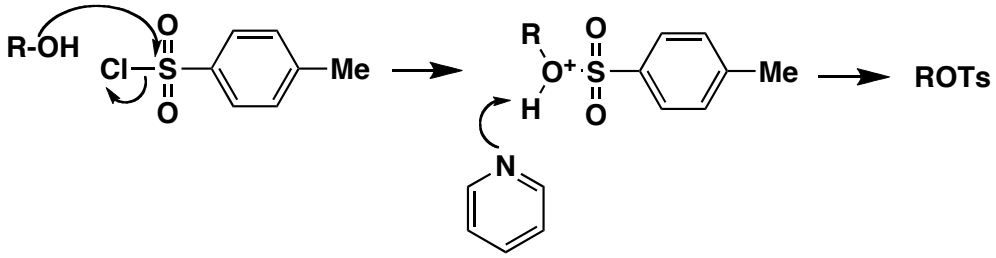
Massachusetts Institute of Technology
Organic Chemistry 5.511

September, 2007
Prepared by Julia Robinson

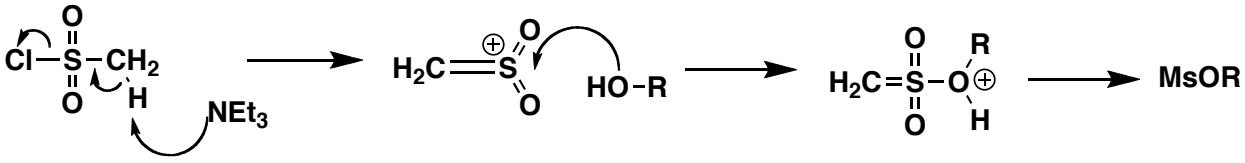
Problem Set 1
Functional Group Transformations Study Guide
SOLUTIONS

Part I - Functional Group Interconversions and Protective Group Chemistry

(1) Tosylate formation

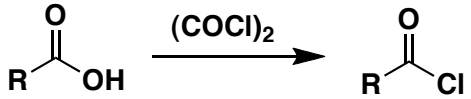


Mesylate formation

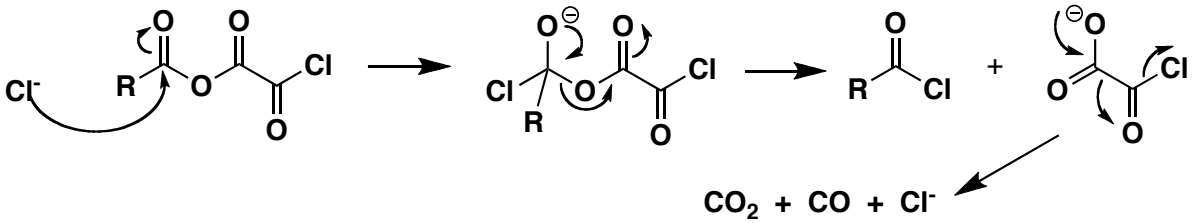


(2) In order to convert a primary alcohol to the corresponding nitrile, the alcohol must first be converted to a sulfonate or halide. DMSO is superior to ethanol as a solvent for the conversion of primary sulfonates or halides to the corresponding nitriles because DMSO solvates cations selectively, resulting in more nucleophilic anions.

(3)



When the pre-formed carboxylate salt is used, these conditions are essentially neutral.



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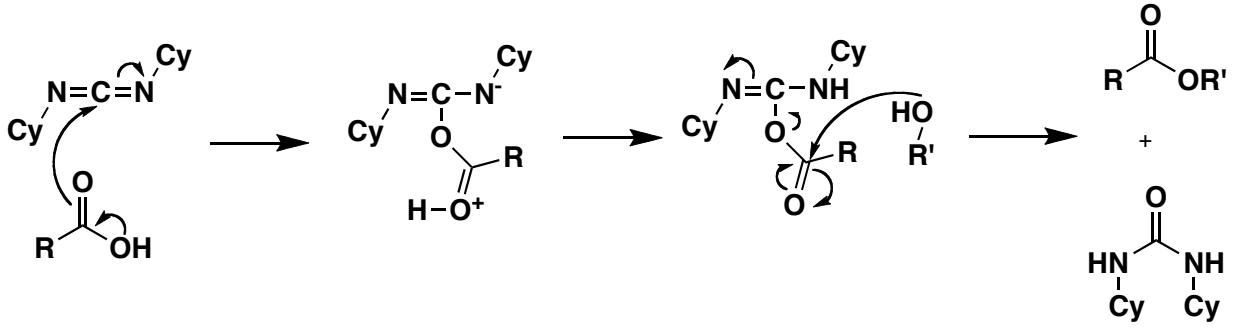

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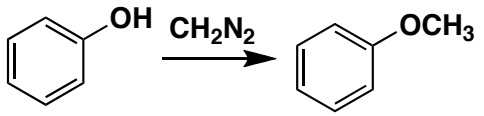
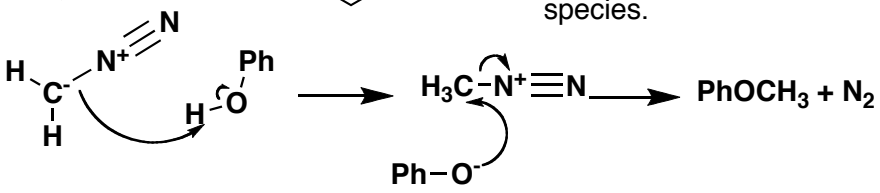


Alcohols do not work for this reaction because their pKa is too high... they do not protonate the diazomethane as phenol does in order to make the activated methylating species.



