

Alkynes Reaction Selectivity and Developing Synthesis

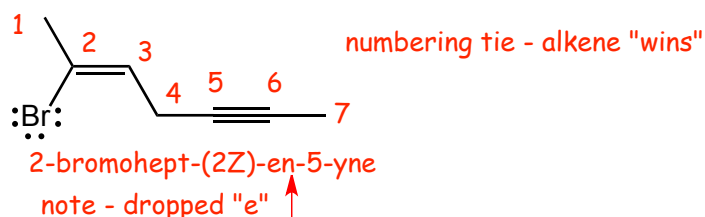
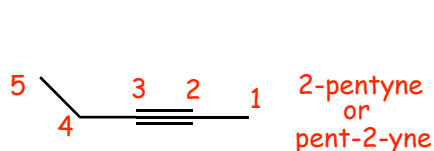
At first glance the chemistry of alkynes looks as if it should be similar to that of alkenes, the reactions will be dominated by additions across the π -bonds, and to a certain extent this is true. However, there are some very significant differences and reactivity that we will need to learn, and more importantly the chemistry of alkynes introduces us to some new and important concepts, these are:

- Many real organic molecules contain more than one functional group, how do we do chemistry of one functional group in the presence of others, i.e., how do we understand chemical reaction selectivity.
- Many reactions this semester will proceed via acid and base catalysis, this section of the notes gives us our first real introduction to these concepts.
- The construction of larger complex organic molecules out of smaller simpler ones requires making new carbon-carbon bonds to join together smaller organic fragments, here we will learn our first useful method for making new carbon-carbon bonds.

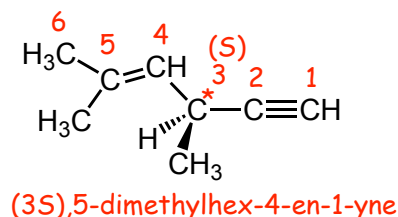
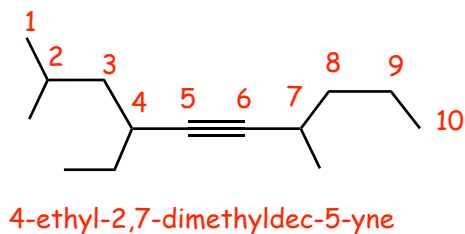
1 Nomenclature

- We must now learn how to name structures that contain more than one functional group. To handle this IUPAC has rules that determine the priorities of the various functional groups. Establishing functional group priority is necessary when naming a structure that contains more than one functional group, the structure then gets named as the highest priority group.
- IUPAC Functional Priority: alkenes = **alkynes** > halides, i.e. number the chain to give either the alkene **or** the alkyne the lowest number, whichever wins.
- **If there is a tie** (and only if there is a tie), **give the alkene the lowest number** (the alkene "wins").
- Alkynes use the suffix **"-yne"**, if the structure contains **both** an alkene and an alkyne, -ene comes before -yne.
- IUPAC has **two** methods for naming alkynes (and alkenes). One puts number specifying the position of the triple bond at the beginning of the name, the second puts the number before the "-yne", which is much more useful when naming structures that contain more than one functional group, since it clearly establishes which number is associated with which functional group.

Examples:



- The method of putting the number directly in front of the functional group to which it refers is used in the example above right, the 2 refers to the position of the double bond and the 5 clearly refers to the position of the triple bond.



- Above **left**, the alkyne is #5 numbering from either end of the chain, the chain is thus numbered from the left to give the first substituent the lowest number, but this is **only** done if the functional group numbering is the same from both directions, the alkyne numbering **takes priority** if possible. The configuration of the two chiral/asymmetric centers is not specified in the structure, and therefore cannot be specified in the name.
- Above **right**, the absolute configuration is specified in the structure, therefore it must be in the name.

Some common (non-IUPAC) names for alkynes:

$\text{CH}\equiv\text{CH}$ *
acetylene

$\text{CH}\equiv\text{C}-\text{CH}_2-\text{CH}_3$
ethyl acetylene

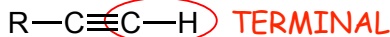
$\text{Ph}-\text{C}\equiv\text{CH}$
phenylacetylene

$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$
diphenylacetylene

* you should know this one

2 Structure and Properties

• First, some notation, alkynes with the triple bonds at the end of the chain (terminal alkynes) have enough different properties from those with the triple bonds in the middle of the chain (internal) alkynes, that terminology that distinguishes them is useful:

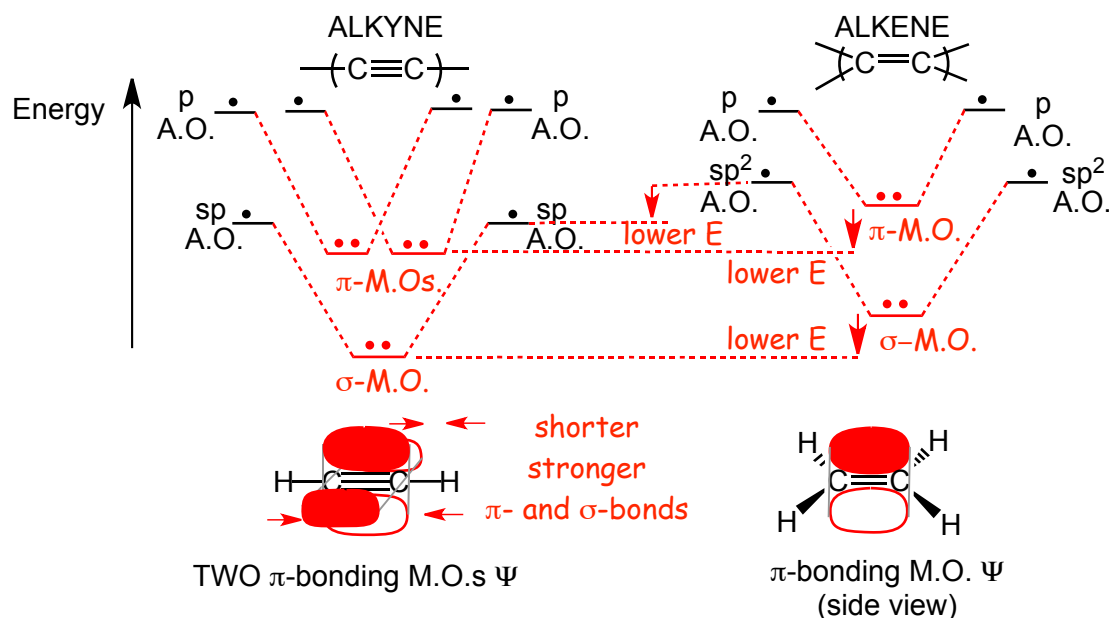


• The sp hybridized carbons give alkynes distinct properties:

	Hybridization	C-C BDE (kcal/mol)	C-C Length (Å)	C-H BDE (kcal/mol)	C-H Length (Å)	Ionization Potential
H ₃ C-CH ₃	sp ³	~90	1.53	~101	1.10	12.84
H ₂ C=CH ₂	sp ²	~174	1.33	~110	1.08	10.58
HC≡CH	sp	~231	1.20	~117	1.00	11.44

π electrons note order
higher energy
lower energy

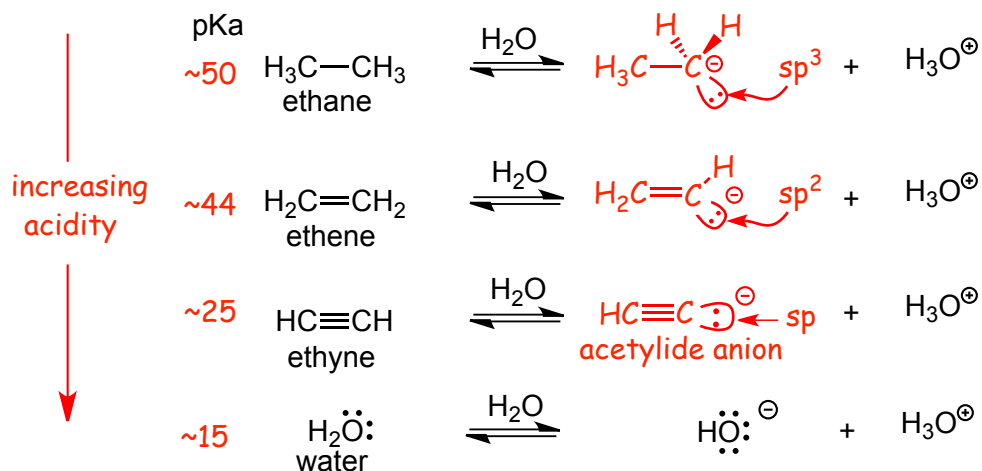
- Bonds to sp hybridized carbons are stronger and shorter bonds, **both the C-H and the C-C bonds**.
- When the carbon atoms are sp hybridized, **all** of the electrons, in both the σ- and the π-bonds, are closer to the nuclei in smaller orbitals (sometimes the sp carbon is described as being more "electronegative" than sp² and sp³ hybridized carbons).
- The **larger I.P. for the alkyne** compared to the alkene shows that **the energy of the electrons in the π-bonds in the alkyne are lower** than those in the π-bonds in alkenes.



• **Both** the π-electrons and the σ-bonding electrons in alkynes are **lower in energy** than the corresponding π- and σ-bonding electrons in alkenes (**but**, see further below).

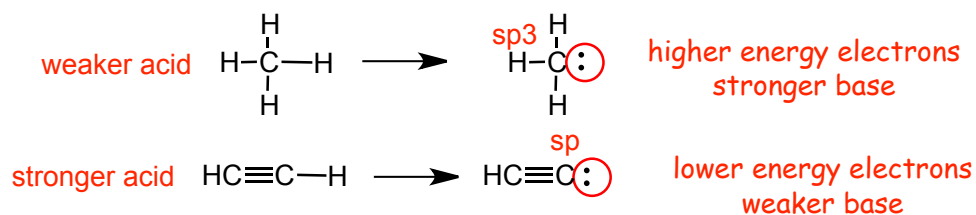
2.1 Alkyne Acidities, Revisit Bronsted Acidity

- Alkynes are stronger Bronsted acids than alkenes and alkanes, although still overall weak, weaker even than conventional weak acids such as ethanol and water.
- The **acetylide** anion (the conjugate base anion of a terminal alkyne) is **relatively** stable for a carbon anion
- As discussed previously, Bronsted acidity increases as hybridization changes, with decreasing p character in the relevant orbital, i.e., sp³ to sp² to sp when comparing an alkane, alkene and alkyne, below.



• **Recall, there are usually two competing factors that control Bronsted acidity**, in this case it is the strength of the C-H bond (which gets larger with decreasing p character in the relevant hybrid orbital) versus the stability of the non-bonding electrons in the Bronsted base, which also increases with decreasing p character, it is the stability of the electrons in the conjugate base anion that "wins" in this case, rather than the bond strength argument, the species with the stronger bond is the stronger acid because the electrons in the base are more stable.

