CHEM 224: Organic Chemistry II

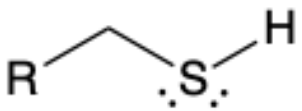
Chapter 14
Ethers/Epoxides and Thiols/Sulfides



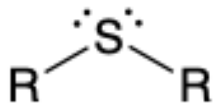
ether



epoxide



thiol



sulfide

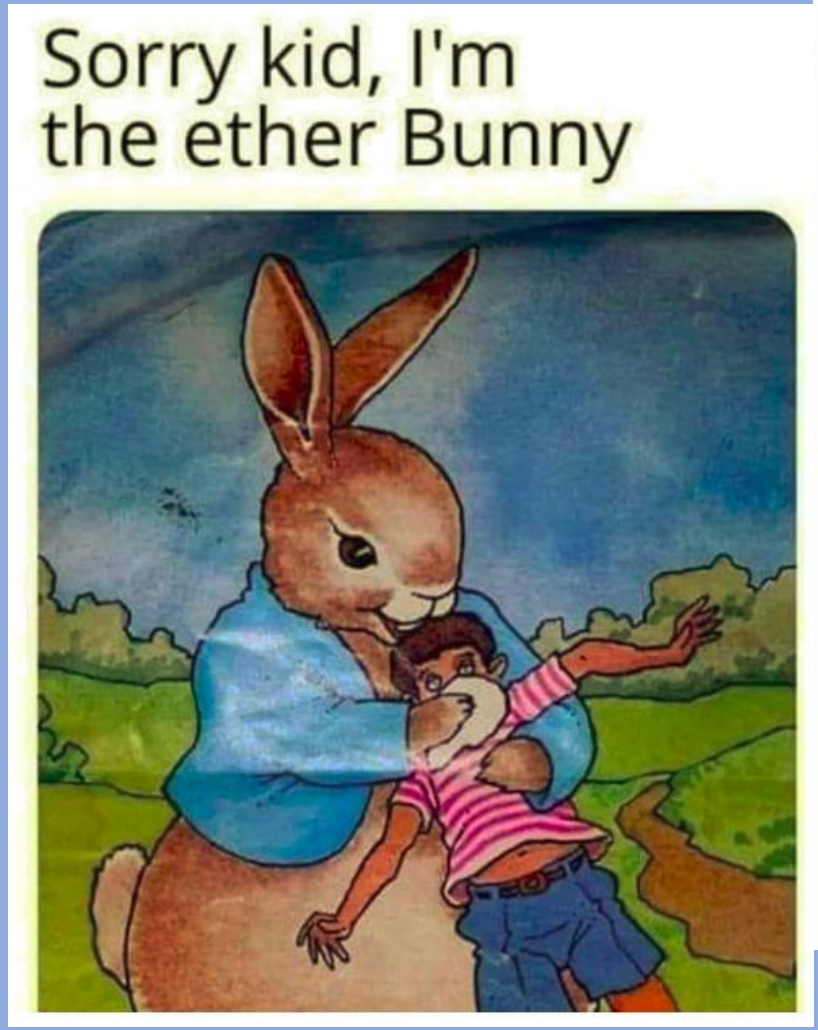
Sections **Not** Covered:

14.12 – SAM Structure

See p. 666. You don’t need to learn the structure of SAM.

Ethers: Properties

- Nomenclature
  - Common
  - IUPAC
- Boiling Points
- Solubility
- Spectroscopy
  - IR
  - H^1-NMR

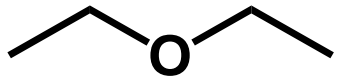




What are Ethers?

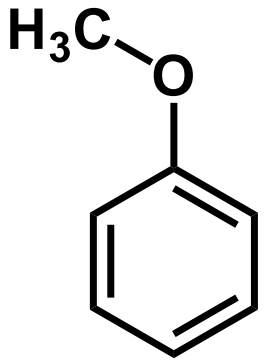
R–O–R, Ar–O–R, or Ar–O–Ar

where R/Ar is any aliphatic/aromatic group



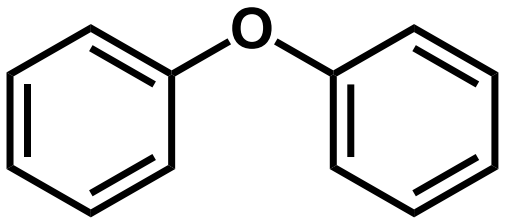
diethyl ether

"ether"



phenyl methyl ether

(anisole)



diphenyl ether

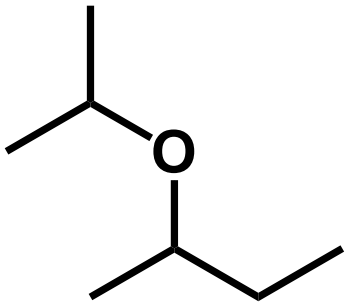


methyl vinyl ether

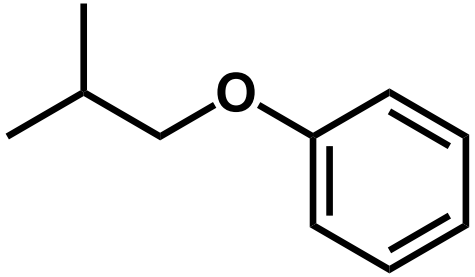
The carbons attached to the oxygen can only be attached to other carbons and/or hydrogen. (More later).

Ethers: Common Name Nomenclature

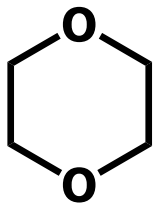
Simple ethers are usually named by **naming the attached groups** to the oxygen, **followed by "ether."** Alphabetical order is common.



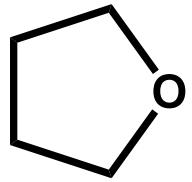
***sec*-butyl isopropyl ether**



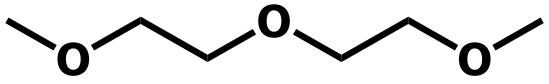
isobutyl phenyl ether



dioxane



tetrahydrofuran (THF)

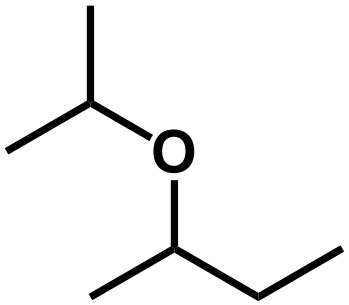


diglyme

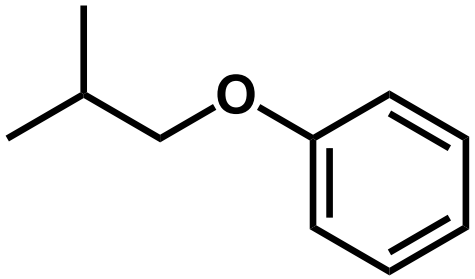
important solvents have common names

Ethers: Common Name Nomenclature

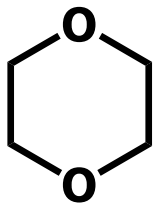
Simple ethers are usually named by **naming the attached groups** to the oxygen, **followed by "ether."** Alphabetical order is common.



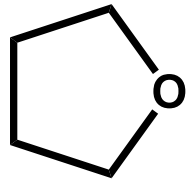
***sec*-butyl isopropyl ether**



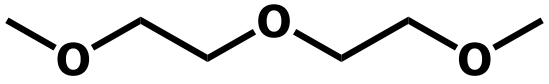
isobutyl phenyl ether



dioxane



tetrahydrofuran (THF)



diglyme

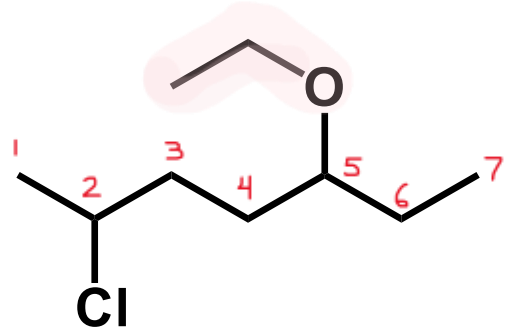
important solvents have common names

For alkyl chains, the numeric prefixes are not considered when alphabetizing (e.g., "sec", "di", or "tert").

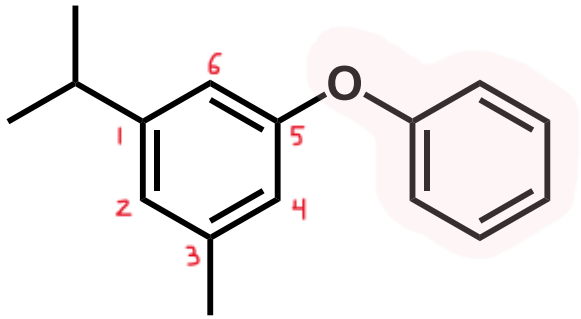
⍟ "Iso" is not a numeric prefix and is considered.

Ethers: IUPAC Nomenclature

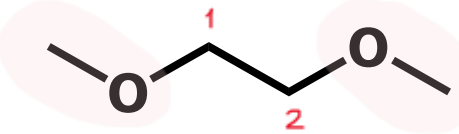
Complex ethers are usually named by according to IUPAC rules, by which **ethers are named as substituents**, as **"alkoxy."**



2-chloro-5-ethoxyheptane

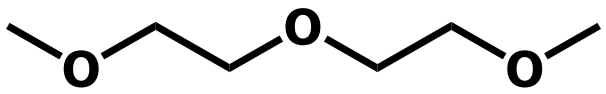


1-isopropyl-3-methyl-5-phenoxybenzene



1,2-dimethoxyethane (DME)

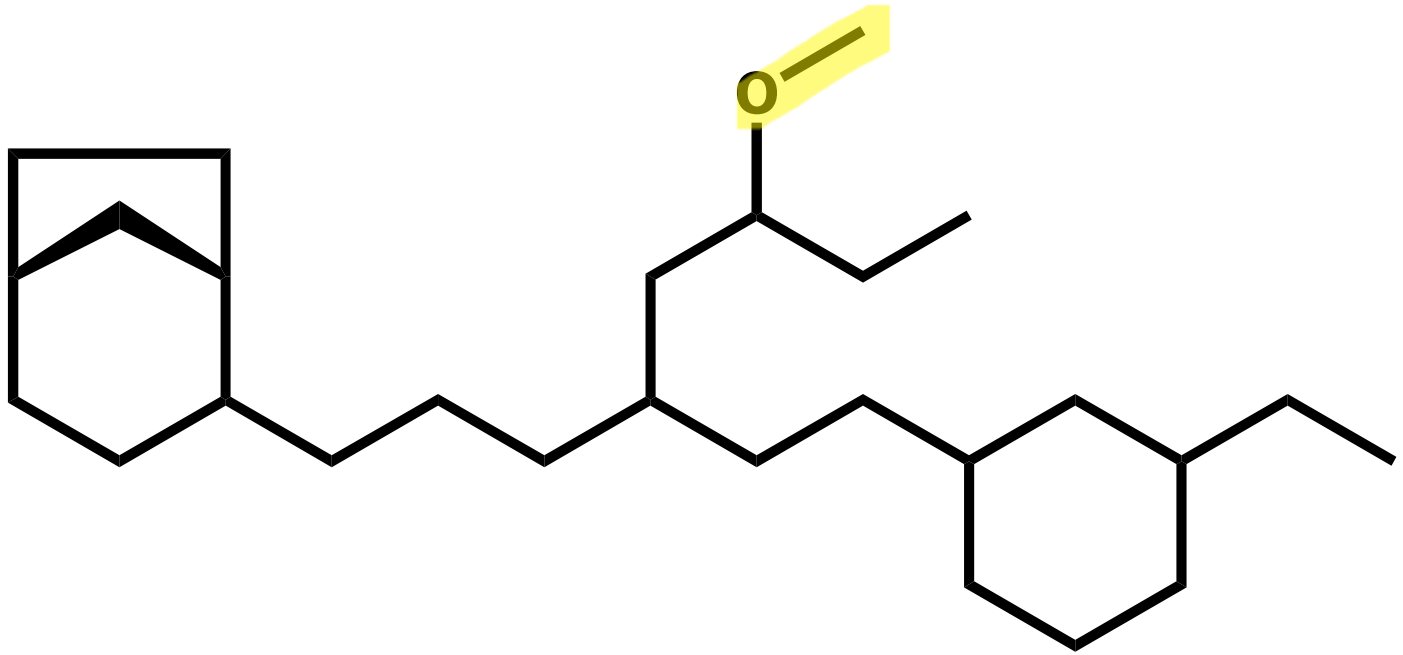
(a glyme solvent)



Diglyme (BP 162°C)

Ether Nomenclature: More Complicated Alkane

(Beyond the scope of our course)



2-(4-(2-(3-ethylcyclohexyl)ethyl)-6-methoxyoctyl)bicyclo[3.2.1]octane

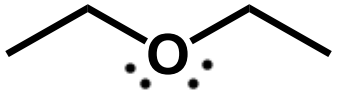
Ethers: Boiling Points

Ethers **cannot** self-hydrogen bond, so most ethers have **boiling points like alkanes** of comparable size.



Pentane

BP = 36°C



Diethyl ether

BP = 35°C

The C–O bond in ethers has a significant bond dipole, yet it has no significant effect on the boiling point.

This is often wrong on the Internet and in many textbooks!

Ethers: Boiling Points

Remember: 1 example does not exhibit a trend.



Propane **– 42°C**



Dimethyl ether (DME) **– 24°C**

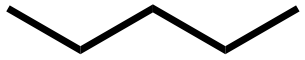


Butane **–1°C**

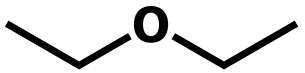


Ethyl Methyl Ether **7°C**

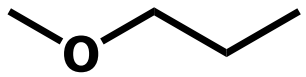
Understandable Exceptions due to the <u>Size</u> of the Ethers: R groups are so <u>small</u> that dipole has greater effect



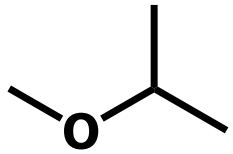
Pentane **36°C**



Diethyl Ether **35°C**



Methyl n-Propyl Ether **37°C**



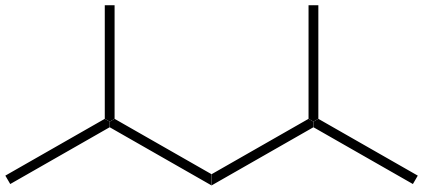
Methyl Isopropyl Ether **32°C**

(Branching lowers BP)

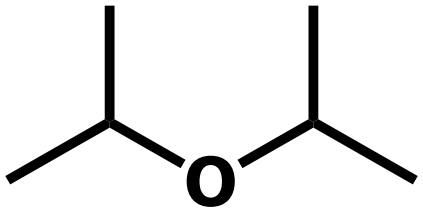
Trend fails to exist in larger & longer ethers.

Ethers: Boiling Points

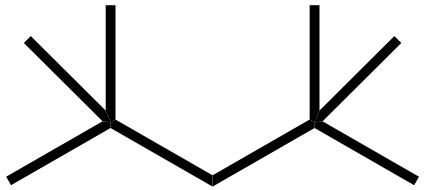
BP's can be flipped from what you'd expect.



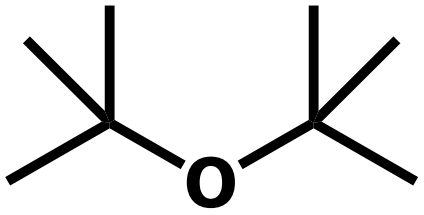
BP 80°C



BP 69°C



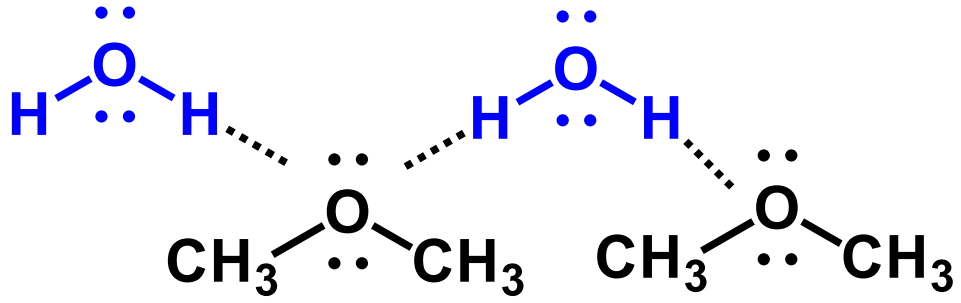
BP 122°C



BP 107°C

Ethers: Solubility

Ethers can hydrogen bond with water.



	Solubility in H_2O
EtOH	miscible
DME	7.1 g/100 mL
n-BuOH	7.3 g/100 mL
EtOEt	6.9 g/100 mL

This is essentially a tie!

Who can explain this discrepancy?

Ethers: Solubility

	Solubility in H_2O	Phase at RT
EtOH	**miscible**	**liquid**
DME	**7.1 g/100 mL**	**gas**
***n*-BuOH**	**7.3 g/100 mL**	**liquid**
EtOEt	**6.9 g/100 mL**	**liquid**

Cf. HCl (g), which is only soluble in water up to 12 M (37% by mass), even though it is completely ionic in water.

DME must fight the **entropic advantage** of being a **gas** to dissolve. *Comparing the solubility of a gas to that of a liquid is **invalid**.*

Ethers: More Solubility Data

Average solubility of the 8 **pentanols** = 3.3 g/100 mL

Average solubility of the 6 C_5 **ethers** = 2.3 g/100 mL

Average solubility of the 5 **hexanes** = 0.002 g/100 mL

Some alcohols are slightly more soluble than ethers, but the differences are hard to predict and often insignificant, especially compared to alkanes. **We can say it's a tie.**

Good Practice: Draw the structures of the 19 isomerics compounds referred to above and name them.

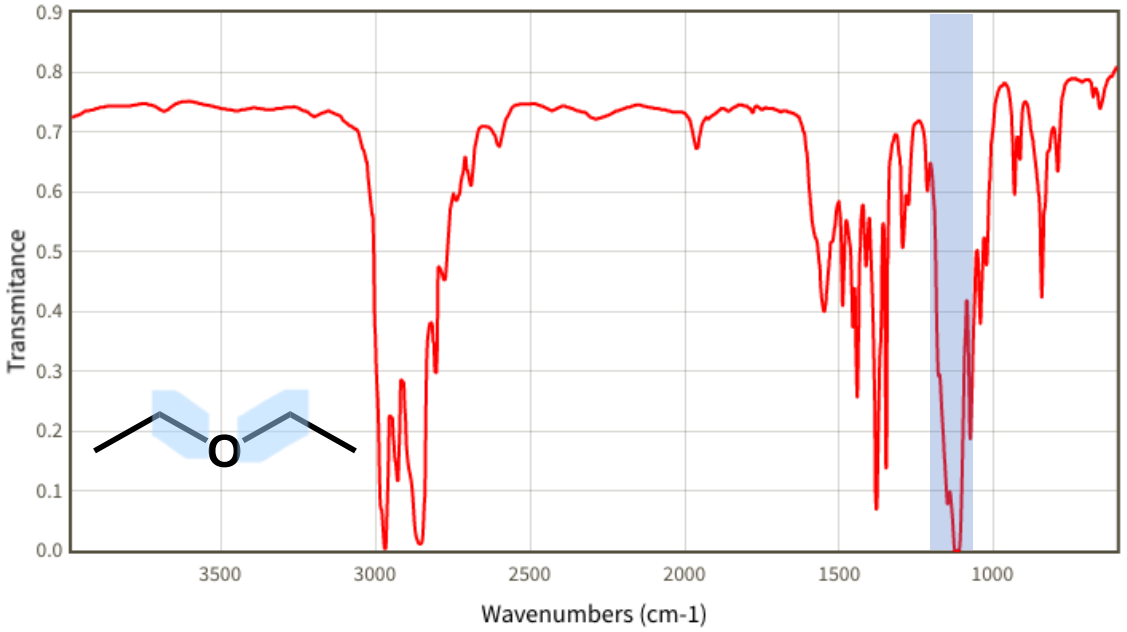
Ethers: Spectroscopy

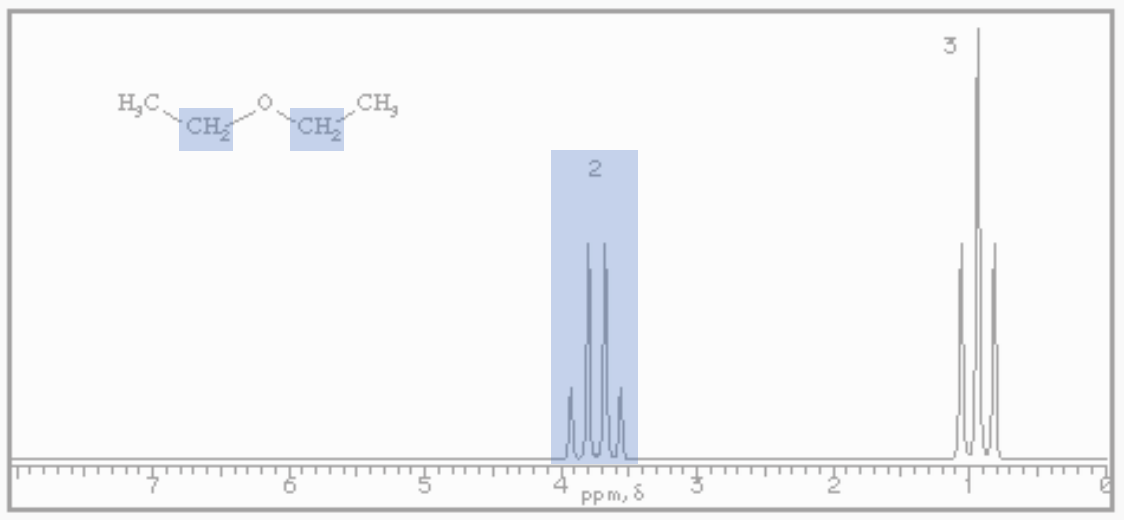
IR Spectroscopy – the C–O stretch appears at 1070-1150 cm^{-1} (*non-diagnostic*)

H^1–NMR – the OCH peaks appear at 3.3-4.0 ppm

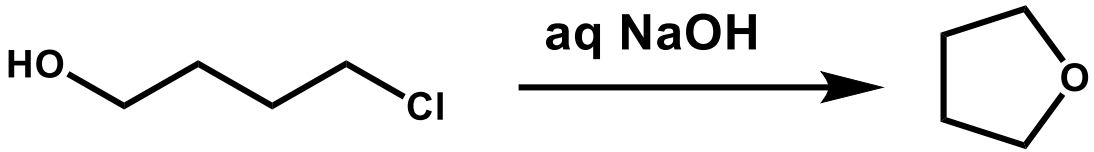
- *Note*: There are many other functional groups that include C–O bonds. If you know you have an oxygen, but there is no carbonyl or OH group, then it is likely an ether.

How would you rule out OH, ester, or COOH via IR? H-NMR?

