

Alcoli, eteri e composti associati



alcohol



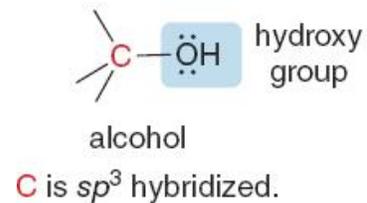
ether



epoxide

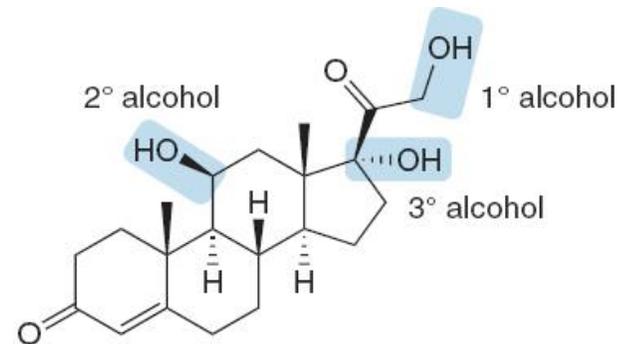
Alcoli, eteri e epossidi contengono in legame C-O

Alcoli: legame C (sp^3) -O



alcohol

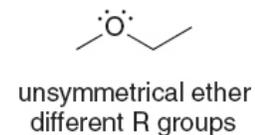
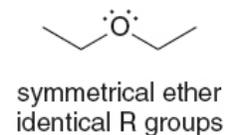
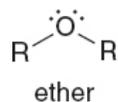
C is sp^3 hybridized.



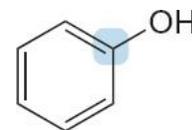
cortisol

anti-inflammatory steroid

Eteri - epossidi



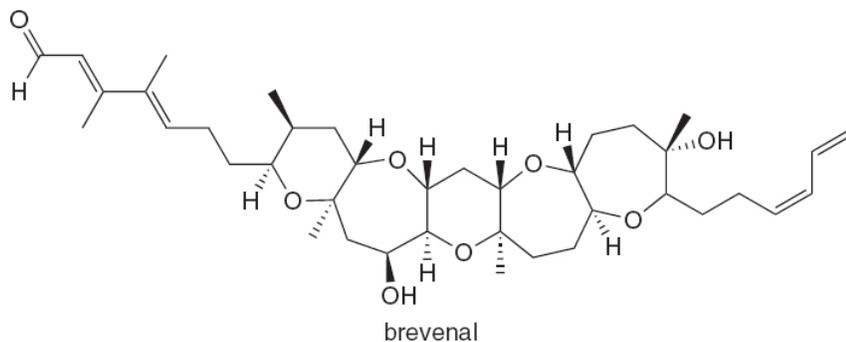
Enoli, fenoli C (sp^2) -O



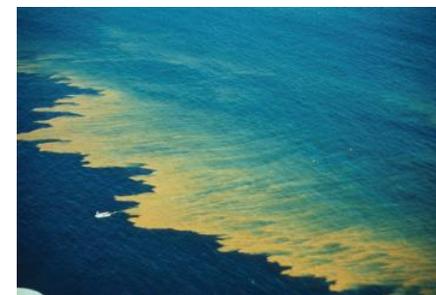
enol

phenol

- C bonded to OH is sp^2 hybridized.

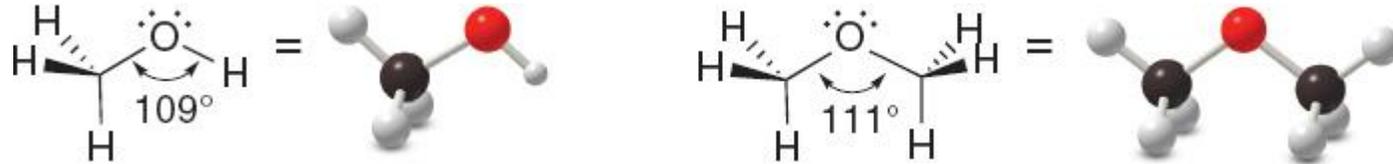


Label each ether and alcohol in brevenal.
Classify each alcohol as 1°, 2°, or 3°.



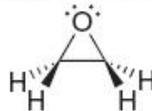
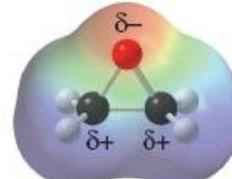
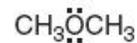
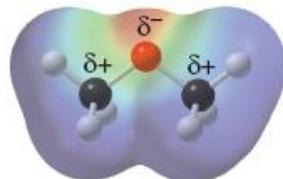
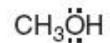
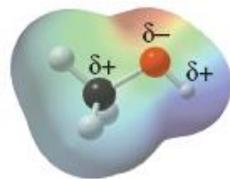
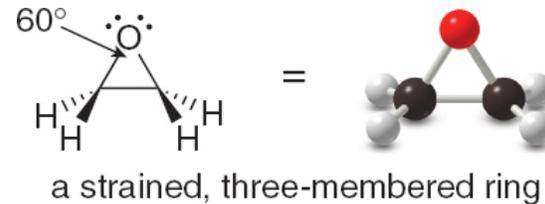
Brevenal is a nontoxic marine polyether produced by *Karenia brevis*, a single-celled organism that proliferates during red tides, vast algal blooms that turn the ocean water red, brown, or green.

Alcoli, eteri e composti associati - struttura



Alcoli, eteri struttura angolata, come l'acqua. Legame C-O polarizzato

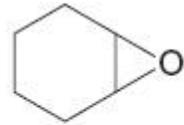
Epossido, anello tensionato



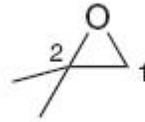
- Electron-rich regions are shown by the red around the O atoms.

Nomenclatura Epossidi

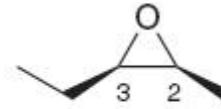
Sono degli eterocicli. Possono essere denominati epossialcani, ossirani, or alchene ossidi



1,2-epoxycyclohexane



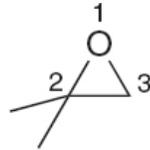
1,2-epoxy-2-methylpropane



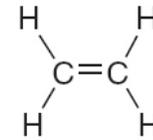
cis-2,3-epoxypentane



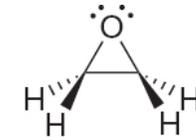
oxirane



2,2-dimethyloxirane

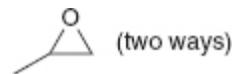
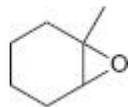


ethylene



ethylene oxide
oxirane

Fornisci un nome ai seguenti composti:



Alcoli/eteri: proprietà fisiche

Gli alcoli/fenoli sono composti polari e formano legami idrogeno

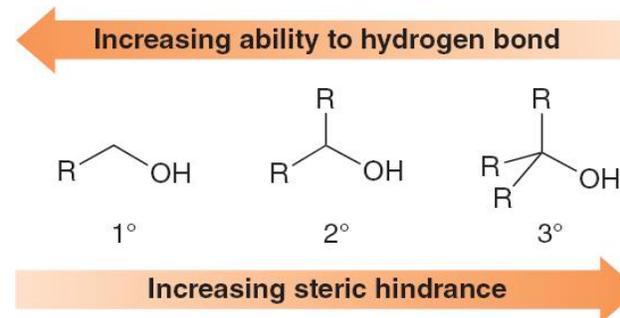
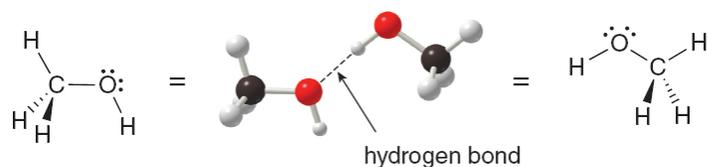
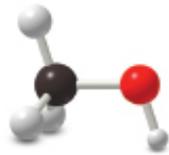


Table 9.1 Physical Properties of Alcohols, Ethers, and Epoxides

Property	Observation
Boiling point and melting point	<ul style="list-style-type: none"> For compounds of comparable molecular weight, the stronger the intermolecular forces, the higher the bp or mp. <div style="text-align: center;"> <p>VDW bp 0 °C VDW, DD bp 11 °C VDW, DD, HB bp 97 °C</p> <p>→ Increasing boiling point</p> </div>
	<ul style="list-style-type: none"> Bp's increase as the extent of hydrogen bonding increases. <div style="text-align: center;"> <p>3° bp 83 °C 2° bp 98 °C 1° bp 118 °C</p> <p>→ Increasing ability to hydrogen bond Increasing boiling point</p> </div>
Solubility	<ul style="list-style-type: none"> Alcohols, ethers, and epoxides having ≤ 5 C's are H_2O soluble because they each have an oxygen atom capable of hydrogen bonding to H_2O (Section 3.4C). Alcohols, ethers, and epoxides having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in H_2O. Alcohols, ethers, and epoxides of any size are soluble in organic solvents.

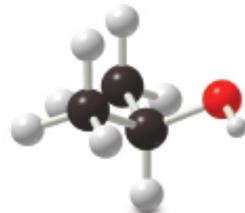
Key: VDW = van der Waals forces; DD = dipole-dipole; HB = hydrogen bonding

Alcoli/eteri



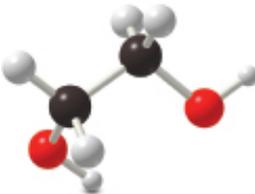
CH₃OH

- **Methanol (CH₃OH)** is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.



(CH₃)₂CHOH

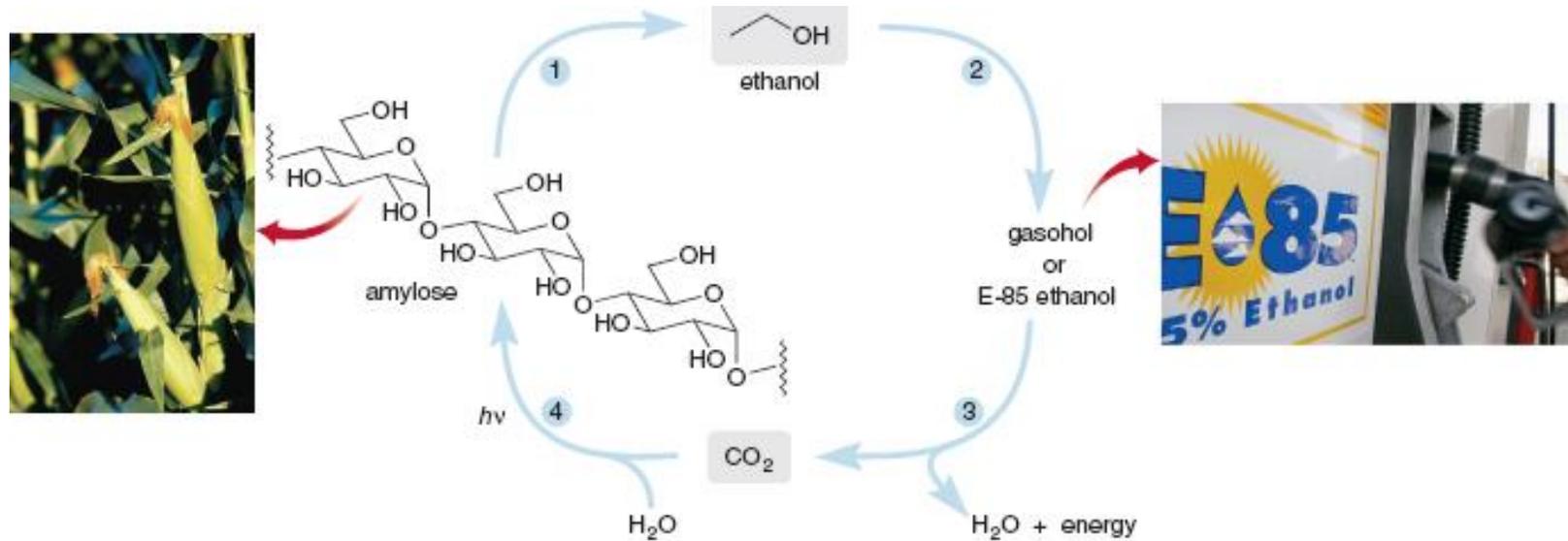
- **Propan-2-ol [(CH₃)₂CHOH]** is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, propan-2-ol is used to clean skin before minor surgery and to sterilize medical instruments.



HOCH₂CH₂OH

- **Ethylene glycol (HOCH₂CH₂OH)** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.16. It is sweet tasting but toxic.

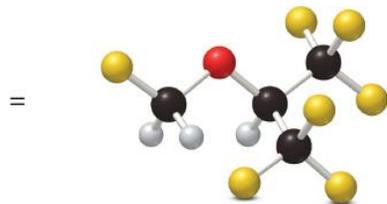
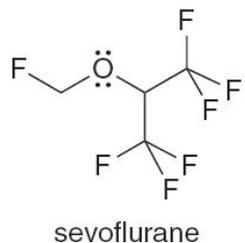
Etanolo: biocarburante (sostenibile)



- Hydrolysis of amylose (one form of starch) and fermentation of the resulting simple sugars (Step [1]) yield ethanol, which is mixed with hydrocarbons from petroleum refining (Step [2]) to form usable fuels.
- Combustion of this ethanol-hydrocarbon fuel forms CO_2 and releases a great deal of energy (Step [3]).
- Photosynthesis converts atmospheric CO_2 back to plant carbohydrates in Step [4], and the cycle continues.

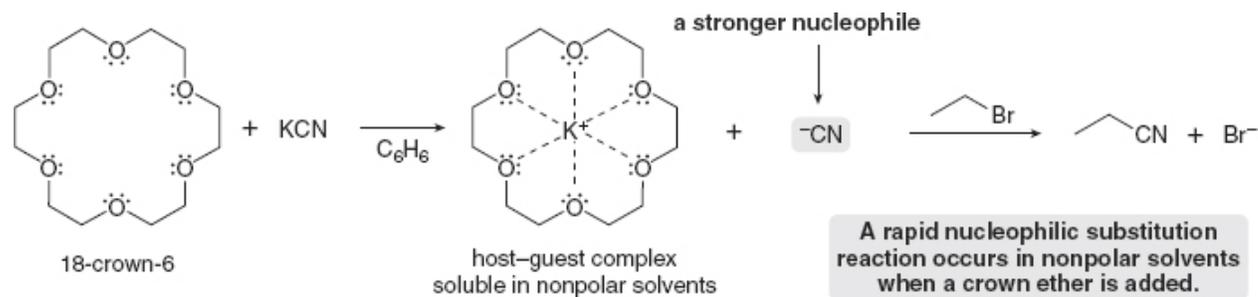
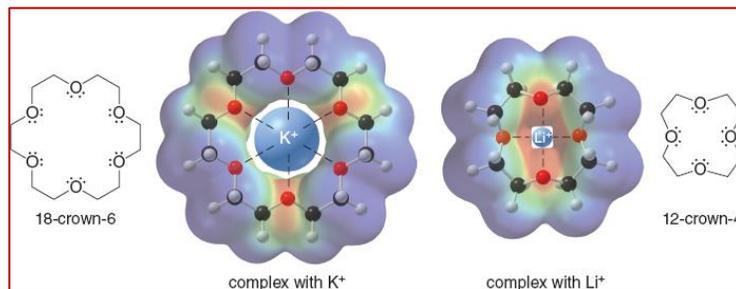
ETERI: Etere Etilico (EtOEt)

primo anestetico (volatile, molto infiammabile, provoca nausea)

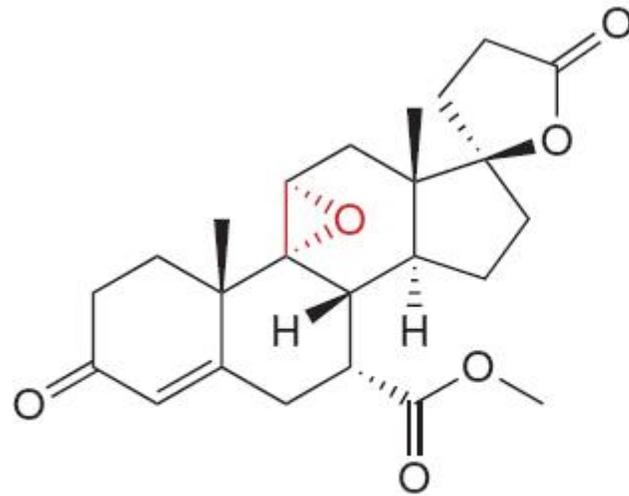


(volatile, poco infiammabile, minori effetti collaterali)

Eteri Corona: solvatano cationi e quindi si possono usare solventi organici apolari

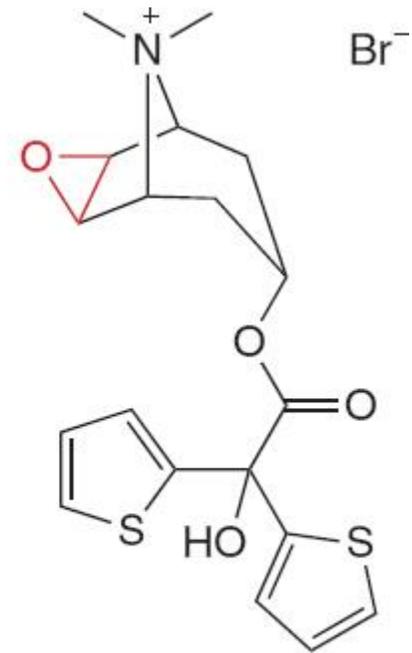


Epossidi: gruppo funzionale in principi attivi



eplerenone

(INSPRA) Riduce il rischio cardiovascolare in pazienti infartuati

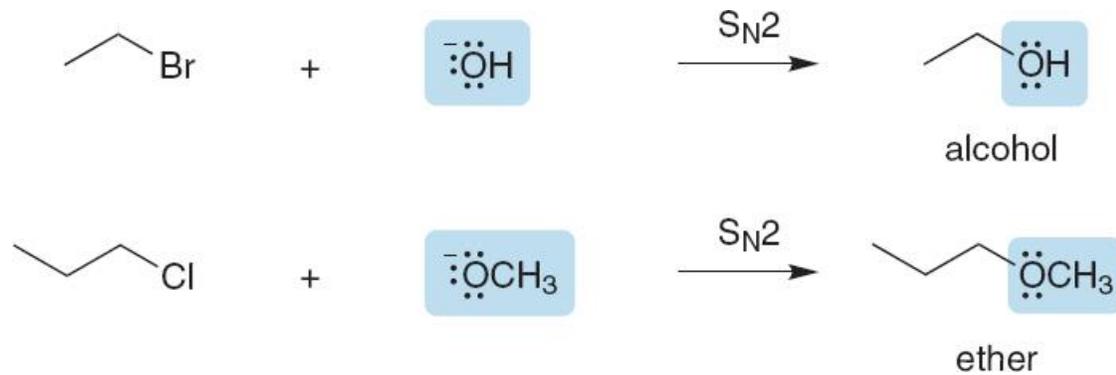


tiotropium bromide

(Spiriva) broncodilatatore

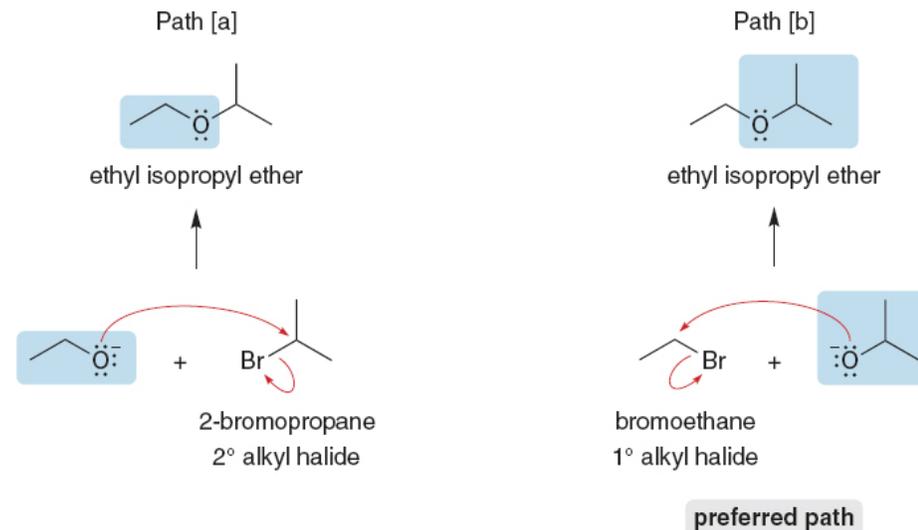
Sintesi di alcoli, eteri

Da alchil alogenuri via reazioni di sostituzione

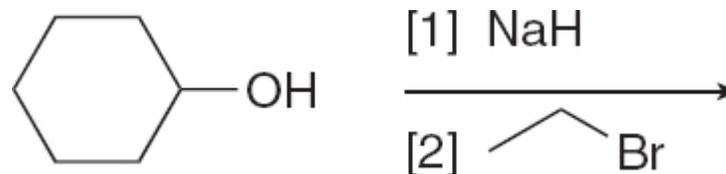


**sintesi di Williamson
(name reaction)**

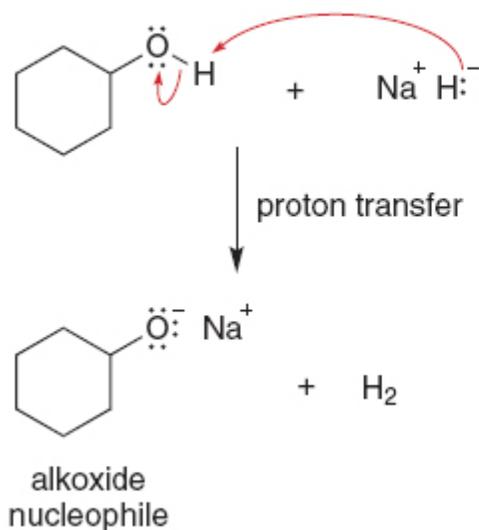
**sintesi di eteri non simmetrici
(elettrofilo più reattivo)**



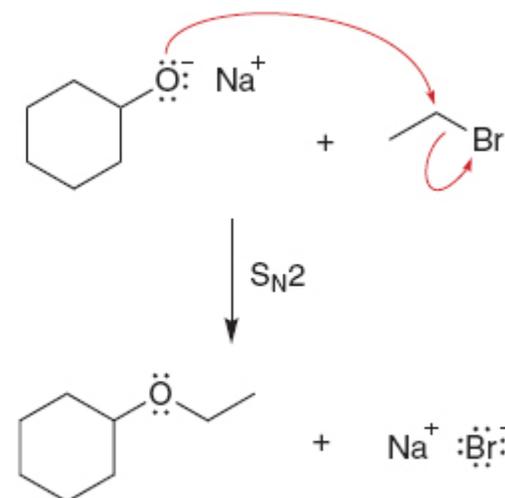
Scrivi il prodotto di questa reazione a due passaggi:



[1] The base removes a proton from the OH group, forming an alkoxide.

