HOMEWORK PROBLEMS: SUBSTITUTION AND ELIMINATION

Substitution vs Elimination: Ask the following questions

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

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

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

E1 vs E2

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

E2 = 3º substrate with a nucleophile that is a strong base (may or may not be hindered – can dictate pdt)
= 2º substrate with a nucleophile that is a strong base (may or may not be hindered – can dictate pdt)
= 1º 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^- , $^t BuO^-$, $RC{\equiv}C^-$, 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 , $HC{=}C\text{-}CH_2\text{-}Br$

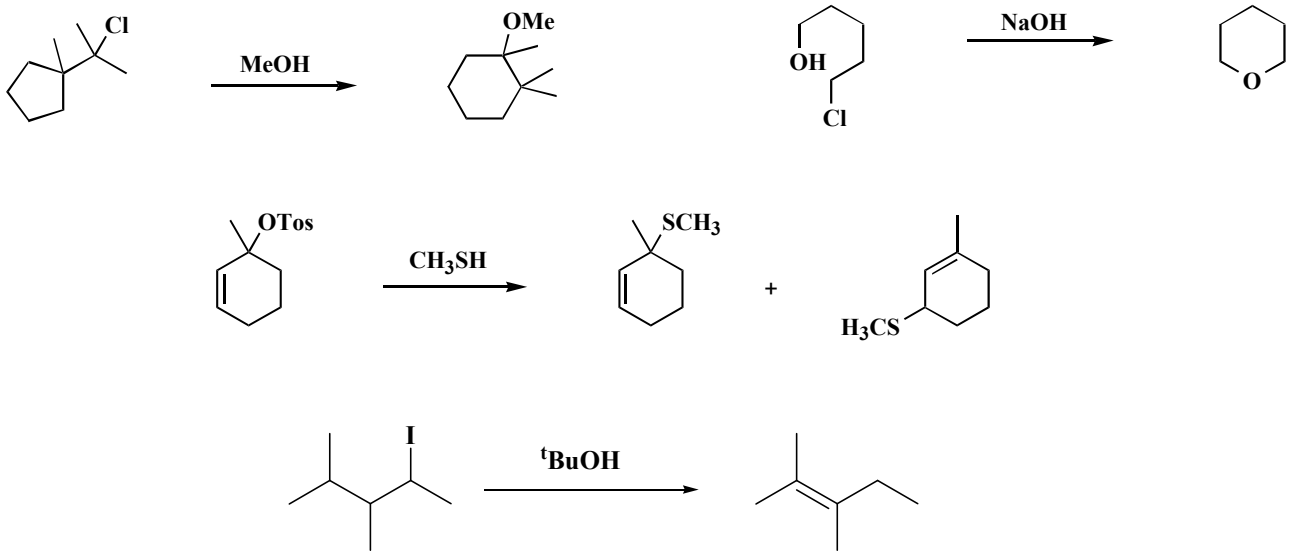
3. For each pair of compounds, circle the stronger nucleophile.

(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.

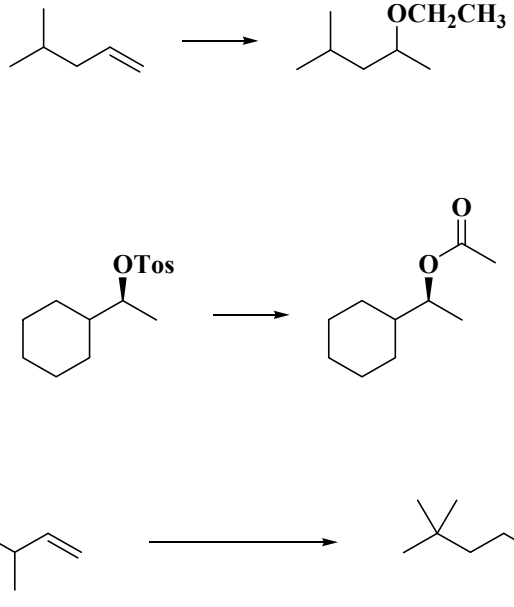
(a) HO^- or H_2O (b) $CH_3SO_3^-$ or $CF_3SO_3^-$
(c) F^-, Cl^-, Br^- or I^- (d) CH_3O^- or $CH_3CO_2^-$

