Synthesis and Retrosynthesis — Putting Reactions Together

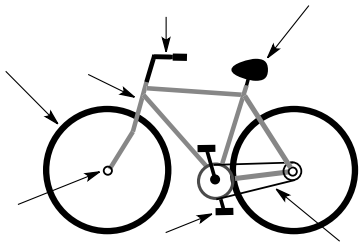
• A large part of organic chemistry involves building more complex molecules from smaller ones using a designed **sequence** of reactions, i.e. chemical synthesis. Especially in more complex cases, synthetic problems are often best solved **backwards** in a process known as retrosynthetic analysis.

But First……..

How to Ride a Bicycle

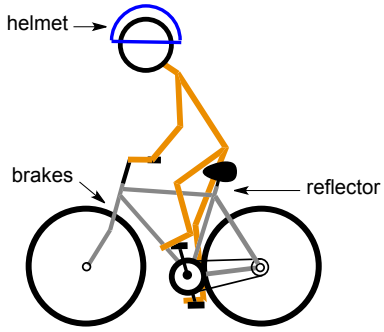
1.1 Parts of the bicycle

• It is important to understand bicycle nomenclature.
• We will not cover IUPAC bicycle nomenclature in this case.



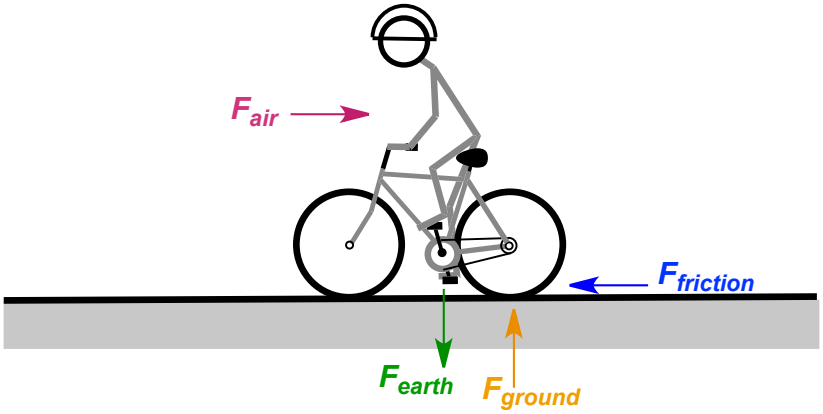
1.2 Bicycle Safety

Question? Which of the following are essential **safety items** when riding a bicycle?



1.3 Physics of Bicycle Riding

• You **must** understand the relevant forces involved, without this understanding you cannot ride a bicycle!

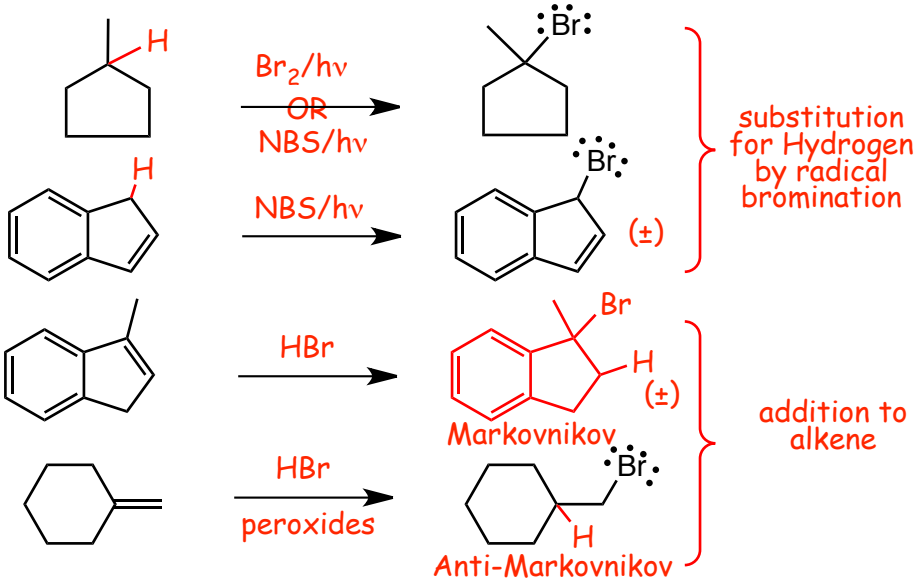


• Review sessions before each exam.
• Chad's Reviews on Bicycle Riding.
• Kahn Academy lectures on Bicycle riding.

1. Summary of First Semester Reactions Useful in Synthesis

1.1 Synthesis of Halides, Reactions that make Bromides

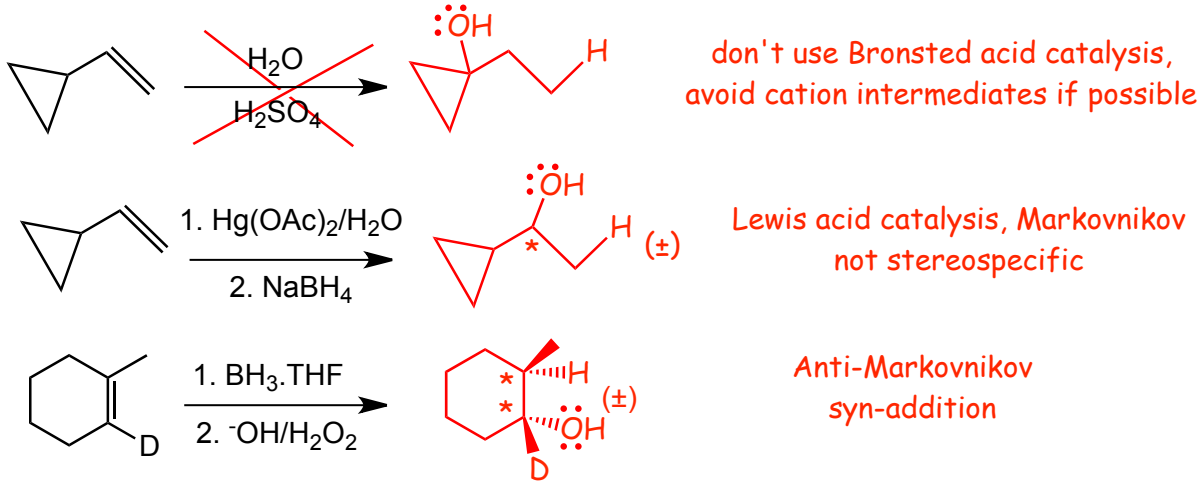
• Bromides are very useful functional groups that do many reactions because they are good leaving groups.



• These all **convert either alkanes** or **alkenes into alkyl bromides.**
• They convert one functional group into another one, t**hey are functional group interconversions (FGI).**

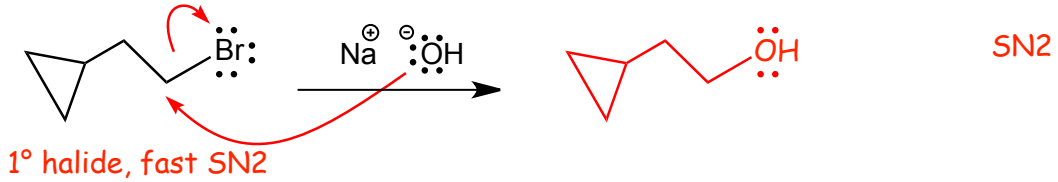
1.2 Synthesis of Alcohols

We know several such reactions that are **additions to alkenes:**



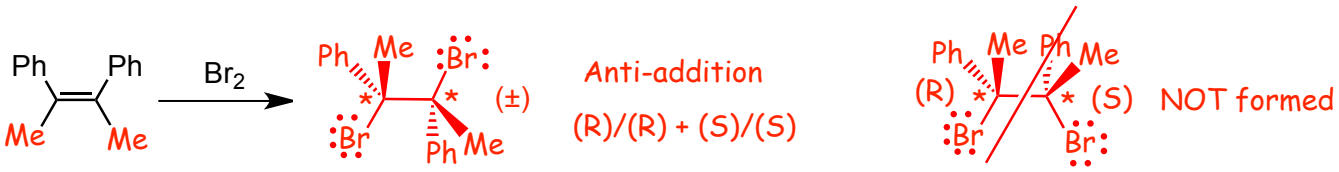
• In the context of synthesis we try to avoid reactions that involve carbocation intermediates, **therefore**, to do Markovnikov addition of water to a C=C bond we will use the Lewis acid catalyzed method with mercuric acetate ($Hg(OAc_2)$) rather than Bronsted acid catalysis using, for example, H_2SO_4.
• These reactions are functional group interconversions (**FGI**), they convert **alkenes into alcohols**.

