Ch 11 HW Set: Substitution and Elimination

Substitution vs Elimination: Ask the following questions

(1) is the substrate (R-LG) sterically hindered?

(2) is the nucleophile hindered? (all 3° and some 2° are hindered)

(3) is the nucleophile a strong base?

If the answer to any 2 of these is yes, then elimination will be favored. If the answer to any 2 of these is no, then substitution will be favored (and obviously if all three answer yes = elimination). The next obstacle to determine (once you know what reaction will occur) is what mechanism is in operation.

S_N1 vs S_N2

S_N1 = 3° substrate (or 2° with resonance) in any solvent with weakly basic, unhindered nucleophile
= 2° substrate (or 1° with resonance) in polar protic solvent with nucleophile that is not both hindered and a strong base

S_N2 = 1° substrate in any solvent with nucleophile that is not both hindered and a strong base
= 2° substrate in polar aprotic solvent with a weakly basic, unhindered nucleophile

E1 vs E2

E1 = 3° substrate with weakly basic, sterically hindered nucleophile typically in polar protic solvent
= 2° substrate with weakly basic, sterically hindered nucleophile typically in polar protic solvent

E2 = 3° substrate with a nucleophile that is a strong base (may or may not be hindered – can dictate pdt)
= 2° substrate with a nucleophile that is a strong base (may or may not be hindered – can dictate pdt)
= 1° substrate with a nucleophile that is a sterically hindered strong base (must be both)

1. For the following list of compounds, circle those which would be classified as a strong base (pKa conjugate acid > 15): (^{t}Bu = $C(CH_3)_3$)

HO^-, $^tBuO^-$, $RC{\equiv}C^-$, RS^-, RCO_2^-, RNH^-, Cl^-, RSO_3^-, H^-, CH_3^-, H_2O, RNH_2

2. For the following compounds, circle those which would be classified as hindered: (notes, Me is an abbreviation for methyl, CH_3, similar to Et, Pr etc. and CO_2^- is shorthand for anion of carboxylic acid)

LDA, MeOH, $tBuO^-$, RCO_2^-, H_2O, CH_3O^-, F^-, CH_3Br, tBu-Br, $HC{=}C\text{-}CH_2\text{-}Br$

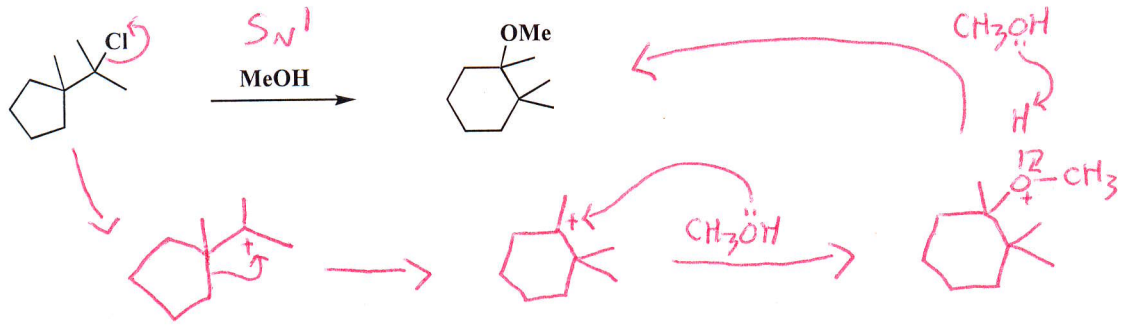
3. For each pair of compounds, circle the stronger nucleophile.

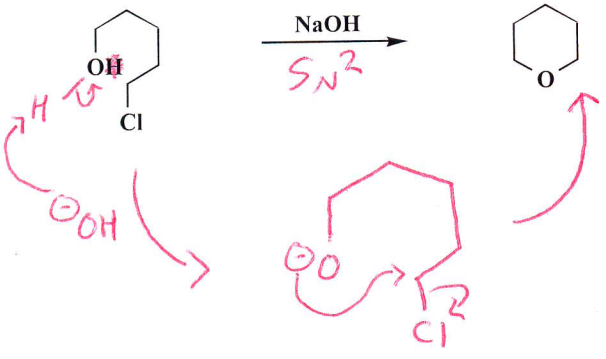
(a) H_2O or ^-OH (b) CH_3O^- or CH_3S^- (c) $HC{\equiv}C^-$ or $N{\equiv}C^-$
(d) $CH_3CO_2^-$ or CH_3O^- (e) Cl^- or I^- (f) CH_3OH or $(CH_3)_3COH$

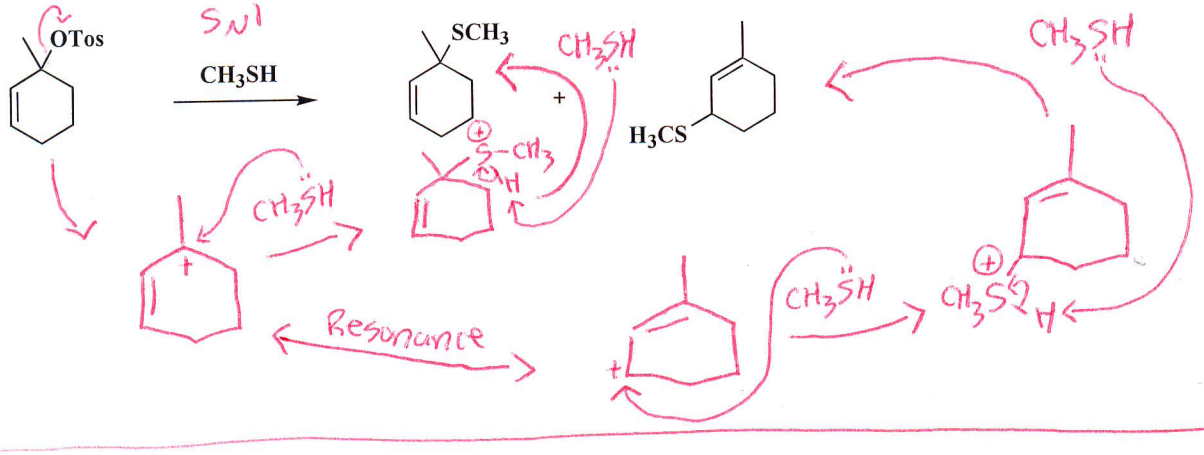
4. For each pair of compounds, circle the better leaving group.

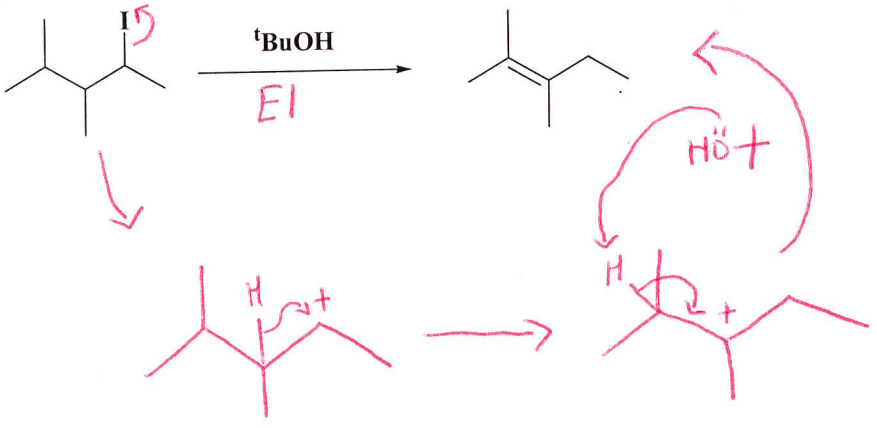
(a) HO^- or H_2O (b) $CH_3SO_3^-$ or $CF_3SO_3^-$ (c) $(CH_3)_2NH^+$ or $(iPr)_2NH^+$ bad question, about equal!
(d) F^-, Cl^-, Br^- or I^- (e) CH_3O^- or $CH_3CO_2^-$ (f) $CH_3SO_3^-$ or $CF_3SO_3^-$
↳ same as b

5. Provide a mechanism for the following reactions.

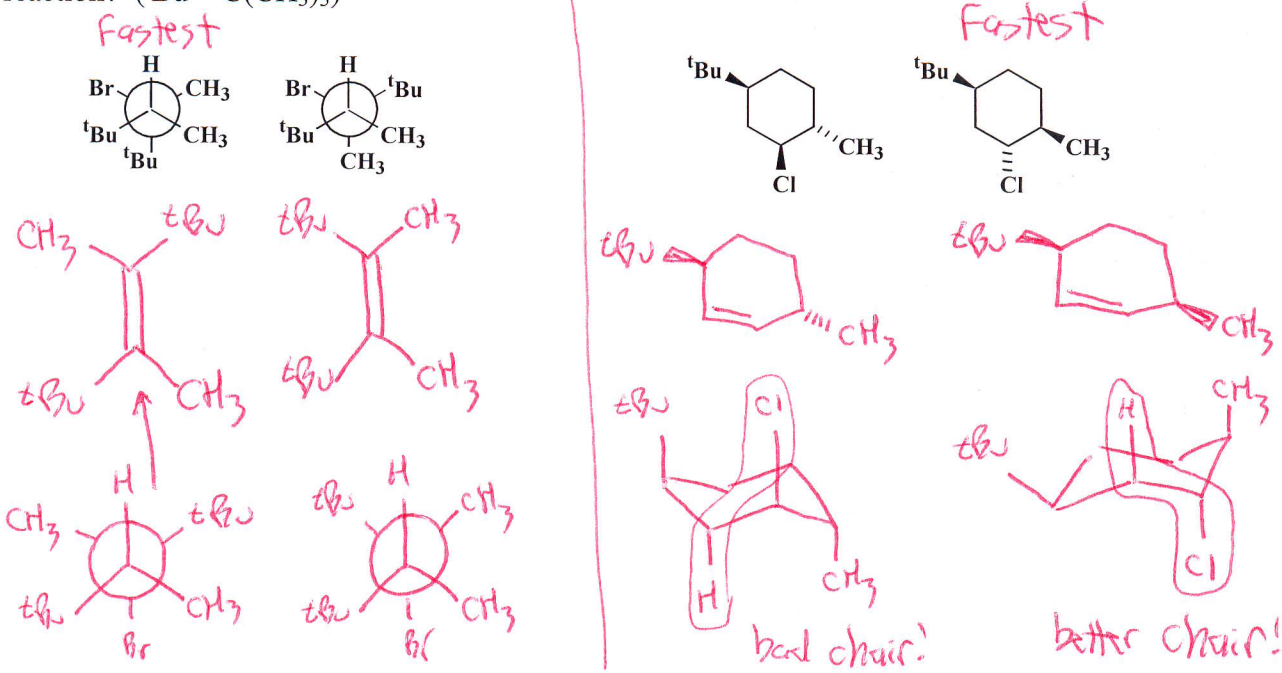




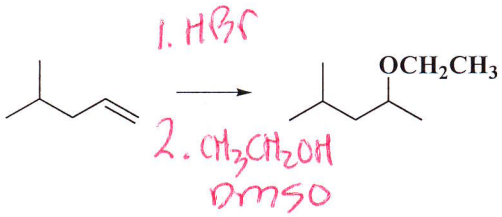


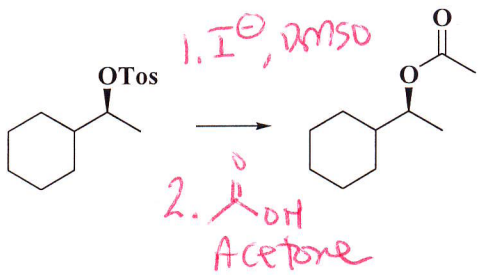


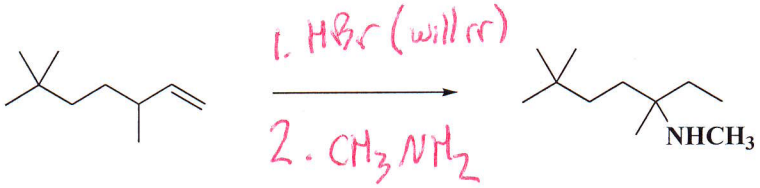
6. For each of the alkyl halides below only one alkene product is produced upon E2 elimination. Draw this product for each of these reactions. For each pair, which would react the fastest in the E2 reaction? (^{t}Bu = C(CH$_3$)$_3$)



