1 Terminology/Properties

- Ethers are generally unreactive, we just saw ethers used as the SOLVENT for Grignard reactions, for example, although Epoxides are an exception as a consequence of the strain in the 3-membered ring.
- Ethers have moderate polarity, and tend to be good Organic Solvents.

2 Nomenclature

- Ethers are named as substituents (like halides), they have the same (low) priority as halides.
- Ether substituents are named as the ALKOXY is equivalent to ALKYL, i.e., -Me is methyl, thus, -OMe is methoxy.
- The "main chain" is determined according to the usual rules, i.e., the longest chain that contains the maximum number of functional groups.

Some Common Ethers and Common Names

- Diethyl ether
- Ethylene oxide (oxirane)
- Oxetane
- Tetrahydrofuran (THF)
- Tetrahydropyran

Those with the star symbol (*) you need to know!

3 Preparation of Ethers

3.1 Williamson Ether Synthesis (SN2 Reaction)

- This is just an SN2 reaction, but we will analyze it using retrosynthetic analysis anyway!

Retrosynthetic strategy:

\[
\begin{align*}
R-O^- & \quad R' \\
(4S)-\text{tert-butoxycyclohexene} \\
\end{align*}
\]

- "Put" the negative charge on the oxygen and a leaving group on the carbon to make the best synthons that have the lowest energy electrons.
The Williamson ether synthesis consists of Two Steps

**FIRST STEP:** preparation of an alkoxide anion (the nucleophile) by **deprotonation of an alcohol**

- which base is useful for this?

\[
\begin{align*}
R\cdot\overset{-}\circ\overset{\cdot}{\circ} & + \text{Na}\cdot\overset{-}\circ\overset{\cdot}{\circ} \cdot \text{H} & \rightarrow & R\cdot\overset{-}\circ\overset{\cdot}{\circ} & \cdot \text{Na} \ + \ \text{H}_2 \\
\text{sodium hydride} & & & \text{sodium alkoxide}
\end{align*}
\]

- sodium hydride is a useful strong base to irreversibly deprotonate an aliphatic alcohol

For Example:

\[
\begin{align*}
\text{H}_3\text{C}\cdot\overset{-}\circ\overset{\cdot}{\circ} & + \text{Na}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow & \text{H}_3\text{C}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \cdot \text{Na} \\
\text{sodium methoxide}
\end{align*}
\]

\[
\begin{align*}
\text{Ph}\cdot\overset{-}\circ\overset{\cdot}{\circ} & + \text{Na}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow & \text{Ph}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \cdot \text{Na} \\
\text{sodium phenoxide}
\end{align*}
\]

- the conjugate base anions of alcohols are alkoxide anions (organic version of hydroxide)
- the phenoxide anion can also be made simply with \(^{-}\text{OH}\)

Stonger acid faster reaction
\[
\begin{align*}
\text{Ph}\cdot\overset{-}\circ\overset{\cdot}{\circ} & + \text{Na}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow & \text{Ph}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \cdot \text{Na} \ + \ \text{H}_2\text{O} \\
p\text{Ka} \sim 10 & & & p\text{Ka} \sim 15
\end{align*}
\]

**SECOND STEP: SIMPLE SN2 reaction with a halide** (coupling reaction)

\[
\begin{align*}
\text{RO}\cdot\overset{-}\circ\overset{\cdot}{\circ} & + \text{R}'\cdot\overset{-}\circ\overset{\cdot}{\circ} \cdot \text{X} & \rightarrow & \text{R}\cdot\overset{-}\circ\overset{\cdot}{\circ} & \cdot \text{R}'
\text{S_N2}
\end{align*}
\]

- preferably primary/allylic halide (S_N2)
- other good leaving groups will also work (S_N2)

Example 1:

\[
\begin{align*}
\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow \overset{-}\circ & \rightarrow \\
1. \text{NaH} & & 2. \text{Br} & 1^\circ \\
\text{preferred method}
\end{align*}
\]

Example 2:

\[
\begin{align*}
\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow \overset{-}\circ & \rightarrow \\
1. \text{NaH} \ & & 2. \text{Br} & 2^\circ \ \\
\text{preferred}
\end{align*}
\]

\[
\begin{align*}
\overset{-}\circ\overset{\cdot}{\circ} & \rightarrow \overset{-}\circ & \rightarrow \\
1. \text{NaH} & & 2. \text{Br} & 3^\circ \\
\text{doesn't work} & & \text{Sn2 on a 3° alkyl halide}
\end{align*}
\]

- only do SN2 at a secondary carbon if you can't avoid it, in this case it can be avoided from the "other" direction
3.2 Preparation Methods for Ethers/Epoxides Seen Before (Review)

- Oxymercuration is the best method for Markovnikov addition of H2O across a C=C bond
- EXACTLY analogously, replacing H2O with an alcohol ROH, results in MARKOVNIKOV addition of the alcohol across a C=C bond, which forms an ETHER

4 Reactions of Ethers/Epoxides (Acids and Bases)

4.1 Cleavage of Ethers Using Acids

- Ethers are mainly unreactive, except ONE reaction that we can WORK OUT based on the reactions of alcohols that we just learned, and reaction principles that we know fairly well.......

