

# CM1501 Tutorial/Assignment Collation

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## Tutorial 1 (Bonding, Structure, Nomenclature)

▼ What is the electronic relationship between a carbanion and a trivalent nitrogen compound such as NH<sub>3</sub>?

The carbanion is isoelectronic with (has the same number of electrons as) trivalent nitrogen compound NH<sub>3</sub>.

▼ Geometry of carbanion?

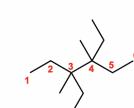
Carbanion is tetrahedral (including the projection of lone pair) at the negatively charged trivalent carbon due to minimized electronic repulsion based on VSEPR.

The geometry is **trigonal pyramid** if projection of lone pair is omitted.

▼ Propose structures and give IUPAC names for

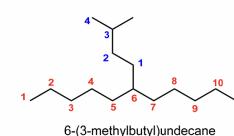
(a) diethyldimethylhexane (b) (3-methylbutyl)-substituted alkane

(a) A diethyldimethylhexane

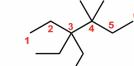


3,4-diethyl-3,4-dimethylhexane

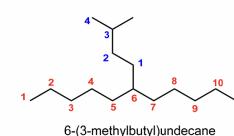
(b) A (3-methylbutyl)-substituted alkane



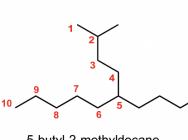
6-(3-methylbutyl)undecane



3,3-diethyl-4,4-dimethylhexane



Parent chain has to be at least a undecane (C11). One less carbon will change the parent chain and the answer will be incorrect; e.g.:



5-butyl-2-methyldecane



cyclopentyne

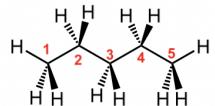
## Assignment 1

▼ Why do you suppose no one has ever been able to make cyclopentyne as a stable molecule?

- In a compound containing a carbon-carbon triple bond, atoms bonded to the sp-hybridized carbons are expected to lie in a linear, straight line due to the required 180° bond angle.
- It is not possible to form a five-membered ring if 4 carbons must have a linear relationship.
- Cyclopentyne will have too high angle strains.

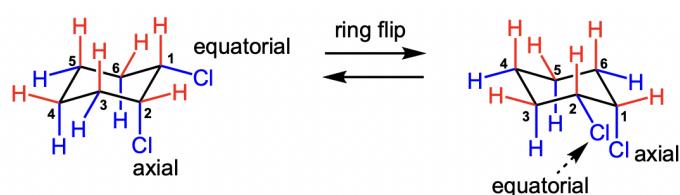
## Assignment 2 (Alkanes)

▼ Draw the most stable conformation of pentane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.



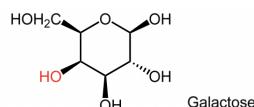
Most stable conformation is the line structure.

- ▼ A 1,2-cis disubstituted cyclohexane, e.g. cis-1,2-dichlorocyclohexane, must have one group axial and one group equatorial. Explain.

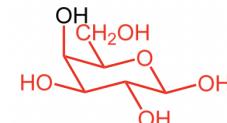


- all cis substituents are on the same side of the ring plane, and that two adjacent cis substituents have an axial-equatorial relationship.
- After the ring flip, the relationship of the two substituents is still axial-equatorial.
- No two adjacent cis substituents can be converted to being both axial or both equatorial by a ring flip.

- ▼ Galactose, a sugar related to glucose, contains a six-membered ring as shown. Draw galactose in its more stable chair conformation.

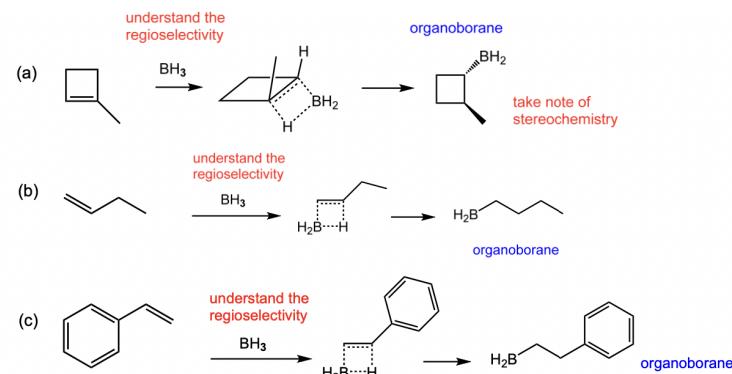


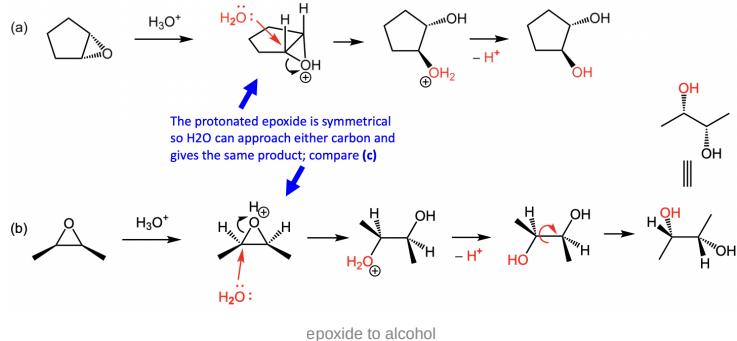
All substituents except the OH groups are in equatorial positions to minimize unfavourable 1,3-diaxial interactions (min steric strains)



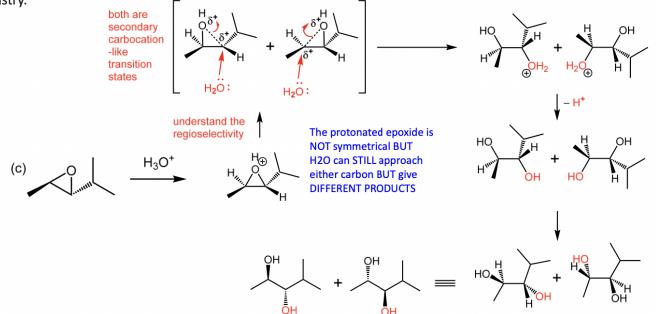
## Tutorial 3 (Alkenes, Alkynes)

Draw the structures of the organoboranes formed when borane reacts with each alkene below, including the regiochemistry and stereochemistry as appropriate. Propose a mechanism for each reaction.

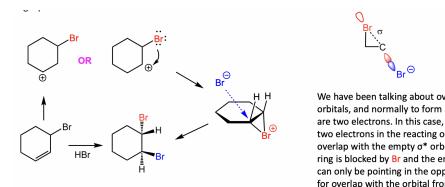
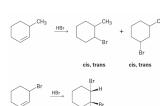




Provide the mechanism and products for the acid-catalyzed epoxide opening reactions below, including appropriate stereochemistry.



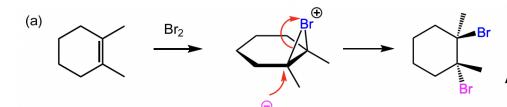
▼ Reaction of  $\text{HBr}$  with 3-methylcyclohexene yields a mixture of four products: cis- and trans-1-bromo-3-methylcyclohexane and cis- and trans-1-bromo-2-methylcyclohexane. The analogous reaction of  $\text{HBr}$  with 3-bromocyclohexene yields trans- 1,2-dibromocyclohexane as the sole product. Draw structures of the possible intermediates, and then explain why only a single product is formed in this reaction.



