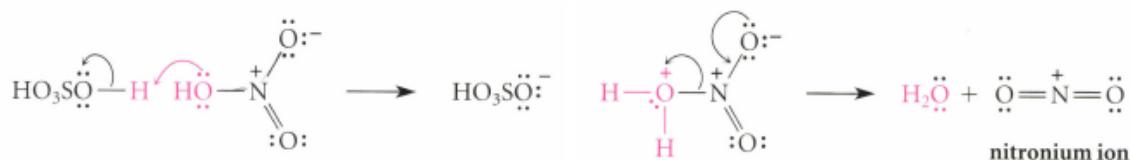


D. Nitration of Benzene

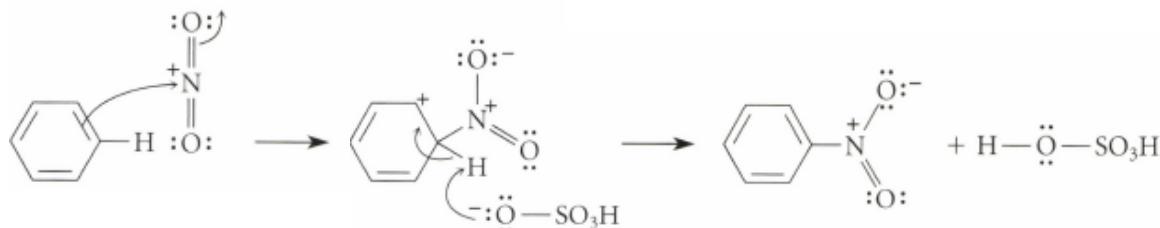
a. Overall reaction: benzene + nitric acid + sulfuric acid (cat) \rightarrow nitrobenzene (Ph—NO₂)

b. Mechanism

i. Step (1): Generation of the electrophile: $^+\text{NO}_2$ (nitronium ion) is formed by acid-catalyzed dehydration of HNO₃ (protonates, then H₂O leaves by S_N1).

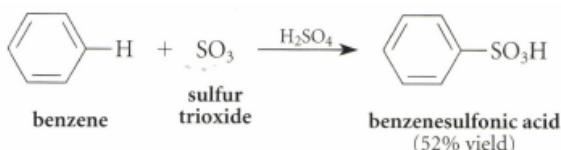


ii. Step (2) and (3): Attack of aromatic e- to form C+ intermediate, then deprotonation.



E. Sulfonation of Benzene

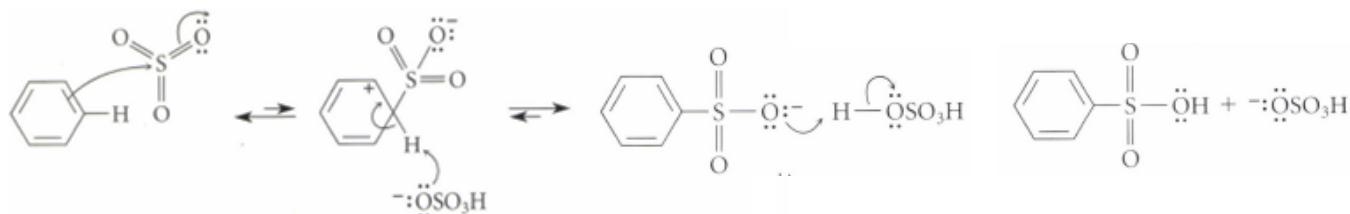
a. Overall reaction: benzene + SO₃ (sulfur trioxide) + H₂SO₄ (cat) \rightarrow benzenesulfonic acid



b. Mechanism

i. Step (1): Electrophile generation: SO₃ in H₂SO₄ available commercially.

ii. Step (2) and (3): Attack of aromatic e- to form C+ intermediate, then deprotonation.

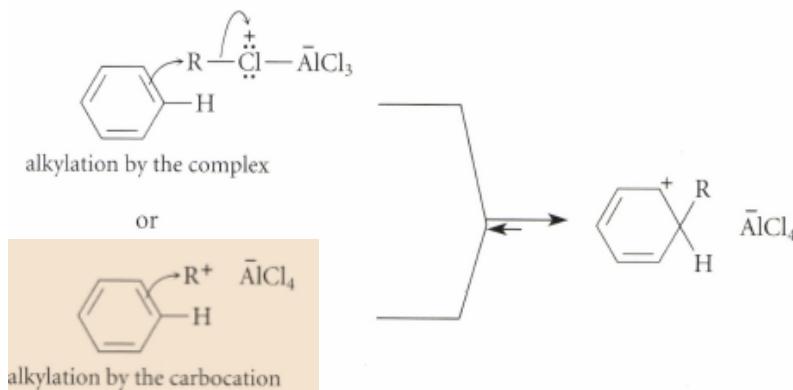


- c. Reversibility: heating with steam displaces SO_3H and reprotonates the ring.
- F. Friedel-Crafts Alkylation of Benzene (sp^2 carbon) – more reactive substituted product
- Overall reaction: Benzene + alkyl halide + AlCl_3 Lewis acid (cat) \rightarrow alkylbenzene
 - Mechanism

- Step (1): Electrophile generation: RX complexes with the Lewis acid.



- Step (2): Either the RX-Lewis acid complex or the derived R+ can serve as the electrophile that receives aromatic pi-electrons to form C+ intermediate.



- Step (3): Deprotonation



- REARRANGEMENT IS POSSIBLE: generally in the complex, not the intermediate.

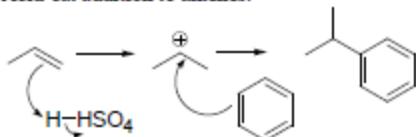
The complex has enough carbocation character to behave like one.



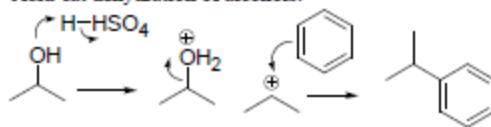
- Reactivity

- Alkylbenzene products are more reactive than benzene itself – can be further alkylated into toluene, ylenes, trimethylbenzenes, etc.
 - Excess benzene promotes monoalkylation.
- e. Friedel-Crafts carbocation electrophiles can also be generated from alkenes by protonation and alcohols by dehydration.

Acid-cat addition to alkenes:



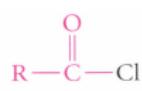
Acid-cat dehydration of alcohols:



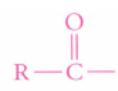
- G. Friedel-Crafts Acylation (sp^2 carbon) – less reactive substituted product

- Acyl group: $-\text{CR}=\text{O}$; generally derived from acid chloride.
- Acylation reaction: an acyl is transferred (analogous to acetylation).
- Overall Reaction: Benzene + Acid Chloride + AlCl_3 Lewis Acid \rightarrow ketone

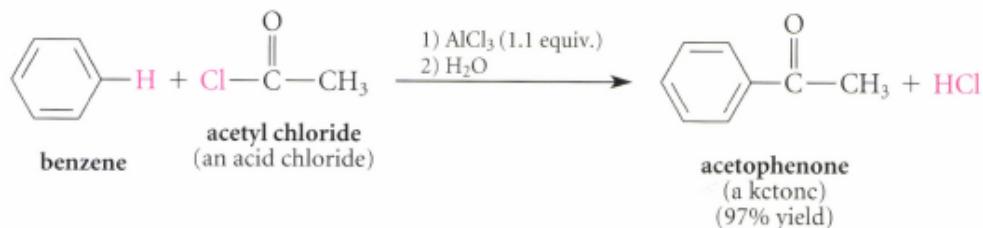
An acyl group is introduced into an aromatic ring as an acylium ion.



an acid chloride

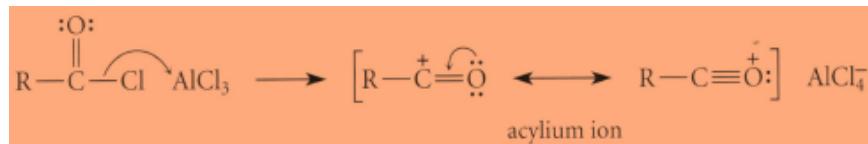


an acyl group

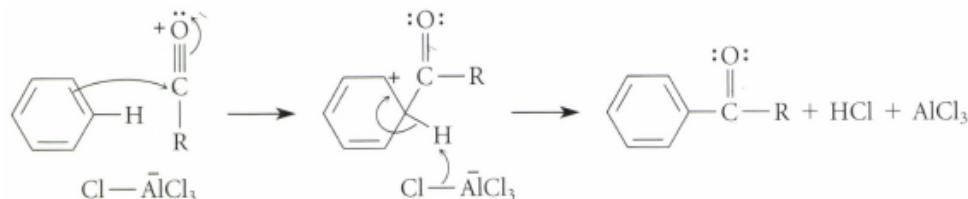


d. Mechanism

i. Step (1): Electrophile generation:



ii. Step (2) and (3): Attack of aromatic pi-electrons to form C+ intermediate and deprotonation.



iii. The weakly basic ketone binds the Lewis acid to form a catalytically inactive complex.

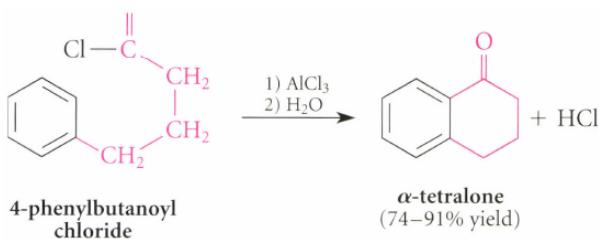
1. At least 1 equivalent of Lewis acid is needed to ensure constant presence.
2. Step (4): The complex must be destroyed before the ketone is isolated.

Pour the reaction mixture into ice water.

e. Intramolecular reactions: may occur in Friedel-Crafts alkylation and acylation.

This only occurs at adjacent ortho positions; other positions are too strained.

Proximity effect: 5/6-member ring formation is faster than intermolecular.



16.5 Electrophilic Aromatic Substitution of SUBSTITUTED Benzenes

A. Directing Effects of Substituents: always ortho, para-directing, or meta-directing.

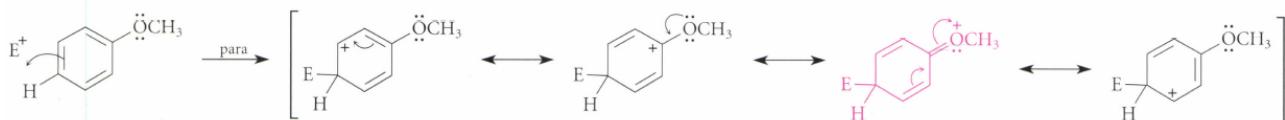
- a. Ortho, para directors: -OH, -OR, -NH₂/NHR/NR₂/NH-COR, -X, -R, -Aryl
- b. Meta directors: -NO₂, -⁺NR₃, -CN, -carboxyl.
- c. Activators: -OH, -OR, -NH₂, -NHR, -NR₂, -acylamino, -R
- d. Deactivators: all meta-directors, and -X.

Substituent group	Name of group	Directing effect	Activating or deactivating
$-\ddot{\text{NH}}_2, -\ddot{\text{NR}}_2$	amino		
$-\ddot{\text{O}}\text{H}$	hydroxy		
$-\ddot{\text{O}}\text{R}$	alkoxy		
$-\ddot{\text{NH}}-\text{C}(=\text{O})-\text{R}$	acylamino	ortho, para directors	activating substituents
$-\text{R}$	alkyl		
$-\ddot{\text{O}}-\text{C}(=\text{O})-\text{R}$	acyloxy		
	phenyl		
$-\ddot{\text{F}}, -\ddot{\text{Br}}, -\ddot{\text{Cl}}, -\ddot{\text{I}}$	halogens		
$-\text{C}(=\text{O})\text{OH}, -\text{C}(=\text{O})\text{NH}_2, -\text{C}(=\text{O})\text{OR}$	carboxy, carboxamido, carboalkoxy		
$-\text{C}(=\text{O})-\text{R}$	acyl	meta directors	deactivating substituents
$-\text{SO}_3\text{H}$	sulfonic acid		
$-\text{CN}$	cyano		
$-\text{NO}_2$	nitro		

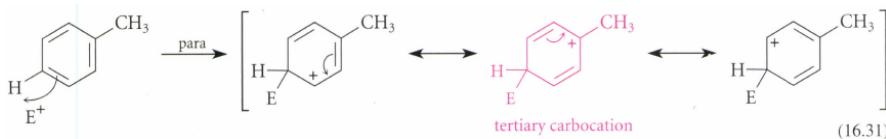
B. Substitution reactions at different ring positions are in competition. Directing effects favor some positions over others.

C. Ortho, para-directing groups are electron-donating, like alkyl groups, or having unshared e- pairs.

a. Reason 1: Resonance-stabilization by the substituent.

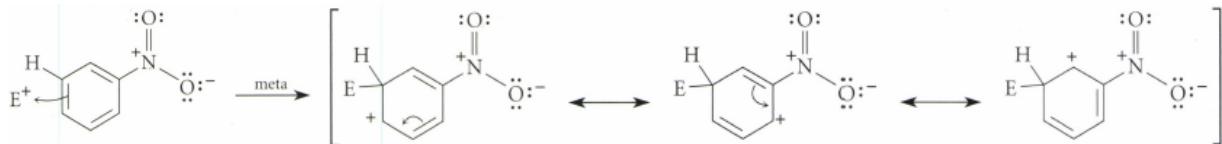


b. Reason 2: Carbocation stabilization



D. Meta-directing substituents are polar groups that do not have unshared electron pairs.

a. Reason: avoids adjacent position charges



- E. Ortho, Para Ratio: In fast reactions, there is a 2:1 ortho preference because of site availability.
In slow reactions, para is preferred because ortho substitution leads to steric repulsions.
- F. Activating and Deactivating Effects of Substituents
- Activating group: increases reactivity of benzene
 - Deactivating group: decreases reactivity of benzene
 - Generalizations:
 - All halogens are deactivating groups
 - All meta-directing groups are deactivating groups
 - All ortho, para-directing groups (except the halogens) are activating groups
 - Reasons:
 - Resonance effect: ability of the substituent to resonance-stabilize the carbocation.
 - Polar effect: tendency of the substituent to:
 - Pull electrons from the ring, creating a partial C+ destabilizing the carbocation
 - Donate electrons to the ring, creating a partial C- stabilizing the carbocation.
 - Methoxybenzene (anisole) has the resonance effect, which outweighs the electron-withdrawing polar effect, making it an activating group.
 - Halogens
 - Deactivating group: strong electro-withdrawing polar effect heavily outweighs minimal resonance effect (orbitals have different sizes and nodes → weak overlap)
 - Ortho, para-director: ortho, para-substitution because there's still SOME resonance effect. Para is preferred because of steric effects.
 - F → Cl → Br → I: polar and resonance effects both weaken → still deactivating.
 - Alkyl groups are activating because of their stabilizing polar effect, but they activate ortho, para better because of C+ stabilization.
 - Nitro groups are deactivating because of their destabilizing polar effect, but they deactivate more at the ortho, para positions.
- G. Substituted Benzenes in Organic Synthesis
- When more than one substituent exerts an effect, the activating/deactivating effects are roughly the sum of the separate effects.
 - Some activators are stronger than others. —OH is so strong that it can be brominated 3 times without a catalyst.
 - In other cases, mixtures of isomers are typically obtained.
 - Activating substituent addition often occurs multiple times, while deactivating substituent addition is usually monosubstitution only.

16.6 Hydrogenation of Benzene

- Benzene + catalyst + heat/pressure → cyclohexane
- Catalyst may be:
 - Rh or Pt @ 10 atm H₂/100°C
 - Ni or Pd @ 200 atm H₂/200°C
- The reaction can't be poisoned → the first step is highly endothermic, but the other two are exothermic and proceed rapidly under reaction conditions.

Chapter 17 – Allylic and Benzylic Reactivity

17.1 Reactions Involving Allylic and Benzylic Carbocations

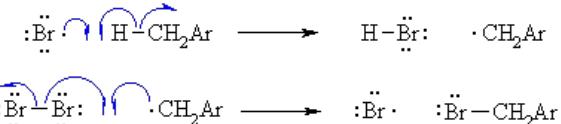
A. Definitions

- Allylic group: group on a carbon adjacent to a double bond.
 - Benzylic group: group on a carbon adjacent to a benzene ring.
- B. Allylic and benzylic groups are highly reactive because resonance can stabilize charges.
- C. Resonance effect stability is about the same = +1 alkyl group (in S_N1 solvolysis).
- D. The creation of a benzylic C⁺ parallels the C⁺ intermediate in electrophilic substitution. The same resonance and polar effects change the reactivity of the benzylic group.
- E. No addition to C⁺ around the ring because it ruins aromaticity.
- F. Multiple products because resonance allows more sites of attack. More substituted sites are more stable and significant products.

Question: why do the benzylics in the triphenol cation need to be aromatic to each other? Do solvent effects play a role?

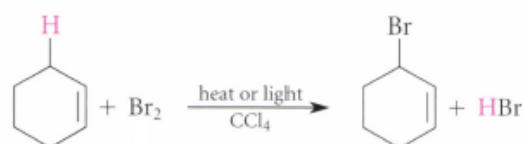
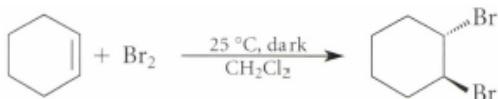
17.2 Reactions involving Allylic and Benzylic Radicals

- Highly stable for the same reasons as above – readily forms reactive radical intermediates.
- Benzylic bromination: benzylic H substitution with Br from Br₂ + hν.
The mechanism proceeds through a benzyl radical and forms HBr side product.



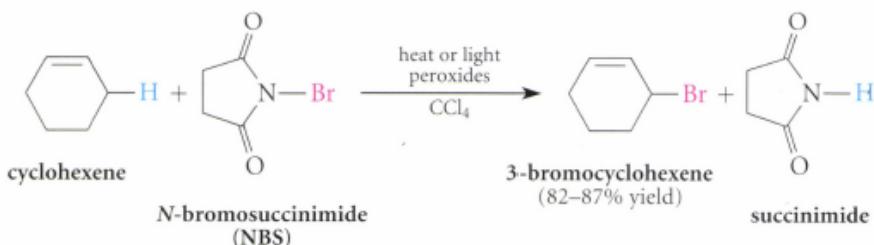
C. Cyclopentene reactions

- Addition: dark; polar CH₂Cl₂ solvent.
- Substitution: heat/light; apolar CCl₄, slow addition of Br₂ to maintain low concentration.



