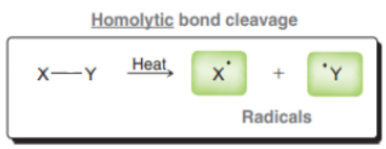
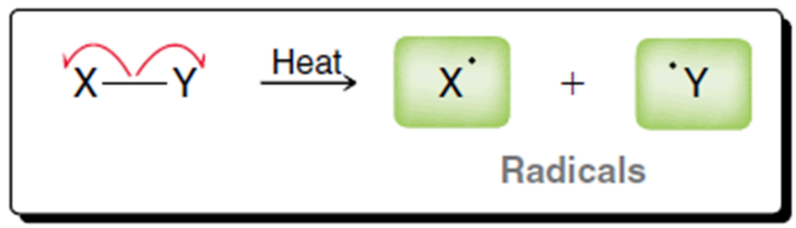
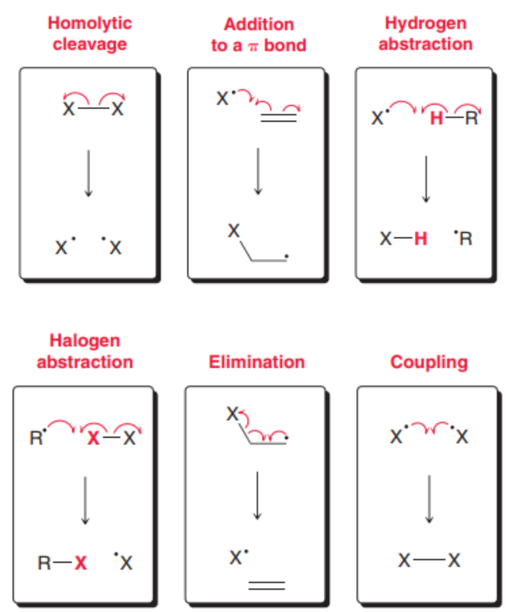
Reference Sheet 5: Organic Chemistry II Mechanisms
Part I

Reaction(s) & Example(s)	Reagent(s)	Example Mechanism
Free Radicals Split covalent bonds homolytically (one electron goes on each atom) into separate molecules (each one has a radical on it). 	Heat →	
Radical Electron Movement Moving radicals; there are **three** steps to which this occurs: • Initiation (radicals are made) • Propagation (radicals typically move from one location to another)- **note that the propagation steps must add together to give the net overall reaction**! • Termination (radicals are destroyed) **See reactions Chlorination to Radical Polymerization for more information.** Consider that there are **six** ways in which radicals move: • Homolytic Cleavage • Addition to a Pi Bond • Hydrogen Abstraction • Halogen (seen as X) Abstraction • Elimination • Coupling	N/A?	

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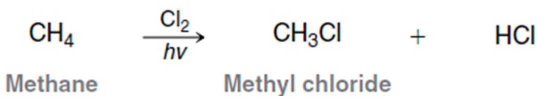
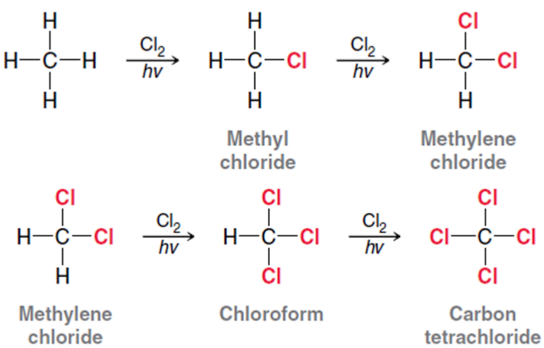
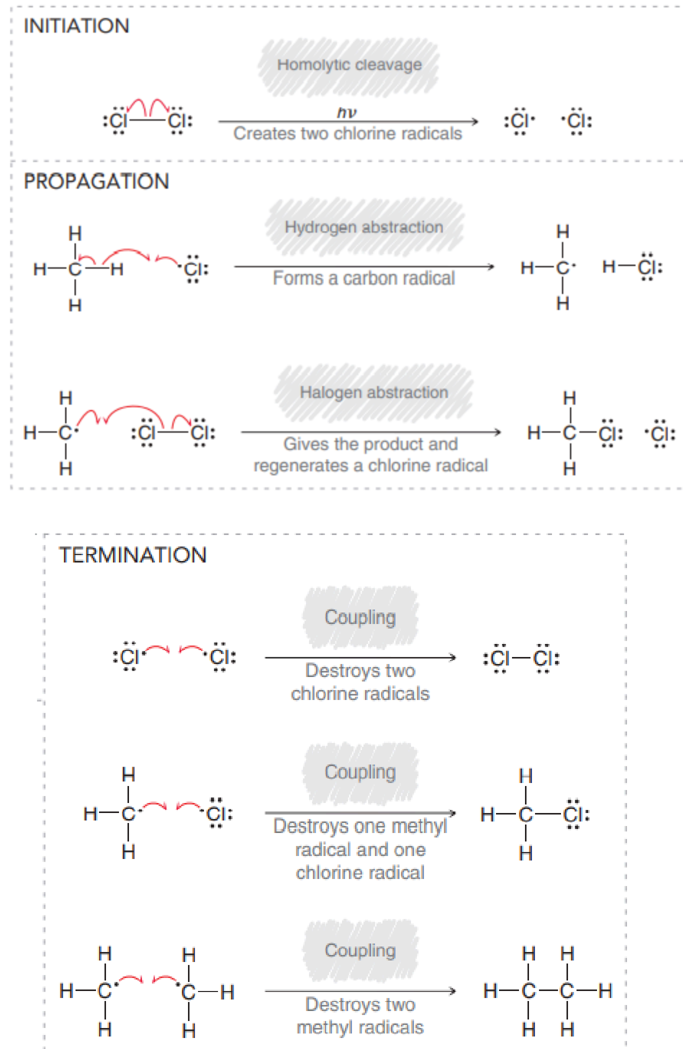
<td><u>Chlorination of Methane</u>

Converting methane into methyl halide (in this case, the chlorine is the halide).



Note that polychlorination could occur, regardless whether there is excess Cl_2 or not:



Once some of the molecules undergo the reaction to form chloromethane, they are more susceptible toward further chlorination (due to the Cl stabilizing radical intermediates through resonance) than remaining unreacted methane molecules.</td>
<td>Cl_2
→
hv</td>
<td>
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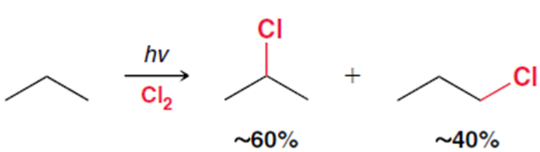
<tr>
<td><u>Chlorination</u>

Taking an alkane and converting it into an alkyl halide (in this case, chlorine is the halide).



***(Depending upon the molecule, the most to least stable radical: tertiary, secondary, primary, methyl; more stable</td>
<td>hv
→
Cl_2</td>
<td>#See mechanism above regarding methane chlorination.</td>
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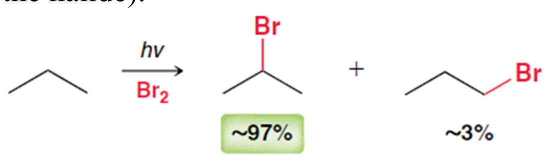
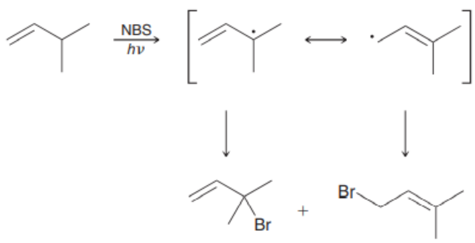
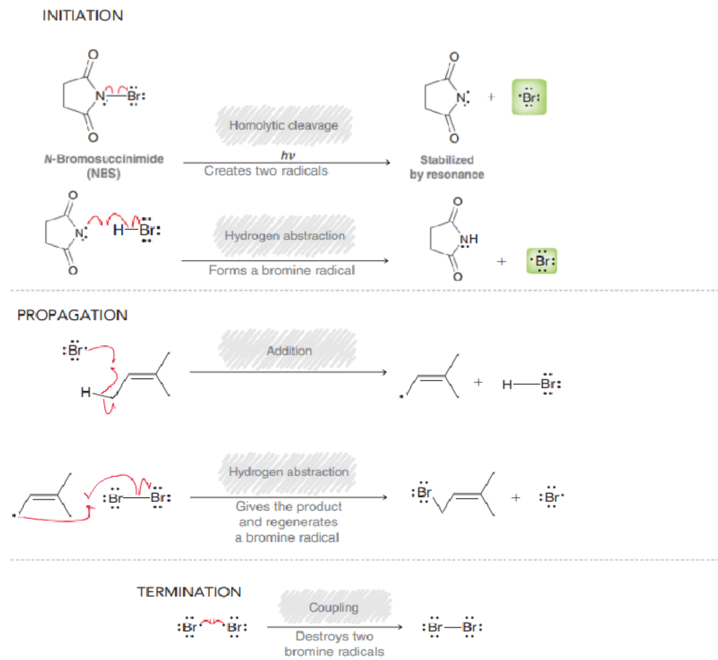
radical leads to the more likely product.**)** With chlorination, one is more prone to get a major product, and potentially other minor products. **Be careful to note any chirality centers that could potentially form enantiomers or diastereomers.**		
<u>Bromination</u> Taking an alkane and converting it into an alkyl halide (in this case, bromine is the halide).  (See "***" above). With bromination, one would most likely to have a lot more of the major product (and little to no minor product). This means that bromination is **more selective**. **Be careful to note any chirality centers that could potentially form enantiomers or diastereomers.**	*hv* → Br_2	#See mechanism above regarding methane chlorination.