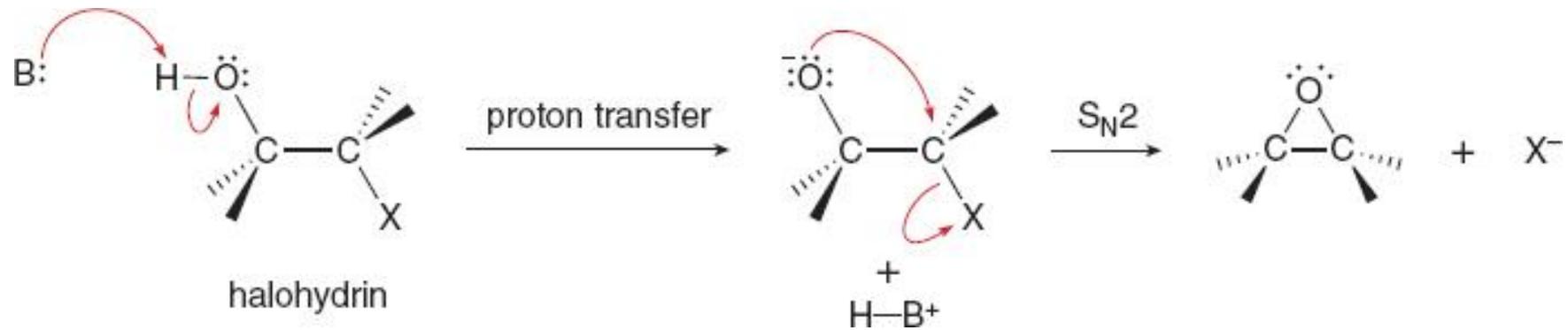


[2] The alkoxide acts as a nucleophile in an S_N2 reaction, forming an ether.



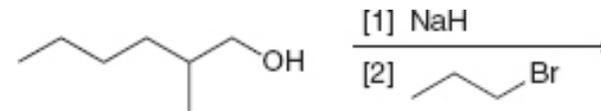
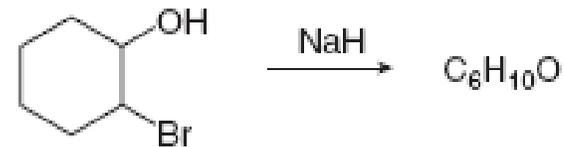
- This two-step sequence converts an alcohol to an ether.

Sintesi di epossidi: da aloidrine (S_N2 intramolecolare)

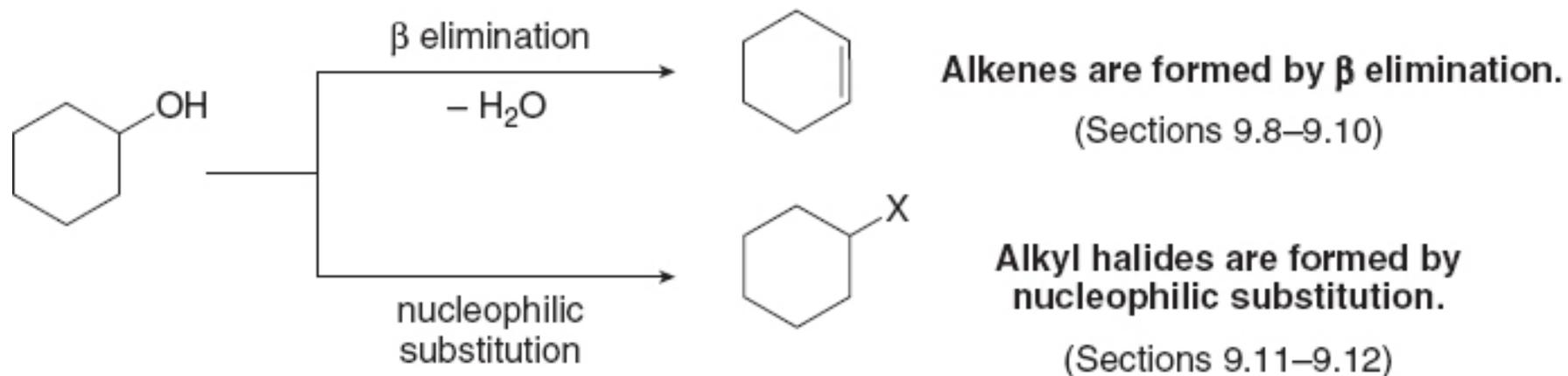


Indicare i prodotti delle seguenti reazioni:

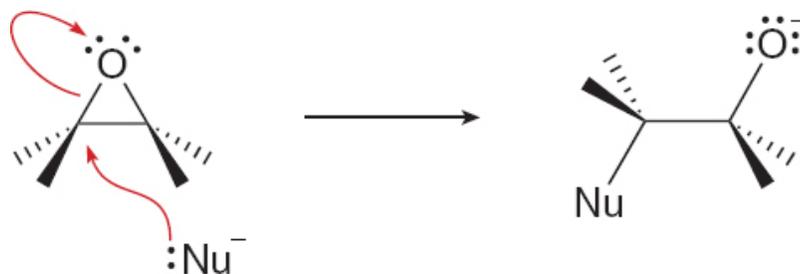
wooclap



Reattività di alcoli, eteri, epossidi

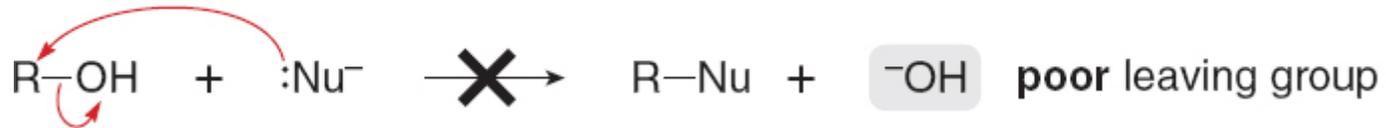
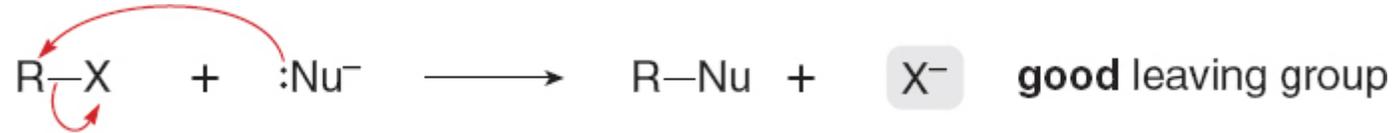


R-R **poor leaving group**



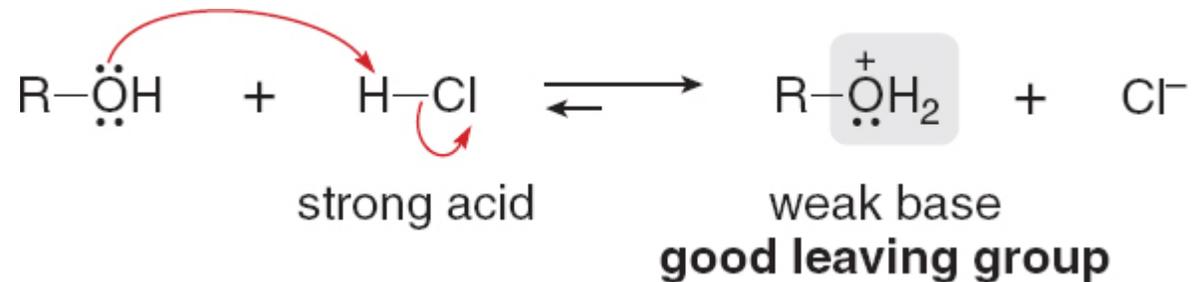
Reattività di alcoli, eteri, epossidi

Alcoli, reazione di sostituzione

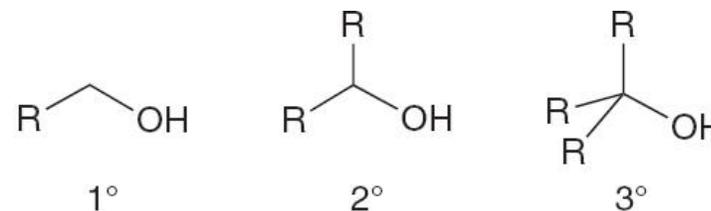
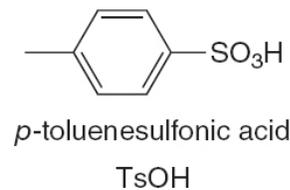
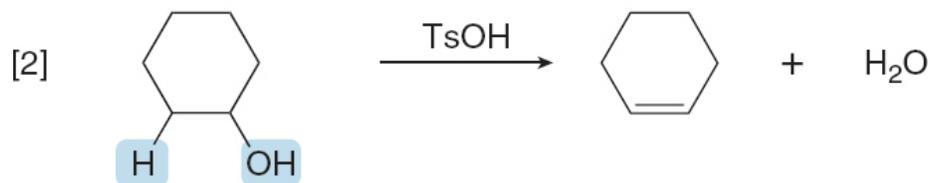
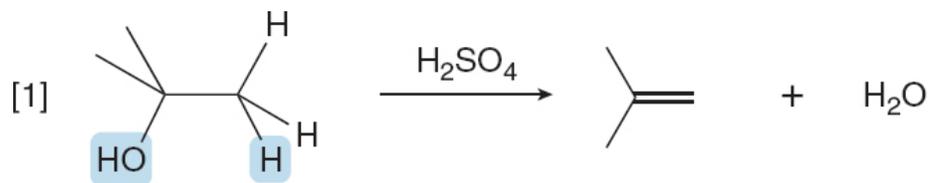
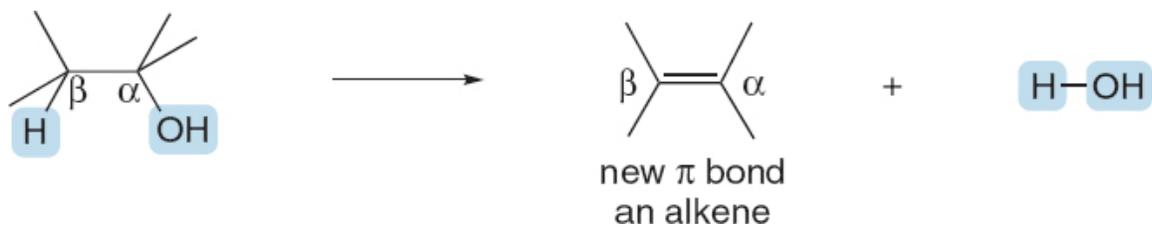


OH⁻ cattivo gruppo uscente: come convertirlo in un miglior gruppo uscente?

Utilizzo di acidi forti (HCl, H₂SO₄)



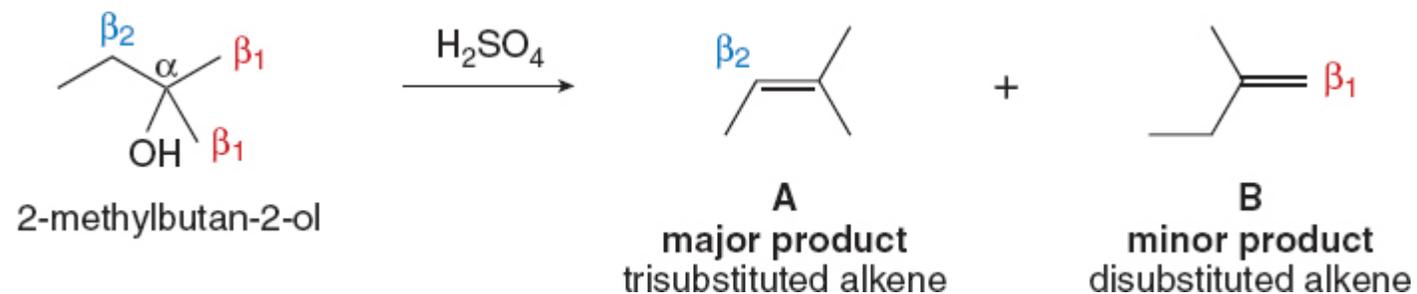
Alcoli - eliminazione: disidratazione (con acidi forti)



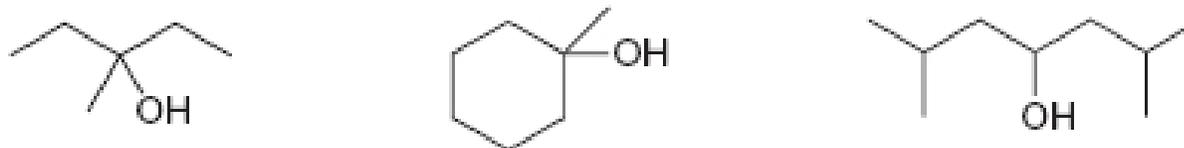
Increasing rate of dehydration

Alcoli - disidratazione (regiochimica)

Segue la regola di Zaitsev: si forma l'alchene più stabile

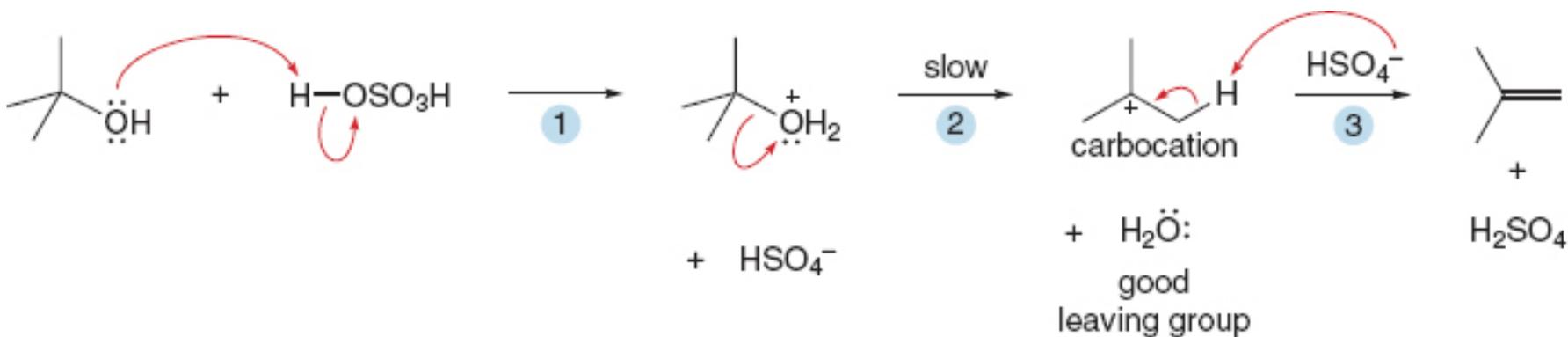


Draw the products formed when each alcohol undergoes dehydration with TsOH, and label the major product when a mixture results.

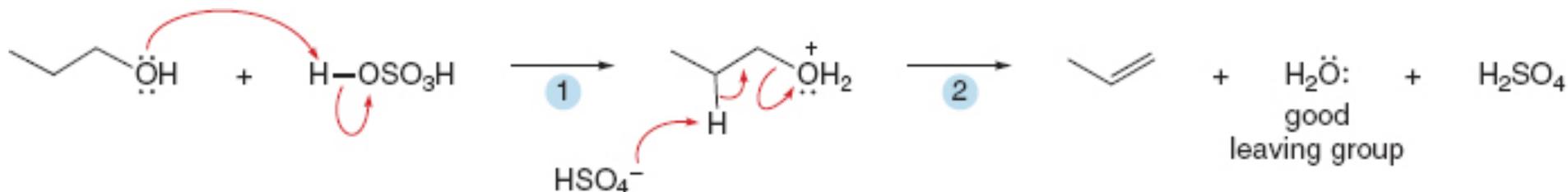


Alcoli - disidratazione (meccanismo)

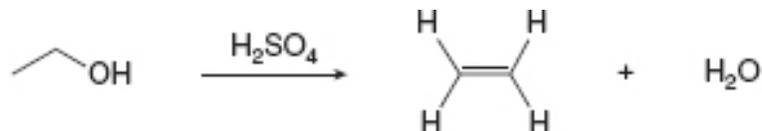
Alcoli secondari e terziari: Meccanismo E1



Alcoli primari: Meccanismo E2



Alcoli - disidratazione - processo endotermico $\Delta H^\circ > 0$



ΔH° calculation:

[1] Bonds broken

	ΔH° (kJ/mol)
$\text{CH}_3\text{CH}_2\text{-OH}$	+393
$\text{HOCH}_2\text{CH}_2\text{-H}$	+410
<hr/>	
Total	+803 kJ/mol

Energy needed to break bonds.

[2] Bonds formed

	ΔH° (kJ/mol)
$\text{CH}_2=\text{CH}_2$ π bond	-267
H-OH	-498
<hr/>	
Total	-765 kJ/mol

Energy released in forming bonds.