5. Provide a mechanism for the following reactions.

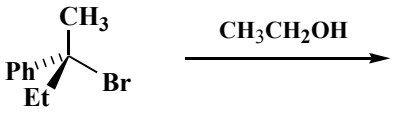


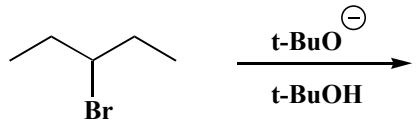
6. For each of the alkyl halides below only one alkene product is produced upon E2 elimination. Draw this product for each of these reactions. For each pair, which would react the fastest in the E2 reaction? (^{t}Bu = $C(CH_3)_3$)

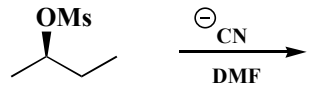
7. Show how you would carry-out a synthesis of the following compound from the indicated starting material. You may use any other reagents you wish.

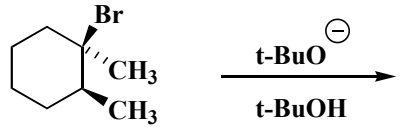


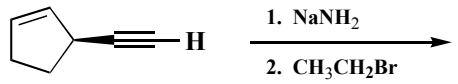
8. Give the structure of the major product(s) expected from each of the following reactions. If necessary, indicate the product stereochemistry. "NO REACTION" may be an acceptable answer.

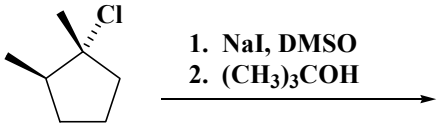


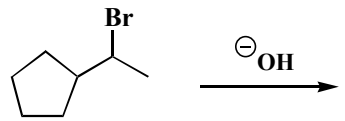








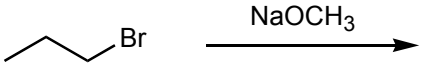




9. Provide mechanisms for the first three reactions in problem 8.

10. 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?

a.



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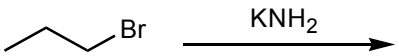

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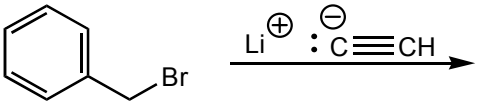

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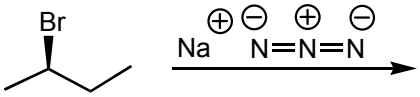
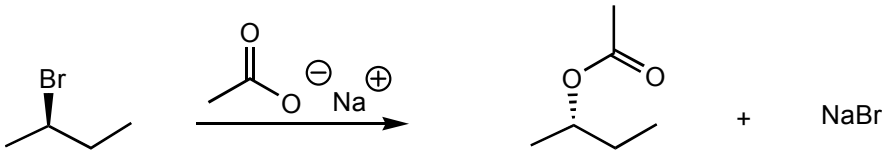
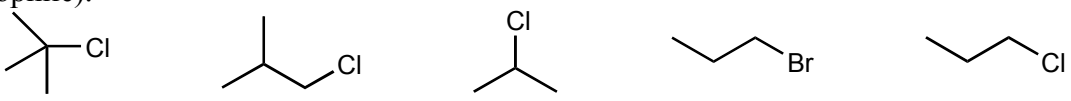


11. Consider the following substitution reaction.



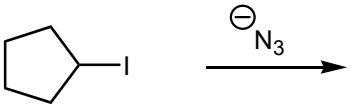
a. Draw a reasonable mechanism that accounts for the observed product. Show all steps and intermediates.
b. Draw a reaction coordinate diagram for the reaction. Label the transition state(s), intermediate(s), the energy of activation(s), and the energy of reaction.
c. Draw the structure(s) of the transition state(s) using the standard conventions.
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?

