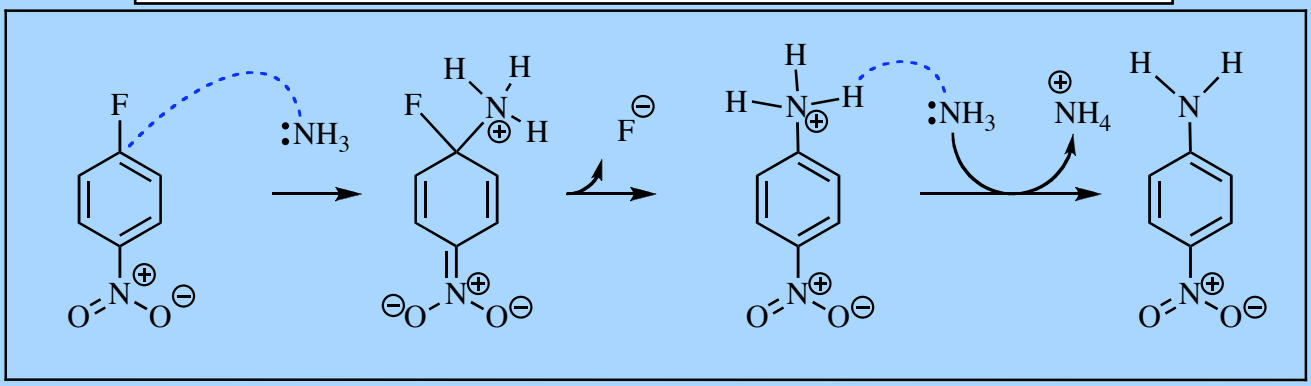
Part D
Demonstration Copy



The Language of Organic Chemistry

A Guide to Organic Chemistry Mechanisms

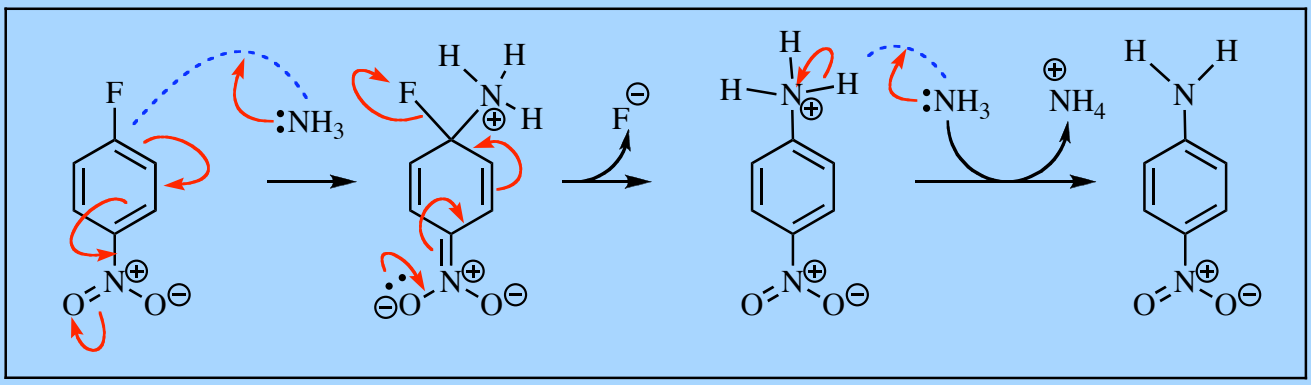


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Table of Contents

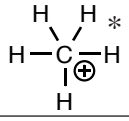
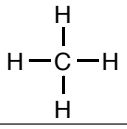
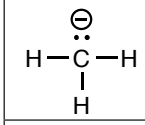
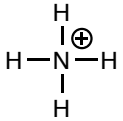
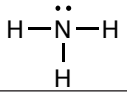
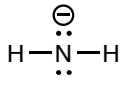
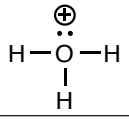
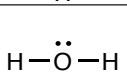
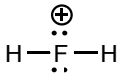
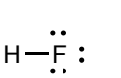
Index

1 - Getting Ready for Reactions

Reaction mechanisms are a challenging part of learning organic chemistry. Before we proceed with some examples, we need some basic knowledge that will be used in the remainder of the book. The two topics we shall examine in Chapter 1 are some basic facts about the atom (also in Parts B and C) and drawing resonance structures.

About the Atom

Complete the following table by adding the number of protons and electrons as needed. I hope you can learn to make some important predictions from this table.

	Charge	protons & electrons	Charge	Bond length	protons & electrons	Charge	protons & electrons
	+1		0			-1	
C		11p, 10e		1.10Å			
N				1.01Å			
O				0.96Å	10p, 10e		
F				0.92Å			9p, 10e

1. What pattern do you note in this table, they all have the same number of _____?

2. For each column, how can the compounds with different elements have the same number of protons?

3. For the column with zero charge, which atom would you expect the valence electrons to be closest to the central nucleus, C, N, O, or F? Explain

4. For the column with zero charge, why might the bond length decrease from C to F? Explain.

5. Why might you expect HF to be a stronger acid than H_2O? How do the electrons of oxygen and fluorine differ? Do the electrons have the same charge?

6. If you had two nitrogen atoms of different base strengths (ability to attract a proton), then which electrons would you predict are held closer to the nitrogen nucleus (to the more basic or less basic)?

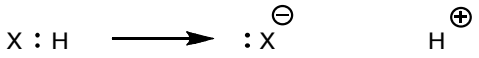
7. In the following problem, an oxygen atom is attached to another (electronegative) atom; predict which compound would be more acidic, HOH (water), HOOH (hydrogen peroxide), or HOCl (hypochlorous acid)? What effect will the atom attached to the oxygen (H, OH, and Cl) have on the proton-oxygen electron pair?

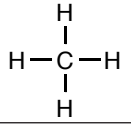
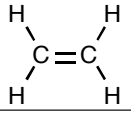
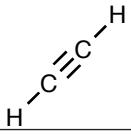
*This is the less common carbocation obtained by protonation of methane. CH_3^+ is more common, but does not fit the principle of the table because it has lost a proton and two electrons.

1 — Getting Ready for Reactions

About the Atom

Let us consider the following type of reaction. A large pK_a is a very weak acid and a very small pK_a is a very strong acid.



Compound	Bond length	pKa
	1.10Å	50
	1.08Å	44
	1.06Å	26
	0.92Å	3.2

Compound	Bond length	Halogen radius	pKa
	1.61Å	1.33Å	-10
	1.41Å	1.14Å	-8
	1.27Å	0.99Å	-7
	0.92Å	0.71Å	3.2

1. Comparing the carbon compounds and HF, how does the bond length correlate with the acidity?
2. Comparing HI, HBr, HCl, and HF, how does the bond length correlate with the acidity?
3. How can we resolve this paradox? Look at the anions (X^-) of HX. Does the total number of electrons increase proton affinity (more electrons, more attraction, therefore less acidic)?
4. If we were to suggest the most important factor in determining acidity was a simplistic model of Coulombic attraction between the positively charged nuclei and the electron pairs, then its force could be determined by the following equation.

   $$F = \frac{kq_1q_2}{r^2}$$

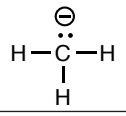
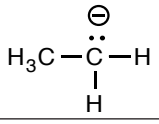
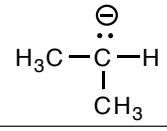
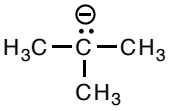
   Where k is a constant, q_1 and q_2 are the charges, and r is the distance. Let us consider HF, q_1=1 and q_2=2 for proton-electron (pair) affinity, and q_1=7, and q_2=2 (disregarding repulsive forces of other electrons) for fluorine-electron (pair) affinity.

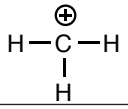
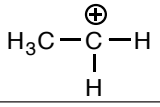
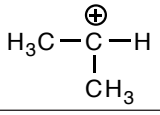
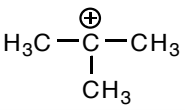
   If electrons are placed between the atoms, which force must be greater, fluorine-electron or proton–electron (pair)?
5. Considering the same principle, how must the proton–electron (pair) force of hydrogen iodide differ from that of hydrogen fluoride?
6. How must the electrons of the carbon-proton bond of methane (CH_4), ethene (CH_2CH_2), and ethyne (HCCH) differ?
7. Can you suggest a common theme that will agree with both sets of compounds?
8. The atomic radii for C, N, O, and F are 70, 65, 60, and 50 pm. What does that suggest about acidity? If the charge of a pair of electrons is always the same, then what one property could you use to predict a compound's acidity? (Hint, use Coulomb's Law)

1 — Getting Ready for Reactions

About the Atom

In the following table, the relative stabilities of some carbanions and carbocations are listed. In the prior tables, we have looked at the effect that different nuclei have on the availability of their electrons. In this instance, we are looking at electron deficient or electron rich carbon atoms.

Carbanion Structure	Relative stability
	1
	2
	3
	4

Carbocation Structure	Relative stability
	4
	3
	2
	1

1. If you compare the carbanion stabilities, what effect does replacing a hydrogen atom with a methyl group have on the stability of the carbanion?

2. If the hydrogen atoms were replaced with fluorine atoms, would a CF_3^- carbanion be more or less stable than a CH_3^- carbanion?

3. The pKa of trifluoromethane is approximately 25 while that of methane is 50. Which carbon-hydrogen electron pair would be closer to the carbon (methane or trifluoromethane)? What effect will that distance have on the proton-electron pair distance?

4. Comparing the carbocation stabilities, what effect does replacing a hydrogen atom with a methyl group have on the stability of the carbocation?

5. Many textbooks state that carbon is a better electron donor than hydrogen. Are the carbocation stabilities consistent with carbon being a better electron donor?

6. Is the stability of the tertiary butyl carbanion, $(CH_3)_3^-$, consistent with carbon being a better electron donor than hydrogen?

7. From your predictions above, which electrons would be held more closely to the carbon nucleus, the methyl carbanion or the tertiary butyl carbanion?

8. Which electrons will be closer to the carbon, those of methane or isobutane [$(CH_3CH(CH_3)_2$] and what effect will that distance have on the proton-electron pair distance?

9. An analogy that I suggest for predicting chemical reactivity is a boxer. The boxer with a longer reach would have an easier time to hit the nucleus of a neighboring atom. Which do you think would have a longer reach, CH_3^- or HO^-?

1 — Getting Ready for Reactions

About the Atom

Part A

1. In the table, they all have the same number of electrons.
2. In the table, the columns have the same number of protons, but a proton that was attached to the nucleus of the upper molecule is in the nucleus of the lower molecule.
3. For the elements C, N, O, and F, because fluorine has the largest number of protons in its nucleus, it should pull its electrons in the most.
4. For the compounds with C, N, O, and F, because fluorine can pull its electrons into the nucleus the most, it should have the shortest bond length, see 3 above.
5. Since H_2O and HF have the same number of electrons and the properties of electrons are constant, the difference in acidity must be do to where the electrons are located. If the electrons of fluorine are held the closest to the nucleus, we might conclude that as a result they are now the further from the hydrogen. If the hydrogen to electron distance is the greatest, they will result in the weakest bond and therefore, most acidic hydrogen.
6. If Number 5 is true, then the base strength of an atom would be proportional to the distance of the electrons to the nucleus. The electrons of nitrogen should be more basic than oxygen or fluorine because there are fewer protons in the nitrogen nucleus to hold them closely. If two nitrogen atoms differ in their basicity, then the less basic nitrogen would have its electrons closer to the nucleus (like oxygen or fluorine).
7. If a pair of electrons on an oxygen atom were pulled away from the nucleus by another atom, then the remaining electrons would feel the attractive force of the nucleus more strongly. If they are pulled in toward the nucleus, that will increase the proton-electron distance and result in a stronger acid. Therefore, acidity would decrease in the following order, HOCl>HOOH>HOH.

Part B

1. The *shorter* the bond length, the stronger the acid.
2. The *longer* the bond length, the stronger the acid.
3. It is the opposite, the iodide anion has the largest total number of electrons and it is the least able to hold a proton.
4. Since we know HF ionizes into H^+ and F^-, we know the hydrogen-electron pair force is weaker than the fluorine-electron pair force.
5. From Number 4, if HI is a stronger acid than HF, we might conclude the proton-electron pair distance of HI must be greater than that of HF.
6. If Number 5 is true, then if ethyne is more acidic than methane, then the terminal ethyne carbon must hold its electrons more tightly than the carbon of methane.
7. It isn't the HX distance that matters as much as the hydrogen-electron pair distance. The greater that distance, the weaker the bond. If you look at the *difference* between bond length and halogen radius, it increases from HF to HI. (The halogen radii were found in www.webelements.com.)
8. The atomic radii for C, N, O, and F are 70, 65, 60, and 50 pm. Since CH_4 is the weakest acid of this group, its proton is the most strongly held. Therefore, the greater the distance that an electron pair can extend beyond a nucleus, the greater the attraction it may have for a proton or another nucleus.

Part C

1. Replacing a hydrogen atom with a methyl group decreases the stability of the carbanion.
2. Because fluorine is more electronegative than hydrogen, a CF_3-carbanion should be more stable than a CH_3-carbanion.
3. Because a fluorine atom can pull its electrons more tightly to its nucleus, we might infer the effect of electrons being pulled away from the carbon will result in the non-fluorine electrons being pulled more tightly to the nucleus. If they are pulled closer to the carbon nucleus, that may increase the hydrogen-electron pair distance and result in an increase in acidity.
4. Replacing hydrogen atoms with methyl groups increases the carbocation stability.
5. If a carbon atom donates electrons, then the carbocation stability should increase as electron donation is increased. The relative stabilities are consistent with carbon being a better electron donor.
6. The carbanion stabilities are consistent with carbon being a better electron donor. Since carbon donates electrons, therefore increasing the number of methyl groups should decrease the stability of a carbanion.
7. A tertiary butyl carbanion is less stable than a methyl carbanion because the methyl groups donate electrons toward the central carbon. Therefore, we might conclude that the donated electrons might increase Coulombic repulsion and increase the distance from the carbon to the non-bonded electron pair.
8. If the carbon-electron pair distance is increased in isobutane, we might conclude that the proton-electron pair distance might decrease. Therefore, isobutane should be less acidic, less stable, and more reactive than methane.
9. The electrons of a CH_3^--carbanion should extend further than a hydroxide anion because there are fewer protons pulling them toward the carbon nucleus. If they extend further, they will be more available for reaction.

For further discussion, see Notes.

Guide to Drawing Resonance Structures

Resonance Structures

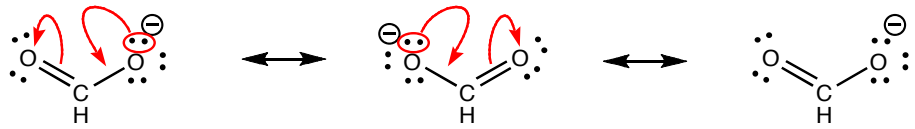
If you are unfamiliar with the use of the curved arrow, refer to the discussion in the Notes section. A good place to start pushing electrons is in drawing resonance structures. They have the elements of electron movement, but the problems will be more limited in scope.

Resonance Structures of Anions

The principle for understanding resonance structures is to understand that electrons will operate by a push-pull mode or model. If there's a net negative charge, it will be the electrons of the atom with the negative charge that will push toward the pi bond. We will start our curved arrow with those electrons. Continue to move them toward any neighboring pi bonds (push) to create and break new bonds. You should note that two curved arrows are required to avoid structures with more than eight valence electrons.

For the following examples, add curved arrows, where needed, to show how the electrons move to form the next structure. For 1-6, the first and last structures are the same. In that case, you are converting it back to the starting structure.

1.



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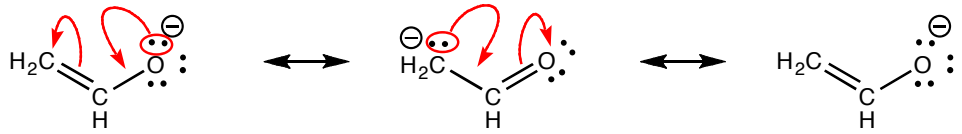

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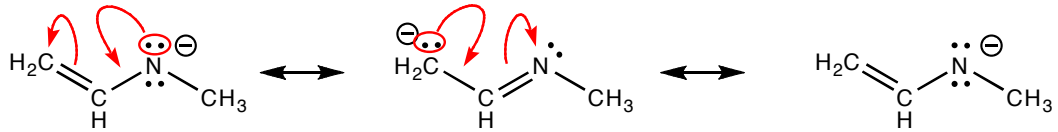

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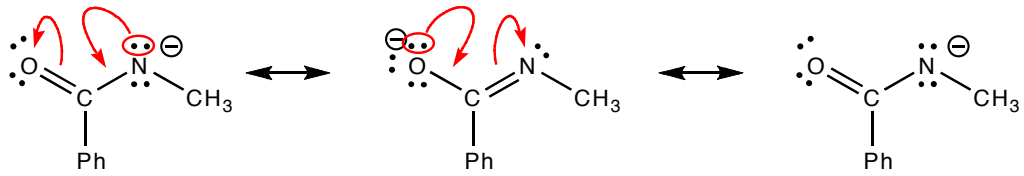

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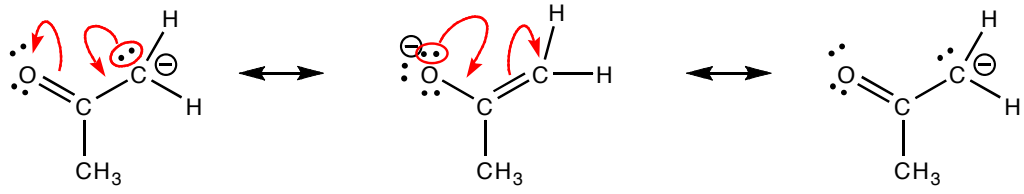

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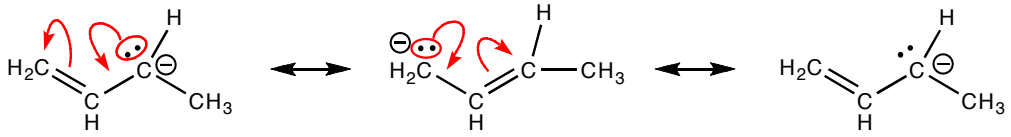

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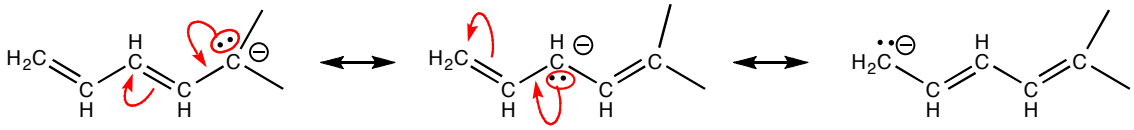

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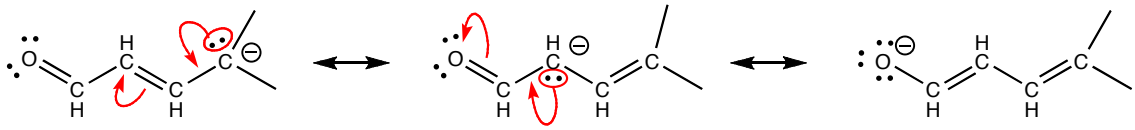


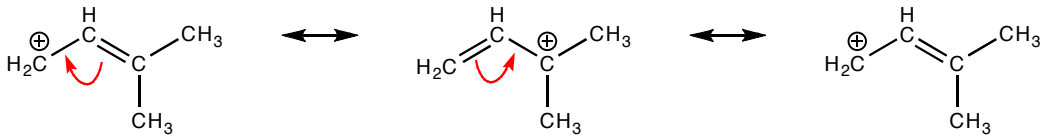
These examples show how the electrons can move, where the resulting charge will form, and how the charge can be distributed. It does not tell you on which atoms the greater charge density might exist nor upon which atom a reaction might next occur. You will note that since the original structure had a negative charge, the only charge that exists on any of the resulting resonance structures is a negative charge.

Resonance Structures of Cations

Conversely, if there is a positive charge, it is the positive charge that will attract (pull) electrons. Start a curved arrow from a neighboring pi or pair of non-bonded electrons and bring it toward the positive charge. You will note that only one curved arrow is necessary to create a new resonance structure. Because the original structure is a cation, completing its octet should not require further electron movement.

Add curved arrows to the following structures. For 9 and 10, the first and last structures are the same. In that case, you are converting it back to the starting structure.

9.



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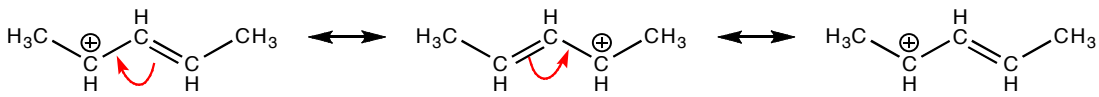

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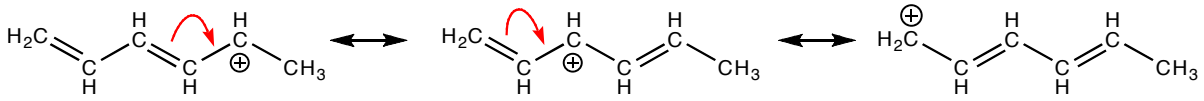

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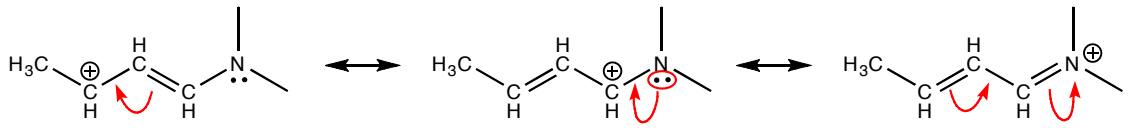

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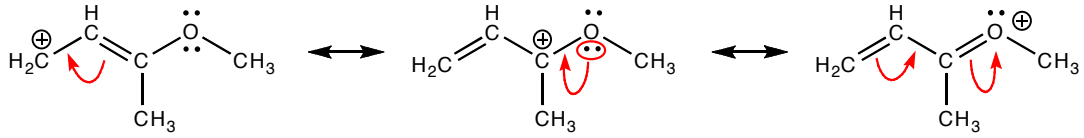


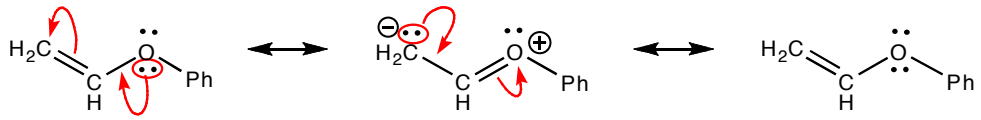
Again, these examples show how the electrons can move, where the resulting charge will form, and how the charge can be distributed. It does not tell you on which atoms the greater charge density might exist nor upon which atom a reaction might next occur. You will note that since the original structure had a positive charge, the only charges that exist on any of the resulting resonance structures are positive charges.

Resonance Structures of Neutral Compounds with Non-Bonded Electrons

If there isn't a charge and there are adjacent non-bonded electrons, then it will be the non-bonded electrons that will move (push) toward a neighboring pi bond. Start a curved arrow with the non-bonded electrons and direct them to the neighboring double bond.

Add curved arrows to the following structures. For 14-17, the first and last structures are the same. In that case, you are converting it back to the starting structure.

14.



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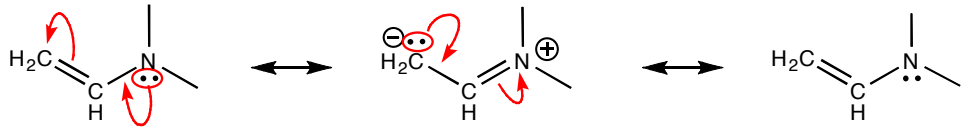

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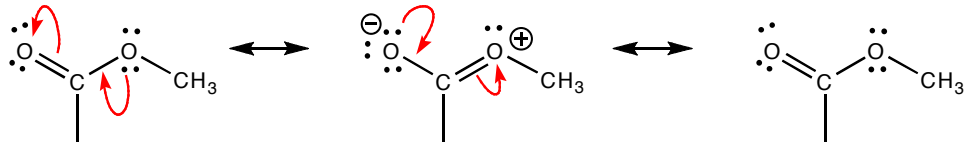

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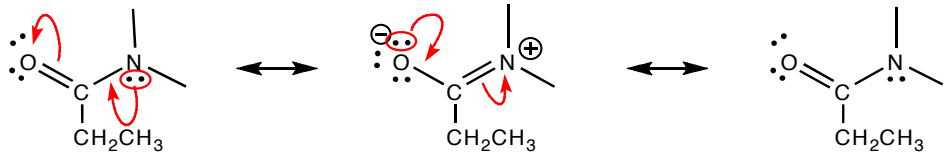

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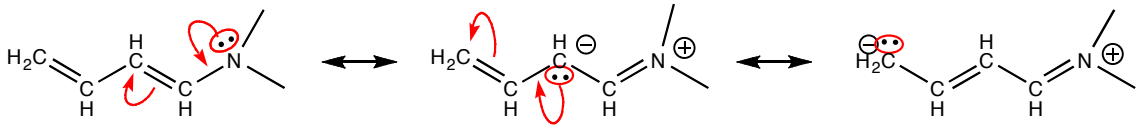

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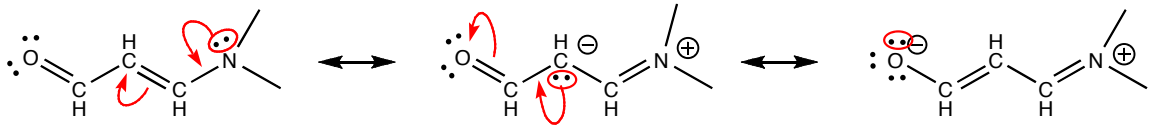
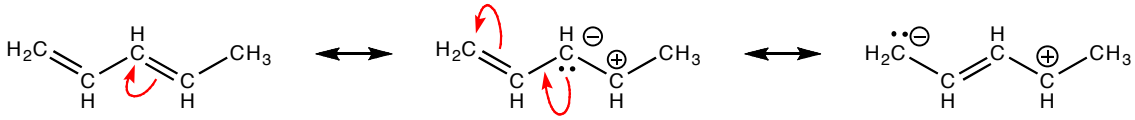


These examples show how the electrons can move, where the resulting charges will form, and how the charges can be distributed. It does not tell you on which atoms the greater charge densities might exist nor upon which atoms a reaction might next occur. You will note that since the original structure was neutral, the net charges that exist on any of the resulting resonance structures are also neutral and only two atoms have a charge.

Resonance Structures of Neutral Compounds without Non-Bonded Electrons

If no charge exists and no neighboring non-bonded electrons, then use the pi electrons of the most substituted double bond (push). Start a curved arrow with the pi electrons of the most substituted double bond and direct them toward the least substituted atom of that double bond.

20.



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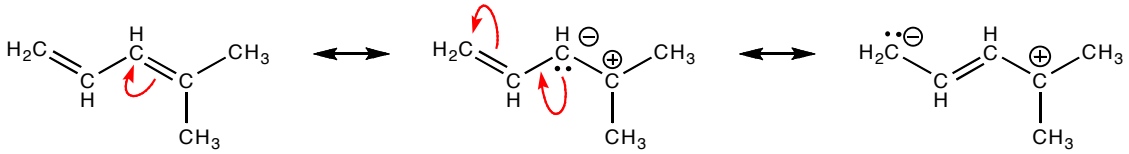
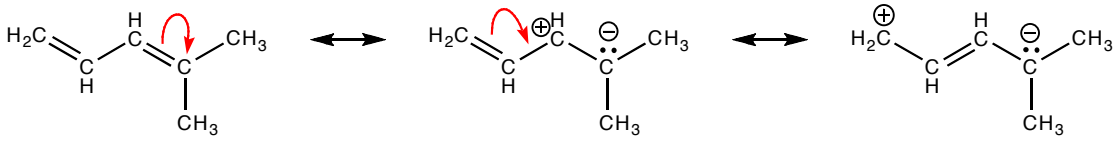


This is the same example as above, however the arrows are pointing in the opposite direction. If you are uncertain in which direction the electrons might move, a good strategy is to draw an arrow in the opposite direction and then to compare the results of the two possibilities. Compare the result below with the one above. Which is the more stable? If you do not recognize the lower arrangement as a lesser contributor, you may need to refer to your textbook for the rules of carbanion, carbocation, and resonance stability.

22.



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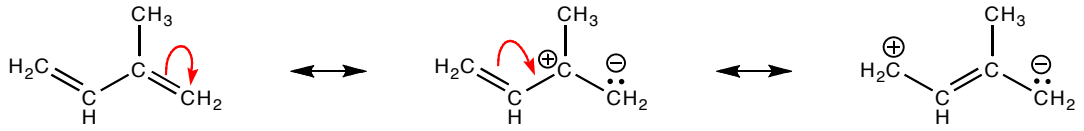

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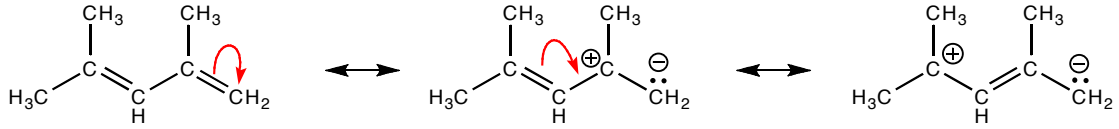

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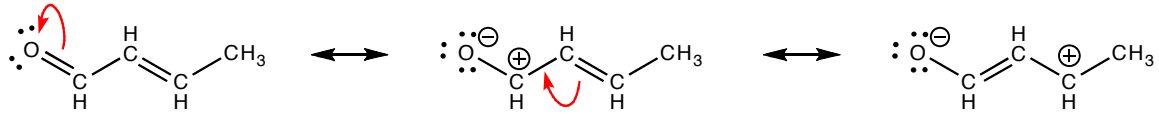
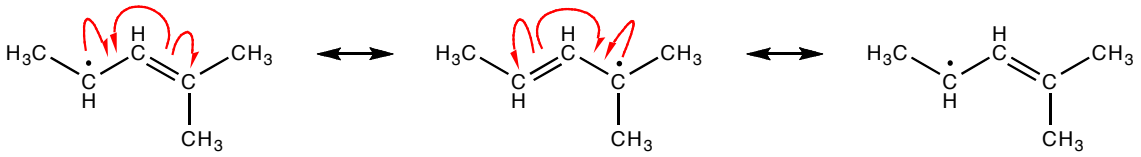


In these examples, we have incorporated chemical principles. The carbocations that are the most substituted are the most stable. Coinciding with this principle is that carbanions with the least substitution (or a heteroatom, last example) are the most stable.

Resonance Structures of Radicals

Radicals, compounds with unpaired electrons, are less stable than those with paired electrons. The fate of radical reactions is to form a paired-electron bond. However, sharing unpaired electrons with neighboring non-bonded or pi-bonds can attain added stability. Also note the curved arrow has a single barb indicating the movement of a single electron. Two arrows are required for a pair of electrons.

26.



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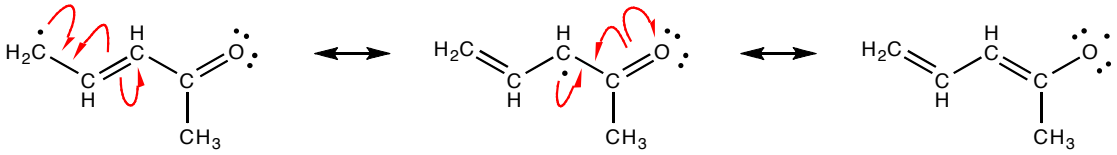


2 — Acid-Base Chemistry

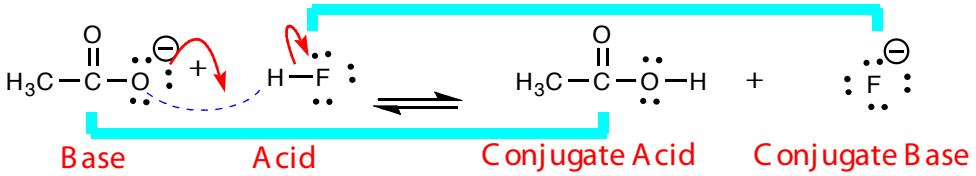
Bronsted-Lowrey Acids and Bases

Acid-base reactions are often the first intermolecular reaction you will encounter. A proton will be exchanged from the strongest acid to the strongest base.

In these examples, you must note the conjugate acid and conjugate base that result in each reaction. You should note the use and meaning of the curved arrows. If the example does not contain a curved arrow, you must supply one. The meaning of the curved arrow is important for you to understand.

- The rule for predicting the product of an acid-base reaction is simple. A reaction will generally give the product that is the weakest base (or conjugate base). The base strength of a compound is related to the acidity of the acid, the stronger the acid, the weaker the base, or the corollary, the weaker the acid, the stronger the base. In order to compare the base strengths, the acidities of the acids and conjugate acid must be determined first.
- Look at each example and write the pK_a under each acid (on the left) and conjugate acid (on the right). Be careful that you correctly identify the acids and the corresponding pK_a. Strong acids have a small pK_a and weak acids have a large pK_a. You may need to use a table to find some values.
- For each acid (or conjugate acid), write the corresponding pK_a beneath it. Write the label "B(ase)" (or "CB") under each base (or conjugate base). Look at the pK_a of the acid or conjugate acid. The strongest acid corresponds with the weakest base. Label it, "weakest base". In example 1, the pK_a of HF is 3.2. It is placed under HF. The pK_a of acetic acid is 4.75 and 4.75 is placed under it. Because HF is the stronger acid (lowest pK_a), its conjugate base will be the weakest base. The equilibrium will shift to the right.
- Label the equilibrium of each reaction, L(eft) or R(ight). Example 1, R.

1. For this example, the acids and bases are labeled. HF is the strongest acid as it has the lower pKa. Therefore, F^-, its conjugate base is the weakest base.

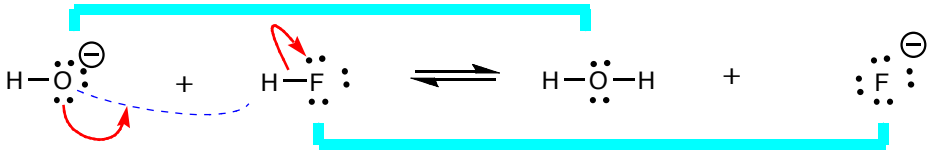


L/**R** pK_a 3.2 pK_a 4.75 weakest base

Notice the curved arrows. They describe the reaction that is taking place. We could write the following sentences to describe the curved arrows.

A bond is being made between the oxygen and hydrogen atom with the electrons from the oxygen atom.
A bond is being broken between the hydrogen and the fluorine atom with the electrons remaining attached to the fluorine atom.

2. Label acids, bases, and conjugate acids and bases.



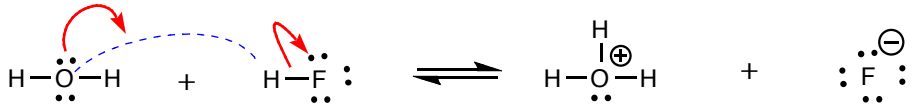
L/**R** base pK_a 3.2 pK_a 15.7 weakest base

Notice the curved arrows. We could write the following sentences to describe the curved arrows.

A bond is being made between the oxygen and hydrogen atom with the electrons from the oxygen atom.
A bond is being broken between the hydrogen and the fluorine atom with the electrons remaining attached to the fluorine atom.

Continue by completing the equation, adding curved arrows, pK_a values, label the direction of equilibrium, and write a sentence(s) describing any bonds being made and broken.

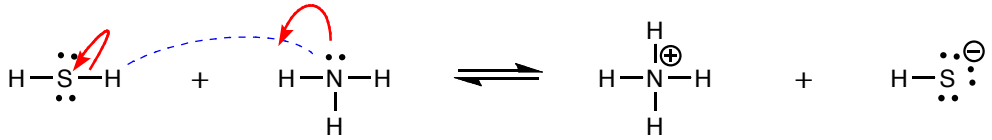
3. Write a sentence(s) describing any bonds being made and broken.



L/R weakest base 3.2 -1.7

A bond is formed between the oxygen and hydrogen with the electrons from the oxygen. The bond between the hydrogen and fluorine is broken with the electrons remaining attached to the fluorine.

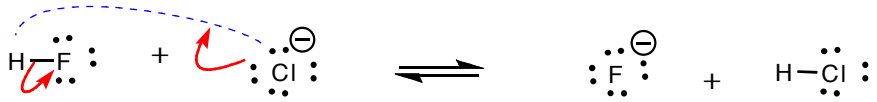
4. Write a sentence(s) describing any bonds being made and broken.



L/**R** 7.0 9.2 weakest base

A bond is formed between the nitrogen and hydrogen with the electrons from the nitrogen. The bond between the hydrogen and sulfur is broken with the electrons remaining attached to the sulfur.

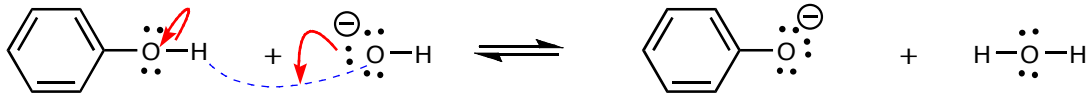
5. Write a sentence(s) describing any bonds being made and broken.



L/R 3.2 weakest base -8

A bond is formed between the chloride and hydrogen with the electrons from the chloride. The bond between the hydrogen and fluorine is broken with the electrons remaining attached to the fluorine.

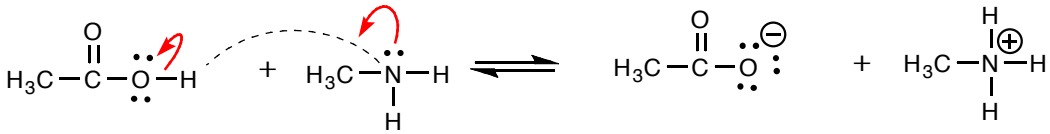
6. Write a sentence(s) describing any bonds being made and broken.



L/**R** 10.0 weakest base 15.7

A bond is formed between the oxygen and hydrogen with the electrons from the oxygen. The bond between the hydrogen and oxygen is broken with the electrons remaining attached to the oxygen.

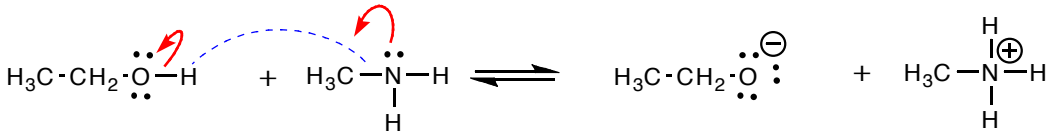
7. Write a sentence(s) describing any bonds being made and broken.



L/**R** 4.75 weakest base 10.5

A bond is formed between the nitrogen and hydrogen with the electrons from the nitrogen. The bond between the hydrogen and oxygen is broken with the electrons remaining attached to the oxygen.

8. Write a sentence(s) describing any bonds being made and broken.

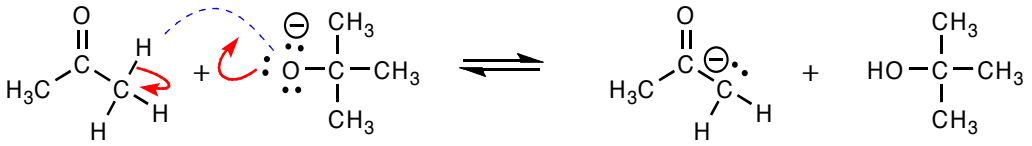


L/R 16.0 weakest base 10.5

A bond is formed between the nitrogen and hydrogen with the electrons from the nitrogen. The bond between the hydrogen and oxygen is broken with the electrons remaining attached to the oxygen.

Continue by completing the equation, adding curved arrows, pK_a values, label the direction of equilibrium, and write a sentence(s) describing any bonds being made and broken.

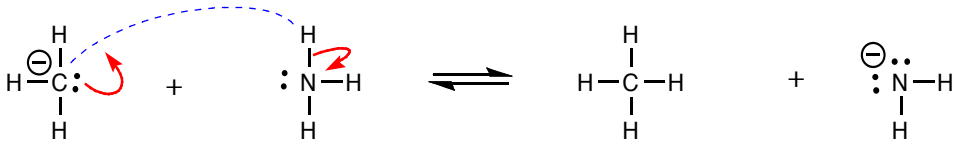
9.



L/R 22 weakest base 19

A new bond is formed between the oxygen and hydrogen with the electrons from the oxygen. The bond between the hydrogen and carbon is broken with the electrons remaining attached to the carbon.

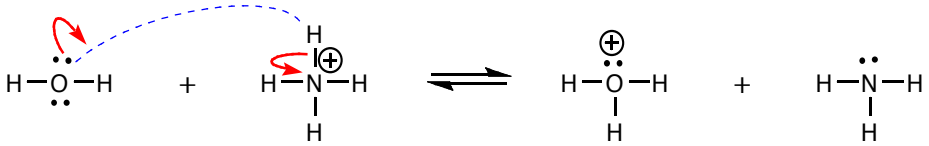
10.



L/**R** 38 50 weakest base

A bond is formed between the carbon and hydrogen with the electrons from the carbon. The bond between the hydrogen and nitrogen is broken with the electrons remaining attached to the nitrogen.

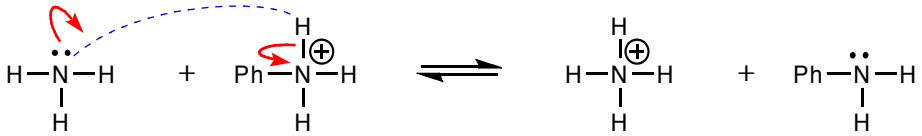
11.



L/R weakest base 9.2 -1.7

A bond is formed between the oxygen and hydrogen with the electrons from the oxygen. The bond between the hydrogen and nitrogen is broken with the electrons remaining attached to the nitrogen.

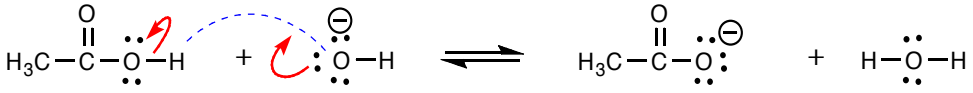
12.



L/**R** 4.6 9.2 weakest base

A new bond is formed between the nitrogen and hydrogen with the electrons from the nitrogen. The bond between the hydrogen and nitrogen is broken with the electrons remaining attached to the nitrogen.

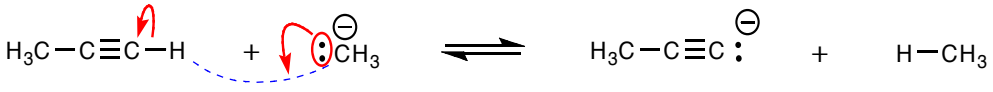
13.



L/**R** 4.75 weakest base 15.7

A bond is formed between the oxygen and hydrogen with the electrons from the oxygen. The bond between the hydrogen and oxygen is broken with the electrons remaining attached to the oxygen.

14.

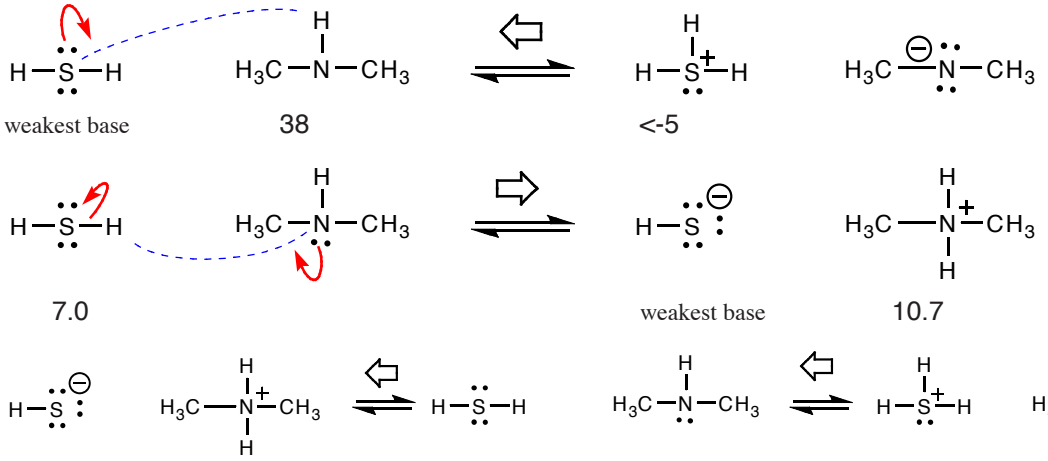


L/**R** 24 weakest base 50

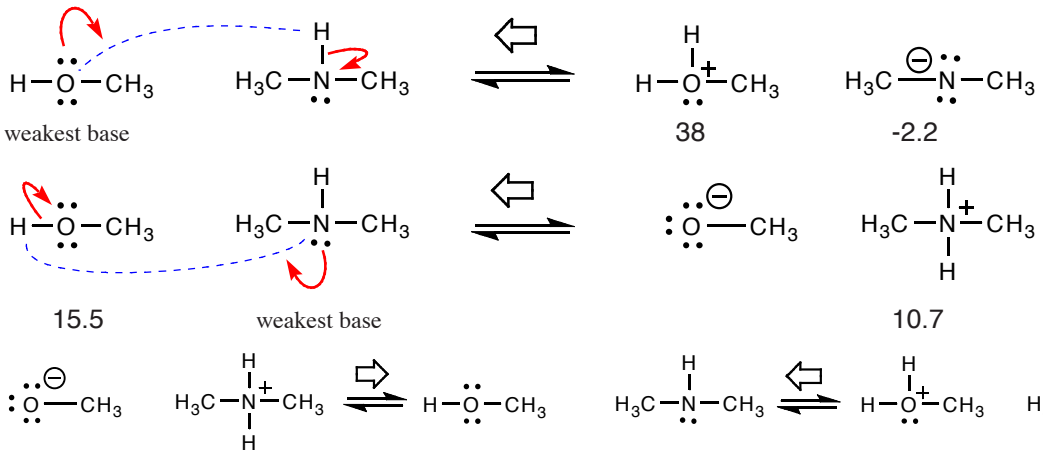
A bond is formed between the carbon and hydrogen with the electrons from the carbon. The bond between the hydrogen and carbon is broken with the electrons remaining attached to the carbon.

15. Sometimes we may be unsure how a reaction might proceed. Will H_2S and $(CH_3)_2NH$ react together? What will the products be if they do? In that case, draw ALL of the possible products and analyze the results. Complete this problem as before.

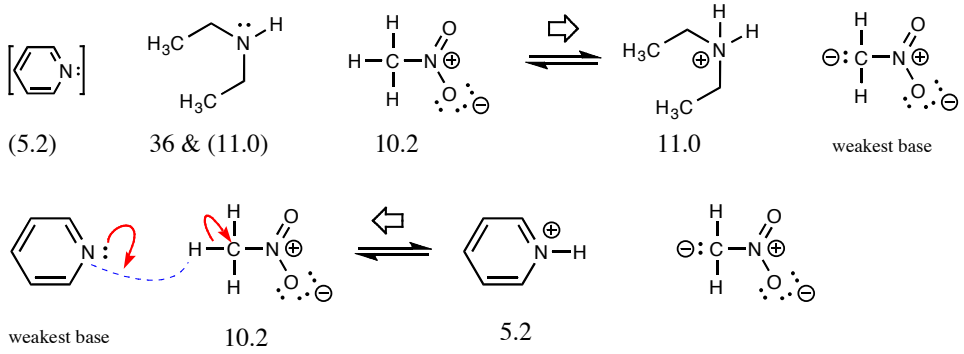
    From the individual equilibria, can you predict the overall result?



16. What is the equilibrium between $HOCH_3$ and CH_3NHCH_3? First, determine the individual equilibria and then predict the overall result.



17. What is the equilibrium when you don't have any idea what will happen? First, determine the individual equilibria. What products will each equilibrium favor? Which equilibria favor the reactants? Which reaction can occur and what will be the products? Circle that reaction.



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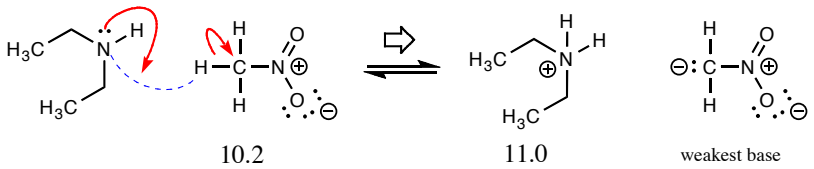
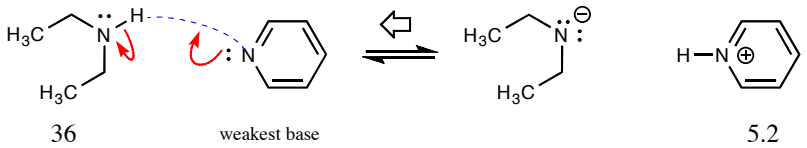
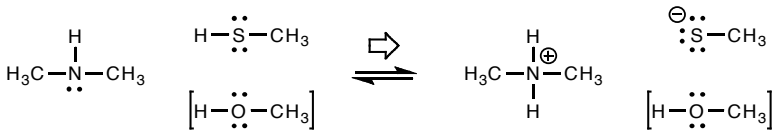


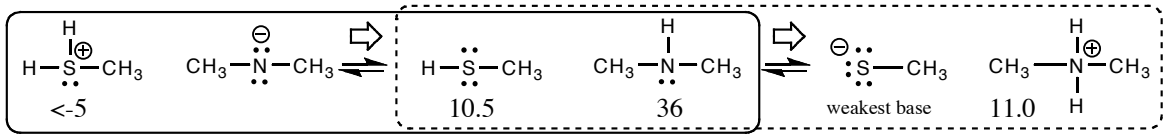


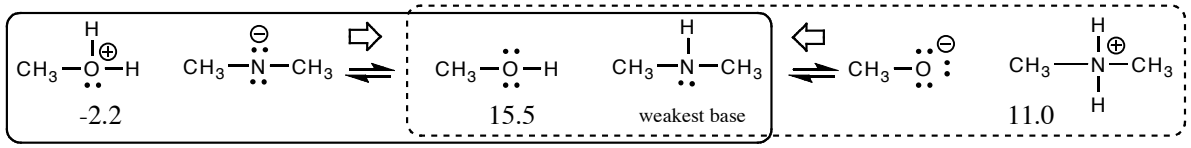
18. What will be the equilibrium mixture between $HSCH_3$, CH_3OH and CH_3NHCH_3? Determine the individual equilibria first.

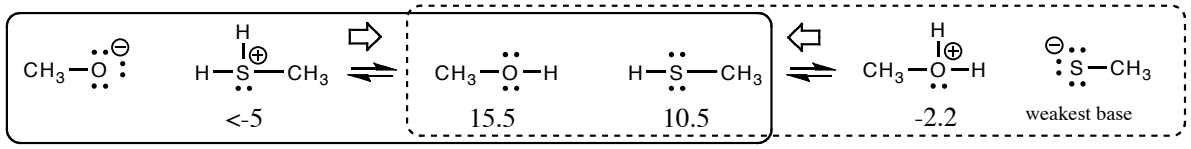


Each individual species is present two times in the individual equilibria. This could have been written as six individual equilibria in which the center reagents are common to both sides. In assaying each equilibrium, note the acid values for each reagent and which will donate a proton in its acid-base reaction. In the first example, the pK_a 36 corresponds to a loss of a proton. The same compound is a base to the conjugate acid of pK_a 11.0.

- Cross out the two acids and two bases that are never favored in any equilibrium.
- Circle the one species that is unchanged in any equilibrium.
- What two remaining species are in equilibria? In which direction does it favor?
- Rewrite this equilibrium as two components and indicate the direction of the equilibrium.
- Write the "solvent" molecule over the equilibrium arrows.



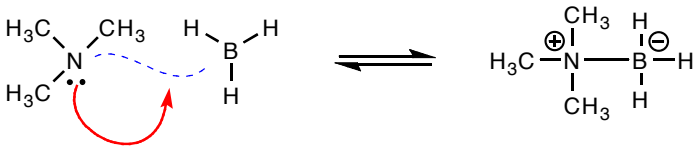
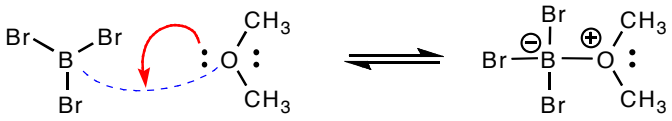
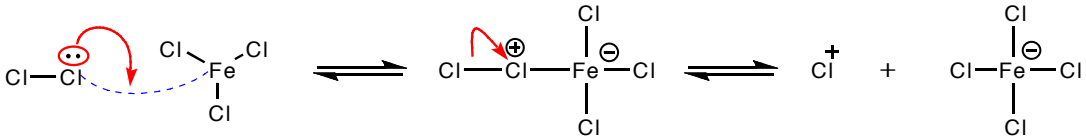
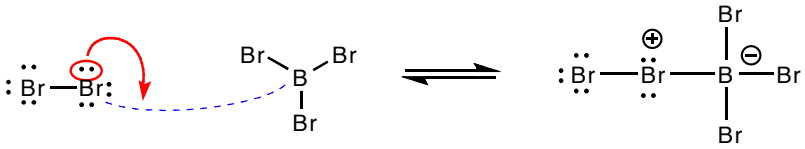
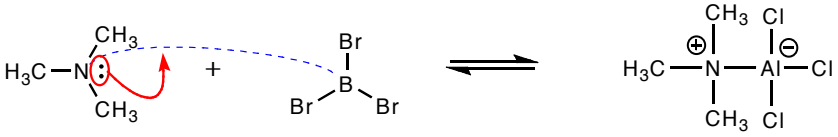
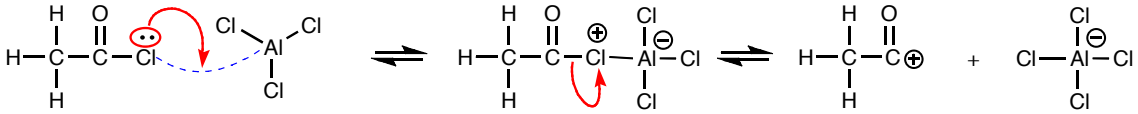
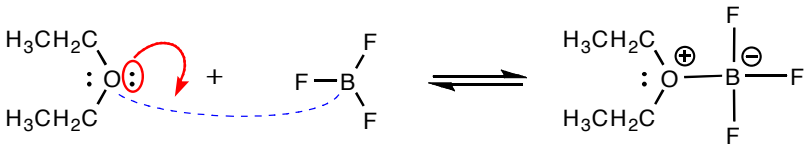
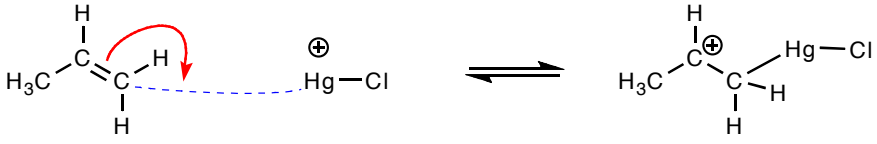




Lewis acids and bases

The prior exercise showed a hydrogen atom accepting electrons. With Lewis acids, other atoms can also accept electrons. See your text for further discussion.

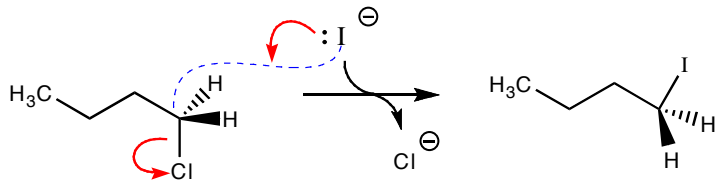
Add structures, non-bonded electrons, curved arrows, and formal charges as needed to complete the following.

19.	
20.	
21.	
22.	
23.	
24.	
25.	
26.	

3 — Substitution Reactions

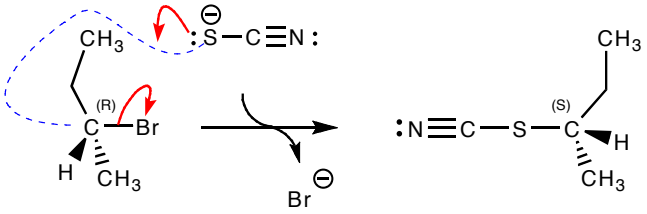
Add curved arrows to the following reactions.

1. An S_N2 reaction of 1-chlorobutane with sodium iodide to give 1-iodobutane.

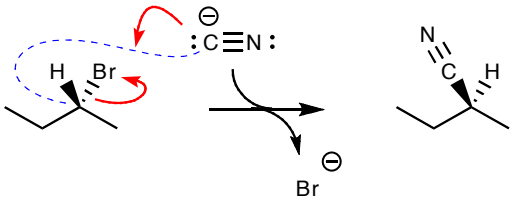


This reaction is usually run in acetone where it is aided by the insolubility of sodium chloride. NaCl precipitates and suppresses the reverse reaction.

2. An S_N2 reaction of I-2-bromobutane with thiocyanate to give (*S*)-2-thiocyanobutane.



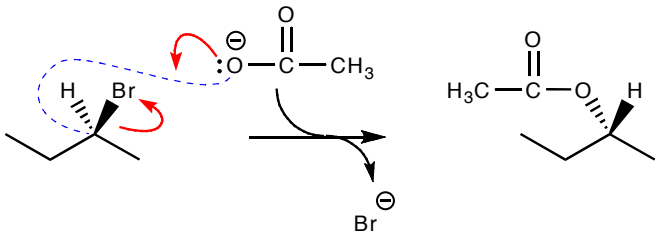
3. An S_N2 reaction of I-2-bromobutane with cyanide to give (*S*)-2-methylbutanenitrile.



