Pericyclic reactions 2: Sigmatropic and electrocyclic reactions

36

Connections

Building on:

- Cycloadditions and the principles of pericyclic reactions (essential reading!) ch35
- Acetal formation ch14
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling alkene geometry ch31

Arriving at:

- The second and third types of pericyclic reaction
- Stereochemistry from chair-like transition states
- Making γ,δ-unsaturated carbonyl compounds
- What determines whether these pericyclic reactions go 'forwards' or 'backwards'
- Special chemistry of N, S, and P
- Why substituted cyclopentadienes are unstable
- What 'con'- and 'dis'-rotatory mean
- Reactions that open small rings and close larger rings

Looking forward to:

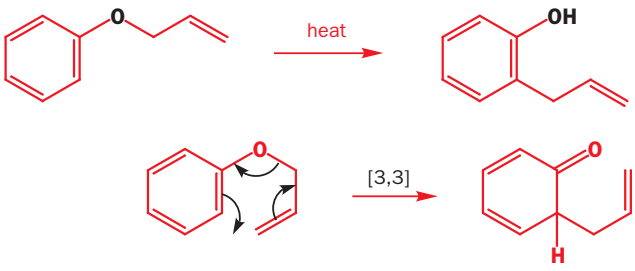
- Rearrangements ch37
- Synthesis of aromatic heterocycles ch44
- Main group chemistry ch46–ch47
- Asymmetric synthesis ch45
- Natural products ch51

Cycloadditions, the subject of the last chapter, are just one of the three main classes of pericyclic rearrangement. In this chapter, we consider the other two classes—sigmatropic rearrangements and electrocyclic reactions. We will analyse them in a way that is similar to our dealings with cycloadditions.

Sigmatropic rearrangements

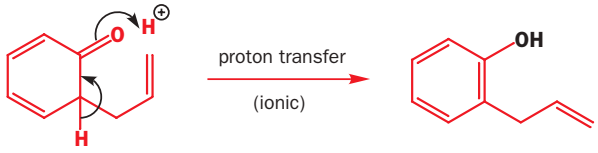
The Claisen rearrangement was the first to be discovered

The original sigmatropic rearrangement occurred when an aryl allyl ether was heated without solvent and an *ortho*-allyl phenol resulted. This is the **Claisen rearrangement**.

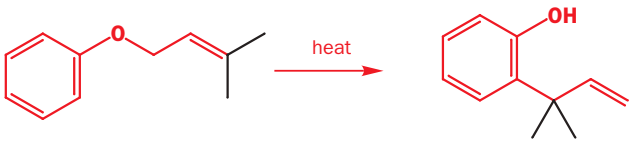


The first step in this reaction is a pericyclic reaction of a type that we will learn to call a **[3,3]-sigmatropic rearrangement**.

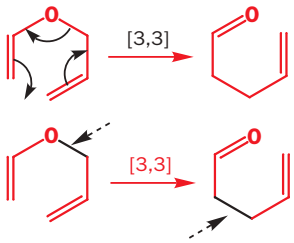
This is a one-step mechanism without ionic intermediates or any charges, just like a cycloaddition. The arrows go round in a ring. The difference between this and a cycloaddition is that one of the arrows starts on a σ bond instead of on a π bond. The second step in the reaction is a simple ionic proton transfer to regenerate aromaticity.



How do we know that this is the mechanism? If the allyl ether is unsymmetrical, it turns 'inside-out' during Claisen rearrangement, as required by the mechanism. Check for yourself that this is right.



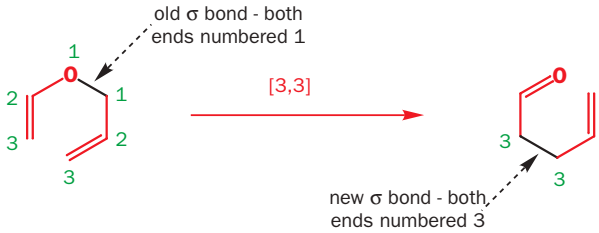
The aliphatic Claisen rearrangement also occurs



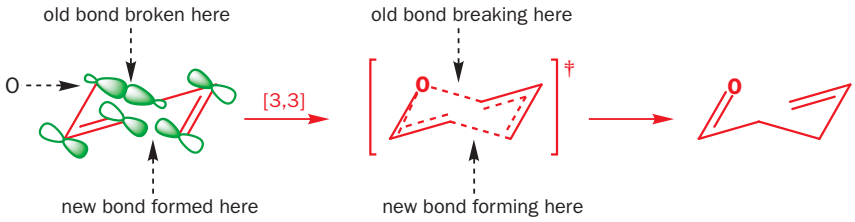
It was later found that the same sort of reaction occurs without the aromatic ring. This is called either the **aliphatic Claisen rearrangement** or the **Claisen–Cope rearrangement**. Here is the simplest possible example.

These reactions are called **sigmatropic** because a σ bond appears to move from one place to another during the reaction. The important bonds are coloured black here.

This particular reaction is called a **[3,3]-sigmatropic rearrangement** because the new σ bond has a 3,3 relationship to the old σ bond. You can see this if you number the ends of the old σ bond '1' and '1' and count round to the ends of the new σ bond in the product. You will find that the ends of the new σ bond both have the number '3'.



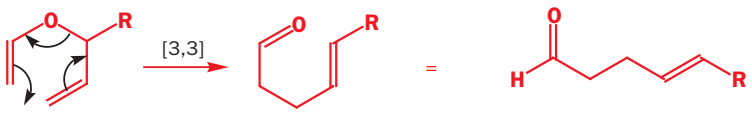
These [3,3]-sigmatropic rearrangements happen through a chair-like transition state, which allows us both to get the orbitals right and to predict the stereochemistry (if any) of the new double bond. The orbitals look something like this.



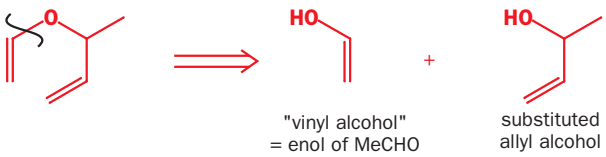
Note that these do not represent any specific frontier orbitals, they simply show that, in this conformation, the new σ bond is formed from two p orbitals that point directly at each other and that the two new π bonds are formed from orbitals that are already parallel.

Alkene stereochemistry in the Claisen rearrangement comes from a chair-like transition state

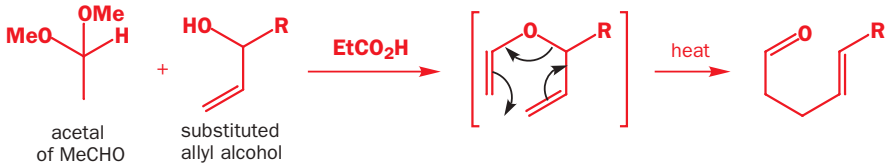
Stereochemistry may arise if there is a substituent on the saturated carbon atom next to the oxygen atom. If there is, the resulting double bond strongly favours the *trans* (*E*) geometry. This is because the substituent prefers an equatorial position on the chair transition state.



The substituent R prefers an equatorial position as the molecule reacts and R retains this position in the product. The new alkene bond is shown in black and the substituents in green. Notice that the *trans* geometry of the alkene in the product is already there in the conformation chosen by the starting material and in the transition state.

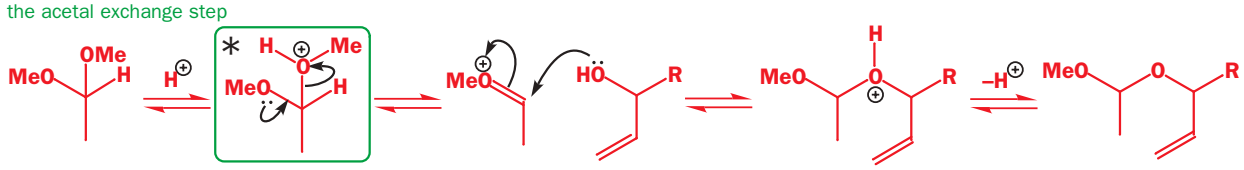


The starting material for these aliphatic Claisen rearrangements consists of ethers with one allyl and one vinyl group. We need now to consider how such useful molecules might be made. There is no problem about the allyl half—allylic alcohols are stable easily made compounds. But what about the vinyl half? 'Vinyl alcohols' are just the enols of aldehydes (MeCHO). The solution is to use an acetal of the aldehyde in an acid-catalysed exchange process with the allylic alcohol.



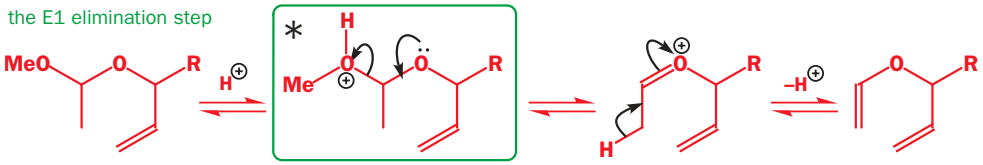
It is not necessary to isolate the allyl vinyl ether as long as some of it is formed and rearranges into the final product. The acid catalyst usually used, propanoic acid, has a conveniently high boiling point so that the whole mixture can be equilibrated at high temperature. The first step is an acetal exchange in which the allylic alcohol displaces methanol.

the acetal exchange step



The methanol is distilled off as it is the most volatile of the components in this mixture. A second molecule of methanol is now lost in an acid-catalysed elimination reaction to give the vinyl group.

