

CFQ & PP: Alcohols and Ethers

Reading

Brown and Foote: Chapters 9 and 11, except sections 9.2, 9.9C, 11.3 and 11.6

Lecture Supplement

Crown Ethers: Introduction to Molecular Recognition (p. 5 of this Thinkbook)

Optional Web Site Reading

The Chemistry of Skunk Spray (<http://www.humboldt.edu/~wfw2/skunkspray.shtml>)

Suggested Text Exercises

Brown and Foote: Chapter 9: 2, 6 – 12, 14, 17, 25 - 47

Chapter 11: 3 - 6, 8, 9, 14 - 40

Review (as needed)

Acids and bases: Brown and Foote Chapter 3

<http://web.chem.ucla.edu/~harding/supread/acidbase.pdf>

Optional Interactive Organic Chemistry CD and Workbook

Mechanisms: Acid-Catalyzed Hydrolysis of an Ether (p. 19)

Acid-Catalyzed Substitution of an Alcohol (p. 19)

Bromination of an Alcohol by Phosphorus Tribromide (p. 22)

Chromic Acid Oxidation of an Alcohol (p. 23)

Dehydration of 2-Butanol (p. 24)

Dehydration of an Unbranched Primary Alcohol (p. 24)

Intermolecular Dehydration of a Primary Alcohol (p. 27)

Propene Hydration (p. 29)

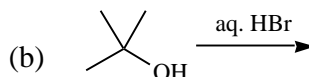
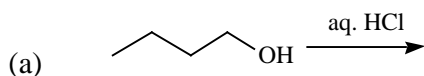
Reaction of an Alcohol with HCl (p. 30)

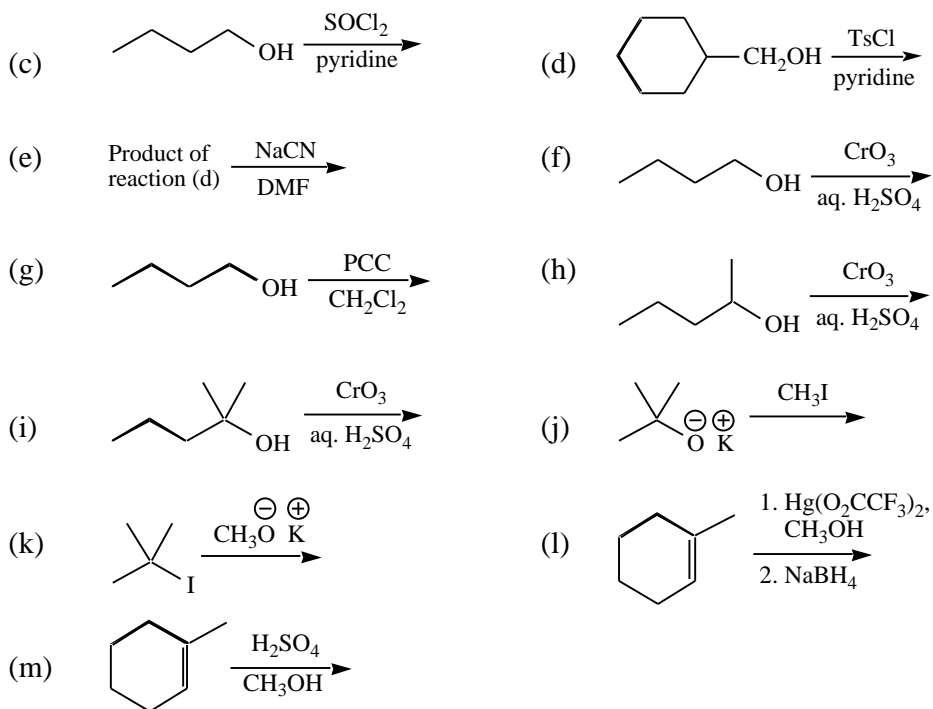
Reactivity Explorer: Alcohols (p. 41)

Ethers (p. 45)

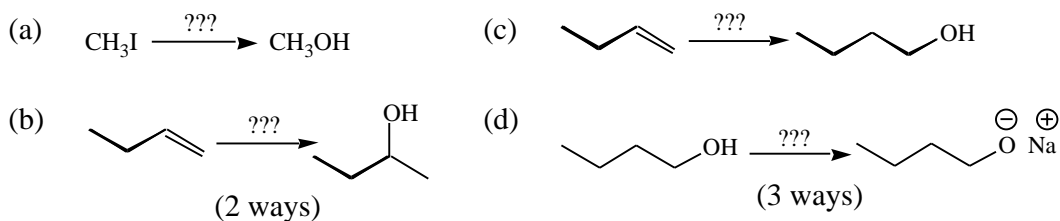
Concept Focus Questions

1. Why are the reactions of alcohols, ethers, and thiols expected to have many similarities? What features make them different?
2. What is the single most important factor that controls the basicity of any alkoxide, or any base at all?
3. Give products of each reaction, and be prepared to write the mechanism for reactions a, b, e, j - m.

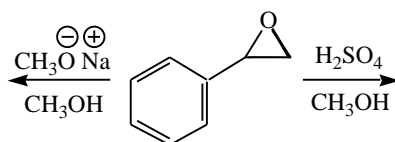




4. Suggest reagents for these transformations.

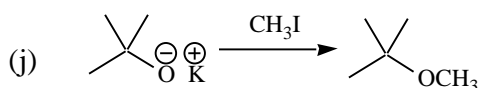
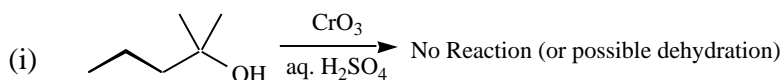
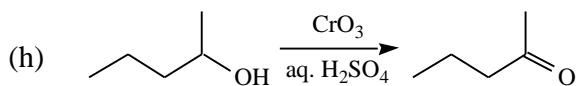
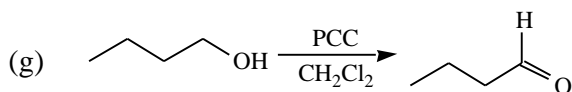
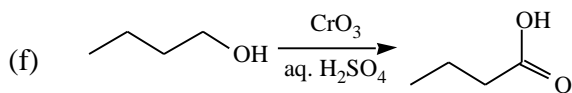
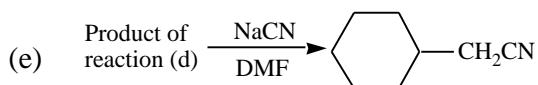
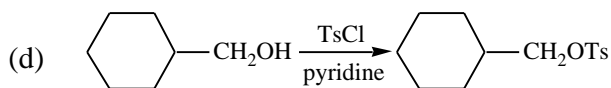
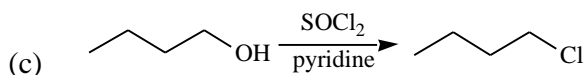
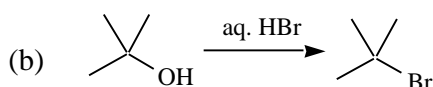
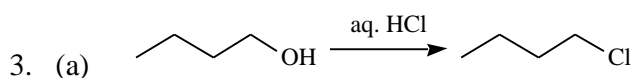