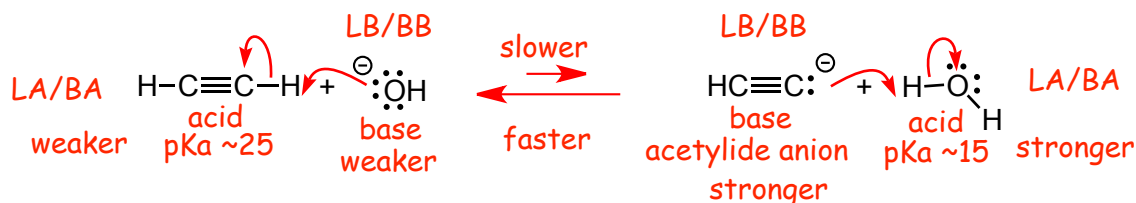
• **Or, simply look at the energy of the electrons in the conjugate base anion**, the lower the energy of the electrons (because of resonance, electronegativity etc., or in this case, hybridization), the more stable the conjugate base anion, the stronger the Bronsted acid.



• Determining base (and therefore acid) strength based on the energy of the electrons in the conjugate base anion **always** works **except** when going down the periodic table (recall H-F, versus H-Cl versus H-I).

2.2 Alkyne Acidity in Water and in Ammonia

• Let's start by understanding alkyne acidity in water:

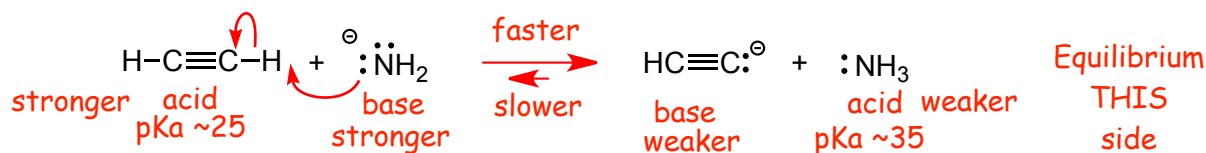


• The stronger acid wins, equilibrium lies on **alkyne** side

• **From this learn that: OH^- is not strong enough base to deprotonate a terminal alkyne.**

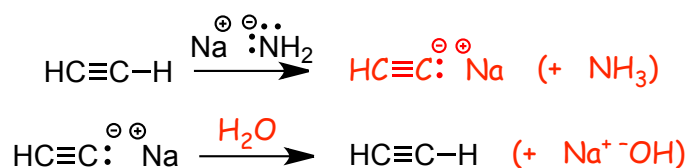
• **From this learn that: H_2O will protonate an acetylide anion.**

• Now, alkyne acidity in ammonia:

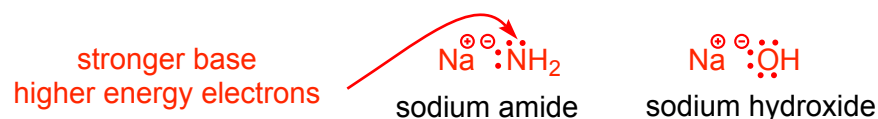


• The stronger acid wins, equilibrium lies on **acetylide anion** side.

- From this learn that: NH_2^- is a strong enough base to deprotonate a terminal alkyne.
- From this learn that: Ammonia will not protonate an acetylide anion.



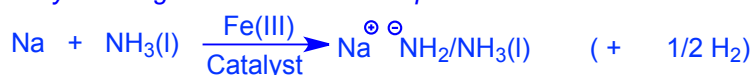
A new reagent, a stronger base:



- Sodium amide (**also sometimes called sodamide**) is a stronger base because the non-bonding electrons are on the less electronegative nitrogen, are higher in energy, more reactive.
- The **number of pairs of non-bonding electrons** is **not important**, they "keep out of each other's way".

more than you really need to know....

sodium amide is made by reacting metallic sodium in liquid ammonia:



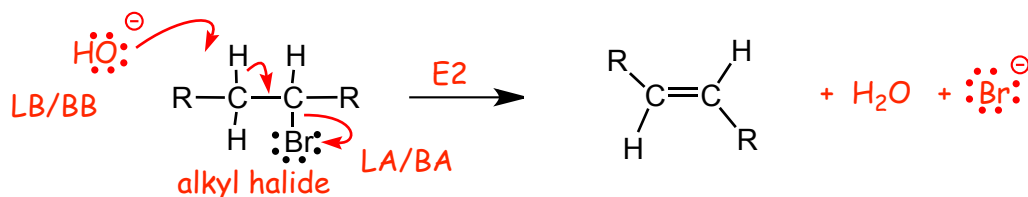
it is usually used as a solution in liquid ammonia (low temperatures) and may be written as

$\text{NaNH}_2/\text{NH}_3(\text{l})$ to emphasize that point, but it is usually just written simply as NaNH_2

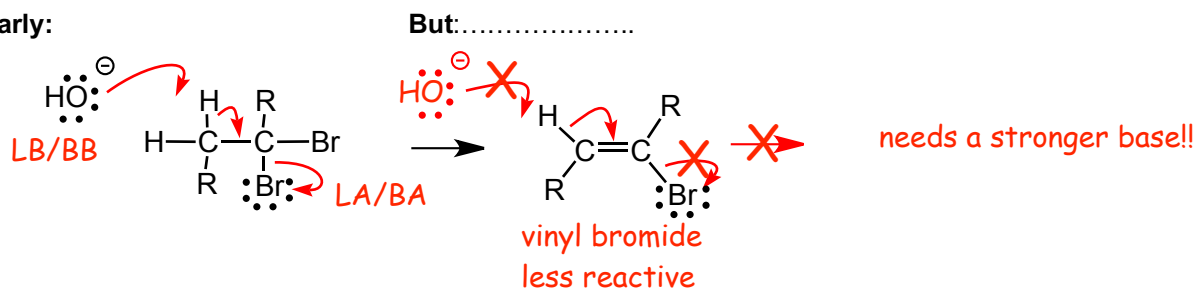
NaNH_2 tends to act as a base rather than a nucleophile simply because it is such a strong base it overwhelms any nucleophilic substitution reactivity

3 Preparation of Alkynes

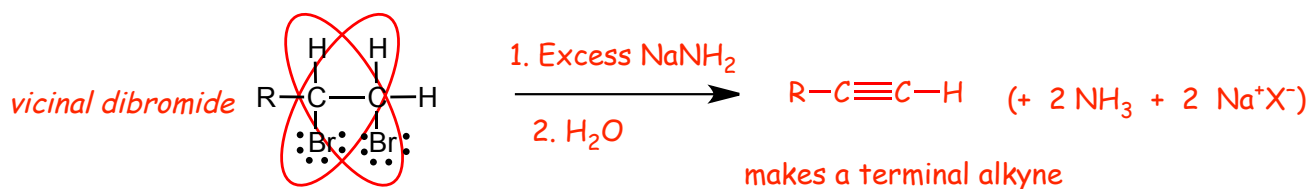
Recall:



Similarly:

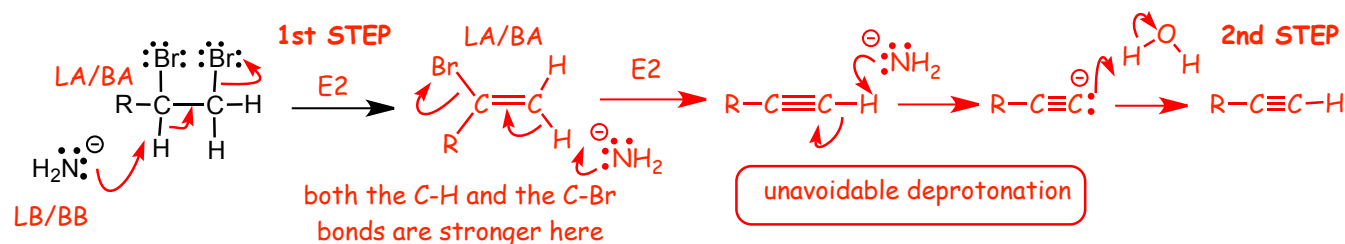


- $\text{S}_\text{N}2$ OR $\text{E}2$ is not possible at an sp^2 hybridized carbon atom (using OH^- as the base at least).
- A **vinyl** bromide is less reactive than an alkyl bromide due to the stronger $\text{C}-\text{Br}$ bond involving an sp^2 hybridized carbon, compared to the Br to sp^3 hybridized carbon in the alkyl halide. We saw this previously, vinyl bromides don't do $\text{S}_\text{N}2$ reactions for partially the same reason (the bond to leaving group is too strong).
- To make **this reaction useful** we need a **stronger base** than hydroxide.
- Luckily, we just learned about a **stronger base** than $\text{Na}^+ \text{OH}^-$, that is $\text{Na}^+ \text{NH}_2^-$.



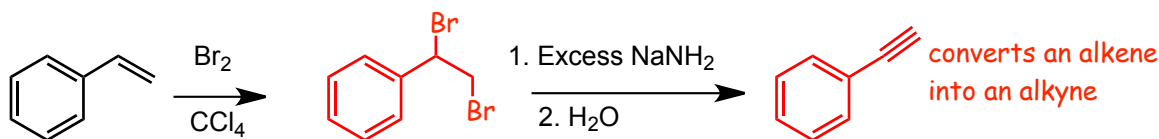
- Note the use of the term "Excess" (XS) - means use more than 1 equivalent of the reagent (more than one mole of reagent per mole of reactant), usually much more than 1 equivalent (more than 2 in this case).
- Why is water required in a second step? To answer this question we need to look at the detailed mechanism.

Mechanism: For the example of a vicinal dibromide:

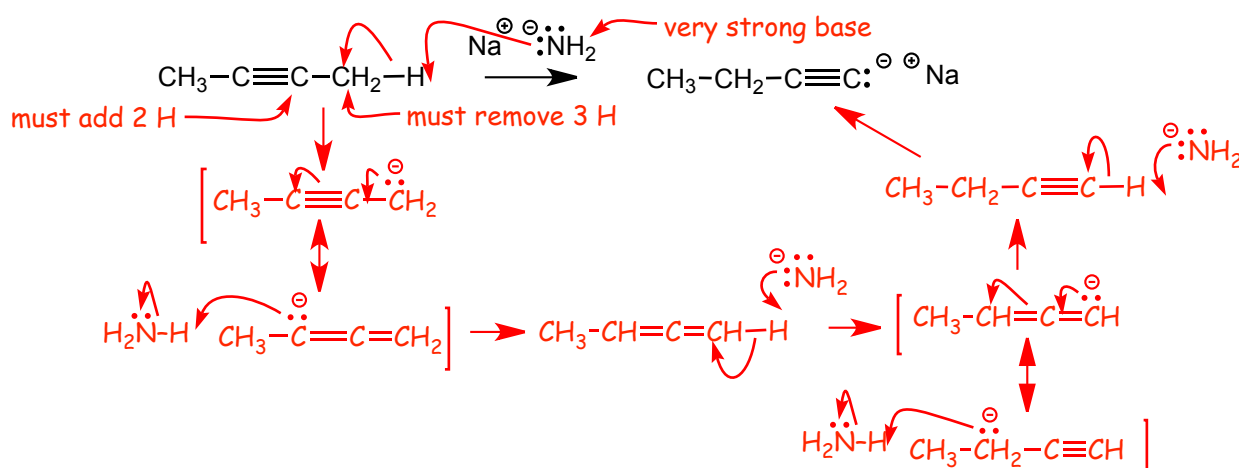


- The mechanism shows why **excess** NaNH₂ is needed, since we need **two** NaNH₂ molecules to do the two deprotonations, and **then**, deprotonation of the terminal alkyne formed in the second E2 reaction is unavoidable
- Therefore, we need the water to put the proton back after the amide anion removed it!
- this overall reaction is useful for making terminal alkynes.