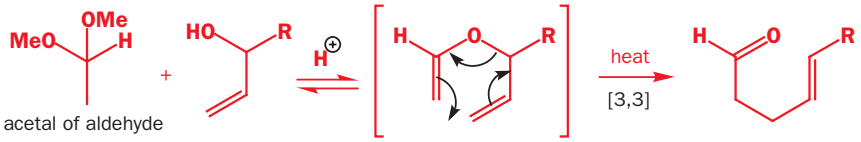
the E1 elimination step

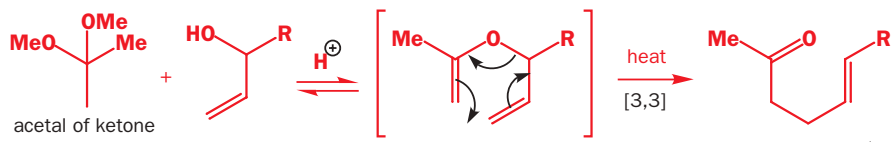


▶ Note that the first molecule of methanol was displaced in an S_N**1** reaction and the second lost in an E**1** reaction. The chemistry of acetals is dominated by the loss of protonated OR or OH groups as in the steps marked *. Never be tempted to use S_N**2** mechanisms with acetals.

The Claisen rearrangement is a general synthesis of γ,δ-unsaturated carbonyl compounds

Finally, the [3,3]-sigmatropic rearrangement can be carried out by heat as part of the same step or as a separate step depending on the compounds. This is a very flexible reaction sequence and can be used for aldehydes (as shown above), ketones, esters, or amides. In each case acetal-like compounds are used—acetals themselves for aldehydes and ketones; orthoesters and orthoamides for the other two (though the orthoamides are often called 'amide acetals').





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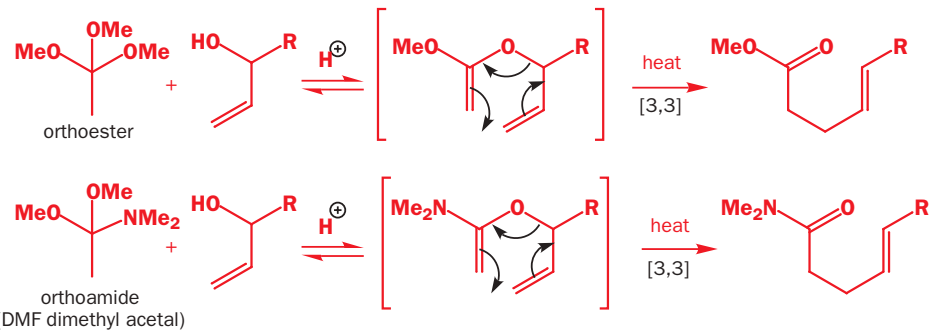


The common feature in the products of these Claisen rearrangements is a γ,δ-unsaturated carbonyl group. If this is what you need in a synthesis, make it by a Claisen rearrangement.

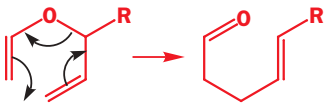
Orbital descriptions of [3,3]-sigmatropic rearrangements

It is possible to give a frontier orbital description of a [3,3]-sigmatropic rearrangement but this is not a very satisfactory treatment because two reagents are not recognizing each other across space as they were in cycloadditions. There are *three* components in these reactions—two nonconjugated π bonds that do have to overlap across space and a σ bond in the chain joining the two π bonds.

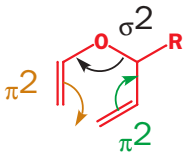
▶ In a thermal pericyclic reaction the total number of $(4q + 2)_s$ and $(4r)_a$ components must be odd.

The Woodward–Hoffmann rules give a more satisfying description and we shall follow the routine outlined for cycloadditions. Note that for stage 3, we can use the three-dimensional diagram we have already made.

1 Draw the mechanism for the reaction (we shall stay with a familiar one)

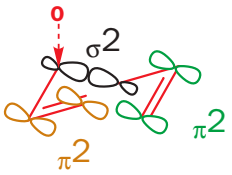


2 Choose the components. All the bonds taking part in the mechanism must be included and no others

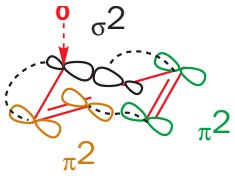


■ Note that we have dropped the shading in the orbital from the previous diagrams earlier in the chapter.

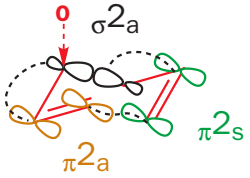
3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)



4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds

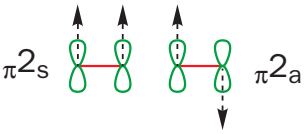


5 Label each component s or a depending whether new bonds are formed on the same or on opposite sides. See below for the σ bond symmetry



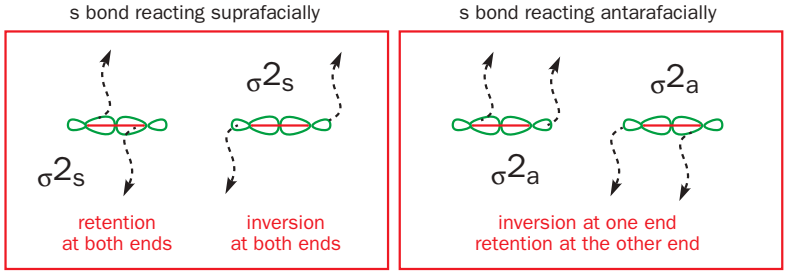
6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed

■ There is *one* $(4q + 2)_s$ component (one alkene) and *no* $(4r)_a$ components. Total = 1 so this is an allowed reaction. The $_\pi 2_a$ and $_\sigma 2_a$ components have irrelevant symmetry and are not counted (see Chapter 35 for a full explanation).



One new aspect of orbital symmetry has appeared in this diagram—how did we deduce a or s symmetry in the way the σ bond reacted? For π bonds it is simple—if both bonds are formed on the same side of the old π bond, it has reacted suprafacially; if on opposite sides, antarafacially.

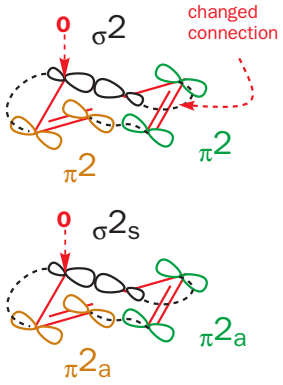
With a σ bond the symmetry is not so obvious. We want to know if it does the *same* thing at each end (s) or a *different* thing (a). But what is the 'thing' it does? It reacts using the large lobe of the sp^3 orbital (retention) or the small lobe (inversion). If it reacts with retention at both ends or inversion at both ends, it reacts *supra*facially, while if it reacts with retention at one end and inversion at the other, it reacts *antara*facially. There are four possibilities.



■ If you are interested in the frontier orbital approach to [3,3]-sigmatropic reactions, you could read about it in Ian Fleming (1976). *Frontier orbitals and organic chemical reactions*. Wiley, Chichester. We shall use that approach when we come to [1,5]-sigmatropic rearrangements.

In the routine above, we chose to use our σ bond so that we got inversion at one end and retention at the other. That was why we identified it as an antarafacial component. If we had chosen another style we should have got different descriptions of the components, but the reaction would still have been allowed—for example, changing just one connecting line.

This changes the symmetry of the σ bond so that it becomes a $_\sigma 2_s$ component but it also changes the symmetry of one of the π bonds so that it becomes a $_\pi 2_a$ component. The net result is still only one component of the Woodward–Hoffmann symmetry, the sum is still one, and the reaction still allowed.



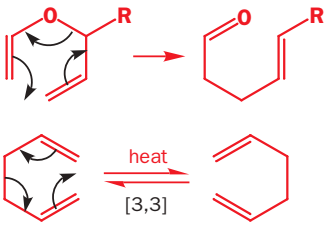
number of $(4q + 2)_s$ components: 1
number of $(4r)_a$ components: 0
sum = 1
so reaction is allowed thermally

The direction of [3,3]-sigmatropic rearrangements

Orbital symmetry tells us that [3,3]-sigmatropic rearrangements are allowed but says nothing about which way they will go. They are allowed in either direction. So why does the Claisen–Cope rearrangement always go in this direction?

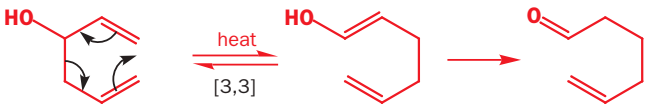
Think back to our discussion on enols and you may recall that the combination of a carbonyl group and a C–C σ bond made the keto form more stable than the enol form with its combination of a C=C π bond and a C–O σ bond. The same is true here. It is the formation of the carbonyl group that drives the reaction to the right.

The **Cope rearrangement** is a [3,3]-sigmatropic rearrangement with only carbon atoms in the ring. In its simplest version it is not a reaction at all.