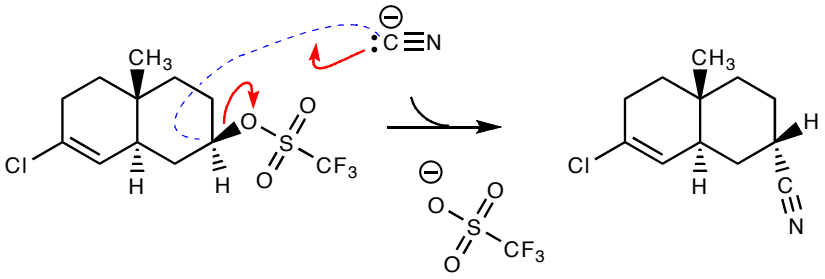
Which electrons can reach furthest from the nucleus, those on carbon or nitrogen?

The carbon, as it has fewer protons in its nucleus to pull the electrons in.

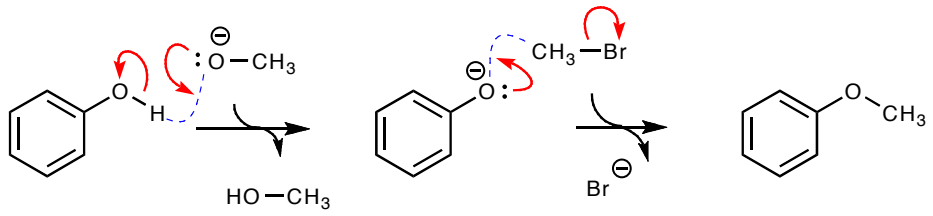
4. An S_N2 reaction of (*S*)-2-bromobutane with acetate to give I-2-butyl acetate.



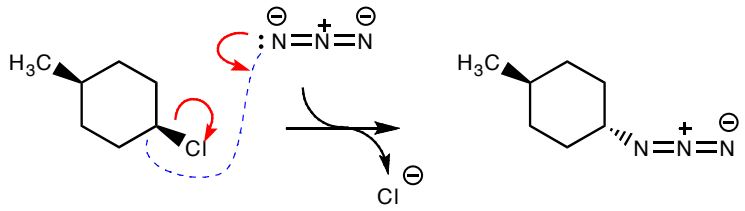
5. An S_N2 reaction of a triflate with potassium cyanide to give a cyano derivative with inversion.



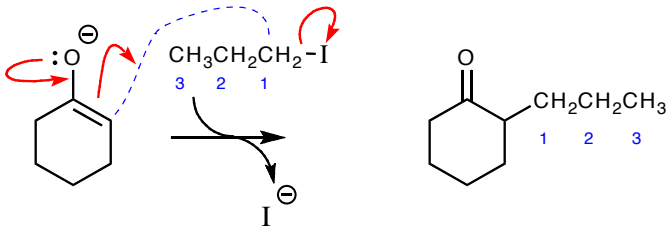
6. An S_N2 reaction of iodomethane with phenoxide to give methoxybenzene (anisole).



7. An S_N2 reaction of *cis*-1-chloro-4-methylcyclohexane with azide to give *trans*-1-azido-4-methylcyclohexane.



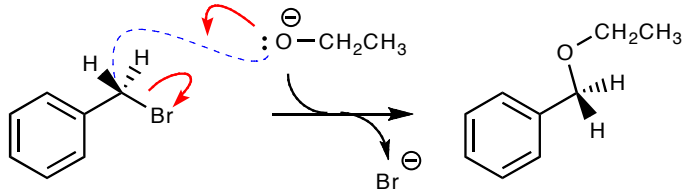
8. An S_N2 reaction of cyclohexanone enolate with iodopropane to give 2-propylcyclohexanone.



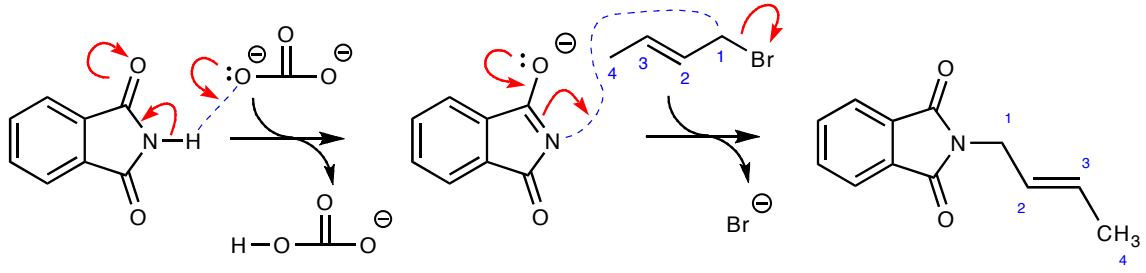
Which electrons of the anion extend further from the nucleus, carbon or oxygen? If you draw the resonance structures, you can put a negative charge on the carbon. Because carbon has fewer protons to pull the electrons toward its nucleus, they may extend further from the carbon.

Note the order of the atoms change. All atoms must be legitimate Lewis structures

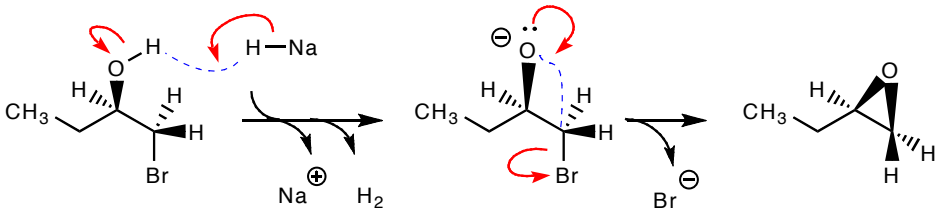
9. An S_N2 reaction of benzyl bromide with sodium ethoxide to give ethyl benzyl ether.



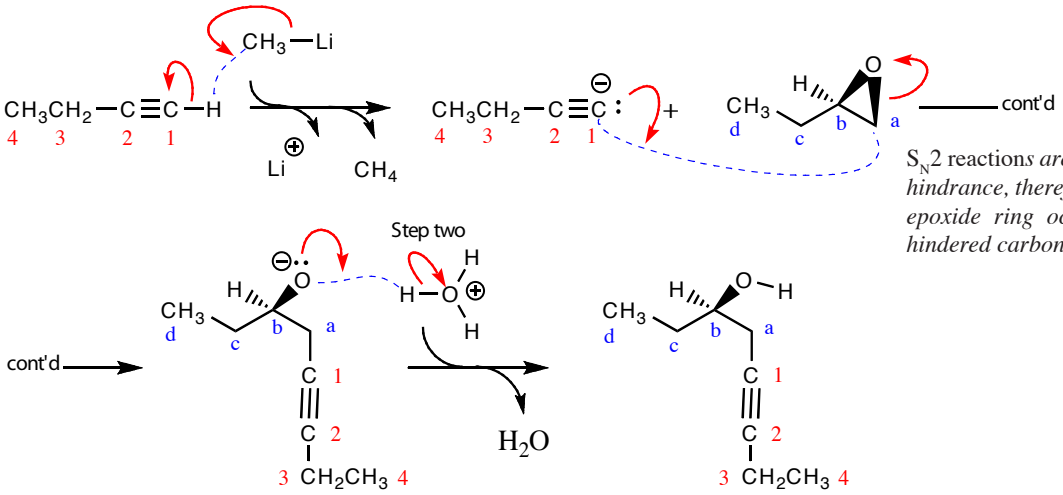
10. A Gabriel amine synthesis, formation of phthalimide anion with potassium carbonate and alkylation with 1-bromo-2-butene.



11. An S_N2 reaction of 1-bromo-2-butanol with sodium hydride to give 2-ethyloxirane (utylenes oxide).

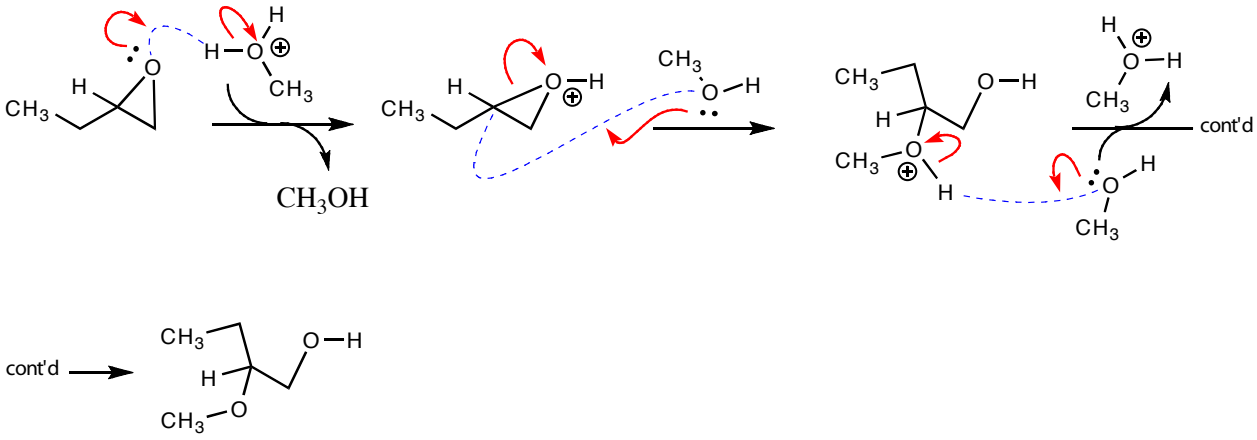


12. An S_N2 reaction of the anion of 1-butyne with I-2-ethyloxirane to give I-hept-5-yn-3-ol.

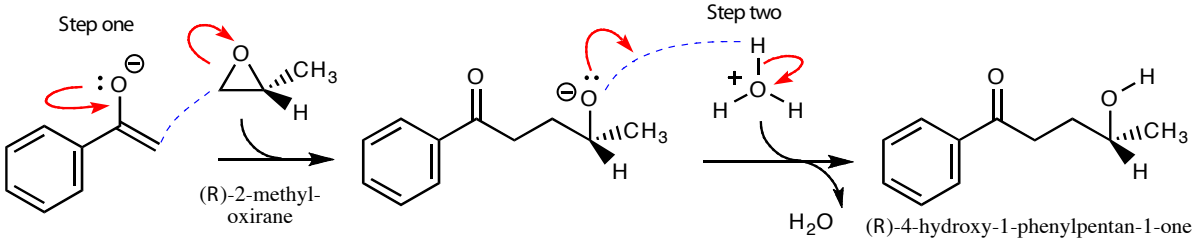


S_N2 reactions *are sensitive to steric hindrance, therefore opening of the epoxide ring occurs at the least hindered carbon.*

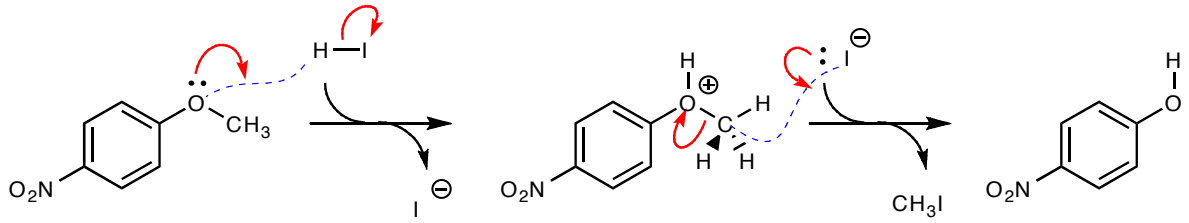
13. An acid catalyzed opening of 2-ethyloxirane with methanol to give 2-methoxybutan-1-ol.



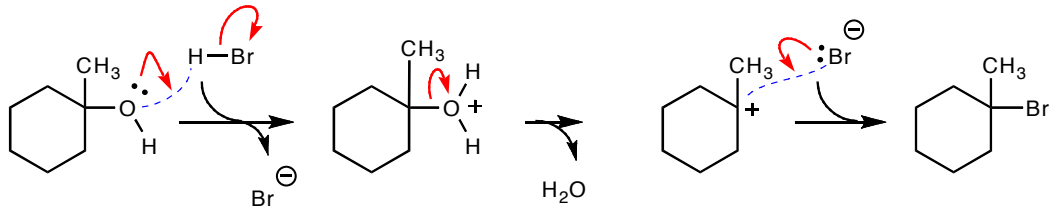
14. An S_N2 reaction of the enolate of acetophenone with I-2-methyloxirane (propylene oxide) to give I-4-hydroxy-1-phenylpentan-1-one.



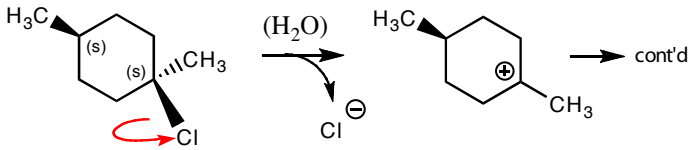
15. An S_N2 cleavage reaction of *p*-nitroanisole to give iodomethane and *p*-nitrophenol.



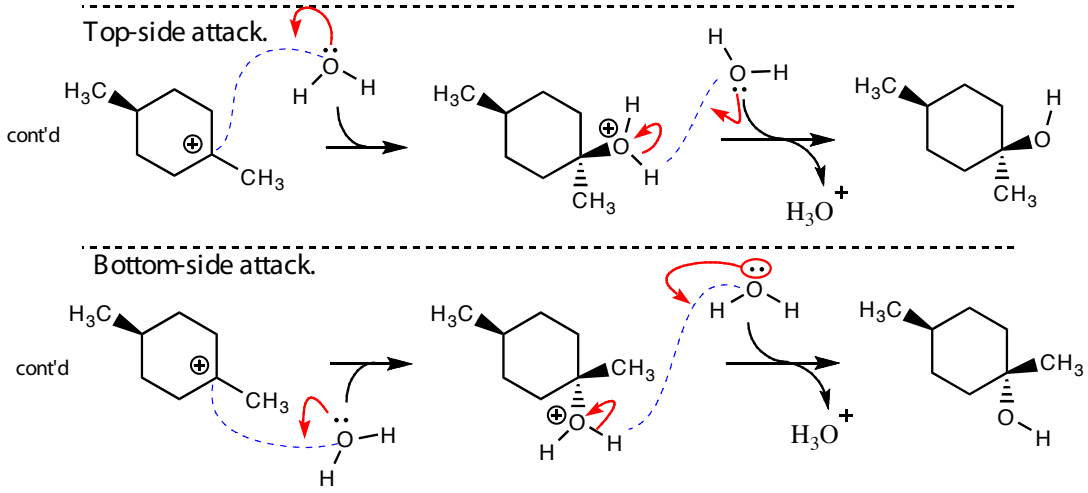
16. An S_N1 reaction of 1-methylcyclohexanol with hydrogen bromide to give 1-bromo-1-methylcyclohexane.



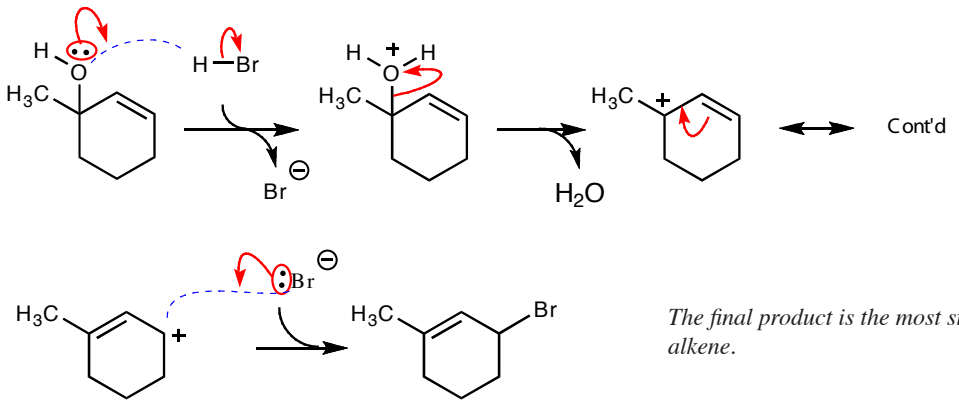
17. An S_N1 solvolysis reaction of 1-chloro-1,4-methylcyclohexane to give *cis*- and *trans*-1,4 dimethylcyclohexanol.



Since the carbocation is planar with a methyl group above or below the plane, the water nucleophile can add from either side. The result is a diastereomeric mixture of cis and trans-isomers.



18. An S_N1 reaction of 1-methyl-2-cyclohex-2-enol with hydrogen bromide to give 1-bromo-1-methylcyclohexane in a two step reaction.



The final product is the most stable alkene.

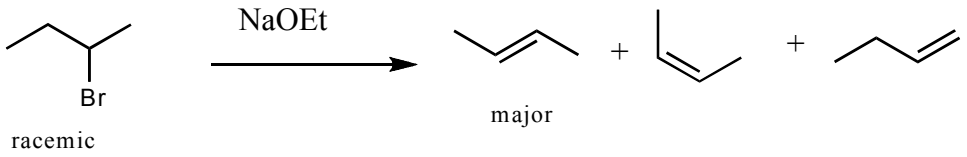
4 — Elimination Reactions

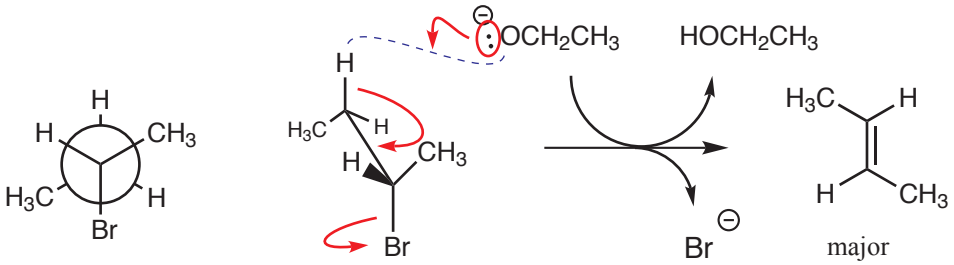
You should consult your textbook for a more complete discussion of elimination reactions. You may think of this reaction as an indirect intramolecular substitution reaction. The reagent that was a nucleophile in a substitution reaction is now a base. As a base, it will remove a proton from a neighboring atom. The remaining electrons displace the leaving group via an S_N2-like reaction. However that product is an alkene rather than a normal substitution product. Understanding these reactions requires noting the conformational constraints required for an intramolecular reaction (backside-attack).

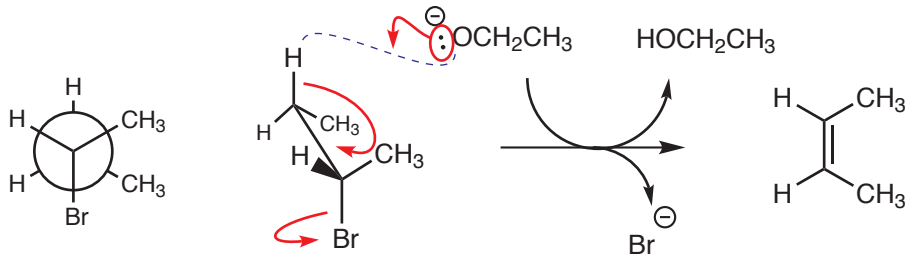
An E2 Elimination

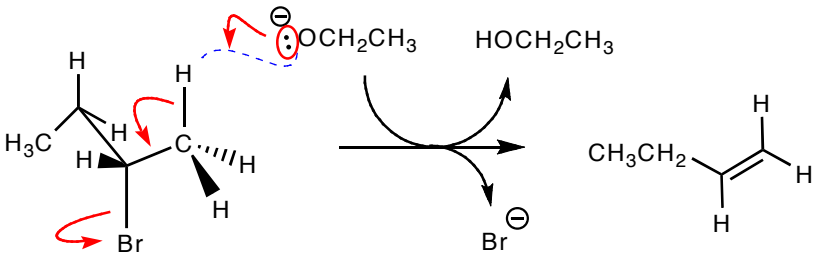
1. An E2 elimination reaction of hydrogen bromide from 1-bromobutane with sodium ethoxide to give trans-2-butene plus other butenes.

   Add the curved arrows to show the formation of the following products.





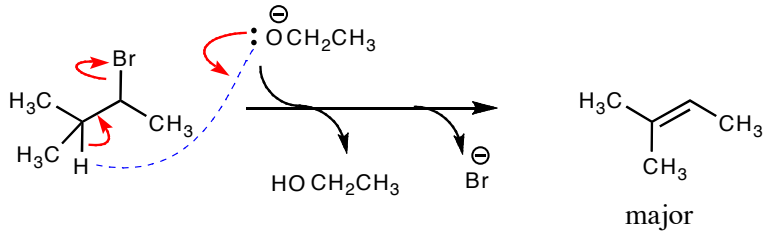




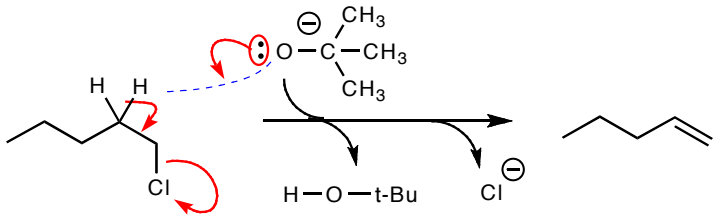
Note the Newman projections. It is the most stable conformation that corresponds with the major product (*trans*-I). The absolute configuration of the carbon with the bromine does not determine the most stable conformation or the eventual product. You could draw a set of mirror image structures that will also give the same products. The configuration shown for 2-bromobutane was arbitrary.

Other Elimination Reactions

2. An E2 elimination reaction from 2-bromo-3-methylbutane to give 2-methyl-2-butene, a Zaitsev product.

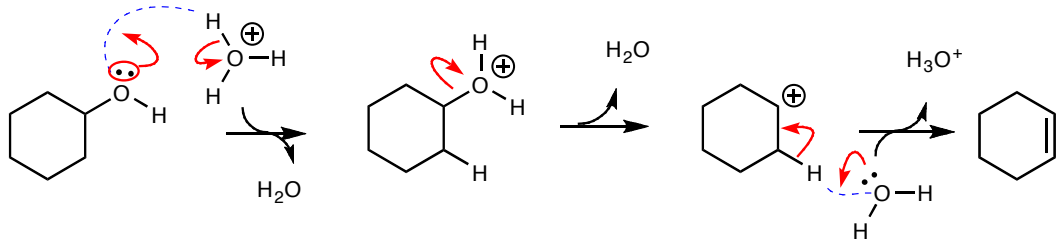


3. An E2 elimination reaction from 1-chloropentane to give 1-pentene.

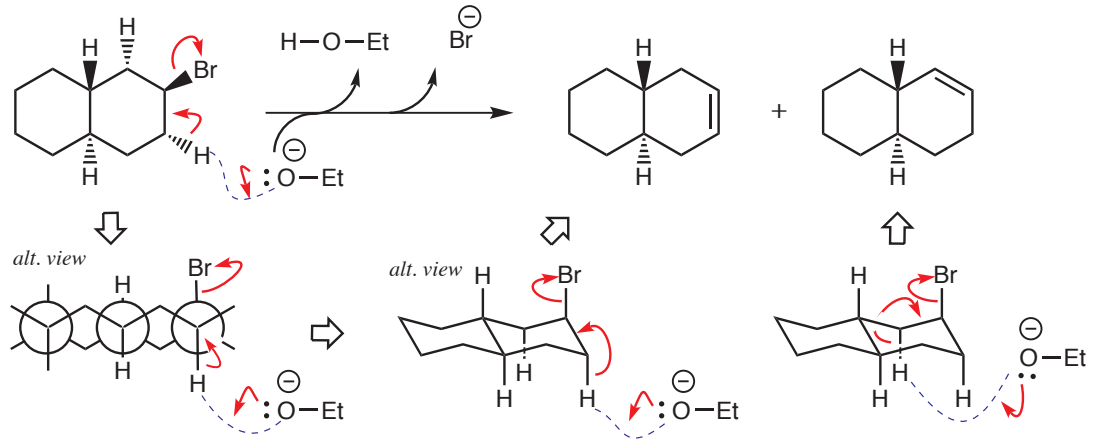


The steric bulk of t-butoxide avoids an S_N2 displacement reaction with the primary halide.

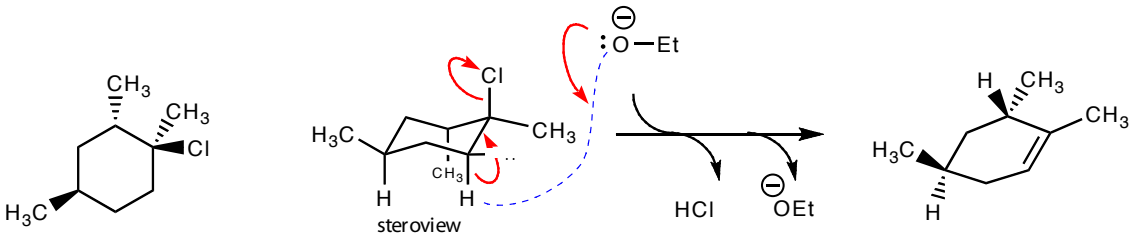
4. An E1 elimination reaction from cyclohexanol by treatment with phosphoric acid to give cyclohexene.



5. An E2 elimination reaction from 2-bromodecalin, a bicyclic halide to an alkene.

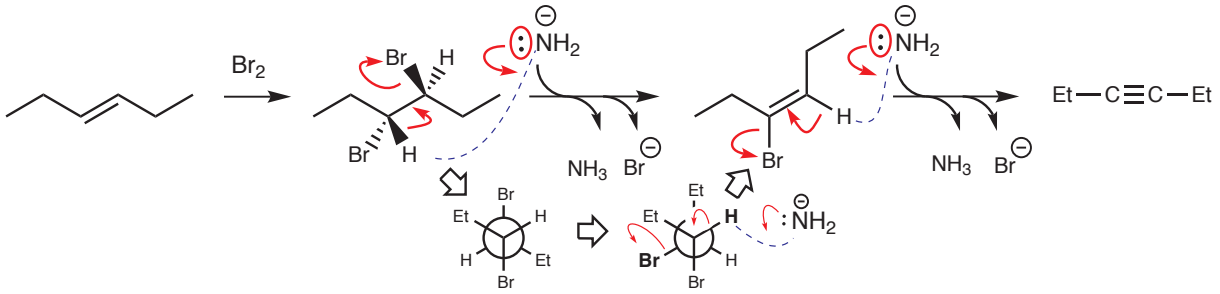


6. An E2 elimination reaction from 1-chloro-1,2,4-trimethylcyclohexane to give 1,4,6-trimethylcyclohex-1-ene.

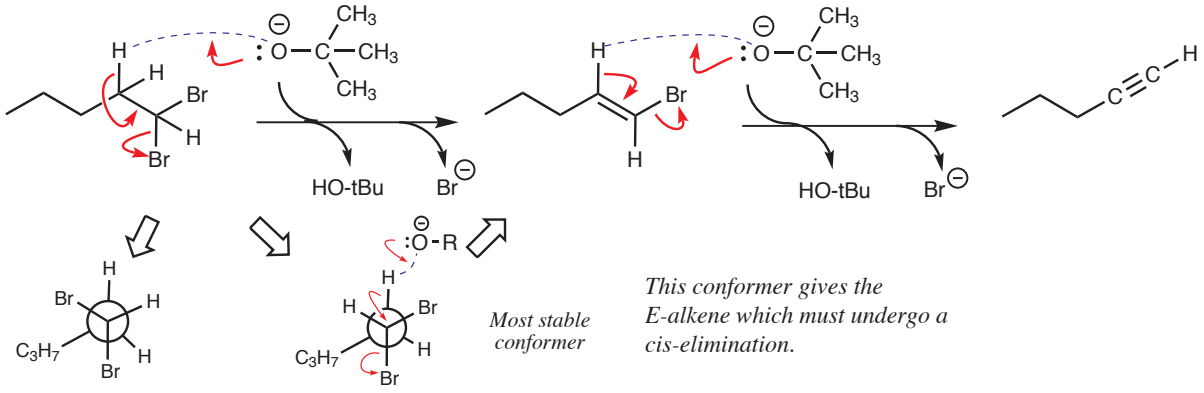


Acetylene Formation

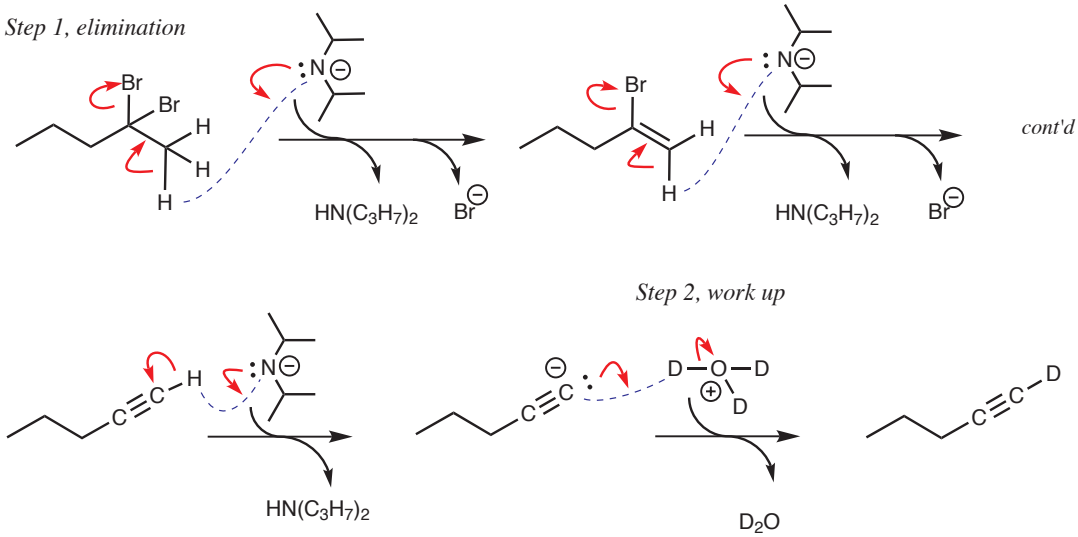
7. A synthesis of 3-hexyne from *trans*-3-hexene by bromination and two elimination reactions.



8. An E2 elimination reaction from 1,1-dibromopentane with *t*-butoxide to give 1-pentyne.

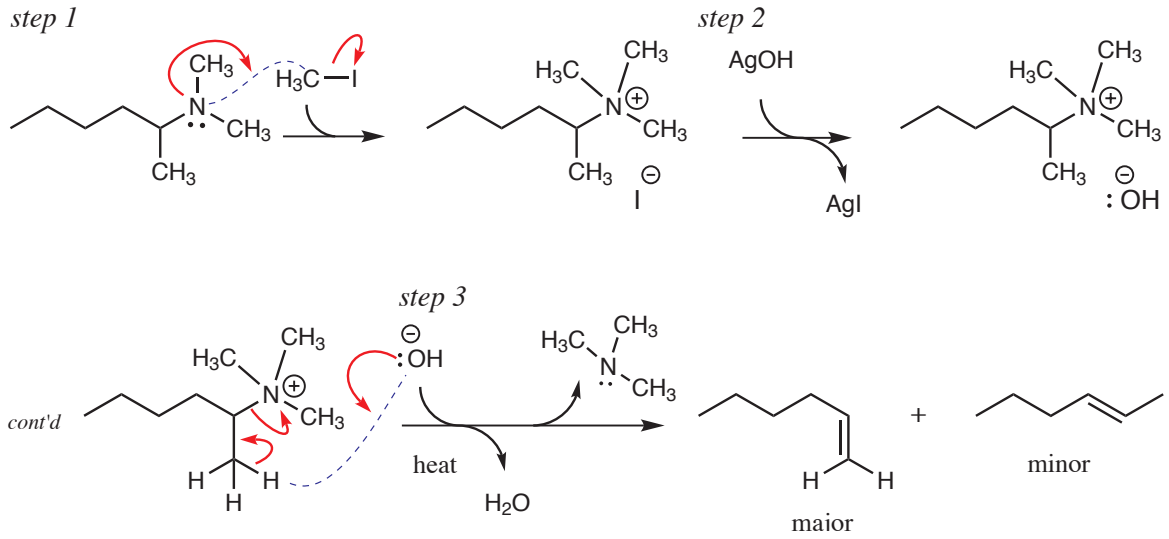


9. An E2 elimination reaction from 2,2-dibromopentane with LDA to give 1-pentyne.



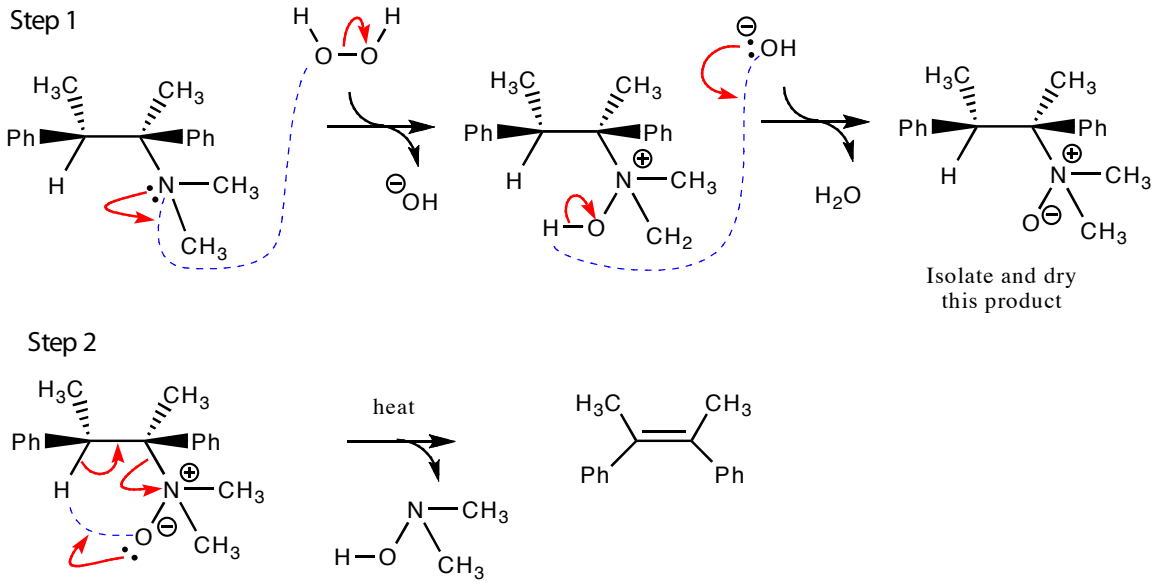
Hofmann Elimination

10. A Hofmann elimination reaction from a trimethylamine to give a 1-alkene. Reaction of *N,N*-dimethyl-2-pentanamine with iodomethane, silver oxide and elimination to give 1-pentene, the Hofmann elimination product.



Cope Elimination

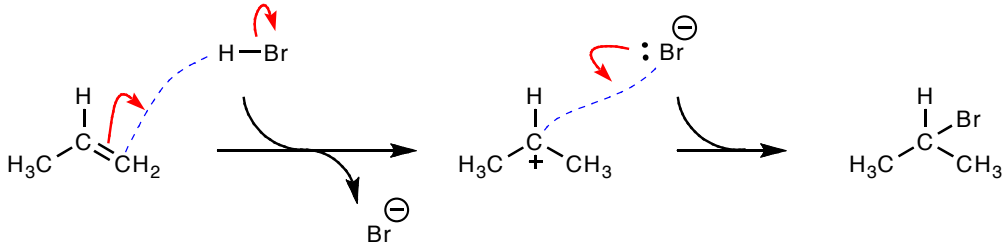
11. A Cope elimination reaction from a dimethylamine-N-oxide. Step 1, reaction of *N,N*-dimethyl-2,3-diphenylbutan-2-amine with hydrogen peroxide. Step 2, heating the *N*-oxide results in an elimination reaction to give *cis*-α,β-dimethylstilbene, the Zaitsev elimination product.



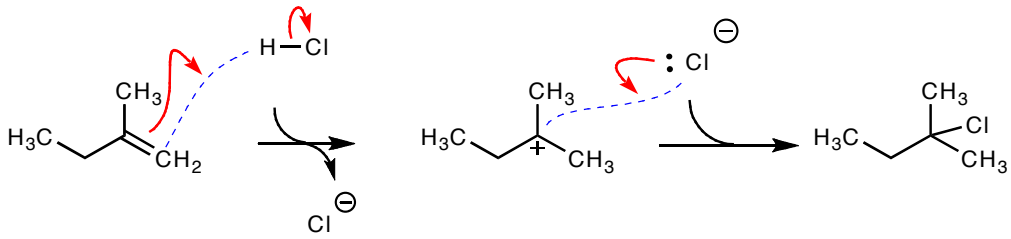
5 — Electrophilic Addition to Alkenes and Alkynes

Addition of HX and H_2O to Alkenes

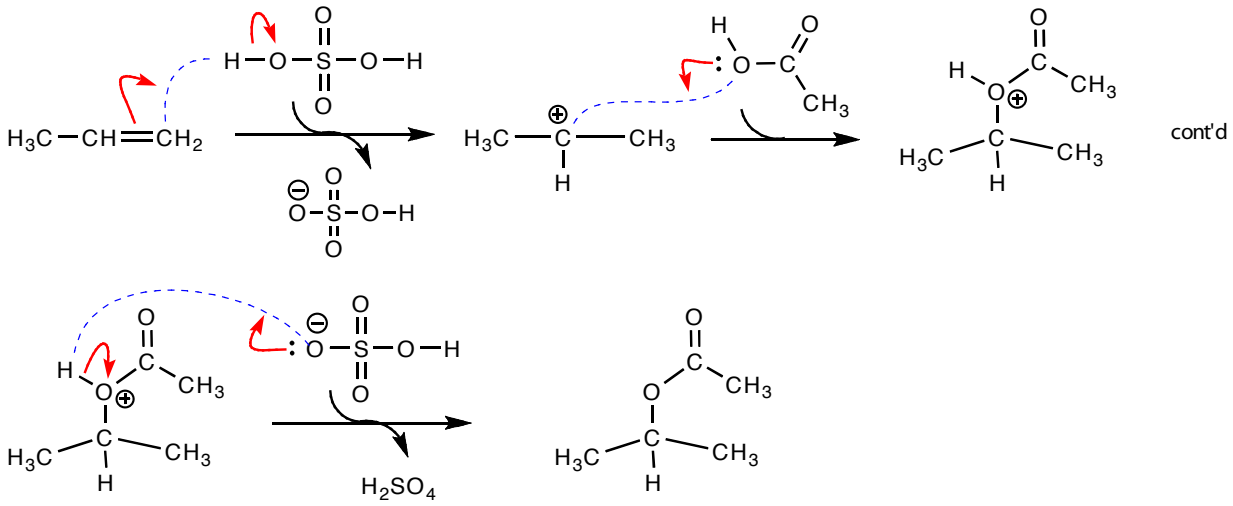
1. Addition of hydrogen bromide to propene to give 2-bromopropane.



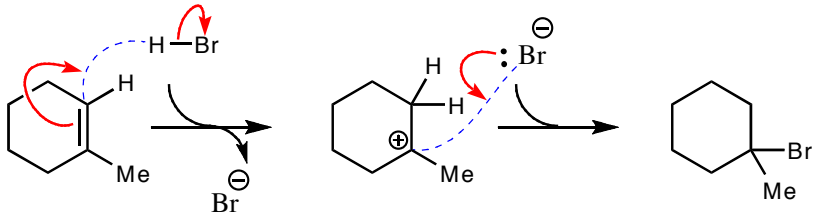
2. Addition of hydrogen chloride to 2-methyl-1-butene to give 2-chloro-2-methylbutane.



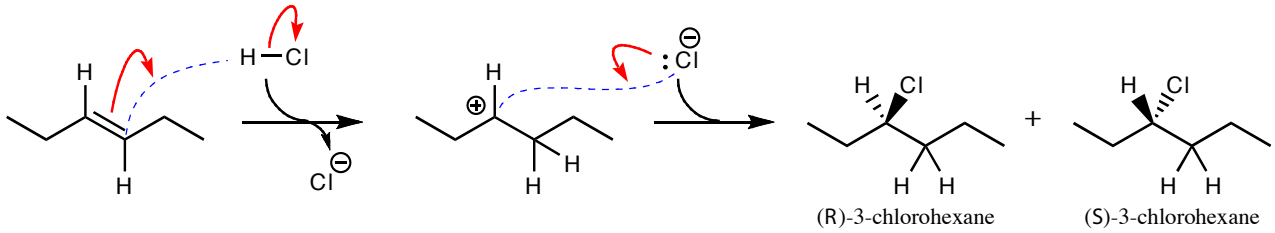
3. Addition of acetic acid to propene catalyzed by sulfuric acid to give 2-propyl ethanoate (isopropyl acetate). (see Notes)



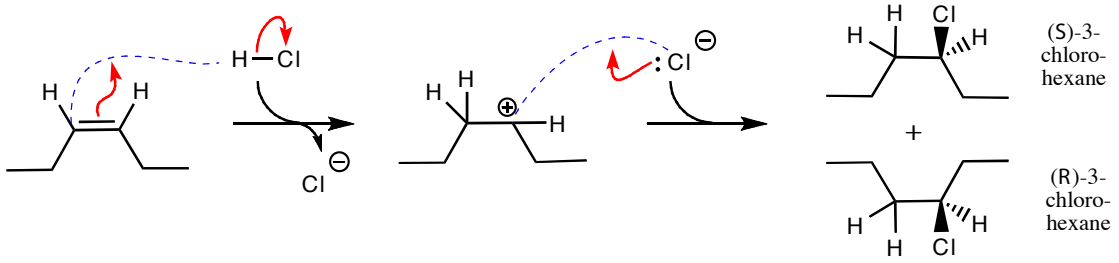
4. Addition of hydrogen bromide to 1-methylcyclohexene to give 1-bromo-1-methylcyclohexane.



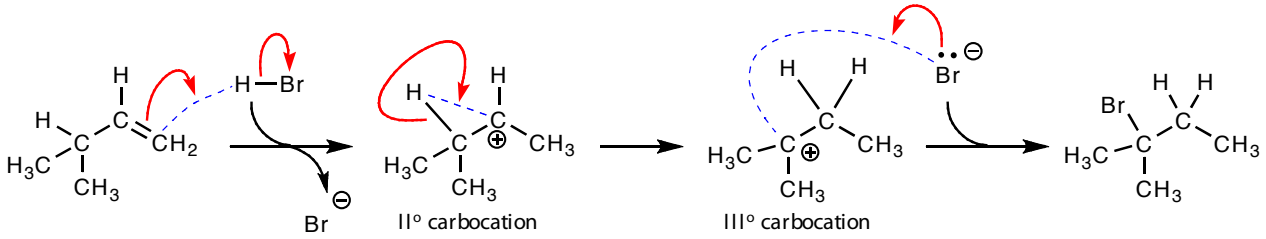
5. Addition of hydrogen chloride to *(E)*-3-hexene to give ®- and *(S)*-3-chlorohexane.



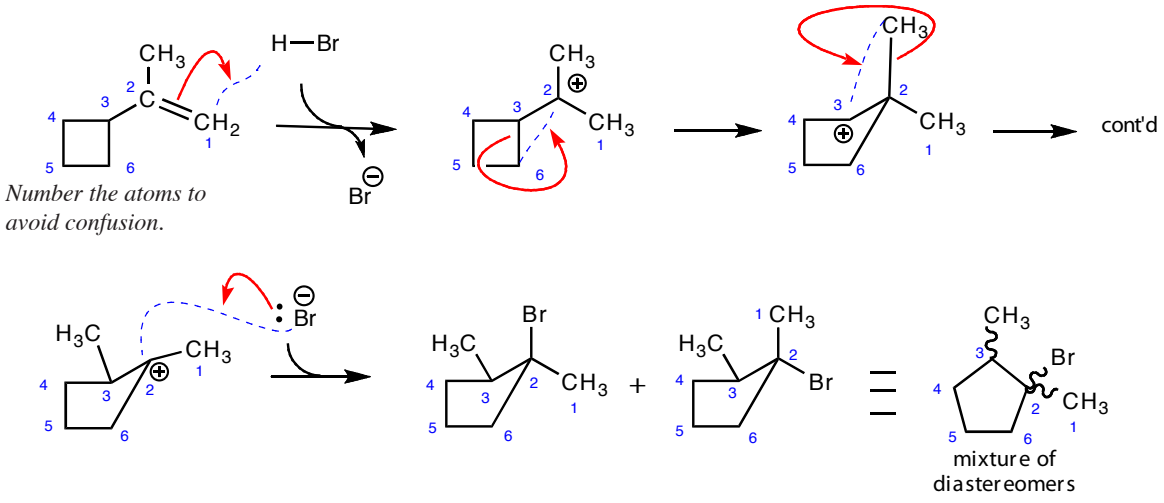
6. Addition of hydrogen chloride to *(Z)*-3-hexene to give ®- and *(S)*-3-chlorohexane



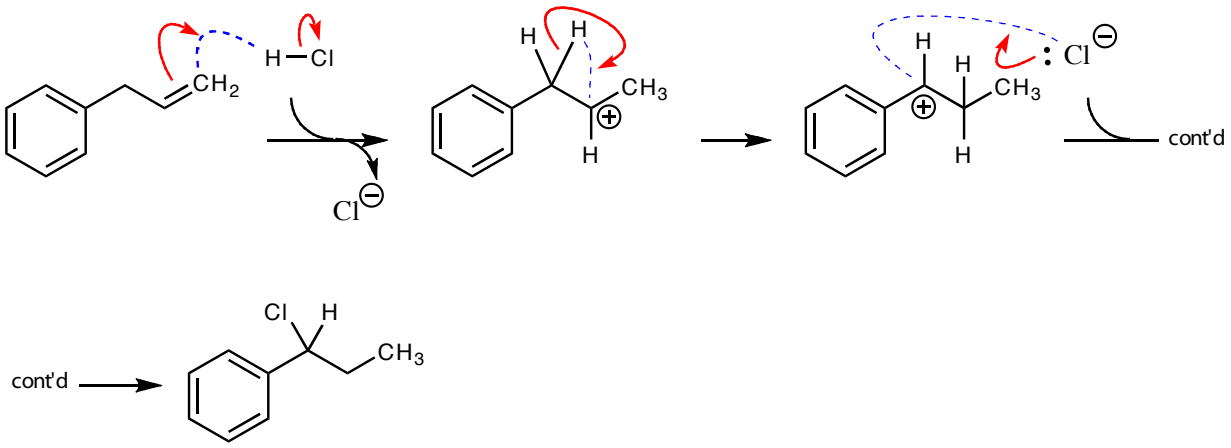
7. Addition of hydrogen bromide to 3-methyl-1-butene to give after rearrangement, 2-bromo-2-methylbutane.



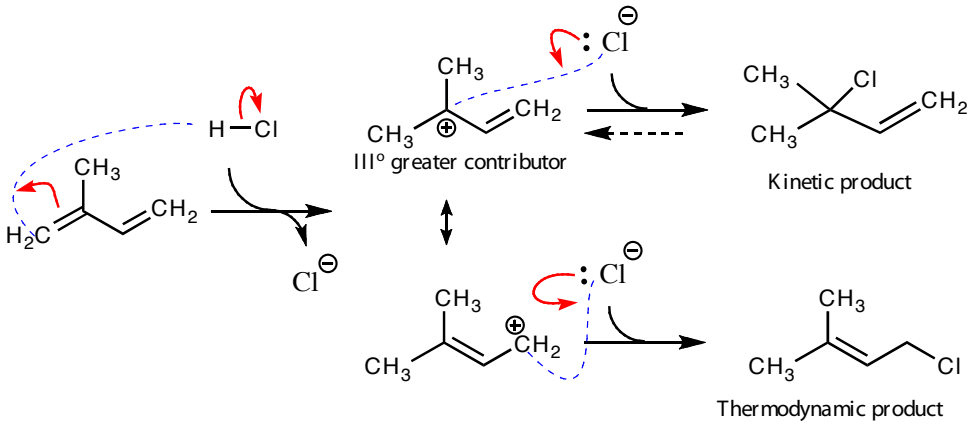
8. Addition of HBr to 1-propen-2-ylcyclobutane to give, after rearrangement, 1-bromo-1,2-dimethylcyclopentane.



9. Addition of hydrogen chloride to allylbenzene to give, after rearrangement, (1-chloropropyl)benzene.

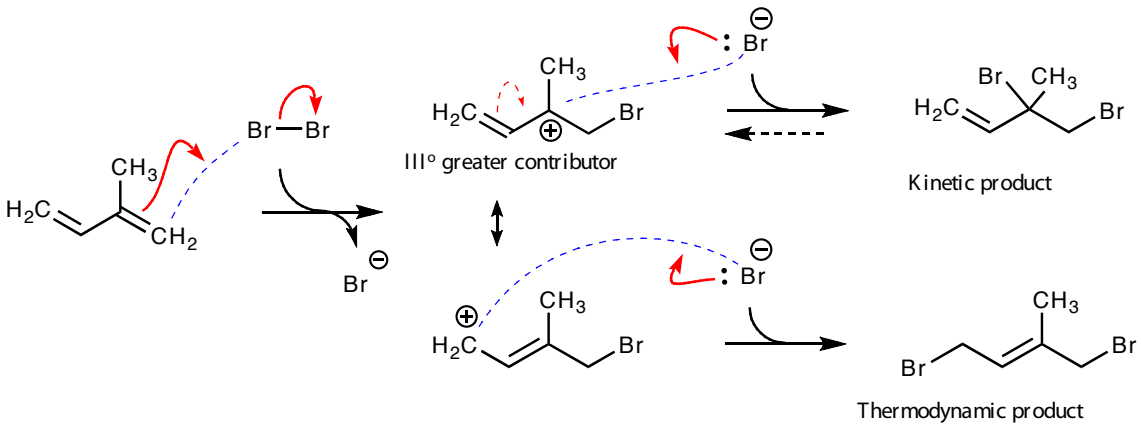


10. Addition of hydrogen chloride to 2-methyl-1,3-butadiene (isoprene) to give, 3-chloro-3-methyl-1-butene, kinetic product, or 1-chloro-3-methyl-2-butene, the thermodynamic product.



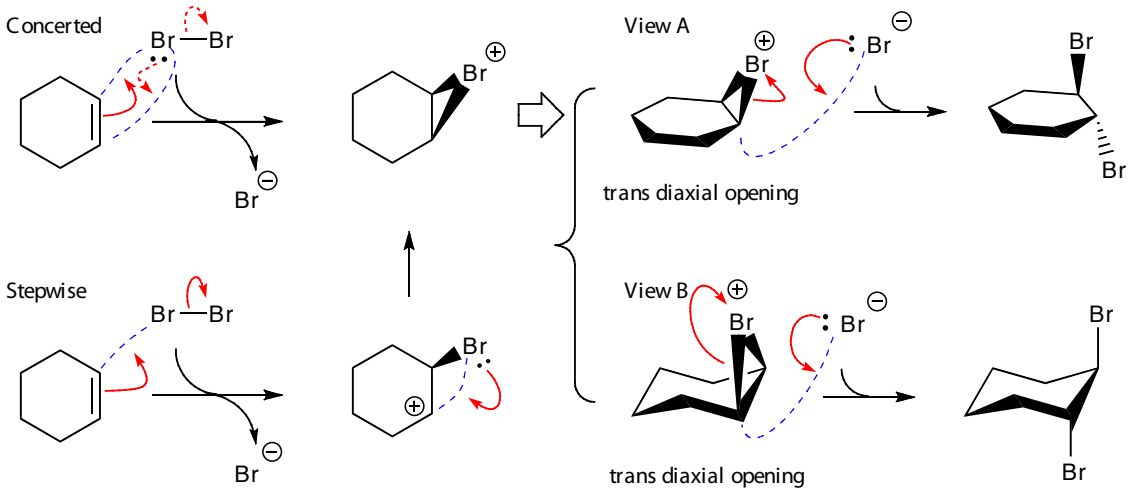
In this case, a III° vs a I° carbocation more strongly favors the III° but less stable kinetic product. The reaction reverses to give the thermodynamic product, the most stable alkene (most substituted). If the reaction can be conducted at low temperatures, the kinetic products may be isolated.

11. Addition of bromine to 2-methyl-1,3-butadiene to give 3,4-dibromo-3-methylbut-1-ene, the kinetic product and 1,4-dibromo-2-methylbut-2-ene, the thermodynamic product.

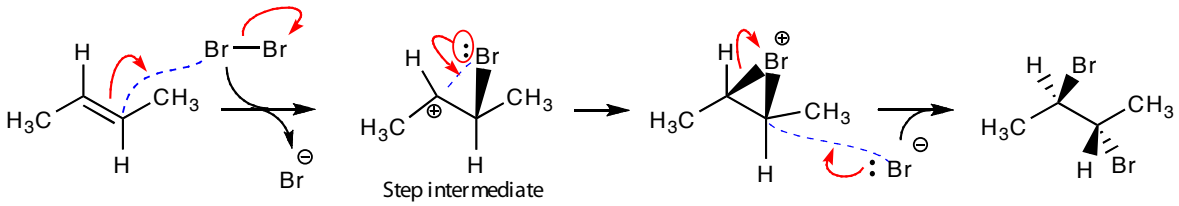


Bromination

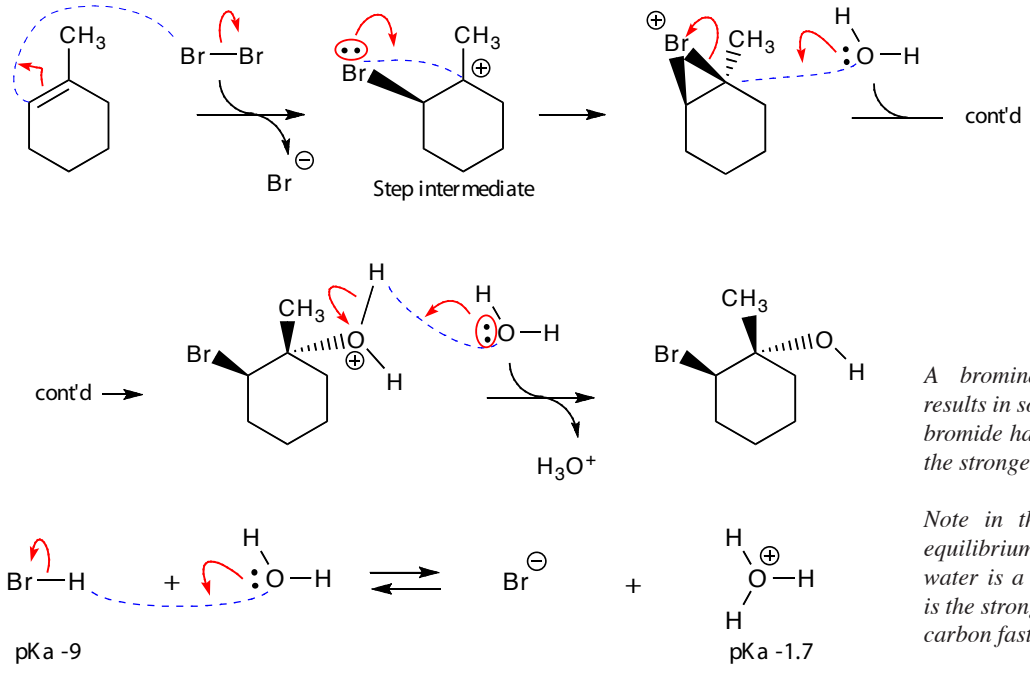
12. Bromination of cyclohexene to give *trans*-1,2-dibromocyclohexane. The formation of the bromonium ion may be written in two slightly different versions. I have written the concerted reaction first, but I favor a step version of the bromination reaction. (see Notes)



13. Bromination of *trans*-2-butene to give (erythro) *(2R,3S)*- and (*2S,3R*)-2,3-dibromobutane.



14. Bromination of methylcyclohexene to give (1*R*,2*R*)- and (1*S*,2*S*)-2-bromo-1-methylcyclohexanol. (see Notes)



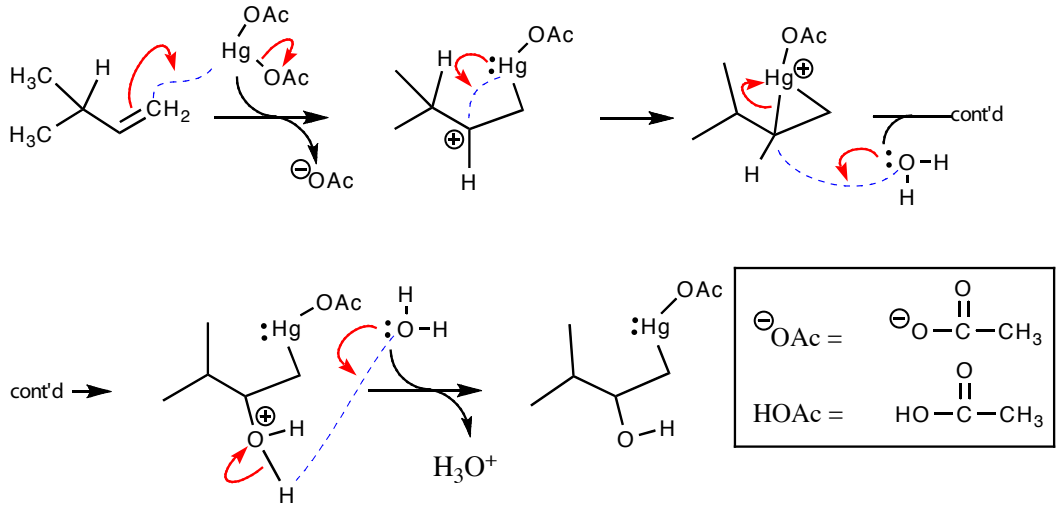
A bromination reaction in water results in some confusion. Even though bromide has a negative charge, it isn't the strongest base.

