STRUCTURE & REACTIVITY IV: REACTIVITY IN ORGANIC, BIOLOGICAL AND INORGANIC CHEMISTRY 2

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Structure & Reactivity IV: Reactivity in Organic, Biological and Inorganic Chemistry 2

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CHAPTER OVERVIEW

1: Reaction Kinetics

1.1: Introduction- Reaction Kinetics

How can you confirm through experiment that a reaction is happening in a particular way? What is the mechanism of the reaction? What intermediates are occurring, and in what order do the bond-making and bond-breaking steps take place?

There are lots of experiments people perform to work out how reactions happen. One of the methods used is chemical kinetics, in which the rate of a reaction is measured. By making changes in the reaction conditions and measuring the effect of the changes on the rate of reaction, we can infer what is going on at the molecular level.

- Chemical kinetics is the measurement of how quickly reactions occur.
- If changes in conditions affect the speed of reaction, we can learn something about how the reaction happens.

Kinetic studies are important in understanding reactions, and they have practical implications, too. For example, in industry, reactions are conducted in reactors in which compounds are mixed together, possibly heated and stirred for a while, and then moved to the next phase of the process. It is important to know how long to hold the reaction at one stage before moving on, to make sure that reaction has finished before starting the next one.

By understanding how a reaction takes place, many processes can be improved. For example, if we know that a particular intermediate is involved in a reaction, we might avoid the use of conditions (such as certain solvents) that are incompatible with that intermediate. We might also be able to think of reagents to add that would make certain steps in the reaction happen more easily.

Not only are kinetic studies important in industry, but they are also used to understand biological processes, especially enzyme-catalyzed reactions. They also play a role in environmental and atmospheric chemistry, as part of an effort to understand a variety of issues ranging from the fate of prescription pharmaceuticals in wastewater to the cascade of reactions involved in the ozone cycle.

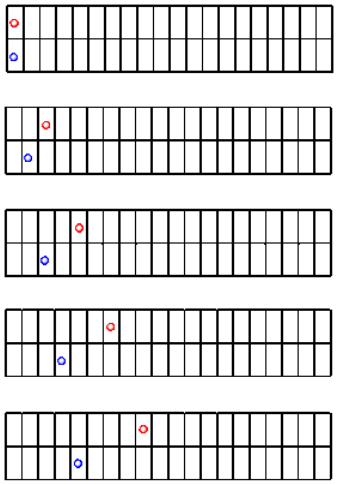
1.2: Reaction Rates

To get started, let's think about what is meant by "rate". The rate of a reaction is just its speed. Just as your speed when driving down the highway can be described in terms of your progress over time (in miles or kilometers per hour), a reaction can be described in terms of the progress of the reaction over time.

- The reaction rate is the progress of the reaction over time.

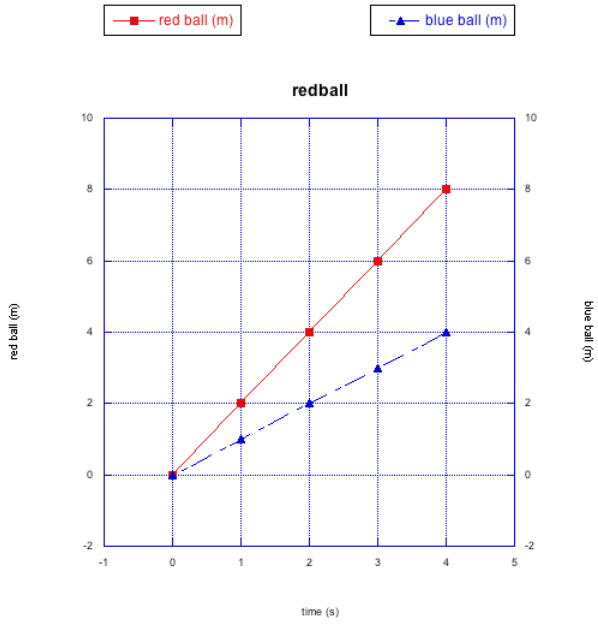
Let's look at a very simple comparison of rates. We'll look at what might happen when we roll a ball along a sidewalk. We'll roll two balls, side by side: a red one and a blue one. We'll give the red ball a slightly harder push, and give the blue one a softer touch. Then we'll snap some pictures of the two balls as they roll along.

The following drawings are a sequence of these pictures. Let's assume we take a picture every second. You will notice that some kid has marked off a line every meter using sidewalk chalk.



What do we see? The red ball is going a little faster than the blue one. It is making more progress over time.

Sometimes, it's useful to make a graph of our observations.



A graph lets us see the relationships among the data we have observed. In this case, the data is just the distance the ball has moved (in meters) and the time (in seconds). This particular relationship is described as a "linear relationship"; that just means that, when

we graph the distance the ball has moved over time, we see a straight line. This is true for both the blue ball and the red ball. In this case, it tells us that both balls are moving at a steady speed.

- Plotting data on a graph lets us see relationships very easily.

However, the red ball is moving more quickly than the blue ball. We can easily use the graph to measure exactly how much more quickly it is moving (you may also be able to do it just by looking at our pictures of the ball rolling along the sidewalk. We can use the slope of the line to determine the rate of change of distance with changing time.

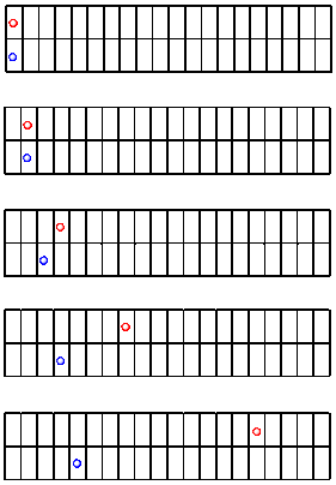
- For a straight line, slope = "rise"/"run"
- "rise"/"run" = distance / time
- distance / time = speed

The red ball moves 8 m in 4 s. Its speed is 2 m/s. The blue ball moves 4 m in 4 s. Its speed is 1 m/s. The red ball is moving twice as quickly as the blue ball.

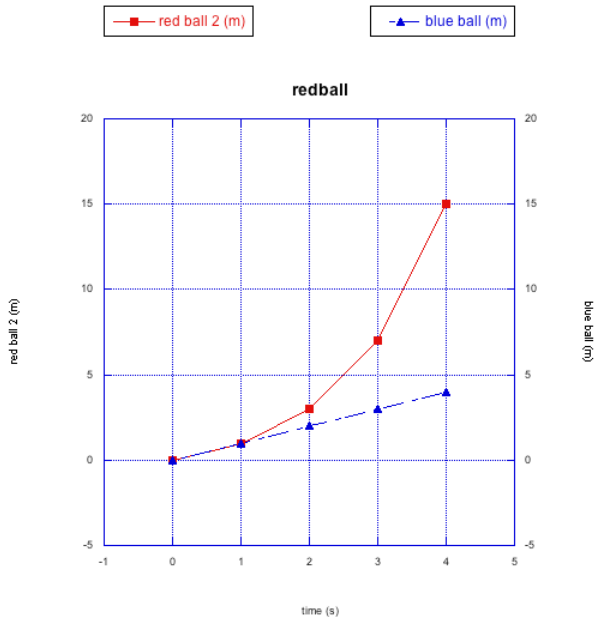
That sort of comparison of rates of change is similar to what is done in chemical kinetics. Furthermore, we might try to explain *why* there is a difference between the two rates (in this case, we pushed the red ball harder than the blue ball).

- Sometimes we can quantify comparisons using graphical analysis.

Let's look at another race between the red ball and the blue ball. This time, who knows? Maybe the blue one will win.



Clearly, the red ball is faster than the blue one again. But let's see what else is made clear by graphing the data.



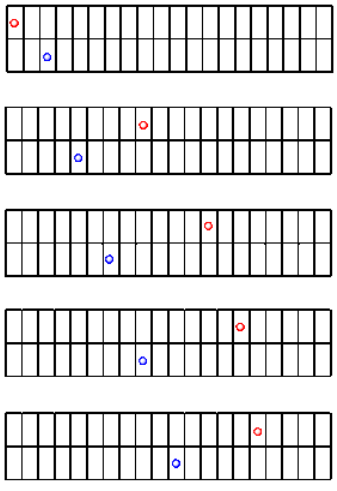
The blue ball is still moving at a steady rate. However, this time the red ball is getting faster and faster. The slope of the line between the last two data points is much higher than it is between the first two data points. In this case the red ball is accelerating; its speed is increasing over time.

The red ball doesn't obey a linear relationship between distance and time. This is a nonlinear relationship, instead. It may fit a polynomial expression, or some other nonlinear function.

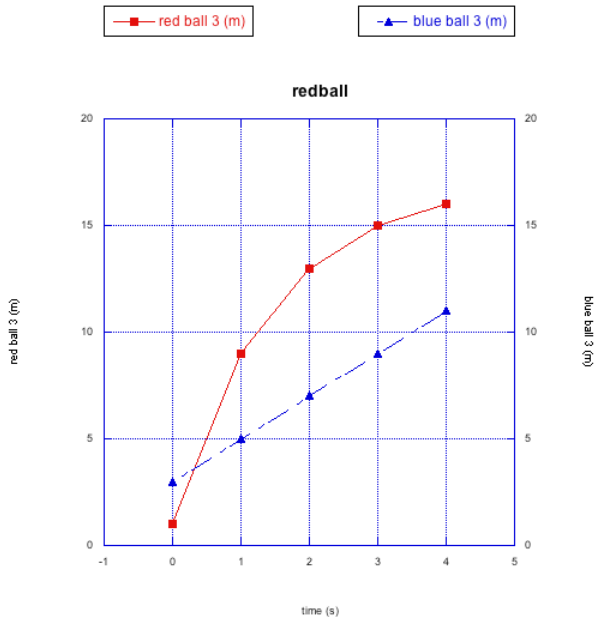
- Sometimes, rates are non-linear. The speed changes over time.

Again, the rate could be interpreted physically. The red ball may be accelerating because of some factor that is making it go faster and faster. Maybe the sidewalk is sloped on one side, so that the red ball is actually rolling slightly downhill.

Let's look at one more race between the red ball and the blue ball. This time, the balls have already been rolling for some time when we start taking pictures.



It looks like the blue ball starts out ahead, but it is soon passed by the red ball. When the progress is graphed, we can see a different kind of nonlinear relationship.



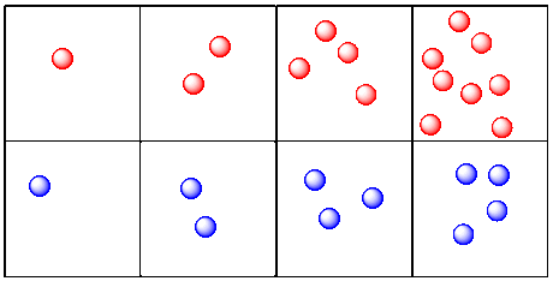
This time the red ball is decelerating. It is getting slower and slower. You can imagine that, if the blue ball keeps rolling steadily along like it has so far, it may eventually pass the red ball again. This deceleration of the red ball is a different type of non-linear relationship.

Why is the red ball slowing down, but the blue one is not? Maybe the sidewalk is uneven again, but this time the red ball is going uphill. You might be able to come up with other reasons, too.

Reaction Rates

Let's take a look at molecules and reactions. This time, instead of tracking distance over time, we will look at the number of molecules present over time. Maybe we are looking at two reactions. One reaction produces red molecules. The other produces blue molecules.

This is more like what we are talking about when we look at chemical kinetics. We are looking at changes in the amount of a compound over time. In this case, the picture makes it look like the red molecules are produced more quickly than the blue molecules. The red molecules and blue molecules are produced at two different rates.



- Reaction kinetics looks at changes in the amount of compounds present over time.

This example may look a little unrealistic. The molecules are appearing from out of nowhere, and of course they can't do that. Something can't be made from nothing. We'll see other examples in which the origin of the new molecules is more clear.

? Exercise 1.2.1

a) Draw a graph showing the rate of production of red molecules in the picture above (graph the number of red molecules vs. time).

b) Draw a graph showing the rate of production of blue molecules.

c) Compare the rates of production of the two kinds of molecules.

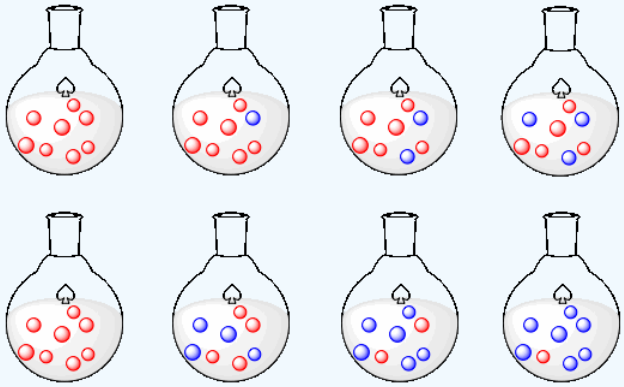
Exercise 1.2.2

a) Make a drawing of molecules changing over time. This time, instead of more molecules appearing over time, make molecules disappear over time, at a constant rate.

b) Draw a graph corresponding with your series of pictures.

Exercise 1.2.3

The following rows of flasks show two different scenarios.



a) Describe what is happening in the first row.

b) Graph what is happeing in the first row.

c) Describe what is happening in the second row.

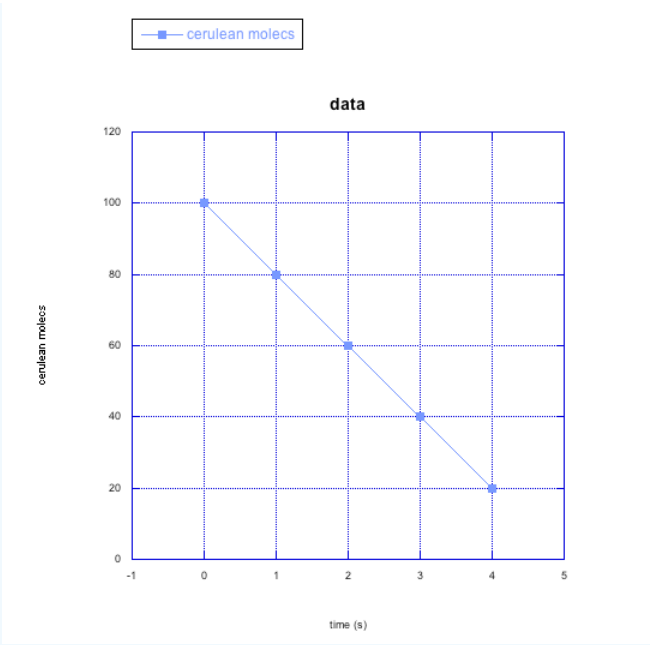
d) Graph what is happening in the second row.

e) Compare what is happening in the first row to what is happening in the second row.

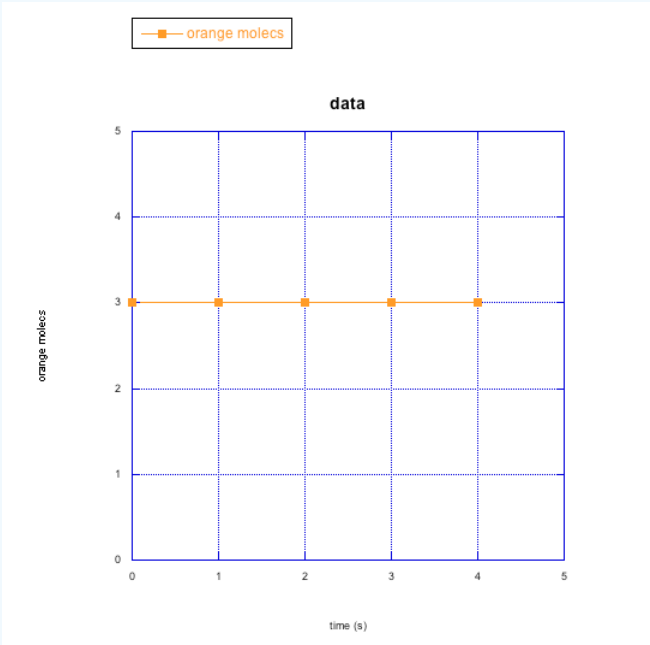
Exercise 1.2.4

The following graphs show changes in the number of molecules over time. Describe what is happening to the number of molecules (increasing? decreasing?) and to the rate at which changes are taking place (staying the same? getting faster? getting slower?).

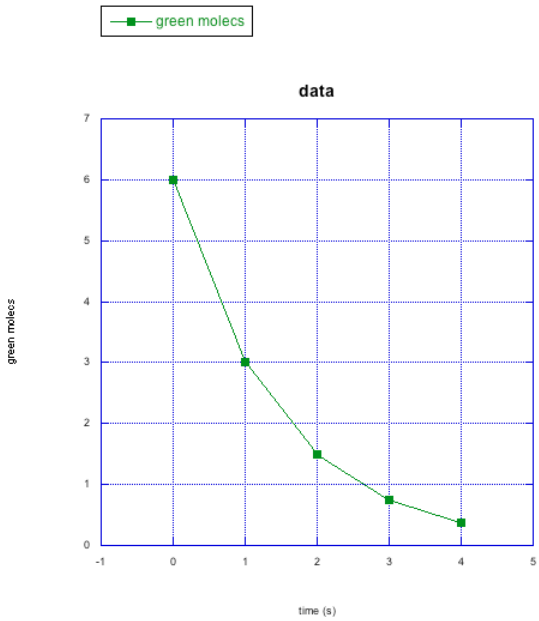
a)


cerulean molecs
data
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
cerulean molecs
time (s)

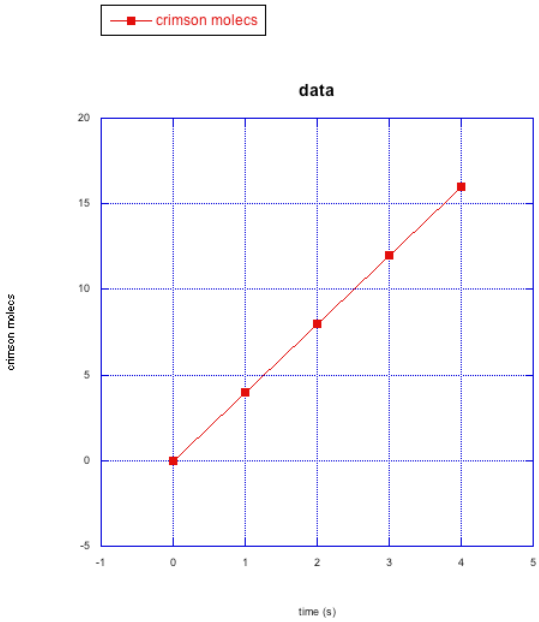
b)


orange molecs
data
5
4
3
2
1
0
0
1
2
3
4
5
orange molecs
time (s)

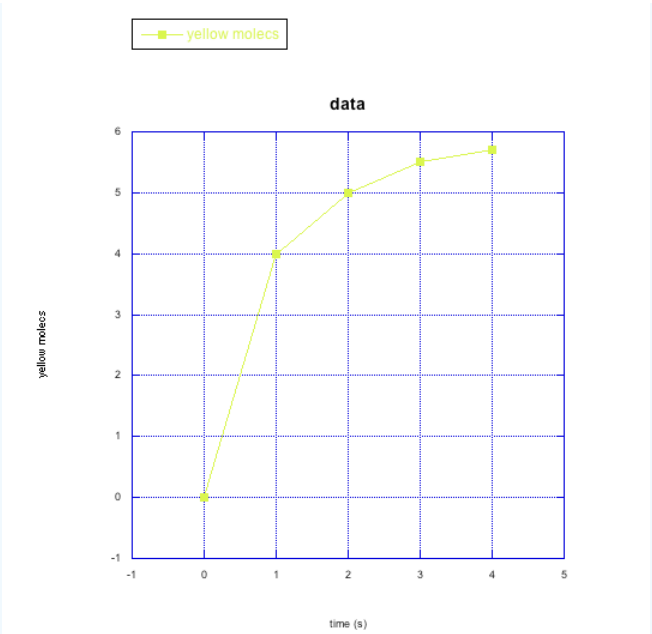
c)


green molecs
data
green molecs
time (s)
0
1
2
3
4
5
6
7
-1
0
1
2
3
4
5

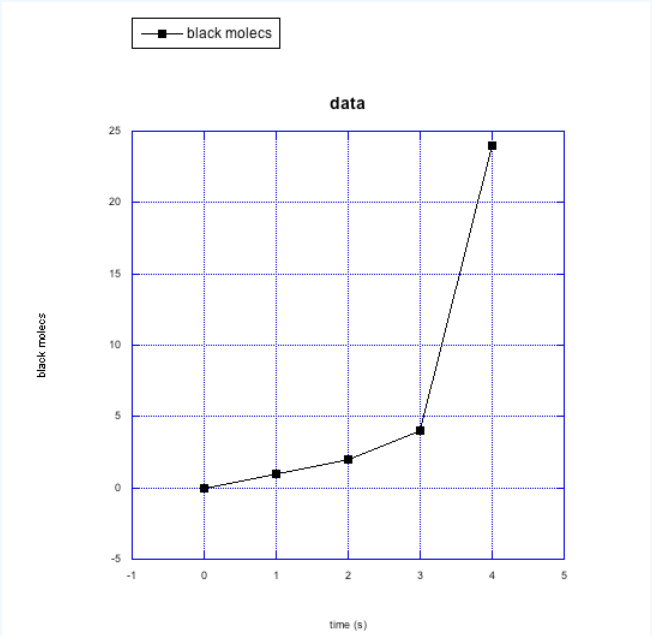
d)


crimson molecs
data
crimson molecs
time (s)
-5
0
5
10
15
20
-1
0
1
2
3
4
5

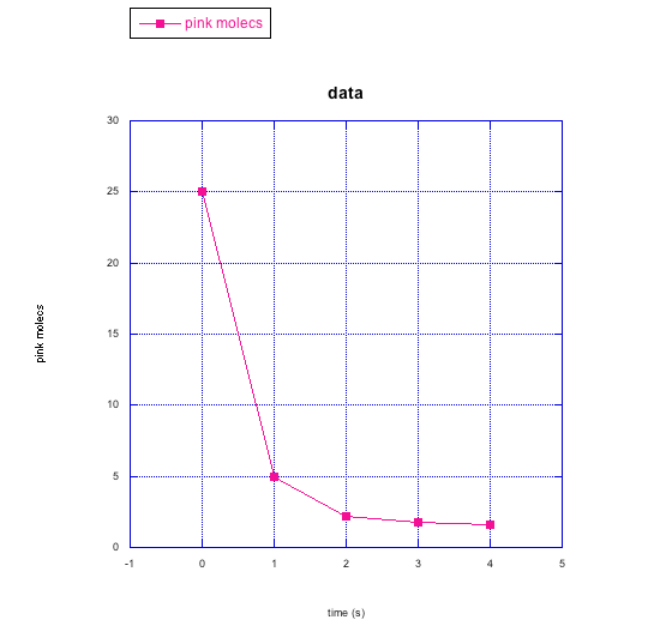
e)


yellow molecs
data
yellow molecs
time (s)
6
5
4
3
2
1
0
-1
-1
0
1
2
3
4
5

f)


black molecs
data
black molecs
time (s)
25
20
15
10
5
0
-5
-1
0
1
2
3
4
5

g)



Exercise 1.2.5

For the following cases in problem RK4, make a qualitative graph showing what you think is happening to the rate of the reaction over time (e.g. Do you think the rate is increasing over time? How would you show that on a graph?)

a) cerulean molecules

b) orange molecules

c) green molecules

d) crimson molecules

e) yellow molecules

f) black molecules

g) pink molecules

Exercise 1.2.6

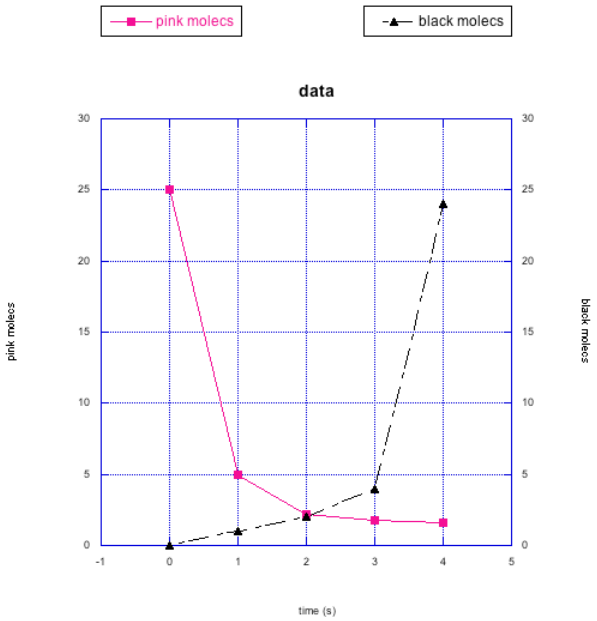
How would you describe the similarities between the changes in the green molecules and the pink molecules in the previous questions? What about the differences?

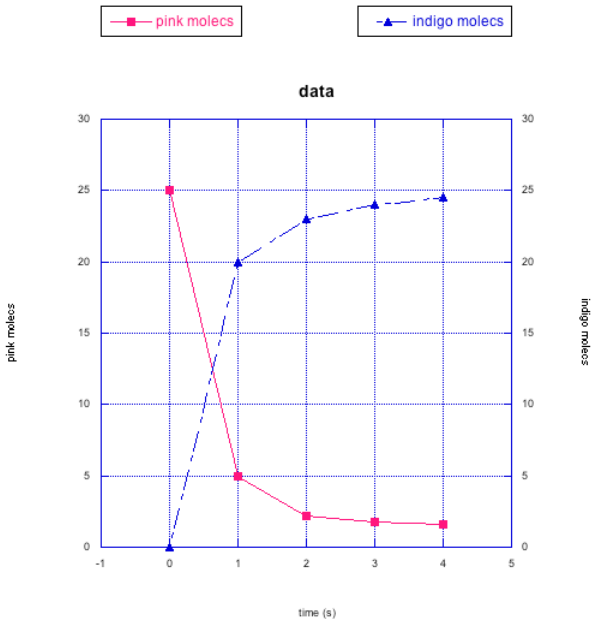
Exercise 1.2.7

Frequently, instead of just plotting changes in one compound, we might graph changes in two things at once. That way, we can look for relationships between them.

In the following graphs, pink molecules are reacting to form another type of molecule.

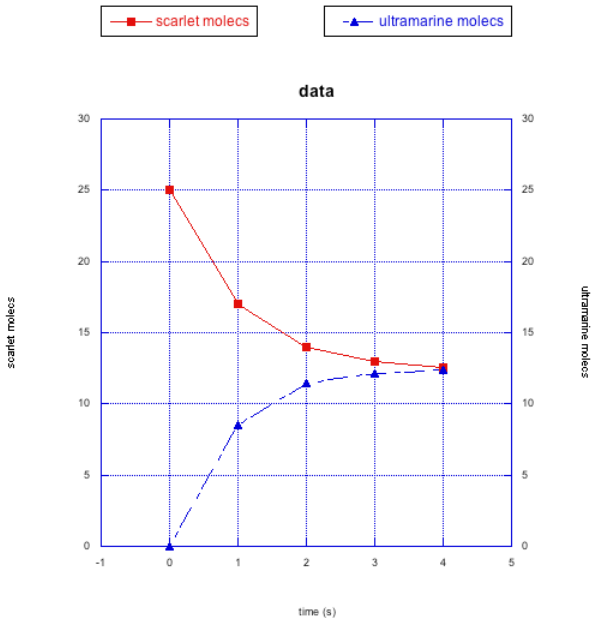
Are the pink molecules turning into black molecules or indigo molecules? How can you tell?

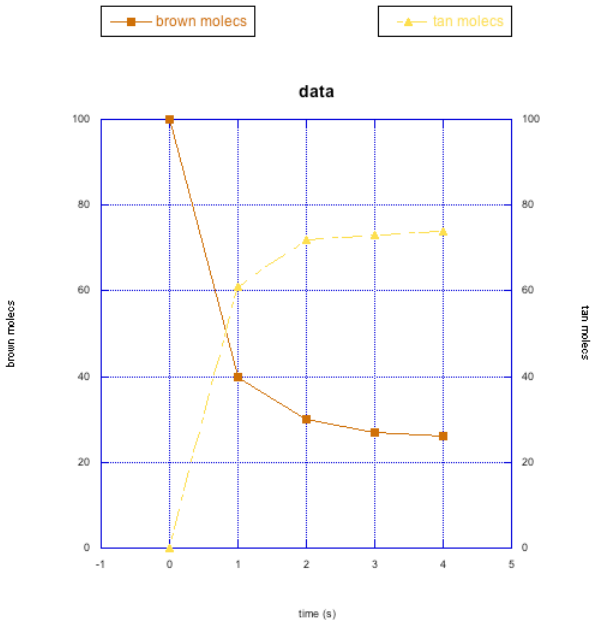


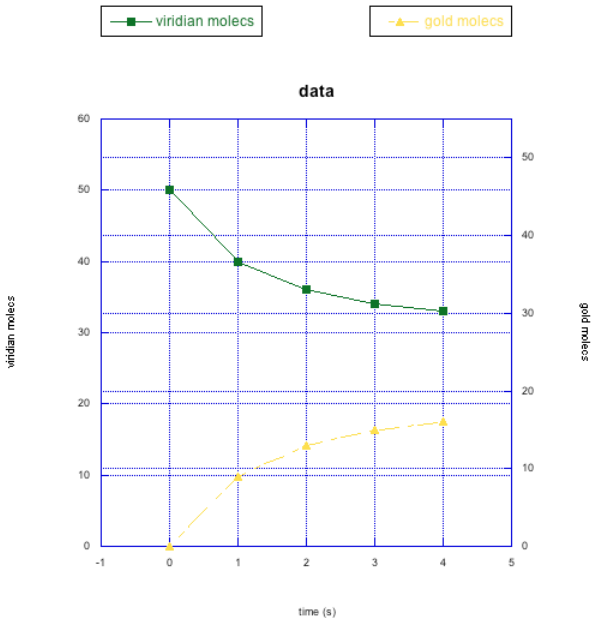


Exercise 1.2.8

The following graphs also show changes in two different compounds at once. Describe what you think is happening in each case.


scarlet molecs
ultramarine molecs
data
scarlet molecs
ultramarine molecs
time (s)


brown molecs
tan molecs
data
brown molecs
tan molecs
time (s)



Answer a

Scarlet molecules are disappearing over time. Ultramarine molecules are appearing over time. However, the number of scarlet molecules seems to stabilize around half its original number; the number of ultramarine molecules reaches about the same level. It is possible that the scarlet molecules are converted into the ultramarine ones, but reach an equilibrium. At this equilibrium, there happen to be about equal amounts of the two compounds.

Answer b

Because the rate of growth of the tan molecules seems to track the rate of loss of the brown ones, it seems likely that the brown ones are being converted to tan molecules. At some point, the change levels out, so an equilibrium is reached. At this equilibrium, tan molecules outnumber brown ones.

Answer c

Viridian molecules seem to be converting into gold ones but the system reaches equilibrium, at which point there are still more viridian molecules than gold ones.

1.3: Activation Barriers

Why do reactions take place at different rates? Why do some happen quickly, and others proceed very slowly? Why might the same reaction proceed at different rates under different conditions? There are a number of factors that influence reaction rates, but the first one that we will look at is the activation barrier.

An activation barrier is a sort of energetic hurdle that a reaction must get over. Some reactions have higher hurdles and some have lower hurdles. It's much easier to get over lower hurdles, so reactions with low activation barriers can proceed more quickly than ones with higher activation barriers.

- A low activation barrier allows a reaction to happen quickly.
- A high activation barrier makes a reaction go more slowly.

A reaction can be exergonic overall (it can give off energy), but it will generally still have an activation barrier at the beginning. Even if the compounds go down in energy by the end of the reaction, they will generally go up in energy before that happens.

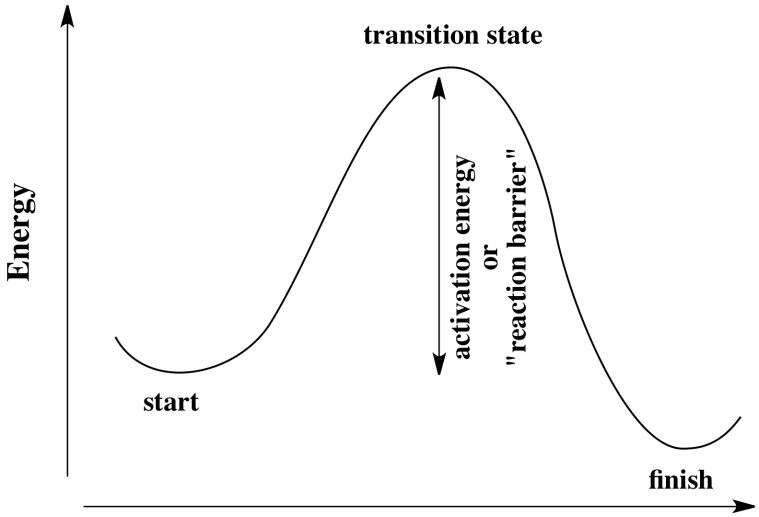
- Even if a reaction gives off energy overall, some energy must be put in at first to get the reaction started.

This situation is a little like investing in a business. A business generally requires some sort of financial investment to get started. If the business is successful, it will eventually make products and pay money back to the investors. If the business is unable to make back its initial investment, it may fail.

Reactions require some initial investment of energy. This energy may come from surrounding molecules or the environment in general. If the reaction is successful, it will proceed to make products and it will give energy back to its surroundings.

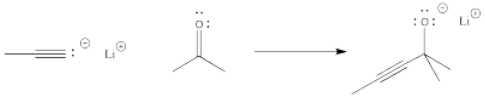
- It always "costs" a molecule energy to enter into a reaction; it "borrows" that energy from its environment.
- That initial investment of energy may be "paid back" as the reaction proceeds.

All reactions must overcome activation barriers in order to occur. The activation barrier is the sum of the energy that must be expended to get the reaction going. An activation barrier is often thought of, cartoonishly, as a hill the molecule has to climb over during the reaction. Once, there, it can just slide down the other side of the hill to become products. At the top of the hill, the molecule exists in what is called the "transition state". At the transition state, the structure is somewhere between its original form and the structure of the products.



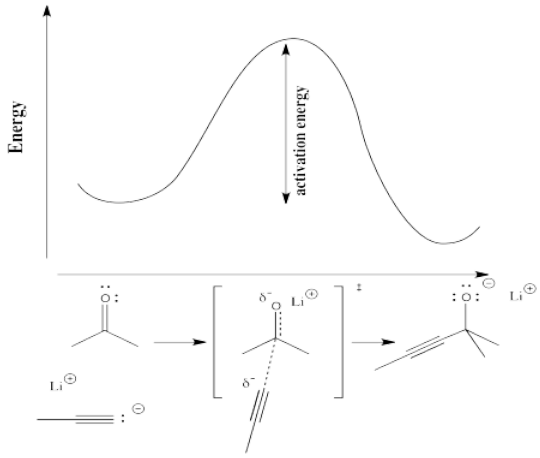
The type of diagram shown above is sometimes called a "reaction progress diagram". It shows energy changes in the system as a reaction proceeds. One or more activation barriers may occur along the reaction pathways, as various elementary steps occur in the reaction.

In order to see more concretely what terms like "reaction progress" and "transition state" mean, let's look at a real reaction. Suppose a nucleophile, such as an acetylide ion, donates its electrons to an electrophilic carbonyl. The π bond breaks and an alkoxide ion is formed.



The reaction progess simply refers to how far the reaction has proceeded. Is it just starting out, is it almost finished, is it just halfway there? The transition state refers specifically to the highest energy point on the pathway from reactants to products. It refers to the structure at that point, and the energy associated with that structure.

In the following diagram, the term "reaction progress" has been replaced by an illustration that shows how far the reaction has proceed by that point in the energy curve that is above the reaction drawing. The structure in the square brackets is the transition state, coresponding to the highest point on the curve. The "double dagger" symbol (a little bit like a Patriarchal or Russian Orthodox cross, with two crosspieces on a vertical post) is the symbol that tells you that you are looking at a transition state structure.



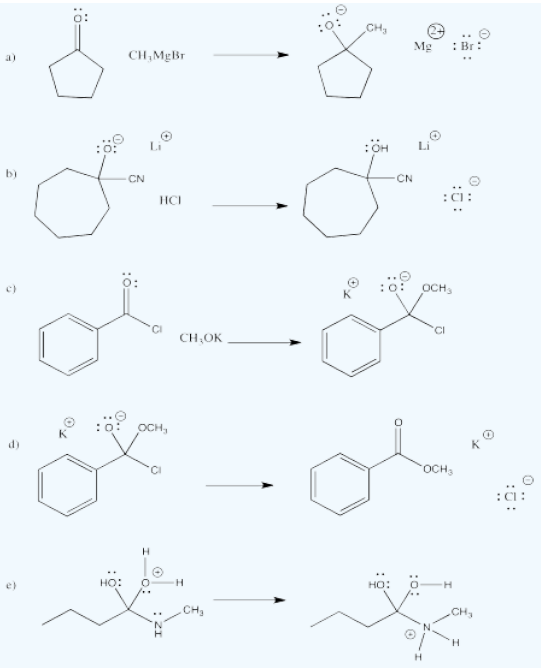
The transition state doesn't refer to a regular chemical structure. It doesn't necessarily obey the rules of Lewis structures, because some new bonds have started to form and some old bonds have started to break; you can't really draw partial bonds in a Lewis structure.

Physically, the transition state structure is not something that can be isolated and stored in a bottle. Because it sits at the top of an energy curve, the transition state is motivated to turn into something else. No matter what direction it goes to change its structure, it will go to lower energy. Remember, things always proceed to lowest energy if possible. As soon as the transition state forms, it will either slide back into the original starting materials or slip forward into the final products.

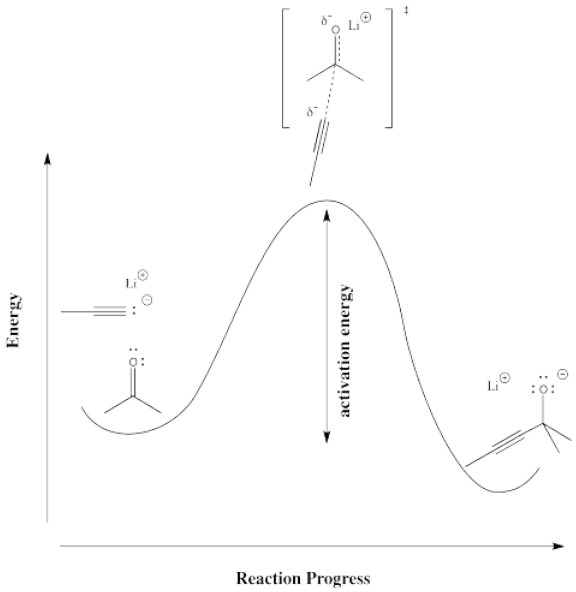
- The transition state is inherently a high-energy, unstable structure, with a very short lifetime. As soon as it comes into existence, it disappears again.

? Exercise 1.3.1

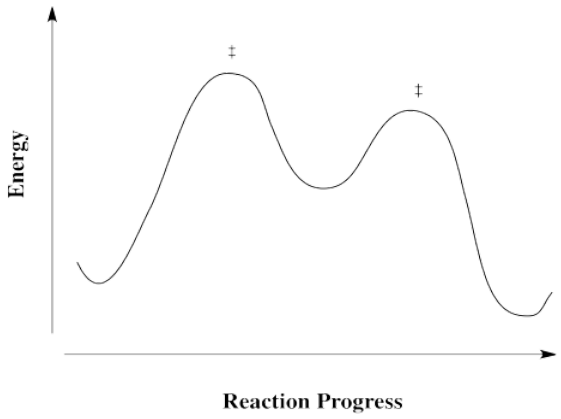
Draw what you think the transition state might look like for the following elementary reactions.



More commonly, reaction progress diagrams aren't drawn like the one above. Instead, structures of reactants, transition states and products are simply shown along the potential energy curve, as shown below.

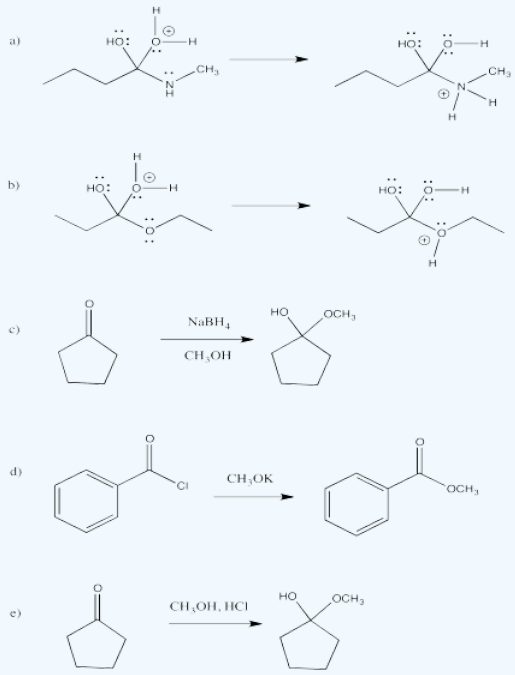


Reactions don't always happen in one step. Sometimes there is an intermediate, or more than one. An intermediate differs from a transition state in that it has finite lifetime. Although it is not as stable as the reactants or the products, it is stable enough that it does not immediately decay. Going either forward to products or back to reactants is energetically uphill.



? Exercise 1.3.2

Draw reaction progress diagrams for the following reactions. Note that the reactions may be composed of more than one elementary step.



Rate Constant

There is a measurable parameter that can be used to get an idea about the activation barrier of a reaction. It is called the rate constant. The rate constant for a reaction is related to how quickly the reaction proceeds. A large rate constant corresponds to a very fast reaction. A very small rate constant corresponds to a slow one.

- The rate constant is an index of the speed of the reaction.

Rate constants have different units depending on how the reaction proceeds, but just to give you a feel for how they vary, a reaction with a "first order" rate constant of 0.001 s^{-1} (or 10^{-3} s^{-1}; you'll learn what "first order" means later) would be over in about an hour. A reaction with a first order rate constant of 10^{-6} s^{-1} might take a couple of weeks.

The rate constant gives direct insight into what is happening at the transition state, because it is based on the energy difference between the reactants and the transition state. Based on that information, we get some ideas of what is happening on the way to the transition state.

The rate constant can be broken down into pieces. Mathematically, it is often expressed as

$$k = \frac{RT}{Nh} e^{-\Delta \frac{G}{RT}}$$

In which R = the ideal gas constant, T = temperature, N = Avogadro's number, h = Planck's constant and D G = the free energy of activation.

The ideal gas constant, Planck's constant and Avogadro's number are all typical constants used in modeling the behaviour of molecules or large groups of molecules. The free energy of activation is essentially the energy requirement to get a molecule (or a mole of them) to undergo the reaction.

? Exercise 1.3.3

For each of the following pairs, use < or > to indicate which quantity is larger.

a) e^{2} or e^{10}

b) $e^{1/4}$ or $e^{1/2}$

c) e^{-3} or e^{-4}

d) $e^{-1/2}$ or $e^{-1/3}$

Answer a

$e^{2} < e^{10}$

Answer b

$e^{1/4} < e^{1/2}$

Answer c

$e^{-3} > e^{-4}$

Answer d

$e^{-1/2} < e^{-1/3}$

Note that k really depends on just two variables:

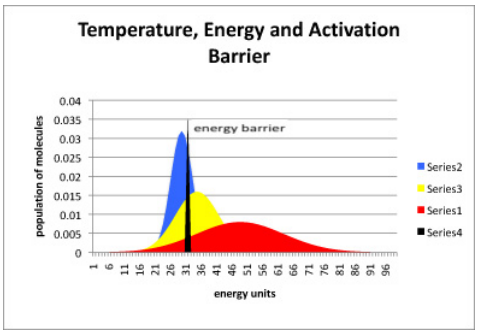
- rate constant depends on ΔG or the energy required for the reactionli>
- rate constant depends on T or the temperature of the surroundings, which is an index of how much energy is available

The ratio of activation free energy to temperature compares the energy needed to the energy available. The more energy available compared to the energy needed, the lower this ratio becomes. As a result, the exponential part of the function becomes larger (since the power has a minus sign). That makes the rate constant bigger, and the reaction becomes faster.

Large groups of molecules behave like populations of anything else. They have averages, as well as outliers on the high and low end. However, the higher the temperature, the more energy a group of molecules will have on average.

In the following drawing, the blue curve represents the energy content in a population of molecules at low temperature. The peak of the curve is near the average energy for this collection of molecules. Some of the molecules have more energy than average (they are further to the right on the blue curve) and some have less (further to the left).

The black slice through this curve indicates how much energy is needed to get over the activation barrier for a particular reaction. Notice that, at low temperature, not that many molecules have enough energy to get over the barrier at any one time. The reaction will proceed very slowly. Nevertheless, more energy is probably available from the surroundings, and so after some time most of the molecules will have obtained enough energy so that they can eventually hop over the barrier.



The yellow curve represents molecules at a higher temperature, and the red curve is a population at a higher temperature still. As the temperature is increased, larger and larger fractions of the molecules have enough energy to get over the activation barrier, and so the reaction proceeds more quickly.

- the rate constant compares energy needed to energy available
- based on that comparison, a specific fraction of the population will be able to react at a time

Free Energy of Activation

There is really more to the activation energy than we have seen so far. The activation free energy is constant for a given reaction at a given temperature. But at different temperatures, ΔG changes. Just as in thermodynamics, it can be broken down in turn to:

$$\Delta G = \Delta H - T\Delta S$$

in which ΔH = activation enthalpy and ΔS = activation entropy.

The activation enthalpy is the part that corresponds most closely with the energy required for the reaction, the way we have been describing the activation barrier so far.

The activation entropy deals with how the energy within the molecule must be redistributed for the reaction to occur. One of the major factors influencing energy distribution over the course of the reaction is molecular geometry.

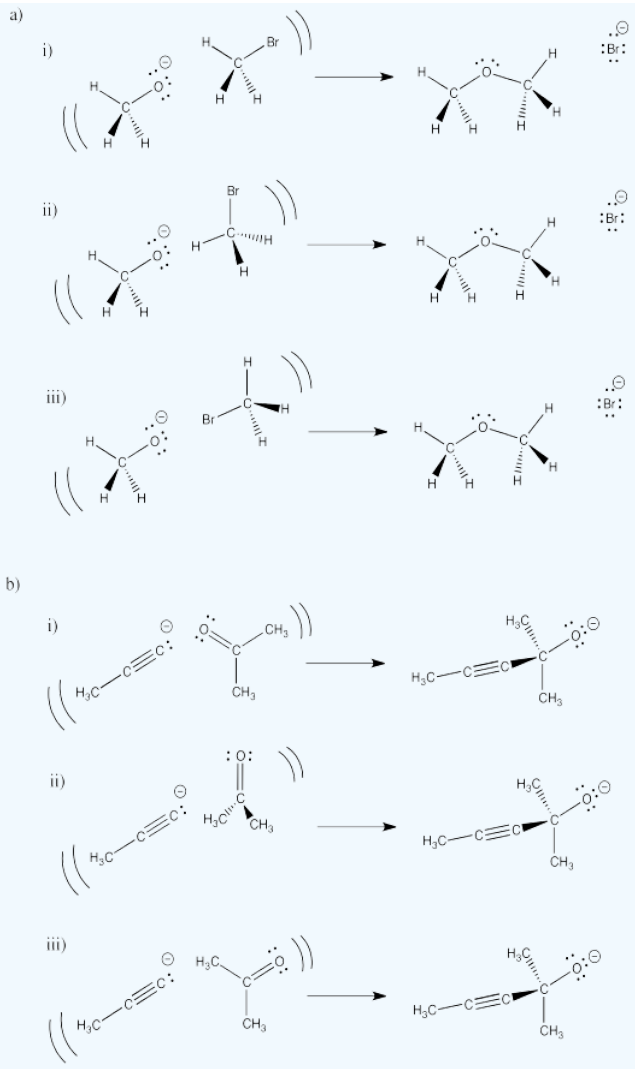
For example, suppose two molecules need to come together for a reaction to take place. They need to collide with each other. However, a reaction might not happen each time the molecules collide. Sometimes, the molecules may be pointing the wrong way when they bump into each other, so that the reaction can't occur. Often, atoms need to be lined up in the proper place where they will be forming a new bond.

When molecules are restricted to only certain orientations or geometries, they have fewer degrees of freedom. With fewer degrees of freedom, energy can be stored in fewer ways. As a result, there is often an entropy cost in initiating a reaction.

On the other hand, a reaction might start in a very different way, with one molecule breaking a bond and dividing into two pieces. Because each individual piece can move independently from the other, the degrees of freedom increase. Energy can be stored in more ways than they could be before the reaction started. As a result, although this reaction would still have an activation barrier, the entropy component may actually lower that barrier a little bit.

? Exercise 1.3.4

In the following drawings, one orientation of reactants is more likely to lead to the product shown. Select which one will be most successful in each set and explain what is wrong with each of the others.



Answer a

Orientation (i) looks most likely to result in connection of the oxygen to carbon with displacement of bromide. In orientation (iii), the oxygen appears ready to collide with the bromine atom. and in oreientation (ii), it may collide with a hydrogen atom.

In addition, you will see later that bringing the the oxygen in along the C-Br axis (but away from the bromine) is also more likely to break the C-Br bond, for reasons involving molecular orbital overlap.

Answer b

Orientation (ii) looks like the carbon anion in the acetylide ion is most likely to bond with the carbonyl carbon. In option (i), the carbon is going to collide with the carbonyl oxygen. In option (iii), it may collide with the alpha carbon, next to the carbonyl. Having the nucleophile approach from outside the plane of the carbonyl, as in option (ii), lowers the chance of collision with atoms other than the carbonyl carbon.

Again, there are also molecular orbital reasons that make this approach the preferred one.

Exercise 1.3.5

Because the activation barrier depends partly on the energy needed to break bonds as the molecule heads into the transition state, comparative bond strength can be a useful factor in getting a qualitative feel for relative activation barriers.

The metal-carbonyl (M-CO) bond strengths of the coordination complexes $M(CO)_6$ have been estimated via photoacoustic calorimetry and are listed below, by metal.

Cr: 27 kcal/mol Mo: 32 kcal/mol W: 33 kcal/mol

a) Based on that information, sketch qualitative activation barriers for the loss of a CO ligand from $Cr(CO)_6$, $Mo(CO)_6$ and $W(CO)_6$.

b) Predict the relative rates for these three reactions (fastest? slowest?).

Answer a

We would expect the lowest barrier for breaking the Cr-CO bond. The barrier to break the Mo-CO bond would be just slightly lower than to break the W-CO bond.

Answer b

Based on this information alone, we might expect the Cr-CO cleavage to occur most rapidly. Mo-CO cleavage would be slightly faster than W-CO cleavage.

Exercise 1.3.6

Comparing the strengths of bonds that will be broken in a reaction is often a good way to get a first estimate of relative activation barriers.

a) Use the following bond strengths to estimate the barriers to addition of a nucleophile (such as $NaBH_4$) to the following double bonds: C=O (180 kcal/mol); C=N (147 kcal/mol); C=C (145 kcal/mol). Make a sketch of the three reaction progress diagrams.

b) In general, C=O bonds are the most reactive of these three groups toward electrophiles, followed by C=N bonds. Are these relative barriers consistent with this observation?

c) What other factor(s) might be important in determining the barrier of the reaction?

d) Modify your reaction progress diagram to illustrate these other factors.

Answer a

On this basis alone, we would expect the lowest barrier for C=C cleavage, followed by C=N and then C=O with the highest barrier.

Answer b

This trend is exactly the opposite of what we just predicted based on bond strengths.

Answer c

There may be a few different reasons for these differences. For example, the electrophilicity of the carbon may be a factor. Based on electronegativity differences, the C=O carbon should be most positive, the C=N carbon less so and the C=C carbon not at all. That electrophilicity may raise the reactant a little in energy.

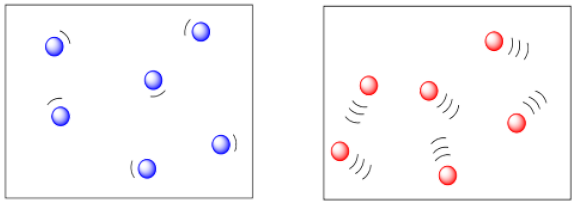
Alternatively, there may be charge stabilization factors in the first-formed intermediate, which may be reflected in the transition state on the way there. These three differing atoms (O, N, C) are all found in a row of the periodic table, so electronegativity differences should dominate charge stability. The alkoxide ion would be most stable, the amide ion of medium stability and the alkyl anion least stable of all. That trend would lower the barrier to alkoxide formation and raise the barrier to formation of a carbon-based alkyl anion.

1.4: Collisions and Phase

Reaction rates depend on the energy required (the activation barrier) and the energy available. They also may involve collisions between molecules.

If two molecules need to collide in order for a reaction to take place, then factors that influence the ease of collisions will be important.

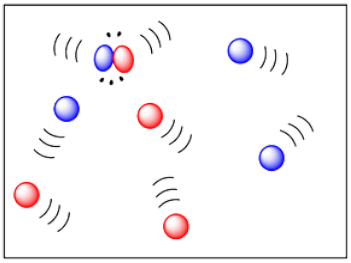
The more energy there is available to the molecules, the faster they will zip around. The faster they zip around, the more likely they are to bump into each other. So higher temperatures ought to lead to more collisions and a greater frequency of reactions between molecules. In the drawing below, the cold, sluggish molecules on the left don't appear to be in danger of colliding with anything, but the hot, zippy molecules on the right look like they are due for a crash at any time.



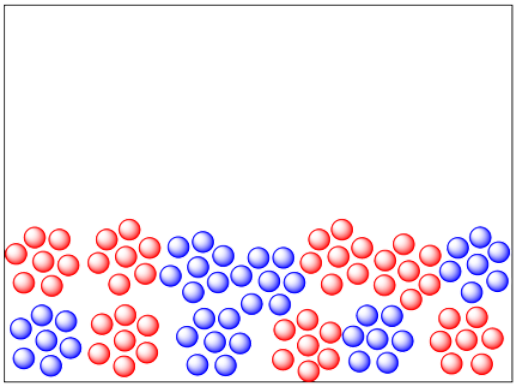
We already knew that higher temperatures increased reaction rates. This new observation is just an additional reason why temperature is important in kinetics.

- Temperature affects molecule mobility
- The higher the temperature, the more mobile the molecules will be, and the more likely they are to collide and react.

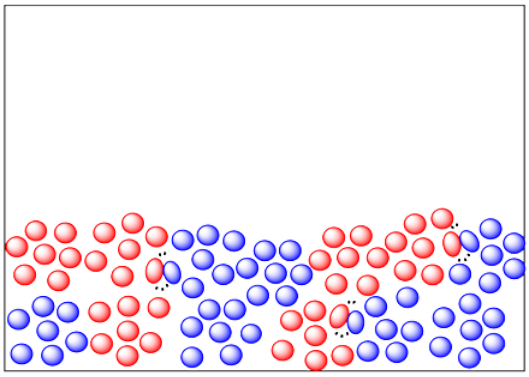
Phase also has a pronounced effect on the mobility of molecules. Molecules in the gas phase are quite free to move around, and they do so pretty quickly. On the other hand, they are pretty well spread out. Nevertheless, collisions in the gas phase happen pretty easily, which might help gas-phase reactions happen more readily.



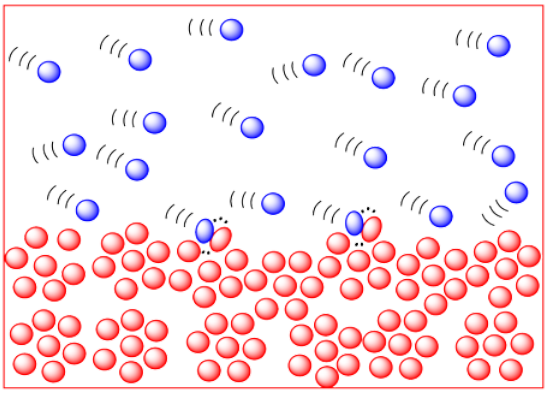
At the opposite extreme, molecules in the solid phase are not very mobile at all. (Reactions may involve atoms or ions, rather than moleules, but the same arguments apply.) Not many collisions happen. As a result, reactions often happen extremely slowly in the solid state. Reactions are mostly limited to the grain boundaries: the surfaces of the grains, where they are in contact with each other. Nothing happens in the middle of a lump of solid, which remains unreacted.



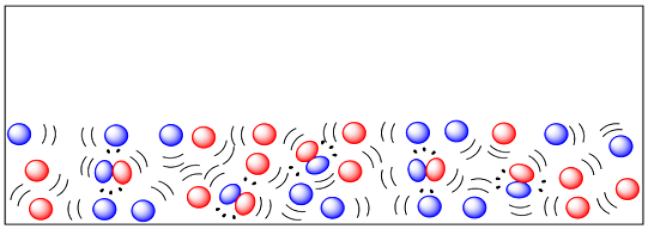
If you heat a solid up, the molecules can move around a little more. They may even leave their crystal lattice (if the solid is a crystalline one) and diffuse very slowly through the solid. Many solid state reactions are run at elevated temperature.



There are also many solid state reactions that are conducted in combination with gas-phase reactants. The solid reactants are often heated in a furnace while gas-phase reactants flow over them.



Many reactions are performed in the liquid state, either because the reactants are already liquid of because the solid reactants are heated past their melting point. In the liquid phase, molecules are much more mobile and collisions are much more frequent than in the solid phase.



It is also very common to run reactions in solution. In solution, a compound that is meant to undergo reaction is dissolved in a solvent. The solvent needs to be a liquid at the temperature at which the reaction will be run, so that molecules will be very mobile, but will still be close together, so collisions are favored.

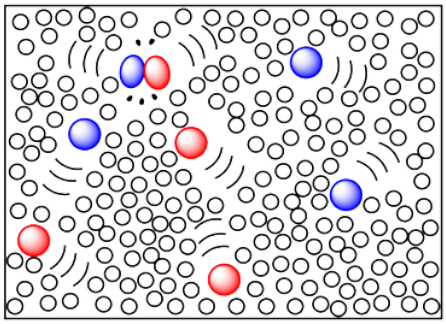
There are many advantages to running reactions in solution. The reactant molecules are very mobile and pretty close together, so that collisions are facilitated. If the reaction is exothermic and gives of a lot of heat, the excess heat can be absorbed by the solvent molecules and carried away. That can be important in controlling reactions and avoiding decomposition. Also, we will see that the rate of collisions can be controlled by adding more solvent or less, in order to slow the reaction down or speed it up. In this way, the reaction rate can be controlled to some extent.

There are many liquids that are commonly used as solvents. Dichloromethane, toluene, dimethylformamide, tetrahydrofuran and acetonitrile are some common "organic" solvents, so called because they are based on carbon, which forms the basis of molecules in organisms. These different solvents offer a range of polarities, so different ones can dissolve different reactants.

Water may be the most common solvent on the planet, and it is non-toxic, so it is very appealing for use in large-scale, industrial reactions. However, it is not very good at dissolving non-polar reactants.

The reactant compound could be a liquid or a solid. It just has to have strong enough intermolecular attractions with the solvent molecules so that it can become dissolved. Individual molecules of the reactant become lost among the solvent molecules and swim

around with ease.

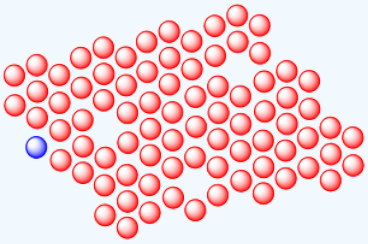


The disadvantage of using a solvent is that the solvent must be removed at the end of the reaction, so that the desired product can be isolated and used. That means the solvent may eventually be thrown away as waste. That practice is less efficient and less environmentally friendly, although the solvent could possibly be recycled.

One method of dissolving reactants that is potentially greener is the use of supercritical fluids. In this approach, gases such as carbon dioxide are pressurized until they turn into liquids. In this form, carbon dioxide is a pretty good solvent, and reactions can be run when reactants are dissolved in it. At the end of the reaction, a valve is opened, releasing the pressure, and the carbon dioxide turns back into a gas. It can be stored and re-pressurized for another reaction.

? Exercise 1.4.1

Diffusion in the solid state is greatly enhanced by defects in the crystal lattice. Show why with the following drawing.



Answer

The vacancies in the crystal lattices give other atoms places to move into, so they act as a path through which atoms can move. Diffusion through the solid is greatly accelerated.

? Exercise 1.4.2

The following drawing represents a reaction between molecules in the gas phase and molecules in the solid phase.

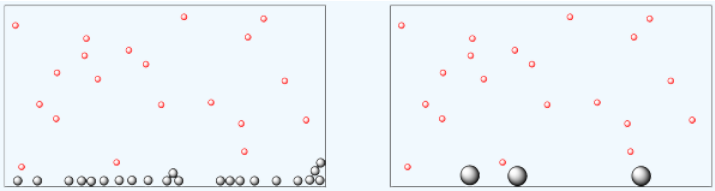
a. Which material is in the gas phase and which one is in the solid phase?
b. Both pictures contain the same mass of each material. One of these materials appears to be distributed differently in each picture, however. Explain how that difference may affect the reaction rate.

Answer a

The small, red dots are in the gas phase, so they are distributed throughout the container. The larger, gray dots are the solid, which lies along the bottom of the container.

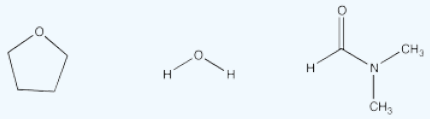
Answer b

The solid on the left is divided into finer particles, with much more surface area. If the gas reacts on the surface of the solid, reaction will be much faster on the left.



Exercise 1.4.3

Three common solvents are shown below. Compare and contrast these three solvents in terms of how they interact with other molecules.



THF water DMF

Answer

All three of these solvents have dipole moments. Also, all three molecules have oxygen lone pairs, so they are able to accept hydrogen bonds from hydrogen bond donors.

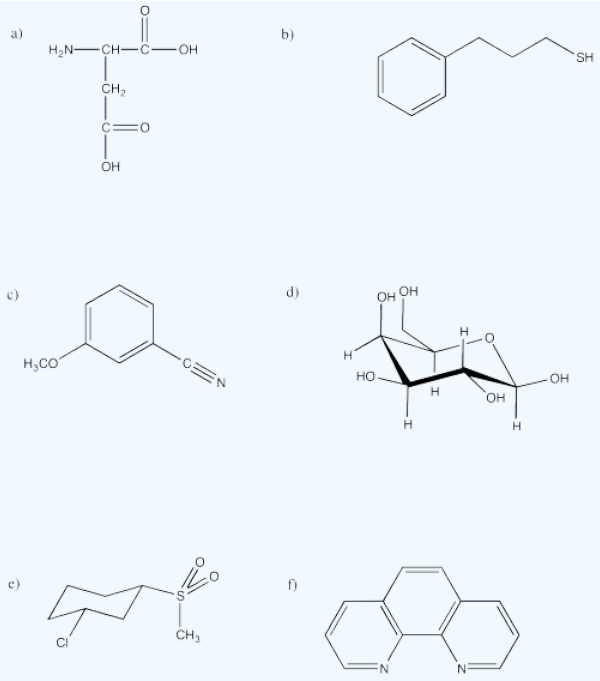
However, some of the solvents are much more polar than others. Water is capable of donating hydrogen bonds, because of its partially positive hydrogen attached to oxygen. It is the most polar of these solvents.

DMF is also very polar, because it has a polar C=O bond. This particular carbonyl is more like $^{+}$N=C-O^{-} because of lone pair donation from the nitrogen, so it is quite polar and will interact strongly with other species via dipole-dipole forces (or ion-dipole forces, if the other molecule is a salt).

THF only has a moderate dipole compared to the others. Although it will still interact via dipole-dipole (or ion-dipole) forces, it does so less effectively than water or DMF.

Exercise 1.4.4

Indicate how well you think each of the three solvents in the above question (THF, water, DMF) could dissolve each of the following compounds. Justify your answers in terms of interactions between molecules.



Answer

Water would be a very good solvent for (a) and (d), because both of those molecules would be very good at hydrogen bonding. Although water may be able to dissolve small amounts of the others, their solubility would be limited by the need for water molecules to release hydrogen bonds to each other in order to make room for the non-polar portions of these molecules.

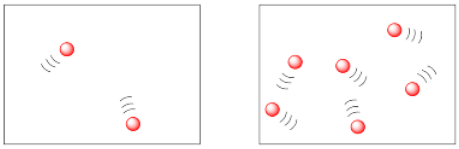
THF would be able to dissolve the other molecules pretty well: (b), (c), (e) and (f). All of those molecules contain polar bonds, like THF, and could interact via dipole-dipole forces. THF would be able to dissolve small amounts of (a) and (d) but may not be polar enough to overcome the stronger intermolecular forces between these molecules.

DMF may be able to dissolve all of these molecules to a moderate extent. Although it is not a protic solvent, its dipole is enough to help overcome hydrogen bonding among (a) and (d).

1.5: Collisions and Concentration

We know that in order for two molecules to react with each other, they must first contact each other. We think of that contact as a "collision". The more mobile the molecules are, the more likely they are to collide. Also, the closer the molecules are together, the more likely they are to collide.

In the following drawings, the molecules are closer together in the picture on the right than they are in the picture on the left. The molecules are more likely to collide and react in the picture on the right.



We might describe the two drawing above in terms of population density. Both drawings appear to offer the same amount of space, but they have different amounts of molecules in them.

The difference is a lot like the difference between human population densities in various locations around the world. Some places, such as Mexico City or Tokyo, are very crowded; they have high population densities. Some places, such as the Australian Outback or the Canadian Arctic, have low population densities.

Exercise 1.5.1

In which location do you think you are likely to bump into another person: the Upper East Side of New York City or 75 degrees north, 45 degrees west, Greenland?

Answer

Upper East Side. Lots more people per square foot.

Exercise 1.5.2

Rank the following places in terms of population density (the number of people per square kilometer).

a. Russia: pop. 143 million; area 17 million km^2
b. Bahrain: pop. 1.2 million; area 750 km^2
c. Argentina: pop. 41 million; area 2.7 million km^2
d. China: pop. 1.3 billion; area 9.6 million km^2
e. Malawi: pop. 15 million; area 118 thousand km^2
f. Vatican City: pop. 850; area 0.44 km^2
g. Jamaica: pop. 2.7 million; area 10,990 km^2

Answer a

8.41 people km^{-2}

Answer b

1,600 people km^{-2}

Answer c

15.2 people km^{-2}

Answer d

13.5 people km^{-2}

Answer e

12.7 people km^{-2}

Answer f

1,930 people km^{-2}

Answer g

24.6 people km^{-2}

Answer

Rank: Bahrain > Vatican > Jamaica > Argentina > China > Malawi > Russia

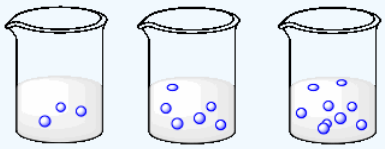
Sometimes, a lot of people are living in a small area, and the population density is high. Sometimes, the population is large, but the area is, too. Population density depends on two different factors: the number of people and the area in which they are spread out.

Concentration is the term we use to describe the population density of molecules (and other chemical entities such as atoms or ions). It describes the number of molecules there are, but also how much room, or volume, they have to move around. Thus, whereas a human population density may be described in terms of people per square kilometer, the concentration of a solution may be described in terms of molecules per liter.

Exercise 1.5.3

Describe what is happening to the concentrations of the three solutions as you go from left to right.

a)



b)

Answer a

The volume is constant, but the number of molecules is increasing. The concentration is increasing.

Answer b

The number of molecules is constant, but the volume is decreasing. The concentration is increasing.

Exercise 1.5.4

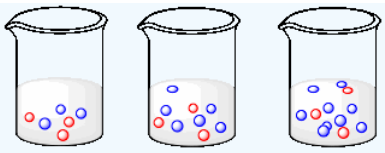
In the cases above, describe what would happen to rates of collisions between molecules as you go from right to left in the drawings.

Answer

In both cases, the molecules are becoming more densely packed. Collisions would become more frequent as we go from left to right.

Exercise 1.5.5

a) In the following drawings, state what is happeing to the concentration of molecules of each type as you go from left to right.



b) Explain what would happen to the rate of collisions between red molecules and blue molecules as you move from left to right.

c) How would your answer about rates change if the situation here were reversed: if the number of blue molecules stayed the same and the number of red molecules increased?

d) How would your answer about rates change if the numbers of both the red and the blue molecules were increasing at the same time?

Answer a

The number of blue molecules is increasing, but the number of red molecules is staying the same.

Answer b

Collisions between red and blue molecules would become more frequent as we go from left to right. The higher density of blue molecules makes collisions more likely.

Answer c

The answer would stay the same.

Answer d

The answer would stay the same qualitatively, but would differ quantitatively. The number of collisions would increase more sharply if the concentrations of both red and blue molecules increased, rather than just one concentration increasing.

We usually don't count individual molecules in a solution. We deal with groups of molecules because it's more convenient. Individual molecules are just too small to work with. In dealing with molecules in bulk, we usually use a unit called a mole, often abbreviated to mol. It's kind of like dealing with eggs by the dozen. Molecules are easier to keep track of by the mole, rather than individually.

? Exercise 1.5.6

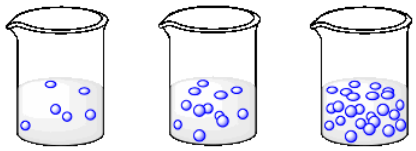
a. In the following solutions, how many dozen blue molecules are there in each case?
b. What is happening to the concentration of the beaker as you go from one beaker to the next? Quantify your answer.

Answer a

A half dozen, a dozen, two dozen.

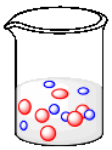
Answer b

The concentration is doubling as we go left to right from one beaker to the next.



In reality, we don't count molecules or even moles of molecules. When we want to work with a compound, we just weigh it out on the balance. We can then use the known weight of the compound to figure out how many moles we have.

Of course, if we are going to be measuring out molecules by weight, we'll need to know how much each molecule weighs. For example, if we need an equal number of red molecules and blue molecules, and red molecules weigh three times as much as blue molecules, we'll need to weigh out three times as much of the red stuff as the blue stuff.



Exercise 1.5.7

You are developing a new "extreme sport" amusement park ride. Each ride (for one person) is powered by one mouse and one elephant. You have plenty of elephants to get started, but will need to go and buy some mice.

a. If an elephant weighs 6,800 kg, how many grams does it weigh?
b. If you have 47,600 kg of elephants, how many rides can you set up?
c. If a mouse weighs 25 g, how many g of mice will you need to buy?
d. Suppose you decide to get three extra mice (sometimes accidents happen around elephants). What is the total weight of mice you would need, including these extras?

Answer a

The elephant weighs 6,800 kg x 1,000 g/kg = 6,800,000 g = 6.8×10^6 g.

Answer b

We have 47,600 kg x 1 elephant/6,800 kg = 7 elephants. Very lucky.

Answer c

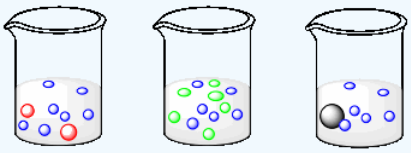
7 mice x 25 g/mouse = 175 g.

Answer d

10 mice x 25 g/mouse = 250 g.

Exercise 1.5.8

Suppose each of the following beakers contains an equal weight of each kind of molecule. The molecular weight of a blue molecule is 60 g/mol. What is the molecular weight of a red, an orange and a grey molecule?



The weight of a molecule can be determined by adding up the weights of all its atoms. For example, a carbon dioxide molecule has a molecular weight of 44 amu (carbon is 12 amu plus two oxygens at 16 amu apiece). The weight of a mole of carbon dioxide is the same as the molecular weight, but in grams instead of amu. A mole of carbon dioxide is 44 g. In other words, the molecular weight (MW) of carbon is 44 g/mol.

Answer

The weight of 7 blue molecules = the weight of 2 red molecules. 1 red molecule = 7/2 x the weight of a blue molecule. $MW_{red} = 3.5 \times MW_{blue} = 3.5 \times 60\ g\ mol^{-1} = 210\ g\ mol^{-1}$.

The weight of 6 blue molecules = the weight of 6 orange molecules. $MW_{orange} = MW_{blue} = 60\ g\ mol^{-1}$.

The weight of 6 blue molecules = the weight of 1 grey molecule. $MW_{grey} = 6 \times MW_{blue} = 6 \times 60\ g\ mol^{-1} = 360\ g\ mol^{-1}$.

Exercise 1.5.9

How much does a mole of each of the following molecules weigh?

a. nitric oxide, NO_2
b. glucose, $C_6H_{12}O_6$
c. benzaldehyde, C_7H_6O
d. phosphorus pentoxide, P_2O_5

Answer a

A mole of material corrsponds to the numerical equivalent of the sum of atomic masses in an molecule, in grams.

atomic masses in NO_2: 14 amu (N) + 32 amu (2 x O) = 46 amu. 1 mol of NO_2 is 46 g of NO_2.

Answer b

180 g

Answer c

106 g

Answer d

142 g

Exercise 1.5.10

How many moles of each of the following compounds are there in the given weights?

a. 3 grams of glucose
b. 10 grams of benzaldehyde
c. 30 grams of phosphorus pentoxide

Answer a

3 g x 1 mol/180 g = 0.017 mol

Answer b

10 g x 1 mol/106 g = 0.094 mol

Answer c

30 g x 142 mol/g = 0.21 mol

Exercise 1.5.11

What is the concentration of each of the following solutions (in moles per liter)?

a. 5 g of glucose in 50 mL of water
b. 11 g of benzaldehyde in 25 mL of THF
c. 9 g of menthol (MW 156 g/mol) in 60 mL of DMF

Answer a

5 g x 1 mol/180 g = 0.028 mol; 0.028 mol / 50 mL = 5.6 x 10^{-4} mol/mL x 1000 mL/L = 0.56 mol L^{-1}.

Answer b

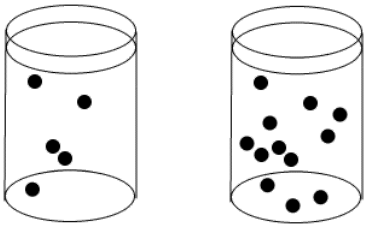
11 g x 1 mol/106 g = 0.104 mol; 0.104 mol / 25 mL = 4.16 x 10^{-3} mol/mL x 1000 mL/L = 4.2 mol L^{-1}.

Answer c

9 g x 1 mol/156 g = 0.058 mol; 0.058 mol / 60 mL = 9.61 x 10^{-4} mol/mL x 1000 mL/L = 0.96 mol L^{-1}.

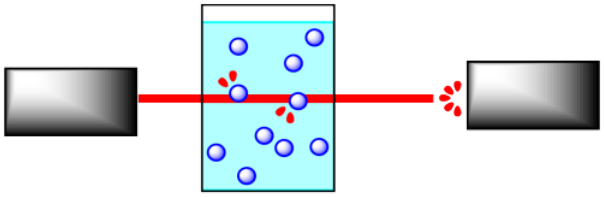
1.6: Rate Laws

So far, we have talked about changes in the number of molecules over time as a reaction progresses. The number of reactant molecules decreases as the number of product molecules increases. Practically, the easiest way to measure the speed of a reaction is to measure the concentration over time. We can measure either the concentration of the reactants or the products. Remember, concentration refers to how densely populated a solution is with a particular compound.

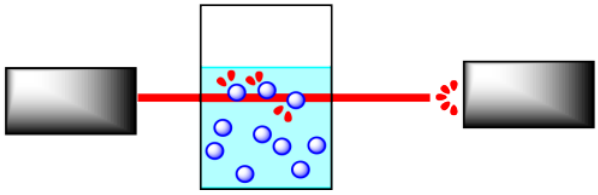


The concentration of black dots is higher in the beaker on the right than in the beaker on the left.

Reactions are often monitored by some sort of spectroscopy. In spectroscopy, "light" or some other frequency of electromagnetic radiation shines through a sample in which a reaction is taking place. The light can interact with the molecules in the sample. The molecules absorb particular frequencies of light, so if the light encounters the molecules on its way through the sample, a little of the light at those frequencies is absorbed. Less light makes it all the way through the sample; the amount that does make it through is measured by a detector on the other side.



If the concentration of the sample is different, a different amount of light from the spectrometer will be absorbed. For instance, suppose the sample is more concentrated. The more molecules there are, the more light is absorbed. And because the beam of light travels through the sample in a straight line, the more concentrated the solution, the more molecules it will encounter.



It is pretty simple to calibrate the instrument to be able to determine concentration from the amount of light absorbed. In addition, the light may interact with the reactant molecules and product molecules in different ways. That means you can monitor the absorption of a frequency that you know is absorbed by reactant molecules, but not by product molecules, and you can detect changes in reactant concentration. You could also do the same thing to detect changes in product concentration.

We sometimes write the rate of the reaction as:

$$Rate = \frac{d[product]}{dt}$$

Meaning, the rate is the change in concentration of product with change in time.

Concentration could be measured in any units. Frequently, we are dealing with a solution, and we use units such as grams per liter or, much more commonly, moles per liter. The change in time is most often measured in seconds.

We could also write the rate of the reaction as:

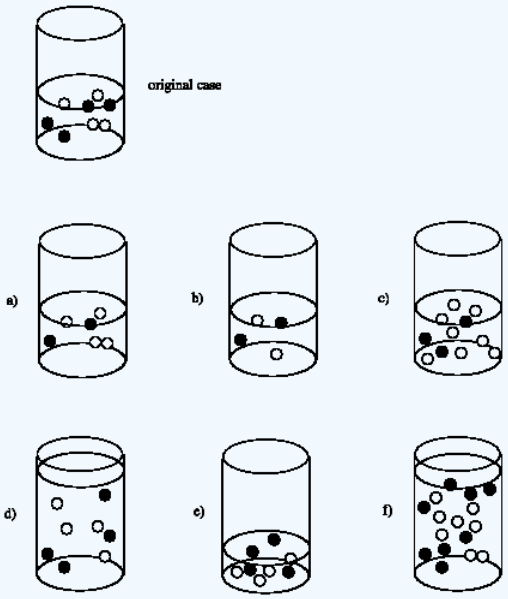
$$Rate = \frac{-d[reactant]}{dt}$$

Meaning, the rate is the change in concentration of reactant with change in time. The minus sign just means that the reaction is getting consumed over time as it turns into product, so its concentration is decreasing.

Kinetic studies are important in understanding reactions. Not only are they important in industry, but they are also used to understand biological processes, especially enzyme-catalyzed reactions. They also play a role in environmental and atmospheric chemistry, as part of an effort to understand a variety of issues ranging from the fate of prescription pharmaceuticals in wastewater to the cascade of reactions involved in the ozone cycle.

? Exercise 1.6.1

Suppose the rate of the reaction between the black circles and the white circles depends only on the concentration of the black circles. That is, rate = k [black circle]. Compare the rate in each case to the rate of the reaction that would occur in the original beaker.



Answer a

Rate of (a) = 1/2 x Rate of original

Answer b

Rate of (b) = 1/2 x Rate of original

Answer c

Rate of (c) = 3/4 x Rate of original

Answer d

Rate of (d) = 1/2 x Rate of original; although the number of molecules is the same as the original, the volume is doubled. As a result, the concentration is cut in half.

Answer e

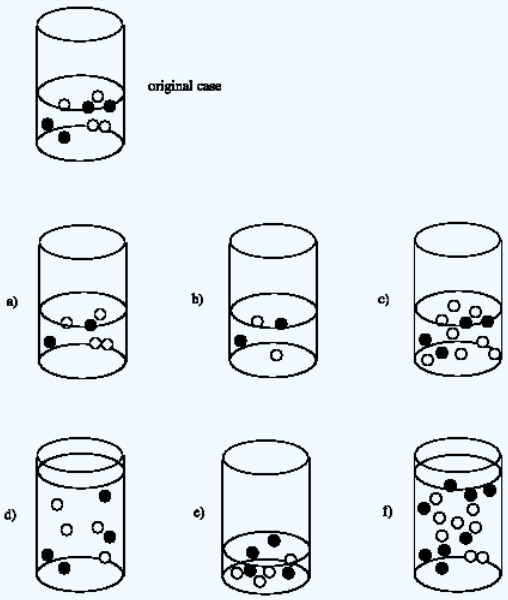
Rate of (e) = 2 x Rate of original; although the number of molecules is the same as the original, the volume is halved. As a result, the concentration is doubled.

Answer f

Rate of (f) = Rate of original; although the number of molecules is doubled, the volume is also doubled, leaving the concentration unchanged.

Exercise 1.6.2

Suppose the rate of the reaction between the black circles and the white circles depends on both the concentrations of the black circles and the white circles. That is, rate = k [black circle][white circle]. Compare the rate in each case to the rate of the reaction that would occur in the original beaker.



Answer a

Rate of (a) = 1/2 x Rate of original

Answer b

Rate of (b) = 1/2 x 1/2 = 1/4 x Rate of original

Answer c

Rate of (c) = 2 x Rate of original

Answer d

Rate of (d) = 1/2 x 1/2 = 1/4 x Rate of original; although the number of molecules is the same as the original, the volume is doubled. As a result, the concentration is cut in half.

Answer e

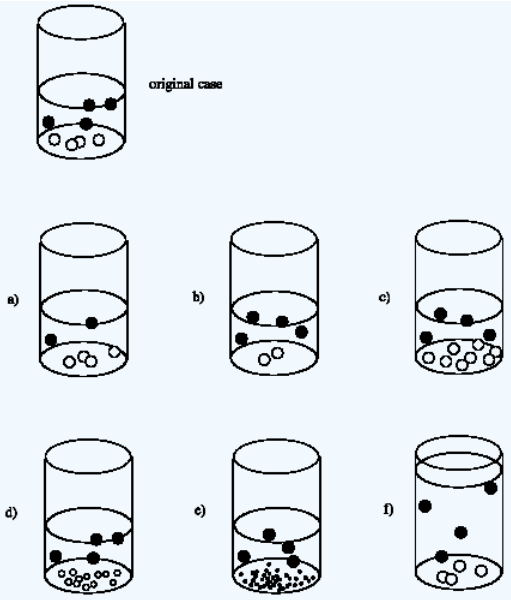
Rate of (e) = 2 x 2 = 4 x Rate of original; although the number of molecules is the same as the original, the volume is halved. As a result, the concentration of each reactant is doubled.

Answer f

Rate of (f) = Rate of original; although the number of molecules is doubled, the volume is also doubled, leaving the concentration unchanged.

Exercise 1.6.3

Suppose the rate of a reaction in the beaker depends on the surface area of the solid at the bottom of the beaker. That is, rate = k x (surface area of white circles). Compare the rate in each case to the rate of the reaction that would occur in the original beaker.



Answer a

Rate of (a) = Rate of original; the surface area of the white solid appears to be the same.

Answer b

Rate of (b) = 1/2 x Rate of original; the surface area of the white solid appears to be cut in half.

Answer c

Rate of (c) = 2 x Rate of original; the surface area of the white solid appears to be doubled.

Answer d

The smaller sizes of the particles in (d) makes it harder to answer this question. Let's assume these white solids are spherical and that the radius of a sphere in (d) is half that of a sphere in the original. The surface area of a sphere is A = 4 π r^2. The ratio of surface areas of one sphere to another is \frac{A_{1}}{A_{2}} = \frac {4 \pi r_{1}^{2}}{4 \pi r_{2}^{2}} = \frac{r_{1}}{r_{2}}^{2}\). The ratio of surface areas of an original sphere to a sphere in (d) is $\frac{A_d}{A_0} = \frac{1}{2}^2 = \frac{1}{4}$. However, there are 12 spheres in (d) and only 4 spheres in the original. Thus, the ratio of total surface areas \(\frac{A_{dT}}{A_{0T}} = \frac{12}{4} \times \frac{1}{4} = \frac{3}{4}. The estimated rate of (d) = 3/4 x the Rate of original.

Answer e

Let's assume these white solids are spherical and that the radius of a sphere in (e) is one quarter that of a sphere in the original. The ratio of surface areas of an original sphere to a sphere in (e) is $\frac{A_e}{A_0} = \frac{1}{4}^2 = \frac{1}{6}$. However, there are 40 spheres in (e) and only 4 spheres in the original. Thus, the ratio of total surface areas $\frac{A_{eT}}{A_{0T}} = \frac{40}{4} \times \frac{1}{16} = \frac{5}{8}$. The estimated rate of (e) = 5/8 x the Rate of original.

Answer f

Rate of (f) = Rate of original; the surface area of the white solid appears to be the same.

? Exercise 1.6.4

Often in studying reaction kinetics, the changing concentration of a reactant or a product is plotted against time. In one method, many data points are collected very early in a reaction (when fewer than 5% of the material has reacted), and the slope of the

resulting line is used to determine the "initial rate". Explain why this method might not work if the data points are plotted all the way until the reaction is finished.

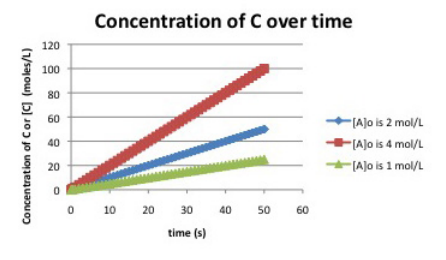
Answer

At the very start of the reaction, the concentrations of reactants have not changed very much. That means the rate of the reaction remains roughly constant as the first few percent of reactants are consumed. Plotting [product] vs. time gives a straight line with the slope = rate. However, over the course of the reaction, the concentration of reactants goes down as the reactants are consumed. That means the rate of product formation slows down and a plot of [product] vs. time becomes curved. We will be unable to measure the slope in a simple way.

Exercise 1.6.5

Suppose the following plots were obtained before 5% conversion for the reaction:

$$A + B \rightarrow C$$



What do you know about the rate law for the reaction?

Answer

The slope of the first curve, with $[A]_0$ = 1 mol L^{-1}, can be estimated by observing that [C] increases from zero to 25 mmol L^{-1} in 50 seconds. The slope is about 25/50 = 0.5 mmol L^{-1} s^{-1}. The slope of the next curve, with $[A]_0$ = 2 mol L^{-1}, is 1.0 mmol L^{-1} s^{-1} (50 mmol L^{-1} / 50 s). The initial concentration is doubled, and the rate doubles. The slope of the final curve, with $[A]_0$ = 4 mol L^{-1}, is 2.0 mmol L^{-1} s^{-1} (100 mmol L-1 / 50 s). The initial concentration is doubled, and the rate doubles. The reaction is linearly dependent on the concentration of A. Whatever happens to [A] also happens to the rate.

In terms of rate laws, there is a mathematical approach to demonstrating this relationship.

Suppose $Rate = k[A]^x$; x is the power of the mathematical relationship.

The ratio of rates in two experiments is $\frac{Rate_1}{Rate_2} = \frac{k[A_1]^x}{k[A_2]^x}$.

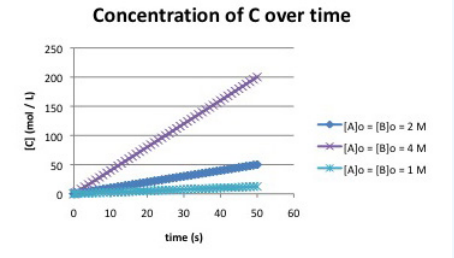
If we take the logarithm of both sides: $ln\frac{Rate_1}{Rate_2} = ln(\frac{[A_1]}{[A_2]})^x = xln\frac{A_1}{A_2}$

Then $x = ln\frac{Rate_1}{Rate_2} / ln\frac{[A_1]}{[A_2]}$

Exercise 1.6.6

Suppose the following plots were obtained before 5% conversion for the reaction:

$$A + B \rightarrow C$$



a) What is a possible rate law for the reaction?

b) Two different rate laws could explain this data. What is the second possible rate law?

c) Propose an experiment to distinguish between these two possible rate laws.

Answer a

Each time the concentrations double (for example, from 2 to 4 mol L^{-1}), the rate quadruples (for example, from 50/50 = 1 mmol L^{-1} s^{-1} to 200/50 = 4 mmol $L^{-1}s^{-1}$). One explanation is $Rate = k[A][B]$

Answer b

Another explanation is $Rate = k[A]^2$ or $Rate = k[B]^2$.

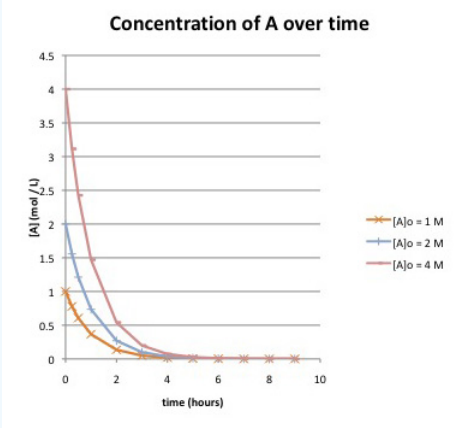
Answer c

We could run a series of experiments in which [A] is changed while holding [B] constant (or vice versa).

Exercise 1.6.7

Suppose the following data were obtained by monitoring the following reaction to completion:

$$A + B \rightarrow C$$



a) How long does it take until the reaction is essentially finished, if the starting concentration of A is:

i) 1 mol/L?

ii) 2 mol/L?

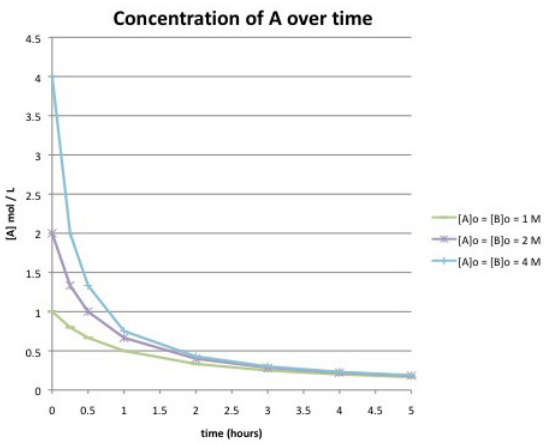
iii) 4 mol/L?

b) What do you know about the rate law for the reaction? Explain.

Exercise 1.6.8

Suppose the following data were obtained by monitoring the following reaction to completion:

$$A + B \rightarrow C$$



Compare this graph to the one in the previous problem. What differences can you detect in the curves? Do you think this reaction has the same rate law as the previous one?

1.7: Elementary Reactions

The mechanism of a reaction is a series of steps leading from the starting materials to the products. After each step, an intermediate is formed. The intermediate is short-lived, because it quickly undergoes another step to form the next intermediate. These simple steps are called elementary reactions.

Because an overall reaction is composed of a series of elementary reaction, the overall rate of the reaction is somehow dependent on the rates of those smaller reactions. But how are the two related?

Let's look at two cases. We'll keep it simple and both cases will be two-step reactions.

The first case begins with a reaction having a pretty low activation barrier. Maybe there is a lot of bond-making involved at the beginning, so this reaction gets an easy start. However, after that, things get harder. The second step has a higher activation barrier.

Both of these reactions occur at particular rates. The first step has a low barrier, so it occurs quickly. The second step has a high barrier, so it happens only slowly.

In that case, the intermediate will be formed quickly and it will sit around for a while before the second step has a chance to happen. The second step is like a bottleneck or a traffic jam. No matter how quickly things were going in the first step, the reaction has to wait to get through the second step. The rate of the overall reaction really depends on the second step. We call this step the "rate-determining step".

Each step has its own rate constant associated with it. We'll call these constants k_1 and k_2. The lower the barrier, the faster the rate, and the larger the rate constant.

We can predict rate laws for elementary reactions (although the same thing isn't true for overall reactions). The rate law for an elementary reaction is simply its rate constant, times the concentrations of any species involved in that step.

The rate of formation of product will be determined by the rate of that second step, the rate-determining step. The rate of that second step is the rate constant, k_2, times the concentration of the intermediate.

$$\frac{d[Product]}{dt} = k_2[Intermediate] \tag{1.7.1}$$

But what is the concentration of the intermediate? The intermediate is produced in the first step, so its concentration depends on how quickly it is produced from the reactants. However, if the activation barrier is low, that first step may be reversible; it may really be an equilibrium reaction. So there is a third step in this reaction, and it goes backwards from the intermediate to the reactant. We'll call the rate constant for this step k_{-1}.

In terms of kinetics, an equilibrium is really just a ratio of forward and reverse steps. If the forward step is much faster, this ratio is bigger than one, and products are favored. If the reverse step is much faster, the ratio is smaller than one, and reactants are favored.

$$K_{eq} = \frac{k_1}{K_{-1}} = \frac{[Intermediate]}{[Reactant]} \tag{1.7.2}$$

Or, rearranging,

$$\frac{k_1}{k_{-1}}[Reactant] = [Intermediate] \tag{1.7.3}$$

Now we know the concentration of the intermediate. That means the rate of the overall reaction is

$$\frac{d[Product]}{dt} = \frac{k_2 k_1}{k_{-1}}[Reactant] \tag{1.7.4}$$

The take-home lesson is this: the second step is the rate determining step, so that step tells us how quickly the product forms. However, that step depends on an intermediate formed in an earlier step, so that earlier step also influences how quickly the product forms.

- The rate-determining step controls the rate of the reaction.
- The steps prior to the rate determining step influence the rate of the reaction by supplying intermediates needed for the rate determining step.

Now let's think about the opposite case. Suppose the first step has a very high barrier and the second step has a lower one. We have to wait and wait and wait for the intermediate to be produced, but once it's there, it reacts pretty quickly to give products.

In this case, the first step is the rate-determining step. That's the step that controls the rate of the reaction. As soon as that step proceeds, the rest of the reaction can occur quickly.

In this case,

$$\frac{d[Product]}{dt} = k_1[Reactant] \tag{1.7.5}$$

- Any steps after the rate-determining step don't influence the rate of the reaction.

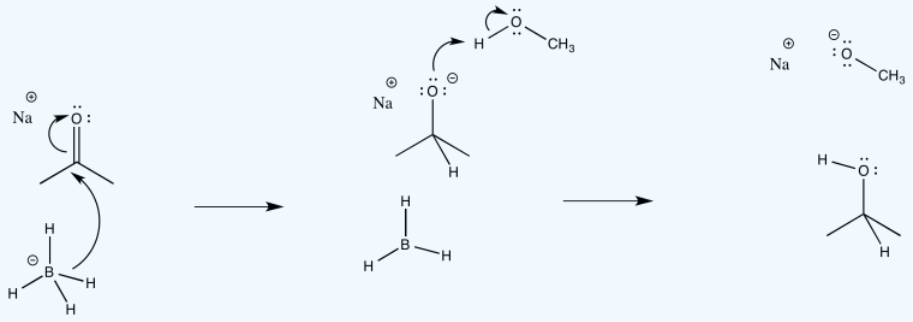
In some cases, we can use our judgement to try to predict which transition states are highest in energy in a multi-step mechanism. However, much of the knowledge about what is happening between the reactant and the product would really come from computational chemistry. In computational chemistry, the energies of the intermediates and the transition states can be calculated using quantum mechanics. This task is not necessarily easy.

? Exercise 1.7.1

Consider the borohydride reduction of a ketone in methanol.

a. Draw a mechanism for this reaction. (If you know about the competing reaction between borohydride and methanol, ignore it. If you didn't know anything about that, forget I said anything.)
b. Assign rate constants (k_1, k_2, k_3...) for each elementary step in the reaction.
c. One of the steps along this reaction is probably reversible. Which one? Why?
d. What do you think is the rate-determining step in this reaction?
e. Draw a reaction progress diagram for this reaction.
f. Predict a rate law for this reaction.

Answer a



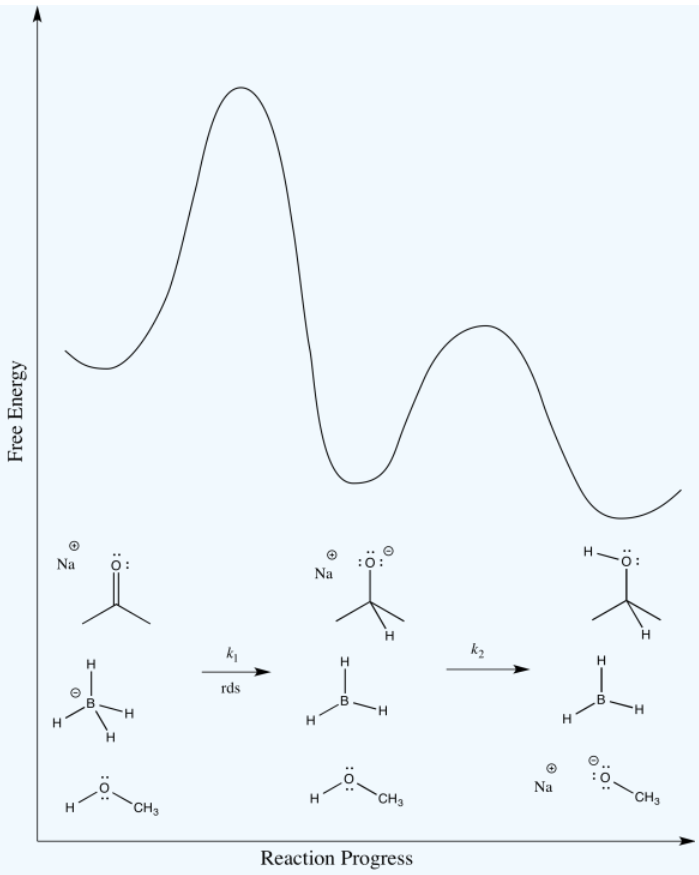
Answer b

The first step proceeds at k_1; the second at k_2.

Answer c

The second step is probably reversible. It is just the exchange of a proton from one OH group to another.

Answer d



Answer e

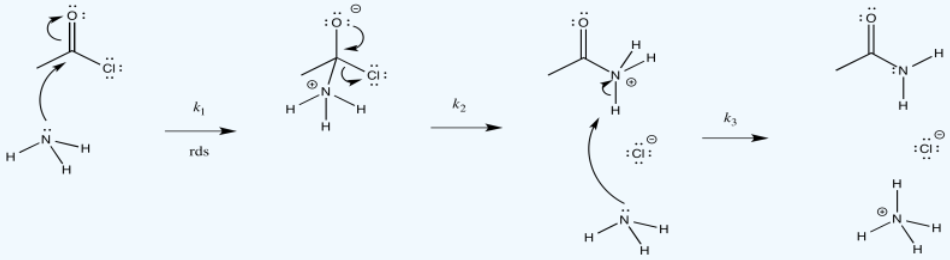
$$Rate = k_1[ketone][NaBH_4]$$

Exercise 1.7.2

Consider the ammonolysis of acetyl chloride.

a. Draw a mechanism for this reaction.
b. Assign rate constants (k_1, k_2, k_3...) for each elementary step in the reaction.
c. Draw alternative reaction progress diagrams for this reaction. In each case, assume a different rate determining step.
d. Predict the rate law corresponding to each of your possible reaction progress diagrams. Can the rate law be used to distinguish between all of the possibilities?
e. Consider your alternative reaction progress diagrams and decide which one is most likely. Justify your choices for eliminating the other one(s).
f. Predict a rate law for this reaction.

Answer a



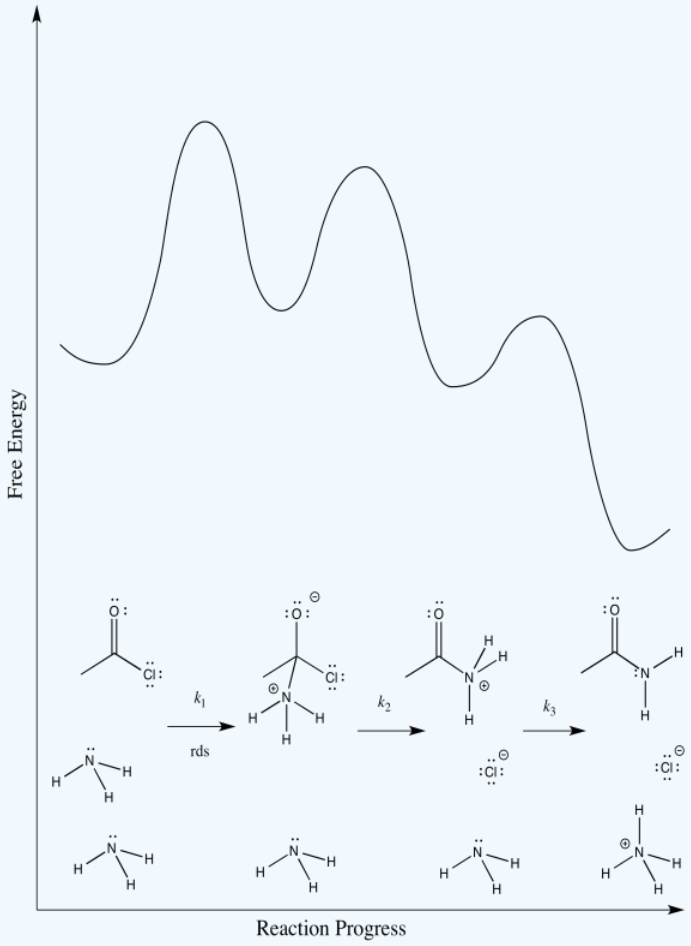
Answer b

The first step proceeds at k_1; the second at k_2; the third at k_3.

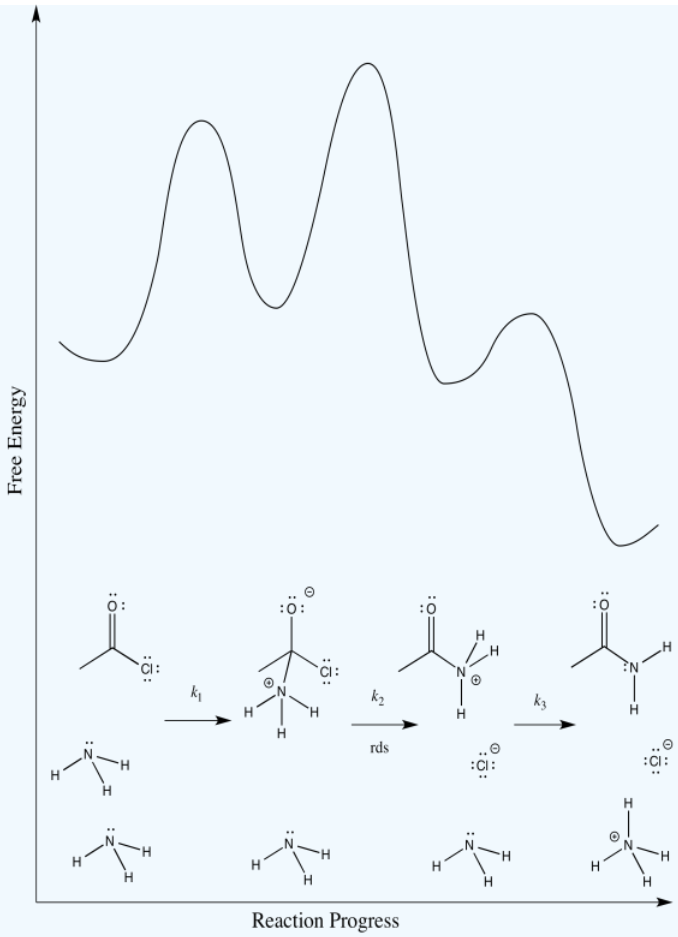
Answer c

There are three different steps, each of which might be rate determining.

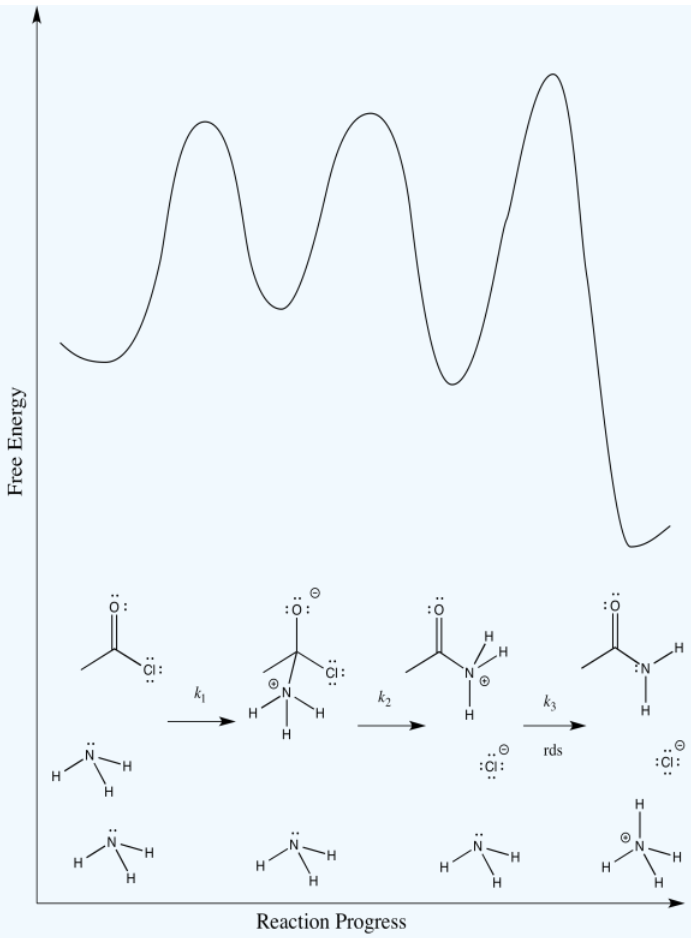
The first:



The second:



The third:



Answer d

First one: $Rate = k_1[CH_3COCl][NH_3]$

Second one: \(Rate = k_{1}k_{2}[CH_{3}COCl][NH_{3}]

Third one: $Rate = k_1k_2k_3[CH_3COCl][NH_3]^2$

The rate law could be used to distinguish the third from the first two. However, it would be impossible to tell the difference between the first two using the rate law alone.

Answer e

We can probably rule out the third possibility right away. Proton transfers tend to happen pretty quickly, especially in the presence of a reasonable base such as ammonia. Measuring the rate law would quickly confirm this assumption.

Scenarios 1 and 2 are much harder to distinguish. In both cases, a bond is being broken as another bond is being made. We could make an educated guess that the formation of the good chloride leaving group is pretty easy; that would make step 1 the rate determining step.

However, we are always left with some ambiguity in subtle cases like this one. In order to get a better idea about which transition states are the highest, we would have to perform computational chemistry.

? Exercise 1.7.3

There are two other possible mechanisms for ammonolysis of acetyl chloride. You already know they aren't the right mechanism, but let's look at the reason we know that.

a. The first possibility is that the chloride ion leaves in the first step. The ammonia comes in afterwards.

   i. Draw this mechanism.

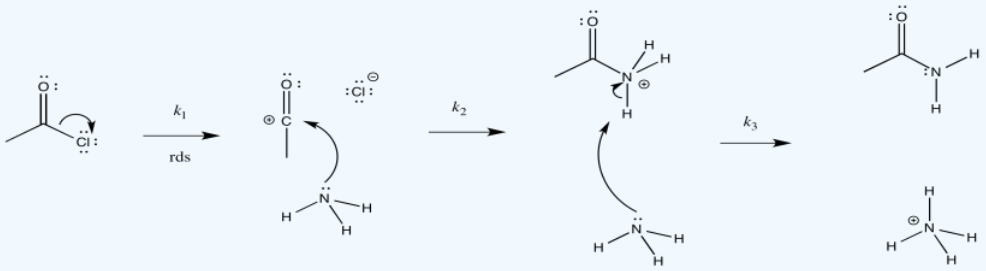
ii. Provide a reaction progress diagram.
iii. Identify the rate determining step and the rate law.

b. The second possibility is that the chloride gets pushed out as the ammonia comes in (instead of the C=O π bond breaking). Draw this mechanism.

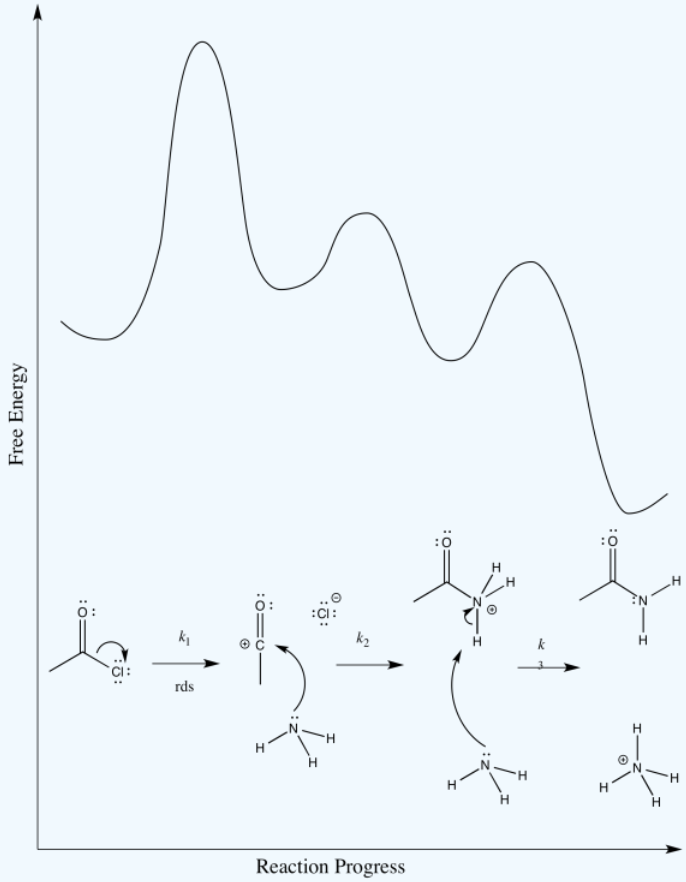
i. Draw this mechanism.
ii. Provide a reaction progress diagram.
iii. Identify the rate determining step and the rate law.

c. Given the experimental rate law, $\mathrm{Rate} = k[\mathrm{CH_3COCl}][\mathrm{NH_3}]$, can either of these possibilities be ruled out?

Answer a i



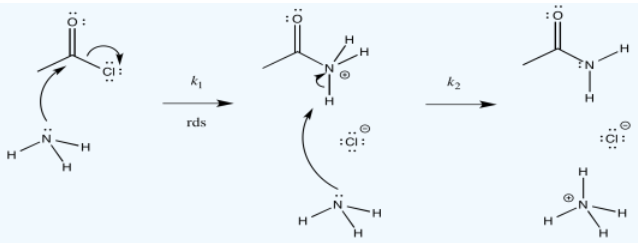
Answer a ii



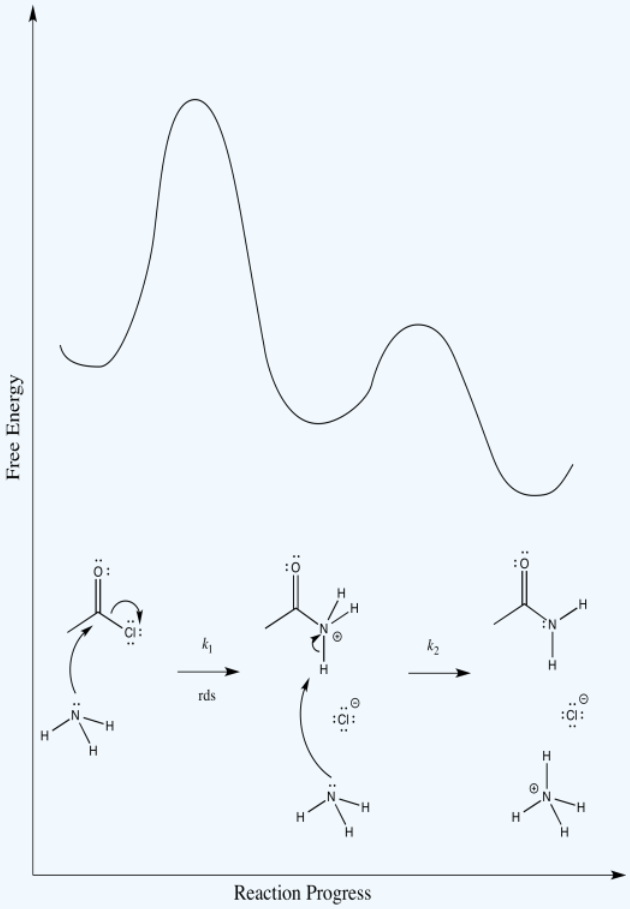
Answer a iii

$$Rate = k_1[CH_3COCl]$$

Answer b i



Answer b ii



Answer b iii

$$Rate = k_1[CH_3COCl][NH_3]$$

Answer c

On the basis of the rate law, possibility (a) can be ruled out, but not possibility (b)

Another commonly used experiment in kinetics is a kinetic isotope effect experiment. Although two isotopes of an atom have almost identical properties, the difference in mass between the two isotopes can cause subtle differences in reaction rates. For rather complicated reasons, two isotopes display different sensitivities to geometry changes that occur up to and including the rate determining step.

For example, if the carbonyl carbon in acetyl chloride is replaced by a ^{13}C isotope (it is normally ^{12}C), it will react at a different rate tthan the normal compound, but only if that carbon undergoes a geometry change at some point before it finishes the rate determining step. If the two compounds react at the same rate, no such geometry change has occurred.

Exercise 1.7.4

The ratio of reaction rates of $CH_3{}^{13}COCl$: $CH_3{}^{12}COCl$ is about 0.9.

a. What does this observation tell you about the mechanism?
b. Does it rule out any possibilities in Exercise 1.7.3?

Answer a

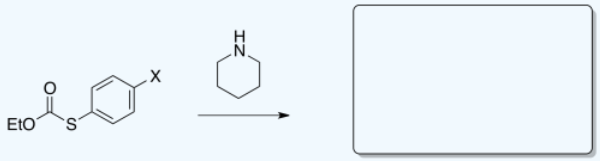
There is a geometry change prior to or during the rate determining step.

Answer b

Possibility (b) can be ruled out.

Exercise 1.7.5

a) Draw the product of the following reaction.



b) Provide a mechanism for the reaction.

c) Briefly describe what is meant by the term "thermodynamics" in the context of reactivity.

d) Briefly define what is meant by the term "kinetics" in this context.

e) In which step of the mechanism is ΔS positive?

f) Write a rate law for the reaction based on your mechanism.

g) What happens to reaction rate as temperature increases?

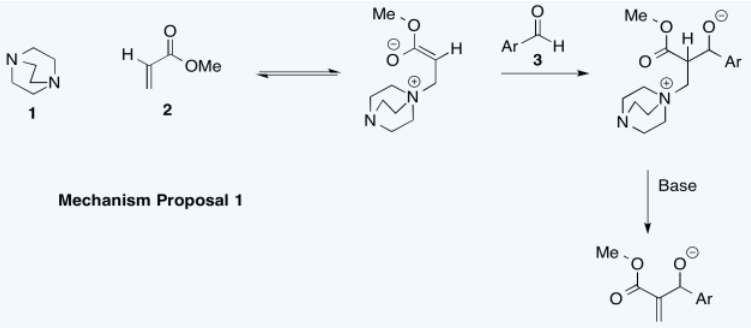
h) What does collision theory tell us about rates of reactions?

i) The following rate constants were observed for the reaction involving different substituents X.

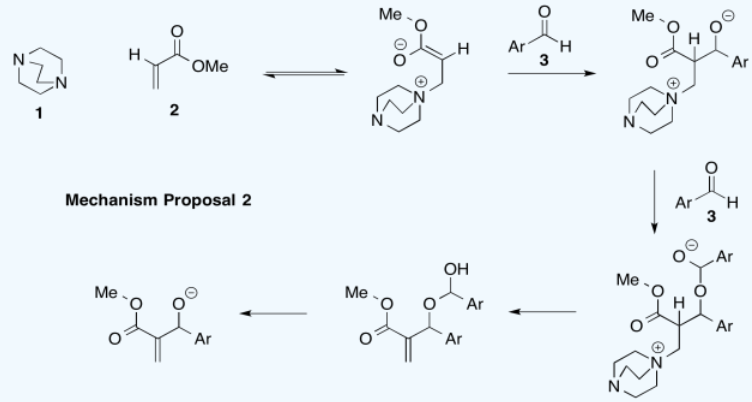
-X	k mol L^{-1} s^{-1}
$-OCH_3$	0.17
-SCN	1.76

Exercise 1.7.6: the Bayliss-Hillman reaction

The Bayliss-Hillman reaction is used extensively in syntheses of pharmaceuticals. However there are two possible mechanisms, shown below (Price, Broadwater, Walker and McQuade, *J. Org. Chem.*, **2005**, *70*, 3980-3987).

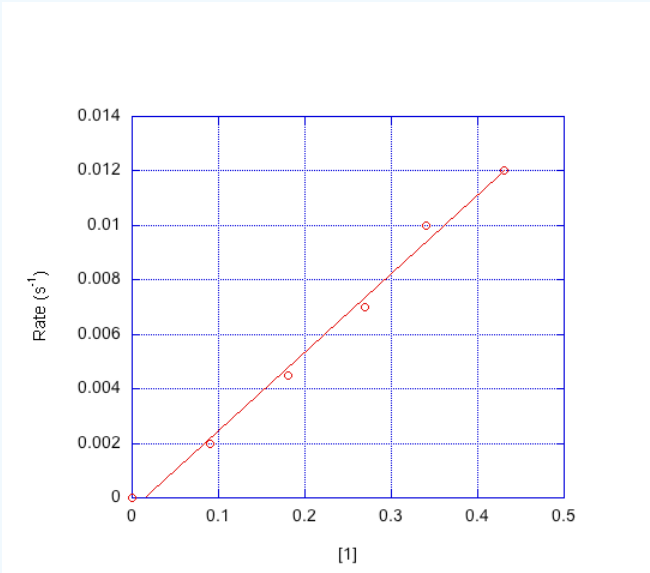


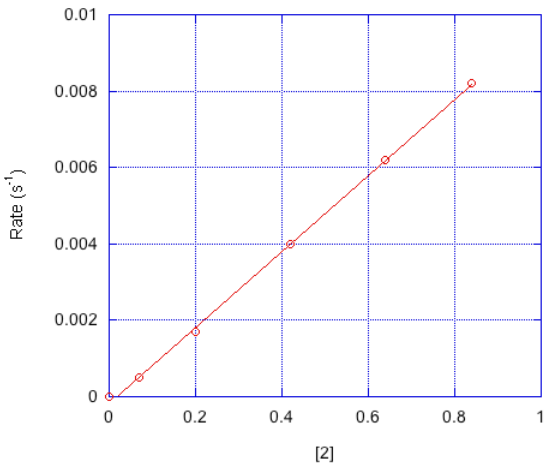
Mechanism Proposal 1

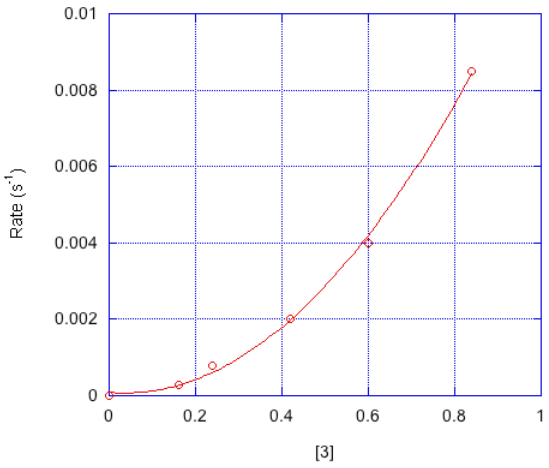


Mechanism Proposal 2

a. Provide arrows to show electron flow for each mechanism.
b. Provide a rate law for each mechanistic proposal, based on concentrations of compounds **1**, **2**, and **3**.
c. Indicate the order in each compound based on the graphs below.

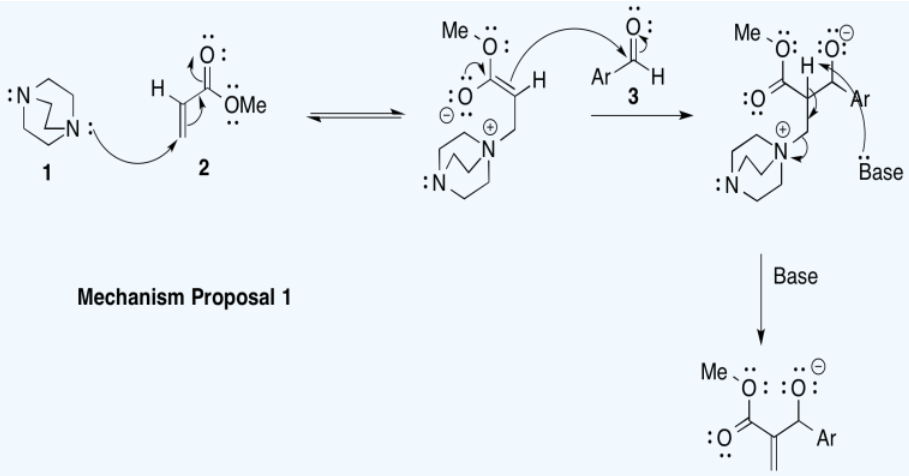


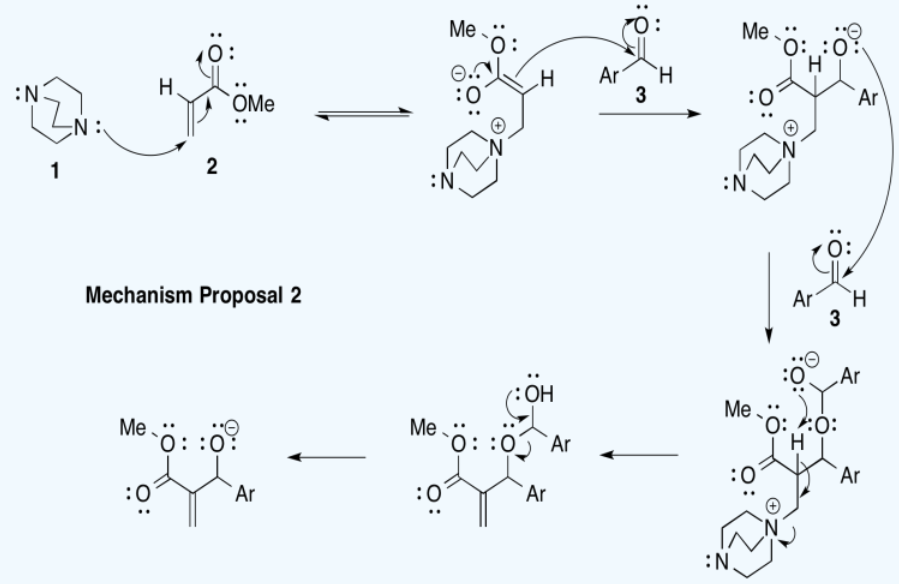




d) Which mechanism is consistent with the data?

Answer a





Answer b

Mechanism 1: k [1][2][3]

Mechanism 2: k [1][2][3]^2

Answer c

First order in [1]; first order in [2]; second order in [3]

Answer d

Mechanism 2.

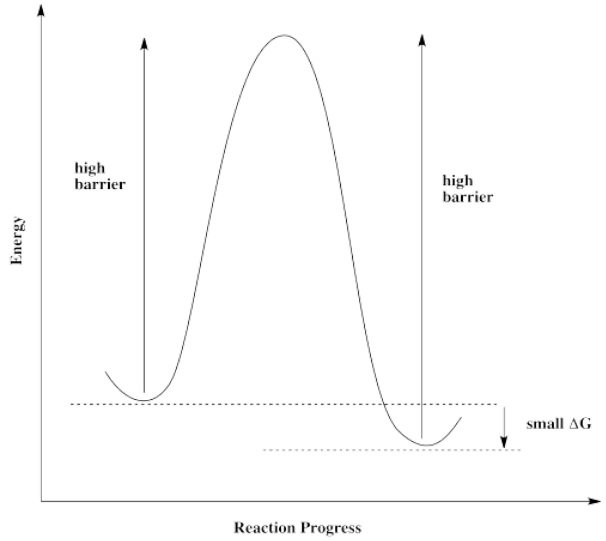
1.8: Catalysis

The mechanism of a reaction is a sequence of elementary steps leading from the starting materials to a series of intermediates and eventually to the products. Each step involves an activation barrier. Each intermediate has some measure of stability. We can keep track of energy changes along this reaction pathway by using a reaction progress diagram.

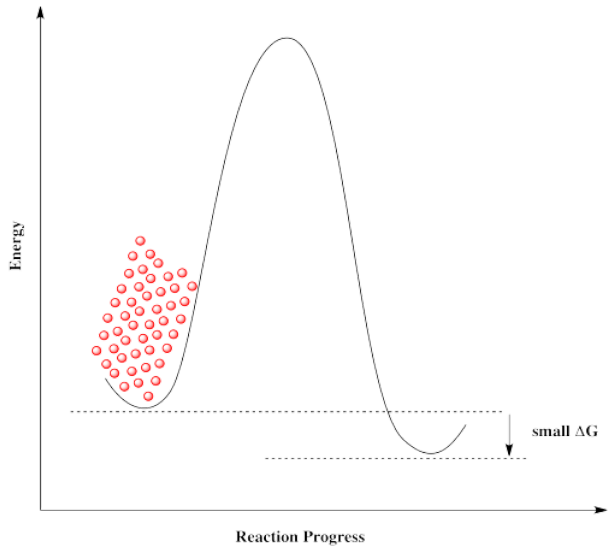
We can change the speed of a reaction by flooding the system with reactant or by adding more energy to help it get over the barrier, but the reaction still follows this same energy pathway.

However, if we add a catalyst, that's no longer true. A catalyst introduces a completely different pathway that was not there before.

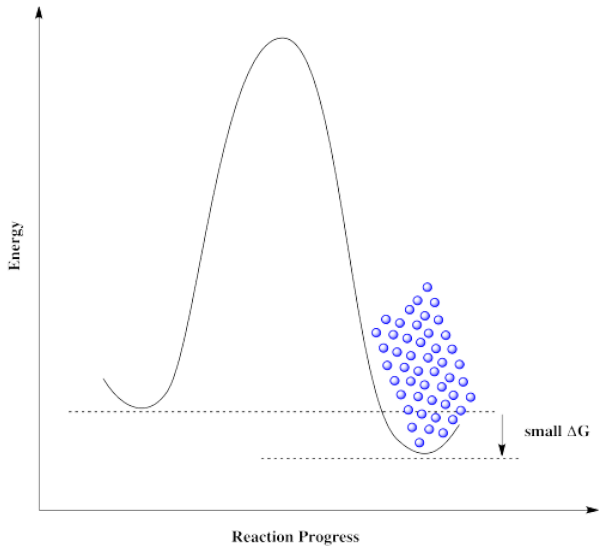
Some reactions simply can't proceed without a catalyst. There is too high a barrier to proceed. That may be true even if the overall reaction is exergonic and *should be* favored to proceed.



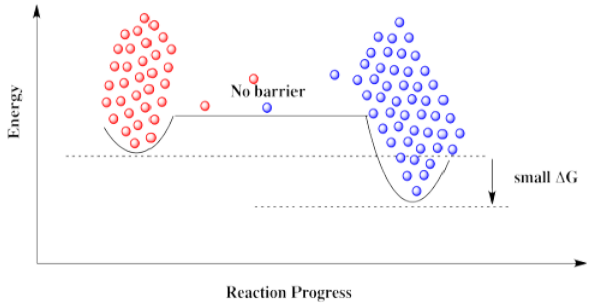
If molecules approach this barrier from the left, they encounter a very large barrier. They can't proceed, even though it would be energetically favorable for them to get to their destination. The molecules get stuck.



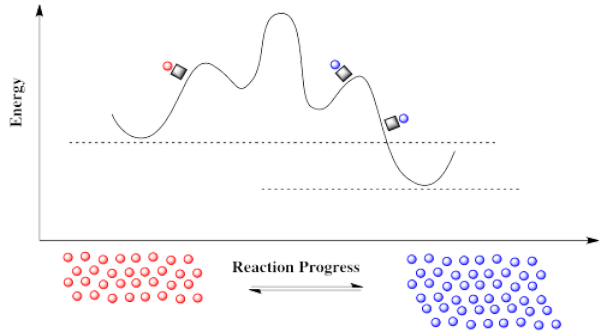
The same is true if molecules approach from the right. They can't get over the barrier, even though thermodynamically their destination is just a short hop. These molecules are stuck.



Everything would be fine if we could just get rid of that darned barrier. The molecules could freely move back and forth, and settle out where they are supposed to be.



A catalyst doesn't remove the barrier, but it offers a new pathway with a lower barrier. The reaction is able to proceed back and forth.



How can there suddenly be a new pathway? A reaction progress diagram plots what happens to the energy along one particular coordinate of interest to the molecule. We may be following a bond as it lengthens and breaks through the course of a reaction. But there are always other energetic possibilities that remain unseen in this diagram. What we are looking at is merely a slice through a potential energy surface. A potential energy surface is like a landscape, a mountain range in which elevation corresponds to energy. The reaction progress diagram depicts a single pathway from one energetic valley to another. In one of these valleys is the reactant; the product is in the other. The path from one valley to another leads uphill, over a mountain pass, and down into the other valley again.

Suppose you are going to visit a friend. You live in one valley and the friend lives in another. Every day you walk the same path to your friend's house. You aren't a fool, so you take the easiest route, over the lowest mountain pass.

One day, instead of visiting our friend on foot, we are going to take the train. The train takes a completely different pathway than the one we are used to. It doesn't even go over the same mountain pass; it may take another route that was inaccessible by foot, or it

may simply tunnel through the mountain. Furthermore, when the train reaches its destination, it picks up more passengers and makes the same journey again, over and over.

In molecular turns, it is the reactant that takes the train, a low-energy pathway, on its way to the product. That train is a catalyst, and it has some very important features.

- A catalyst takes a reaction pathway that is lower in energy than the usual one.
- A catalyst returns again and again to take more molecules through the reaction.

That recycling of the catalyst is sometimes referred to as "turnover". The *turnover number* of a catalyst is the number of times the catalyst is able to return and carry out the reaction again. (Eventually something may go wrong and the catalyst may stop working.) The reactant in a catalytic reaction is often called the *substrate*, particularly in cases in which the catalyst is an enzyme of a transition metal catalyst. The speed at which the catalyst is able to carry out the reaction on new substrates is called the *turnover frequency*. These are important parameters in describing the efficiency of a catalyst.

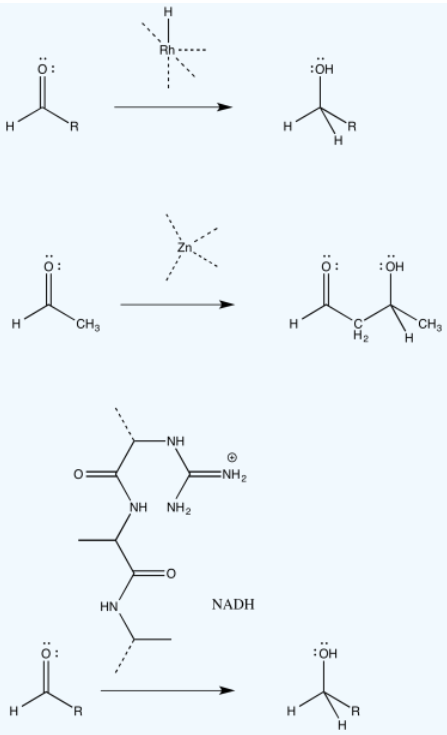
? Exercise 1.8.1

Polymerization catalysts take small molecules called monomers and connect them together using the same reaction over and over again to make a long polymer chain. What was the minimum turnover number of the catalyst used to make each of the following polymers? (M_n = number average molecular weight, a statistical estimate of the average size of polymer chain.)

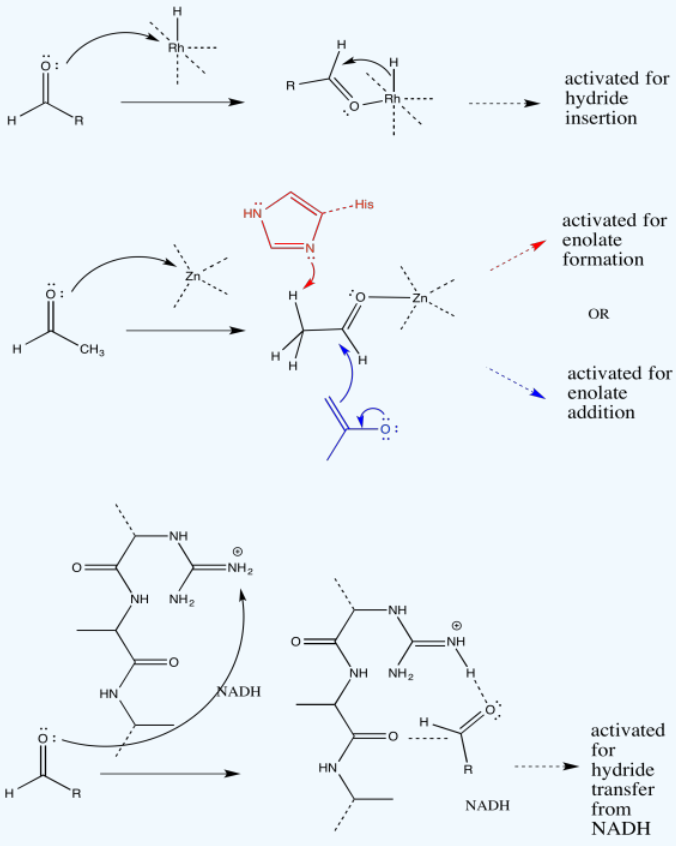
a. polylactide, M_n = 3,000, from lactide, $C_6H_8O_4$.
b. polystyrene, M_n = 250 thousand, from styrene, $C_6H_5C_2H_3$.
c. high-modulus polyethylene (HMPE), M_n = 6 million, from ethene, C_2H_4.

? Exercise 1.8.2

Catalysis often begins with a binding step, followed by one or more subsequent steps needed to carry out the reaction. For the following catalysed reactions, draw the binding step using curved arrows.



Answer



1.9: Solutions to Selected Problems

Exercise 1.2.7:

a) Scarlet molecules are disappearing over time. Ultramarine molecules are appearing over time. However, the number of scarlet molecules seems to stabilize around half its original number; the number of ultramarine molecules reaches about the same level. It is possible that the scarlet molecules are converted into the ultramarine ones, but reach an equilibrium. At this equilibrium, there happen to be about equal amounts of the two compounds.

b) Because the rate of growth of the tan molecules seems to track the rate of loss of the brown ones, it seems likely that the brown ones are being converted to tan molecules. At some point, the change levels out, so an equilibrium is reached. At this equilibrium, tan molecules outnumber brown ones.

c) Viridian molecules seem to be converting into gold ones but the system reaches equilibrium, at which point there are still more viridian molecules than gold ones.

Exercise 1.3.3:

a) $e^{2} < e^{10}$

b) $e^{1/4} < e^{1/2}$

c) $e^{-3} > e^{-4}$

d) $e^{-1/2} < e^{-1/3}$

Exercise 1.3.4:

a) Orientation (i) looks most likely to result in connection of the oxygen to carbon with displacement of bromide. In orientation (iii), the oxygen appears ready to collide with the bromine atom. and in oreientation (ii), it may collide with a hydrogen atom.

In addition, you will see later that bringing the the oxygen in along the C-Br axis (but away from the bromine) is also more likely to break the C-Br bond, for reasons involving molecular orbital overlap.

b) Orientation (ii) looks like the carbon anion in the acetylide ion is most likely to bond with the carbonyl carbon. In option (i), the carbon is going to collide with the carbonyl oxygen. In option (iii), it may collide with the alpha carbon, next to the carbonyl. Having the nucleophile approach from outside the plane of the carbonyl, as in option (ii), lowers the chance of collision with atoms other than the carbonyl carbon.

Again, there are also molecular orbital reasons that make this approach the preferred one.

Exercise 1.3.5:

a) We would expect the lowest barrier for breaking the Cr-CO bond. The barrier to break the Mo-CO bond would be just slightly lower than to break the W-CO bond.

b) Based on this information alone, we might expect the Cr-CO cleavage to occur most rapidly. Mo-CO cleavage would be slightly faster than W-CO cleavage.

Exercise 1.3.6:

a. On this basis alone, we would expect the lowest barrier for C=C cleavage, followed by C=N and then C=O with the highest barrier.
b. This trend is exactly the opposite of what we just predicted based on bond strengths.
c. There may be a few different reasons for these differences. For example, the electrophilicity of the carbon may be a factor. Based on electronegativity differences, the C=O carbon should be most positive, the C=N carbon less so and the C=C carbon not at all. That electrophilicity may raise the reactant a little in energy.

Alternatively, there may be charge stabilization factors in the first-formed intermediate, which may be reflected in the transition state on the way there. These three differing atoms (O, N, C) are all found in a row of the periodic table, so electronegativity differences should dominate charge stability. The alkoxide ion would be most stable, the amide ion of medium stability and the alkyl anion least stable of all. That trend would lower the barrier to alkoxide formation and raise the barrier to formation of a carbon-based alkyl anion.

Exercise 1.4.1:

The vacancies in the crystal lattics give other atoms places to move into, sothey act as a path through which atoms can move. Diffusion through the solid is greatly accelerated.

Exercise 1.4.2:

a) The small, red dots are in the gas phase, so they are distributed throughout the container. The larger, gray dots are the solid, which lies along the bottom of the container.

b) The solid on the left is divided into finer particles, with much more surface area. If the gas reacts on the surface of the solid, reaction will be much faster on the left.

Exercise 1.4.3:

All three of these solvents have dipole moments. Also, all three molecules have oxygen lone pairs, so they are able to accept hydrogen bonds from hydrogen bond donors.

However, some of the solvents are much more polar than others. Water is capable of donating hydrogen bonds, because of its partially positive hydrogen attached to oxygen. It is the most polar of these solvents.

DMF is also very polar, because it has a polar C=O bond. This particular carbonyl is more like $^{+}$N=C-O^{-} because of lone pair donation from the nitrogen, so it is quite polar and will interact strongly with other species via dipole-dipole forces (or ion-dipole forces, if the other molecule is a salt).

THF only has a moderate dipole compared to the others. Although it will still interact via dipole-dipole (or ion-dipole) forces, it does so less effectively than water or DMF.

Exercise 1.4.4:

Water would be a very good solvent for (a) and (d), because both of those molecules would be very good at hydrogen bonding. Although water may be able to dissolve small amounts of the others, their solubility would be limited by the need for water molecules to release hydrogen bonds to each other in order to make room for the non-polar portions of these molecules.

THF would be able to dissolve the other molecules pretty well: (b), (c), (e) and (f). All of those molecules contain polar bonds, like THF, and could interact via dipole-dipole forces. THF would be able to dissolve small amounts of (a) and (d) but may not be polar enough to overcome the stronger intermolecular forces between these molecules.

DMF may be able to dissolve all of these molecules to a moderate extent. Although it is not a protic solvent, its dipole is enough to help overcome hydrogen bonding among (a) and (d).

Exercise 1.5.1:

Upper East Side. Lots more people per square foot.

Exercise 1.5.2:

a) 8.41 people km^{-2}

b) 1,600 people km^{-2}

c) 15.2 people km^{-2}

d) 13.5 people km^{-2}

e) 12.7 people km^{-2}

f) 1,930 people km^{-2}

g) 24.6 people km^{-2}

Rank: Bahrain > Vatican > Jamaica > Argentina > China > Malawi > Russia

Exercise 1.5.3:

a) The volume is constant, but the number of molecules is increasing. The concentration is increasing.

b) The number of molecules is constant, but the volume is decreasing. The concentration is increasing.

Exercise 1.5.4:

In both cases, the molecules are becoming more densely packed. Collisions would become more frequent as we go from left to right.

Exercise 1.5.5:

a) The number of blue molecules is increasing, but the number of red molecules is staying the same.

b) Collisions between red and blue molecules would become more frequent as we go from left to right. The higher density of blue molecules makes collisions more likely.

c) The answer would stay the same.

d) The answer would stay the same qualitatively, but would differ quantitatively. The number of collisions would increase more sharply if the concentrations of both red and blue molecules increased, rather than just one concentration increasing.

Exercise 1.5.6:

a) A half dozen, a dozen, two dozen.

b) The concentration is doubling as we go left to right from one beaker to the next.

Exercise 1.5.7:

a) The elephant weighs $6800kg \times 1000\frac{g}{kg} = 6800000g = 6.8 \times 10^6 g$

b) We have $47600kg \times \frac{1elephant}{6800kg} = 7elephants$. Very lucky.

c) $7mice \times 25\frac{g}{mouse} = 175g$

d) $10mice \times 25\frac{g}{mouse} = 250g$

Exercise 1.5.8:

The weight of 7 blue molecules = the weight of 2 red molecules. 1 red molecule = 7/2 x the weight of a blue molecule. $MW_{red} = 3.5 \times MW_{blue} = 3.5 \times 60\frac{g}{mol} = 210\frac{g}{mol}$

The weight of 6 blue molecules = the weight of 6 orange molecules. $MW_{orange} = MW_{blue} 60\frac{g}{mol}$

The weight of 6 blue molecules = the weight of 1 grey molecule. $MW_{grey} = 6 \times MW_{blue} = 6 \times 60\frac{g}{mol} = 360\frac{g}{mol}$

Exercise 1.5.9:

A mole of material corrsponds to the numerical equivalent of the sum of atomic masses in an molecule, in grams.

a) atomic masses in NO_2: 14 amu (N) + 32 amu (2 x O) = 46 amu. 1 mol of NO_2 is 46 g of NO_2.

b) 180 g

c) 106 g

d) 142 g.

Exercise 1.5.10:

a) $3g \times \frac{1mol}{180g} = 0.017mol$

b) $10g \times \frac{1mol}{106g} = 0.094mol$

c) $30g \times \frac{142mol}{g} = 0.21mol$

Exercise 1.5.11:

a) $5g \times \frac{1mol}{180g} = 0.028mol$; $\frac{0.028mol}{50mL} = 5.6 \times 10^{-4}\frac{mol}{mL} \times 1000\frac{mL}{L} = 0.56\frac{mol}{L}$

b) $11g \times \frac{1mol}{106g} = 0.104mol$; $\frac{0.104mol}{25mL} = 4.16 \times 10^{-3}\frac{mol}{mL} \times 1000\frac{mL}{L} = 4.2\frac{mol}{L}$

c) $9g \times \frac{1mol}{156g} = 0.058mol$; $\frac{0.058mol}{60mL} = 9.61 \times 10^{-4}\frac{mol}{mL} \times 1000\frac{mL}{L} 0.96\frac{mol}{L}$

Exercise 1.6.1:

a) Rate of (a) = 1/2 x Rate of original

b) Rate of (b) = 1/2 x Rate of original

c) Rate of (c) = 3/4 x Rate of original

d) Rate of (d) = 1/2 x Rate of original; although the number of molecules is the same as the original, the volume is doubled. As a result, the concentration is cut in half.

e) Rate of (e) = 2 x Rate of original; although the number of molecules is the same as the original, the volume is halved. As a result, the concentration is doubled.

f) Rate of (f) = Rate of original; although the number of molecules is doubled, the volume is also doubled, leaving the concentration unchanged.

Exercise 1.6.2:

a) Rate of (a) = 1/2 x Rate of original

b) Rate of (b) = 1/2 x 1/2 = 1/4 x Rate of original

c) Rate of (c) = 2 x Rate of original

d) Rate of (d) = 1/2 x 1/2 = 1/4 x Rate of original; although the number of molecules is the same as the original, the volume is doubled. As a result, the concentration is cut in half.

e) Rate of (e) = 2 x 2 = 4 x Rate of original; although the number of molecules is the same as the original, the volume is halved. As a result, the concentration of each reactant is doubled.

f) Rate of (f) = Rate of original; although the number of molecules is doubled, the volume is also doubled, leaving the concentration unchanged.

Exercise 1.6.3:

a) Rate of (a) = Rate of original; the surface area of the white solid appears to be the same.

b) Rate of (b) = 1/2 x Rate of original; the surface area of the white solid appears to be cut in half.

c) Rate of (c) = 2 x Rate of original; the surface area of the white solid appears to be doubled.

d) The smaller sizes of the particles in (d) makes it harder to answer this question. Let's assume these white solids are spherical and that the radius of a sphere in (d) is half that of a sphere in the original. The surface area of a sphere is $A = 4\pi r^2$. The ratio of surface areas of one sphere to another is $\frac{A_1}{A_2} = \frac{4\pi r_1^2}{4\pi r_2^2} = (\frac{r_1}{r_2})^2$. The ratio of surface areas of an original sphere to a sphere in (d) is $\frac{A_d}{A_0} = (\frac{1}{2})^2 = \frac{1}{4}$ However, there are 12 spheres in (d) and only 4 spheres in the original. Thus, the ratio of total surface areas $\frac{A_{dT}}{A_{0T}} = (\frac{12}{4}) \times (\frac{1}{4}) = \frac{3}{4}$. The estimated rate of (d) = 3/4 x the Rate of original.

e) Let's assume these white solids are spherical and that the radius of a sphere in (e) is one quarter that of a sphere in the original. The ratio of surface areas of an original sphere to a sphere in (e) is $\frac{A_e}{A_0} = (\frac{1}{4})^2 = \frac{1}{16}$. However, there are 40 spheres in (e) and only 4 spheres in the original. Thus, the ratio of total surface areas $\frac{A_{eT}}{A_{0T}} = (\frac{40}{4}) \times (\frac{1}{16}) = \frac{5}{8}$ The estimated rate of (e) = 5/8 x the Rate of original.

f) Rate of (f) = Rate of original; the surface area of the white solid appears to be the sam

Exercise 1.6.4:

At the very start of the reaction, the concentrations of reactants have not changed very much. That means the rate of the reaction remains roughly constant as the first few percent of reactants are consumed. Plotting [product] vs. time gives a straight line with the slope = rate. However, over the course of the reaction, the concentration of reactants goes down as the reactants are consumed. That means the rate of product formation slows down and a plot of [product] vs. time becomes curved. We will be unable to measure the slope in a simple way.

Exercise 1.6.5:

The slope of the first curve, with $[A]_o$ = 1 mol L^{-1}, can be estimated by observing that [C] increases from zero to 25 mmol L^{-1} in 50 seconds. The slope is about $\frac{25}{50} = 0.5 \frac{mmol}{Ls}$. The slope of the next curve, with $[A]_0 = 2 \frac{mol}{L}$, is $1.0 \frac{mmol}{Ls} (\frac{50 \frac{mmol}{L}}{50s})$. The initial

concentration is doubled, and the rate doubles. The slope of the final curve, with $[A]_0 = 4\frac{mol}{L}$, is $2.0\frac{mol}{Ls}(\frac{100\frac{mmol}{L}}{50s})$. The initial concentration is doubled, and the rate doubles. The reaction is linearly dependent on the concentration of A. Whatever happens to [A] also happens to the rate.

In terms of rate laws, there is a mathematical approach to demonstrating this relationship.

Suppose $Rate = k[A]^x$; x is the power of the mathematical relationship.

The ratio of rates in two experiments is $\frac{Rate_1}{Rate_2} = (\frac{k[A_1]^x}{k[A_2]^x}) = (\frac{[A_1]}{[A_2]})^x$

If we take the logarithm of both sides: $\ln(\frac{Rate_1}{Rate_2}) = \ln((\frac{[A_1]}{[A_2]})^x) = x\ln(\frac{[A_1]}{[A_2]})$

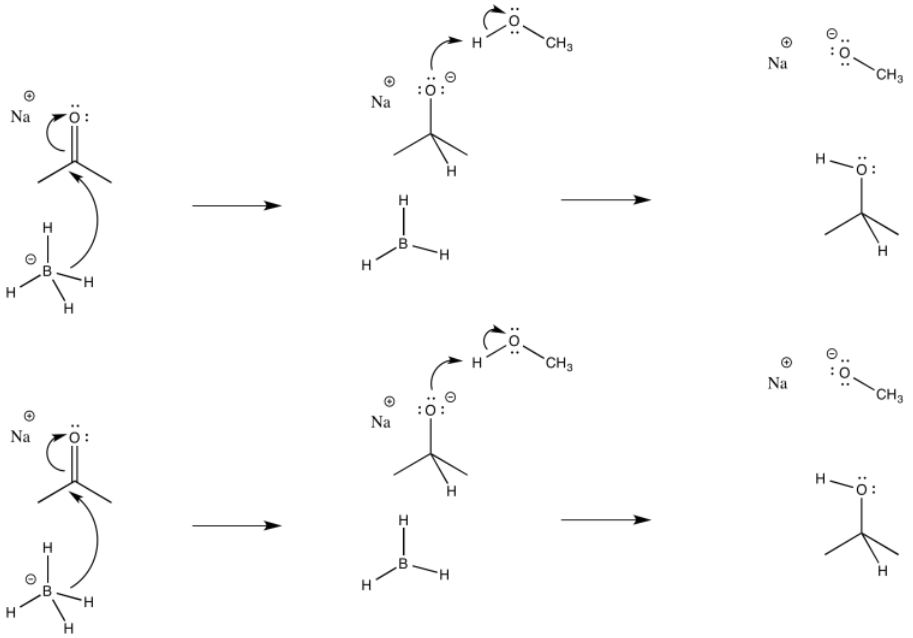
Then $x = \frac{ln(\frac{Rate_1}{Rate_2})}{ln(\frac{[A_1]}{[A_2]})}$

Exercise 1.6.6:

a. Each time the concentrations double (for example, from 2 to 4 mol L^{-1}), the rate quadruples (for example, from 50/50 = 1 mmol L^{-1} s^{-1} to 200/50 = 4 mmol $L^{-1}s^{-1}$). One explanation is Rate = k[A][B].
b. Another explanation is $Rate = k[A]^2$ *or* $Rate = k[B]^2$
c. We could run a series of experiments in which [A] is changed while holding [B] constant (or vice versa).

Exercise 1.7.1:

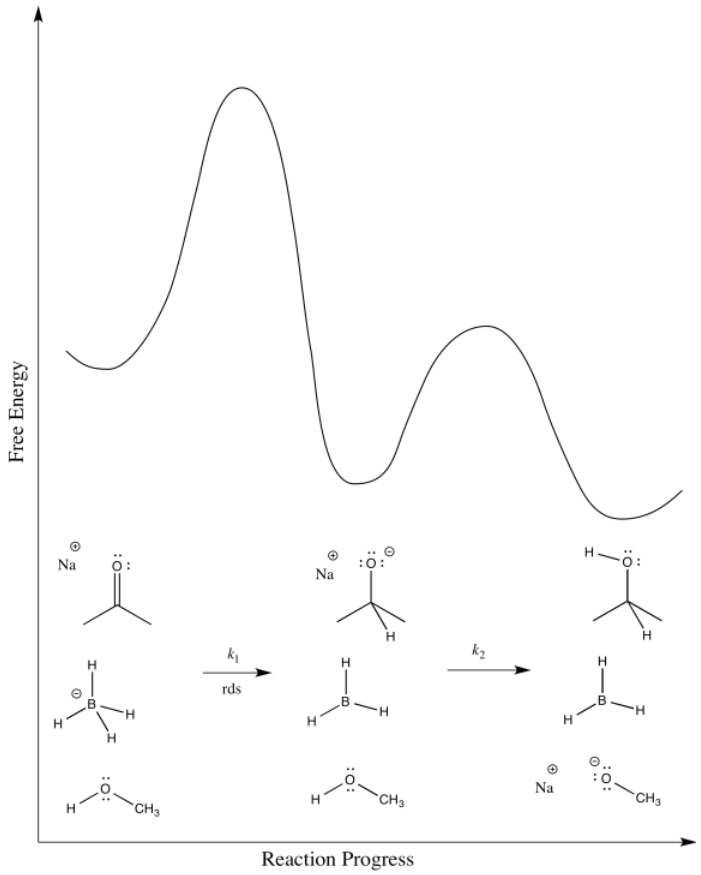
a)



b) The first step proceeds at k_1; the second at k_2.

c) The second step is probably reversible. It is just the exchange of a proton from one OH group to another.

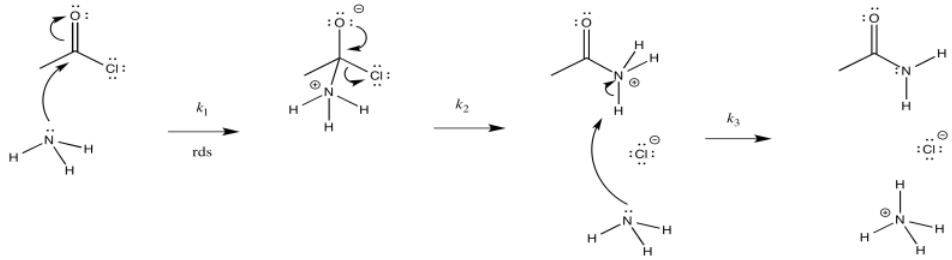
d)



e) $Rate = k_1[ketone][NaBH_4]$

Exercise 1.7.2:

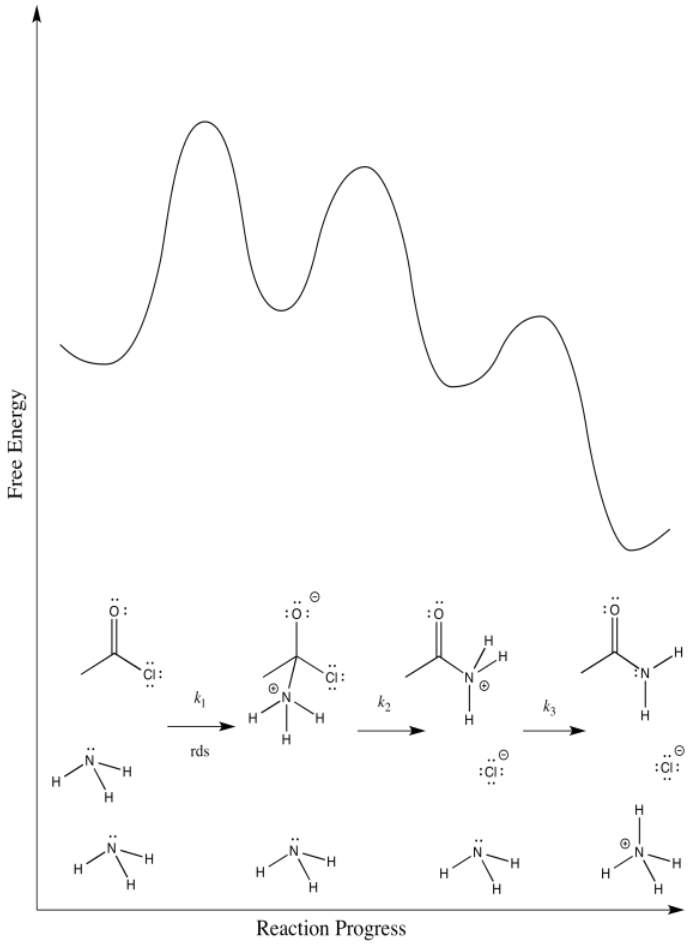
a)



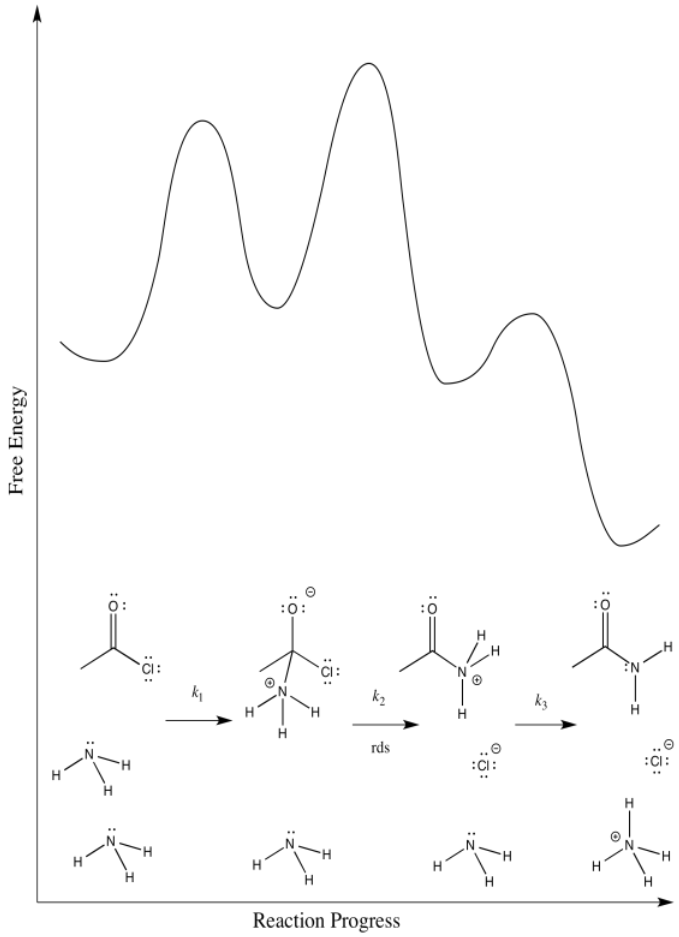
b) The first step proceeds at k_1; the second at k_2; the third at k_3.

c) There are three different steps, each of which might be rate determining.

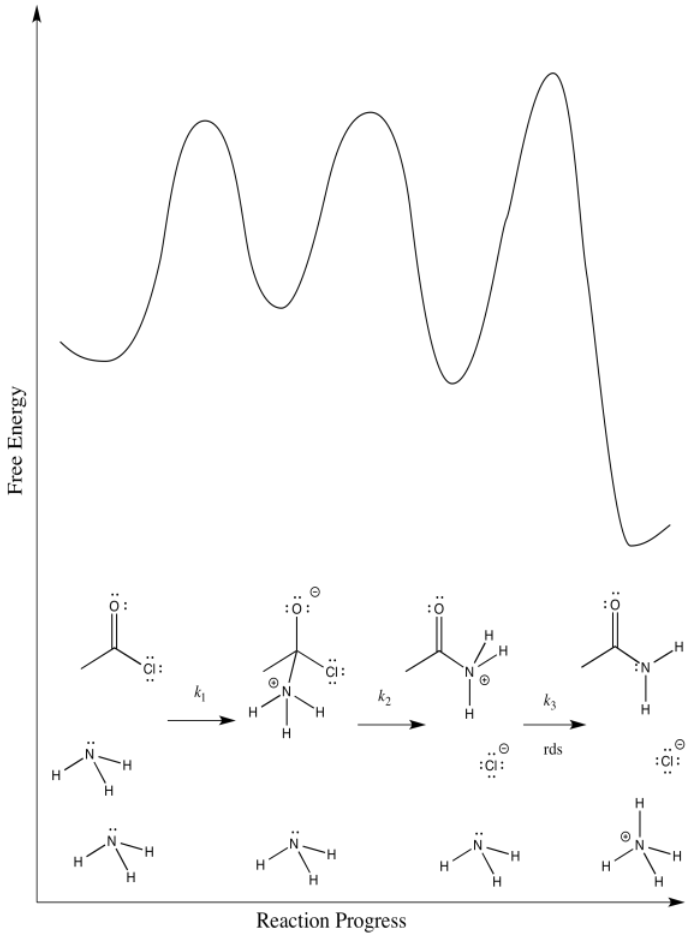
The first:



The second:



The third:



d) First one: $Rate = k_1[CH_3COCl][NH_3]$

Second one: $Rate = k_1k_2[CH_3COCl][NH_3]$

Third one: $Rate = k_1k_2k_3[CH_3COCl][NH_3]^2$

The rate law could be used to distinguish the third from the first two. However, it would be impossible to tell the difference between the first two using the rate law alone.

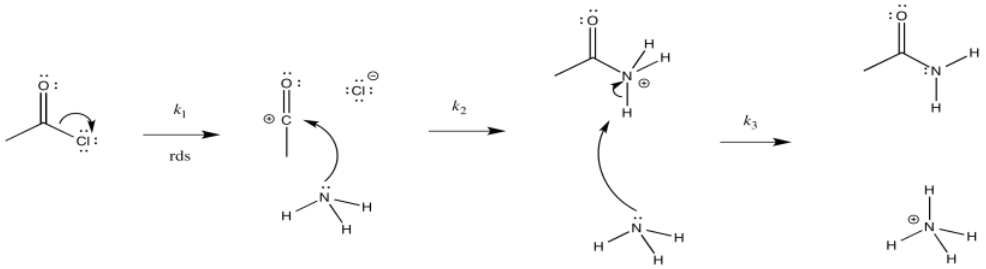
e) We can probably rule out the third possibility right away. Proton transfers tend to happen pretty quickly, especially in the presence of a reasonable base such as ammonia. Measuring the rate law would quickly confirm this assumption.