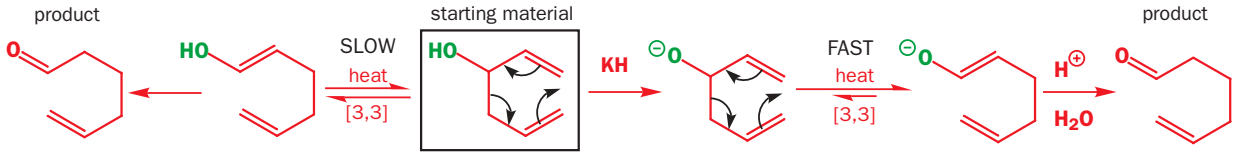


Directing the Cope rearrangement by the formation of a carbonyl group

The starting material and the product are the same. We can drive this reaction too by the formation of a carbonyl group if we put an OH substituent in the right place.

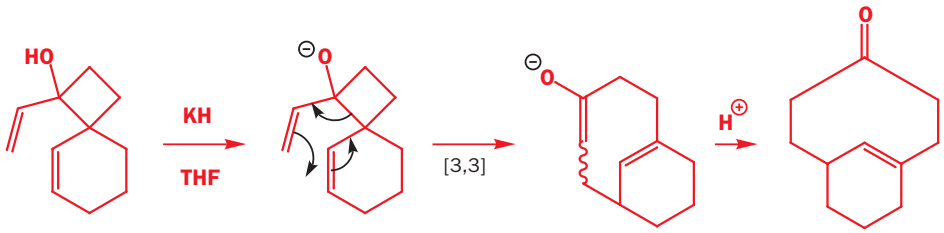


The product of the sigmatropic step is the enol of the final product. It turns out that the reaction is accelerated if the starting alcohol is treated with base (KH is the best) to make the alkoxide. The product is then the potassium enolate, which is more stable than the simple potassium alkoxide starting material. As the reaction proceeds, conjugation is growing between O^- and the new π bond.

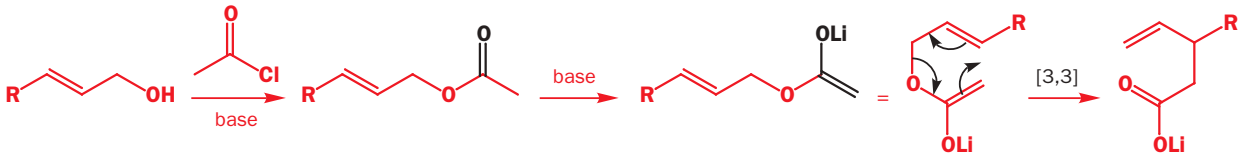


■ Bredt's rule forbidding bridgehead alkenes and the reasons are discussed in Chapter 19.

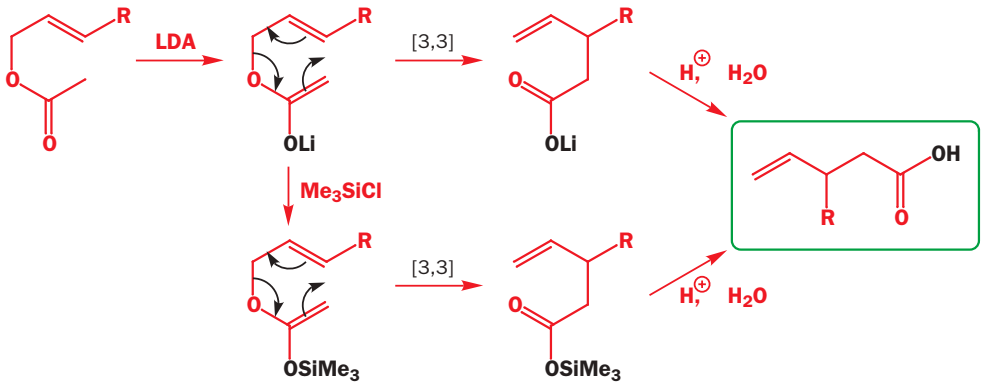
Some remarkable compounds can be made by this method. One of the strangest—a 'bridgehead' alkene—was made by a potassium-alkoxide-accelerated Cope rearrangement in which a four-membered ring was expanded into an eight-membered ring containing a *trans* double bond.



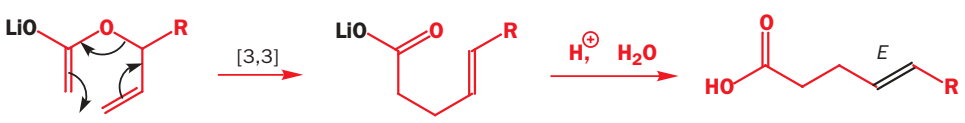
A combination of an oxygen atom in the ring and another one outside the ring is very powerful at promoting [3,3]-sigmatropic rearrangements and easy to arrange by making the lithium enolate of an ester of an allylic alcohol.



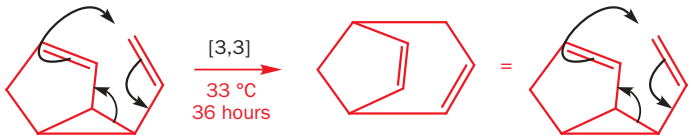
Sometimes it is better to convert the lithium enolate into the silyl enol ether before heating to accomplish the [3,3]-sigmatropic rearrangement. In any case, both products give the unsaturated carboxylic acid on work-up.



This reaction is known as the **Ireland–Claisen rearrangement** as it was a variation of the Claisen rearrangement invented by R.E. Ireland in the 1970s and widely used since. If the substituents are suitably arranged, it shows the same *E* selectivity as the simple Claisen rearrangement and for the same reason.



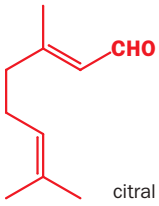
In some cases simple Cope rearrangements without any oxygen atoms at all can be directed by an unstable starting material or a stable product. The instability might be strain and the stability might simply be more substituents on the double bonds. In this case the driving force is the breaking of a weak σ bond in a three-membered ring. This reaction goes in 100% yield at only just above room temperature, so it is very favourable.



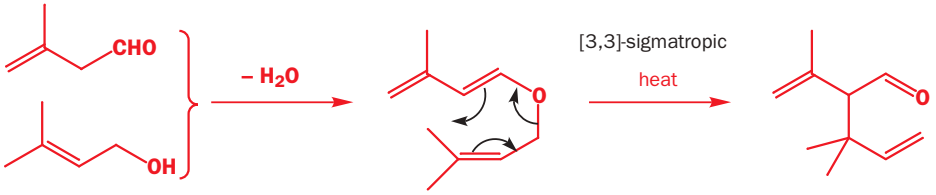
In this second example, the trisubstituted double bonds inside the five-membered rings of the product are more stable than the exomethylene groups in the starting material.

An industrial synthesis of citral

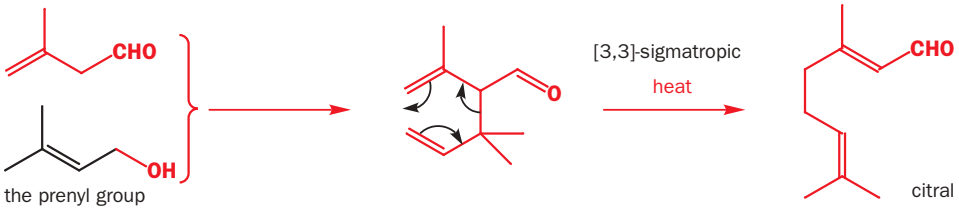
'Citral' is a key intermediate in the synthesis of vitamin A, and in Chapter 31 you had a go at designing a synthesis of it. BASF manufacture citral by a remarkable process that involves two successive [3,3]-sigmatropic rearrangements, a Claisen followed by a Cope.



The allyl vinyl ether needed for the Claisen rearrangement is an enol ether of an unsaturated aldehyde with an unsaturated alcohol. The two starting materials are themselves derived from a common precursor, making this a most efficient process! Heating the enol ether promotes [3,3]-sigmatropic rearrangement propelled by the formation of a carbonyl group.



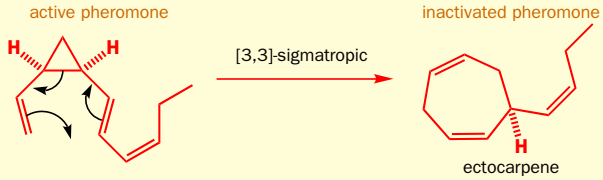
But the product of this rearrangement is now set up for a second [3,3]-sigmatropic rearrangement, this time made favourable by a shift into conjugation and the formation of two trisubstituted double bonds from two terminal ones. Overall, the prenyl group walks from one end of the molecule to the other, inverting twice as it goes.



Sex for seaweeds censored by a [3,3]-sigmatropic rearrangement

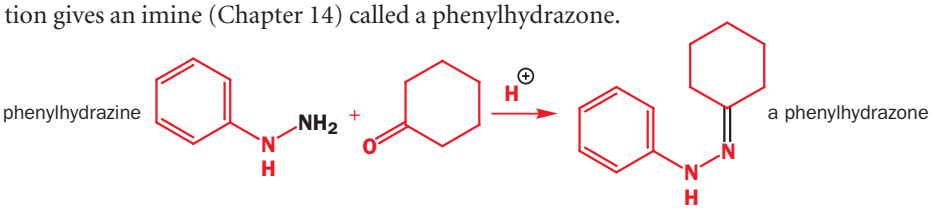
In order to reproduce, the female gametes of marine brown algae must attract mobile male gametes. This they do by releasing a pheromone, long thought to be the cycloheptadiene ectocarpene. In 1995 results were published that suggested that, in fact, the pheromone was a cyclopropane, and that ectocarpene was ineffective as a pheromone

How had the confusion arisen? Well, the remarkable thing is that the cyclopropyl pheromone inactivates itself, with a half-life of several minutes at ambient temperature, by [3,3]-sigmatropic rearrangement to the cycloheptadiene, driven by release of strain from the three-membered ring. This not only confused the earlier pheromone chemists, but it also provides a marvellously precise way for the algae to signal their presence and readiness for reproduction without saturating the sea water with meaningless pheromone.

