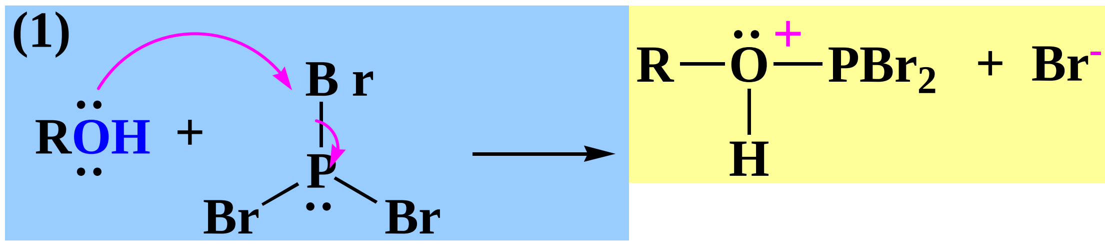
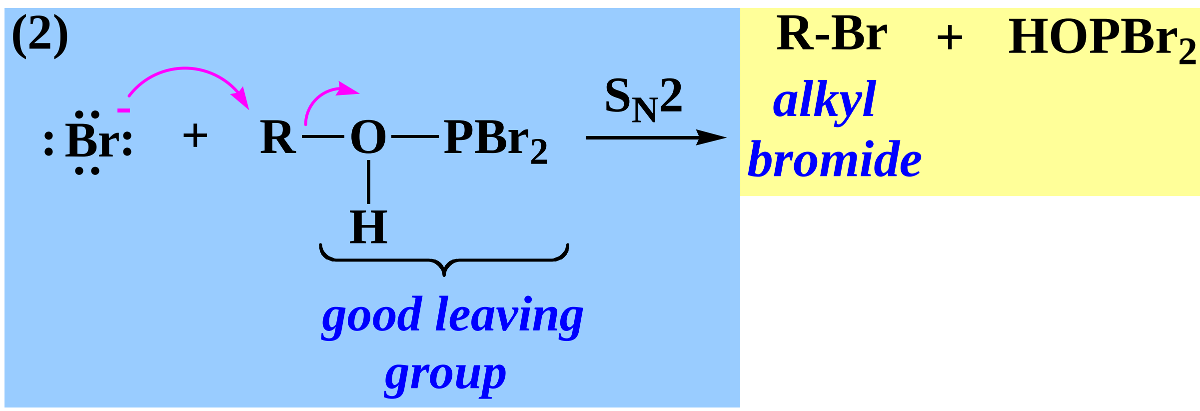
Section 9--Alkyl Halides from the Reactions of Alcohols with PBr_3 or $SOCl_2$

Reaction of Alcohols with Phosphorous Tribromide

A general synthesis of alkyl bromides is the reaction of alcohols with PBr_3 (a colorless, fuming liquid, bp 173º C). An advantage of this procedure is the absence of carbocation rearrangements.





This reaction proceeds well with primary and secondary alcohols. The overall stoichiometry is:

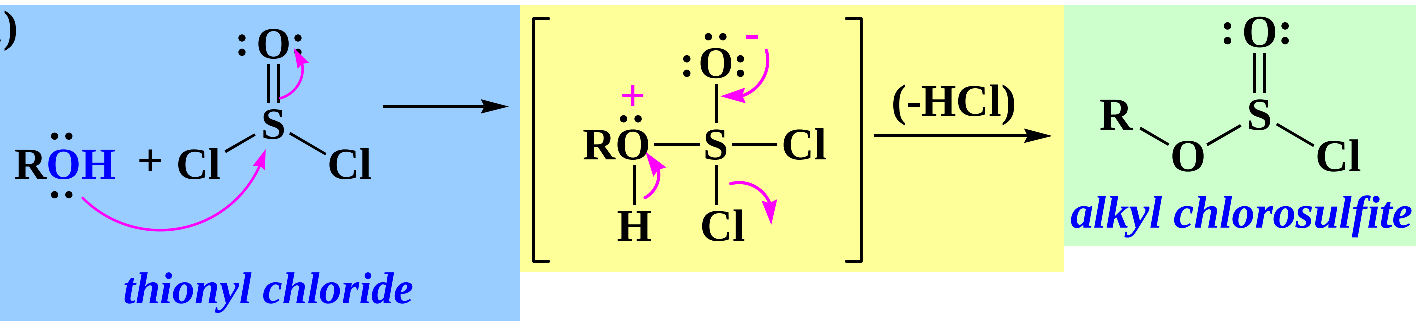
$$3\ ROH + PBr_3 \longrightarrow 3\ RBr + 3\ H_3PO_3$$

phosphorous acid

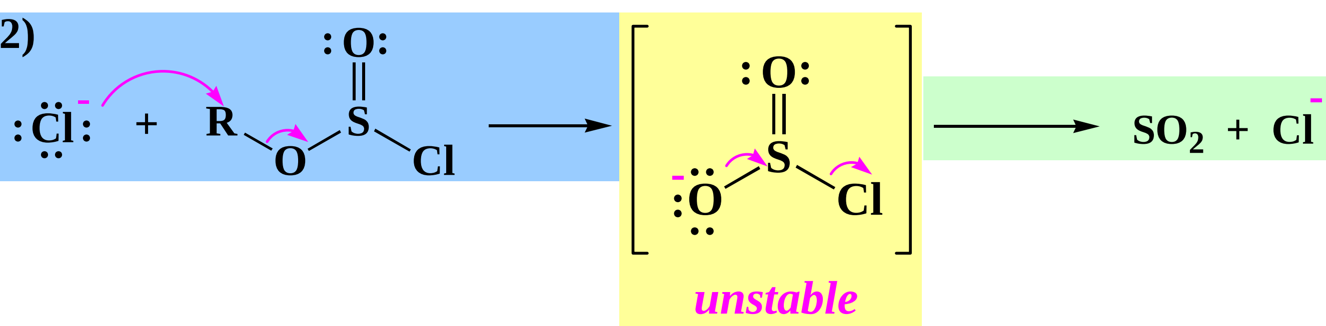
Reaction of Alcohols with Thionyl Chloride

A similar reaction occurs with primary and secondary alcohols and $SOCl_2$ to yield alkyl chlorides.

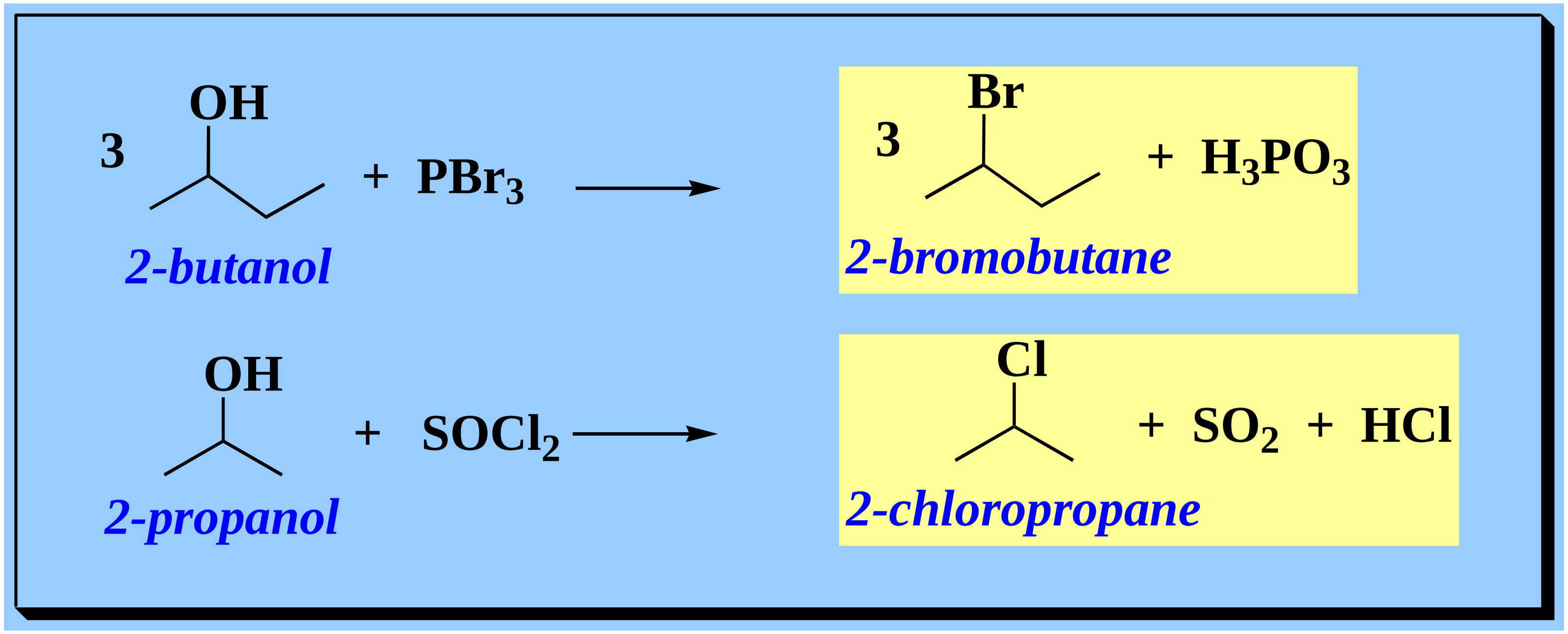
(1)



(2)



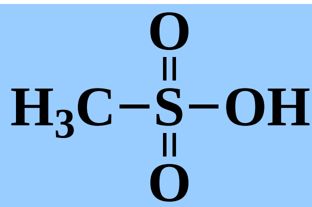
Examples


3
OH
+ PBr3
2-butanol
3
Br
+ H3PO3
2-bromobutane
OH
+ SOCl2
2-propanol
Cl
+ SO2 + HCl
2-chloropropane

Section 10--Tosylates, Mesylates and Triflates: Leaving Group Derivatives of Alcohols

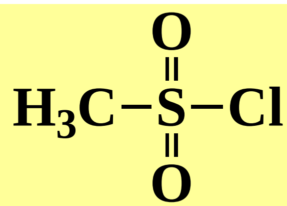
Sulfonate Esters: Better Leaving Groups

It is relatively easy to convert the hydroxyl group into a sulfonate ester that is a much better leaving group. The alcohol is reacted with derivatives of alkyl or aryl sulfonic acids called sulfonyl chlorides.