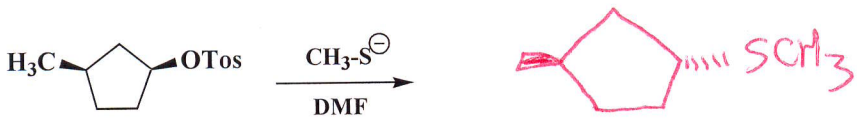
7. Show how you would carry-out a synthesis of the following compound from the indicated starting material. You may use any other reagents you wish.

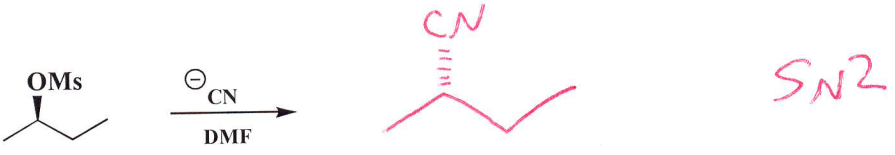


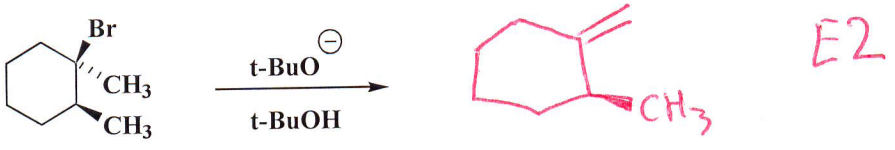


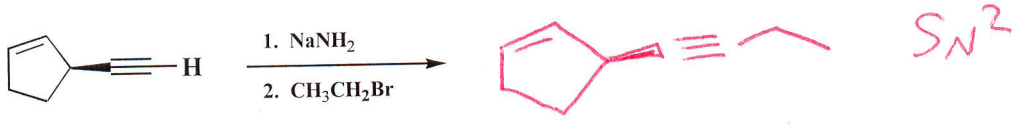


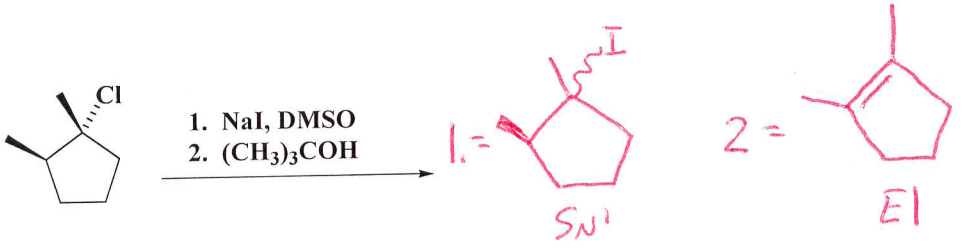
8. Give the structure of the major product(s) expected from each of the following reactions. If necessary, indicate the product stereochemistry. "NO REACTION" may be an acceptable answer.

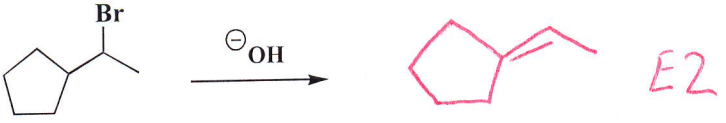




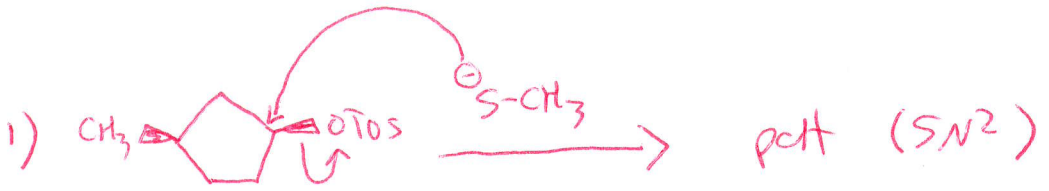


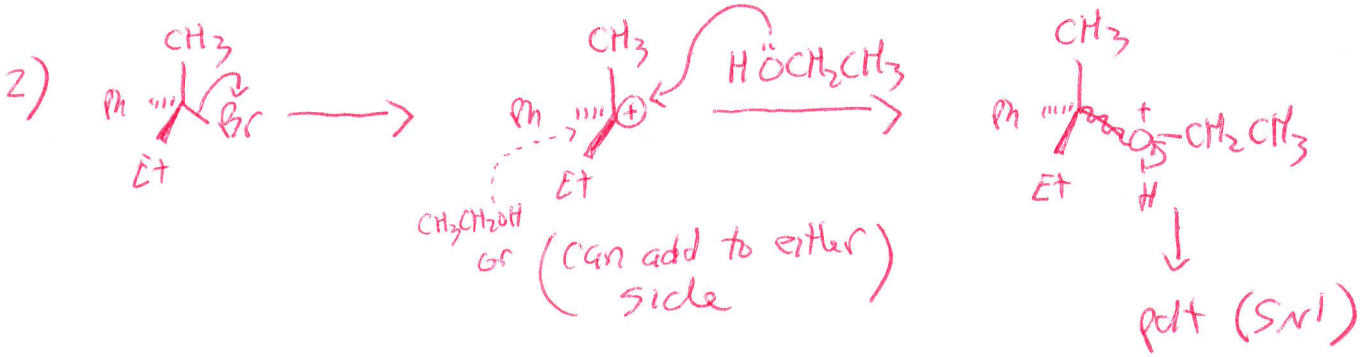


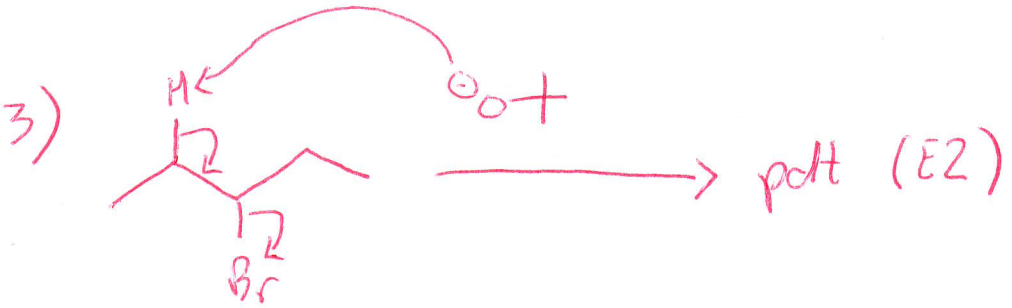




9. Provide mechanisms for the first three reactions in problem 8.





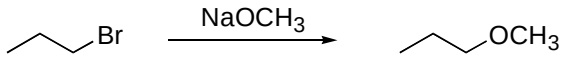


10. HW assigned from the text: 25, 26, 27, 28, 29, 30, 31, 33, 35, 36, 37, 40, 41, 44, 51, 57, 68

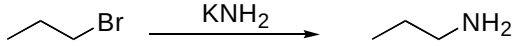
10. For the following substitution reactions, determine the nucleophile and electrophile, and predict the product. For extra fun, draw the mechanism of these reactions. Note that the last one has an interesting stereochemical outcome. Recalling what we discussed to be the best approach to displace the Br, what should be the stereochemistry of the product?

In all cases, the electrophile is the starting halide compound, and the nucleophile is over the reaction arrow. All the mechanisms are SN2.

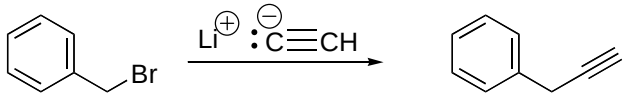
a.



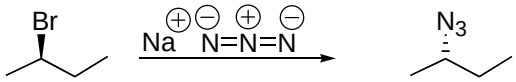
b.



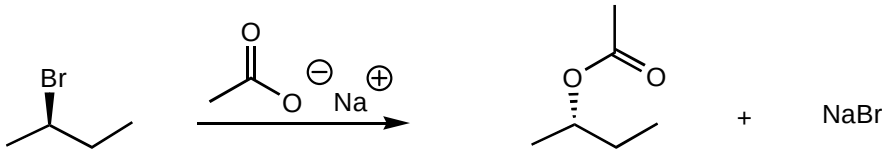
c.



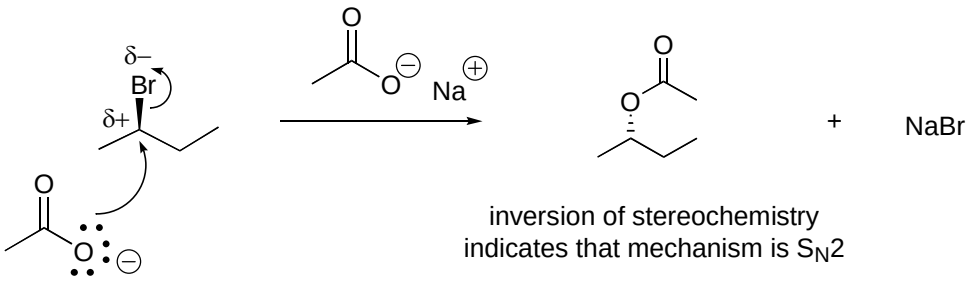
d.