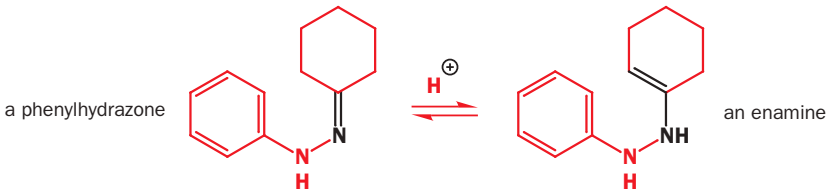


Applications of [3,3]-sigmatropic rearrangements using other elements

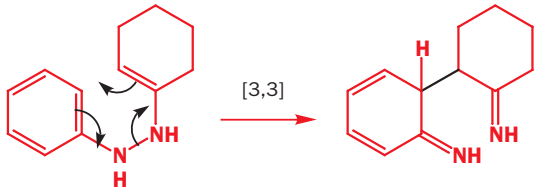
There is no need to restrict our discussion to carbon and oxygen atoms. We shall finish this section with two useful reactions that use other elements. The most famous synthesis of indoles is a nineteenth century reaction discovered by Emil Fischer—the **Fischer indole synthesis**—and it would be a remarkable discovery even today. Reaction of phenylhydrazine with a ketone in slightly acidic solution gives an imine (Chapter 14) called a phenylhydrazone.



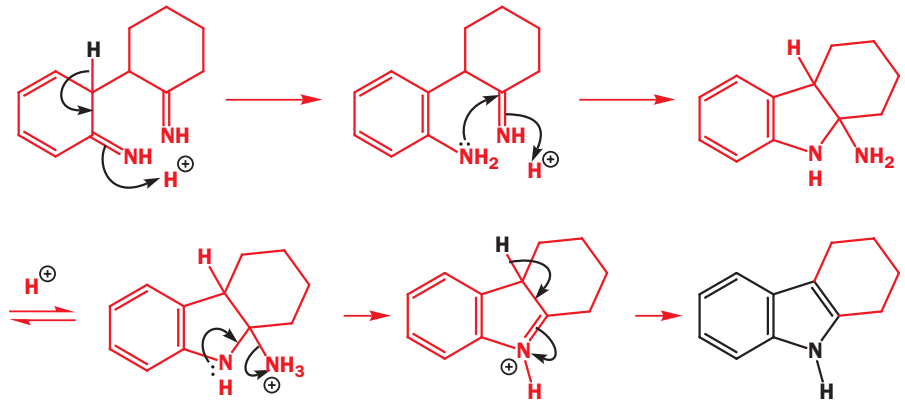
If the ketone is enolizable, this imine is in equilibrium with the corresponding enamine. The important bonds are given in black in the diagram.



The enamine is ideally set up for a [3,3]-sigmatropic rearrangement in which the σ bond to be broken is the weak N–N σ bond and one of the π bonds is in the benzene ring.



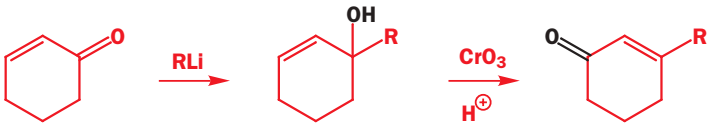
The product is a highly unstable double imine. Aromaticity is immediately restored and a series of proton shifts and C–N bond formation and cleavage give the aromatic indole. In the last diagram the ten-π-electron indole is outlined in black.



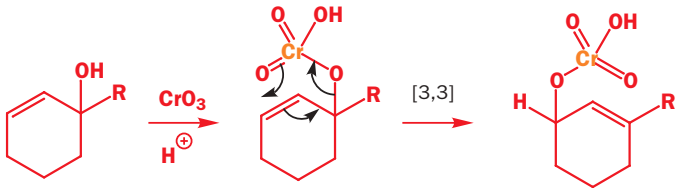
■ A detailed discussion of this reaction as a synthesis of indoles appears in Chapter 44.

Indoles are of some importance in biology and medicine and the Fischer indole synthesis is widely used. Sometimes the complete reaction occurs, as in this example, under the slightly acidic conditions needed to make the phenylhydrazone. More commonly, the phenylhydrazone is isolated and converted into the indole with a Lewis acid such as $ZnCl_2$.

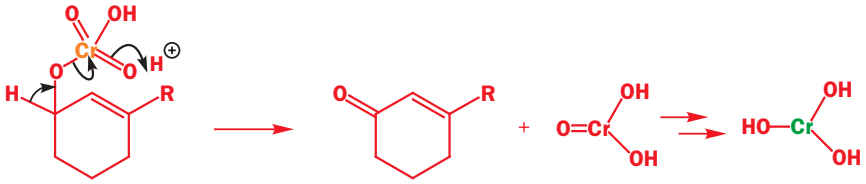
That was a [3,3]-sigmatropic reaction involving two nitrogens. There follows one with two oxygens and a chromium atom. When tertiary allylic alcohols are oxidized with CrO_3 in acid solution, no direct oxidation can take place, but a kind of conjugate oxidation occurs.



The first step in Cr(VI) oxidations can take place to give a chromate ester (Chapter 24) but this intermediate has no proton to lose so it transfers the chromate to the other end of the allylic system where there is a proton. The chromate transfer can be drawn as a [3,3]-sigmatropic rearrangement.

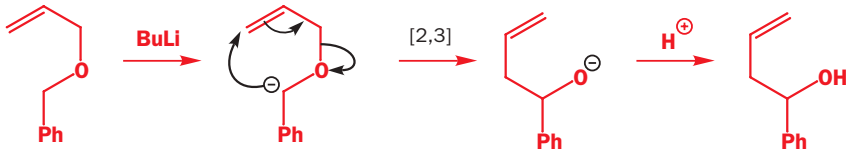


The final step is the normal oxidation (Chapter 24) in which chromium drops down from orange Cr(VI) to Cr(IV) and eventually by disproportionation to green Cr(III).

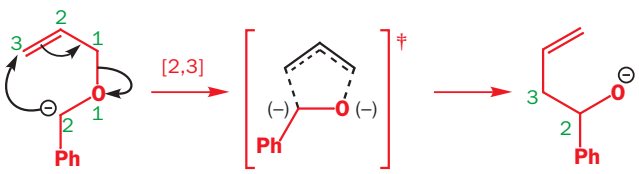


[2,3]-Sigmatropic rearrangements

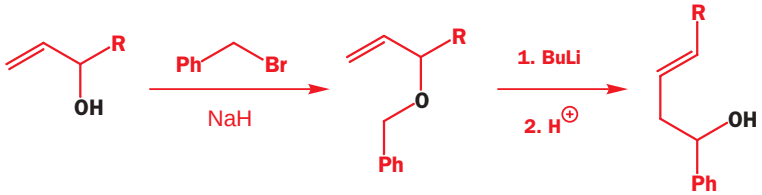
All [3,3]-sigmatropic rearrangements have six-membered cyclic transition states. It is no accident that the size of the ring is given by the sum of the two numbers in the square brackets as this is universally the case for sigmatropic rearrangements. We are now going to look at [2,3]-sigmatropic rearrangements so we will be needing five-membered cyclic transition states. There is a problem here. You cannot draw three arrows going round a five-membered ring without stopping or starting on an atom. One way to do this is to use a carbanion.



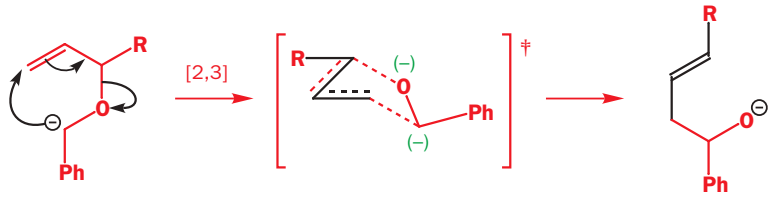
The starting material is a benzyl allyl ether and undergoes [2,3]-sigmatropic rearrangement to make a new C–C σ bond at the expense of a C–O σ bond—a bad bargain this as the C–O bond is stronger. The balance is tilted by the greater stability of the oxyanion in the product than of the carbanion in the starting material. The new bond has a 2,3 relationship to the old and the transition state is a five-membered ring.

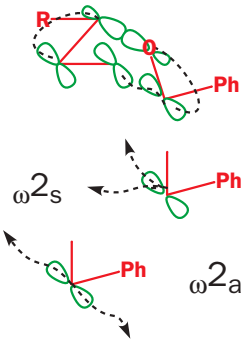


The transition state can be quite chair-like so that the new π bond will be *trans* if it has a choice. There will be a choice if the ether has been made from a substituted allyl alcohol.



