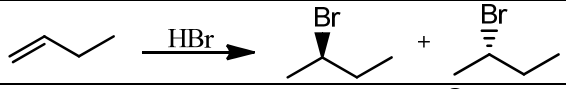
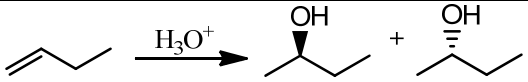
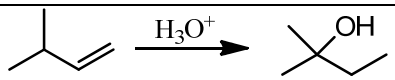
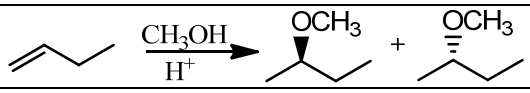
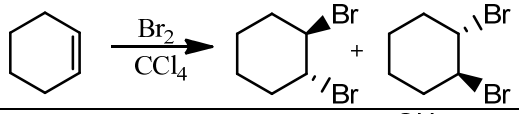
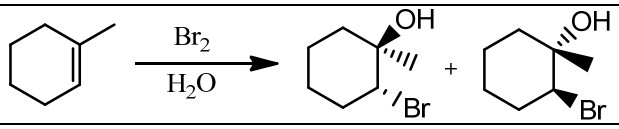
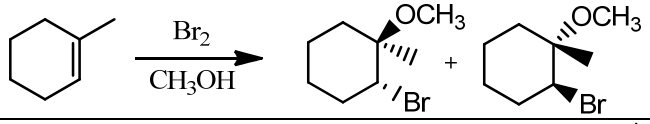
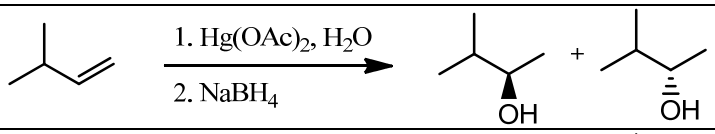
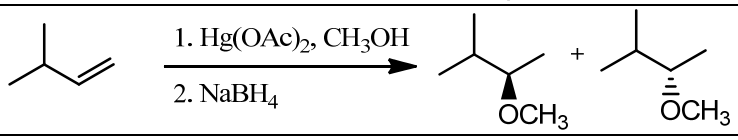
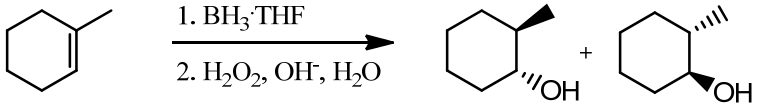
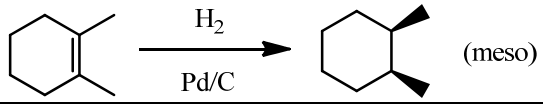
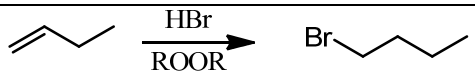
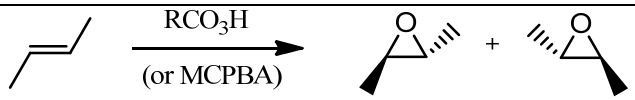
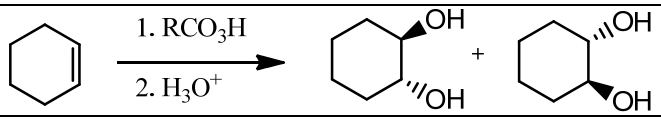
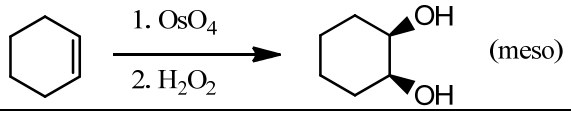
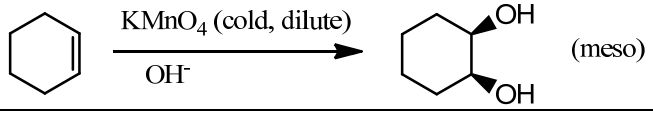
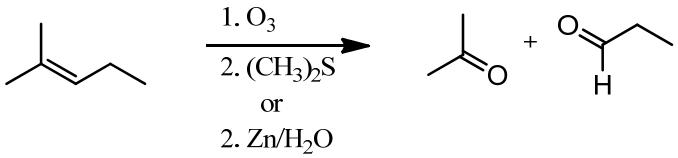
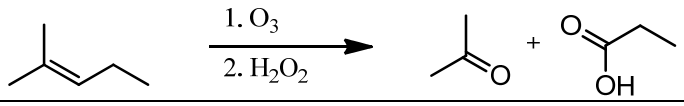
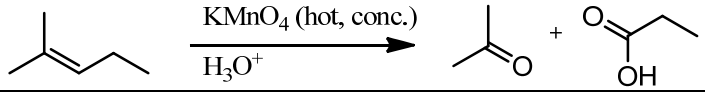
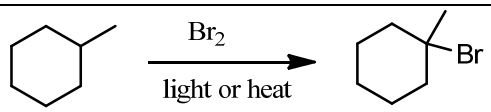
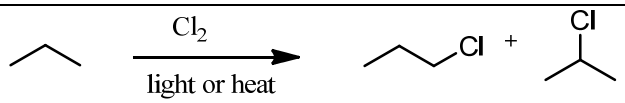
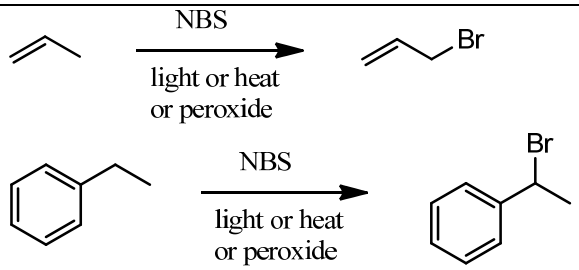
Alkene Rxns

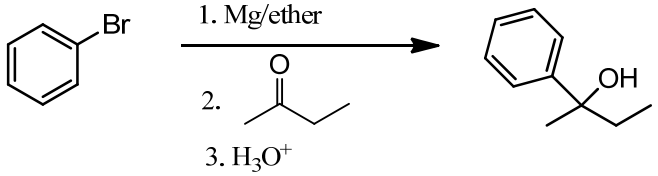
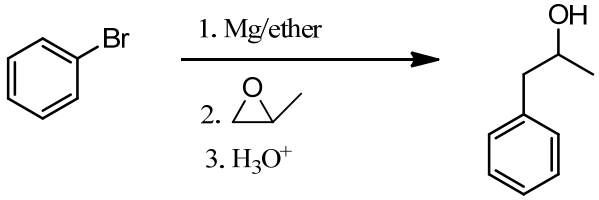
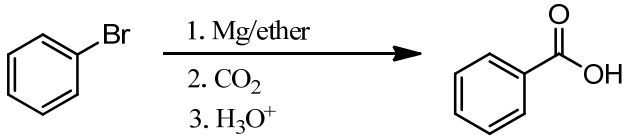
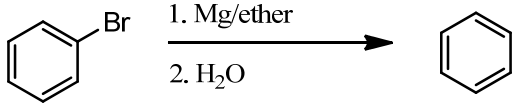
Hydrohalogenation	
Hydration	
Hydration (with rearrangement)	
Addition of Alcohol	
Bromination	
Bromination in H_2O	
Bromination in Alcohol	
Oxymercuration-Demurcuration	
Alkoxymercuration-Demurcuration	
Hydroboration-Oxidation	
Catalytic Hydrogenation (Catalytic Reduction)	
Hydrobromination with Peroxide	
Epoxidation	
Anti-Hydroxylation	
Syn-Hydroxylation	
Syn-Hydroxylation	
Ozonolysis under Reducing Conditions	

Ozonolysis under Oxidizing Conditions	
Oxidative Cleavage	

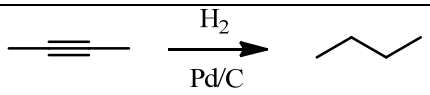
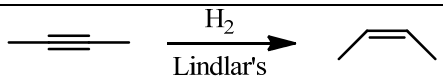
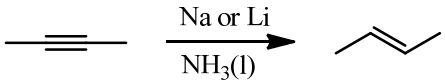
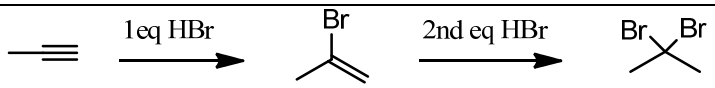
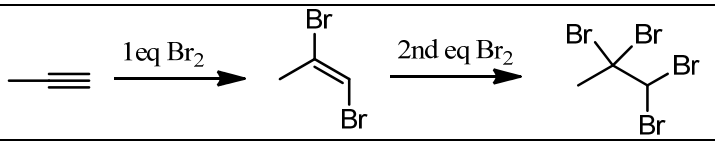
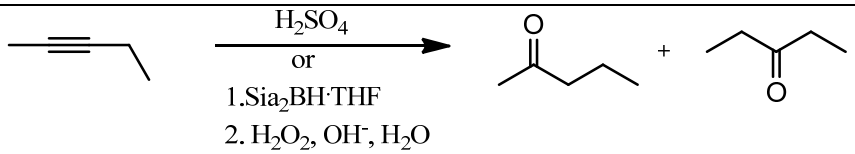
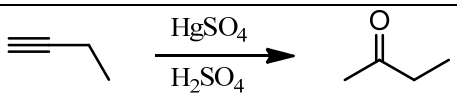
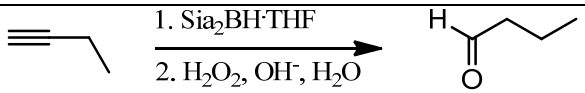
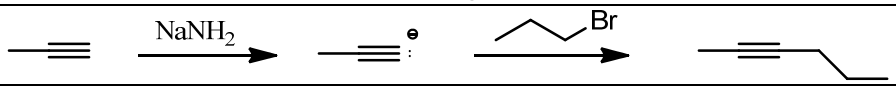
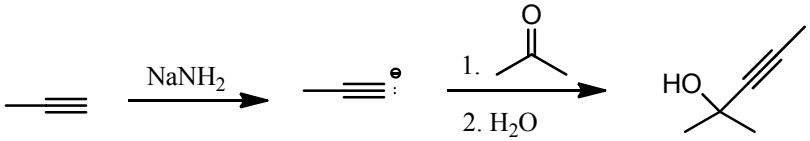
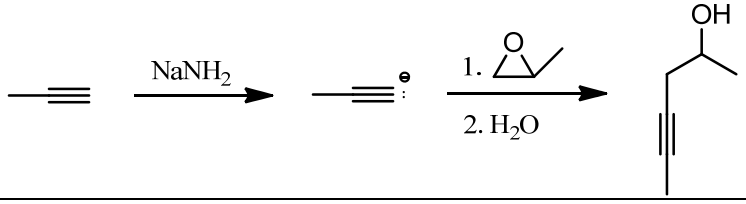
Free Radical Halogenation

Free Radical Bromination (high selectivity)	
Free Radical Chlorination (low selectivity)	
Allylic/Benzylic Bromination	

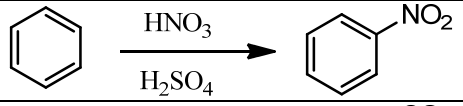
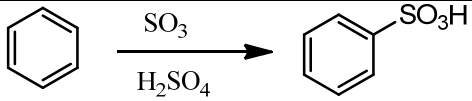
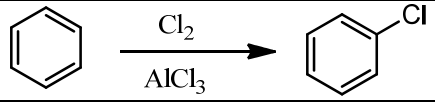
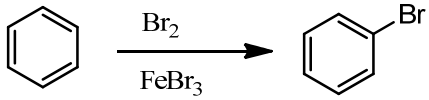
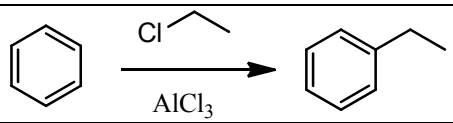
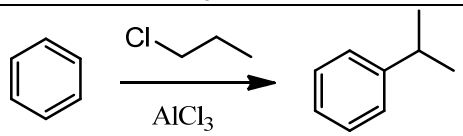
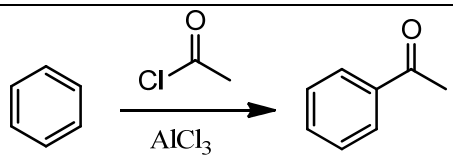
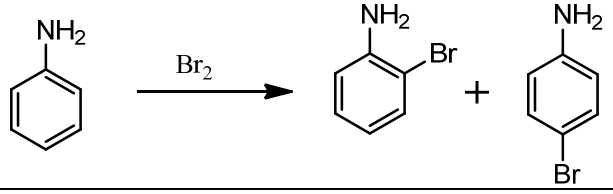
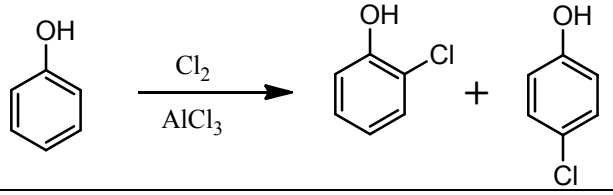
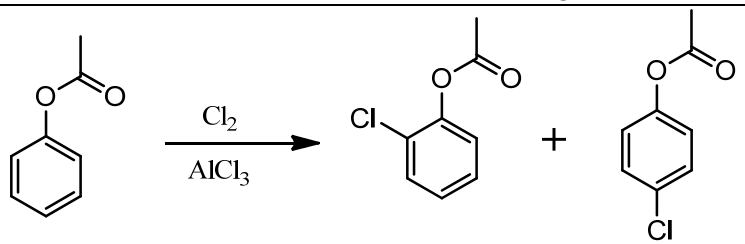
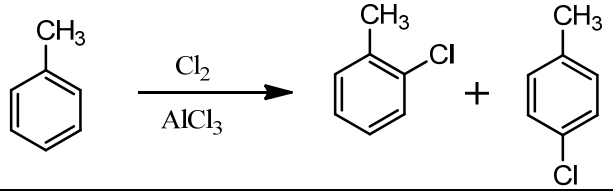
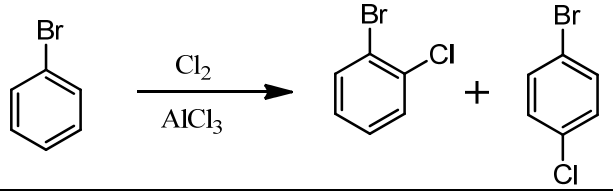
Grignard Rxns

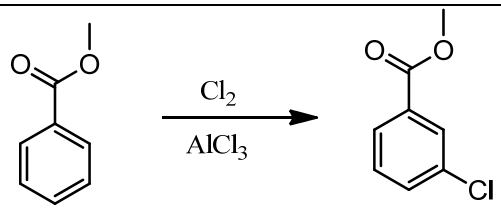
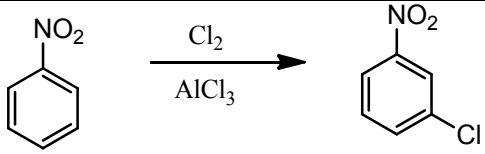
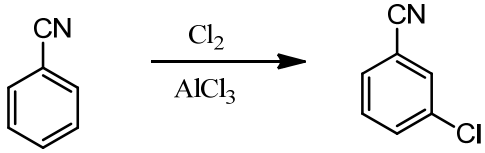
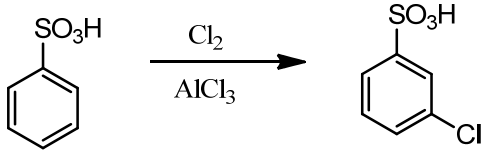
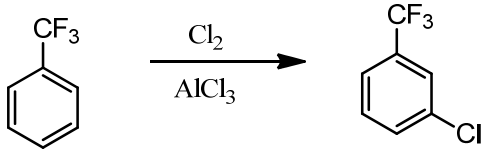
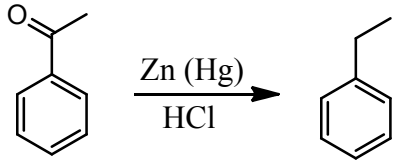
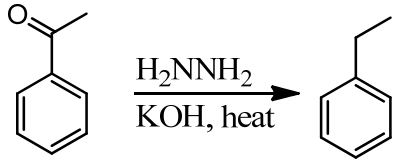
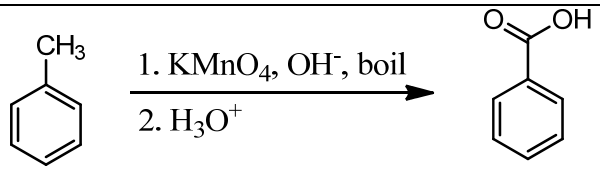
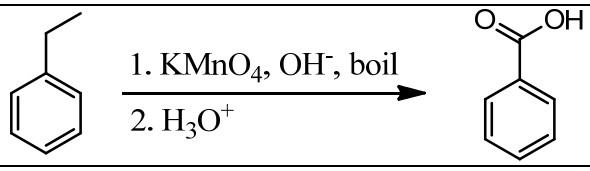
Nucleophilic Addition of a Grignard Reagent to a Ketone	
Nucleophilic Addition of a Grignard Reagent to an Epoxide (attacks less substituted side)	
Nucleophilic Addition of a Grignard Reagent to CO_2	
Protonation of a Grignard Reagent (Grignards are protonated in protic solutions)	

Alkyne Rxns

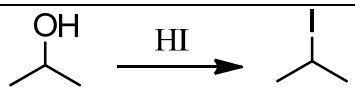
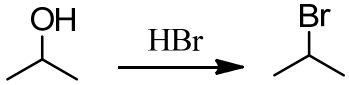
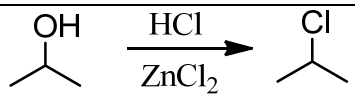
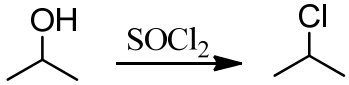
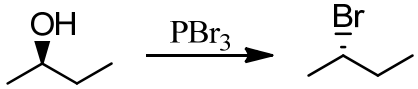
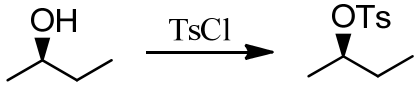
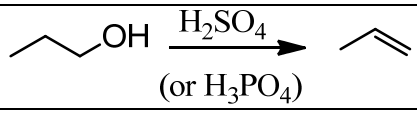
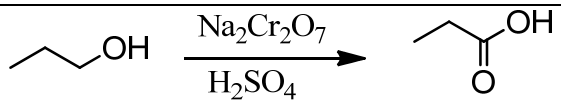
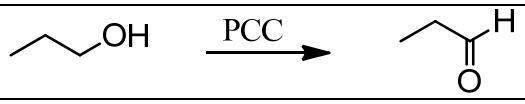
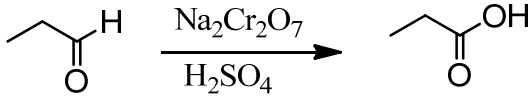
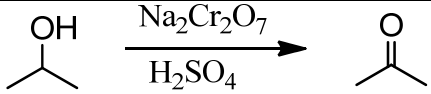
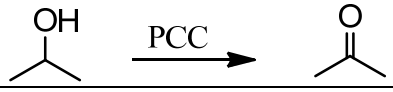
Catalytic Hydrogenation (Catalytic Reduction)	
Reduction to cis-alkene	
Reduction to trans-alkene	
Hydrohalogenation	
	
Hydration of an Internal Alkyne	
Hydration (Markovnikov)	
Hydration (Anti-Markovnikov)	
S_N2 Addition of an Acetylide Ion	
Addition of an Acetylide Ion to a Ketone	
Addition of an Acetylide Ion to an Epoxide	

Benzene Rxns

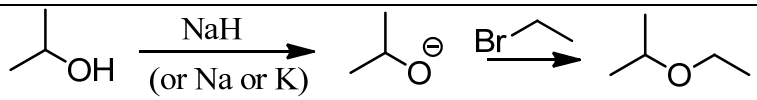
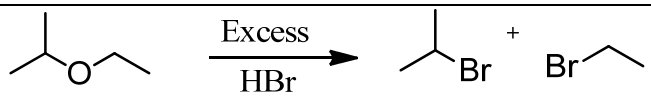
Nitration (EAS)	
Sulfonation (EAS)	
Chlorination (EAS)	
Bromination (EAS)	
Friedel-Crafts Alkylation (EAS)	
Friedel-Crafts Alkylation (EAS) (with rearrangement)	
Friedel-Crafts Acylation (EAS)	
Bromination (EAS) -NH_2 is an ortho/para director and doesn't require a catalyst like $FeBr_3$	
Chlorination (EAS) -OH is an ortho/para director	
Chlorination (EAS) -OR is an ortho/para director	
Chlorination (EAS) -CH_3 is an ortho/para director	
Chlorination (EAS) -Br is an ortho/para director	