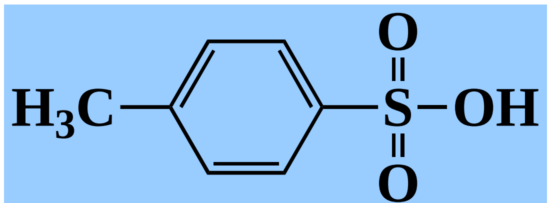


methanesulfonic acid

pK_a = -7

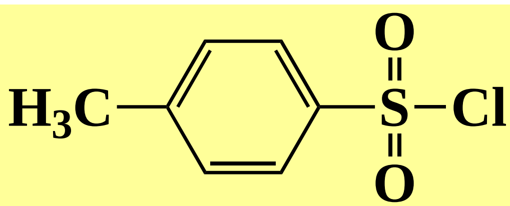


methanesulfonyl chloride



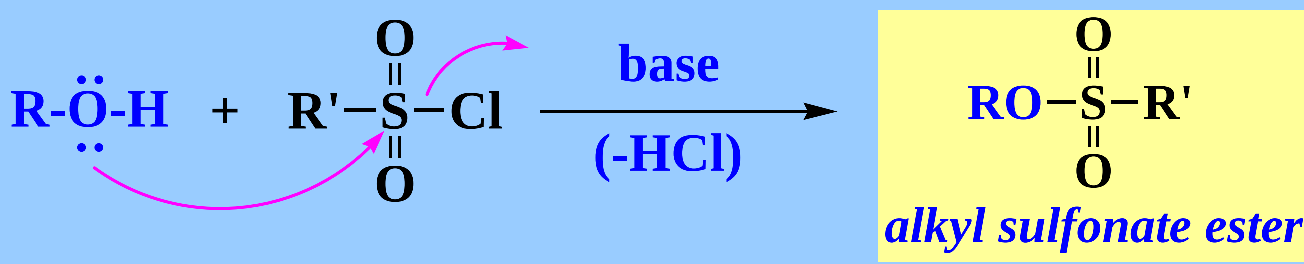
p-toluenesulfonic acid

$pK_a \approx -7$



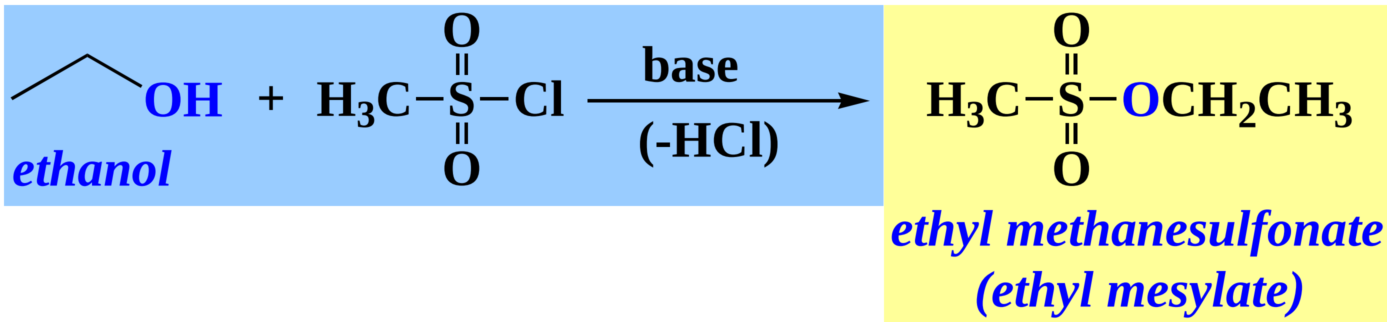
p-toluenesulfonyl chloride

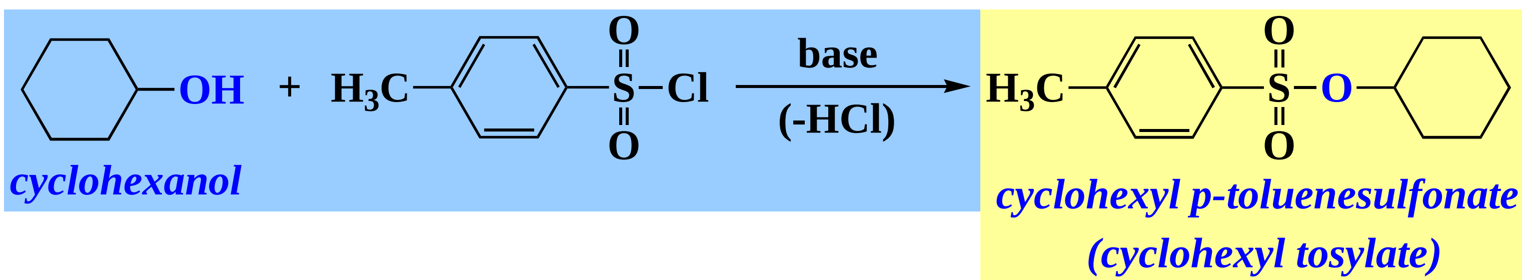
The Synthesis of Sulfonate Esters from Alcohols



Alcohols react readily with sulfonyl chlorides in the presence of amine bases producing sulfonate esters.

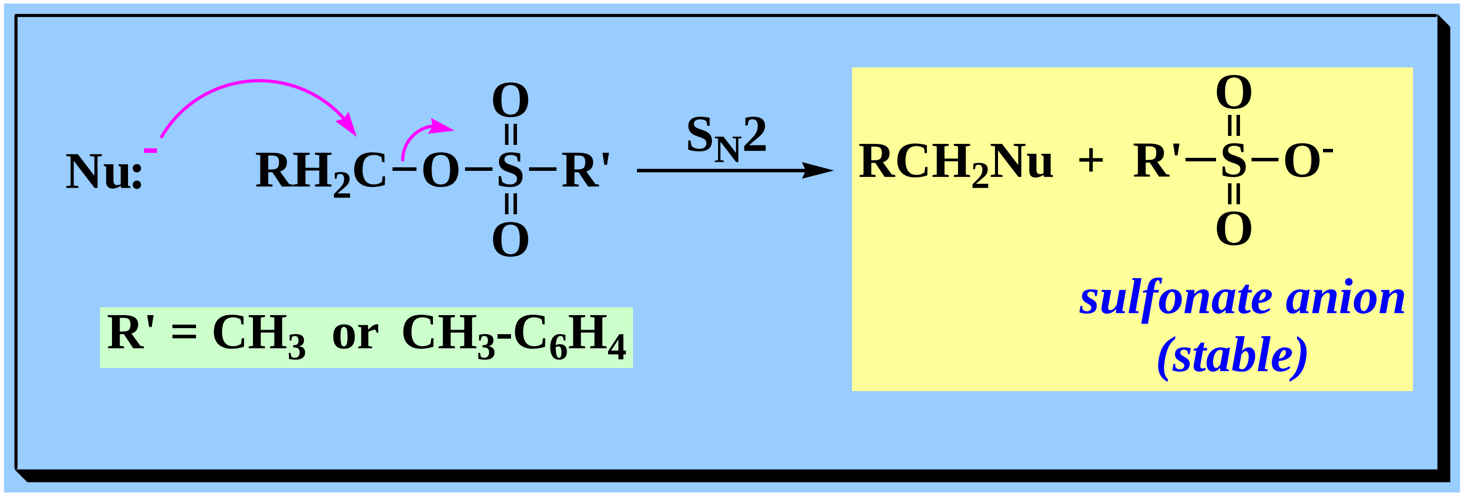
Examples


OH
ethanol
+
$H_3C-S(=O)_2-Cl$
base
(-HCl)
$H_3C-S(=O)_2-OCH_2CH_3$
ethyl methanesulfonate
(ethyl mesylate)


OH
cyclohexanol
+
H_3C
S
O
O
Cl
base
(-HCl)
H_3C
S
O
O
O
cyclohexyl p-toluenesulfonate
(cyclohexyl tosylate)

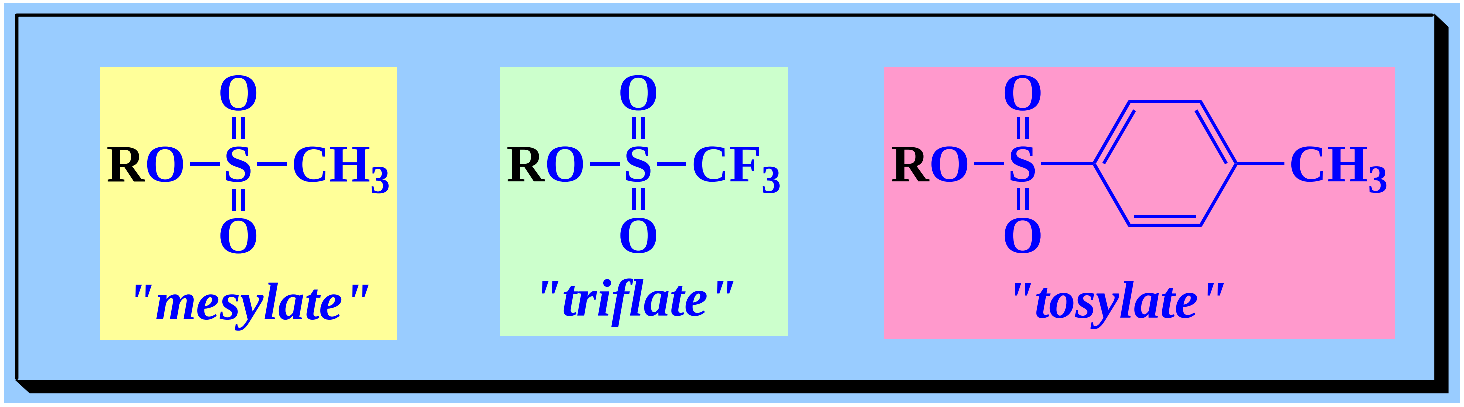
Mesylates and Tosylates in S_N2 Reactions

Sulfonate esters are often used as substrates in S_N2 reactions because the sulfonate anion is a good leaving group.



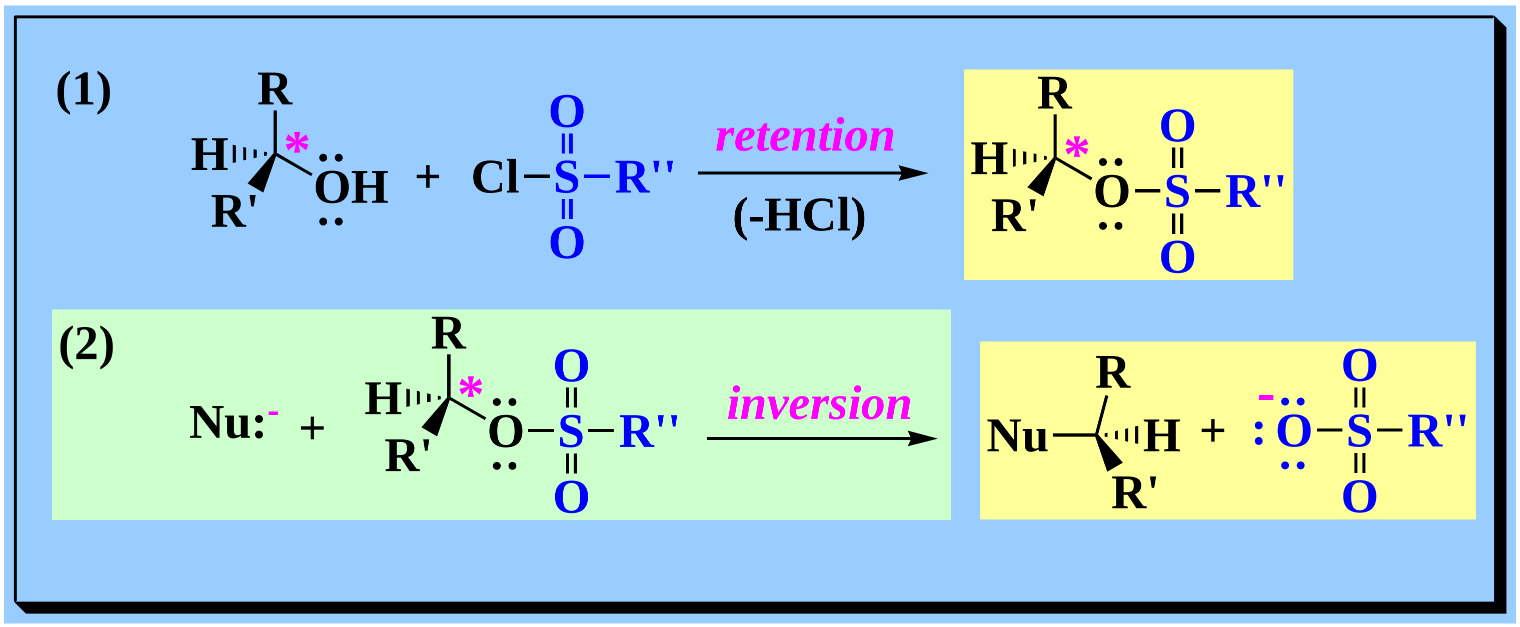
Alkylsulfonate Ester Leaving Groups

An even better leaving group is the trifluoromethanesulfonate anion, $F_3CSO_3^-$. The fluorine atoms stabilize the anion through the inductive effect. This group is called triflate.