Scenarios 1 and 2 are much harder to distinguish. In both cases, a bond is being broken as another bond is being made. We could make an educated guess that the formation of the good chloride leaving group is pretty easy; that would make step 1 the rate determining step.

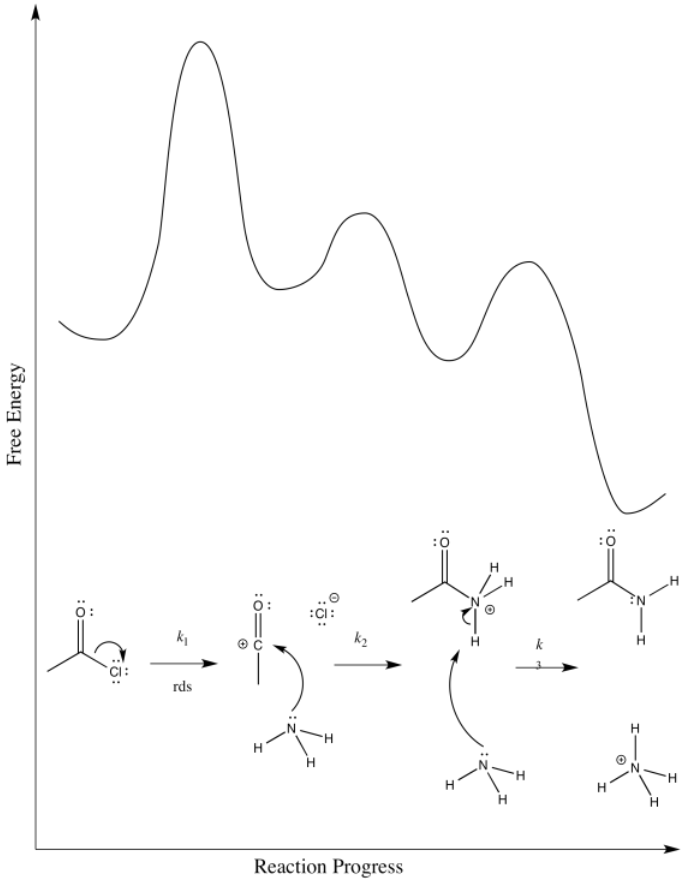
However, we are always left with some ambiguity in subtle cases like this one. In order to get a better idea about which transition states are the highest, we would have to perform computational chemistry.

Exercise 1.7.3:

a) i)

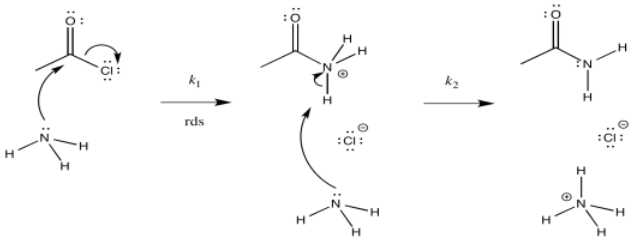


ii)

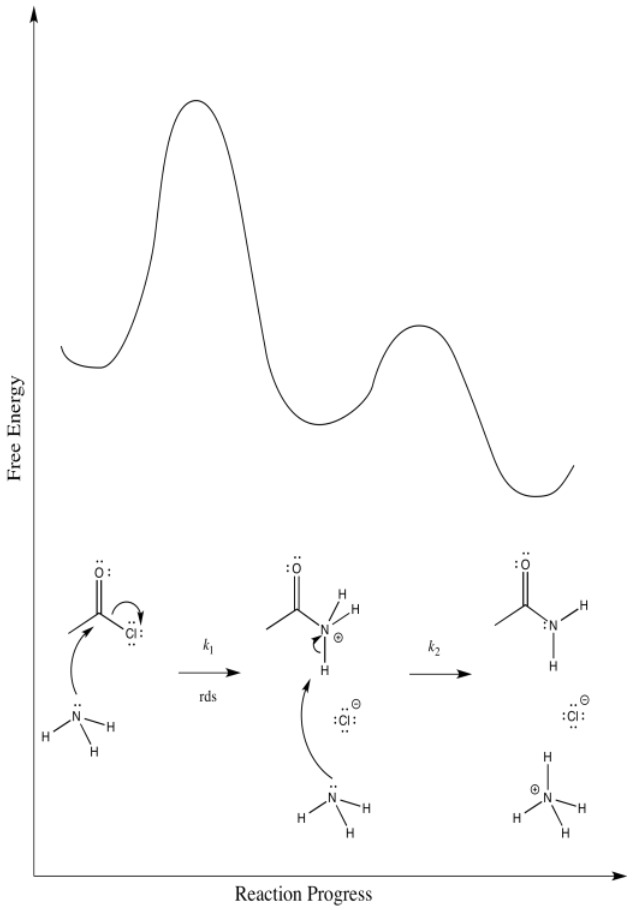


iii) $Rate = k_1[CH_3COCl]$

b) i)



ii)



iii) $Rate = k_1[CH_3COCl][NH_3]$

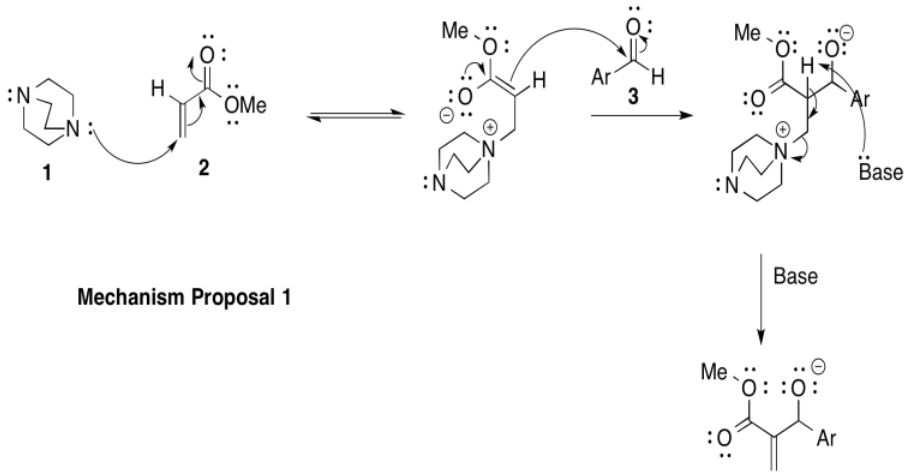
c) On the basis of the rate law, possibility (a) can be ruled out, but not possibility (b)

Exercise 1.7.4:

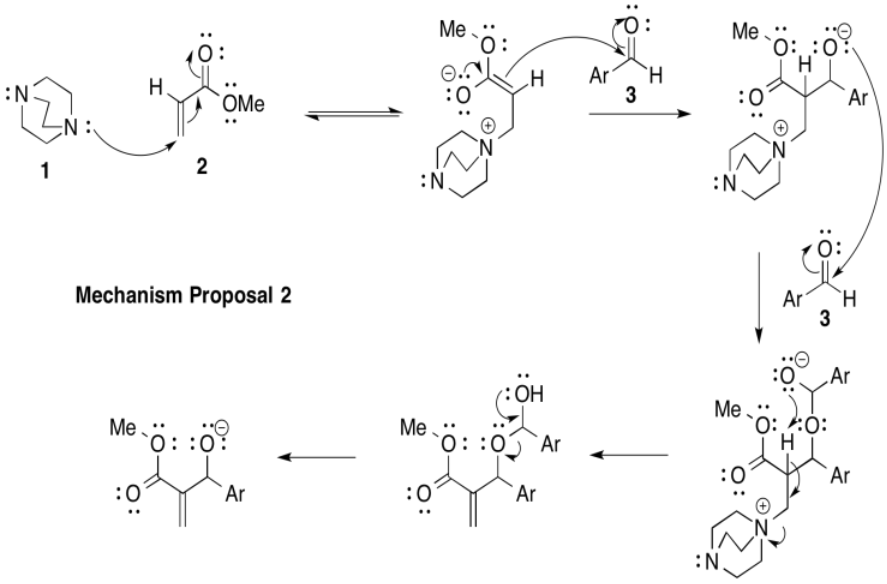
a. There is a geometry change prior to or during the rate determining step.
b. Possibility (b) can be ruled out.

Exercise 1.7.6

a)



Mechanism Proposal 1



Mechanism Proposal 2

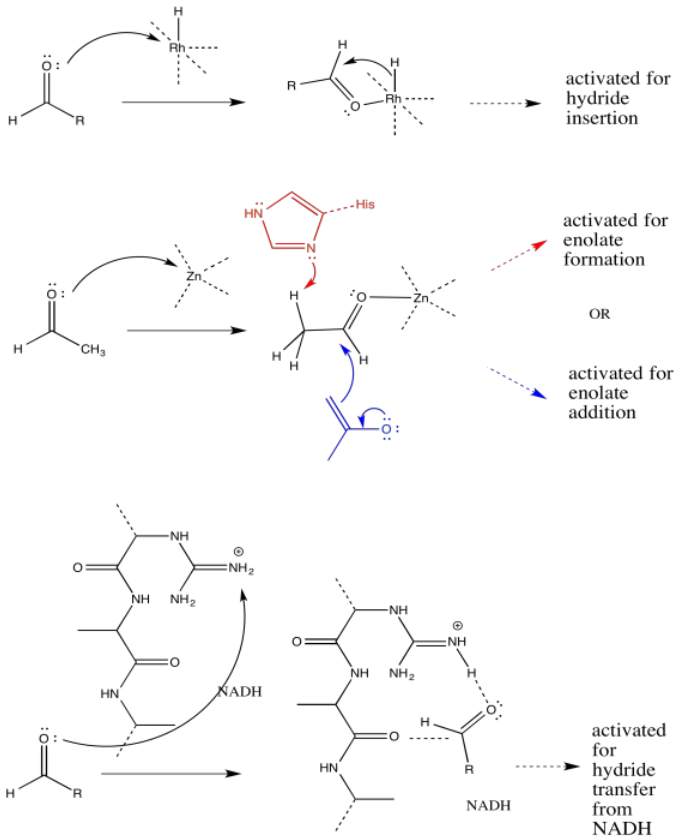
b) Mechanism 1: $k[1][2][3]$

Mechanism 2: $k[1][2][3]^2$

c) First order in [1]; first order in [2]; second order in [3]

d) Mechanism 2.

Exercise 1.8.2:



CHAPTER OVERVIEW

2: Mathematical Tools in Reaction Kinetics

2.1: Determination of Activation Parameters

Intuitively, you know that a reaction goes faster as the temperature is raised, as more reactant molecules have the energy needed to overcome the activation barrier to the reaction. The Arrhenius equation relates reaction rate constants (k) and temperature. One of the forms of the Arrhenius equation is:

$$lnk = \frac{-Ea}{RT} + lnA$$

where Ea is the activation energy for the reaction, T is the absolute temperature (in Kelvin) at which a corresponding k is determined, R is the gas constant, and A is a pre-exponential factor. The activation energy may then be extracted from a plot of ln k vs. 1/T, which should be linear. This plot is called an "Arrhenius plot".

Exercise 2.1.1

Recall that y = mx + b.

a. In a so-called “Arrhenius plot” plot, what is the slope?
b. What is the intercept?

Exercise 2.1.2

Using the following data, construct an Arrhenius plot and determine the activation energy (in both kcal/mol and kJ/mol) and the pre-exponential factor.

1/T (K^{-1})	ln k (unitless)
0.00152	3.7
0.00157	3.2
0.00160	2.9
0.00165	2.2
0.00170	1.6

Exercise 2.1.3

Using the following data, construct an Arrhenius plot and determine the activation energy (in both kcal/mol and kJ/mol) and the pre-exponential factor.

T (°C)	k (mol L^{-1} s^{-1})
40	1.3 x 10^{-4}
50	2.2 x 10^{-4}
60	4.0 x 10^{-4}
70	7.5 x 10^{-4}
80	1.4 x 10^{-3}

In practice, activation energies are not often cited in the current literature. Instead, a similar but more useful equation called the Eyring equation is used. The Eyring equation is:

$$ln(\frac{k}{T}) = \frac{-\Delta H^{\ddagger}}{RT} + ln(\frac{k_B}{h}) + \frac{\Delta S^{\ddagger}}{R}$$

where k, T and R are the same as in the Arrhenius equation, k_B is Boltzmann's constant, h is Planck's constant and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are the enthalpy and entropy of activation, respectively.

Exercise 2.1.4

a. What should be plotted to make an Eyring plot?
b. What is equal to the slope?
c. What is equal to the intercept?

Note that the activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) are not the same as the entropy and enthalpy of the reaction, which can usually be calculated from tables of values. Since they depend on how the reaction proceeds, not just the initial and final states of the reaction, they must be determined experimentally. Once that has been done, interpretation of the numerical values provides insight into the mechanism of the reaction.

2.2: The Rate Law Takes Different Forms

Sometimes it is useful to think of the rate law in different ways.

First Order Rate Law

For a first order reaction, we have seen the following rate law:

$$Rate = \frac{d[P]}{dt} = k[R] \tag{2.2.1}$$

In this case, R is a reactant and P is the product. This rate law indicates that as reactant concentration increases, the rate of formation of the product increases proportionally. On the other hand, the concentration of reactant will decrease as it is converted into product, so we could also describe the rate of reactant consumption by the same rate law.

$$Rate = \frac{-d[R]}{dt} = k[R] \tag{2.2.2}$$

Sometimes, it can be useful to look at that rate law a different way. If we use a little algebra on the original rate law, we can cross-multiply and get an equivalent expression:

$$d[R] = -k[R]dt \tag{2.2.3}$$

or, going one step further,

$$\frac{d[R]}{[R]} = -kdt \tag{2.2.4}$$

What we are doing here is separating out these two differential terms so that we can integrate the expression. Insetad of looking at what is happening in, for example, an infinitesimal unit of time, we are going to step back and see what happens in a much larger block of time.

$$\int \frac{d[R]}{[R]} = \int -kdt \tag{2.2.5}$$

We can pull any constants in front of the integral.

$$\int \frac{d[R]}{[R]} = -k \int dt \tag{2.2.6}$$

We can integrate the two halves of the equation separately. The right hand side is simple. The integral of dt is just t, time. It is the elapsed time from the start of the experiment until the current time.

$$\int \frac{d[R]}{R} = -k(t - t_0) \tag{2.2.7}$$

Or if the experiment started at t = 0

$$\int \frac{d[R]}{[R]} = -kt \tag{2.2.8}$$

The left side is not very complicated either; the integral of 1/x dx is ln(x), the natural log. Again, it would be the current value of ln(x) minus the value of ln(x) at the beginning of the experiment.

$$\ln([R]) - ln([R]_0) = -kt \tag{2.2.9}$$

Or, using the rules of logarithms,

$$\ln(\frac{[R]}{[R]_0}) = -kt \tag{2.2.10}$$

This is called the integrated form of the rate law. The form we started with is called the differential form of the rate law. Both are useful. The reason people use an integrated form is to easily plot linear relationships. In this form, if we plot ln([R]/[R0] on the y

axis and time on the x axis, and the reaction is first order, we will get a straight line. The slope will be -*k*. This is an easy way to find a rate constant.

Another useful outcome of the integrated form of the rate law is the the relationship between "half life" and the rate constant. Half life is the time it takes for a first order reaction to be 50% complete; half the reactants have been converted to product. In other words, the ratio $[R]/[R]_0 = 0.5$. At that point,

$$\ln(0.5) = -kt_{\frac{1}{2}} \tag{2.2.11}$$

In which $t_{1/2}$ just refers to the half life, the time to get to 50% completion of the reaction.

Once again, the rules of logarithms can help simplify things.

$$-\ln(0.5) = ln(2) \tag{2.2.12}$$

so

$$\ln(2) = kt_{\frac{1}{2}} \tag{2.2.13}$$

$$0.693 = kt_{\frac{1}{2}} \tag{2.2.14}$$

or

$$t_{\frac{1}{2}} = \frac{0.693}{k} \tag{2.2.15}$$

So if we know the half life, we can easily calculate the rate constant, and vice versa.

Second Order Rate Law

We can take a similar approach for a rate law that is second order in reactant. The integrated rate law provides a different treatment that can be useful.

$$Rate = \frac{-d[R]}{dt} = k[R]^2 \tag{2.2.16}$$

Cross-multiplying allows us to separate the two differential terms.

$$\frac{d[R]}{[R]^2} = -kdt \tag{2.2.17}$$

We can integrate each side. This time, we have the integral of $1/x^2$, or x^{-2}, which is just 1/x, or x^{-1}.

$$\int \frac{d[R]}{[R]^2} = -k \int dt \tag{2.2.18}$$

$$\frac{1}{[R]} - \frac{1}{[R_0]} = -kt \tag{2.2.19}$$

Like the integrated form of the first order rate law, the integrated form of the second order rate law allows concentration data to be plotted against time, giving a linear relation. This time, the reciprocal of the reactant concentration is plotted, 1/[R]. The slope once again provides the rate constant via -*k*. The y intercept is the reciprocal of the starting concentration of reactant.

2.3: Determining the Rate Law Experimentally

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2.4: Elementary Reactions and the Rate Law

How can you confirm a particular rate law through experiment?

The rate law is just the mathematical expression that shows how the rate of production of the product varies with concentrations of reactants.

$$\text{Rate} = \frac{d[P]}{dt} = k[R]^x \tag{2.4.1}$$

In other words, the rate of the reaction can be defined as the change in product concentration over changing time. It is proportional to some rate constant, *k*, as well as some reactant concentrations. The relationship may not be linear, so the exponent x indicates that the rate will vary with reactant concentrations to some power; x might be a whole number or it might be a fraction.

If all we know is the overall equation for the reaction (these reactants are converted into those products), it is difficult to tell what the rate law will be. The rate law will depend on the series of steps that occur to transform the reactant into product. However, if we think we know what those individual steps are, we can use that knowledge to make educated guesses about what the rate law will look like. In other words, knowing the mechanism of the reaction allows us to predict the rate law. Conversely, knowing the rate law for the reaction can help us to determine the mechanism.

Consider the simplest reaction of all: one that occurs in only one step. A is transformed into B.

$$A \rightarrow B \tag{2.4.2}$$

The most common examples of these kinds of reactions are in nuclear chemistry. Elements occur in a number of isotopes, some of which are less stable than others. Unstable atoms tend to spontaneously decay. A mother atom turns into a daughter atom. They don't do it all at once, but according to a sort of clock: a certain fraction of the nuclei will decay in a certain period of time. That same fraction of the remaining nuclei will decay in the next period of time, and so on. That fraction per unit time corresponds to the rate constant of the reaction.

Of course, if it is always a certain fraction of atoms decaying per unit time, then the more atoms we have the more quickly we will be producing daughter atoms. The rate of production of daughter atoms depends on the amount of mother atoms. Consequently, the rate depends both on the concentration of mother atoms and the rate constant.

$$Rate = \frac{d[B]}{dt} = k[A]$$

$$Rate = \frac{d[daughter\ atom]}{dt} = k[mother\ atom]$$

Now let's look at another, relatively simple reaction. Consider an aliphatic nucleophilic substitution reaction. The kind we will think about involves the direct displacement of a leaving group by a nucleophile. The two molecules come together and, in one step, form the products.

$$A + B \rightarrow C + D \tag{2.4.3}$$

Now, this reaction will also depend on a rate constant. At a given temperature, over a given period of time, a specific fraction of these molecules will have enough energy to undergo reaction and they will collide in the proper orientation for the substitution to take place.

What happens if the concentration of available nucleophile is doubled? The electrophile is twice as likely to collide with a nucleophile. What happens if the concentration of electrophile is doubled? The nucleophile is twice as likely to collide with the electrophile. The rate varies linearly with the concentration of both the electrophile and nucleophile.

$$Rate = \frac{d[C]}{dt} = k[A][B] \tag{2.4.4}$$

For example, in the substitution of bromomethane with sodium methylsulfide to make dimethyl thioether,

$$\mathrm{NaSCH_3CH_3Br \longrightarrow CH_3SCH_3 + NaBr} \tag{2.4.5}$$

In the most likely reaction pathway, the reaction happens all in one step: reactants come together to produce the products. The rate law is:

$$Rate = \frac{d[CH_3SCH_3]}{dt} = k[NaSCH_3][CH_3Br] \tag{2.4.6}$$

Those two scenarios form the building blocks of rate laws. An elementary step may involve one molecule or intermediate undergoing a change by itself. The rate of that step will depend on the concentration of the intermediate and the rate constant of the process. Alternatively, an elementary step may involve a collision between two species. The rate of that step will depend on the concentration of both species and the rate constant for the reaction.

- unimolecular steps depend on the concentration of one species only
- bimolecular steps depend on the concentration of two species

Multi-Step Reactions and the Steady State Approximation

If we look at another reaction, very similar to the last one, we will see a slightly more complicated case. In cases of more sterically crowded alkyl halides, substitution reactions can take place via initial ionization, especially if the resulting carbocation is relatively stable.

For example, in the following reaction:

$$\mathrm{Ph_3CCl + NaN_3 \longrightarrow Ph_3CN_3 + NaCl} \tag{2.4.7}$$

(P. v. R. Schleyer, D. J. Raber, J. M. Harris, R. E. Hall, *J. Am. Chem. Soc.* **1971**, *93*(9), 4821-4828.)

initial ionization appears to give rise to a cationic intermediate.

$$\mathrm{Ph_3CCl{=}Ph_3C^+ + Cl^-} \tag{2.4.8}$$

Here, the equals sign suggests an equilibrium case.

Subsequently, the azide ion combines with the triphenylmethyl cation (sometimes nicknamed "trityl" cation):

$$\mathrm{Ph_3C^+ + N_3^- \rightarrow Ph_3CN_3} \tag{2.4.9}$$

If we think about the rate of reaction in terms of the rate of product formation, then we are looking at a simple elementary step. Azide and trityl cation come together to make the product.

$$Rate = \frac{d[Ph_3CN_3]}{dt} = k_2[Ph_3C^+][N_3^-]$$

Because sodium azide is an ionic compound, the azide concentration is equal to the dissolved concentration of sodium azide. We know what the azide concentration is because we know how much sodium azide we dissolved.

What about the trityl cation? What is its concentration? The thing about reactive intermediates such as cations is that they often exist so fleetingly that we don't directly observe them. It's not like the sodium azide, which we weigh out on a balance and add to the reaction flask. We don't really know how much of the trityl cation is in the flask at a given time.

We do know where the trityl cation comes from. We can use that knowledge to work out what its concentration should be. The trityl cation comes from the trityl chloride, and that would be measured on a balance and added to the reaction mixture.

That tells us how quickly trityl cation could be produced.

$Rate = \frac{d[Ph_3C^+]}{dt} = k_1[Ph_3CCl]$,

if k_1 is the elementary rate constant for the forward equilibrium step in equation 1.

We also know that the trityl cation is a reactive intermediate, so it is probably converted into products as soon as it is formed. Either that, or it collapses back to the trityl chloride from which it came in the first place. We can look at that rate of consumption. That will depend on the elementary steps that use up the cation:

$Rate = \frac{-d[Ph_3C^+]}{dt} = k_{-1}[Ph_3C^+][N_3^-]$ if k_{-1} is the reverse step in the initial equilibrium

If the reactive intermediate is consumed as soon as it is produced, then the rate of formation equals the rate of consumption.

$$\frac{d[Ph_3C^+]}{dt} = \frac{-d[Ph_3C^+]}{dt} \tag{2.4.10}$$

or

$$k_1[Ph_3CCl] = k_{-1}[Ph_3C^+][Cl^-] + k_2[Ph_3C^+][N_3^-] \tag{2.4.11}$$

The right hand side has some common terms.

$$k_1[Ph_3CCl] = [Ph_3C^+](k_{-1}[Cl^-] + k_2[N_3^-]) \tag{2.4.12}$$

We can isolate the trityl cation concentration.

$$[Ph_3C^+] = \frac{k_1[Ph_3CCl]}{(k_{-1}[Cl^-] + k_2[N_3^-])} \tag{2.4.13}$$

That means we can express that unknown concentration in terms of other quantities, and we may be able to use that to simplify things.

We already knew the rate law for product formation:

$$Rate = \frac{d[Ph_3CN_3]}{dt} = k_2[Ph_3C^+][N_3^-] \tag{2.4.14}$$

But now we can replace that unknown quantity:

$$Rate = \frac{d[Ph_3CN_3]}{dt} = \frac{k_1k_2[Ph_3CCl][N_3^-]}{(k_{-1}[Cl^{-1}] + k_2[N_3^-])} \tag{2.4.15}$$

So the steady state approximation, the assumption that a reactive intermediate is consumed as soon as it is formed, leads to a rate law that is independent of that unknown intermediate concentration. That may not make you very happy, because the rate law looks a little complicated. That's normal. The key part now is looking at specific cases in which the rate law may simplify, and thinking about what that simplification tells us.

Looking at Limiting Cases

This rate law would be pretty straightforward if it were not for that denominator. The denominator has two additive terms, and that makes analysis complicated. It would be more straightforward if we did not have two things adding together.

The question we need to ask now is whether there are situations in which one of those additive terms can be ignored? In general, that's true if one of the terms is a whole lot bigger than the other. There are some different situations in which that could occur. Maybe the chloride concentration is much, much smaller than the azide concentration, so small that those two terms added together are not much different from the second term alone:

i.e. if $k_{-1}[Cl^-] + k_2[N_3^-] = k_2[N_3^-]$, approximately

In that case, the rate law simplifies to a form that is easier to use:

$$Rate = \frac{d[Ph_3CN_3]}{dt} = \frac{k_1k_2[Ph_3CCl][N_3^-]}{k_2[N_3^-]}$$

or $Rate = \frac{d[Ph_3CN_3]}{dt} = k_1[Ph_3CCl]$

So there may be some reaction conditions under which the rate law becomes much simpler.

For the purposes of thinking about mechanism, it can also be useful to think about cases in which those elementary rate constants are very large or very small. For example, suppose $k_{-1} >> k_2$.

In that case,

$$Rate = \frac{d[Ph_3CN_3]}{dt} \frac{k_1k_2[Ph_3CCl][N_3^-]}{(k_{-1}[Cl^-] + k_2[N_3^-])} = \frac{k_1k_2[Ph_3CCl][N_3^-]}{k_{-1}[Cl^{-1}]}$$

That suggests a bimolecular reaction, but one that is inhibited by the leaving group.

On the other hand, suppose $k_2 >> k_{-1}$.

In that case,

$$Rate = \frac{d[Ph_3CN_3]}{dt} = \frac{k_1 k_2 [Ph_3CCl][N_3^-]}{(k_{-1}[Cl^-] + k_2[N_3^-])} = \frac{k_1 k_2 [Ph_3CCl][N_3^-]}{k_2[N_3^-]}$$

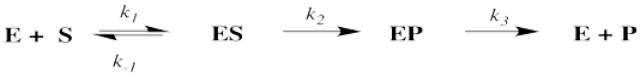
Or $Rate = k_1[Ph_3CCl]$

And that is what we think of as a first order rate law for an S_N1 reaction. In other words, in that kind of reaction, the step in which the cation and anion combine is rapid compared to the initial equilibrium for ion formation.

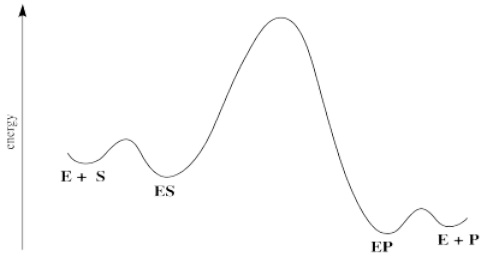
2.5: Enzyme Kinetics and Inhibition

The kinetics of reactions involving enzymes are a little bit different from other reactions. First of all, there are sometimes lots of steps involved. Also, the reaction involves a huge, complicated molecule, the enzyme. Sometimes it's hard to figure out what's going inside that enzyme.

Nevertheless, we can think about that reaction and break it down into just a few different steps. First, the enzyme has to bind the substrate. Second, the enzyme has to transform that substrate into the product. Third, the product must be released.



A reaction progress diagram for this process looks something like this:



There are some energetic considerations on this diagram that we should think about. In normal reactions, the intermediates that form along the reaction pathway are higher in energy than either the reactants or the products. We can think of the reactants climbing up a hilly mountain range and sliding down the other side, all the way to products.

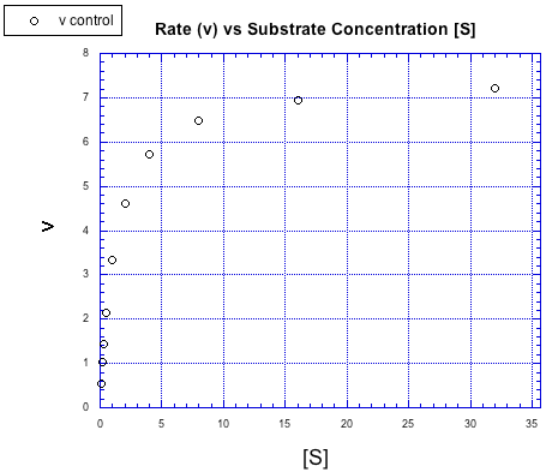
In many cases of catalysis, the enzyme-substrate complex (ES) is actually lower in energy than the free enzyme and substrate. That's because of the intermolecular attractions that hold the substrate in place within the enzyme. That's good; if the enzyme is able to hold the substrate tightly, it will be able to do its work. Of course, if the ES is too stable, it will just sit there; nothoing will ever happen to it.

The middle hump of the diagram actually represents any number of steps. In reality, we might better represent those steps as a series of individual hills and valleys. We're simplifying a little bit by picturing it this way. Nevertheless, it may often be the case that the highest energy, slowest step of this reaction falls somewhere among these steps.

When we looked at reaction kinetics earlier, we made the assumption that anything after the rate determining step had little effect on the rate of the reaction. We'll make that approximation here, too, and think about two main components of the reaction. First, the substrate must be bound in an enzyme-substrate complex. Second, the enzyme has to do something with that substrate, and turn it into somethings else.

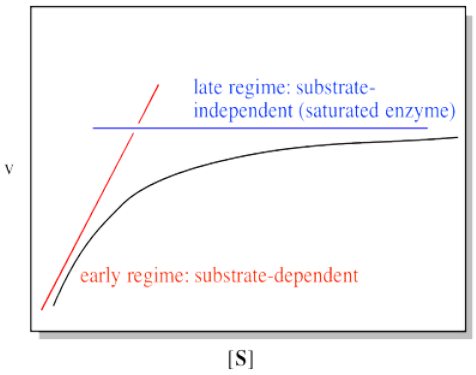
Before we start thinking very hard about rate constants, we'll take a look at what data typically looks like in an enzyme-catalysed reaction. Presumably, substrate is required to get anywhere in the reaction, and so the rate of the reaction should go faster if the substrate concentration increases. The more substrate we have reacting, the fatser we should make product.

That's true, but only up to a point. Suppose we add more and more substrate to an enzymatic reaction. Look at the following graph of what happens to the rate (usually represented in biochemistry as *v* for velocity).



Instead of forming a straight line, the concentration / rate plot is curved. At first, the rate increases with added substrate. Eventually, however, the rate levels off, no matter how much substrate is added.

We can think about the plot falling into two regimes. There is the early regime, at low substrate concentration. Across this range of substrate concentrations, the rate increases with added substrate. There is also the late regime, at high substrate concentration. Across that range of substrate concentrations, the rate remains flat.

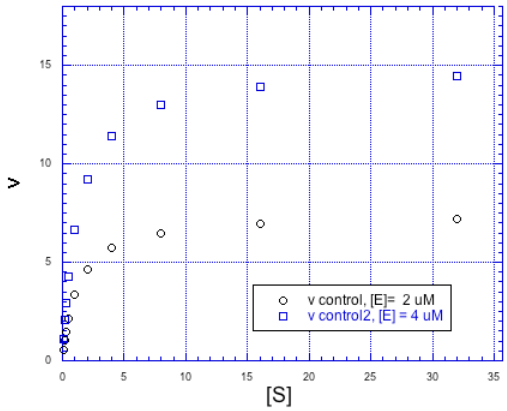


There is a simple explanation for this behaviour. It has to do with how enzymatic reactions are carried out, and with catalytic reactions in general. The whole point of a catalyst is that, in addition to facilitating a reaction, it is regenerated. It gets recycled: each enzyme molecule is used multiple times to convert many substrate molecules into product. Consequently, only a very tiny amount of enzyme is needed to efficiently carry out the reaction. The ratio of substrate to enzyme molecules in a typical reaction may be in the millions.

That's all very good in terms of efficiency. However, at some point, it seems like some of those substrate molecules are going to be left waiting around while enzymes are busily working on others. If the enzyme has to bind the substrate and do some work on it, we could easily have a situation in which all the enzyme molecules are full. Additional substrate molecules have to wait their turn. At that point, adding additional substrate doesn't speed up the reaction. We refer to the enzyme as "saturated" at that point, meaning it can't add any more substrate.

- the reaction reaches a maximum rate at high substrate levels
- additional substrate does not increase the rate beyond that point
- the enzyme is saturated with substrate and cannot accommodate more

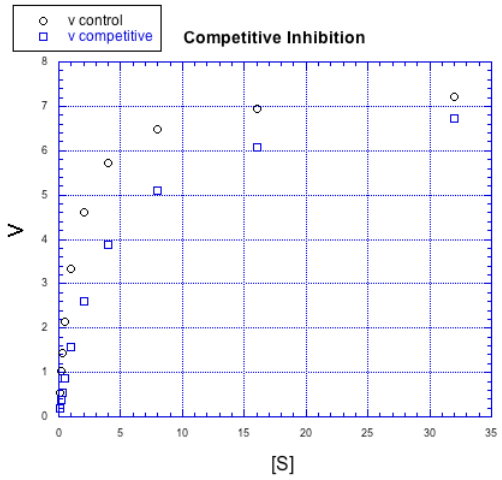
Of course, if we added more enzyme, we could handle more substrate, too. Doubling the amount of anzyme would double the maximum rate of the reaction.



We study the rates of enzymes reactions to learn more about how they work. One of the most important things we can look at is the response of enzymes to inhibitors. Inhibitors are compounds that can slow the enzymatic reaction.

From a purely scientific point of view, how an inhibitor interacts with the enzyme is an interesting question. However, there are many applications for this question in the pharmaceutical industry. Suppose a disease can be controlled by slowing down a particular enzyme that is over-producing some small compound. Inhibitors might make useful pharmaceuticals. However, we would want to have a good idea about how that drug is working. That knowledge might tell us someting about how to build a better drug, for instance.

Inhibitors can work in different ways. The effect an inhibitor has on the rate / concentration plot can tell us something about what the inhibitor is doing. For example, look at the following plot. The regular reaction involving the enzyme and the substrate is plotted with black circles. The blue squares show the same reaction in the presence of an inhibitor.



If we compare individual data points from both curves at the same value of [S], it is clear that the speed of the reaction is always slower when the inhibitor is present. For example, when the substrate concentration is about 16 units, the rate of the regular reaction is about 7 units, but the rate of the reaction with added inhibitor is only 6 units.

But something interesting is happenning. By the time we get to the next data point, [S] = 32 units, the rate of the inhibited reaction has almost caught up with the regular one. If you look closely, the inhibited reaction is steadily closing the gap throughout the graph.

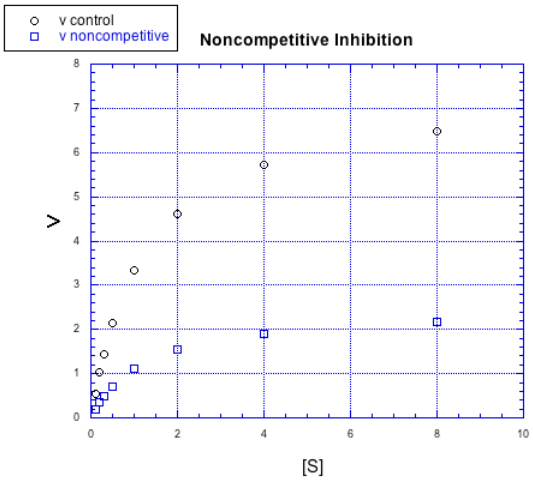
That means that if you add enough substrate, you can neutralize the effect of the inhibitor. How does it do that?

The simplest explanation is that the inhibitor can bind to the enzyme in place of the substrate. There is an equilibrium constant for enzyme-inhibitor binding, just as there is an equilibrium constant for enzyme-substrate binding. However, if we add enough substrate, we can displace the inhibitor altogether, binding only substrate. Remember le Chatelier? The more substrate we have, the more the equilibrium shifts toward enzyme-substrate complex.

This type of inhibition is called competitive inhibition. The inhibitor and the substrate are competing for the same binding site on the enzyme.

- A competitive inhibitor competes with the substrate for the binding site on the enzyme.
- As substrate concentration increases, it eventually displaces the inhibitor.
- The reaction rate approaches the normal rate at higher substrate concentrations.

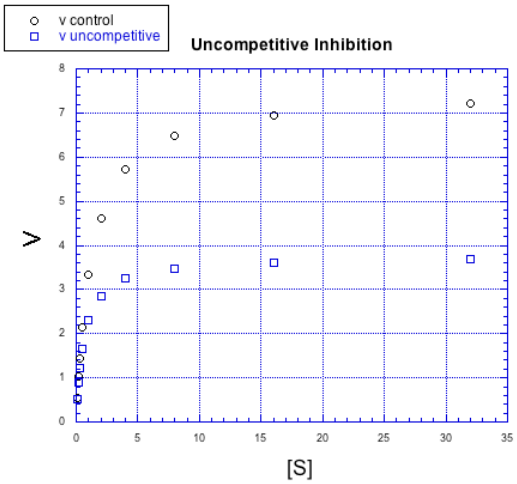
There are other kinds of inhibitors, too. For example, the inhibitor in the following case does not behave the same way.



No matter how much substrate is added in this case, the reaction with the inhibitor can't catch up. There is more going on here than just competition for the binding site.

In this case, the inhibitor is directly interfering with the product-forming steps of the reaction. The inhibited reaction starts behind and never catches up. This case is called non-competitive inhibition.

There are other, more subtle variations of inhibition, too. For example, in the following case, the inhibited reaction behaves a little bit differently than in the other cases, but the difference is hard to see at first.



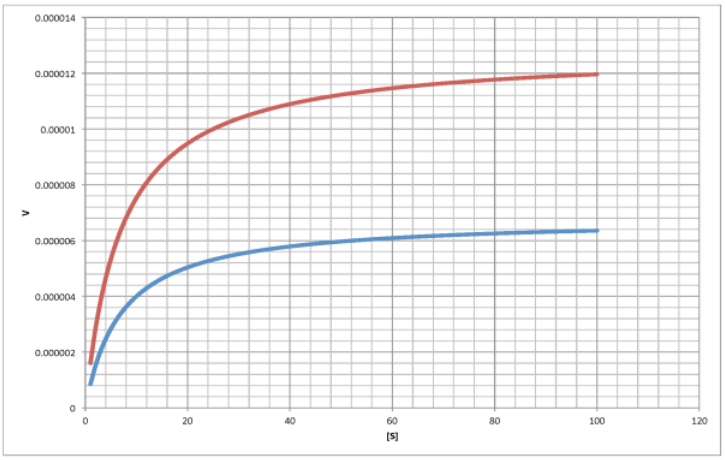
This time, the inhibited reaction seems to be doing OK at first, but it gradually falls off. It can't keep up with the regular reaction. Again, something is interfering with the product-forming steps; that's why added substrate doesn't eventually overcome the inhibitor. But in the early stages, this case looks different from non-competitive inhibition. This case is given the very similar name "uncompetitive inhibition".

To get a little more insight into these inhibitors, we will have to take a look at a mathematical treatment of the kinetics.

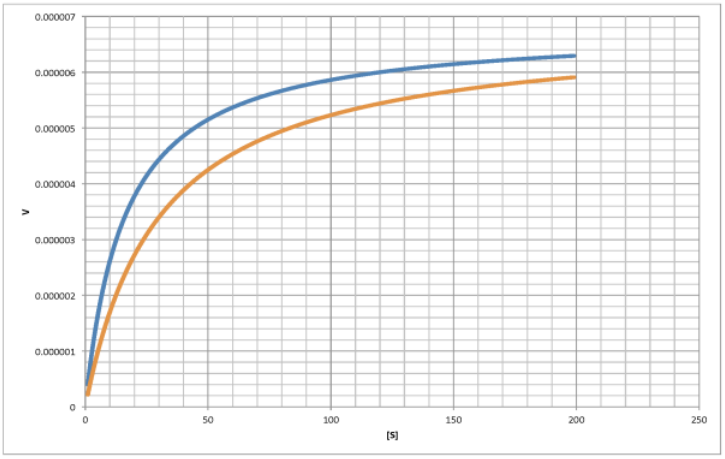
? Exercise 2.5.1

Characterise the following graphs as representing either competitive or non-competitive inhibition.

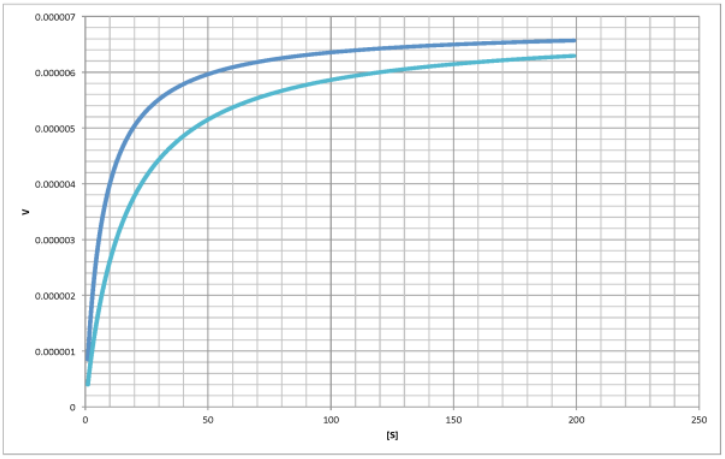
a)


0.000014
0.000012
0.00001
0.000008
0.000006
0.000004
0.000002
0
v
0
20
40
60
80
100
120
[s]

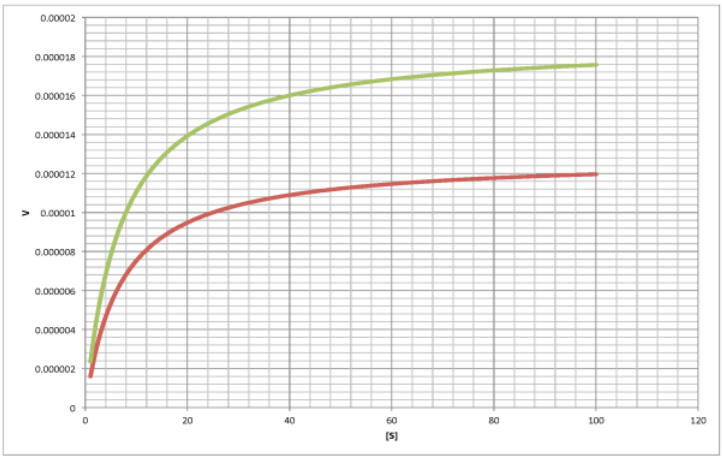
b)


0.000007
0.000006
0.000005
0.000004
0.000003
0.000002
0.000001
0
v
0
50
100
150
200
250
[s]

c)



d)



Answer a

non-competitive

Answer b

competitive

Answer c

competitive

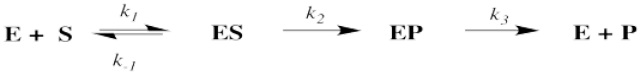
Answer d

non-competitive

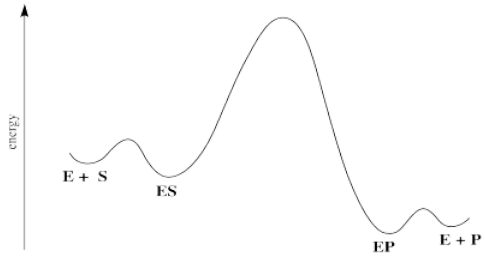
2.6: Characterization- The Mathematics Behind Enzyme Kinetics

Michaelis-Menten Plots

An enzyme-catalysed reaction can be roughly divided into three stages: enzyme-substrate binding, "catalysis" and product release. "Catalysis" refers to all the steps that happen to convert substrate into product. Sometimes, these steps are too fast to distinguish from each other. To simplify, we sometimes refer to this whole sequence of events as though they were just one step.



Often, but not always, that catalysis part is the rate determining step. Product release is sort of an afterthought.



In that case, we might simplify and only consider those steps up through catalysis.

If we do that, we find that enzyme reactions can be summarized by a relation called the Michaelis-Menten equation, named after the early 20th century biochemist Leonor Michaels and his collaborator, the immensely talented artist, physician and biochemist, Maud Menten.

$$\text{rate} = v = \frac{k_2[\mathbf{S}][\mathbf{E}_{\mathbf{tot}}]}{[\mathbf{S}] + K_m}$$

The numerator in this equation should make sense -- of course the rate should increase when we add either more substrate or more enzyme and the relationship will depend on the speed of that product-forming step.

The denominator is a little more complicated and contains the composite constant K_m, the Michaelis-Menten constant.

$$K_m = \frac{k_2 + k_{-1}}{k_1}$$

This relationship can be understood most easily by examining its limits. For instance, suppose the substrate concentration is still very low. Perhaps it is much smaller than K_m. How does that affect the rate of the reaction?

It is useful to keep in mind that a large number added to a small number is just a large number. One million plus one is about a million. One million plus three is also about a million. One million plus five is pretty close to a million. We can often ignore the small quantity in additions. In that sense, if [**S**] is small, we can ignore it in the denominator, and think of the denominator instead as "approximately K_m".

$$v = \frac{k_2[\mathbf{S}][\mathbf{E}_{\mathbf{tot}}]}{[\mathbf{S}] + K_m}$$

$$v \simeq \frac{k_2[\mathbf{S}][\mathbf{E}_{\mathbf{tot}}]}{K_m}$$

$$v = k[\mathbf{S}][\mathbf{E}_{\mathbf{tot}}]$$

We can't ignore [**S**] in the numerator, of course, even if it is very small. That's because a number multiplied by a very small number also becomes a very small number; the small number really counts when it is multiplied by something.

On the other hand, when [**S**] gets very large, we can ignore Km. That means Km disappears from the denominator, leaving only [**S**]. At that point, the [**S**] in the denominator and numerator cancels.

$$v = \frac{k_2[\mathbf{S}][\mathbf{E_{tot}}]}{[\mathbf{S}] + K_m}$$

$$v \simeq \frac{k_2[\mathbf{S}][\mathbf{E_{tot}}]}{[\mathbf{S}]}$$

$$V_{max} = k_2[\mathbf{E_{tot}}]$$

Remember, when [**S**] gets very large, the reaction has reached its maximum possible rate, because the enzyme is saturated. Adding more substrate doesn't speed things up, because the extra substrate just has to wait around until an enzyme becomes available. We call that maximum rate V_{max}.

- The limits of the Michaelis Menten equation explains the shape of the curve describing the rate dependence on substrate.

There is another piece of useful information we can get from this equation. It comes at an intermediate point between the two cases we have considered so far. What if the numerical value of K_m and [**S**] are exactly equal? In that case, the value of the denominator, K_m + [**S**], is the same as [**S**] + [**S**]. The denominator becomes 2[**S**]. Just as in the limiting case that gave us the value of V_{max}, the [**S**] cancels, but this time there is still a 2 in the denominator, so we get $V_{max}/2$.

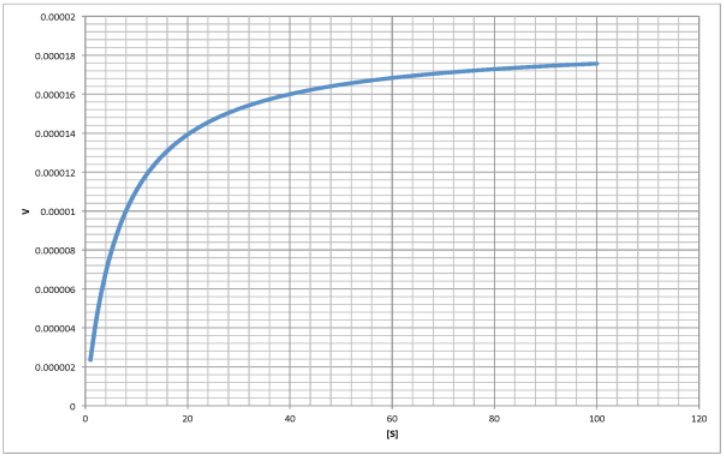
Turning that conclusion around, if we find the point on a Michaelis Menten plot where the rate is half the maximum rate, we can drop a line down to the x axis. The value of [S] at the intercept will be numerically the same as the value of Km.

- V_{max} is the point on the y axis where the rate has completely leveled off.
- K_m is the point on the x axis corresponding to y = $V_{max}/2$.

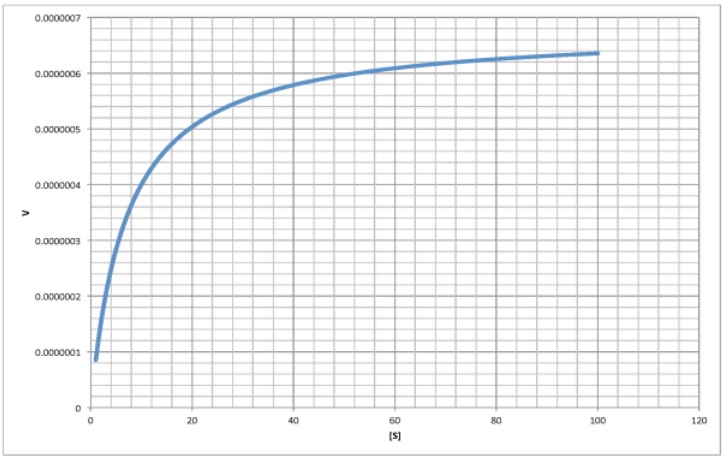
? Exercise 2.6.1

Determine V_{max} and K_m in each of the following cases. Assume the units of [S] are millimoles per liter and the units of V are moles per liter per second.

a)



b)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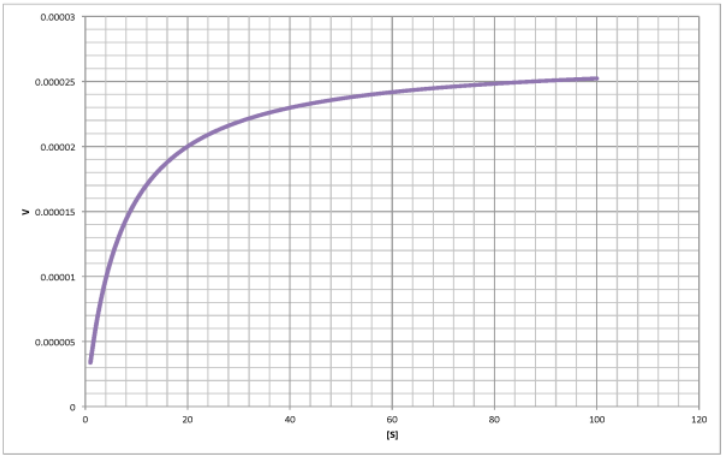
0.0000005
0.0000004
0.0000003
0.0000002
0.0000001
0
V
0
20
40
60
80
100
120
[S]

c)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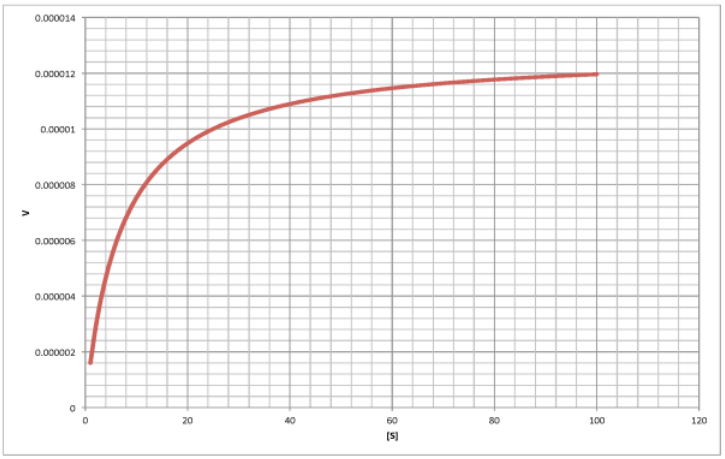
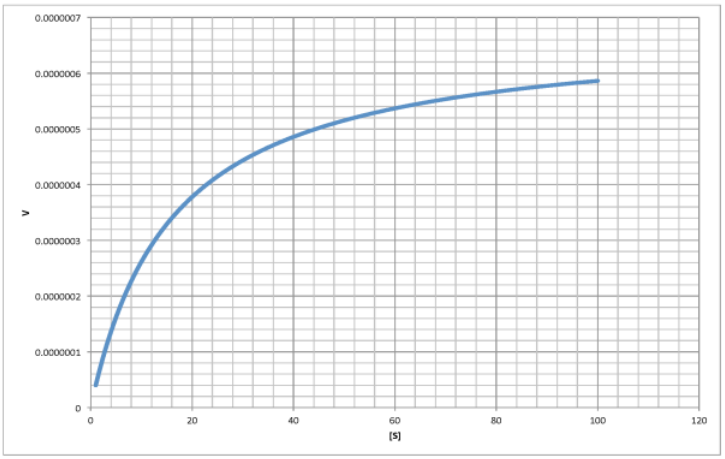
0.000025
0.00002
0.000015
0.00001
0.000005
0
V
0
20
40
60
80
100
120
[S]

d)



e)



Answer a

$$V_{max} = 1.8 \times 10^{-5} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 9 \times 10^{-6} \frac{mol}{Ls} \backslash) so \backslash (K_m = 6 \frac{mol}{L}$$

Answer b

$$V_{max} = 6.5 \times 10^{-7} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 3.25 \times 10^{-7} \frac{mol}{Ls} \backslash) so \backslash (K_m = 7 \frac{mol}{L}$$

Answer c

$$V_{max} = 2.6 \times 10^{-5} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 1.3 \times 10^{-5} \frac{mol}{Ls} \backslash) so \backslash (K_m = 6 \frac{mol}{L}$$

Answer d

$$V_{max} = 1.2 \times 10^{-5} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 6 \times 10^{-6} \frac{mol}{Ls} \backslash) so \backslash (K_m = 6 \frac{mol}{L}$$

Answer e

$$V_{max} = 6.0 \times 10^{-7} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 3 \times 10^{-7} \frac{mol}{Ls} \backslash) so \backslash (K_m = 13 \frac{mol}{L}$$

Turnover Frequency and Efficiency

If we're running an experiment, we know what the total concentration of enzyme is, because we're the ones who put it in there. That means that we can also figure out exactly what that rate constant is for catalysis.

$$k_{cat} = k_2 = \frac{V_{max}}{[\mathbf{E_{tot}}]}$$

That quantity, k_{cat}, is sometimes referred to by biochemists as the "turnover number". The turnover number essentially means the number of molecules of product made by an enzyme in the specified period of time (usually the units of k_{cat} are expressed as s^{-1}, but they could also be written in min^{-1}, etc).

In industrial catalysis, k_{cat} is instead referred to as the "turnover frequency", but of course it still means the same thing. There is an important reason for this difference in terms. The "turnover number" in industry refers to the number of molecules of product made before the catalyst stops working. Catalyst death can occur for any number of reasons, but you might imagine something going wrong via a side reaction that renders the catalyst unreactive toward the substrate. This is a very important consideration in industry. The engineer in charge of the production plant would like to replace the catalyst with a new batch *before* it stops working, to avoid an unscheduled halt in the process that could prove very costly. They need to have an idea about when that is likely to happen, so they need to be aware of the turnover number in this sense.

Another consideration that is sometimes useful is enzymatic efficiency. Remember, the reaction does not depend only on the catalysis step. The binding step also matters. The faster the catalysis step, the faster the production of product. In addition, the greater the proportion of substrate bound, the faster the production of product.

Combining those two ideas:

$$Efficiency = \frac{k_{cat}}{K_m}$$

In this relationship, K_m is a stand-in for the equilibrium constant for enzyme-substrate dissociation. It's not quite the same thing, but it's the closest we've got. By extension, $1/K_m$ stands for the enzyme-substrate binding constant. The greater the binding constant and the faster the catalysis, the more efficient the enzyme.

Note that the units of K_m are concentration units (mol L^{-1}, for instance). The units of efficiency will therefore be something like L mol^{-1} s^{-1}.

Lineweaver-Burk Plots

The Michaelis-Menten equation is useful in other ways, too. If we take its inverse, we get a new relationship.

$$v = \frac{k_2[\mathbf{S}][\mathbf{E}_{tot}]}{[\mathbf{S}] + K_m}$$

If we take the reciprocal of v, we'll have to do the same thing to the other side.

$$\frac{1}{v} = \frac{[\mathbf{S}] + K_m}{k_2[\mathbf{S}][\mathbf{E}_{tot}]}$$

Now it looks like we're just adding two fractions together, so let's show it that way

$$\frac{1}{v} = \frac{[\mathbf{S}]}{k_2[\mathbf{S}][\mathbf{E}_{tot}]} + \frac{K_m}{k_2[\mathbf{S}][\mathbf{E}_{tot}]}$$

Now the [S] cancels in that left term.

$$\frac{1}{v} = \frac{1}{k_2[\mathbf{E}_{tot}]} + \frac{K_m}{k_2[\mathbf{S}][\mathbf{E}_{tot}]}$$

It's still a little complicated, but we already know that $V_{max} = k_2[\mathbf{E}_{tot}]$.

$$\frac{1}{v} = \frac{1}{V_{max}} + \frac{K_m}{V_{max}[\mathbf{S}]}$$

Which is really the same thing as:

$$\frac{1}{v} = \frac{1}{V_{max}} + \left(\frac{K_m}{V_{max}}\right)\frac{1}{[\mathbf{S}]}$$

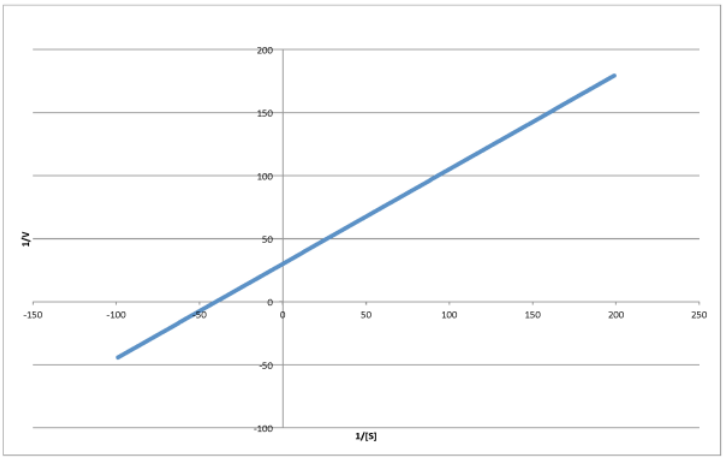
That's useful because it's really an expression for a straight line. If we plot 1/v against 1/[S], we get a straight line. The slope is K_m/V_{max} and the y intercept is $1/V_{max}$.

- Lineweaver-Burk plot gives a straight line for the rate data.
- y intercept = $1/V_{max}$
- slope = K_m/V_{max}
- the x intercept = $-1/K_m$, too

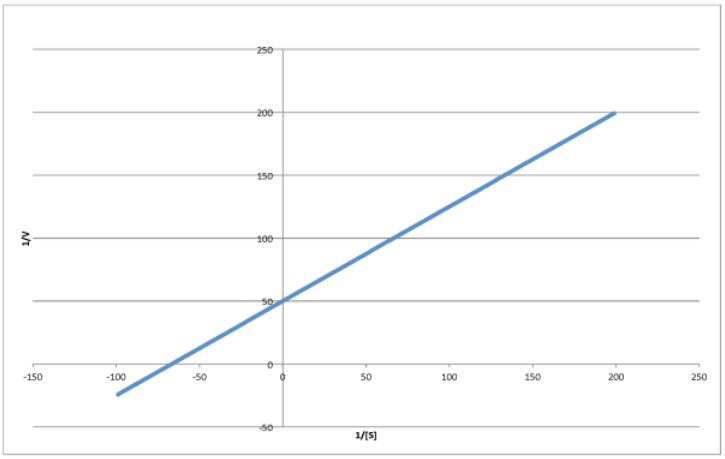
Exercise 2.6.2

Determine the values of Vmax and Km in each of the following cases. Assume the units of [S] are millimoles per liter and the units of V are moles per liter per second.

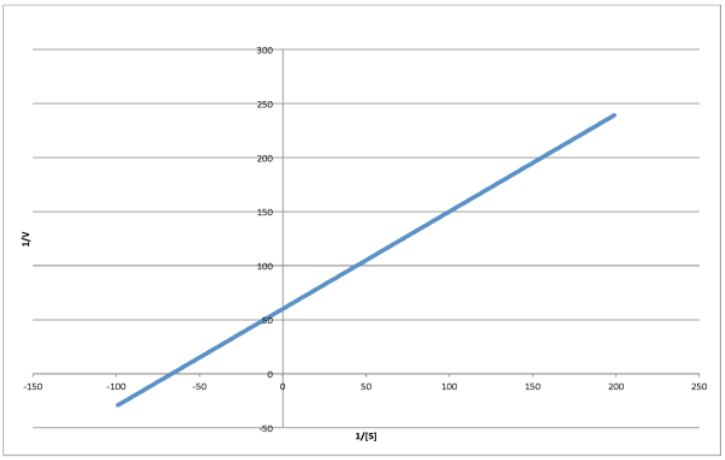
a)



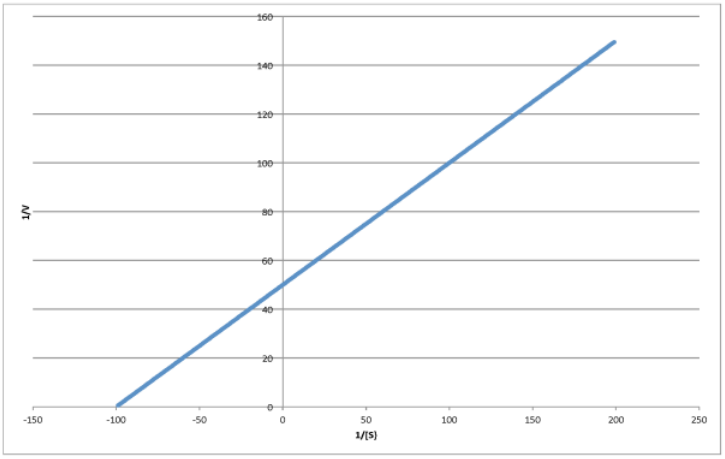
b)



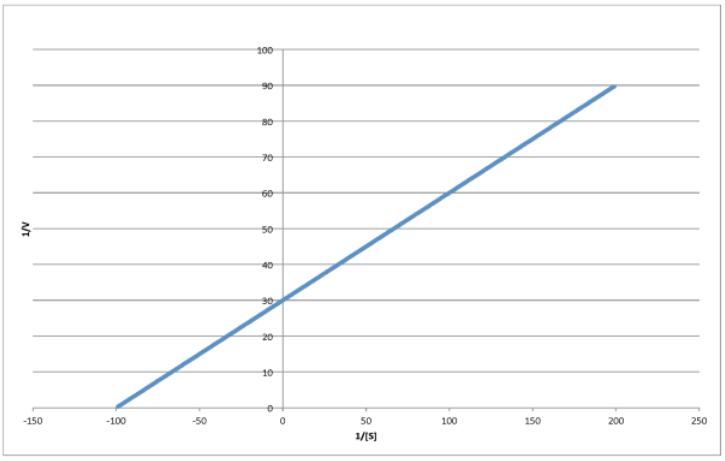
c)



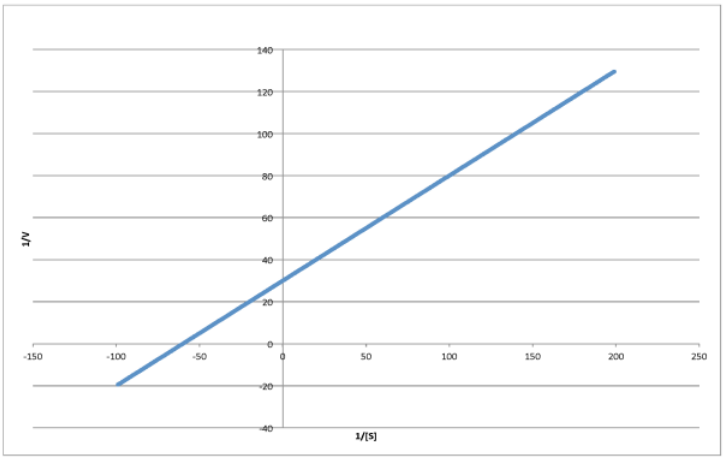
d)



e)



f)



Answer a

$$\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \backslash) so \backslash (V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$$

\frac{-1}{K_{m} = -40 \frac{L}{mmol}\) so \(K_{m} = 2.5 \times 10^{-2} \frac{M}{L} \nonumber

Answer b

$$\frac{1}{V_{max}} = 50 \frac{Ls}{mol} \backslash) so \backslash (V_{max} = 2. - \times 10^{-2} \frac{mol}{Ls}$$

\frac{-1}{K_{m} = -70 \frac{L}{mmol}} so $K_m = 1.4 \times 10^{-2} \frac{M}{L}$

Answer c

\frac{1}{V_{max} = 60 \frac{L s}{mol}\) so \(V_{max} = 1.7 \times 10^{-2} \frac{mol}{L s} \nonumber

$$\frac{-1}{K_m} = -70 \frac{L}{mmol} \text{ so } K_m = 1.4 \times 10^{-2} \frac{M}{L}$$

Answer d

$$\frac{1}{V_{max}} = 50 \frac{Ls}{mol} \backslash) so \backslash (V_{max} = 2.0 \times 10^{-2} \frac{mol}{Ls}$$

$$\frac{-1}{K_m} = -100 \frac{L}{mmol} \text{ so } K_m = 1.0 \times 10^{-2} \frac{M}{L}$$

Answer e

$$\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \backslash) so \backslash (V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$$

$$\frac{-1}{K_m} = -100 \frac{L}{mmol} \text{ so } K_m = 1.0 \times 10^{-2} \frac{M}{L}$$

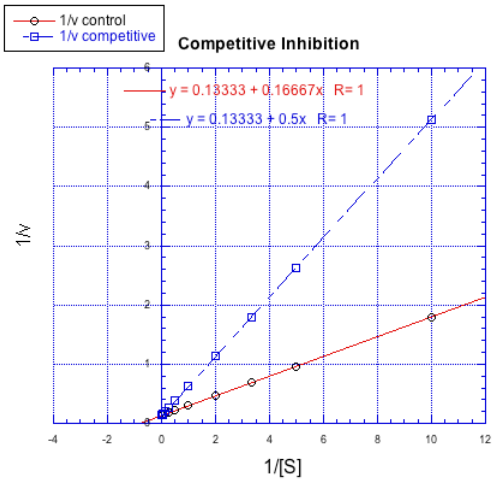
Answer f

$$\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \backslash) so \backslash (V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$$

$$\frac{-1}{K_m} = -60 \frac{L}{mmol} \text{ so } K_m = 1.7 \times 10^{-2} \frac{M}{L}$$

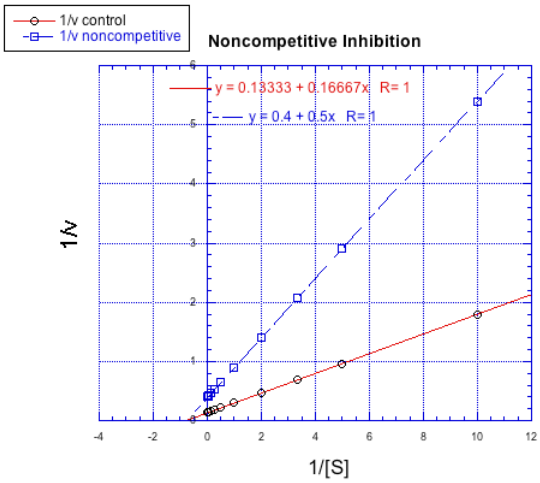
Inhibition and Lineweaver-Burk Plots

Lineweaver-Burk plots allow additional insight into the mechanism of inhibition. The following plot, for example, shows competitive inhibition.

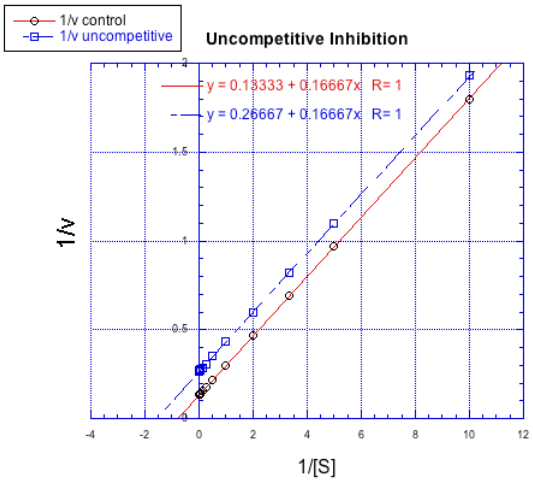


Because the plot uses 1/v on the y axis, the slower reaction is actually the top line. The bottom line is the regular reaction without an inhibitor. Remember, the y intercept is equal to $1/V_{max.}$ In competitive inhibition, the inhibited reaction eventually reaches (or at least approaches) the same V_{max} as the uninhibited reaction. The Lineweaver-Burk plot shows both lines meet the y axis at the same place.

In contrast, the following plot shows noncompetitive inhibition. Once again, the regular line is the lower one, whereas the upper line is the inhibited one. The two lines do not share the same y intercept, however. However, they do share the same x intercept. That's because noncompetitive inhibition does not directly affect binding of substrate (which is reflected in K_m), but interferes with the catalysis step (linked to V_{max}).

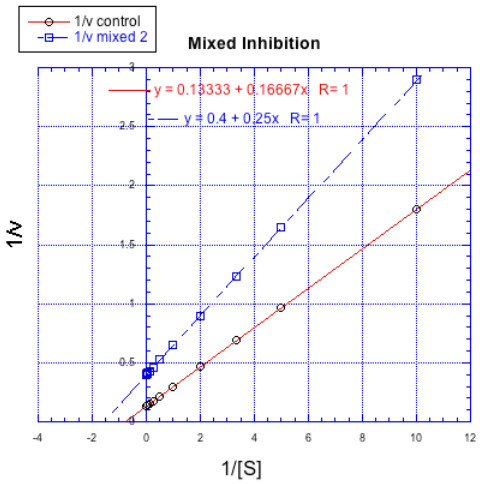


The difference between noncompetitive and uncompetitive inhibition, very subtle in a Michaelis-Menten plot, is quite clear in Lineweaver-Burk. The case illustrated below is thought of as "pure" uncompetitive inhibition. Once again, the inhibited reaction is shown by the upper line. In this case, the inhibited and uninhibited reactions produce parallel lines in the Lineweaver-Burk plot; that feature is actually the definition of uncompetitive inhibition.



If you think about it, pure uncompetitive inhibition only happens under very specific circumstances. The K_m clearly differs when an inhibitor is added; we can see that in the different x intercept. However, the slope is the same. The slope is K_m/V_{max}. That means that, because K_m is different, V_{max} must differ in exactly the same way, keeping the slope the same. For example, if K_m is cut in half in the inhibited reaction, then V_{max} must also be cut in half. That would keep the slope the same.

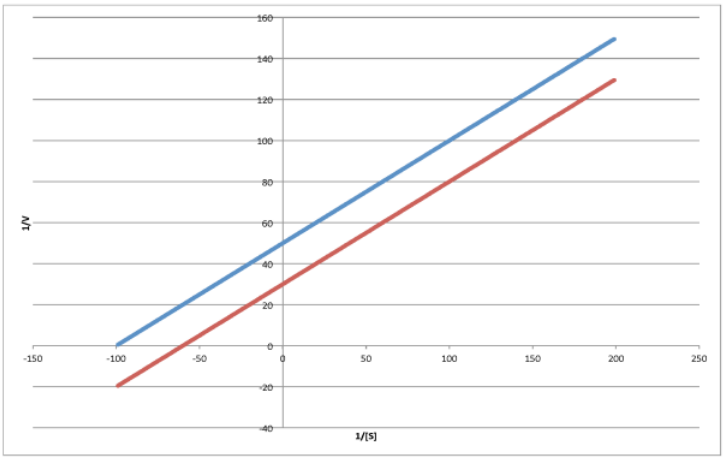
On the other hand, a situation in which the inhibited reaction does not give a line parallel to the regular reaction is called "mixed inhibition". Like uncompetitive inhibition, mixed inhibition results in changes in both K_m and V_{max}. However, the changes in this case do not scale exactly the same way as in uncompetitive inhibition.



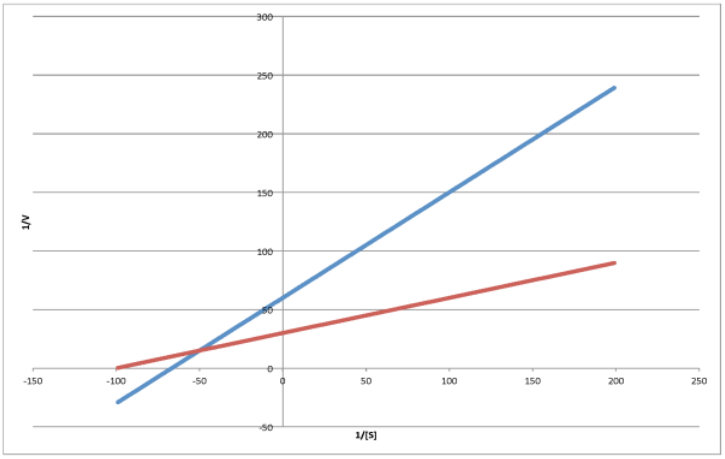
Exercise 2.6.3

Characterise each of the following graphs as representing competitive, noncompetitive, uncompetitive, or mixed inhibition.

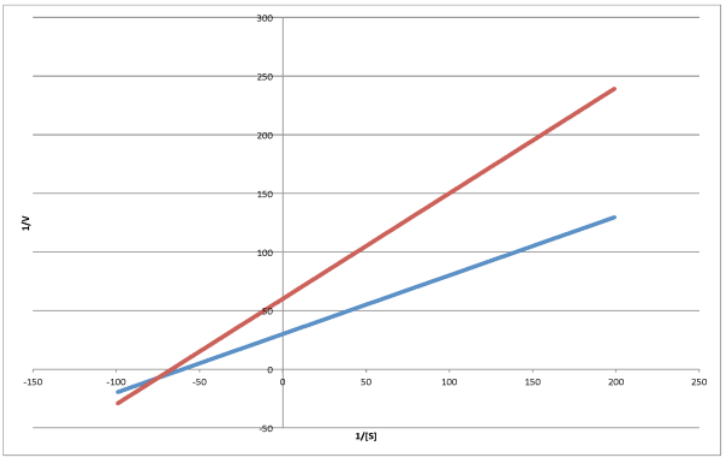
a)


160
140
120
100
80
60
40
20
0
-20
-40
1/V
-150
-100
-50
0
50
100
150
200
250
1/[S]

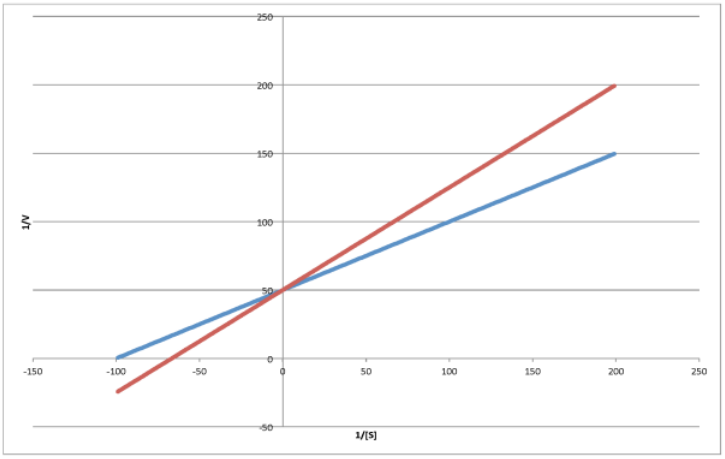
b)


300
250
200
150
100
50
0
-50
1/V
-150
-100
-50
0
50
100
150
200
250
1/[S]

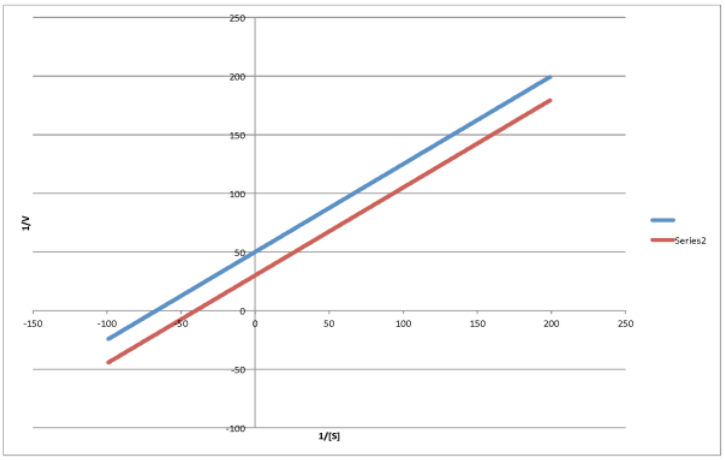
c)



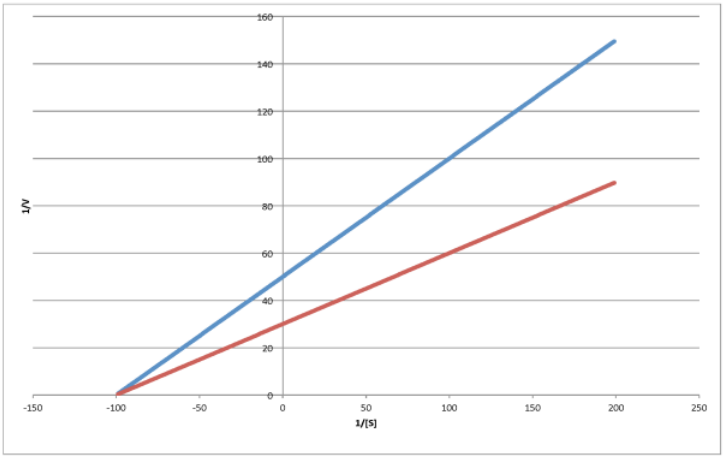
d)



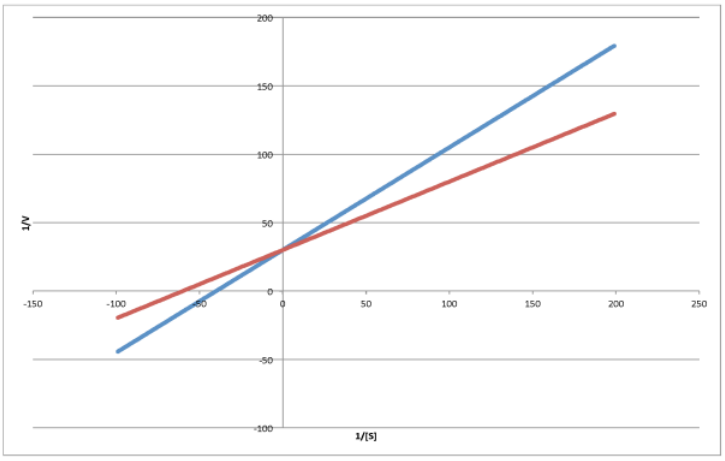
e)



f)



g)



Answer a

uncompetitive

Answer b

mixed

Answer c

noncompetitive

Answer d

competitive

Answer e

uncompetitive

Answer f

noncompetitive

Answer g

competitive

The Origin of the Michaelis-Menten Equation

But where does the Michaelis-Menten relationship come from? That takes a little bit of heavy lifting with kinetics. If you feel the need to know, then we'll start with the approximation that the reaction essentially boils down to two steps: substrate binding and the stuff after that. The binding step is described as k_1/k_{-1}. The stuff after that is summed up in k_2.

The rate of product formation really depends on the rate of the elementary step k_2. That rate depends upon the amount of enzyme substrate complex and its rate of passage through the subsequent step.

$$\mathbf{E} + \mathbf{S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{ES} \xrightarrow{k_2} \mathbf{E} + \mathbf{P}$$

$$v = \text{rate} = \frac{d[\mathbf{P}]}{dt} = k_2 [\mathbf{ES}]$$

The trouble is, the enzyme substrate complex is an intermediate. We don't know exactly how much of it we have. We might assume that, as a reactive intermediate, the complex doesn't have much of a lifetime. It gets used up pretty much as soon as it forms.

That assumption helps us to express the concentration of enzyme substrate complex in terms of other things we might know more about: the enzyme and the substrate. Of course, the enzyme and the substrate react together to make the enzyme substrate complex. They react together with rate constant k_1.

Two possible fates await the enzyme substrate complex. Either it is released back to enzyme and free substrate, with rate constant k_{-1}, or else it goes on to make product, with rate constant k_2. In a steady state approximation, the enzyme substrate complex is consumed as soon as it is formed.

$$\text{rate of formation of } \mathbf{ES} = \text{rate of consumption of } \mathbf{ES}$$

$$k_1\,[\mathbf{E}]\,[\mathbf{S}] = k_2\,[\mathbf{ES}] + k_{-1}\,[\mathbf{ES}]$$

Again, we don't know how much free enzyme there is. We don't know how much enzyme-substrate complex we have. We do know how much enzyme is added at the beginning of the kinetics experiment. We'll call that concentration $[\mathbf{E_{tot}}]$, meaning the total amount of enzyme. Some of that enzyme remains free, and some of it is bound as enzyme-substrate complex.

$$[\mathbf{E_{tot}}] = [\mathbf{E}] + [\mathbf{ES}]$$

$$[\mathbf{E_{tot}}] - [\mathbf{ES}] = [\mathbf{E}]$$

It's useful to express the concentration of free enzyme as the total enzyme minus that portion bound with substrate. That way, we'll be able to eliminate the term for free enzyme from the rate equation. A few steps of algebra let us express the concentration of the enzyme-substrate complex solely in terms of the total enzyme concentration, the substrate concentration and some rate constants.

$$k_1\,[\mathbf{S}](\,[\mathbf{E_{tot}}] - [\mathbf{ES}]) = [\mathbf{ES}](\,k_2 + k_{-1}\,)$$

Let's put all the parts that contain $[\mathbf{ES}]$ together on one side.

$$k_1\,[\mathbf{S}][\mathbf{E_{tot}}] = k_1[\mathbf{S}][\mathbf{ES}] + (k_2 + k_{-1})[\mathbf{ES}]$$

$[\mathbf{ES}]$ is a common factor on the right hand side. We'll factor it out.

$$k_1\,[\mathbf{S}][\mathbf{E_{tot}}] = [\mathbf{ES}](\,k_1[\mathbf{S}] + k_2 + k_{-1})$$

We're interested in an expression for $[\mathbf{ES}]$ so that we can use it in the rate law. If we divide both sides by the stuff in the parentheses, we'll get $[\mathbf{ES}]$ by itself.

$$\frac{k_1\,[\mathbf{S}][\mathbf{E_{tot}}]}{(\,k_1[\mathbf{S}] + k_2 + k_{-1}\,)} = [\mathbf{ES}]$$

If we multiply *both* the top and the bottom by $1/k_1$, it won't change the value of anything; $(1/k_1)/(1/k_1)$ i still 1. However, it will simplify the expression just a little bit.

$$\frac{[\mathbf{S}][\mathbf{E_{tot}}]}{\left([\mathbf{S}] + \dfrac{k_2 + k_{-1}}{k_1}\right)} = [\mathbf{ES}]$$

Remember, the rate of product formation just depends on the amount of enzyme-substrate complex and the rate constant for the catalysis step.

$$\text{rate} = k_2\,[\mathbf{ES}] = \frac{k_2\,[\mathbf{S}][\mathbf{E_{tot}}]}{\left([\mathbf{S}] + \dfrac{k_2 + k_{-1}}{k_1}\right)}$$

That collection of constants in the denominator is just a group of numbers. It's a constant. We'll call it the Michaelis-Menten constant.

$$K_m = \frac{k_2 + k_{-1}}{k_1}$$

That brings us back to the Michaelis-Menten equation.

$$\text{rate} = v = \frac{k_2\,[\mathbf{S}][\mathbf{E_{tot}}]}{[\mathbf{S}] + K_m}$$

2.7: Potential Energy Surfaces

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Click the Edit page button in your user bar. You will see a suggested structure for your content. Add your content and hit Save.

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2.8: Kinetic Isotope Effects

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2.9: Linear Free Energy Relationships

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2.10: Solutions to Selected Problems

Exercise 2.4.1:

a) non-competitive

b) competitive

c) competitive

d) non-competitive

Exercise 2.5.1:

a) $V_{max} = 1.8 \times 10^{-5} \frac{mol}{Ls}$

$$\frac{V_{max}}{2} = 9 \times 10^{-6} \frac{mol}{Ls} \; so \; K_m = 6 \frac{mol}{L}$$

b) $V_{max} = 6.5 \times 10^{-7} \frac{mol}{Ls}$

$$\frac{V_{max}}{2} = 3.25 \times 10^{-7} \frac{mol}{Ls} \; so \; K_m = 7 \frac{mol}{L}$$

c) $V_{max} = 2.6 \times 10^{-5} \frac{mol}{Ls}$

$$\frac{V_{max}}{2} = 1.3 \times 10^{-5} \frac{mol}{Ls} \; so \; K_m = 6 \frac{mol}{L}$$

d) $V_{max} = 1.2 \times 10^{-5} \frac{mol}{Ls}$

$$\frac{V_{max}}{2} = 6 \times 10^{-6} \frac{mol}{Ls} \; so \; K_m = 6 \frac{mol}{L}$$

e)

$$V_{max} = 6.0 \times 10^{-7} \frac{mol}{Ls}$$

$$\frac{V_{max}}{2} = 3 \times 10^{-7} \frac{mol}{Ls} \; so \; K_m = 13 \frac{mol}{L}$$

Exercise 2.5.2:

a) $\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \; so \; V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -40 \frac{L}{mmol} \; so \; K_m = 2.5 \times 10^{-2} \frac{M}{L}$

b) $\frac{1}{V_{max}} = 50 \frac{Ls}{mol} \; so \; V_{max} = 2.0 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -70 \frac{L}{mmol} \; so \; K_m = 1.4 \times 10^{-2} \frac{M}{L}$

c) $\frac{1}{V_{max}} = 60 \frac{Ls}{mol} \; so \; V_{max} = 1.7 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -70 \frac{L}{mmol} \; so \; K_m = 1.4 \times 10^{-2} \frac{M}{L}$

d) $\frac{1}{V_{max}} = 50 \frac{Ls}{mol} \; so \; V_{max} = 2.0 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -100 \frac{L}{mmol} \; so \; K_m = 1.0 \times 10^{-2} \frac{M}{L}$

e) $\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \; so \; V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -100 \frac{L}{mmol} \; so \; K_m = 1.0 \times 10^{-2} \frac{M}{L}$

a) $\frac{1}{V_{max}} = 30 \frac{Ls}{mol} \; so \; V_{max} = 3.3 \times 10^{-2} \frac{mol}{Ls}$

$\frac{-1}{K_m} = -60 \frac{L}{mmol}$ so $K_m = 1.7 \times 10^{-2} \frac{M}{L}$

Exercise 2.5.3:

a. uncompetitive
b. mixed
c. noncompetitive
d. competitive
e. uncompetitive
f. noncompetitive
g. competitive

CHAPTER OVERVIEW

3: Ligand Substitution in Coordination Complexes

3.1: Introduction to Substitution

Ligand substitution refers to the replacement of one ligand in a coordination complex with another ligand.

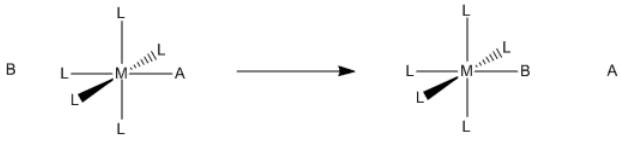


Figure 3.1.1: Substitution of one ligand for another in a coordination complex.

Remember, a ligand in coordination chemistry is just a Lewis base that binds to a metal atom or ion. It does so by donating a lone pair (or other pair of electrons). Generallly, this donation is reversible. The donor can always take its electrons back. Typically, there may be some balance between the metal's need for more electrons and the donor's attraction for its own electrons; donor atoms are frequently more electronegative than the metal.

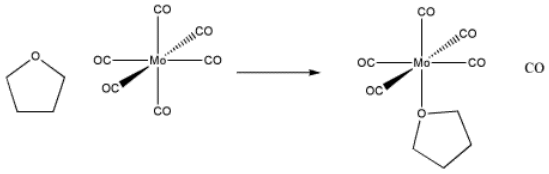


Figure 3.1.2: An example of ligand substitution. THF replaces a carbon monoxide in this molybdenum complex.

Even though the reaction is pretty simple, it can occur in different ways.

That is, the elementary steps involved in the reaction can occur in different orders. The elementary reactions are the individual bond-making or bond-breaking events that lead to an overall change. Sometimes the order of steps is referred to as the mechanism or the mechanistic pathway.

- The mechanism is the order of elementary reaction steps.
- Elementary reaction steps are individual bond-making and breaking steps.

You may have seen reaction mechanisms before. For example, carbonyl addition chemistry can involve lengthy mechanisms, in which a number of proton transfers and other bond-making and bond-breaking steps must occur to get from one state to another. Because ligand substitution is simpler than that, it is a good place to study mechanism in a little more depth, without getting overwhelmed by the details.

The sequence of steps in the mechanism influences how different factors will impact the reaction. For example, changing concentrations of different components in a reaction mixture can affect the time it takes for a reaction to finish.

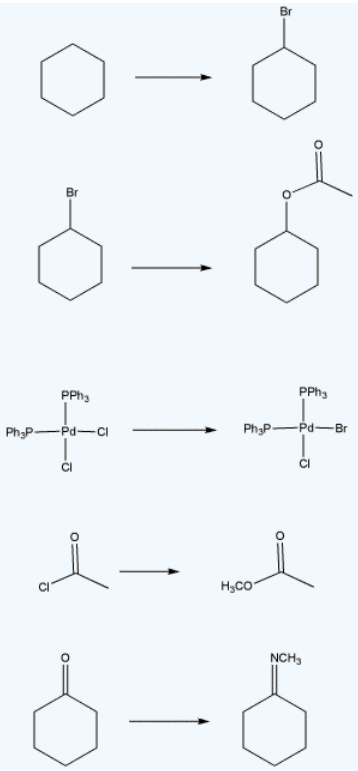
- The mechanism can have a dramatic impact on the outcome of the reaction under different circumstances.

These kinds of considerations have a dramatic impact on industrial processes such as pharmaceutical production. In that setting, chemical engineers need to make decisions about how much of each reactant must be admitted to a reaction mixture and how long they should be allowed to react together. If they allow the reaction to proceed for too, long, there may be “side-reactions” that start to occur, interfering with the quality of the product, and they will waste valuable time in the production pipeline. If they don’t allow it to react long enough, the reaction may not finish, and the product will be contaminated with leftover starting materials.

In this chapter, we will look at how this simple reaction can occur in different ways. We will see some different methods that are used to tell which way the reaction occurs (i.e. evidence of what is really happening). We will also look at some different factors that may influence whether the reaction is likely to occur one way or the other (i.e. reasons it is happening that way, or reasons we expect it will happen that way).

? Exercise 3.1.1

Some kind of substitution occurs in each of the following reactions: an atom or group replaces another. In each case, identify what is being replaced, and what replaces it.



Answer a

a bromine atom replaces a hydrogen atom

Answer b

an acetate group (ethanoyl ester) replaces a bromine atom

Answer c

a bromine atom replaces a chlorine atom (or ions)

Answer d

a methoxy group replaces a chlorine atom

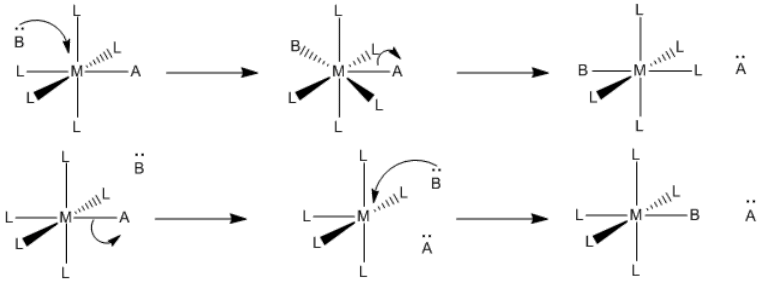
Answer e

a methylamino group replaces an oxygen atom

3.2: Mechanistic Possibilities

There are two basic steps in ligand substitution: association and dissociation. Association, in this case, refers to the binding of a ligand to the metal. The ligand donates an electron pair to the metal and the two molecules come together to form a new bond. Dissociation, in this case, refers to the release of a ligand from a metal. The metal-ligand bond breaks and the ligand leaves with its electron pair.

Two mechanistic possibilities seem pretty obvious. Either the new ligand binds first and then the old one leaves, or the old ligand leaves first and then the new one binds.



- Associative mechanism is association first. The new ligand binds and then the old one leaves.
- Dissociative mechanism is dissociation first. The old ligand leaves and then the new one binds.

Knowing the mechanism is important because the mechanism has an impact on what factors affect the reaction. For example, if the reaction is associative, adding lots more new ligand may speed up the reaction, because then it becomes more likely that the new ligand will find the metal complex and bind with it. However, if the old ligand is supposed to leave before the new ligand arrives, then it doesn't matter how much new ligand is around. It has to wait for the old ligand to leave before it can bind, anyway, so adding a lot more new ligand won't speed things up.

? Exercise 3.2.1

a) Which kind of step costs more energy: bond-making or bond-breaking?

b) What would be the rate-determining step in the associative mechanism?

c) What would be the rate-determining step in the dissociative mechanism?

d) What would be the rate law for the associative mechanism?

e) What would be the rate law for the dissociative mechanism?

Answer a

Energy is released when bonds are formed. Energy must be added to break bonds. In general, bond-breaking costs more energy than bond-making.

Answer b

On the basis of question (a), we would assume that the second, bond-breaking step is the rate determining step in association mechanisms.

Answer c

The first, dissociative step would be the rate-determining step, on the basis of question (a).

Answer d

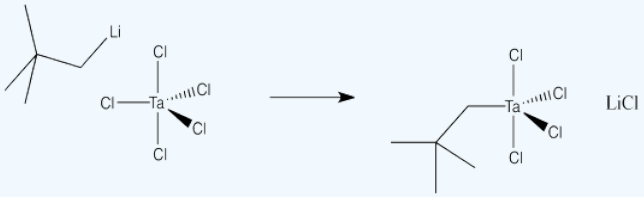
The rate law would include steps prior t the rate determining step. $Rate = k[MLn][X]$ if MLn is the complex and X is the new ligand.

Answer e

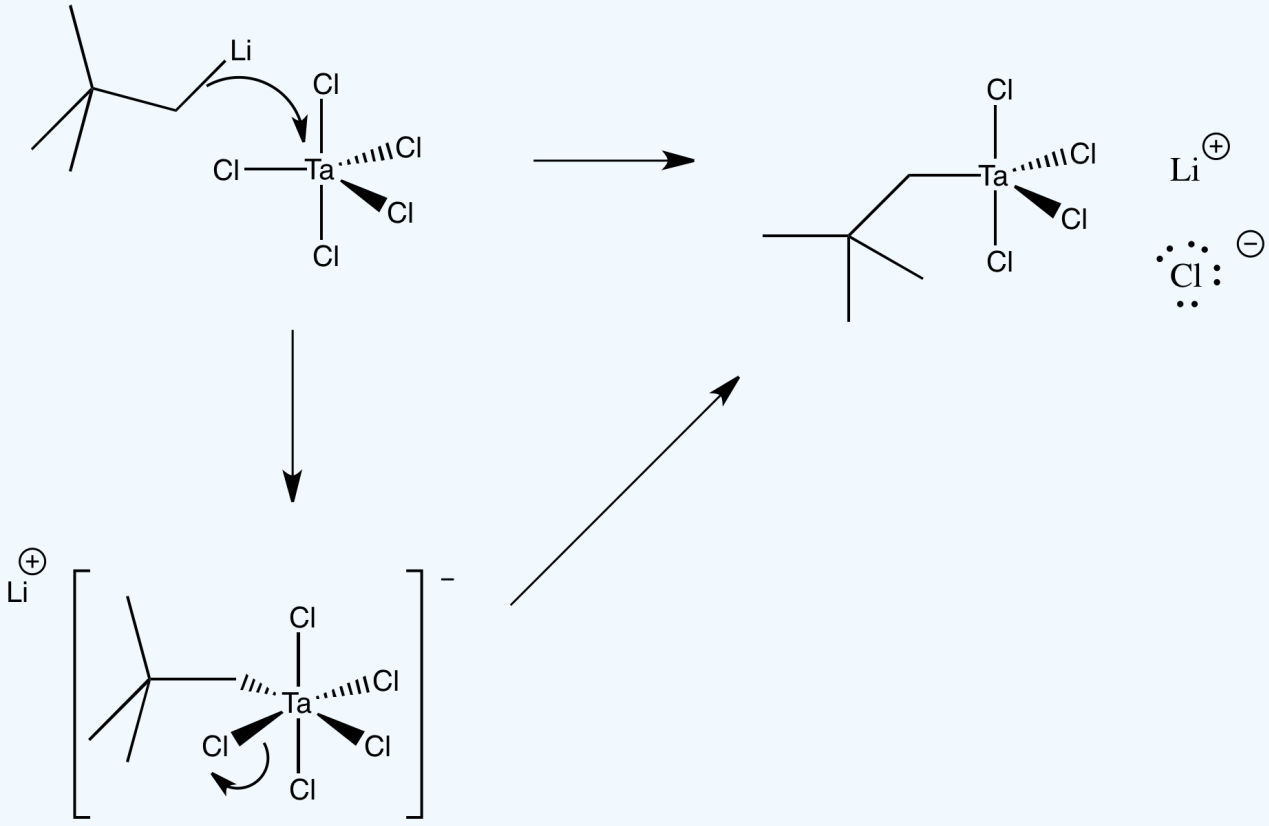
$$Rate = k[MLn]$$

Exercise 3.2.2

Draw a mechanism, with arrows, for the following substitution. Assume an associative mechanism.

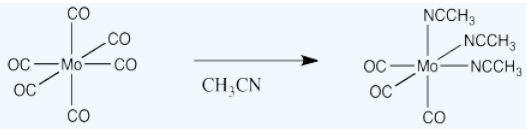


Answer

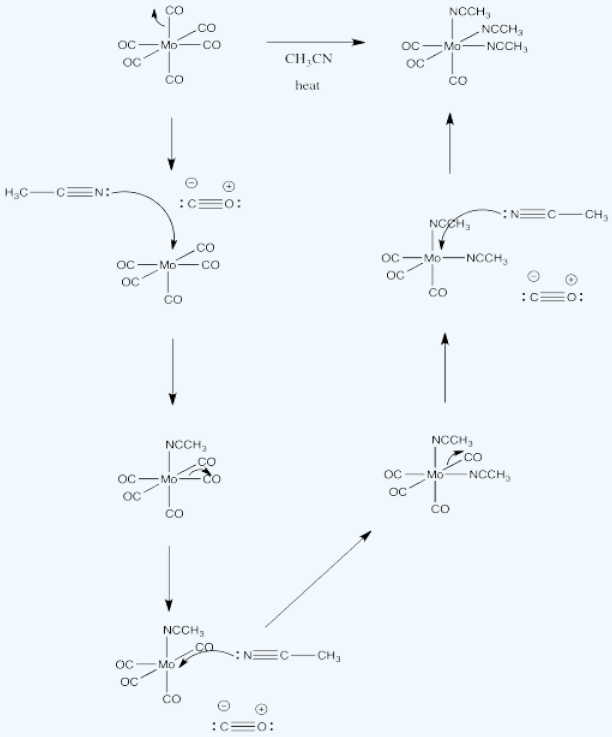


Exercise 3.2.3

Draw a mechanism, with arrows, for the following substitution. Assume a dissociative mechanism.

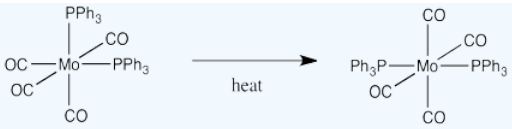


Answer

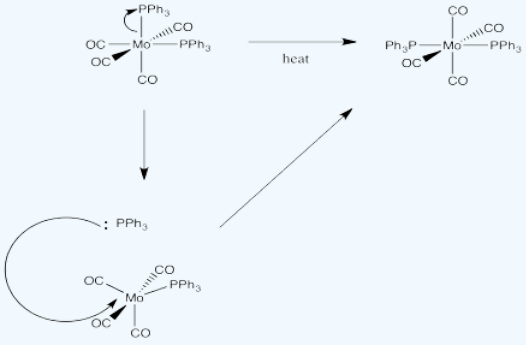


? Exercise 3.2.4

Draw a mechanism, with arrows, for the following isomerization.



Answer



Exercise 3.2.5

The ability to substitute for a ligand depends partly on its ability to leave. Rank the following ligands, from the easiest to replace to the hardest to replace:

CO Cl^- PPh NH_3 NO_3^- H_2O

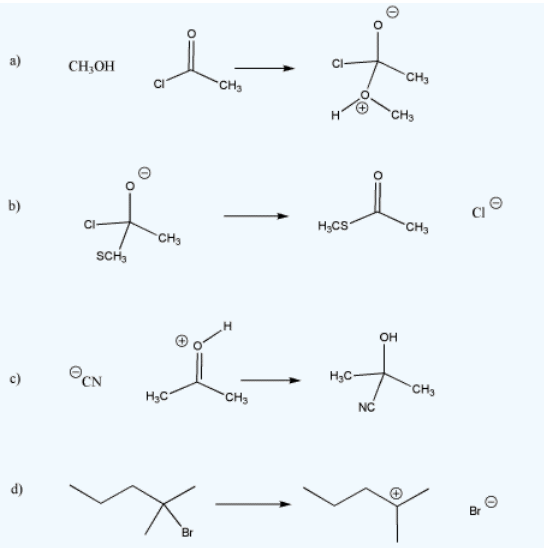
Answer

This problem is answered through consideration of the spectrochemical series.

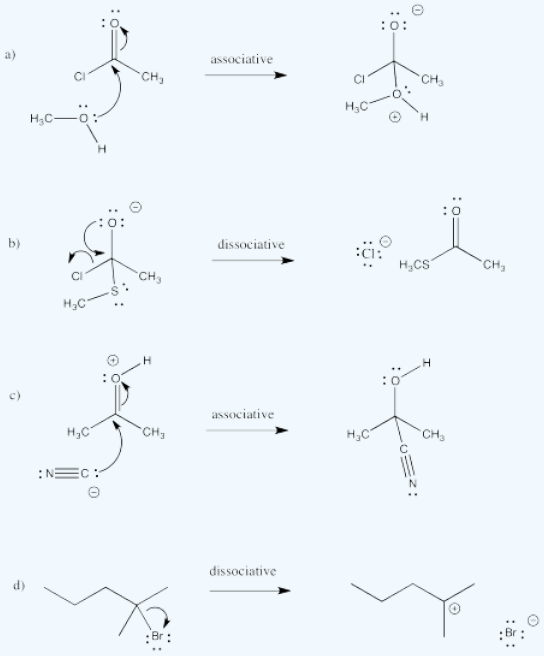
from easiest to hardest to replace: NO_3^- Cl^- H_2O NH_3 PPh_3 CO

Exercise 3.2.6

Draw curved arrows for the following steps. Classify each step as associative or dissociative.



Answer



3.3: Associative Mechanism and Kinetics

We can measure the rate of an associative reaction and make changes in the reaction conditions to see how the rate is affected. For example, we could easily change the concentrations of the two reactants. All we have to do is change the amount of reactant we dissolve in the solution.

If we did that, we would find a linear relationship between each concentration and rate. If we double the concentration of new ligand, the rate of reaction doubles. If we triple it, the rate triples.

Also, if we double the amount of metal complex, the rate doubles and so on.

We can write the following expression, called the rate law, to describe this relationship:

Rate Law: $Rate = \frac{-d[ML_n]}{dt} = k[ML_n][L']$

This type of reaction is sometimes called a second order reaction. That term just refers to the mathematical form of the rate law, which depends on concentration times concentration, or concentration squared. The "order" of the reaction is the number of concentrations multiplied together in the rate law.

Why does the associative mechanism depend on concentrations in this specific way?

This is a case of two molecules coming together. If both compounds are dissolved in solution, they must “swim around” or travel through the solution until they bump into each other and react. The more concentrated the solution is, or the more crowded it is with molecules, the more likely are the reactants to bump into each other. If we double the amount of new ligand in solution, an encounter between ligand and complex becomes twice as likely. If we double the amount of metal complex in solution, an encounter also becomes twice as likely.

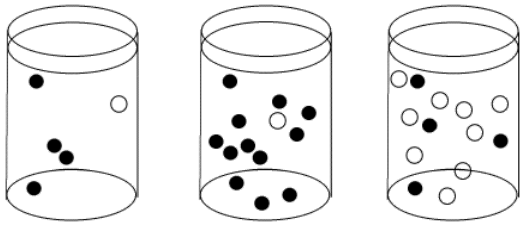


Figure 3.3.1: The effect of concentration on collision probability. In the first beaker, there is a chance that a black molecule and white molecule will meet and react together. The chance of a meeting is much higher in both the second beaker, where there are lots more black molecules, and in the third beaker, where there are many more white molecules.

? Exercise 3.3.1

Given the associative rate law above, what would happen to the reaction rate for an associative substitution in the following cases?

a. the concentration of ligand is doubled, and the concentration of metal complex is doubled
b. the concentration of ligand is tripled, and the concentration of metal complex is doubled
c. the concentration of ligand is tripled, and the concentration of metal complex is tripled
d. the concentration of ligand is halved, and the concentration of metal complex is doubled

Answer a

Associative Rate Law: $Rate = [ML_n][X]$, if ML_n is the complex and X is the new ligand.

Rate will quadruple: $Rate = (2 \times [ML_n]_0) \times (2 \times [X]_0) = 4 \times [ML_n]_0[X]_0$, if $[X]_0$ and $[ML_n]_0$ are the original concentrations.

Answer b

Rate will sextuple: $Rate = (3 \times [ML_n]_0) \times (2 \times [X]_0) = 6 \times [ML_n]_0[X]_0$.

Answer c

Rate will nonuple: $Rate = (3 \times [ML_n]_0) \times (3 \times [X]_0) = 9 \times [ML_n]_0[X]_0$.

Answer d

Rate will stay the same: $Rate = (0.5 \times [ML_n]_0) \times (2 \times [X]_0) = 1 \times [ML_n]_0[X]_0$.

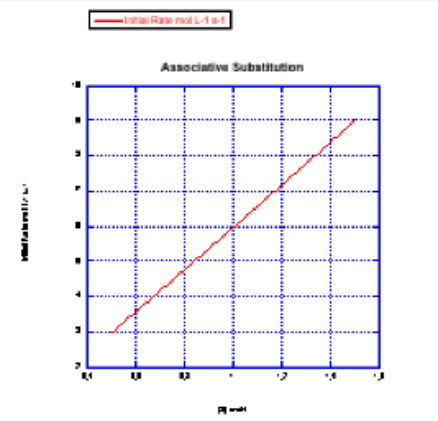
Exercise 3.3.2

Plot graphs of initial rate vs. concentration to show what you would see in associative substitution.

a) The concentration of new ligand, [X], is held constant at 0.1 mol/L and the concentration of metal complex is changed from 0.5 mol/L to 1 mol/L and then to 1.5 mol/L.

b) The concentration of metal complex, [ML_n], is held constant at 0.1 mol/L and the concentration of ligand is changed from 0.5 mol/L to 1 mol/L and then to 1.5 mol/L.

Answer



Exercise 3.3.3

In the previous problem, the experiment was run in a particular way for particular reasons.

a) Why was one concentration held constant while the other one was changed? Why not change both?

b) Why does the graph report "initial rate" -- just the rate at the very beginning of the reaction?

Answer a

Changing both concentrations at once would leave some doubt about whether one concentration had affected the rate, or the other concentration, or both. In practice, one concentration is usually held constant while the other is kept in excess and varied.

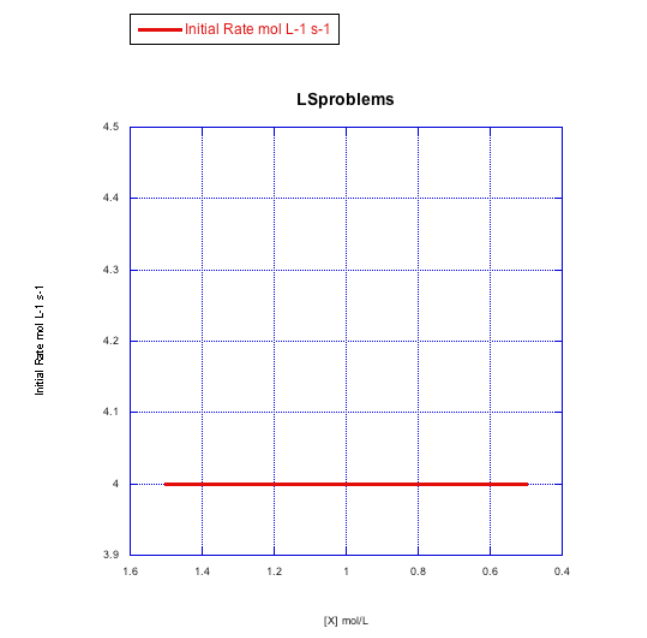
Answer b

Rate changes over time because the concentrations of reactants change as they are consumed. By reporting only the initial rate (usually meaning less than 5% or 10% complete, but possibly even less than that if a lot of data can be gathered very quickly), the concentrations are still about what you started with. That means you can report a rate that corresponds to a given concentration with confidence.

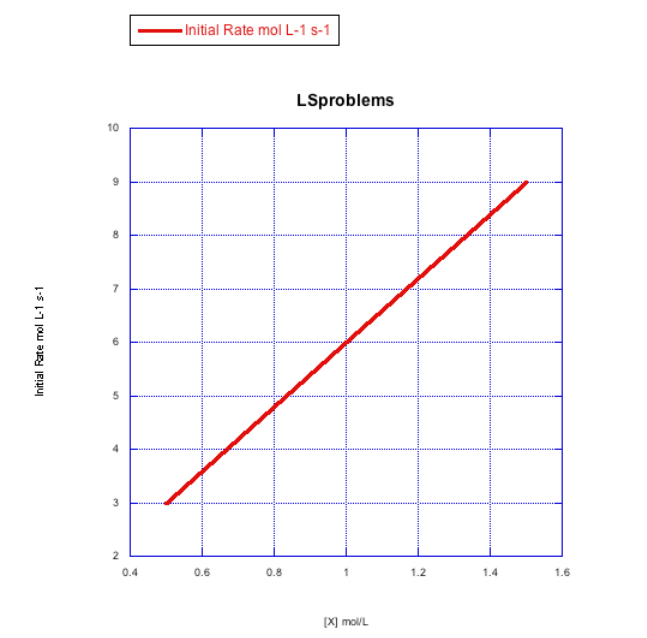
Exercise 3.3.4

Given the following sets of initial rate data (rates measured at the beginning of a reaction), determine whether each case represents an associative substitution.

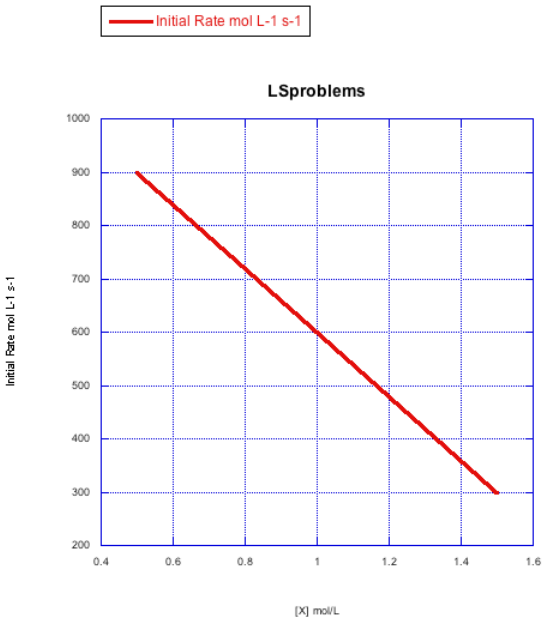
a)



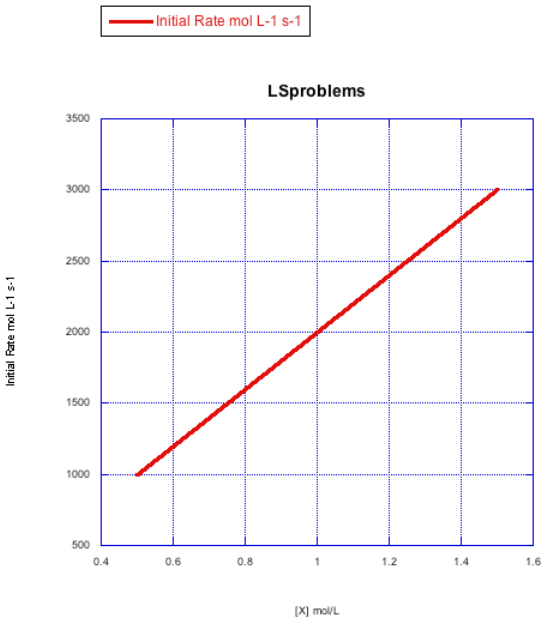
b)



c)



d)



Answer a

The rate would change with the ligand concentration if associative. This rate is constant over a range of ligand concentrations, so the reaction is not associative.

Answer b

The rate increases linearly with ligand concentration. This reaction proceeds via an associative mechanism.

Answer c

The rate changes over the concentration range, but it decreases. This is the opposite of what should happen. This reaction does not follow a simple associative pathway.

Answer d

The rate increases linearly with ligand concentration. This reaction proceeds via an associative mechanism.

? Exercise 3.3.5

What information can be gained from the slopes of lines in Exercise 3.3.4 (Problem LS3.4.)?

Answer

Because $Rate = k[ML_n][L]$ is held constant while [L] is varied, then the slope of the line is k [ML_n]. Since you would know the value of [ML_n], you could obtain the rate constant from the quantity (slope/ [ML_n]).

3.4: Dissociative Mechanism and Kinetics

What about a dissociative reaction? Does it also depend on concentration?

We could also change concentrations of the two reactants, the new ligand and the metal complex, in a dissociative reaction. If we did that, we would find a linear relationship between the concentration of metal complex and rate. If we doubled the amount of metal complex, the rate would double and so on.

However, changes in concentration of the new ligand would have little effect on the rate. If we double the concentration of new ligand, the rate wouldn't change.

We can write the following expression, called the rate law, to describe this relationship:

Rate Law: $Rate = \frac{-d[ML_n]}{dt} = k[ML_n]$

This type of reaction is sometimes called a first order reaction. That means the rate law depends on only one concentration term.

Why does the dissociative mechanism depend on concentrations in this specific way?

This is a case of one molecule losing a ligand. Once it does so, a second ligand can replace the one that left. However, losing a ligand may be harder to do than gaining a new one. To lose a ligand, a bond must be broken, which costs energy. To gain a new ligand, a bond is made, releasing energy. That first step is harder to do, so it takes longer. It is a bottleneck that slows the reaction down. It is called the rate-determining step.

- The rate-determining step is the slow step of the reaction.
- The rate-determining step controls the rate of the overall reaction; everything else has to wait for that step to happen.
- Once the rate-determining step has occurred, everything else follows very quickly.

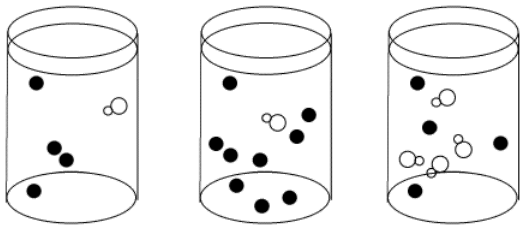


Figure 3.4.1: A bottleneck in a reaction. If the reaction must wait for the white molecule to dissociate, it doesn't matter how many black molecules there are; the reaction still goes just as slow. However, the more white molecules there are, the more frequently they will be able to react with the black molecules as dissociation occurs.

No collision is necessary for the metal complex to lose a ligand. Instead, a bond in the metal complex has to break. That just takes time and energy. As a result, concentrations matter very little.

We should think a little more about energy requirements, available energy and reaction rate. It takes a certain amount of energy to break a bond. Over any given period of time, a specific amount of energy is available in the surroundings to use. That energy is not available uniformly. Some molecules will get more energy from their surroundings and others will get less. There will be a statistical distribution, like a bell curve, of energy available in different molecules. That means bond-breaking events are governed by statistics.

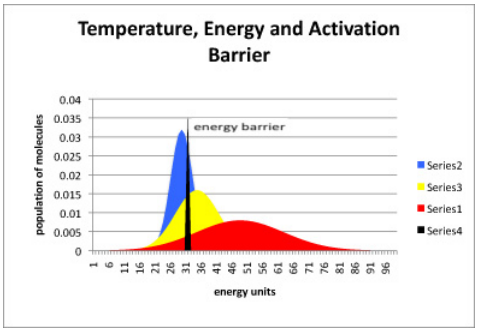


Figure 3.4.2: The relationship between temperature, energy available, and energy barrier. The black line represents energy needed to start the reaction, also called the energy barrier or the activation barrier. The blue curve is the distribution of available energy in a group of molecules at a cooler temperature. The yellow curve is for a group of molecules that is a little warmer, and the red curve even warmer.

In figure 3.4.2, most of the molecules at the low temperature (blue) do not have enough energy to begin the reaction. A small portion do, and so the reaction will proceed, but very slowly. In the yellow curve, there is more energy available, and so a large fraction of molecules have the energy necessary to begin the reaction. In the red curve, the vast majority have sufficient energy to react. Thus, one of the factors governing how quickly a reaction will happen is the energy needed, or activation barrier. A second factor is the energy available, as indicated by the temperature.

Of course, even if there is enough energy for the reaction, the reaction might not occur yet. Energy is necessary but not sufficient to start a reaction. There are also statistical factors in terms of whether a molecule has its energy allotted into the right places, or in some cases, whether two molecules that need to react together are oriented properly.

Suppose at a given temperature it takes a specific amount of time for half the molecules to gain enough energy so that they can undergo the reaction. That amount of time is called the half life of the reaction. After one half life, half the molecules have reacted and half remain. After a second half life, half the remaining molecules (another quarter, for three quarters of the original material in all) have also reacted, and a quarter still remain. After a third half life, half the remaining ones (another eighth, making it seven eighths reacted in total) will have reacted, leaving an eighth of the original material behind.

- Exponential decay is based on a statistical distribution of energy availability.
- The concept of half life is related to exponential decay.
- It takes a fixed period of time for a half of the metal complex obtain enough energy to dissociate.

Thus, the time it takes for the reaction to happen does not really depend on the concentration of anything.

However, the change in *concentration* over time -- the quantity that we can usually measure most easily -- depends on the original concentration, and for that reason the concentration of the metal complex appears in the rate law.

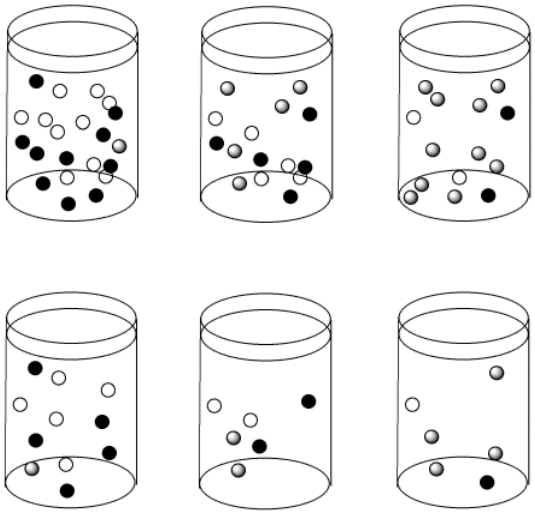


Figure 3.4.3: The reactions in the top row and bottom row are proceeding with the same half-life as we move from left to right. However, the top row starts out more concentrated than the bottom row. As a result, the *concentrations* in the top row are changing more quickly than in the bottom row.

Suppose the half life for a particular case of ligand substitution is one second. After a half life, a 1 M solution becomes 0.5 M, so the rate of change in concentration per time is 0.5M/s. But after the same half life, a 0.5 M solution becomes 0.25 M, so the change in concentration is 0.25 M/s.

? Exercise 3.4.1

If a first order reaction has a half-life of 120 seconds, how much of the original material is left after

a) four minutes? b) six minutes? c) eight minutes? d) ten minutes?

Answer a

4 minutes = 240 seconds = 2 x 120 second = 2 half lives.

Material left = 50% x 50% = 0.5 x 0.5 = 0.25 = 25% left

Answer b

6 minutes = 360 seconds = 3 x 120 second = 3 half lives.

Material left = 0.5 x 0.5 x 0.5 = 0.125 = 12.5% left

Answer c

8 minutes = 480 seconds = 4 x 120 second = 4 half lives.

Material left = 0.5 x 0.5 x 0.5 x 0.5 = 0.0625 = 6.25% left

Answer d

10 minutes = 600 seconds = 5 x 120 second = 5 half lives.

Material left = 0.5 x 0.5 x 0.5 x 0.5 x 0.5 = 0.03125 = 3.125% left

Exercise 3.4.2

Given the dissociative rate law above, what would happen to the reaction rate for substitution in each of the following cases?

a. the concentration of ligand is doubled, and the concentration of metal complex is doubled
b. the concentration of ligand is tripled, and the concentration of metal complex is halved
c. the concentration of ligand is doubled, and the concentration of metal complex is tripled
d. the concentration of ligand is halved, and the concentration of metal complex is halved

Answer a

Dissociative Rate Law: Rate = $[ML_n]$, if ML_n is the complex. There is no dependence on [X], if X is the new ligand.

Rate will double: Rate = 2 x $[ML_n]_0$, if $[ML_n]_0$ is the original concentration.

Answer b

Rate will be halved: Rate = 0.5 x $[ML_n]_0$.

Answer c

Rate will triple: Rate = 3 x $[ML_n]_0$.

Answer d

Rate will be halved: Rate = 0.5 x $[ML_n]_0$.

Exercise 3.4.3

Plot graphs of initial rate vs concentration to show what you would see in dissociative substitution.

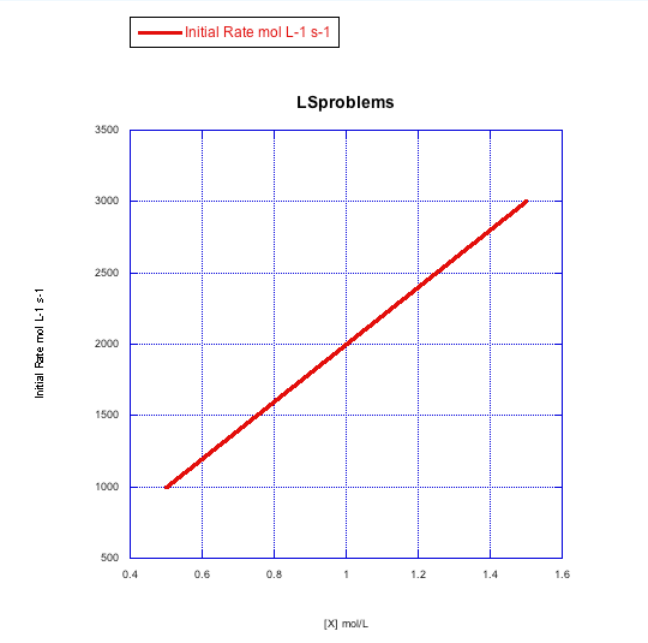
a) The concentration of metal complex, $[ML_n]$, is held constant at 0.1 mol/L and the concentration of ligand is changed from 0.5 mol/L to 1 mol/L and then to 1.5 mol/L.

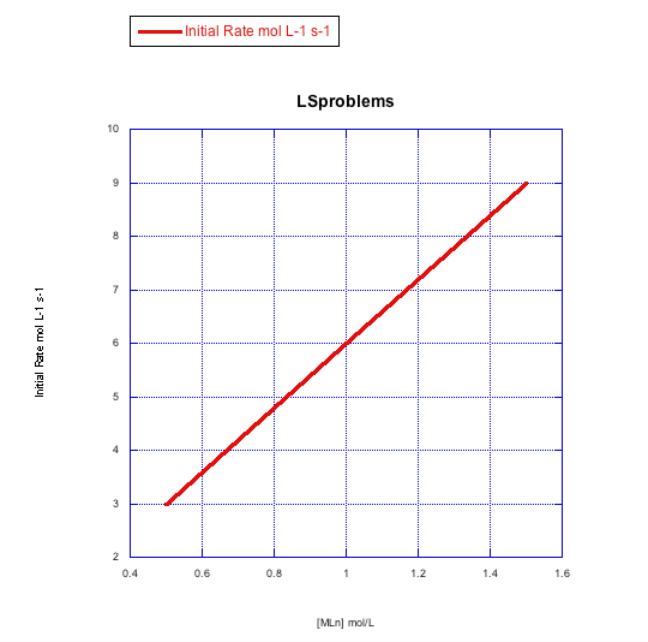
b) The concentration of new ligand, [X], is held constant at 0.1 mol/L and the concentration of metal complex is changed from 0.5 mol/L to 1 mol/L and then to 1.5 mol/L

Exercise 3.4.4

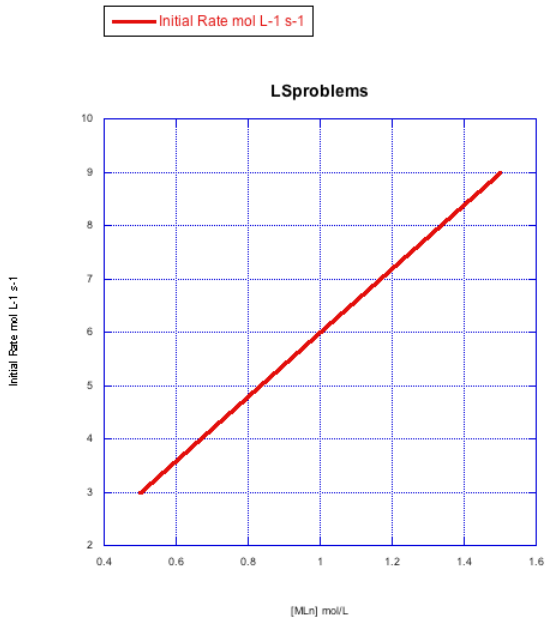
Given the following sets of initial rate data, determine whether each case represents a dissociative substitution. [MLn] = concentration of the coordination complex; [X] = concentration of incoming ligand.

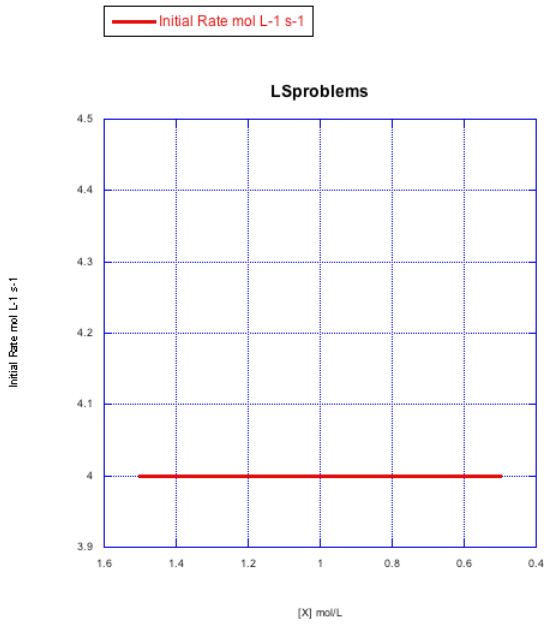
a)





b)





Answer a

The rate increases with both concentration of metal complex and incoming ligand. This looks like an associative mechanism.

Answer b

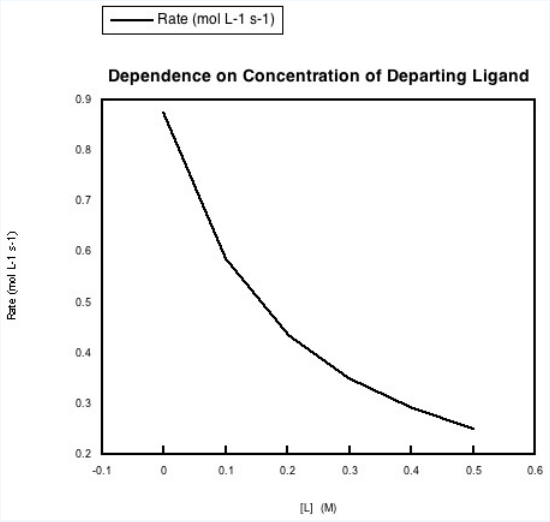
The rate depends on concentration of the metal complex, but not the incoming ligand. This looks like a dissociative mechanism.

Answer c

The rate depends on the concentration of incoming ligand, but not the metal complex. Whatever is going on here, it isn't a simple dissociative mechanism.

Exercise 3.4.5

In the following data, the concentration of the metal complex and the incoming ligand were held constant, but more of the departing ligand was added to the solution.



a) Explain what the data says about rate dependence on this concentration.

b) Explain this rate dependence in terms of the reaction.

Answer a

The rate of the reaction is depressed when the concentration of the departing ligand is increased.

Answer b

This dependence could indicate an equilibrium in the dissociative step. The more departing ligand is added, the more the equilibrium is pushed back towards the original metal complex. With less dissociated metal complex around, the entering ligand cannot form the new complex as quickly.

Exercise 3.4.6

In certain solvents, such as THF, acetonitrile and pyridine, the rate law for substitution often appears to be Rate = $k_1[ML_n] + k_2[ML_n][X]$, in which X is the incoming ligand and ML_n is the metal complex.

a) What do these solvents have in common?

b) What is a possible explanation for this rate law?

c) This rate law has been shown to be consistent with an entirely associative mechanism. How is that possible?

Answer a

These solvents all have lone pairs. They could be Lewis bases or nucleophiles.

Answer b

It looks like two competing mechanisms. On term suggests a dissociative mechanism, whereas the other term suggests a dissociative mechanism. They could be happening in competition with each other.

Answer c

On the other hand, it could be that there is one mechanism with two different nucleophiles. If the incoming ligand is the nucleophile, the term on the right shows up in the rate law. If the solvent is the nucleophile, forming a third complex, the term on the left shows up in the rate law. That's because we would typically change the amount of metal complex and the amount of ligand that we add to the solution in order to determine the rate law, but we wouldn't normally be able to change the concentration of the solvent, so it would be a constant. (How could you confirm this explanation in an experiment?)

3.5: Activation Parameters

The rate law shows how the rate of a reaction depends on concentrations of different species in solution. The proportionality constant, k, is called the rate constant. It contains other information about the energetic requirements of the reaction.

All reactions must overcome activation barriers in order to occur. The activation barrier is the sum of the energy that must be expended to get the reaction going. An activation barrier is often thought of, cartoonishly, as a hill the molecule has to climb over during the reaction. Once, there, it can just slide down the other side of the hill to become products. At the top of the hill, the molecule exists in what is called the "transition state". At the transition state, the structure is somewhere between its original form and the structure of the products.

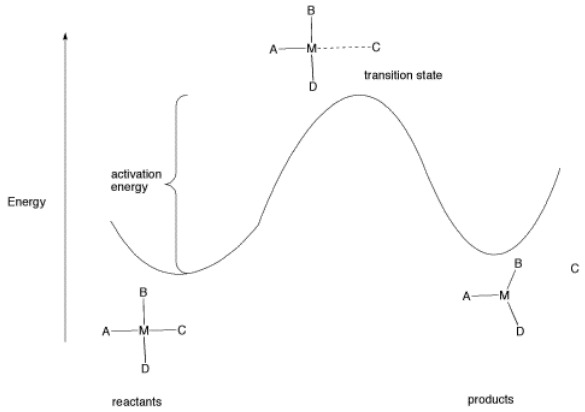


Figure 3.5.1: The activation barrier for a ligand dissociation step.

The type of diagram shown in figure LS6.1 is sometimes called a "reaction progress diagram". It shows energy changes in the system as a reaction proceeds. One or more activation barriers may occur along the reaction pathways, as various elementary steps occur in the reaction. In the above case, it is easy to imagine the source of the energy barrier, because some energy must be expended to break the bond to ligand C.

However, after that barrier is passed, energy is lowered again. This can happen for several reasons. Once C has separated from the metal complex, it is free to vibrate, tumble, roll and zip around all on its own. That means it can put its energy into any of those modes, independently of the metal complex. As a result, the entropy of the system increases. That lowers the overall "free energy" of the system. In addition, there may be some relief of crowding as the molecule changes from a four-coordinate complex to a three-coordinate complex, so strain energy is also lowered.

? Exercise 3.5.1

Make drawings depicting the relationship between reaction progress and energy for the following cases:

a) a new ligand binds to a four-coordinate complex, forming a five coordinate complex.

b) a two-step process in which a new ligand binds to a four-coordinate complex, forming a five coordinate complex, and then an old ligand dissociates to form a new, four-coordinate complex.

The rate constant gives direct insight into what is happening at the transition state, because it gives us the energy difference between the reactants and the transition state. Based on that information, we get some ideas of what is happening on the way to the transition state.

The rate constant can be broken down into pieces. Mathematically, it is often expressed as

$$k = (\frac{RT}{Nh})e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

In which R = the ideal gas constant, T = temperature, N = Avogadro's number, h = Planck's constant and $\Delta G^{\ddagger}$ = the free energy of activation.

The ideal gas constant, Planck's constant and Avogadro's number are all typical constants used in modeling the behaviour of molecules or large groups of molecules. The free energy of activation is essentially the energy requirement to get a molecule (or a

mole of them) to undergo the reaction.

Note that k depends on just two variables:

- Δ $G^{‡}$ or the energy required for the reaction
- T or the temperature of the surroundings, which is an index of the available energy

The ratio of activation free energy to temperature compares the energy needs to the energy available. The more energy available compared to the energy needed, the lower this ratio becomes. As a result, the exponential part of the function becomes larger (since the power has a minus sign). That makes the rate constant bigger, and the reaction becomes faster.

The activation free energy is constant for a given reaction. It can be broken down in turn to:

$$\Delta G^{‡} = \Delta H^{‡} - T\Delta S^{‡}$$

in which Δ $H^{‡}$ = activation enthalpy and Δ $S^{‡}$ = activation entropy.

The activation enthalpy is the energy required for the reaction. The activation entropy deals with how the energy within the molecule must be redistributed for the reaction to occur. These two parameters can be useful in understanding events leading to the transition state.

For example, in ligand substitution, an associative pathway is marked by low enthalpy of activation but a negative entropy of activation. The low enthalpy of activation results because bonds don't need to be broken before the transition state, so it doesn't cost much to get there. That's favorable and makes the reaction easier. However, a decrease in entropy means that energy must be partitioned into fewer states. That's not favorable and makes the reaction harder. The reason the energy must be redistributed this way is that two molecules (the metal complex and the new ligand) are coming together to make one bigger molecule. They can no longer move independently of each other, and all of their combined energy must be reapportioned together, with a more limited range of vibrational, rotational and translational states to use for that purpose.

- Associative pathway: more bond making than bond breaking; lower enthalpy needs
- Associative pathway: two molecules must be aligned and come together; fewer degrees of freedom for energy distribution; decrease in entropy

On the other hand, the dissociative pathway is marked by a higher enthalpy of activation but a positive entropy of activation. The higher enthalpy of activation results because a bond must be broken in the rate determining step. That's not favorable. However, the molecule breaks into two molecules in the rate determining step. these two molecules have more degrees of freedom in which to partition their energy than they did as one molecule. That's favorable.

- Dissociative pathway: more bond breaking in rate determining step, higher enthalpy needs
- Dissociative pathway: one molecule converts to two molecules in rate determining step, greater degrees of freedom in two independently moving molecules, entropy increases

Thus, looking at the activation parameters can reveal a lot about what is going on in the transition state.

? Exercise 3.5.2

What factor(s) other than entropy might raise the free energy of the transition state going into an associative step between a metal complex and an incoming ligand? (What factor might make the first, associative step slower than the second, dissociative step?)

Answer

The metal centre is becoming more crowded as the new ligand arrives, so an increase in energy owing to steric hindrance may also play a role in the transition state energetics.

? Exercise 3.5.3

Other mechanisms for ligand substitution are also possible. The following case is referred to as an associative interchange (I_A).

a) Describe in words what happens in an associative interchange.

b) Predict the rate law for the reaction.

c) Qualitatively predict the activation entropy and enthalpy, compared with

i) an associative mechanism and

ii) a dissociative mechanism.

Answer a

The new ligand, B, is arriving at the same time as the old ligand, A, is departing. We might also describe it as new ligand B pushing old ligand A out of the complex.

Answer b

$Rate = k[ML_5A][B]$, which looks like an associative rate law.

Answer c

This is a thought-provoking question without a definite answer. Associative mechanisms typically have lower activation enthalpy than dissociative mechanisms, because there has also been some bond-making prior to the bond-breaking in the rate determining step. The associative interchange would be a little more like the associative mechanism than dissociative. The mix of bond-making and bond-breaking at the transition state would make the enthalpy of activation relatively low.

Associative mechanisms have negative activation entropies, whereas dissociative mechanisms have positive activation entropies. The associative interchange could be in between the two, given that the elementary step would be close to entropically neutral overall. What happens at the transition state is a little harder to imagine, but it might reflect the small changes in entropy through the course of the reaction, producing a small entropy of activation. On the other hand, if the incoming ligand is forced to adopt some specific approach as it comes into the molecule (to stay out of the way of the departing ligand, for example) then that restriction could show up as a small negative activation entropy.

? Exercise 3.5.4

For the following mechanism:

a) Describe in words what is happening.

b) Predict the rate determining step.

c) Predict the rate law for the reaction.

d) Qualitatively predict the activation entropy and enthalpy, compared with

i) both an associative mechanism and

ii) a dissociative mechanism.

e) Suggest some ligands that may be able to make this mechanism occur.

Answer a

The lone pair donation from one ligand appears to push another ligand out.

Answer b

The first step is probably rate determining, because of the bond breaking involved.

Answer c

If the first step is rate determining, $Rate = k[ML_5A]$.

Answer d

Another question without a very clear answer. Compared with an associative mechanism, the activation entropy is probably much more positive, because additional degrees of freedom are being gained as the molecule heads over the activation barrier and one of the ligands separates to be on its own. However, the activation entropy may be less positive than in a regular dissociation, because in this case the breaking of one bond has to be coordinated with the formation of another.

The enthalpy of activation has both a bond-making and bond-breaking component, a little like in an associative mechanism. However, the amount of bond making here is probably less important, because pi bonds are typically not as strong as sigma bonds. The activation enthalpy is probably higher than an associative pathway but not as high as a dissociative one.

Answer e

The donor ligand must have a lone pair. Oxygen donors would be good candidates, because even if one lone pair is already donating in a sigma bond, an additional lone pair may be available for pi donation. The same thing is true for halogen donors. It would also be true for anionic nitrogen donors but not for neutral nitrogen donors, because a neutral nitrogen has only one lone pair.

3.6: Some Reasons for Differing Mechanisms

We usually look for physical reasons why a given compound might undergo a reaction via one mechanism and not another. That ability adds to our understanding of chemistry. If we can take information and give it predictive value, then we may be able to make educated decisions about what is probably happening with new reactions.

Why might a reaction undergo a dissociative reaction rather than an associative one? What factors might prevent an associative pathway?

One reason may be that there is not enough room. In an associative step, an additional ligand comes in and binds to the metal. If it is already crowded, that may be difficult.

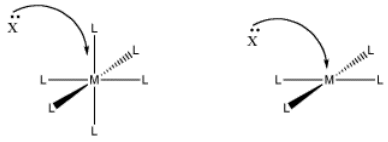


Figure 3.6.1: The role of steric crowding in ligand substitution. In one of these cases, the associative mechanism is less favored because of crowding that will occur in the transition state.

- Steric crowding may lead to a dissociative, rather than associative, mechanism.

Another reason has to do with electronics. Maybe the compound cannot easily accept an additional bonding pair. That may be the case if the compound already has eighteen electrons.

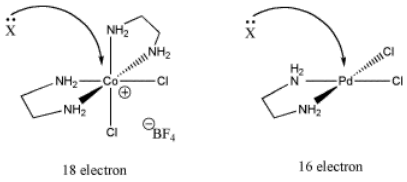


Figure 3.6.2: The role of electron count in ligand substitution. In one of these cases, the associative mechanism is less favored because the metal is already electronically saturated.

- Electronic saturation may lead to a dissociative, rather than associative, mechanism.

However, if there is less crowding, and more electrons can be accommodated, an associative pathway may result.

? Exercise 3.6.1

i) Draw structures for the following reactions. Pay attention to geometry.

ii) Predict whether each of the substitutions would occur through associative or dissociative mechanisms.

a) $AuCl_3py + Na\ N_3 \rightarrow Na^+\ [AuCl_3N_3]^- + py$

b) $Rh(C_2H_4)_2(acac) + C_2D_4 \rightarrow Rh(C_2D_4)_2(acac) + C_2H_4$

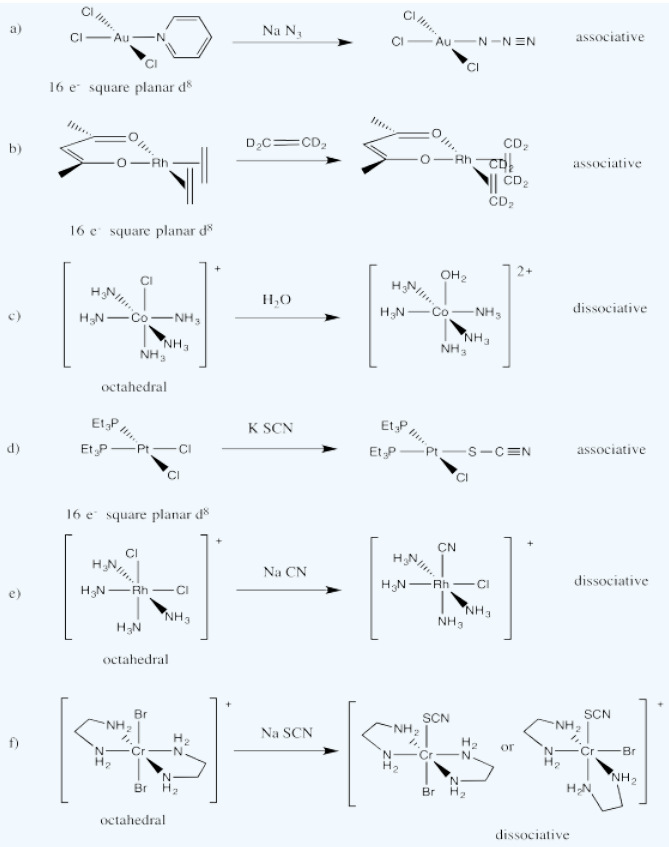
c) $[Co(NH_3)_5Cl]^{2+} + H_2O \rightarrow [Co(NH_3)_5(OH_{2)}]^{2+} + Cl^-$

d) *trans*-$(Et_3P)_2PtCl_2 + {}^-SCN \rightarrow$ *trans*-$(Et_3P)_2PtCl(SCN) + Cl^-$

e) $Rh(NH_3)_4Cl_2^+ + {}^-CN \rightarrow Rh(NH_3)_4Cl(CN)^+ + Cl^-$

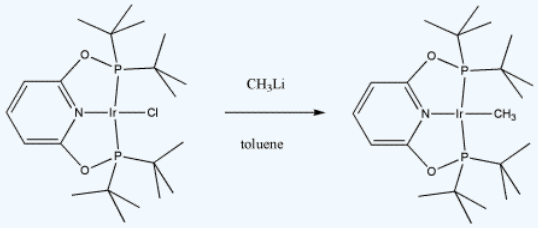
f) *trans*-$[Cr(en)_2Br_2\ ]^+ + {}^-SCN \rightarrow$ *cis*- and *trans*-$[Cr(en)_2Br(SCN)]^+ + Br^-$

Answer



Exercise 3.6.2

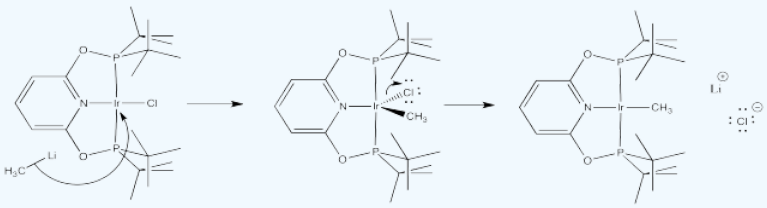
Maurice Brookhart of UNC, Chapel Hill, makes organometallic compounds in order to study fundamental questions about reactivity. In this case, he has reported making a new compound capable of "C-H activation", a reaction in which unreactive C-H bonds can be forced to break. This process holds the future promise of converting coal and natural gas into important commodities currently obtained from petroleum.



a) Draw, with curved arrows, a mechanism for the ligand substitution in the synthesis of this C-H activating complex.

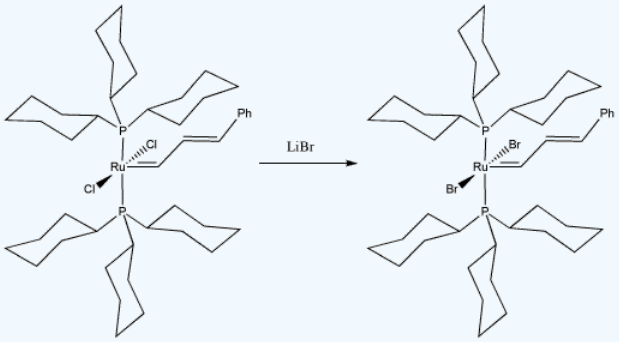
b) Explain your reasons for your choice of reaction mechanism.

Answer



Exercise 3.6.3

Bob Grubbs of Cal Tech was awarded the Nobel Prize in chemistry for his development of catalysts for olefin metathesis. Olefin metathesis is important both in the reforming of petroleum and in the synthesis of important commodities such as pharmaceuticals. In the following study, he replaced chlorides on a "Grubbs Generation I catalyst" to study the effect on the olefin metathesis reaction.

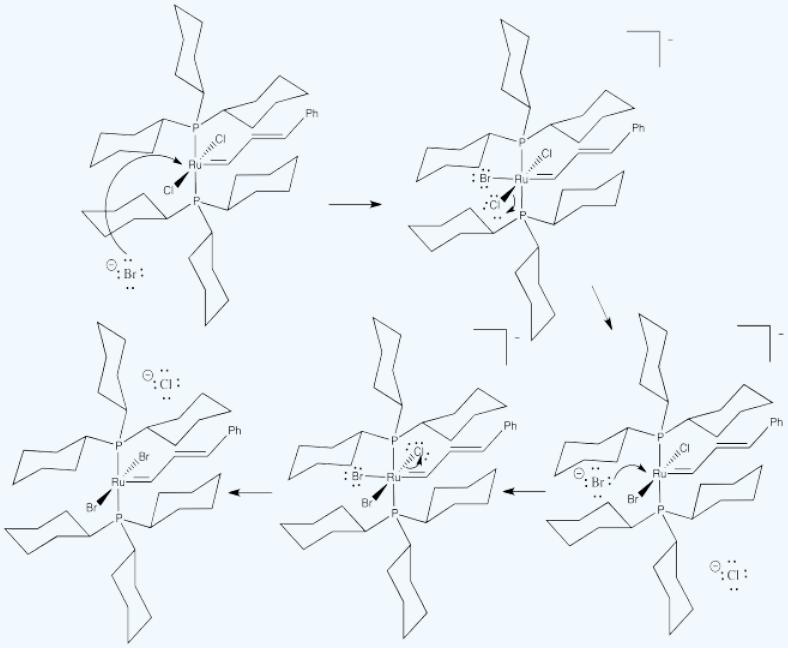


a) Draw, with curved arrows, a mechanism for the ligand substitution in this complex.

b) Explain your reasons for your choice of reaction mechanism.

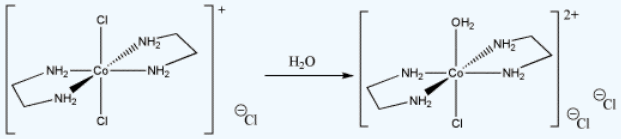
c) What factor(s) do you think Grubbs hoped to study by making this substitution in the catalyst?

Answer



Exercise 3.6.4

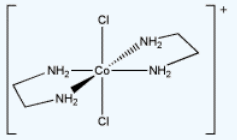
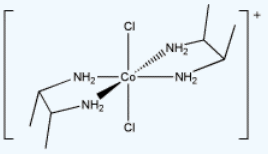
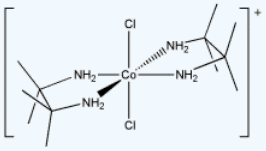
Sometimes, kinetic studies can give insight into a reaction if controlled changes in the reaction produce measurable results.



a) Draw, with curved arrows, a mechanism for the ligand substitution in this reaction.

b) Explain your reasons for your choice of reaction mechanism.

c) Explain the following kinetic data.

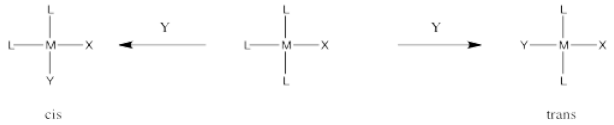
complex	substitution rate constant
	$3.2 \times 10^{-5}\ s^{-1}$
	$4.1 \times 10^{-3}\ s^{-1}$
	too fast to measure easily

Exercise 3.6.5

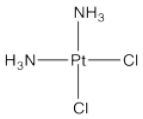
Several different structures were proposed for $Ni(cysteine)_2^{2-}$. Kinetic studies of substitution in this complex showed the rate was dependent in the concentration of both the metal complex and the incoming ligand. Which structure do you think is correct? Why?

3.7: The Trans Effect

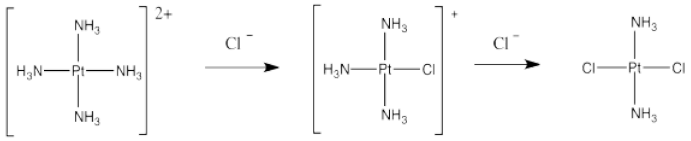
Occasionally in ligand substitution there is a situation in which there are two identical ligands that could be replaced, but two different products would result depending on which ligand left. This situation often happens in square planar complexes, for example. Replacement of one ligand would lead to a *cis* product. Replacement of the other one would lead to a *trans* product.



An important example of this issue is in the synthesis of cis-platin, an antitumour medication frequently used to treat ovarian and testicular cancer.

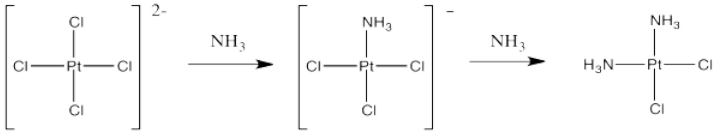


Cis-platin could be made from treatment of tetraammineplatinum(II) with chloride salts. The chloride ion could replace two of the ammonia ligands.



But that doesn't work. That synthesis results in the formation of *trans*-platin, a compound that has all of the nasty side effects of the *cis* isomer but with none of the therapeautic benefit.

If instead you were to start with tetrachloroplatinate salts and treat them with ammonia, you could replace two of the chloride ligands. That works really well, and it provides *cis*-platin, not *trans*-platin.



? Exercise 3.7.1

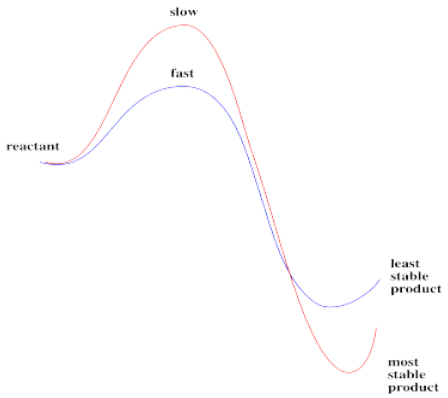
What do you think is the mechanism of substitution of the two reactions above? Why?

Answer

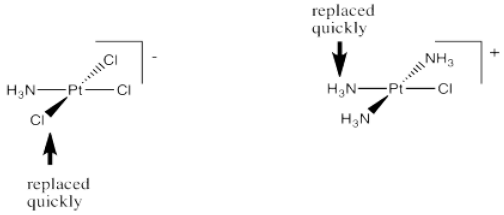
This is probably an associative mechanism because of the square planar geometry.

This reaction, if run under these conditions, is clearly not always under thermodynamic control. Two different products result, depending on how the reaction is done. One of those isomers is probably more stable than the other; if thermodynamics were in charge, it would form the same thing both times.

Instead, there may be an element of kinetic control for at least one of the pathways. A given product might be made, not because it is more stable, but simply because it forms more quickly than the other one.



Take another look at those two reactions. One of the things that they have in common is that the ligand that gets replaced is *trans* to a chloride. It is not *trans* to an ammonia. Maybe the other ligands in the complex can influence how quickly one ligand can leave.



Specifically, the "*trans* effect" is the role of *trans*-ligands in influencing substitution rates in square planar complexes.

The following kinetic data were obtained for substitutions on square planar platinum complexes, in the reaction:

$$trans-(PEt_3)_2PtLCl+py \rightarrow trans-(PEt_3)_2PtLpy^+ + Cl^-$$

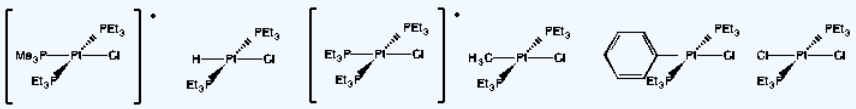
L	k_{obs} (s^{-1})	T, °C
PMe_3	0.20	0
H^-	0.047	0
PEt_3	0.041	0
CH_3^-	6.0 x 10^{-4}	25
$C_6H_5^-$	1.2 x 10^{-4}	25
Cl^-	3.5 x 10^{-6}	25

Ref: Cooper Langford & Harry Gray, *Ligand Substitution Processes*, W.A. Benjamin, NY, 1965, p. 25.

? Exercise 3.7.2

Draw structures for each of the complexes listed in the table.

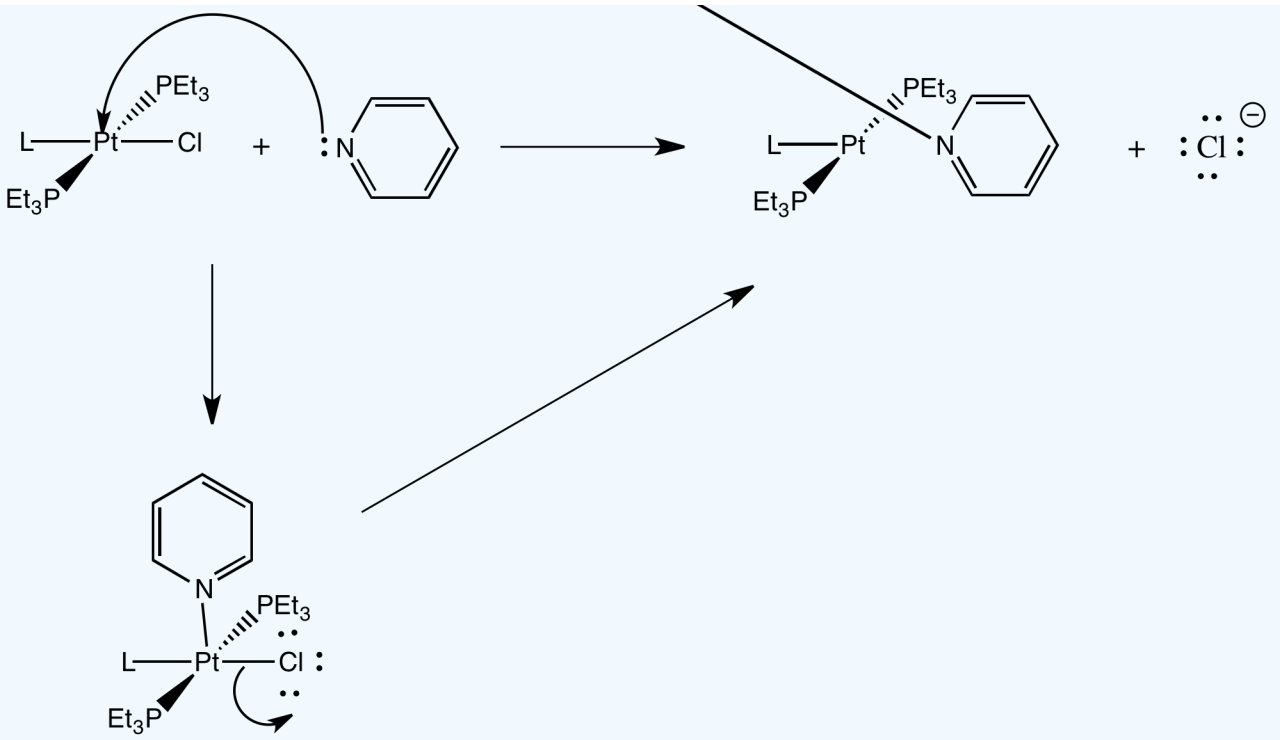
Answer



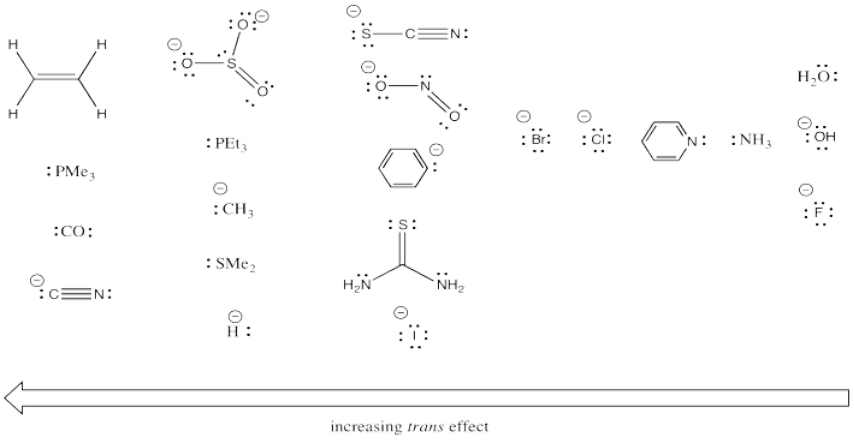
? Exercise 3.7.3

Provide a mechanism with arrows for the reaction studied in the table.

Answer



Clearly that *trans* ligand has a dramatic effect on how quickly the chloride can be substituted in the above study. Additional studies like this one have led to some general trends. Below, the ligands on the left have strong *trans*-effects. Ligands *trans* to them are substituted very quickly. The ligands on the right have very modest *trans* effects. Ligands *trans* to them are substituted only slowly.



Exercise 3.7.4

Look for empirical trends in the series of ligands above. Without trying to explain exactly why, find chemically relevant factors that may be responsible for these reactivity trends.

Answer

There is an electronegativity trend: the less electronegative, the greater the *trans* effect (see the halogens, as well as the series O,N,C and also the orders within several pairings: S,P; O,S and N,P).

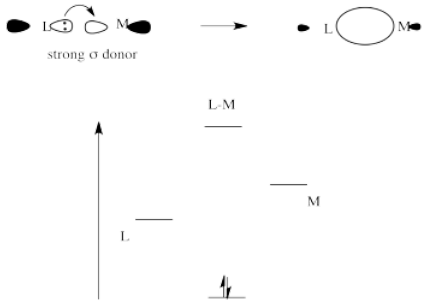
Alternatively, some of the above could be described by a polarizability trend: more polarizable atom, greater *trans* effect (for example, the halogens).

Most of the ligands containing π-bonds have strong *trans* influence (but not all).

Most of the π-donors have a weaker *trans* influence. However, these ligand cover a very broad range in this series.

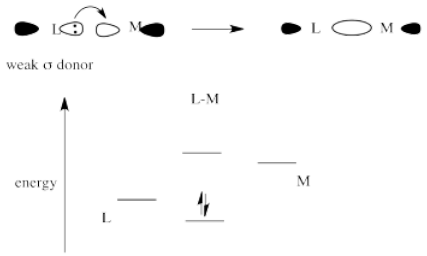
In general, explanations of the trans effect have focused on two separate types of ligands. These are strong sigma donors and strong pi acceptors.