We cannot draw a complete chair as we would need a six-membered ring for that (see discussion of [3,3]-sigmatropic rearrangements above), but the part that is to become the new π bond can be in a chair-like part of the five-membered ring. The substituent R prefers an equatorial position and the resulting *trans* arrangement of the groups is outlined in black.

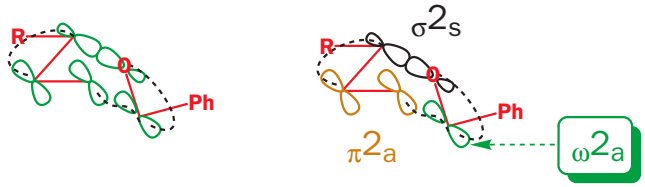




We can use the same conformational diagram to show how the orbitals overlap as the new bond is formed.

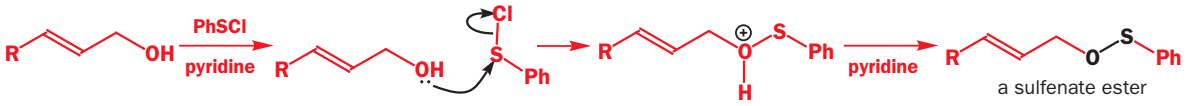
When we come to use the Woodward–Hoffmann rules on these [2,3]-sigmatropic rearrangements, we find something new. We have a π bond and a σ bond and a carbanion. How are we to represent a carbanion (or a carbocation) that is just a p orbital on an atom? The new symbol we use for a simple p orbital is ω. A carbanion is an $_{\omega}2$ component and a carbocation is an $_{\omega}0$ component as it has zero electrons. If the two new bonds are formed to the same lobe of the p orbital of the carbanion, we have an $\omega 2_s$ component but, if they are formed to different lobes, we have an $\omega 2_a$ component.

Without going through the whole routine again, the [2,3]-sigmatropic rearrangement we have been discussing can be described as an $\omega 2_a + \sigma 2_s + \pi 2_a$ reaction. There is one $(4q + 2)_s$ and no $(4r)_a$ components so the reaction is thermally allowed.

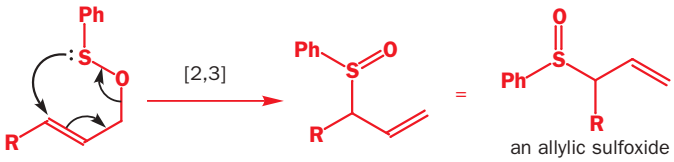


Sulfur is good at [2,3]-sigmatropic rearrangements

There are many [2,3]-sigmatropic rearrangements involving a variety of heteroatoms as well as carbon. We shall describe just one more because it involves no ions at all. The key is an element that is prepared to change its oxidation state by two so that we can start and finish an arrow on that element. The element is sulfur, which can form stable compounds at three oxidation states: S(II), S(IV), or S(VI).

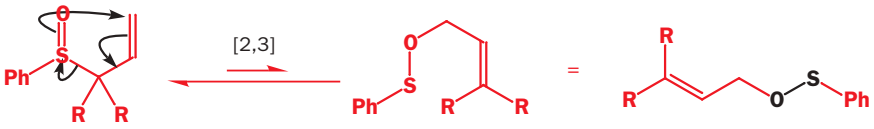


Reaction of an allylic alcohol with PhSCl gives an unstable sulfenate ester that rearranges on heating to an allylic sulfoxide by a [2,3]-sigmatropic rearrangement involving both O and S.

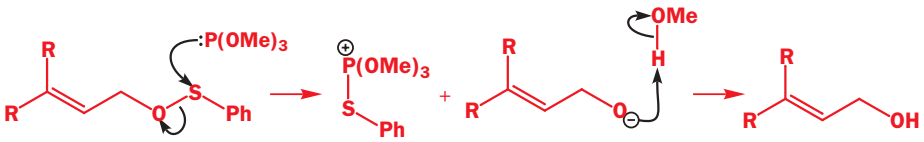


Notice that arrows both start and stop on the sulfur atom, which changes from S(II) to S(IV) during the reaction. The new functional group with an S=O bond is called a **sulfoxide**. This is a good preparation of allylic sulfoxides. The product forms an anion stabilized by sulfur, which can be alkylated.

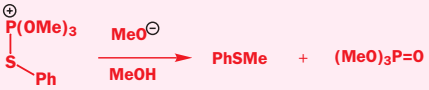
We have said that all these sigmatropic rearrangements are reversible but now we can prove it. If this product is heated in methanol with a nucleophile such as $(MeO)_3P$, which has a liking for sulfur, the [2,3]-sigmatropic rearrangement runs backwards and a sulfenate ester is again formed.



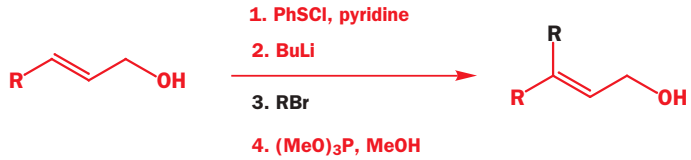
This is an unfavourable reaction, because the equilibrium lies over on the sulfoxide side. But the nucleophile traps the sulfenate ester and the methanol ensures that the alkoxide ion formed is immediately protonated so that we get another allylic alcohol.



▶ The other products are actually PhSMe and $(MeO)_3P{=}O$. You might like to work out a mechanism for these stages of the reaction.



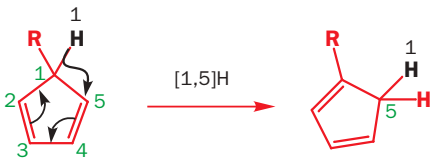
So what is the point of going round in circles like this? The net result is the alkylation of an allylic alcohol in a position where alkylation would not normally be considered possible.



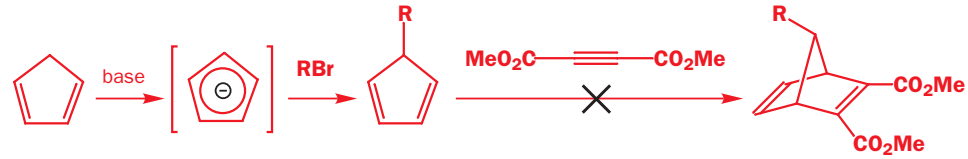
[1,5]-Sigmatropic hydrogen shifts

When one of the numbers in square brackets is '1', the old and new σ bonds are to the same atom, so we are dealing with the migration of a group around a conjugated system. In the case of a [1,5] shift the transition state is a six-membered ring (remember—just add together the numbers in square brackets). Here is an important example.

Let us first check that this is indeed a [1,5]-sigmatropic rearrangement by numbering the position of the new σ bond with respect to the old. Note that we must go the long way round the five-membered ring because that is the way the mechanism goes.

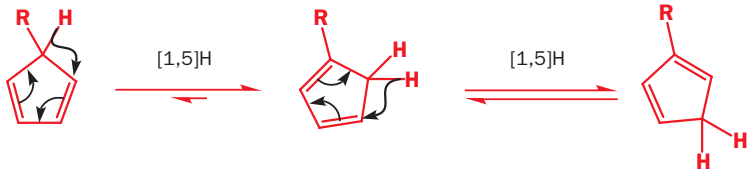


It *is* a [1,5]-sigmatropic rearrangement. The figure '1' in the square brackets shows that the same atom is at one end of the new σ bond as was at one end of the old σ bond. One atom has moved in a 1,5 manner and these are often called [1,5]-sigmatropic *shifts*. This is often abbreviated to **[1,5]H shift** to show which atom is moving. This particular example is important because sadly it prohibits a most attractive idea. The cyclopentadiene anion is very stable (Chapter 8) and can easily be alkylated. The sequence of alkylation and Diels–Alder reaction looks very good.

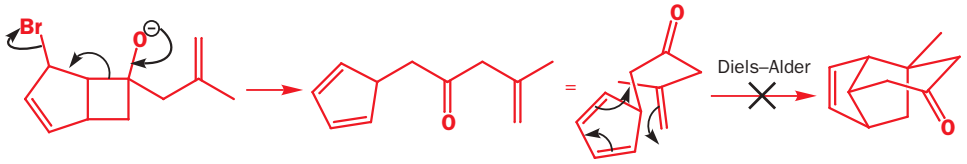


Sadly this sequence is, in fact, no good at all. A mixture of three Diels–Alder adducts is usually obtained resulting from addition to the three cyclopentadienes present in solution as the result of

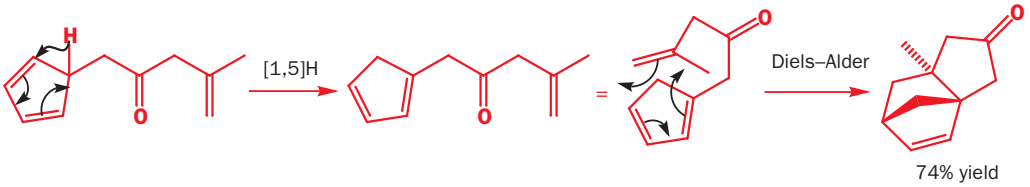
rapid [1,5]H shifts. The one drawn above is a minor product because there is more of the other two dienes, which have an extra substituent on the double bonds.