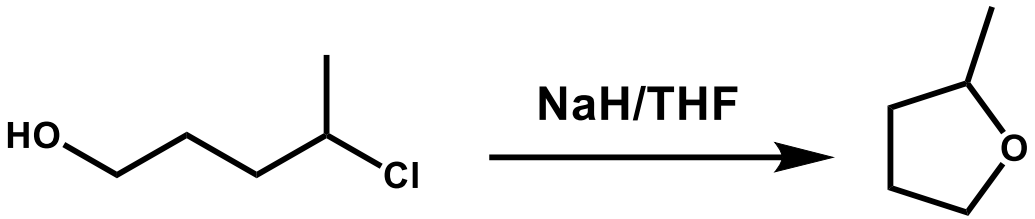




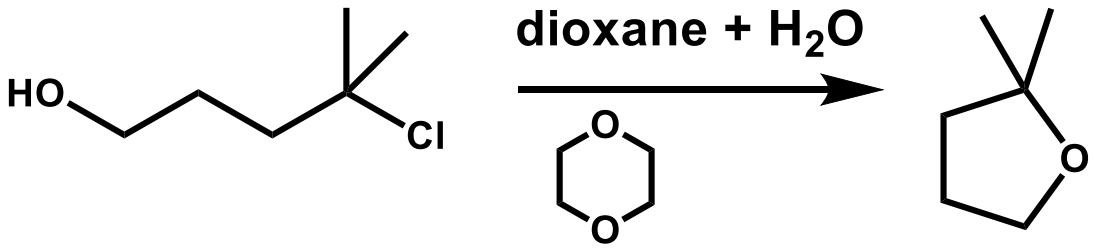
Ether Synthesis: Intramolecular



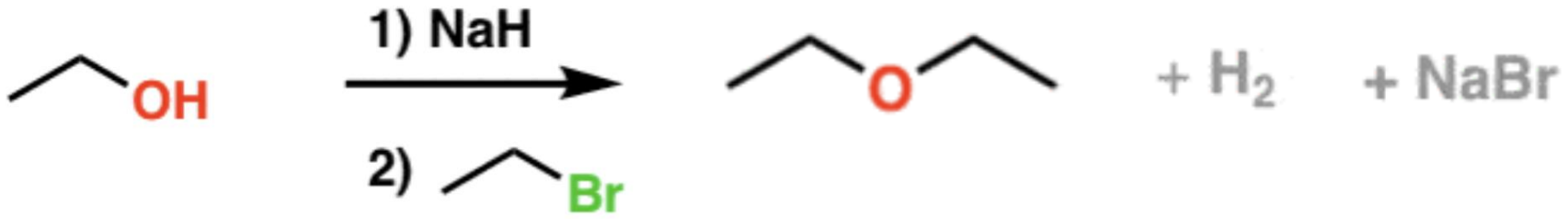
NOTE: Little, if any, of the diol is formed

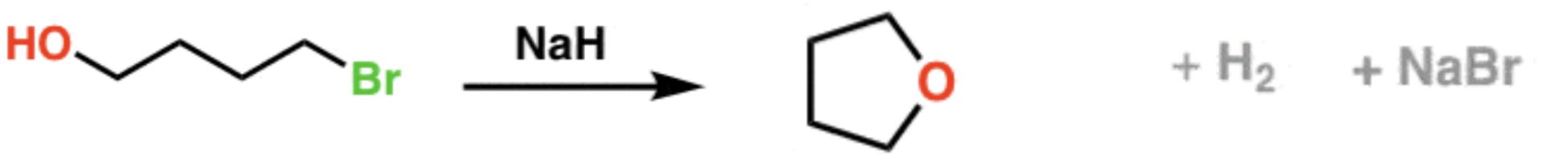


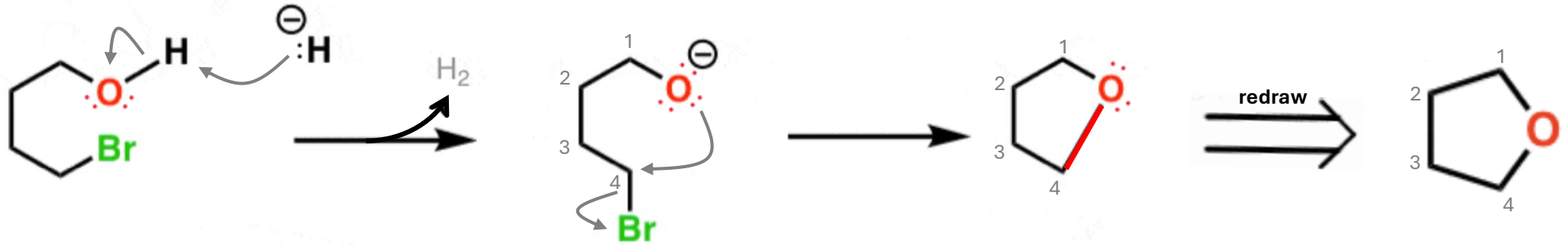
NOTE: the 2^{o} RX intramolecular reactions are sometimes better



Ether Synthesis: Intramolecular via S_N2

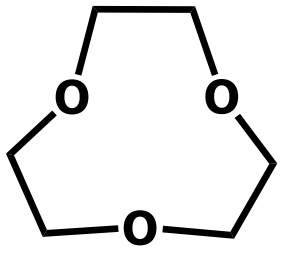




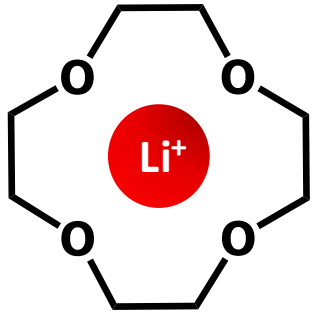


Special Solvents: Crown Ethers

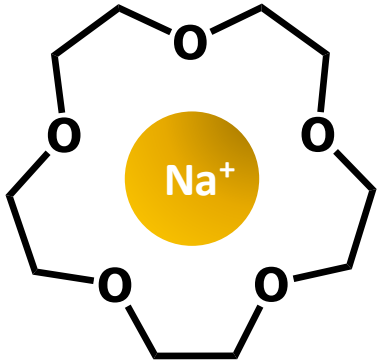
Metal cations (as Lewis bases) always complex to ether oxygens (as Lewis acids). Crown ethers do it better and more selectively.



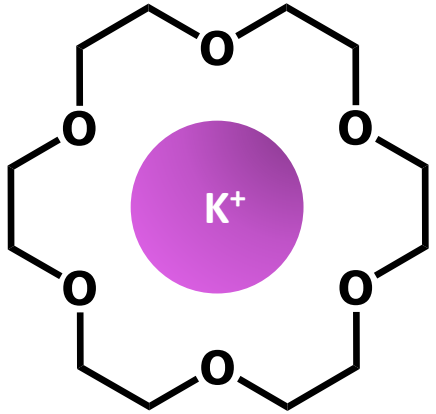
9-crown-3



12-crown-4

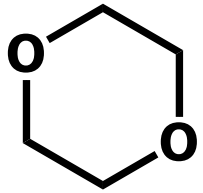


15-crown-5



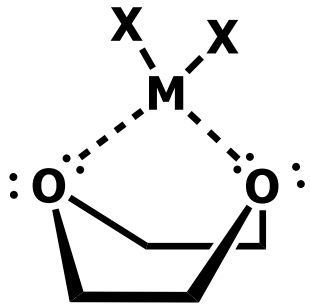
18-crown-6

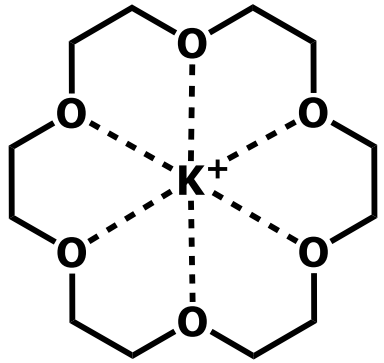
The poor man's crown ether
=
1,4-dioxane or "dioxane" is also **6-crown-2**



MX_2 ligand

M = Mg, Cu, Ge
X = Cl, Br

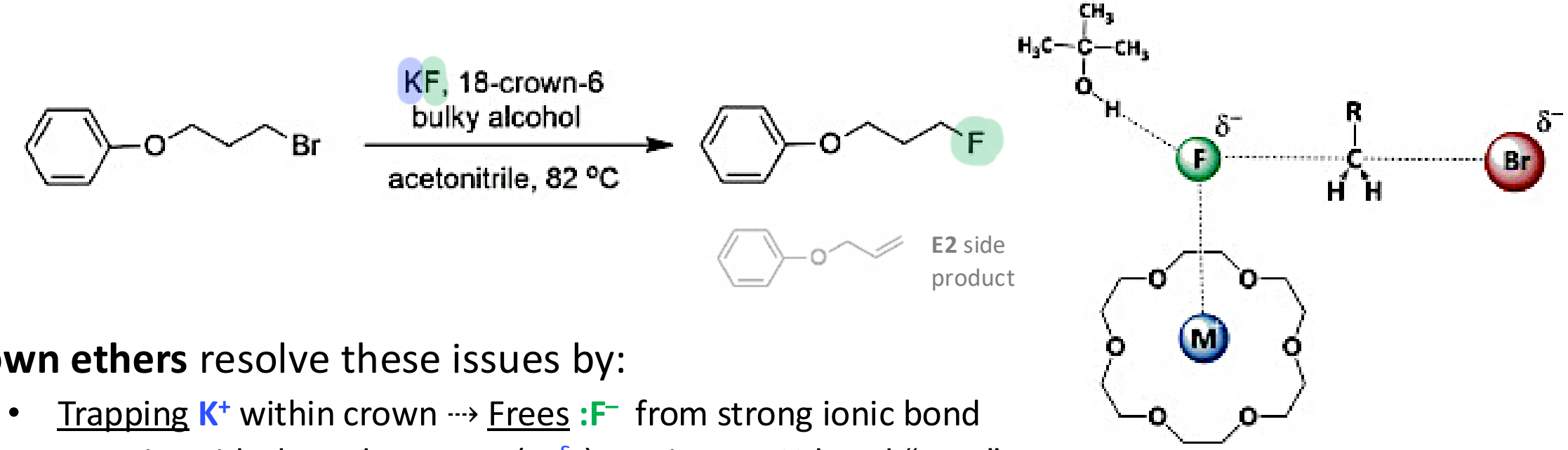




Special Solvents: Crown Ethers

KF is a salt of K^+ and $:F^-$ ions, but fluoride is not typically reactive for (2) reasons:

- The large **Δ**EN between K and F (EN_K = 0.8, EN_F = 4) forms a strong ionic pairing.
- Even freed, $:F^-$ is strongly solvated in protic solutions within H-bond "cage," which weakens its nucleophilicity (c.f. alkene addition of Br_2 in CH_2Cl_2 vs. in H_2O).

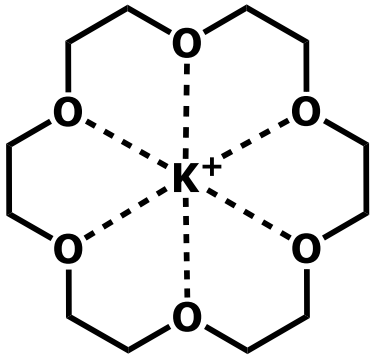


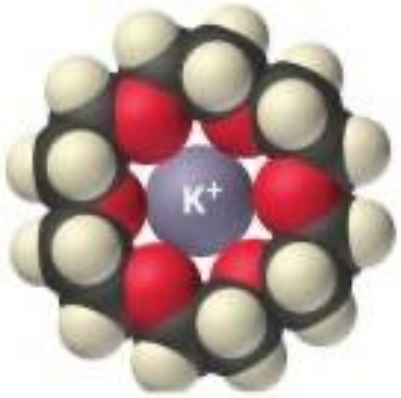
Crown ethers resolve these issues by:

- Trapping K^+ within crown ⇢ Frees $:F^-$ from strong ionic bond
- $:F^-$ pairs with the polar crown ($M^{\delta+}$) ⇢ Disrupts H-bond "cage"
  - Using a bulky alcohol also helps with this, since steric hindrance makes it harder to pack around $:F^-$.

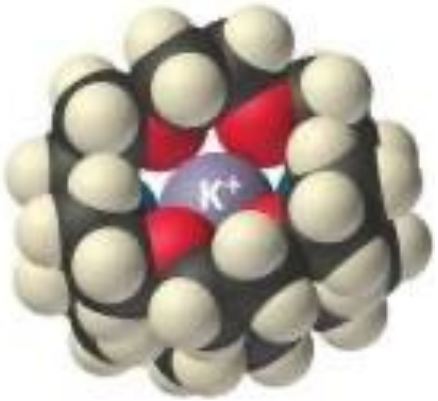
Special Solvents: Crown Ethers

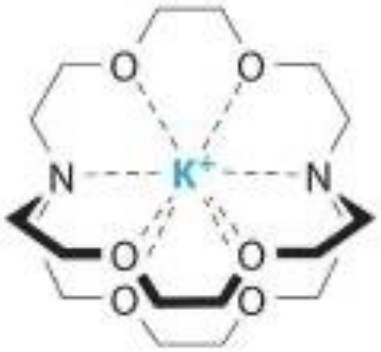
Examples of **guest-host complexes**





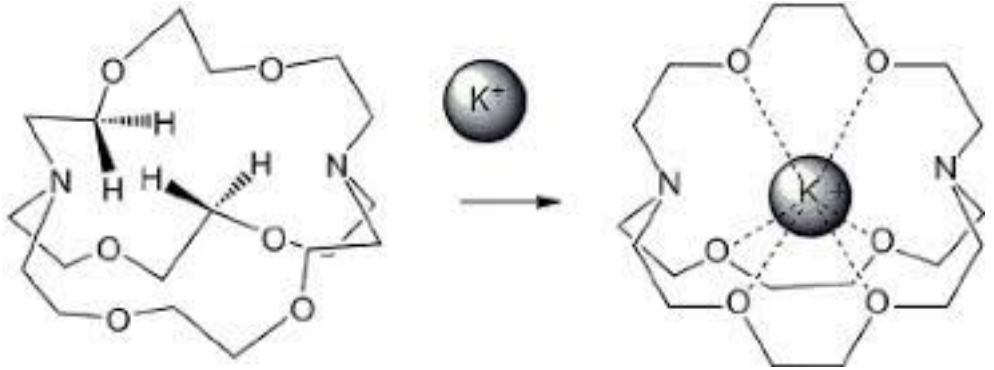
18-crown-6





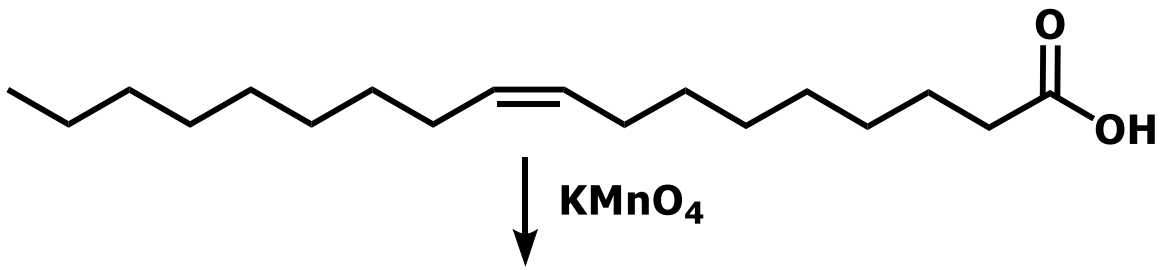
[2.2.2]cryptand

Cryptand "hosts" are polycyclic multidentate ligands that can fully encapsulate "**guest**" ions and increase solubility similar to crown ethers.

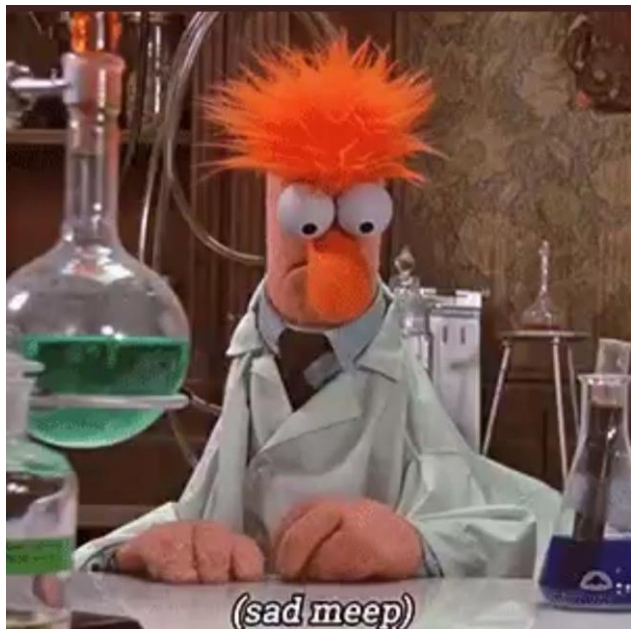


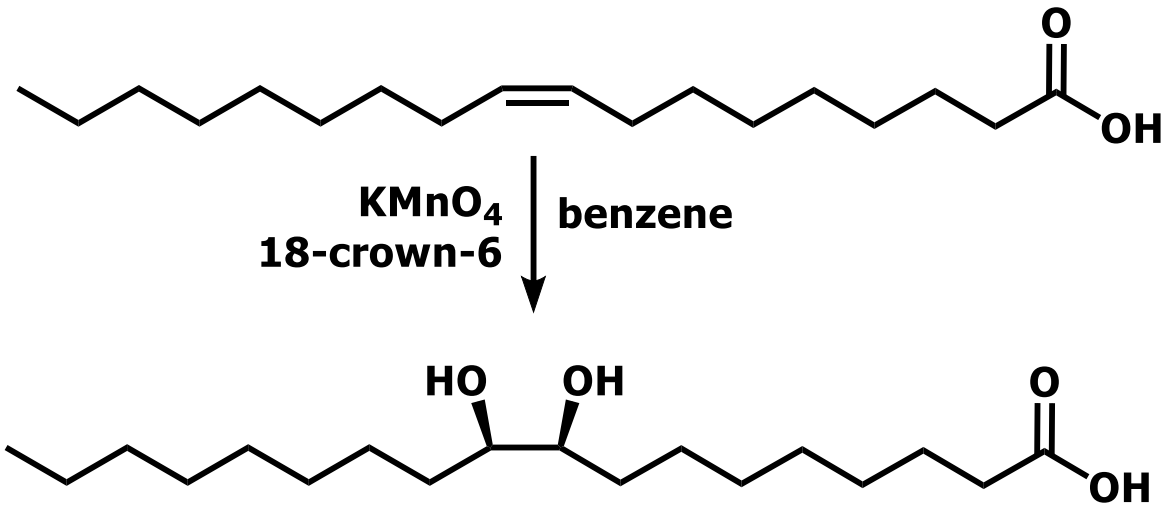
Special Solvents: Crown Ethers

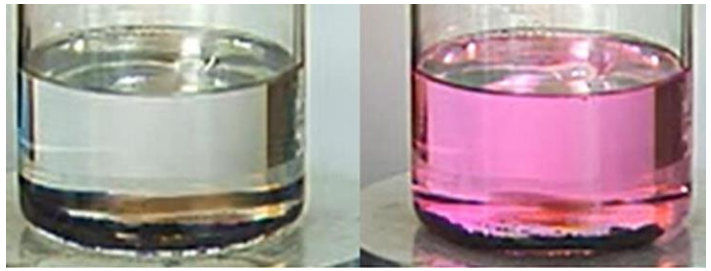
Improves solubility of ionic compounds in non-polar solvents.



poor reaction, no matter the solvent







without **18-crown-6**

with **18-crown-6**

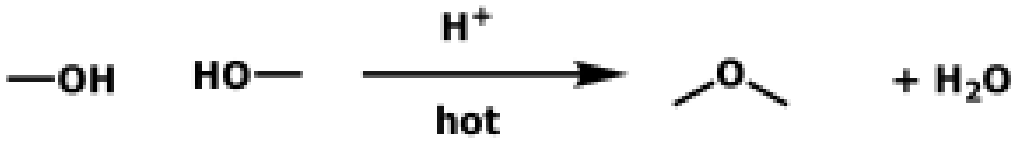
Ethers: Reactions

- Synthesis
  - Acid-Catalyzed Dehydration
  - Acid-Catalyzed Addition of Alcohol
  - Solvolysis of 3° Alkyl Halides
  - **Williamson Ether Synthesis**
- Cleavage
  - **Acid Cat. Cleavage** w. conc. HI OR HBr
  - **Lewis Acid Cat. Cleavage** w. BBr_3 OR TMSI

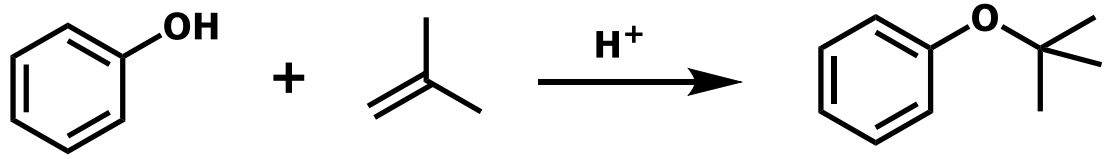
Williamson Ether Synthesis	
	**ATTACKING 2° or 3° ALKYL HALIDES**
	**ATTACKING Me or 1° ALKYL HALIDES**

Ether Synthesis: Common Methods

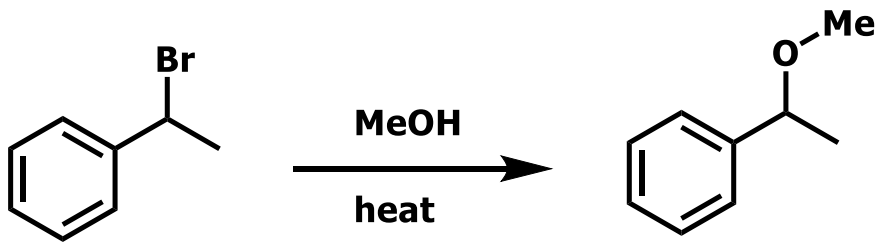
1 ACID-CATALYZED DEHYDRATION



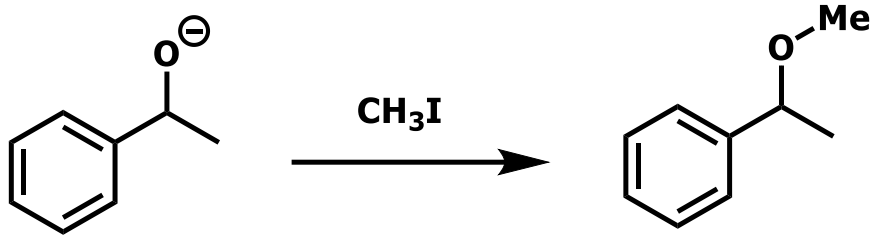
2 ACIDIC CAT. of ALCOHOL & ALKENE



3 SOLVOLYSIS of 3° RX w. ALCOHOLS

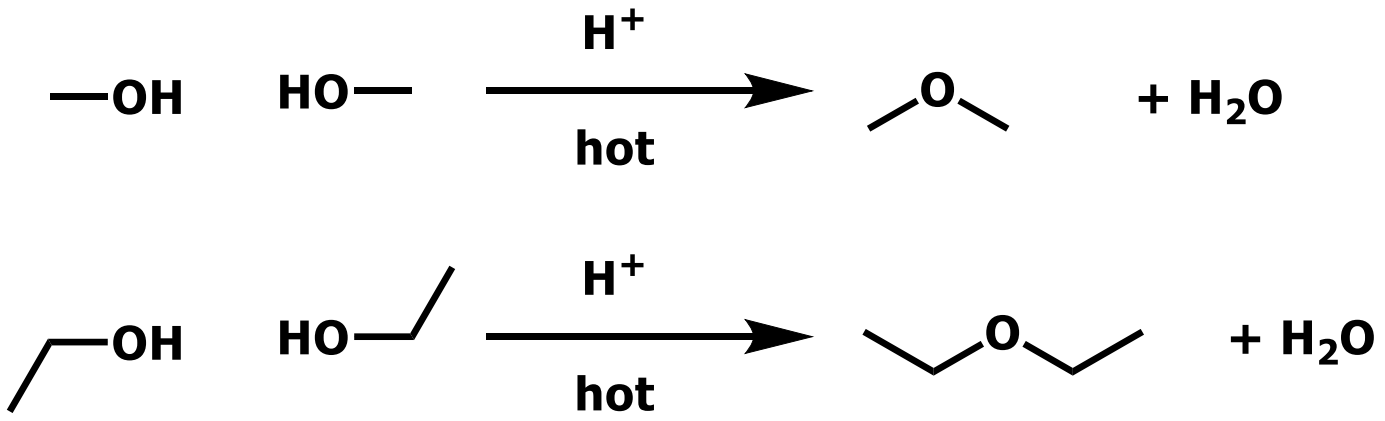


4 WILLIAMSON ETHER SYNTHESIS



There are other methods, learned in Orgo 1.

Ether Synthesis: Acid Catalyzed Dehydration



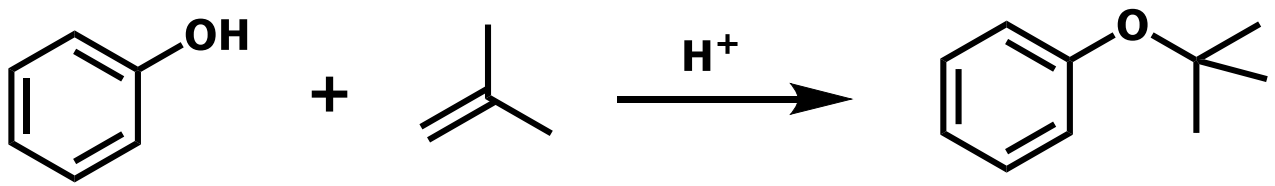
Useful for small unbranched alcohols, resulting in symmetrical ethers only.

t-BuOH does not work for this reaction – **WHY?**

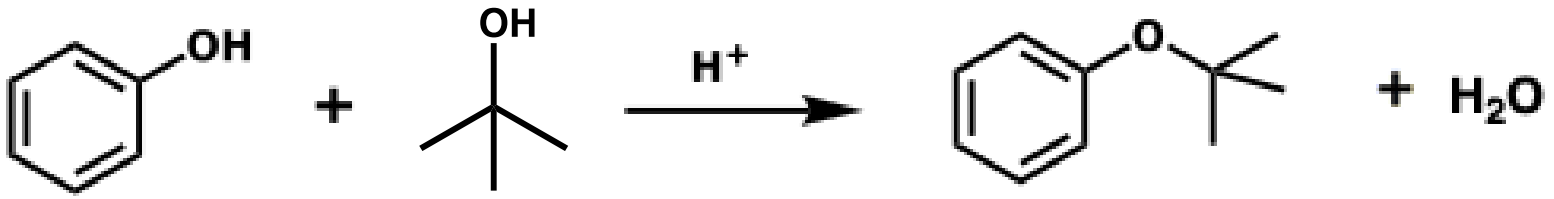
You should be able to draw a mechanism,

and no carbocations, please!

Ether Synthesis: Alcohol, Acid & Alkene



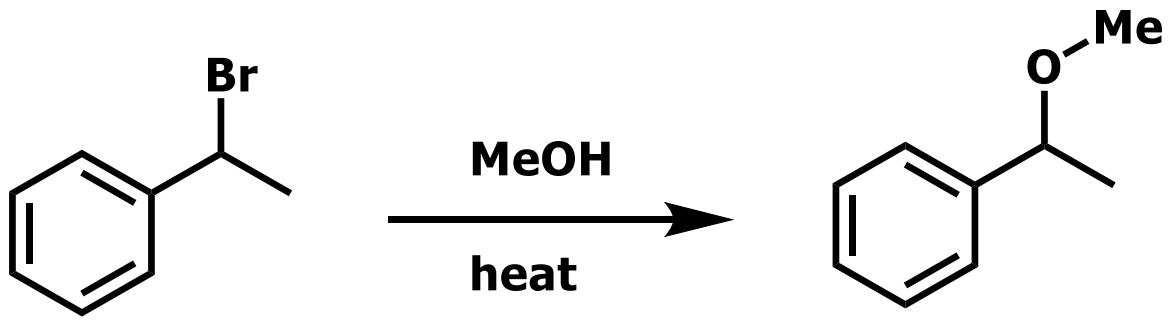
Also works with t-BuOH instead of isobutylene, but with isobutylene, no water generated. Done in a pressure flask.



