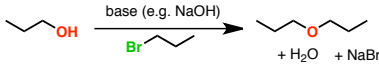
Introduction to Alcohols and Ethers

"Master Organic Chemistry"
masterorganicchemistry.com
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

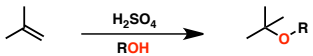
Ethers from alcohols and alkyl halides

The Williamson Ether synthesis: alcohol, base, alkyl halide (or tosylate)



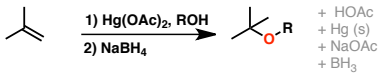
This is an S_N2 reaction; it works best for primary alkyl halides (and alkyl tosylates)

Ethers from alkenes



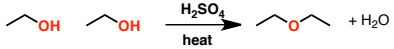
The reaction is similar to the hydration of alkenes with aqueous acid. Acid leads to the formation of a carbocation, which is then trapped by the alcohol as solvent.
Carbocation rearrangements (hydride and alkyl shifts) can occur in certain cases.

Ethers from alkenes through oxymercuration



The reaction is similar to the hydration of alkenes with aqueous acid. The **key difference** is that it does **not** proceed through a carbocation, so **no rearrangements** can occur.

Ethers from alcohols through dehydration

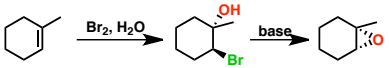


Strong acid (and heat) leads to protonation of the alcohol, followed by nucleophilic attack of a second molecule of alcohol to give the ether. Only practical for the synthesis of *symmetrical* ethers.

Epoxides from alkenes

m-CPBA (meta-chloroperoxybenzoic acid, a peroxyacid) converts alkenes to epoxides, a cyclic ether. Other peroxyacids can be used (e.g. CH_3CO_3H)

Epoxides from halohydrins



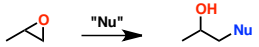
Formation of the halohydrin from the alkene is stereospecific for the **trans** product. Deprotonation of the alcohol by base results in S_N2 (with inversion at carbon bearing the leaving group) to give the epoxide.

Opening of epoxides

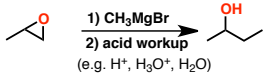
Due to ring strain, epoxides are highly reactive towards nucleophiles. They will react with nucleophiles under both acidic and basic conditions. However the *patterns* are different.

Under basic conditions

Under basic conditions, nucleophiles will attack epoxides at the ***least sterically hindered position*** (primary [fastest] > secondary > tertiary [slowest]) The reaction is essentially an S_N2 reaction!

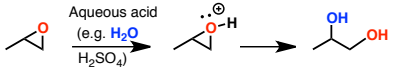


Example: reaction of epoxides with Grignard reagents

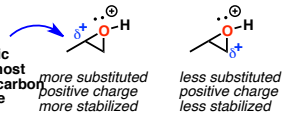


Under acidic conditions

Under acidic conditions, the epoxide oxygen is protonated:

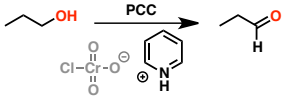


The nucleophile will attack the carbon best able to stabilize positive charge - which is the more substituted carbon Just like Markovnikov's rule!



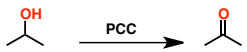
Oxidation of alcohols

Oxidation of primary alcohols to aldehydes



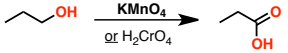
PCC = pyridinium chlorochromate

Oxidation of secondary alcohols to ketones



Can also use $KMnO_4$ or H_2CrO_4 (or DMP or Swern, see right)

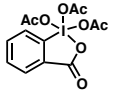
Oxidation of primary alcohols to carboxylic acids



Common source of confusion:
Another way of writing H_2CrO_4 is $K_2Cr_2O_7$ / H_2SO_4 or $Na_2Cr_2O_7/H_2SO_4$

Alternative reagents for oxidation of primary alcohols to aldehydes and secondary alcohols to ketones (not seen in all courses):

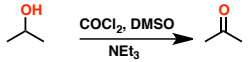
Dess-Martin Periodinane (DMP)



- oxidizes primary alcohols to aldehydes
- oxidizes secondary alcohols to ketones

Swern oxidation

- oxidizes primary alcohols to aldehydes
- oxidizes secondary alcohols to ketones



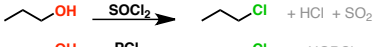
(often just written, "Swern")

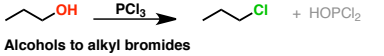
$(COCl)_2$ is oxalyl chloride
DMSO is dimethyl sulfoxide
and NEt_3 is triethylamine (base)

Conversion of alcohols to good leaving groups

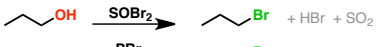
The hydroxide group (HO^-) of alcohols is a strong base and a poor leaving group. Converting to a halogen or "sulfonate" (e.g. tosylate or mesylate) greatly facilitates substitution reactions.

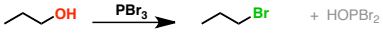
Alcohols to alkyl chlorides



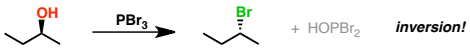


Alcohols to alkyl bromides

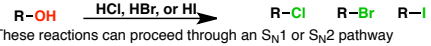




One thing to note - these reactions occur with inversion of configuration. For example:



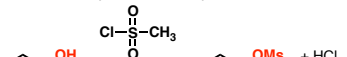
Alcohols to alkyl halides by using acids



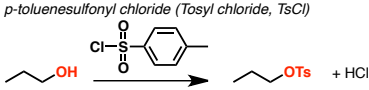
These reactions can proceed through an S_N1 or S_N2 pathway depending on the structure of the alcohol

Alcohols to tosylates and mesylates ("sulfonate esters")

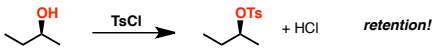
Methanesulfonyl chloride (mesyl chloride, MsCl)



p-toluenesulfonyl chloride (Tosyl chloride, TsCl)

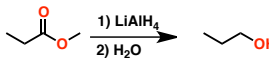


One thing to note - these reactions do not change the stereochemistry of the alcohol.

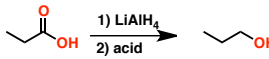


Alcohols through reduction

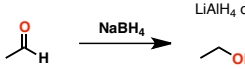
Reduction of esters by lithium aluminum hydride ($LiAlH_4$)



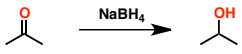
Reduction of carboxylic acids by lithium aluminum hydride ($LiAlH_4$)



Reduction of aldehydes by sodium borohydride ($NaBH_4$)
$LiAlH_4$ can also do this reaction.



Reduction of ketones by sodium borohydride ($NaBH_4$)
$LiAlH_4$ can also do this reaction.



Omissions, Mistakes, Suggestions?

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Introduction to the Diels Alder Reaction

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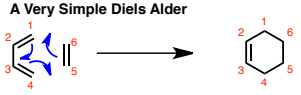
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

1. The Basics

The Diels-Alder reaction is a **concerted** reaction between a compound with two adjacent double bonds (a "diene") and an alkene (the "dienophile"), usually attached to an electron withdrawing group. The transition state is "pericyclic", meaning it has cyclic geometry and is concerted
The Diels-Alder reaction **always** forms a six-membered ring with an alkene.

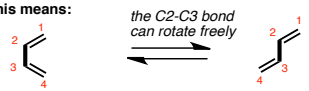
A Very Simple Diels Alder



Form	Break
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

Rule #1 The diene must always be in the "s-cis" conformation

What this means:



note how the two alkenes are on the same side of the C_2–C_3 sigma bond

"s-cis"

The end carbons (C_1 and C_4) are close together

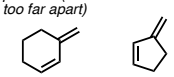
note how the two alkenes are on opposite sides of the C_2–C_3 sigma bond

"s-trans"

The end carbons (C_1 and C_4) are too far apart

no Diels-Alder reaction possible

When the diene is "locked" in an s-trans configuration, no Diels-Alder reaction is possible (the two ends are too far apart)



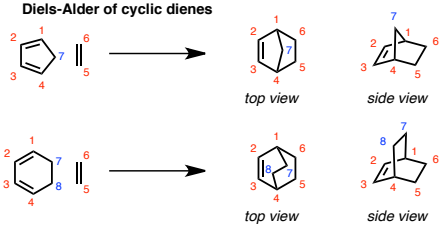
These dienes cannot participate in the Diels-Alder

2. Special Cases

Diels-Alder Reactions of Cyclic Dienes:

These look a little weird, but they're no different than a normal Diels-Alder

Diels-Alder of cyclic dienes



Form	Break
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

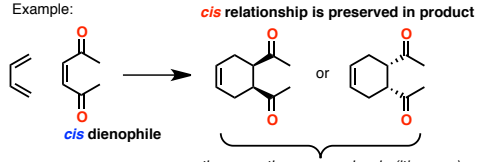
note how the pattern of bonds forming and bonds breaking is exactly the same as for the simple case, above.