Example:



- This method for alkyne synthesis is really only useful for synthesis of **terminal** alkynes, because of the following triple bond migration effect:



- Think about this apparently complex mechanism **as a mechanism problem**.
- What bonds have to be made, what bonds have to be broken, how to we make/break these bonds in reasonable order using the Lewis/Bronsted acid base reactions that we know or could predict?
- Need to both add and remove hydrogen atoms in the form of protons, in the presence of a base,
- In the presence of base, **first** remove protons and then reprotoate using the acid that you just generated.
- It is the irreversible formation of the terminal acetylide anion, the last step in the mechanism, that "traps" the terminal alkyne and prevents further migration.

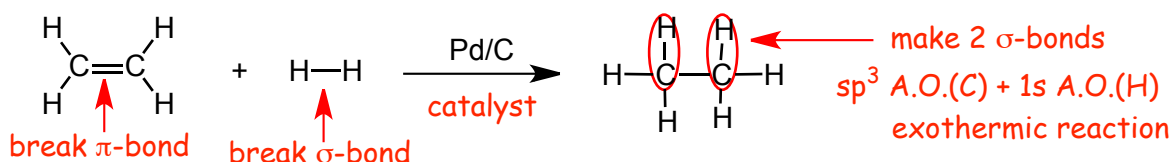
- The amide anion is a **catalyst**, it never gets consumed, but it helps the reaction to "go".
- Note: This process **isn't really a reaction that you can use in, for example, synthesis**, in practice it is not possible to convert an internal alkyne into a terminal alkyne with high yield, it is given here purely as a **mechanism problem**.

4 Reactions of Alkynes: Reactions of One Functional Group in the Presence of Another

- Here we start our discussion of the reactions of the alkyne functional group, but also do something much more important: We learn how to control reactions of one functional group **in the presence** of another.
- Organic molecules often have many functional groups, how do we do a reaction **selectively** at one functional group and leave the others alone? Here is we start to find out how to do this.

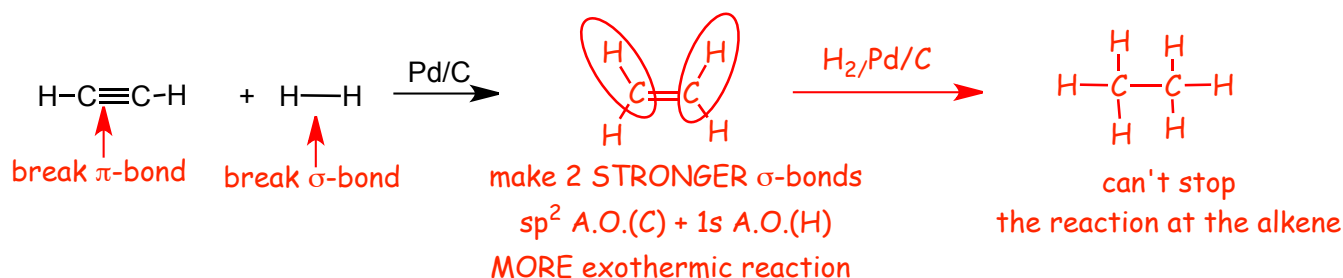
4.1 Selective Syn-Addition of Hydrogen (Reduction)

Recall:

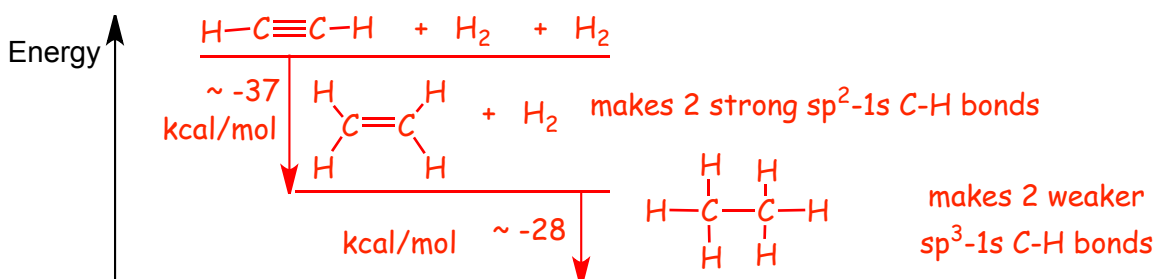


- This reaction is exothermic because it converts a σ - and a π - bond into a σ - and a σ -bond, and σ -bonds are stronger than π -bonds, the electrons in σ -bonds are lower in energy in σ -bonds compared to π -bonds.

Similarly:



- The reaction can't be stopped after one addition of H_2 , the alkene formed in the first step will be further reduced to the alkane, **but**, the two reactions are not the same, they don't have the same exothermicity:

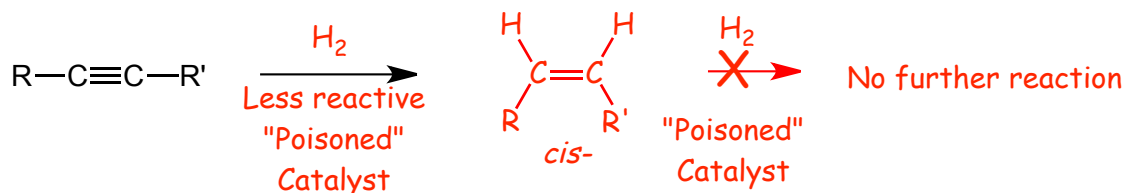


- Note: Alkyne reactions **are generally more exothermic than corresponding alkene reactions**, even though they have lower energy electrons in their π -bonds.
- When considering chemical reactivity, we have to think about **all** of the bonds that are broken **and** formed.
- The reaction exothermicity takes into account the energy of the electrons in the alkene and the alkyne π -bonds, **and**, the energy of the electrons in the **products** that are formed.
- **Even though** alkynes have lower energy electrons in their π -bonds, the two $C(sp^2)$ -H that are formed are **stronger** than the $C(sp^3)$ -H bonds that are formed when an alkene reacts, which is why the alkyne reactions are more exothermic.

- Therefore, **the reactions of alkynes and alkenes** could, in principle, be **distinguished** or selected on the basis that the additions reactions have **different thermodynamics**, and as we will see, this works!

The two new sigma bonds that are made when the H_2 adds to the alkyne are $C(sp^2)-H$, whereas the two new sigma bonds that are made when the H_2 adds to the alkene are $C(sp^3)-H$. Therefore, the addition reaction of H_2 to the alkyne makes stronger sigma-bonds than the addition reaction of H_2 to an alkene. Now, a lot of other stuff also happens in these reactions, for example, when the H_2 adds, the existing C-H bonds in the alkyne change from $C(sp)-H$ to $C(sp^2)-H$, and, stronger pi-bonds are broken in the alkyne reaction, but it is the new sigma bonds that are formed that is the major difference between the two reactions, and is the main reason why addition of H_2 to an alkyne is more exothermic than addition to an alkene

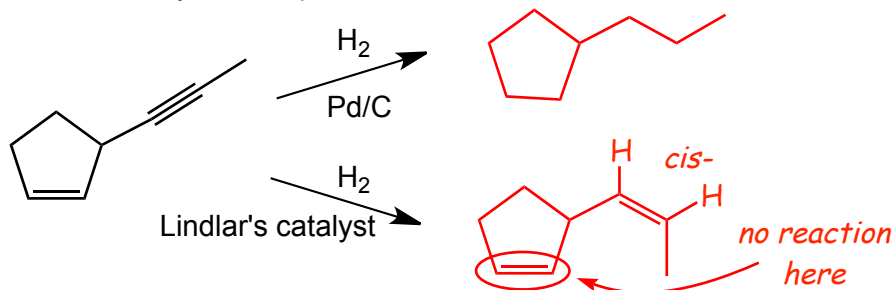
Compare: Syn-Addition of H_2 across the carbon-carbon triple bond of an alkyne:



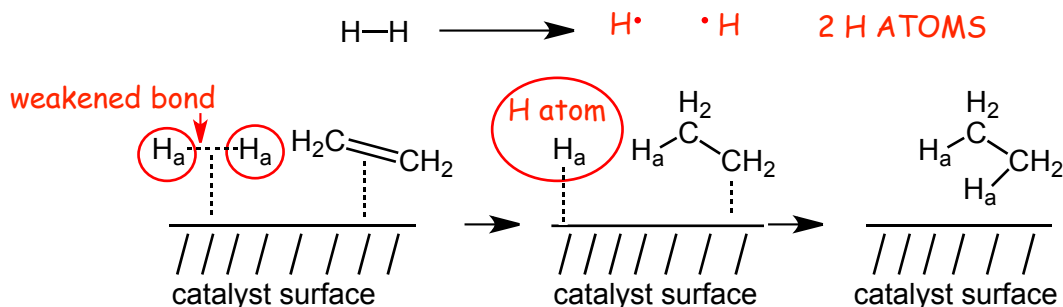
- Syn-addition (same as to alkenes) leads to formation of *cis*-product.
- A poisoned catalyst = Pd on $CaCO_3$ with PbO_2 and quinoline can be used to reduce activity. This less reactive catalyst is called Lindlar's catalyst (there are other recipes for the Lindlar catalyst, it can get confusing, and so we will just refer to the Lindlar catalyst using its name).
- The alkyne reaction is **more** exothermic, which aids selectivity based on **thermodynamics** (although in reality it is a bit more complicated than this since the alkyne also adsorbs preferentially to the surface).
- The details about exactly how the catalyst works, and indeed its composition, are not worth the effort to learn.
- However**, you **do** need to know this method for synthesizing a *cis*-alkene from an alkyne.

Example:

A stereospecific reaction of an alkyne in the presence of an alkene:

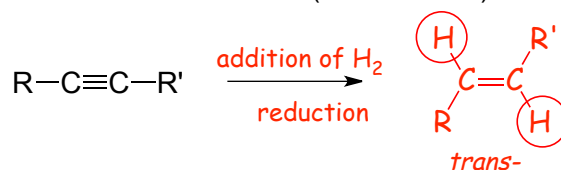


- Using the Lindlar catalyst, the alkyne can be made to react selectively, **and**, a single alkene stereoisomer is formed as a result of this reaction!
- The alkyne reacts preferentially to the alkene because the reactions have **different exothermicities** and the alkyne tends to adsorb **preferentially** to the catalyst.
- To get two hydrogen atoms from a hydrogen molecule, a way is needed to break the strong H-H bond, that is the role of the catalyst.

