CHM 224 • Organic Chemistry II
Spring 2013, Des Plaines • Prof. Chad Landrie

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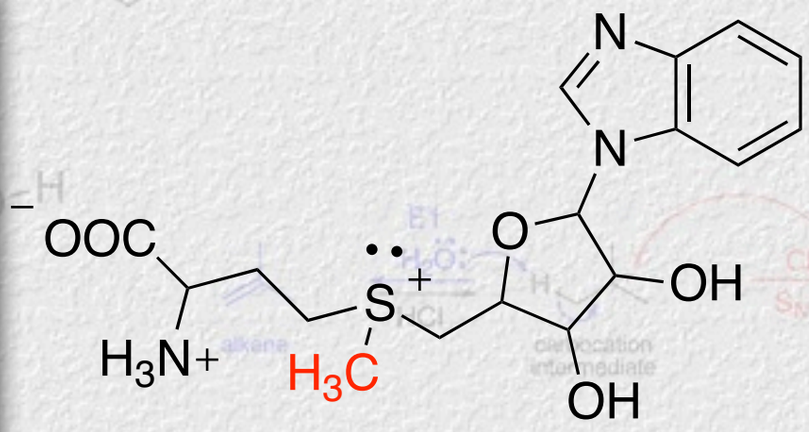

S-adenosylmethionine

Lecture 4: January 24, 2013

- Reactions of Ethers (18.3-18.4)
- Ring-opening of Epoxides (18.6)
- Epoxides in Biological Processes (18.6)
- Sulfides (18.8)

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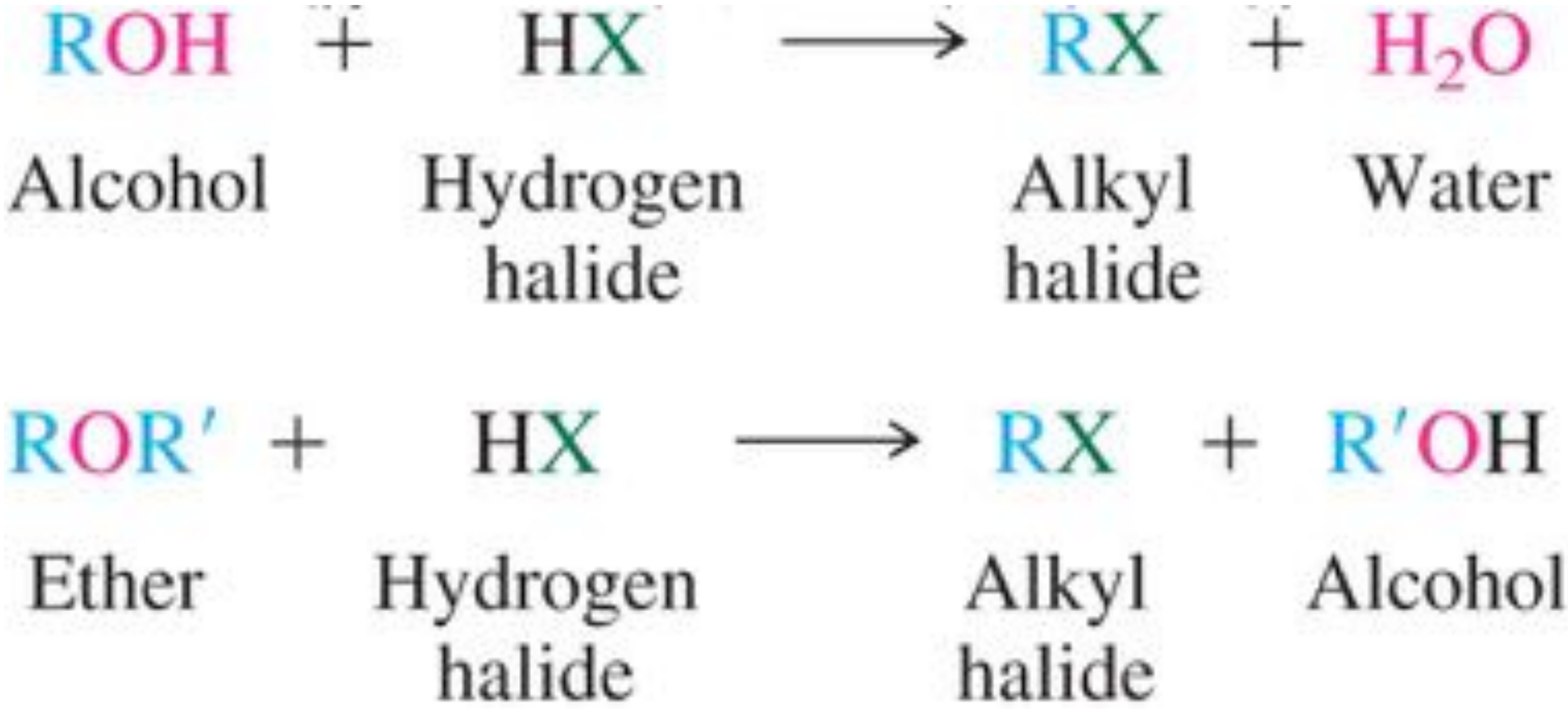
Reactions of Ethers

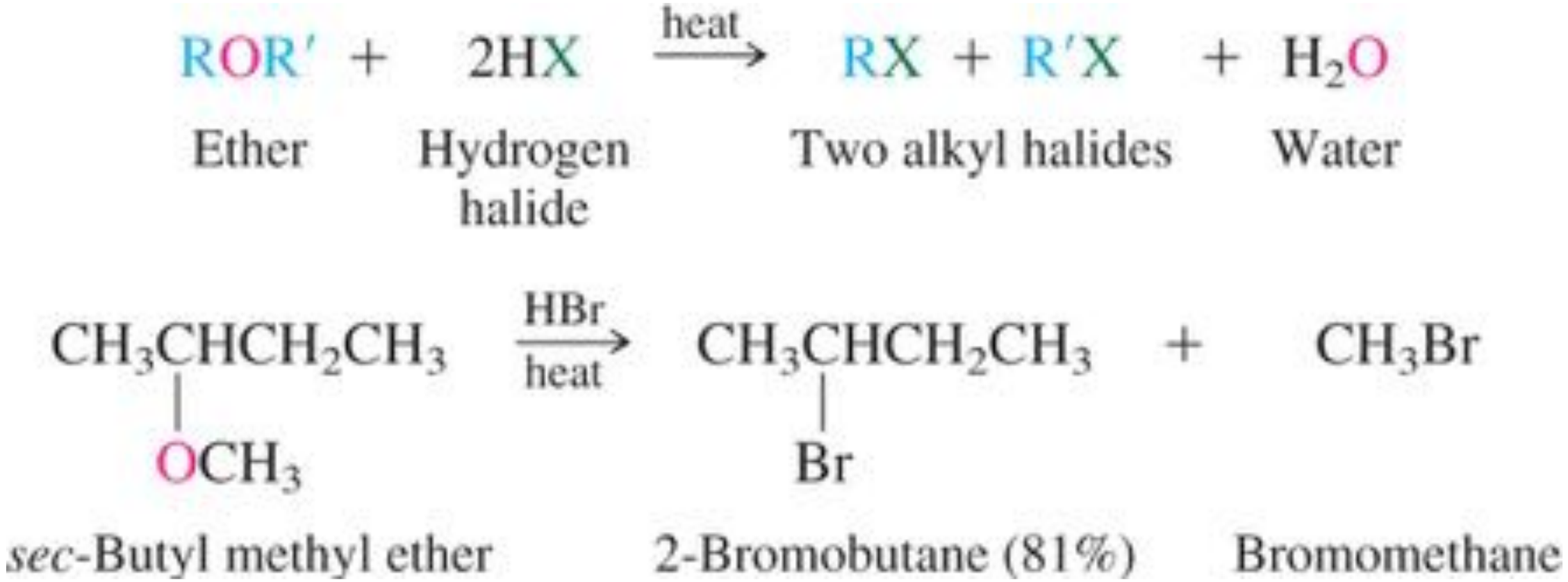
Cleavage (18.3)

Cleavage of Ethers



- Ether are cleaved (the C–O bonds are broken) with hydrogen halides.
- Analogous process to S_N of alcohols by hydrogen halides

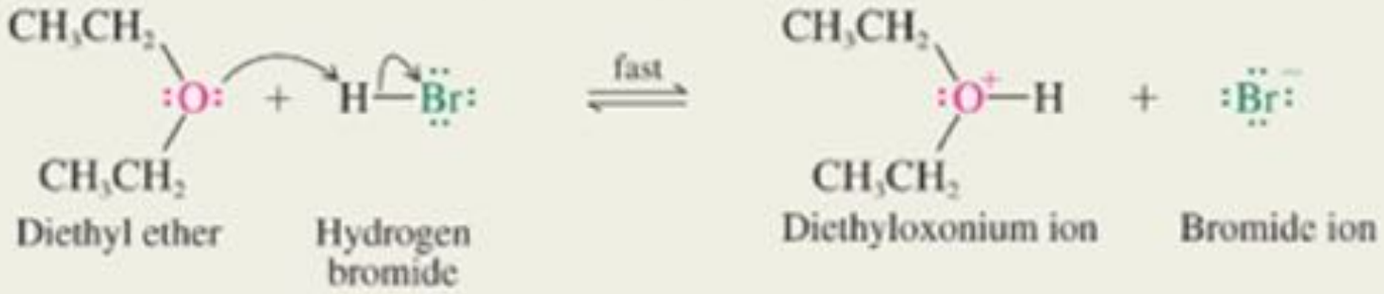
Cleavage of Ethers



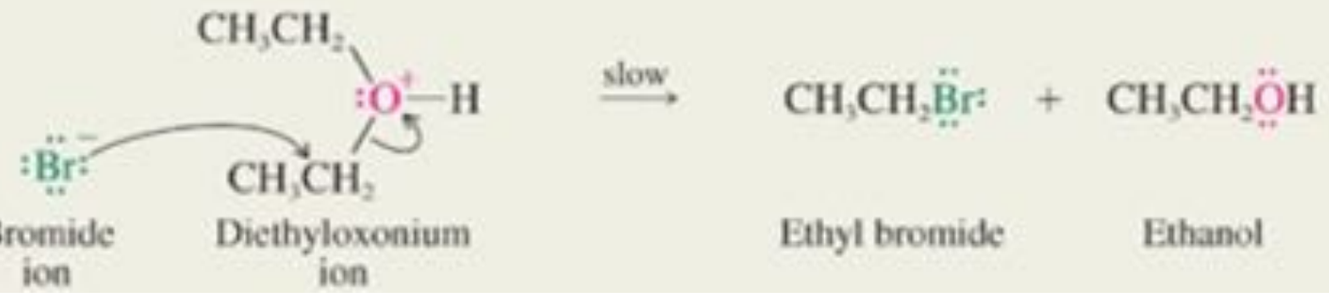
- The alcohol produced after cleavage of the first C–O bond is immediately converted to an alkyl halide by S_N
- Overall pattern: Ethers are cleaved into two alkyl halides

Cleavage of Ethers

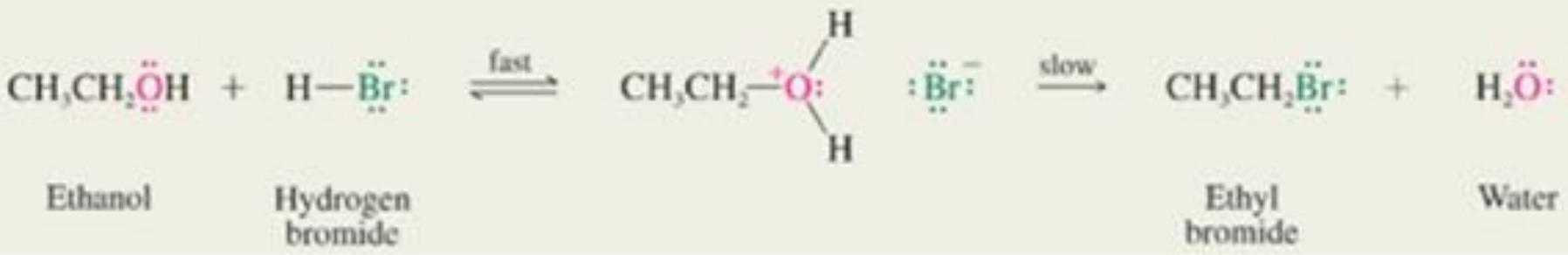
STEP 1: Proton transfer to the oxygen of the ether to give a dialkyloxonium ion.