<u>Allylic Halogenation</u> In preventing any potential of adding halogens to a pi bond, and rather remove an allylic hydrogen and replace it with a halogen, one would convert an alkene to an alkene with a halogen (in this case, bromine) allylic to the pi bond:  *Consider the resonance of the radicals from which other products could be made. **Be careful to note any chirality centers that could potentially form enantiomers or diastereomers.**	NBS → *hv*	

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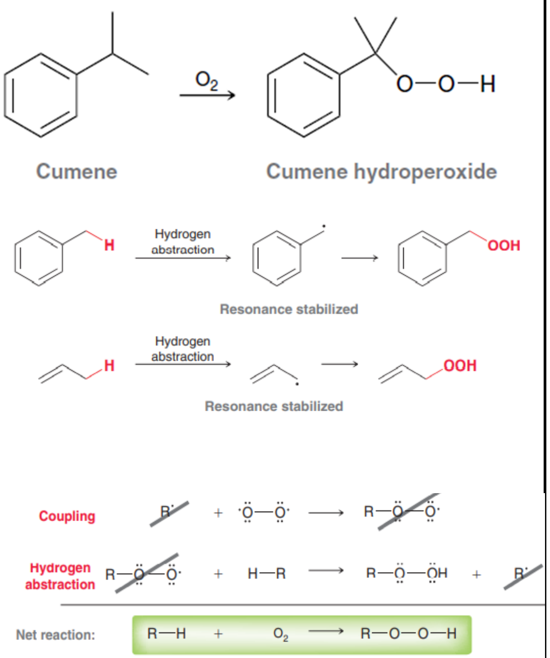
<u>Autoxidation</u>

Organic compounds react with oxygen to form hydroperoxide (ROOH):



This process occurs very slowly.

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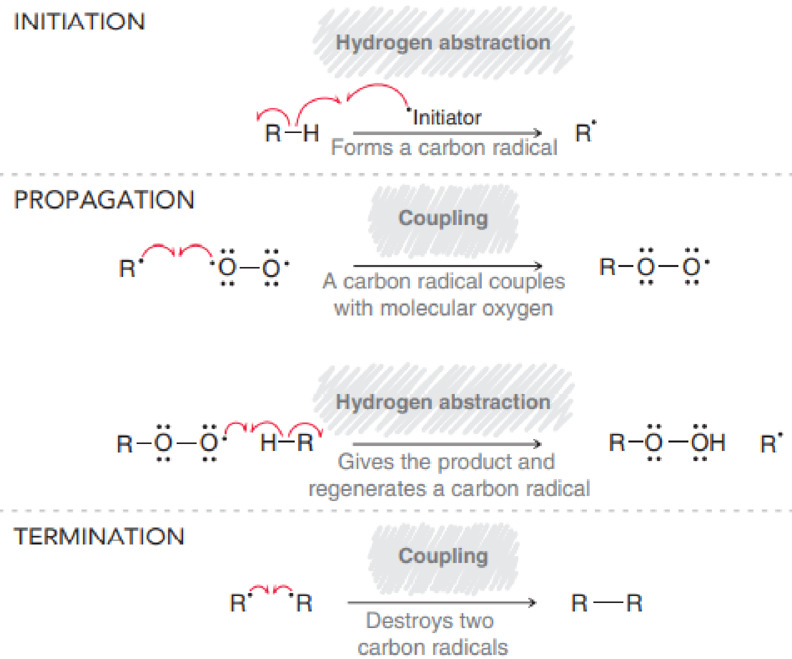
O_2
→

</td>
<td>



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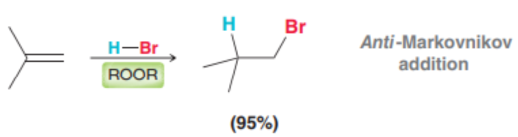
<u>Radical Addition of HBr</u>

Using peroxide, an alkene, and HX (where X in this case is the halogen Br), the alkene converts into an alkyl halide:



<u>Anti-Markovnikov</u><u>- Hydrogen goes on</u> **<u>most</u>** <u>substituted carbon (in terms of most substituted, in reference to the most number of carbon groups on a given carbon).</u>

Be careful to note any chirality centers that could potentially form enantiomers or diastereomers.

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HBr
→
ROOR (This is the peroxide! :O)

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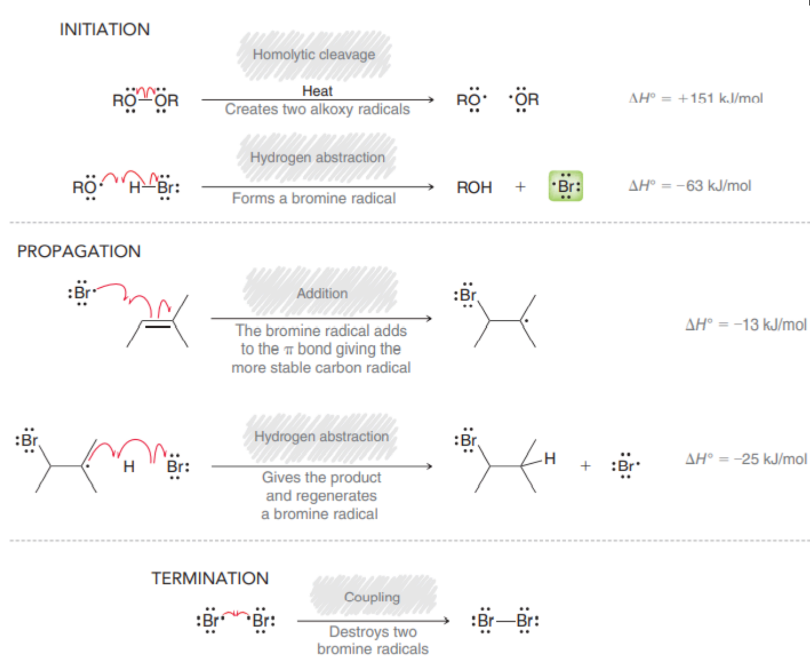

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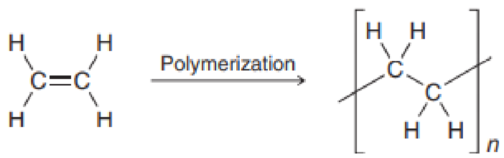
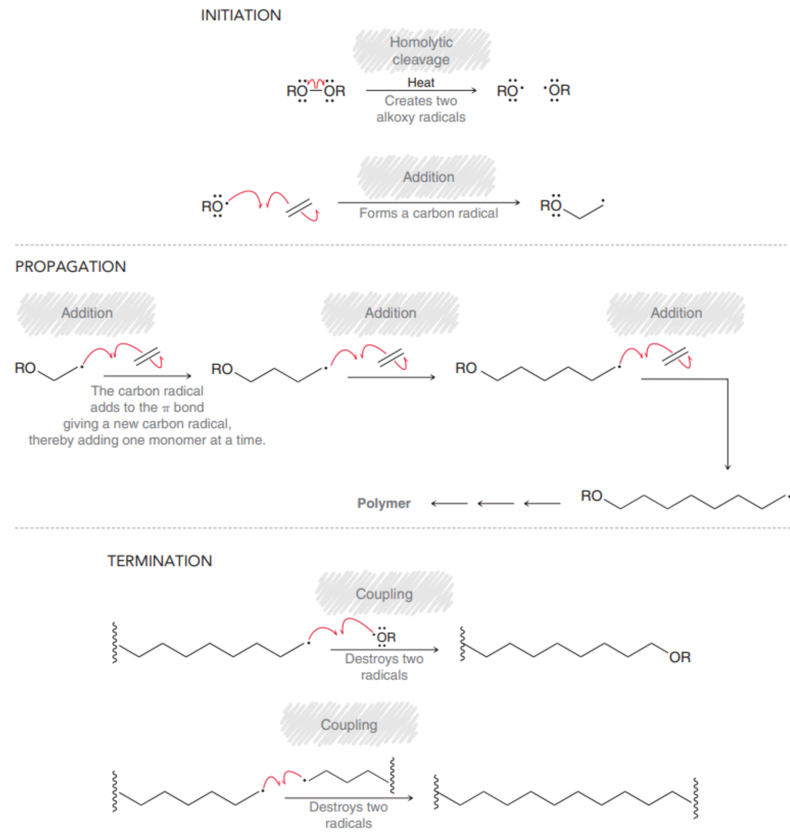
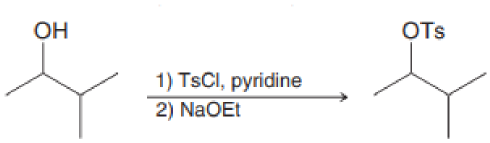
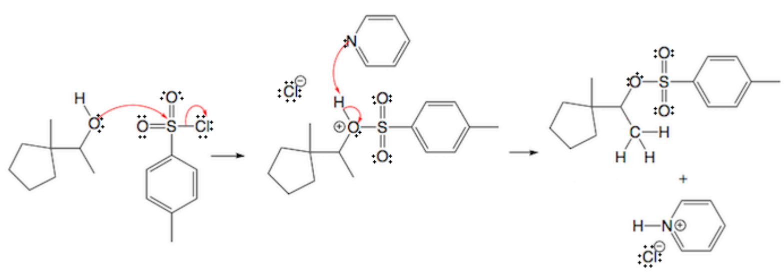
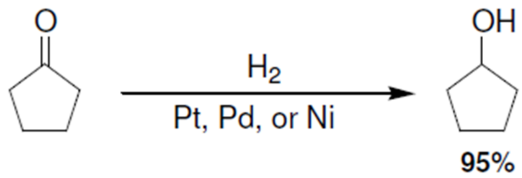
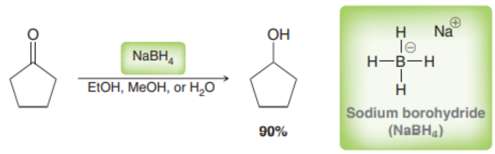
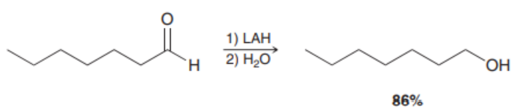
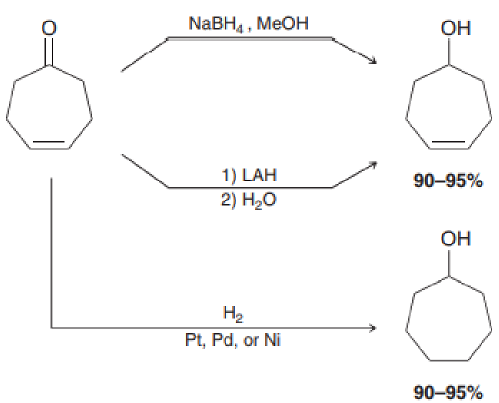
<u>Radical Polymerization</u> Form polymers from an alkene:  Ethylene Polyethylene The brackets ([ ]) represent the repeating unit (monomer) that makes up the polymer (consisting of more than one unit).	N/A	
<u>Converting OH into a Good Leaving Group</u> Replacing a hydrogen with Ts (p-toluenesulfonylchloride or tosyl chloride): 	TsCl, pyr (pyr, aka pyridine) →	
<u>Alcohol Prep via Reduction</u> Converts a carbonyl (i.e. ketones and aldehydes) into an alcohol:	H_2 → Pt, Pd, or Ni **^(This is done at high temperatures and/or high**	Reduction of a Ketone or Aldehyde with H_2: **Mechanism isn't required. (N/A)**