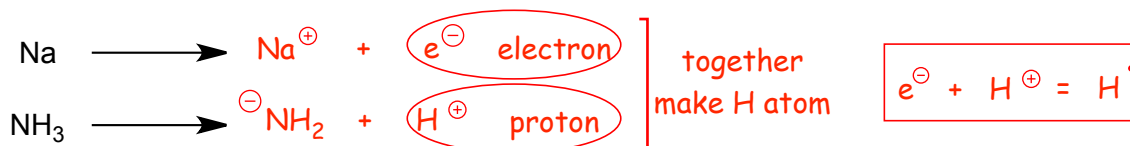


4.2 Selective Anti-Addition of Hydrogen (Reduction)

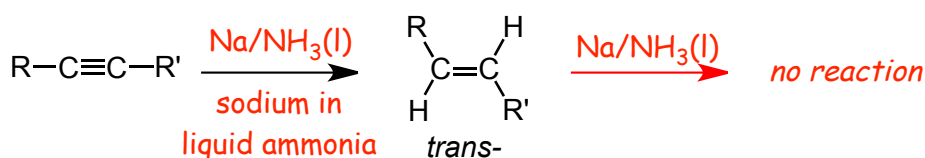
- How **do** we add H_2 specifically to make the **trans**-isomer (**anti-addition**)?



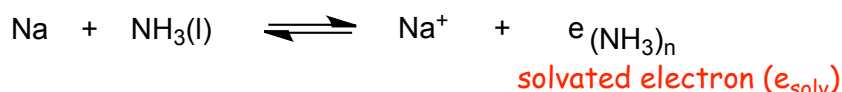
- Formation of a **trans-alkene** from an alkyne requires a different **New Reagent** and a new mechanism.



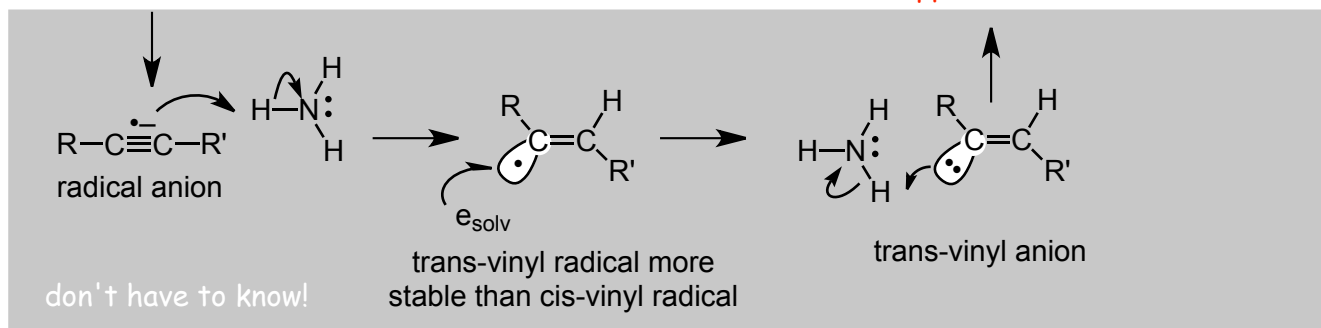
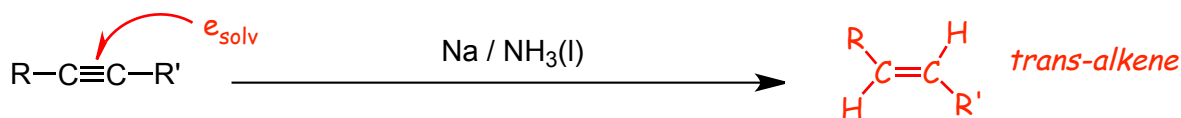
- A sodium atom can provide an electron and a hydrogen atom containing solvent (NH_3 , ammonia in this case) can provide a proton, together they constitute a hydrogen atom **and** a very different way of adding hydrogen atoms to an organic structure, via a very different mechanism to catalytic hydrogenation
- A hydrogen atom is equivalent to a **proton and an electron**, adding a proton and an electron to a molecule is equivalent to adding a hydrogen atom.
- Mixing sodium metal and ammonia provides H atoms in the form of electrons and protons



- This reagent reduces (adds H atoms) to an alkyne but not an alkene, the addition to the alkyne is **anti**-, a **trans**-alkene is produced.
- The sodium metal dissolves in the ammonia solvent (at low temperature) to generate an electron in the ammonia solvent, a solvated electron, $Na/NH_3(l)$ is an example of a **dissolving metal reducing agent** (we will see these again later in the course).
- The solvated electron (in ammonia):

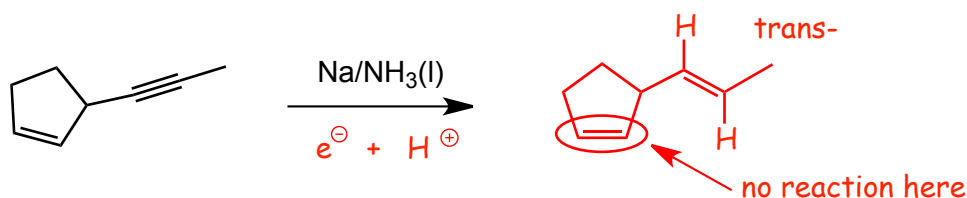


The Mechanism is not a conventional Lewis acid/base mechanism, and you are unlikely to be asked to reproduce it on an exam, the key intermediates are a **trans**-vinyl radical and a **trans**-vinyl anion.



- The intermediate vinyl radical and anion are more stable in the **trans**-form, which explains the overall stereochemistry of the reaction.

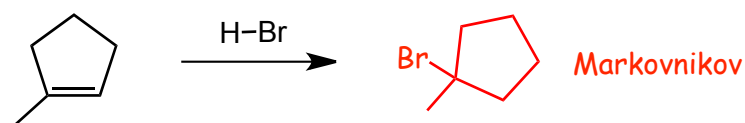
Example:



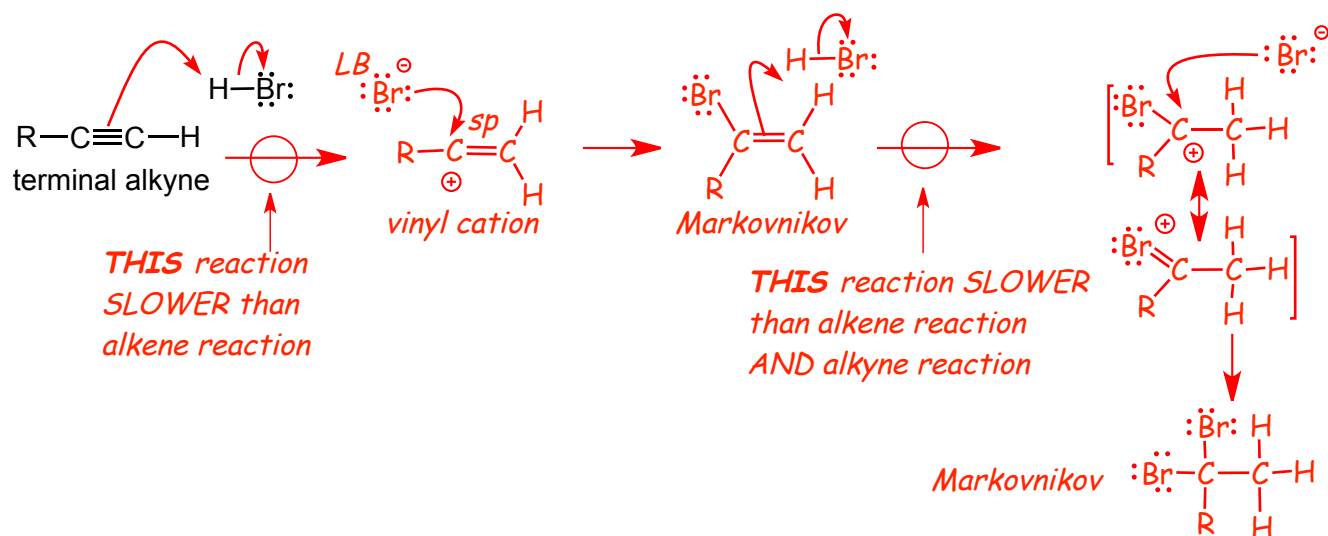
- Again, here we have **reaction of one functional group** (alkyne) **in the presence of another** (alkene) and with specific stereochemistry.

4.3 Addition of H-Br

Remember the following reaction:

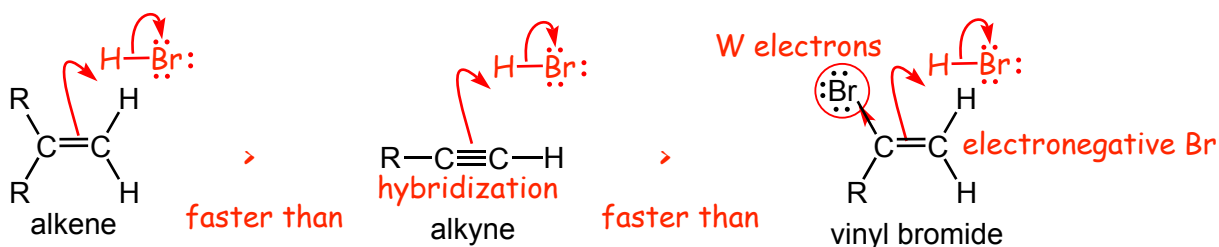


Compare:



- The second cation is resonance stabilized, which explains the second Markovnikov addition.
- Note: the kinetics and thermodynamics of alkyne reactions compared to alkene reactions are tricky, alkyne reactions tend to be **both** slower **and** more exothermic.