## Assignment 3

### Alkenes

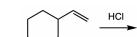
- $\text{H-X}$ : normal carbocation intermediate
- $\text{X-X} / \text{X}^+ / \text{Hg(OAc)}_2$ : 3-membered ring intermediate, no need draw TS (dotted bonds)
- for synthesis, just write conditions and products, don't need arrow pushing mechanism, unless stated in the qns specifically (mechanism)

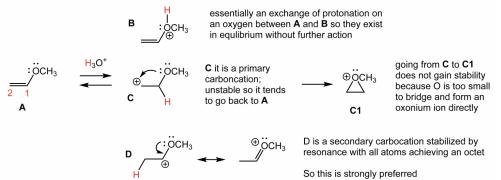
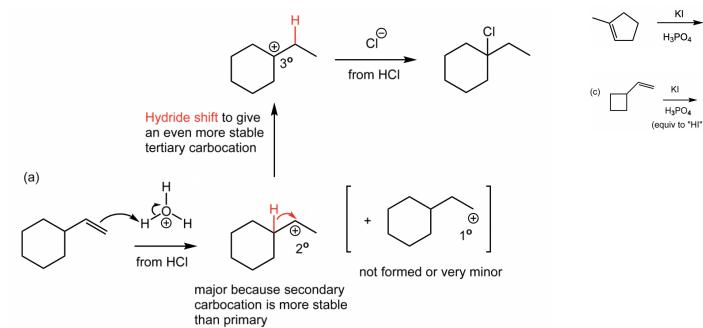


- The C=C double bond is planar, so the  $\text{Br}^-$  could approach either from the top or the bottom side of the averaged molecular plane, leading to A and B.
- A and B are a pair of enantiomers.
- In similar questions like this, you may use either reaction to show the general mechanism. YOU DO NOT NEED TO SHOW BOTH UNLESS YOU ARE TOLD TO DO SO.

if asked to show stereochemistry

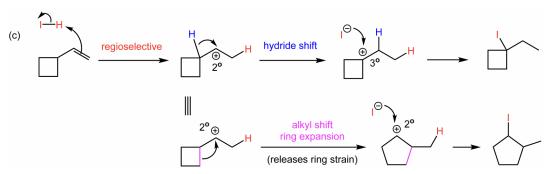
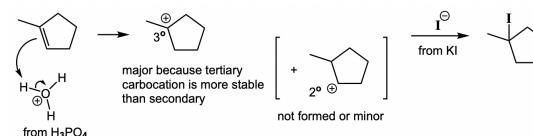
- ▼ Predict the major product and show the complete mechanism for each electrophilic reaction below.



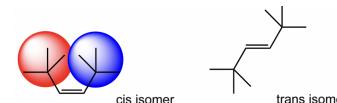
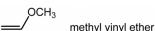


▼ trans-But-2-ene is a more stable than cis-but-2-ene by only 4 kJ mol<sup>-1</sup>, but trans-2,2,5,5-tetramethylhex-3-ene is more stable than its cis isomer by 39 kJ mol<sup>-1</sup>. Explain.

- As expected, the two trans compounds are more stable than their cis counterparts. The cis-trans difference is much more pronounced for the tetramethyl compound, however.
- Due to the bulky nature of the t-butyl groups, there is extreme crowding of the overall electron clouds of the two cis t-butyl groups. Steric strain is much more significant than the dimethyl case, making the cis isomer much less stable than the trans isomer.



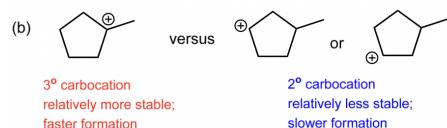
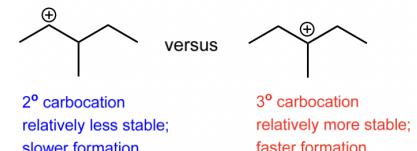
▼ When methyl vinyl ether reacts with a strong acid, the proton adds to C2 exclusively, instead of C1 or the oxygen atom. Draw the three protonated forms of methyl vinyl ether and explain this observation.



▼ Qualitatively determine which alkene in each pair would be expected to form a carbocation faster in an electrophilic addition reaction.

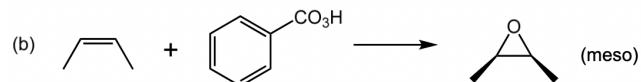
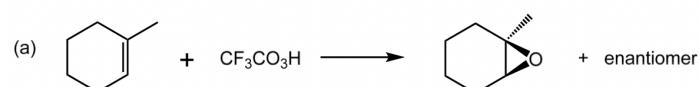
- Consider protonation as a simple electrophilic addition reaction.

- In the formation of carbocation in EACH reaction, recognise the regioselectivity.
- Compare the relative stability of the carbocations.
- A more stable carbocation will form more rapidly than a less stable one.



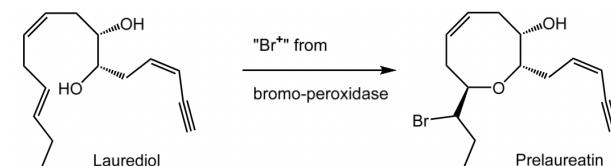
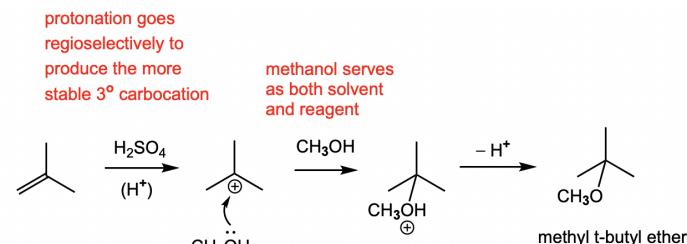
▼ m-CPBA is not the only peroxyacid capable of epoxide formation. For each reaction below, predict the product or products.

(use wedge and dash)



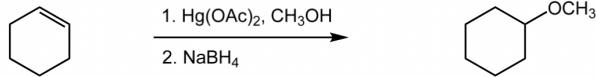
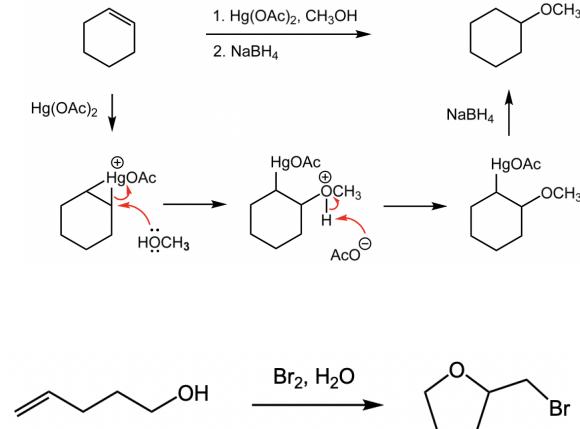
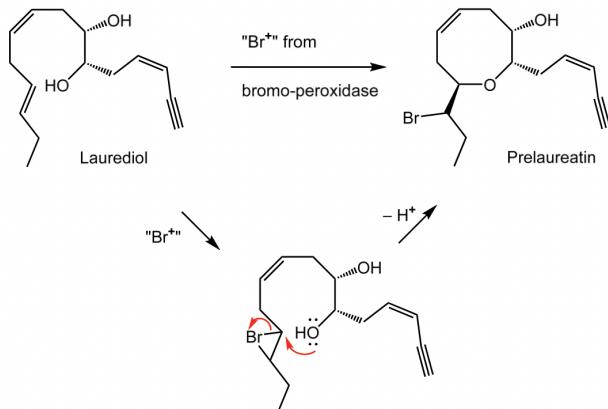
▼ Reaction of 2-methylpropene with CH<sub>3</sub>OH in the presence of H<sub>2</sub>SO<sub>4</sub> catalyst yields methyl *tert*-butyl ether, CH<sub>3</sub>OC(CH<sub>3</sub>)<sub>3</sub>, by a mechanism analogous to that

of acid-catalysed alkene hydration. Write the mechanism, using curved arrows for each step.



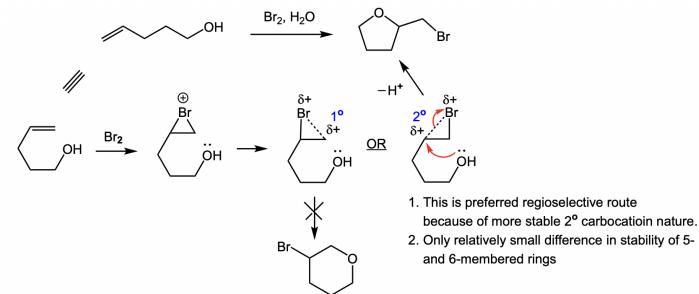
▼ Isolated from marine algae, Prelureatin is thought to be biosynthesised from laurediol by the following route. Propose a mechanism.

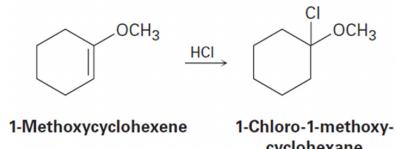
3-membered ring intermediate



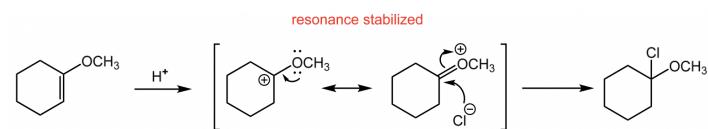
▼ Reaction of cyclohexene with mercury(II) acetate in CH<sub>3</sub>OH rather than H<sub>2</sub>O, followed by treatment with NaBH<sub>4</sub>, yields cyclohexyl methyl ether rather than cyclohexanol. Suggest a mechanism.