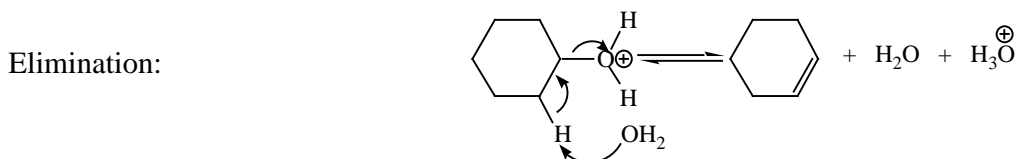
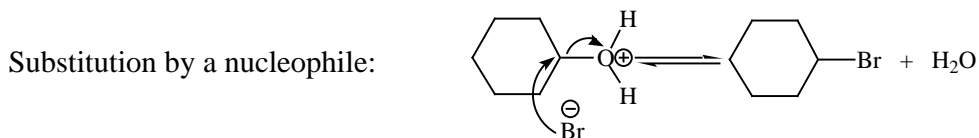
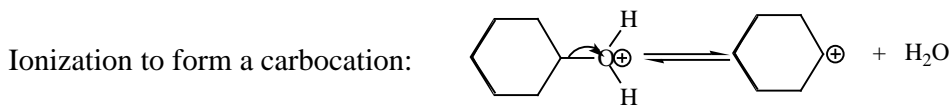
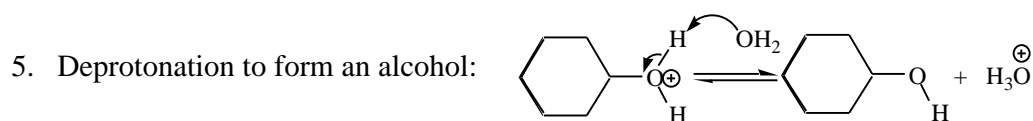
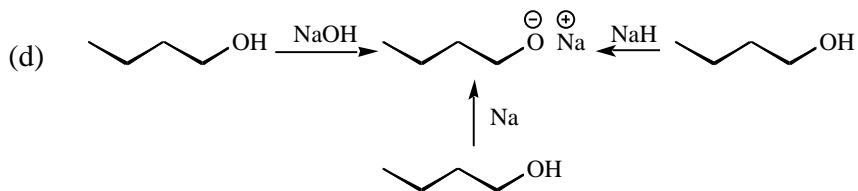
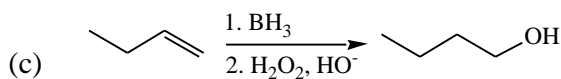
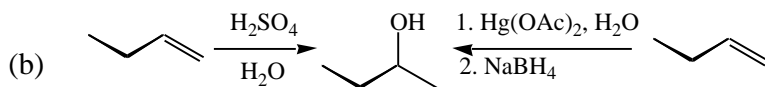
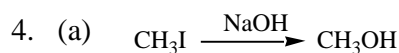
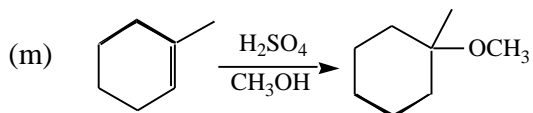
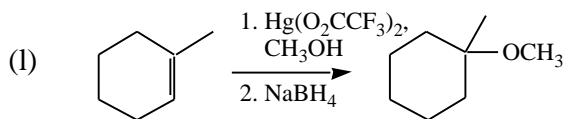
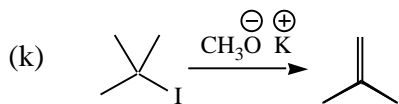
- List and illustrate the four fundamental mechanism steps of a protonated alcohol.
- Define oxidation and reduction from an organic perspective, and give specific examples.
- Why does ethylene oxide react readily with nucleophiles such as ammonia, whereas THF is inert to nucleophilic attack by ammonia?
- Give the products and mechanism of each reaction shown below. Explain why nucleophilic attack on the epoxide occurs at different sites in the two reactions.



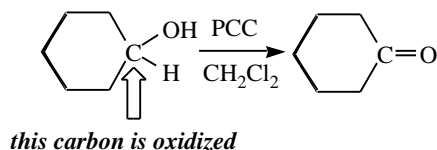
Concept Focus Questions Solutions

1. Reactions and reactivity are controlled by the electronic structure of functional groups. The alcohol, ether, and thiol functional groups have very similar electronic structures. Each has two lone pairs on the heteroatom (oxygen or sulfur), rendering that atom nucleophilic. Oxygen is more electronegative than carbon, so alcohols and ethers both have a polar carbon - oxygen bond. The alcohol and thiol groups also both have a heteroatom-hydrogen bond. Differences in electronegativity and polarizability of oxygen and sulfur, the lack of a heteroatom-hydrogen bond in an ether, and the fact that carbon and sulfur have equal electronegativities account for the differences in reactivity and reactions.
2. The single most important factor that controls the basicity of any base (including alkoxides) is the ability or driving force for the base to donate electrons to a proton.

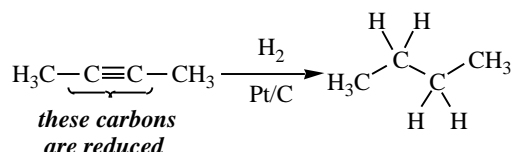




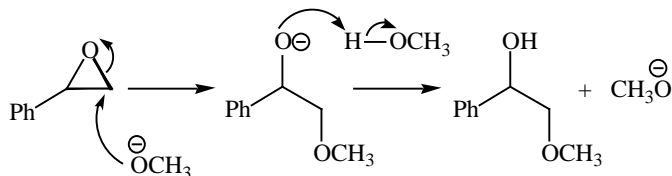
6. **Oxidation:** A carbon atom is oxidized when there is an increase in the number of bonds between that carbon and atoms that are more electronegative than carbon, usually oxygen. Example: The indicated carbon atom is oxidized because the number of bonds between carbon and oxygen is increased from one to two.



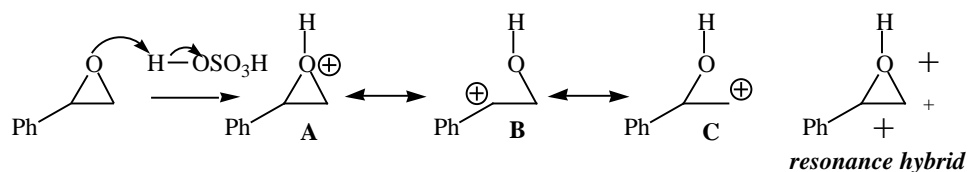
Reduction: A carbon atom is reduced when there is an increase in the number of bonds between that carbon and atoms that are less electronegative than carbon, usually hydrogen. Example: The indicated carbon atoms are reduced because the number of bonds between carbon and hydrogen is increased from zero to two.



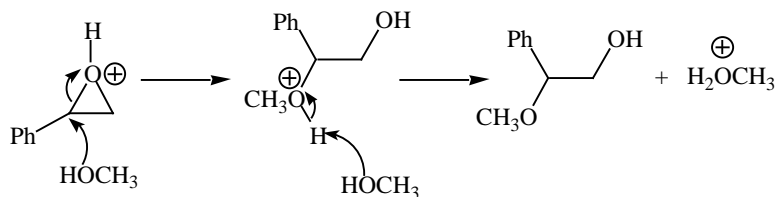
7. The carbon-oxygen bond of a generic ether R-O-R is inert to nucleophilic attack because an alkoxide (RO⁻) is a poor leaving group. Thus, we expect THF to be inert to nucleophilic attack. An epoxide has significant ring strain (about 27 kcal mol⁻¹). Breaking the C-O bond relieves this ring strain. This release of ring strain lowers the transition state energy enough to overcome the poor leaving group ability of RO⁻, so that the C-O bond of an epoxide can be cleaved by a strong nucleophile.
8. Attack by a strong nucleophile such as CH₃O⁻ (methoxide) on an epoxide occurs at the least hindered carbon, similar to an S_N2 reaction. Because methoxide is regenerated in the last step, this mechanism suggests that only a catalytic amount of CH₃O⁻ is needed.