Note in the equilibrium below, the equilibrium lies to the right. Therefore, water is a stronger base. Since water is the stronger base, it will react on the carbon faster than bromide ion.

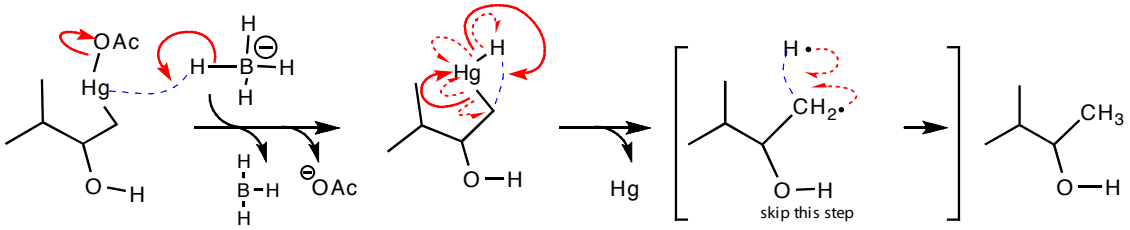
Two of 12 valence electrons of mercury are shown. A hydrogen atom is staged for migration to give a tertiary carbocation. The 6s electrons on mercury prevent that migration.

Oxymercuration

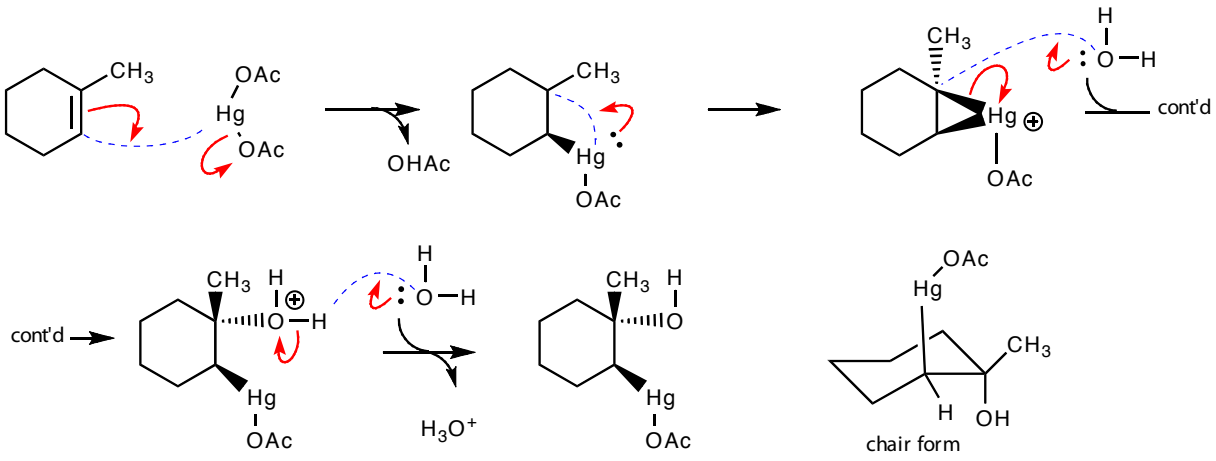
15. Step 1, oxymercuration of 3-methyl-1-butene to give 3-methyl-2-butanol.



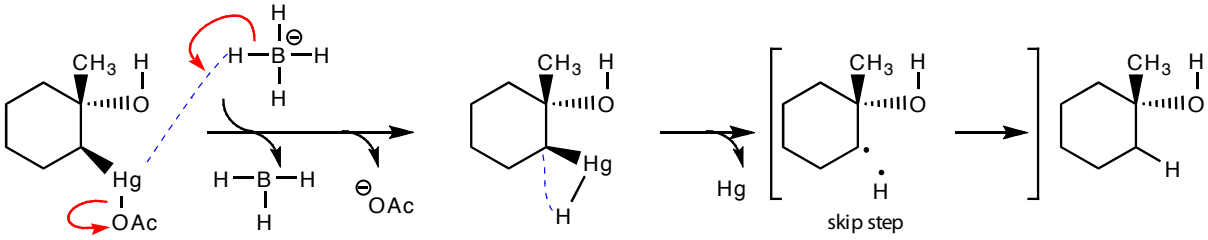
Step 2, reductive demercuration. Few texts show a mechanism for this reaction. (see Notes)



16. Oxymercuration of 1-methylcyclohexene to give 1-methylcyclohexanol, step 1.



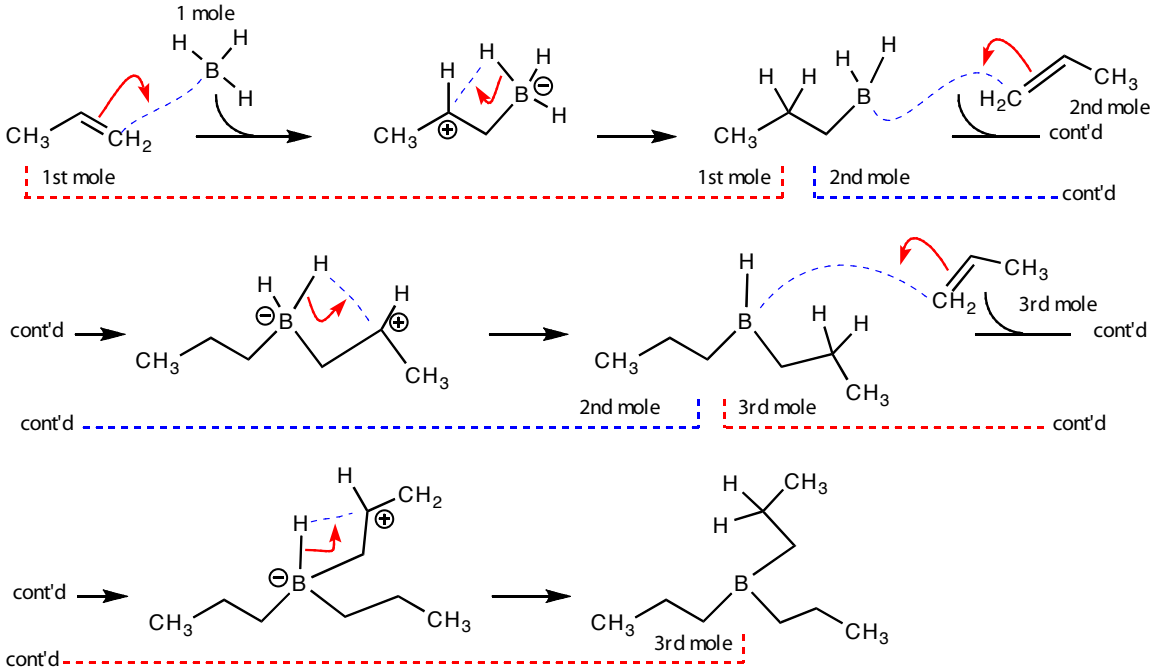
Step 2, reductive demercuration.



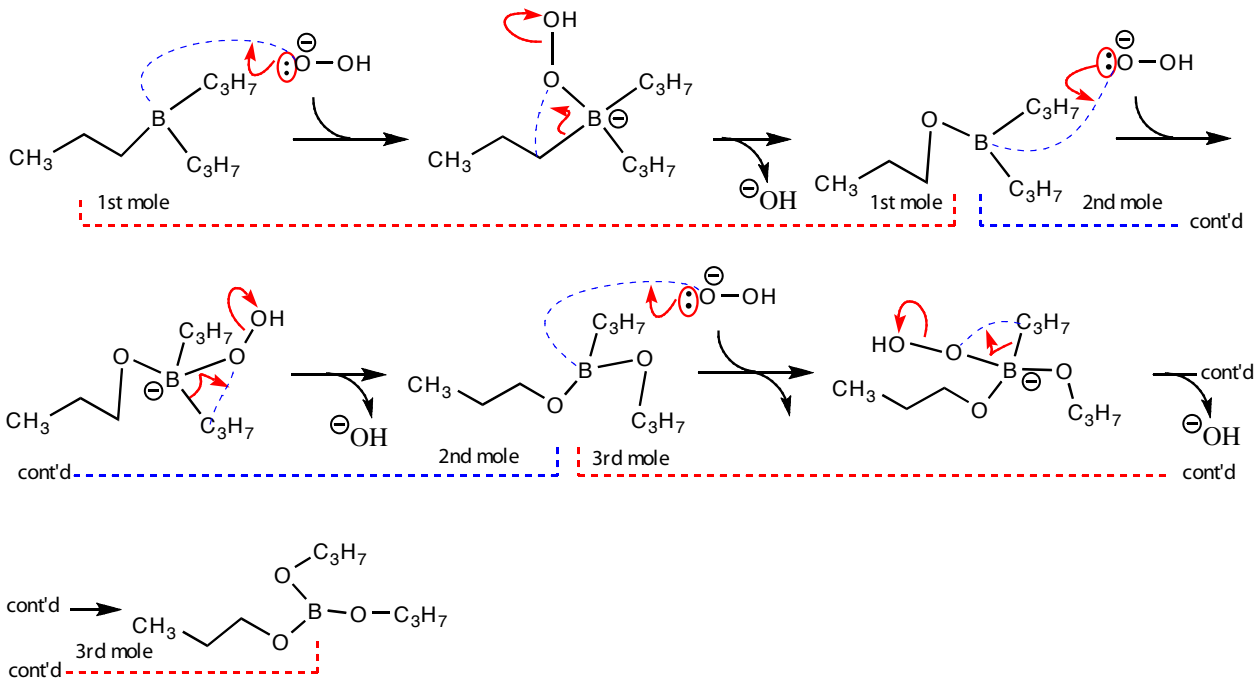
Hydroboration-oxidation of Alkene

17. Hydroboration-oxidation of propene to give 1-propanol.

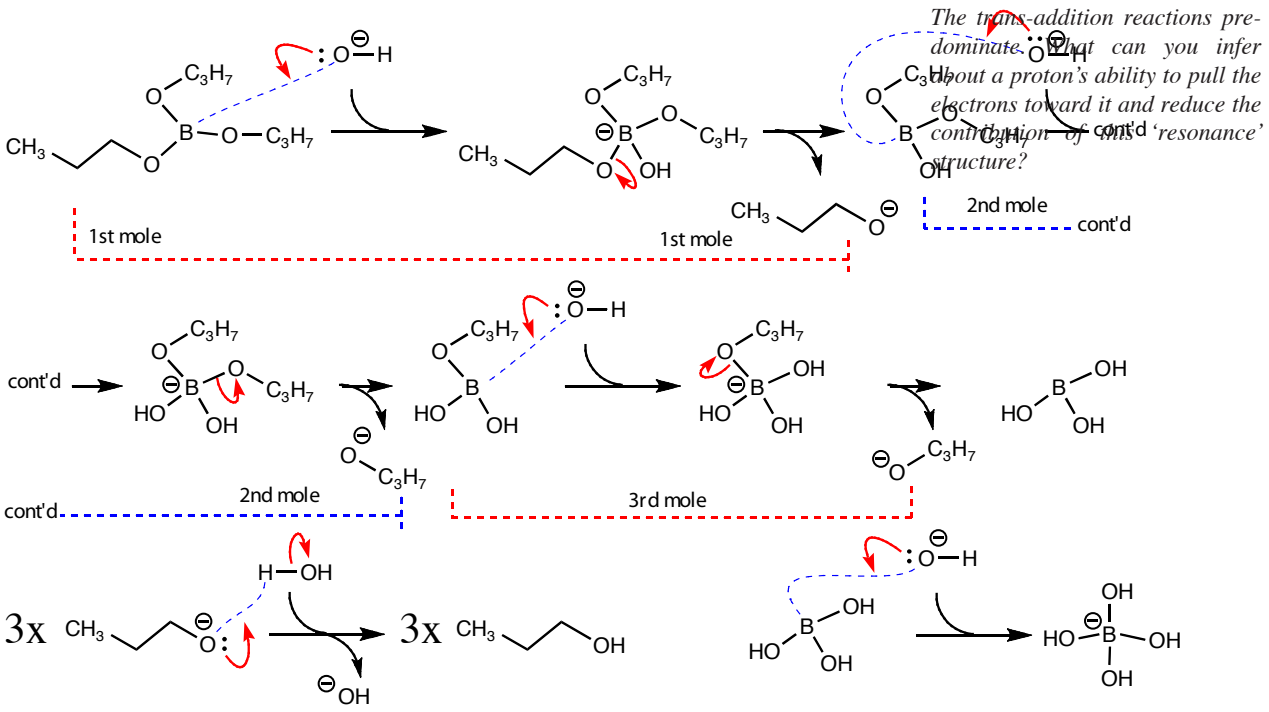
Step 1, hydroboration. Each bracket represents one of three hydroboration steps. (see Notes)



Step 2, oxidation. Each bracket represents one of three oxidation steps. (see Notes)



Step 3, borate ester hydrolysis to 1-propanol. Each bracket represents one of three hydrolysis steps. (see Notes)

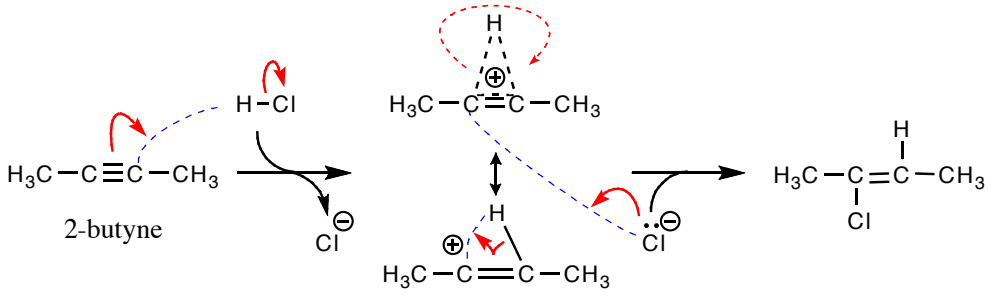


The trans-addition reactions predominate. What can you infer about a proton's ability to pull the electrons toward it and reduce the contribution of this 'resonance' structure?

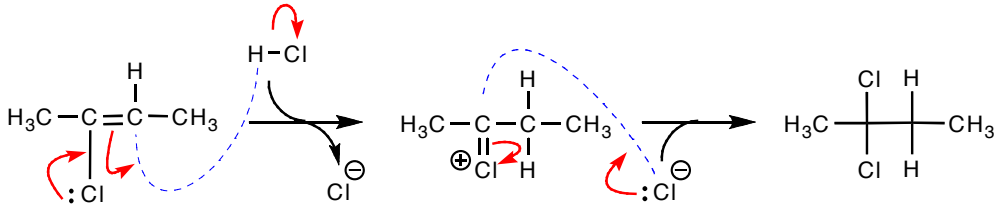
Carbon-carbon Triple Bond Electrophilic Reactions

Addition to an Internal Acetylene (see Notes)

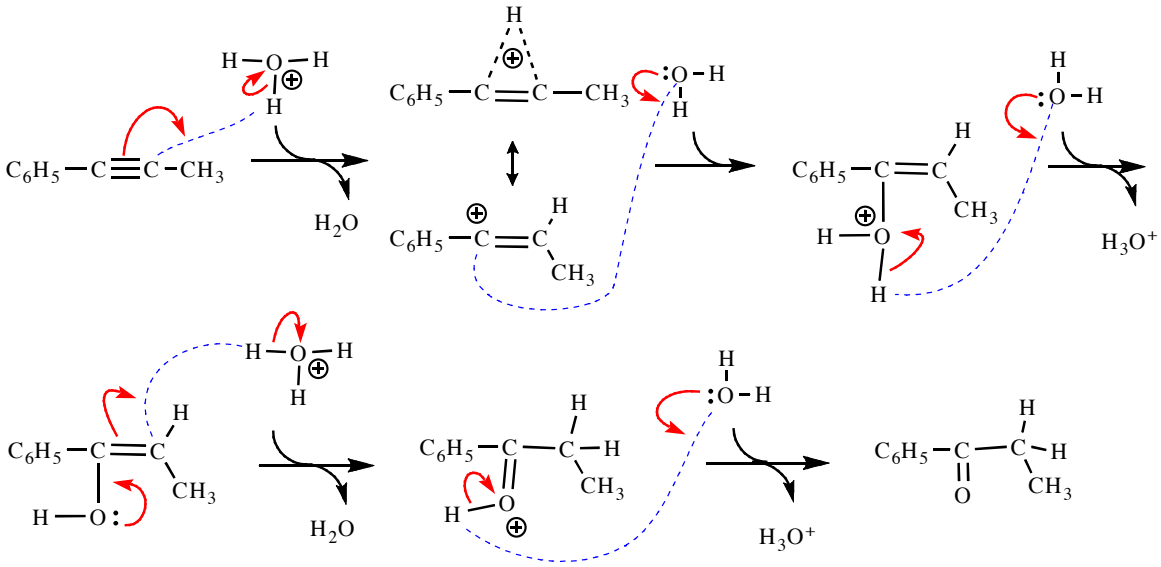
18. Addition of HCl to 2-butyne (dimethyl acetylene) to give *E*-2-chloro-2-butene and 2,2-dichlorobutane.



2nd Equivalent of HCl

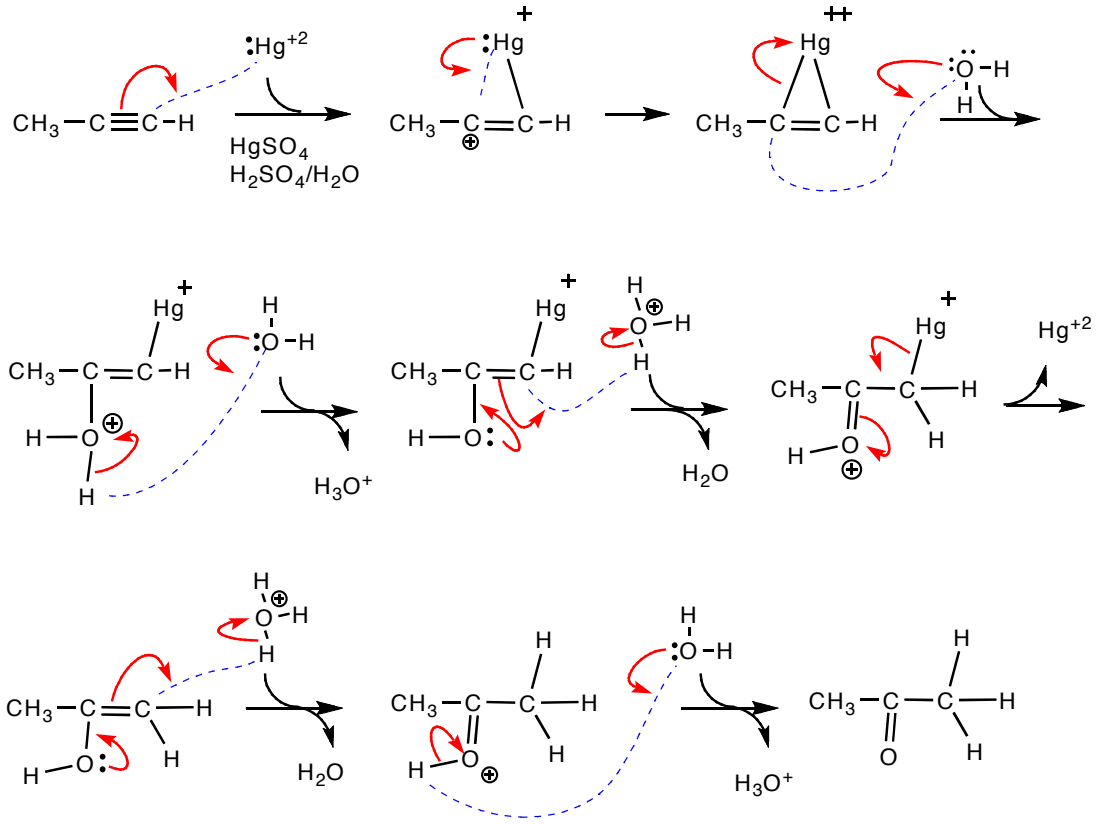


19. Sulfuric acid catalyzed hydration of 1-propynylbenzene to give 1-phenyl-1-propanone.



Addition to a Terminal Acetylene

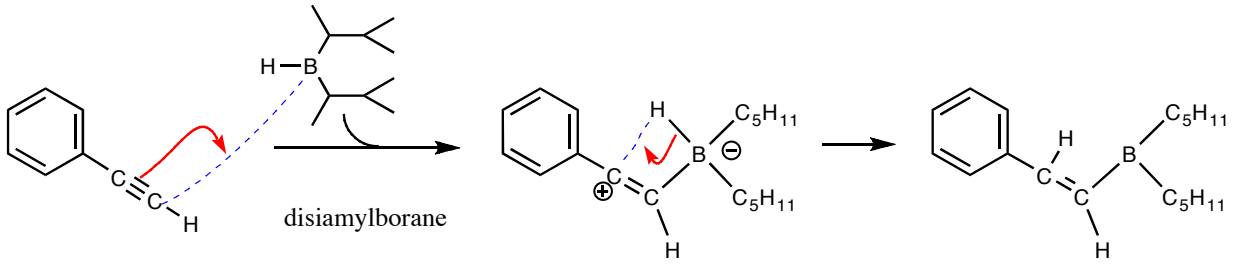
20. Mercury catalyzed hydration of propyne (methyl acetylene) to give 2-propanone (acetone).



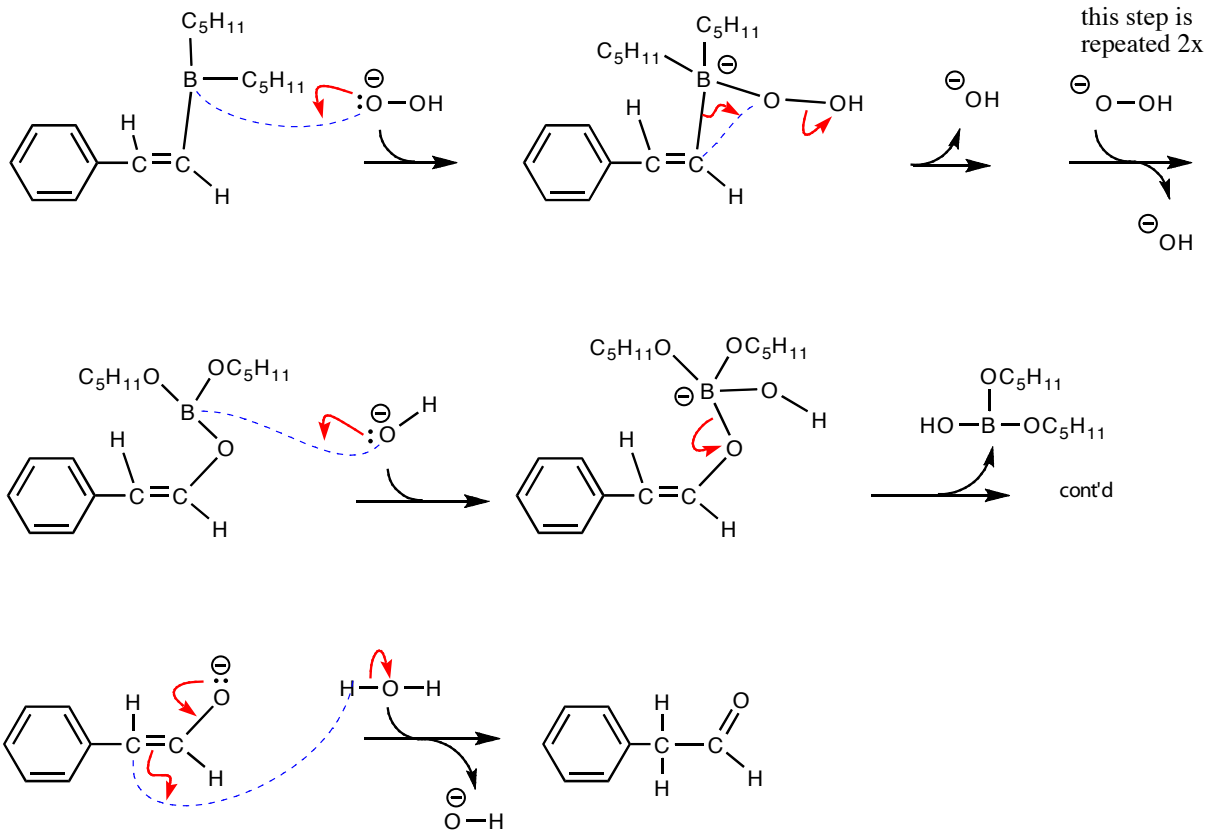
Disiamylborane Hydroboration–Oxidation of an Acetylene

21. Addition of disiamylborane to phenyl acetylene and oxidation to give phenyl acetaldehyde.

Step 1, hydroboration:



Step 2, oxidation.

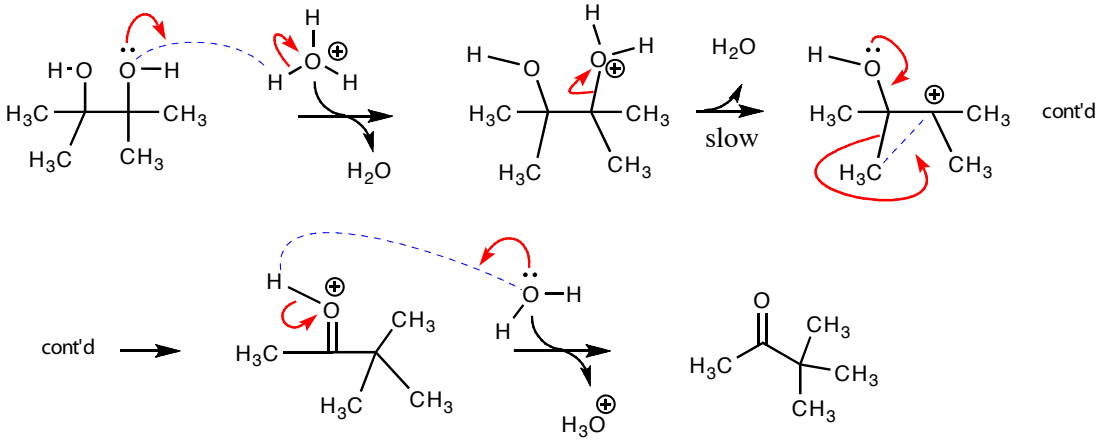


6 — Rearrangement Reactions

Pinacol Rearrangement, Baeyer-Villiger Oxidation, Benzilic Acid Rearrangement, Dakin Reaction, and Acetone from Benzene. Also see the Oxidation step of Hydroboration-Oxidation.

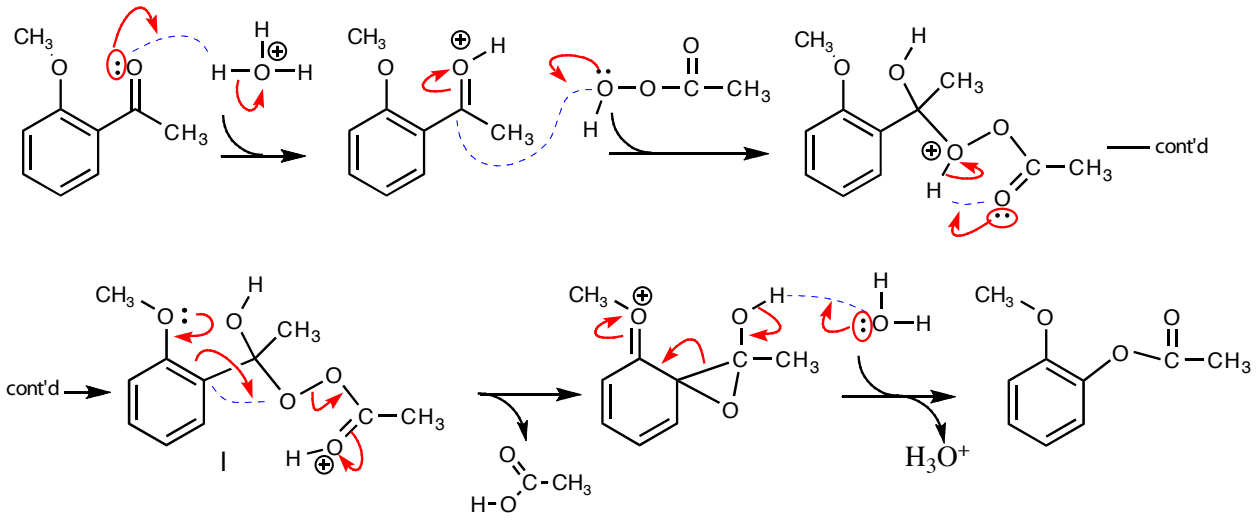
Pinacol Rearrangement

1. Rearrangement of pinacol to pinacolone, methyl *t*-butyl ketone (see Notes).



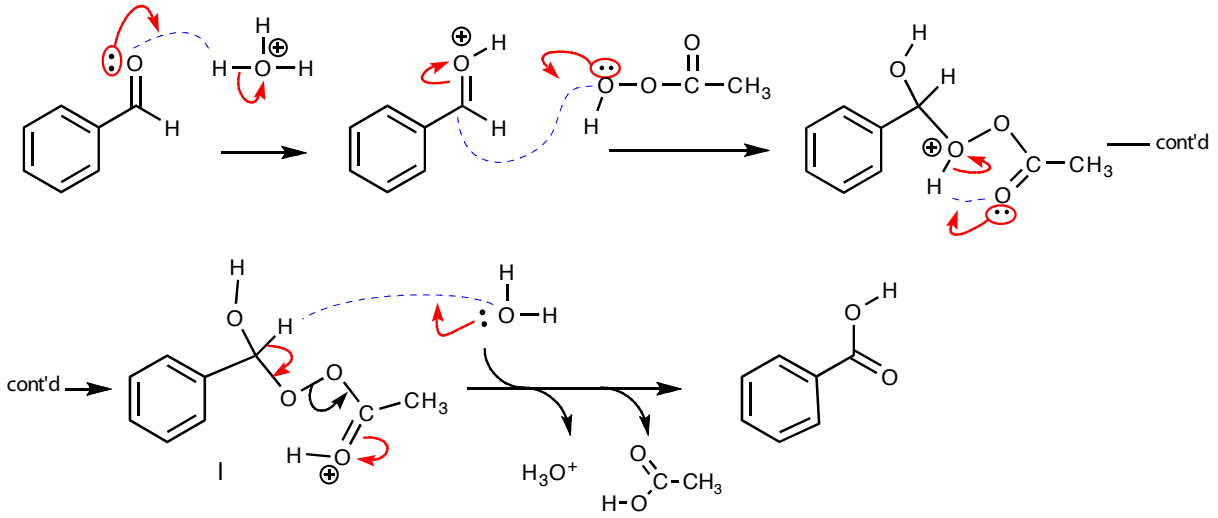
Baeyer-Villiger Oxidation

2. (Acid catalyzed) Baeyer-Villiger oxidation of *o*-methoxyacetophenone to 2-methoxyphenyl acetate with peracetic acid. (see Notes)



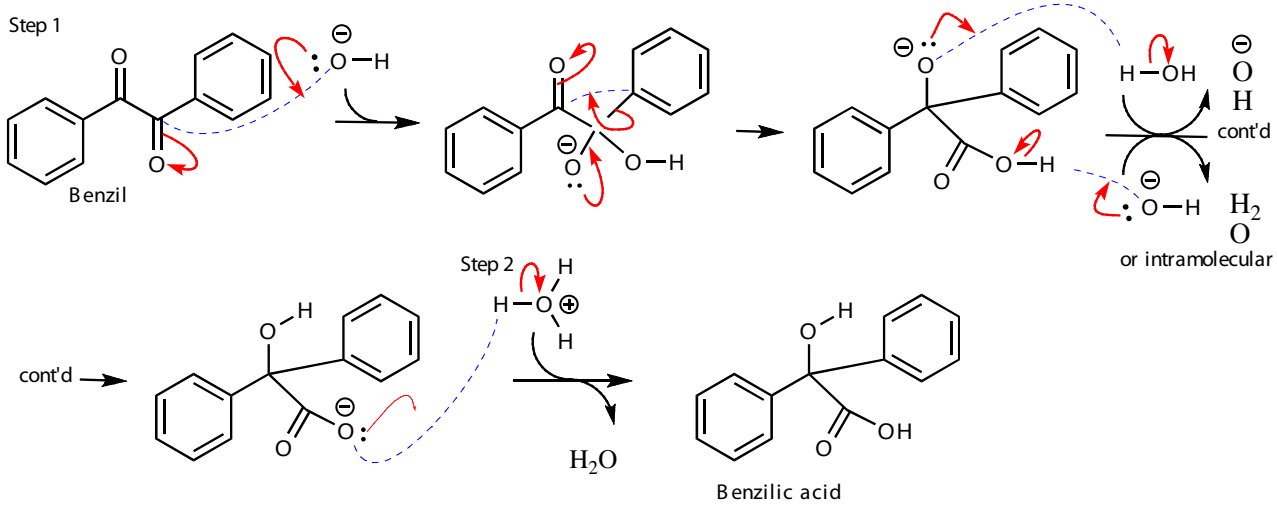
The key to predicting the Baeyer-Villiger oxidation products is being able to predict which group of the tetrahedral intermediate (**I**) will migrate, here phenyl or methyl. The order of migration is hydrogen > tertiary alkyl > secondary alkyl > phenyl > primary alkyl > methyl. If there are two aromatic rings, the more electron rich ring migrates most quickly, but there are many exceptions based on the peracid used, reaction conditions, and stereochemistry. The migrating group can be described as the one best able to stabilize a carbocation. The electron movement is similar to elimination reactions with the moving electrons preferring an anti arrangement.

3. (Acid catalyzed) Baeyer-Villiger oxidation of benzaldehyde to benzoic acid with peracetic acid.



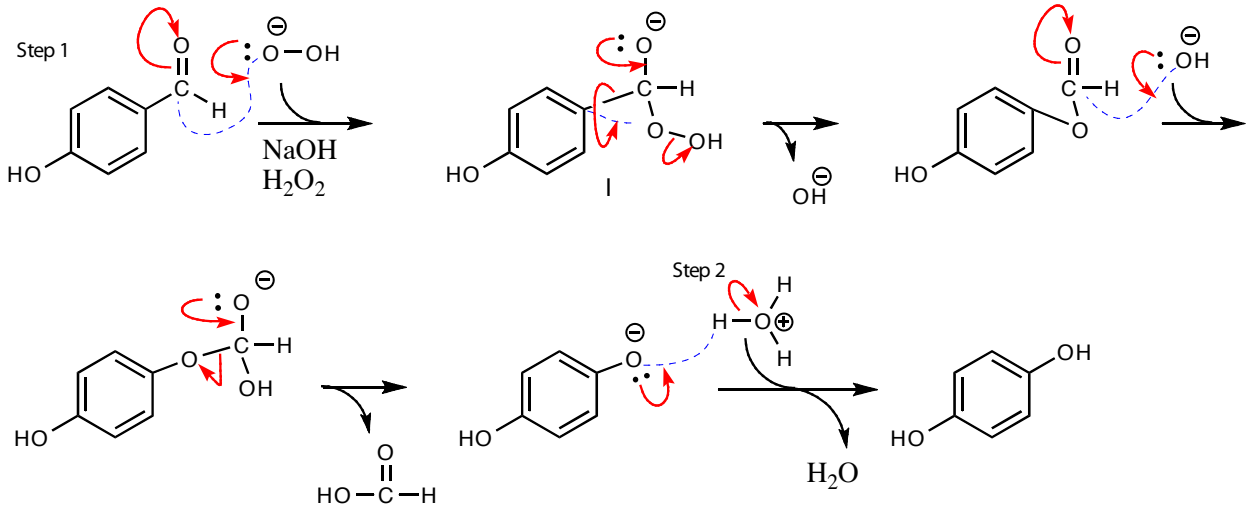
Benzilic Acid Rearrangement

4. Reaction of benzil with hydroxide to give benzilic acid after rearrangement.



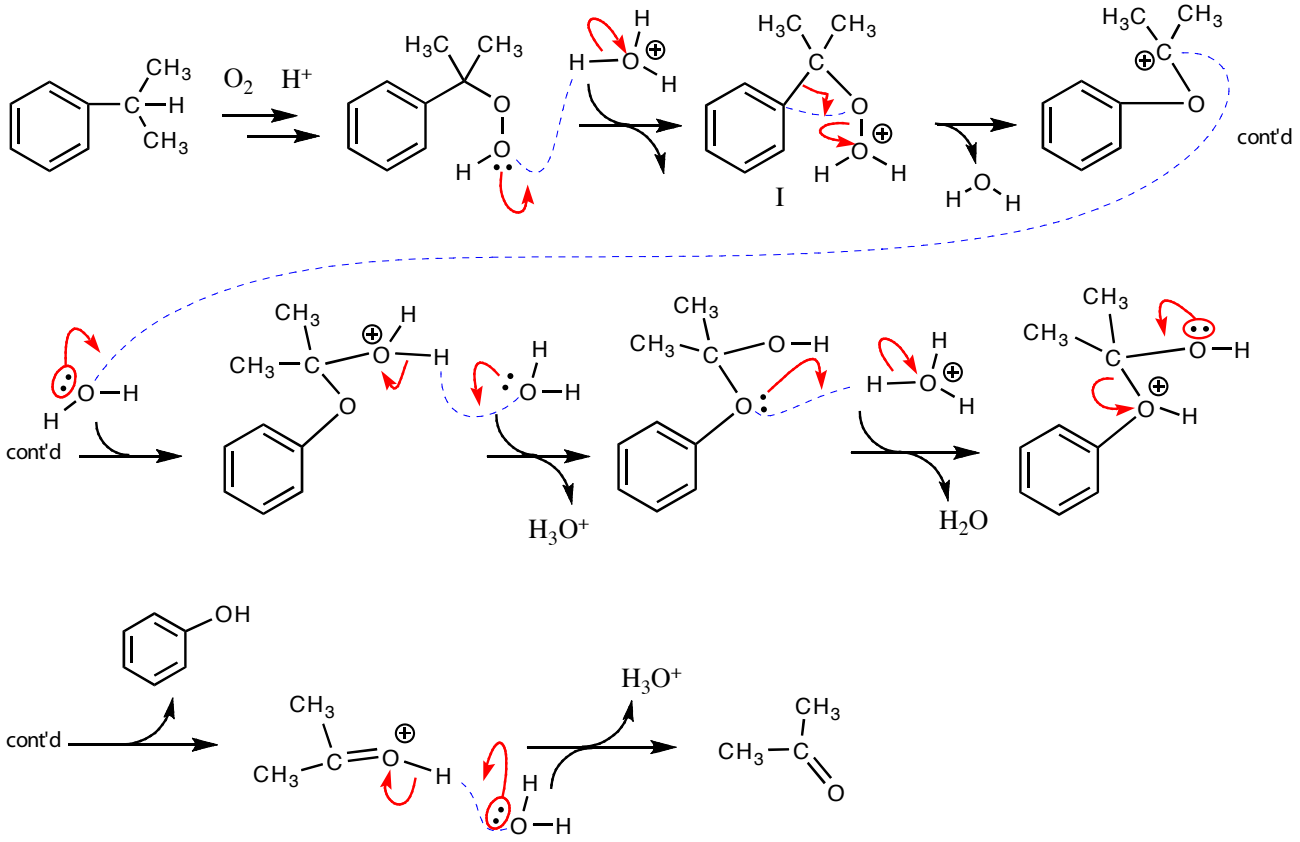
Dakin Reaction

5. Reaction of an *o*- or *p*-hydroxybenzaldehyde with basic hydrogen peroxide to give a phenol.



Acetone from Cumene

6. Conversion of isopropylbenzene (cumene) to acetone and phenol.

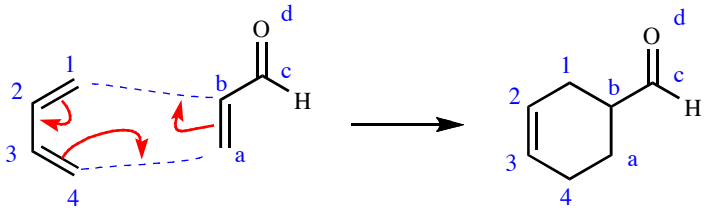


7 — Electrocyclic reactions

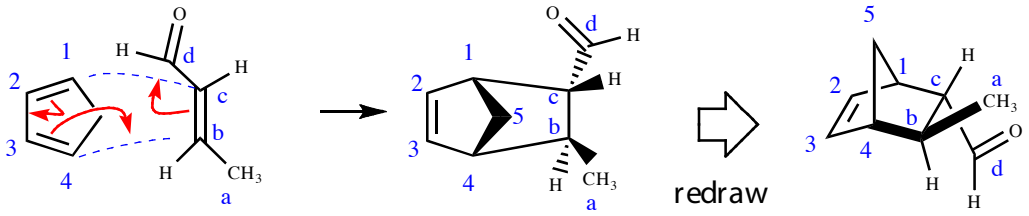
Diels Alder Reactions

This reaction is simple, but errors are common. The best aid to make the right connections is to label each reactant. Then complete the bonds, label the product, and make sure the bonds correspond with the labels. For bicyclic products, I suggest breaking this into two operations. First, make the correct bonds for the product. Then, convert the two-dimensional structure into a correct three-dimensional structure. I can make an error if trying to do both at the same time. Add curved arrows for the following examples.

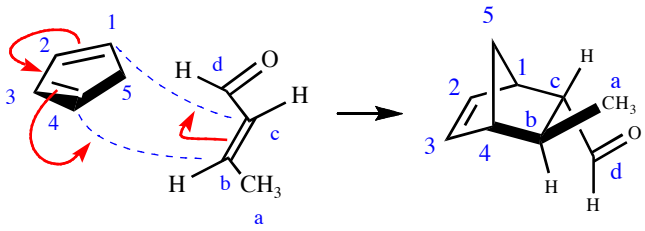
1. A Diels-Alder reaction between 1,3-butadiene and 2-propenal (acrolein).



2. A Diels-Alder reaction between 1,3-cyclopentadiene and (*E*)-2-butenal (trans-crotonaldehyde).

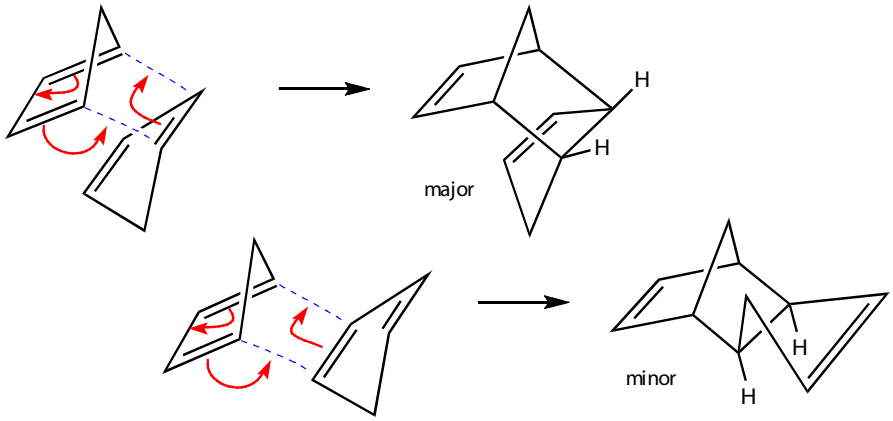


The preferred orientation of the dienophile is below. You should check with your text for further details.

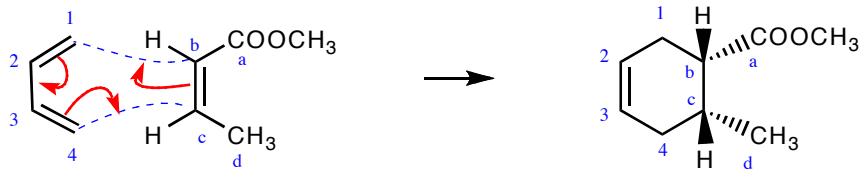


This is the same example as above. Many students find this more difficult to negotiate the atom movements, congestion, and drawing the final product all at one. I wrote the upper example as it is easier to visual and convert to the bicyclic product. You just have to remember the dienophile electron-withdrawing group prefers to overlap with the diene, if possible.

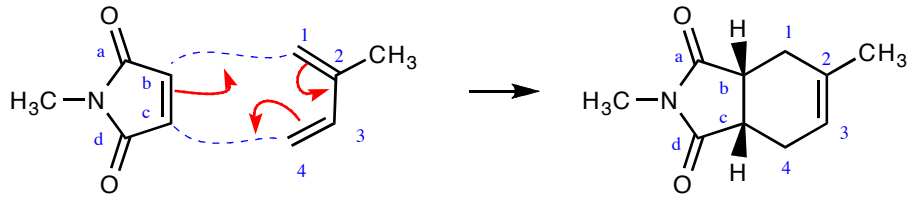
3. The Diels-Alder dimer of cyclopentadiene.



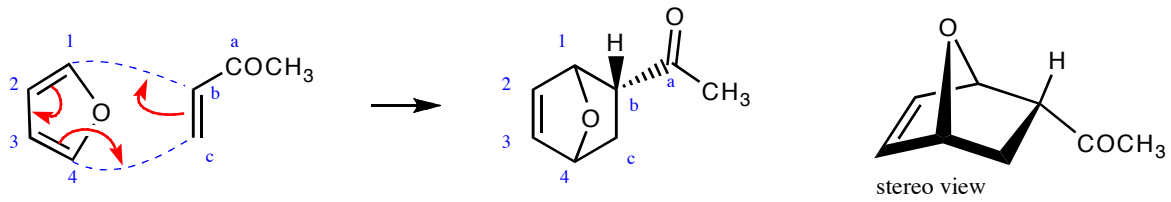
4. A Diels-Alder reaction between 1,3-butadiene and methyl (*Z*)-2-butenoate.



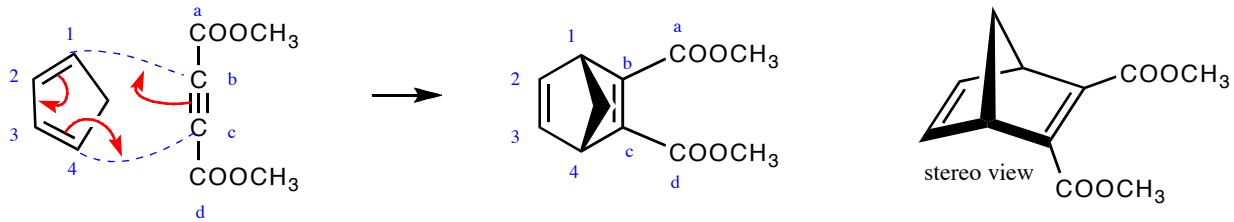
5. A Diels-Alder reaction between 2-methyl-1,3-butadiene and *N*-methylmaleimide.



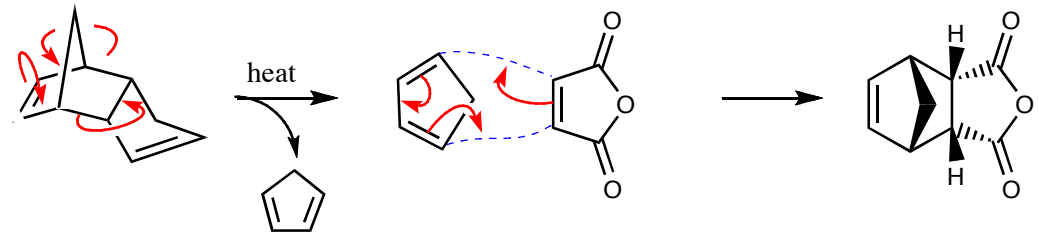
6. A Diels-Alder reaction between furan and but-3-en-2-one (methyl vinyl ketone, MVK).



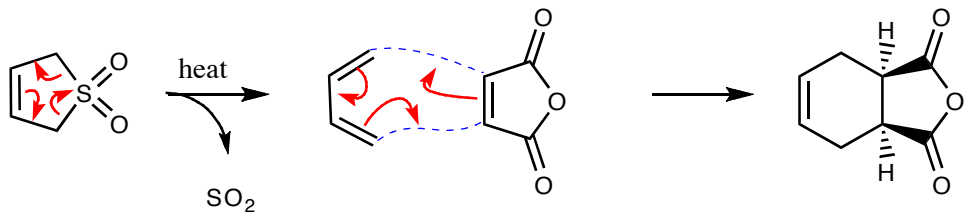
7. A Diels-Alder reaction between cyclopentadiene and dimethyl acetylenedicarboxylate.



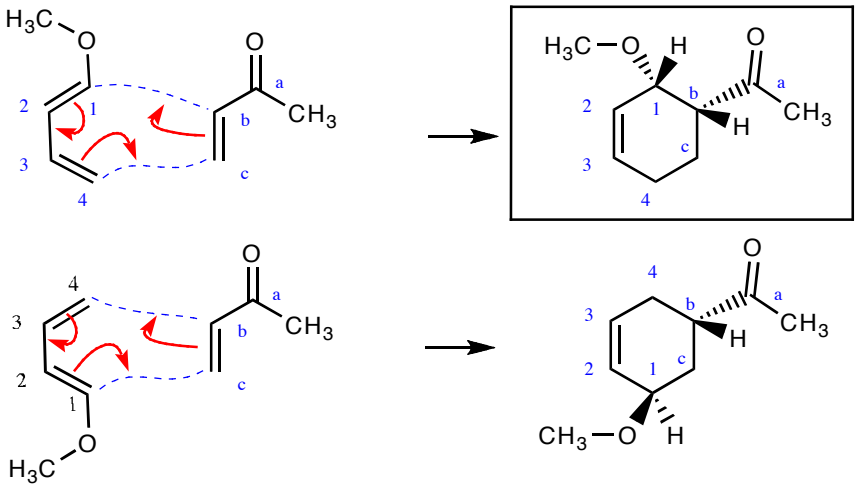
8. A reverse-forward Diels-Alder reaction between cyclopentadiene and maleic anhydride.



9. A reverse-forward Diels-Alder between butadiene (sulfone) and maleic anhydride.

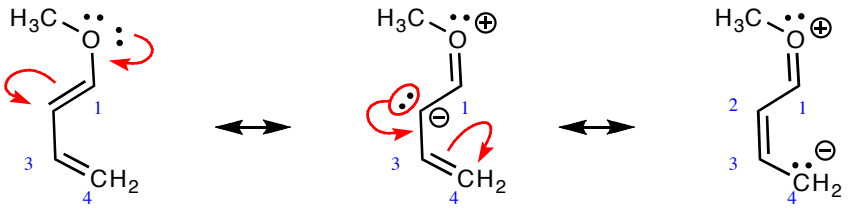


10. A Diels-Alder reaction between 1-methoxy-1,3-butadiene and but-3-en-2-one (methyl vinyl ketone) gives a major product. To determine the structure of the major product, work down to #13.



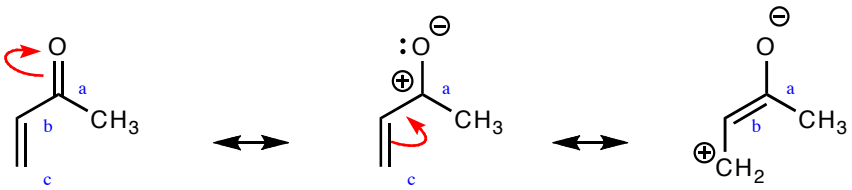
11. Examine the electrostatic charges of the starting materials by drawing the resonance structures.

    Add curved arrows



12. Examine the electrostatic charges of the starting materials by drawing the resonance structures.

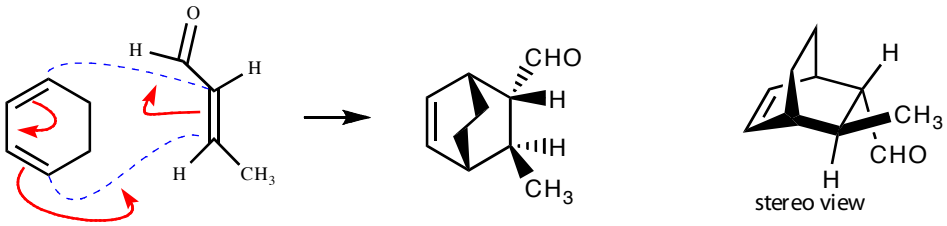
    Add curved arrows



13. How do resonance structures shown in 11 and 12 predict the product for 10? Which structure will be the major product?

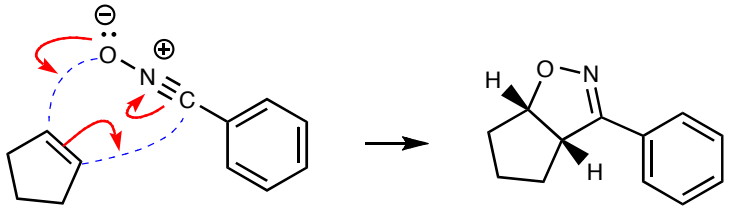
    The boxed structure is the preferred product as it matches the opposite charges in the resonance structures (which might contribute to the transition state). If the reaction were truly concerted, that is, an equal donation and acceptance of electrons would cancel out any charges and therefore no charge effects would be expected.

14. Draw the Diels-Alder product for the reaction of 1,3-cyclohexadiene and 2-butenal (crotonaldehyde).

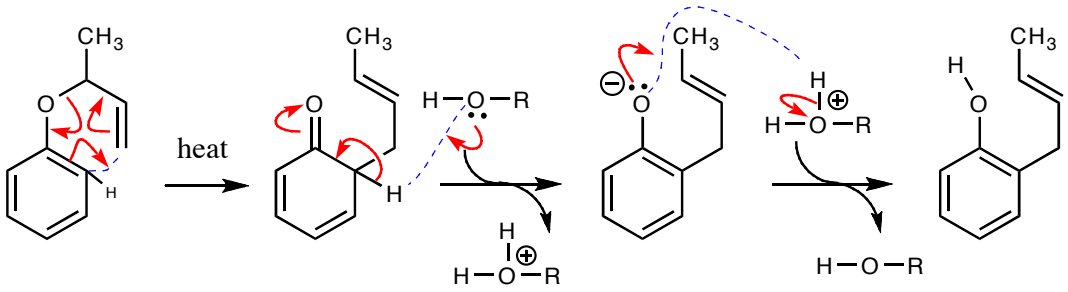


Other Electrocyclic Reactions

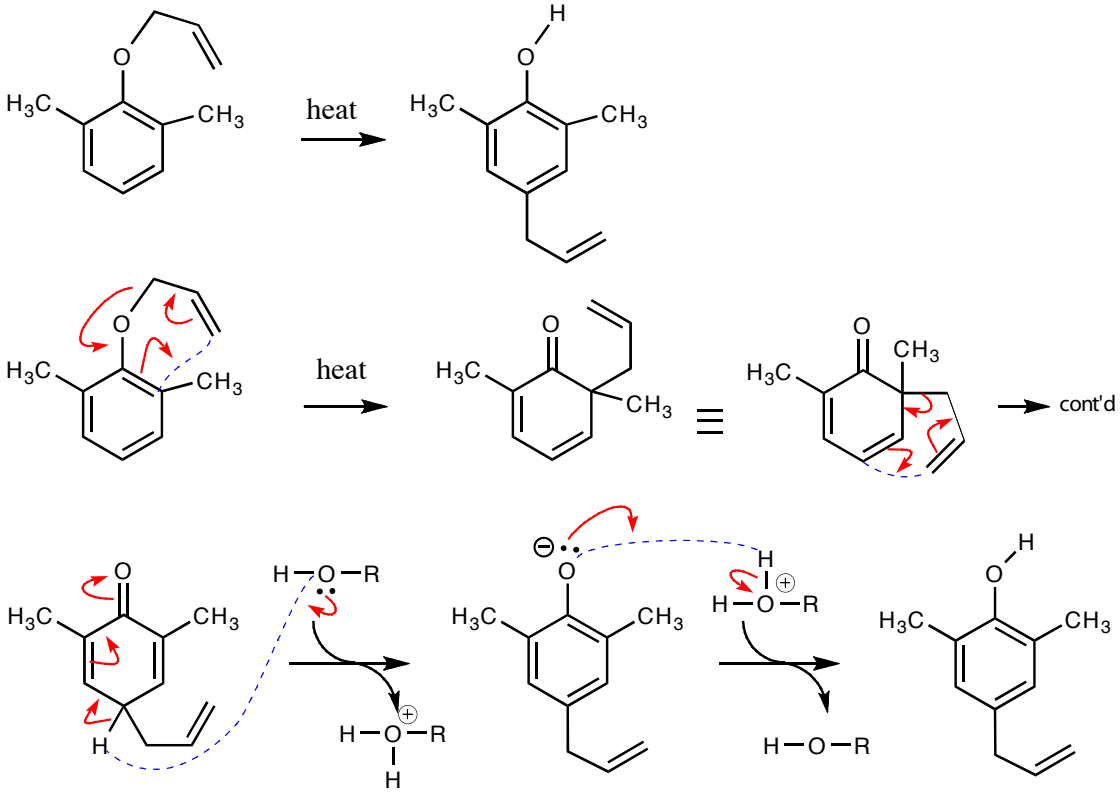
15. A 3+2 cycloaddition between cyclopentene and benzonitrile oxide. How many pairs of electrons (curved arrows) move to complete the formation of product. Compare the number of electrons that move in this reaction with the Diels-Alder reaction. Is it the same?