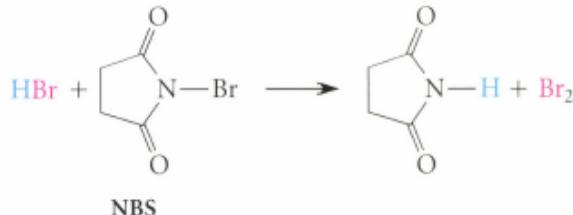
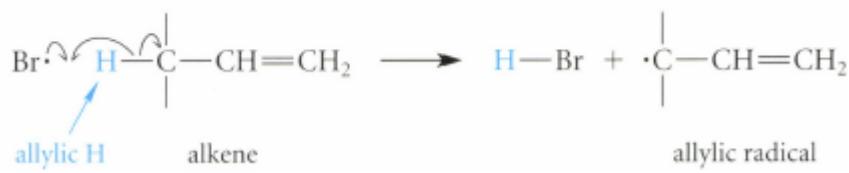
- Br-substitution may also be accomplished using N-bromosuccinimide (NBS).

This keeps the Br₂ concentration low.



- Initiation: homolytic cleavage of N-Br to form N· and Br·.

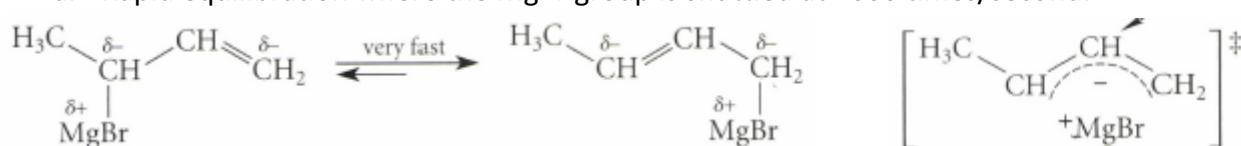
e. Propogation:



f. Termination: any two of the radicals combine.

17.3 Reactions Involving Allylic and Benzylic Anions

- A. Anions are stabilized by the resonance effect and the polar effect (electronegativity helps pull away and delocalize electron density).
 - B. Allylic Grignard Reagents

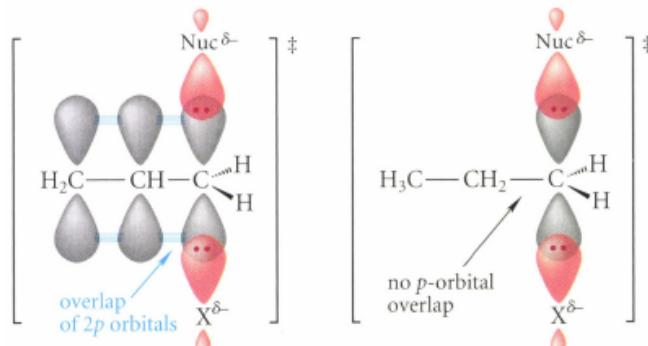


- b. Allylic rearrangement: simultaneous movement of a group and a double bond that interconverts allylic isomers. NO RESONANCE; two distinct species in equilibrium.

 - The same mixture of reagents is obtained from either of two allylic alkyl halides.
 - When Grignard reagents undergo subsequent reaction to form a mixture of products.

17.4 Allylic and Benzylic E2/S_N2 Reactions

- A. E2 Eliminations Involving Allylic or Benzylic Hydrogens
 - c. Allylic or benzylic character promote elimination by enhancing the acidity of β -hydrogens.
 - d. The transition state involves a partial allylic/benzylic carbanion that can be stabilized.
 - B. Allylic or benzylic character promote S_N2 because additional overlap from the pi bonds stabilizes the $2p$ orbital created in the sp^2 transition state.



17.5 Allylic and Benzylic Oxidation

A. Oxidation of Allylic and Benzylic Alcohols

- Oxidized selectively by MnO_2 suspension \rightarrow carbonyls.
- Activated MnO_2 is obtained by redox reaction of KMnO_4 with Mn^{2+} salt (MnSO_4) under acidic/basic conditions. Water competes with alcohol for MnO_2 sites, so drying is necessary.

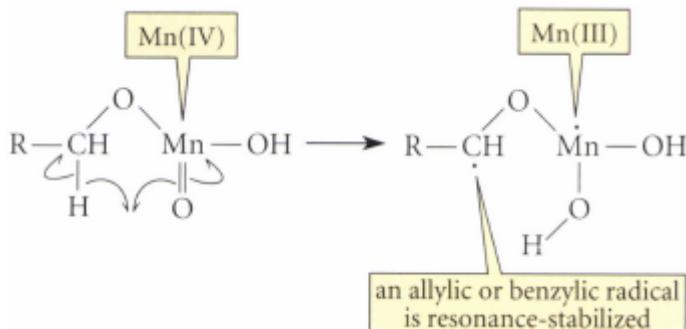


- MnO_2 oxidation is SELECTIVE for allylic and benzylic alcohols, which are the only ones that can react rapidly
- Mechanism:

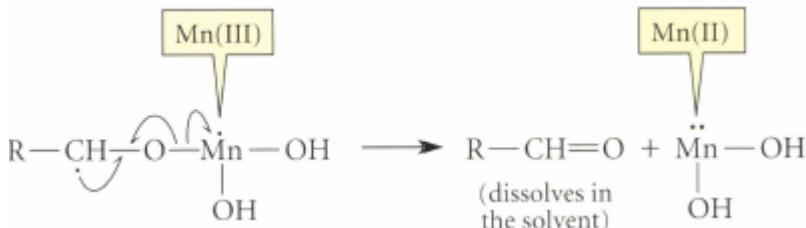
- Step (1): OH adds to MnO_2 \rightarrow ester



- Step (2): [rate-limiting] $\text{Mn}(\text{IV}) + \text{e}^- \rightarrow \text{Mn}(\text{III})$; H is transferred from the allylic/benzylic carbon to the oxidant oxygen. The benzylic/allylic resonance-stabilization of the radical is what confers selectivity.

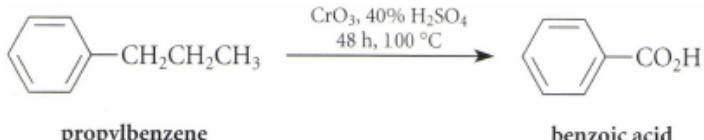


- $\text{Mn}(\text{III})$ is reduced to $\text{Mn}(\text{II})$ and $\text{C}=\text{O}$ forms to give the carbonyl.



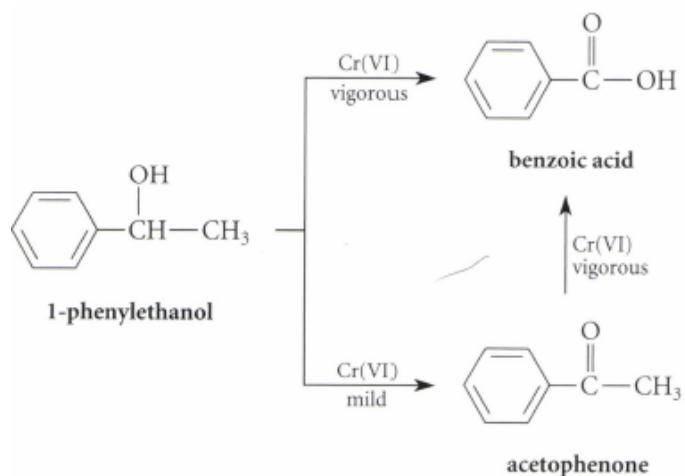
B. Benzylic Oxidation of Alkylbenzenes

- Alkyl side chains on benzene may be oxidized to carboxylic acids. Oxidants include $\text{Na}_2\text{Cr}_2\text{O}_7$ or CrO_3 , KMnO_4 , O_2 and special catalysts.



- The length of the alkyl side chain is irrelevant.
- Oxidation of alkyl side chains requires a benzylic hydrogen ($t\text{B}$ -benzene is unreactive).
- Reaction conditions

- Vigorous conditions lead to complete oxidation: heat, high concentration of oxidant, and long reaction times.
- Mild conditions may lead to less extensive oxidations.



17.6 Terpenes – NOT COVERED

A. The Isoprene Rule

- Essential oils: substance possessing a key characteristic (odor/flavor) of the natural material.
- Terpenes (isoprenoids): natural products containing a 5:8 C:H ratio composition.
Common structural feature: repeating units of isoprene (double-bonds unimportant).



the carbon skeleton
of isoprene

- The basis of terpene/isoprenoid classification is only the connectivity of the carbon skeleton.

Chapter 18 – Aryl and Vinylic Halides and Transition-Metal Catalysis

18.1 Lack of Reactivity of Vinylic and Aryl Halides under S_N2 Conditions

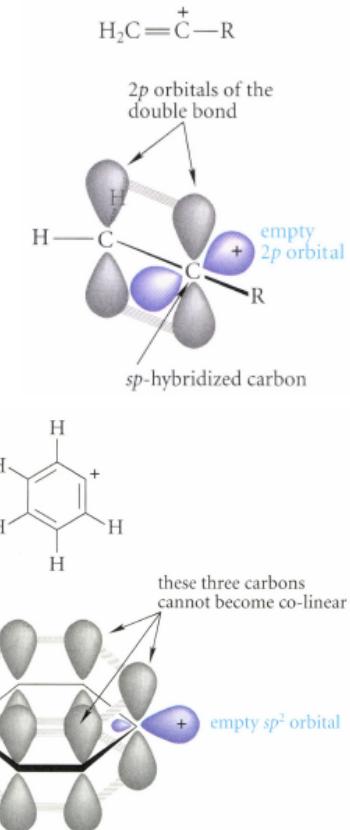
- G. Hybridization barrier: Vinylic/aryl halides would have to dehybridize to sp to give a free p-orbital for S_N2 attack, which has such high energy (21 kJ/mol) that it slows down S_N2 by ~1000x.
- H. Steric barrier: the nucleophile approaches in the plane of the alkene, leading to terrible repulsions.

18.2 Elimination Reactions of Vinylic Halides

- A. β-elimination occurs under harsh conditions (heat or very strong base) to form alkynes.

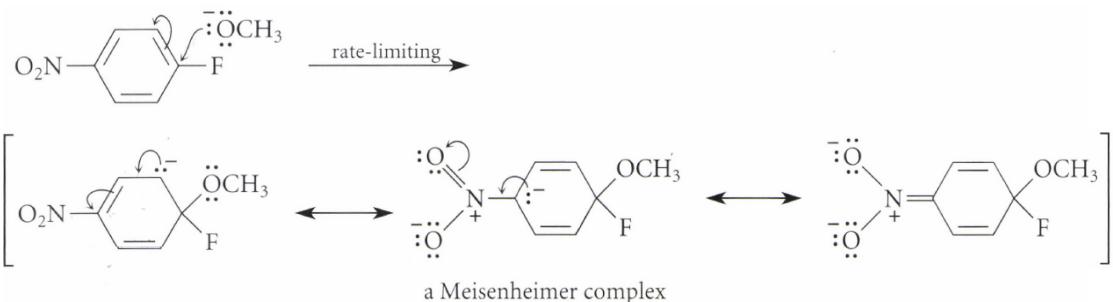
18.3 Lack of Reactivity of Vinylic and Aryl Halides under S_N1/E1 conditions.

- A. Vinyl halide dissociation results in highly unstable vinylic cations.
 - a. The electron-withdrawing double-bond and the sp² C—X bond keeps electrons from leaving to form the cation.
 - b. Vinyl cations want a linear formation → high-energy sp-hybridization.
- B. Aryl halides dissociation results in highly unstable aryl cations.
 - a. The electron-withdrawing ring double-bonds keep electrons from leaving to form the cation.
 - b. Aryl cations cannot adopt a linear formation for a new p-orbital, so bond strain.
 - c. The aryl cation is NOT the same as the carbocation intermediate formed in electrophilic aromatic substitution because it is orthogonal to the pi-electron system and cannot be resonance-stabilized.

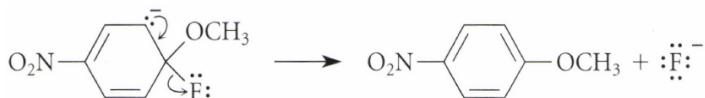


18.4 Nucleophilic Aromatic Substitution Reactions of Aryl Halides

- A. Nucleophilic aromatic substitution: occurs in aryl halides with EWGs ortho/para to the halogen.
- B. 2nd order bimolecular: rate = k[ArX][Nuc] – but no concerted backside mechanism.
- C. Possible nucleophiles: OH[−], OR[−], SR[−], NR₂[−]
- D. Mechanism
 - a. Step (1): The nucleophile reacts above/below the plane of the ring (rate-limiting step).
 - b. This yields a resonance-stabilized anionic Meisenheimer complex, where the negative charge in this complex is delocalized onto the nitro group.



c. Step (2): The Meisenheimer complex loses the halide ion to form product.



E. Implications of mechanism

- The reaction is faster with more EWGs ortho/para to the halogen. Each has a huge effect.
- Effect of halogen type on reactivity is reversed from S_N2: Ar—F >> Ar—Cl/Br/I
This is because (a) more electronegative helps stabilize the anion by polar effect, and
(b) the loss of halide is not rate-limiting, so increased H-X acidity doesn't affect reaction rate.
- The reaction is NOT concerted. The Meisenheimer complex is an actual intermediate.

18.5 Intro to Transition-Metal Catalyzed Reactions

A. Transition Metals and Their Complexes

- Schepartz triangle: used to gather the orbital configurations.
- The energy levels of the higher s and lower d orbitals are very similar, so both are considered valence shells. For example, Ni is [Ar]4s²3d⁸, but it has 10 valence electrons.
- Coordination compounds are when ligands surround transition metals to form transition-metal complexes. These may be neutral, or complex ions.
- Ligands are Lewis bases that donate electron pairs to transition metals.
 - L-ligand: uncharged when dissociated. Upon dissociation, L-ligands keep their electrons. Removal does not affect formal charge. L-ligands form dative bonds with the metal. R₃P, R₃N, pi-bonds.
 - X-ligand: (-1) charge when dissociated. X-ligands keep one electron, and the metal keeps the other electron. Removal +1 to the metal and -1 to the ligand.
Halogens, methyl, vinyl, aryl, NH₂, H, RO, RS.
- Alkenes, alkynes, or aromatic rings may act as ligands by donating pi electrons to a metal.

Ligand	Name	Abbreviation	Type	Electron count*
H ₃ N:	ammine		L	2
H ₂ O:	aquo		L	2 [†]
R ₃ P: (R = alkyl, aryl)	trialkylphosphino, triarylphosphino		L	2
:C=O:	carbonyl	CO	L	2 [‡]
H ₂ C=CH ₂ [§]	ethylene		L	2
CH ₃ C≡N:	acetonitrile	MeCN	L	2 ^{§§}
	benzene		L ₃	6
F ⁻ , Cl ⁻ , Br ⁻ , I ⁻	halo (e.g., chloro)	X	X	2 [†]
H ⁻	hydrido		X	2
H ₃ C—C(=O)—O ⁻	acetato	AcO	X	2 [†]
R: ⁻ e.g., H ₃ C: ⁻	alkyl (e.g., methyl)		X	2
:C≡N:	cyano	CN	X	2 [‡]
H ₂ C=CH—CH ₂	allyl		LX	4**
	cyclopentadienyl	Cp	L ₂ X	6

*The sum of all electrons in the bond(s) between the ligand and the metal.

[†]Only one electron pair is involved in the ligand–metal interaction.

[‡]Only the electron pair on carbon is involved in the ligand–metal interaction.

[§]Ethylene is listed as a prototype for many alkenes.

^{§§}Donation of the nitrogen unshared electron pair.

**Allyl can also bind to metals as an X-type ligand. In such a situation, the π bond is not involved in coordination and the electron count is 2 (as with alkyl).

B. Oxidation State

- Oxidation state: the charge of the metal if all covalently bonds dissociated.
- Oxidation state of M = #X-ligands + Q_M** (Q_M is actual charge of M before dissociation).
L-ligands do not contribute to the oxidation state.

C. The dⁿ Notation

- dⁿ notation: n is the number of the unshared valence electrons on a metal.

A complex with 4 unshared valence electrons pairs \rightarrow d⁸ complex

- n = valence e- in neutral M – oxidation state of M.**

n = valence e- in neutral M – Q_M – #X-ligands.

D. Electron Counting: The 16- and 18-Electron Rules

a. Electron count = $n + 2$ (#ligands)

Electron count = valence e- in neutral M – oxidation state of M + 2(#ligands)

Electron count = valence e- in neutral M – Q_M – #X-ligands + 2(#ligands)

Electron count = valence e- in charged M + #X-ligands + 2(#L-ligands)

E. Electron configuration and stability

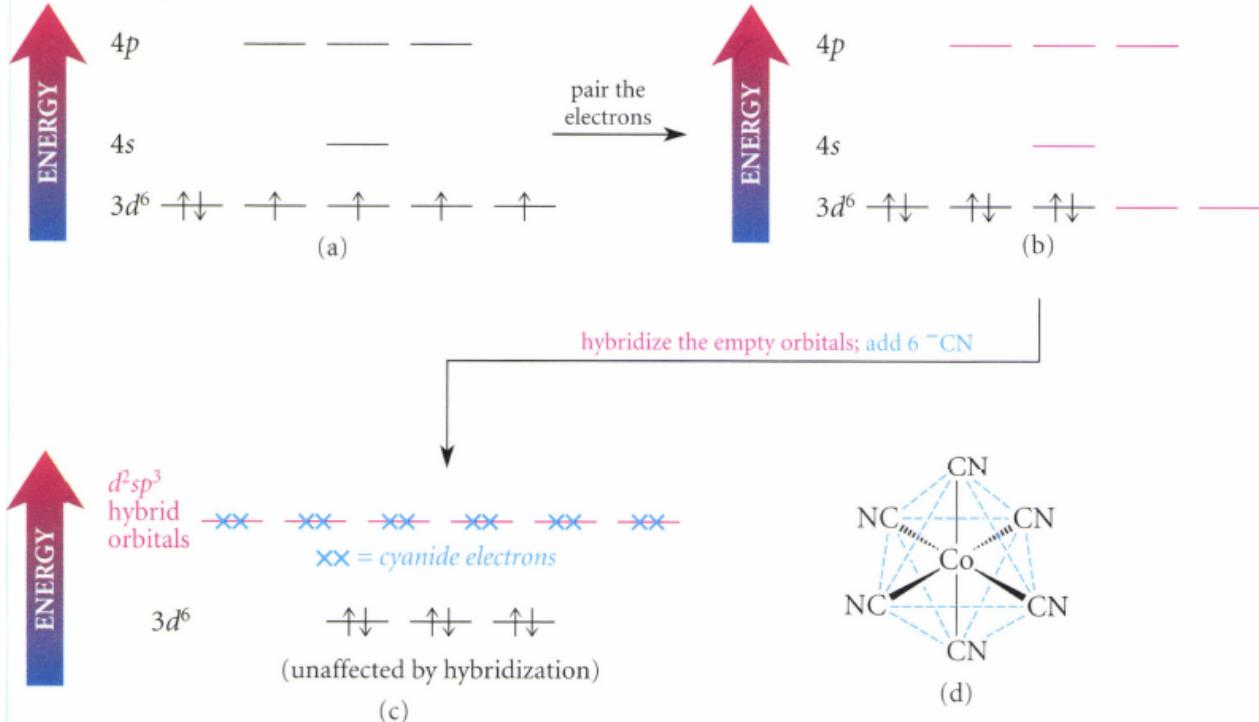
a. 18-electron rule: the transition-metal analog of the octet rule for stability.

b. 16-electron rule: stable exceptions to the 18-electron rule, often found in the 8-11 valence electron group (Ni, Pd).