Stereochemical Features

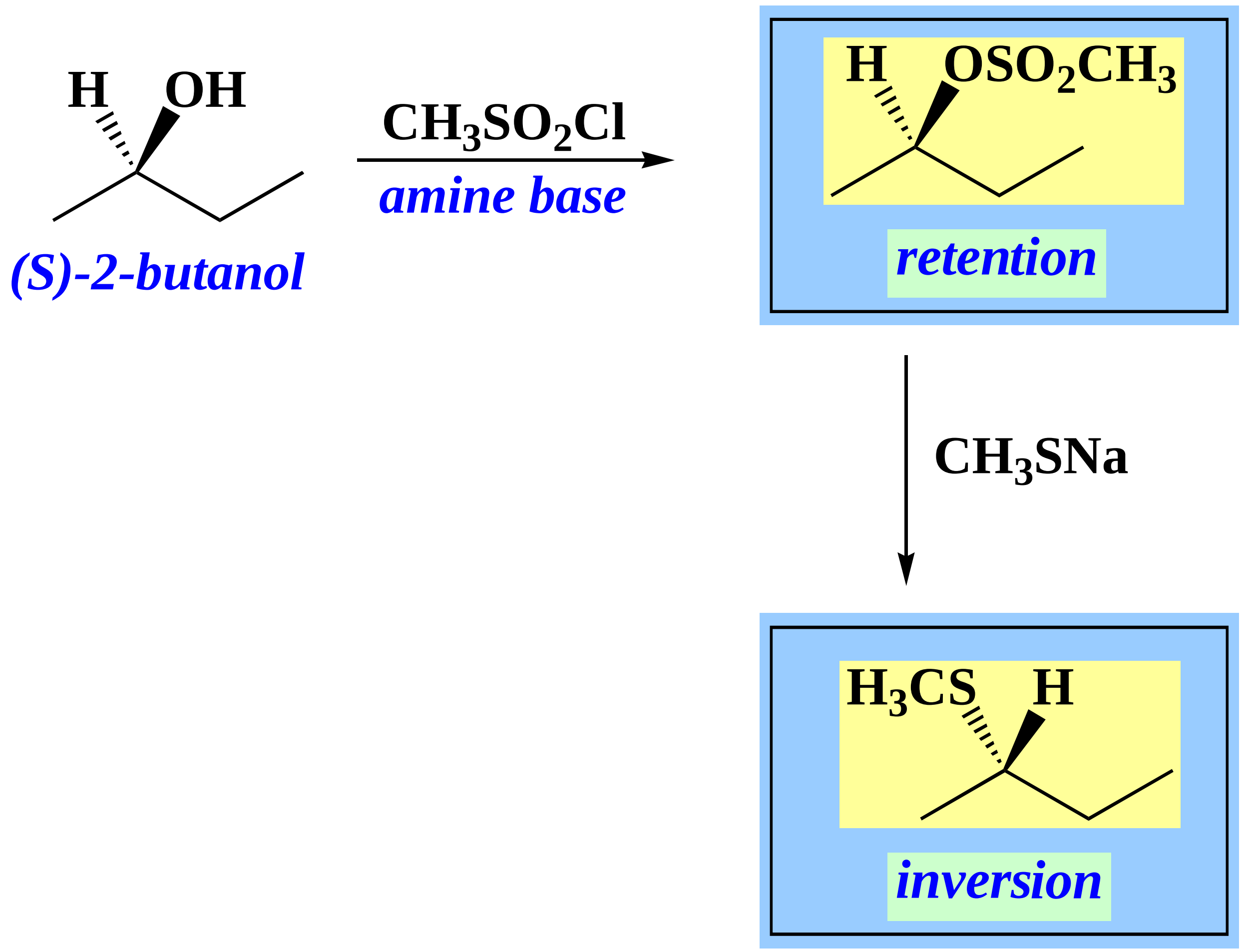
When the hydroxyl group is directly attached to a stereocenter, a well-defined stereochemical reaction pathway is possible:



Such predictable stereochemical pathways are useful in both mechanistic studies and synthesis.

Quiz Chapter 11 Section 10

Provide the products, including stereochemical details, for the following reaction sequence.



Section 4--Synthesis of Alcohols from Alkenes

Addition of Sulfuric Acid to Alkenes

Alkenes dissolve in cold concentrated H_2SO_4 because of an addition reaction that produces alkyl hydrogen sulfates:

electrophilic addition

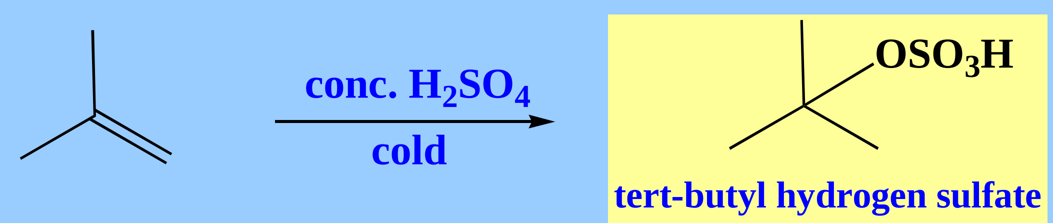
$$CH_3CH{=}CH_2 + H\text{-}O\text{-}S(=O)_2\text{-}O\text{-}H \longrightarrow CH_3\overset{+}{C}HCH_3 + {}^{-}O\text{-}S(=O)_2\text{-}O\text{-}H$$

nucleophilic addition

$$CH_3\overset{+}{C}HCH_3 + {}^{-}O\text{-}S(=O)_2\text{-}O\text{-}H \longrightarrow CH_3CH(O\text{-}SO_3H)CH_3$$

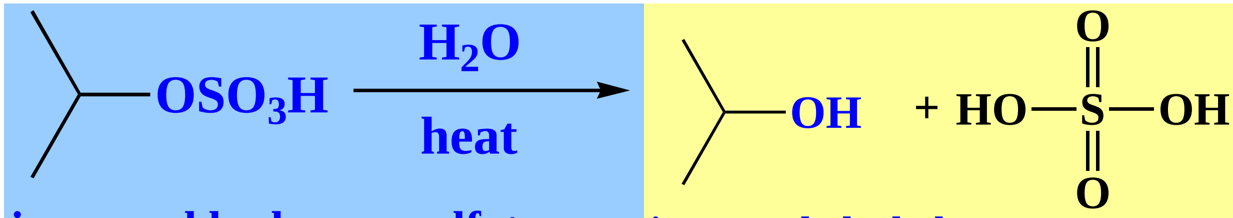
isopropyl hydrogen sulfate

This reaction is regioselective and follows Markovnikov's rule:



Alcohols by Hydrolysis of Alkyl Hydrogen Sufates

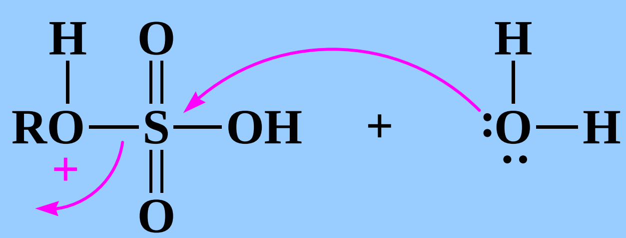
Alcohols (ROH) are formed by heating alkyl hydrogen sulfates in water. The sulfate ester bond is hydrolyzed:



isopropyl hydrogen sulfate

isopropyl alcohol

via

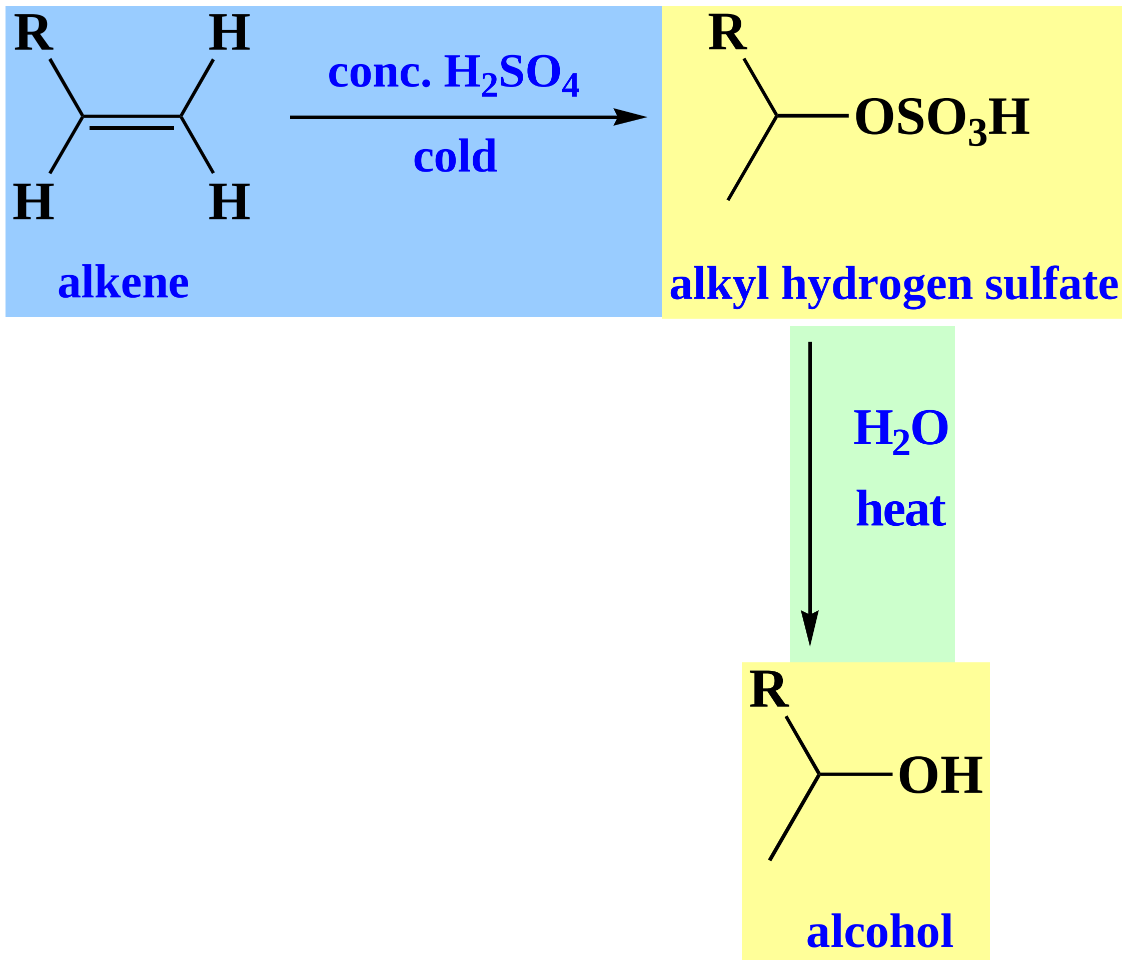


alkyl hydrogen sulfate

The nucleophilic water attacks the sulfate ester function releasing the alcohol.

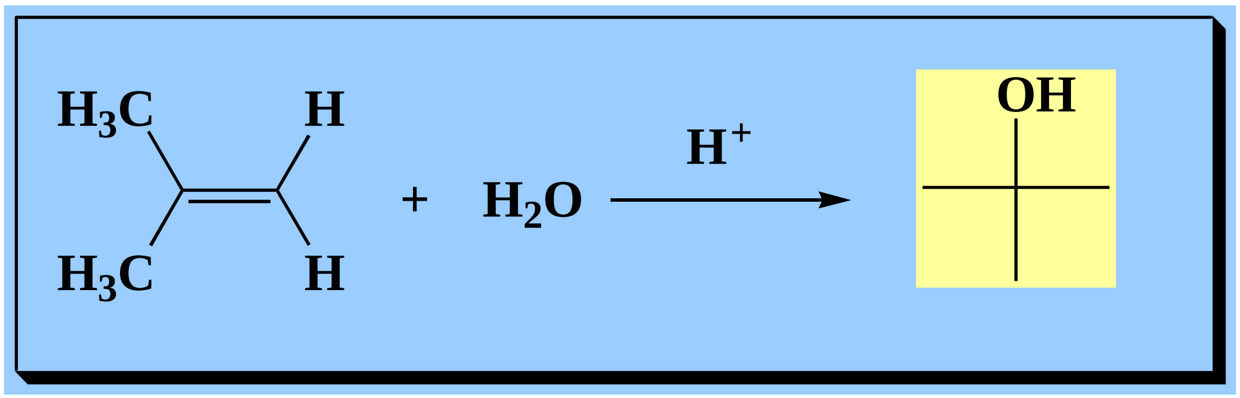
Note: A better leaving group is formed by protonation of the oxygen.

Overall Scheme: A Two-Step Hydration of Alkenes



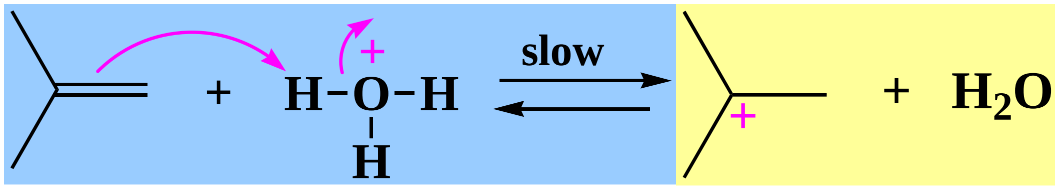
Acid-Catalyzed Direct Hydration of Alkenes

Alkenes react with water in the presence of acids to give alcohols directly. Addition does not occur in the absence of acids.