11. Consider the following substitution reaction.



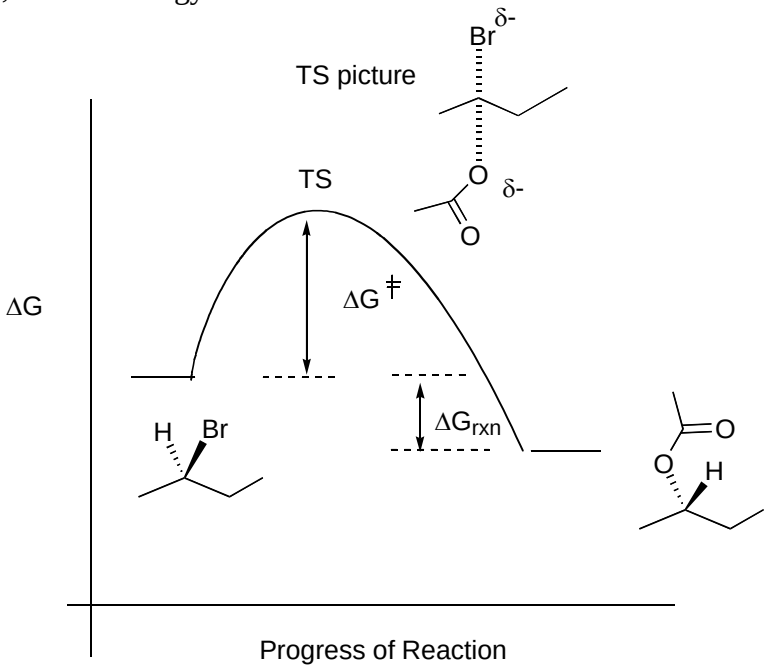
a. Draw a reasonable mechanism that accounts for the observed product. Show all steps and intermediates.



inversion of stereochemistry indicates that mechanism is S_N2

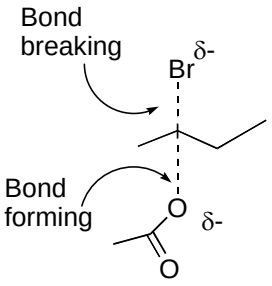
Nucleophile must approach from the opposite side of the leaving group -- 180° approach

b. Draw a reaction coordinate diagram for the reaction. Label the transition state(s), intermediate(s), the energy of activation(s), and the energy of reaction.

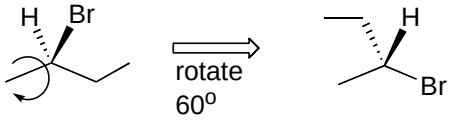


c. Draw the structure(s) of the transition state(s) using the standard conventions. We did not do

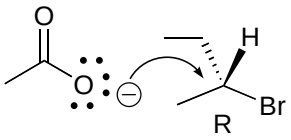
Note: we can't really show the change in stereochemistry with dashed/partial bonds (a dashed-wedge or a dashed-dash?), so we show the stereochemistry change using the modified pictures below

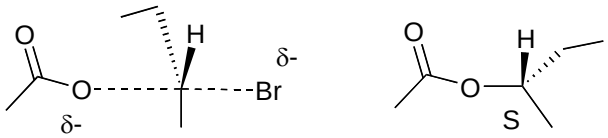


first rotate



Mechanism:





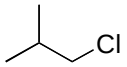
TS picture that shows sterechemistry changing

d. Carefully examine the stereochemistry of the product. How would you describe the change of stereochemistry that occurred from the reactant to the product? To produce the stereochemistry of the product, how did the nucleophile, CH_3CO_2Na, approach the reactant, (R)-2-bromobutane -- from the top face or the bottom face of the molecule?

S_N2 reactions cause inversion of stereochemistry as seen here. The nucleophile approaches the carbon from the opposite side (180° relative approach angle) of the leaving group. As drawn, the Br was coming out toward us, which can be considered being on the top face. As a result, the acetate must have approached from the bottom face.

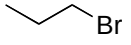
12. Rank the following alkyl halides in order of increasing S_N2 reaction rate as electrophiles (when reacted with a nucleophile).

1 = slowest
no S_N2 at 3° carbons

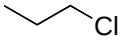


3
1° halide with beta branching

2
2° halide



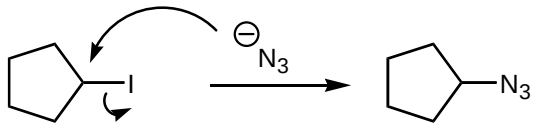
5 = fastest
1°, and Br is better leaving group than Cl



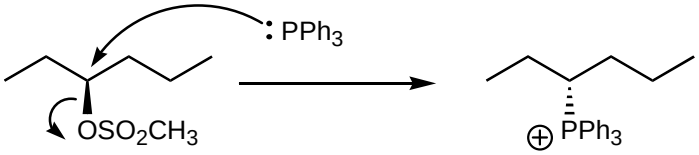
4
1° halide, no beta branching

13. Give the expected major products for the following S_N2 reactions. Draw the movement of electrons for each reaction using mechanistic arrows.

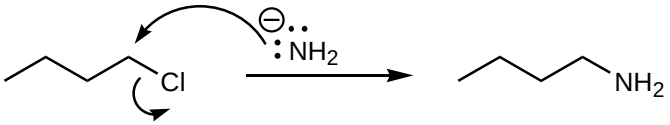
a.



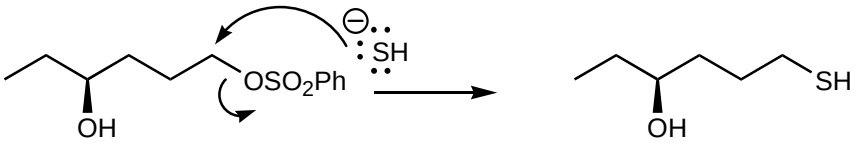
b.



c.

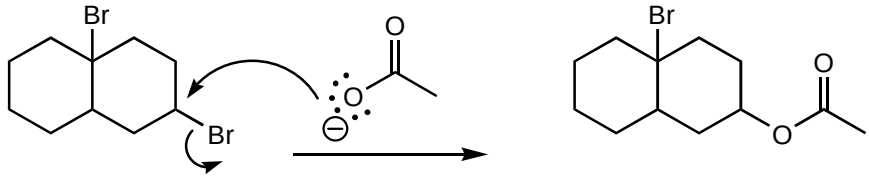


d.



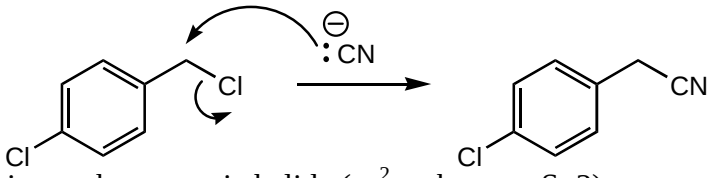
no reaction at the alcohol -- not a good leaving group

e.



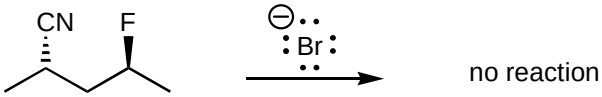
no reaction at the 3° bromide

f.



no reaction at the aromatic halide (sp^2 carbon, no SN2)

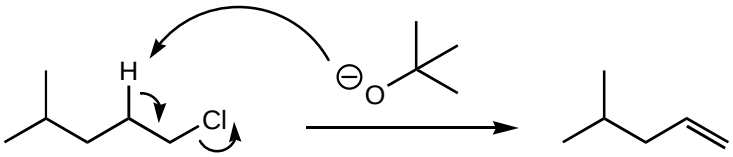
g.



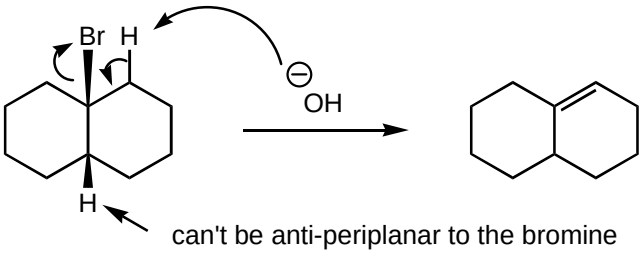
no good leaving groups in the substrate

14. Give the expected major products for the following E2 reactions. Draw the movement of electrons for each reaction using mechanistic arrows.

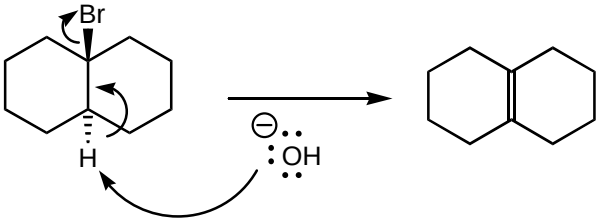
a.



b.

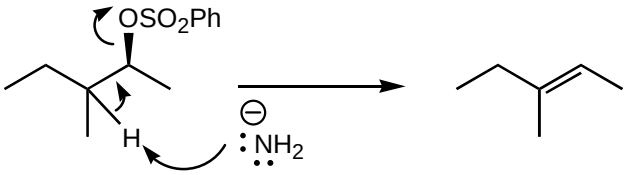


c.

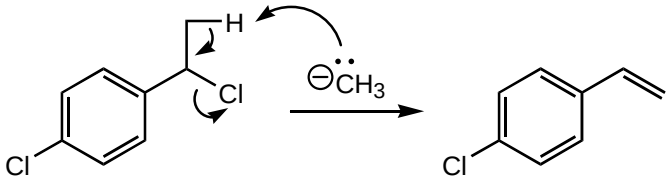


more substituted alkene product

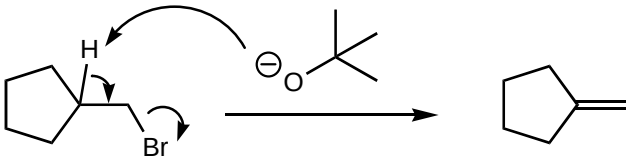
d.



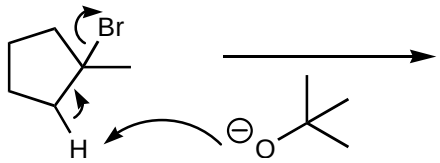
e.



f.



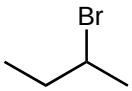
g.



ERROR - Less sub alkene typically major to give same answer as f.

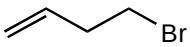
15. When the following substrates are reacted with NaOH, will they participate in a SN2 reaction, an E2 reaction, both, or neither? Briefly explain why.

a.



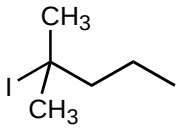
2° substrate, expect E2 with basic nucleophile

b.



1° substrate, expect SN2 -- good nucleophile

c.