16. A Claisen rearrangement (electrocyclic) reaction to give transfer a group from oxygen to carbon.



17. A double Claisen rearrangement (electrocyclic) reaction to give transfer a group from oxygen to carbon to carbon. Count the number of electrons that move in each step.

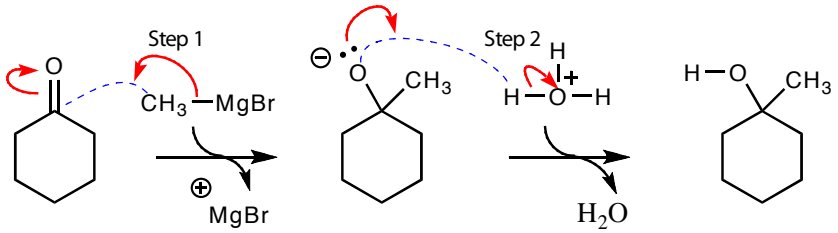


8 — Carbonyl Addition and Addition-Elimination Reactions

Additions by C, N, and O. Addition by hydrogen nucleophiles are discussed in Chapter 11, Reduction.

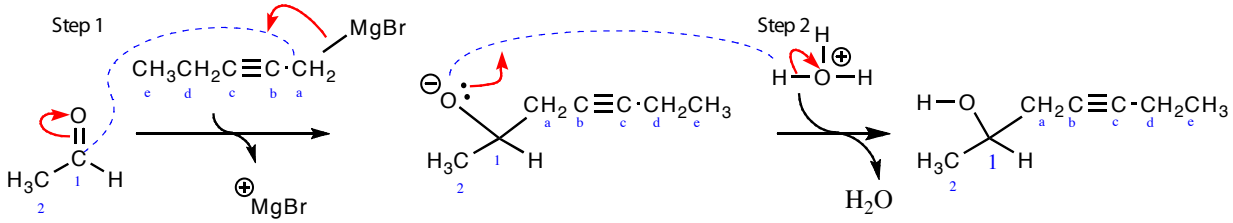
Grignard Addition to a Carbonyl Group

1. Addition of methyl magnesium bromide to cyclohexanone to give 1-methylcyclohexanol. (see Notes for formation of Grignard reagents)



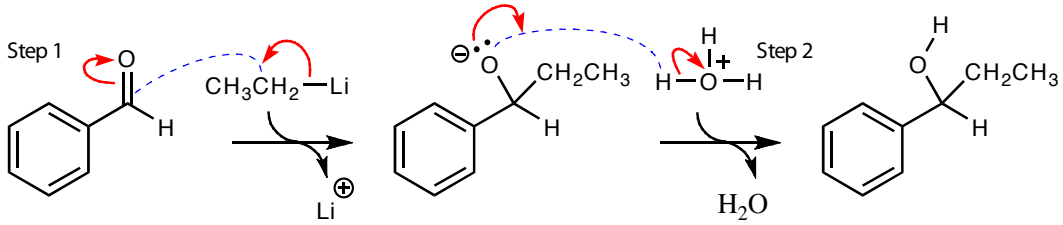
2. Addition of a functionalized Grignard reagent to acetaldehyde to give 2-methylhept-4-yn-2-ol.

   In this example, the order of the atoms becomes snaked around. This is a good example where numbering, lettering or numbering and lettering the reactants and products is useful.

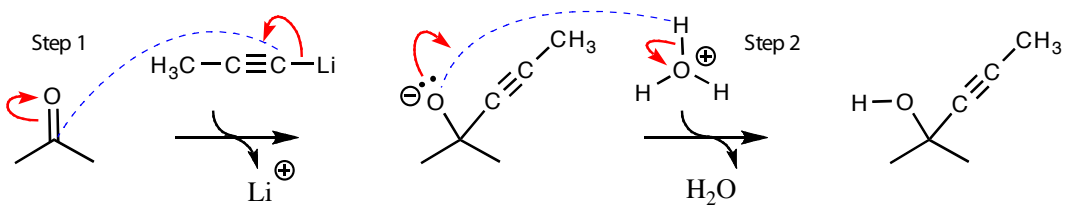


Alkyllithium Addition to a Carbonyl Group

3. Addition of ethyllithium to benzaldehyde to give 1-phenylpropanol. (see Notes for formation of lithium reagents)

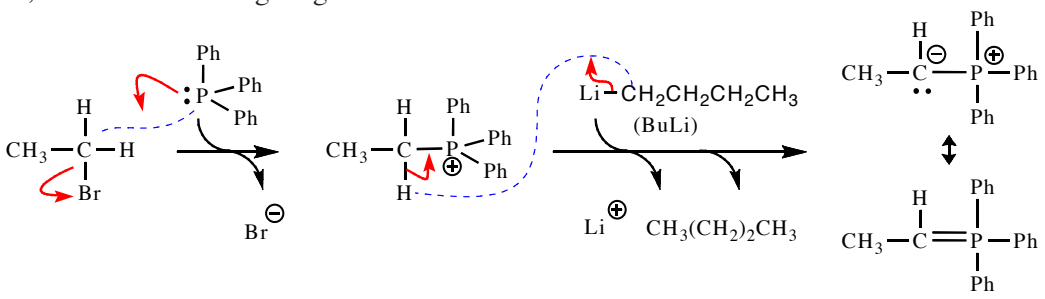


4. Addition of propargyllithium to acetone to give 2-methylpent-3-yn-2-ol. (see Chapter 2.14)

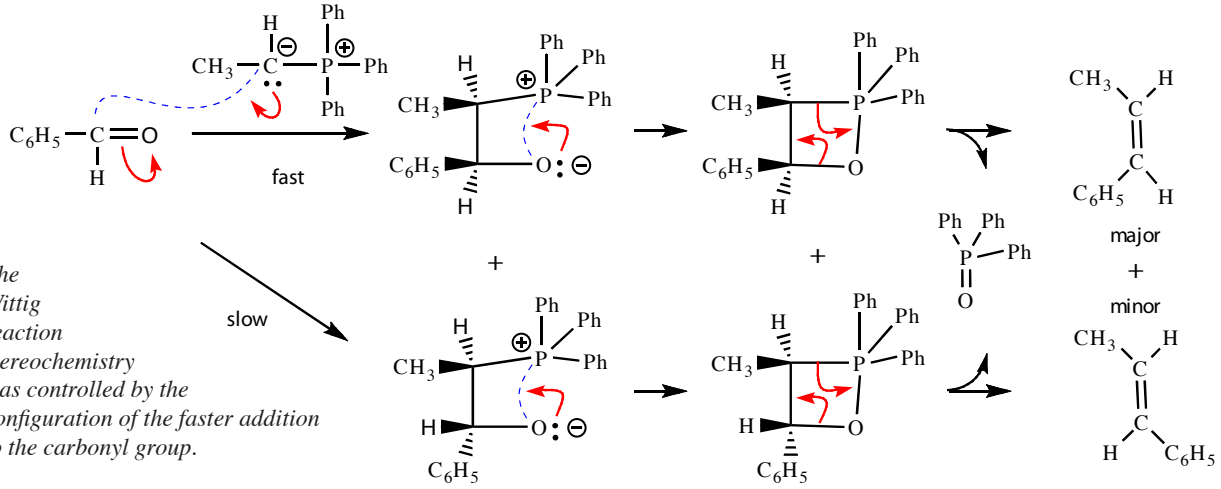


Wittig Reaction

5. Step 1, formation of Wittig reagent

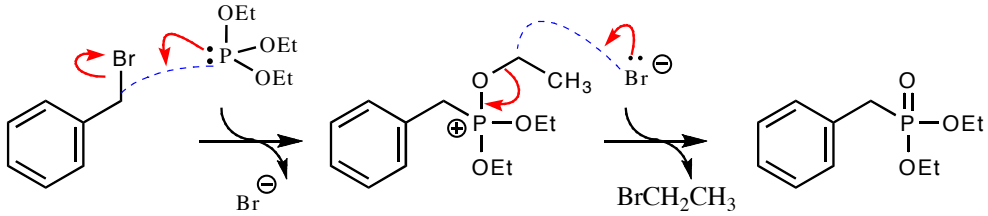


Step 2, reaction with benzaldehyde

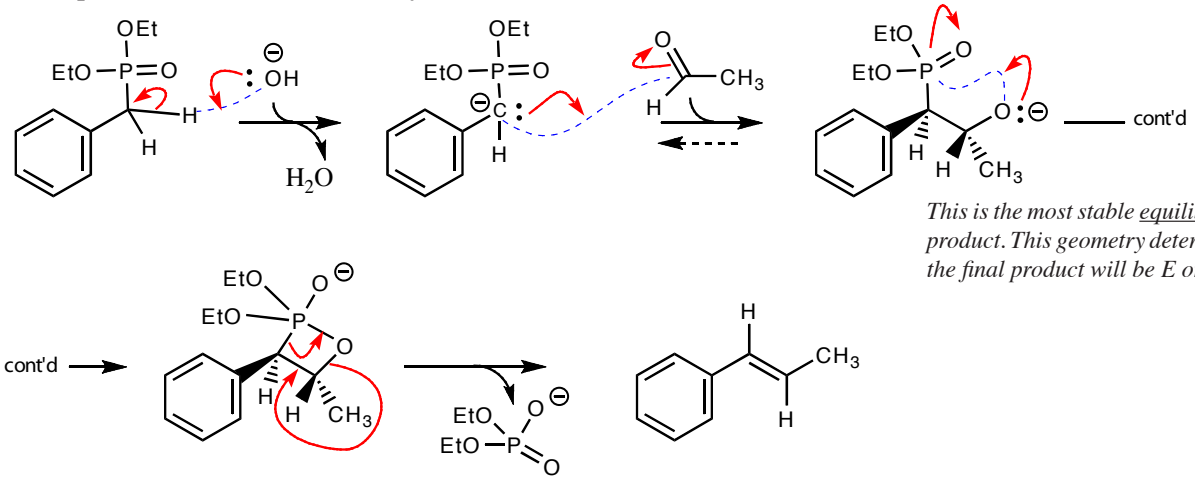


The Wittig reaction stereochemistry was controlled by the configuration of the faster addition to the carbonyl group.

6. Step 1, formation of Horner-Emmons reagent



Step 2, reaction with benzaldehyde

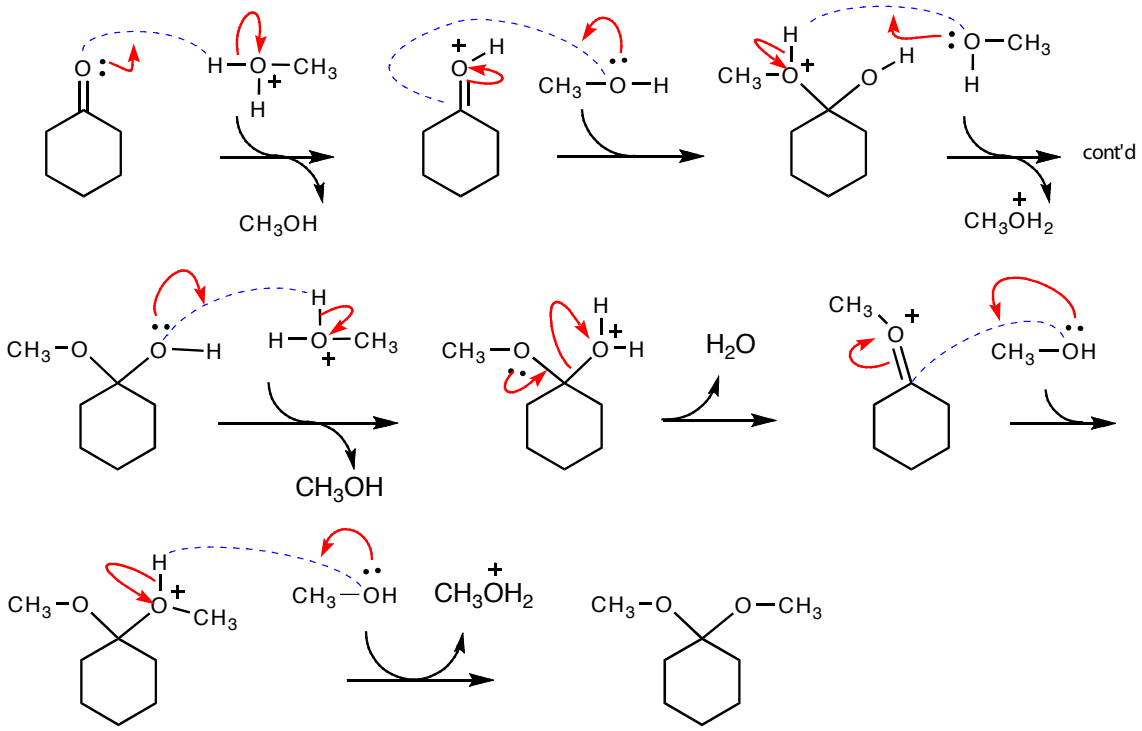


This is the most stable equilibrium addition product. This geometry determines whether the final product will be E or Z.

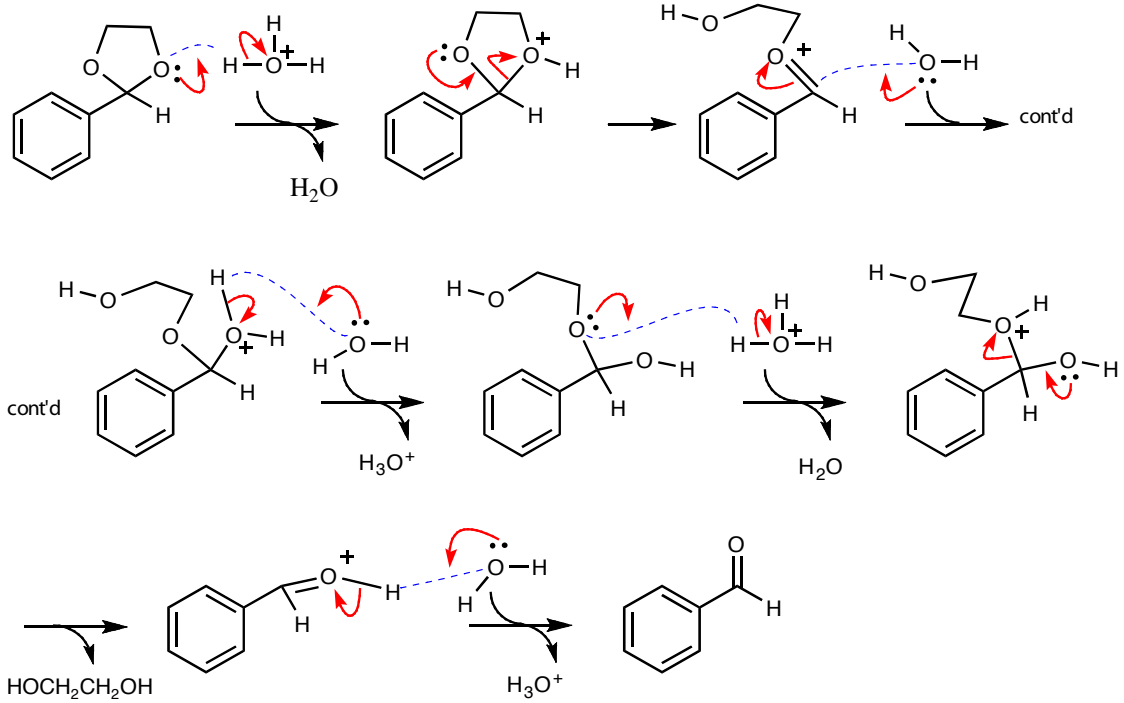
Addition-Elimination Reactions (Reversible Additions)

Ketal Formation and Hydrolysis

7. Acid catalyzed ketalization of cyclohexanone.

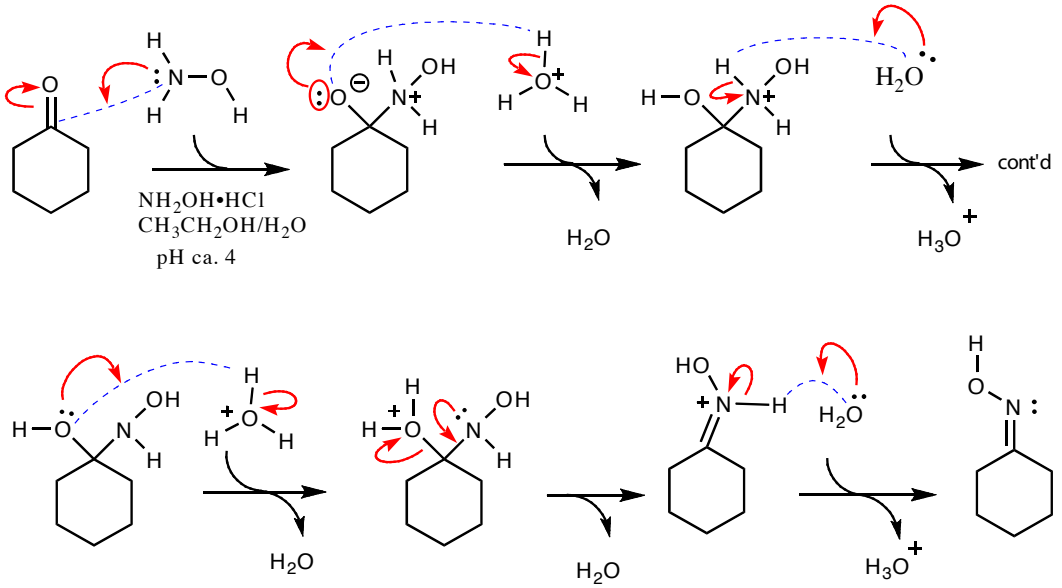


8. Acid catalyzed hydrolysis of the dioxolane ketal of benzaldehyde.



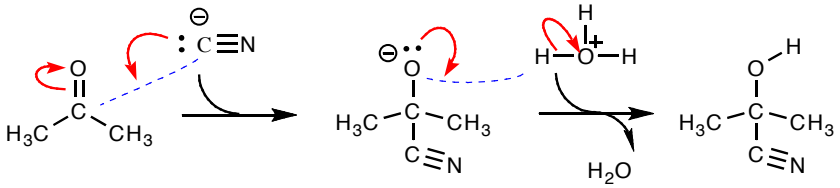
Oxime Formation

9. Formation of the oxime of cyclohexanone.

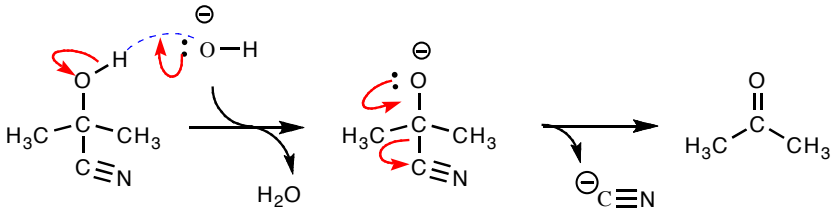


Addition of Cyanide to a Carbonyl Group

10. Formation of the cyanohydrin (2-hydroxy-2-methylpropanenitrile) from acetone.



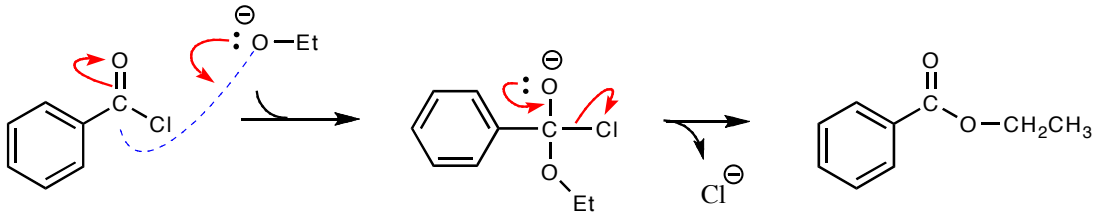
11. Reversion of the cyanohydrin (2-hydroxy-2-methylpropanenitrile) to form acetone.



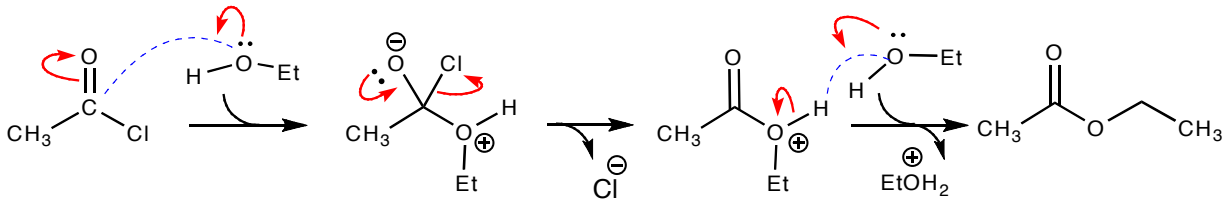
Reactions of Acyl Chlorides, Anhydrides, Esters, and Amides

Esters from Acid Chlorides or Anhydrides

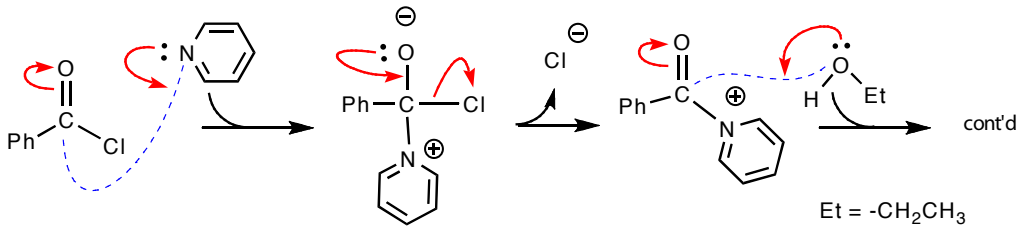
12. Reaction of benzoyl chloride with ethoxide to give ethyl benzoate.

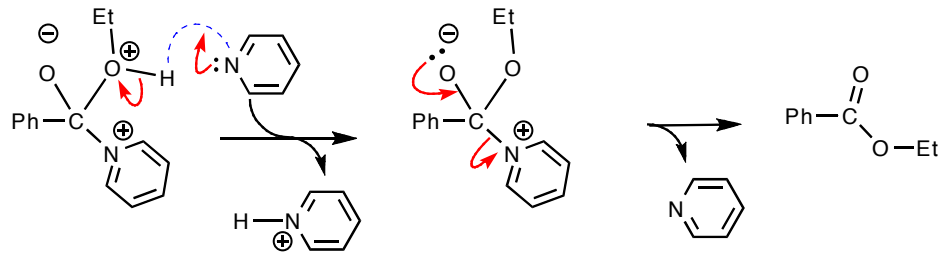


13. Direct reaction of ethanol with acetyl chloride to give ethyl acetate. (see Notes)

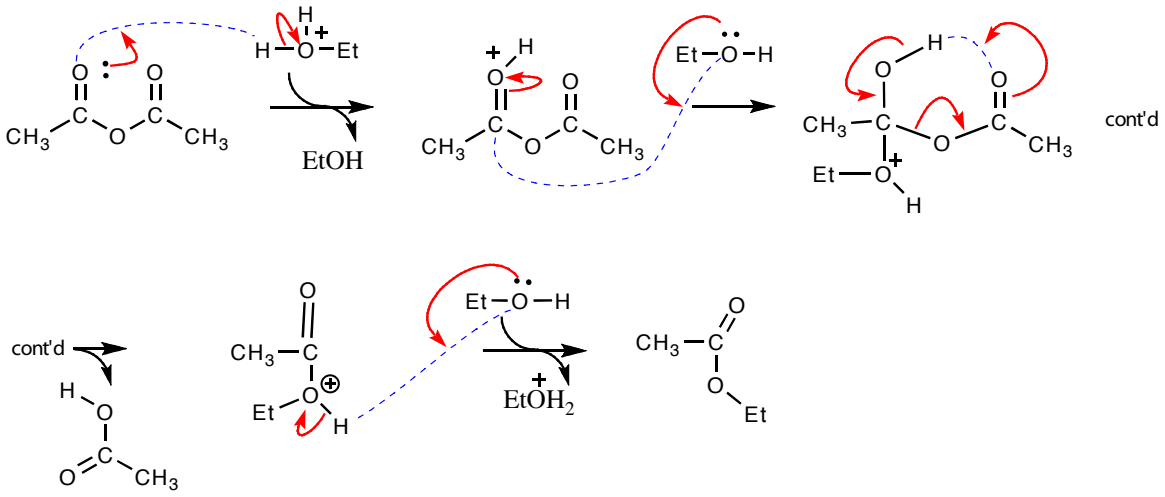


14. Pyridine catalyzed acylation with benzoyl chloride to give ethyl benzoate.



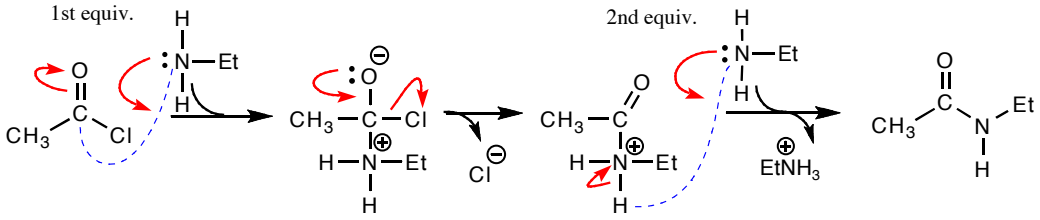


15. Reaction of acetic anhydride with ethanol catalyzed by sulfuric acid.

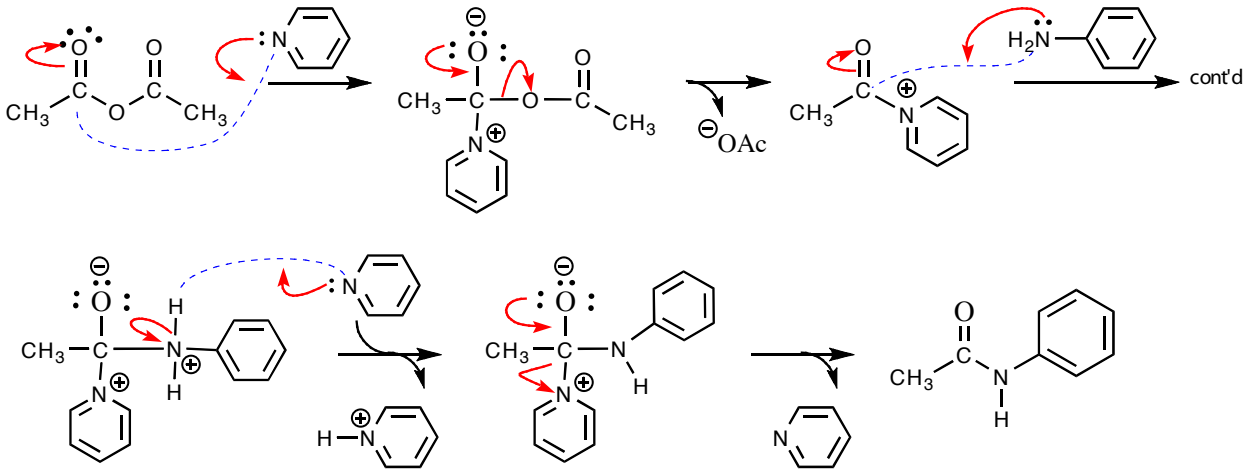


Amides from Acid Chlorides or Anhydrides

16. Reaction of acetyl chloride with ethylamine to give *N*-ethylacetamide.

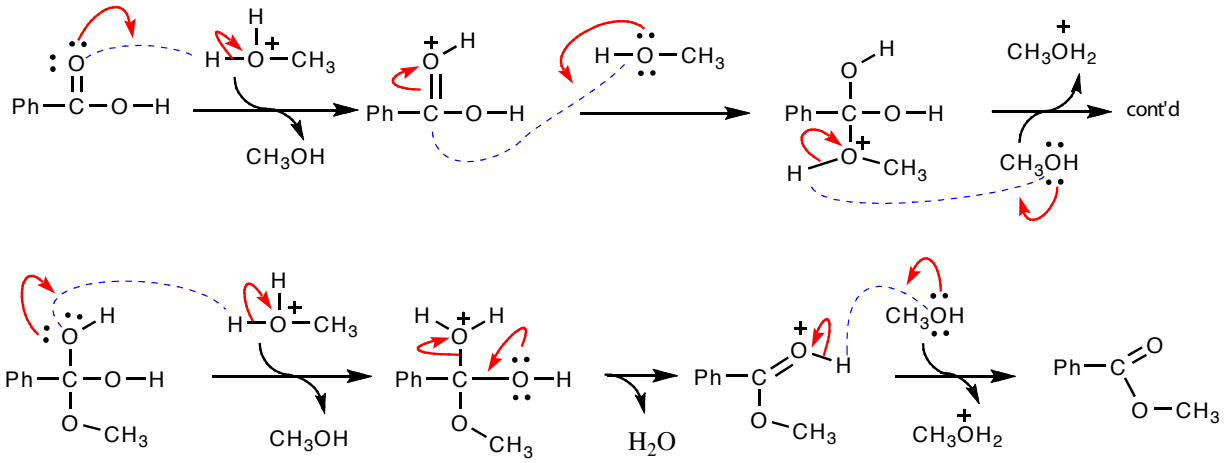


17. Reaction of acetic anhydride with aniline (and pyridine) to give acetanilide.

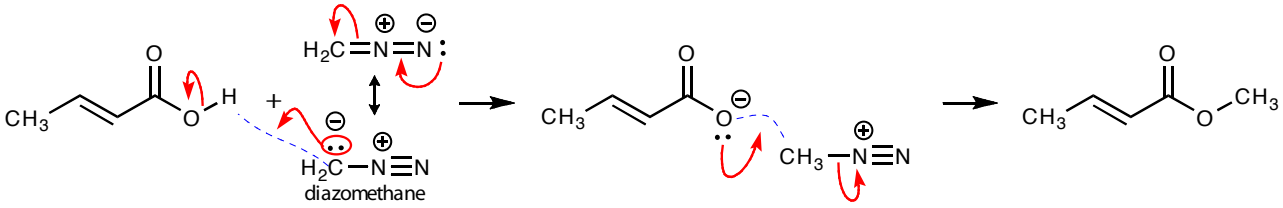


Ester from Acid with Mineral Acid Catalysis (Fischer Esterification)

18. Acid catalyzed esterfication. Formation of methyl benzoate from benzoic acid and methanol with sulfuric acid or hydrogen chloride.

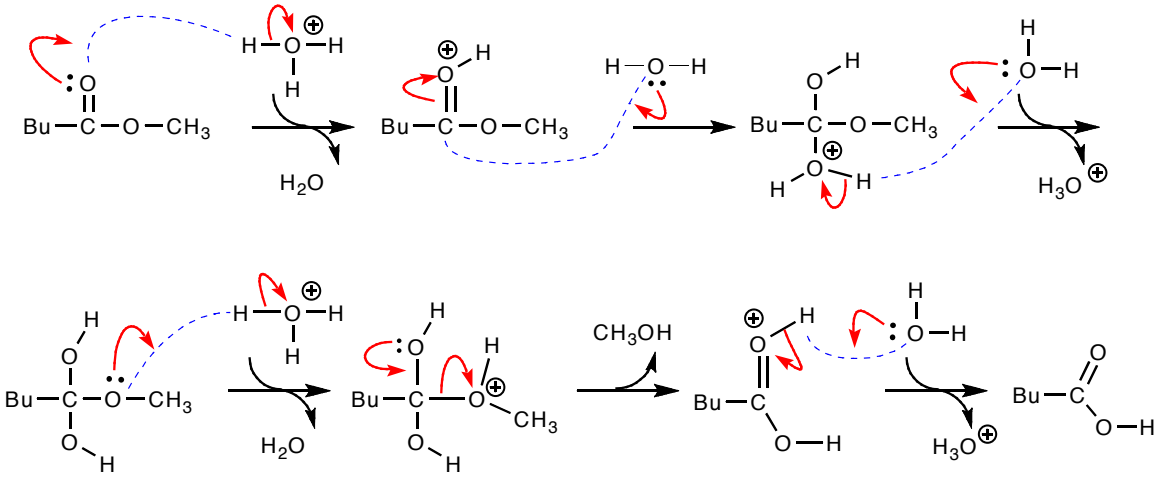


19. Reaction of diazomethane with a carboxylic acid to form methyl 2-butenoate (methyl crotonate).



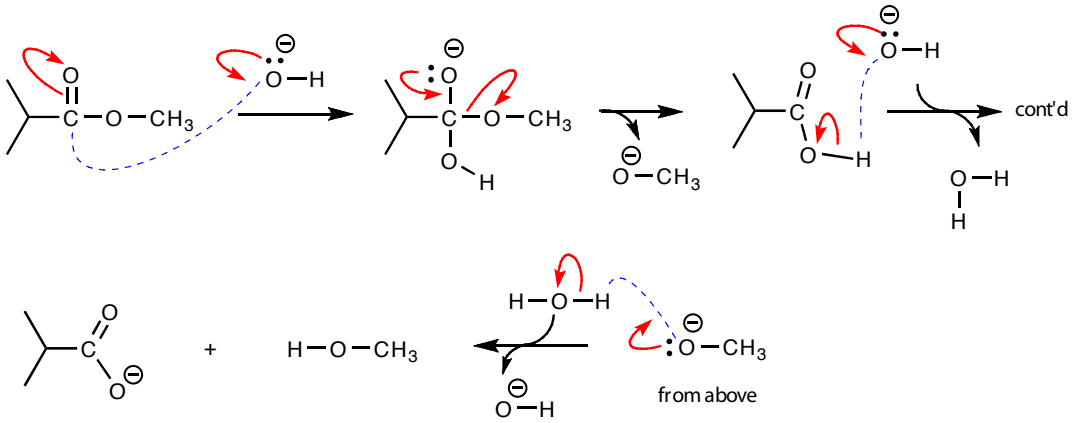
Acid Catalyzed Hydrolysis of an Ester

20. Acid catalyzed hydrolysis of methyl pentanoate (valerate) to pentanoic (valeric) acid plus methanol.

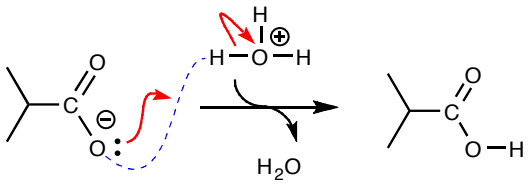


Base Catalyzed Hydrolysis of an Ester (Saponification)

21. Base catalyzed hydrolysis of methyl isobutyrate to give methanol and isobutyric acid. Step 1, treatment with base.

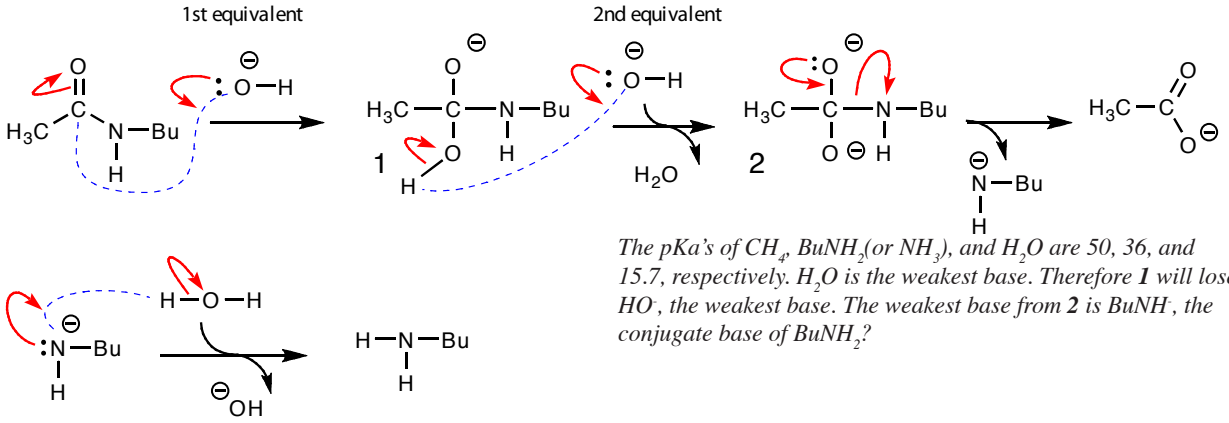


Step 2, acidification of isobutyrate and isolation of isobutyric acid.



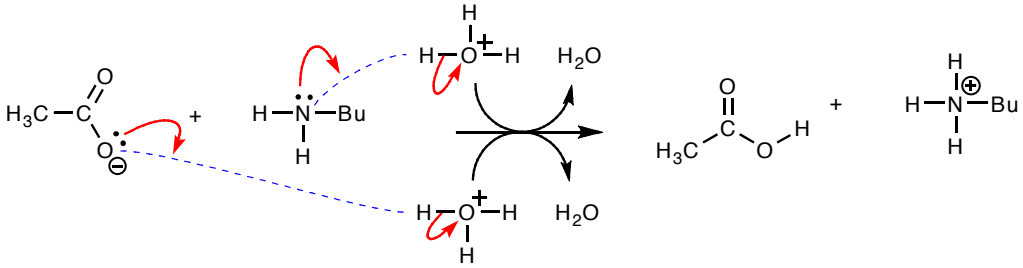
Hydrolysis of an Amide

22. Base catalyzed hydrolysis of *N*-butylacetamide to give n-butylamine and acetic acid. Step 1, treatment with base.

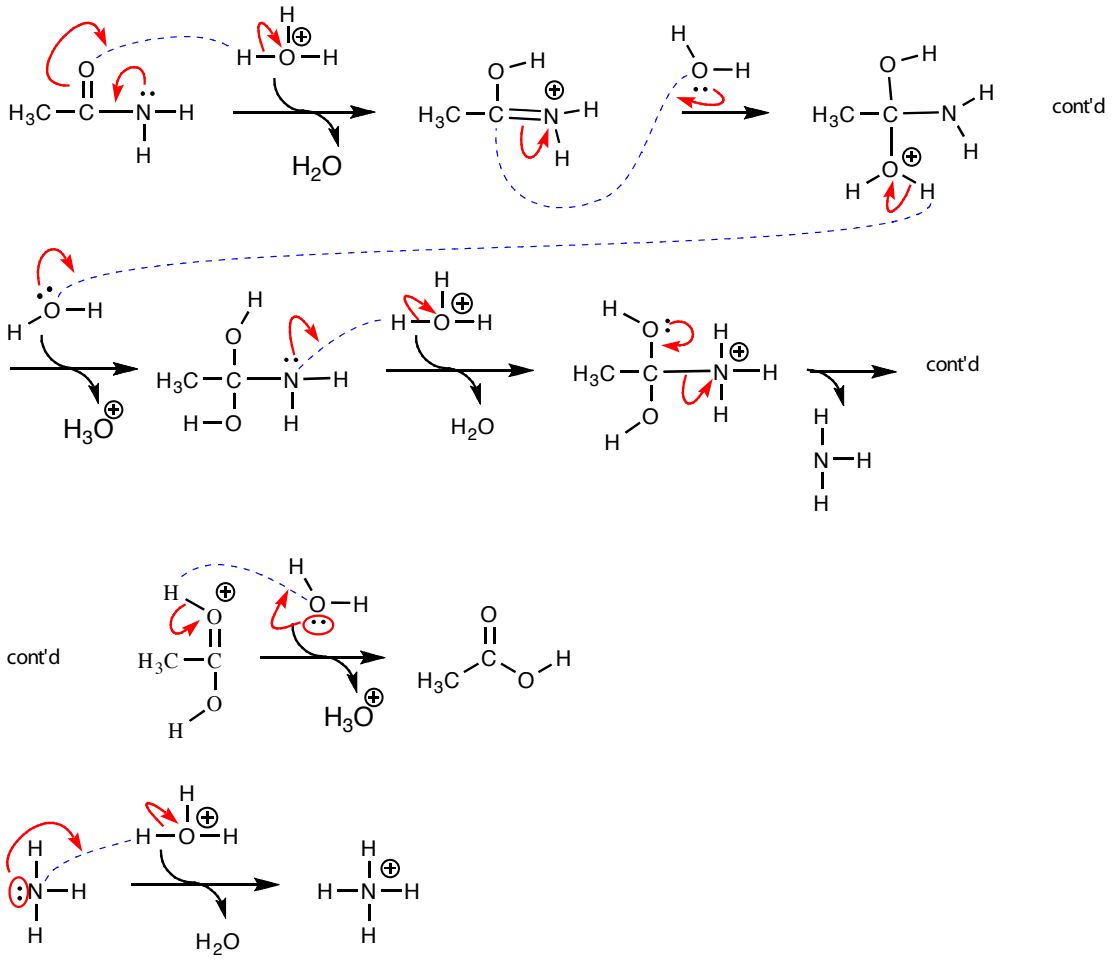


*The pKa's of CH_4, $BuNH_2$(or NH_3), and H_2O are 50, 36, and 15.7, respectively. H_2O is the weakest base. Therefore **1** will lose HO^-, the weakest base. The weakest base from **2** is $BuNH^-$, the conjugate base of $BuNH_2$?*

Step 2, acidification and isolation of the carboxylic acid, acetic acid.

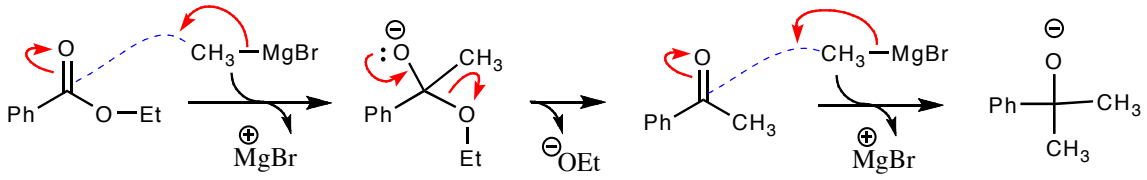


23. Acid catalyzed hydrolysis of acetamide to give acetic acid and ammonia.

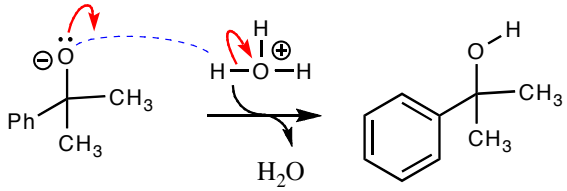


Grignard Addition to an Ester

24. Addition of methyl magnesium bromide to ethyl benzoate to give 2-phenyl-2-propanol. Step 1, addition of Grignard reagent.

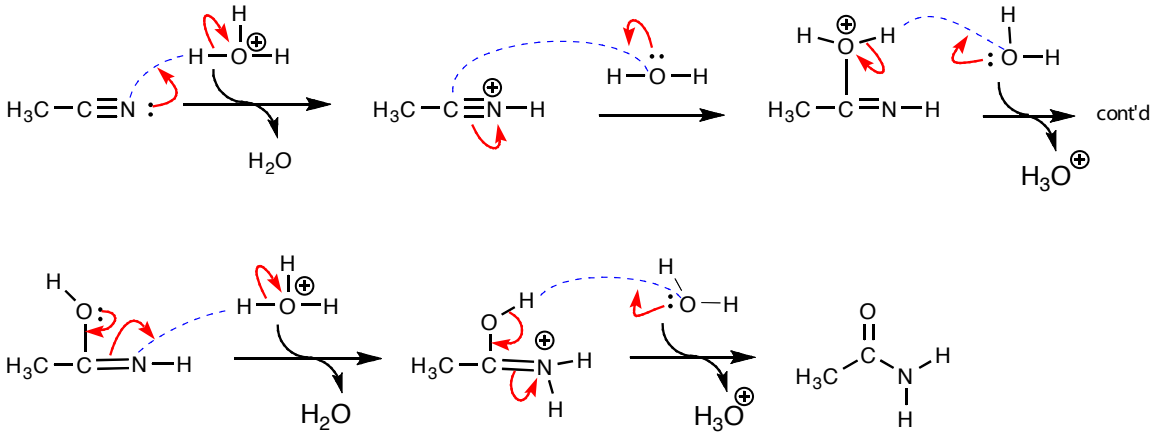


Step 2, acidification and isolation of the product.

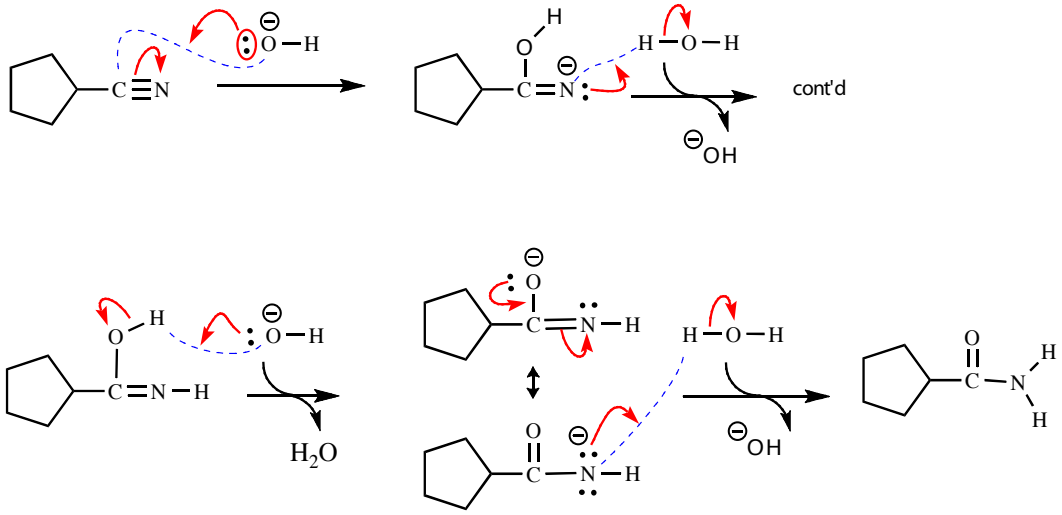


Addition to a Nitrile

25. Acid catalyzed hydrolysis of a nitrile, conversion of acetonitrile to acetamide.

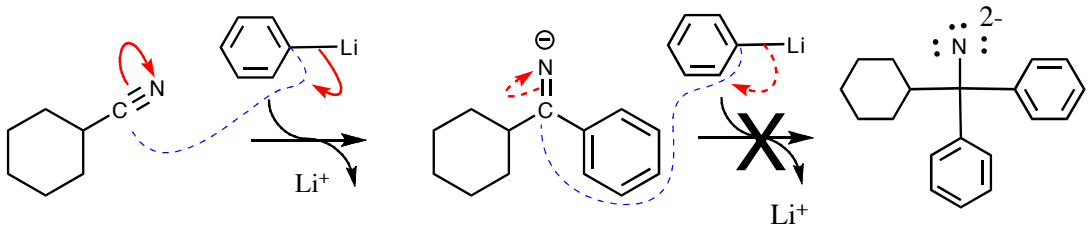


26. Base catalyzed hydrolysis of a nitrile, conversion of cyclopentanecarbonitrile to cyclopentanecarboxamide.

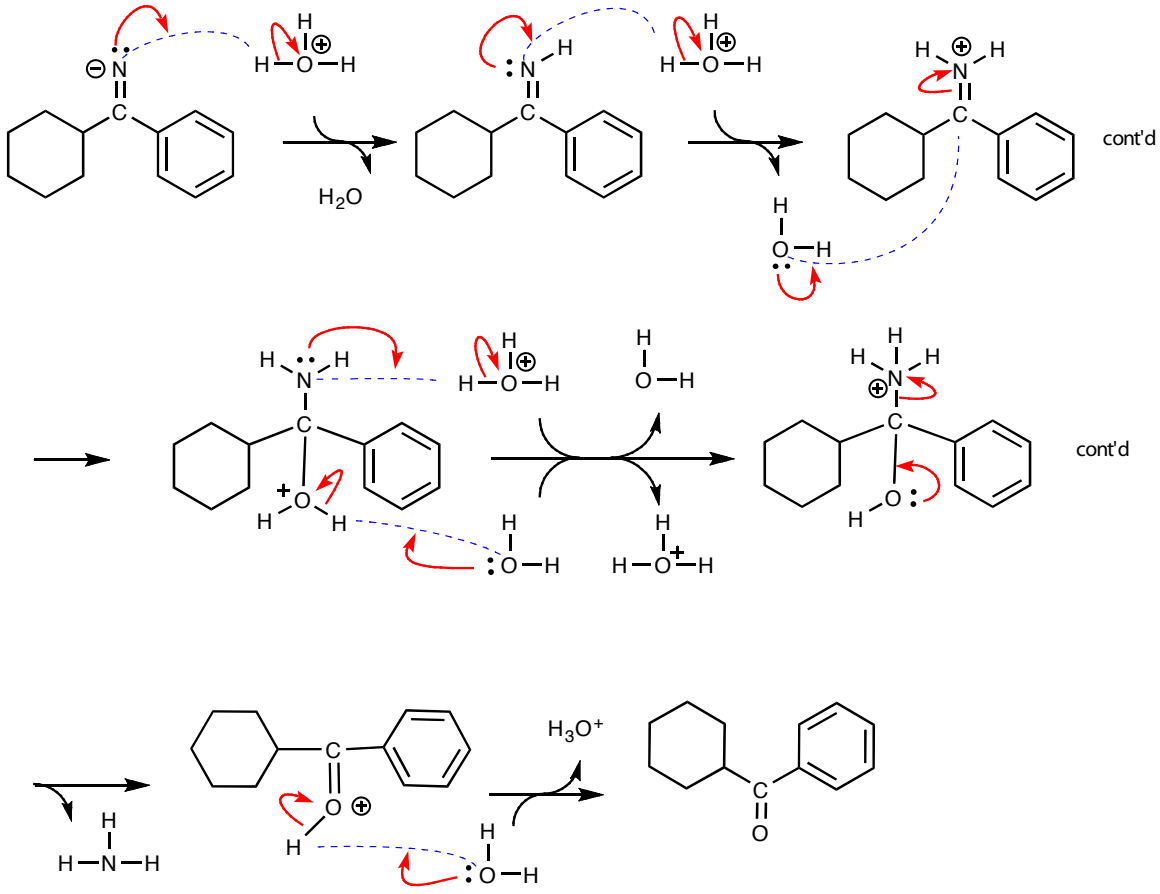


27. Addition of phenyl lithium to a nitrile to give, after hydrolysis, cyclohexyl phenyl ketone.

Step 1, addition to the nitrile.



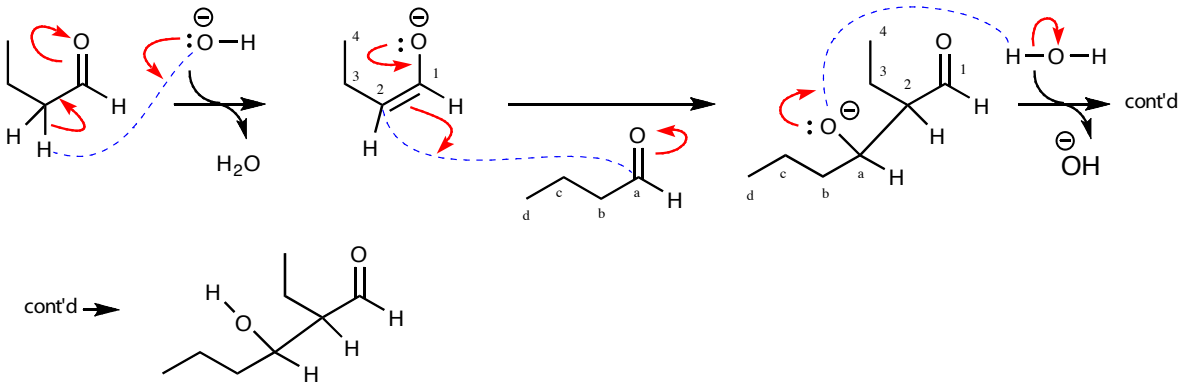
Step 2, hydrolysis of the imine.



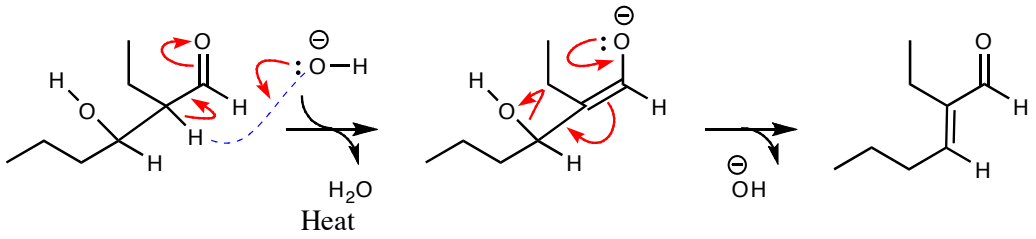
9 — Reactions of Enols and Enolates

Aldol Reaction

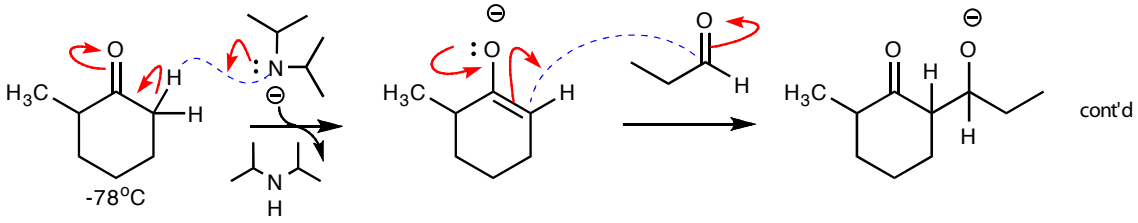
1. Base catalyzed aldol condensation of butanal (butyraldehyde). (see Notes)



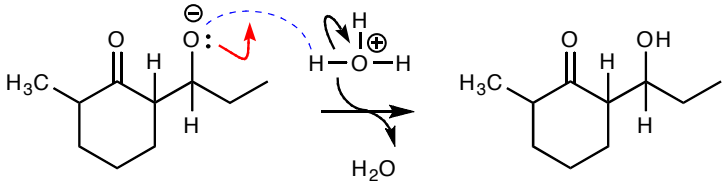
Base catalyzed dehydration step. Under concentrated base or heating, the dehydration reaction may occur spontaneously.



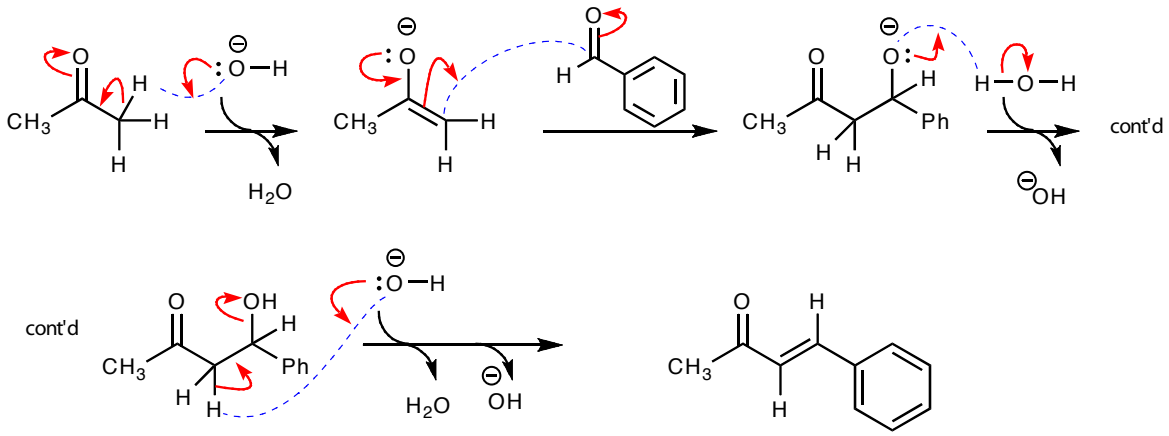
2. Directed kinetic aldol condensation of 2-methylcyclohexanone with propanal (propionaldehyde). Step 1, enolate formation; step 2, reaction with propanal.



Step 3, work-up and isolation of aldol product.