STEP 2: Nucleophilic attack of the halide anion on carbon of the dialkyloxonium ion. This step gives one molecule of an alkyl halide and one molecule of an alcohol.



STEPS 3 AND 4: These two steps do not involve an ether at all. They correspond to those in which an alcohol is converted to an alkyl halide (Sections 4.8–4.12).



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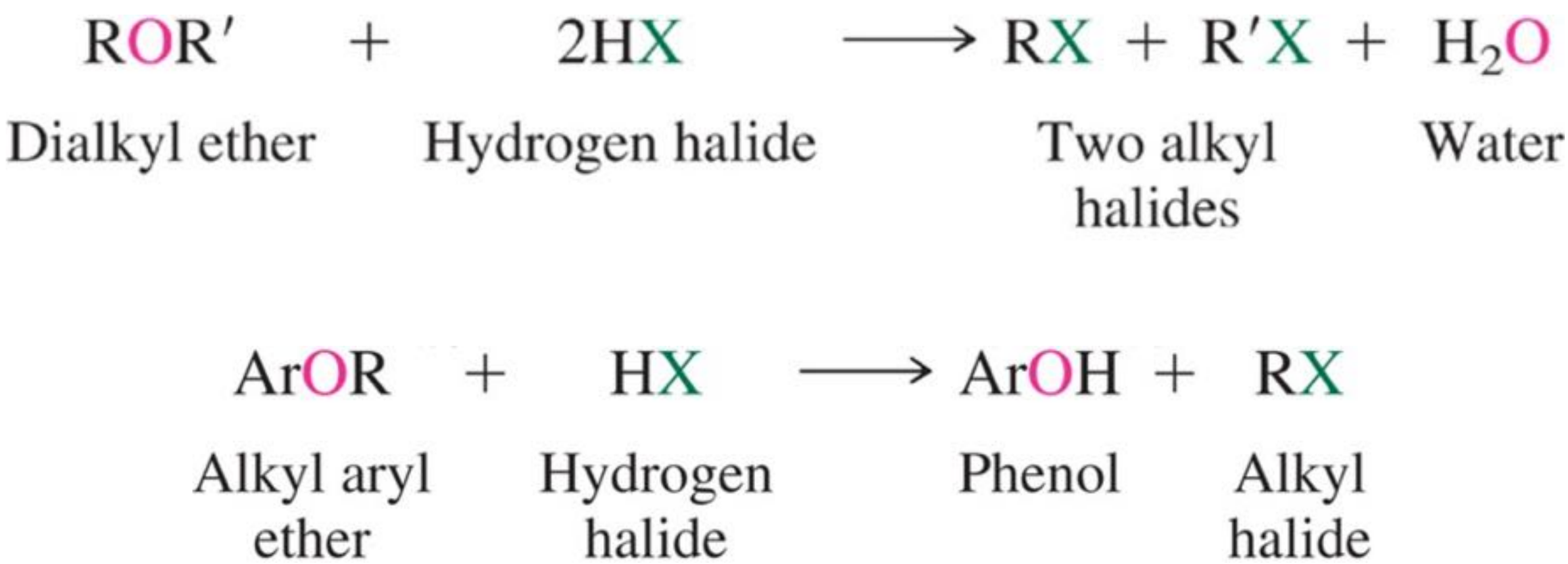
Cleavage of Aryl Ethers



- Dialkyl ethers are cleaved to produce halides from both alkyl groups
- Alkyl aryl ethers are cleaved to provide phenol and the alkyl halide
- **Why the difference?**

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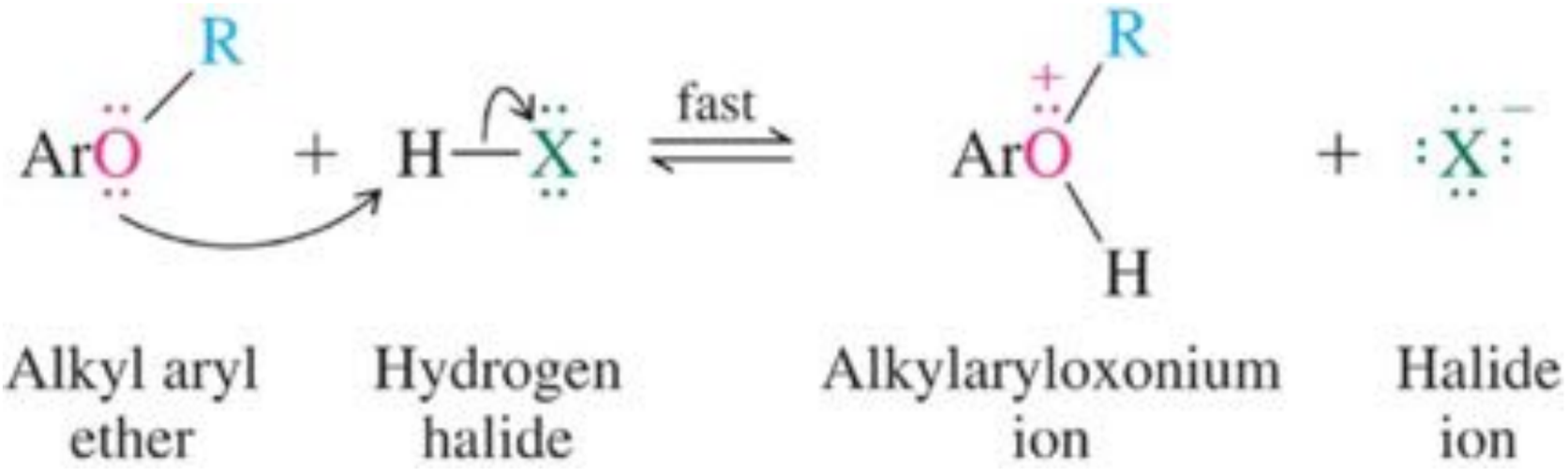
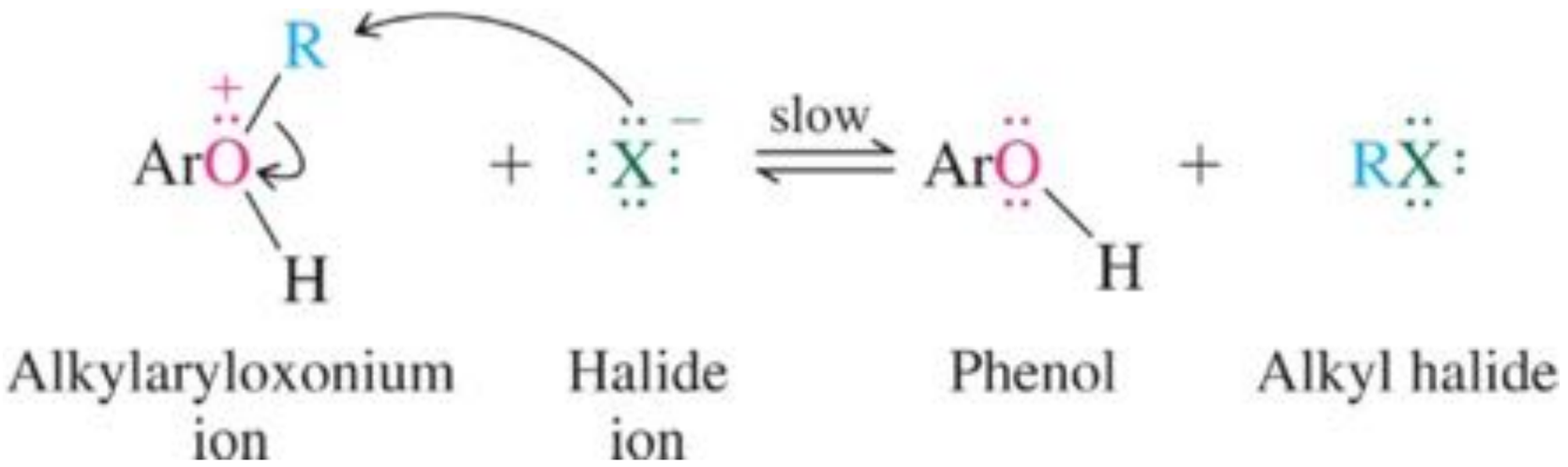
Cleavage of Aryl Ethers

1. *Only the O-Alkyl bond is broken.*
2. *Phenol cannot be converted to aryl halides by hydrogen halides.*