Don't forget about the SN2 reaction we know that can be an **FGI** that converts a bromide into an alcohol:



1.3 Synthesis of Dibromides

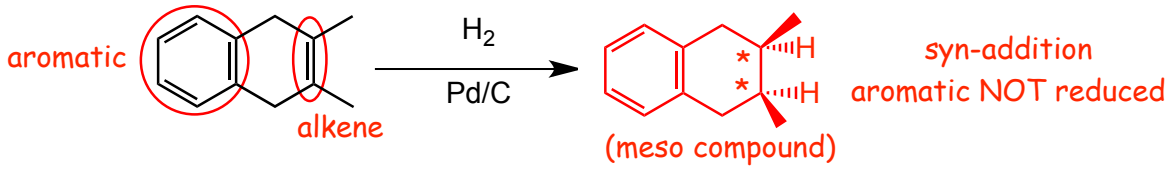
• Another addition reaction to an alkene that is required for further synthesis of alkynes (see later):



• **Note**: This addition is **anti-**, even though there is no possibility of *cis-*/*trans*-isomers in this reaction we still **need the wedged/dashed bonds** because the **product has two chiral centers**, and thus stereoisomers can be formed, our answer **must** specify these stereoisomers.
• This particular reaction forms a pair of (R)/(R) and (S)/(S) enantiomers, and we need to distinguish these from the (R)/(S) diastereomer (the meso compound) that is **not** formed.
• This reaction is an **FGI**, it converts an **alkene** into a **dibromide**.

1.4 Synthesis of Alkanes

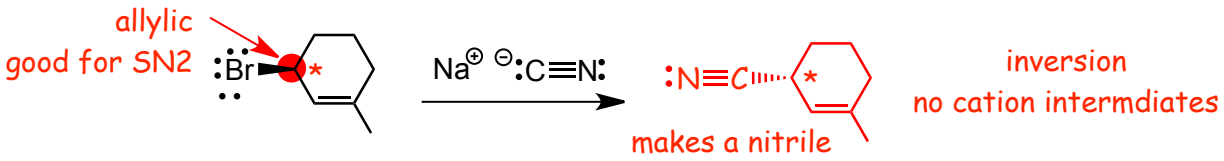
• This is more useful than it looks!



• Other catalysts you may to perform this reaction see include Raney Ni or Pt
• This reaction converts an alkene into an alkane (**FGI**).

1.5 SN2 Reactions

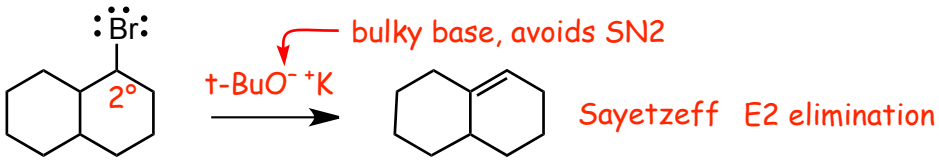
• SN2 reactions are extremely useful in many reactions that require formation of a new bond, especially with alkyl bromides and other halides, structures with good leaving groups that can be substituted.
Example:



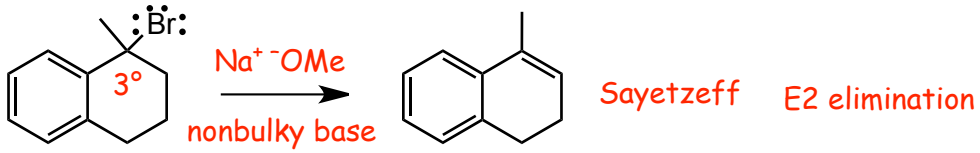
You will need to be able to use these reactions forwards and backwards (we will practice this).
• SN2 reactions are so useful that they can be used to many kinds of FGI (the example above converts an alkyl bromide into a nitrile). They can also be used to make carbon-carbon bonds, i.e. to make larger molecules from smaller ones. This will be discussed in more detail later.

1.6 Synthesis of Alkenes, Eliminations of Alkyl Bromides Using E2 (Strong Bases)

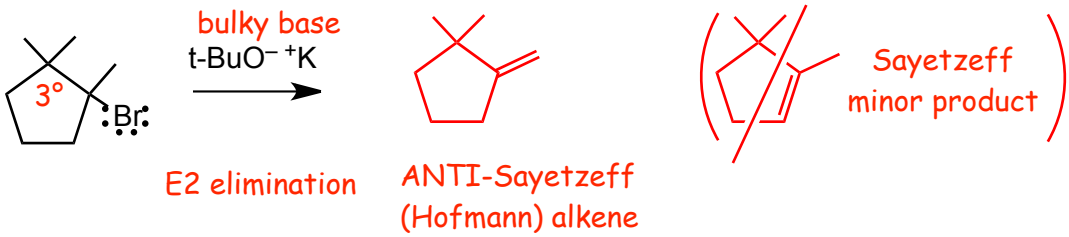
• As previously discussed, alkenes are formed in elimination reactions in a FGI from alkyl bromides in a **FGI**.
• In a synthesis context we try to avoid reactions that involve carbocation rearrangements if at all possible. Therefore, we use **E2 elimination** rather than E1 wherever possible to **avoid** carbocation intermediates.



• Use a **strong bulky** base with a **2° halide** (to avoid SN2) to form the **Saytzeff** (or **Zatisev**, spell it any way you like), i.e. the more substituted alkene product.



• SN2 is not possible for a 3° bromide, therefore use a **non-bulky** base with a **3° halide** to get the **Saytzeff/Zaitsev** (spell this name anyway you like) alkene product.



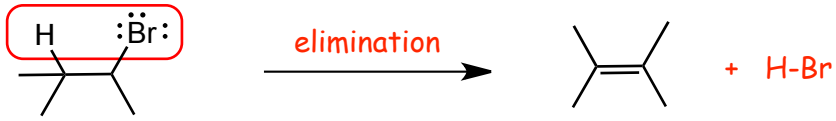
• Use a **bulky** base with a **3° halide** to get the **anti-Saytzeff** (also called the **Hofmann**) least substituted alkene product.

2. Synthesis of Alkenes from Alcohols

2.1 Water as a Leaving Group: Important new Concept!

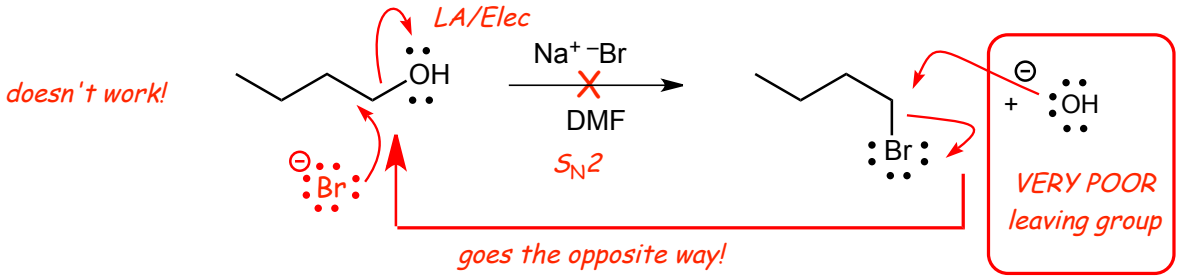
• In principle, an alkene can be formed by elimination reactions of not only alkyl halides:

Schematically



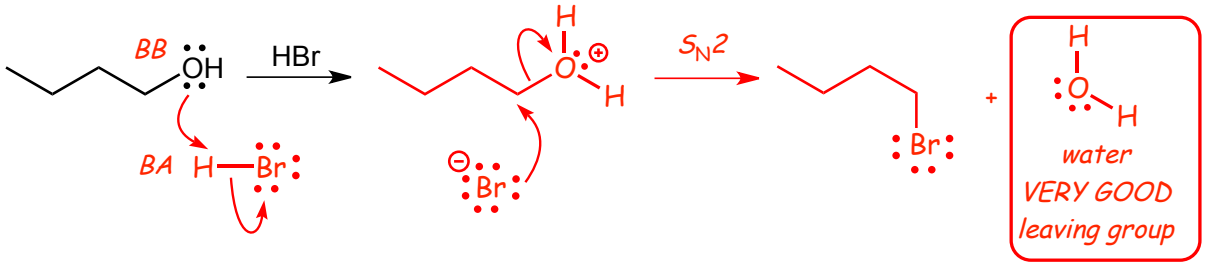
By Analogy

• **Water** is a potential **good leaving group** in **any substitution or elimination reaction.**
• In fact, **water is an excellent leaving group**
• **Good leaving groups** are **stable anions**, but **water** isn't even an anion, it is a **stable neutral molecules.**
Stable neutral molecules are often even better leaving groups than stable anions.
• However, consider the following, let's try to do an SN2 reaction on an alcohol:



• This reaction doesn't work! In fact, goes in reverse $^{-}$OH will substitute for X^{-} (think about a standard SN2 reaction that has **-OH as the nucleophile** and **Br- as the Leaving group**), this reaction has the **opposite**!
• **$^{-}$OH is too poor a leaving group**, we need to make a better leaving group.