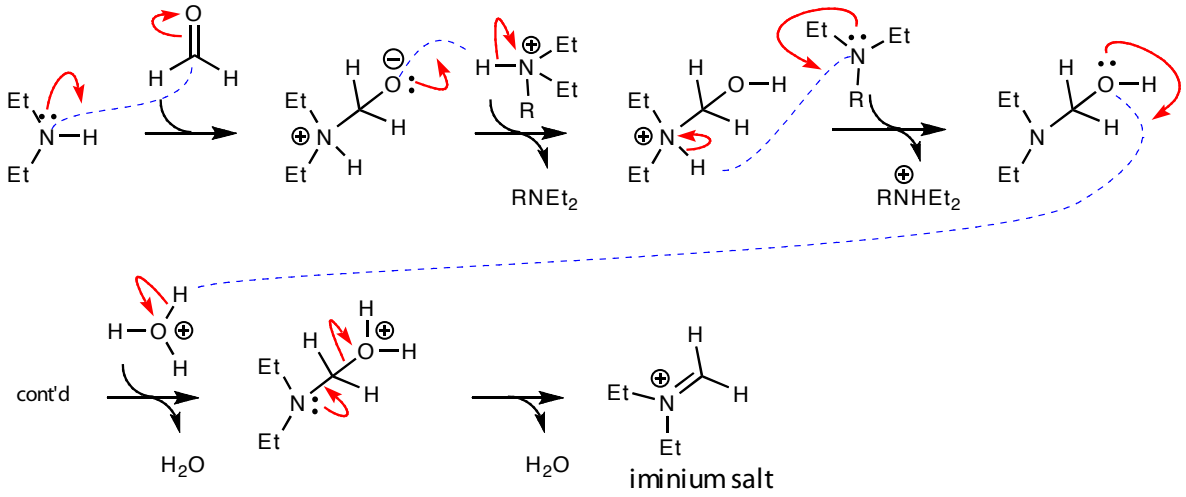


3. Base catalyzed mixed or crossed aldol condensation of acetone and benzaldehyde.

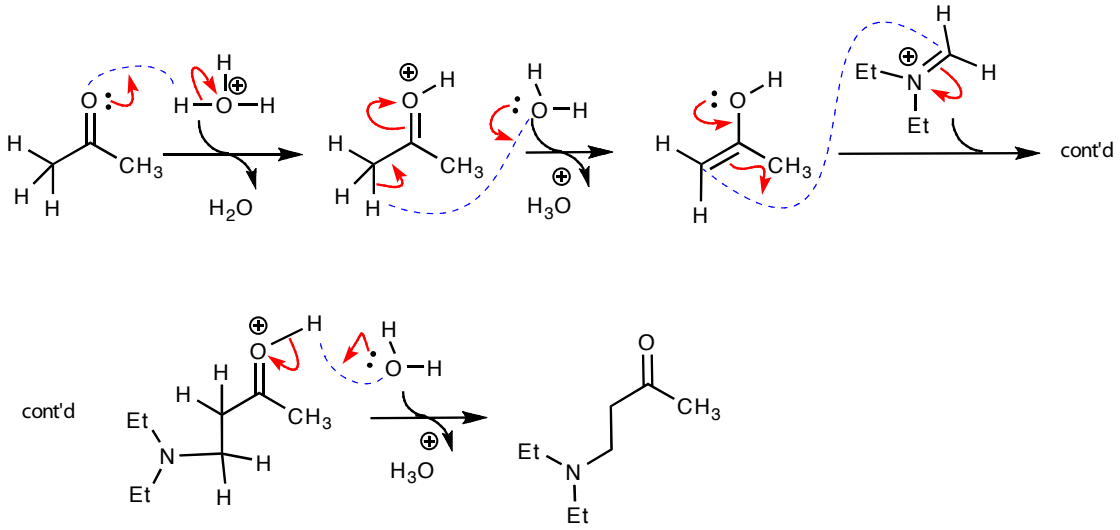


4. Mannich reaction, acid catalyzed enolization of 2-propanone in a reaction of with diethylamine, formaldehyde, and 2-propanone to give 4-(diethylamino)butan-2-one. (see Notes)

Step 1, formation of iminium salt

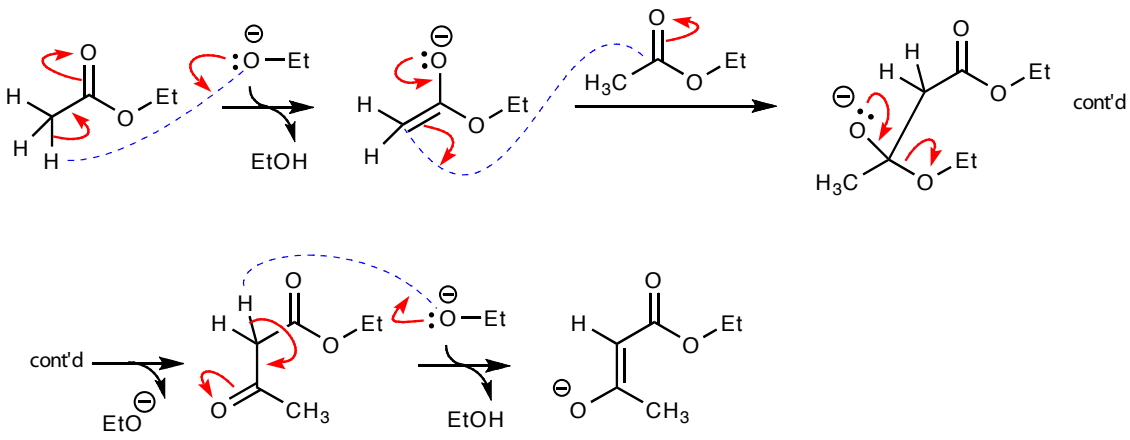


Step 2, enolization of acetone and condensation with iminium salt.

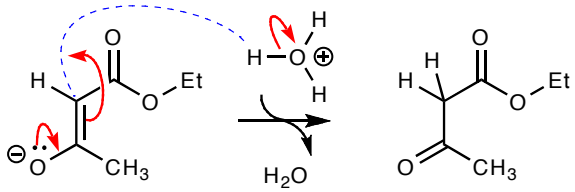


Claisen Condensation

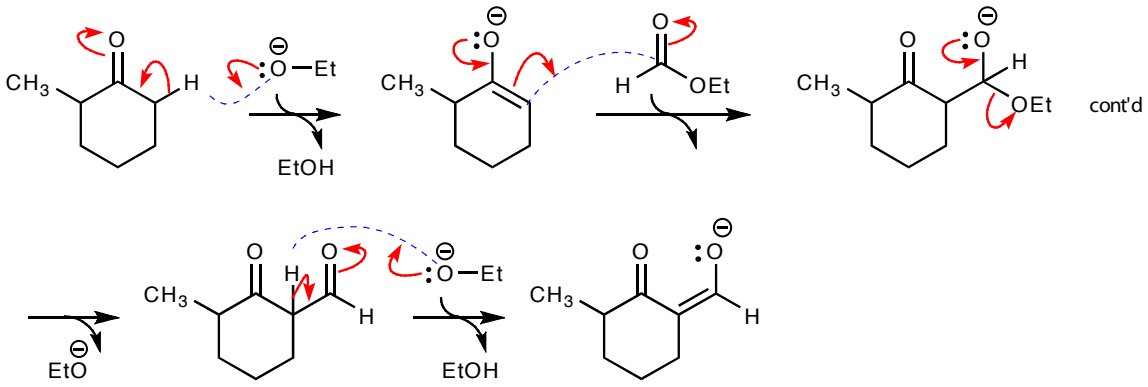
5. Step 1, ethoxide catalyzed Claisen condensation of ethyl acetate to ethyl acetoacetate (ethyl 3-oxobutanoate). (see Notes)



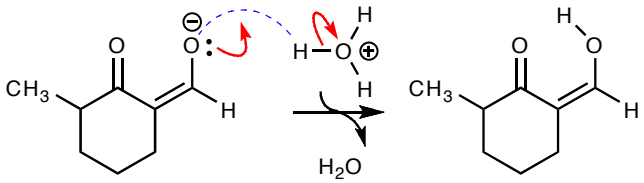
Step 2, acidification and product isolation.



6. Step 1, ethoxide catalyzed crossed-Claisen condensation of cyclohexanone and ethyl formate. (see Notes)

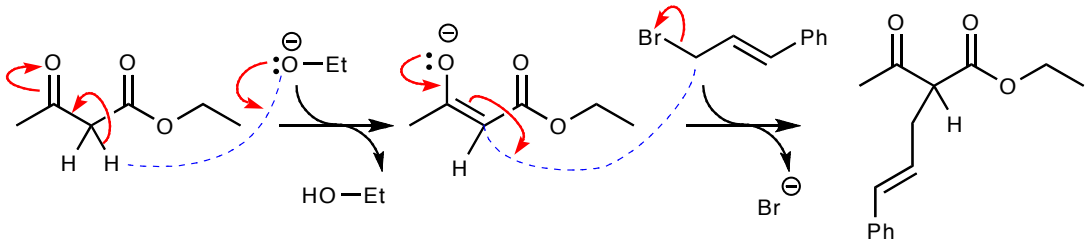


Step 2, acidification and product isolation.

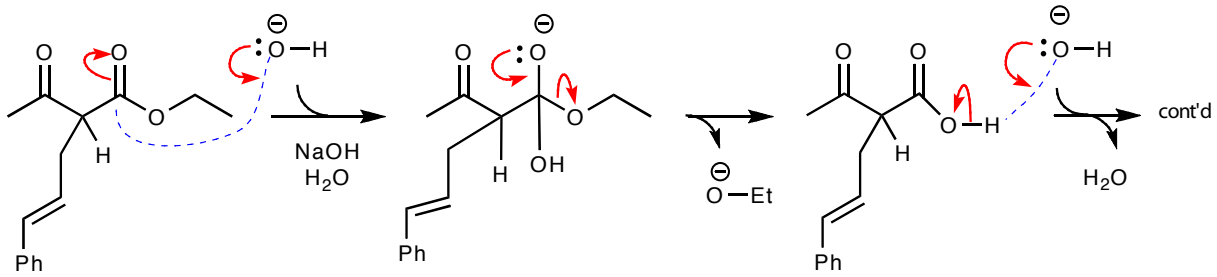


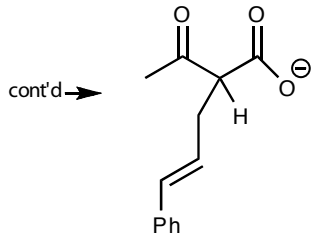
Acetoacetate Synthesis

7. Step 1, S_N2 alkylation of acetoacetate.

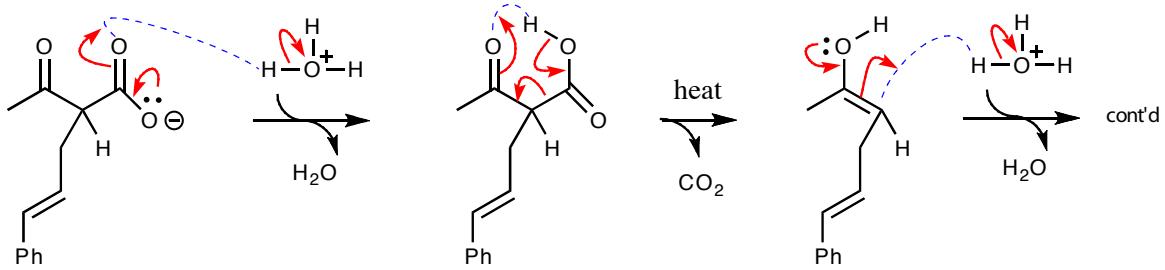


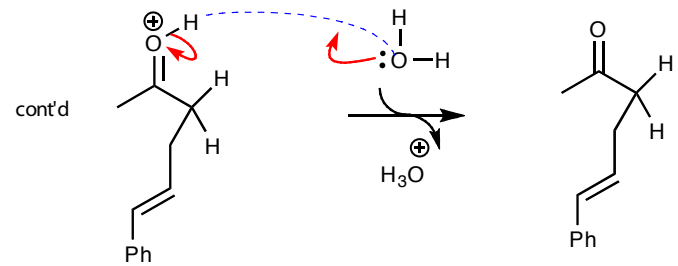
Step 2, sodium hydroxide hydrolysis of ester (saponification).





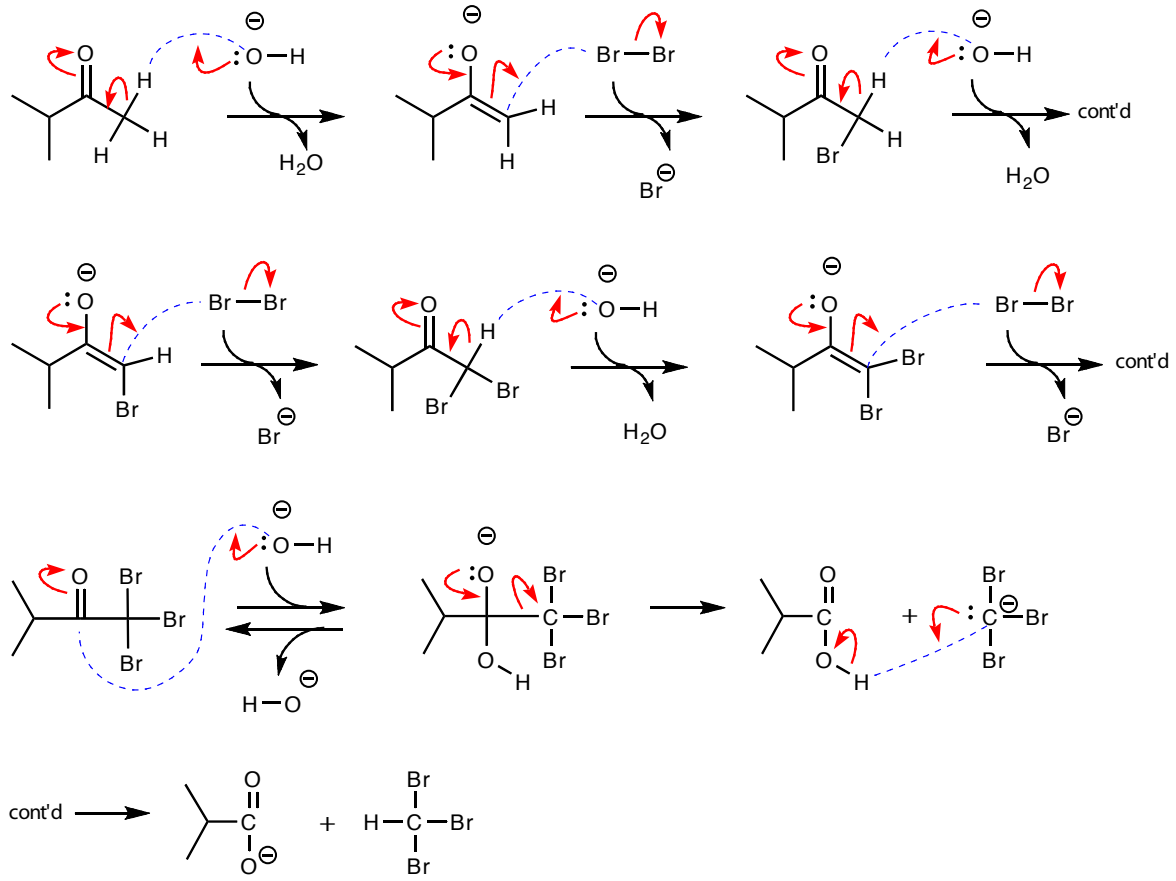
Step 3, acidification of carboxylate, decarboxylation, and tautomerization.



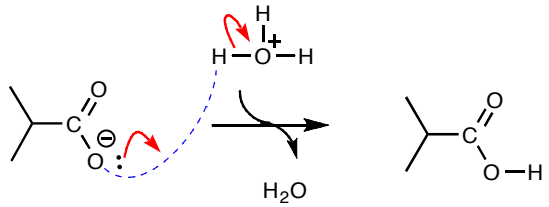


Halogenation of Carbonyl Compounds

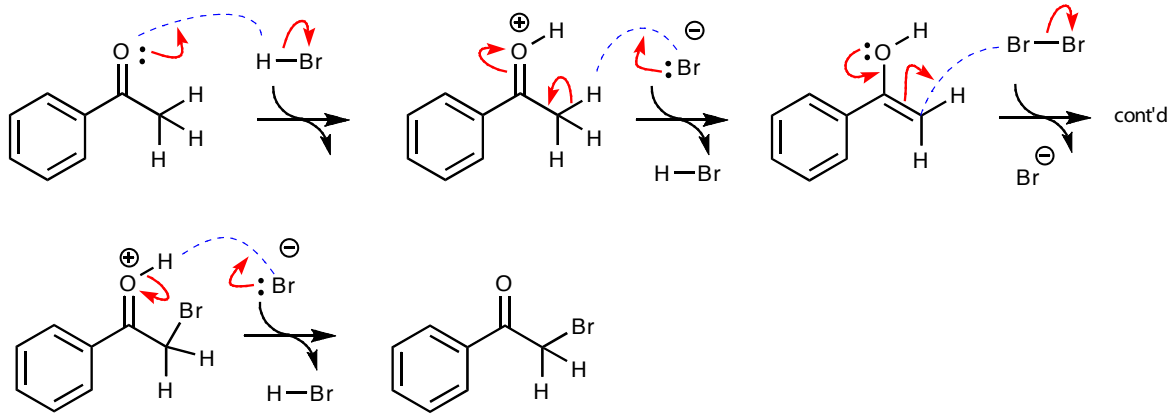
8. Basic bromination of 3-methyl-2-butanone with sodium hydroxide and bromine, bromoform reaction.



Step 2, acidification and isolation of isobutyric acid.

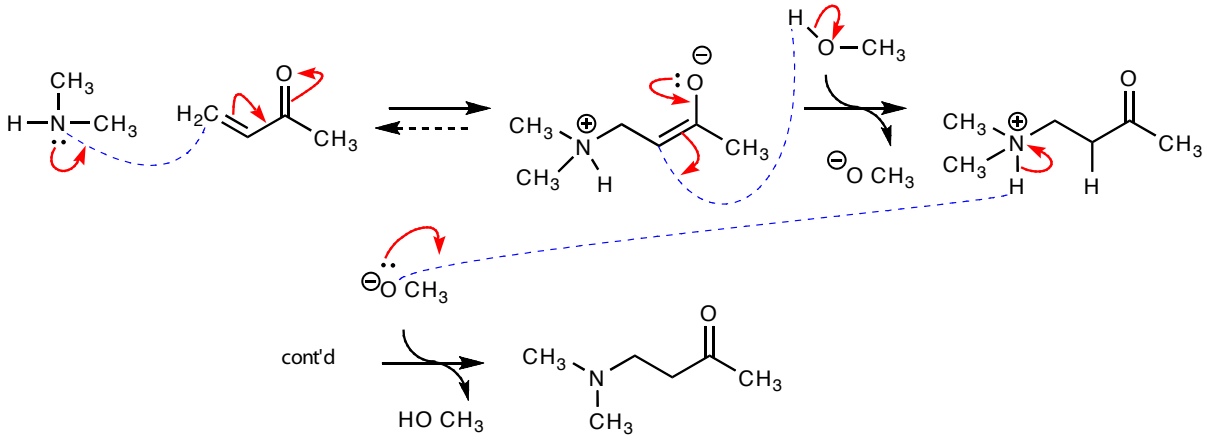


9. Acid catalyzed bromination of acetophenone to give α-bromoacetophenone

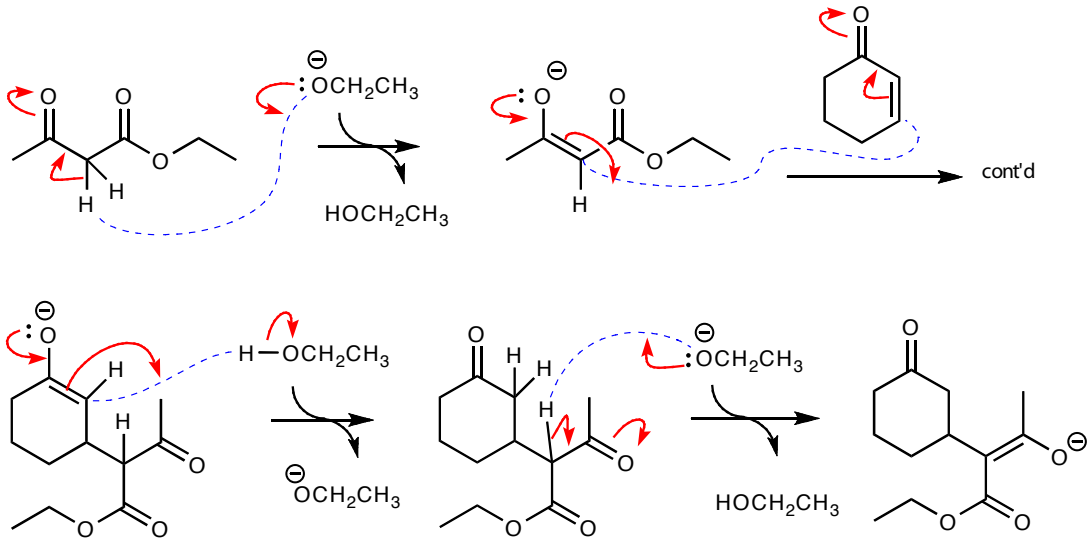


Michael or 1,4-Conjugate Addition Reaction

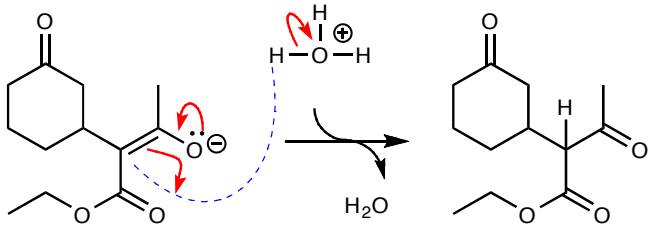
10. Michael addition reaction of dimethylamine to 3-buten-2-one (methyl vinyl ketone – MVK).



11. Michael addition reaction of ethyl acetoacetate to cyclohexenone.

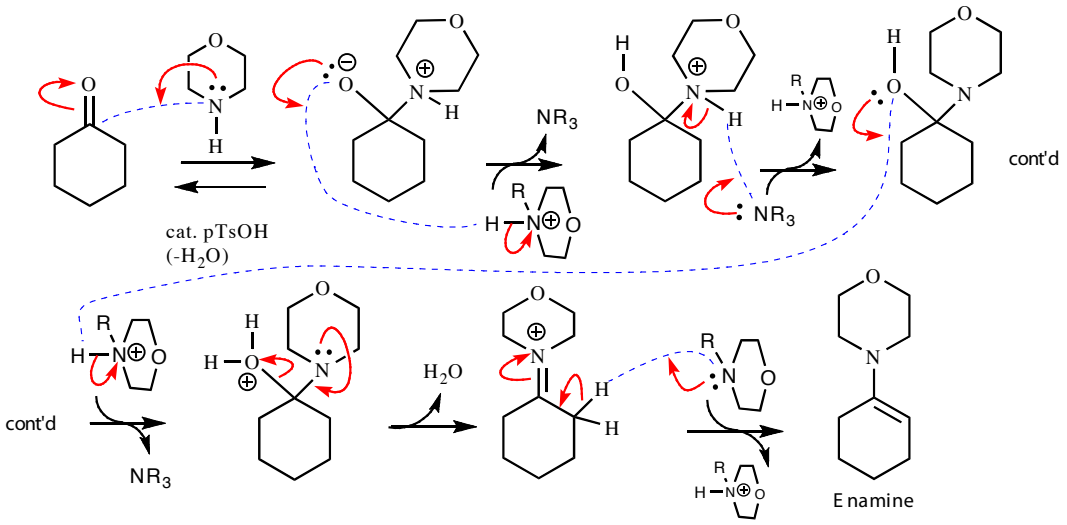


Step 2, neutralization of reaction mixture.

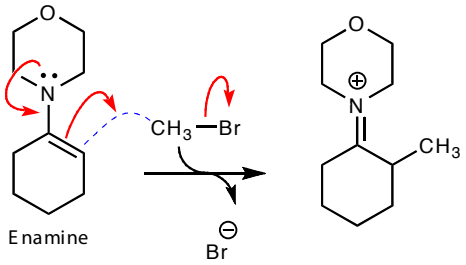


Enamine Alkylation

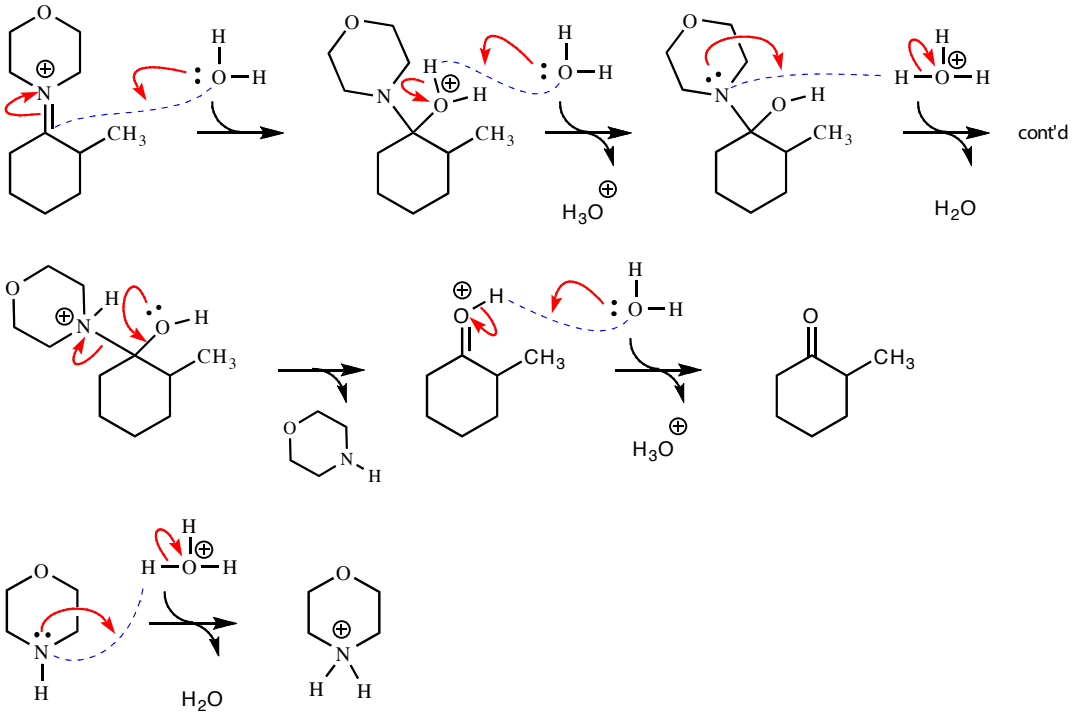
12. Step 1, formation of the morpholine enamine of cyclohexanone.



Step 2, enamine alkylation with methyl iodide.



Step 3, hydrolysis of iminium salt and isolation of substituted cyclohexanone.

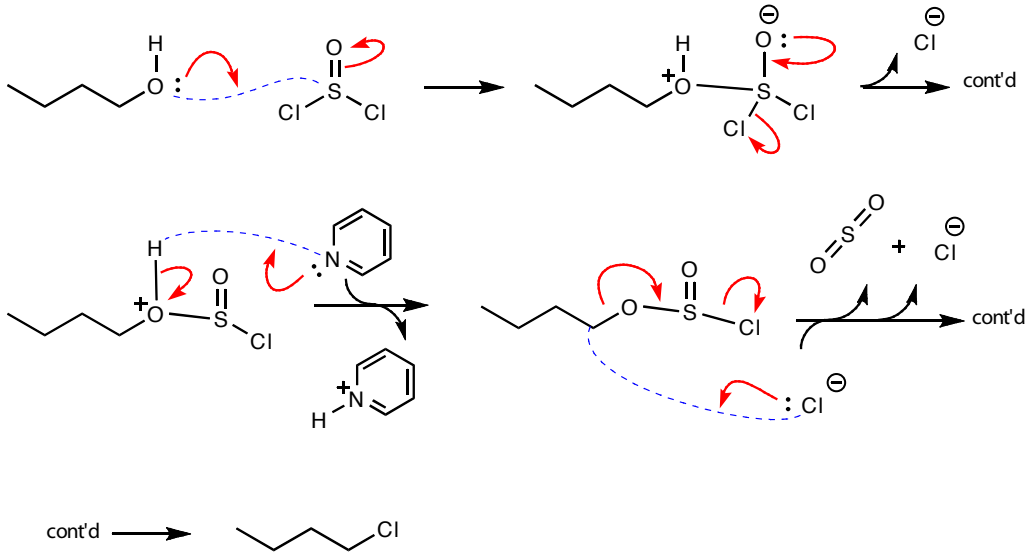


10 — Dehydration Agents

This chapter will deal with reagents that result in a net removal of water in which the oxygen atom becomes absorbed by the reagents. For example, one can perform an S_N2 nucleophilic substitution of an alcohol in the presence of HBr to give an alkyl bromide and water, see Chapter 3. In this chapter, we will see similar reactions, but water will not be formed as the leaving group.

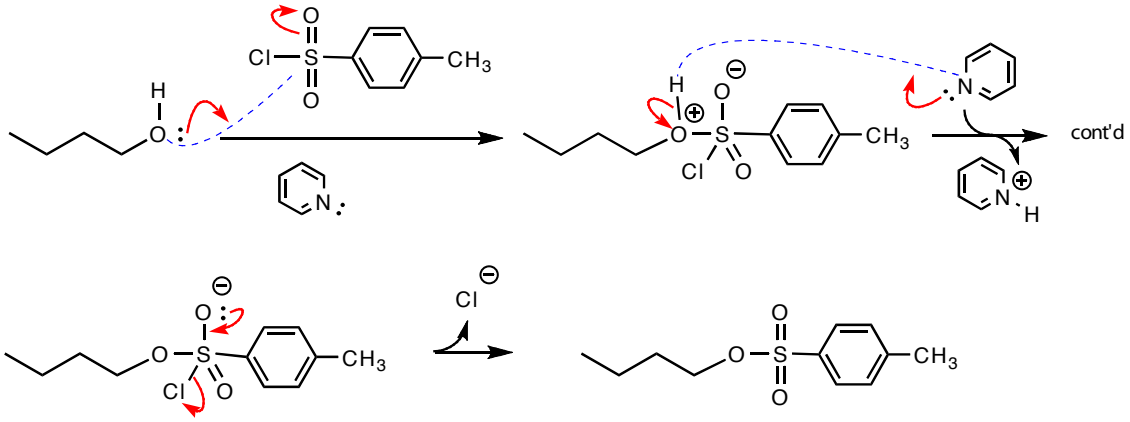
Thionyl Chloride Reaction with an Alcohol

1. S_N2 reaction of thionyl chloride with 1-butanol to give chlorobutane.



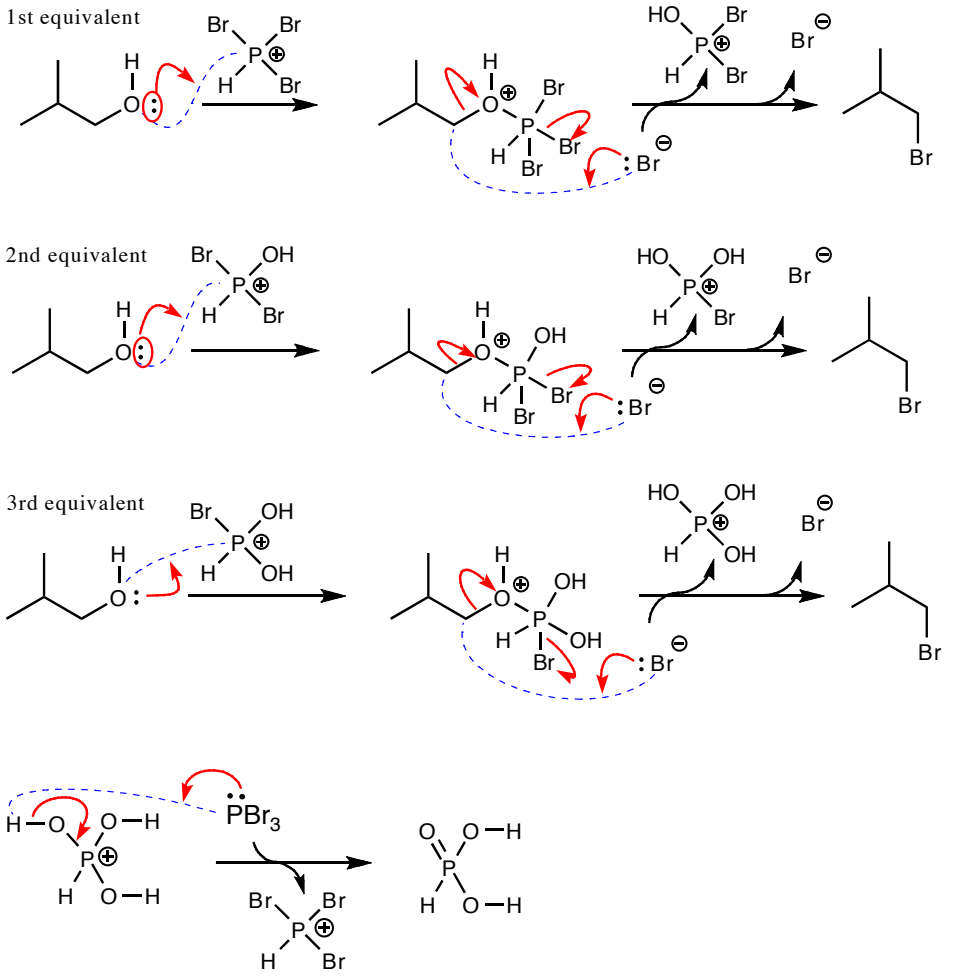
Reaction of Toluenesulfonyl Chloride with an Alcohol

2. Reaction of 1-butanol with tosyl chloride and pyridine to give butyl tosylate. (see Notes)

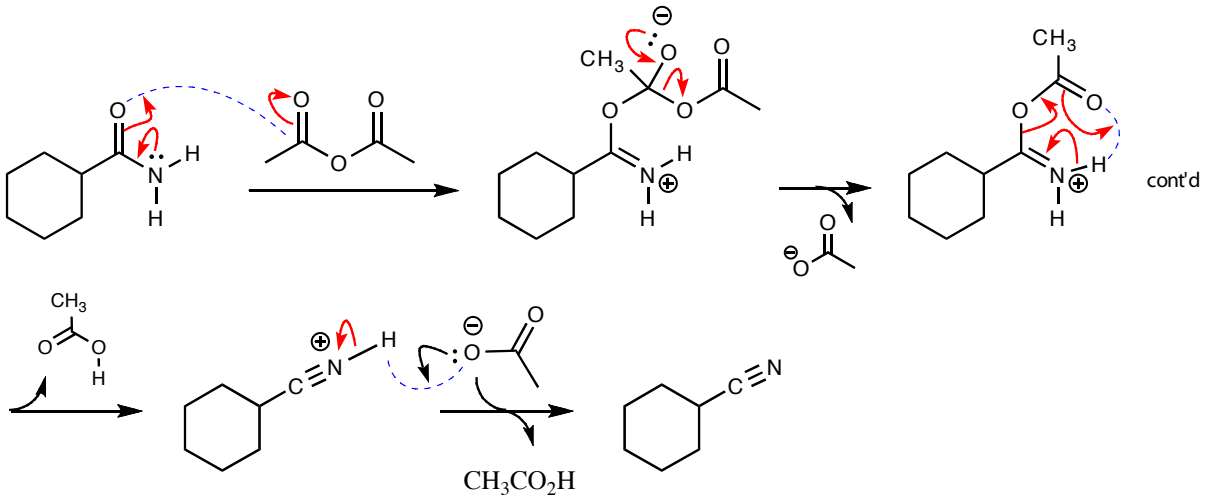


Reaction of Phosphorus Tribromide with an Alcohol

3. Reaction is isobutyl alcohol with phosphorous tribromide to give isobutyl bromide.

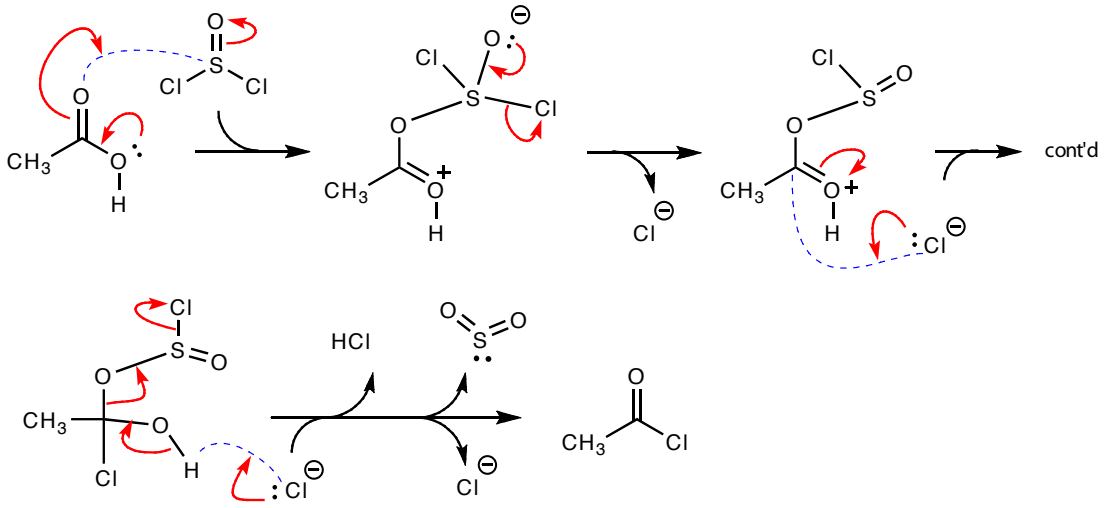


4. Reaction of cyclohexanecarboxamide with acetic anhydride to give cyclohexanecarbonitrile.



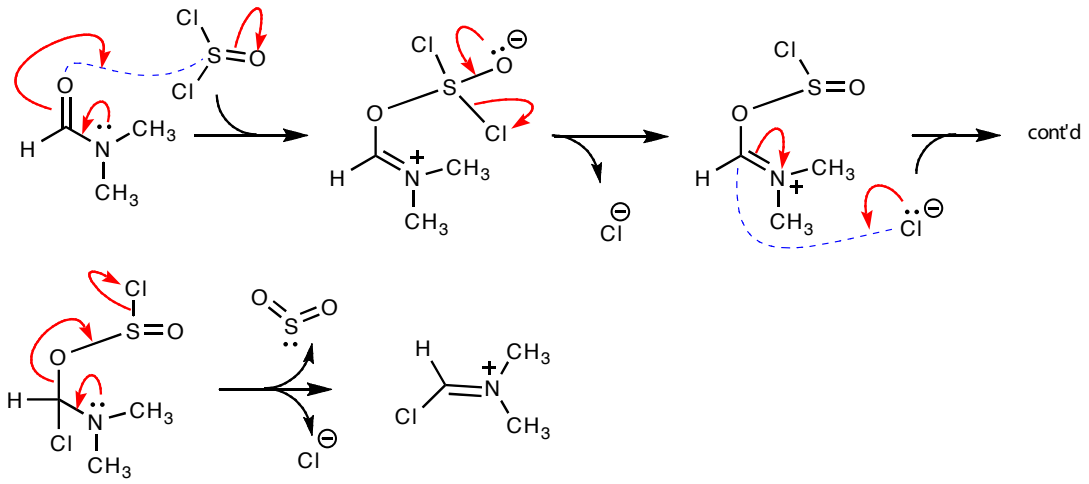
Reaction of a Carboxylic Acid with Thionyl Chloride

5. Conversion of acetic acid to acetyl chloride with thionyl chloride.

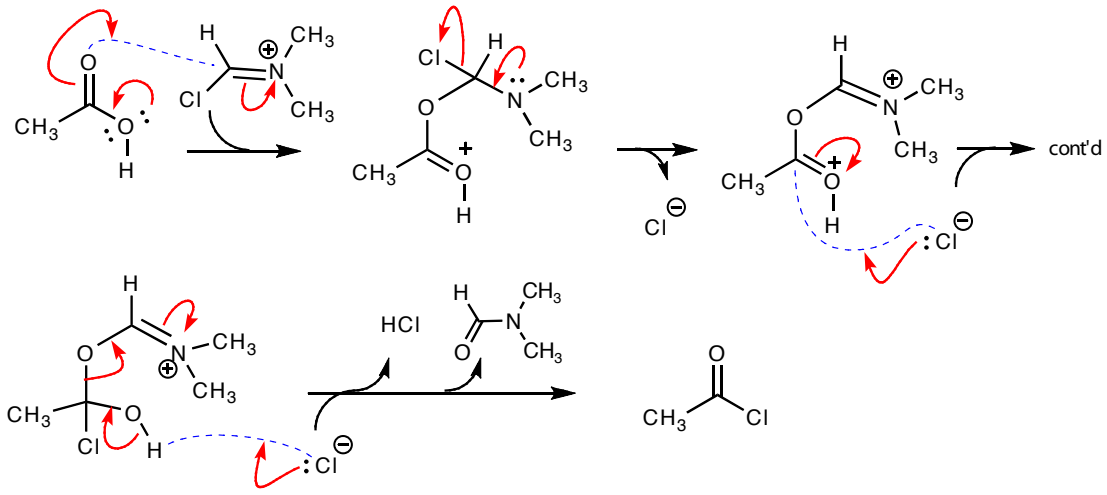


Reaction of a Carboxylic Acid with Thionyl Chloride and DMF as Catalyst

6. Part 1, reaction of thionyl chloride with DMF to form iminium salt



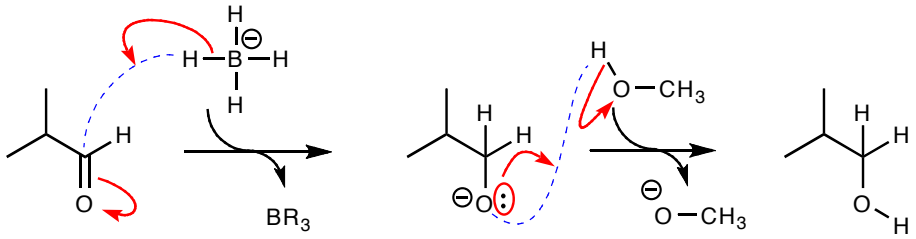
Part 2, reaction of iminium salt with carboxylic acid



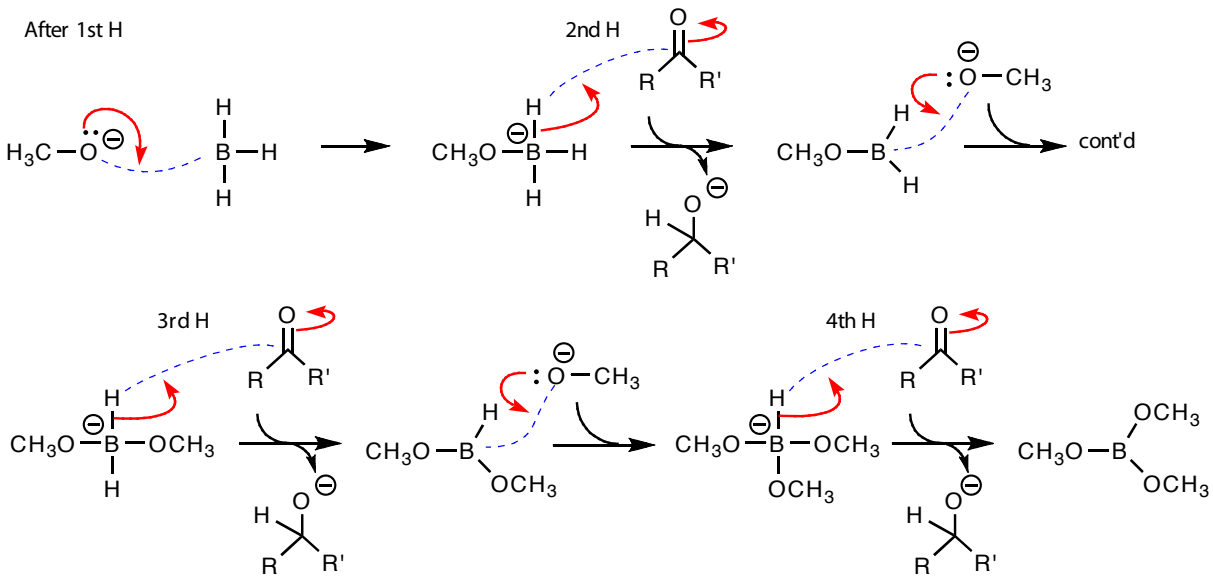
11 — Reduction Reactions

Sodium Borohydride Reductions

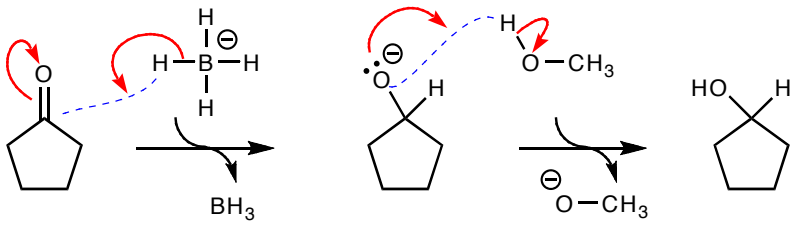
1. Sodium borohydride reduction of 2-methylpropanal (isobutyraldehyde) to 2-methyl-1-propanol (isobutyl alcohol).



The transfer of all hydrogens of borohydride to carbonyl groups in reduction reaction.

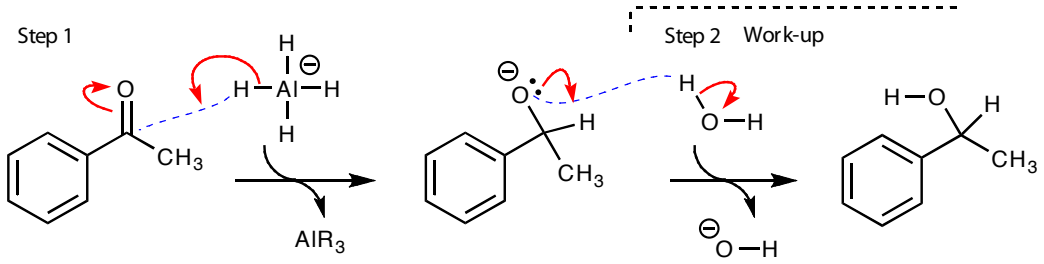


2. Sodium borohydride reduction of cyclopentanone to cyclopentanol.

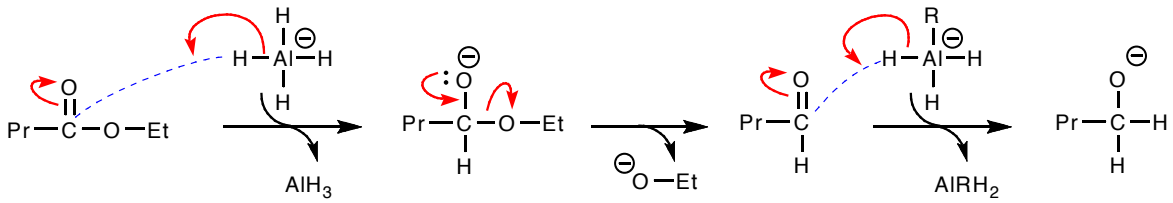


Lithium Aluminum Hydride Reductions

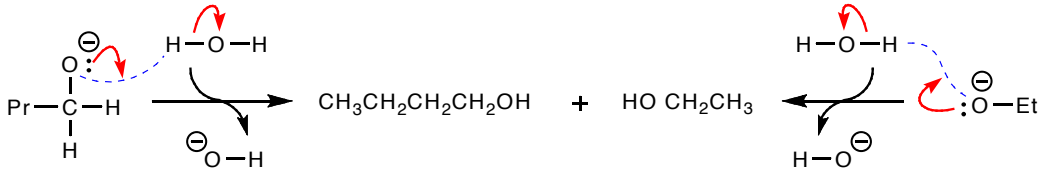
3. Lithium aluminum hydride reduction of acetophenone to 1-phenylethanol.



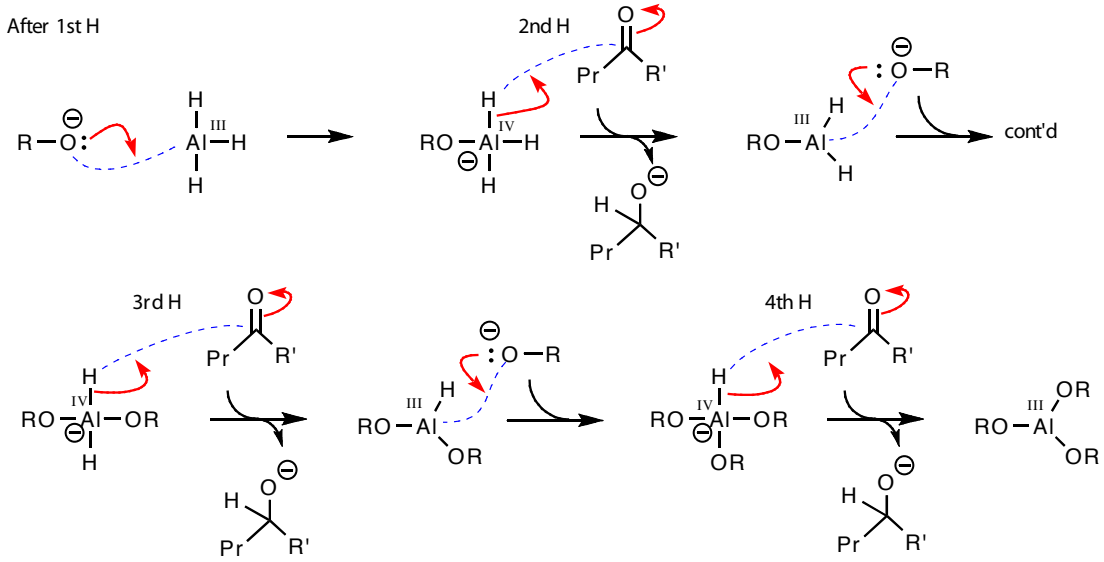
4. Step 1, lithium aluminum hydride of ethyl butanoate (butyrate) to give ethanol and butanol.



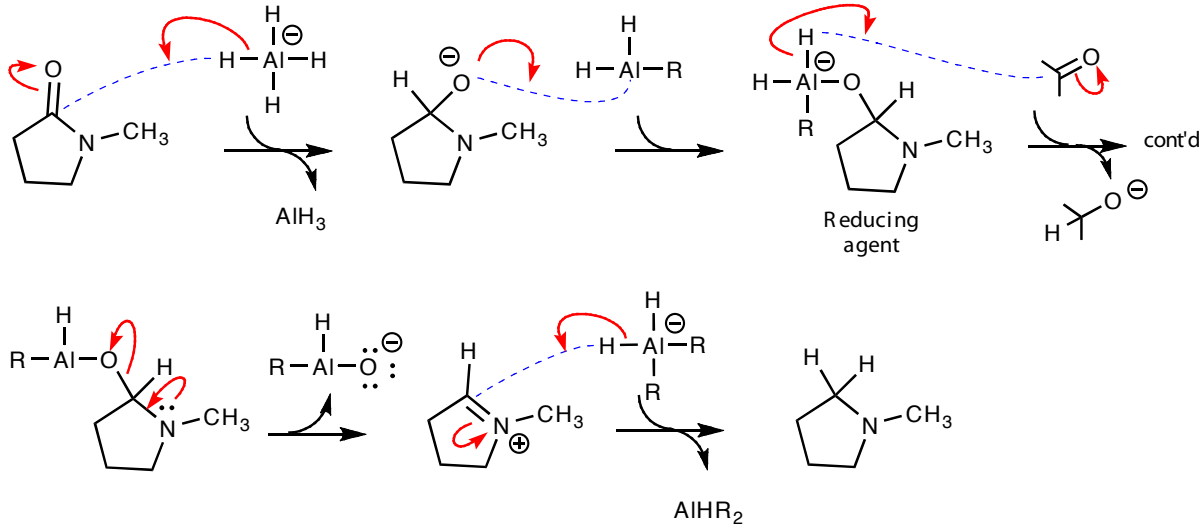
Step 2, quench of reaction mixture and isolation of product.



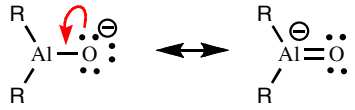
Regeneration of aluminum (IV) reductant to use all four hydrogens of lithium aluminum hydride.



5. Lithium aluminum hydride reduction of ethyl butanoate (butyrate) to give ethanol and butanol. (see Notes) See previous example (5), for regeneration of aluminum (IV) reductant.

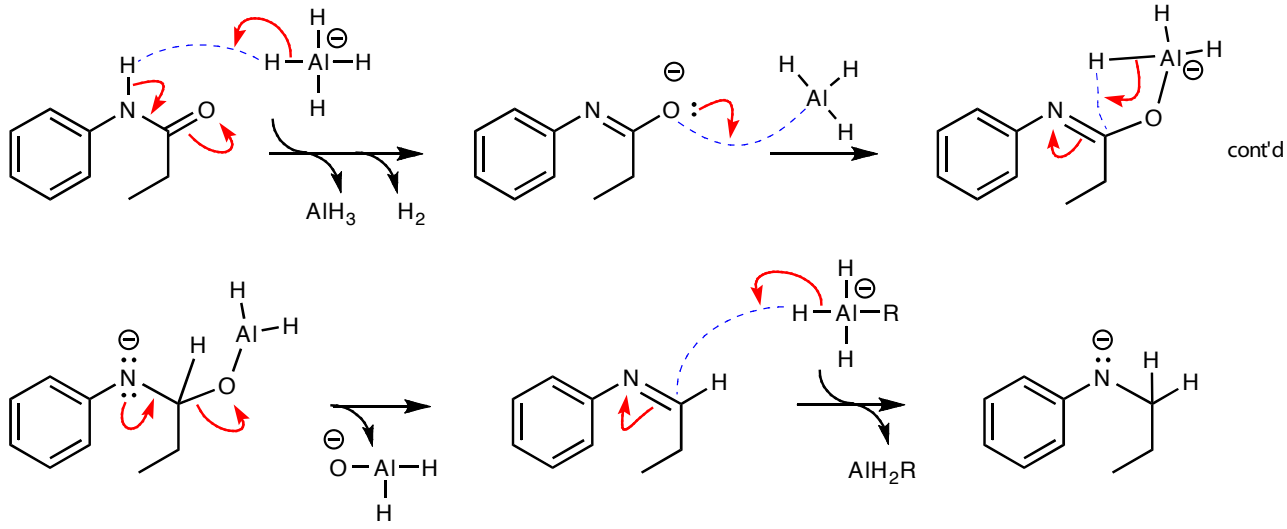


Preferred leaving group for lithium aluminum hydride reductions.

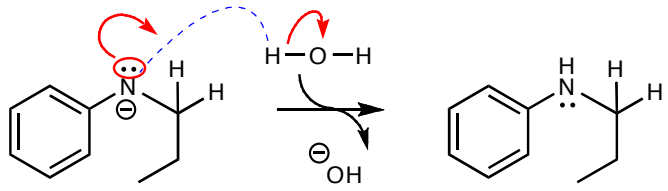


6. Lithium aluminum hydride reduction of propionyl anilide to *N*-propylaniline.

Step 1, reduction.

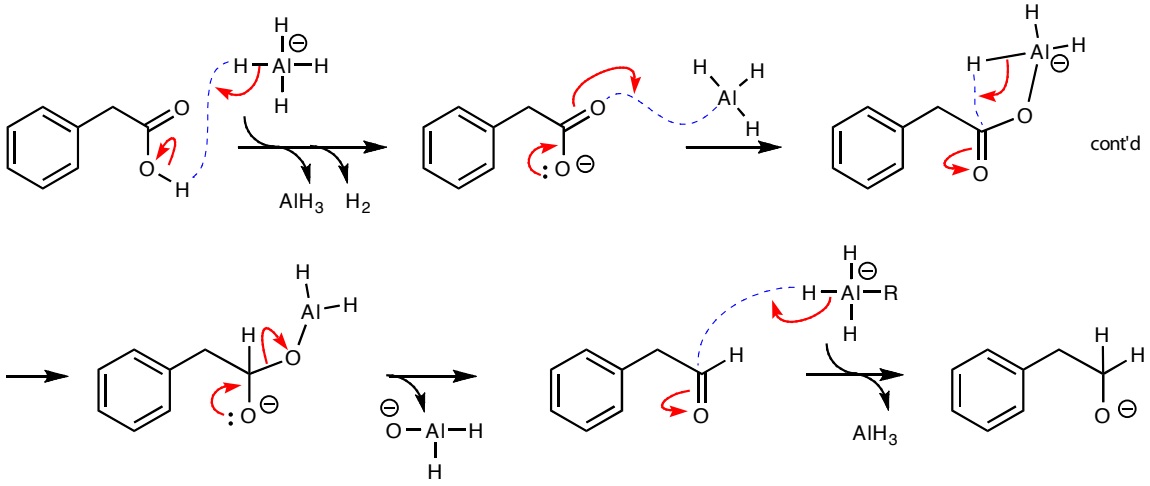


Step 2, work up.

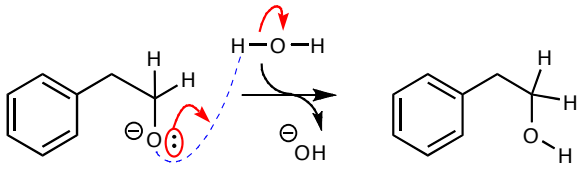


7. Lithium aluminum hydride reduction of phenylacetic acid to 2-phenylethanol. (see Notes)

Step 1, reduction.

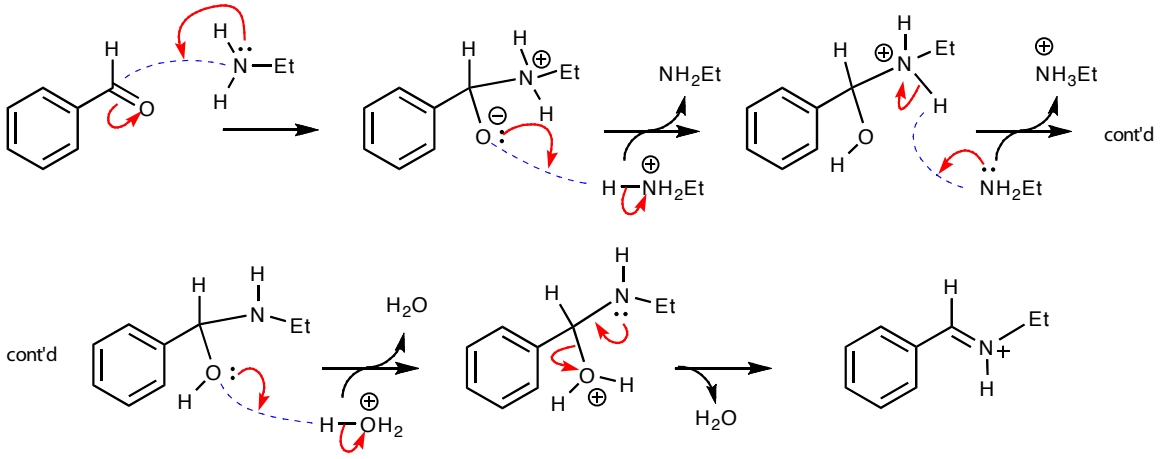


Step 2, work up.