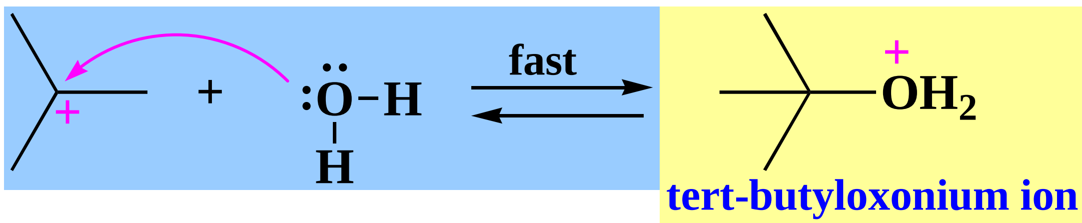


Mechanism of Direct Hydration of Alkenes

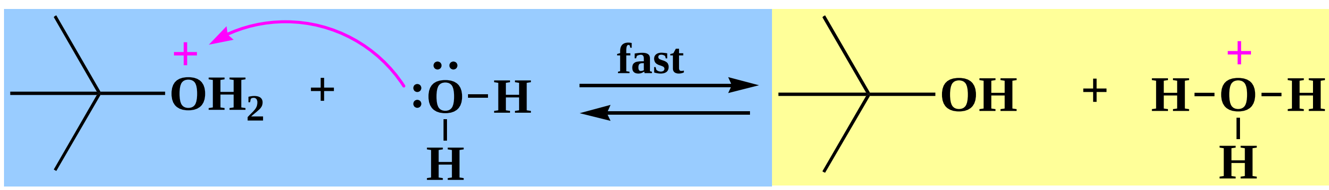
Step 1: electrophilic addition



Step 2: nucleophilic addition



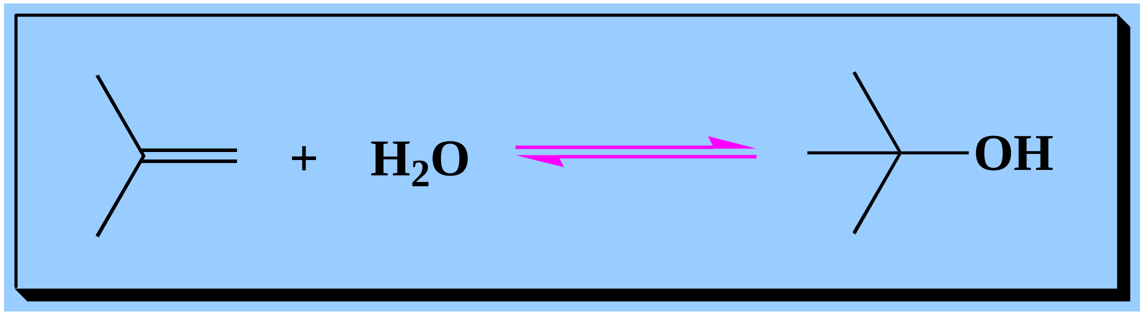
Step 3: deprotonation



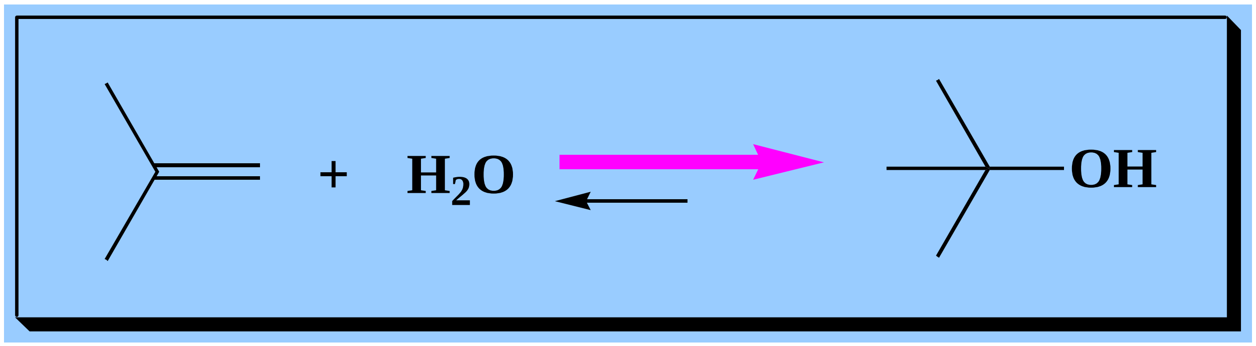
Note: Hydronium ion is reformed, so the reaction is catalyzed by acid.

A Reversible Reaction

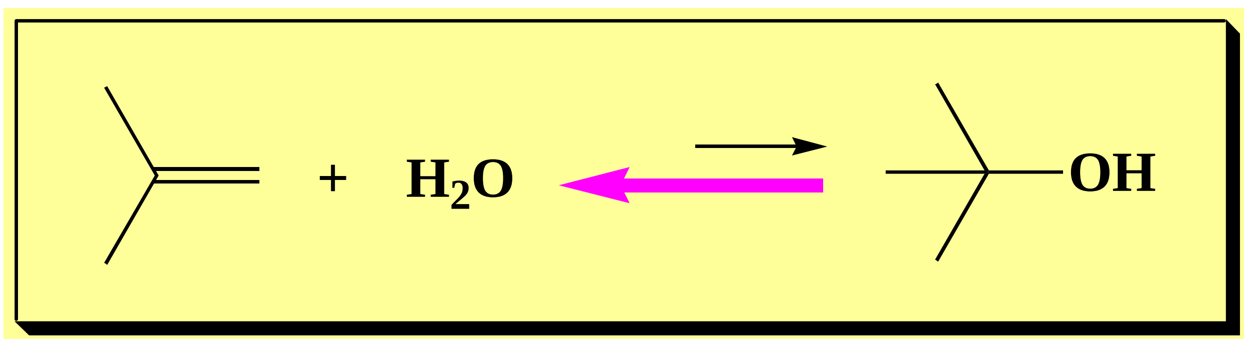
The hydration of an alkene is a reversible reaction. The product isolated depends on the reaction conditions.



To hydrate an alkene, moderately concentrated acid solutions are used so that ample water is present to drive the reaction to the alcohol.

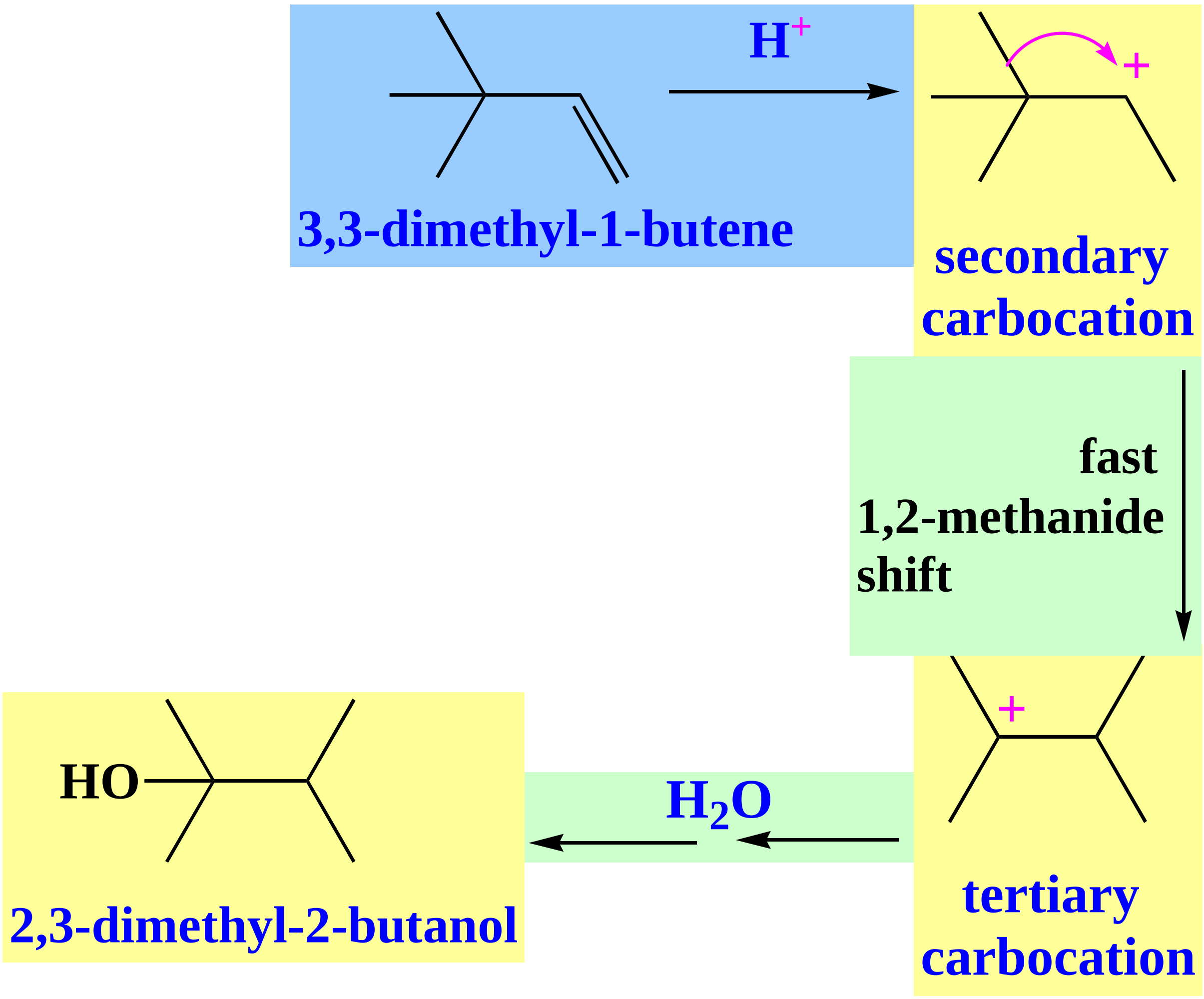


To dehydrate an alcohol, concentrated acid solutions are used (little water) and the alkene product is often removed by distillation as it is formed.



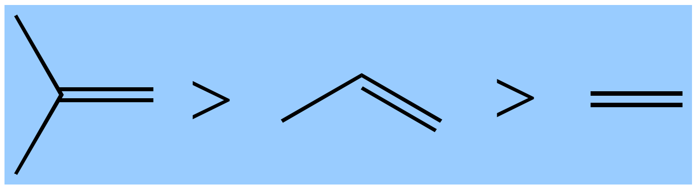
Rearrangements

Rearrangements may occur during the acid-catalyzed hydration of alkenes at the carbocation stage:

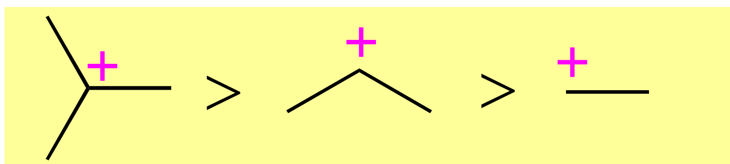


Some Key Observations about the Acid-Catalyzed Hydration Reaction of Alkenes

The **reactivity order** of alkenes:



parallels the **stability order** of the carbocation intermediates:



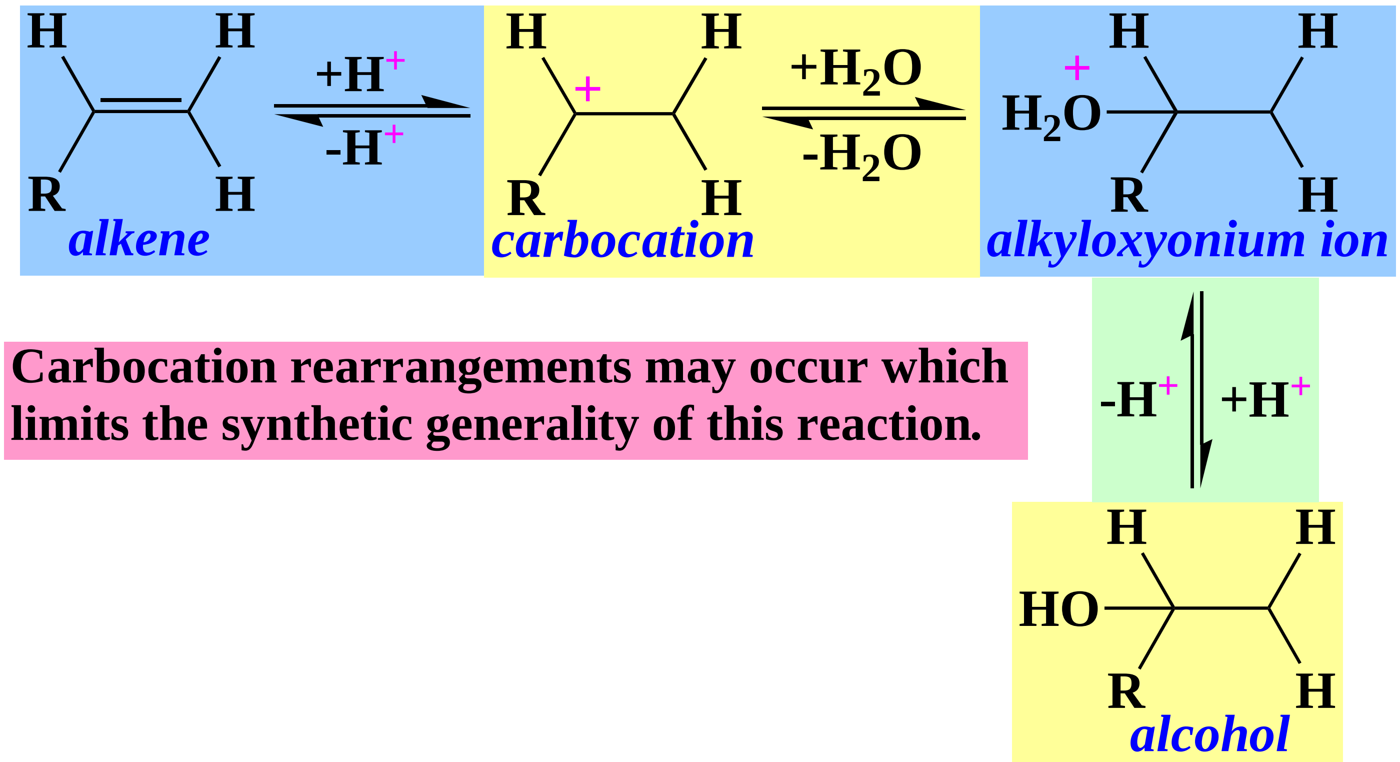
tertiary secondary primary

that are formed in the **rate-determining step.**

Rearrangements may occur at the carbocation stage.