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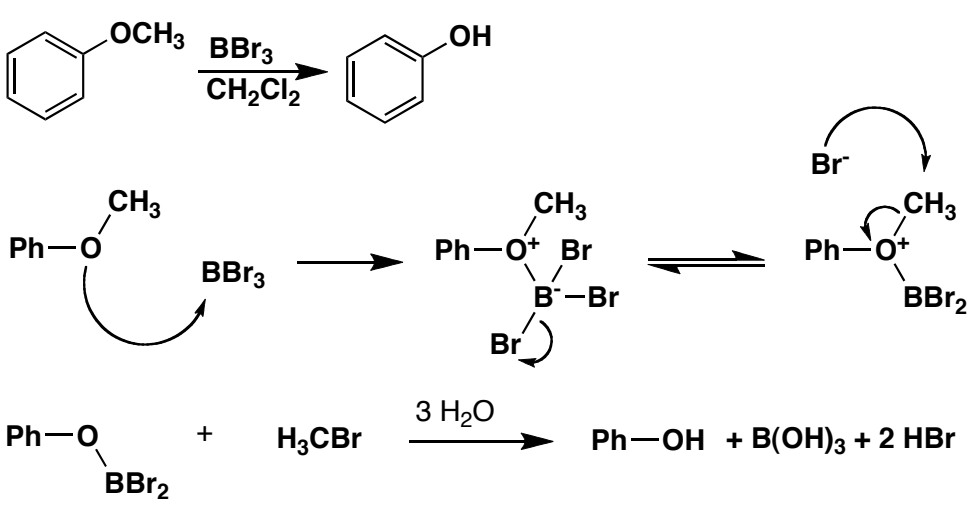

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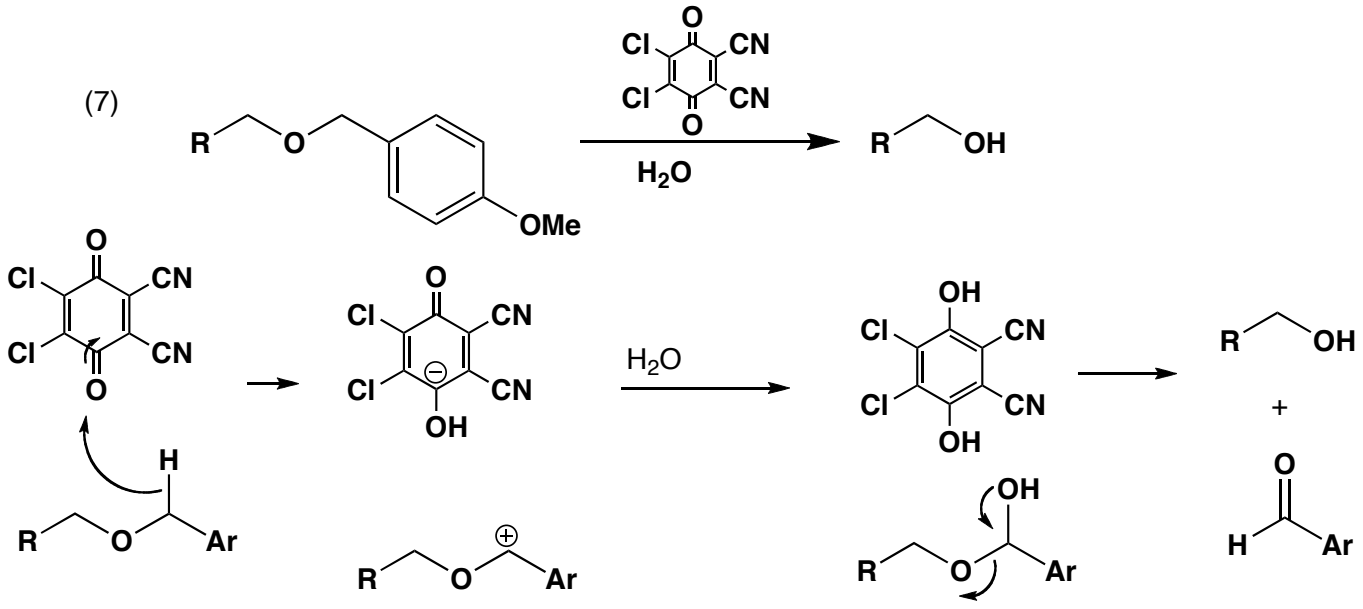
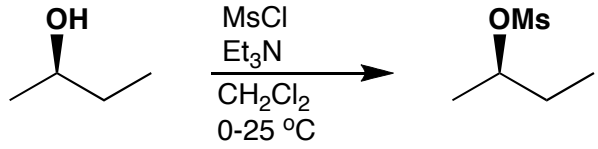
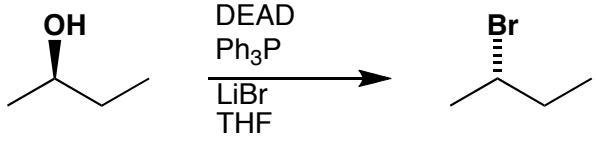
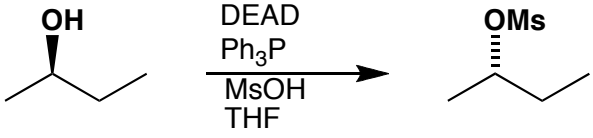
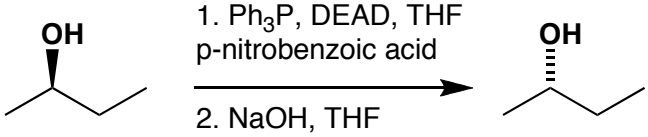


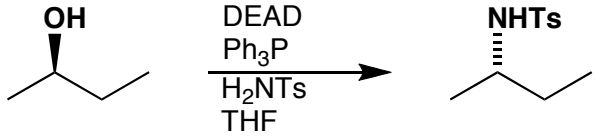
Provide conditions for effecting each of the following transformations. In this and related problems in 5.511, you will be expected to indicate reagents, an appropriate solvent, and in cases where it is critical to the success of the reaction, the number of equivalents of reagents and the reaction temperature.