Cleavage of Aryl Ethers

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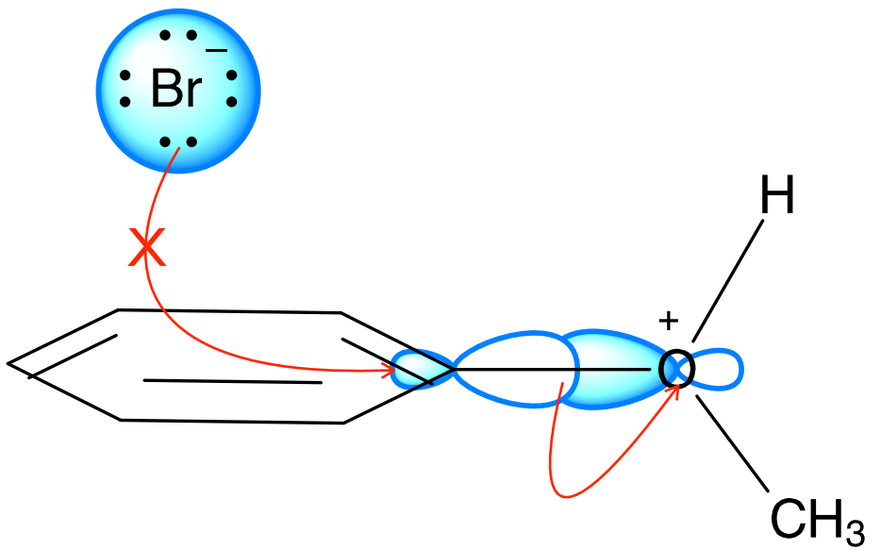
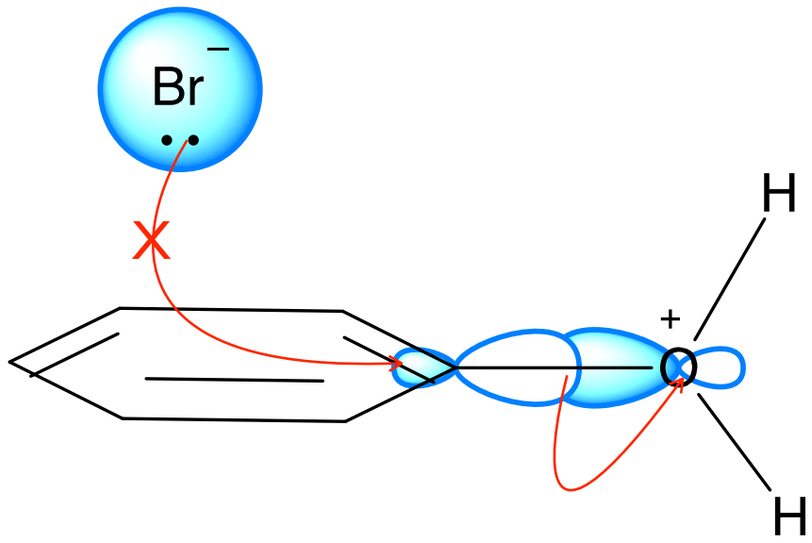
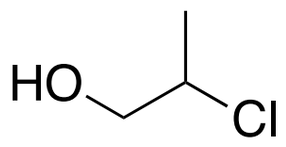
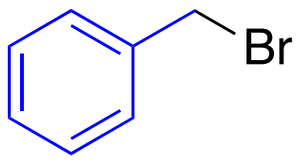




Backside attack in a S_N2 process is not possible on the sp^2–hybridized carbon of the aromatic ring.

Benzyl Ethers as Protecting Groups

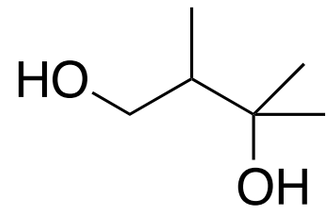




benzyl bromide (BnBr)

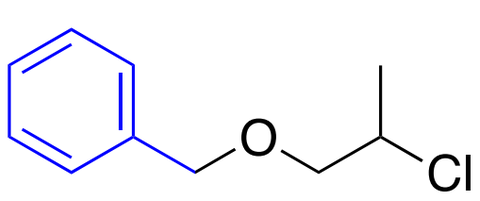
NaH

protection by S_N2



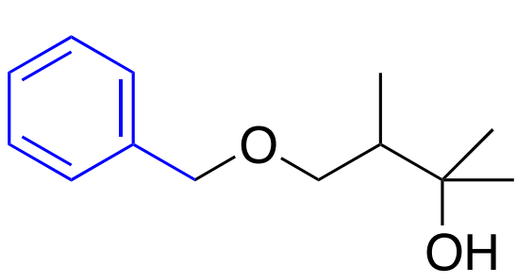
deprotection by hydrogenolysis

H_2, Pd/C
EtOH



1. Mg, Et_2O
2. acetone

3. H_3O^+/H_2O



- Benzyl ethers are stable to (do not react under) mildly acidic conditions and strongly basic conditions
- Protection = Williamson ether synth.: requires NaH to deprotonate alcohol to alkoxide
- Deprotection: hydrogen gas, metal catalysts, usually alcohol solvent (e.g., EtOH)
- Cannot deprotect benzyl groups in the presence of alkenes or alkynes; they will undergo hydrogenation (unless this is concomitantly desired)

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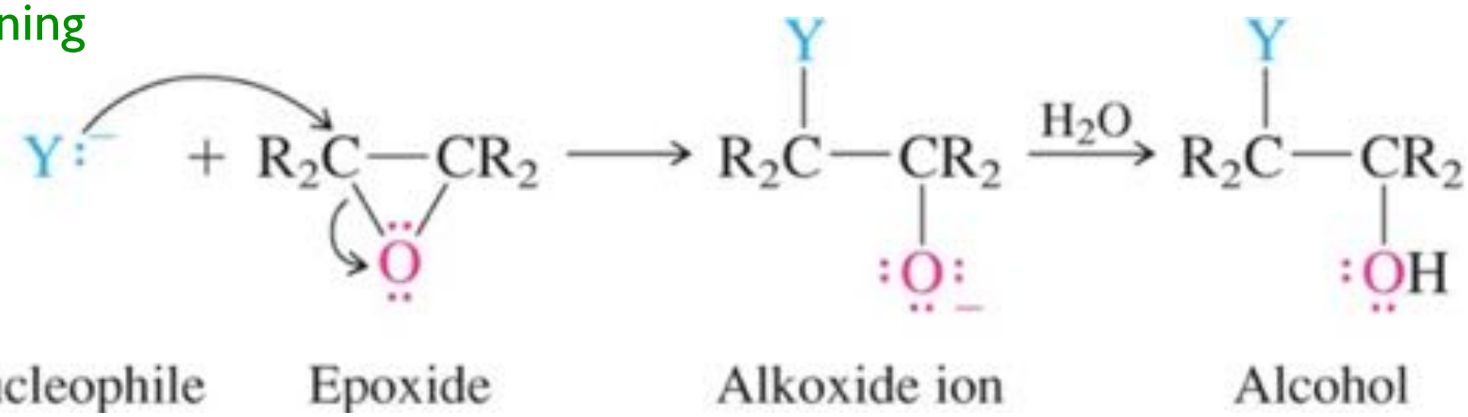
Reactions of Ethers

Ring-Opening of Epoxides (18.6)

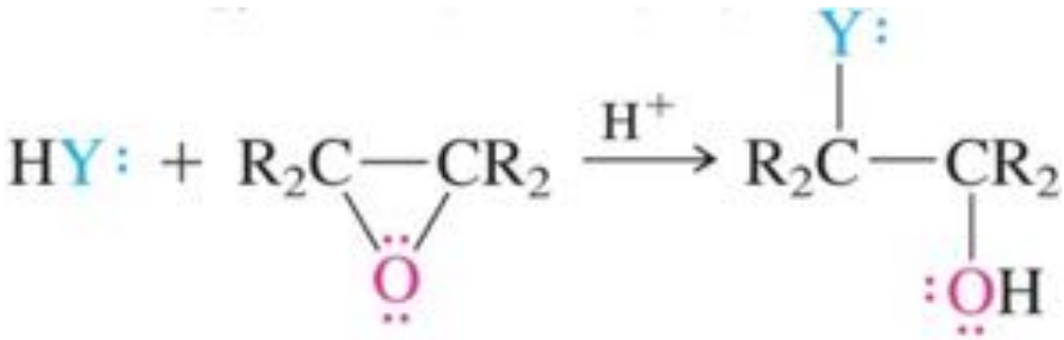
Reactions of Epoxides

Nucleophilic Ring Opening



Nucleophile Epoxide Alkoxide ion Alcohol

Acid-Catalyzed Ring Opening



Epoxide Alcohol

- Epoxides are very reactive species since the three membered ring is highly strained (Baeyer strain).
- Epoxides can undergo nucleophilic ring opening or acid catalyzed ring opening.
- The conditions dictate the regioselectivity of addition.

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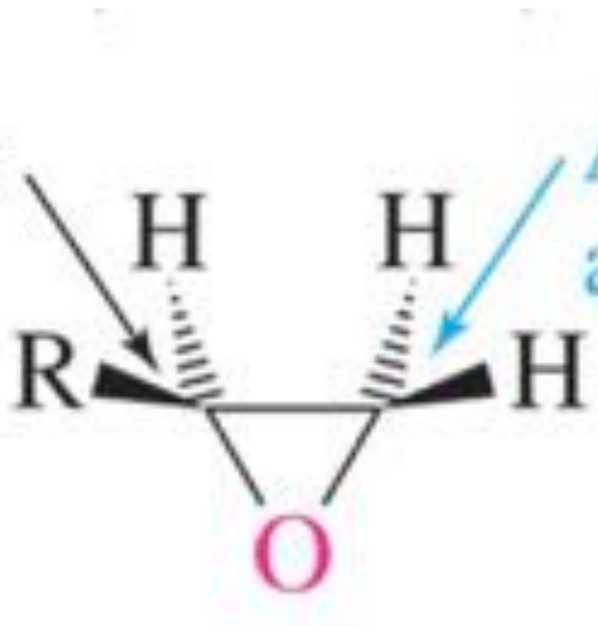
Reactions of Epoxides

Nucleophiles attack here when reaction is catalyzed by acids.

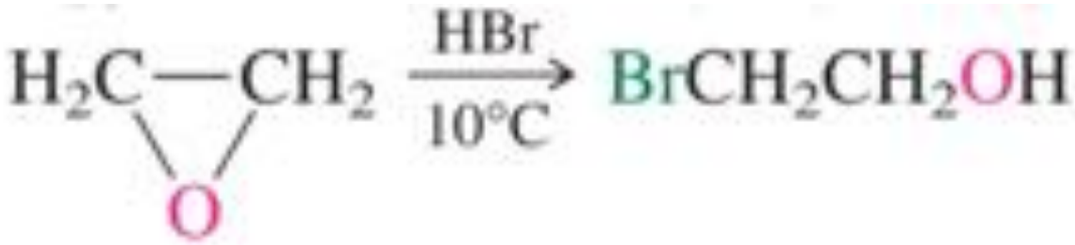


Anionic nucleophiles attack here.

- Epoxides are very reactive species since the three membered ring is highly strained (Baeyer strain).
- Epoxides can undergo nucleophilic ring opening or acid catalyzed ring opening.
- The conditions dictate the regioselectivity of addition.