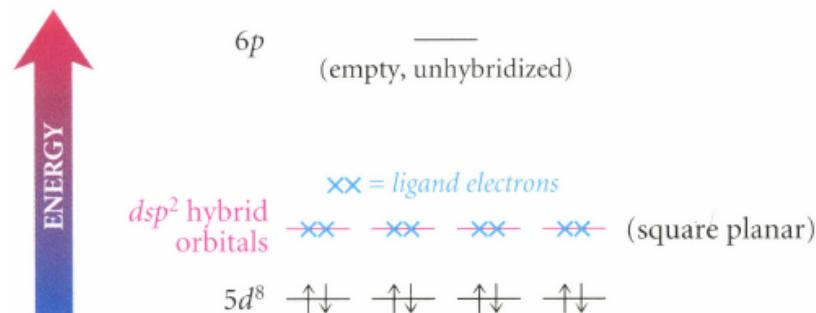
c. 14-electrons: highly reactive.

F. Hybridization derivation of the 18-electron rule: 6 empty orbitals all hybridize.

Unhybridized Co^{3+} (d^6):



Hybridization derivation of the 16-electron rule: 5 empty orbitals; only 4 hybridize.



G. Given VE; calculate OS, d^n , EC.

H. Fundamental Reactions of Transition-Metal Complexes

a. Notation: $L_nM + L' \rightarrow L + L_{n-1}ML'$ ($n = \#$ Ligands)

L leaves and L' binds; can be concerted or stepwise (L leaves first).

b. Ligand Dissociation-Association; Ligand Substitution

i. Dissociation: ligands depart from the metal with its pair of electrons, leaving a vacant orbital. This changes the electron count but not the oxidation state.

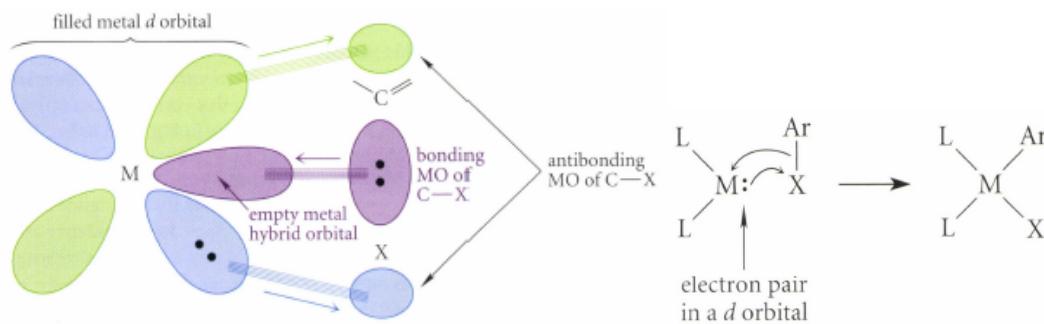
ii. Association: the reverse of dissociation: attacking at vacant orbitals.

iii. Substitution: combined dissociation/association of ligands (mostly same X/L type)

c. Oxidative Addition

i. Metal M inserts into $X-Y$ to form $X-M-Y$ and is oxidized (e.g. Grignard formation)

ii. Essentially, X and Y both becomes ligands of M. M's previous ligands are preserved.



d. Reductive Elimination

i. Opposite of oxidative addition

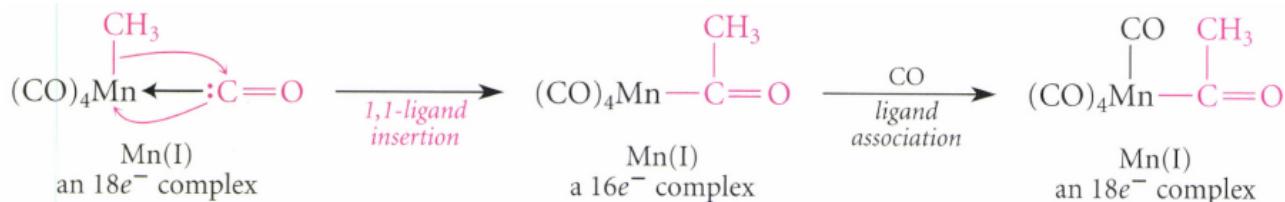
ii. Can form new C—C bonds with full retention of stereochemistry, esp. olefins.

e. Ligand Insertion

i. 1,1-insertion: new bond formed one atom down.

Step (1): $C=O$ inserts into the $Mn-CH_3$ bond, leaving an empty orbital on Mn.

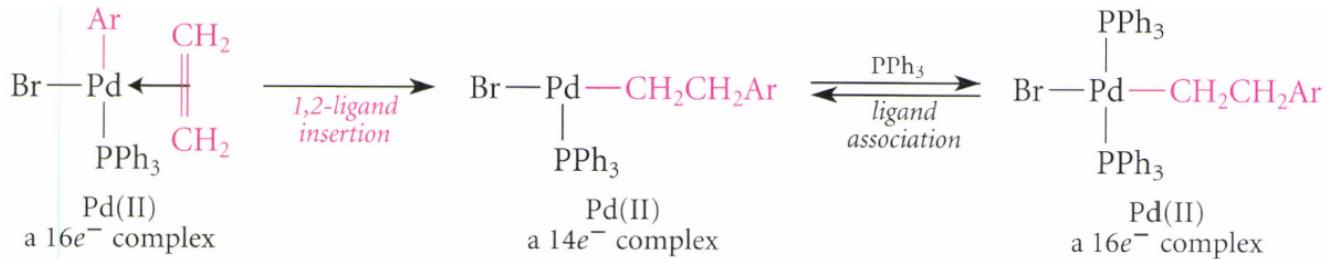
Step (2): The empty Mn orbital is filled by CO ligand association from solution.



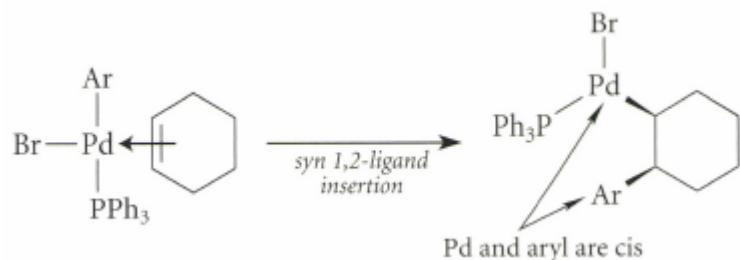
ii. 1,2-insertion: migrating group moves two atoms down.

Step (1): $H_2C=CH_2$ inserts into the $Pd-Ar$ bond, leaving an empty orbital on Pd.

Step (2): The empty Pd orbital is filled by PPh_3 ligand association from solution.



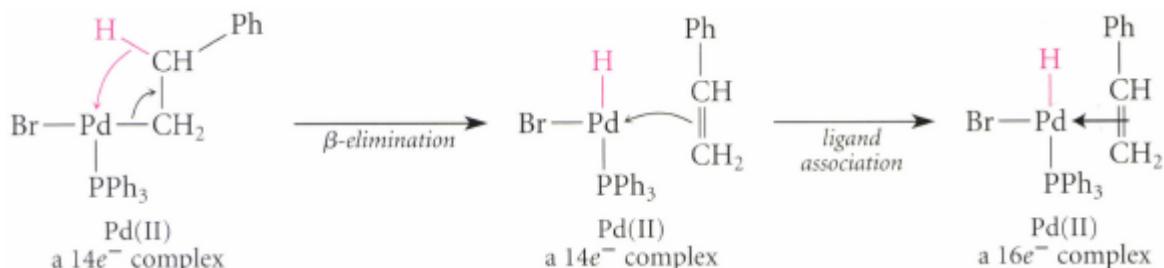
iii. 1,2-insertion is concerted intramolecular addition, so the two new bonds are formed by syn-addition, and must be cis to each other.



iv. JUST RECOGNIZE/IDENTIFY WHAT KIND OF REACTION IT IS, PREDICT THE PRODUCT.

f. β -hydrogen elimination

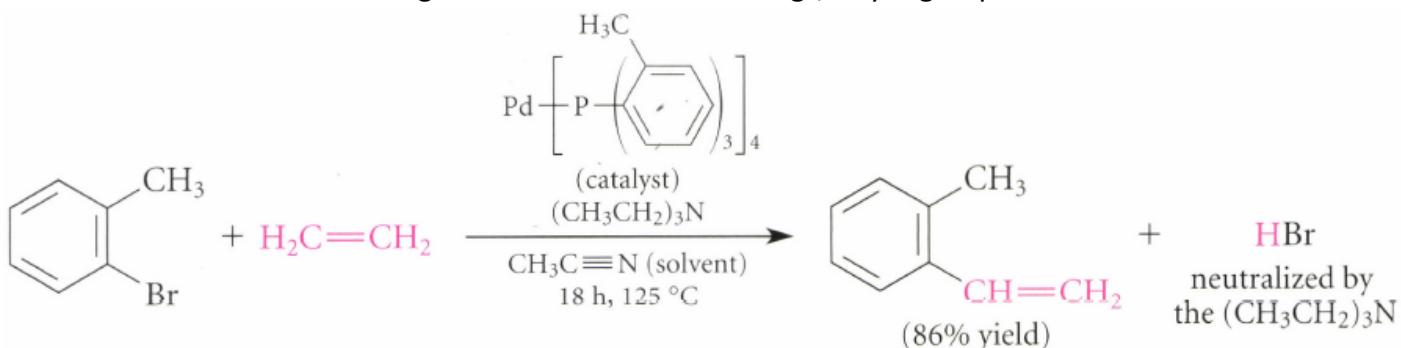
- Opposite of ligand insertion. A β -hydride migrates (with bonding e- pair) to the metal.
- $M-X_\alpha-Y_\beta-H \rightarrow H-M-(X=Y)$
- Requires an empty orbital on the metal.
- Intramolecular: must occur as syn-elimination.



18.6 Examples of Transition-Metal-Catalyzed Reactions

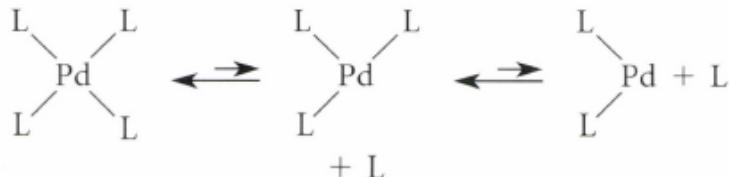
A. The Heck Reaction

- Alkene substitutes for Br/I in an aryl group, under Pd(0) catalyst – $Pd(PPh_3)_4$, $Pd(OAc)_2$
- Useful for forming C–C bonds to aromatic rings/vinylic groups.

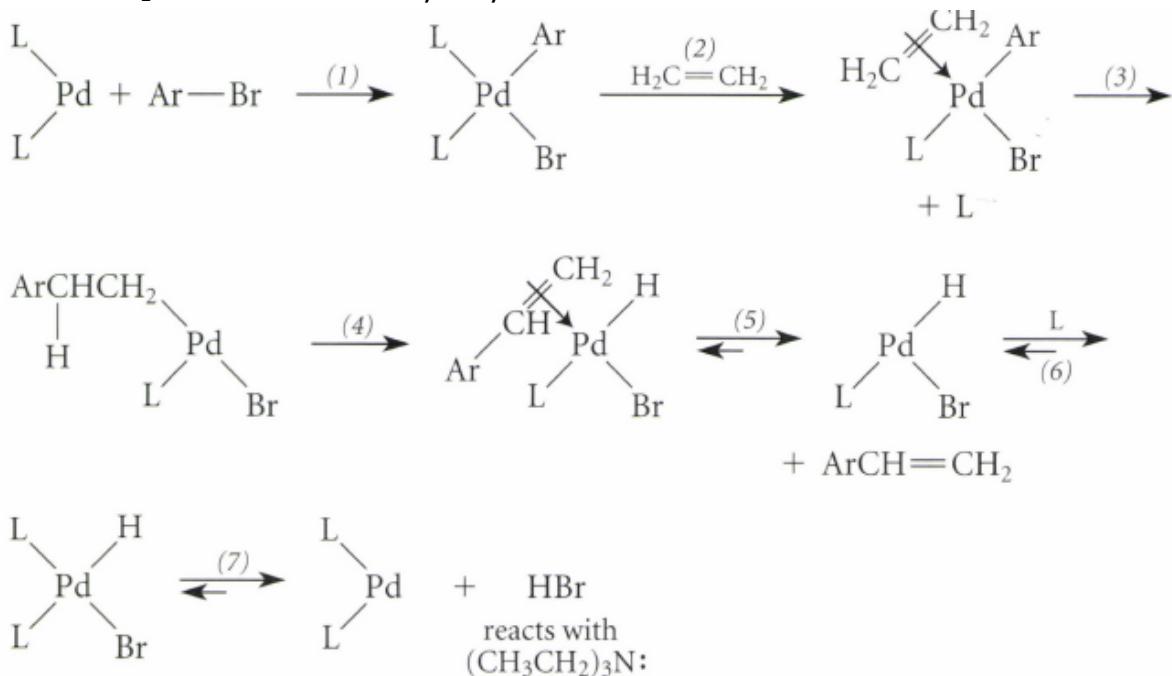


c. Mechanism:

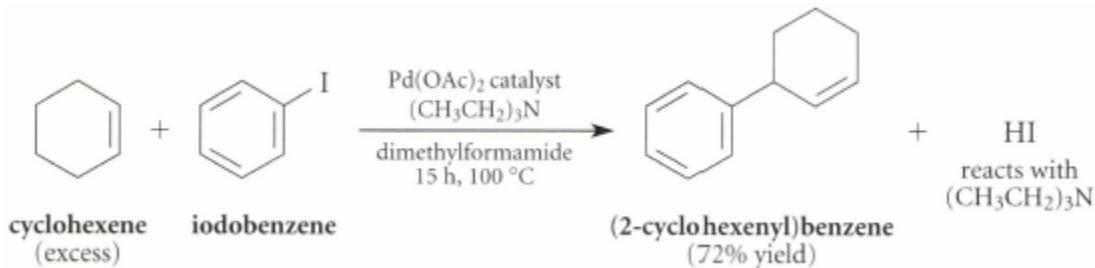
- The catalytically active species is PdL_2 , formed by 2 ligand dissociations:



ii. PdL_2 enters into the catalytic cycle



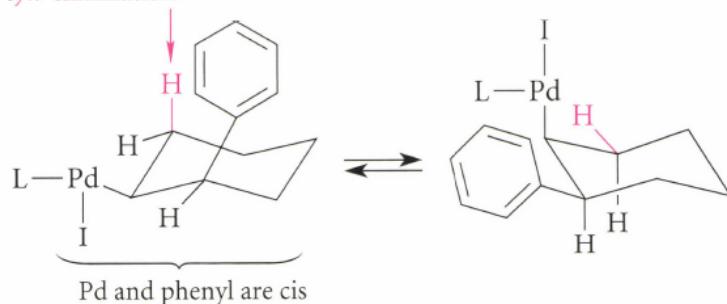
d. In some cases, $\text{Pd}(\text{II})$ may be used to generate $\text{Pd}(0)$ [the catalyst] for ease and convenience.



e. Regiochemistry: the site of coupling is 1 carbon removed.

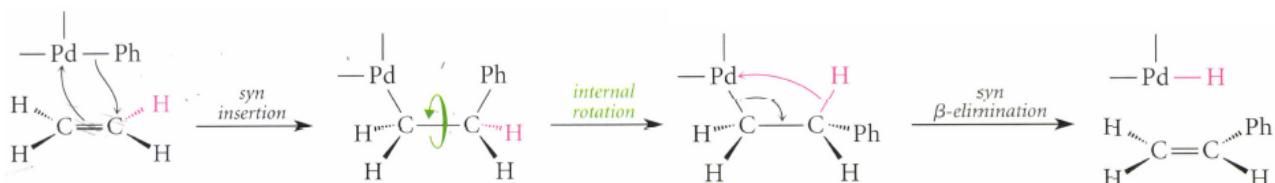
f. Stereochemistry: Syn insertion occurs in the intramolecular reaction.

the only β -hydrogen available for syn-elimination

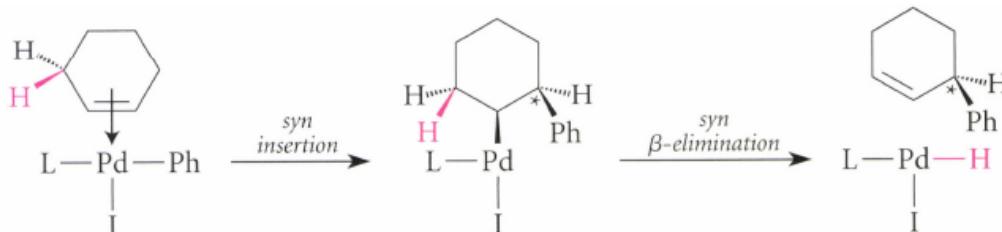


g. β -hydrogen elimination is also a syn process.

i. If a noncyclic alkene is used, internal rotation makes the hydride on the carbon at which insertion occurs, eliminable.