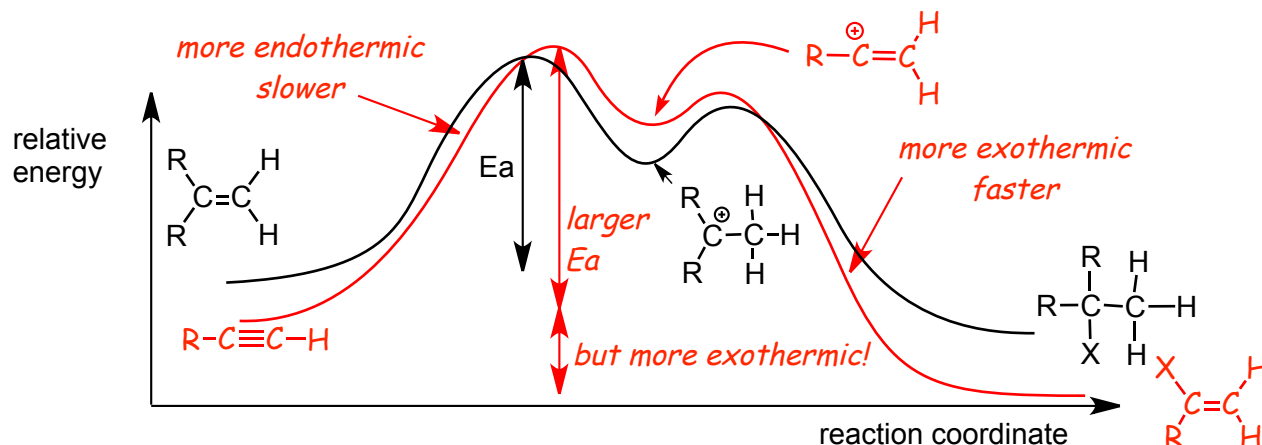
Different types of π -bond react at different rates with HBr:



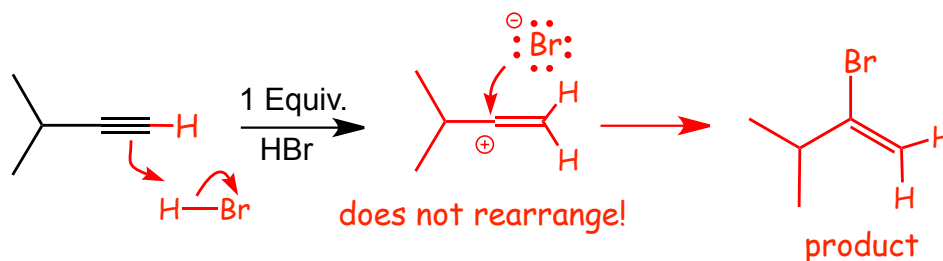
- Alkynes react slower than alkenes because of the stronger π -bond.
- The vinyl bromide reacts slower than **both** the alkyne and the alkene because of the electron energy lowering effect of having the bromine atom attached directly to the $\text{C}=\text{C}$ double bond.
- This reactivity order can't be predicted from first principles, but it is understandable and explains some important reactivity differences between alkynes and alkenes
- Therefore, the reactions of **alkynes and alkenes could, in principle, be distinguished or selected on the basis that the additions reactions have different kinetics**, and as we will see, this works!

- This is a **second way in which alkenes and alkyne reactivity can be differentiated** and selected
- We previously saw that reductions by **adding hydrogen (hydrogenation) with catalysts such as the Lindlar catalyst**, could distinguish alkenes and alkynes based on how exothermic the reactions are, i.e. **based on thermodynamics**.

- **Note:** The Hammond postulate is **not** disobeyed, it works for **each step** of the mechanism (energy diagram below).
- The Hammond postulate can only be used to analyze single step reactions or a single step in a mechanism:

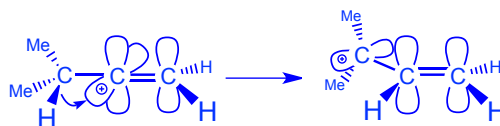


Example: One Equivalent of HBr:



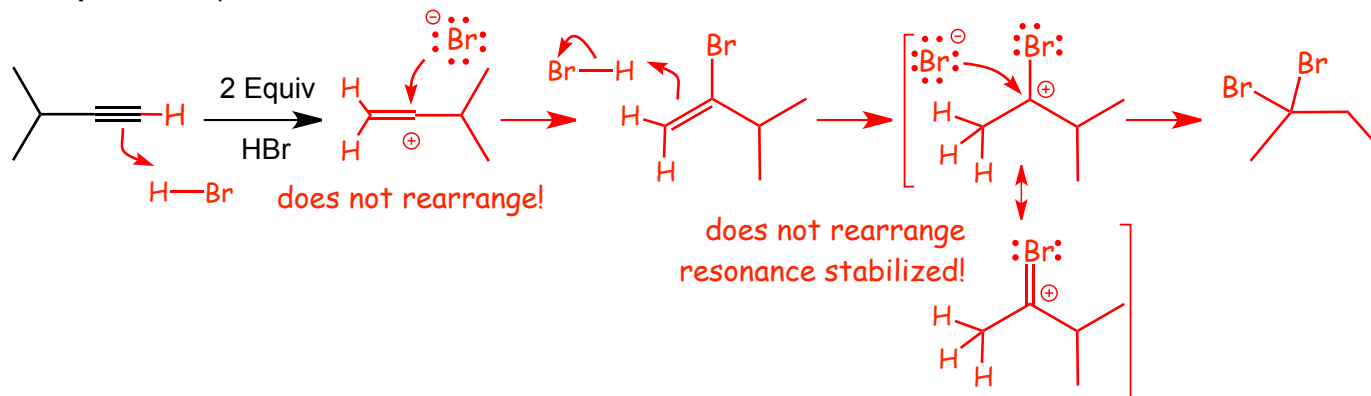
- Addition of a single (1 Equivalent of) HBr to an alkyne is possible, the product of the first addition, the vinyl bromide, reacts slower than the reactant alkyne, and so some of the HBr does not also react with the vinyl bromide making a complex mess. **This is selectivity based on kinetics.**
- Note that the intermediate **vinyl cations** tend to rearrange **slowly** due to a stereoelectronic effect associated with the relevant orbitals, therefore in this course we assume that they **don't rearrange**.

more than you really need to know.....

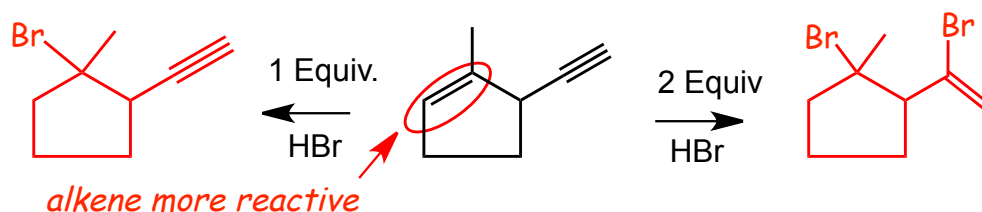


hydride transfer to a vinyl cation should produce a resonance stabilized allyl cation, however, the newly formed empty p A.O. is orthogonal to the pi-system of the C=C double bond, there is no large energy gain associated with rearrangement until rotation, which makes rearrangement of vinyl cations slow

Example: Two Equivalents of HBr:



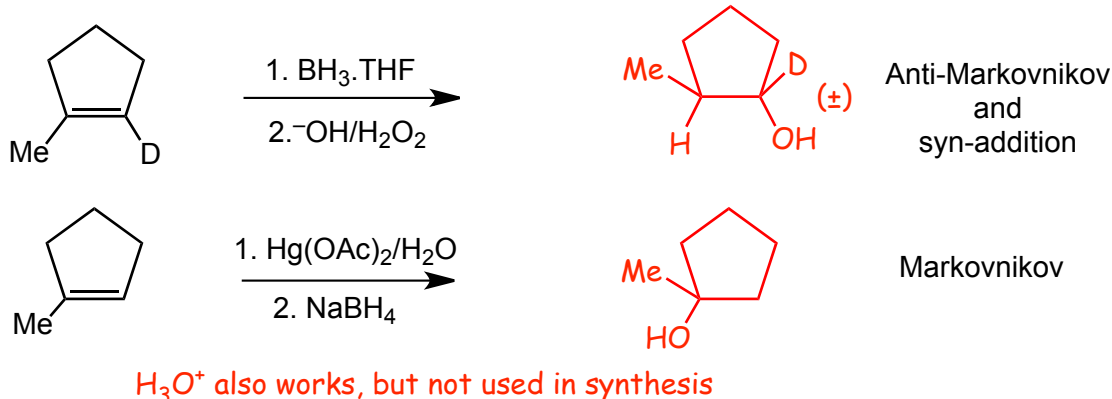
Example: Alkene versus Alkyne:



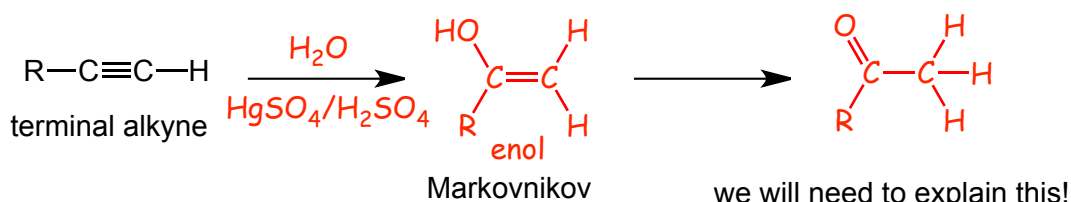
- Reaction of 1 Equivalent of HBr with a structure that has both an alkene and an alkyne functional group results in reaction of the alkene and not the alkyne.
- This is actually a pretty important point, this is our first example of preferential reaction of one functional group in the presence of another very similar one! The small change in hybridization is sufficient to allow this selectivity.

4.4 Addition of Water

Recall:



Analogously: Markovnikov addition of water to an alkyne:



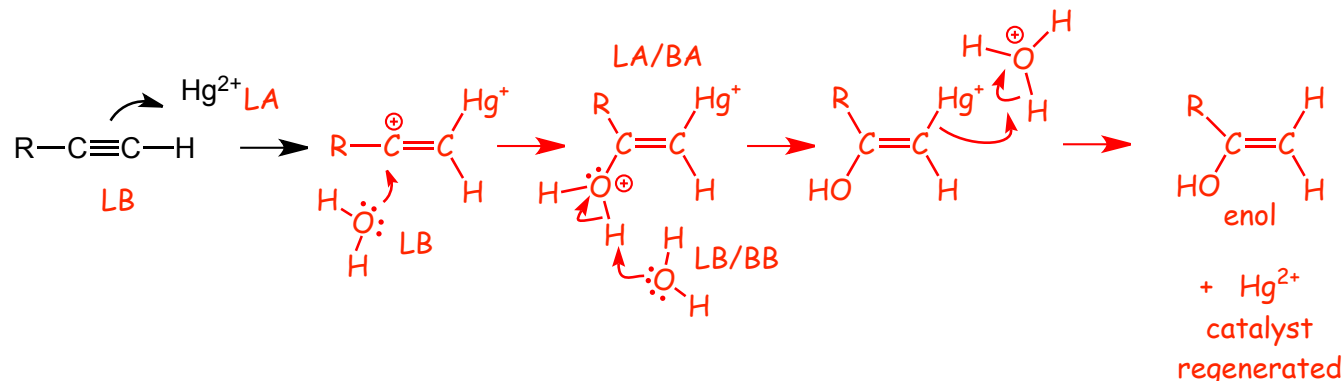
- Aqueous acid actually reacts pretty slowly with alkynes, even slower than with alkenes, and the Hg^{2+} catalyst is usually required to allow water addition to the alkyne.
- $\text{Hg}(\text{OAc})_2$ is not reactive enough as a catalyst to make the alkyne reaction go with a reasonable rate.