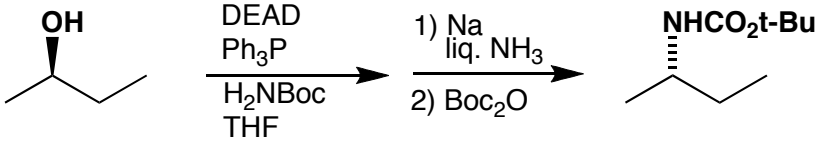


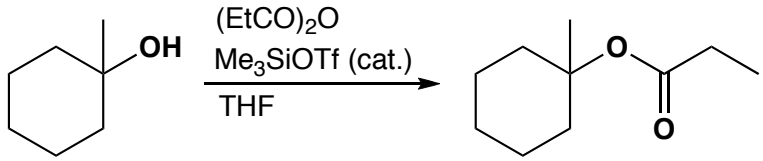


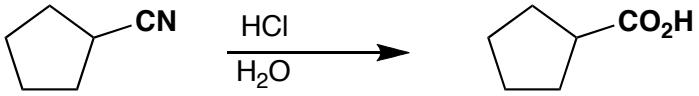


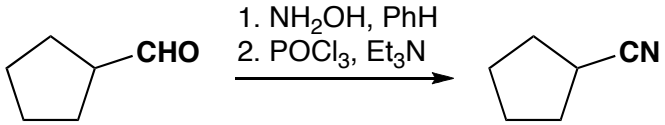


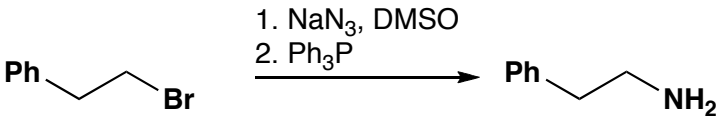


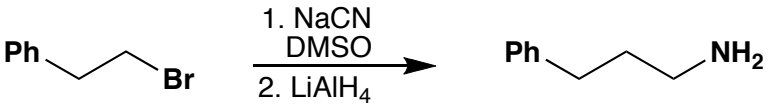


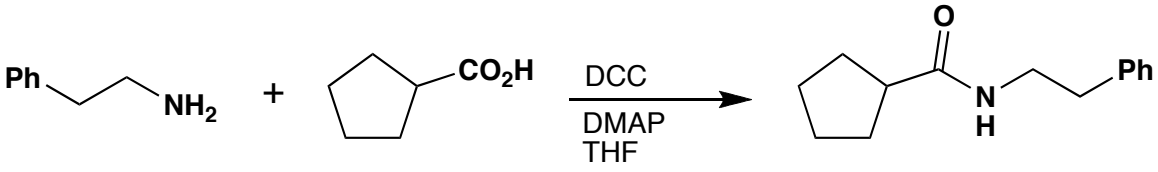


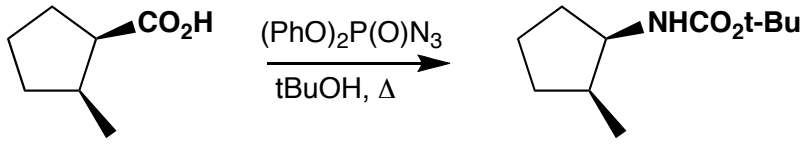




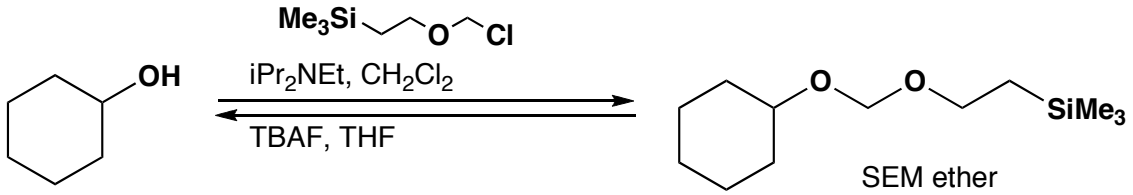






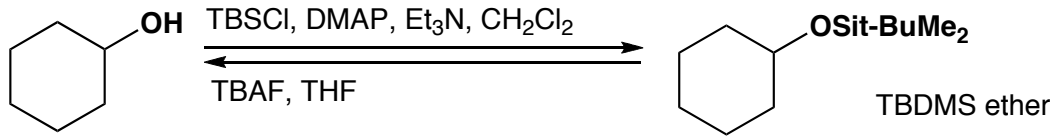


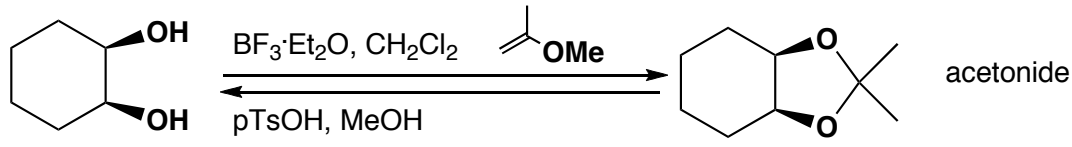
Provide conditions for the formation of each of the following protected functional groups and for their deprotection.