Chlorination (EAS) Carbonyl is a meta director	
Chlorination (EAS) -NO_2 is a meta director	
Chlorination (EAS) -CN is a meta director	
Chlorination (EAS) -SO_3H is a meta director	
Chlorination (EAS) -CF_3 is a meta director	
Clemmensen Reduction	
Wolff-Kishner Reduction	
Side-chain Oxidation (Benzylic Oxidation)	
Side-chain Oxidation (Benzylic Oxidation)	

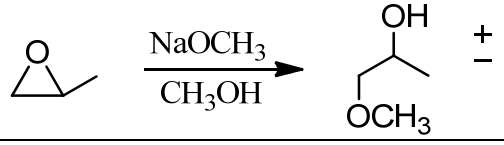
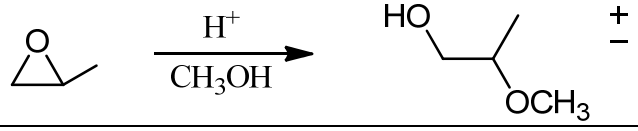
Alcohol Rxns

Conversion to an alkyl iodide	
Conversion to an alkyl bromide	
Conversion to an alkyl chloride	
Conversion to an alkyl chloride with thionyl chloride (only for 1° and 2°)	
Conversion to an alkyl bromide (only for 1° and 2°)	
Conversion to a tosylate ester	
Acid-catalyzed Dehydration	
Chromic Acid Oxidation of a 1° Alcohol (Chromic Acid can also be written as H_2CrO_4 or CrO_3/H_2SO_4)	
PCC Oxidation of a 1° Alcohol	
Chromic Acid Oxidation of an Aldehyde	
Chromic Acid Oxidation of a 2° Alcohol	
PCC Oxidation of a 2° Alcohol	

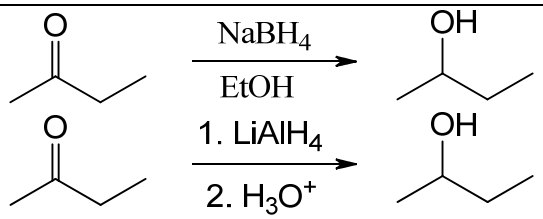
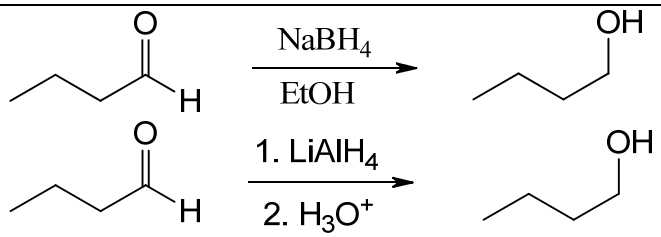
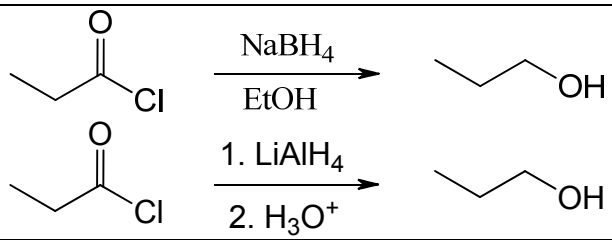
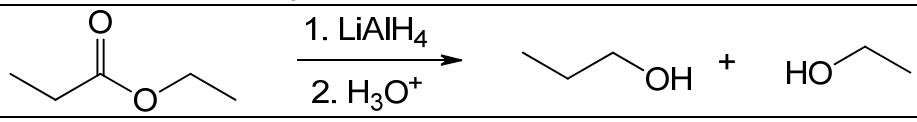
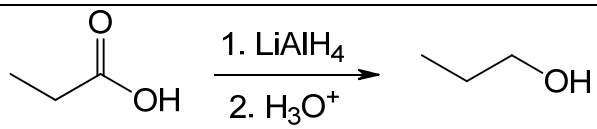
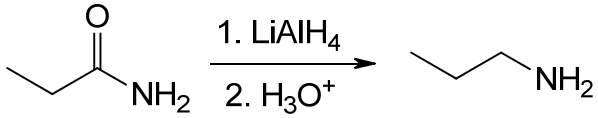
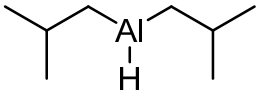
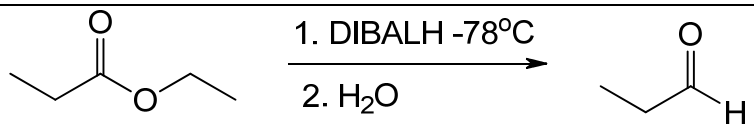
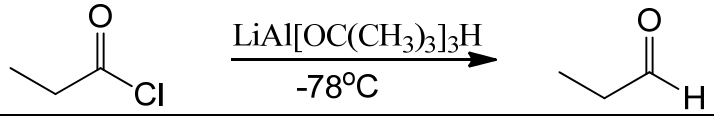
Ether Rxns

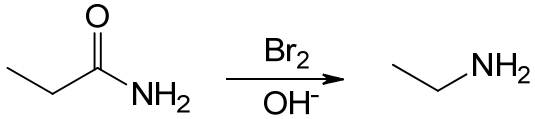
Williamson Ether Synthesis (2^{nd} step is S_N2)	
Acid-Catalyzed cleavage of Ethers (also works with HI and HCl)	

Epoxide Rxns

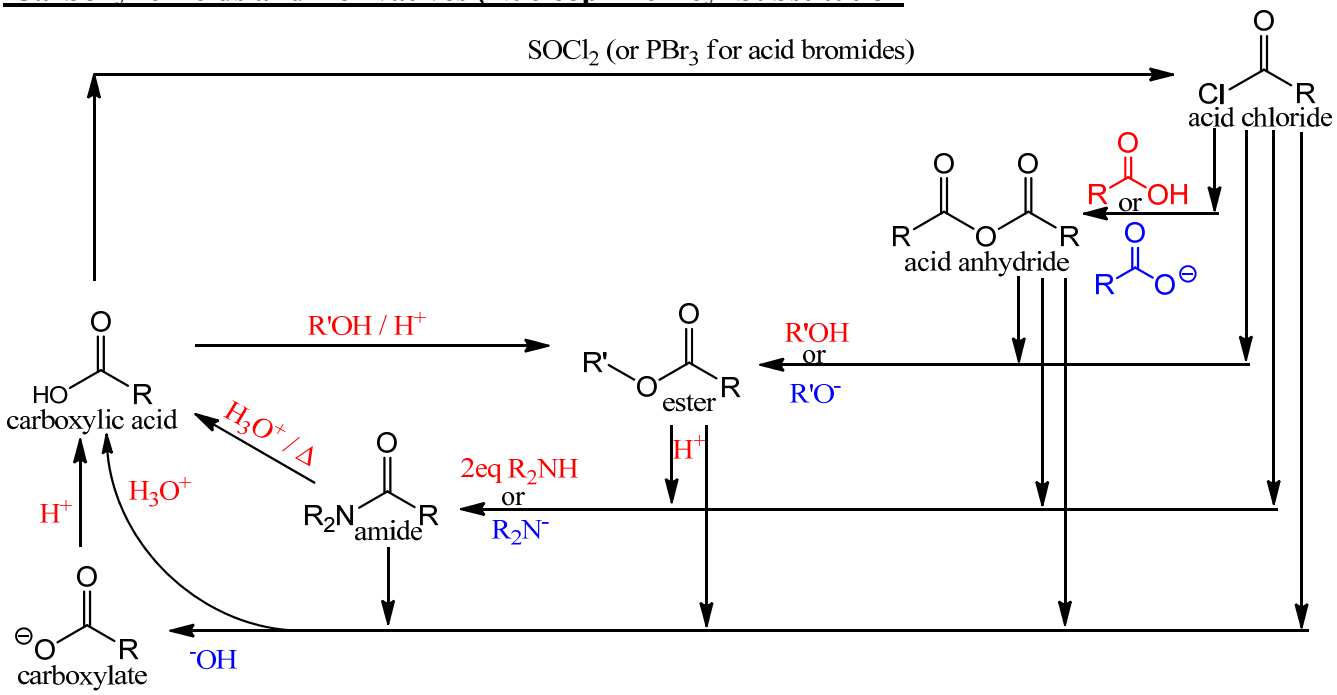
Base-Catalyzed Ring Opening of an Epoxide (Attacks less-substituted side)	
Acid-Catalyzed Ring Opening of an Epoxide (Attacks more-substituted side)	

Hydride Reduction Rxns

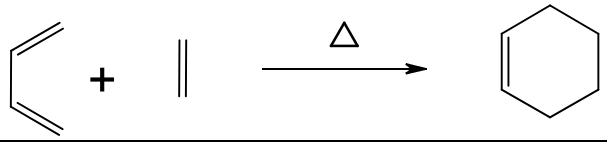
Reduction of a ketone to a 2° alcohol	
Reduction of a aldehyde to a 1° alcohol	
Reduction of an acid chloride to a 1° alcohol	
Reduction of an ester to two alcohols	
Reduction of a carboxylic acid to a 1° alcohol	
Reduction of an amide to an amine	
Reduction of an ester to an aldehyde using DIBALH (also called DIBAH) DIBALH is diisobutylaluminum hydride (shown below) 	
Reduction of an acid chloride to an aldehyde using tri-*t*-butoxyaluminum hydride	

Hoffman Rearrangment Converts an amide to an amine with the loss of a carbon (note the difference with reduction of an amide with $LiAlH_4$ where there is no loss of carbon)	

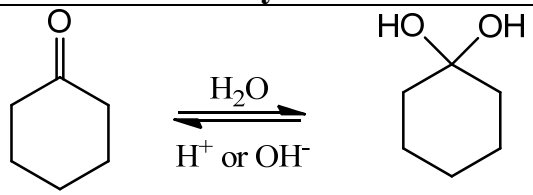
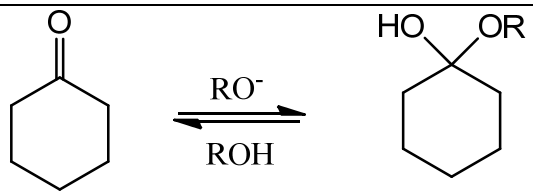
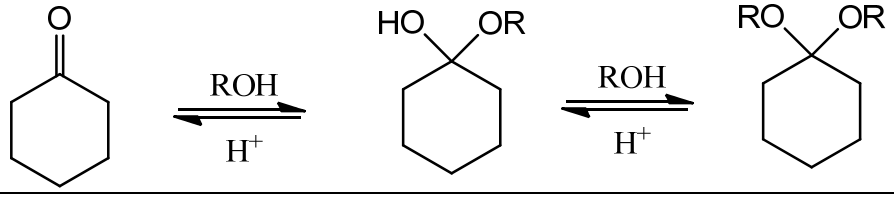
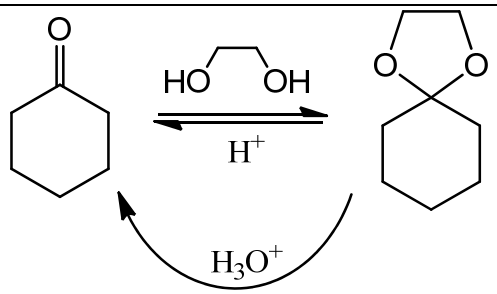
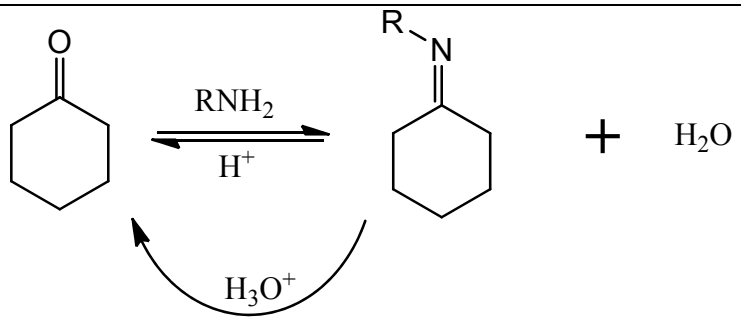
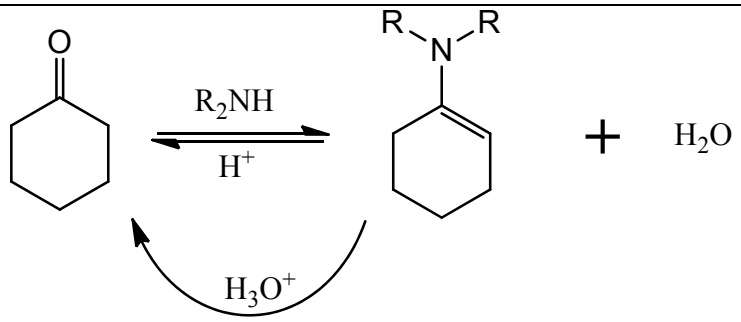
Carboxylic Acids and Derivatives (Nucleophilic Acyl Substitution

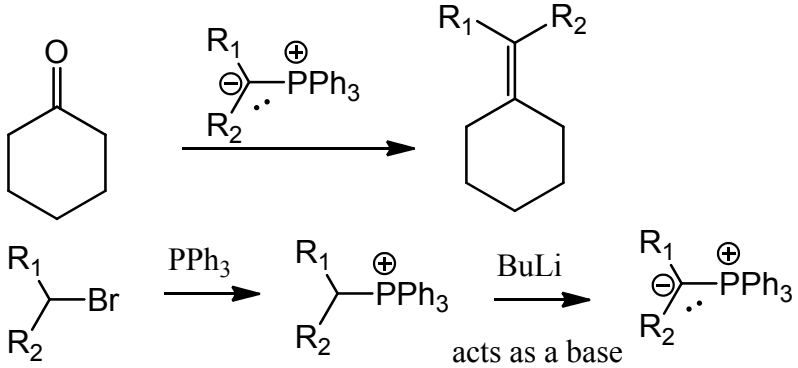
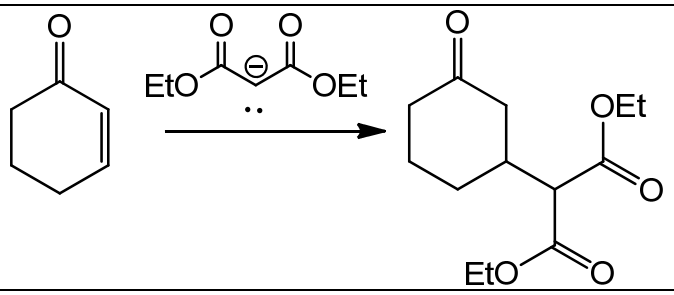
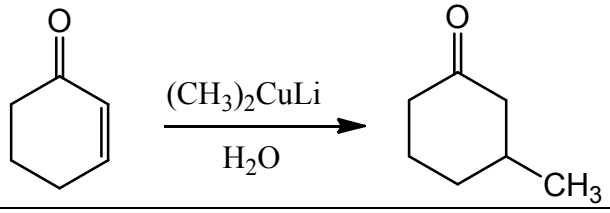


Diels-Alder Rxns

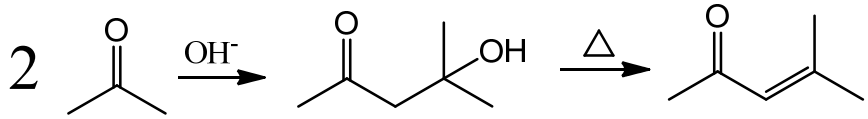
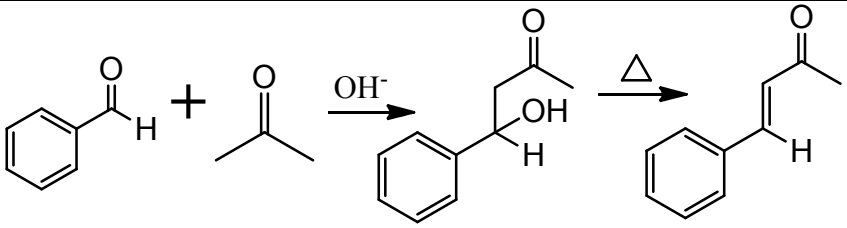
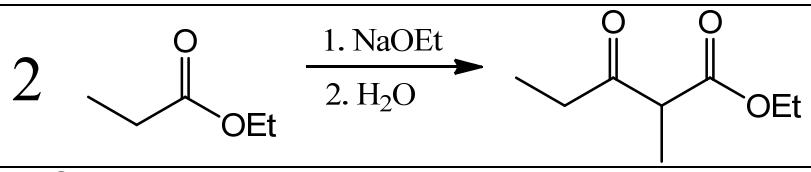
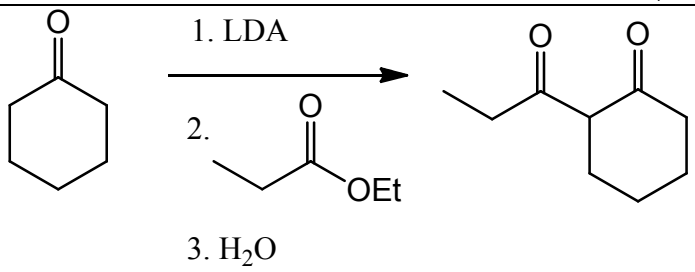
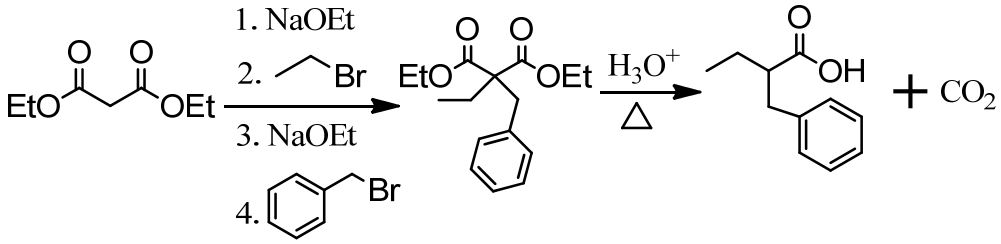
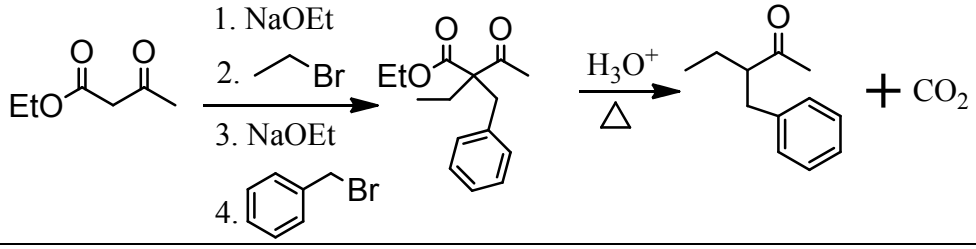
Basic Diels-Alder Rxn (a 4+2 cycloaddition rxn)	