12. Rank the following alkyl halides in order of increasing SN2 reaction rate as electrophiles (when reacted with a nucleophile).



13. Give the expected major products for the following S$_N$2 reactions. Draw the movement of electrons for each reaction using mechanistic arrows.

a.



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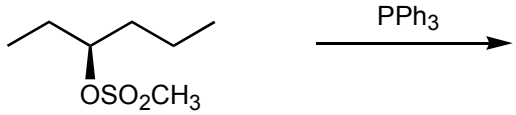

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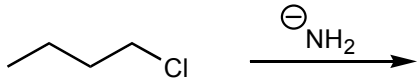

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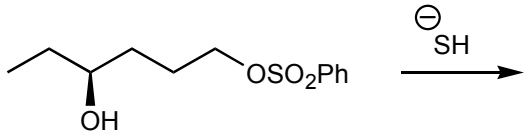

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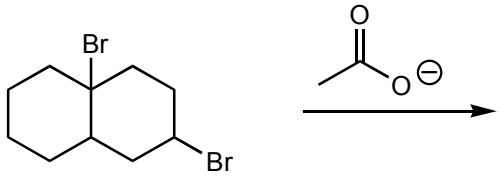

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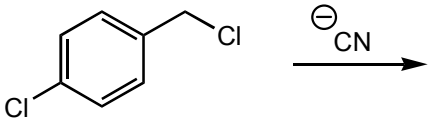

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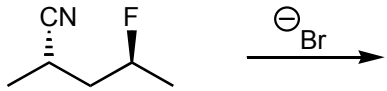
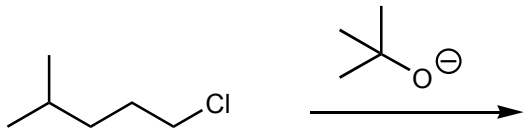


14. Give the expected major products for the following E2 reactions. Draw the movement of electrons for each reaction using mechanistic arrows.

a.



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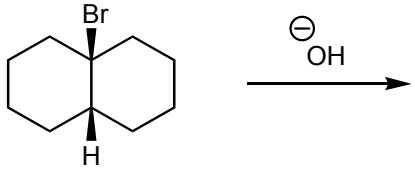

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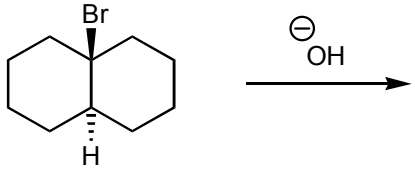

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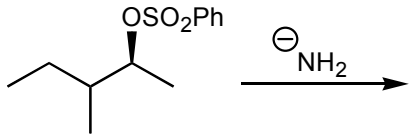

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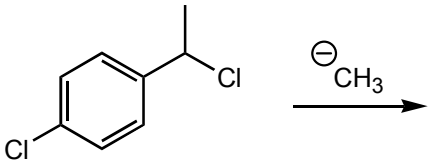

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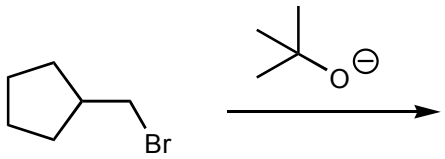

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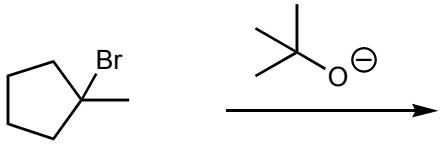
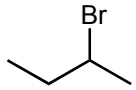


15. When the following substrates are reacted with NaOH, will they participate in a SN2 reaction, an E2 reaction, both, or neither? Briefly explain why.

a.



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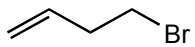

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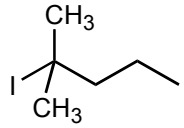
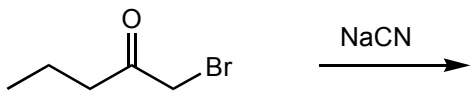


d. CH_3I

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

a.