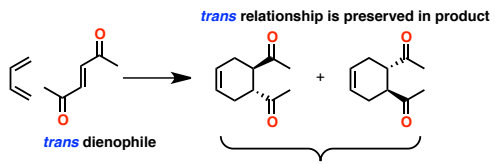
3. Stereochemistry: The Dienophile

How the stereochemistry of the dienophile works:

Rule #2: *Stereochemistry in the dienophile is always preserved*

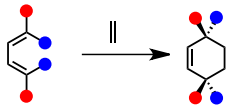
Example:





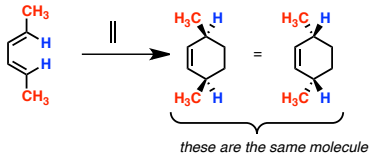
4. Stereochemistry: The Diene

How the stereochemistry of the diene works:



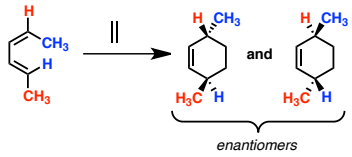
Rule #3: *The two "outside" groups (red)and the two "inside" groups (blue) always end up on the same side of the new cyclohexene*

Example 1:



Note how the two "outside" groups (CH_3 and CH_3) end up on the same side of the ring, as do the two "inside" groups (H and H)

Example 2:



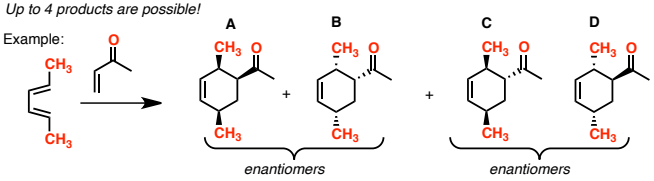
Note how the two "outside" groups (CH_3 and H) end up on the same side of the ring, as do the two "inside" groups (CH_3 and H)

5. The Endo Rule

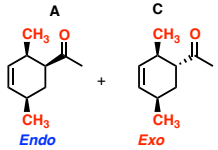
What if there's a substituted diene *and* a substituted dienophile?

Up to 4 products are possible!

Example:



Let's just pick one set of diastereomers. A and C.



Note how in A, the two methyl groups are on the same side of the ring as the electron withdrawing group (ketone), whereas in C, they are on the opposite side of the ring

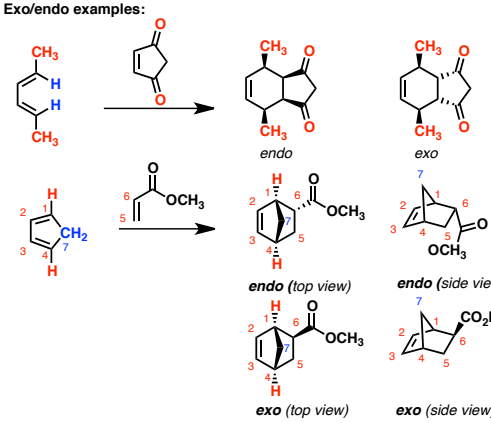
A is referred to as the **endo** product. C is referred to as the **exo** product (note: B is also endo, and D is also exo)

Rule #4: Under normal conditions, endo products dominate

How to tell if a product is exo or endo

One way to do it: if the outside groups (red) end up on the **same** side of the ring as the electron withdrawing group, the product is **endo.**
If the outside groups end up on the ***opposite*** side of the ring as the electron withdrawing group, the product is **exo**.

Exo/endo examples:



Omissions, Mistakes, Suggestions?

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Introduction to Aromaticity

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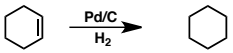
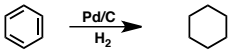
1. An introduction to resonance energy and aromaticity

Hydrogenation of alkenes liberates 119 kJ/mol of energy



ΔH = –119 kJ/mol (28.4 kcal/mol)

We would expect hydrogenation of benzene to liberate 3 × 119 = 357 kJ/mol.



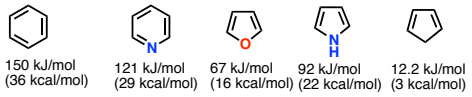
ΔH = –207 kJ/mol (49 kcal/mol)

Instead, 207 kJ/mol is liberated (150 kJ mol less than we expect!)
So it is 150 kJ/mol (36 kcal/mol) **more stable**.

The extra stability of benzene is called the "resonance energy".

Benzene has a particularly large resonance energy, which leads us to classify it as "aromatic".

Resonance energy of some compounds:



150 kJ/mol (36 kcal/mol)	121 kJ/mol (29 kcal/mol)	67 kJ/mol (16 kcal/mol)	92 kJ/mol (22 kcal/mol)	12.2 kJ/mol (3 kcal/mol)
aromatic	**aromatic**	**aromatic**	**aromatic**	**not aromatic**

2. Two major ways in which reactions of aromatic compounds differ from alkenes

Hydrogenation: more difficult with aromatic compounds

Alkene

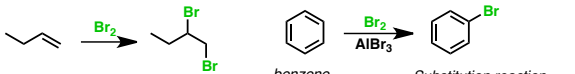
easy

benzene

difficult

no reaction at normal temperature and pressure

Reaction with electrophiles (such as bromine): aromatics give substitution, not addition



Alkene

Addition reaction

easy

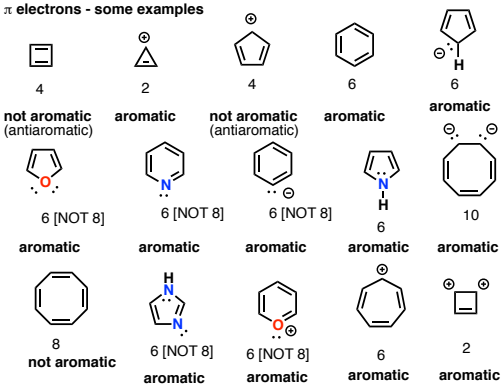
benzene

Substitution reaction

difficult

no reaction without a catalyst such as $AlCl_3$

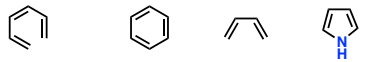
π electrons - some examples



4	2	4	6	6
not aromatic (antiaromatic)	**aromatic**	**not aromatic** (antiaromatic)	**aromatic**	**aromatic**
6 [NOT 8]	6 [NOT 8]	6 [NOT 8]	6	10
aromatic	**aromatic**	**aromatic**	**aromatic**	**aromatic**
8	6 [NOT 8]	6 [NOT 8]	6	2
not aromatic	**aromatic**	**aromatic**	**aromatic**	**aromatic**

3. How to tell if a molecule is aromatic?

Rule 1. *It must be a ring. No acyclic molecule is aromatic. Ever.*

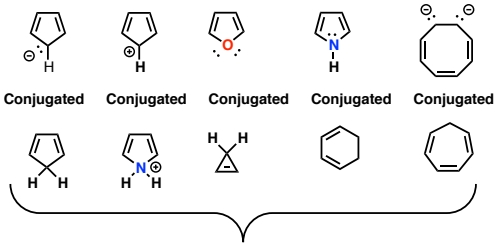


1,3,5 hexatriene *not aromatic*	benzene *aromatic*	butadiene *not aromatic*	pyrrole *aromatic*

Rule 2. *The molecule must be conjugated*

Meaning: there must be a continuous line of p orbitals around the ring.
p orbitals can come from 1) π-bonds 2) lone pairs 3) carbocations

A good test. Can you push electrons all the way around the ring through resonance? If not, it's not conjugated.



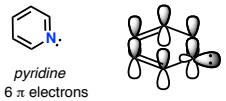
Conjugated	Conjugated	Conjugated	Conjugated	Conjugated

Not Conjugated

Rule 3. *There must be 4n + 2 π electrons* i.e. 2, 6, 10, 14.... π electrons

π electrons can come from double bonds or lone pairs. Note: A carbocation indicates the *absence* of π electrons.
One tricky part: for a given atom, you can only count electrons from a lone pair if the atom is not part of a π bond. And in that case you can only count a maximum of **one** lone pair.

This is due to the fact that each atom can only share one p orbital with the π system of the molecule.

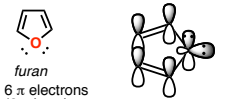


pyridine
6 π electrons
(3 π bonds,
2 electrons
per π bond)

the electrons from the lone pair on N are at 90° to the π system, and do not contribute to aromaticity.

Similar example: lone pair on this anion does not contribute towards aromaticity.

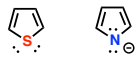
ignore lone pair for this calculation



furan
6 π electrons
(2 π bonds,
2 electrons
per π bond)
+ 2 electrons
from lone pair

only one of the lone pairs can align itself with the pi system at any given time, so only one lone pair is counted towards aromaticity.

Similar examples: only count one lone pair



only count one lone pair for this calculation

For more examples, see section on left

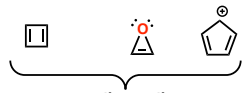
Rule 4. *It must be flat*

Most molecules that obey the first 3 rules are also flat.
One exception is [10]-annulene, which is bent due to repulsion of the hydrogens.

not aromatic

4. Antiaromaticity

Molecules that obey rules 1,2 and 4 but have (4n) π electrons instead of (4n +2) π electrons have *special instabiity.*
This *special instability* is called "antiaromaticity".



antiaromatic

- cyclic
- conjugated
- 4π electrons

extremely unstable

cyclooctatetraene has 8π electrons, but can adopt a "tub" shape, "escaping" antiaromaticity.

5. Some physical evidence for aromaticity:

1. Shows a different reactivity profile than for alkenes (see section on reactivity at left)

2. All π bonds are of the same length & do not alternate

All bonds in benzene are the same length (1.4 Angstrom)

Compare this to cyclobutadiene, which has short double bonds and long single bonds - like a rectangle.

3. Ring currents in NMR

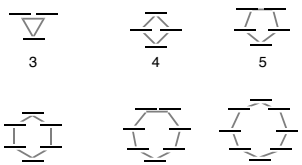
Resonances for aromatic protons in NMR typically show up in the region 6.8–8.0 ppm, whereas those for "normal" alkenes show up in the region from 5.0–6.5 ppm.

6. "Frost circles" - a trick for obtaining the molecular orbital structures of aromatic rings.

General idea: Inscribe a polygon of **n** sides in a circle. Make sure one of the apices is pointing down. Then, each apex will represent a level in the molecular orbital energy diagram.

Frost, J. Chem. Phys. **1953**, *21*, 572

Examples:



3	4	5
6	7	8

this shows the arrangement of molecular orbitals for benzene

Omissions, Mistakes, Suggestions?