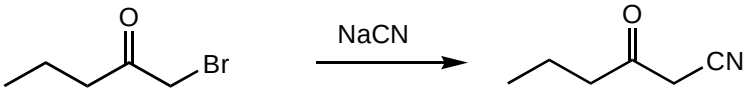
3° substrate, SN2 not possible -- NaOH is strong base, so expect E2

d. CH_3I

no elimination possible, so expect SN2

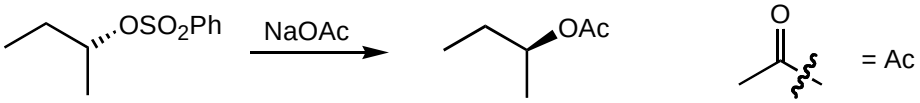
16. Give the expected products for the following reactions, and when possible indicate the type of mechanism by which the reaction proceeds.

a.



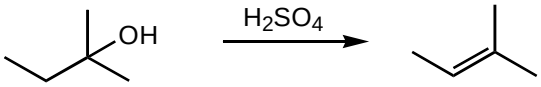
1° halide; good nucleophile (weak base) -- SN2

b.



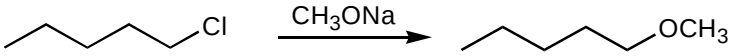
Good leaving group, 2° substrate; good nucleophile, weak base -- SN2; note inversion of stereochemistry

c.



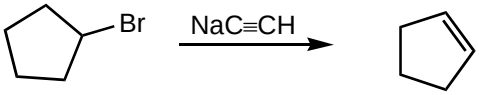
3° alcohol, sulfuric acid -- special case of deliberate E1; note most substituted double bond is major product

d.



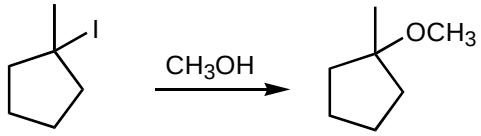
1° halide; good nucleophile (strong base, but ok with 1°) -- SN2

e.



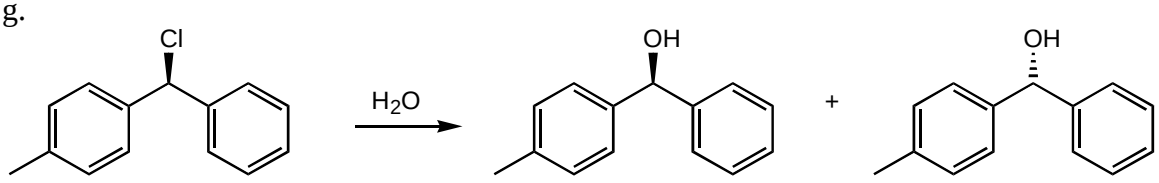
2° halide; good nucleophile but very strong base (conj. acid pKa 25) -- E2

f.



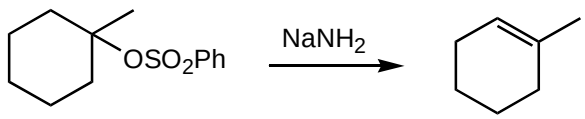
3° halide; weak nucleophile, but weak base -- SN1

g.



2° halide but benzylic on both sides (special case); weak nucleophile, weak base -- SN1; note racemization owing to cation intermediate

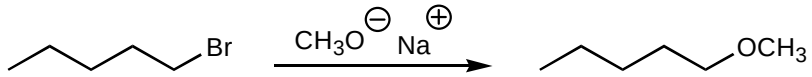
h.



3° substrate, good leaving group; very strong base (conj. acid pKa 35) -- E2; note most substituted double bond

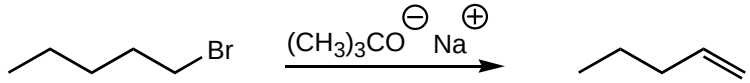
17. Give the major product of the reaction and the mechanism by which it is produced (SN2 and E2 only for this set of reactions; we will add in SN1 /E1 later). Be sure to include the stereochemical outcome.

a.



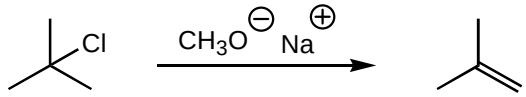
1° halide, good nucleophile, SN2

b.



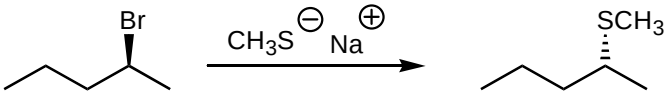
special case: 1° halide but non-nucleophilic, strong base, E2

c.



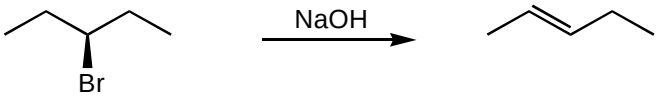
3° halide, SN2 not possible; with strong base, E2 (conjugate acid pKa >15)

d.



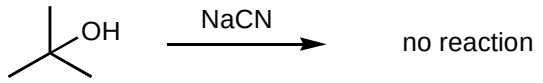
2° halide, but non-basic (conj. acid pKa <12), good nucleophile, so SN2 -- note inversion of stereocenter

e.



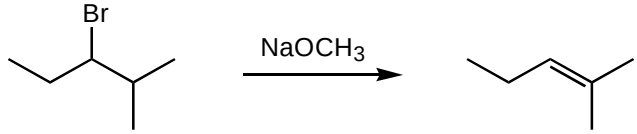
2° halide, strong base, E2

f.



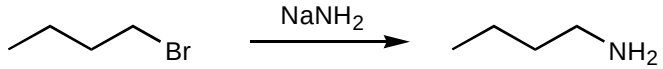
No good leaving group plus 3°, so no SN2. Nucleophile not in class that can cause any other reaction we know.

g



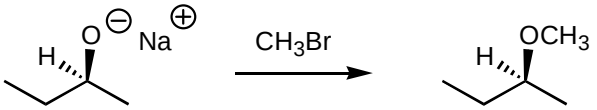
2° halide, strong base, E2; note more substituted double bond product

h.



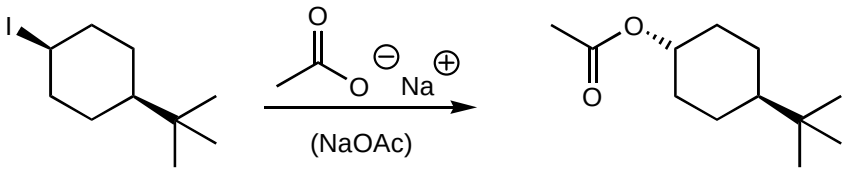
1° halide, good nucleophile, SN2

i.



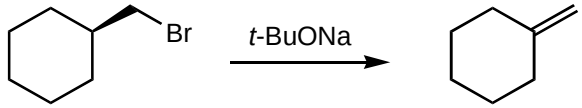
methyl substrate can't eliminate, so SN2; note that reaction is not occuring at the stereocenter, so the stereochemistry remains unchanged.

j.



2° halide, with weak base/good nucleophile, so SN2; note stereochemical inversion

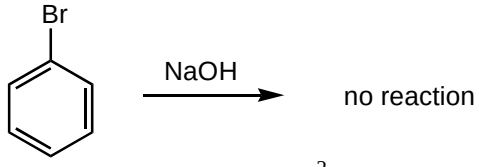
k.



special case: 1° halide but non-nucleophilic, strong base, E2

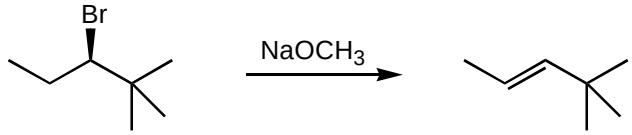
18. Give the <u>major product</u> of the reaction and the mechanism by which it is produced (SN1, SN2, E1, E2). Be sure to include the stereochemical outcome.

a.



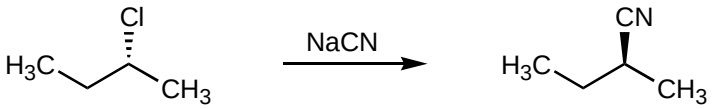
no SN2 possible at an sp^2 carbon; no current reaction we know works with an aromatic halide

b.



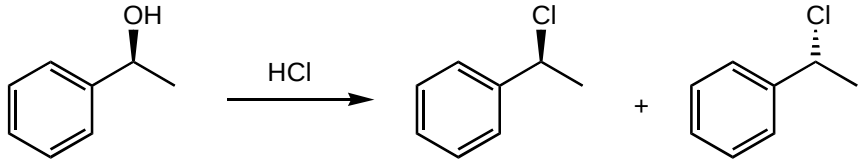
2° halide, strong base, E2

c.



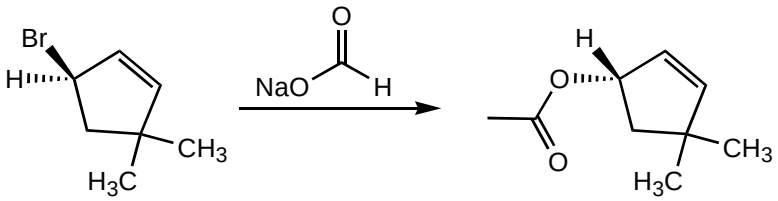
2° halide, good, non-basic nucleophile, SN2; note inversion of stereochemistry

d.



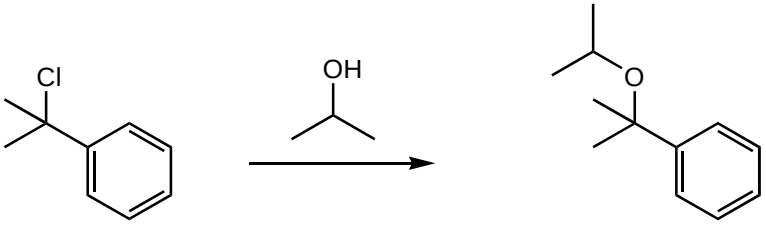
special case: this substitution occurs by an SN1 mechanism; substrate is just good enough at 2° with resonance stabilization; carbocation intermediate leads to racemic mixture

e.



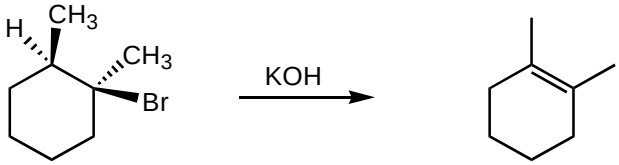
2° halide, good, non-basic nucleophile, SN2; note inversion of stereochemistry

f.



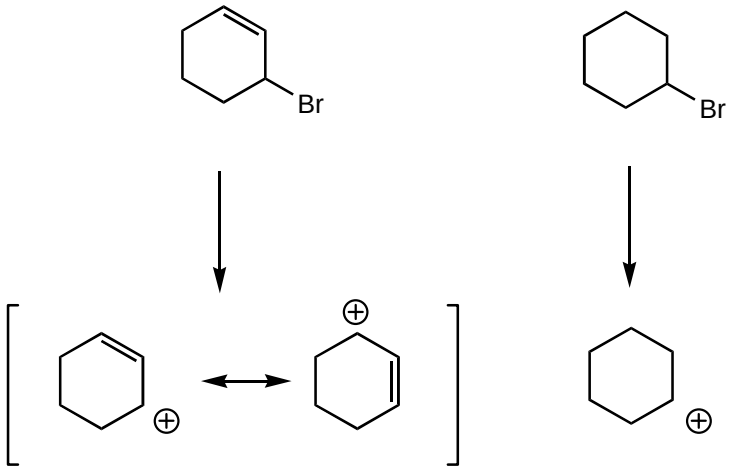
3° halide with a weak nucleophile, weak base. Actually, E1 more likely since sub and nuc hindered, so answer above is incorrect.