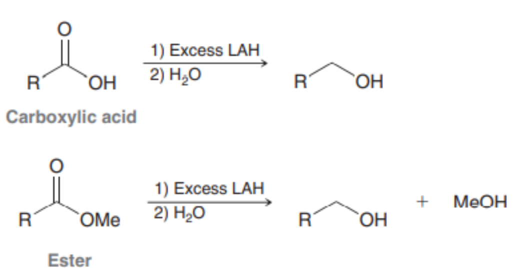




Note: H_2 can be added to an alkene, whereas the reactions concerning LAH and $NaBH_4$ **cannot**:



Also consider that $NaBH_4$ only reacts with ketones and aldehydes, whereas LAH reacts with <u>ALL</u> C=O (including carboxlic acids and esters).



pressures, so it may not be practical for most structures)

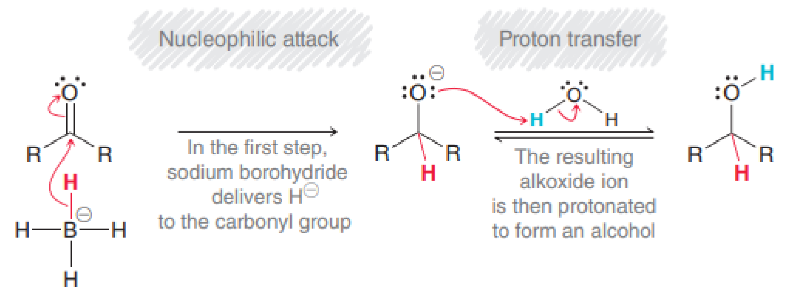
OR

$NaBH_4$
→
EtOH, MeOH, or H_2O

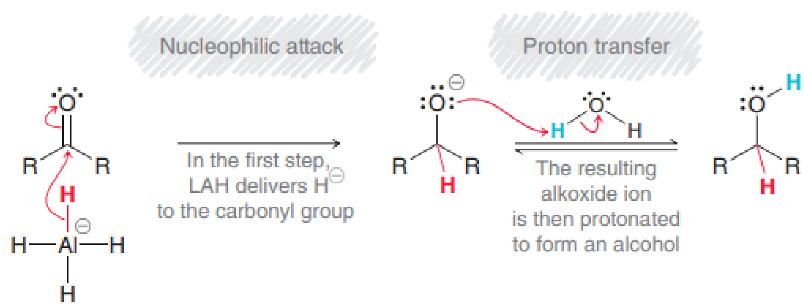
OR

1) LAH
→
2) H_2O

Reduction of a Ketone or Aldehyde with $NaBH_4$:

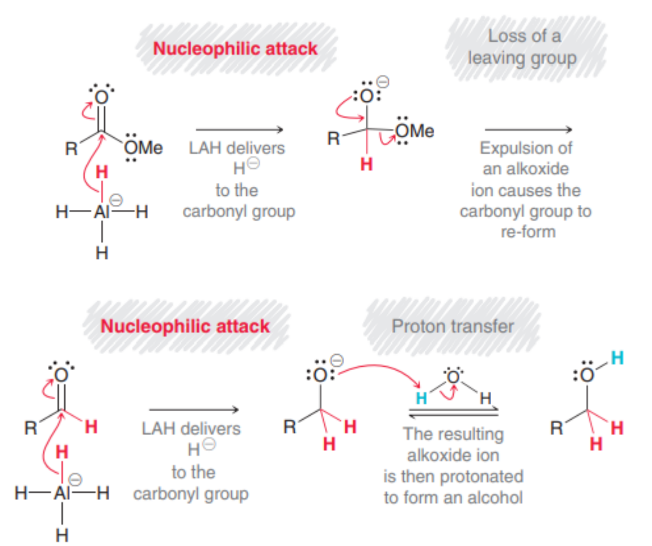


Reduction of a Ketone or Aldehyde with LAH:



^This is also true for when an LAH reacts with an aldehyde.

Reduction of an Ester with LAH:



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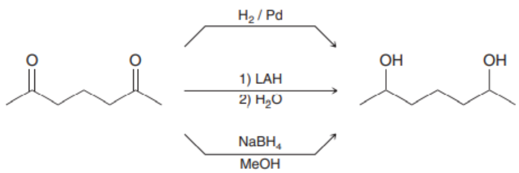
<u>Preparation of Diols</u>

A dicarbonyl converts into a diol (two C=O to two hydroxyl (OH) groups).



Note that the mechanism is the same in the formation of the OH groups, with exception of the fact that in converting each C=O group, they **DON'T** occur **simultaneously**!

Also consider that **two hydrogens total** are also added to make the product.

#See Reference Sheet 3 for *syn* and *anti* dihydroxylation.

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H_2
→
Pt, Pd, or Ni

^(This is done at high temperatures and/or high pressures)

OR

$NaBH_4$
→
EtOH, MeOH, or H_2O

OR

1) LAH
→
2) H_2O

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*See "<u>Alcohol Prep via Reduction</u>" above.

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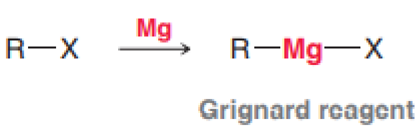
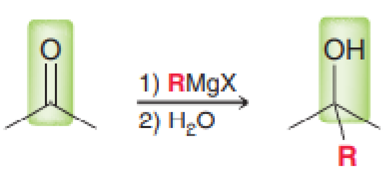
<u>Preparation of Alcohols via Grignard Reagents</u>

Making a Grignard Reagent requires magnesium (Mg) and an alkyl halide:



Using the Grignard reagent and a dicarbonyl, this will eventually convert into a diol (two C=O to two hydroxyl (OH) groups). Also consider that **an R (a carbon group)** is added to the carbon that once had an carbonyl:



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Formation of the Grignard:

R-X (X could be a Cl or a Br)

Mg
→

Formation of the alcohol given a ketone or an aldehyde:

1) RMgX (R could be an alkyl; X could be Cl or Br)
→
2) H_2O

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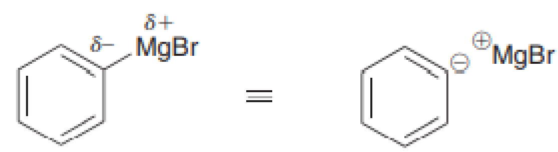
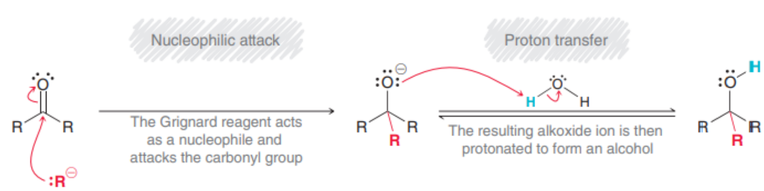
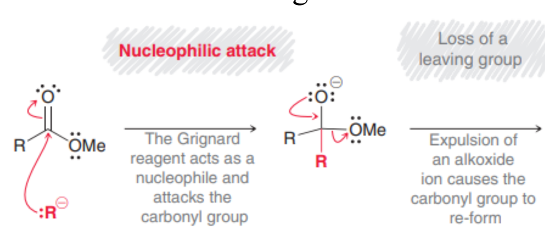




Have an ester as a given molecule:



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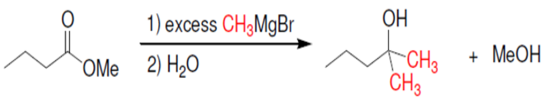
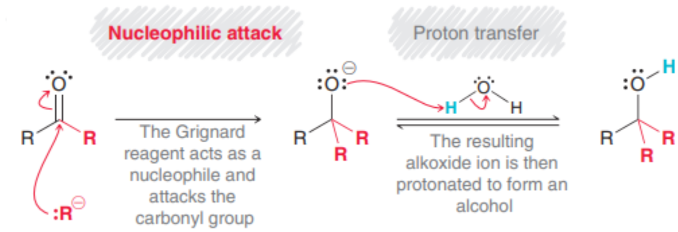
<tr>
<td>Note that the mechanism is the same in the formation of the OH groups, with exception of the fact that in converting each C=O group, they DON'T occur simultaneously!

If one is dealing with an ester, use excess Grignard Reagent!!!

</td>
<td>Formation of the alcohol given an ester:

1) xs RMgX (R could be an alkyl; X could be Cl or Br)
→
2) H_2O</td>
<td>
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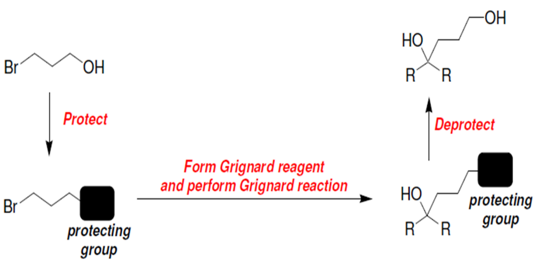
<td><u>Protection of Alcohols</u>

In achieving a product in which a given reactant's hydroxyl group is present, one must note that the OH can act like an acid, especially when a Grignard is present. One must utilize a protecting group to shield the OH from reacting:

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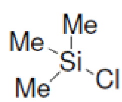
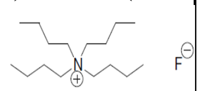
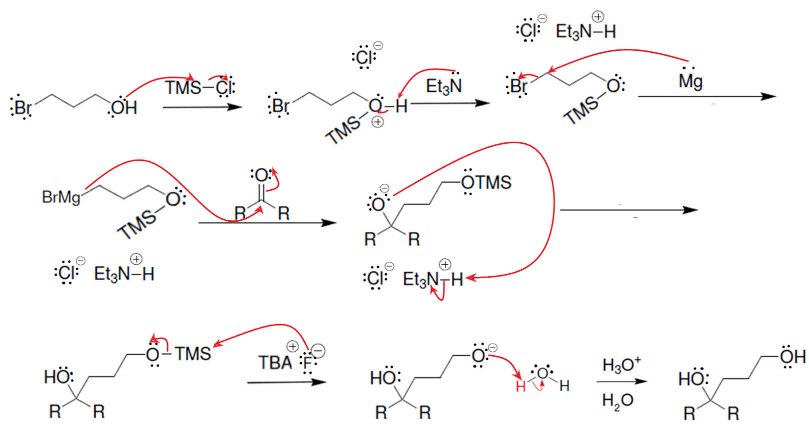
<td>1) TMsCl (aka
)
2) Et_3N
→
3) Mg
4) Ketone, Aldehyde, or any Carbonyl of one's choice
5) TBAF (aka

)
6) H_3O^+ / H_2O</td>
<td></td>
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<td colspan="3"><u>Reactions of Alcohols</u></td>
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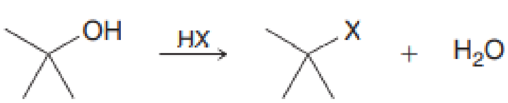
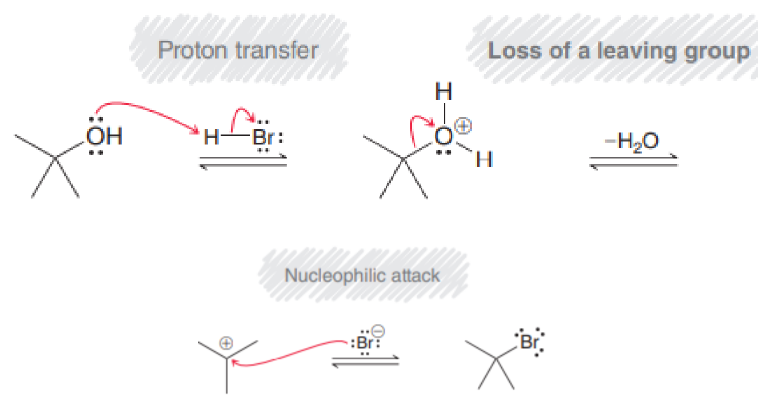
<td><u>S_N1 Reactions with Alcohols:</u>

Tertiary alcohols will undergo a substitution reaction when treated with a hydrogen halide:
</td>
<td>HX (X could be Cl, Br, or I)
→</td>
<td>
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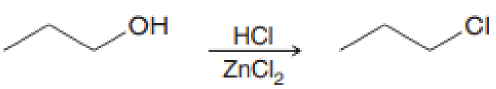
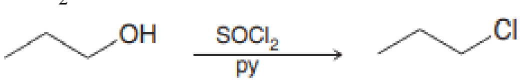
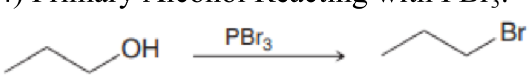
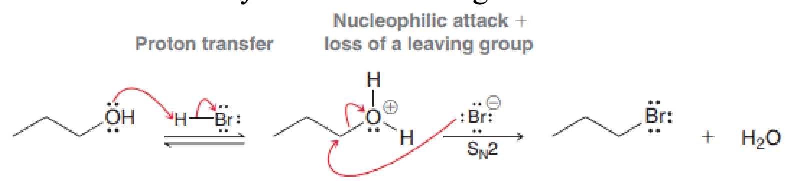
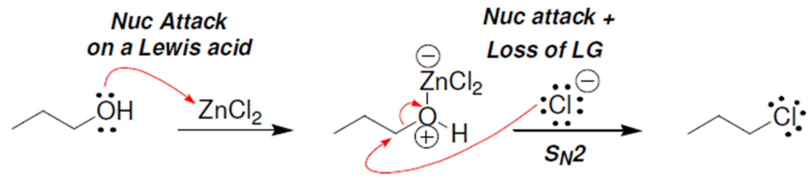
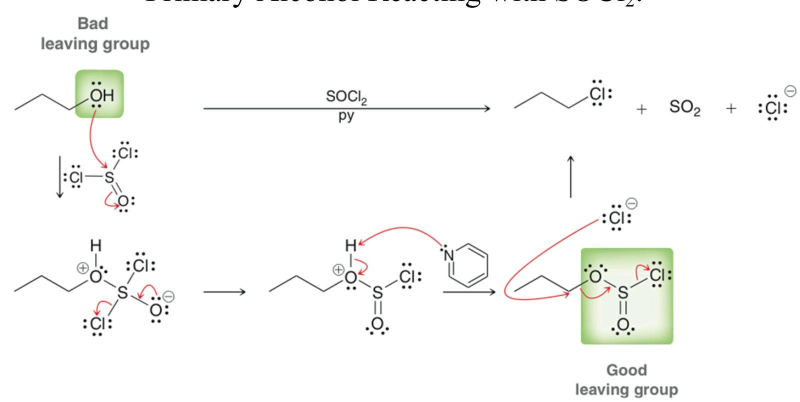
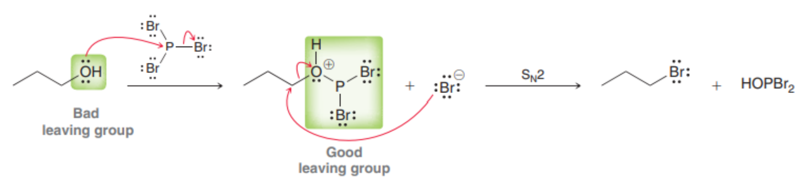
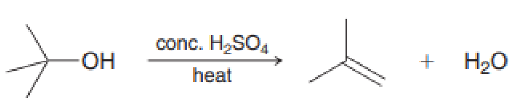
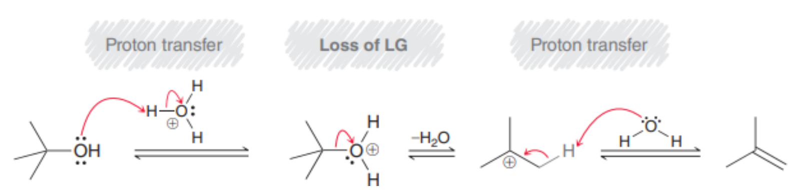
<u>S_N2 Reactions with Alcohols</u> Primary and secondary alcohols will undergo substitution reactions with a variety of reagents, all of which proceed via an S_N2 process. One is **mainly** focused on the three following S_N2 reactions: 1) Primary Alcohol Reacting with HX:  2) Primary Alcohol Reacting with $ZnCl_2$:  3) Primary Alcohol Reacting with $SOCl_2$:  4) Primary Alcohol Reacting with PBr_3:  (In all of these reactions, one is converting an alcohol to an alkyl halide).	HX (X could be Cl, Br, or I) → **OR** HCl → $ZnCl_2$ **OR** $SOCl_2$ → pyr (aka pyridine: ) **OR** PBr_3 →	Primary Alcohol Reacting with HX:  Primary Alcohol Reacting with $ZnCl_2$:  Primary Alcohol Reacting with $SOCl_2$:  Primary Alcohol Reacting with PBr_3: 
<u>E1 and E2 Reactions with Alcohols</u> <u>*(Examples below)</u> E1: Given a tertiary alcohol and a **weak base**, one would convert this into an alkene: 	E1: conc. H_2SO_4 → heat E2: 1)TsCl → pyr (aka	E1: 