Unusually challenging to make ethers of 3° ROH

You should be able to draw mechanisms for each (Hint: think carbocations!)

Ether Synthesis: Solvolysis of 2°/3° RX



Solvolysis (**S_N1**) works well with **3° substrates** and **<u>stabilized</u>* 2°/1° substrates**.

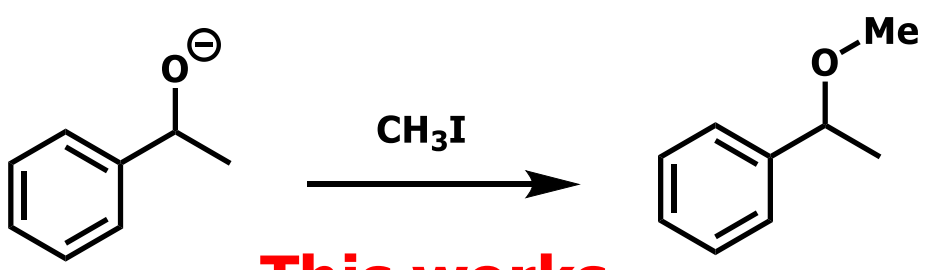
Note: This reaction can be promoted by $AgNO_3$ (**WHY?**)

Other nucleophiles are possible, if they behave as protic solvent, e.g. AcOH.

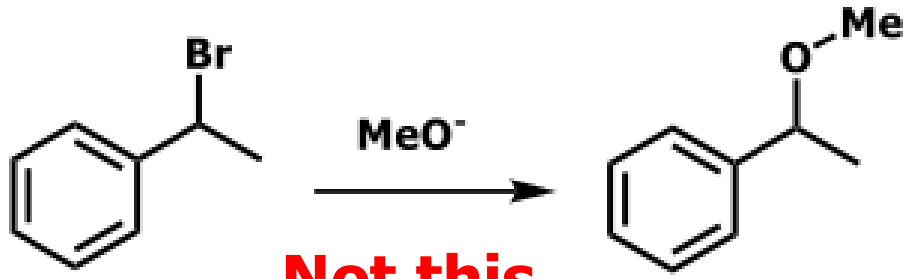
Note: E1 is always a side product, when possible.

*<u>stabilized</u> = benzylic, allylic, propargylic ($–CH_2–C{\equiv}CH$)

Ether Synthesis: Williamson Ether Synthesis



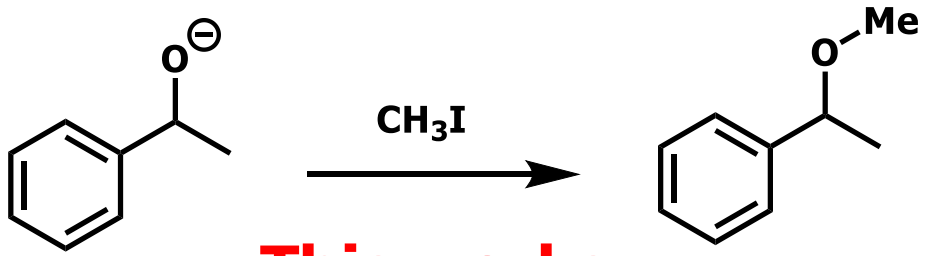
This works.



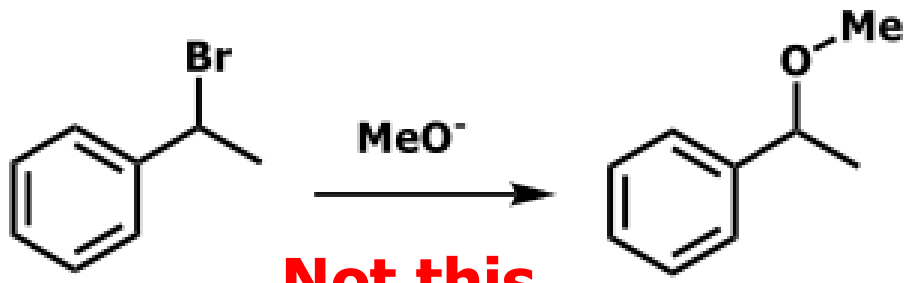
Not this.

WHY NOT?

Ether Synthesis: Williamson Ether Synthesis

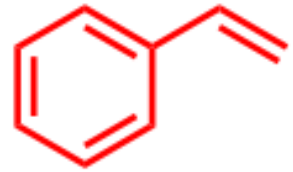


This works.



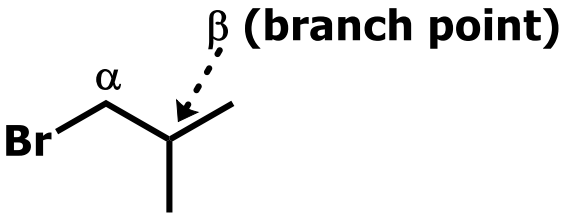
Not this.

MeO^- is a base too and **prefers E2** for 2°/3°.

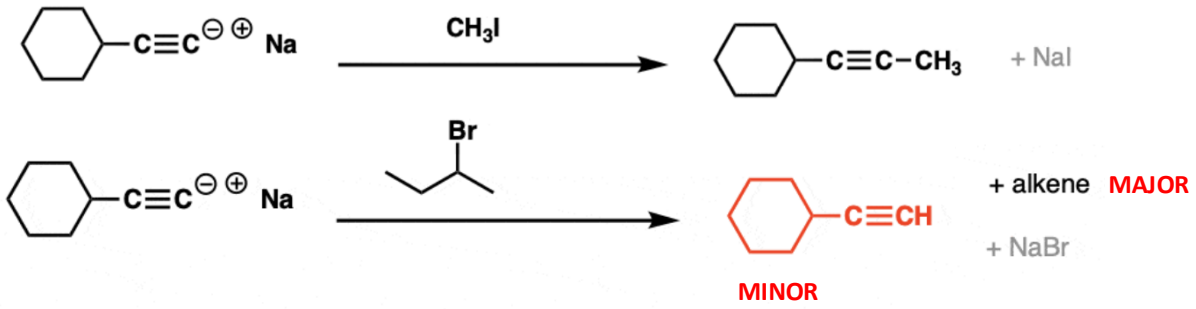


<u>What We Know</u>:

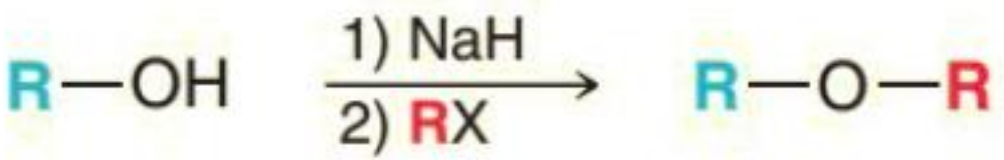
- only **1°** alkyl halides prefer **S_N2**
- only **1°/2°** alkoxides are good $^-$:Nuc
- lower yield if there is β-branching
  - e.g., substrate is <u>isobutyl bromide</u>



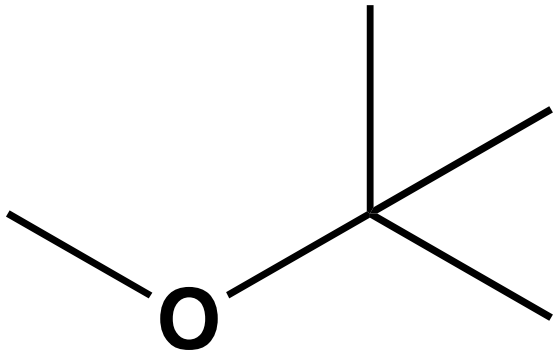
Similar restrictions exist with all strongly basic nucleophiles w. **Me/1° RX**, e.g. RC≡CH (**pKa = 25**)



Ether Synthesis: Williamson Ether Mechanism



Williamson Ether Syntheses must be strategized like any other **S_N2 reaction**:

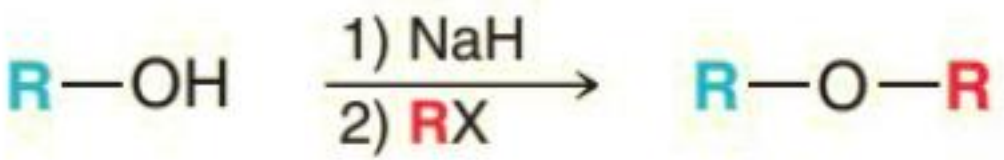


What are the possible strategies for synthesis?

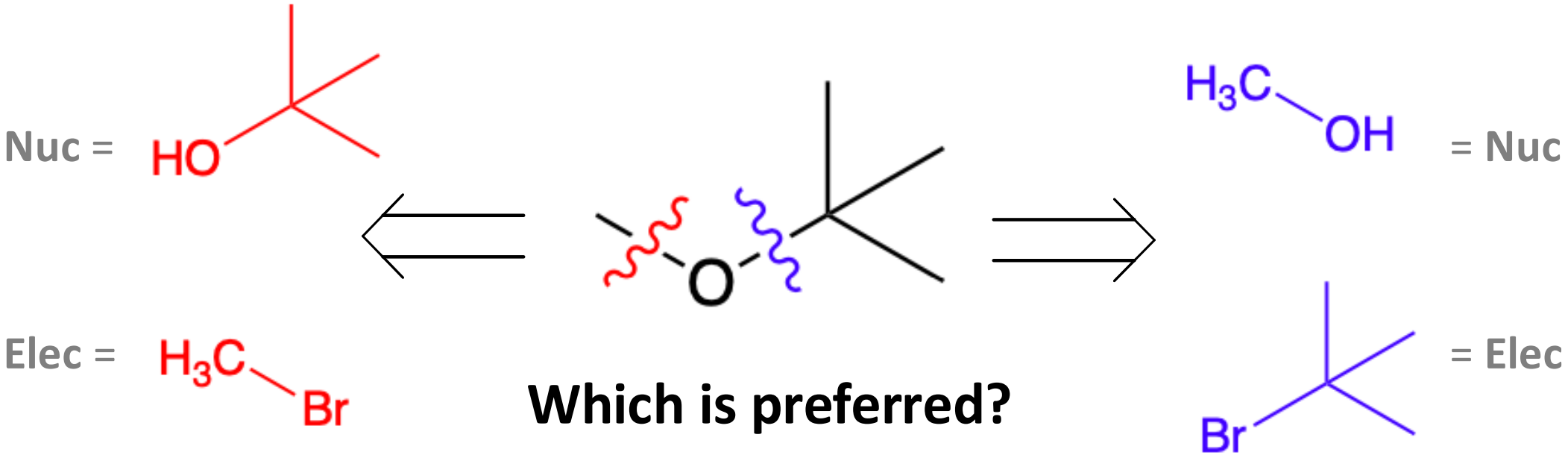
1 R group must come from the alkyl halide

1 R group come from the alcohol.

Ether Synthesis: Williamson Ether Mechanism



Williamson Ether Syntheses must be strategized like any other **S_N2 reaction**:



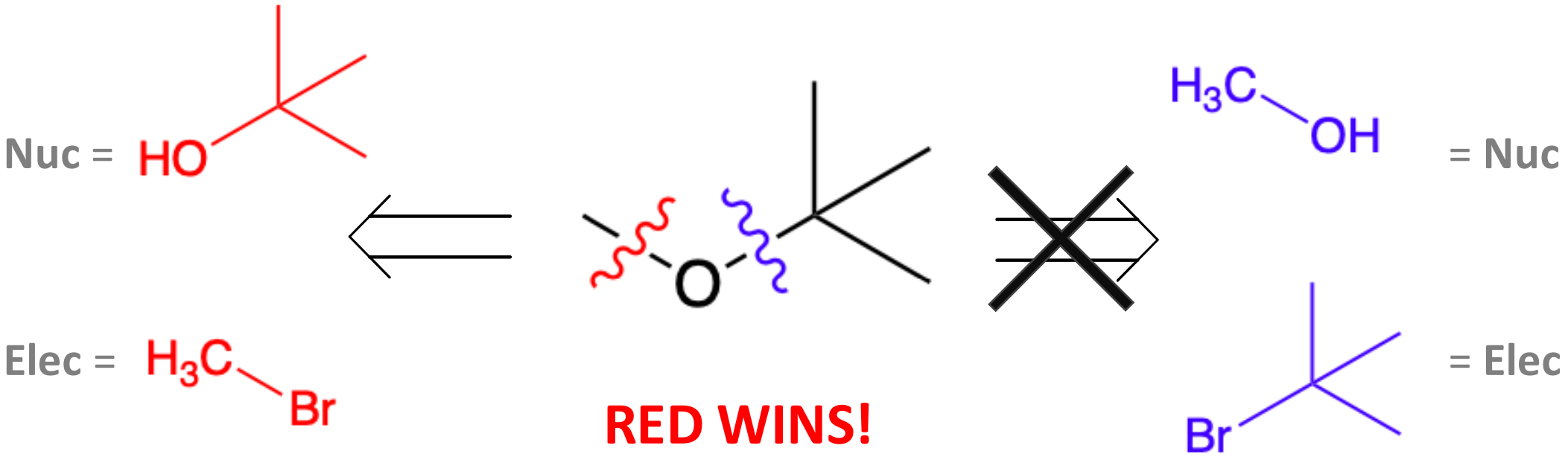
Which is preferred?

Ether Synthesis: Williamson Ether Mechanism

Williamson Ether Syntheses must be strategized like any other **S_N2 reaction**:

Red pathway is more preferred: t-BuO:$^-$ attacks Me alkyl halide via S_N2.

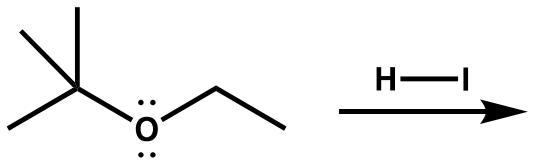
Blue pathway is slower: MeO:$^-$ attacks 3° alkyl halide via E2.



Ether Cleavage: Strong Acids

1





Ethers are composed of C—O bonds that are stable and difficult to break without concentrated strong acids.

Order of reactivity: **HI > HBr > HCl**

WHY THIS ORDER?

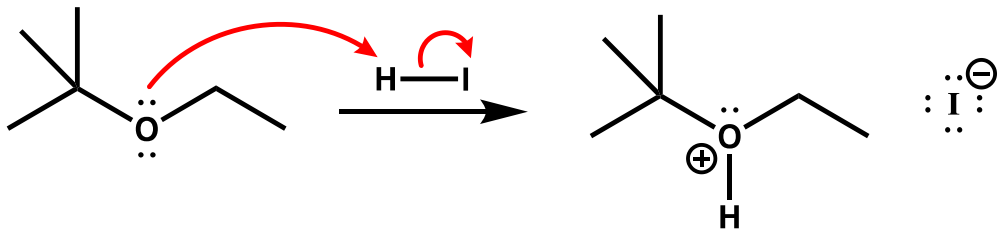
These cleavages occur via **S_N1/S_N2**.

S_N2 reactions occur faster than S_N1.

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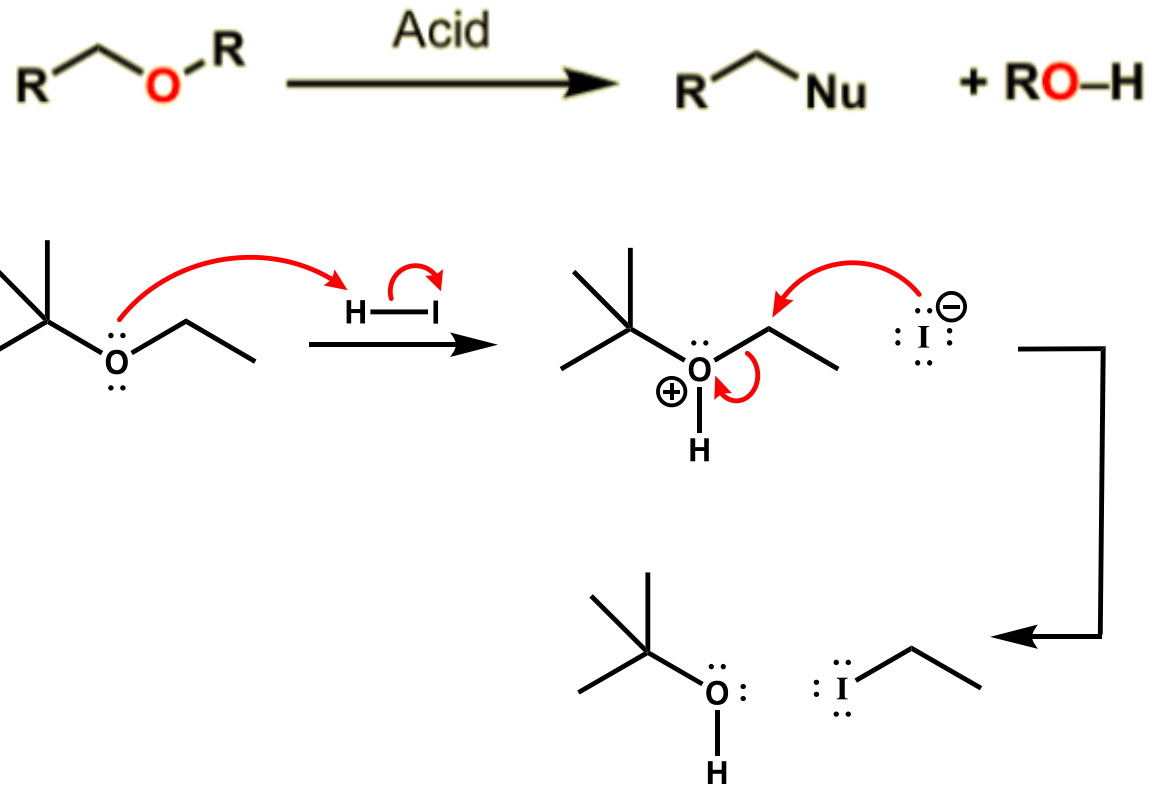
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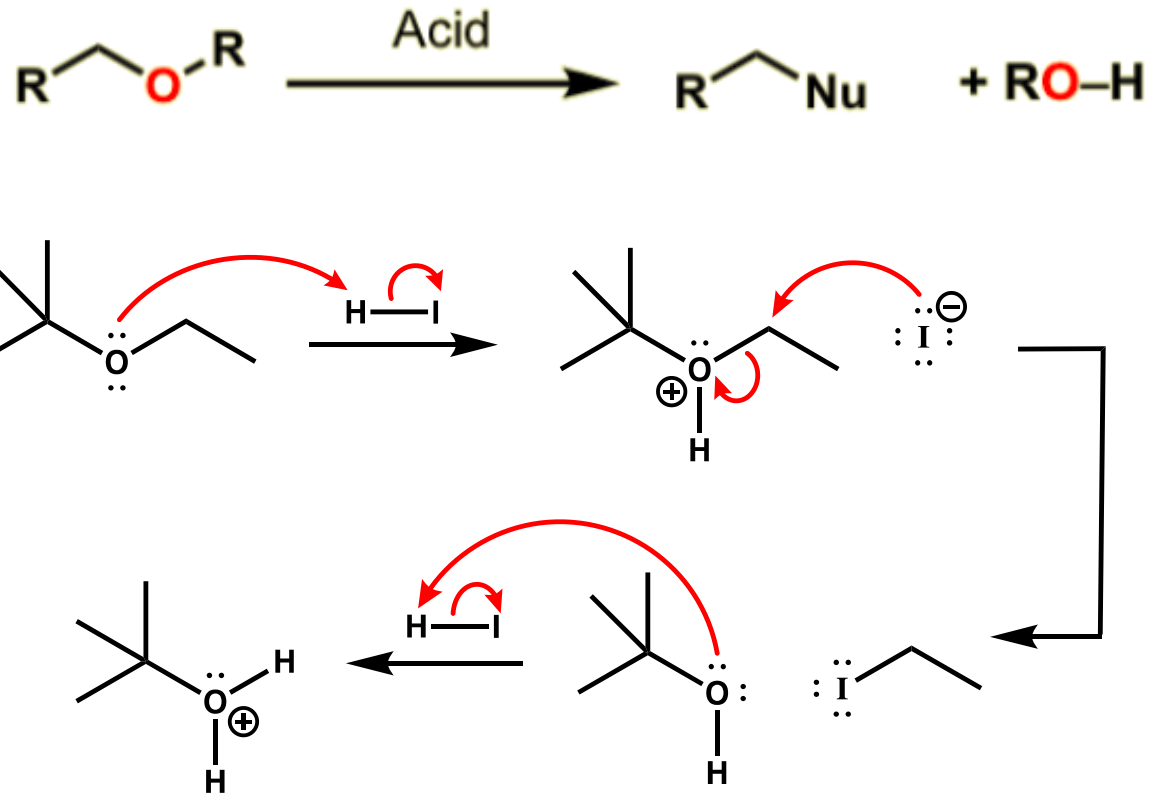
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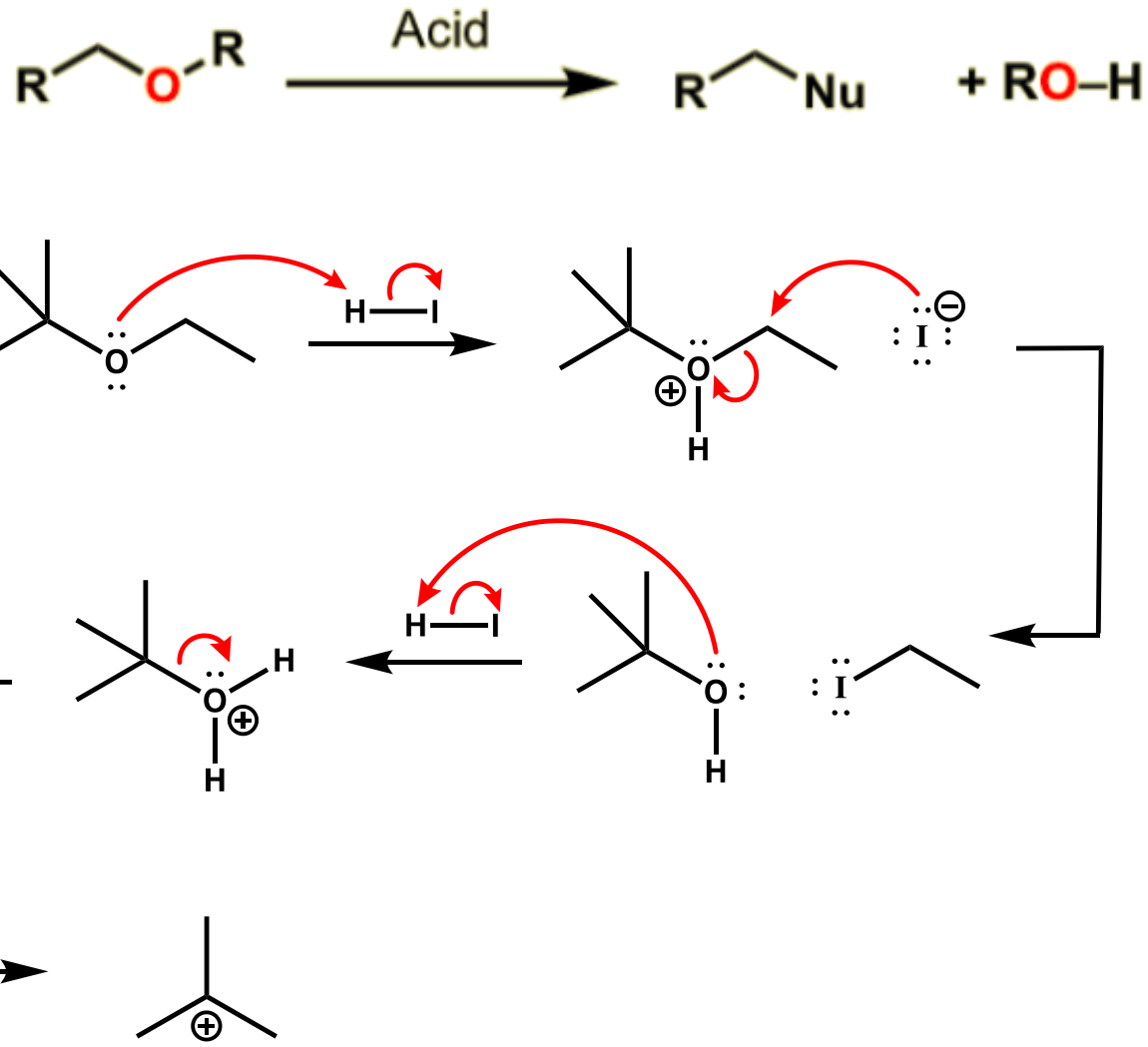
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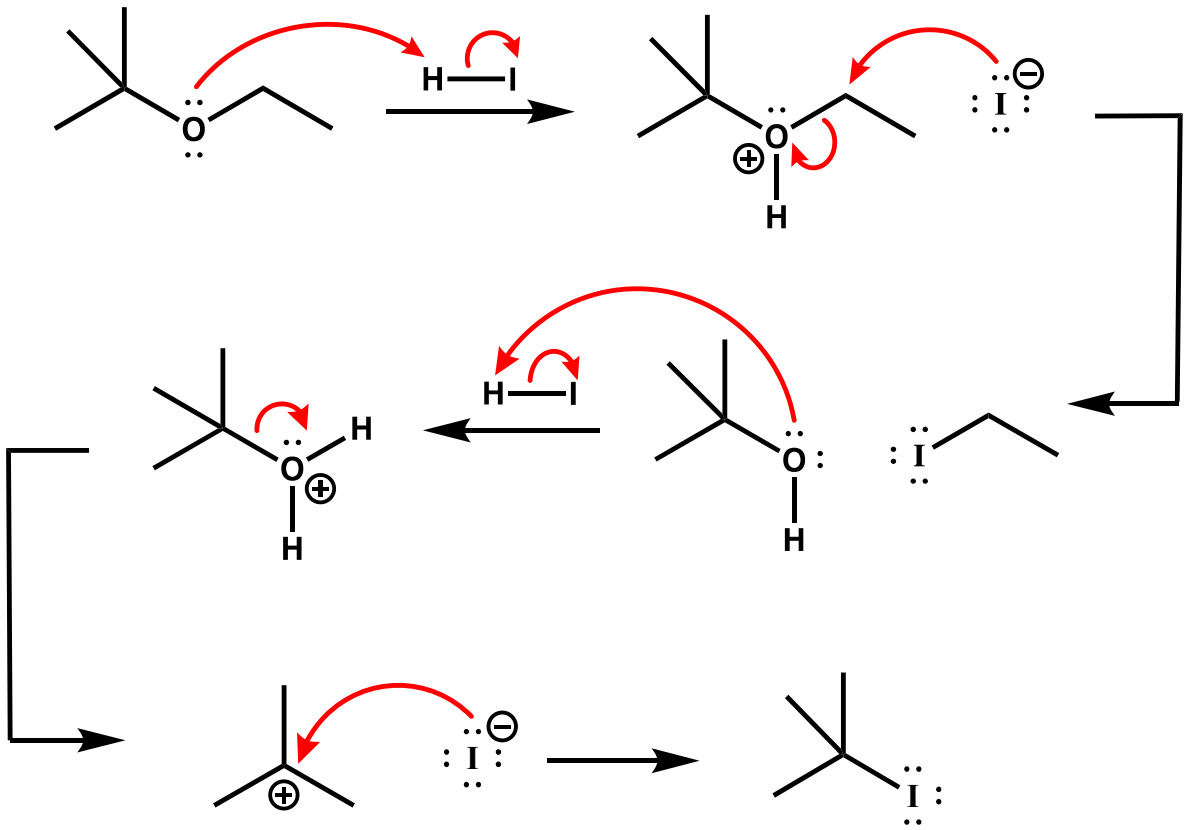
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Ether Cleavage: Strong Acids