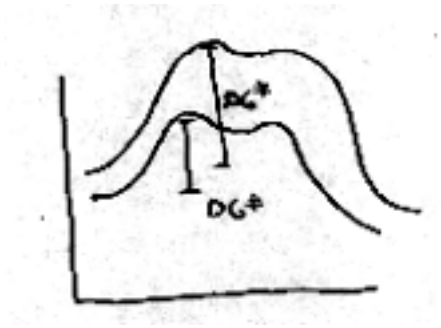
g.



3° halide with strong base, E2; stereochemistry allows formation of most substituted double bond

19. Assume that both of the following compounds happen to undergo an SN1 reaction. Draw what the intermediate would be for each compound. Which, if either intermediate, is more stable? Why? As a result, which should be formed faster?



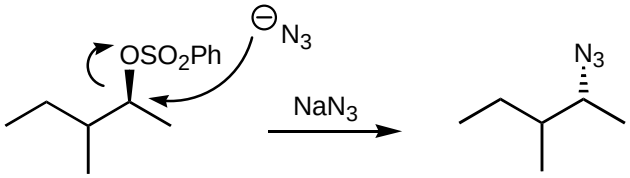


intermediate is stabilized by resonance no resonance

The allyl cation is a more stable intermediate because it is stabilized by resonance. In the energy diagram on the right, the lower curve might represent the SN1 reaction profile for the 3-bromocyclohexene (left, **A**), and the higher curve would then represent the SN1 reaction profile for the bromocylcohexane (right, **B**). We know that the energy gap between the starting material and the intermediate is less if the intermediate is more stable, so that distance is less on the profile for **A**. The Hammond postulate says that a transition state most closely resembles the intermediate nearest to it in energy. If the intermediate is more stable for **A**, the transition state for forming that intermediate is also more stable than the corresponding transition state for **B**. That means that the activation energy ($\Delta G‡$) is lower for the reaction of **A** than it is for the reaction of **B**, and therefore 3-bromocyclohexene reacts faster.

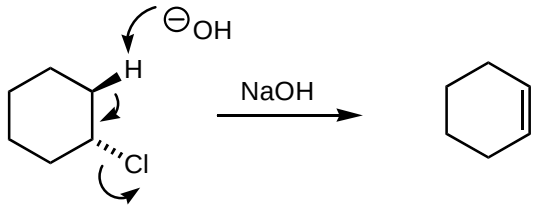
20. Give the expected major product for each of the reactions shown below. Indicate the type of mechanism by which it is formed. Draw out the mechanism by which it is formed.

a.



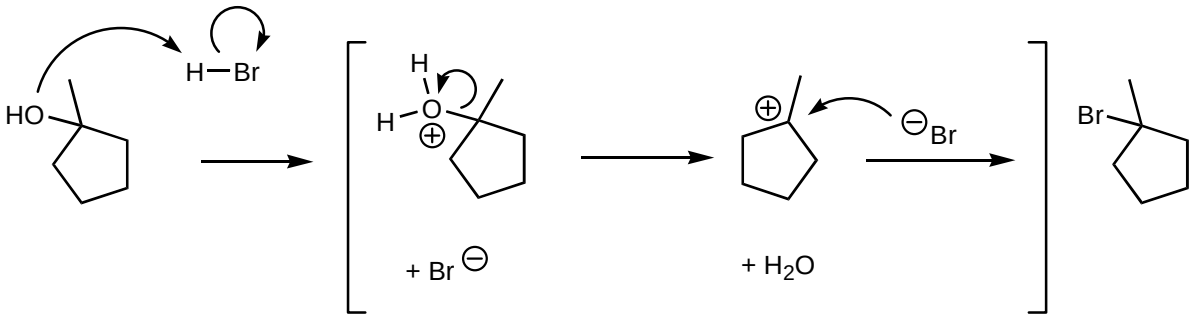
SN2 reaction -- inversion of stereochemistry; 2° substrate; weak base, good nucleophile

b.



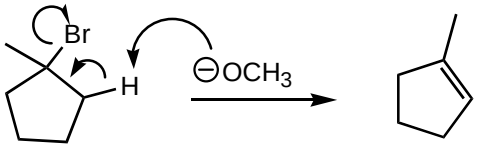
E2 reaction -- I emphasized that the anti hydrogen is removed; 2° substrate, strong base

c.



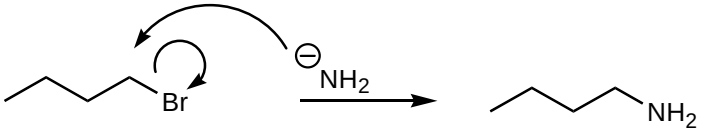
SN1 reaction; note that first step is to make OH into a good leaving group; 3° alcohol; protonation gives us good leaving group; very non-basic

d.



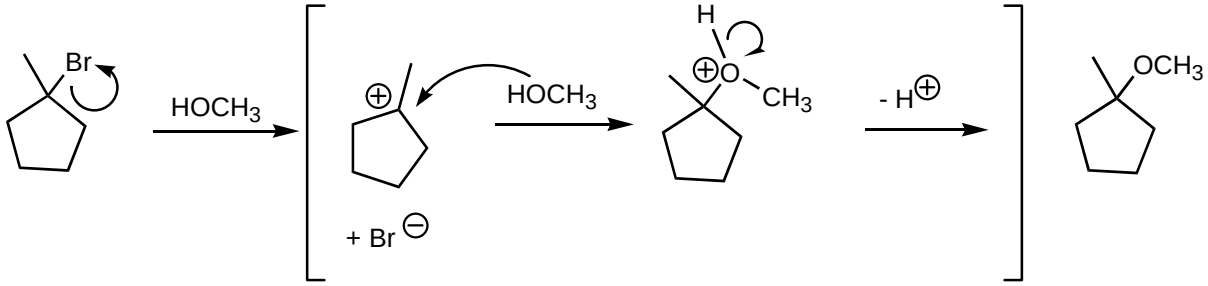
E2 reaction; major product is most substituted double bond; 3° substrate; strong base

e.



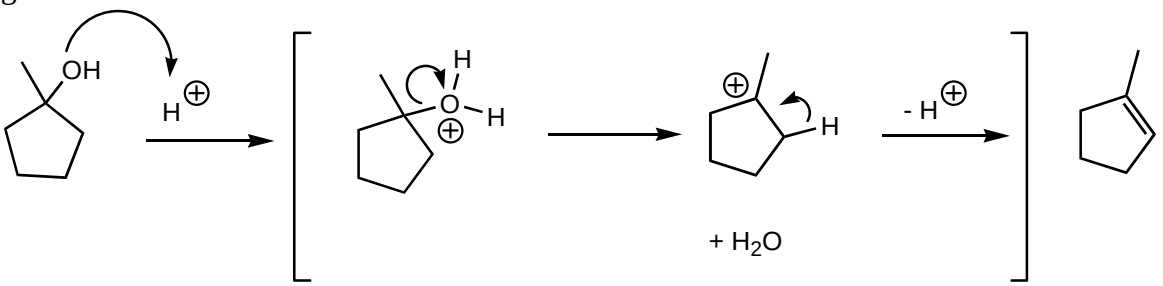
SN2 reaction; 1° substrate, good nucleophile

f.



SN1 reaction; 3° substrate, non-basic, weak nucleophile

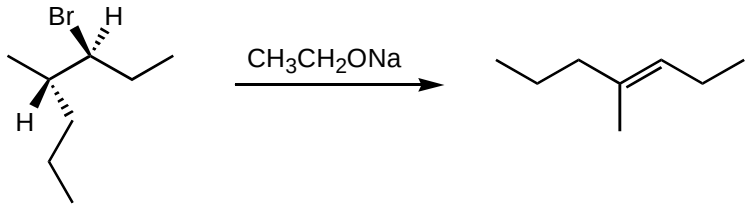
g.



E1 reaction; special case of 3° alcohol and sulfuric acid

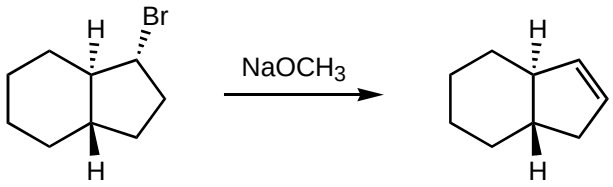
21. Using what you know about the mechanism, predict the elimination product. Be sure to clearly show the stereochemistry of the proposed product.

a.



Remember that the elimination only occurs when the Br and H are anti-periplanar. That means that you have to rotate to that conformation to accurately predict the stereochemistry of the resulting double bond.

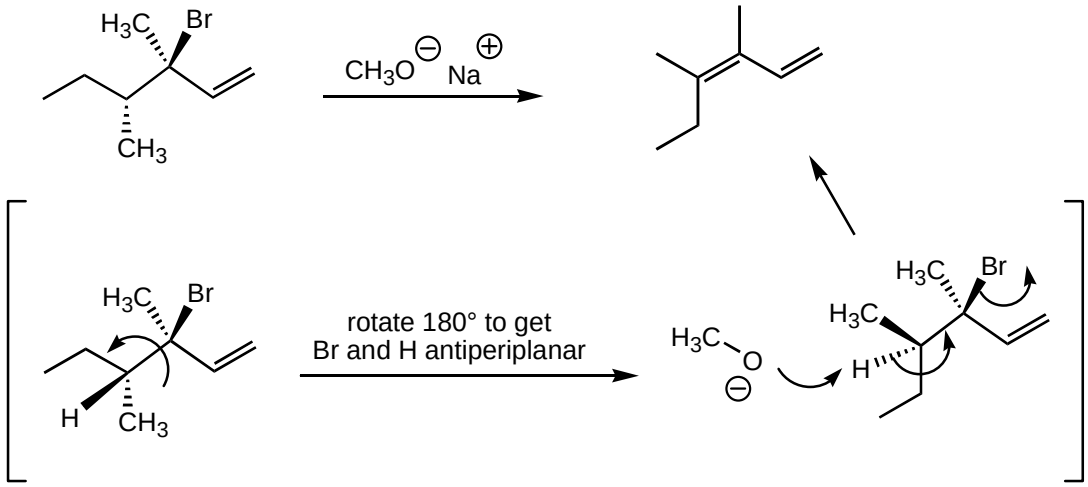
b.