Breaking C-O bonds in the presence of ACID:
- We just learned how to do that when we covered conversion of an alcohol to an alkyl bromide
- Protonate the oxygen to form a GOOD LEAVING GROUP than can be substituted by SN2 or SN1

![Diagram of cleavage of ethers using acids]

- protonation of oxygen makes a good leaving group, which allows C-O to be broken
- In this case the reaction is substitution, which will proceed via the SN2 OR SN1 mechanism, depending upon the substituents on the alcohol (SN2 on primary, SN1 on secondary and tertiary)

The Corresponding Ether Reaction: Cleavage of C-O bonds and substitution, with Acid
- The overall reaction is essentially the SAME as the one above for alcohols, protonate the oxygen to form a good leaving group, followed by SN1 and/or SN2.

\[
\text{R-O-R'} \xrightarrow{\text{Excess HX/Heat}} \text{R-X + R'-X + H}_2\text{O}
\]

The Mechanism:

![Diagram of the mechanism of cleavage of ethers using acids]

- the substitutions may be by the SN2 or SN1 mechanisms, depending upon whether the protonated oxygen is attached to a 1°, 2° or 3° carbon, as usual

Examples
• protonate the oxygen to create a good leaving group as usual, then……
• SN2 at the 1° carbon happens FIRST, because SN2 is always faster than SN1
• SN1 at the 3° carbon

Example with ONE Equivalent of Acid:

• Note 1 Equivalent of acid, only allows ONE substitution, substitution occurs at the carbon where SN2 is FASTEST, in the example above it is the methyl carbon atom
• Note, H-I is also a strong Bronsted acid, reacts the same way as H-Br
• Iodide is a WEAK Lewis base/nucleophile, but the protonated ether is a STRONG Lewis acid/electrophile

4.2 Formation of Epoxides and trans-Diols
New reagent:

peroxy acid
peroxide
carboxylic acid
meta-chloroperbenzoic acid (MCPBA)
**Mechanism:**

- **CONCERTED mechanism** - all bonds made and broken at the same time - **STEREOCHEMISTRY**!
- no chance for bond rotation "in the middle" - **CONCERTED REACTION** means a **STEREOSPECIFIC** reaction!

**Examples:**

- The reaction is **STEREOSPECIFIC** (because it is concerted)

**Anti-Addition of two -OH across a C=C bond in an alkene:**
- Synthesis of a trans-Diol
- formation of an epoxide followed by **ACID CATALYZED HYDROLYSIS of the epoxide**
- **lysis** = bond breaking, and **hydro** = with water, **hydrolysis** = bond breaking using water

- when $\text{H}_3\text{O}^+$ is a reagent, this means aqueous acid (e.g. HCl or $\text{H}_2\text{SO}_4$ in water)
- the intermediate is an **oxonium ion** (onium means more than usual valence, in this case 3 for oxygen), compare with bromonium etc.,
- the driving force for opening the protonated epoxide (oxonium ion) is provided by release of ring strain energy
- this reaction sequence makes a trans-diol when cis-/trans-isomers are possible, the overall addition of the two -OH is ANTI- in all cases.

**NOTE:** the (R)/(R) and (S)/(S) stereoisomers are formed in the above example (as a pair of enantiomers).
Although cis-/trans-isomers cannot be formed in this case, we still need to distinguish formation of the (R)/(R) and the (S)/(S) pair of enantiomers from a (R)/(S) and (S)/(R) diastereomers because the addition is ANTI- and we can tell in this example.
Recall: 3-membered onium rings are attacked at most substituted carbon
- In these reactions the attacking species is a WEAK nucleophile/Lewis base (Br-, H2O, ROH etc.)