Strong sigma donors donate electrons very effectively to the metal via a sigma bond. Because the ligand trans to this donor would be bonding via donation to the same metal p orbital, there is a competition. The metal p orbital bonds more favorably with the strong sigma donor, and the ligand trans to it is left with a weaker bond.



The strong sigma donor gets good overlap with the metal orbital and the resulting interaction goes down low in energy.

The weak sigma donor gets poorer overlap with the metal orbital and only weak stabilization of the donor electrons.



Place these two choices together, and the metal orbital will engage in a strong bonding interaction with the strong σ-donor. Doing so lowers the electronic energy significantly. It won't interact very much with the weak σ-donor, because doing that won't result in as much lowering of electronic energy. The result is a strong bond on one side of the metal and a weak bond on the other. That weak bond will break easily and that ligand will be replaced easily.

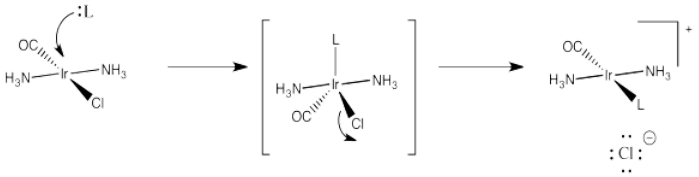
Exercise 3.7.5

Which of the ligands in the *trans* effect series are probably strong σ-donors? Why?

Answer

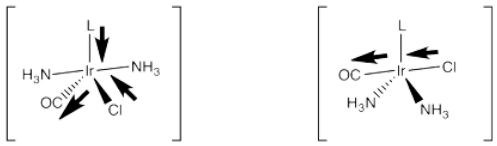
The strongest σ-donors are typically those with more polarizable donor atoms (such as S, P, I) as well as those with less electronegative donor ions such as C^- and H^-.

Strong pi acceptors exert their trans effect in a different way. They are thought to stabilize a particular geometry of the five-coordinate intermediate in substitution of square planar complexes. We haven't worried too much about the geometry of that intermediate, but it is probably trigonal bipyramidal. It would have three ligands in an equatorial plane and two more directly opposite each other, in the axial positions.



Essentially, the incoming ligand pushes two of the ligands down from the square plane to form this trigonal bipyramid. When it comes time for a ligand to leave, it is probably going to be one of these ligands that is already on the move. They are already on a trajectory out of the square plane, anyway.

A strong pi acceptor like CO exerts its *trans* effect by making sure it, along with the ligand opposite it, gets into that equatorial plane. It does that by a stabilizing delocalization that happens when the π-acceptor is in the electron-rich equatorial plane. In that position, it can draw electron density via π-donation from two different donors. If it were in an axial position, it could still delocalize electrons this way, but it would draw most effectively from just one donor rather than two.



favoured

So which of those two ligands is going to keep moving and leave the complex? It certainly won't be the one that is exerting a stabilizing, delocalizing effect on the complex via its strong bonding interactions. It will be the unlucky *trans* ligand that got dragged along with it.

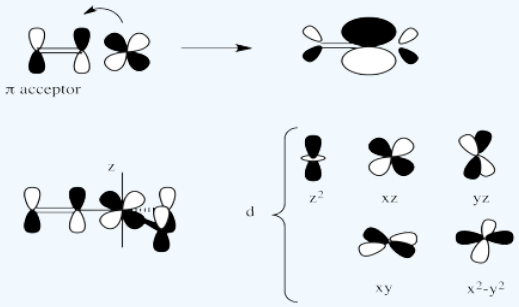
Exercise 3.7.6

Which of the ligands in the *trans*-effect series are probably strong π-acceptors? Show why.

Exercise 3.7.7

Draw an orbital picture showing the -delocalization described in the trigonal bipyramidal intermediate. Label the orbitals, assuming the z axis is along the axis of the trigonal bipyramid (i.e. the equatorial plane is the xy plane).

Answer



Exercise 3.7.8

Substitution of trans ligands in μ-oxo-bis(μ-acetato)diruthenium complexes: Synthesis and kinetic studies. Hussain, Bhatt, Kumar, Thorat, Padhiyar and Shukla, *Inorganica Chemica Acta*, **2009**, *362*, 1101-1108.

Given the structure $[Ru_2O(L)_6(acetate)_2](PF_6)_2$, in which L is a neutral donor,

a) Draw the structure of the counterion, PF_6^-.

b) Provide an account of the valence electron count in the ruthenium coordination complex.

Valence electrons on metal	
Total charge on ligands	
Charge on the metal	
Revised count on metal	

Electrons donated by ligands	
Total electrons on metal in complex	

Data shows that the ligands L are *trans* to the bridging oxo ligand are labile.

c) Use orbital cartoons and words to provide an explanation for this effect.

When water is added to an acetone solution of $[Ru_2O(pyridine)_4(L)_2(acetate)_2](PF_6)_2$, then $[Ru_2O(pyridine)_4(H_2O)_2(acetate)_2](PF_6)_2$ is formed.

d) Draw the product of this reaction.

When pyridine is added to $[Ru_2O(pyridine)_4(H_2O)_2(acetate)_2](PF_6)_2$, then $[Ru_2O(pyridine)_6(acetate)_2](PF_6)_2$ is formed. The following rate constants were observed for this reaction.

[pyridine] mol L^{-1}	k_{obs} s^{-1} (x 10^{-3})
0.005	1.75
0.012	2.53
0.025	9.7
0.049	16.7
0.100	35.2

e) Use the data from this table to determine the order in pyridine. Provide an explanation for your conclusion.

f) Draw a mechanism for the reaction, consistent with the data.

g) Write a rate law for the reaction.

h) The authors studies the same reaction with different ligands instead of pyridine. They observed an increase in rate constants with increasing basicity of the incoming ligands. Provide an explanation for this observation.

Answer a

5 valence electrons - 6 bonds - 0 nonbonding = -1

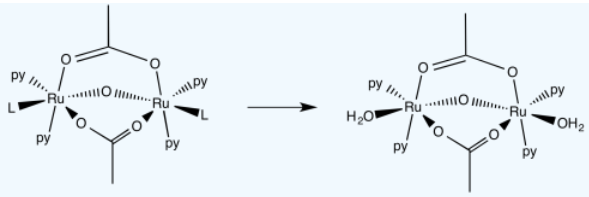
Answer b

Valence electrons on metal	8
Total charge on ligands	-4 (-2 per Ru)
Charge on the metal	+2
Revised count on metal	6
Electrons donated by ligands	12
Total electrons on metal in complex	18

Answer c

The oxo is a strong sigma donor and hogs the orbital with the metal thus leaving very little room for orbital bonding trans to the sigma donor.

Answer d



Answer e

First order. Although there is some amount of error in the data, doubling the pyridine concentration generally results in a doubling of the rate.

Answer f

The mechanism you draw would have to involve a first associative step; because the complex is already 18 electrons, associative interchange is likely.

Answer g

$$Rate = k[ML_n][py]$$

Answer h

Basic ligands have stronger attraction to the metal thus accelerating the reaction.

3.8: Solutions to Selected Problems

Exercise 3.1.1:

a) a bromine atom replaces a hydrogen atom

b) an acetate group (ethanoyl ester) replaces a bromine atom

c) a bromine atom replaces a chlorine atom (or ions)

d) a methoxy group replaces a chlorine atom

e) a methylamino group replaces an oxygen atom

Exercise 3.2.1:

a) Energy is released when bonds are formed. Energy must be added to break bonds. In general, bond-breaking costs more energy than bond-making.

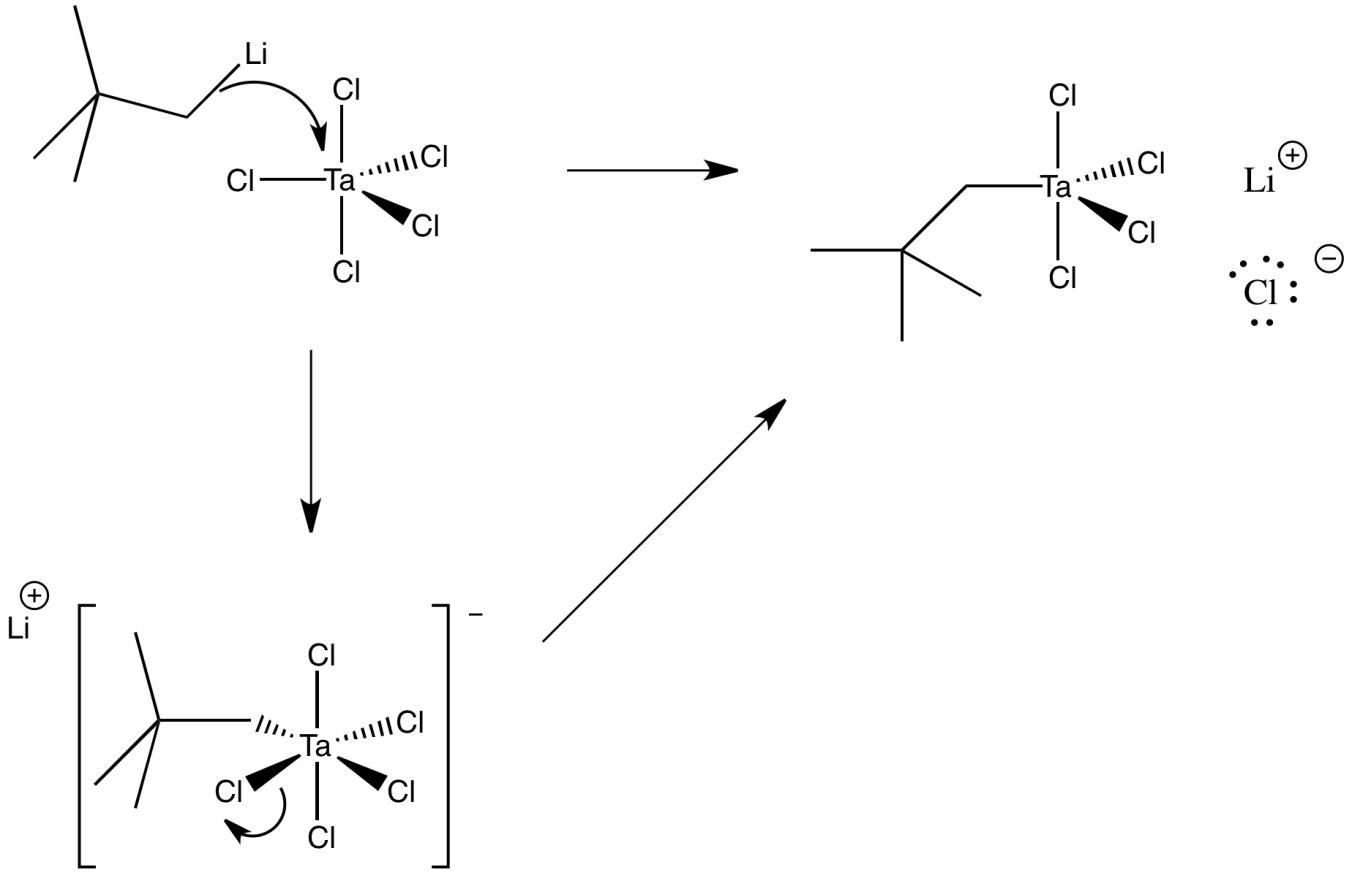
b) On the basis of question (a), we would assume that the second, bond-breaking step is the rate determining step in association mechanisms.

c) The first, dissociative step would be the rate-determining step, on the basis of question (a).

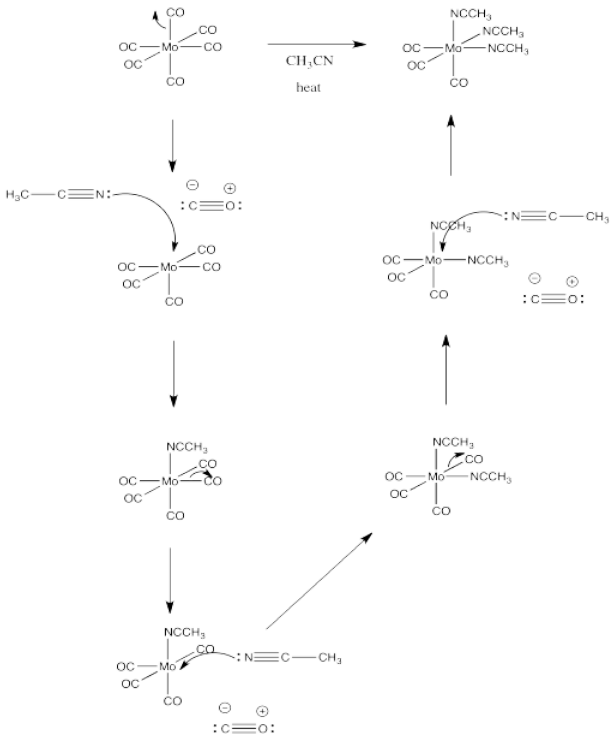
d) The rate law would include steps prior t the rate determining step. $Rate = k[MLn][X]$ if MLn is the complex and X is the new ligand.

e) $Rate = k[MLn]$

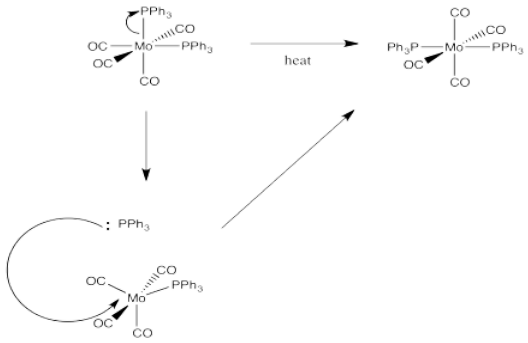
Exercise 3.2.2:



Exercise 3.2.3:



Exercise 3.2.4:

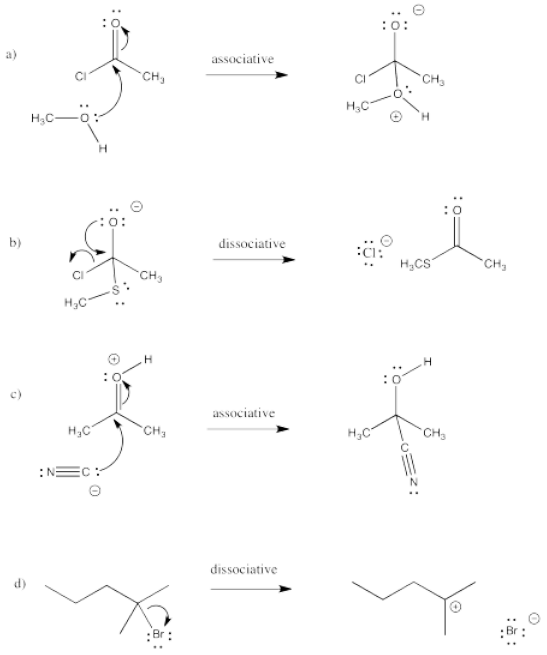


Exercise 3.2.5:

This problem is answered through consideration of the spectrochemical series.

from easiest to hardest to replace: NO_3^- Cl^- H_2O NH_3 PPh_3 CO

Exercise 3.2.6:



Exercise 3.3.1:

Associative Rate Law: $Rate = [ML_n][X]$, if ML_n is the complex and X is the new ligand.

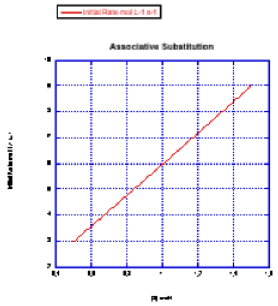
a) Rate will quadruple: $Rate = (2 \times [ML_n]_0) \times (2 \times [X]_0) = 4 \times [ML_n]_0[X]_0$ if $[X]_0$ and $[ML_n]_0$ are the original concentrations.

b) Rate will sextuple: $Rate = (3 \times [ML_n]_0) \times (2 \times [X]_0) = 6 \times [ML_n]_0[X]_0$

c) Rate will nonuple: $Rate = (3 \times [ML_n]_0) \times (3 \times [X]_0) = 9 \times [ML_n]_0[X]_0$

d) Rate will stay the same: $Rate = (0.5 \times [ML_n]_0) \times (2 \times [X]_0) = 1 \times [ML_n]_0[X]_0$

Exercise 3.3.2:



Problem LS3.3.

a) Changing both concentrations at once would leave some doubt about whether one concentration had affected the rate, or the other concentration, or both. In practice, one concentration is usually held constant while the other is kept in excess and varied.

b) Rate changes over time because the concentrations of reactants change as they are consumed. By reporting only the initial rate (usually meaning less than 5% or 10% complete, but possibly even less than that if a lot of data can be gathered very quickly), the concentrations are still about what you started with. That means you can report a rate that corresponds to a given concentration with confidence.

Exercise 3.3.4:

a) The rate would change with the ligand concentration if associative. This rate is constant over a range of ligand concentrations, so the reaction is not associative.

b) The rate increases linearly with ligand concentration. This reaction proceeds via an associative mechanism.

c) The rate changes over the concentration range, but it decreases. This is the opposite of what should happen. This reaction does not follow a simple associative pathway.

d) The rate increases linearly with ligand concentration. This reaction proceeds via an associative mechanism.

Exercise 3.3.5:

Because $Rate = k[ML_n][L]$ and [ML_n] is held constant while [L] is varied, then the slope of the line is k [ML_n]. Since you would know the value of [ML_n], you could obtain the rate constant from the quantity $(\frac{slope}{[ML_n]})$.

Exercise 3.4.1:

a) $4\ minutes = 240\ seconds = 2 \times 120\ seconds = 2\ half\ lives.\ Material\ left\ = 50\% \times 50\% = 0.5 \times 0.5 = 0.25 = 25\%\ left$

b) $6\ minutes = 360\ seconds = 3 \times 120\ seconds = 3\ half\ lives.\ Material\ left\ = 0.5 \times 0.5 \times 0.5 = 0.125 = 12.5\%\ left$

c) $8\ minutes = 480\ seconds = 4 \times 120\ seconds = 4\ half\ lives.\ Material\ left\ = 0.5 \times 0.5 \times 0.5 \times 0.5 = 0.0625 = 6.25\%\ left$

d) $10\ minutes = 600\ seconds = 5 \times 120\ seconds = 5\ half\ lives.\ Material\ left\ = 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 = 0.03125 = 3.125\%\ left$

Exercise 3.4.2:

Dissociative Rate Law: $Rate = [ML_n]$, if ML_n is the complex. There is no dependence on [X], if X is the new ligand.

a) Rate will double: $Rate = 2 \times [ML_n]_0$, if $[ML_n]_0$ is the original concentration.

b) Rate will be halved: $Rate = 0.5 \times [ML_n]_0$

c) Rate will triple: $Rate = 3 \times [ML_n]_0$

d) Rate will be halved: $0.5 \times [ML_n]_0$

Exercise 3.4.4:

a) The rate increases with both concentration of metal complex and incoming ligand. This looks like an associative mechanism.

b) The rate depends on concentration of the metal complex, but not the incoming ligand. This looks like a dissociative mechanism.

c) The rate depends on the concentration of incoming ligand, but not the metal complex. Whatever is going on here, it isn't a simple dissociative mechanism.

Exercise 3.4.5:

a) The rate of the reaction is depressed when the concentration of the departing ligand is increased.

b) This dependence could indicate an equilibrium in the dissociative step. The more departing ligand is added, the more the equilibrium is pushed back towards the original metal complex. With less dissociated metal complex around, the entering ligand cannot form the new complex as quickly.

Exercise 3.4.6:

a) These solvents all have lone pairs. They could be Lewis bases or nucleophiles.

b) It looks like two competing mechanisms. On term suggests a dissociative mechanism, whereas the other term suggests a dissociative mechanism. They could be happening in competition with each other.

c) On the other hand, it could be that there is one mechanism with two different nucleophiles. If the incoming ligand is the nucleophile, the term on the right shows up in the rate law. If the solvent is the nucleophile, forming a third complex, the term on the left shows up in the rate law. That's because we would typically change the amount of metal complex and the amount of ligand that we add to the solution in order to determine the rate law, but we wouldn't normally be able to change the concentration of the solvent, so it would be a constant. (How could you confirm this explanation in an experiment?)

Exercise 3.5.2:

The metal centre is becoming more crowded as the new ligand arrives, so an increase in energy owing to steric hindrance may also play a role in the transition state energetics.

Exercise 3.5.3:

a) The new ligand, B, is arriving at the same time as the old ligand, A, is departing. We might also describe it as new ligand B pushing old ligand A out of the complex.

b) $Rate = k[ML_5A][B]$, which looks like an associative rate law.

c) This is a thought-provoking question without a definite answer. Associative mechanisms typically have lower activation enthalpy than dissociative mechanisms, because there has also been some bond-making prior to the bond-breaking in the rate determining step. The associative interchange would be a little more like the associative mechanism than dissociative. The mix of bond-making and bond-breaking at the transition state would make the enthalpy of activation relatively low.

Associative mechanisms have negative activation entropies, whereas dissociative mechanisms have positive activation entropies. The associative interchange could be in between the two, given that the elementary step would be close to entropically neutral overall. What happens at the transition state is a little harder to imagine, but it might reflect the small changes in entropy through the course of the reaction, producing a small entropy of activation. On the other hand, if the incoming ligand is forced to adopt some specific approach as it comes into the molecule (to stay out of the way of the departing ligand, for example) then that restriction could show up as a small negative activation entropy.

Exercise 3.5.4:

a) The lone pair donation from one ligand appears to push another ligand out.

b) The first step is probably rate determining, because of the bond breaking involved.

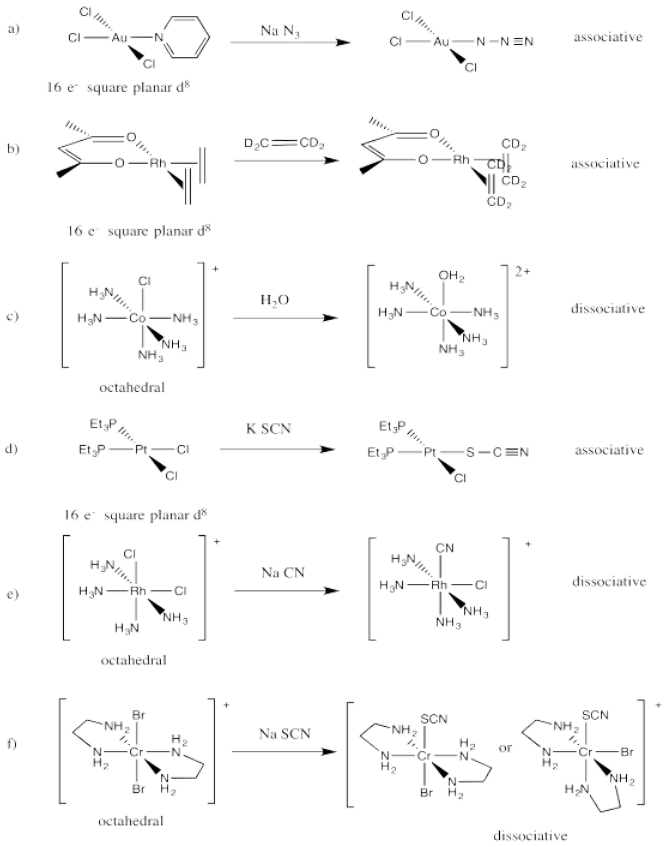
c) If the first step is rate determining, $Rate = k[ML_5A]$

d) Another question without a very clear answer. Compared with an associative mechanism, the activation entropy is probably much more positive, because additional degrees of freedom are being gained as the molecule heads over the activation barrier and one of the ligands separates to be on its own. However, the activation entropy may be less positive than in a regular dissociation, because in this case the breaking of one bond has to be coordinated with the formation of another.

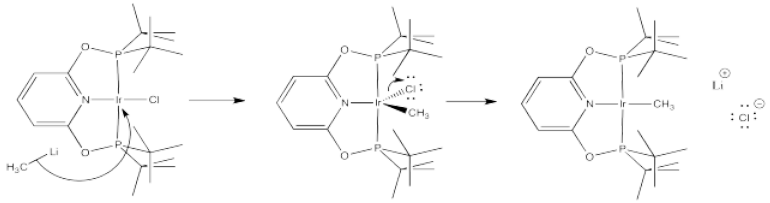
The enthalpy of activation has both a bond-making and bond-breaking component, a little like in an associative mechanism. However, the amount of bond making here is probably less important, because pi bonds are typically not as strong as sigma bonds. The activation enthalpy is probably higher than an associative pathway but not as high as a dissociative one.

e) The donor ligand must have a lone pair. Oxygen donors would be good candidates, because even if one lone pair is already donating in a sigma bond, an additional lone pair may be available for pi donation. The same thing is true for halogen donors. It would also be true for anionic nitrogen donors but not for neutral nitrogen donors, because a neutral nitrogen has only one lone pair.

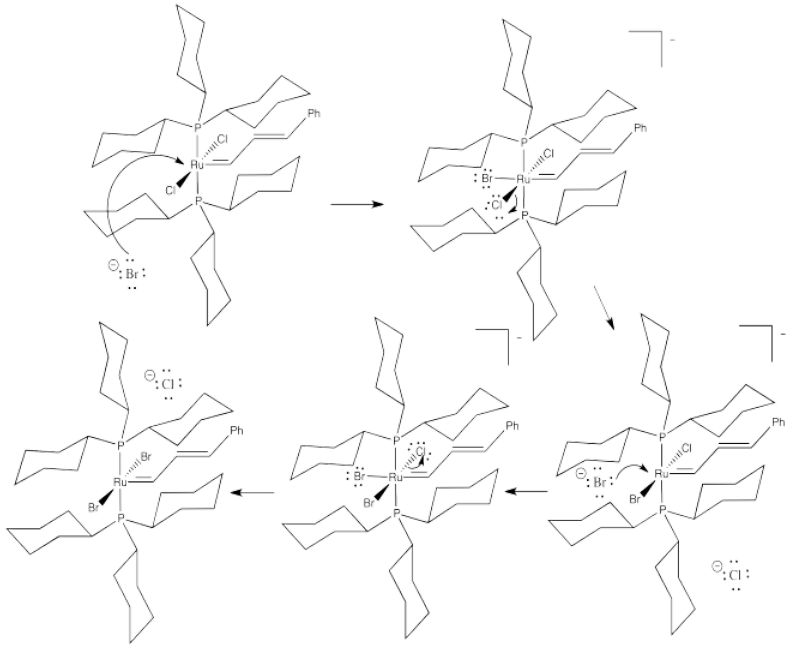
Exercise 3.6.1:



Exercise 3.6.2:



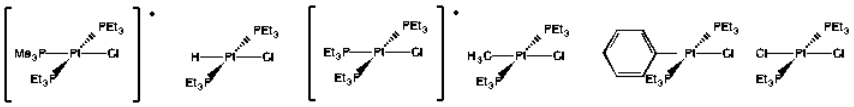
Exercise 3.6.3:



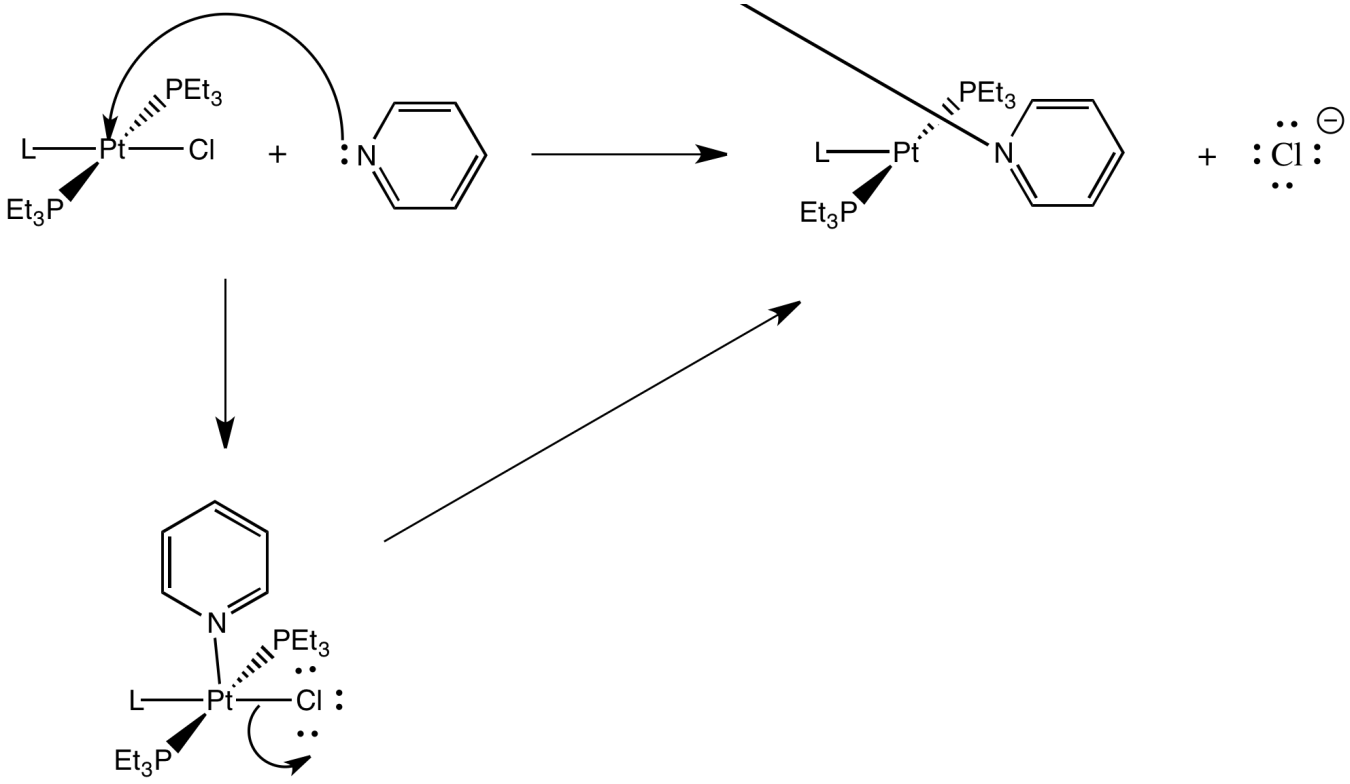
Exercise 3.7.1:

This is probably an associative mechanism because of the square planar geometry.

Exercise 3.7.2:



Exercise 3.7.3:



Exercise 3.7.4:

There is an electronegativity trend: the less electronegative, the greater the *trans* effect (see the halogens, as well as the series O,N,C and also the orders within several pairings: S,P; O,S and N,P).

Alternatively, some of the above could be described by a polarizability trend: more polarizable atom, greater *trans* effect (for example, the halogens).

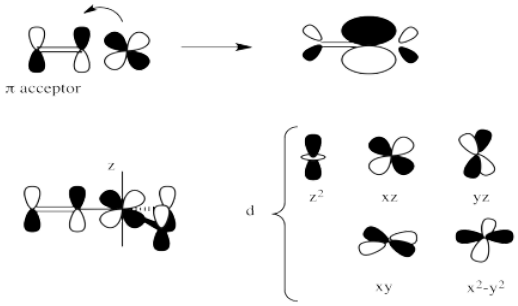
Most of the ligands containing π-bonds have strong *trans* influence (but not all).

Most of the π-donors have a weaker *trans* influence. However, these ligand cover a very broad range in this series.

Exercise 3.7.5:

The strongest σ-donors are typically those with more polarizable donor atoms (such as S, P, I) as well as those with less electronegative donor ions such as C^- and H^-.

Exercise 3.7.7:



Exercise 3.7.8:

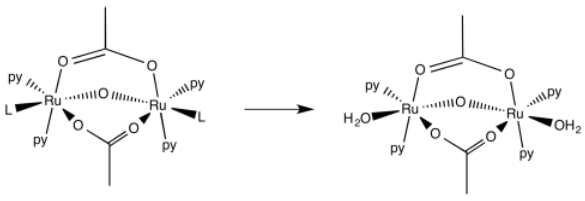
a)

b)

Valence electrons on metal	8
Total charge on ligands	-4 (-2 per Ru)
Charge on the metal	+2
Revised count on metal	6
Electrons donated by ligands	12
Total electrons on metal in complex	18

c) The oxo is a strong sigma donor and hogs the orbital with the metal thus leaving very little room for orbital bonding trans to the sigma donor.

d)



e) First order. Although there is some amount of error in the data, doubling the pyridine concentration generally results in a doubling of the rate.

f) The mechanism you draw would have to involve a first associative step; because the complex is already 18 electrons, associative interchange is likely.

g) $Rate = k[ML_n][py]$

h) Basic ligands have stronger attraction to the metal thus accelerating the reaction.

CHAPTER OVERVIEW

4: Aliphatic Nucleophilic Substitution

4.1: Introduction to Aliphatic Nucleophilic Substitution

Aliphatic nucleophilic substitution is a mouthful, but each piece tells you something important about this kind of reaction.

In *substitution* reactions, one piece of a molecule is replaced by another. For example, ligands can be replaced in transition metal complexes. Oxygen atoms in organic carbonyl compounds can be replaced by nitrogen atoms or sulfur atoms, in a particular variation of carbonyl addition reactions.

These reactions all involve the addition of a *nucleophile* to an electrophilic atom or ion. They are all nucleophilic substitution reactions.

Aliphatic systems involve chains of saturated hydrocarbons, in which carbons are attached to each other only through single bonds. Aliphatic nucleophilic substitution is the substitution of a nucleophile at a tetrahedral or sp^3 carbon.

Aliphatic nucleophilic substitutions do not play a glamourous, central role in the world of chemistry. They don't happen in every important process, the way carbonyl additions and carboxyloid substitutions appear to in biochemistry. Instead, they are ubiquitous little reactions that play important, small roles in all kinds of places.

For example, polyethylene gloycol (PEG) is a commonly used polymer in lots of biomedical applications. PEG frequently has hydroxyl groups at each end of the polymer. Capping the ends of the polymer through reaction with another group can lead to very different physical properties.

For another example, many biochemical processes require prenylation of proteins. That would involve a nucleophilic substitution in which a sulfur in a cysteine residue adds to a tetrahedral carbon in a prenyl group, replacing a phosphate group.

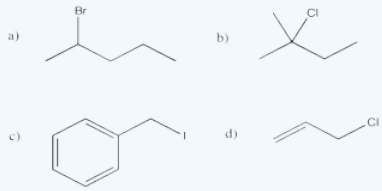
In order to be an electrophile, that tetrahedral carbon should have at least some partial positive charge on it. In the simplest cases, this electrophilic carbon is attached to a halogen: chlorine, bromine or iodine. These compounds are called alkyl halides (or alkyl chlorides, alkyl bromides and alkyl iodides).

? Exercise 4.1.1

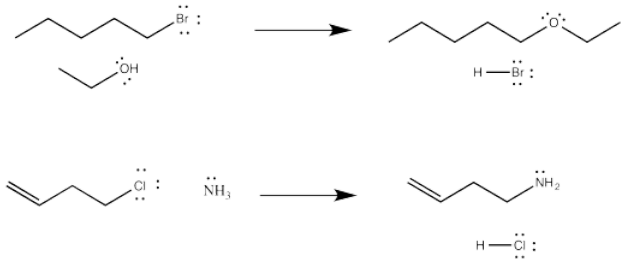
Draw structures of the following alkyl halides.

a) 2-bromopentane b) 2-methyl-2-chlorobutane c) benzyl iodide d) allyl chloride

Answer



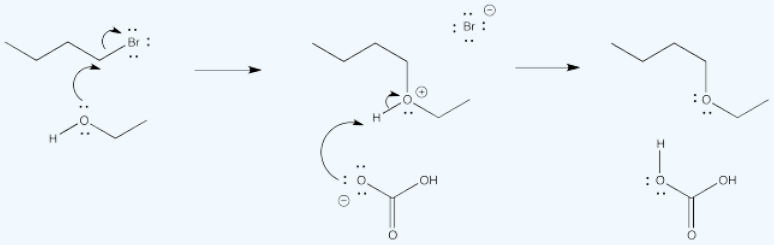
Lots of things can be nucleophiles in these reactions. Sometimes, the nucleophile is a neutral compound with a lone pair, such as ammonia or water (or, by extension, an amine or an alcohol).



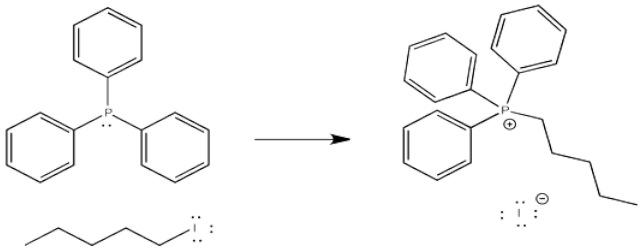
Exercise 4.1.2

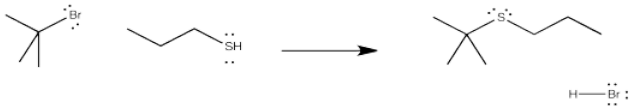
Sometimes, addition of a mild base is helpful in reactions of neutral nucleophiles. Show, with mechanistic arrows, how sodium carbonate (K_2CO_3) would play a role in the reaction.

Answer

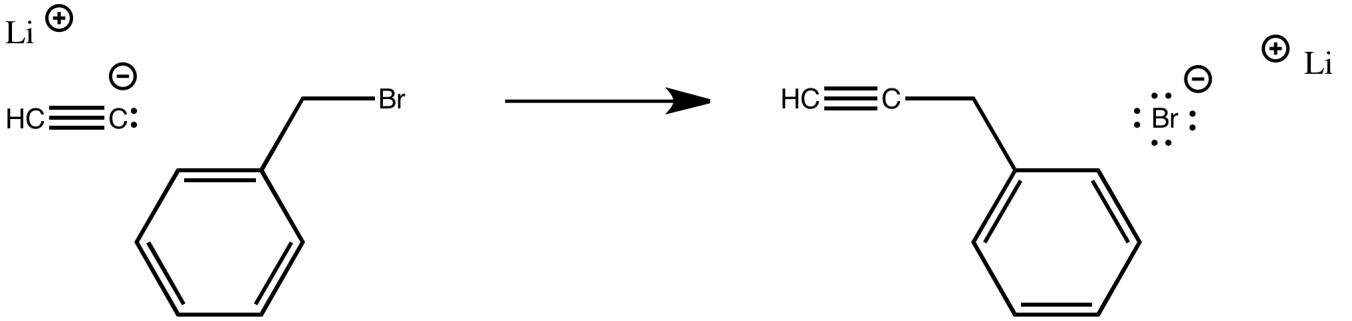


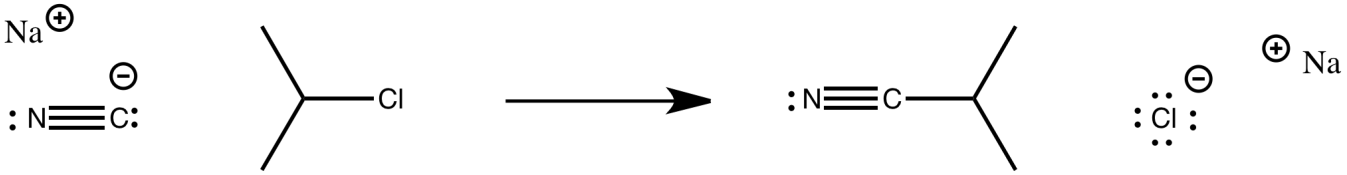
The third row analogs of these nucleophiles, in which the nucleophlic atom is a phosphorus or a sulfur, are also good nucleophiles in these reactions.





Sometimes, the nucleophile is an anion. Cyanide anion is a good nucleophile, as are the structurally similar acetylides.



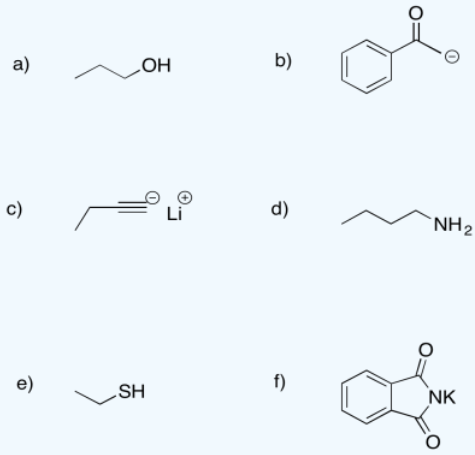


Enols, enolates and enamines are also very good nucleophiles in this type of reaction.

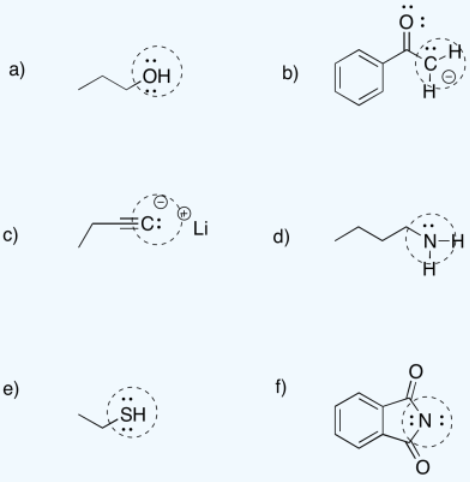
Semi-anionic nucleophiles such as Grignard (or organomagnesium) reagents and alkyl lithium reagents can sometimes act as nucleophiles in this reactions, but they are not very reliable. Complications often lead to other reactions instead. Gilman (or organocopper) reagents, in which a carbon atom is attached to a copper atom, can usually react with alkyl halides. However, they probably act via a different mechanism from the ones described in this chapter.

Exercise 4.1.3

Put a box around the nucleophilic portion of the following molecules. Note: lone pairs have not been drawn in.



Answer



4.2: Mechanism of Aliphatic Nucleophilic Substitution

Aliphatic nucleophilic substitution clearly involves the donation of a lone pair from the nucleophile to the tetrahedral, electrophilic carbon bonded to a halogen. We might expect this carbon to be electrophilic because of the halogen attached to it. For that reason, it attracts to nucleophile. However, the mechanism of the reaction might happen in a couple of different ways.

? Exercise 4.2.1

Compare the electronegativity of carbon to that of fluorine, chlorine, bromine and iodine.

a. On this basis alone, explain why the carbon attached to the halogen would be electrophilic.
b. Which compound should be most electrophilic based on electronegativity: fluoromethane, chloromethane, bromomethane or iodomethane?
c. Use the following bond strengths to estimate the qualitative trend in activation barriers for nucleophilic substitution in the four compounds in part (b): C-F 115 kcal/mol; C-Cl 84 kcal/mol; C-Br 72 kcal/mol; C-I 58 kcal/mol.
d. Fluorocarbons are quite stable towards aliphatic nucleophilic substitution; in general, they do not undergo this reaction. Explain why.

Answer a

The electronegativity of carbon (2.55 on Pauling scale) is less than that of fluorine (3.98), chlorine (3.16), bromine (2.96) or iodine (2.66).

On that basis, the carbon attached to a halogen is electrophilic because it has a partial positive charge resulting from the polar carbon-halogen bond.

Answer b

We would expect an alkyl fluoride to be the most electrophilic of these compounds, based on electronegativity.

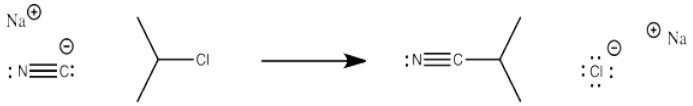
Answer c

Assuming the energy required for breaking the carbon-halogen bond plays a major role in the activation barrier (not guaranteed), we would expect the activation barrier to be lowest with the alkyl iodide, then the alkyl bromide, then the alkyl chloride and finally the alkyl fluoride. This prediction contrasts with what we might expect based on electronegativity.

Answer d

The stability of alkyl fluorides towards this reactions suggests that there is, in fact, a prominent role played by bond strengths, at least in that case. The carbon-fluoride bond is strong enough to hinder nucleophilic substitution in this compound.

In considering possible mechanisms for this reaction, we ought to think about overall bond-making and bond-breaking steps. In the addition of sodium cyanide to alkyl chloride to make an alkyl nitrile, there is one bond-making step (the C-C bond) and one bond-breaking step (the C-Cl bond). The simplest reaction mechanism would involve some combination of these steps.



Two possibilities immediately present themselves:

Mechanism A

The C-C bond forms and then the C-Cl bond breaks.

Mechanism B

The C-Cl bond breaks and then the C-C bond forms.

However, some familiarity with bonding in the second row of the periodic table may suggest to you that mechanism A is not very likely. That mechanism would require forming five bonds to carbon before the C-Cl bond eventually breaks. We can safely ignore this possibility.

Instead, there may be a third possibility to consider.

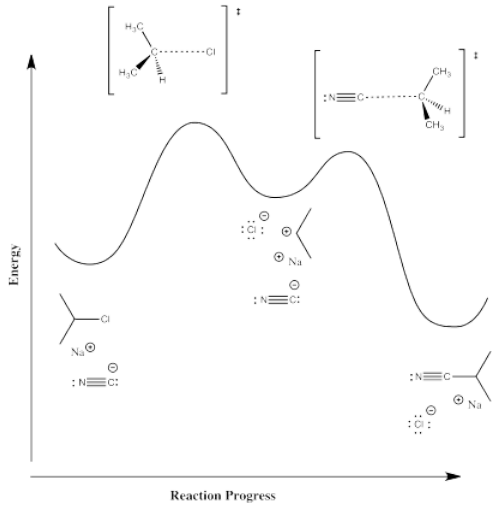
Mechanism C

The C-Cl bond breaks and the C-C bond forms at the same time.

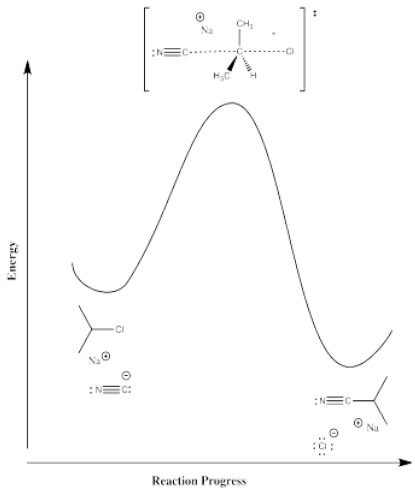
Mechanism C is a concerted mechanism; two bond-making and -breaking events happen at once. However, no octet rules are violated.

Reaction progress diagrams for these two reactions would look like the illustrations below.

Mechanism B, ionization and then addition of nucleophile:



Mechanism C, direct displacement of leaving group by nucelophile:



? Exercise 4.2.2

Compare mechanism B and C in terms of your expectations of the following parameters:

a. Activation enthalpy.
b. Activation entropy.

Answer a

In mechanism B, the dissociative one, we would expect a higher activation enthalpy. The first step, which appears to be rate determining, is a bond-breaking step, which will cost energy. In mechanism C, the bond-breaking is compensated by some bond-making; overall, this probably costs less energy.

Answer b

In mechanism B, the dissociative case, we expect a more positive entropy of activation. As the bond to the halide begins to break, the halide and carbocation fragments begin to move independently of each other, gaining degrees of freedom and increasing in entropy. In mechanism C, the incoming nucleophile appears to coordinate its motion with that of the departing halide; as a result, there are fewer degrees of freedom in this case.

There isn't necessarily a reason to believe that mechanism B is the correct mechanism and mechanism C is the wrong one, or vice versa. Either one may be possible. You may need to do some work in order to figure out which one really happens. Some experiments may help to highlight what is going on.

? Exercise 4.2.3

If charged intermediates are suspected along a reaction pathway, insight can sometimes be gained by running a reaction in a more polar solvent and comparing its rate to that of the reaction in a less polar solvent.

a. Are charged intermediates present, either in mechanism B or C?
b. Explain how each of these mechanisms might behave in a more polar solvent.

Answer a

Charged intermediates are present in the dissociative mechanism (B).

Answer b

It seems like a more polar solvent would favor both mechanisms, because both involve the interaction of an anionic nucleophile with an electrophile and loss of an anionic leaving group. However, the dissociative case (B) involves a build-up of charge in the intermediate. It is possible that a more epolar solvent could reduce the barrier to that buildup of charge separation, accelerating this mechanism.

? Exercise 4.2.4

Sometimes, a distinction between two possible mechanisms can be gained by comparing rate laws expected from each mechanism.

a. What do you think is the likely rate-determining step in mechanism B?
b. What do you expect will be the rate law for mechanism B?
c. What do you think is the likely rate-determining step in mechanism C?
d. What do you expect will be the rate law for mechanism C?

Answer a

The rate-determining step is probably the bond-breaking one (the first one).

Answer b

Because the nucleophile has not yet participated at that point, $Rate = k[R-X]$, if R-X = the alkyl halide.

Answer c

There is only one step; it is the rate-determining step, by default.

Answer d

$Rate = k[R-X][Nu]$.

4.3: Aliphatic Nucleophilic Substitution - Rate Laws

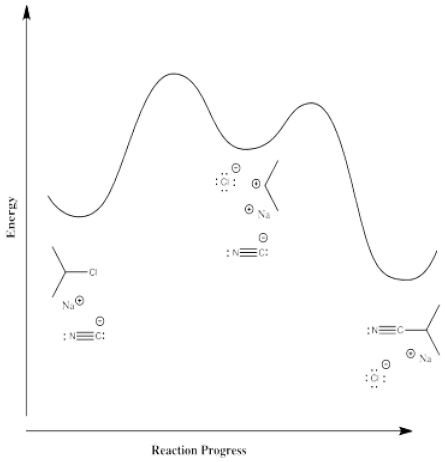
In aliphatic nucleophilic substitution, a nucleophile (abbreviated Nu) replaces a halogen "leaving group" (abbreviated LGp) from a tetrahedral carbon. Aliphatic nucleophilic substitution may take place through two different mechanisms:

- C-LGp bond breaking, followed by C-Nu bond formation.

or

- C-Nu bond formation at the same time as C-LGp bond breaking.

A look at the reaction progress diagrams for these two reactions illustrates some big differences. We will look at cyanide anion, a nucleophile, substituting for chloride in 2-chloropropane.



In the first case, some energy must be added in order to break the carbon-chlorine bond. The chlorine forms an anion, leaving a cation on the carbon. This ion pair is an intermediate along the reaction pathway. The cyanide ion then connects with this cation to form the nitrile product. Thus, there are two elementary steps in this mechanism.

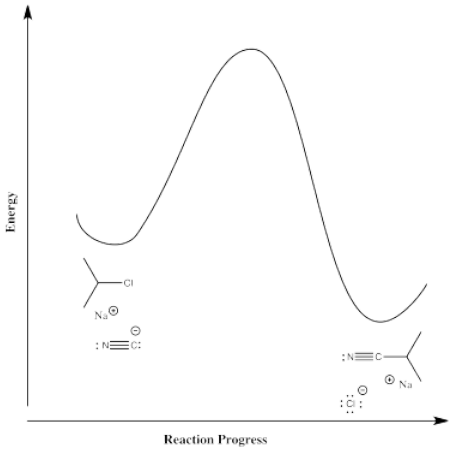
Most likely, the first step is the rate-determining step. Breaking bonds costs energy, whereas making bonds releases energy. It is hard to imagine that there could be a significant barrier to the second step; the anion and cation should come together almost automatically.

The rate law for this stepwise mechanism is:

$$Rate = k[PrCl]$$

that is, the rate depends on the first elementary step, but not on the second one. The second step happens pretty much automatically as soon as the first one has finally gotten around to happening.

In the second case, the nucleophile displaces the chloride directly in one step. There is only one elementary step in this reaction, and it requires both compounds to come together at once.



The rate law for this concerted mechanism is:

$$Rate = k[PrCl][^{-}CN]$$

These two rate laws are very different, and offer an additional way for us to tell how this reaction is taking place. In principle, if we try the reaction with different concentrations of cyanide (but keep the 2-chloropropane concentration constant), we can see whether that has an effect on how quickly the product appears. If it has the predictable effect, maybe the reaction happens in one step. If not, maybe it is a two-step reaction.

Because the rate laws for these two mechanisms are so different, there has arisen a catchy shorthand for describing these reactions based on their rate laws, coined by C.K. Ingold. The rate of the stepwise reaction depends only on one concentration and is referred to as a "unimolecular reaction"; Ingold's shorthand for this kind of nucleophilic substitution was "S_N1".

The rate of the concerted reaction depends on two different concentrations and is referred to as a bimolecular reaction; Ingold's shorthand for this reaction was "S_N2".

? Exercise 4.3.1

Suppose you run this reaction with three different concentrations of cyanide: 0.1 mol/L, 0.2 mol/L and 0.3 mol/L. You keep the 2-chloropropane concentration constant at 0.05 mol/L.

a. The reaction turns out to be proceeding via a S_N1 mechanism. Plot a graph of rate vs.[$^{-}$CN].
b. The reaction turns out to be proceeding via a S_N2 mechanism. Plot a graph of rate vs.[$^{-}$CN].

Now you switch things up and run this reaction with three different concentrations of 2-chloropropane: 0.1 mol/L, 0.2 mol/L and 0.3 mol/L. You keep the 2-chloropropane concentration constant at 0.05 mol/L.

c. The reaction turns out to be proceeding via a S_N1 mechanism. Plot a graph of rate vs.[^{i}PrCl].
d. The reaction turns out to be proceeding via a S_N2 mechanism. Plot a graph of rate vs.[^{i}PrCl].

Why would the mechanism proceed in one way and not the other? Molecular choices between pathways like this are often described on the basis of "steric and electronic effects"; in other words, it's either something to do with charge or something to do with crowdedness. We will see soon how these effects can influence the course of the reaction, and how the mechanism can itself have consequences in the formation of different products.

? Exercise 4.3.2

How might crowdedness or steric effects influence the pathway taken by the reaction between cyanide and 2-chloropropane?

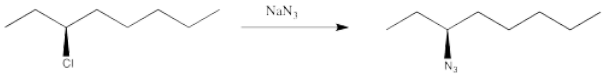
? Exercise 4.3.3

How might charge stability influence the pathway taken by the reaction between cyanide and 2-chloropropane?

4.4: Stereochemistry

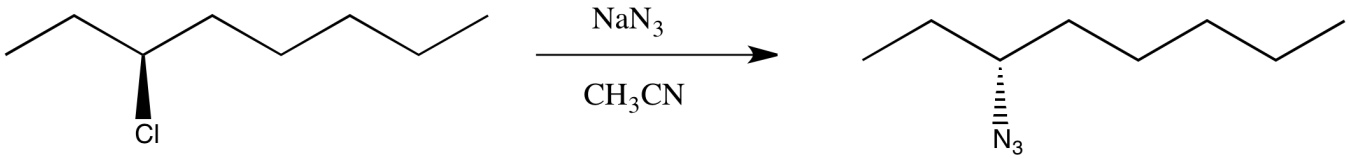
Apart from measuring rates of reaction and deducing the rate law, there are other lines of evidence that can suggest how the reaction is occurring. For aliphatic nucleophilic substitution, stereochemistry of the products provides some additional evidence.

Suppose you carry out a nucleophilic substitution reaction using a chiral starting material. You decide to convert (*S*)-3-chlorooctane into the corresponding azide. Azides are pretty widely used reagents (but slightly dangerous and potentially explosive). They are employed in a class of reactions called "click chemistry"; you've just heard about these reactions and you want to try one out for yourself.



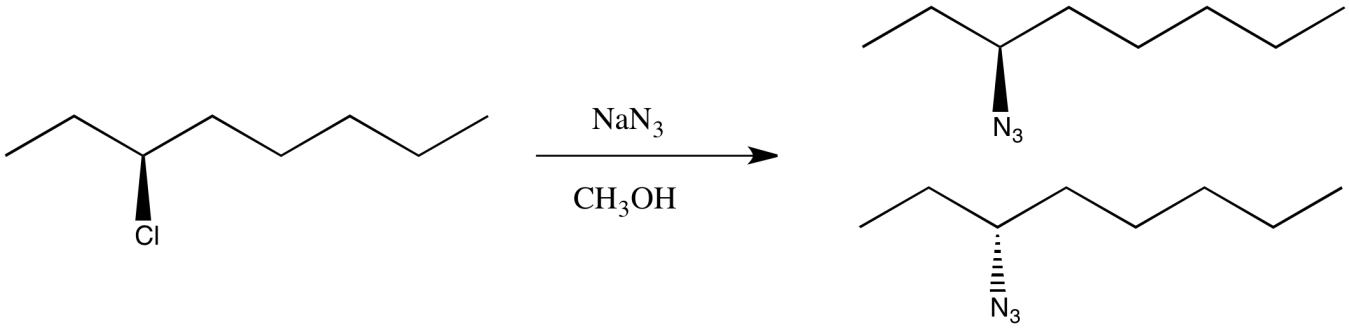
You have complete control over the mechanism of the reaction (not so easy in reality, but in this thought experiment you can set the dial on your stir plate to the desired mechanism). You choose to make the reaction occur through an S_N2 pathway.

You know the product will be chiral, so you plan to check its optical rotation. The trouble is, once you have finished the reaction, the optical rotation is exactly the opposite of what you were expecting, based on the values of other compounds like this one. You did the reaction successfully but got the unexpected enantiomer.



You're not worried. You've been taking this nifty chemistry class and you have an idea of something else to try. This time you select an S_N1 pathway.

You finish the reaction and get the right product, but it shows no optical rotation whatsoever. This time you got a racemic mixture.



This is just a thought experiment, but what would it all mean? Why might changing mechanism influence the stereochemistry?

This is just a thought experiment, but the results are generally true: in an S_N2 reaction, the chiral center undergoes an inversion. The three-dimensional arrangement of groups around the chiral center is the opposite of how it started. In an an S_N1 reaction, the chiral center undergoes racemization. There is a 50:50 mixture of enantiomers.

? Exercise 4.4.1

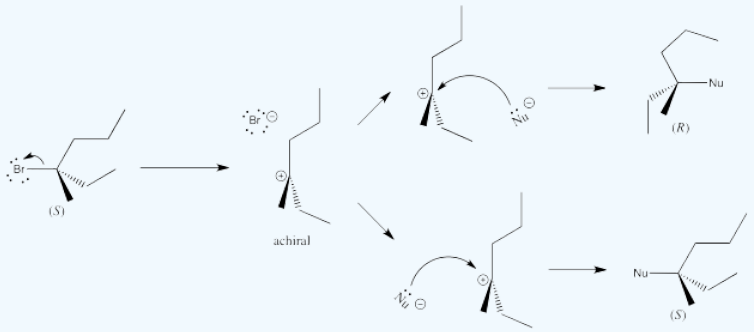
a. Propose reasons why the stereochemistry would flip in an S_N2 reaction. A drawing will help.
b. Propose reasons why an equal mixture of stereoisomers would result from an S_N1 reaction. A drawing will help.

Answer

Exercise 4.4.2

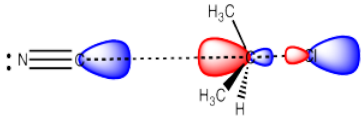
You may have noticed that two different solvents were used in the two reactions above. Propose a reason why this change in solvent may lead to a change in mechanism.

Answer



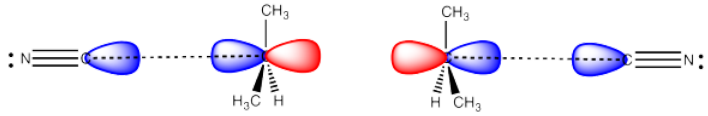
In an S_N2 reaction, the nucleophile donates electrons to the electrophilic carbon, displacing the leaving group from the other side. The nucleophile donates its electrons to the lowest unoccupied molecular orbital, which displays a lage lobe on the side of the carbon opposite the leaving group.

As a result, the nucleophile always approaches from the opposite side of the electrophilic carbon as the location of the leaving group, and ends up on the opposite side from where the leaving group group was.



- S_N2 reactions at chiral centers lead to reversal or "inversion" of the chiral center.

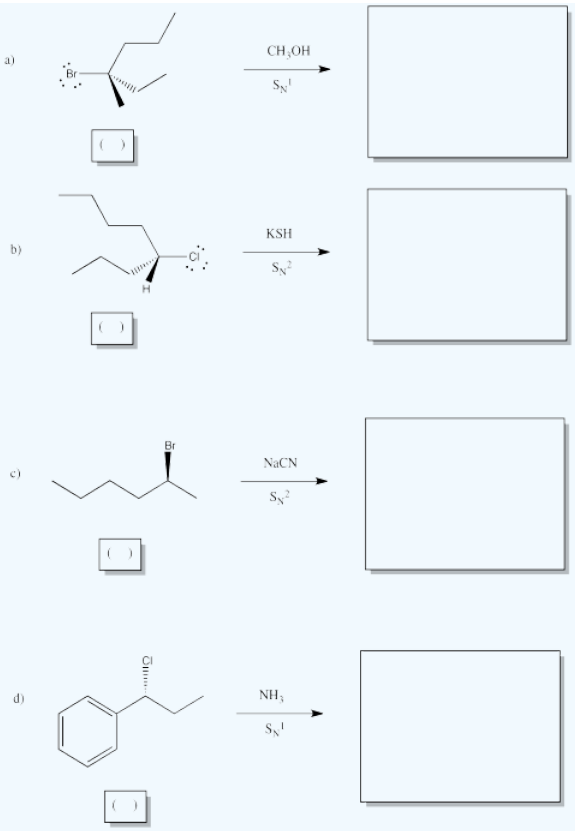
On the other hand, in an SN1 reaction, the nucleophile enters only after the leaving group has left. At that point, the electrophilic carbon is a cation, so it is trigonal planar because it only has three groups attached to it. The nucleophile could easily approach from either side.



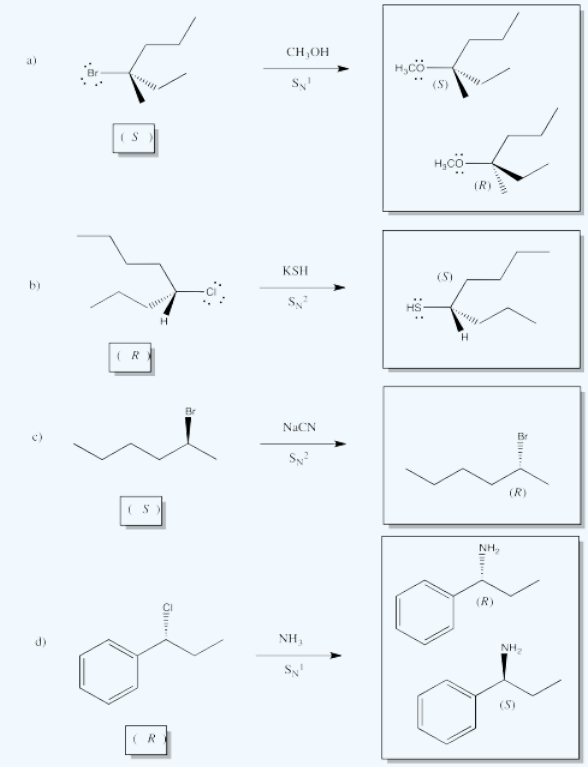
S_N1 reactions at chiral centers lead to racemic mixtures.

Exercise 4.4.3

Show the products of the following reactions, and indicate stereochemical configuration of bothe the starting material and the product in each case.



Answer



? Exercise 4.4.4

The lesson here can be restated as follows: the mechanism affects the stereochemical outcome of the reaction. Explain why that fact is important in the context of making a chiral drug for the pharmaceutical market.

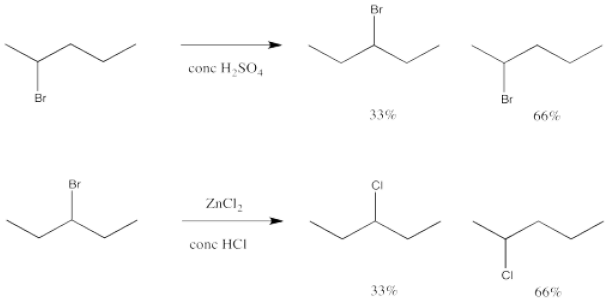
4.5: Regiochemistry

Regiochemistry is the term for where changes take place in a reaction. It can be another indication of how the reaction occurred.

In aliphatic nucleophilic substitution, the answer seems pretty obvious: the reaction takes place at the electrophilic carbon, the one attached to the electronegative halogen. That's where the leaving group is. When the leaving group is replaced, that's where the nucleophile will be. But this isn't always true.

- In an S_N2 reaction, the nucleophile is always found on the carbon where the leaving group used to be.
- In an S_N1 reaction, the nucleophile is usually found on the carbon where the leaving group used to be. Sometimes it moves.

Under some circumstances, unexpected changes occur. The following two reactions are examples of such surprises. These reactions happen to take place via an S_N1 mechanism.



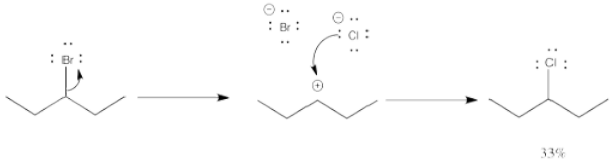
So, the regiochemistry of this reaction may be more complicated than we thought.

What is happening in these two reactions? In one of them, the bromine is just hopping from one place to another along the molecule. Some of the original compound remains, too, so there is a mixture. If you look carefully, though, the bromine has switched places with a hydrogen atom. It doesn't seem like that hydrogen atom could come off very easily.

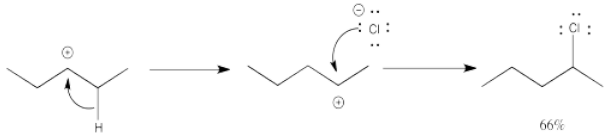
In the other reaction, something very similar is happening. Bromide and chloride both have lone pairs, so they can both be nucleophiles as well as leaving groups, and one can replace the other. There is lots of chloride around, so it beats any bromide to the electrophilic carbon. Once again, though, some of the chloride seems to end up in the wrong place.

This sort of behaviour is characteristic of carbocations. It is called a rearrangement, in which part of the molecule unexpectedly switches places.

Again, one of the products forms in a simple enough way.



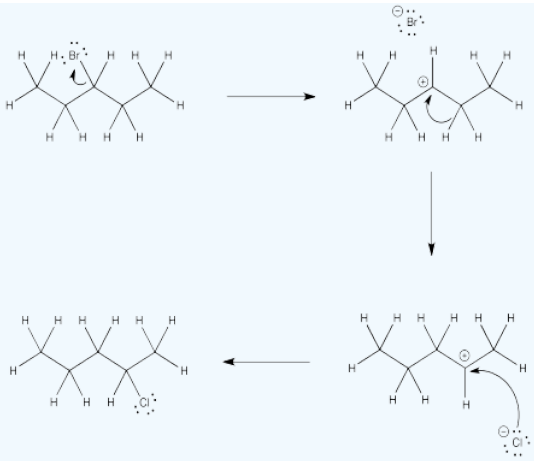
The formation of the other product involves a "1,2-hydride shift". In this event, a hydrogen anion hops from one carbon to the next, leaving a cation where it used to be.



Exercise 4.5.1

Draw the reaction above with all the hydrogens drawn in the structures, to confirm the formal charges and the positions of the hydrogens.

Answer

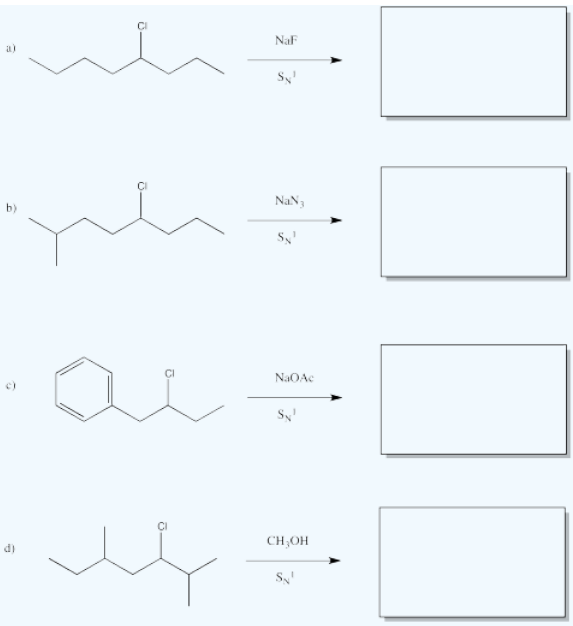


Exercise 4.5.2

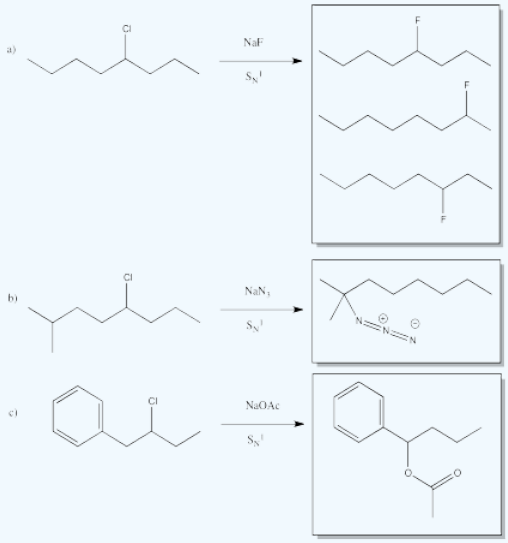
Explain the observed product ratios in the above reaction.

Exercise 4.5.3

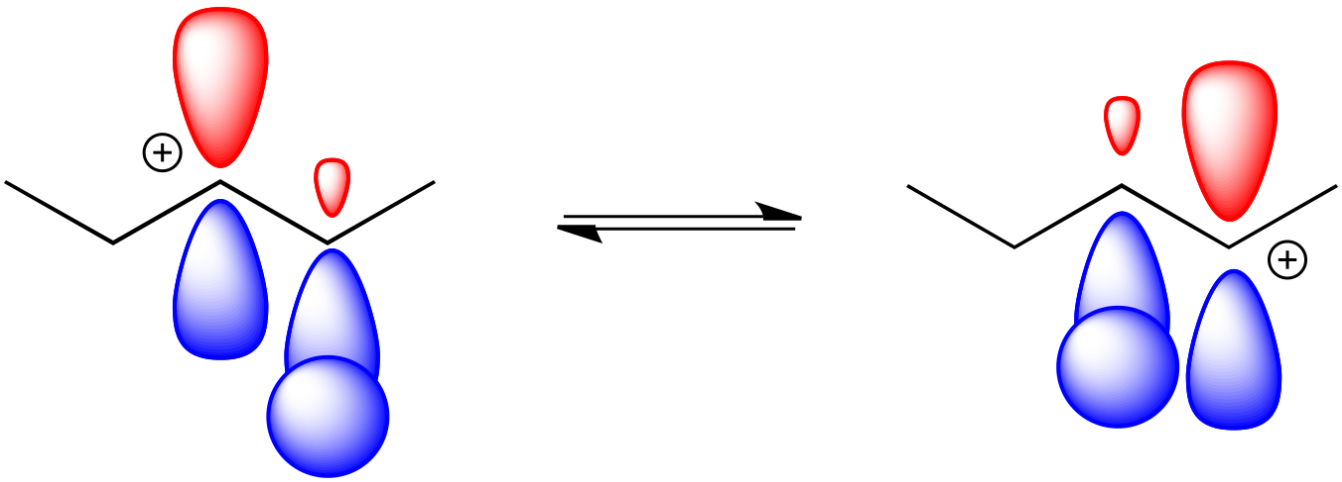
Predict the products of the following reactions.



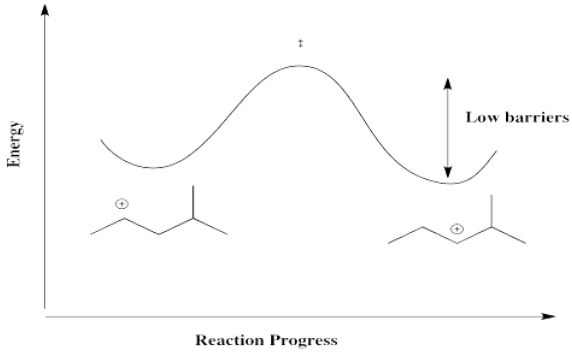
Answer



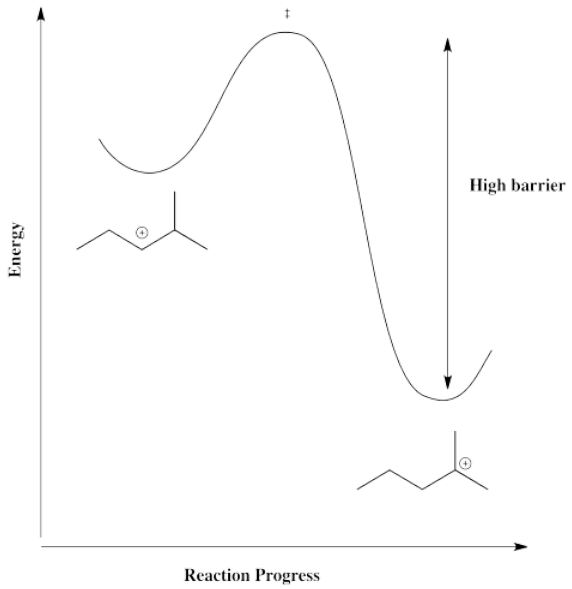
The hydride can hop one carbon away because of the proximity to the empty p orbital with which it can overlap and form a new bond.



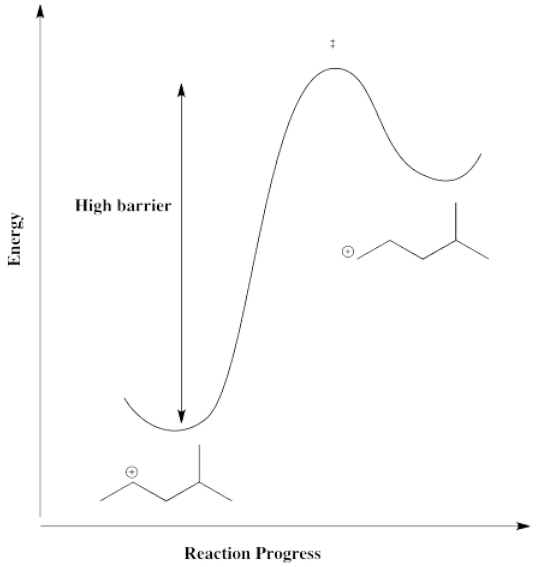
The barrier for a hydride shift is not very high, provided a carbocation is available on the very next carbon. As a result, an equilibrium between cations is established pretty quickly. Below, there is an equilibrium between two secondary cations on the 2-methylpentyl skeleton.



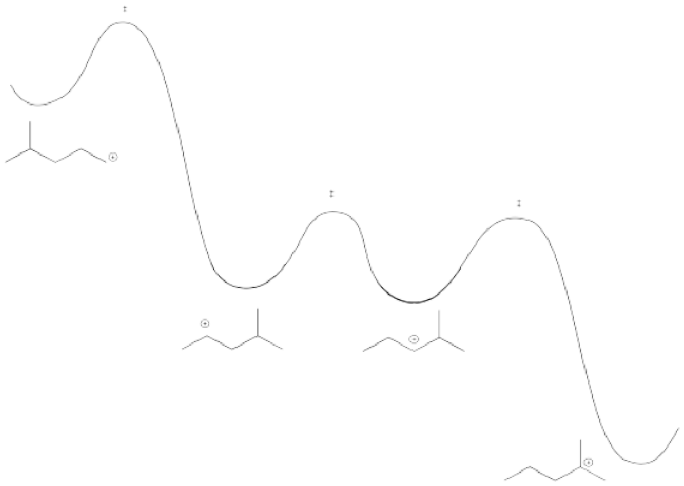
However, that particular structure has another possible cation that is more stable. Once a tertiary cation forms, the hydride isn't likely to hop back.



On the other hand, there is also a primary position. A hydride shift could give a primary cation, but that isn't likely to happen, because it would be too far uphill.

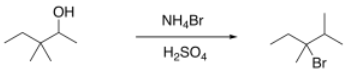


Altogether, there is an energy surface linking several different possible cations. In this case, however, one tertiary cation would quickly dominate.



It isn't just hydride ions that are able to undergo 1,2-migrations. Alkyl anions (such as methyl, CH_3^-) and aryl anions (such as phenyl, $C_6H_5^-$) can also undergo 1,2-shifts, rearranging to give stable cations.

For example, the following reaction is apparently just a substitution of a bromo group for a hydroxy group. The regiochemistry indicates a cation was formed, however, because the new group is found at the site of the most stable carbocation.



The mechanism here involves protonation of the hydroxy group; the reaction takes place in strong, concentrated acid. The resulting cation is able to undergo a 1,2-methyl shift leading to a new carbocation. The bromide ion connects at that new position.

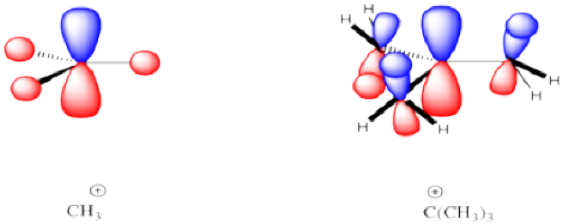
4.6: Structural Factors Influencing the Mechanism

If two possible mechanisms can occur, there may be some factors that have an influence on the course of the reaction, tipping it one way or the other. One of the most important factors determining the mechanism of aliphatic nucleophilic substitution is the structure of the alkyl halide.

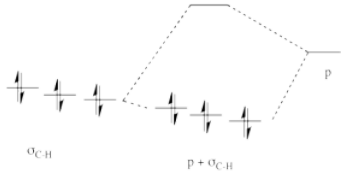
The S_N1 mechanism involves formation of a carbocation. Ion stability is often a very important factor influencing how easily a reaction occurs. It stands to reason that, the more stable the cation that forms, the more easily an S_N1 mechanism can occur.

There is a simple trend that more substituted carbocations are more stable than less-substituted ones. By more-substituted, we mean carbocations in which the carbon bearing the positive charge is attached to more carbons and fewer hydrogens. A tertiary carbocation is more stable than a secondary, a secondary is more stable than a primary carbocation, and a primary is more stable than a methyl cation.

This trend is usually explained by hyperconjugation in the more substituted cation. In hyperconjugation, neighbouring σ-bonding orbitals overlap with the empty π-orbital that is the center of the carbocation.



That electronic donation from the occupied σ-bonding orbitals helps delocalize the positive charge, lowering the positive charge on the central carbon and placing a little of it on the surrounding ones. Energetically, the interaction is favorable because the electrons in the σ-bonding orbitals are lowered stabilized by delocalization.

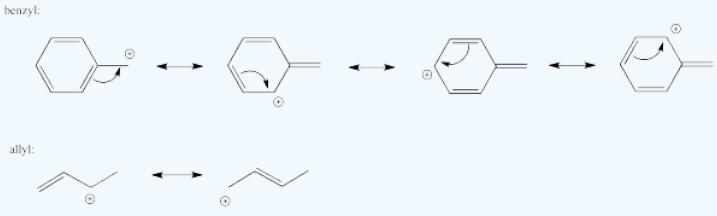


Overall, S_N1 reactions occur much more easily when the halide is attached to a more substituted carbon. The resulting carbocation forms more readily in what is otherwise the hardest step in the reaction. S_N1 reactions occur most easily at tertiary carbons, moderately well at secondary ones, and very sluggishly at primary ones, if at all.

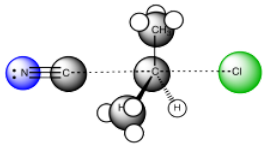
? Exercise 4.6.1

Although they may be considered primary alkyl halides, compounds like benzyl chloride and allyl bromide are capable of undegoing S_N1 reactions. Show why.

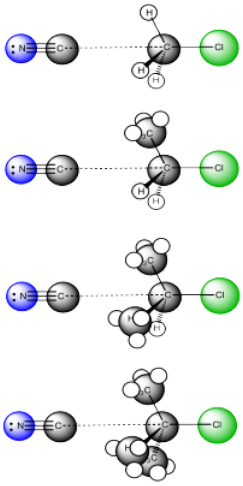
Answer



S_N2 reactions do not undergo highly charged intermediates, so ion stability is less important in that pathway. On the other hand, there is a stark contrast between S_N1 reactions and S_N2 reactions in terms of steric effects. S_N1 reactions occur via a trigonal planar intermediate, which is less sterically crowded than the starting material. S_N2 reactions do not occur via an intermediate, but the transition state through which they proceed is actually five-coordinate; the electrophilic carbon gets more crowded as the reaction proceeds. Steric effects are much more important in this concerted pathway.



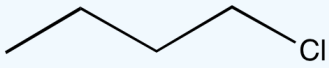
Comparing the approach to the transition state in a series of alkyl halides of different substitution, we can see some steric differences. The pictures shows a snapshot very early in the reaction, when the nucleophile is just approaching the electrophile but the reaction is not really committed yet. Comparing these pictures, it seems most likely that the nucleophile will keep going forward in the top case, with the methyl. In the bottom case, with the tertiary halide, chances are that the nucleophile will just bounce off the methyl groups before it can connect with the electrophilic carbon.

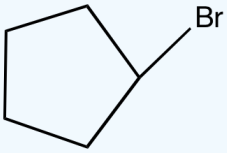


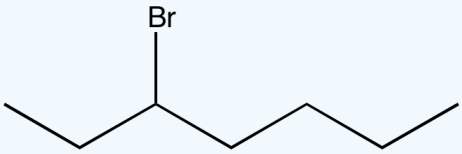
As a result, S_N2 reactions are more likelyto occur with less substituted alkyl halides. They occur very easily with methyl halides and primary alkyl halides. They occur moderately well at secondary alkyl halides, but only with difficulty at tertiary alkyl halides.

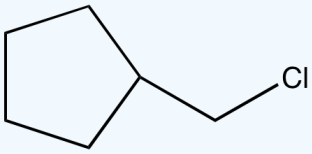
? Exercise 4.6.2

In each of the following cases, is nucleophilic substitution likely to proceed via an S_N1 or an S_N2 reaction?

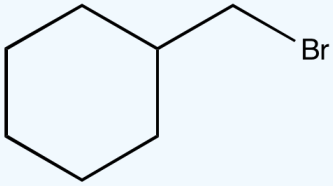
a) 

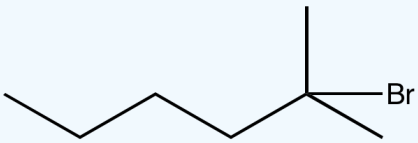
b) 

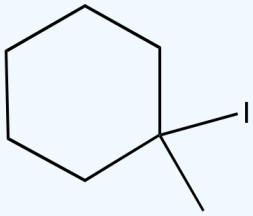
c) 

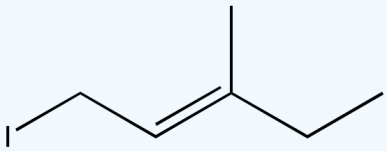
d) 

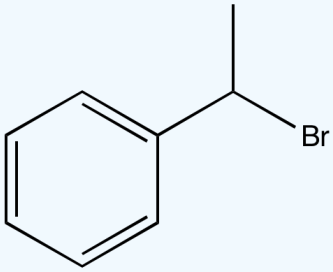
e) CH_3Br

f) 

g) 

h) 

i) 

j) 

Answer a

Keep in mind that there are other factors that can influence the reaction pathway; what we have here are just the most likely mechanisms.

S_N2

Answer b

Both pathways are very possible

Answer c

Both pathways are very possible

Answer d

S_N2

Answer e

S_N2

Answer f

S_N2

Answer g

S_N1

Answer h

S_N1

Answer i

S_N1

Answer j

S_N1

4.7: Solvent Effects

There are often several factors that can influence the course of a reaction. Probably the most important is the structure of the alkyl halide, but the solvent can also play a role.

The crucial difference between S_N1 and S_N2 reactions is the ionization step in the S_N1 pathway. Factors that stabilize ions, and assist in ionization, promote this pathway.

In general, more polar solvents are often helpful in nucleophilic substitutions; the nucleophile may be an ionic compound itself, and a more polar solvent will help it to dissolve. However, especially polar solvents may provide additional stability to ions.

The most polar solvents tend to be those that are capable of hydrogen bonding, such as water and alcohols. These are sometimes called "polar, protic solvents". The "protic" part refers to hydrogen bonding; in hydrogen bonding, the hydrogen atom attached to a very electronegative oxygen or nitrogen develops a significant positive charge, like a proton.

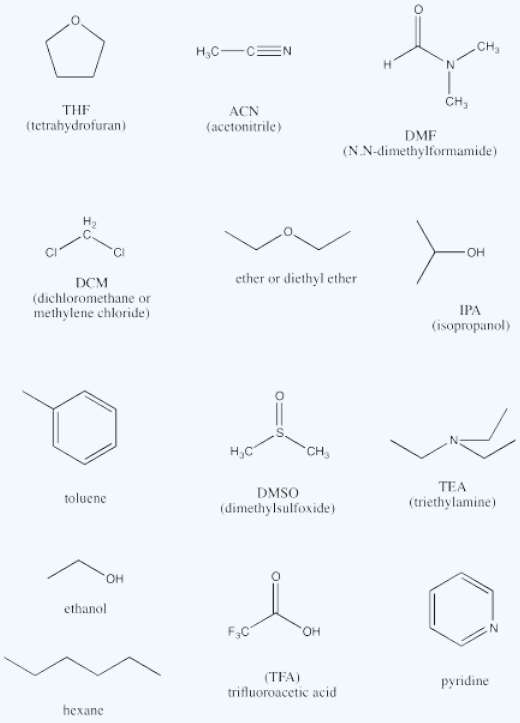
Polar, protic solvents can stabilize ions through very strong intermolecular attractions. The protic hydrogen can strongly interact with anions, whereas the lone pair on the oxygen atom can stabilize cations.

These stabilizing interactions can strongly stabilize the intermediates in S_N1 reactions. In the same way, the transition state leading into the intermediate is also significantly stabilized. The barrier for this reaction is lowered and the reaction can occur more quickly.

In addition, polar, protic solvents may play an additional role in stabilizing the nucleophile. If the nucleophile is stabilized, it is less likely to react until a sufficiently strong electrophile becomes available. As a result, polar, protic solvents may also depress the rate of S_N2 reactions. Once the alkyl halide ionizes and a more attractive electrophile becomes available, the nucleophile can spring into action.

? Exercise 4.7.1

The following are a baker's dozen of potential solvents.



a. Identify the protic solvents in this group.
b. Identify the completely non-polar solvents in this group.
c. Identify the polar, aprotic solvents.
d. Rank the polar solvents from most polar to least polar.
e. Identify two basic compounds, frequently used to facilitate proton transfers in reactions.

Answer a

ethanol, isopropanol, trifluoroacetic acid

Answer b

hexane, toluene

Answer c

THF, acetonitrile, DMF, dichloromethane, ether, DMSO, triethylamine, pyridine

Answer d

DMSO > DMF > ACN > pyridine > DCM > THF > ether > TEA, based on dielectric constants. In general, the ones with multiple bonds between two different atoms are the most polar.

Answer e

pyridine and triethylamine. The lone pair on the nitrogen atom is basic toward protons. The trend in basicity is triethylamine > pyridine >> acetonitrile; as the percent s character in the lone pair increases, the electrons are lower in energy and less available for donation.

? Exercise 4.7.2

Describe the S_N1 reaction as slow, medium or fast in the following cases.

a. NaCN and $PhCH_2Cl$ in acetonitrile, CH_3CN.
b. NaSH and 2-bromo-2-methylheptane in methanol.
c. KI and 1-chloropentane in 2-propanol.

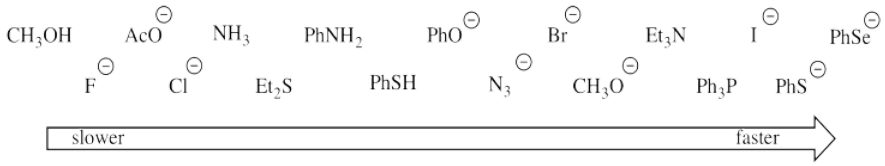
? Exercise 4.7.3

Describe the S_N2 reaction as slow, medium or fast in the following cases.

a. $LiCCCH_3$ and 2-bromopentane in THF.
b. NaN3 and 3-chloro-3-methyloctane in DMF.
c. LiOPh and 1-bromohexane in methanol.

4.8: Nucleophilicity

The nucleophile can sometimes play a pronounced role in nucleophilic substitutions. The following relative rates have been observed when these nucleophiles reacted with methyl bromide in methanol:



note: Ph = phenyl, C_6H_5; Ac = acetyl, $CH_3C{=}O$; Et = ethyl, CH_3CH_2.

Presumably, some of the species react much more quickly with methyl bromide because they are better nucleophiles than others.

Exercise 4.8.1

Sometimes we can draw general conclusions about kinetic factors by looking at sub-groups among the data. Determine how the following factors influence nucleophilicity (the ability of a species to act as a nucleophile). Support your ideas with groups of examples from the data (preferably more than just a pair of entries).

a. charge on the nuclophile
b. size of the atom bearing the charge
c. electronegativity of the atom bearing the charge
d. delocalization of charge

Exercise 4.8.2

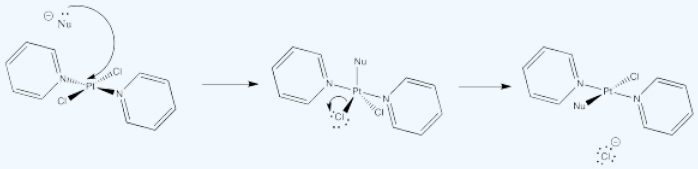
Nucleophilicity plays a strong role in the rate of one type of substitution mechanism, but not the other.

a. In which mechanism is it important? Support your idea.
b. Is the reaction of methyl bromide likely to proceed via this mechanism? Why or why not?

Exercise 4.8.3

A trend very similar to the data above is found in substitution reactions of py_2PtCl_2 (py = pyridine) in methanol. Draw a mechanism for this substitution and explain why nucleophilicity plays an important role.

Answer



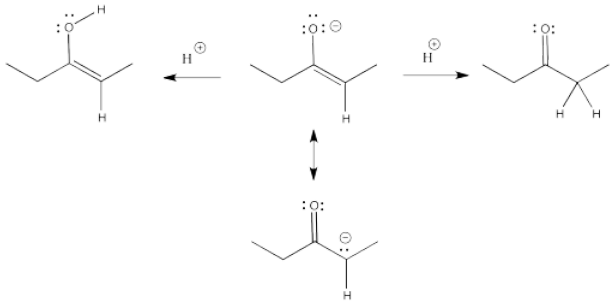
Exercise 4.8.4

Very fast nucleophiles are sometimes more likely to undergo S_N2 reactions than S_N1 reactions. Explain why.

4.9: Enolate Nucleophiles

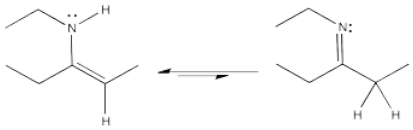
Enolates and related nucleophiles deserve a closer look because they are very common and because they have their own issues of regiochemistry.

Remember, an enolate is just the conjugate base of an enol. An enolate can also be thought of as the conjugate base of a related carbonyl. Because the enolate is a delocalized anion, it can be protonated in two different places to get two different conjugates.

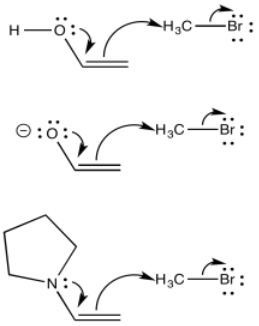


Enols typically are not seen because of a rapid equilibrium with that related carbonyl compound. As soon as an enol forms, if there is any way for it to transfer a proton to get to the carbonyl, it will do so. This kind of equilibrium is called "tautomerism", involving the transfer of one proton from one place to another within the molecule. The enol and its related carbonyl are referred to as "tautomers". "Tautomers" describes the relationship between these two molecules.

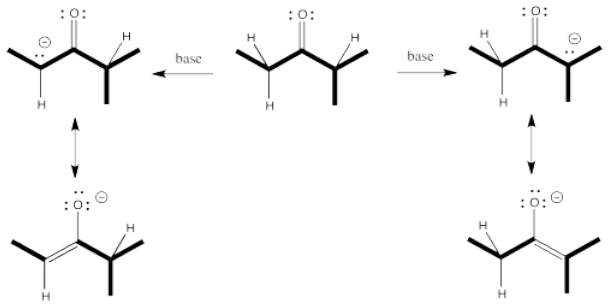
Enamines are very similar to enolates, but with a nitrogen atom in place of the oxygen. Hence, they are amines instead of alcohols.



Enamine, enolates and enols are all turbo-charged nucleophiles. The nucleophilic atom is the alpha carbon. Although that carbon can be thought of as a double bonded carbon, with no lone pair, that position is motivated to donate electrons because of pi donation from the oxygen (or nitrogen).



One of the issues with these nucleophiles has to do with asymmetry about the carbonyl (or the would-be carbonyl). If one alpha position next to the carbonyl isn't the same as the other one, two possible enolates could result from removal of a proton.

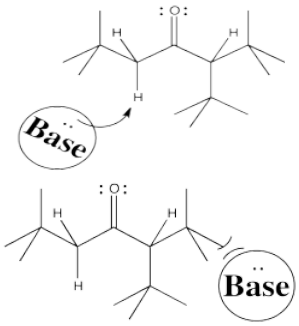


That means we potentially have two different nucleophiles from the same starting compound. Sometimes, mixtures of products result from enolate reactions.

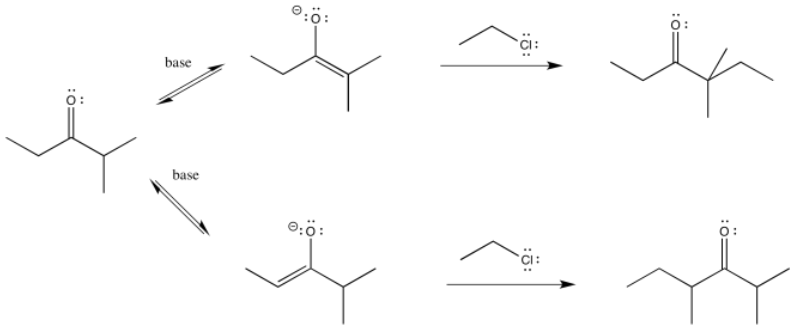
Nevertheless, enolates and enamines are very broadly used in the synthesis of important things like pharmaceuticals, precisely because they can be controlled so well. If you want the enolate on one side of the carbonyl -- we'll call it the more-substituted side -- then you can have it. If you want the enolate on the other side of the carbonyl -- the less-substituted side -- you can have that, instead.

To get the proton off and turn a carbonyl compound into an enolate requires a base. Some control over which proton is removed might come from the choice of base. Let's think about what is different about those two sides of the carbonyl. One side is more substituted. It has more stuff on it. It's more crowded. Maybe to get the proton off the more crowded position, you need a smaller base.

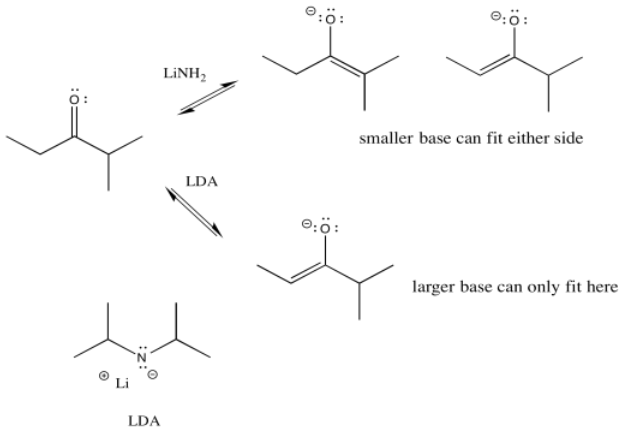
Conversely, to get the proton exclusively from the least crowded position, and have very little chance of getting it from the more crowded spot, you could use a really big base.



So let's go all the way through a reaction, looking at two possible nucleophilic substitution products. Suppose we take 2-methylpentan-3-one, deprotonate it to make an enolate anion, and add chloroethane to complete the reaction. The overall reaction is called an α-alkylation, because the alkyl electrophile that is added goes to the alpha position, next to the carbonyl.



You can see the two different products of the reactions: one of them is 4,4-dimethylhexan-3-one. The other one is 2,4-dimethylhexan-3-one. From what we have said so far, if we use a big base, maybe it won't fit as well on the more hindered side (the top pathway above), so it will go to the least-hindered side (the bottom path).



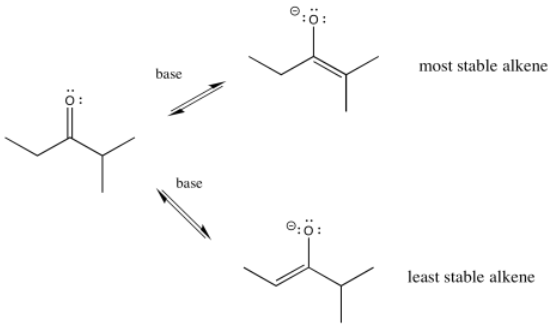
We can make the base bulkier by adding alkyl substituents. If it just has little hydrogens attached to the basic atom, it won't be very crowded. Also, in this case we used amide bases because they are very strong bases. (Amide is the inorganic chemistry term for the conjugate base of ammonia, or NH_2^-.) There is an equilibrium between a ketone and an enolate. A stronger base pushes the equilibrium all the way to the enolate side, with no leftover ketone.

- Bulky bases can promote deprotonation on the least substituted side (the least crowded side) of the carbonyl.

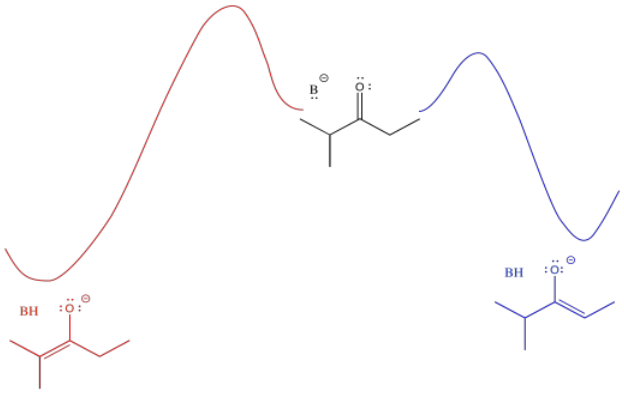
So if we need to take the lower pathway, we have found a way to do it. LDA (lithium diisopropylamide) will take the least hindered proton and alkylation will occur on that side. The trouble is, the much smaller lithium amide can fit on either side. It has no preference, so it leads to a mixture of products.

How can we force things through the upper pathway?

There's something else about enolates that is apparent only when you look at the ions in one resonance form. Enolate ions can be thought of as alkenes, of course. Depending on which proton we remove, we get two different alkenes. There may be factors that make one of these two alkenes more stable. If so, there may be ways to form that one instead of the other.



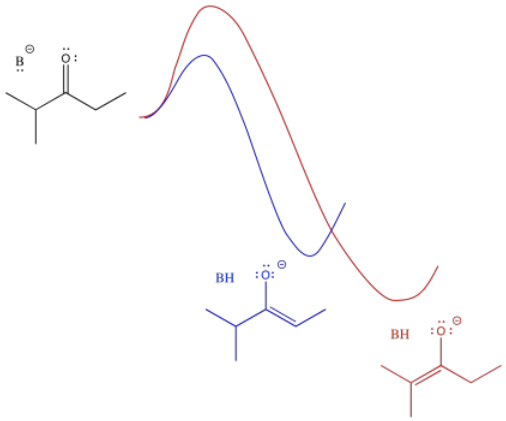
In general, more-substituted alkenes are more stable than less-substituted ones. The more substituted alkene is formed via loss of the proton at the more crowded position. Enolate stability should influence things, and it does, but there are some subtleties involved. To understand the subtleties, we are going to need to look at the potential energy diagram for enolate formation.



The barrier might be a little higher going from the middle of the picture to the left than going from middle to right (it's more crowded, after all). However, once the reaction gets over that barrier, it settles out in a more stable place (the enolate is more stable). An initially greater investment, in this case, yields a greater return in the end.

- The thermodynamic product refers to the one that is more stable. In this case, it also happens to be harder to get to, becuas eof a higher barrier.
- The kinetic product refers to the one that is formed more easily, because of a lower barrier. in this case, it also happens to be less stable.

An alternative view of that surface places the reactant on the left and both products on the right. The two possible pathways are then superimposed on each other. The conclusion we draw is the same: the barrier is higher along the red path than the blue path because of steric hindrance. Eventually, the red path leads to the lower energy product.



Just looking at the diagram, we can infer that it takes more energy to get over the barrier leading to the more stable enolate. If we supply more energy to start with, we might have a better chance of reaching the more stable enolate. Of course, the easiest way to do that is to heat the reaction up. If we don't want to form the more stable enolate, we could cool the reaction down. That way, there wouldn't be enough energy to get to the more stable enolate.

- Warmer temperatures can lead to formation of the thermodynamic product.
- Colder temperatures will encourage formation of the kinetic product.

Forming a product based on its relative stability means relying on thermodynamics. Getting to the thermodynamic product means you have to give the system a chance to find its way there. One way to do that is to allow the deprotonation to happen reversibly. Given multiple chances, the more stable enolate will form eventually.

- Time is a key factor in forming the thermodynamic product. The longer the reaction time, the more likely the system will eventually reach the most stable position.

An obvious way to allow reversibility is to conduct the reaction in a protic solvent, such as ethanol. If the enolate takes a proton from ethanol, it becomes a ketone again. It has a second chance to get deprotonated again. Eventually, it should form the most stable enolate.

- Protic solvents allow reversibility in enolate formation. Conducting enolate formation in a protic solvent should allow eventual formation of the more stable enolate.

On the other hand, if you intend to take the proton off the least substituted position, you don't want any reversibility. Given the chance, the wrong enolate will eventually form. You want to just take what you get the first time, which is more likely to be the blue pathway because of its lower barrier. Earlier, we used a bulky amide base to form the least stable enolate because we didn't want to allow the possibility of second chances.

This is a case in which we need kinetic control to get one product: we want the least-substituted enolate, and we depend on it forming more quickly than the ther enolate. After all, if the other enolate forms, it is more stable; it isn't likely to come back.

- Base strength can be important in formation of a thermodynamic enolate. A strong base, such as hydroxide or alkoxide, forms a protic conjugate acid that could easily reprotonate the enolate.
- A very strong base, such as amide, forms a protic conjugate acid that is much less likely to reprotonate the enolate.

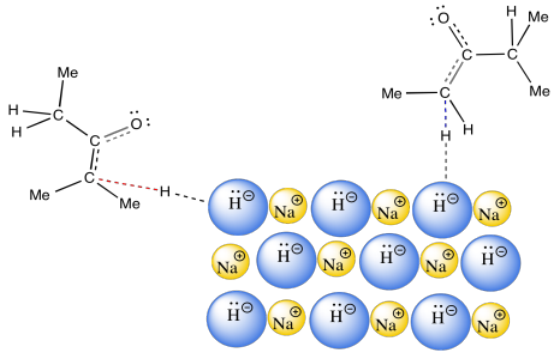
There are some even more subtle factors that are used to help things along just a little bit more. For example, the counterions for the bases can have a modest effect one way or the other. The effect has to do with the degree of covalency between the counterion and the enolate. For example, lithium is a smaller, harder alkali ion that forms strong bonds with oxygen. Potassium is a larger, softer alkali ion that forms weaker bonds with oxygen. We are just using these terms in a relative way; lithium and potassium ion are both hard, but lithium ion is even harder than potassium ion.

If the enolate is bound to its counterion, it is less likely to undergo reversal to the ketone. Lithium counterions are sometimes used to promote formation of the kinetic enolate. Potassium counterions are sometimes used to promote formation of the thermodynamic enolate.

- Smaller counterions like lithium promote formation of the kinetic enolate; larger counterions promote the formation of thermodynamic enolates.

There is one final factor to talk about, which comes up in the case of sodium hydride. The use of sodium hydride generally leads to the thermodynamic enolate. That may be a surprise. After all, sodium hydride is a very strong base. We would not expect the counterion, H_2, to be acidic. That means the use of sodium hydride allows only one chance to get to the thermodynamic product. So how does NaH manage to do that?

The answer appears to be related to phase. NaH is an insoluble solid. As a result, the reaction between NaH in the solid phase and the ketone in the solution phase happens only at the surface of the NaH. This reaction is very slow. It happens over a long period of time. Remember, time was one of the factors that favored formation of the thermodynamic product.

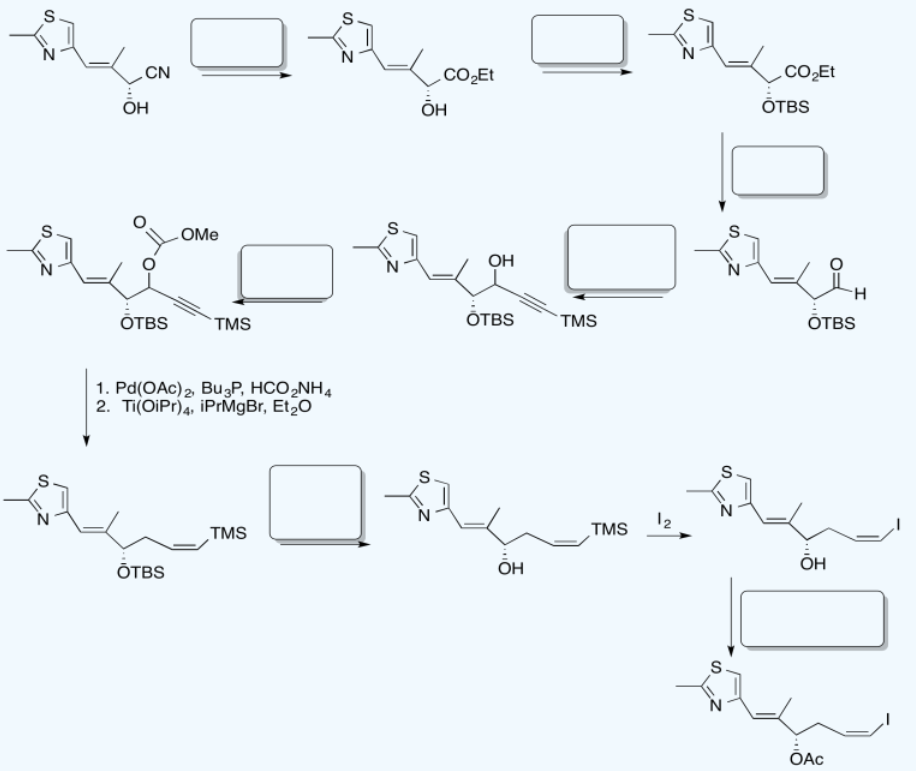


? Exercise 4.9.1

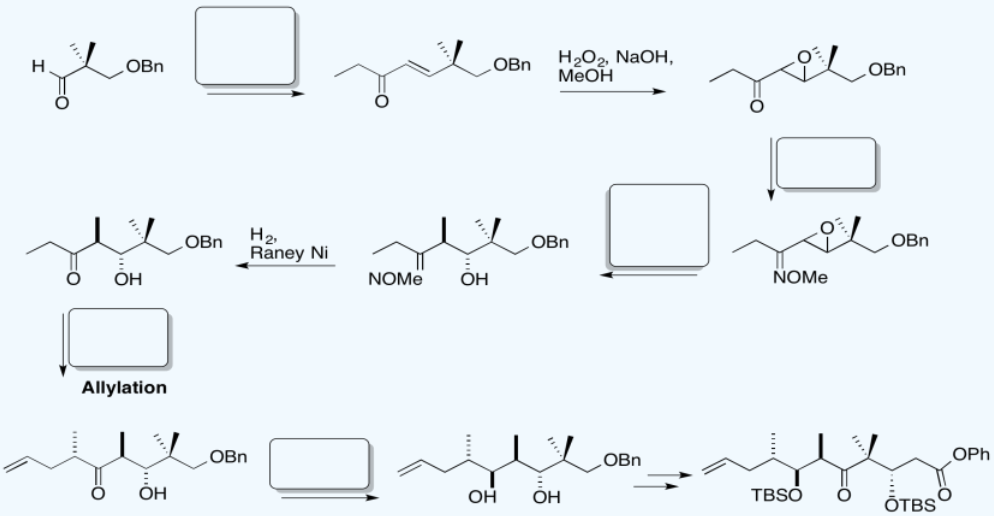
Fill in the blanks in the following synthesis. Includes: aliphatic nucleophilic substitution, silyl ethers, carboxylic substitution, carbonyl addition (anionic nucleophiles, neutral nucleophiles, enolates)

Enantioselective Total Synthesis of Epothilone A
Sawada, Kanai, Shibasaki, *J. Am. Chem. Soc.*, **2000**, *122*, 10521-10532.

1. Synthesis of Fragment A



2. Synthesis of Fragment C



3. Stereocontrol of the allylation step:

Is the base used a kinetic or a thermodynamic base? Why?

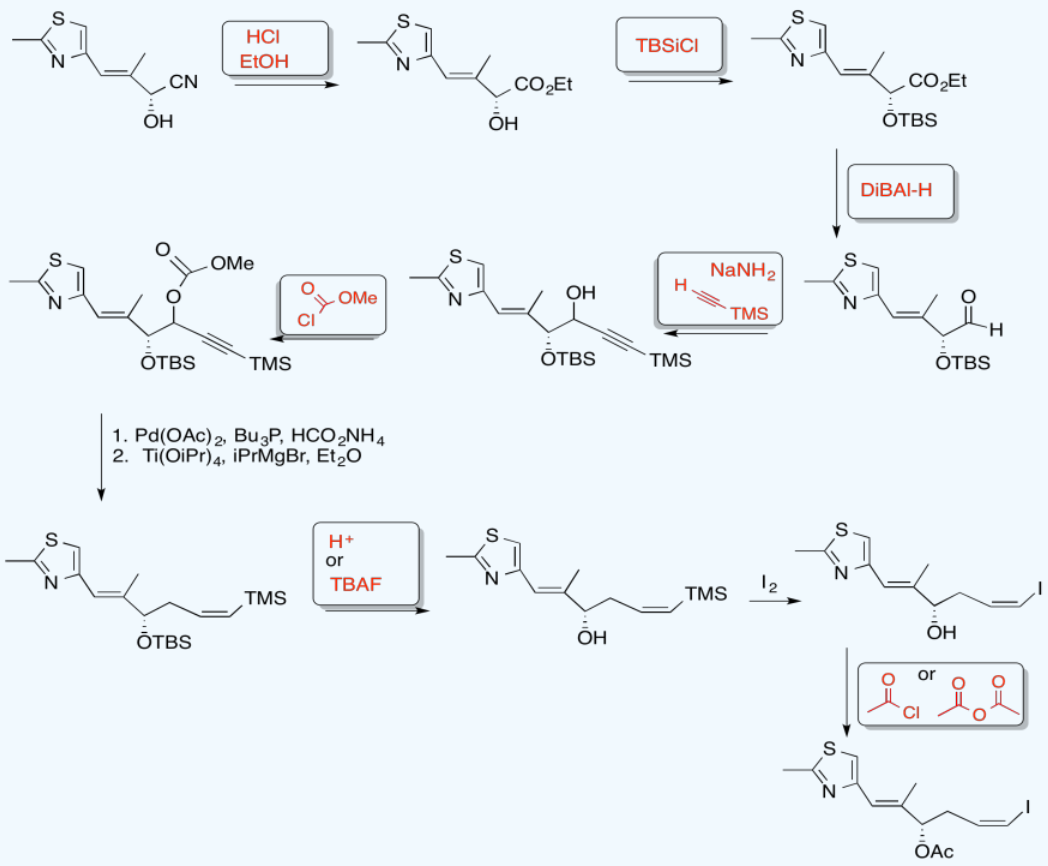
Explain the stereocontrol of the allylation step in the preparation of Fragment C (shown here). Be sure to include pictures.

Answer

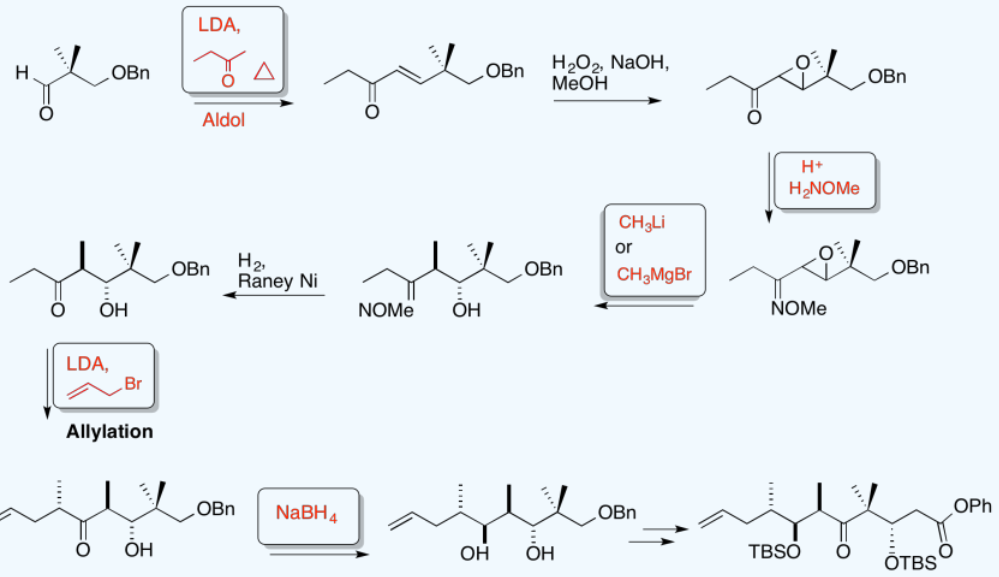
Enantioselective Total Synthesis of Epothilone A

Sawada, Kanai, Shibasaki, *J. Am. Chem. Soc.*, **2000**, *122*, 10521-10532.

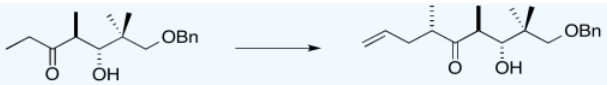
1. Synthesis of Fragment A

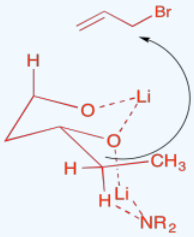


2. Synthesis of Fragment C



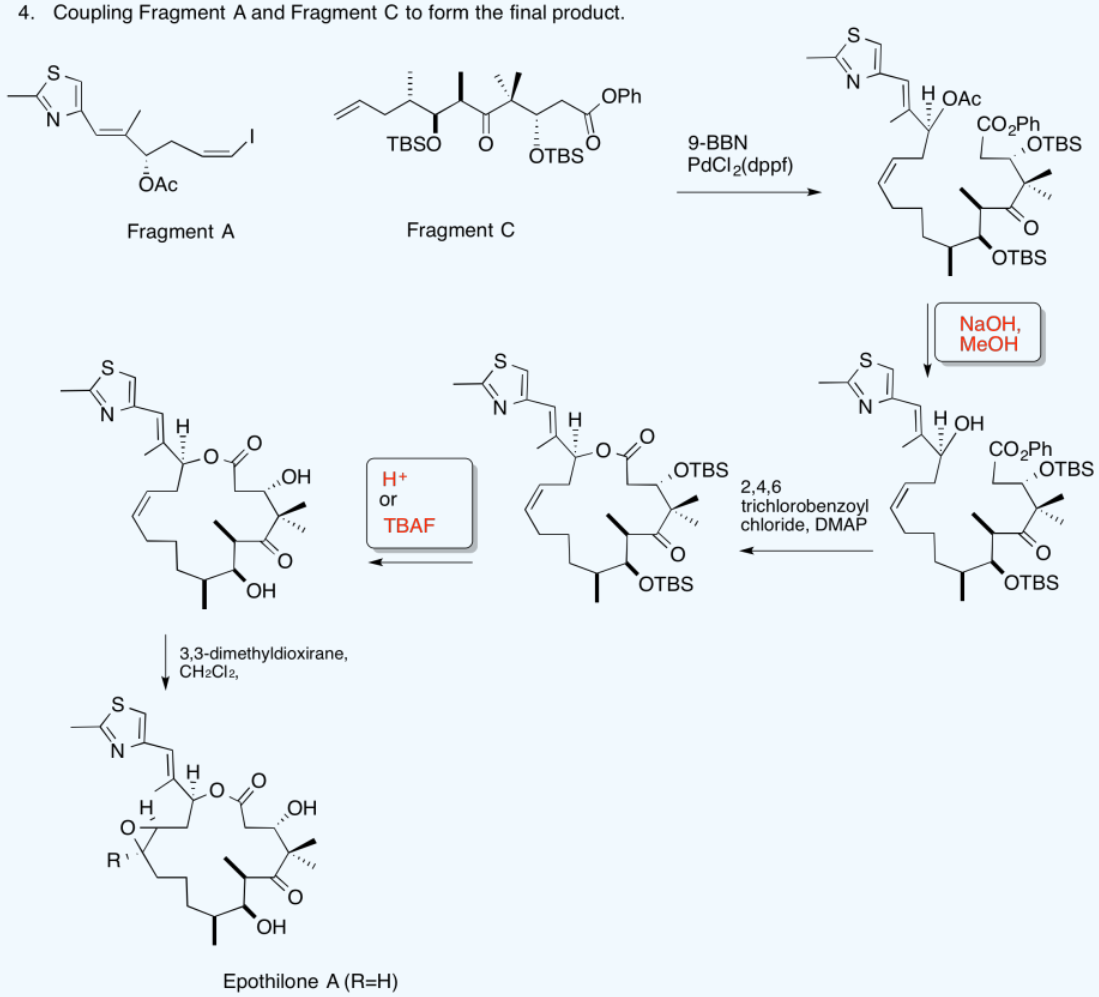
3. Kinetic -- to fully deprotonate (not equilibrate or you lose stereocontrol) and for the chelation control.





Due to chelation effects shown above, the LDA preferentially removes one hydrogen to form only the Z-enolate that will then do the SN2 to allyl bromide on only one face.

4. Coupling Fragment A and Fragment C to form the final product.

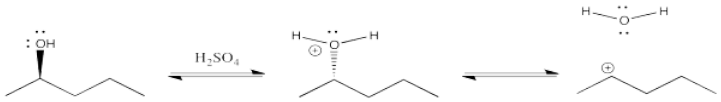


4.10: Leaving Group Formation

Aliphatic Nucelophilic Substitutions can be useful reactions. A minor drawback is the low natural occurrence of alkyl halides. Alcohols are much more common.

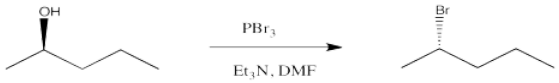
We could do nucleophilic substitutions on alcohols. The trouble is, oxygens are less polarizable than halides. A hydroxide ion is less stable, and harder to form than a halide ion. They don't make very good leaving groups, comparatively.

One way around that problem would be to protonate the oxygen. Attached to the carbon, it is a cation. Once it leaves, it becomes a neutral. The issue of ion stability is sidestepped. The trouble is, plunking a compound into concentrated acid is not always a reliable way to get things done.



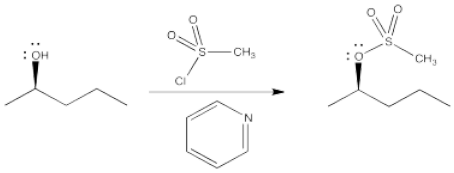
For that reason, it is pretty helpful to be able to turn alcohols into alkyl halides, or otherwise turn hydroxyls into stable, anionic leaving groups.

One of the most common synthetic methods of converting alcohols into good candidates for nucleophilic substitution is to convert the hydroxyl into a halide through the use of a phosphorus reagent. Phosphorus tribromide is frequently used to make alkyl bromides from alcohols.

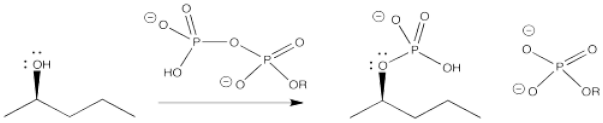


This reaction itself involves a sequence of nucleophilic substitution reactions. In the first, the oxygen atom in a hydroxyl group acts as the nucleophile and replaces a bromide on phosphorus. In the second, the displaced bromide ion rebounds to displace the oxygen atom from the tetrahedral carbon. This mechanism is aided by the strength of the strong phosphorus-oxygen bond that is formed. The phosphite that forms is a very good leaving group.

Another common method is to turn the hydroxyl into a sulfonate ester, such as a mesylate or tosylate. Again, the oxygen atom acts as a nucleophile, displacing a halide from the sulfur in a sulfonyl chloride. This is very similar to the bromination with phosphorus tribromide, but the sulfonate ester waits, poised to be displaced by a nucleophile. In fact, tosylates are generally even better leaving groups than halides.



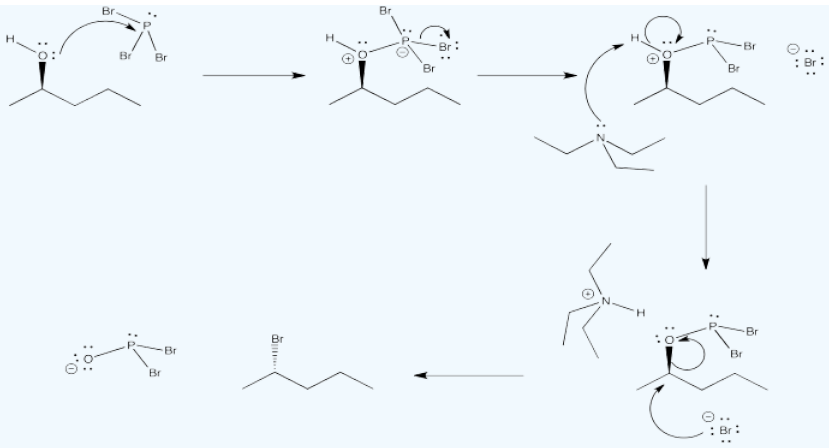
Biologically, something very similar to both of these processes sometimes happens. The alcohol unit is converted into a phosphate. The alcohol can be phosphorylated by a molecule of ATP. Again, the phosphate portion of the molecule is a very good leaving group.



? Exercise 4.10.1

Provide a mechanism for the reaction of phosphorus tribromide with 2-pentanol, based on the description provided.

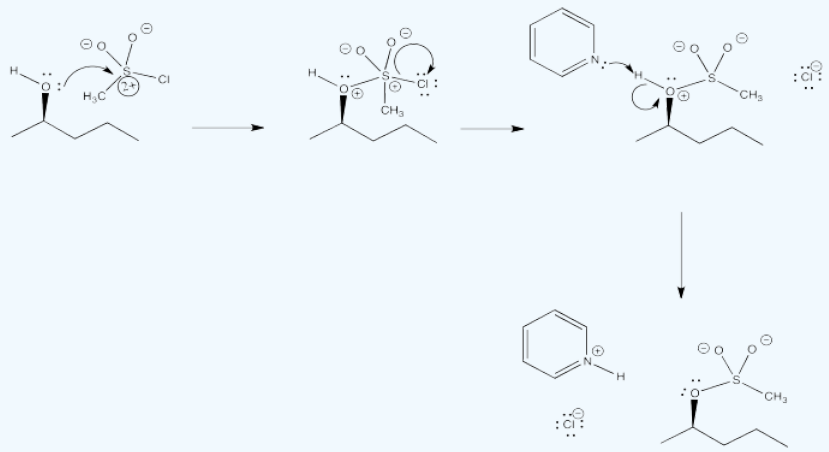
Answer



Exercise 4.10.2

Provide a mechanism for the reaction of mesyl chloride with 2-pentanol, based on the description provided.

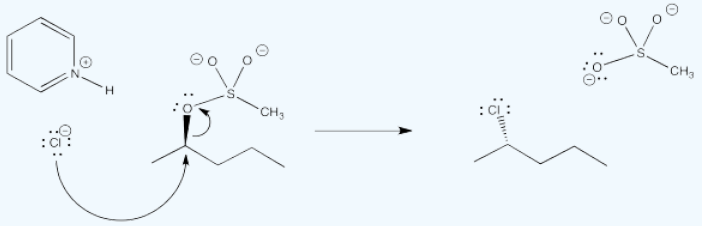
Answer



Exercise 4.10.3

Sometimes in formation of sulfonate esters, halogenation occurs by accident, forming an alkyl chloride. Show how that might happen by continuing on from the mechanism of formation of a mesylate ester from mesyl chloride and 2-pentanol.

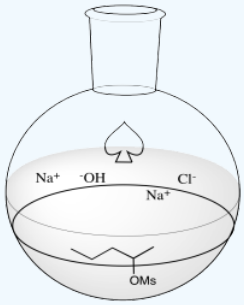
Answer



Exercise 4.10.4

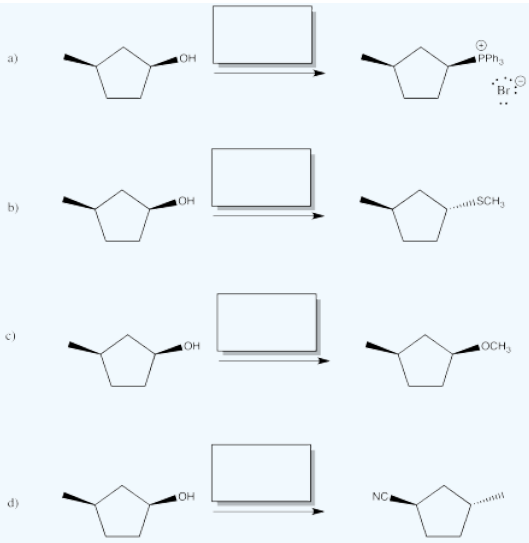
One way of preventing side reactions during synthesis of sulfonate esters, like the one in the previous question, is to perform a two-phase reaction. For example, the reaction might be performed in a mixture of water and dichloromethane, with a little added sodium hydroxide to act as a base. Show how this approach would limit the chlorination reaction.

Answer

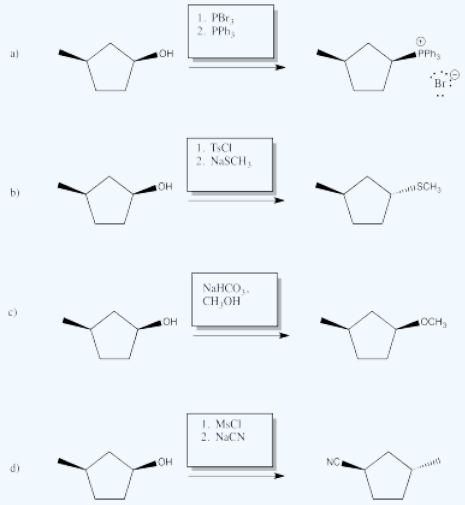


Exercise 4.10.5

Provide reagents (or series of reagents) to accomplish the following transformations.



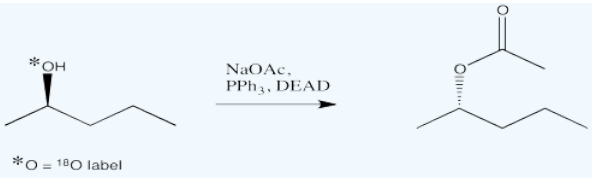
Answer



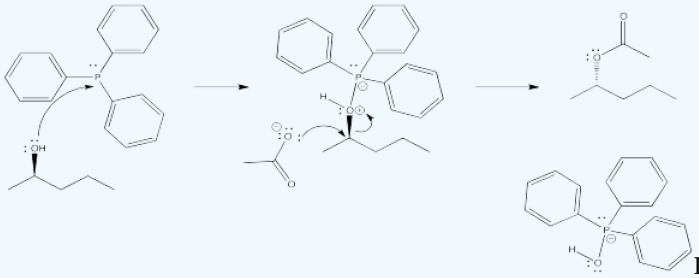
Exercise 4.10.6

Mitsunobu addition is a one-step method of replacing an alcohol's OH group with a nucleophile. In the following case, the original oxygen atom has been completely replaced. You may be able to guess where it goes based on other reactions you have seen here.

Propose a mechanism for this reaction, but don't worry about what DEAD does (that is a more advanced topic).



Answer



DEAD acts as an oxidizing agent to convert the phosphorus product to a stable side-product, triphenylphosphine oxide, $Ph_3P{=}O$.

4.11: Addition to Strained Rings - Epoxides

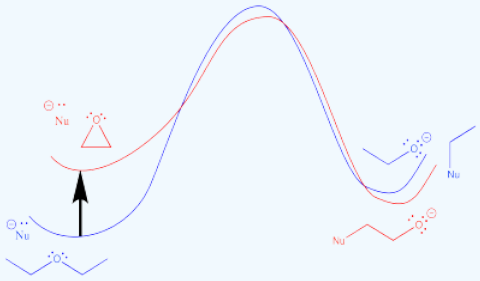
Oxygen is a very common element in all kinds of compounds, whether they are biological molecules, minerals from the earth or petrochemicals. Exploiting oxygen's electronegativity and giving it a little help to become a leaving group is a common way to make connections and build new molecules in nature, the laboratory or the production facility.

Sometimes oxygen doesn't need much help to become a leaving group. Epoxides, or oxiranes, are three-membered ring ethers. They are good electrophiles, and a C-O bond breaks easily when a nucleophile donates electrons to the carbon.

? Exercise 4.11.1

Explain why the C-O bond in an epoxide breaks easily.

Answer



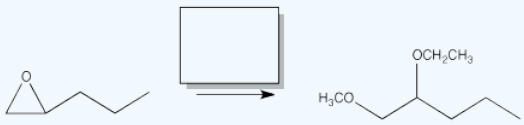
? Exercise 4.11.2

Use a potential energy diagram to show why epoxides are susceptible to react with nucleophiles, whereas other ethers are not.

Epoxides are very useful in the synthesis of important molecules. The Nu-C-C-O motif that is formed in nucleophilic addition to an epoxide is very valuable. Whereas other nucleophilic additions simply replace a halide or leaving group with a nucleophile, exchanging one reactive site with another, addition to an epoxide makes a product that has gone from having one reatcive site to two reactive sites. That can open the door to lots of useful strategies when trying to make a valuable commodity.

? Exercise 4.11.3

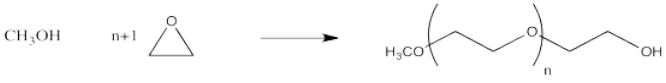
Show how you could carry out the following transformation. More than one step is involved.



? Exercise 4.11.4

One of the most widespread uses of epoxides is in making polymers. The polyethylene glycol produced in polymerization of an epoxide is frequently used in biomedical applications. Provide a mechanism with arrows for the following polymerization of ethylene oxide, in the presence of:

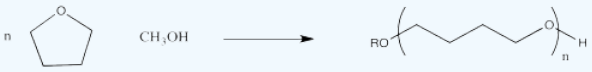
a. an acid catalyst
b. a basic catalyst.



Exercise 4.11.5

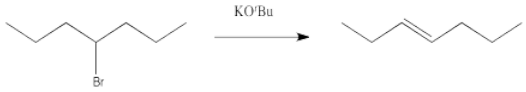
Tetrahydrofuran can also be polymerized, forming polytetramethylene glycol.

a. Compare the rate of polymerization of THF with that of ethylene oxide.
b. Polymerization of THF generally requires an acid catalyst, rather than a basic one. Why?

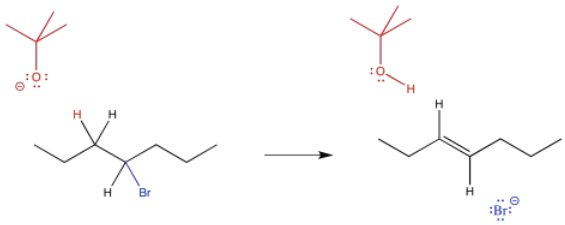


4.12: Elimination

Sometimes, elimination reactions occur instead of aliphatic nucleophilic substitutions. In an elimination reaction, instead of connecting to the electrophilic carbon, the nucleophile takes a proton from the next carbon away from it. The halide or other leaving group is still displaced. A double bond forms between the two carbons.



Thus, there are actually more than two competing mechanisms occurring at once here. In addition to unimolecular and bimolecular substitution, a reaction involving deprotonation is also possible.

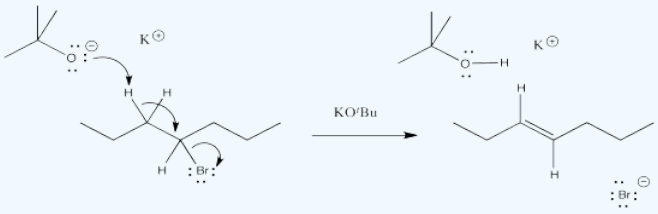


Instead of acting as a nucleophile, the tert-butoxide anion acts as a base. It forms a bond to a proton, becoming tert-butanol. This proton must always come from the carbon next to the leaving group. The bromide still leaves, and the two adjacent carbons form a second bond together.

Exercise 4.12.1

Draw a mechanism for the elimination reaction above. Assume the reaction is bimolecular and concerted, so that the C-H bond and the C-Br bond break at the same time, forming the C=C bond.

Answer

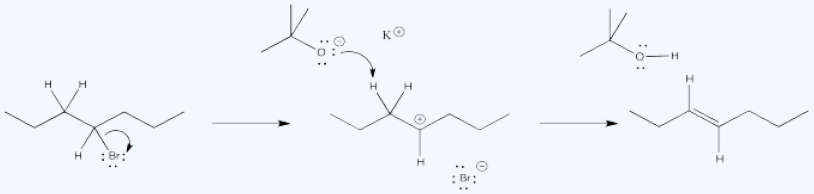


The mechanism of an elimination reaction is almost exactly the same as an aliphatic nucleophilic substitution, except that the nucelophile misses its mark. It hits a proton instead of a carbon and acts as a base instead of a nucleophile. This process can happen at the same time as the leaving group's departure or it can happen afterwards. These mechanisms are called E1 and E2.

Exercise 4.12.2

Draw another mechanism for the elimination reaction above, but this time, suppose the reaction is unimolecular.

Answer



? Exercise 4.12.3

Given the mechanism in Exercise 4.12.2, other products would also be expected.

a. What are they? (Think about the reactive intermediate and what else could happen to it.)
b. What does their absence in the original reaction scheme above suggest about the most probable mechanism of the reaction?

Answer a

products of cation rearrangement via hydride shifts: 2-heptene instead of 3-heptene.

Answer b

The absence of rearrangement suggests the absence of cations. The mechanism for the reaction shown must be concerted rather than via the ionic intermediate.

Why might a reaction undergo elimination rather than substitution? The most important reason concerns the nature of the nucleophile. The more basic the nucleophile, the more likely it will induce elimination.

- Basic nucleophiles lead to elimination.

What makes something basic, rather than nucleophilic? As a very rough rule of thumb, we can beging by thinking of bases as less stable versions of nucleophiles. Nucleophiles are very often anions, and bases are generally less stable anions. So what factors make anions more stable? Those factors would make the anion more like a nucleophile and less like a base.

One of the most important factors here is polarizability. Remember, polarizable atoms are large atoms. In the main group of the periodic table, they include sulfur, phosphorus, chloride, bromide, iodide, etc. These anions are stable because the negative charge is spread out over a larger atom. Any time charge is spread out, it tends to result in greater stability. On the other hand, smaller, less polarizable atoms include oxygen, nitrogen and carbon. Anions of carbon, nitrogen and oxygen tend to be more basic. Anions of bromine, iodine, and sulfur are not basic. What, never? No, never. Well, hardly ever.

- Large, polarizable atoms such as Br, I, or S make stable anions.
- These stable anions are more likely to be nucleophiles than bases.

You might remember this factor from a discussion of anion stability in acid-base chemistry. Other considerations from acidity will be useful, too.

A second important factor that helped to stabilize anions was resonance. If a negative charge can be delocalised via resonance, the anion becomes much more stable. For example, an alkoxide ion, such as methoxide, might be very basic, because the negative charge is on an oxygen atom. Oxygen is not a large, polarizable atom. However, an adjacent carbonyl in an acetate anion makes all the difference. This anion is resonance stabilised.

- Resonance stabilised anions are relatively stable.
- These stable anions are more likely to be nucleophiles than bases.

Another factor sometimes plays a role in the case of carbon or nitrogen. It is the idea of hybridisation. Remember that the geometry of an atom determines which atomic orbitals are involved in bonding. Tetrahedral carbons are thought of as sp^3 hybridised, meaning that the carbon uses an s electron and three p electrons in sigma bonding. A trigonal planar carbon is sp^2 hybridised. That means it uses only two p orbitals and an s orbital in forming sigma bonds.

Different hybridisation leads to some subtle differences in properties. For example, the C-H bonds of sp^2 carbons are a little stronger than those of sp^3 carbons (maybe 105 to 110 kcal/mol for the former, and 95 to 100 kcal/mol for the latter). That's because the electrons in the sp^2 C-H bonds are at slightly lower energy. That, in turn, is because an s orbital is a little lower in energy than a p orbital.

For similar reasons, an sp^2 carbanion is more stable than an sp^3 carbanion. The electrons on the sp^2 carbon are lower in energy than the electrons on the sp^3 carbon. An sp carbanion is more stable, still. As a result, although an ethyl anion ($CH_3CH_2^-$) is extremely basic and a vinyl anion ($H_2C{=}CH^-$) is still highly basic, an acetylide or alkynyl anion ($HC{\equiv}C^-$), though basic, is much more nucleophilic than the other two.

- A sp hybridized carbon anion is much more stable than an sp^2 or sp^3 carbon anions.

- These relatively stable anions (remember, we are still talking about an anion on carbon), although pretty basic, are usually nucleophiles.

If any of these three factors apply (polarizability, resonance, sp hybridization in carbon), the anion is more likely to be a nucleophile than a base.

There is a fourth factor which is almost a non-sequitur. It goes without saying that a neutral compound -- in the sense that the compound that has no charge at all -- does not require charge stabilisation at all. Thus, if a nucleophile has no charge, it is relatively stable, and will often act as a nucleophile rather than a base.

- Neutral (uncharged) compounds are stable; they do not require charge stabilisation.
- Neutral compounds are usually nucelophiles rather than bases.

A fifth factor -- relative electronegativity within a row -- does play a minor role here. Remember, within a row of the periodic table, size changes are minor. All of the atoms are small. Differences in polarizability are not much of a factor. Instead, differences in electronegativity influence anion stability. The more electronegative the atom, the more stable the anion. As a result, an oxygen anion is more stable than a nitrogen anion or carbon anion. As a result, we sometimes make a distinction here, referring to hydroxide ion and alkoxide ions as strong bases, but amide anions and alkyl anions as very strong bases.

? Exercise 4.12.4

Classify the following anions as very strong base, strong base, or weak base.

a) $NaNH_2$ b) NaOH c) CH_3CO_2Na d) NaH e) CH_3OH

f) NaBr g) CH_3COCH_2Li h) $CH_3CH_2CH_2CH_2Li$ i) KI j) H_2O

k) CH_3CCNa l) $(CH_3CH_2)_3N$ m) Na_2CO_3 n) LiCl o) CH_3OK

p) $CH_3C_6H_4ONa$ q) NaSH r) $[(CH_3)_2CH]_2NLi$ s) $(CH_3)_3P$ t) $(CH_3)_3COK$

Answer a

very strong

Answer b

strong

Answer c

weak (resonance)

Answer d

very strong

Answer e

weak (neutral)

Answer f

weak (polarizable)

Answer g

weak (resonance)

Answer h

very strong

Answer i

weak (polarizable)

Answer j

weak (neutral)

Answer k

medium-weak (C anion but sp)

Answer l

weak (neutral)

Answer m

weak (resonance)

Answer n

weak (polarizable)

Answer o

strong

Answer p

weak (O anion but delocalised)

Answer q

weak (polarizable)

Answer r

very strong

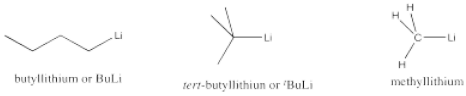
Answer s

weak (polarizable)

Answer t

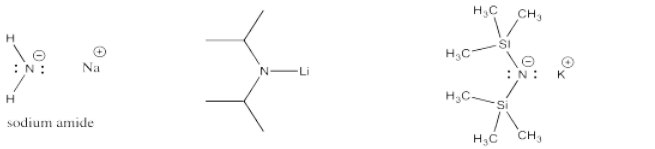
strong

Very strong bases include carbon and nitrogen anions and semi-anions. Examples include butyllithium and sodium amide. Very strong bases are highly likely to engage in elimination, rather than substitution.



butyllithium or BuLi | *tert*-butyllithiun or ^{t}BuLi | methyllithium

Strong bases include non-stabilized oxygen anions. Examples include sodium hydroxide as well as alkoxides such as potassium tert-butoxide or sodium ethoxide. Strong bases favor elimination, too. Nevertheless, they can sometimes undergo either elimination or substitution, depending on other factors (see below).



sodium amide | lithium diisopropylamide or LDA | potassium hexamethyldisilazide (KHMDS) or potassium bis(TMS)amide

Weak bases include cyanide, stabilized oxygen anions such as carboxylates and aryloxides, sulfur anions, fluoride ion and neutral amines. Weak bases are much more likely to undergo substitution than elimination.

phenoxide or phenolate anion (an aryloxide) | acetate or ethanoate anion (a carboxylate)

Very weak bases include heavy halides such as chloride, bromide or iodide, as well as neutral phosphorus or sulfur nucleophiles. Very weak bases undergo elimination only rarely.

Exercise 4.12.5

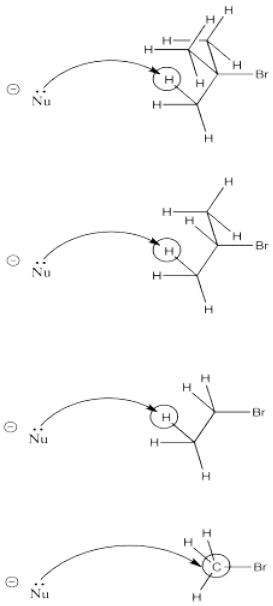
Typically, strong bases and very strong bases are more likely to react via the E2 mechanism; they react so quickly that the deprotonation step triggers C-LGp ionization, rather than the other way around. However, E1 mechanisms also occur with these bases, especially at low concentrations. Explain why.

Exercise 4.12.6

Why is it that an anion such as cyanide is a weak base, whereas CH_3Li is a strong base?

Another factor is sterics. The more crowded the electrophile, the more likely the nucleophile will encounter a proton on its way to the electrophilic carbon.

As a nucleophile approaches *tert*-butyl bromide, coming from the side opposite the bromine in order to undergo nucleophilic substitution, it is pretty likely to collide with a proton on its way to the electrophilic carbon. The same thing has a good chance of happening with *iso*-propyl bromide. However, it is much less likely to happen with bromoethane. Finally, bromomethane doesn't even have a beta-hydrogen, so the chance of elimination in that case is zero.



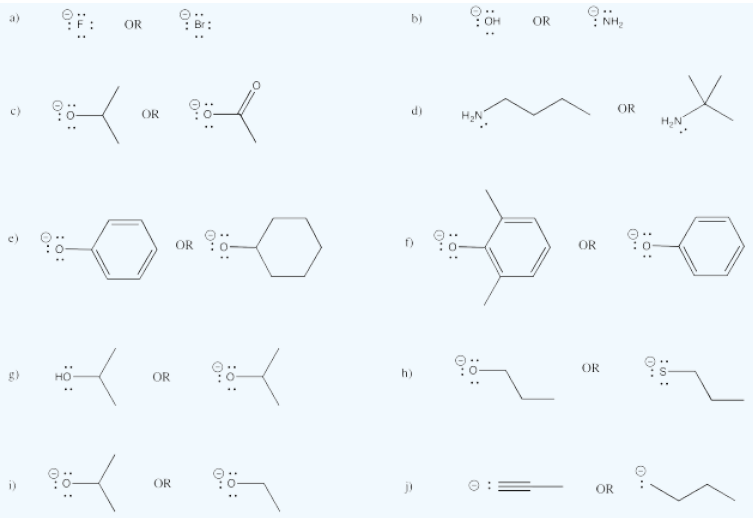
- Crowding leads to elimination.

Note that the crowding could involve either the structure of the base or the structure of the electrophile. A large, bulky base may be more likely to deprotonate than find its way in to the electrophilic carbon atom.

- Bulkier nucleophiles can act as bases.

Exercise 4.12.7

Given the following pairs of nucleophiles, which one is more likely to undergo elimination?



? Exercise 4.12.8

Although acetylides (such as sodium acetylide, Na CCH) are actually more basic than alkoxides (such as sodium isopropoxide, Na $OCH(CH_3)_2$), acetylides frequently undergo substitution rather than elimination. Propose a reason for this difference.

A third factor is temperature. An elimination reaction involves the cleavage of two bonds, whereas a substitution reaction requires only one bond to break. Thus, an elimination reaction is more energy-intensive, and it is more likely to occur at higher temperatures, when more energy is available.

- Higher temperatures lead to elimination.

? Exercise 4.12.9

An additional factor in the energy dependence of eliminations and substitutions is entropy.

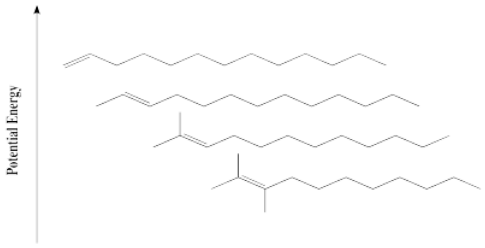
a. Use simple rules about to determine which products are favored by entropy: Elimination or substitution?
b. Given the relationship $\Delta G = \Delta H - T\,\Delta S$, which thermodynamic factor dominates free energy change at high temperature?
c. Therefore, which product is favored at high temperature?

4.13: Regiochemistry in Elimination

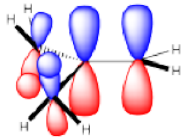
Sometimes, an elimination reaction could lead to formation of a double bond in more than one place. If the halide is on one carbon and there are protons that could be removed on either side, then taking one proton or the other might lead to two different products. This reaction could have different regiochemical outcomes, meaning it could happen at two different places in the molecule.

What factors might influence which product forms? We might think about product stability, in case there are corresponding differences in barriers leading to those products. We already know about stereochemical effects in alkene stability, but what about other effects?

It is well-established that alkene stability is influenced by degree of substitution of the double bond. The greater the number of carbons attached to the double bond, the more stable it is.

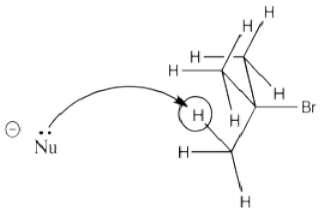


That effect is related to hyperconjugation. Specifically, it's an interaction between bonding orbitals and antibonding orbitals on neighbouring carbons. The interaction allows the bonding electrons to drop a little lower in energy through delocalization. The interaction also pushes the antibonding orbitals a little higher in energy, but since they have no electrons, they don't contribute to the real energy of the molecule. Overall, the molecules goes down in energy.

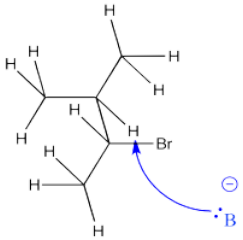


- In most cases, the most-substituted alkene results from elimination reactions.

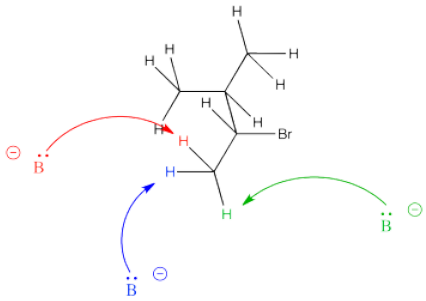
However, alkene stability isn't the only factor that plays a role in elimination. Steric hindrance can play a role, too.



In a case in which there are two different hydrogens from which to select, the one leading to the more-substituted double bond is sometimes a little bit crowded. That leaves the base with fewer viable pathways to approach the proton.



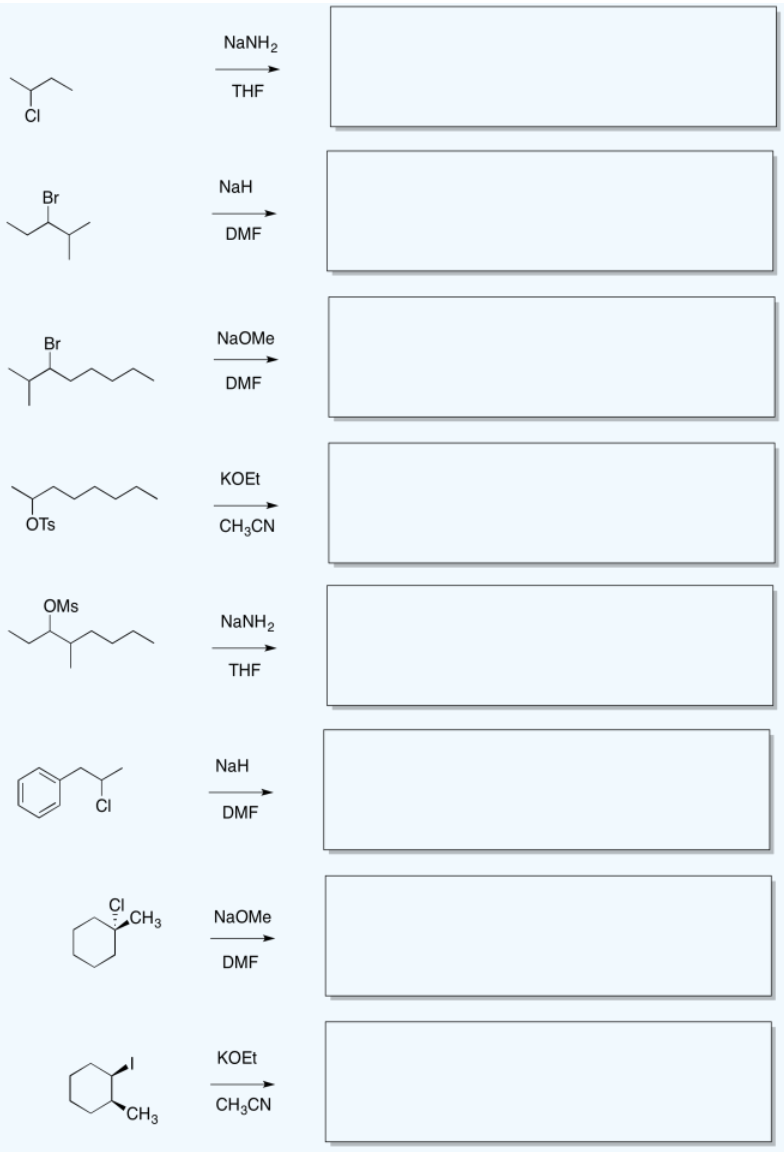
On the other hand, the removal of a proton leading to the less stable alkene is often less crowded, allowing the base to approach much more easily from a number of angles.



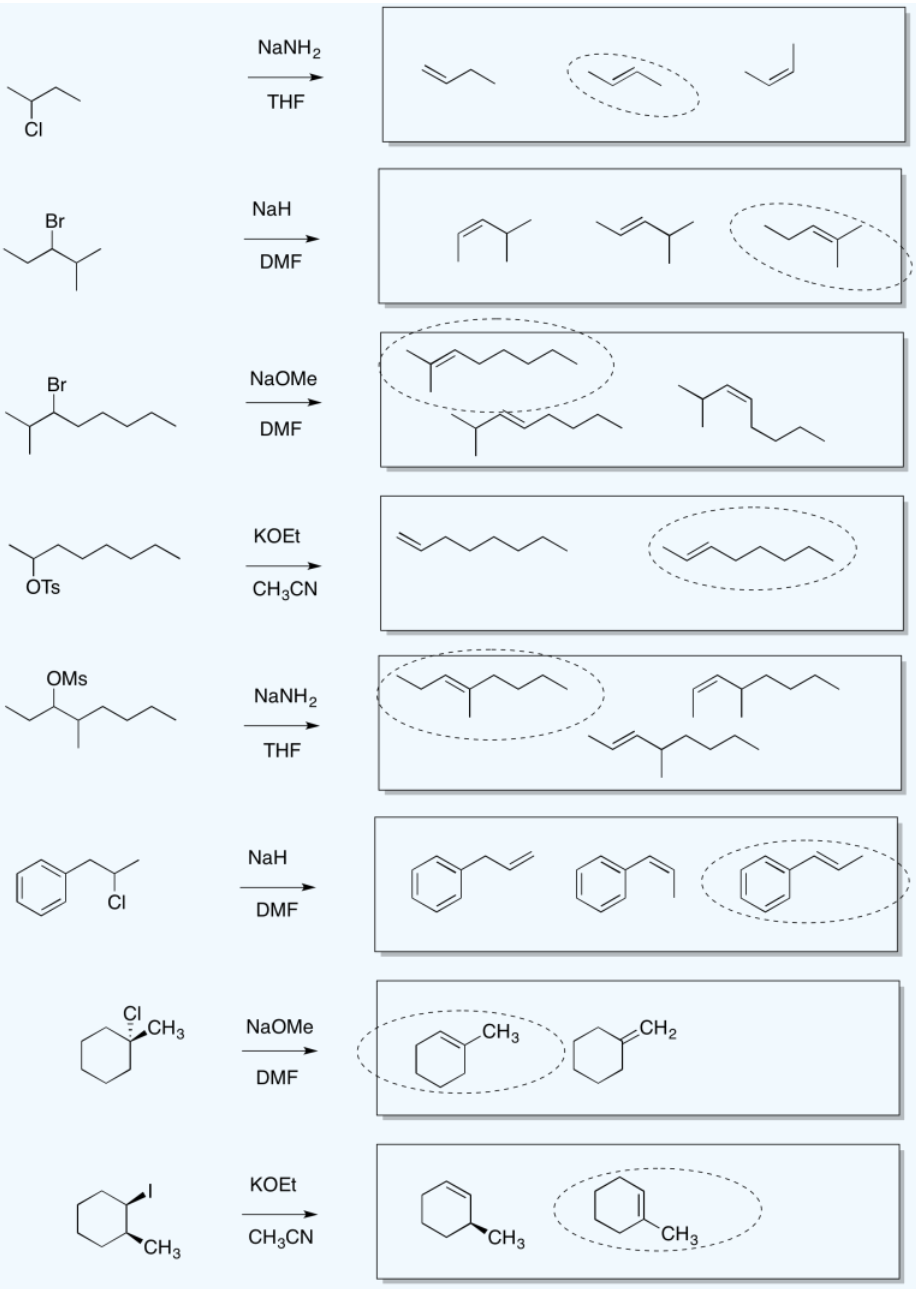
- In some cases, especially with very bulky bases, the least substituted alkene forms, even though it is less stable.

Exercise 4.13.1

In the following reactions, more than one elimination product is possible. Draw the products. Circle the most stable product.

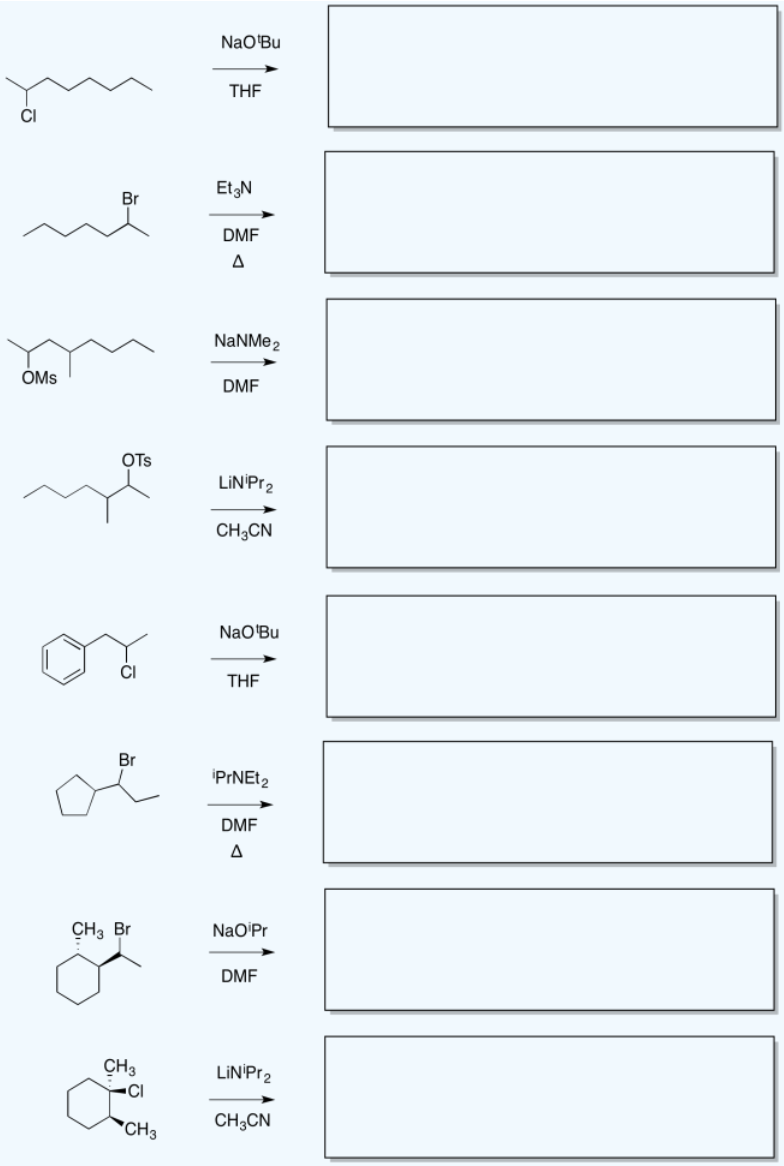


Answer

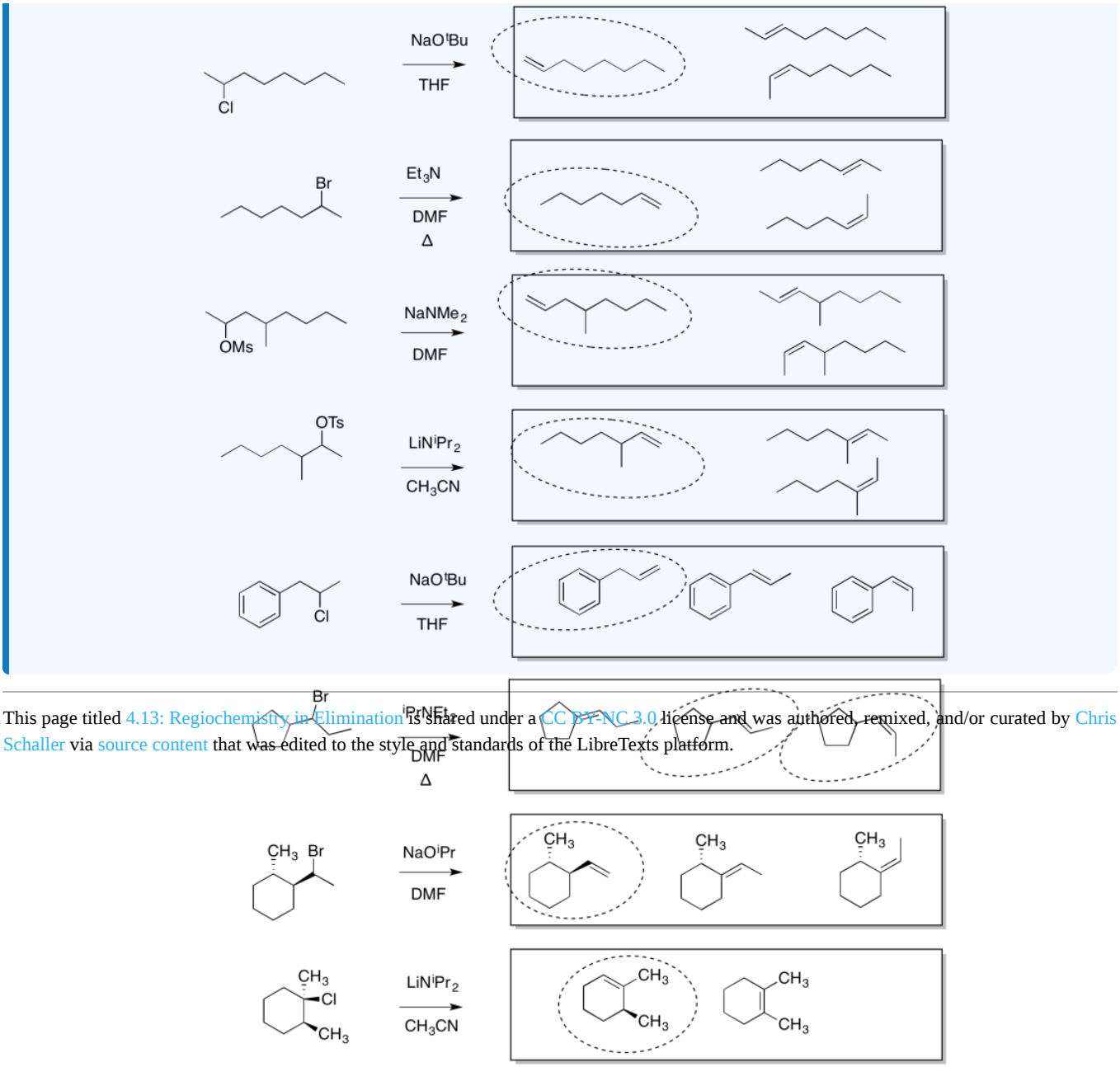


Exercise 4.13.2

In the following reactions, more than one elimination product is possible. Draw the products. Circle the product formed via removal of the most accessible proton.