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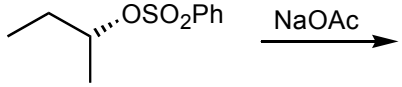

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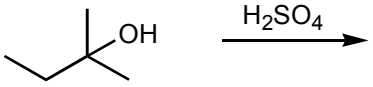

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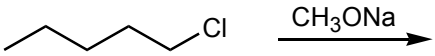

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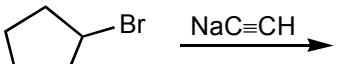

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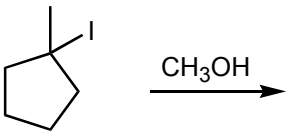

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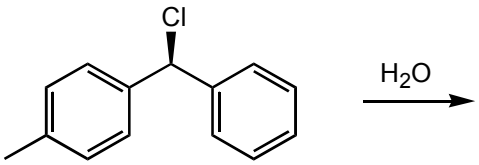
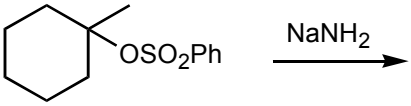
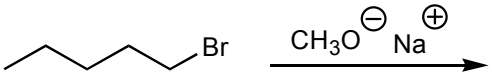




17. Give the major product of the reaction and the mechanism by which it is produced (SN2 and E2 only for this set of reactions; we will add in SN1 /E1 later). Be sure to include the stereochemical outcome.

a.


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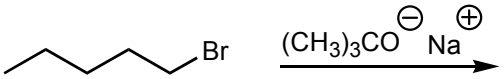

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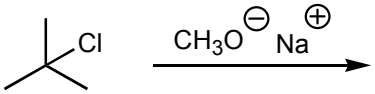

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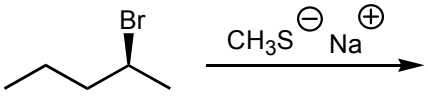

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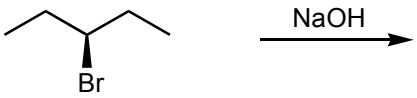

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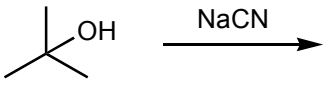

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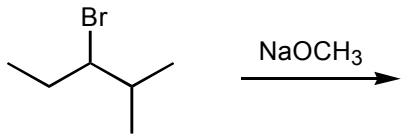

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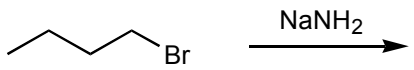
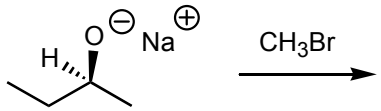
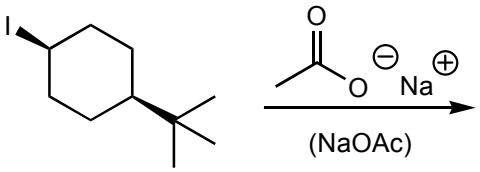


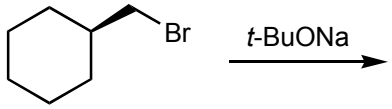
i.



j.

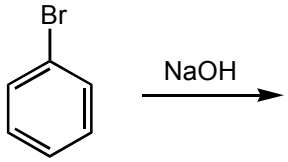


k.

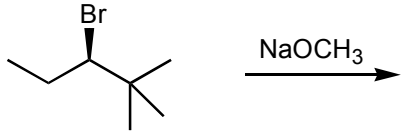


18. Give the <u>major product</u> of the reaction and the mechanism by which it is produced (SN1, SN2, E1, E2). Be sure to include the stereochemical outcome.

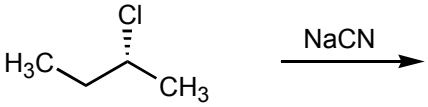
a.



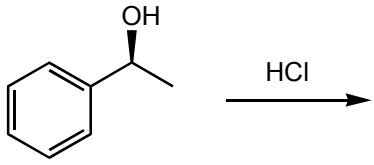
b.



