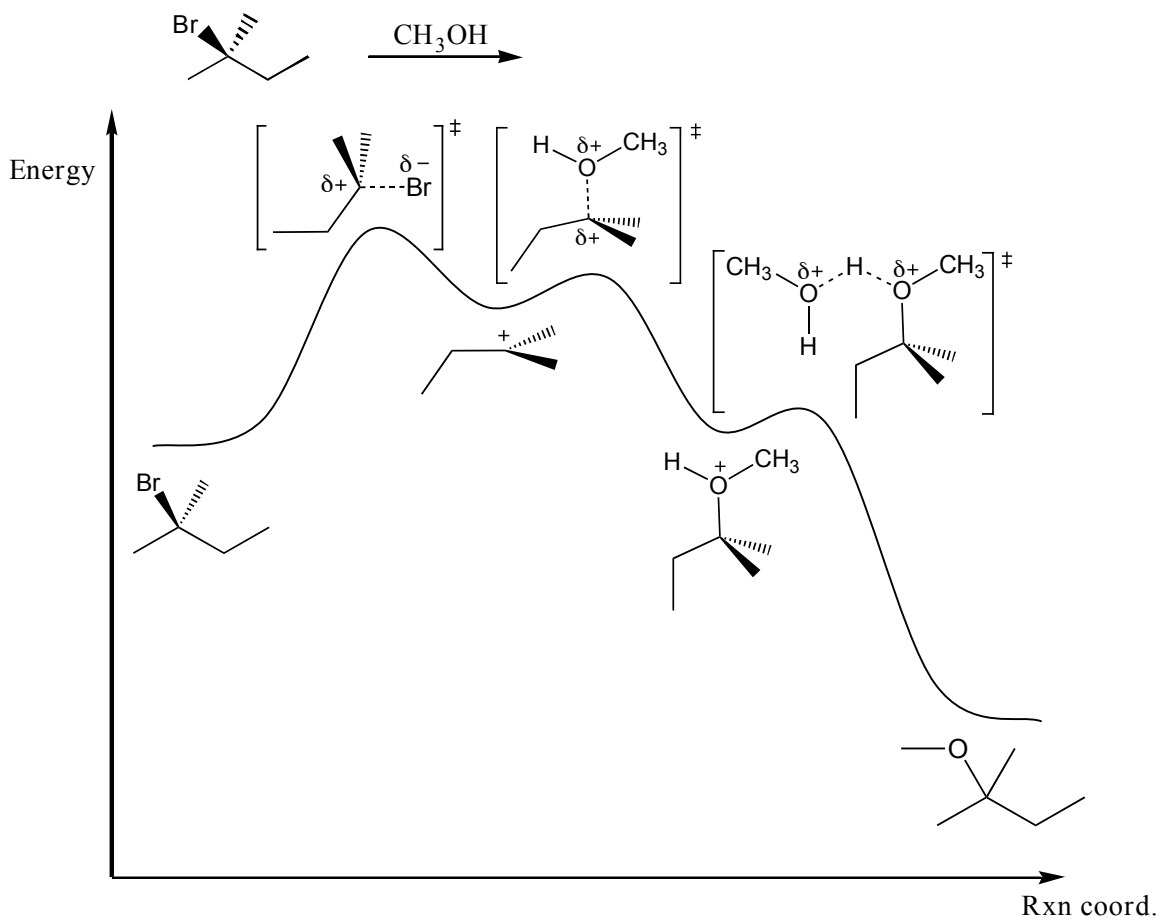


Chem 141
Problem Set 11
Friday 5th December 2008

1. Draw free energy diagram to represent the following reaction. Include structures of the transition state(s) and intermediate.



The hindered electrophile and the weak nucleophile suggest an S_N1 reaction. There is no base, so we can rule out an $E2$ reaction. $E1$ is likely to compete.

2. Explain when an E1 mechanism is likely to occur compared to an E2 mechanism. Use two reactions as examples.

E1 mechanism:

Typical of tertiary and some secondary substituted alkyl halides.

No antiperiplanar requirement.

Reaction mostly occurs in complete absence of base or presence of only a weak base.

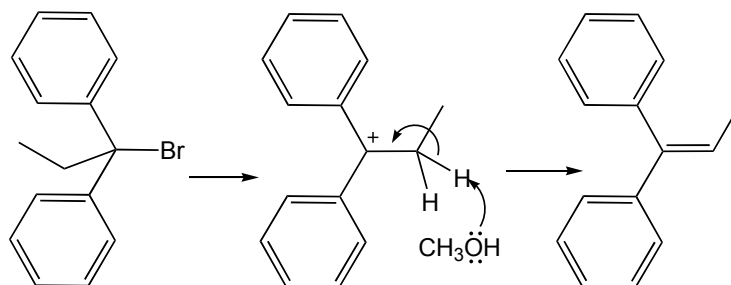
E1 eliminations happen with highly substituted alkyl halides due to 2 main reasons.