Answer



4.14: Stereochemistry in Elimination

Sometimes, elimination reactions may lead to multiple stereoisomers; that is, they could lead to either the *cis* or the *trans* isomer, or in more complicated structures, either the *Z* or the *E* isomer.

Of course, if there were some inherent stability difference between these isomers, that could be a factor that plays a role in influencing the outcome. Elimination reactions aren't generally reversible, so products are not directly determined by alkene isomer stabilities. Nevertheless, sometimes the barrier leading to a more stable product is a little lower than the barrier leading to a less stable product.

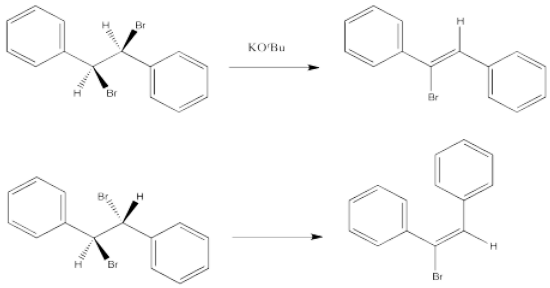
We do know that in simple *cis vs. trans* cases, the *trans* isomer is generally lower in energy because of fewer steric interactions between the substituents on the double bond. In the absence of other information, we could take that as a starting point. Let's see whether elimination reactions generally lead to *trans* isomers.

It turns out that sometimes this is true: eliminations often lead to the more stable product. Sometimes it isn't true, though. The answer depends on the mechanism.

- E1 eliminations generally lead to the more stable stereochemistry.
- E2 eliminations may or may not lead to the more stable stereochemistry.

Instead, in an E2 reaction, stereochemistry of the double bond -- that is, whether the *E* or *Z* isomer results -- is dictated by the stereochemistry of the starting material, if it is diastereomeric. In other words, if the carbon with the hydrogen and the carbon with the halogen are both chiral, then one diastereomer will lead to one product, and the other diastereomer will lead to the other product.

The following reactions of potassium ethoxide with dibromostilbene (1,2-dibromo-1,2-diphenylethane) both occurred via an E2 mechanism. Two different diastereomers were used. Two different stereoisomers (*E* vs. *Z*) resulted.



? Exercise 4.14.1

Provide the stereochemical configurations of the following compounds from the above reactions:

a. 1,2-dibromo-1,2-diphenylethane (upper example)
b. 1-bromo-1,2-diphenylethene (upper example)
c. 1,2-dibromo-1,2-diphenylethane (lower example)
d. 1-bromo-1,2-diphenylethene (lower example)

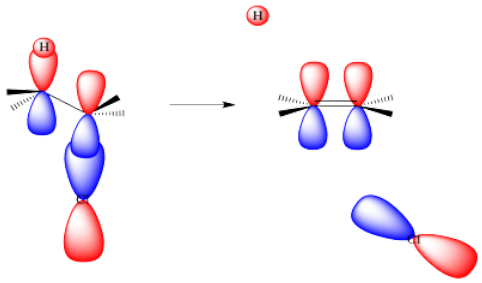
In E2 eliminations, the spatial relationship between the proton and leaving group determines the product stereochemistry. That's because pi bond formation happens at the same time that the halide leaves and at the same time that the base removes the proton. All of these events have to be coordinated together. The central, tricky event is the pi bond formation. The leaving group can leave in any direction, and the base can approach from many directions, but unless the pi bond is ready to form, nothing else happens.

Let's slow the reaction down and imagine it takes place in slightly different stages.

As the leaving group leaves, it takes its electrons with it. It begins to leave a positive charge behind. That positive charge will be centered on the carbon from which the halide is departing. That carbocation, if it fully formed, would have only three neighbors to bond with. It would be trigonal planar. It would have an unoccupied, non-bonding p orbital.

As the base takes the proton, the hydrogen leaves behind the electrons from the C-H bond that held it in place. These electrons stay behind on the carbon atom. They are left in a non-bonding carbon valence orbital, a p orbital or something quite like it.

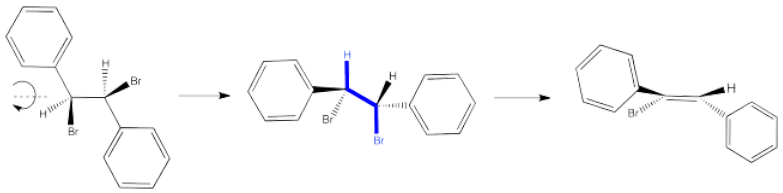
Now we have a filled p orbital next to an empty p orbital. They overlap to form a pi bond.



Of course, in an E2 reaction, things don't happen in stages. Everything happens at once. That means that, as the base removes the proton, the pi bond must already start forming. Because a pi bond requires parallel alignment of two p orbitals, and the p orbitals are forming from the C-H and C-LGp bonds, then those bonds must line up in order for the elimination to occur.

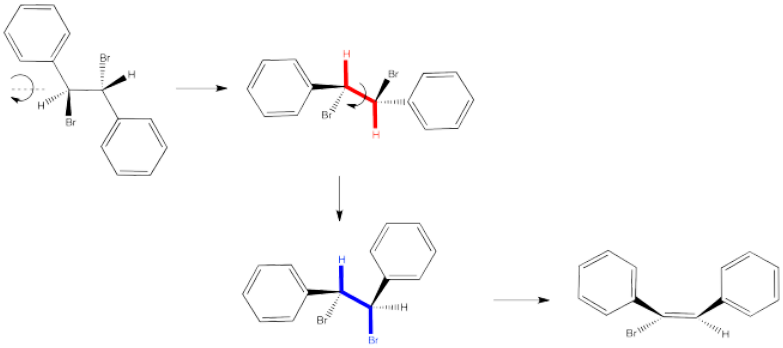
So let's look again at that dibromostilbene example.

In the first case, we need to spin the molecule so that we can see how the H on one carbon and the Br on the other are aligned and ready to eliminate via an E2 reaction. The substituents coming towards us in the reactant will still be coming towards us in the product. The substituents pointing away from us in the reactant will still be pointing away from us in the product.



So the relationships between the substituents on the nascent double bond are determined by their relationship once the reactant is aligned for the E2 reaction.

In the second case, we can spin the molecule but quickly realize the C-H and C-Br bonds are not lined up in this conformer. We need a bond rotation. Once we have made a conformational change, the C-H and C-Br bonds line up. It doesn't matter if this conformer is not favored; if there is going to be any E2 reaction at all, this is the conformer it will have to go through.



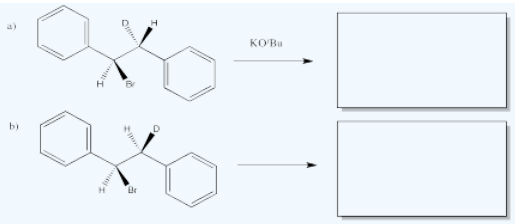
Again, the relationships between on the new double bond are determined by their relationship once the reactant is aligned for the E2 reaction.

? Exercise 4.14.2

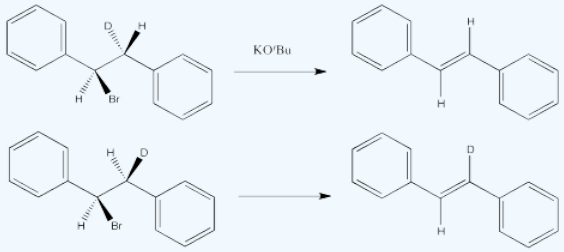
Sometimes it is easier to see the relationships between substituents by using a Newman projection. Draw Newman projections showing how the two isomers above proceed to different products in an E2 reaction.

? Exercise 4.14.3

Predict the product of each of the following E2 reactions. Note that the compounds differ in the incorporation of a ^{2}H isotope (deuterium, or D) in place of a regular ^{1}H isotope (protium, or H).



Answer

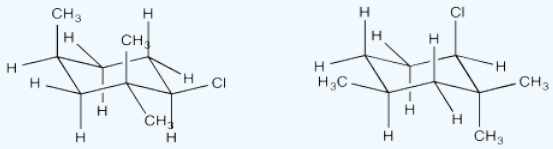


Conformational analysis of cyclohexanes requires the use of diamond lattice projections ("chairs"). In a chair, a periplanar requirement would only be met when two neighbouring groups are both axial. One would be "axial up" whereas the other would be "axial down". In contrast, if two neighbouring groups are both equatorial, they are actually gauche to one another. The dihedral angle between them would be 60 degrees, and so a π bond would not readily form during an E2 elimination. If one group were axial and the other equatorial, the two groups would still be gauche to each other.

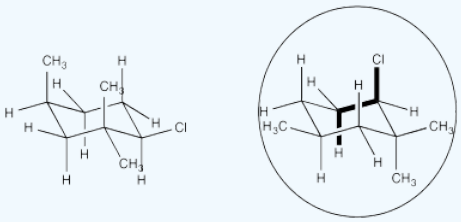
- An E2 elimination can only happen if a hydrogen and a neighbouring leaving group are anti to each other in a chair.
- These two groups must be trans to each other.
- These two groups must both be in axial positions.

Exercise 4.14.4

In which of these two chair conformations is an E2 reaction ready to occur?

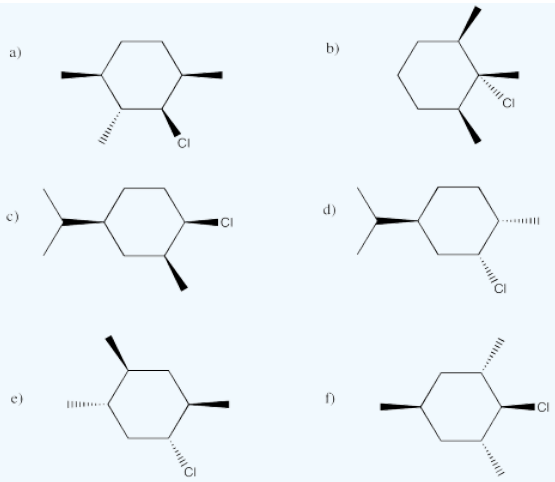


Answer

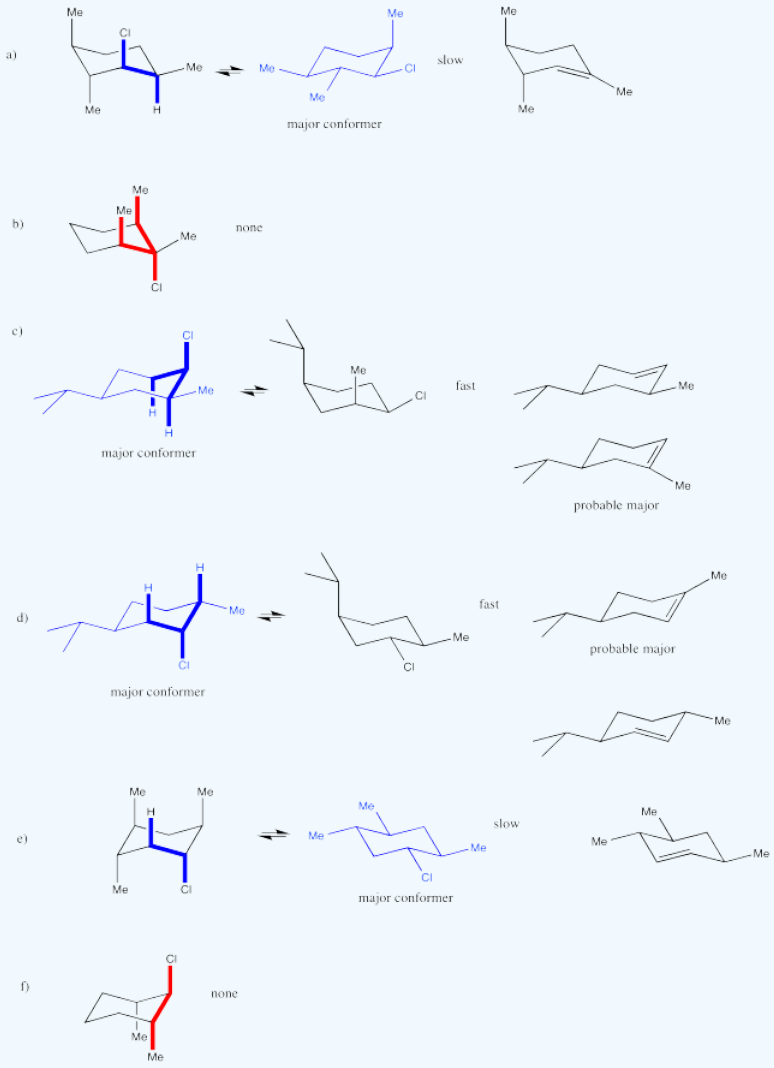


Exercise 4.14.5

In the following cases, elimination might proceed very quickly, very slowly or not at all. Indicate the propensity to react through an E2 mechanism in each of the following compounds. If it could react via this mechanism, show the product.

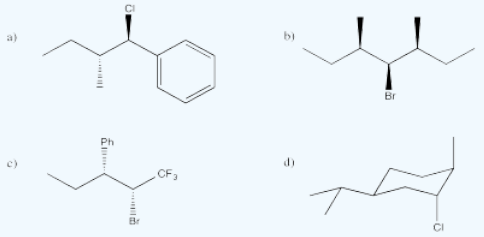


Answer

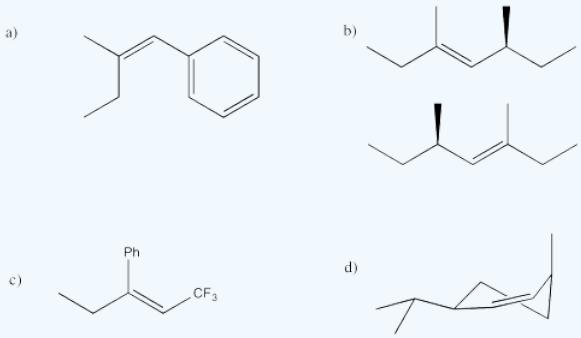


Exercise 4.14.6

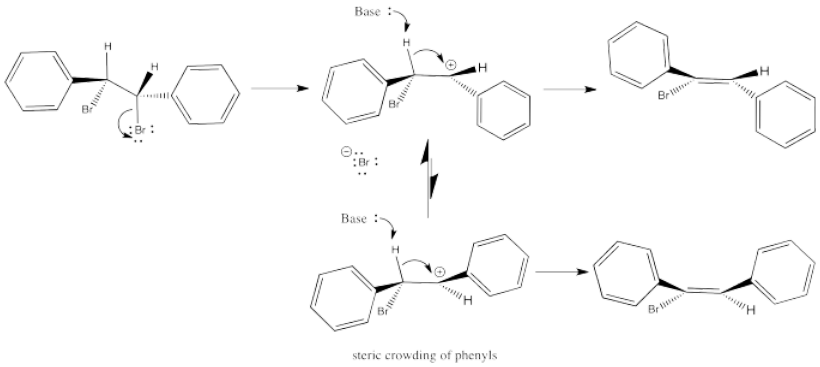
Predict the E2 elimination products from the following compounds.



Answer



In contrast to E2 reactions, E1 reactions do not occur in one step. That means there is time for reorganization in the intermediate. Once the leaving group leaves, the cation can sort itself into the most stable conformer. When the proton is taken, generally the most stable stereoisomer results because it comes from the most stable conformer of the cation. Any steric interactions in the alkene would also have occurred in the cation, so this interaction would have been sorted out at that point.

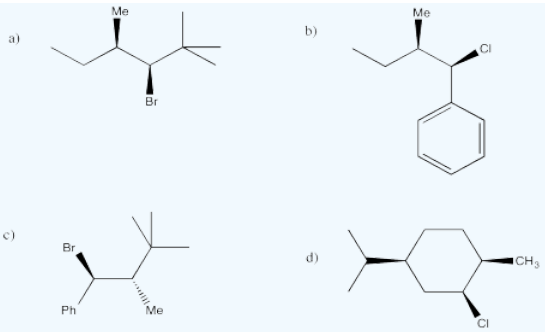


Thus, in the case of the dibromostilbenes examined before, E1 elimination would result in the same product in either case.

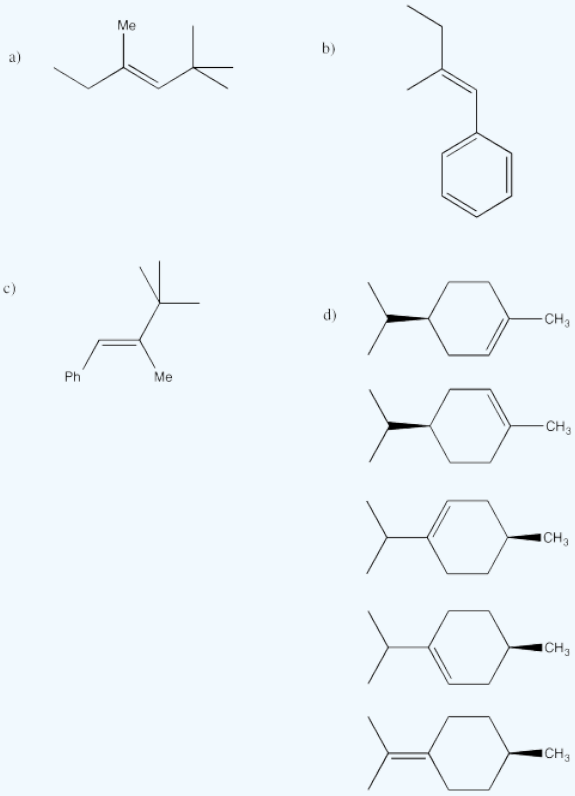
- E1 reactions can, in principle, lead to either stereochemistry of alkene.
- Free rotation around bonds in the carbocation intermediate allows the cation to adopt either conformer prior to elimination.
- However, steric interactions will lead to a preponderance of one conformer.
- The more stable conformer will lead to the more stable alkene.

Exercise 4.14.7

Predict the products of the following compounds under E1 conditions.



Answer



4.15: Factors Influencing the Elimination Mechanism

The factors that influence whether an elimination reaction proceeds through an E1 or E2 reaction are almost exactly the same as the factors that influence the S_N1/S_N2 pathway. Cation stability, solvents and basicity play prominent roles. However, basicity may be the single most important of these factors.

? Exercise 4.15.1

By analogy with substitution reaction, in which elimination mechanism does cation stability play a strong role: E1 or E2?

Answer

Cation stability is important in an E1 reaction.

? Exercise 4.15.2

Draw an example of an alkyl halide that is likely to undergo an E1 elimination.

Answer

Any tertiary alkyl halide would be a good example. Benzylic alkyl halides would also be good examples if they are either secondary or tertiary.

? Exercise 4.15.3

By analogy with substitution reactions, what mechanism would be promoted by protic solvents: E1 or E2?

Answer

Protic solvents could promote E1 reactions.

? Exercise 4.15.4

Basicity refers to the strength of the base. Which mechanism is more likely to occur with strong bases: E1 or E2?

Answer

A strong base could promote an E2 reaction.

Because strong bases can be thought of as very reactive nucleophiles, it might not be surprising that they tilt the likely reaction towards E2. These compounds are so reactive that they are much more likely to abstract a proton than be guided to the electrophilic carbon. They are also sufficiently reactive that they can intercept the electrophile on a timescale faster than it takes for the electrophile to ionize. Even under conditions that might otherwise be expected to lead to an S_N1 or E1 reaction, if the base is strong, E2 will frequently prevail.

Of course, that general rule is subject to limitations. If there is no beta-hydrogen to abstract, then there will be no elimination of any kind. The compound will be limited to substitution reactions. Furthermore, if the C-H bond cannot line up with the C-LGp bond in such a way as to allow them to break together, forming a pi bond at the same time, then an E2 mechanism would be impossible. However, the lack of possibility for an antiperiplanar relationship is not that common. If we are dealing with an alkyl chain, rotations around sigma bonds will be sufficient to bring the C-H and C-LGp bonds into alignment. Only in cyclic structures, in which rotation is much more restricted, would there be a possibility that an antiperiplanar relationship would be completely prevented.

So we need to keep E2 in mind when we are dealing with strong bases. Those compounds are generally unstabilized oxygen anions: hydroxide and alkoxides (such as CH_3O^- or $CH_3CH_2O^-$). Very strong bases would also fall into this category. These bases are generally unstabilized carbon and nitrogen anions or semianions (such as amide, NH_2^-, or alkyllithiums such as CH_3Li or

$CH_3CH_2CH_2CH_2Li$). Bases that are stabilized in some way, such as resonance stabilized carboxylates (like $CH_3CO_2^-$) or enolates (like $CH_3COCH_2^-$) are much weaker, and are much more likely to act as nucleophiles than as bases.

E1 reactions, like S_N1 reactions, are really only possible when cation stability allows them to occur. Remember that cation formation is the slow step in these mechanisms. If the cation is too unstable to form in the first place, then there is no going down this road. That means tertiary alkyl halides are good candidates for E1, but primary alkyl halides are not. Under the right conditions, such as in the presence of a protic solvent, secondary cations might also be coaxed into being.

Whether at that point the cation undergoes an S_N1 or an E1 reaction depends less on the nucleophile than you might expect. At this point we are dealing with more or less weak bases; a strong base would have carried out an E2 while it had the chance. Instead, the two possibilities may compete, giving mixtures of products, but temperature is often the major factor determining which way the reaction will go. At higher temperature, E1 reactions are favored for entropic considerations. At lower temperature, S_N1 may dominate.

Sometimes, E1 reactions can be carried out in the presence of a strong base, but the base is very dilute. As a result, the base is not as likely to encounter the alkyl halide until the alkyl halide has already had time to dissociate into anion and cation. At that point, the base just comes in and deprotonates the cation.

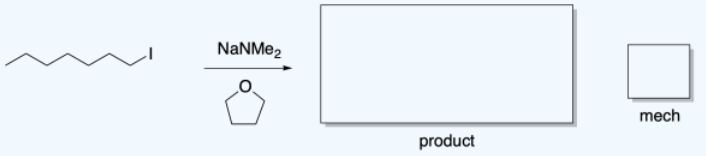
? Exercise 4.15.5

Predict the major products of the following reactions, and the mechanism type (S_N1, S_N2, E1, E2) by which the products are formed.


Br
O
O
Me S Me
product
mech


I
KO^{t}Bu
O
H NMe$_2$
Δ
product
mech

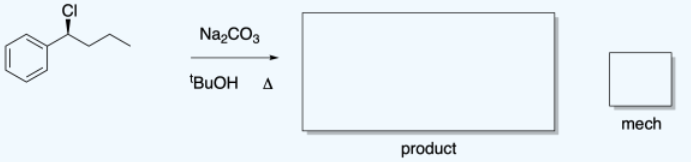

OTs
CH$_3$CH$_2$SNa
CH$_3$CH$_2$OH
product
mech

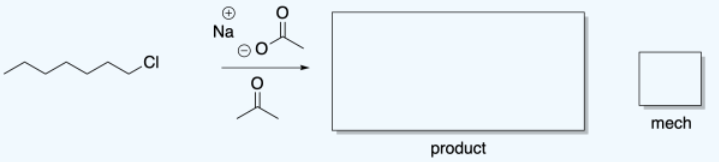

I
NaNMe$_2$
O
product
mech

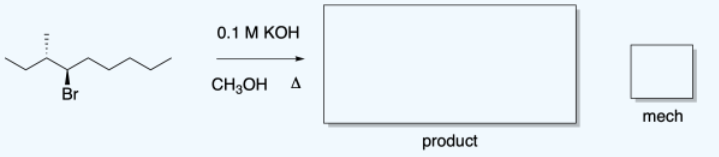

Br
Na
N=N=N
CH$_3$CN
product
mech


O
CF$_3$
Cl
KOCH$_3$
O
product
mech

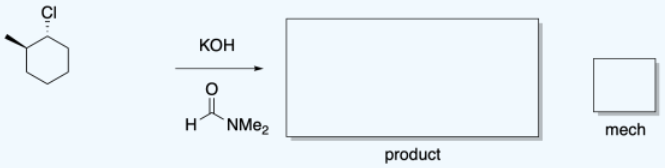

Cl
Na$_2$CO$_3$
MeOH
product
mech


Cl
Na$_2$CO$_3$
^{t}BuOH
Δ
product
mech


Cl
Na
O
O
O
product
mech

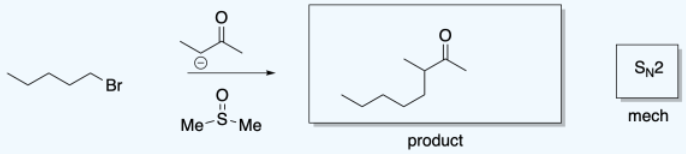

Br
0.1 M KOH
CH$_3$OH
Δ
product
mech

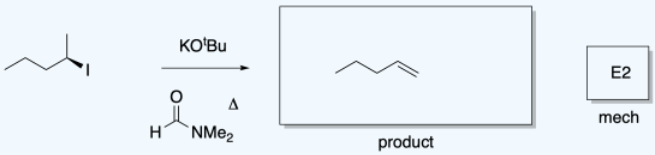

Cl
NaSCH3
CH3OH
product
mech

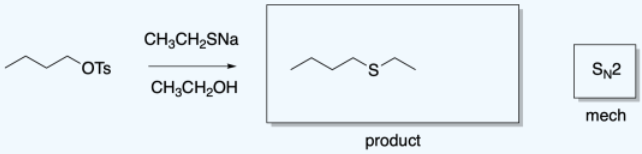

Cl
KOH
O
H
NMe2
product
mech

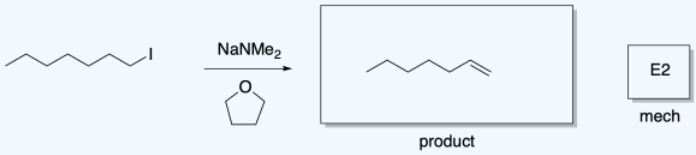

Br
Na2CO3
CH3CH2OH
Δ
product
mech

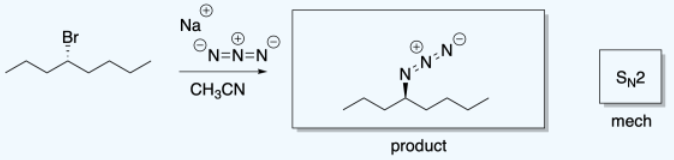
Answer

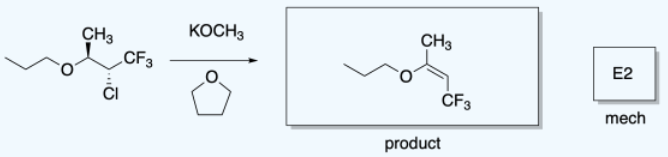

Br
O
Me
S
Me
product
SN2
mech

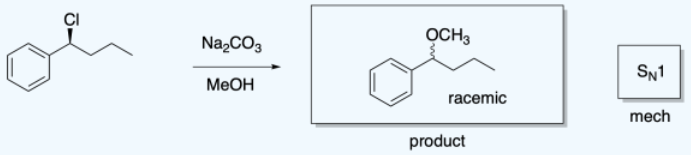

I
KO^tBu
Δ
H
NMe2
product
E2
mech

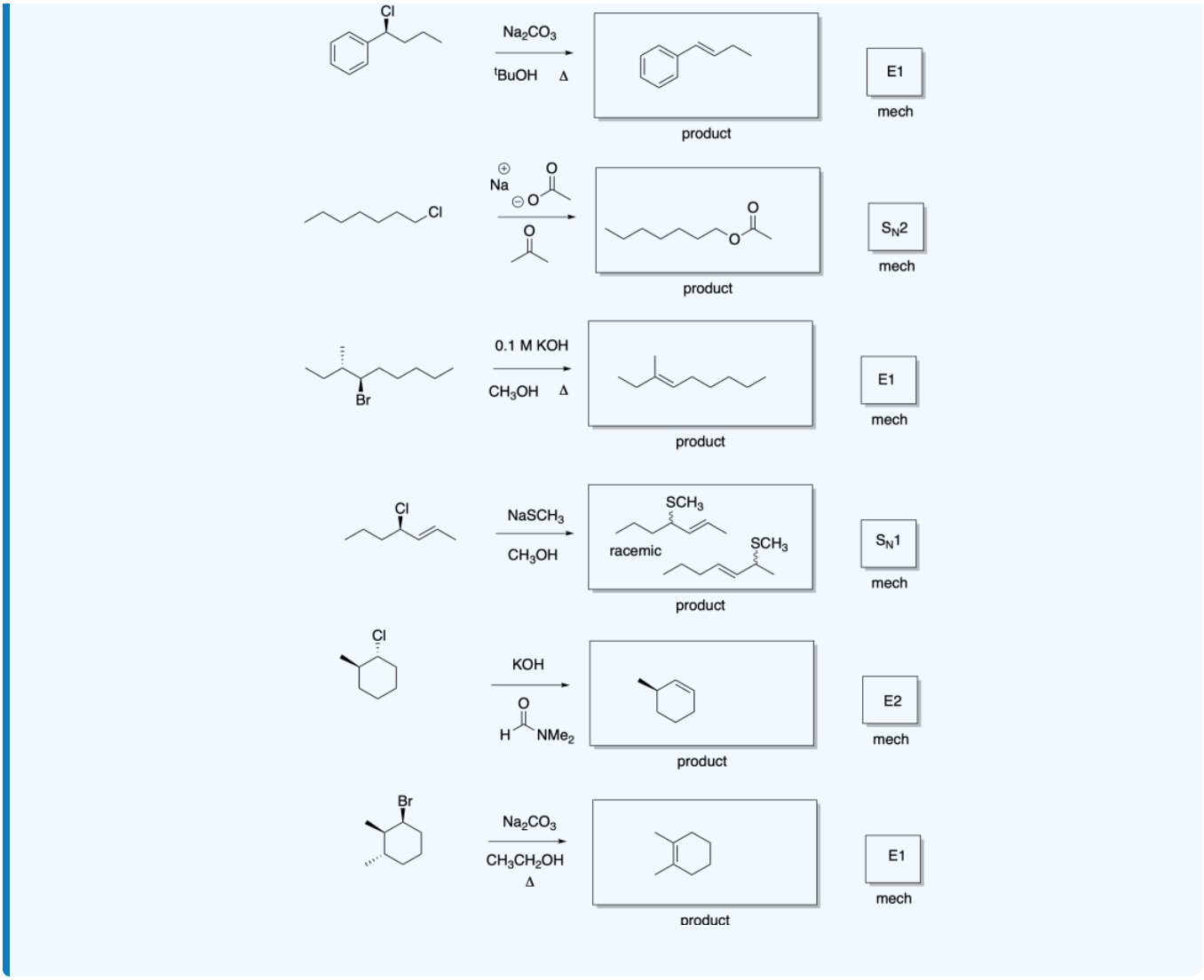

OTs
CH3CH2SNa
CH3CH2OH
S
product
SN2
mech


I
NaNMe2
O
product
E2
mech


Br
Na
N=N=N
CH3CN
product
SN2
mech

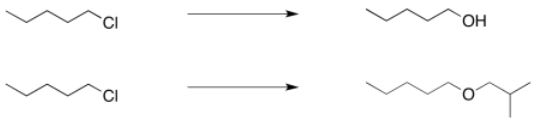

CH3
CF3
O
Cl
KOCH3
O
CH3
O
CF3
product
E2
mech


Cl
Na2CO3
MeOH
OCH3
racemic
product
SN1
mech

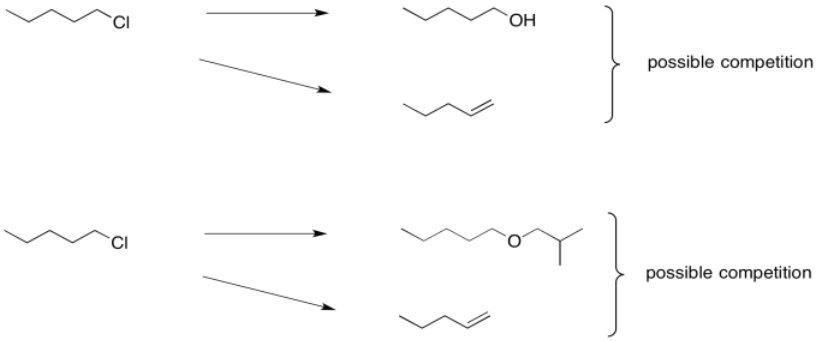


4.16: Nucleophilic Substitution in Synthesis - Alcohols and Ethers

Nucleophilic substitution reactions can be useful in organic synthesis. Mostly they are used for the interconversion of functional groups. For example, an alkyl halide might be transformed into an alcohol, or into an ether.



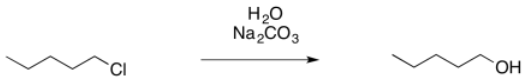
The trouble is, these seemingly simple steps can be very difficult. That's because the hydroxide needed to make an alcohol from an alkyl halide is really quite basic. So is the alkoxide that would be needed in order to turn an alkyl halide into an ether. Instead of substitution, you may get an elimination reaction.



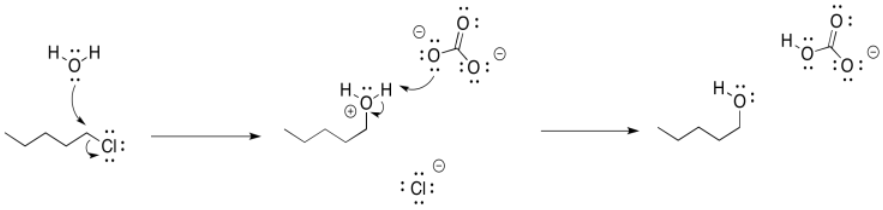
Who cares? Well, you would care if you were working on the synthesis of an antimalarial drug that could save millions, or an anticancer drug, or anything of that nature. Maybe that ether forms the last crucial part of the pharmacophore that will bind the drug to its target. Without this reaction, it may be thousands of times less effective. So this little reaction could be very important.

Clearly, the best thing to do would be to make sure a substitution reaction happened, and not that elimination. We need the reagent to be a nucleophile, not a base.

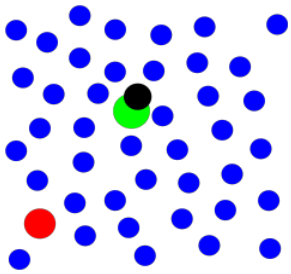
In the case of the alcohol synthesis, we could use water as the nucleophile, rather than hydroxide. Water is certainly less basic than hydroxide ion. It is still nucelophilic, though, because it still has a lone pair. If we add it to an alkyl chloride, the water will displace the chloride, and then the extra proton will be plucked off the positive oxygen atom by the chloride, leaving us with the alcohol.



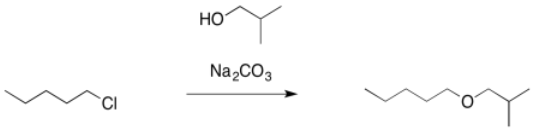
That last step would form hydrogen chloride, a corrosive acid, and that could cause problems. To counteract that possibility, we will want to add a weak base so that the HCl gets neutralized. Sodium carbonate (Na_2CO_3) or sodium bicarbonate ($NaHCO_3$) may be good options, because they are mildly basic and they dissolve in water.



Alternatively, we could just use sodium hydroxide as the base. That gets us back to the original problem. However, in order to avoid elimination, we would use very dilute sodium hydroxide. We would keep its concentration low enough that the alkyl halide is much more likely to react with the water than with the hydroxide ion, for the simple reason that it is much more likely to run into a water molecule than a hydroxide ion. However, once that oxygen donor atom picked up a positive charge, it would be more attractive to the hydroxide ion, and the hydroxide would then come in for the proton.



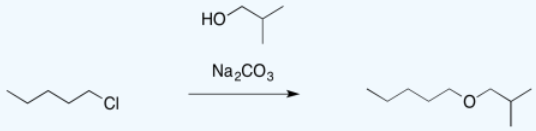
In the same way, if we wanted to make an ether, we might use an alcohol as the nucleophile rather than the much more basic alkoxide ion. We would add a weak base to sponge up the extra proton and avoid formation of a strong acid.



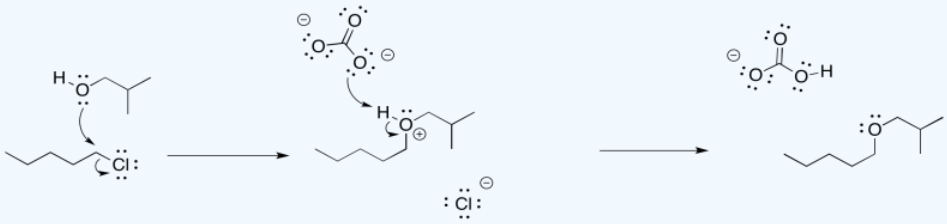
- A neutral nucleophile is less basic than an anionic one, and may avoid elimination reactions
- A weak base can be used to scavenge protons from the reaction

? Exercise 4.16.1

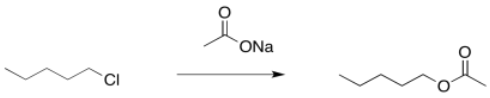
Provide a mechanism for the following reaction.



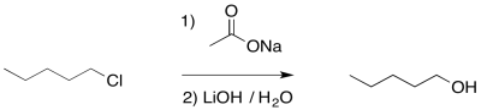
Answer



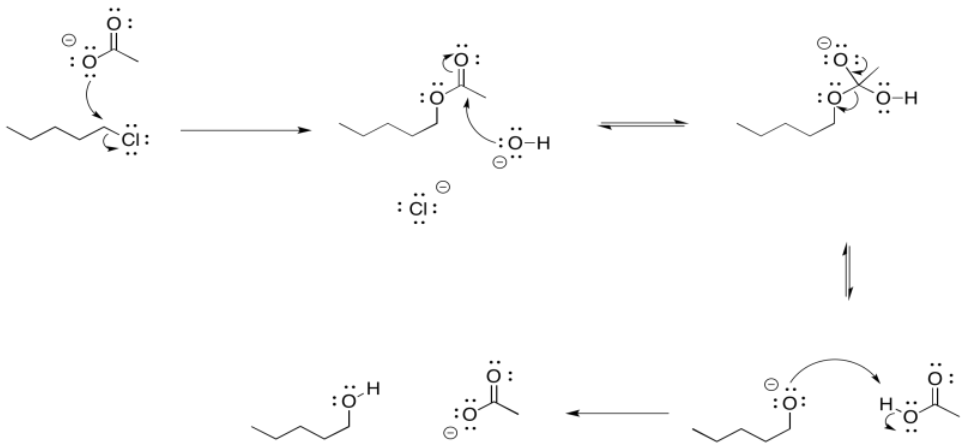
There is another approach to limiting the amount of elimination during a substitution step to form an alcohol. It also involves the use of a more stable nucleophile than a hydroxide ion. However, it employs a more reactive anionic nucleophile, rather than the neutral water. If an acetate ion is used instead, very little elimination usually occurs. An ester is formed as a product. There isn't much elimination because the acetate ion is resonance stabilised. More stable nucleophiles often undergo substitution rather than elimination.



Of course, we didn't want an ester; we wanted an alcohol. No problem. Esters can be saponified relatively easily -- that is, broken down into an alcohol and a carboxylate. Just add a hydroxide and water. Now the stronger carbonyl electrophile is a better target for the hydroxide and the reaction is pretty well assured to get to the right place.

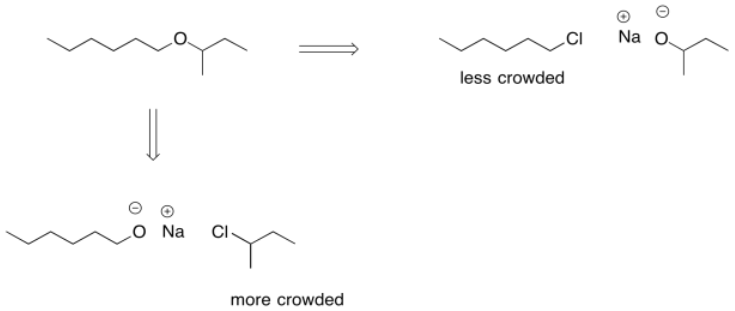


Overall, the reaction is actually a sequence of several events.



- Acetate esters are readily converted into alcohols under basic conditions
- By turning an alkyl halide into an ester first, and then into an alcohol, we can limit competition with elimination

We can't take the same approach in ether synthesis. An ether is an oxygen bridge between two tetrahedral or sp^3 carbons; we can't have resonance stabilisation and still have those two sp^3 carbons. Instead, another strategy is sometimes employed during addition of an anionic nucleophile to an alkyl halide. An alkoxide ion is still employed, but care is taken in how the alkoxide and the alkyl halide are chosen. Because the ether is symmetric -- it is two tetrahedral carbons attached to an oxygen -- either side could originate as the alkoxide and either side could originate as the alkyl halide.



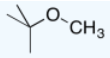
If the alkyl halide is chosen so that steric crowding is minimized, there is a lower chance of an accidental collision between the alkoxide and a beta hydrogen on that alkyl halide. In some cases, we might even be able to choose the alkyl halide so that elimination is not possible at all. If possible, we can use an alkyl halide that doesn't have any beta hydrogens.

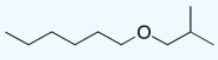
In general, the use of alkoxide ions as nucleophiles can be pretty successful if done carefully, and this approach to making ethers even has its own name. It's called the Williamson ether synthesis.

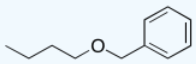
- In the Williamson ether synthesis, the less crowded half of the ether is formed from the alkyl halide
- In some cases, an alkyl halide may also be chosen because elimination is not physically possible with that structure

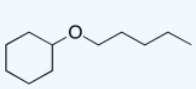
? Exercise 4.16.2

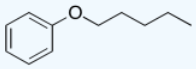
Propose Williamson ether syntheses of the following compounds.

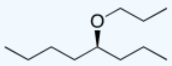
a) 

b) 

c) 

d) 

e) 

f) 

Answer

a) 

b) 

c) 

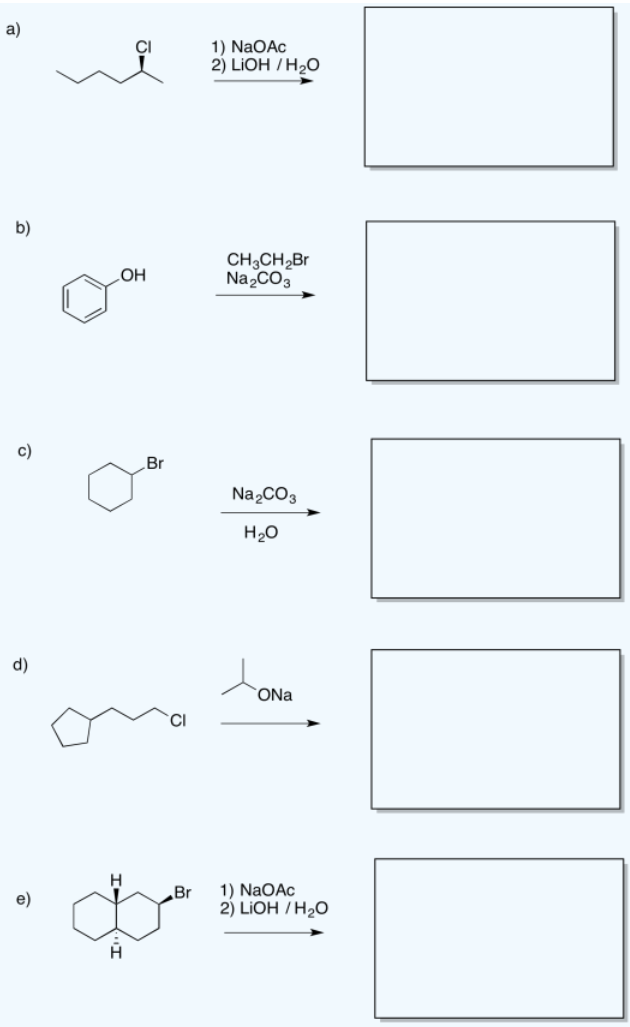
d) 

e) 

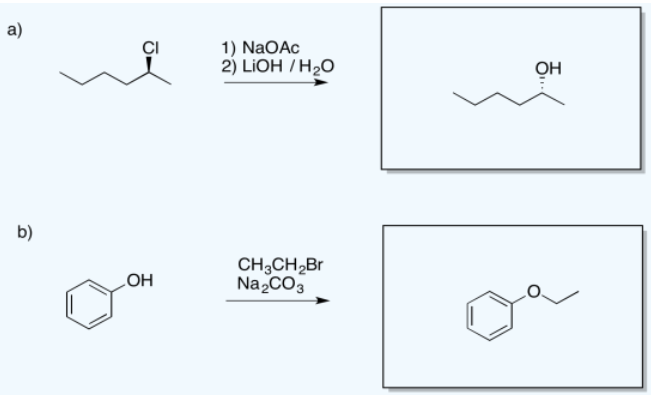
f) 

Exercise 4.16.3

Provide products of the following reactions.

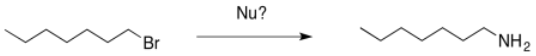


Answer

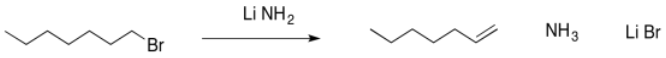


4.17: Nucleophilic Substitution in Synthesis- Amines

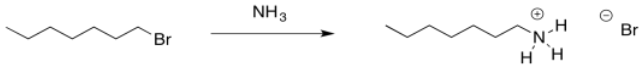
Amines can be synthesized through nucleophilic substitution. Using an alkyl halide and the proper nucleophile, the halide can be replaced by an amino group.



If an amide ion were used as the nucleophile, elimination would be a pretty sure thing. An amide ion is even more basic than a hydroxide ion. The nitrogen atom is less electronegative than the oxygen atom of hydroxide. This was the same problem with making alcohols and ethers with hydroxide or alkoxide ions, but now the problem is more severe.

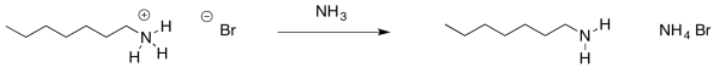


In the case of alcohol and ether syntheses, one approach was to simply use a neutral form of the nucleophile rather than an anion. We could do that in this case. Ammonia still has a lone pair and it is a pretty good nucleophile. We don't need a negative charge on the nitrogen for it to displace a halogen from an alkyl halide.

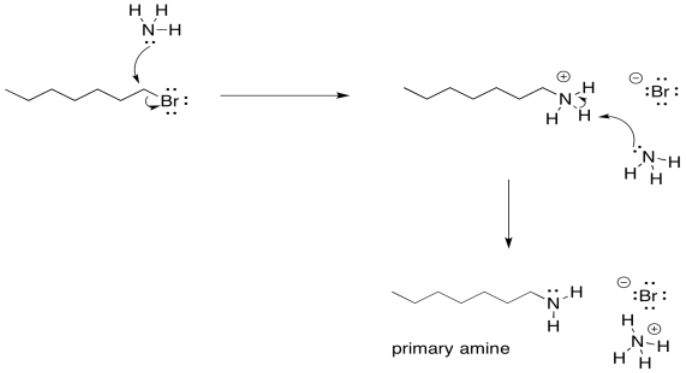


Because nitrogen is a litle less electronegative than oxygen, ammonia is a better nucleophile than water. This substitution works even better than the substitution of water for a halide. However, there are other problems.

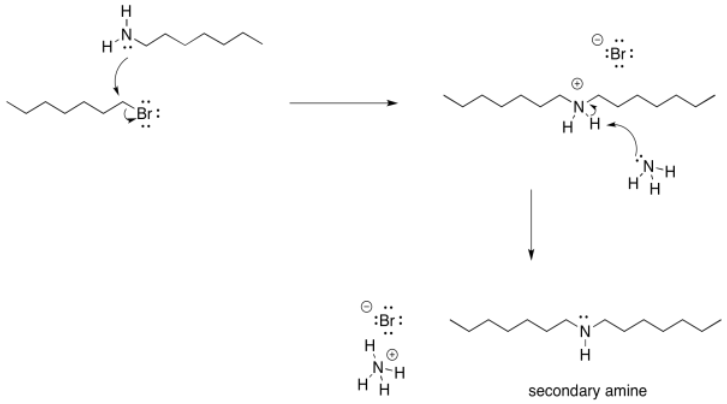
Ammonia is nucleophilic, but it is also basic. That can be helpful. In the synthesis of alcohols and ethers, addition of a neutral nucleophile had to be accompanied by a weak base, otherwise the buildup of acid in the reaction might cause unexpected side reactions, including the breaking of ether linkages that you were trying to make. However, it means that half of the ammonia that you put into the reaction would get used up in acid-base reactions. You would need to add twice as much ammonia as alkyl halide. One molecule of ammonia would act as the nucleophile in each reaction, and one would act as the base.



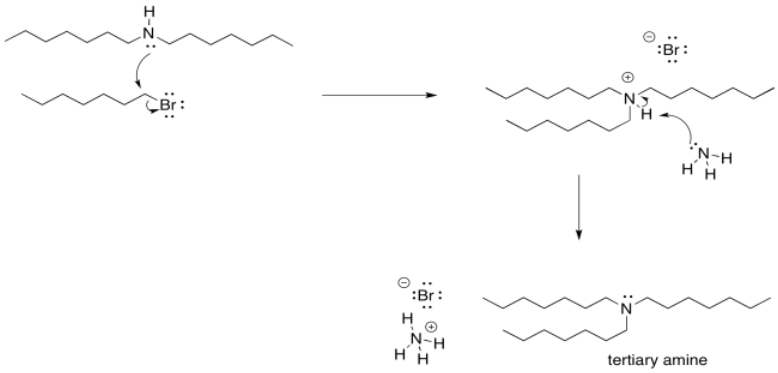
Remember, the order of steps does matter here. Sure, you could imagine some miniscule equilibrium in which one ammonia has plucked a proton off another, but a quick look at a pKa table tells you that's not very likely. The proton will only be removed after the first ammonia has donated its lone pair and the neutral nitrogen atom becomes part of a much more acidic ammonium ion.



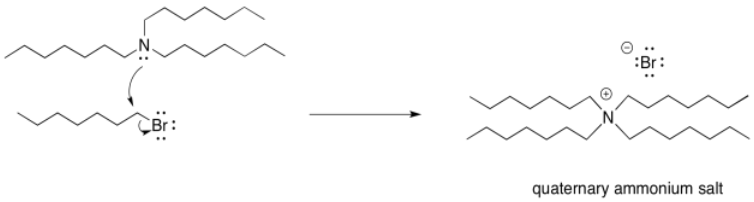
There is another problem, though. Once that ammonium ion has been deprotonated, the nitrogen gets its lone pair back again. It becomes nucleophilic again. Because nitrogen is pretty nucleophilic, there is nothing stopping this newly-formed amine from reacting with another alkyl halide. It will do so, pretty reliably. That will lead to formation of some secondary amine, in addition to the primary amine that you may have been aiming for. A secondary amine has two alkyl groups attached to the nitrogen, rather than just one.



Of course, now that we have started down that road, there's no going back. As soon as that secondary ammonium ion is deprotonated, it gets a lone pair restored. Once it has a lone pair, it becomes pretty nucleophilic. It will donate to another alkyl halide and form a tertiary ammonium ion. That tertiary ammonium ions will get deprotonated almost immediately.



As soon as the tertiary amine forms, of course it is just going to do the same thing. It will donate its lone pair to an alkyl halide. It forms a quaternary ammonium ion. This time, however, there is no proton on the nitrogen. It can't easily be deprotonated. It remains as a quaternary ammonium salt. Quaternary ammonium salts are really quite stable; they are used in household consumer products all the time. Surfactants (like those used in cleaning sprays) and anti-static agents (which might show up in dryer sheets and shampoos) frequently use quaternary ammonium salts.

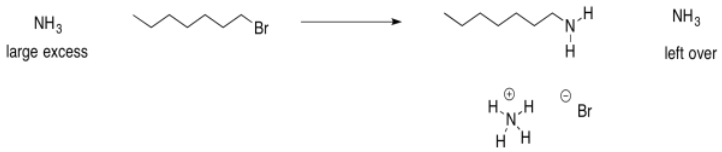


Now, let's think about our ratio again. Suppose we started with that 2:1 ratio of ammonia to alkyl halide, knowing that as soon as a first ammonia molecule bonded with an alkyl, a second ammonia would immediately take a proton. By forming a quaternary ammonium salt, we have actually used up four alkyl halides with one ammonia nucleophile. We have also used up three other ammonia molecules as bases. We have used the reactants up in a 1:1 ratio and we will have half of the ammonia left over.

So it sounds like a 2:1 ratio of ammonia to alkyl halide might get us a primary amine, but a 1:1 ratio might get us to a quaternary ammonium salt. What if we had stopped at a secondary amine? Then we would use up two alkyl halides as electrophiles, one ammonia as a nucleophile, and two ammonias as bases. That's a 3:2 ratio of ammonia to alkyl halide, or 1.5:1. Similar analysis would tell you that stopping at a teriary amine would require a 1.3:1 ratio of ammonia to alkyl halide.

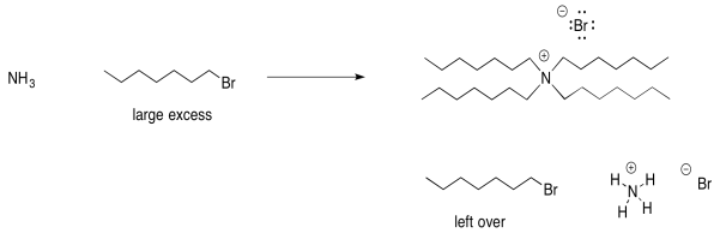
The point is, formation of these different amines require ratios of ammonia to alkyl halide that are really very similar. Realistically, there is no way we could add these exact ratios of reagents to a reaction and expect things to stop at the right place. Remember, a reaction is taking place with millions of molecules at once, and probability says that all four pathways will be followed by significant fractions of the reactants. All of these ratios of ammonia to alkyl halide will lead to the same thing: a mixture of all possible products. There would invariably be some leftover amine or leftover alkyl halide, too, once the other reagent had run out.

Practically speaking, there are only two products that you can make from this reaction. You could make a primary amine if you used a vast excess of ammonia, so that you ensured that any alkyl halide was much more likely to run into an ammonia molecule long before it ran into an amine molecule.



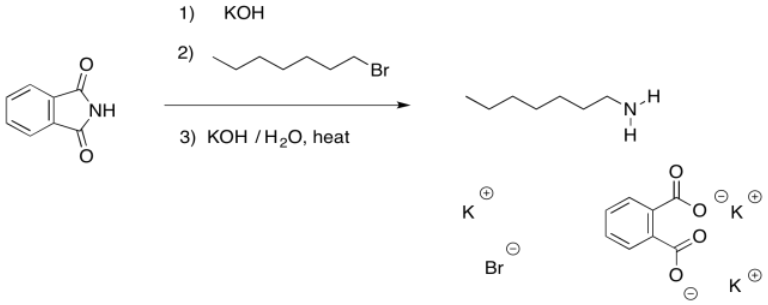
In this case, you would have leftover ammonia. That should be pretty easy to remove because of its low boiling point.

Alternatively, you could make a quaternary ammonium salt if you used a large excess of alkyl halide.

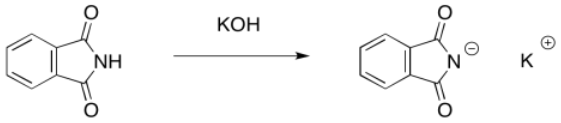


In this scenario, you would have leftover alkyl halide. The difference in solubility between the alkyl halide and the quaternary ammonium salt could help separate these two materials.

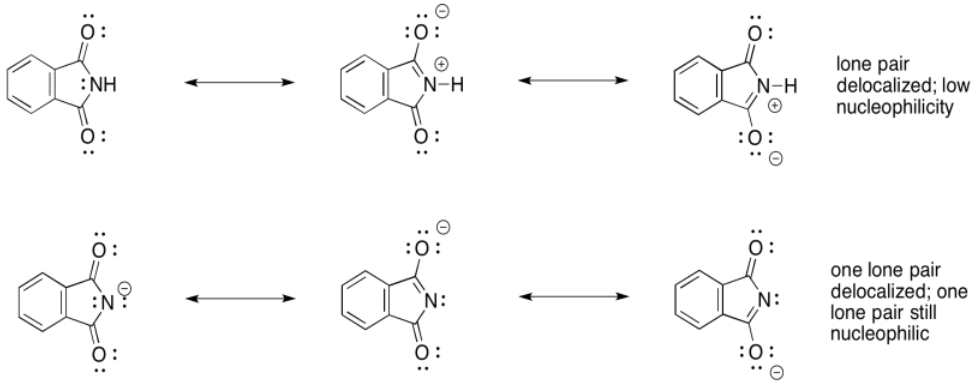
You might recall that in the section on the synthesis of alcohols and ethers, an alternative strategy used a resonance-stabilised, anionic oxygen nucleophile to make alcohols. The same strategy is often used with the synthesis of amines. This approach is called a Gabriel amine synthesis.



The nucleophile in this case is a phthalimide ("FTAL-im-id" or "FTAL-im-eyed") ion. The phthalimide ion is easily formed by a strong base such as potassium hydroxide, becaus the anion obtained is pretty stable. Even though the negative charge is on a nitrogen atom, the two carbonyls serve to delocalise the charge and make this ion less reactive.

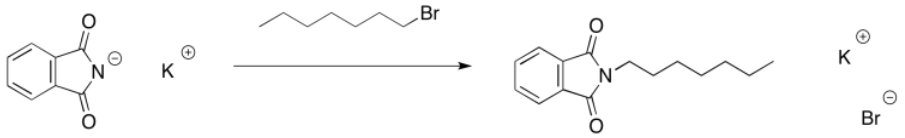


Notice the difference in nucleophilicity between the neutral phthalimide and the phthalimide ion. In the neutral compound, the single lone pair on the nitrogen is delocalised. It is not available to act as a nucleophile. This is generally true with amides and imides; the neighbouring carbonyl ties up the nitrogen lone pair so that it is neither basic nor nucleophilic.

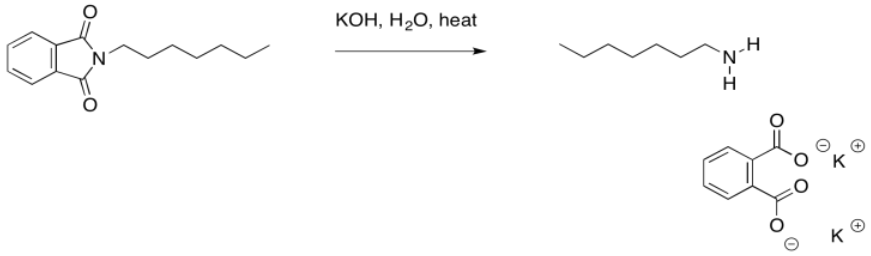


However, the phthalimide ion has a spare lone pair. If one of the lone pairs is delocalised, then the other is still available to act as a nucleophile. Both lone pairs cannot be delocalized because they are orthogonal to each other -- that means they are forced to be in different areas of space in order to minimize electron repulsion.

The phthalimide anion is thus able to act as a nucleophile. It can donate to an alkyl halide and displace the halide anion.



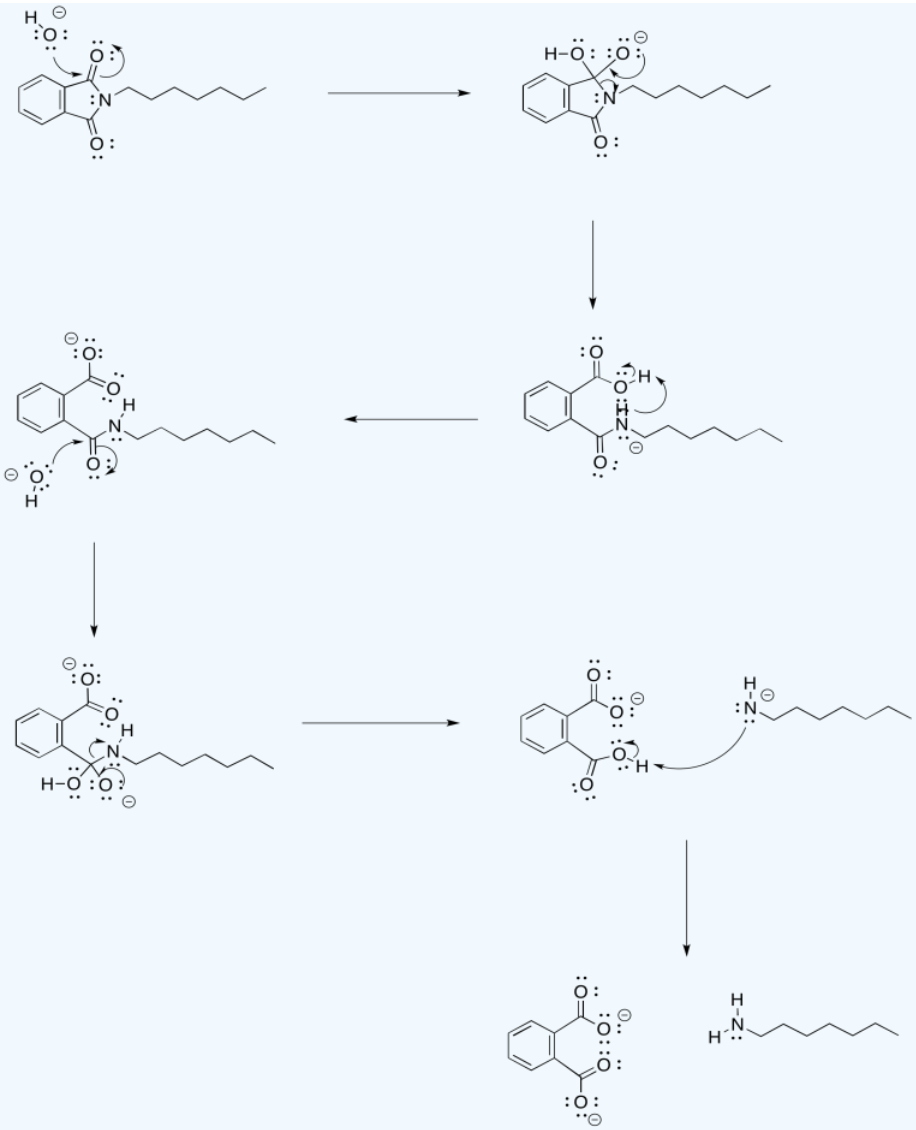
The phthalate part of the molecule has now served its purpose. It was just there to deliver the nitrogen in a way that was stable, yet suitably reactive. We can get rid of it now through base-catalysed hydrolysis. Remember, that is a carboxyloid substitution reaction. The resulting phthalate salt is easily removed because of its very different solubility properties.



? Exercise 4.17.1

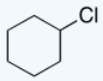
Provide a mechanism for the hydrolysis of the imide shown above.

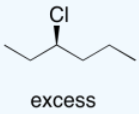
Answer

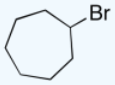


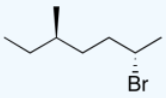
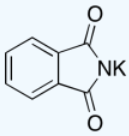
Exercise 4.17.2

Provide products of the following reactions.

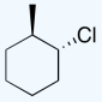
a)  excess NH_3 →

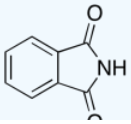
b)  excess NH_3 →

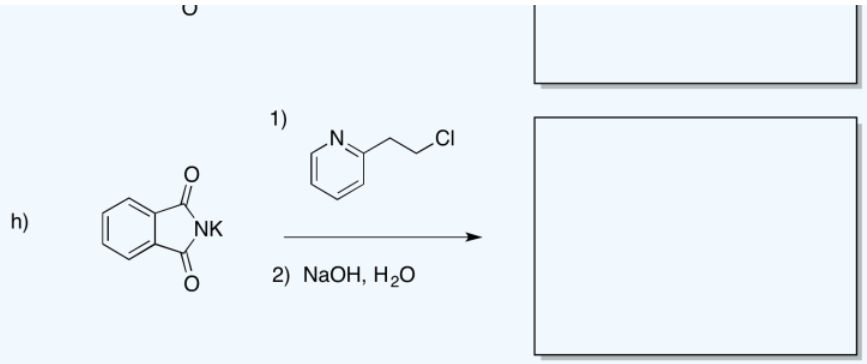
c)  iPr_2NLi →

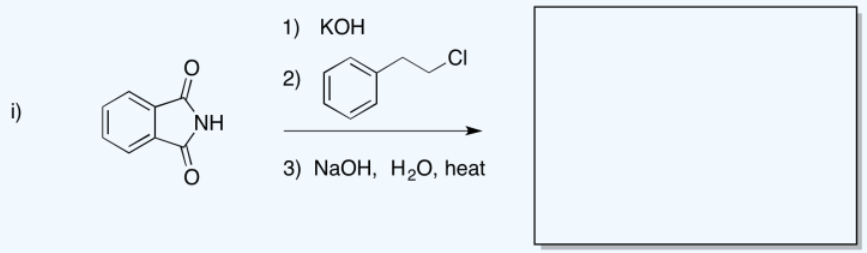
d)  1)  2) NaOH, H_2O, heat →

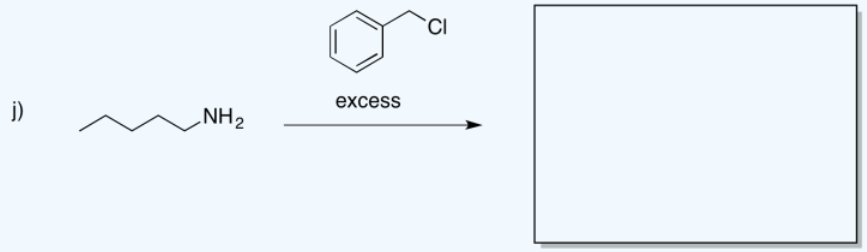
e)  excess ammonia →

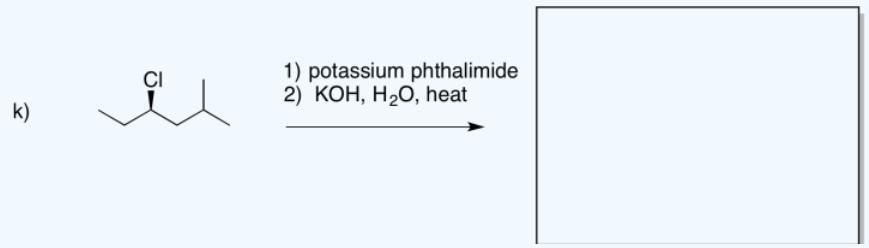
f)  $NaNH_2$ →

g)  1) KOH 2) $(CH_3)_2CH_2CH_2Br$ 3) KOH, H_2O, heat →

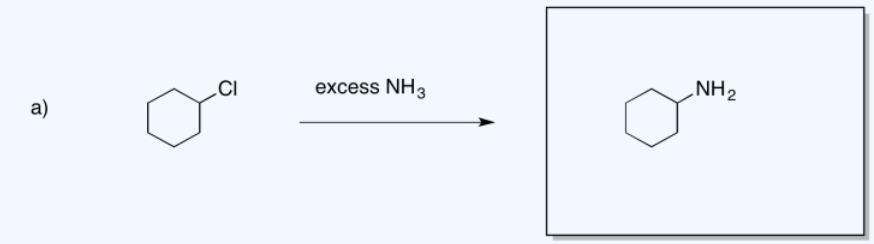


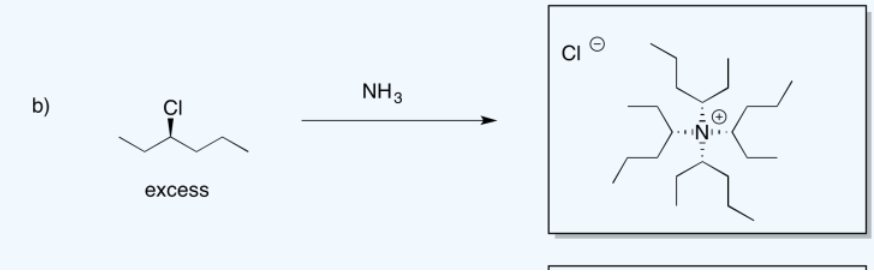




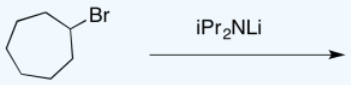


Answer

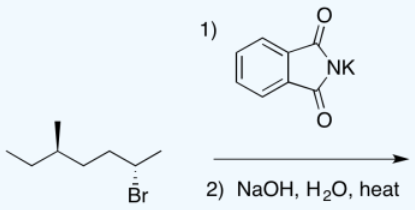




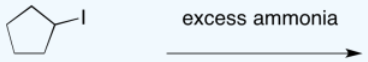
c)



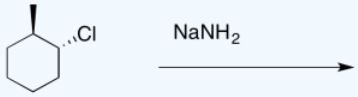
d)



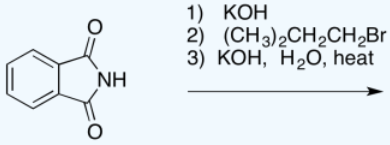
e)



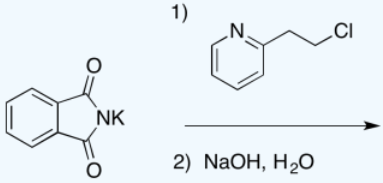
f)



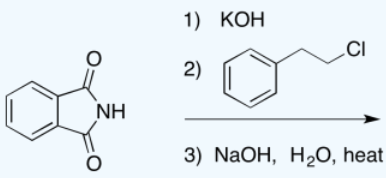
g)

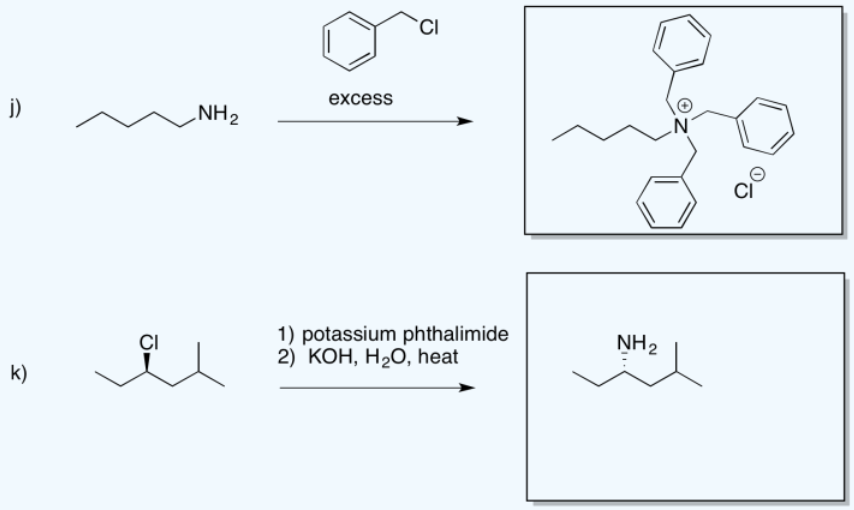


h)



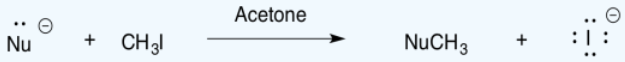
i)





Exercise 4.17.3

For the reaction of nucleophile with iodomethane in acetone, rank the nucleophiles in order of reactivity (1 = fastest, 3 = slowest).



a. _ HO^- _ HS^- _ H_2O
b. _ H_2O _ H_3O^+ _ NH_3
c. _ $CH_3CH_2NH_2$ _ $(CH_3)_2CHNH_2$ _ $(CH_3)_3CNH_2$

Answer a

2 HO^- 1 HS^- 3 H_2O; the anions are more nucleophilic than the neutral, but sulfur is more polarizable than oxygen

Answer b

2 H_2O 3 H_3O^+ 1 NH_3; the neutrals are more nucleophilic than the cation, but nitrogen is less electronegative than oxygen

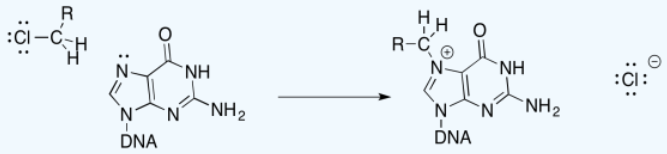
Answer c

1 $CH_3CH_2NH_2$ 2 $(CH_3)_2CHNH_2$ 3 $(CH_3)_3CNH_2$; steric effects

Exercise 4.17.4

DNA bases (adenine, guanine, cytosine, and thymidine) contain nucleophilic nitrogen atoms, which is why many halogenated compounds are carcinogenic. Alkylated DNA can still function in its process of replication, though it will do so abnormally, resulting in mutations in the DNA and, ultimately, cancerous cells.

a) Propose a mechanism, with arrows, for the alkylation of guanine:

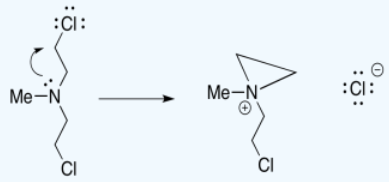


Guanine

Damaging DNA via alkylation can also be used to treat cancer. The key is that cancer calls grow and divide more rapidly than normal calls, and thus are more susceptible to mechanisms that damage DNA and impair its functions. Mechlorethamine is one

such drug that cross-links DNA.

The mechanism for the activation of mechlorethamine is shown below:



Mechlorethamine Aziridinium ring

b) Using that step, provide a mechanism, with arrows, for the formation of two cross-linked guanine molecules.

c) What makes the aziridinium ring so electrophilic?

Answer a & b

Guanine

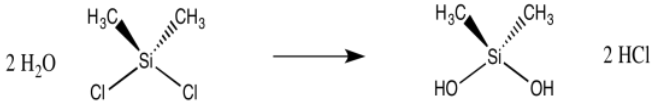
Answer c

Ring strain promotes opening of the ring.

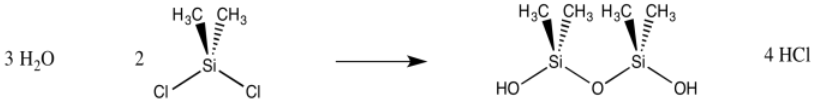
4.18: Nucleophilic Substitution at Silicon

Silicon is in the same group as carbon in the periodic table, so in some ways it might be expected to behave in some ways that are similar to carbon. It might not be surprising that silicon can undergo nucleophilic substitution reactions like carbon. However, there are differences in both the mechanism and the reactions that are likely to occur.

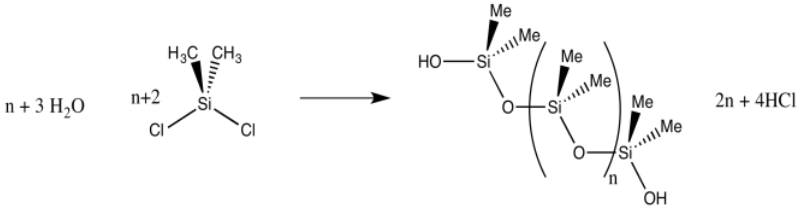
Probably the most common example of nucleophilic substitution at silicon occurs during the formation of silicone polymers. Silicon forms a pretty strong bond to oxygen, so a chloride leaving group is easily displaced from silicon to form a silanol. If a dichlorosilane is exposed to water, a silane diol is produced.



Just by adjusting the ratio of silicon that is reacting with water, we could imagine forming different products. A 2:1 ratio of H_2O : Me_2SiCl_2 might lead to a silane diol, $Me_2Si(OH)_2$. However, a 3:2 ratio could end up forming a silicone dimer, $Me_2(HO)SiOSiMe_2(OH)$. That's because the hydroxy group on the first silicon atom is still a nucleophile, and it could donate to a second silicon atom, forming a bridge between two silicon atoms.

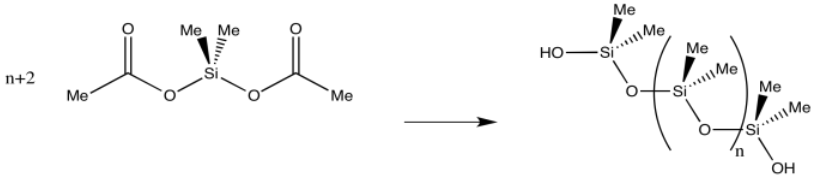


If the water is introduced gradually to the dichlorosilane, polymerization results, because a chlorosilane is more likely to react with a neighbouring silanol than with scarce water molecules. Lots of Si-O-Si bridges form, leading to a polymeric material: silicone rubber.

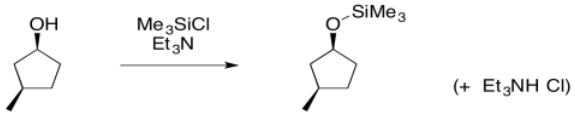


- Silicones are polymers containing -(R_2SiO)- repeating units.
- Silicones are formed via polymerization of dichlorosilane compounds with water.

The side product of this reaction is hydrogen chloride, HCl. When it contacts water, HCl dissociates to give hydrochloric acid. Hydrochloric acid is a strong acid and a severe health risk. Because of that, there are alternative formulations for making silicone that are a little safer. If the chlorine is replaced with an acetate group, polymerization is still possible upon exposure to water. However, the side product is the somewhat safer acetic acid. This route is used in commercially available silicones for household use. For example, silicone caulk can be used to waterproof around a bathtub or sink. The strong smell of vinegar when it is left to cure is the acetic acid being produced when the acetoylsilane reacts with moisture in the air.



Apart from its use in polymer materials, substitution at silicon plays an important role in organic synthesis. Silyl ethers can be made in ways similar to the formation of regular ethers. The usual approach is through addition of an alcohol to a chlorosilane. The presence of a weak base, such as a tertiary amine, prevents the buildup of corrosive hydrochloric acid. That's what would result if the chloride leaving group were the only base available to pick up the extra proton.



Exercise 4.18.1

Draw structures for the following silyl ethers.

a) the trimethylsilyl ether of cyclohexanol

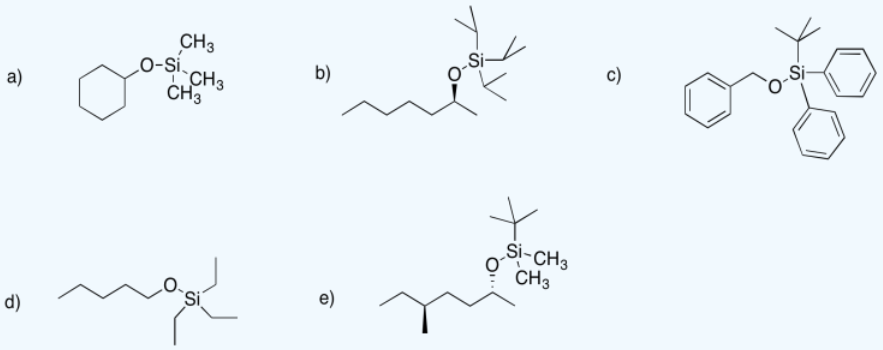
b) the triisoproylsilyl ether of (S)-2-heptanol

c) the *tert*-butyldiphenylsilyl

d) the triethylsilyl ether of pentanol

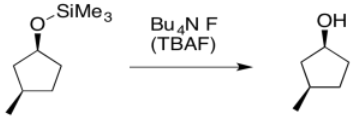
e) the *tert*-butyldimethylsilyl ether of (S)-5-methylheptan2-ol

Answer

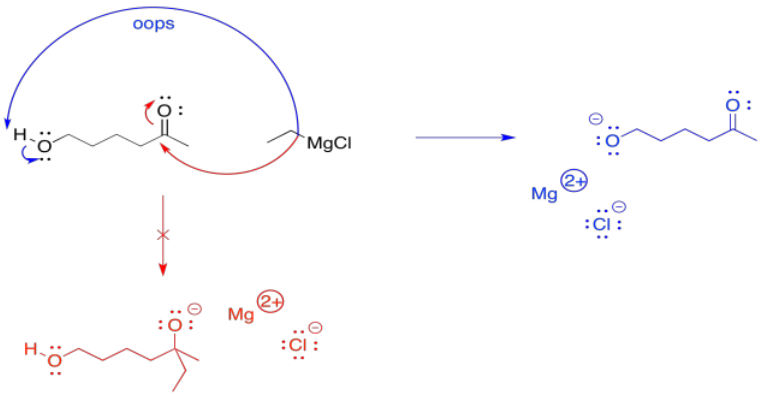


The chief utility of silyl ethers is that they are just as easy to break down as they are to make in the first place. They can be converted back to alcohols in the presence of hydrochloric acid, although the process can be very slow. That's one of the reasons that HCl must be removed during siliyl ether formation. There is an equilibrium at work here, and at some point a buildup of HCl would drive the reaction backward, preventing further formation of the silyl ether.

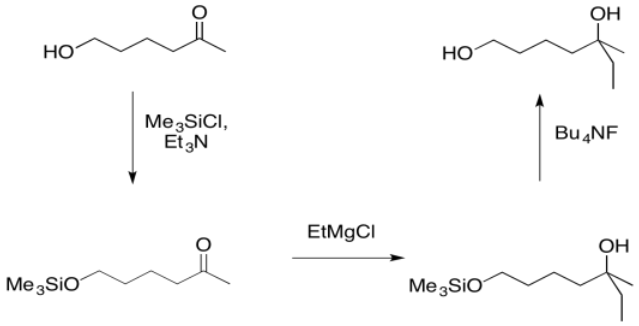
Silyl ethers can be cleaved much more quickly in the presence of fluoride ion. The usual reagent for this transformation is tetrabutylammonium fluoride (TBAF). The tetrabutylammonium ion is pretty soluble in most organic solvents; that makes the reagent much easier to use.



The reason that reversibility is useful is because it offers a way to temporarily "cover up" and alcohol group. Alcohols can be problematic during many reactions. The slightly acidic OH group, like the slightly acidic OH group of a water molecule, can interfere with sensitive reagents. Compounds that are highly basic, such as alkylmetal compounds (e.g. BuLi, EtMgBr, etc) and metal amides (e.g. $NaNH_2$, LDA, etc) will deprotonate that OH group instead og going on with their intended business with the reactant. For example, if a Grignard reagent is supposed to add to a carbonyl, but it encounters a hydroxy group, it will simply pull the proton from the hydroxy group. Then it will be neutralised. It won't be a nucleophile anymore, so nothing will happen after that.



Instead, if the hydroxy group is first protected, the reaction will proceed with no possibility of an accidental acid-base event. Later, the hydroxy group can easily be replaced.



- Silyl ethers can be used to protect mildly acidic alcohols
- Silyl ethers can be removed easily when protection is no longer needed

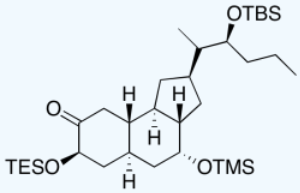
Common silyl ethers include trimethyl silyl (Me_3Si, or TMS); triethylsilyl (Et_3Si, or TES); tri-*iso*-propylsilyl (iPr_3Si, or TIPS); *tert*-butyldimethylsilyl ($tBuMe_2Si$, or TBS); and *tert*-butyldiphenylsilyl ($tBuPh_2Si$, TBDPS). The fact that a variety of silyl ethers are commonly available allows chemists to choose from different ones. As a result, several different silyl ethers might be used to protect alcohols in different positions in a more complicated molecule. They can then choose which silyl group to remove, in which order. Selective removal of silyl ethers is possible because they are very sensitive to steric effects. The more crowded the silyl ether, the harder it is to remove.

- Less crowded silyl ethers are removed most easily
- More crowded silyl ethers are removed more slowly
- Less crowed silyl ethers can be removed, leaving more crowded ones intact

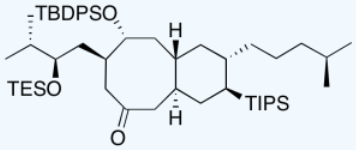
? Exercise 4.18.2

In each of the following cases, rank the order in which the silyl ethers could be removed.

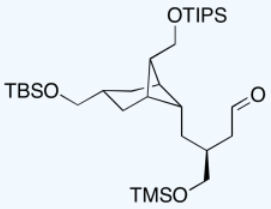
a)



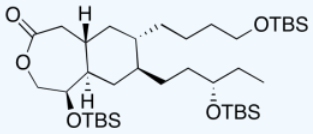
b)



c)

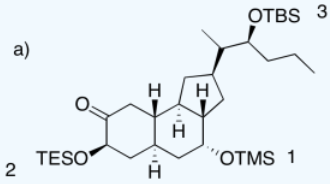


d)

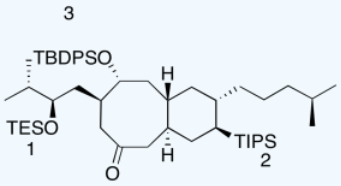


Answer

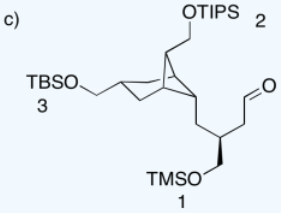
a)



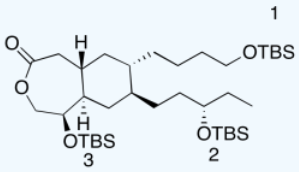
b)



c)



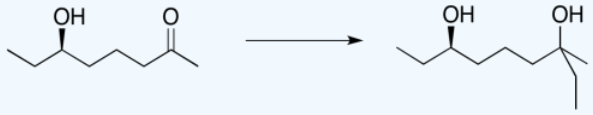
d)



Exercise 4.18.3

Use a triethylsilyl ether to help complete the following transformations.

a)



b)

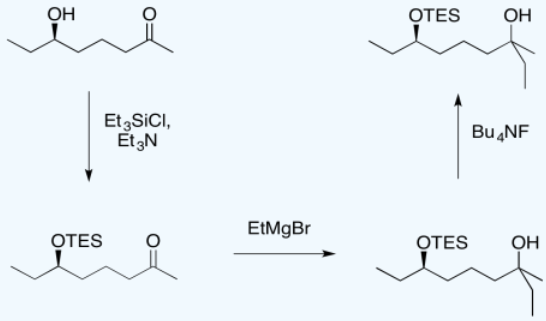
c)

d)

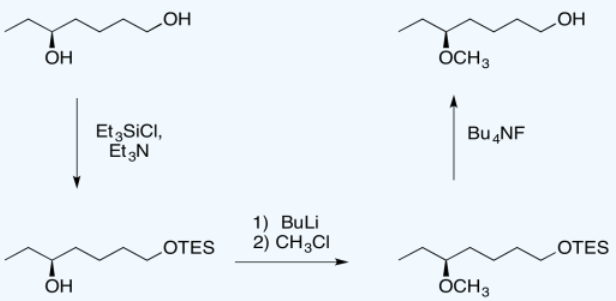
e)

Answer

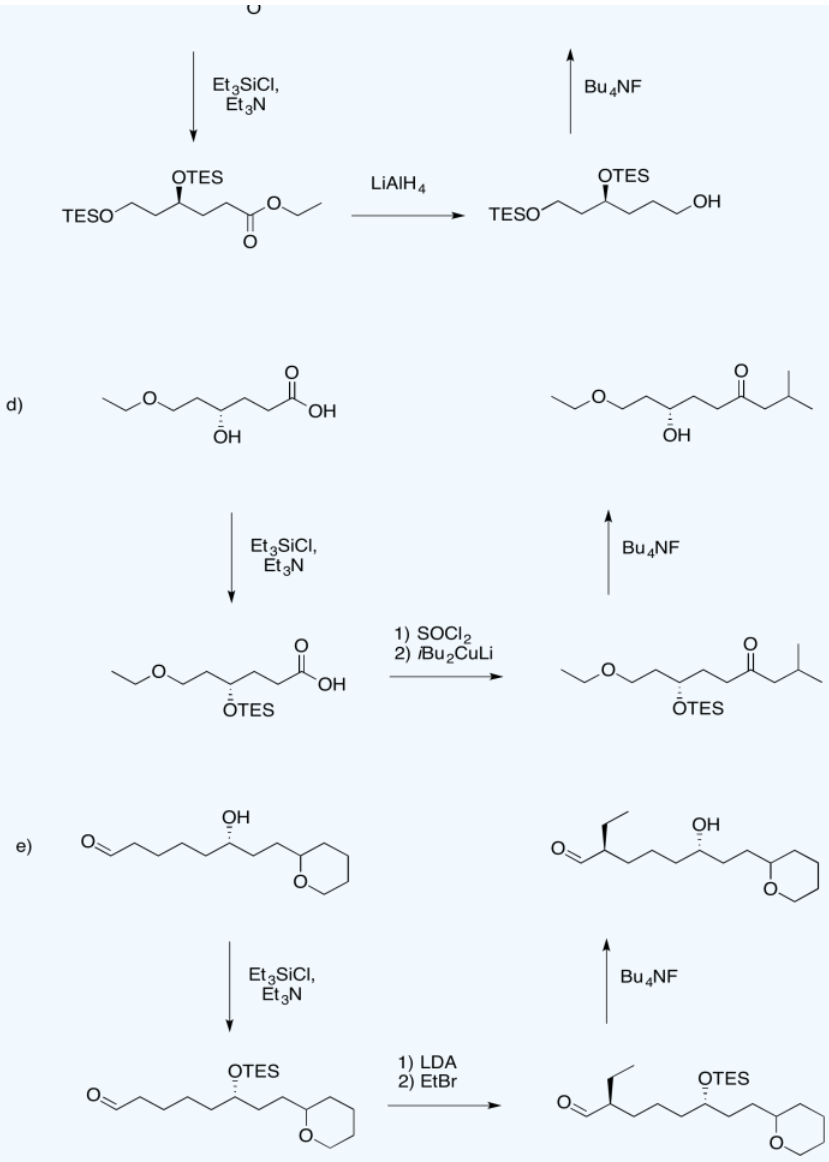
a)



b)



c)

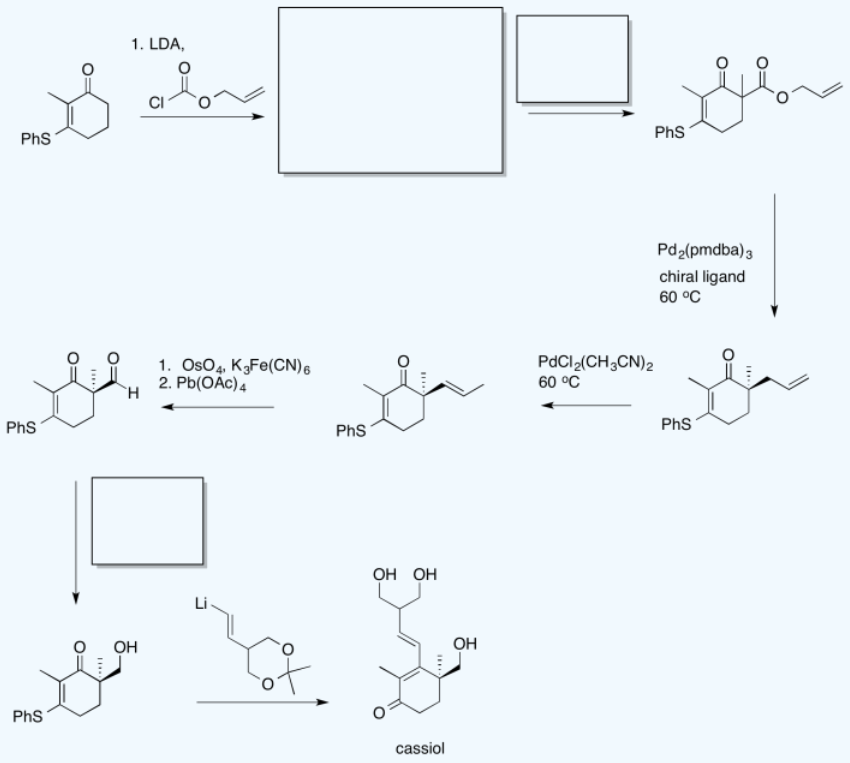


4.19: Extra Problems with Nucleophilic Substitution and Elimination

Exercise 4.19.1

Fill in the missing items in the following synthesis. Includes: aliphatic nucleophilic substitution, carboxylic substitution, enolates, addition to carbonyl (anionic nucleophiles).

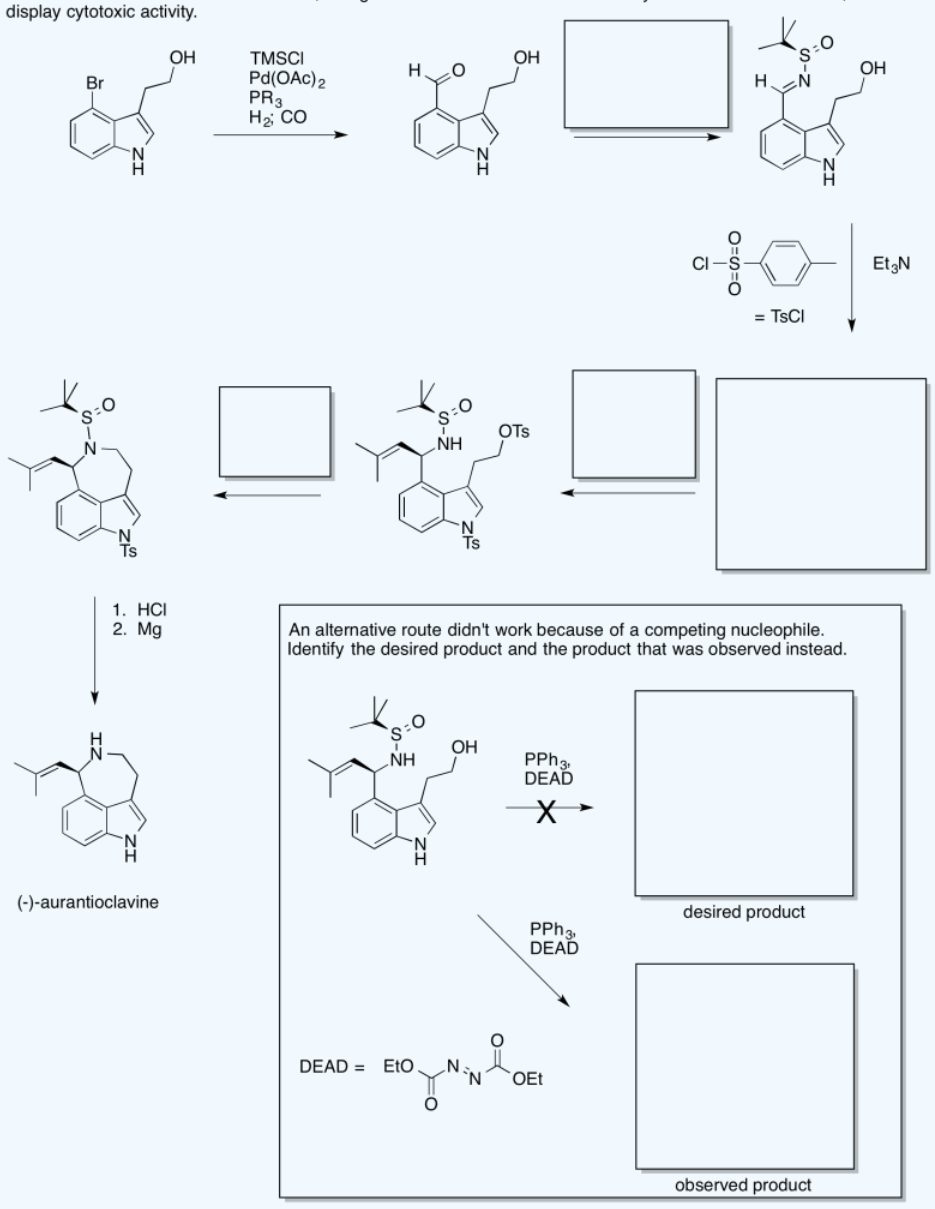
Synthesis of (+)-Cassiol
Stoltz (Caltech) 2008
Cassiol is a natural product of *Cinnamomium cassia* that displays potent antiulcerogenic activity in rats.



Exercise 4.19.2

Fill in the missing items in the following synthesis. Includes: addition to carbonyls (anionic nucleophiles, neutral nucleophiles, aliphatic nucleophilic substitution, Mitsunobu reaction).

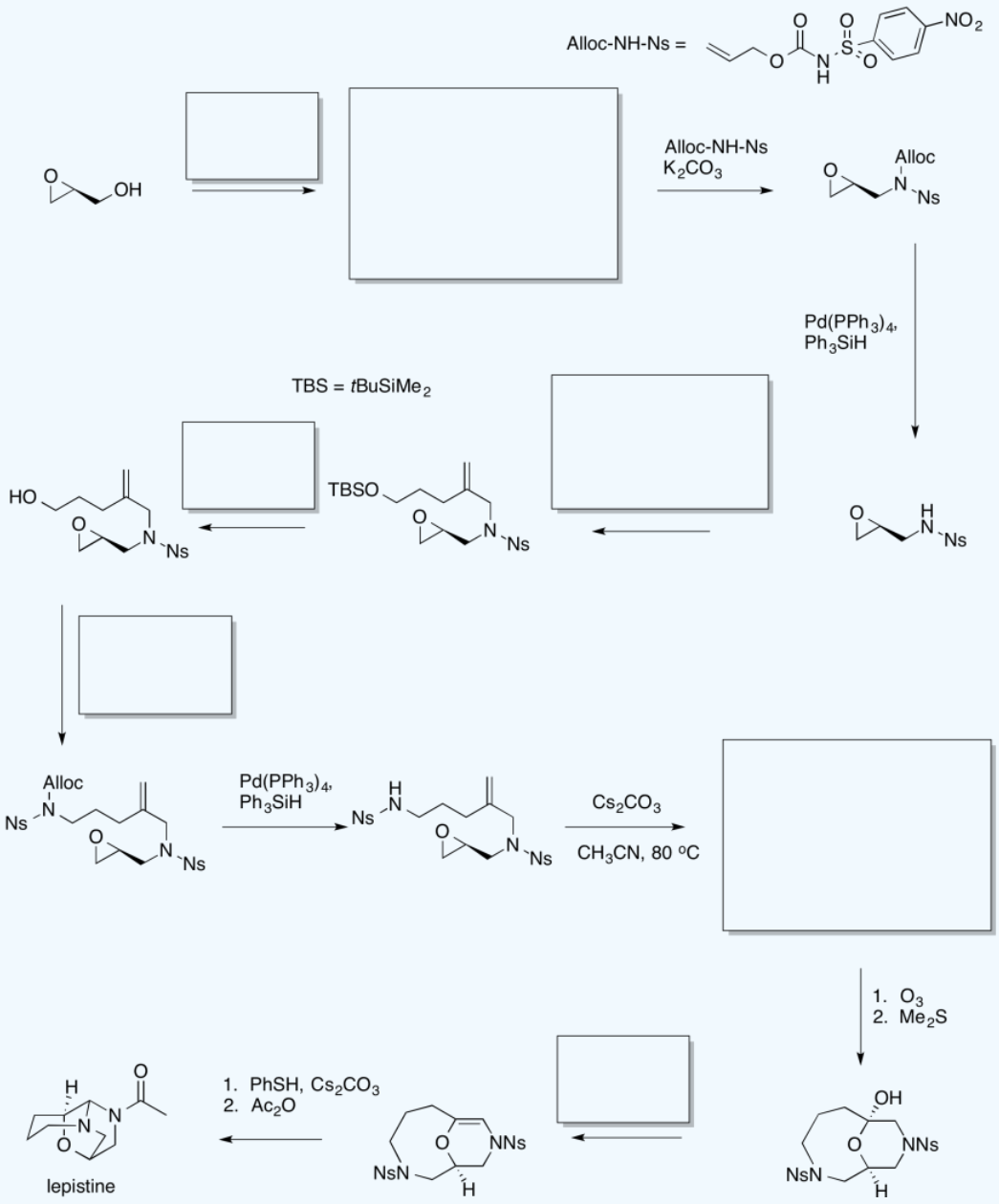
Synthesis of (-)-Aurantioclavine
Ellman (Berkeley) 2010
Isolated from Penicillium aurantiovirens; thought to be an intermediate in the biosynthesis of communesins, which display cytotoxic activity.



? Exercise 4.19.3

Fill in the missing items in the following synthesis. Includes: aliphatic nucleophilic substitution,sulfonate substitution, Mitsunobu reaction, silyl ether cleavage, nucleophilic substitution of epoxides, elimination / dehydration.

Total Synthesis of (-) Lepistine
Yokoshima & Fukuyama (Nagoya, Japan) 2014
Natural product of the mushroom Clitocybe fasciculate. With no known biological properties, the synthesis was undertaken because of its unusual structure.

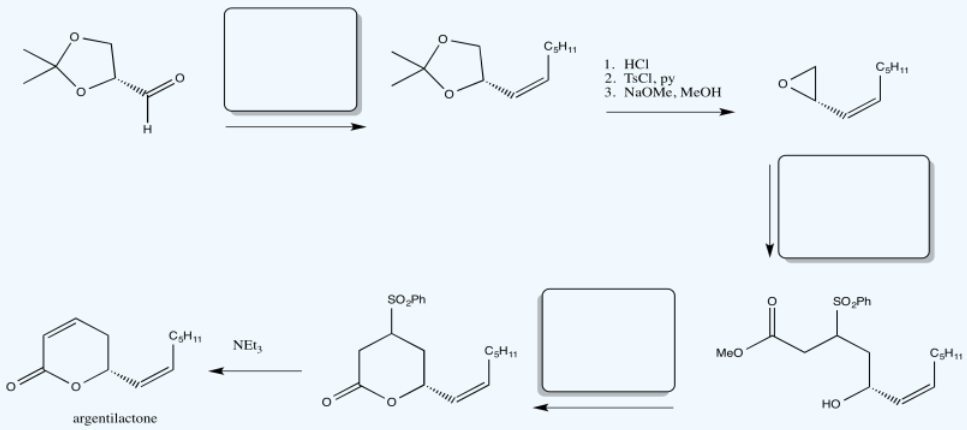


? Exercise 4.19.4

Fill in the missing items in the following synthesis. Includes: addition to carbonyls (ylides), nucleophilic substitution of epoxides, carboxylic substitution.

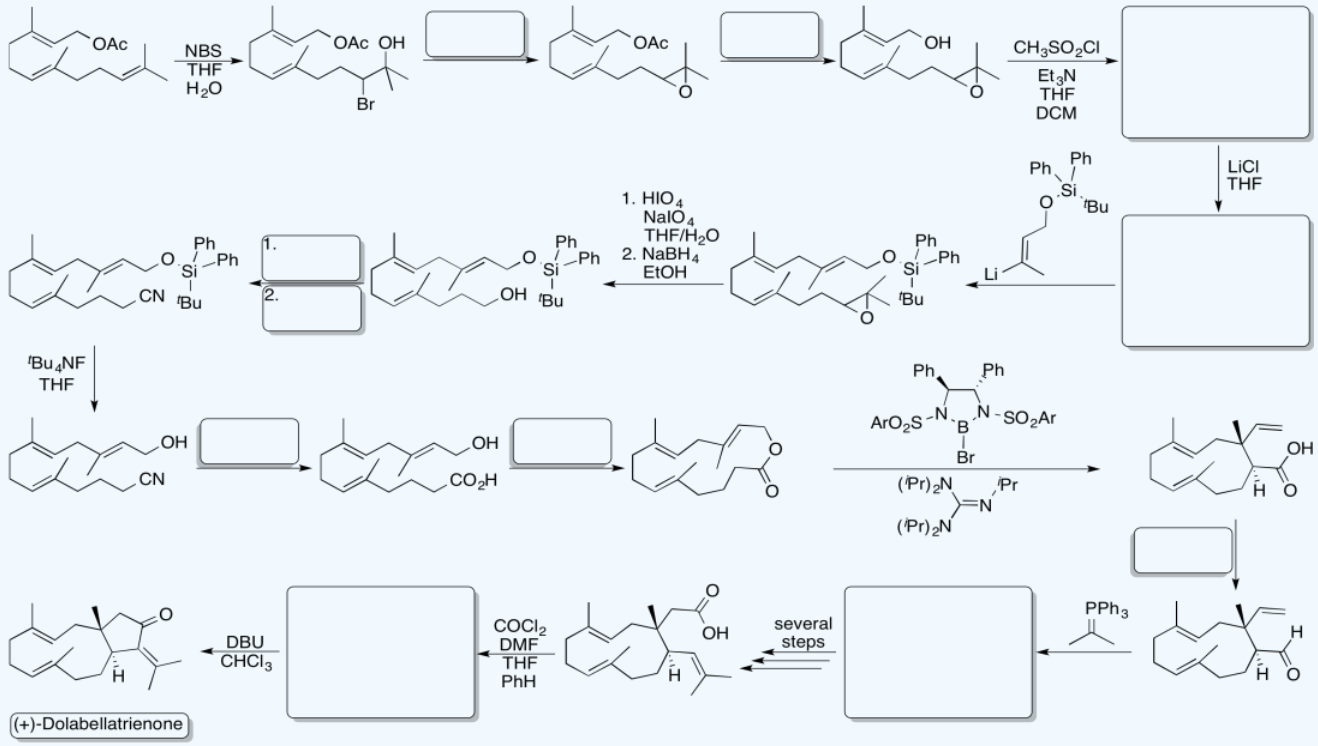
Argentilactone

Carretero and Ghosez, *Tetrahedron Lett.*, **1988**, *29*, 2059.



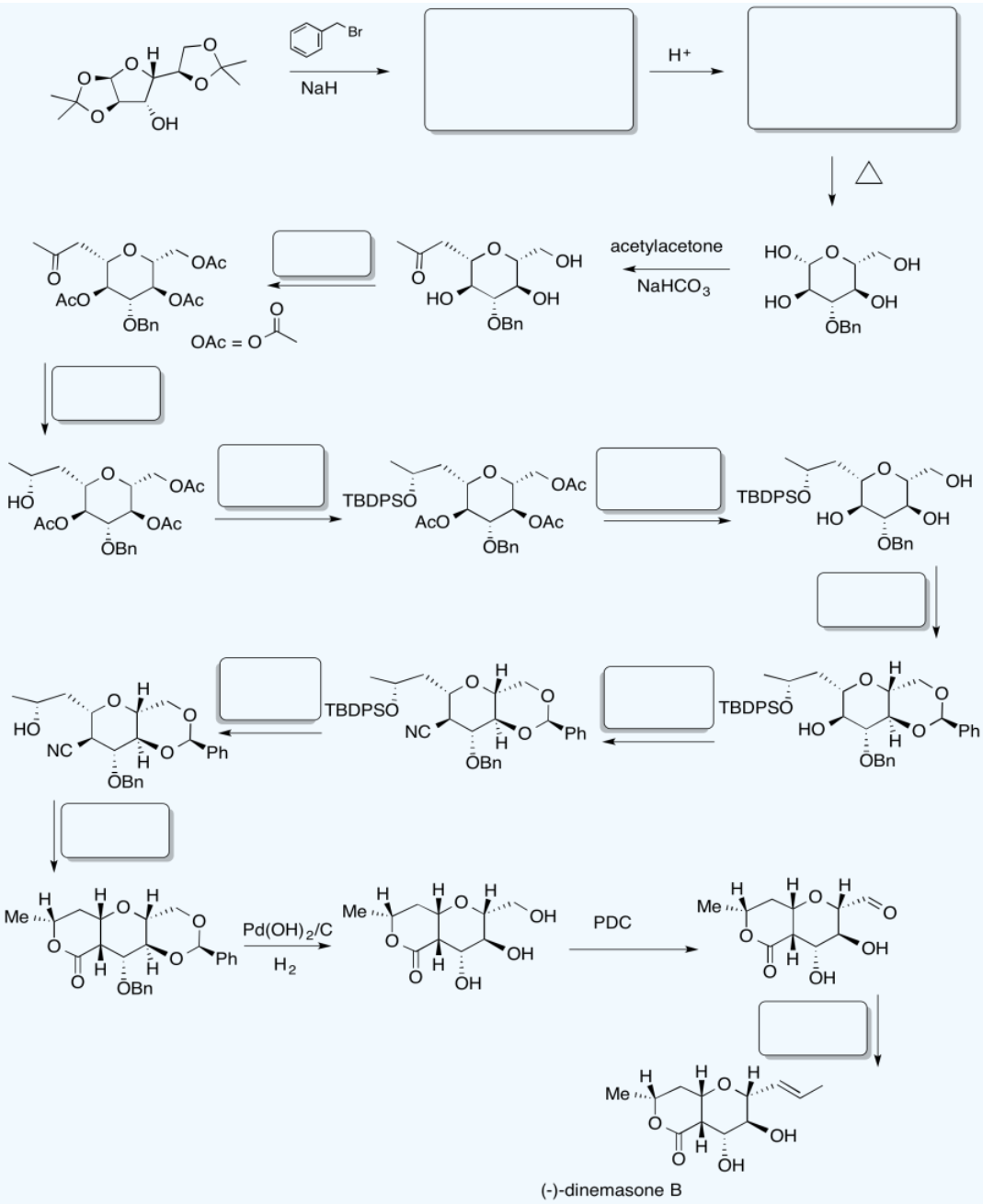
Exercise 4.19.5

Fill in the missing items in the following synthesis. Includes: aliphatic nucleophilic substitution, carboxylic substitution, sulfonate substitution, addition to nitriles, addition to carbonyls (ylides).



Exercise 4.19.6

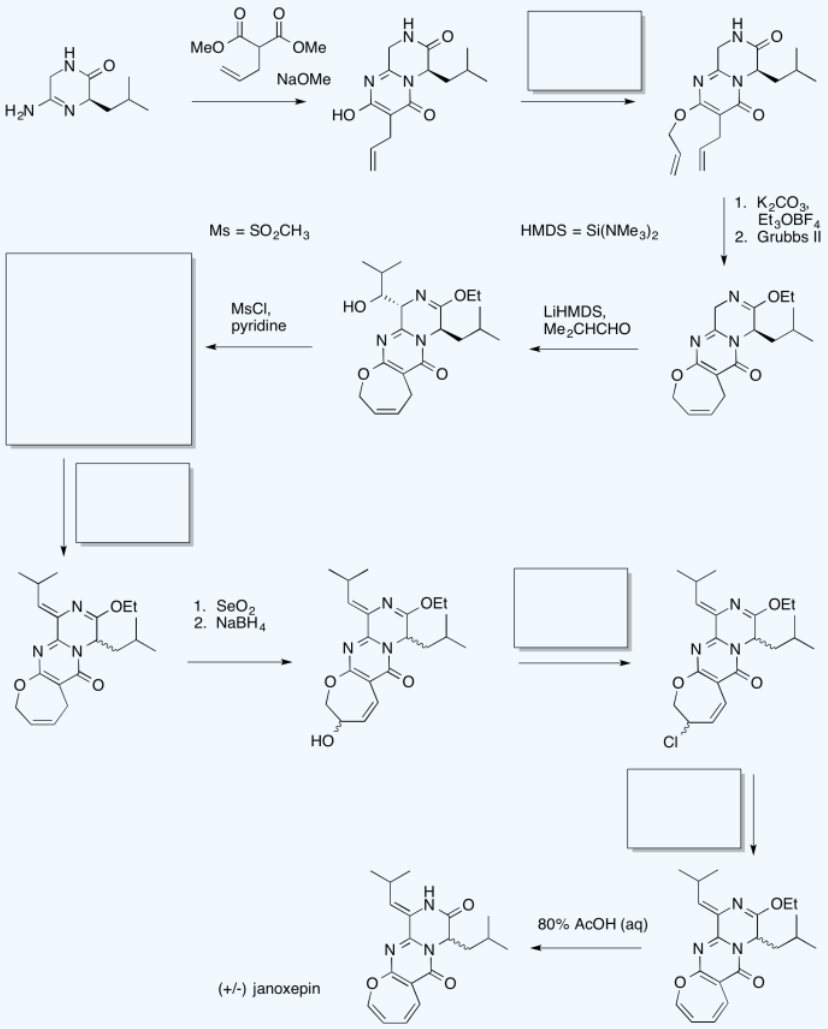
Fill in the missing items in the following synthesis. Includes: aliphatic nucleophilic substitution, carbonyl addition (anionic nucleophiles, acetals, ylides), carboxylic substitution, silyl ethers.



? Exercise 4.19.7

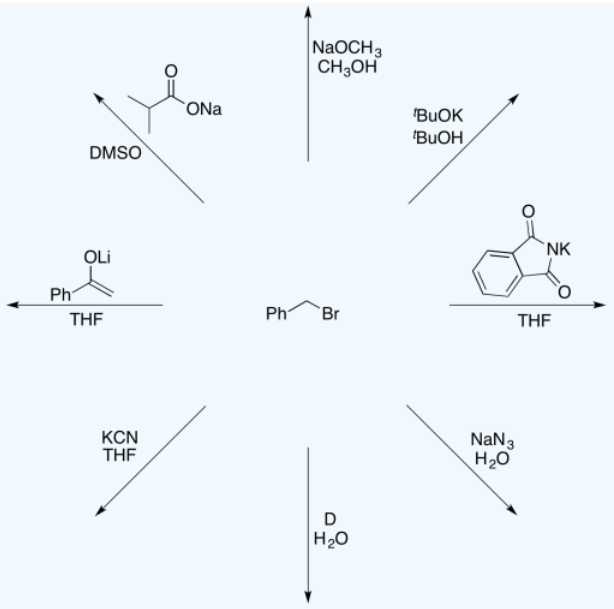
Fill in the missing items in the following synthesis. Includes: aliphatic nucleophilic substitution, sulfonate substitution, elimination.

Synthesis of janoxepin
Richard Taylor et al, University of York, 2012
A fungal metabolite from *Aspergillus janus*, effective against the malaria parasite *Plasmodium falciparum*.



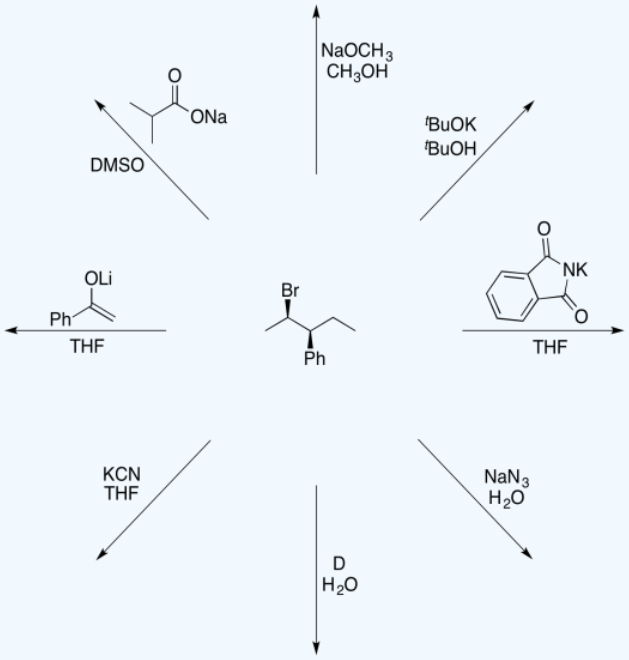
Exercise 4.19.8

Predict products of the following reactions.



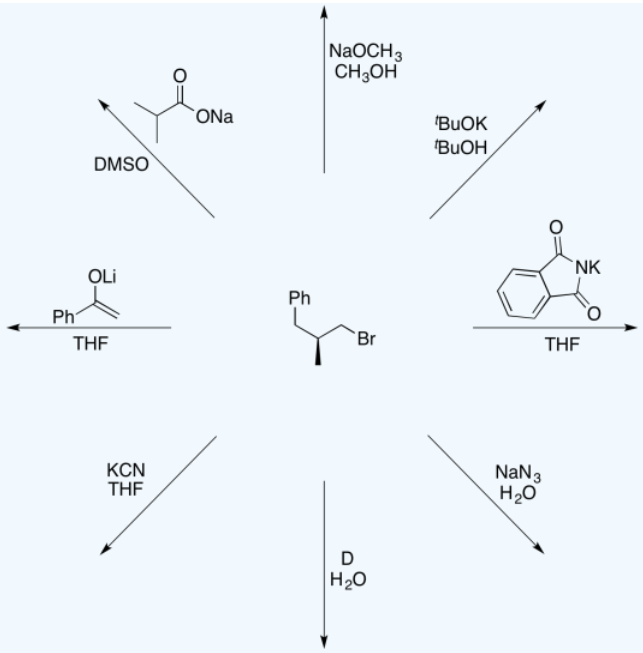
Exercise 4.19.9

Predict products of the following reactions.



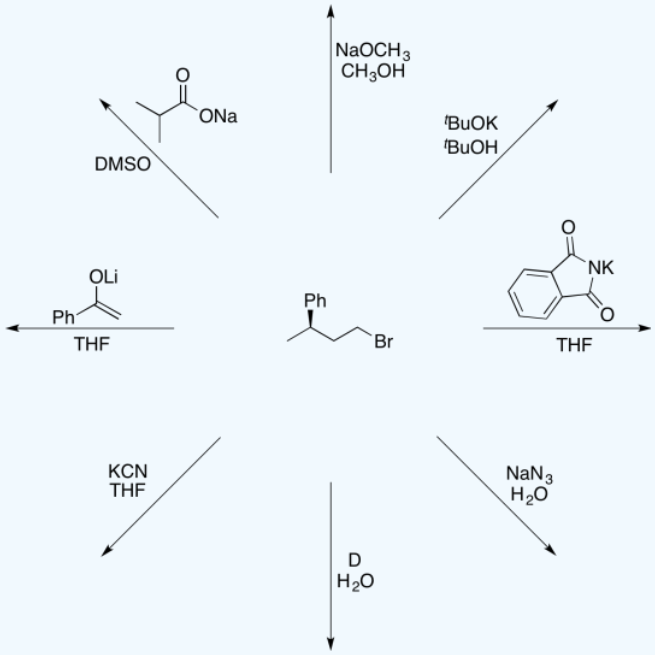
Exercise 4.19.10

Predict products of the following reactions.



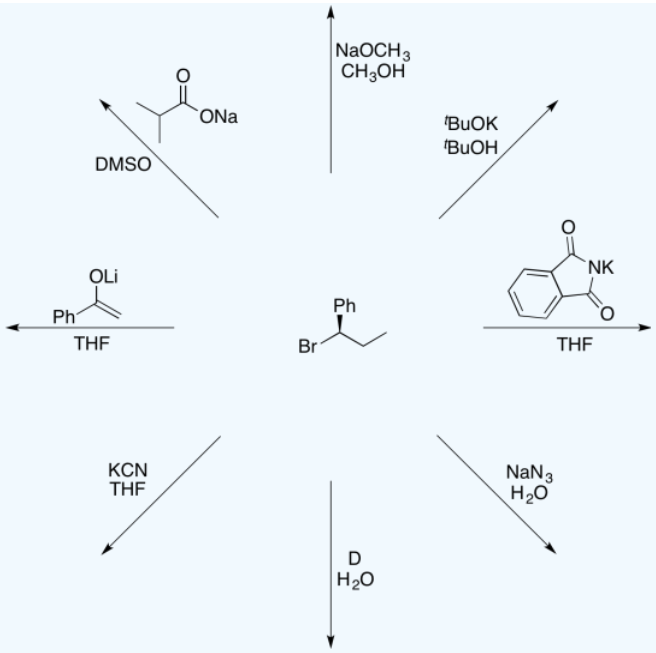
Exercise 4.19.11

Predict products of the following reactions.



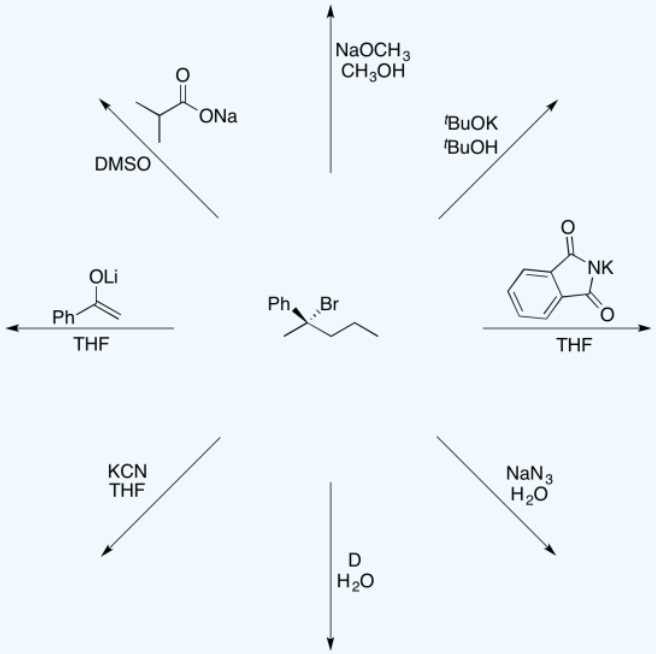
Exercise 4.19.12

Predict products of the following reactions.



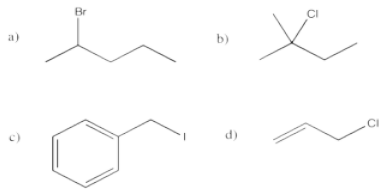
Exercise 4.19.13

Predict products of the following reactions.

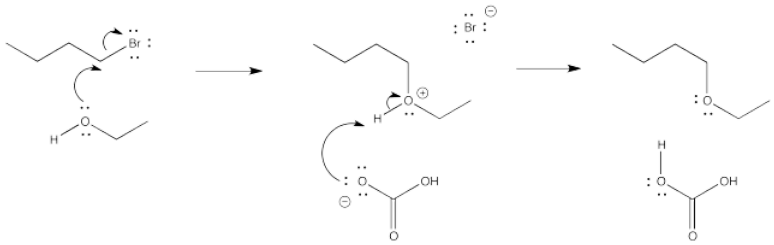


4.20: Solutions to Selected Problems

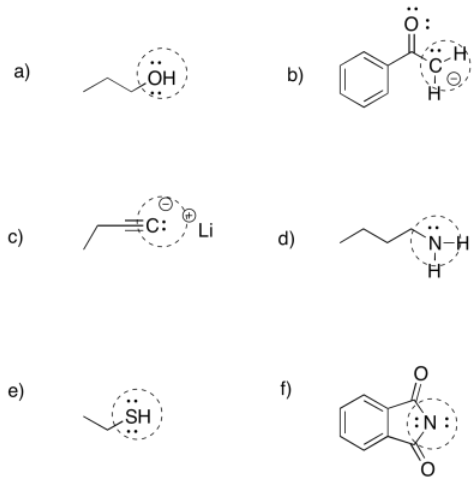
Exercise 4.1.1:



Exercise 4.1.2:



Exercise 4.1.3:



Exercise 4.2.1:

The electronegativity of carbon (2.55 on Pauling scale) is less than that of fluorine (3.98), chlorine (3.16), bromine (2.96) or iodine (2.66).

a. On that basis, the carbon attached to a halogen is electrophilic because it has a partial positive charge resulting from the polar carbon-halogen bond.
b. We would expect an alkyl fluoride to be the most electrophilic of these compounds, based on electronegativity.
c. Assuming the energy required for breaking the carbon-halogen bond plays a major role in the activation barrier (not guaranteed), we would expect the activation barrier to be lowest with the alkyl iodide, then the alkyl bromide, then the alkyl chloride and finally the alkyl fluoride. This prediction contrasts with what we might expect based on electronegativity.
d. The stability of alkyl fluorides towards this reactions suggests that there is, in fact, a prominent role played by bond strengths, at least in that case. The carbon-fluoride bond is strong enough to hinder nucleophilic substitution in this compound.

Exercise 4.2.2:

a. In mechanism B, the dissociative one, we would expect a higher activation enthalpy. The first step, which appears to be rate determining, is a bond-breaking step, which will cost energy. In mechanism C, the bond-breaking is compensated by some bond-making; overall, this probably costs less energy.

b. In mechanism B, the dissociative case, we expect a more positive entropy of activation. As the bond to the halide begins to break, the halide and carbocation fragments begin to move independently of each other, gaining degrees of freedom and increasing in entropy. In mechanism C, the incoming nucleophile appears to coordinate its motion with that of the departing halide; as a result, there are fewer degrees of freedom in this case.

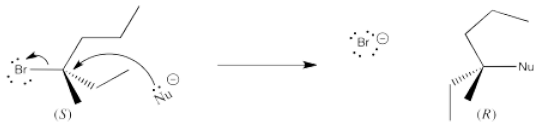
Exercise 4.2.3:

a. Charged intermediates are present in the dissociative mechanism (B).
b. It seems like a more polar solvent would favor both mechanisms, because both involve the interaction of an anionic nucleophile with an electrophile and loss of an anionic leaving group. However, the dissociative case (B) involves a build-up of charge in the intermediate. It is possible that a more epolar solvent could reduce the barrier to that buildup of charge separation, accelerating this mechanism.

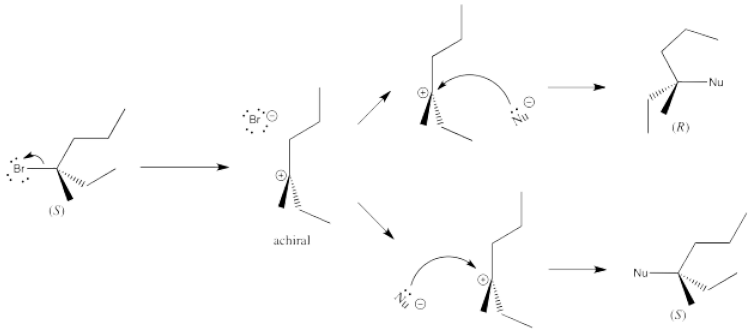
Exercise 4.2.4:

a. The rate-determining step is probably the bond-breaking one (the first one).
b. Because the nucleophile has not yet participated at that point, $Rate = k[R-X]$, if R-X = the alkyl halide.
c. There is only one step; it is the rate-determining step, by default.
d. $Rate = k[R-X][Nu]$.

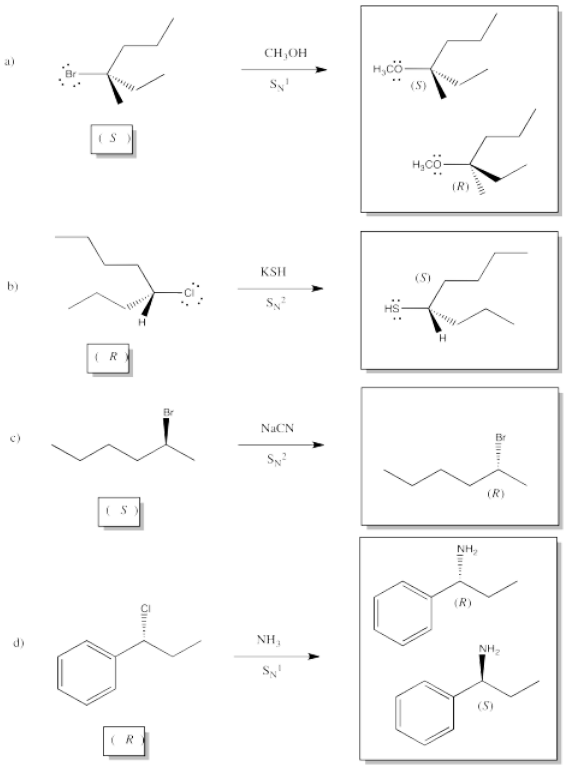
Exercise 4.4.1:



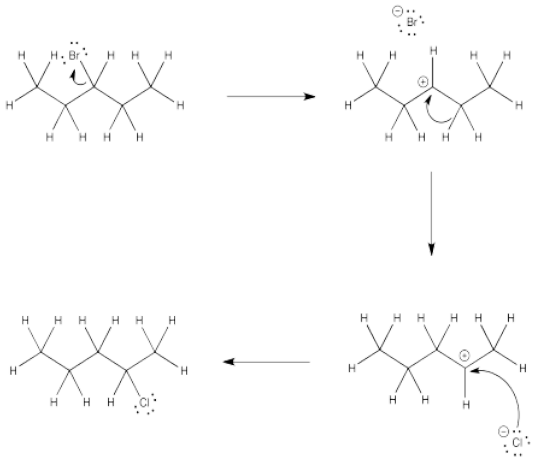
Exercise 4.4.2:



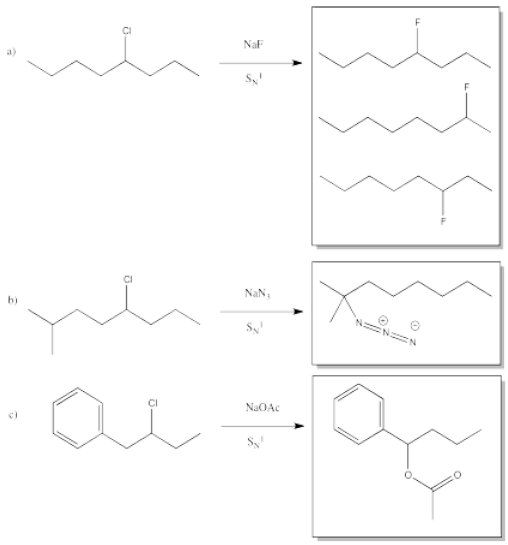
Exercise 4.4.3:



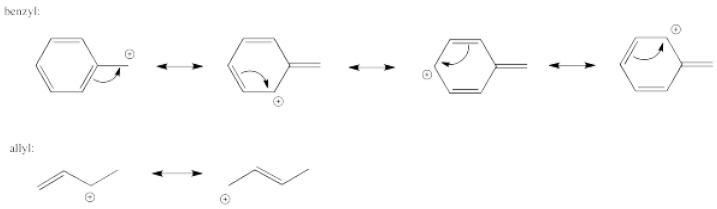
Exercise 4.5.1:



Exercise 4.5.3:



Exercise 4.6.1:



Exercise 4.6.2:

Keep in mind that there are other factors that can influence the reaction pathway; what we have here are just the most likely mechanisms.

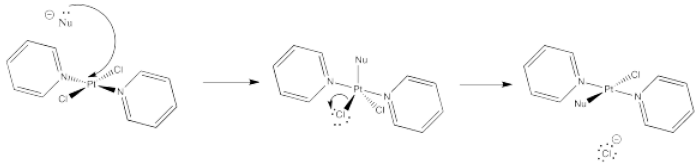
a) S_N2 b) Both pathways are very possible c) Both pathways are very possible d) S_N2

e) S_N2 f) S_N2 g) S_N1 h) S_N1 i) S_N1 j) S_N1

Exercise 4.7.1:

a. ethanol, isopropanol, trifluoroacetic acid
b. hexane, toluene
c. THF, acetonitrile, DMF, dichloromethane, ether, DMSO, triethylamine, pyridine
d. DMSO > DMF > ACN > pyridine > DCM > THF > ether > TEA, based on dielectric constants. In general, the ones with multiple bonds between two different atoms are the most polar.
e. pyridine and triethylamine. The lone pair on the nitrogen atom is basic toward protons. The trend in basicity is triethylamine > pyridine >> acetonitrile; as the percent s character in the lone pair increases, the electrons are lower in energy and less available for donation.

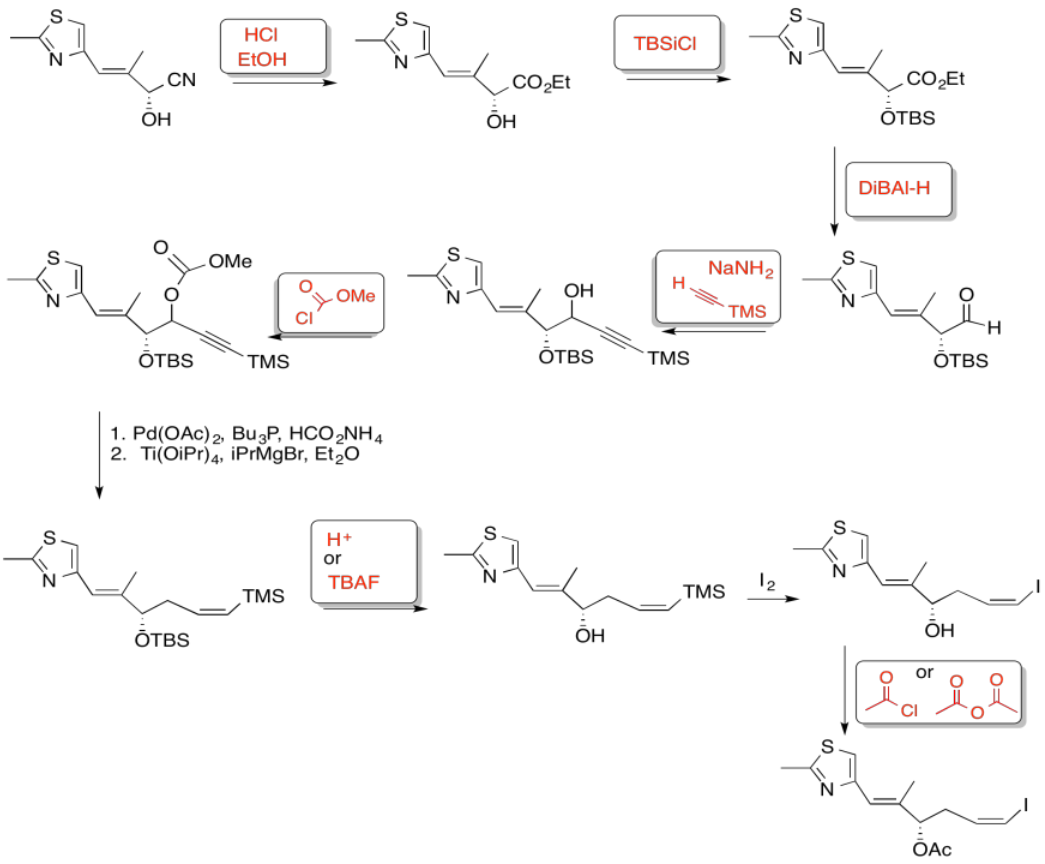
Exercise 4.8.3:



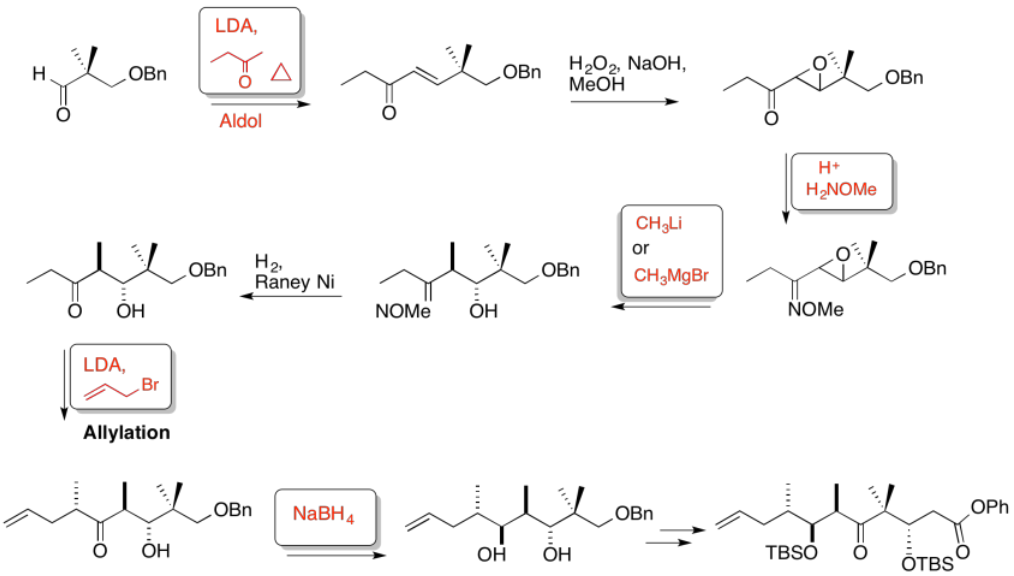
Exercise 4.9.1:

Enantioselective Total Synthesis of Epothilone A
Sawada, Kanai, Shibasaki, *J. Am. Chem. Soc.*, **2000**, *122*, 10521-10532.

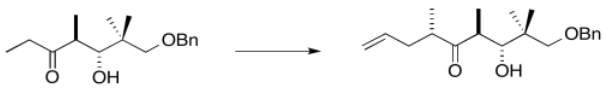
1. Synthesis of Fragment A

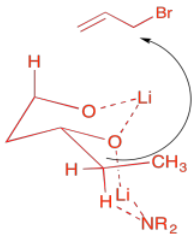


2. Synthesis of Fragment C



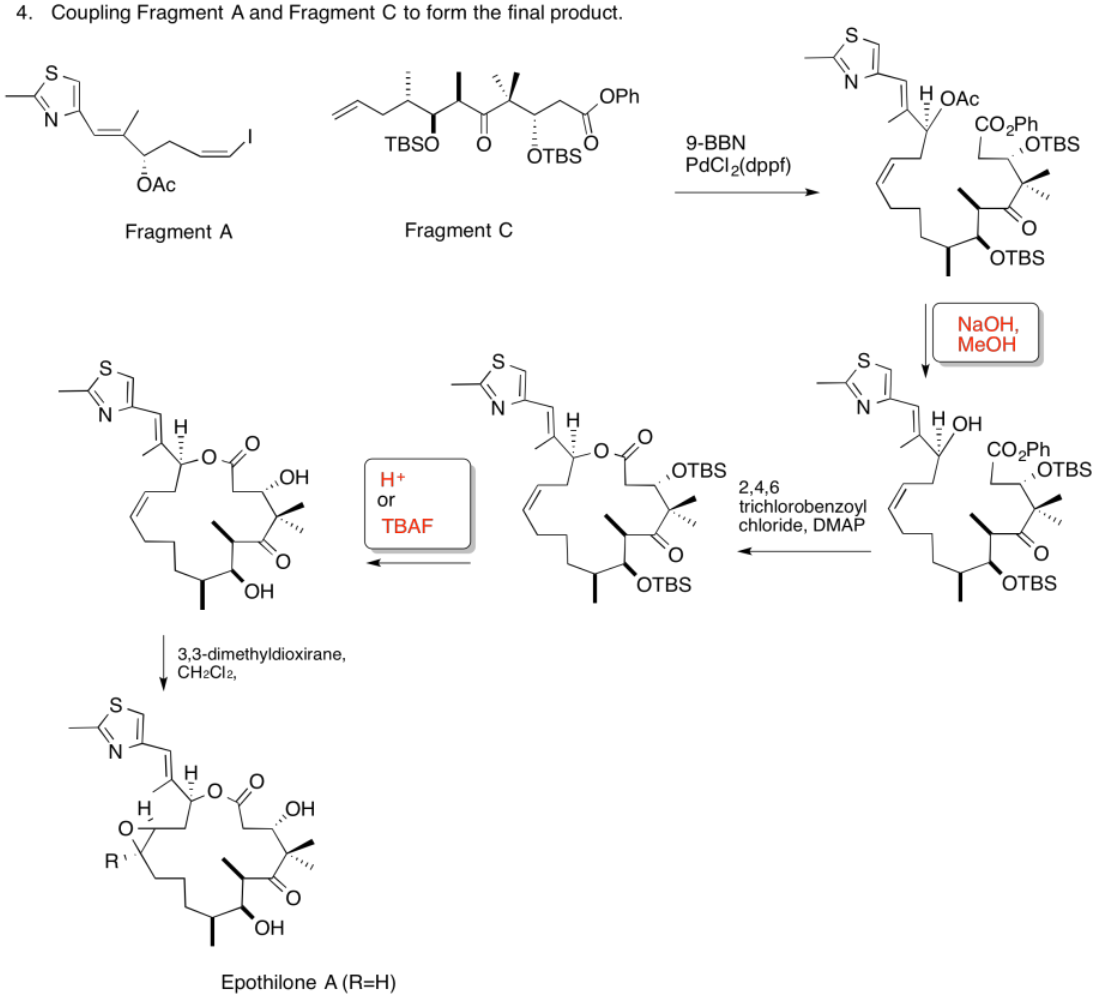
3. Kinetic -- to fully deprotonate (not equilibrate or you lose stereocontrol) and for the chelation control.



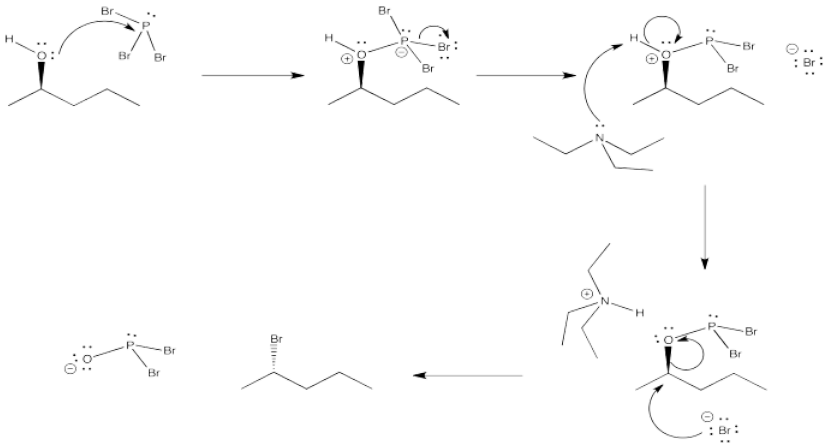


Due to chelation effects shown above, the LDA preferentially removes one hydrogen to form only the Z-enolate that will then do the SN2 to allyl bromide on only one face.

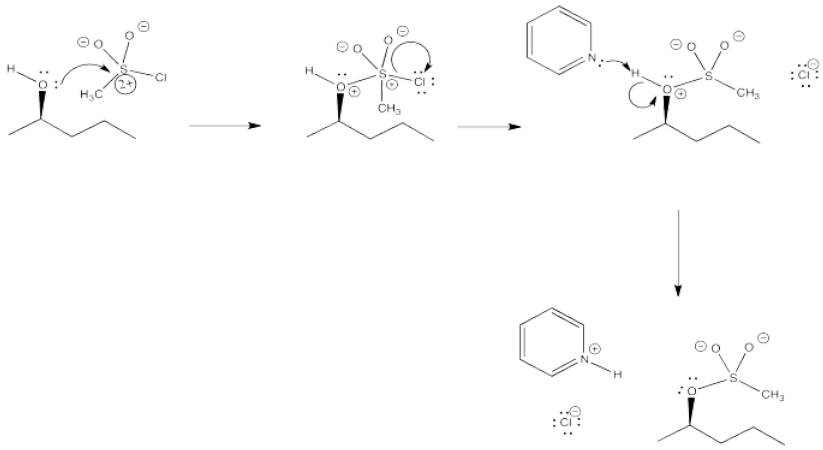
4. Coupling Fragment A and Fragment C to form the final product.



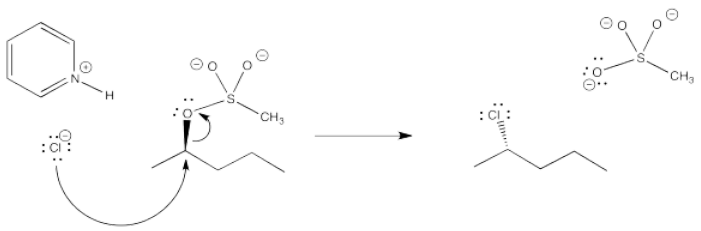
Exercise 4.10.1:



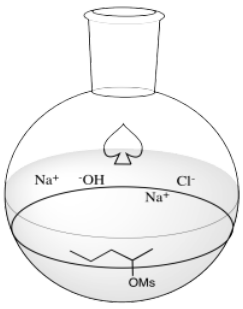
Exercise 4.10.2:



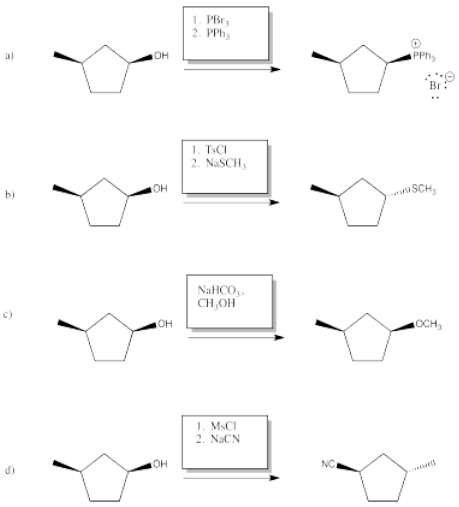
Exercise 4.10.3:



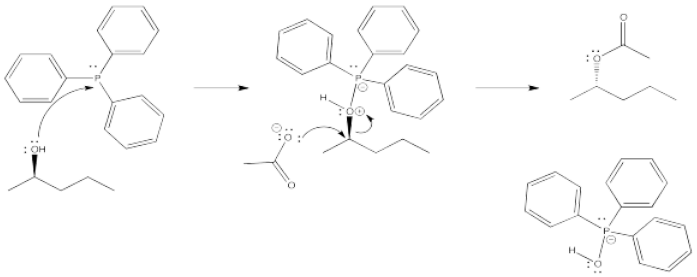
Exercise 4.10.4:



Exercise 4.10.5:

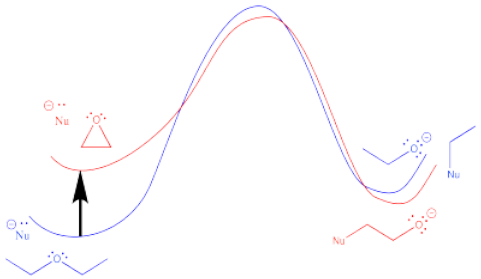


Exercise 4.10.6:

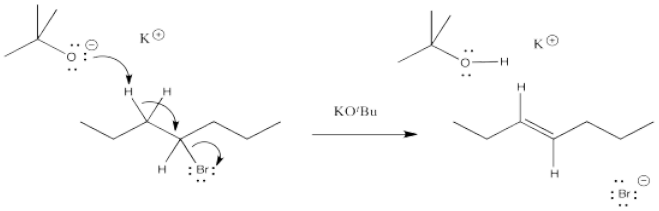


DEAD acts as an oxidizing agent to convert the phosphorus product to a stable side-product, triphenylphosphine oxide, $Ph_3P{=}O$.

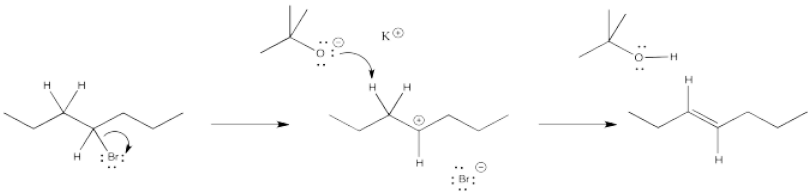
Exercise 4.11.1:



Exercise 4.12.1:



Exercise 4.12.2:



Exercise 4.12.3:

a. products of cation rearrangement via hydride shifts: 2-heptene instead of 3-heptene.
b. The absence of rearrangement suggests the absence of cations. The mechanism for the reaction shown must be concerted rather than via the ionic intermediate.

Exercise 4.12.4:

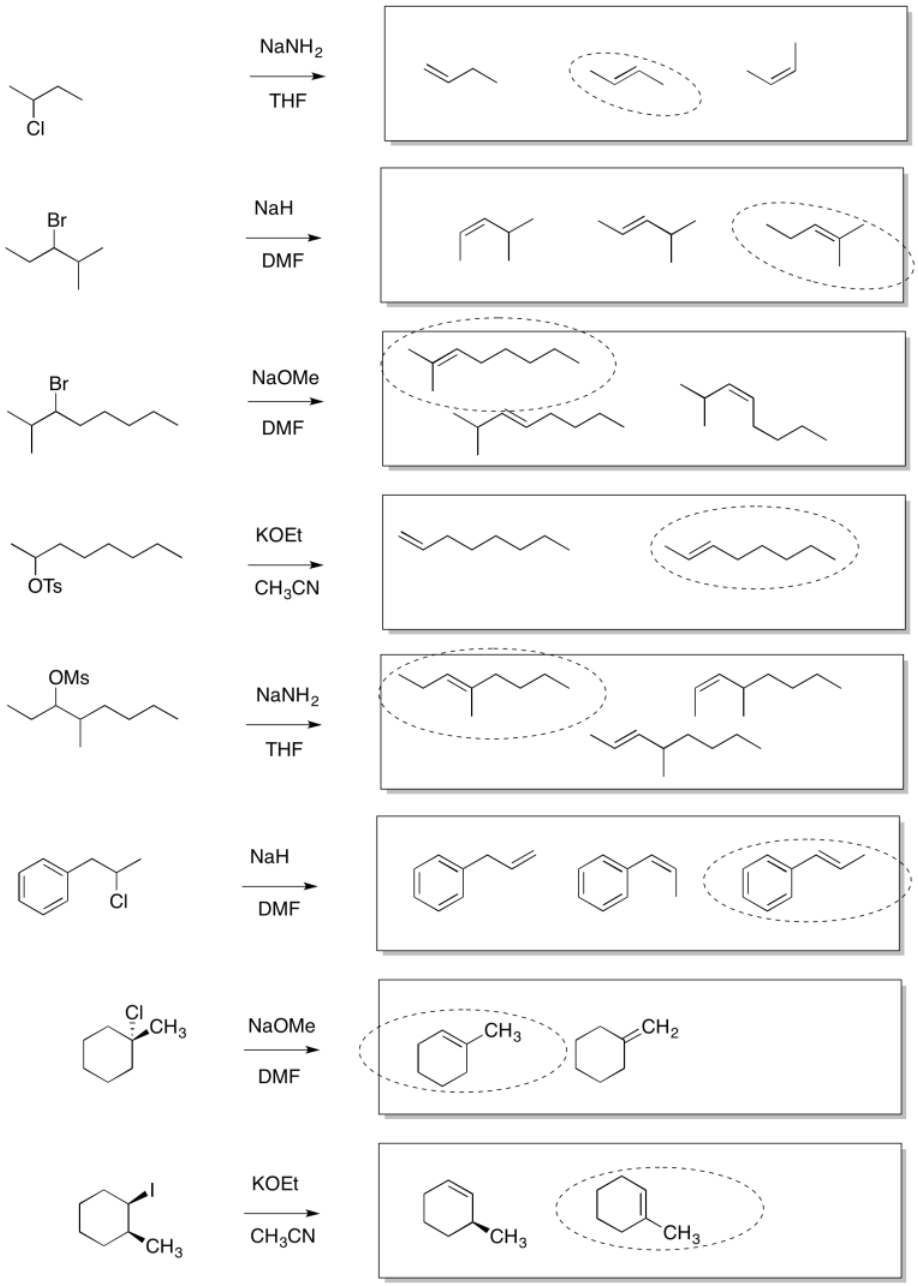
a) very strong b) strong c) weak (resonance) d) very strong e) weak (neutral)

f) weak (polarizable) g) weak (resonance) h) very strong i) weak (polarizable) j) weak (neutral)

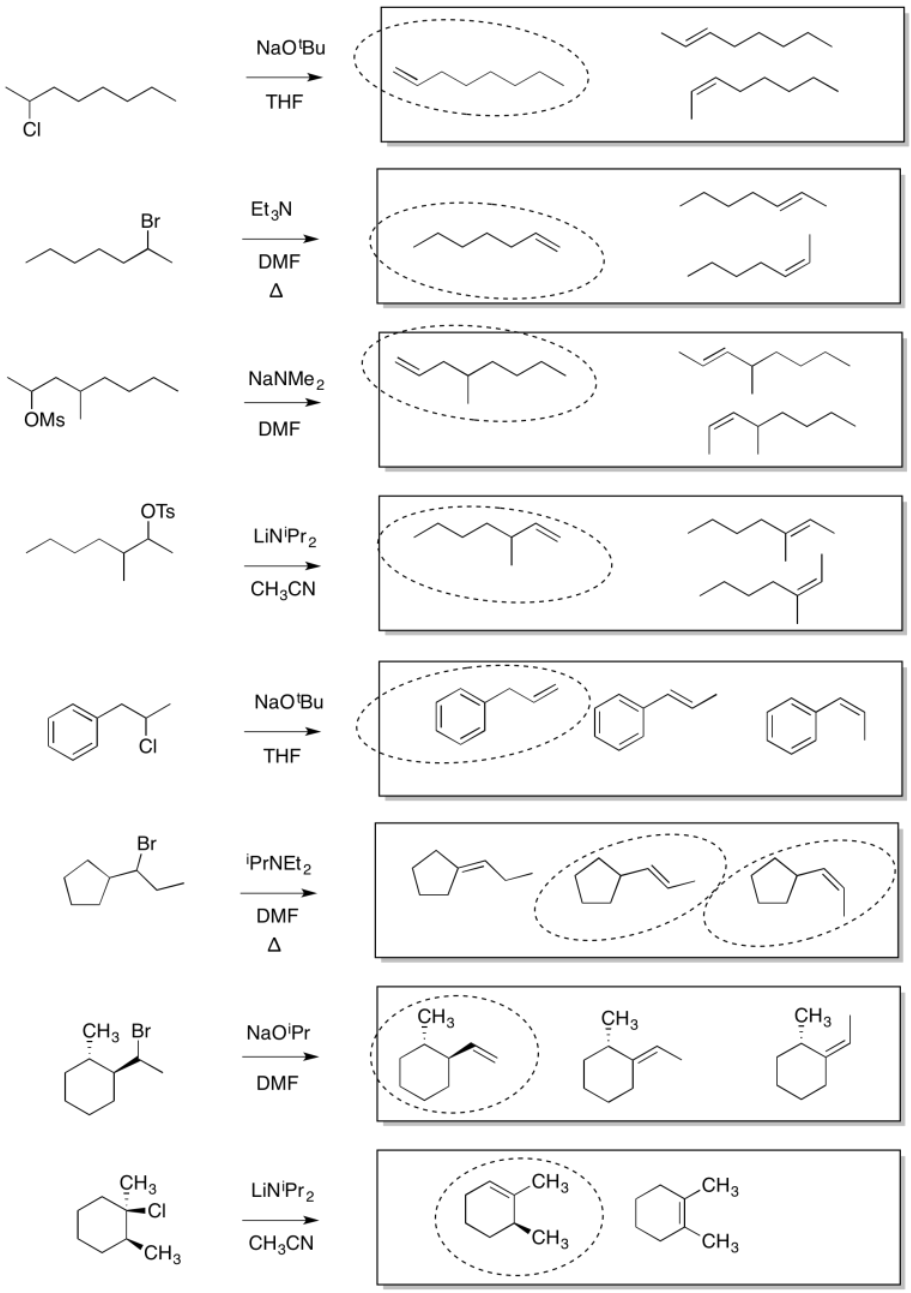
k) medium-weak (C anion but sp) l) weak (neutral) m) weak (resonance) n) weak (polarizable) o) strong

p) weak (O anion but delocalised) q) weak (polarizable) r) very strong s) weak (polarizable) t) strong

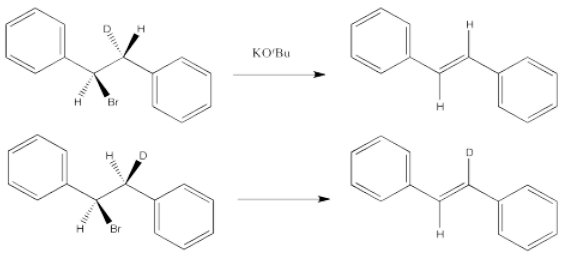
Exercise 4.13.1:



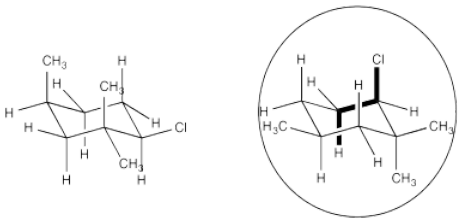
Exercise 4.13.2:



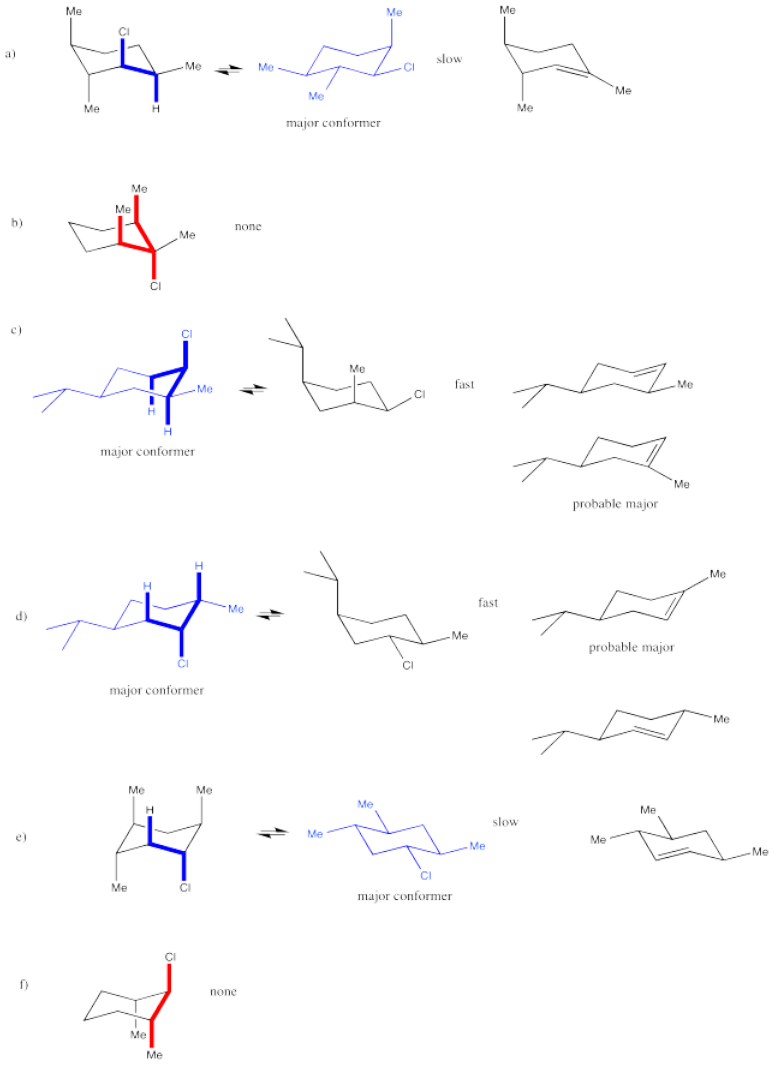
Exercise 4.14.3:



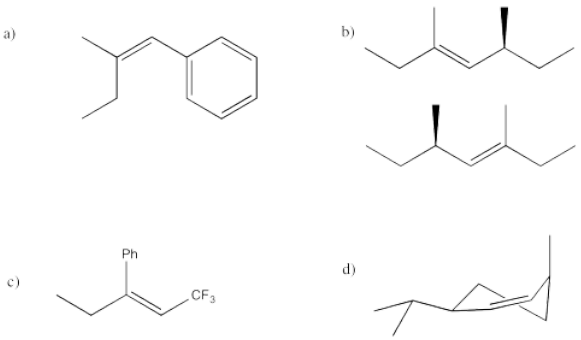
Exercise 4.14.4:



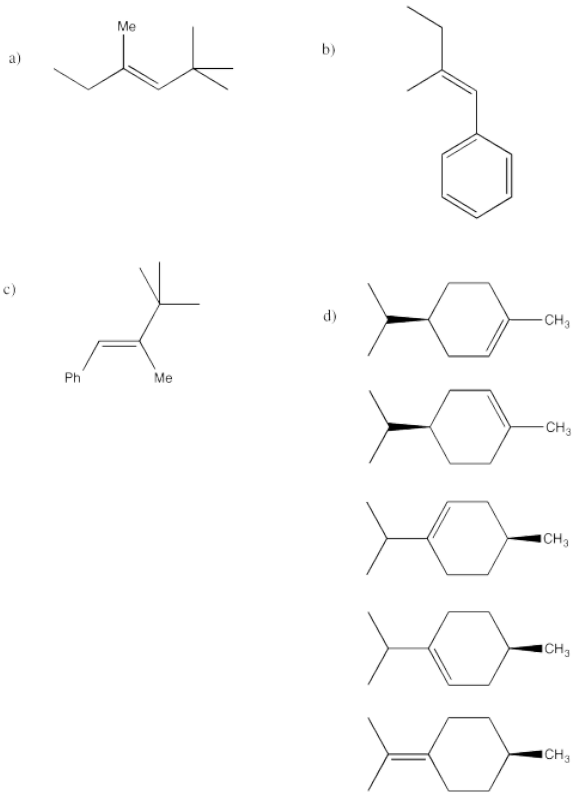
Exercise 4.14.5:



Exercise 4.14.6:



Exercise 4.14.7:



Exercise 4.15.1:

Cation stability is important in an E1 reaction.