Consider the following reaction instead:

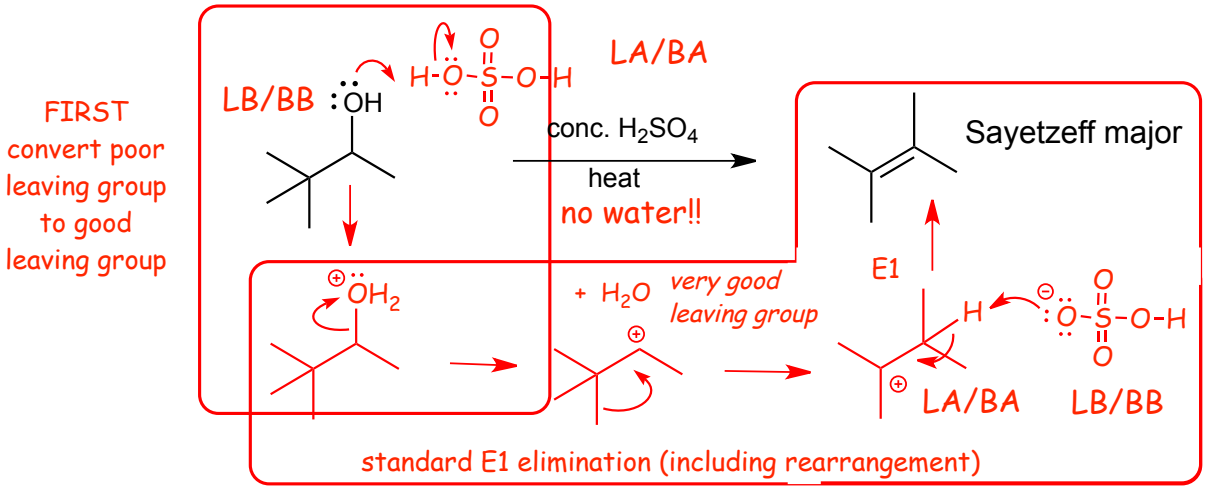


• The first step is a standard Bronsted acid/base reaction, with H-Br as the strong Bronsted acid
• **Now,** we have a very good potential leaving group, H_2O, the next step is standard **SN2 and it works well,** even though the bromide anion is a poor nucleophile.
• We will return to SN2 reactions with protonated alcohols later, for now we are more interested in eliminations.
• **The concept of protonating oxygen to turn it from a poor leaving group into a good leaving group is critical, we will see it again, multiple times!**

2.1 Water as a Leaving Group: Elimination of Alcohols (E1 and E2)

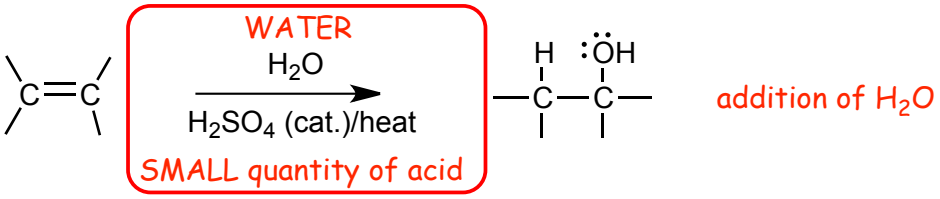
• **Alkenes** can also be made **from alcohols** in a **FGI** that is an **elimination reaction**, if we **protonate the oxygen** first to convert it **from a poor leaving group** into a **good leaving group.**
• Water is then a leaving group in a standard E1 and/or E2 mechanisms after that.
• In this case we will not be able to avoid E1 reactions, but the alcohol to alkene FGI is so useful that we use this reaction anyway.

Example Problem: Give the mechanism for the following elimination reaction.



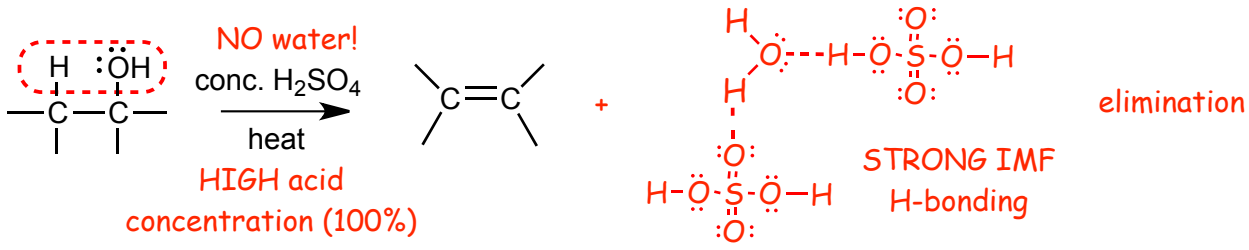
• Sulfuric acid protonates the -OH in a Bronsted acid/base reaction to convert the -OH into a good leaving group
• Water is such a good leaving group that the elimination is almost always **E1 with 3° and 2° alcohols.**
• Water is such a good leaving group that E1 is occurs even at a secondary carbon to make a secondary cation
• **Carbocation intermediates mean rearrangements!** (that hasn't changed, of course).
• The conjugate base anion of the sulfuric acid, the bisulfate anion, is the most likely base to deprotonate the carbocation intermediate, thus regenerating the acid catalyst.
• The alkene formed will be the Sayetzeff (Zaitsev), there are no stereochemical constraints in the E1 mechanism and the most stable alkene will form.

Why does the alcohol make an alkene + water when previously we learned that water + alkene gives an alcohol?
• **This** is what we learned previously:



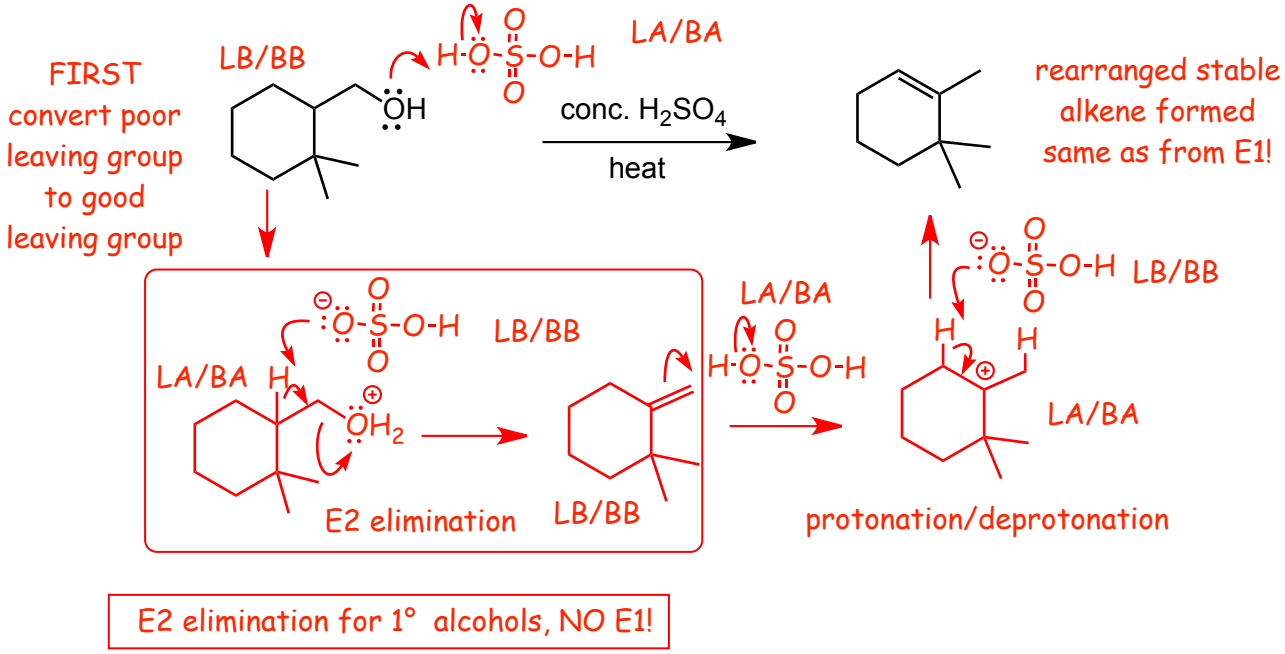
• The addition reaction "goes" because the weaker pi-bond is converted into a stronger sigma-bond.
• The reagents/conditions have a **larger quantity of water** and a **small quantity of sulfuric acid.**

• **This** is what we now learned:



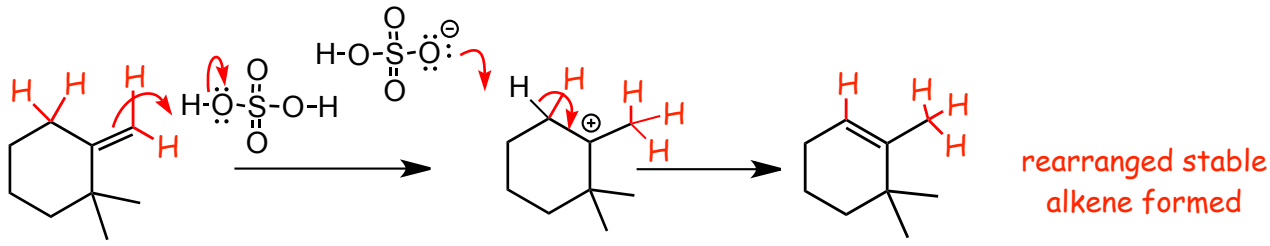
• The reagents have **zero water** and a **high concentration of sulfuric acid** (opposite of previous reaction)
• The elimination reaction "goes" because the water is highly solvated in the concentrated sulfuric acid
• Note a special kind of **so0lvent effect** here! In an aqueous medium, acid catalyzes water **addition** to the alkene to make an alcohol. In conc. sulfuric acid medium, the acid helps to **remove** water from an alcohol to make an alkene (the sulfuric acid **dehydrates** the alcohol).
• Alternate reagents and conditions are H_2SO_4/P_2O_5, and others….