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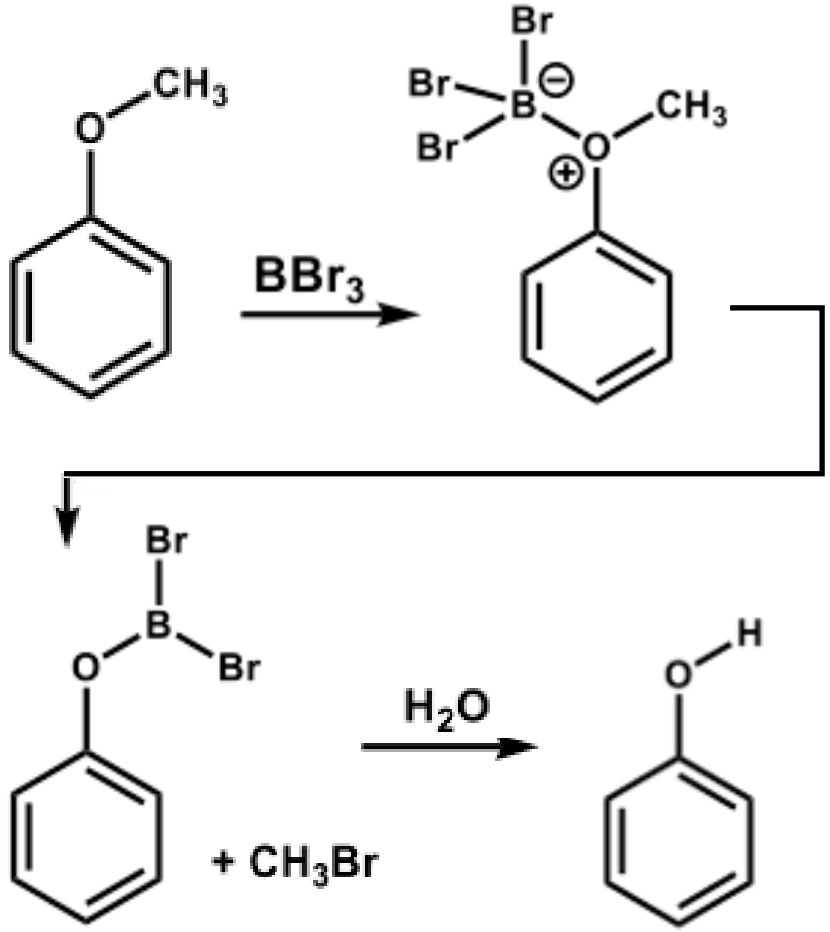
WHY THIS ORDER?

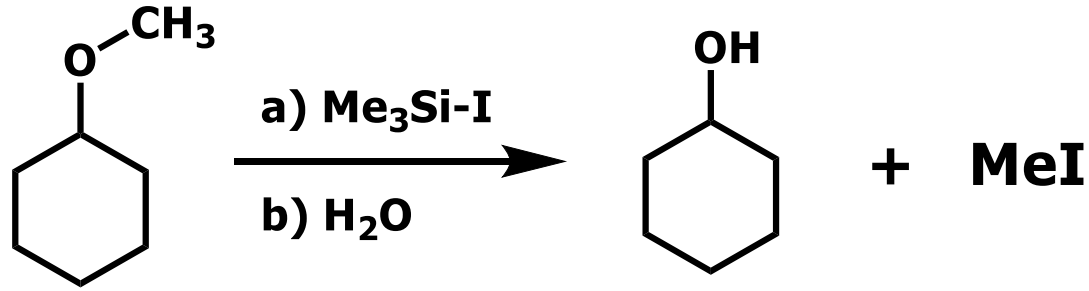
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Ether Cleavage: Strong *<u>Lewis</u>* Acids

2 **Lewis Acid Catalysts: BBr_3** OR **TMS-I** – both followed by H_2O hydrolysis





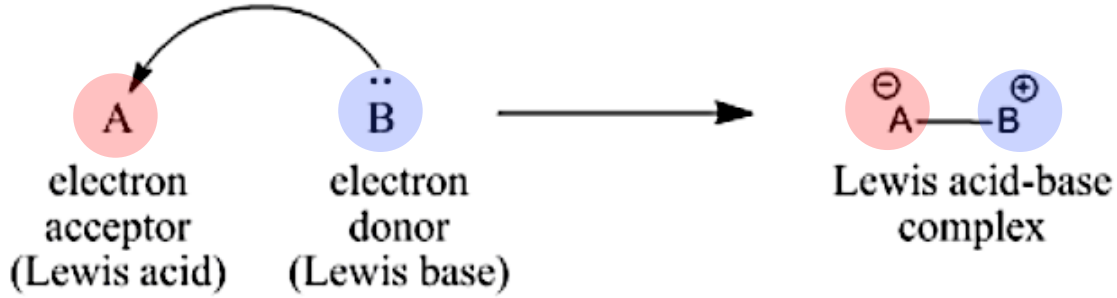
Silicon (Row 3) is bigger than **Carbon** (Row 2), so Si can be pentavalent (but, R_3Si^+ cations are unknown).

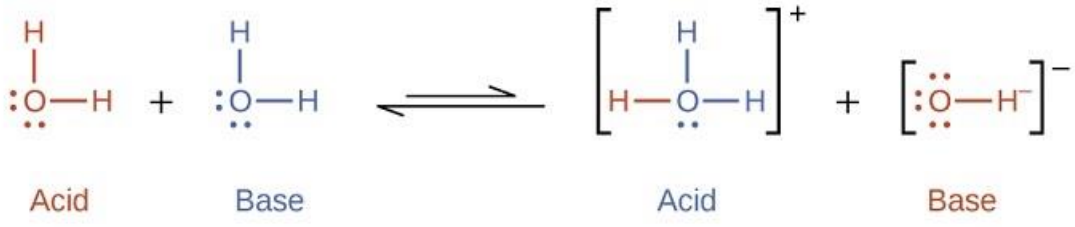
We won't learn Si mechanisms

But you don't remember what a Lewis Acid is…?

NEXT SLIDE!

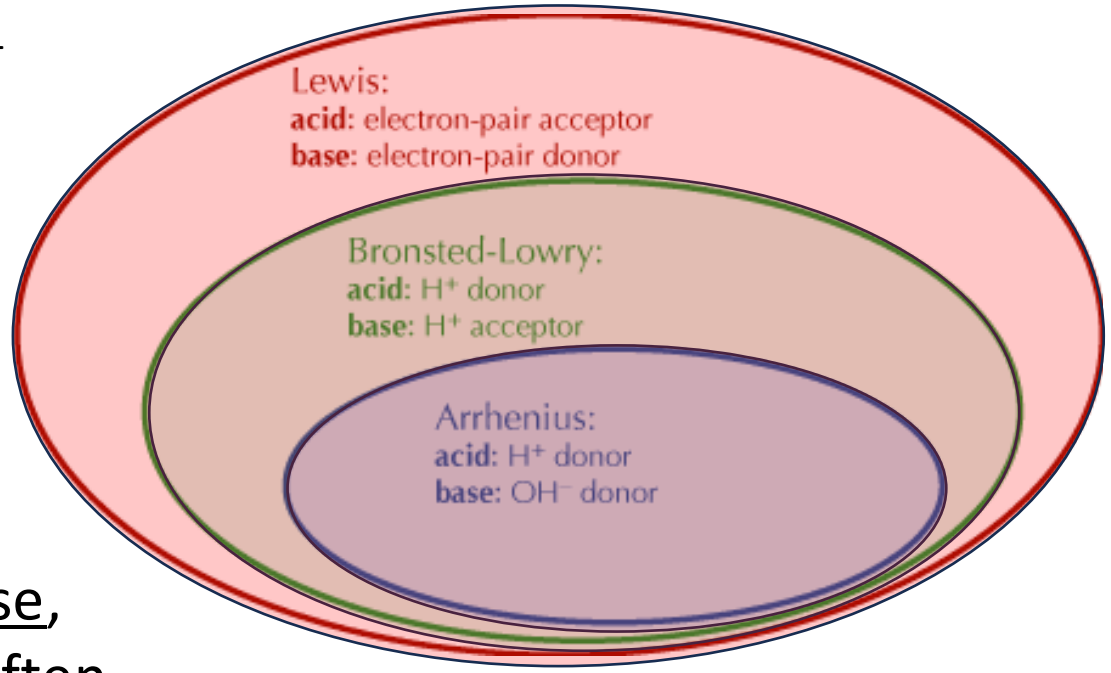
Mini-Break: **Lewis Acid** & **Lewis Bases**





Lewis acids <u>accept</u> e^- H_2O, H_3O^+, H_2SO_4, $^+NH_4$

Lewis bases <u>donate</u> e^- H_2O, $^-$:OH, $^-$:Br, :NH_3

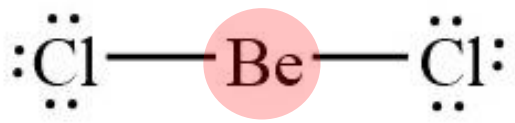


<u>Lewis</u> definitions are the **<u>broadest</u>**, focusing on transfer of **<u>electrons</u>** (not H^+).

Therefore, **<u>all</u>** <u>Acids</u> and **<u>all</u>** <u>Bases</u> can be categorized as either a <u>Lewis Acid</u> or a <u>Lewis Base</u>, plus a few reagents that we haven't used very often...

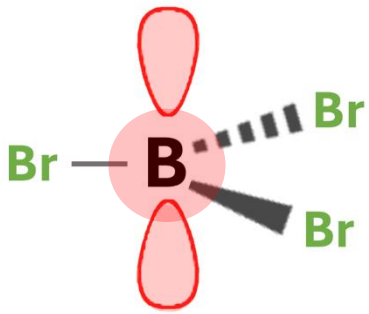
Mini-Break: **Lewis Acids**

There are some compounds that can only be categorized as a **Lewis acid** (i.e., it can **accept electrons**) while not being a Bronsted acid (i.e., it has no H^+ to donate).

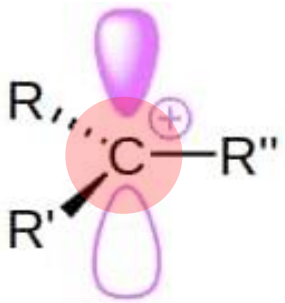


Beryllium Chloride
(BCl_2)

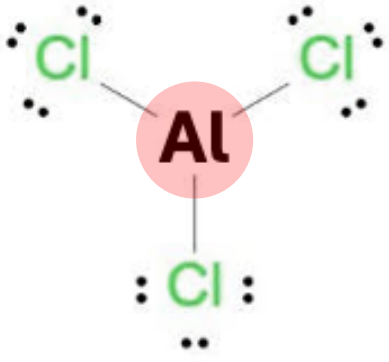
2nd Row Elements with **Empty *p* Orbitals**



Boron Tribromide
(BBr_3)

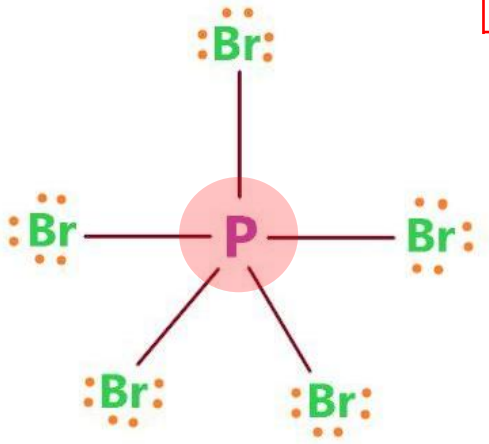


3° Carbocation
(R_3C^+)

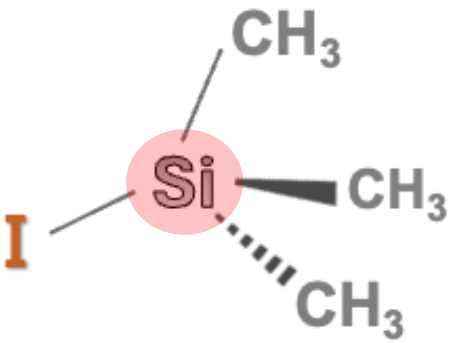


Aluminum Trichloride
($AlCl_3$)

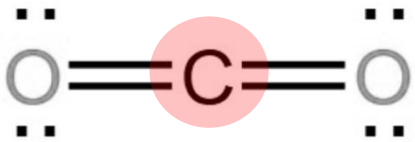
3rd Row Elements with **Expandable "Octets"**



Phosphorous Pentabromide
(PBr_5)



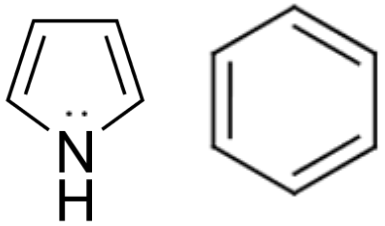
Trimethylsilyl iodide
(TMS-I)



Carbon Dioxide
or **2nd Row w. Polar π Bond**

Mini-Break: **Lewis Bases**

There are also compounds that can only be categorized as a **Lewis bases** (i.e., it can **donate electrons**) while not being a Bronsted base (i.e., bad at accepting H^+), which can sometimes (and ironically) make them **bad "bases"** and **better nucleophiles**.

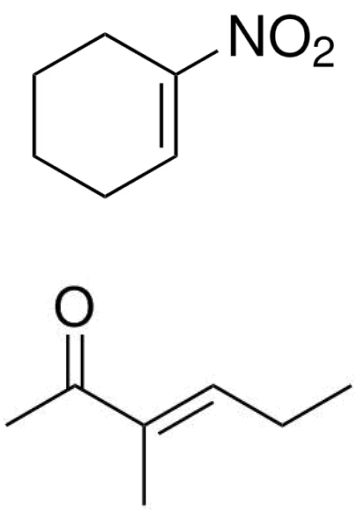


AROMATIC π Systems

that

CANNOT BREAK 4n+2 RULE

(equal sharing of pi *e*– is caring)

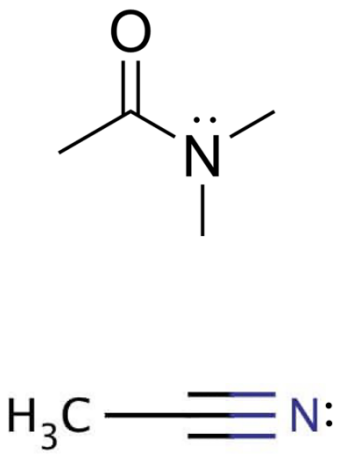


***e*⁻ POOR CONJ. Systems**

due to

EWGs w. STRONG RESONANCE

(can't handle the extra + charge)

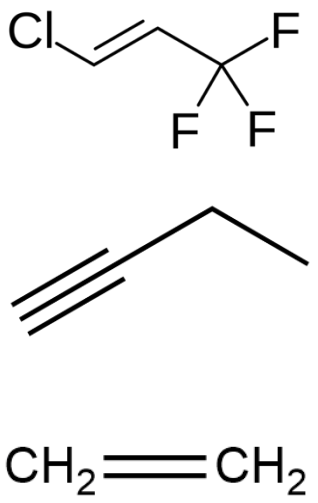


TIGHTLY HELD LPs

due to

EWGs or *sp* ORBITALS

(happy w. what they're doing)

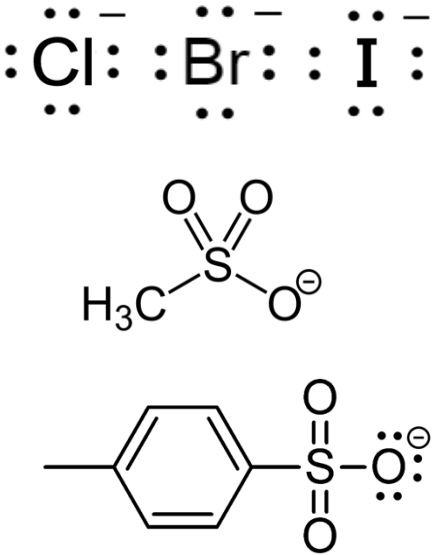


Resultant UNSTABLE C+

due to

STRONG EWG or NO R GROUPS

(new carbocation is clinically unstable)



STRONG ACID Conj. BASE

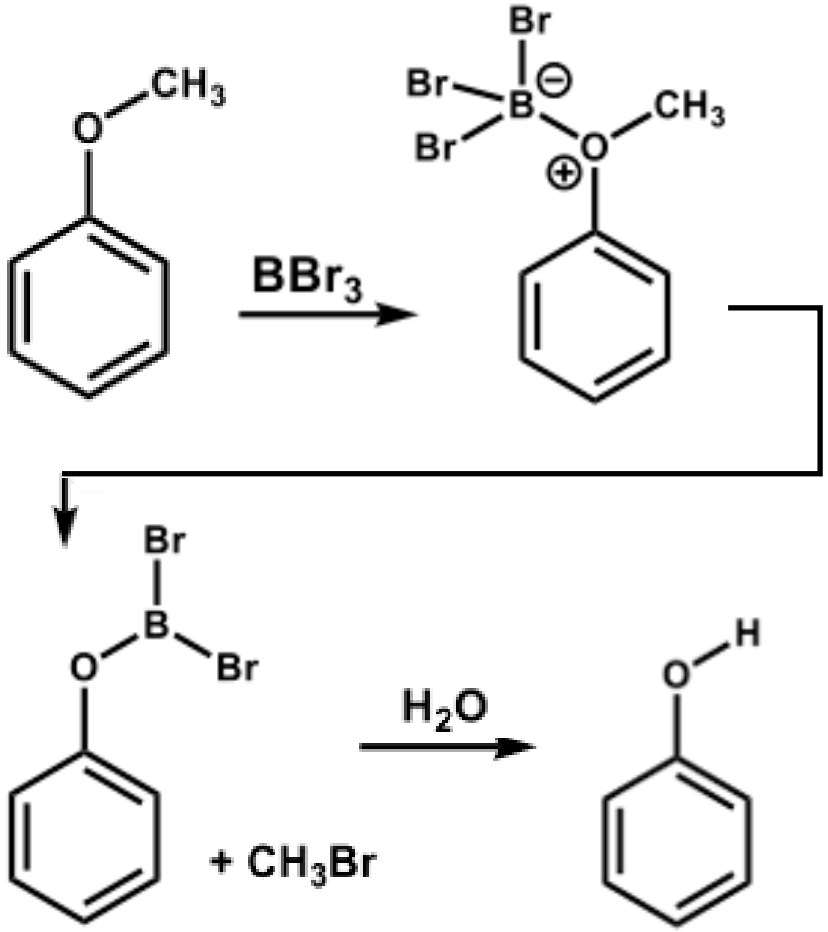
that is

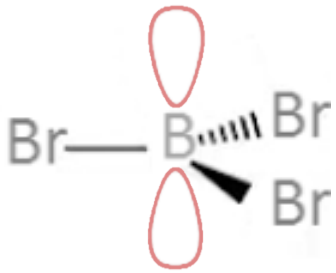
HAPPIER WITHOUT the H^+

(dude, they *just* got rid of it)

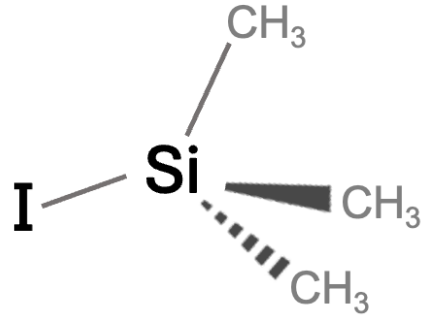
Return To → Ether Cleavage: Strong *Lewis* Acids

2 **Lewis Acid Catalysts: BBr_3** OR **TMS-I** – both followed by H_2O hydrolysis

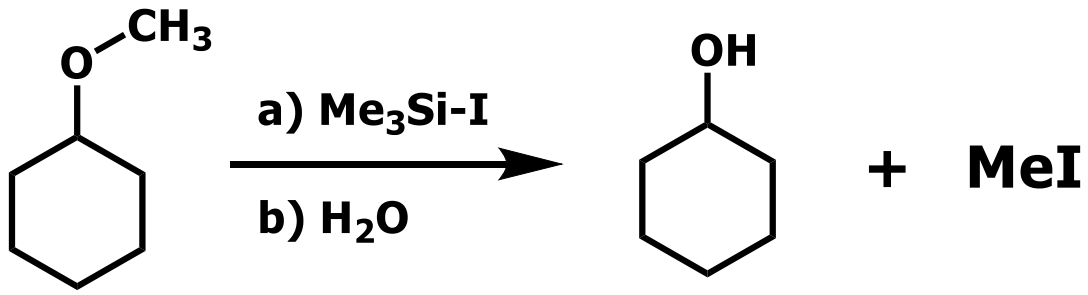




Boron Tribromide



Trimethylsilyl iodide

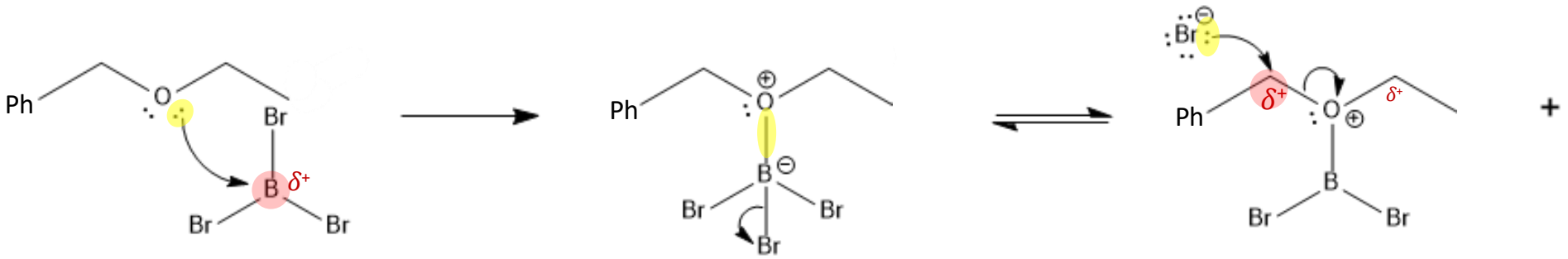


Silicon (Row 3) is bigger than **Carbon**, so it can be pentavalent.

We won't learn Si mechanisms

Ether Cleavage: Strong *Lewis* Acid Mechanism

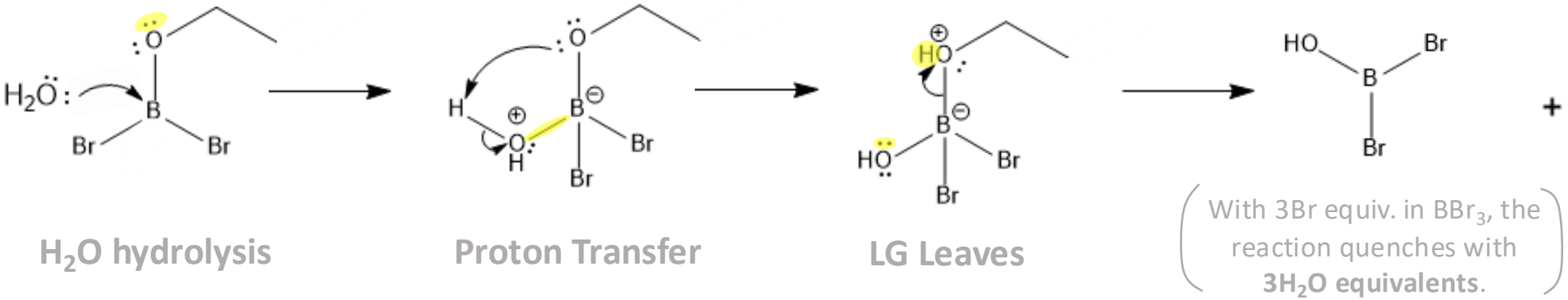
2 **Lewis Acid Catalysts: BBr_3** — followed by H_2O hydrolysis



Weak Nuc attacks Boron's *p orbital* (induction = **big δ+**)

Oxygen is now **Oxidized** (oxygen with + formal charge)

⁻:Nuc attacks larger δ+ due to electronic effect.