[3] Overall $\Delta H^\circ =$

sum in Step [1]

+

sum in Step [2]

+803 kJ/mol

-765 kJ/mol

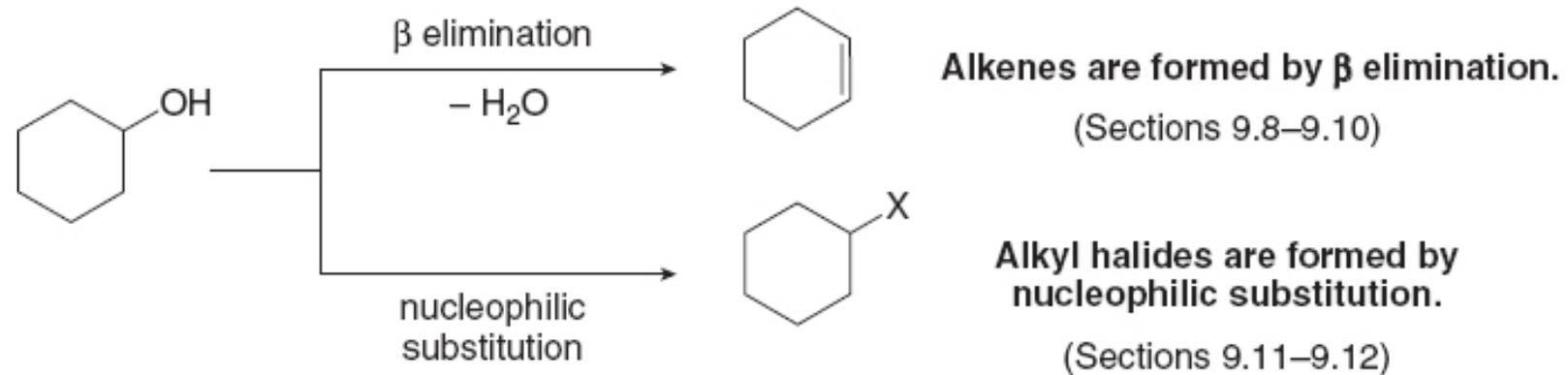
$\Delta H^\circ = +38$ kJ/mol

The reaction is endothermic.

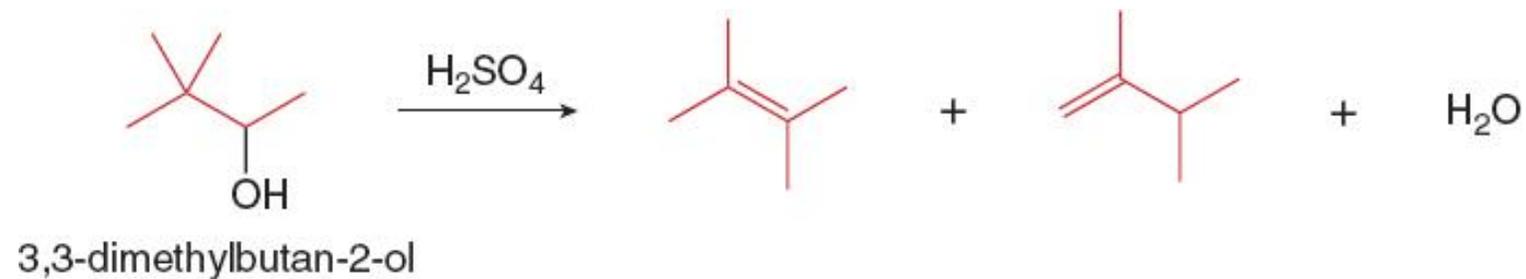
[Values taken from Appendix C.]

Rimozione di H_2O (principio di Le Châtelier) o alte temperature favoriscono l'eliminazione

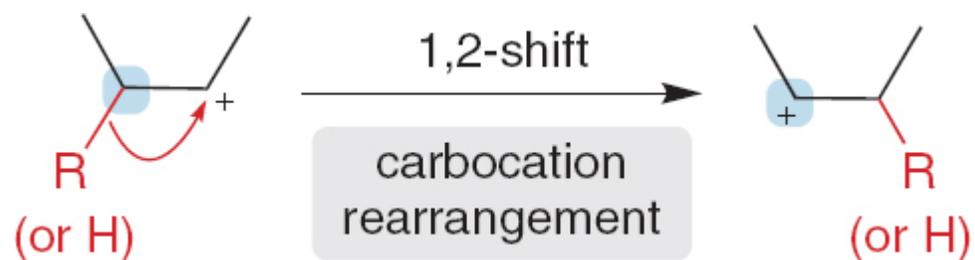
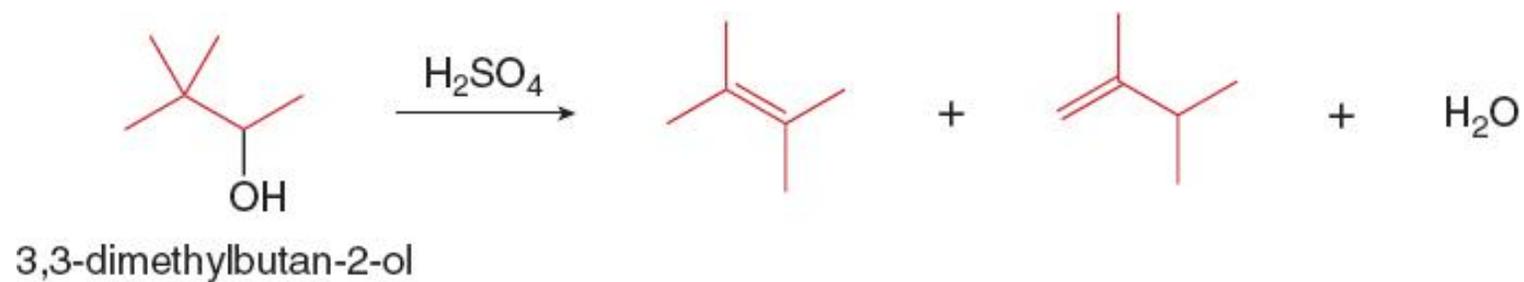
Alcoli, reazione di sostituzione/eliminazione



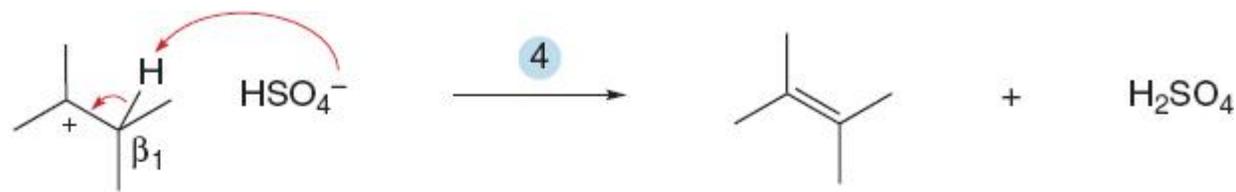
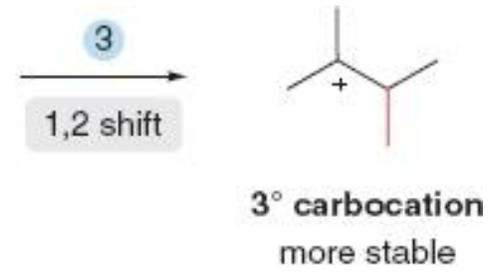
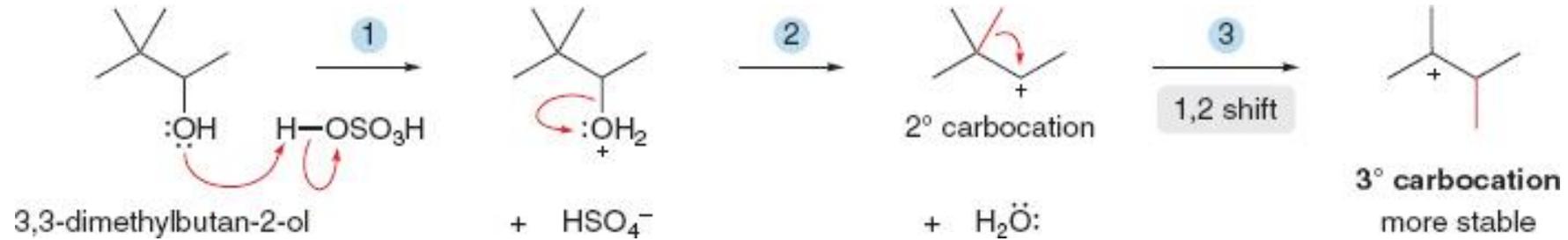
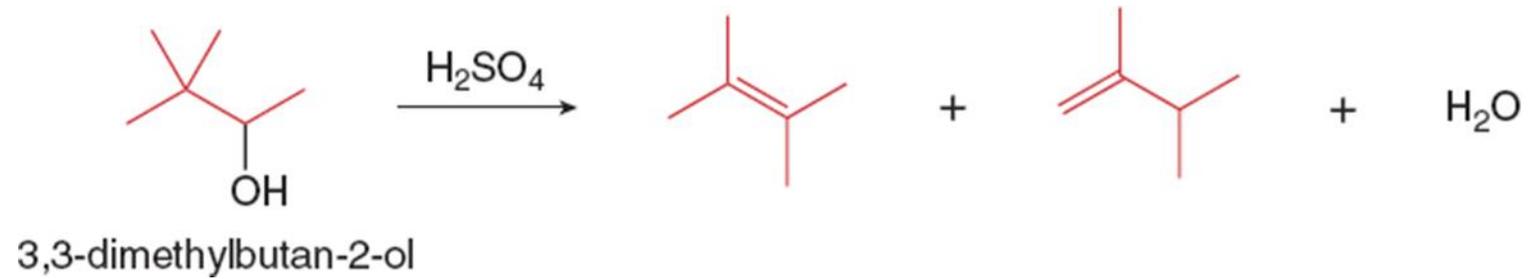
E1: riarrangiamenti



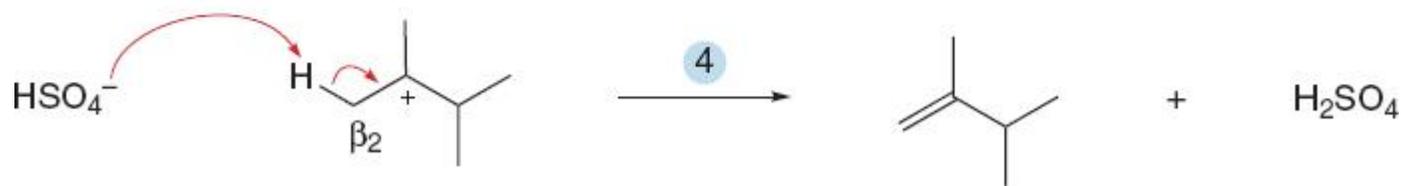
E1: riarrangiamenti



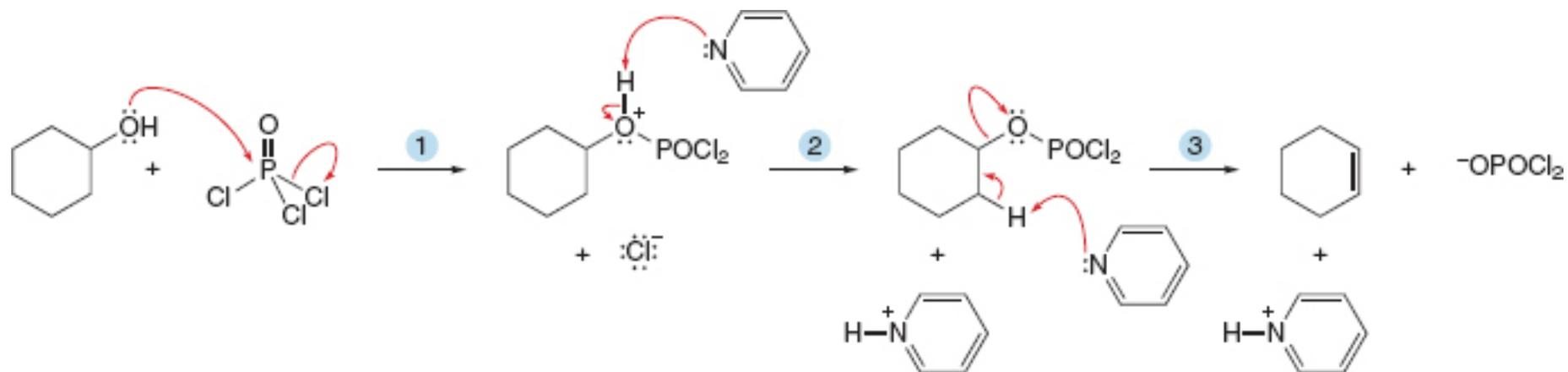
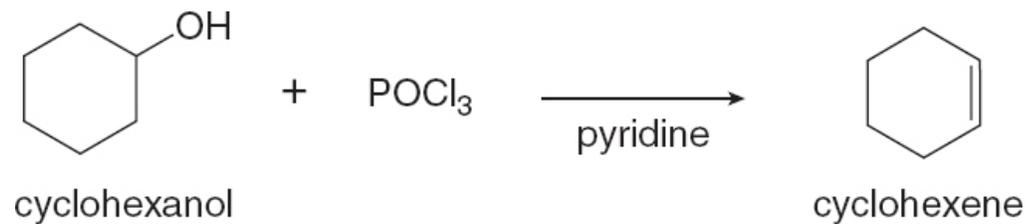
E1: riarrangiamenti (meccanismo e regiochimica)



or

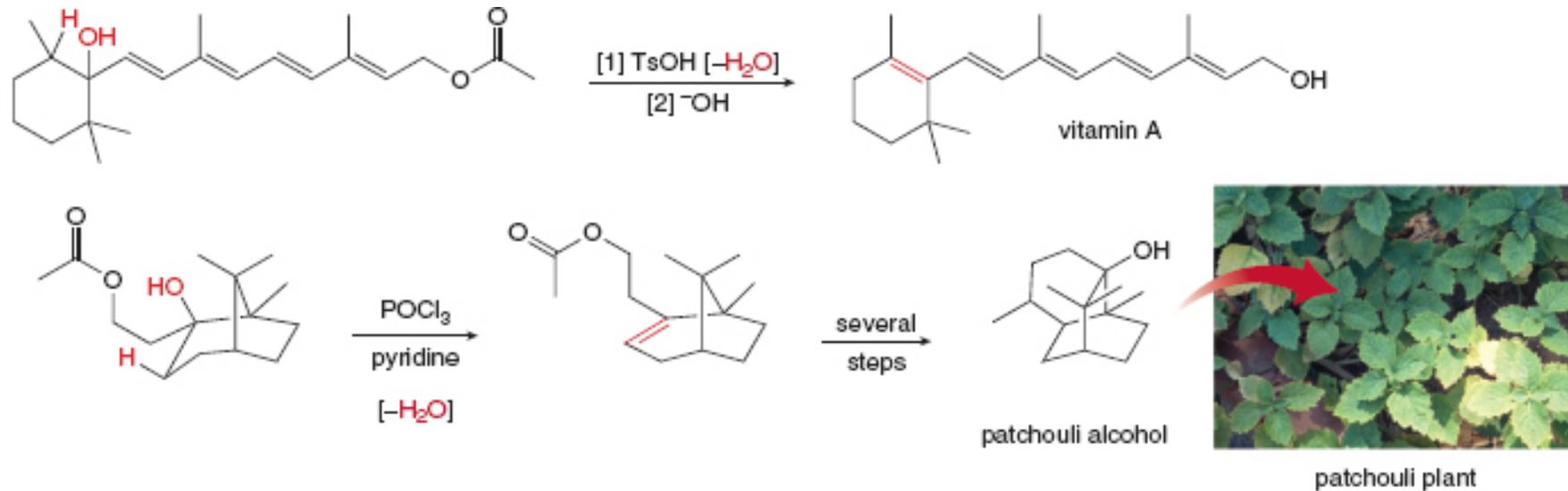


Disidratazioni con POCl_3 /piridina (E2) (alcoli non stabili in acidi forti)



Nessun riarrangiamento

Disidratazioni nella sintesi di prodotti naturali



- New double bonds formed by dehydration are shown in red.
- **Patchouli alcohol**, obtained from the patchouli plant native to Malaysia, has been used in perfumery because of its exotic fragrance. In the 1800s, shawls imported from India were often packed with patchouli leaves to ward off insects, thus permeating the clothing with the distinctive odor.

Conversione di alcoli in alogenuri alchilici



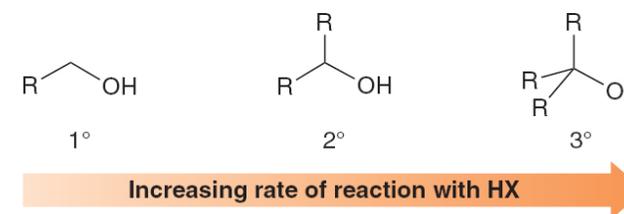
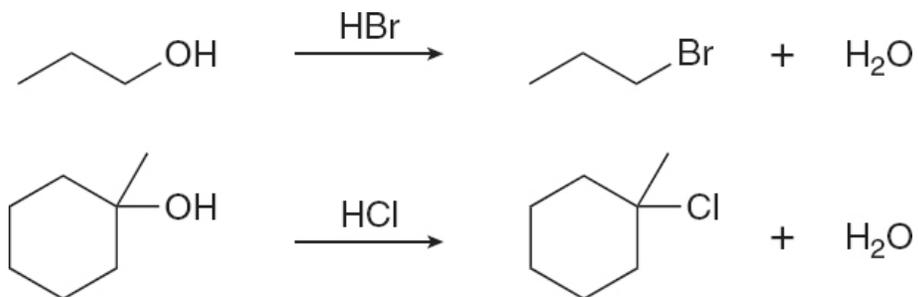
poor leaving group
Reaction does *not* occur.



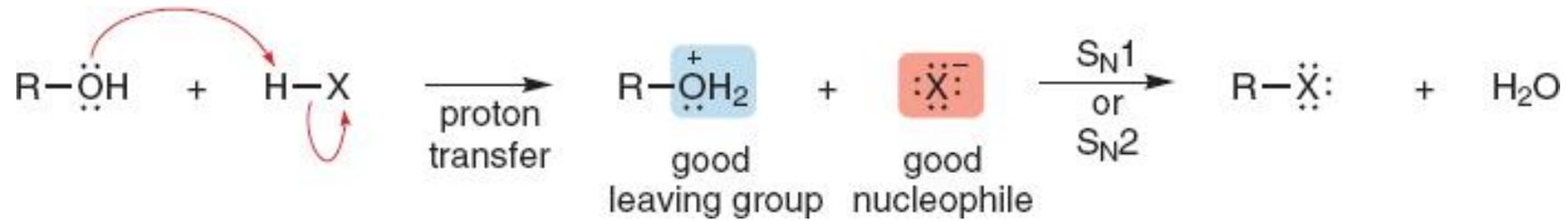
good leaving group
Reaction occurs.

alkyl halide

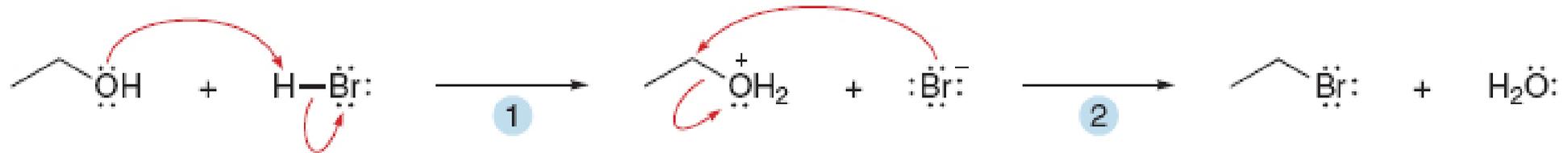
Reazione con HX (X=Cl, Br, I): metodo per preparare alogenuri 1°, 2° e 3°



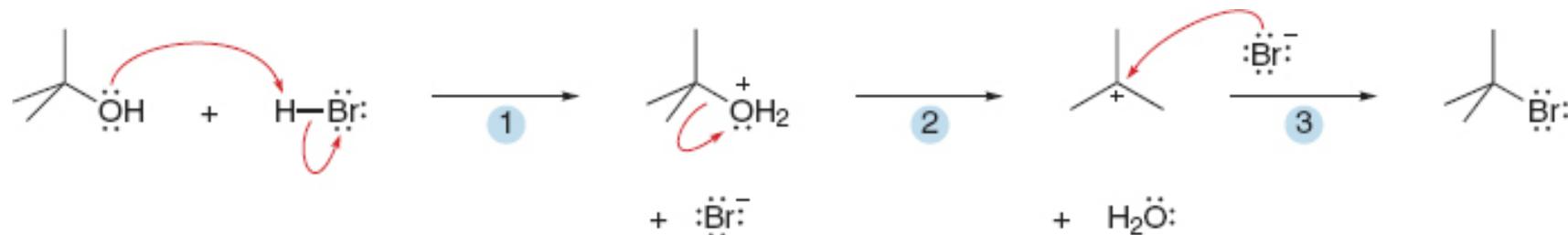
Conversione di alcoli in alogenuri alchilici