Example: Primary (1°) Alcohols: E2 elimination (with rearrangement):



• With a **primary alcohol** the **mechanism must be E2, formation of a primary carbocation can't occur.**
• **But**, even though the elimination does not involve a rearrangement, the final alkene product is usually the same one that would have been formed via an E1 reaction due to protonation followed by deprotonation (isomerization) of the primary alkene into a final more stable product.

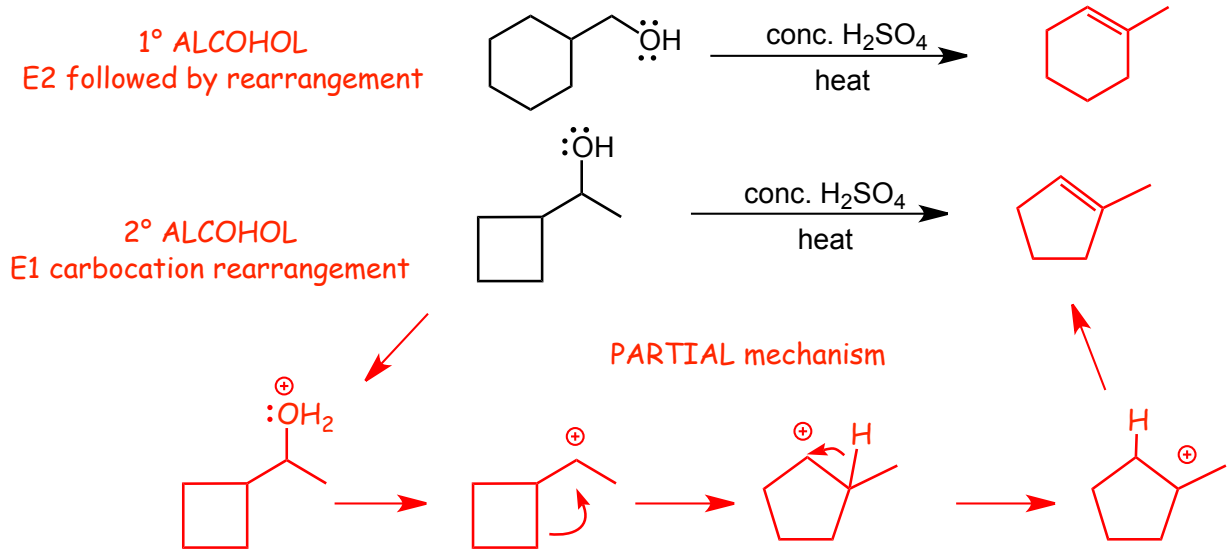
Let's look again at the second part of the mechanism, the rearrangement:



• This effectively converts a less stable less substituted alkene into a more stable more substituted alkene, this is why this **isomerization** reaction "goes".
• To solve the mechanism problem, **add some hydrogen atoms back to the line-angle structure**, the H atoms tell you exactly where you need to protonate and deprotonate.
• In the presence of acid, **protonation** will occur first, followed by deprotonation.
• A less **rearrangement: A** less stable alkene is converted into a more substituted/more stable alkene.
• This is a **rearrangement**, the acid is only the catalyst (no atoms are overall added or subtracted).
• In a strong acid, especially with heat, protonation and deprotonation can **often** occur, and if this can result in formation of a more stable alkene, then the more stable alkene will form, and you should always include this step when doing acid catalyzed dehydrations of alcohols.

The final product is the same most substituted, whether the mechanism is E1 followed by cation rearrangement (2° and 3° alcohols) or E2 followed by protonation/deprotonation (1° alcohols)

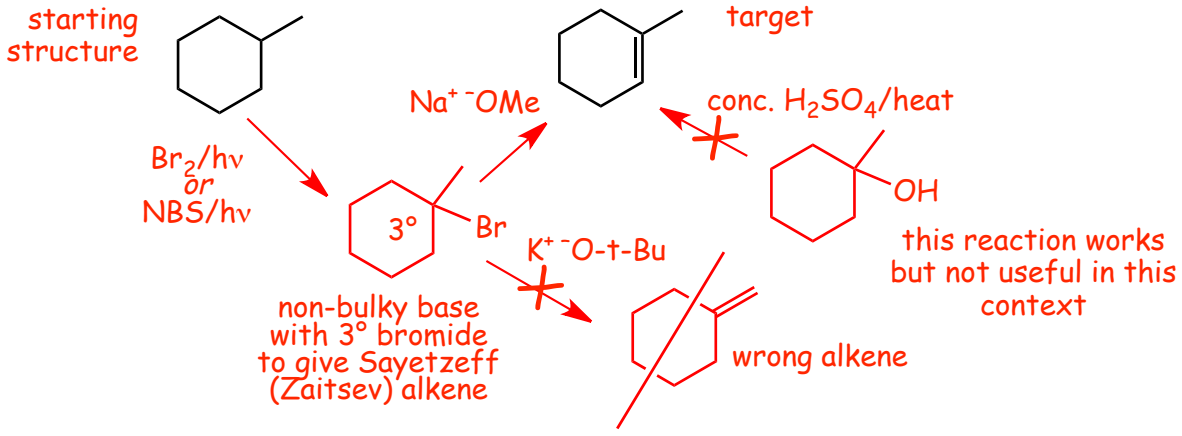
Examples:



3. Multi-Step Synthesis

• Multi-step chemical synthesis involves building larger or more complex molecules from smaller ones using a designed **series** of reactions.
• This involves putting a series of reactions together **in sequence** (in reaction multiple steps).
• Here we will look at some simple examples.
• To do these problems you need to **know the reactions**, and **practice**, practice, practice, practice.....

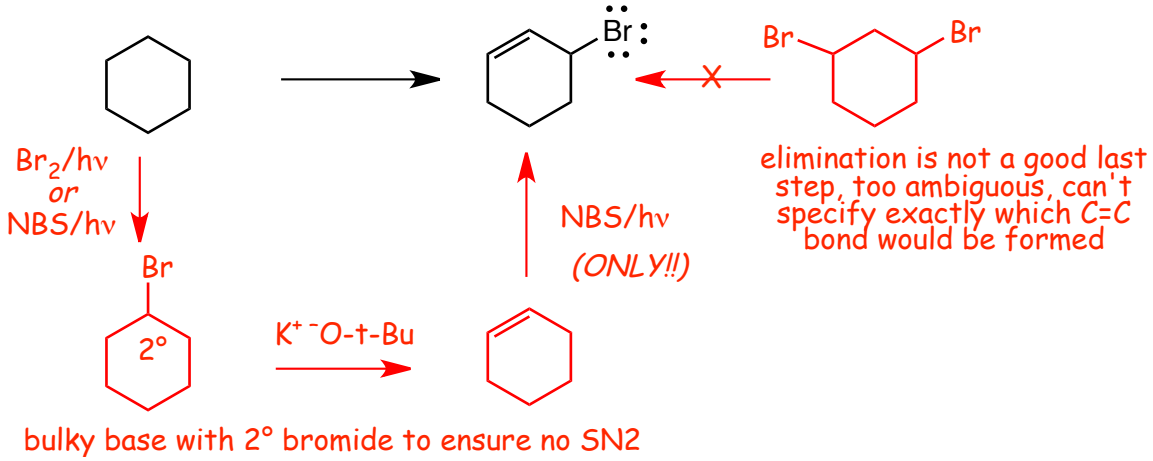
Example Problem 1: Synthesize the molecule on the right from the one on the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step.



• The **first reaction working backwards** must have an alkene as the product.

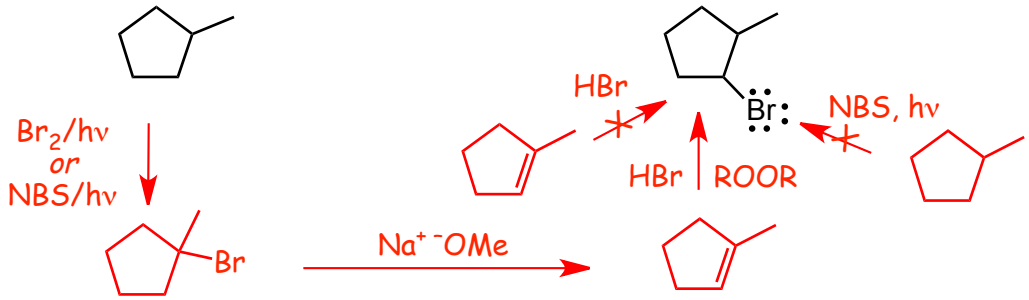
• Alkenes can be formed by elimination from either a halide or an alcohol, but a halide works better here.
• Note: the first bromination is of an alkane, **either** Br_2/light or NBS/light can be used, if we were brominating in an allylic position only NBS/light could have been used.
• Then E2 elimination, which is the standard way to make an alkene avoiding cation intermediates.

Example Problem 2: Synthesize the molecule on the right from the one on the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step.