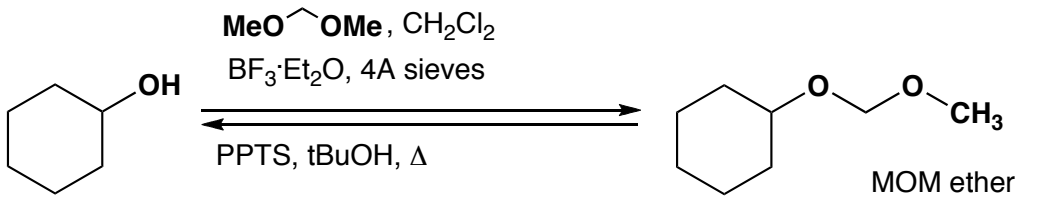


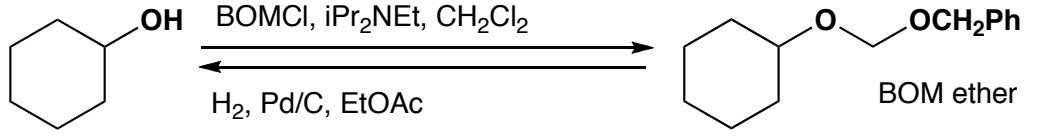
SEM ether

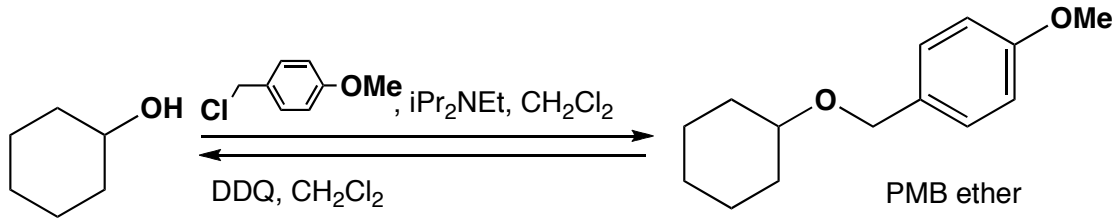

NaH, NaI, ClCH2SCH3,
DME
HgCl2, H2O, CH3CN
OH
O
SMe
MTM ether

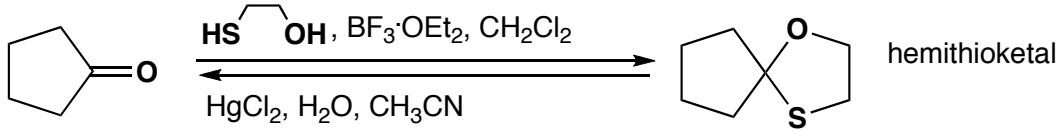

TBSCl, DMAP, Et3N, CH2Cl2
TBAF, THF
OH
OSit-BuMe2
TBDMS ether

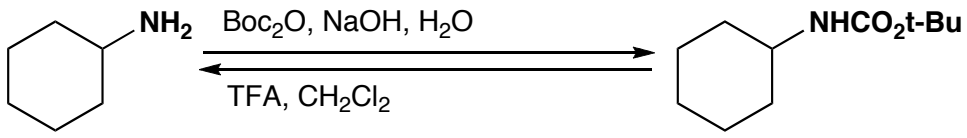

BF3·Et2O, CH2Cl2
OMe
pTsOH, MeOH
OH
OH
O
O
acetonide


MeO
OMe
, CH2Cl2
BF3·Et2O, 4A sieves
PPTS, tBuOH, Δ
OH
O
O
CH3
MOM ether


BOMCl, iPr2NEt, CH2Cl2
H2, Pd/C, EtOAc
OH
O
OCH2Ph
BOM ether

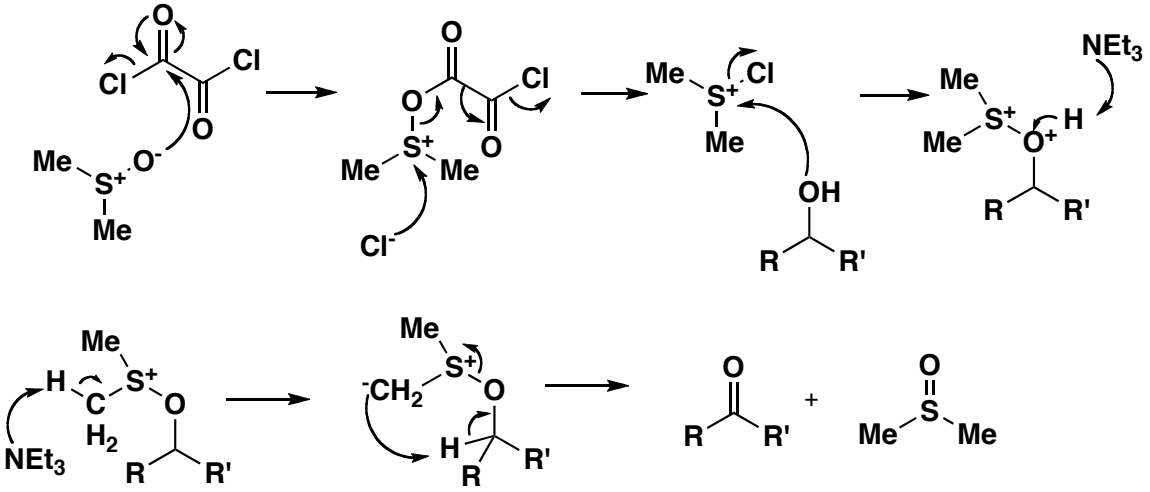

Cl
OMe
, iPr2NEt, CH2Cl2
DDQ, CH2Cl2
OH
OMe
O
PMB ether


HS
OH
, BF3·OEt2, CH2Cl2
HgCl2, H2O, CH3CN
O
O
S
hemithioketal

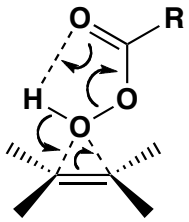

Boc2O, NaOH, H2O
TFA, CH2Cl2
NH2
NHCO2t-Bu

Part II - Oxidation Methods

(1) Swern oxidation of a secondary alcohol

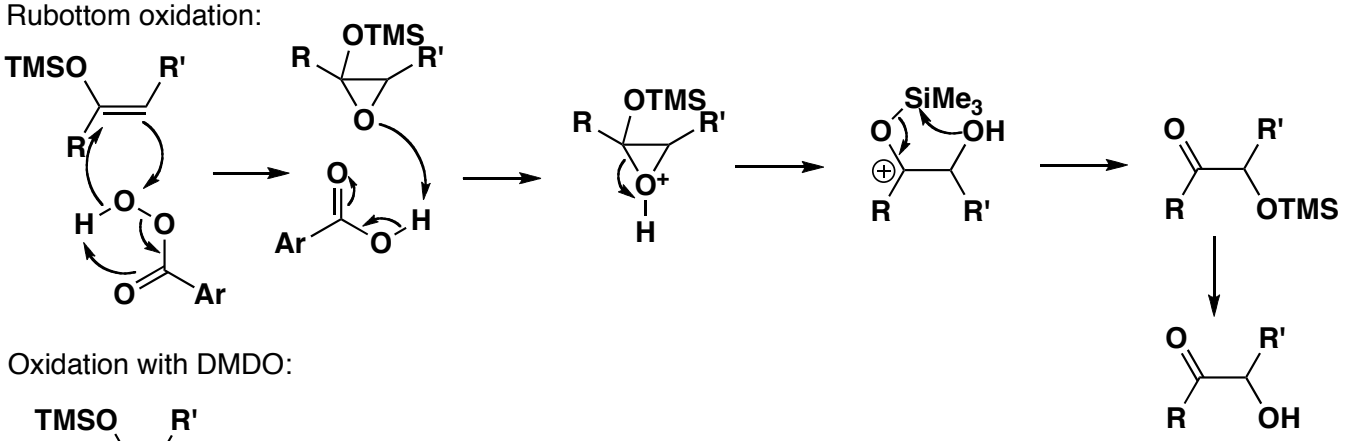


(2) Transition state for epoxidation of an alkene with a peracid

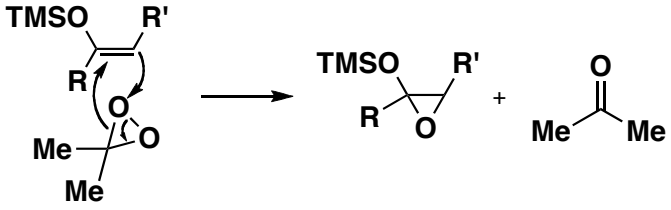


(3) Reaction of enol ethers with peracids such a *m*-CPBA (the "Rubottom Oxidation") produce α-silyloxy ketones (usually hydrolyzed in situ or during workup to the α-hydroxy derivatives). However, oxidation with DMDO often allows isolation of the epoxides. Provide a mechanism for each transformation and explain the different outcome of the reactions.