- In reality, dissolving HgSO_4 in water is more complicated than indicated here, but what we show here is sufficient to make the point that a **monocation** mercury catalyst is sufficient to allow the alkene/ H_2O reaction to occur, but a **dication Lewis acid can be the stronger electrophile needed for the alkyne/water reaction.**

The alkyne mechanism can be broken down into **two** important parts

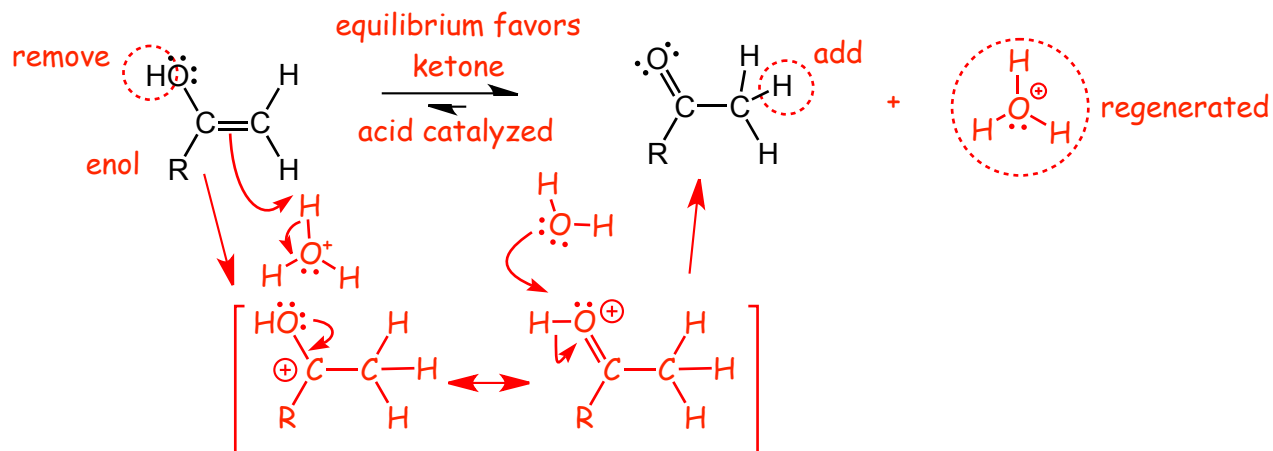
Mechanism part 1: Formation of the enol:



- Alkynes will not react with aqueous acid (alkynes are less reactive than alkenes) without a catalyst.
- The Hg^{2+} cation is a **stronger electrophile** (works with alkynes) than Hg^+OAc (works with alkenes).

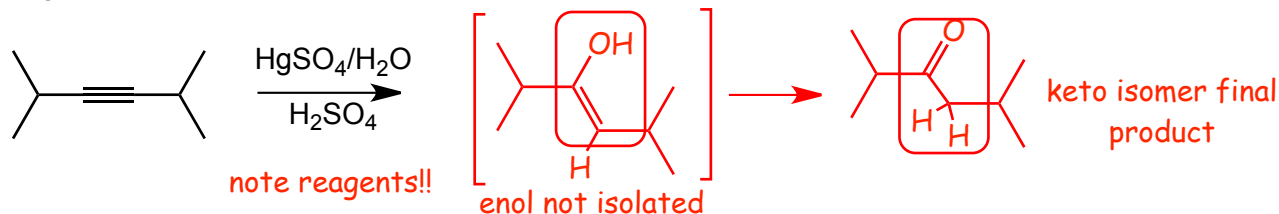
Mechanism part 2: tautomerization of the enol

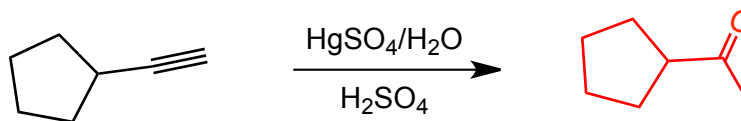
- Keto-enol **tautomerization**: Is equilibrium between proton shift isomers.
- **Tautomerization** is interconversion between isomers, where the only difference between the isomers is the position of on H atom and one double bond.
- We need to add (first) H and remove (second) H in presence of **acid** (i.e., in the form of H^+).



- **Critical point** - with **acid**, **add a proton first**, remove a proton second.
- The enol and the ketone are **isomers**, the reaction is a **keto-enol tautomerization**.
- Equilibrium favors the stronger $\text{C}=\text{O}$ bond compared to the weaker $\text{C}=\text{C}$ bond in enol.
- The acid is not overall consumed, the acid that used in the first step is regenerated in the second step, the acid acts as a true catalyst.

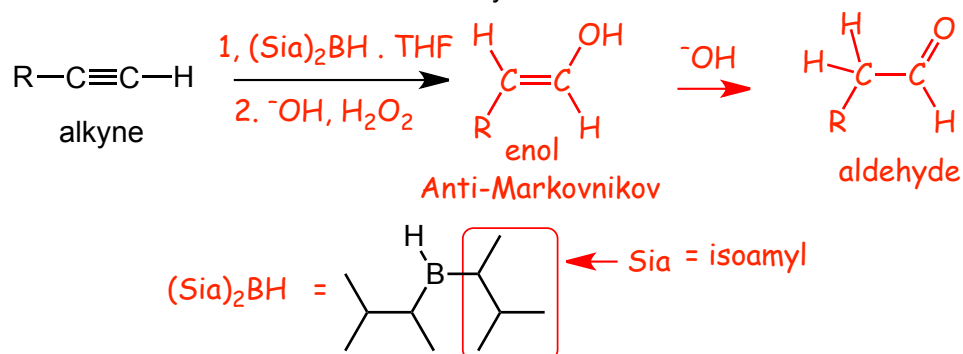
Example:



Example:

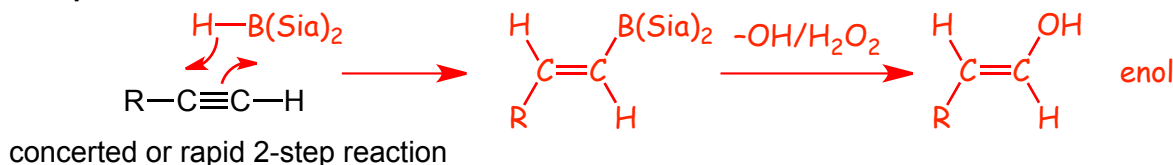
- This reaction works well with symmetrical or terminal alkynes, otherwise you get a mixture of isomeric products.

Analogously: Anti-Markovnikov addition of H₂O to an alkyne:



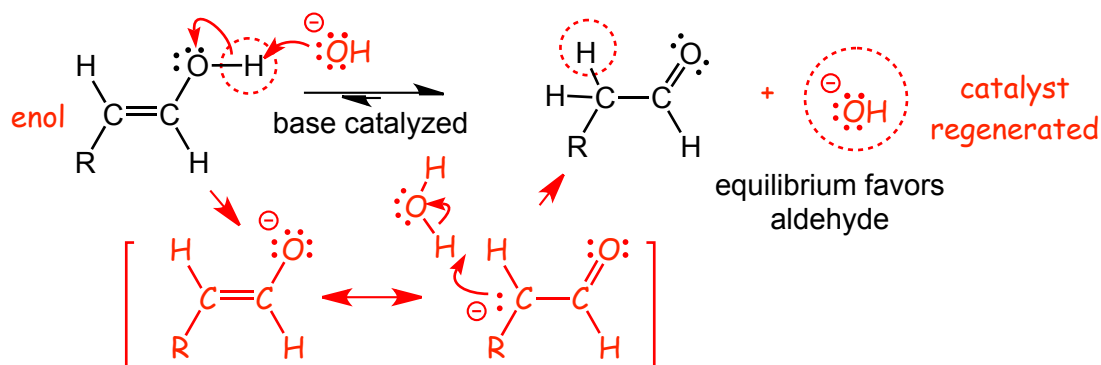
(Sia)₂BH : Is a very bulky borane, it prevents 2 molecules from adding to the alkyne.

Mechanism part 1: Formation of the enol:



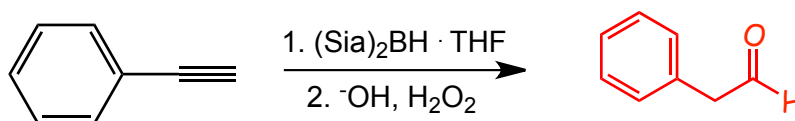
Mechanism part 2: Tautomerization of the enol:

- This reaction is **base catalyzed**, the base that is consumed in the first step of the mechanism is regenerated in the second step, the base is a true catalyst
- Need to add and remove "H" with **base** (i.e. remove first, a base will **not** provide protons)
- Treat this a mechanism **problem**, think about the order of making and breaking bonds and what the best order is given the provided reagents/condition, in this case **base**....



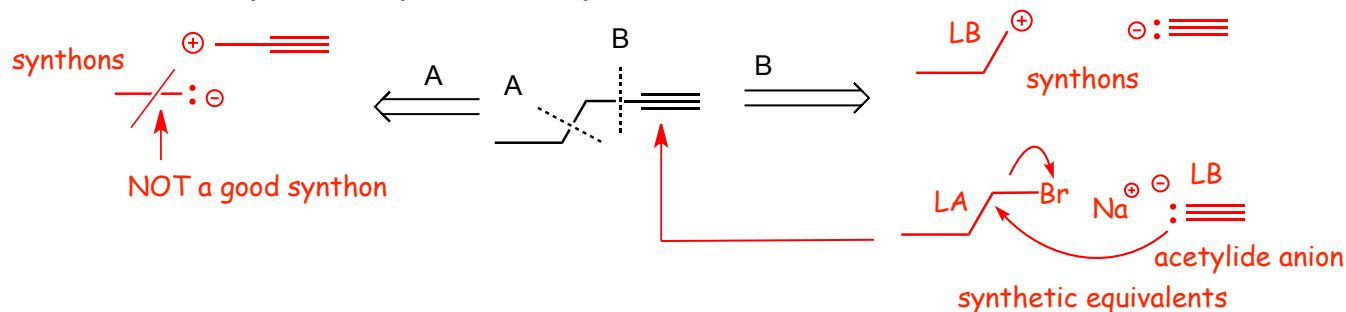
- With a **base**, **first remove a proton**, add a proton second.
- Recall this reaction is a **keto-enol tautomerization** (the enol and the aldehyde are isomers).
- Equilibrium favors stronger C=O bond compared to weaker C=C bond in the enol.

Example Reaction:



5 Acetylide Anions : Retrosynthesis and Carbon-Carbon Bonds

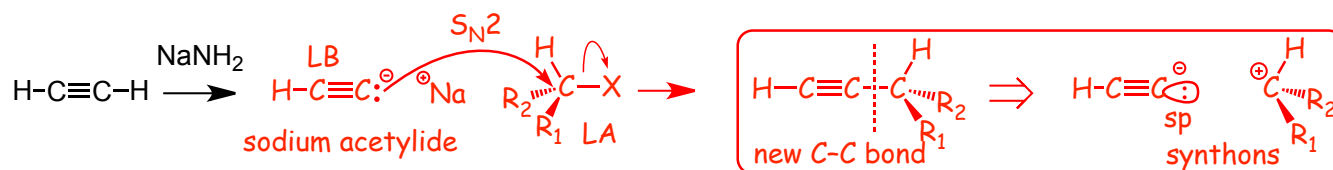
- Suppose we want to make one of the C-C bonds in the structure shown.
- Consider the retrosynthetic analysis indicated by the disconnections **A** and **B**.