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Reactions of Aromatic Compounds

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Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Six reactions for electrophilic aromatic substitution

- **Chlorination** — Cl_2, $FeCl_3$
- **Bromination** — Br_2, $FeBr_3$
- **Nitration** — HNO_3, H_2SO_4
- **Sulfonation** — SO_3, H_2SO_4
- **Friedel-Crafts Alkylation** — R–Cl, $AlCl_3$ (or $FeCl_3$)
- **Friedel-Crafts Acylation** — $R-\overset{O}{\overset{\|}{C}}-Cl$, $AlCl_3$ (or $FeCl_3$)

Electrophilic aromatic substitution: Mechanism

Step 1: attack of the double bond at the electrophile ($E^{\oplus}$) — *Step 2: Removal of a proton from the carbon regenerates the aromatic group*

This forms a carbocation. — *[Breaks C–C, forms C–E]* — ***rate determining step*** — *[Breaks C–H, forms C–C (and X–H)]*

Certain substituents will stabilize this carbocation
Stabilize the carbocation, speed up the reaction

Substituents that stabilize this carbocation (relative to H) are called activating groups.

Ortho-meta-para : What does it mean?

1,2 (ortho) — **1,3 (meta)** — **1,4 (para)**

"ortho - meta - para" only applies to di-substituted benzenes

What if there's already a group on the ring?

The group X on the ring will affect the stability of the carbocation

ortho — *meta* — *para*

Activating vs. Deactivating : What does it mean?

An **activating group** is a group that causes electrophilic aromatic substitution to be ***faster, relative to H***

A **deactivating group** is a group that causes electrophilic aromatic substitution to be ***slower, relative to H***

	CH_3	Cl	CO_2Me
relative rate for nitration:	1	24	.03	.004

CH_3 is activating

Cl and CO_2Me are deactivating

Question 1: Ortho or para: what product dominates?

HNO_3, H_2SO_4

para (Major) — *ortho (Minor)*

Key concept: para is generally favored due to steric hindrance

Resonance forms *A* and *B* are KEY

If **X** has an electron pair, these resonance forms will be **stabilized** through formation of a double bond:

This resonance form is available for the ortho and para adducts, but NOT the meta.

This is why the following groups are ortho-para "directors"

$-NH_2$ $-NHR$ $-NR_2$ $-OR$ $-OH$ $-F$ $-Cl$ $-Br$ $-I$ $-SH$ $-SR$

Alkyl groups such as CH_3, CH_2CH_3, etc. are also ortho-para directors. Why? Notice the partial charge:

The partial negative charge on the carbon will stabilize an adjacent positive charge.

Similarly, if there is a partial positive charge on the atom adjacent to the ring, this will **destabilize** resonance forms A and B

bad! *ortho* — *bad!* *para* — *meta*

Destabilized! adjacent positive charges — *Not as unstable*

This is why the following groups are meta directors. (Although "ortho-para *avoider*" is more appropriate)

$-NO_2$ $-CF_3$ $-CN$ $-OH$ $-NR_3$

Transformations of aromatic functional groups

- **Reduction of nitro groups** — *conditions*: Fe / HCl, Sn / HCl, Zn / HCl, Pd-C, H_2 (either of these conditions will work)
- **Oxidation of side chain** — $KMnO_4$ → COOH (will convert any carbon with a C–H bond to a carboxylic acid) — *Benzylic oxidation*
- **Halogenation of side chain** — NBS, light (hν) → CH_2Br — *Benzylic halogenation* — NBS = *N*-bromosuccinimide
- **Reduction of ketone to alkane** — *conditions*: NH_2NH_2/ KOH *(Wolff-Kishner)*; Zn(Hg) / HCl *(Clemmensen)*; Pd/C / H_2 (5 atm) (all of these conditions will convert a ketone to an alkane)
- **Conversion of ketone to ester** — *m*-CPBA — *Baeyer-Villiger reaction*

Formation and reactions of diazonium salts

NH_2 → (H_3PO_2) H; (HNO_2, acid (e.g. HCl)) → *Diazonium salt*; CuBr → Br; CuCN → CN; KI → I; CuCl → Cl; NaOH, heat → OH

Question 2. When two groups "direct" to different carbons What product dominates?

strongly activating o/p director — *deactivating o/p director*

HNO_3, H_2SO_4

NOT OBSERVED

Key concept: more activating donor wins

Strongly activating o-p

$-O^{\ominus}$ $-NH^{\ominus}$ $-NH_2$ $-NHR$ $-NR_2$ $-OH$ $-OR$

Moderately activating o-p

$-CH_3$ $-R$ $-SH$ $-SR$

Deactivating o-p directors

$-F$ $-Cl$ $-Br$ $-I$

Moderately deactivating meta directors

$-CN$ $-OH$ $-OR$ $-H$ $-R$

Strongly deactivating meta directors

$-CF_3$ $-NO_2$ $-NR_3^{\oplus}$

Omissions, Mistakes, Suggestions?

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Key Reactions of Aldehydes and Ketones

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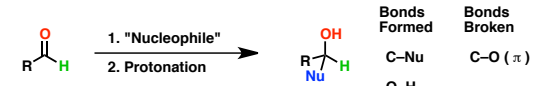
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

A Simple "Formula" for Seven Key Reactions of Aldehydes & Ketones



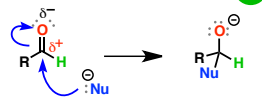
Aldehyde (but also applies to ketones)

Reaction	Nucleophile	Product
Grignard Reaction	R–MgX	
Addition of Organolithiums	R–Li	
Reduction by sodium borohydride ($NaBH_4$)	Na H–BH_3	
Reduction by lithium aluminum hydride ($LiAlH_4$)	Li H–AlH_3	
Addition of cyanide ion to form cyanohydrins	:CN	
Addition of hydroxide ion to form hydrates	:OH	
Addition of alkoxide ions to form hemiacetals	:OR	

Each of these reactions follows a "two-step" pattern: 1) addition 2) protonation

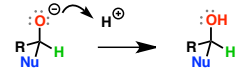
How to draw the mechanism for this pattern:
Step 1 is donation of a lone pair of electrons ***from*** the nucleophile ***to*** the carbonyl carbon, which bears a partial positive charge [oxygen is more electronegative than carbon]. A bond forms between the nucleophile and carbon, and the carbon-oxygen double bond [π bond] breaks. The oxygen then bears a negative charge.

Step 1: Addition of nucleophile (A)



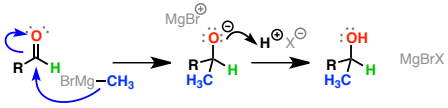
Bonds formed	Bonds broken
C–Nu	C–O (π)

Step 2: Protonation of oxygen (P)
In the second step of this reaction, acid is added the oxygen is protonated to give a neutral hydroxyl [O-H] group:



Specific example: Grignard addition

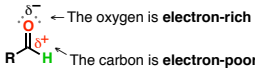
Step 1: Addition of nucleophile **Step 2: Protonation**



draw the arrow as coming from the Mg–C bond

What factors affect the reactivity of aldehydes and ketones?

1. Electronic effects
In aldehydes and ketones, the C=O bond is polarized; due to the greater electronegativity of oxygen relative to carbon [3.4 vs. 2.5]; the carbon bears a partial positive charge and the oxygen bears a partial negative charge



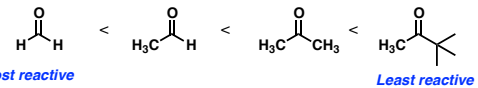
Most of the reactions of aldehydes and ketones involve an electron-rich *nucleophile* forming a bond with the electron-poor *electrophile* that is the carbonyl carbon of the aldehyde or ketone.

The more *electron-poor* the aldehyde or ketone, the more reactive it will be with nucleophiles

more electrophilic ***less electrophilic***

this aldehyde is more electron-poor than the aldehyde on the right due to the electron-withdrawing fluorines

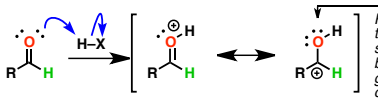
2. Steric effects
The larger the group adjacent to the carbonyl carbon, the more difficult it will be for nucleophiles to attack. This is referred to as *steric hindrance*.



Most reactive ***Least reactive***

Aldehydes are more reactive than ketones largely for this reason.

3. Acid catalysis
When acid ("HX" is added to an aldehyde or ketone it can make the carbonyl carbon more electrophilic (and thus more reactive)



Protonation of oxygen makes this resonance form more significant than it normally would be, and therefore there is a greater positive charge on carbon in the resonance hybrid

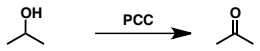
bottom line: carbon is more electrophilic

The only "catch" with using acid to accelerate a reaction is that it can't be used with strongly basic nucleophiles, because it will protonate them irreversibly. For instance using strong acid to accelerate a Grignard reaction would **not** work because Grignard reagents are strong bases; once protonated, they can't be regenerated.

Acid catalysis works well with neutral nucleophiles like H_2O, ROH, and amines, and also with weakly basic nucleophiles like $^{\ominus}CN$

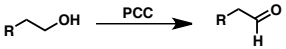
Synthesis of aldehydes and ketones

Through oxidation of alcohols



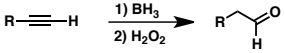
Secondary alcohols can also be oxidized to ketones with oxidizing agents such as H_2CrO_4 and others.

PCC = pyridinium chlorochromate



PCC is a mild oxidant that does not oxidize the aldehyde further to the carboxylic acid

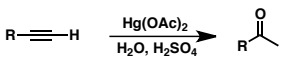
Hydroboration of alkynes



This first forms the enol, which then tautomerizes to the aldehyde.

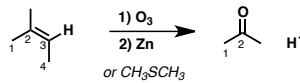
Synthesis of Aldehydes and Ketones (continued)

Oxymercuration of alkynes



This adds water to the more substituted end of the alkyne, forming an enol, which then tautomerizes to the ketone.