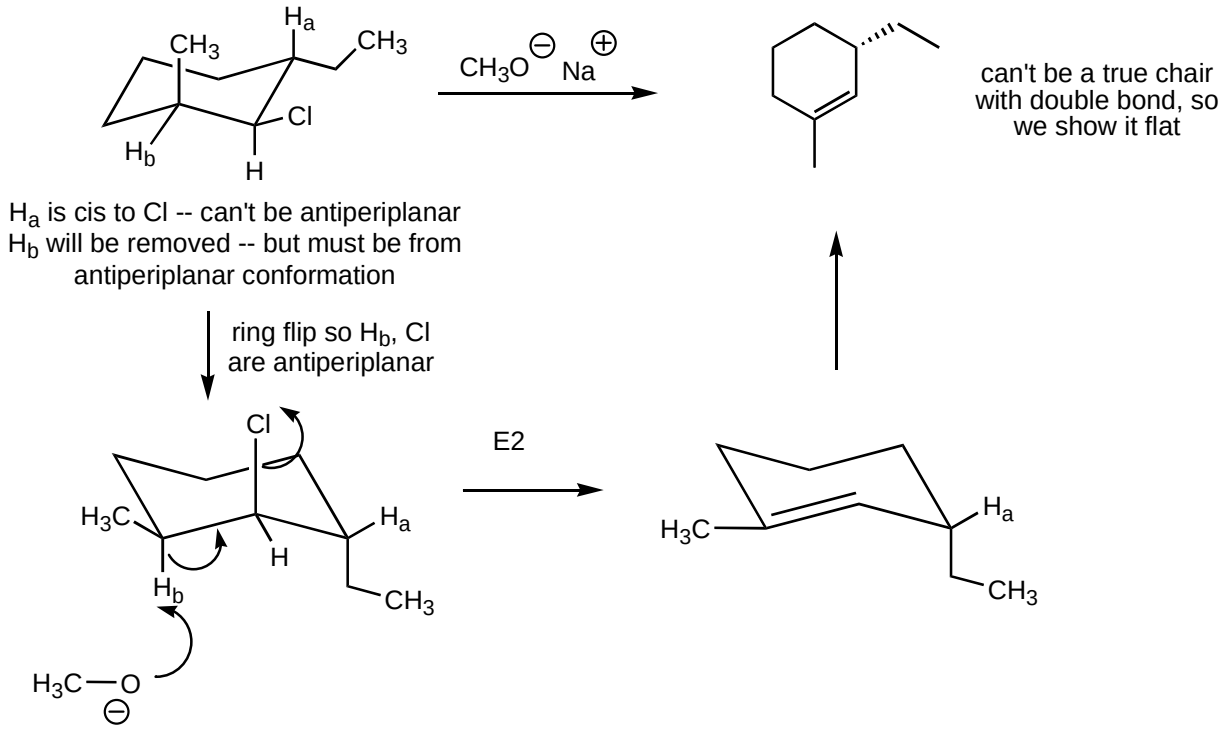
The bridgehead hydrogen (at the 3° carbon next to the Br) can never be antiperiplanar to the Br. The rings make that conformation impossible. As a result, we get the less substituted double bond.

22. Using what you know about the mechanism, predict the elimination product. Be sure to clearly show the stereochemistry of the proposed product.

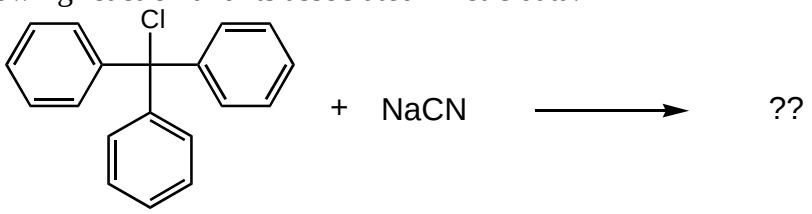
a.



b.



23. Consider the following reaction and its associated kinetic data.

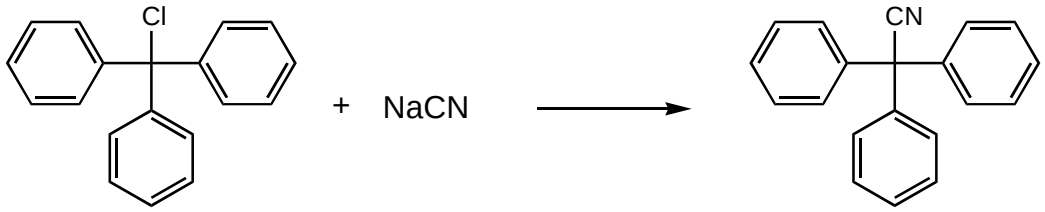


A **B**

Change in Reactant Concentration	Effect on Rate
2 x [A]	rate doubles
2 x [B]	no change in rate
2 x [A], 2 x [B]	rate doubles
4 x [A]	rate quadruples (x 4)

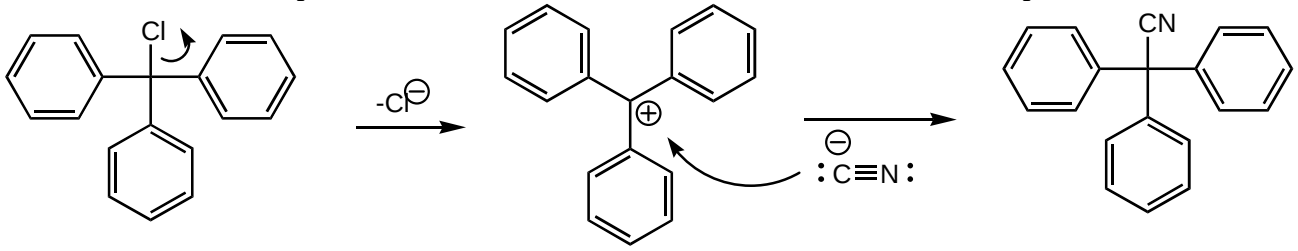
a. Determine the reaction mechanism (SN1, SN2, E1 or E2), provide a reasonable rate expression, and predict the reaction product.

Only the concentration of the substrate **A** affects the reaction rate, so we have a unimolecular reaction. Of the choices, that means SN1 or E1. With **A**, no elimination is possible, so it must be SN1. A reasonable rate expression is rate = k[**A**], and our predicted product is:

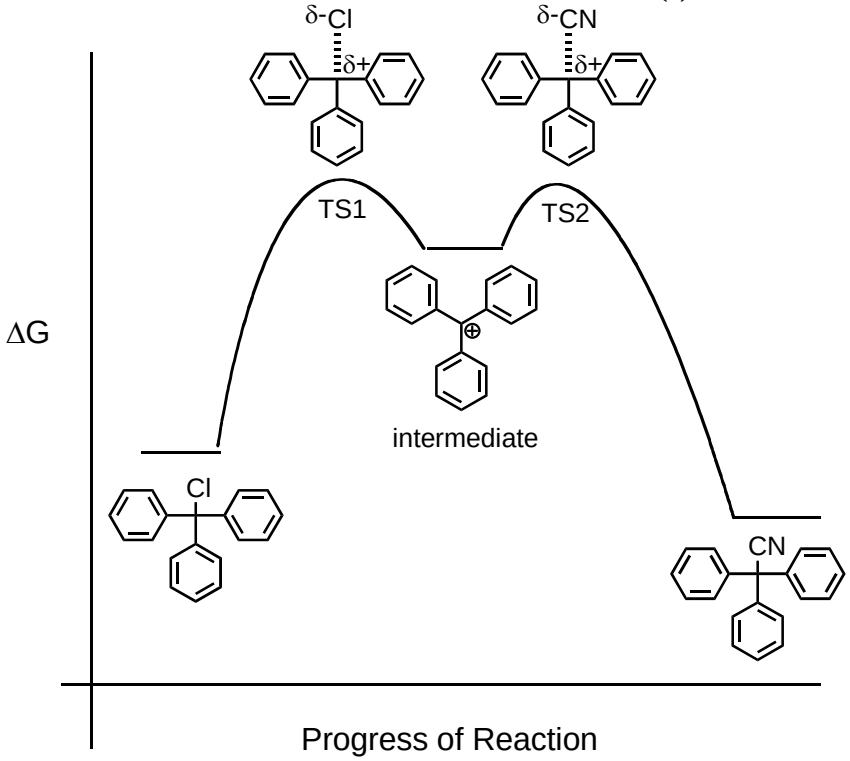


A **B**

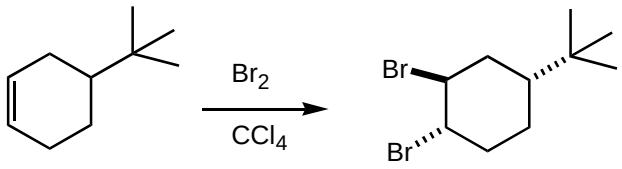
b. Draw a reasonable, stepwise reaction mechanism. Be sure to show all of the steps!!!

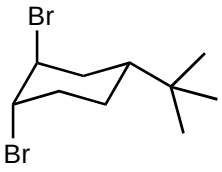


c. Draw a reaction coordinate diagram for the reaction. Label the transition state(s) and intermediate(s), and draw structures that are reasonable estimates of the transition state(s).



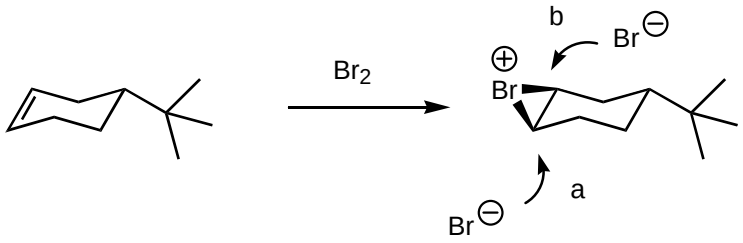
24. Explain the following observations. These problems are difficult but interesting.
a. In the following reaction, the only product had the relative stereochemistry shown. Why? Use your knowledge of the E2 mechanism to explain.





most stable conformation

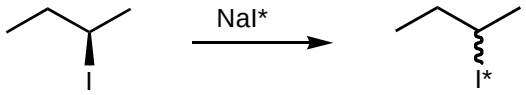
Let's start by looking at the most stable conformation for the product. We know that the tBu must be equatorial, so both the bromines are axial. As a result, they are anti and periplanar (more simply antiperiplanar). How would this product have been formed? We have to look at the mechanism.



The reaction goes via the bromonium ion, as we've learned previously. This intermediate can react with the bromide in two ways. Both are from underneath the ring, but **a** is axial and **b** is equatorial.

If bromide does the axial attack via **a**, we get the experimentally observed product. If bromide attacks equatorially via **b**, we would get the unobserved diequatorial product. Why is **a** favored? Only by this pathway can there be an overlap of all the orbitals involved in the forming of the new bonds and the breaking of the pi bond. Why is this question even on the problem set? This example is completely analogous to what we learned about E2 eliminations and their requirement for antiperiplanar H and leaving group. Essentially, this reaction can be thought of as a reverse reaction for the elimination. Microscopic reversibility tells us that what is true for the forward reaction is also true for the reverse.