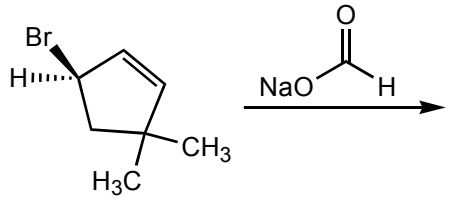
c.



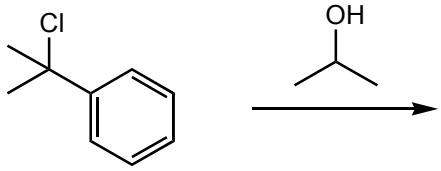
d.



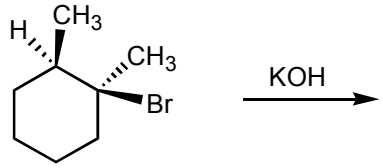
e.



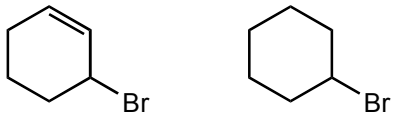
f.



g.

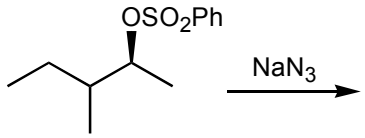


19. Assume that both of the following compounds happen to undergo an SN1 reaction. Draw what the intermediate would be for each compound. Which, if either intermediate, is more stable? Why? As a result, which should be formed faster?

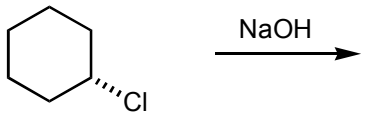


20. Give the expected major product for each of the reactions shown below. Indicate the type of mechanism by which it is formed. Draw out the mechanism by which it is formed.

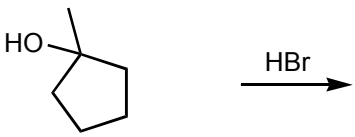
a.



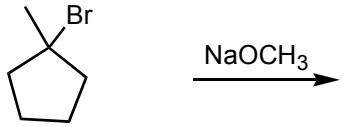
b.



c.

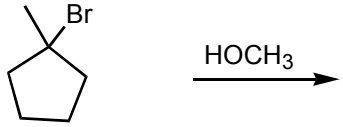


d.

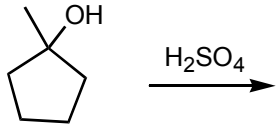


e.

f.

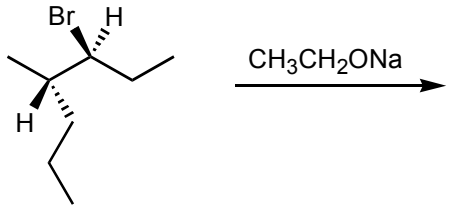


g.

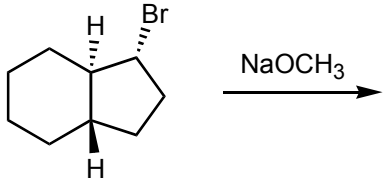


21. Using what you know about the mechanism, predict the elimination product. Be sure to clearly show the stereochemistry of the proposed product.

a.

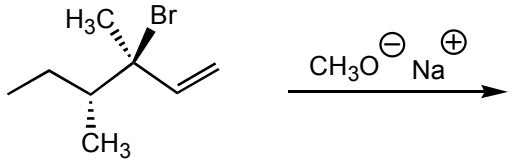


b.

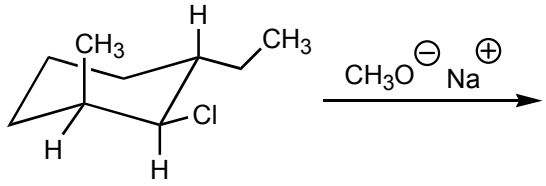


22. Using what you know about the mechanism, predict the elimination product. Be sure to clearly show the stereochemistry of the proposed product.