Ozonolysis of alkenes

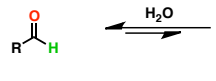


Ozonolysis cleaves C–C π bonds. If a "reductive workup" is used, C–H bonds attached to the alkene are preserved, leading to aldehydes.

or CH_3SCH_3
this is "reductive workup"

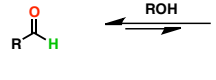
Other Key Reactions of Aldehydes and Ketones

Hydration



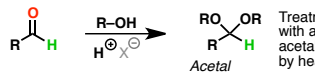
Water will add to aldehydes and ketones to give hydrates.
Equilibrium favors the starting aldehyde/ketone
The reaction is made faster by acid.

Hemiacetal formation



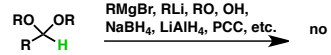
Alcohols will add to aldehydes/ketones to give hemiacetals.
Equilibrium usually favors the starting aldehyde/ketone, except in cases where a ring is formed.
The reaction is made faster by acid. Electron withdrawing groups on the aldehyde favor hemiacetal formation

Acetal formation



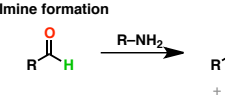
Treatment of an aldehyde or ketone with an alcohol in acid leads to an acetal. The acetal can be removed by heating with aqueous acid.

Acetals as protecting groups



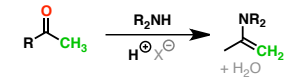
Acetals only react with aqueous acid. So forming an acetal is a method of "masking" a carbonyl group.

Imine formation



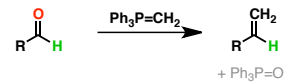
Aldehydes/ketones treated with a primary amine will give **imines.**
Mild acid can be used to promote this reaction

Enamine formation



Aldehydes/ketones treated with a **secondary** amine give **enamines.**
Acid catalyzes their formation.

Wittig Reaction



Treatment of an aldehyde/ketone with a phosphorus ylide leads to formation of an alkene. This is the Wittig Reaction.

Omissions, Mistakes, Suggestions?
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Key Reactions of Carboxylic Acid Derivatives

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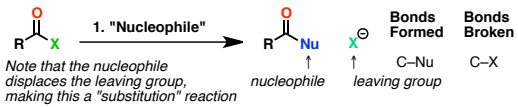
Nucleophilic acyl substitution

A key pattern for reactions of carboxylic acid derivatives

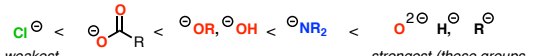


Note that the nucleophile displaces the leaving group, making this a "substitution" reaction

The biggest factor in whether this reaction proceeds is *base strength.*

If the base strength of the nucleophile is stronger than the leaving group, the reaction proceeds. If the nucleophile is a weaker base than the leaving group, the reaction does not proceed under these conditions.

Base strength:



Summary: Reactions of negatively charged nucleophiles with carboxylic acid derivatives (excluding H⊖ and R⊖)

Nucleophile \ Electrophile	Acid chloride	Anhydride	Ester	Amide
Cl^- halide	——	NR (no reaction)	NR	NR
carboxylate	*	NR	NR	NR
RO^- alkoxide	**	NR	NR	NR
OH^- hydroxide	***			
NR_2^- (or NHR/NH_2) amide				NR

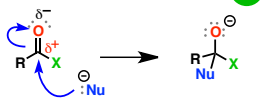
* If an anhydride is treated with a large excess of a carboxylate nucleophile with a different R group, a new anhydride will be formed.

**If an ester is treated with a large excess of an alkoxide nucleophile with a different R group, a new ester will be formed (this is called "transesterification")

*** Conversion of an amide to a carboxylic acid by adding HO(-) is not favorable unless a *lot* of heat is added.

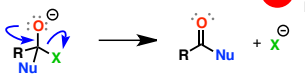
Each of these reactions follows a "two-step" pattern: 1) addition 2) elimination

Step 1: Addition of nucleophile A



Bond forming: C–Nu
Bonds broken: C–O (π)

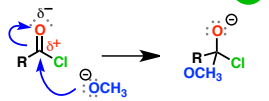
Step 2: Elimination of leaving group E



Bond forming: C–O (π)
Bonds broken: C–X

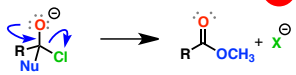
Specific example of nucleophilic acyl substitution:

Step 1: Addition of nucleophile A



Bond forming: C–O
Bonds broken: C–O (π)

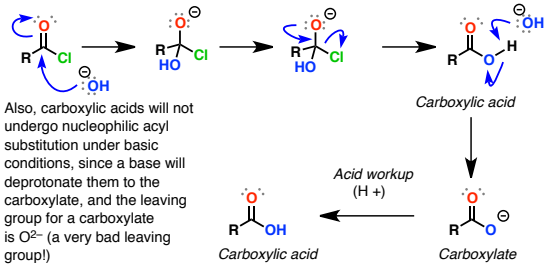
Step 2: Elimination of leaving group E



Bond forming: C–O (π)
Bonds broken: C–Cl

Special Cases: 1. Formation of carboxylic acids

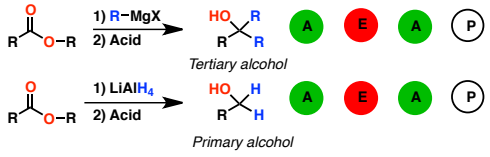
When the main product is a carboxylic acid, an "acid workup" step is necessary, since the carboxylic acid will be deprotonated to a carboxylate under the reaction conditions.



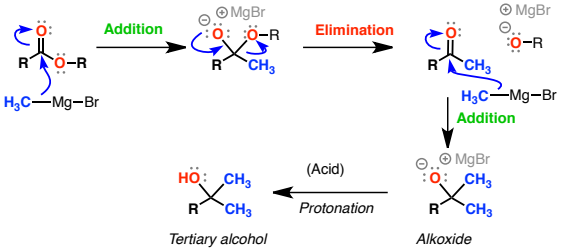
Also, carboxylic acids will not undergo nucleophilic acyl substitution under basic conditions, since a base will deprotonate them to the carboxylate, and the leaving group for a carboxylate is O^{2-} (a very bad leaving group!)

Special Cases: 2. Addition of Grignard reagents/ $LiAlH_4$ to esters

Esters will undergo "double addition" with Grignard reagents and the strong reducing agent $LiAlH_4$. This is because addition/elimination results in a ketone (or aldehyde, in the case of $LiAlH_4$), which then reacts with another equivalent of nucleophile to give an alkoxide. Addition of acid then give a neutral alcohol.

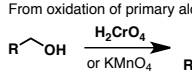


Example: "Double addition" of Grignard reagent to an ester

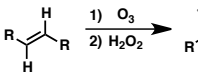


Synthesis of carboxylic acids

From oxidation of primary alcohols:



From ozonolysis of alkenes (oxidative workup)

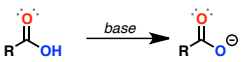


Ozonolysis followed by H_2O_2 leads to oxidation of the C–H bond to a C–OH bond (a carboxylic acid)

This is called "oxidative workup"

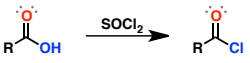
Other Important Reactions of Carboxylic Acids (and derivatives)

Deprotonation of carboxylic acids



Treatment of a carboxylic acid with base leads to formation of its conjugate base, called a "carboxylate"

Conversion of carboxylic acids to acid chlorides



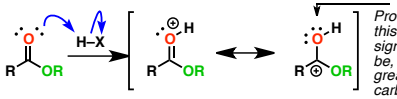
This is how to convert a carboxylic acid into a better electrophile

The role of acid in reactions of carboxylic acid derivatives

Acid can't be used as a catalyst with nucleophiles that are strong bases, since it will react irreversibly with them (i.e. protonate them) - Grignard reagents, for example.

With *poor* nucleophiles like H_2O and alcohols (ROH) it's possible to use acids to catalyze reactions. Acid serves two purposes:

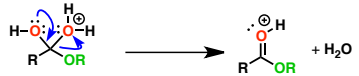
1) it makes carbonyl carbons more electrophilic (increasing the rate of **addition)**



Protonation of oxygen makes this resonance form more significant than it normally would be, and therefore there is a greater positive charge on carbon in the resonance hybrid

bottom line: carbon is more electrophilic

2) Acid also increases the rate of **elimination,** because it improves leaving group ability

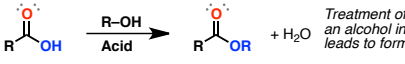


H_2O is a much better leaving group than HO^-

Thus, acid increases the rate of the elimination step

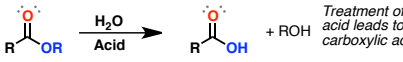
All of these reactions employ acid catalysis:

Fischer Esterification: Formation of esters from carboxylic acids



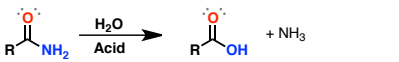
Treatment of a carboxylic acid with an alcohol in the presence of acid leads to formation of an ester

Aqueous hydrolysis of esters to carboxylic acids

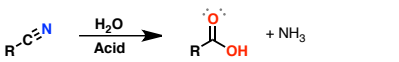


Treatment of an ester with aqueous acid leads to the formation of a carboxylic acid