Attack by a weak nucleophile such as methanol (CH₃OH) can occur only when the epoxide has been protonated so that a better leaving group is formed. Under these conditions, the epoxide C-O bonds are weakened because the leaving group has been improved. The protonated epoxide can be viewed as a resonance hybrid.



A weak nucleophile attacks the resonance hybrid carbon with the greatest $+$. The magnitude of the $+$ is determined by the relative importance of the resonance contributors. (Review the resonance tutorial on the Hardinger web site if necessary.) Resonance contributor **A** is the most important because all atoms have a full octet. Contributor **B** is a secondary carbocation with benzene ring resonance whereas contributor **C** is a primary carbocation, so contributor **B** is more important than **C**. Weighing these relative contributions in the resonance hybrid reveals that the benzylic carbon has more $+$ than the primary carbon, so the nucleophile attacks at the benzylic carbon. (This same reasoning applies to any three-membered ring with two carbons and a third atom bearing a positive charge, such as a protonated epoxide, a halonium ion, or a mercurinium ion.)

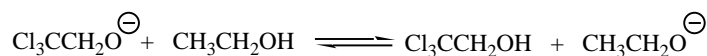


Because the proton source is regenerated in the last step, this mechanism suggests that only a catalytic amount of acid is needed.

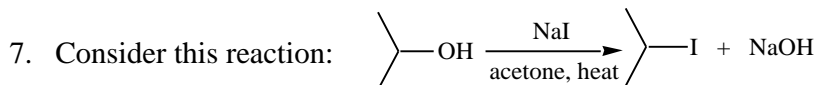
Practice Problems

- List two significant similarities between alcohols and ethers. Clearly illustrate each similarity with a pair of reactions or other drawings.
- List two significant differences between alcohols and ethers. Clearly illustrate each difference with a pair of reactions or other drawings.
- Select the strongest and weakest acid: CH_3OH , $\text{CF}_3\text{CH}_2\text{OH}$ and $(\text{CH}_3)_3\text{COH}$.
- Give an example of an alcohol that has a higher $\text{p}K_a$ than cyclohexanol. (Use the index of your text to find the structure of this molecule if necessary.) Briefly explain your answer.
- Select the most stable alkoxide: $\text{Cl}_3\text{CCH}_2\text{O}^-$, $\text{F}_3\text{CCH}_2\text{O}^-$, $(\text{CH}_3)_3\text{CCH}_2\text{O}^-$ and $\text{CH}_3\text{CH}_2\text{O}^-$.

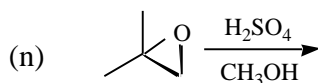
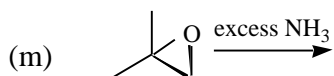
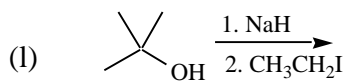
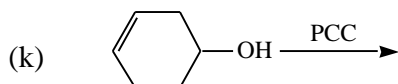
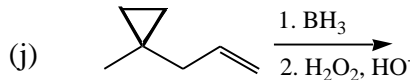
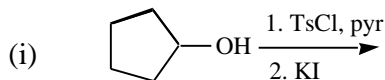
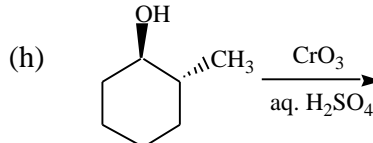
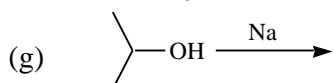
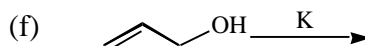
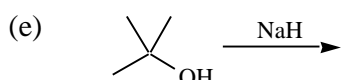
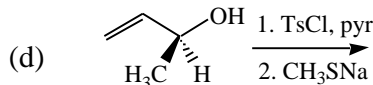
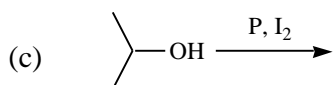
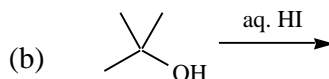
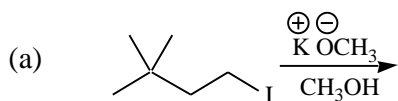
6. Consider this equilibrium.

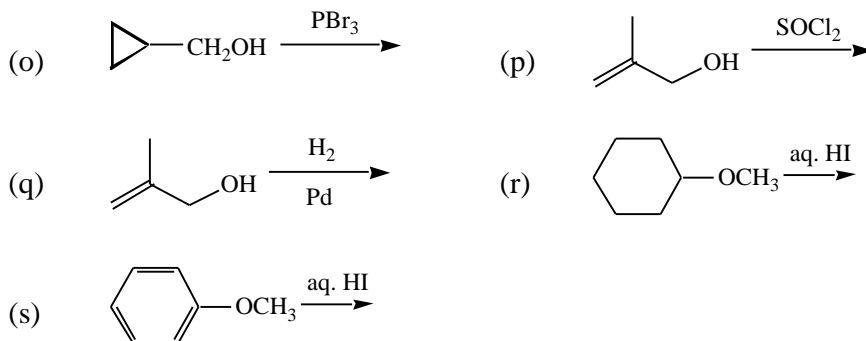


- Where does the equilibrium lie? Briefly explain your reasoning.
- Give the structure of an alcohol which is more acidic than the strongest acid in this equilibrium. Briefly explain your reasoning.
- Give the structure of an alcohol which is less acidic than the weakest acid in this equilibrium. Briefly explain your reasoning.

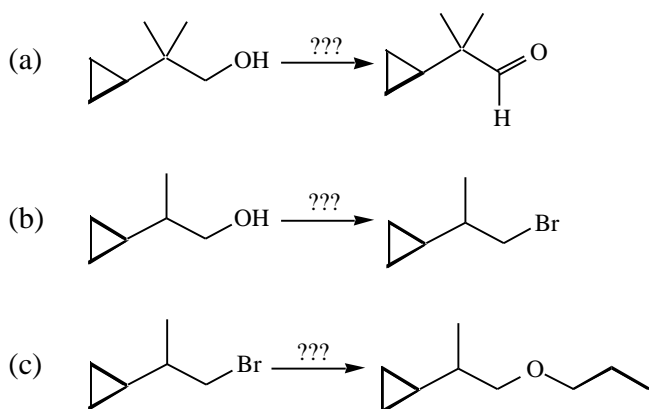


- Very briefly explain why the reaction does not occur as written.
 - Changing only the alcohol or NaI (not both) modify the reaction so that it does occur. Write a complete mechanism for your new reaction.
8. Provide the organic product(s) of the following reactions. Pay careful attention to stereochemistry. If more than one product is formed, indicate which product (if any) is the major product. If no reaction occurs, write "NR."

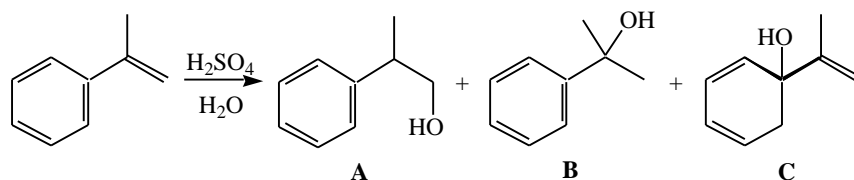




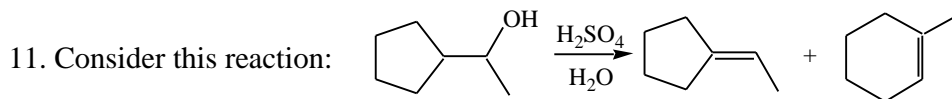
9. Write the best reagents above each reaction arrow. If the transformation cannot be achieved in a single step by any reagents, write "NR."