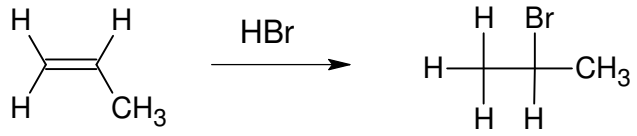
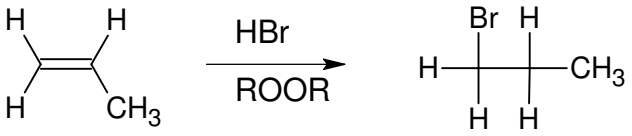
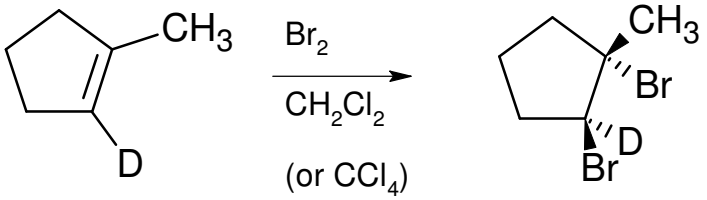
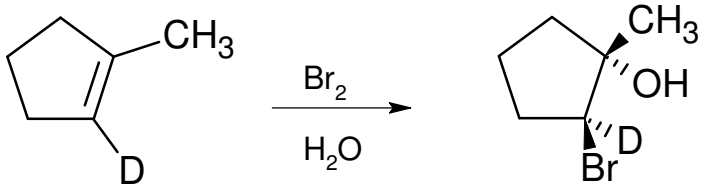
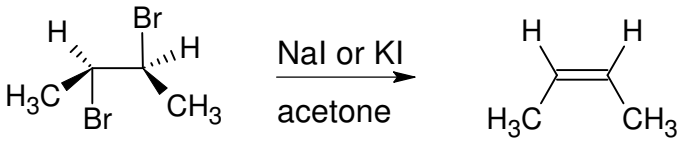
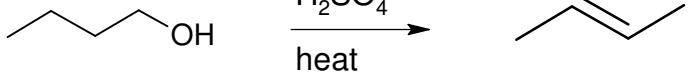
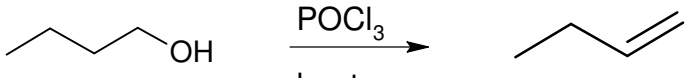
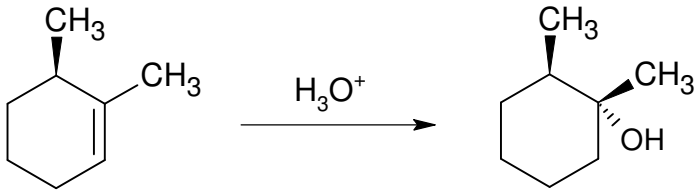
Nucleophilic Addition to Ketones and Aldehydes

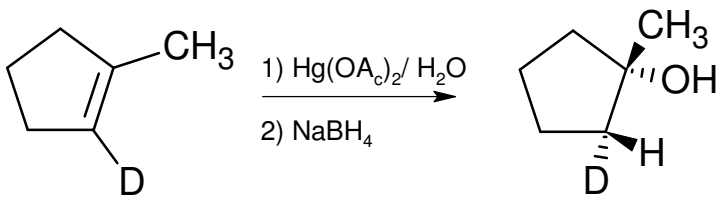
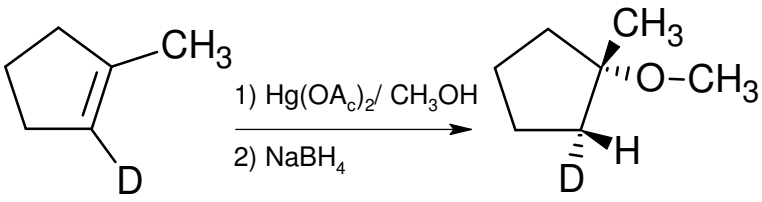
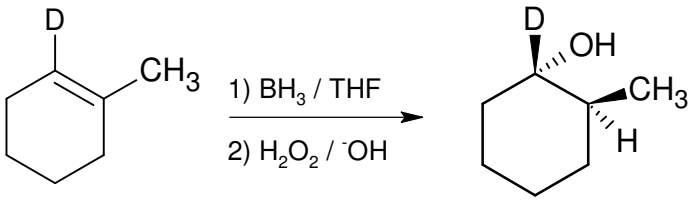
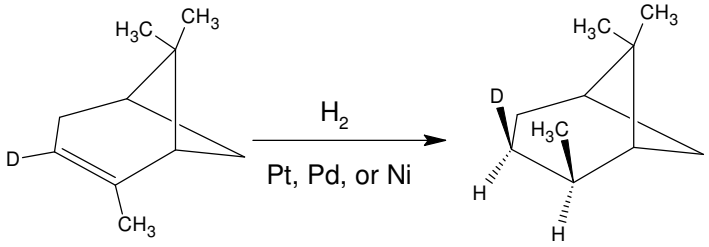
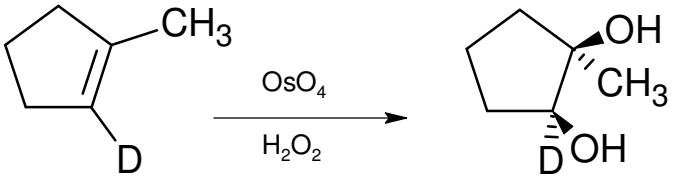
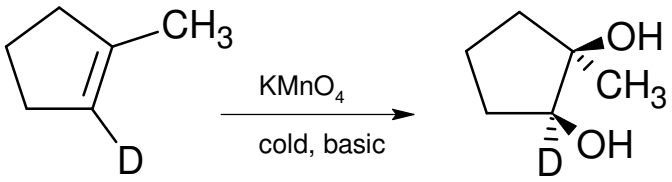
Addition of water to form a hydrate	
Addition of an alcohol under basic conditions to form a hemi-ketal	
Addition of 1eq of an alcohol in acid to form a hemi-ketal and then a 2nd eq to form a ketal	
Addition of ethylene glycol to from a cyclic ketal which functions as a protecting group for ketones and aldehydes H_3O^+ is used to de-protect	
Addition of a 1° amine to form an imine (can be reversed with H_3O^+)	
Addition of a 2° amine to form an enamine Forms on less substituted side if there's a difference (can be reversed with H_3O^+)	

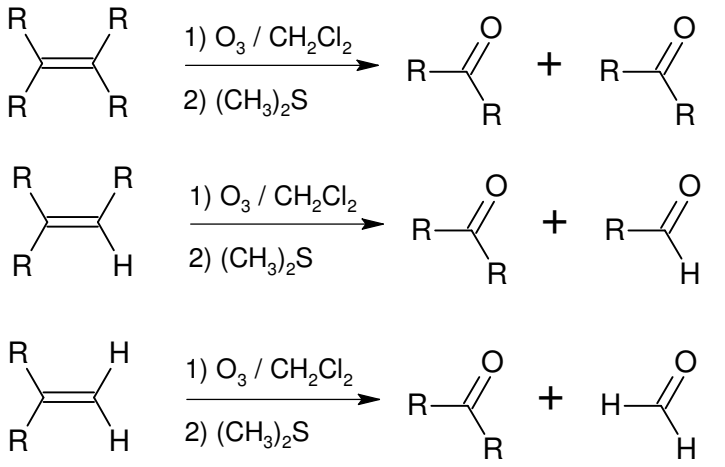
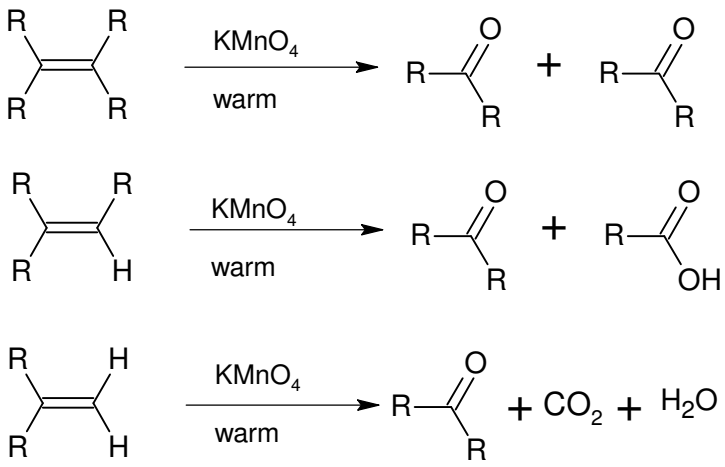
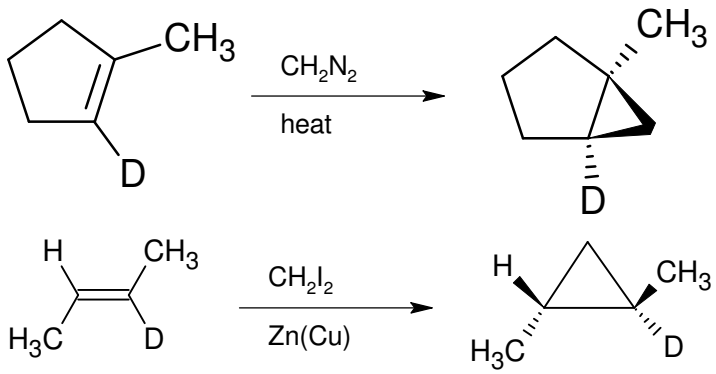
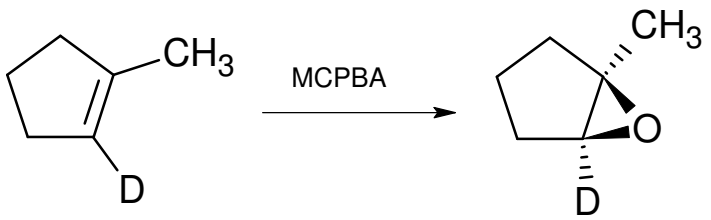
Wittig Rxn Addition of a phosphylide to form an alkene Formation of a phosphoylide from an alkyl halide	
Michael Addition (also called β-addition or conjugate addition)	
Michael Addition with a lithium dialkylcuprate	

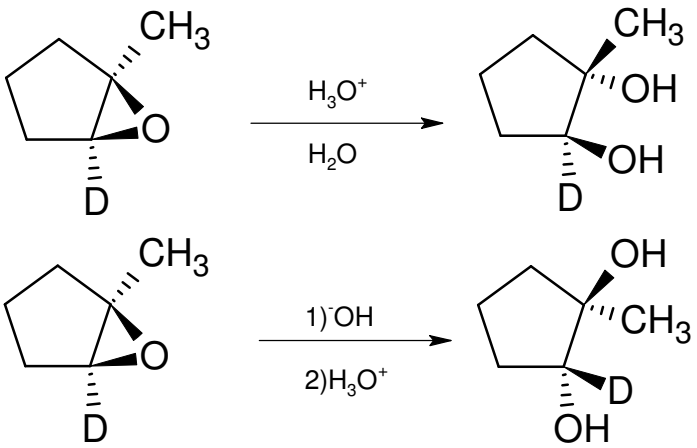
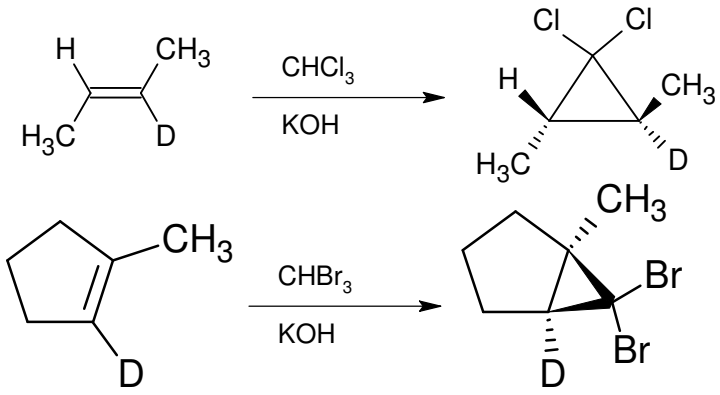
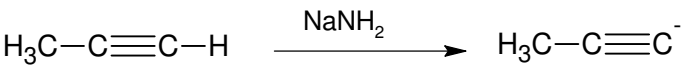
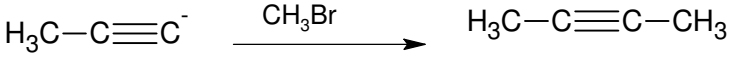
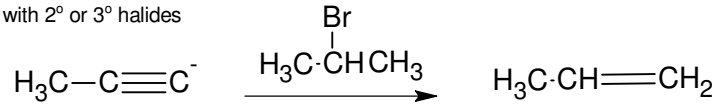
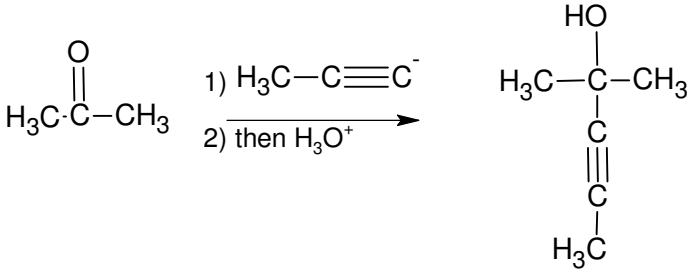
Alpha Addition Rxns

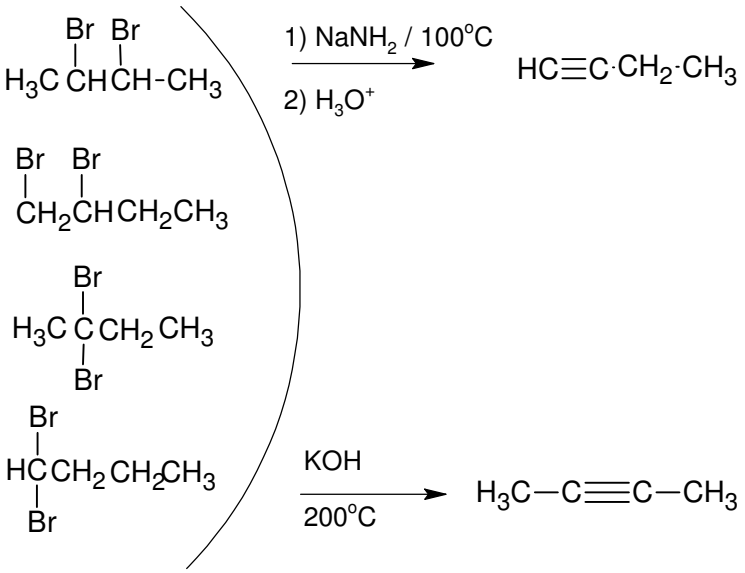
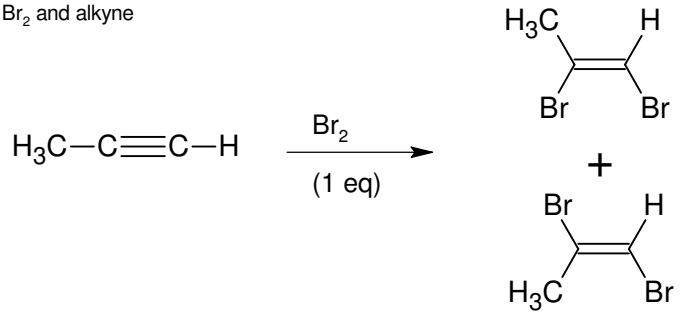
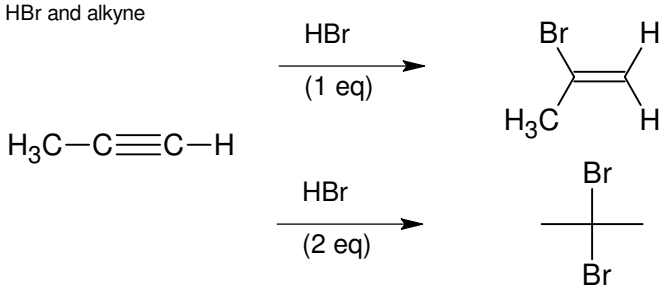
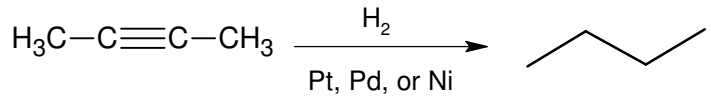
Self Aldol Condensation	
Mixed Aldol Condensation	
Self Claisen Condensation	
Mixed Claisen Condensation	
Malonic Ester Synthesis	
Acetoacetic Ester Synthesis	

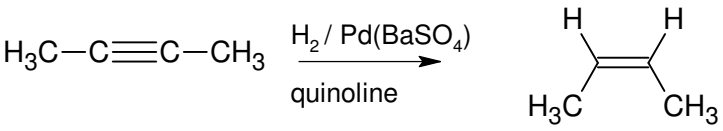
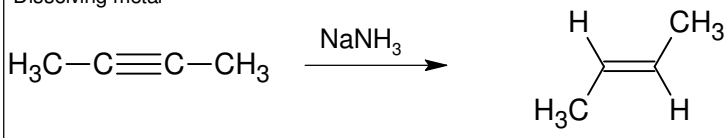
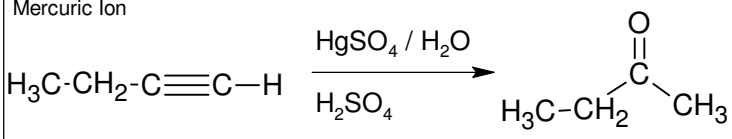
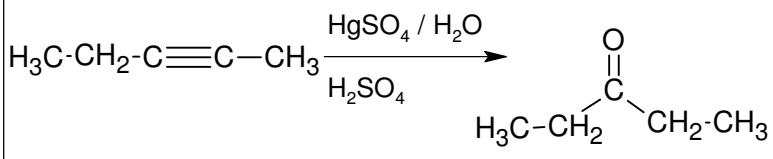
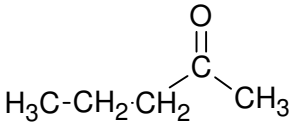
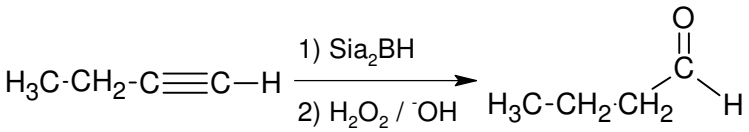
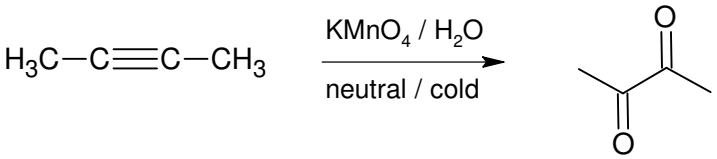
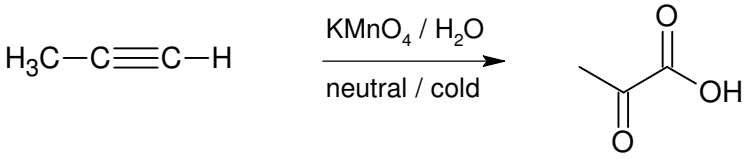
Task	Reaction	Notes
Addition of HX (Mark)		*Adds a halide to more substituted carbon.
Addition of HX (Anti-Mark)		*Adds a halide to least substituted carbon.
Add two Br's anti to alkene		*Anti and co planar
Adding a Br and OH (Mark w/ Br as H and anti-planar)		*Anti and co planar
Forming alkene from vicinal dihalide		*Wedges with wedges and dashes with dashes *E2 Like!
Dehydration to alkene		*E1 like and it cannot give terminal alkene
		*SPECIAL REACTION: dehydrates to form terminal alkene.
Addition of OH (direct and mark)		*CANNOT CONTROL STEREOCHEM! *Low yield! *C+ formation!