• The first bromination is of an alkane, **either** Br_2/light or NBS/light can be used
• Br_2/light **cannot** be used for the last bromination of the alkene, we need to avoid Br_2 addition to the C=C bond
• it may be a good idea to always use NBS and for all radical brominations then you don't have to remember which bromination reagent works best in which case, this one works in all cases.
• E2 with a **bulky base**, which is the standard way to avoid SN2 to make an alkene, then brominate again in the allylic position (same reagents).
• Formation of an alkene in the last step is **not** a good idea, there is more than one leaving group, double eliminations may occur, or the C=C bond may be formed in the wrong place with respect to the other bromine.

Example Problem 3:



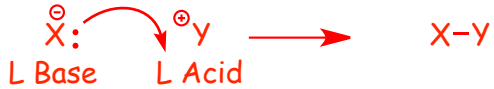
• We need to add Br at a position that is not possible by direct bromination, the obvious way is by addition of HBr to an alkene Anti-Markovnikov, so first, make an alkene as usual.
• We have two ways to make an alcohol, SN2 or water addition to an alkene, the best thing to "do" with the starting alcohol is make an alkene, which decides for us which alcohol synthesis method to use.

4 Retrosynthetic Analysis : The Synthon

The most important concept from First Semester Organic Chemistry:

Lewis Acid/Base reactions explains bond **formation.**

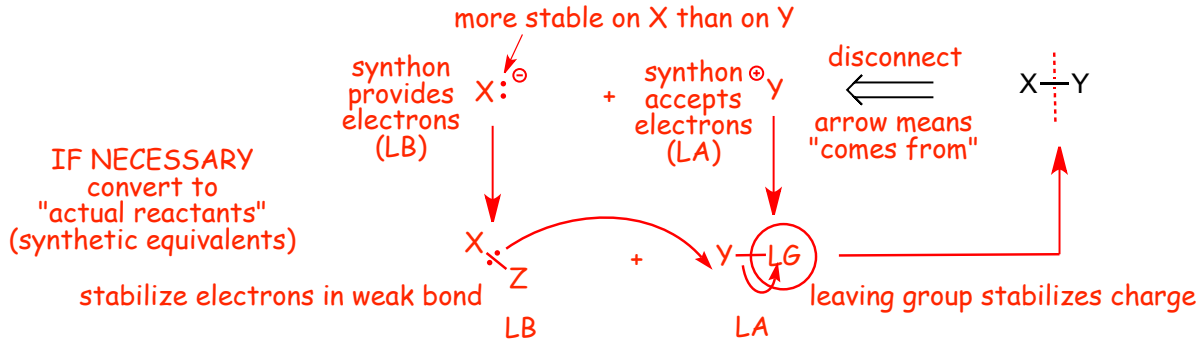
• The Lewis Base **provides** the electrons and the Lewis Acid **accepts** the electrons to make the bond:



• Lewis acid base theory is extremely useful in **predicting** the products of organic reactions.
• Although it works as a fundamental theory, we will find that occasionally we have to just "know" some reagents, the same will apply for reaction in reverse, next…….

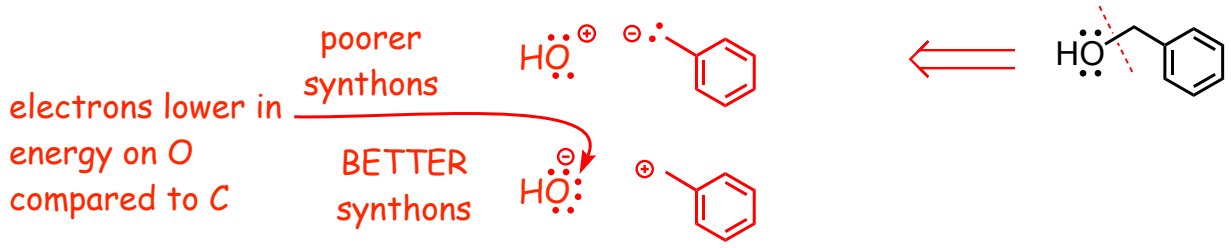
• **Lewis acid/base theory** helps us to understand **what the product of a reaction will be.**
• Lewis acid/base theory helps us to generate the product of a reaction when we are provided with the reactants.

New concept: The synthon, explains bond formation from **reactants, Lewis acid/base theory in reverse.**
• **Synthon theory** helps us to understand **where reaction products come from** (it is the reverse of Lewis acid/base theory).
• **Synthon** theory helps us to figure out **what Lewis acid/base reaction to do** to form a bond.
• Retrosynthetic analysis helps us to generate the reactants when we are provided with the product.

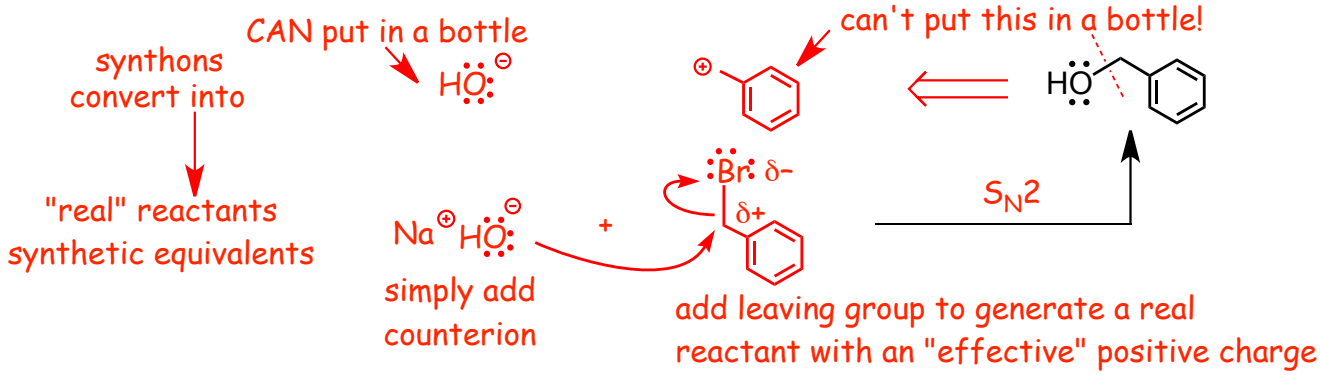


• Synthons indicate where the electrons come from to make the bond, they help us to identify which fragment is the Lewis base and which fragment is the Lewis acid do make the desired bond.
• Synthons **don't exist**, they are the products of a **thought experiment**, they need to be converted into "real" reactants, or synthetic equivalents.
• One synthon must carry the electron pair (LB), the other accepts the electrons to make the bond (LA).
• Somewhat counter-intuitive is that the synthon with the electrons (LB) is usually the one where the **electrons would be most stable** (lowest in energy).
• The idea here is that the synthon that carries the electrons would be most useful if it could be kept "in a bottle", if the electron pair is very high in energy then that synthon may be impossible to make and the retrosynthetic strategy would fail.
• Very often, even putting the electrons where they are most stable results in one or more of the synthons being so unstable, and they have to be actually used in the form of "synthetic equivalents" or "actual reagents", these are stable chemicals that do the same thing as the synthons.

Example 1:
• Disconnect the O-C bond and "put" the electrons on the synthon where they would be most "temporarily" stable:



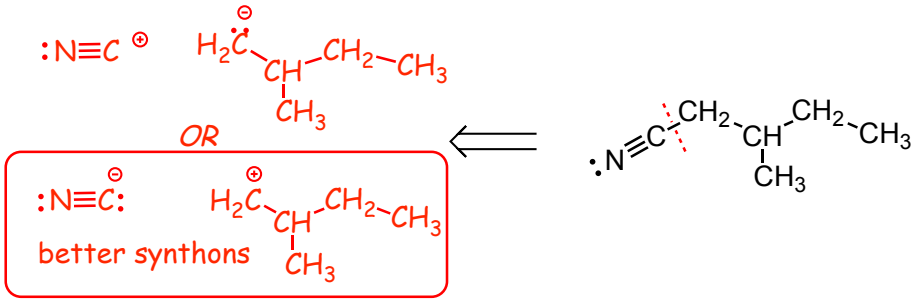
• **Next**, ask the following question about each synthon "can it be put into a bottle (with an appropriate counter ion)?", if the answer is yes then the synthon is also the reagent, if the answer is no, then we need to convert the synthon into an actual useable reagent, i.e. a synthetic equivalent.
• Reacting the synthetic equivalents makes the required alcohol.



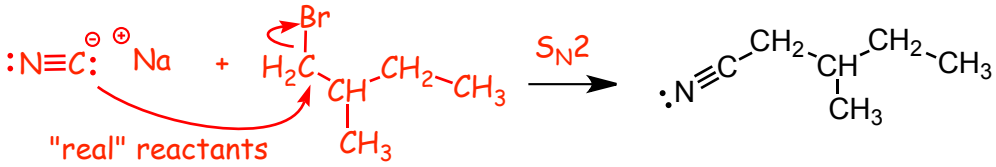
Example 2:

• Disconnect the indicated C-C bond.