▼ Treatment of 4-penten-1-ol with aqueous Br<sub>2</sub> yields a cyclic bromo ether rather than the expected bromohydrin. Suggest a mechanism, using curved arrows to show electron movement.

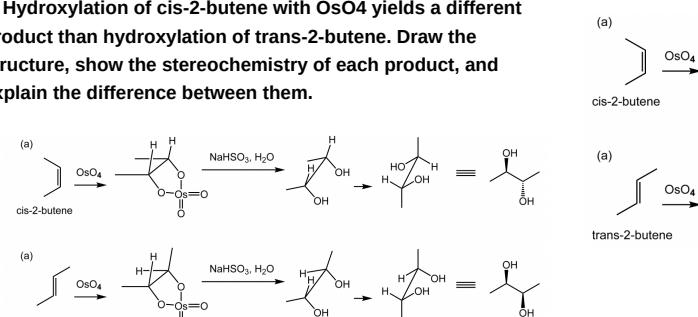




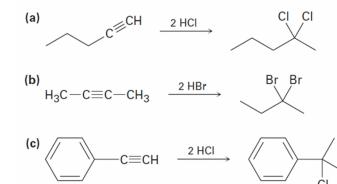
▼ Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as a sole product. Use resonance structures of the carbocation intermediate to explain why none of the alternate regioisomer is formed.



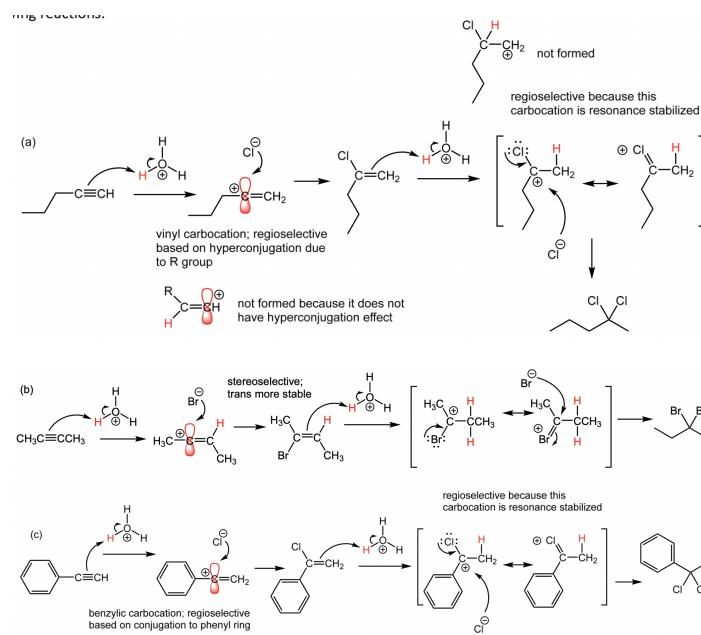
▼ Hydroxylation of cis-2-butene with OsO<sub>4</sub> yields a different product than hydroxylation of trans-2-butene. Draw the structure, show the stereochemistry of each product, and explain the difference between them.



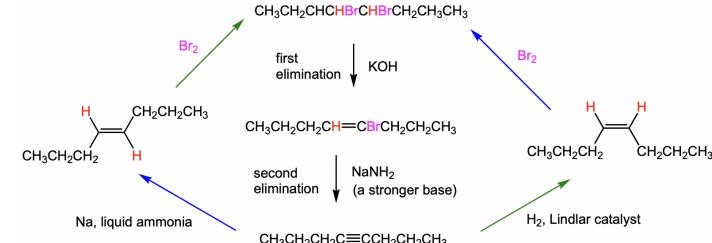
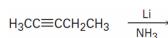
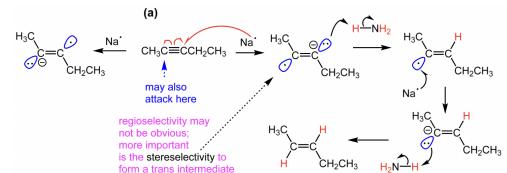
## Alkynes



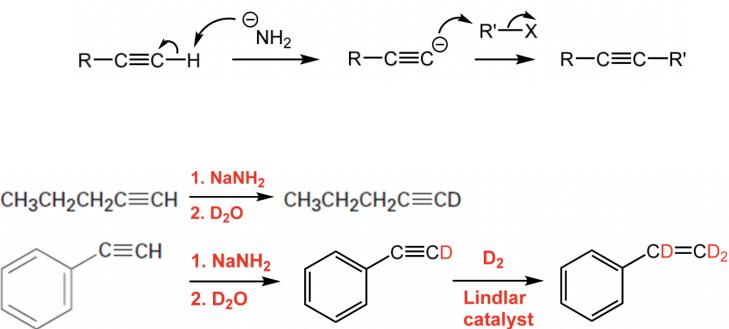
▼ Assuming that strong acids add to alkynes in the same manner as they add to alkenes, propose a mechanism for each of the following reactions.



▼ Alkyne to alkene via Na, NH<sub>3</sub>



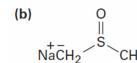
▼ Alkylation of terminal alkynes via  $\text{NaNH}_2$ ,  $\text{CH}_3\text{I}$



▼ Alkene to Alkyne: trans-5-decene → cis-5-decene and vice-versa

▼ Which of the following bases could be used to deprotonate 1-butyne?

(a) KOH – **No**  $\text{HO}^-$  is a weaker base than  $\text{C}\equiv\text{C}^-$  because oxygen is highly electronegative and can accommodate the negative charge better.



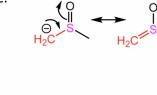
– **Yes**

For (b), (c) and (d):  
(1) For C-H acidity, the **GENERAL** decreasing order is:  $\text{spC-H} > \text{sp}^2\text{C-H} > \text{sp}^3\text{C-H}$

(2) So the **GENERAL** decreasing basicity order of the corresponding carbanions is:  
•  $\text{sp}^3\text{C}^- > \text{sp}^2\text{C}^- > \text{spC}^-$

(3) The above explains why (b) & (c) is “Yes” because it involves a  $\text{sp}^3\text{C}^-$ ; Although the negative charge in (b) could be stabilized by resonance, the mismatch of C and S orbitals makes this resonance less effective than that in (4). So the  $\text{sp}^3\text{C}^-$  in (b) is still sufficiently basic to deprotonate 1-butyne.

(4) Answer for (d) is “No”. Although it is a  $\text{sp}^3\text{C}^-$ , the negative charge is stabilized by resonance, so it is not sufficiently basic to deprotonate 1-butyne.



## Tutorial 4 (Unsaturation, Conjugation, Isomerism, Stereochemistry)

optically inactive

1. achiral (no chiral centre - 4 diff subst)
2. meso (chiral with internal plane of symmetry)

3. racemic mixture (50:50) - derived from planar intermediate (carbocation, carboradical, C=O)
- depending on steric hindrance, if one product is more favourable  $\Rightarrow$  no 50:50  $\Rightarrow$  optically active
  - sometimes there's another chiral centre which is not affected  $\Rightarrow$  optically active

Stability of alkene products formed

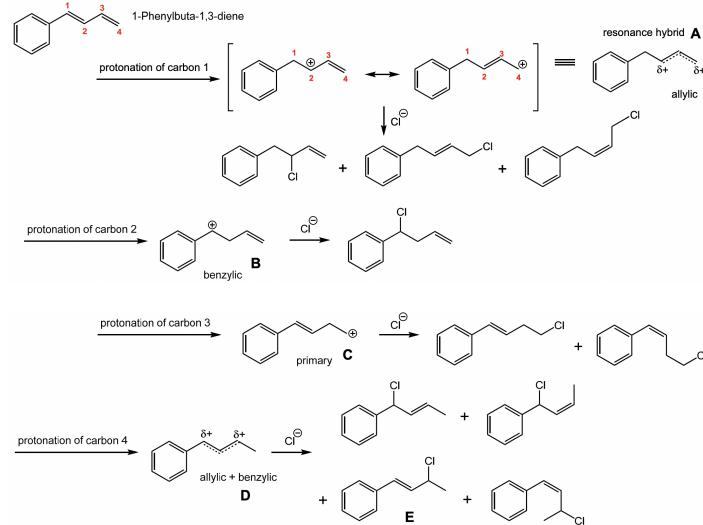
- stability of carbocation
  - most stable: benzylic + allylic
  - secondary + benzylic, secondary + allylic
  - primary
- substitution
- trans > cis
- conjugation

▼ Draw the possible products resulting from addition of 1 equivalent of HCl to 1-phenyl-1,3-butadiene. Which would you expect to predominate, and why?