10. Consider this reaction:

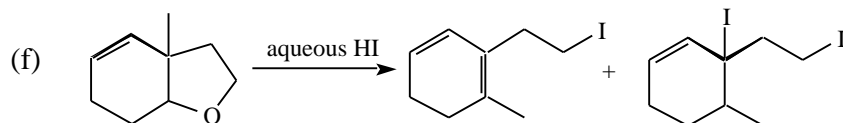
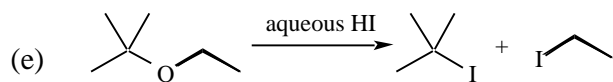
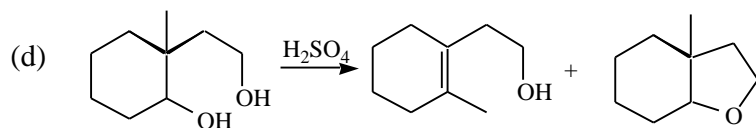
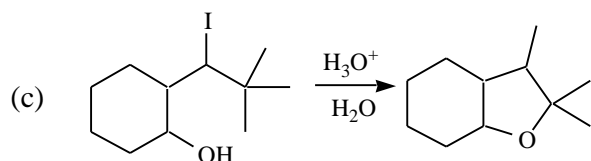
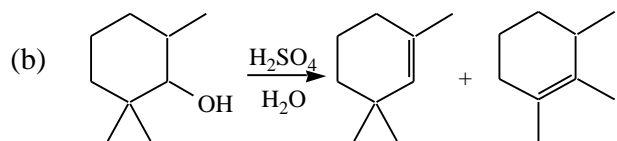
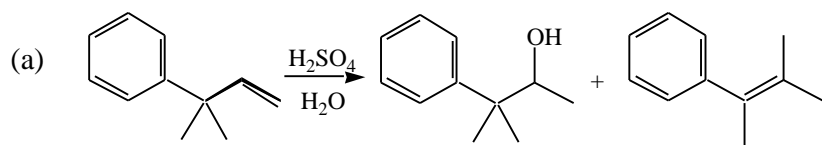


- (a) Provide a complete mechanism for the formation of the major product.
 (b) Briefly explain your choice of major product.

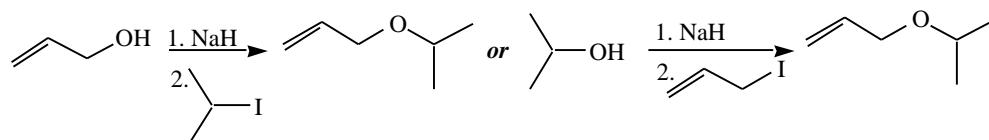


- (a) Provide a mechanism. Label the rate-determining step with "rds."
 (b) Very briefly explain why this reaction does not proceed in the absence of H_2SO_4 .

12. Provide detailed mechanisms for the following reactions.



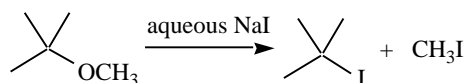
13. Which of the following two routes to allyl isopropyl ether is more efficient? Explain.



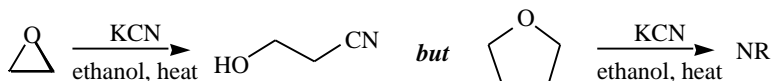
14. Choose the best synthetic route to $(\text{CH}_3)_3\text{COCH}_3$:

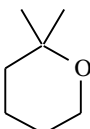

- React $(\text{CH}_3)_3\text{COH}$ with K, then add CH_3I
- React $(\text{CH}_3)_3\text{COH}$ with NaOH, then add CH_3I
- React CH_3OH with K, then add $(\text{CH}_3)_3\text{CI}$

15. Briefly explain why this reaction does not occur as written.



16. Explain why ethylene oxide is attacked by cyanide ion, but THF is not.

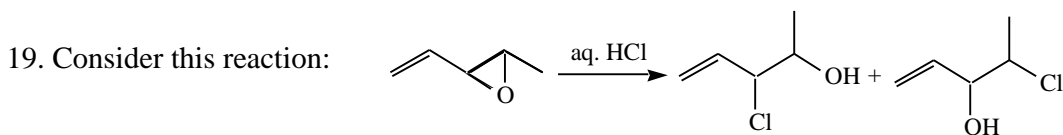


17. Consider the reaction of  and  with aqueous HI.

- (a) Give the mechanism and product of the faster reaction.
 (b) Explain your choice of the faster reaction.

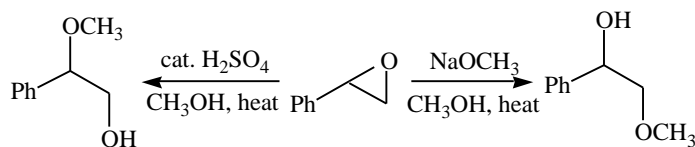
18. Alcohols and ethers are often used as reaction solvents, because they are inert to nucleophiles such as iodide ion. Epoxides would be poor reaction solvents because they react with a wide variety of nucleophiles.

- (a) Write a chemical equation that illustrates the reaction of an epoxide with iodide ion in CH_3OH .
 (b) Why do epoxides react with iodide ion, but ethers and alcohols are inert to iodide ion?

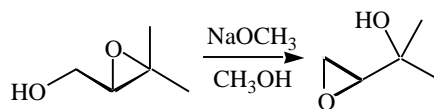


- (a) Provide a complete mechanism for the formation of the major product.
 (b) Briefly explain your choice of major product.

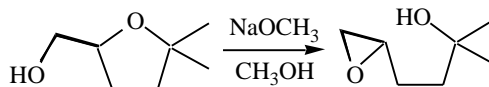
20. Explain why these reactions give different products.



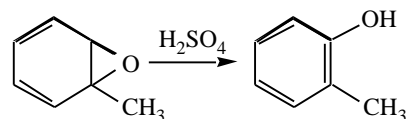
21. The reaction shown below is an example of the Payne rearrangement.



- (a) Write a mechanism for this reaction. Hint: The mechanism has three steps.
 (b) Briefly explain why the similar reaction shown below does not occur.



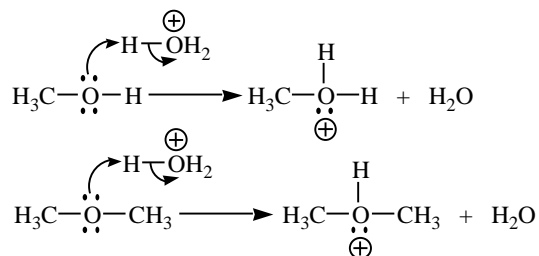
22. List two significant driving forces for this reaction:



Practice Problems Solutions

1. Similarity #1: Both have oxygen atoms bear two lone pairs, so both can function as poor nucleophiles or weak bases.

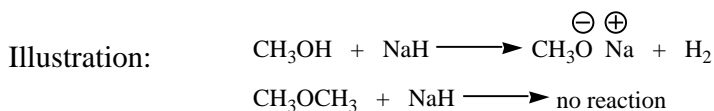
Illustration:



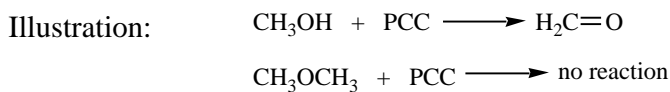
Similarity #2: Hydroxide and alkoxide ions are not good leaving groups, so both are inert to nucleophilic attack in the absence of strong acid.

Illustration: CH_3OH or $\text{CH}_3\text{OCH}_3 \xrightarrow{\text{NaI}}$ no reaction

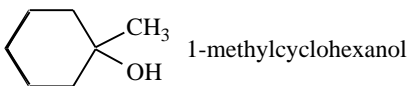
2. Difference #1: Alcohols have a hydrogen atom that may be removed by base; ethers do not.