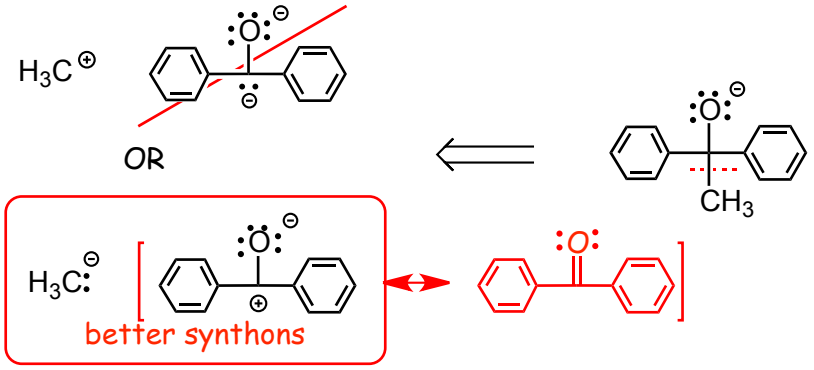
• One of the carbons must carry the electron pair, one the leaving group, which is best?



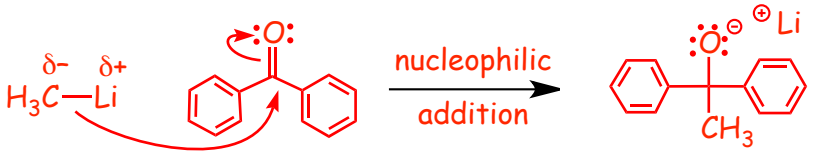
• Convert to "real" reactants (synthetic equivalents):



Example 3: Disconnect the indicated bond (this is a reaction you have not yet seen).



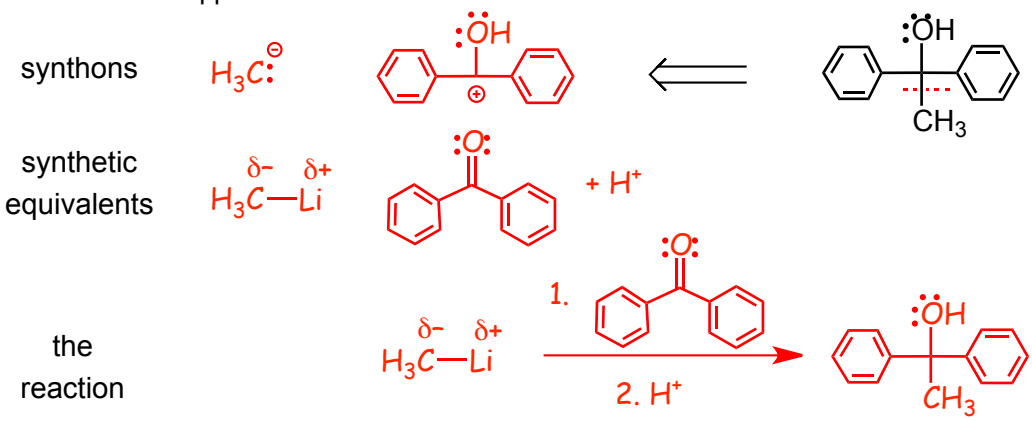
• Convert to "real" reactants (synthetic equivalents):



• In this case the "leaving group" is the C-O π-bond.

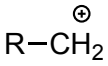
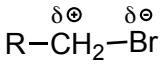
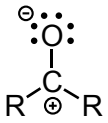
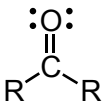
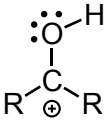
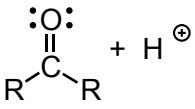
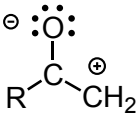
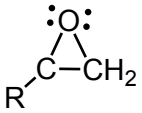
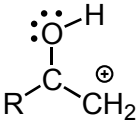
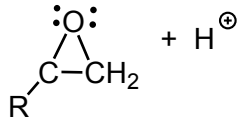
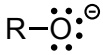
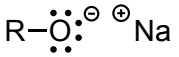
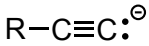
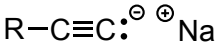
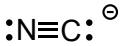
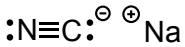
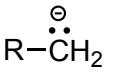
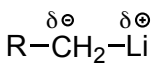
• Later we will see why the metal used this time is Lithium and not sodium, and why we draw a bond between the carbon and the lithium.

Example 4: a more realistic application



• Synthons and **retrosynthetic strategy** is an advanced organic chemistry concept.
• However, we **don't** analyze every forward reaction in terms of Lewis acid/base, we don't have time, we just **know the reactions forwards.**
• Similarly, we **won't** analyze every reverse reaction in terms of synthons, we won't have time, we **will** just **know the reactions backwards.**
• It sometimes takes experience and practice to recognize how to convert the synthons into synthetic equivalents, so you should expect to find some of these difficult to do at first.
• We will return to synthons as we work our way through the semester.

Summary of Synthetic Equivalents
• The hardest part of retrosynthetic analysis using synthons is knowing exactly which synthons are stable and are already synthetic equivalents, and which need to be "translated" into synthetic equivalents, A summary of the ones we have come across so far is given below.

positive synthon	**synthetic equivalents**	
		alkyl halide
		aldehyde/ketone
		aldehyde/ketone + H_3O^+
		epoxide
		epoxide + H_3O^+
negative synthon	**synthetic equivalents**	
		
		
		
		

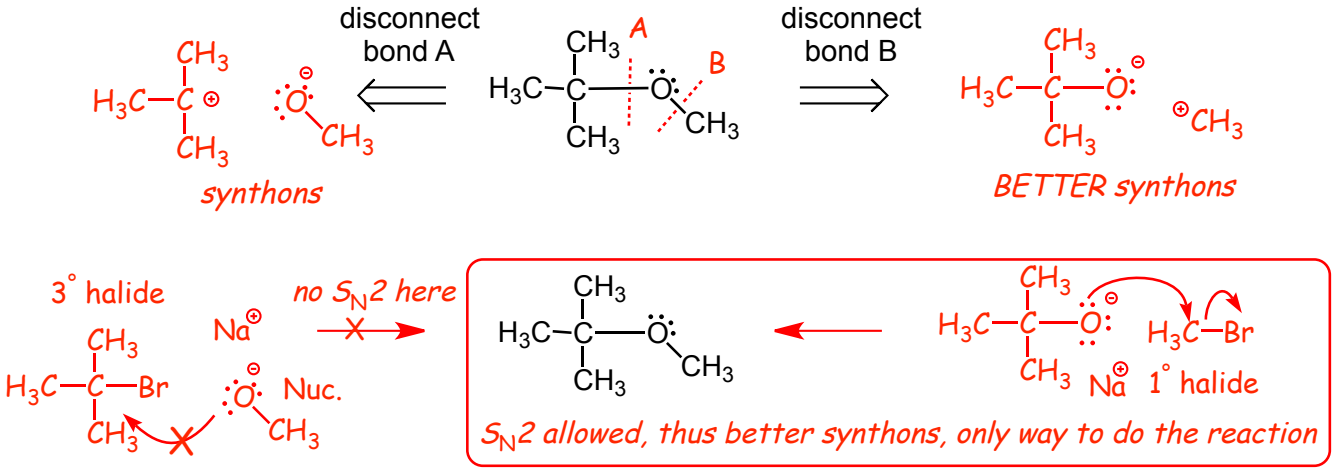
• Do **not** try to memorize these, instead, learn them by using them, refer to this table when solving synthesis problems so that you learn by using!
• Later we will find out why sp3 hybridized carbons as negative synthons require a lithium metal rather than a sodium metal counter ion and why we draw a covalent bond in this case.
• We will return to these synthons and retrosynthetic analysis throughout the course, repeated exposure will also facilitate learning.

5. SN2 Reactions Revisited : Practice Doing Reactions in Reverse

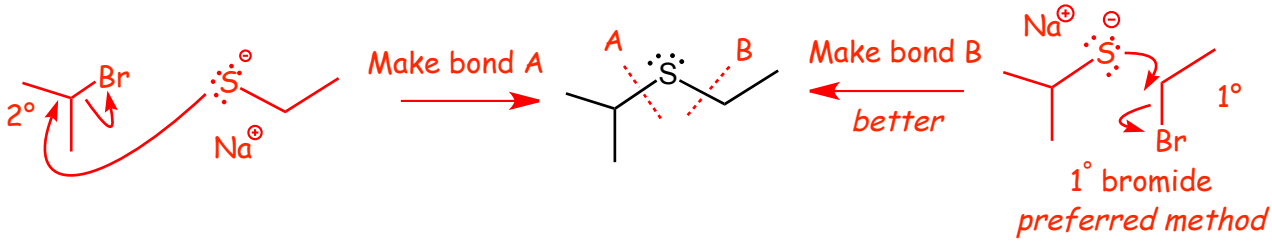
How would you make the following molecules using the S_N2 reaction?

• The emphasis is on recognizing which bond you can make, and identifying the synthons and thus reactants...