Exercise 4.15.2:

Any tertiary alkyl halide would be a good example. Benzylic alkyl halides would also be good examples if they are either secondary or tertiary.

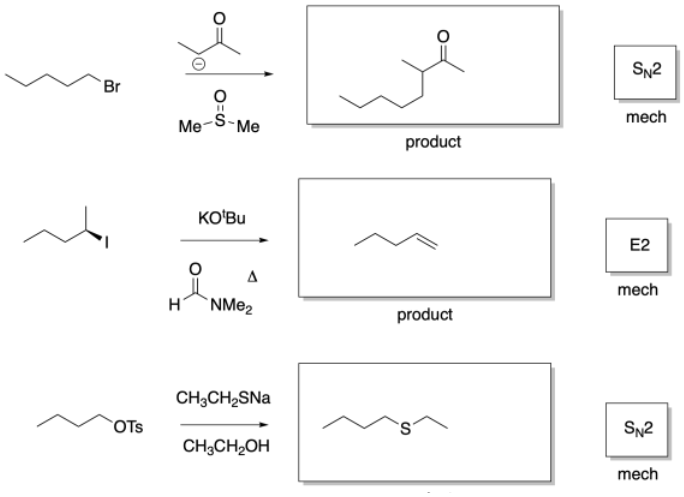
Exercise 4.15.3:

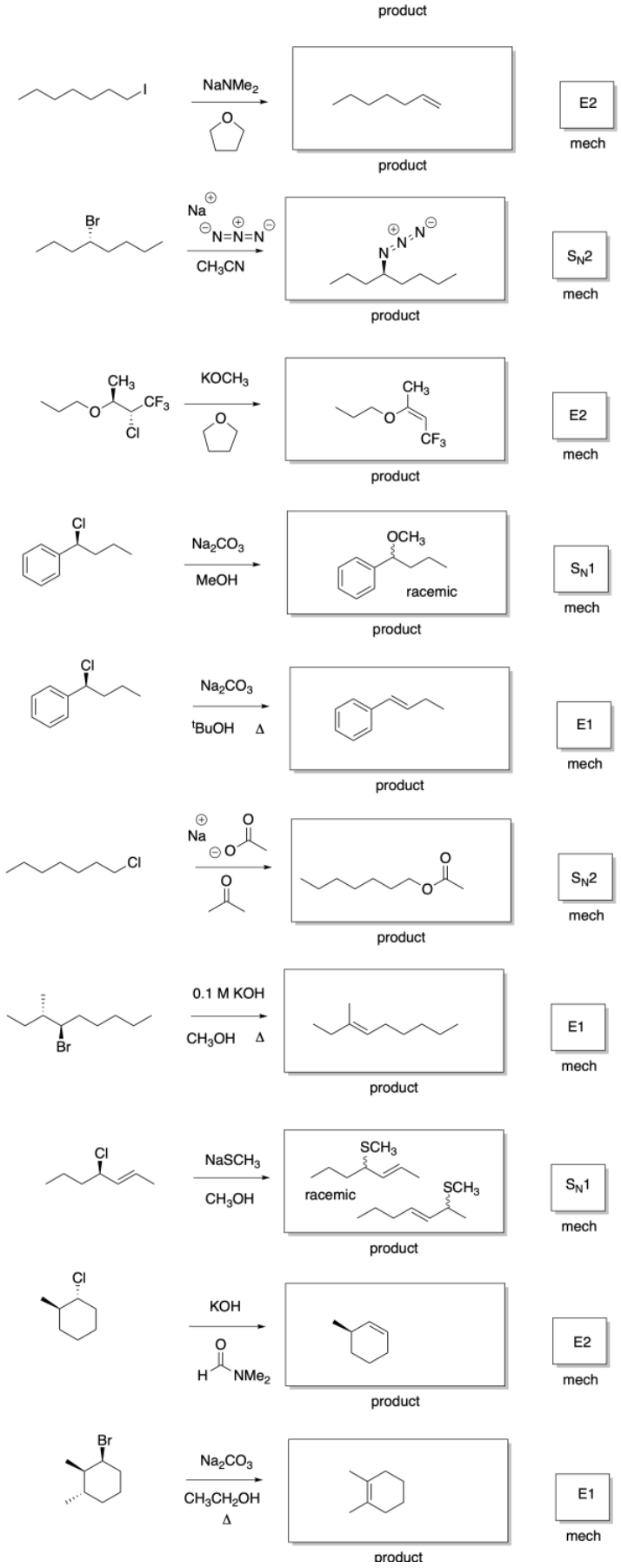
Protic solvents could promote E1 reactions.

Exercise 4.15.4:

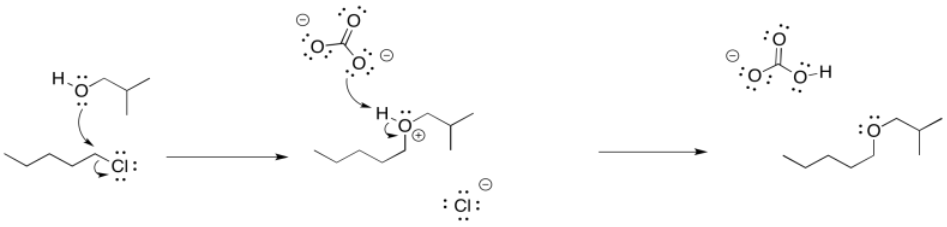
A strong base could promote an E2 reaction.

Exercise 4.15.5:

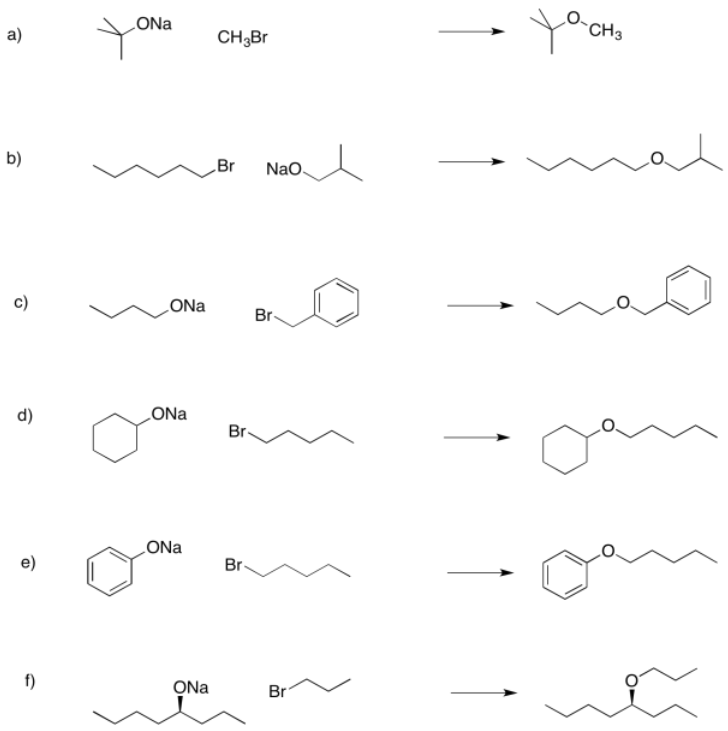




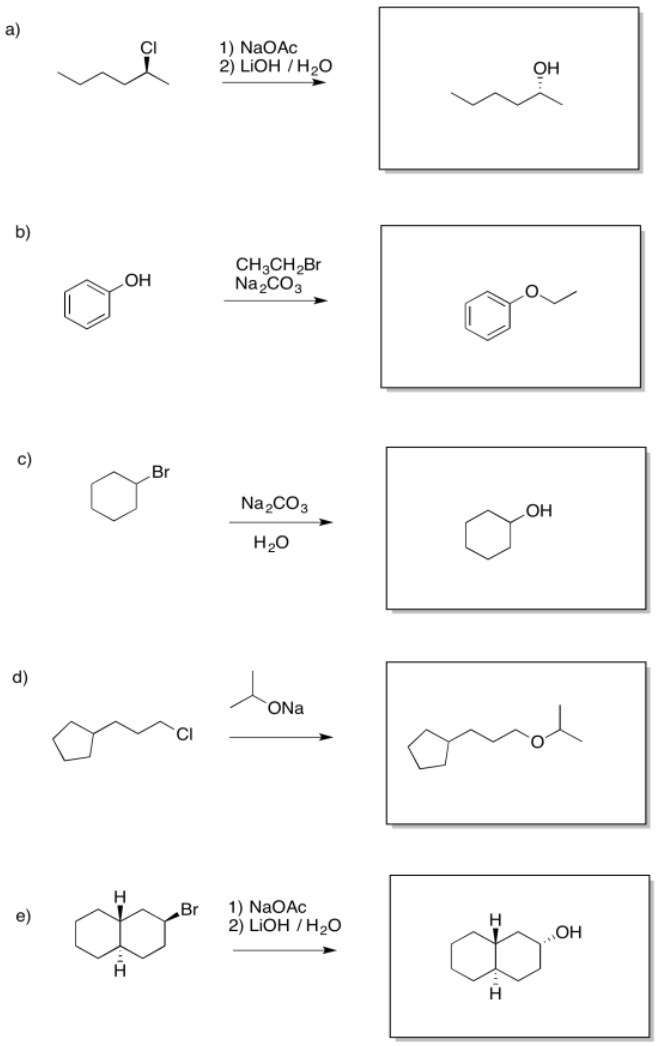
Exercise 4.16.1:



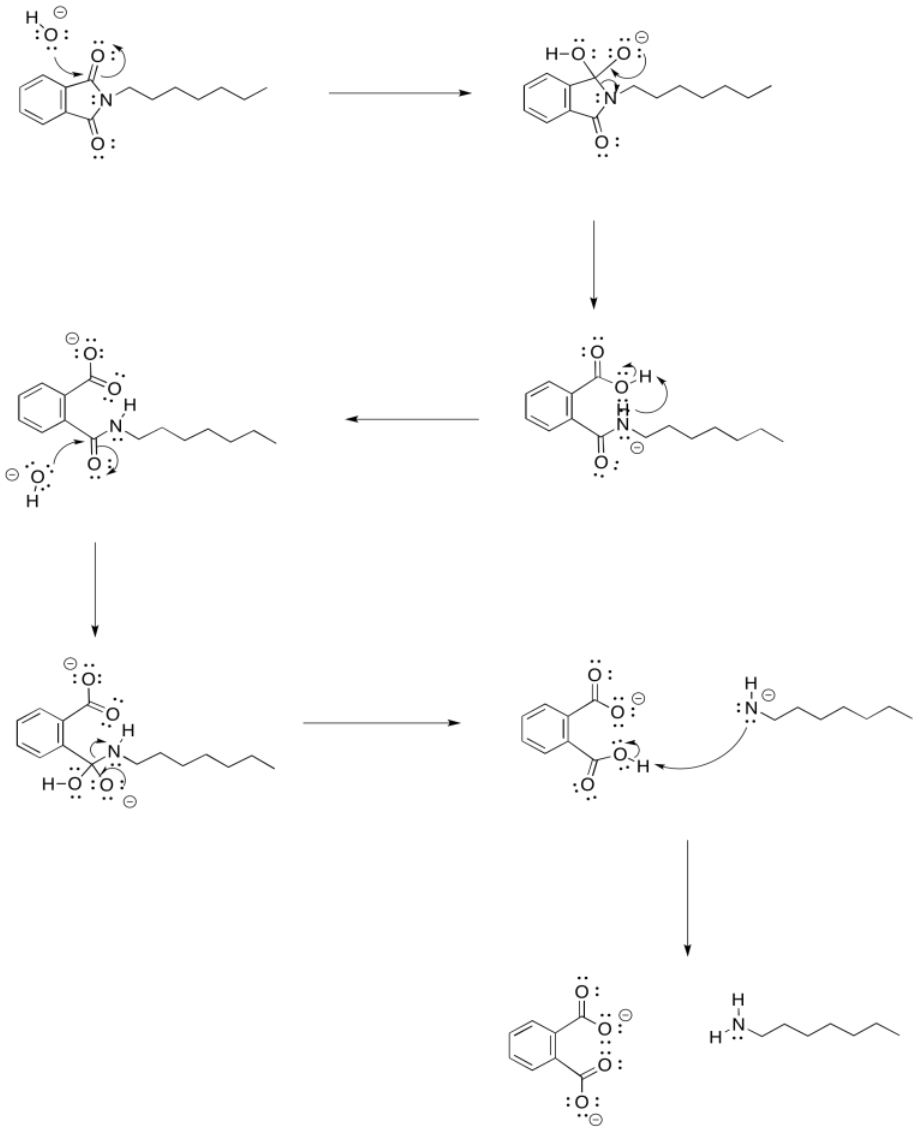
Exercise 4.16.2:



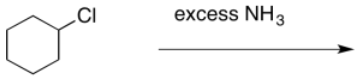
Exercise 4.16.3:

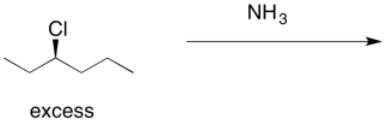


Exercise 4.17.1:

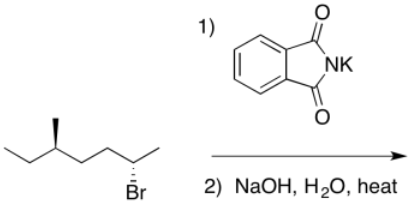


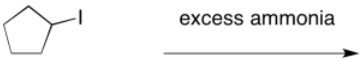
Exercise 4.17.2:

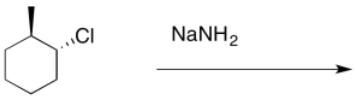
a) 

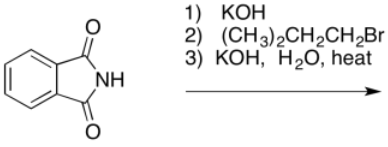
b) 

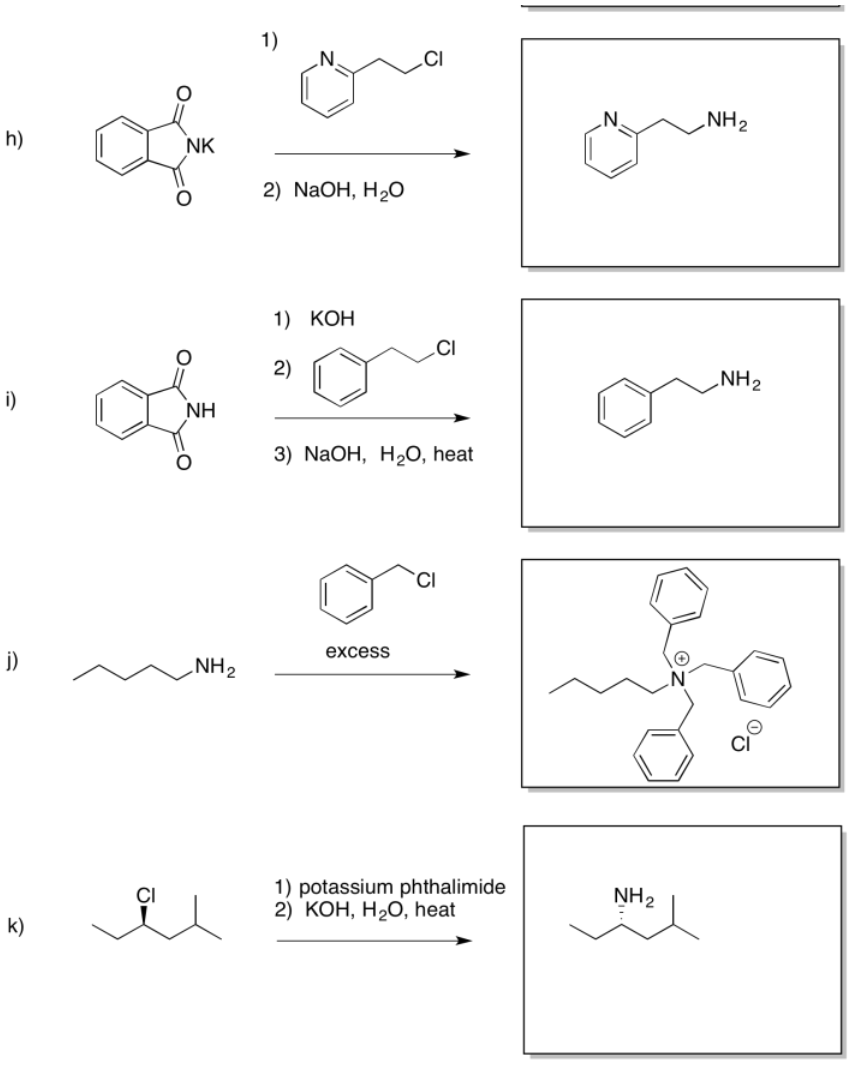
c) 

d) 

e) 

f) 

g) 



Exercise 4.17.3:

a. 2 HO^- 1 HS^- 3 H_2O; the anions are more nucleophilic than the neutral, but sulfur is more polarizable than oxygen
b. 2 H_2O 3 H_3O^+ 1 NH_3; the neutrals are more nucleophilic than the cation, but nitrogen is less electronegative than oxygen
c. 1 $CH_3CH_2NH_2$ 2 $(CH_3)_2CHNH_2$ 3 $(CH_3)_3CNH_2$; steric effects

Exercise 4.17.4:

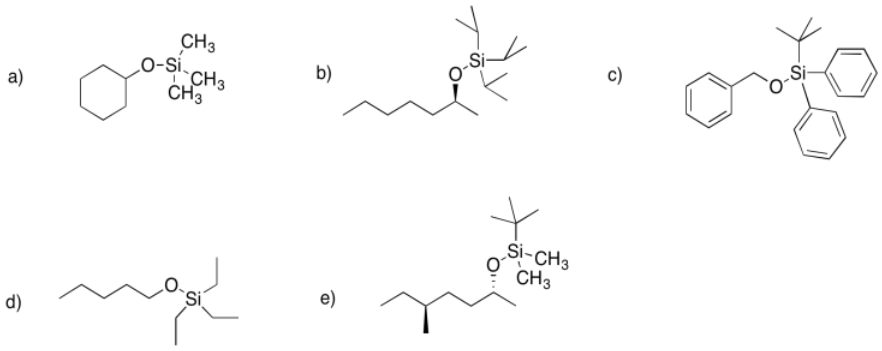
a)

Guanine

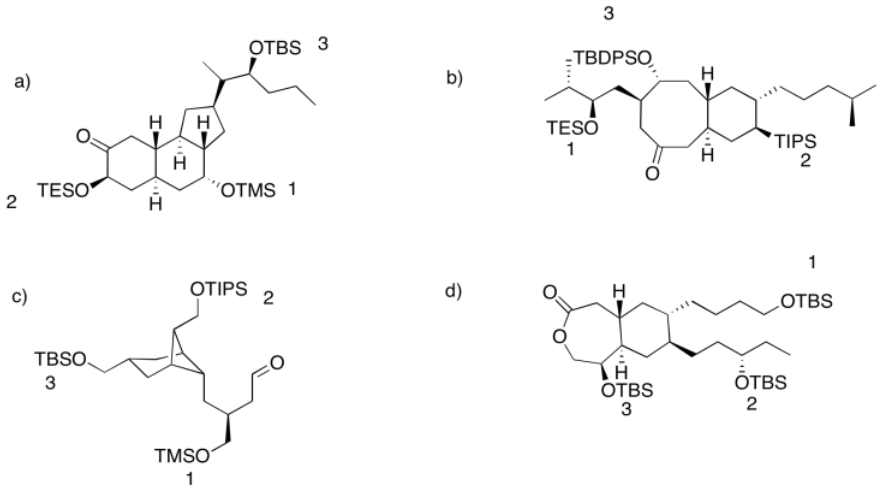
b)

c) Ring strain promotes opening of the ring.

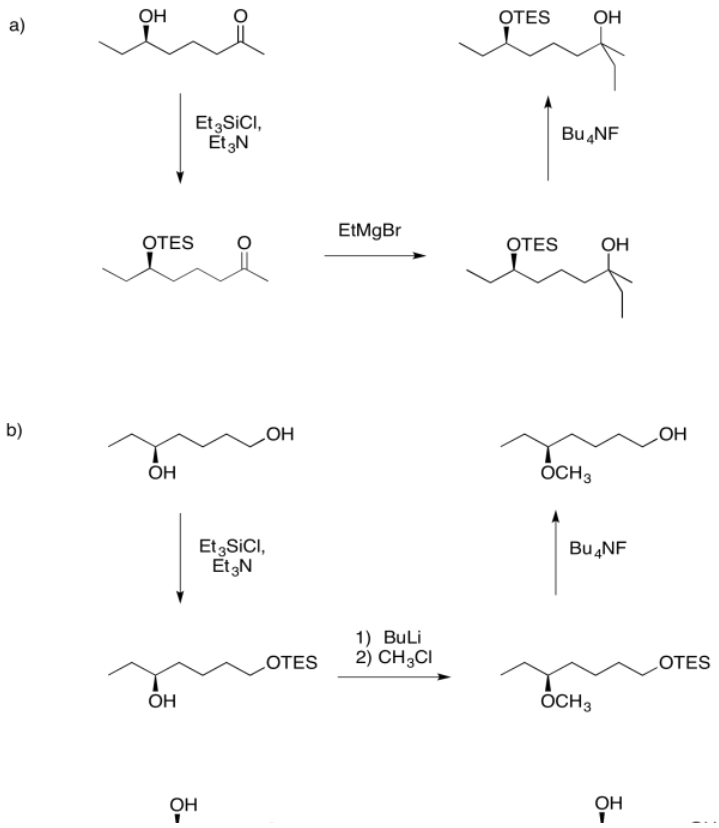
Exercise 4.18.1:

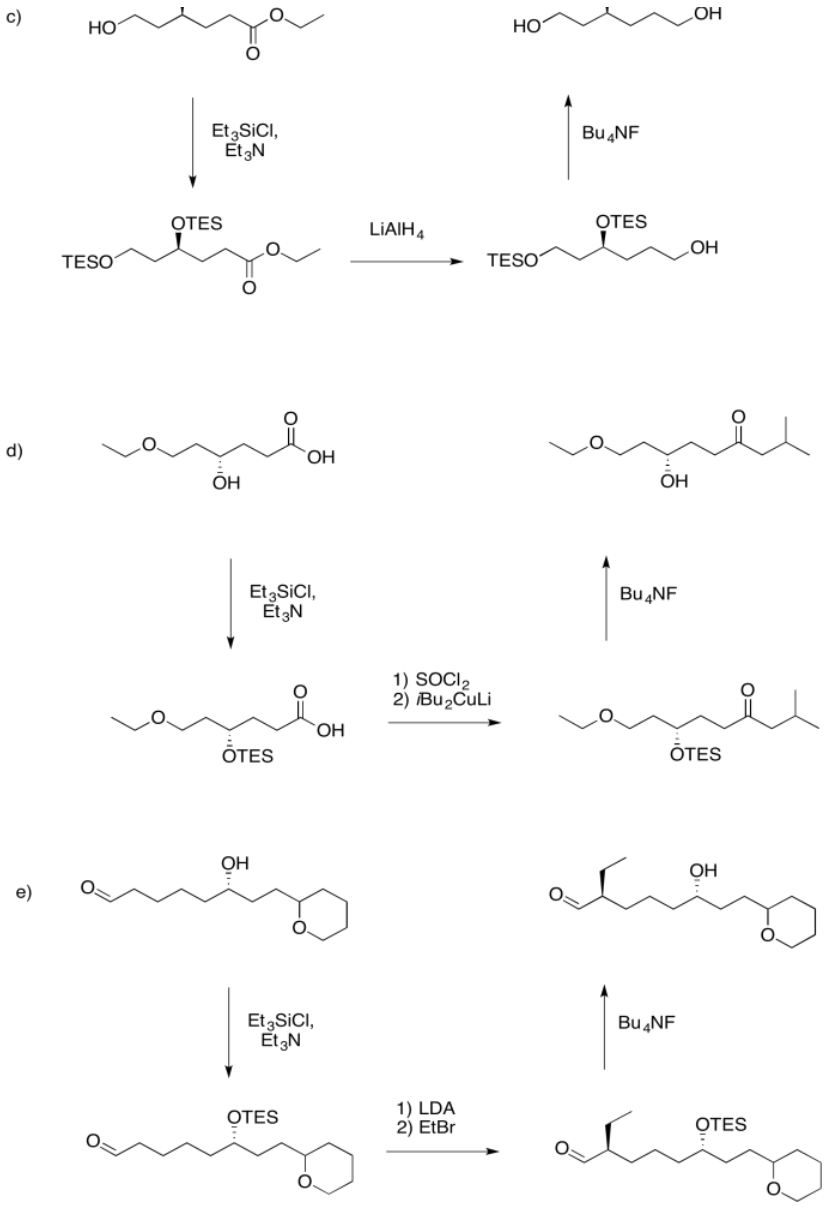


Exercise 4.18.2:



Exercise 4.18.3:

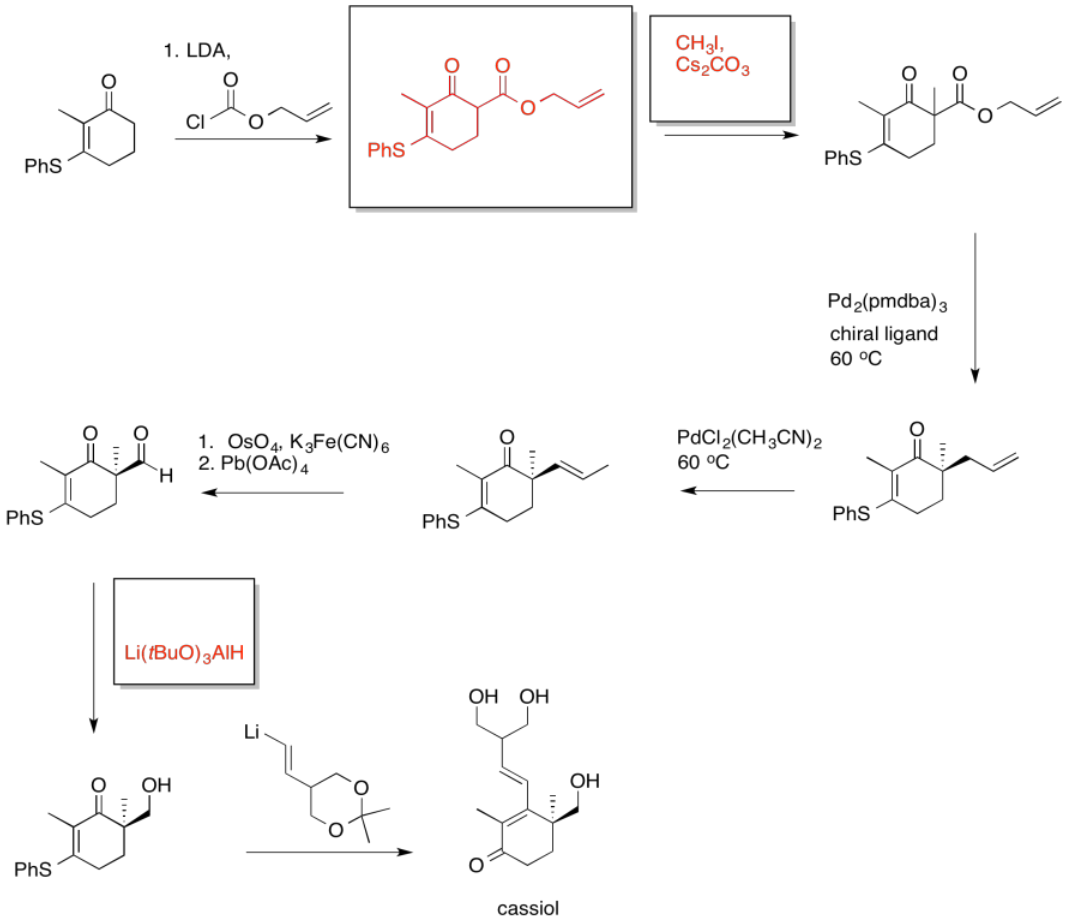




Exercise 4.19.1:

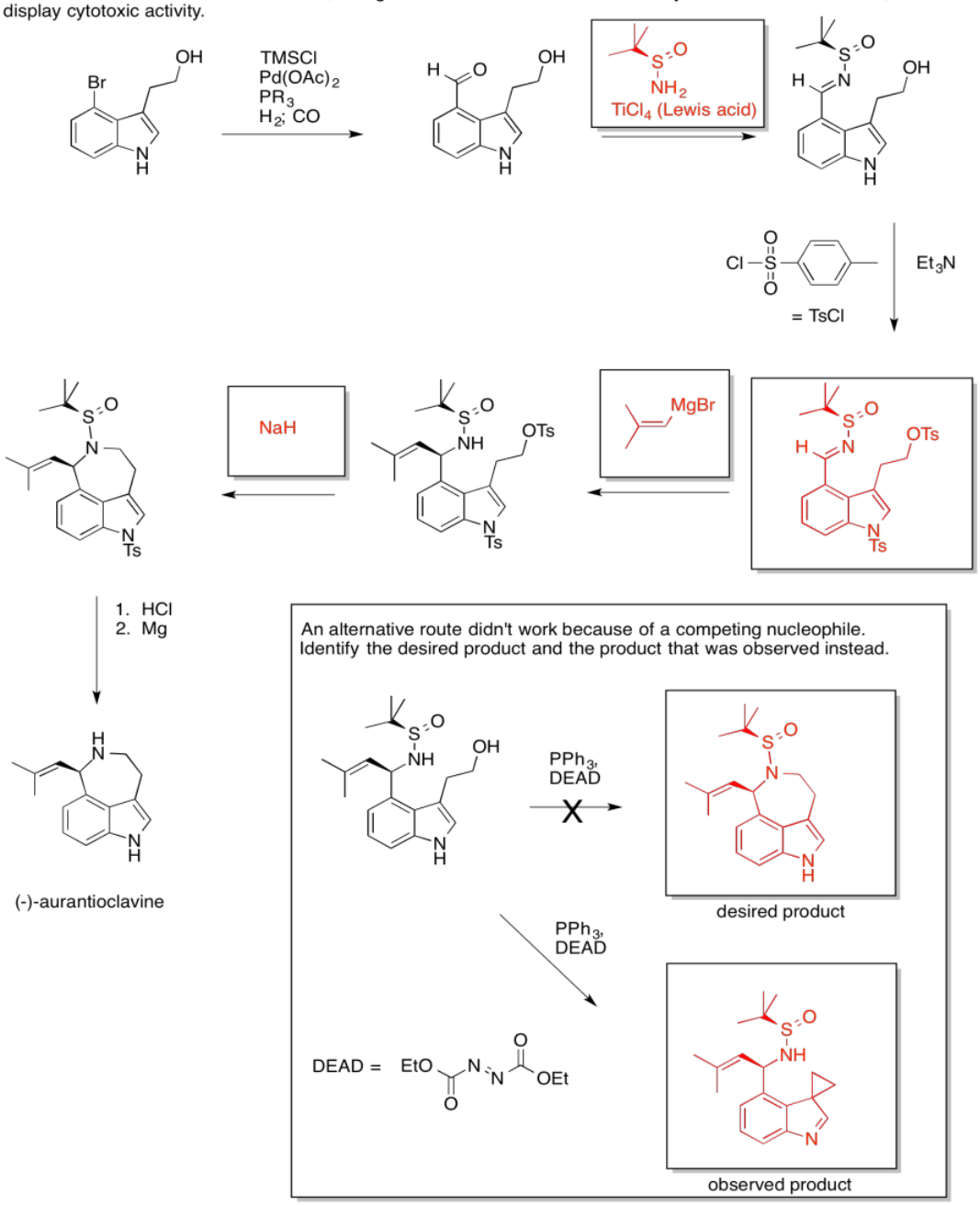
Answers may assume aqueous workup after the reagents shown. Only one answer shown per box; similar answers may also work.

Synthesis of (+)-Cassiol
Stoltz (Caltech) 2008
Cassiol is a natural product of *Cinnamomium cassia* that displays potent antiulcerogenic activity in rats.



Answers may assume aqueous workup after the reagents shown. Only one answer shown per box; similar answers may also work.

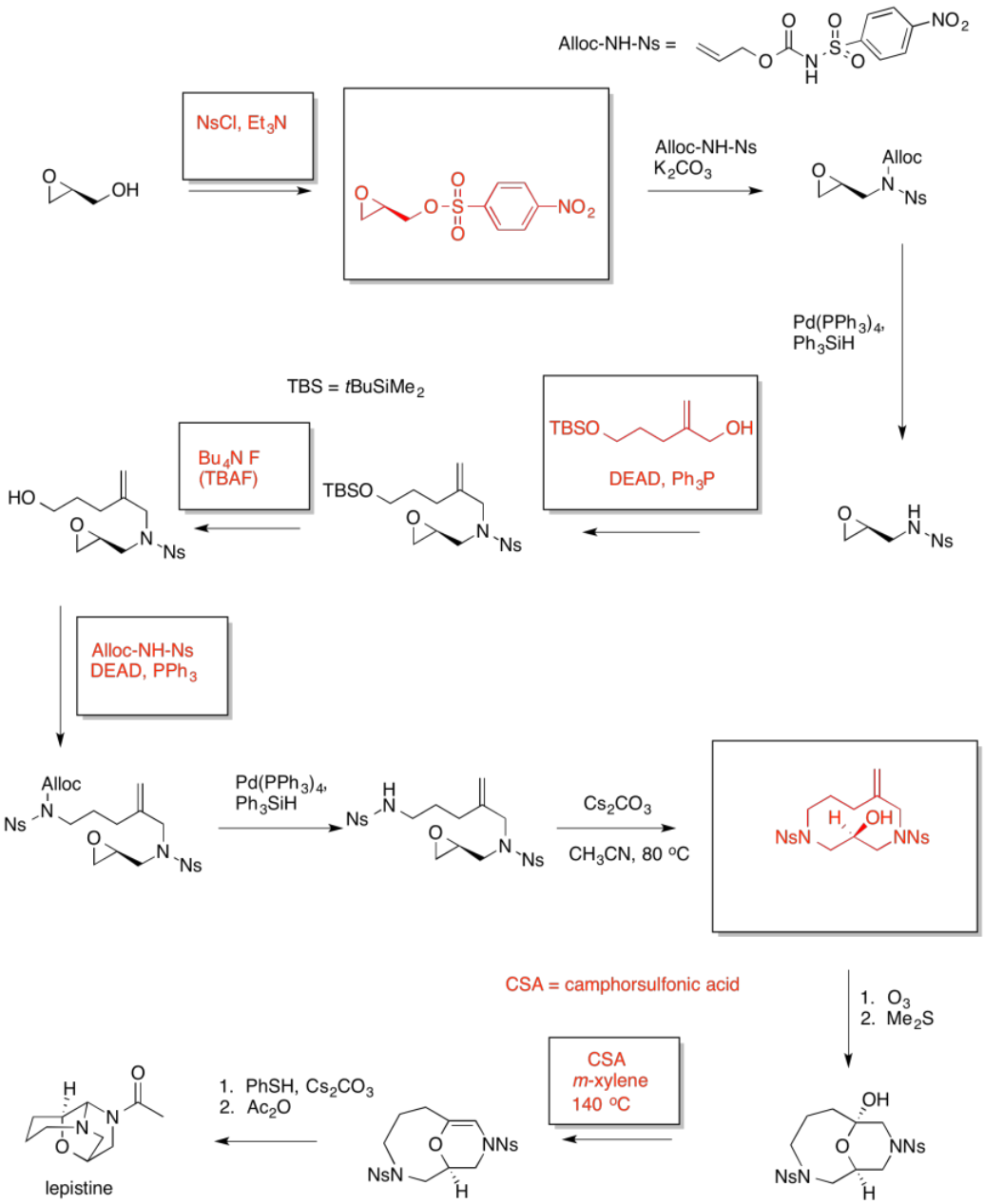
Synthesis of (-)-Aurantioclavine
Ellman (Berkeley) 2010
Isolated from Penicillium aurantiovirens; thought to be an intermediate in the biosynthesis of communesins, which display cytotoxic activity.



Exercise 4.19.3:

Answers may assume aqueous workup after the reagents shown. Only one answer shown per box; similar answers may also work.

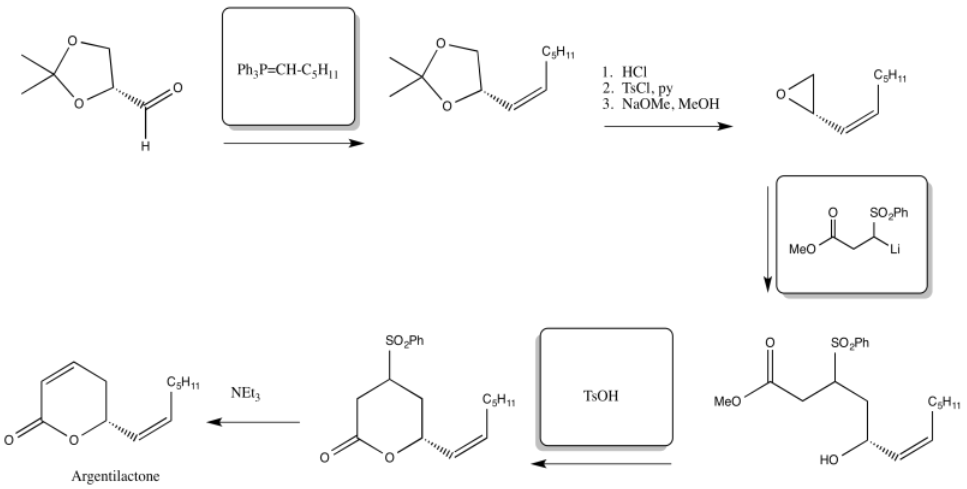
Total Synthesis of (-) Lepistine
Yokoshima & Fukuyama (Nagoya, Japan) 2014
Natural product of the mushroom Clitocybe fasciculate. With no known biological properties, the synthesis was undertaken because of its unusual structure.



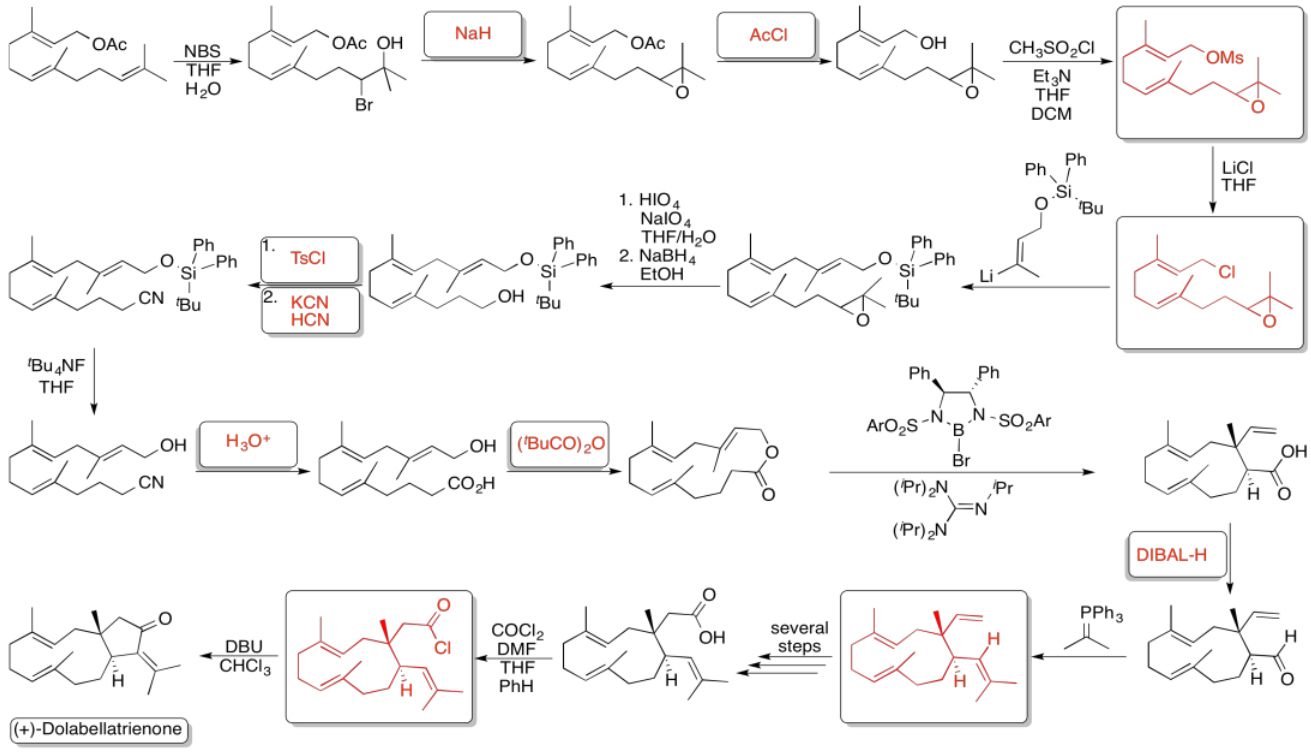
Exercise 4.19.4:

Argentilactone

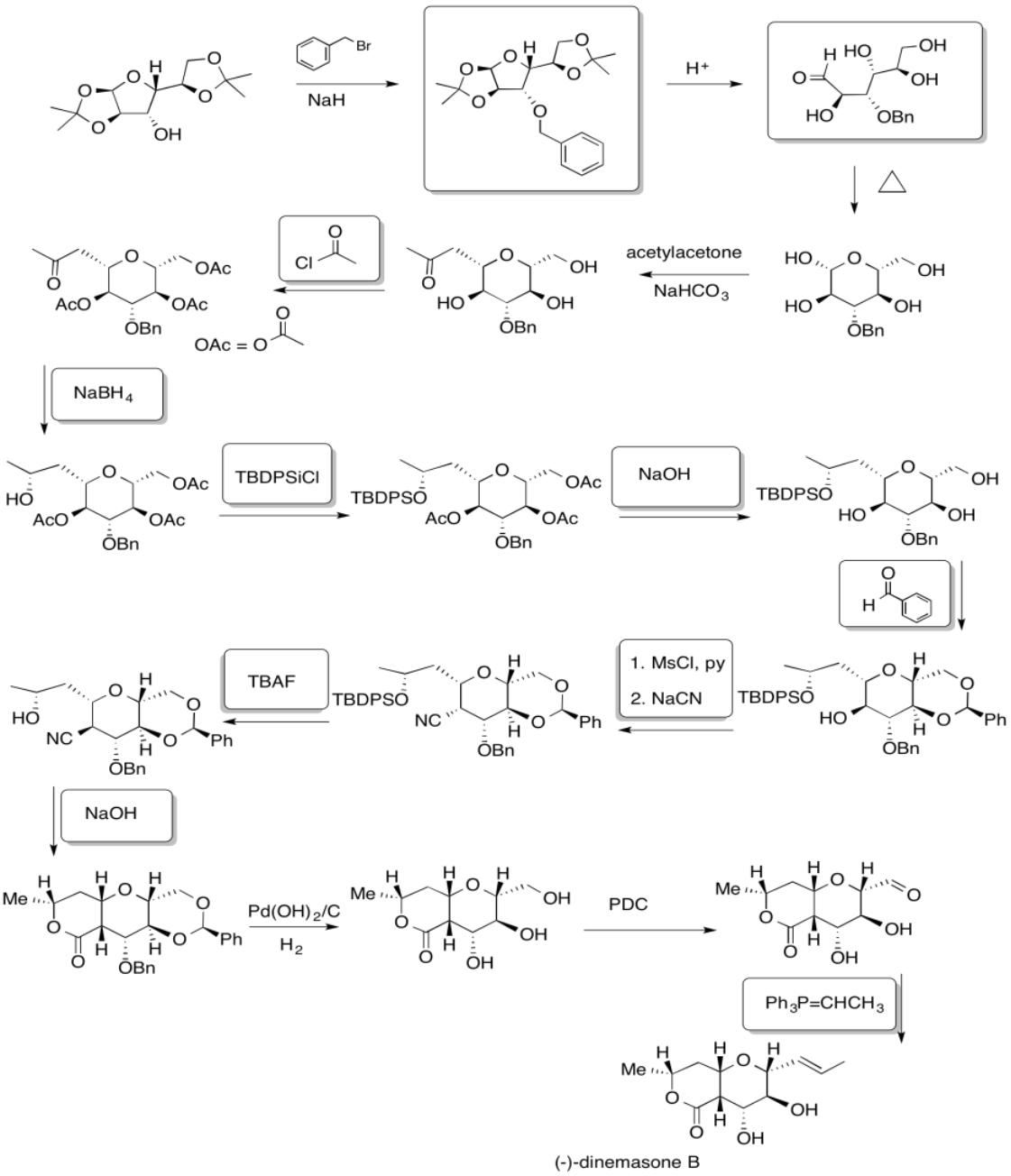
Carretero and Ghosez, *Tetrahedron Lett.*, **1988**, *29*, 2059.



Exercise 4.19.5:

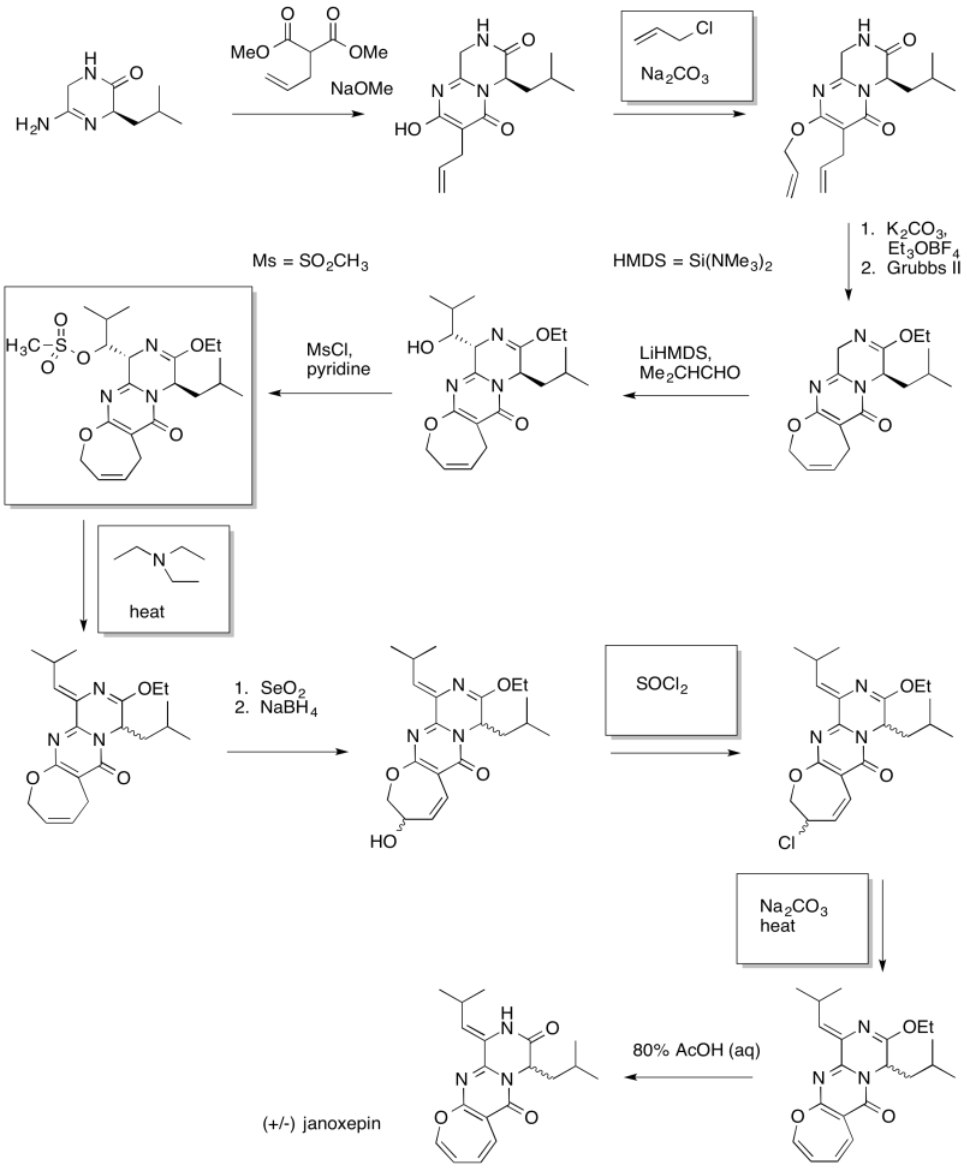


Exercise 4.19.6:

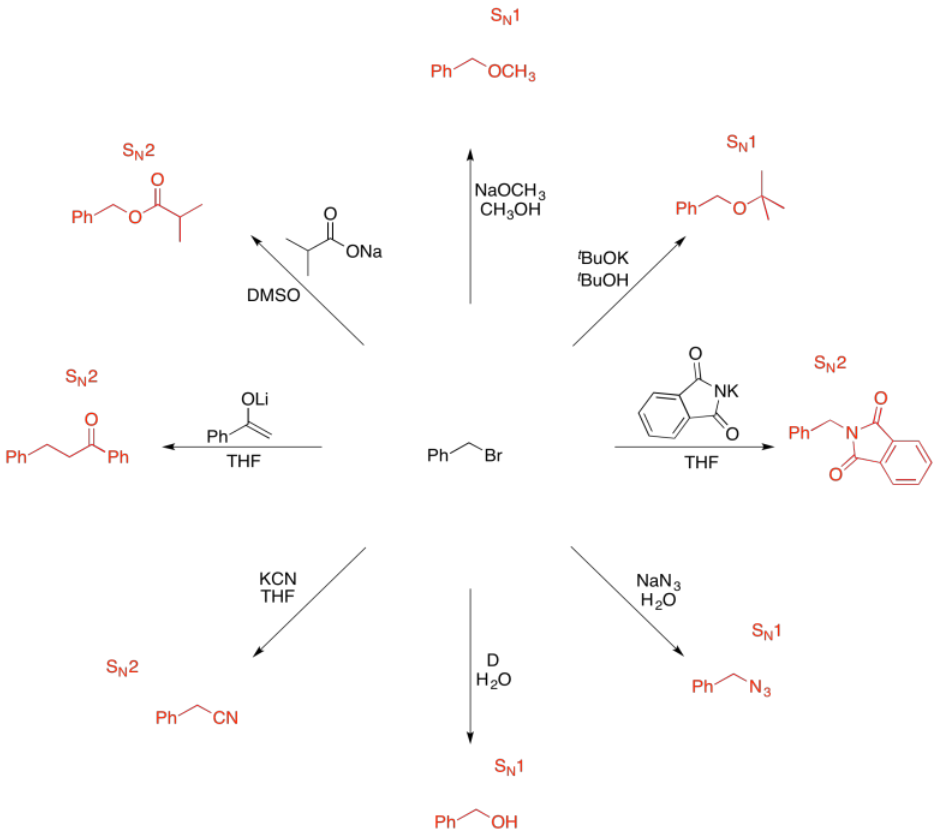


Exercise 4.19.7:

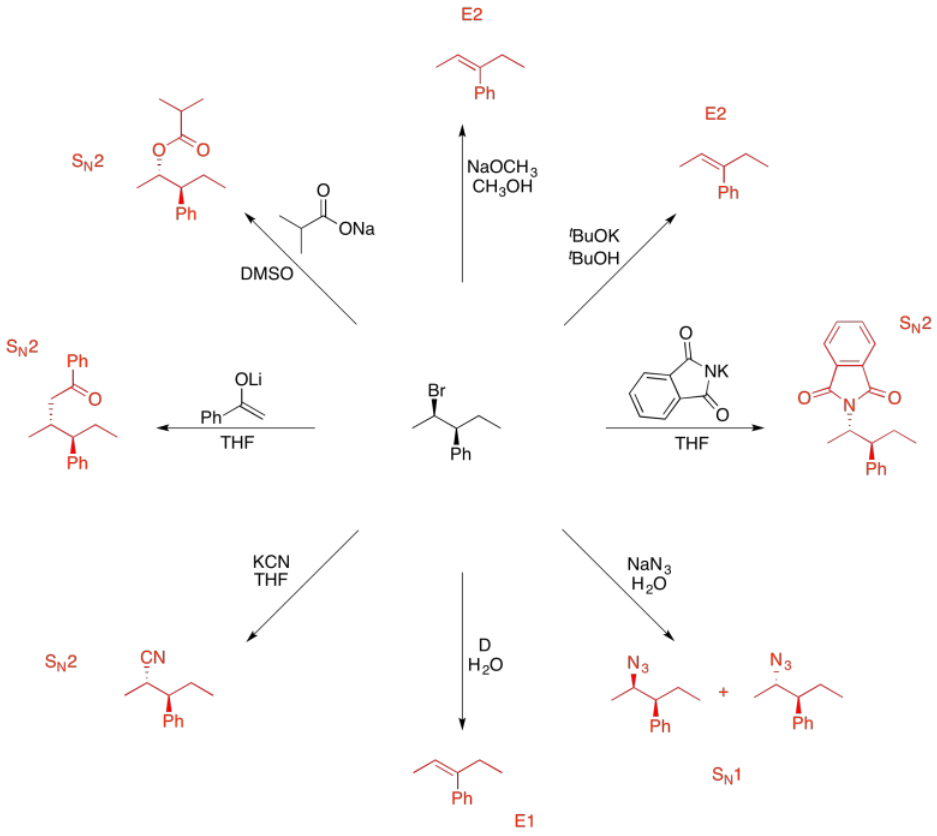
Synthesis of janoxepin
Richard Taylor et al, University of York, 2012
A fungal metabolite from *Aspergillus janus*, effective against the malaria parasite *Plasmodium falciparum*.



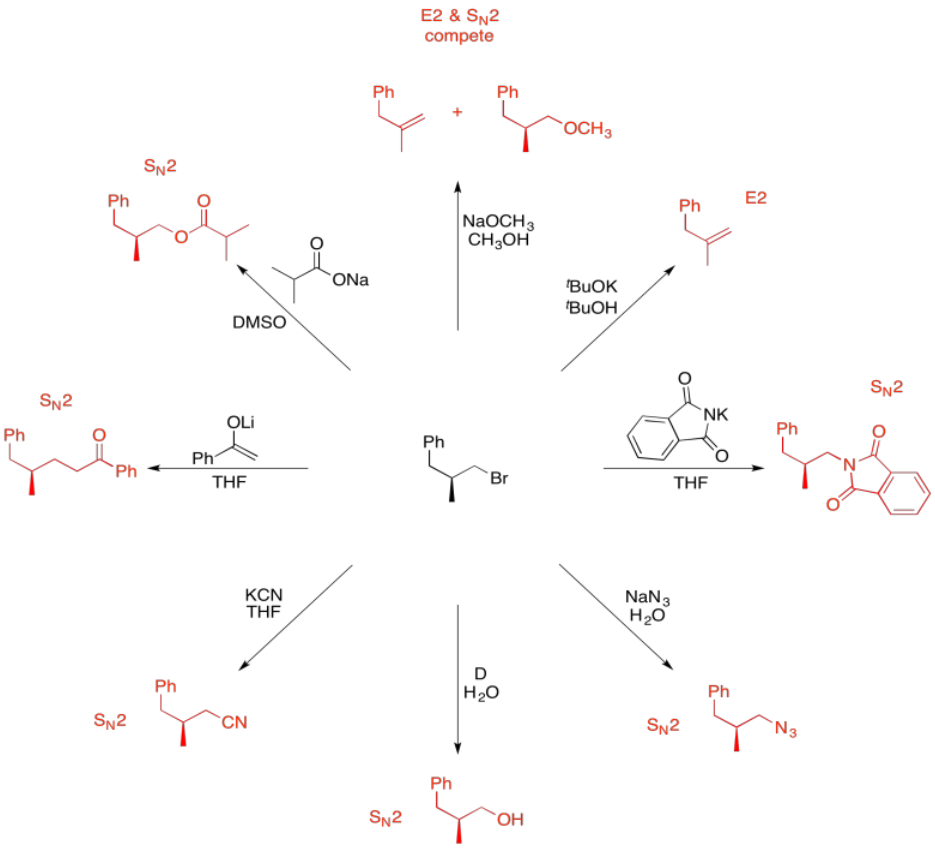
Exercise 4.19.8:



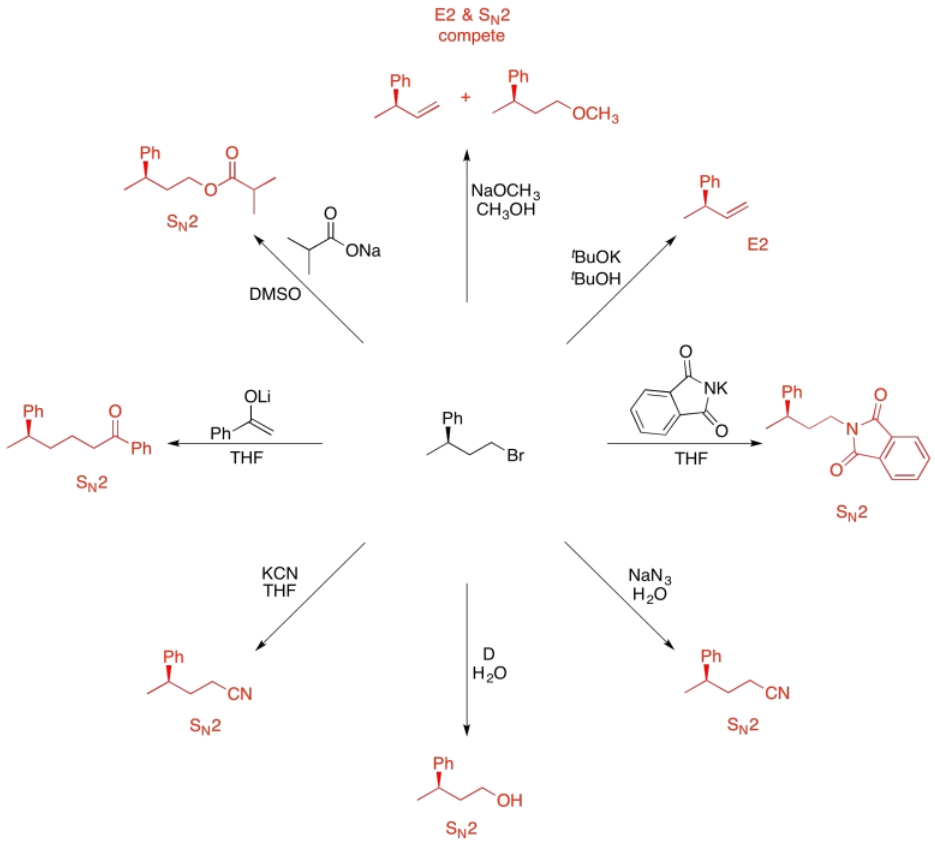
Exercise 4.19.9:



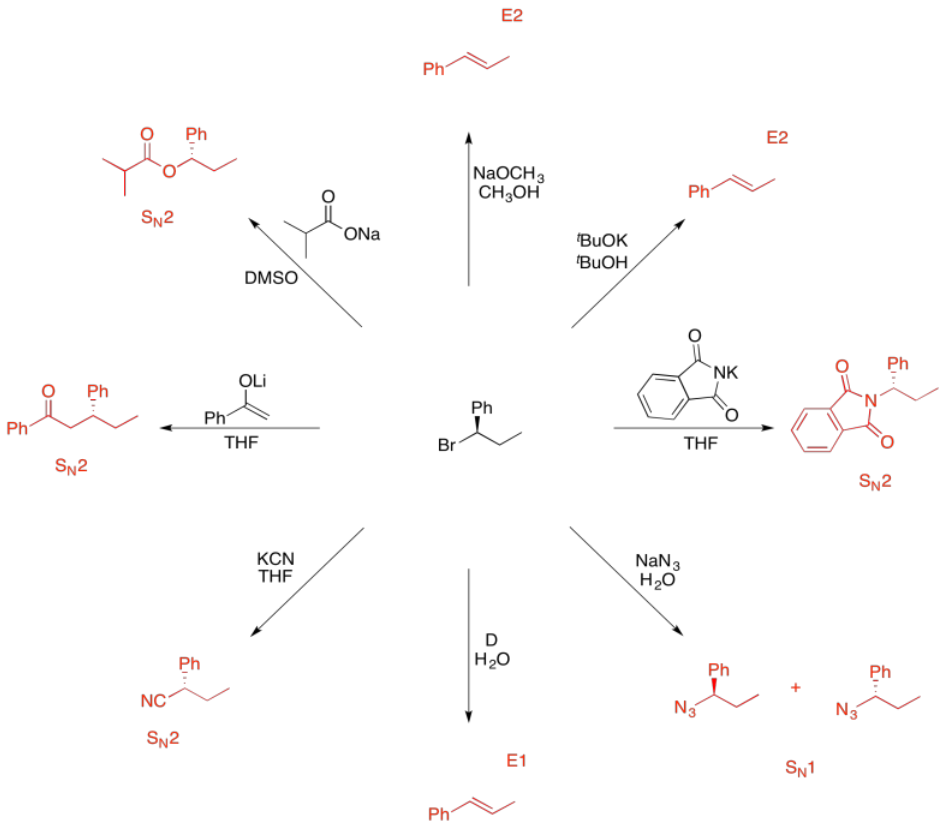
Exercise 4.19.10:



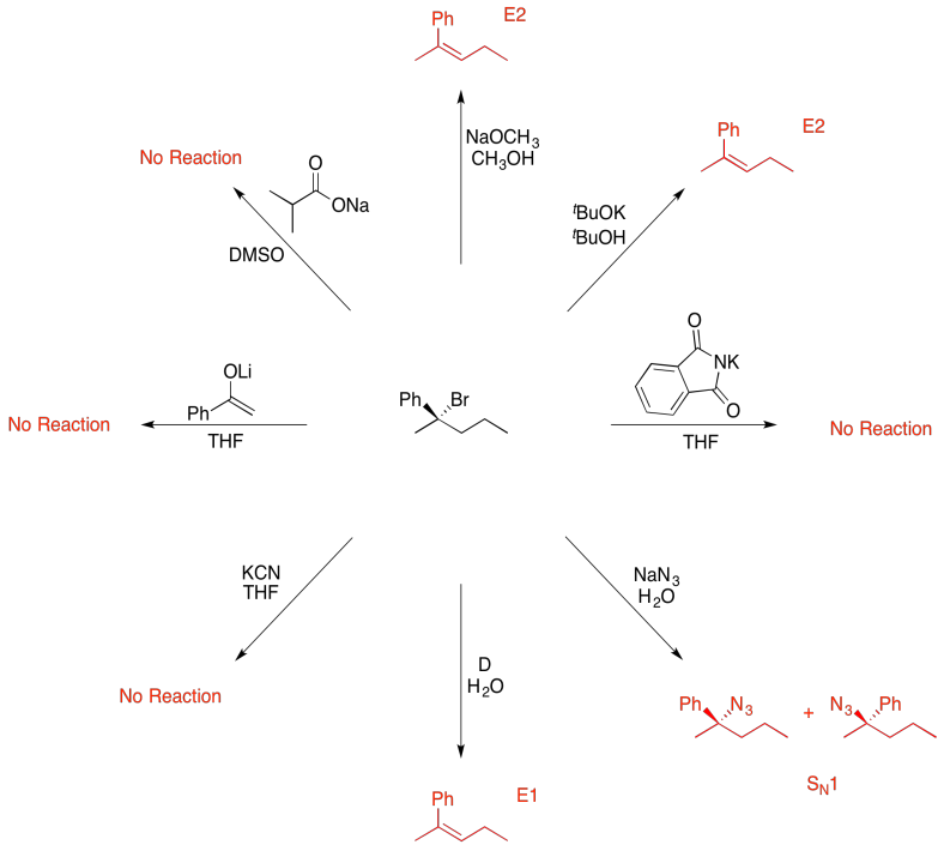
Exercise 4.19.11:



Exercise 4.19.12:



Exercise 4.19.13:



CHAPTER OVERVIEW

5: Oxidative Addition and Reductive Elimination

5.1: Introduction

Oxidative addition and reductive elimination are key steps in industrial catalysis. Oxidative addition is used to activate substrates. Substrates that normally might not react get ready to react with something. Then they sit on the metal atom and wait for something else to come along and react with them.

Figure 5.1.1: A generalized oxidative addition.

Bonds can be broken via oxidative addition that cannot easily be broken via other reactions. For example, although the H-H bond is very strong, it can be cleaved in the presence of a variety of metal atoms and ions. Transition metals possess the right tools to coax the two hydrogen atoms apart from each other.

Figure 5.1.2: A generalized oxidative addition of dihydrogen.

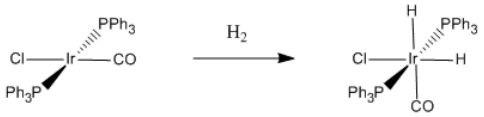


Figure 5.1.3: A specific case of oxidative addition of dihydrogen. When hydrogen adds to Vaska's complex, the oxidation state of iridium changes from +1 to +3.

Reductive elimination, in turn, is used to couple different groups together to form useful products. Once two groups are sitting beside each other on a transition metal atom or ion, they can bond to each other rather than the metal and go off together as a new molecule.

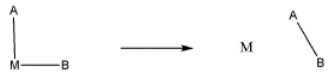


Figure 5.1.4: A general scheme for reductive elimination.

Clearly, a reductive elimination is just an oxidative addition in reverse. The reaction can go in either direction. That means it can, conceivably, occur in equilibrium. At this level, you would not be expected to know which direction would be favored for a particular reaction. However, you might be able to predict which direction a reaction would proceed based on factors such as le Chatelier's principle.

- le Chatelier's principle says that a change in the reaction conditions will lead to a shift in product:reactant ratio that offsets the change

For example, adding more reactant to the reaction shifts equilibrium to the right. More product is made, and some of the extra reactant is used up, so that the system can come back to its natural equilibrium. If products are somehow removed from the system, the reaction will also shift to the right, using up reactants and replacing the missing product. If the reaction is exothermic (produces heat) and more heat is added to the system, the reaction would shift to the left, using up some products and making more reactants in order to remove excess heat.

The reversibility of oxidative addition / reductive elimination actually serves very well in catalytic processes. For example, one of the most important catalytic processes in the world is catalytic hydrogenation, in which two hydrogen atoms are added across a double bond (usually a C=C bond, but sometimes a C=O or C=N bond). The process requires oxidative addition of hydrogen to a metal, but it also requires reductive elimination of an alkyl and a hydride to form the final product, forming a hydrocarbon.

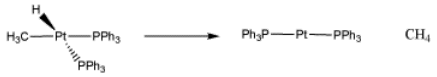


Figure 5.1.5: A reductive elimination of a methyl and a hydride to form methane.

The addition of dihydrogen to Vaska's complex and other transition metals is a reversible reaction. The hydrogen can be released again if the reaction moves to the left in a reductive elimination. That reversibility makes transition metal compounds useful for hydrogen storage. Hydrogen gas is voluminous, flammable and generally dangerous. By cleaving H_2 and binding hydrogen to metal atoms, hydrogen can be more safely stored and released again under the right conditions.

In reductive elimination, bonds can be made that cannot be formed via other reactions. That makes it a useful part of strategies to make commodity chemicals and complex organic molecules such as pharmaceuticals.

Exercise 5.1.1

Based on le Chatelier's principle, propose conditions under which:

a) Vaska's complex could bind hydrogen

b) the resulting dihydride adduct of Vaska's complex could release dihydrogen again.

Answer a

under an atmosphere of hydrogen gas.

Answer b

under an atmosphere of an inert gas such as nitrogen or argon, especially if there is a way for hydrogen gas to escape.

Exercise 5.1.2

Draw products of oxidative addition of the following compounds to $(PPh_3)_2Pd$.

a) HBr b) H_2 c) I_2 d) CH_3-Br

Answer

5.2: Reaction Overview

Oxidative addition is a general term for the insertion of a metal between two atoms that were previously bonded together.

Figure 5.2.1: Our general scheme for an oxidative addition of hydrogen to a metal.

Oxidative addition is a reaction type rather than mechanism. Several different mechanisms are possible, including polar reactions, non-polar / concerted reactions and radical reactions. For example the formation of Grignard nucleophiles by treatment of alkyl halides with magnesium could be described as an oxidative addition.

Figure 5.2.2: Formation of a Grignard reagent could be described as an oxidative addition, although the mechanism does not resemble the ones that we will look at here.

However, Grignard formation is believed to occur via a radical reaction, and has very little relationship to the addition of hydrogen to Vaska's complex, for instance. In this section, we will look at polar oxidative additions and concerted oxidative additions. Radical oxidative additions will be left for a later chapter on radical chemistry.

Where do the terms "oxidative addition" and "reductive elimination" come from? Think back to how we learned to count valence electrons in transition metal complexes. One of the first things we did was remove the ligands from the complex to see whether there would be a charge on the metal without the ligands.

Figure 5.2.3: Deconstruction of a metal complex to discern the charge on the metal.

If each H ligand in Figure OA2.2 is a hydride (reasonable because H is more electronegative than the metal), then removing them would leave the metal with a 2+ charge. That means the metal is in the (II) oxidation state, even if it doesn't formally have a charge on it in the complex. Addition of H_2 to a metal atom, M, is accompanied by increase in formal oxidation state at the metal (by +2).

Reductive Elimination is microscopic reverse of oxidative addition.

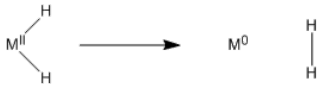


Figure 5.2.4: Deconstruction of a metal complex to discern the charge on the metal.

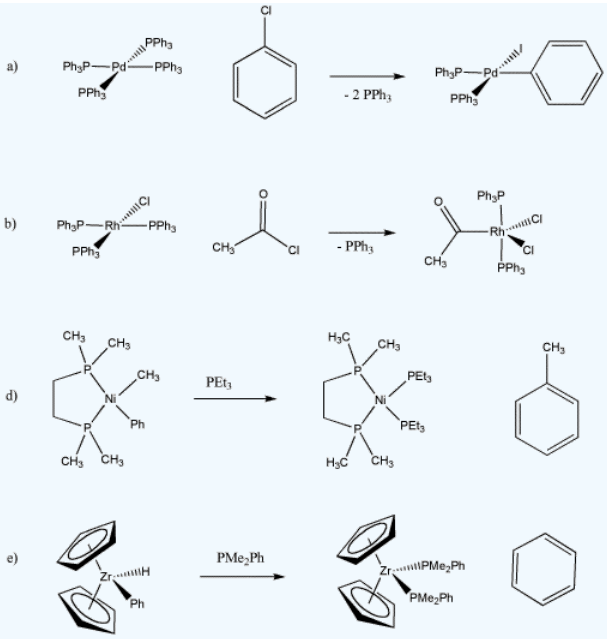
Two atoms that were bonded to one metal atom become bonded to each other, instead. Keep in mind the formal oxidation state of the metal. This elimination is accompanied by decrease in formal oxidation state at the metal (by -2).

Remember, oxidation state can often be determined by giving each ligand the pair of electrons it shares with the metal. Sort out the formal charge on the donor atom in the ligand, and you will know the charge or oxidation state of the metal.

For example, in the example of MH_2 in Figure OA2.3., assume each bond between M and H is a pair of electrons that belongs with the hydrogen. A hydrogen with two electrons is an anion. As a result, the metal must have an oxidation state of +2 (usually written with Roman numeral II).

? Exercise 5.2.1

Determine the oxidation state on the metal before and after each of the following reactions.



Answer a

Pd(0) to Pd(II) (I and Ph are negative)

Answer b

Rh(I) to Rh(III) (Cl and acyl are negative)

Answer d

Ni(II) to Ni(0) (Methyl and phenyl are negative)

Answer e

Zr(IV) to Zr(II) (Cp, H and Ph are negative)

? Exercise 5.2.2

Propose a reason why the addition of a ligand such as a phosphine can sometimes result in reductive elimination from a coordination complex.

Answer

Increased steric crowding in the coordination sphere may force two gorups to reductively eliminate together.

5.3: Polar Oxidative Addition

The polar oxidative addition mechanism is very similar to an aliphatic nucleophilic substitution (S_N1 or S_N2) reaction.

Figure 5.3.1: An example of a polar oxidative addition.

In an oxidative addition, the metal can act as a nucleophile in the first step in an S_N2 process. In the second step, the liberated halide binds to the metal. That doesn't happen in a normal nucleophilic substitution. In this case, the metal has donated its electrons and is able to accept another pair from the halide.

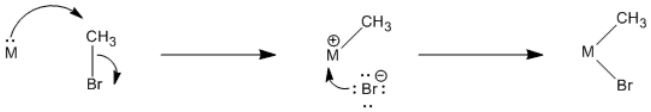


Figure 5.3.2: Mechanistic steps in a polar oxidative addition.

Polar oxidative addition has some requirements similar to a regular S_N1 or S_N2 reaction:

- Requires good leaving group
- Requires tetrahedral carbon (or a proton) as electrophile

Exercise 5.3.1

a) What do you think is the most difficult step (i.e. the rate-determining step) for the reaction in Figure 5.3.2 (OA3.2)? Why?

b) Suggest the probable rate law for this reaction.

Answer a

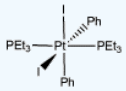
Probably the first step is the hardest (slowest) step, involving bond breaking in the alkyl halide. The donation of the resulting anion to the cation should be pretty fast.

Answer b

$$Rate = k_1[ML_n][CH_3Br]$$

Exercise 5.3.2

The platinum compound shown below is capable of reductively eliminating a molecule of iodobenzene.



a) Show the products of this reaction.

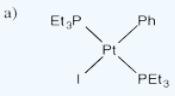
The starting platinum compound is completely stable in benzene; no reaction occurs in that solvent. However, reductive elimination occurs quickly when the compound is dissolved in methanol instead.

b) Explain why the solvents may play a role in how easily this compound reacts.

The reaction in methanol is inhibited by added iodide salts, such as sodium iodide.

c) Provide a mechanism for the reductive elimination of iodobenzene from the platinum complex, taking into account the solvent dependence and the inhibition by iodide ion.

Answer a

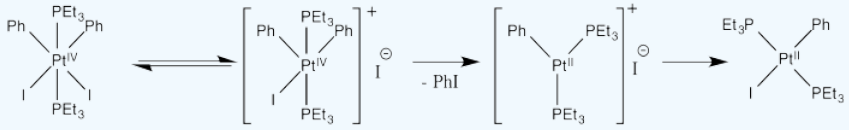


Answer b

Methanol is more polar than benzene. The acceleration of the reaction in methanol suggests that there is increasing polarity in the transition state, or polar intermediates.

Answer c

Inhibition by iodide ion suggests that iodide is a product of a reversible step during this reaction. Adding iodide pushes that step backward, decreasing the rate of product formation. The mechanism below is consistent with these observations:



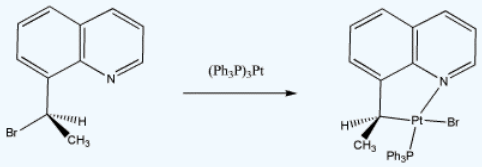
Thus reductive elimination occurs as we go from the second to the third intermediate.

Presumably, the increased positive charge (and general decrease in electron density, owing to loss of a ligand) results in reductive elimination because of destabilization of the Pt(IV).

Alternatively, we might suppose that after loss of iodide, the iodide ion donates directly to a phenyl ligand, displacing the platinum as a leaving group in an S_N2 reaction. That would lead directly to the product from the first intermediate, which is a simpler route. However, the precedent for aliphatic nucleophilic substitution involves nucleophilic donation to tetrahedral carbons, not to trigonal planar ones. That mechanism is unlikely.

Exercise 5.3.3

For the following reaction,



a) Identify the oxidation state at platinum in the reactant and the products.

b) Assign stereochemical configuration in the product and the reactant.

c) Explain the stereochemistry of the reaction.

Answer a

Pt(0) to Pt(II)

Answer b

Changes from (*R*) to (*S*)

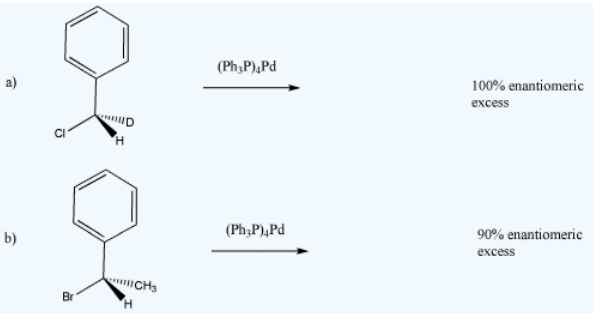
Answer c

This is an S_N2 reaction, so the platinum displaces the bromide from the opposite side.

Exercise 5.3.4

Reaction of the following deuterium-labeled alkyl chloride with tetrakis(triphenylphosphine) palladium produces an enantiomerically pure product (equation a). Draw the expected product.

However, reaction of a very similar alkyl halide produces a compound that is only 90% enantiomerically pure. Draw the major product and explain the reason that there is some racemization

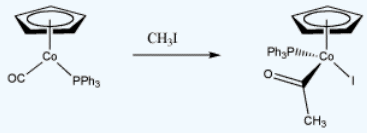


Answer

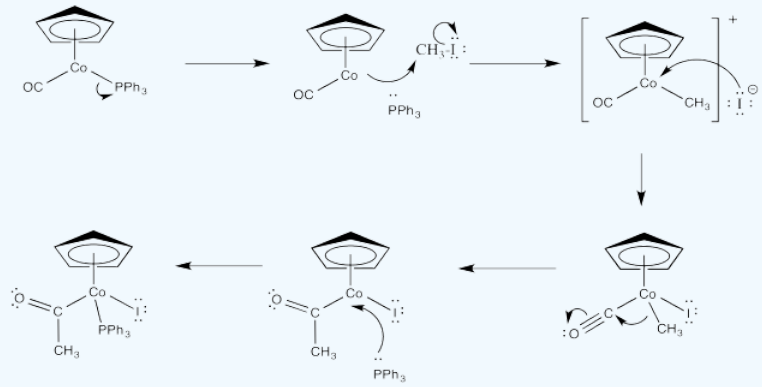
In case (a), the reaction appears to be S_N2, presumably with complete inversion of configuration from (*S*) to (*R*). In case (b), there is probably a competing S_N1 pathway because the resulting cation is both benzylic and secondary, so it is pretty stable. On the other hand, if the reaction proceeded entirely through an S_N1 pathway, the reaction would result in nearly complete racemization, with 0% ee.

Exercise 5.3.5

Frequently, oxidative additions and reductive eliminations are preceded or followed by other reactions. Draw a mechanism for the following transformation.



Answer



5.4: Concerted Oxidative Addition

Concerted oxidative addition is a more general reaction than polar addition, in the sense that it is not restricted to compounds that can undergo aliphatic nucleophilic substitution. It could also be thought of as non-polar oxidative addition, because it does not involve charged intermediates as seen in the polar mechanism.

Aryl halides, for example, do not undergo nucleophilic substitution, but they do undergo concerted oxidative addition.

Instead of proceeding step by step, the addition of both fragments is synchronized. They add to the metal at the same time.

Figure 5.4.1

At first, it's difficult to understand this mechanism in terms of nucleophiles and electrophiles. The reaction is generally explained in terms of molecular orbital interactions, however, that can be thought of as nucleophile-electrophile interactions.

There are interactions involved in a concerted or non-polar oxidative addition.

- There is sigma bond donation from a bonding orbital in the substrate into a metal p orbital. This interaction is shown on the left of figure OA4.2.
- There is donation from a metal d orbital into an antibonding orbital on the substrate. This interaction is shown in the middle of figure OA4.2.
- Overall, a pair of electrons are donated from the substrate to the metal, and a pair of electrons are donated from the metal to the substrate.

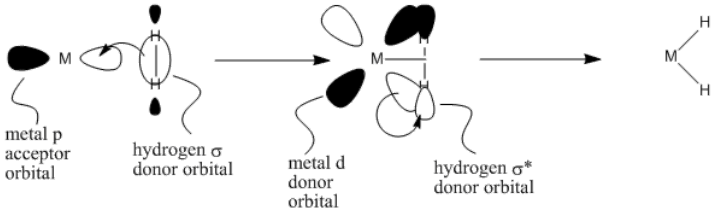
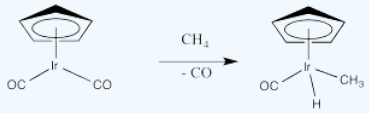


Figure 5.4.2: Molecular orbital interactions in a non-polar oxidative addition.

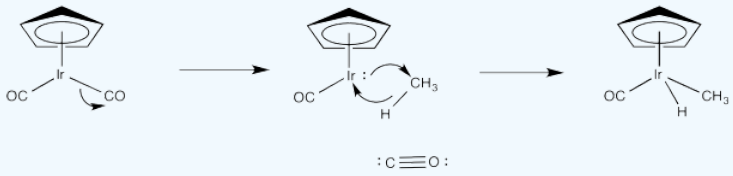
Figure 5.4.3: A curved arrow representation of non-polar oxidative addition.

Exercise 5.4.1

Provide a mechanism, with curved arrows, for the following reaction.

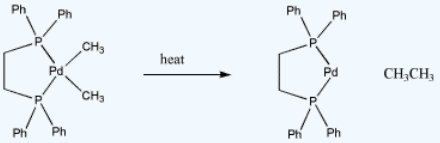


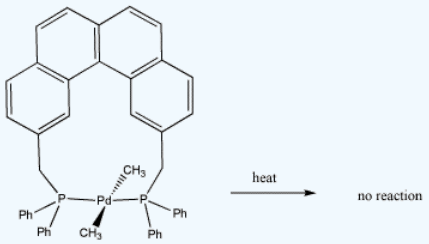
Answer



Exercise 5.4.2

Propose a reason for the fact that one of the following dimethyl palladium compounds undergoes reductive elimination, but the other one does not.





Answer

Concerted oxidative addition is the mechanism that occurs when a polar mechanism (S_N2) is not possible. It is sometimes called "cis" oxidative addition. Because the two fragments added to the metal form bonds to the metal at the same time, they must be cis to each other.

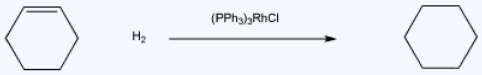
By the principle of microscopic reversibility, reductive elimination works the same way. The ligands have to be cis to each other in order to reductively eliminate, unless they are eliminating via a polar mechanism. Since both alkyl groups would have the same charge, a polar mechanism is unlikely.

Both of these platinum(II) complexes are d^8 and they would adopt square planar geometry. In the second case, the alkyls would be trans to each other and would be unable to undergo reductive elimination.

Exercise 5.4.3

Frequently, oxidative addition and reductive elimination are combined with other reactions into catalytic cycles. These cycles form the basis of important processes used to make valuable materials. Propose catalytic cycles for the following reactions. You don't need to draw curved arrows; just provide the intermediate formed after each reaction step.

a) catalytic hydrogenation

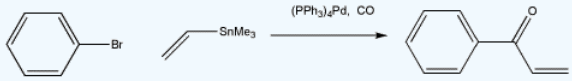


b) Monsanto Acetic Acid Process

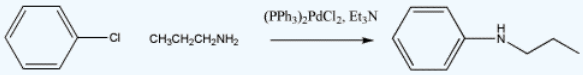
(probably involves acid-catalysed conversion of methanol to bromomethane)

c) Suzuki Coupling

d) Stille Coupling (Carbonylative Variation)

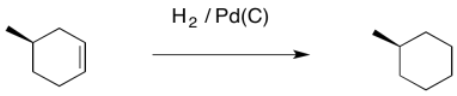


e) Buchwald-Hartwig Coupling



5.5: Oxidative Addition in Action- Catalytic Hydrogenation

Catalytic hydrogenation is a tremendously important reaction. It is an essential step in the synthesis of many fine chemicals as well as bulk commodities. In catalytic hydrogenation, a pair of hydrogen atoms are added across a double bond, turning an alkene into an alkane.



In general, the reaction requires a large excess of hydrogen gas, often under high pressure. The reaction can be performed under either homogeneous or heterogeneous conditions. Homogeneous reactions employ a soluble catalyst. Soluble catalysts are those that dissolve under the reaction conditions; they often provide superior control over the reaction. Heterogeneous catalysts do not dissolve; they are solids that sit on the bottom of the reaction, like sand in a lakebed. One of the advantages of heterogeneous catalysts is that they can easily be filtered away from the rest of the reaction, making purification of the product much more straightforward.

? Exercise 5.5.1

Indicate whether the following mixtures are homogeneous or heterogeneous.

a) Kool-aid b) a glass of pop with ice c) orange juice d) cranberry juice

Answer a

homogeneous

Answer b

heterogeneous

Answer c

heterogeneous

Answer d

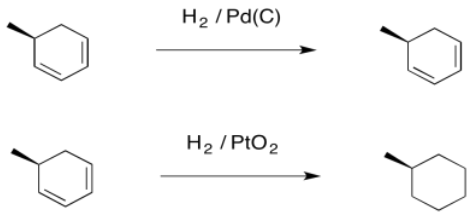
homogeneous

Because of the importance of hydrogenation, a number of catalysts have been developed over the years that are capable of performing the reaction. There are a number of motivations for working on catalyst development. One reason is speed: the faster the catalyst, the more product can be made and the more economical the process. Another reason is selectivity. Suppose there are two double bonds present in a molecule. Maybe you only want to hydrogenate one of these double bonds. By choosing the proper catalyst, you may be able to do that.

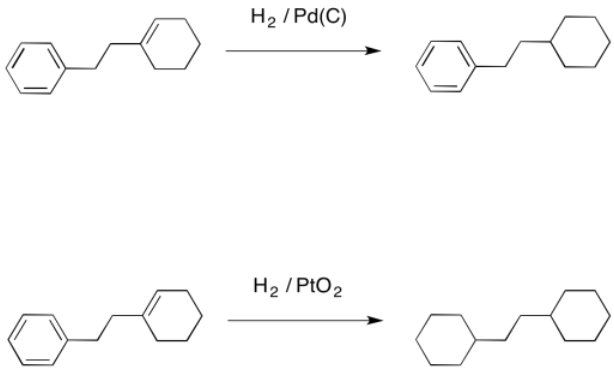
Let's take a look at a few different examples of catalysts with different selectivities.

Perhaps the most commonly used catalyst is palladium metal, a heterogeneous catalyst. Very often, expensive metals like palladium are not used in their pure state. For example, palladium is often dispersed on a "solid support", such as carbon. There are a couple of benefits of doing that. First, the expensive palladium metal is stretched a little further by mixing it with carbon, which is much cheaper. Usually, this mixture is about 5% palladium and 95% carbon, although different compositions can be used. In addition, use of a solid support helps to spread the metal particles out spatially. When the metal isn't all clumped together, it has an increased surface area. That means there are more places available for hydrogen and alkenes to bind and undergo the hydrogenation reaction. Finally, a solid support often tunes the reactivity of the metal that is stuck to it. The solid support might change the rate of the reaction or alter the selectivity because of interactions between the metal and the support.

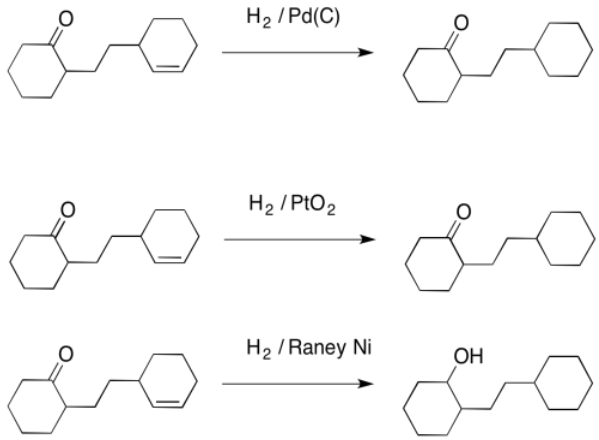
Palladium on carbon, or Pd/C, provides an example of what we mean by selectivity. It is very good at adding hydrogen to alkenes. It can hydrogenate alkynes, too. However, it is not very good at hydrogenating more stable double bonds, such as those in conjugated dienes, or in benzene or other aromatics. In contrast, platinum oxide is much more general, hydrogenating regular alkenes and also conjugated ones.



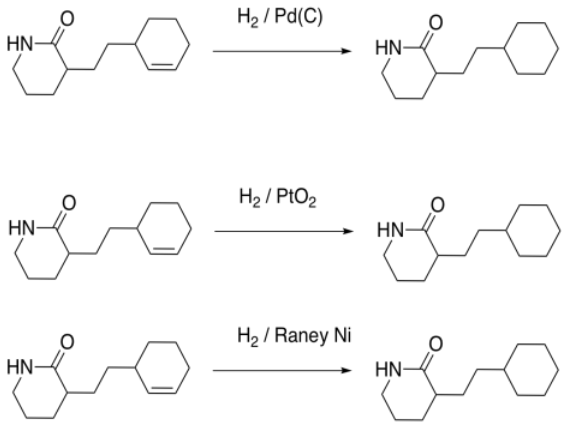
Under the right conditions, platinum oxide can even be used to hydrogenate benzene. That usually means very high pressure of hydrogen gas.



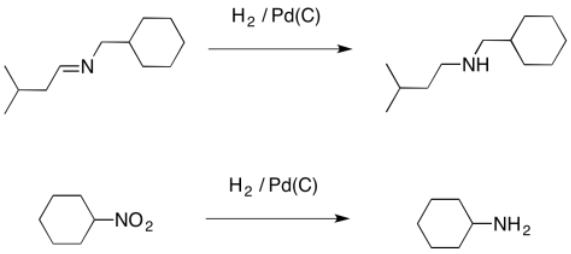
Also, hydrogenation with palladium doesn't work very well with carbonyls. It usually won't reduce aldehydes or ketones. You may remember that other reducing agents (compounds that add hydrogen to carbon atoms) such as $LiAlH_4$ can react with carbonyls quite easily, so palladium with hydrogen is very complementary to those reagents. Even PtO_2 can't induce hydrogen to add across a carbonyl, although another heterogeneous catalyst, a ferocious one called Raney Nickel, can do the job.



However, not even Raney Nickel does very well at hydrogenating more stable carbonyls, such as amides, esters and carboxylic acids. Those are the ones at the bottom of the energetic "ski hill", so they are the least reactive carbonyls. They are difficult to hydrogenate, and are usually left alone.

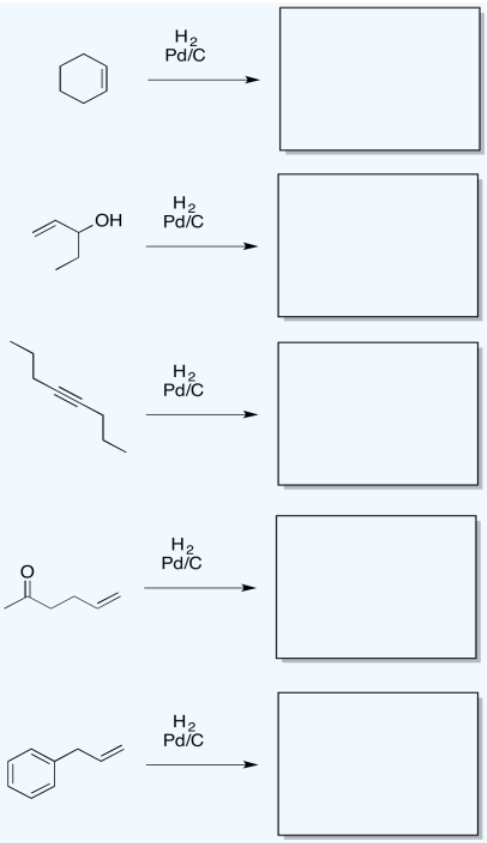


On the other hand, palladium does just fine with some seemingly related compounds, containing imines and nitro groups. Although these groups contain multiple bonds and nitrogen, they do not have the same stability of amides. Imines and nitro groups behave a little more like simple carbonyl compounds when it comes to hydrogenation.

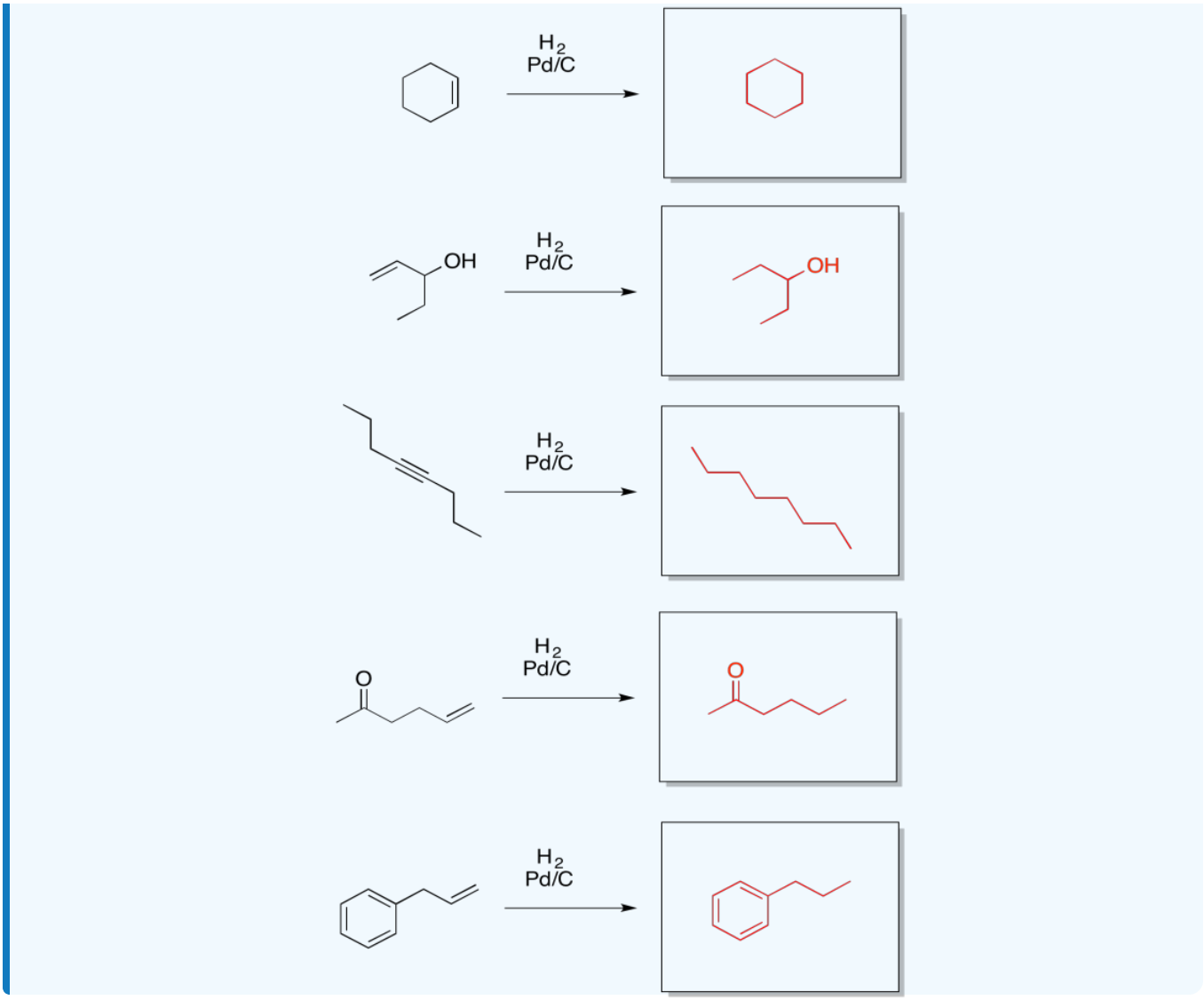


? Exercise 5.5.2

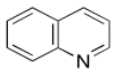
Provide products for the following reactions.



Answer

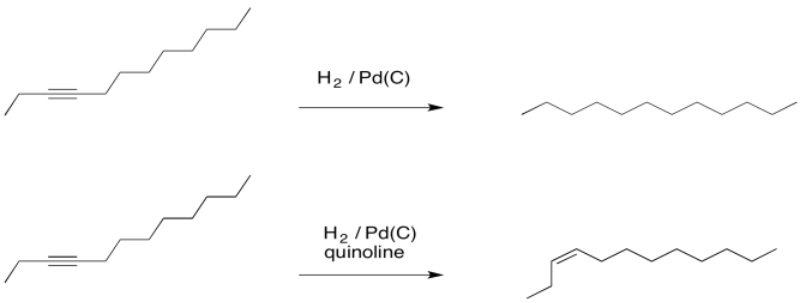


We can make the palladium catalyst even more selective by preparing it in a different way. Lindlar's catalyst is a very dramatic example of how reactivity can be tuned by using different compositions. To make Lindlar's catalyst, palladium is supported on calcium carbonate rather than carbon, together with other components, such as lead acetate and quinoline. That last component turns out to be the key to Lindlar's catalyst. It tunes the reactivity so that the catalyst can react with alkynes but not with alkenes.



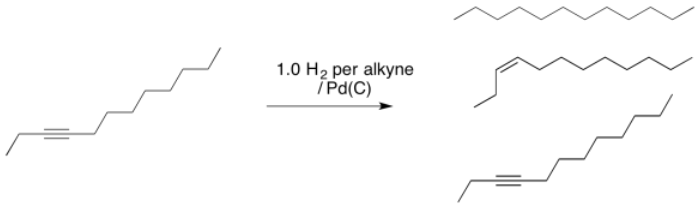
quinoline

As a result, if a compound is hydrogenated with a palladium catalyst in the presence of quinoline, an alkene is produced. Without the quinoline, you would get an alkane.



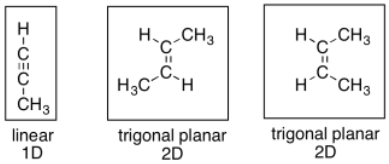
Normally, if a catalyst hydrogenates an alkyne, no alkene is observed. That's because the alkene also reacts under the same conditions and is quickly converted to an alkane.

Not so fast, you say. If we just add one equivalent of hydrogen (that is, one molecule of hydrogen for every molecule of alkyne) then the reaction will stop after forming an alkene. That's very clever of you. However, you've missed a couple of important concepts. First of all, we are never dealing with individual molecules when we run a reaction; instead, we are dealing with vast numbers of molecules at a time. That means we will deal with statistical distributions. Maybe some molecules of hydrogen react with alkyne to produce alkene. Maybe some molecules go ahead and react with that alkene to produce alkane. Now, if we only added enough hydrogen for every alkyne to react with one H_2, and some of them have already reacted with two, then somebody will be left out. There will be some leftover alkyne, too. That means we have made a mixture of alkyne, alkene and alkane.

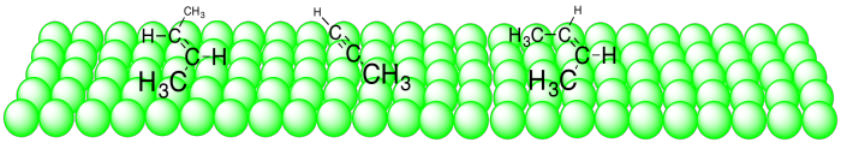


The other missing concept is that hydrogenation reactions usually run under a high pressure of hydrogen gas. That means many equivalents of hydrogen are needed in order to push the reaction forward.

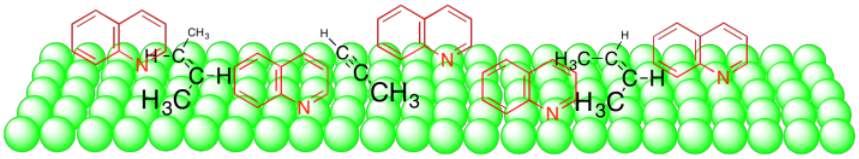
How does the presence of quinoline change the catalyst so dramatically? It seems that the answer is based on steric crowdedness. Although alkenes are flat, and don't seem very crowded, they may be crowded compared to an alkyne, which is linear. That difference makes alkynes even more reactive than alkenes with respect to hydrogenation.



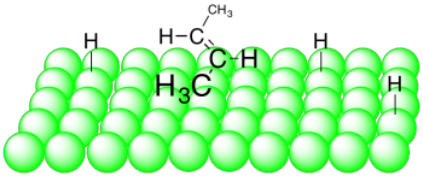
When these compounds bind to the surface of the catalyst, the alkyne takes up less space than the alkenes. It mostly lies along one dimension, whereas the alkenes are spread out into two dimensions.



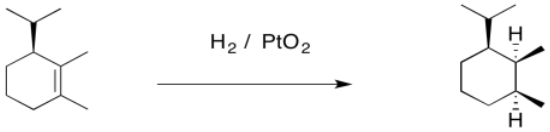
The quinoline seems to simply take up space when it binds to the surface of the catalyst. As a result, the wider alkene can't bind as well as the narrow alkyne.



So it turns out that Lindlar's catalyst is a big deal. It provides a very selective reaction: production of an alkene from an alkyne. Furthermore, it doesn't just make any alkene. It only makes *cis*-alkenes. That's because the hydrogen atoms are both delivered from the surface of the metal. The alkyne binds to the surface of the metal and accepts the hydrogen atoms from that surface. As a result, both hydrogens end up on the same side of the new double bond. The alkene formed is then a *cis*-alkene.

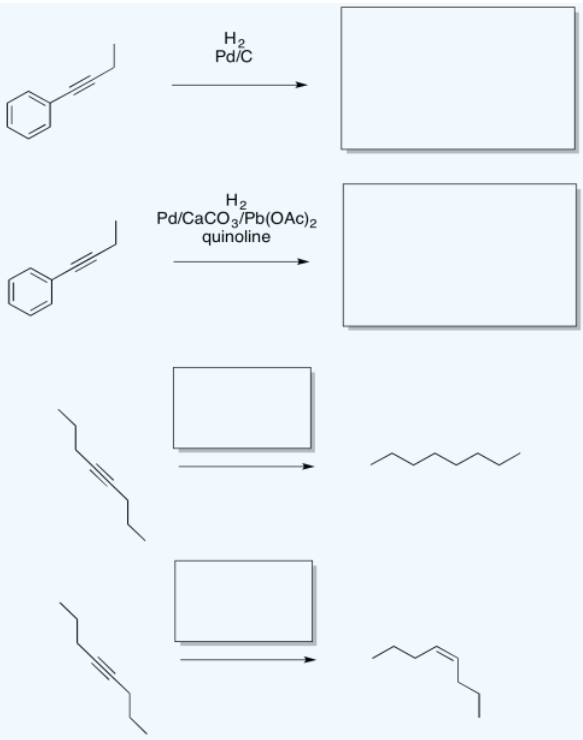


The addition of two hydrogen atoms to the same side of the molecule is not limited to Lindlar's catalyst. It's a general feature of catalytic hydrogenation. As a result, catalytic hydrogenations are often diastereoselective; they result in the formation of one diastereomer, but not the other.

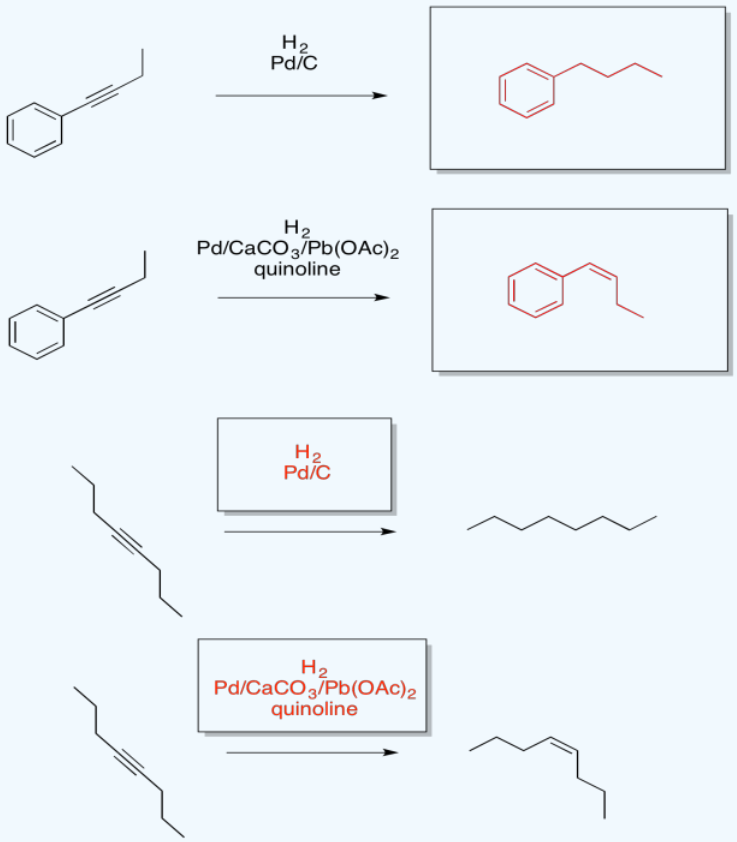


Exercise 5.5.3

Provide the missing reagents or products for the following reactions.

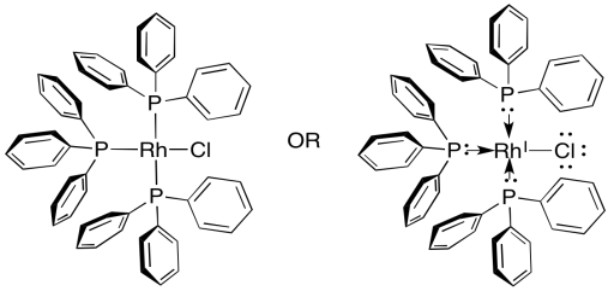


Answer

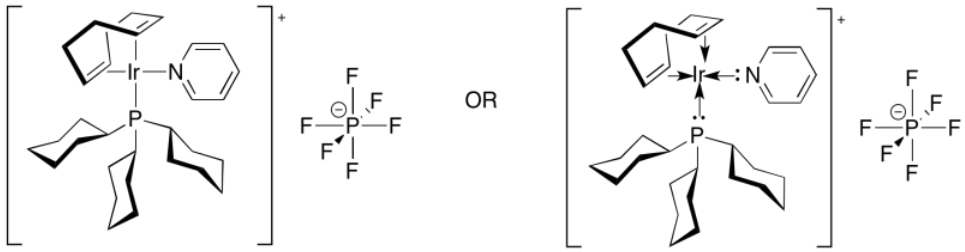


What about homogeneous catalysts? The most common one is Wilkinson's catalyst, $(Ph_3P)_3RhCl$. Wilkinson's catalyst, like Pd/C, is good at reacting with alkenes but leaving polar bonds alone. It is also highly selective, reacting only with the least sterically

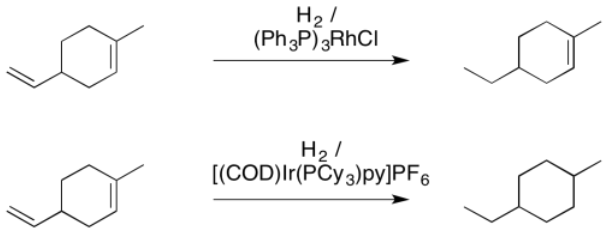
crowded alkenes. It only reacts with monosubstituted and disubstituted alkenes. If an alkene has fewer than two hydrogens attached to the double bond, Wilkinson's catalyst leaves it alone.



In contrast, Crabtree's catalyst, $[(COD)(PCy_3)(py)Ir]PF_6$ is a much more reactive catalyst. In part, that's because it is a more electrophilic, cationic catalyst; the PF_6 is a non-reactive counterion. In addition, Crabtree's catalyst contains a sacrificial alkene ligand. COD is cyclooctadiene, a bidentate ligand that contains two double bonds. What happens to that ligand when the catalyst is exposed to hydrogen? It gets hydrogenated, of course. Without double bonds, it can no longer be a ligand. That leaves the catalyst with two open coordination sites, although really these sites are occupied by solvent molecules. Nevertheless, the solvent molecules bind only loosely, and can easily leave to make room for an alkene.

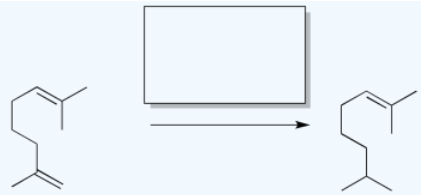


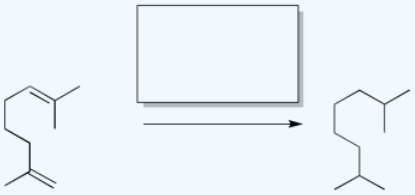
As a result, Crabtree's catalyst is much less sensitive to steric crowding. Unlike Wilkinson's catalyst, it is perfectly capable of hydrogenating trisubstituted or even tetrasubstituted alkenes.

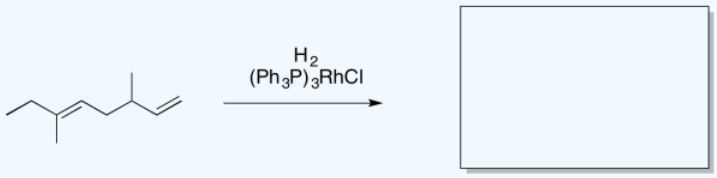


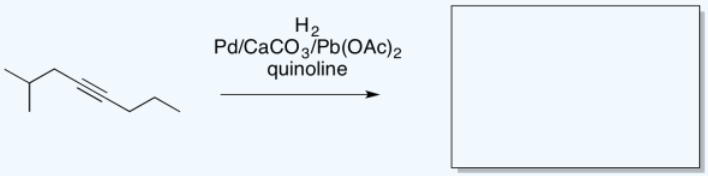
? Exercise 5.5.4

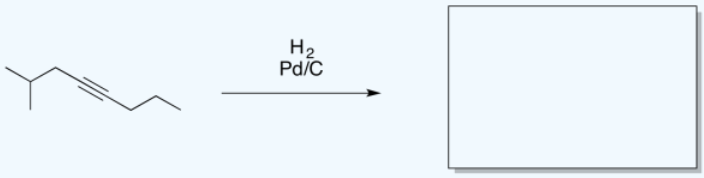
Provide the missing reagents or products in the following reactions.











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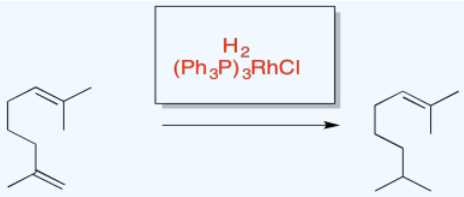
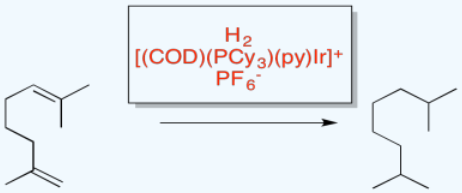
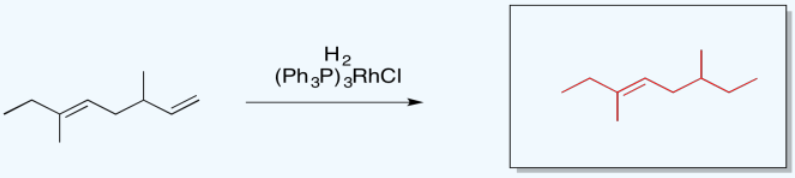
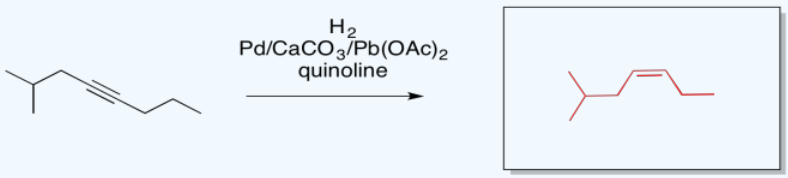


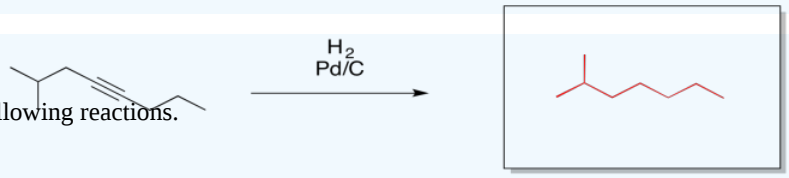


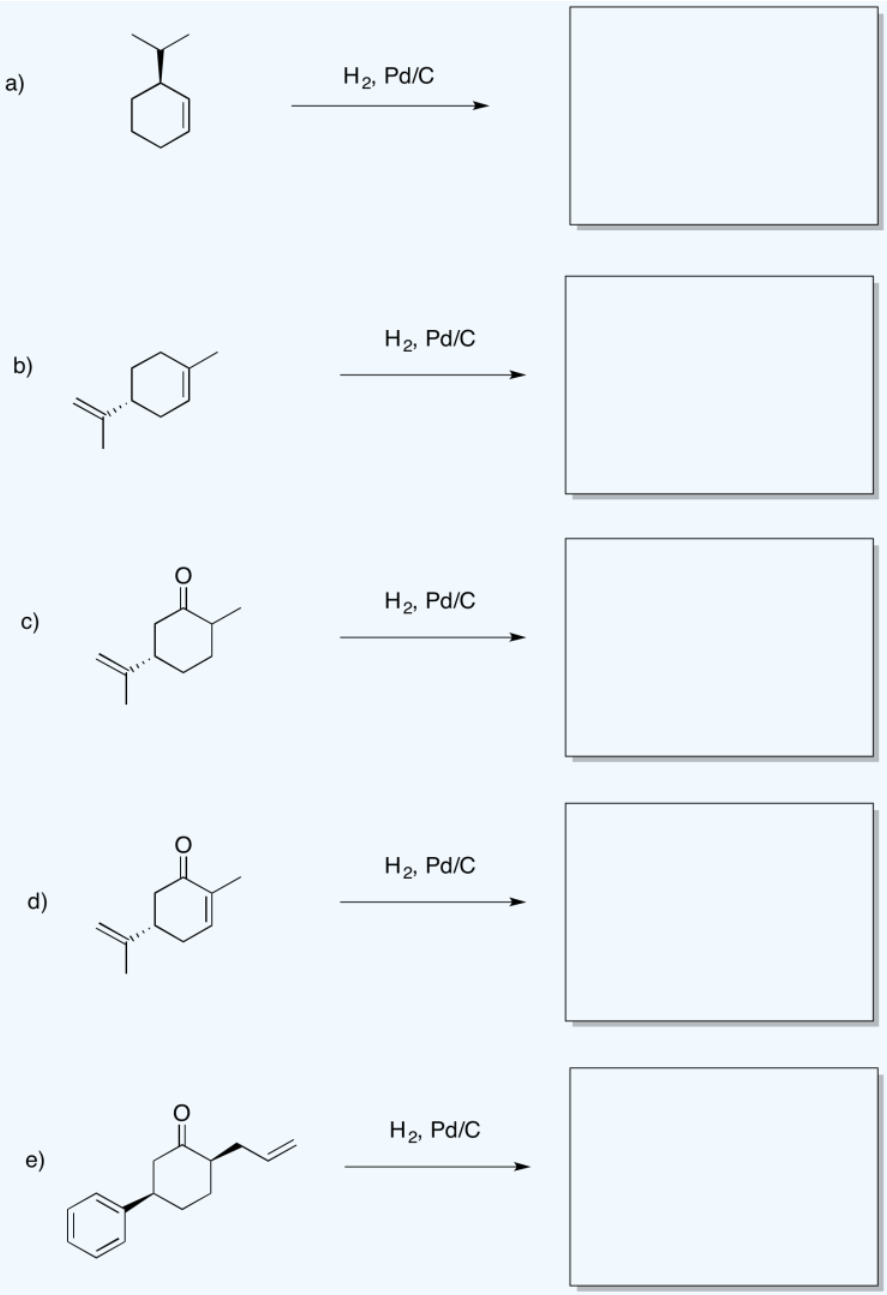




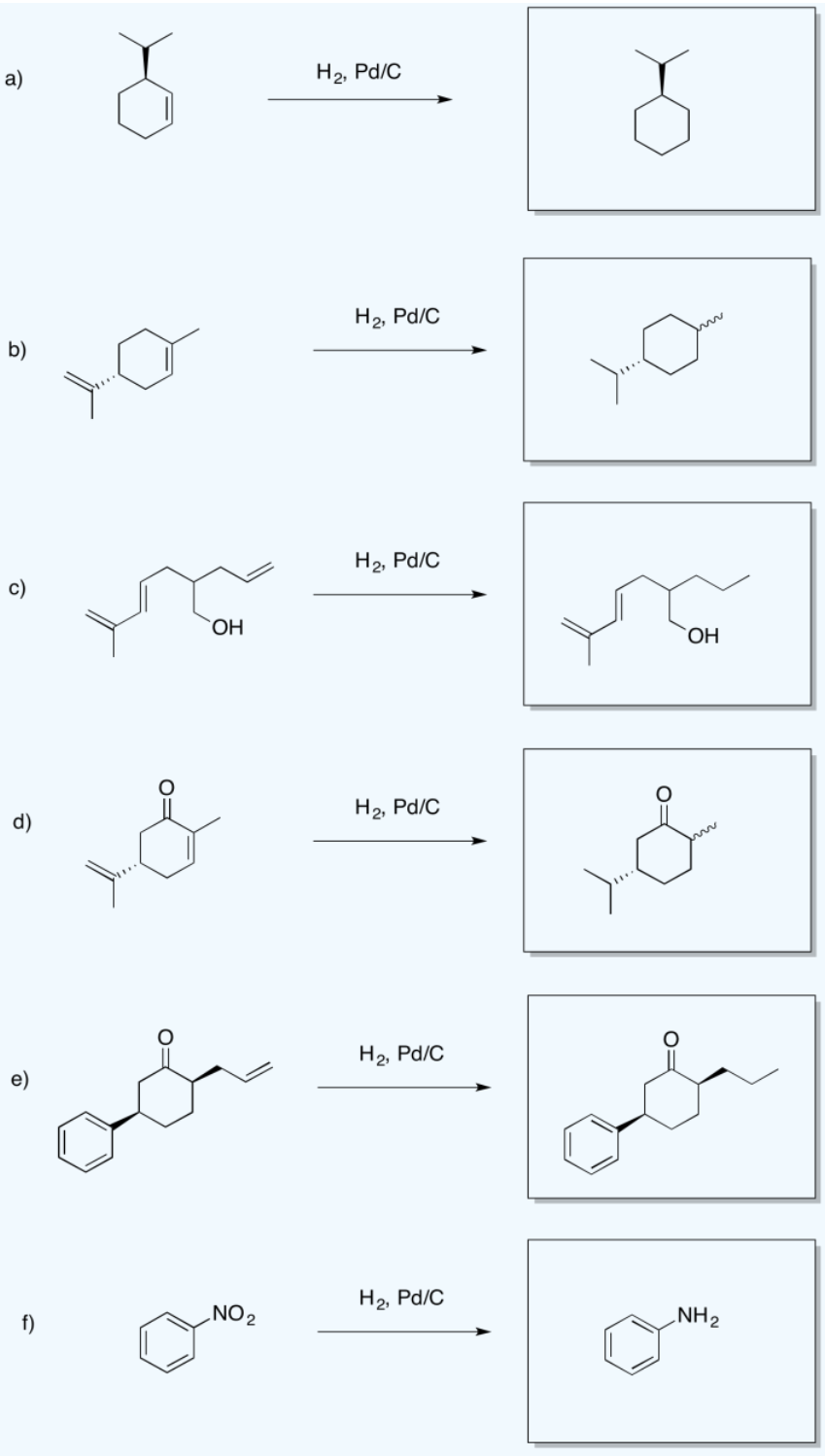
? Exercise 5.5.5

Provide products for the following reactions.



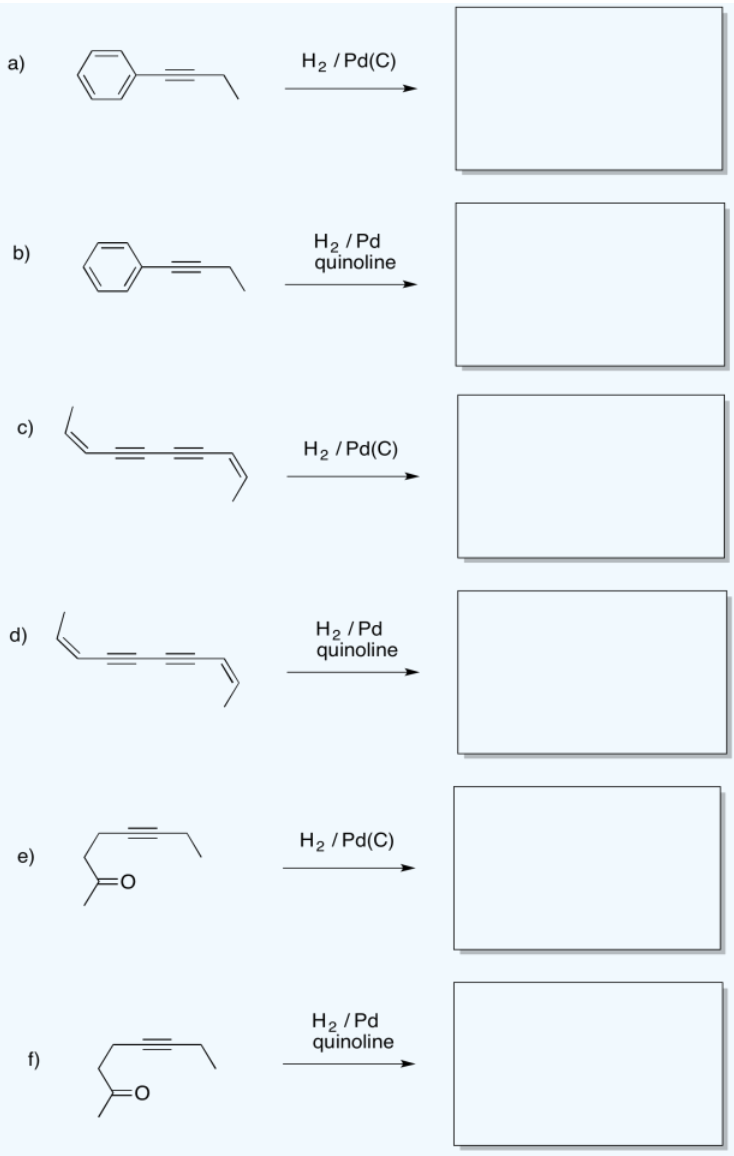


Answer

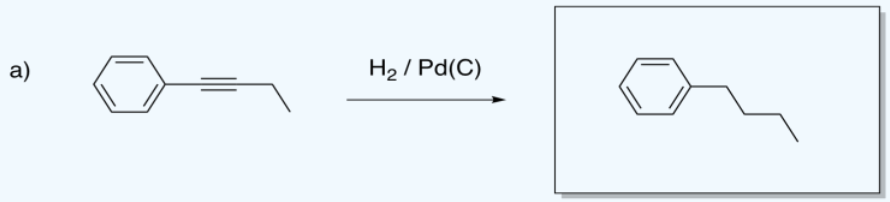


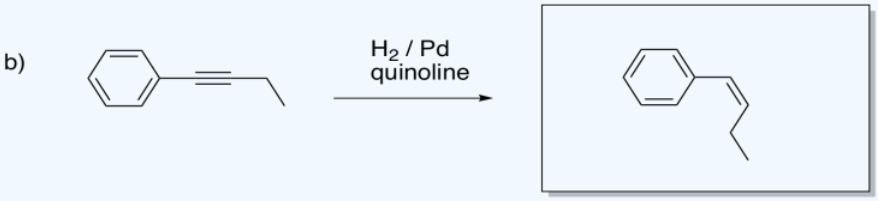
Exercise 5.5.6

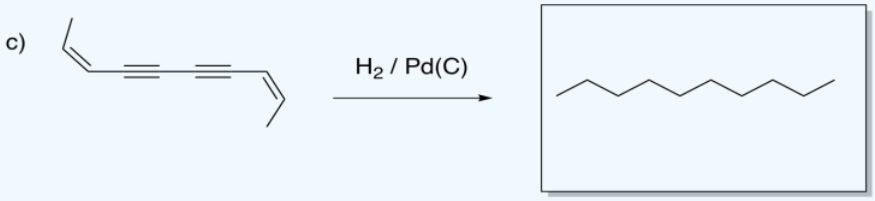
Provide products for the following reactions.

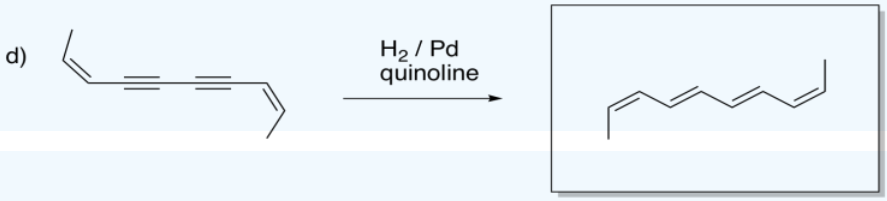


Answer



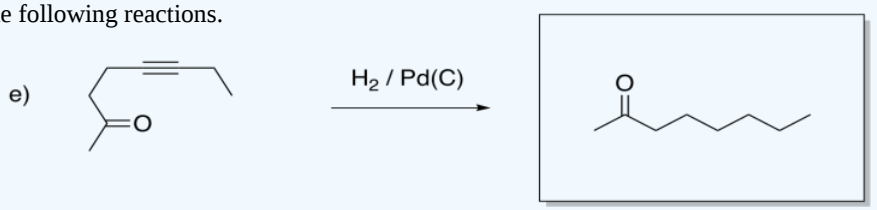


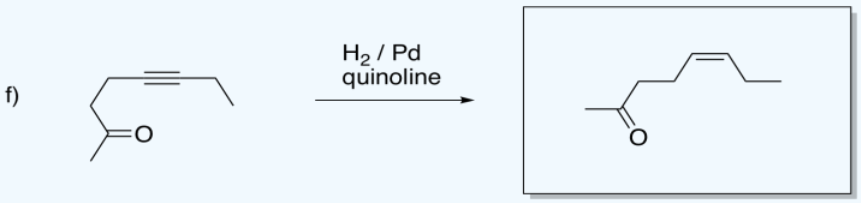




? Exercise 5.5.7

Provide reagents for the following reactions.



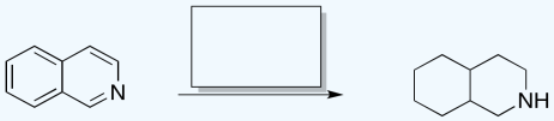


a) 

b) 

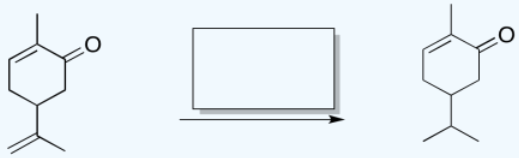
c) 

d) 

e) 

f) 

g) 

h) 

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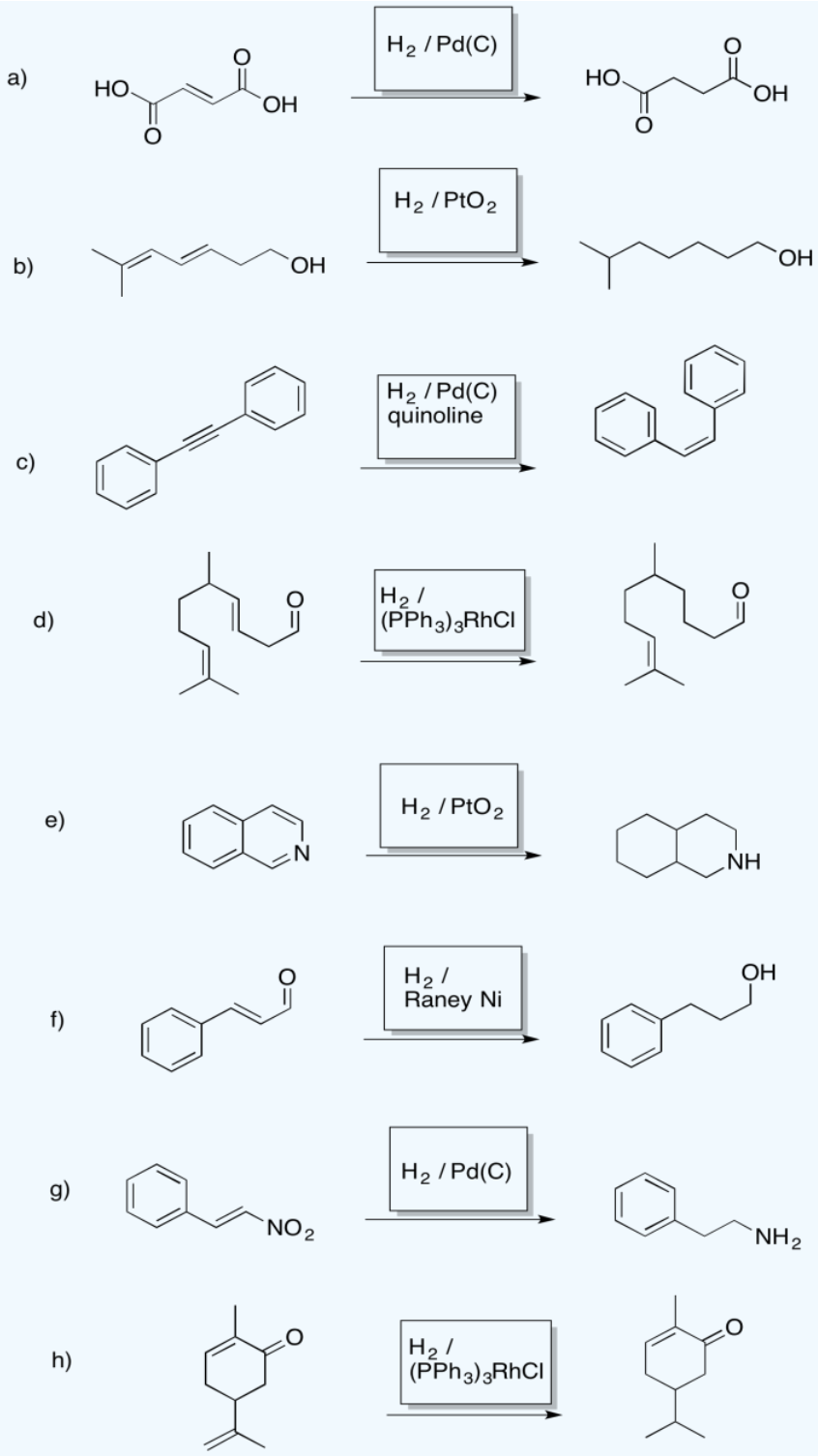


5.6: Coupling Reactions in Organic Synthesis

Oxidative addition and reductive elimination are key steps in industrial catalysis. For example, both steps are featured in palladium-catalyzed cross-coupling reactions, the subject of the 2010 Nobel Prize in Chemistry. The prize was awarded to Richard Heck of the University of Delaware, Ei-Ichi Negishi of Purdue University and Akira Suzuki of Hokkaido University. With these reactions, workers in a variety of fields can make molecules that otherwise would be quite difficult to make. These molecules in turn may be important pharmaceuticals or useful compounds for electronic displays in computers and other devices, to name just a couple.

The Negishi reaction involves catalytic addition of alkylzinc nucleophiles to vinyl halides.

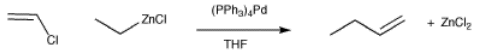


Figure 5.6.1: The Negishi cross-coupling reaction.

The catalytic cycle believed to operate for this reaction involves the crucial oxidative addition of the vinyl halide to the metal. The alkylzinc probably delivers the alkyl nucleophile to the metal via more conventional nucleophilic substitution. Once both pieces are both on the metal, they can reductively eliminate together.

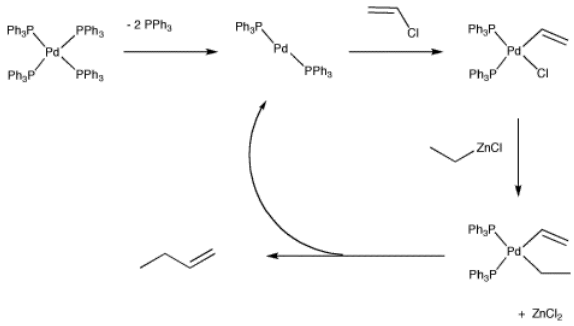


Figure 5.6.2: Catalytic cycle for the Negishi cross-coupling reaction.

? Exercise 5.6.1

Explain why the vinyl halide pictured in the example above would not react directly with the alkylzinc reagent.

? Exercise 5.6.2

Label each step of the catalytic cycle for the Negishi reaction with the appropriate term (oxidative addition, etc).

? Exercise 5.6.3

Draw the mechanism for the Negishi reaction using curved arrow notation.

There are many other examples of coupling reactions in organic synthesis. The Suzuki reaction is somewhat similar to the Negishi reactions.

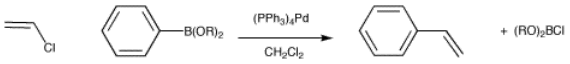


Figure 5.6.4: The Suzuki reaction.

The Heck reaction involves activation of a vinylic or aryl C-H bond.

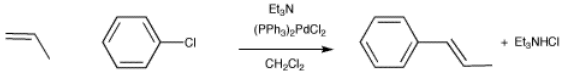


Figure 5.6.5: The Heck reaction.

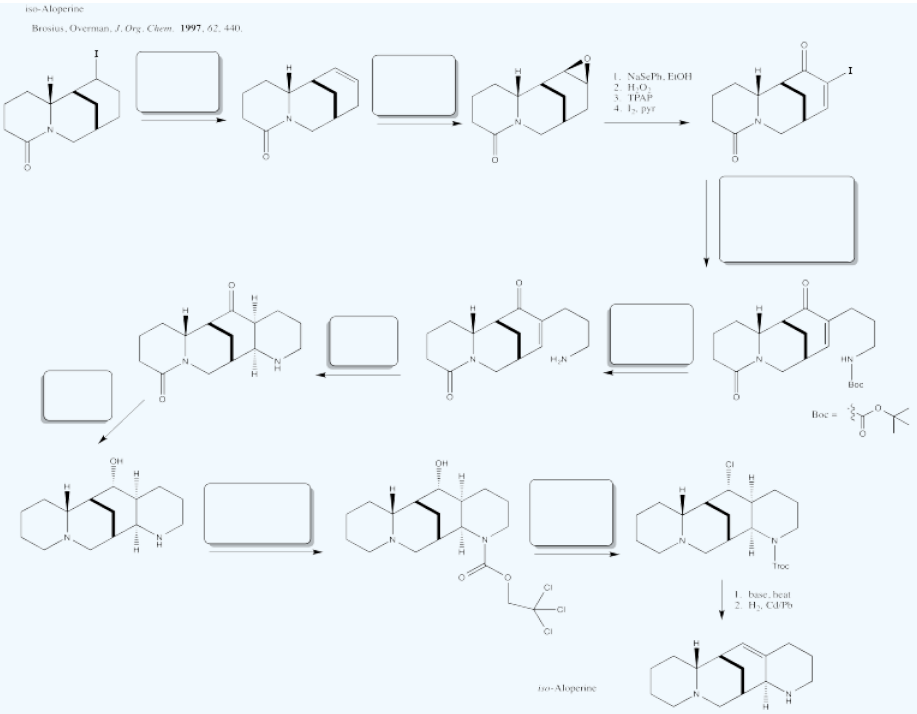
Exercise 5.6.4

By analogy with the Negishi reaction, propose a catalytic cycle for the Suzuki reaction.

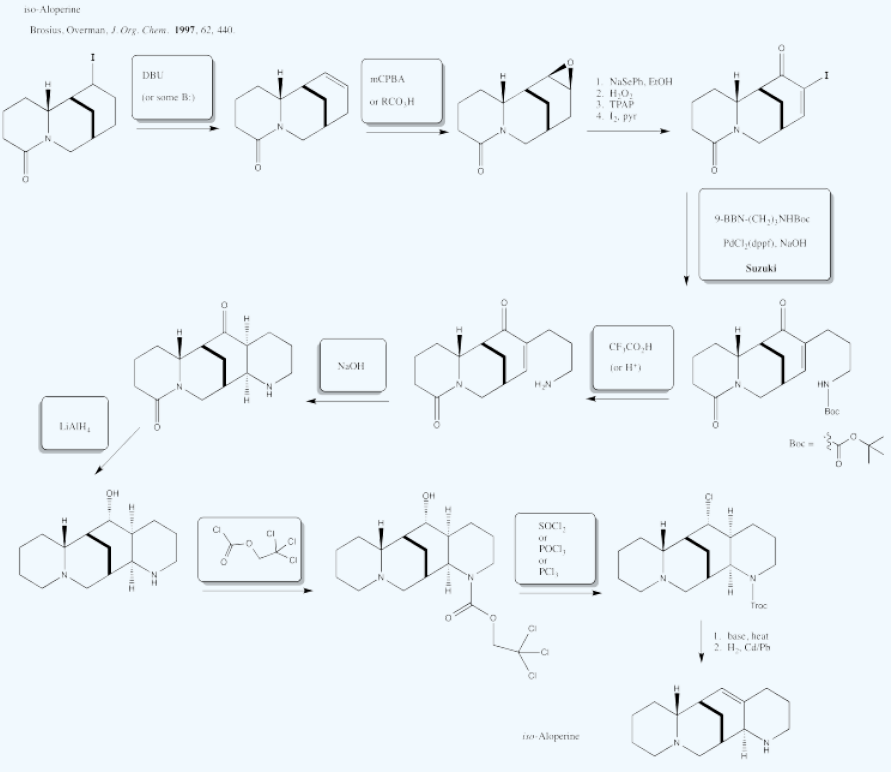
Exercise 5.6.5

Propose a catalytic cycle for the Heck reaction.

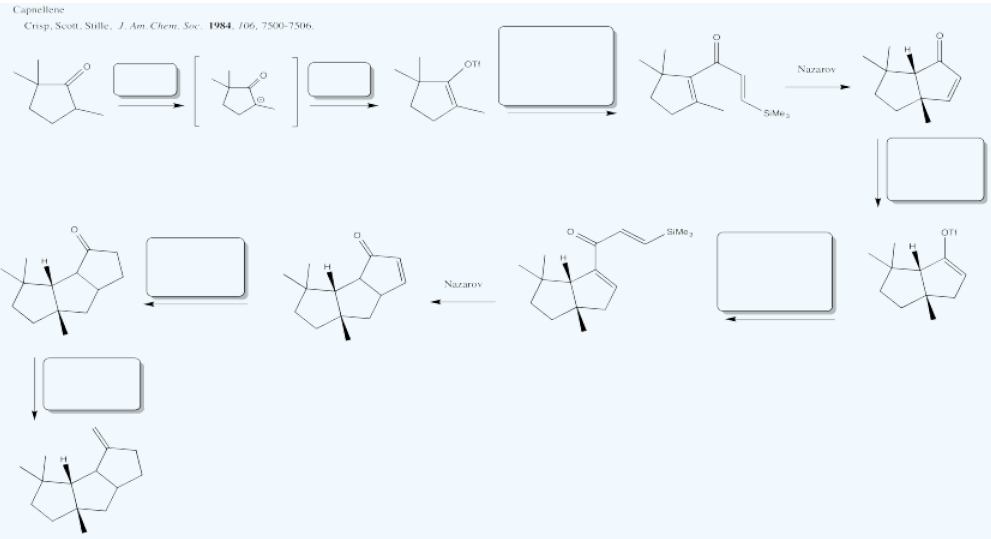
Exercise 5.6.6



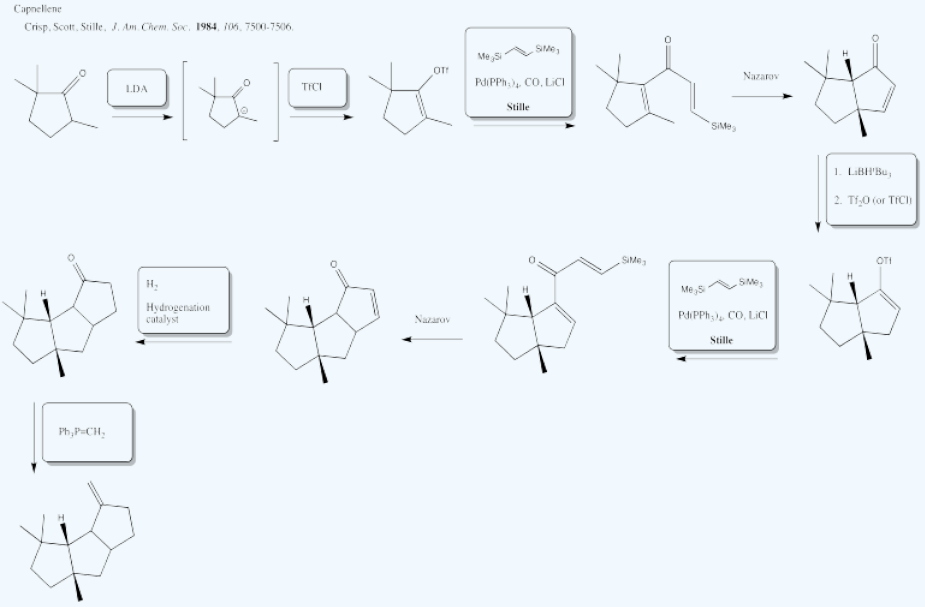
Answer



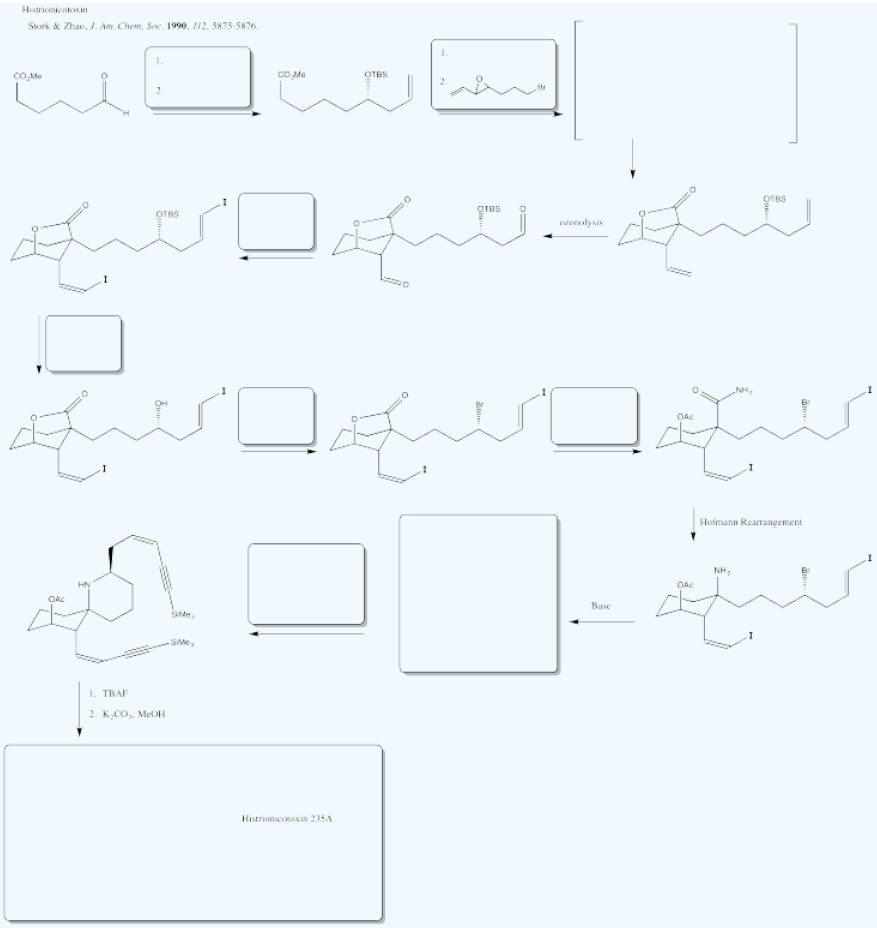
? Exercise 5.6.7



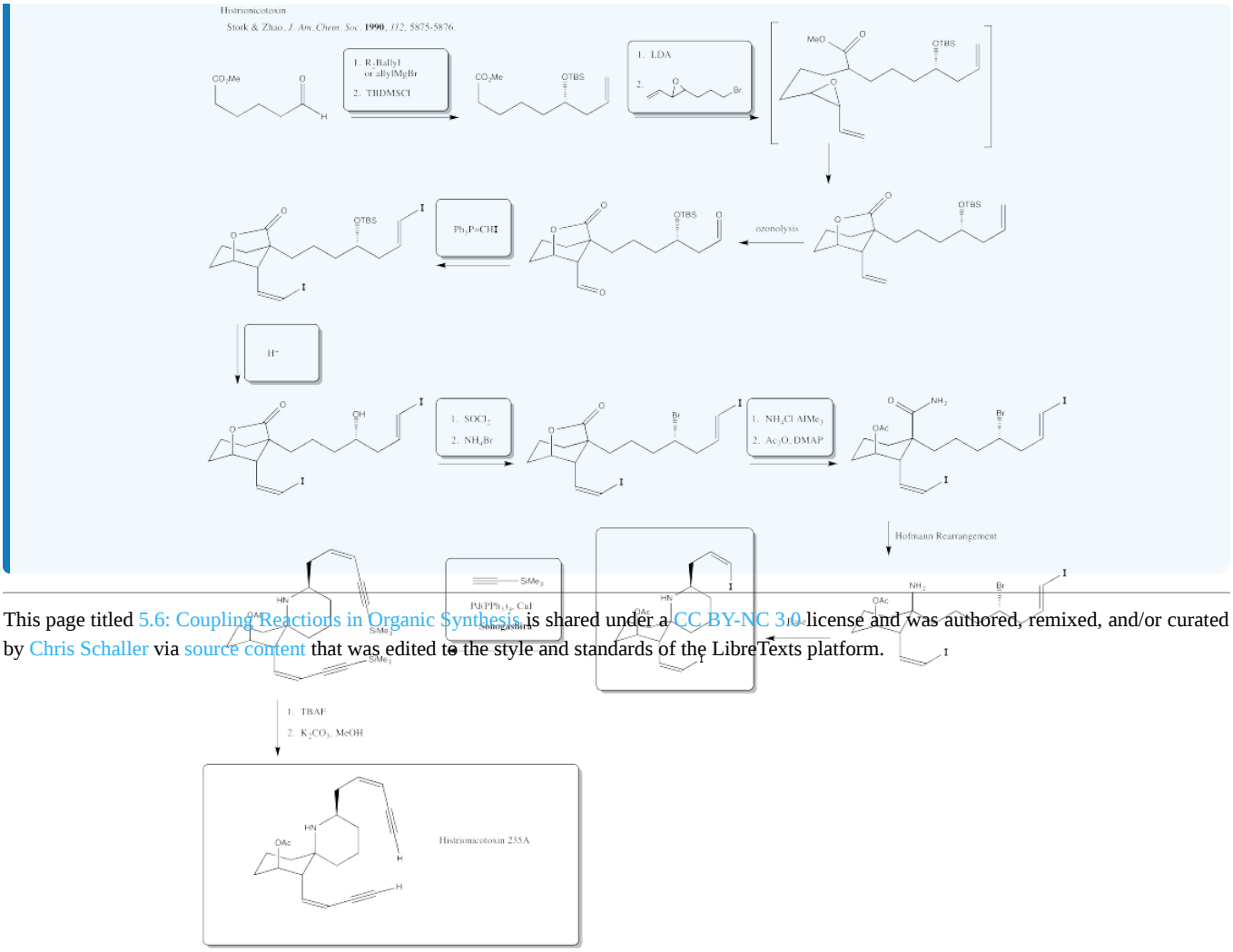
Answer



? Exercise 5.6.8


Histrionicotoxin
Stork & Zhao, *J. Am. Chem. Soc.* **1990**, *112*, 5875-5876.
ozonolysis
Hofmann Rearrangement
Base
1. TBAF
2. K_2CO_3, MeOH
Histrionicotoxin 235A

Answer



5.7: Solutions to Selected Problems

Exercise 5.1.1:

a. under an atmosphere of hydrogen gas.
b. under an atmosphere of an inert gas such as nitrogen or argon, especially if there is a way for hydrogen gas to escape.

Exercise 5.1.2:

Exercise 5.2.1:

a. Pd(0) to Pd(II) (I and Ph are negative)
b. Rh(I) to Rh(III) (Cl and acyl are negative)
c. Ni(II) to Ni(0) (Methyl and phenyl are negative)
d. Zr(IV) to Zr(II) (Cp, H and Ph are negative)

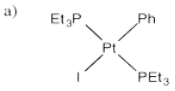
Exercise 5.2.2:

Increased steric crowding in the coordination sphere may force two gorups to redcutively eliminate together.

Exercise 5.3.1:

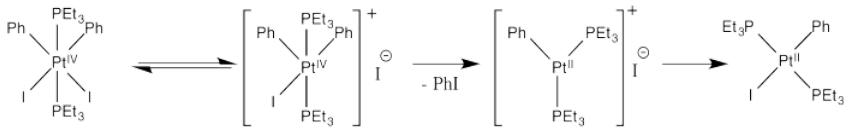
a. Probably the first step is the hardest (slowest) step, involving bond breaking in the alkyl halide. The donation of the resulting anion to the cation should be pretty fast.
b. $Rate = k_1[ML_n][CH_3Br]$

Exercise 5.3.2:



b) Methanol is more polar than benzene. The acceleration of the reaction in methanol suggests that there is increasing polarity in the transition state, or polar intermediates.

c) Inhibition by iodide ion suggests that iodide is a product of a reversible step during this reaction. Adding iodide pushes that step backward, decreasing the rate of product formation. The mechanism below is consistent with these observations:



Thus reductive elimination occurs as we go from the second to the third intermediate.

Presumably, the increased positive charge (and general decrease in electron density, owing to loss of a ligand) results in reductive elimination because of destabilization of the Pt(IV).

Alternatively, we might suppose that after loss of iodide, the iodide ion donates directly to a phenyl ligand, displacing the platinum as a leaving group in an S_N2 reaction. That would lead directly to the product from the first intermediate, which is a simpler route. However, the precedent for aliphatic nucleophilic substitution involves nucleophilic donation to tetrahedral carbons, not to trigonal planar ones. That mechanism is unlikely.

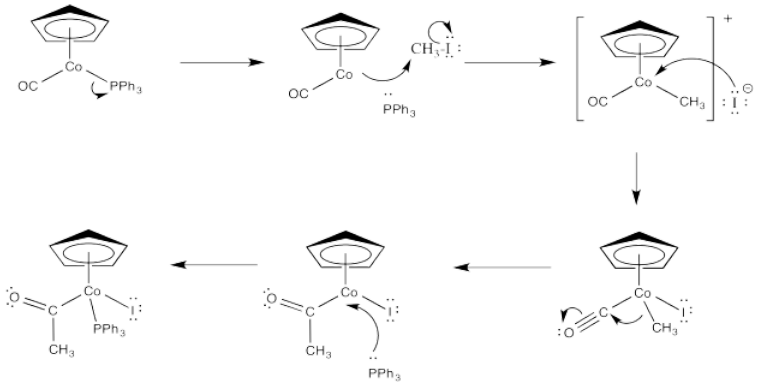
Exercise 5.3.3:

a. Pt(0) to Pt(II)
b. Changes from (*R*) to (*S*)
c. This is an S_N2 reaction, so the platinum displaces the bromide from the opposite side.

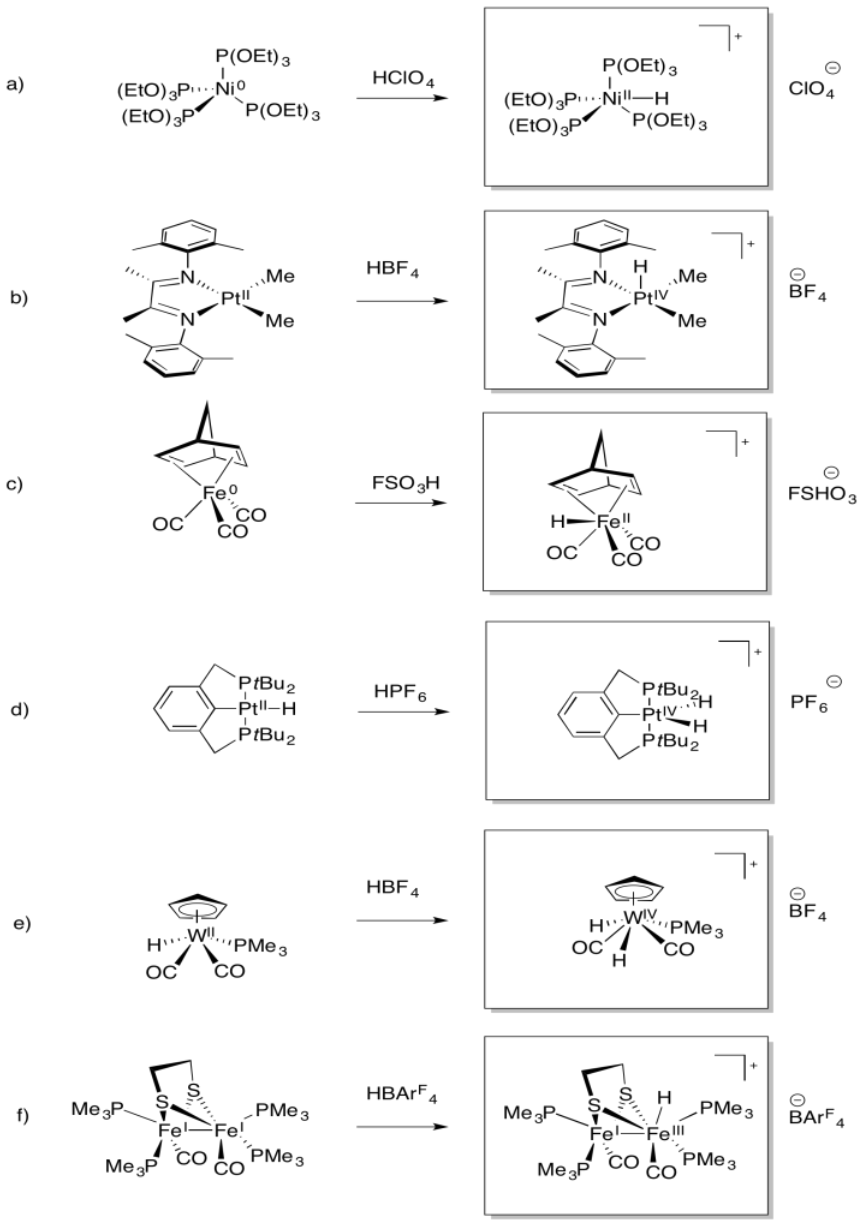
Exercise 5.3.4:

In case (a), the reaction appears to be S_N2, presumably with complete inversion of configuration from (*S*) to (*R*). In case (b), there is probably a competing S_N1 pathway because the resulting cation is both benzylic and secondary, so it is pretty stable. On the other hand, if the reaction proceeded entirely through an S_N1 pathway, the reaction would result in nearly complete racemization, with 0% ee.

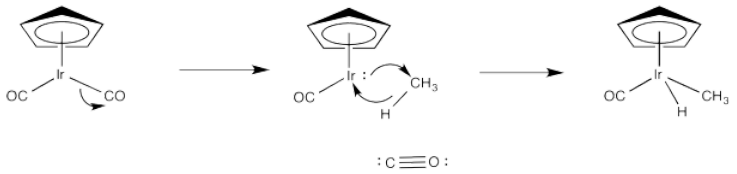
Exercise 5.3.5:



Exercise 5.3.6:



Exercise 5.4.1:



Exercise 5.4.2:

Concerted oxidative addition is the mechanism that occurs when a polar mechanism (S_N2) is not possible. It is sometimes called "cis" oxidative addition. Because the two fragments added to the metal form bonds to the metal at the same time, they must be cis to each other.

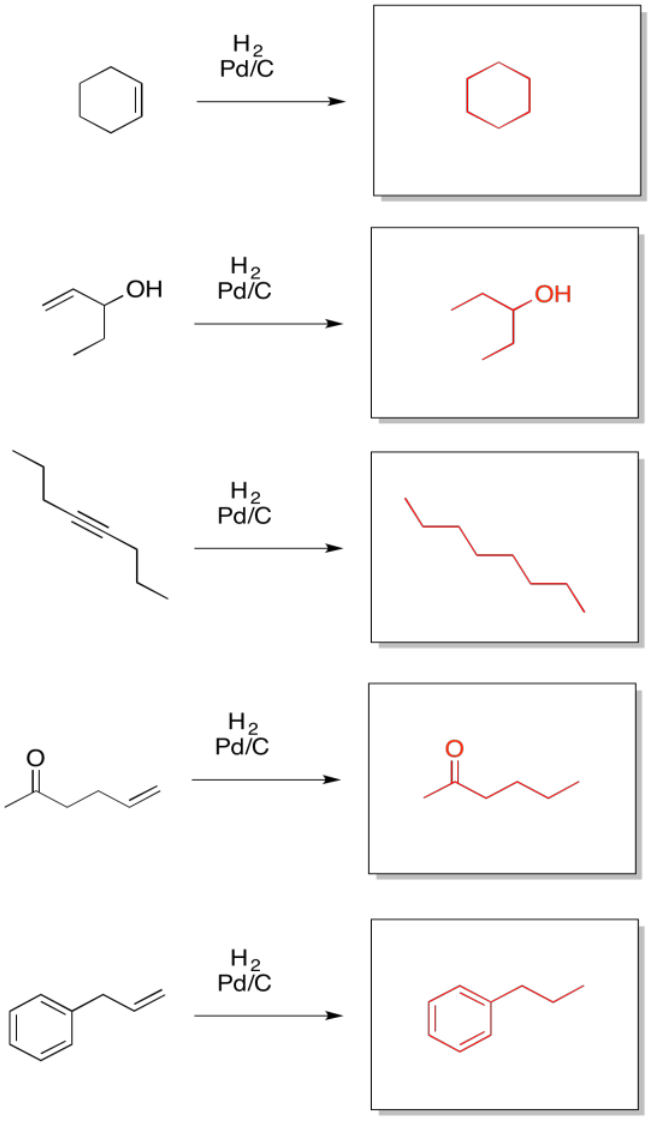
By the principle of microscopic reversibility, reductive elimination works the same way. The ligands have to be cis to each other in order to reductively eliminate, unless they are eliminating via a polar mechanism. Since both alkyl groups would have the same charge, a polar mechanism is unlikely.

Both of these platinum(II) complexes are d^8 and they would adopt square planar geometry. In the second case, the alkyls would be trans to each other and would be unable to undergo reductive elimination.