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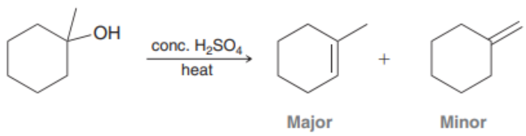
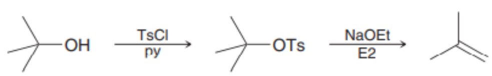


E2: Given an alcohol and a **strong base**, one would convert an alcohol into an alkene:



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pyridine:

)
2) Strong Base (see Reference Sheet #5)
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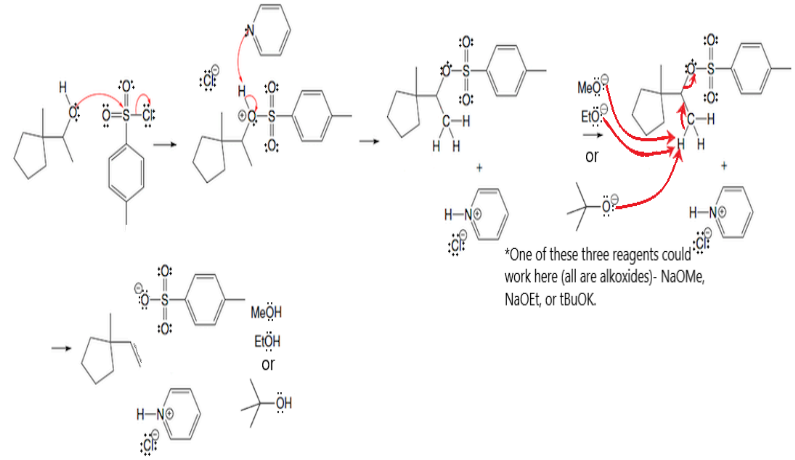
E2:



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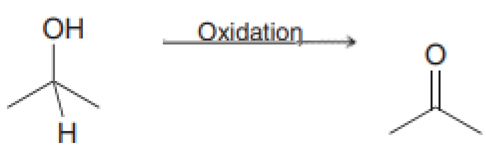
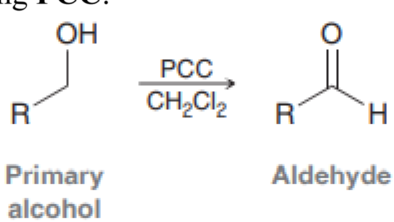
<u>Reactions of Alcohols: Oxidation</u>

(Note that tertiary alcohols generally **don't** undergo oxidation!)

When examining **secondary** alcohols, would convert this into a **ketone** by using **chromic acid or PCC**:



When examining **primary** alcohols, would convert this into an **aldehyde** by using **PCC**:



One could also convert a **primary** alcohol (**or an aldehyde**) into a **carboxylic acid** using **chromic acid**:
</td>
<td>
Secondary Alcohol:

PCC
→
CH_2Cl_2

OR

($Na_2Cr_2O_7$
→
H_2SO_4, H_2O)

3

Primary Alcohols to:

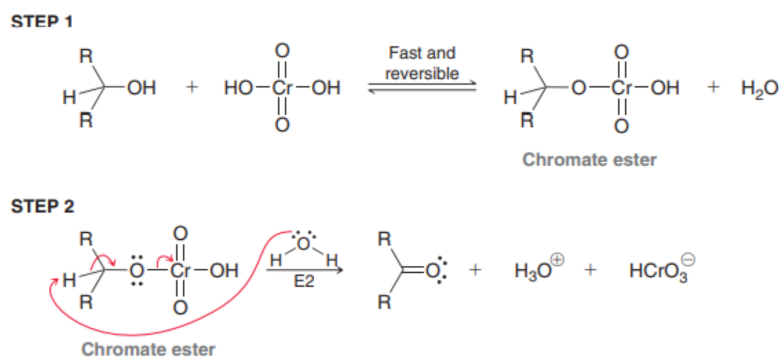
Aldehyde:

PCC
→
CH_2Cl_2

Carboxylic Acid:

H_2CrO_4
→
</td>
<td>
Reactions with PCC: N/A

Reactions with Chromic Acid- Ketone:



Reactions with Chromic Acid- Carboxylic Acid: N/A
</td>
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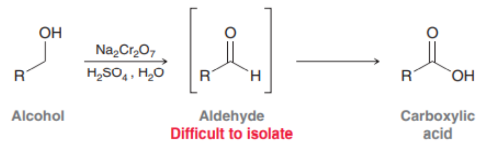
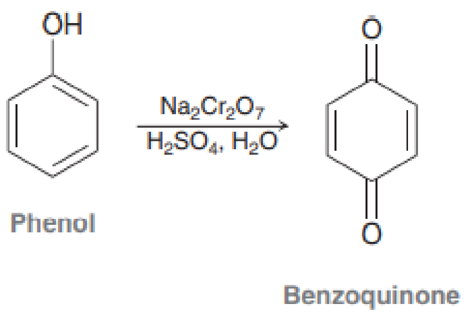
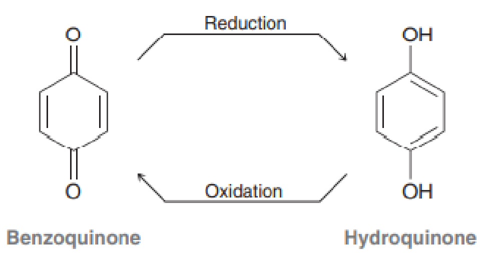
<tr><td>
</td><td>acetone</td><td></td></tr>
<tr><td><u>Oxidation of Phenol</u>

Converting a phenol (hydroxyl group attached to a benzene ring) into benzoquinone:


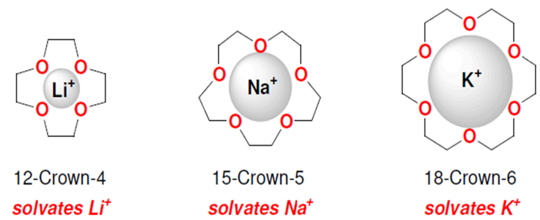
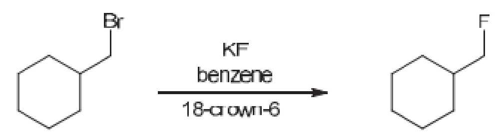
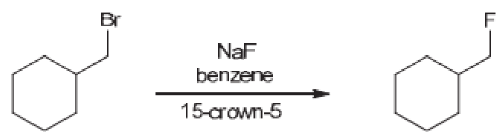
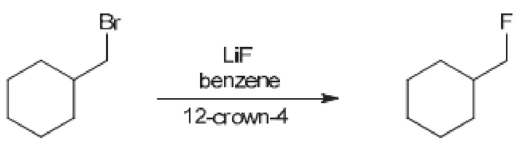
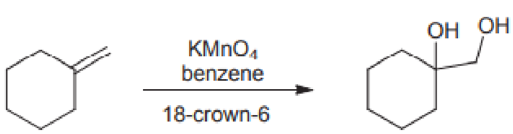
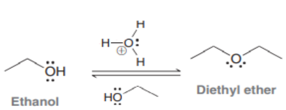
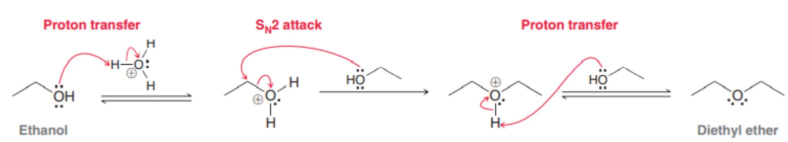
Note this:

</td><td>Phenol or Hydroquinone to Benzoquinone

CrO_3
→
H_3O^+, acetone</td><td>N/A</td></tr>
<tr><td colspan="3"><u>END OF “REACTIONS OF ALCOHOLS”</u></td></tr>
<tr><td><u>Crown Ethers</u>