Synthesis of Alcohols from Alkenes--Hydration of Alkenes

Alkenes react with water in the presence of an acid catalyst to give alcohols. The regiochemistry of the addition reaction follows Markovnikov's rule.



Carbocation rearrangements may occur which limits the synthetic generality of this reaction.

Two General Syntheses

Two standard procedures for converting alkenes to alcohols with controlled regiochemistry and some degree of controlled stereochemistry are:

(1) The Oxymercuration-Demercuration Procedure (Markovnikov product)

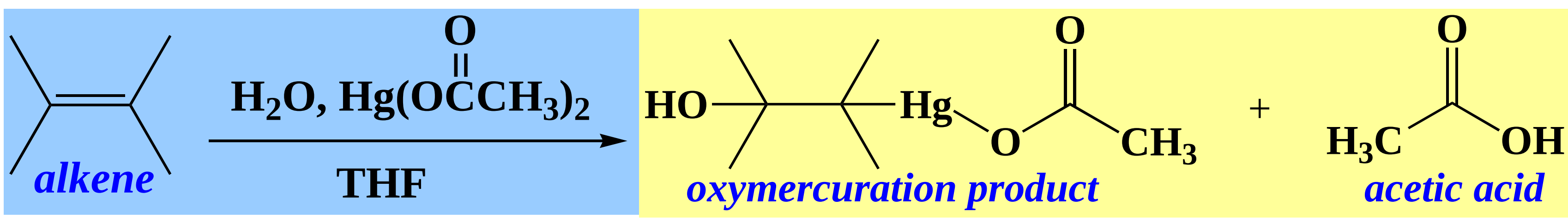
(2) The Hydroboration-Oxidation Method (anti-Markovnikov product)

The Oxymercuration-Demercuration Procedure

There are two steps in this method:

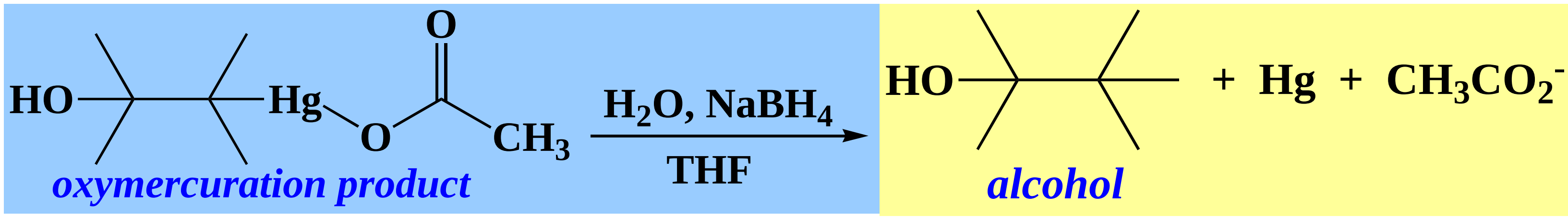
(1) Oxymercuration

An alkene reacts with water in the presence of mercuric acetate, $Hg(OAc)_2$, (an electrophile) in a mixture of THF and water. The role of theTHF is to help dissolve the alkene.



(2) Demercuration

After the first step, sodium borohydride, $NaBH_4$, reduces the alkyl mercury (II) compound under basic conditions.

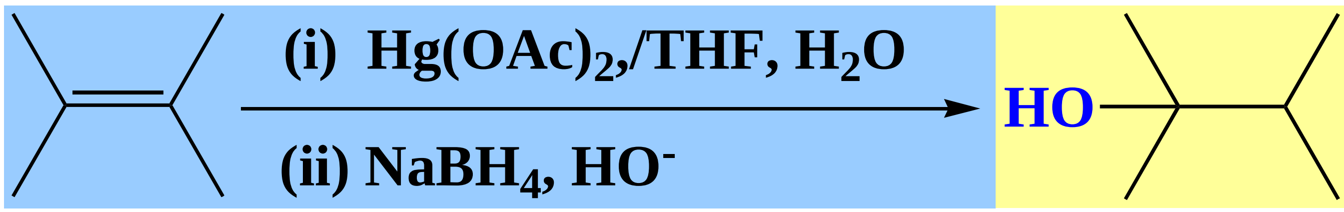


A Simple Procedure with High Yields

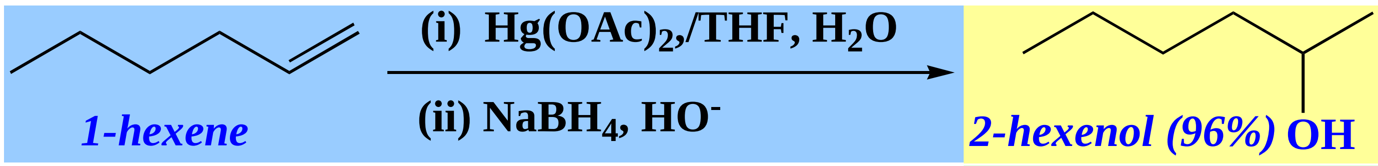
The two steps are carried out in the same reaction flask at room temperature or below. The oxymercuration step usually goes to completion within a few minutes. The second demercuration step is completed in less than an hour with overall yields of close to 90%.

Oxymercuration-Demercuration Reaction--Regiochemistry

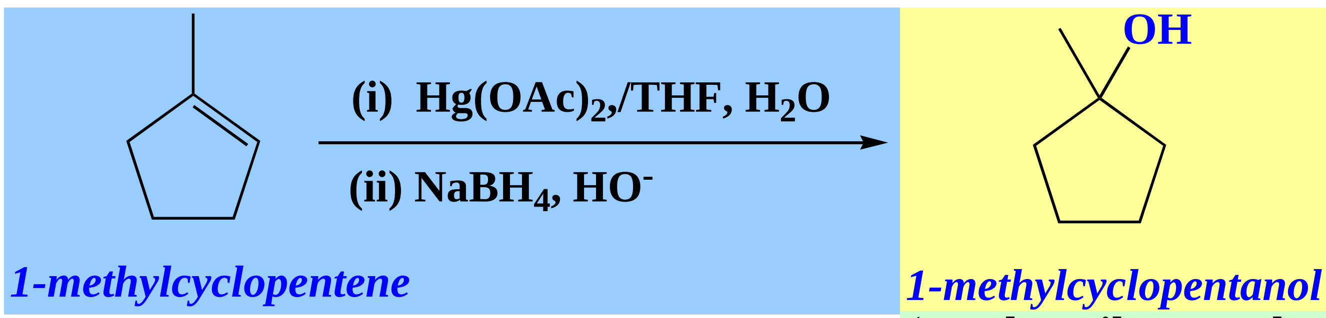
This reaction is **highly regioselective** with the overall addition of **-H** and **-OH** following **Markovnikov's Rule**.



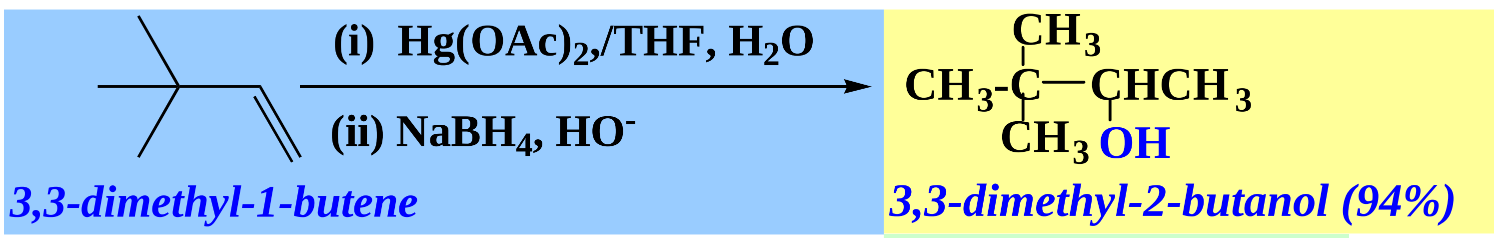
Examples



(Markovnikov product)



(Markovnikov product)



(Markovnikov product)

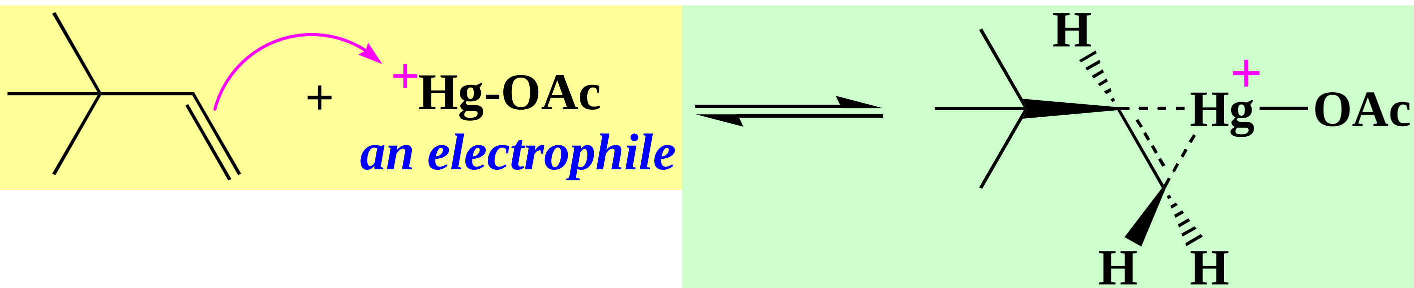
The third example strongly suggests that a true carbocation intermediate is not formed during the oxymercuration step. Why?

A Mechanism for the Oxymercuration-Demercuration Reaction

There is general agreement the reaction begins with electrophilic attack of mercury (II), possibly as $^{+}$Hg(OAc), on the π-bond of the alkene.

(1) $Hg(OAC)_2 \rightleftharpoons {}^{+}Hg\text{-}OAc + {}^{-}OAc$

(2)

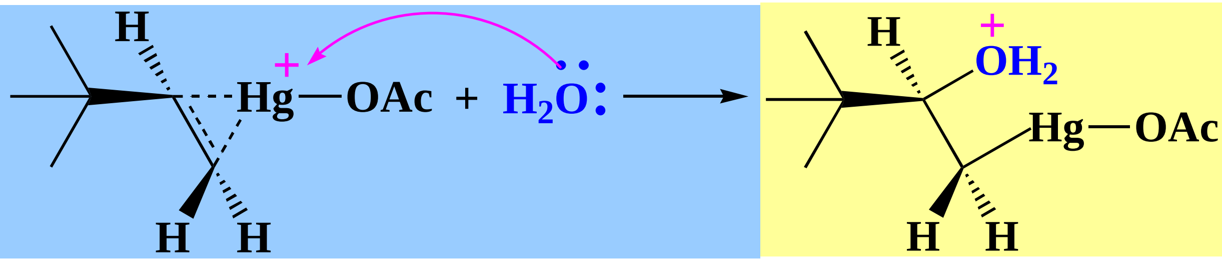


A bridging mercurinium ion is believed to form rather than a free carbocation since typical carbocation rearrangements do not occur.