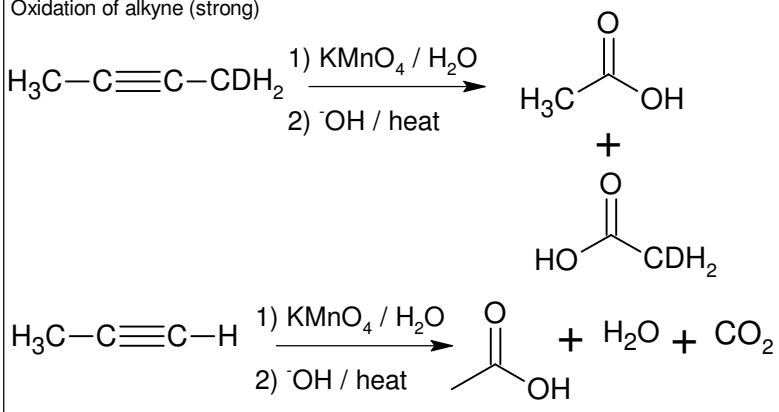
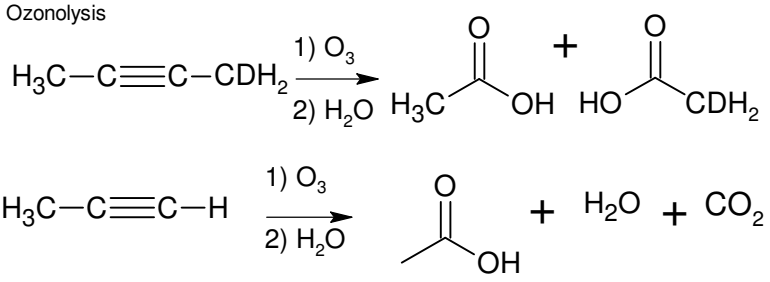
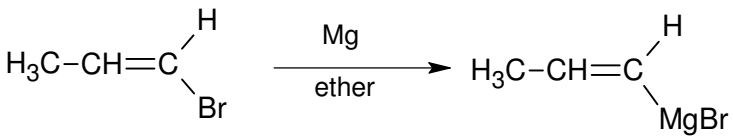
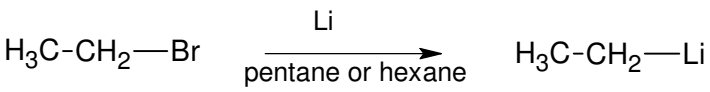
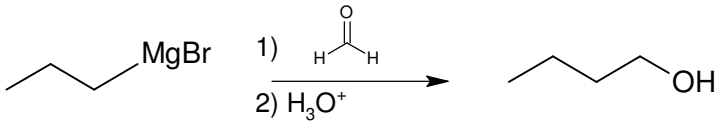
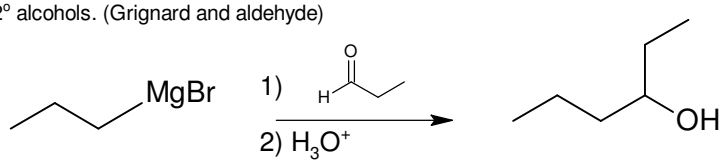
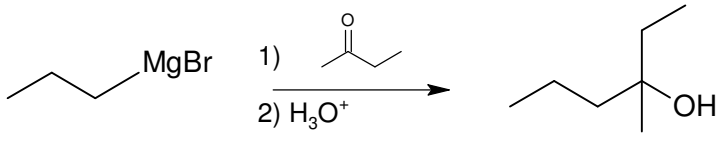
Task	Reaction	Notes
Oxymercuration/ demercuration *(Add OH from alkene mark and antiplanar)*		*Complex mechanism *Mark and antiplanar
SPECIAL: Adds alcohol instead to form ethers!		*Complex mechanism *Mark and antiplanar *WILL BE SEEING THIS MORE IN ORGO II
Hydroboration *(Add Oh anti-mark and syn planar)*		*Anti-mark *Notice Peroxide
Catalytic Hydrogenation (Alkenes -> Alkane, Syn Addition of H)		*Steric factors must be payed attention to *Can use D_2 instead
Formation of Vicinal Diols (Syn)		*expensive *toxic *great yield
		*cheaper *safer *poor yield

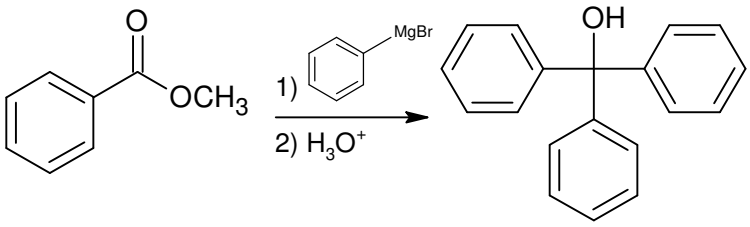
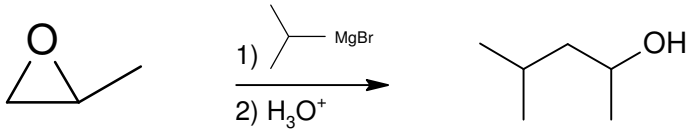
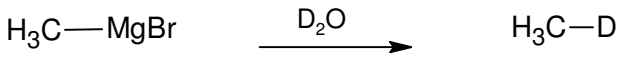
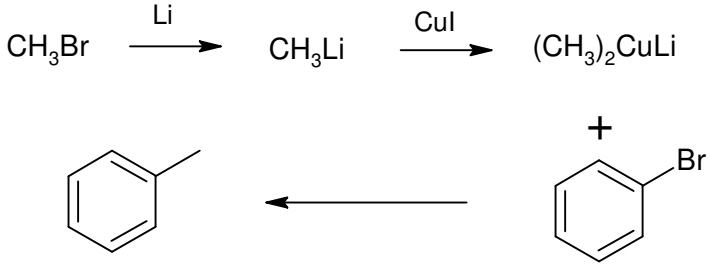
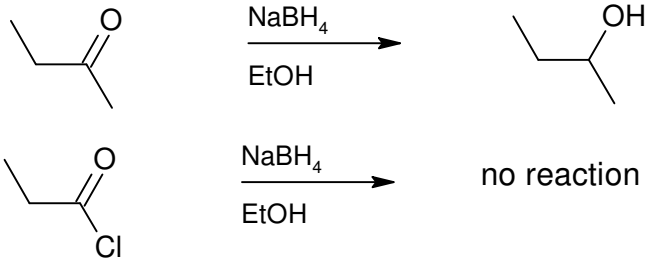
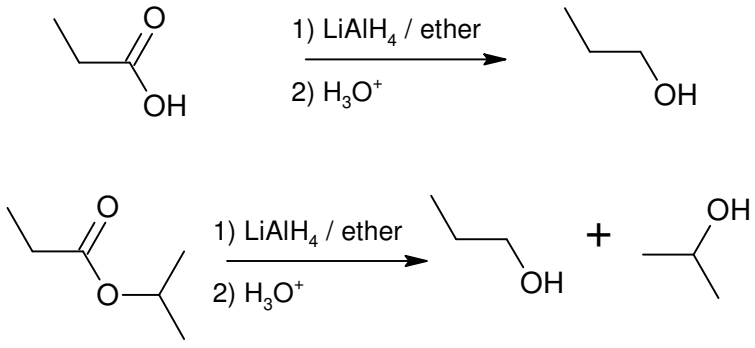
Task	Reaction	Notes
Ozonolysis (double bond cleavage)		*Can use Zn/acetic acid instead of $(CH_3)_2S$ *Can isolate the formaldehyde.
Warm $KMnO_4$ cleavage		*further oxidizes to form carboxylic acids *cannot isolate the formaldehyde
Carbene / Carbenoid addition (formation of cyclopropane)		*syn *stereochem is preserved *Second reaction uses the Simmons-Smith reagent
Formation of epoxides from alkenes		*useful for synthesis (ESPECIALLY IN ORGO II)

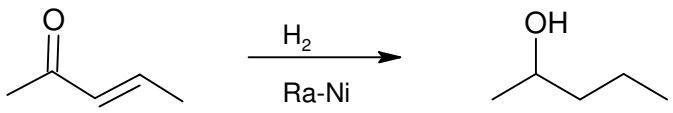
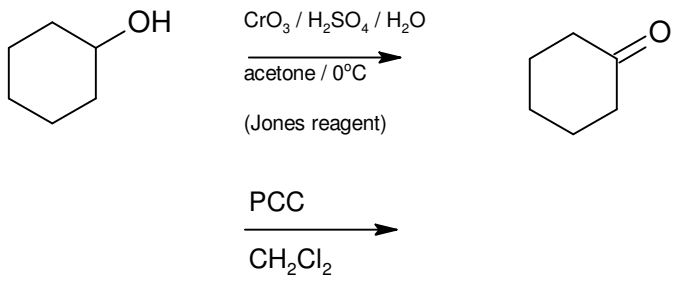
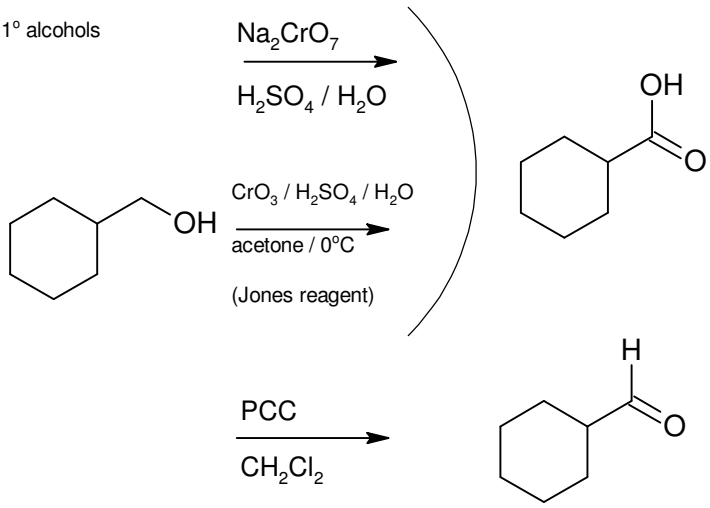
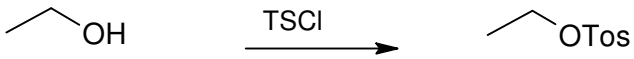
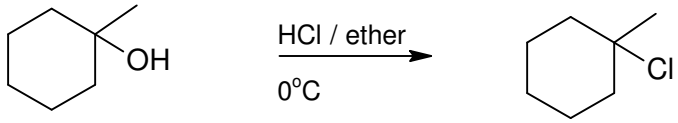
Task	Reaction	Notes
Opening of Epoxides NOTE: Can use RO^- to form ethers. You will see this in Orgo II.		*acidic conditions opens from more substituted side. *Basic are like SN2 (least substituted side) *Please look up mechanism.
Formation of Dibromocarbenes and Dichlorocarbenes		*please look up the mechanism so you can see how the carbene is formed
Formation of the acetylide anion		*forms the nucleophile that is handy when connecting carbons!
Uses of the acetylide anion	with methyl or 1° halides 	*SN2 because of the exception we learned from before!!!!
	with 2° or 3° halides 	*E2 remember from last test!!!
	with carbonyl groups (ketones, aldehydes, and formaldehydes) 	*acetylide anion attacks partially positive carbon *DO NOT FORGET then H_3O^+

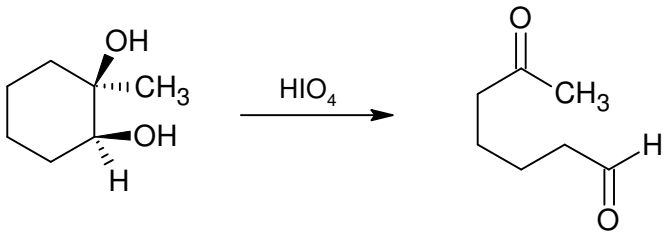
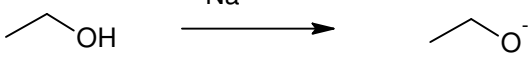
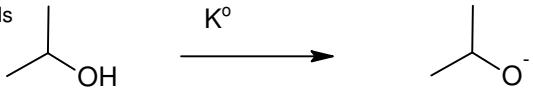
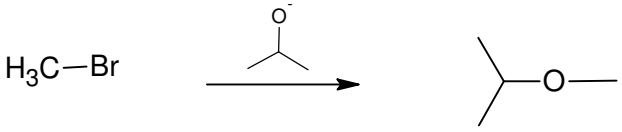
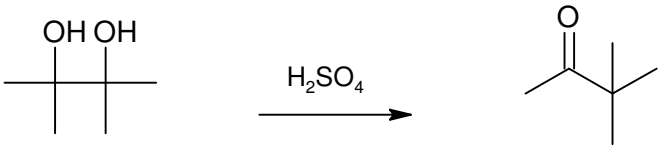
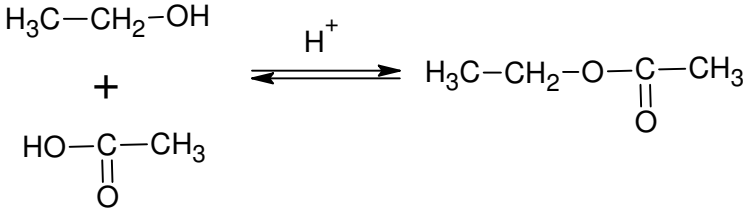
Task	Reaction	Notes
Synthesis of Alkynes		*Need either geminal or vicinal dihalides *Look up mechanism *$NaNH_2$ gives terminal *KOH gives internal
Halogenation of alkynes	Br_2 and alkyne 	*Stereochem cannot be controlled
	HBr and alkyne 	*Mark *syn addition
	HBr and alkyne 	*Anti mark *syn addition
Catalytic reduction with reactive catalyst		*Takes it all the way back to alkane *generally bad yield

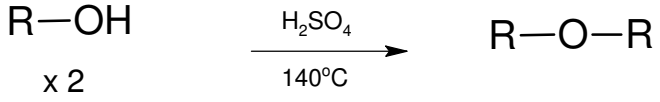
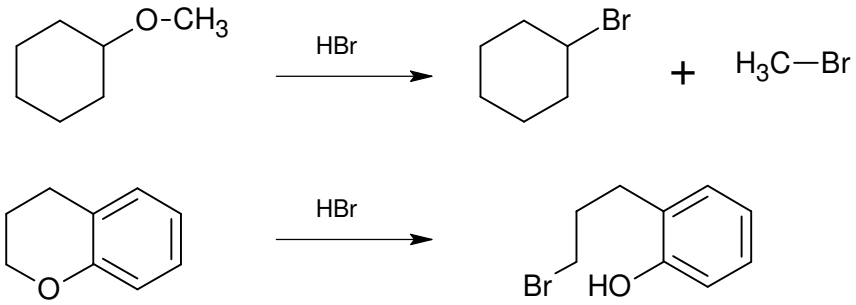
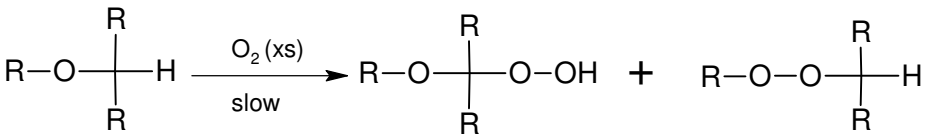
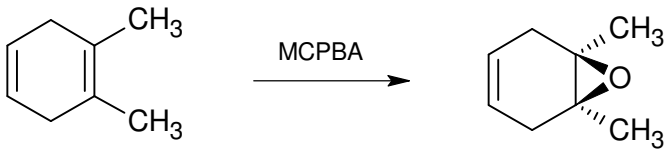
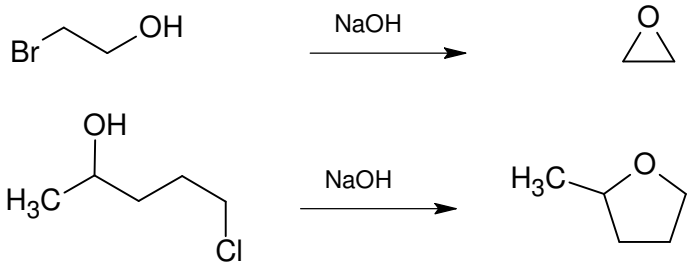
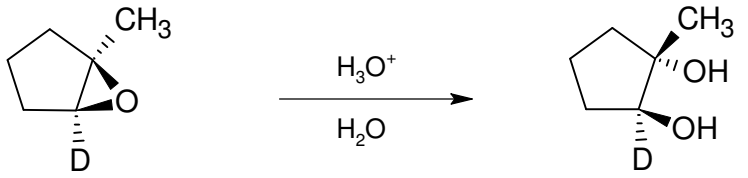
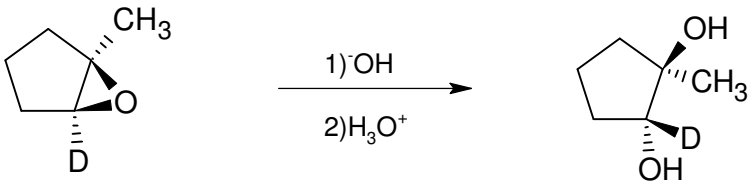
Task	Reaction	Notes
Alkyne to Alkene: TRIPLE to DOUBLE	Lindlar's catalyst 	*isolates an alkene with a SYN addition of H
	Dissolving metal 	*isolates an alkene with an ANTI addition of H
Addition of H-OH to alkynes	Mercuric Ion   + 	*Mark addition *If not terminal, you will get a mixture. ***Formation of ketone**
	Hydroboration 	*Antimark addition *will get a mixture if not terminal ***Formation of aldehyde**
Oxidation of alkynes (mild conditions)	 	*Forms vicinal carbonyls *further oxidizes terminal alkynes to form carboxylic acid.

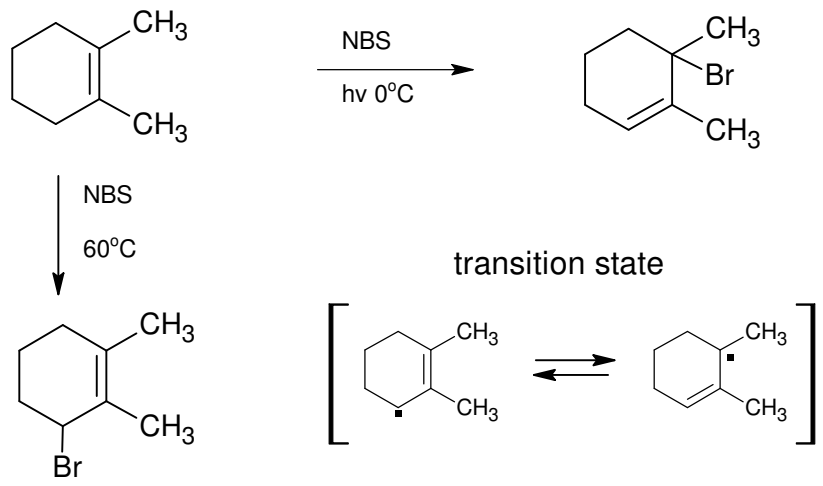
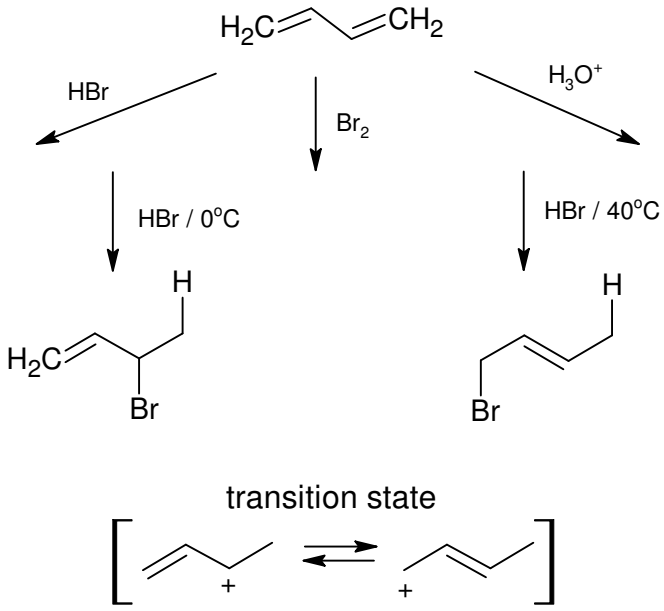
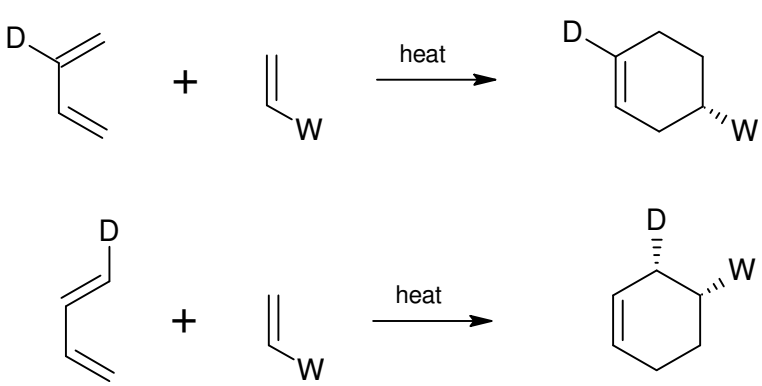
Task	Reaction	Notes
Cleavage of Alkynes:	Oxidation of alkyne (strong) 	*Forms H_2O and CO_2 if terminal.
	Ozonolysis 	*Same products as previous
The Grignard Reagent		*Forms from 1°, 2°, 3°, allyl, vinyl, and aryl carbons.
The Organolithium Reagent		*This reagent acts like grignard but is stronger.
Formation of alcohols from Grignard	1° alcohols. (Grignard and formaldehyde) 	*Know this mechanism! *Carbon attachment
	2° alcohols. (Grignard and aldehyde) 	*Know this mechanism! *Carbon attachment
	3° alcohols. (Grignard and ketone) 	*Know this mechanism! *Carbon attachment