Difference #2: Primary and secondary alcohol can be oxidized to aldehydes or ketones; ethers cannot be oxidized to aldehydes or ketones.



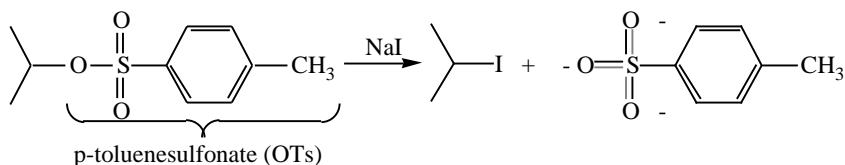
3. To determine relative acidity, examine the basicity of the corresponding conjugate bases (review the Organic Acids and Bases CFQ on the Hardinger web site if needed). The role of a base is to share a pair of electrons with a hydrogen atom to form a new covalent bond, so the driving force for sharing of this electron pair influences basicity. The driving force is a result of the oxygen atom's preference to be neutral, and to form new bonds by sharing lone pairs. Any structural feature that decreases the magnitude of negative charge or lone pair electron density on the oxygen atom decreases basicity. The question then is this: How do the changes in structure (CF_3 or CH_3 replacing the hydrogen atoms of methanol) influence the electron density of the oxygen atom? Trifluoromethyl (CF_3) is an electron-withdrawing group, so it decreases the electron density on oxygen by the inductive effect. This makes $\text{CF}_3\text{CH}_2\text{O}^-$ (trifluoroethoxide) a weaker base than CH_3O^- (methoxide). Alkyl groups such as methyl are weak electron-donating groups, resulting in an increase in electron density on the oxygen atom, also by the inductive effect. This makes $(\text{CH}_3)_3\text{CO}^-$ (*tert*-butoxide) a stronger base than methoxide. (A more rigorous examination of the problem would also consider other factors at work such as steric effects on solvation.) Thus for basicity we predict: $\text{CF}_3\text{CH}_2\text{O}^-$ (weakest base) $<$ CH_3O^- $<$ $(\text{CH}_3)_3\text{CO}^-$ (strongest base). Since stronger conjugate bases have weaker conjugate acids, the acidity prediction is: $\text{CF}_3\text{CH}_2\text{OH}$ (strongest acid) $>$ CH_3OH $>$ $(\text{CH}_3)_3\text{COH}$ (weakest acid).
4. Higher $\text{p}K_a$ means weaker acid, which in turn means stronger conjugate base. Thus, we need to design a molecule which is more basic (more nucleophilic toward a proton) than the conjugate base of cyclohexanol. Amplifying the electron density on the oxygen increases basicity. This effect can be achieved by adding electron-donating groups close to the OH group. Thus, we expect the anion of the tertiary alcohol 1-methylcyclohexanol to be a stronger base, and the alcohol to have a higher $\text{p}K_a$ than cyclohexanol. (The extra methyl group also has a steric effect on solvation of the alkoxide that results in increased basicity.)



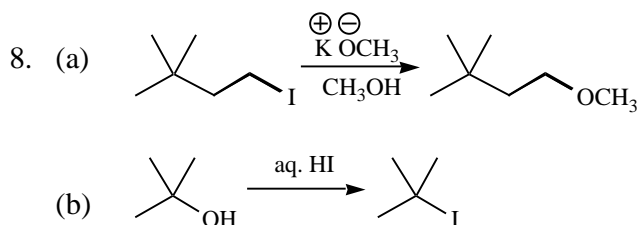
5. The most stable alkoxide has the smallest magnitude of negative charge on the oxygen (and thus also be the weakest base). In this series of alkoxides, we can compare the effect of replacing a hydrogen atom (the last structure) with a chlorine atom (first structure), fluorine atom or methyl group. Chlorine and fluorine are both electron withdrawing by the inductive effect, resulting in decreased charge density on the oxygen atom and increased stability. Fluorine is more electronegative than chlorine so the oxygen atom of the trifluoro alkoxide has a small electron density than the oxygen atom of the trichloro alkoxide. Alkyl groups such as methyl are weak electron donors, resulting in an increase in the charge density of the oxygen atom.

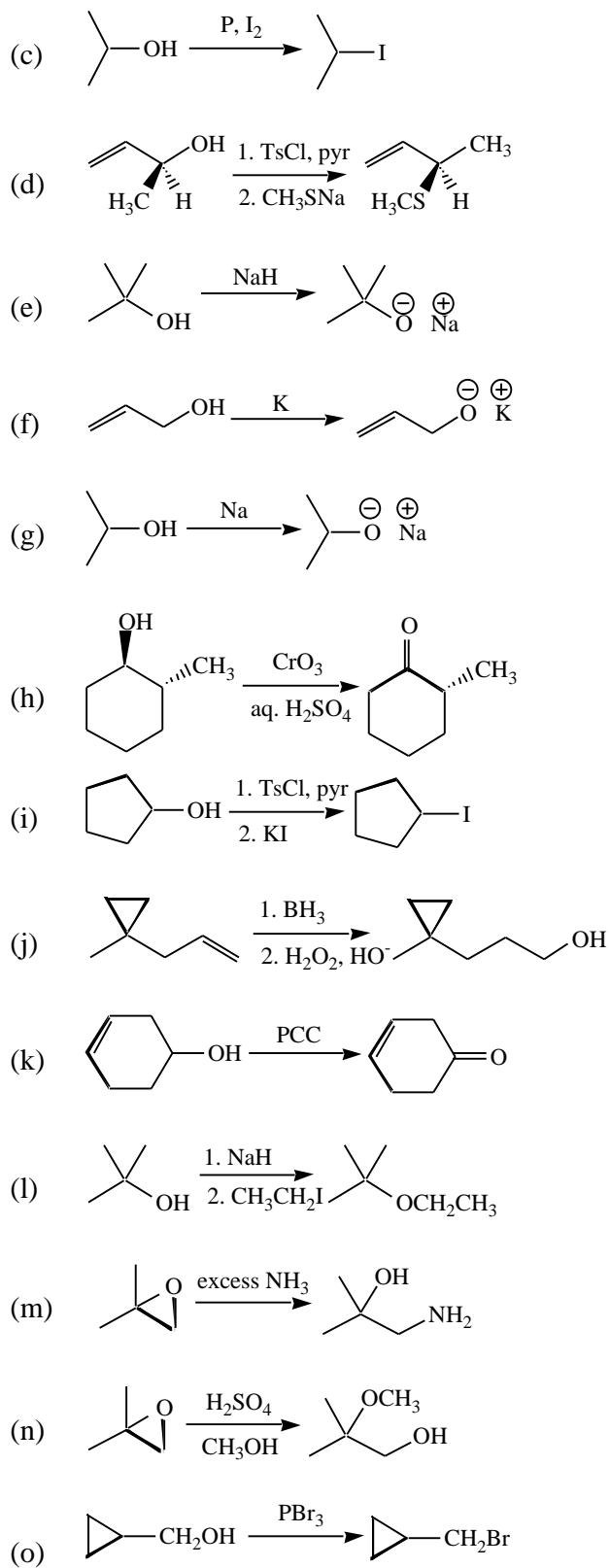
Thus the order of basicity and stability is: $\text{F}_3\text{CCH}_2\text{O}^-$ (most stable; weakest base) $>$ $\text{Cl}_3\text{CCH}_2\text{O}^- > \text{CH}_3\text{CH}_2\text{O}^- > (\text{CH}_3)_3\text{CCH}_2\text{O}^-$ (least stable; strongest base).