Example 1:

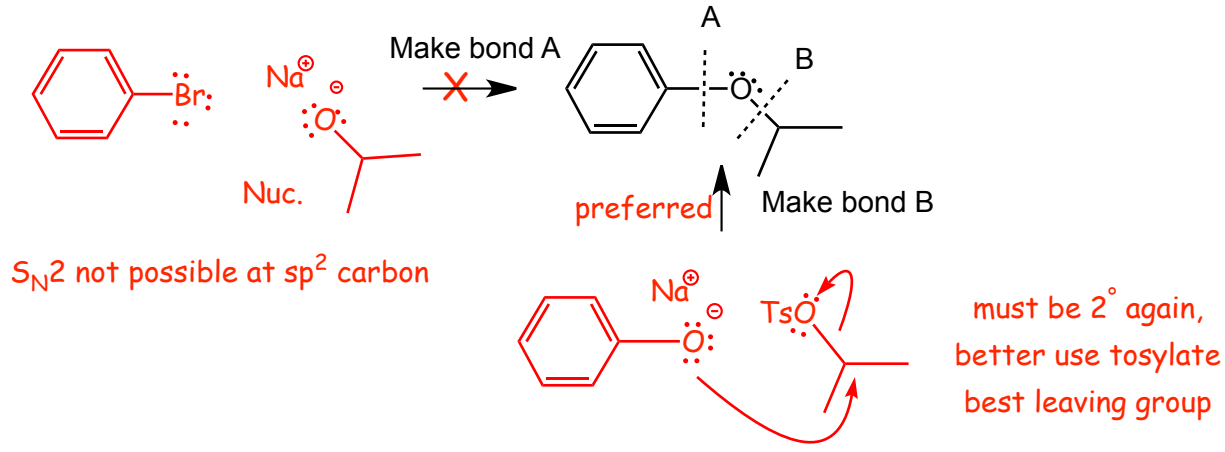


Example 2:

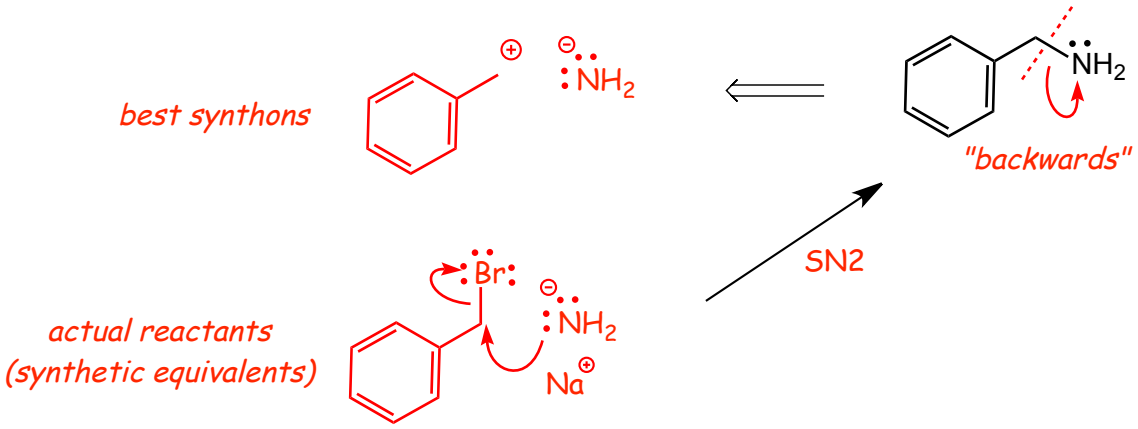


• It is not impossible to do an SN2 reaction at a secondary (2°) carbon, but is there is a choice then always choose the primary (1°) carbon.

Example 3:

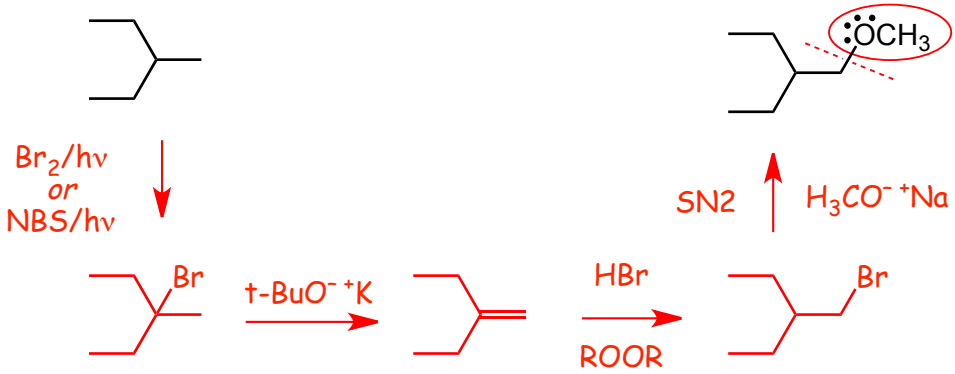


Example 4:



• You can "make up" your own SN2 reaction, just look for obvious bond to make, do reaction "backwards" to get the synthons and reactants.

An Example in Synthesis:

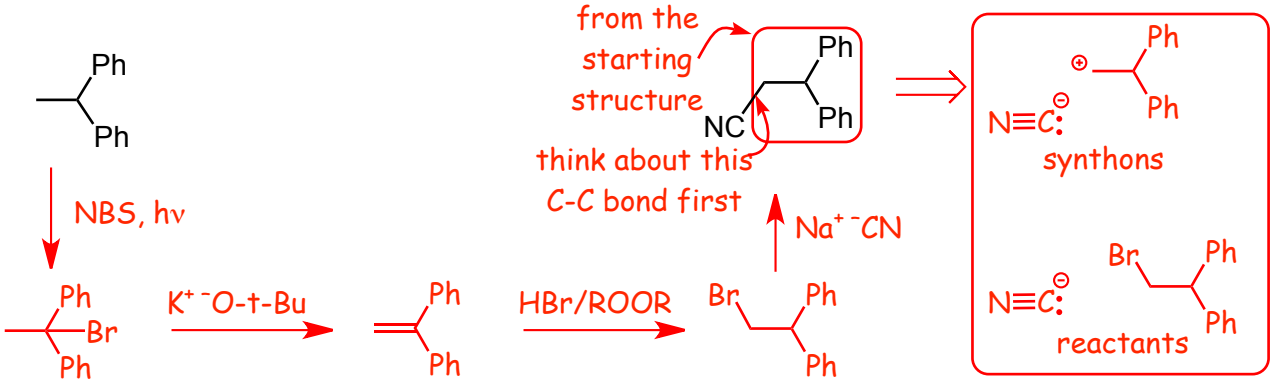


• We can't add -OMe to an alkane, so we need to a **leaving** group at that carbon.
• An SN2 reaction works well to make the required C-O bond.
• Going backwards from there, back to the starting structure, involves simple reactions we have used previously.

6. Putting it all Together : A Retrosynthesis Strategy

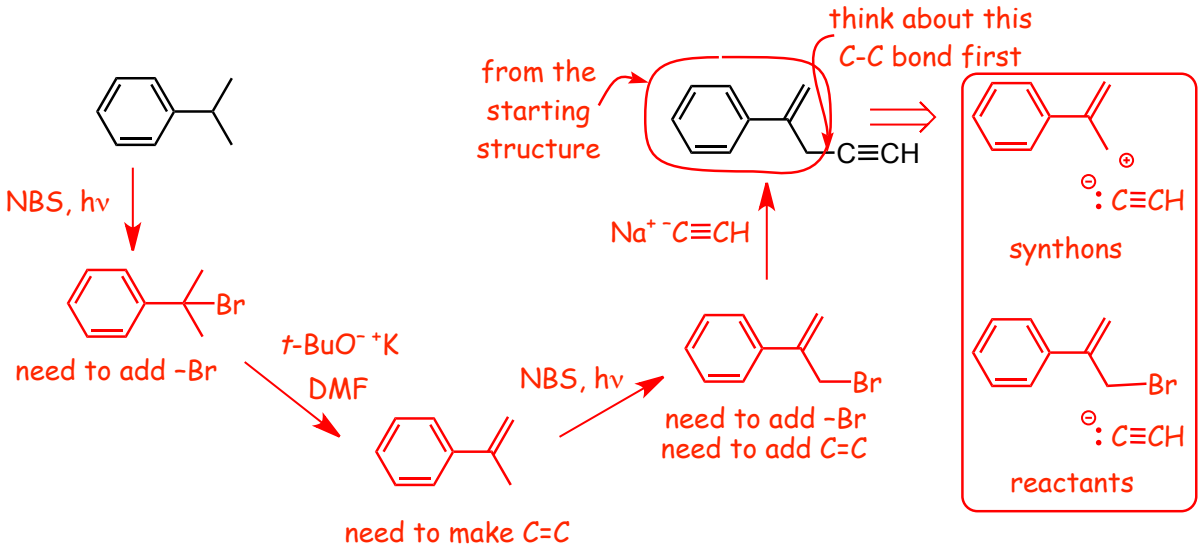
• Look for the reactant "in" the target molecule.
• Identify the required **Functional Group Interconversions** (FGI) and C–C (C–X) bond making reactions.
• Generally, try to make C–C (C–X) bonds first, or do an FGI that will allow you to do so.
• If your first route doesn't work, go back a step and change the approach.
• **Don't** look at the starting material (at first), it *doesn't help you*!

Example 1: Synthesize the (target) molecule on the right from the starting molecule the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step. Do not show any mechanisms or transient intermediates.