(i) Highly substituted alkyl halides are bulky, limiting the room for the E2 one-step mechanism; therefore, the two-step E1 mechanism is favored.

(ii) Highly substituted carbocations are more stable than methyl or primary substituted.

Such stability gives time for the two-step E1 mechanism to occur.

Eg



E1 competes with $\text{S}_{\text{N}}1$. Higher temperatures favor the elimination.

E2 mechanism

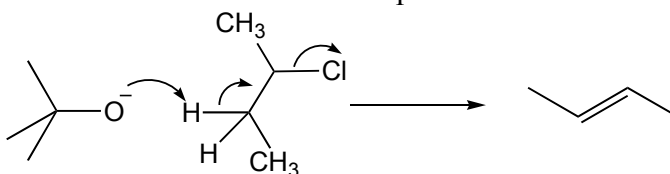
Typical of secondary or tertiary substituted alkyl halides, or primary alkyl halides if a hindered base is used.

The two leaving groups need to be antiperiplanar.

Reaction often requires a strong base.

E2 reactions must not be too hindered at the site of proton abstraction.

Eg



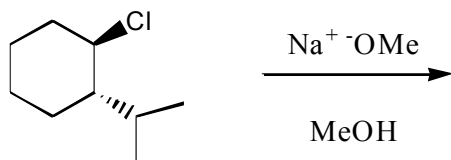
Note the use of a sterically hindered strong base to reduce the possibility of a competing $\text{S}_{\text{N}}2$ reaction. Also, a poorer leaving group minimizes the competing E1 mechanism.

3. Define Zaitsev's rule with an example.

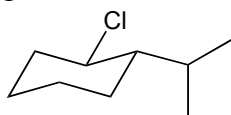
If multiple elimination products are possible, the most substituted alkene is favored.

The E2 example above shows how the internal alkene is favored over the terminal alkene that would result from attack of t-butoxide at the 1-methyl position.

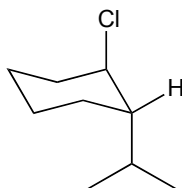
4. What is (are) the product(s) of the following reaction? Draw the mechanism(s).



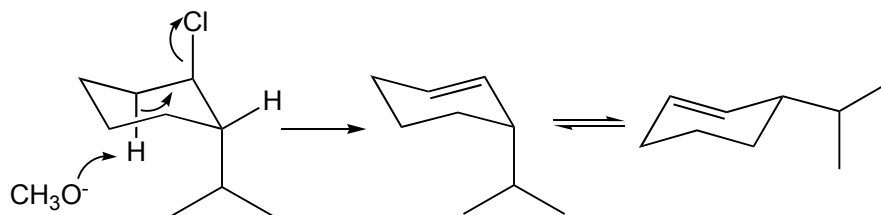
The strong nucleophile suggests $\text{S}_{\text{N}}2$, but the hindered electrophile points to elimination as the more likely outcome. The protic solvent confirms this. Cl isn't such a good leaving group, so $\text{E}2$ is the most likely mechanism here. Is the electrophile set up with appropriate *trans*-diaxial substituents? The isopropyl group will prefer to be equatorial, so we'll have the following conformer:



Both substituents are equatorial; good for stability but not set up for elimination. Let's flip the ring:



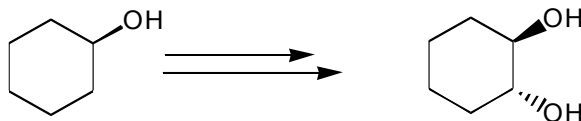
The leaving group is axial, but the H on C2 is equatorial. We can only eliminate using the axial hydrogen on C6:



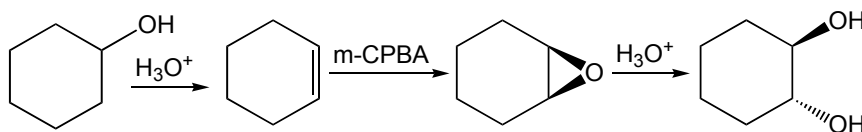
Note that the product disobeys Zaitsev's rule!