- ii. If a cyclic alkene is used, no internal rotation means that the other β -hydride is the only one available.

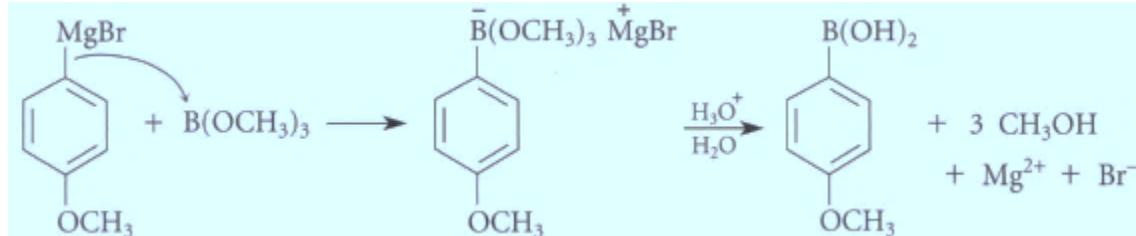


- When the Heck reaction is applied to unsymmetrical alkenes, two products are possible (insertion could occur at either alkene carbon).
- When the R-group is Ph, CO_2R , CN, or another EWG, ArX tends to react at the unsubstituted carbon to give $\text{R}-\text{CH}=\text{CH}-\text{Ar}$. Alkyl groups give a mix of products.

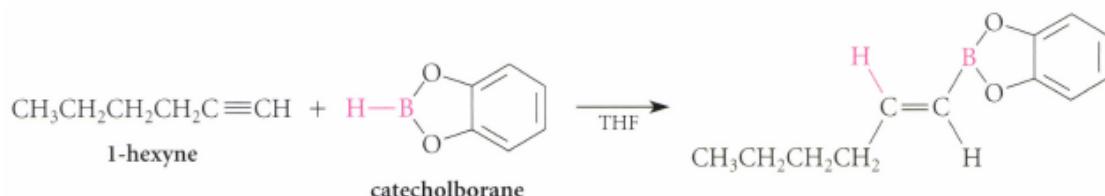
B. The Suzuki Coupling Reaction

- Prepares biaryls, aryl-substituted alkenes, and conjugated alkenes with retention of alkene stereochemistry WITHOUT regiochemistry issues that arise from the Heck reaction.
- Preparation of reagents

- Grignard reaction with trimethyl borate: $\text{B}(\text{OCH}_3)_3$

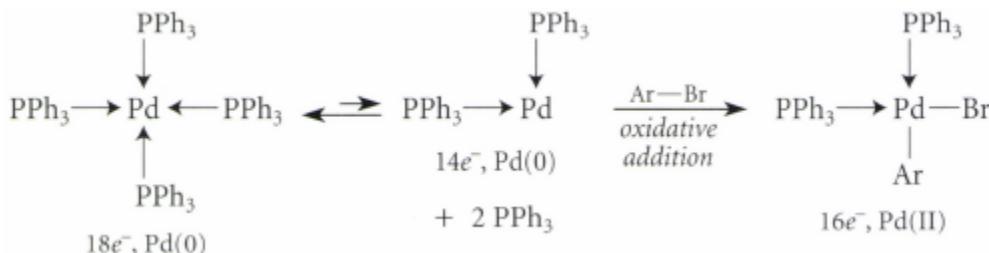


- Hydroboration of 1-alkanes to form conjugated alkenes.

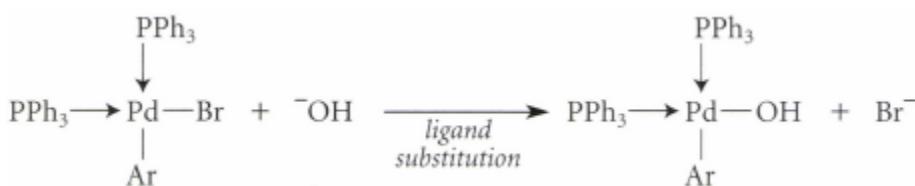


c. Mechanism:

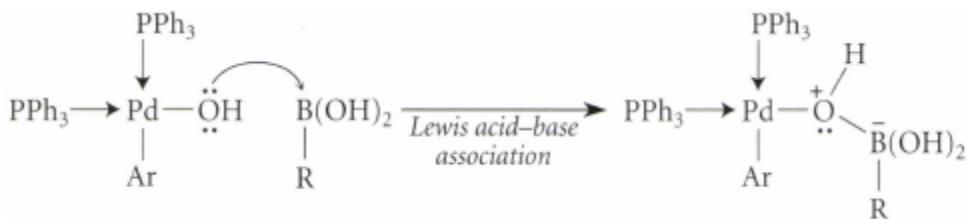
- Ligand dissociation gives a 14e- complex followed by oxidative addition of $\text{Ar}-\text{X}$.



- Another ligand substitution where the base displaces the halide ion.

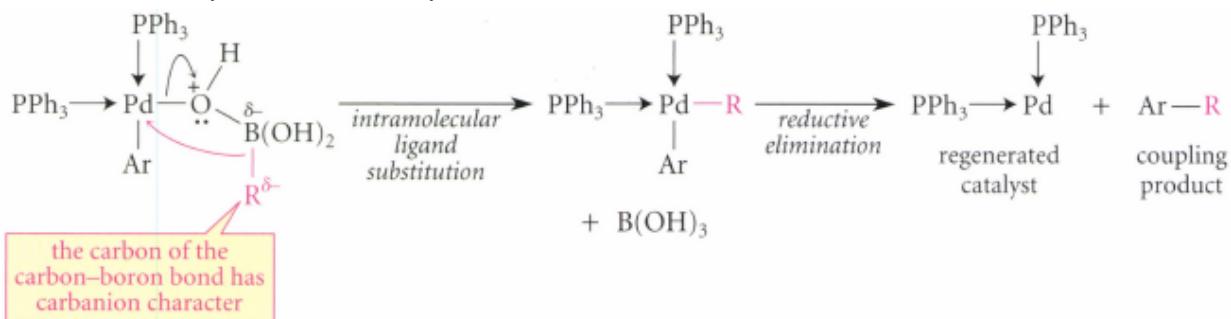


iii. A Lewis acid-base association brings boron to the metal.



Formal charges are deceiving – carbon is more electronegative than boron, and has significant carbanion character.

iv. Intramolecular substitution of this basic carbanion for the weaker base transfers the R-group to the metal. Reductive elimination gives the coupling product and provides the catalyst for the next cycle.



Chapter 19 – Aldehydes and Ketones: Carbonyl Addition

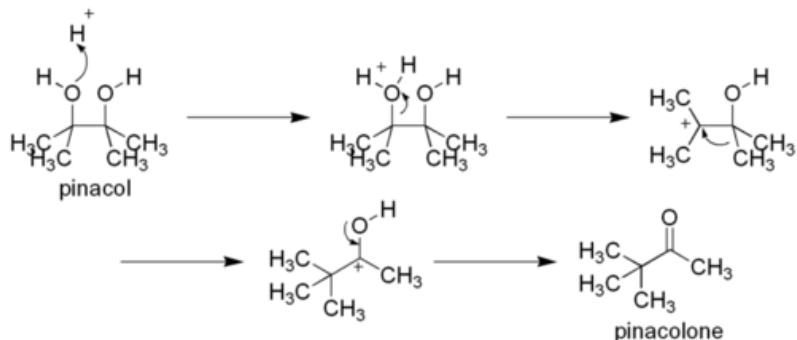
19.5 Introduction to Aldehyde and Ketone Reactions

The carbonyl O is nucleophilic/weakly basic. The carbonyl C is electrophilic.

19.6 Basicity of Aldehydes and Ketones

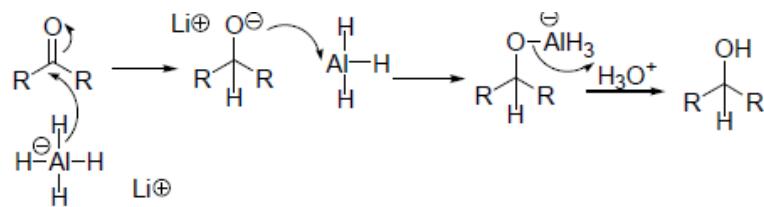
- A. β -hydrogens are more acidic because the negative charge on the conjugate base is stabilized by the enolate resonance. After deprotonation, the nucleophilic β -carbon can attack electrophiles.
When does this even happen?

- B. Pinacol Reaction:



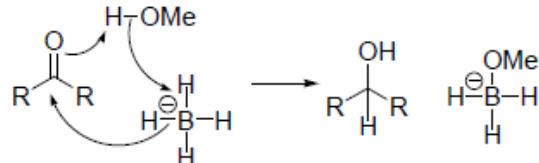
- C. Reversible Addition Reactions of Carbonyl Groups

- Geometry is important: carbon's hybridization goes from sp^2 to sp^3 .
 - Nuc: attacks at the π^* orbital, and this weakens the C=O bond.
 - Nuc: attacks from either above or below the carbonyl plane = potential stereocenter.
- Basic/neutral conditions: the base attacks the carbonyl carbon to form a tetrahedral intermediate. These intermediates have choices!
 - Protonation yields an alcohol-base tetrahedral molecular structure
 - Protonation ejects the base (return to original state).
- Acidic conditions: $\text{C=O}^+\text{H}$ makes the carbon more electrophilic. After attack of OH_2 :
 - Deprotonate ${}^+\text{OH}_2$
 - Eject ${}^+\text{OH}_2$ (return to original state).
- Additional alkyl groups (a) donate electron density to the carbonyl carbon and make it less electrophilic, and (b) destabilize the intermediate by steric effects. Ketone is less reactive.
- Polar effect: trifluoro-ketones are a lot more electrophilic.
- Reduction reactions: carbonyl reduced with hydride, then workup to an alcohol.
- Reagents:
 - $1. \text{LiAlH}_4 \quad 2. \text{H}_3\text{O}^+$ (reduces alcohols, CN, carboxylic acids, nitriles, etc) [no water]
 - NaBH_4 (only aldehydes and ketones) [protic solvent].
 - H_2/Ni^0 at high pressure.
- Reaction of NaLiH_4
 - Step (1) Addition of H^- forms an R_4AlLi intermediate.
 - Step (2) H_3O^+ work-up exchanges each R-group for H^+ from water.



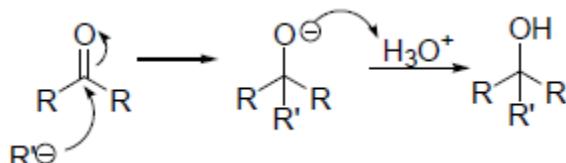
i. Reaction of NaBH_4

- i. Concerted reaction: the protic solvent donates H^+ , the bond goes to NaBH_4 , which donates H with its e- pair to the carbonyl carbon.



19.9 Reactions with Organometallics

- A. Step (1): An organometallic attacks the carbonyl. Step (2) H_2O work-up.



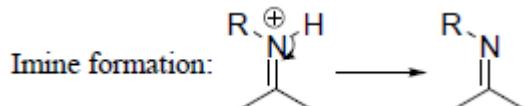
- B. Organometallic may be: Grignard reagents, organolithiums, and acetylenic anions

- C. CAVEAT: if the organometallic deprotonates a beta hydrogen and forms an enol, the carbon is no longer electrophilic.

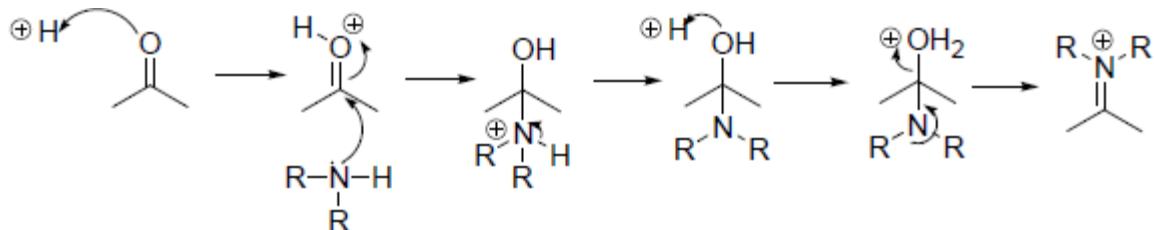
19.11 Reactions of Aldehydes and Ketones with Amines

- A. Imine: nitrogen analog of a carbonyl, where $\text{C}=\text{O}$ becomes $\text{C}=\text{NR}$.

Iminium ion: protonated imine



- B. Reactions with 1° amines: (note- nitrogen has an invisible lone pair after deprotonation)



- a. Rate-limiting step: loss of water

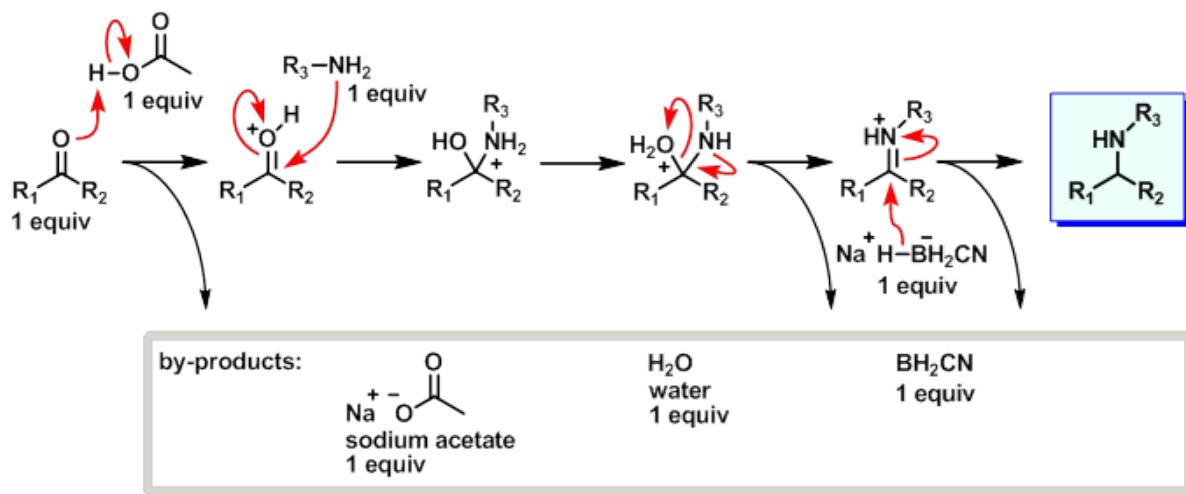
- b. Stereochemistry: trans-conformation preferred: R is closer to the smaller group (sterics)

- C. Reductive Amination

- a. Basically: imines/iminium ions can be reduced by NaCnBH_3 to form the amine ($\text{R}-\text{:NH}-\text{R}'$)

- b. Iminium ions can be reduced selectively by NaCnBH_3 (sodium cyanoborohydride)

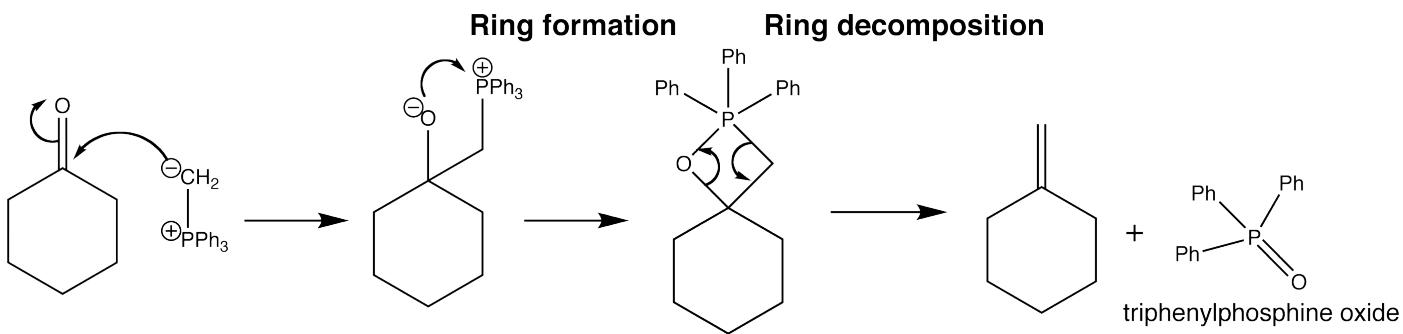
- c. The hydride attacks the DBC and pushes the pi electrons onto nitrogen.



d. NaCnBH_3 does not reduce aldehydes and ketones at pH 6.

D. Wittig Reaction

a. Add a ylide (anion-cation) that forms a 4-membered cyclic intermediate that decomposes to replace a carbonyl with an alkene with 100% precision.



Chapter 20 – Carboxylic Acids

20.2 Structure, Physical Properties, and Acidity of Carboxylic Acids

- A. Carboxylic Acid: basically carbonyl + hydroxyl.
- B. Both oxygens sp^2 hybridized – maintains partial double-bonds from resonance.
- C. Same rules of acidity apply (polar, resonance, distance, charge) $pK_a = 4-5$ range.
- D. The acid has resonance just like the conjugate base, but separation of charge makes it less stable.
- E. Ionized forms are more soluble.