Rubottom oxidation:



Oxidation with DMDO:



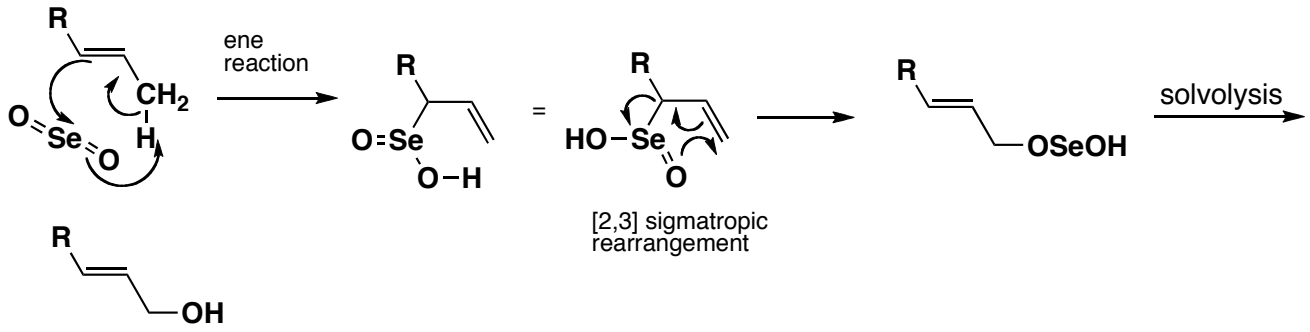
Peracid epoxidation results in the formation of a carboxylic acid which protonates the epoxide, leading to epoxide-opening and 1,4-silyl migration. Epoxidation with DMDO occurs under neutral conditions, so the epoxide does not open.

(4) Oxone = 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

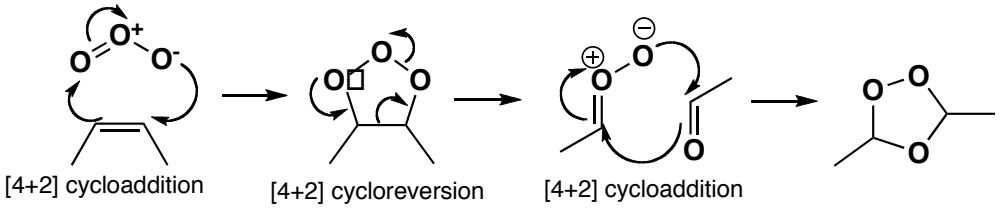
(5) Ground state oxygen Excited state "singlet" oxygen

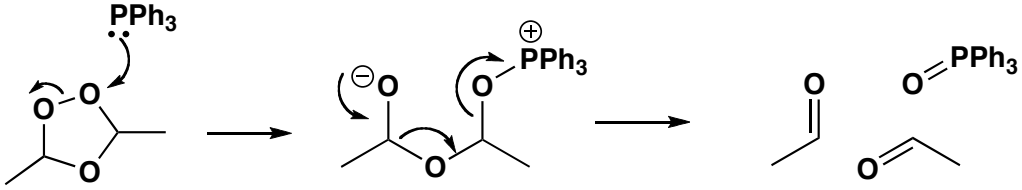
(6) A photosensitizer is a compound that absorbs light and is promoted to an excited state, then transfers that excitation to triplet oxygen in order to form singlet oxygen and regenerate the ground-state photosensitizer. This is the most common method for generation of singlet oxygen.