H_2O hydrolysis

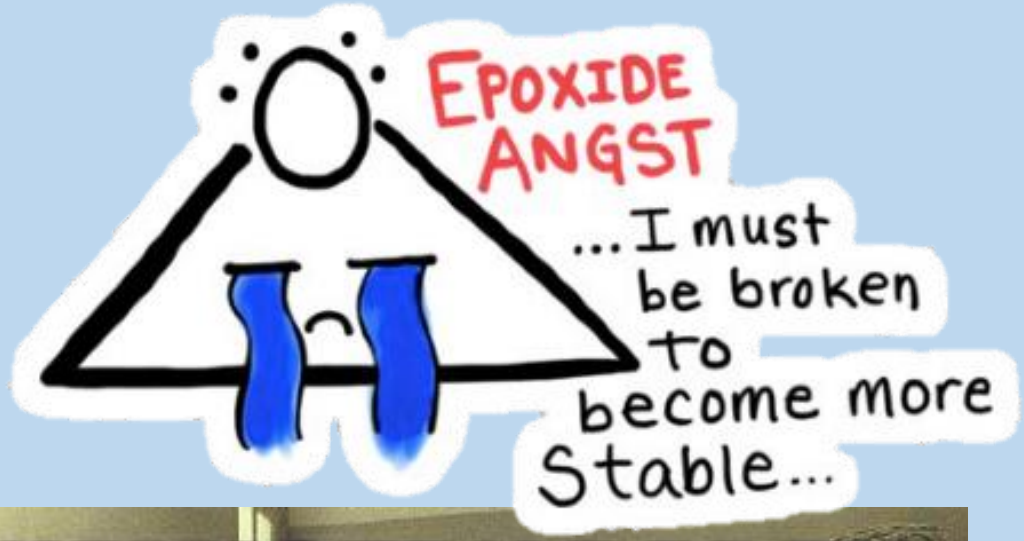
Proton Transfer

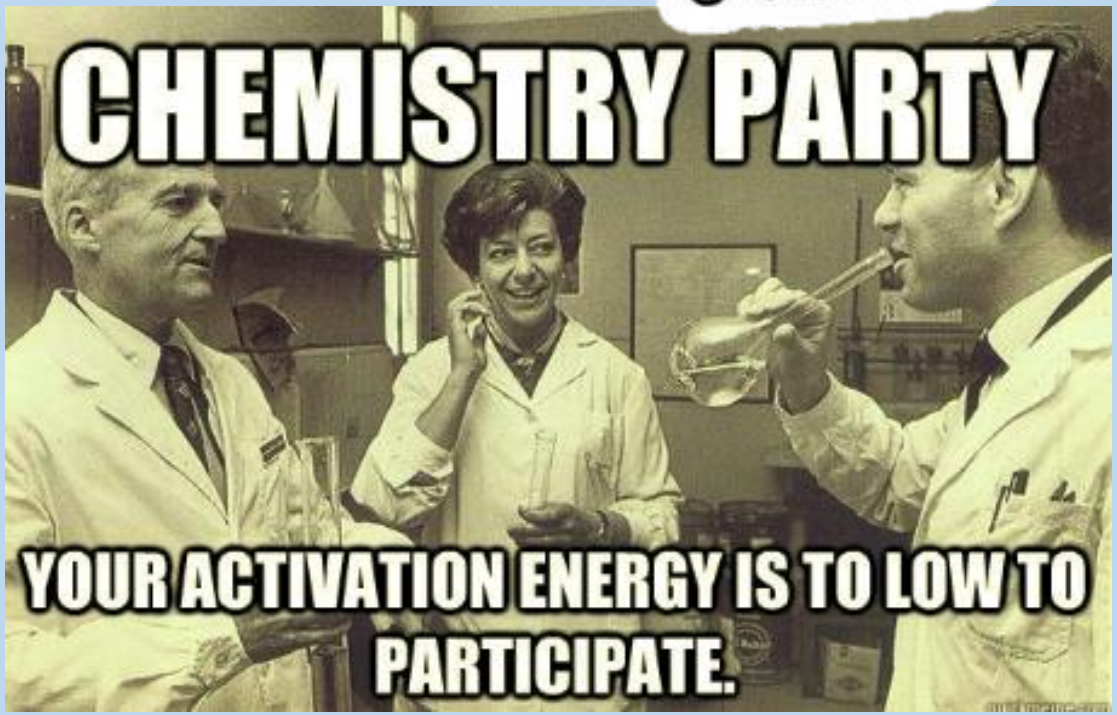
LG Leaves

With 3Br equiv. in BBr_3, the reaction quenches with **$3H_2O$ equivalents**.

Epoxides:

- Nomenclature
- Chemical Properties: BP
- **Synthesis**
  - Via Peracids
  - Via Halohydrins
  - Sharpless
- **Epoxide Opening**
  - Acidic
  - Basic





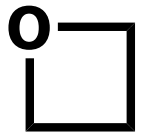
Epoxides: Reactive Ethers

An **epoxide** (**oxirane**) is a 3-member ring ether.



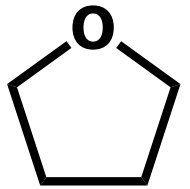
oxirane

very strained
most reactive



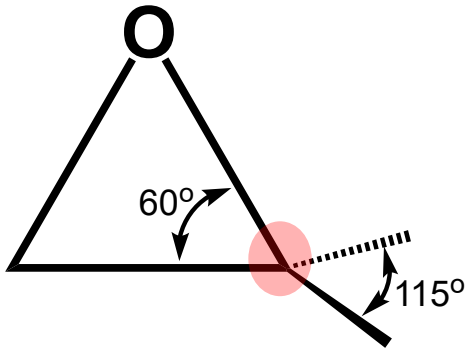
oxetane

strained
more reactive



tetrahydrofuran

low strain
normal reactivity



Angle strain results in **atypically weak C–O bonds.**

- **More accessible than regular sp^3 carbon**
- **C-O bond in epoxide much weaker than ether C-O bond**

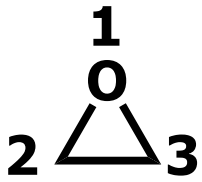
Epoxides: Nomenclature

Three different methods for naming:

(1) as **oxirane** derivative ("**oxiranyl**" as substituent) = IUPAC

(2) as "**epoxy**" substituent (with <u>divalent</u> numbering)

(3) as **oxides** of the corresponding alkene

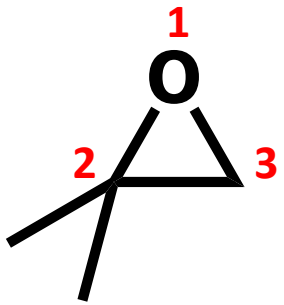


common heterocyclic numbering

2,2-dimethyl**oxirane**

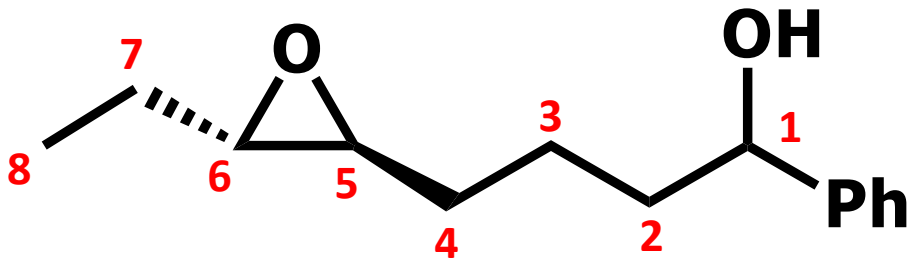
1,2-epoxy-2-methylpropane

isobutene **oxide**



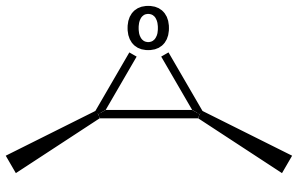
rac-4-((2S,3S)-3-ethyl**oxiran-2-yl**)-1-phenylbutan-1-ol

trans-5,6-**epoxy**-1-phenyl-1-octanol

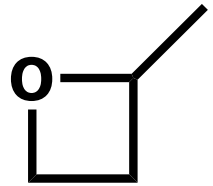


Epoxides: Properties

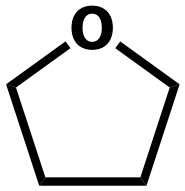
Larger dipoles result in **higher boiling points**.



BP 60°C



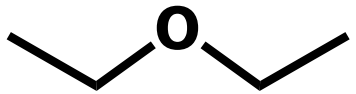
BP 60°C



1.63 D

BP 65°C

miscible



1.15 D

BP 33°C

6.9 g/100 g H_2O

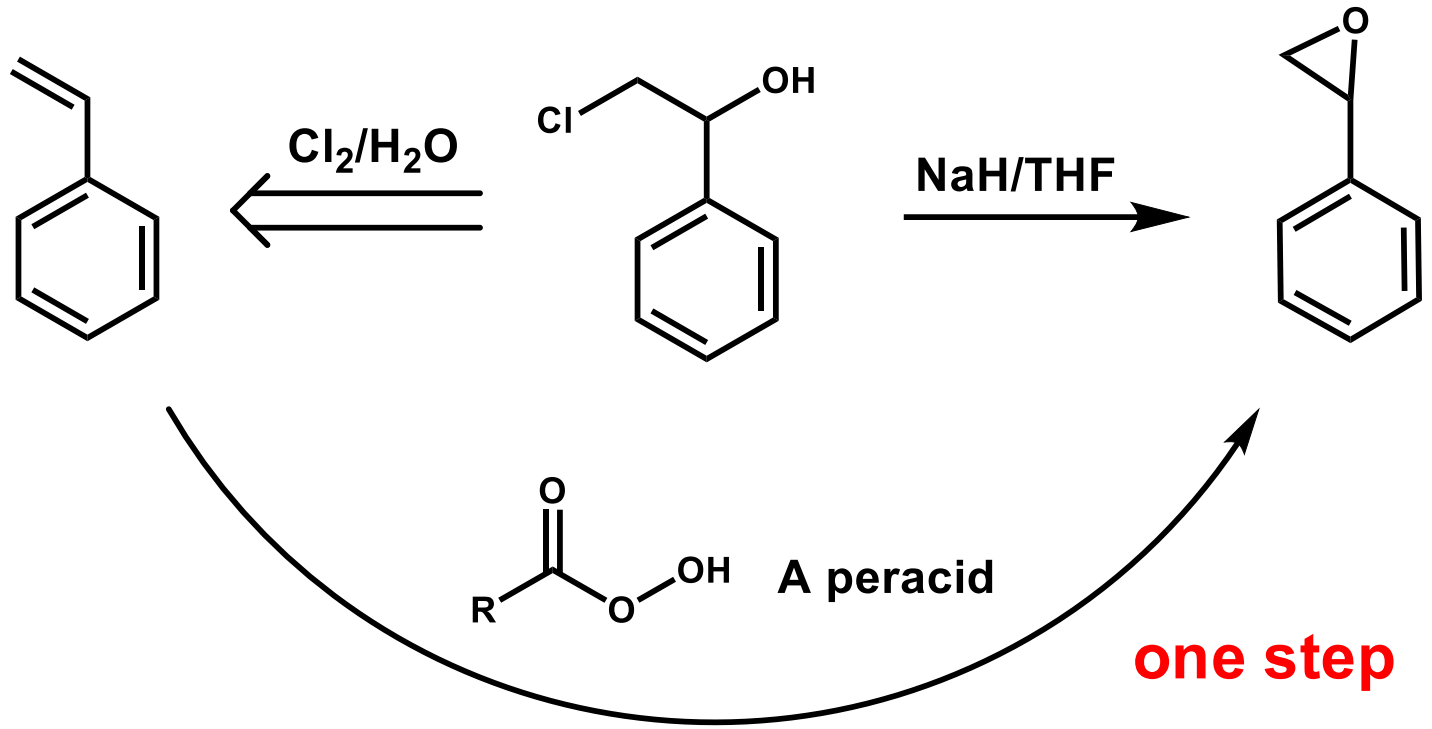
The C–O dipoles aren't that different,

but they are more exposed.

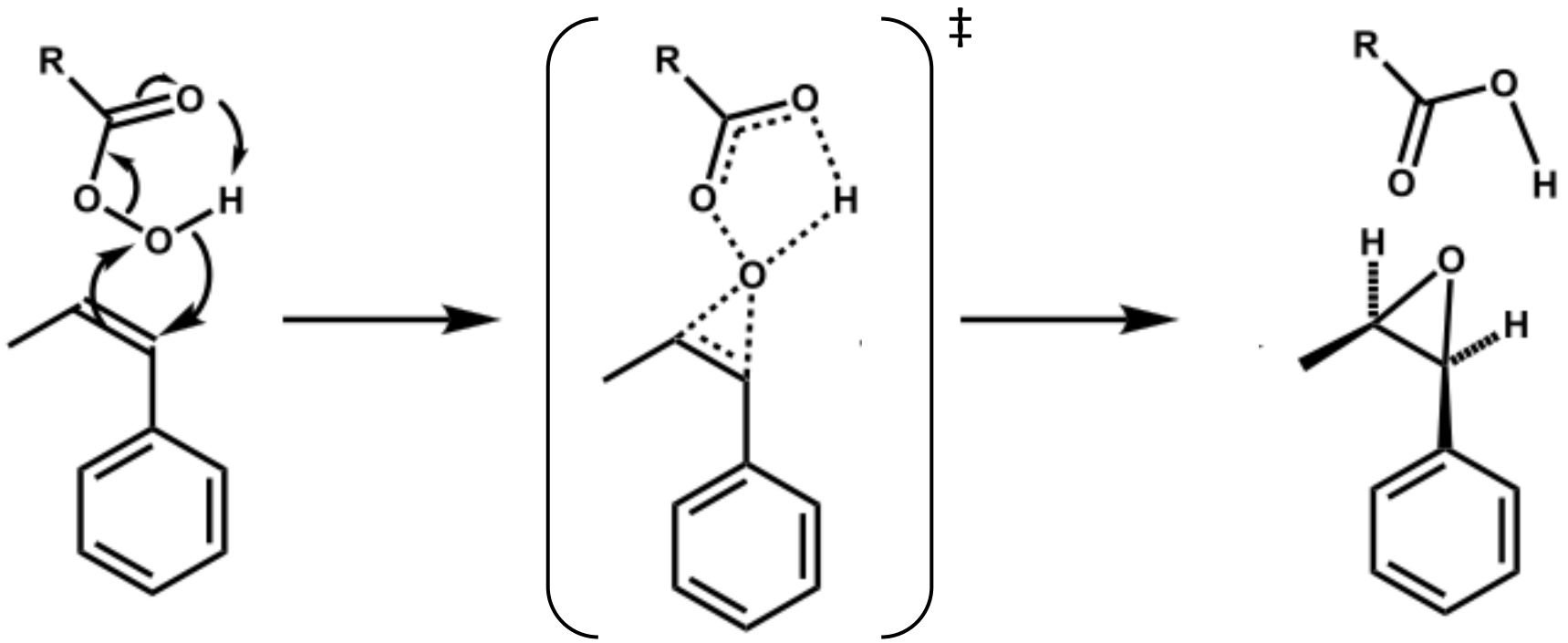
Epoxides: Synthesis

Olefins are often converted to an epoxide by:

1. **Halohydrin formation then treatment with base**
2. **Reaction with a peracid**



Epoxides: Peracid Mechanism



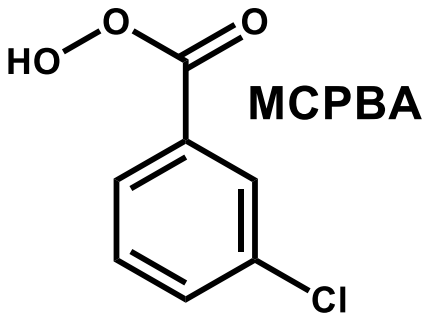
Reaction is **stereospecific**

<u>Common Peracids</u>

peracetic acid (CH_3CO_3H)

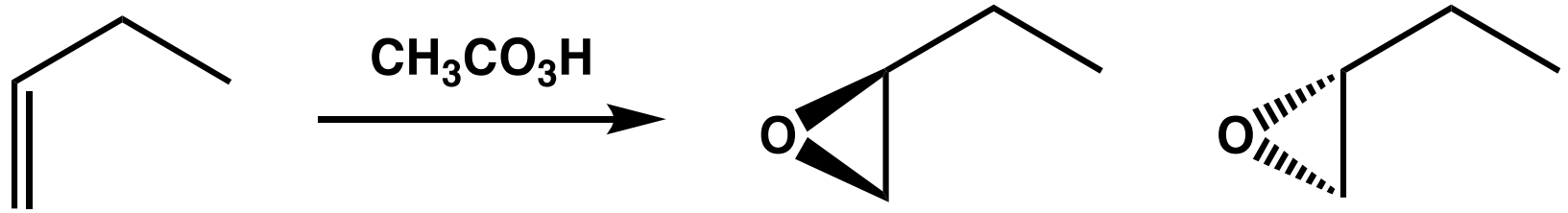
m-chloroperbenzoic acid (mCPBA)

monoperphthalic acid

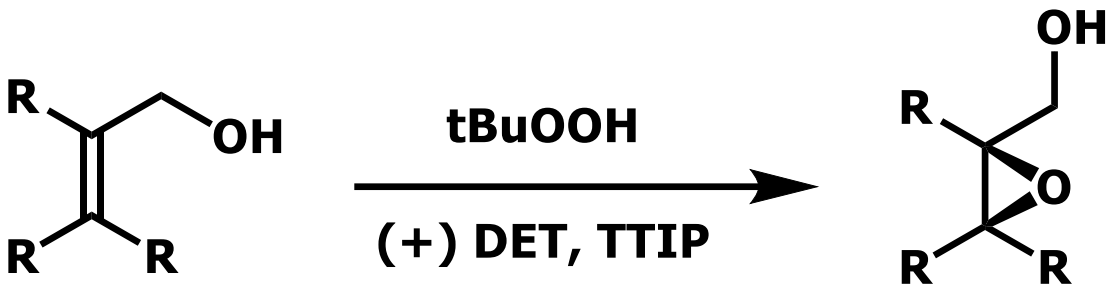


Asymmetric Epoxides: Sharpless

Typically forming epoxides from alkenes results in a mixture of enantiomers.



Sharpless Epoxidation forms a specific enantiomer but requires an **allylic OH group**.



!!!

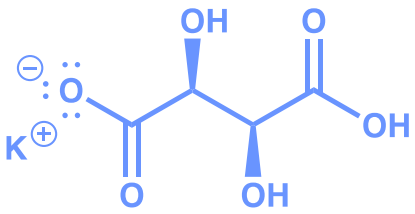
Stereospecific

very high *ee* of products

BIG NOBEL-PRIZE-WINNING DEAL

Asymmetric Epoxides: Sharpless Reagents

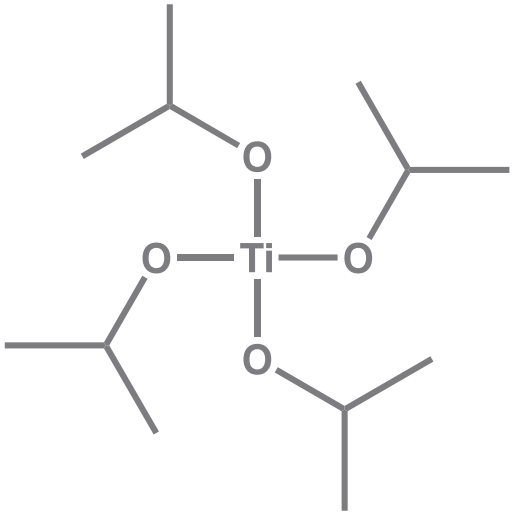




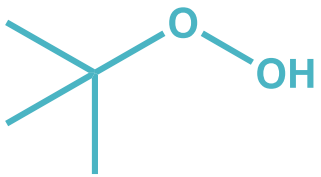
tartrate crystals on a wine cork

$TiCl_4$ is a common Lewis acid.

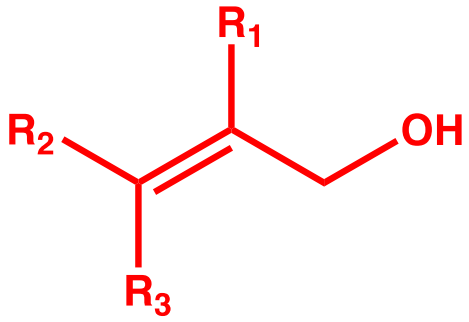
$Ti(O\text{-}iPr)_4$ (TTIP) is milder.



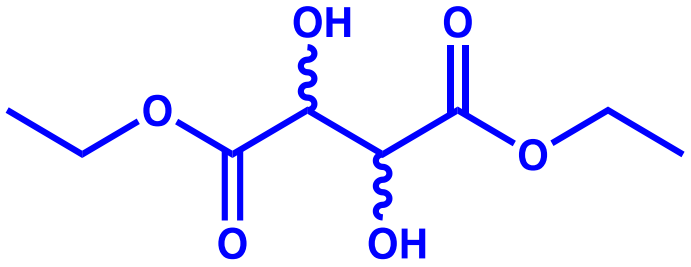
tBu-OOH (TBHP) is the oxidizing agent.



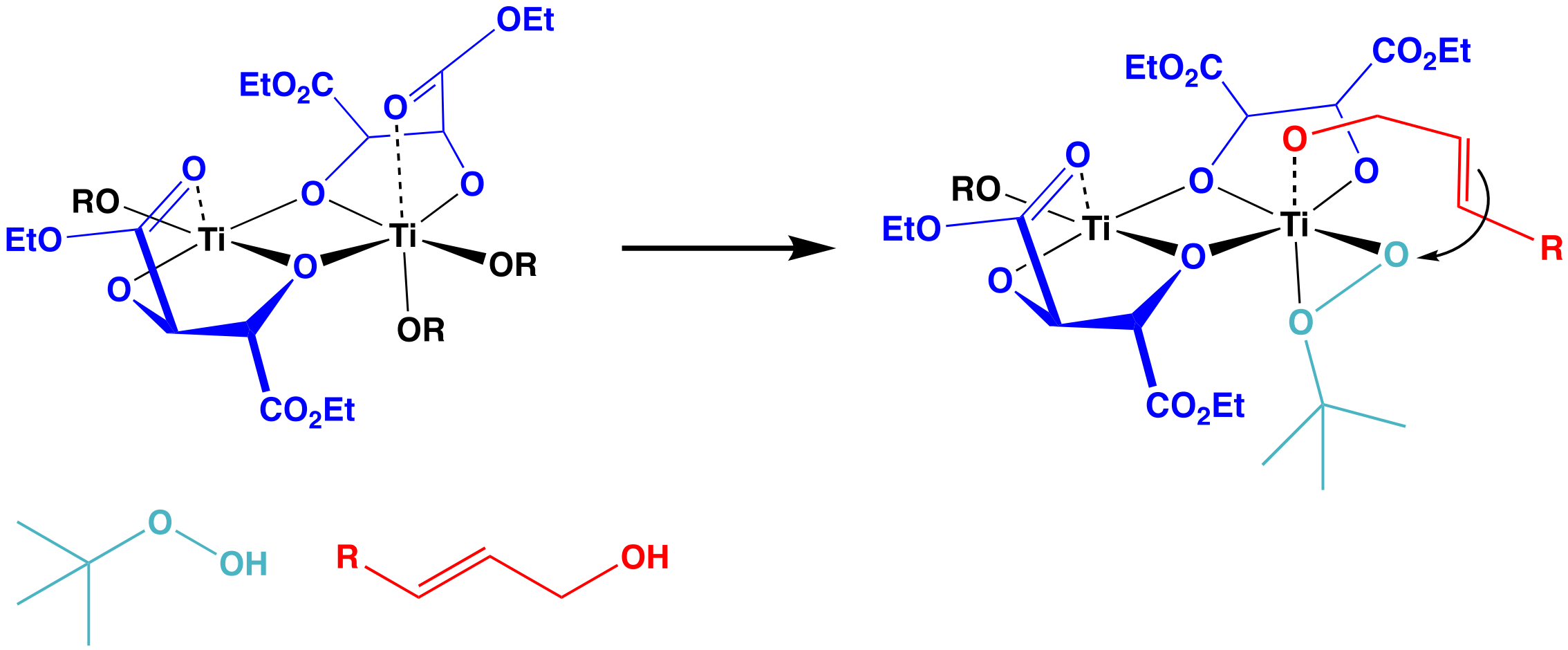
Requires an allylic alcohol



(S,S) and (R,R) diethyl tartrate (+/– DET) are the source of chirality.