Example:

Example NOT using aqueous acid:
- In the polar solvent methanol the HCl is almost all dissociated, just as in water, and so the acid catalyst is NOT H3O+ but the protonated form of methanol, MeOH2+, the methanol equivalent of H3O+
- NOTE, the solvent here is NOT water, this is not hydrolysis, it is "methanolysis" (bond breaking using methanol)
- Other strong organic acid catalysts (catalysts that can be dissolved in organic solvents) that can be used here (when H3O+ cannot be used) include……

   F3C-C-OH  
   trifluoroacetic acid: TFA

   O

   p-toluene sulfonic acid: TsOH

LET'S TAKE A CLOSER LOOK at the Walden Inversion for protonated epoxide ring-opening
- Let's look at an example with a chiral/asymmetric center

   "leaving group" (S)  
   backside attack

   these pushed "away"

   still wedged and dashed but now "up"

   WALDEN INVERSION

- This is a real Walden inversion, exactly the same as we saw when we first encountered SN2 reactions
NOTE: an SN2 with a Walden inversion doesn't ALWAYS result in a change of configuration $R > S$ or $S > R$, but it often does, and this is shown here to make the point that the Walden inversion doesn't; change what is on the wedged/dashed bonds, but it pushes them "away"

NOW: Let's rotate and reorient the protonated epoxide molecule so that the reaction looks more like a conventional SN2 reaction

- And so we see that the effect of the SN2 type attack on the protonated epoxide is to "push" the two substituents on the carbon that is attacked, "up"

A Related Example:
- You should be able to extrapolate to examples such as this by knowing the mechanism.

- In his case the acid is the reagent, it ADDS to the epoxide, it is not just a catalyst
- Obviously $\text{H}_3\text{O}^+$ can't be used here since we do not have water as the solvent
- when the chloride anion acts as the nucleophile/LB it is doing an SN2 reaction on the carbonatom, the SN2 proceeds with a Walden inversion, the wedged -Me and the dashed -H change from both pointing "down" to both pointing "up", but the wedged bond remains wedged and the dashed bond remains dashed when we look at the reaction from the perspective shown

The regiospecificity associated with attack at the most substituted carbon of a protonated epoxide is not a strong as that for reaction of a strong nucleophile with a non-protonated epoxide, where the least substituted carbon is attacked. For example, primary carbon and secondary carbons in a protonated epoxide are often attacked equally. Therefore, it is only fair to ask students about cases in which there is a tertiary carbon atom, where the positive charge effect is overwhelming and the nucleophile unambiguously attacks the more substituted carbon.
4.3 Base Catalyzed Opening of Epoxides: Strong versus Weak Nucleophiles

Epoxides are WEAK Lewis acids/Electrophiles:
- Weak Lewis acids/Electrophiles generally do not react with WEAK Lewis bases/Nucleophiles
- For an epoxide to react with a weak nucleophile/LB, the epoxide must be PROTONATED!
- Protonation gives the epoxide a positive charge and turns it into a MUCH STRONGER Lewis acid/electrophile
- WEAK Lewis Bases/Nucleophiles attack the MOST SUBSTITUTED CARBON of the epoxide, because that is where the largest partial positive charge is

Examples of WEAK Lewis bases/Nucleophiles are water, neutral alcohols etc.

Compare Reaction with STRONG Lewis Bases/Nucleophiles:
- Epoxides will react with STRONG Lewis bases/Nucleophiles DIRECTLY (no need for protonation)
- You already KNEW THIS, we have seen these reactions previously

<table>
<thead>
<tr>
<th>Epoxide - WEAK LA/Electrophile</th>
<th>PROTONATED Epoxide - STRONG LA/Electrophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC\equiv C\textsuperscript{+}</td>
<td>Weakest Nuc/LB attacks the LEAST substituted carbon when the oxygen is not protonated</td>
</tr>
<tr>
<td>Grignard</td>
<td>WEAK Nuc/LB attacks the MOST substituted carbon when the oxygen is protonated</td>
</tr>
</tbody>
</table>

Strong nucleophiles have a negative charge, such as the acetylide anion, the Grignard reagent etc.
- The reaction of a strong nucleophile with an epoxide is essentially an SN2 reaction, and the nucleophile attacks the LEAST SUBSTITUTED carbon of the epoxide for steric reasons, just like any SN2 reaction
- WHICH CARBON IS ATTACKED (MOST or LEAST Substituted) DEPENDS UPON WHETHER THE EPOXIDE IS PROTONATED OR NOT!