- Generate the synthons that have the lowest energy electron energy.
- Disconnection **A** generates a negative synthon with the charge on an sp³ hybrid carbon, very high energy electrons.
- The **much** better disconnection **B** generates a negative synthon with the negative charge in an sp hybridized carbon, much lower energy electrons, disconnection B is the better one!
- The negative synthon from **B** can be "put into a bottle" as a sodium salt, since the synthetic equivalent in this case is simply an **acetylide anion**.
- The positive synthon is converted into a synthetic equivalent as a bromide, as usual
- Acetylide anions are by far the most useful carbon anion synthons, and are **very important for the synthesis of carbon-carbon bonds**.

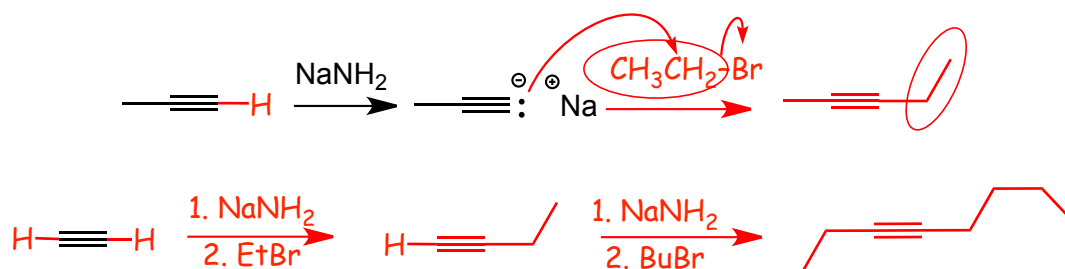
5.1 S_N2 Reaction with Alkyl Halides

- We **know** how to make the acetylide anion, by deprotonation of a terminal alkyne using our new favorite strong base, sodium amide (NaNH₂).

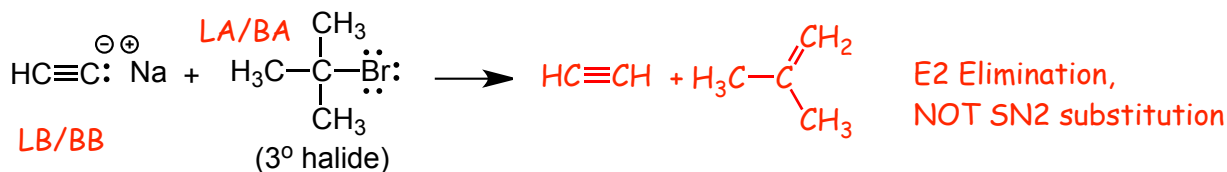


- The acetylide anion reaction is simply an S_N2 reaction **and**, makes a new C-C bond.
- It proceeds via the usual concerted **backside attack mechanism**, with a **Walden inversion**.
- Recall:** S_N2 reactions work best at primary and allylic carbons atoms.

Examples:



- Important**, Note 1..... 2..... notation, which means **first** reaction with NaNH₂ (and wait until that reaction is complete), and then **second** then react what you get in the first step with the alkyl halide.
- As usual, the S_N2 reaction works best with primary/allylic halides, otherwise you get the usual S_N2/E2 elimination/substitution competition.

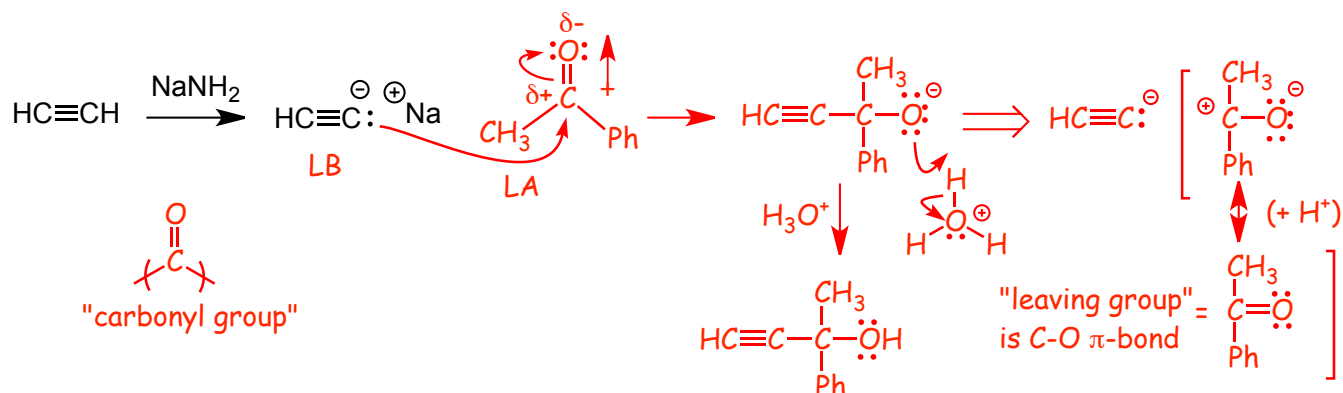


- The acetylide anion is a **strong Bronsted base**, it will do standard E2 elimination with a tertiary halide, and as with any Lewis base/nucleophile, **cannot** do SN2 (substitution) at a tertiary carbon atom.

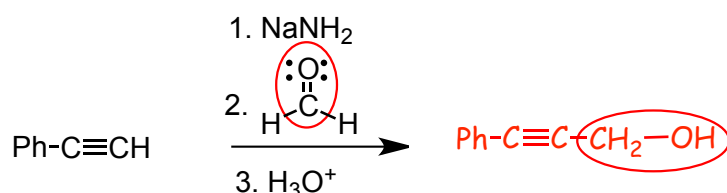
5.2 Addition to Carbonyls and Epoxides

- The acetylide anion reacts with an alkyl halide via SN2, the carbon it attacks has a partial positive charge.
- The acetylide anion can also attack other electrophilic carbons that have partial positive charges, e.g. the carbon in a carbonyl (C=O) bond.

Example with a carbonyl (C=O bond):

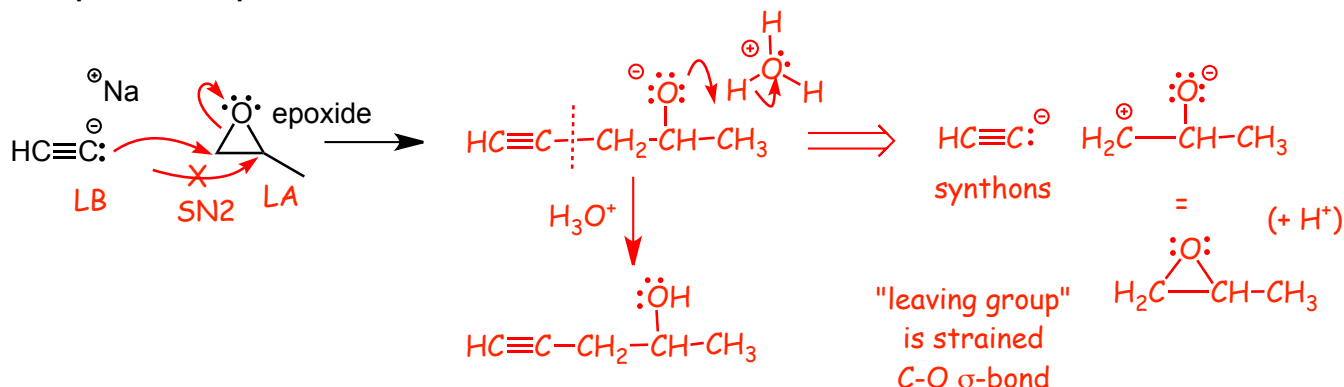


- This makes a new C-C bond **and** makes an alcohol.
- The C=O π -bond is the "leaving group" in this case.
- H_3O^+ is required to add the proton to the oxygen with the negative charge in the second step.
- Here we have a (slightly) more complex conversion of **synthon** to **synthetic equivalent**, for the positive synthon, the synthetic equivalents are a carbonyl (aldehyde or ketone) **and** the proton (H^+).
- The carbon** involved in the **new C-C bond** has an **oxygen atom "attached"**, this is the key structural feature that indicates **addition to a C=O bond**!



- Note 1... 2.... 3.... notation, it is **important**!

Example with an epoxide:

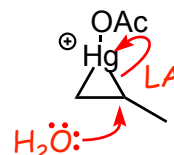
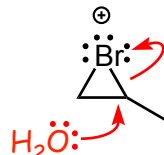
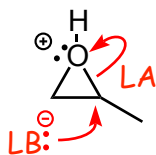
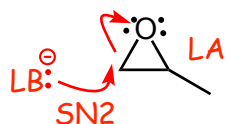


- This makes a C-C bond **and** makes an alcohol.
- The strained C-O sigma-bond is the "leaving group" in this case.
- H_3O^+ is required to add the proton to the oxygen with the negative charge in the second step.
- Here we have a (slightly) more complex conversion of **synthon** to **synthetic equivalent**, for the positive synthon, the synthetic equivalents are an epoxide **and** the proton (H^+).
- The carbon** involved in the **new C-C bond** has an **oxygen atom on the adjacent carbon**, this is the key structural feature that indicates **addition to an epoxide**!

- The **acetylide** anion adds to **least substituted side of epoxide** for steric reasons.

Compare:

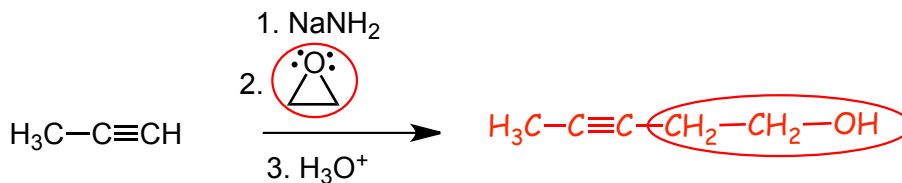
NO positive charge, steric effects dominate



positive charge attracts electrons

- When the 3-membered ring has a **positive charge**, a Lewis base attacks the **most substituted** carbon. This is an energy of the electrons effect. As the Lewis base approaches the more substituted carbon it "feels" a slightly higher positive charge, which lowers the energy of its electrons more, it is "attracted" to the slightly higher partial positive charge.
- When the 3-membered ring is **neutral**, a Lewis base attacks the **least substituted** carbon for the usual SN2 steric effect reasons, the least substituted carbon is less sterically hindered.