Reactions of Epoxides

Acid-Catalyzed Ring Opening



Ethylene oxide — 2-Bromoethanol (87–92%)

Ethylene oxide — 2-Ethoxyethanol (85%)

- Epoxide is protonated in acid-catalyzed version.
- Nucleophile adds to the most substituted carbon atom.
- Addition is *anti* to the leaving oxygen atom = inversion of configuration
- Reaction is S_N2-like

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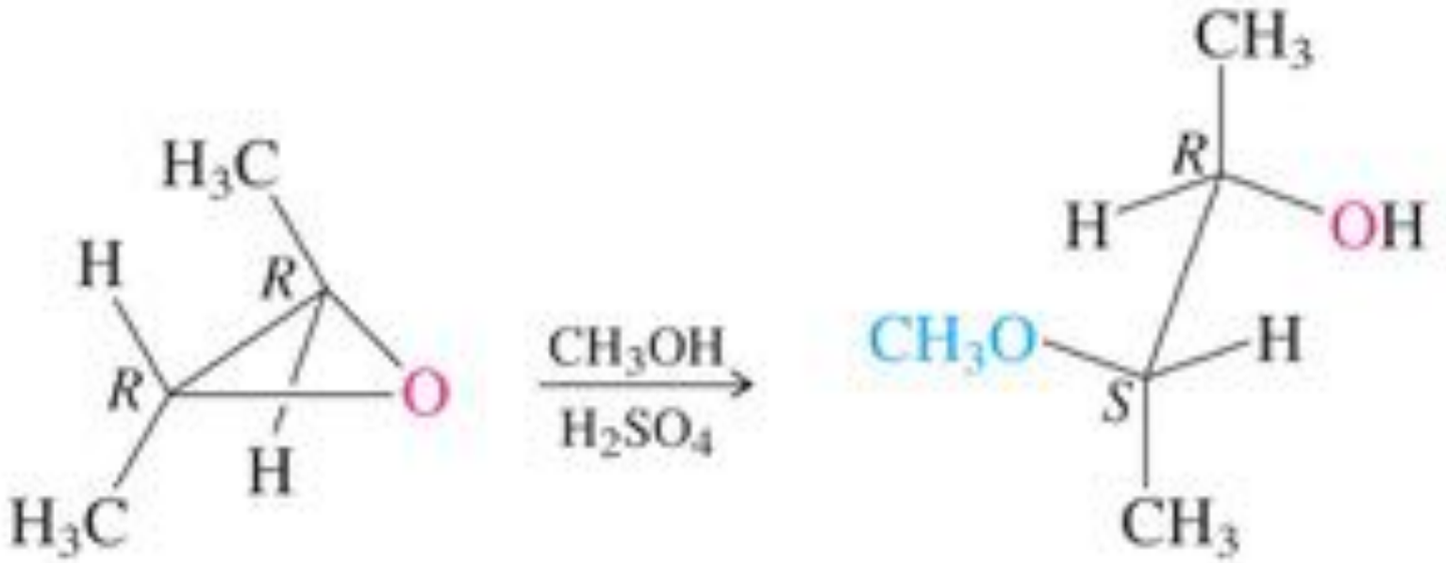
Reactions of Epoxides

Acid-Catalyzed Ring Opening



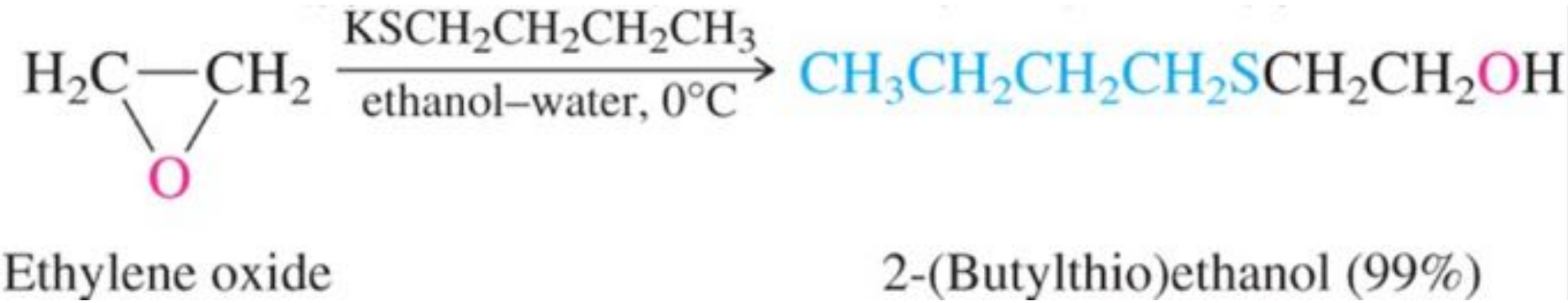
(2*R*,3*R*)-2,3-Epoxybutane

(2*R*,3*S*)-3-Methoxy-2-butanol
(57%)

- Epoxide is protonated in acid-catalyzed version.
- Nucleophile adds to the most substituted carbon atom.
- Addition is *anti* to the leaving oxygen atom = inversion of configuration
- Reaction is S_N2-like

Reactions of Epoxides

Anionic Nucleophilic Ring Opening



- Anionic nucleophiles add to neutral epoxides.
- Nucleophiles add to least sterically hindered carbon atoms.
- Reaction is S_N2 = inversion of configuration at chirality centers.

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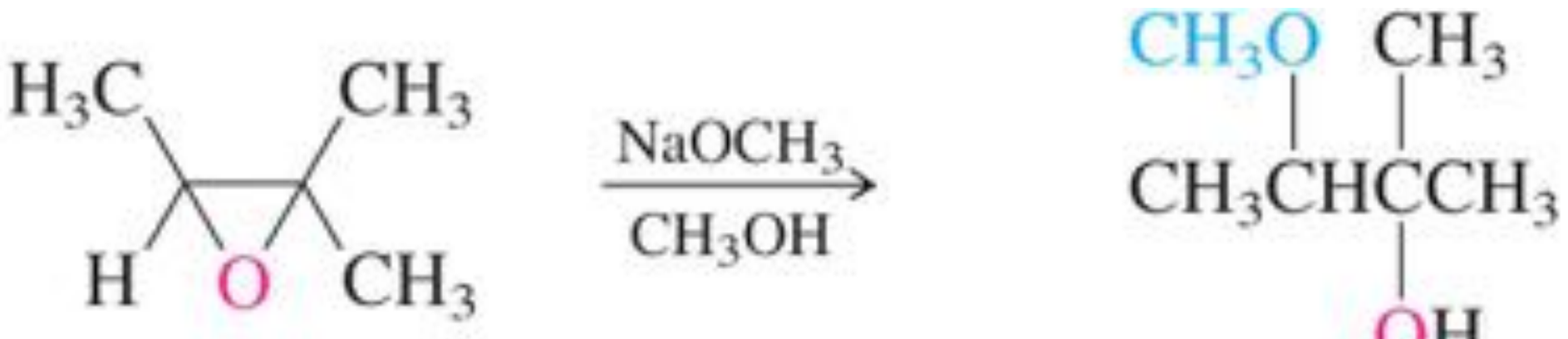
Reactions of Epoxides

Anionic Nucleophilic Ring Opening

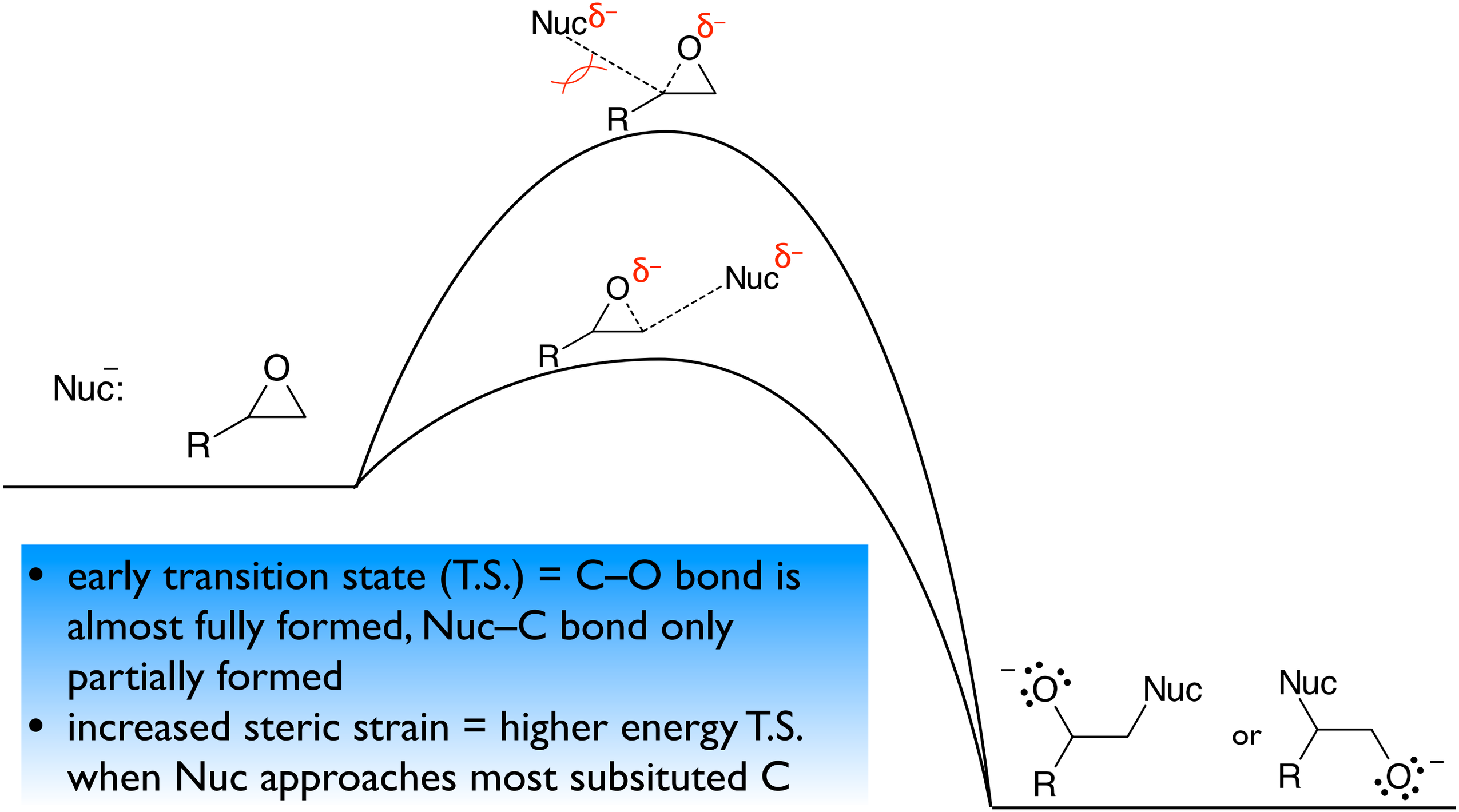


2,2,3-Trimethyloxirane

3-Methoxy-2-methyl-2-butanol
(53%)

- Anionic nucleophiles add to neutral epoxides.
- Nucleophiles add to least sterically hindered carbon atoms.
- Reaction is S_N2 = inversion of configuration at chirality centers.