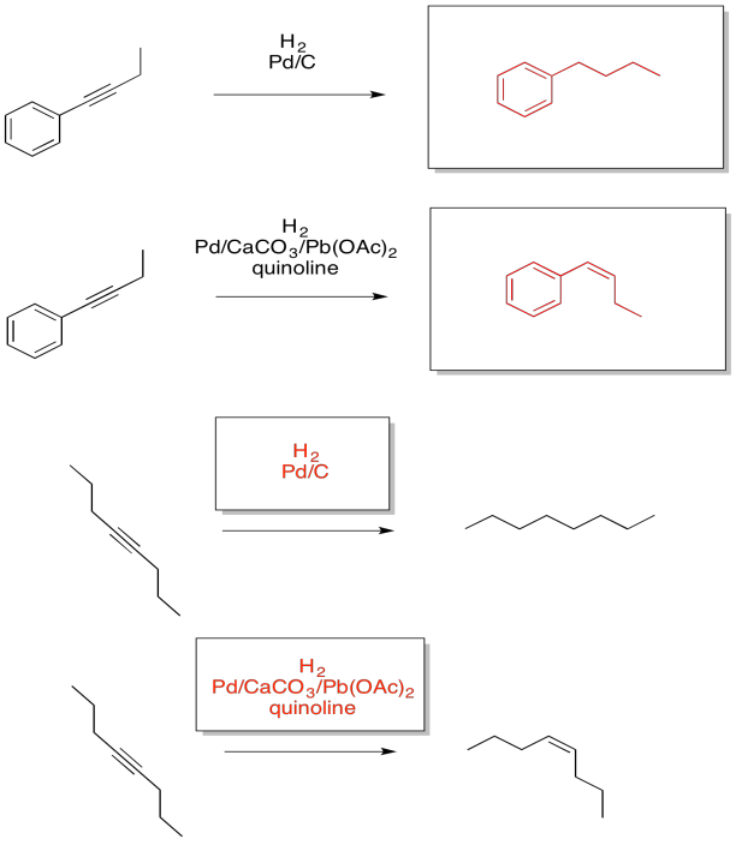
Exercise 5.5.1:

a) homogeneous b) heterogeneous c) heterogeneous d) homogeneous

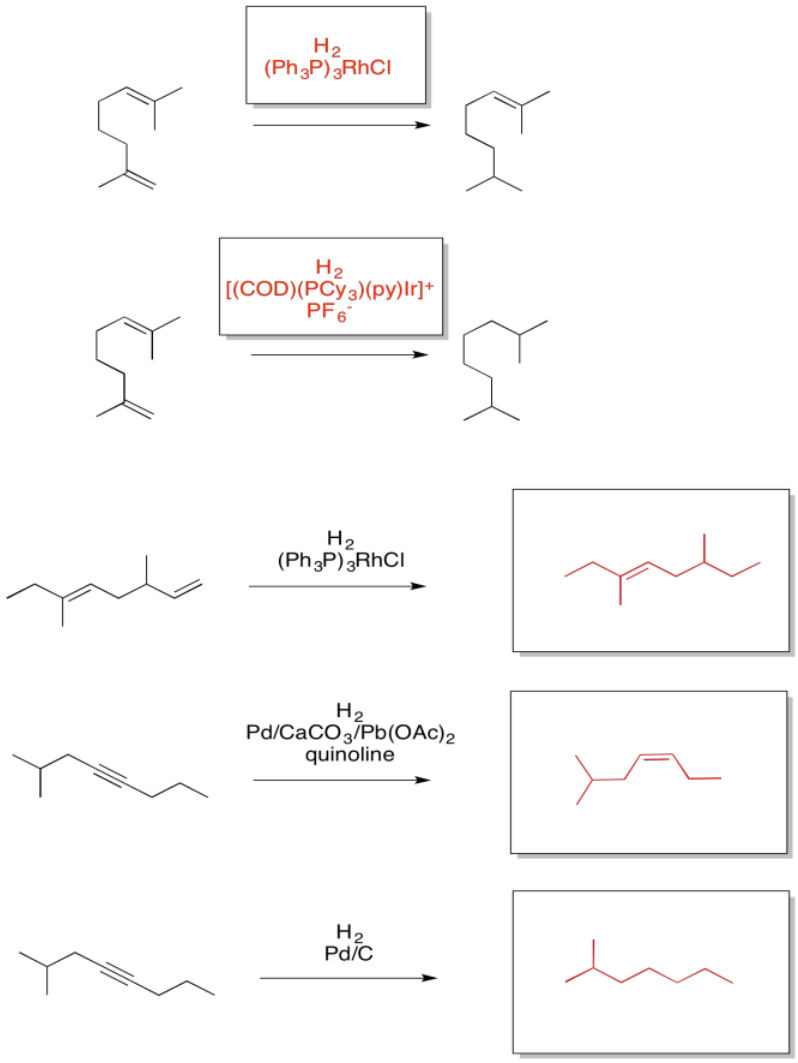
Exercise 5.5.2:



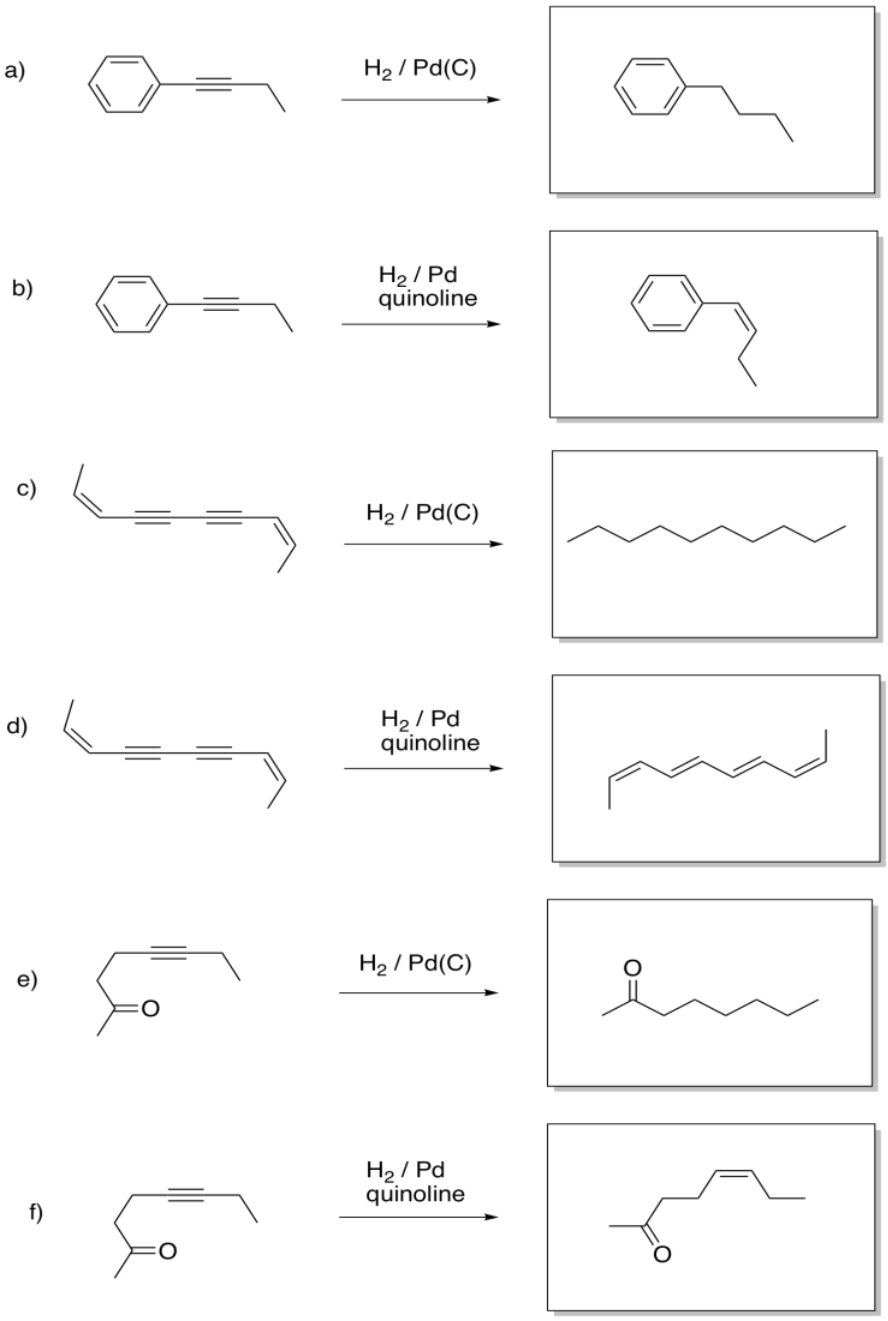
Exercise 5.5.3:



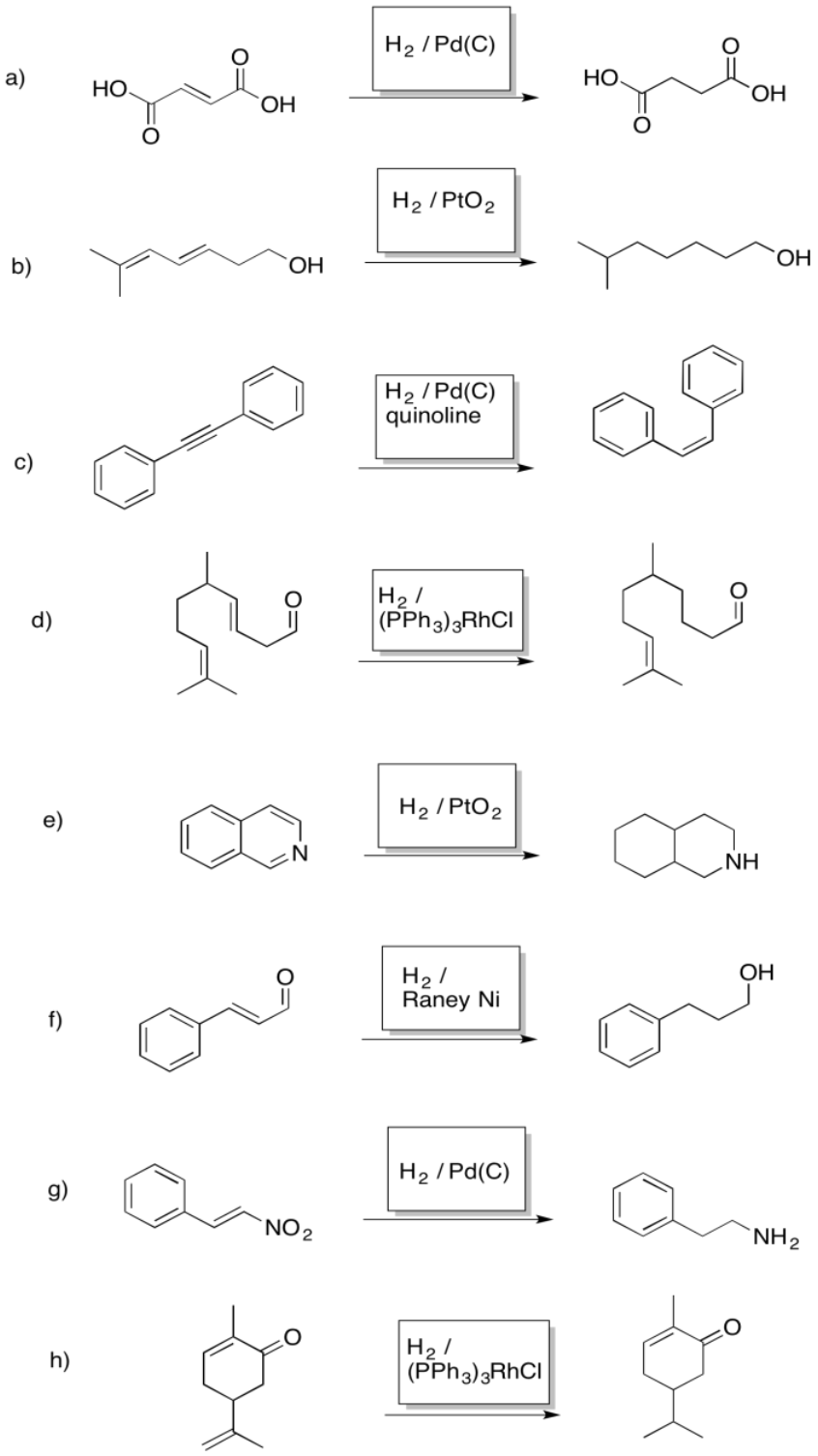
Exercise 5.5.4:



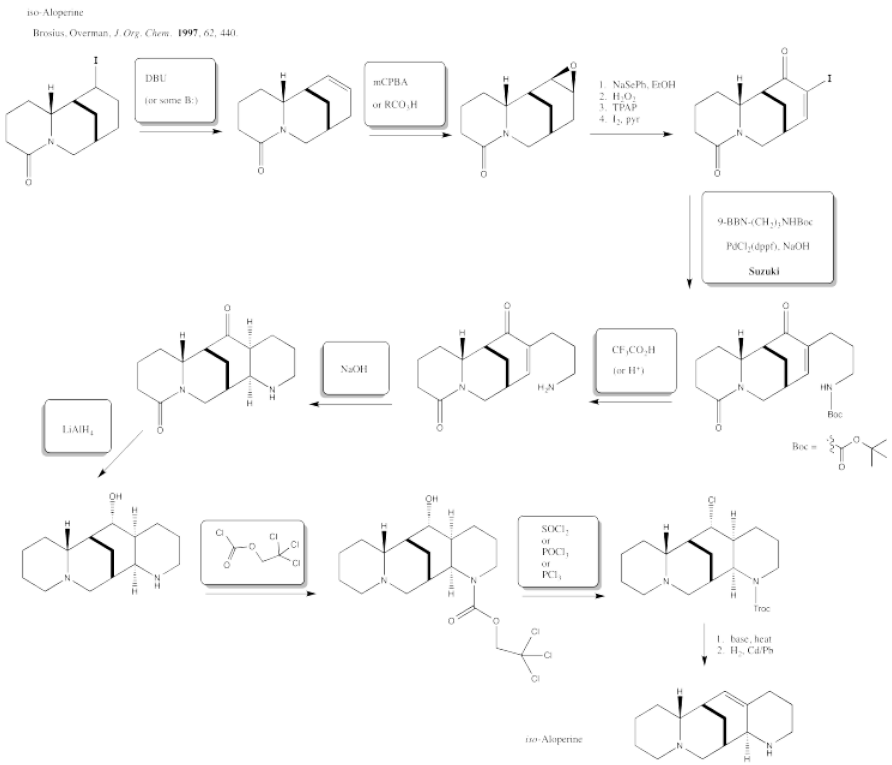
Exercise 5.5.6:



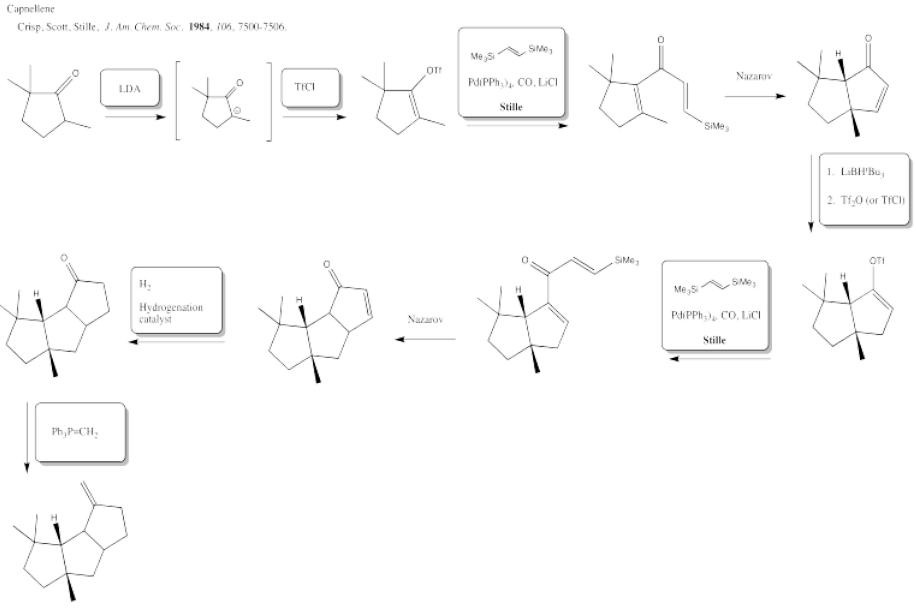
Exercise 5.5.7:



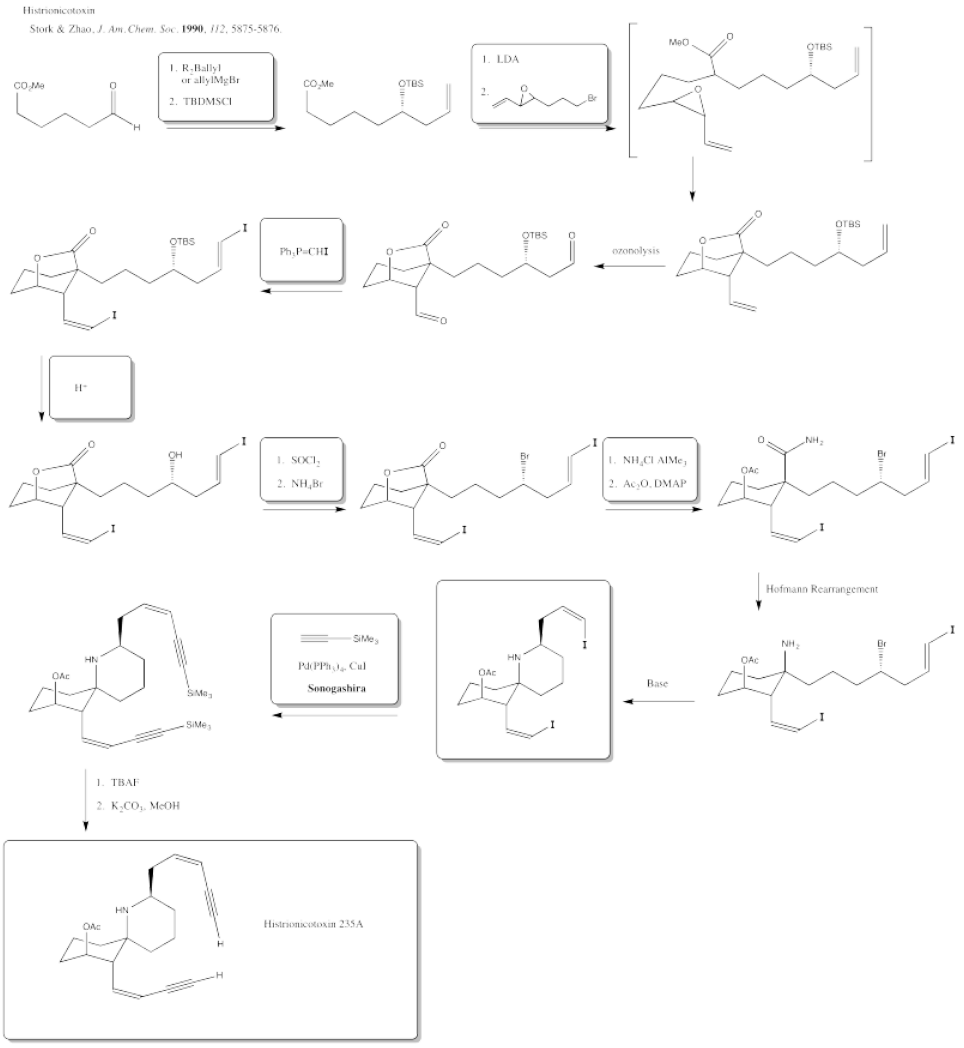
Exercise 5.6.6:



Exercise 5.6.7:



Exercise 5.6.8:



CHAPTER OVERVIEW

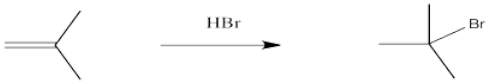
6: Electrophilic Addition to Alkenes

6.1: Introduction to Electrophilic Addition

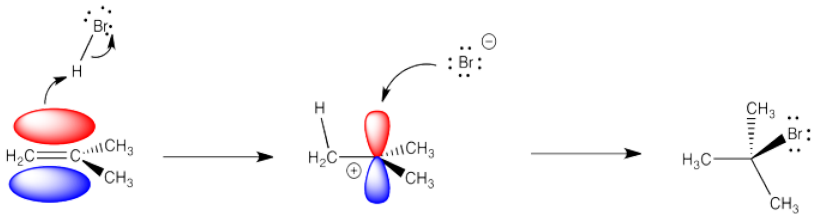
Alkenes are found throughout nature. They form the basis of many natural products, such as terpenes, which play a variety of roles in the lives of plants and insects. The C=C bonds of alkenes are very different from the C=O bonds that are also common in nature. The C=C bonds of alkenes are electron-rich and nucleophilic, in contrast to the electron-poor C=O bonds of carbohydrates, fatty acids and proteins. That difference plays a role in how terpenes form in nature.

Alkenes, or olefins, are also a major product of the petroleum industry. Reactions of alkenes form the basis for a significant porion of our manufacturing economy. Commonly used plastics such as polyethylene, polypropylene and polystyrene are all formed through the reactions of alkenes. These materials continue to find use in our society because of their valuable properties, such as high strength, flexibility and low weight.

Alkenes undergo addition reactions like carbonyls do. Often, they add a proton to one end of the double bond and another group to the other end. These reactions happen in slightly different ways, however.



Alkenes are reactive because they have a high-lying pair of π-bonding electrons. These electrons are loosely held, being high in energy compared to σ-bonds. The fact that they are not located between the carbon nuclei, but are found above and below the plane of the double bond, also makes these electrons more accessible.



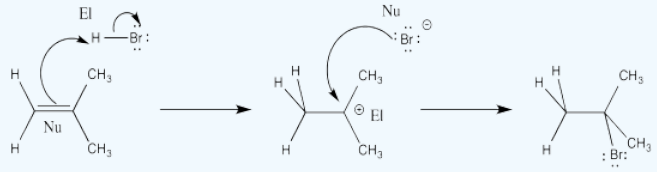
Alkenes can donate their electrons to strong electrophiles other than protons, too. Sometimes their reactivity pattern is a little different than the simple addition across the double bond, but that straightforward pattern is what we will focus on in this chapter.

Exercise 6.1.1

The reaction of 2-methylpropene (or isobutylene) with HBr, as depicted above, is really a 2-step process. Draw this mechanism again and in each of the two steps label both the nucleophile and the electrophile (so, that's four labels).

Answer

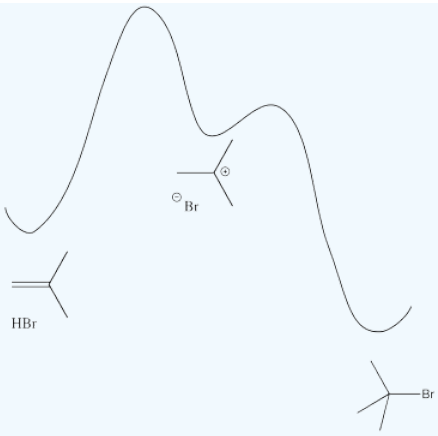
El = electrophile; Nu = nucleophile



Exercise 6.1.2

Draw a reaction progress diagram for the reaction of 2-methylpropene with hydrogen bromide.

Answer



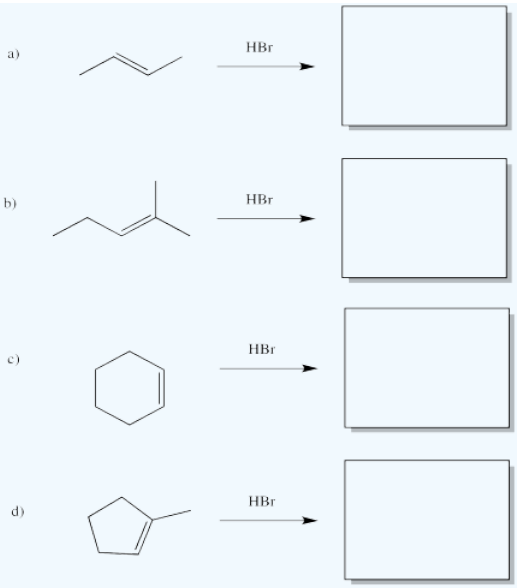
Exercise 6.1.3

Predict the rate law for the reaction of 2-methylpropene with hydrogen bromide.

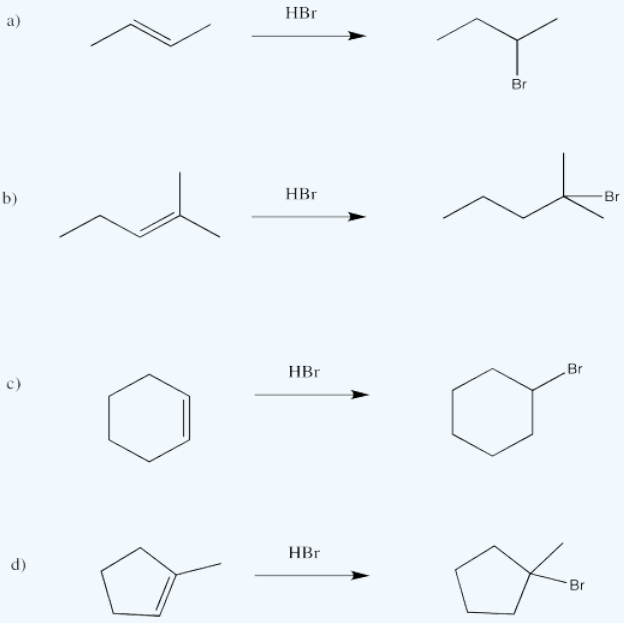
Answer

Rate = d[alkyl bromide] / dt = k [alkene] [HBr]

Exercise 6.1.4

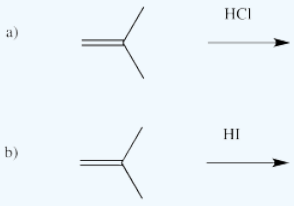


Answer



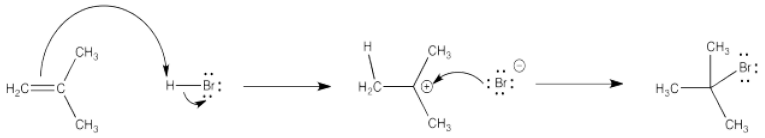
Exercise 6.1.5

Acids other than HBr can add to alkenes. Based on the reaction with HBr, draw products for the following reactions.



6.2: Cations in Electrophilic Addition

Many of the reactions of alkenes begin with a protonation step. The cation that forms then undergoes a second step in which it combines with the counterion from the acid.

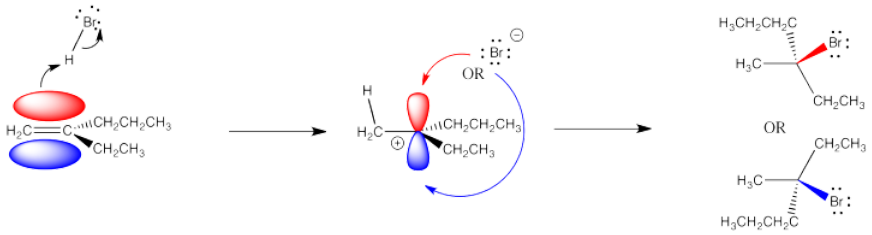


In the first step, the alkene's π bond is the nucleophile and the proton is the electrophile. In the second step, the bromide is the nucleophile and the cation is the electrophile.

If you are familiar with nucleophilic aliphatic substitution, you will already know that the presence of a cationic intermediate signals some potential complications in this reaction.

One issue is the problem of stereochemical control. A carbocation is trigonal planar, because the carbon with the positive charge has only three groups attached to it. Because the cation is trigonal planar, the bromide ion that combines with it can approach from either side. It can come from above or below the trigonal plane.

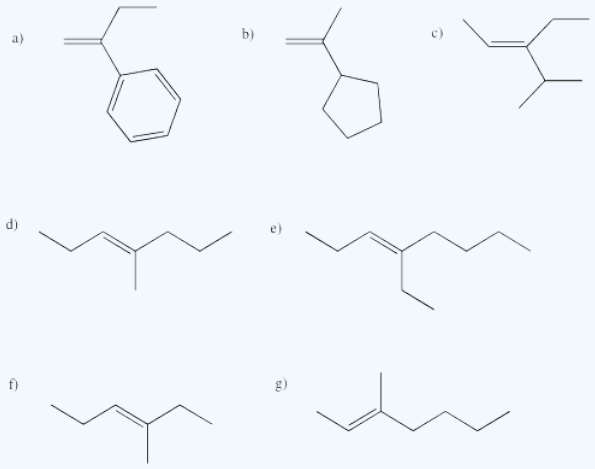
That fact may have no effect whatsoever. However, if the alkene (and the cation it forms) is prochiral, meaning it has the potential to form a new chiral center during this reaction, then there is a choice of which enantiomer to make.



A prochiral carbocation is easy to recognize because the cationic carbon has three different groups attached to it. The fourth group added, the nucleophile, would result in four different groups attached to that carbon, making it a chiral center. In order to recognize a prochiral alkene, you can picture what the alkene would look like after the reaction has taken place: will there be four different groups?

? Exercise 6.2.1

Which of the following alkenes are prochiral?



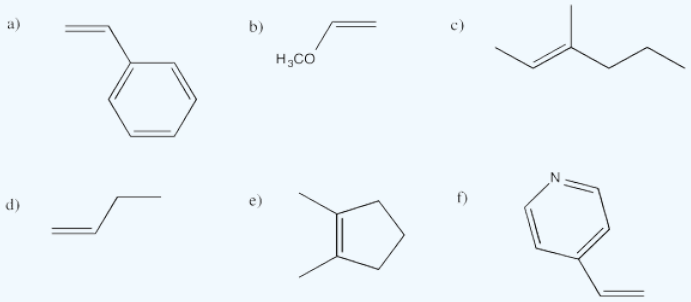
Answer

a, e, f, g are prochiral.

Exercise 6.2.2

Addition of the nucleophile to one face of the alkene will result in a stereocentre with R configuration. That face is called the *re* face. Adding it to the other will lead to formation of S configuration. That face is called the *si* face.

In the following alkenes, identify whether we are looking at the *re* face or the *si* face in terms of the product we would get through addition of HBr.



Answer a

a) re

Answer b

b) si

Answer c

c) re

Answer d

d) si

Answer e

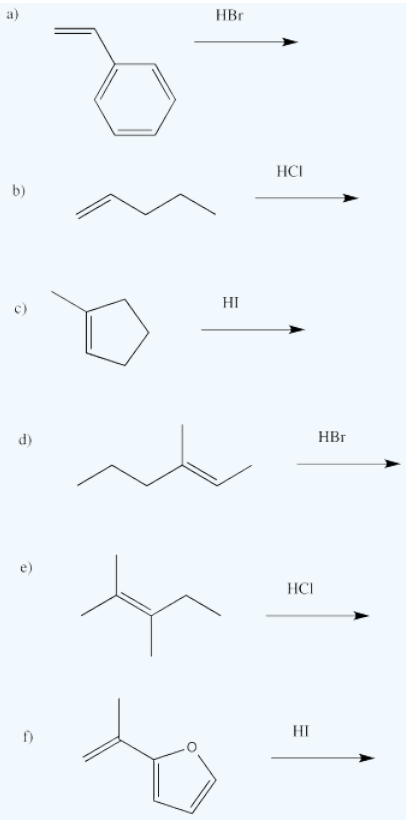
e) either; if the Br adds on one end of the double bond it is re, but at the other it is si

Answer f

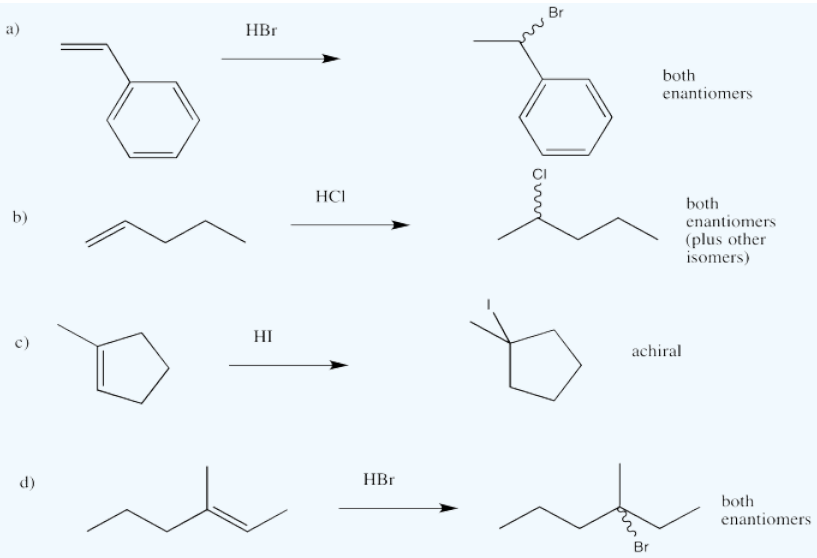
f) re

Exercise 6.2.3

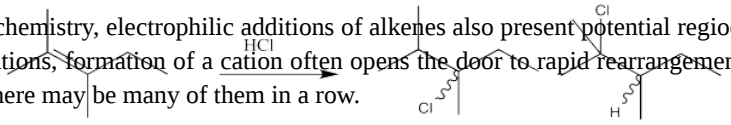
Draw the products of the following reactions, paying attention to stereochemistry.



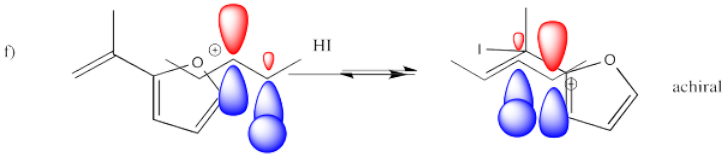
Answer



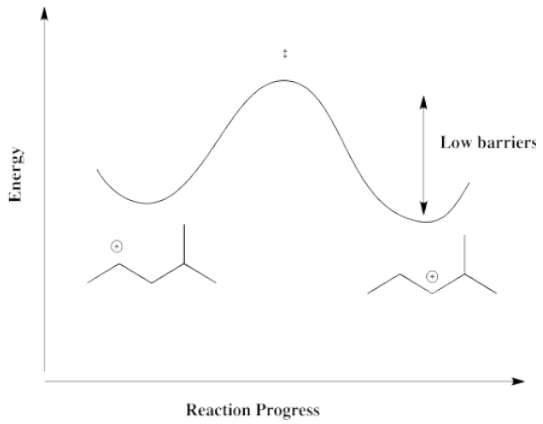
In addition to the problem of stereochemistry, electrophilic additions of alkenes also present potential regiochemical complications. As in aliphatic nucleophilic substitutions, formation of a cation often opens the door to rapid rearrangement via 1,2-hydride shifts. There may be one hydride shift or there may be many of them in a row.



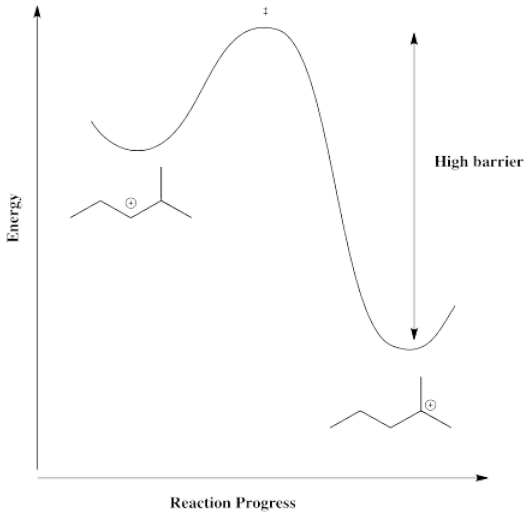
These hydride shifts happen pretty easily. Overlap of a hydrogen atom with the empty p orbital of the the adjacent cation leads to a short hop from one carbon to the next.



A hydride shift from one secondary carbon to the next, as illustrated in the above example, is thermodynamically pretty neutral. Because the barrier is low, it happens quickly, but there isn't a driving force fo the hydride to shift one way or the other. Instead, both cations result. There is a mixture.



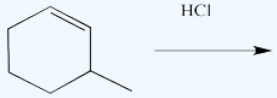
However, in a case in which the cation can form in a more stable position, such as a tertary position, there is a driving force for the reaction to go one way. The barrier would be too high for it to get back.

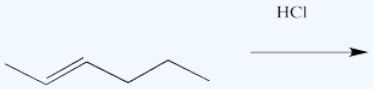


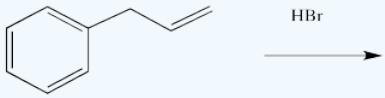
As a result, when the counterion combines with the cation, it may do so in a position away from the original double bond.

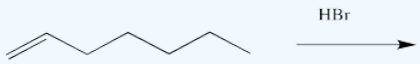
? Exercise 6.2.4

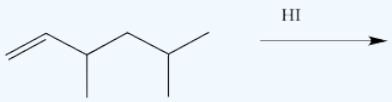
Draw the products of the following reactions, paying attention to regiochemistry.

a) 

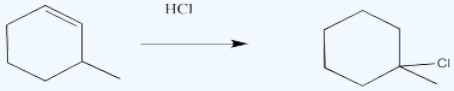
b) 

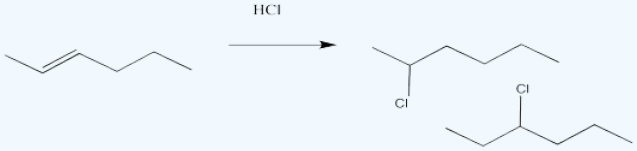
c) 

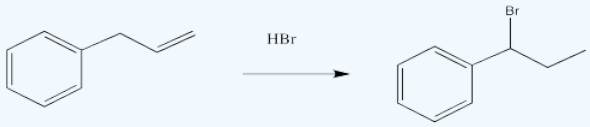
d) 

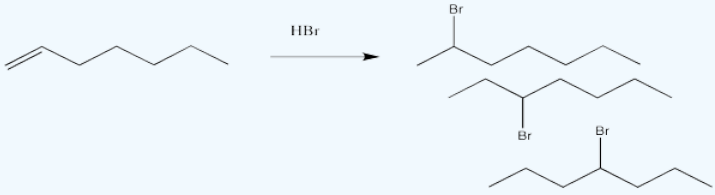
e) 

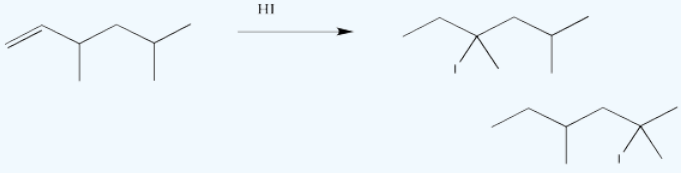
Answer

a) 

b) 

c) 

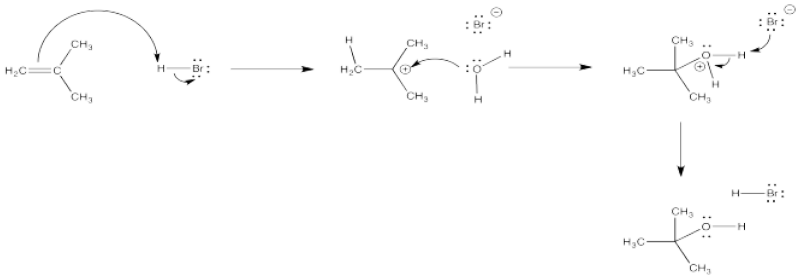
d) 

e) 

6.3: Solvent Participation in Electrophilic Addition

Alkenes can donate their electrons to strong electrophiles and the resulting carbocations combine with the counterion of the electrophile to undergo an overall addition reaction. However, there may be some cases in which the counterion does not combine with the carbocation.

Hydrobrominations of the type we have looked at only occur under certain conditions. Other conditions can lead to other products. For example, a solvent such as water can also participate in the reaction.



The oxygen-based cation (or oxonium ion) that results can easily lose its charge through loss of a proton. As a result, a molecule of water adds to the alkene overall. The alkene becomes an alcohol. This reaction is called an "acid-catalyzed hdration" of an alkene.

Exercise 6.3.1

Explain how the hydration of an alkene in the presence of acid is a catalytic reaction.

Answer

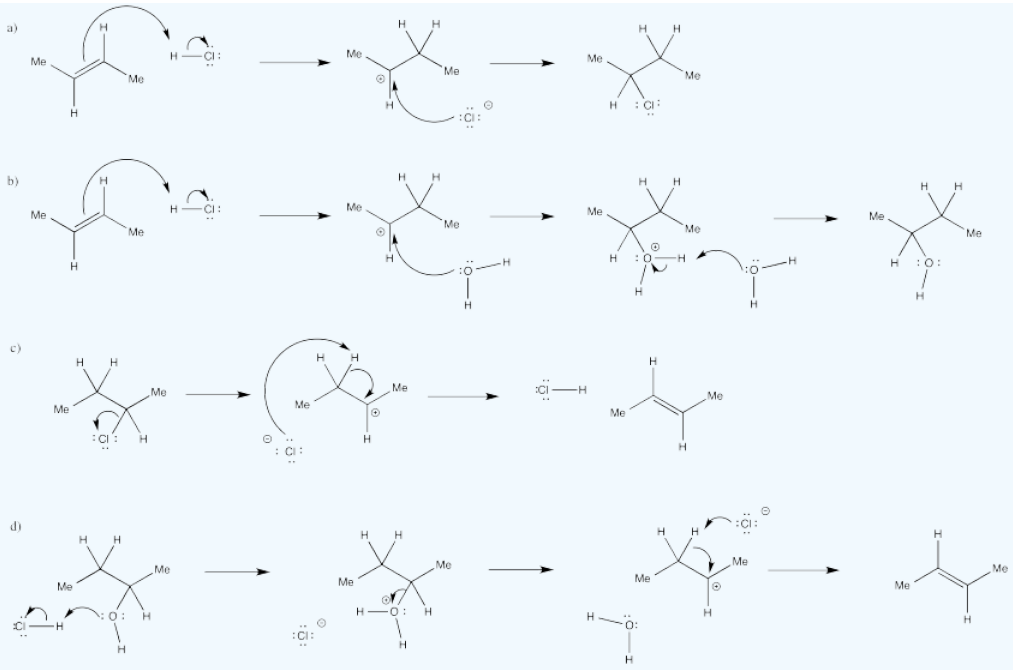
If the acid is regenerated at the end of the reaction, it isn't a reagent. It is a catalyst. It makes addition of water to the double bond occur much more quickly than if water acted alone, since water would never manage to protonate the alkene.

Exercise 6.3.2

In many cases, equilibrium mixtures of multiple products may result from the addition of acids to alkenes. Show mechanisms, with curved arrows, for the following reactions.

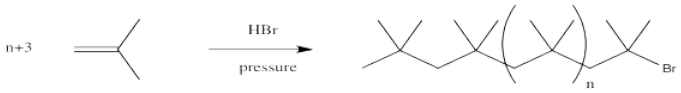
a. The conversion of 2-butene to 2-chlorobutane with aqueous HCl.
b. The conversion of 2-butene to 2-butanol with aqueous HCl.
c. The conversion of 2-chlorobutane to 2-butene with aqueous HCl.
d. The conversion of 2-butanol to 2-butene with aqueous HCl.

Answer



On the other hand, in the absence of any solvent, the bromide ion might still have some competition in the second step. The neat reaction (neat means "without solvent" of an alkene with a small amount of acid can result in polymerization. The alkene, which acted as a nucleophile in the first step, can also act as a nucleophile in the second step.

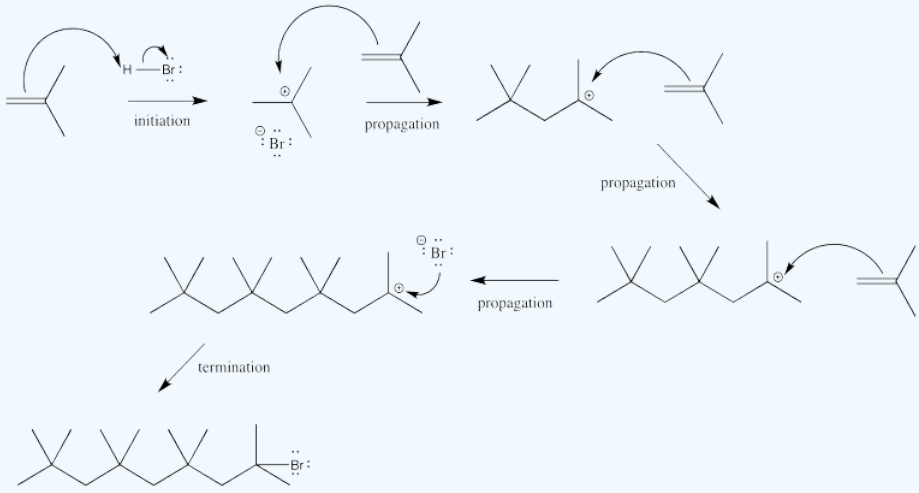
It is important to remember that in any reaction, millions of molecules are involved. Even if one alkene molecule reacts with acid in the first step of a reaction, there are still plenty of other alkene molecules around to act as nucleophile in the second step.



? Exercise 6.3.3

Provide a mechanism for the polymerization shown above. Assume there are four 2-methylpropene molecules and one hydrogen bromide molecule to begin.

Answer

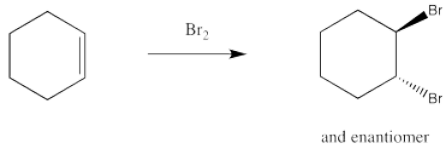


? Exercise 6.3.4

Chain reactions involve an *initiation step*, in which a reactive species is generated; *propagation steps*, in which the reactive species reacts to make a new reactive species; and a *termination step*, in which the reactive species reacts to make a stable molecule. Label each of the steps in your mechanism from the previous question.

6.4: Stabilized Cations in Electrophilic Addition

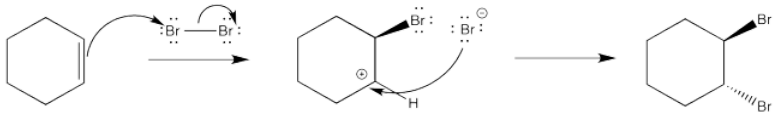
Electrophilic addition to alkenes generally takes place via donation of the π-bonding electron pair from the alkene to an electrophile. So far, we have only looked at protic electrophiles, but the reaction proceeds with others, as well. For instance, alkenes react quite easily with bromine.



and enantiomer

Dripping a solution of bromine into a solution of alkene provides a clear sign of reaction. The red-brown colour of bromine disappears almost instantly.

Although bromine isn't an obvious electrophile, most of the common diatomic elements can behave that way; the exception is dinitrogen. A fleeting asymmetry of electrons can polarize the molecules to one end. That event leaves one atom partially positive and the other end partially negative. Because these elements tend to form somewhat stable anions, the partially negative atom can be displaced fairly easily.



As before, a nucleophile connects with the cation in a second step. In this case, a dibromide compound is formed. However, it isn't formed in quite the way that is shown below.

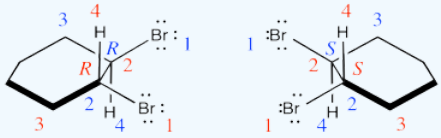
We know that the mechanism shown above does not convey the whole picture because it isn't consistent with the stereochemistry of the reaction. The stereochemical outcome is shown below. The enantiomer is formed as well.

Exercise 6.4.1

Assign configurations R or S to the product shown in the above mechanism.

Answer

Two products are formed and they are enantiomers.



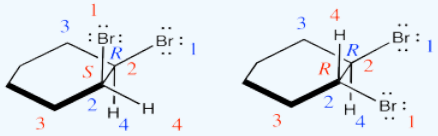
However, although two enantiomers are formed in the reaction, the corresponding diastereomer is not. The following step does not occur.

Exercise 6.4.2

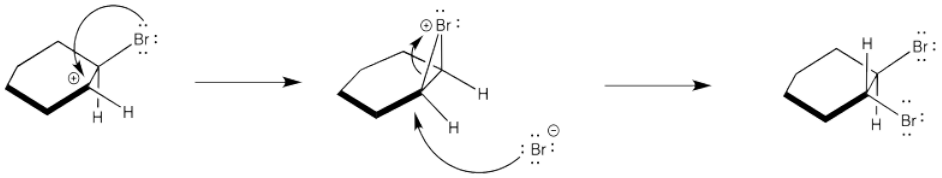
Assign configurations R or S to the product shown in the above mechanism and explain why it is not an enantiomer to the compound in problem EA4.1.

Answer

They are diastereomers. One chiral center has the same configuration in both compounds but the others are opposite.



Instead, the cation that forms in the reaction appears to be stabilized by lone pair donation from bromine. The intermediate species below is called a cyclic bromnium ion. The bromine prevents approach of the nucleophilic bromide from one side, ensuring formation of product through *anti* addition only. The *trans* product forms as a result.

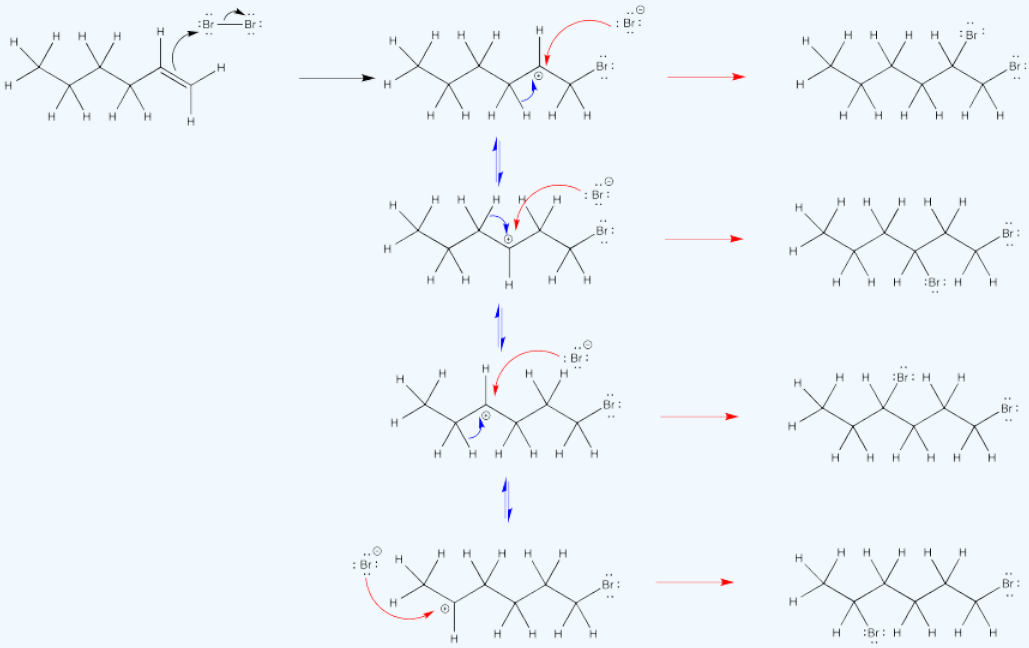


Exercise 6.4.3

Additional evidence of the stabilized bromonium comes from the observation of just one product in the bromination of 1-hexene. How many products would be expected in the absence of a stabilized cation? Explain with a mechanism.

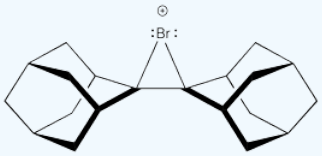
Answer

The second bromine could occupy any of the secondary positions if there were a true carbocation. That doesn't happen; the second bromine occupies only the position next to the other bromine.



Exercise 6.4.4

Bromonium ions like the one shown below have been isolated and characterized by X-ray crystallography in at least one case. Explain why the intermediate was isolated in this case, rather than a dibromo product.



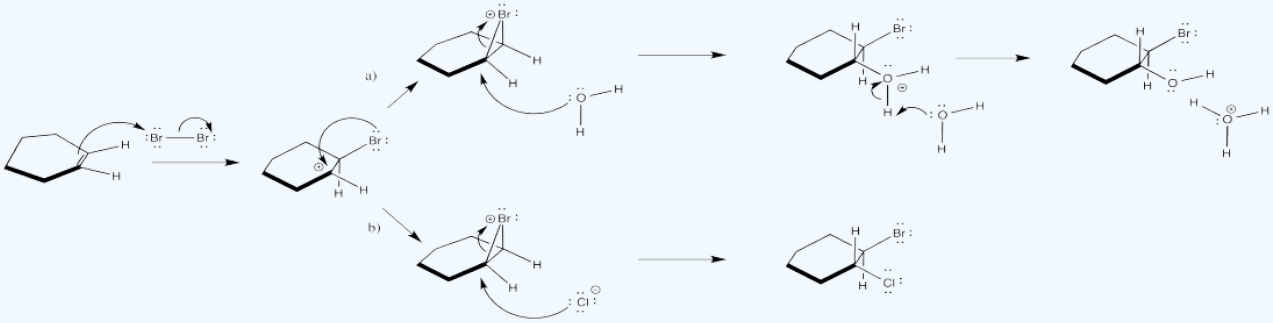
Exercise 6.4.5

In some cases, the reaction of an alkene with bromine does not provide dibromo products. Show products of the reaction of cyclohexene under the following conditions and justify your choices with mechanisms.

a) Br_2 in water b) Br_2 and NH_4^+ Cl^- in THF

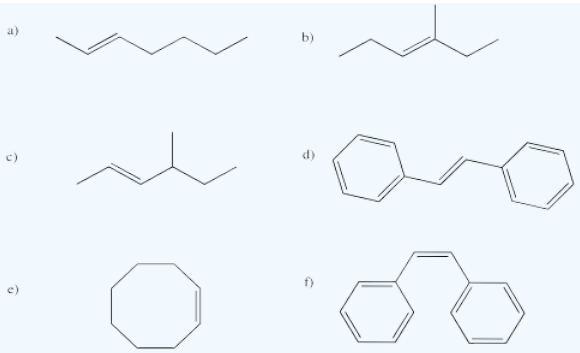
Answer

The nucleophile in the second step changes under different conditions.

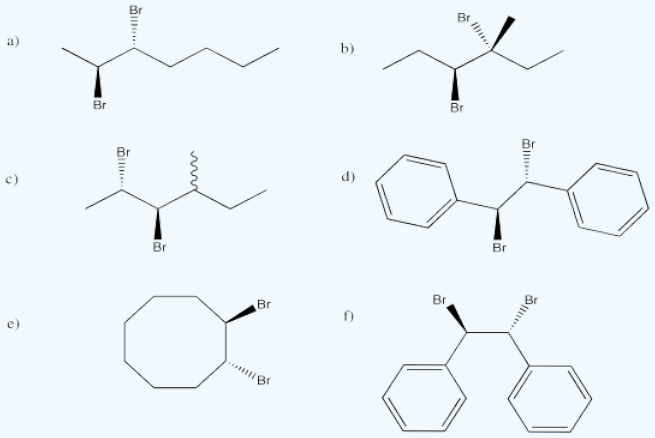


Exercise 6.4.6

Provide products for the reaction of bromine with each of the following compounds.



Answer

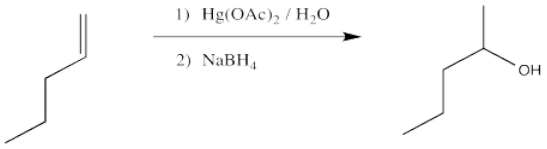


& enantiomer in each case

6.5: Addition to Coordinated Alkenes

Alkenes can coordinate to transition metals to form alkene complexes. In some cases, coordination of the alkene to a metal leaves it susceptible to reaction with a nucleophile such as water.

The classic case of nucleophilic donation to a coordinated alkene occurs with mercury (II) salts such as mercuric chloride, $HgCl_2$, or mercuric acetate, $Hg(OAc)_2$. The reaction, or rather the sequence of reactions, is called oxymercuration - demercuration or oxymercuration - reduction.



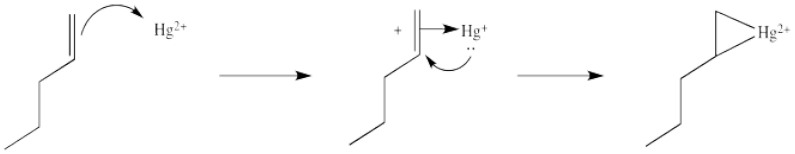
? Exercise 6.5.1

Compare the product of the reaction above to that obtained from treatment of 1-pentene with aqueous sulfuric acid.

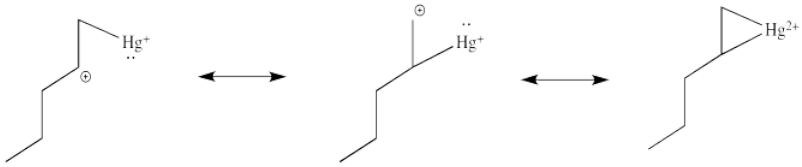
We will break the two different reactions in this sequence apart and focus only on the first one: oxymercuration. This reaction qualifies as an electrophilic addition because, as in the previous cases, it begins with donation of a π-bonding pair to an electrophile. In this case, we will consider the electrophile to be aqueous Hg^{2+} ion.

That electrophilic addition (from the alkene's perspective) results in the formation of an alkene complex. In reality, the mercury ion is also coordinated by several water molecules, but we will ignore them for simplicity.

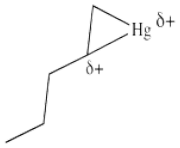
You may know that alkene complexes are not observed with d^0 transition metals. Although π-to-metal donation is the key event in the formation of such complexes, the alkene is just a little more sticky if the metal has d electrons. These electrons are able to "back-donate" into the alkene portion of the complex, adding extra stability to the interaction.



This situation is something like formation of a cyclic bromonium ion.

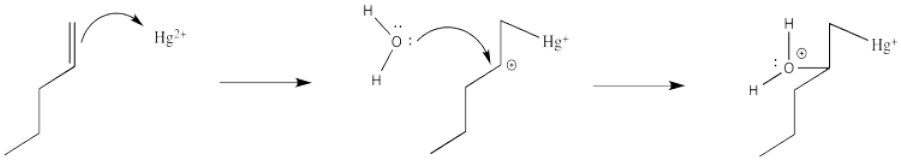


Note that the overall transfer of electrons is still from alkene to metal. That imbalance isn't apparent in a Lewis structure sense, in which case you can draw the structure so that there appears to be an equal trade. In a computational chemistry approach, in which we rely on basic principles of quantum mechanics and let computers churn out high-level calculations, we would still predict a little bit of positive charge on the alkene.



In the structure below, we have over-emphasized that charge, just to see what happens next in the reaction. When we draw it that way, it looks a lot more like simple addition of electrophile , such as H^+, to alkene. We know it's more subtle than that. We'll get back to the real mechanism after a small detour.

Of course, the next step is donation of a lone pair from a nucleophile to the almost-cationic carbon.

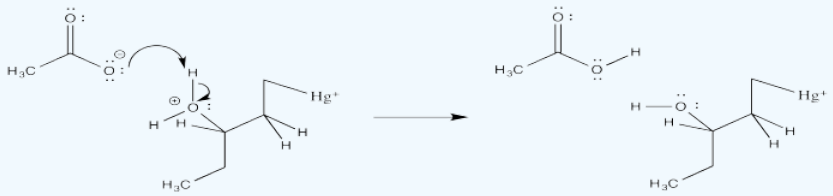


That looks easy. After that, deprotonation would result in the formation of a hydroxy group.

? Exercise 6.5.2

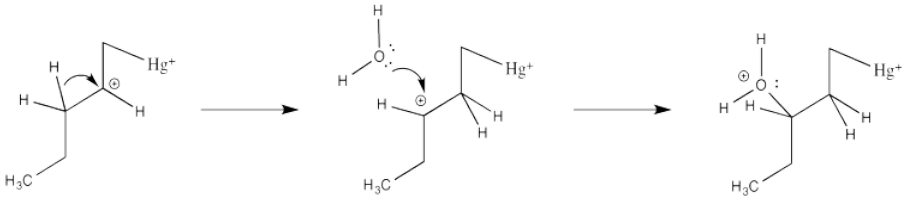
Suppose deprotonation is carried out by the acetate ion in solution. Draw a mechanism for this step.

Answer



How do we know the reaction doesn't happen through this simple cation?

Partly we know that because we know about alkene complexes. There are thousands of examples, structurally characterized by NMR spectroscopy and X-ray crystallography. In addition, we know it isn't a simple cation because nothing like the following scenario plays out during oxymercuration.



There are no hydride shifts. The cation stays put. The hydroxy group forms right where the alkene used to be. That means there is not a full carbocation like the one shown above.

If there isn't a real carbocation, though, why does the nucleophile end up at one particular end of the alkene? The hydroxy does end up at the position that would form the more stable cation. (In other words, this reaction results in what is called "Markovnikov addition".)

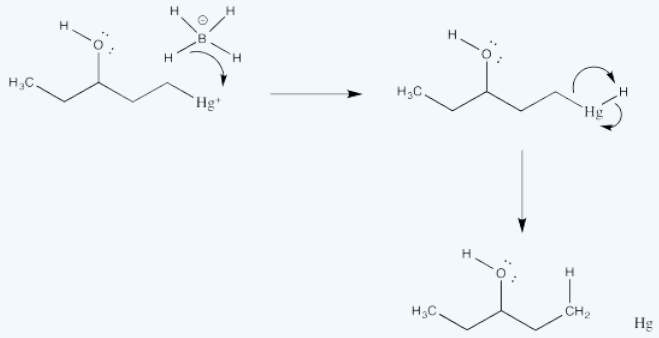
There are a couple of reasons that could play a role. Foremost, the alkene isn't bound symmetrically. One end is held a little closer to the mercury than the other. Mostly that's because of sterics. Any other ligands on the mercury (such as those water molecules) push that more crowded end away a little bit. That slight asymmetry allows a little more charge to build on the more substitutted end of the alkene, which is therefore more electrophilic.

The final part of the reaction sequence is displacement of mercury from the hydroxyalkylmercury complex, effected through addition of sodium borohydride. The details of the reaction are usually dismissed in textbooks because they have little to do with electrophilic addition, the topic we are focusing on. However, the result is that the mercury is replaced by a hydrogen atom. The metal is converted to silvery, liquid, elemental mercury.

Exercise 6.5.3

Suppose the demercuration reaction takes place via addition of hydride nucleophile to mercury, followed by reductive elimination. Draw this mechanism.

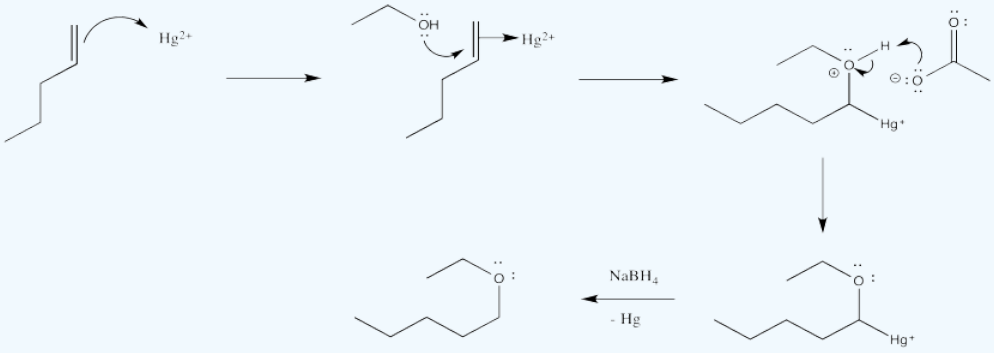
Answer



Exercise 6.5.4

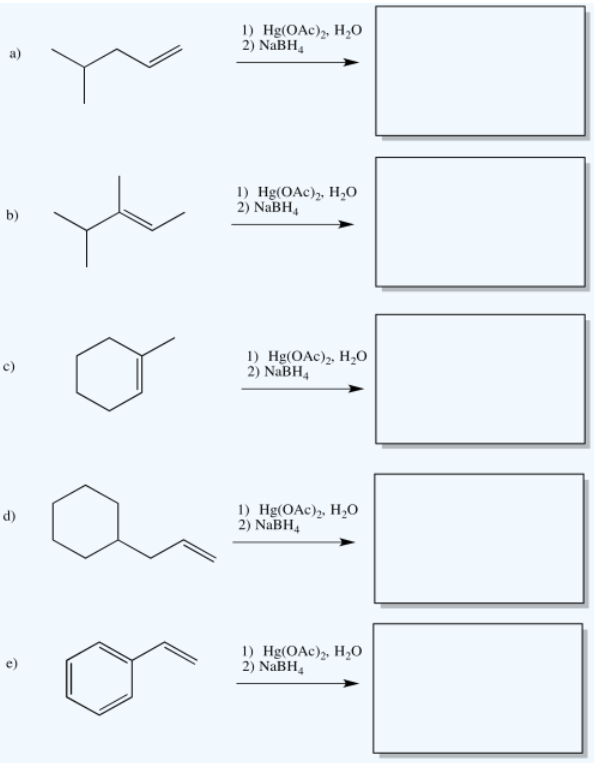
When mercuration takes place in a ethanol instead of water, an ether product results rather than an alcohol. Work through the mechanism and show the result of mercuration-demercuration in ethanol.

Answer

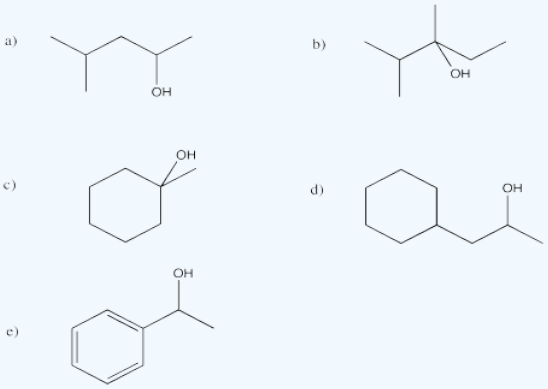


Exercise 6.5.5

Show the products of the following reactions.

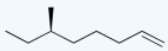


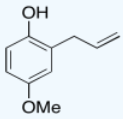
Answer

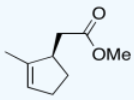


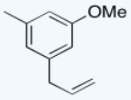
? Exercise 6.5.6

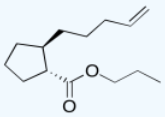
Predict the products of the following reactions.

a)  1) $Hg(OAc)_2$, MeOH 2) $NaBH_4$ →

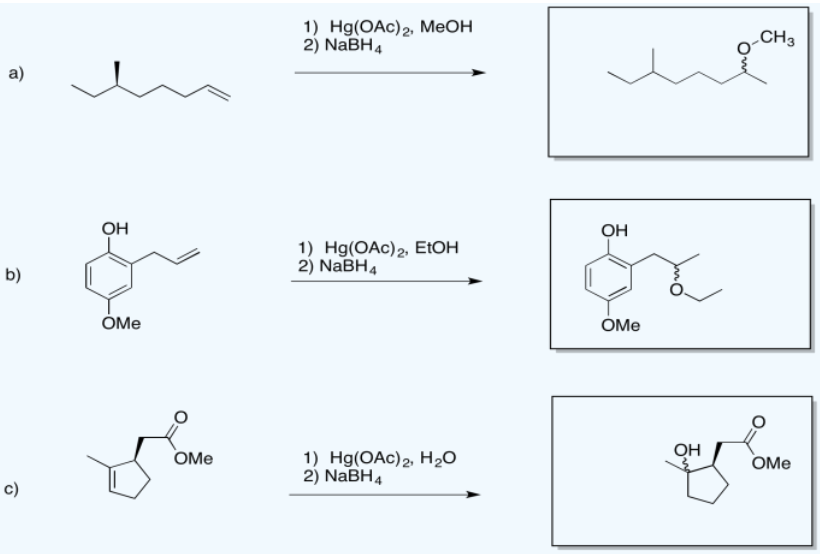
b)  1) $Hg(OAc)_2$, EtOH 2) $NaBH_4$ →

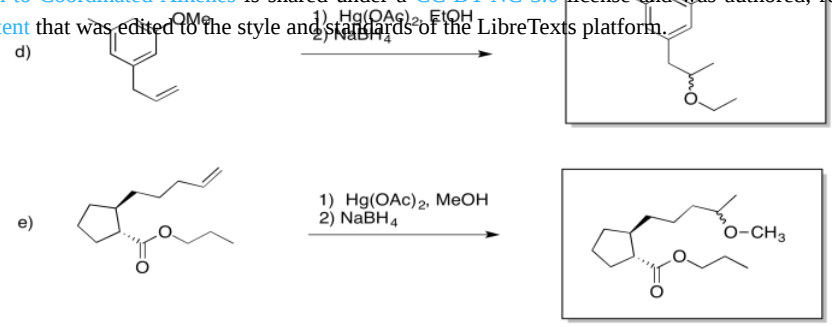
c)  1) $Hg(OAc)_2$, H_2O 2) $NaBH_4$ →

d)  1) $Hg(OAc)_2$, EtOH 2) $NaBH_4$ →

e)  1) $Hg(OAc)_2$, MeOH 2) $NaBH_4$ →

Answer





6.6: Insertion at Coordinated Alkenes

Metal alkoxides can undergo 1,2-elimination (or beta-elimination) to give organic carbonyl compounds. This reaction is the reverse of a nucleophilic addition of a metal hydride to an organic carbonyl.

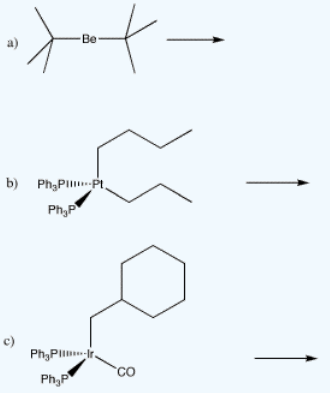
Metal alkyls can also undergo 1,2-elimination. In this case, an alkene is formed. Like the carbonyl compounds formed from 1,2-elimination, the alkene usually remains bound to the metal. It can dissociate to form the free alkene, though. For more information on alkene binding, take a look at this page.

These reactions are sometimes called "beta hydride eliminations", emphasizing that the hydrogen attached to the metal usually acts as a nucleophile. Thus, when the hydrogen transfers to the metal, it is forming a hydride.

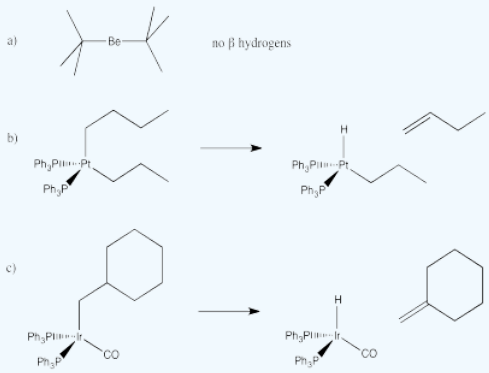
- Alkyl groups that are coordinated to metals can also undergo elimination.
- In order to undergo elimination, an alkyl group must have a hydrogen.
- When a metal alkyl undergoes elimination, it forms an alkene.

Exercise 6.6.1

Draw the elimination products in the following cases.

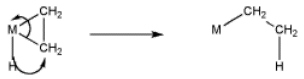


Answer

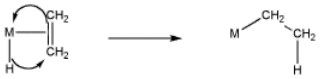


The reverse of a 1,2-elimination is a 1,2-insertion. Just like aldehydes and ketones, alkenes can undergo 1,2-insertions (also called beta hydride insertions). In terms of electrophiles and nucleophiles, this reaction is a little harder to imagine. However, we can still think of the hydride as a nucleophile. Maybe the alkene is an electrophile. Given that it is donating its pi electrons to the metal, we can think of it as "activated", a little bit like an activated carbonyl.

The formalisms of drawing a beta alkene insertion are tricky. If we use the metallacycle drawing of a bound alkene, it might look like this:



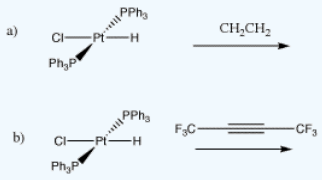
More often, bound alkenes are drawn as shown as in the picture below. In that case, we could try to show the pi bond forming a new carbon-metal bond. The bond between the metal and alkene on the picture to the left does not really stand for a separate pair of electrons in this case; it just stands for the pi bond donating to the metal.



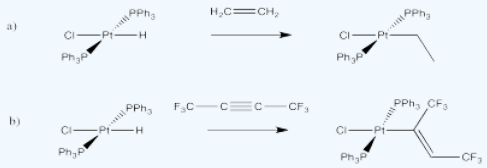
- The reverse of elimination is insertion.
- A coordinated alkene is sometimes considered electrophilic because it is giving electrons to the metal.
- A coordinated alkene is activated, like a coordinated carbonyl compound.

Exercise 6.6.2

Draw the insertion products in the following cases.

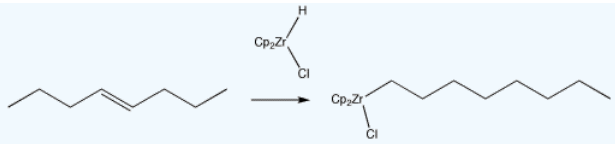


Answer

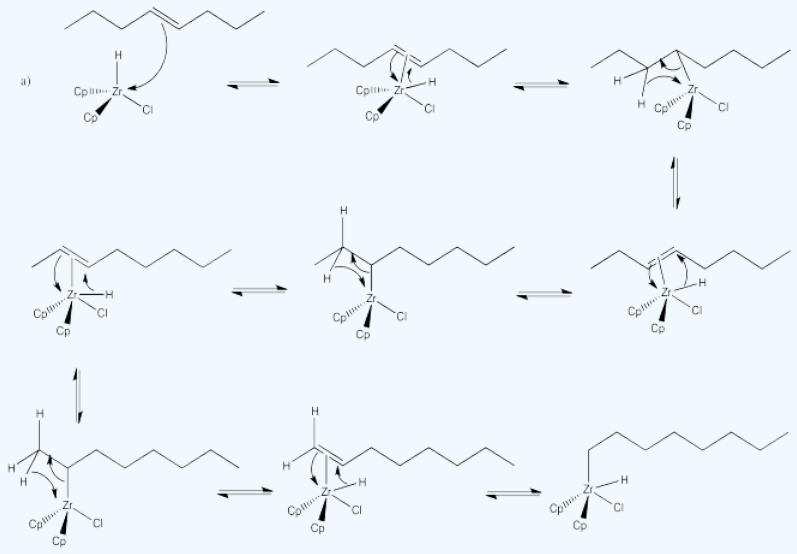


Exercise 6.6.3

Alkenes can be converted into other compounds through the use of organometallic reagents, such as "Schwartz's reagent" (below). In this case, the resulting alkyl compound can easily be converted into a long-chain alkyl halide or alcohol through the addition of appropriate reagents. Provide a mechanism for the reaction shown below.

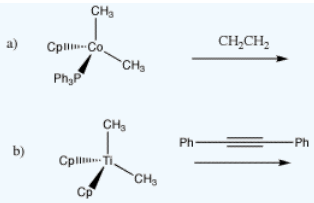


Answer

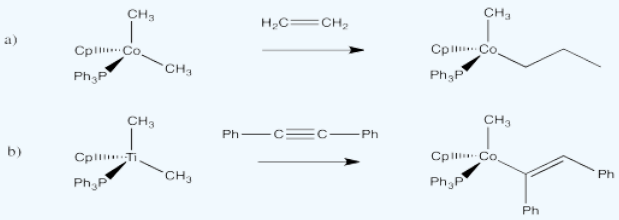


Exercise 6.6.4

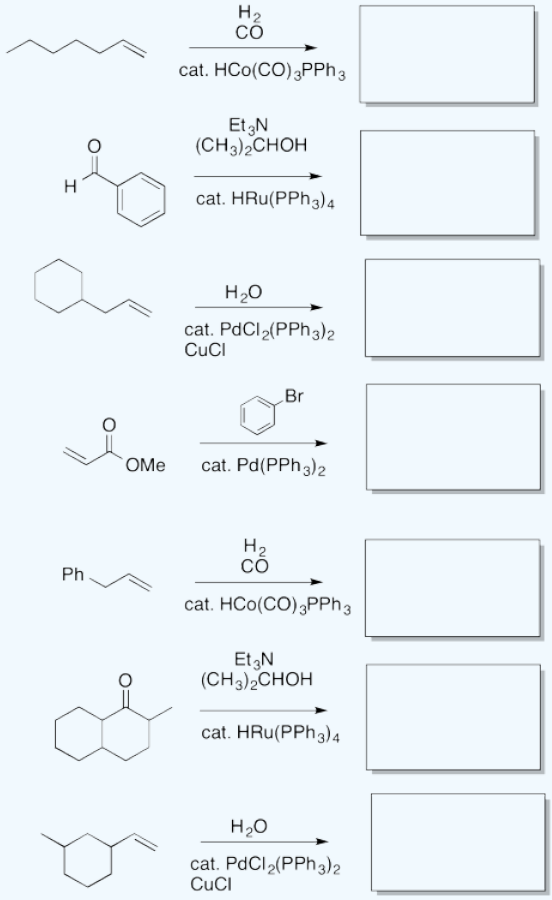
1,2-alkyl insertions and -eliminations are also known in a few cases, although they are much slower than 1,2-hydride insertions and -eliminations. Show the 1,2-insertion products for the following cases.



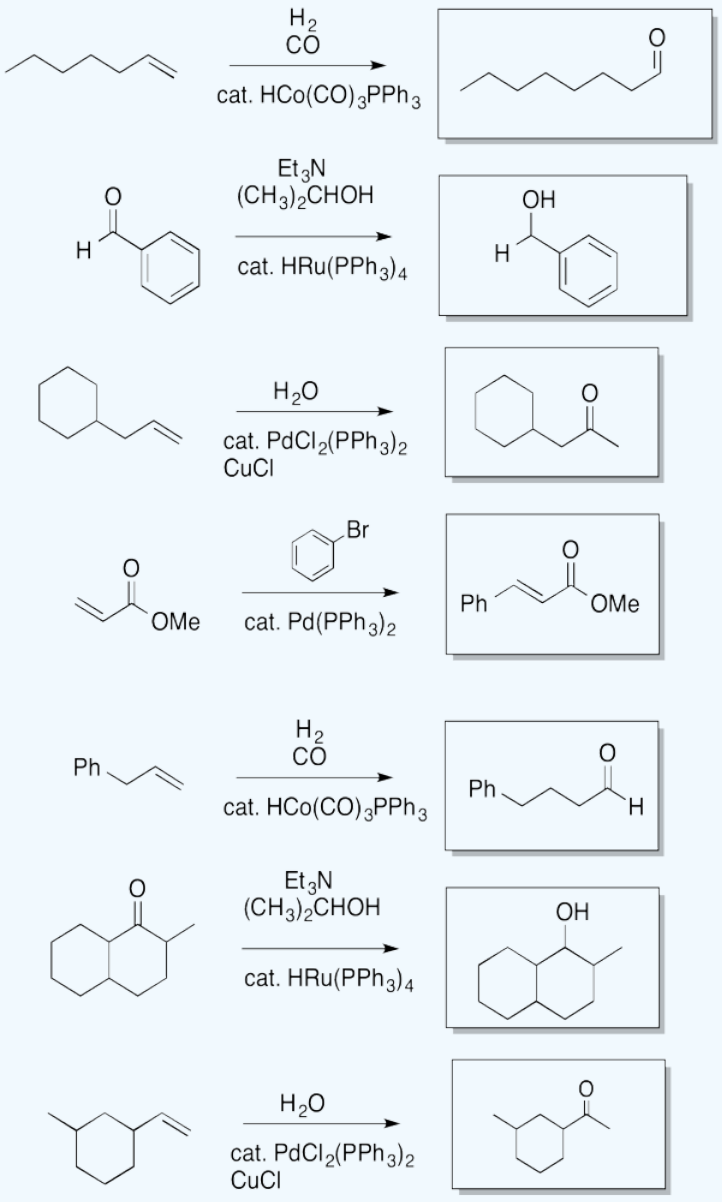
Answer



? Exercise 6.6.5

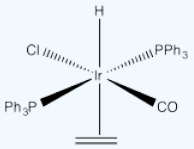


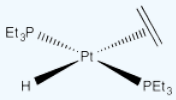
Answer



? Exercise 6.6.6

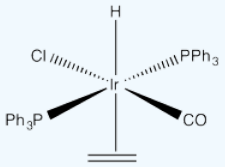
Why don't either of these complexes undergo hydride insertions at room temperature?

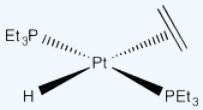




Answer

Why don't either of these complexes undergo hydride insertions at room temperature?

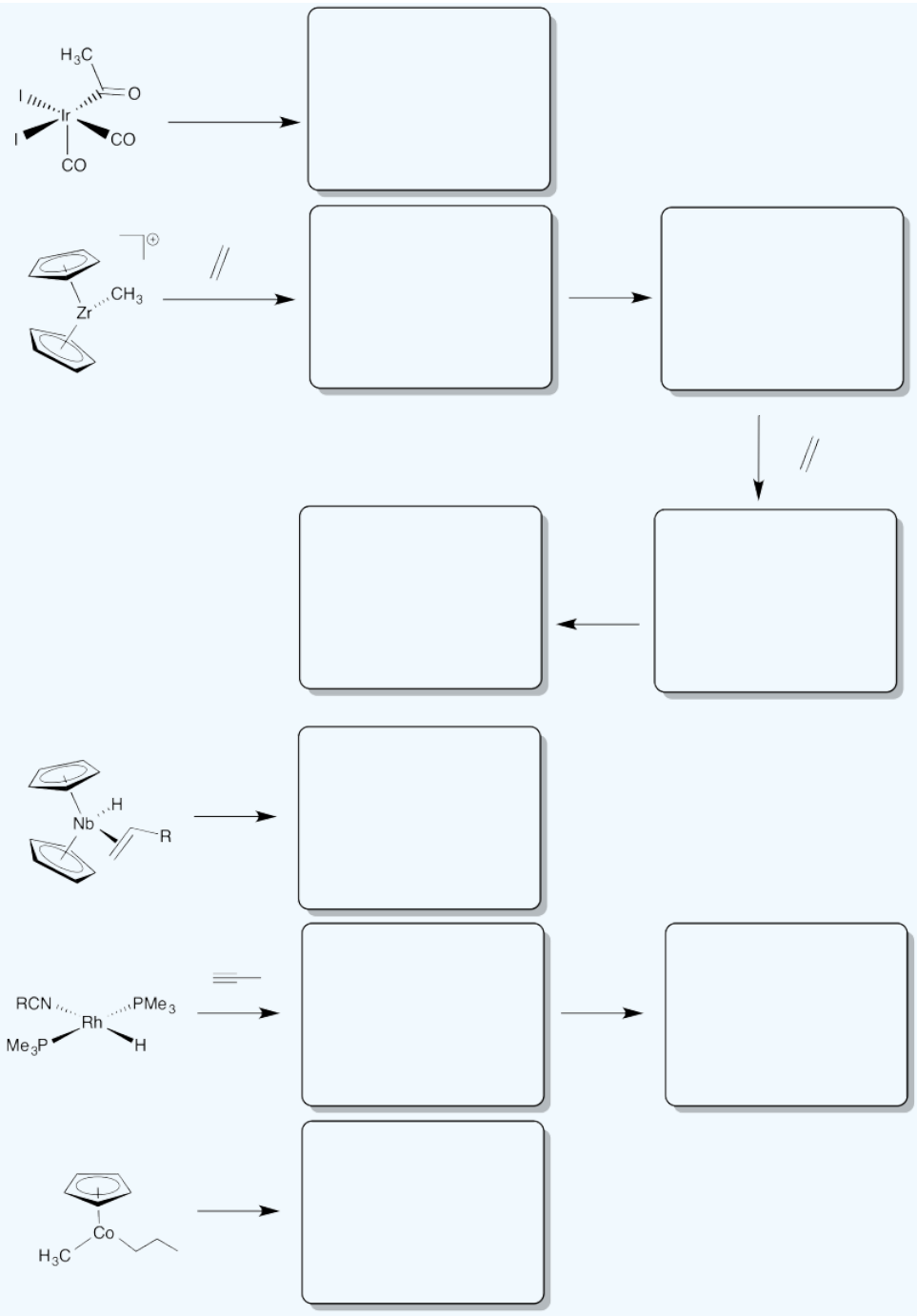




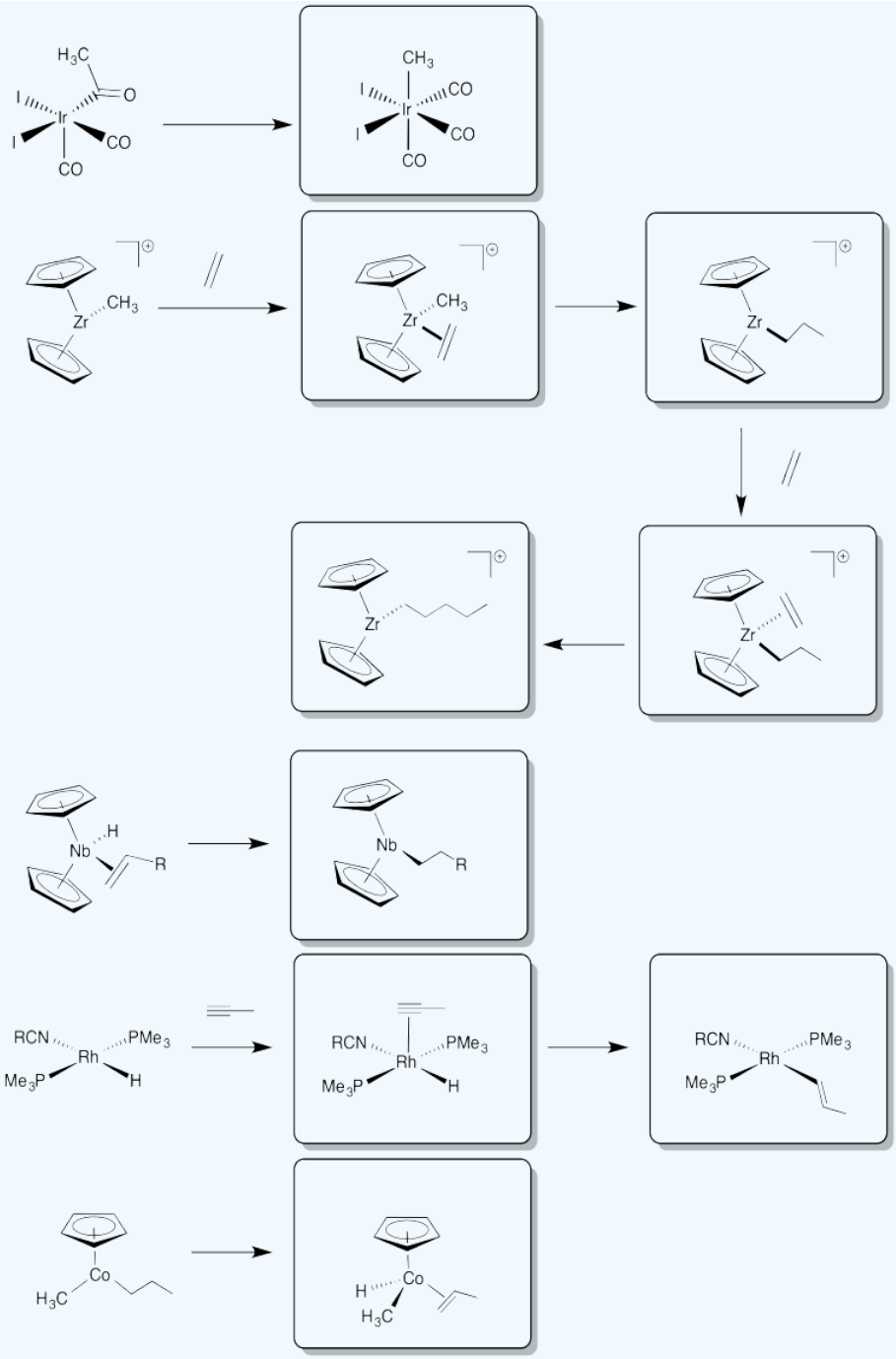
The hydride and the alkene group are trans to each other in this complex. In order for ar insertion reaction, the two ligands need to be closer.

Exercise 6.6.7

Fill in the missing insertion / elimination products.



Answer



Exercise 6.6.8

The following multi-part problem is based on an article in the primary research literature.

Scorpionate Ligands: A Ligand with a Greater Propensity to Sting?

Dyson, Zech, Rawe, Haddow, Hamilton and Owen, *Organometallics*, **2011**, *30*, 5844-5850.

1. A ligand that we have seen before, **COD**.

COD

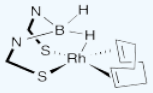
a. What will the denticity of this ligand be? _____
b. Circle the sites that bind to the metal.

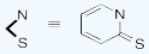
2. Show a molecular orbital cartoon showing how the orbitals of COD that bind to the M.

3. New Ligand, **Bmp**.
   a. Add formal charges to these two resonance structures.

When rhodium is complexed with Bmp and the COD, the following complex is formed.

4. What is the geometry of the rhodium in this complex?



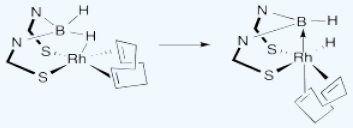


Geometry: _____

5. What is the valence electron count on Rh in this complex?

Valence electrons on Metal: _____
Charge on the ligands: _____
Charge on the Metal: _____
Revised Count on the Metal (accounting for charge): _____
Number of electrons donated from the ligands: _____
Total electrons in this complex: _____

6. Upon formation, the hydride quickly moves to the metal.

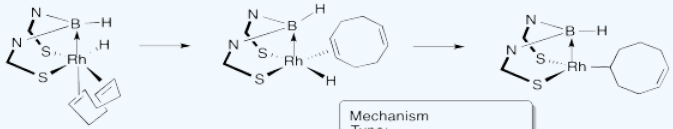


a. Why did this occur?

b. Why is there an arrow toward the B in the product?

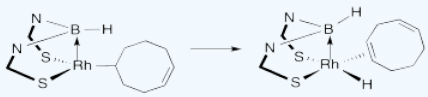
For the rhodium complex, a novel "chain-walking mechanism" is observed.

7. In this reaction, the COD partially dissociates and then the first step of the "chain-walking" occurs. Show the mechanism and provide a name for the mechanism type.



Mechanism Type:_____

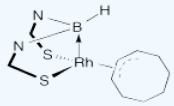
8. The second step of the "chain-walking" occurs. Show the mechanism and provide a name fo the mechanism type.



Mechanism Type:_____

9. Eventually the hydride "walks" to the final position. Show the rest of the mechanism.

10. The final product can also be represented in the following way. Show how this structure is equivalent to the one above.



11. Considering structure and thermodynamics, why is this the final product?

Answer

Scorpionate Ligands: A Ligand with a Greater Propensity to Sting?
Dyson, Zech, Rawe, Haddow, Hamilton and Owen, *Organometallics*, **2011**, *30*, 5844-5850.

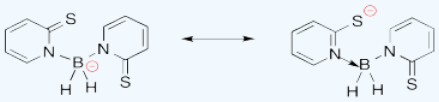
1. A ligand that we have seen before, **COD**.

COD

a. What will the denticity of this ligand be? ____2_____
b. Circle the sites that bind to the metal.

2. Show a molecular orbital cartoon showing how the orbitals of COD that bind to the M.

3. New Ligand, **Bmp**.
   a. Add formal charges to these two resonance structures.



When rhodium is complexed with Bmp and the COD, the following complex is formed.

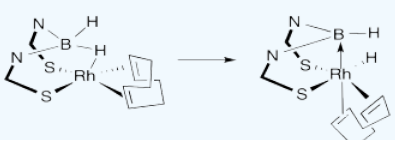
4. What is the geometry of the rhodium in this complex?

Geometry: distorted square pyramidal

5. What is the valence electron count on Rh in this complex?

Valence electrons on Metal:	___9___
Charge on the ligands:	___-1___
Charge on the Metal:	___+1___
Revised Count on the Metal (accounting for charge):	___8___
Number of electrons donated from the ligands:	___10___
Total electrons in this complex:	___18___

6. Upon formation, the hydride quickly moves to the metal.

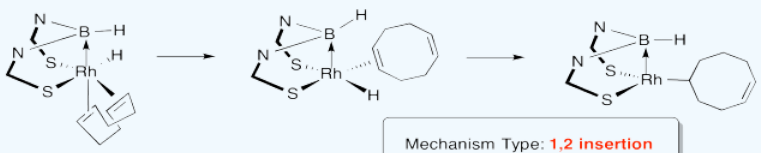


a. Why did this occur?

b. Why is there an arrow toward the B in the product?

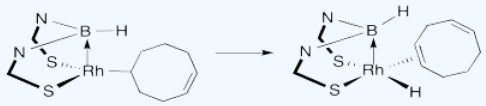
For the rhodium complex, a novel "chain-walking mechanism" is observed.

7. In this reaction, the COD partially dissociates and then the first step of the "chain-walking" occurs. Provide a name for the mechanism type.



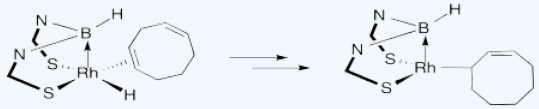
Mechanism Type: 1,2 insertion

8. The second step of the "chain-walking" occurs. Provide a name for the mechanism type.



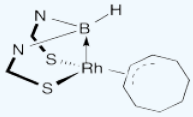
Mechanism Type: beta elimination

9. Eventually the hydride "walks" to the final position. Show the rest of the mechanism.



Chain walking is a series of 1,2 insertions and beta eliminations

10. The final product can also be represented in the following way. Show how this structure is equivalent to the one above.



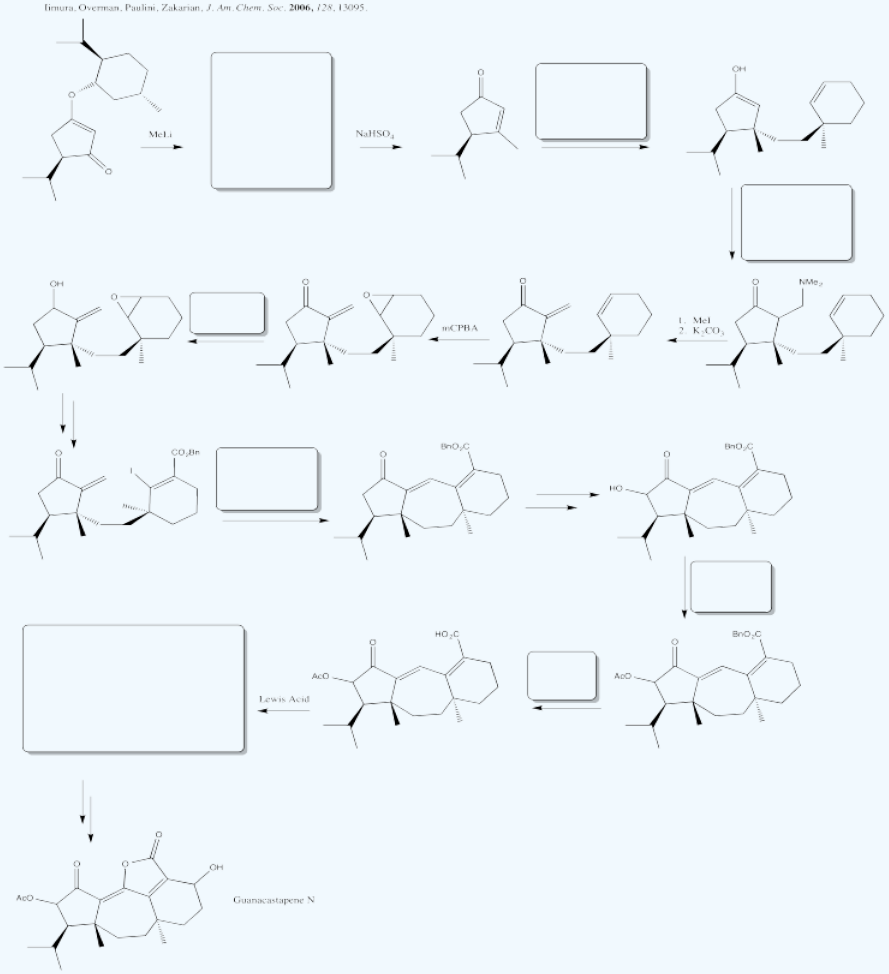
11. Considering structure and thermodynamics, why is this the final product?

resonance stabilized

Exercise 6.6.9

Guanacastepene N

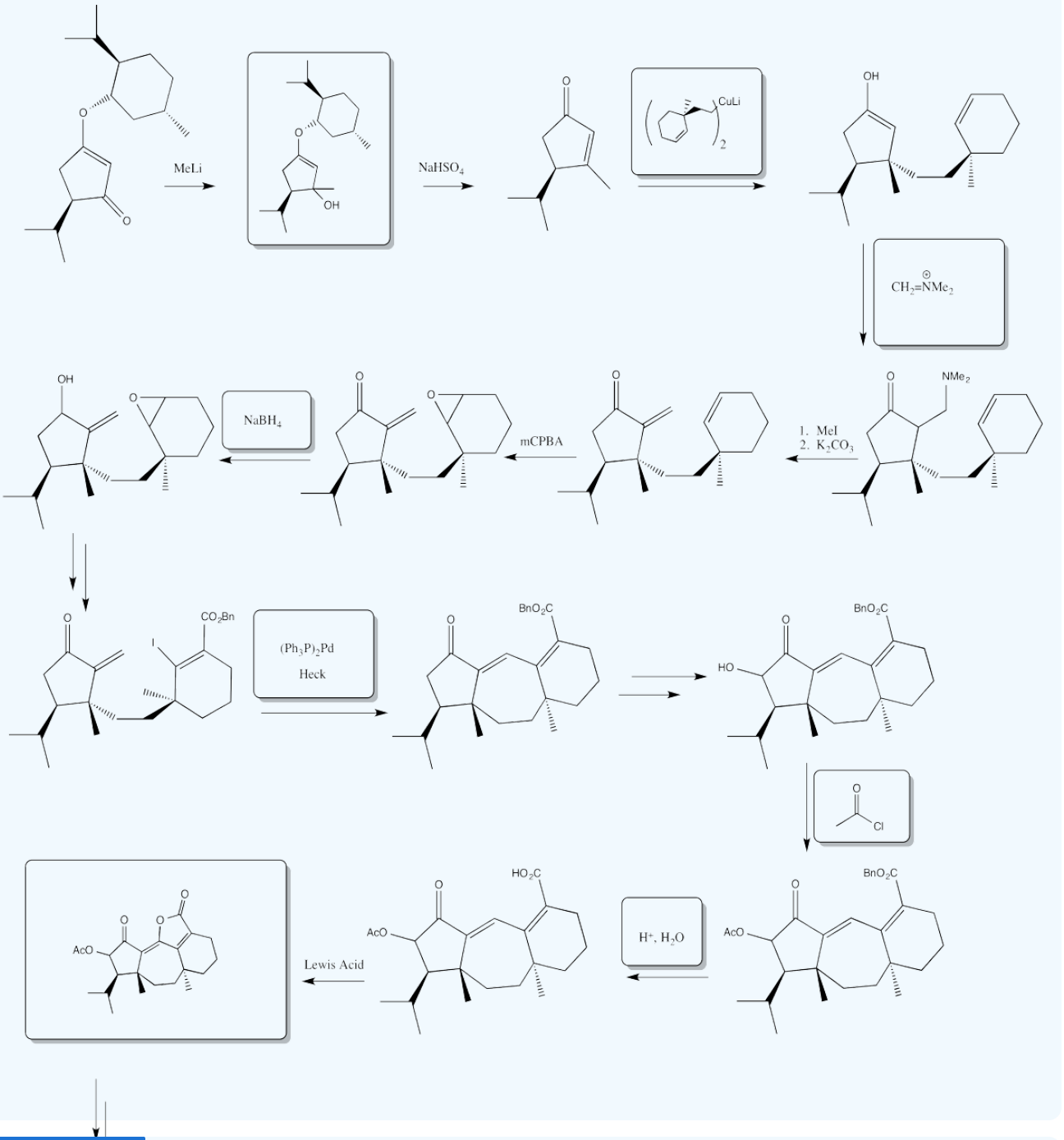
Iimura, Overman, Paulini, Zakarian, *J. Am. Chem. Soc.* **2006**, *128*, 13095.



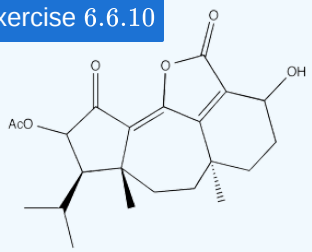
Answer

Guanacastepene N

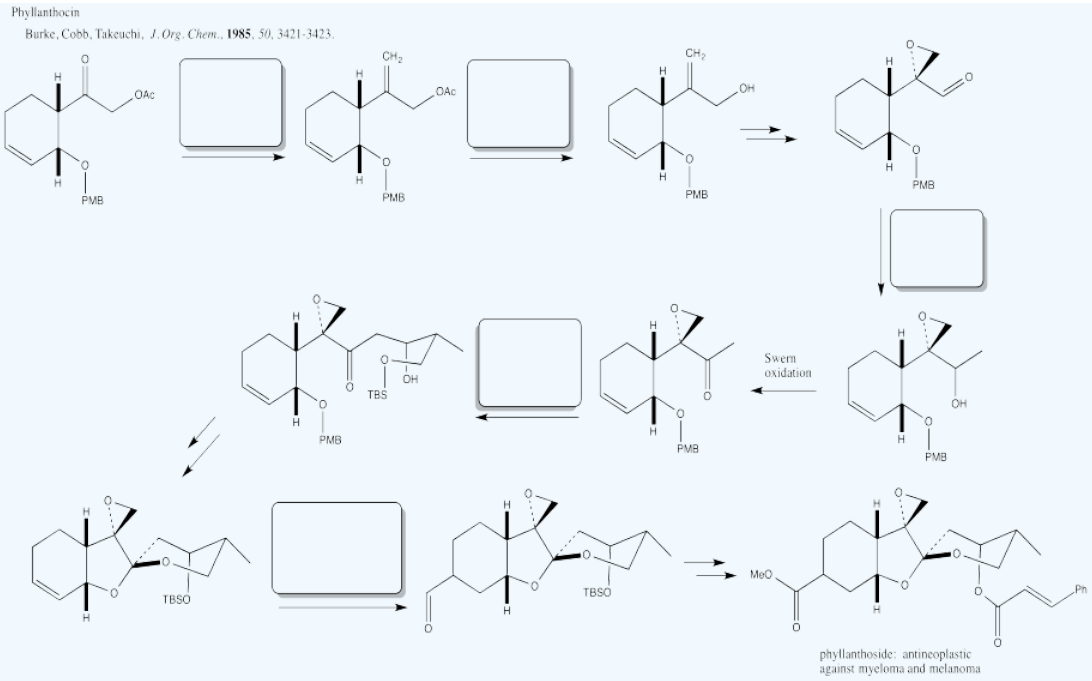
Iimura, Overman, Paulini, Zakarian, *J. Am. Chem. Soc.* **2006,** *128*, 13095.



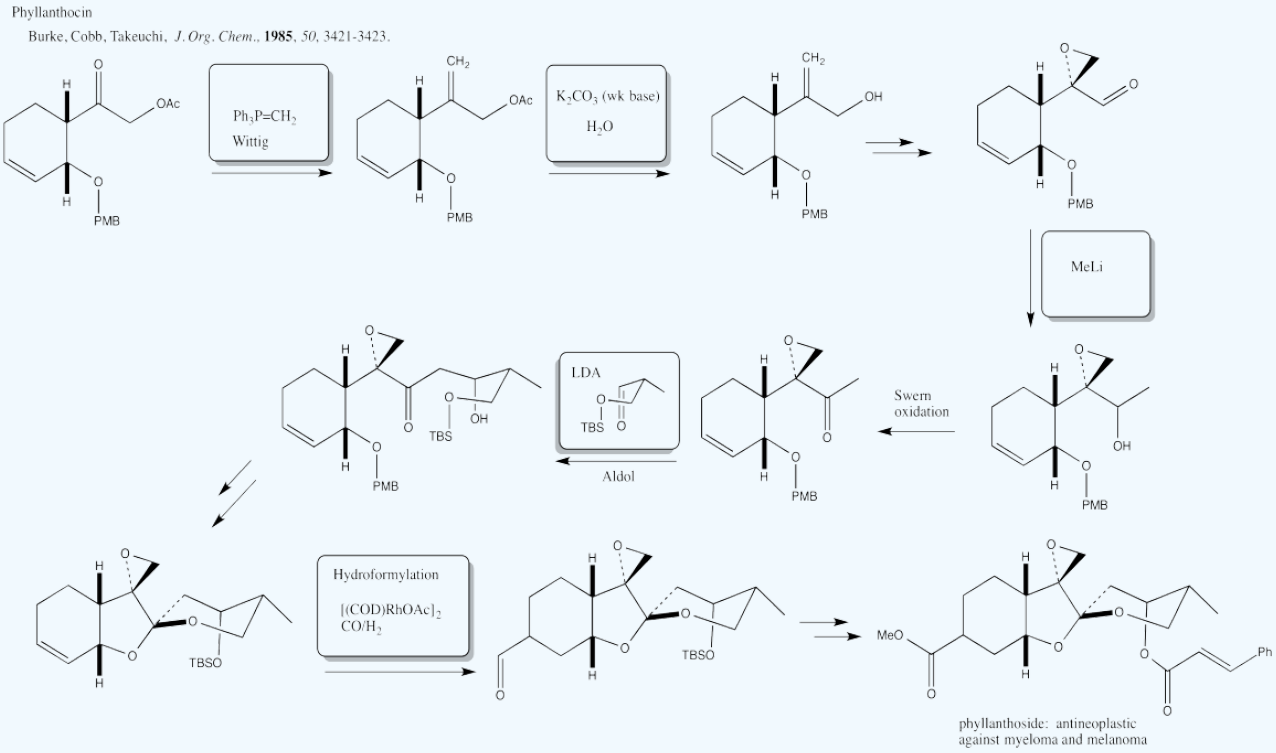
? Exercise 6.6.10



Guanacastapene N



Answer



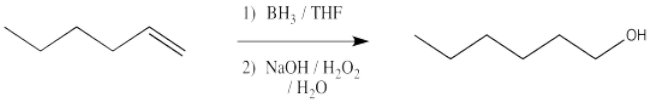
6.7: Concerted Addition to Alkenes

Alkenes can be treated with aqueous acids or, much more efficiently, with aqueous mercuric salts, followed by sodium borohydride, to produce alcohols. In those cases, the hydroxyl group is found in different places. Treatment with acid often results in a mixture of alcohols in which the OH groups are found in the most substituted positions in the structure, regardless of the position of the original alkene. Oxymercuration - demercuration results in the hydroxyl being fixed at the most substituted end of the former C=C bond.

Those reactions are generally called hydration reactions because they result in the overall addition of H-OH across the double bond.

- Hydration reactions place an OH on one end and a H on the other end of a former double bond.

Hydroboration - oxidation is a two-step sequence of reactions that also results in hydration of a double bond. However, this reaction is complementary to oxymercuration - demercuration.



Instead of leaving an OH group at the most substituted end of the double bond, the hydroxy group is placed at the least substituted end of the double bond.

Let's modify that statement a little bit. In reality, the reaction scheme above just shows the major product. The minor product has the hydroxy group at the more substituted position of the double bond. These two products might be found in different ratios, maybe even as close as 55:45, but the least substituted product always predominates. We will see more efficient hydroboration methods soon, leading to ratios above 95:5, or almost entirely the least substituted product.

The product of non-hydrogen addition (i.e. OH group addition) at the most substituted end of the alkene is called a Markovnikov addition product. The product of non-hydrogen addition at the least substituted end of the alkene is called an anti-Markovnikov addition product.

- Oxymercuration - demercuration results in Markovnikov hydration.
- Hydroboration - oxidation results in anti-Markovnikov hydration.

This selectivity is important in synthetic applications. We use natural products all the time as pharmaceuticals, vitamins and other health and beauty applications, but we can't always obtain these compounds directly from nature, for a number of reasons. It could be that the organism needs to be killed in order to harvest its products, or that there isn't enough of the source in nature ro meet demand. Frequently it is more economical to produce commercially useful compounds from convenient chemical feedstocks. Over the last century and a half, those feedstocks have come from coal tar and, later, petroleum. Currently, there is rapid progress underway to develop chemical feedstocks from sources such as vegetable and algal oil (i.e. oil from seaweed).

These feedstocks are just compounds that can be converted synthetically into pharmaceuticals as well as in plastics, paints, coatings and other materials. Frequently, the starting materials for these processes contain C=C bonds that can be functionalized through electrophilic addition. Thus, electrophilic addition and related reactions are among the most important in the world, economically speaking. It's very valuable to be able to control the outcome of these reactions in order to make processes more efficient, producing fewer wasteful by-products.

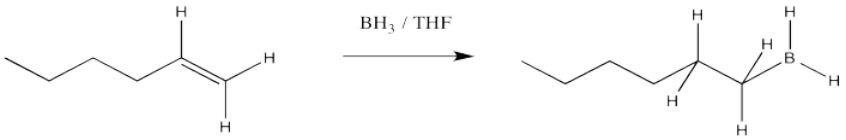
- Regioselectivity, or control over where a reaction occurs, is very important.
- The Markovnikov versus anti-Markovnikov additions available in hydration are good examples of regiochemical control.

? Exercise 6.7.1

List advantages and disadvantages of producing materials based on

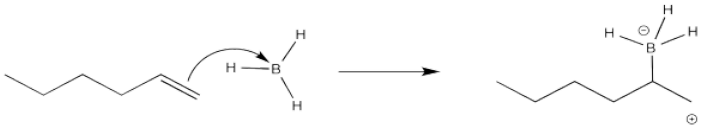
a. petroleum
b. vegetable oil
c. algae
d. harvesting desired compounds directly from nature

Again, we are going to focus on the first of the two reactions in this sequence. That part is where the placement of the new substituent is decided. After the addition of the borane, an alkylborane is formed. The major isomer results from anti-Markovnikov addition.



It seems pretty clear at this point that this reaction must proceed like other electrophilic additions to alkenes. The π electrons donate to the electrophile. In this case that's boron, which is strongly Lewis acidic because it lacks an octet. The boron ends up at the least substituted end of the double bond.

That outcome would certainly be favored over this one:



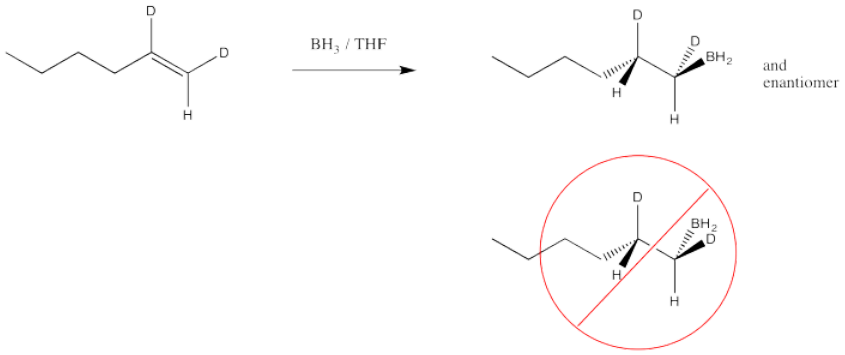
That boron is beginning to look less electrophilic and more nucleophilic. We can easily imagine a hydride nucleophile being delivered to the carbocation.

So far, the picture of how the alkylboration reaction works fits pretty well within our electrophilic addition framework. Unfortunately, there are some problems with this model.

First of all, maybe 55% of the boration takes place in a Markovnikov sense, but the other 45% is added to form an anti-Markovnikov product. Certainly the secondary cation is favored over the primary one, but if the reaction is proceeding through a carbocation, then the primary one shouldn't happen at all.

Something is wrong with our model.

Another hole is torn in the argument when we look at the results of stereochemical studies. We could, for example, take the following deuterium-labelled hexene and treat it with borane. We could look at the products via ^{1}H NMR spectroscopy, and if we could see the coupling constant between the two protons shown in the structure, then we would know their relative arrangement in space. We would know their stereochemistry.



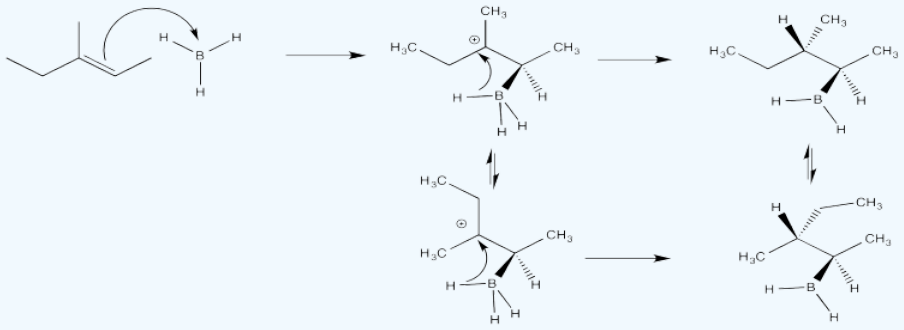
If we did that experiment, then we would see that the hydrogen and the boron from the borane are added to the same face of the alkene. We don't get addition of boron to one face and hydrogen to the other. This type of addition is called *syn* addition; it is the opposite of *anti* addition.

- Hydroboration results in *syn* addition to the alkene.

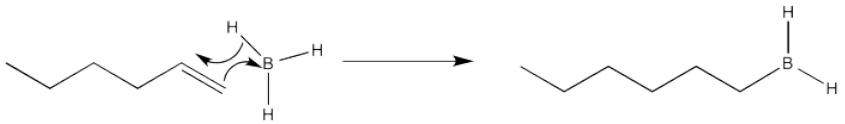
Exercise 6.7.2

Show how a cationic intermediate and conformational changes would allow both *syn* and *anti* addition of borane to propene.

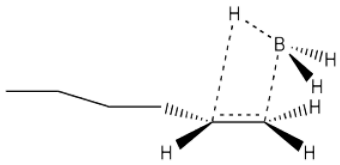
Answer



That result means that, although some elements of our mechanism may reflect reality, we at least have a problem with timing. How can the hydride be delivered before the conformation has a chance to change? It has to happen pretty quickly. What if it happens at the same time as π bond donation to the boron?

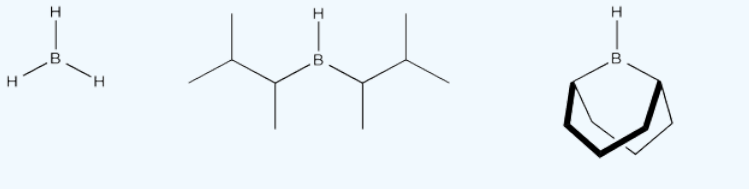


This reaction would best be described as a concerted addition. Two groups are added to the two ends of the double bond at the same time. During the transition state, two bonds would be breaking and two would be forming at the same time.



Exercise 6.7.3

We can further improve our model of how the alkylboration works if we consider that disiamylborane and 9-BBN are much more effecient than borane in terms of regioselectivity. These reagents can produce close to 100% anti-Markovnikov addition. Explain how with the help of drawings.



borane | disiamylborane | 9-borabicyclo[3.3.1]borane 9-BBN

Answer

Crowding is more severe in the structure on the left than in the structure on the right. The structure on the right, representing an approach to the transition state of the reaction, is more favourable than the other one.

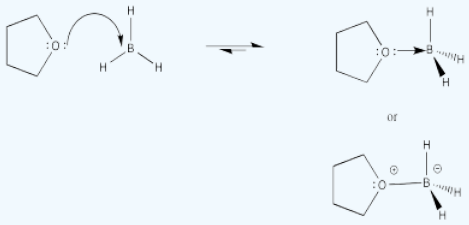
The subsequent reaction in this series involves removal of the boron and replacement with a hydroxyl group. The mechanism of this reaction may not be worth memorizing becuase it doesn't fit well within categories we have looked at so far.

The important thing to know is that the oxygen ends up in exactly the same place as the boron. There is no change in stereochemistry at that position. Overall, the hydrogen and the hydroxy effectively group undergo *syn* addition, although they are added in different steps.

Exercise 6.7.4

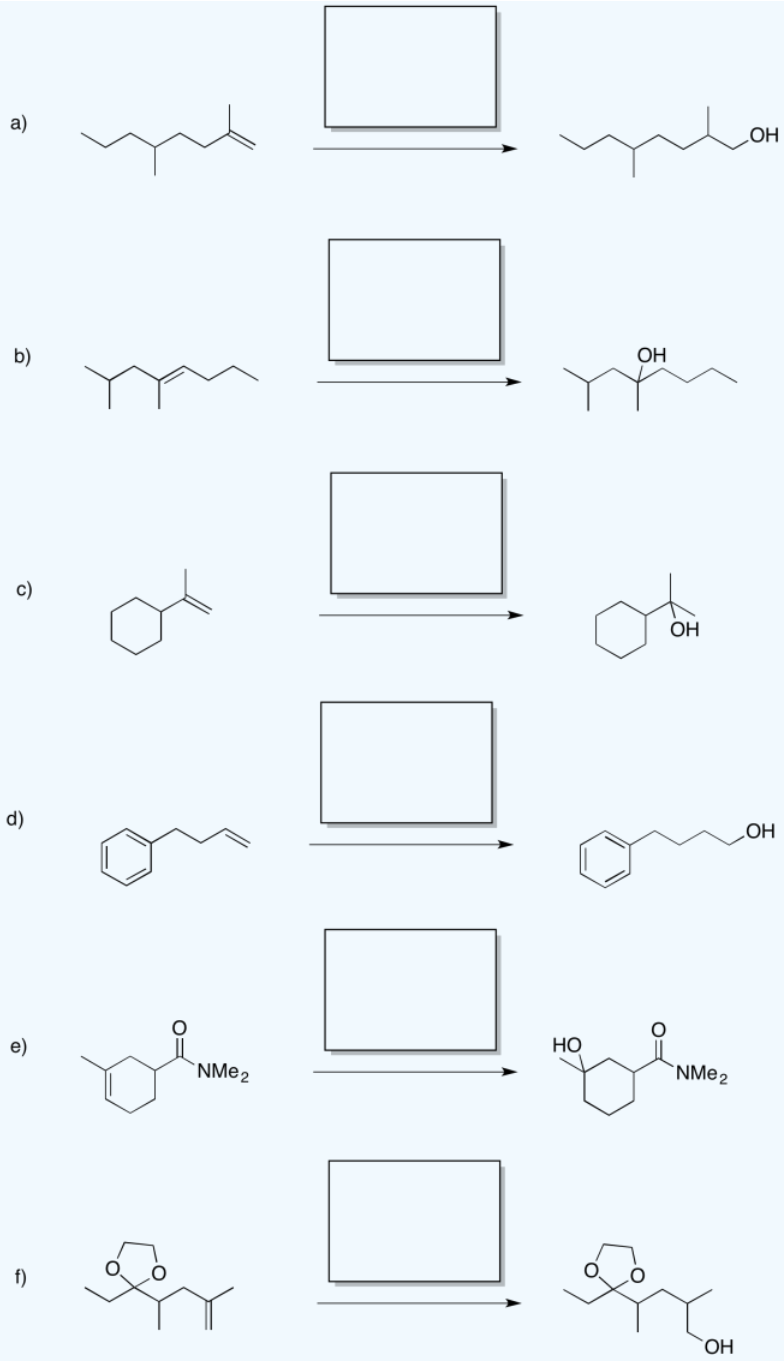
Borane is frequently used in THF because borane alone is not very stable; it is quite pyrophoric, bursting into flame upon contact with air. In THF, borane forms an equilibrium with a Lewis-acid-base complex. Show this equilibrium reaction.

Answer

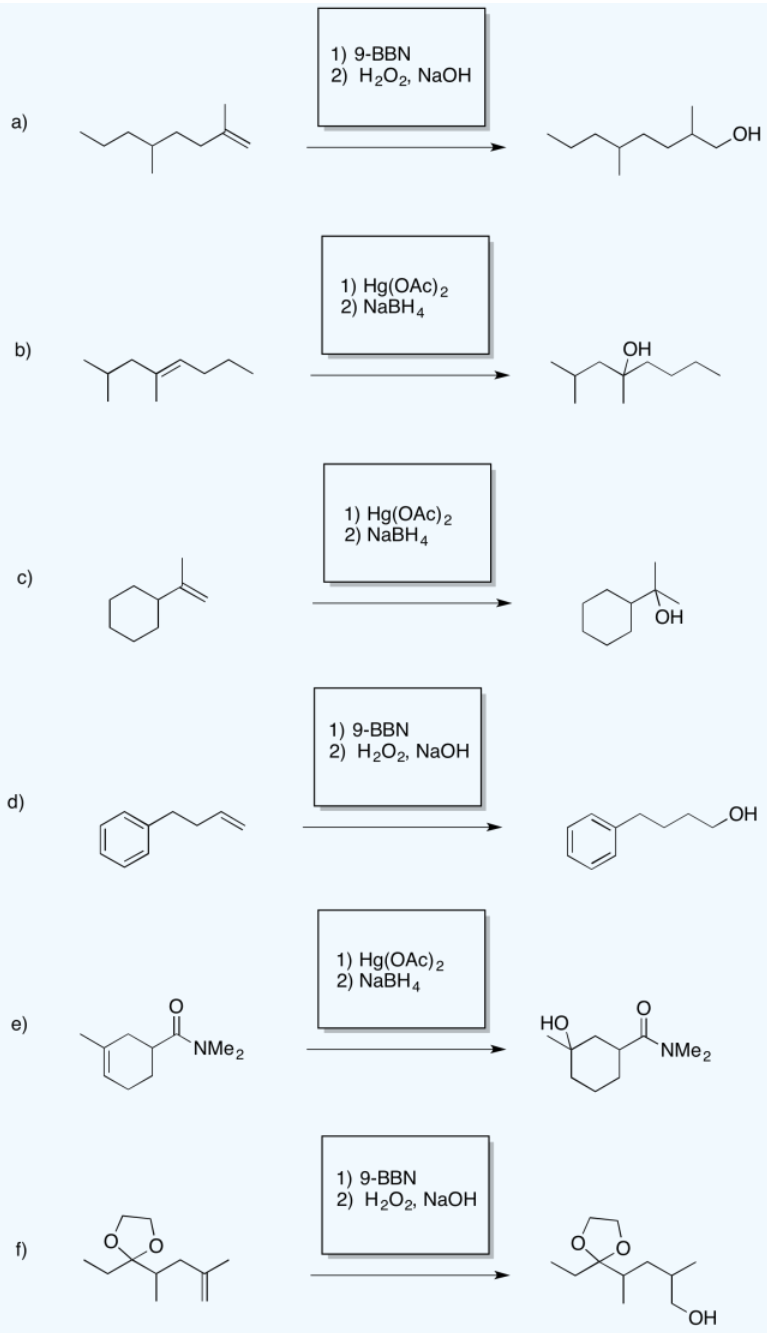


Exercise 6.7.5

Provide reagents for the following reactions

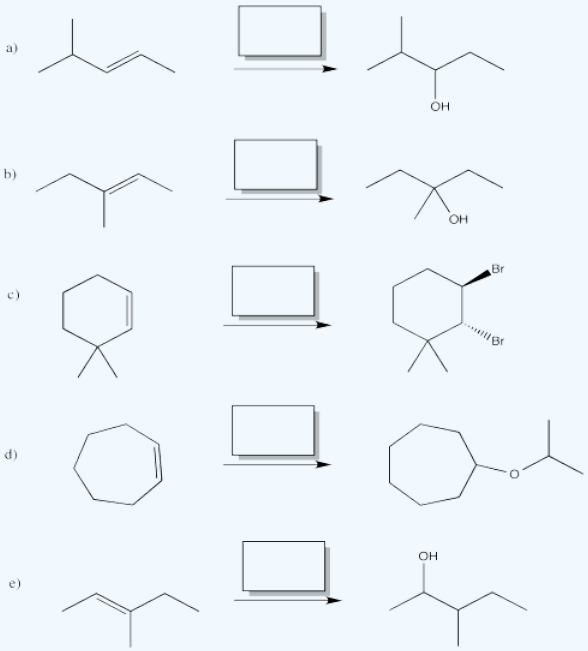


Answer

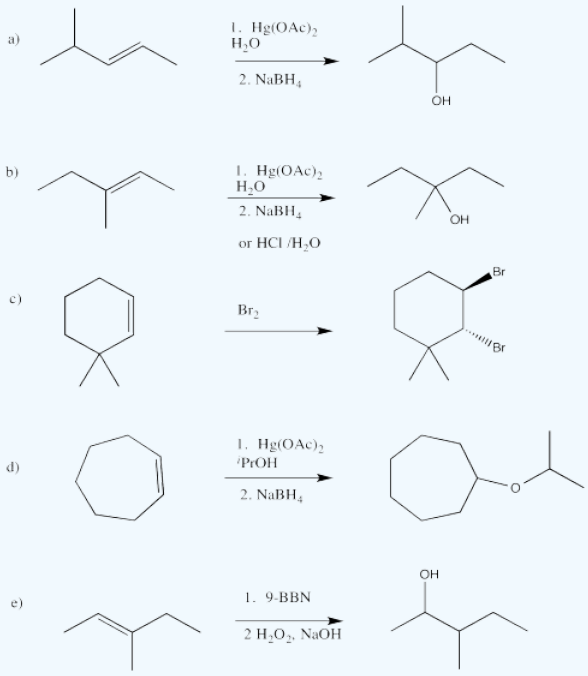


Exercise 6.7.6

Provide reagents for the following reactions

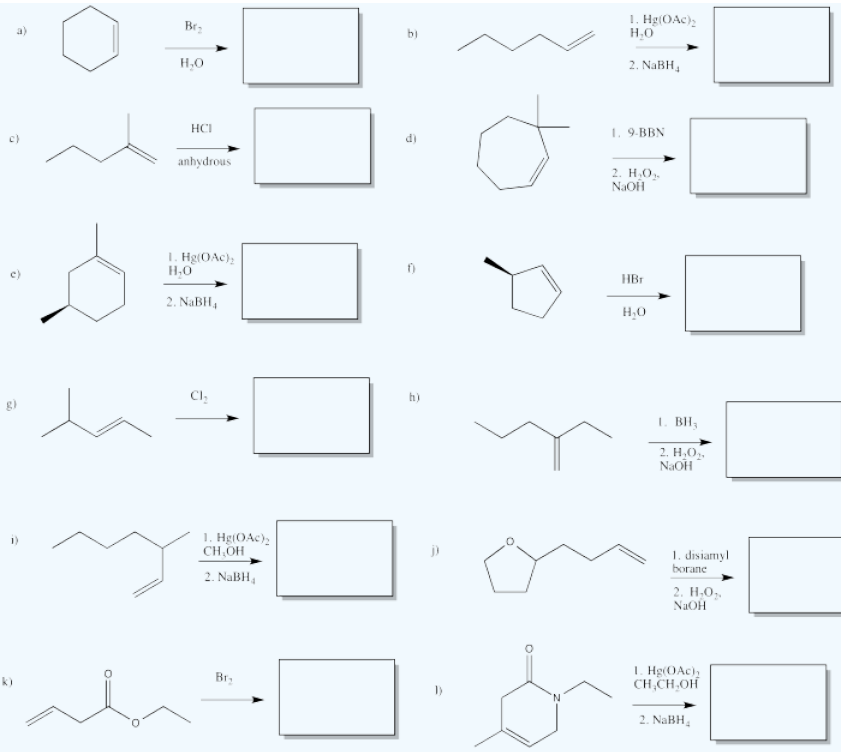


Answer

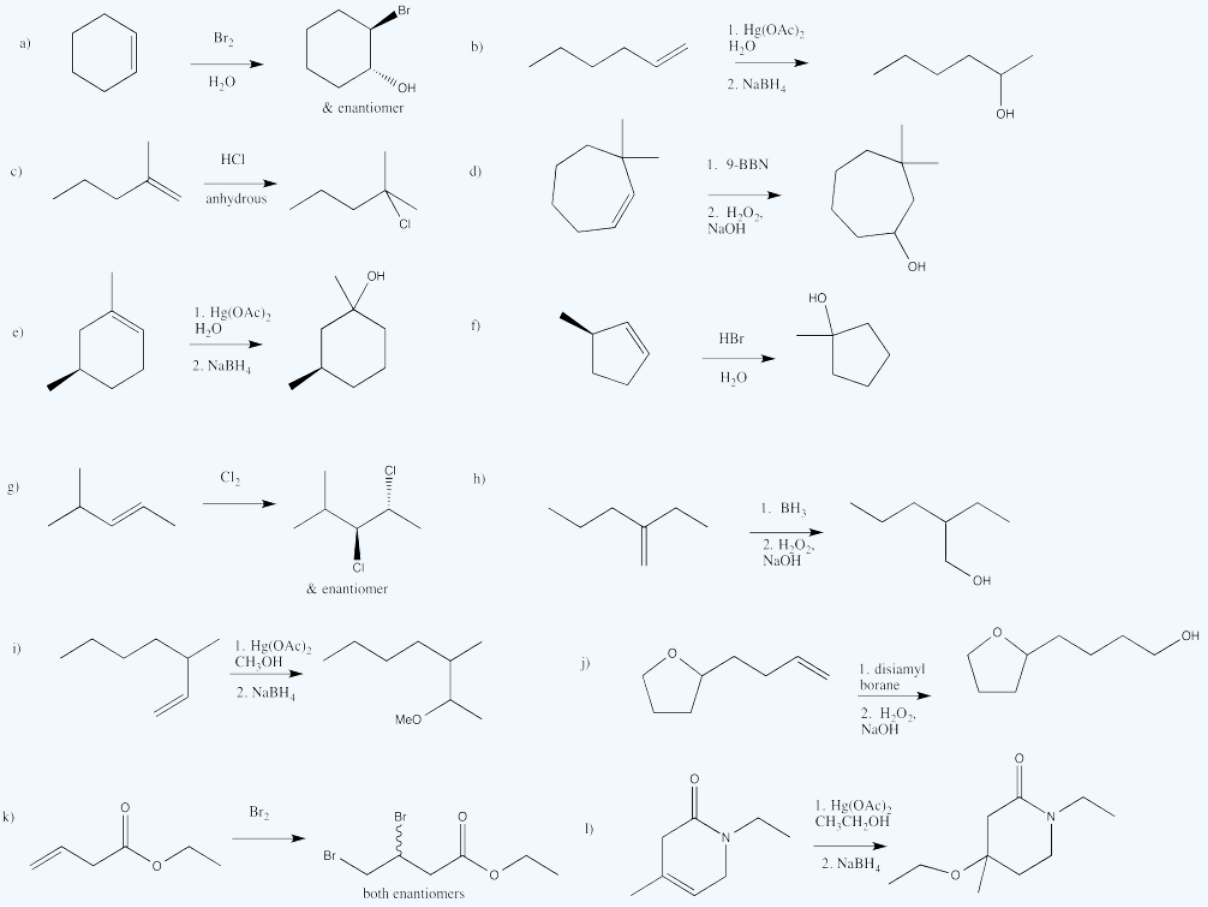


Exercise 6.7.7

Show products of the following reactions.

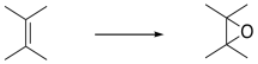


Answer

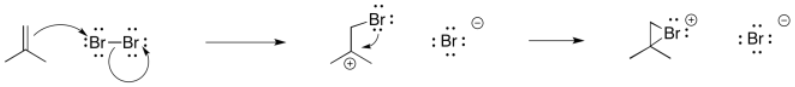


6.8: Epoxidation

Epoxidation is the addition of a single oxygen atom across a C=C double bond.

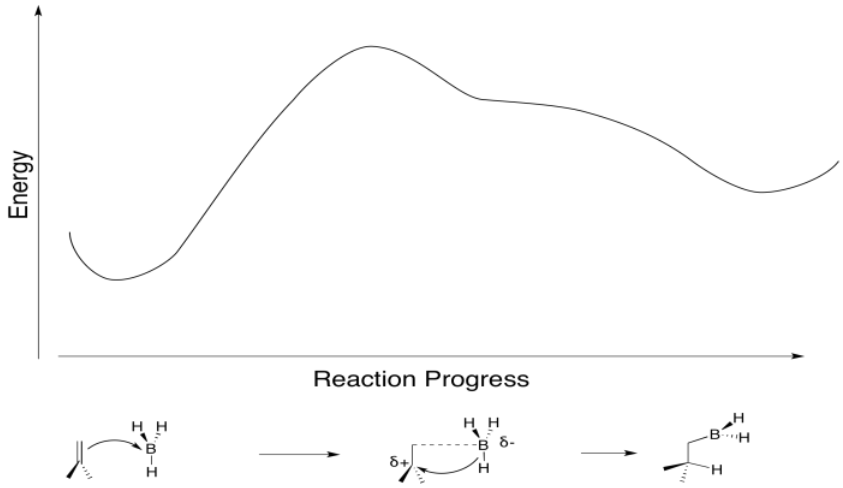


Earlier, we saw that alkenes can donate their pi electrons to electrophiles such as "Br^+". In the bromonium ion that results, a lone pair on the bromine can donate back to the incipient carbocation, leading to a more stable intermediate.

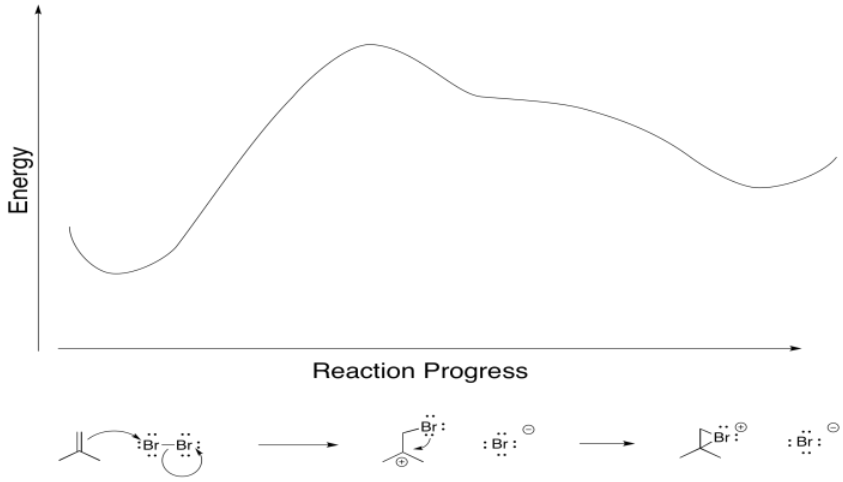


We have also seen that addition to alkenes can sometimes be concerted, happening all at once, rather than one step at a time. For example, in hydroboration, the boron and the hydrogen add to the double bond at the same time.

The boron is adding just slightly ahead of the hydrogen. The initial interaction is donation from the pi bond to the Lewis acidic boron. However, as soon as positive charge starts to build up on carbon, and negative charge starts to build up on boron, the hydride is immediately donated. Time is not allowed for the charged intermediate to fully form before proceeding.



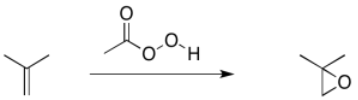
Really, that's what is happening to the bromine, too. As the alkene starts to donate its pi electrons to the bromine and begins to build up positive charge, the bromine's lone pair is drawn back to the alkene. As a result, the intermediate that we imagine with a full positive charge on carbon and no charge on bromine exists too fleetingly to be considered an intermediate at all. As soon as it begins to form, it is already turning into something else.



That sort of concerted addition happens with some other electrophiles, too. If an atom is electrophilic, but also has a lone pair to donate, that cyclic transition state can lead to the product in one step.

Alkene epoxidation is another example of this kind of reaction. An epoxidation is the transfer of an oxygen atom from a peroxy compound to an alkene. Peroxides contain O-O bonds, which are relatively weak and reactive.

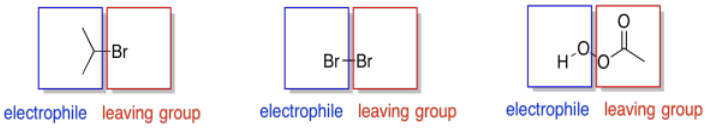
To simplify a little bit, just look at the reaction from the point of view of the alkene. It's just picking up an oxygen atom, because the peroxide had an extra one.



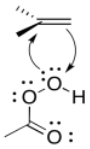
When the oxygen atom is transferred, it forms an epoxide (sometimes called an oxirane). It is a three-membered ring containing two carbons and an oxygen.

- Epoxidation results in transfer of an oxygen atom from a peroxide to an alkene.
- Peroxides are compounds containing weak O-O bonds.

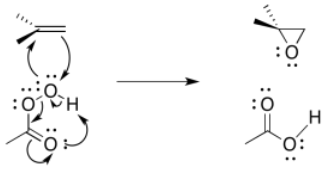
Like in a bromination, the electrophile is deceptive. It is an oxygen atom, which we more naturally think of as a nucleophile. However, just as Br_2 contains an atom attached to a good leaving group (Br^-), so do the kinds of oxygen compounds used in epoxidation. Most often, these are "peroxy acids", carboxylic acids containing an extra oxygen.



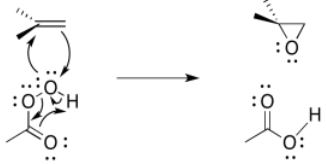
As in the bromination, as soon as the alkene begins donating to the electrophile, a lone pair can donate back, so that an unstable cation does not have to form.



The entire mechanism is believed to be concerted, based on a number of lines of experimental evidence. A number of things need to be accomplished; in addition to the oxygen donation, the leaving group must leave, and a proton must be transferred.



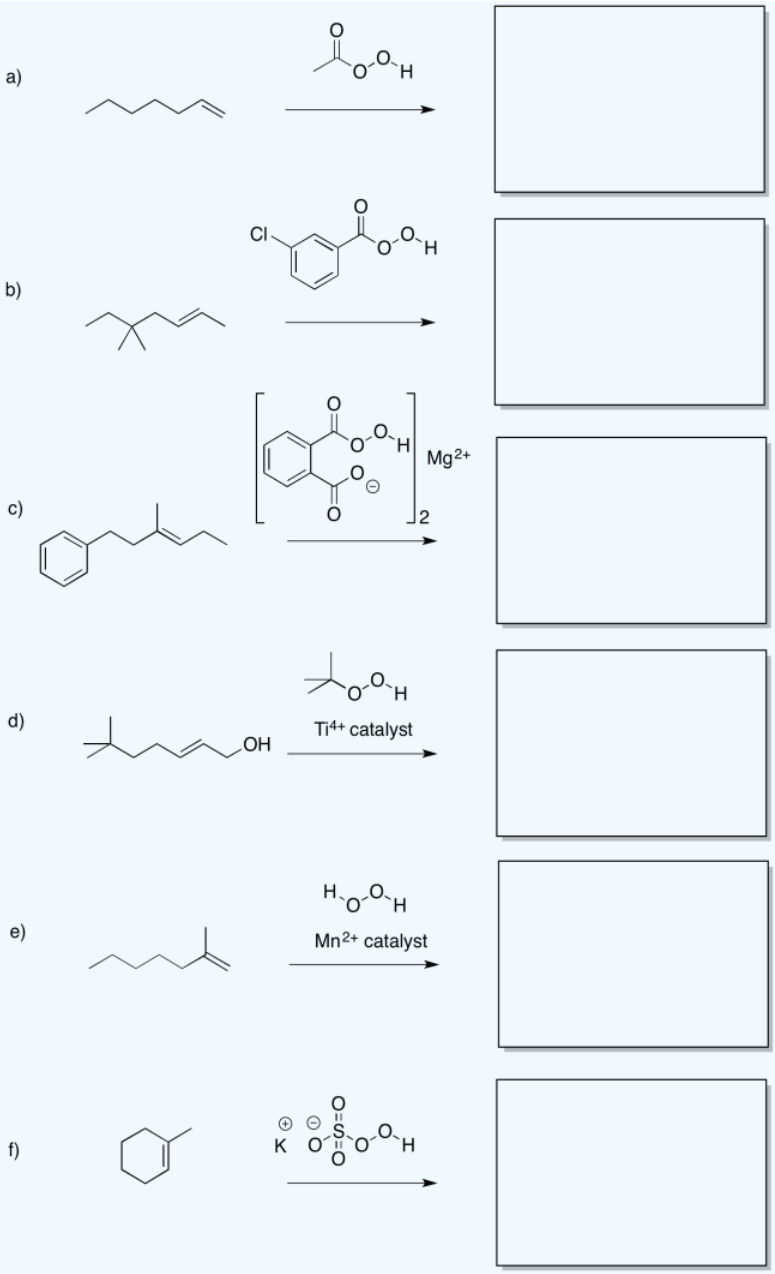
The reaction mechanism can be cleaned up slightly because it is thought to be an example of a pericyclic reaction. Pericylcic reactions frequently involving three pairs of electrons moving in a circle. Like the three pairs of electrons in a benzene ring, this structure is thought to be unusually stable.



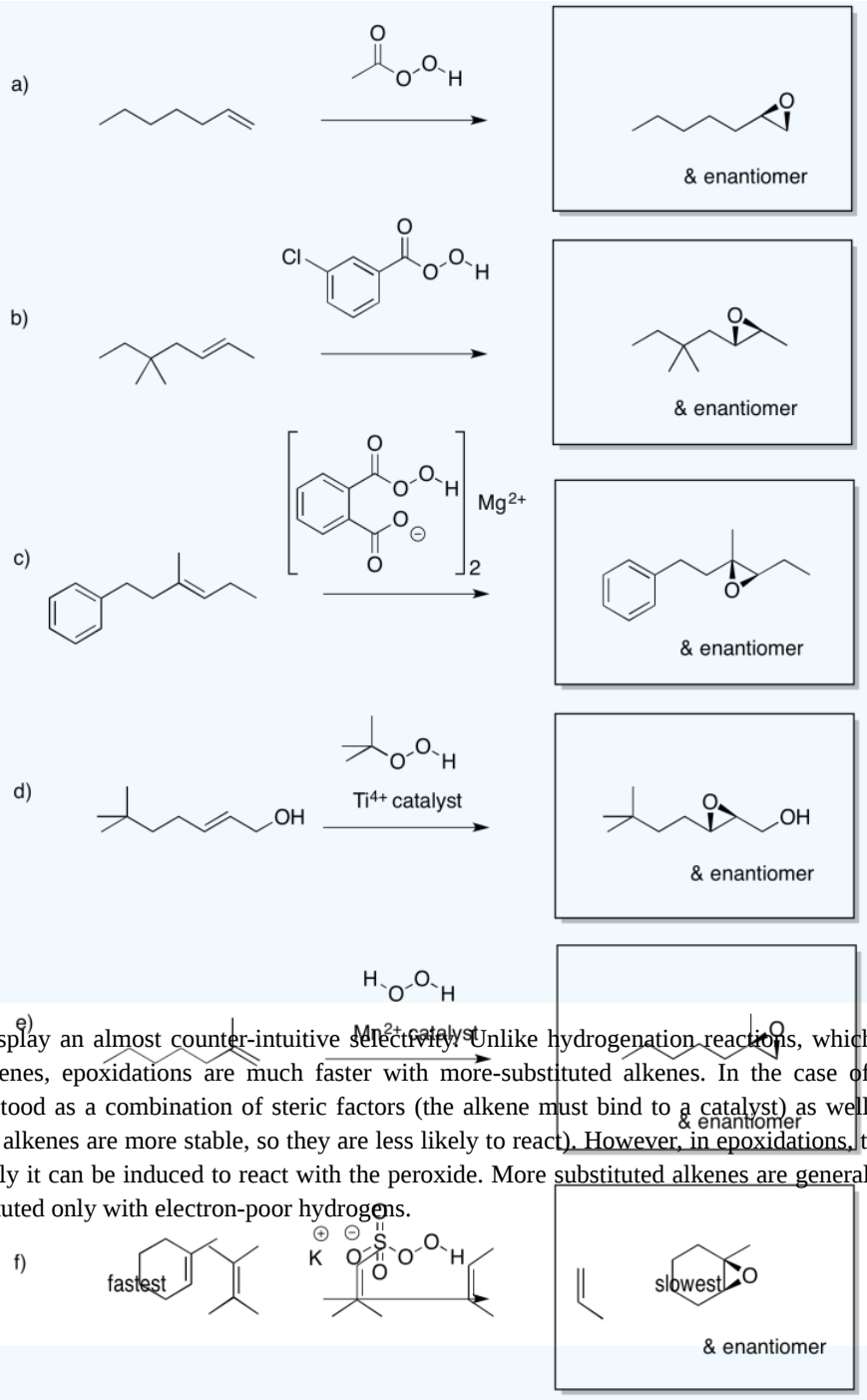
Apart from peroxy acids, many other peroxides can be involved in epoxidations, as well as some metal oxides. In some cases, the reaction is extremely slow, but works better in the presence of a catalyst.

Exercise 6.8.1

Predict the products of the following reactions.



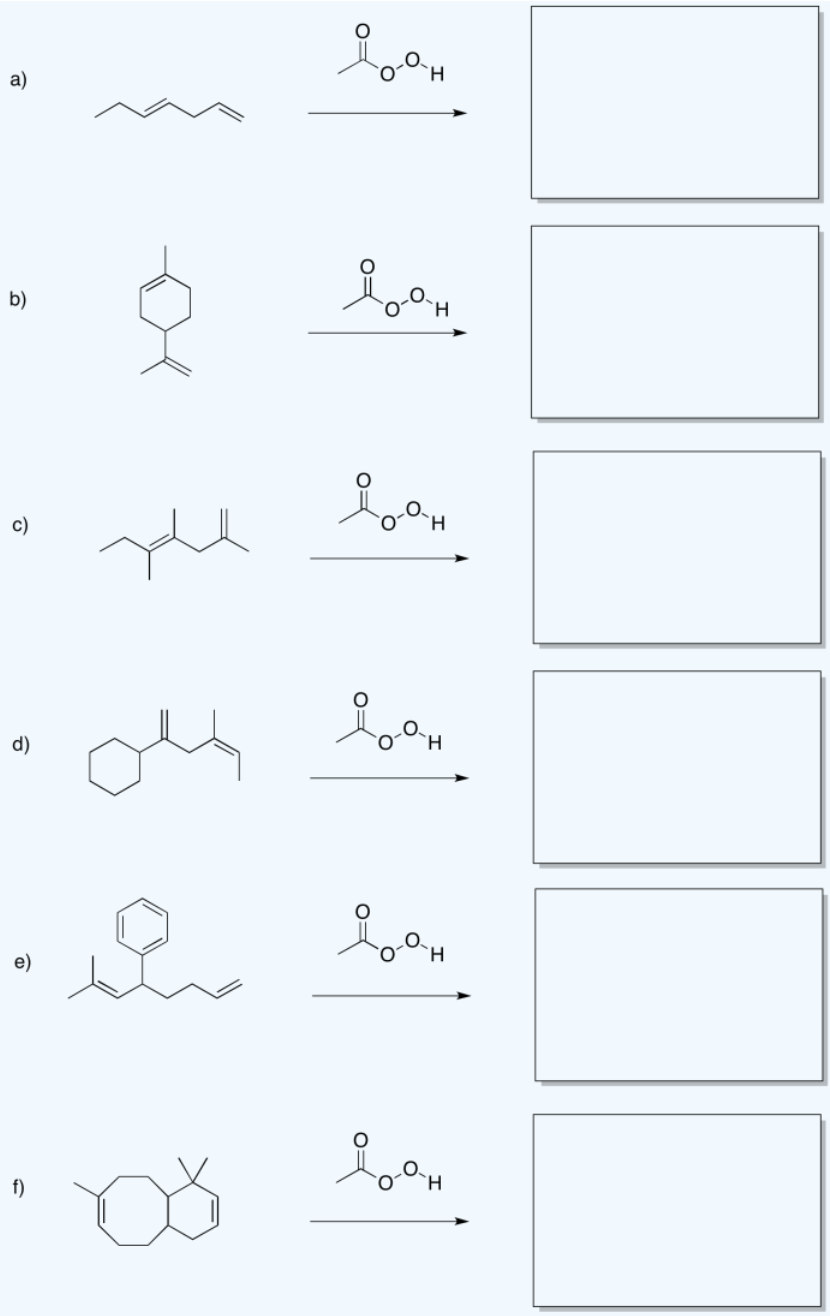
Answer



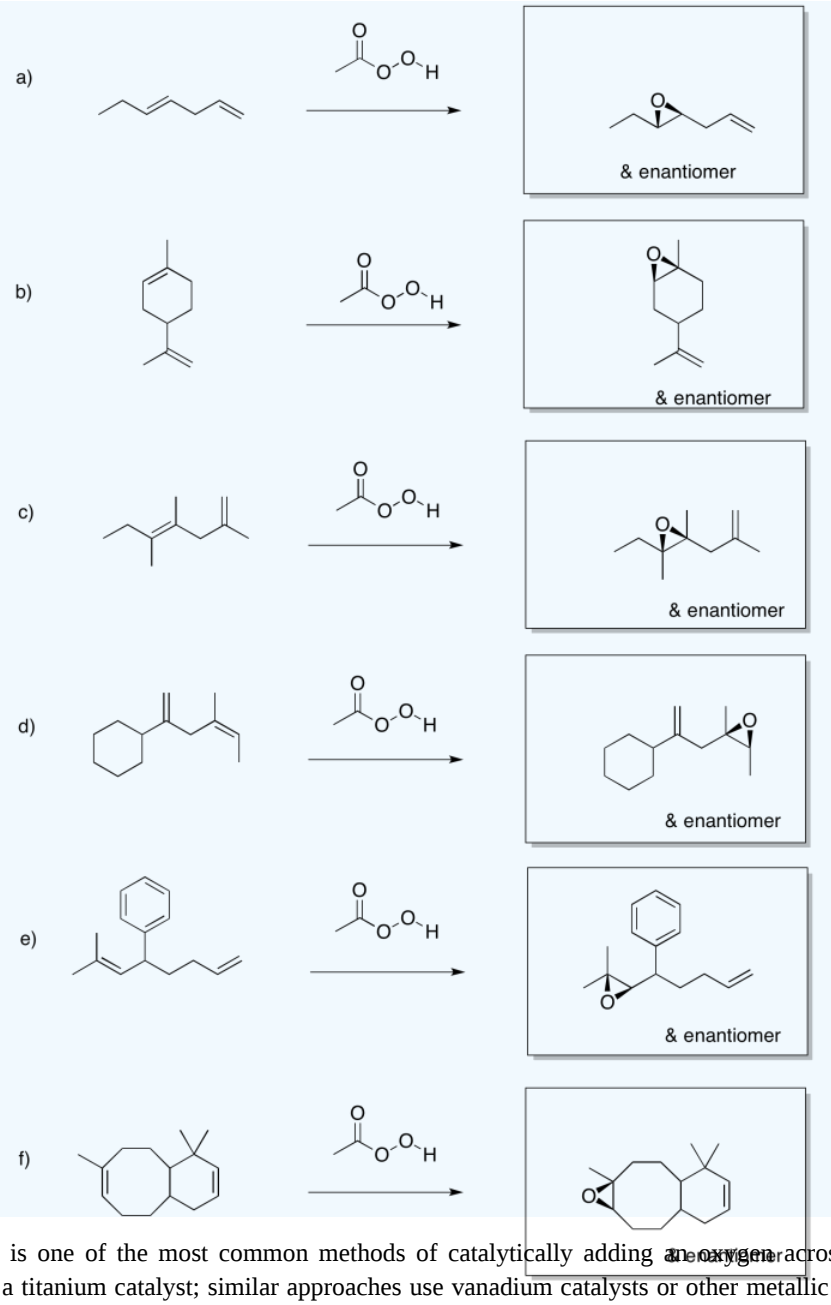
Epoxidation reactions display an almost counter-intuitive selectivity. Unlike hydrogenation reactions, which are generally easier with less-substituted alkenes, epoxidations are much faster with more-substituted alkenes. In the case of hydrogenations, the selectivity can be understood as a combination of steric factors (the alkene must bind to a catalyst) as well as thermodynamicic factors (more substituted alkenes are more stable, so they are less likely to react). However, in epoxidations, the more electron-rich the alkene, the more easily it can be induced to react with the peroxide. More substituted alkenes are generally more electron-rich than those that are substituted only with electron-poor hydrogens.

Exercise 6.8.2

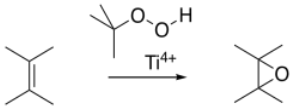
Predict the products of the following reactions.



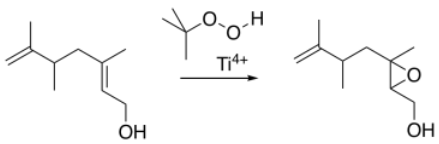
Answer



The Sharpless epoxidation is one of the most common methods of catalytically adding an oxygen across a double bond. The method generally employs a titanium catalyst; similar approaches use vanadium catalysts or other metallic species. As mentioned before, metal ions can sometimes accelerate epoxidations.

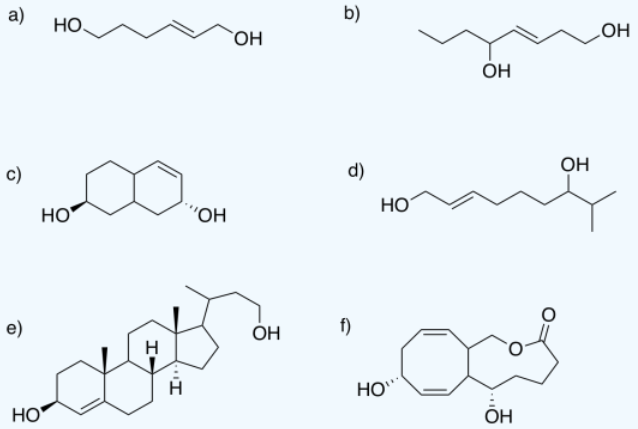


The Sharpless epoxidation is important partly because it selectively epoxidizes allylic alcohols: compounds containing a C=C-C-OH unit. That means that, in addition to being able to selectively epoxidize more-substituted double bonds in the presence of less-substituted double bonds, we can also select double bonds that are close to alcohols.

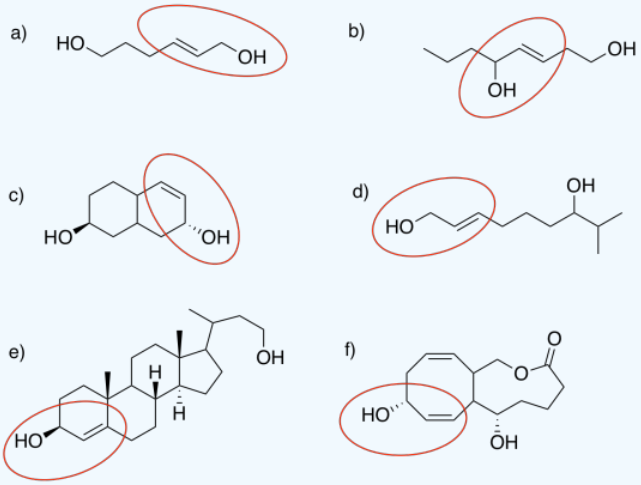


Exercise 6.8.3

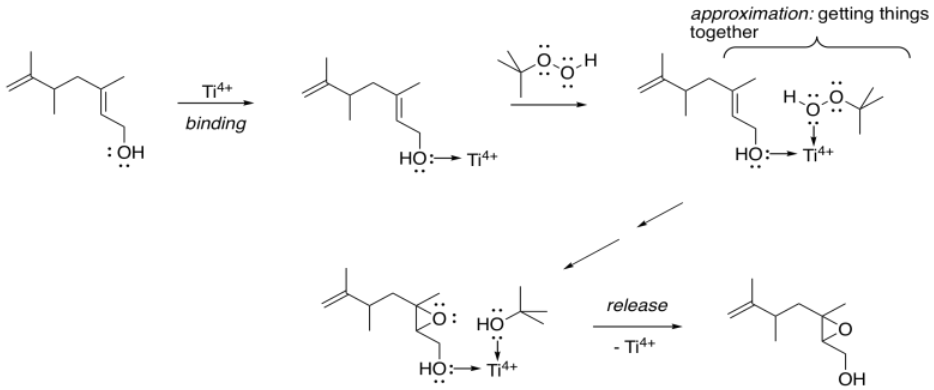
Circle the allylic alcohol in each of the following compounds.



Answer

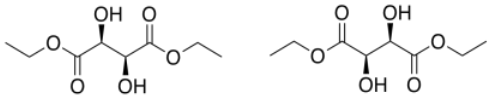


How does the metal catalysis selectively identify that position? Remember, one of the important strategies in enzyme catalysis is approximation: the act of bringing two things together. An alcohol is a potential lone pair donor, so it could become a ligand for a metal ion. Ti^{4+} and V^{4+} happen to be very oxophilic -- they bind well to oxygen -- and so they are particularly suited for this task.



In this scheme, we're not worrying about exactly how the titanium ion gets to peroxide to give up its extra oxygen to the alkene; that's complicated. However, the fact that both the allylic alcohol and the peroxide can bind to the titanium gets them closer together, and makes them more likely to react with each other.

That's only part of the story of the Sharpless epoxidation. The other reason this method is important is its stereoselectivity. To get stereoselectivity, a chiral ligand is added for the titanium. It's usually diethyl tartrate (DET) or diisopropyl tartrate (DIT). Tartrate is chiral; there is a D-(-)-enantiomer and a L-(+)-enantiomer. The D and L are common symbols used to designate enantiomers in sugars; they relate the structure back to the biochemical grandparents of all sugars, D-glyceraldehyde and L-glyceraldehyde. The (-) and (+) symbols refer to the characteristics of this particular compound in polarimetry; the (+) enantiomer rotates plane polarized light in a clockwise direction, whereas the (-) enantiomer rotates plane polarized light in a counter-clockwise direction.



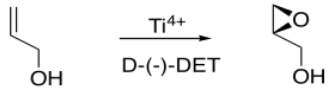
? Exercise 6.8.4

Assign stereochemical configurations (R and S) to the tartrates to confirm that they are enantiomers of each other.

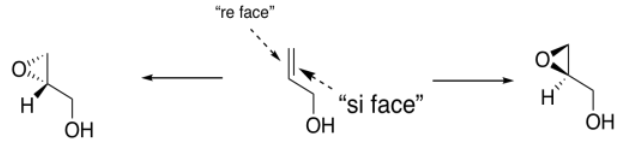
Answer

D-(-)-tartrate is the (*2S*,*3S*)-isomer. L-(+)-tartrate is the (*2R*,*3R*)-isomer.Each chiral center is configured opposite to the corresponding one in the other molecule, so the molecules are enantiomers.

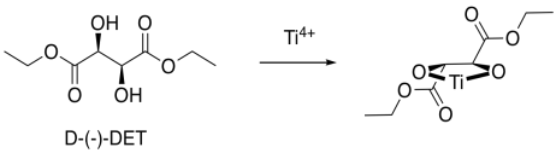
If the D-(-)-isomer is added, one possible enantiomer of the product is obtained. If the L-(+)-isomer is added, the other possible enantiomer is obtained.



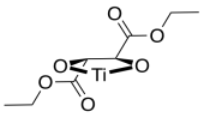
In general, we would get one enantiomer if the oxygen were added to one face of the alkene and the other enantiomer if the oxygen were added to the other face. In the drawing below, the face of the alkene towards us is sometimes called the "re face" (pronounced, ray face). The face of the alkene away from us is called the "si face" (see face). These words sound related to *R* and *S* configuration, and they sort of are like that, but they are used to describe two different faces of a flat molecule. Adding oxygen to the re face gives on enantiomer; addign oxygen to the si face gives another.

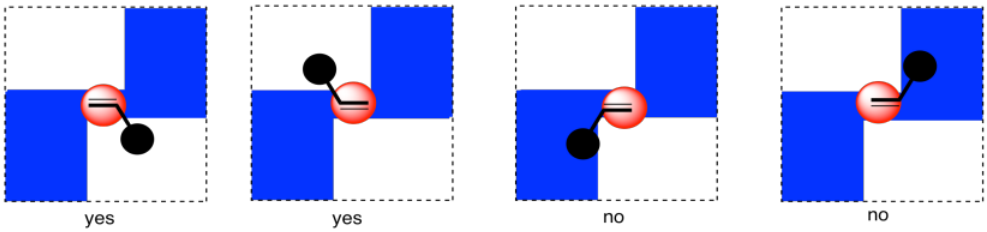


How does this preferred reactivity work? How does the metal manage to add the oxygen to one face but not to the other? Tartrates are oxygen-rich and so they bind very well to titanium. Remember, if we have a reaction site and we make it chiral, one enantiomer of the product is generally preferred. Enzymes are very compicated, chiral molecules, and they are good at producing one enantiomer of a product. By comparison, the titanium DET complex is a relatively simple chiral molecule, but it uses the same idea.



Now, it is really very difficult to look at these conditions and predict exactly which enantiomer would be formed in a reaction. However, we can look at a factor that might illustrate an underlying reason for the preference. In quadrant analysis, we look at the general shape formed by that bidentate tartrate ligand on the metal. In the pictures below, the red ball is the metal atom. The tartrate ligand extends up and to the right as it sits on the metal, and also down and to the left; it is cartooned in blue. As a result, if we think of the metal as sitting in the middle of a square, alternating corners of that square are filled, and the other corners are empty.





Imagine the alkene approaching that metal. The alkene will probably have a preferred orientation in which it will bind. Just for example, maybe it needs to bind with the double bond in the same plane as the ring formed by the titanium and the oxygens (horizontally in the picture). If it does that, it can reduce steric interactions with the ligand by binding one face of the alkene preferentially to the metal, keeping the biggest substituent on the alkane (the black ball) in a relatively open space. The alkene could also bind if rotated upside down compared to the first picture, but the same face would still be towards the titanium.