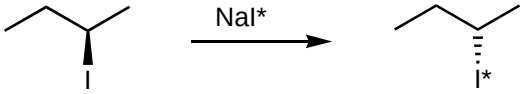
b. Workers studying nucleophilic substitutions reacted optically active 2-iodobutane with radioactive iodine (I*) as shown below. When they stopped the reaction, they found that the product was 40% radioactive, but only 20% enantiomerically pure (20% ee). Does this result confirm or contradict the SN2 mechanism we would have predicted? Explain.



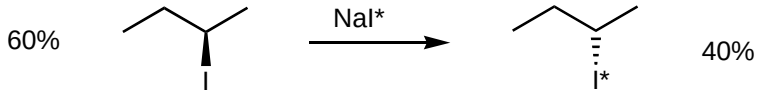
no radioactivity
100% ee

40% radioactive
20% ee

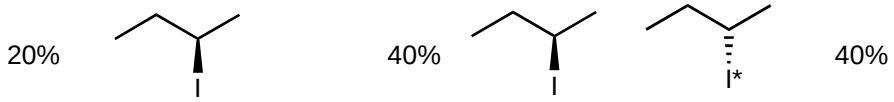
This result is exactly what we would expect, and in fact it was used to confirm the mechanism for the SN2 reaction. Let's see why. Everytime we substitute with I*, we both incorporate radioactivity and invert the stereochemistry of the chiral center, as shown below.



Now, if the reaction has gone to 40% completion, we have 60% starting material (not radioactive) and 40% product (radioactive).



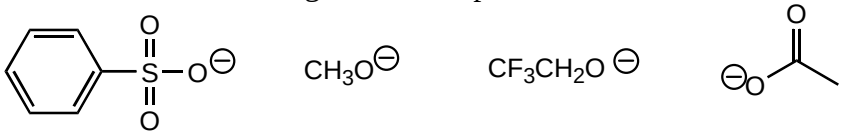
Now, let's think about the stereochemistry. This mixture is the same as 20% of the original isomer and a 80% racemic mixture -- 40% product and 40% starting isomer. This combination therefore exhibits a 20% enantiomeric excess. As a result, 40% radioactivity and 20% ee is exactly what we expect for a mechanism that always involves inversion -- as we said was true for SN2



excess

racemic mixture

25. Rank the following species in order of their strength as nucleophiles.

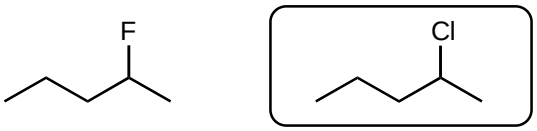


conjugate acid pKa	-7	16	12	5
nucleophilicity rank	4	1	2	3

As a first approximation, we can simply make our ranking based on the basicities. Because in each case we have an oxygen anion, the more basic anions will be more nucleophilic. The basicity can be judged by the pKa of the conjugate acids, which leads us to the ranking above. At the same time, it is useful to consider in more general terms why some anions are more basic than the others. A useful concept is that to whatever degree an anion is better stabilized (happy at home), it is less likely to be donated in a reaction (leave the house). In this group we have the methoxide anion, which is the most basic because it

has no additional stabilization (other than being on the electronegative oxygen). Next is the trifluoroethoxide anion, which is somewhat stabilized by the inductive withdrawal of the highly electronegative fluorine atoms. Following is the acetate anion, which is stabilized by resonance. Last comes the benzenesulfonyl anion, which is stabilized both be several resonance forms and special characteristics of the sulfur. For practice, I suggest taking the time to draw pictures that represent these effects -- particularly the resonance forms. It is also worth noting a general trend: resonance is a more stabilizing force than inductive effects.

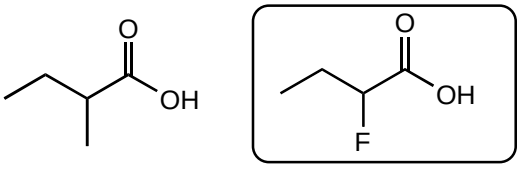
26. Evaluate the sets of compounds according to the given criterion and explain your reasoning. I like these questions a lot, and you can expect to see them regularly on exams.
a. Which substrate reacts faster in SN2 reactions (2 different sets)?



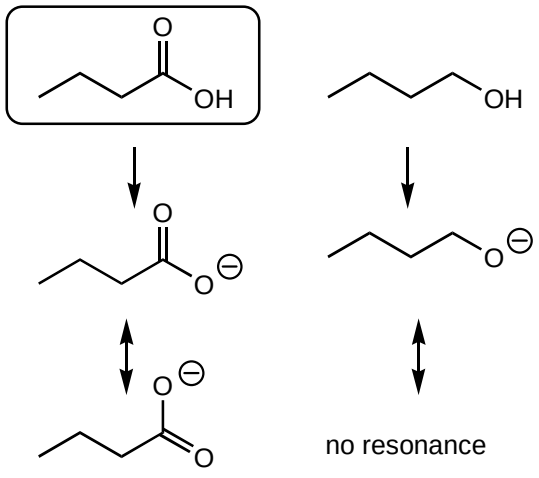
Chloride ion (conj. acid pKa -2) is a much better leaving group than fluoride ion (conj. acid pKa 3). The arguments can be complicated and depend somewhat on the solvent, so we'll leave it at that.

Both are primary and unbranched, so sterics isn't really a factor. The positive charge on the carbon in the transition state can be stabilized by conjugation with the pi bond of the alkene. The idea is more complicated than but similar to why the allyl substrate is better for an SN1 reaction. In that case we can draw direct resonance.

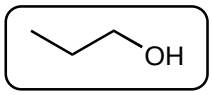
b. Which is a stronger acid (3 different sets)?



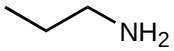
The fluorine atom is highly electronegative and inductively withdraws electrons. That withdrawal helps stabilize the oxyanion of the conjugate base. For the other acid, if anything the methyl group is inductively donating.



We can let the picture do the talking. Both conjugate bases are oxygen anions. One is stabilized by resonance, and the other is not. The more stable conjugate base correlates with the stronger acid.



pKa 16



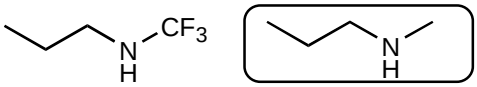
pKa 40

When we look at the conjugate bases, we see an oxygen anion vs. a nitrogen anion. The charge is much better stabilized on the more electronegative atom. The trend here is unambiguous because oxygen and nitrogen are in the same row of the periodic table, so size isn't a factor.

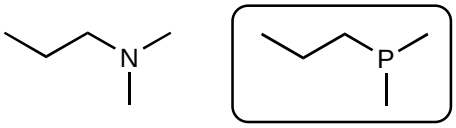
c. Which is a better nucleophile (4 different sets)?

The basicities of the two amines should be about the same, so that isn't the deciding factor. The sterics, however, differ greatly. The extra alkyl group on the secondary amine can get in the way for the nitrogen lone pair to be donated as a nucleophile. As a result, the primary amine is the better nucleophile.

Oxygen is more electronegative than nitrogen, which means that it holds on to its lone pairs more tightly. If you hold on tighter, you're less willing to give them up, which is what you need to do to be a good nucleophile. The amine is therefore the better nucleophile.



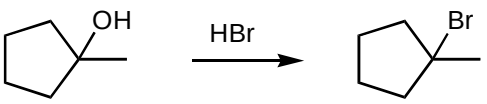
Sterics are roughly the same, and they're both amines. Here we return to a difference based on inductive effects. The highly electronegative fluorine atoms withdraw some of the electron density of the nitrogen lone pair. In a sense that makes it less negative and certainly less available for donation as a nucleophile. The non-fluorinated amine should be better.



Here's a trend we don't talk about as often --atom size. The two compounds differ only in whether they have a nitrogen or a phosphorous. Which lone pair is easier to donate? In general, bigger atoms (here the P) can more easily donate their lone pairs. The lone pair electrons are always in an outermost electron shell, and the bigger the atom, the farther these electrons are from the draw of the nuclear charge. As a result, it is easier to donate them.

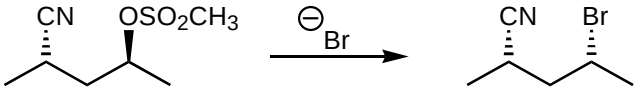
27. Give the expected major products for the following reactions, and when possible indicate the type of mechanism by which the reaction proceeds.

a.



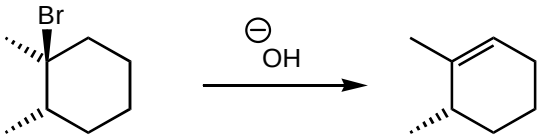
protonation
then SN1

b.



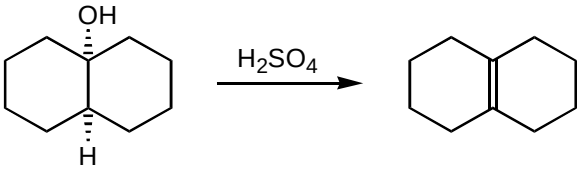
SN2

c.



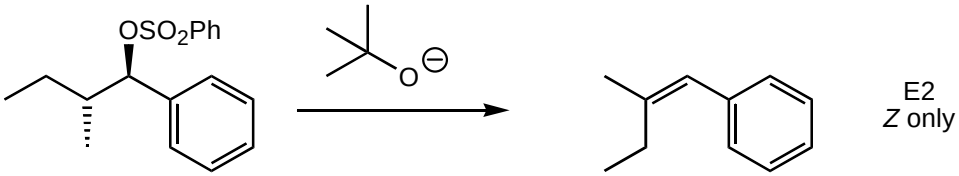
E2

d.



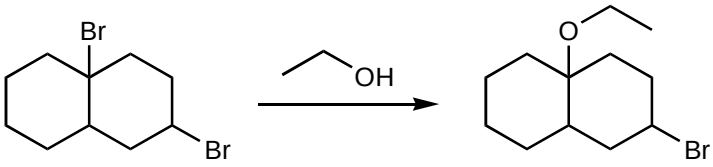
E1

e.



E2
Z only

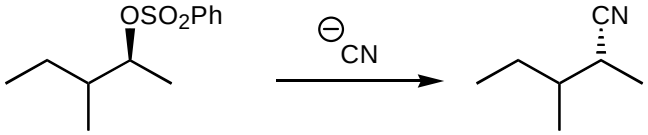
f.



SN1

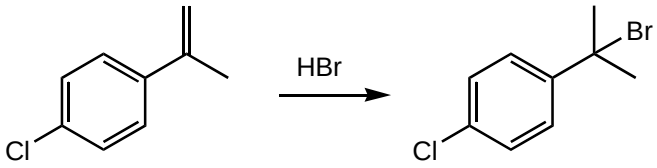
(could also replace second Br)

g.