Task	Reaction	Notes
Grignard and esters or acid halides		*Reaction goes until completion *Know this mechanism!
Grignard and Epoxides (opening of epoxides)		*SN2 like (attacks least substituted side) *Know this mechanism!
Attaching Deuterium to carbons		*This is just good to know.
Corey-House Reaction		*not well understood (do not need to know mechanism) *another way to attach carbons.
Hydride reduction of carbonyls	mild conditions ($NaBH_4$ as reagent) 	*reduces only **aldehydes** and **ketones**. *use alcohols as a solvent.
	strong conditions ($LiAlH_4$ as reagent) 	*reduces **aldehydes**, **ketones**, **esters**, **acid halides**, **carboxyllic acids**. *Use ethers solvents *Two step process

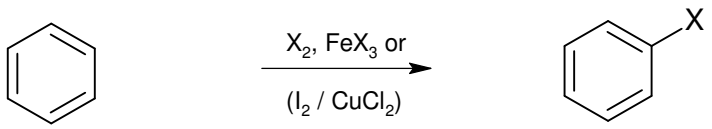
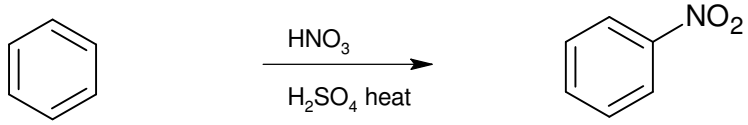
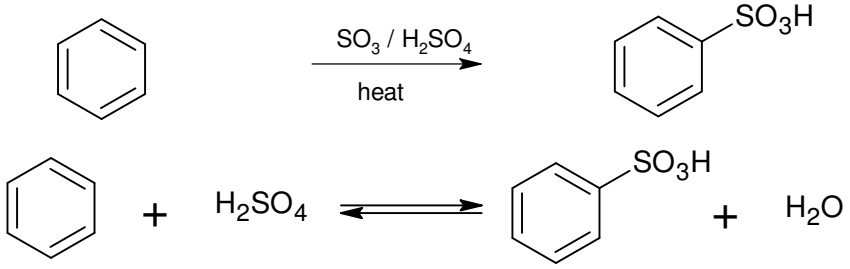
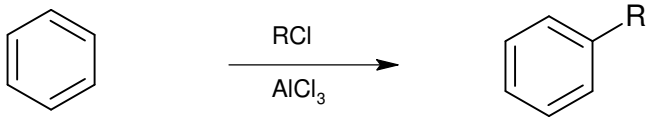
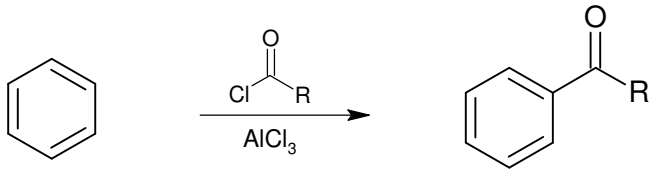
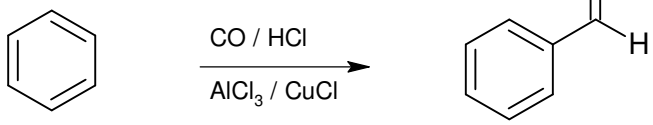
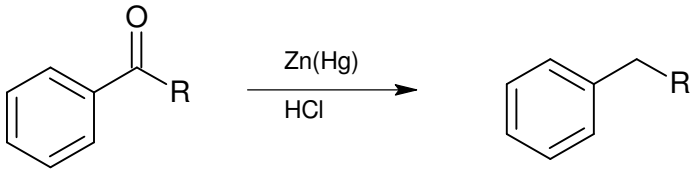
Task	Reaction	Notes
Raney Nickel		*Reduces both carbonyl and alkene.
Oxidation of alcohols	2° alcohols 	*any [ox] can be used ***$KMnO_4$** and **NO_3** can be used but they are harsh.
	1° alcohols 	*PCC is the only one that can isolate the formaldehyde.
Formation of the Tosylate Ester		***RETENTION** from where alcohol was originally **(SN2 purposes)**
Formation of alkyl halide from 3° alcohols		

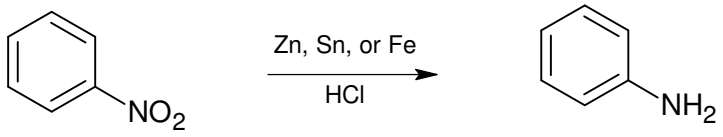
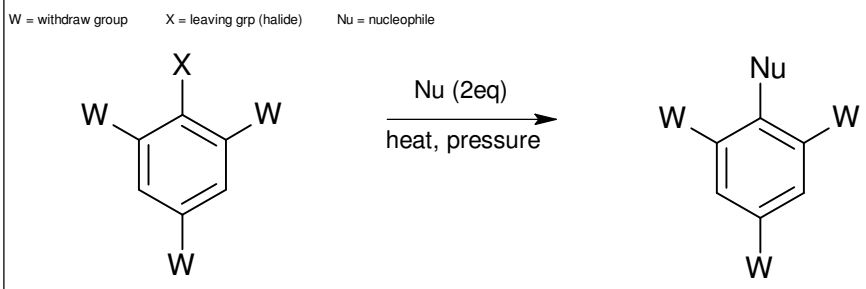
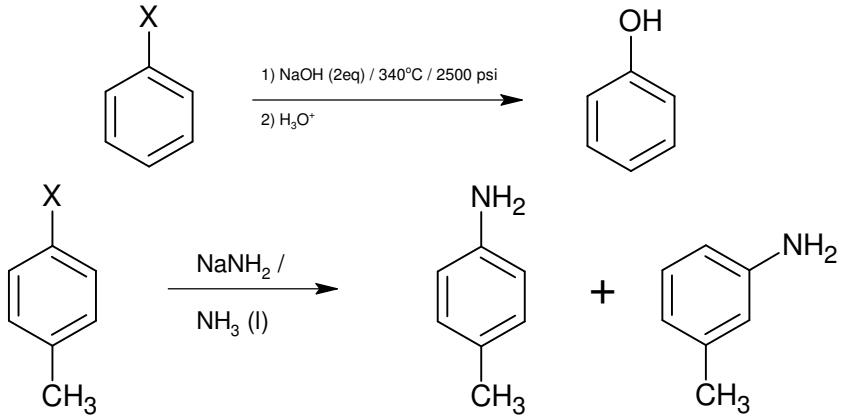
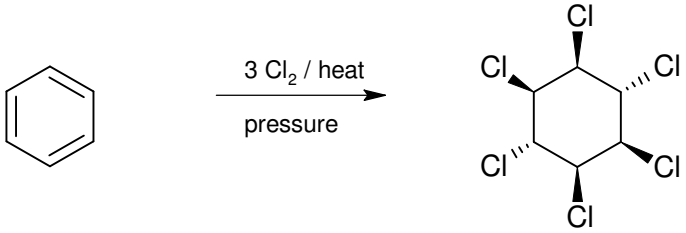
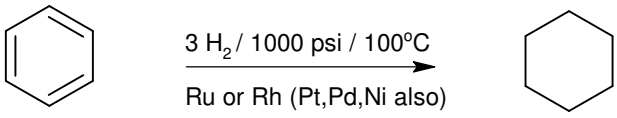
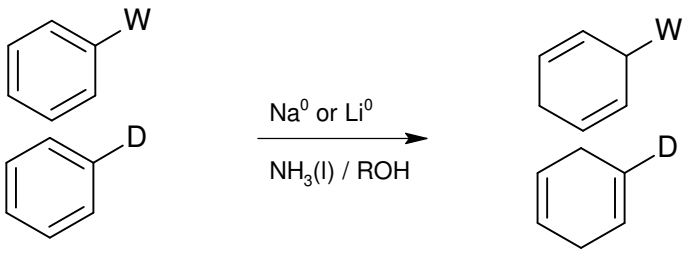
Task	Reaction	Notes
Formation of $1^o/2^o$ alkyl halides from $1^o/2^o$ alcohols	$H_3C-OH \xrightarrow[CH_2Cl_2]{PBr_3} Br-CH_3$ $H_3C-OH \xrightarrow[CH_2Cl_2]{PCl_3} Cl-CH_3$ $H_3C-OH \xrightarrow[CH_2Cl_2]{P / I_2} I-CH_3$	*Basically an SN2 reaction. (Inversion from original alcohol) *Can also use $SOCl_2$ for Cl, but it undergoes a special mechanism!
Unique cleavage with HIO_4		*Vicinal diols **must be syn**
Formation of Alkoxide Anion	1° or 2 ° alcohols  2° or 3° alcohols 	
Williamson ether synthesis		*Basically that SN2 exception we learned in test 2
Ethers from intermolecular dehydration	$2x\ CH_3CH_2-OH \xrightarrow[140^oC]{H_2SO_4} CH_3CH_2-O-CH_2CH_3$	***Must be identical alcohols** or else you will get a mixture!!!
Pinacol - Pinacolone Rearrangement		*Need vicinal diols *Know mechanism (methyl shift!)
Fischer Estherification		***CAN USE ACID HALIDE** instead of carboxyllic acid!!!

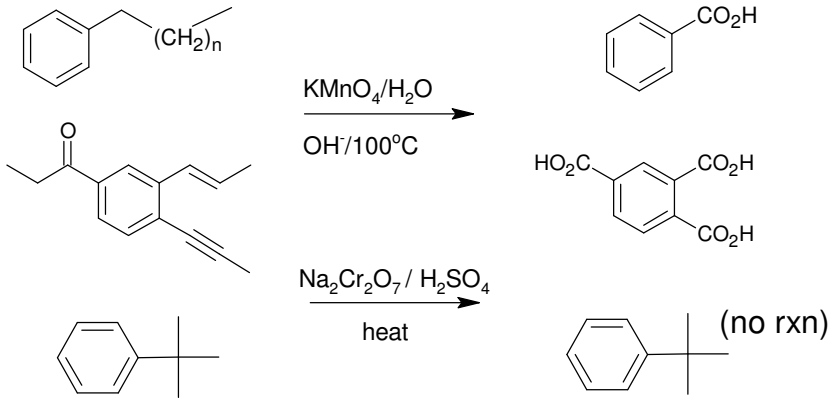
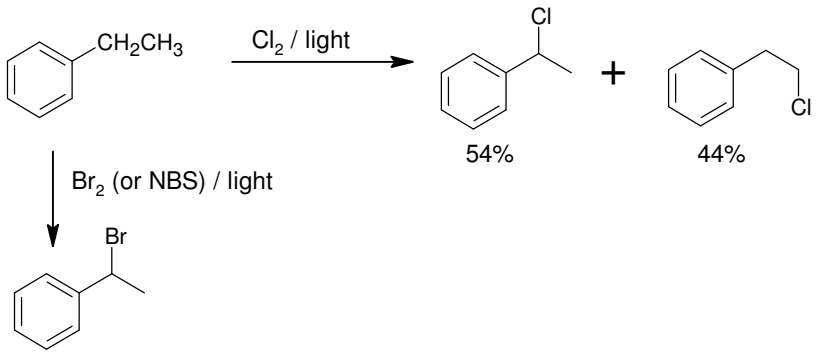
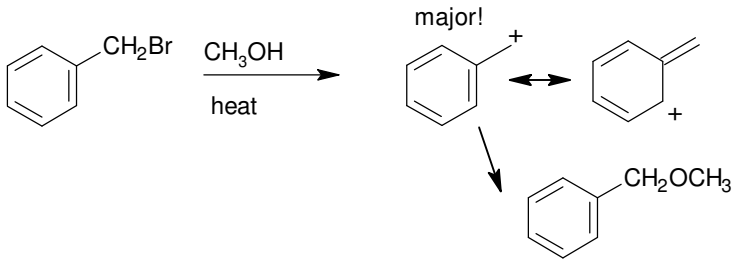
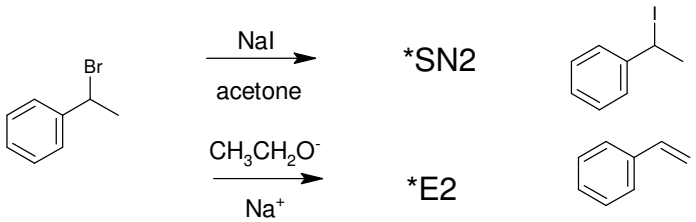
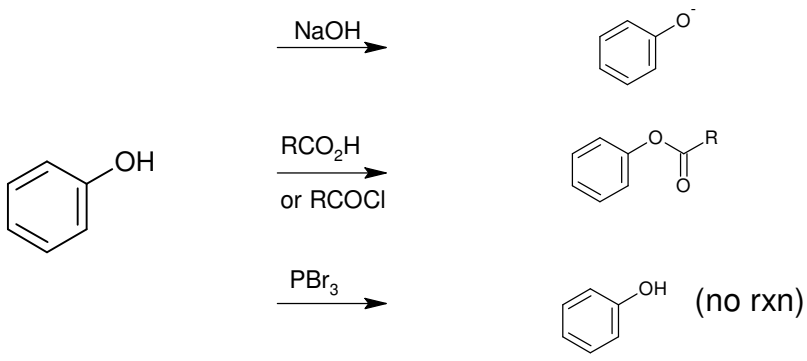
Task	Reaction	Notes
Symmetrical ethers through dehydration of 1° alcohols		*cannot be unsymetrical (you will get mixtures!)
Cleavage of ethers byvstrong acids		*can also use HI, HCl, etc * vinyl or aryl do not get cleaved (NO SN2 ON SP2)
Autoxidation		*basically forms peroxides.... which EXPLODE!
MCPBA		*epoxide will form along the more substituted alkene
Intramolecular Williamson		*SN2 like *forms O^- that attacks halogenated C
Opening of Epoxides		***activate** the O first *weak Nu are good ***more substituted** side attacked
		***SN2 like (least subs)** so strong Nu and base *Grignard reagent and acetylide anion can work tooo

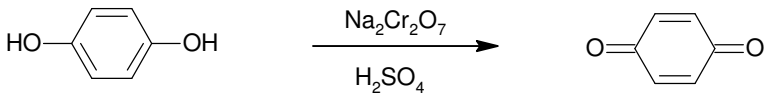
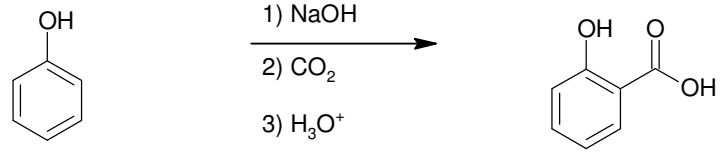
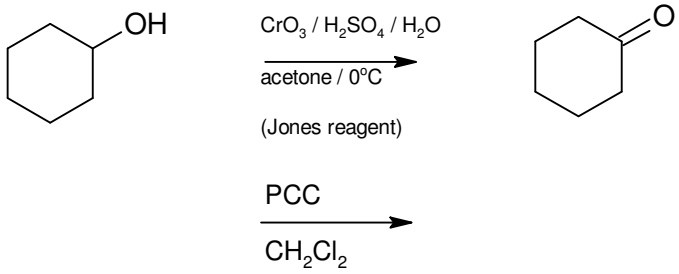
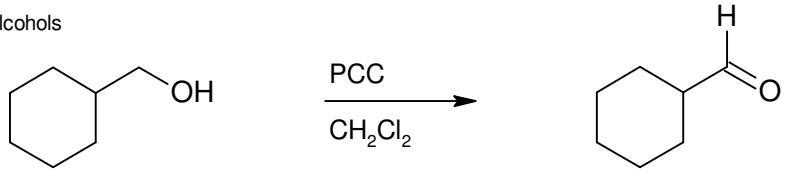
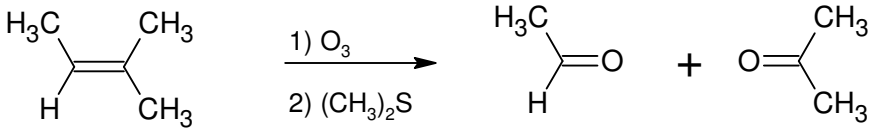
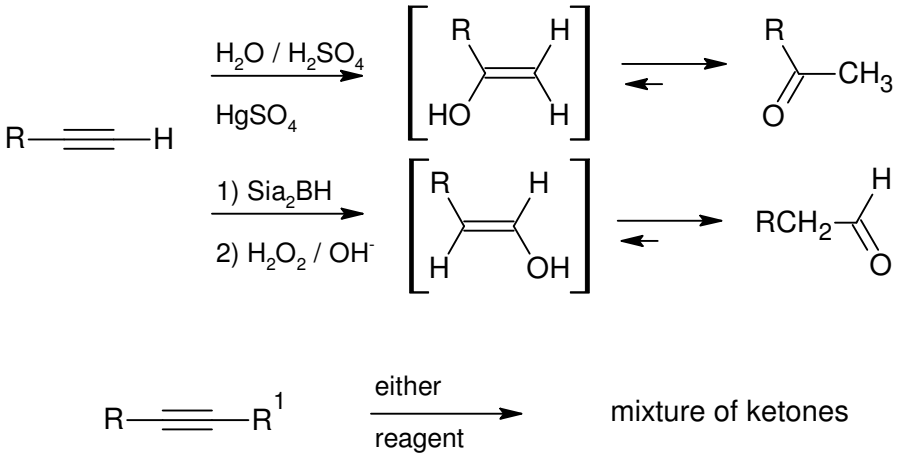
Task	Reaction	Notes
Free Radical Halogenation Expanded		*__Low T:__ more stable TS *__High T:__ more stable compound
Conjugated Systems	*in this example we will examine the case of HBr 	*__Low T:__ more stable TS *__High T:__ more stable compound *NOTE: If more than one conjugated system possibly exists, examine the transition states of each one and do the reactions with the more stable transtion states!
Diels-Alder Reaction	D = donating group W = withdraw group 	*1,2 or 1,4 adduct *know endo rule *Diene and Dienophile *Know Stereochem *PRACTICE THIS!!!