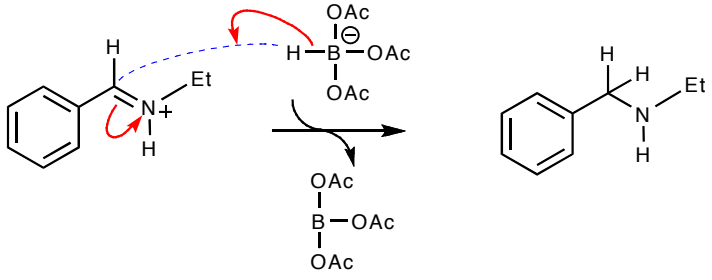


Reductive Amination

8. Step 1, formation of imine from benzaldehyde and ethylamine. (see Notes)



Step 2, reduction

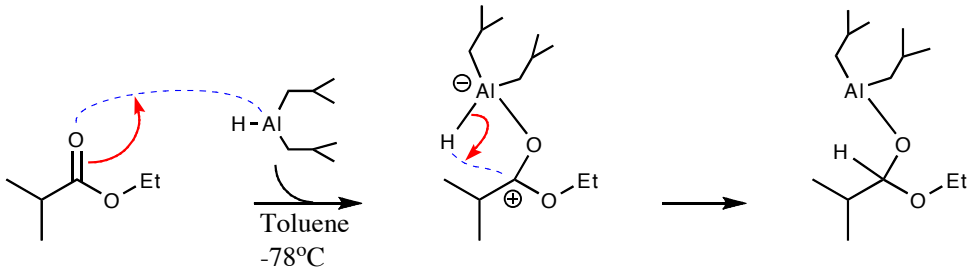


Even though this is written as a two-step process, which it is, both steps can be carried out at the same time. The imine, as it forms, can be reduced.

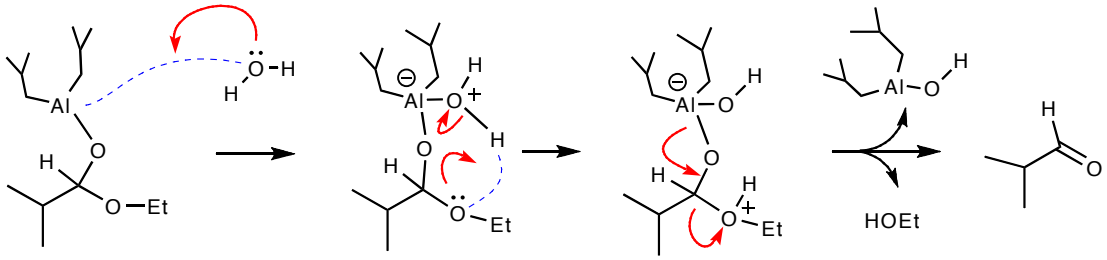
Triacetoxyborohydride is one of several reagents that one can use. Others are sodium cyano-borohydride ($NaBH_3CN$) or hydrogen with a palladium or nickel catalyst.

Diisobutylaluminum Hydride Reduction of an Ester

9. Step 1, addition of DIBAH or DIBAL(H) (diisobutylaluminum hydride) to ethyl isobutyrate. Reduction to give isobutyraldehyde (2-methylpropanal).



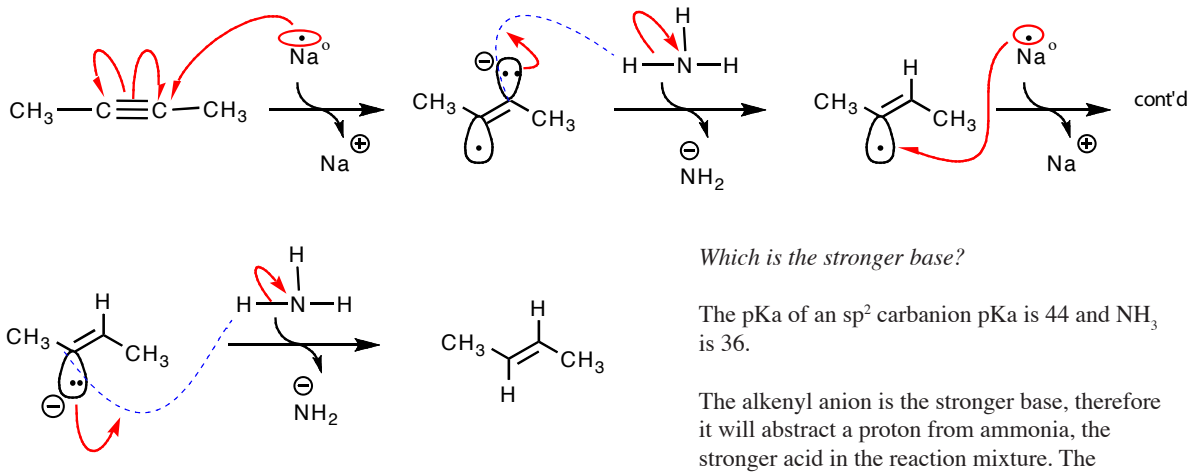
Step 2, work-up



Reduction of alkyne with sodium ammonia

10. Sodium and ammonia *trans*-reduction of 2-butyne to *trans*-2-butene.

Note, use a single barbed arrow for one-electron transfers reaction.



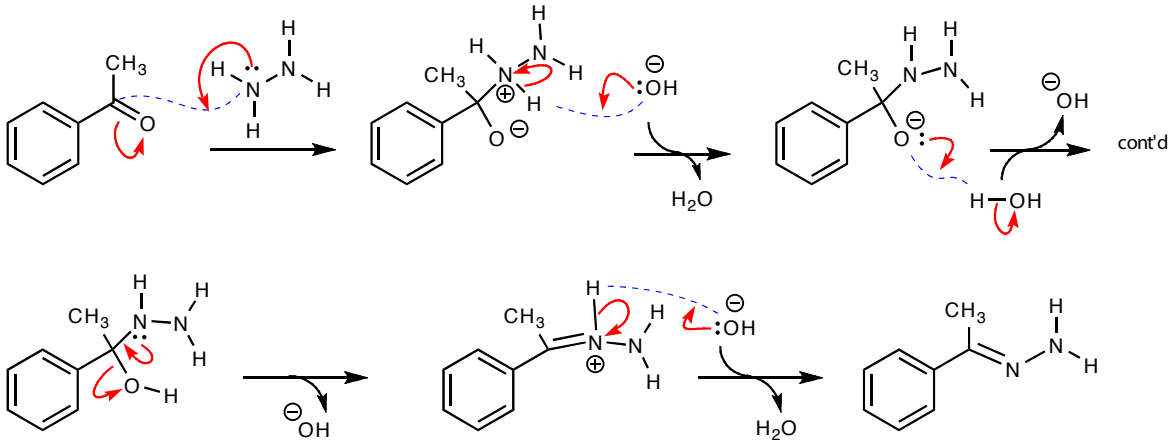
Which is the stronger base?

The pKa of an sp^2 carbanion pKa is 44 and NH_3 is 36.

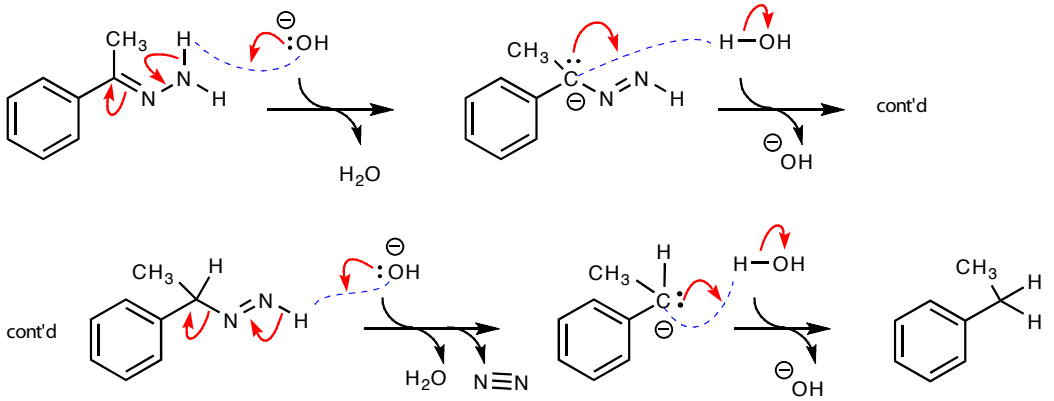
The alkenyl anion is the stronger base, therefore it will abstract a proton from ammonia, the stronger acid in the reaction mixture. The equilibrium favors formation of sodium amide as the conjugate base.

Wolff Kischner reduction

11. Reaction of the ketone with hydrazine under basic conditions to form the hydrazide.



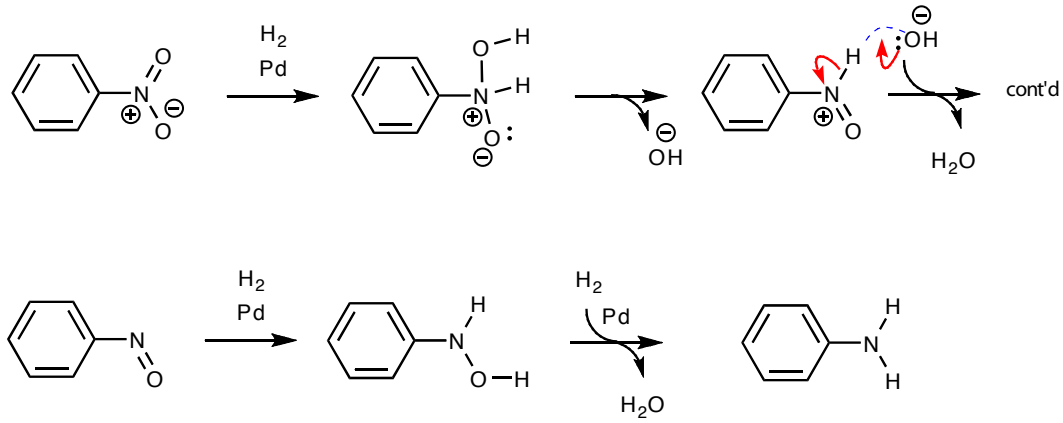
Reaction of the *in situ* formed hydrazide with KOH to form the methylene.



Catalytic Reduction of Nitrobenzene

Catalytic reduction of nitrobenzene to aniline. This isn't a mechanism. It shows that hydrogen can add across N-O single and double bonds. It is a very facile reduction. One can see that the oxygen atoms form water and the reduction takes three moles of hydrogen.

12. Catalytic reduction of nitrobenzene to aniline.



12 — Oxidation Reactions

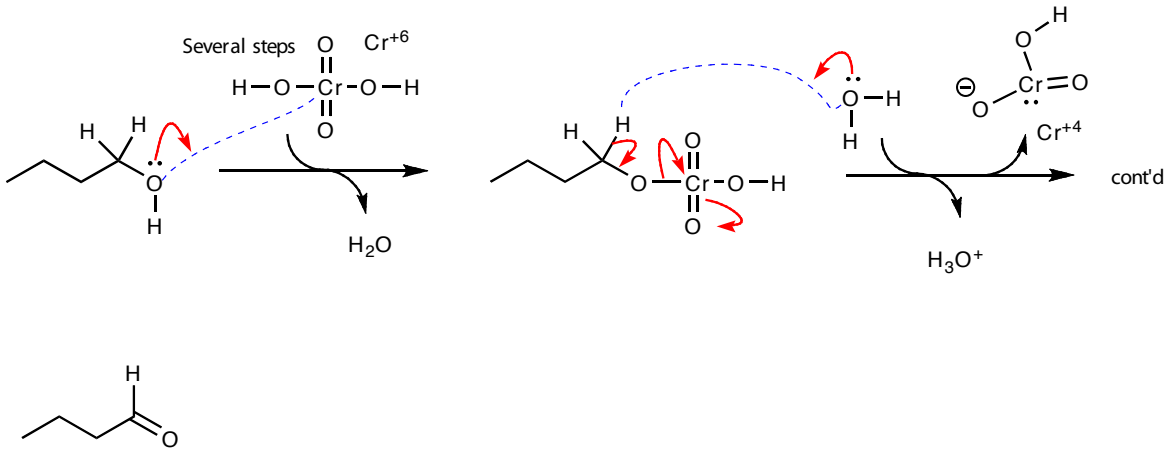
General Form For Oxidations

See Notes for further discussion of oxidation reactions.

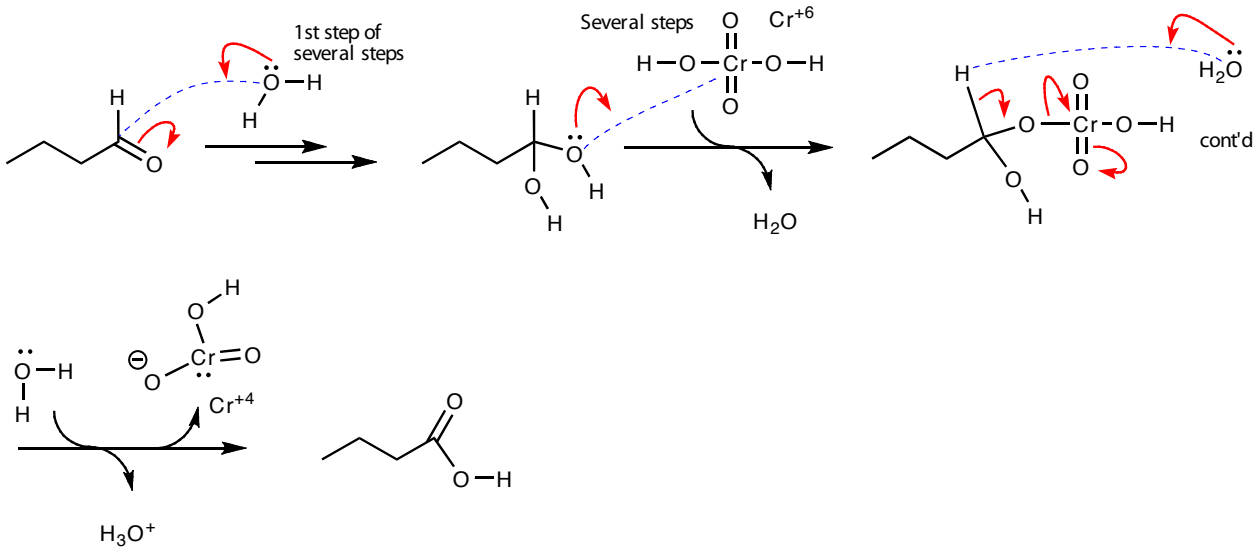
Chromic Acid Oxidation

1. Chromic acid oxidation of 1-butanol to butanoic acid.

   Step 1, form chromate ester and oxidize to aldehyde

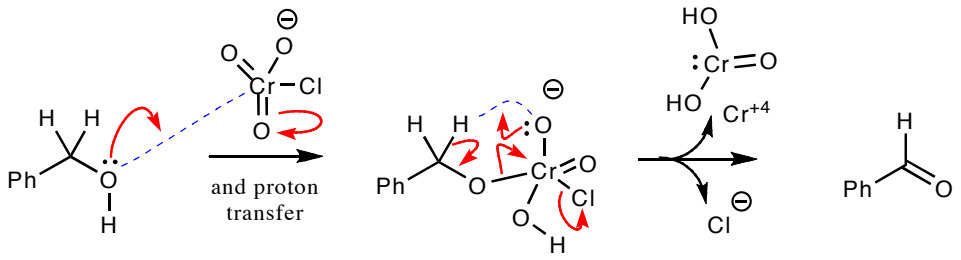


   Step 2, hydration of aldehyde and oxidation of hydrate to butanoic acid (butyric acid).



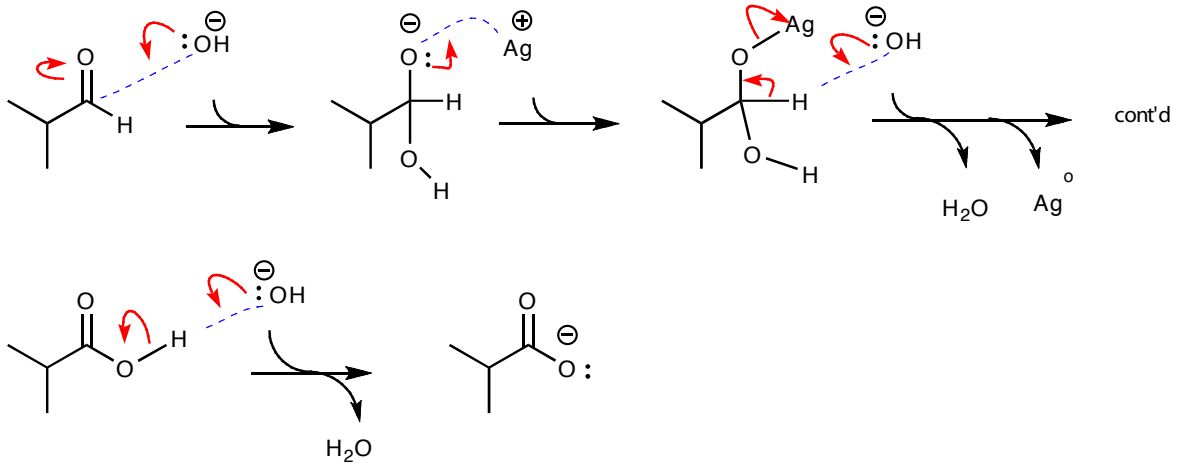
Pyridinium Chlorochromate Oxidation

2. Pyridinium chlorochromate oxidation of benzyl alcohol to benzaldehyde.

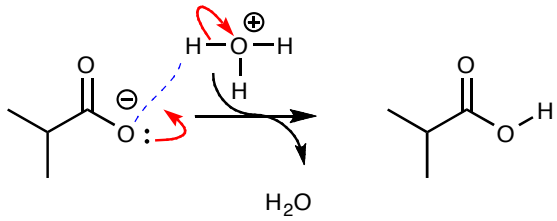


Tollens Oxidation

3. Step 1, oxidation of 2-methylpropanl (isobutyraldehyde) with silver oxide (or hydroxide).

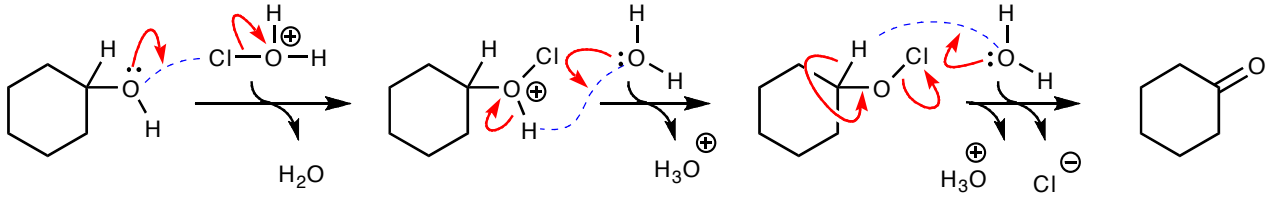


Step 2, acidification and isolation of 2-methylpropanoic acid (isobutyric acid).



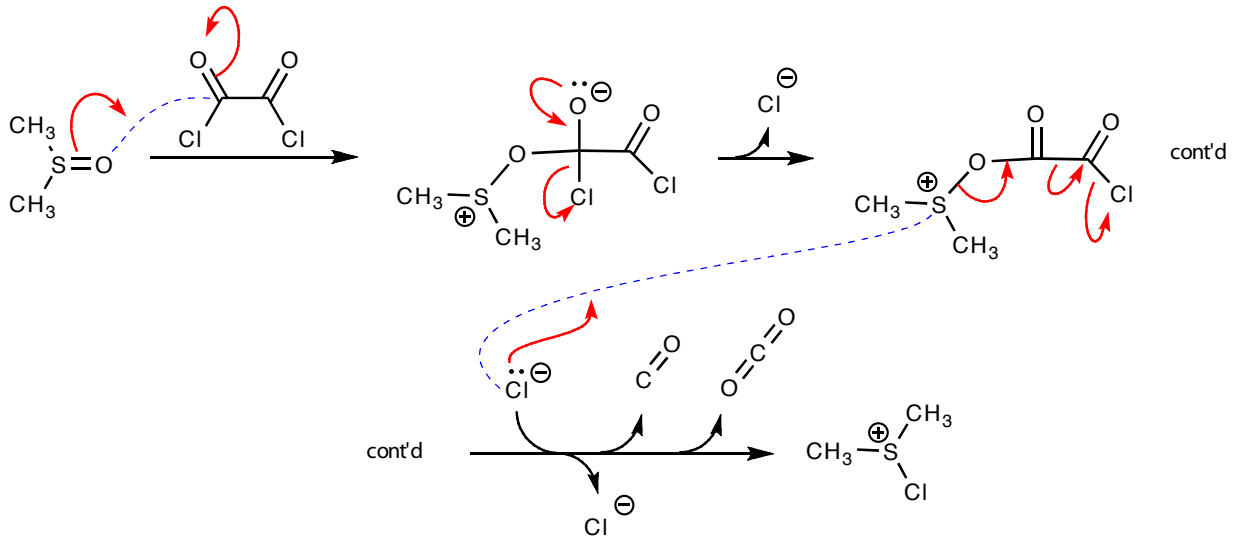
Hypochlorite Oxidation

4. Oxidation of cyclohexanol to cyclohexanone with sodium hypochlorite (NaOCl, bleach).

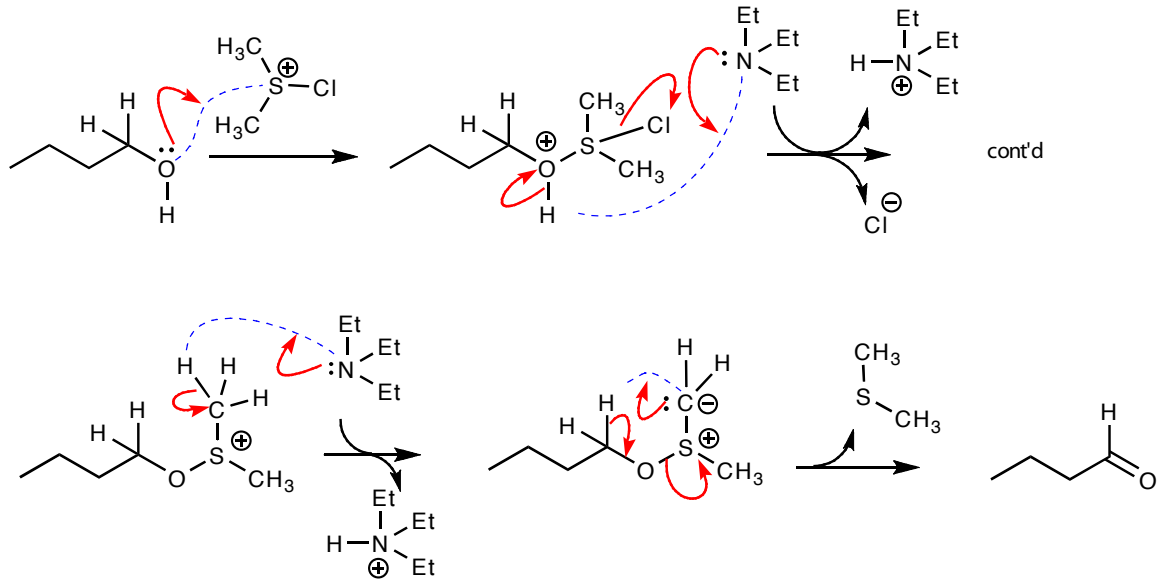


Swern Oxidation

5. Step 1, Swern oxidation, preparation of chlorosulfonium salt

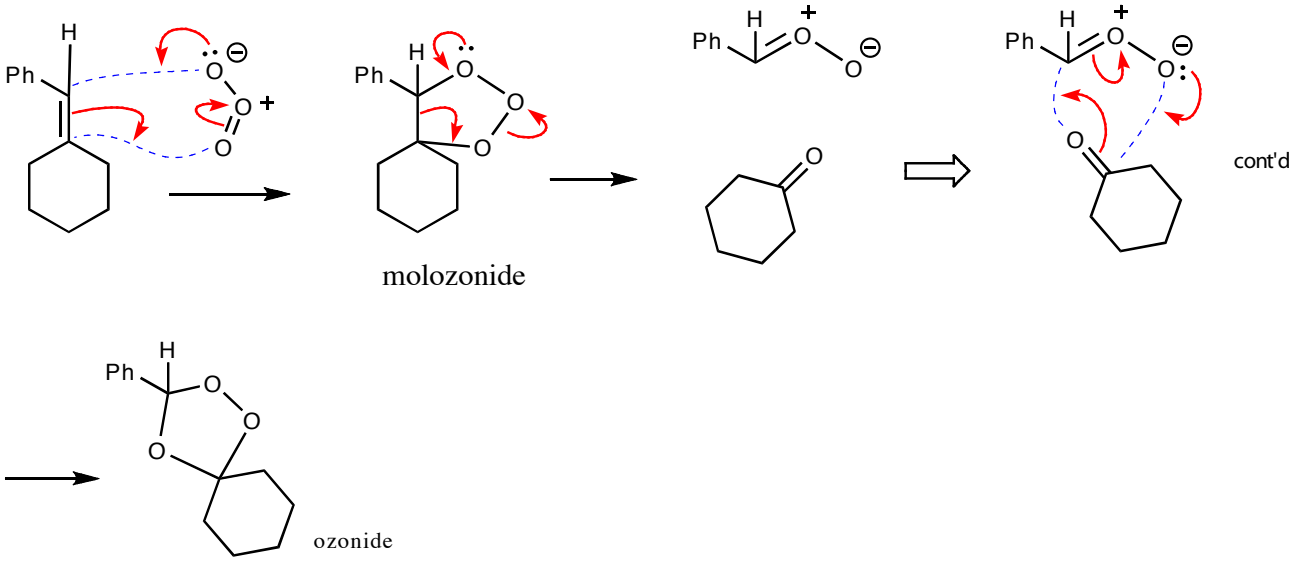


Step 2, Swern oxidation, oxidation step

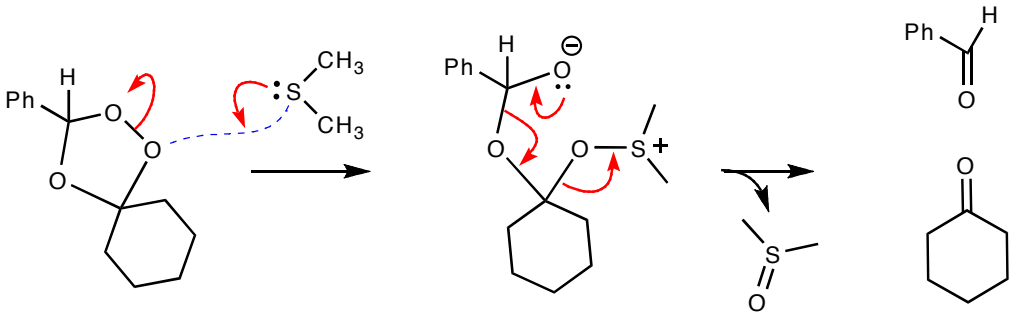


Ozone Oxidation

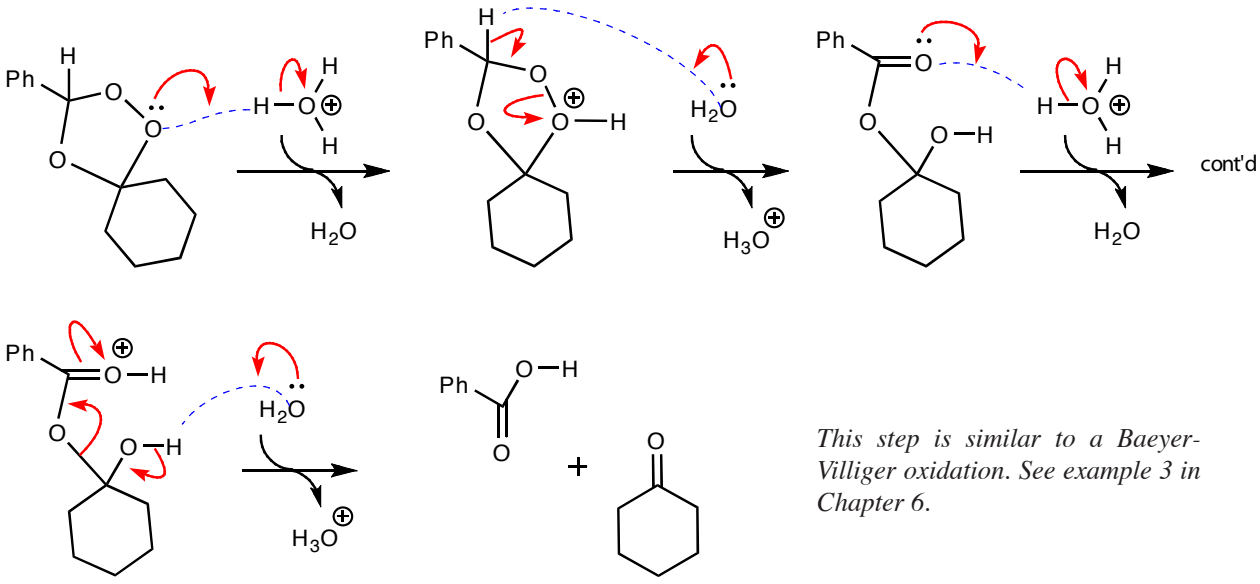
6. Step 1, ozone reaction with an alkene to give an ozonide.



Step 2, reduction of ozonide to two carbonyl compounds.



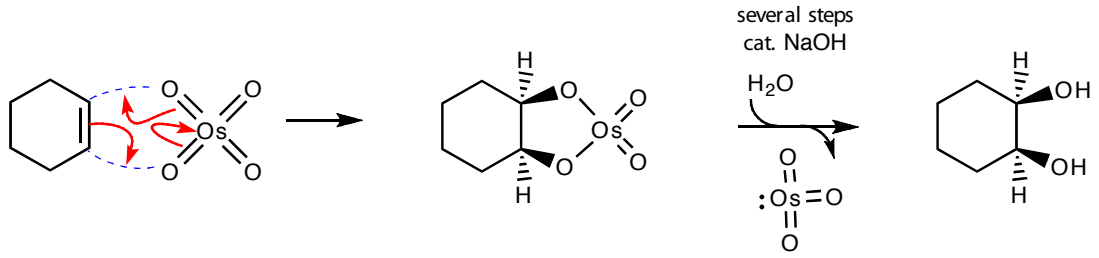
Alternate step 2, oxidative destruction of ozonide.



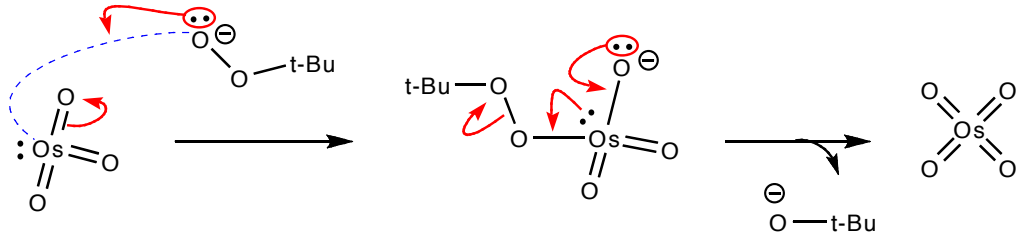
This step is similar to a Baeyer-Villiger oxidation. See example 3 in Chapter 6.

Osmium Tetroxide, Potassium Permanganate, and Periodate Oxidations

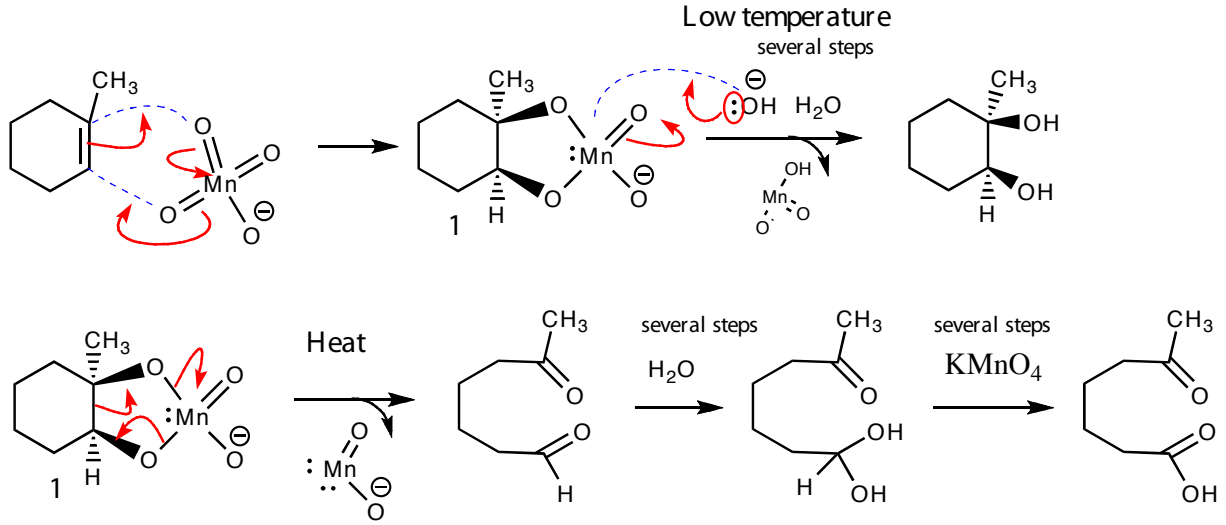
7. Osmium tetroxide oxidation of cyclohexene to give *cis*-1,2-cyclohexanediol



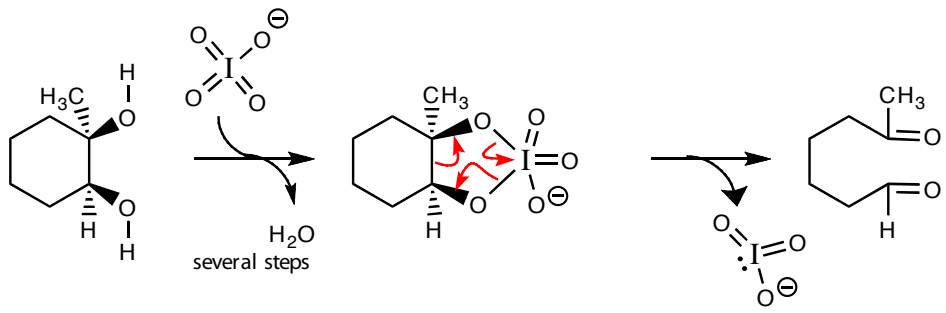
Regeneration of oxidant with *tert*-butylperoxide.



8. Potassium permanganate oxidation of methylcyclohexene to 1-methylcyclohexane-1,2-diol at low temperature or cleavage at high temperature.



9. Periodate cleavage of a 1,2-diol to give a dicarbonyl compound.

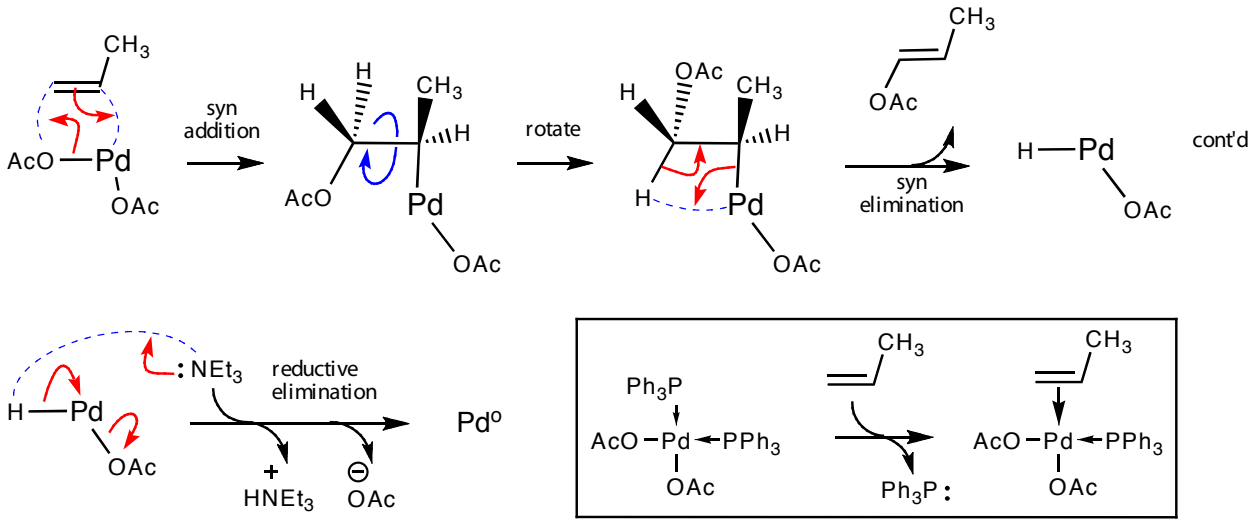


13 — Organometallic Reactions

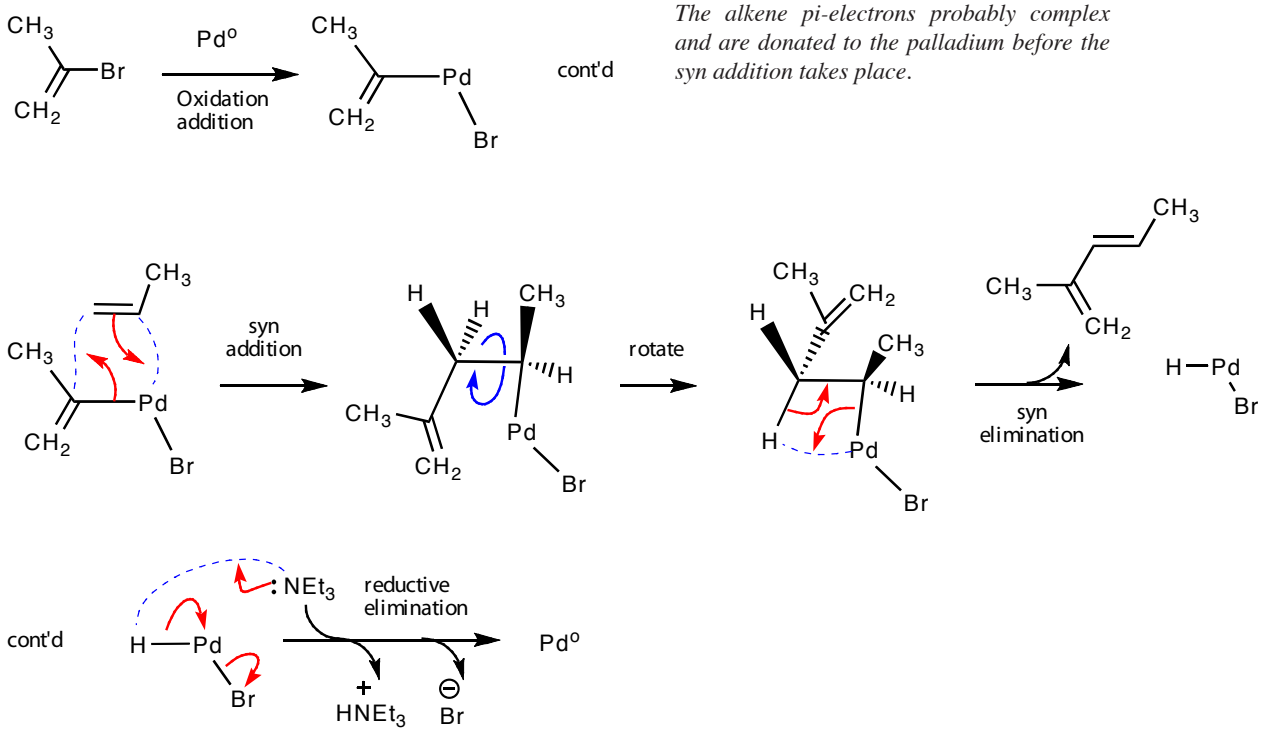
The (transition) organometallic reactions in this chapter of are of increasing importance. The reactions included recount the steps more than the actual mechanisms. Significantly absent are the concept of 18 valence electrons about the catalytic palladium atom.

Acyclic Heck Reaction

1. Step 1, reduction of palladium (II) to zero valent palladium with propene.

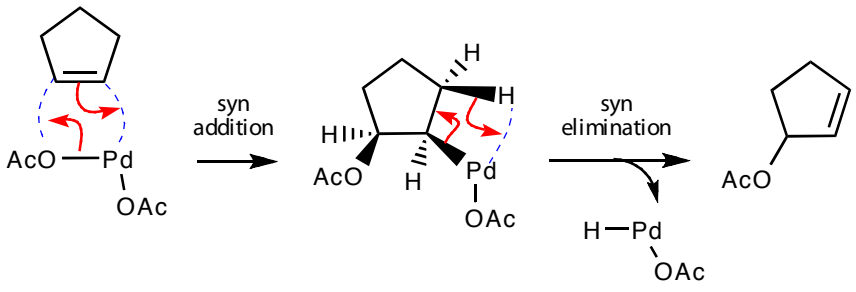


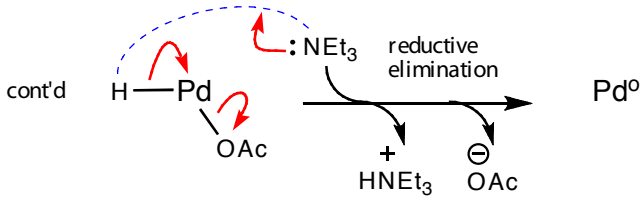
Step 2, the catalytic cycle (oxidative addition, syn addition, syn elimination, and reductive elimination) with 2-bromopropene and propene.



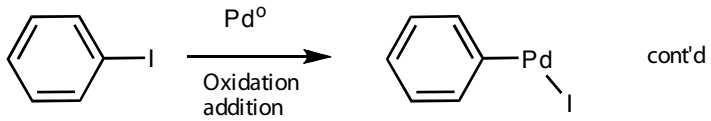
Cyclic Heck Reaction

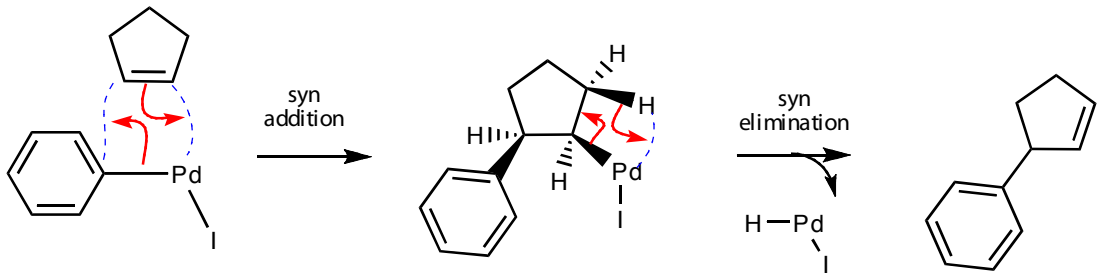
2. Step 1, reduction of palladium (II) to zero valent palladium with cyclopentene.

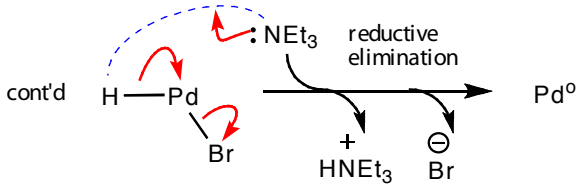




Step 2, the catalytic cycle (oxidative addition-syn addition-syn elimination-reductive elimination) with iodobenzene and cyclopentene.

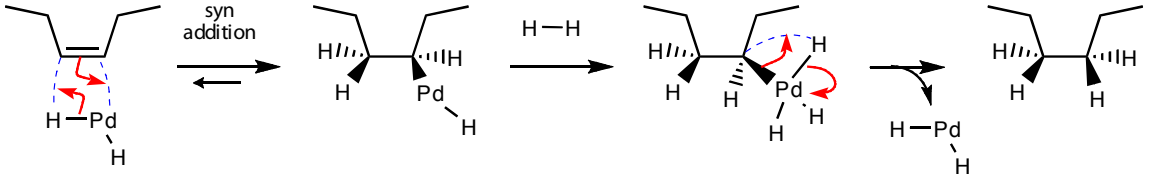




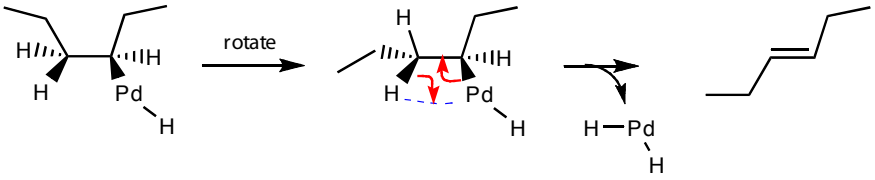


Catalytic Reduction of an Alkene

3. Catalytic hydrogenation of *cis*-3-hexene to hexane.

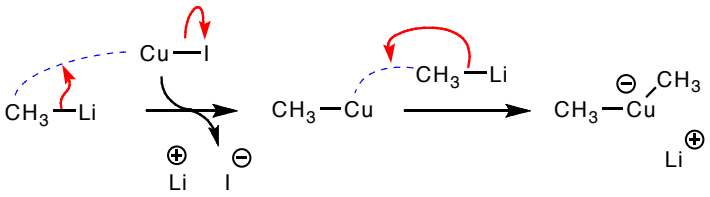


If there isn't enough hydrogen to complex with the palladium, then the *cis*-addition can reverse. If you started with a *cis*-alkene, you would end up with the *trans*. This is how *trans*-fatty acids are formed in vegetable oils.

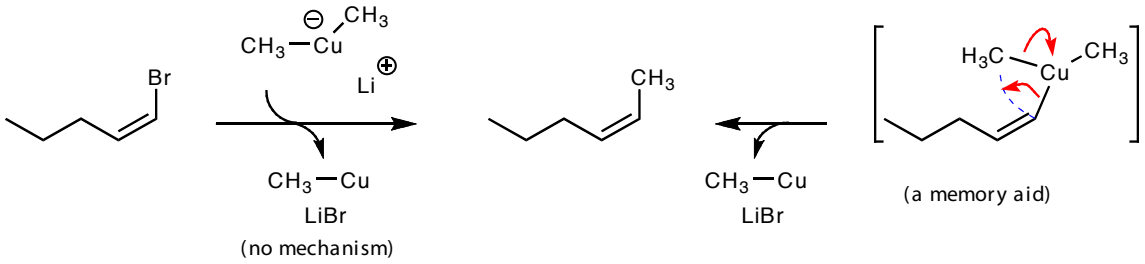


Gilman Reagent

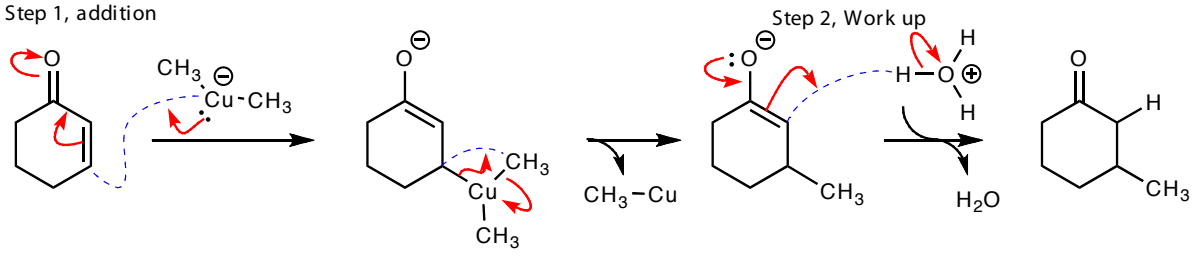
4. Formation of Gilman reagent, lithium dimethylcuprate.



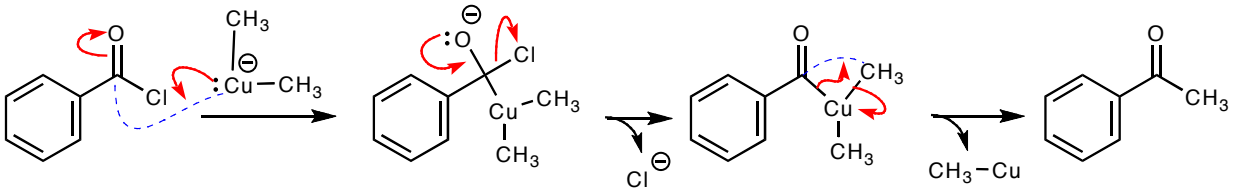
Coupling of Gilman reagent, lithium dimethylcuprate with *Z*-1-bromopent-1-ene to give *cis*-2-hexene. (see Notes)



5. A 1,4-conjugate addition of lithium dimethylcuprate to 2-cyclohexenone to give 3-methylcyclohexanone.



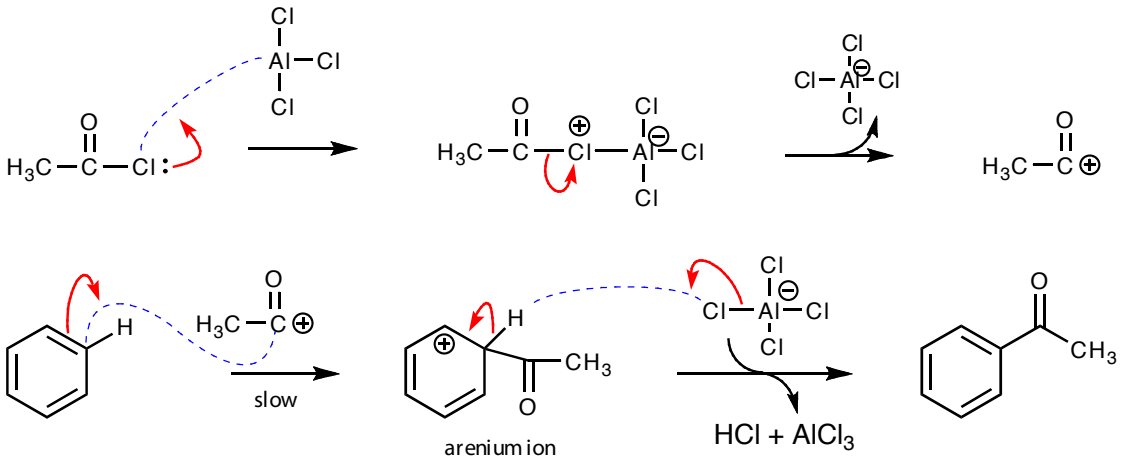
6. Reaction of lithium dimethylcuprate to benzoyl chloride to give acetophenone.



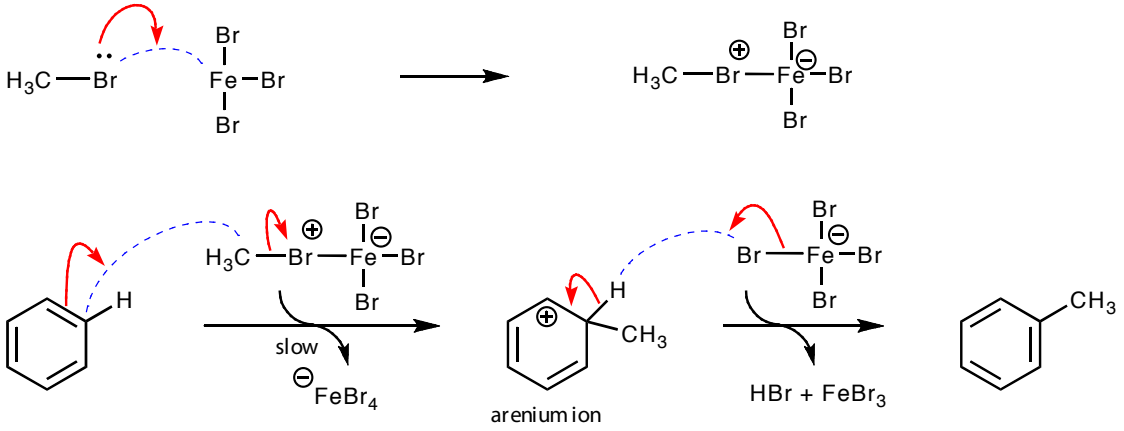
14 — Aromatic Substitution Reactions

Electrophilic Aromatic Substitution

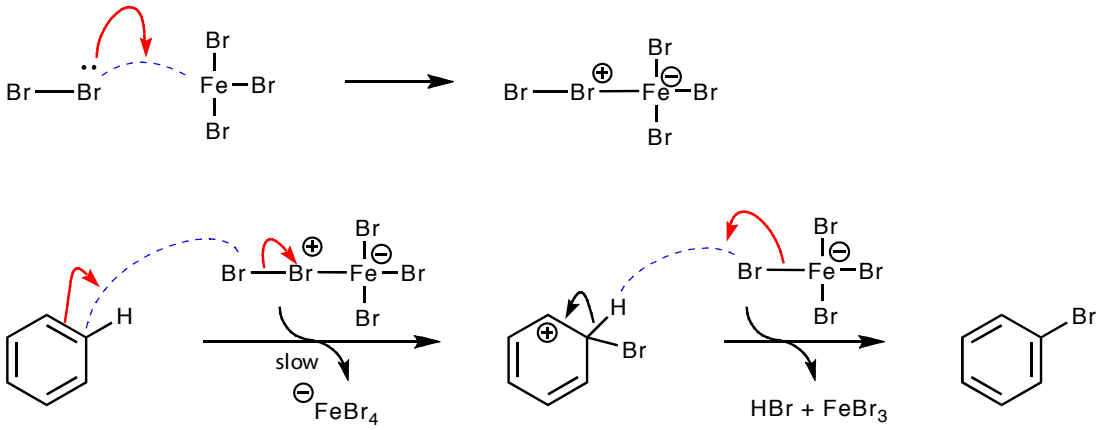
1. Friedel Crafts acylation of benzene



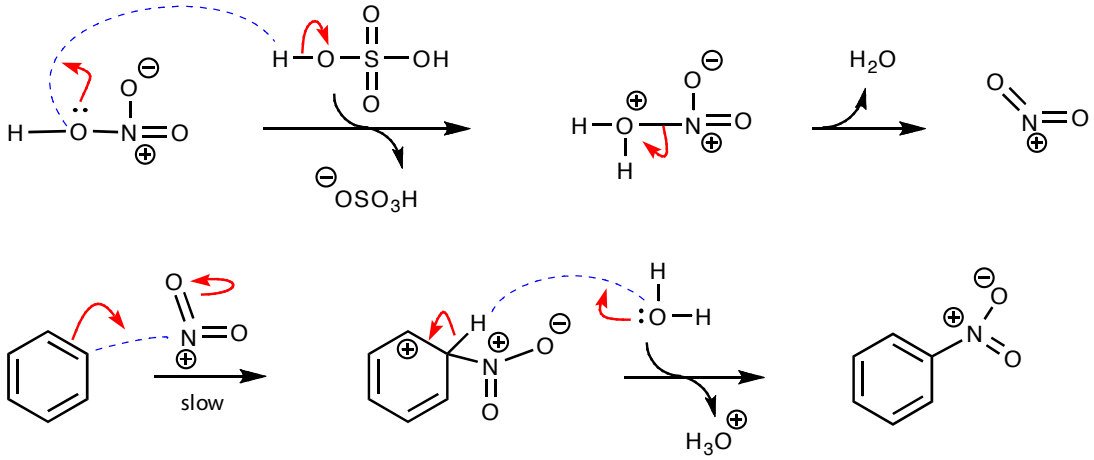
2. Friedel Crafts alkylation of benzene



3. Ferric bromide bromination of benzene



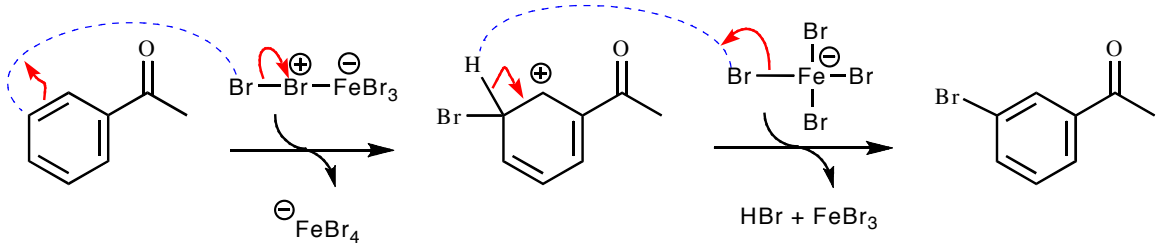
4. Nitration of benzene with nitric and sulfuric acids.