Anionic Nucleophilic Ring Opening of Epoxides



- early transition state (T.S.) = C–O bond is almost fully formed, Nuc–C bond only partially formed
- increased steric strain = higher energy T.S. when Nuc approaches most subsituted C

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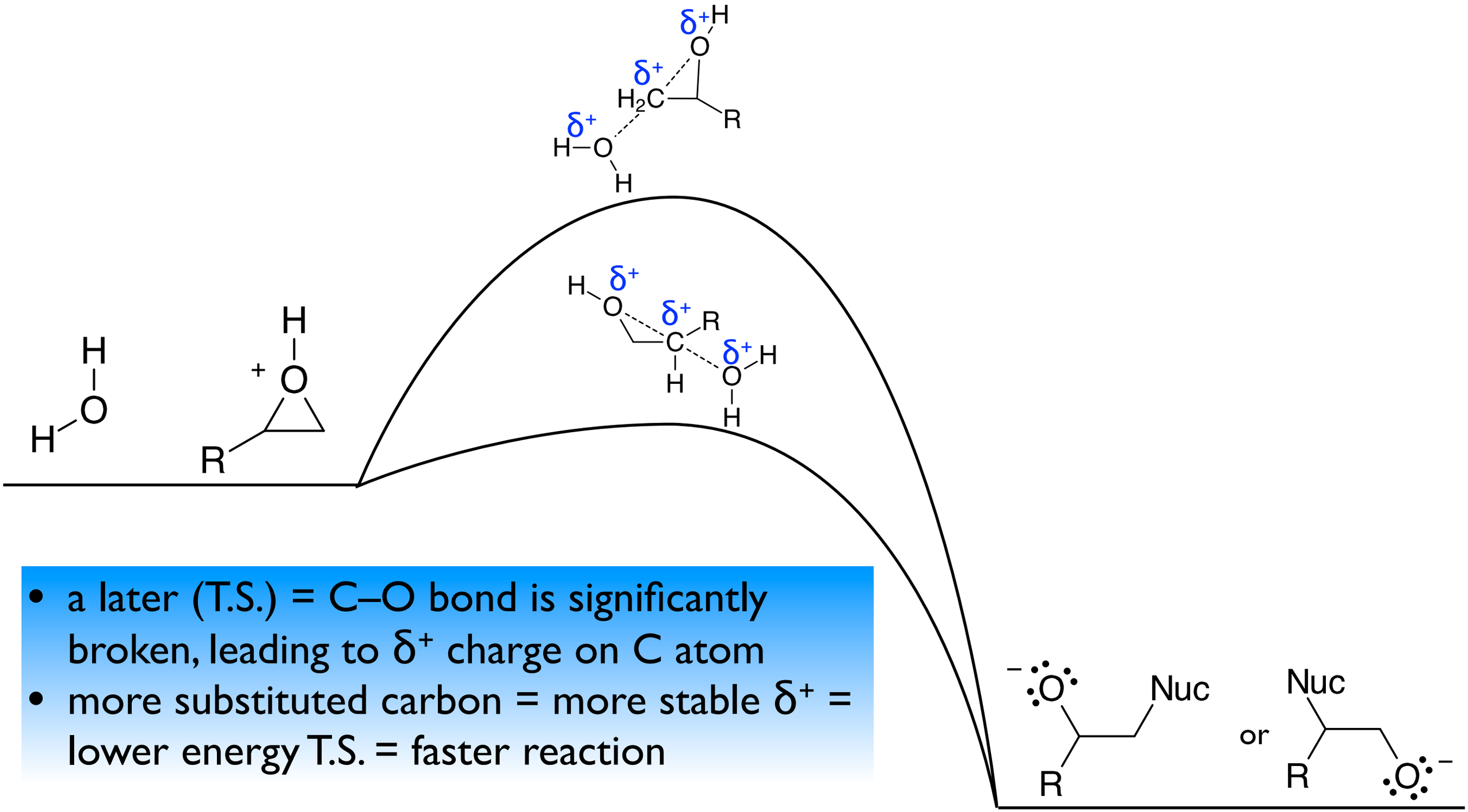
Acid-Catalyzed Ring Opening



- a later (T.S.) = C–O bond is significantly broken, leading to δ^+ charge on C atom
- more substituted carbon = more stable δ^+ = lower energy T.S. = faster reaction

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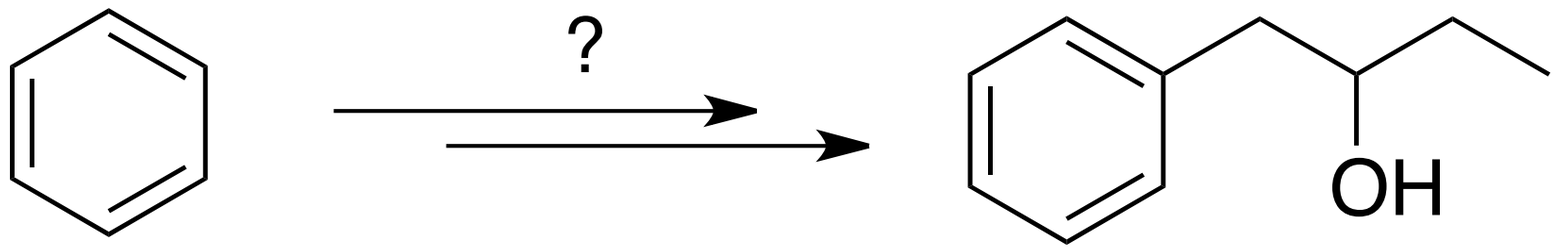
Synthetic Challenge



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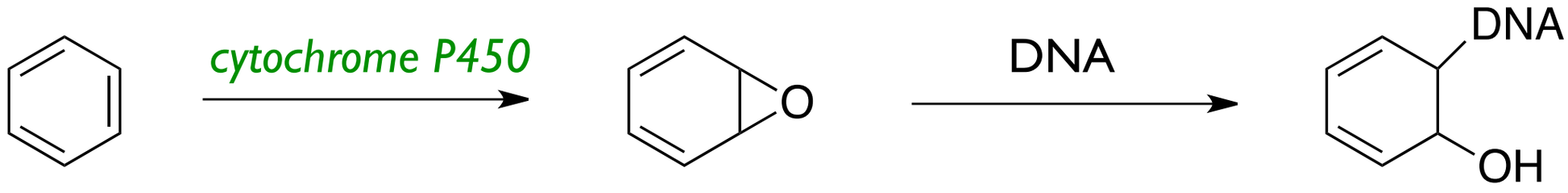
Metabolism of Arenes



- benzene can be oxidized by enzymes to give arene epoxides
- powerful alkylating reagents; can alkylate nucleophilic sites in DNA and proteins leading to toxicity and carcinogenicity

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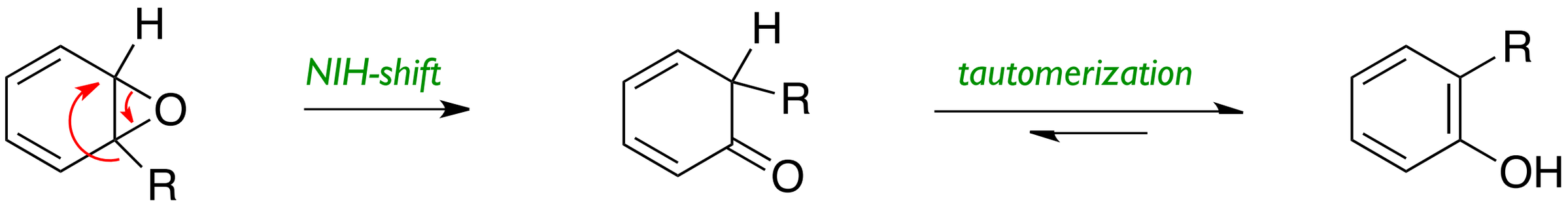
Biosynthetic Oxidation Through NIH-Shift

NIH-Shift: Rearrangement of an epoxide through a 1,2-sigmatropic shift (hydride shift or alkyl shift) to form a ketone.



- Discovered by scientists National Institute of Health (NIH)
- Catalyzed by Bronsted acids and Lewis acids (e.g. BF_3)
- 2,4-dienones are initial products that undergo tautomerization to give enol product (rearomatized = more stable)

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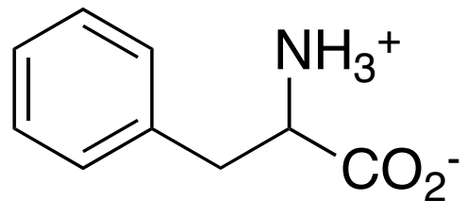
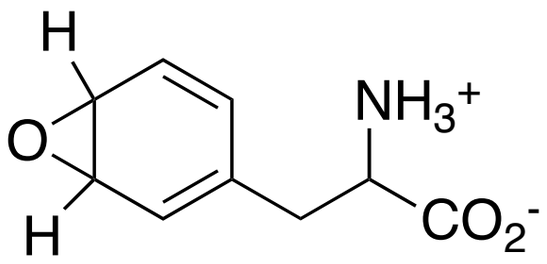
Biosynthetic Oxidation Through NIH-Shift

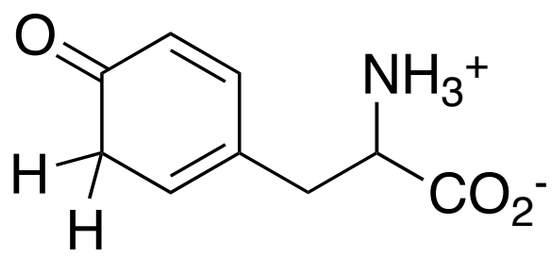


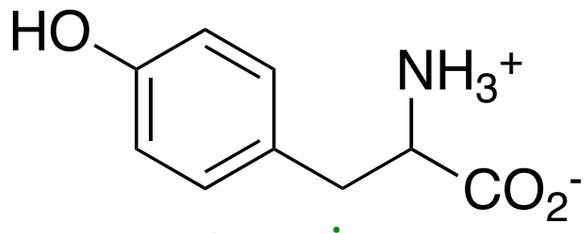
phenylalanine

phenylalanine hydroxylase (monooxygenase)



NIH-shift





tyrosine

tautomerization

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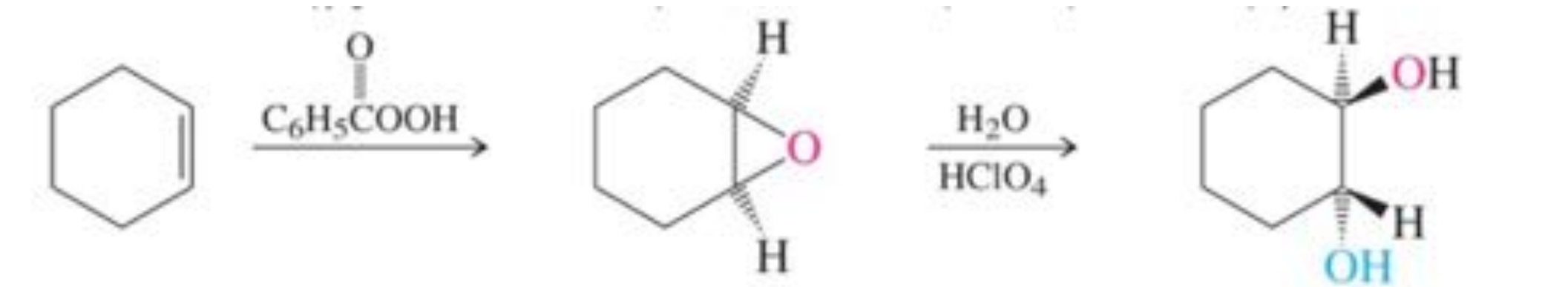
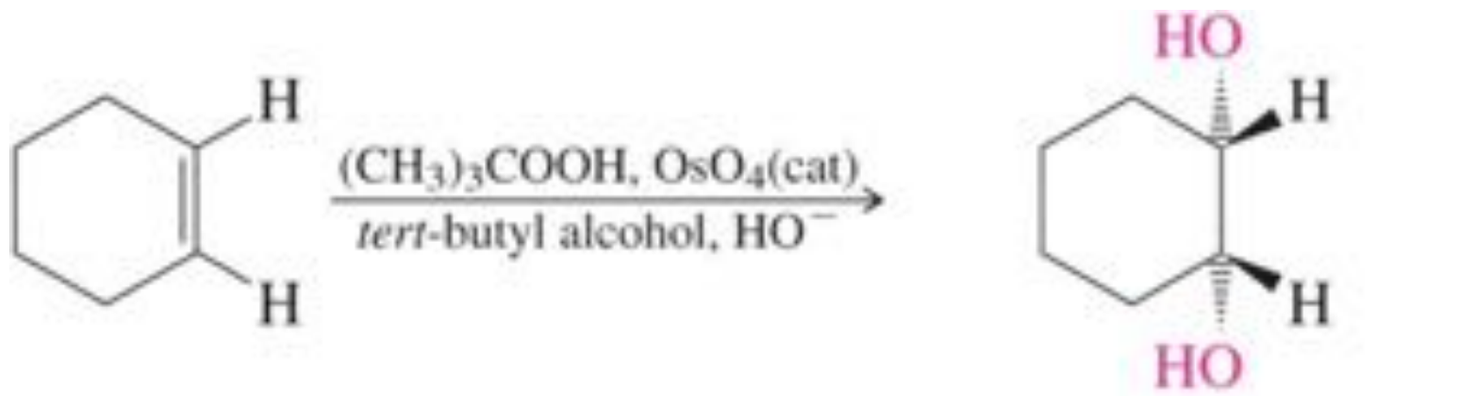
Dihydroxylation Strategies