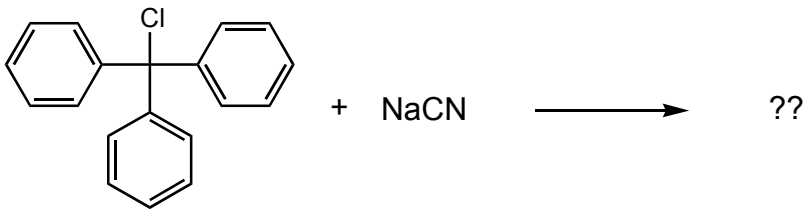
a.



b.



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

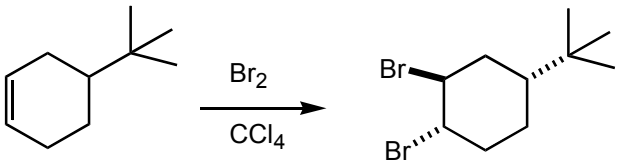


A **B**

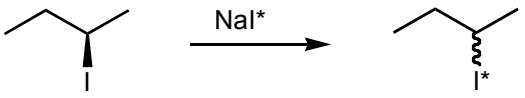
Change in Reactant Concentration	Effect on Rate
2 x [A]	rate doubles
2 x [B]	no change in rate
2 x [A], 2 x [B]	rate doubles
4 x [A]	rate quadruples (x 4)

a. Determine the reaction mechanism (SN1, SN2, E1 or E2), provide a reasonable rate expression, and predict the reaction product.
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), intermediate(s), the energy of activation(s), and the energy of reaction.. Include transition state pictures as well.

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.



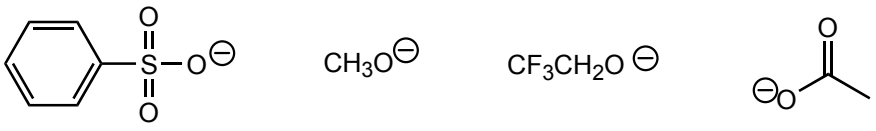
b. Workers studying nucleophilic substitutions reacted optically active 2-iodobutane with radioactive iodine (I*) as shown below. When they stopped the reaction, they found that the product was 40% radioactive, but only 20% enantiomerically pure (20% ee). Does this result confirm or contradict the SN2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



no radioactivity
100% ee

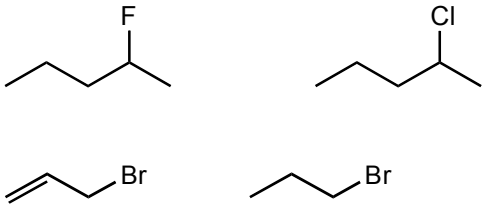
40% radioactive
20% ee

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

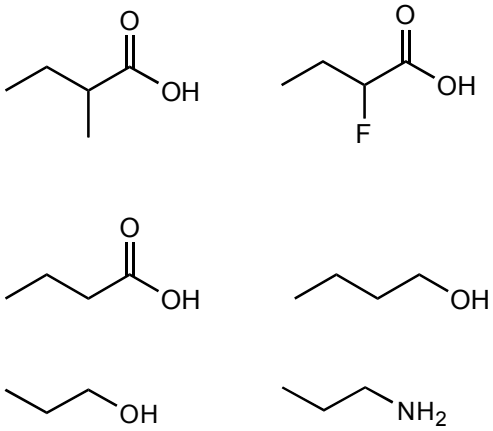


26. Evaluate the sets of compounds according to the given criterion and explain your reasoning. I like these questions a lot, and you can expect to see them regularly on exams.

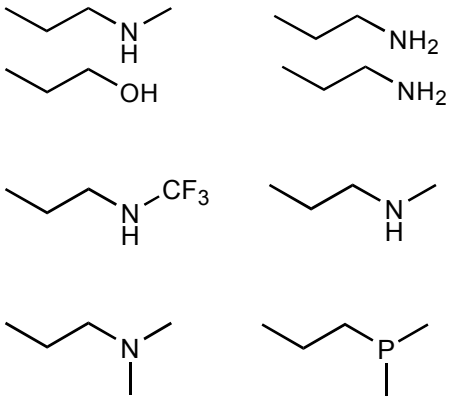
a. Which substrate reacts faster in SN2 reactions (2 different sets)?