Aqueous hydrolysis of amides to carboxylic acids



Aqueous hydrolysis of nitriles to carboxylic acids



Omissions, Mistakes, Suggestions?
james@masterorganicchemistry.com

The Oxidation Ladder

"Master Organic Chemistry"
http://masterorganicchemistry.com
2015 Version

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Oxidation state of carbon

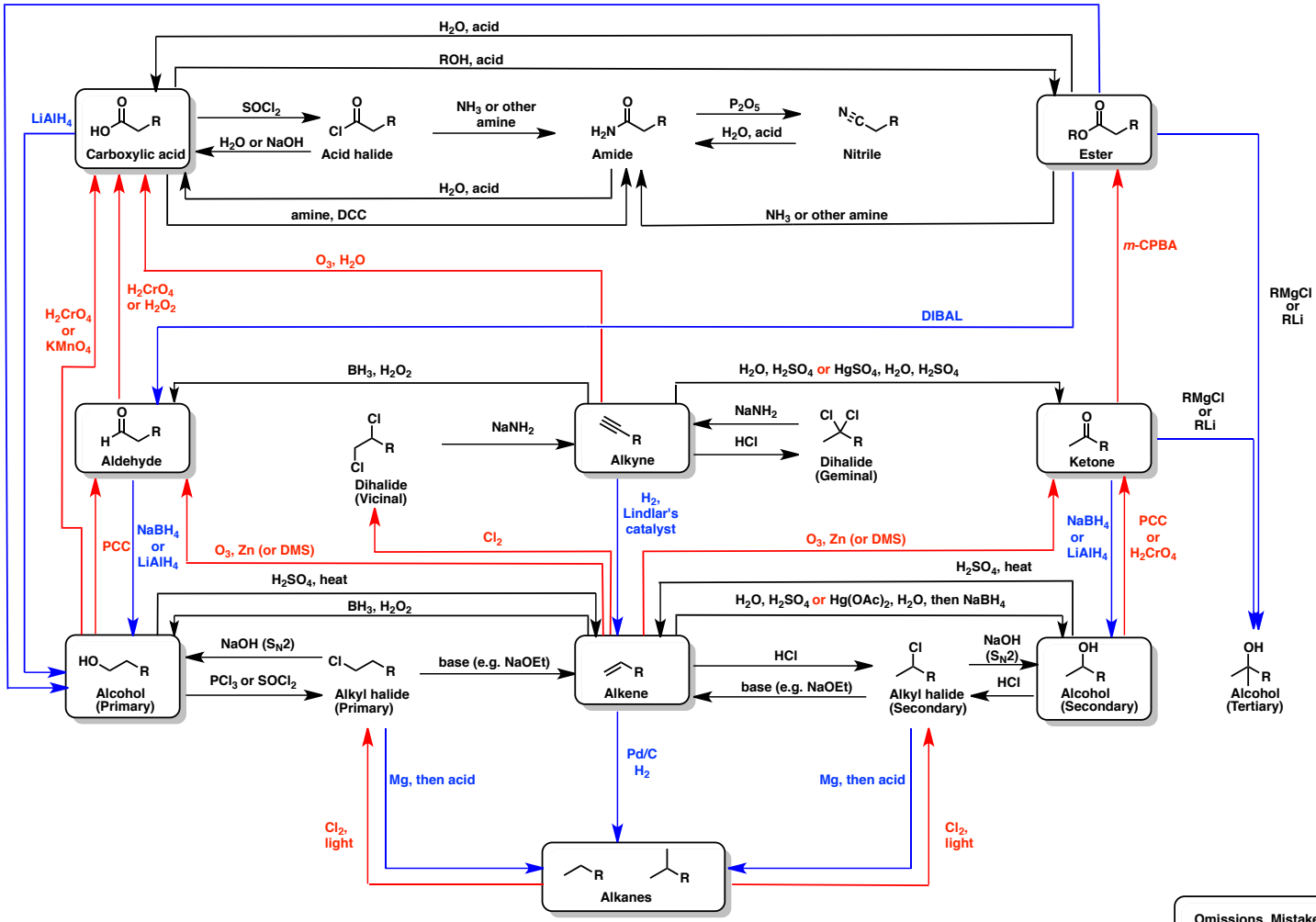
Indicates oxidations
Indicates reductions
Functional group transformations

CO_2
Carbon dioxide
(from combustion!)

- To keep things relatively simple, several common functional groups (amines, epoxides, ethers, and many more) have been omitted.
- All alkyl halides are drawn as chlorides ("Cl"). For Br and I, the corresponding reagent containing those atoms should be employed.
- Oxidation here is defined as: loss of a C–H bond or gain of a C–O bond (or equivalent)
  Reduction here is defined as: gain of a C–H bond or loss of a C–O bond (or equivalent)

REDUCTION

OXIDATION



Omissions, Mistakes, Suggestions?

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Enols and Enolates

Name	Structure	Example	pKA* of H
aldehyde			17
ketone			20
ester			25
lactone (cyclic ester)			
amide			30
lactam (cyclic amide)			
carboxylic acid			Note 1
acid chloride			Note 2
anhydride			Note 2
nitrile	R–CN	Me-CN	25

NH_2 = 1° amide
NHR = 2 ° amide
NR_1R_2 = 3 ° amide

Note 1: The carboxylic acid is deprotonated at oxygen first. Subsequent deprotonation of the α-carbon would form a dianion, which has a high activation barrier due to charge repulsion. It can be done, but requires a very strong base.

Note 2: It is difficult to measure the pKa of these species due to their reactivity.

*source: P.Y. Bruice, "Organic Chemistry"

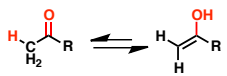
Note that some of these values differ slightly from textbook to textbook and instructor to instructor. However, there is universal agreement that for a given structure, pKas increase in the order:
aldehyde < ketone < ester < amide

1) evans.harvard.edu/pdf/evans_pka_table.pdf
2) www.chem.wisc.edu/areas/reich/pkatable/

Structural Features of the Carbonyl Group:

- Carbon, oxygen: sp^2 hybridized
- O–C–C bond angle ~120 °
- C=O bond strongly polarized toward oxygen.
- Carbonyl carbon is partially positive therefore **electrophilic!**
- Lone pairs render oxygen weakly nucleophilic (will react with strong acid)

Key Concept: Tautomerism



keto form enol form

Tautomerism: *a form of isomerism where a keto converts to an enol through the movement of a proton and shifting of bonding electrons*

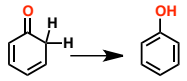
For acetone (R=CH_3) the keto:enol ratio is ~6600:1 at 23 °C. Main reason is the difference in bond strengths between the two species.

The enol tautomer is most significant for ketones and aldehydes. (You may also encounter it with acid chlorides in the mechanism of the Hell-Volhard-Zolinsky reaction). Esters and amides are less acidic and exist almost exclusively as the keto form (e.g. >10^6 : 1 keto: enol for ethyl acetate)

Acetone in D_2O will slowly incorporate deuterium at the α–carbon. The enol form is responsible for this behavior. *The rate of keto/enol tautomerism is greatly increased by acid* (see below right)

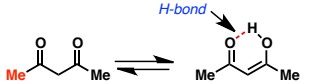
Five factors that influence the relative proportion of keto/enol:

1. Aromaticity



Not observed *Exclusive*

2. Hydrogen bonding stabilizes the enol form.

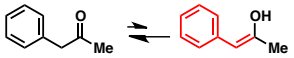


H-bond

24 : 76 (at 23 °C)

3. Strongly hydrogen bonding **solvents** can disrupt this, however. The above equilibrium is 81:19 using water as solvent.

4. Conjugation is stabilizing.

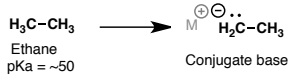


Preferred enol form

5. As with alkenes, increasing **substitution** increases thermodynamic stability (assuming equal steric factors)

Effects on acidity of alkyl groups

The carbonyl is an electron withdrawing π system with low-lying π* orbitals. It stabilizes adjacent negative charge.



Ethane pKa = ~50 Conjugate base

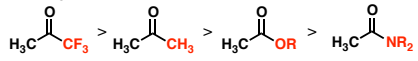
Methyl propionate pKa = ~25 Conjugate base (enolate)

~10^{25} more acidic just by replacing H with a carbonyl!

Why the huge difference in acidity? **The lone pair is stabilized by donation into the carbonyl π system.**

Enolate (Carbanion resonance form) Enolate (oxy-anion resonance form)

Question: How do you explain the relative acidity of the following series?



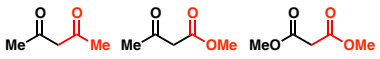
most acidic *least acidic*

***Answer**: The more electron-poor the carbonyl, the greater will be its ability to stabilize negative charge. Conversely, the greater the donating ability of a substitutent on the carbonyl, the less it will be able to stabilize negative charge.*

The aromatic electrophilic substitution chart is a good proxy for the ability of a functional group to donate to a carbonyl:

NR_2 , O⊖ > OH > OR, NHAc > CH_3, R > Cl, Br, F, I > C(O)OR > CF_3, etc.

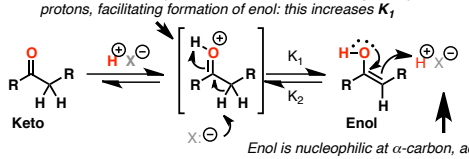
Substitution of the α-carbon by a second carbonyl derivative makes the α-proton even more acidic:



pKa = 9 pKa = 11 pKa = 13

The rate of keto/enol interconversion isgreatly enhanced by acid:

Acid makes carbonyl more electrophilic, increasing acidity of α-protons, facilitating formation of enol: this increases K_1



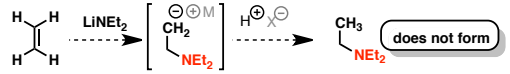
Keto Enol

Enol is nucleophilic at α-carbon, acid is excellent electrophile: this increases K_2

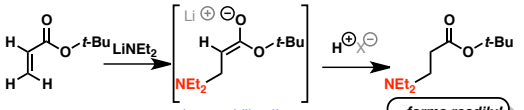
Net result: Addition of acid speeds proton exchange between the keto and enol forms.