Cyclohexene

1,2-Epoxycyclohexane

trans-1,2-Cyclohexanediol
(80%)



Cyclohexene

cis-1,2-Cyclohexanediol
(62%)

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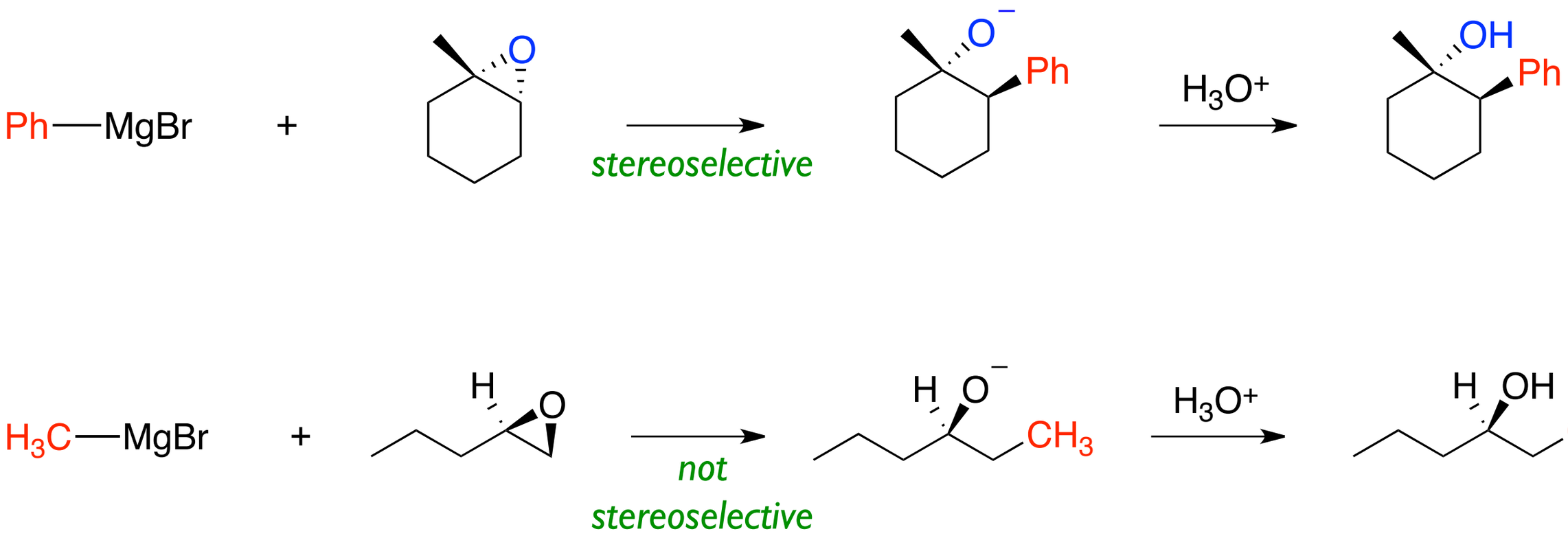
Grignard Addition to Epoxides



- Grignard reagents are considered anionic nucleophiles
- Addition takes place at least substituted c-atom of epoxide
- S_N2 = inversion of configuration at chirality centers
- can be stereoselective = trans alcohols and alkyl group

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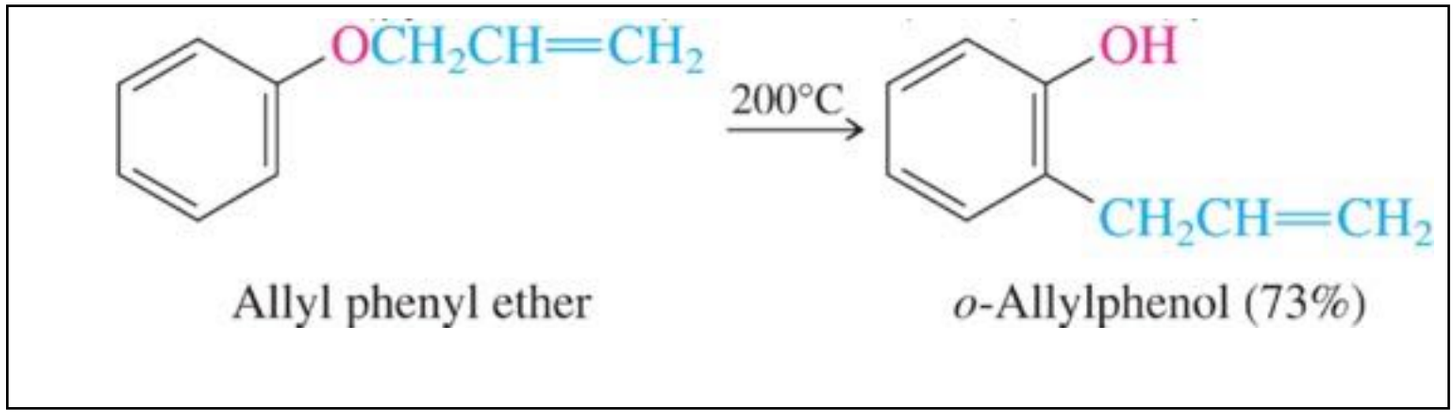
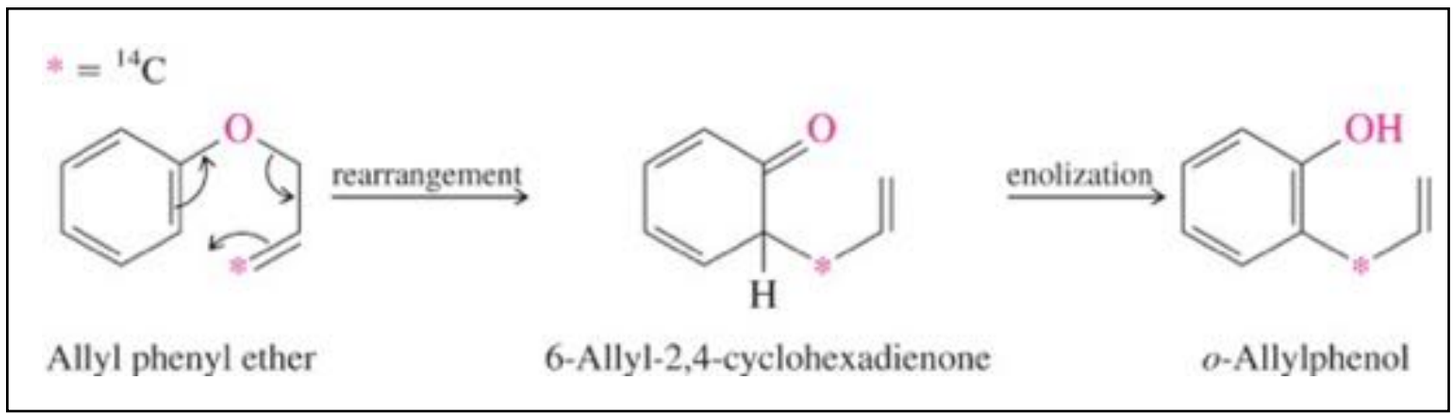
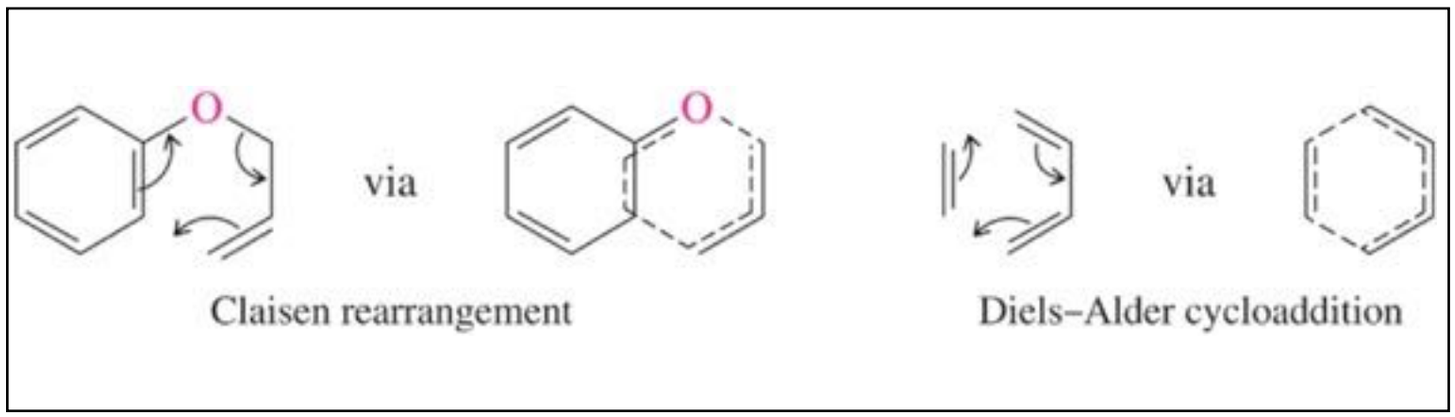
Reactions of Ethers

Claisen Rearrangement (18.4)

Claisen Rearrangement







- Claisen rearrangement occurs for allyl phenyl ethers (and some allyl vinyl ehthers)
- sigmatropic rearrangement: sigma bond is migrating from one end of a π-system to the other
- pericyclic reaction (like Diels-Alder): cyclic transition state
- ketone immediately tautomerizes to the enol form to regenerate aromatic ring

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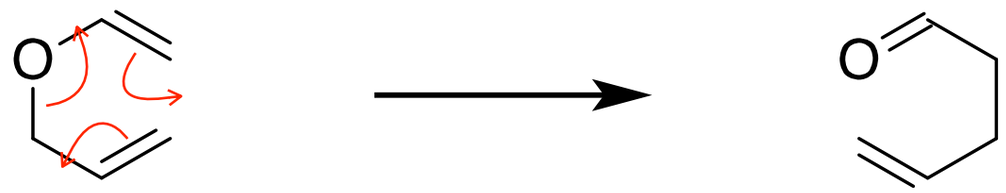
Claisen & Cope Rearrangements