(7) Selenium dioxide oxidation of alkenes to allylic alcohols

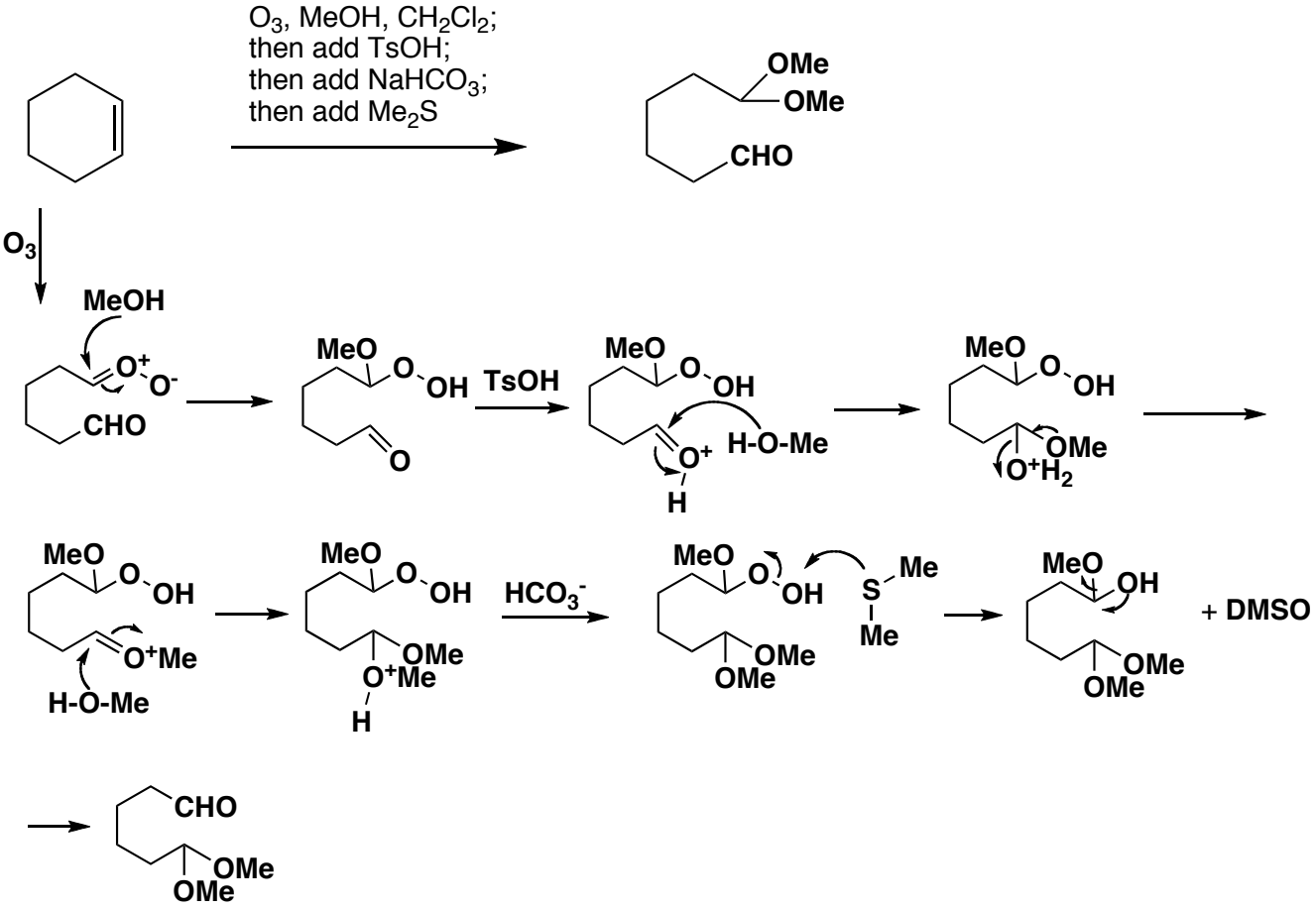


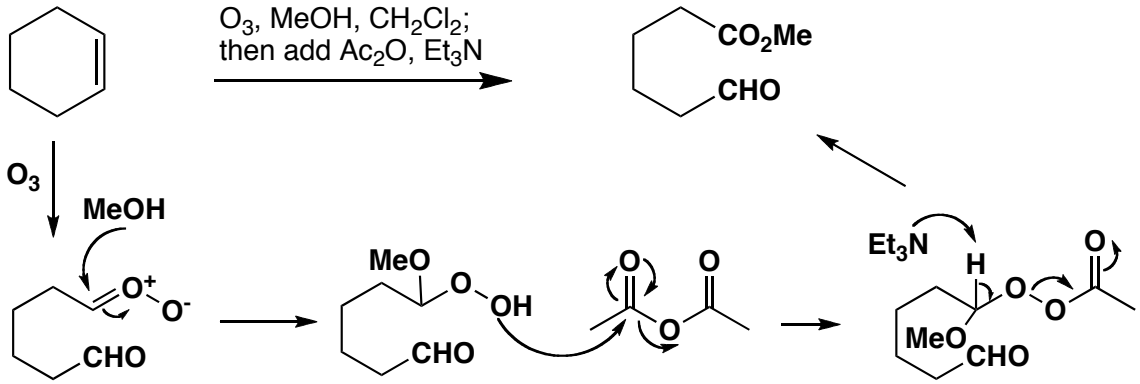
(8) Ozonolysis of a simple alkene in dichloromethane

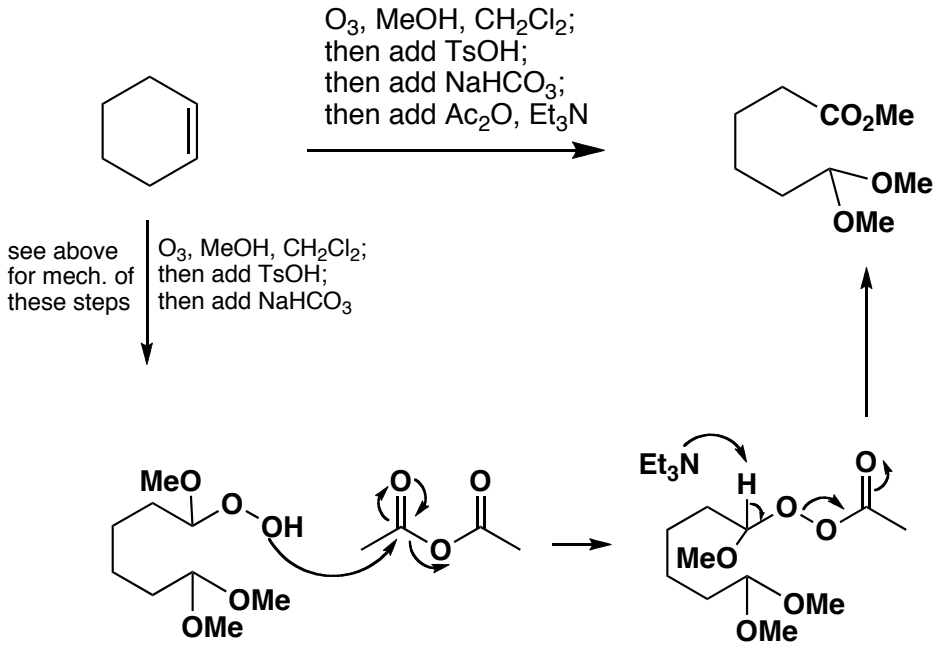




(9) *Org. Syn.* **1986**, *64*, 150



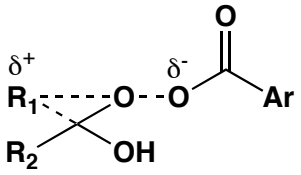




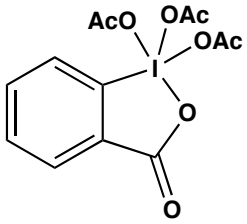
(10) Migratory aptitude in the Baeyer-Villiger oxidation:

tert-alkyl, *sec*-alkyl > benzyl, phenyl > cyclopropyl > methyl

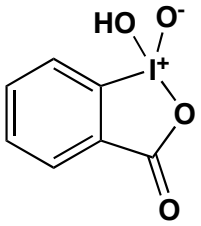
Migratory aptitude is based on the ability of a group to accomodate partial positive charge. In the transition state of the reaction, one of the alkyl groups develops a partial positive charge.