20.6 Synthesis of Carboxylic Acids

- A. Ozonolysis: (alkene) + 1. O_3 , 2. $H_2O_2 \rightarrow$ diacid
- B. Oxidation of 1° OH or COH or Ar—?: $(ROH) + H_2CrO_4, H_2O \rightarrow$ acid
- C. Grignard addition to CO_2 : $(R-Br) + 1. Mg, 2. CO_2, 3. H_3O^+ \rightarrow$ acid
- D. Hydrolysis of Nitriles: $(R-C\equiv N) + 1. H_3O^+/H_2O, 2. heat \rightarrow$ acid + ammonium ion.
 - a. From RX via $Sn2$: $(R-X) + NaCN \rightarrow R-C\equiv N$
 - b. From cyanohydrin: $RCO_2H + 1. HCN, 2. H_3O^+ \rightarrow ROH-CO_2H$ (α -hydroxy acid)

20.7-20.9 Formation of Carboxylic Acid Derivatives

- A. Carbonyl substitution: Nuc: replaces OH. Carboxylate oxygen (Nuc:) can attack electrophiles.
- B. Ester Formation
 - a. $Sn2$: $RCOO^-$ anion attacks $R'X \rightarrow$ ester, $RCOO^-$ generated by K_2CO_3 base.
 - b. Alkylation: CO_2H is deprotonated by $H_2C^{(-)}-^{(+)}N\equiv N$; and then attacks by $Sn2 \rightarrow$ methyl/benzylic ester
 - c. Fischer Esterification: $CO_2H + ROH(xs) \rightarrow$ acid \rightarrow ester. Driven by Le Châtelier's principle.
Basic conditions do not work.
- C. Lactone Formation: substitution on a 1,4 or 1,5 acid alcohol (to form a 5-6 membered ring)
- D. Acid Halide Formation: $SOCl_2$ or PCl_5 binds to the carbonyl oxygen, releasing one of the Cl^- anions to attack the activated carbonyl carbon. The $OSOCl$ group leaves and kicks off Cl^- to form $HCl + SO_2$.
- E. Anhydride Formation:
 - a. From acid chloride: $ROCl + RO_2H \rightarrow$ anhydride
 - b. From two acids: $RO_2H + P_2O_5 \rightarrow$ anhydride.
 - c. Cyclization: 1,4 and 1,5 diacids + heat \rightarrow cyclic anhydride (5-6 membered ring)

20.10 Reduction of Carboxylic Acids to Primary Alcohols

- A. $LiAlH_4$ reduces $CO_2H \rightarrow OH$. $NaBH_4$ is weaker: reduces $C=O$, but not in CO_2H .
 - a. Step (1): H: (hydride) deprotonates $CO_2H \rightarrow H_2 + COO^-$
 - b. Step (2): COO^- attacks and complexes with $AlH_3 \rightarrow R/H/O^-/OAlH_3$ intermediate
 - c. Step (3): $OAlH_3$ reduces the carbonyl and gets ejected \rightarrow aldehyde
 - d. Step (4): A new AlH_4 reduces the aldehyde to form $R/H/H/OLi$
 - e. Step (5): H_3O^+ workup replaces Li with H
- B. Decarboxylation of diacids with β -carbonyls
 - a. Cyclic mechanism: diacid + $H_3O^+/H_2O \rightarrow$ enol-keto tautomer + CO_2

Synthesis of esters:

- acid-catalyzed esterification of carboxylic acids (Sec. 20.8A)
- alkylation of carboxylic acids or carboxylate salts (Sec. 20.8B)
- reaction of acid chlorides and anhydrides with alcohols or phenols (Sec. 21.8A)
- transesterification of other esters (Sec. 21.8C)

Synthesis of acid chlorides:

- reaction of carboxylic acids with SOCl_2 or PCl_5 (Sec. 20.9A)

Synthesis of anhydrides:

- reaction of carboxylic acids with dehydrating agents (Sec. 20.9B)
- reaction of acid chlorides with carboxylate salts (Sec. 21.8A)

Synthesis of amides:

- reaction of acid chlorides, anhydrides, or esters with amines (Sec. 21.8A,C)

Synthesis of nitriles:

The synthesis of nitriles is an important exception to the generalization that carboxylic acid derivatives are usually prepared from other carboxylic acid derivatives. Two syntheses of nitriles are:

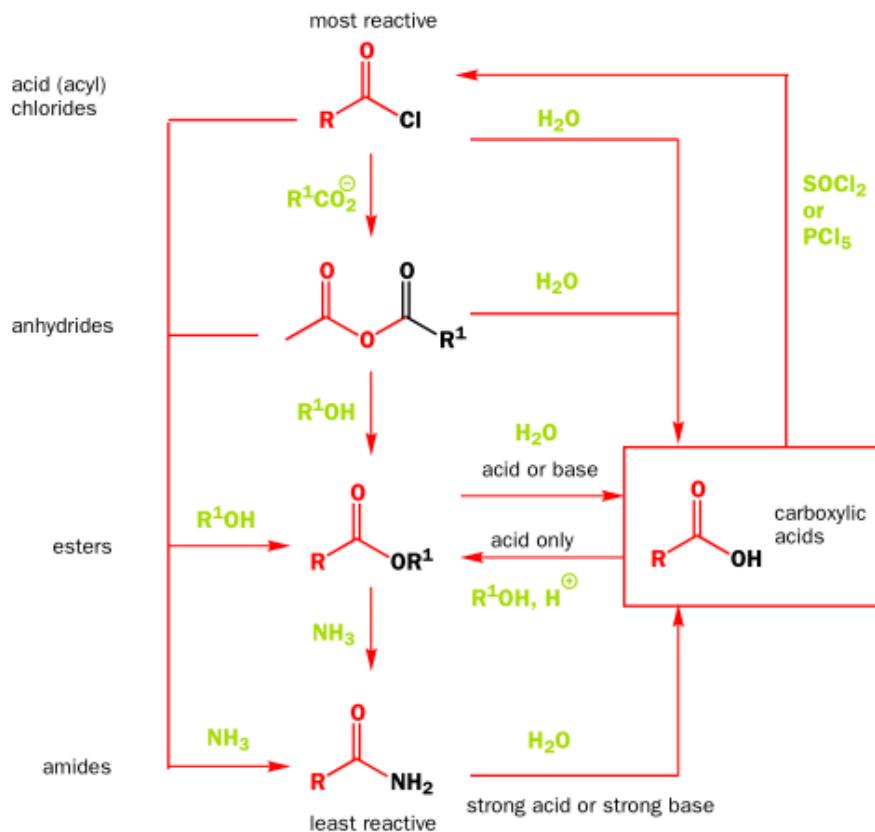
- cyanohydrin formation (Sec. 19.7)
- $\text{S}_{\text{N}}2$ reaction of cyanide ion with alkyl halides or sulfonate esters

The $\text{S}_{\text{N}}2$ reaction was discussed thoroughly in Sec. 9.4, and the reaction of alkyl halides with cyanide ion was used as an example in Table 9.1 on p. 379. Let's now focus on that reaction as a useful organic synthesis. Recall that an $\text{S}_{\text{N}}2$ reaction of cyanide ion, like all $\text{S}_{\text{N}}2$ reactions, requires a primary or unbranched secondary alkyl halide or sulfonate ester, as in the following examples.

Chapter 21 – Carboxylic Acid Derivatives

21.1 Classification of Carboxylic Acid Derivatives

F. Handy-Dandy Chart

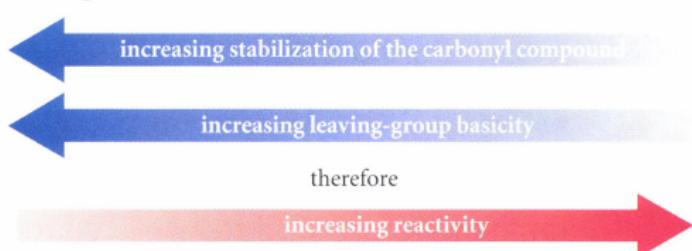
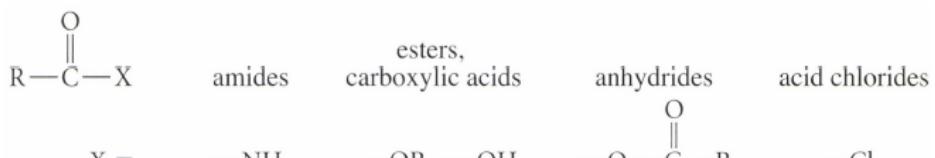


G. Nitriles are kind of at the bottom of this list.

H. Lactone: cyclic ester. Lactam: cyclic amide

21.5 Structures and Physical Properties of Carboxylic Acid Derivatives

- In acyl substitution reactions, the pK_a of the leaving group predicts the stability of the species. Lower pK_a (more acidic) has electronegativity and overlap effects that make good leaving groups.
- Basicity follows hybridization state: more s character = more electronegative = more stable negative charge on conjugate base = more acidic.
- This reactivity order means that you can selectively hydrolyze groups with precise conditions.

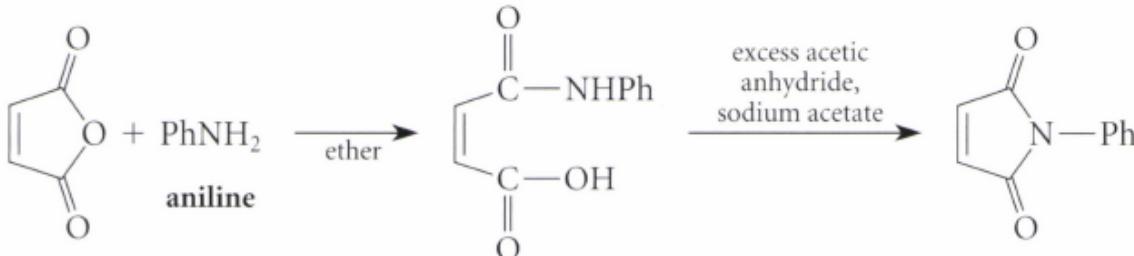


21.7 Hydrolysis of Carboxylic Acid Derivatives

- A. Acyl substitution: substitution at the carbonyl carbon of an acyl group. Often nucleophilic.
- B. Hydrolysis of Esters by Acyl Substitution
 - a. Basic conditions: OH replaces OR in an ester (saponification). Irreversible because the final product is the carboxylic acid salt, which is effectively removed from equilibrium. -OH is NOT catalytic; 1 eq is required. Must be followed by H₃O⁺.
 - b. Acid-catalyzed: requires excess water, strong acid, reversible.
- C. Hydrolysis of Amides by Acyl Substitution: strong acid/base, heat, time (severe conditions)
- D. Hydrolysis of Nitriles by Addition: very harsh conditions produces an amide intermediate that decomposes to a carboxylic acid.
- E. Hydrolysis of Acid Chlorides and Anhydrides by Acyl Substitution
 - a. Rapid reaction with water to form carboxylic acids.
 - b. Not a useful synthesis technique – just avoid contaminating acid chlorides/anhydrides
- F. Note on Reactivity: the stability of the carbonyl reactant affects activation energy. A more stable reactant means a greater energy difference between it and the tetrahedral intermediate.

21.8 Reactions of Carboxylic Acid Derivatives with Nucleophiles

- A. Acid Chloride Reactions
 - a. Acid Chlorides + Ammonia/Amines → Amides + HCl
 - i. Replaces Cl with the amine. (NH_xR_y attacks, kicks off Cl, and is deprotonated).
 - ii. Pyridine base and 2 equivalents of NH_xR_y are used to neutralize HCl. Rapid and irreversible.
 - b. Acid Chlorides + Alcohols/Phenols → Esters + HCl
 - i. Replaces Cl with the alcohol. (OH attacks, kicks off Cl, and is deprotonated).
 - ii. Pyridine base is used to neutralize HCl.
 - c. Reaction of Acid Chlorides with Carboxylate Anions → Anhydride
 - i. Replaces Cl with the carboxylate anion. (COO⁻ attacks and kicks off Cl⁻)
 - ii. Na⁺ from the salt neutralizes Cl⁻
- B. Anhydride Reactions
 - a. Exact same products as acid chlorides, except COO⁻ is the leaving group.
 - b. Useful in producing half-esters and half-amides from cyclic anhydrides.
These may then be cyclized to imides by dehydration + heat.



C. Ester Reactions

- a. Reacts with ammonia/amines → amides.
- b. Reacts with R'OH(xs) to form new esters.

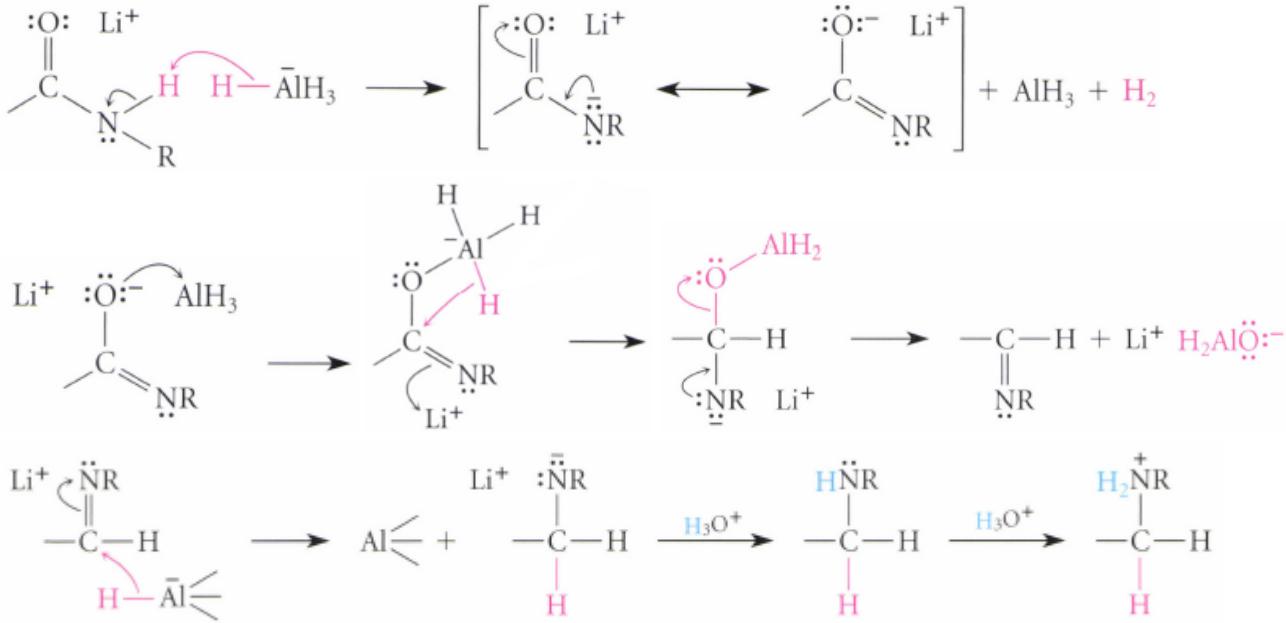
21.9 Reduction of Carboxylic Acid Derivatives

A. Reduction of Esters \rightarrow 1° Alcohols by LiAlH₄

- a. LiAlH₄ first cleaves off the OR group, then reduces the C=O to C—OH, forming 2 alcohols (after H₃O⁺)
- b. This also works for acid chlorides and anhydrides, but that's generally useless.

B. Reduction of Amides \rightarrow Amines by LiAlH₄

- a. LiAlH₄ reduces C=O to C—OH, then reduces it again to eject OH, leaving R—CH₂—NH₂.
- b. 2. H₃O⁺ and 3. OH⁻ workup needed.
- c. OH is ejected because NH₂ is an awful leaving group.



C. Reduction of Nitriles \rightarrow Primary Amines

- a. LiAlH₄: hydride attack gives the imine, which is reduced to the amine in the same way.
- b. H₂ + Raney nickel: catalytic hydrogenation: also proceeds through the imine.

D. Reduction of Acid Chlorides \rightarrow Aldehydes

- a. Rosenmund reduction: H₂ + Pd/C poisoned with quinoline/sulfur.
- b. LiAl(tB-O)₃H replaces 3 H's with tert-butoxy groups that lower reactivity of the remaining hydride.

21.10 Reactions of Derivatives with Organometallics

A. Esters + Grignard Reagents

- a. Step (1): Acyl substitution: 1st Grignard replaces OR \rightarrow ROH
- b. Step (2): 2nd Grignard attacks the carbonyl \rightarrow —OH

B. Acid Chlorides + Lithium Dialkylcuprates (R₂CuLi)

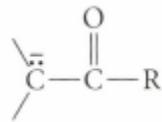
- a. Lithium dialkylcuprates are less reactive – does not react with ketones or esters.
- b. Reaction with acid chlorides give ketones and stop there.

Chapter 22 – Enols, Enolates, and α,β -Unsaturated Carbonyls

22.1 Acidity of Carbonyls

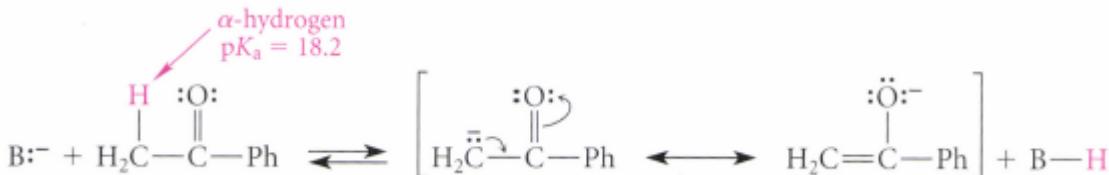
A. Definitions

- Enol: vinylic alcohol.
- Enolate ion: conjugate-base anion of a carbonyl after removal of an α -hydrogen.
- α,β -unsaturated carbonyl compounds: carbonyl group conjugated with C=C

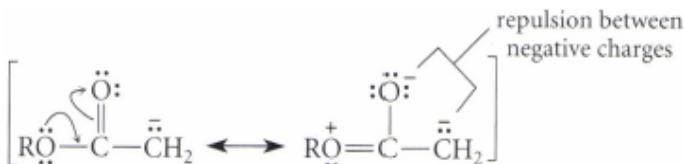


B. Formation of Enolate Anions

- α -Hs are acidic: 10^{30} times more than alkane Hs.
- Deprotonation of α -carbon gives an enolate anion.



- Since resonance can delocalize most of the negative charge to electronegative oxygen through the pi system, the enolate is pretty stable. Even the contributor with C- is stabilized by the polar effect of the oxygen.
- Aldehydes and ketones are far more acidic than esters. The resonance that stabilizes the ester does NOT stabilize the enolate.



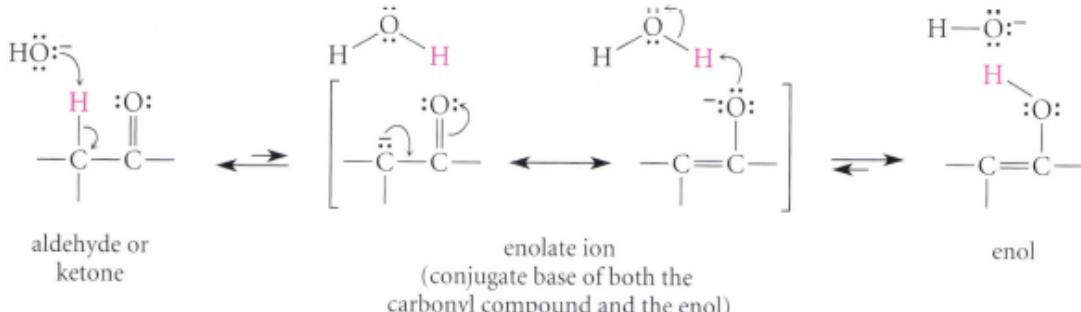
- Enolates are the carbon analogs of carboxylic acids and amides. The acidity order c-acids > amides > aldehydes/ketones follows electronegativity (element effect).