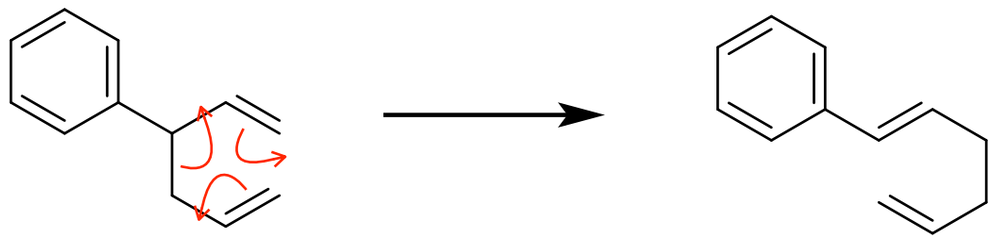
Aliphatic Claisen



allyl vinyl ether

γ,δ-unsaturated carbonyl

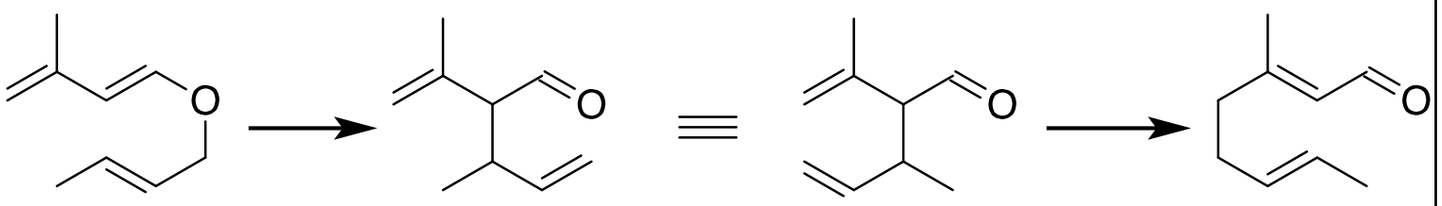
Cope Rearrangement (carbon analog of Claisen)



1,5-diene

1,5-diene

Tandem Claisen-Cope



- Claisen rearrangement also occurs for allyl vinyl ethers
- Cope Rearrangement is the carbon analog. Usually proceeds in the direction that gives most substituted and most conjugated alkenes
- Tandem Claisen-Cope possible with allyl 1,4-dienenyl ethers

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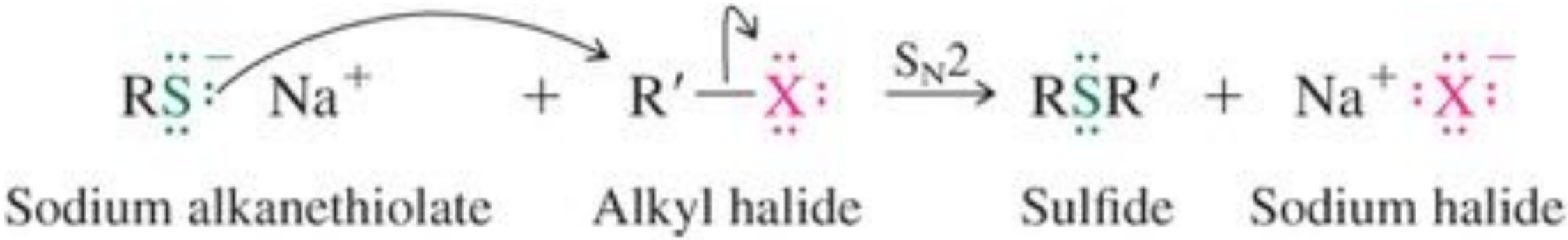
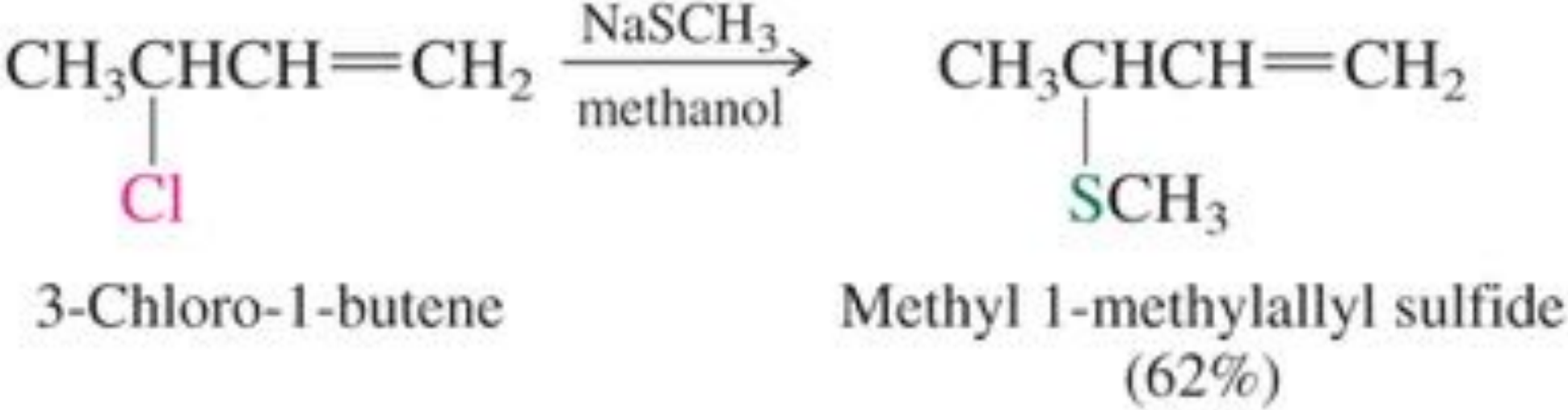
Preparation and Reactions of Thiols and Sulfides

18.8

Preparation of Sulfides



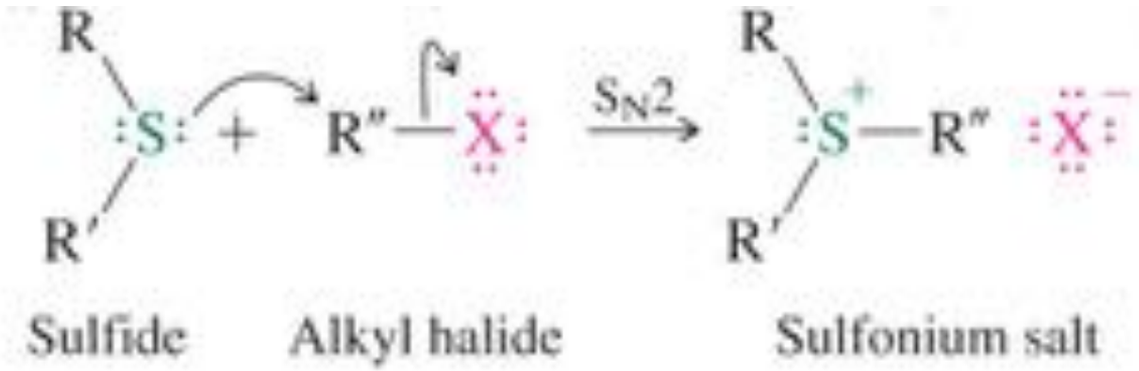
Sodium alkanethiolate Alkyl halide Sulfide Sodium halide



3-Chloro-1-butene Methyl 1-methylallyl sulfide (62%)

- Sulfides are prepared in a similar way to ethers.
- Sodium alkanethiolates do not have to be prepared separately. Since thiols are more acidic than alcohols, they can easily be prepared by deprotonating with NaOH

Alkylation of Sulfides: Sulfonium Salts



Sulfide Alkyl halide Sulfonium salt

Dodecyl methyl sulfide Methyl iodide Dodecyldimethylsulfonium iodide

- Sulfides (sulfur) are much more nucleophilic than ethers (oxygen).
- Sulfides are so nucleophilic, even neutral species can be alkylated.
- Sulfonium salts are stable and can be isolated.
- Important transformation in biological processes.

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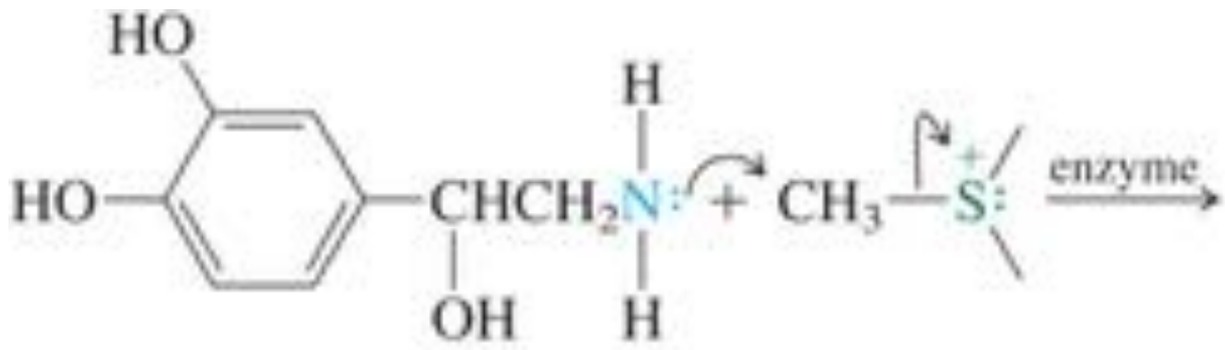
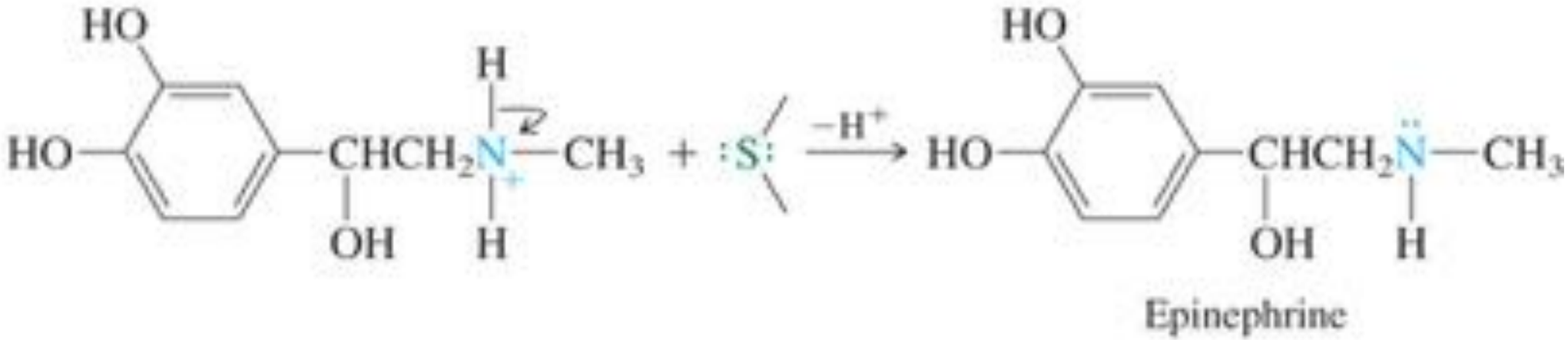
Alkylation of Sulfides: Sulfonium Salts



Norepinephrine SAM



Epinephrine

- Sulfides (sulfur) are much more nucleophilic than ethers (oxygen).
- Sulfides are so nucleophilic, even neutral species can be alkylated.
- Sulfonium salts are stable and can be isolated.
- Important transformation in biological processes.