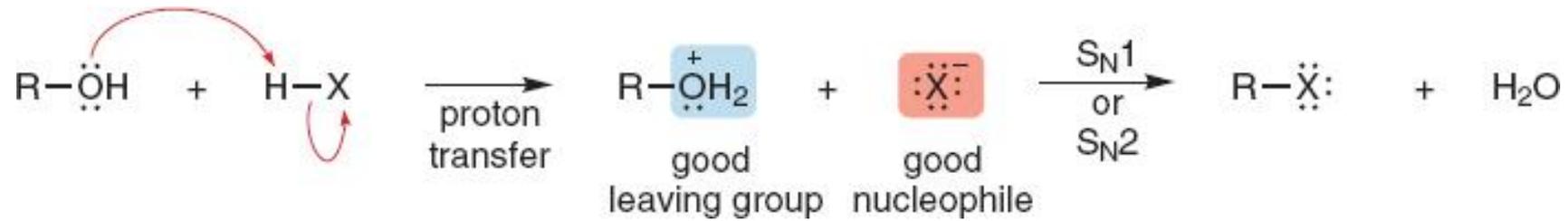
Alcoli primari: Meccanismo S_N2



Alcoli secondari e terziari: Meccanismo S_N1



Conversione di alcoli in alogenuri alchilici



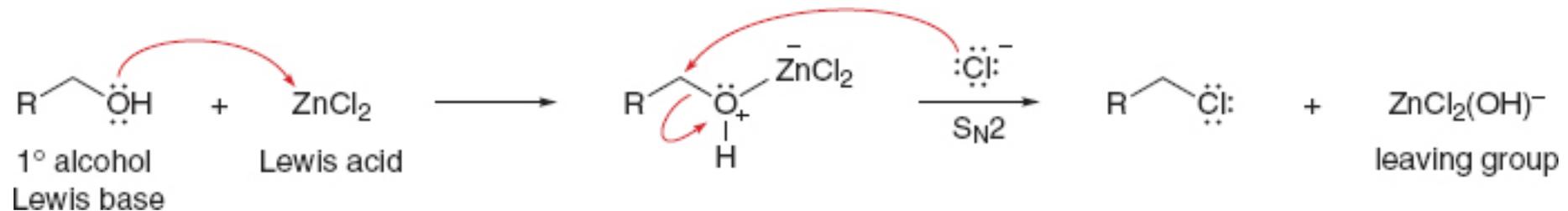
H-Cl

H-Br

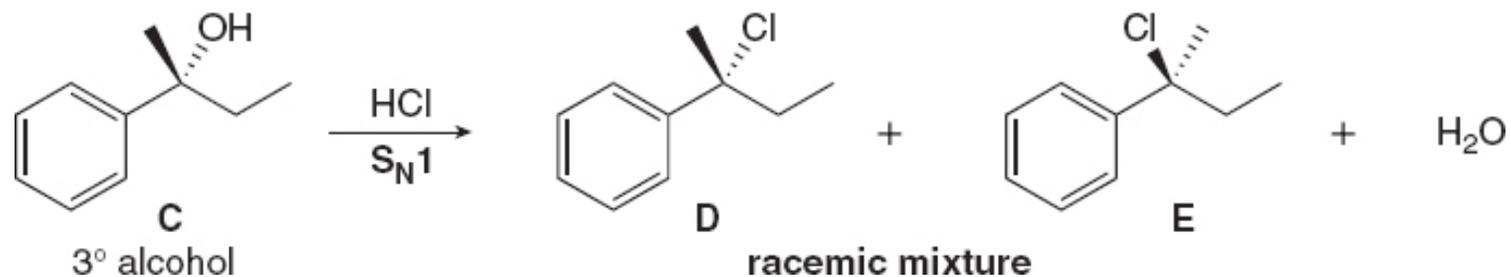
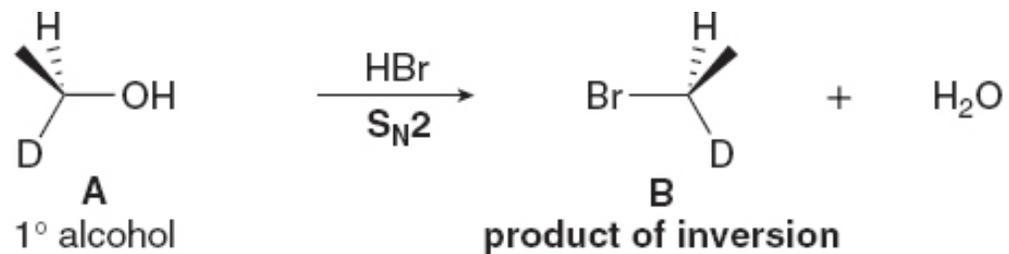
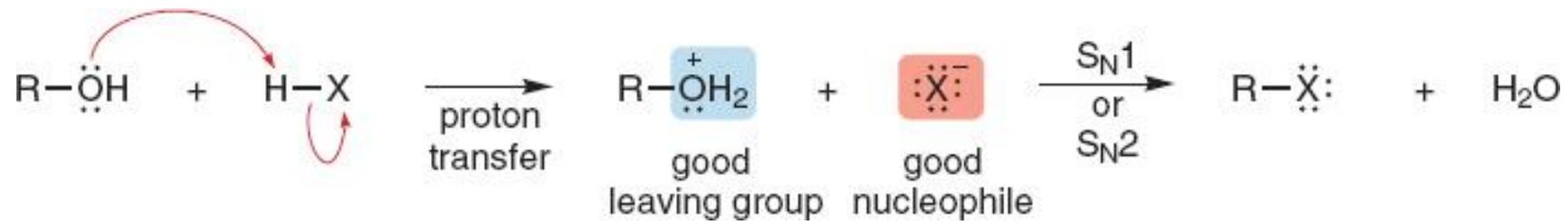
H-I

Increasing reactivity toward ROH

Alcoli primari/HCl poco reattivi: si aggiunge un acido di Lewis (ZnCl_2)

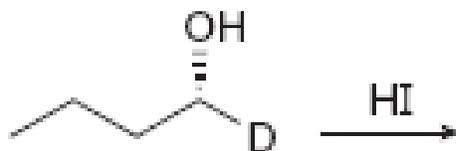
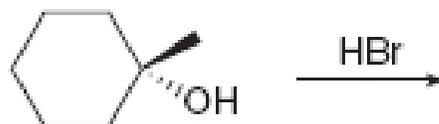


Conversione di alcoli in alogenuri alchilici (stereochemica)



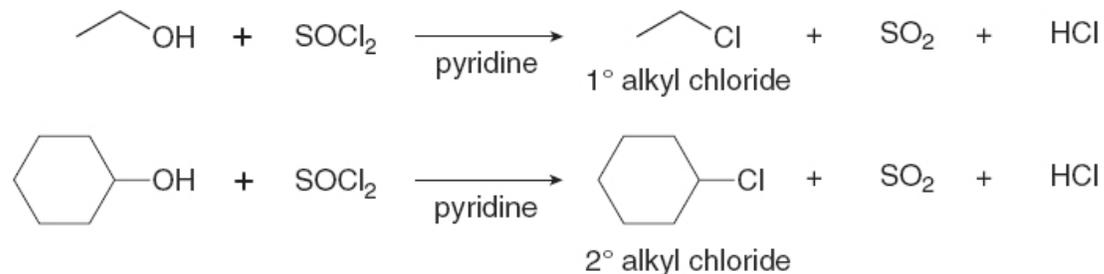
Conversione di alcoli in alogenuri alchilici con HX (stereochemica)

Draw the products of each reaction, indicating the stereochemistry around any stereogenic centers.

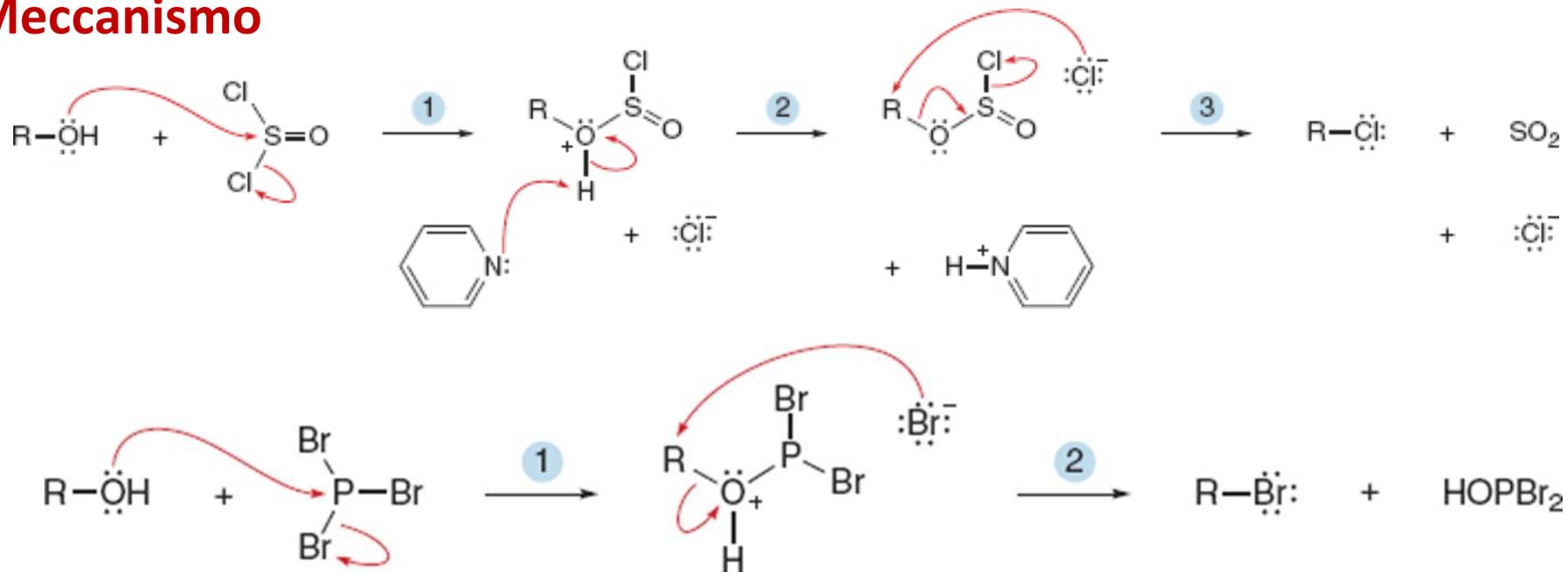


Conversione di alcoli 1° e 2° in alogenuri alchilici con SOCl₂ e PBr₃

- SOCl₂ (cloruro di tionile) converte alcoli nei corrispondenti alchilcloruri
- PBr₃ (fosforo tribromuro) converte alcoli nei corrispondenti alchil bromuri



Meccanismo

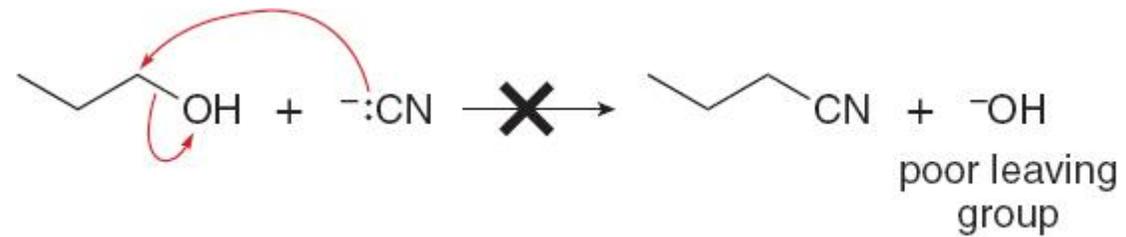
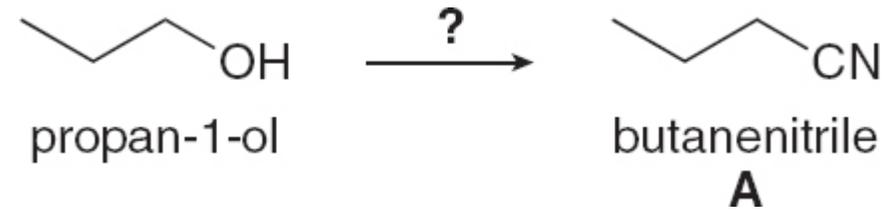


Conversione di alcoli in alogenuri alchilici (X=Cl, Br, I)

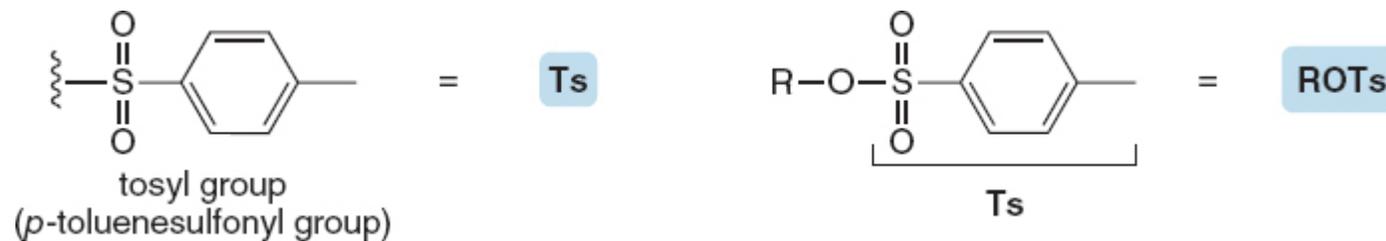
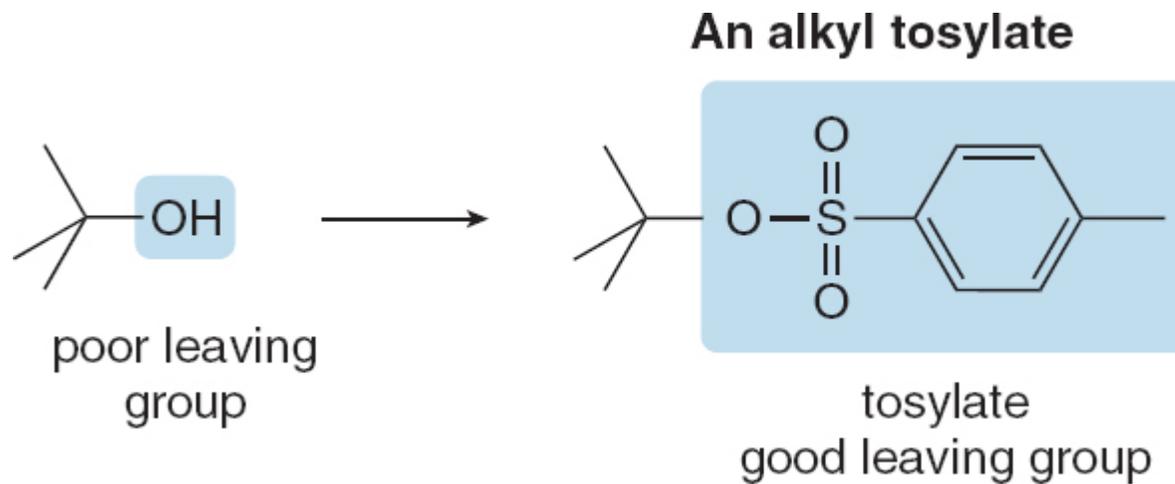
Table 9.2 Summary of Methods for ROH → RX

Overall reaction	Reagent	Comment
ROH → RCl	HCl	<ul style="list-style-type: none">• Useful for all ROH• An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH₃OH and 1° ROH
	SOCl ₂	<ul style="list-style-type: none">• Best for CH₃OH, and 1° and 2° ROH• An S_N2 mechanism
ROH → RBr	HBr	<ul style="list-style-type: none">• Useful for all ROH• An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH₃OH and 1° ROH
	PBr ₃	<ul style="list-style-type: none">• Best for CH₃OH, and 1° and 2° ROH• An S_N2 mechanism
ROH → RI	HI	<ul style="list-style-type: none">• Useful for all ROH• An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH₃OH and 1° ROH

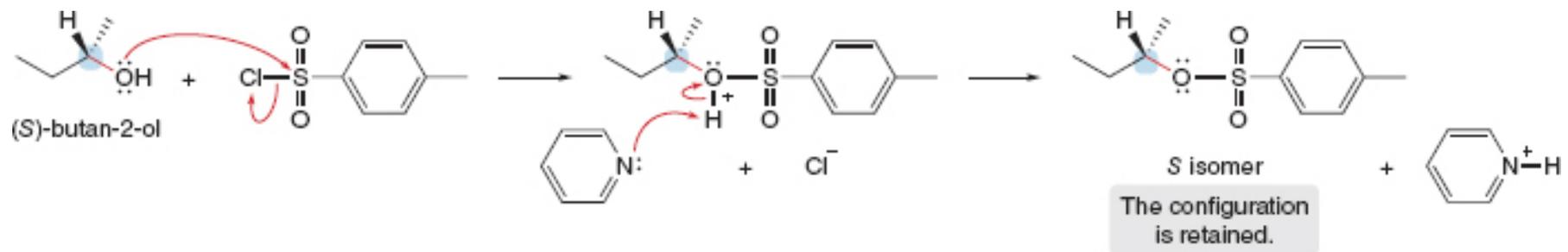
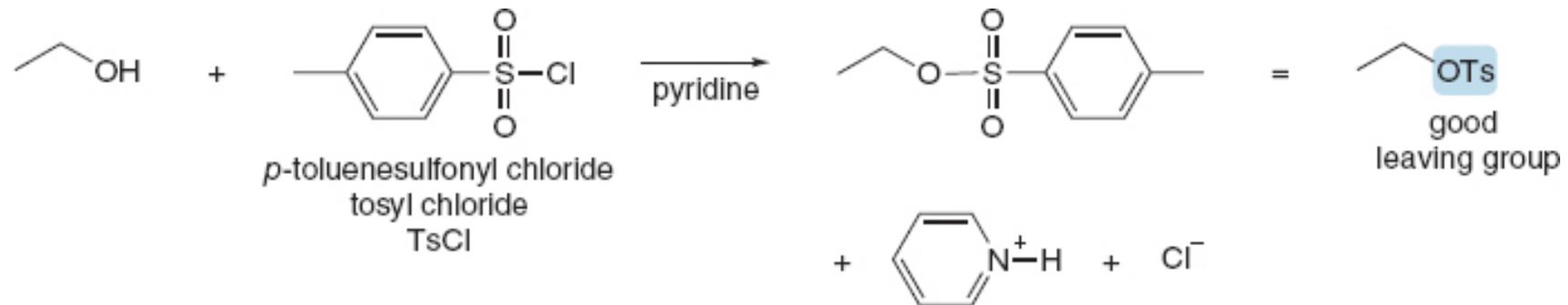
Sintesi multistadio via alogenuri alchilici