Effect on reactivity of alkenes:

Likewise, the presence of a carbonyl group activates alkenes toward nucleophilic attack:

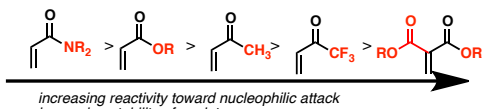


highly unstable does not form



enolate: stabilized! *forms readily!*

The reactivity of the alkene toward nucleophilic attack is directly related to the stability of the enolate that forms -

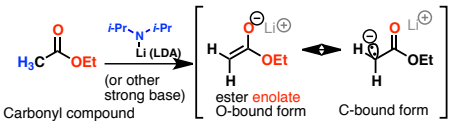


increasing reactivity toward nucleophilic attack
increasing stability of enolate

This means we can predict the course of the reaction by pKa!

Key Reaction: Enolate Formation

Enolate = deprotonated enol



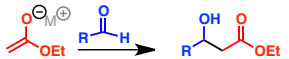
Carbonyl compound (or other strong base) ester enolate O-bound form C-bound form

Important: the Enolate is a NUCLEOPHILE

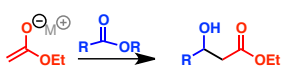
Amphiphilic =nucleophilic at both O and C; here we focus on the reactions at C.

note: though an ester enolate is shown here, the reaction of any enolate with an aldehyde is generally called an "Aldol".

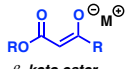
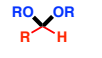
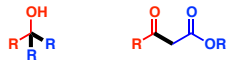
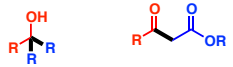
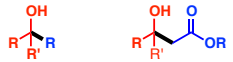
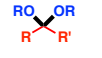
Two key examples:



Aldol reaction



Claisen Condensation

	1	2	3	4	5	6	7	8	9	10	11
	R–MgX ***Grignard***	 ***Ester enolate***	 ***Ketone enolate***	 ***Enamine***	 ***β–keto ester enolate***	R–NH$_2$ ***amine (primary amine)***	M–CN ***Cyanide***	R–OH/ R–OM ***alcohol/ alkoxide***	H$_2$O/ M–OH ***water/ hydroxide***	NaBH$_4$ ***Sodium borohydride***	LiAlH$_4$ ***Lithium aluminum hydride***
A	 ***Aldehyde***	 ***2° alcohol***	***Aldol Reaction***	***Aldol Reaction***	 ***Knoevenagel Condensation***	 ***Imine (aldimine)***	 ***Cyanohydrin***	 ***Acetal*** *Requires acid catalysis to form*	 ***Hydrate*** *(usu. thermodynaically disfavored, except for electron poor aldehydes) If aldehyde is enolizable, hydroxide can form enolate.*	 ***1° alcohol***	 ***1° alcohol***
		*heating under basic conditions will lead to elimination of OH - **Aldol condensation also note** that reaction can be reversible under basic conditions : **Retro-aldol reaction***									
B	 ***Acyl chloride***	 ***3° alcohol***	 ***β–keto ester***			 ***Amide (Schotten-Bauman reaction)***	 ***Acid nitrile***	 ***Ester***	 ***Carboxylic acid***	 ***1° alcohol***	 ***1° alcohol***
C	 ***Anhydride***	 ***3° alcohol***				 ***Amide***	 ***Acid nitrile***	 ***Ester***	 ***Carboxylic Acid***	*Borderline*	 ***1° alcohol***
D	 ***Ketone***	 ***3° alcohol***	***Aldol Reaction***	***Aldol Reaction***		 ***Imine (ketimine)***	 ***Cyanohydrin***	 ***Acetal*** *Requires acid catalysis*	 ***Hydrate*** *see above: even less favored than with aldehydes due to sterics*	 ***2° alcohol***	 ***2° alcohol***
		Note: best when ketones are identical or when only one can enolize (to avoid scrambling)									
E	 **α, β unsaturated ketone (enone)**	*Varies with conditions: 1,2 adduct is kinetic pdt.*	 ***Michael Reaction***	 ***Michael Reaction***			 *Note: in both cases, very prone to the reverse reaction (elimination)*		 *Note: Easily reversible*	*Varies with conditions: 1,2 adduct is kinetic product, 1,4 adduct is thermodynamic.*	
F	 ***Ester***	 ***3° alcohol***	 ***β–keto ester: Claisen Condensation***	 ***1,3 diketone: Claisen Condensation***	*Borderline*	*Borderline*	 ***Amide***	NR	 ***Transesterification*** *Can be done under basic or acidic conditions.*	 ***Saponification*** *(basic conditions) Can also hydrolyze with aqueous acid*	NR	 ***1° alcohol***
G	 ***Carboxylic acid***	*Deprotonation*	*Deprotonation*	*Deprotonation*	*NR*	*Deprotonation*	 ***Usually requires dehydration agent (e.g. DCC)***	NR	 ***Fischer esterification*** *(requires acid, heat)*	——	NR	 ***1° alcohol***
H	 ***Amide***	*Deprotonation*	*1° and 2° amides: deprotonation 3°amides: NR*	*1° and 2° amides: deprotonation 3°amides: NR*	NR	NR	NR	*Borderline reaction: requires strong acid, alcohol as solvent, heat*	 ***Amide Hydrolysis*** *Requires strong conc. acid, heat*	NR	 ***Amine***
I	 ***Alkyl halide***	Mix of addition /deprotonation	 ***Enolate Alkylation***	 ***Enolate Alkylation***	 ***Stork enamine reaction*** *note: capable of alkylating a second time*	 ***Amine*** ***caution! product is a good nucleophile; multiple alkylations usually result***		 ***Williamson Ether Synthesis*** *requires basic conditions*	 *requires basic conditions*	NR	 ***Alkane***

Identifying the Patterns in Carbonyl Reaction Mechanisms

Grignard Reaction — R–MgX — A P

Cyanohydrin formation — NaCN — A P

Ketone or aldehyde reduction — $NaBH_4$ or $LiAlH_4$ — A P

Base-catalyzed aldol reaction — base — D A P

Addition of neutral nucleophiles to acid halides or anhydrides (e.g.amines, alcohols, water) — RNH_2 — A E D

Addition of anionic nucleophiles to acid halides or anhydrides (e.g.RO^-, H_2N^-, HO^-) — A E

Claisen condensation — base — D A E *note 1

1,4 addition of Gilman reagent — R_2CuLi — 14A P

Michael reaction — base — D 14A P

1,4 addition of neutral nucleophiles — RNH_2 — 14A PT

Reactions of neutral nucleophiles with alkyl halides — SN2 D

Reactions of anionic nucleophiles with alkyl halides — SN2

Enolate alkylation (ketones or esters) — base — D SN2

Reduction of esters — $LiAlH_4$ — A E A P

Grignard Reaction + acid chloride, ester, or anhydride — RMgX — A E A P

Imine formation — RNH_2 — acid — P A PT E D

Fischer esterification — ROH — acid — P A PT E D

Amide hydrolysis — H_2O — acid — P A PT E D

Formation of acetals — ROH — acid — P A PT E A D

Hydrolysis of acetals — H_2O — acid — P E A PT E D

Acid catalyzed aldol — acid — P T A PT T 14E D

*note 1 - There is actually a fourth step; base removes a proton from the acidic alpha-carbon, rendering the reaction irreversible. Acidic workup gives the final product.

The Nine Mechanistic Components (with examples)

A — Addition to carbonyl [1,2-addition]

E — Elimination [1,2-elimination]

SN2 — S_N2

D — Deprotonation

Removal of a proton from substrate

PT — Proton Transfer

Intramolecular acid-base reaction example:

This can either be drawn as an intramolecular reaction (one step) or as a deprotonation (D)followed by a protonation (P)

14A — [1,4] addition

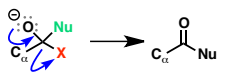
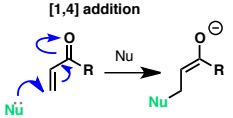
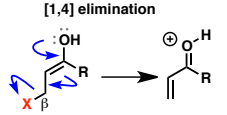
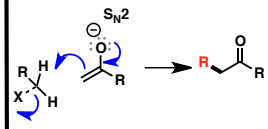
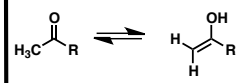
14E — [1,4] elimination

T — Keto-Enol Tautomerization

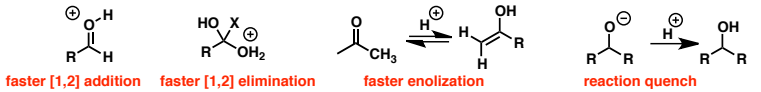
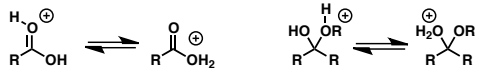
P — Protonation