- Carbocation stability: benzylic + allylic > sec + benzylic ~ sec + allylic > primary
- Substitution of alkene
- trans > cis
- conjugation of final product

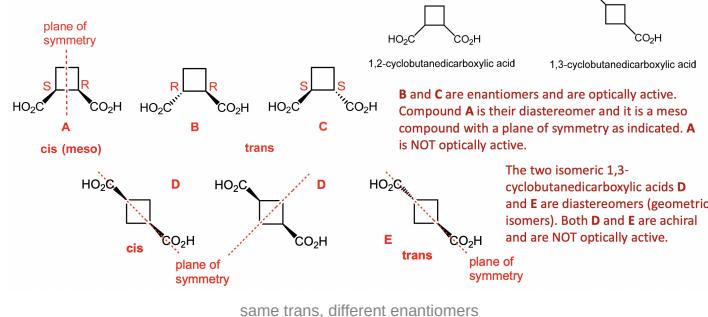
Carbocation resonance hybrid D is most stable because the positive charge is stabilized by an allylic system and a benzylic system, i.e. into the benzene ring.

(E)-3-Chloro-1-phenylbut-1-ene is the major product because the double bond is conjugated with the benzene ring and the double bond is the more stable trans isomer



▼ Draw all possible stereoisomers of 1,2-cyclobutanedicarboxylic acid, and indicate the inter-relationships. Which, if any, are optically active? Do the same for 1,3-cyclobutanedicarboxylic acid.

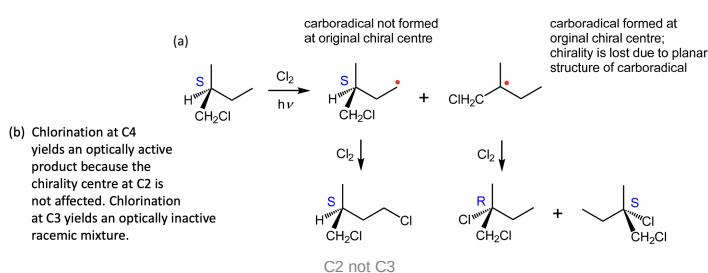
Draw all possible stereoisomers of 1,2-cyclobutanedicarboxylic acid, and indicate the inter-relationships. Which, if any, are optically active? Do the same for 1,3-cyclobutanedicarboxylic acid.



▼ (S)-1-Chloro-2-methylbutane undergoes light-induced reaction with Cl<sub>2</sub> to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane

(a) Write the reaction, showing the correct stereochemistry of the reactant.

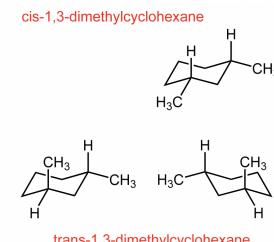
(b) One of the two products is optically active, but the other is optically inactive. Which is which?



▼ Draw both cis- and trans-1,3-dimethylcyclohexane in their more stable chair conformations.(a) How many stereoisomers are there of cis-1,3-dimethylcyclohexane, and how many of trans-1,3-dimethylcyclohexane?

(b) Are any of the structures chiral?

(c) What are the stereochemical relationships among the various stereoisomers of 1,3-dimethylcyclohexane?

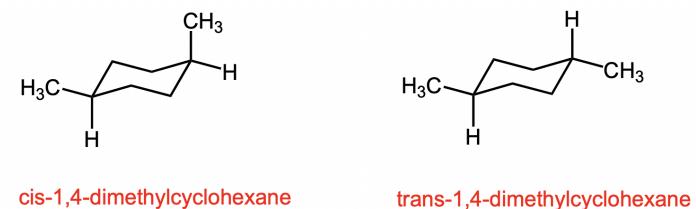


- a) There is only one stereoisomer of cis-1,3-dimethylcyclohexane, and there are two stereoisomers of trans-1,3-dimethylcyclohexane.
- b) cis-1,3-Dimethylcyclohexane is an achiral meso molecule; trans-1,3-dimethylcyclohexane exists as a pair of chiral enantiomers.
- c) The two trans stereoisomers are enantiomers; and both are diastereomers of the cis stereoisomer.

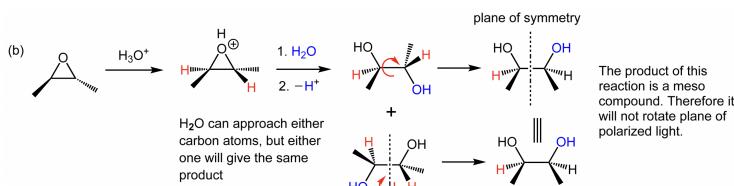
▼ Draw both cis- and trans-1,4-dimethylcyclohexane in their more stable chair conformations.(a) How many stereoisomers are there of cis-1,4-dimethylcyclohexane, and how many of trans-1,4-dimethylcyclohexane?

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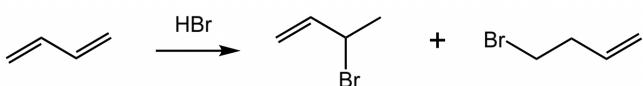
(c) What are the stereochemical relationships among the various stereoisomers of 1,4-dimethylcyclohexane?



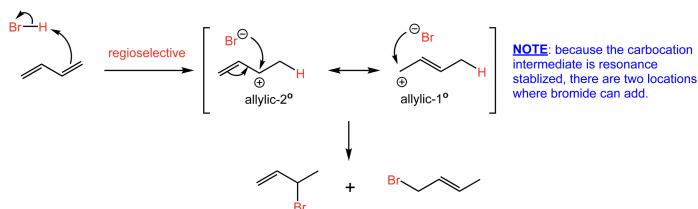
- (a) There is only one stereoisomer of each of the 1,4-dimethylcyclohexanes.
- (b) Neither 1,4-dimethylcyclohexane is chiral because there is a plane of symmetry in each molecule.
- (c) The two 1,4-dimethylcyclohexanes are diastereomers (geometric isomers).



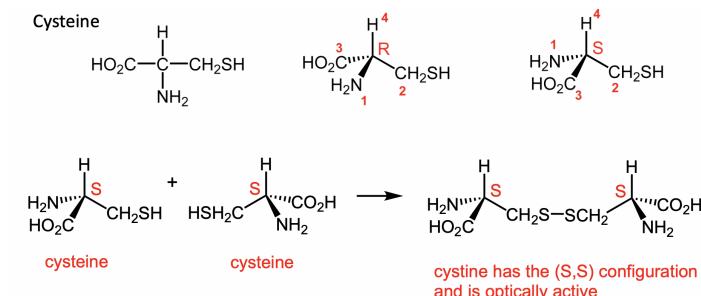
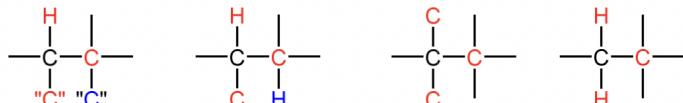
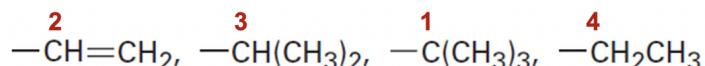
## Assignment 4



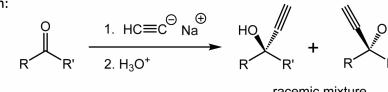
▼ When 1,3-butadiene reacts with one mole of HBr, two isolable products result.  
Propose a mechanism to explain this



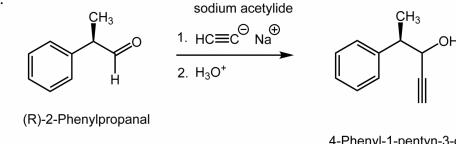
▼ Sequence rule: look at all substituents to the C atom



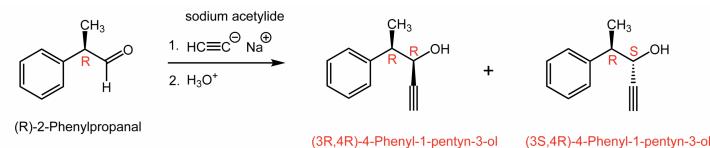
Background information:



Imagine that a reaction similar to that in the above is carried out between sodium acetylide and (R)-2-phenylpropanal to yield 4-phenyl-1-pentyn-3-ol:



- (a) Is the product chiral?  
(b) Draw all possible products. Is the product mixture optically active? Explain.