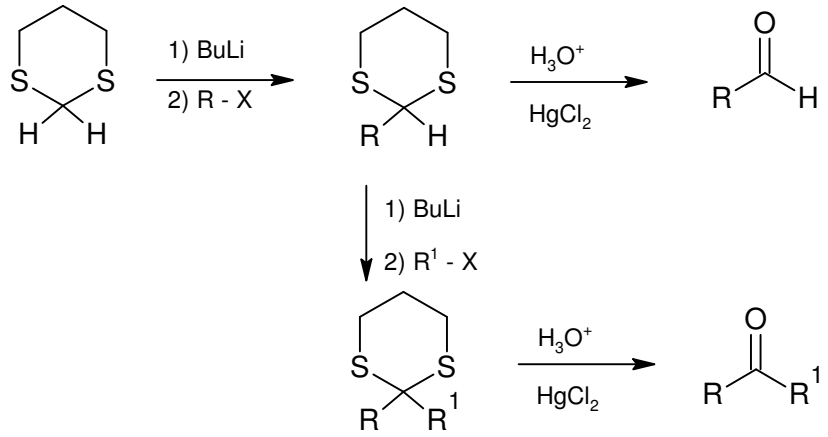
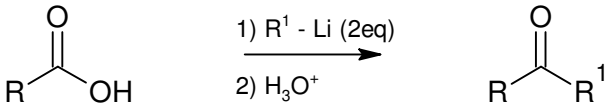
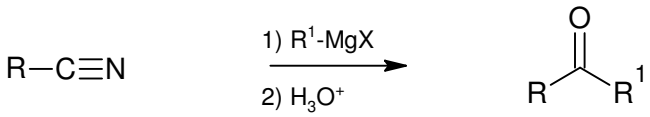
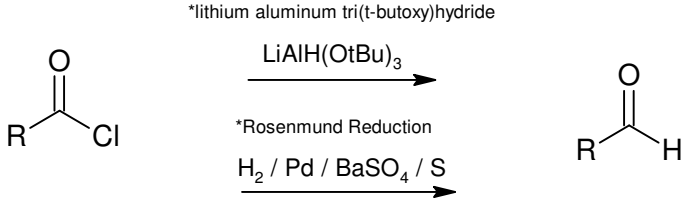
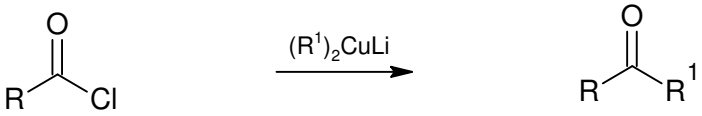
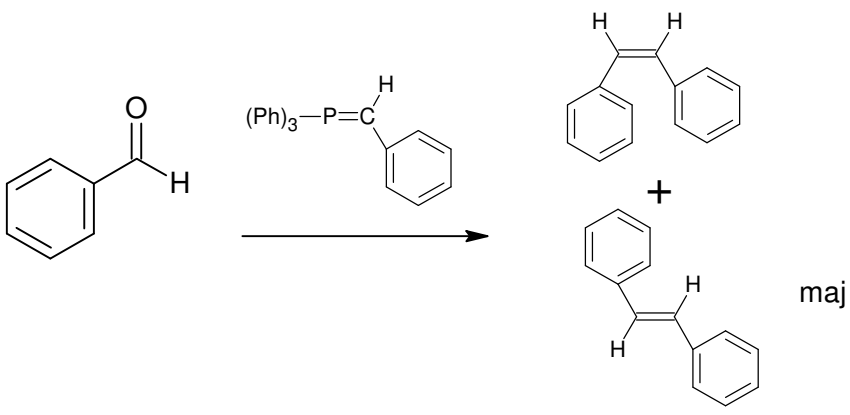
NOTE: FROM HERE, YOU HAVE TO KNOW YOUR **META, ORTHO, AND PARA** DIRECTORS

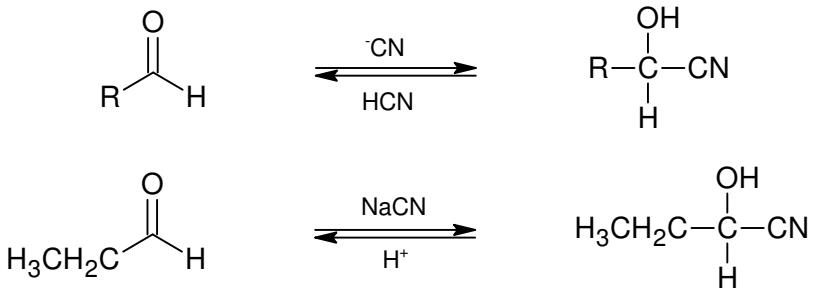
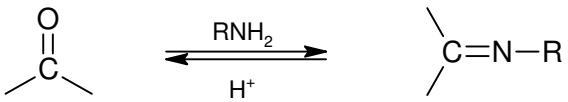
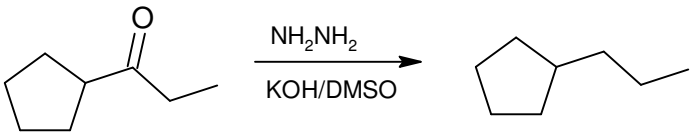
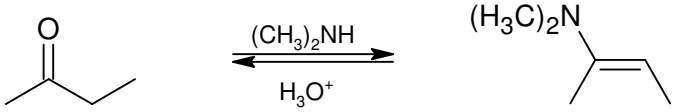
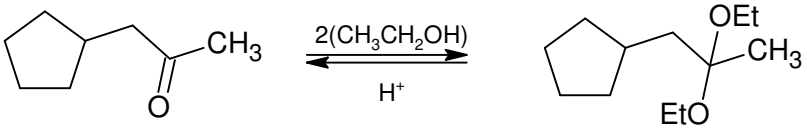
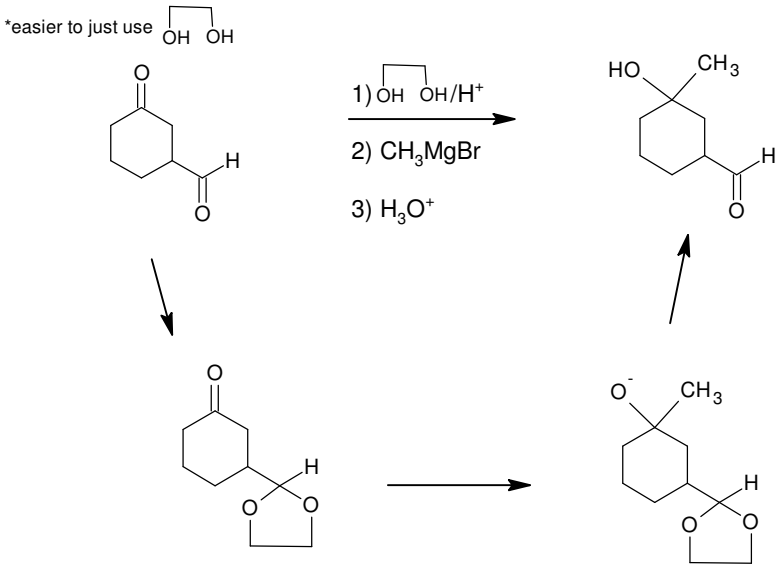
Task	Reaction	Notes
Halogenation of Benzene		*X = Cl or Br
Nitration of Benzene		*H_2SO_4 acts as a catalyst
Sulfonation (fuming sulfuric)		***REVERSIBLE DUE TO ENTROPY**
Friedel-Crafts Alkylation		*watch rearrangement! *no strong deactivators (no strong W grps) *no amino groups *watch for polyalkylation
Friedel-Crafts Acetylation		*no strong deactivators (no strong W grps) *no amino groups
Gatterman-Koch Formation (forming benzaldehyde)		*no strong deactivators (no strong W grps) *no amino groups
Clemmensen Reduction		*avoid using this reactant in the presence of alkenes, alkynes, alcohols and amines.

Task	Reaction	Notes
Reduction of Nitro group into Amino Group		*Do not confuse with Clemmenson Red.
Nucleophilic Aromatic Substitution of Aryl Halides: **Addition / Elimination**		*need **Strong W groups ortho and/or para to leaving group**. *Nu can be OH^-, RO^-, NH_3. *NOTE: If $^-OCH_3$ is the Nu, only need 1 eq
Nucleophilic Aromatic Substitution of Aryl Halides: **Elimination / Addition**		*occurs **when Strong W group is not O/P** *formation of benzyne in mechanism * Nu can be OH^-, RO^-, $^-NH_2$. *will get a mixture (like second example)
Chlorination of Benzene		*8 different stereochems actually occur *this particular molecule is the commercial compound **Rid** (lice killer)
Catalytic Hydrogenation		
Birch Reduction		*withdraw groups -> sp3 *donating groups -> sp2

Task	Reaction	Notes
Side Chain Rxn: Oxidation		*Can use either reagent *Does not work for bulky groups.
Halogenation of side chains		*If aromatic ring is activated, use NBS instead of Br_2 *Pay attention to Temp (if it's low or high) *WILL EXPLAIN THIS BETTER IN CLASS
Nucleophilic Subs of Benzylic Halides	*SN1 	*SN1 or SN2 or E2? Depends on conditions! *Resonance form that does not disrupt the aromaticity is more stable
		
Rxns of phenols similar to alochols		*2nd rxn is Fischer Estherification *3rd rxn is only one that is different!

Task	Reaction	Notes
Oxidation of Phenols to Quinones		*This reaction forms a D-A dienophile!
Formation of Salycilic Acid		*Phenoxide anion can react with the weak electrophile because it is so strongly activated.
REVIEW: Oxidation of alcohols	2° alcohols 	*any [ox] can be used *$KMnO_4$ and NO_3 can be used but they are harsh.
	1° alcohols 	*Only use PCC because Jones reagent will yield carboxyllic acid
REVIEW: Cleavage of Alkenes by Ozonolysis		
REVIEW: Hydration of Alkynes		*Really know the mechanism now and how the enols tautomerize.

Task	Reaction	Notes
Dithiane Synthesis of Aldehydes and Ketones		*Dithiane will be given *BuLi = $CH_3(CH_2)_2CH_2$-Li *Halide must be methyl or 1°
Ketones from Carboxylic Acids		*2 eq because first is used to make salt
Ketones from Nitriles		
Aldehydes from Acid Chlorides		
Ketones from Acid Chlorides		*Make sure you know how to form Gilman Reagent (refer to Corey-House in previous rxn sheet)
Wittig Reaction: Ald and Ketones ONLY		*Know how to prep the phosphorous ylide! *trans is more stable because you want bulky groups to be furthest away from each other.

Task	Reaction	Notes
Aldehydes and Ketones: Formation of Cyanohydrins		*Aldehydes or unhindered ketones *will use this as a reagent in the future.
Aldehydes and Ketones: Addition of 1° Amines		*non AQ favors reactant *AQ favors product
Wolf-Kishner Reaction		*avoid halogens and other good LGs. (Use Clemmensen instead)
Aldehydes and Ketones: Addition of 2° Amines		
Acetal Formations "protected carbonyls"		
		*aldehyde protected before ketone because it is more reactive

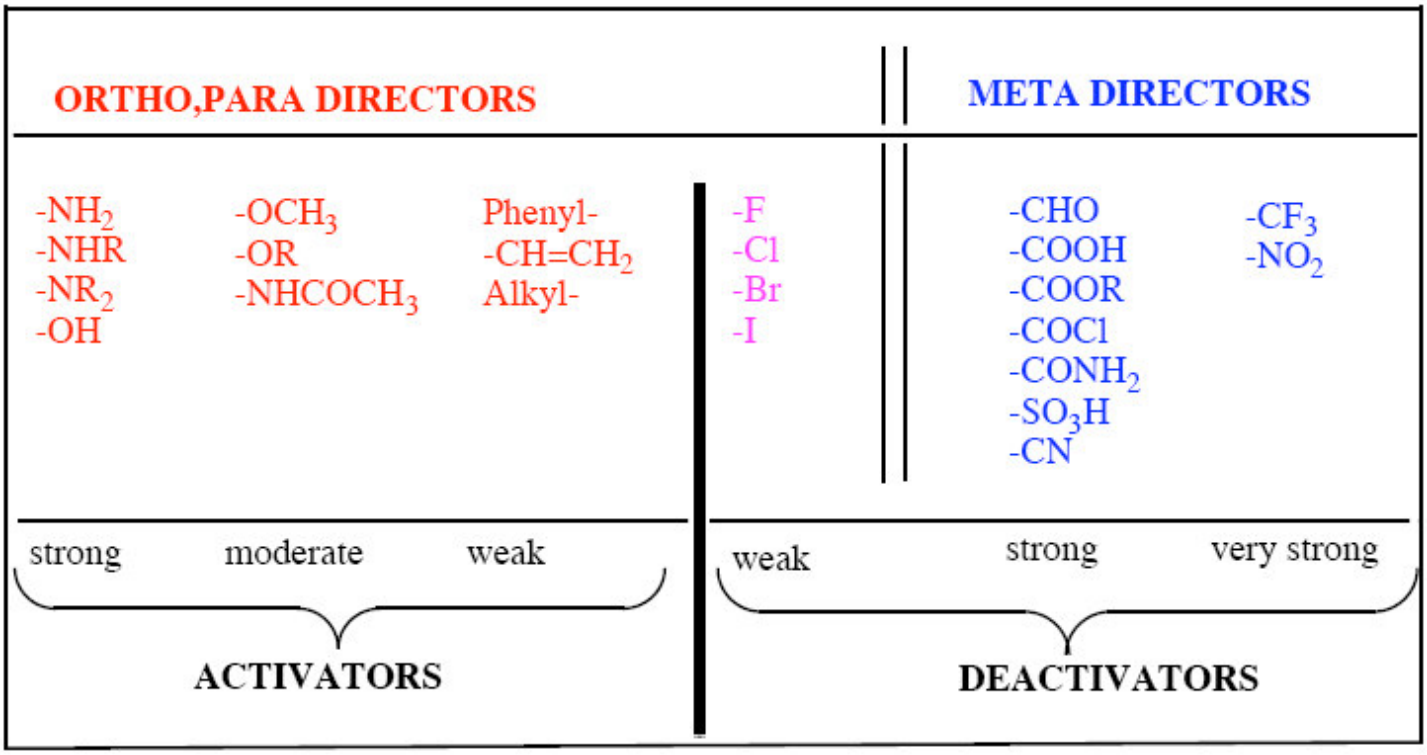
Substituent Effects in Aromatic Substitution

First group on the ring determines the reactivity of the ring toward further substitution relative to benzene itself, and also determines the where the second incoming group will go. These are two separate aspects to consider in further substitution on the ring.

An **activating group** makes the ring more reactive than benzene to further substitution. In some cases the activation is so great that polysubstitution occurs and cannot be controlled.

A **deactivating group** makes the ring less reactive than benzene to further substitution. In some cases the ring is deactivated sufficiently to prevent certain reactions from occurring.

With one group already on the ring, a second substituent can come on the ring in ortho, meta or para positions.

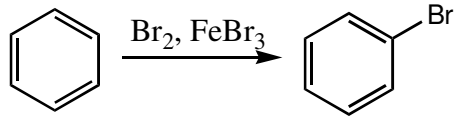


Two effects are working here. One is **induction**, which is an effect that occurs through the sigma bond system. Electron withdrawing groups will "pull" electron density away from the ring making the electrons of the ring less available for attack by an electrophile. Electron donating groups do the opposite. Induction also plays a role in some of the directional effects.

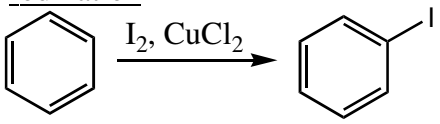
The other effect is **resonance**, which occurs through the pi system of bonds in the molecule. Resonance plays an important role in the stability of intermediates of the reactions.

Chapter 16 Overview:

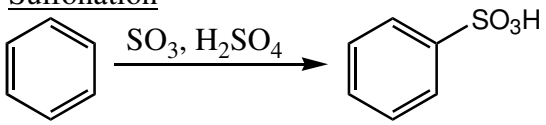
Bromination



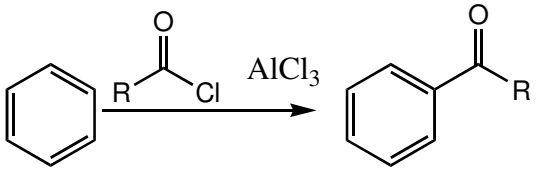
Iodination



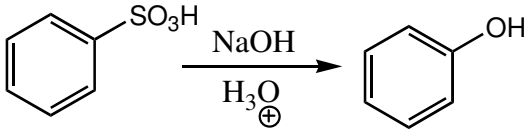
Sulfonation



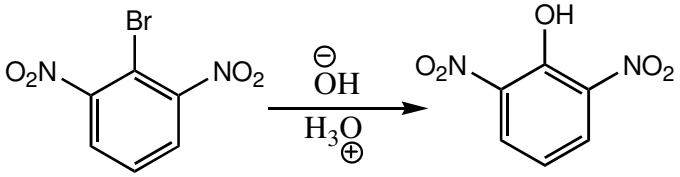
Friedel-Crafts Acylation



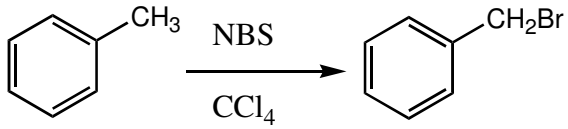
Alkali Fusion of Aromatic Sulfonates



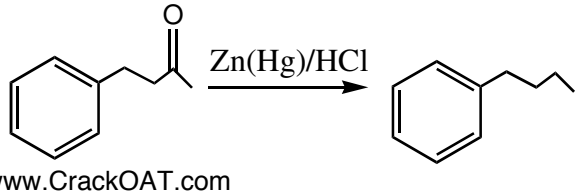
Addition/Elimination to an Activated Aryl Halide



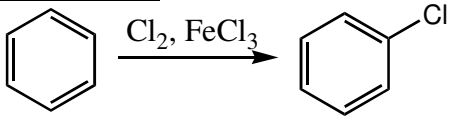
Benzylic Bromination of Alkylbenzenes with NBS



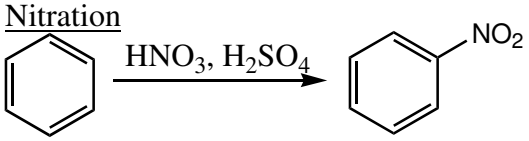
Clemeson Reduction of Dialkyl Ketones



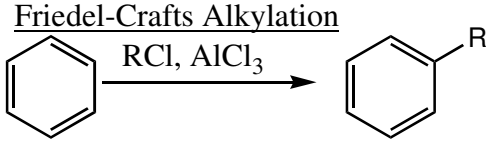
Chlorination



Nitration

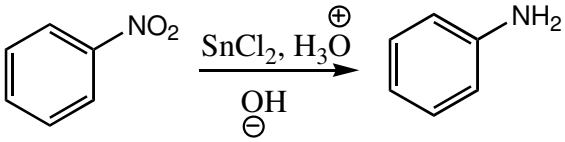


Friedel-Crafts Alkylation

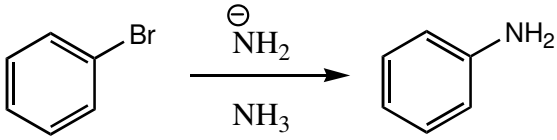


R group may rearrange
Substrate must be at least as reactive as a halobenzene
Deactivated rings don't react

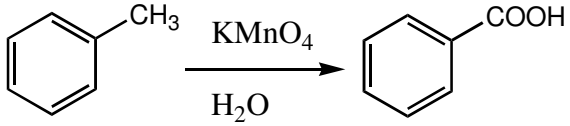
Nitro Reduction to an Amine



Benzyne Intermediate for Amination

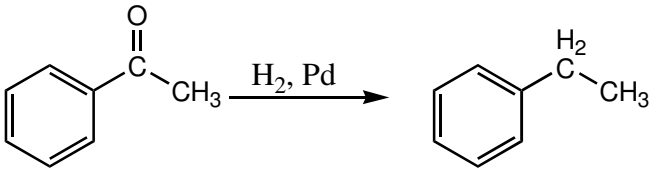


Oxidation of Alkylbenzene Side Chains



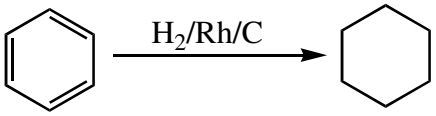
reaction doesn't work with tertriary alkanes