Addition of a proton to substrate

Nine Key Mechanisms In Carbonyl Chemistry

Mechanism	Description	Promoted by	Hindered by	Examples
Addition **[sometimes "[1,2] addition"]** 	Attack of a nucleophile at the carbonyl carbon, breaking the C–O π bond.	*Anything that makes the carbonyl carbon a better electrophile (more electron-poor)* Electron withdrawing groups on α carbon Electron-withdrawing X groups that are poor π-donors (e.g. Cl, Br, I, etc.) Addition of acid (protonates carbonyl oxygen, making carbonyl carbon more electrophilic. Note: acid must be compatible with nucleophile;alcohols are OK, strongly basic nucleophiles (e.g. Grignards) are not.	*1) Anything that makes the carbonyl carbon a poorer electrophile (more electron-rich)* *2) Sterically bulky substituents next to the carbonyl* X-groups that are strong π-donors (e.g. amino, hydroxy, alkoxy) Sterics: X=H (fastest) > 1° alkyl > 2° alkyl > 3° alkyl (most hindered, slowest) X=Cl (poorest π-donor, fastest addition) > OAc > OR > NH_2/NHR/NR_2 (best π donor, slowest rate)	Grignard reaction Imine formation Fischer esterification Aldol reaction Acetal formation Claisen condensation
Elimination **[sometimes "[1,2] elimination"]** 	Lone pair on carbonyl oxygen comes down to carbonyl carbon, forming new π-bond and displacing leaving group X.	The better the leaving group X, the faster the reaction will be. The rate follows pKa very well. Acid can turn poor leaving groups (NR_2, OH) into good leaving groups (HNR_2, H_2O) $I^- > Br^- > Cl^- > H_2O > OAc^- > SR^- > OR^- >> NR_2$, O^{2-} H alkyl –9 –8 –7 –2 4 12 17 35 >40	X groups that are strong bases are poor leaving groups. Alkyl groups and hydrogens never leave. Amines and hydroxy are poor leaving groups under basic conditions, but are much better leaving groups under acidic conditions.	Fischer esterification Formation of amides by treatment of acid halides with amines. Claisen condensation
[1,4] addition 	Nucleophile attacks alkene polarized by electron withdrawing group, leading to formation of enolate.	So-called "soft" nucleophiles such as Gilman reagents (organocuprates) will add [1,4], as will amines, enolates etc. The more stable the conjugate base (enolate) of the carbonyl, the faster the reaction. Extra electron withdrawing groups on the α-carbon will promote the reaction.	[1,2]-addition can compete in the example of Grignard reagents. The more electron rich the carbonyl, the slower will be the rate of reaction (less able to stabilize negative charge). So addition to α,β-ketones > α,β–esters > α,β-amides.	MIchael reaction Addition of Gilman reagents (organocuprates)
[1,4] elimination 	Lone pair on oxygen comes down to form carbonyl, enol double bond displaces leaving group on the β-carbon	Facilitated if X is a good leaving group (just like [1,2]-elimination) In the aldol condensation, addition of acid helps OH group leave as H_2O. Note that in the Aldol reaction run under basic conditions, the enolate is a stronger base than OH(–), so in the base-promoted Aldol reaction, the [1,4]-elimination is favorable.	As with [1,2]elimination, X groups that are strong bases are poor leaving groups. Addition of acid will promote elimination of groups such as NR_2 and OH/OR.	Aldol condensation Knovenagel condensation
	Backside attack of nucleophile onto electrophile (alkyl halide or equivalent)	Facilitated by good leaving group on electrophile (alkyl halide or tosylate). Polar aprotic solvent is ideal. Enolate α-carbon is excellent nucleophile for S_N2 The higher the pKa of the carbonyl compound, the more reactive the conjugate base will be in the S_N2.	Rate of reaction will go primary alkyl halide > secondary alkyl halide Tertiary alkyl halides unreactive in S_N2.	Enolate alkylation Carboxylate alkylation
Keto-Enol Tautomerization 	Internal oxygen ↔ proton transfer with change in hybridization of oxygen and carbon.	Facilitated by acid The enol form is stabilized by internal hydrogen bonding if there is a carbonyl present at the β position.	Tautomerism under acidic conditions only significant for ketones, aldehydes, and acid halides (the latter under the conditions of the Hell-Vollhard-Zolinski reaction).	Acid-catalyzed aldol Acid-catalyzed bromination of ketones

Acid Base Reactions

Deprotonation	The conjugate base is always a better nucleophile than the conjugate acid. Deprotonation increases nucleophilicity. E.g. enolate > enol, alkoxide > alcohol, $NH_2(-) > NH_3$ Conjugate base can perform reactions the conjugate acid cannot. Deprotonation is also the last step in acid-catalyzed reactions, in order to generate the final (neutral) product	 *forms alkoxide* (more nucleophilic) deprotonation at end of acid-catalyzed acetal formation provides neutral product
Protonation	1) catalyzes [1,2] addition to carbonyls 2) promotes [1,2] elimination 3) to promote tautomerization. 4) quench (e.g. enolate from 1,4.	 faster [1,2] addition faster [1,2] elimination faster enolization reaction quench
Proton Transfer	An internal acid-base reaction. Not mechanistically distinct from the above, but often drawn as one step. Can proceed either intramolecularly or intermolecularly (both pathways operate) hence distinct arrow pushing steps often not drawn, and we just say "proton transfer"	

Introduction to Carbohydrates

"Master Organic Chemistry"
masterorganicchemistry.com

Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

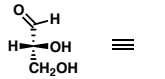
What's a Carbohydrate?

Carbohydrates have the molecular formula $C_n(H_2O)_n$

For example:
- Glucose $C_6H_{12}O_6$ = $C_6(H_2O)_6$ a hexose
- Fructose $C_6H_{12}O_6$ = $C_6(H_2O)_6$ a hexose
- Sucrose $C_{12}H_{24}O_{12}$ = $C_{12}(H_2O)_{12}$ a disaccharide
- Glyceraldehyde $C_3H_6O_3$ = $C_3(H_2O)_3$ a triose

The Fischer Projection

A 3-D molecule is "projected" as a flat molecule.



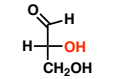
Fischer projection

Mnemonic:
"the arms come out to hug you" (or strangle if you prefer)

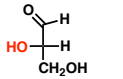
What's D and L?

D and L are arbitrary terms assigned by Emil Fischer in 1891 to denote the enantiomers of glucose. The absolute configuration wasn't determined until 1951.

He guessed right!



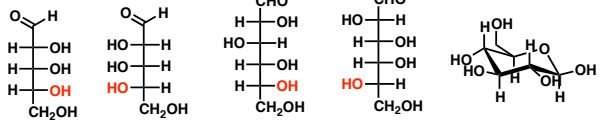
D-glyceraldehyde



L-glyceraldehyde

In the Fischer projection, assign D and L by placing the most oxidized carbon of the sugar (i.e. the aldehyde) at the top, and then if the stereocenter furthest from it is on the **right**, it's **D**. If it's on the **left**, it's **L**.

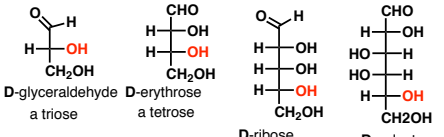
Examples



D-Ribose **L-Ribose** **D-Glucose** **L-Galactose** **D-Glucose**

Triose, Tetrose, Pentose, Hexose

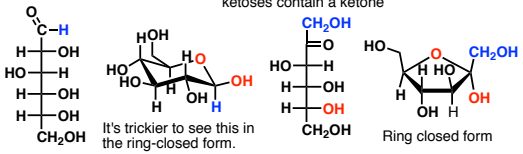
Each of these terms simply denotes the number of carbons in the sugar



D-glyceraldehyde a triose
D-erythrose a tetrose
D-ribose a pentose
D-galactose a hexose

Aldoses and Ketoses

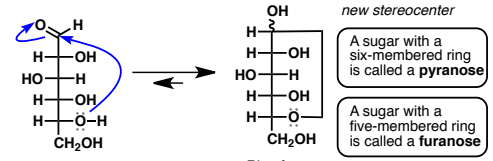
Aldoses contain an aldehyde; ketoses contain a ketone



D-glucose (an **ald**ose)
It's trickier to see this in the ring-closed form.
D-Fructose (a **ket**ose)
Ring closed form

Chain and Ring Forms of Sugars

Sugars can exist as mixtures of their open chain and ring forms.



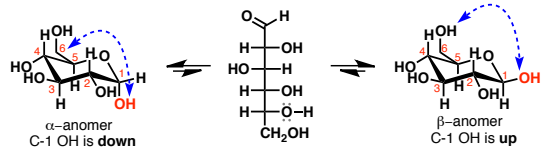
Open chain form *Ring form* *new stereocenter*

A sugar with a six-membered ring is called a **pyranose**

A sugar with a five-membered ring is called a **furanose**

The alcohol on C_5 attacks the aldehyde on C_1, forming a cyclic hemiacetal (after proton transfer)

Note that a stereocenter is formed on C_1 ! This leads to two isomers of the cyclic sugar, called "anomers" (designated alpha and beta)



α–anomer
C-1 OH is **down**
Mnemonic: "α" looks like a **fish**, which swims ***down*** *in the sea*

Open chain form

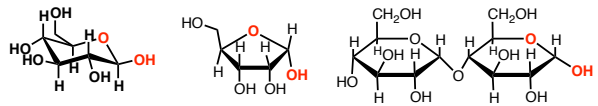
β–anomer
C-1 OH is **up**
Mnemonic: "β" stands for **bird**, which flies ***up*** in the sky

The two anomers (α and β) are in equilibrium with each other. A pure sample of either α-D-glucose (optical rotation +112°) or β-D-glucose (optical rotation +19°) will change over time to +52.7° which is an equilibrium mixture of 64% alpha and 36% beta. This change in optical rotation is known as **mutarotation**.

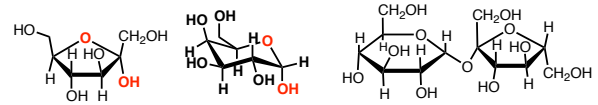
"Reducing Sugars"

A cyclic sugar with a hemiacetal is in equilibrium with the open chain form. And since the open chain form can be reduced to an alcohol with $NaBH_4$, it is termed a "reducing sugar".

Examples of reducing sugars (the hemiacetal is highlighted in **red**)



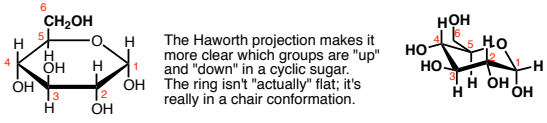
β–**D-Glucose** α–**D-Ribose** **Maltose**



α–**D-Fructose** β–**D-Galactose** **Sucrose**

not a reducing sugar - no hemiacetal!

Haworth Projections

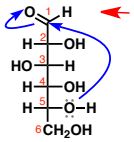


α–**D-Glucose** (Haworth)

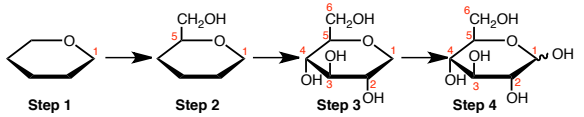
The Haworth projection makes it more clear which groups are "up" and "down" in a cyclic sugar. The ring isn't "actually" flat; it's really in a chair conformation.