C. Reactions of Enolate Ions

- α -H's are interchanged with the solvent, and α -carbons can be deuterated.
- Asymmetric α -carbons are racemized as they constantly re-shift from $sp^3 \rightarrow sp^2$. This happens much more quickly in aldehydes/ketones than esters.
- Enolates are nucleophilic and attack alkyl halides or carbonyls.

22.2 Enolization of Carbonyl Compounds

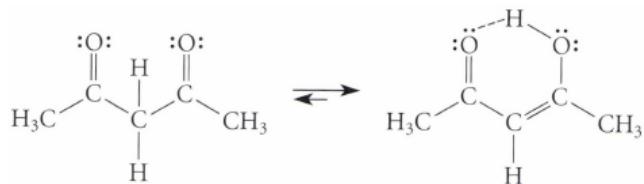
A. Rapid interconversion of tautomers (constitutional isomers), acid/base catalyzed.



- Enols are generally unstable: C=O is more stable than C=C.

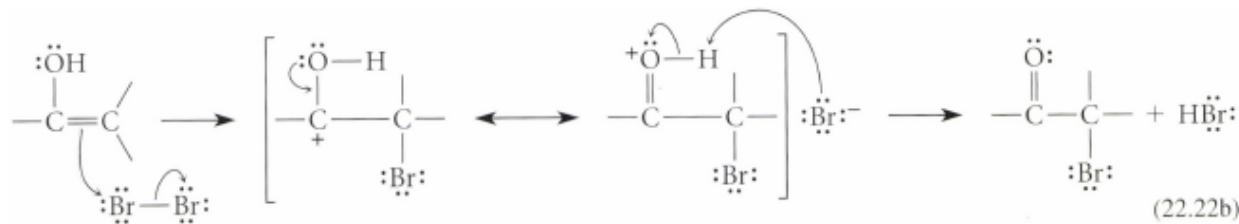
C. Phenols remain enols because this maintains aromaticity.

D. β -dicarbonyl compounds have stable enols: conjugation and intramolecular H-bonding



22.3 α -Halogenation of Carbonyl Compounds

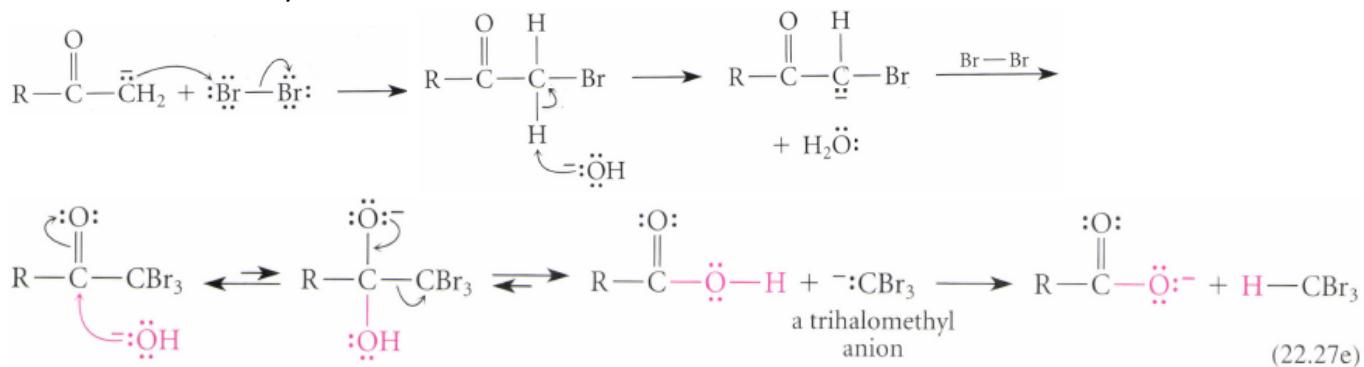
A. Acid-Catalyzed α -Halogenation of Aldehydes and Ketones



- Rate = $k[\text{ketone}][\text{H}_3\text{O}^+]$. INDEPENDENT of [X] – NOT involved in the transition state.
This is because the rate-limiting step is enolization.
- Acid always results in the replacement of ONE α -hydrogen with X, a second bromine addition would be destabilized by the polar effect of the first bromine.

B. The Haloform Reaction: Halogenation of Aldehydes and Ketones in Base

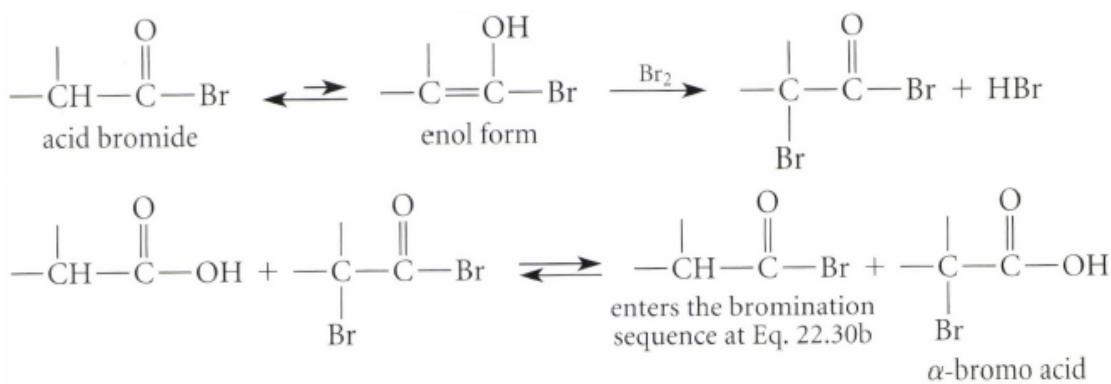
- Haloform: HCX_3 (trihalomethane)
- ALL α -H's are substituted by X \rightarrow trihalo carbonyl \rightarrow carboxylic acid + HCX_3
- Each substitution is more favorable than the last because the polar effect of the halogen actually stabilizes the enolate ion.



- The tribrominated carbon is a good enough leaving group to break the C–C bond.
- The final deprotonation of the carboxylic acid by the haloform salts out the product and drives the reaction to completion.
- Can be used to prepare carboxylic acids from methyl ketones (loss of carbon).

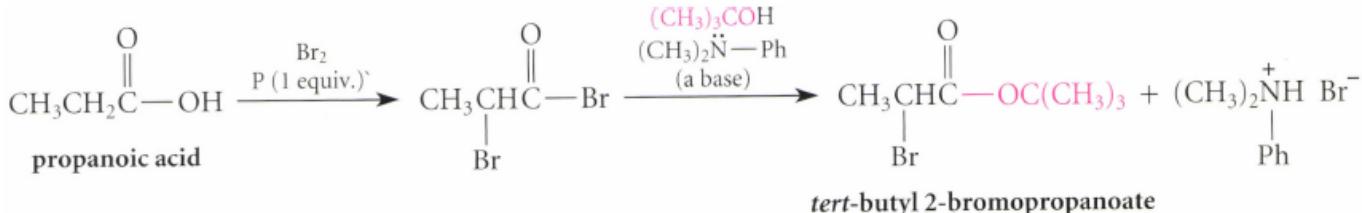
C. Hell-Volhard-Zelinsky (HVZ) Reaction: α -Bromination of Carboxylic Acids

- Carboxylic acids + $\text{Br}_2 \rightarrow (\text{P or } \text{PBr}_3) \rightarrow \alpha$ -brominated acid + HBr
- Carboxylic acid \rightarrow acid bromide by PBr_3 , then bromination of the enol as usual.
- If a catalytic amount of PBr_3 is used, the product is the α -bromo acid.



d. If a full equivalent of PBr_3 is used, the reaction product is the α -bromo acid Br.

This can be treated further to give α -bromo carboxylic acid derivatives.



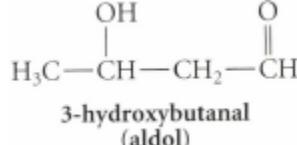
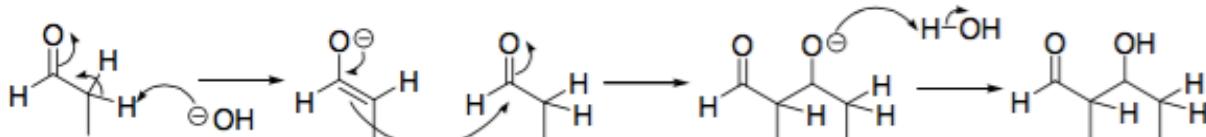
D. Substitution Reactions of α -Halo Carbonyl Compounds

- α -halo carbonyls readily undergo $\text{Sn}2$. $\text{Sn}2$ reactivity is 35,000x faster with the adjacent carbonyl because it can resonance-stabilize the anion.
- $\text{Sn}1$ does NOT happen because $\alpha\text{-C}^+$ cannot be resonance-stabilized (results in O^+) and is destabilized by the polar effect.

22.4 Aldol Addition and Condensation

A. Base-Catalyzed Aldol Reactions

- Aldol: β -hydroxy aldehyde.
- Aldol addition: aldehyde + aldehyde \rightarrow aldol.
- One aldehyde is deprotonated to its enolate, and the carbanion attacks another aldehyde carbonyl to produce the aldol. This is reversible.



B. Ordinary Aldol Condensation: aldol addition + dehydration \rightarrow α,β -unsaturated carbonyls.

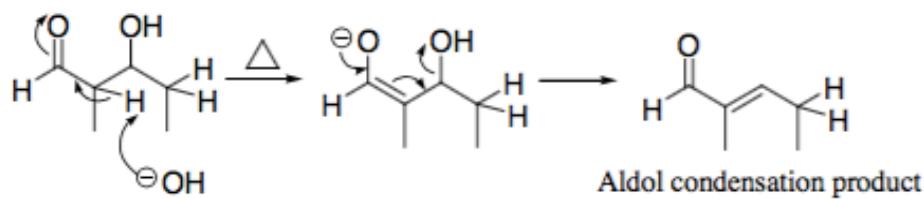
- Heat** favors the elimination of $\beta\text{-OH}$ and $\alpha\text{-H}$ by dehydration.

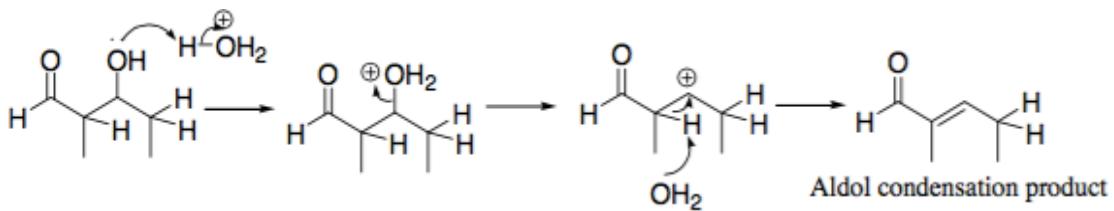
This occurs in two distinct steps and is NOT concerted.

(1) deprotonation gives the enolate, (2) this pushes electrons to kick off OH.

- Ordinary alcohols dehydrate in acid and NOT base, but β -hydroxy carbonyls are different. First, they have relatively acidic $\alpha\text{-H}'s$. Second, the product is stabilized by conjugation.
- In acid: an enol pi bond attacks a protonated carbonyl.

In base: an enolate carbanion attacks a neutral carbonyl.





C. Crossed Aldol Reactions: 2 different carbonyl reactants

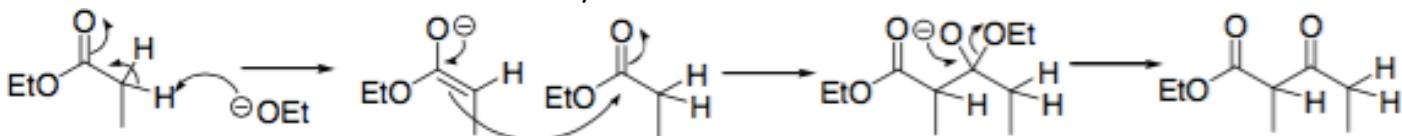
- Results in complex mixtures, hard to isolate
- Claisen-Schmidt condensation: ketone (+ α -H's) is condensed with aldehyde (- α -H's) under acidic conditions. Only one product is formed.
- Ketones must do the attacking because aldehydes can't form nucleophilic enolates.
- Aldehydes must be the ones attacked because they're more electron-deficient and thus more reactive electrophiles AND used in excess.
- Intramolecular Aldol Condensation: especially favorable with 1,4/1,5 carbonyls \rightarrow 5/6-rings.

D. Retrosynthesis with the Aldol Condensation: split along the double-bond of an α,β -unsaturated carbonyl, replace with C=O and CH₂ and then ensure the mixture is separable.

22.5 Condensation Reactions Involving Ester Enolate Ions

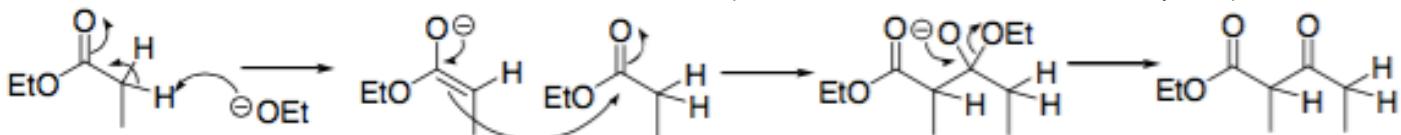
A. Claisen Self-Condensation (1,3-dicarbonyl)

- (2 eq) esters + (>1 eq) alkoxide \rightarrow β -keto ester. Needs (2) H⁺/H₂O workup.
- The ester/alkoxide/alcohol MUST be matched to prevent transesterification.
- Needs at least 2 α -Hs for (1) condensation, and (2) acid-base ion formation.
- Esters are also great electrophiles because they don't like forming nucleophilic enolates that break their resonance stability. Ketones hate it even more.



B. Claisen Two Different Esters/Ketones

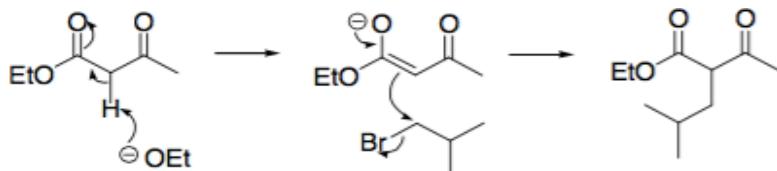
- Ester and ketone: ketone attacks ester/C (ketones more acidic, less electrophilic)

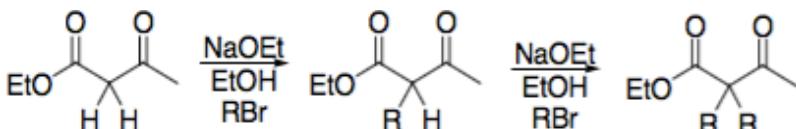


C. Ester Alkylation

- Malonic ester alkylation: a center H is deprotonated to form a nucleophilic pi bond that attacks R-X; product is slightly less acidic/reactive; you can add just one R or a different R'.
- Preparing α -alkyl acids (malonic acid: 2EtO) and α -alkyl ketones (acetoacetate: EtO/R)

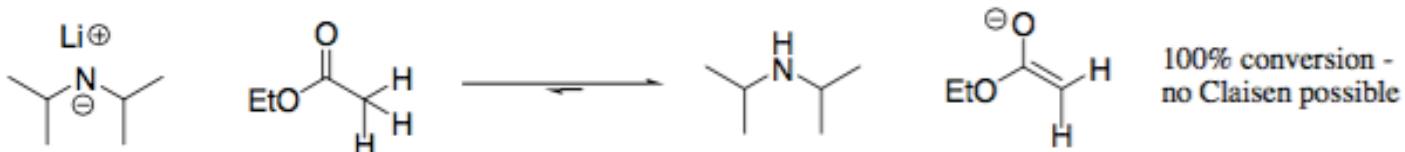
 - Treat dicarbonyl with base to form the enolate, attack RX, add acid to protonate, and then heat to decarboxylate.





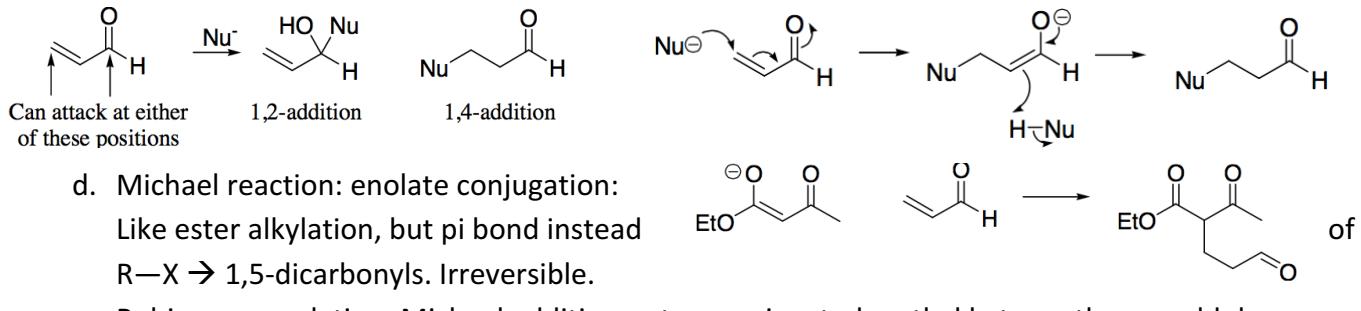
D. Problems with Direct Ester Alkylation

- The enolate formation is so low (10^{-9}) you'll alkylate the alkoxide first.
- MUST use hindered strong base: lithium diisopropyl amide (LDA) that forms 100% enolate. Must be stepwise to prevent LDA attack at R—X. (1) LDA, THF (aprotic solvent) (2) R—X
- Only stable enough to produce quaternary products

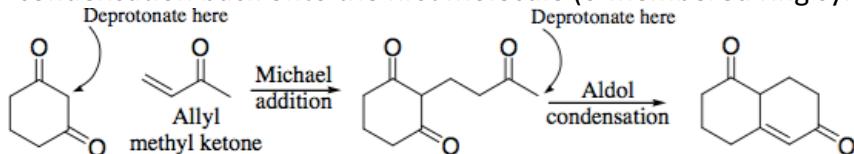


E. a,b-unsaturated carbonyl compounds: dual reactivity

- 1,4-conjugate addition is thermodynamic product: reversible, C=O bond more stable.
- 1,2-carbonyl addition is kinetic product: irreversible, carbonyl C most electrophilic.
- 1,2-addition: RLi, LiAlH₄** **1,4-addition: CN⁻, RS⁻, R₂NH, R₂CuLi**



- Michael reaction: enolate conjugation:
Like ester alkylation, but pi bond instead
 $R-X \rightarrow 1,5\text{-dicarbonyls}$. Irreversible.
- Robinson annulation: Michael addition onto a conjugated methyl ketone, then an aldol condensation back onto the first molecule (6-membered ring synthesis).