Reduction of Aryl Alkyl Ketones



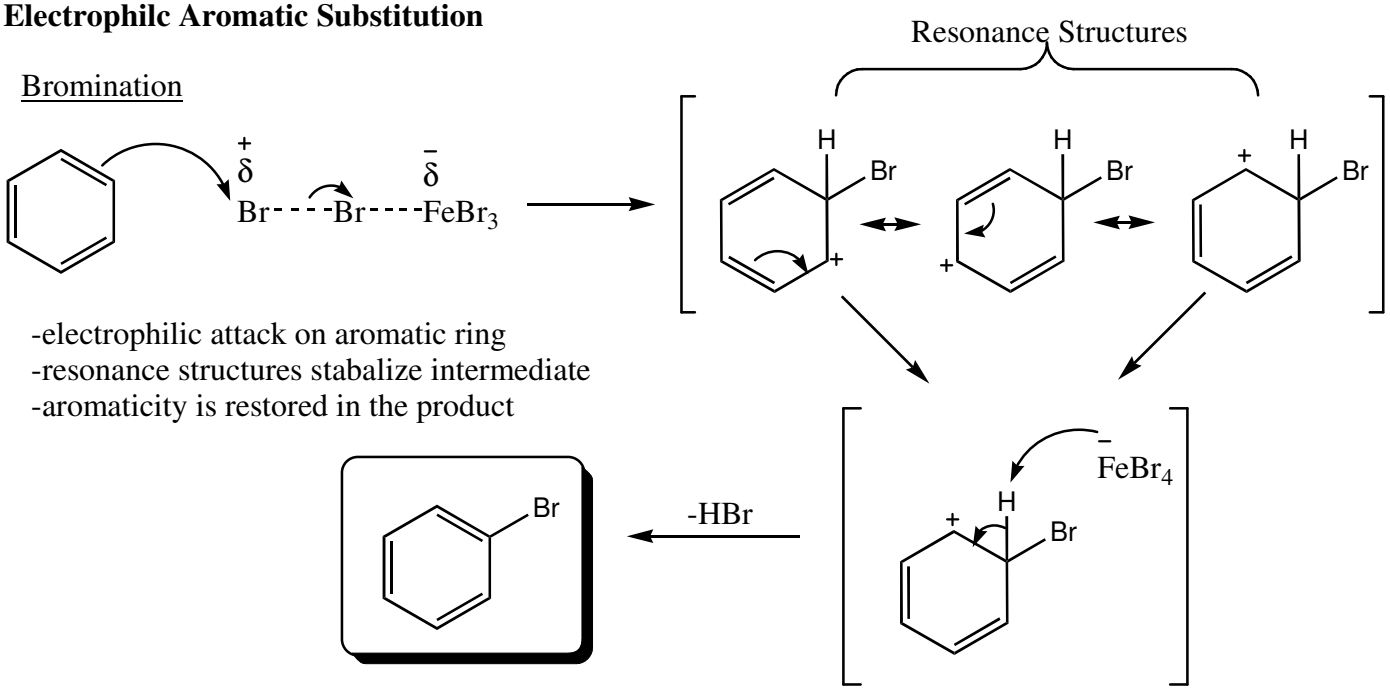
only works with benzylic ketones

Catalytic Hydrogenation



Electrophilc Aromatic Substitution

Bromination

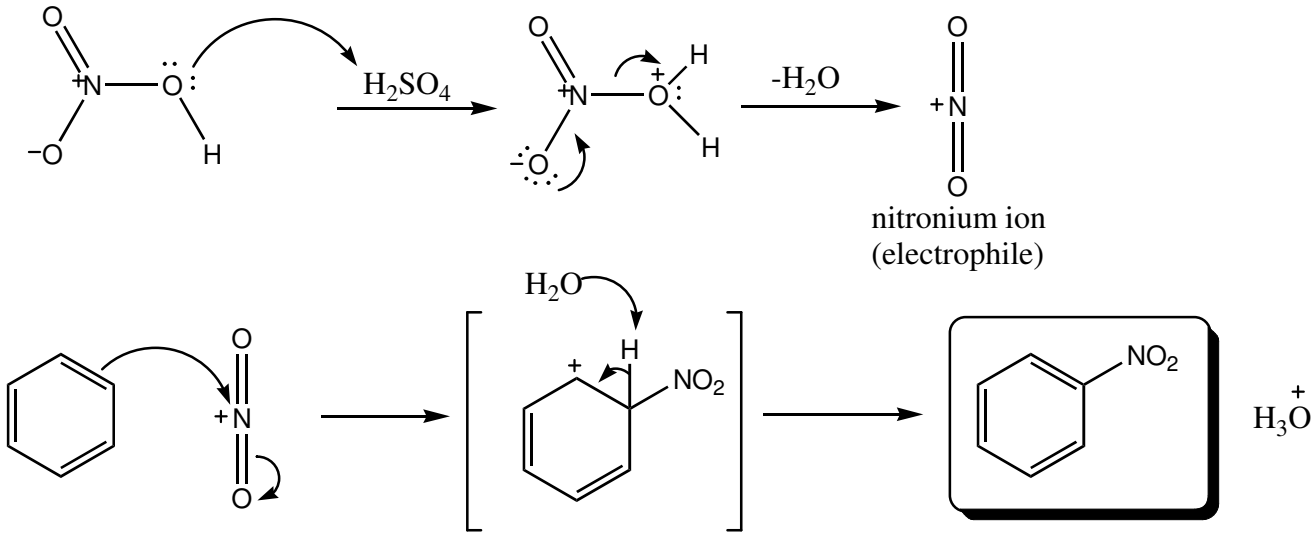


-electrophilic attack on aromatic ring
-resonance structures stabalize intermediate
-aromaticity is restored in the product

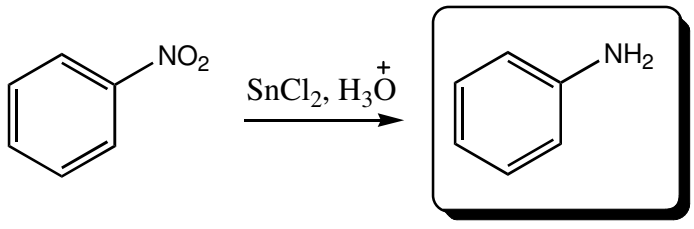
Aromatic chloronation and iodonation happen in the same manner but use different lewis acid catalysts: $FeCl_3$ and $CuCl_2$ respectively.

Aromatic Nitration

begins with formation of the nitronium ion: $+NO_2$

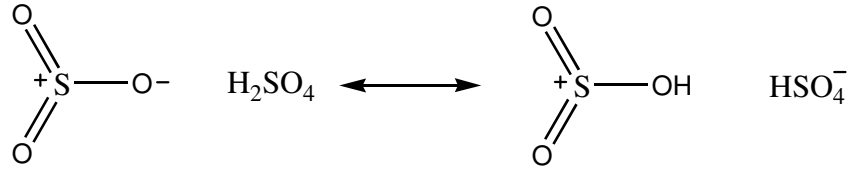


Remember: Reduction of a nitro group to form an amino group

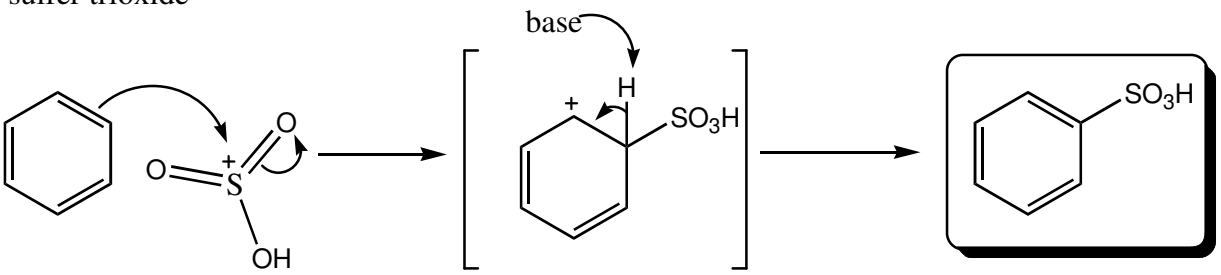


Aromatic Sulfonation

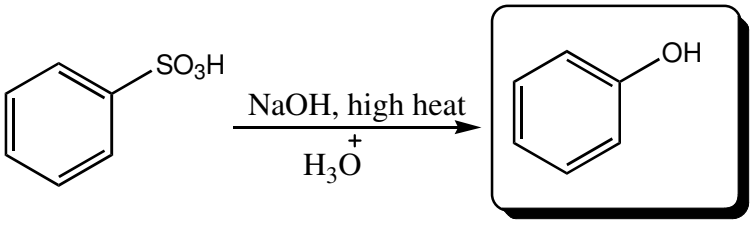
useful for sufonation, protecting group and as an intermediate to phenols



sulfer trioxide



Remember: alkali fusion to produce phenol



Note: the alkali fusion reaction requires harsh solvent free conditions, therefore it is typically only useful with alkyl goups present on the ring

---

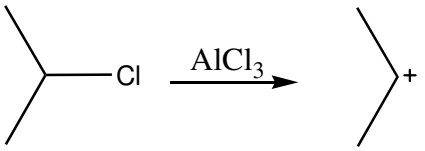
Friedel-Crafts Alkylation

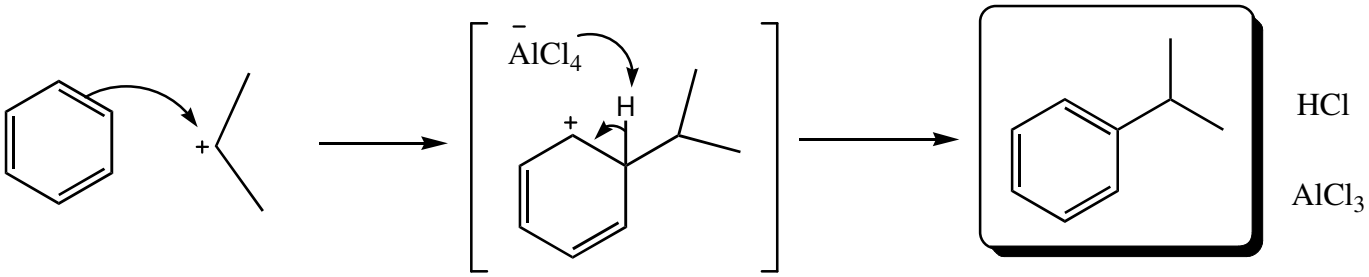
problems/limiations

-prone to carbocation rearrangements

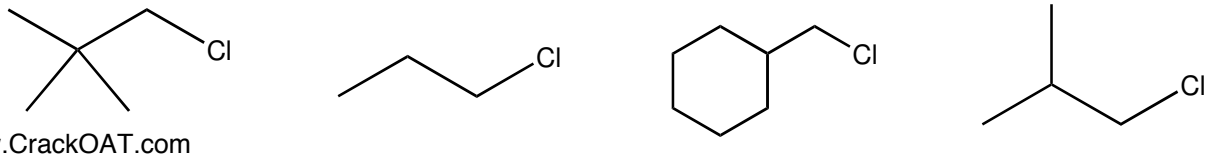
-will not work on an aromatic ring with electron withdrawing groups or amino groups

-poly-alkylation certain to occur



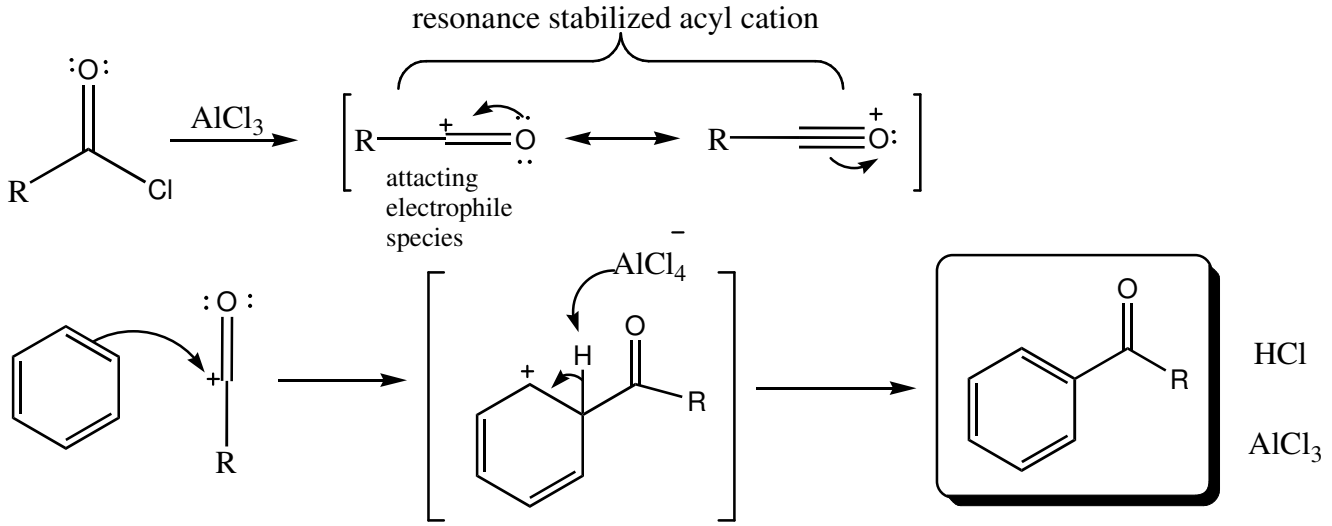


These are examples of alkyl halides that can rearrange:



Friedel-Crafts acylation reaction

Acid chloride can be made from a carboxylic acid and $SOCl_2$



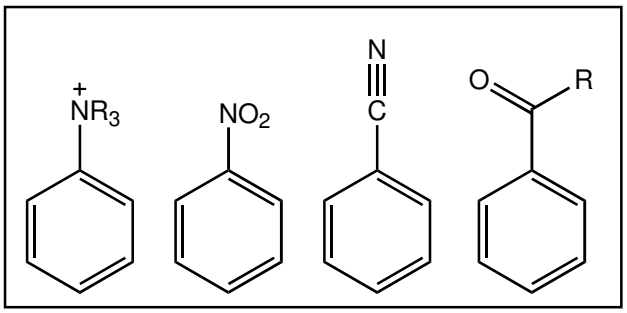
Acylation does not occur more than once since the acylated product is less reactive than the starting material, due to the electron withdrawing nature of the group.

Substituent Effects in Substituted Aromatic Rings

The substitutents on an aromatic ring determine the reactivity of the aromatic substrate in subsequent reactions (either activating or deactivating). Examples:

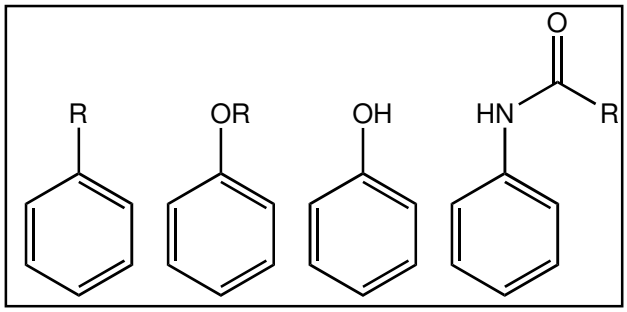
They will also direct the incoming reagent to a specific site on the ring (either ortho/para or meta).

Deactivators/Meta Directors: EWG



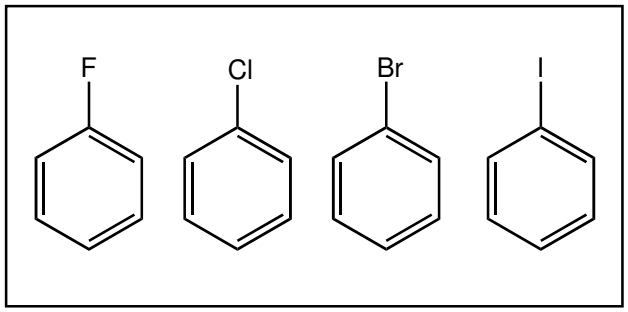
R=any alkyl group or H

Activators/Ortho-Para Directors: EDG



R=any alkyl group or H

Dectivators/Ortho-Para Directors: EWG



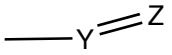
Reactivity and directing ability in electrophilic aromatic substitutions are controlled by inductive effects and resonance.

Inductive Effect-withdrawal or donation of electrons (electron density) through σ bonds. This is a result of a polarization in electronegativity.

Resonance Effect-withdrawal or donation of electrons through π bonds. Resonance structures can be drawn to explain the placement of electron density.

General Structures:

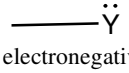
Electron-withdrawing groups(EWG):



Z is a more electronegative atom then Y

destabalize the intermediate carbocation therefore the ring is less reactive

Electron-donating groups(EDG):



Y is an electronegative atom

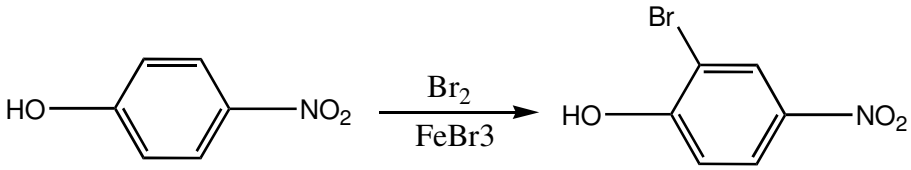
stabalize the intermediate carbocation therefore the ring is more reactive

Halogens, despite the fact that they are electron-donating groups, deactivate the ring since they have stronger electron-withdrawing capabilities.

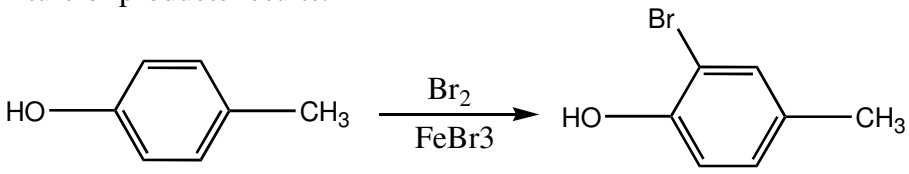
Resonance Structures for electron-donating groups show that the most stable electrophilic attacks take place in the ortho and para positions; electron-withdrawing groups show that the most stable elctrophlic attacks take place in the meta postion.

Trisubstituted Benzene: Considerations of Different Effects

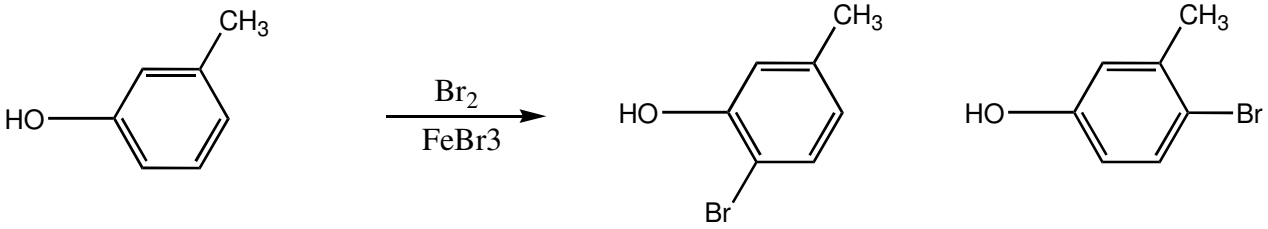
1. If two directing groups direct to the same place then the incoming reagent will react in this position.



2. If two groups oppose each other then the more powerful activating group has the major influence. Often a mixture of products results.



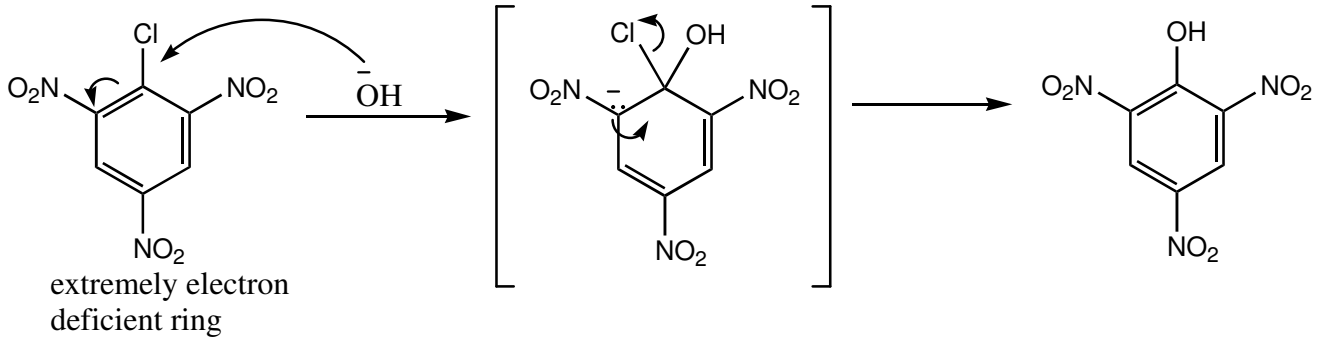
3. If two groups are meta to one another they are usually two bulky to allow attack between them. The incoming reagent will be directed to another site on the ring.



Nucleophilic Aromatic Substitution

Only takes place on electron deficient rings! EWG must be present!

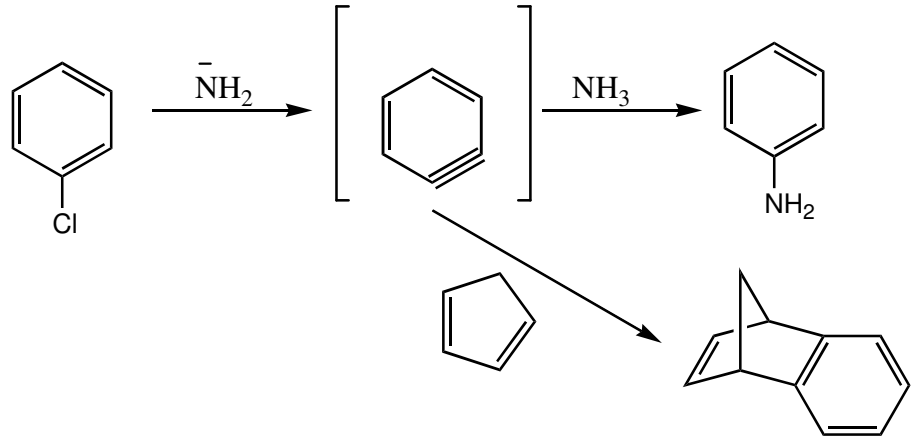
Proceed through an addition/elimination mechanism

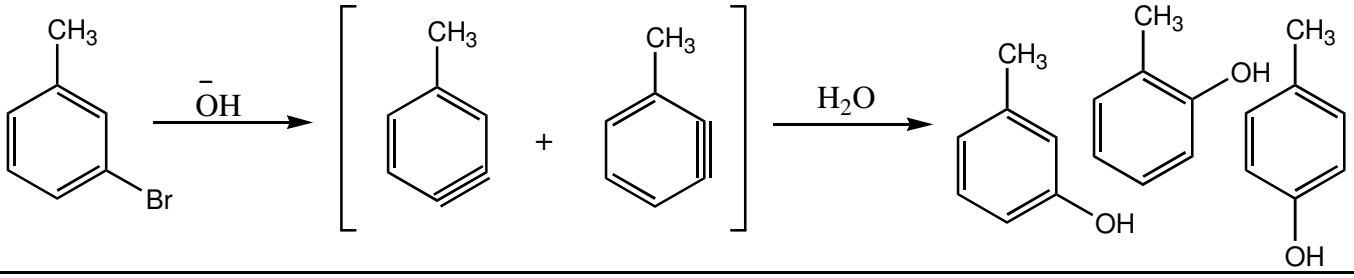


extremely electron deficient ring

Benzyne: Triple bond in an aromatic ring.