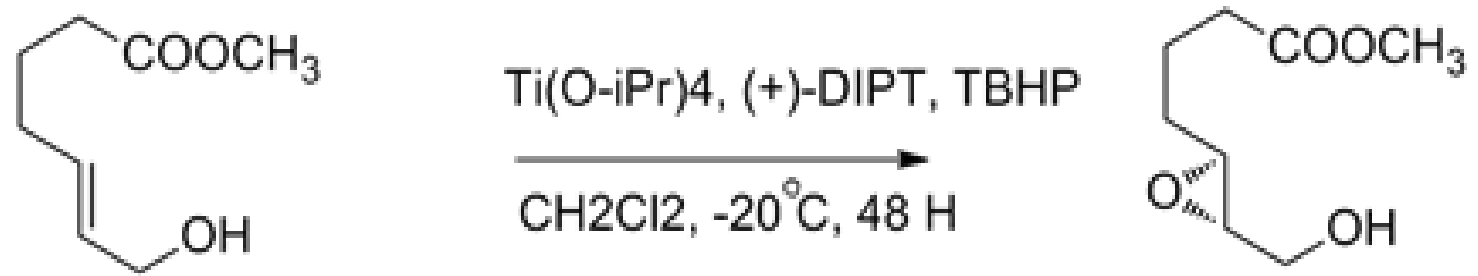


Asymmetric Epoxides: Sharpless



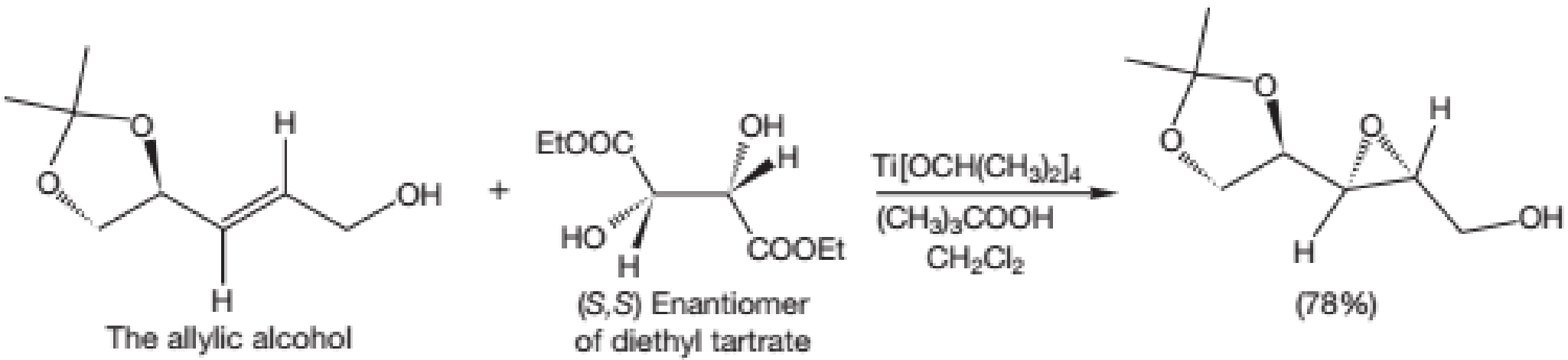
Structures of complexes for appreciation only

Asymmetric Epoxides: Sharpless Examples



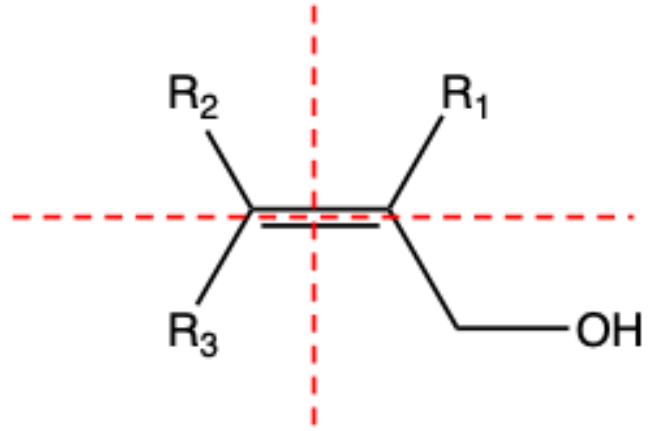
leukotriene C-1

80% yield
95% ee



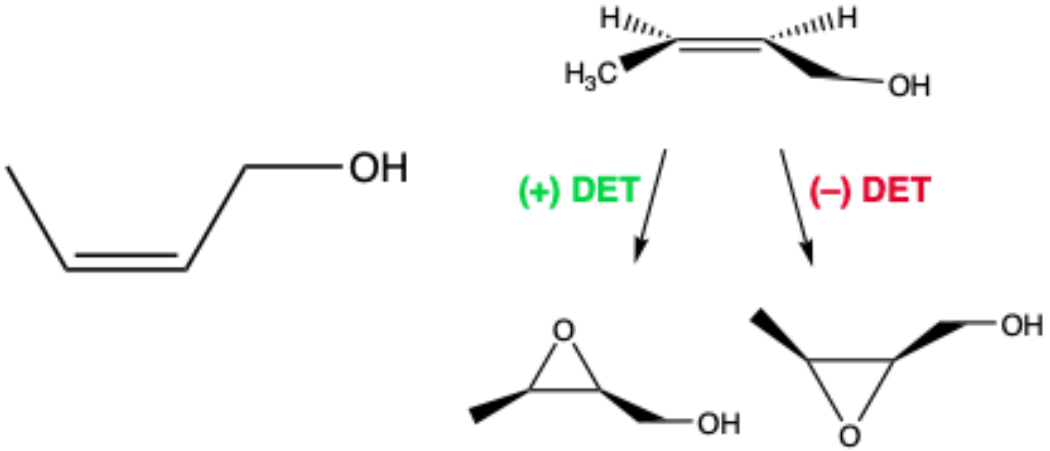
Asymmetric Epoxides: Sharpless

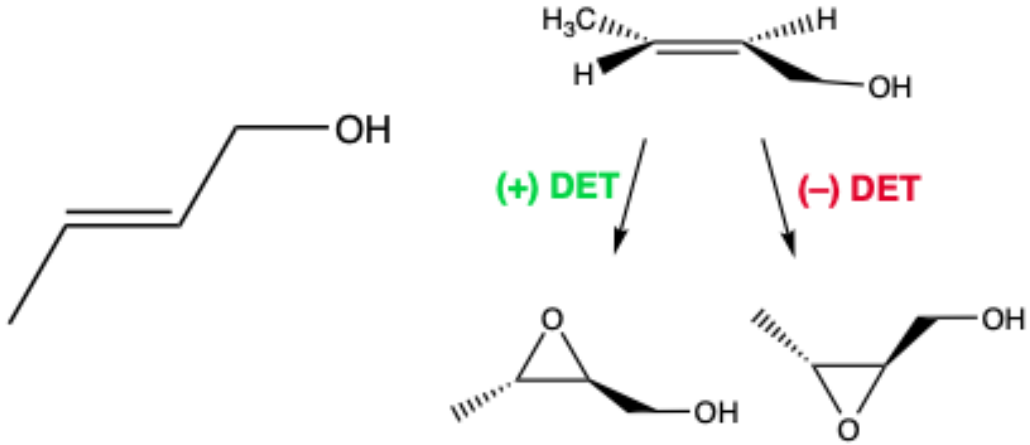
Selecting (+)/(–) DET and placing the **allylic OH in the lower right** quadrant, helps to predict the enantiomeric product.



(+) DET – epoxide forms *above*

(–) DET – epoxide forms *below*

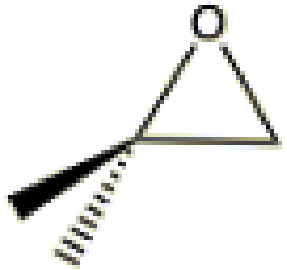




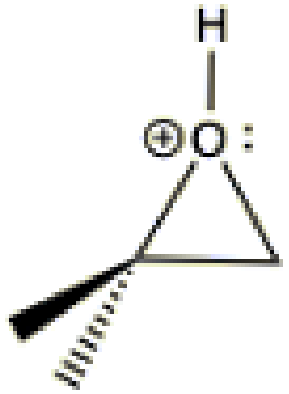
Epoxides: Opening in Different Conditions

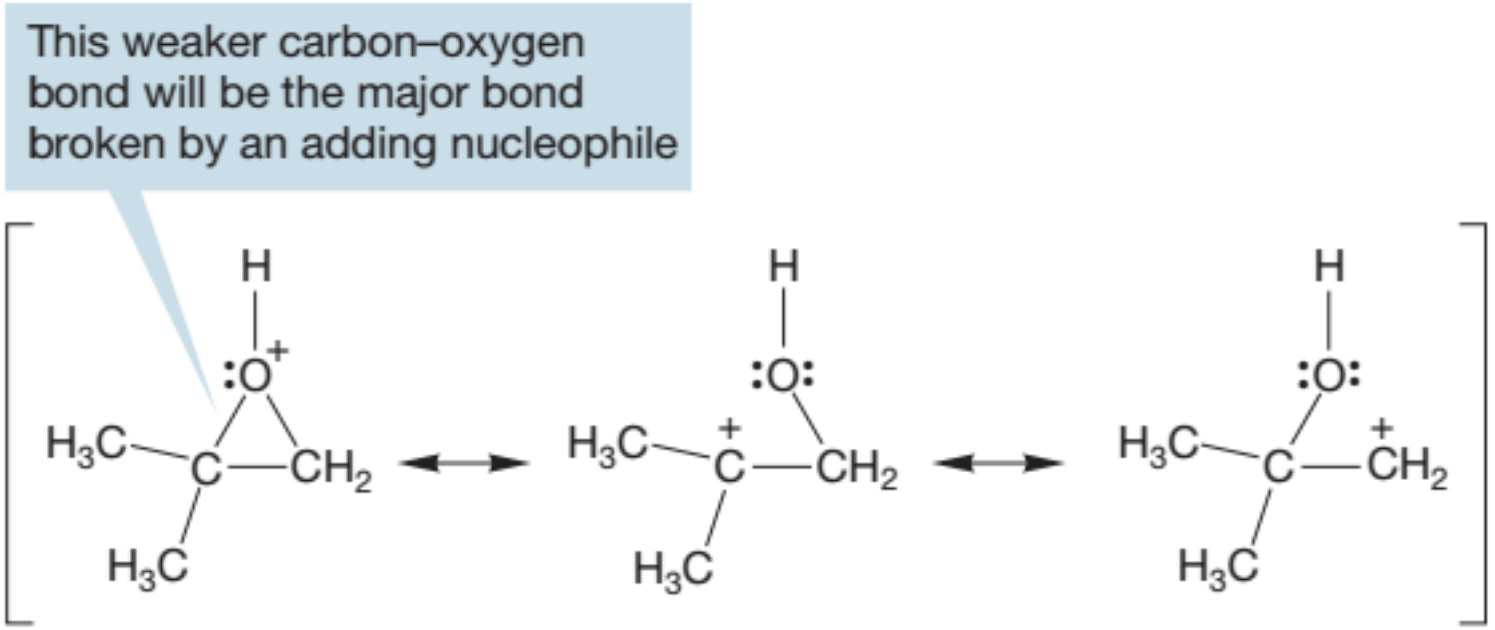
For asymmetric epoxides, the nucleophile can attack either side, but there is regioselectivity based on the reaction conditions. **Epoxides** will be **neutral** in **basic conditions** and **protonated** in a **strong acid**.

Epoxide
In **BASE**



Epoxide
In **ACID**



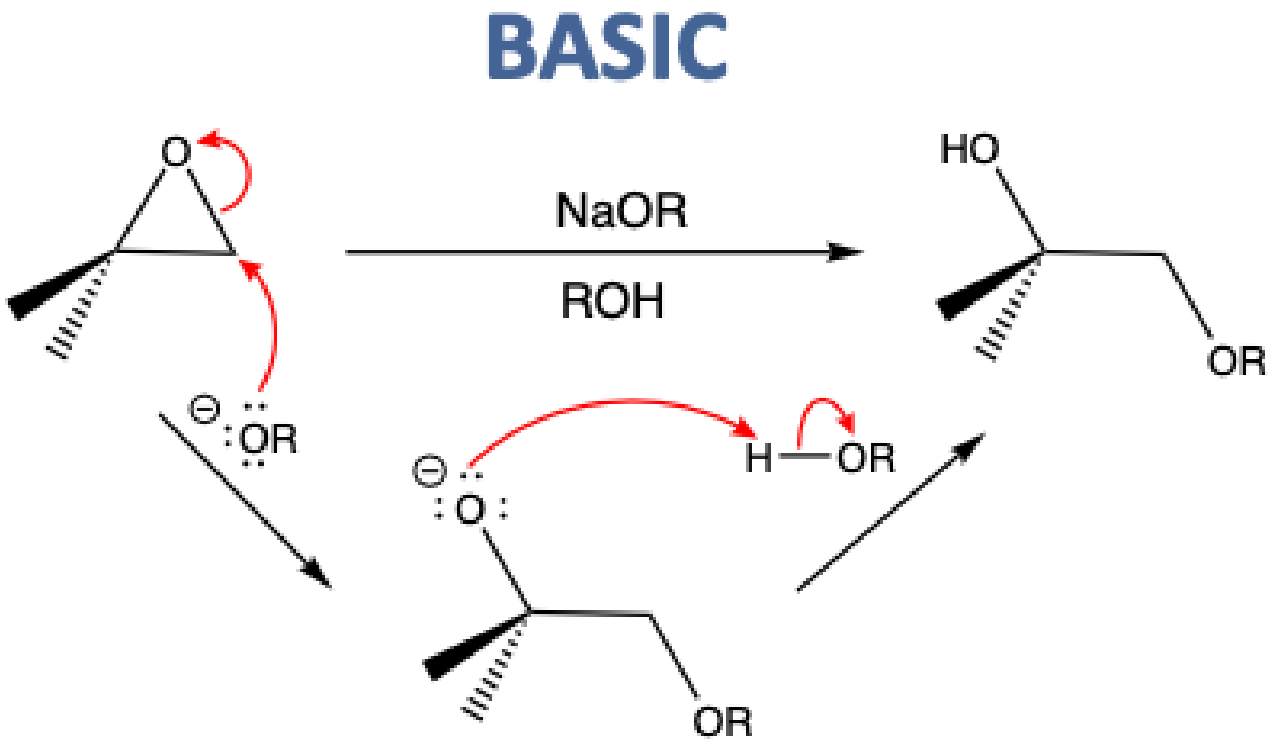


Epoxides: Opening in Different Conditions

Nucleophiles attack the **LESS substituted** side in **basic** conditions.

This follows the rules of S_N2, in which the nucleophile attacks the more exposed, weaker bond.

(1) S_N2 Nuc Attack
(2) Acid-Base H^+-Transfer



Basic Nucleophiles:
- ^-OH
- ^-OR
- ^-SR
- $^-NH_2$
- ^-CN
- ^-Nuc (etc…)
- ^-R (via Grignard)
- ^-H (via LAH)

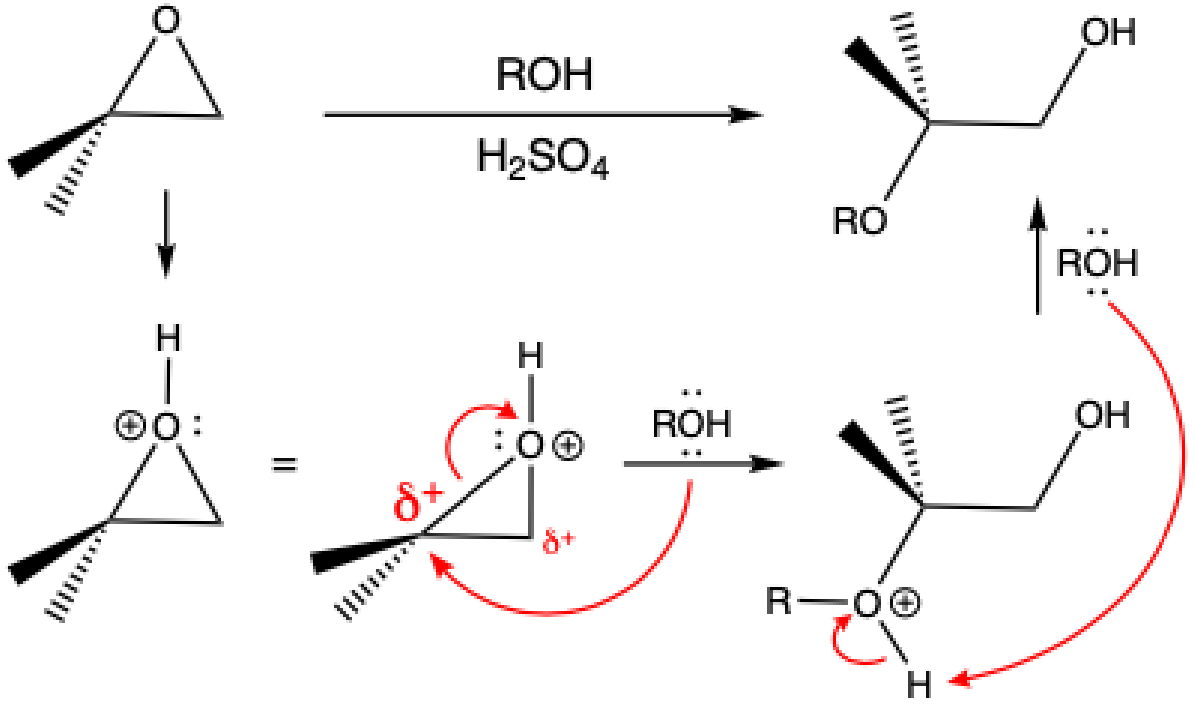
Epoxides: Opening in **ACIDIC** Conditions

Nucleophiles attack the **MORE substituted** side in **acidic** conditions.

This also follows the rules of **S_N2**, with the Elec$^+$ being the best "partial carbocation" (*see 2 slides ago*).

(1) Acid-Base H^+ Transfer
(2) S_N2 Nuc Attack
(3) Acid-Base H^+ Transfer

Acidic Nucleophiles:
- H_2O, H^+
- ROH, H^+
- SH_2, H^+
- HBr or HCl

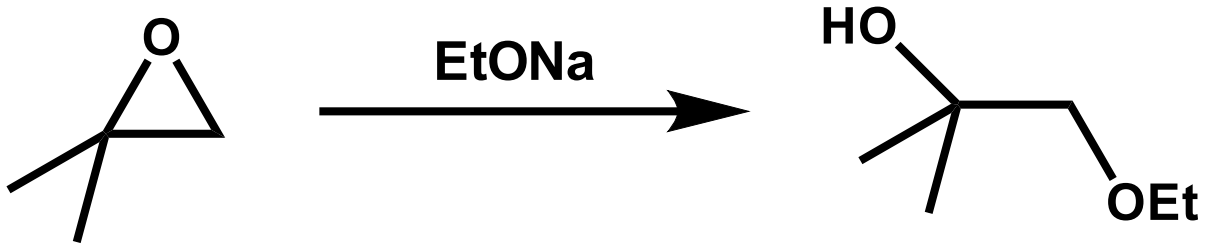


Oxonium (+) charge is held by O and two neighboring C atoms (*see resonance on slide 50*).

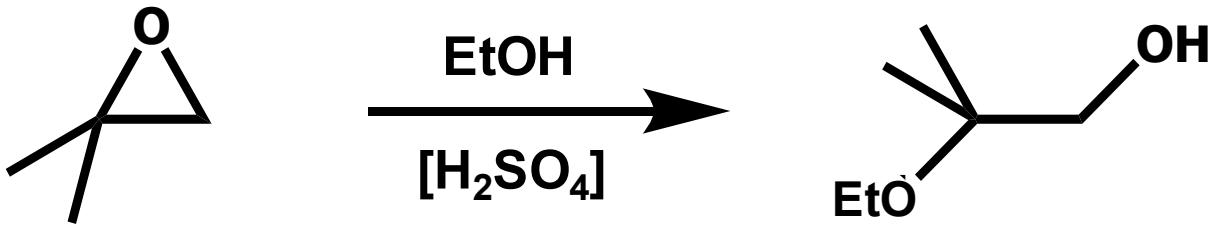
The 3° side holds the (+) better, lowering the E_A for a Nuc^- attack.

Epoxides: Opening in **ACID**/**BASE**

AGAIN, which regioisomer is formed depends on conditions.



S_N2-like



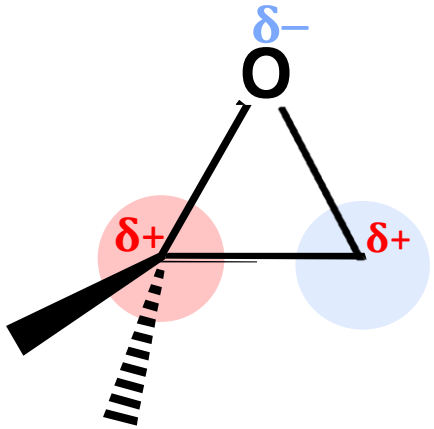
Not S_N1 -

NO “true” CARBOCATION!

Stereochemical outcome *inconsistent* with carbocation intermediate.

Epoxide Opening: Steric vs. Electronics

Epoxide <u>regioselectivity</u> depends on whether steric or electronic effects dominate:

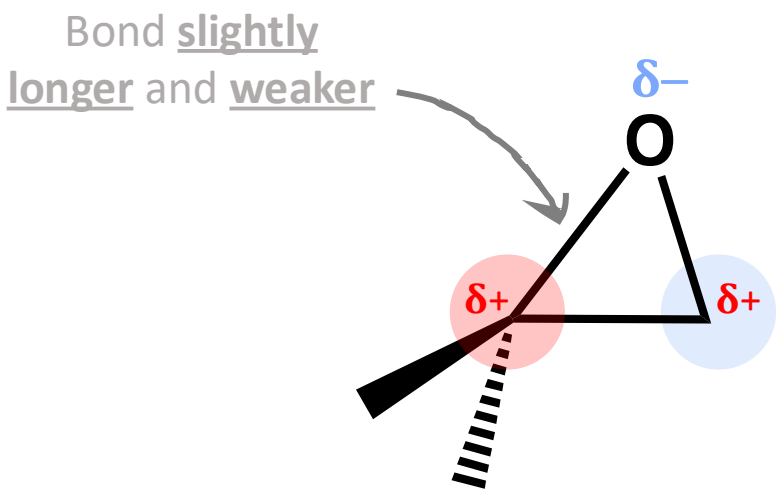


- **Steric Hinderance**
  - Crowding blocks nucleophile approach
  - Minimal steric stabilizes transition state
  - Dominates in S_N2 / strong nucleophile
- **Electronic polarization**
  - Developing positive charge stabilizes transition state
  - More steric stabilizes δ+ better
  - Dominates in acidic / weak nucleophile

Worse Steric **<u>Better</u> Electronics**	**<u>Better</u> Steric** **Worse Electronics**

Epoxide Opening: Steric vs. Electronics

Under **basic conditions**, oxygen is not protonated and nucleophiles are negatively charged (⁻**:Nuc**), which affects likelihood of attacking either side:



- **Strong Nuc** wants easiest, fastest side reaction.
- **Steric hindrance** raises the activation energy (E_A) for attack at more substituted carbons
  - **In Base: Steric increases E_A at 3° side**
- **Electronics** have little effect due to insignificant polarization of the C–O bond w/o protonation
  - **In Base**: Electronics minimal w. lesser polarity

Collision unlikely
Raises E_A due to
↑ steric effects at **3°**

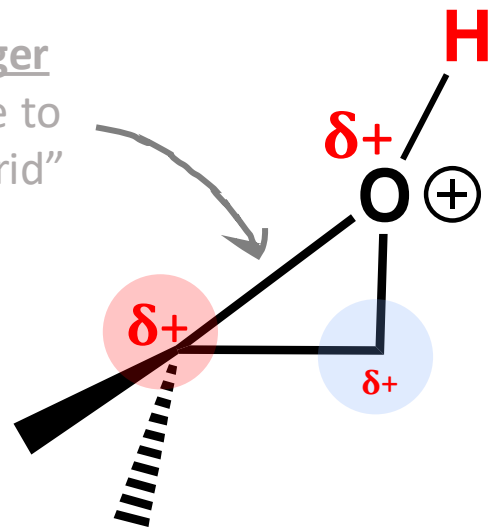
Collision likely
Relatively
Lower E_A

For Strong Nucleophiles in Base,
STERICS Win!

Epoxide Opening: Steric vs. Electronics

Under **acidic conditions**, oxygen is protonated and nucleophiles are neutral (**HNuc**), which affects likelihood of attacking either side:

Bond **even longer** and **weaker** due to resonance "hybrid" structure



- **Weak Nuc** waits for strong electronics to attract it.
- **Electronics** have greater effect due to significant polarization with protonated oxygen
  - **In Acid: Electronics lower E_A at 3° side**
- **Steric hindrance** has less impact due to elongated bond from partial bond character (see resonance)
  - **In Acid**: Steric less effective due to longer bonds

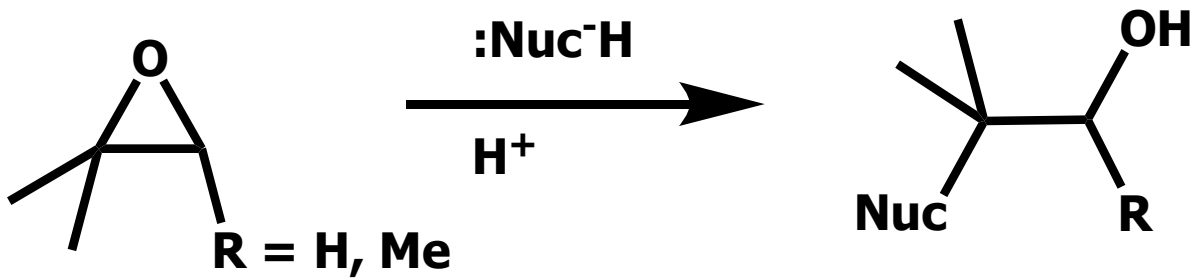
Collision more likely
Lowers E_A due to
↑ **electronics** at **3°**

Collision less likely
Higher E_A due to
↑ **electronics**

For Weak Nucleophiles in Acid,
ELECTRONICS Win!