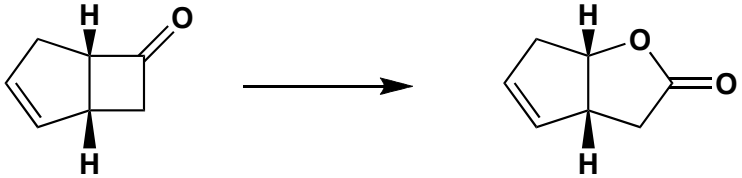
(11) Dess Martin reagent



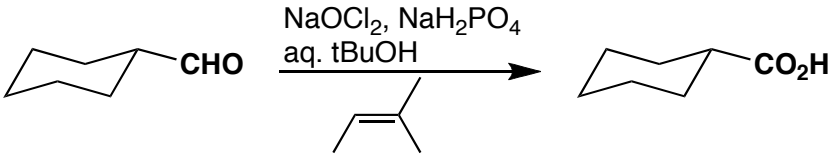
IBX

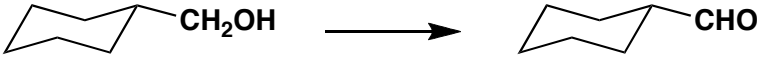


(12) H_2O_2 works for B-V oxidation in this case (even though it doesn't work for cyclohexanone) because the ring strain of the cyclobutanone makes it more reactive.



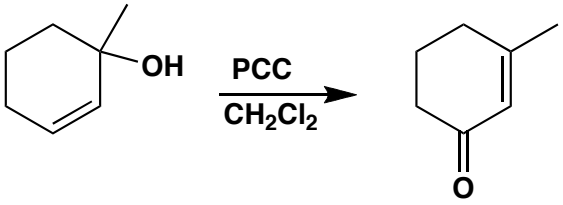
Provide detailed conditions for effecting each of the following transformations.

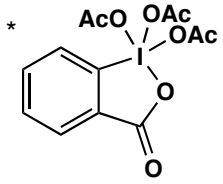


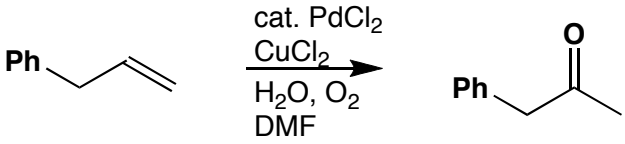


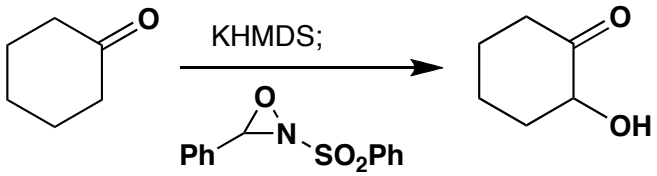
5 methods:

1. PCC, CH_2Cl_2
2. $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N
3. $CrO_3 \cdot pyr_2$, CH_2Cl_2
4. Dess-Martin periodinane*, CH_2Cl_2
5. TEMPO (cat), NaOCl, CH_2Cl_2



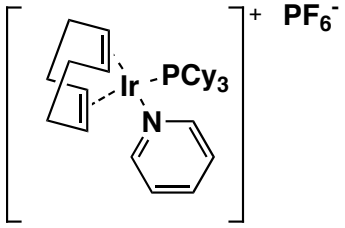




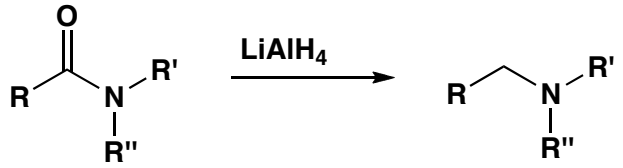


Part III - Reduction Methods

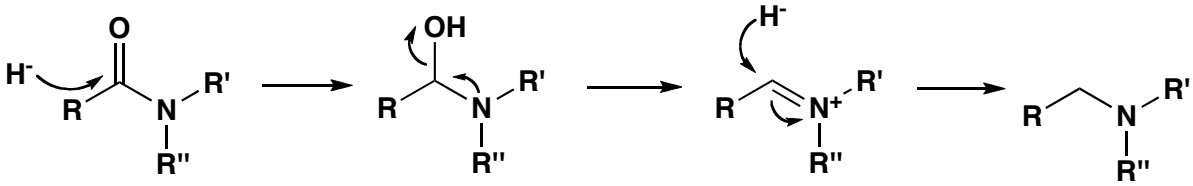
(1) Crabtree's catalyst is especially useful for hydroxyl-directed hydrogenations because the hydroxyl group coordinates very strongly to the cationic iridium center.



(2)



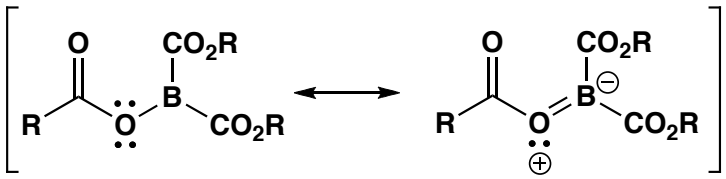
Amines are the products of this reaction because R_2N^- is a terrible leaving group compared to HO^-, so the iminium is formed rather than the aldehyde, and the iminium is reduced to the amine.



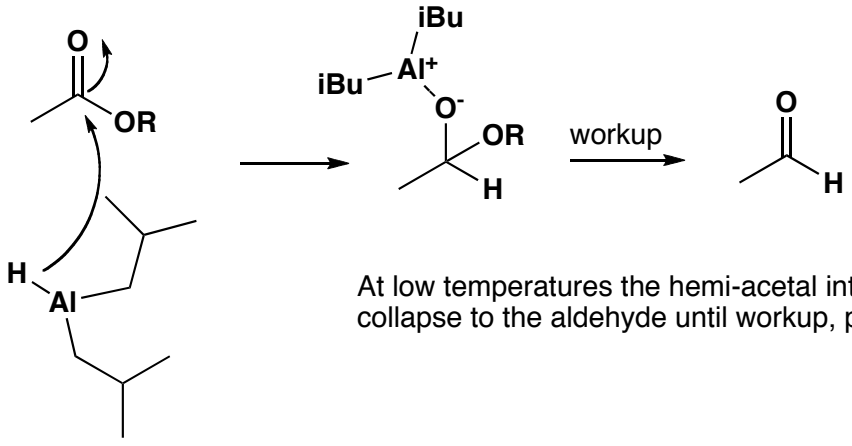
(3) In reduction of ketones and aldehydes the reactivity order is $Zn(BH_4)_2 > NaBH_4 > NaBH_3CN$ because zinc is a stronger Lewis acid than sodium, and the cyano group of $NaBH_3CN$ reduces the nucleophilicity of the hydrides due to its electron-withdrawing effect.