α–**D-Glucose** (Chair)

Converting a Fischer to a Ring Form



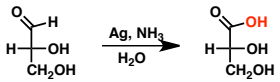
1. A bond is forming between the oxygen on C-5 and C-1 . So draw a six membered ring with oxygen at the top right.
2. Since the sugar is D, on C-5, place the CH_2OH pointing "up" on the ring (if it was L, CH_2OH would point "down")
3. For C-2, C-3, and C-4, every group on the **right** of the Fischer will be **down** on the ring, and every group on the **left** of the Fischer will be **up** on the ring.
4. The configuration of the anomeric carbon (C-1) will be a mixture of alpha (α) and beta (β)



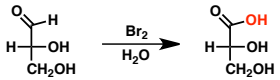
Step 1 **Step 2** **Step 3** **Step 4**

Reactions (not a complete list)

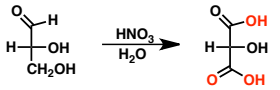
Tollens Test: Ag^+, NH_3, H_2O : oxidizes aldehyde to carboxylic acid



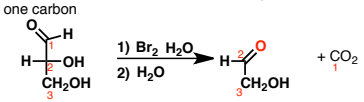
Aldonic Acid synthesis: Br_2, H_2O; oxidizes aldehyde to carboxylic acid



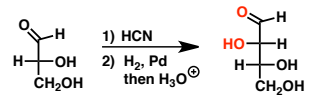
Aldaric acid synthesis: HNO_3, H_2O; oxidizes both ends to acids



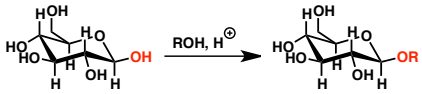
Ruff degradation: Br_2, H_2O, then $FeCl_3$, H_2O_2; shortens sugar by one carbon



Kiliani-Fischer Synthesis: Convert aldehyde to cyanohydrin, then reduce and hydrolyze. Extends sugar chain by one carbon.



Glycosides: Acetal formation



Omissions, Mistakes, Suggestions?

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Introduction to Amines

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2015 Version

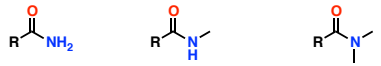
Note - this sheet is not meant to be comprehensive. Your course may provide additional material, or may not cover some of the reactions shown here. Your course instructor is the final authority.

Important nitrogen-containing functional groups

Amines An amine is classifed as primary, secondary, or tertiary depending on how many carbons the nitrogen is attached to

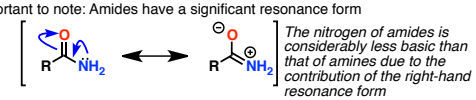
Primary amine (1° amine) | **Secondary amine** (2° amine) | **Tertiary Amine** (3° amine) | **Quaternary ammonium** technically not an amine *not a base (no lone pair)*

Amides An amide has a carbonyl group adjacent to an amine nitrogen



A primary amide | **A secondary amide** | **A tertiary amide**

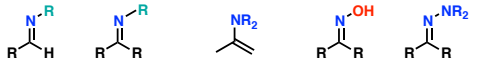
Important to note: Amides have a significant resonance form



The nitrogen of amides is considerably less basic than that of amides due to the contribution of the right-hand resonance form

Imines and Enamines

Imines are the nitrogen-containing analogues of ketones and aldehydes. Enamines are the nitrogen-containing analogues of enols



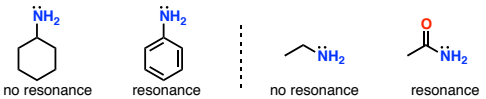
imine "Aldimine" | **imine** "Ketimine" | **enamine** | **oxime** | **hydrazone**

"exotic" variations of imines, less frequently seen

Basicity of amines

Factors that affect the basicity of amines
The more stable the lone pair, the less basic it will be. Examples of factors that stabilize the lone pair are 1) resonance 2) electron donating/withdrawing groups, and 3) orbitals

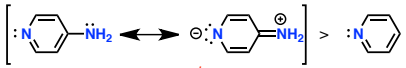
1. Resonance



no resonance stabilization ***more basic*** | resonance stabilization ***less basic*** | no resonance stabilization ***more basic*** | resonance stabilization ***less basic***

2. Electron donating and withdrawing groups

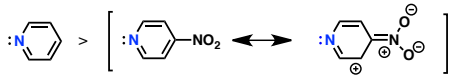
Electron donating groups will make the nitrogen more electron rich, and therefore more unstable (more basic)



more basic | *key resonance form* | ***less basic***

Other examples of electron donors - OH, OR, CH_3, NR_2

Electron withdrawing groups will make the nitrogen less electron-rich, and therefore more stable (less basic)

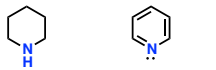


more basic | ***less basic***

Basicity of amines (cont'd)

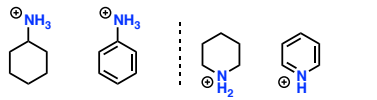
3. Orbitals

The more s-character the orbital, the more stable the nitrogen lone pair will be (and therefore less basic)



sp^3 hybridized ***more basic*** | sp^2 hybridized ***less basic*** | sp hybridized ***least basic***

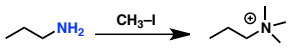
Acidity of amine derivatives (ammonium salts)
The weaker the base, the stronger the conjugate acid.



less acidic | ***more acidic*** | ***less acidic*** | ***more acidic***

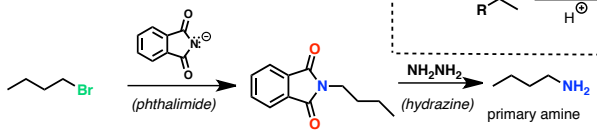
Synthesis of amines

Alkylation of amines with alkyl halides is not a good way of making amines; it will lead to ammonium salts



doesn't stop after just one reaction. Goes on to form ammonium salt.

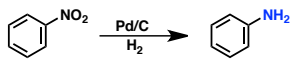
Gabriel synthesis - a way of making primary amines



(phthalimide) | *(hydrazine)* | primary amine

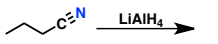
Alkylation of phthalimide with alkyl halides stops after one alkylation. The phthalimide is then removed with hydrazine (NH_2NH_2) to give the free amine.

Reduction of nitro groups



Nitro groups can be reduced to amines with Pd-C/H_2, or Zn/HCl, or Sn/HCl

Reduction of nitriles



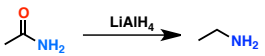
Nitriles can also be reduced with Pd-C or Pt-C and H_2

Reduction of azides

Both nitriles and azides can be prepared through S_N2 reactions with alkyl halides

An azide "R–N_3" | can also use $LiAlH_4$

Reduction of amides

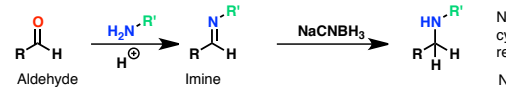


Depending on the type of amide (primary, secondary, tertiary) the corresponding amine will be formed.

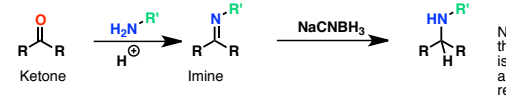
Synthesis of amines (cont'd)

Reductive amination

A very versatile method for amine synthesis involves making the imine, and then reducing it to the amine. Primary or secondary amines can be used; often, imine formation and reduction is done under slightly acidic conditions.



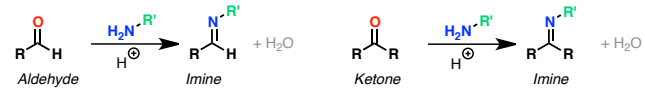
Aldehyde | Imine | $NaCNBH_3$ is sodium cyanoborohydride, a reducing agent. $NaBH(OAc)_3$ is also sometimes used



Ketone | Imine | Note: under acidic conditions, the conjugate acid of the imine is formed ("the iminium ion") and this is what is actually reduced here

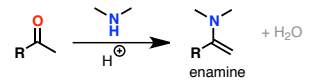
Formation of imines

When ketones or aldehydes are treated with a primary amine, imines are formed. Mild acid can catalyze this reaction. The byproduct is one equivalent of water, so this is a *condensation* reaction. Imines can be hydrolyzed back to the aldehyde/ketone by adding water.



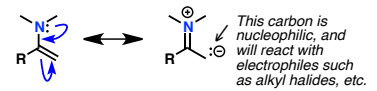
Aldehyde | *Imine* | *Ketone* | *Imine*

Formation of enamines
When ketones (or aldehydes) are treated with a *secondary* amine and acid, an *enamine* is formed. This is also a condensation reaction.



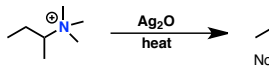
enamine

Enamines are good nucleophiles, due to the importance of this resonance form:



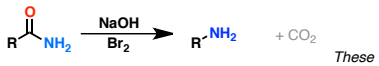
This carbon is nucleophilic, and will react with electrophiles such as alkyl halides, etc.

The Hoffmann elimination of ammonium salts



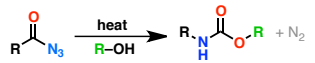
The less substituted alkene is formed here.
Non-Zaitsev product

The Hofmann rearrangement:



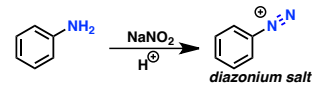
These reactions both proceed through an isocyanate intermediate

The Curtius Rearrangement



isocyanate

Formation of diazonium salts



diazonium salt

For reactions of diazonium salts, see the summary sheet on aromatic chemistry

Omissions, Mistakes, Suggestions?

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