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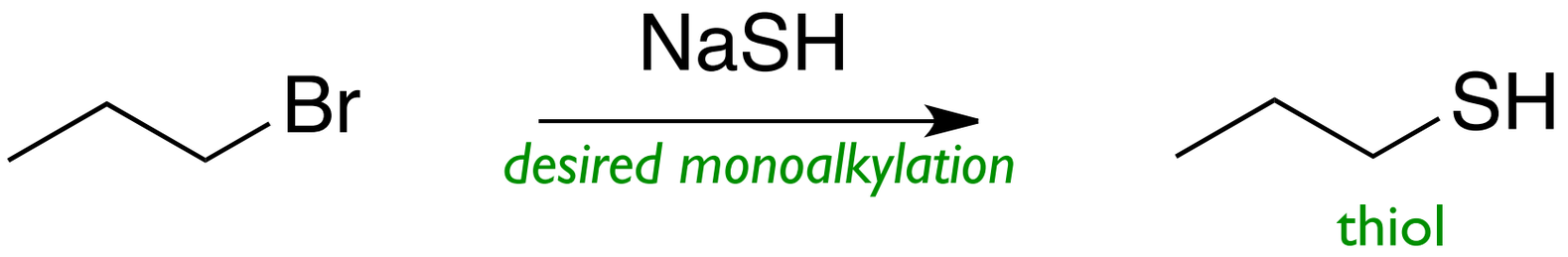
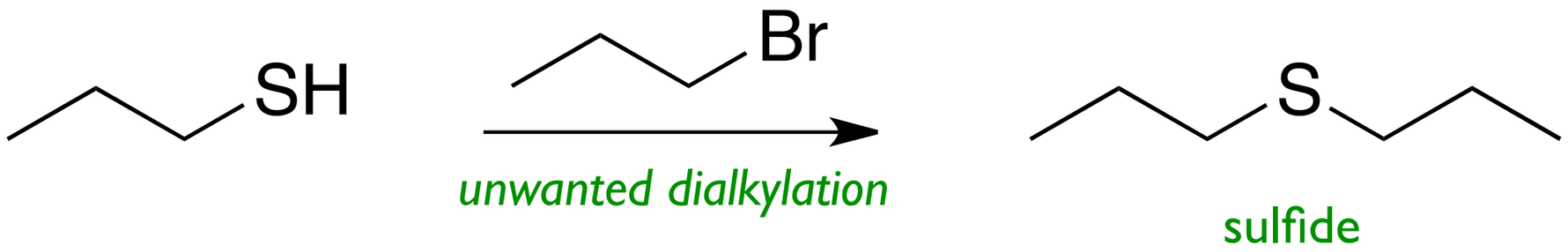
Synthesis of Thiols





- Preparation of thiols by addition of sulfide (SH^-) often gives dialkylation.
- Sulfur is a very good nucleophile; difficult to stop the thiol from reacting with a second molecule of alkyl halide

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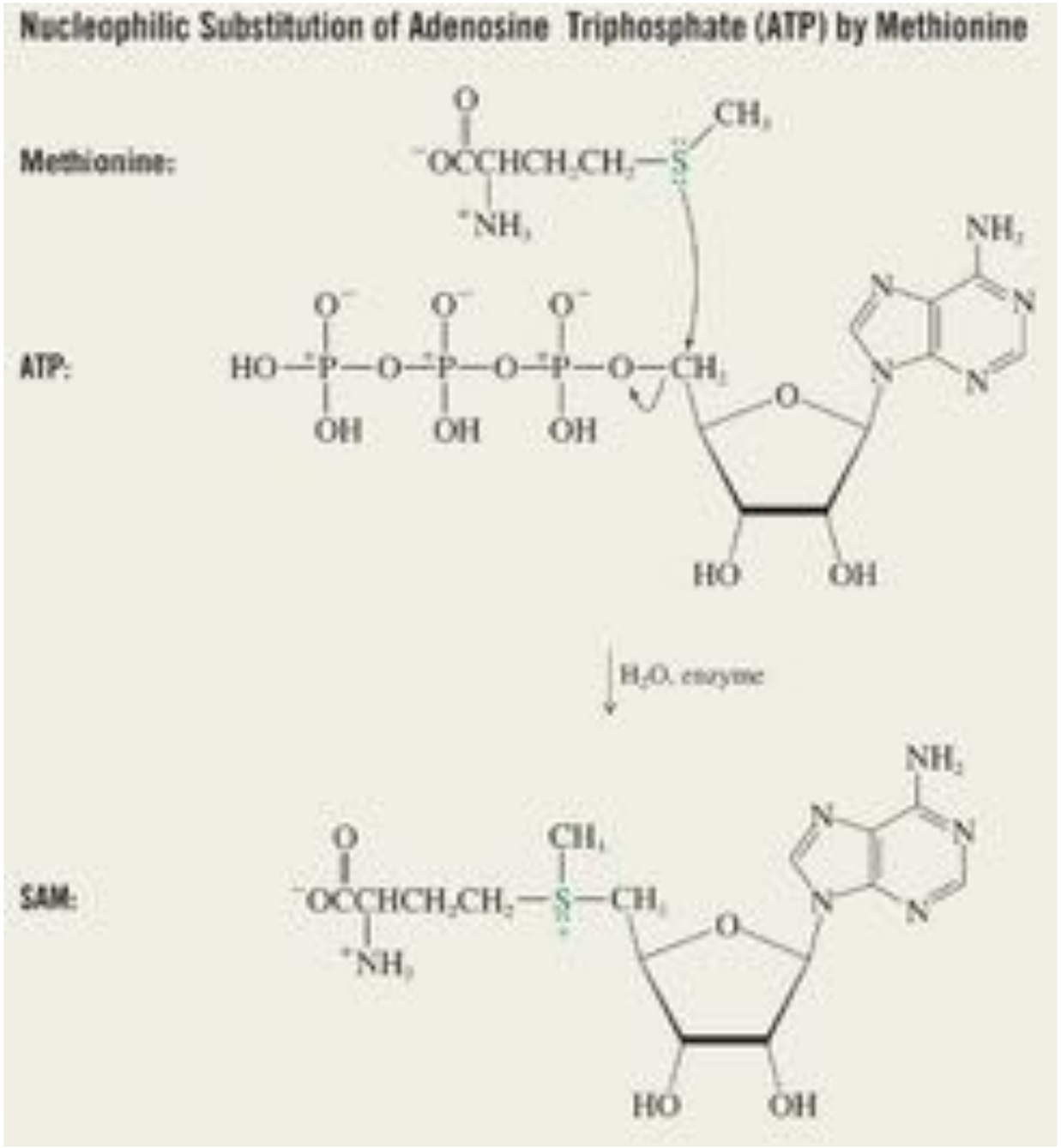
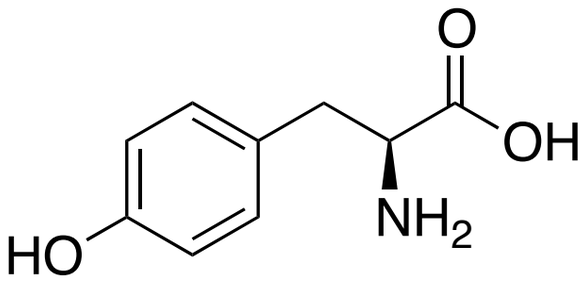
Alkylation of Sulfides: Sulfonium Salts

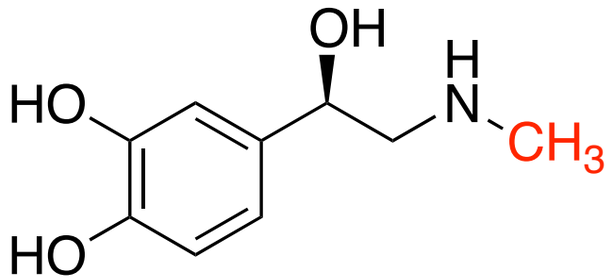


- SAM (S-adenosylmethionine)
- SAM sold as nutritional supplement
- Claimed to treat symptoms related to arthritis, depression and Alzheimers

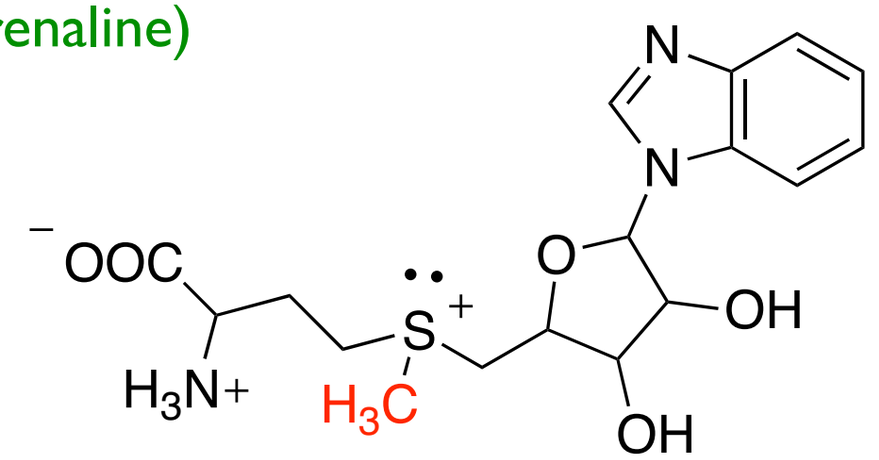
Biosynthetic Methylation by S-adenosylmethionine



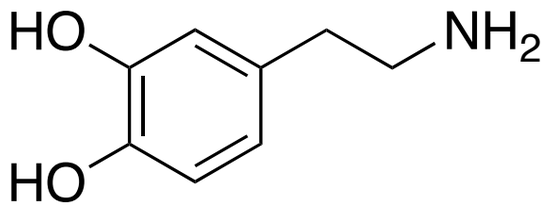
L-tyrosine



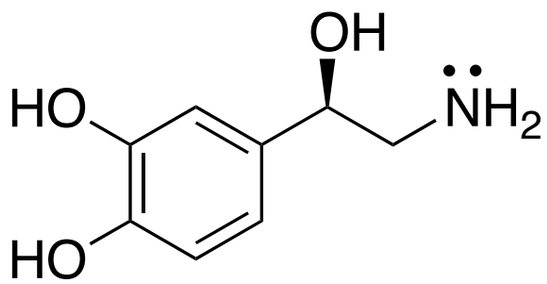
epinephrine (adrenaline)



SAM



dopamine



norepinephrine (noradrenaline)

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CHM 224 • Organic Chemistry II
Spring 2013, Des Plaines • Prof. Chad Landrie

Oakton Community College

Next Lecture. . .

Preview of Carbonyl Chemistry

Naming aldehydes & ketones (19.1)

Nucleophilic Additions (19.4-19.6)