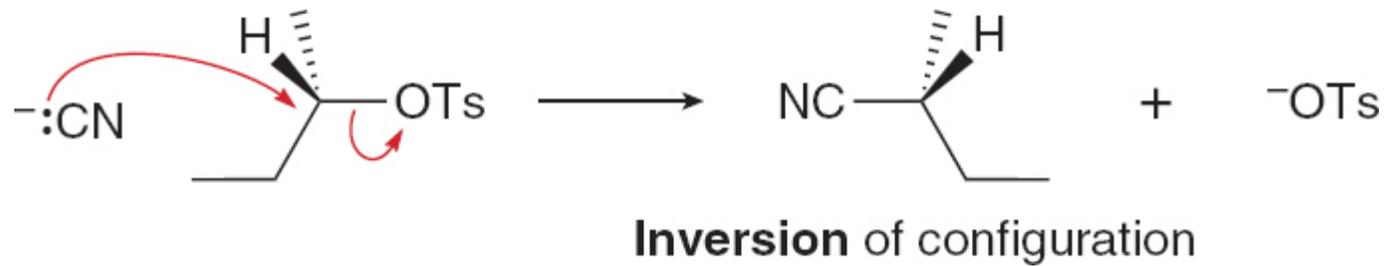
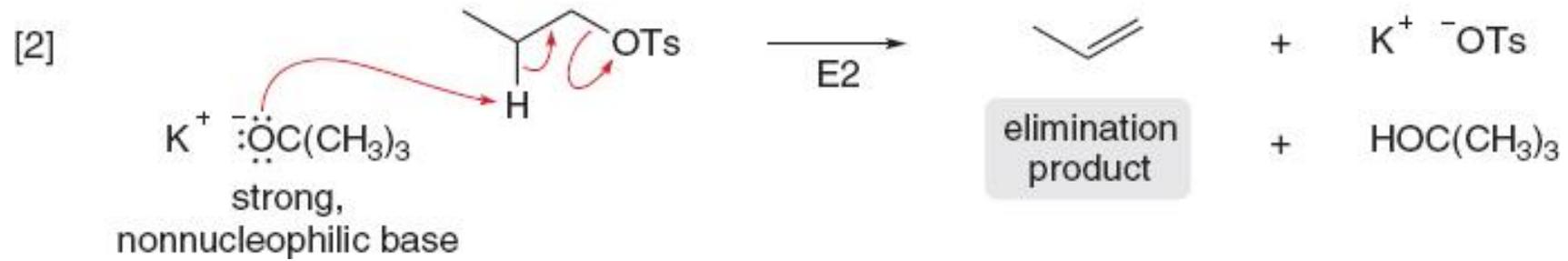
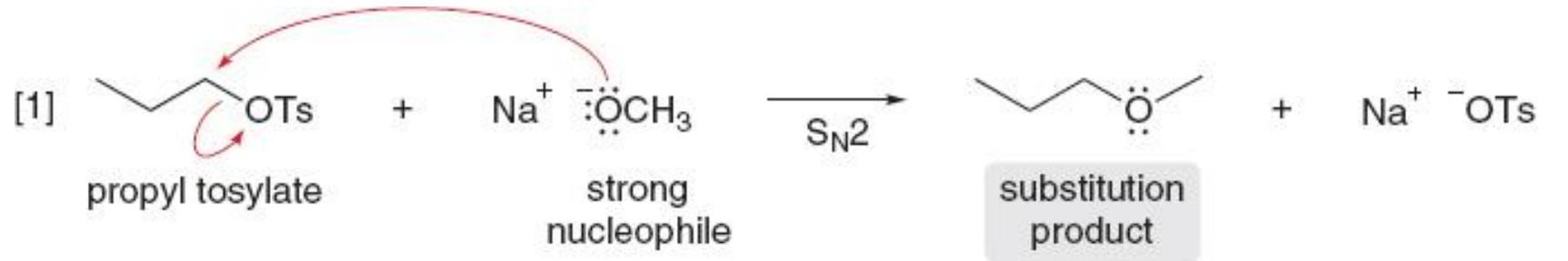
Conversione di alcoli in alogenuri alchilici via tosilati



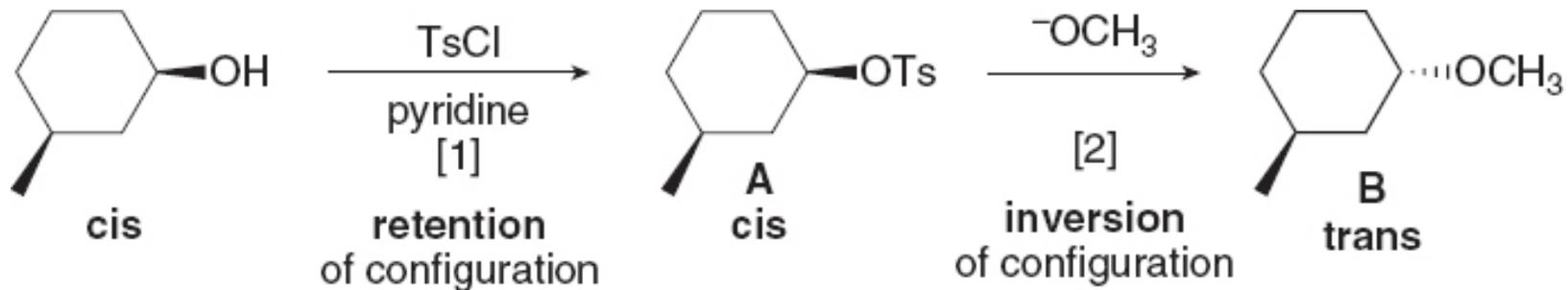
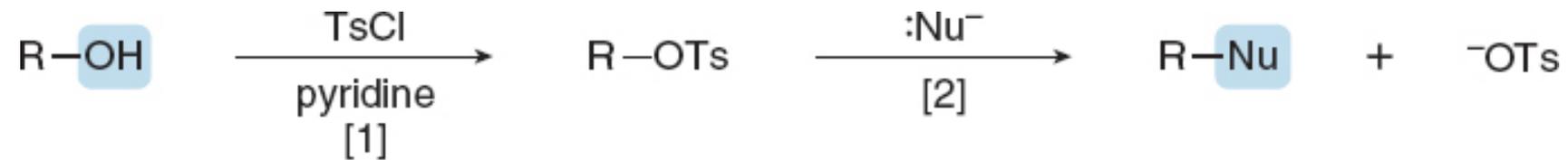
Tosilati: sintesi



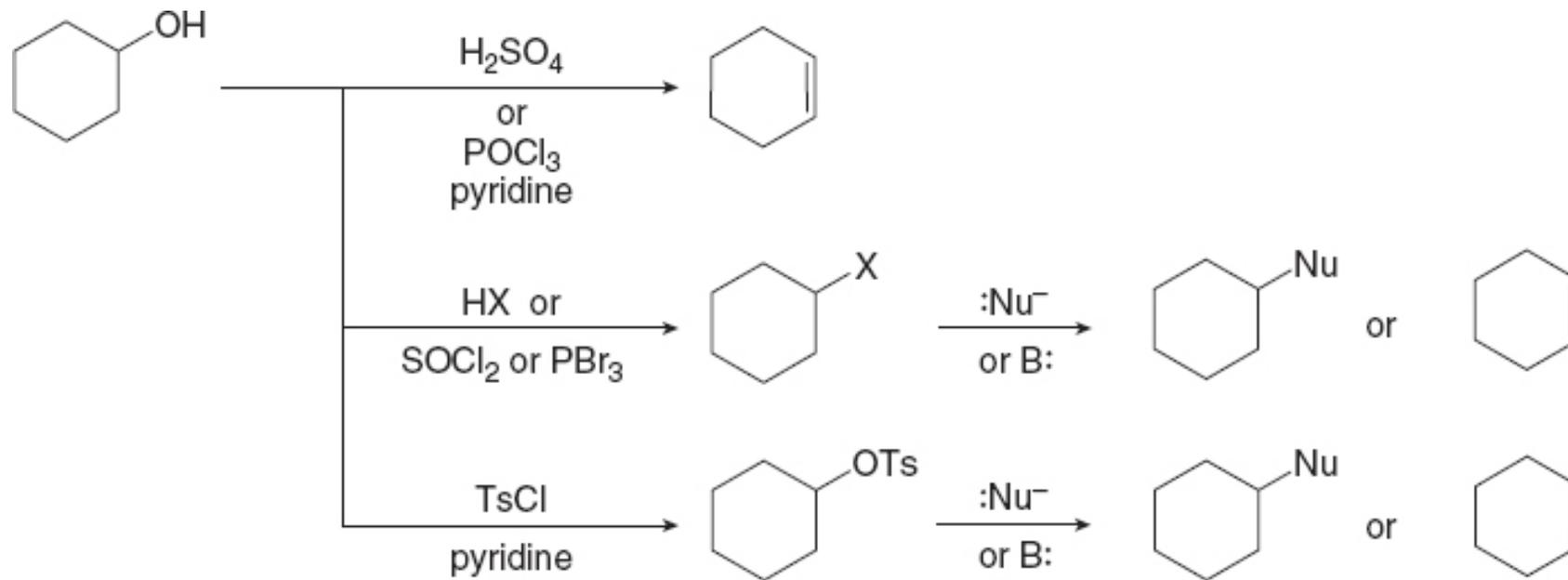
Tosilati: reattività (E2, S_N2 – reazioni stereospecifiche)



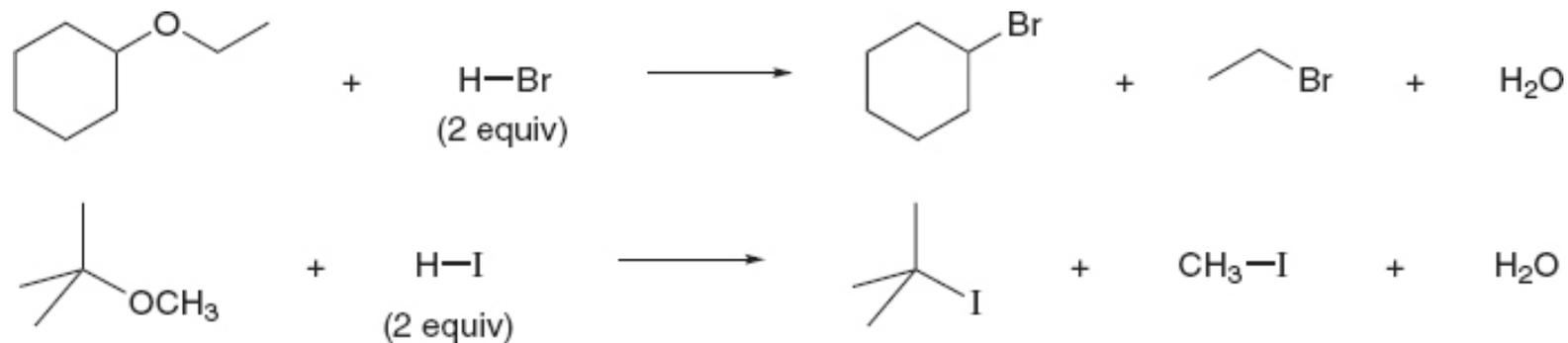
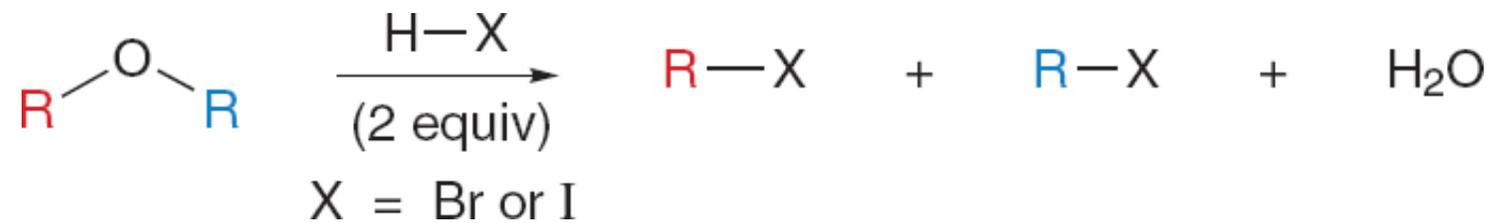
Reazioni in 2 passaggi: trasformazioni di alcoli



Trasformazioni di alcoli (eliminazioni e sostituzioni)



Reazione di Eteri con Acidi Forti



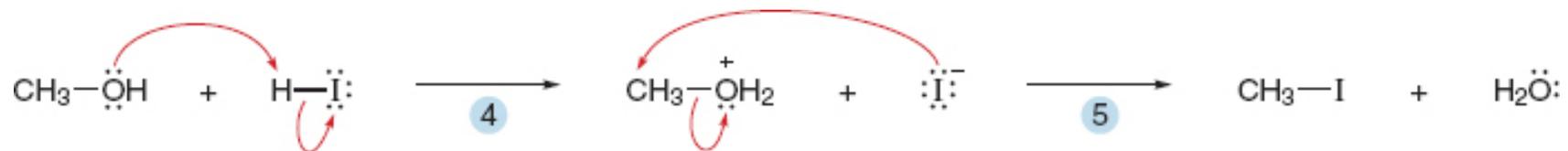
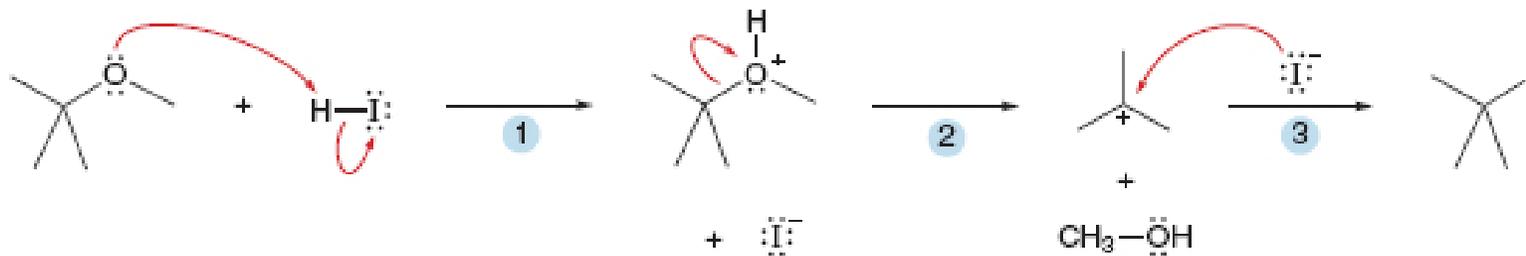
Il meccanismo della scissione degli eteri è $\text{S}_{\text{N}}1$ o $\text{S}_{\text{N}}2$, a seconda della natura di R

Reazione di Eteri con Acidi Forti (meccanismo)

S_N1 (R=2° o 3°) S_N2 (R=1°)

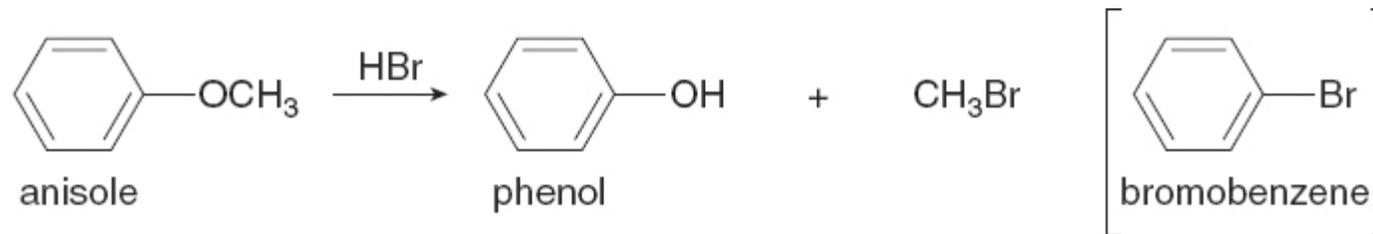
Bond to the 3° C is
cleaved by an S_N1 reaction.

Bond to the methyl C is
cleaved by an S_N2 reaction.

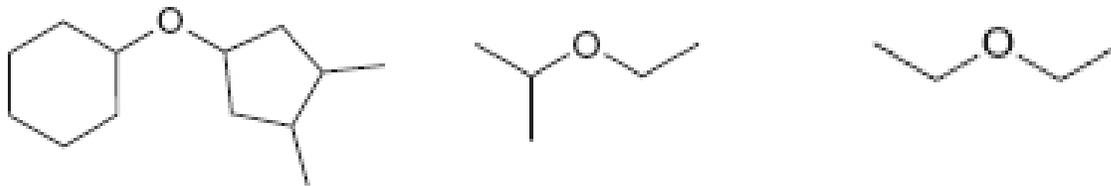


Reazione di Eteri con Acidi Forti

Spiega la seguente reazione (non si forma bromobenzene)

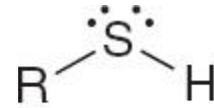


What alkyl halides are formed when each ether is treated with HBr ?

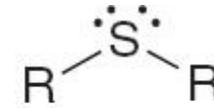


Tioli e solfuri (tioeteri)

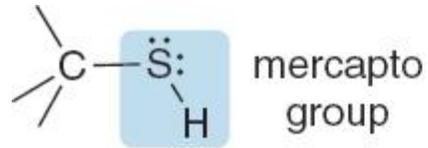
Analoghi agli alcoli e eteri



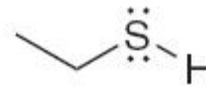
thiol



sulfide

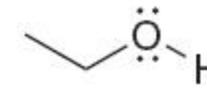


thiol



ethanethiol

bp 35 °C



ethanol

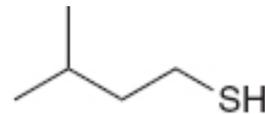
bp 78 °C

Hanno un cattivo odore



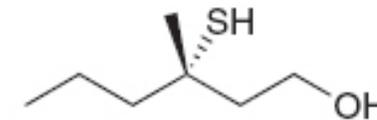
propane-1-thiol

onion odor



3-methylbutane-1-thiol

skunk odor

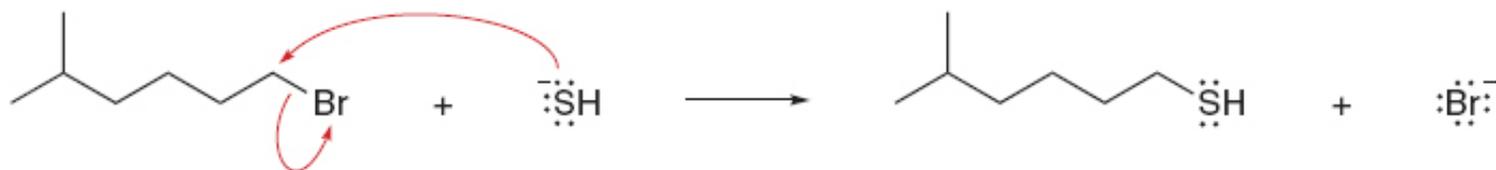


(S)-3-methyl-3-sulfanylohexan-1-ol

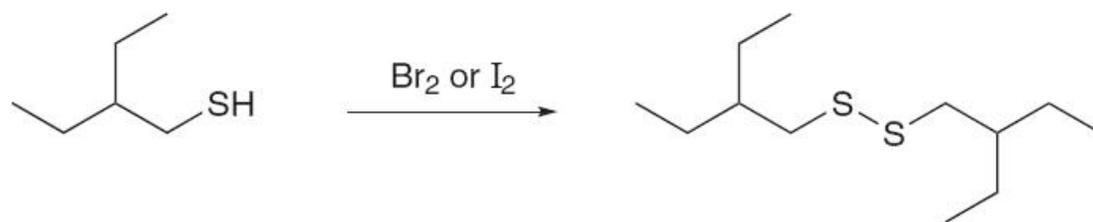
onion-like odor in human sweat

Tioli e solfuri – Sintesi - reattività

Da alogenuri alchilici

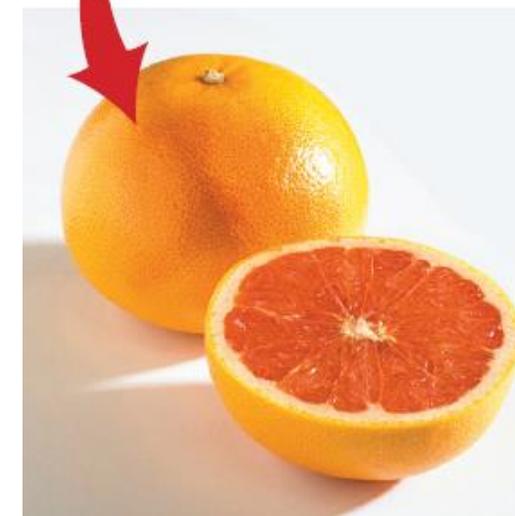
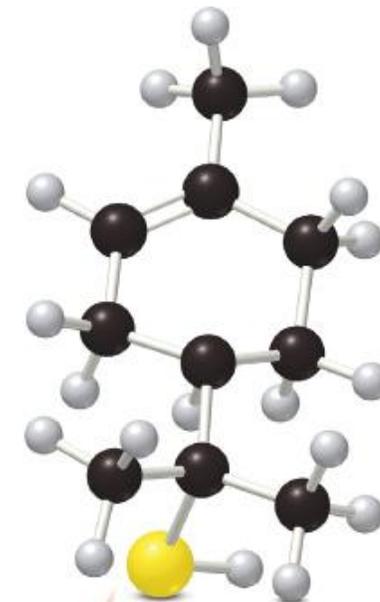
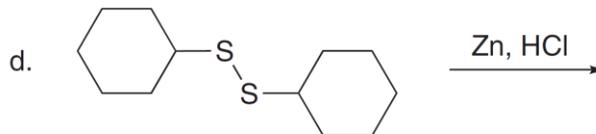
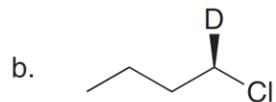
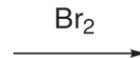
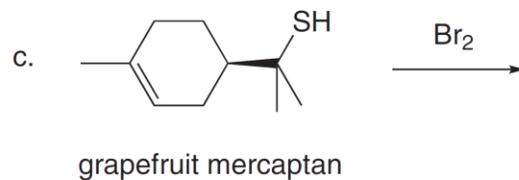
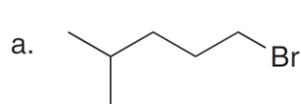


Si ossidano facilmente a disolfuri (Br_2 , I_2) che a loro volta possono essere ridotti facilmente con Zn/HCl



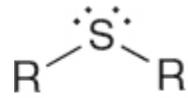
Tioli e solfuri – Sintesi reattività

Problem 9.31 Draw the product of each reaction.