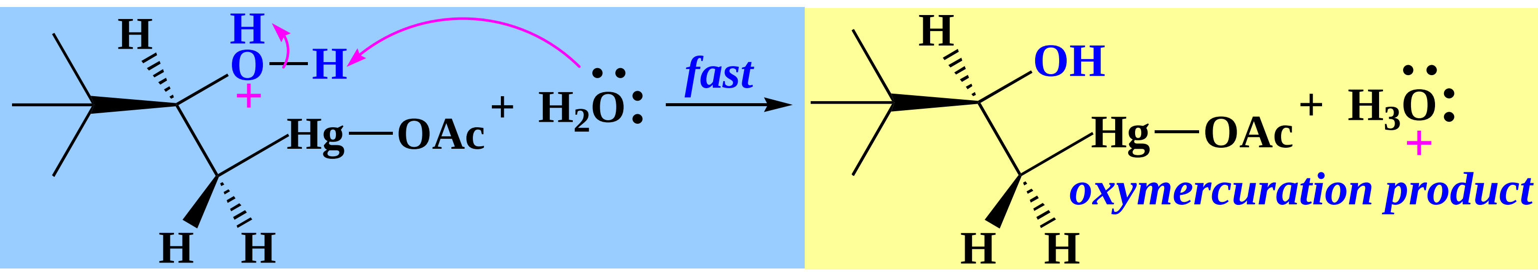
Regioselective Reaction of the Mercurinium Ion

The mercurinium ion reacts with a nucleophile (H_2O) preferentially at the carbon with the greater positive charge density:

(3)



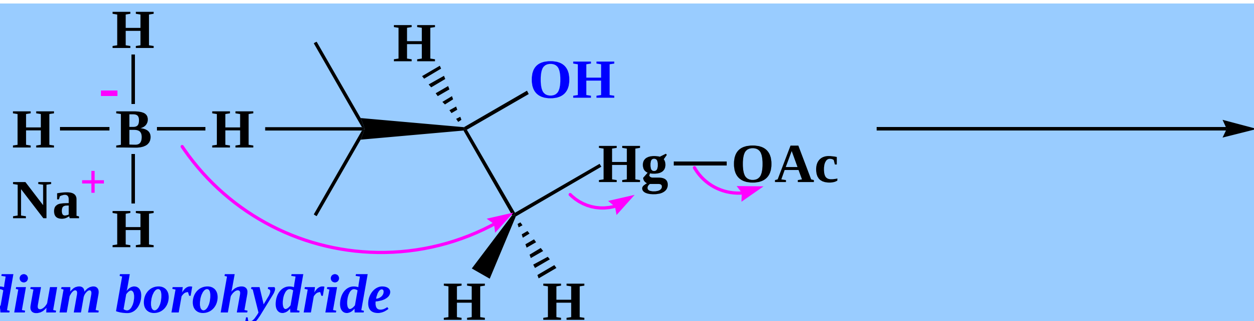
(4)



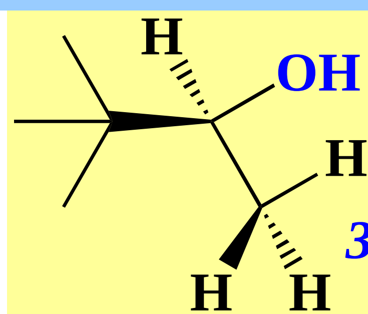
At this stage the regiochemistry is set. Reduction yields the Markovnikov product.

Reduction of the Oxymercuration Product

Reduction of the alkylmercury acetate with sodium borohydride is not a well defined reaction. A free radical may be involved. The net result is reductive cleavage of the C-Hg(II) bond by hydride, replacing the metal with H, and producing Hg(0).

(5) 

sodium borohydride



+ Hg^{o} + $CH_3CO_2^-$

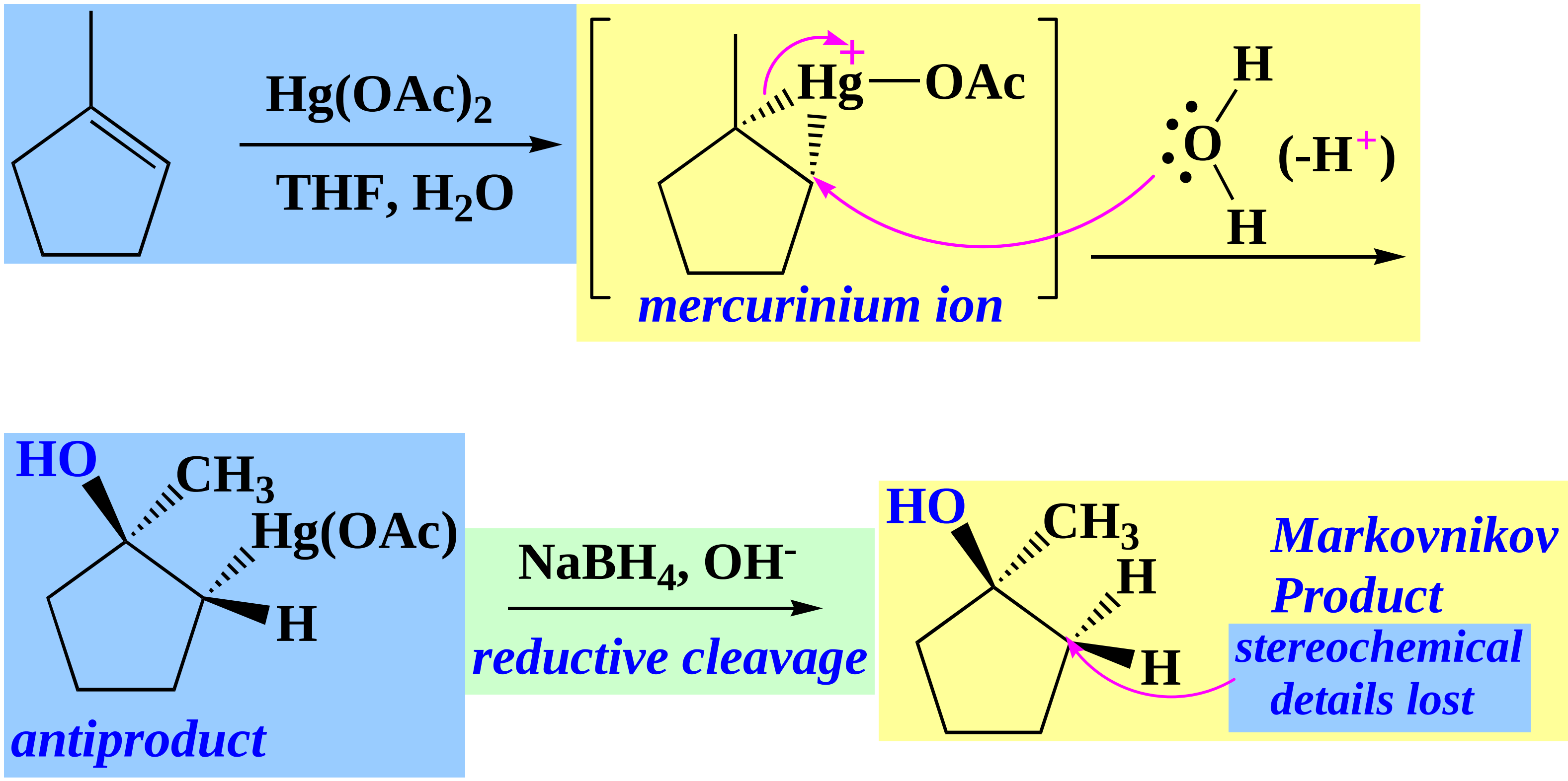
3,3-dimethyl-2-butanol

(Markovnikov Addition Product)

Reaction is shown as a two-electron reduction.

Stereochemistry of the Oxymercuration Reaction

The oxymercuration reaction proceeds with overall anti-addition to the alkene, as observed in bromination (section 8.7):



Key Features of the Oxymercuration-Demercuration Procedure

1. **Overall Markovnikov Addition Product**

2. **No Carbocation-type Rearrangements**

3. **Good Yields**

4. **Oxymercuration Step occurs with Anti-addition**

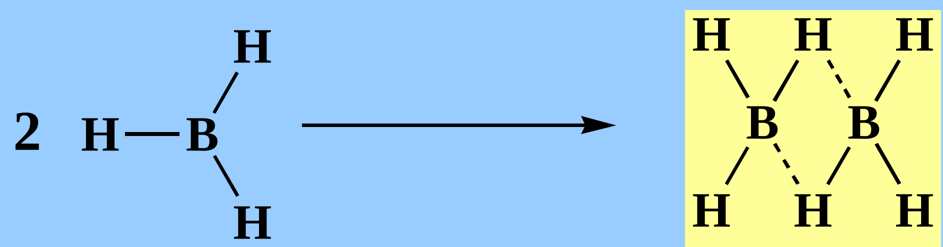
5. **Reduction Step has Unknown Stereochemical Details**

The Hydroboration-Oxidation Procedure

Alcohols may be prepared from alkenes by the general two-step procedure of hydroboration-oxidation.

Borane and Diborane

Boron forms a trihydride, BH_3, called borane. Because trivalent boron is electron-deficient, a dimer, B_2H_6, called diborane forms in the gas phase and non-associating solvents.

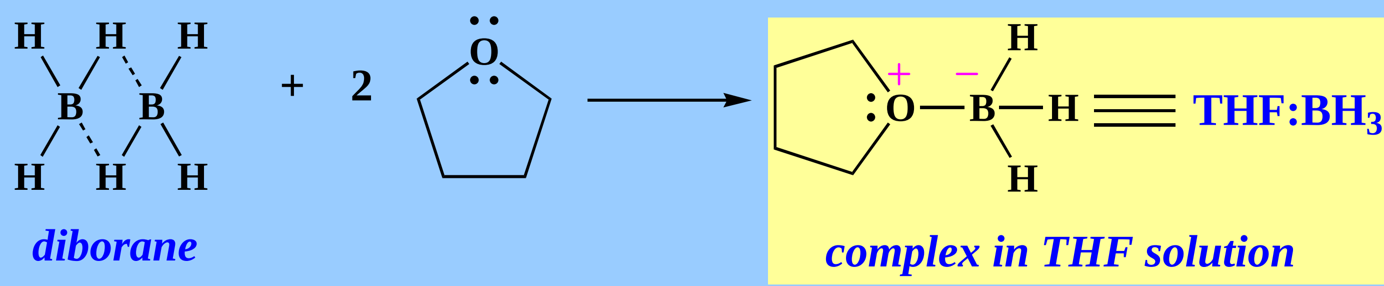


borane

diborane

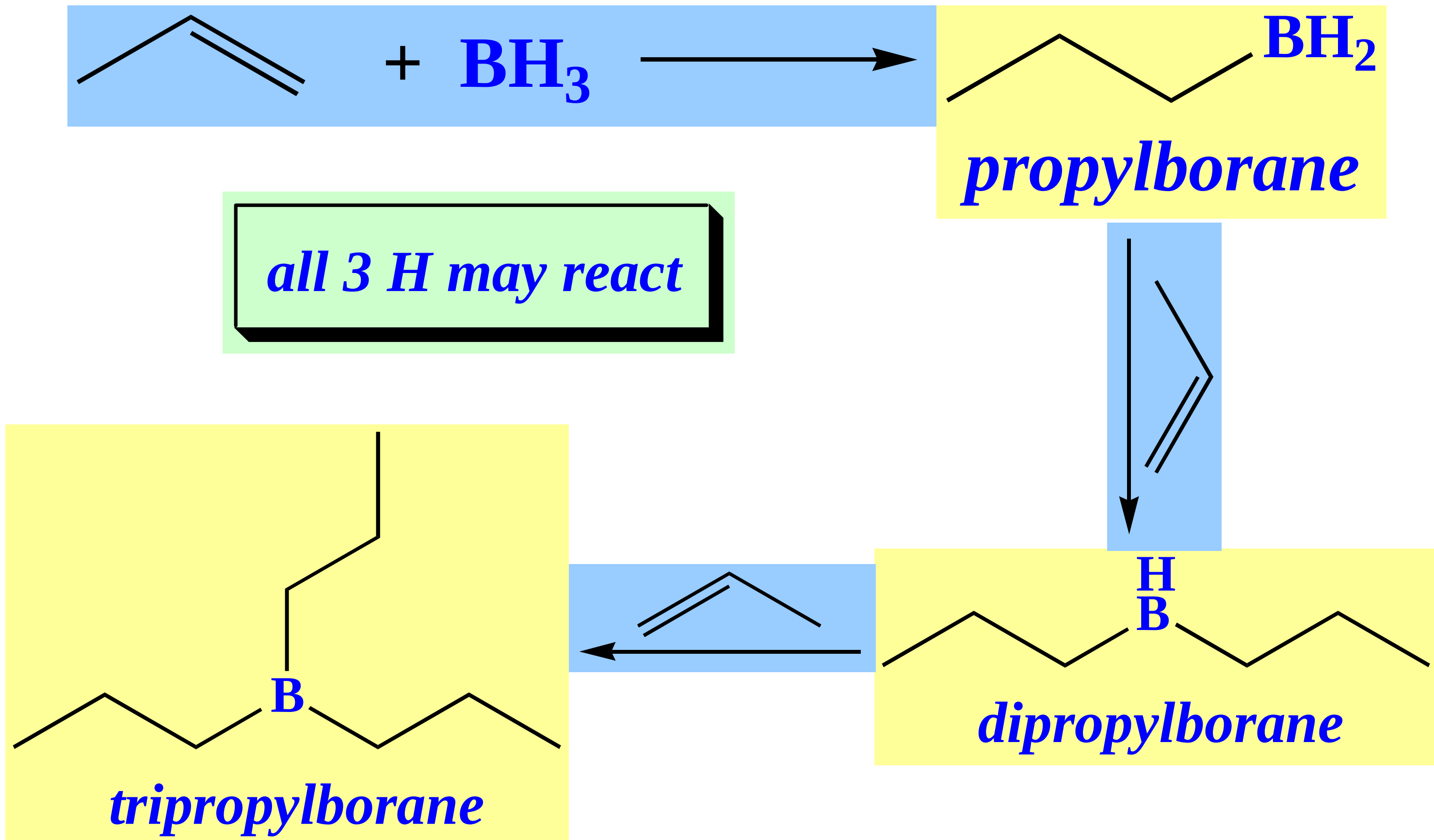
Laboratory Scale Reactions

Diborane ignites in air. Commercial solutions of borane in tetrahydrofuran (THF) are much more stable, and allow laboratory procedures to be performed under an inert atmosphere (argon or nitrogen).