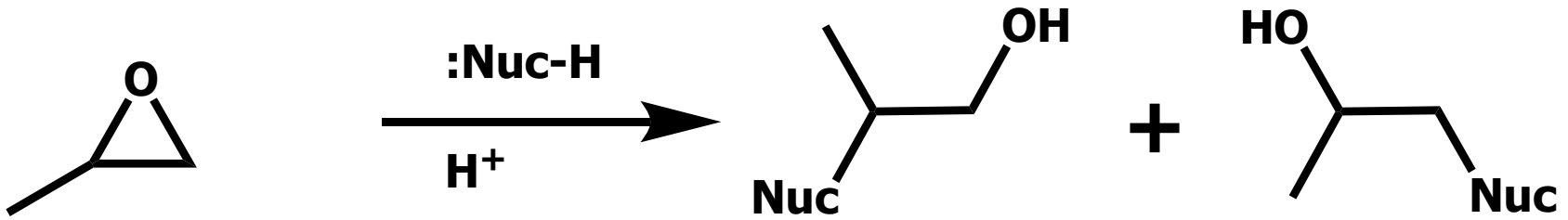
Epoxide Opening: Not Black-and-White

In **acidic conditions**, attacking the most substituted side *does not always* result in the major product. When a **NucH** chooses between a **1°** or **a 2°**, we tend to get a mixture:



ELECTONICS
WINS

[1° vs. 3°] OR **[2° vs. 3°]**



[1° vs. 2°]

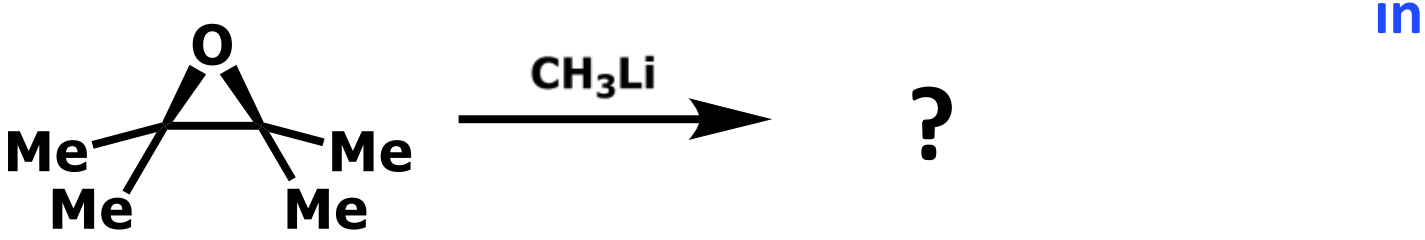
STERICS &
ELECTRONICS
COMPETE

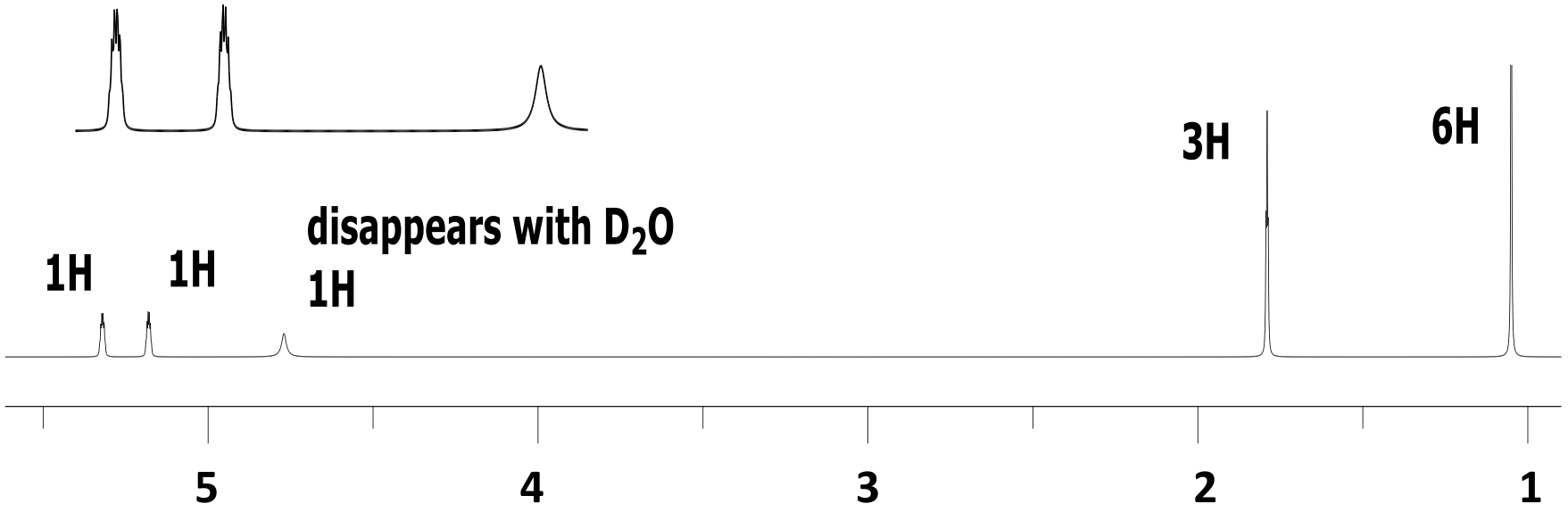
E_A is more comparable when there is **NO 3° carbocation** available.

Epoxide Opening: Steric & Strong $^{-}$:Nuc

What about in **basic conditions**, if there is <u>no possibility</u> of S_N2: **(1) Why not?**

(2) What happens instead?

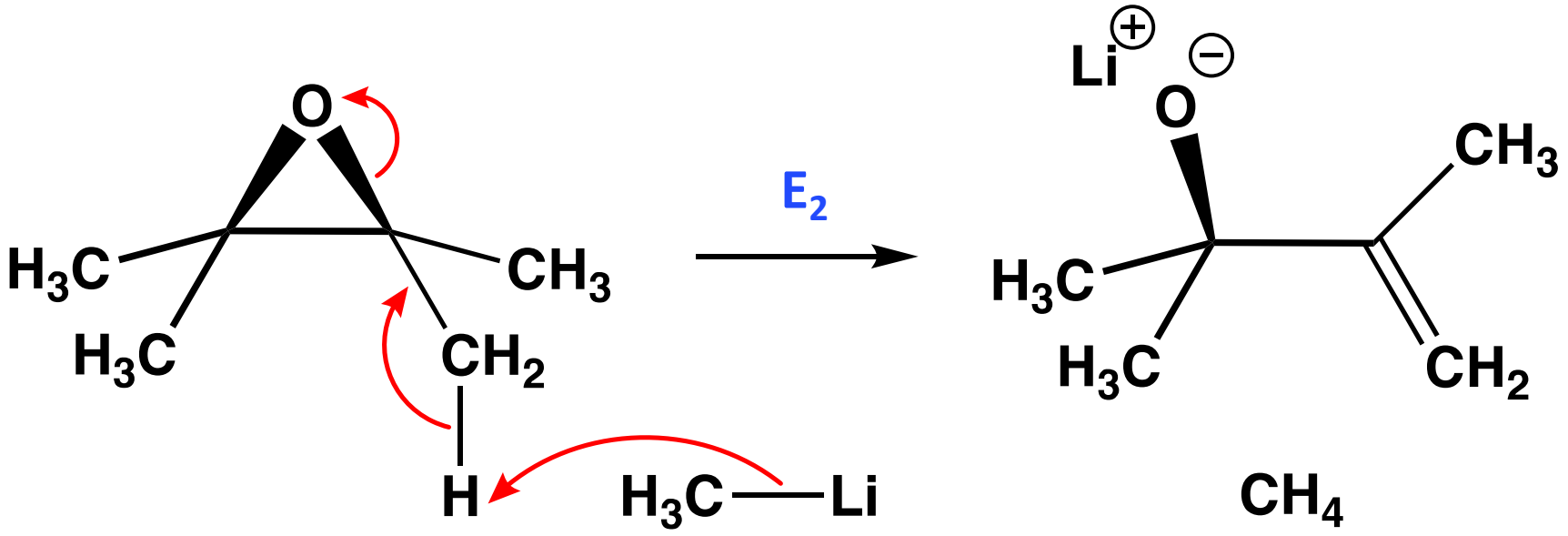




H-NMR spectrum of the product.

Epoxide Opening: Steric & Strong ⁻:Nuc

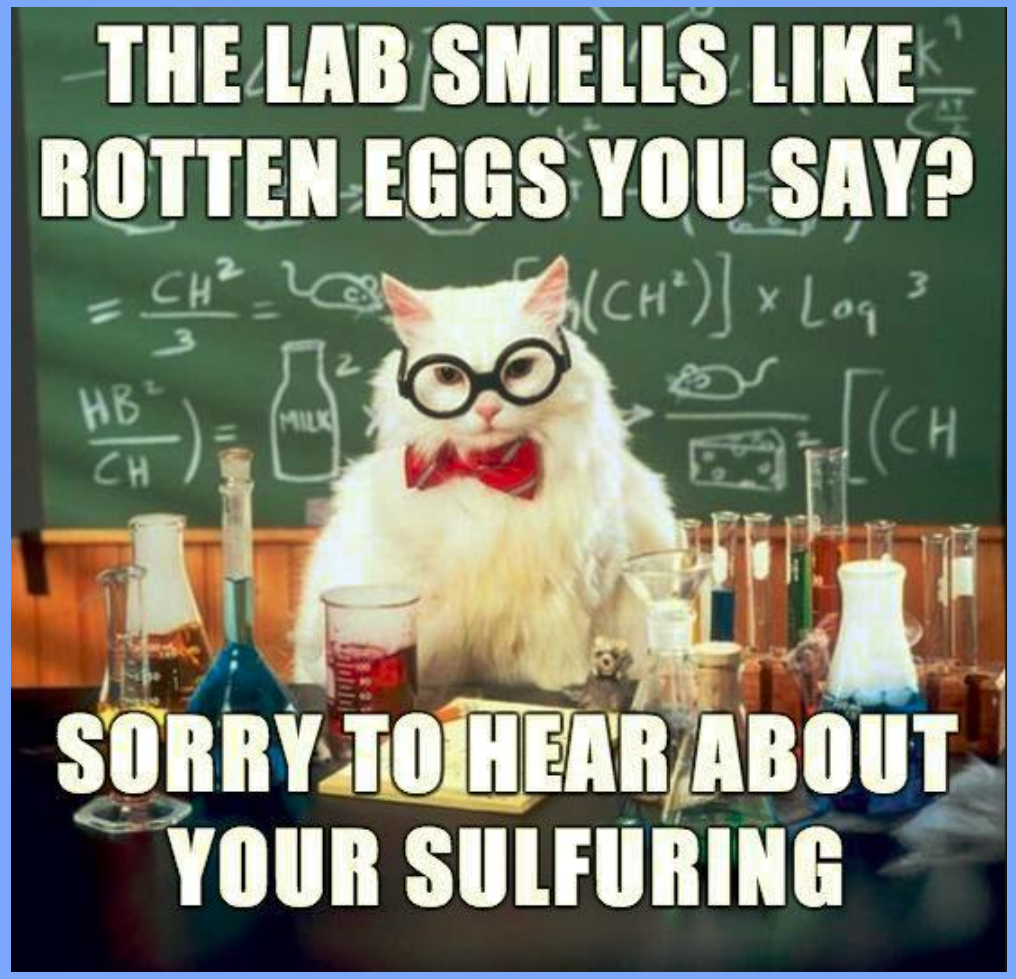
In **basic conditions**, but there is no possibility of S_N2:



Too sterically-hindered to undergo S_N2 reaction, so E2 outcompetes.

Sulfides & Thiols

- Oxygen vs. Sulfur
- Acidity (of Thiols)
- Reactivity
  - **Synthesis** via S_N2 – NaSH or SH_2
  - **Reduction** via Zn/HCl or H_2/Ni
  - Mild **Oxidation** via I_2
  - Strong **Oxidation** via $NaIO_4$ or H_2O_2



ROH/ROR vs. RSH/RSR: Sulfur vs. Oxygen

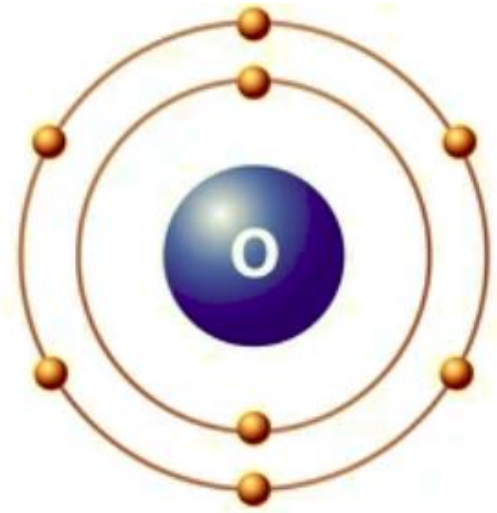
A useful analogy for predicting thiol and sulfide properties is the similarities and differences between O and S (same group of PT)

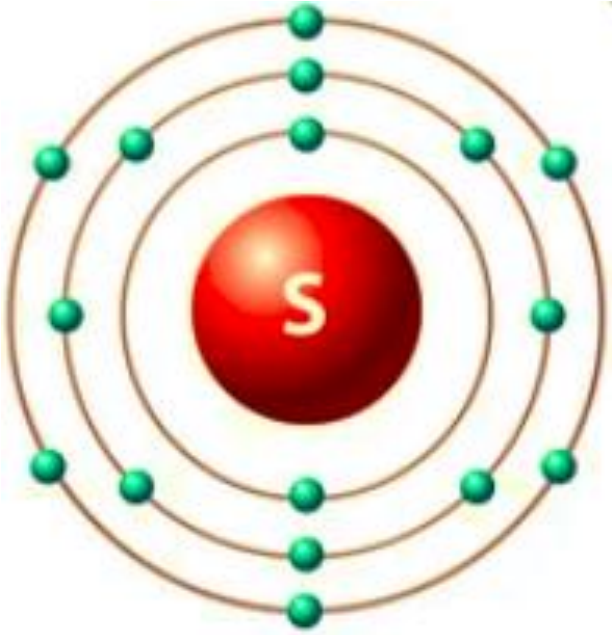
This **group 6A analogy** exists for oxygen, sulfur, and selenium and their resultant alcohols, thiols, and *selenols.

Smaller atom
(8 p^+, 8 n, 8 e^-)

More EN (3.5)

Less Polarizable
(due to smaller volume)



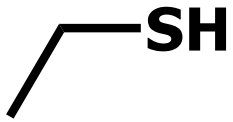


Larger atom
(16 p^+, 16 n, 16 e^-)

Less EN (2.5)

More Polarizable
(due to larger volume)

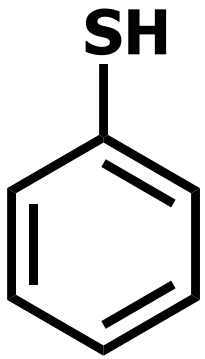
ROH vs. RSH: Acidity



Ethyl mercaptan

pKa 10.6

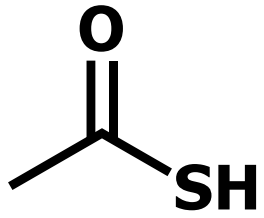
(*c.f.* **EtOH** – pKa **15.9**)



Thiophenol

pKa 6.6

(*c.f.* **PhOH** – pKa **10.0**)

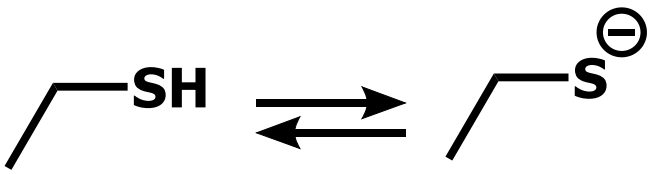


Thioacetic acid

pKa 3.3

(*c.f.* **AcOH** – pKa **4.7**)

ROH vs. RSH: Acidity

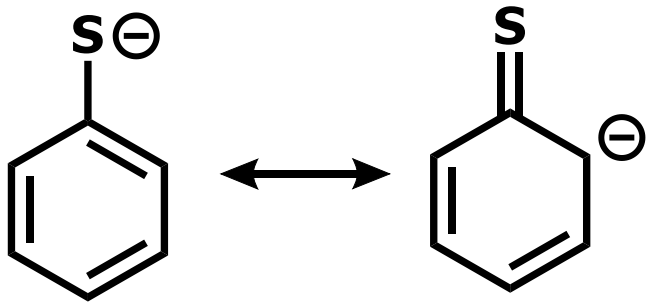


Ethyl mercaptan

pKa 10.6

(*c.f.* **EtOH** – pKa **15.9**)

3rd row atoms carry charge better (due to larger atomic volume)

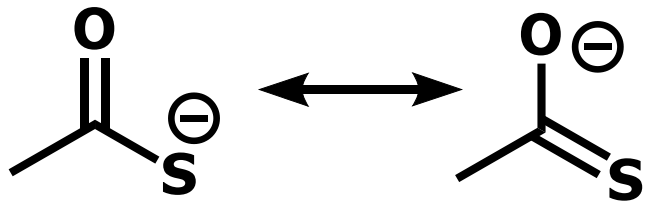


Thiophenol

pKa 6.6

(*c.f.* **PhOH** – pKa **10.0**)

Sulfur weakly π-bonds with 2nd row (diff. size *p* orbitals) – **reduces contribution of resonance**



Thioacetic acid

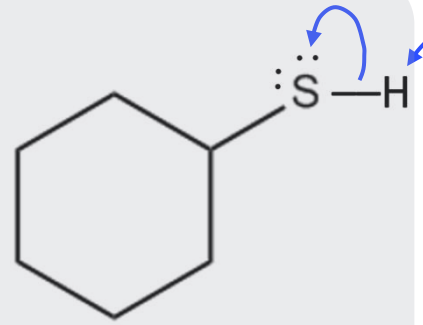
pKa 3.3

(*c.f.* **AcOH** – pKa **4.7**)

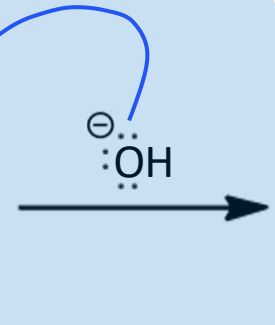
Same reasoning as Thiophenol vs. Phenol

Thiols: Thiol Deprotonation

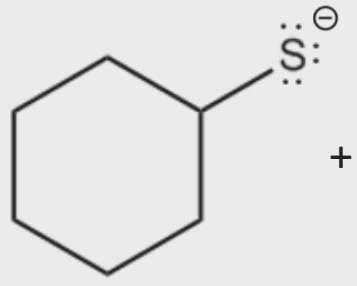
While thiols and sulfides are inherently nucleophilic, thiols contain an **acidic hydrogen (H^+)** that can be removed by a relatively **stronger base** to form a **strong nucleophile.**



THIOL
$pK_a \simeq$ **10-11**



Base



THIOLATE
(Conj. Base)

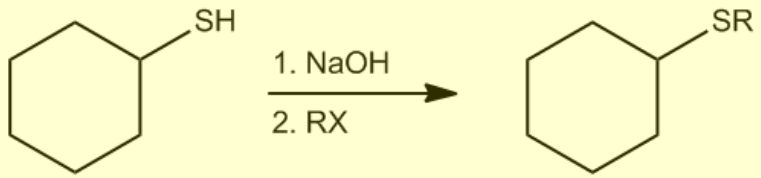
+ H_2O

Conj. Acid
pK_a **= 15.7**

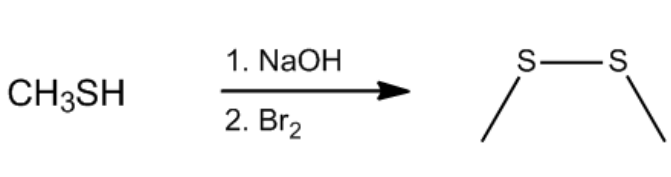
Bases to Deprotonate Thiols:

- **tBuOK** —— C.A. pK_a = **18**
- **NaOEt** —— C.A. pK_a = **16**
- **Et_3N** —— C.A. pK_a = **10.7**
- **iPr_2EtN** — C.A. pK_a = **10.8**
- **iPr_3N** —— C.A. pK_a = **11**

Sulfide Synthesis

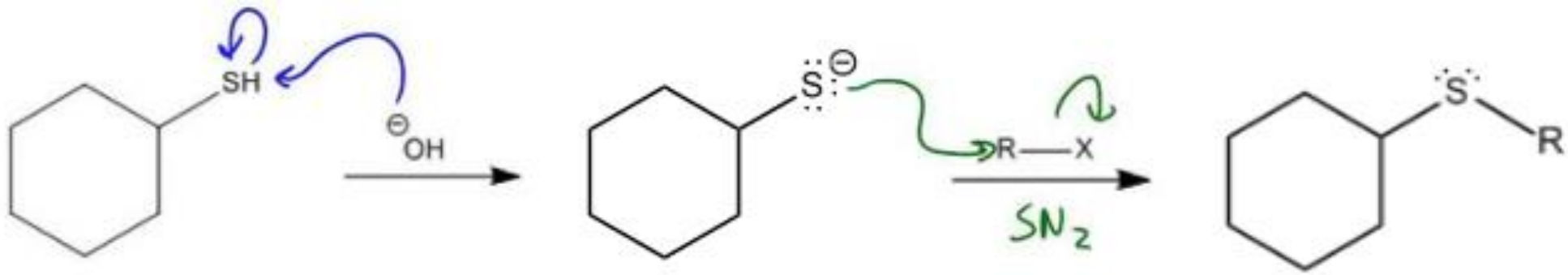


Disulfide Synthesis

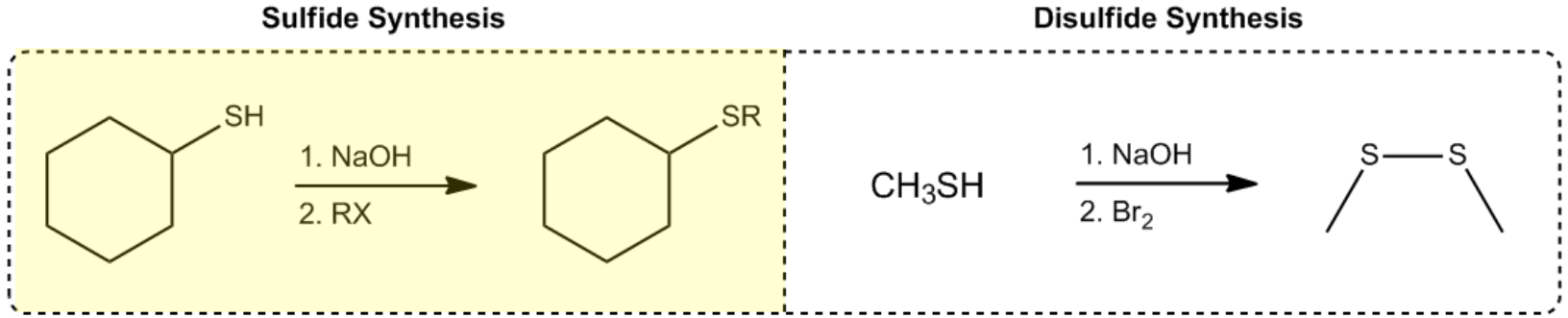


Thiols: Sulfide Synthesis

Once the **THIOLATE** has been formed, it can be used as a **strong nucleophile** to attack **sterically-unhindered substrates** (**Me**/**1°**) via **S_N2**, though 2° substrates can *slowly* (and inefficiently) undergo S_N2.