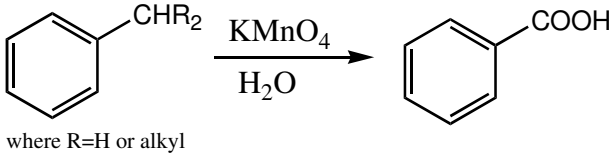
Strong base (either OH or NH_2) eliminates HX (via an E2 mechanism) where X is Cl or Br producing benzyne. Benzyne is then subject to a nucleophilic attack as well as other reactions such as Diels-Alder



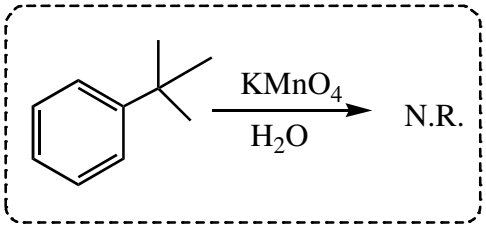


Oxidation of alkylbenzene side chains to carboxylic acids.

Must have a benzylic proton. Tert-butyl won't react!

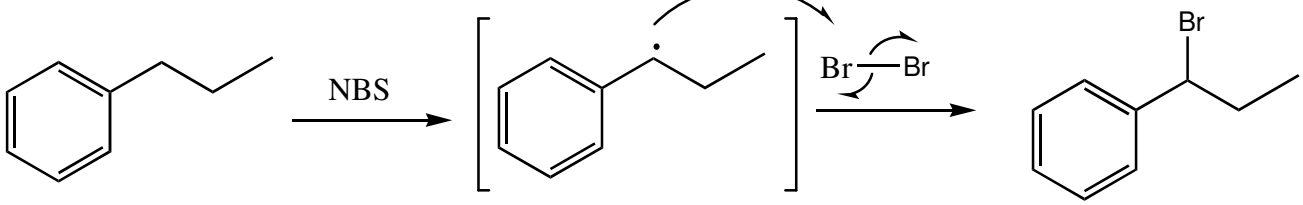


where R=H or alkyl



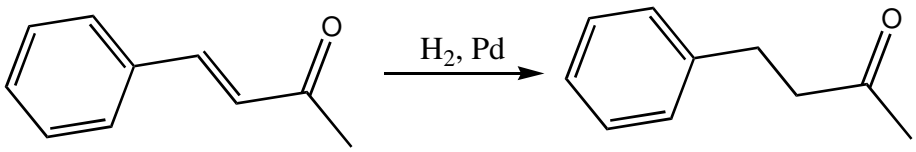
Bromination of Alkylbenzene Side Chains

Radical mechanism, benzylic radical very stable, typical initiation, propogation, termination steps.

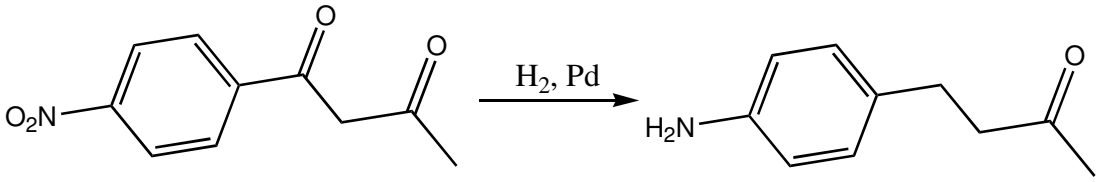


Reduction with aromatic rings

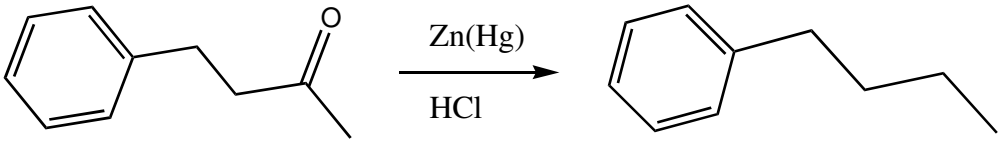
Hydrogen with Pd or Pt catalysts won't reduce aromatic rings or non-benzylic carbonyls.



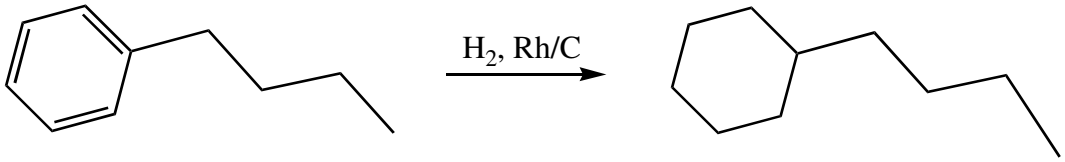
It will reduce aryl alkyl ketones to alkanes and aromatic nitro groups to amino groups



Clemmensen Reduction will reduce all carbonyls, it will also reduce aromatic nitro groups to amino groups

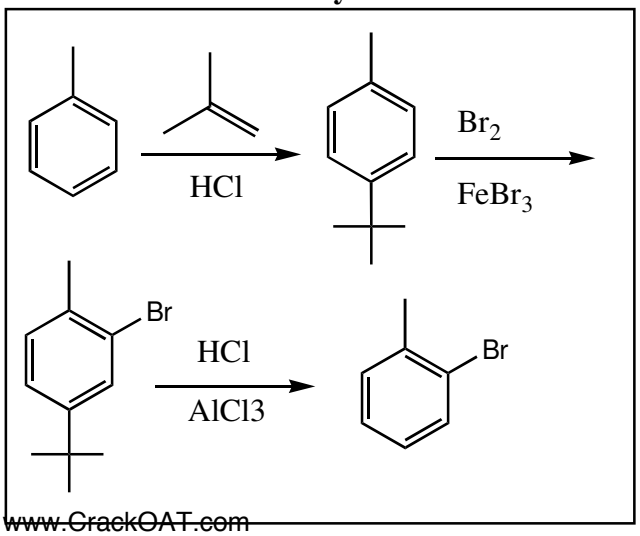


Hydrogen with Rhodium Catalyst will reduce the aromatic ring to cyclohexane

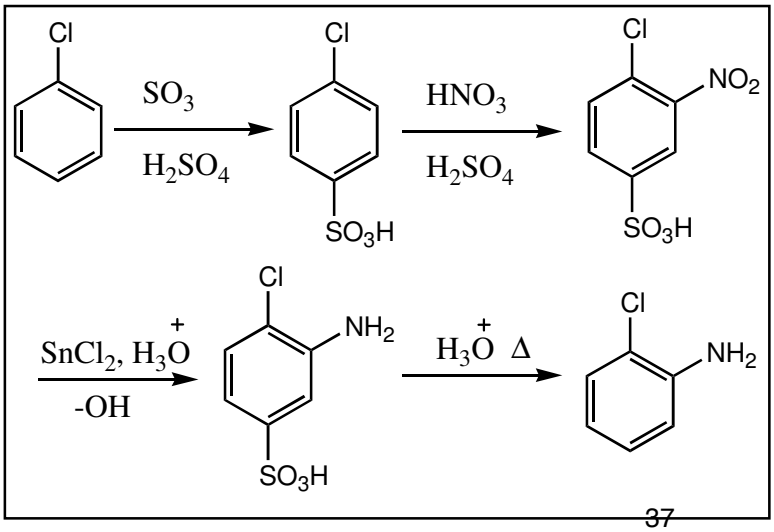


Protecting Groups for Synthesis: put in a place holder group so the position it occupies is not attacked.

tert-butyl



sulfonate



SUBSTRATE	REAGENT catalyst	REACTION	MECHANISM	MAJOR PRODUCT	BYPRODUCT	NOTE
ALKANES						
CH_4	Cl_2 or Br_2	Radical Halogenation	S_R	CH_3Cl	HCl	
ALKENES						
$CH_2=CH_2$	H_2 (Pt, Ni, Pd)	Catalytic Hydrogenation (Reduction)	Cis A_E	CH_3-CH_3		
$CH_2=CH_2$	HX	Hydrohalogenation	Trans or anti A_E	CH_3CH_2X Organic monohalide		X on more substituted C; H on less substituted C
$CH_2=CH_2$	X_2	Halogenation	Trans or anti A_E	CH_2XCH_2X Vicinal dihalide		
$CH_2=CH_2$	HOH H_2SO_4	Hydration	Trans or anti A_E	CH_3CH_2OH Alcohols		
$CH_2=CH_2$	Neutral or basic $KMnO_4$ (aq.)	Hydroxylation	REDOX (Oxidation)	Diols		
$CH_2=CH_2$	Acidic $KMnO_4$	Oxidative Multiple Bond Cleavage	REDOX (Oxidation)	If terminal = $CO_2 + H_2O$ If internal = RCOOH		
$CH_2=CH_2$	Peroxyacid	Epoxidation	REDOX (Oxidation)	Epoxide	RCOOH	
$CH_2=CH_2$	X_2 , H_2O	Halohydration	Trans A_E	Halohydrins HO-C-C-X	HX	
ALKYNES						
HCCH	H_2 (Lindlar's Catalyst)	Catalytic Hydrogenation (Reduction)	Cis A_E	$CH_2=CH_2$		

HCCH	HOH H_2SO_4, $HgSO_4$	Hydration	Trans or anti A_E	Enol H_2=CHOH Ketone R_2CO		Markovnikov's rule Keto-enol Tautomerism
HCCH	HX	Hydrohalogenation	Trans or anti A_E	CH_2=CHX		
HCCH	X_2	Halogenation	Trans or anti A_E	CH_2X=CH_2X		
HCCH	Neutral or basic $KMnO_4$ (aq.)	Hydroxylation	REDOX (Oxidation)	Diols		
HCCH	Acidic $KMnO_4$ (aq.)	Oxidative Multiple Bond Cleavage	REDOX (Oxidation)	If terminal = CO_2 + H_2O If internal = RCOOH		
HCCH	$NaNH_2$	Acetylide Formation	Acid-base reaction (or S_N)	Acetylide	NH_3	
AROMATIC COMPOUNDS						
Benzene	X_2 FeX_3 or AlX_3	Halogenation	S_E	Halobenzene	HX	Note activators and deactivators
Benzene	Conc. HNO_3 and Conc. H_2SO_4	Nitration	S_E	Nitrobenzene	HOH	
Benzene	Fuming H_2SO_4 (conc. H_2SO_4 + SO_3)	Sulfonation	S_E	Benzenesulfonic Acid	HOH	
Benzene	RCOX (Acid halide) AlX_3	Friedel-Crafts Acylation	S_E	Aromatic ketone	HX	Cannot undergo friedel-craft if the ring contains a deactivator
Benzene	RX (Alkyl halide) AlX_3	Friedel-Crafts Alkylation	S_E	Arenes	HX	
Benzene	Zn(Hg), conc. HCl heat	Clemmenson Reduction	S_E	Acyl to Alkyl		
Ethyl Benzene	$KMnO_4$, H_2O	REDOX (Oxidation)	S_E	If terminal = CO_2 + H_2O If internal = RCOOH		

				(Benzoic Acid)		
ALKYL HALIDES						
R-X	Mg^{o}	Synthesis of Grignard Reagent	A_N	R-Mg-X Grignard reagent		Condensation Reaction (A_NE)
R-Mg-X	H_2O	Hydrolysis	E	R-H	Mg(OH)X Basic magnesium halide	
R-X	Strong or weak nucleophile; dependent on substrate; polar protic solvent		S_N1	Racemization (enantiomeric products)		$3^{o}>2^{o}>1^{o}$
R-X	Strong nucleophile; dependent on both substrate and nucleophile; polar aprotic or nonpolar solvent		S_N2	Inversion prod.		$1^{o}>2^{o}>3^{o}$
R-C-X	Nu^- heat	elimination	E_1	R=C	X^-	
R-C-X	Nu^- (basic) heat	elimination	E_2	R=C	X^-	Major product in more substituted C atom
ALCOHOLS AND PHENOLS						
R-OH	H-X Hydrogen halide ether	Hydrohalogenation	S_N1	R-X	H_2O	Most reactive with 3^{o} alcohols
R-OH	p-TosCl Toluenesulfonyl chloride pyridine		S_N1 or S_N2	ROTos	Pyridine HCl	
CH_3CH_2-OH	H_3O^+, THF	dehydration	E_1	$CH_2=CH_2$ More substituted alkene product	Less substituted alkene product	Follows Zaitsev's rule
R-OH (1^{o}) (2^{o})	$KMnO_4/CrO_3$/ $Na_2Cr_2O_7$	REDOX	oxidation	Aldehydes → Carboxylic acids Ketones		
R-OH (1^{o})	Dess-martin periodinane CH_2Cl_2	REDOX	oxidation	RCHO		

Ar-OH phenol	$Na_2Cr_2O_7$ H_2O	REDOX	Oxidation	Benzoquinone		
Quinone	$SnCl_2$ H_2	REDOX	Reduction	Hydroquinone		
ETHERS						
ROR'	HBr or HI	Acidic Cleavage	S_N2: If 1^O or 2^O S_N1: If 3^O	R'Br or R'Cl + ROH		Br or I will bond with the less sterically hindered R between 1^o and 2^o If there is a tertiary R, Br and I will automatically bond with it
EPOXIDES (AKA OXIRANES)						
ROH	Na^O metal or NaH	Williamson Ether Synthesis		$RONa^+$ (Alkoxide Ion)	H_2	In short: $ROH+NaH \rightarrow H_2+RONa$ $RONa+RX \rightarrow NaX+ROR$
RONa	R-X		S_N2: If 1^O or 2^O S_N1: If 3^O	ROR'	NaX	
EPOXIDE	HX, Ether	Ring Opening	S_N2 like: If 1^O or 2^O S_N1 like: If 3^O is present S_N2 (accdg to Torres)	Halohydrin		X or the halogen will bond with the 1^O (between 1^O and 2^O) X will bond with 3^O if it is present
EPOXIDE	H^+, HOH	Ring Opening	S_N2	1,2 diol (glycol)		
ALDEHYDES						
RCHO	$KMnO_4/CrO_3$/ $Na_2Cr_2O_7$	REDOX	Oxidation	RCOOH		
RCHO	H_2O (basic OH^-) or (acidic H^+)	Hydration	A_N	Hydrate (gem diol)		

RCHO	HCN	Cyanohydrin formation	A_N	nitriles		
RCHO	$NaBH_4$;ethanol	REDOX	reduction	Primary alcohols		
RCHO	R-Mg-X	Addition of grignard reagent	A_N	Secondary alcohols		
RCHO	RNH_2	Imine formation	A_NE	RCH-Imine		
RCHO	R_2NH	Enamine formation	A_NE	Enamine		
RCHO	H_2NNH_2 KOH	Wolff-Kishner	A_N	RCH_3	$N_2 + H_2O$	
RCHO	ROH Acid catalyst	Acetal formation	A_NE	Hemiacetal → acetal	H_2O	
KETONES						
R_2CO	H_2O (basic OH^-) or (acidic H^+)	Hydration	A_N	Hydrate (gem diol)		
R_2CO	HCN	Cyanohydrin formation	A_N	Nitriles		
R_2CO	$NaBH_4$;ethanol	REDOX	reduction	Secondary alcohols		
R_2CO	R-Mg-X	Addition of grignard reagent	A_N	Tertiary alcohols		
R_2CO	RNH_2	Imine formation	A_NE	R_2C-Imine	H_2O	

R_2CO	R_2NH_2	Enamine formation	A_NE	Enamine	H_2O	
R_2CO	H_2NNH_2 KOH	Wolff-Kishner	A_N	R_2CH_2	$N_2 + H_2O$	
R_2CO	ROH Acid catalyst	Ketal formation	A_NE	Hemiketal → ketal	H_2O	
CARBOXYLIC ACIDS						
RCOOH	$SOCl_2$		S_NAcyl	RCOCl		
RCOOH	PBr_3, Ether		S_NAcyl	RCOBr		
RCOOH (2 moles acetic acid)	heating			Acetic anhydride	H_2O	Only acetic anhydride is prepared this way
RCOOH	ROH Acid catalyst	Fischer Esterification	S_NAcyl	Ester (RCOOR')	H_2O	
RCOOH	NH_3(alc.) DCC	ammonolysis	S_NAcyl	Amide ($RCONH_2$)	H_2O	
RCOOH	RNH_2(alc.) DCC	aminolysis	S_NAcyl	Amide (RCONHR')	H_2O	
RCOOH	1. $LiAlH_4$, ether 2. H_3O^+	REDOX	Reduction	Primary alcohol (RCH_2OH)		
ACID HALIDES (CARBOXYLIC ACID DERIVATIVE)						
RCOX	H_2O	Hydrolysis	S_NAcyl	RCOOH	HX	
RCOX	Carboxylate anion		S_NAcyl	Acid Anhydride (symmetrical or unsymmetrical)		
RCOX	ROH	Alcoholysis	S_NAcyl	Ester (RCOOR')	HX	
RCOX	R'-NH_2 (alc)	Aminolysis	S_NAcyl	Amides (RCONHR')	HX	Trisubstituted amines can't be used
RCOX	NH_3 (alc)	Ammonolysis	S_NAcyl	$RCONH_2$	HX	

RCOX	1. $LiAlH_4$, ether 2. H_3O^+	REDOX (reduction)	S_NAcyl	Primary alcohol (RCH_2OH)	HX	
RCOX	2 R-Mg-X (Grignard reagent)	Grignard	S_NAcyl	Tertiary alcohols		
RCOX	R_2CuLi Lithium diorganocopper (Gilman) reagent	Diorganocopper	S_NAcyl	Ketone (RCOR')	R'Cu	
ACID ANHYDRIDES (CARBOXYLIC ACID DERIVATIVE)						
$(RC(O))_2O$	H_2O	Hydrolysis	S_NAcyl	RCOOH	RCOOH	
$(RC(O))_2O$	ROH	Alcoholysis	S_NAcyl	Ester (RCOOR')	RCOOH	
$(RC(O))_2O$	R'-NH_2 (alc)	Aminolysis	S_NAcyl	Amide (RCONHR')	RCOOH	
$(RC(O))_2O$	1. $LiAlH_4$, ether 2. H_3O^+	REDOX	reduction	2 Primary alcohol 2 (RCH_2OH)		
ESTERS (CARBOXYLIC ACID DERIVATIVE)						
RCOOR'	H_2O, NaOH H_3O^+	Hydrolysis saponification	S_NAcyl	RCOOH	R'OH	
RCOOR'	NH_3 ether	Aminolysis	S_NAcyl	RCO-NH_2	R'OH	
RCOOR'	1. ROH 2. H_3O^+ or base	Trans esterification	S_NAcyl	Ester (RCOOR')	R'OH Primary alcohol	Double bond O will become ester Ester must not have the same
RCOOR'	1. $LiAlH_4$, ether 2. H_3O^+	REDOX	reduction	RCOH Primary alcohol	R'OH Primary alcohol	
RCOOR'	R-Mg-X (Grignard reagent)	Grignard	S_NAcyl	Tertiary alcohol		
AMIDES (CARBOXYLIC ACID DERIVATIVE)						
$RCONH_2$	H_2O, NaOH H_3O^+	Hydrolysis	S_NAcyl	RCOOH	NH_3	
$RCONH_2$	1. $LiAlH_4$, ether	REDOX	reduction	RCH_2NH_2	H_2O	

	2. H_3O^+					
NITRILES						
RC≡N	H_2O	Hydration	A_N	amide $RCONH_2$		
RC≡N	H_2O, NaOH H_3O^+	Hydrolysis		RCOOH	NH_3	
RC≡N	$LiAlH_4$, ether	REDOX	reduction	RNH_2 Primary amine		
RC≡N	R-Mg-X (Grignard reagent), H_2O			R_2CO	NH_3	