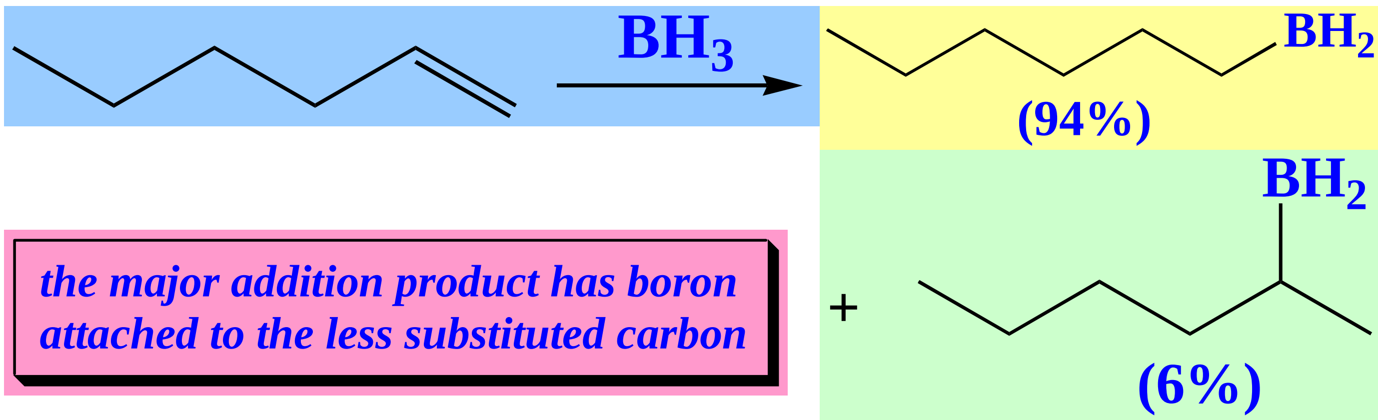


The nucleophilic THF associates with BH_3 to form a Lewis acid-base complex.

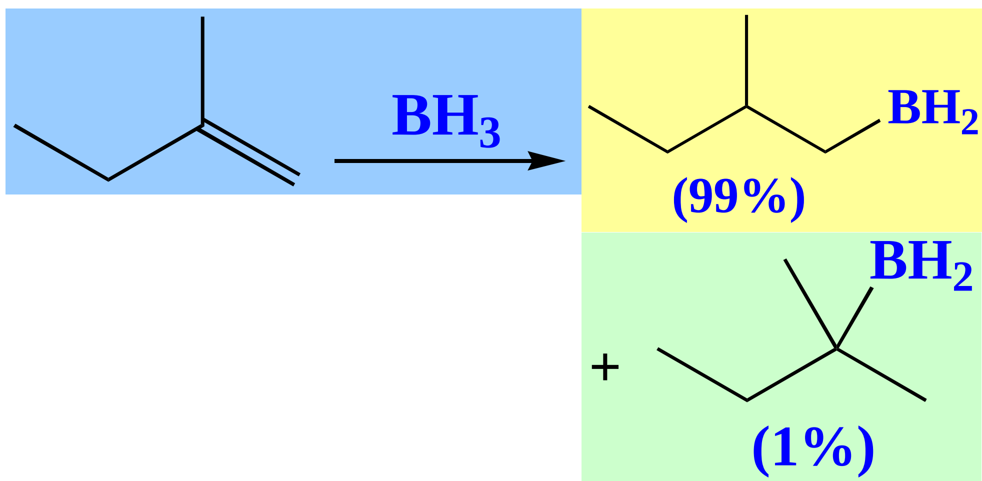
Stoichiometry of the Hydroboration Reaction



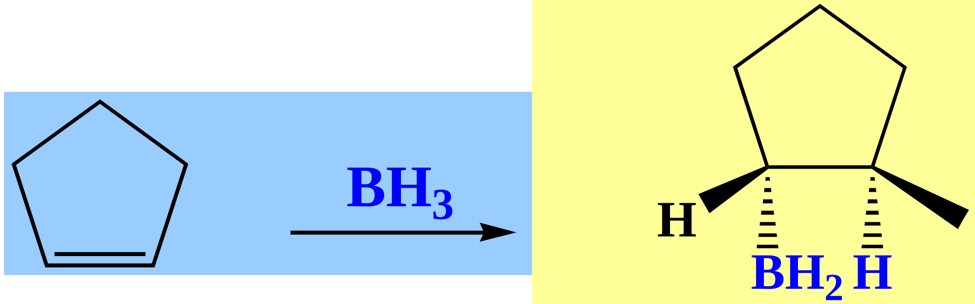
Regiochemistry



the major addition product has boron attached to the less substituted carbon



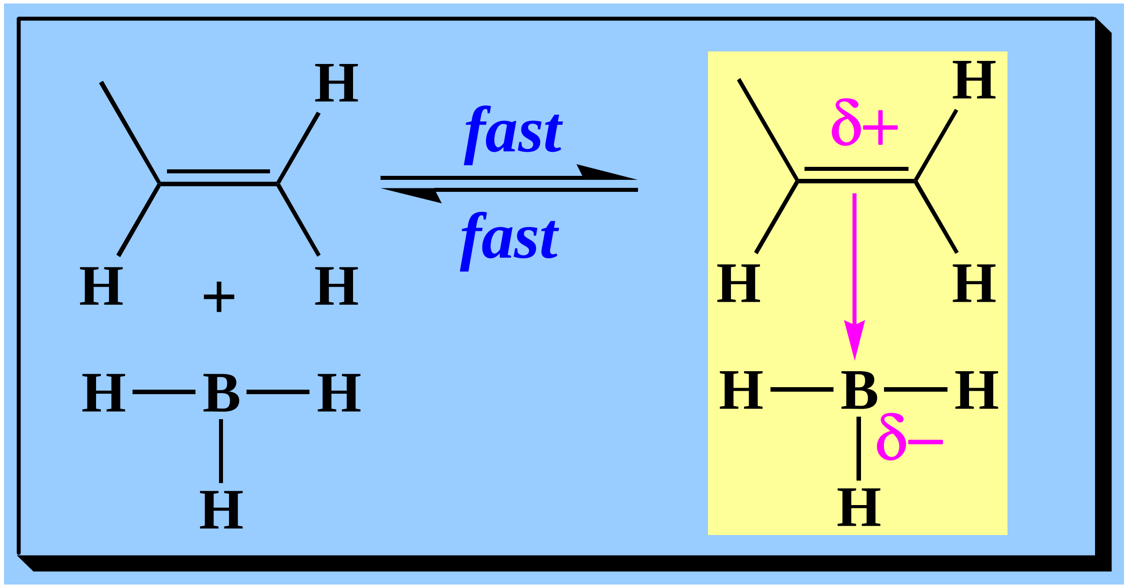
Stereochemistry



product of syn-addition

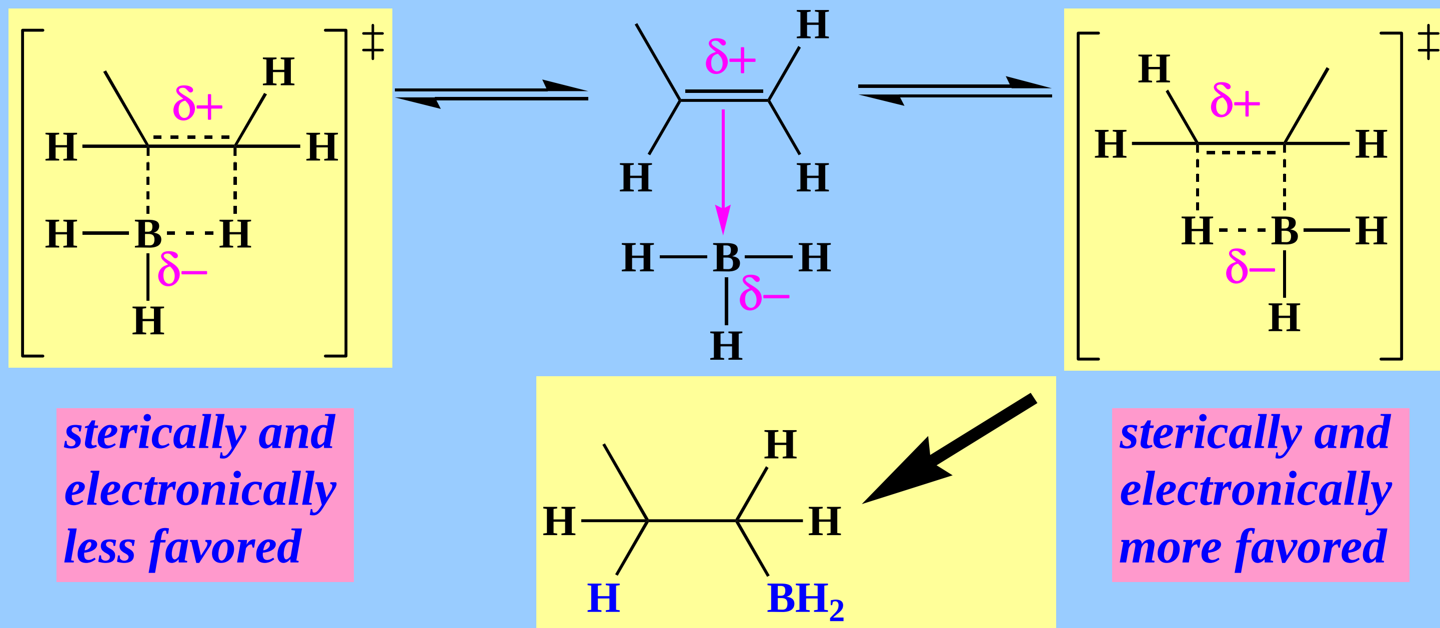
hydroboration is a syn-addition

The Mechanism of Hydroboration



The electron-deficient borane (Lewis acid) is believed to form a π-complex with the π-bond of the alkene.

The π-complex reacts by way of a four-center transition state that determines the regiochemistry of the addition reaction. The two competing modes of reaction are shown on next slide.