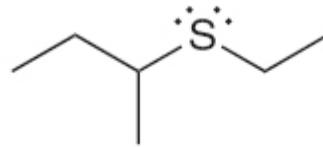


The potent odor of grapefruit mercaptan contributes to the characteristic aroma of grapefruit.

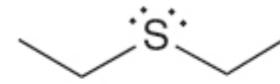
Solfuri – Sintesi/reattività



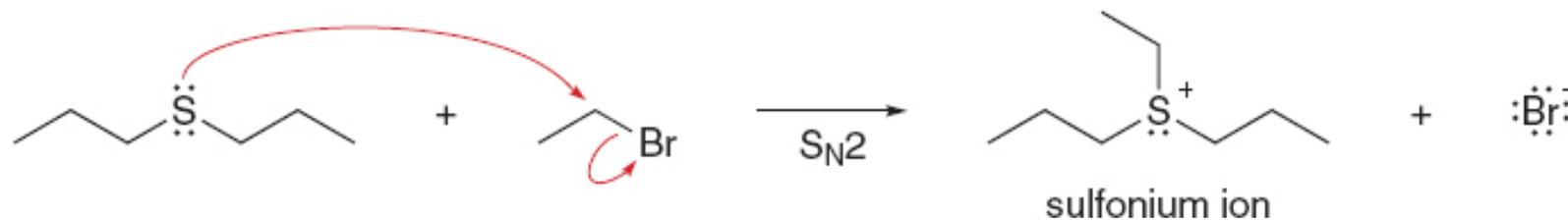
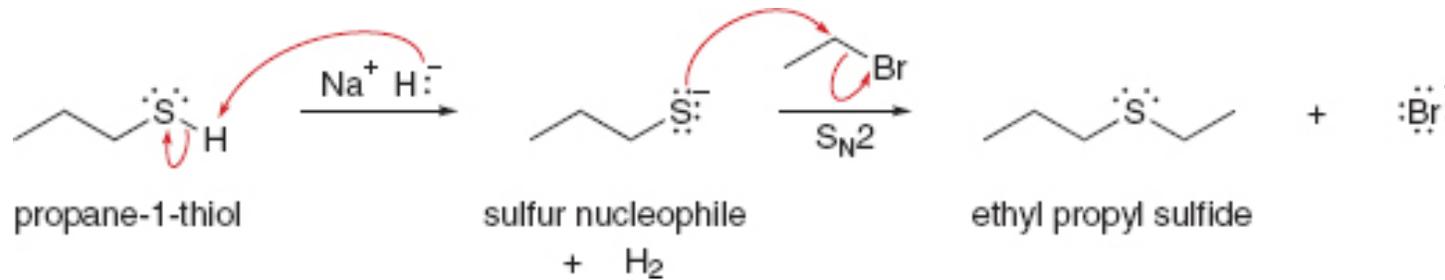
sulfide



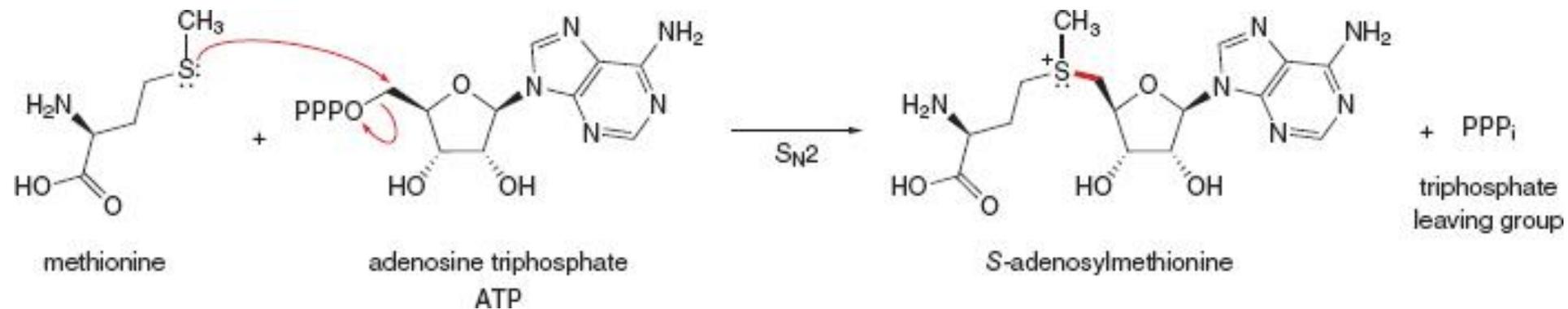
sec-butyl ethyl sulfide



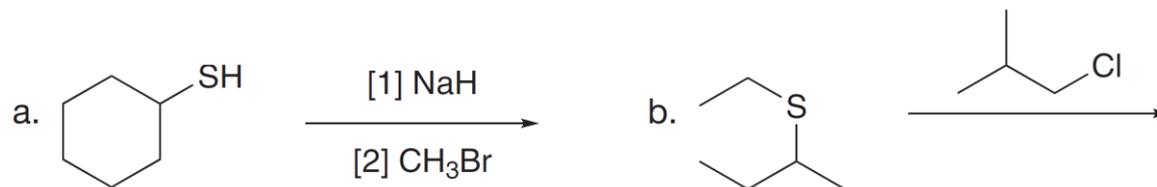
diethyl sulfide



Sintesi di SAM, un sale di solfonio, agente metilante



Draw the product of each reaction.

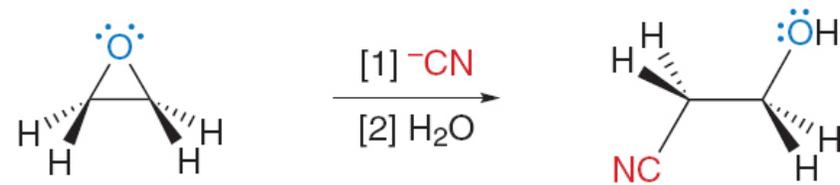
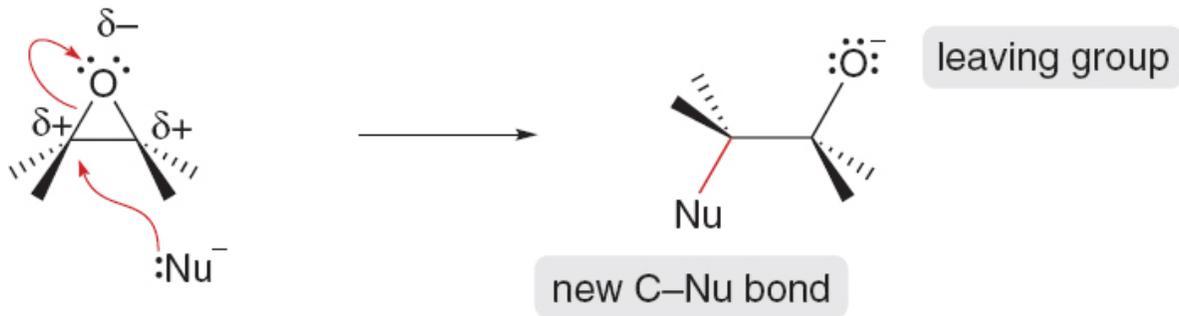


Eteri e Epossidi, reazione di sostituzione

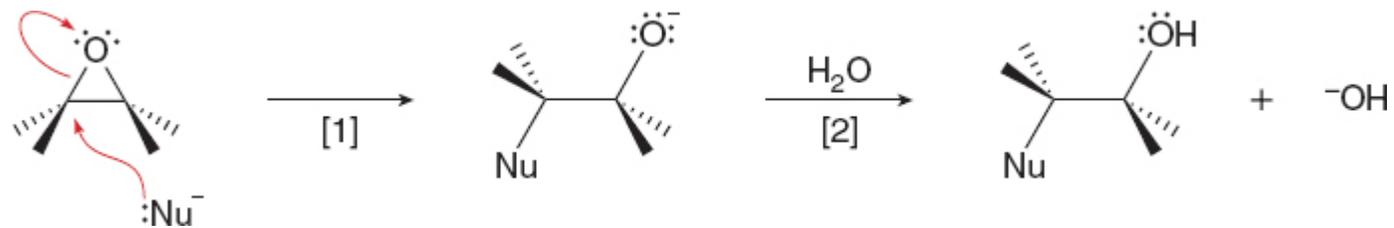
Eteri sono poco reattivi



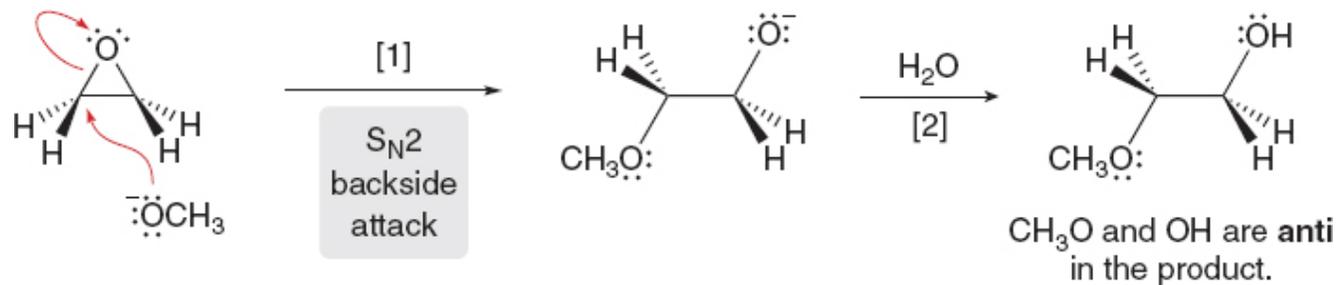
Epossidi: anello a tre membri, tensionato. Anche senza attivazione l'attacco nucleofilo fornisce un prodotto molto più stabile. **Servono forti nucleofili**



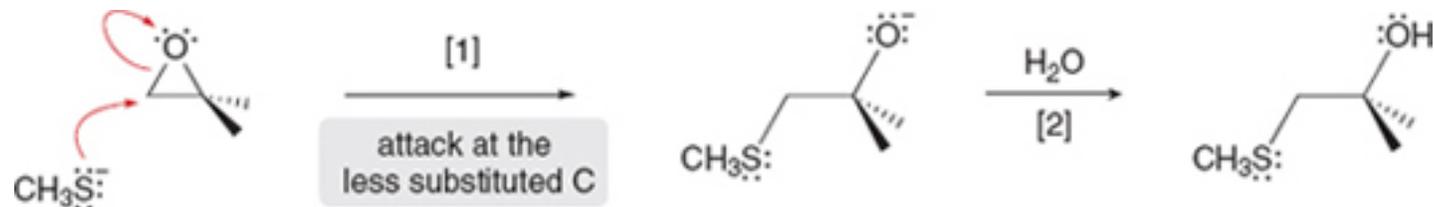
Apertura Epossidi con forti nucleofili - meccanismo



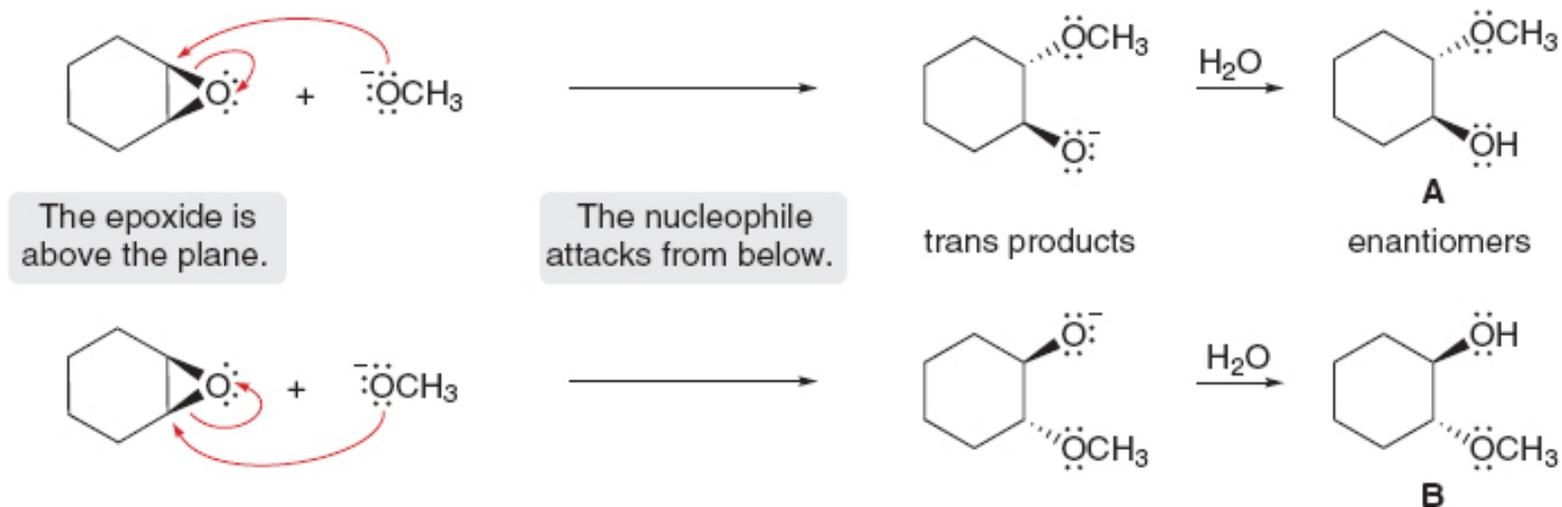
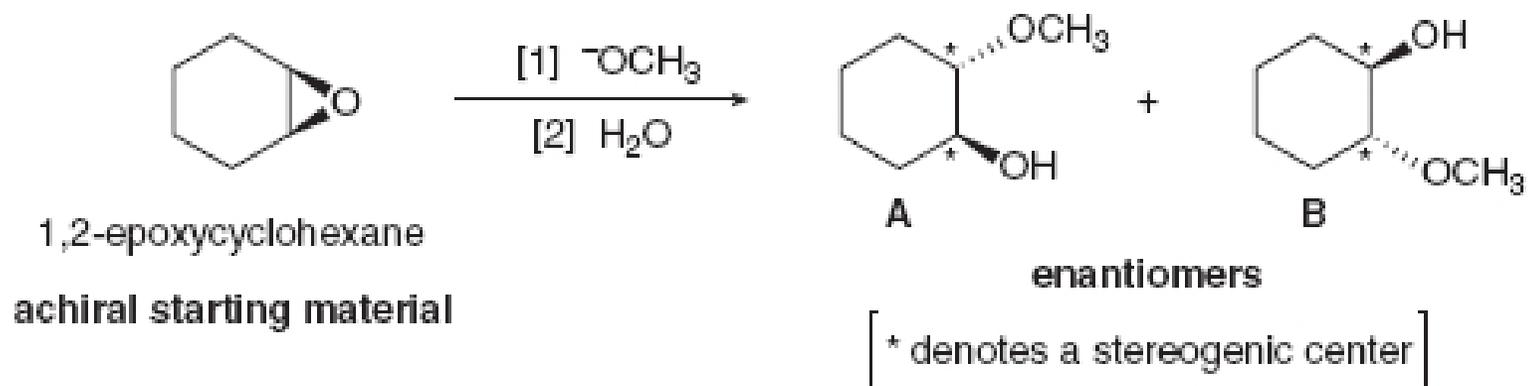
Reazione $\text{S}_{\text{N}}2$ Stereospecifica, regioselettiva



Attacco al carbonio meno sostituito

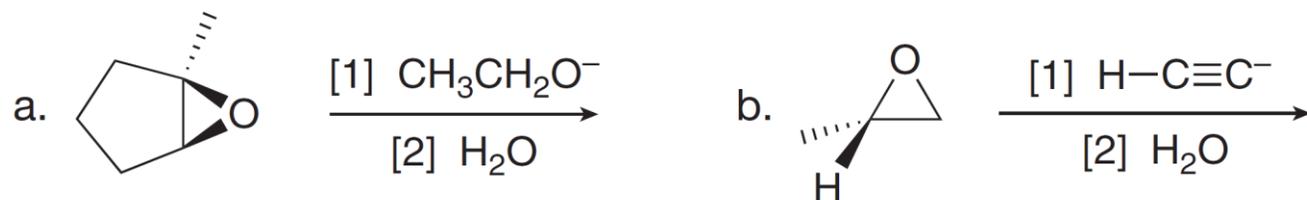


Apertura Epossidi con forti nucleofili - cicloesene ossido

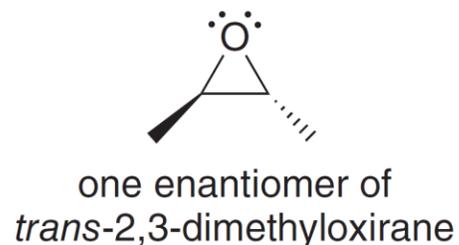
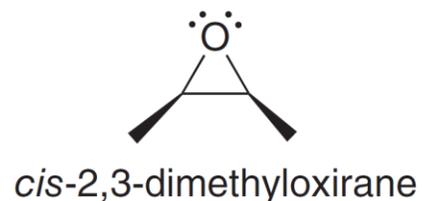


Apertura Epossidi con forti nucleofili - esercizi

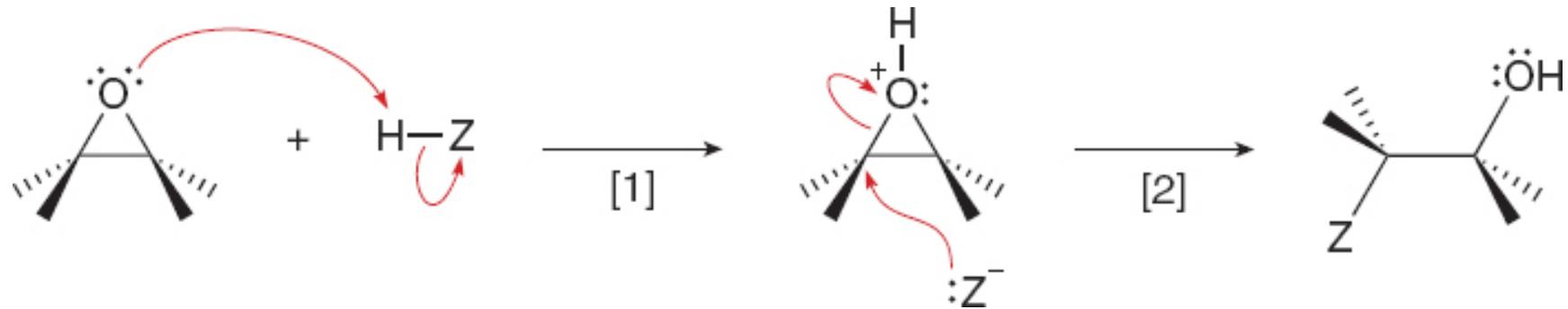
Draw the product of each reaction, indicating the stereochemistry at any stereogenic center.



The cis and trans isomers of 2,3-dimethyloxirane both react with ^-OH to give butane-2,3-diol. One stereoisomer gives a single achiral product, and one gives two chiral enantiomers. Which epoxide gives one product and which gives two?