(4) Diborane reduces carboxylic acids to alcohols but reacts very slowly with carboxylic esters because diborane reacts with carboxylic acids to give a triacyloxyborane intermediate via protonolyis of the B-H bonds. In this intermediate the carbonyl exhibits enhanced reactivity towards the reducing agent because the ester oxygen donates some electron density to the boron, decreasing donation to the carbonyl, and thus increasing the electrophilicity of the carbonyl compared to an ester carbonyl.

$$3\ RCO_2H + BH_3 \longrightarrow (RCO_2)_3B + 3H_2$$



(5) DIBAL reduction of esters to aldehydes without over-reduction to alcohols



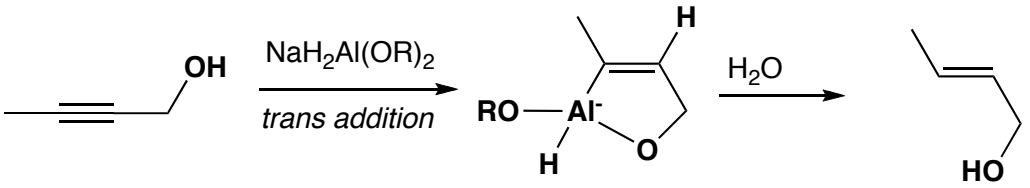
At low temperatures the hemi-acetal intermediate is stable and does not collapse to the aldehyde until workup, preventing over-reduction.

(6) Esters react slowly with borane and alane (AlH_3) but tertiary amides and lactams are reduced smoothly to amines because borane and alane form a Lewis acid-base complex with the carbonyl of the amide or lactam and then deliver the hydride in an intramolecular fashion. The carbonyl oxygen of tertiary amides and lactams are more Lewis basic than the carbonyl oxygens of esters because nitrogen is more electron-donating than oxygen, so the Lewis acid-base adduct forms more readily with tertiary amides and lactams.

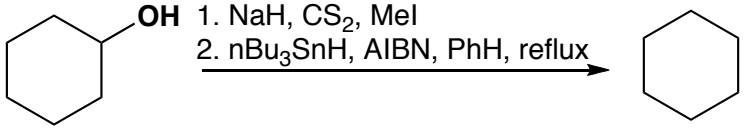
(7) Suggest several reagents that effect selective 1,2-reduction of conjugated enones to produce allylic alcohols and explain why these reagents favor 1,2-reduction while the use of $NaBH_4$ and $LiAlH_4$ often leads to mixtures of 1,2 and 1,4-addition products.

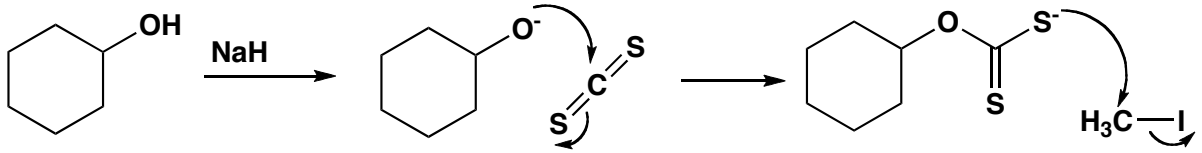
$NaBH_4$ + $CeCl_2$ (Luche reduction), DIBAL, and 9-BBN all give exclusive carbonyl reduction because the reactivity of the carbonyl group is enhanced by Lewis acid complexation at oxygen, and these reagents are more Lewis acidic than sodium borohydride and lithium aluminum hydride.

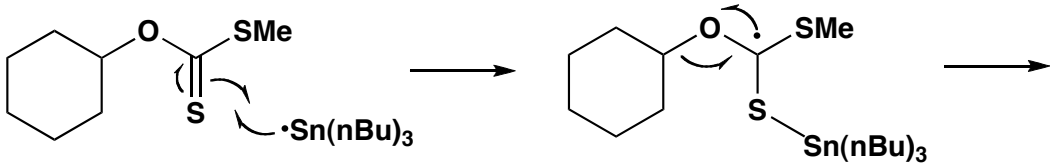
(8) The reduction of propargylic alcohols with Red-Al to (*E*)-allylic alcohols:



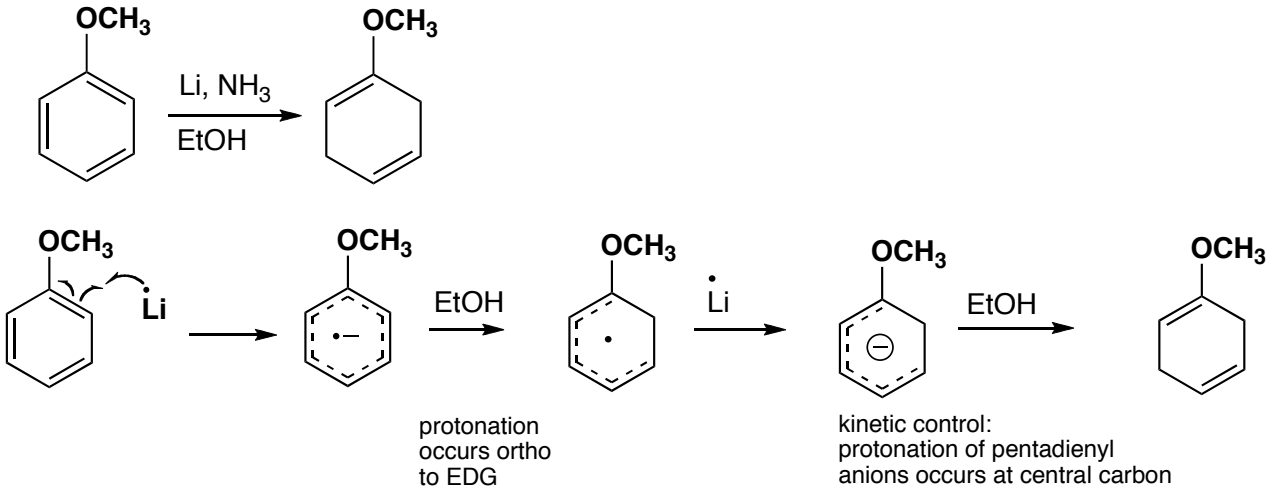
(9)







(10) Birch reduction of anisole: explain regiochemical course of reaction



Provide conditions for effecting the following transformations.