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

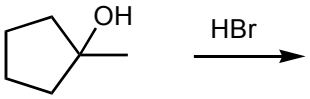


c. Which is a better nucleophile (4 different sets)?

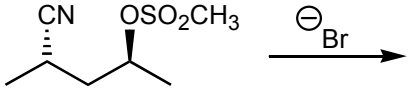


27. Give the expected major products for the following reactions, and when possible indicate the type of mechanism by which the reaction proceeds.

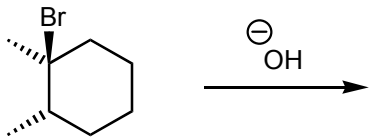
a.



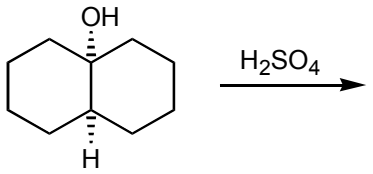
b.



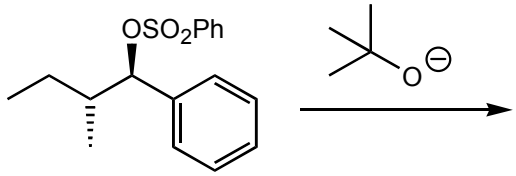
c.


Br
⊖
OH

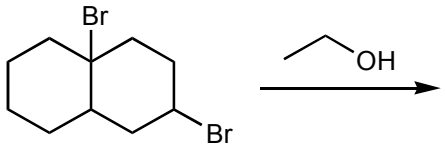
d.


OH
H2SO4
H

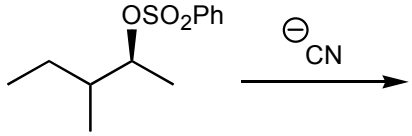
e.


OSO2Ph
O⊖

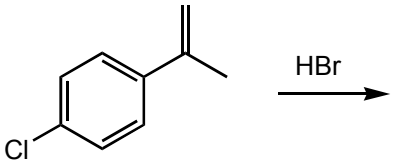
f.


Br
OH
Br

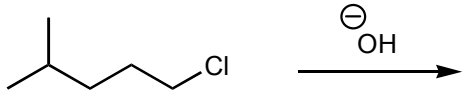
g.


OSO2Ph
⊖
CN

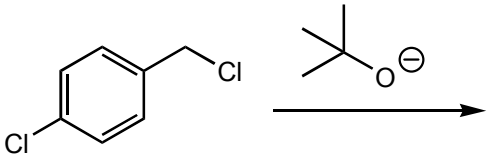
h.


HBr
Cl

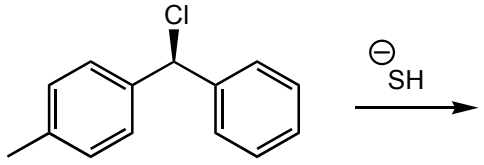
i.


⊖
OH
Cl

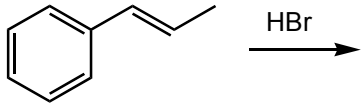
j.


Cl
O⊖
Cl

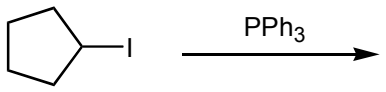
k.


Cl
⊖
SH

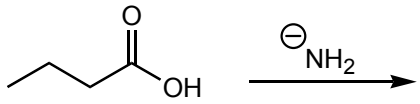
l.


HBr

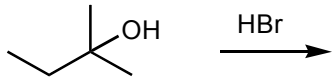
m.



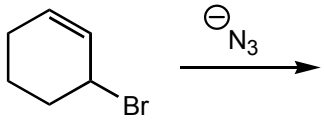
n.



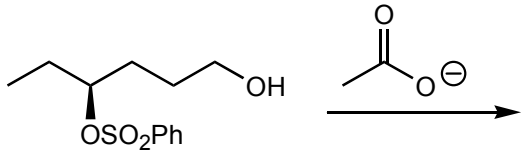
o.



p.