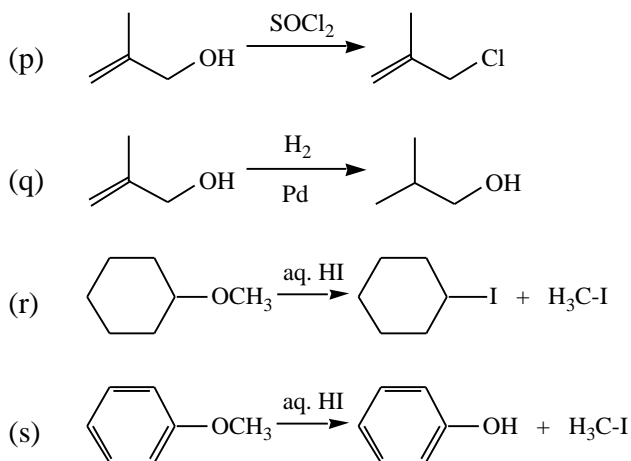
6. (a) Any equilibrium favors the most thermodynamically stable side. For an acid/base equilibrium, this is the side of the equilibrium with the weakest acid and base. Because $\text{Cl}_3\text{CCH}_2\text{O}^-$ is a weaker base than $\text{CH}_3\text{CH}_2\text{O}^-$ (see previous question), this equilibrium lies to the left.
- (b) The strongest acid in the equilibrium is $\text{Cl}_3\text{CCH}_2\text{OH}$. Thus, we need to design a base which is weaker than $\text{Cl}_3\text{CCH}_2\text{O}^-$. A weaker base would have a smaller degree of alkoxide oxygen charge, as discussed in the previous answer. Fluorine is more electronegative than chlorine, so $\text{F}_3\text{CCH}_2\text{O}$ has less charge on the oxygen than $\text{Cl}_3\text{CCH}_2\text{O}^-$. This means $\text{F}_3\text{CCH}_2\text{O}^-$ is a weaker base than $\text{Cl}_3\text{CCH}_2\text{O}^-$, and $\text{F}_3\text{CCH}_2\text{OH}$ is a stronger acid than $\text{Cl}_3\text{CCH}_2\text{OH}$.
- (c) Using the same logic as in the part (b) answer, we need an alkoxide that has more negative charge on the oxygen than does $\text{CH}_3\text{CH}_2\text{O}^-$. This can be achieved with electron-donating groups, such as alkyl groups. Thus, $(\text{CH}_3)_3\text{CCH}_2\text{OH}$ is a weaker acid than $\text{CH}_3\text{CH}_2\text{OH}$.
7. (a) The reaction does not proceed as written because hydroxide is a poor leaving group. It cannot be replaced in a substitution reaction without prior conversion to a better leaving group.
- (b) Replacing the hydroxide with a better leaving group will allow the reaction to proceed. A sulfonate such as p-toluenesulfonate (OTs) is a superior leaving group due to the resonance stabilization gained when it leaves.



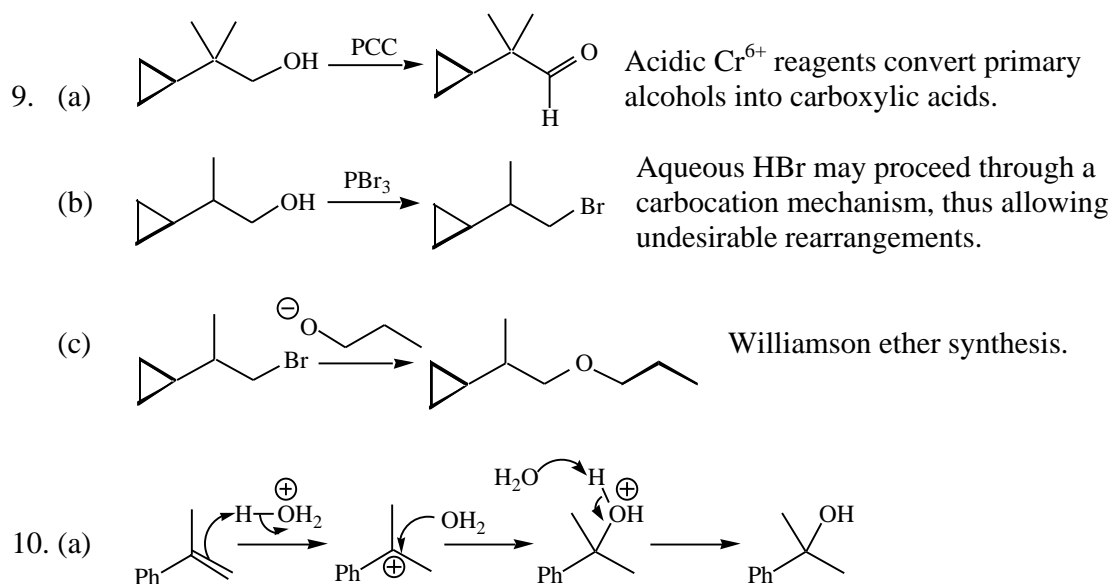
Alternate answer: NaI can be replaced with a reagent that converts the OH into a better leaving group prior to nucleophilic attack by iodide. Such reagents include PBr_3 , SOCl_2 , aqueous HI, or P/I_2 .





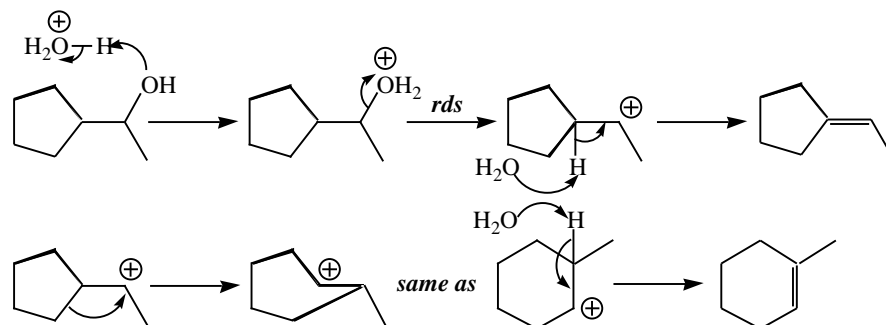


A phenyl cation ($C_6H_5^+$ or Ph^+) is harder to form than other types of secondary carbocations.

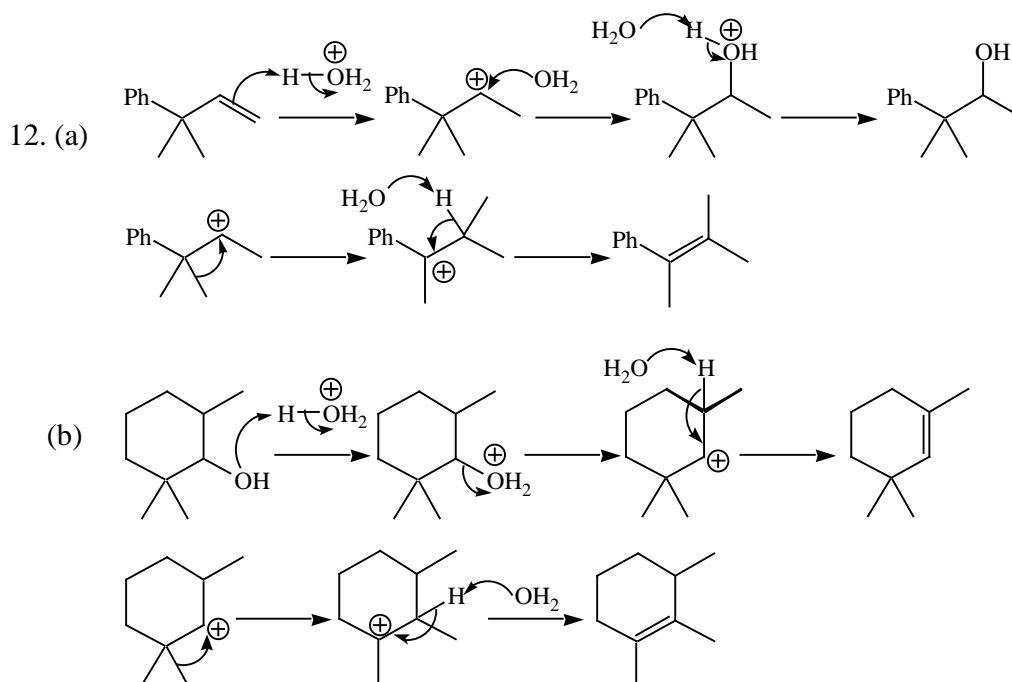


(b) Initial reaction of the alkene with H_3O^+ can form two carbocations. The more stable benzylic tertiary carbocation (shown in the mechanism above) is formed in preference to the less stable primary carbocation. This is the rate-determining step, and thus controls the product distribution. Formation of the more stable carbocation is the mechanistic basis for Markovnikov's rule.