- Intramolecular aldols and Claisen - only forms 5,6-membered rings.
- Reduction: hydride addition to the carbonyl to turn the conjugated C=O to C—OH
- Organometallic addition: racemic products
 - Organolithium: carbonyl addition: $R-Li/aq$ workup
 - Organocuprates: R_2CuLi/aq workup \rightarrow conjugate addition (transitional metal process).

Chapter 23 – Amines

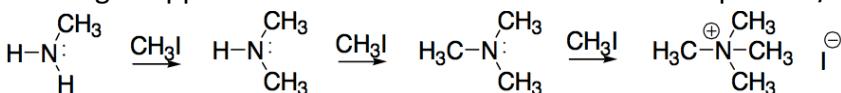
23.5 Amine Basicity

- A. Amines are mildly basic. Aromatic amines are less so (resonance stabilizes charge).

23.7 Amine Alkylation and Acylation Reactions

I. Direct Alkylation of Amines

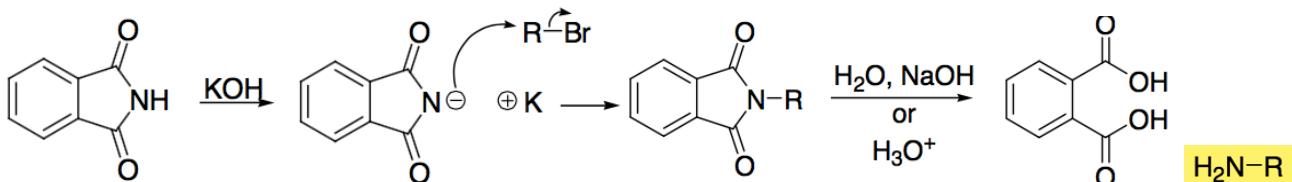
- a. Alkyl halide addition: multiple alkylations lead to a complex product mixture because H^+/X^- exchange happens much faster than S_n2 . Also true of epoxides/a,b-unsaturated carbonyls.



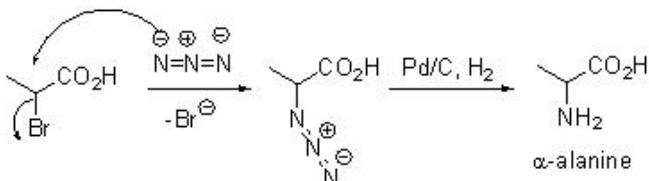
- b. Quaternization of Amines: $3^\circ R_3N: + RX \text{ (xs)} \rightarrow 4^\circ R_4N+$.

J. Gabriel Synthesis of Primary Amines with primary/unbranched-secondary Alkyl Halides

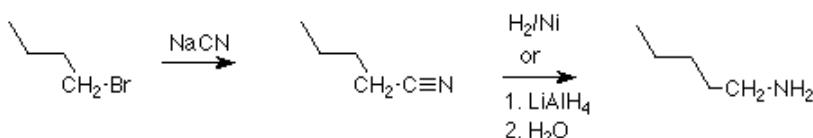
- a. Protects the amine nitrogen against multiple alkylations. Hydrolyze with strong acid/base.



K. Alkyl Azides: $(Na)N_3$ attacks RX by S_n2 and is reduced to an amine.

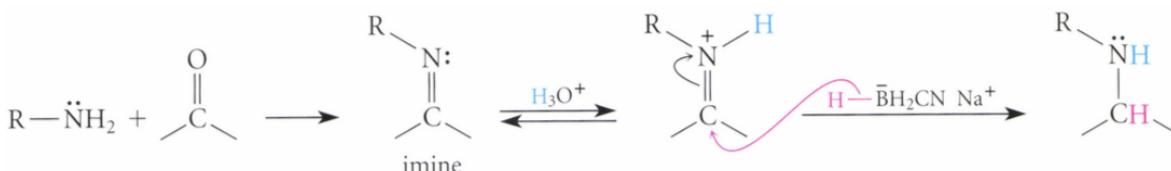


L. Nitrile reduction: $(Na)CN$ attacks RX by S_n2 and is reduced to an amine.



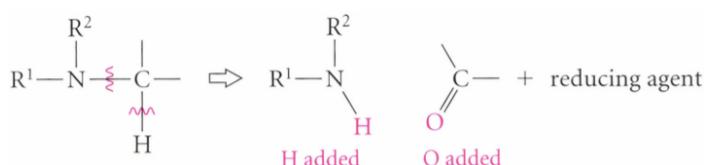
M. Reductive amination

- a. Amides \rightarrow amine: $LiAlH_4$, H_3O^+ workup.
 b. Ketones/Aldehydes: add the amine to replace the carbonyl, then use the Borch reaction >>
 c. Borch reaction: $NaBH_3CN$ (weaker than $NaBH_4$), can reduce imines, but not carbonyls.



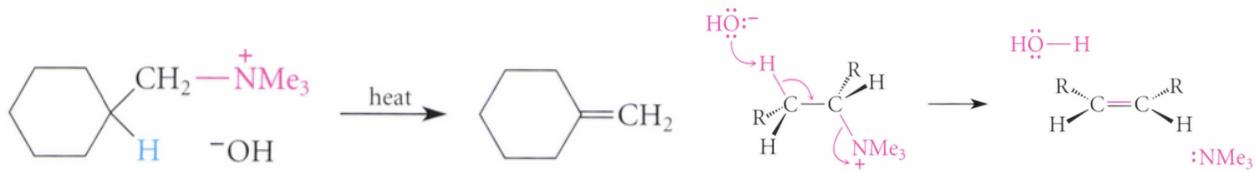
- d. Reduction of formaldehyde: too small to stop multiple alkylation $\rightarrow 3^\circ RN(Me)_2$

e. Synthesis:



23.8 Hofmann Elimination of Quaternary Ammonium Hydroxides:

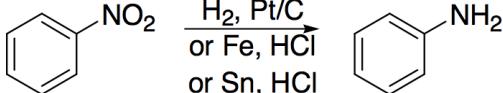
Add NaOH to a compound with R_4N^+ leaving group to kick it off via E2. R_4N^+ created by RX (xs).



23.10 Diazotization on Aryl Groups

A. Diazotization: reaction of primary amines with HNO_2 to form diazonium salts ($\text{R}^+\text{N}\equiv\text{N:X}^-$).

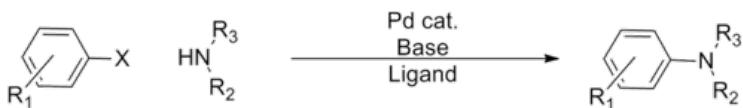
B. Making aromatic anilines via nitro-group reduction



Amination of $\text{Ar}-\text{X}$

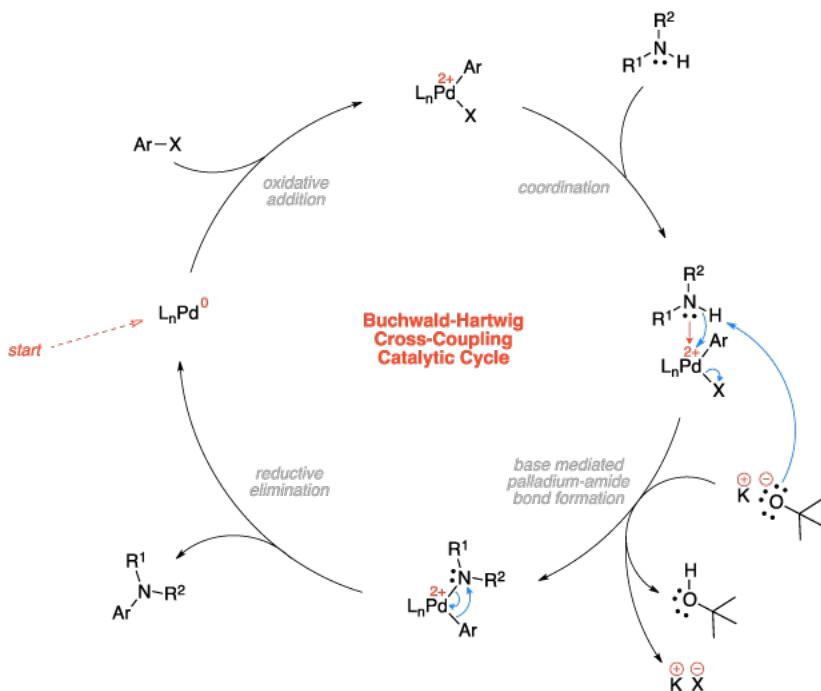
C. Buchwald-Hartwig

a. Ligand is usually $\text{Pd}(\text{PR}_3)_4$, base is usually $\text{K}^+ \text{tBO}^-$, K_2CO_3 , etc. Ignore R_1 .



$\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{OTf}$
 $\text{R}_2 = \text{Alkyl, Aryl, H}$
 $\text{R}_3 = \text{Alkyl, Aryl}$

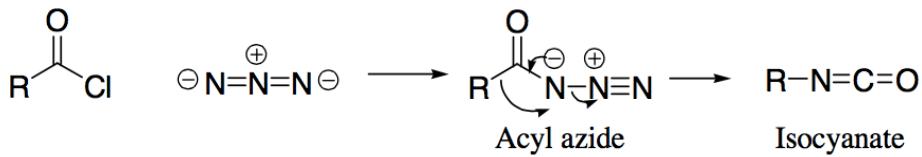
b. Mechanism



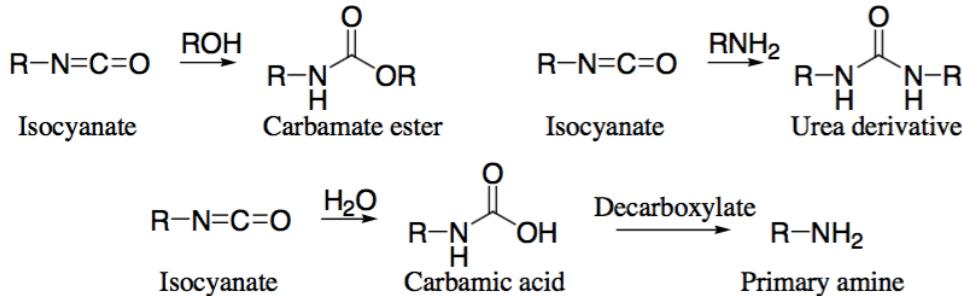
23.11 Rearrangement Synthesis of Amides

A. Curtius Rearrangement

- a. Make the acyl azide by acid chloride + NaN_3 (sodium azide).

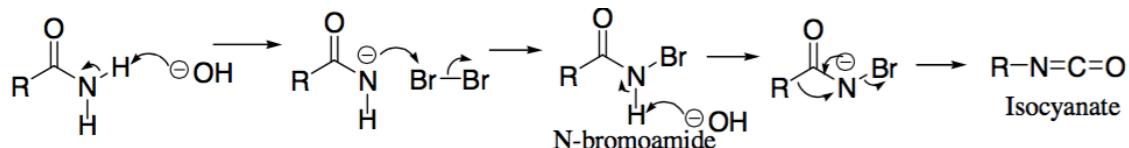


- b. Isocyanate is unstable, and a synthetic equivalent for a lot of stuff.

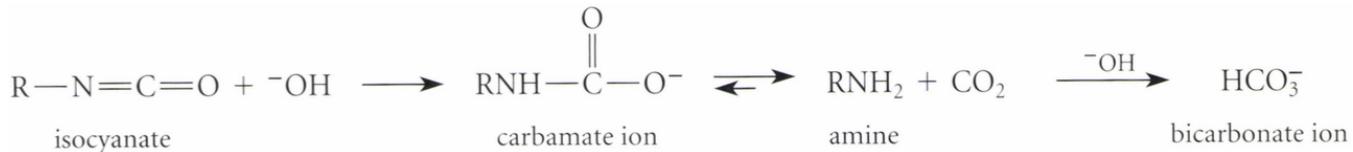


B. Hofmann Rearrangement

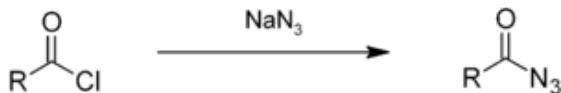
- a. Amide + X_2 + NaOH (xs) + $\text{H}_2\text{O} \rightarrow 1^\circ$ amine. Excises carbon; retention of stereochemistry.
 b. $\text{Cl}_2 + -\text{OH} \rightarrow \text{ClO}\text{H}$ (hypochlorite) – actual active agent.



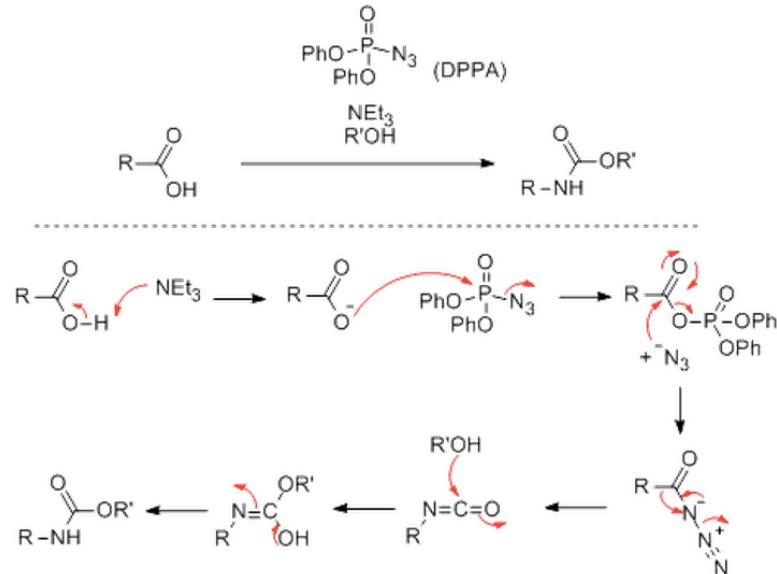
C. Isocyanate Decomposition



Preparation of acyl azides from acid chlorides



Preparation of acyl azides with DPPA



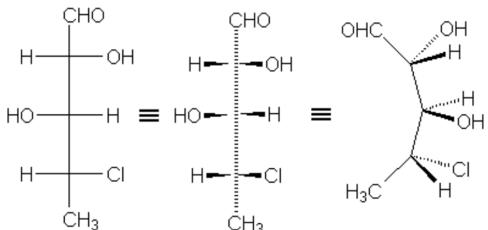
Chapter 24 – Carbohydrates

24.1 Classification and Properties of Carbohydrates

- N. Aldose: contains an aldehyde // Ketone: contains a ketone
- O. Hexose: 6 carbons // Pentose: 5 carbons
- P. Monosaccharides: cannot be converted to simpler sugars by hydrolysis.

24.2 Fischer Projections

- A. Most sugar carbons are asymmetric, giving 2^n stereocenters.
- B. Carbons are in a vertical line. Vertical means away from you; horizontal means toward you.



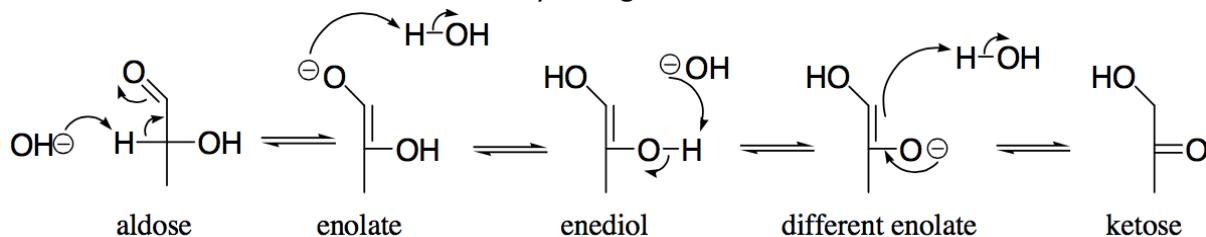
- C. Mirror plane converts to enantiomer. This is a good check for meso compounds.

Cyclization

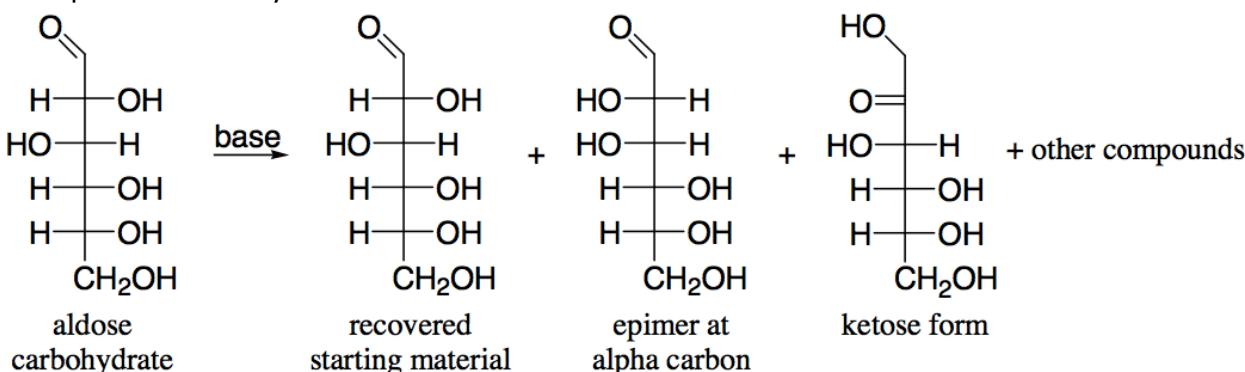
- A. Any sugar OH can attack a carbonyl to form a 5,6-cyclic hemiacetal.
- B. Anomeric carbon: the former carbonyl carbon, now attached to OH; becomes a new stereocenter one carbon away from the ring oxygen. Top attack \rightarrow alpha, bottom attack \rightarrow beta.