5. Provide synthetic strategies for the following transformations.

(a)



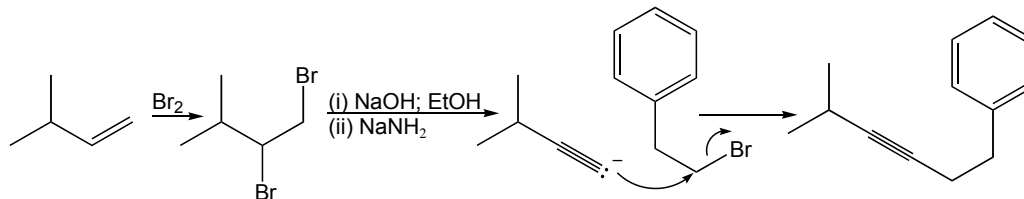
The *trans* vicinal diol could come from an acid-catalyzed epoxide ring opening in H₂O. The epoxide could be prepared from cyclohexene, and we can easily get to cyclohexene using an acid-catalyzed E1 elimination of cyclohexanol.



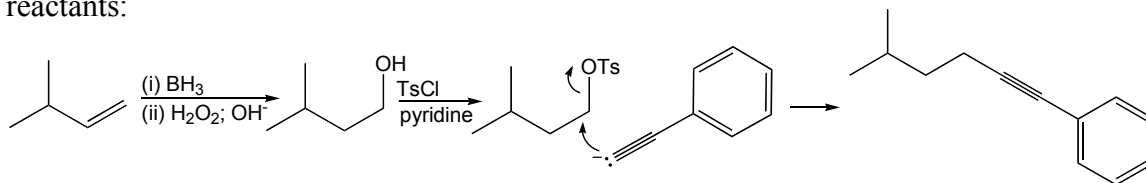
(b)



We have to lengthen the carbon chain, so an S_N2 reaction between an acetylide anion and a haloalkane is in order. We can get to the alkyne by dibromination of the alkene followed by a double elimination. The haloalkane of choice would be 2-phenylbromoethane. Catalytic hydrogenation using Pd/C gives the final product.

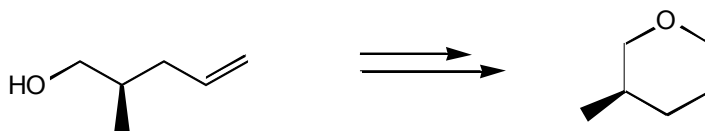


While this is OK, the acetylide is such a strong base that it would likely cause elimination of the phenylbromoethane to give styrene. A better strategy would be to “reverse” the reactants:

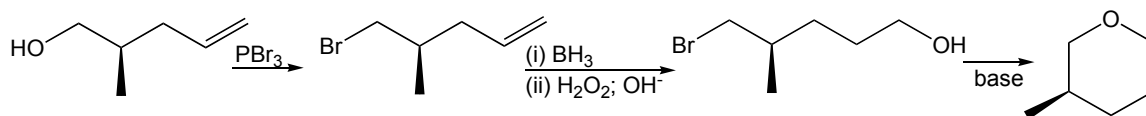


Again, we finish with catalytic hydrogenation.

(c)

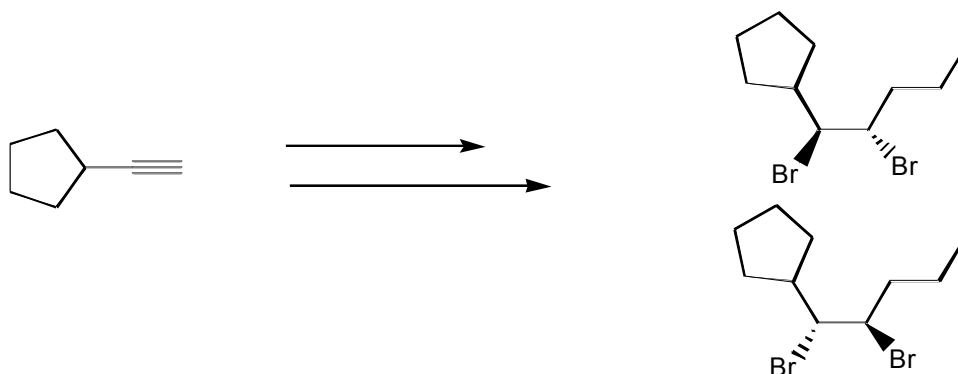


This looks like an intramolecular cyclization. Epoxidation of the alkene is attractive, but an acid-catalyzed epoxide opening will give the 5-membered ring. If we use the OH as a nucleophile, we'll need to install a leaving group on C1. Hydrobromination will go Markovnikov, to give the 2-bromo compound. Dibromination will give a mixture of 5- and 6-ring products. If we do a non-Markovnikov addition of water, we'll get a diol (OH on both ends of the molecule), and we won't be able to convert one of the alcohols selectively to a leaving group. Our only choice is to make the OH into a leaving group first:

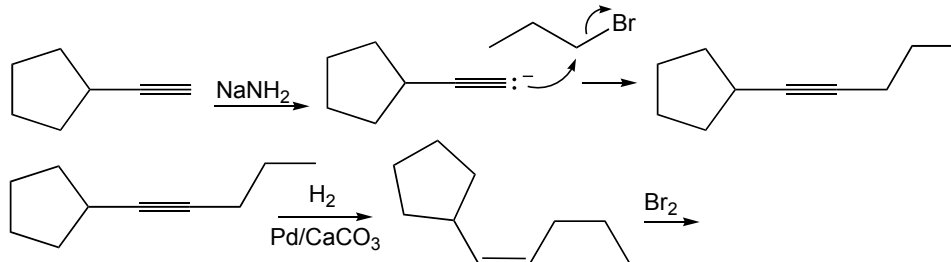


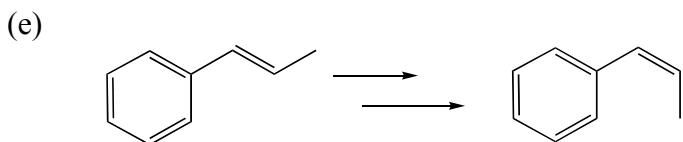
This still isn't absolutely optimal, because the base used to deprotonate the alcohol in the last step will likely cause some elimination of the Br.

(d)

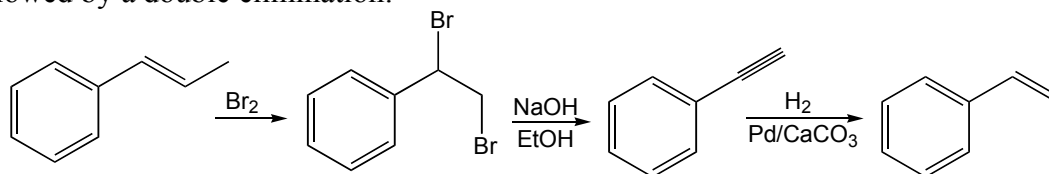


The *anti* bromines will come from bromination of a *Z*-alkene. We can get the *Z*-alkene by hydrogenation of an alkyne using Lindlar's catalyst, and the required alkyne can be had by addition of our starting material to bromopropane:

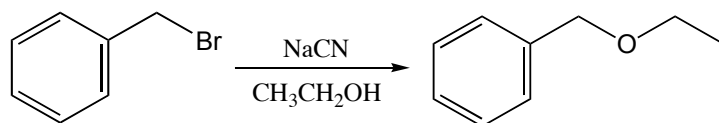




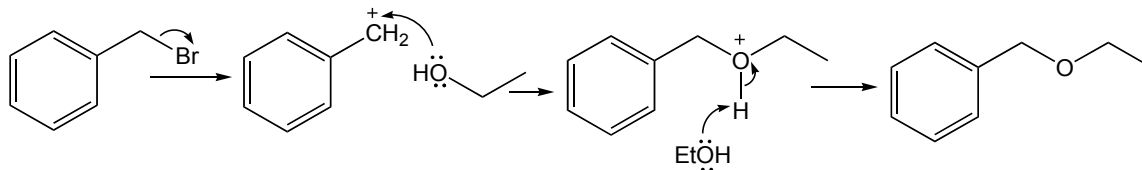
We can get the *Z*-alkene by hydrogenation of the corresponding alkyne using Lindlar's catalyst. Conversion of the *E*-alkene to the alkyne is simply a matter of dibromination followed by a double elimination:



6. The following is a recent example from a lab at UVM. The target molecule is phenylacetone nitrile (phenylmethylcyanide), $C_6H_5CH_2CN$, which could presumably be made by an S_N2 reaction. This is what happened:



Draw a mechanism for this reaction, and suggest how the reaction conditions could be changed to get the desired product.



The highly stable benzylic carbocation allows an S_N1 mechanism to dominate and we get a solvolysis reaction. To fix the problem, we need conditions that favor an S_N2 mechanism:

- (i) use a polar aprotic solvent such as CH_3CN or DMF
- (ii) use a poorer leaving group (eg chloride) so that the spontaneous dissociation is less likely.