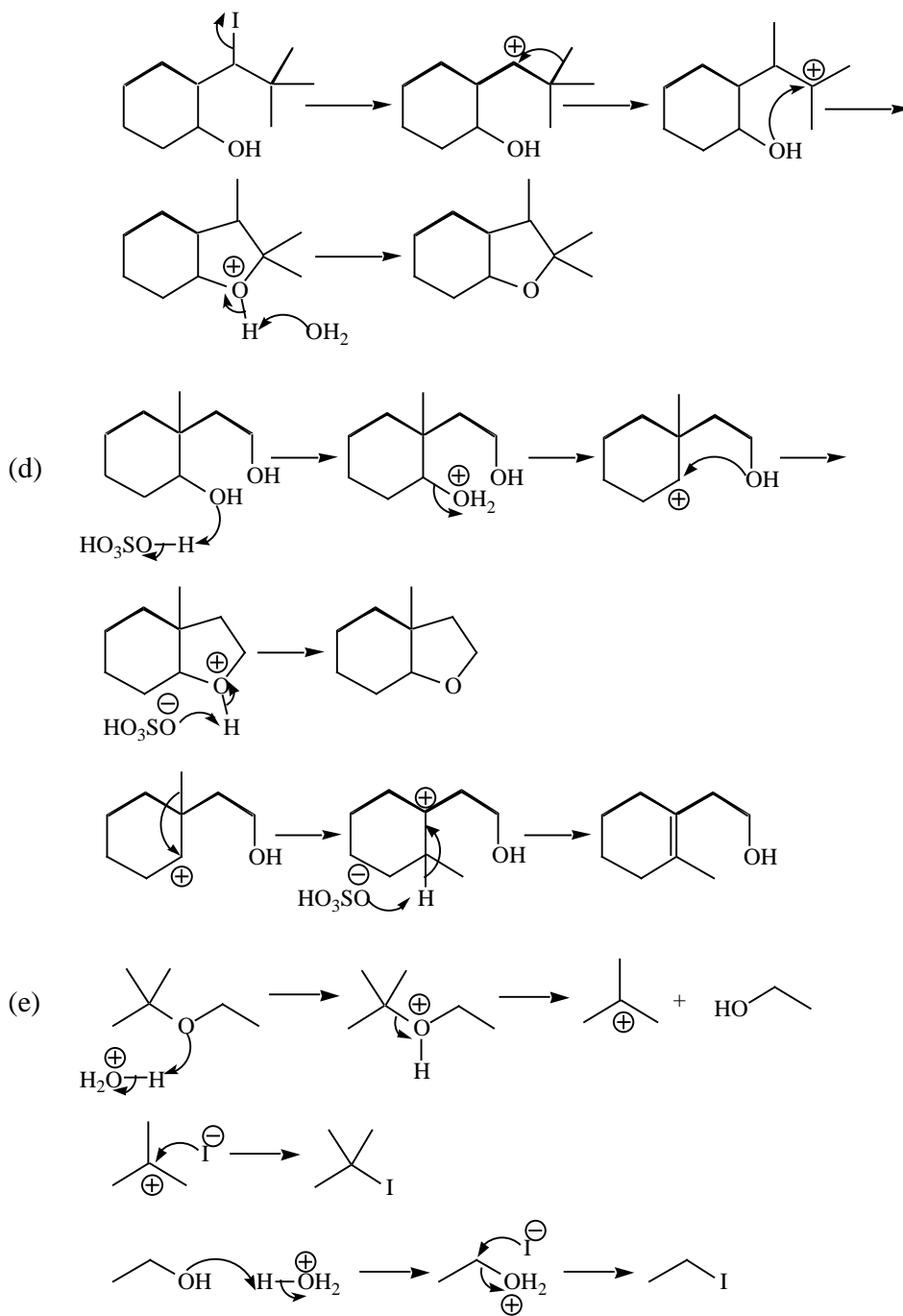
11. (a) In water, H_2SO_4 is completely ionized to form H_3O^+ . Only in instances in which there is no water, or in which the number of moles of water is less than the number of moles of H_2SO_4 will there be any non-ionized H_2SO_4 in solution. Thus, in aqueous H_2SO_4 , the material that protonates the alcohol is H_3O^+ , not H_2SO_4 .



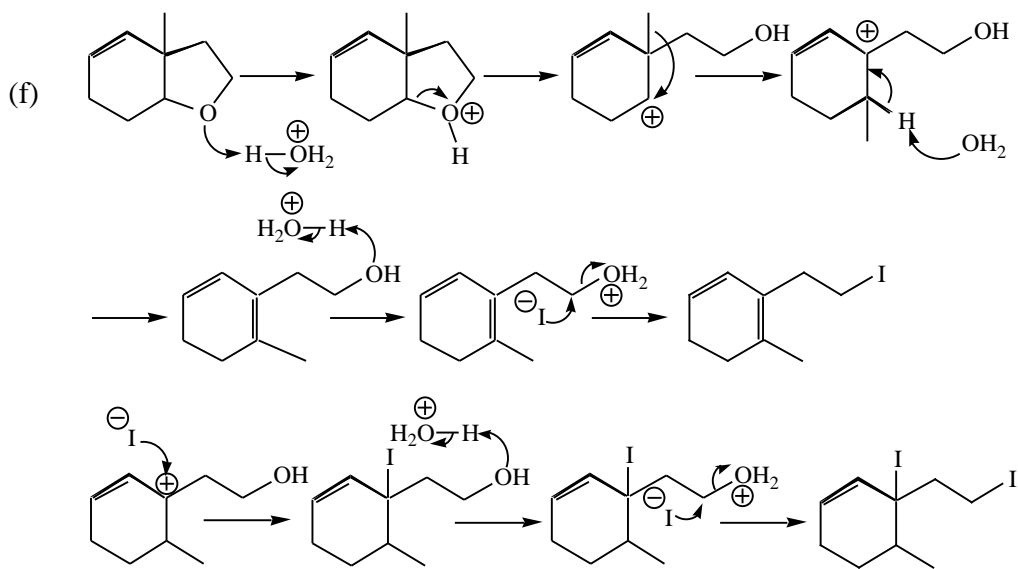
(b) Hydroxide ion is a very poor leaving group (primarily due to the low polarizability of oxygen and the negative charge), so the reaction cannot proceed. Hydroxide ion will only leave when some other factor stabilizes the transition state, such as formation of a conjugated or aromatic structure. After protonation by hydronium ion derived from sulfuric acid, water is the leaving group. Because it would leave as a neutral molecule, water is a better leaving group than hydroxide, and thus the reaction can proceed. (Considering leaving groups as a whole, water is a moderate leaving group, about equal to chloride or bromide.)