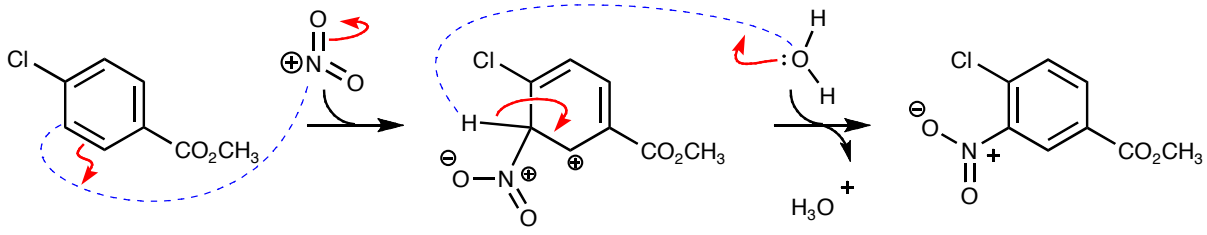
Electrophilic Substitution of Substituted Aromatic Compounds

5. Bromination of acetophenone to give *m*-bromoacetophenone.

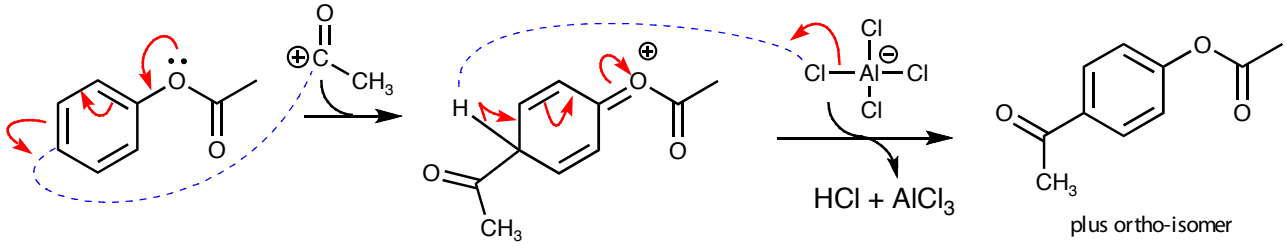
(For 5, 6, and 7, also answer the question, "Will it react faster than benzene?")



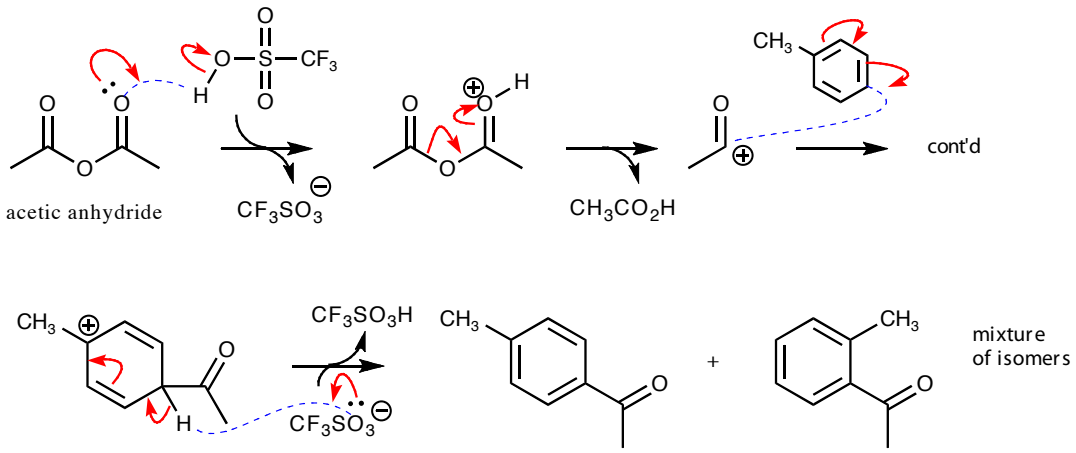
6. Nitration of methyl *p*-chlorobenzoate to give methyl 4-chloro-3-nitrobenzoate.



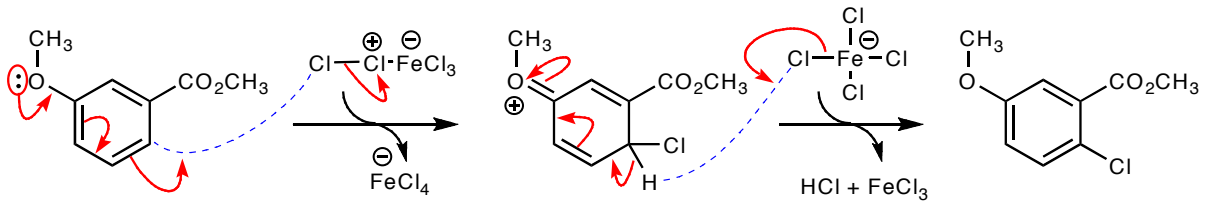
7. Friedel-Crafts acylation of phenyl acetate with acetyl chloride and aluminum chloride.



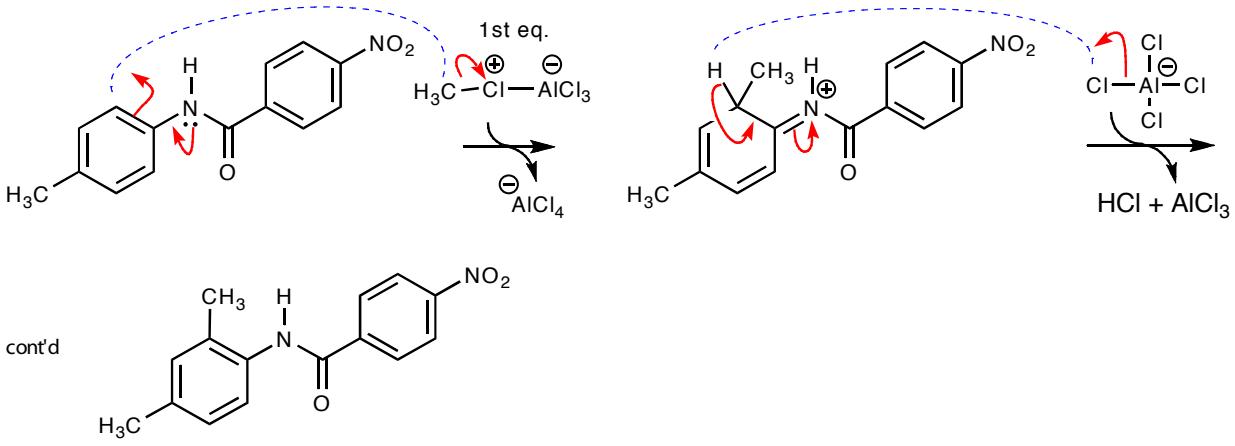
8. Triflic acid catalyzed acetylation of toluene to give *o*- and *p*-methylacetophenone.



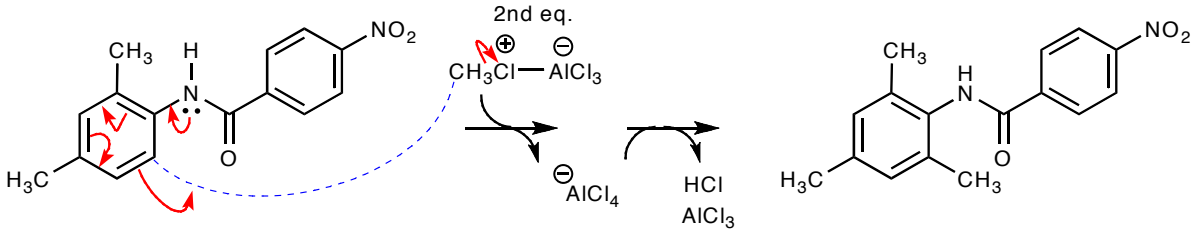
9. Aluminum chloride catalyzed chlorination of methyl 3-methoxybenzoate (methyl *m*-anisate) to give methyl 2-chloro-5-methoxybenzoate.



10. Friedel-Crafts alkylation of 4-nitro-*N*-*p*-tolylbenzamide with two equivalents of iodomethane. (see Notes)

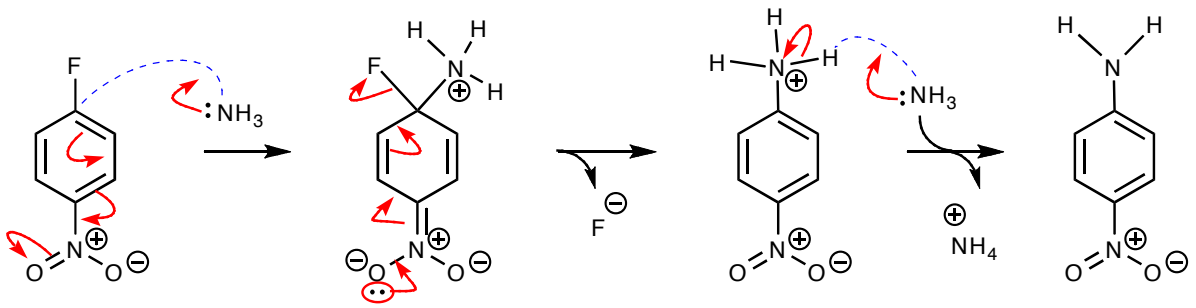


Reaction of the second equivalent of chloromethane and aluminum chloride.

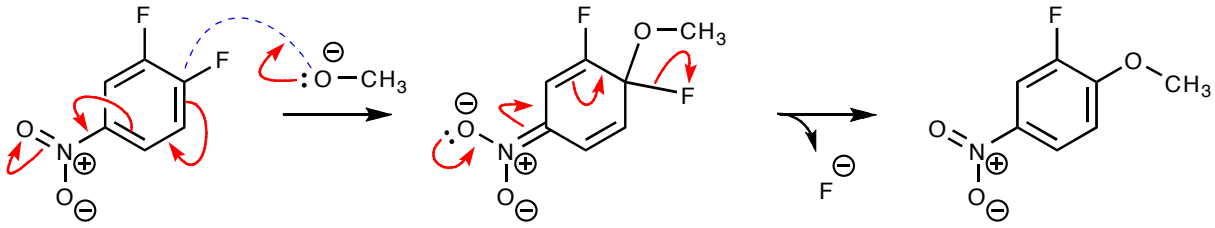


Nucleophilic Aromatic Substitution

11. Nucleophilic aromatic substitution of 1-fluoro-4-nitrobenzene with ammonia to give 4-nitroaniline.

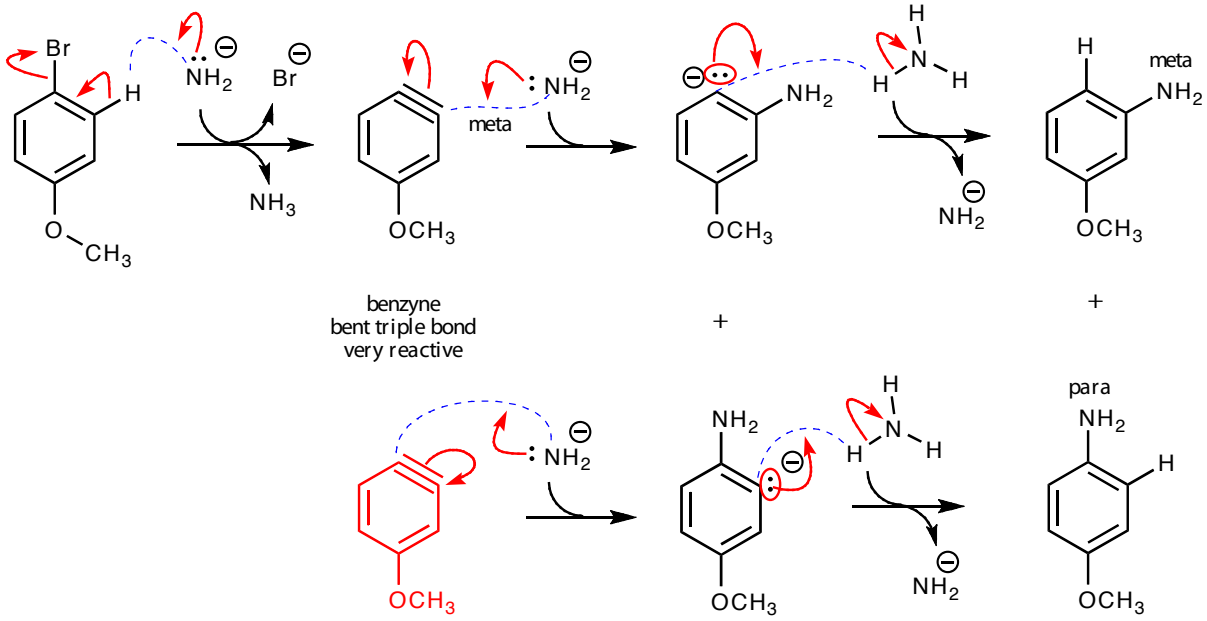


12. Nucleophilic aromatic substitution of 1,2-difluoro-4-nitrobenzene with sodium methoxide to give 2-fluoro-1-methoxy-4-nitrobenzene.



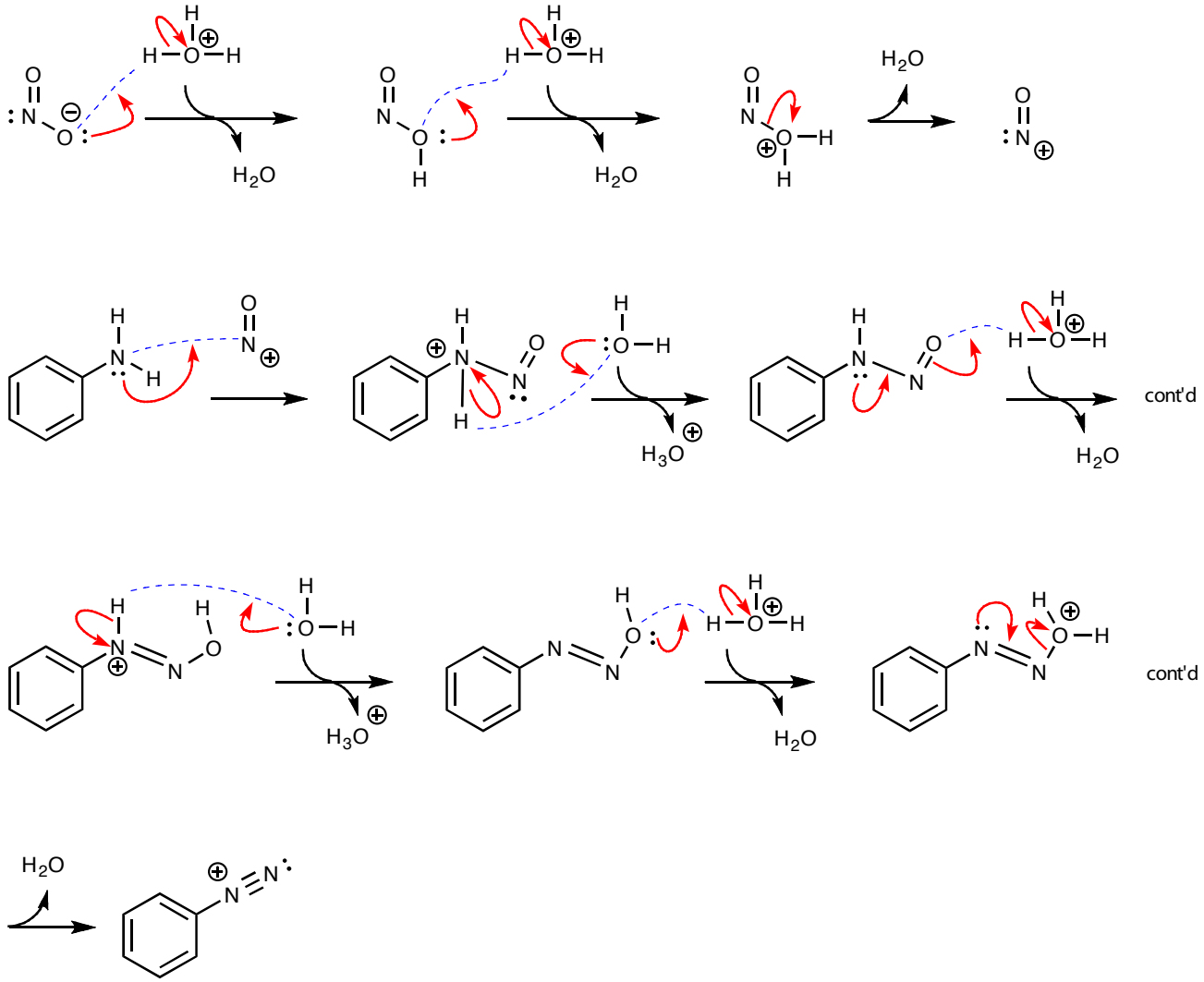
Benzyne Reaction

13. Reaction of 4-bromoanisole and sodamide to give 3- and 4-methoxyaniline via a benzyne intermediate.

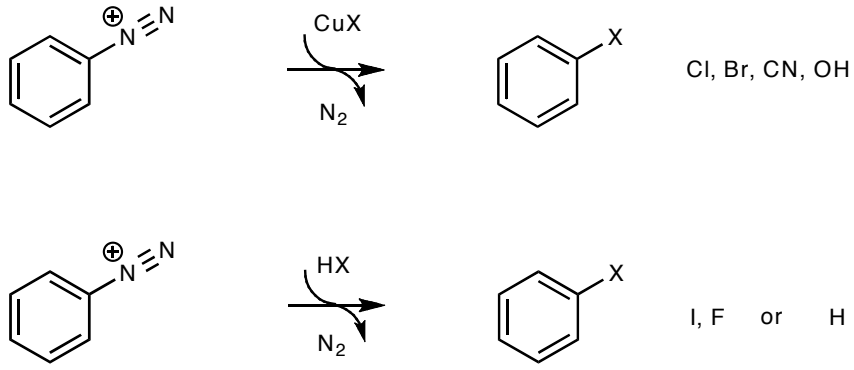


Diazonium Chemistry

14. Formation of a diazonium salt from aniline.



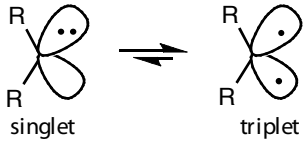
Reaction of Diazonium Salts



15 — Carbene and Nitrene Reactions

Carbene Reactions

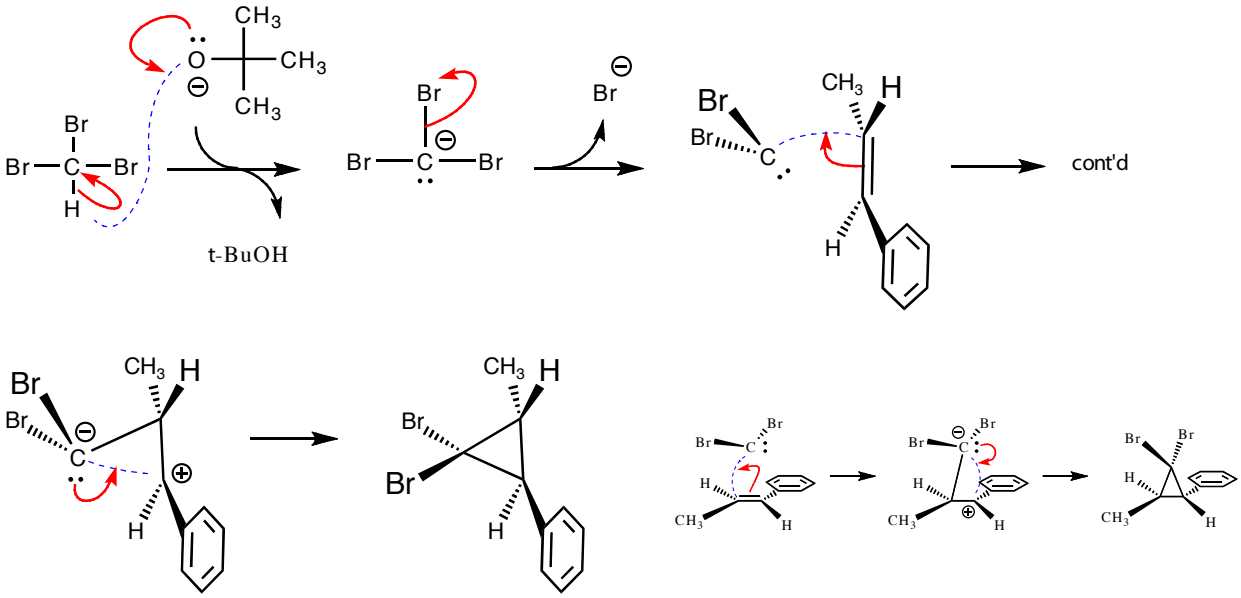
This may be stretching carbenes and introductory organic chemistry. There are two types of carbenes, singlet and triplet, and have differing rates of reactivity and stereochemical outcomes. In general, singlet carbenes are more reactive and experience less loss of stereochemistry than an equivalent triplet carbene.



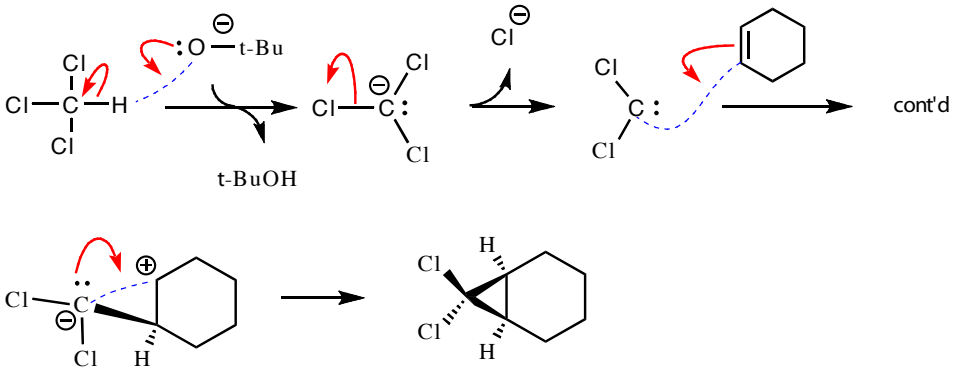
The two forms can interconvert. Often, the triplet is the more stable form. When it reacts with an alkene, it reacts as a diradical. It will generate a new diradical which can loose its stereochemistry. The singlet is closer to a carbocation in its characteristics. It does not have a complete octet and acquires one upon reaction.

Carbene Addition

1. Dihalocarbene addition to (*E*)-1-phenylpropene to give a dibromocyclopropane.

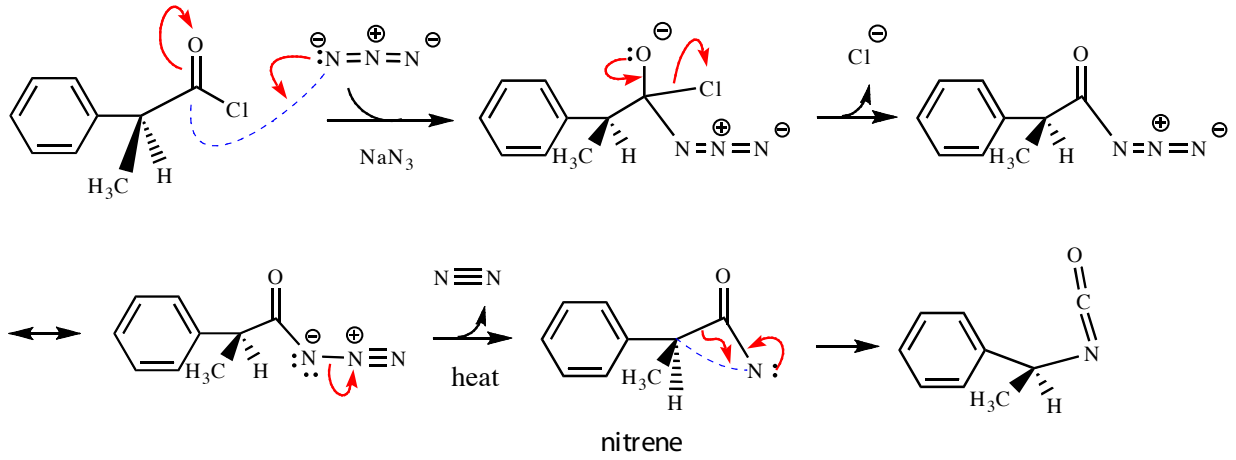


2. Dihalocarbene addition to cyclohexene to give 7,7-dichlorobicyclo[4.1.0]heptane.

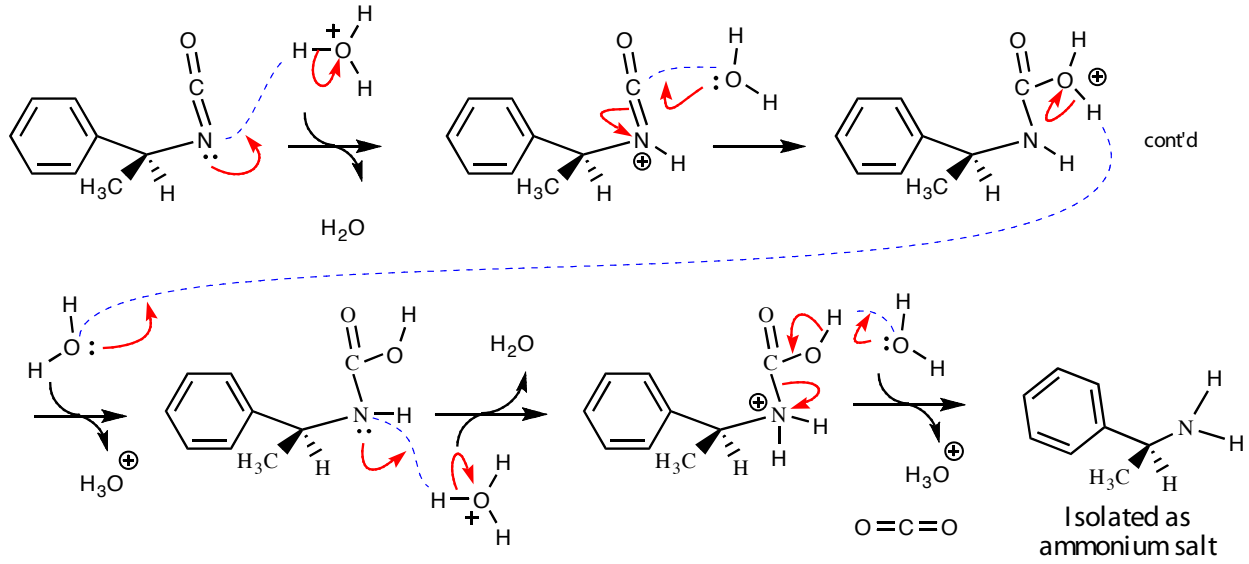


Curtius Rearrangement

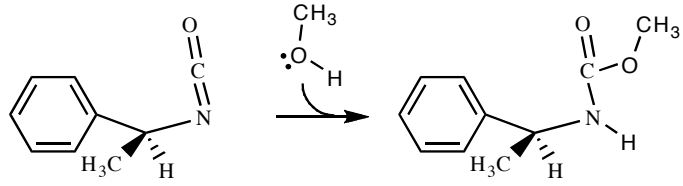
3. Step 1, Curtius rearrangement, reaction of acid chloride with azide and rearrangement via a nitrene intermediate.

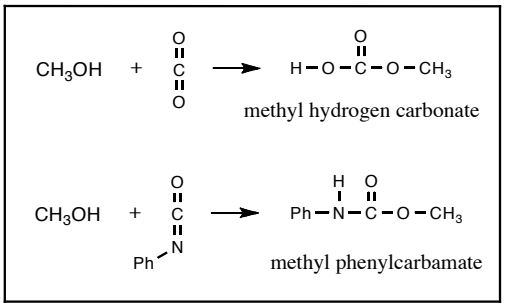


Step 2, hydrolysis of isocyanate to an amine.



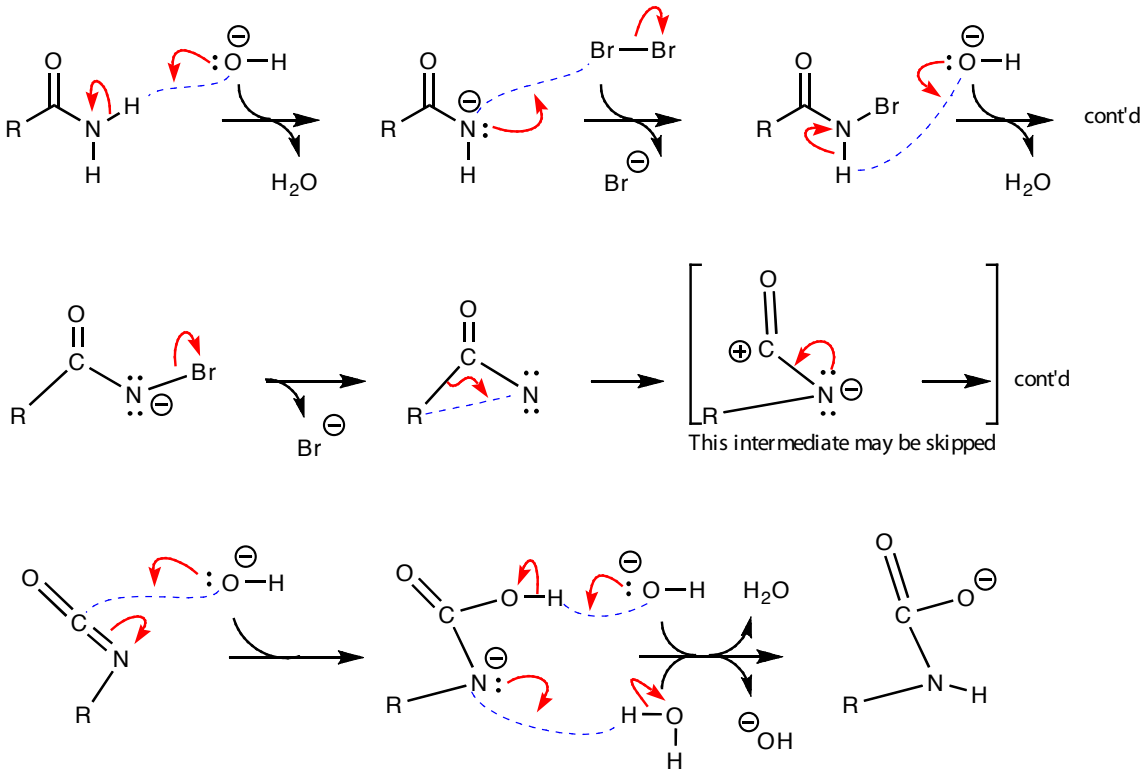
Alternate Step 2, hydrolysis of isocyanate to a carbamate. A carbamate is a nitrogen analog of a carbonate ester. The steps are similar to above with an alcohol replacing the water.



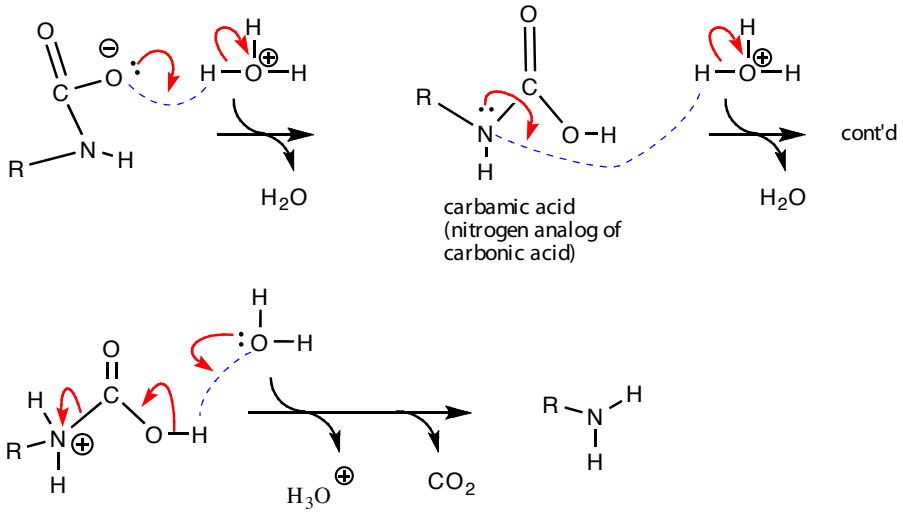


Hoffmann Rearrangement

4. Step 1, Hoffmann rearrangement of a primary amide to give the corresponding amine. The reaction of the amide with sodium hydroxide and bromine.



Step 2, Acidification and decarboxylation to give the amine.

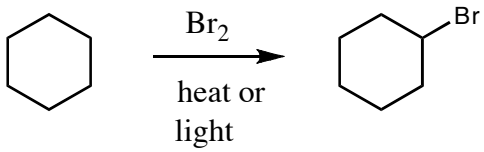


16 — Radical Reactions

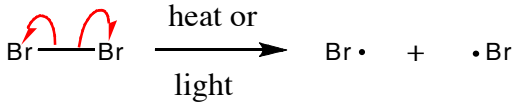
Free Radical Bromination (or Chlorination) Reaction

1. Free radical bromination of cyclohexane to give bromocyclohexane.

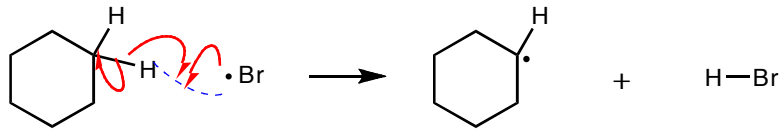
Overall reaction

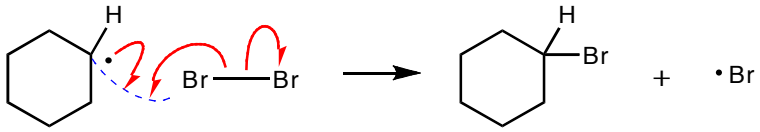


Initiation

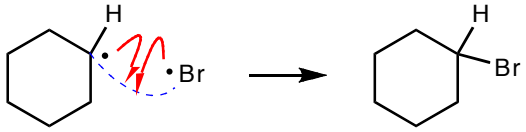


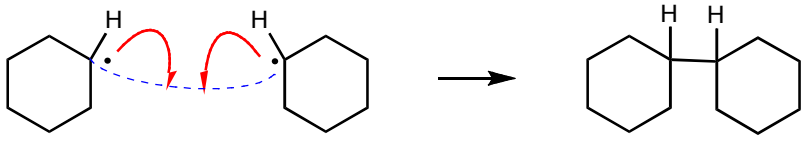
Propagation





Termination

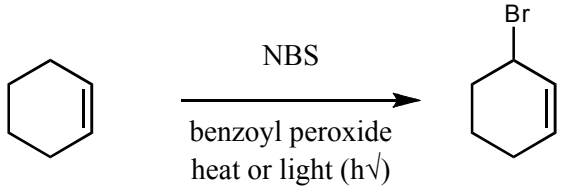




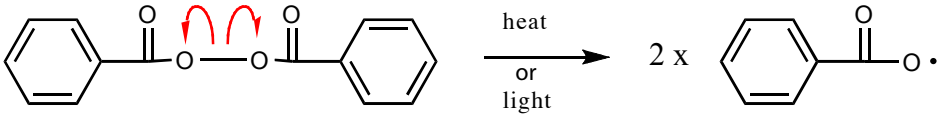
Allylic Bromination with NBS

2. Free radical bromination of cyclohexene with N-bromosuccinimide, an allylic bromination.

Overall reaction



Initiation (see Notes)



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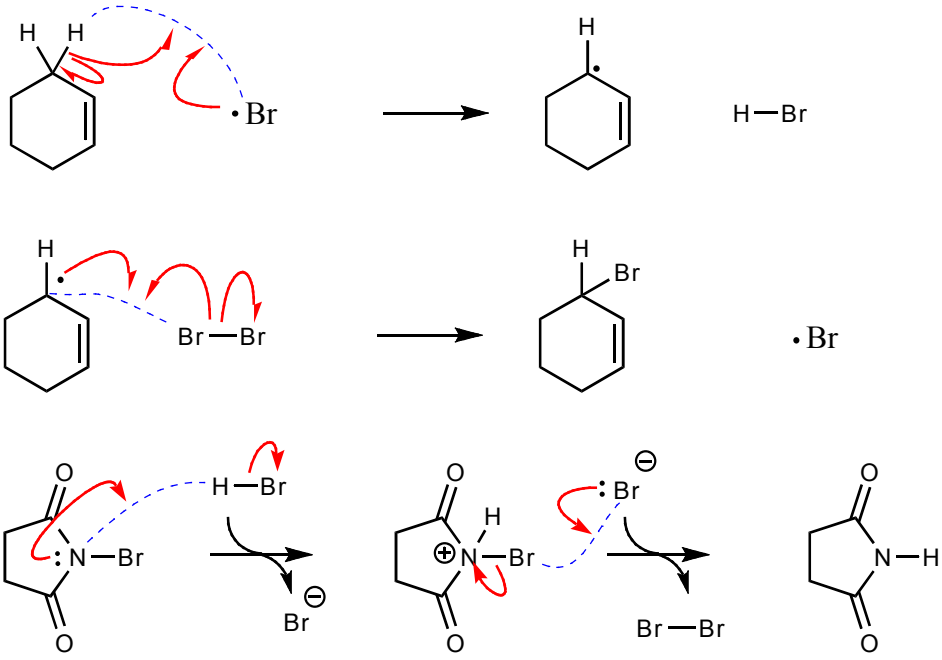
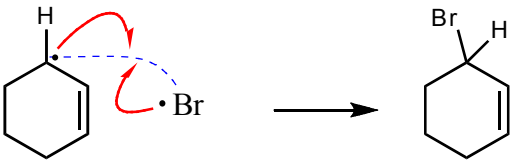


Termination

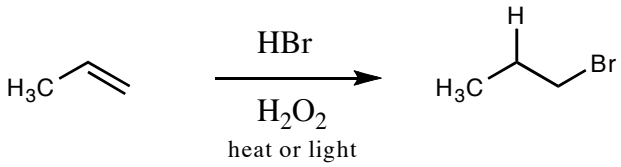


+ others

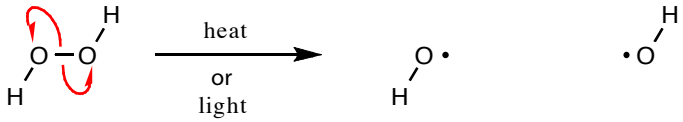
Radical Addition of Hydrogen Bromide

3. Free Radical Addition of HBr/H_2O_2 to 1-propene to give 1-bromopropane via an anti-Markovnikov addition of hydrogen bromide. (see Notes)

Overall reaction



Initiation (see Notes)



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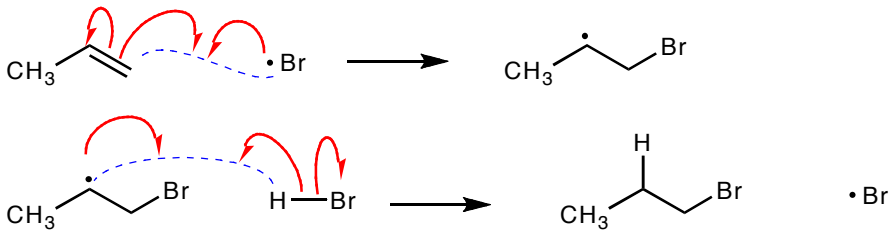
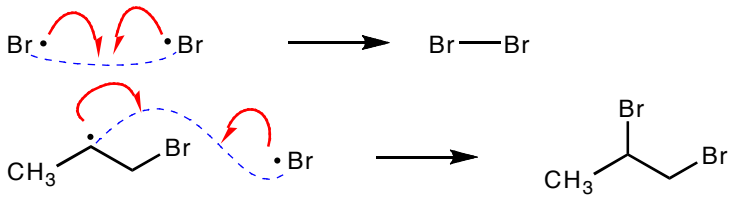


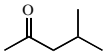
Termination

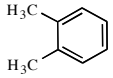
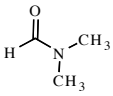
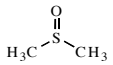


others

Common Names and Abbreviations for Compounds or Prefixes

Solvents

	Methylene chloride	CH_2Cl_2
	Chloroform	$CHCl_3$
MeOH	Methyl alcohol	CH_3OH
	Acetonitrile	CH_3CN
HOAc or AcOH	Acetic acid	CH_3COOH
EtOH	Ethyl alcohol	CH_3CH_2OH
EtOAc	Ethyl acetate	$CH_3CO_2CH_2CH_3$
Et_2O	Diethyl ether, ethyl ether, or ether	$(CH_3CH_2)_2O$
	Acetone	CH_3COCH_3
MEK	Methyl ethyl ketone	$CH_3COCH_2CH_3$
MIBK	Methyl isobutyl ketone	
MVK	Methyl vinyl ketone	$CH_3COCH{=}CH_2$
	toluene	$C_6H_5CH_3$

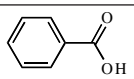
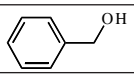
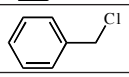
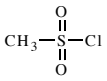
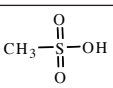
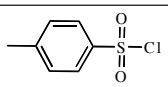
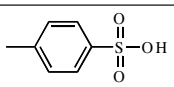
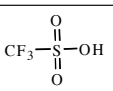
	o-xylene(s)	
IPA	Isopropyl alcohol	$(CH_3)_2CHOH$
DMF	Dimethyl formamide	
DMSO	Dimethyl sulfoxide	
MTBE	Methyl t-butyl ether	$CH_3OC(CH_3)_3$
DME	Dimethoxyethane or glyme	$CH_3OCH_2CH_2OCH_3$
THF	Tetrahydrofuran	
	1,4-dioxane	
	ethylene glycol	$HOCH_2CH_2OH$
	diethylene glycol	$(HOCH_2CH_2O)_2$

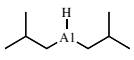
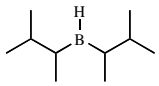
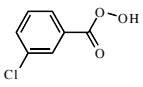
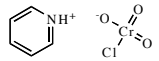
Prefixes

Me	methyl	$-CH_3$
OMe	methoxy	$-OCH_3$
Et	ethyl	$-CH_2CH_3$
Pr	propyl	$-CH_2CH_2CH_3$
iPr	isopropyl	$-CH(CH_3)_2$
n-Bu	n-butyl	$-CH_2CH_2CH_2CH_3$
s-Bu	sec-butyl	$-CH(CH_3)CH_2CH_3$
i-Bu	i-butyl	$-CH_2CH(CH_3)_2$

t-Bu	t-butyl	$-C(CH_3)_3$
	vinyl	$-CH{=}CH_2$
	allyl	$-CH_2CH{=}CH_2$
Bzl	benzyl	$-CH_2C_6H_5$
Ph	phenyl	$-C_6H_5$
	tolyl	$-C_6H_4CH_3$
Ac	acetyl	$-COCH_3$
Bz	benzoyl	$-COC_6H_5$

Reagents

AcCl	Acetyl chloride	CH_3COCl
Ac_2O	Acetic anhydride	$(CH_3CO)_2O$
BzOH	Benzoic acid	
BzlOH	Benzyl alcohol	
BzlCl	Benzyl chloride	
MsCl	mesyl chloride	
MsOH	methanesulfonic acid	
p-TsCl or TsCl	Tosyl chloride	
p-TsOH or TsOH	tosic acid or toluenesulfonic acid	
TFA	trifluoroacetic acid	CF_3CO_2H
TfOH	triflic acid or trifluoromethanesulfonic acid	

TEA	Triethylamine	$N(CH_2CH_3)_3$
pyridine		
LDA	Lithium diisopropylamide	
	Sodamide	$NaNH_2$
	Oxalyl chloride	
borane		BH_3
DIBAH or DIBALH	Diisobutyl-aluminum hydride	
Disiamylborane	Disiamylborane	
MCPBA	meta-chloroperoxybenzoic acid	
PCC	Pyridinium chlorochromate	
	Ozone	

Reference

Notes

Intro

A challenge to maintaining the utility of this book as a guide is to maintain the organization of the different parts. While it would be useful to have continuing notes in the different parts, doing so makes it very difficult to maintain the overall organization of the book. It is easier to keep the commentary to a minimum within each part and to place notes elsewhere. This is the start of the additional comments.

Chapter 1

$F = \frac{kq_1q_2}{r^2}$

It is commonly held that, "There is a strong correlation between the length and strength of a covalent bond." This notion is based upon Coulomb's Law:

However, the foundation of that length and strength correlation assumes that atoms exist as ions and their bond strengths are dependent on their mutual attraction. It seems plausible that one could consider a simple alternate model in which bonds are made up of electron pairs that are mutually attracted to pairs of positively charged nuclei. In that case, the key to predicting bond strength is the distance between a pair of electrons and the nucleus and its charge. Thus in predicting acidity, there are two important distances, the distance of the electrons to the main nucleus and the distance to the proton. If two bonds had an equal length, then the atom best able to pull the electrons closest to its nucleus would increase the distance to a proton. The greater distance will result in a weaker bond as determined by Coulomb's Law. The weaker bond will correspond with greater acidity.

The model in Chapter 1 is in agreement with the acidities for the atoms C, N, O, and F. It can also explain why a proton connected to a triple bond, which is shorter, can be more acidic than a proton attached to a double or single bond. Because the C-H bond lengths are the shortest in a terminal triple bond, I conclude that a) the electrons are closest to the carbon nucleus in a triple bond and b) the electron-proton distance is larger and therefore more acidic. This is counter to the cited principle.

A corollary to 'a tightly held pair of electrons results in a weak bond' is that 'a loosely held pair of electrons can form a stronger bond'. The analogy for an electron's ability to attract protons is, "The electrons are like a boxer, and the electrons with a longer reach will be able to snatch a proton more easily."

Although we haven't discussed resonance structures to this point, you will find that the principle of resonance has a great effect on atom acidity. The effect of creating resonance structures is the electrons can be shared with neighboring atoms. If a neighboring atom can pull electrons away, then the remaining electrons will now be held more tightly. Conversely, if a pair of electrons can be distributed over two different atoms, especially if there is a negative charge, then a reaction will be most likely to occur on the atom which holds the electrons the least tight. That is, if a pair of electrons can exist on two different atoms, the least electronegative atom (C>N>O) will be the most likely site of reaction.

Drawing Resonance Structures

It is important that everyone be successful in drawing the curved arrows and resonance structures because they are precursors to writing reaction mechanisms. Therefore, I have included some overly organized examples that will be very simple or serve as reference examples.

Chapter 2

p. 7 *Bronsted-Lowrey Acids and Bases*

The problems have been laid out in Parts A, B, and C to increase in difficulty. I have also included using sentences to represent the electron movement illustrated by the curved arrows. Understanding the curved arrows is as important as understanding acid-base equilibria.

Many times, students face problems in which they do not know how to proceed. 'Trial and error' is

Reference

Notes

an undervalued and underused strategy to solve chemistry problems. Several problems have been written to illustrate how one can arrive at the same answer if two possible options exist.

The chemical properties that can be illustrated by a pK_a can be widely used to predict the course of a reaction. The method laid out here is a model for how new problems may be solved.

While the underlying principle prefers the weakest base, you might also recognize the electrons of the weakest base will correspond with the electrons least available to react. For example, because bromide and iodide hold their electrons so tightly, they are more difficult to form bonds with.

Chapter 3

p. 13 *Substitution Reactions*

Substitution reactions can be described in two extremes, S_N1, and S_N2. In an S_N1 reaction, the rate-limiting step is formation of a carbocation. The leaving group must pull the electrons from the carbon. It is assumed that no bond formation occurs until a carbocation exists long enough for the leaving group to diffuse away and the group having left does not influence any incoming nucleophile. If the RX compound had been optically active, then the product of the reaction would be completely racemic.

In an S_N2 reaction, the bond formation precedes and controls the product formation. The nucleophile must push into the carbon nucleus. If the RX group were optically active, the product would retain that optical activity but it will be of the opposite configuration due to an inversion process that must take place.

In between these extremes will be the reactions for which you have to predict the products. For every rule or principle, there are ambiguities or exceptions. Therefore, I find that predicting the products can be challenging. However, there are some simple principles,

> An S_N1 reaction requires conditions that favor carbocation formation, namely a good leaving group, a polar solvent, usually water, and weak nucleophiles (often uncharged). Primary halides (unless allylic or benzylic) never undergo S_N1 reactions. Tertiary halides never undergo an S_N2 reaction.
>
> S_N2 reactions require conditions in which a pair of electrons is able to attack the carbon attached to the leaving group. That attack must precede bond cleavage. In order to extend the reach of the electrons, anions and especially anions of weak acids are common. High nucleophile concentrations and polar aprotic solvents (DMF, DMSO) are common.
>
> The ease of nucleophilic substitution is: methyl halide>primary halide>secondary halide. Tertiary halides fail to react via S_N2 mechanisms. In order to displace a tertiary halide, the halide must leave before the nucleophile can attack (S_n1 reaction). If not, elimination will occur. In between primary and tertiary are the secondary halides. They are the most ambiguous and the conditions of the reaction are most important in predicting the products.

For a given set of problems, students will not experience many difficulties in substitution reactions. However, they may have trouble writing the products simply because they are not grasping the details of the bond making and breaking process. In order to focus more attention on that aspect, the problems were selected in which the orientation of the nucleophiles and substrates were varied, included additional atoms or preceding steps. I have also used nucleophiles of ambident anions. These have two different atoms that may be the nucleophile. Throughout the book, I have generally written the greatest resonance contributor. The greatest resonance contributor best predicts the stability of an intermediate. However, reactions often occur on the resonance isomer. It may be useful to write the

Reference

Notes

resonance structure and consider why a reaction might occur on one atom versus another.

Chap 3.3 & 3.5 The cyanide anion in Example 3 and 5 could hypothetically react with the electrons of either the nitrogen or carbon. I would argue that it isn't the negative charge that we write on the carbon that determines its reactivity, but rather the distance the electrons can extend from the carbon that makes it the site of reaction.

Also, note in Example 5 that while the triflate can be displaced, the chloride cannot. The key here is that the chloride is attached to an sp^2 carbon. *Direct substitution reactions cannot take place on sp^2 carbons*. Although this chloride would be difficult to displace by any means, later we will see how chlorine attached to sp^2 carbons can be displaced via an addition-elimination reaction.

Chap 3.8 In Example 8, the enolate of cyclohexanone, the negative charge can be written on the oxygen atom or the carbon atom. The question I suggest answering is, "from which atom can the electrons reach furthest to react with iodopropane?" From our prior analysis, I hope you think that if the electrons can easily move from atom to atom, they can reach the furthest from the carbon atom (because it has the fewest protons in its nucleus). That analogy will correctly allow prediction of the product in the majority of cases.

That analysis works well for most cases. However, if the atoms in question are in different rows, the greater electron attraction of the larger nucleus may dominate the reaction. Even though we may write a resonance structure with the charge on a less electronegative atom, that charge may be so low that little reaction takes place at that site. Example 2 fits this model.

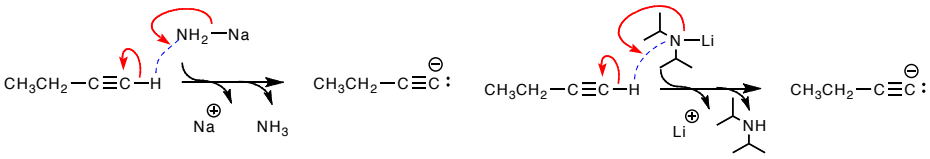
Chap 3.11 Note the use of sodium hydride as a base. It is a convenient and often used reagent to generate an alkoxide. I further wanted an example of an intramolecular substitution, especially to form an epoxide. Epoxides are frequently encountered and therefore a good example to use. Even though sodium hydride is illustrated in this example, sodium hydroxide would be just as effective and a more likely base because it is cheaper and safer to use.

Chap 3.12 I wanted to highlight how epoxides react under S_N2 conditions (strong nucleophile) at the least substituted carbon. This is a push reaction in that bond making drives the reaction. Under those conditions, the least substituted carbon is the site of attack. I describe it as a push reaction because there is relatively little bond polarization of the carbon-oxygen bond. The oxygen is not a weak base. It is not a good leaving group. The nucleophile must begin bond formation in order to succeed in breaking the carbon-oxygen bond.

I also wanted an acetylide nucleophile because acetylene is often the first anion used in carbon-carbon bond formation. It is a good example because you must also follow which atoms are joined to which atoms to correctly draw the product.

Finally, this reaction is illustrated with methyllithium, a commonly used commercially available

Chap 3.12 base for this reaction. However, depending on your class and textbook, you may find other bases illustrated that can also be used. Note the same reaction with sodium amide (left) or lithium diisopropylamide (right) for the same reaction. Sodium amide (sodamide) is an older base that is less frequently used in the modern organic chemistry laboratory.



Reference

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Chap 3.13 This is a good example of how an epoxide can be made to react with a very weak nucleophile, an uncharged methanol. Epoxides aren't as reactive as primary halides so acidification will pull electrons toward the oxygen to make it a better leaving group. This reaction blurs the line between S_N1 and S_N2 reactions. The reaction does not occur on the least substituted carbon, which would typify an S_N2 reaction, yet the reaction occurs with inversion of the carbon, which is not characteristic of an S_N1 reaction. The intramolecular nature of the oxygen atom leaving group allows the reaction dynamics to change as a result.

Chap 3.15 This reaction shows an S_N2 reaction does not have to occur under basic conditions. Also, note the CH_3-O bond is cleaved but not the aryl-C-O bond. The aryl C-O bond is sp^2 hybridized and they cannot undergo S_N2 displacement reaction.

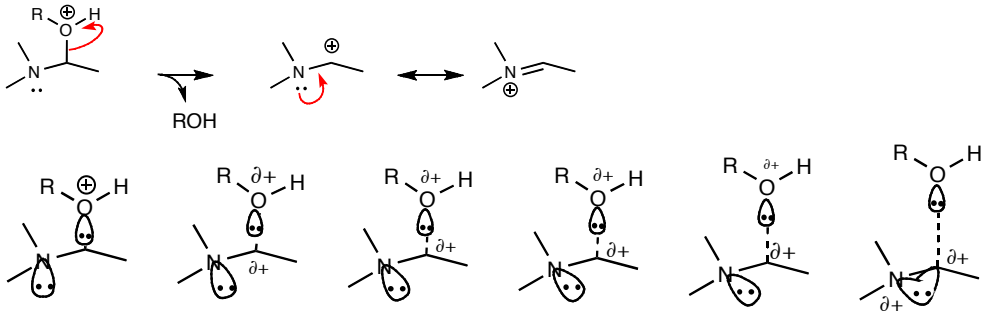
Chap 3.17 A solvolysis reaction means the solvent causes the bond to break. Note that water as a solvent or co-solvent will accelerate the reaction.

Chap 3.18 In Example 18, you want the water concentrations to be low so it does not react. Practically, I think water might still compete but the acid present would cause any alcohol that might form to continue to be converted into the bromide product. Remember, that it would be easier to protonate oxygen than a bromine so the alcohol would be more easily converted to the bromide.

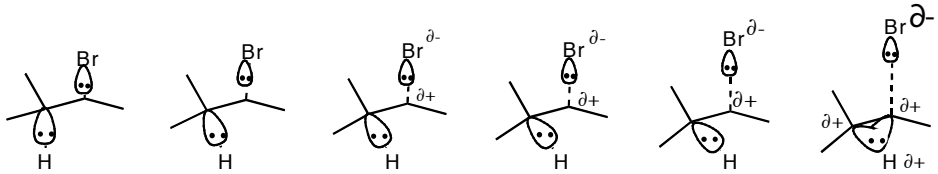
Chapter 4 *About Elimination Reactions*

You should consult your textbook for a more complete discussion of elimination reactions.

An elimination reaction is like a nucleophilic substitution reaction in which the electrons that displace the leaving group come from a neighboring atom. If we were not considering an elimination reaction, then other examples of electron participation are common. The electrons of a nitrogen are donated in formation of an imine. A nitrogen analog of an elimination reaction is illustrated below. Because nitrogen has a pair of non-bonded electrons, they are easily attracted to the developing positive charge and indeed accelerate the loss of the pair of electrons from the neighboring carbon. Below, I've written a step reaction equivalent of this process. In this case, we recognize the participation of the neighboring electrons in the resonance structure.



We can draw an analogy to the imine formation above with the first steps of an elimination reaction. As the leaving group bond lengthens, a charge develops and other electrons will be attracted to the positive charge. The electron pair with a hydrogen attached can easily move. Remember, that it is the electrons that are being attracted to the nucleus of the carbon. It seems plausible that the electrons being shared with a proton could move reasonably easily. If a proton with its electrons did move, then the result is the microscopic reverse of an HX addition reaction in which the X is the same leaving group in the original substrate.



Reference

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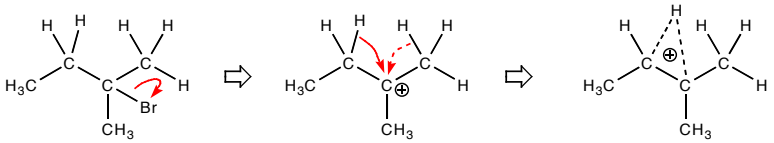
The first consideration for electron donation is availability. Stereochemistry and electronic effects determine electron availability. For an example of stereochemical effects, see bromobutane elimination, Chapter 4.1. The stereochemistry of a molecule is crucial. The electrons that are opposite to the leaving group could approach the back of the carbon nucleus most easily. Electronically, the electrons most available for shifting are those attached to a carbon with the least number of hydrogens (because carbons are electron donating, see page 1-C). Thus, if one had 2-methyl-2-bromobutane, the proton on the methylene group would shift rather than one from a methyl group.



Concomitant with the electrons (and its proton) becoming attracted to a carbon nucleus is that the carbon will be shielded from attack by a nucleophile. Therefore, if a proton-electron pair has shifted over to the carbon nucleus, then the nucleophile will abstract that proton and leave the pair of electrons. This is a net elimination reaction. Because the electrons being donated are from the second most stable carbocation (tertiary>secondary>primary), that carbon will be central to the elimination product. It agrees with the most stable alkene and consistent with Zaitzev's rule.

Paradoxically, a "hard" negative charge characteristic of a good nucleophile will also be most able to abstract a proton to cause an elimination reaction to occur.