Isomerization

- A. Since cyclization is reversible, the alpha and beta forms interconvert.
- B. Enolate conversion can move the carbonyl along the chain.

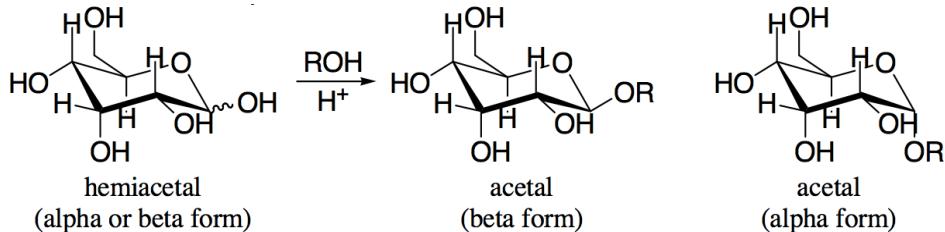


- C. Exposure to base yields three different isomers

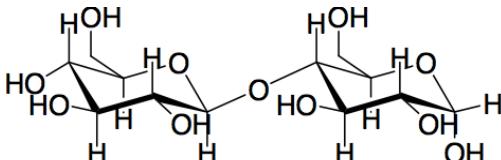


D. Glycosides

- a. Hemiacetals can be converted into the alpha/beta full acetals with alcohol addition.



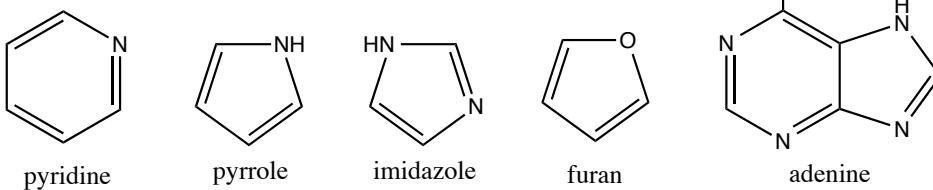
- b. The ring oxygen dumps e- to form a double bond with the leaving group. If it attacks from the top face, it's beta. If it attacks the bottom face, it's alpha.
c. This can be hydrolyzed again by acid, like any other ether.
d. Other carbohydrates can be attached instead of simple alcohols.



- e. If the bonding oxygen is beta to a ring oxygen, it's a glycosidic bond (8). If the receiving oxygen is also beta to a ring oxygen, the linkage happens through 2 glycosidic bonds (4).

Chapter 25 – Aromatic Heterocycles

25.1 Examples



The electronegative atom disrupts symmetry and resonance; some structures have charge separation.

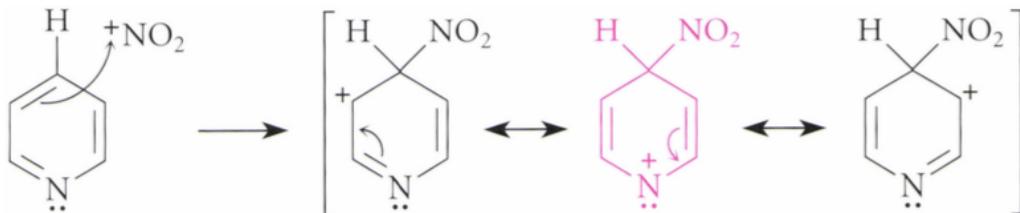
Basicity and aromaticity: aromatic lone pairs are not protonated.

25.3 Reactions of 5-Membered Rings: faster than benzene

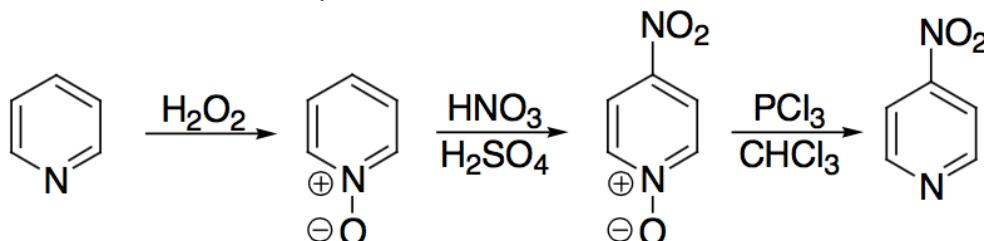
- Bromination rate: pyrrole (N) > furan (O) > thiophene (S) >> benzene.
- S is slower because its 3rd shell has poor overlap, O is slower because it's more electronegative than N and O⁺ is unstable. Heterocycles are faster than benzene; Z+ has a full octet and C+ doesn't.
- Unsubstituted
 - 2-substitution: 3 resonance structures: **MAJOR PRODUCT**
The C+ is conjugated to the other double-bond.
 - 3-substitution: 2 resonance structures: **MINOR PRODUCT**
 - Milder conditions: Br₂, AcOH v. Br₂, FeBr₃ // anhydride, BF₃ v. acid chloride, AlCl₃
- Substituted: same trends as for benzene.
 - High regioselectivity when substitution/heterocycle preferences **match**
 - Count around the carbon framework, NOT through the heterocycle, to determine o, m, p.
 - Conflicting preferences → mess.

25.4 Electrophilic Addition Reactions of 6-Membered Rings: slower than benzene

- 3-substitution: 3 resonance structures: **MAJOR PRODUCT**
- 4-substitution: 2 resonance structures: **MINOR PRODUCT** (the middle one is bad/irrelevant)

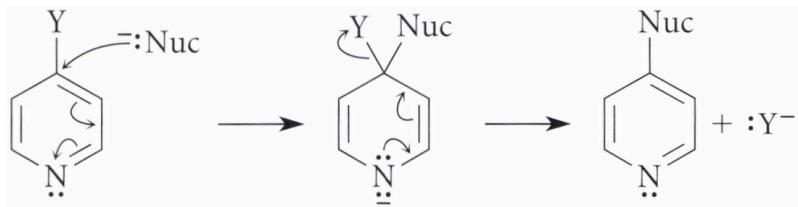


- Pyridine N-oxide: oxidation with H₂O₂ makes N electron-withdrawing, which forces 4-substitution. N-oxide can be removed by reduction with H₂, Pd/C or PCl₃

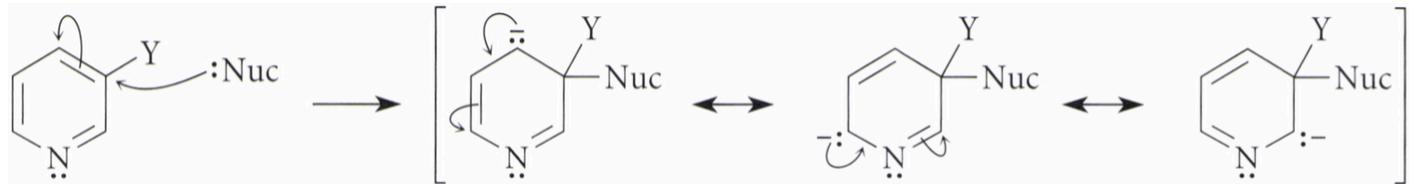


25.5 Nucleophilic Addition Reactions of 6-Membered Rings with Leaving Groups at 2' or 4' position.

A. 2-substitution and **4-substitution** place negative charge on N.



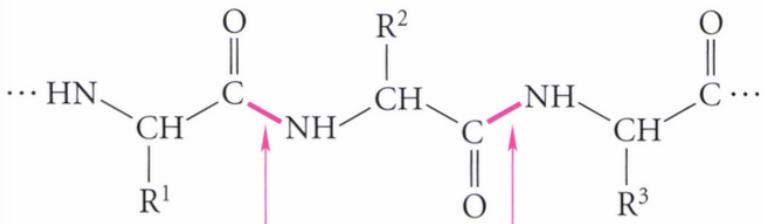
B. 3-substitution is bad: the negative charge does not end up on N.



Chapter 26 – Amino Acids, Peptides, and Proteins

26.1 Amino Acids Properties

Q. General Peptide Structure (peptide bonds labeled)



R. Glycine is achiral, but the other AAs are all S-chiral

S. Amino Acids are bi-functional and zwitterionic (opposite charges on the same molecule).

26.2 Alpha Amino Acid Synthesis

A. Gabriel AA Synthesis

1. Starting material prep created

by enolate Sn2

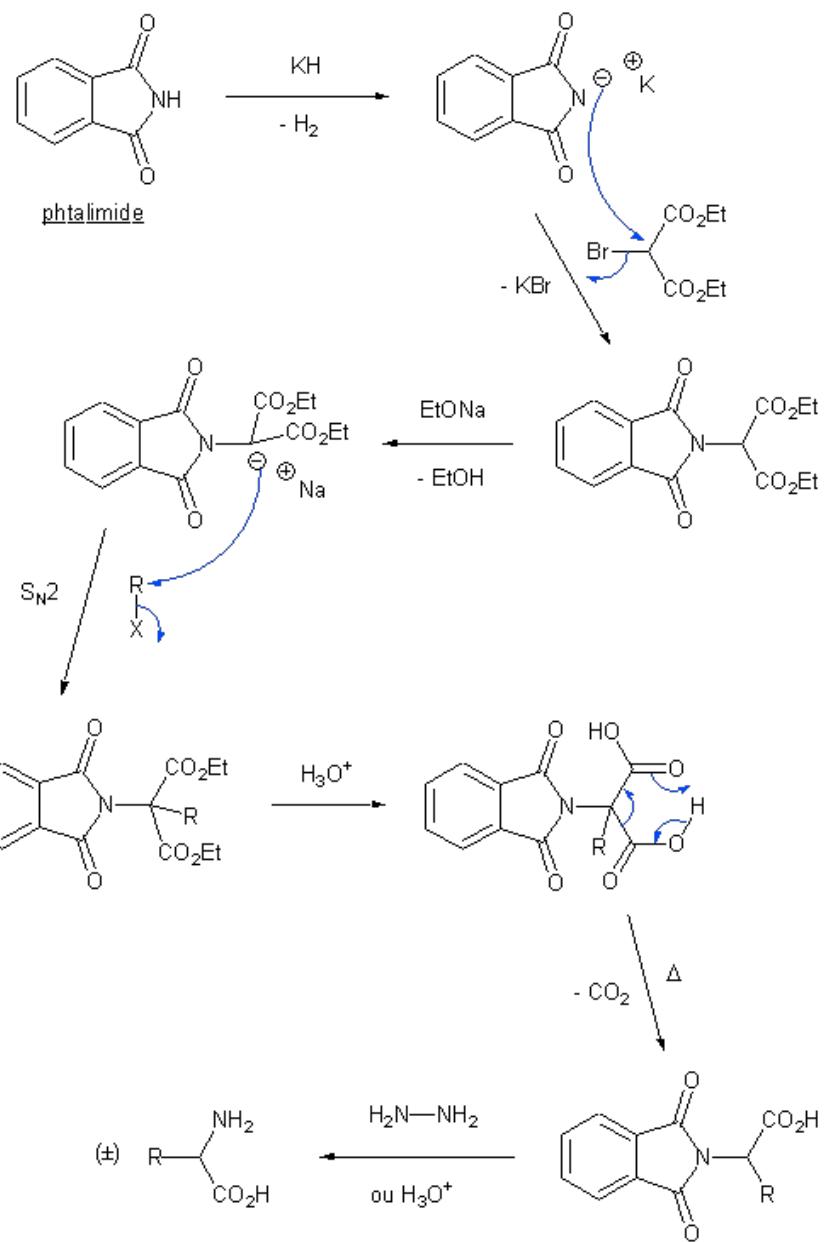
2. A second Sn2 introduces the R group via RX.

3. Vigorous acidic workup yields:

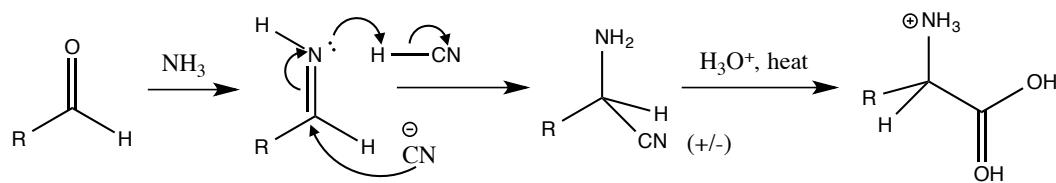
(a) phthalimide hydrolysis,

(b) ester hydrolysis

(c) decarboxylation

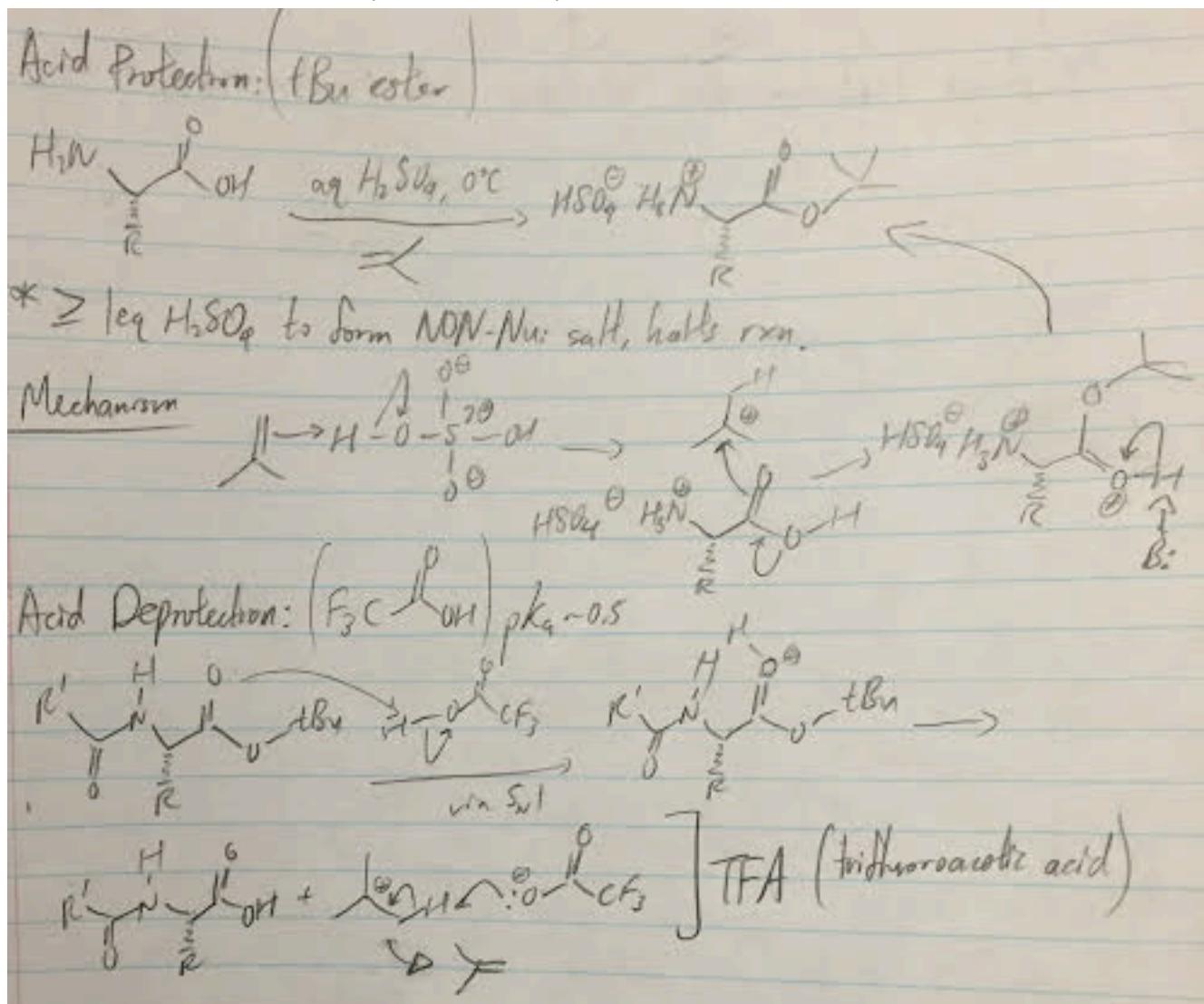


4. Strecker AA Synthesis (condensed)



26.3 Amide bond formation with AAs

- A. Complicated because bi-functional. Adding two different AAs via SOCl_2 will yield a mess, because of dimerization/polymerization. Synthesis necessitates protection.
- B. Acid Protection with tBu ester (H_2SO_4 , 0°C / \rightleftharpoons)



Part 2:

- A. Amine Protection: make non-nucleophilic with carbamate
- B. Amine Protection 2: protect with fluorenylmethoxycarbonyl (Fmoc) group
 - a. This acts as an acid chloride; reacts at the amine → Fmoc amino acid.
 - b. Stable under acidic conditions; easily cleaved by base.
- C. Deprotection: fast E2 with basic piperidine to kick out Fmoc and CO₂.
- D. Loss of the highly acidic center-H yields a 14 e- aromatic compound.
- E. Standard peptide coupling
 - a. DCC, HOBr (insert mechanism).
- F. Solid-phase synthesis (SPS): peptides, DNA, RNA
 - a. Benefits
 - i. Isolation/purification: reaction product by filtration.
 - ii. Complete reaction conversion by excess reagents is okay
 - iii. Automation: uniform and standard steps
 - b. Polymer for SPS peptide synthesis: **styrene** → radical chain polymerization → **polystyrene** → modify 10% by linkers.
 - c. Operation 1: attach 1st amino acid to solid support
 - i. Add the Fmoc-bound AA via Sn2
 - d. Operation 2: peptide synthesis: Fmoc deprotection and AA coupling
 - i. Repeat 1 by 1 until synthesis is complete.
 - e. Operation 3: remove from solid support (E1 by TFA attack).
- G. Side chain protection: acids protected as tBu-tert-butyloxycarbonyl, and amines protected as Boc carbamates.