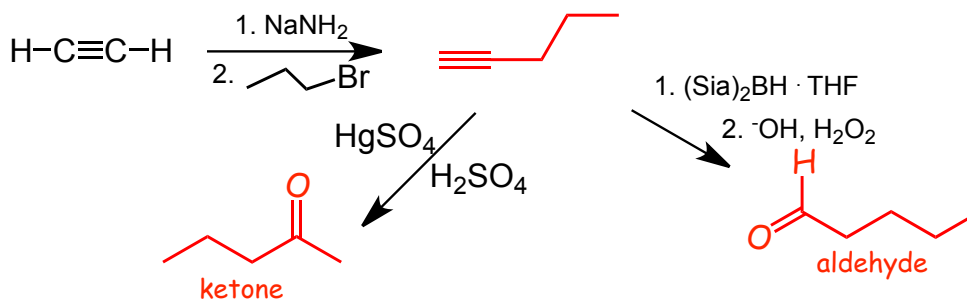
Example:



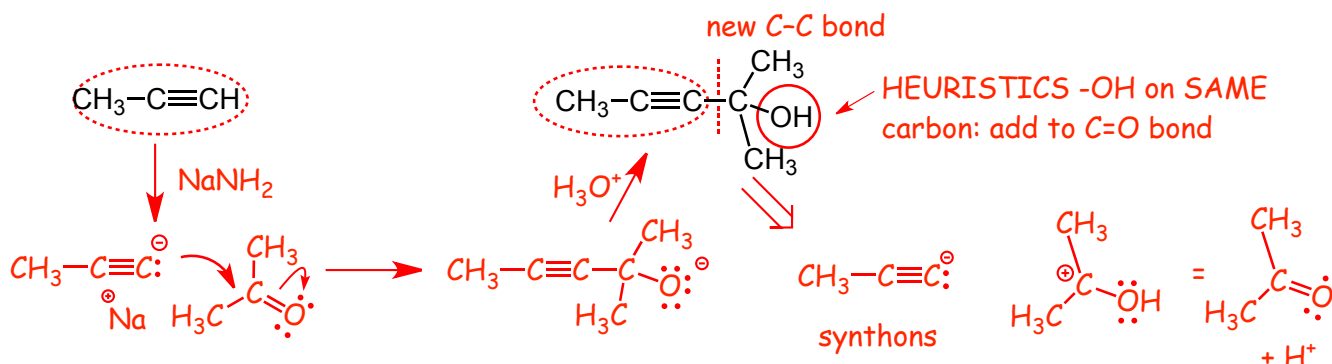
- Note 1... 2.... 3.... notation, it is **important!**

5.3 Examples in Synthesis

As a simple example of a multi-step reaction that forms a new C-C bond followed by two different **functional group interconversions** (FGI or F.G.I.):

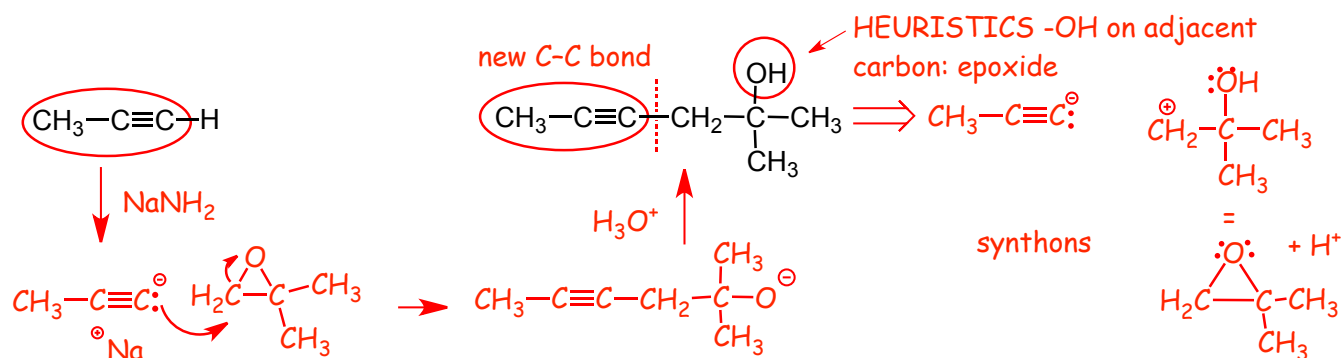


Synthesis Example 1:



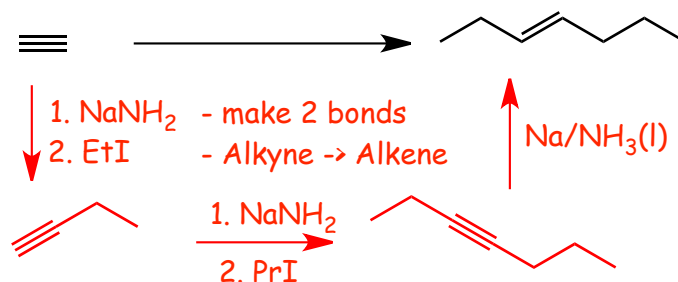
- Look for starting materials in product (circled)
- Any C-C bonds to make? (yes)
- Heuristics:** The -OH is on the **same** carbon as new C-C bond, therefore, the reaction must be addition to a **carbonyl (C=O bond)**.

Synthesis Example 2:

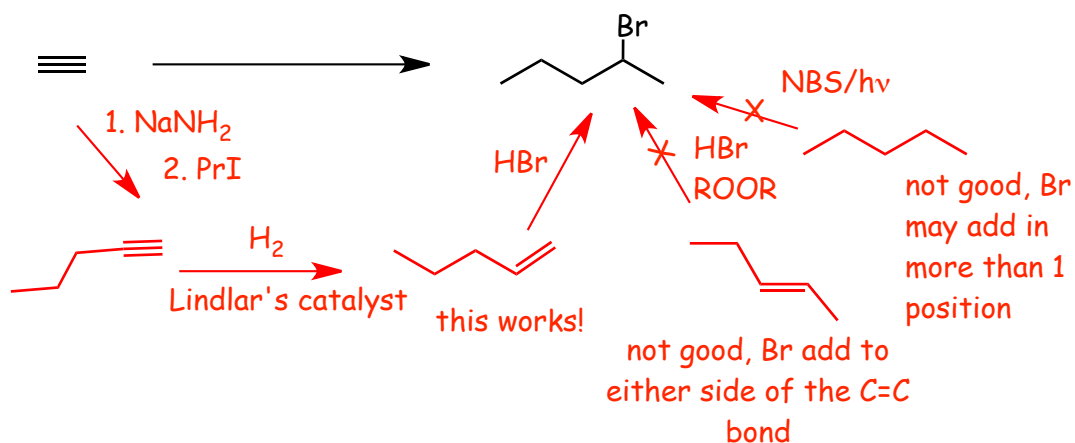


1. Look for starting materials in product (circled)
2. **Heuristics:** The -OH is on a carbon that is **adjacent** to the carbon involved in making the new C-C bond, therefore, this must be addition to an **epoxide**.

Synthesis Example 3:

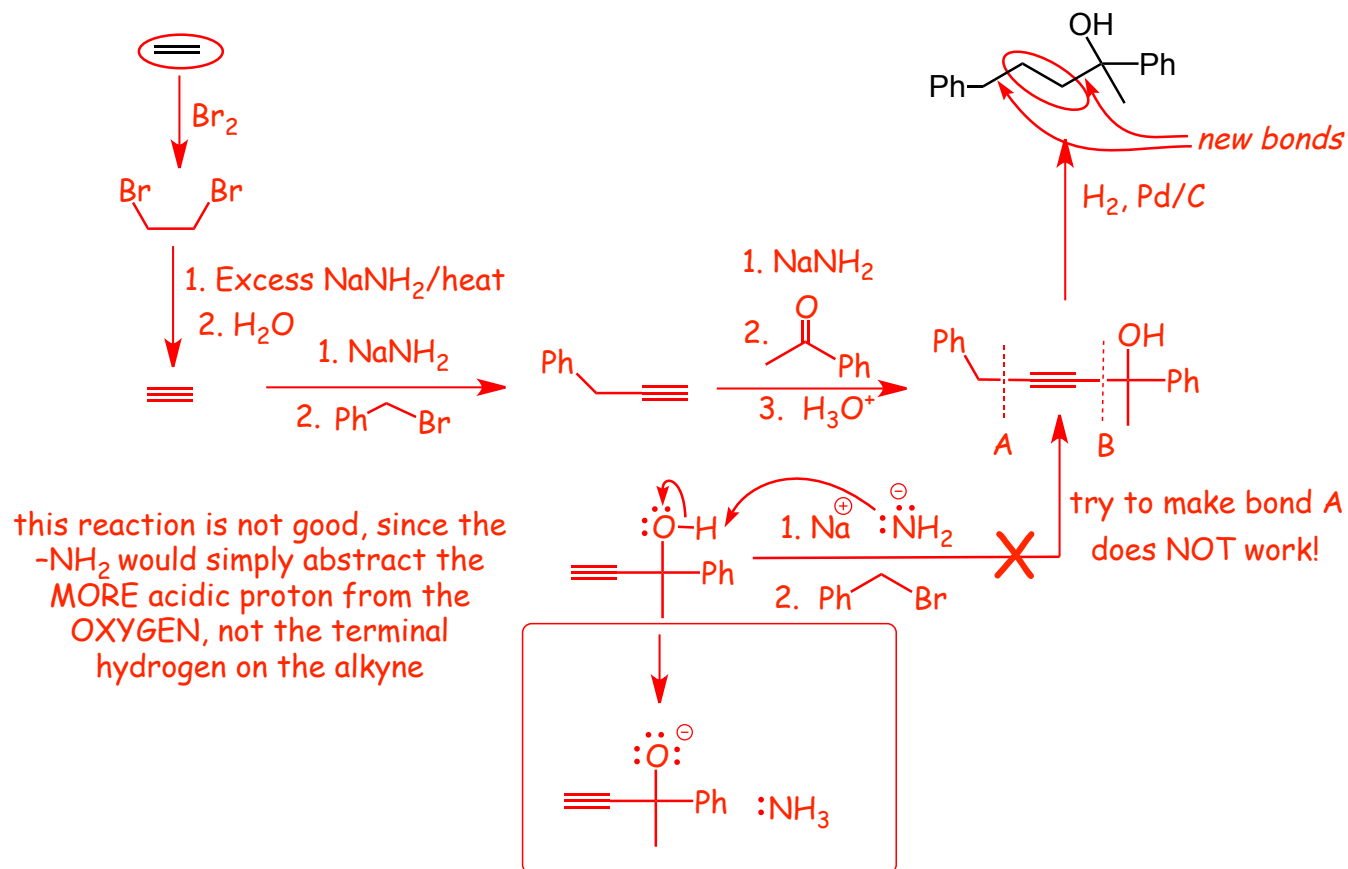


Synthesis Example 4: Synthesize the target structure on the right from the starting alkyne on the left



- There is only one good way of getting the bromine onto the required carbon in the last step in the synthesis
- Conversion of the alkyne to the alkene does not involve stereochemistry, therefore, $\text{Na}/\text{NH}_3(\text{l})$ could have been used equally well for this step.

Synthesis Example 5: Synthesize the target structure on the right from the starting alkene on the left:



- The order in which the two C-C bonds are made is important.
- If we try to make bond **A** **after** making bond **B**, then we will have a problem, the sodium amide (NaNH_2) will not deprotonate the terminal alkyne to make an acetylide anion, instead it will simply deprotonate the -OH alcohol group as shown above.
- This is a common issue when dealing with organic structures that have multiple functional groups, we need to pay attention to all possible reactions!

6 Alkynes : 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.