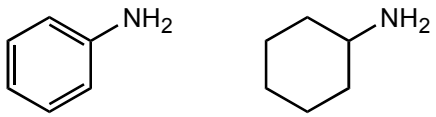
q.



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

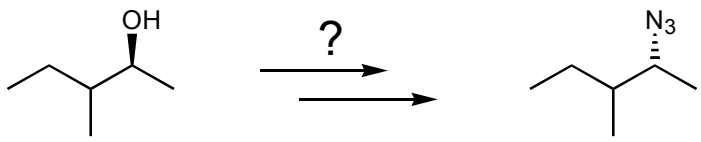
a. Which substrate reacts faster in SN1 reactions?

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

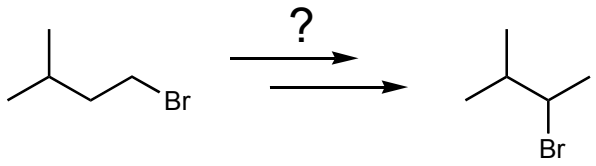


29. Provide a synthetic sequence to go from the given starting material to the desired product. Show all reagents and synthetic (not reaction) intermediates. All these syntheses can be accomplished in two steps.

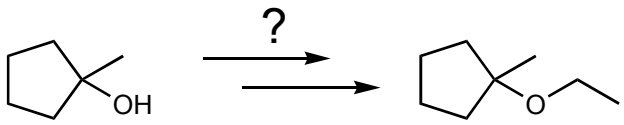
a.



b.

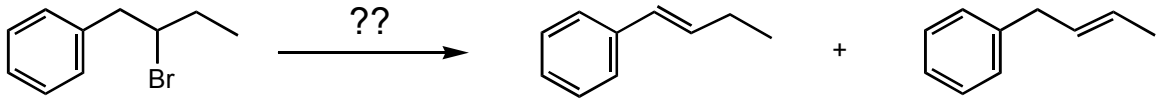


c.

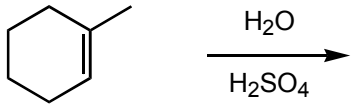


30. Supply the missing reagent or product. If more than one product can formed, give all possible products, and indicate which would be the major product. Be sure to indicate the stereochemistry and regiochemistry of the products where appropriate.

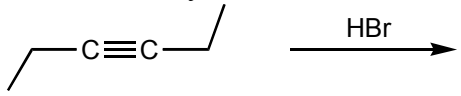
a.



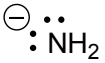
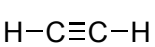
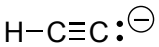
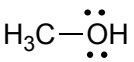
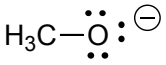
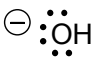
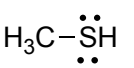
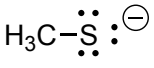
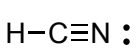
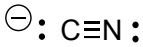
b.



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.



pKa Table: Acidity and Basicity

	Acid		Conjugate Base	
Weak Acid		49		Strong Base
		36		
		25		
		16		
		15.7		
		11		Increasing Nucleophilicty
		9.2		
		9.1		
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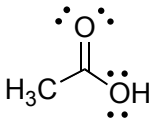
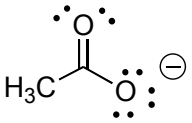
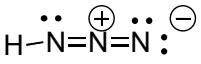
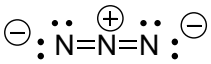
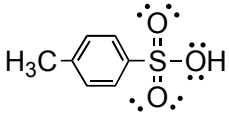
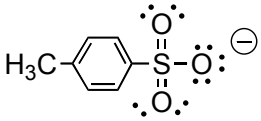
		4.8		
		4.7		
		3.2		
		-1.7		
**	 p-toluene sulfonic acid	-6.5	 p-toluene sulfonate or Tosylate	** Increasing Leaving Group Capabilities
		-7.0		
		-9.0		
Strong Acid		-10.0		Weak Base