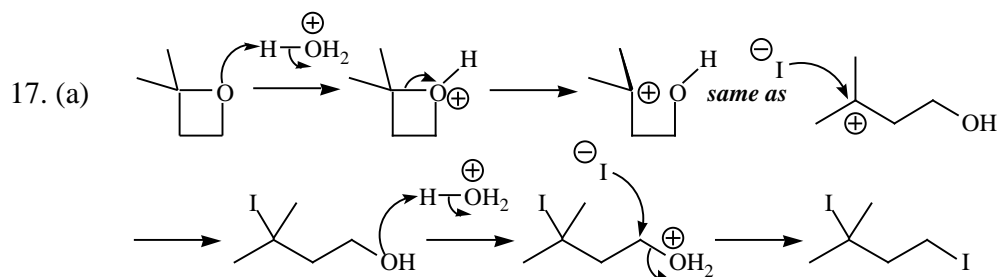
(c) The skeletal rearrangement suggests that this reaction involves a carbocation.



Other reasonable mechanisms are possible.

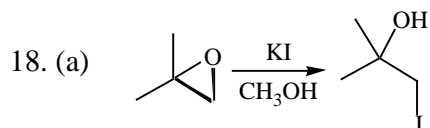


13. The reaction of NaH with an alcohol (ROH) yields an alkoxide (RO^-). Alkoxides are generally strong bases. If an alkoxide is reacted with a methyl or primary alkyl halide, $\text{S}_{\text{N}}2$ substitution can be made to proceed in good yield. If the alkyl halide is secondary or tertiary, then elimination predominates. In this example, the second reaction (primary alkyl iodide) will give the better ratio of substitution vs. elimination products.
14. The best synthetic route to $(\text{CH}_3)_3\text{COCH}_3$ is route (a). In route (b), the difference in basicity of hydroxide and *tert*-butoxide, the conjugate base of $(\text{CH}_3)_3\text{COH}$, is not sufficiently large to allow essentially complete deprotonation of the alcohol. When CH_3I is added to the reaction mixture, there will be two alkoxides (hydroxide and *tert*-butoxide) competing for reaction. In route (c), reaction of CH_3O^- (a strong base) with a tertiary alkyl halide will give E2, not $\text{S}_{\text{N}}2$, products.
15. By itself, $(\text{CH}_3)_3\text{CO}^-$ is not a good enough leaving group to allow iodide to attack the methyl carbon in an $\text{S}_{\text{N}}2$ fashion. Protonation of the oxygen converts the leaving group to methanol (CH_3OH), which is good enough to leave when iodide attacks.
16. These reactions involve $\text{S}_{\text{N}}2$ attack of cyanide ion on the C-O bond of the ethers, with the alkoxide as the leaving group. We normally consider alkoxides to be poor leaving groups. This explains why THF is inert in this reaction. However, the epoxide has ring strain that is relieved when the ring is opened. This additional driving force overcomes the fact that alkoxides are normally poor leaving groups. Epoxides can be ruptured by $\text{S}_{\text{N}}2$ attack of a good nucleophile such as cyanide ion.

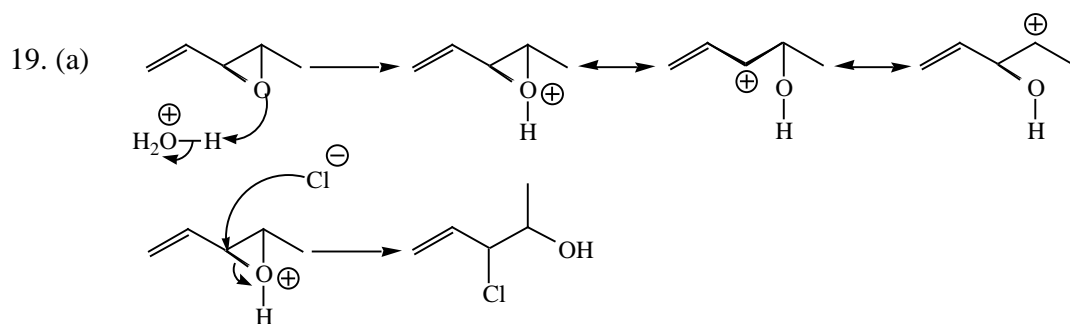


Several variations on this mechanism are acceptable, as long as they make chemical sense and lead to the same diiodide.

- (b) A significant difference between these two reactants is the presence of ring strain in the four-membered ring ether (called an oxetane). This ring strain is absent in the six membered ring ether (called a tetrahydropyran). Relief of this ring strain would make the oxetane cleavage reaction faster than the tetrahydropyran cleavage reaction.

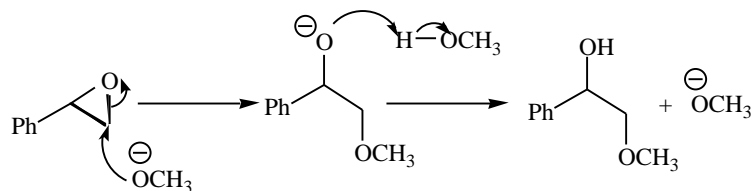


- (b) Ethers and alcohols are inert to most nucleophiles (like iodide ion) because HO^- and RO^- are poor leaving groups. The ring strain energy released during the transition state of the reaction of an epoxide with iodide ion compensates for the normally poor propensity an alkoxide to leave.

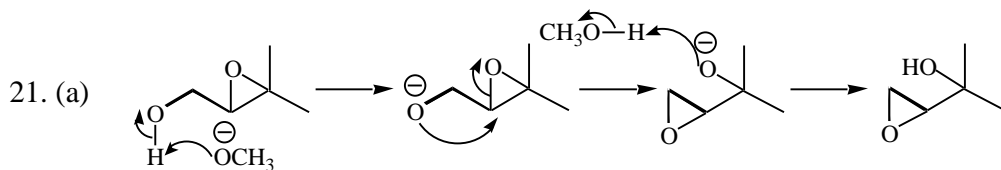
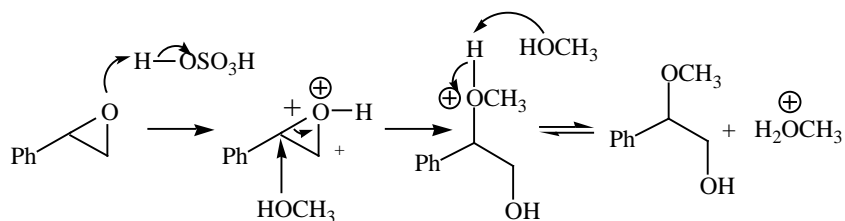


- (b) As discussed in the answer to CFQ #8, nucleophilic attack occurs at the carbon that would bear the most stable carbocation in the ring-opened resonance contributors. In this case, both carbocations are secondary but the one with resonance is more stable. Thus the chloride ion attacks the allylic carbon. (An allylic carbon atom is directly attached to an alkene.)

20. When reacting with strong nucleophiles, epoxides react by an $\text{S}_{\text{N}}2$ mechanism. Attack occurs at the least hindered carbon atom.



When reacting with weak nucleophiles under acidic conditions, epoxides react by a S_N1 -like mechanism. Because the nucleophile is weak, it attacks the carbon with the greatest amount of δ^+ charge, regardless of steric hindrance. This greatest charge resides where it is most stable; in this case, on the more substituted carbon. Additional charge stabilization results from resonance with the benzene ring.



(b) Both of the reactions involve an alkoxide (RO^-) leaving group. Normally this is a poor leaving group. The relief of ring strain when an epoxide opens, however, is sufficient driving force to overcome the poor leaving group propensity of alkoxides. There is no such ring strain in the equation with the tetrahydrofuran ring, so the alkoxide remains a poor leaving group, and the reaction cannot occur.

22. Relief of epoxide ring strain and gain of aromaticity.