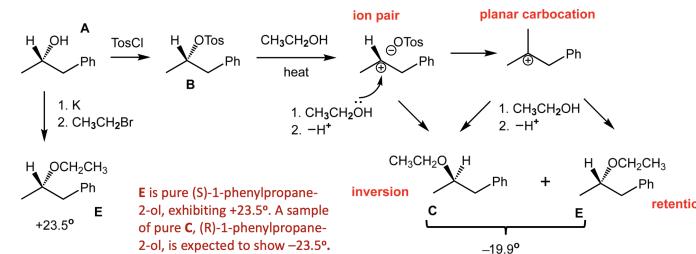
- (a) The above reaction gives two products. The  $\text{C}=\text{O}$  function is planar so the acetylide anion could approach from either side of the  $\text{C}=\text{O}$  plane to give the two products expected to be in equal amounts.

The original R chiral center in the starting material remains the same in both products because the reaction does not involve this chiral center.

The new chiral center in the products are however different to give the R and S configuration.

b) The two products are then a mixture of the (3R,4R) and (3S,4R) diastereomers of 4-phenyl-1-pentyn-3-ol. The product ratio cannot be predicted.

Since the products are diastereomers, each is optically active and so the product mixture is also optically active.

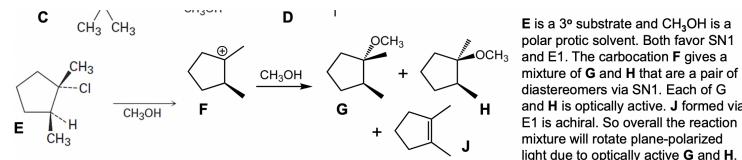
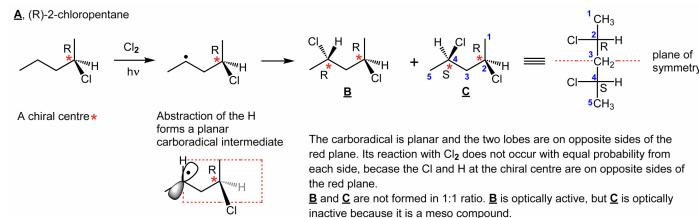


From ion pair, the product is **C** with inversion. From carbocation, it should give a 1:1 mixture of **C** (inversion) and **E** (retention). So the presence of **E** as minor product reduces the optical activity to -19.9°.

CH3CH2OH is a poor Nu, and a polar protic solvent → favours SN1; complete racemization forms optical inactive mixture but optical activity of -19.9 is observed.

## Tutorial 5 (R-X)

▼ Assume that you have carried out a radical chlorination reaction on (R)-2-chloropentane and have isolated (in low yield) 2,4-dichloropentane. How many stereoisomers of the product are formed, and in what ratio? Are any of the isomers optically active?

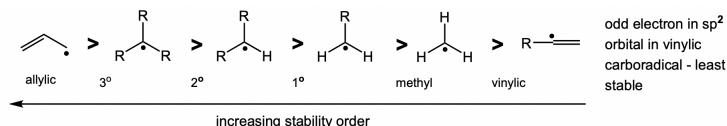


CH<sub>3</sub>CH<sub>2</sub>OH is a poor nucleophile, and it is also a polar protic solvent. The conditions favor SN1.

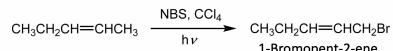
If it is complete racemization, then the product mixture should be optically inactive. But optical activity of -19.9° is observed.

## Assignment 5

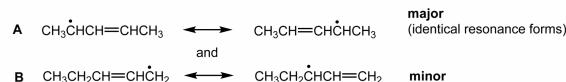
- inversion does NOT necessarily mean R/S exchange
- vinylic organic halides do not undergo nucleophilic substitution (CH<sub>2</sub>=CHBr)
- tertiary carbocation is stable, hence tertiary halides can react with HCl at 0 deg Cel as well
- racemizes → carbocations are generally formed as intermediate



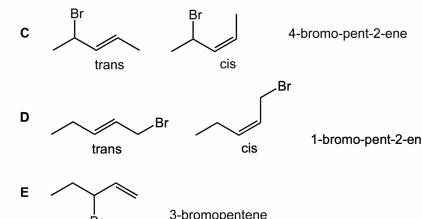
A chemist requires a large amount of 1-bromo-2-pentene as starting material for a synthesis and decides to carry out an NBS allylic bromination reaction. What is wrong with the following synthesis plan? What side products would form in addition to the desired product?



Abstraction of hydrogen by  $\text{Br}^+$  can produce either of two allylic carboradicals **A** and **B**. **A** is allylic+2°, so it is more likely to be formed because it is more stable than the allylic-1° **B**. Moreover, **A** is a more stabilized, identical pair of resonance structures.

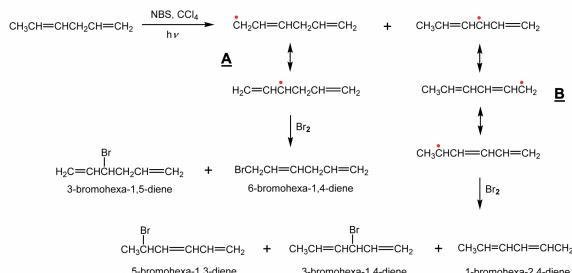


note the resonance forms of the radicals



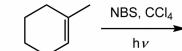
The major product is 4-bromo-2-pentene **C**, derived from **A**, and not the desired product, 1-bromo-2-pentene **D** from **B**. Take note that 3-bromo-pentene **E** is also formed as a minor product from **B**.

What product(s) would you expect from the reaction of hexa-1,4-diene with NBS? What is the structure of the most stable radical intermediate?

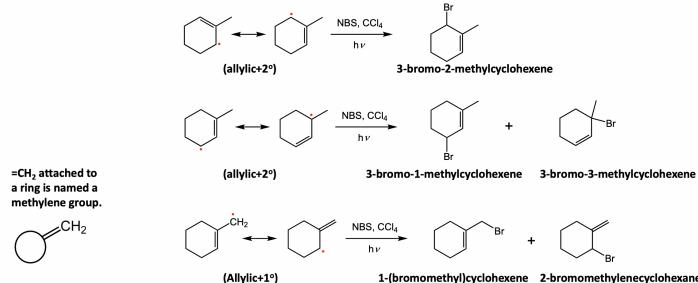


The intermediate **B** is more stable because the unpaired electron is delocalized over more atoms than in the intermediate **A**, and the resulting products from **B** should predominate.

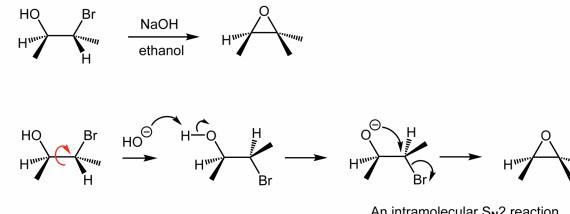
What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?



Three different allylic carboradical intermediates can be formed. Bromination of these intermediates can yield as many as five bromoalkenes. This is definitely not a good reaction to use in synthesis even if the products could be separated.



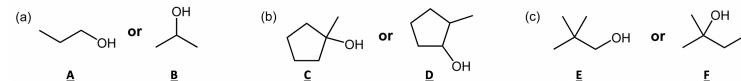
Bromohydrins can be converted into epoxides when treated with base. Propose a mechanism, using curved arrows to show the electron flow.



An intramolecular  $S_N2$  reaction

▼ Retention of configuration via 2  $S_N2$  mechanisms

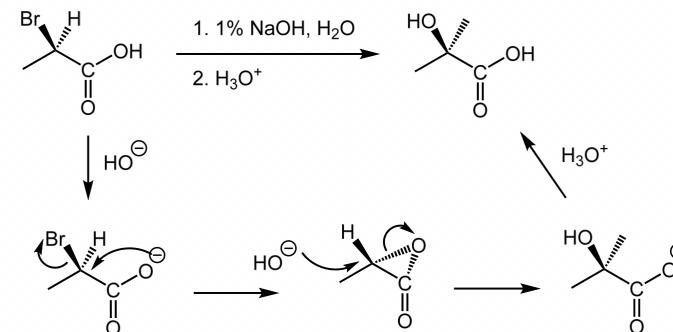
Choose the alcohol from each pair below that would react faster with  $\text{HX}$  to form the corresponding alkyl halide.