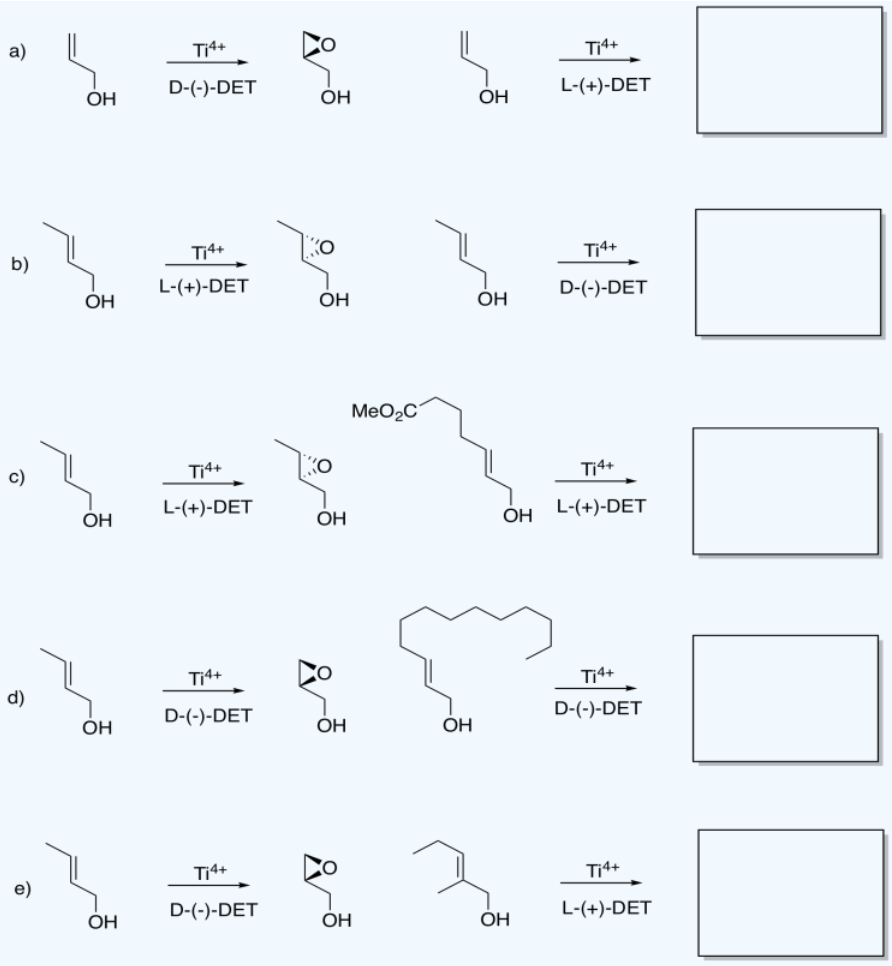
On the other hand, if the alkene tries to bind through the other face of the pi bond, the largest substituent would be in a more crowded space. That might be less favorable.

Overall, if the alkene has a preferred face that it will bind to the metal, then anything delivered from that metal will land on that face, and not the opposite one.

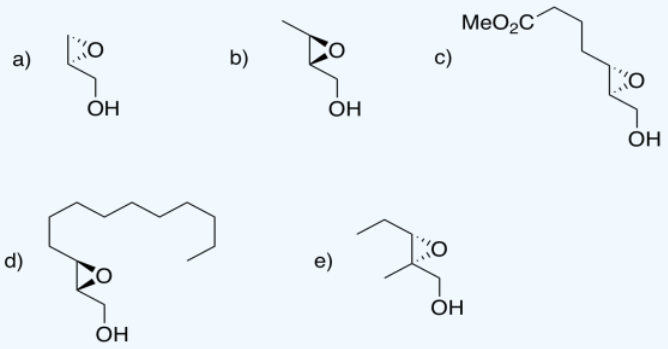
There are lots of variations on this model. Maybe it isn't steric interactions that influence how the alkene approaches the metal. Maybe it is some other factor, like hydrogen bonding, that pulls in the alkene oriented in one direction and not another. Nevertheless, although the details of a particular case make the outcome very difficult to predict, the general idea is a familiar one: a chiral molecule will fit preferentially one way with another molecule, because of its asymmetric shape.

? Exercise 6.8.5

Although you may not be able to predict off the top of your head which enantiomer is formed in a Sharpless epoxidation, given one result, you may be able to guess another. Given the reaction on the left, see what you can tell about the reaction on the right.



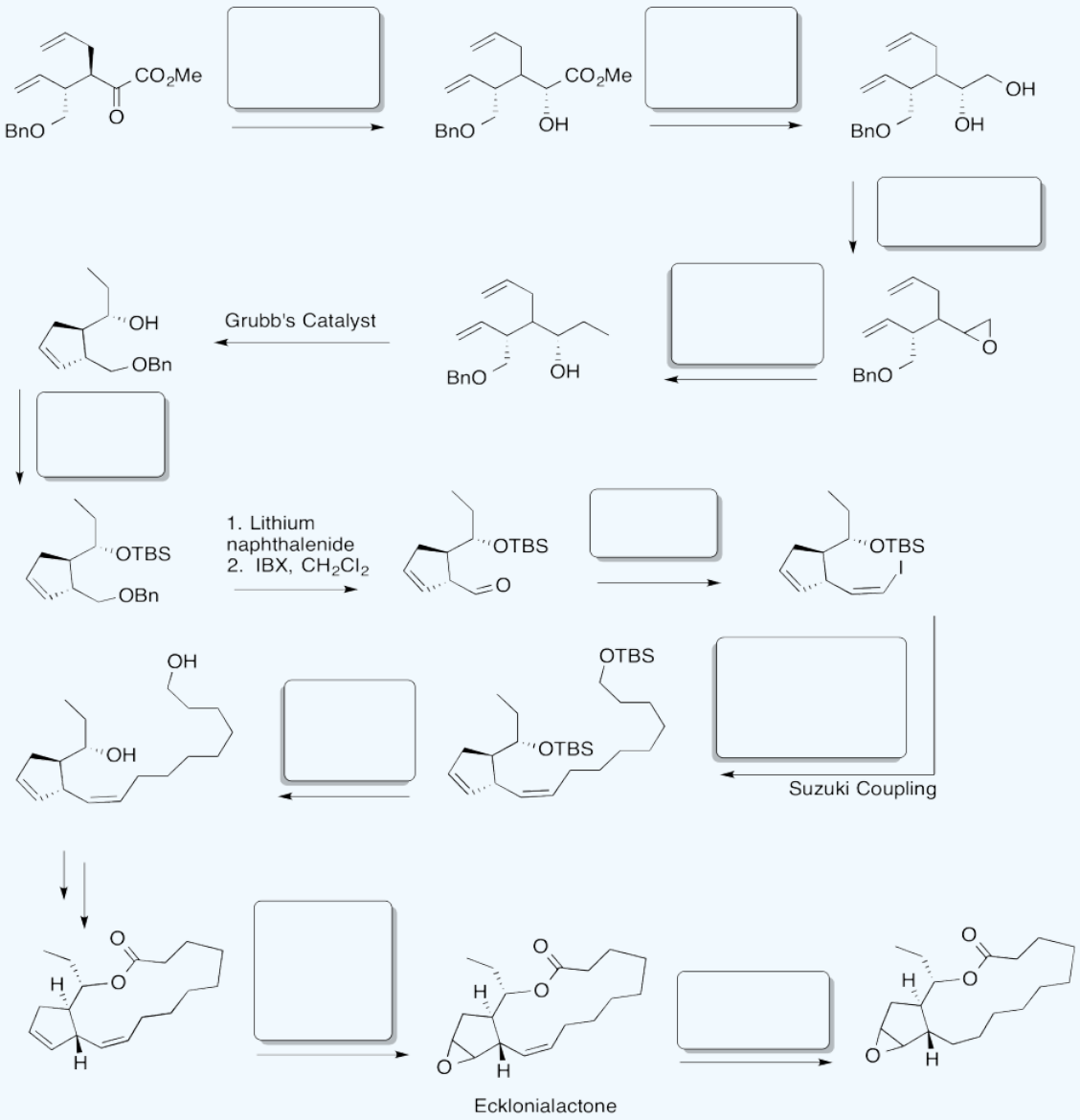
Answer



? Exercise 6.8.6

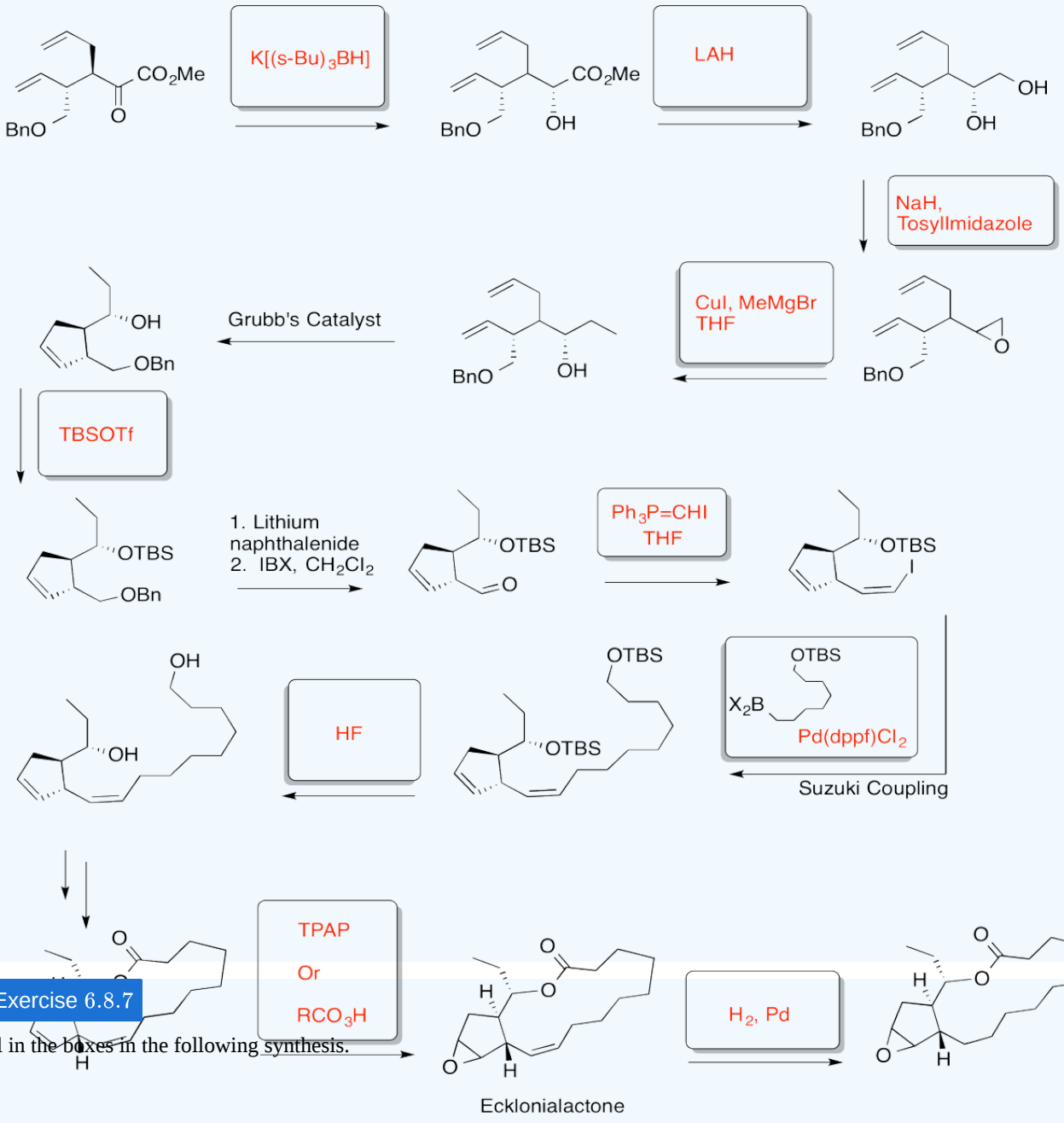
Fill in the boxes in the following synthesis.

Becker, Butt, Kiedrowski, Mieschler, Quentin and Hiersemann, Total Synthesis of (-)-Ecklonialactone B, *Org. Lett.*, **2013**, *15* (23), 5982-5985.



Answer

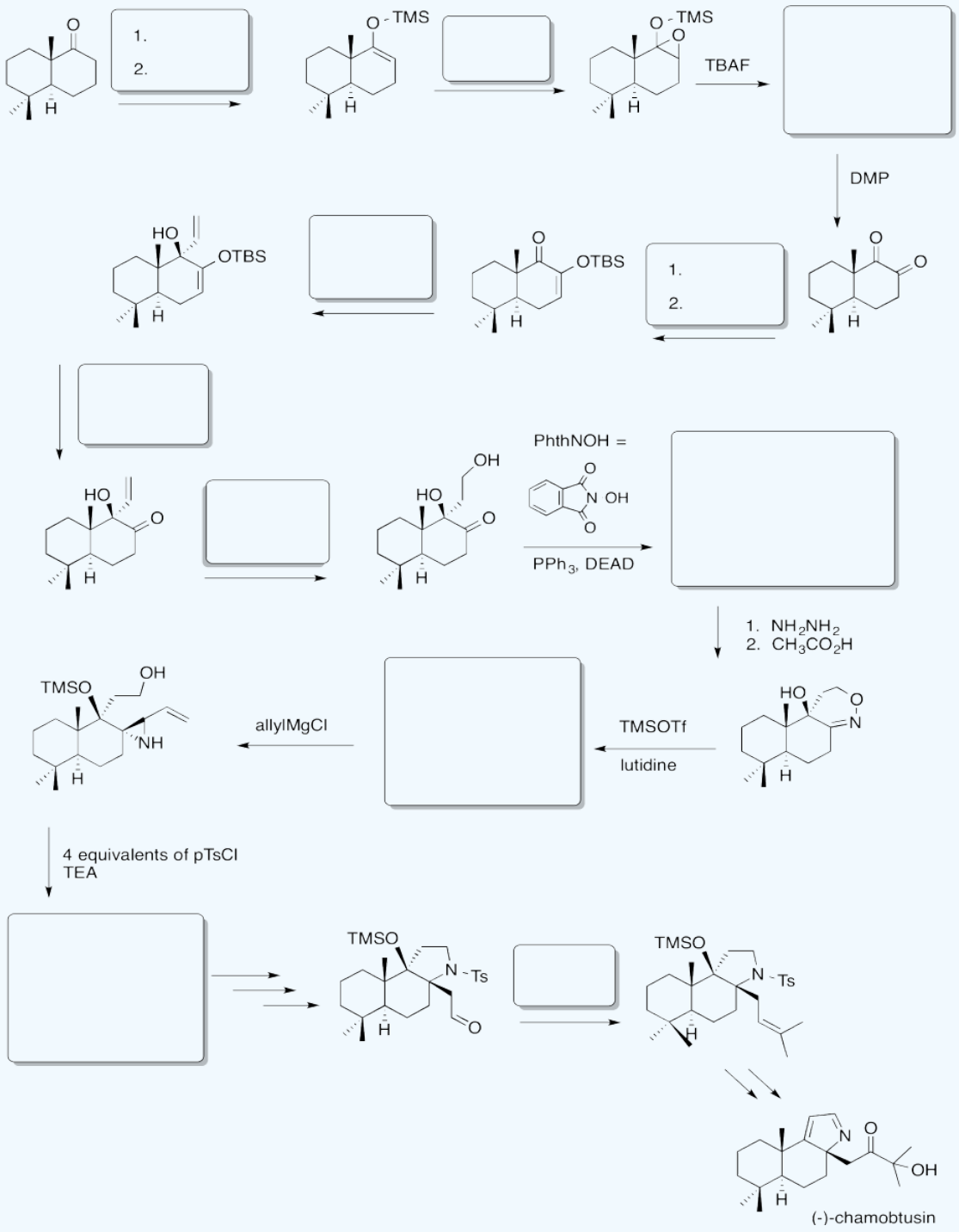
Becker, Butt, Kiedrowski, Mieschler, Quentin and Hiersemann, Total Synthesis of (-)-Ecklonialactone B, *Org. Lett.*, **2013**, *15* (23), 5982-5985.



? Exercise 6.8.7

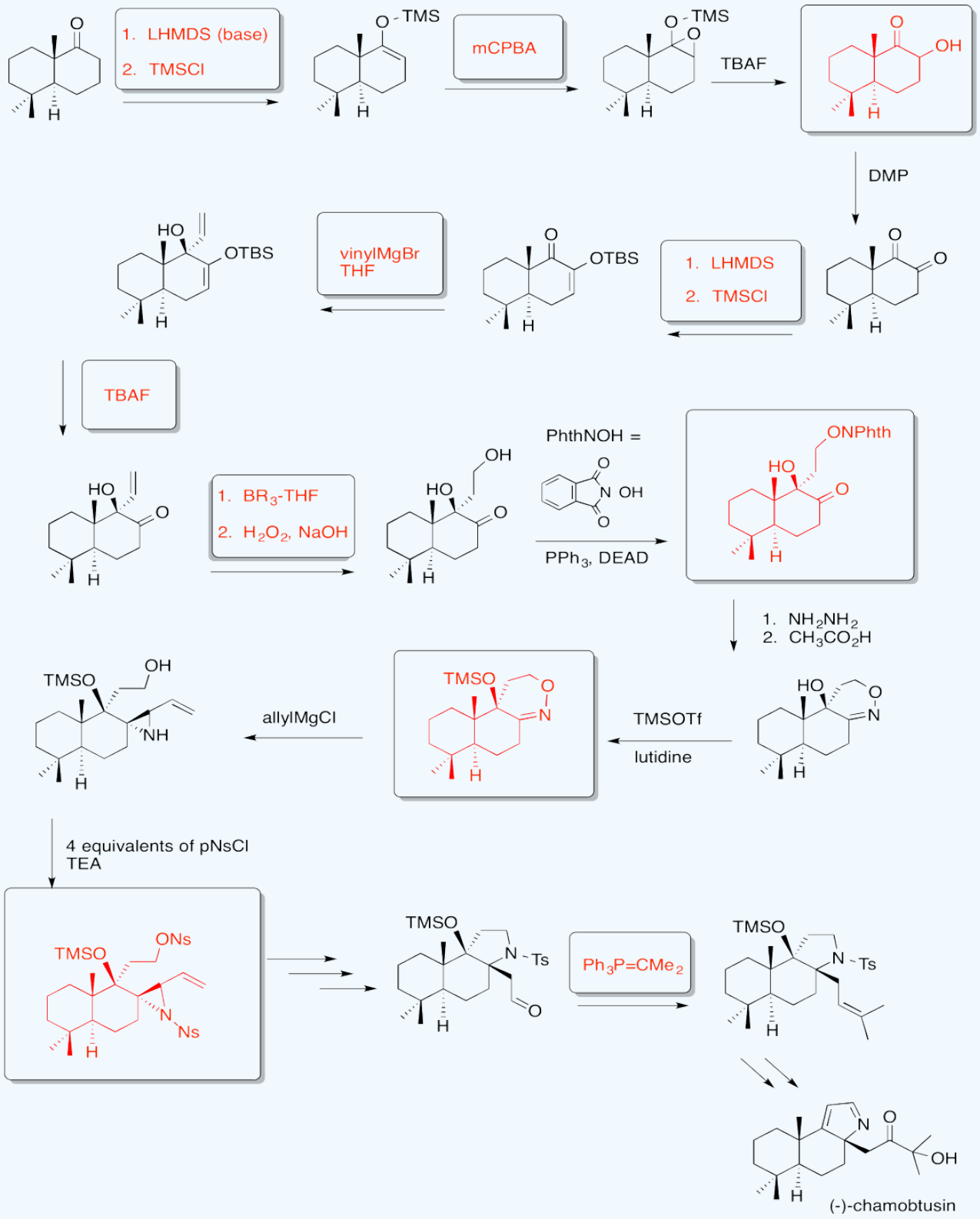
Fill in the boxes in the following synthesis.

Suzuki and Aoyagi, Total Synthesis of (-)-Chamobtusin A, *Org. Lett.*, **2012**, *14* (24), 6374-6376.



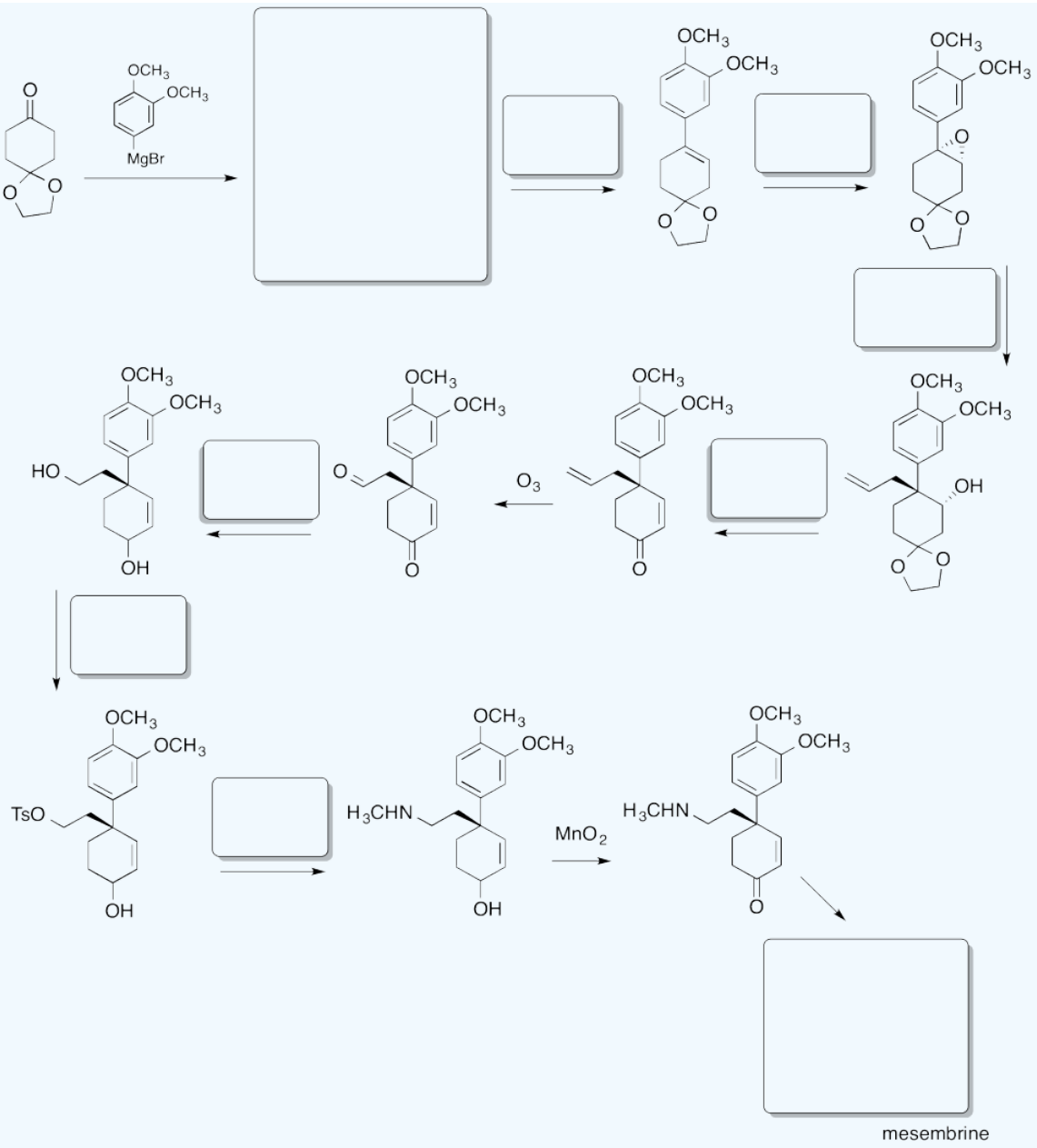
Answer

Suzuki and Aoyagi, Total Synthesis of (-)-Chamobtusin A, *Org. Lett.*, **2012**, *14* (24), 6374-6376.



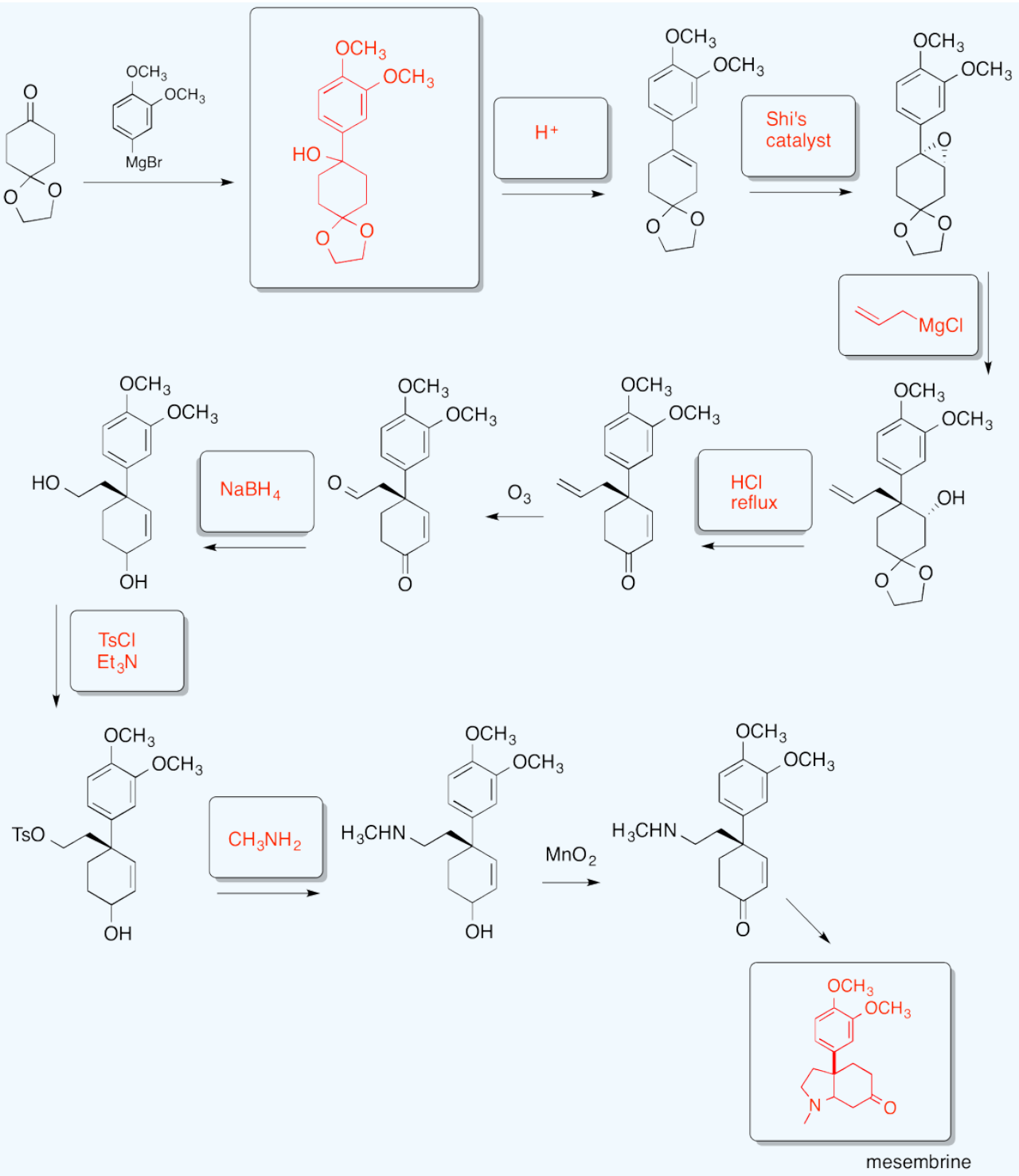
Exercise 6.8.8

Fill in the boxes in the following synthesis.



Taber and He, Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (-)-Mesembrine, *J. Org. Chem.*, **2005**, *70*, 7711-7714.

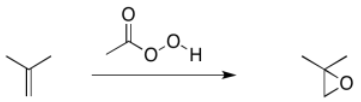
Answer



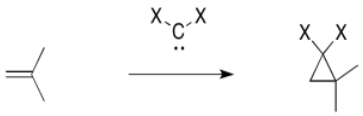
Taber and He, Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (-)-Mesembrine, *J. Org. Chem.*, **2005**, *70*, 7711-7714.

6.9: Cyclopropanation

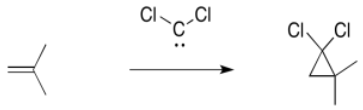
Earlier, we saw that alkenes can donate their pi electrons to oxygen electrophiles in peroxides. The result is transfer of an oxygen atom from the peroxide to the alkene. An epoxide or oxirane ring is formed.



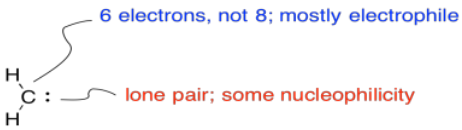
Another, related example is cyclopropanation of an alkene. In alkene cyclopropanation, an alkene is converted into a cyclopropane. A carbon atom is donated to the alkene.



A classic example is the addition of dichlorocarbene to an alkene.



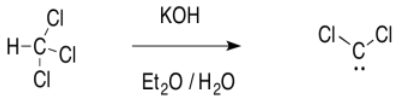
Carbenes are electrophiles because the carbon does not have an octet. The carbon has only two bonds and one lone pair. That's just three electrons, not eight.



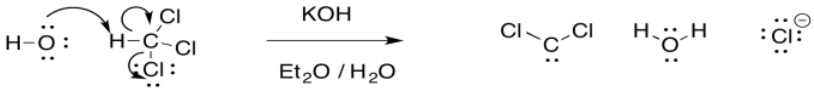
On the other hand, there is a lone pair. The carbene can be nucleophilic, too.

The reaction involves addition of the alkene to an electrophilic carbene. At the same time, that lone pair can donate back, so that a carbocation does not actually form.

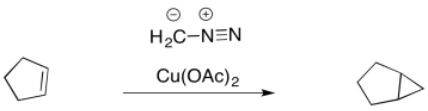
The carbene is sometimes formed through an unusual "alpha"-elimination in the presence of strong base. Strong bases are often alkyllithium reagents, such as CH_3Li, but KOH will work with some compounds.



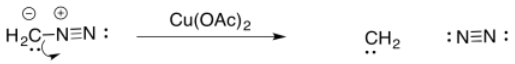
The reaction is unusual because a proton is abstracted from one carbon atom, and a leaving group departs from the same atom. It is much more common to see the leaving group depart from the next atom over, in a beta-elimination.



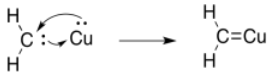
Carbenes are frequently formed from diazo compounds. These include diazomethane, CH_2N_2.



In diazo compounds, an N_2 group is hanging on by a thread. It can easily leave, resulting in a carbene. This reaction is often promoted by metal catalysts, such as copper (II) salts.



The carbene, CH_2, is even less stable than CCl_2. However, in the presence of metal salts, it can be stabilised as a metal carbene complex.

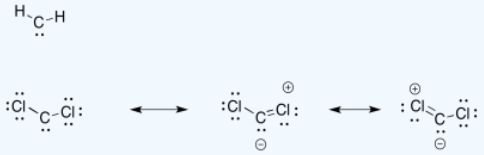


Exercise 6.9.1

Why is a carbene more stable with chlorine atoms attached?

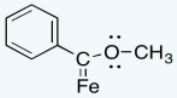
Answer

The chlorines can (weakly) share their electrons to fill the octet on carbon.



Exercise 6.9.2

Some metal carbene complexes, such as the one shown below, are particularly stable. Explain why.

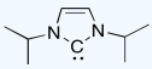


Answer

The oxygen can π-donate to help fill the octet on the carbon.

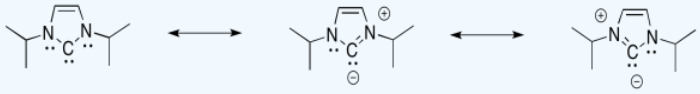
Exercise 6.9.3

Free carbenes, those not attached to a metal ion, are typically so unstable that they can only be generated briefly in solution before they react with a nucleophile, such as an alkene. Arduengo carbenes, such as the one below, are stable enough to be put in a bottle and stored in the refrigerator. Explain why.



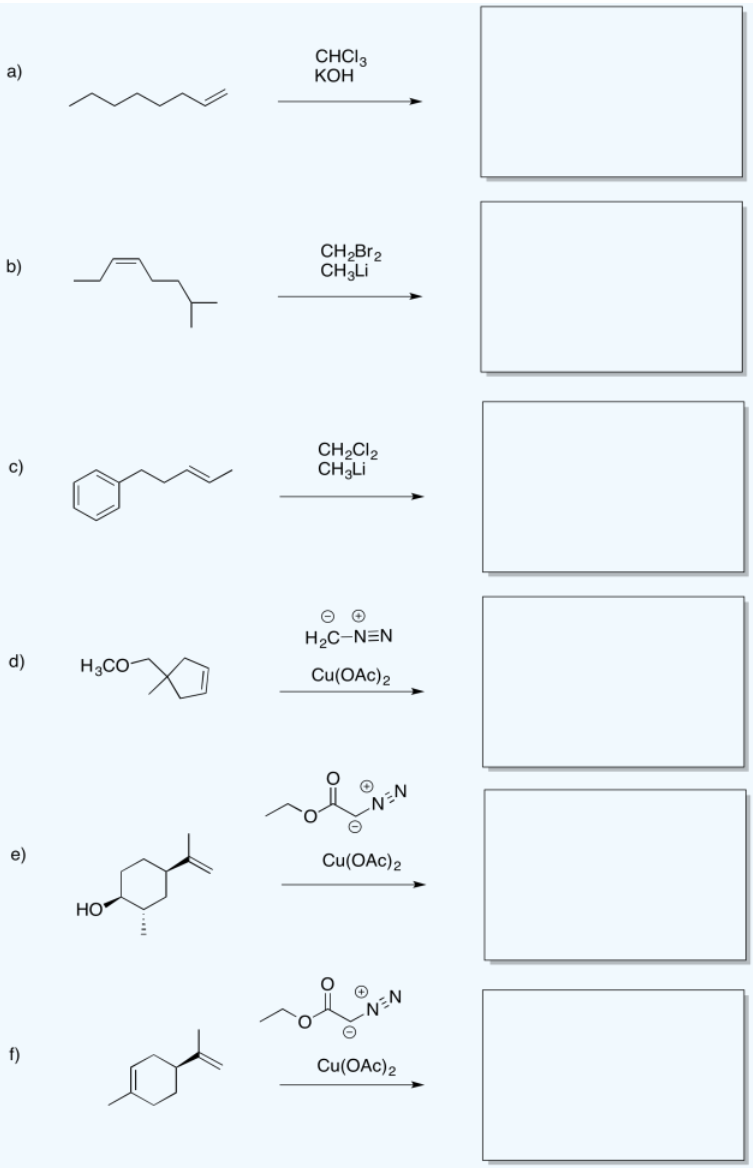
Answer

Not only can the nitrogens π-donate to help fill the octet on carbon, but this is an aromatic system. It is planar, cyclic, fully conjugated, with an odd number of electron pairs in the π-system.

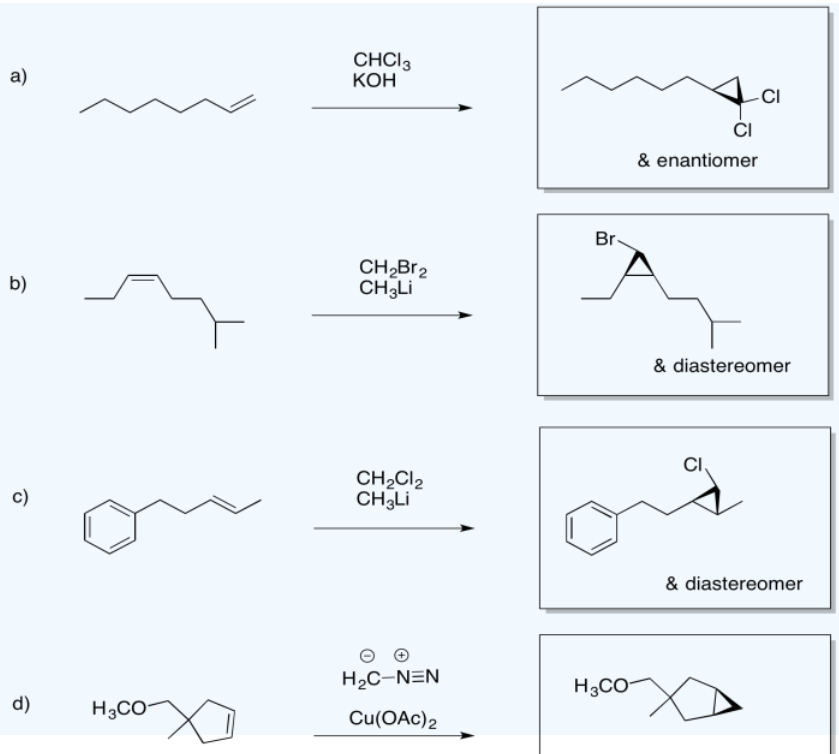


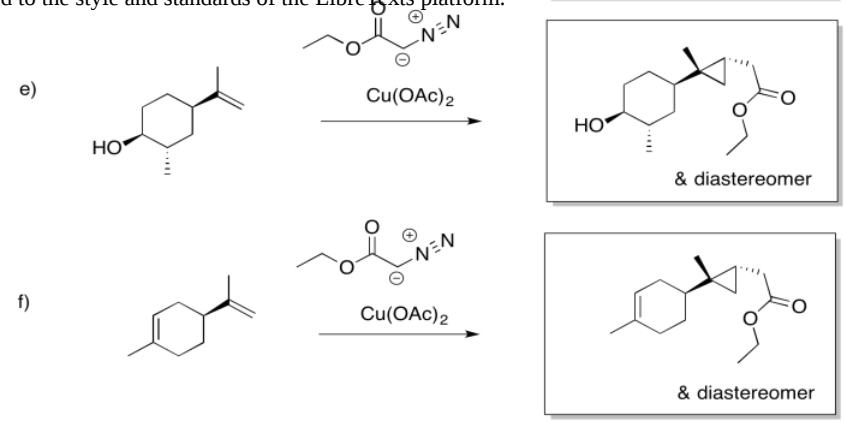
Exercise 6.9.4

Predict the products of the following reactions.



Answer

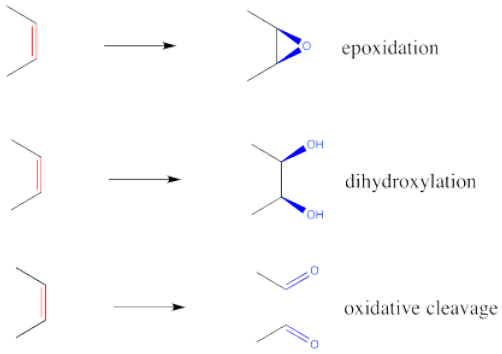




6.10: Alkene Oxidations

There are a number of other additions to alkenes that occur via concerted mechanisms. Alkene oxidations are among the most synthetically useful of these reactions because they are able to convert simple hydrocarbon starting materials into oxygen-containing compounds. The resulting heteroatomic functional groups may open up new avenues of synthetic utility or they may reflect aspects of a target natural product.

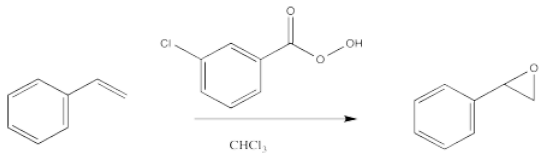
The three most common alkene oxidations are epoxidation, dihydroxylation and oxidative cleavage.



Epoxidation

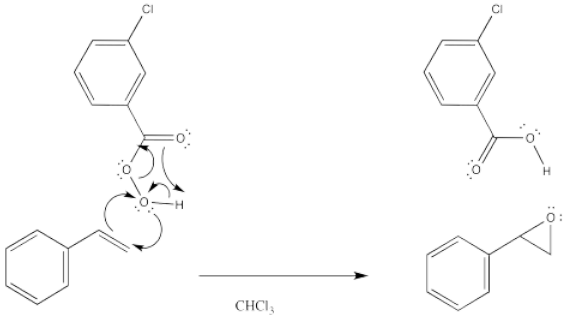
Epoxidation is a method for converting an alkene into an epoxide. The reagent required is always a peroxo species. A peroxo species looks very much like a normal oxygen-containing compound, but with an extra oxygen in it. Historically, the most common such reagent was *m*-chloroperbenzoic acid (*m*CPBA).

However, other reagents can also be used, such as hydrogen peroxide (H_2O_2) or potassium hydrogen persulfate ($KHSO_5$), marketed under the trade name Oxone. The latter methods are considered "greener" or more environmentally friendly, because the side poducts (water or sulfate, respectively) are pretty innocuous. These methods are generally slower and are often used with a catalyst. Catalysts used with hydrogen peroxide include Lewis acidic species such as sodium tungstate (Na_2WO_4) needed to activate the peroxide. A similar reaction using titanium (IV) and chiral ligands leads to an enantiomerically pure epoxide; this reaction is called "Sharpless epoxidation". With oxone, ketones are used as oxygen transfer catalysts in a method referred to as "Shi oxidation".



The electrophilicity of peroxy compounds continues a theme seen in halogens such as chlorine and bromine. When two oxygen atoms are connected to each other, one of the can act as an electrophile, just as when two halogens are connected together.

During the epoxidation, the peroxy compound simply delivers its extra oxygen to the double bond. The oxygen atom both accepts a pair of electrons from the double bond and donates an electron pair to the double bond at the same time.



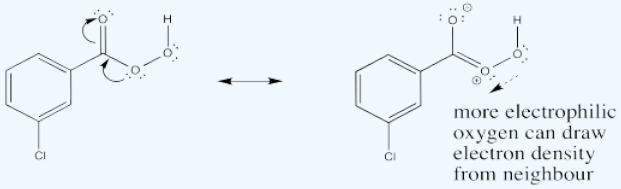
The reaction has something in common with pericyclic reactions. In pericyclic reactions and other reactions that take place under control of orbital symmetry, it is common to see six electrons circulating in a ring as a central feature of the mechanism. This picture is reminiscent of the aromatic structure of benzene. In fact, that aromatic stabilization is thought to play a role in stabilizing

the transition states of various reactions. In this case, the three electron pairs involve delivery of the oxygen, proton transfer and π donation to the carbonyl in mCPBA. However, a similar set of arrows might not be found in the reaction of hydrogen peroxide.

? Exercise 6.10.1

Show how the carbonyl in *m*CPBA may help activate the donor oxygen toward reaction with the alkene.

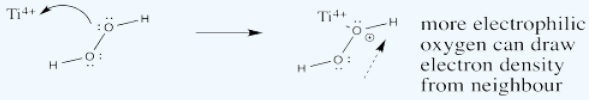
Answer



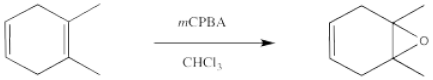
? Exercise 6.10.2

Show how a titanium (IV) ion may help activate the donor oxygen in hydrogen peroxide toward reaction with the alkene.

Answer

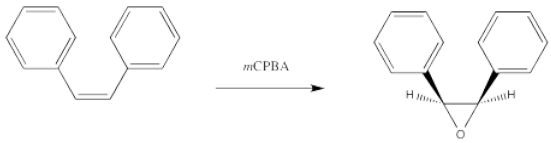


The electrophilic nature of the peroxy compound is seen in the selectivity of the epoxidation reaction. Alkenes that are more electron rich tend to react much more quickly than other ones. For example, more substituted alkenes, often regarded as being electron-rich, can be selectively epoxidized in the presence of other alkenes.



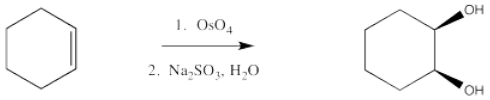
Furthermore, although enones can sometimes be epoxidized, the reaction is generally slower than with regular alkenes. Of course, the carbonyl attached to the alkene in an enone makes the alkene very electron-poor.

Part of the evidence for a concerted mechanism for epoxidation comes from the stereochemistry of the reaction. In general, if a *cis*-alkene is epoxidized, the two groups that were *cis* to each other in the alkene remain *cis* to each other in the epoxide. If the groups start out *trans* to each other, they remain *trans* in the epoxide. Just as in hydroboration, there is no opportunity for these stereochemical relationships to change.

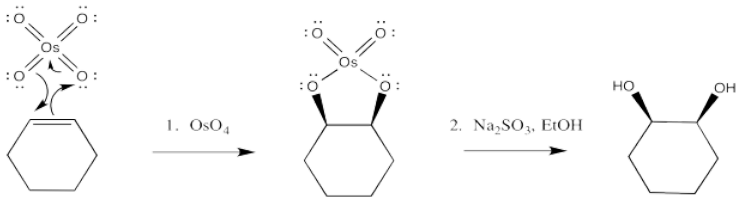


Dihydroxylation

Dihydroxylation is the addition of an OH group to both sides of an alkene. Typically, when reagents such as osmium tetroxide are used, the hydroxyl groups are added to the same face of the double bond. This reaction is therefore called a *syn*-dihydroxylation.

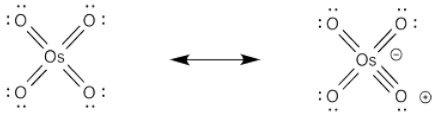


Osmate esters can be isolated from this reaction, resulting from the concerted addition of osmium tetroxide to the alkene. Once again, this step can be compared to a pericyclic reaction. However, the osmate ester is usually decomposed *in situ* through the addition of a "reducing agent" such as sodium sulfite.



Once again, the concerted nature of the reaction is seen in the stereochemistry of the product. The fact that both oxygens, which come from the osmium, are delivered to the same face of the alkene suggests that they are added at the same time.

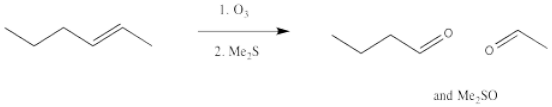
It isn't uncommon for oxygen atoms to form additional π bonds to transition metals such as osmium. In this case, we could think of the osmium as forming an 18 electron complex as a result. Whether or not that resonance contributor is an important representation of osmium tetroxide, it is a helpful device to think of how the oxygen might form an initial attraction to the alkene.



Because of osmium tetroxide's high cost, potent toxicity and alarming propensity to rapidly sublime, other reagents are preferred. It is quite common to still use a catalytic amount of osmium tetroxide, though, along with a co-oxidant. Co-oxidants can be things like Fe(III) salts and air, although hydrogen peroxide is often used.

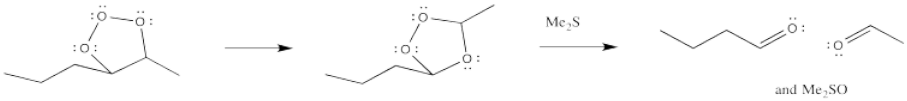
Oxidative Cleavage: Ozonolysis

Ozonolysis results in the complete cleavage of a double bond into two parts. The resulting fragments are each capped by an oxygen atom.



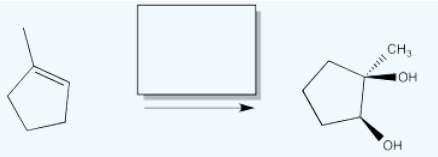
Once again, this reaction starts out with a concerted addition of the ozone to the alkene.

However, the first-formed adduct, termed a molozonide, quickly rearranges to a second product, termed an ozonide. Both of these species can be isolated. However, in practice this is rarely done because of the appalling tendency of molozonides and ozonides to explode unexpectedly. The ozonide is instead decomposed through the addition of a reducing agent, such as dimethylsulfide or zinc, leaving two oxygen-containing fragments behind.

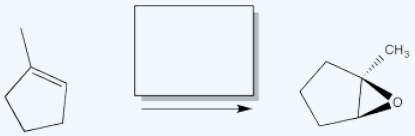


? Exercise 6.10.3

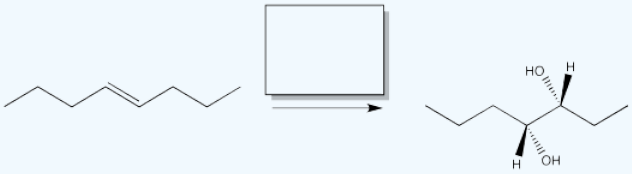
Fill in the reagents for the following alkene oxidations.



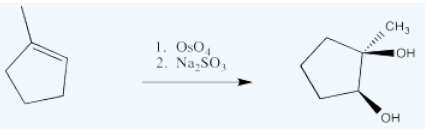
& enantiomer



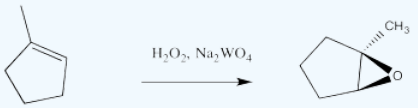
& enantiomer



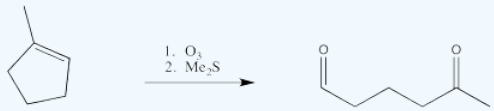
Answer

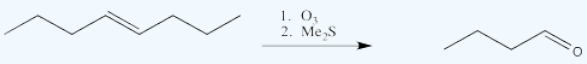


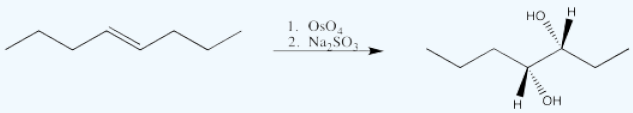
& enantiomer

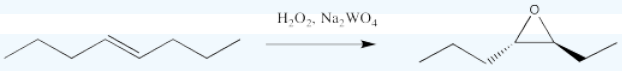


& enantiomer



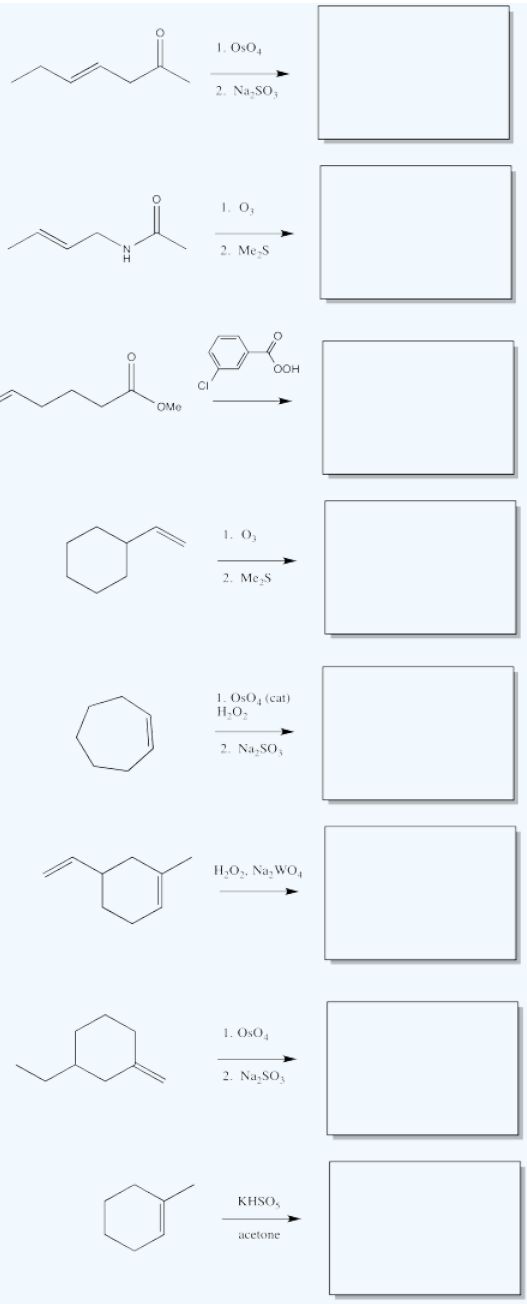




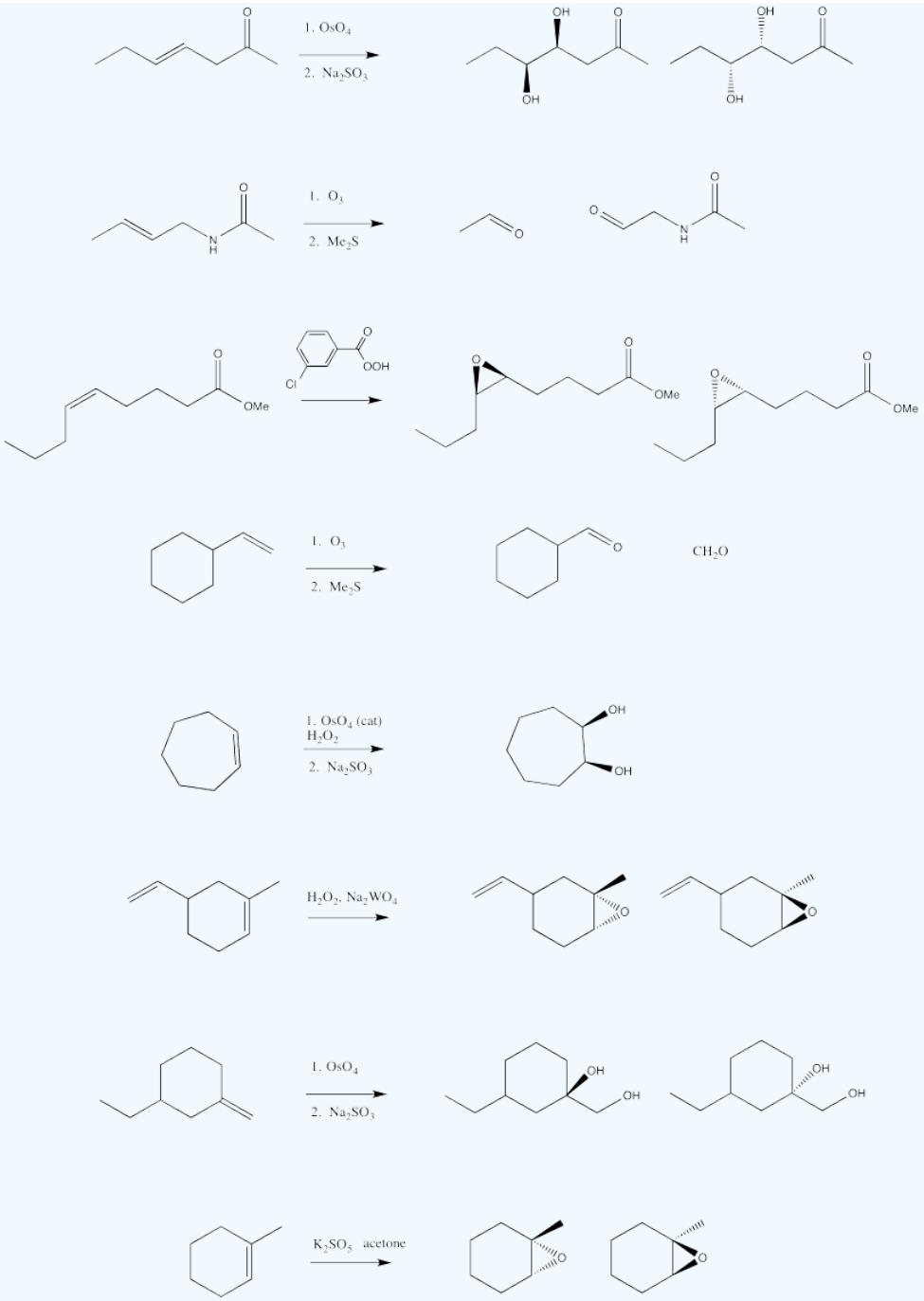


Exercise 6.10.4

Fill in the products of the following alkene oxidations.


1. OsO_4
2. Na_2SO_3
1. O_3
2. Me_2S
OMe
Cl
OOH
1. O_3
2. Me_2S
1. OsO_4 (cat)
H_2O_2
2. Na_2SO_3
H_2O_2, Na_2WO_4
1. OsO_4
2. Na_2SO_3
$KHSO_5$
acetone

Answer

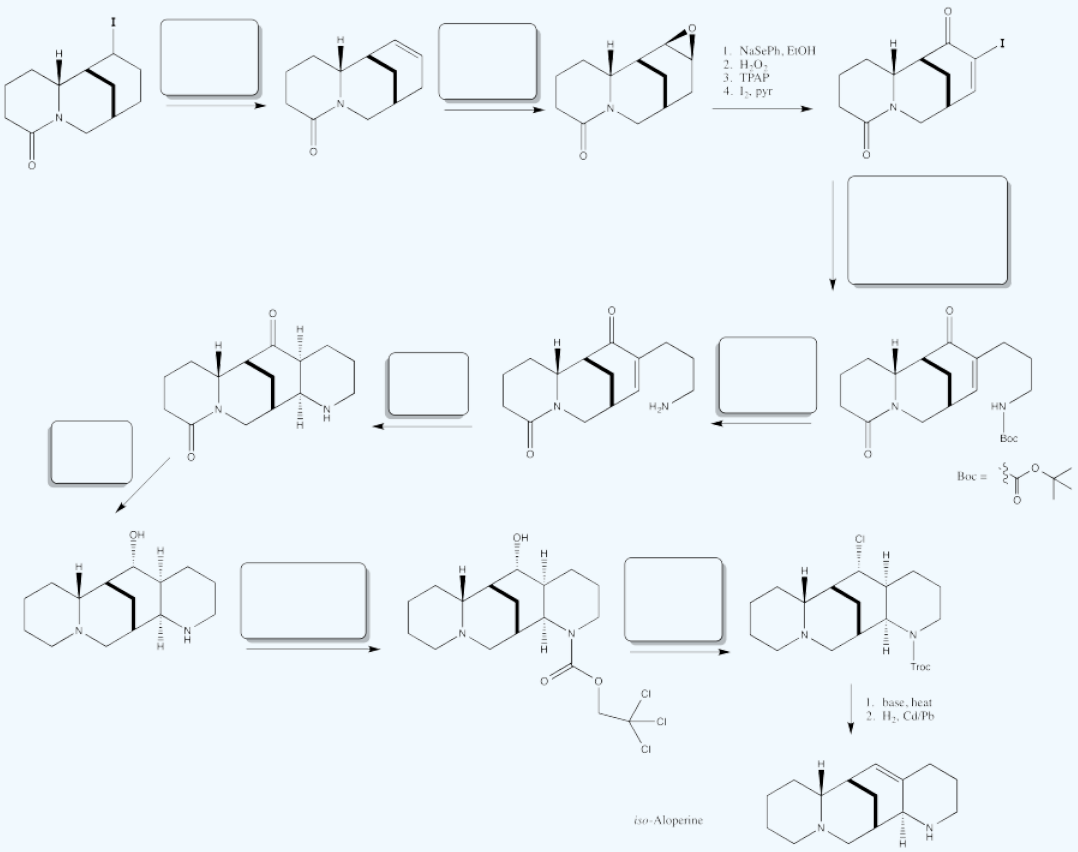


Exercise 6.10.5

Fill in the blanks in the following synthesis.

iso-Aloperine

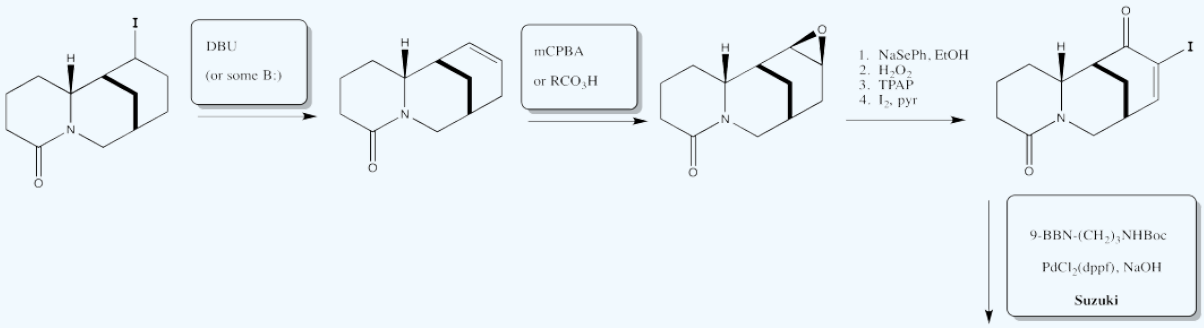
Brosius, Overman, *J. Org. Chem.* **1997**, *62*, 440.

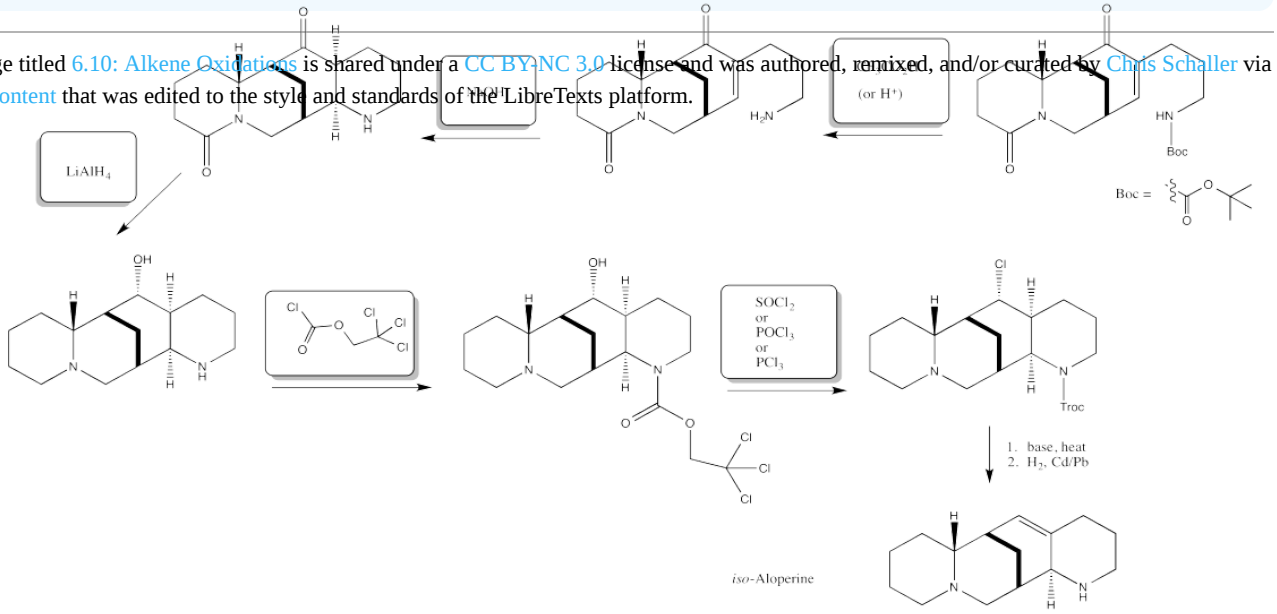


Answer

iso-Aloperine

Brosius, Overman, *J. Org. Chem.* **1997**, 62, 440.

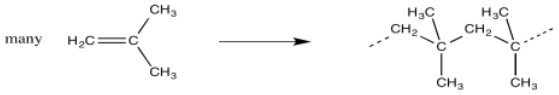




6.11: Alkene Polymerisation

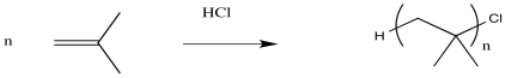
We have already seen the general concept that alkenes can be polymerised through a series of electrophilic additions. In this section, we will look at this topic in more depth.

In polymerisation, a large group of monomers are pulled together into a single, large molecule. In most cases, the monomers are connected in a row, forming a long chain. This process is sometimes called "enchainment".

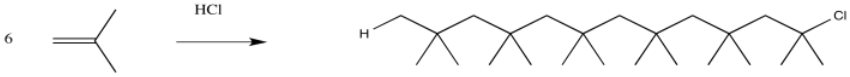


Looking at the structure of the polymer, we can see where the monomers have ended up. They are linked together along the chain in a repetitive fashion. When the monomers become enchained, they turn into the "repeat units" of the polymer.

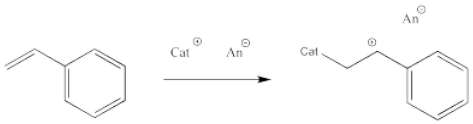
The structure of a polymer is often depicted using the repeat unit in parentheses. A subscript *n* stands for an integer, meaning that *n* of these repeat units are linked together in a chain.



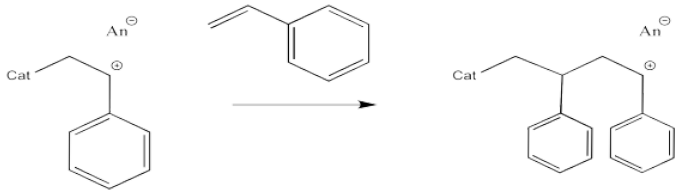
Of course, this chain has to end somewhere. At either end of the chain there will be something else attached; these parts of the polymer are called the "end groups". The identity of these groups can vary; it depends on how the polymer was made. One of these end groups gets incorporated into the polymer when the polymer starts growing; it was the "initiator". The other end group gets incorporated when the polymer stops growing, in a chain termination step. We'll see more about termination soon.



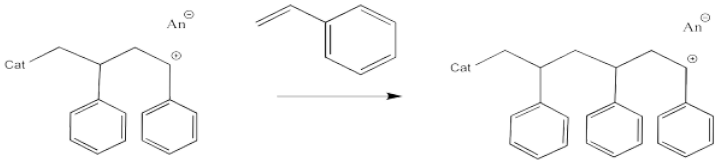
Let's take a look at how a macromolecule grows via cationic polymerisation. The initiator is a cation that reacts with the alkene. When it does so, it forms a new cation from the old alkene.



This sort of reaction is called a chain reaction because one reactive species reacted to form a new reactive species; this cycle then keeps repeating in a chain.



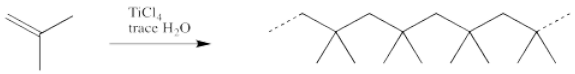
The process keeps repeating so that more and more monomers become enchained. In the picture below, only three monomers have been enchained so far, but you get the idea.



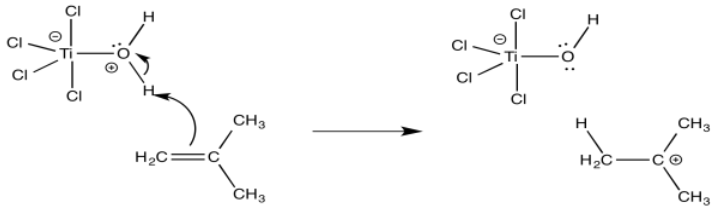
Most cationic polymerisations are initiated by a proton. That means that one of the end groups can be thought of as a proton. Alternatively, the first monomer can be thought of as having a slightly different structure than the repeat units that follow.

Perhaps the most obvious method of providing a proton is to add a protic acid, such as sulfuric acid (H_2SO_4) or trifluoromethanesulfonic acid (CF_3SO_3H or often abbreviated as TfOH). However, although that seems easy on paper, polymerisations typically don't work extremely well under those conditions. Usually, something goes wrong and the polymer stops growing when it is still a fairly short chain.

More commonly, commercial polymerisation involves a two-component mixture that together can initiate the reaction. One of these components is a Lewis acid. Some common Lewis acids used for this purpose include BF_3, $AlCl_3$, $TiCl_4$ or $SnCl_4$. The other component is usually a small amount of water or alcohol.

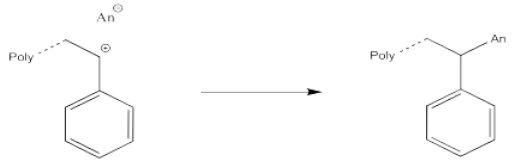


The role of the Lewis acid is to activate the water or alcohol, providing a proton to initiate a growing chain. Because the water or alcohol is the actual source of the proton, it is referred to as the initiator, whereas the Lewis acid is called a co-initiator.

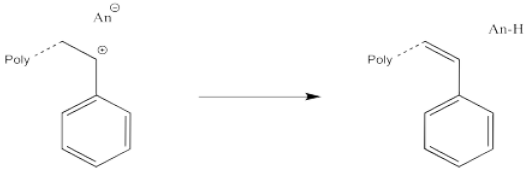


The other end group in the polymer is formed during termination, when something happens that stops the polymer from going. In termination, the cation in the growing chain would be lost. That event can happen through a few different pathways.

The simplest thing that might happen to stop chain growth is for some anion to connect irreversibly with the cation of the growing chain. That might happen accidentally while the polymerisation is supposed to be occurring. Alternatively, it might be forced to happen on purpose. When the polymer has grown for a long enough time to reach the desired weight, we might simply add some aqueous acid (like dilute HCl, for example). In that case, chloride ions might connect with the cations. Also, water molecules might connect with the cations, leaving the chains terminated by hydroxyl groups after loss of a proton.



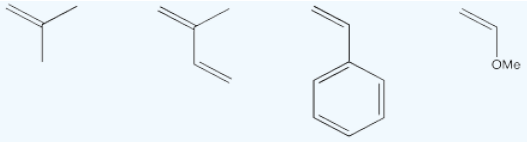
Other accidental pathways for chain termination include "chain transfer" events. In chain transfer, a proton is lost, either to an anion or to an alkene. This event results in an elimination reaction, forming an alkene at the end of the chain. However, the transferred proton results in initiation of a new growing chain. These accidental terminations can be a problem because some chains just get started growing after others have already been growing for a long time. As a result, the material obtained has a variety of chain lengths. The material has a high polydispersity, which means the properties of the material are difficult to control.



Termination events also raise the possibility that there will be some leftover monomer at the end of polymerisation. We wouldn't want these small molecules in the material we are making, because they would slowly leach out of the material over time. Sometimes, these monomers are removed via a precipitation step. The polymer mixture is simply dumped into a solvent in which the monomers will dissolve but the polymer will not. The solvent is then poured off, taking the monomers with it, leaving behind a purified polymer.

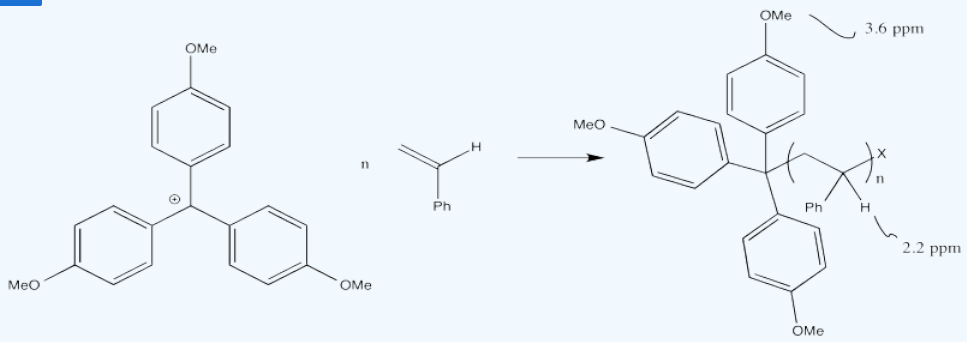
? Exercise 6.11.1

The following monomers are readily polymerised via cationic polymerisation. Show why, using drawings of the intermediates invlved in the reaction in each case.



isobutylene isoprene styrene methyl vinyl ether

? Exercise 6.11.2



6.12: Alkene Polymerisation- Living Cationic Methods

The trouble with reactive intermediates such as cations is that they are so reactive. Sometimes, cations do unexpected things. For example, we have already seen how they frequently undergo 1,2-hydride shifts. They can undergo nucleophilic addition, but they may undergo elimination instead. Sometimes, there may be competition between different nucleophiles racing to combine with the cation; you may end up with a mixture of products.

In other words, all kinds of things could go wrong during a cationic polymerisation.

What are the consequences of a polymerisation gone bad? The biggest problem is that the polydispersity gets too high. The polymer chains obtained in the reaction are not uniform in size; there are some much, much longer chains as well as some much, much shorter chains.

Remember, the polydispersity is an important component of how we think about the size of polymer chains. Because polymers are a collection of molecules formed through tandem growth of chains -- lots of chains growing at the same time -- we will always have a range of chain lengths. The polydispersity tells us how broad is that distribution. If the polydispersity is too high, it means there is too great a range of chain lengths (and molecular weights) in the material. Because the physical properties of polymers depend in part on the chain length, when the polydispersity gets too high, we have less and less control over the properties of the material. It might not perform the way we want it to perform.

Why do these unexpected reactions of cations lead to a wider range of molecular weights? It's because they often stop a chain from growing. We call these reactions "random termination events".

As a result of random termination events, some chains stop growing when they are still too short. Other chains keep growing and gobble up the rest of the monomer. There is extra monomer left over, because some chains didn't use theirs, so the chains that keep growing get extra long. There is a very wide range of chain lengths.

A secondary symptom of this problem is that the measured molecular weight of the polymer is sometimes *higher* than expected. That doesn't make any sense at first; if the chains stop growing, how can the molecular weight be higher than we thought it would? Wouldn't it be lower?

Well, sometimes that's true. If *all* of the chains were to stop growing early, then the molecular weight wouldn't reach our expectations, and there would be a lot of monomer left over. However, we're talking about *random* termination. Some chains stop growing. Others don't.

Remember that at the end of a polymerization, the polymer is usually precipitated. Any leftover monomers stay dissolved and are decanted off. At the same time, many of the very short chains also stay dissolved, and they are lost, too. We are left with the bigger chains, and the average weight of the chains has shifted higher. In addition, there are physical methods for measuring the size of polymers that are more strongly influenced by the bigger molecules, and that fact may artificially inflate our estimate of molecular weight.

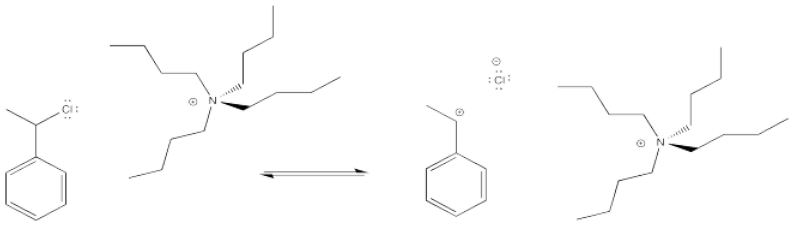
In contrast to this scenario, a "living polymerisation" is a process in which the polymer chains keep growing uniformly and the molecular weight agrees closely with expectations. Furthermore, after a living polymerization has finished, you can add more monomer and the chains will start growing again. The growing chains don't die out and stop growing. When they run out of monomer, they remain "dormant" (it's like they are just sleeping) until more monomer is available.

A key strategy for living polymerisation is to limit the number of reactive species at a given time. The fewer reactive species there are, the fewer random termination events will occur.

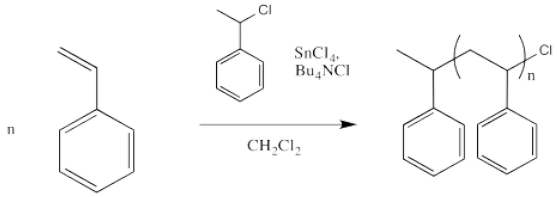
That scenario might seem to pose a different problem: if there are fewer reactive species, then there are fewer growing chains. If there are fewer growing chains, won't the polymerisation be much slower? Yes, it will be slower. We are looking for an optimum point at which polymerisation proceeds at a reasonable rate but the termination rate is very low.

However, there is a way to keep the number of reactive species low, but still have lots of growing chains, or at least potentially growing chains. We just exploit an equilibrium in which chains spend part of their time actually growing and part of their time dormant.

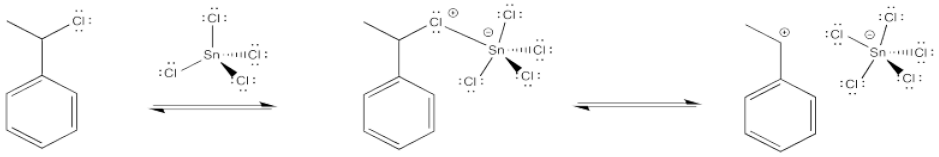
The idea is to have an anion that can cap the cation, so that we have an alkyl halide rather than a cation. In a very simple case, we might think about adding some halide salts to the polymerisation reaction. The halide anions might bind reversibly to the cationic intermediate, sending it into a dormant phase. Occasionally, the halide would dissociate again, and the polymer would grow again.



However, the halide must leave once in a while, producing a cation that can undergo polymerisation. In order to help that halide leave, a Lewis acid might be employed. The following example shows tin(IV) chloride added to the mix.



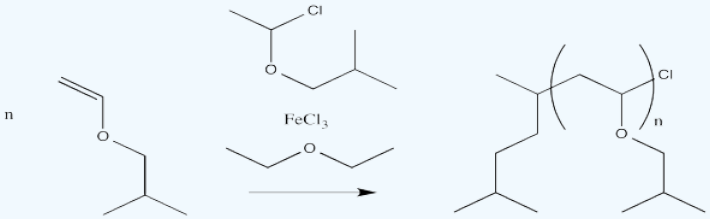
The halide coordinates to the Lewis acid, which polarises the carbon-halogen bond. Tin, iron or titanium compounds are some exampes of Lewis acids that are sometimes used for this purpose, but there are others, as well.



This method may actually change the mechanism of the reaction slightly. Maybe the halide ion never actually leaves completely, and the cation never fully forms. Instead, there may be enough polarization in the presence of the Lewis acid so that the alkene donates to the incipient (almost-formed) cation.

? Exercise 6.12.1

Provide a mechanism, with arrows, for the following living cationic polymerisation reaction.



6.13: Ziegler-Natta Polymerization

Polyethylene and polypropylene are two enormously important materials on the market. The fact that their use continues to persist despite legitimate environmental concerns is a testament to how useful these materials have become over the years.

Polyethylene and polypropylene can be thought of as polymers of the very simple alkenes, ethene and propene. In fact, that's exactly where these materials come from.

? Exercise 6.13.1

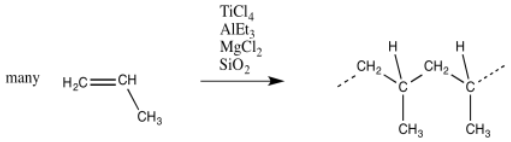
Draw the first intermediate formed after the initiation step in the cationic polymerization of:

a. ethene
b. propene

Unlike other polymers of alkenes that we have looked at, polyethylene and polypropylene are not polymerised via cationic methods.

Instead, these monomers are enchained through a process called "Ziegler-Natta polymerisation." This process is named after a German and an Italian chemist who are independently credited with its development in the 1950's.

In Ziegler-Natta polymerisation, monomers are treated with a catalyst, such as a mixture of titanium chloride (or related compounds, like oxovanadium chloride) with triethylaluminum (or trimethylaluminum). Other components are often added, such as magnesium chloride, to modify the catalyst and improve performance. The mixture described here produces a heterogeneous catalyst; it is an insoluble solid.



Now, the catalyst isn't really titanium chloride, because all of these components react together to make something new. Exactly what they make may be hard to determine. It's a complicated gmish.

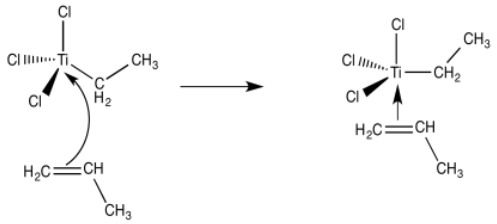
Despite the complicated catalyst mixture, we do know a little bit about the mechanism of reaction. Partly this information comes from studies of model compounds. Model compounds are simpler than the industrial catalysts, but they still have some structural features in common with their hard-working cousins. They have enough in common to be able to carry out polymerization catalysis, although maybe not as well as the industrial heavyweights.

So, what do we think happens? It seems pretty clear that one of the things that the trialkylaluminum does is provide an alkyl group to titanium. That shouldn't be too surprising. The triethylaluminum, like ethyllithium or ethylmagnesium bromide, ought to be a source of nucleophilic ethyl groups. The titanium tetrachloride ought to be a pretty good electrophile, complete with halide leaving groups. We can imagine at least one of those chlorides getting replaced by an ethyl ligand.

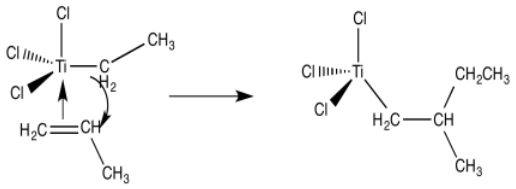
? Exercise 6.13.2

Provide a mechanism for the ethylation of titanium tetrachloride with triethylaluminum.

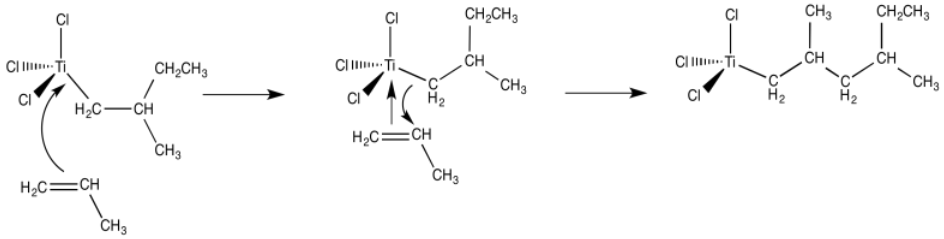
The next step, presumably, could be the binding of an alkene ligand to the transition metal.



Now we are looking at an organo transition metal compound. We should be thinking about organometallic reaction mechanisms. For example, a 1,2-insertion of the alkene into the metal-carbon bond would provide a new metal alkyl.



From there, and using these same elementary steps in succession, it is easy to imagine how polymerization of propene might occur. Bnding of an additional alkene, followed by the 1,2-insertion of the propene into the metal-carbon bond, results in formation of the propene dimer (with a methyl end group).



- The mechanism of Ziegler-Natta polymerization involves alkene binding and insertion into metal-carbon bonds

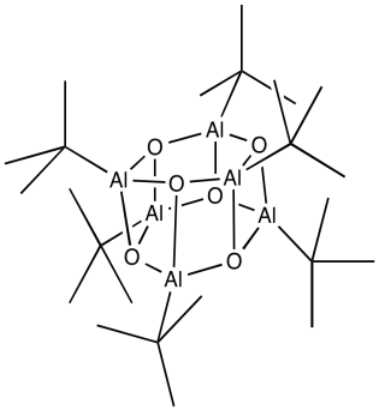
Let's pause for a moment and look a little more closely at the role of the aluminum compound. This topic is peripheral to electrophilic addition although important to the subject of catalysis.

In catalysis, "promoters" and "supports" are sometimes added to improve catalyst function. They might do so in a number of ways. They may take part directly in the reaction, providing additional Lewis acidic or Lewis basic sites, in much the same way that amino acid residues surrounding the active site of an enzyme may help catalyse a reaction. They may play a more subtle role, affecting physical properties of the catalyst (such as its solubility) or even tuning up the chemical properties of the catalyst. For example, maybe the promoter adds a little more electron density to the catalyst, making it a little less electrophilic. That might make the catalyst more stable; maybe it becomes more selective, reacting more carefully instead of with wild abandon. Maybe it makes the catalyst last longer.

Although classic Ziegler-Natta polymerization involves heterogeneous catalysis, lots of variations have been developed, including model systems to study the basics of the reaction as well as other, working homogeneous catalysts. One very successful variation, developed by Walter Kaminsky at University of Hamburg, uses Cp_2ZrCl_2 as catalyst and methylalumoxane (MAO) as a promoter. This zirconium species, in which the zirconium atom is wedged between two cyclopentadienly ligands, is commonly called a "zirconocene".

MAO is another poorly-defined species. It is obtained by treating trimethylaluminum with a trace of moisture. If you remember anything about Grignard reagents or alkyllithiums, you might think that isn't such a good idea. In truth, it is an even worse idea with trimethylaluminum with either of those other two metal alkyls. The trimethylaluminum is quickly decomposed into something else, a poorly-defined species called "methylalumoxane".

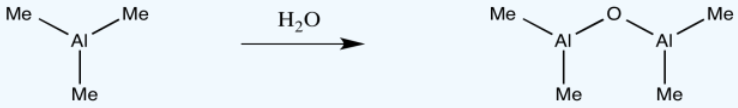
What we know about the structure of MAO may be a little bit fuzzy. Once again, some light can be shed on the subject via model studies. In some beautiful work done in Andrew Barron's lab at Rice University, alkyl aluminum oxide clusters were obtained via the careful treatment of tri(^{t}butyl)aluminum with water. Aluminum oxide clusters resulted, containing two, three, four or six aluminum atoms, depending on the reaction conditions. A drawing of one example, a hexamer, is shown below.



Some of the alkyl groups have been replaced by oxide ligands. We can imagine something similar would happen with trimethylaluminum. The aluminum forms bonds with oxygen, which bridges between different aluminum atoms. The structure is probably oligomeric itself, forming large clusters of aluminum oxide, although it must retain some methyl groups as well.

? Exercise 6.13.3

Provide a mechanism for the formation of an oxy-bridged aluminum dimer via treatement of trimethylaluminum with water.



? Exercise 6.13.4

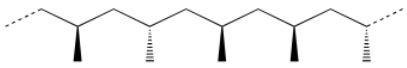
Why does tri(^{t}butyl)aluminum with water produce well-defined structures, whereas trimethylaluminum with water leads to a mess?

Just as in the original Ziegler-Natta catalyst, the "extra stuff" plays an important role. The MAO may tune up the qualities of the zirconium catalyst, in addition to providing an alkyl group.

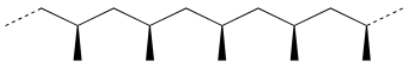
Kaminsky's "zirconocene" catalysts are used commercially to produce polypropylene. They have been particularly important in developing ways to control the stereochemistry of the reaction.

Consider a polypropylene chain. Each methyl group that hangs from the zig-zagging backbone of the polymer could have two possible orientations. It could be coming forward, shown with a wedge. It could be going backward, shown with a dash.

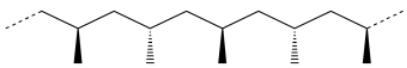
The stereochemical relationship between those wedges and dashes is called "tacticity". Tacticity basically comes in three flavours: random, alternating and same. A random stereochemical arrangment is described as an "atactic" polymer. If all the methyl groups are on the same side in a regular zig-zag projection of the backbone (either all wedges or all dashes) the arrangement is described as "isotactic". If instead the methyl groups alternate (wedge-dash-wedge-dash), the arranement is called "syndiotactic".



atactic

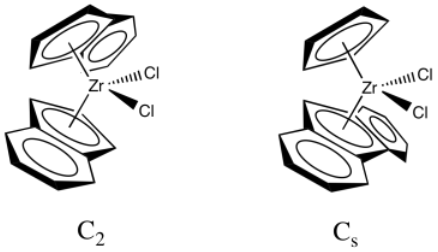


isotactic



syndiotactic

In a collaboration with Hans-Herbert Brintzinger at Konstanz University, Kaminsky developed zirconocene catalysts that could control the tacticity of the polymer chain. Use of the original zirconocene, Cp_2ZrCl_2, resulted in an atactic polymer. However, modified zirconocene catalysts selectively make either the isotactic or the syndiotactic polypropylene. We will look at two examples. The first one is sometimes described as a C_2 catalyst and leads to formation of isotactic polypropylene. The second is sometimes described as a C_s catalyst and leads to formation of syndiotactic polypropylene. (The labels, C_s and C_2, are symmetry point groups that describe the shape of the catalyst, but we won't go into that idea any further.)



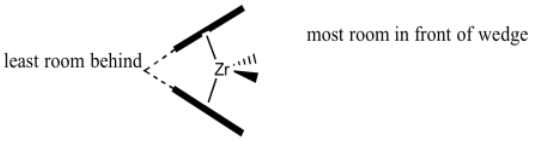
C_2 C_s

? Exercise 6.13.5

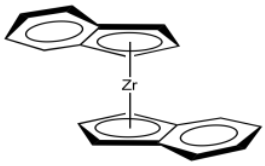
One of these catalysts (C_2 vs. C_s) is chiral; the other one isn't. Which is which?

Let's look at the C_2 catalyst. We'll strip it down to just the zirconocene part, leaving off the chlorides. The chlorides are likely replaced by methyl groups or else lost via dissociation (presumably leaving Cp'_2ZrCl^+ ion).

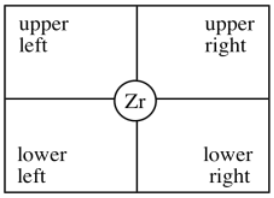
We will rotate the catalyst fragment to look at it from the "front": the more open part of the zirconocene "wedge", which is the direction from which a newly coordinating propene would approach.



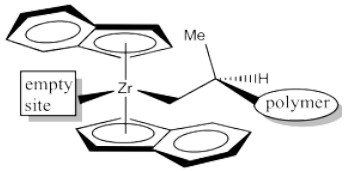
Here is the view from in front of the wedge. This is the surface that the propene will interact with as it approaches.



In our discussion, we will use "quadrant analysis", a standard tool for trying to analyse stereocontrol in transition metal catalysis. In quadrant analysis, we try to imagine differences in steric barriers in each of four quadrants around the metal centre. How will the arrangement of bulky groups influence the approach of a substrate?



In the C_2 catalyst we are using, it looks like there will be more room in the upper right and lower left quadrants. The upper left and lower right are blocked by those rings. When the propene is approaching, the polymer chain will present the largest obstacle, because it is extending a significant distance away from the zirconium atom. To minimize steric interactions,the chain may extend into the relatively empty upper right quadrant.

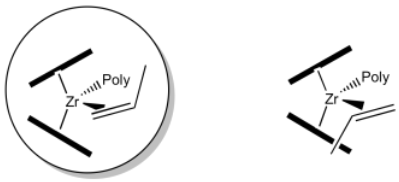


Alternatively, the polymer change could extend into the relatively open lower left quadrant, but that would really give us the same drawing, just rotated by 180 degrees.

? Exercise 6.13.6

Make a drawing of the complex with the polymer in the lower left quadrant.

As we think about bringing the propene into the empty coordination site next to the polymer chain, there are two questions we need to consider about orientation. The first is about which end of the alkene to bring into the wedge. The propene has two different ends: one end sports two hydrogen atoms, whereas the other end has a hydrogen and a methyl. It seems likely that the propene will fit best if the narrow end, the one with the two hydrogen atoms, extends into that narrow wedge.

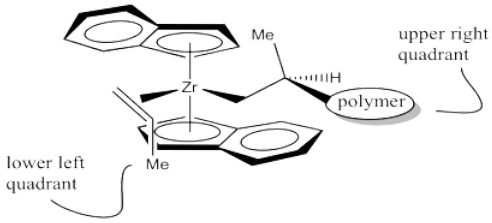


not likely

Now we need to think about which of the propene's two faces will coordinate to the zirconium. To think about the faces of propene, hold your hand out flat, with the thumb forming a right angle with the rest of your hand. The back of your hand represents one face of the propene; the palm of your hand represents the other. The propene will enter in such a way as to minimise steric interactions.

It looks like the easiest way is as shown below. The methyl group is placed in the lower left quadrant. You can think of it as keeping the methyl group away from the upper ring or keeping it away from the polymer chain, which is also in an upper quadrant.

If your left hand is propene, we have coordinated the back of your hand to the zirconium, with the thumb pointing down. If we had coordinated your palm, the thumb would be pointed up.

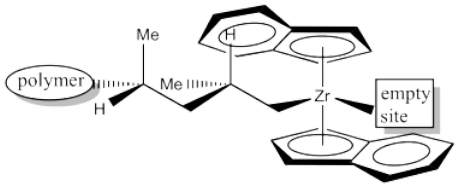


Once again, if we started with the polymer in the lower left quadrant, the entire drawing just rotates 180 degrees. It is still the same face that coordinates (the back of your left hand).

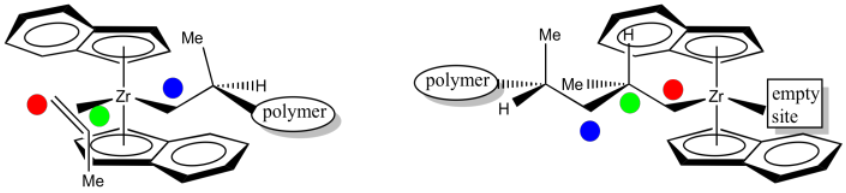
? Exercise 6.13.7

Make a drawing of the complex with the polymer in the lower left quadrant and the propene coordinating to the right.

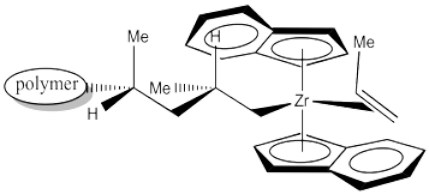
The next event is 1,2-insertion of the alkene into the metal-alkyl bond. That leaves us with the following structure. Notice that we have formed a new stereocentre. Because the methyl group of coordinated propene was pointing down, and the hydrogen adjacent to it was therefore up, then in the new stereocenter the methyl is still in the lower of two possible positions and the hydrogen is in the upper of two possible positions. Furthermore, the methyl is pushed back and to the left because the alkyl came from the right.



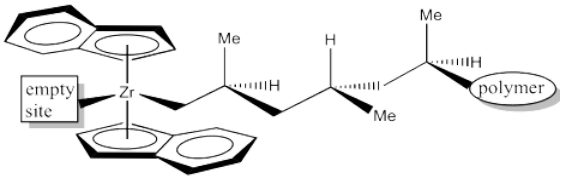
In order to help keep track of that insertion step, here is a drawing with colour labels. The narrow end of the propene is now attached to the zirconium via a sigma bond. The wider end of the proene has formed the new chiral center. The carbon that used to form a sigma bond to zirconium is now just another carbon along the growing polymer chain. The youngest part of the polymer is found at the growing end.



When another propene approaches to occupy the empty position, it will coordinate using the same face as the previous propene.



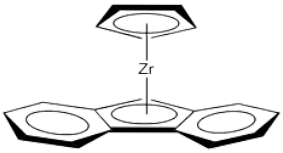
The 1,2-insertion produces a new chiral centre. The C_2 catalyst is producing an isotactic polymer chain. The is an example of "site control" of polymerization. The chiral C_2 catalyst has influenced the stereochemistry of the growing chain.



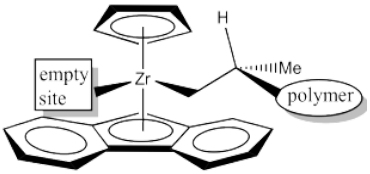
? Exercise 6.13.8

Assign configuration (*R* or *S*) to each of the chiral centres along the polymer chain in the above drawing to confirm isotacticity. Keep in mind that "polymer" stands for a long chain of carbons.

Now let's look at the C_s catalyst. We'll strip it down like we did before.



Where will a growing polymer chain go? Obviously it should go into one of the upper quadrants.



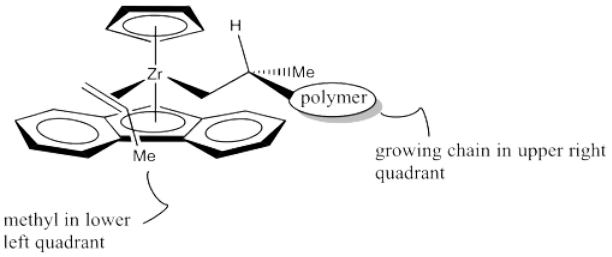
It isn't obvious whether it should be upper right or upper left. This time, it makes a difference, because the picture would not be the same.

? Exercise 6.13.9

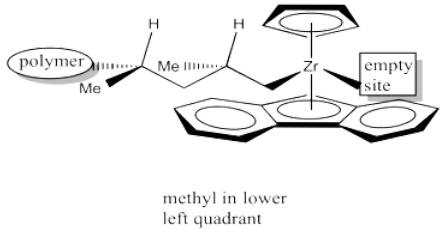
Draw the catalyst site with the polymer chain in the upper left quadrant.

However, once the propene approaches, a clear preference occurs. The chiral centre on the polymer chain is shown with the hydrogen up towards the Cp ring, since it is small and won't cause too much steric interaction. The polymer chain is extending forward, into the big, open space of the wedge. The leaves the methyl pointing to one side of the wedge.

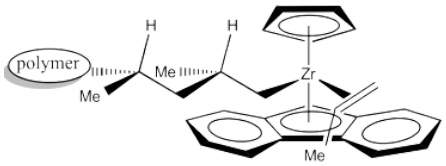
Which way will the propene approach? Will it come in on the same side as the methyl, or the opposite side? Probably the opposite side, as shown below.



Researchers suspect the methyl group points "down" in the above drawing, rather than "up", because the polymer chain is a bigger steric obstacle than the lower aromatic ring, and the polymer chain is in an upper quadrant. Once again, the approach of the propene is sterochemically controlled, although this time the stereochemistry of an existing chiral centre in the growing polymer chain influenced how things proceeded.



Once again, upon 1,2-insertion, a new chiral centre is formed. The C_s catalyst is forming a syndiotactic polymer chain.



Because of the influence of an existing choral centre on the stereochemical outcome of the reaction, this catalyst is considered to work through "chain-end control". The catalyst site simply amplifies the influence of that chiral centre upon the chiral centre that forms next. It does so by bringing the reactants together into a small space where the steric differences of two subtly different pathways become more important.

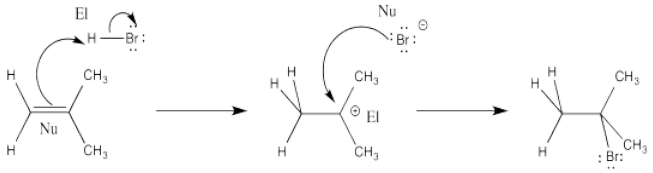
? Exercise 6.13.10

Label the configurations (R or S) of the chiral centres in the above drawing to confirm syndiotacticity.

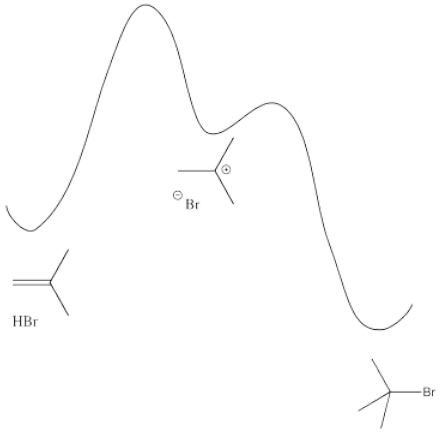
6.14: Solutions for Selected Problems.

Exercise 6.1.1:

El = electrophile; Nu = nucleophile



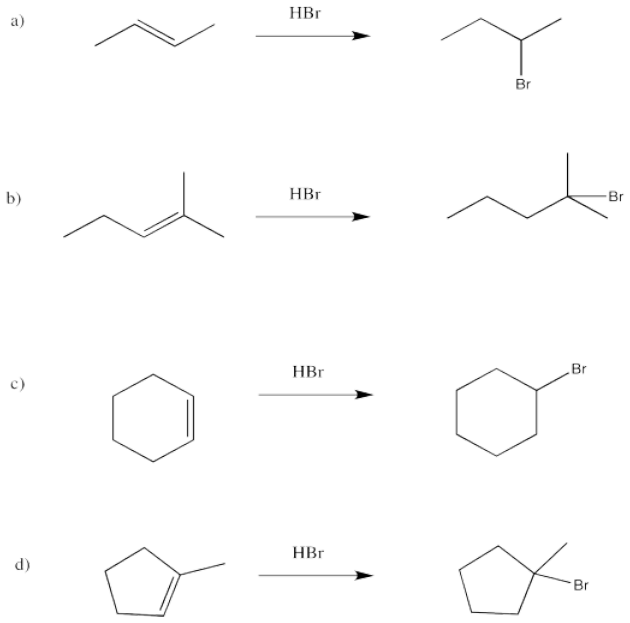
Exercise 6.1.2:



Exercise 6.1.3:

$$Rate = \frac{d[alkyl\ bromide]}{dt} = k[alkene][HBr]$$

Exercise 6.1.4:



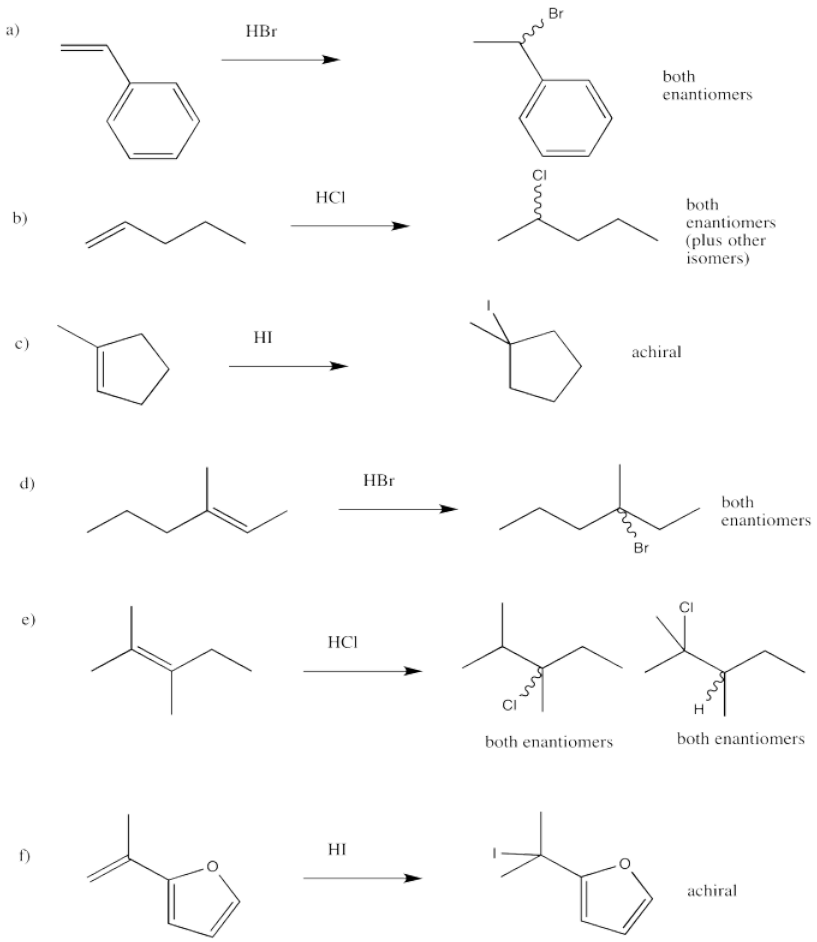
Exercise 6.2.1:

a, e, f, g are prochiral.

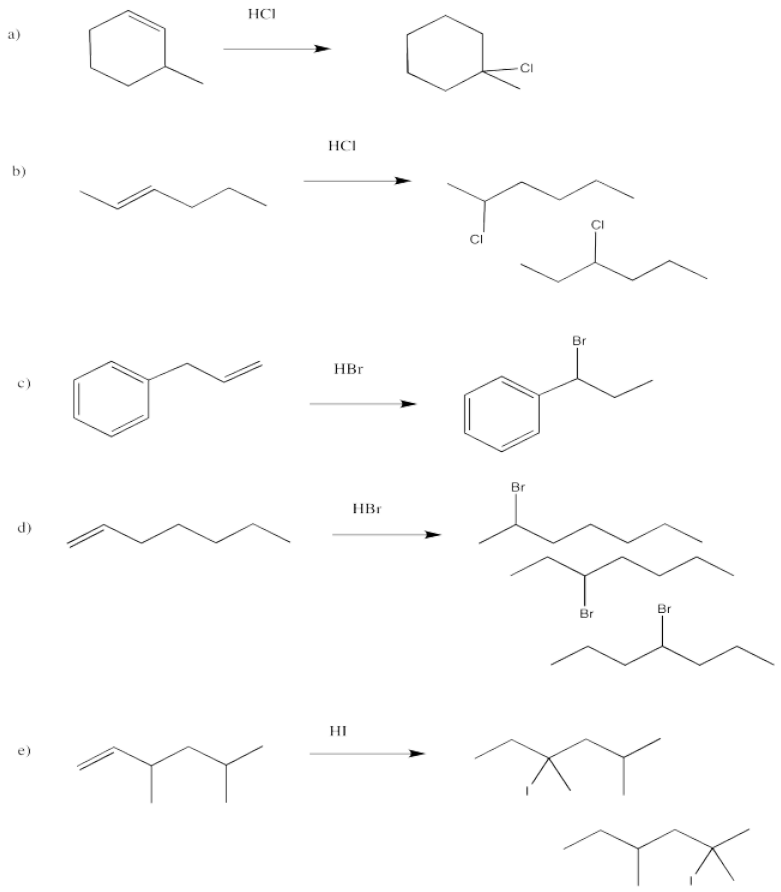
Exercise 6.2.2:

a) re b) si c) re d) si e) either; if the Br adds on one end of the double dond it is re, but at the other it is si f) re

Exercise 6.2.3:



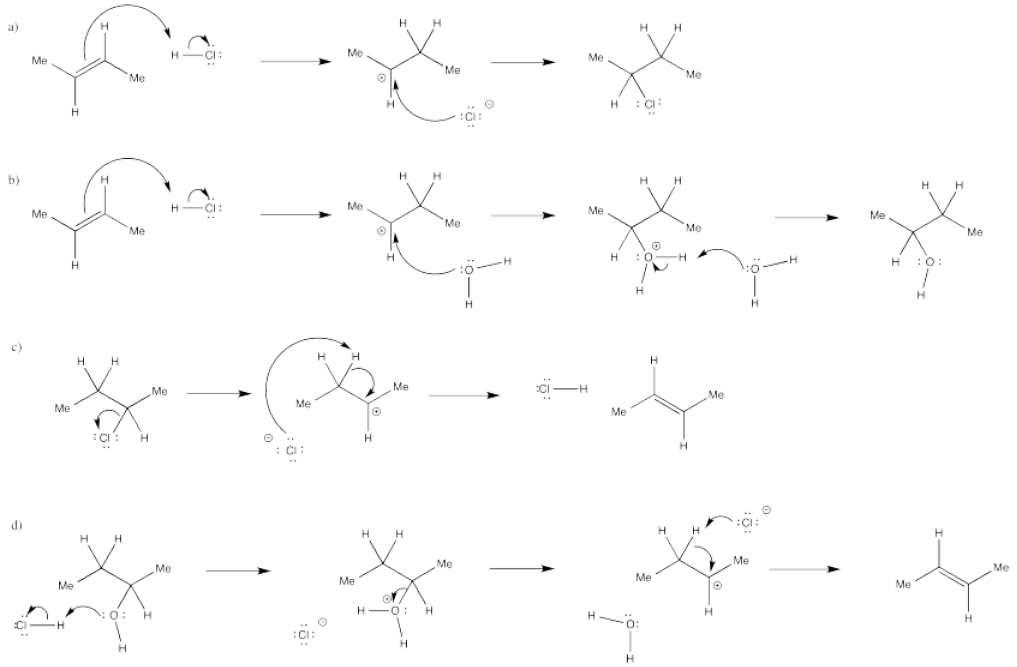
Exercise 6.2.4:



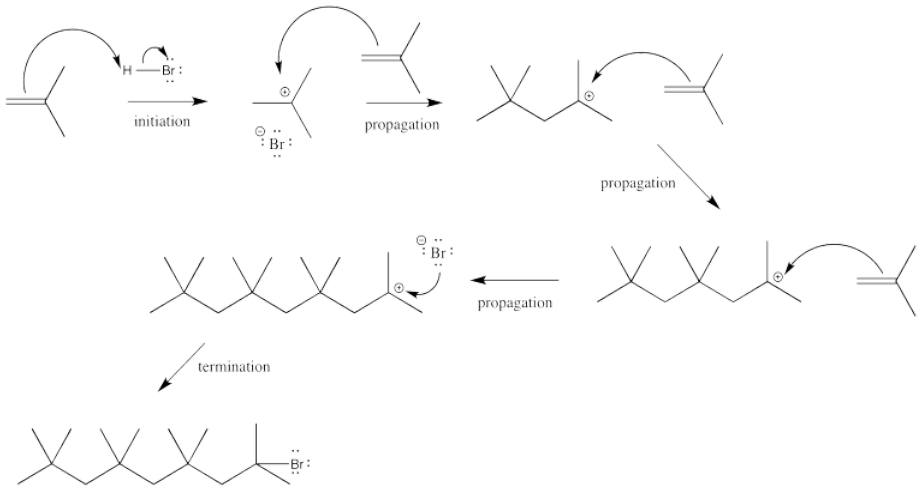
Exercise 6.3.1:

If the acid is regenerated at the end of the reaction, it isn't a reagent. It is a catalyst. It makes addition of water to the double bond occur much more quickly than if water acted alone, since water would never manage to protonate the alkene.

Exercise 6.3.2:

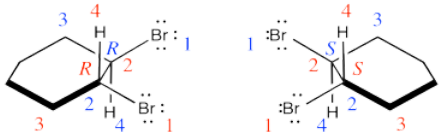


Exercise 6.3.3:



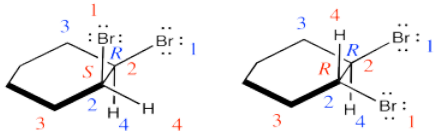
Exercise 6.4.1:

Two products are formed and they are enantiomers.



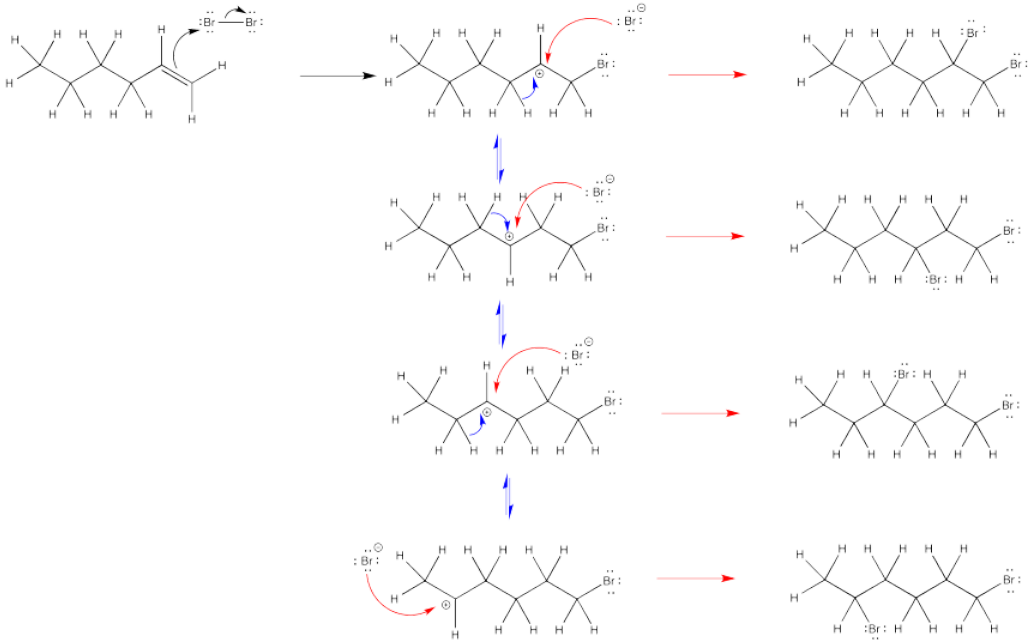
Exercise 6.4.2:

They are diastereomers. One chiral center has the same configuration in both compounds but the others are opposite.



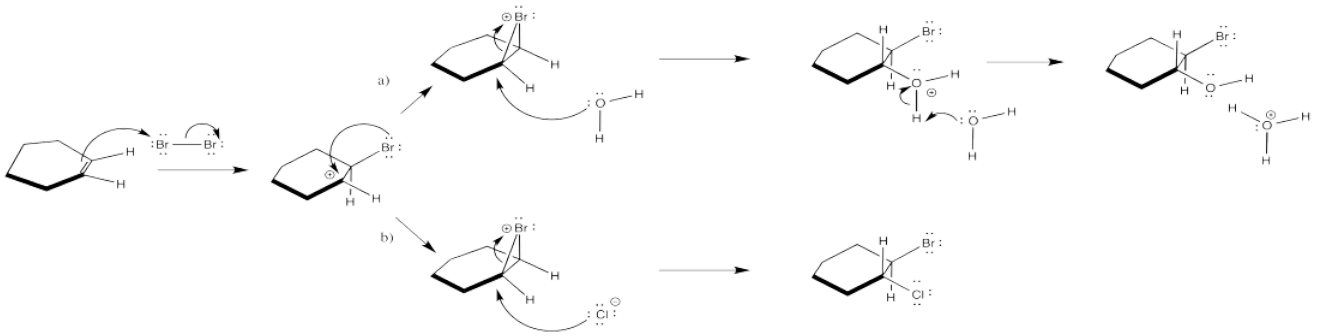
Exercise 6.4.3:

The second bromine could occupy any of the secondary positions if there were a true carbocation. That doesn't happen; the second bromine occupies only the position next to the other bromine.

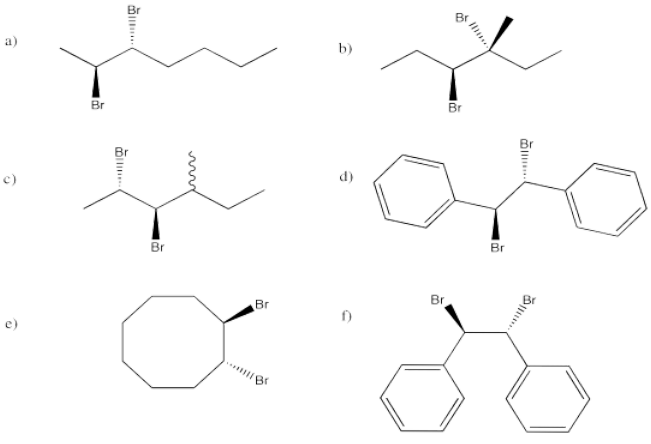


Exercise 6.4.5:

The nucleophile in the second step changes under different conditions.

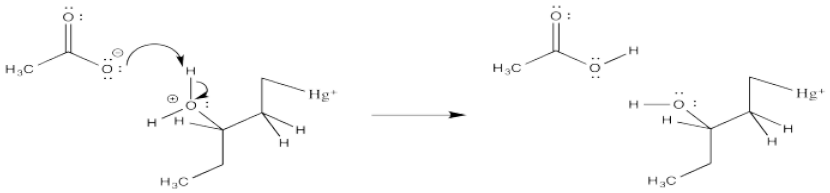


Exercise 6.4.6:

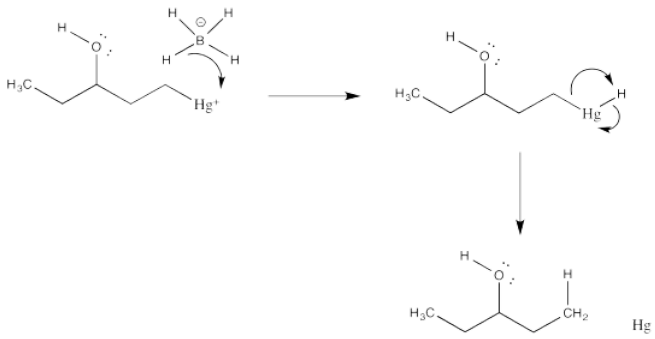


& enantiomer in each case

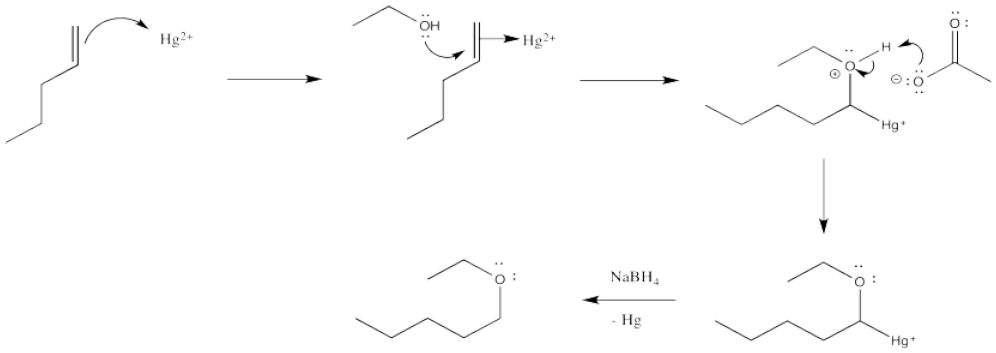
Exercise 6.5.2:



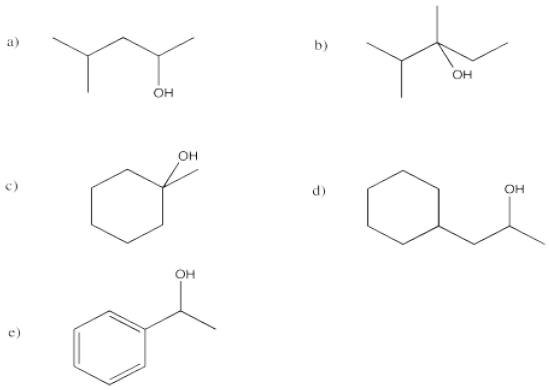
Exercise 6.5.3:



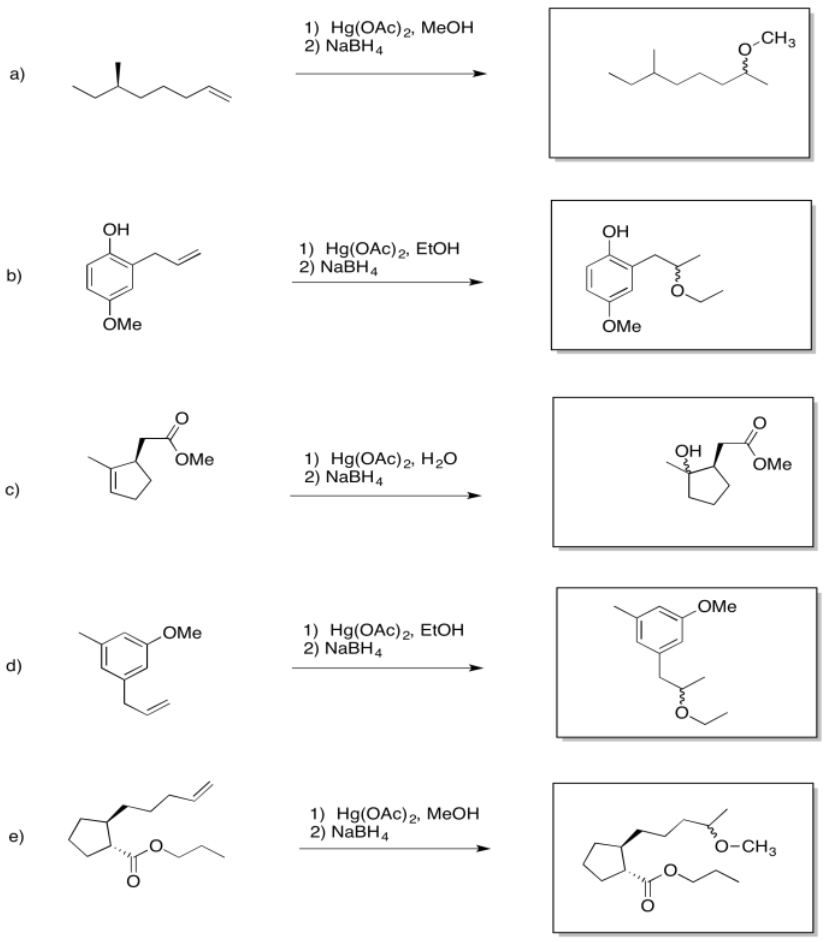
Exercise 6.5.4:



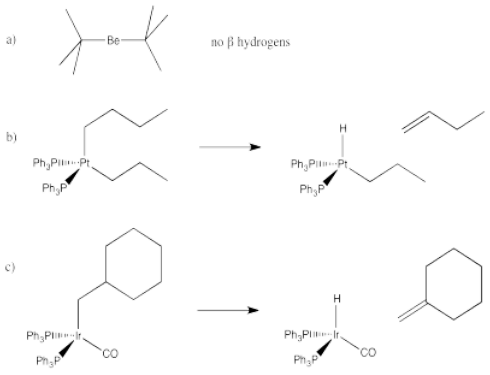
Exercise 6.5.5:



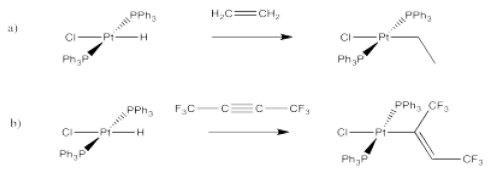
Exercise 6.5.6:



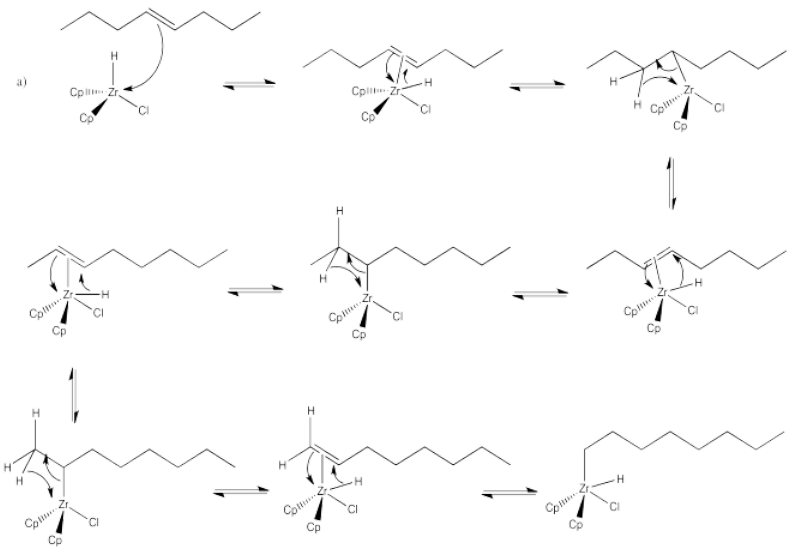
Exercise 6.6.1:



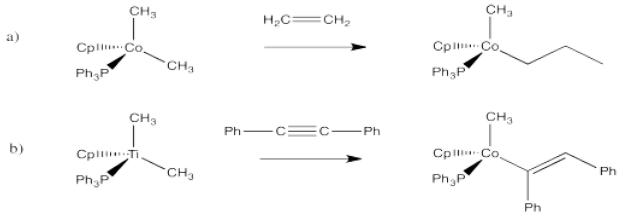
Exercise 6.6.2:



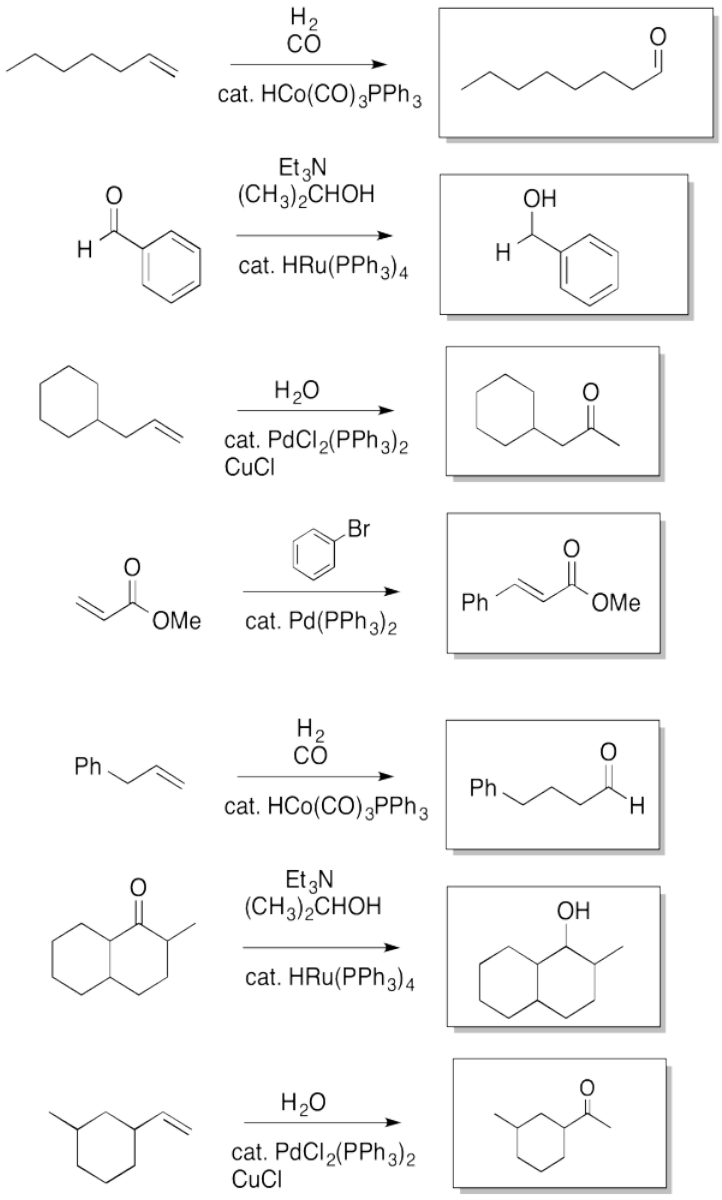
Exercise 6.6.3:



Exercise 6.6.4:

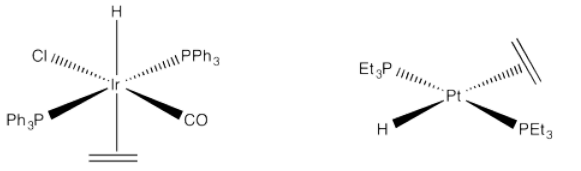


Exercise 6.6.5:



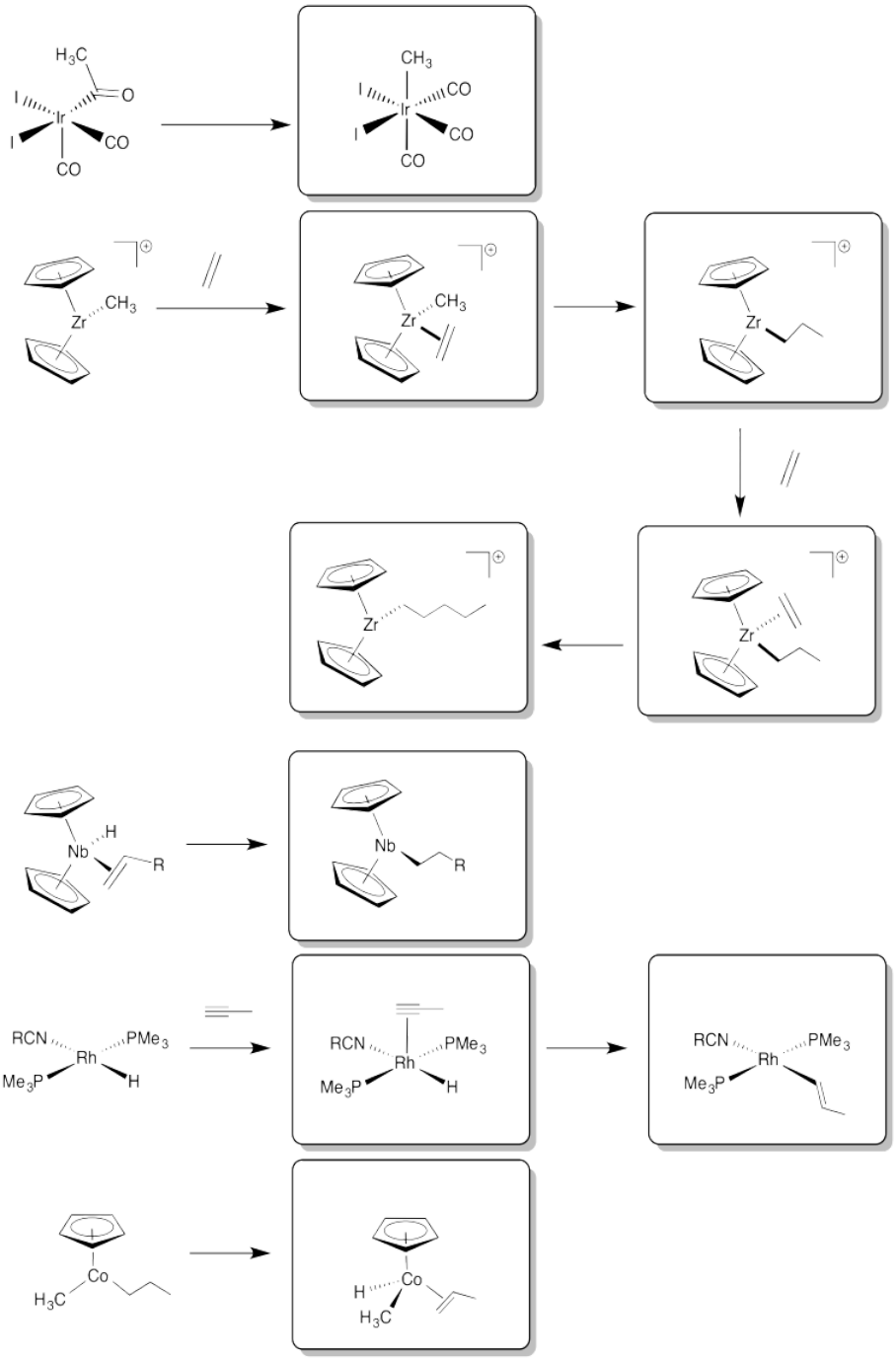
Exercise 6.6.6:

Why don't either of these complexes undergo hydride insertions at room temperature?



The hydride and the alkene group are trans to each other in this complex. In order for ar insertion reaction, the two ligands need to be closer.

Exercise 6.6.7:



Exercise 6.6.8:

Scorpionate Ligands: A Ligand with a Greater Propensity to Sting?
Dyson, Zech, Rawe, Haddow, Hamilton and Owen, *Organometallics*, **2011**, *30*, 5844-5850.

1. A ligand that we have seen before, **COD**.

COD

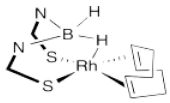
a. What will the denticity of this ligand be? ____2____
b. Circle the sites that bind to the metal.

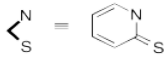
2. Show a molecular orbital cartoon showing how the orbitals of COD that bind to the M.

3. New Ligand, **Bmp**.
   a. Add formal charges to these two resonance structures.

When rhodium is complexed with Bmp and the COD, the following complex is formed.

4. What is the geometry of the rhodium in this complex?



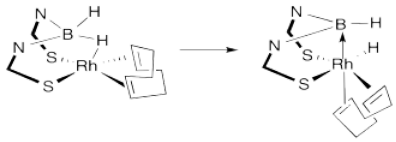


Geometry: **distorted square pyramidal**

5. What is the valence electron count on Rh in this complex?

Valence electrons on Metal:	9
Charge on the ligands:	-1
Charge on the Metal:	+1
Revised Count on the Metal (accounting for charge):	8
Number of electrons donated from the ligands:	10
Total electrons in this complex:	18

6. Upon formation, the hydride quickly moves to the metal.

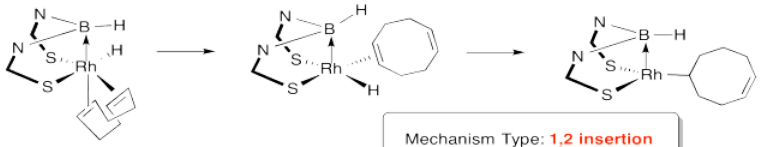


a. Why did this occur?

b. Why is there an arrow toward the B in the product?

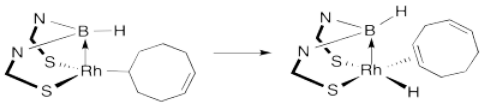
For the rhodium complex, a novel "chain-walking mechanism" is observed.

7. In this reaction, the COD partially dissociates and then the first step of the "chain-walking" occurs. Provide a name for the mechanism type.



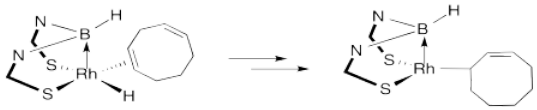
Mechanism Type: **1,2 insertion**

8. The second step of the "chain-walking" occurs. Provide a name for the mechanism type.



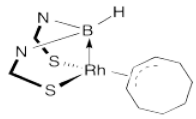
Mechanism Type: **beta elimination**

9. Eventually the hydride "walks" to the final position. Show the rest of the mechanism.



Chain walking is a series of 1,2 insertions and beta eliminations

10. The final product can also be represented in the following way. Show how this structure is equivalent to the one above.



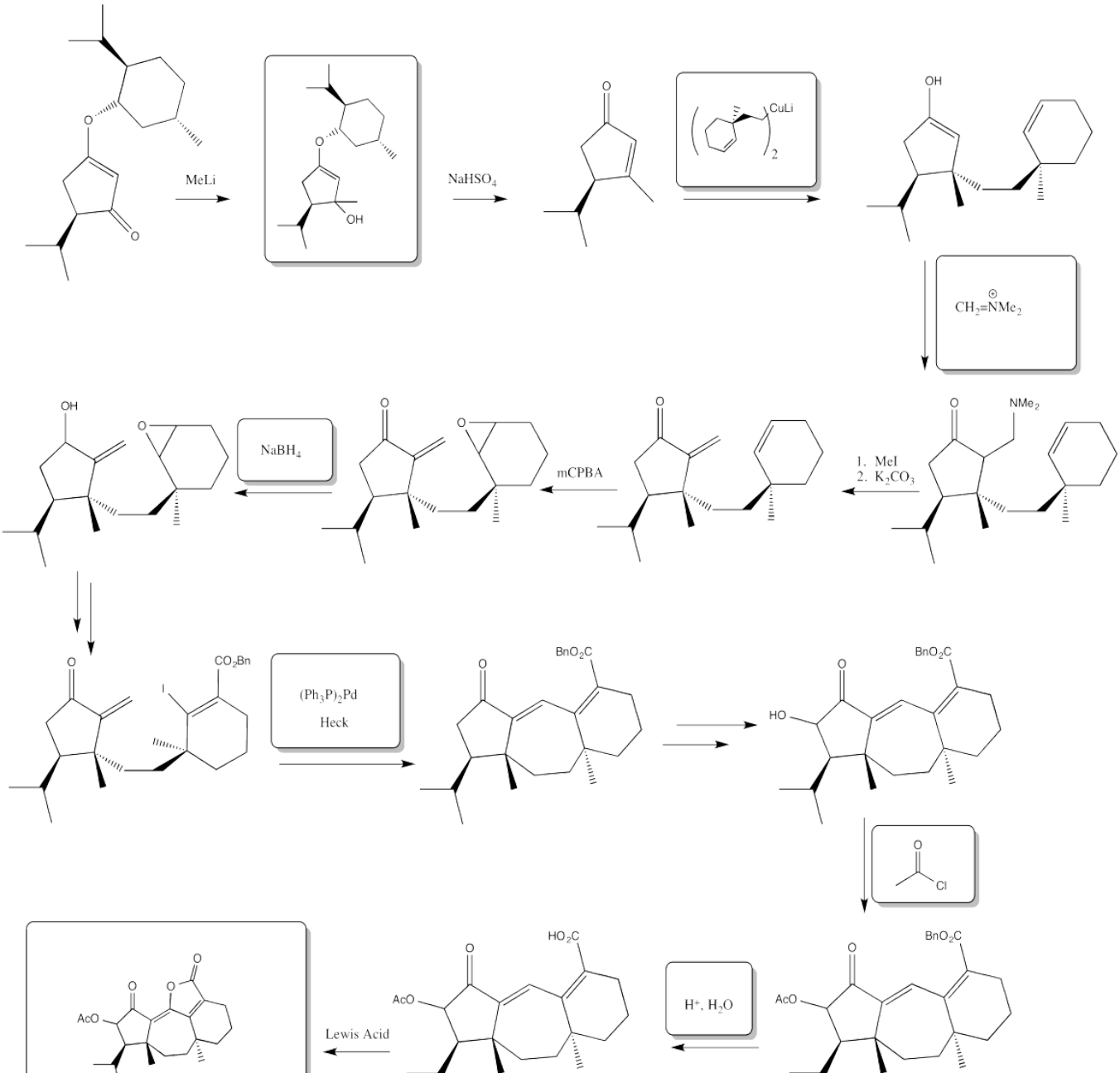
11. Considering structure and thermodynamics, why is this the final product?

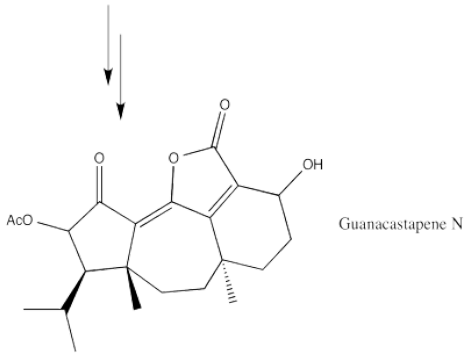
resonance stabilized

Exercise 6.6.9:

Guanacastepene N

Iimura, Overman, Paulini, Zakarian, *J. Am. Chem. Soc.* **2006,** *128*, 13095.



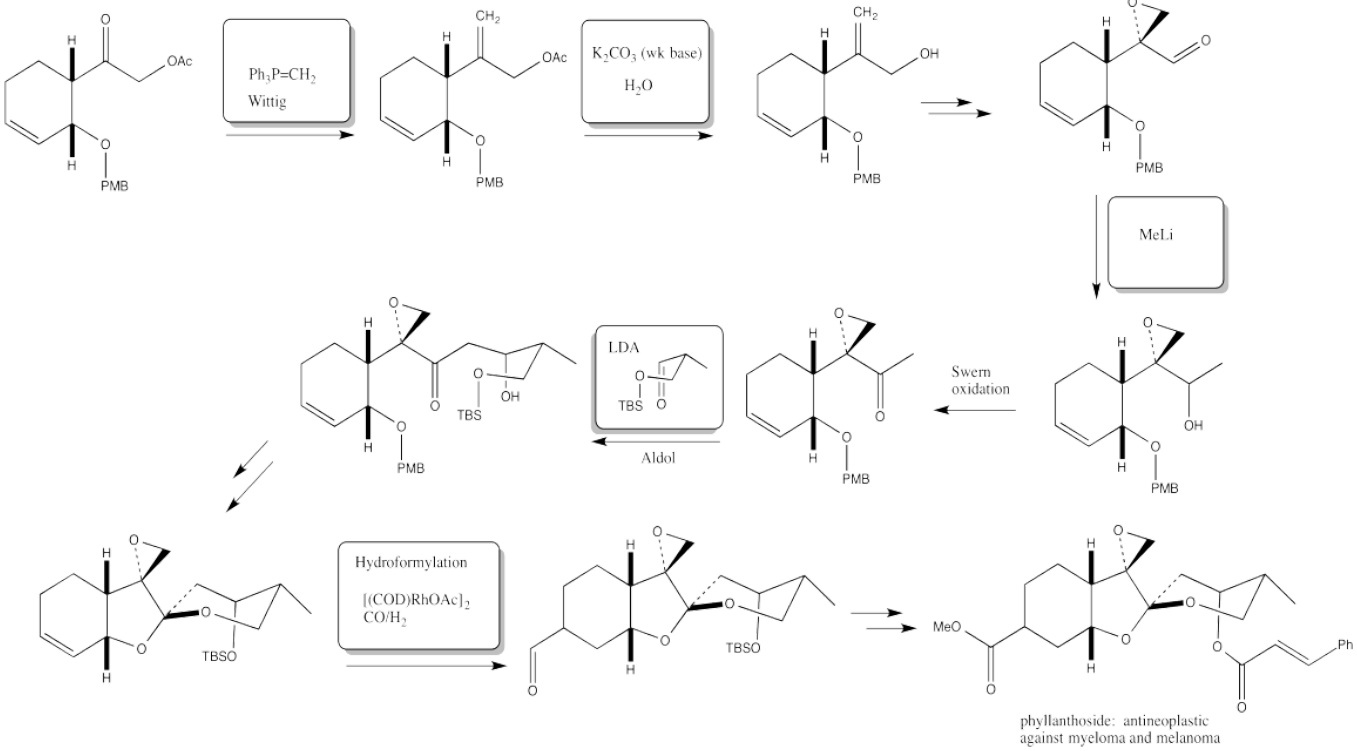


Guanacastapene N

Exercise 6.6.10:

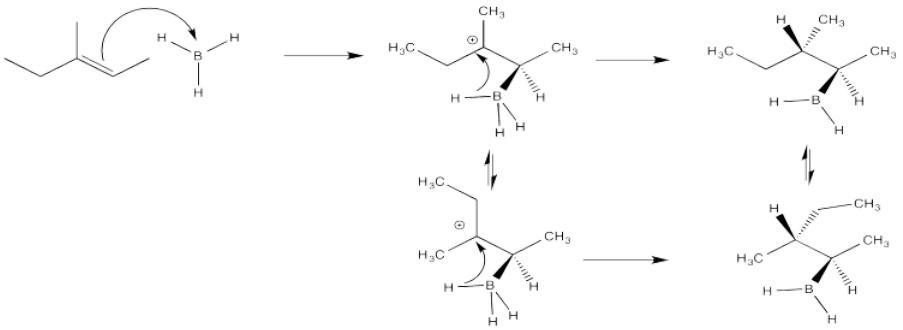
Phyllanthocin

Burke, Cobb, Takeuchi, *J. Org. Chem.*, **1985**, *50*, 3421-3423.



phyllanthoside: antineoplastic against myeloma and melanoma

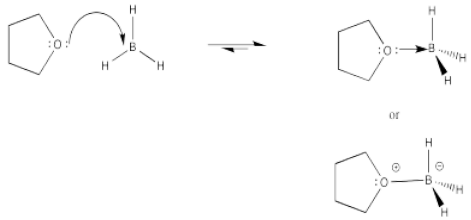
Exercise 6.7.2:



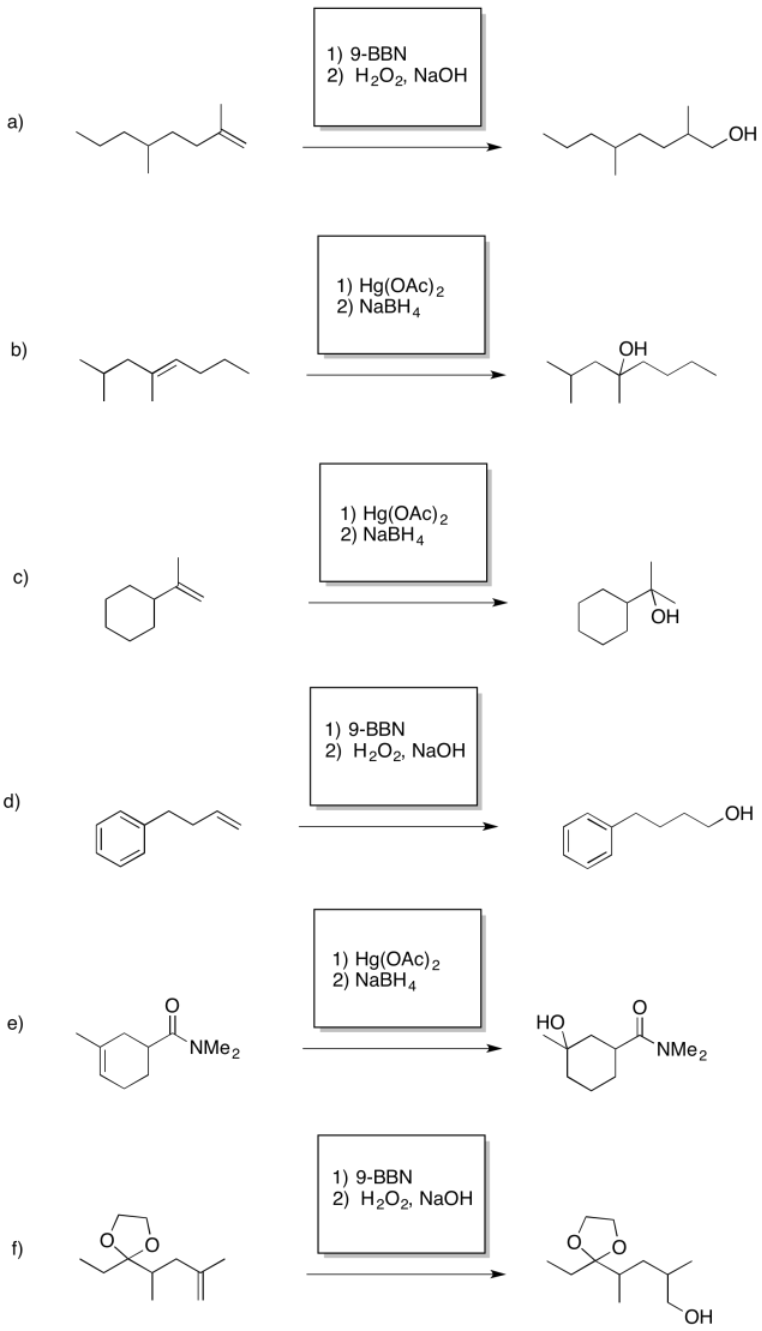
Exercise 6.7.3:

Crowding is more severe in the structure on the left than in the structure on the right. The structure on the right, representing an approach to the transition state of the reaction, is more favorable than the other one.

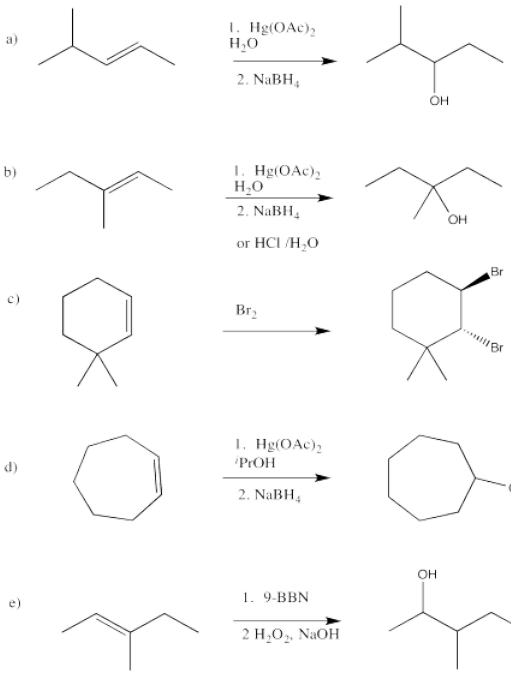
Exercise 6.7.4:



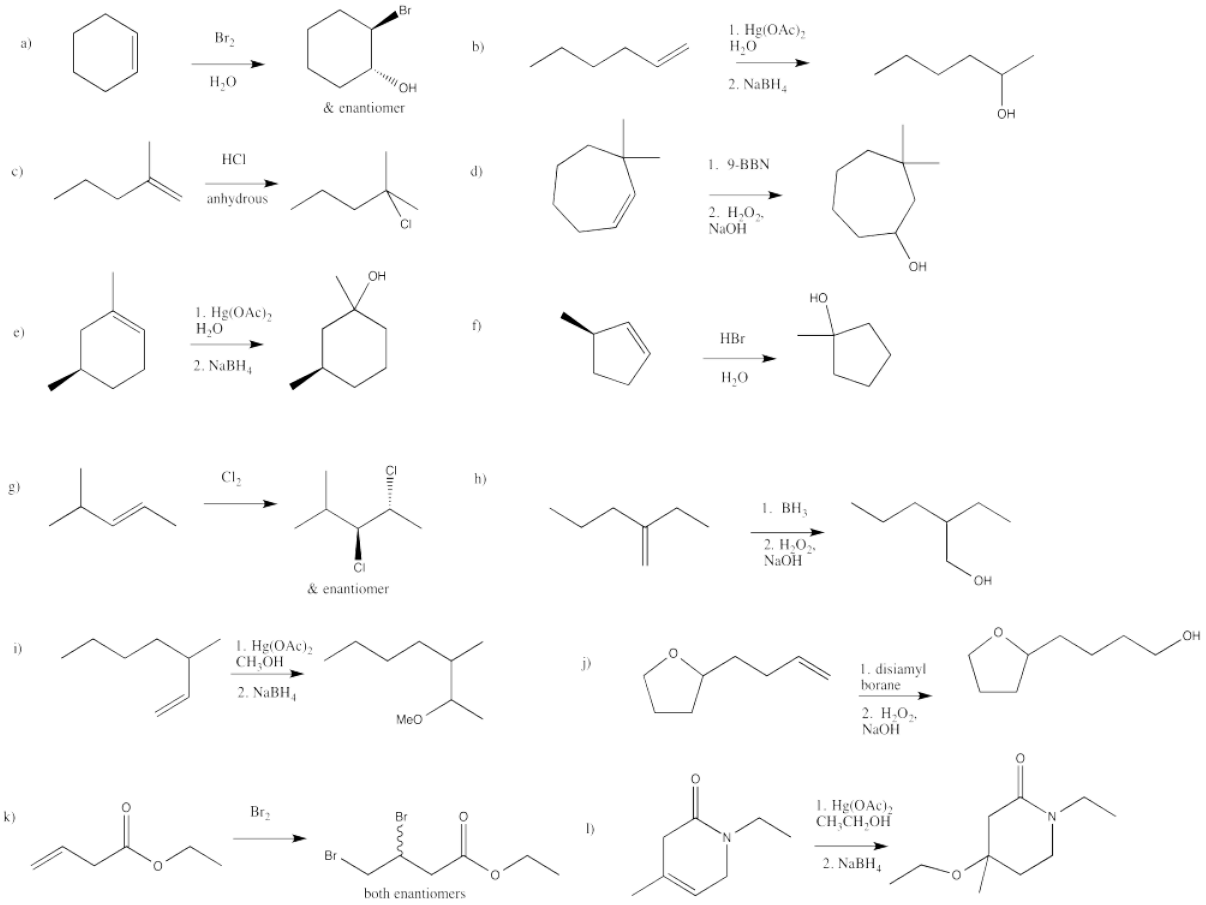
Exercise 6.7.5:



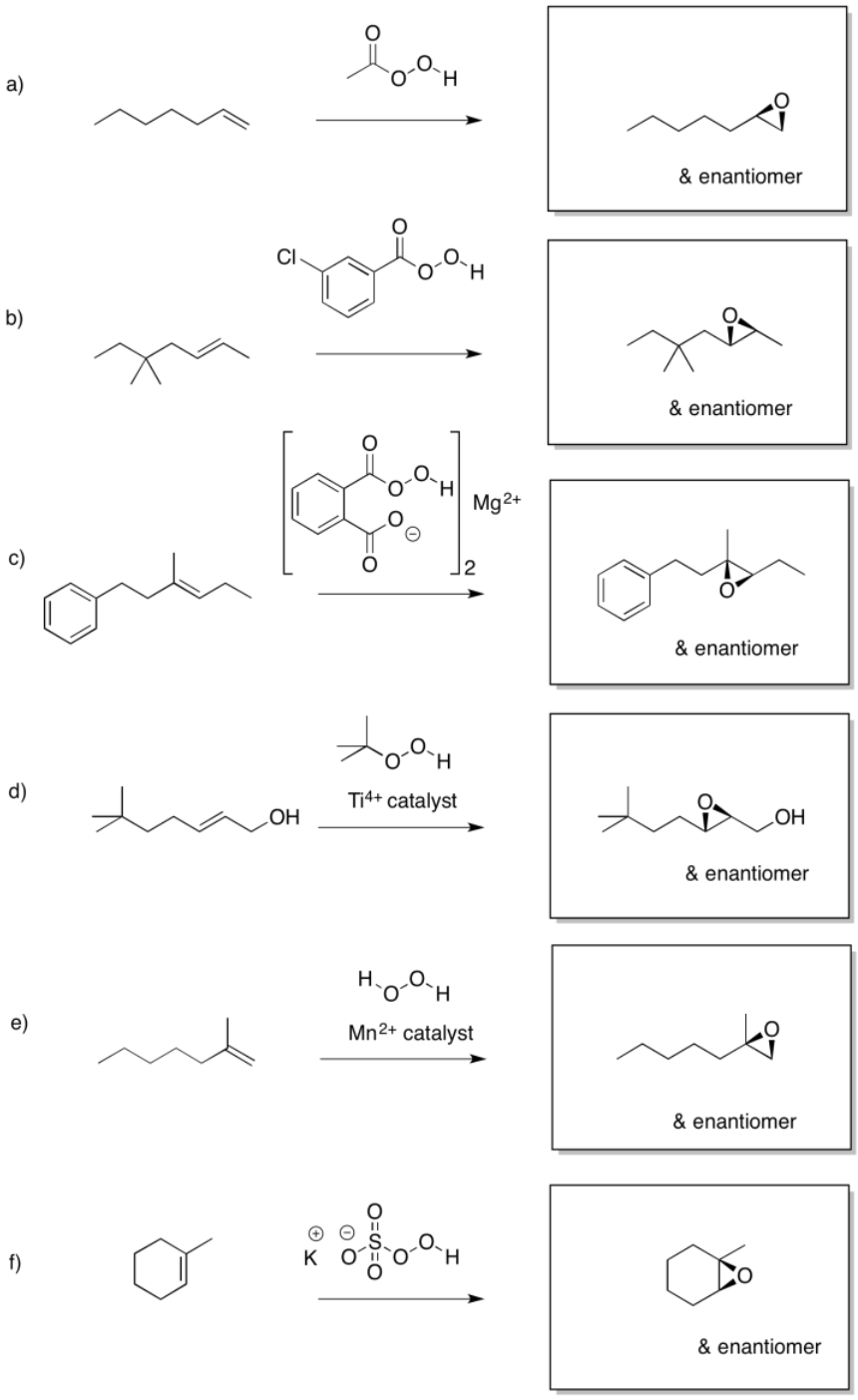
Exercise 6.7.6:



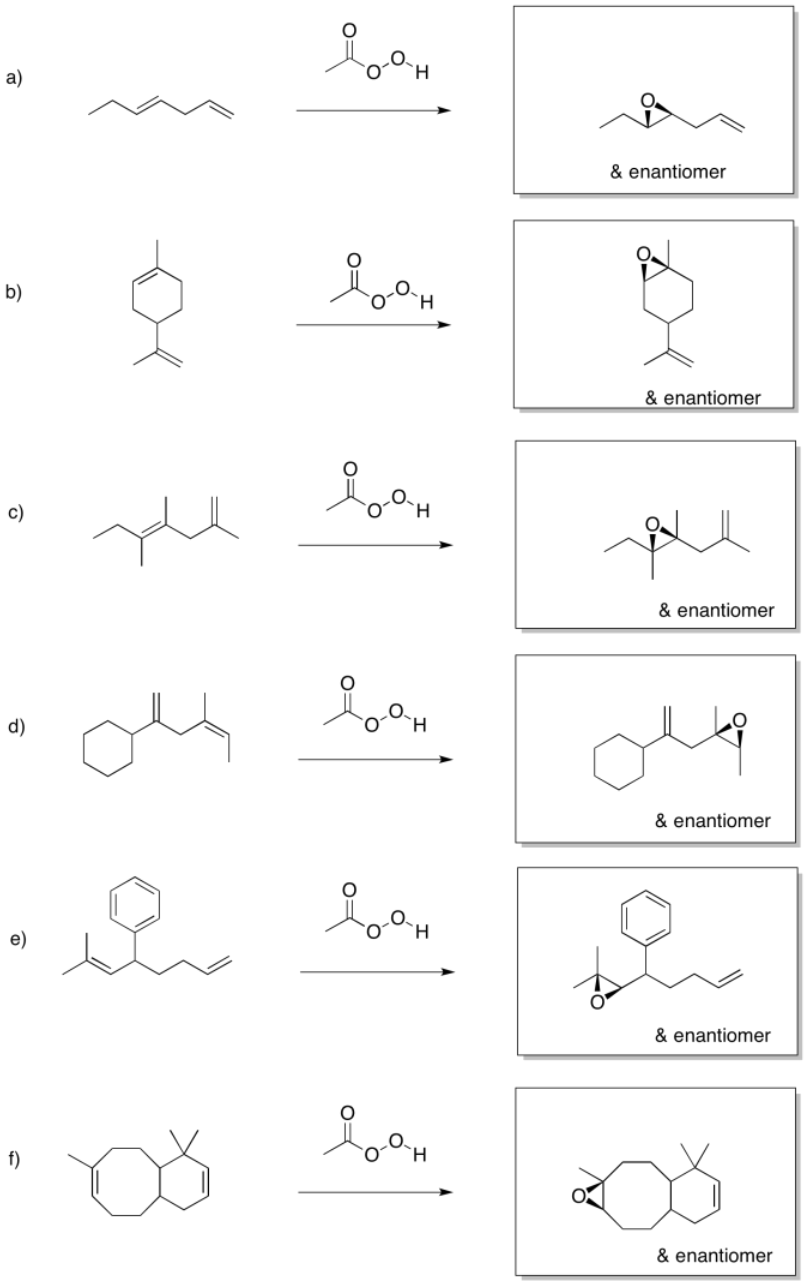
Exercise 6.7.7:



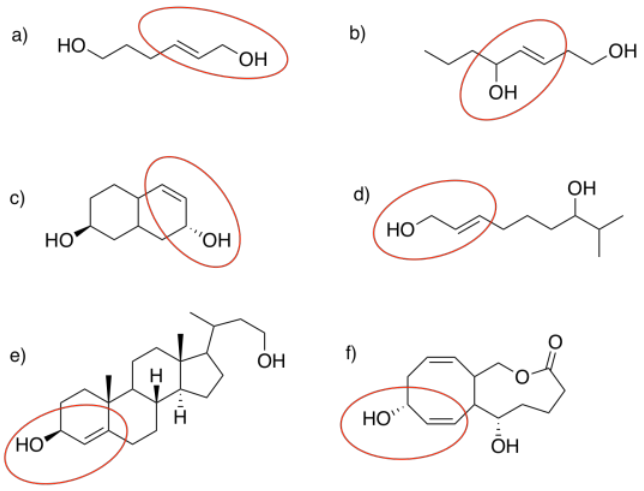
Exercise 6.8.1:



Exercise 6.8.2:



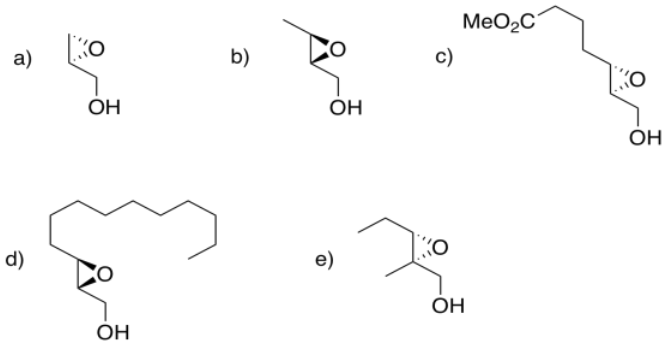
Exercise 6.8.3:



Exercise 6.8.4:

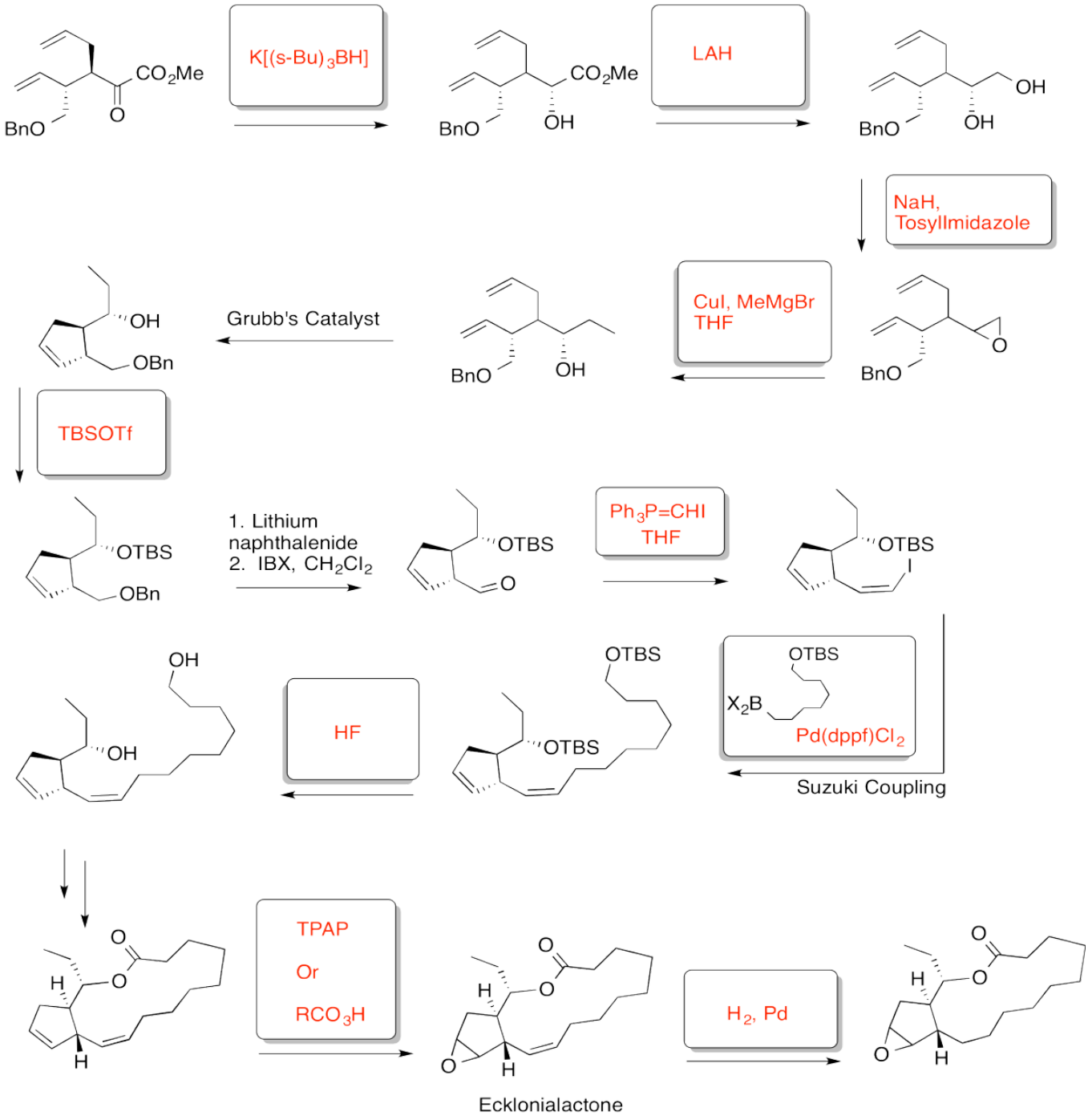
D-(-)-tartrate is the (*2S*,*3S*)-isomer. L-(+)-tartrate is the (*2R*,*3R*)-isomer. Each chiral center is configured opposite to the corresponding one in the other molecule, so the molecules are enantiomers.