Apertura Epossidi con Acidi HZ (S_N2)

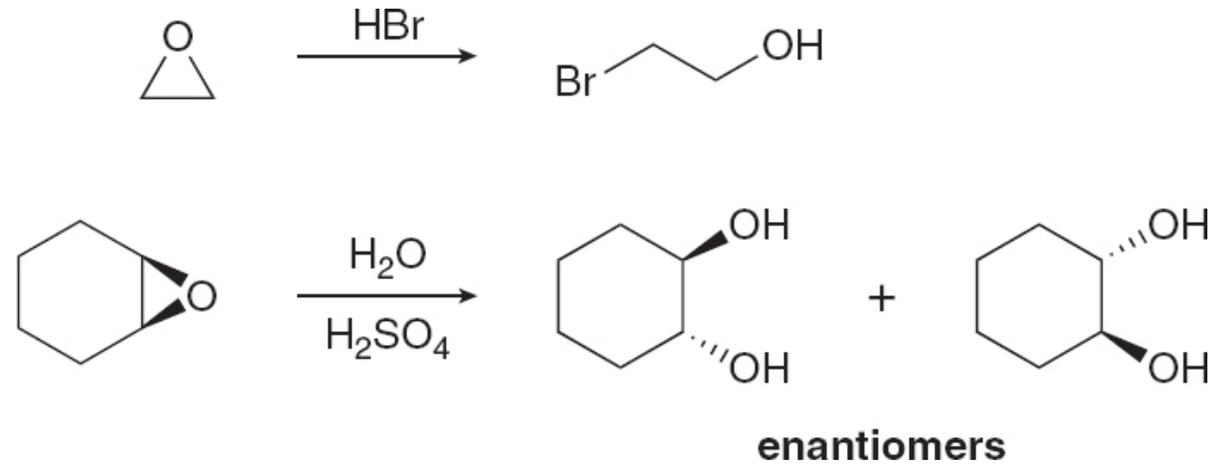


- **Step [1]:** protonazione dell'ossigeno dell'eossido con HZ rende l'ossigeno dell'eossido un miglior gruppo uscente. Si genera anche un buon nucleofilo in soluzione (Z^-) che può aprire l'anello epossidico.

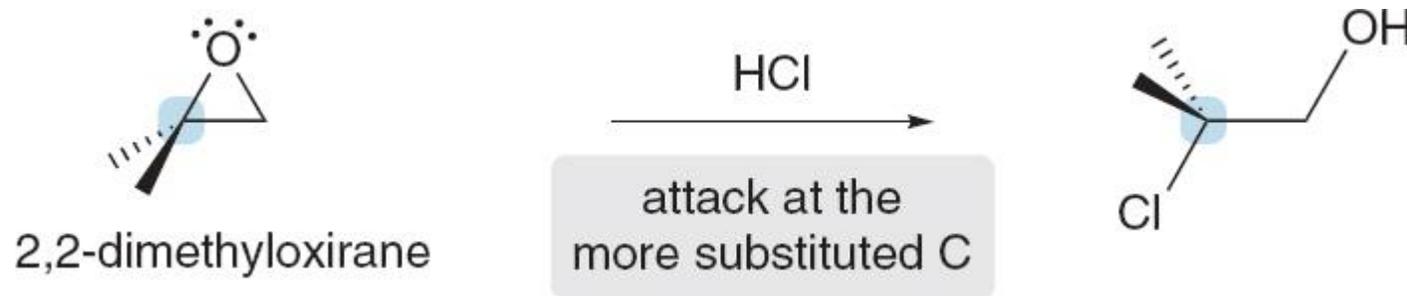
- **Step [2]:** il nucleofolo Z^- apre l'eossido con un attacco dalla parte opposta (S_N2)

- HZ: HCl, HBr, HI, H_2O/H_2SO_4 ; ROH/ H_2SO_4

Apertura Epossidi con Acidi HZ (S_N2)

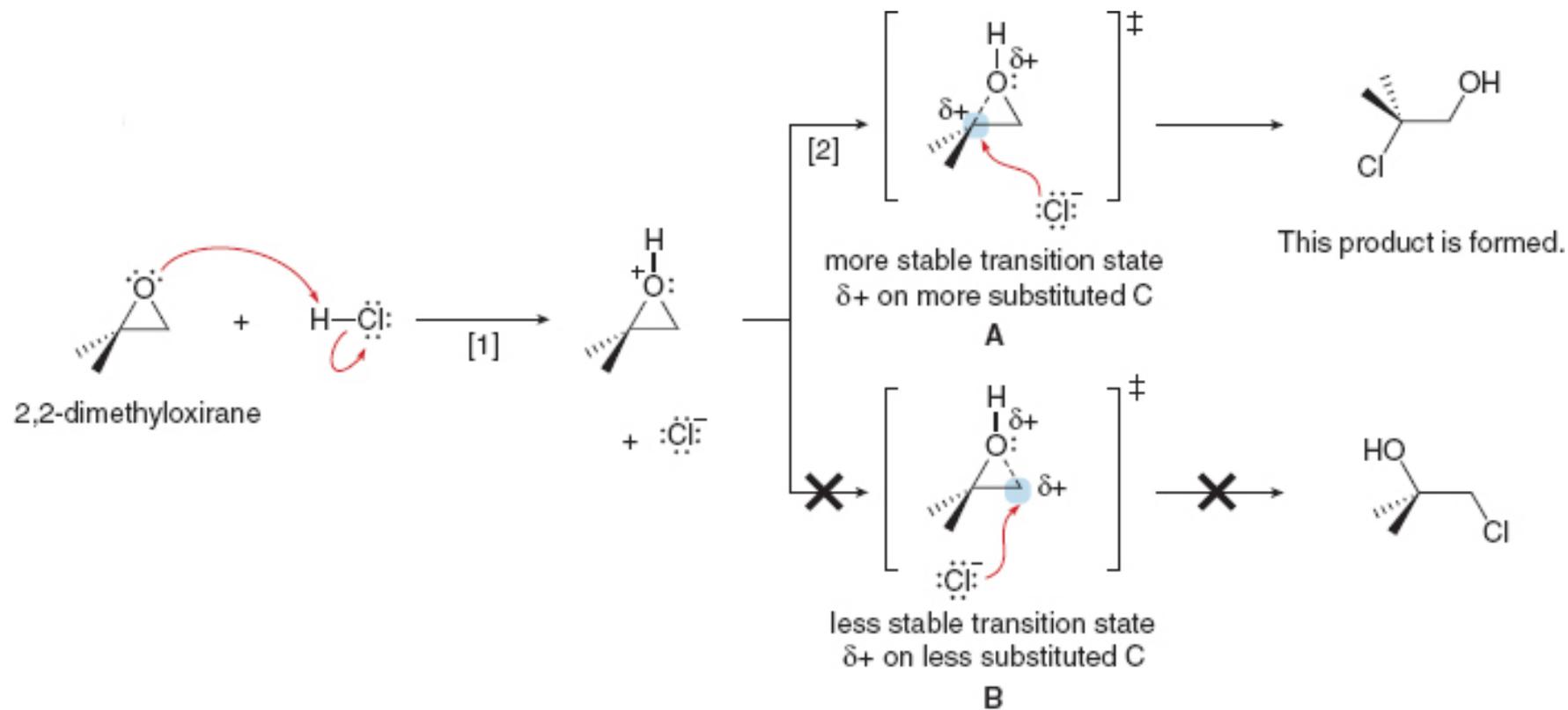


Regiochimica



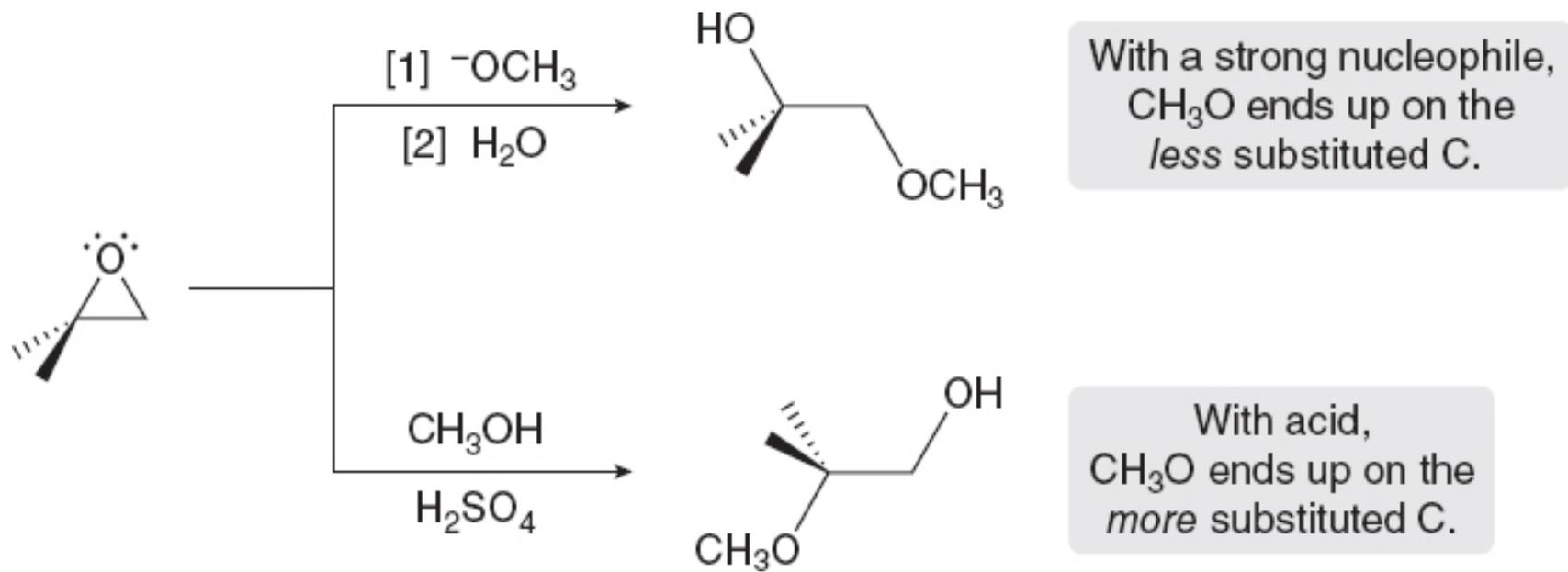
Apertura Epossidi con Acidi HZ (S_N2) – regiochimica

Attacco al carbonio più elettrofilo (+ sostituito)

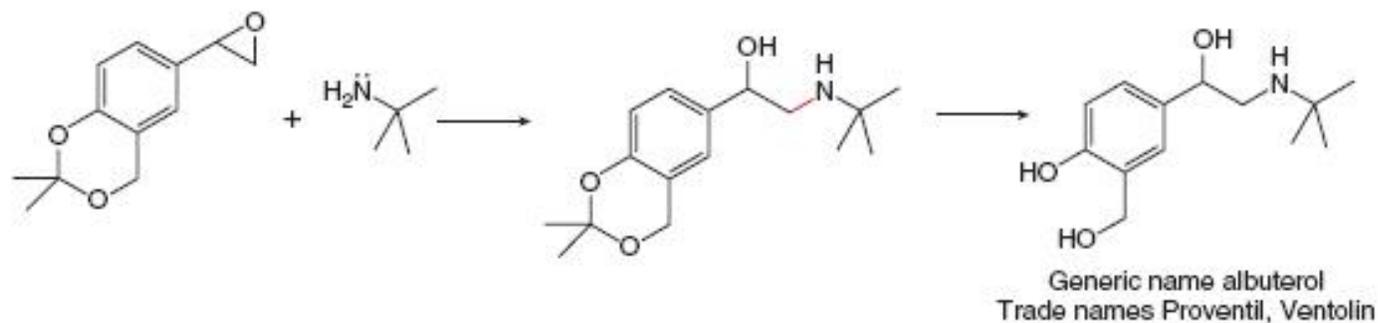
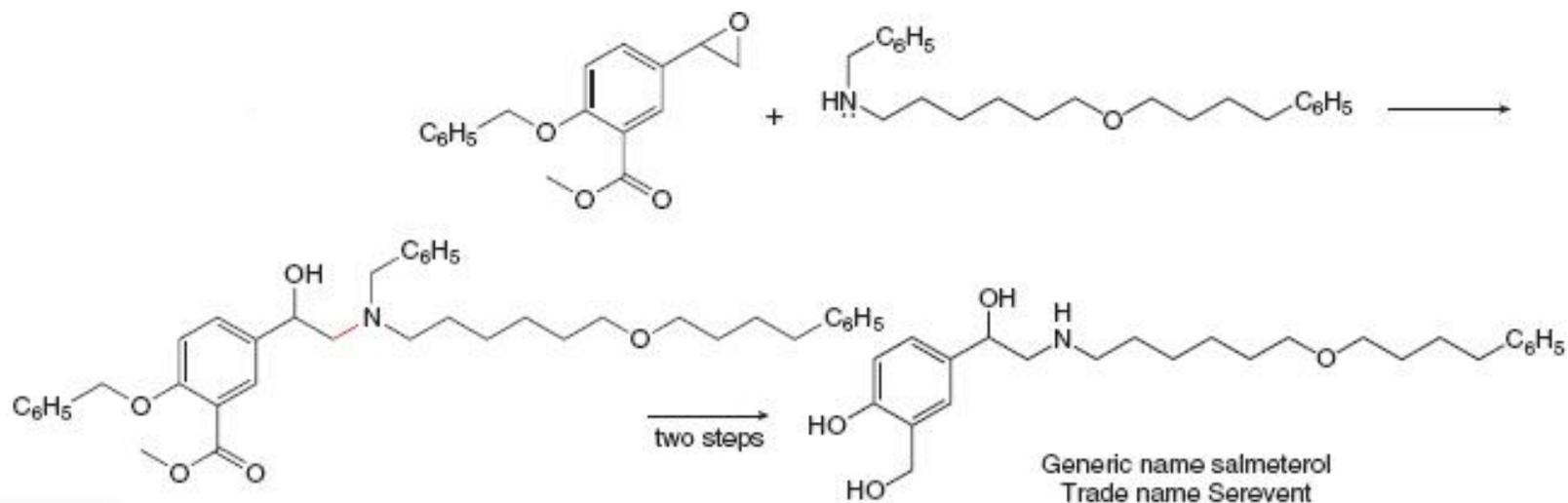


- Transition state **A** is lower in energy because the partial positive charge (δ^+) is located on the more substituted carbon. In this case, therefore, nucleophilic attack occurs from the back side (an S_N2 characteristic) at the more substituted carbon (an S_N1 characteristic).

Apertura Epossidi con Acidi HZ (S_N2) – Controllo della regiochimica di apertura



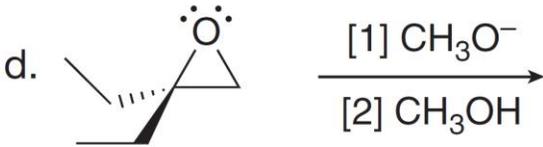
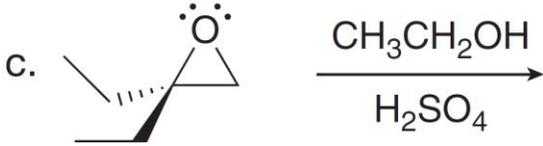
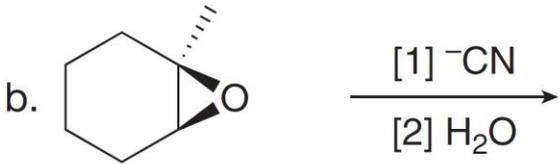
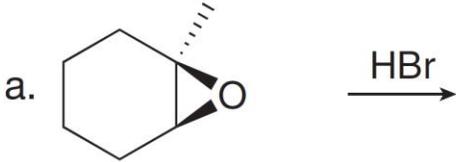
Apertura Epossidi nella sintesi di principi attivi



- A key step in each synthesis is the opening of an epoxide ring with a nitrogen nucleophile to form a new C-N bond, shown in red.

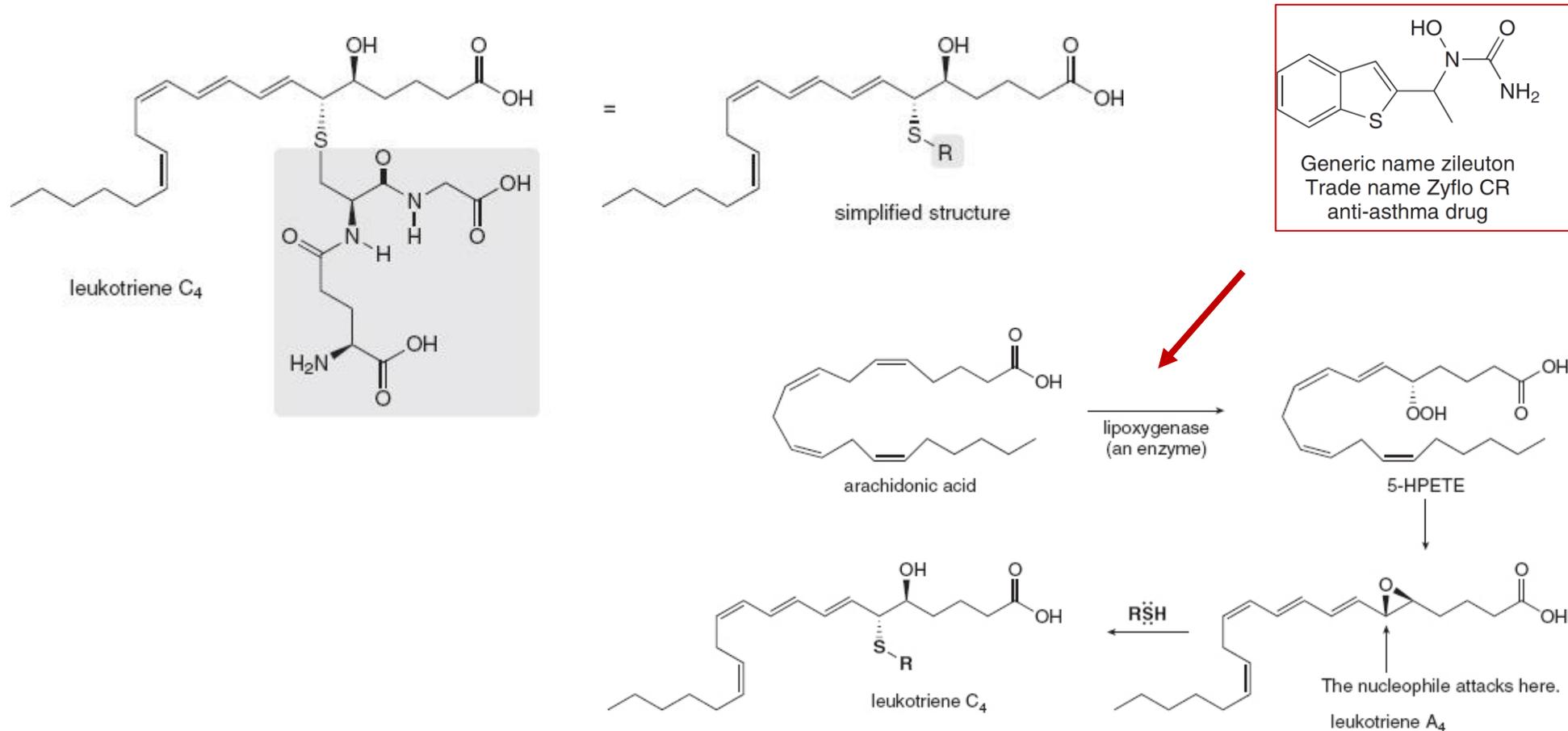
Epossidi esercizi

Draw the product of each reaction.