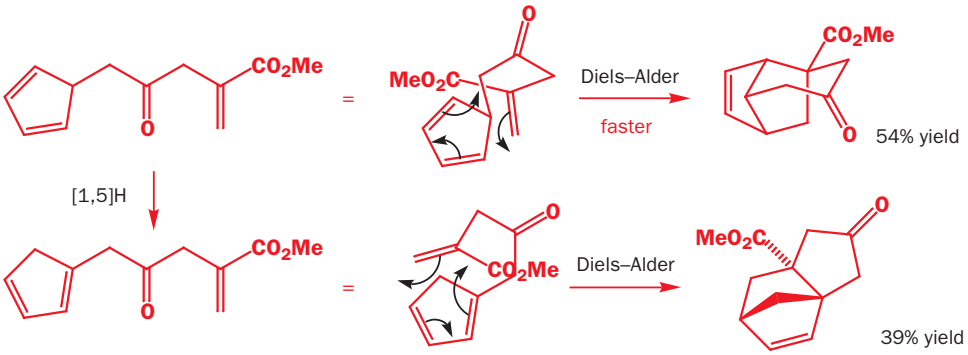
An excellent example comes from the intramolecular Diels–Alder reactions explored by Dreiding in 1983. One particular substituted cyclopentadiene was made by a fragmentation reaction (see Chapter 38). It might have been expected to give a simple Diels–Alder adduct.



There is nothing wrong with this reaction; indeed, the product looks beautifully stable, but it is not formed because the [1,5]H shift is too quick and gives a more stable cyclopentadiene with more substituents on a double bond. *Then* it does the Diels–Alder reaction.



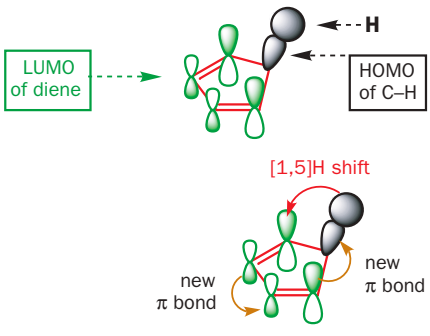
Notice that in these compounds the ketone is not conjugated to any of the alkenes and so does not influence the reaction. If we increase the reactivity of the dienophile by putting an ester group in conjugation with it, most of the compound does the Diels–Alder reaction *before* it does the [1,5]H shift.



Orbital description for the [1,5]H sigmatropic shift

It is equally satisfactory to use frontier orbitals or the Woodward–Hoffmann rules for these reactions. We can take the diene as one component (HOMO or LUMO or $\pi 4$) and the C–H bond as the other (LUMO or HOMO or $\sigma 2$). Let us start by using the LUMO of the diene and the HOMO of the C–H bond.

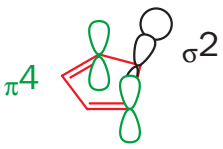
If the circle around the H atom surprised you, perhaps it will also remind you that hydrogen has only a 1s orbital which is spherical. You can probably see already that all the orbitals are correctly lined up for the reaction.



▶ You should satisfy yourself that the other frontier orbital combination—HOMO of the diene and LUMO of the C–H bond—works equally well.

The hydrogen atom slides across the top face of the planar cyclopentadiene ring. We call this a **suprafacial migration**. This name has got nothing to do with the components in the Woodward–Hoffmann rules—it just means that the migrating group leaves from one face of the π system and rejoins that same face (the top face in this example). **Antarafacial migration** would mean leaving the top face and rejoining the bottom face—a clear impossibility here.

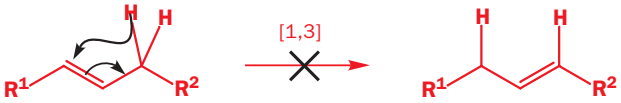
If you use the Woodward–Hoffmann rules, you need to note that the hydrogen atom must react with retention. The 1s orbital is spherically symmetrical and has no node, so wherever you draw the dotted line from that orbital it always means retention. Choosing the components is easy—the diene is a $_{\pi}4$ and the C–H bond a $_{\sigma}2$ component.



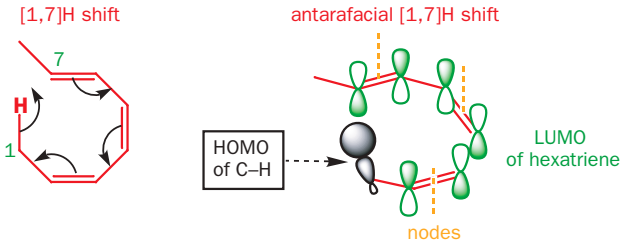
The easiest way to join them up is to link the hydrogen atom's 1s orbital to the top lobe of the p orbital at the back of the diene and the black sp^3 orbital to the top lobe at the front of the diene. This gives us $_{\pi}4_s$ and $_{\sigma}2_s$ components and there is one $(4q + 2)_s$ and no $(4r)_a$ components so the sum is odd and the reaction is allowed. Both approaches give us the same picture—a suprafacial migration of the hydrogen atom with (inevitably) retention at the migrating group.

These [1,5]-sigmatropic shifts are not restricted to cyclopentadienes. In Chapter 35 we bemoaned the lack of Diels–Alder reactions using *E,Z*-dienes. One reason for this dearth is that such dienes undergo [1,5]H shifts rather easily and mixtures of products result.

The complete rules for sigmatropic hydrogen shifts are simple. In thermal reactions, [1,5]H shifts occur suprafacially but [1,3]H and [1,7]H shifts must be antarafacial. It is just as well that antarafacial [1,3]H shifts are impossible (though allowed) as otherwise double bonds would wander about organic molecules like this.



Antarafacial [1,3]H shifts are impossible because a rigid three-carbon chain is too short to allow the H atom to transfer from the top to the bottom—the H atom just can't reach. When we come to [1,7]H shifts, the situation is different. Now the much longer chain is just flexible enough to allow the transfer.



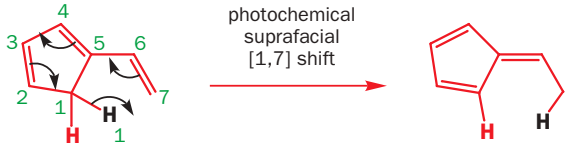
The hydrogen atom leaves the top side of the triene and adds back in on the bottom side. Antarafacial migration is allowed and possible.

Summary of thermal sigmatropic hydrogen shifts

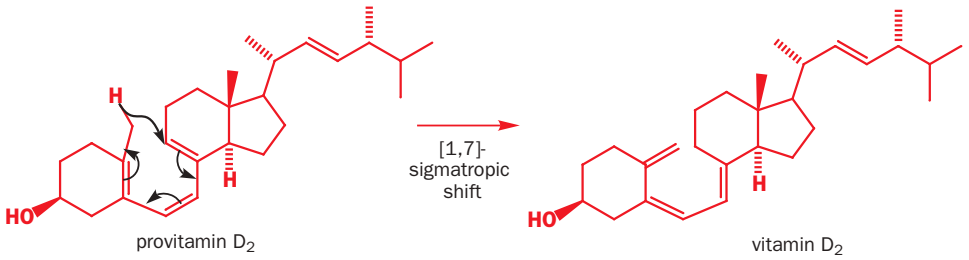
	[1,3]H shift	[1,5]H shift	[1,7]H shift
stereochemistry	antarafacial	suprafacial	antarafacial
feasibility	impossible	easy	possible

Photochemical [1,*n*]H sigmatropic shifts follow the opposite rules

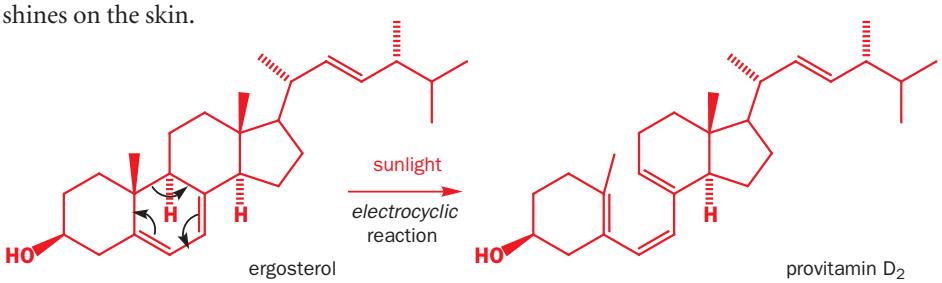
As you should by now expect (p. 000), all this is reversed in photochemical reactions. Here is an example of a [1,7]H shift that cannot occur antarafacially because the molecule is a rigid ring, but that can and does occur photochemically.



A [1,7]H shift occurs in the final stages of the human body's synthesis of vitamin D from cholesterol. Here is the last step of the biosynthesis.



This step happens spontaneously, without the need for light, so the shift must be antarafacial. The reason the body *does* need light to make vitamin D is the previous step, which only occurs when light shines on the skin.