Note that the crown ether’s size must match the size of the metal to form a strong attraction (12-Crown-4 solvates Li^+, 15-Crown-5 solvates Na^+, and 18-Crown-6 solvates K^+):</td><td>Formation of an Alkyl Fluoride from an Alkyl Halide:

KF
benzene
→
18-crown-6

OR</td><td>N/A</td></tr>
</table>

 One could convert an alkyl halide (with Cl, Br, or I) into an alkyl fluoride:    One could also convert an alkene into a diol using $KMnO_4$: 	NaF benzene → 15-crown-5 **OR** LiF benzene → 12-crown-4 Formation of a Diol from an Alkene: $KMnO_4$ benzene → 18-crown-6	
<u>Preparation of Ethers</u> Converting an alcohol into an ether using the following: Acid-Catalyzed Dehydration:  Williamson Ether Synthesis:	Acid-Catalyze-d Dehydration: H_3O^+ → HOR (R can be any carbon group) Williamson Ether	Acid-Catalyzed Dehydration:  Williamson Ether Synthesis:

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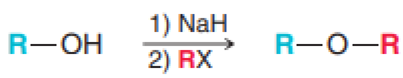
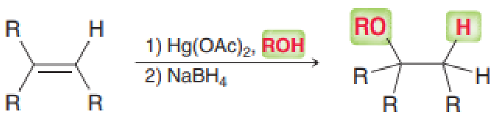


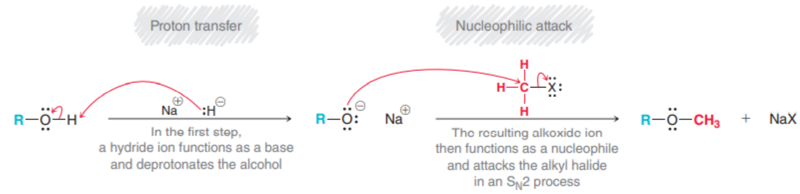
Alkoxymercuration-Demercuration:



</td>
<td>
Synthesis:

1) NaH
→
2) RX (where R can be any carbon group, with the exception of tertiary and quaternary carbons).

Alkoxymercuration-Demercuration:

1) $Hg(OAc)_2$, ROH
→
2) $NaBH_4$
</td>
<td>


Alkoxymercuration-Demercuration: Note that this mechanism is like that of "Oxymercuration-Demercuration." See Reference Sheet #3 for more information regarding the mechanism.
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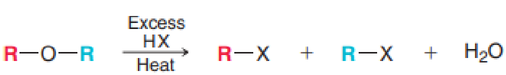
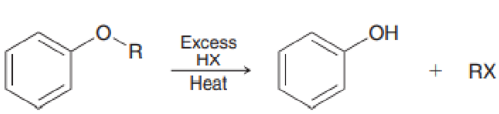
<u>Acidic Cleavage</u>

When heated with a concentrated solution of a strong acid, an ether will undergo acidic cleavage, in which the ether is converted into two alkyl halides:



When a phenyl ether is cleaved under acidic conditions, the products are phenol and an alkyl halide:

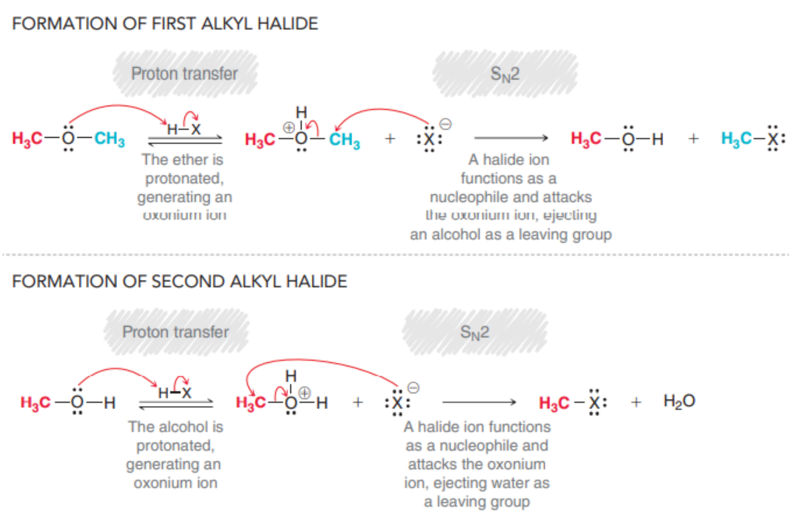


Phenol

The phenol is not further converted into a halide- neither S_N2 nor S_N1 processes are efficient at sp_2 -hybridized centers.
</td>
<td>
Acidic Cleavage:

xs HX (where X could be Br or I)
→
Heat

(Note: Both HI and HBr can be used to cleave ethers. HCl is less efficient, and HF does not cause acidic cleavage of ethers.)
</td>
<td>
Acidic Cleavage:



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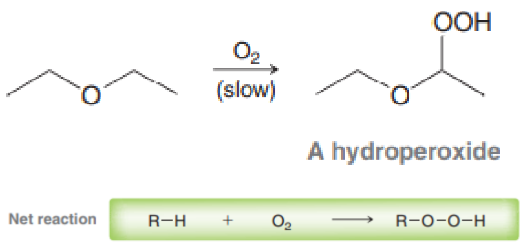
<u>Autoxidation of Ethers</u>

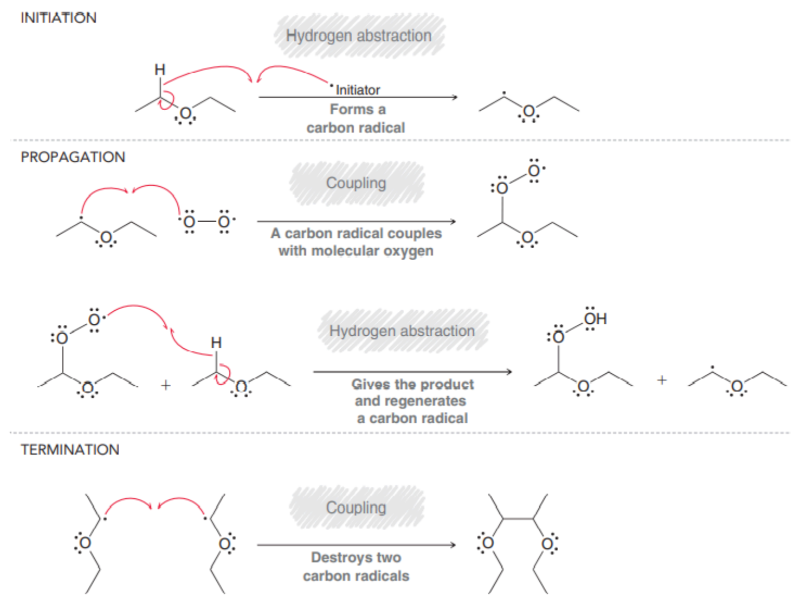
Ethers undergo autoxidation in the presence of atmospheric oxygen to form hydroperoxides:



</td>
<td>

O_2
→
(slow)

</td>
<td>



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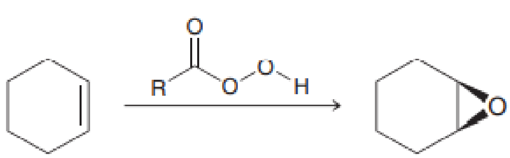
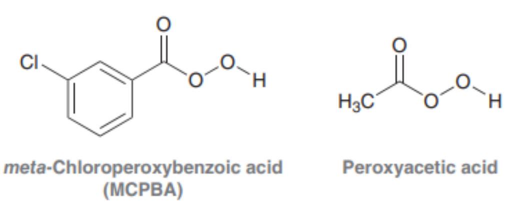
<u>Preparation of Epoxides</u>

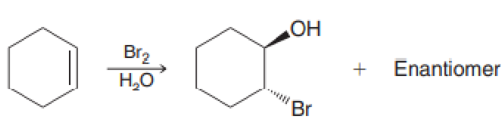
Using a peroxy acid and an alkene, one is able to create an epoxide:



Examples of Peroxy Acids:



One could also prepare an epoxide using the Halohydrin Reaction, as well as a strong base:



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Making an Epoxide:

MCPBA
→

OR

Peroxyacetic Acid
→

OR

1) Br_2, H_2O
→
2) NaOH

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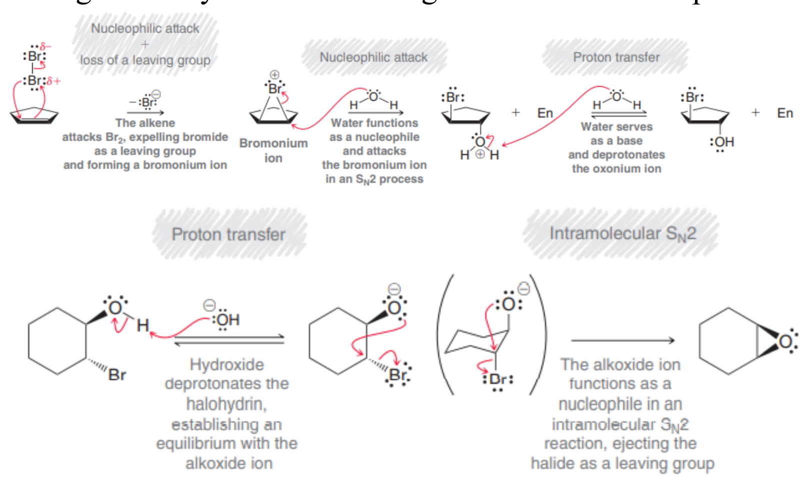
Using MCPBA or Peroxyacetic Acid to Form the Epoxide:
N/A