Exercise 6.8.5:



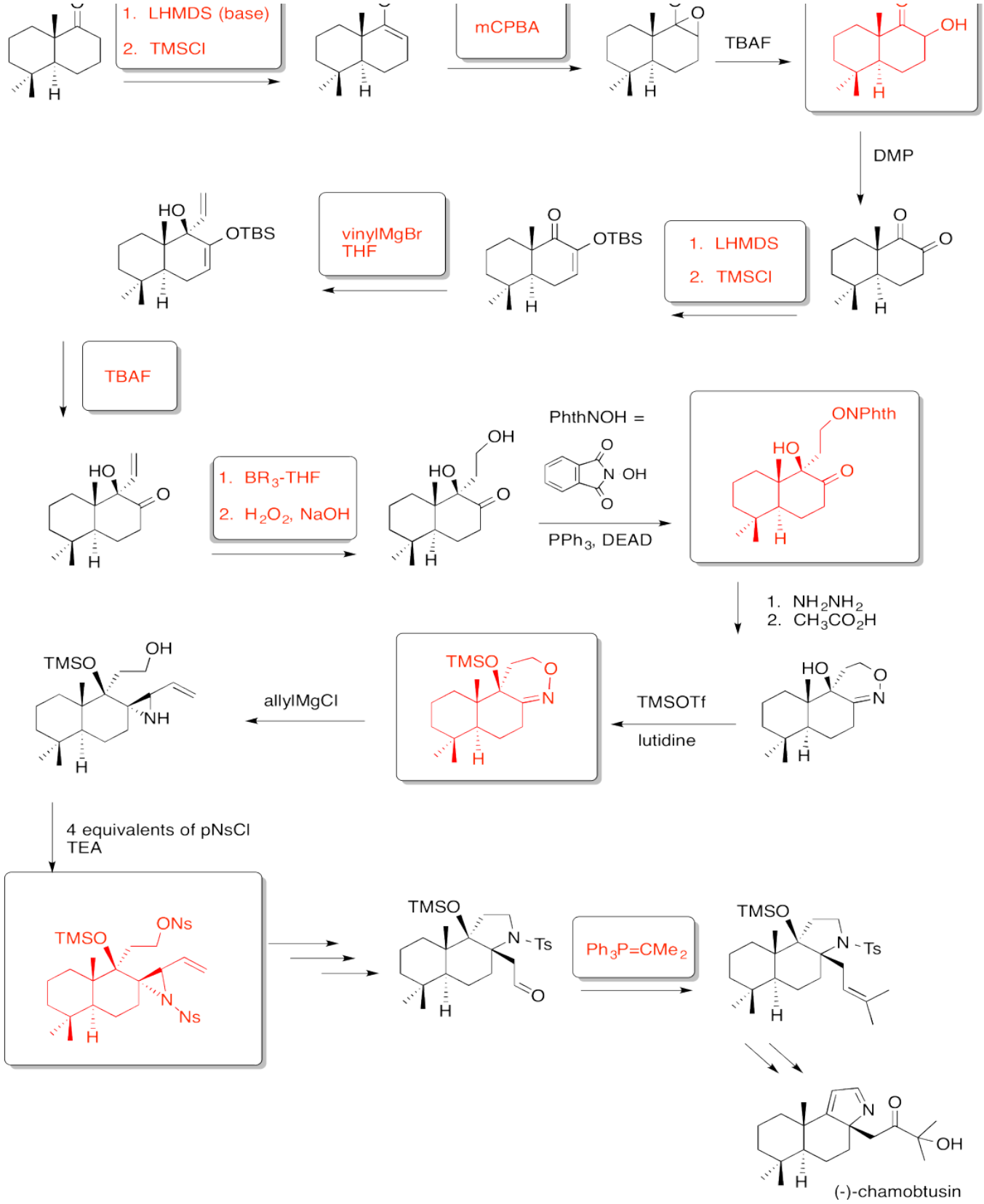
Exercise 6.8.6:

Becker, Butt, Kiedrowski, Mieschler, Quentin and Hiersemann, Total Synthesis of (-)-Ecklonialactone B, *Org. Lett.*, **2013**, *15* (23), 5982-5985.

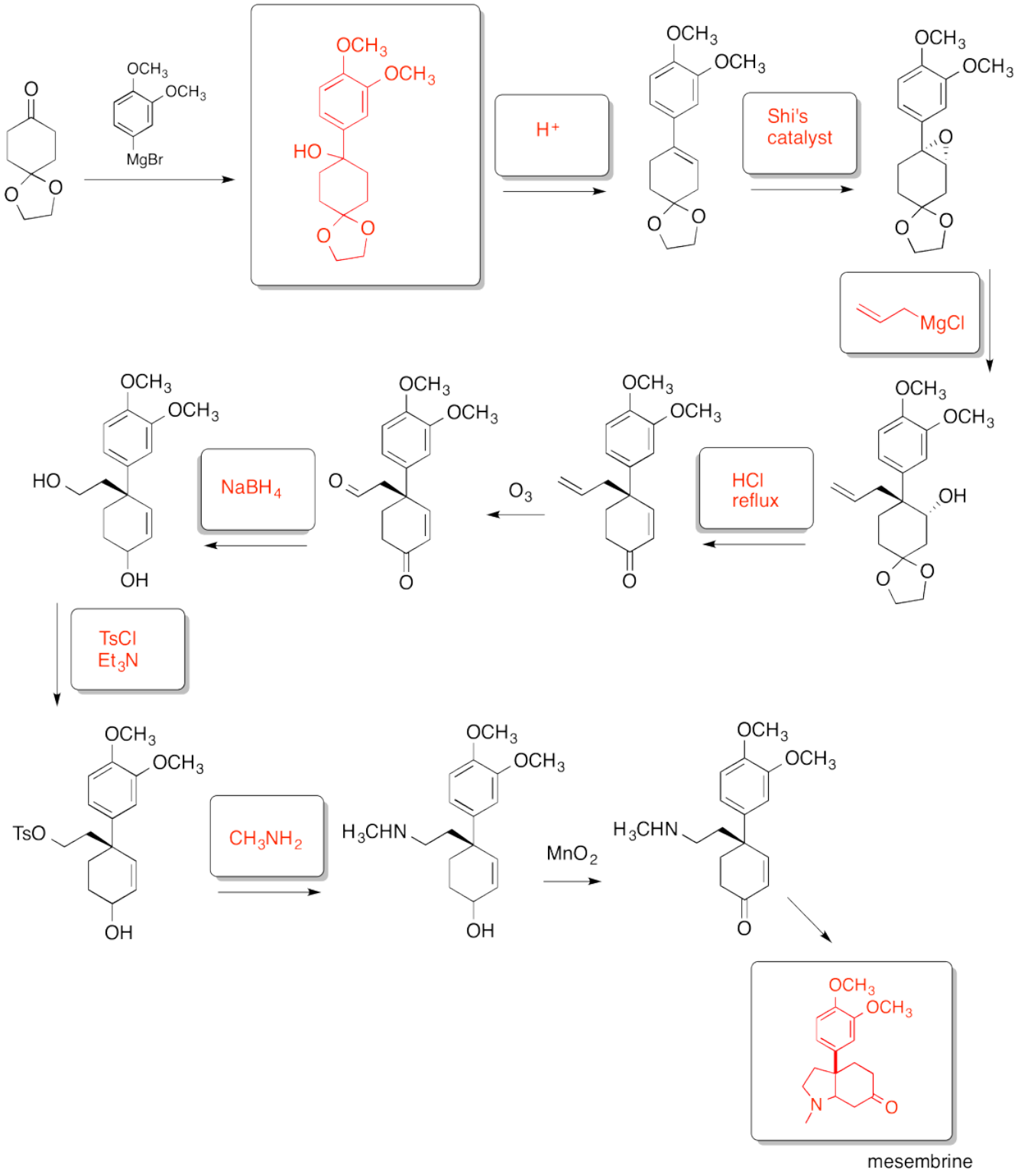


Exercise 6.8.7:

Suzuki and Aoyagi, Total Synthesis of (-)-Chamobtusin A, *Org. Lett.*, **2012**, *14* (24), 6374-6376.



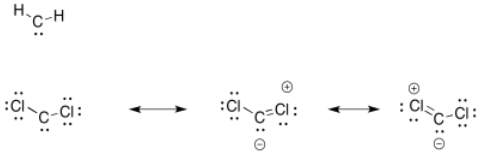
Exercise 6.8.8:



Taber and He, Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (-)-Mesembrine, *J. Org. Chem.*, **2005**, *70*, 7711-7714.

Exercise 6.9.1:

The chlorines can (weakly) share their electrons to fill the octet on carbon.

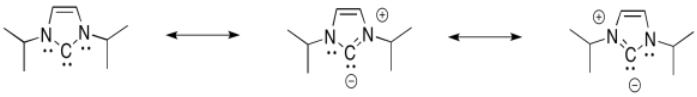


Exercise 6.9.2:

The oxygen can π-donate to help fill the octet on the carbon.

Exercise 6.9.3:

Not only can the nitrogens π-donate to help fill the octet on carbon, but this is an aromatic system. It is planar, cyclic, fully conjugated, with an odd number of electron pairs in the π-system.



Exercise 6.9.4:

a) $CHCl_3$, KOH → & enantiomer

b) CH_2Br_2, CH_3Li → & diastereomer

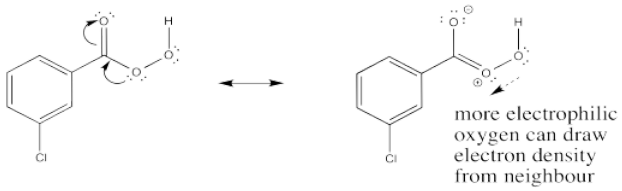
c) CH_2Cl_2, CH_3Li → & diastereomer

d) $H_2C{-}N{\equiv}N$, $Cu(OAc)_2$ → & enantiomer

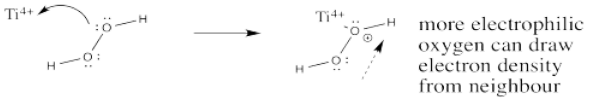
e) $Cu(OAc)_2$ → & diastereomer

f) $Cu(OAc)_2$ → & diastereomer

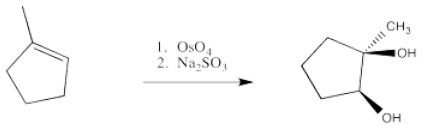
Exercise 6.10.1:



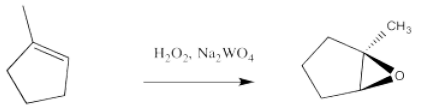
Exercise 6.10.2:



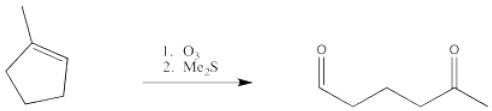
Exercise 6.10.3:

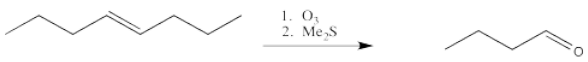


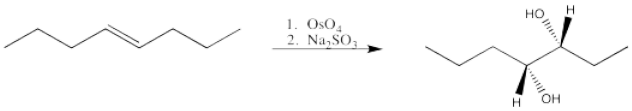
& enantiomer

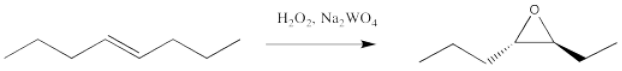


& enantiomer

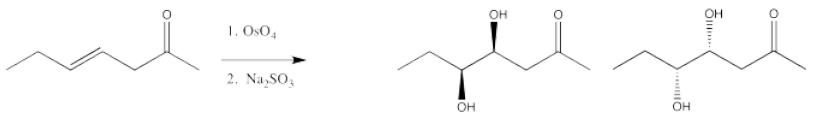


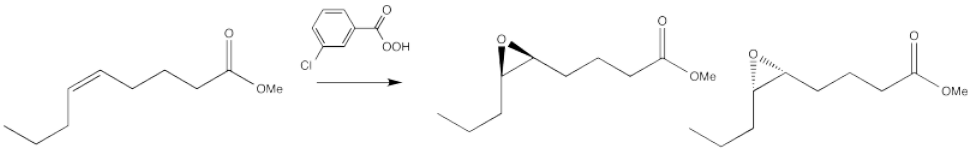


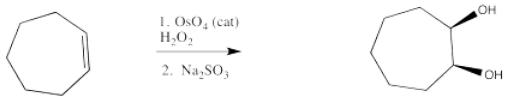


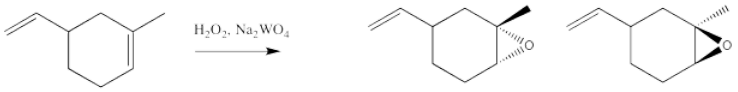


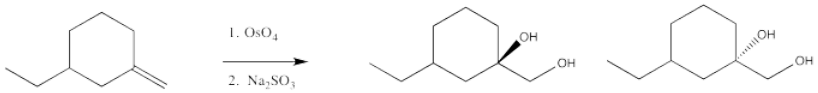
Exercise 6.10.4:

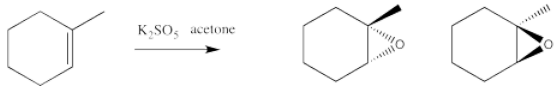








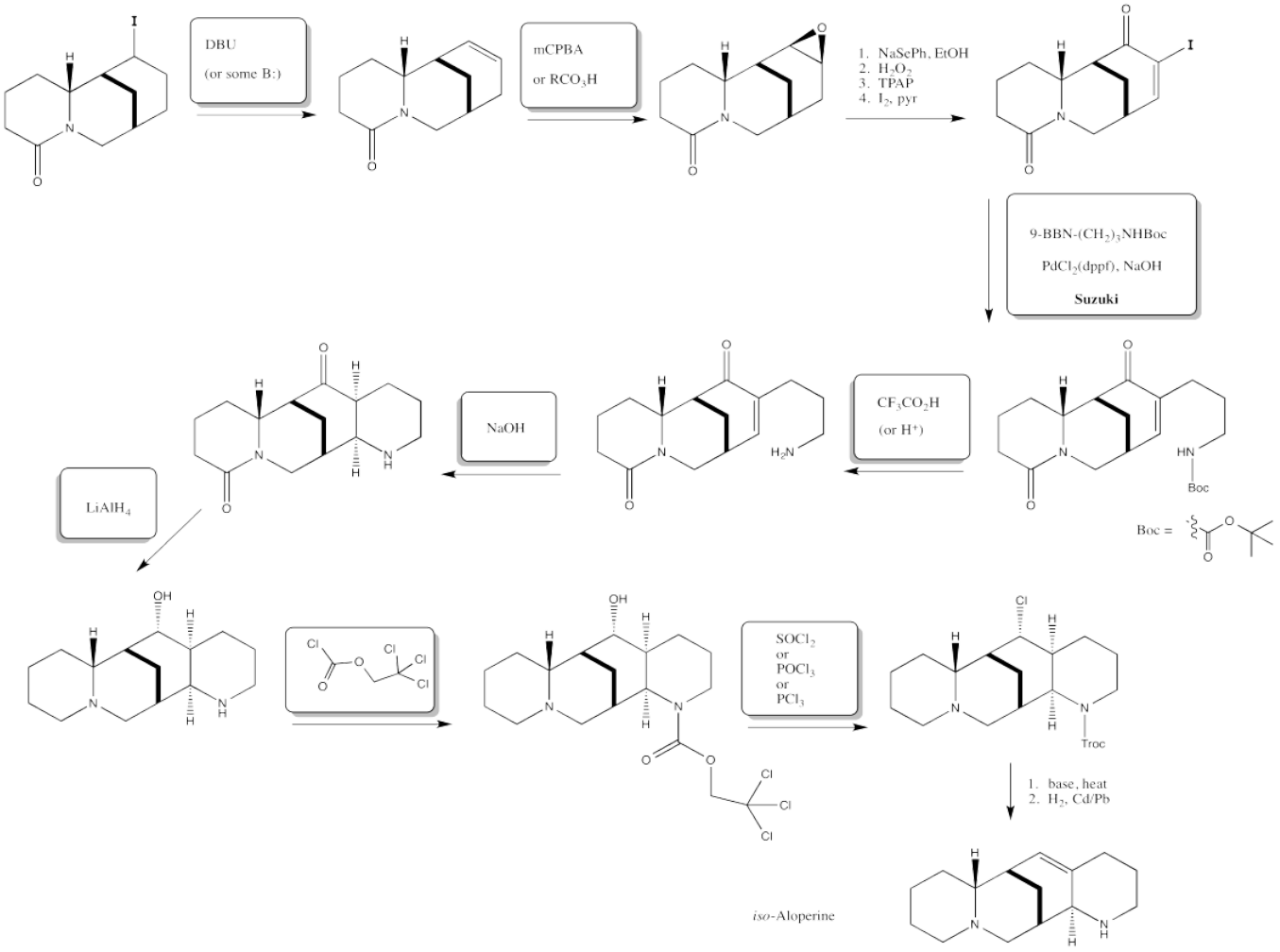




Exercise 6.10.5:

iso-Aloperine

Brosius, Overman, *J. Org. Chem.* **1997**, *62*, 440.



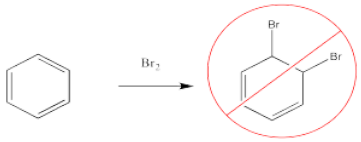
CHAPTER OVERVIEW

7: Electrophilic Aromatic Substitution

7.1: Introduction to Electrophilic Aromatic Substitution

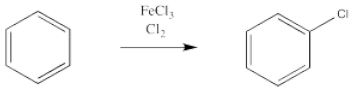
Aromatics, or arenes, are derivatives of benzene or other compounds with aromatic ring systems. That is, they are cyclic, planar, fully conjugated and have an odd number of π-electron pairs. Like alkenes, aromatics have π-electrons that are loosely held and are easily attracted to electrophiles. However, aromatics don't undergo the typical reactions of alkenes.

For example, bromine will not add across the double bond of benzene.

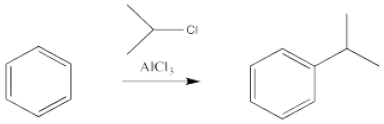


Instead, a bromine atom replaces one of the hydrogen atoms on the benzene. This reaction is greatly accelerated in the presence of Lewis acids, such as ferric chloride.

A similar reaction happens with chlorine. If treated with chlorine gas and a metal catalyst, a chlorine atom from chlorine gas can replace a hydrogen atom on benzene. However, the same thing doesn't work as smoothly with the other halogens, iodine and fluorine.

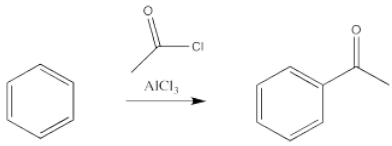


The reactions of chlorine and bromine with benzene and other aromatics can be catalysed by a variety of Lewis acidic metal catalysts. So can the reactions of alkyl halides and acyl halides, which we don't normally think of as electrophiles for alkene addition.



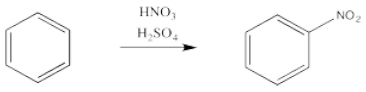
There are some limitations on what kind of groups can be added in this way. The carbon attached to the halide should be tetrahedral. Typically, it is much easier to add secondary or tertiary alkyls than primary ones. That is, the carbon attached to the halogen had best be attached to two or three other carbons as well. Methyls are very, very difficult to add in this way.

There is an exception. The carbon attached to the halogen need not be tetrahedral, provided it is a carbonyl carbon. That reaction is called an acylation.

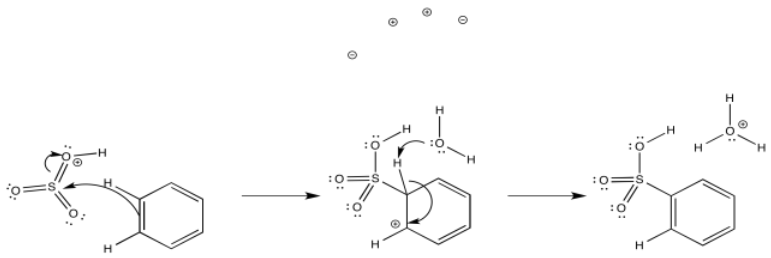


In these cases, it is the alkyl or acyl, rather than the halogen, that replaces a hydrogen atom on the benzene. Remember, benzene is most likely acting as a nucleophile in this reaction, even though it is following a different pathway than an alkene would. It is reacting with the most electrophilic part of the alkyl halide or acyl halide.

Aromatics have a limited repertoire of electrophiles with which they commonly undergo reaction. In addition to these Lewis acid-catalysed reactions, there are also reactions strong acidic media, such as a mixture of nitric and sulfuric acid.



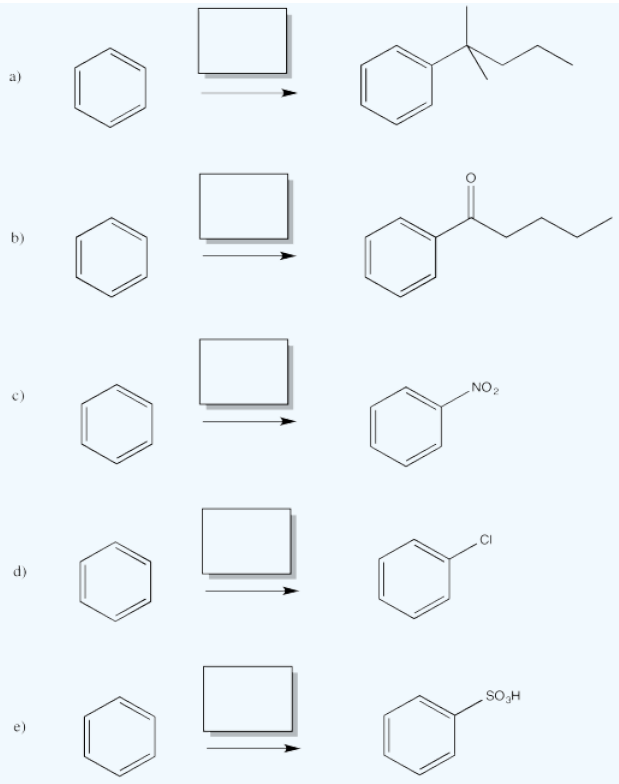
Another acidic medium, referred to as "fuming sulfuric acid", is really a mixture of sulfuric acid and sulfur trioxide.



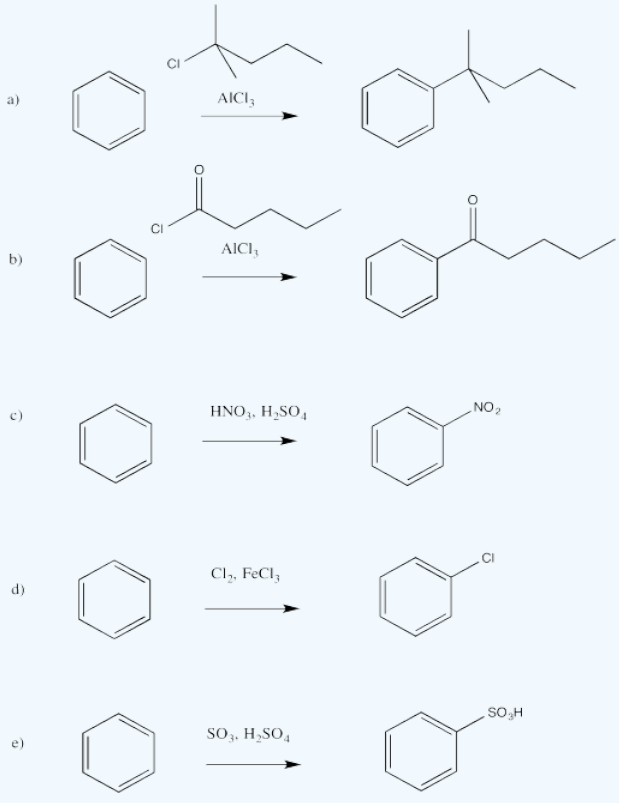
Just as with the acid-catalysed reactions, the nitro group and the sulfonate group just replace a hydrogen atom on the benzene ring. The overall reaction involves bond formation between a benzene carbon and the electrophile, and bond cleavage between the same carbon and a proton.

? Exercise 7.1.1

Fill in the missing reagents in the following reactions.

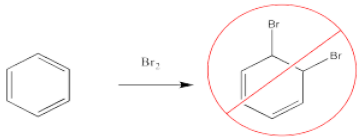


Answer

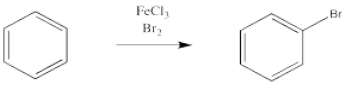


7.2: Mechanism of Electrophilic Aromatic Substitution

Bromine will not add across the double bond of benzene.



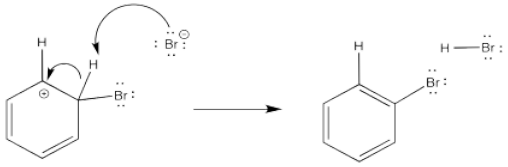
Instead, a bromine atom can replace one of the hydrogen atoms on the benzene. This reaction is especially easy in the presence of a catalyst.



How does that outcome happen? Why does that outcome happen?

There has been a good deal of study of these reactions and there is strong evidence of the steps through which they occur. As expected, the reaction involves donation of π electrons from the benzene. For the moment, we'll assume the electrophile is a bromine cation; we will deal with its exact structure later.

The problem is, that initial step results in the loss of aromaticity. The aromatic system confers a little extra stability on the π system, so the molecule is motivated to restore the aromaticity. The easiest way to do that, and get rid of a positive charge at the same time, would be to deprotonate the cation. Some base will pick up the proton; it is likely a bromide ion in this case. We will see later where that bromide comes from.



- Electrophilic aromatic substitution proceeds through a cationic intermediate.
- The intermediate forms via donation of π electrons from the arene to an electrophile.
- Aromaticity is restored through loss of a proton from this cation.

How do we know that the mechanism unfolds this way? There are three basic steps that are clearly accomplished during the course of the reaction: the C-H bond is broken, the C-Br bond is formed, and the Br-Br bond is broken.

When is the C-H bond broken? That question can be answered by looking for what is called an "isotope effect". The most common isotope of hydrogen is ^{1}H, or protium, but ^{2}H is also available; it is called "deuterium". Deuterium is often represented by the symbol D and protium by the symbol H. Deuterium is twice as heavy as the common protium. That mass difference leads to a lower vibrational frequency of a C-D bond than a C-H bond. The C-H bond vibrates more rapidly and energetically than a C-D bond; as a consequence, the C-H bond is more easily broken than the C-D bond.

If we take a sample of ordinary benzene, C_6H_6, and a sample of deuterated benzene, C_6D_6, we can measure how quickly they each undergo a bromination reaction. Very often, a reaction that involves C-H bond cleavage will slow down if a C-D bond is involved. This outcome is observed in E2 eliminations, for instance. This slowing of the reaction with the heavier isotope is called the deuterium isotope effect.

However, no deuterium isotope effect is observed during bromination, or other aromatic electrophilic substitution reactions. That absence of an isotope effect usually means the C-H bond cleavage is a sort of an afterthought. The hard part of the reaction is already done. Both the C-H and C-D bonds are broken so quickly and easily, by comparison, that we don't really notice the difference between them.

There is even more evidence. In a few exceptional cases, the cationic intermediate in this reaction is stable enough to be isolated and crystallized. X-ray diffraction shows that there is a tetrahedral carbon in the ring, indicating that the C-H bond has not broken yet.

The C-H bond is broken at the end of the reaction. When is the Br-Br bond broken?

That question is a little harder to answer. We can't use the same isotope strategy that we used with the C-H bond. Although deuterium is twice as heavy as protium, producing a substantial isotope effect, ^{81}Br is only 2.5% more massive than ^{79}Br. Any difference in rates involving these isotopes is undetectable. The exact nature of the bromine species in the reaction is complicated, and may even be different under different conditions.

Exercise 7.2.1

In the case of uncatalyzed bromination reactions, the addition of salts such as NaBr has no effect on the reaction rate, indicating that the arene reacts directly with Br_2 rather than Br^+. Explain this line of reasoning.

Answer

In the case of uncatalyzed bromination reactions, there is clear evidence that the Br-Br bond-breaking step does not start the reaction off. If that were the first step, there would presumably be an equilibrium between Br_2 and Br^+/Br^- ions. That equilibrium would be shifted back toward Br_2 if bromide salts were added. In that case, the amount of bromine cation would be suppressed and the reaction would slow down. No such salt effects are observed, however. That evidence suggests that, in the uncatalyzed reaction, the aromatic reacts directly with Br_2.

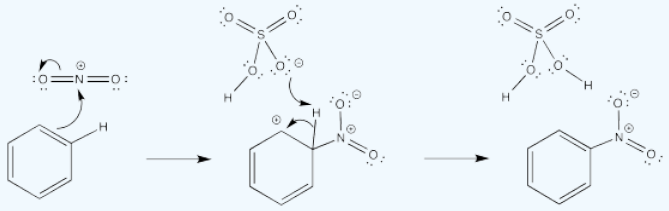
Exercise 7.2.2

Given each of the following electrophiles, provide a mechanism for electrophilic aromatic substitution.

a) NO_2^+ b) $CH_3CH_2^+$ c) SO_3H^+ d) CH_3CO^+

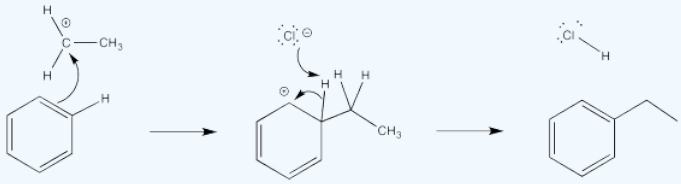
Answer a

In each case, a base must remove the proton from the cationic intermediate. An anion that would be present in solution has been chosen for this role.



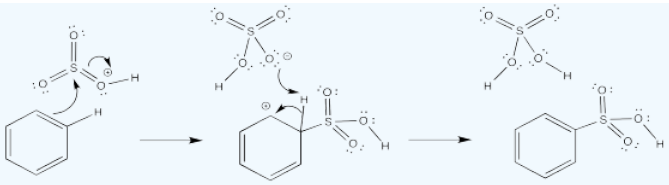
Answer b

In each case, a base must remove the proton from the cationic intermediate. An anion that would be present in solution has been chosen for this role.



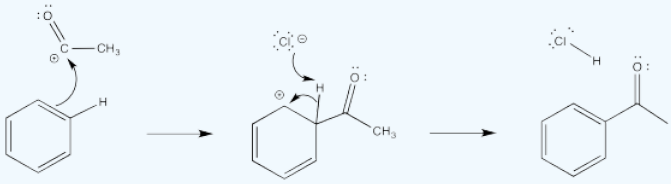
Answer c

In each case, a base must remove the proton from the cationic intermediate. An anion that would be present in solution has been chosen for this role.



Answer d

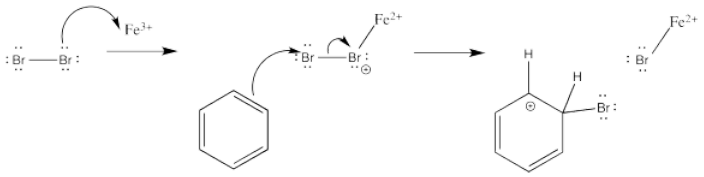
In each case, a base must remove the proton from the cationic intermediate. An anion that would be present in solution has been chosen for this role.



7.3: Formation of the Electrophile

The mechanism of electrophilic aromatic substitution follows two elementary steps. First, donation of a pair of π electrons to the electrophile results in a loss of aromaticity and formation of a cation. Second, removal of a proton from that cation restores aromaticity.

How does the electrophile form in the first place? The details of that part of the reaction vary from case to case. With the catalysed bromine reaction, the Lewis acid activates the halogen to render it more electrophilic. The activation may even go so far as to form a bromine cation, as suggested earlier. Otherwise, the positive charge on the bromine atom that ligates the Lewis acid can be nullified, indirectly, when the arene donates to the terminal bromine atom.

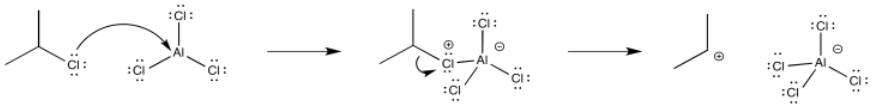


The appearance of a bromide ion to deprotonate the cation simply results fom the equilibrium of the Lewis acid-base complex.

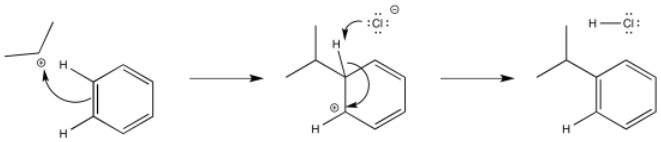
? Exercise 7.3.1

Show the mechanism for chlorination of benzene in the presence of ferric chloride.

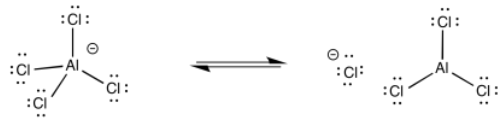
The reactions of alkyl and acyl halides also involve Lewis acid catalysts; frequently, aluminum chloride ($AlCl_3$) is employed. These two reactions are called Friedel-Crafts reactions after the French and American co-discoverers of the reaction. Typically, Friedel-Crafts reactions are believed to occur through initial formation of cationic electrophiles, which then react with aromatics in the same way as halogen electrophiles.



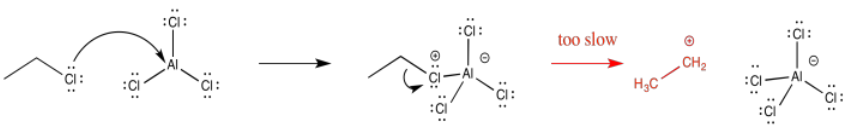
The alkyl cation is a potent electrophile. It is able to temporarily disrupt the aromaticity of the aromatic ring, forming an arenium ion.



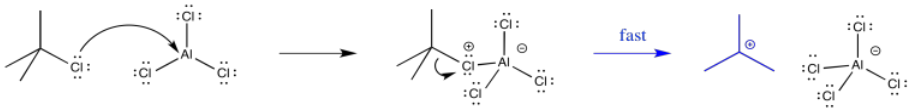
The arenium ion intermediate is probably deprotonated by halide ion; some amount of these ions would be in equilibrium with the Lewis acid-base adduct.



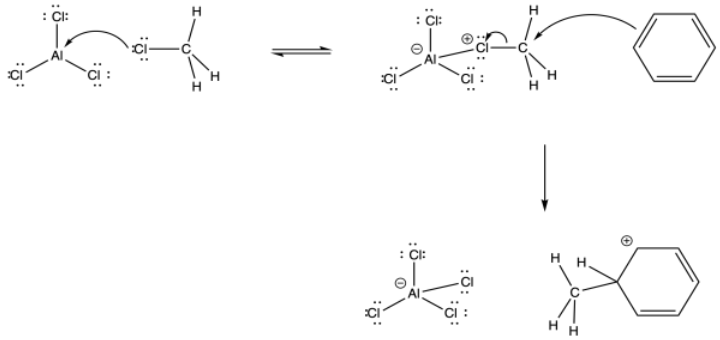
Because Friedel-Crafts alkylations occur via alkyl cations, the reactions of primary alkyl halides are generally pretty slow. Those cations just aren't stable enough to form. Although it sometimes seems like formation of a stable intermediate would slow things down, because it would not be motivasted to react further, usually the reverse is true. Because an intermediate is at high energy, it is inherently difficult to form in the first place. This difficulty acts as a blockade on the reaction, so that it doesn't proceed very easily.



Forming the intermediate more easily, therefore, allows the reaction to proceed more quickly. For example, the tert-butyl cation is relatively stable, so that intermediate is formed relatively easily. Alkylation of aromatics rings with tertiary alkyl halides is especially easy to accomplish.



In some cases, formation of a cation probably does not happen at all. Instead, the activated Lewis acid-base complex acts as the electrophile directly. This pathway seems to occur with methyl electrophiles. However, there are also indications that primary alkyl halides undergo this mechanism in parallel with the cationic mechanism.

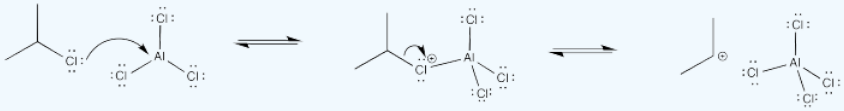


It is worth noting that in some cases, multiple products may result via rearrangements. These observations provide additional evidence for the cationic nature of the intermediates as well as competing pathways.

? Exercise 7.3.2

Show the mechanism for the Friedel-Crafts alkylation of benzene with 2-chloropropane in the presence of aluminum chloride.

Answer

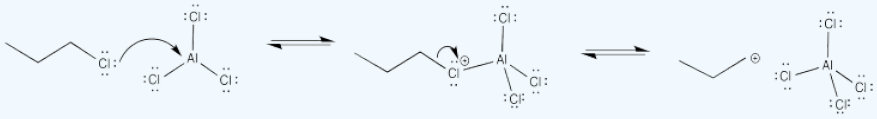


? Exercise 7.3.3

Why is the Friedel-Crafts reaction of 1-chloropropane so much slower than the reaction of 2-chloropropane? Explain using a mechanism and intermediates.

Answer

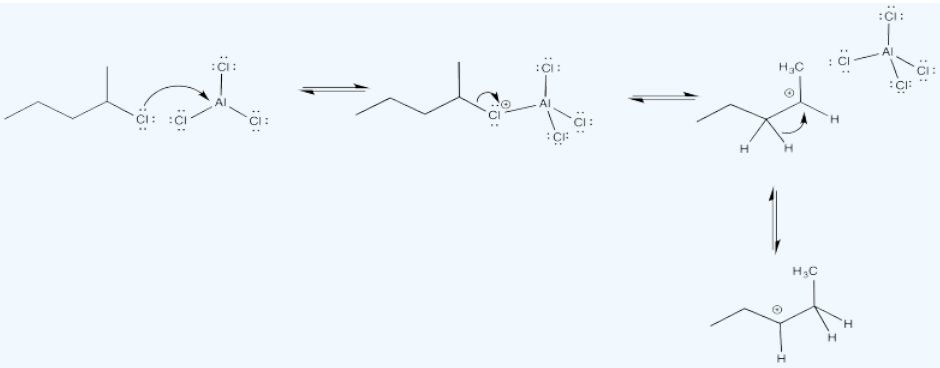
The primary cation formed is very unstable. As a result, there is a high barrier to cation formation.



? Exercise 7.3.4

Show why Friedel-Crafts alkylation of benzene with 2-chloropentane results in the formation of two different products.

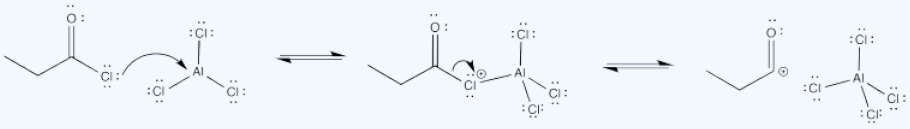
Answer



Exercise 7.3.5

Show the mechanism for the Friedel-Crafts acylation of benzene with ethanoyl chloride (acetyl chloride) in the presence of aluminum chloride.

Answer



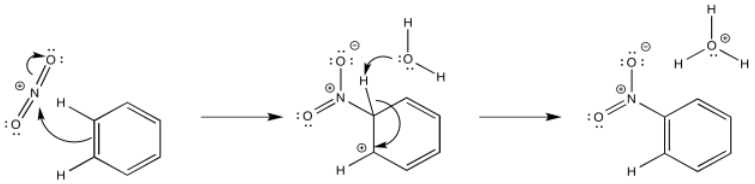
Exercise 7.3.6

Show why the Friedel-Crafts acylation of benzene with pentanoyl chloride results in only one product, with no rearrangement.

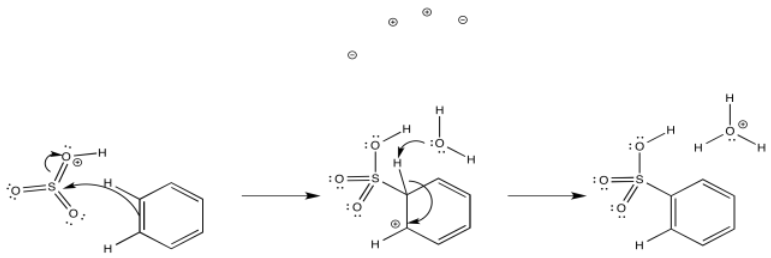
Answer

The cation that results is stabilized via π-donation from oxygen.

Nitration and sulfonation reactions differ from the other substitutions that we have seen because they do not utilize Lewis acid catalysis. These reactions depend on equilibria that occur in strongly acidic media. When nitric acid is dissolved in sulfuric acid, there is spectroscopic evidence than NO_2^+ forms, providing an electrophile. That electrophile adds readily to the aromatic ring.



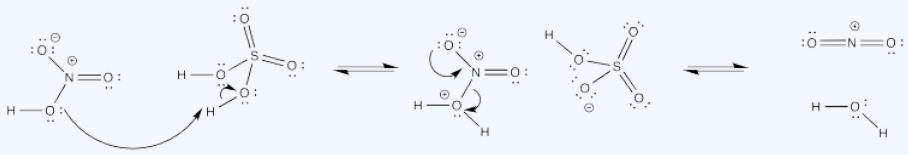
Similarly, when sulfuric acid is concentrated by boiling off residual water, sulfur trioxide results. Under these acidic conditions, the latter easily forms SO_3H^+, the electrophile in sulfonation.



Exercise 7.3.7

Provide a mechanism for the formation of NO_2^+ from nitric and sulfuric acid.

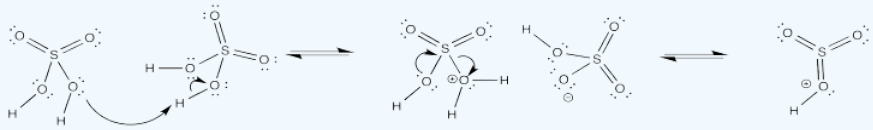
Answer



Exercise 7.3.8

Provide a mechanism for the formation of SO_3H^+ from sulfuric acid.

Answer



7.4: Activation and Deactivation

Because the benzene acts as a nucleophile in electrophilic aromatic substitution, substituents that make the benzene more electron-rich can accelerate the reaction. Substituents that make the benzene moor electron-poor can retard the reaction.

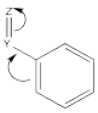
In the mid-twentieth century, physical organic chemists including Christopher Ingold conducted a number of kinetic studies on electrophilic aromatic substitution reactions. In the table below, you can see that some substituents confer a rate of reaction that is much higher than that of benzene (R = H). Phenol, C_6H_5OH, undergoes nitration a thousand times faster than benzene does. Nitrobenzene, $C_6H_5NO_2$, undergoes the reaction millions of times more slowly.

Rate of nitration in benzene derivatives	
R in C_6H_5R	Relative rate
OH	1,000
CH_3	25
H	1
CH_2Cl	0.71
I	0.18
F	0.15
Cl	0.033
Br	0.030
CO_2Et	0.0037
NO_2	6×10^{-8}
NMe_3^+	1.2×10^{-8}

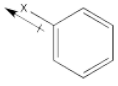
These observations are consistent with the role of the aromatic as a nucleophile in this reaction. Substituents that draw electron density away from the aromatic ring slow the reaction down. These groups are called deactivating groups in this reaction. Substituents that readily donate electron desnity to the ring, or that effectively stabilize the cationic intermediate, promote the reaction. These groups are called activating groups in this reaction.

The roles of these groups are related to their electronic interactions with the electrons in the ring. Some groups might be π-donors, providing additional electron density to the benzene ring via conjugation.

Other groups may be π-acceptors, drawing electron density away from the ring via conjugation.



Still others may be σ-acceptors, drawing electron density away from the ring via a simple inductive effect which arises from the electronegativity of a substituent.



In some cases, there may be multiple effects, and the overall influence of the substituents is determined by the balance of the effects. One effect may be stronger in one case than the other, so it wins out in one case and loses in another.

Exercise 7.4.1

Explain why a fluorine atom would slow down an electrophilic substitution on an adjacent benzene ring.

Exercise 7.4.2

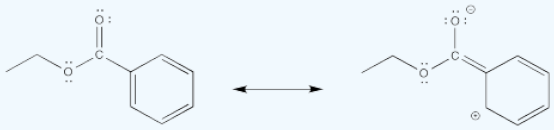
Show, with structures, how the OH group in phenol makes the benzene ring more nucleophilic.

Answer

Exercise 7.4.3

Show, with structures, how the CO_2Et group makes the benzene ring less nucleophilic.

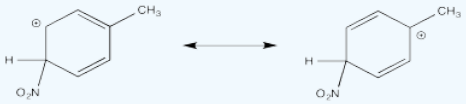
Answer



Exercise 7.4.4

Show, with structures, how a methyl group stabilizes the cationic intermediate during a nitration reaction.

Answer



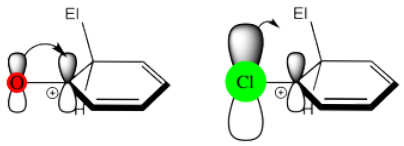
In general, deactivating groups fall into two classes. Π-acceptors, such as carbonyls, if placed directly adjacent to the aromatic ring, slow down the reaction. Highly electronegative atoms, typically halogens, attached directly to the aromatic ring also slow down the reaction.

- deactivating groups make electrophilic aromatic substitutionslower than in benzene
- π-acceptors are deactivating groups
- halogens are deactivating groups

Activating groups also fall into two categories. Π-donors, typically oxygen or nitrogen atoms, accelerate the reaction. This observation is true even though these atoms are also highly electronegative. Alkyl groups attached to the aromatic ring also accelerate the reaction.

- activating groups make electrophilic aromatic substitution faster than in benzene
- oxygen and nitrogen π-donors are activating groups
- alkyls are activating groups

Note that halogens are also π-donors, but they are less effective in this regard than nitrogen or oxygen. That's because nitrogen and oxygen are similar in size to carbon, and they form effective π-overlap with the adjacent carbon on the benzene ring. In the halogens, electronegativity wins by default, because their π-donating effects are not good enough to make them activators.

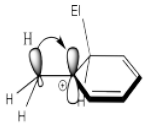


Conversely, nitrogen and oxygen are both very electronegative, but their exceptional π-donating ability makes them activators rather than deactivators. Thus, in many cases, there is a subtle balance between activating and directing effects. In some cases, the activating effect is more pronounced, and that is what is observed. In other cases, it is the deactivating effect that wins out.

mostly deactivating mostly activating

Alkyl groups behave almost as sigma donors, although that may be a misleading way to think about them.

Instead, their mild activating effect arises from hyperconjugation, in which a pair of C-H bonding electrons can weakly interact with a cationic site, providing a little extra stability to the cation.



Exercise 7.4.5

One of the groups in the table, CH_2Cl, does not quite fit the general rules. It is very slightly deactivating. Explain why this group acts in this way.

Answer

This is a substituted alkyl group. An alkyl group should be moderately activating, but the presence of a halogen exerts an inductive electron-withdrawing effect. The cation-stabilizing effect of the alkyl substituent is completely counteracted by the halogen.

Exercise 7.4.6

Predict whether each of the following groups would be activating or deactivating towards electrophilic aromatic substitution.

a) NH_2 b) CN c) OCH_3 d) SMe_2^+ e) $C(O)CH_3$

Answer a

a) activating

Answer b

b) deactivating

Answer c

c) activating

Answer d

d) deactivating

Answer e

e) deactivating

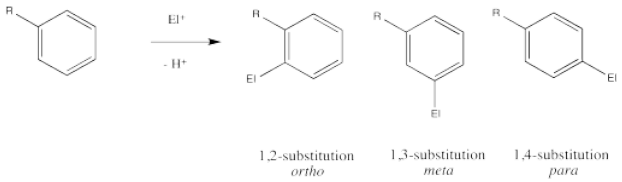
Exercise 7.4.7

Explain the trend in activating effects among the different halogens.

7.5: Directing Effects

In addition to exerting an effect on the speed of reaction, substituents on the benzene ring also influence the regiochemistry of the reaction. That is, they control *where* the new substituent appears in the product.

Remember, there are three different position on the bezene ring where a new substituent can attach, relative to the original substituent. Substitution could actually occur on five positions around the ring, but two pairs are related by symmetry. Isomerism in disubstituted benzenes can be described by numbering the substituents (1,2- etc) or by the relationships *ortho*-, *meta*- and *para*-. There are two positions *ortho*- to the initial substituent and two positions *meta*- to it.



Ingold and colleagues investigated the question of regiochemistry in nitration. They reported the following observations:

Substitution patterns during nitration of benzene derivatives

R in C_6H_5R	% *o*- product	% *m*- product	% *p*- product
CH_3	56	3	41
F	10	0	90
Cl	30	0	70
Br	38	0	62
OH	10	0	90
CHO	19	72	9
CO_2Et	28	68	3
CN	17	81	2
NO_2	6	94	0

In looking at the table, you might see that there are two groups of substituents. One group reacts to make mixtures of *ortho*- and *para*- products. There may be different ratios of *ortho*- to *para*- and there may be small amounts of *meta*-, but don't get bogged down in the details right now. Focus on the bigger picture. Some groups are "*ortho*-/*para*-directors".

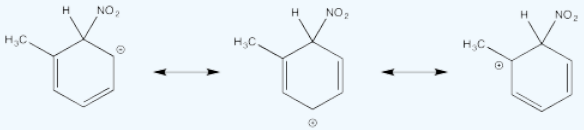
The other group reacts to makemostly *meta*-substituted products. There may be small amounts of*ortho*- and *para*- products, but don't worry about that. Focus on the bigger picture. Some groups are "*meta*-directors".

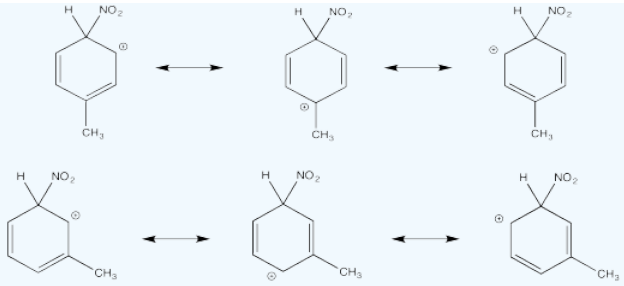
These regiochemical effects are very closely related to the activating and directing effects we have already seen. If we want to understand this data, we need to think about things like π-donation, π-acceptance, inductive effects and cation stability.

? Exercise 7.5.1

Show resonance structures for the cationic intermediate that results during nitration of toluene (methylbenzene). Explain why a mixture of *ortho*- and *para*- substitution results.

Answer



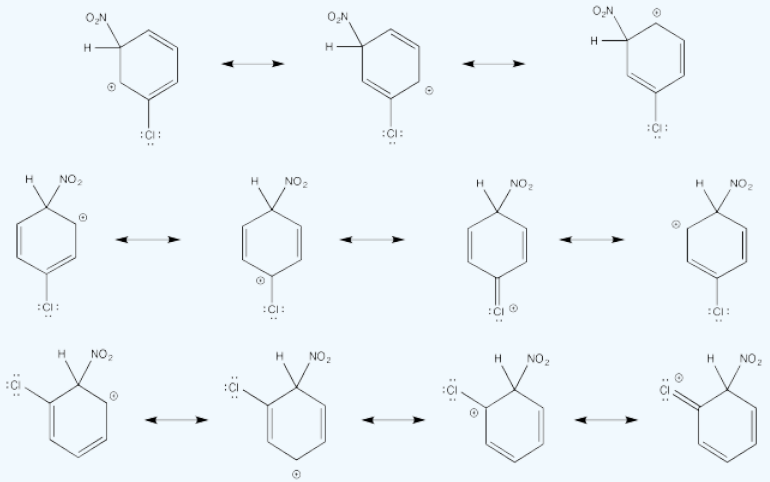


The tertiary cations that result during *ortho*- and *meta*- substitution offer extra stability, leading to preferential formation of these cations.

Exercise 7.5.2

Show resonance structures for the cationic intermediate that results during nitration of chlorobenzene. Explain why a mixture of *ortho*- and *para*- substitution results.

Answer

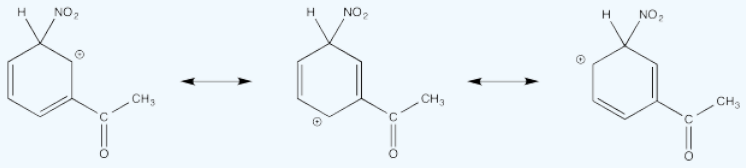


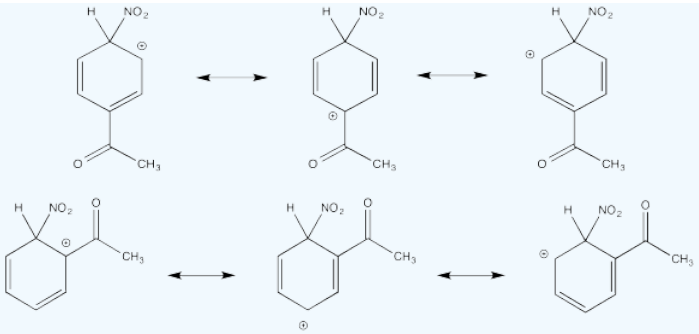
The π-donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

Exercise 7.5.3

Show resonance structures for the cationic intermediate that results during nitration of acetophenone ($C_6H_5COCH_3$). Explain why mostly *meta*- substitution results.

Answer



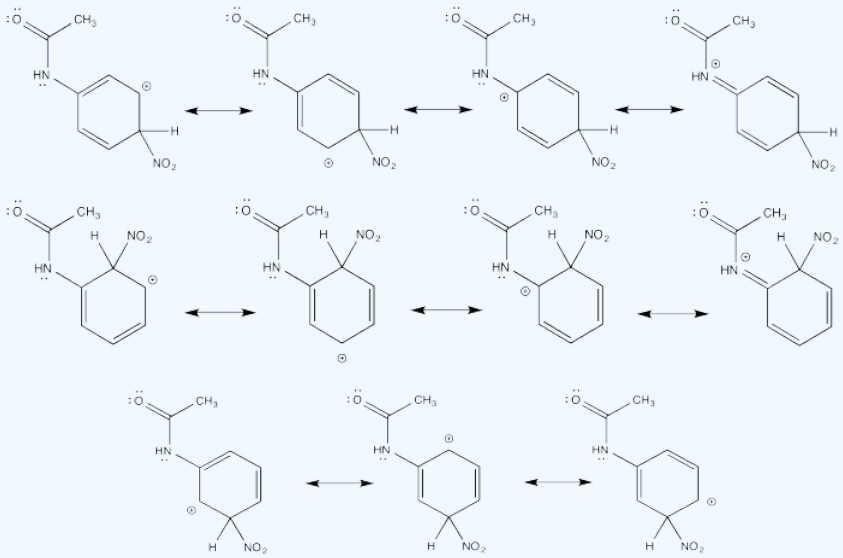


The cation directly adjacent to the carbonyl is destabilized by the electron withdrawing effect of the ketone. By default, the other intermediate is preferentially formed.

Exercise 7.5.4

Show resonance structures for the cationic intermediate that results during nitration of acetanilide ($C_6H_5NH(CO)CH_3$). Explain why a mixture of *ortho*- and *para*- substitution results.

Answer



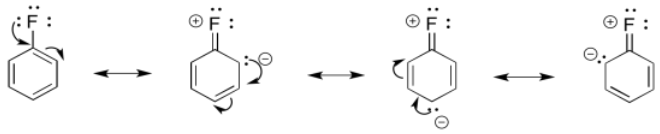
The π-donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

In general, we can divide these substituents into three groups:

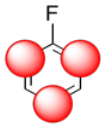
- π-acceptors are *meta*- directors.
- π-donors are *ortho*-/*para*- directors.
- alkyls are *ortho*-/*para*- directors.

Note that, once again, we may have two competing effects in one substituent, such as a halogen. In halogens, although the net effect may be to slow the reaction down, that weak π-donation is still enough to tilt the balance of products in favor of ortho- and para- substitution.

For example, fluorine has a lone pair. It can be a π-donor.

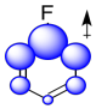


We could illustrate the effects with the following cartoon. It shows negative charge buildup, illustrated in red, on three of the carbons on the benzene ring.

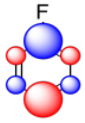


Fluorine is also very electronegative. It can be an electron withdrawing group. Because it withdraws electrons through its sigma bond rather than through resonance effects, we think of it as "inductively" electron withdrawing. Nonetheless, a considerable amount of electron density from the benzene is attracted to the fluorine.

Again, we could illustrate the effects with a cartoon. It shows positive charge buildup, illustrated in blue, on the carbons that are closest to the fluorine. Remember, electrostatic interactions decrease rapidly with distance, so the farther the carbons are from the fluorine, the lower the effect that they will experience.

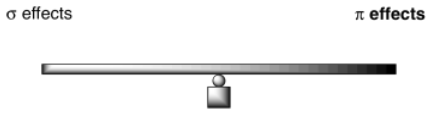


The sum of these effects can be illustrated in a composite cartoon that shows different amounts of positive or negative charge built up on different carbons.

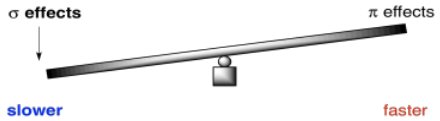


Thus, although fluorine is generally an electronegative and deactivating group, it may still manage to place some extraelectron density on particular carbons.

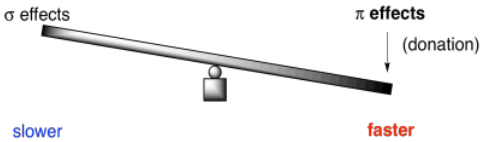
Whether something is overall activating or deactivating depends on a similar balance of factorsIn general, we can think about competing effects in terms of a see saw.



For an electronegative π-donor like fluorine or another halogen, the stronger those σ-withdrawing effects, the slower the reaction. It pulls more electron density away from the benzene than it puts back. As a result, the benzene is less nucleophilic than it would be if the halogen were not there.

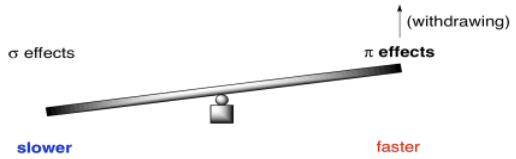


On the other hand, the better the π-donation, the faster the reaction. Good π-donors include oxygen and nitrogen. They are just the right size to lend a lone pair to a neighbouring carbon in the benzene ring. Halogens, on the other hand, are relatively clumsy donors. Either they are just a little too electronegative to be useful, like fluorine, or else they are a little too big to share wtih carbon. That's the case with chlorine, bromine and iodine.



Remember, the same argumants are true in carbonyl chemistry. The general reactivity of carboxyloid derivatives depends on a similar balance between donating and withdrawing effects. As a result, esters and amides are relatively stable and unreactive, whereas chlorides are very reactive.

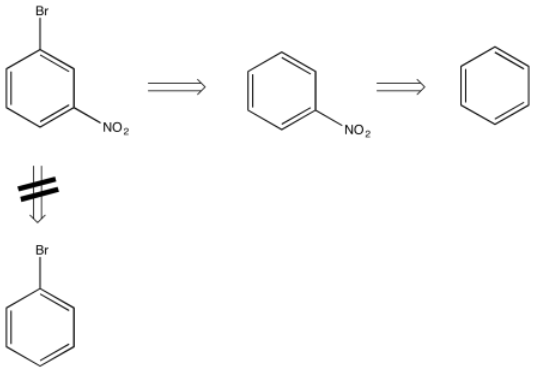
Of course, a π-acceptor would work in the opposite way. That would be true if the atom attached to the benzene is multiply bonded to another atom, especially if that other atom is something electronegative (an oxygen or a nitrogen).



Retrosynthetic Planning

Sometimes in synthetic work it is useful to look at a compound and imagine what it might be made from. This practice is used in industrial chemistry, when a researcher might be trying to decide on the most economical routed to make a particular compound. There may be readily available materials that a useful pharmaceuticla can be made from. By working backwards one step at a time, the researcher may more easily see different possibilities for starting materials. In a similar way, a biological chemist might be able to identify what biological precursors could lead to the formation of a particular compound in biology.

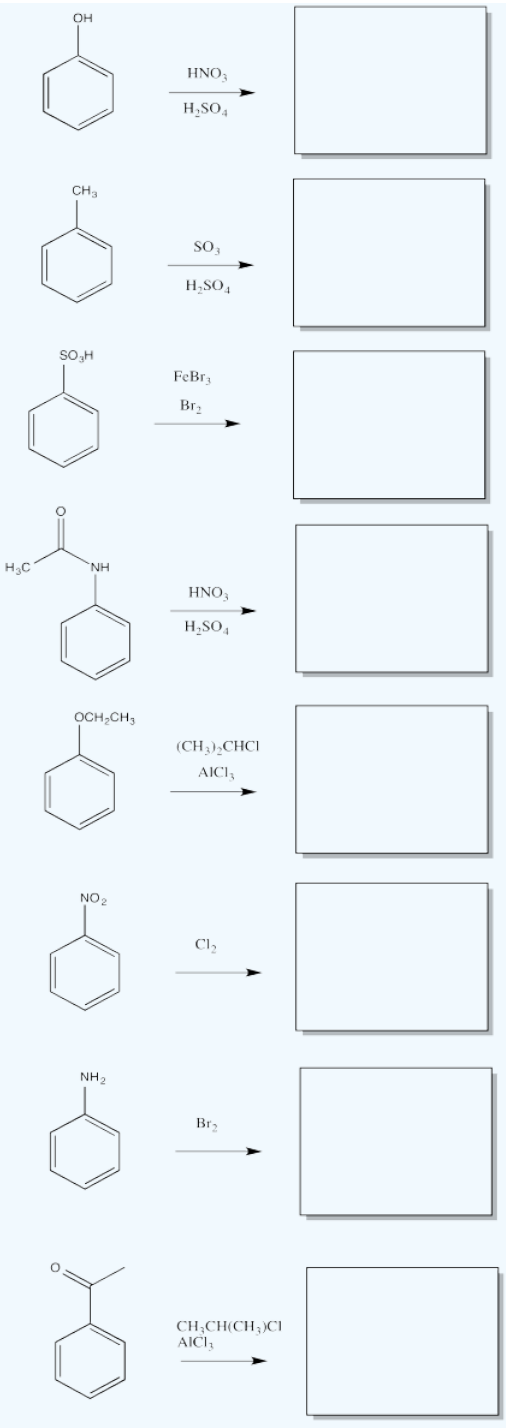
For example, by looking at the structure of *m*-bromonitrobenzene, you could imagine that the compound could be made by the bromination of nitrobenzene, but not by the nitration of bromobenzene. That's because nitro groups are *meta*-directors, but bromo-groups are *ortho*-, *para*-directors.



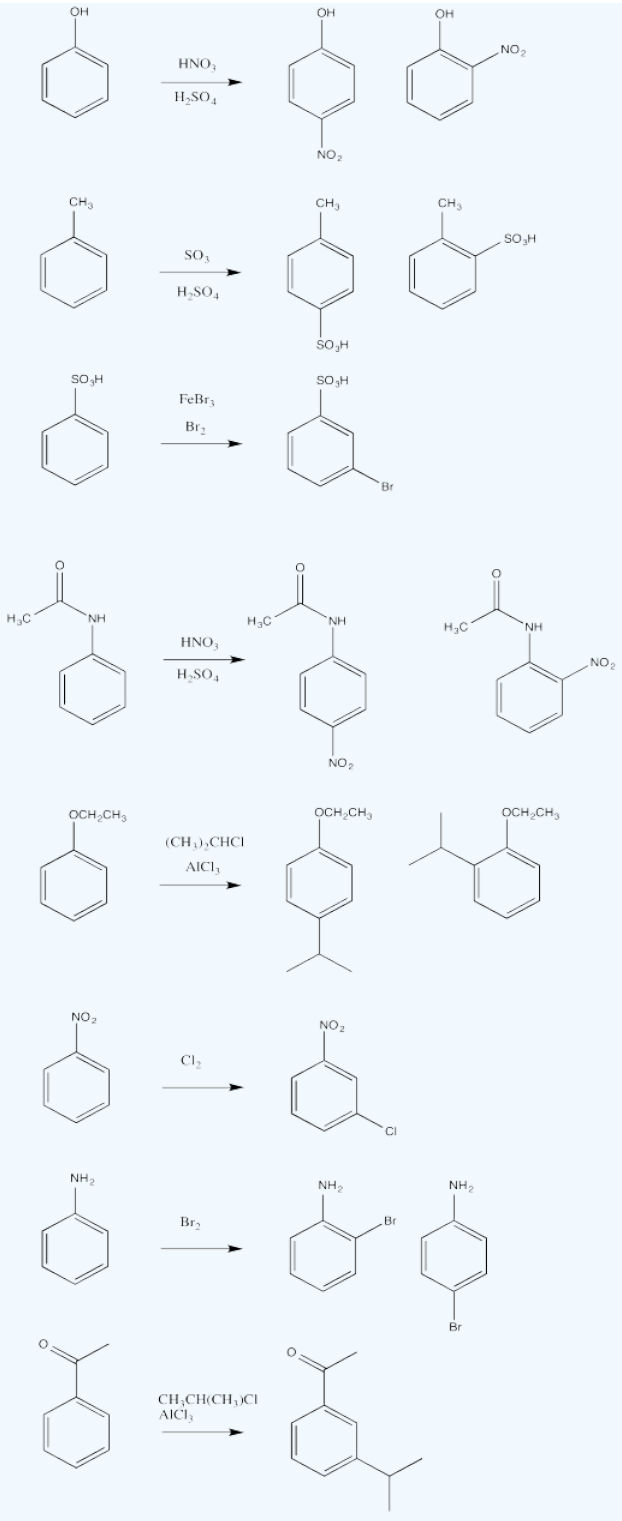
This method of working backward from the target compound is called "retrosynthetic analysis". By making a retrosynthetic plan, we can more efficiently arrive at the possible ways to make a specific compound.

? Exercise 7.5.5

Fill in the major organic products of the following reactions.

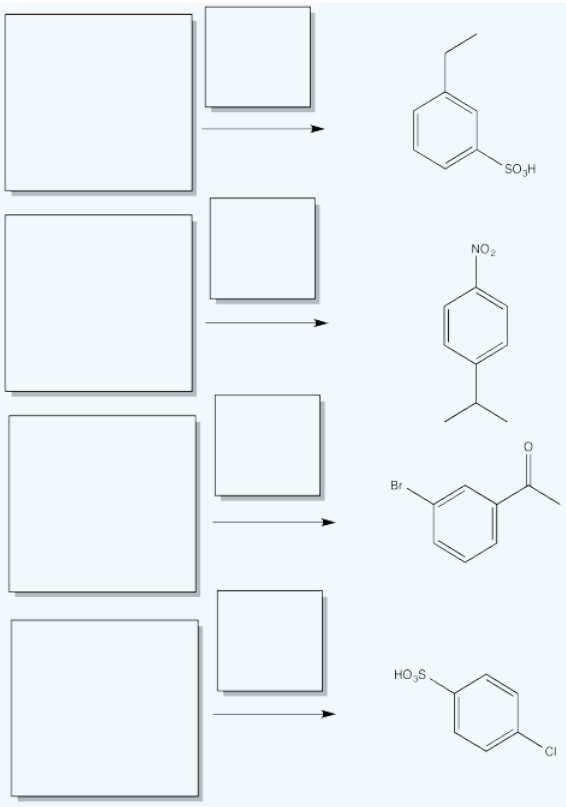


Answer

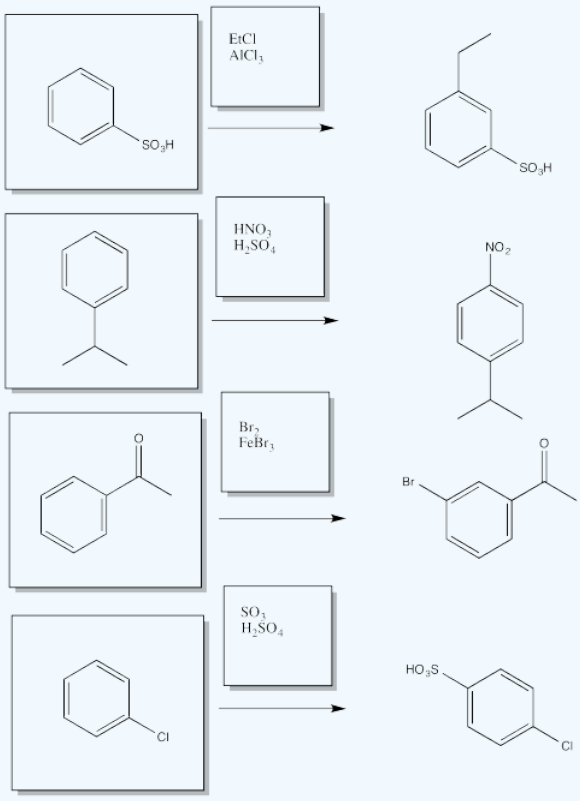


Exercise 7.5.6

Fill in the starting materials and reagents needed to obtain the major product shown via electrophilic aromatic substitution.

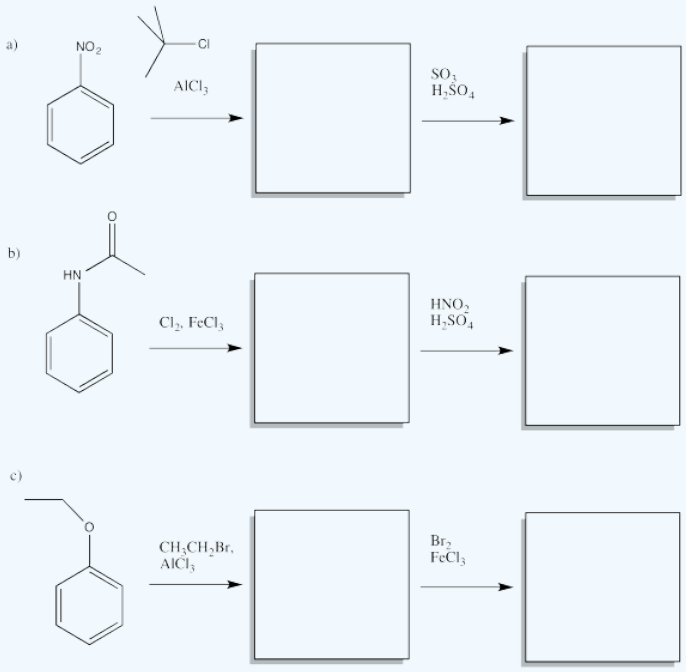

SO3H
NO2
Br
O
HO3S
Cl

Answer


EtCl
AlCl3
SO3H
HNO3
H2SO4
NO2
Br2
FeBr3
O
Br
SO3
H2SO4
HO3S
Cl

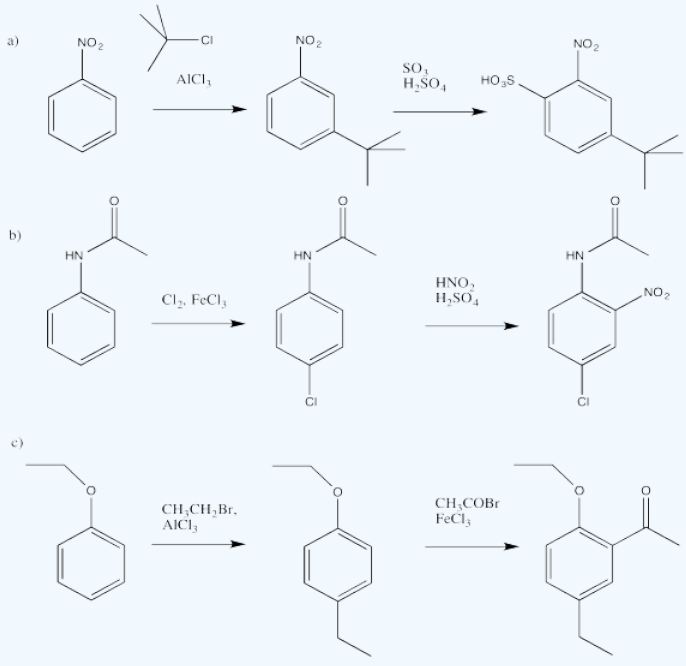
Exercise 7.5.7

Given two different substituents on a benzene, there can sometimes be a conflict in predicting which substitution pattern will result. Generally, the group with the stronger activating effect wins out. Predict the major products of the following reactions.



Answer

In cases leading to mixtures of *ortho* and *para* products, only one product was chosen, based on minimal steric interactions.

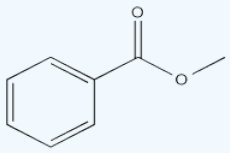


Exercise 7.5.8

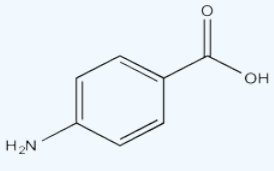
Problem AR5.8

Starting from benzene and any monofunctional group compound, propose a synthesis for the following.

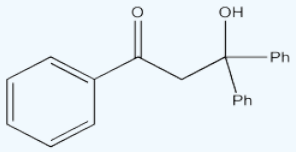
A)



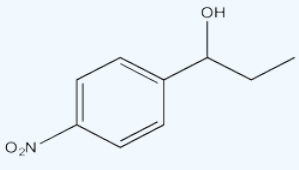
B)



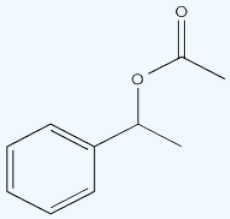
C)



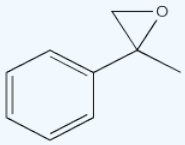
D)



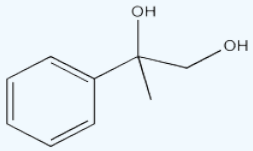
E)



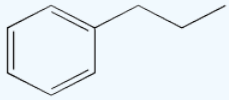
F)



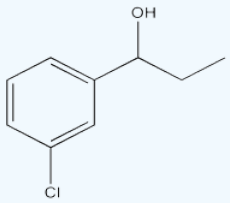
G)



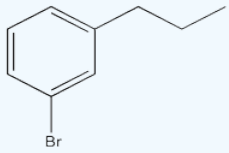
H)



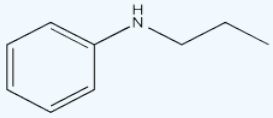
I)



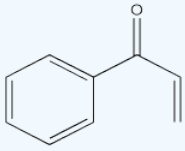
J)



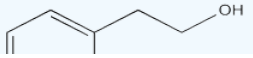
K)



L)



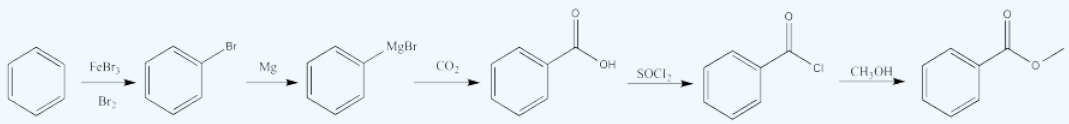
M)



Answer

Starting from benzene and any monofunctional group compound, propose a synthesis for the following. There may be more than one answer than is presented here.

A)



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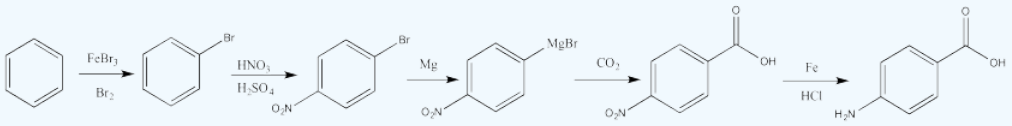
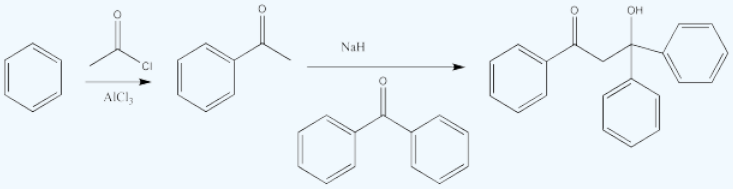


C)



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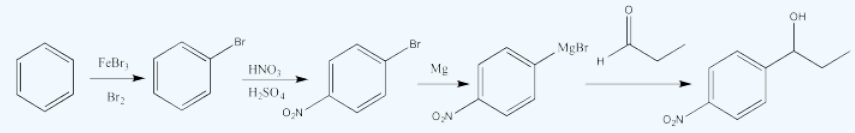
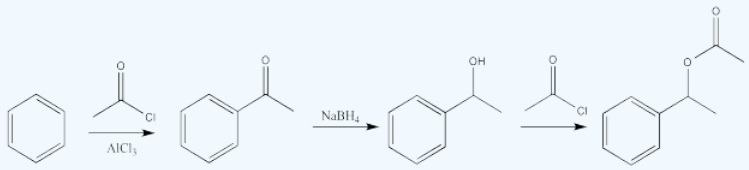


E)



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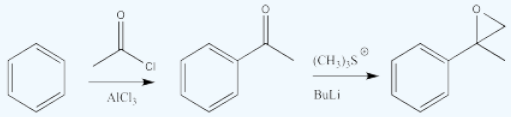
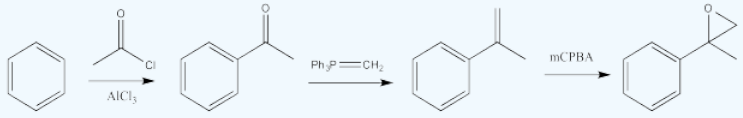
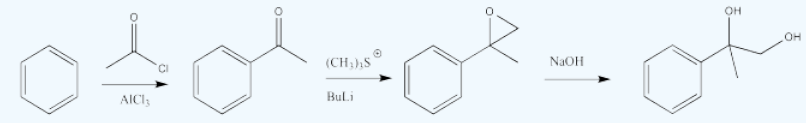
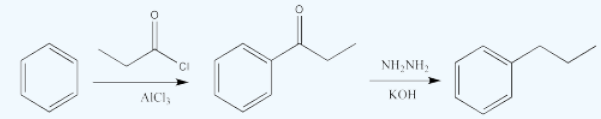


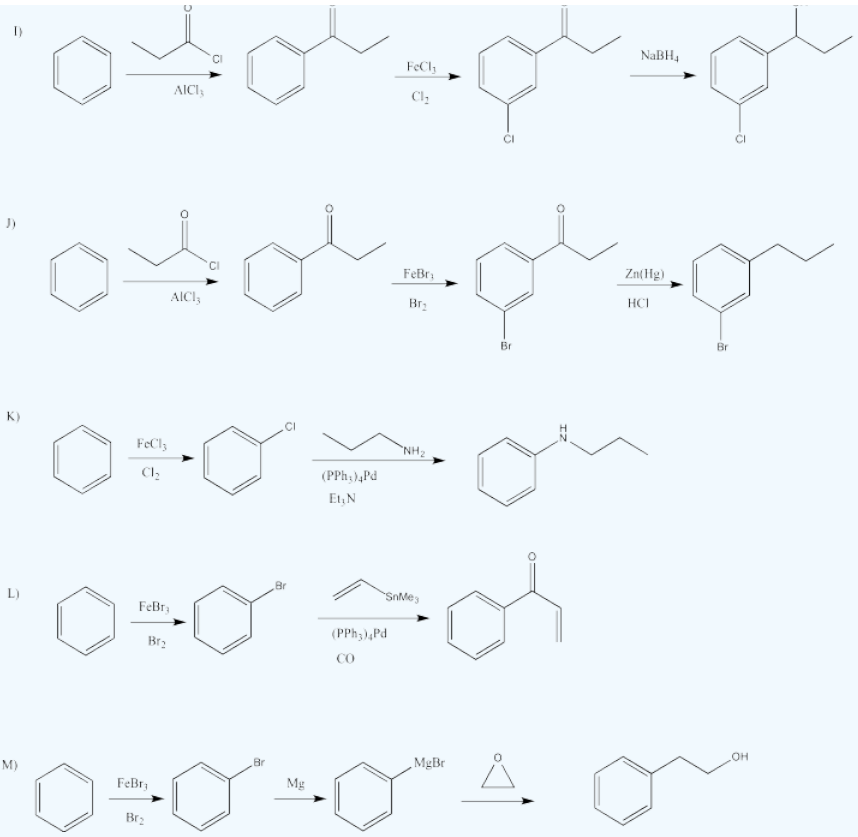


G)



H)

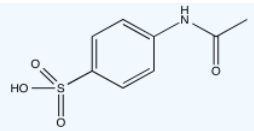




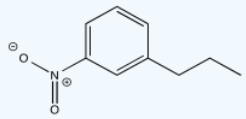
Exercise 7.5.9

Provide a retrosynthetic plan for each of the following compounds, going back to benzene.

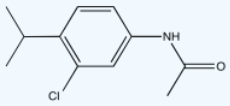
a)



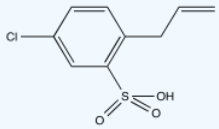
b)



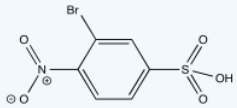
c)



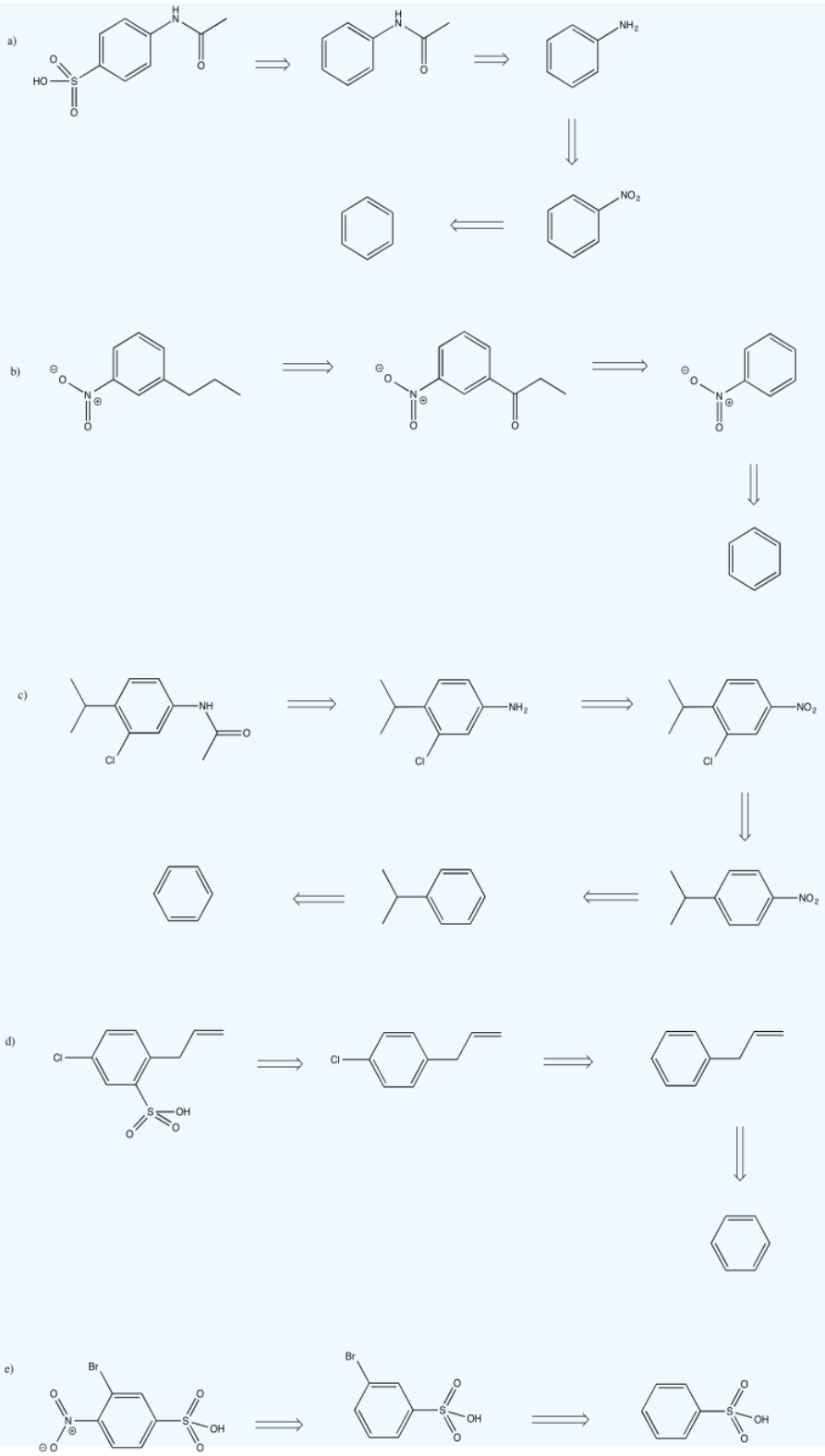
d)



e)



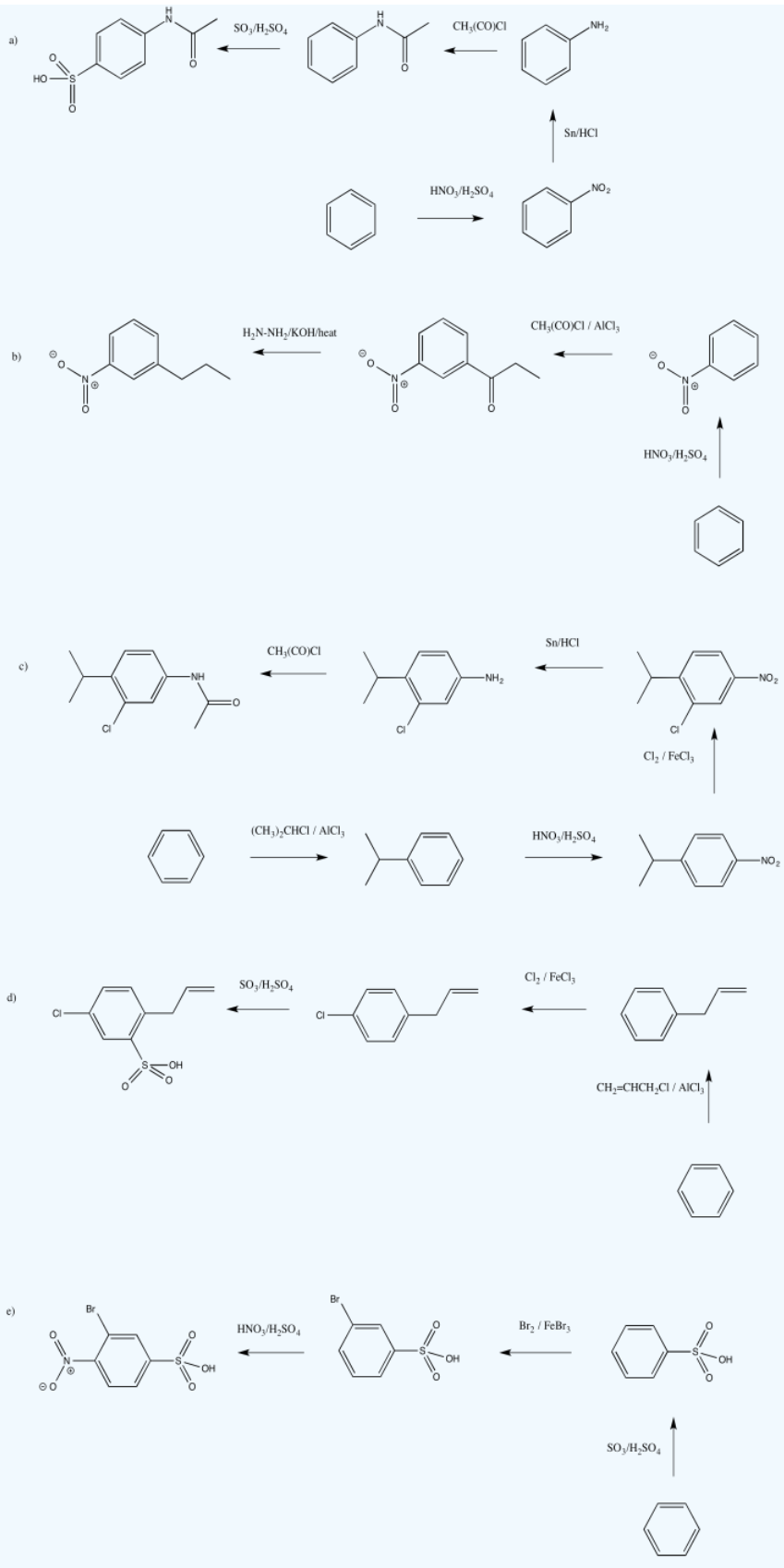
Answer



Exercise 7.5.10

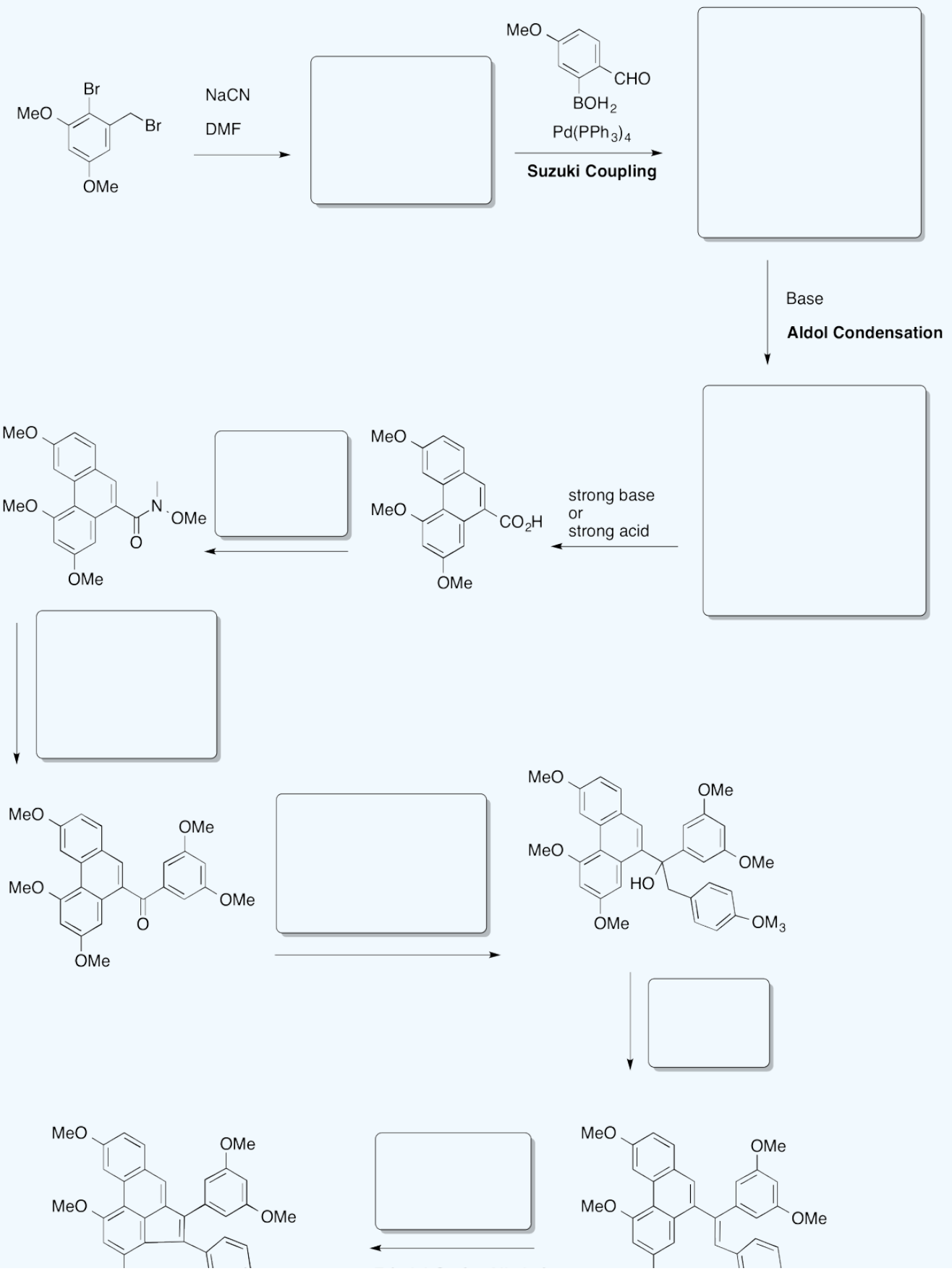
Turn the retrosynthetic plans from the previous problem into syntheses.

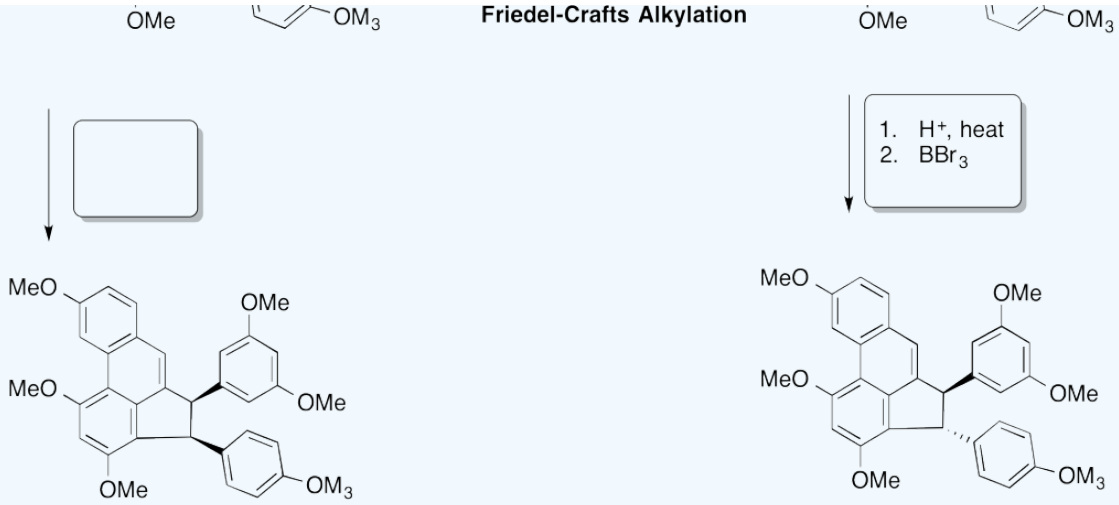
Answer



Exercise 7.5.11

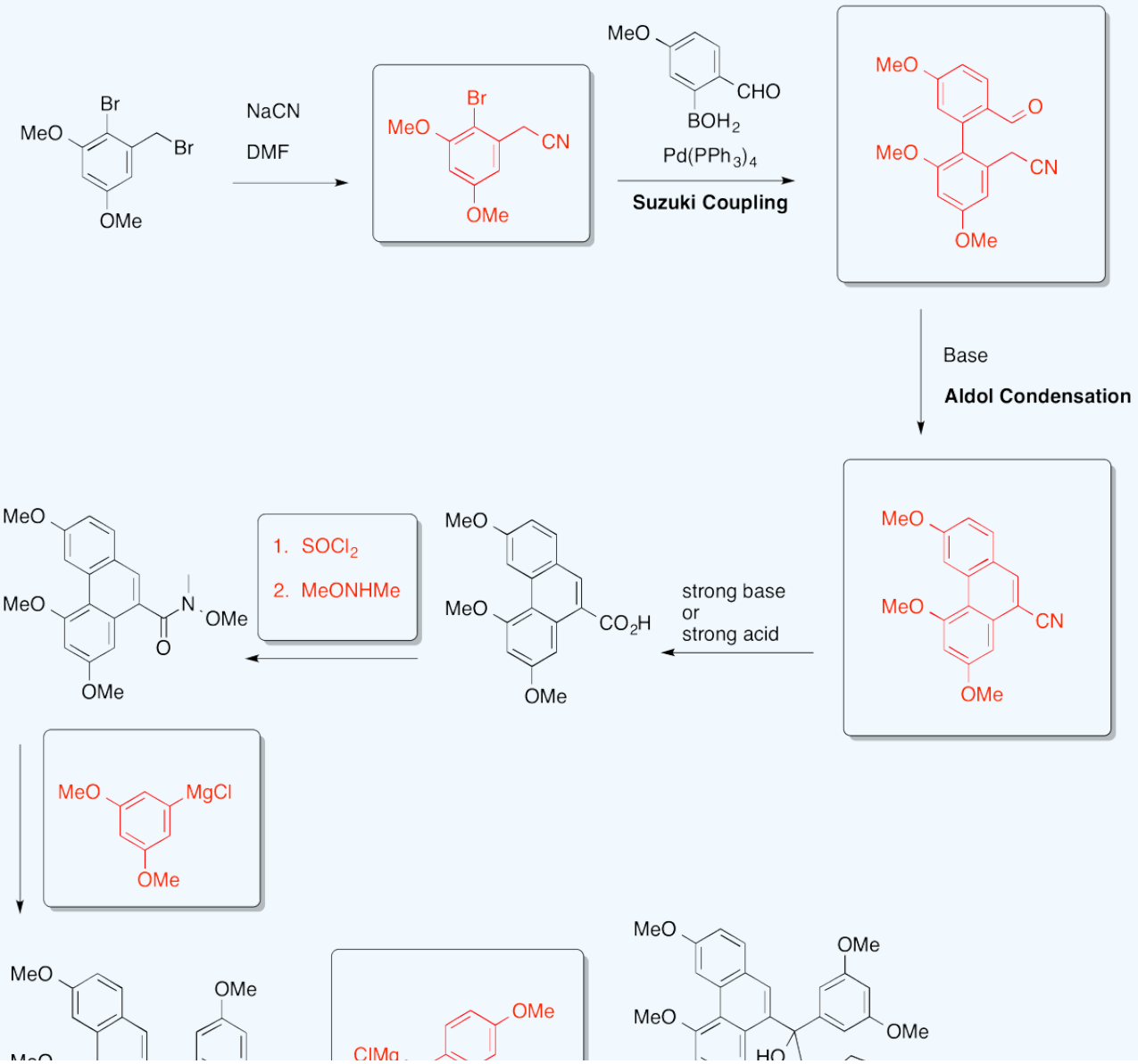
Choi, Kim and Heo, Total Synthesis of Laetevirenol A, *J. Org. Chem.*, **2012**, *77*, 8762-8767.

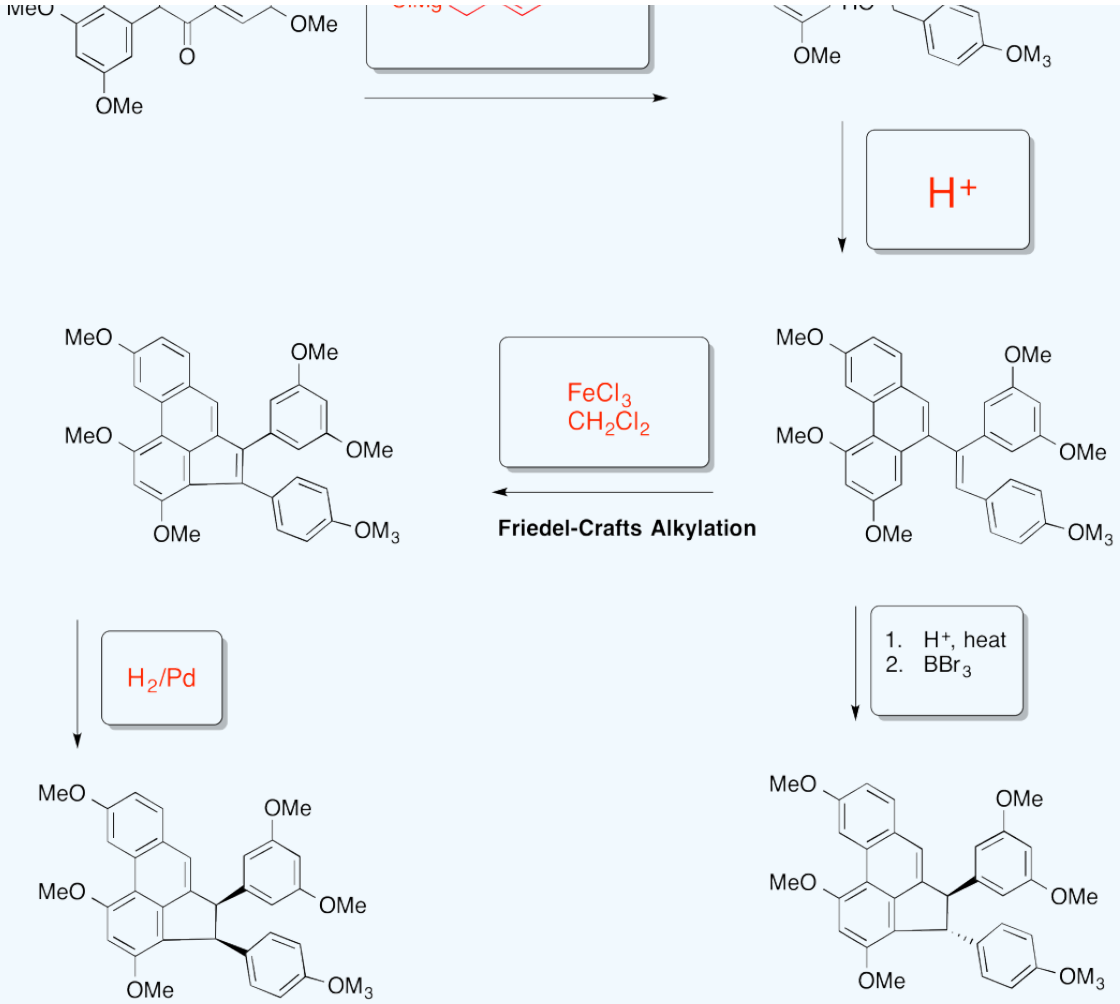




Answer

Choi, Kim and Heo, Total Synthesis of Laetevirenol A, *J. Org. Chem.*, **2012**, *77*, 8762-8767.

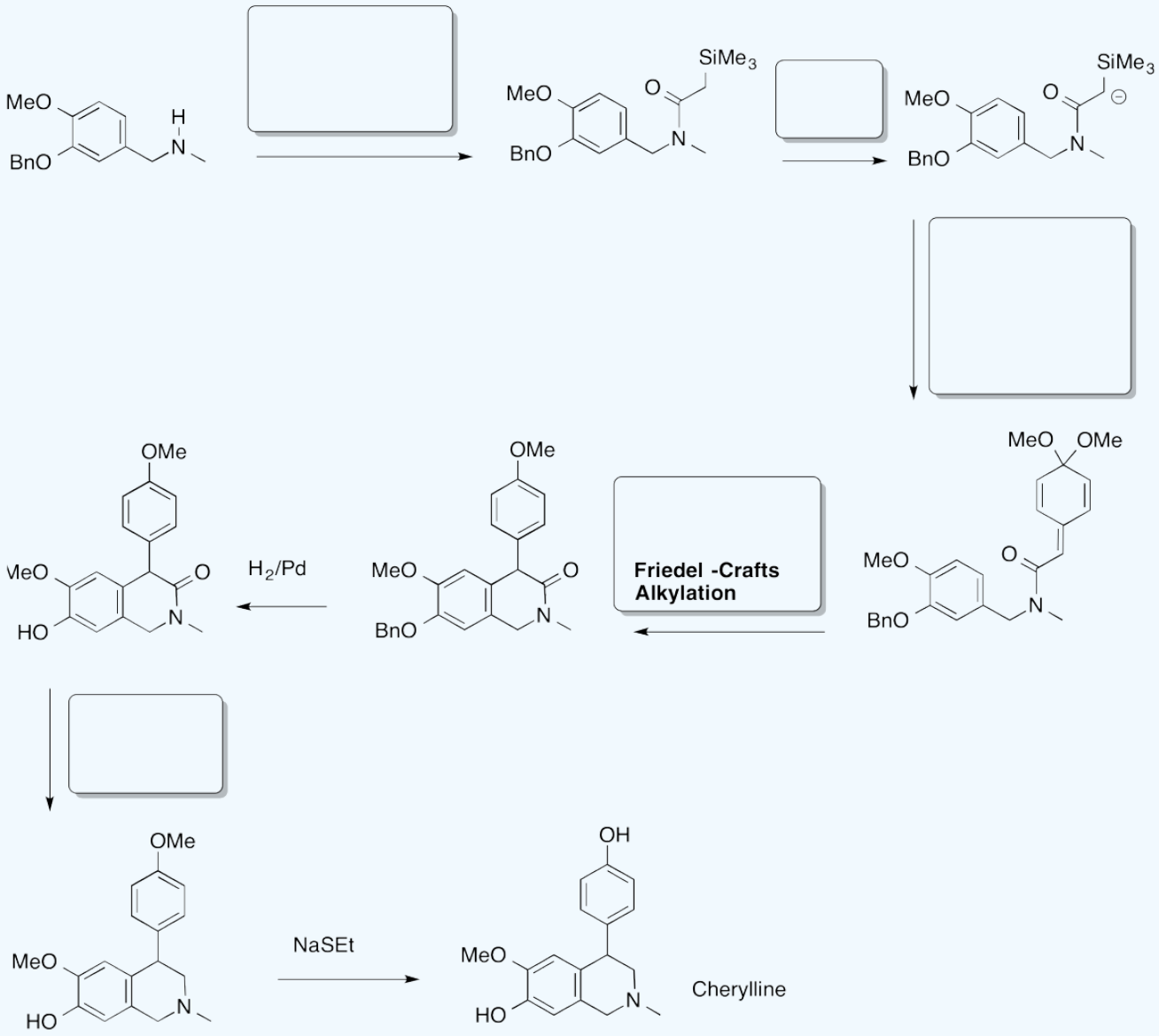




Exercise 7.5.12

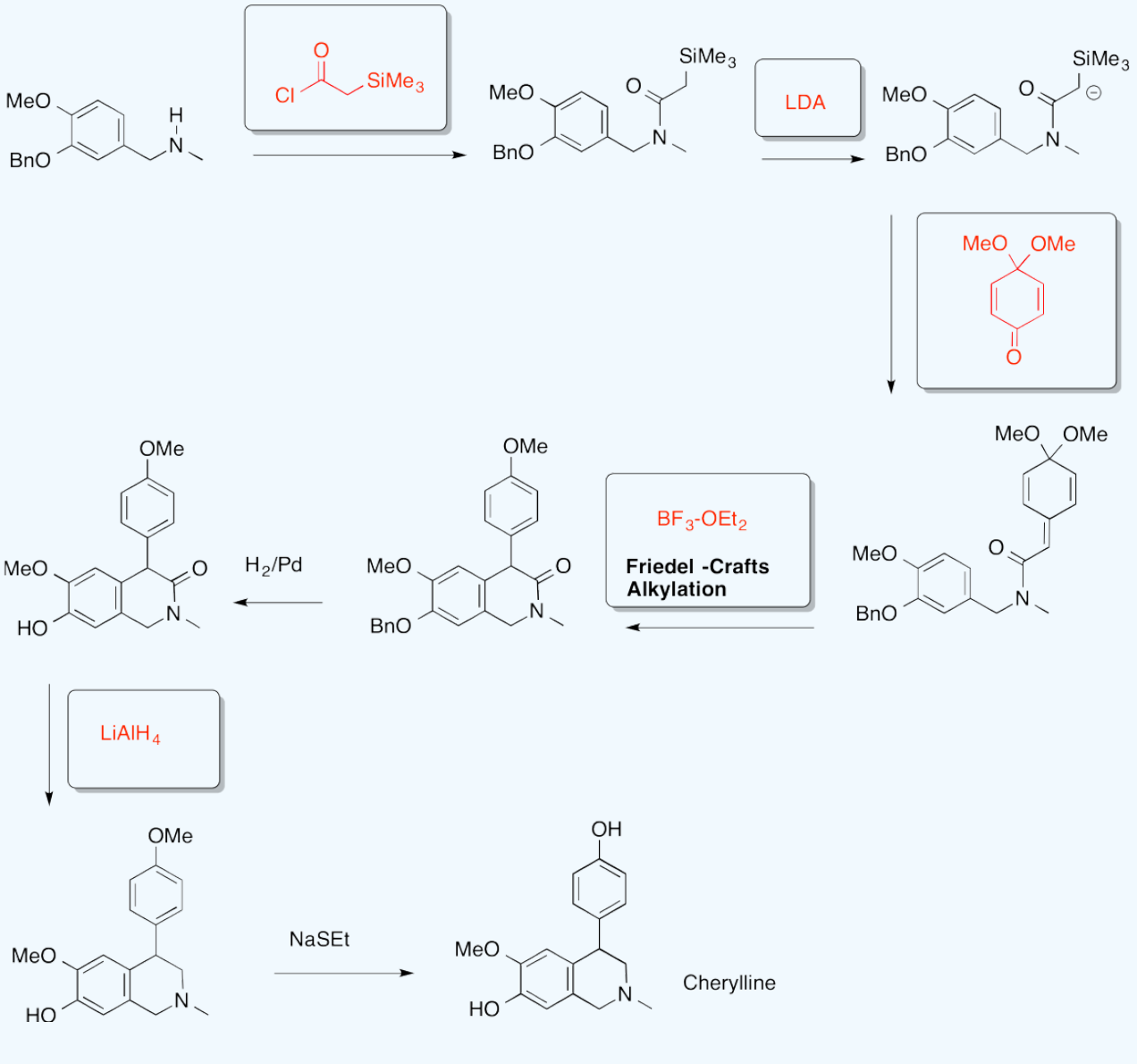
Problem AR5.12.

Hart, Cain, Evans, Approaches to the synthesis of masked p-quinone methides. Applications to the total synthesis of cherylline, *J. Am. Chem. Soc.*, **1978**, *100* (5), 1548-1557.



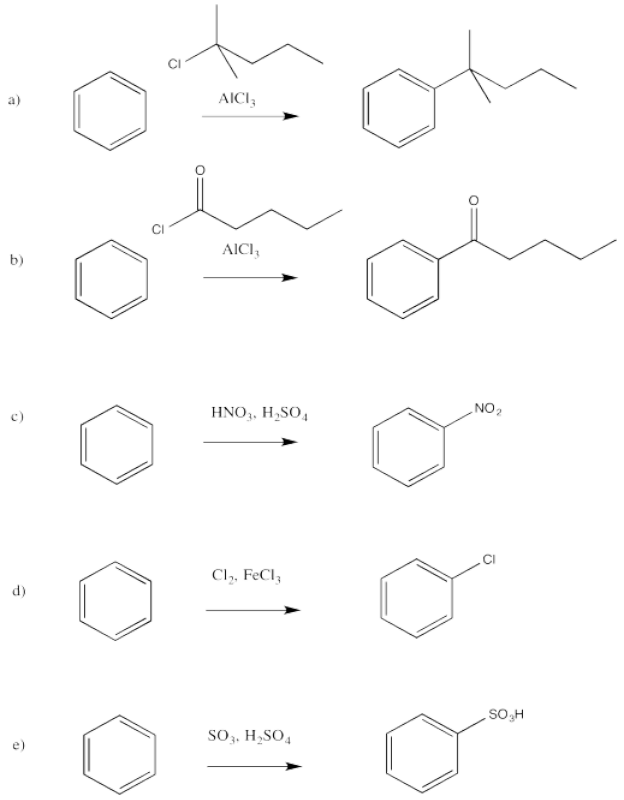
Answer

Hart, Cain, Evans, Approaches to the synthesis of masked p-quinone methides. Applications to the total synthesis of cherylline, *J. Am. Chem. Soc.*, **1978**, *100* (5), 1548-1557.



7.6: Solutions to Selected Problems

Exercise 7.1.1:



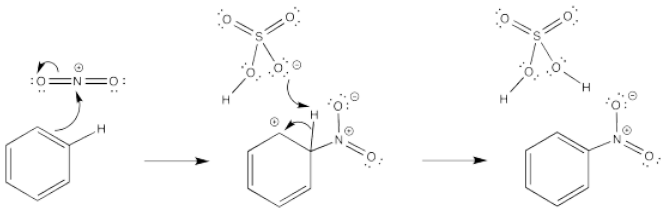
Exercise 7.2.1:

In the case of uncatalyzed bromination reactions, there is clear evidence that the Br-Br bond-breaking step does not start the reaction off. If that were the first step, there would presumably be an equilibrium between Br_2 and Br^+/Br^- ions. That equilibrium would be shifted back toward Br_2 if bromide salts were added. In that case, the amount of bromine cation would be suppressed and the reaction would slow down. No such salt effects are observed, however. That evidence suggests that, in the uncatalyzed reaction, the aromatic reacts directly with Br_2.

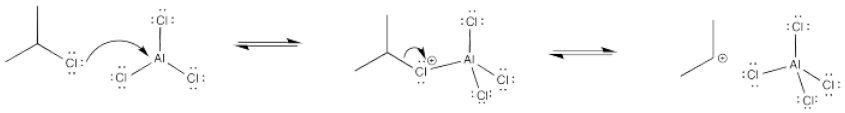
Exercise 7.2.2:

In each case, a base must remove the proton from the cationic intermediate. An anion that would be present in solution has been chosen for this role.

a)

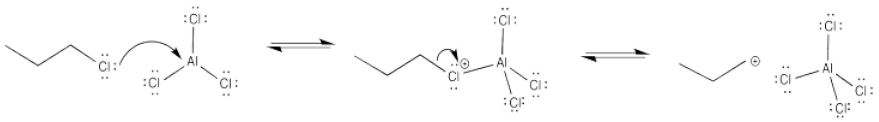


Exercise 7.3.2:

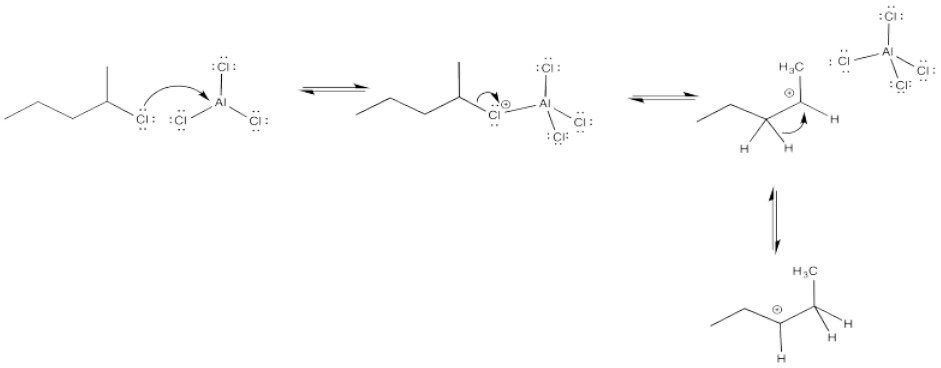


Exercise 7.3.3:

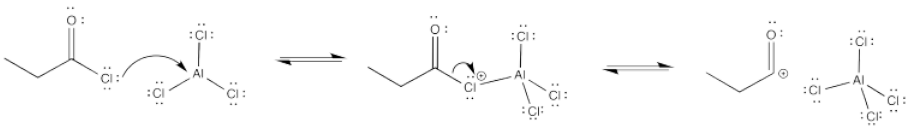
The primary cation formed is very unstable. As a result, there is a high barrier to cation formation.



Exercise 7.3.4:



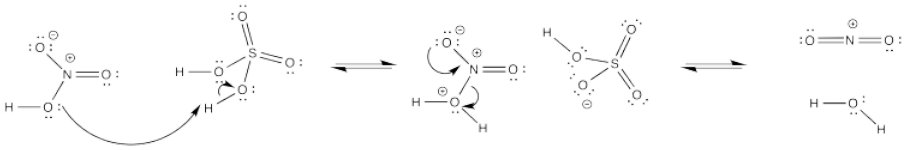
Exercise 7.3.5:



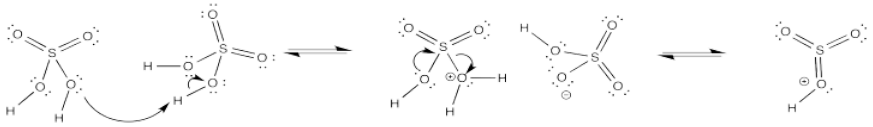
Exercise 7.3.6:

The cation that results is stabilized via π-donation from oxygen.

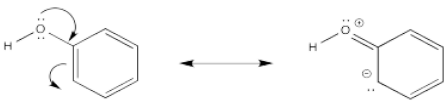
Exercise 7.3.7:



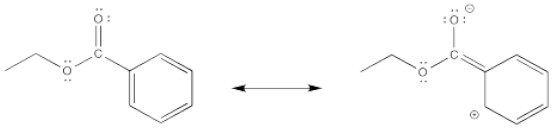
Exercise 7.3.8:



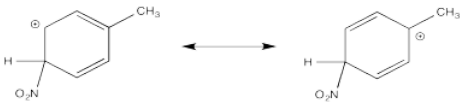
Exercise 7.4.2:



Exercise 7.4.3:



Exercise 7.4.4:



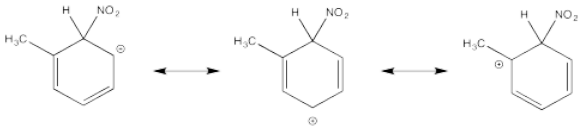
Exercise 7.4.5:

This is a substituted alkyl group. An alkyl group should be moderately activating, but the presence of a halogen exerts an inductive electron-withdrawing effect. The cation-stabilizing effect of the alkyl substituent is completely counteracted by the halogen.

Exercise 7.4.6:

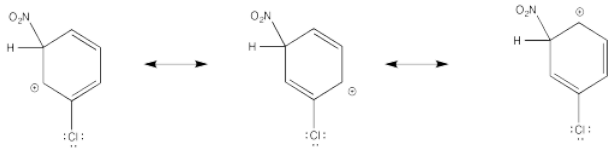
a) activating b) deactivating c) activating d) deactivating e) deactivating

Exercise 7.5.1:



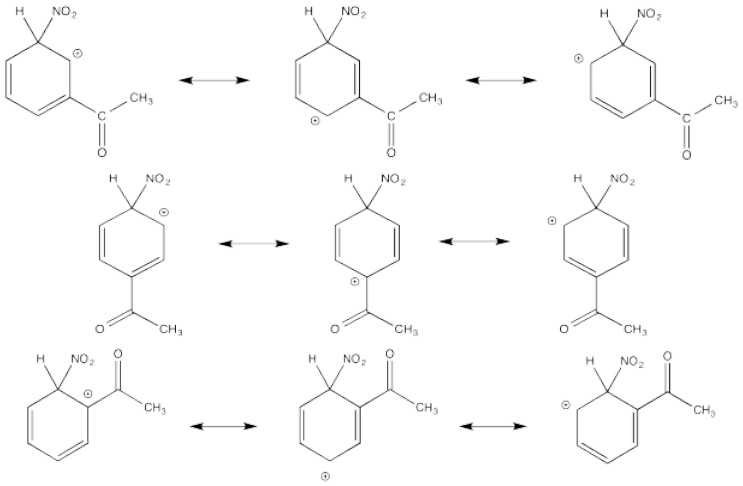
The tertiary cations that result during *ortho*- and *meta*- substitution offer extra stability, leading to preferential formation of these cations.

Exercise 7.5.2:



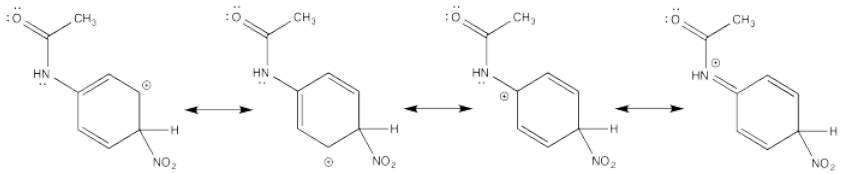
The π-donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

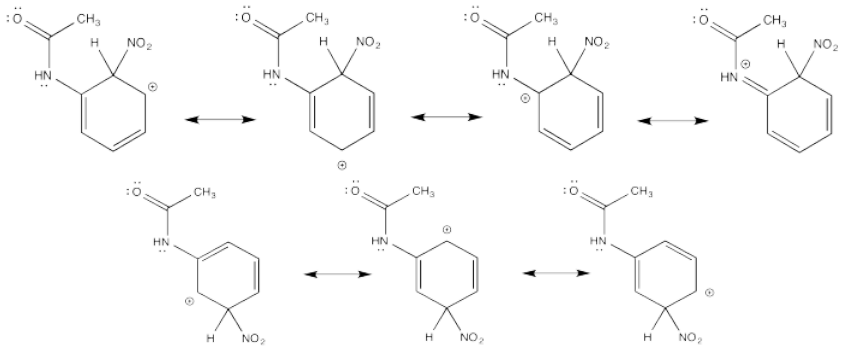
Exercise 7.5.3:



The cation directly adjacent to the carbonyl is destabilized by the electron withdrawing effect of the ketone. By default, the other intermediate is preferentially formed.

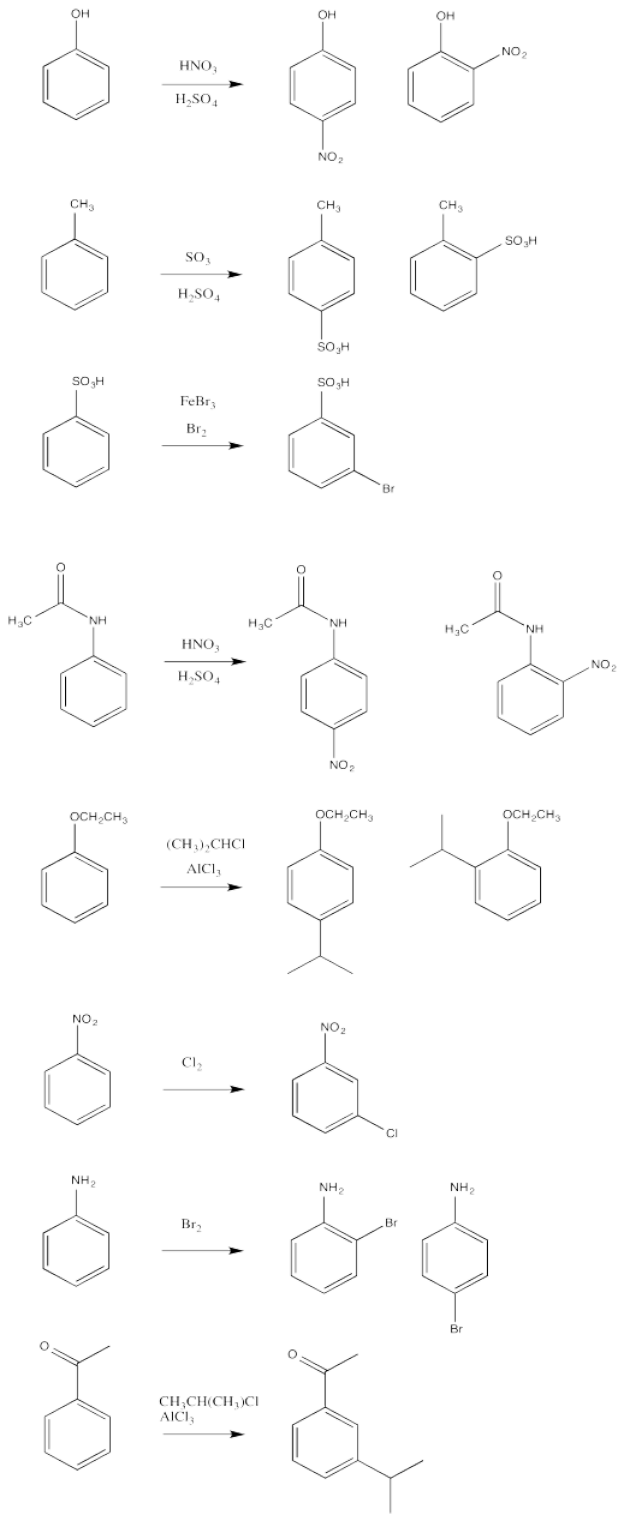
Exercise 7.5.4:



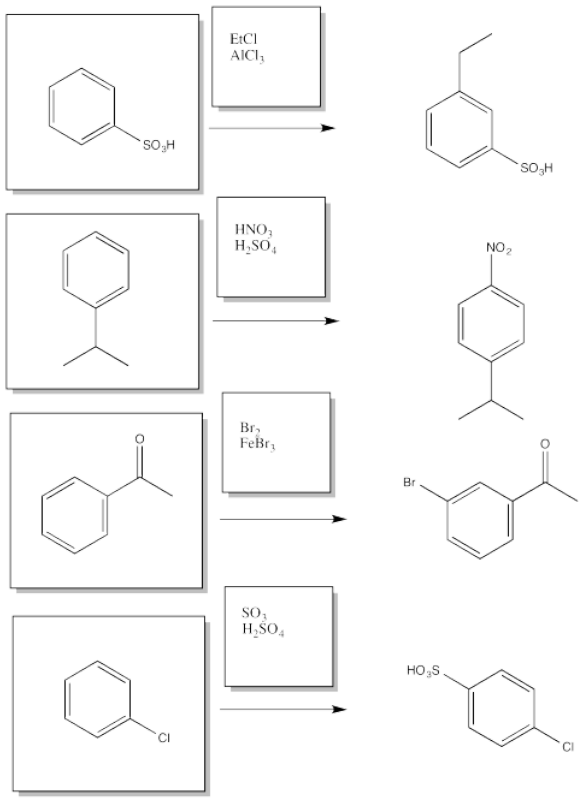


The π-donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

Exercise 7.5.5:

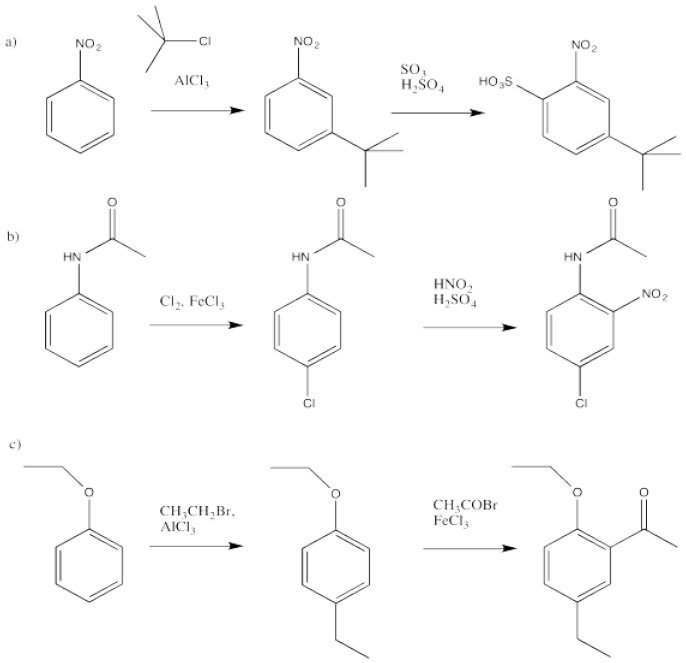


Exercise 7.5.6:



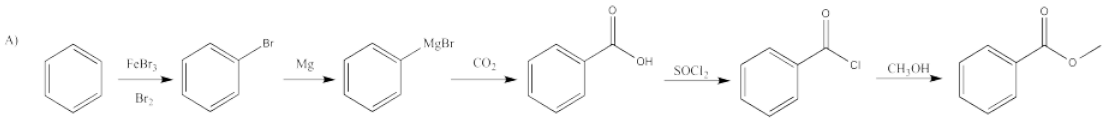
Exercise 7.5.7:

In cases leading to mixtures of *ortho* and *para* products, only one product was chosen, based on minimal steric interactions.

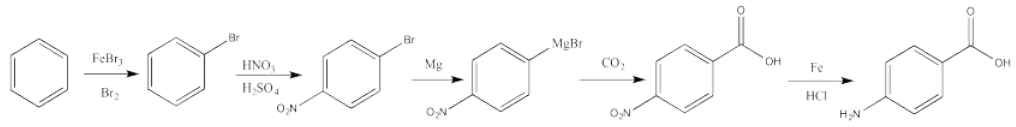


Exercise 7.5.8:

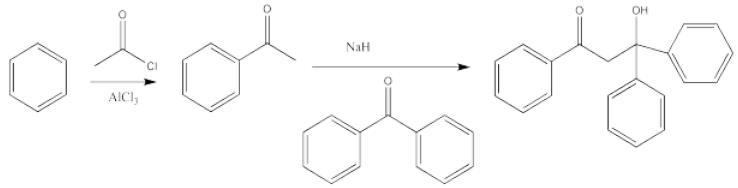
Starting from benzene and any monofunctional group compound, propose a synthesis for the following. There may be more than one answer than is presented here.



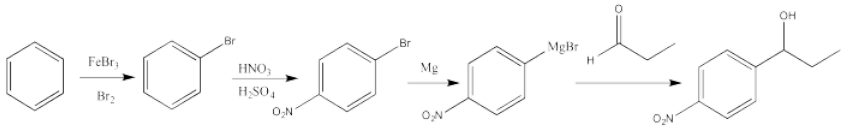
B)


FeBr3
Br2
HNO3
H2SO4
Mg
MgBr
CO2
OH
Fe
HCl

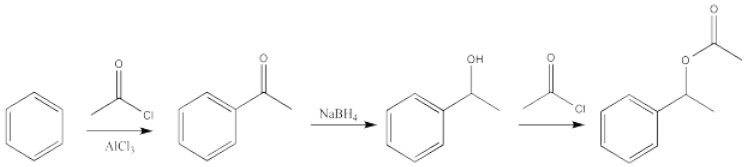
C)


Cl
AlCl3
NaH
OH

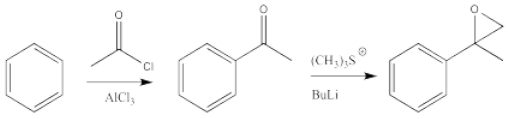
D)

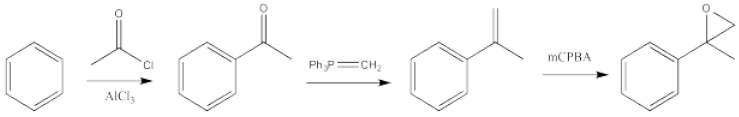

FeBr3
Br2
HNO3
H2SO4
Mg
MgBr
OH

E)

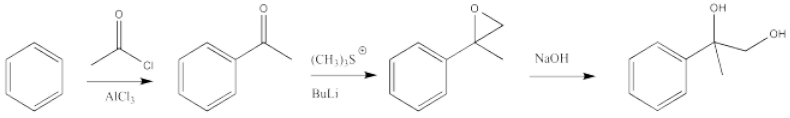

Cl
AlCl3
NaBH4
OH

F)

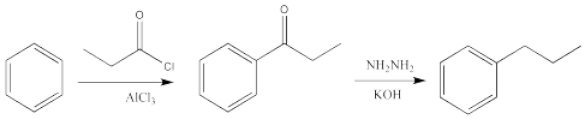

Cl
AlCl3
(CH3)3S
BuLi


Cl
AlCl3
Ph3P=CH2
mCPBA

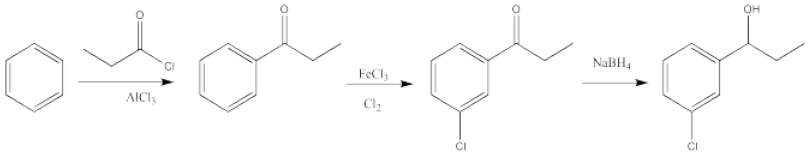
G)


Cl
AlCl3
(CH3)3S
BuLi
NaOH
OH

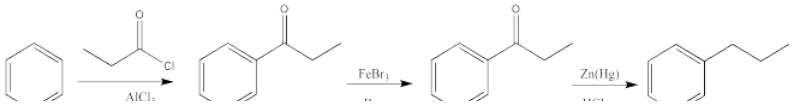
H)

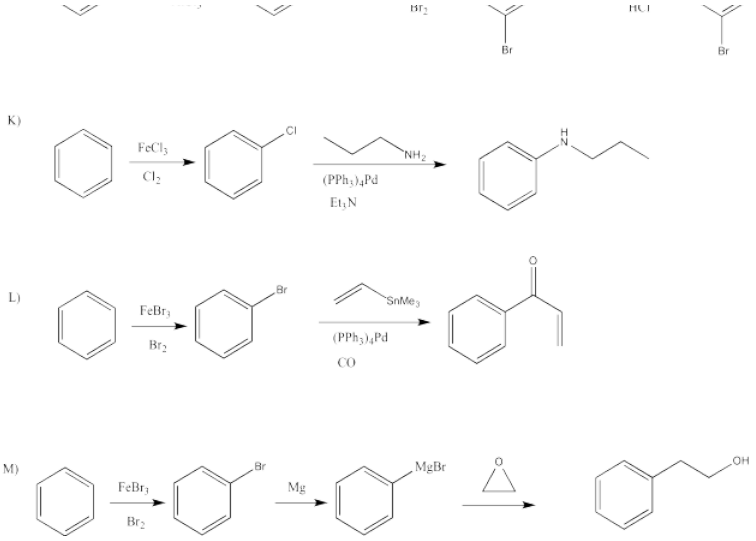

Cl
AlCl3
NH2NH2
KOH

I)


Cl
AlCl3
FeCl3
Cl2
NaBH4
OH

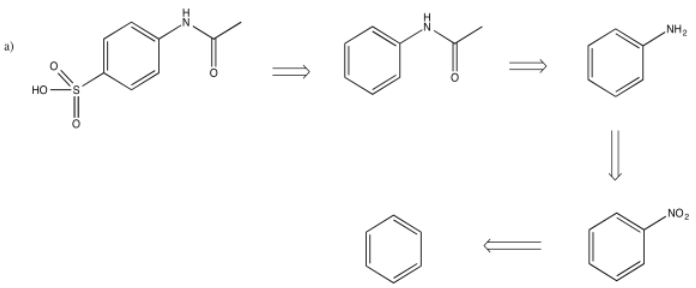
J)


Cl
AlCl3
FeBr3
Zn(Hg)

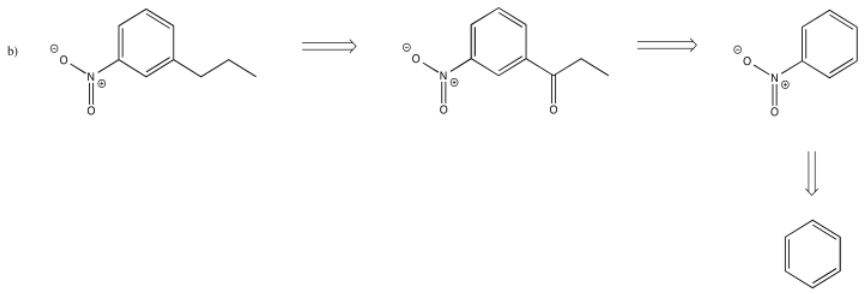


Exercise 7.5.9:

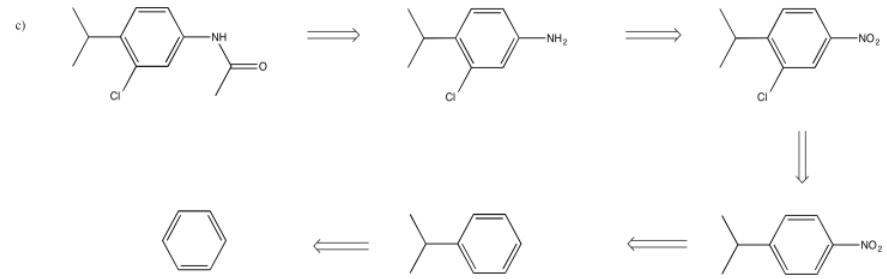
a)



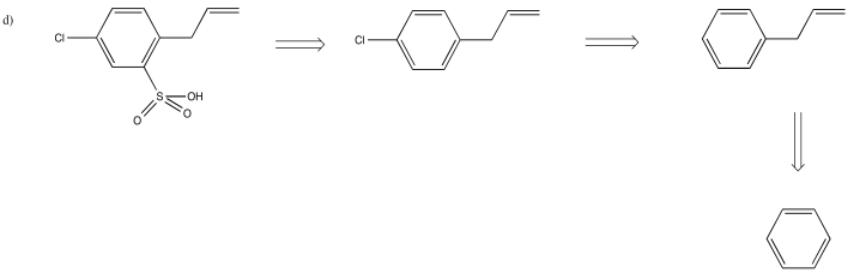
b)



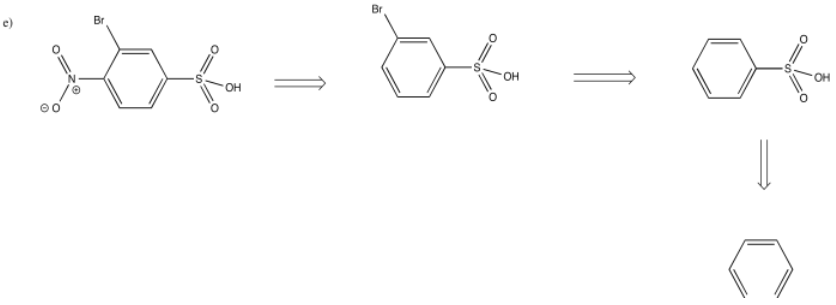
c)



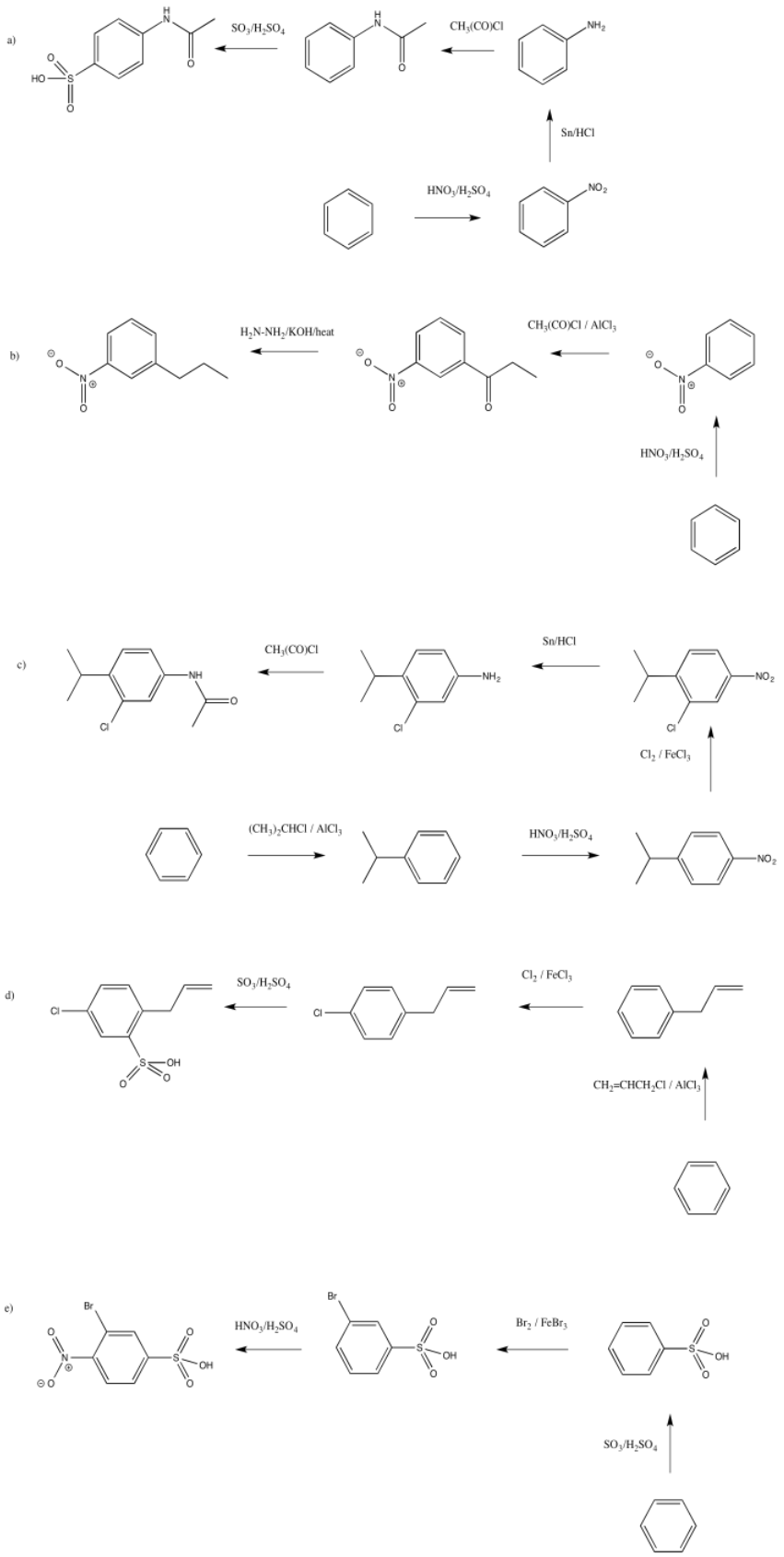
d)



e)

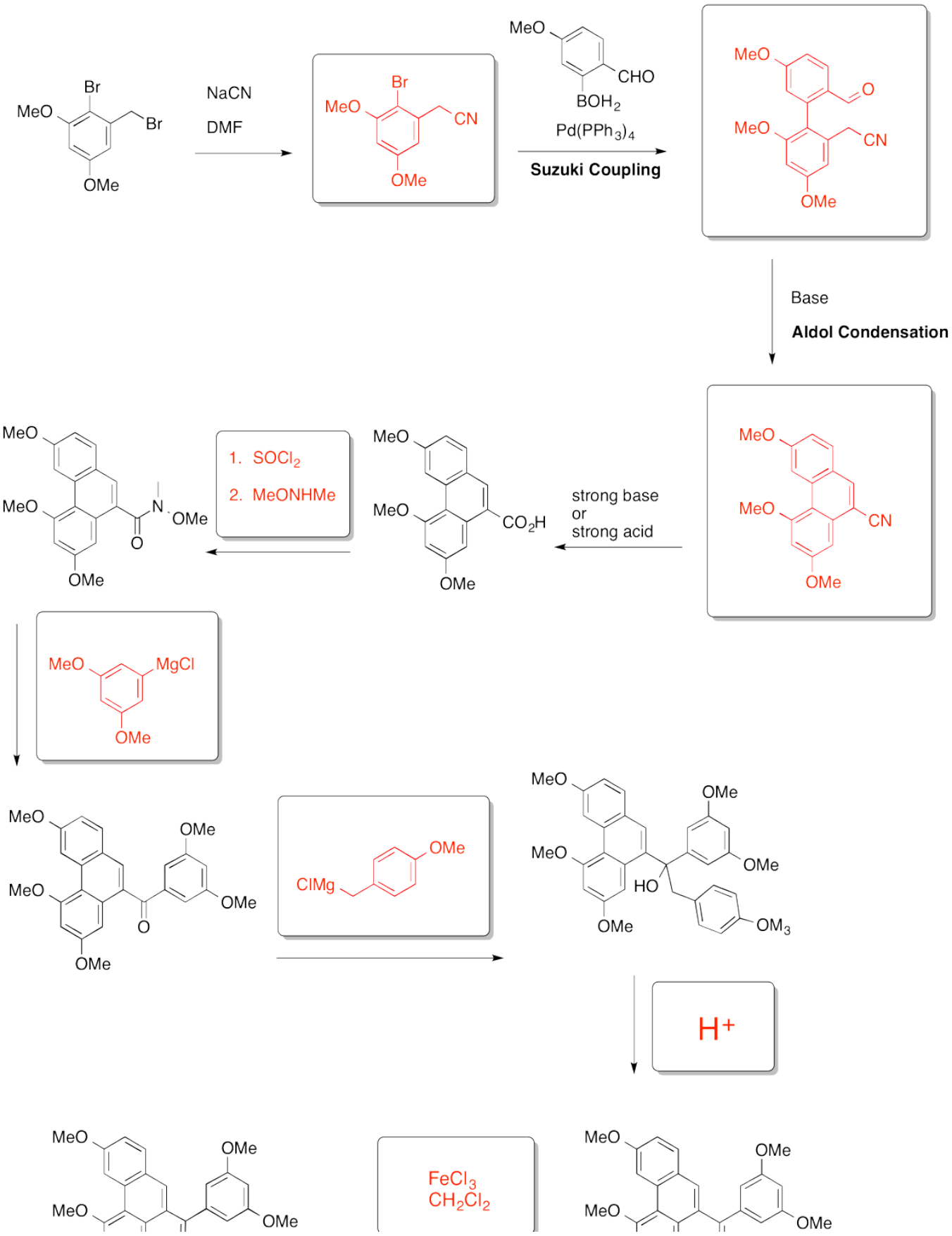


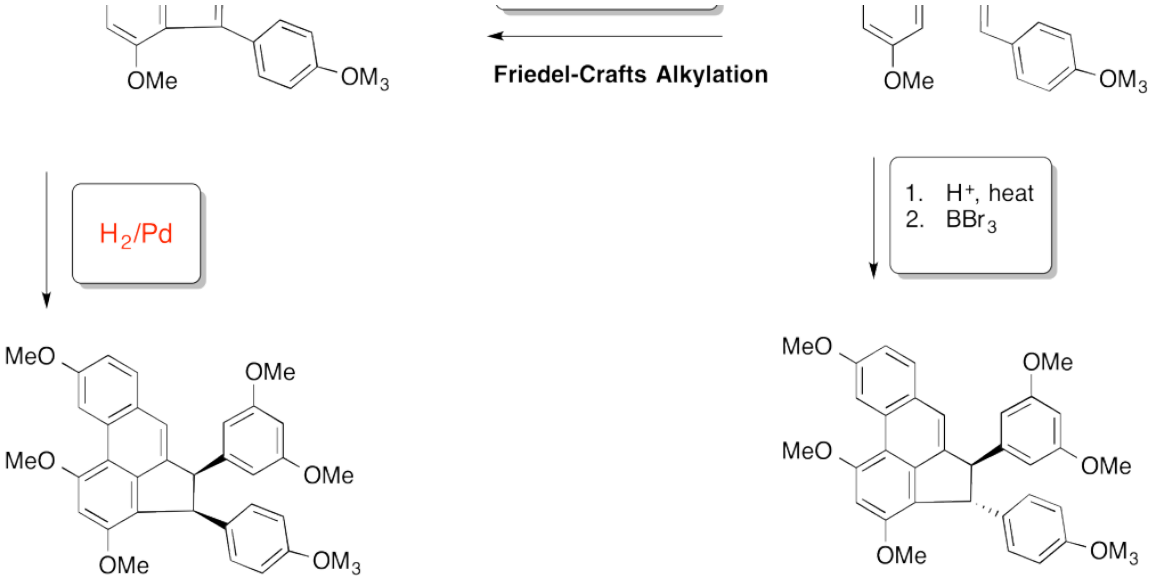
Exercise 7.5.10:



Exercise 7.5.11:

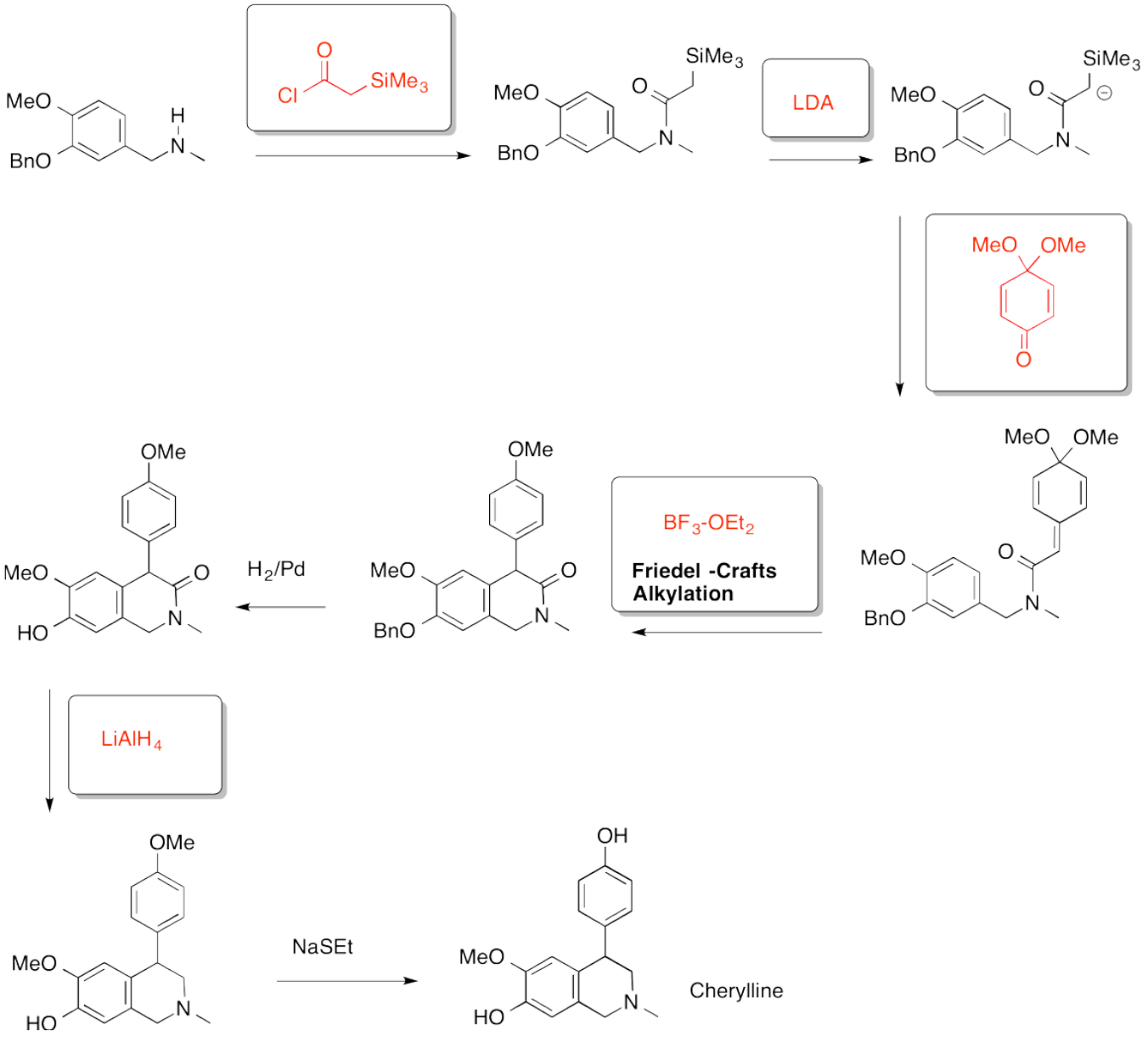
Choi, Kim and Heo, Total Synthesis of Laetevirenol A, *J. Org. Chem.*, **2012**, *77*, 8762-8767.





Exercise 7.5.12:

Hart, Cain, Evans, Approaches to the synthesis of masked p-quinone methides. Applications to the total synthesis of cherylline, *J. Am. Chem. Soc.*, **1978**, *100* (5), 1548-1557.



CHAPTER OVERVIEW

8: Organic Synthesis

8.1: Road Maps in Total Synthesis of Natural Products

Topics required for successful completion are listed under each link.

Abyssomicin, Sorensen, 2006

alkene addition

carbonyl addition

carboxylic substitution

nucleophilic substitution

oxidation of alcohols

pericyclics

Amphilectolide, Trauner, 2014

carbonyl addition

carbonyl reduction

"Claisen condensation"-type carboxylic substitution

cuprate addition

ester reduction

nitrile hydrolysis

Annamoxic Acid, Corey, 2004

> *alkene addition*
>
> *carbonyl addition*
>
> *elimination*
>
> *pericyclics*

Anominine, Nicolaou, 2012

> *aldol reaction*
>
> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxyl substitution*
>
> *elimination*
>
> *oxidation of alcohols*
>
> *radicals*

Aplykurodinone, Danishefsky, 2010

> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *elimination*

oxidation of alcohols

Atisine, Fukumoto, 1990

esterification & amidification

Michael addition

reduction of esters

Wittig & Horner-Wadsworth-Emmons reactions

Aurantioclavine, Ellman, 2010

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

Aza-epothilone B, Danishefsky, 2000

with bioassay study

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

Brevenal, Crimmins, 2010

(partial synthesis)

carbonyl addition, anionic & semianionic nucleophiles

carbonyl addition, aldols

carbonyl addition, ylides

Brevetoxin, Crimmins, 2009

aliphatic nucleophilic substitution

electrophilic addition to alkenes

carbonyl addition

Briarellin, Crimmins, 2011

nucleophilic addition to epoxide

aliphatic nucleophilic substitution

silyl protecting groups

carboxylic substitution

carbonyl addition

electrophilic addition to alkenes

ylide addition

oxidation of alcohols

Bryostatin, Burke, 2004

dihydroxylation

Horner-Wadsworth-Emmons or Wittig reaction

hydroboration - oxidation

oxidation of alcohols

reduction of esters and ketones

ring-closing olefin metathesis

Callipeltoside, MacMillan, 2008

> *aliphatic nucleophilic substitution*
>
> *electrophilic addition to alkenes*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *oxidation of alcohols*

Cassiol, Stoltz, 2008

> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*

Cavicularin, Beaudry, 2013

> *Diels Alder*
>
> *etherification*
>
> *palladium coupling*
>
> *Wittig or Tebbe reactions*

Clavolonine, Fujioka, 2011

aliphatic nucleophilic substitution and elimination

Deoxytetracycline, Stork, 1996

> *carbonyl addition (anionic and neutral nucleophiles)*
>
> *carboxylic substitution*
>
> *conjugate addition*

Dedihydrosemofalin, Overman, 2003

alpha-alkylation

aza-Cope rearrangement

catalytic hydrogenation

Diels Alder

iminium ion formation

oxidation of alcohols

ozonolysis

reduction of esters

silylation of alcohols

silylation of enolates

silyl ether cleavage

Wittig & Horner-Wadsorth-Emmons reactions

Dendrobine, Carreira, 2012

> *carbonyl addition*
>
> *carboxylic substitution*

Doliculide, Ghosh, 2001

> *aliphatic nucleophilic substitution*
>
> *electrophilic addition to alkenes*

Dynemicin, Danishefsky, 1996

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

elimination

oxidation of alcohols

pericyclics

Echinopine, Nicolaou, 2010

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

Epothilone, Altmann, 2008

aldol reaction

alpha deprotonation

Grignard reactions

Wittig and Horner-Wadsworth-Emmons reactions

Fischerindole, Baran, 2008

aliphatic nucleophilic substitution

carbonyl addition,

carboxylic substitution,

electrophilic addition to alkenes

oxidation of alcohols

radicals

Ginkgolide, Corey, 1988

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

conjugate addition

electrophilic addition to alkenes

enolates

rearrangements

radicals

Glucosylceramide, Overkleeft, 2007

> *contains a bioassay exercise*
>
> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *elimination*
>
> *oxidation of alcohols*

Juvenile Hormone 1, Corey, 1968

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

cuprate addition

electrophilic addition to alkenes

oxidation of alcohols

Wittig reaction

Lepistine, Yokoshima & Fukuyama, 2014

aliphatic nucleophilic substitution

elimination

Longifolene, Corey, 1961

> *aliphatic nucleophilic substitution*
>
> *alkene oxidation*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *elimination*
>
> *oxidation of alcohols*

Lycopladine, Weinreb, 2015

acetal/ketal cleavage

acetal/ketal formation

catalytic hydroformylation of alkenes

Grignard reactions

reductive amination

Manzacidin A, Kawabata, 2013

carboxylic substitution: esterification and amidification

conjugate addition

Nahuoic Acid, Smith, 2017

acetal / ketal formation

alkene reduction

carbonyl reduction

cuprate addition

Diels Alder reaction

epoxide opening (organometallic)

ester hydrolysis

keto-enol tautomerism

methoxymethyl ether formation

olefin metathesis

silyl ether formation & cleavage

syn dihydroxylation

thioacetal / thioketal cleavage

Nakadomarin, Kerr, 2007

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

conjugate addition

elimination

oxidation of alcohols

Norzoanthamine, Theodorakis, 2011

Robinson annulation

conjugate addition

anionic addition to carbonyls

carboxylic substitution

Octalactin, Buszek, 1994

alkene reduction

epoxidation

hydroboration / oxidation

Lindlar's catalyst

silyl ether cleavage

Okilactomycin, Smith, 2007

aldol condensation

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

elimination

oxidation of alcohols

pericyclics

Perhydrohistrionicotoxin, Corey, 1975

aliphatic nucleophilic substitution

carbonyl addition

carboxylic substitution

conjugate addition

elimination

enolates

oxidation of alcohols

radicals

Periplanone, Still, 1979

> *aldol condensation*
>
> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution,*
>
> *elimination*
>
> *oxidation of alcohols*
>
> *pericyclics*

Platensimicin, Ghosh, 2009

> *aliphatic nucleophilic substitution*
>
> *electrophilic addition to alkenes*

Polyanthellin, Johnson, 2009

> *electrophilic addition to alkenes: halogenation, hydroboration, oxymercuration, epoxidation, cyclopropanation*
>
> *aliphatic nucleophilic substitution*

Polycavernoside, Sasaki, 2017

> *epoxidation*
>
> *epoxide ring-opening*
>
> *esterification*
>
> *oxidation of alcohols*
>
> *silyl ether cleavage*

Prostaglandin A2, Corey, 1972

> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *elimination*
>
> *oxidation of alcohols*

Quinine, Stork, 2001

> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*

Quinocarcin, Stoltz, 2008

> *carbonyl addition*
>
> *carboxylic substitution*

Salvileucalin, Reisman, 2011

> *carbonyl addition*
>
> *carboxylic substitution*

Saxitoxin, Du Bois, 2006

> *Contains a bioassay exercise.*
>
> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution*
>
> *electrophilic addition to alkenes*
>
> *oxidation of alcohols*

Scholarisine, Smith, 2012

> *aliphatic nucleophilic substitution*
>
> *carbonyl addition*
>
> *carboxylic substitution,*

Serotobenine, Fukuyama & Kan, 2008

> *aliphatic nucleophilic substitution*
>
> *alkene oxidation*
>
> *carbonyl addition*
>
> *carboxylic substitution*

elimination

oxidation of alcohols

pericyclics

Solamine, Stark, 2006

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

elimination

oxidation of alcohols

Spongidepsin, Cossy, 2006

activation of carboxylic acids

esterification & amidification

Grignard reactions

hydrolysis of amides

reduction of esters

Wittig & Horner-Wadsworth-Emmons reactions

Strychnine, Overman, 1993

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

conjugate addition

elimination

enolates

Exercise: catalytic cycles in transition metal organometallics.

Taiwaniaquinol, Fillion, 2005

aldol condensation

alpha alkylation

conjugate addition

electrophilic aromatic substitution

etherification

palladium coupling

Taxol, Nicolaou, 1994

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

elimination

oxidation of alcohols

pericyclics

radicals

Tetrodotoxin, Kishi, 1972

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

electrophilic addition to alkenes

oxidation of alcohols

pericyclics

rearrangements

Tubingensin, Li, 2012

carbonyl addition

carboxylic substitution, aldol

Tulearin, Cossy, 2009

carbonyl addition, anionic & semianionic nucleophiles

carbonyl addition, aldols

carbonyl addition, ylides

Vermiculine, Corey, 1975

carbonyl addition

carboxylic substitution

Vibsanin, Takeo, 2015

addition to carbonyl (organometallic)

allylic substitution

ester hydrolysis

ester reduction

esterification

ether formation

Mitsunobu reaction

silyl ether formation and cleavage

Wittig / Horner-Wadsworth-Emmons

Vinigrol, Berriault, 2005

acetals & ketals

Claisen rearrangement

Diels Alder

syn-dihydroxylations

esterification

Grignard reagents

hydride additions

oxidation of alcohols

silyl ethers

Vittatalactone, Breit, 2010

Aliphatic nucleophilic substitution

Zaragozic acid, Nicolaou, 1994

aliphatic nucleophilic substitution

alkene oxidation

carbonyl addition

carboxylic substitution

organo-transition metal reactions

oxidation of alcohols

radicals

sulfur ylides

Zincophorin, Hsung, 2007

aliphatic nucleophilic substitution

electrophilic addition to alkenes

Index

Glossary

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