(a) The  $1^\circ$  alcohol **A** would go exclusively through an  $S_N2$  mechanism. The  $2^\circ$  alcohol **B** will undergo a mixture of  $S_N1$  and  $S_N2$  substitution. However, formation of a secondary carbocation from **B** is relatively slow, and steric effect in **B** is higher than that in **A**. Thus **A** will undergo a faster reaction.

(b)  $3^\circ$  alcohol **C** undergoes the fastest of  $S_N1$  reactions through a  $3^\circ$  carbocation, while  $2^\circ$  alcohol **D** is a relatively slow substrate for both  $S_N1$  and  $S_N2$  as mentioned in (a). Thus the  $3^\circ$  alcohol **C** would be expected to react faster.

(c)  $3^\circ$  alcohol **E** undergoes the fastest of  $S_N1$  reactions through a  $3^\circ$  carbocation. Alcohol **E** is  $1^\circ$  so it does not undergo  $S_N1$ . Though **E** is  $1^\circ$ , the steric effect of the adjacent bulky t-butyl group slows down the  $S_N2$  reaction of **E**. Thus the  $3^\circ$  alcohol **E** would be expected to react faster.

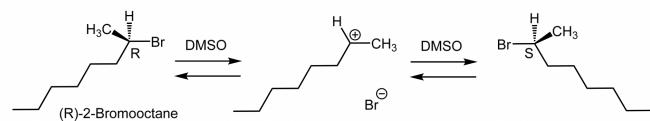


Two consecutive intramolecular  $S_N2$  reactions;  
two inversions of configuration = a net retention of configuration

▼ What effect would you expect to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane ( $\text{SN}1$ ) when the concentration of the ethanol is halved by adding diethyl ether as an inert solvent?

Halving the concentration of ethanol by dilution with diethyl ether reduced the polarity of the solvent and **decreases the rate**.

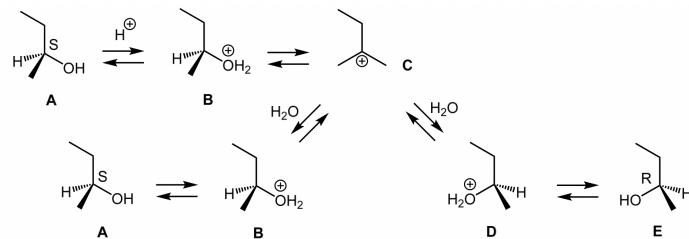
▼ (R)-2-Bromoocetane undergoes racemization to give ( $\pm$ )-2-bromoocetane when treated with NaBr in dimethyl sulfoxide. Explain.



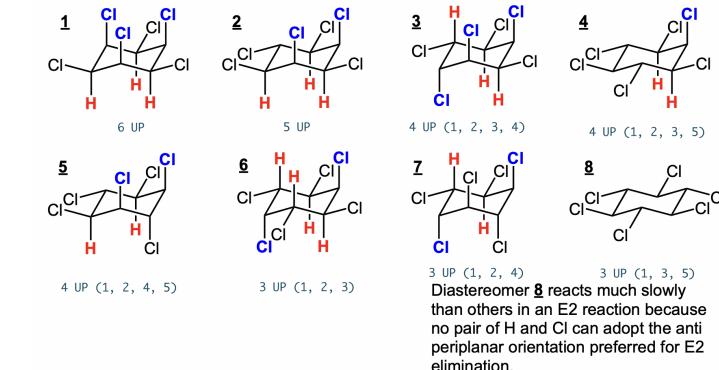
(R)-2-Bromoocetane is 2° and could undergo either S<sub>N</sub>1 or S<sub>N</sub>2. The polar solvent DMSO however encourages formation of carbocation so it favors S<sub>N</sub>1. When the carbocation is formed, Br<sup>-</sup> could attack from either side of the planar carbocation. After 50% of the starting material has reacted, the reaction mixture consists of 50% R enantiomer and 50% S enantiomer. Take note that the S enantiomer could also undergo the reversed S<sub>N</sub>1. So at equilibrium, the R starting material is completely racemized, i.e. a mixture of R and S stereoisomers is formed.

▼ (S)-2-Butanol slowly racemizes on standing in dilute sulfuric acid. Explain.

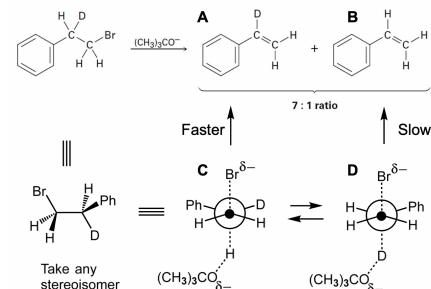
Protonation of A gives B that forms the carbocation C. Water then reacts with C from either side of the carbocation plane to return to B and also form its mirror image D. B and D after deprotonation give the pair of enantiomers A and E, respectively. So on standing, an equilibrium is reached to give a racemic mixture of A and E.



▼ There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

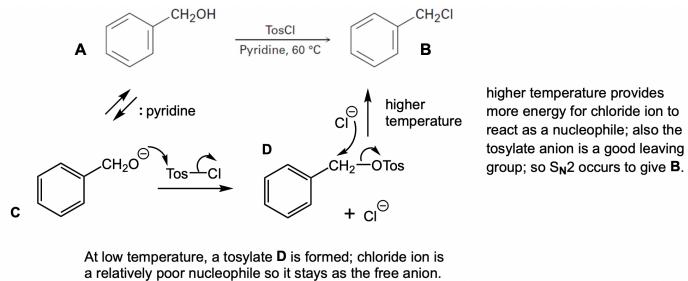


▼ Treatment of 1-bromo-2-deutero-2-phenylethane with strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in an approximately 7:1 ratio. Explain.

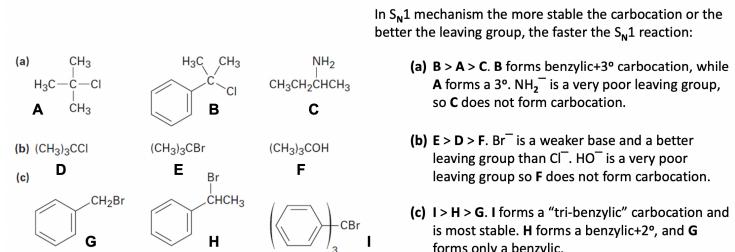
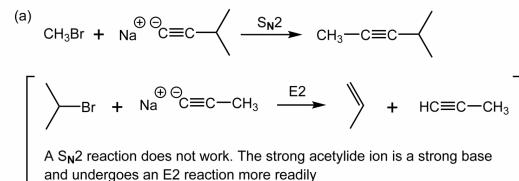
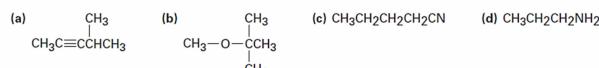


Carbon-deuteron bond is relatively stronger than carbon-hydrogen bond due to the heavier deuterium atom. In an E2 elimination, the transition state could be either C or D. Removing deuterium in D is relatively slower and requires higher energy. So E2 of C goes faster to give a larger proportion of A.

▼ When a primary alcohol is treated with p-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at higher temperature, an alkyl chloride is often formed. Explain.

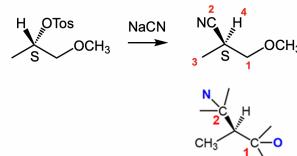


How might you prepare each of the following molecules using a nucleophilic substitution reaction at some step?



- LG: OTos- > Br- > OCH3-

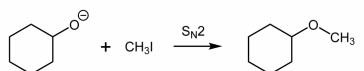
Reaction of the following  $S$  tosylate with cyanide ion yields a nitrile product that also has  $S$  stereochemistry. Explain.



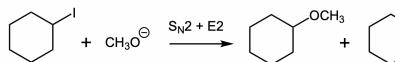
Starting material is 2° substrate that could go either  $S_N1$  or  $S_N2$ . But  $\text{CN}^-$  is a very good nucleophile that favors  $S_N2$ . Thus it is expected to give the product with inversion of configuration.