If the bond breaking process does not precede nucleophilic attack (on carbon or hydrogen), then the elimination reaction will be bimolecular (E2). The less the bond is polarized, the more the reaction will depend on releasing the electrons by the action of a base, an E2 elimination reaction. Also, the less the bond is polarized, then an elimination reaction may be controlled by hydrogen acidity. Hydrogen acidity for alkanes is primary>secondary>tertiary. For weakly polarized bonds, the greatest negative charge can be formed on a methyl group, which is the opposite directing effect of Zaitzev's rule. Fluoride leaving groups and Hofmann elimination reactions give the greatest amount of products that are exceptions to Zaitzev's rule.

If the substrate is an iodide or bromide in a polar solvent, such as sodium ethoxide in ethanol, generally Zaitzev's rule will apply. This solvent is the most similar to E1 elimination reaction conditions. Therefore the product will be the most substituted alkene because the hydrogens on the most substituted carbons are most able to move (and block attack by a nucleophile).

If the substrate is a primary iodide or bromide, then an S_N2 nucleophilic substitution reaction is likely to occur unless a sterically hindered nucleophile/base is be used (tertiary butoxide or diisopropylamide). If the halide is tertiary and the nucleophile has a negative charge (except conjugate bases of strong acids), then elimination is likely. If the halide is secondary, and the nucleophile is strongly basic, then elimination will likely compete well with substitution and may be the major product.

Chapter 5

Chap 5.3 The hydration of an alkene may be found in some organic chemistry textbooks. However, although this reaction can be preformed, it is not a general reaction. If water added, the alcohol is more basic than the starting alkene. As a result, the dehydration reaction is favored. A sulfate ester may be formed instead, and subsequently hydrolyzed. That reaction can work, but that is still an awkward reaction for common usage. In the laboratory, it is better to perform an oxymercuration-reduction or addition of acetic acid and hydrolyze the ester.

Reference

Notes

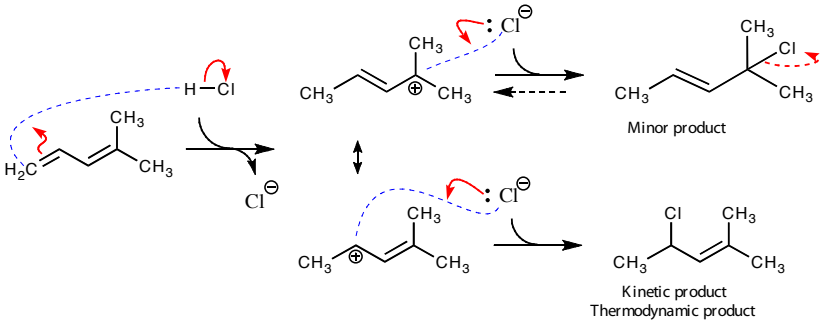
Chap 5.7 Often I am uncertain about whether a rearrangement reaction will take place and the amount that rearranges. This example may be found in many texts, but I doubt it is as generally successful as the mechanism suggests.

Chap 5.8 Relief of ring strain is a common reason for rearrangement. I usually assume that if the atoms are arranged with a carbocation adjacent to a strained ring, then a rearrangement will occur. I always suggest to students to anticipate a rearrangement reaction with 3, 4, and 5-membered rings. .

Chap 5.9 This rearrangement will occur in a high yield. Any reactions that increase conjugation are generally favored reactions.

Chap 5.10 & 5.11 In most reactions, the kinetic and thermodynamic products are the same. Dienes are good examples where the thermodynamically or kinetically controlled products can be isolated (and mixtures are common). If the activation energy of a reaction is low, the reaction will be fast (to give a kinetic product). However, it may not be the most stable product. That product may continue to react under those conditions to give the more stable (thermodynamic) product. How would you know that a kinetic or thermodynamic product should be chosen? A signal that a kinetic product might be expected is if the reaction is carried out at a low temperature.

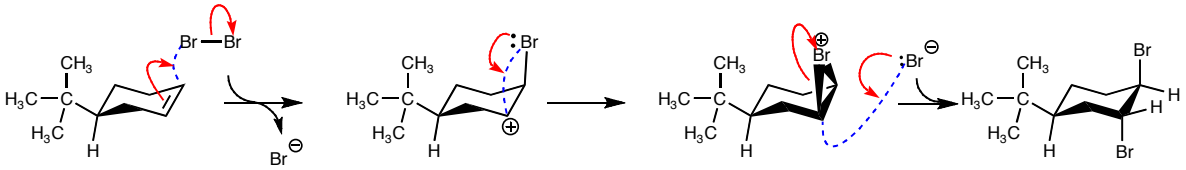
You shouldn't assume that the addition will occur in a 1,4-manner. In this example, the 1,2-adduct is the kinetic and thermodynamic product.

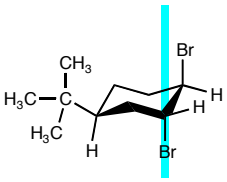


Chap 5.12 *Bromination*

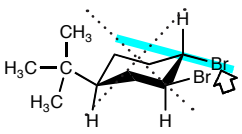
Many textbooks show the bromination as a concerted reaction in which three bonds form and break simultaneously. However, electron-rich alkenes react faster than electron poor ones. This difference in reactivity is more easily conveyed in a stepwise reaction than a concerted one.

In the bromination of cyclohexene, it doesn't matter at which carbon the bromide enters, as it is symmetrical. It only matters that the entering bromide is on the opposite side of the bond being broken. If an anchoring t-butyl group were present, then opening the bromonium ion would prefer to give the diaxial product. The entering and leaving electrons would be aligned in an S_N2 like reaction as shown below. Note how an axial bromine remains aligned to entering trajectory.





If the light line represents the axis of an S_N2 reaction having taken place, it is easier to imagine the departing Br being on the axis on the left than on the right. On the left, the electrons are aligned with that axis, but the angle on the right is not.



Reference

Notes

Chap 5.14 The stereo and regiochemistry play a role in this reaction. In this case, the nucleophile (water) attacks the most substituted carbon and results in inversion. The stereochemical consequences of this reaction are the same as an S_N2 reaction. However, as a general rule, we said S_N2 reactions do not take place on tertiary carbons. How is this different? Generally, in an S_N2 reaction, the process of bond formation precedes bond cleavage. For that to happen, one needs a good nucleophile to force bond formation before the bond to the leaving group is completely broken.

In this instance, you can think that unlike the S_N2 reaction, in which little bond cleavage has occurred to expose the nucleus to attack, the bond may be considered highly polarized and thus the carbon contains considerable positive charge. Therefore, the reaction is more S_N1 like than S_N2 like. The atom best able to support that charge is now the site of an S_N2-like reaction.

Alternately, you may think that of it as though a three membered ring were not present (though untrue). The reaction is then like an S_N1 reaction in which the neighboring atom and its non-bonded electrons blocks one face of the carbocation and results in attack from the opposite side.

For the opening of the bromonium ion, while it is written in a distorted manner, the electrons are attacking the carbon nucleus from the opposite side of the leaving electrons. You may wish to draw a Newman projection of this process in a cyclohexane to convince yourself this is the best description of the process.

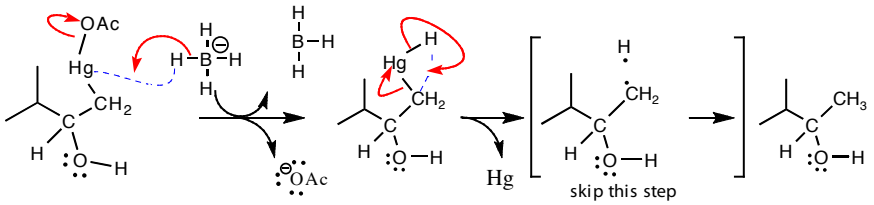
Chap 5.15 *Oxymercuration*

This reaction is a good analog to the bromination reaction. In this case, we write the reaction with an electrophilic mercury atom. We might know it is electrophilic because we may see it written with a positive charge (although I didn't), therefore an alkene should be the nucleophile. What we might forget is that mercury still has ten valence electrons. Therefore, after it reacts with an alkene, it has a number of electrons that are available to react with a neighboring positive charge, just as the bromine atom did.

If the non-bonded electrons of the mercury did not interact with the carbocation, then a rearrangement might take place.

Reductive Demercuration

The mercury is removed by a borohydride reduction followed by loss of metallic mercury. The loss of mercury is reportedly a radical reaction. However, for expediency, I suggest you write the reaction as indicated and skip the intermediate in brackets unless directed otherwise by your instructor.



Chap 5.17 *Hydroboration-oxidation of Alkene*

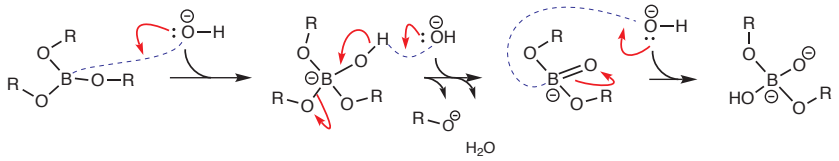
You may also find this reaction written as a concerted reaction. You should note how similar this reaction is to the prior reactions in this section. Boron is the electrophile and reacts with the electrons from the alkene. The second part of this reaction takes place before any atom movement can take place. The electrons from the negatively charged boron are donated to the carbocation. In this case, a proton is attached to the donated electrons.

You may also use this alternate mechanism for the hydrolysis. I like the deprotonation to promote the loss of the alkoxide. However, the product of that elimination is an sp^2-hybridized boron with

Reference

Notes

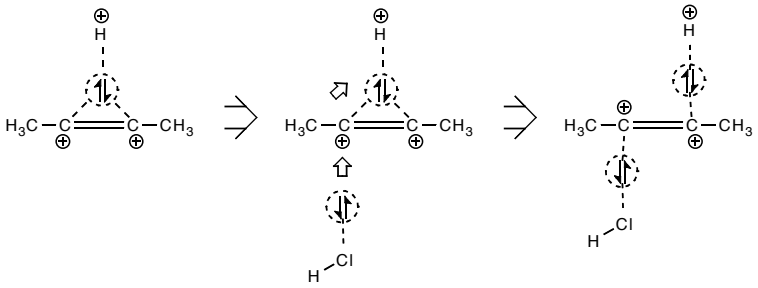
Chap 5.17 cont'd a negative charge. The next step requires that boron to attract an additional pair of electrons. The product of that addition is an sp^3-hybridized boron with an alkoxide oxygen neighbor.



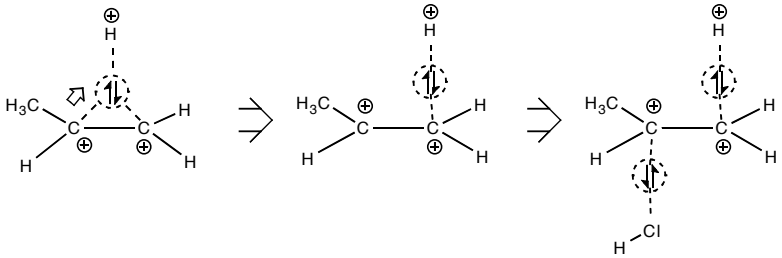
While I do not favor this mechanism, if your textbook or your instructor uses it, then you may consider this alternative. However, you may also contemplate the merits of this mechanism compared to the mechanism in example 17.

Chap 5.18 *Addition to an Internal Acetylene*

This example contains a kind of misrepresentation. The three membered ring immediate in the addition of HCl to the acetylene is misleading. This is an example of a three-centered two-electron bond. As written, it implies two bonds to hydrogen. I believe a better representation is shown below. If addition of a proton was on a pair of electrons, an intermediate such as on the left would result. The charge of the nuclei would be unchanged, but overall an imbalance would exist. Because the acetylene carbons are sp2 hybridized, one less bond is present to add electron density to each carbon. As a result, you may think of the electrons as still attached to the acetylene carbons. When the electrons approach one of the carbons, it will only be at that stage that bond cleavage occurs. I like this model to explain why addition of HCl gives a high amount of *trans*-addition.



If we compare the above with addition of HCl to propene, the electron density about the carbocation is sufficient to allow the connection with the pair of electrons to break. This gives the most stable carbocation and is consistent with a Markovnikov addition of HCl.



Chap 5.19 In Example 20, sulfuric acid is a good acid to use because its conjugate base, bisulfate ion, is a weak nucleophile. One again has a similar three membered-ring intermediate forming, although in this case, it doesn't matter if the intermediate opens trans as the stereochemistry is eventually lost. The reaction has an additional carbon protonation step to give a ketone as the final product. In the last deprotonation step, which proton is more acidic, the one on the oxygen (to give the ketone) or the one on the carbon (to regenerate the enol)?

Reference

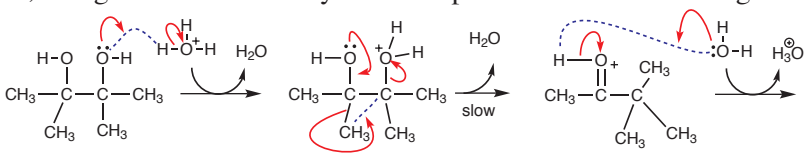
Notes

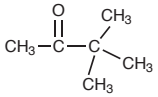
Chap 5.20 While sulfuric acid could proton an internal acetylene, if a carbon is replaced with a less electron donating hydrogen, the acetylene is not nucleophilic enough to react. A mercuric salt can react with the terminal acetylene in an oxymercuration reaction that parallels the alkene reaction. However, mercury gives up its electrons at the end to reform mercuric ion and provides a ketone.

Chap 5.21 A hindered borane is necessary to avoid over reduction of the acetylene.

Chapter 6

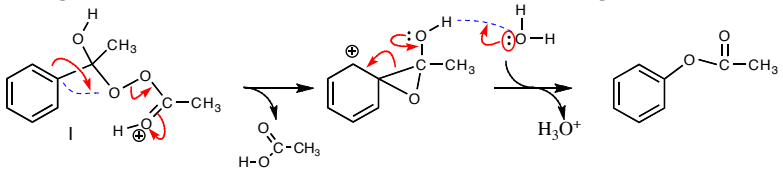
Chap 6.1 I had earlier written the pinacol rearrangement with one less intermediate. It went directly from protonation of the alcohol to the rearranged product. I used the non-bonded electrons of the adjacent oxygen to facilitate migration of the methyl group and loss of water. That could be a suitable mechanism, though I was troubled by the three pairs of electrons moving concurrently.



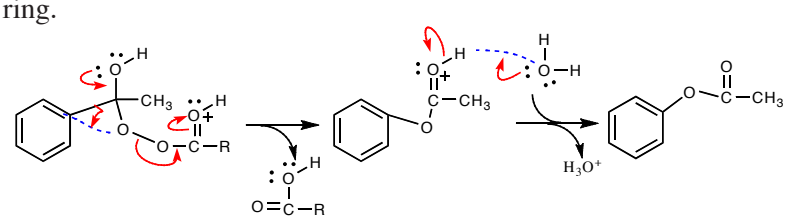


Chap 6.2 *Baeyer-Villiger Oxidation*

A mechanism in which the phenyl group utilized the electrons of the aromatic ring better explained why an electron-donating group would prefer to migrate. Reasonably, any group that can stabilize a positive charge or that donate electrons would facilitate migration.



In a concerted migration, the electron pushing from the oxygen does not require any demands of the phenyl ring.



Chapter 7

Chap 7.17, 7.18, & 7.19 *Other Electrocyclic Reactions*

These reactions are often excluded from introductory texts. I have included them as they fit the general model for electrocyclic reactions and extend the model.

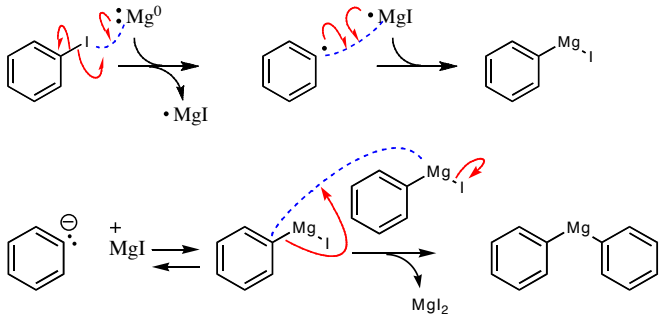
Chap 7.18 It is an exaggeration that hydronium ion is necessary for the tautomerization to take place. The product phenol is a more likely acid that catalyzes the tautomerization. Drawing the phenol as the acid would have been awkward.

Reference

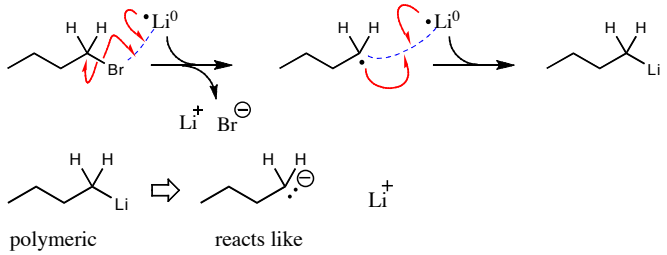
Notes

Chapter 8

Chap 8.1 The formation of Grignard reagents is thought to be a single electron transfer process. Magnesium metal donates electrons to iodobenzene (I>Br>Cl). The product is phenyl magnesium iodide or phenyl Grignard. This reagent reacts as though it were the anion. Because it is very basic, it is very reactive and must be protected from water. Anhydrous ether is the most common solvent to use with Grignard reactions. Other solvents may be chosen that precipitate the inorganic disproportionation product, magnesium iodide, and give a solution of diphenyl magnesium, which has similar properties to the normal Grignard reagent.



Chap 8.3 In a reaction similar to the Grignard formation, lithium metal donates an electron to a halide. The product from the first transfer is the single electron radical plus the lithium salt of the halide. Radicals are very reactive and thus quickly react with a second equivalent of lithium metal to form the organolithium reagent. In the case of butyllithium, it is structurally a polymer. However, many compounds depolymerize it so it can react as though it were the butyl anion.



Chap 8.7 & 8.8 Even though ketal formation and hydrolysis reactions are written with single arrows, these reactions are reversible. They are controlled by Le Chatelier's principle. Water drives a hydrolysis and dehydration drives ketal formation. If water is added to a reaction mixture, a hydrolysis will result. In order to form a ketal, water has to be removed or absorbed by one of the reactants. Another common method to absorb water react the target ketone or aldehyde with an acetal, ketal, or enol ether that will absorb the water.

Chap 8.9 *Oxime Formation*

This mechanism is common for other imine reactions. If the OH group is replaced with an alkyl group, this will result in formation of an imine. Many students do not recognize other imine forming reactions. Hydrazine, phenylhydrazine, methylamine, etc., all react similarly to this mechanism.

Chap 8.24 *Grignard Addition to an Ester*

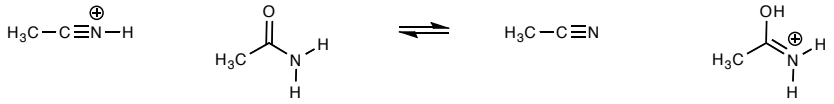
In the course of the reaction, the intermediate methyl ketone is more reactive than the starting ester, therefore if less than 2 equivalents of Grignard reagent is used, then the intermediate methyl ketone will react faster than the unreacted ester and some ester will be found as a by-product.

Reference

Notes

Chap 8.25 *Hydrolysis of a Nitrile*

The following equilibrium should explain why an acid catalyzed hydrolysis of a nitrile is difficult to stop at an amide. An amide is more basic than the nitrile and will tend to react faster than the nitrile. One method to stop the reaction is to limit the amount of water to the shoichiometric amount.



pKa -10 pKa -0.5

Chapter 9

Chap 9.1 *Aldol Reaction*

The base (and acid) catalyzed aldol reactions confuse many students. One reason is because of how these reactions are represented. How should a self-condensation reaction be represented? If you indicate that it takes two moles, then it is suggestive of the stoichiometry of the other reagents. Because the aldol only requires a catalytic amount of acid or base, that would be an incorrect inference. Polymerization reactions do not indicate that 100 or more molecules are being self-condensed. I've placed a (2) before the aldehyde. It is there as a reminder that a self-condensation reaction is taking place.

The enol and carbonyl forms are in equilibrium. Therefore both molecular forms are present and the enol (in acid) or enolate (in base) can react with the unenolized aldehyde.

The dehydration step is frequently accomplished by heat, strong acid, or strong base. I infer from any of those notations to expect a dehydration to occur. The dehydration step could also have been written as a one step reaction.

Chap 9.2 The signal that a mixed or cross-aldol condensation will take place is the low temperature (-78°C) for the formation of a kinetic enolate. If those conditions were not employed, the ketone and aldehyde would undergo a variety of self and mixed aldol condensation reactions.

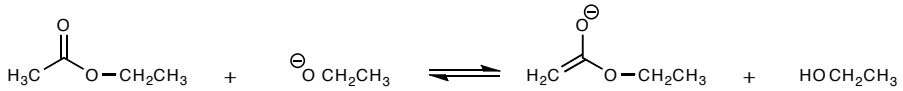
Chap 9.4 The Mannich reaction is conducted under mildly acidic conditions. I interpret this to mean that nearly all of the nitrogen atoms will be protonated as ammonium ions. Since they are greatest in concentration, this will be the most prevalent acid. In order to protonate the alcohol, a small amount of hydronium ion seemed logical.

There is also a slight error in the mechanism. The final product of that reaction, as shown should be the ammonium salt of the product. In order to isolate the product from the reaction, it must be treated with base. I chose to skip the illustration of that process to avoid making a long reaction longer.

Chap 9.5 *Claisen Condensation*

This is another self-condensation reaction. Again, don't confuse a prefix with stoichiometry. This reaction does not require two moles of ester per mole of ethoxide, quite the contrary. It requires an excess of sodium ethoxide.

The pK_a of ethyl acetate is greater than ethanol. Therefore, in the presence of ethoxide, the concentration of enolate in the reaction mixture would be low.

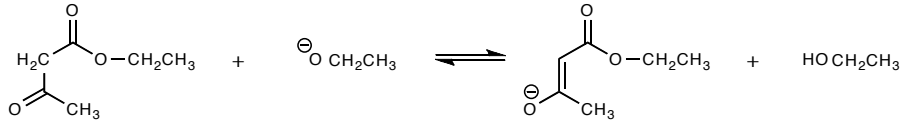


After the formation of the β-ketoester, whose pKa is lower than ethanol, the enolate concentration will again fall. In order to generate the enolate of the ester, excess ethoxide is needed to overcome the

Reference

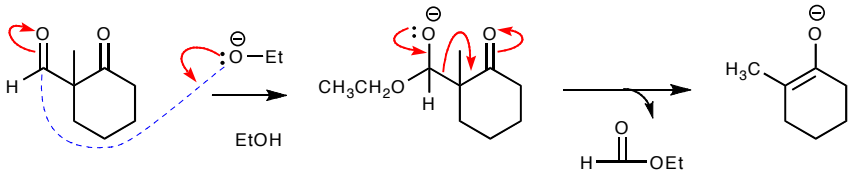
Notes

Chap 9.5 cont'd formation of the salt of the product.

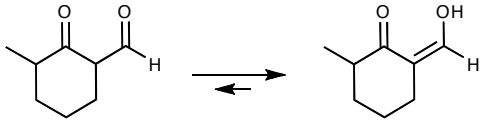


Chap 9.6 *Mixed Claisen Condensation*

The requirement for a mixed or cross Claisen condensation is to use an ester that does not have any enolizable hydrogens, therefore it cannot form a nucleophile. With the ketone, methylcyclohexanone, two possible condensation products can form. However, the hindered product cannot form a stable enolate. Therefore, the product of that enolate reverses to reform the enolate.



Finally, the neutral product prefers the enol form of the aldehyde because it can be conjugated with the ketone and aldehydes are very easily enolized.



Chap 9.8 *Halogenation of Carbonyl Compounds*

Under basic conditions, the addition of each halogen increases the acidity of the remaining hydrogen atoms. As a result, the unhalogenated ketone is the least reactive species in the reaction. One the methyl group is completely halogenated (I, Br, or Cl), the pKa of the trihalomethane is now low enough that it can form an anion from the tetrahedral intermediate.

Chap 9.9 Where does HBr come from for the acid catalyzed bromination? If bromine reacts with acetic acid, the products are HBr and CH_3COOBr. Also, a by-product of the reaction is HBr, so the reaction becomes more acidic as it progresses.

The rate-limiting step in a acid catalyzed bromination is enolization of the ketone. The enol will be produced from the protonated ketone. Under acidic conditions, bromination will reduce the electron density around the carbonyl oxygen making it more difficult to protonate the halogenated ketone versus the starting ketone. Therefore, a monobromination reaction is much easier to achieve under acidic conditions.

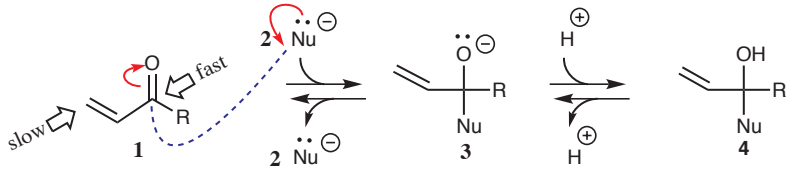
Chap 9.10 & 9.11 *Michael Addition Reaction*

Below is a model I like to explain Michael addition reactions. In reactions of enone **1** with nucleophile **2**, the fast reaction gives the 1,2-addition product (**4**) and the slow reaction gives 1,4-addition product (**6**). The selectivity is a function of enone **1** and changes with substitution. The best nucleophiles (**2**) for 1,2-addition are conjugate bases of weak acids, e.g., Grignard reagents, alkyllithium reagents, and (boron or) aluminum hydrides. The intermediate of the addition (**3**) is the weakest base. Therefore, the reaction will not reverse and **4** will be the product. If the nucleophile **2** is the conjugate base of a strong acid or at least stronger than **4**, the product of the reaction will be the weakest base. If **2** is the weakest base, the tetrahedral intermediate **3** may revert back to starting materials.

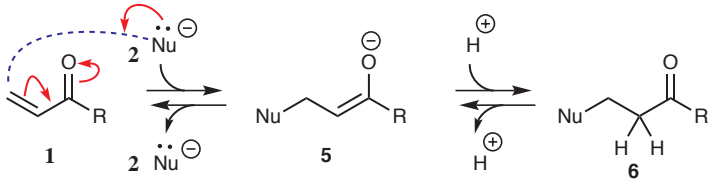
Reference

Notes

Chap 9.10 & 9.11 cont'd



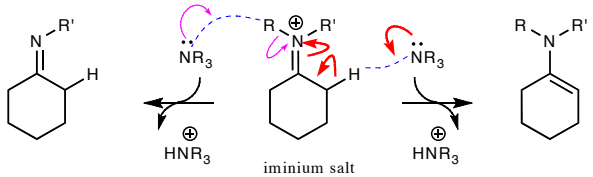
If the nucleophile **2** is less basic than **3**, not only will **3** regenerate **2**, but if **2** were to do a Michael addition or 1,4-conjugation addition reaction with **1**, the product would be **6**. If the nucleophile **2** added to **1**, the intermediate could become protonated to form **6**. Because nucleophile **2** is a weak base, it would be unable to regenerate enolate **5**. While ienolate **5** can lead to the weaker base as the product, its formation is dependent on nucleophile **2** being able to deprotonate **6**. If MeSH were the nucleophile (in the presence of a basic catalyst), intermediate **3** would lose the thiolate nucleophile **2** because it would be a weaker base (pKa 10.4 of conjugate acid of **2**) than **4** (pKa ~18). If the 1,4-addition reaction took place and protonation also occurred, the nucleophile **2** would not be basic enough to regenerate the enolate (pKa ~20 of **6**) to reverse the reaction. Therefore, the conditions favor the an accumulation of the 1,4-addition product **6**.



This principle applies to the aldol condensation as well. Because the intermediate of the aldol is an example of product **6**, we can apply the same principles. The pKa of the nucleophile is ~16 (the conjugate acid of the base catalyst, hydroxide), it is basic enough to generate small amounts of enolate **5**. If enolate **5** can form a weaker base, that reaction will take place. Therefore enolate **5** will lose hydroxide to regenerate the enone **1**. If insufficient base is present, then little enolization will take place and the formation of the enone may not occur and the product will be the analog of **6**.

Chap 9.12 *Enamine formation*

The mechanism of this reaction parallels other nucleophilic additions to carbonyl groups. A nitrogen is able to add to a carbonyl and thus does not need a catalysis. Catalysis is likely involved in the dehydration steps of the formation. It is similar to the formation of an oxime. If the pH were too low, the amine would be complexed with the acid. If the pH were too high, it would be difficult to lose water because it couldn't be lost as neutral water. After water is lost the product is an iminium salt, a nitrogen analog of a protonated carbonyl group. If R is H, then a deprotonation reaction occurs to give an imine (see Chap 8.9). If R is not H, then the alkyl hydrogen is lost and an enamine results.



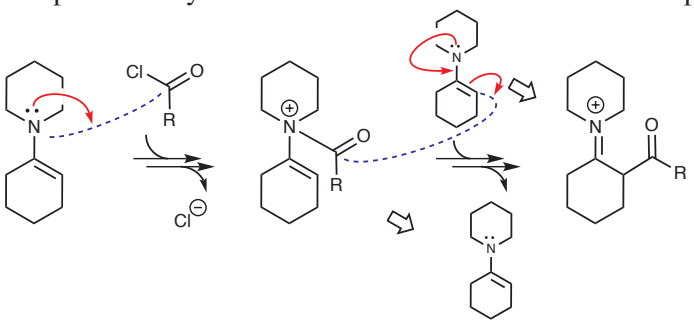
Enamine Alkylation

Why does an enamine react on carbon rather than the nitrogen atom? A key is to draw the resonance structure of the enamine. The resonance structure has a negative charge on the carbon. On which atom will the electrons extend the furthest? In which form would you predict the electrons are best able to react?

Reference

Notes

Chap 9.12 cont'd However, many reactions also involve direct reaction on the nitrogen atom. If it is an acylation reaction, that product may be reversible and leads to the same final product.



Chapter 10

Chap 10.2 *Reaction of Toluenesulfonyl Chloride with an Alcohol.*

With tosyl chloride, the product is a sulfonate ester rather than a chloride. Why doesn't the chloride by product displace the tosylate ester? The answer is a difference in rates. If the reaction time is left too long, the chloride will accompany the tosylate.

Chap 10.3 *Reaction of Phosphorus Tribromide with an Alcohol*

I have been troubled by how a pair of electrons of an alcohol should be able to attack a phosphorous atom since there are many other examples where the opposite occurs, see the Wittig reaction or $PCl_3 + Cl_2 \rightarrow PCl_5$. I thought that if HBr were liberated, it could protonate the phosphorous and convert it from a nucleophile to an electrophile.

Chap 10.4 *Conversion of an Amide to a Nitrile with Acetic Anhydride*

Acetic anhydride is one of many reagents for this conversion. The mechanisms are fundamentally the same. The initial complexation is with the oxygen atom to convert it into a better leaving group. While this explanation seems counter to the enamine explanation (Chap 9.12), it shows how important resonance structures are in revealing the ability of nitrogen to share it electrons with the neighboring oxygen. The effect of the electron donation will pull the electrons of nitrogen closer to its nucleus while extending the electrons of oxygen. That effect will make it easier for a reaction to occur on the oxygen atom. That effect can also be seen in the IR spectrum of an amide.

I like using acetic anhydride because it has a high boiling point and the by-products are all volatile organic compounds.

Chap 10.6 *Reaction of a Carboxylic Acid with Thionyl Chloride and DMF as Catalyst*

This is one of the best ways to make an acid chloride. It also parallels reaction 10.5 and demonstrates some of an amide's reactions.

Chapter 11

p 59 *Lithium Aluminum Hydride Reductions*

Lithium aluminum hydride will react violently with water or low mw alcohols. Reductions are carried out in aprotic solvents such as ether, tetrahydrofuran, or dimethoxyethane.

Chap 11.6 An oxygen atom must be removed to get the final amine product. I think this might be the most difficult step in the reaction and reductions which involve loss of a complexed oxygen are more sluggish than other $LiAlH_4$ reductions. For example, references often show the use of an excess of $LiAlH_4$ to give a successful reduction of an amide.

Reference

Notes

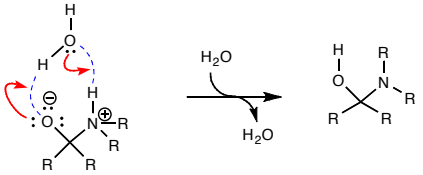
Chap 11.7 Notice the first step of the lithium aluminum hydride reduction of a carboxylic acid is abstraction of the hydrogen and generation of hydrogen gas. Lithium aluminum hydride reacts similarly with water (or alcohol) at the start of a reaction and therefore reductions must be carried out in the absence of moisture. This reaction is also evident from unreacted aluminum hydrides when quenching the reaction mixture during work up. It is also wise to exclude oxygen or air to prevent the released hydrogen from igniting.

Chap 11.8 *Reductive-Amination*

Even though the reductive-amination reaction is written as two separate reactions, which it is, both reactions can be carried out at the same time. The reactions are compatible with one another and are frequently carried out in a single flask. The imine, as it forms, can be reduced.

Triacetoxyborohydride is one of several reductants that one can use. Others are sodium cyanoborohydride ($NaBH_3CN$) or hydrogen with a palladium or nickel catalyst.

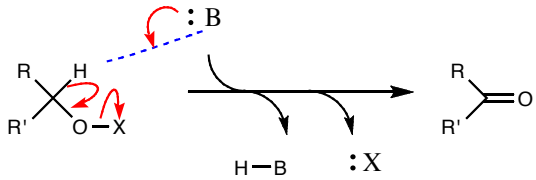
In step 1, the aldehyde is converted into an imine. I've written this as a stepwise process while others have suggested an intermolecular protonation-deprotonation reaction.



Chapter 12

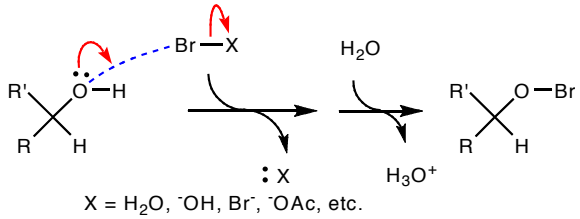
p 64 *General form for oxidations*

The key step in an oxidation reaction is transfer electrons onto some group X, Equation 1. The X-group can be a halogen, oxygen, or a metal, frequently Cr, Mn, Ag, and others.



(1)

The first step in that process is to create an O-X bond. For monovalent oxidants (Br, Cl, Ag), that can be a simple displacement reaction, Equation 2. Those reactions are simple and generally don't need further discussion.



(2)

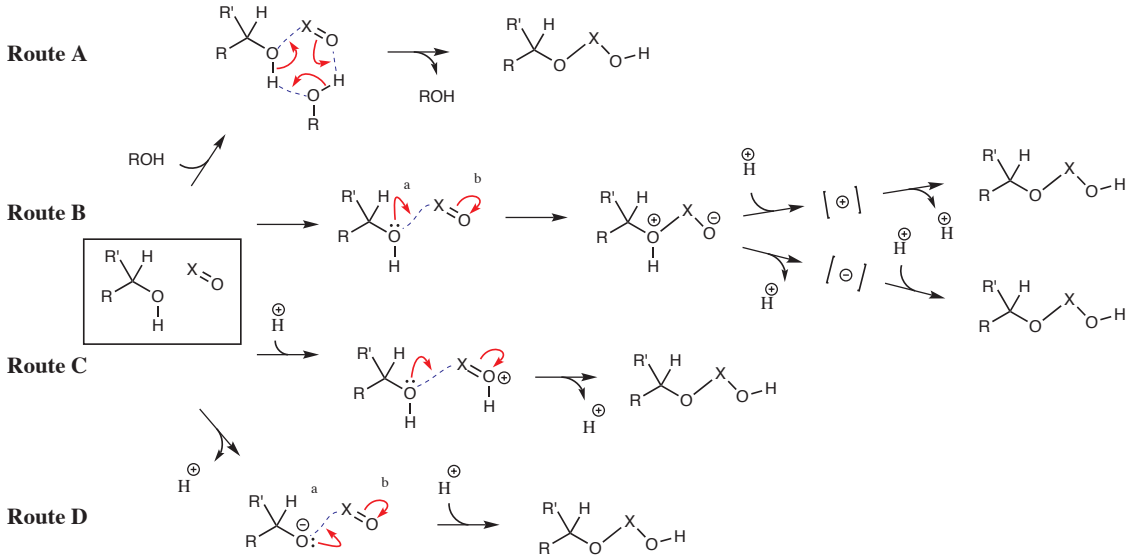
For polyvalent oxidants, formation of an O-X bond is lengthier. It is usually a series of additions and proton transfer reactions. However, these proton transfer reactions often distract from the oxidation mechanism itself. Therefore, I am going to display the principles of those reactions, some variances to consider, and an example or two. After that, I will not write out all steps. I will leave it to you to devise plausible steps to complete the reaction.

Reference

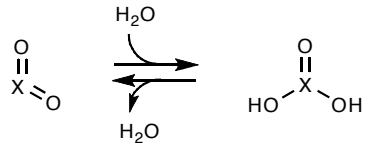
Notes

p 64 cont'd

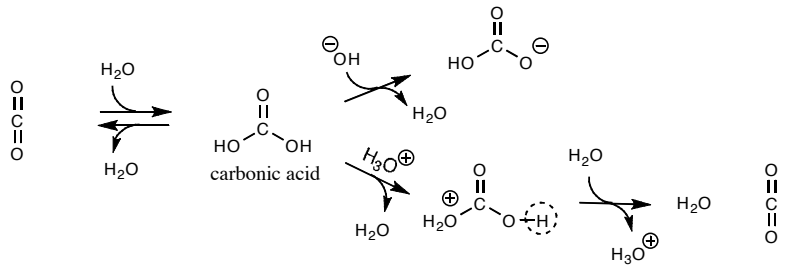
In the scheme below, four general routes to form an O-X (ester) bond are shown. The routes differ by the timing of addition-proton transfer reactions, concurrent, zwitterionic, early protonation, or early deprotonation. Route **A** is electronically neutral, but places a high entropic requirement on the reaction. Route B in an ionic route and one must determine whether these intermediates are consistent with the pH requirements of the reaction. Route **C** is a low pH mechanism while Route **D** is a high pH one. Because these routes are fast, not rate limiting, and precede the oxidation step their mechanisms are not known. Little literature data exists to guide us in determining which route to choose. Therefore, the steps showing the formation of the esters of the oxidants are not described.



Overall, any structures that can be written as shown below or contains similar structures may form by a series of addition-proton transfer steps. These reactions take place in protic solvents and are therefore capable of following any of the routes described earlier. An example of this reaction is the formation of carbonic acid.



At a high pH, deprotonation of carbonic acid occurs. Because carbonic acid can distribute the negative charge over two atoms, it is more stable than hydroxide. Therefore, the anion does not lose carbon dioxide. At a low pH, carbonic acid is protonated. The protonated form decomposes to carbon dioxide and water in either a concerted or stepwise reaction. The stepwise reaction is Route **B** above. Whether stepwise or concerted, the circled hydrogen must be removed.

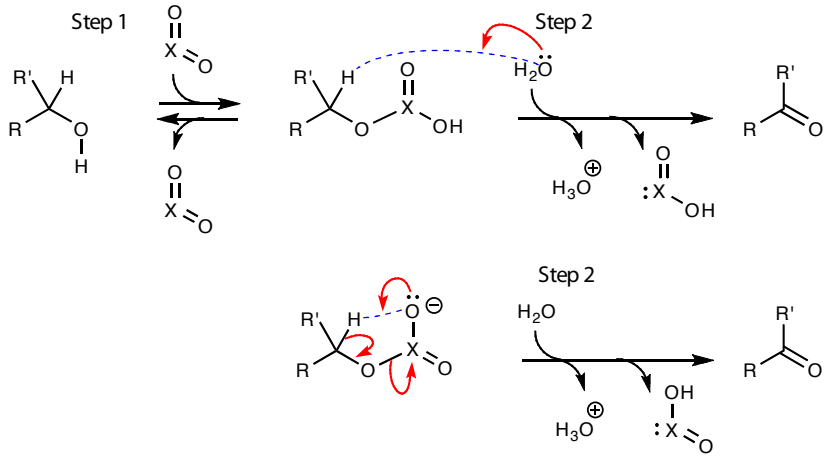


Reference

Notes

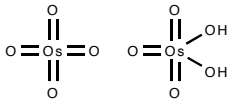
p 64 cont'd

Now that we have discussed the addition-proton transfer reactions that take place in an oxidation reaction, it is the second step that determines the product. In that step, a pair of electrons is transferred to the metal oxidant. For chromic acid oxidations, that step is rate limiting. The base could be water, but other bases are possible or it may be an intramolecular reaction.

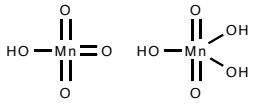


In order to simplify oxidations and since step two is the most important step, formation of the oxidant-esters will not be shown. Therefore, in this section, we will concentrate on the oxidation step rather than its formation. You may suggest a plausible route for their formation on your own. You may consult your textbook, your instructor, or you may send me an email message for additional help.

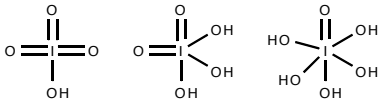
Because these oxidation reactions form metal esters by addition to the metal oxide, I have written the structures of several common oxidants and their hydrated forms. The hydrated form is the product of water addition and any oxidation may be thought to involve either of those forms (unless there is experimental evidence indicating otherwise).



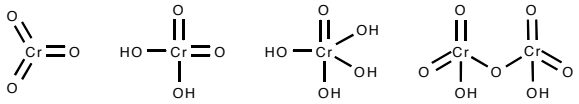
osmic acid



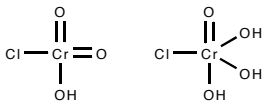
permanganic acid



periodic acid



chromic acid



chlorochromic acid

Chap 12.6 *Ozone Oxidation*

An ozonide is actually a peroxy diacetal. For reductive Step 2, two goals are accomplished, 1) reduction of the O-O bond and 2) conversion of the acetals or ketals to a two carbonyl groups. In alternate Step 2, the O-O bond is used to convert an acetal to a carboxylic acid. If a dicarboxylic acid were desired, then an additional mole of hydrogen peroxide would be required.

Since the oxidation of an ozonide is related to the Baeyer-Villiger oxidation, Baeyer-Villiger products are frequent by-products. It is sometimes advantageous to separate the second oxidation step to avoid such by-products. That is, to first employ a reductive work-up, isolate the aldehydes and ketones, and then oxidize the aldehyde in a separate step.

Reference

Notes

Chapter 13

Chap 13.1 The Heck reaction is an example of an organometallic reaction in which the steps seem fairly well understood. It is a very useful reaction because it only requires a catalytic amount of palladium, the reaction conditions are very mild, and a wide variety of functional groups are compatible with it. We will study two similar examples, reactions of acyclic and cyclic alkenes. Before the coupling reaction takes place, zero valent palladium metal, the active catalyst, must be formed in a sub-reaction. Palladium acetate reacts with an alkene (much like mercuric acetate, but in an anti-Markovnikov orientation). The intermediate is unstable and loses hydridopalladium acetate, which in the presence of base forms an ammonium acetate and zero valent palladium (Pd^0).

The first step of the coupling sub-reaction is insertion into a carbon-halogen bond, in this instance a carbon-bromine bond. This reaction is similar to the formation of a Grignard reagent. The rest of the process is similar to the palladium reduction sub-reaction. The thus formed organopalladium compound inserts into an alkene double bond. In order for an elimination to occur, the bonds must rotate. Elimination gives the coupled product and hydridopalladium bromide. The hydridopalladium bromide will lose hydrogen bromide and regenerate palladium zero.

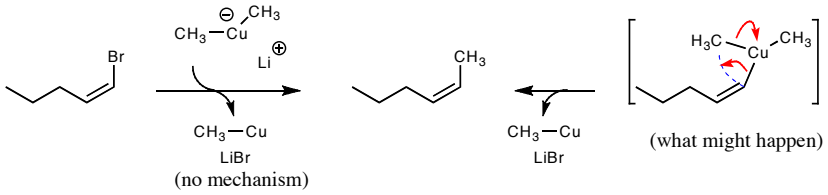
Also important to the reaction are the ligands that donate electrons to palladium. I followed the model of prior reactions by not showing atoms that are not part of a reaction, like by-stander ions or solvents. Presumably, the electrons of the alkene replace the electrons of one of the ligands that coordinate with the palladium. Therefore, the ligands are vital to the success of the reaction. They must be exchangeable in the reaction.

Chap 13.3 *Catalytic Reduction*

This mechanism is hypothetical. It was extrapolated from the Heck reaction to similar mechanisms and other metals. This mechanism can broadly explain formation of the products and by-products of catalytic reduction reactions, for example, how *trans*-fatty acids are produced.

p. 71 *Gilman Reagents*

These mechanisms are hypothetical. The mechanisms of the Gilman reagents are not known. I've written them to broadly agree with how these reagents might react. The groups couple without losing the stereochemistry. While I don't know how that might occur, I anticipated that just as zero-valent palladium could insert into a carbon-halogen bond, so too must the copper insert into the carbon-bromine bond. If it did, then the intermediate on the right would occur. The decomposition of this intermediate parallels that of the palladium (Heck) and mercury (reduction step of oxymercuration) reactions.



Let's discuss the insertion and elimination steps a bit further. The mechanism by which magnesium inserts into a carbon-halogen bond in a Grignard reaction is uncertain. It is believed to be a radical reaction, but the actual mechanism is infrequently shown. If you consider the properties of the other reagents that are reacting with an alkyl, alkenyl, or aryl bromide, the metals are all able to donate electrons in breaking the carbon-halogen bond. In a Gilman reagent, I presume that replacing an iodide atom of copper iodide with a methyl group would increase the electron density on copper.

Reference

Notes

72 If another methyl group were also added to the copper, then it is again plausible that the electrons on copper would be more available still. Now, without explaining the mechanism of the reaction, each of these reagents, Gilman, magnesium, lithium, and palladium, donate electrons to the carbon-halogen bond in breaking that bond and leading to a net insertion.

For the loss of copper in the Gilman reactions, if you look back to the de-mercuration step of the oxymercuration reaction, this is reported in the literature to be a radical reaction. The decomposition of the alkylcuprate can also be written as a radical reaction. However, I like to write this as a two-electron process, which is similar to other reactions in this book, e.g., oxidation of boranes, Baeyer-Villiger oxidation, loss of PdH_2, and others. I like the two-electron mechanism as this nicely parallels these other reactions. By using a parallel, I think the reactions are now written in a more plausible manner. By being plausible, it makes the reactions easier to understand, remember, and use (which is the objective of this book).

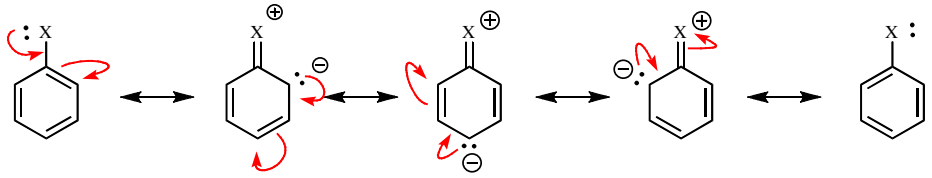
Chapter 14

p. 73 *Electrophilic substitution of substituted aromatic compounds*

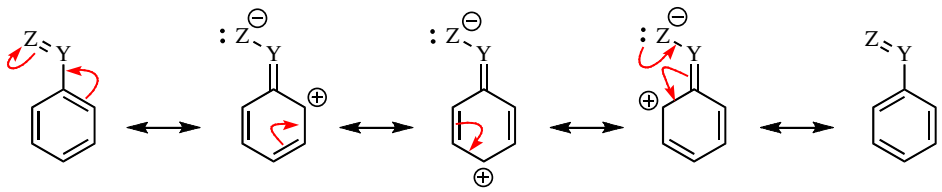
The method I prefer to predict the products of electrophilic aromatic substitution reactions is from an analysis of the resonance structures of the reactants. First, draw the resonance structures for the substituted benzenes, shown below. Because the resulting resonance structures have a charges, they are not the major resonance contributors. However, they do predict whether the atoms of the benzene ring will be **more** or **less** electron rich. Examine the resonance structures and answer; compared to benzene, will the compound react faster or more slowly than benzene in an electrophilic substitution reaction (such as bromination or nitration)? Where on the molecule will the highest electron density be found? At the *ortho-para* or *meta* position?

I like this method of examining the resonance structures of the reactants to predict the regiochemistry of the reaction. I believe the reaction profile is more consistent with the slow step being addition to an aromatic ring (and disrupting aromaticity) I am also more satisfied by how the resonance structures predict reactivity because those that add electron density to the ring will be more reactive while those, which remove electron density, are less reactive. However, halogens do not follow that pattern in that they contribute electrons by resonance, but are less reactive. However, this is consistent with halogens having non-bonded electrons to donate, but because of their electronegativity, are reluctant to do so.

Electron donating groups (usually, X = N, O, halogen), *ortho-para* directors



Electron withdrawing groups (usually Y = C, N, P, or S; Z = N, O, or S), *meta* directors



Reference

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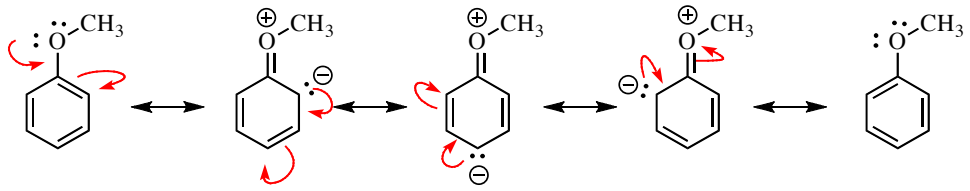
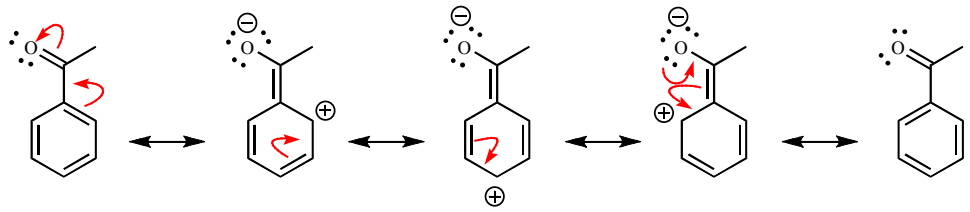
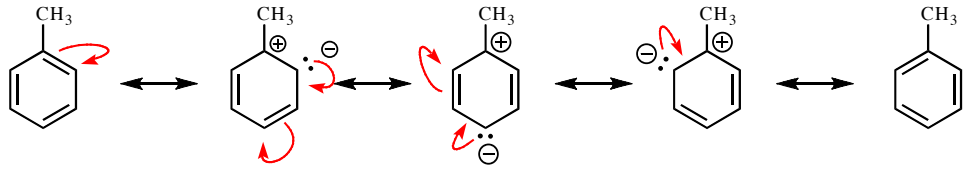
p. 73 cont'd Anisole, *ortho-para* director



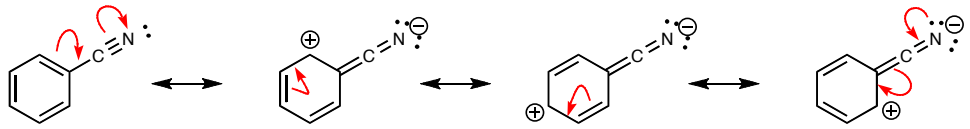
Acetophenone, *meta* director



Toluene, weak *ortho-para* director

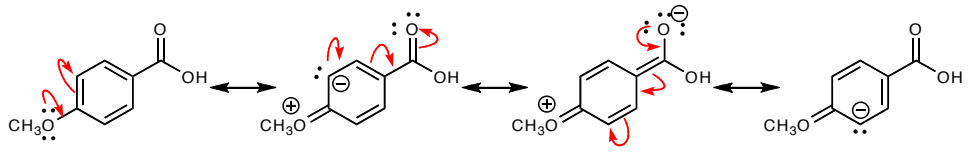


Benzonitrile, *meta* director



If a multi-substituted benzene reacts, the **activating substituents have the greatest effect on determining the regiochemistry of the products**. In the methoxybenzoic acid shown below, the methoxy group controls the substitution pattern whether the carboxy group is *ortho*, *meta*, or *para* to it. In the nitroanisole example, the upper series of resonance structures will predict the product distribution while the lower will not. The upper show the resonance structures of the activating methoxy group while the lower show the resonance structures of the deactivating nitro group.

p-Methoxybenzoic acid, *ortho-para* director to CH_3O and *meta* director to COOH

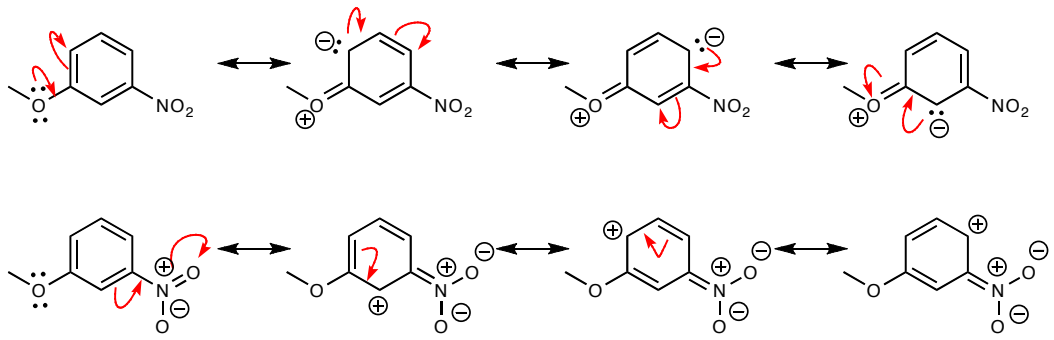


meta-Nitroanisole, CH_3O-, *ortho-para* director of reduced reactivity, less regioselective. The upper series of resonance structures show where electron density will be increased and therefore direct substitution to those positions. The lower series of resonance structures shows the effect of the nitro group has. It will <u>not</u> control the regiochemistry, but it will decrease the electron density (and thus

Reference

Notes

p. 73 cont'd reactivity) of the methoxy group.



Chap 14.10 In the reaction of the second equivalent of chloromethane and aluminum chloride, no reaction occurs on the *p*-nitrobenzamide ring. Since Friedel-Crafts reactions are the least reactive of electrophilic reagents, no reaction occurs on the ring with the two electron withdrawing groups.

Chap 14.11 *Nucleophilic Aromatic Substitution*

If you react a substituted aromatic compound with a nucleophile rather than an electrophile, the aromatic ring cannot donate electrons to the nucleophile. The nucleophile may add to the aromatic ring provided the aromatic ring contains enough electron withdrawing groups. The electron withdrawing groups must be able to absorb the negative charge of the nucleophile. The reaction is an addition-elimination reaction in a manner similar to an acid chloride. The most effective electron-withdrawing group is a nitro group, but other groups will work at lower rates.

Chap 14.13 *Benzyne Reaction*

If you react a nucleophile with a halobenzene, no reaction will take place if no strong electron withdrawing groups are present. If a sufficiently strong base were used, a deprotonation may take place which may generate a benzyne intermediate. The resulting benzyne, because constraining a triple bond in a six-membered ring, will be very reactive. Therefore, the regiochemistry of the original halobenzene becomes lost as the nucleophile can add to either side of the triple bond of the benzyne.

Chap 14.14 *Diazotization*

The diazotization reaction is not as complicated as it may look. It has six proton transfer reactions (acid-base chemistry), two dehydration reactions, and a condensation of NO^+ with aniline. One of the steps is like an acid catalyzed enolization except the carbon atoms are replaced by two nitrogen atoms. However, the most frequent error that I have noted has been due to an incorrect Lewis structure for sodium nitrite.

Chapter 15

Chapter 16

Chap 16.2 *Allylic Bromination with NBS*

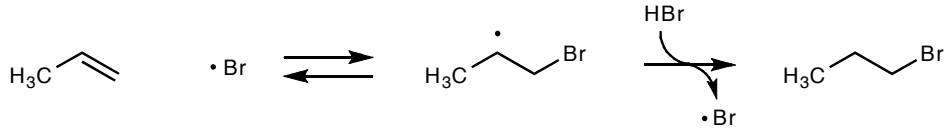
A number of different catalysts are capable of initiating radical reactions. Benzoyl peroxide and azoisobutyronitrile (AIBN) are commonly used. While the reaction generates an oxygen radical to start the reaction, it becomes transferred over to a bromine radical.

Reference

Notes

16.3 *Radical Addition of Hydrogen Bromide*

Why does NBS lead to an allylic bromination while a radical addition of HBr leads to addition? Both are reactions of a bromine radical with an alkene. If addition of a bromine radical is the expected product, how can one get allylic bromination (eq 2) to occur if the addition of a radical to a terminal position (eq 1) is a faster reaction? If the addition of the bromine radical to a terminal alkene is a fast but reversible reaction, then its success would be aided by quenching the intermediate radical with HBr. If the concentration of HBr is low or absent, then the reaction may reverse. Then a competing abstraction of the allylic hydrogen in a bromination reaction might occur. The use of N-bromosuccinimide is effective as the HBr generated by the allylic bromination is consumed by NBS to give succinimide.



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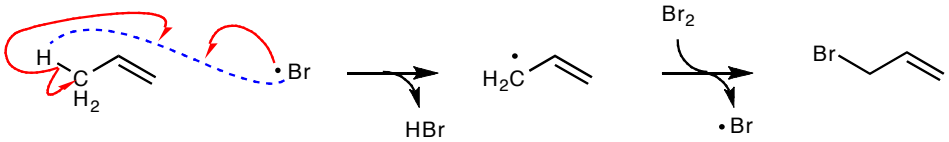

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