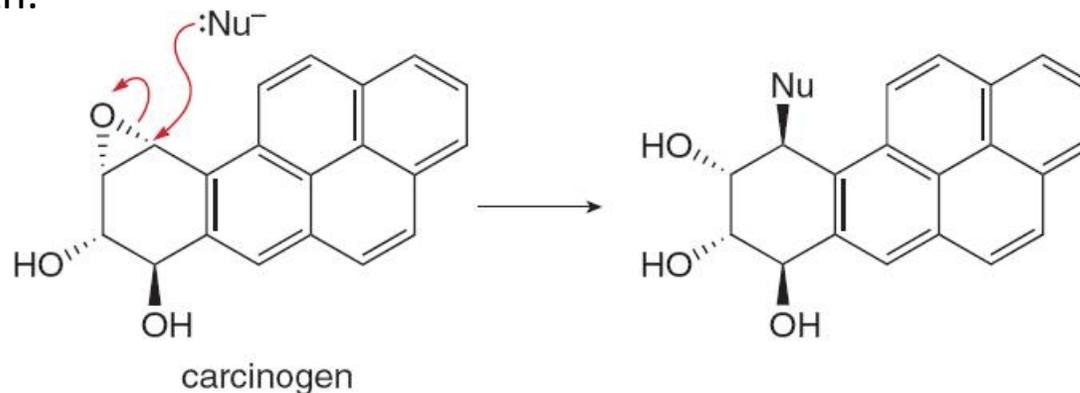
Epossidi, Asma e Leucotrieni

I leucotrieni contribuiscono alla risposta asmatica, sono molecole molto instabili ed efficaci in bassissimo dosaggio. Si ottengono dall'acido arachinoico, via sintesi di un epossido e attacco nucleofilo con un residui cisteinico



Benzo[*a*]pyrene, Epossidi e Cancro

Benzo[*a*]pyrene is a widespread environmental pollutant, produced during the combustion of all types of organic material—gasoline, fuel oil, wood, garbage, and cigarettes. It is a **polycyclic aromatic hydrocarbon (PAH)**. After this nonpolar and water-insoluble hydrocarbon is inhaled or ingested, it is oxidized in the liver to a diol epoxide. Oxidation is a common fate of foreign substances that are not useful nutrients for the body. The oxidation product has three oxygen-containing functional groups, making it much more water soluble, and more readily excreted in urine. It is also a potent carcinogen. The strained three-membered ring of the epoxide reacts readily with biological nucleophiles $:\text{Nu}^-$ (such as DNA or an enzyme), leading to ring-opened products that often disrupt normal cell function, causing cancer or cell death.



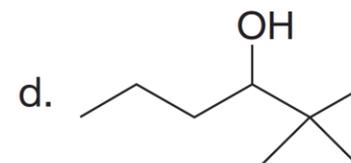
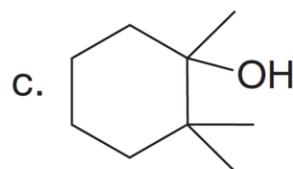
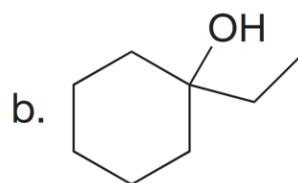
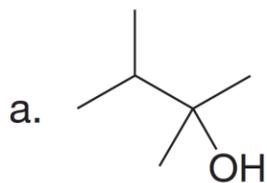
alcoli, eteri, epossidi - esercizi

Alcohols

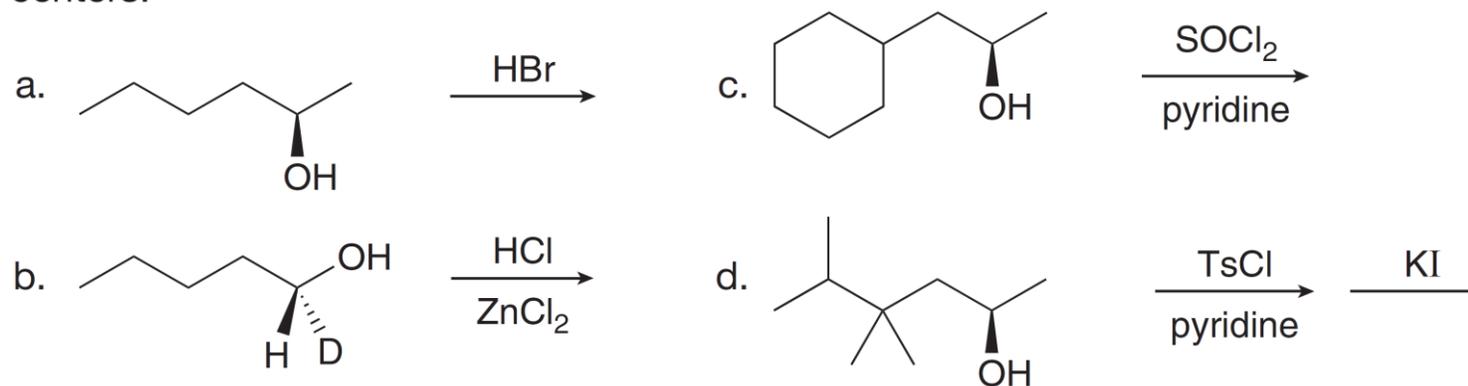
9.45 Draw the organic product(s) formed when $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$ is treated with each reagent.

- | | | |
|---------------------------------|---|---------------------------------|
| a. H_2SO_4 | e. SOCl_2 , pyridine | i. [1] TsCl, pyridine; [2] NaSH |
| b. NaH | f. PBr_3 | j. POCl_3 , pyridine |
| c. $\text{HCl} + \text{ZnCl}_2$ | g. TsCl, pyridine | |
| d. HBr | h. [1] NaH; [2] $\text{CH}_3\text{CH}_2\text{Br}$ | |

9.46 What alkenes are formed when each alcohol is dehydrated with TsOH? Label the major product when a mixture results.

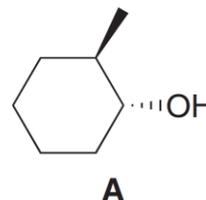


9.48 Draw the products of each reaction and indicate stereochemistry around stereogenic centers.

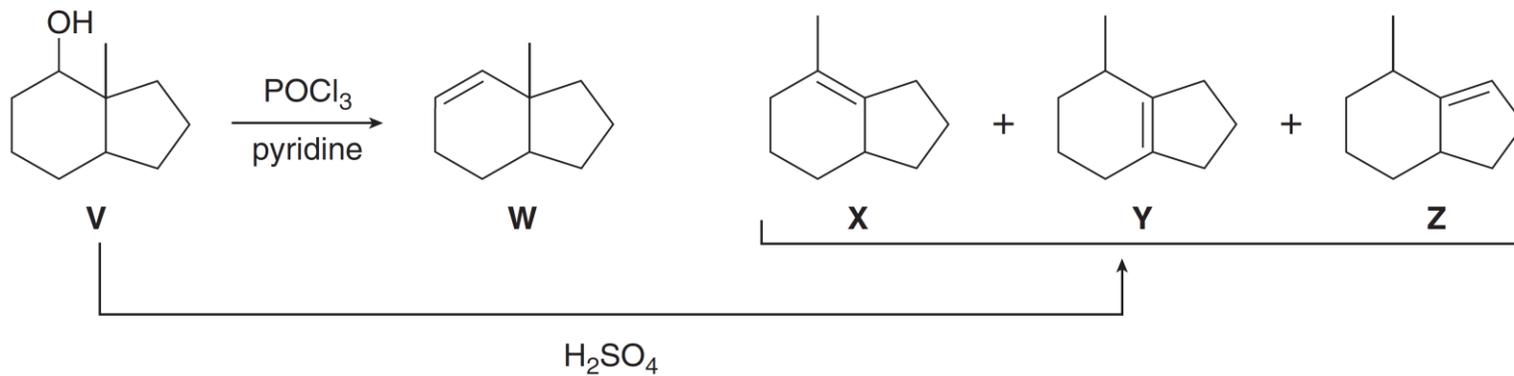


9.50 Draw the substitution product formed (including stereochemistry) when (*R*)-hexan-2-ol is treated with each series of reagents: (a) NaH, followed by CH₃I; (b) TsCl and pyridine, followed by NaOCH₃; (c) PBr₃, followed by NaOCH₃. Which two routes produce identical products?

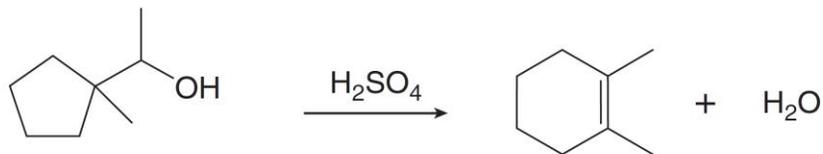
9.51 (a) What is the major alkene formed when **A** is dehydrated with H₂SO₄? (b) What is the major alkene formed when **A** is treated with POCl₃ and pyridine? Explain why the major product is different in these reactions.



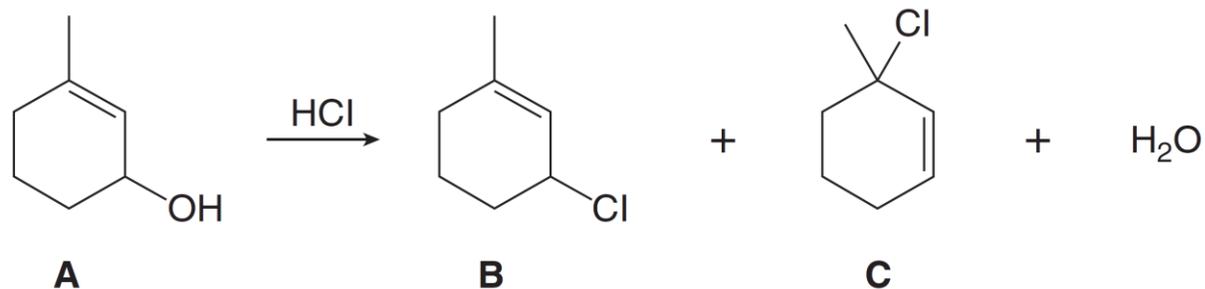
9.53 Although alcohol **V** gives a single alkene **W** when treated with POCl_3 and pyridine, three isomeric alkenes (**X-Z**) are formed on dehydration with H_2SO_4 . Draw a stepwise mechanism for each reaction and explain why the difference occurs.



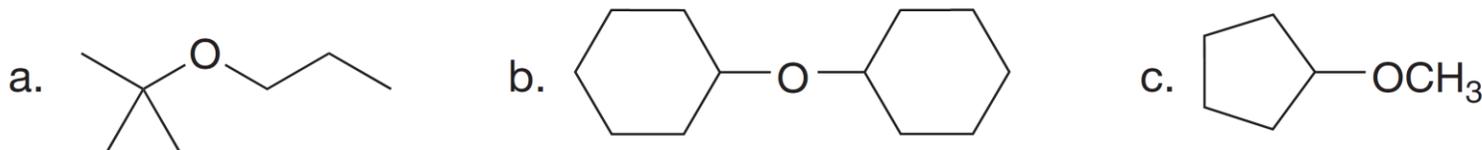
9.54 Sometimes carbocation rearrangements can change the size of a ring. Draw a stepwise, detailed mechanism for the following reaction.



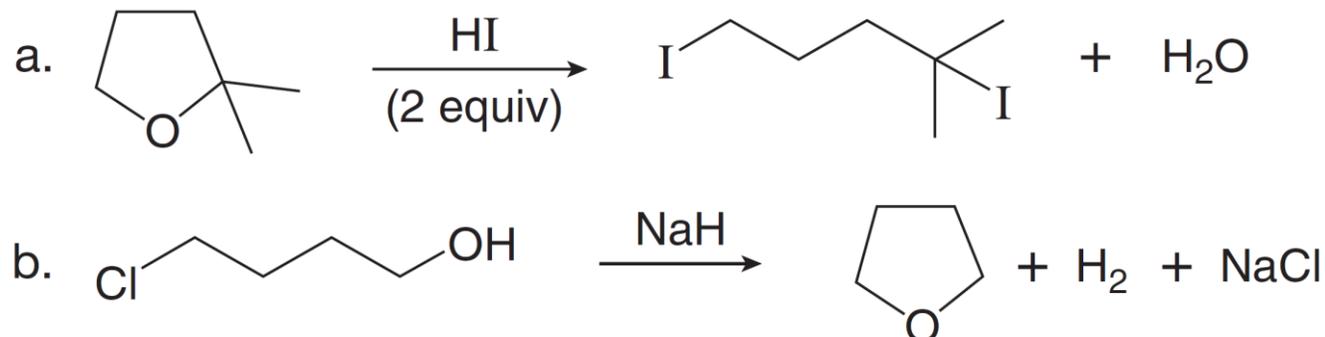
9.56 An allylic alcohol contains an OH group on a carbon atom adjacent to a C–C double bond. Treatment of allylic alcohol **A** with HCl forms a mixture of two allylic chlorides, **B** and **C**. Draw a stepwise mechanism that illustrates how both products are formed.



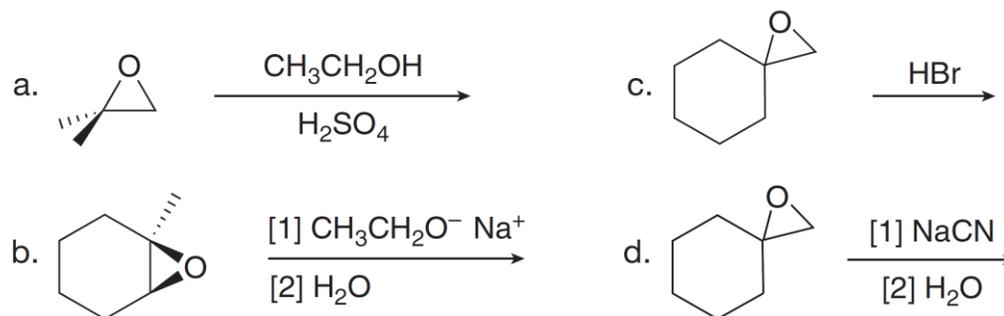
9.61 Draw the products formed when each ether is treated with two equivalents of HBr.



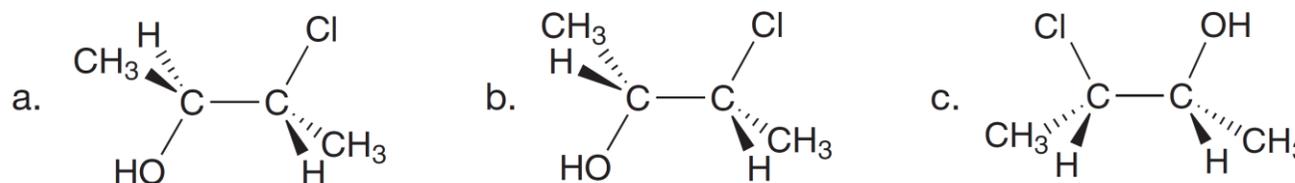
9.62 Draw a stepwise mechanism for each reaction.



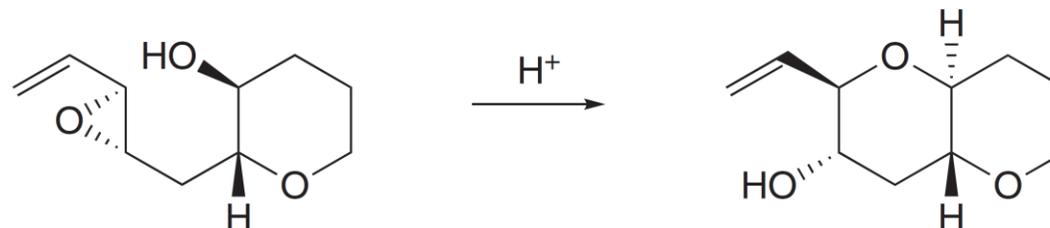
9.65 Draw the products of each reaction.



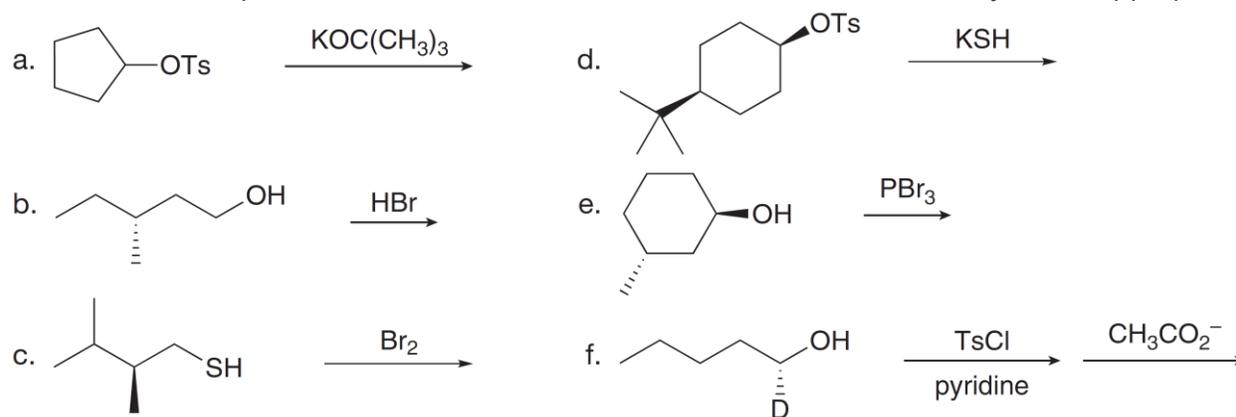
9.66 When each halohydrin is treated with NaH, a product of molecular formula C_4H_8O is formed. Draw the structure of the product and indicate its stereochemistry.



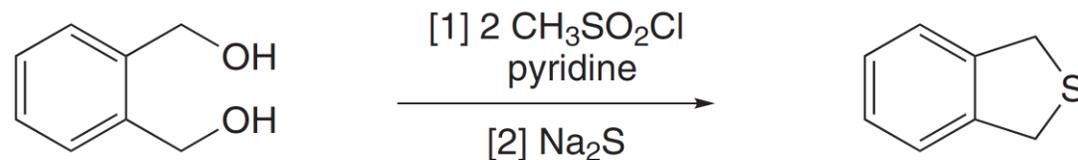
9.68 Draw a stepwise mechanism for the following reaction and explain the stereochemistry of the product.



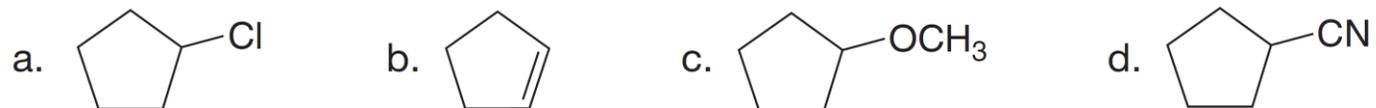
9.69 Draw the products of each reaction, and indicate the stereochemistry where appropriate.



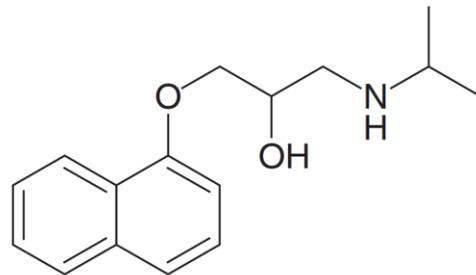
9.70 The following two-step procedure was used to prepare a sulfide from a diol. Draw the intermediate formed in Reaction [1] and draw a mechanism for Reaction [2].



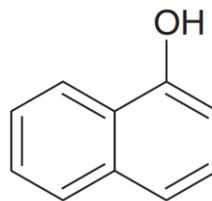
9.71 Prepare each compound from cyclopentanol. More than one step may be needed.



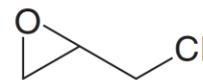
9.73 **Propranolol**, an antihypertensive agent used in the treatment of high blood pressure, can be prepared from 1-naphthol, epichlorohydrin, and isopropylamine using two successive nucleophilic substitution reactions. Devise a stepwise synthesis of propranolol from these starting materials.



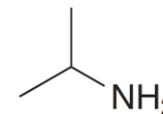
propranolol



1-naphthol

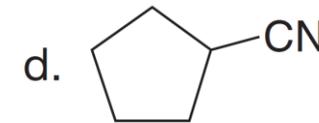
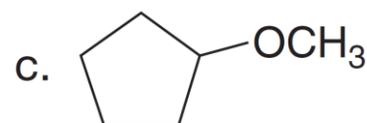
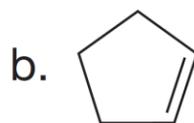


epichlorohydrin



isopropylamine

9.71 Prepare each compound from cyclopentanol. More than one step may be needed.



9.72 Identify the reagents (a–h) needed to carry out each reaction.