Applying the Sequence Rules, the 1-2-3-4 priorities are as shown will still give a  $S$  configuration for the product.

Ethers can often be prepared by  $S_N2$  reaction of alkoxide ions,  $\text{RO}_2^-$ , with alkyl halides. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the two possible routes shown below would you choose? Explain.



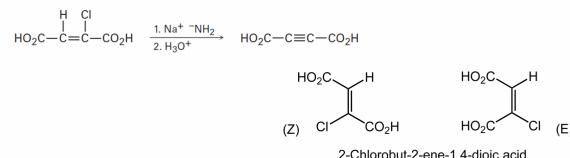
This is an excellent method of ether preparation because iodomethane is very reactive in  $S_N2$  reaction. The alkoxide is a strong nucleophile also favoring  $S_N2$ . Although the alkoxide is also a strong base, there is no possible elimination reaction.



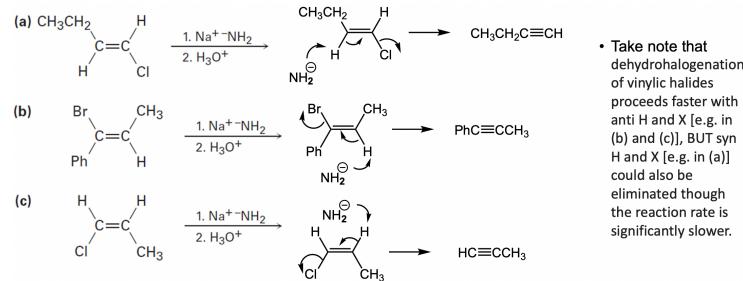
Reaction of a 2° substrate with a strong nucleophile that is also a strong base normally results in both substitution and elimination reaction. This is a less satisfactory method of ether preparation.

## Dehydrohalogenation of Vinylic Halides

Alkenes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (Z)-2-chloro-2-butenedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?



H and Cl are anti to each other in the Z isomer and are syn in the E isomer. Since Z isomer reacts 50 times faster than the E isomer, elimination must proceed more favorably when the H and Cl to be eliminated are anti to one another. This is similar to the stereochemical result that occurs in E2 elimination of alkyl halides.

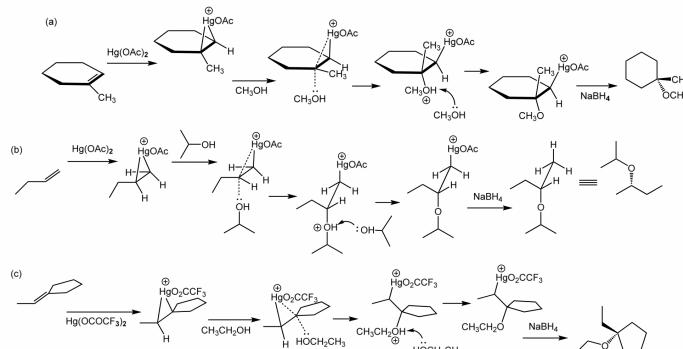


## Alkoxymercuration

The alkoxymercuration of alkenes involves the formation of an organomercury intermediate (**I**), which is reduced with NaBH4 to give an ether product.

- ▼ For each reaction below, predict the ether product and provide the mechanism formation.

- NOTE: In each answer, the double bond is planar, so the mercurinium ion could be formed from either side of the plane.
- Only one enantiomer is given in each answer.

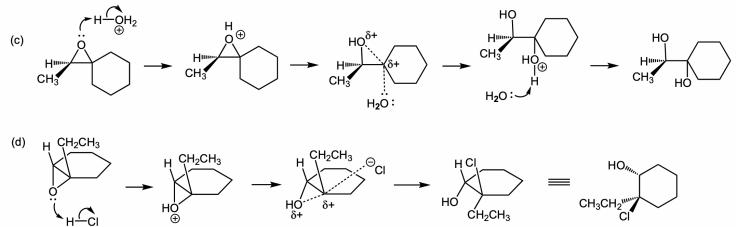


## Tutorial 6 (Alcohol, Ethers, Epoxides, Aldehyde, Ketons, Carboxylic Acids, Nitriles)

### Epoxide Mechanism

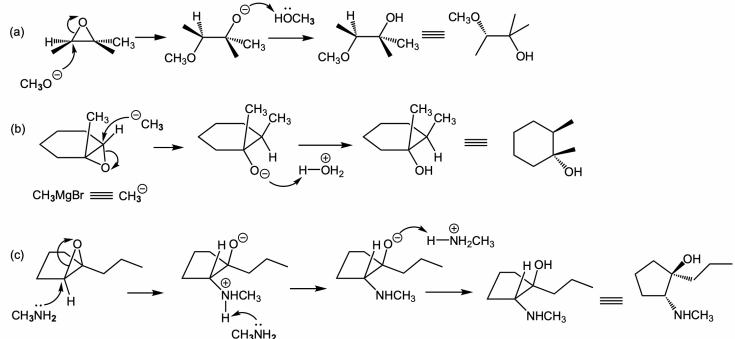
#### Acidic condition

- Protonation of epoxide occurs first
- Stability of  $\delta+$  is the key consideration (i.e. attacks the C that with more alkyl groups)
- e.g. HCl or HBr in ether

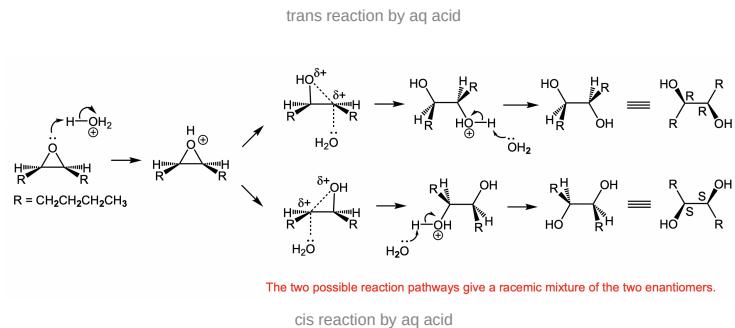
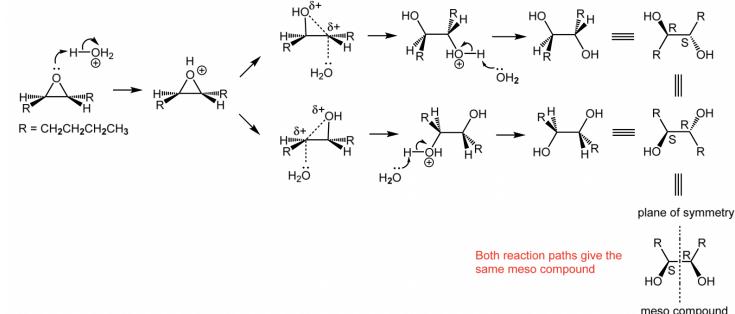


### Neutral / Basic conditions

- Nu attacks directly by SN2.
- Steric effect is the key consideration (i.e. attacks the C with less alkyl/bulky groups).
- e.g.  $\text{CH}_3\text{MgBr}$  followed by  $\text{H}_3\text{O}^+$



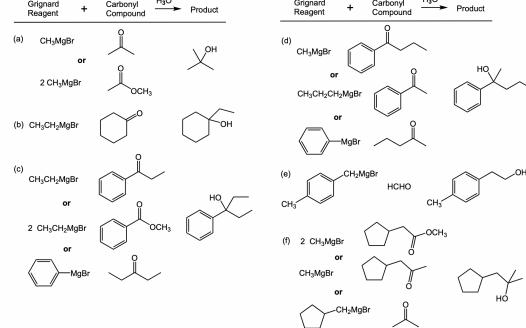
## Epoxide Hydrolysis Mechanism



- substituent resonance effect is stronger than inductive effect

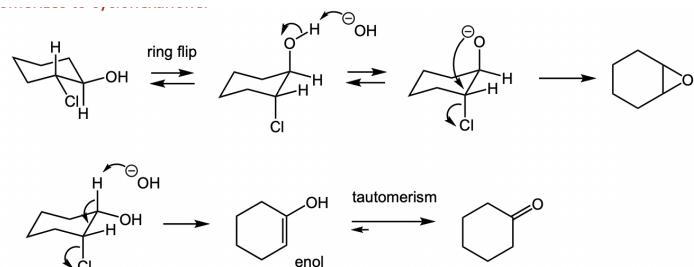
What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

- In general, the smaller Grignard reagents such as  $\text{CH}_3\text{MgBr}$ ,  $\text{CH}_3\text{CH}_2\text{MgBr}$  and  $\text{PhMgBr}$  are commercially available.