Base Catalyzed Hydrolysis of Epoxides:
- recall, hydrolysis means breaking bonds using water, here, bonds in the epoxide ring)
- Catalysis using BASE means means reaction of the epoxide with STRONG LB/Nucleophile

- The STRONG Lewis Base/Nucelophile attacks the LEAST SUBSTITUTED carbon of the epoxide, because the epoxide is not protonated
Example with different strong LB/nucleophile:

- the STRONG LB/nucleophile methoxide attacks the least substituted side for steric reasons (seen previously!)
- RECALL: a different product (structural/REGIO isomer) is formed in the corresponding from acid catalyzed reaction!

In THIS EXAMPLE, the ACID and BASE catalyzed reactions give DIFFERENT STRUCTURAL ISOMERS, the reactions are REGIOSPECIFIC
- an abbreviated mechanism is shown here, you can solve problems using an ALGORITHMIC APPROACH, where if you follow the correct algorithm (the mechanism in this context) you MUST get the correct answer
- OR, you develop HEURISTIC PROBLEM solving skills that allow you to “jump” to the answer without writing out the entire mechanism, this is much faster and the way that “real” chemists work out the products of reactions
- the more problems you solve the better developed your heuristic problem solving becomes

4.4 Formation of cis-Diols ; TWO Sets of Reagents/Conditions
- We already saw how to add two -OH substituents across a C=C bond to give a TRANS-DIOL, via acid catalyzed hydration of an epoxide, which is usually made by reacting the alkene with a perepoxide such as MCPBA

We can also make a CIS-DIOL from an alkene using a different kind of reaction:

The mechanisms:
- These are BOTH CONCERTED REACTIONS in the first step, the reactions are therefore STEREOSELECTIVIC, and in this case, SYN-ADDITION
- Although are obviously a bit complex, the important part is that the MnO₄⁻ ion and the OsO₄ both start the reaction by adding to both ends of the alkene at the same side, which is why a cis-diol must be formed
- note that in mechanisms involving metal atoms, the metal has enough electrons and empty orbitals to give and take electrons on its own, almost at will (almost like cheating to an organic chemist!!)
CONCERTED REACTION:
• In the first step, the reaction is concerted, therefore STEREOSPECIFIC, and in this case, SYN-ADDITION

Why do we need TWO reagents?
KMnO₄ – is inexpensive, used for large scale reactions, variable yields
OsO₄ – is expensive, but extremely toxic! good yields, is catalytic, used in small scale syntheses
This illustrates the principle that in general there will always be more than one reagent to accomplish any transformation even if we only discuss one in this course

Example REACTIONS:

achiral \[ \begin{array}{c}
\text{H}_3C \\
\text{C} = \text{C} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} \] \quad OsO₄ / H₂O₂ \quad \begin{array}{c}
\text{H}_3C \\
\text{C} \quad \text{C} \quad \text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}
\] \quad \text{achiral meso}

achiral \[ \begin{array}{c}
\text{H}_3C \\
\text{C} = \text{C} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} \] \quad OsO₄ / H₂O₂ \quad \begin{array}{c}
\text{H}_3C \\
\text{C} \quad \text{C} \quad \text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}
\] \quad \text{achiral meso} syn-addition

achiral \[ \begin{array}{c}
\text{H}_3C \\
\text{C} = \text{C} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array} \] \quad OsO₄ / H₂O₂ \quad \begin{array}{c}
\text{H}_3C \\
\text{C} \quad \text{C} \quad \text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}
\] \quad \text{achiral meso} syn-addition

\text{syn-addition} (S,S) and (R,R) products formed racemic mixture
Compare:

4.5 Examples of Ether Reactions in Synthesis

Example 1:

- in this case the C-O bond that we are tempted to make to construct the ether (bond A) is not as good as bond B, since to make bond A we would need to do an SN2 reaction on a secondary carbon atom
- in ether synthesis you need to select the BEST C-O bond to make in an SN2 reaction

Example 2:

- can't make required C-C bond in last step, need to do a FGI that will allow the C-C bond to be made
- convert (backwards) into an alkyne, NOW can make the C-C bond
5 Summary of Reactions

Do NOT start studying by trying to memorize the reactions here!

Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on eth reagents/conditions, and so that you can learn and practice solving reaction problems. Use this list AFTER you have worked all of the problems, and just before an exam. By then you will have learned a lot of the reagents/conditions just by using them and you will only have to memorize what you haven't learned yet. Then do the following:

• Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if COMPLETELY correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
• Keep coming back to this list and so the same thing only for those reactions you circled N, until all are circled Y.

Knowing the reagents/conditions on this page is INSUFFICIENT to do well on an exam since you will ALSO need to recognize how to use and solve reaction problems in different contexts, this page ONLY helps you to learn the reagents/conditions that you have not YET learned by working problems.