Using a Halohydrin and a Strong Base to Form the Epoxide:



#(The second part of forming the epoxide (utilizing the strong base) is an Intramolecular Williamson Ether Synthesis. An alkoxide ion is formed, which then functions as a nucleophile in an intramolecular S_N2-like process). :O

Also, consider this: for these reactions, the overall stereochemical outcome is the same as direct epoxidation with MCPBA. That is, substituents that are *cis* to each other in the starting alkene remain *cis* to each other in the epoxide, and substituents that are *trans* to each other in the starting

</td>
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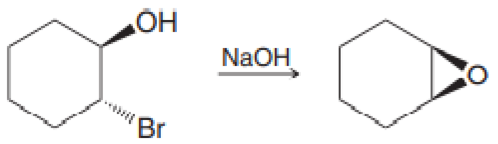
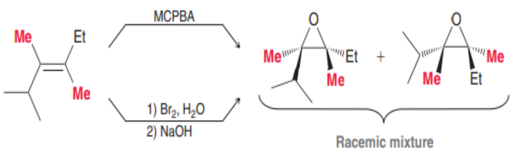
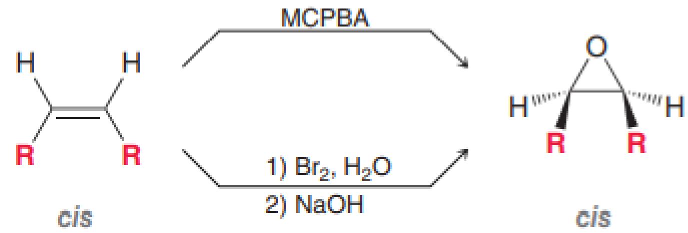


Enantioselective Epoxidation:

When forming an epoxide that is chiral, both of the methods mentioned previously will provide a racemic mixture:



alkene remain *trans* to each other in the epoxide:

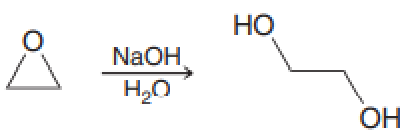


Enantioselective Epoxidation: (See mechanism above).

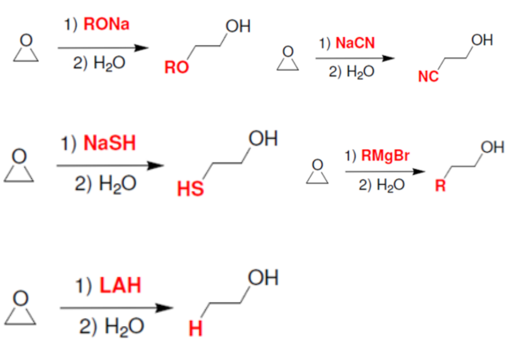
The two enantiomers are formed in equal amounts, because the epoxide can be formed on either face of the alkene with equal likelihood (in other words, the epoxide can form from above or below the plane equally).

Ring-Opening Reactions of Epoxides

When an epoxide is subjected to attack by a strong nucleophile, the ring opens:



Other examples also include:



One could form a diol, an alcohol with an OR, CN, or an SH group, an alcohol with an extended carbon chain (with carbons), or an alcohol. It depends upon what one desires for the product.

Note: There are two factors to consider here:

Formation of a Diol:

1) NaOH → 2) H_2O

Formation of an Alcohol with an RO:

1) RONa → 2) H_2O

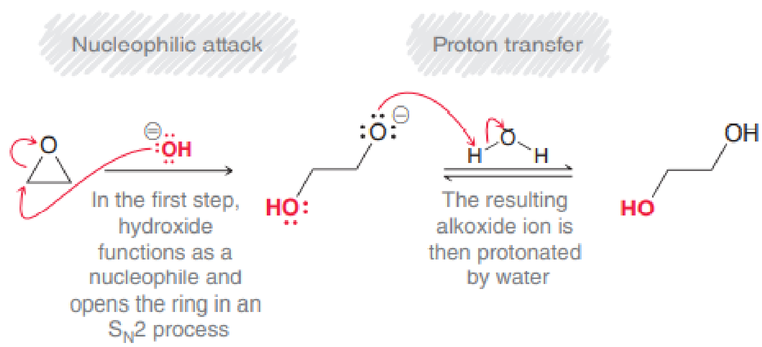
Formation of an Alcohol with a CN:

1) NaCN → 2) H_2O

Formation of an Alcohol with an SH:

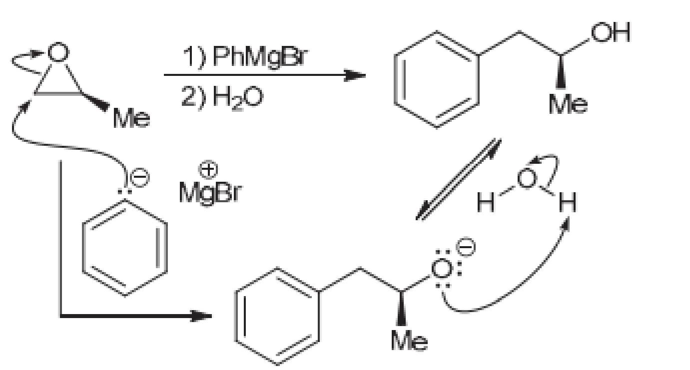
1) NaSH → 2) H_2O

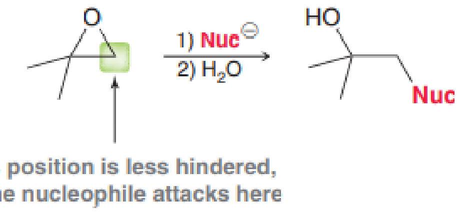
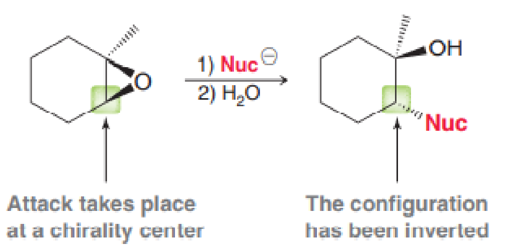
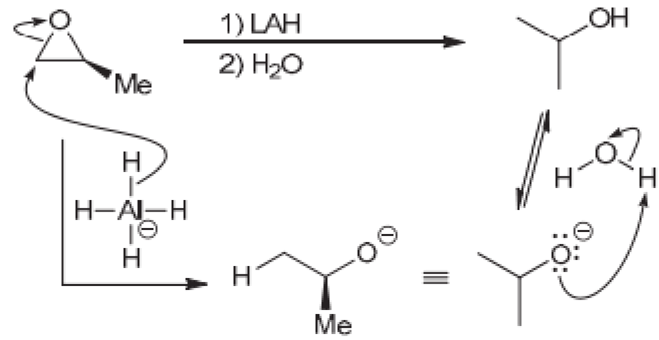
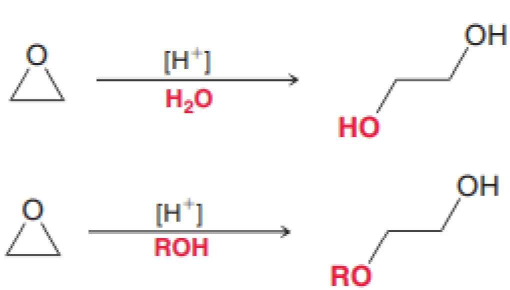
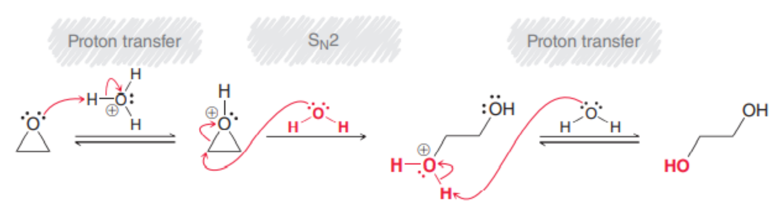
Formation of a Diol:



Using NaOR, NaCN, or NaSH: See mechanism above as an example.