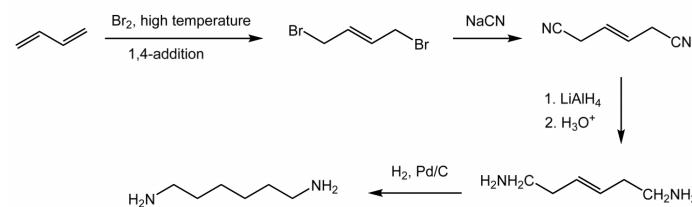
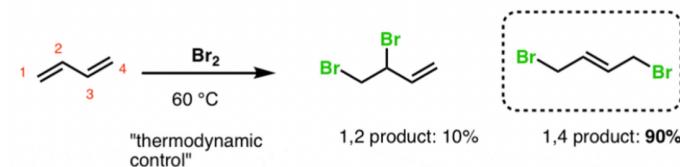
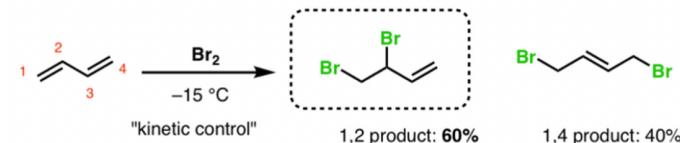
▼ Treatment of trans-2-chlorocyclohexanol with  $\text{NaOH}$  yields 1,2-epoxycyclohexane, but reaction of the cis isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions and explain why the different results are obtained.

- In the trans isomer, the OH and Cl are in the trans orientation that allows epoxide formation to occur via a  $\text{SN}2$ -type reaction.
- However, epoxidation cannot occur for the cis isomer.
- Instead the base  $\text{HO}^-$  brings about E2 elimination, producing an enol that tautomerizes to cyclohexanone.



### ▼ Synthesis of 1,6-hexanediamine from 1,3-butadiene

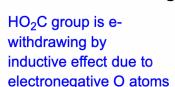
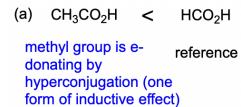
#### 1,2 and 1,4-addition of $\text{Br}_2$ to butadiene as a function of temperature



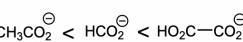
### Acidity Comparison

- the more stable is the anion formed, the more acidic is the acid.
- The negative charge on an anion could be stabilised by inductive or resonance effect of an electron-withdrawing atom or group.
- resonance effect > inductive effect

▼ acetic acid < formic acid < oxalic acid



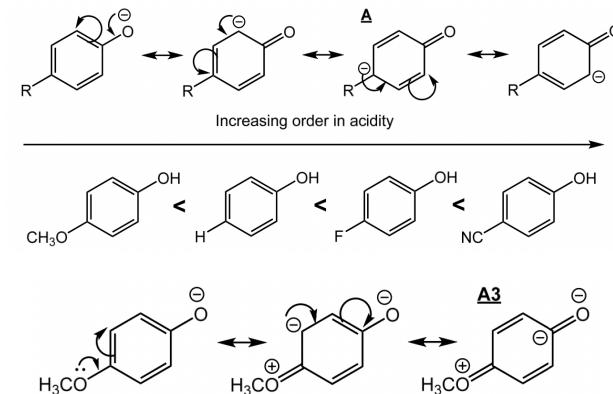
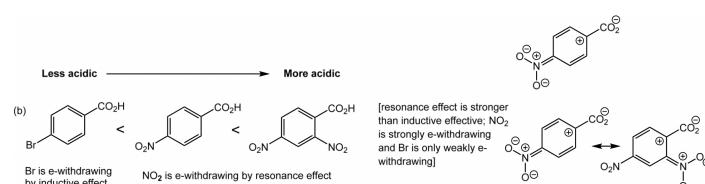
Consider the relative stability of :



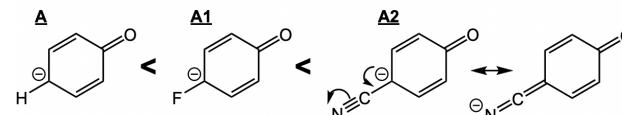
▼ 3-fluoropropanoic acid < iodoacetic acid < Fluoroacetic acid

- Mainly by inductive effect due to EN.
- F is more EN than I.
- Inductive effect decreases significantly in distance.
- Hence, 3-fluoropropanoic acid is least acidic.

▼ p-Bromobenzoic acid < p-nitrobenzoic acid < 2,4-dinitrobenzoic acid



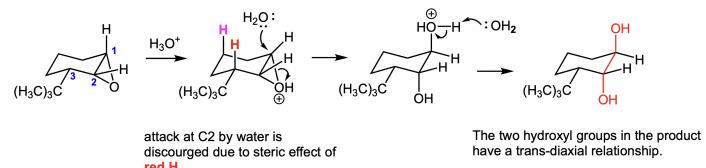
- Using phenol as reference
- The -CH<sub>3</sub>O group is e-donating group. As illustrated, the O lone pair is delocalised into the ring by resonance, and forms a negative charge next to the phenoxide ion in A3. This is least stable. So the phenol is least acidic.



- In A1, the negative charge could be further stabilised by the e-withdrawing F due to its high electronegativity.
- In A2, the negative charge is stabilised by stronger resonance effect by placing the negative charge on electronegative N.

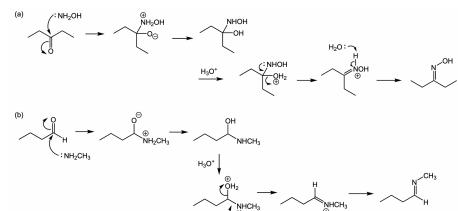
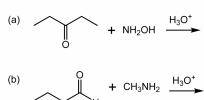
## Assignment 6

▼ Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a trans-diaxial 1,2-diol. What product would you expect to obtain from acidic hydrolysis of cis-3-t-butyl-1,2-epoxycyclohexane?



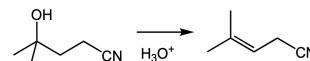
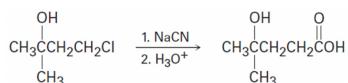
▼ Give the mechanisms and products.

In both mechanisms, after the nucleophilic addition, protonation and dehydration occurs to remove water and forms the C=N bond.

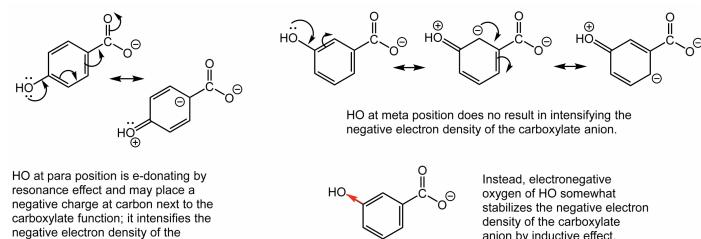


▼ What's wrong with the synthesis?

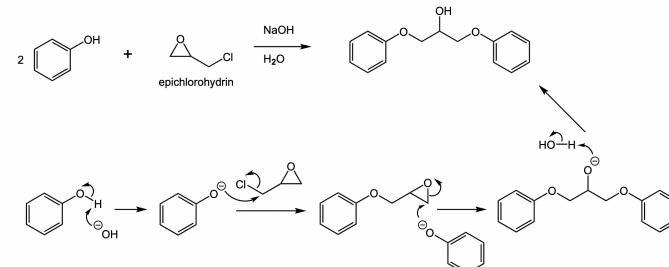
- The intermediate before hydrolysis of nitrile is a tertiary alcohol;
- acidic conditions applied also favour E1 elimination.



▼ Explain why a hydroxyl group in the para (4) position decreases the acidity while a hydroxyl group in the meta (3) position increases the acidity.



▼ In the formation of the prepolymer used to make epoxy resins, a bisphenol reacts with epichlorohydrin in the presence of a base. Show the product and mechanism when two moles of phenol react with epichlorohydrin.



▼ When the alcohol below is treated with POCl<sub>3</sub> and pyridine, the expected elimination product is formed. Propose a mechanism.