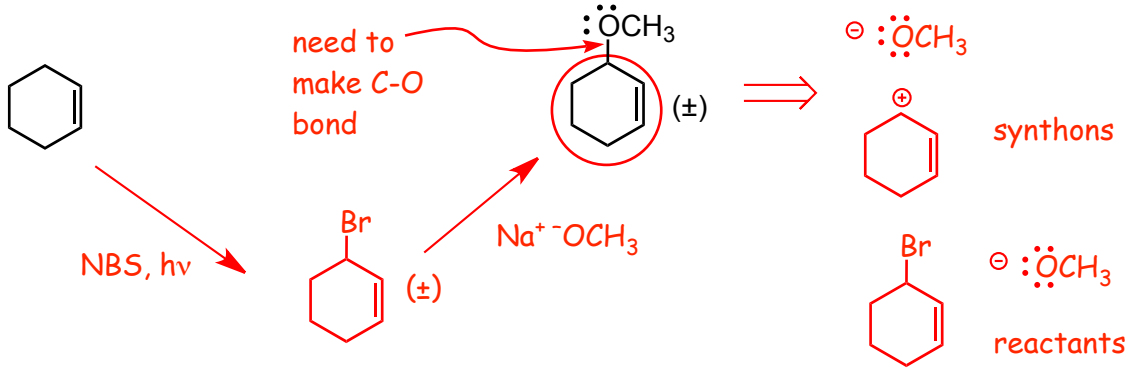
• Look for the starting structure in the target molecule.
• Identify the new C-C bond that has to be made, do this first (going backwards, step 4).

Example 2:

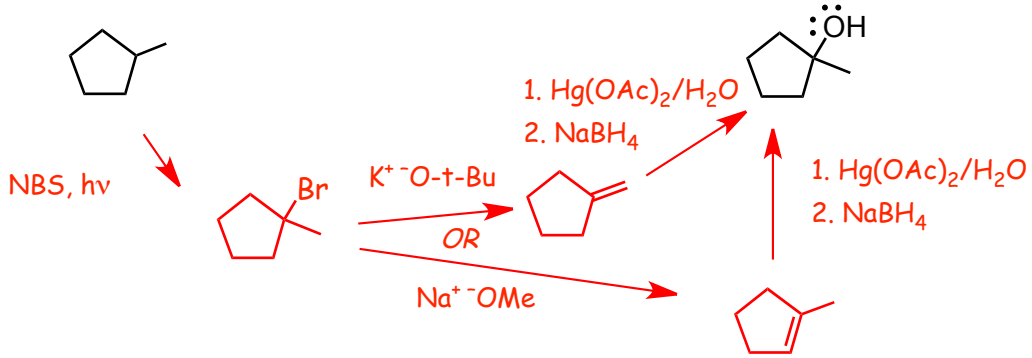


• Look for starting structure in target molecule and for any new C-C bonds.
• **Make the C-C bond (backwards) first if possible (as in this case).**
• Identify FGI's, in this case making an allylic bromide is the obvious one.
• Making an alkene must be next step.
• Making the bromide must be the first step.

Example 3:



Example 4:



• There will sometimes be more than one correct way of solving these problems.
• Note the bulky base with the tertiary halide gives the least substituted non-Sayetzeff alkene.
• Note the **non**-bulky base with the tertiary halide gives the most substituted Sayetzeff alkene.

7 Retrosynthesis : Summary of Reactions

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

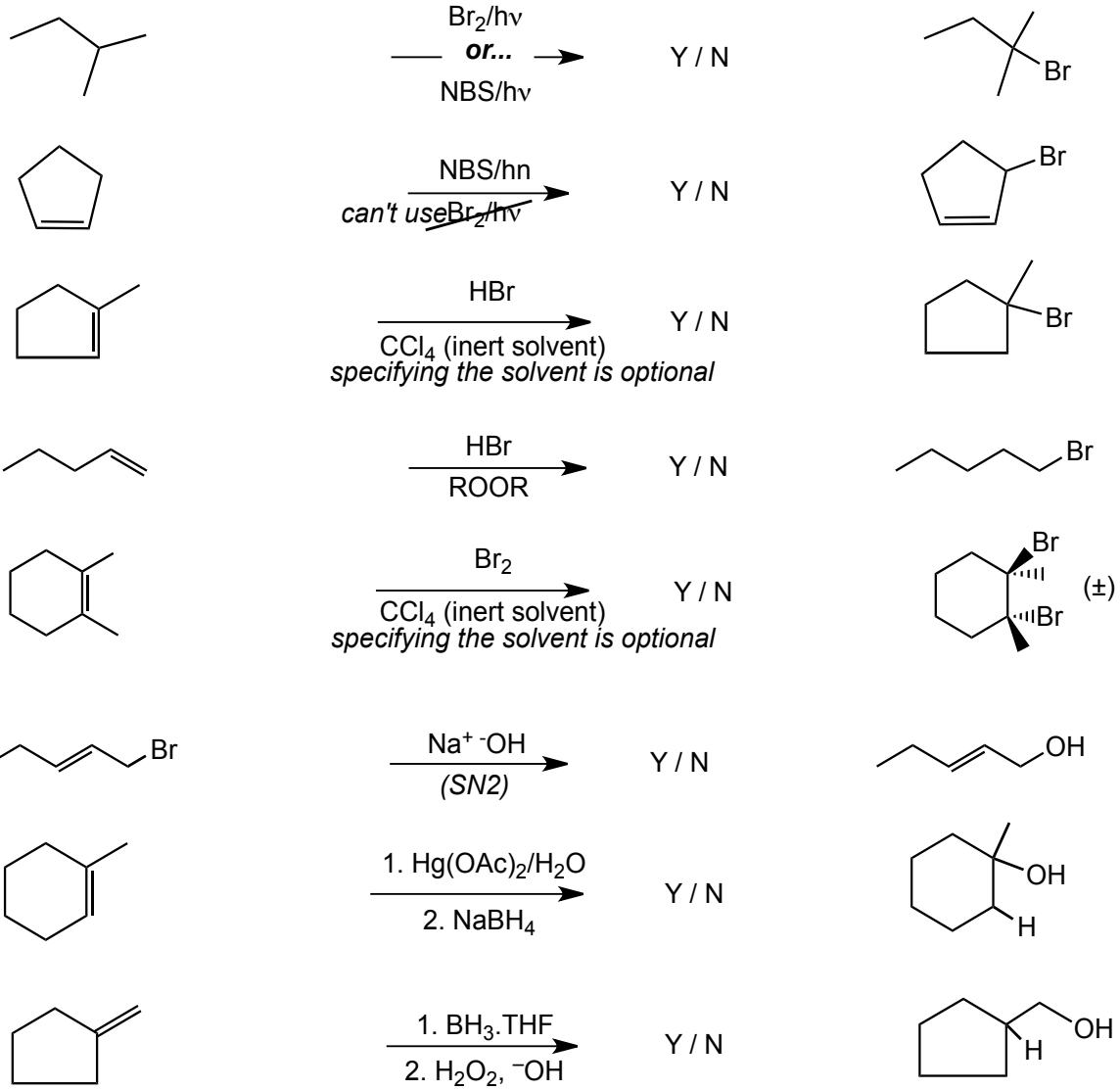
Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on eth reagents/conditions, and so that you can learn and practice solving reaction problems. Use this list **after** you have worked 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:

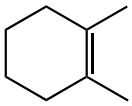
• Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if **completely** correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track 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.

Obviously we like to minimize memorization in a class that is designed to help you understand organic chemistry, but you can't work everything out from first principles, and there is nothing wrong with **a little bit of memorization**. There is a reason that it is useful to "just know" some material. Material that you just know can be used more quickly and accurately than material you have to "work out". This is why we memorize multiplication tables, for example.

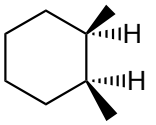


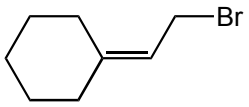


H_2

Pd/C (or Pt or Raney Ni)

Y / N

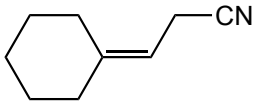


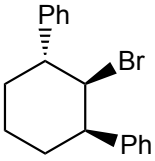


$Na^+ {}^-CN$

Y / N

this is a generic SN2 reaction
you will generally need to WORK
OUT the reagents for SN2 reactions

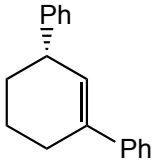


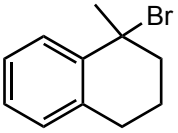


$Na^+ {}^-O\text{-}t\text{-}Bu$

Y / N

2° halide requires bulky base to
avoid SN2, gives Sayetzeff alkene

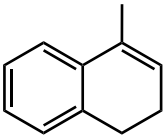


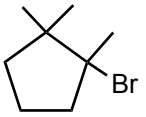


$Na^+ {}^-OMe$

Y / N

3° halide with NON-bulky base
gives Sayetzeff alkene

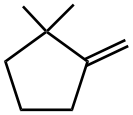


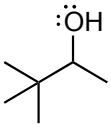


$t\text{-}BuO^- {}^+K$

Y / N

3° halide with BULKY base gives
Anti-Sayetzeff (Hoffman) alkene

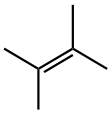




conc. H_2SO_4

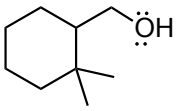
heat

Y / N



E1

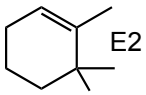
rearranged



conc. H_2SO_4

heat

Y / N



E2

most stable alkene