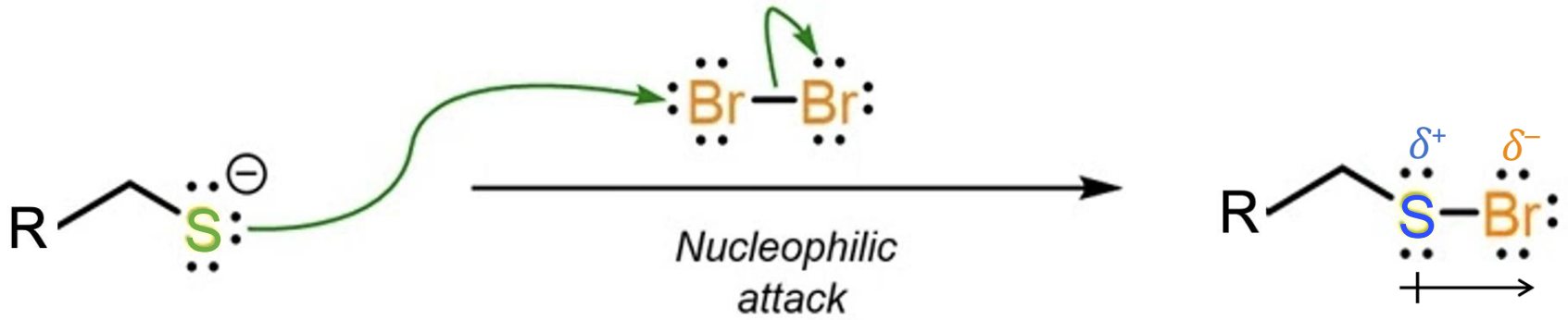


THIOLATE

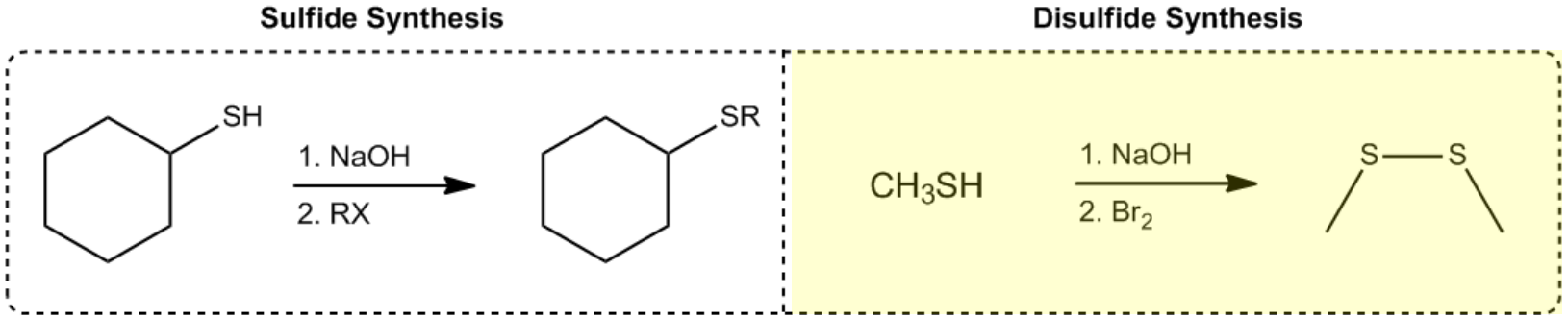


Thiols: Disulfide Synthesis

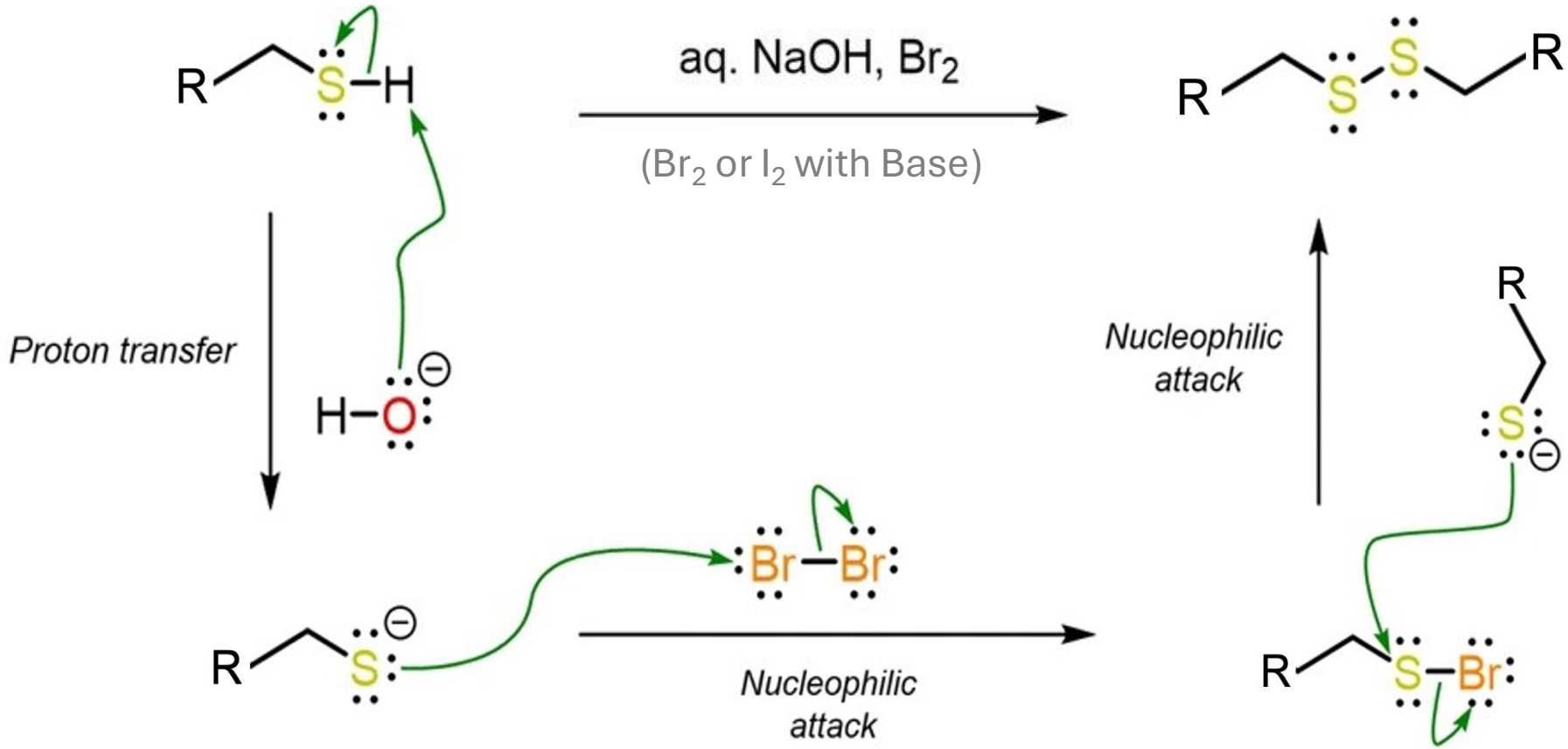
Thiolates are also used to form **disulfide bonds** via sulfenyl halide intermediate (RSX). To form the intermediate, **nucleophilic sulfur** converts into an **electrophilic sulfur**, via an oxidative reaction with Br_2 or I_2. The sulfenyl halide is then primed to be attacked by another equiv. of thiolate.



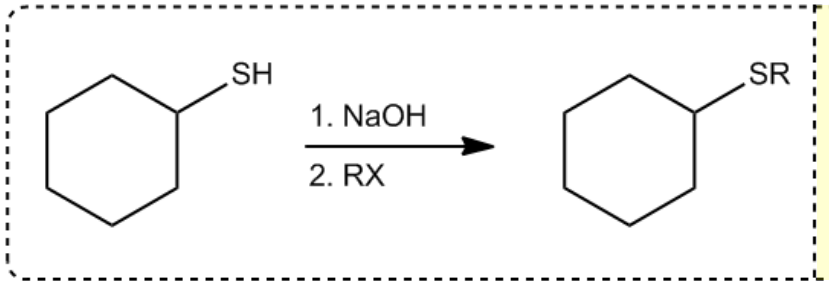
Nucleophilic Sulfur **[Oxidation Step]** **Electrophilic Sulfur**



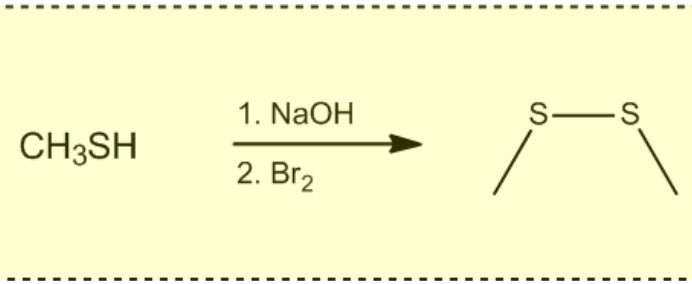
Thiols: Disulfide Synthesis



Sulfide Synthesis



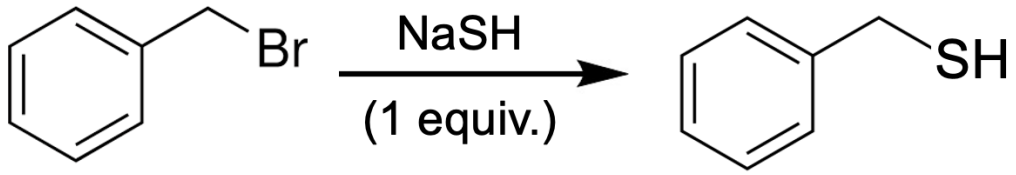
Disulfide Synthesis



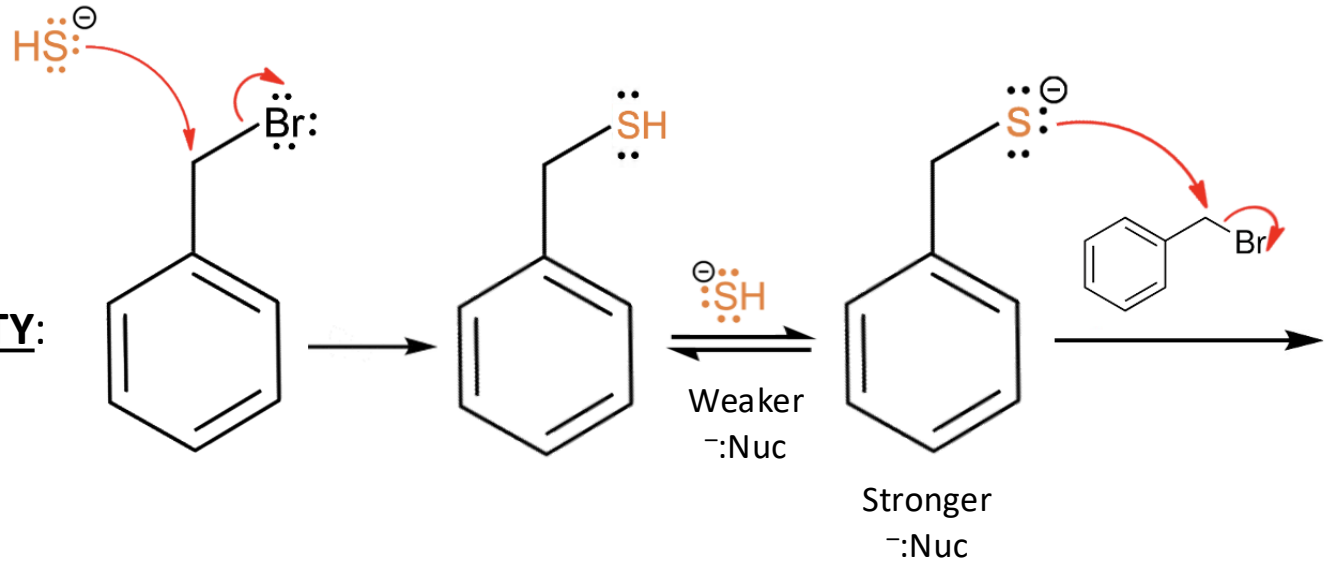
Thiols: Sulfur Hydride and Alkyl Halides

Because thiols are such great nucleophiles (and decent acids), they often exceed the expectations of the reaction. This is especially notable if starting with sodium hydrogen sulfide (NaSH), that can both behave as a weak base and a strong nucleophile.

EXPECTATION:



REALITY:

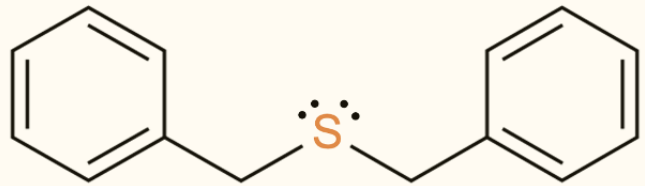


NaSH used up before all the substrate reacts, yielding a mix of products.



Thiol
(Once Reacted)

Starting Material
(Unreacted)



Sulfide
(Twice Reacted)

Thiols: Sulfur Hydride and Alkyl Halides

Since $HS:^-$ is a weaker nucleophile relative to $RS:^-$, manipulating concentrations can help to favor the reactivity of $HS:^-$ and give the desired thiol as the only product.

1 equiv. NaSH (Excess RBr)		
Nuc:⁻	**Concentration**	**As Reaction Proceeds**
HS^-	low	decreases as it's used
RS^-	—	increases with RT (becomes comparable)

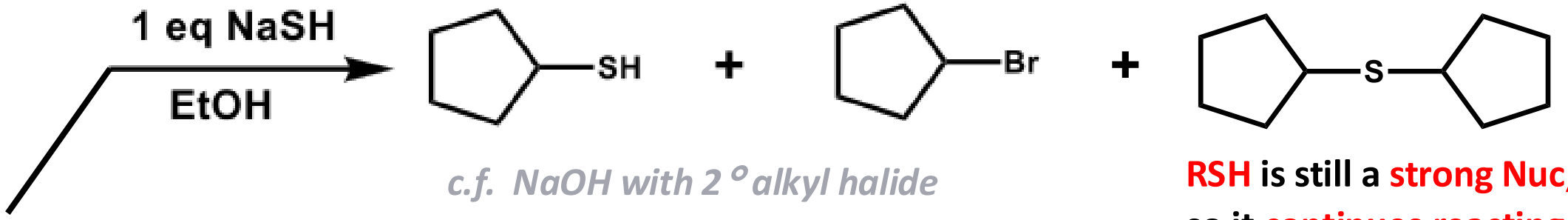
Excess NaSH (1 equiv. RBr)		
Nuc:⁻	**Concentration**	**As Reaction Proceeds**
HS^-	high (excess)	stays abundant
RS^-	—	stays low (per acid-base equilibrium)



Acid-Base equilibrium favors the weaker Nuc ($^-$:SH), keeping [$RS:^-$] low.

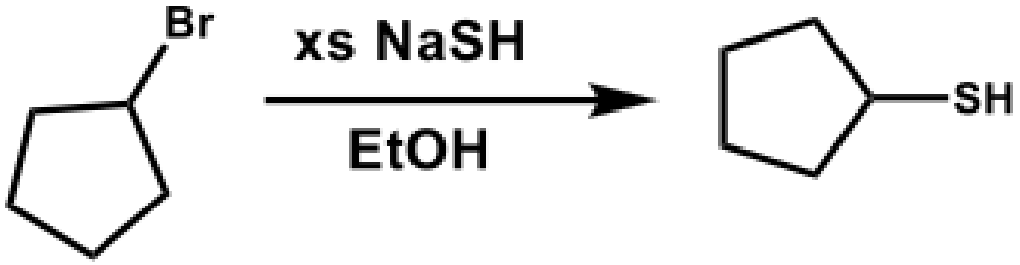
- If **NaSH** is also **low**, the small amount of **thiolate** formed **can outcompete**.
- If **NaSH** is in **excess**, it becomes the **default nucleophile** since **thiolate remains minimal**.

Synthesis Summary: Thiols, Sulfides, & Thioester

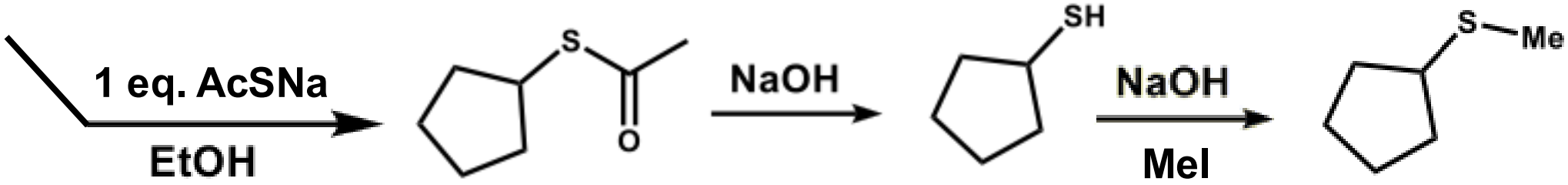


c.f. NaOH with 2° alkyl halide

RSH is still a strong Nuc, so it continues reacting.



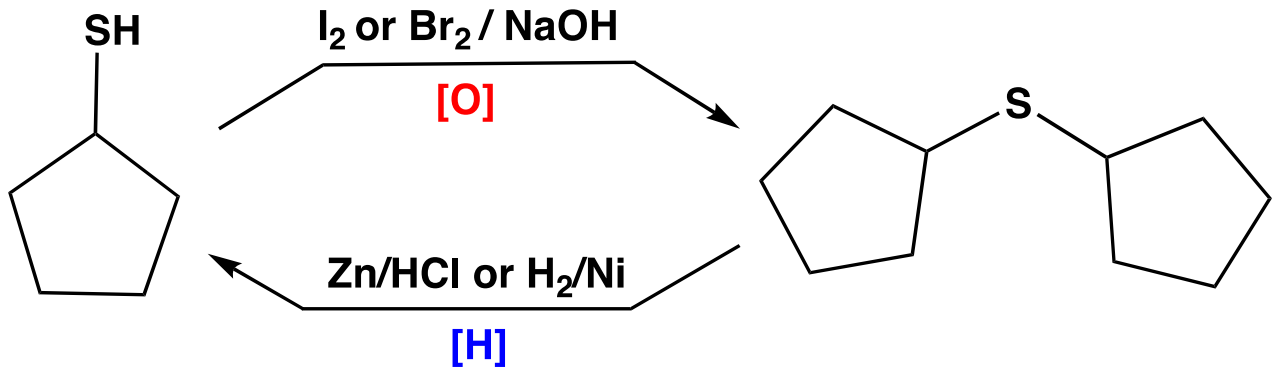
High concentrations of NaSH can favor the formation of thiol *only* due to limiting reagent R–Br.



⁻:OH attacks carbonyl C, releasing RCOOH & RS:⁻

***c.f.* Williamson Ether Synthesis**

Synthesis Summary: Thiols, Sulfides, & Disulfides



a disulfide

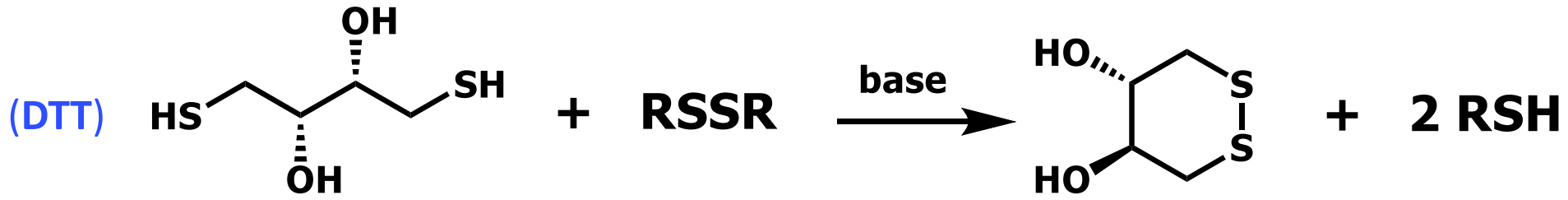
(dicyclopentyl disulfide)

Thiols are oxidized by almost any oxidant: (1) elemental halogen (X_2) with base

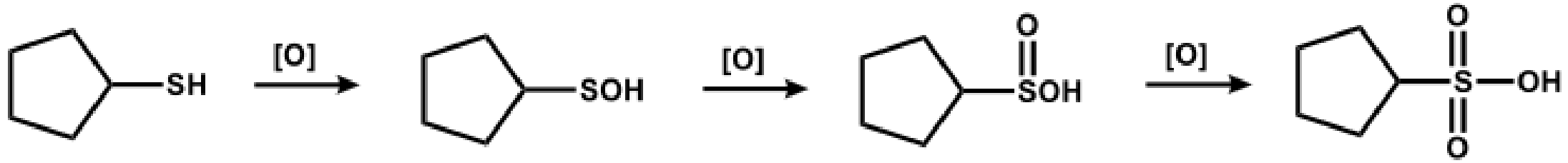
Disulfides are reduced by almost any reducing agent: (1) Zn/HCl

(2) H_2/metal

(3) dithiothreitol (DTT)



Thiols: Strong Oxidation

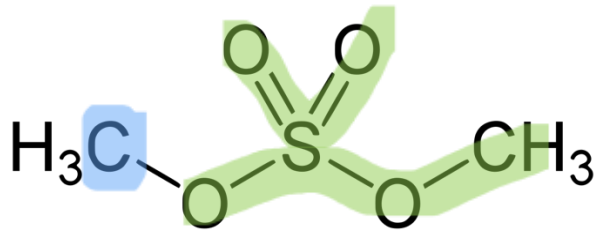


cyclopentylthiol **cyclopentylsulfenic acid** **cyclopentanesulfinic acid** **cyclopentanesulfonic acid**

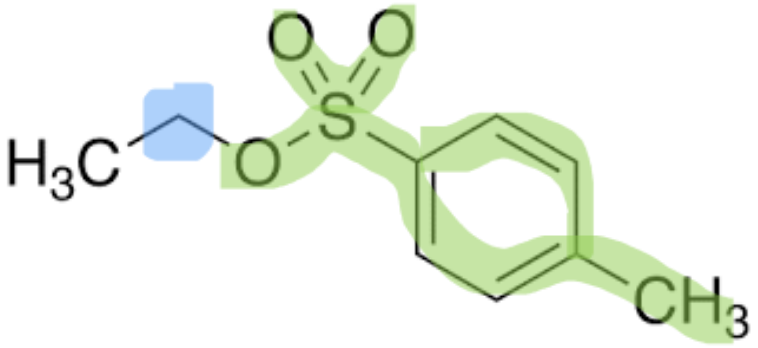
c.f. TsOH

Multiple equivalents of H_2O_2 can be used to oxidize thiols along this pathway.
Almost any oxidant works for this pathway.

Alkyl sulfonates and sulfates are good for S_N2 : $^-$:OTs is good LG; R is electrophile.

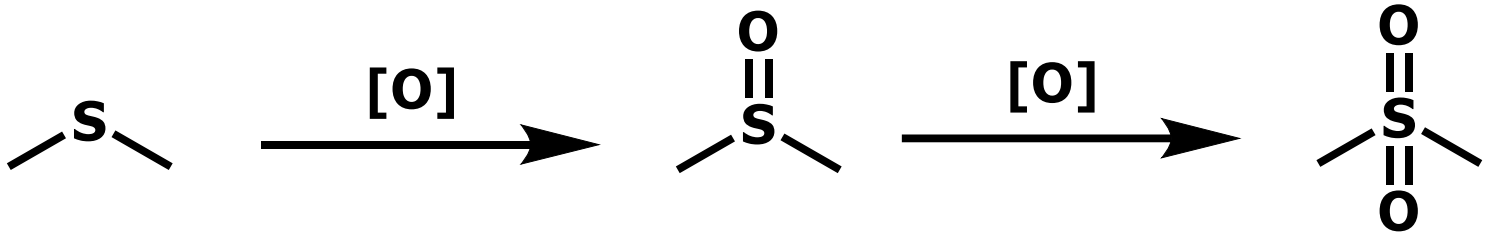


dimethylsulfate



ethyltosylate (EtOTs)

Sulfides: Strong Oxidation

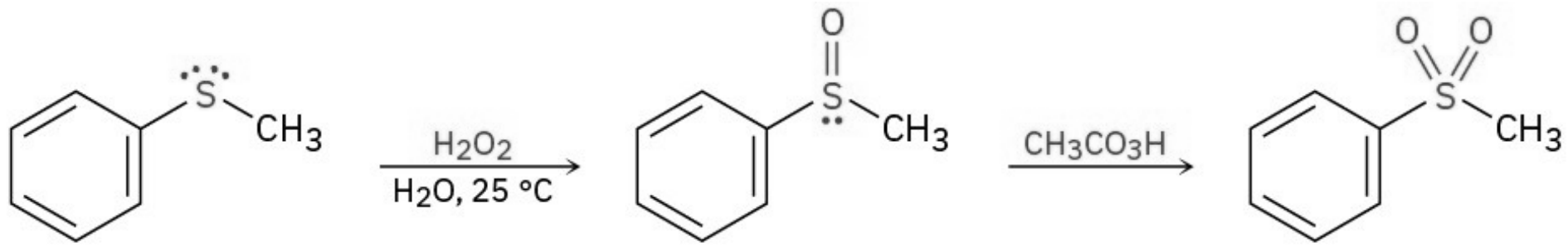


[O] = almost any oxidant

dimethyl Sulfide
(DMS)
(useful solvent*)

dimethyl Sulfoxide
(DMSO)
(useful solvent*)

dimethyl Sulfone



Methyl phenyl sulfide

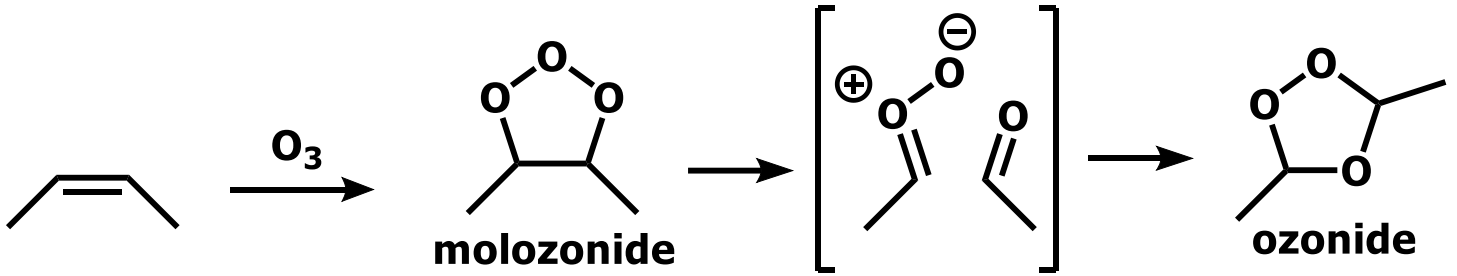
Methyl phenyl sulfoxide

Methyl phenyl sulfone

** see next slide*

DMS & DMSO: Oxidation of Alkenes

OZONOLYSIS MECHANISM



DMS acts as a reducing agent, so it becomes oxidized into DMSO.