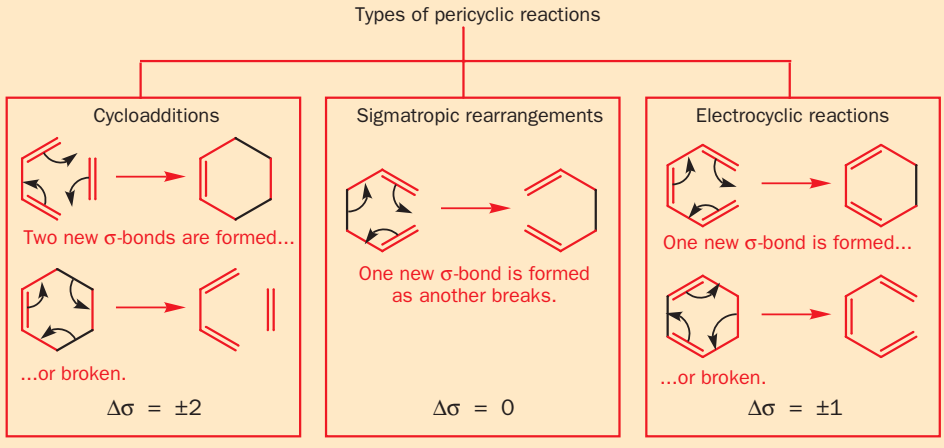


This ring opening is clearly pericyclic—the electrons go round in a ring, and the curly arrows could be drawn either way—but it is neither a cycloaddition (only one π system is involved) nor a sigmatropic rearrangement (a σ bond is broken rather than moved). It is, in fact, a member of the third and last kind of pericyclic reaction, an *electrocyclic reaction*.

Electrocyclic reactions

In an **electrocyclic reaction** a ring is always broken or formed. Rings may, of course, be formed by cycloadditions as well, but the difference with electrocyclic reactions is that just one new σ bond is formed (or broken) across the ends of a single conjugated π system. In a cycloaddition, two new σ bonds are always formed (or broken), and in a sigmatropic rearrangement one σ bond forms while one breaks.

The types of pericyclic reactions are distinguished by the number of σ bonds made or broken



One of the simplest electrocyclic reactions occurs when hexatriene is heated to 500 °C.

It is a pericyclic reaction because the electrons go round in a ring (you could equally draw the arrows going the other way); it's electrocyclic because a new σ bond is formed across the ends of

a π system. The reaction goes because the σ bond that is formed is stronger than the π bond that is lost. The opposite is true for the electrocyclic reaction shown in the margin—ring strain in the four-membered ring means that the reverse (ring-opening) reaction is preferred to ring closure.

Rules for electrocyclic reactions

Whether they go in the direction of ring opening or ring closure, electrocyclic reactions are subject to the same rules as all other pericyclic reactions—you saw the same principle at work in Chapter 35 where we applied the Woodward–Hoffmann rules both to cycloadditions and to reverse cycloadditions. With most of the pericyclic reactions you have seen so far, we have given you the choice of using either HOMO–LUMO reasoning or the Woodward–Hoffmann rules. With electrocyclic reactions, you really have to use the Woodward–Hoffmann rules because (at least for the ring closures) there is only one molecular orbital involved.

▶ In one famous case, the release of ring strain is almost exactly counterbalanced by the formation of a σ bond at the expense of a π bond. Cycloheptatriene exists in equilibrium with a bicyclic isomer known as norcaradiene. Usually cycloheptatriene is the major component of the equilibrium, but the norcaradiene structure is favoured if R is an electron-withdrawing group.

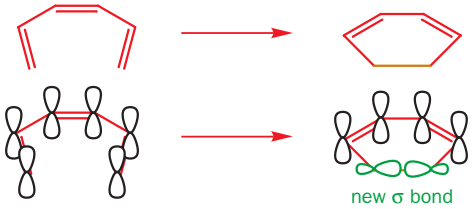
cycloheptatriene (R = H) norcaradiene (R = H)

Electrocyclic reactions

- An **electrocyclic reaction** is the formation of a new σ bond across the ends of a conjugated polyene or the reverse

It is important that you do not confuse electrocyclic reactions with pericyclic reactions. Pericyclic is the name for the family of reactions involving no charged intermediates in which the electrons go round the outside of the ring. *Electrocyclic* reactions, *cycloadditions*, and *sigmatropic* rearrangements are the three main classes of *pericyclic* reactions.

Let's start with the hexatriene ring closure, first looking at the orbitals, and then following the same procedure that we taught you for cycloadditions and sigmatropic rearrangements to see what the Woodward–Hoffmann rules have to say about the reaction. As a preliminary, we should just note that hexatriene is, of course, a 6 π electron ($_{\pi}6$) conjugated system and, on forming cyclohexadiene, the end two orbitals have to form a σ bond.

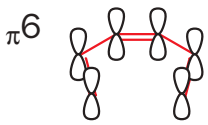


▶ *Reminder.* In a thermal pericyclic reaction the total number of $(4q + 2)_s$ and $(4r)_a$ components must be odd.

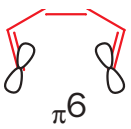
So, now for the Woodward–Hoffmann treatment.

1 Draw the mechanism for the reaction

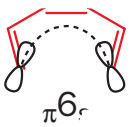
2 Choose the components. All the bonds taking part in the mechanism must be included and no others



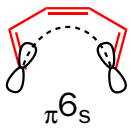
3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)



4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds



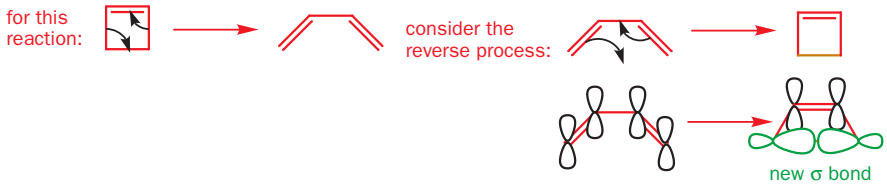
5 Label each component s or a depending on whether new bonds are formed on the same or on opposite sides



6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed

■ There is **one** $(4q + 2)_s$ component and **no** $(4r)_a$ components. Total = 1 so this is an allowed reaction

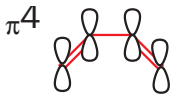
Notice that we called the reaction 's' because the top halves of the two π orbitals were joining together. We can give the same treatment to the cyclobutene ring-opening reaction—the Woodward–Hoffmann rules tell us nothing about which way the reaction will go, only if the reaction is allowed, and it is invariably easier with electrocyclic reactions to consider the ring-closing reaction even if the ring opening is favoured thermodynamically. This is the process we need to consider.



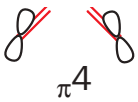
And the Woodward–Hoffmann treatment again.

1 Draw the mechanism for the reaction

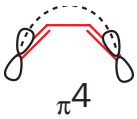
2 Choose the components. All the bonds taking part in the mechanism must be included and no others



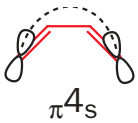
3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)



4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds



5 Label each component s or a depending whether new bonds are formed on the same or on opposite sides



6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed.

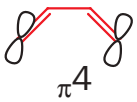
■ There are **no** $(4q + 2)_s$ components and **no** $(4r)_a$ components. Total = 0 so this is a *dis*allowed reaction.

Oh dear! We know that the reaction works, so something must be wrong. It certainly isn't Woodward and Hoffmann's Nobel-prize-winning rules—it's our way of drawing the orbital overlap that is at fault. We were fine till stage 3 (we had no choice till then)—but look at what happens if we make the orbitals overlap in a different way.

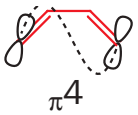
1 As before

2 As before

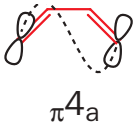
3 Make a three-dimensional drawing of the way in which the components come together for the reaction, putting in orbitals at the ends of the components (only!)



4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds



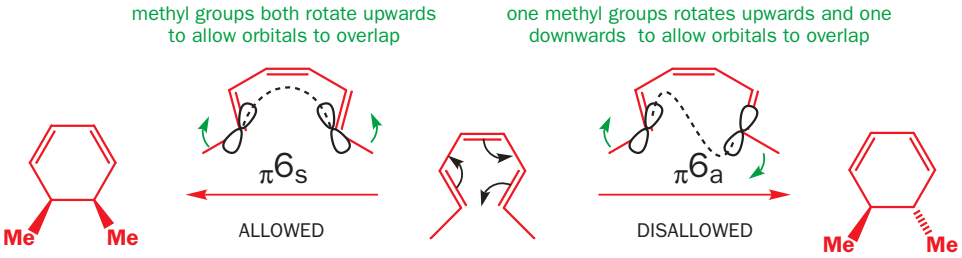
5 Label each component s or a depending on whether new bonds are formed on the same or on opposite sides



6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed.

■ There are **no** $(4q + 2)_s$ components and **one** $(4r)_a$ component. Total = 1 so this is an allowed reaction.

Now it works! In fact, extension of this reasoning to other electrocyclic reactions tells you that they are *all* allowed—provided you choose to make the conjugated system react with itself *supra*-facially for $(4n + 2)$ π systems and *antara*facially for $(4n)$ π systems. This may not seem particularly informative, since how you draw the dotted line has no effect on the reaction product in these cases. But it can make a difference. Here is the electrocyclic ring closure of an octatriene, showing the product from (a) suprafacial reaction and (b) antarafacial reaction.