Using RMgBr:



Regiochemistry→ When the starting epoxide is asymmetrical, the nucleophile attacks at the less substituted (less hindered) position:  This steric effect is what one would expect from an S_N2 process. Stereochemistry→ When the attack takes place at a chirality center, inversion of configuration is observed:  This result is also expected for an S_N2 process as a consequence of the requirement for back-side attack of the nucleophile. *Note that the configuration of the other chirality center isn't affected by the process.* **Only the center being attacked undergoes an inversion of configuration.**	Formation of an Alcohol with an extended carbon group: 1) RMgBr → 2) H_2O Formation of an Alcohol: 1) LAH → 2) H_2O	Using LAH: 
<u>Acid-Catalyzed (AC) Ring Opening</u> Under acidic conditions, one could open a ring:  	Formation of a diol (AC): [H^+] (aka [H_2SO_4]) → H_2O This can also be rewritten as:	Formation of a diol (AC): 

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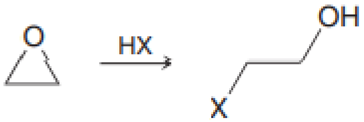
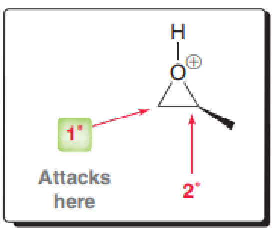


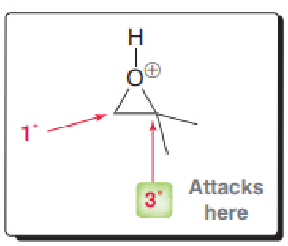
Note this: when the given epoxide is asymmetrical, **the regiochemical outcome of acid-catalyzed ring opening depends on the nature of the epoxide.**

Primary vs. secondary



Dominant factor=<u>steric effect</u>

Primary vs. tertiary



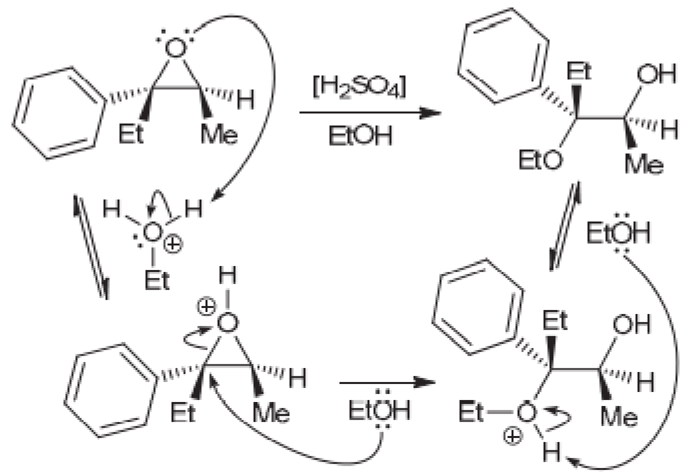
Dominant factor=<u>electronic effect</u>
</td>
<td>
H_3O^+
→

Formation of an alcohol with an OR (AC):

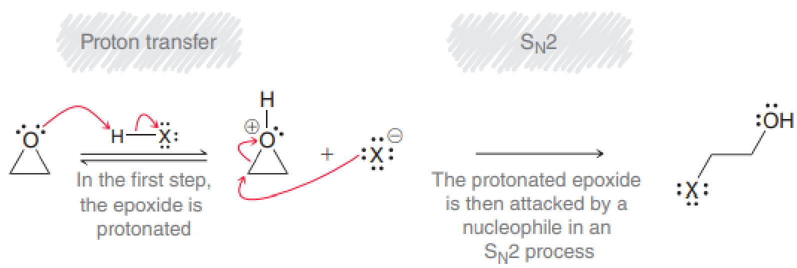
$[H^+]$ (aka $[H_2SO_4]$)
→
ROH

Formation of an alcohol with a halogen attached (AC):

HX (X could be Cl, Br, or I)
→
</td>
<td>
Formation of an alcohol with an OR (AC):



Formation of an alcohol with a halogen attached (AC):



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<td>
<u>Formation of a Thiol</u>

Convert an alkyl halide into a thiol (a sulfur analog of alcohol):

S_N2:

(Note: This reaction can occur even at
</td>
<td>
NaSH
→
</td>
<td>
(See Reference Sheet #5 for S_N2 reaction mechanism example).
</td>
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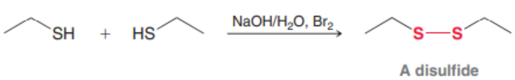
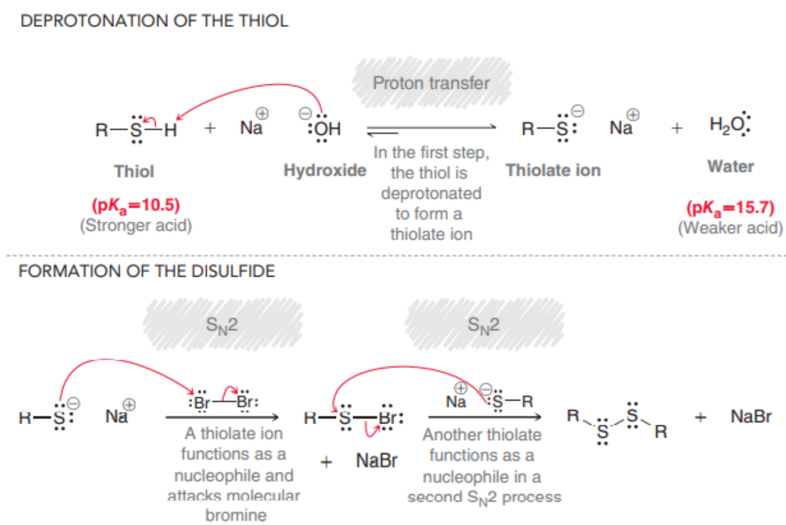
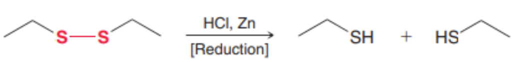
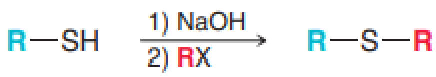
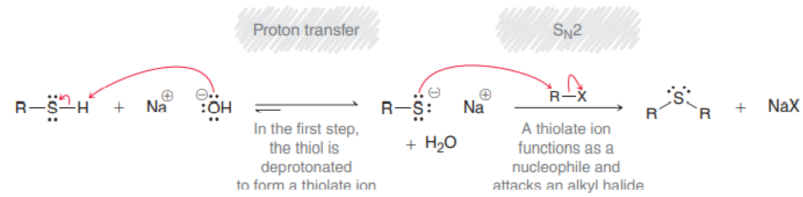
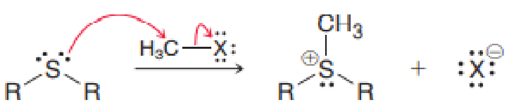
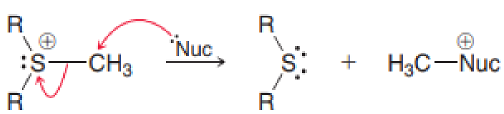
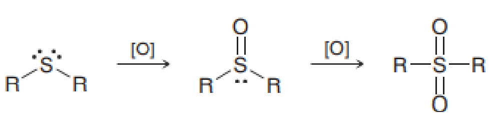
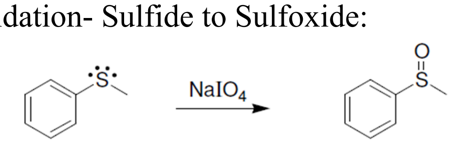
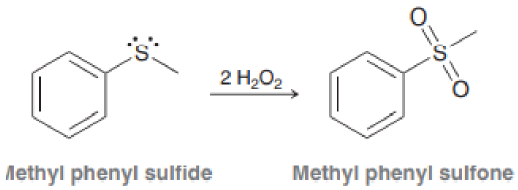
</table>

secondary substrates without competing E2 reactions, because the hydrosulfide ion (HS-) is an excellent nucleophile and a poor base).		
<u>Oxidation of Thiols</u> Thiols easily undergo oxidation to produce disulfides: 	$NaOH/H_2O$, Br_2 →	
<u>Reduction of Thiols</u> Disulfides are easily reduced back to thiols with a reducing agent, (i.e. HCl with zinc):  (Note: The interconversion between thiol and disulfide can also occur directly via a free radical mechanism.)	HCl, Zn →	N/A Note that it is essential to know what's happening in the reaction: the neutral Zn is providing two electrons to become Zn^{2+}. The electrons attach to the S atoms as they break their S-S bond, making both S atoms negatively charged. This causes them to pick up protons from the HCl. Consider that there arises the potential that one of the S atoms could be protonated before any of the other steps happen. So, the order in which the reaction occurs is irrelevant.

<u>Preparation of Sulfides</u> Sulfides can be prepared from thiols using the sulfur analog of the Williamson ether synthesis:  Note that this mechanism could work with primary or secondary alkyl halides, **never** with tertiary alkyl halides!	1) NaOH → 2) RX	
<u>Reactions of Sulfides</u> Sulfides will attack alkyl halides in an S_N2 process:  The product of this step is a powerful alkylating agent, because it is capable of transferring a methyl group to a nucleophile:  Sulfides also undergo oxidation to give sulfoxides and then sulfones:  Sulfide Sulfoxide Sulfone Oxidation- Sulfide to Sulfoxide:  *methyl phenyl sulfide* *methyl phenyl sulfoxide*	Utilizing a sulfide to give a methyl group to a nucleophile: Given a sulfide, use: 1) CH_3X (X could be Cl, Br, or I) → 2) Nucleophile Sulfide to Sulfoxide: $NaIO_4$ → **OR** H_2O_2 →	Reaction of Sulfide & Alkyl Halides: Given on the left. Oxidation of Sulfides to Sulfoxides; Oxidation of Sulfides to Sulfones: N/A (Don't be afraid to go on your *sulfone* and message Dr. Beil via Discord/Canvas if you have any questions!) :)

Oxidation- Sulfide to Sulfone: 	Sulfide to Sulfone: 2 H_2O_2 $\rightarrow$	