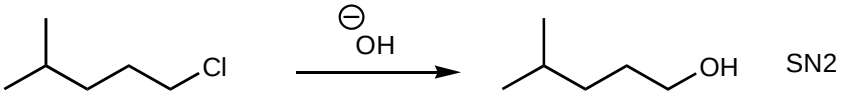


SN2

h.

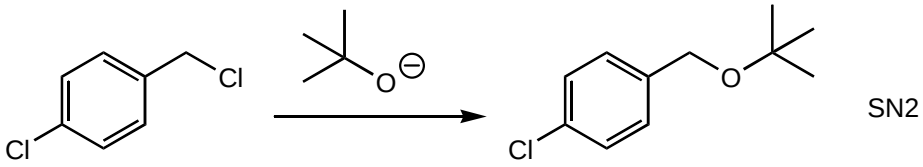


i.



SN2

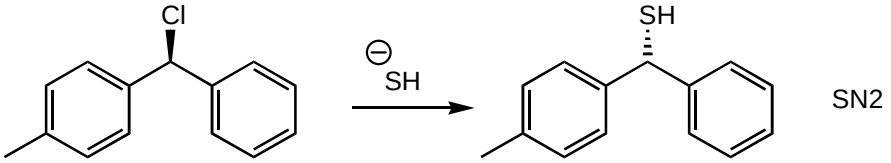
j.



SN2

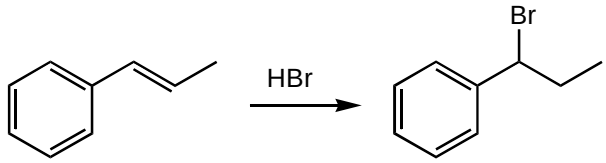
may be slow, but no elimination is possible

k.



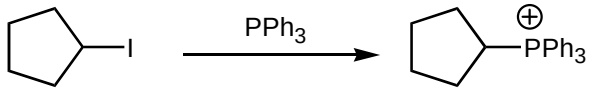
SN2

l.



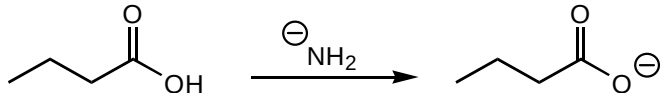
the cation intermediate for this product also has resonance

m.

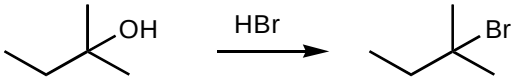


SN2

n.

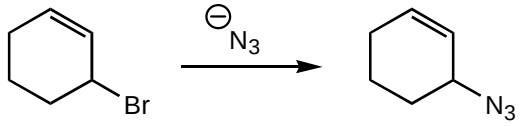


o.



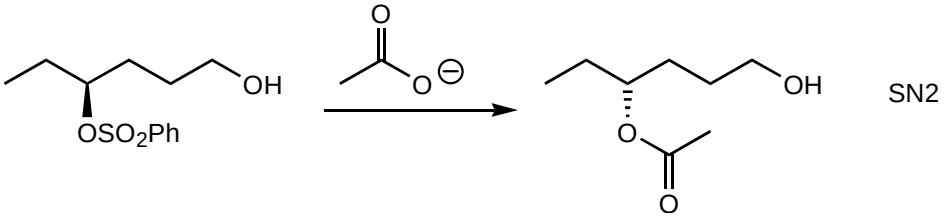
protonation
then SN1

p.



SN2

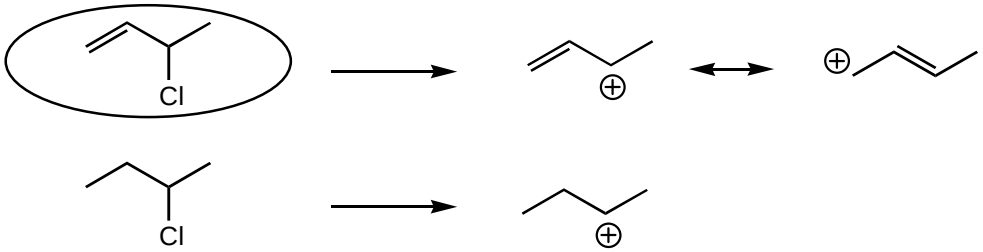
q.



SN2

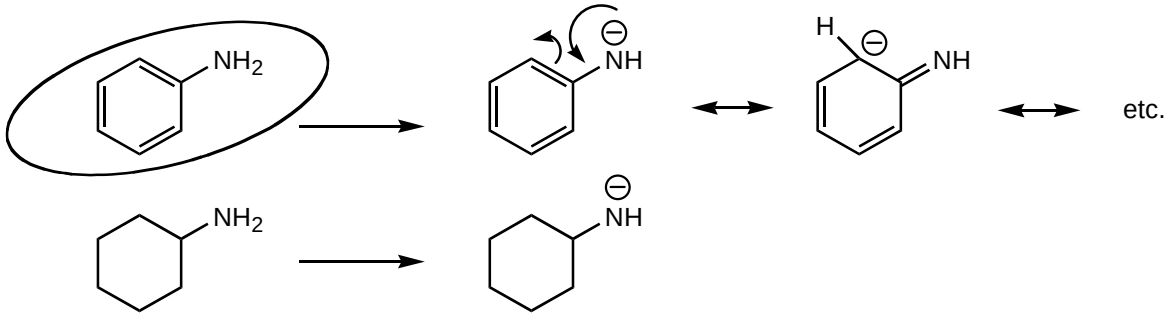
28. Evaluate the sets of compounds according to the given criterion and explain your reasoning.

a. Which substrate reacts faster in SN1 reactions?

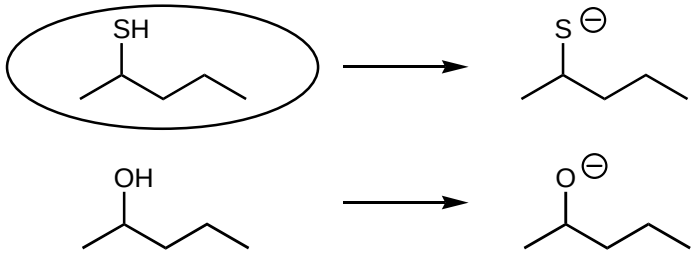


in the top case, the cation intermediate has resonance, but it the second case it doesn't (both are 2°). Expect the more stable cation to be formed faster, which means a faster SN1 reaction.

b. Which is a stronger acid (2 different sets)?



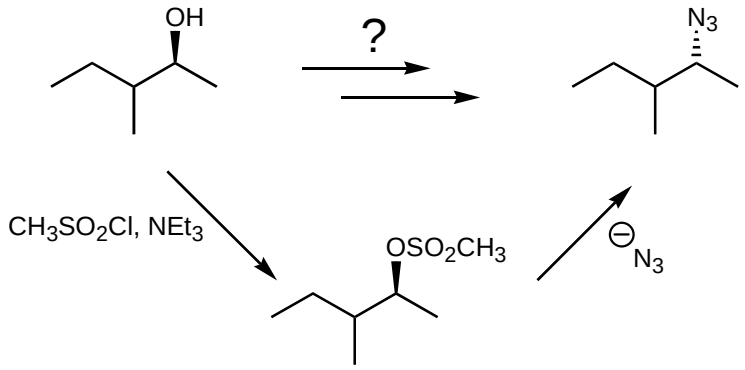
better conjugate base is the one stabilized by resonance. more stable conjugate base correlates with the stronger acid.



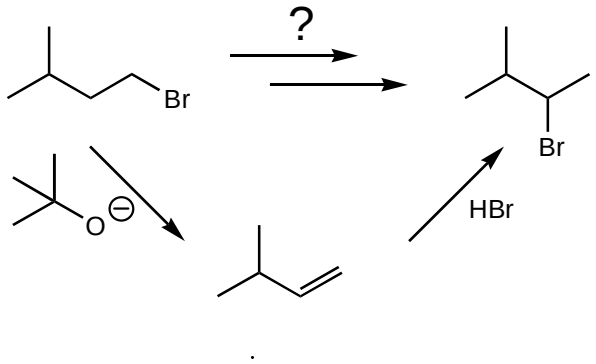
O and S are in the same column of the periodic table. The charge is better stabilized on the larger atom, so the thiol will be more acidic.

29. Provide a synthetic sequence to go from the given starting material to the desired product. Show all reagents and synthetic (not reaction) intermediates. All these syntheses can be accomplished in two steps.

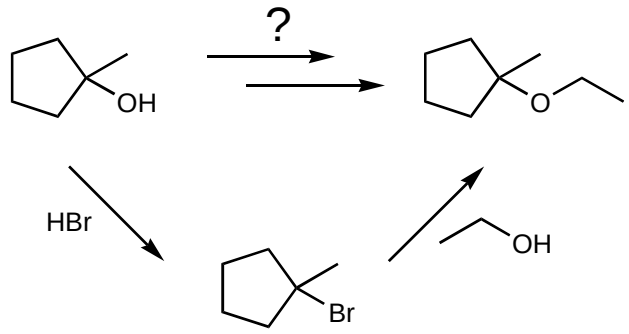
a.



b.

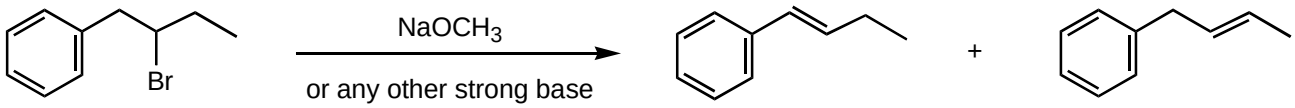


c.



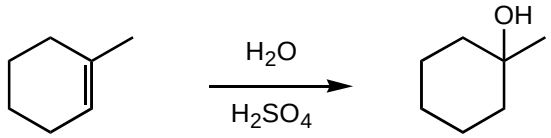
30. Supply the missing reagent or product. If more than one product can formed, give all possible products, and indicate which would be the major product. Be sure to indicate the stereochemistry and regiochemistry of the products where appropriate.

a.



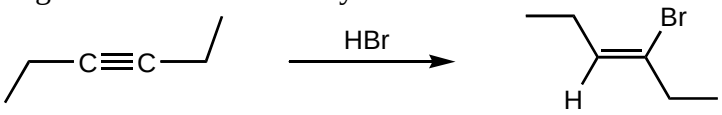
major -- favored because double bond is in conjugation with the benzene ring; think about resonance stabilization

b.



analogous to HBr addition

c. Although we have not covered reactions of alkynes yet, use what you know about HBr addition to predict the product. What is the sterochemistry of the double bond in the product? Assume one mole of HBr adding to one mole of the alkyne.



trans product