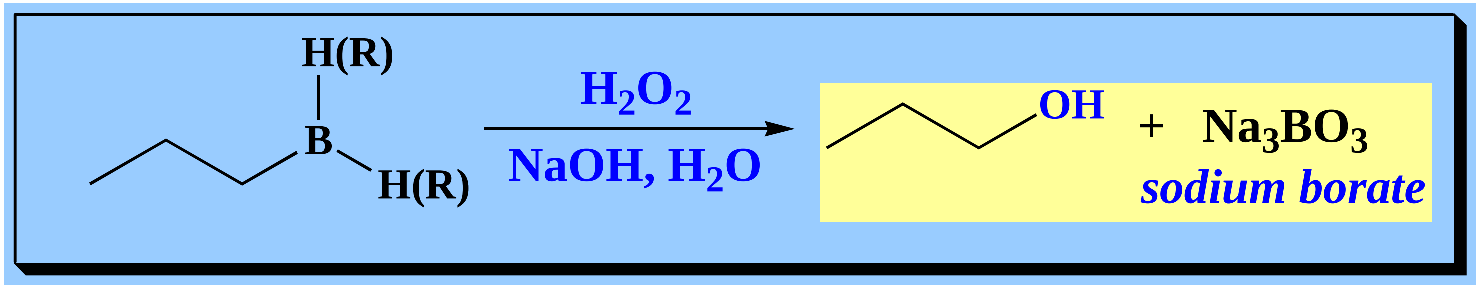


major product shows ***SYN ADDITION*** *and*
ANTI-MARKOVNIKOV ADDITION OF BORANE

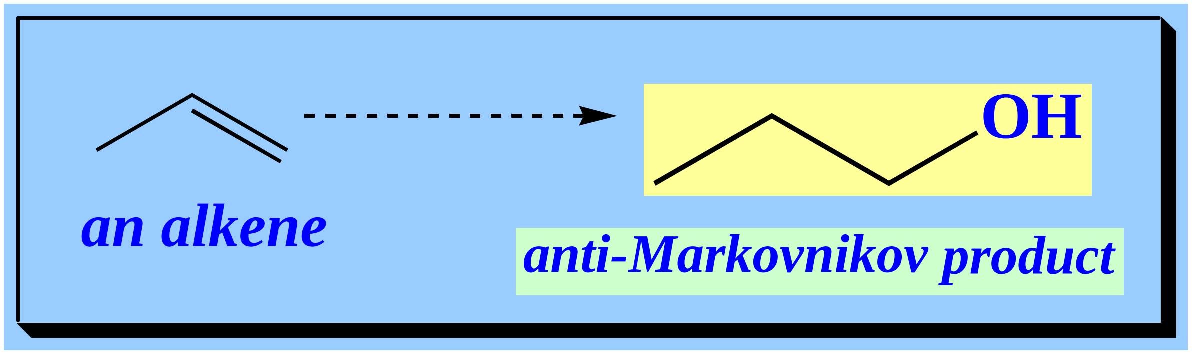
Note: The syn stereochemistry of hydroboration necessarily follows from the four-center transition state.

Alcohols through Oxidation of Alkylboranes

Reaction of an alkylborane with hydrogen peroxide (H_2O_2) and base (NaOH) leads to replacement of the borane group with a hydroxyl group.

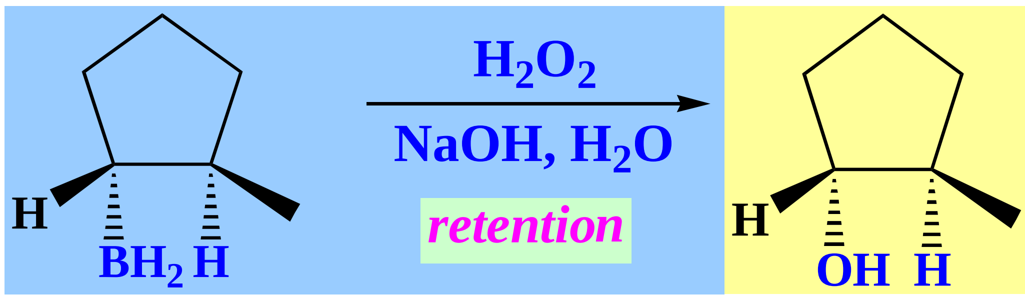


The sequence of hydroboration-oxidation of an alkene yields an alcohol with anti-Markovnikov orientation.



Stereochemistry of the Oxidation Reaction

The hydroxyl group replaces the borane group with retention.



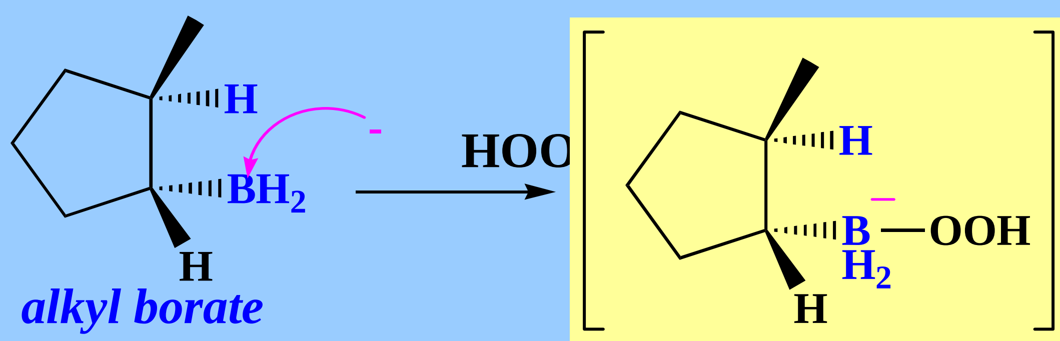
Mechanism of the Oxidation Reaction

In the aqueous basic solution used, hydrogen peroxide (pK_a = 11.6) is converted into its anion:

$$HOOH + HO^- \longrightarrow HOO^- + HOH$$

formic acid *peroxy anion*

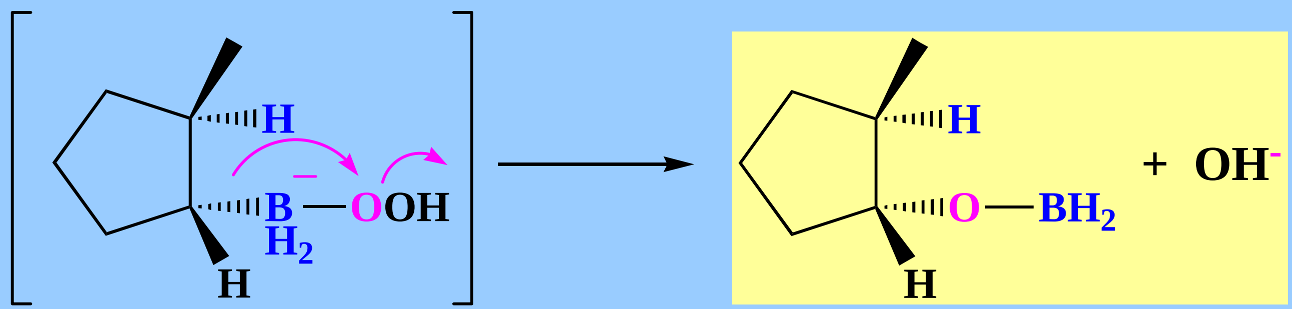
The peroxy anion adds to the electron-deficient alkylborane producing an unstable peroxyborate intermediate:



peroxyborate
unstable

A Molecular Rearrangement

The peroxyborate intermediate reacts by migration of the alkyl group from boron to oxygen with retention at the stereocenter, and with concurrent heterolysis of the weak peroxy bond:

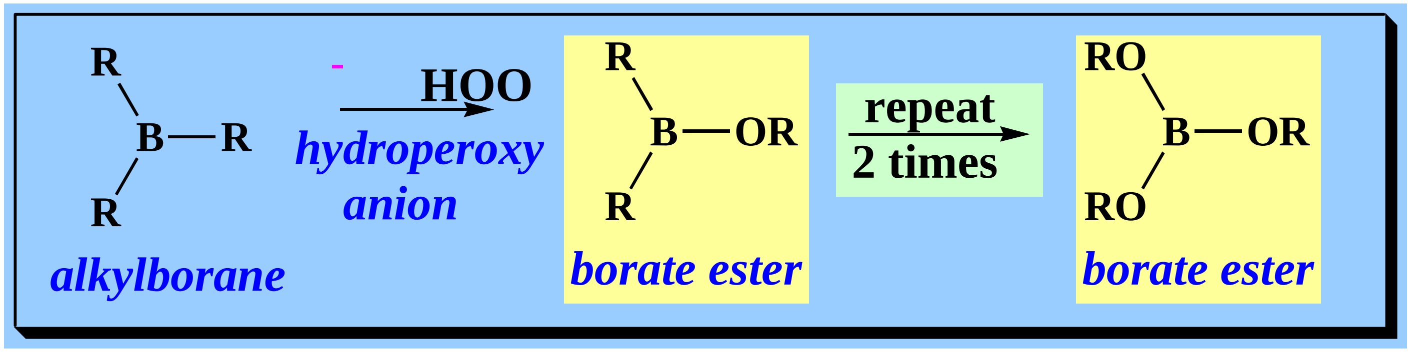


peroxyborate
unstable

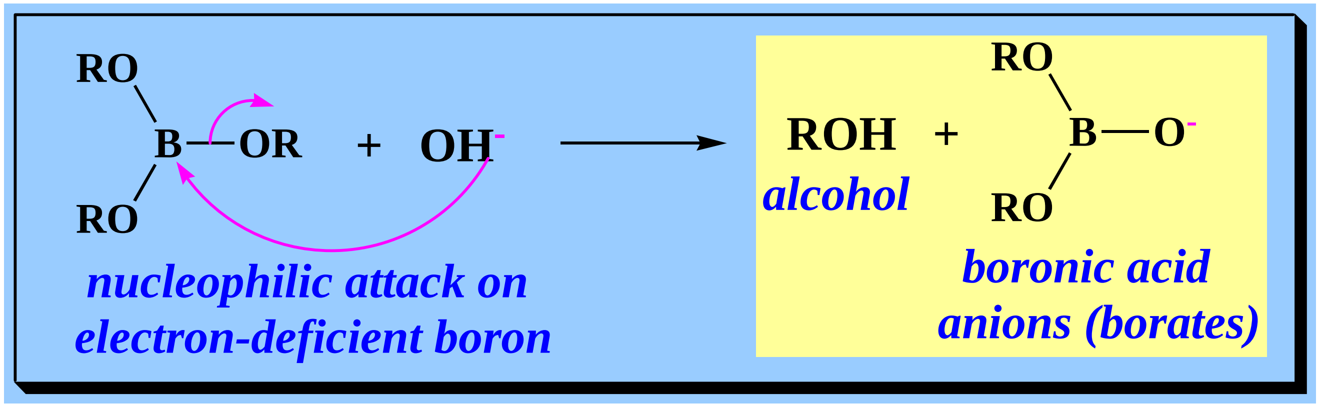
retention at the stereocenter

Overview of the Oxidation Reaction--General Scheme

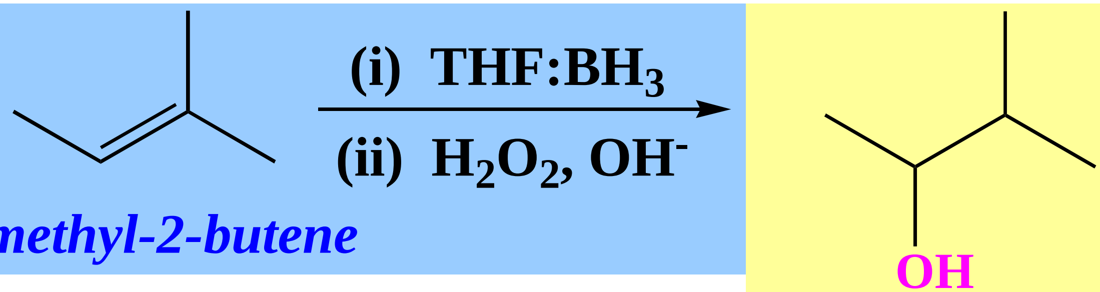
Formation and reaction of unstable peroxyborate intermediates yield borate esters with retention in any migrating stereocenter.



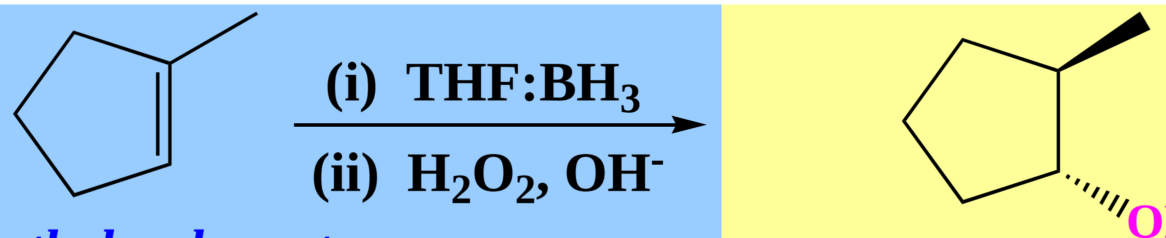
The borate ester produced after the rearrangement step hydrolyzes in the aqueous basic solution:



The Overall Reaction--Specific Examples



2-methyl-2-butene → *3-methyl-2-butanol* *(59%)*



1-methylcyclopentene → *trans-2-methylcyclopentanol* *(86%)*

Summary of Alkene Hydration Reactions

Hydration Reaction	Regiochemistry	Stereochemistry
Acid-Catalyzed Hydration	Markovnikov	Racemic
Oxymecuration-Demercuration	Markovnikov	Racemic
Hydroboration-Oxidation	Anti-Markovnikov	Syn

NOTE: The acid-catalyzed hydration proceeds through a carbocation and can lead to rearrangements.