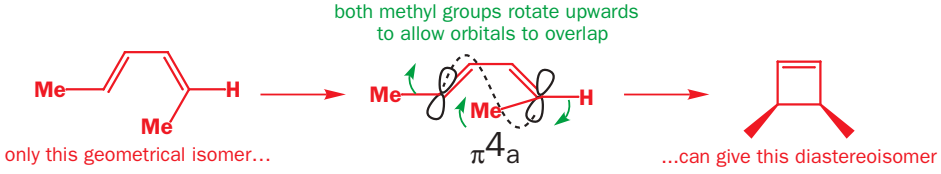
The meanings of con- and disrotation

Whether the reaction is supra- or antarafacial ought to be reflected in the relative stereochemistry of the cyclized products—and indeed it is. This reaction gives solely the diastereoisomer on the left, with the methyl groups *syn*—clear proof that the reaction is suprafacial. This is a difficult result to explain without the enlightenment provided by the Woodward–Hoffmann rules!

This electrocyclic cyclobutene ring opening also gives the product as a single stereoisomer.

syn-1,2-dimethylcyclobutene — *E, Z*-hexa-2,4-diene

Again, if we draw the reverse reaction, we can see that the reaction required has to be antarafacial for the stereochemistry to be right.



We have drawn little green arrows on the two diagrams to show how the methyl groups move as the new σ bonds form. For the allowed suprafacial reaction of the 6π electron system they rotate in

▶ The green arrows in this and subsequent diagrams are merely mechanical devices to show the way in which the substituents move. They are nothing to do with real, mechanistic curly arrows.

opposite directions so the reaction is called **disrotatory** (yes, they both go up, but one has to rotate clockwise and one anticlockwise) while for the allowed antarafacial reaction of the 4π electron system they rotate in the same direction so the reaction is called **conrotatory** (both clockwise as drawn, but they might equally well have both gone anticlockwise). We can sum up the course of all electrocyclic reactions quite simply using these words.

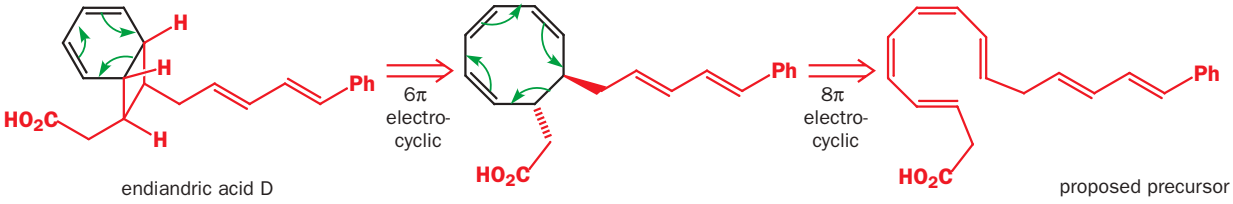
Rules for electrocyclic reactions

- All electrocyclic reactions are allowed
- Thermal electrocyclic reactions involving $(4n + 2)$ π electrons are *disrotatory*
- Thermal electrocyclic reactions involving $(4n)$ π electrons are *conrotatory*
- In *conrotatory* reactions the two groups rotate in the *same* way: *both* clockwise or *both* anticlockwise
- In *disrotatory* reactions, *one* group rotates *clockwise* and *one anticlockwise*

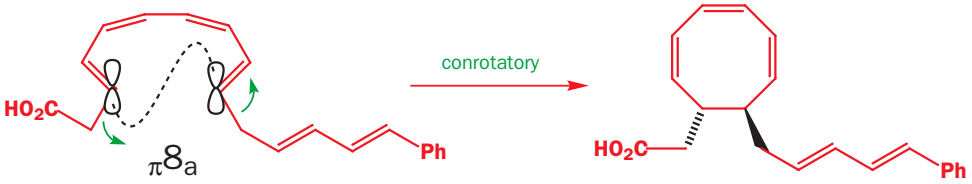
This rotation is the reason why you must carefully distinguish electrocyclic reactions from all other pericyclic reactions. In cycloadditions and sigmatropic rearrangements there are small rotations as bond angles adjust from 109° to 120° and vice versa, but in electrocyclic reactions, rotations of nearly 90° are required as a planar polyene becomes a ring, or vice versa. These rules follow directly from application of the Woodward–Hoffmann rules—you can check this for yourself.

Electrocyclic reactions occur in nature

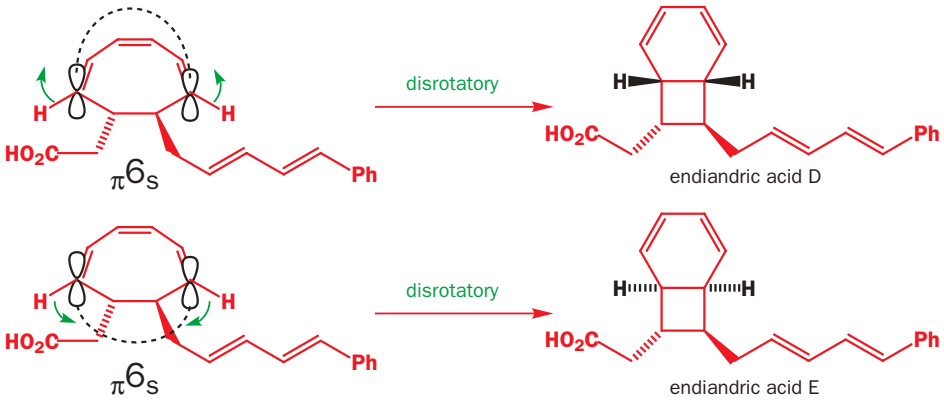
A beautiful example of electrocyclic reactions at work is provided by the chemistry of the endiandric acids. This family of natural products, of which endiandric acid D is one of the simplest, is remarkable in being racemic—most chiral natural products are enantiomerically pure (or at least enantiomerically enriched) because they are made by enantiomerically pure enzymes (we discuss all this in Chapter 45). So it seemed that the endiandric acids were formed by non-enzymatic cyclization reactions, and in the early 1980s their Australian discoverer, Black, proposed that their biosynthesis might involve a series of electrocyclic reactions, starting from an acyclic polyene precursor.



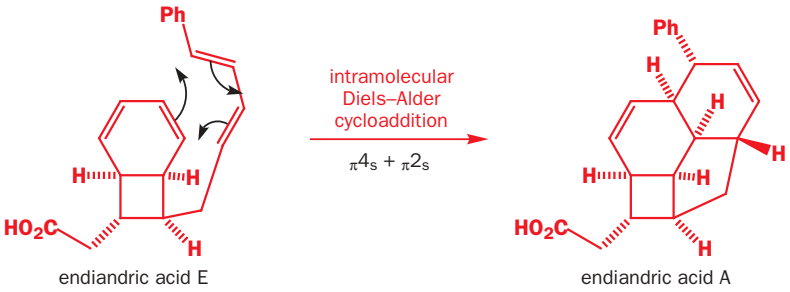
What made his proposal so convincing was that the stereochemistry of the endiandric acid D is just what you would expect from the requirements of the Woodward–Hoffmann rules. The first step from the precursor is an 8π electrocyclic reaction, and would therefore be conrotatory.



This sets up a new 6π system, which can undergo an electrocyclic reaction in disrotatory fashion. Because there are already chiral centres in the molecule, there are, in fact, two possible diastereoisomeric products from this reaction, both arising from disrotatory cyclization. One is endiandric acid D; one is endiandric acid E.



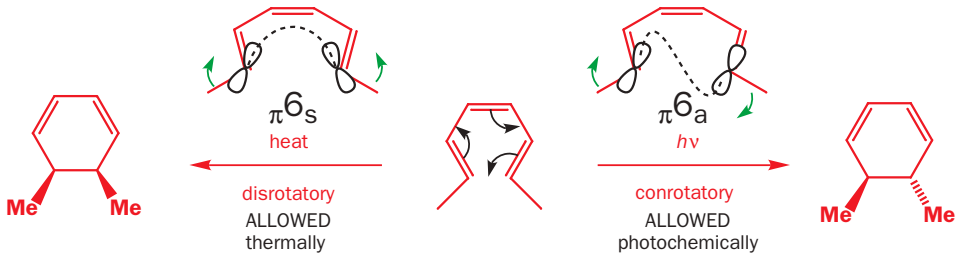
Of course, this was only a theory—until in 1982 K.C. Nicolaou's group synthesized the proposed endiandric acid precursor polyene—and in one step made both endiandric acids D and E, plus endiandric acid A, which arises from a further pericyclic reaction, an intramolecular Diels–Alder cycloaddition of the acyclic diene on to the cyclohexadiene as dienophile.



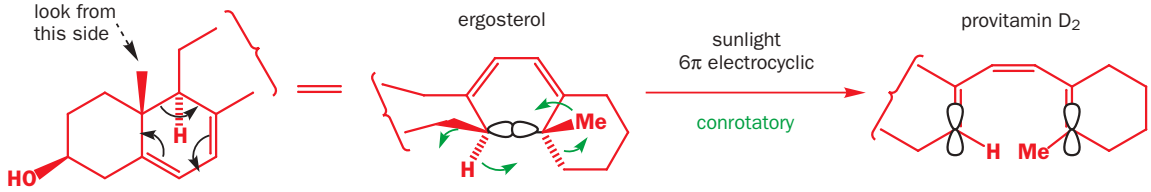
Endiandric acid A has four rings and eight stereogenic centres and yet is formed as a single diastereoisomer in one step from an acyclic polyene! And it's all controlled by pericyclic reactions.

Photochemical electrocyclic reactions

After your experience with cycloadditions and sigmatropic rearrangements, you will not be surprised to learn that, in photochemical electrocyclic reactions, the rules regarding conrotatory and disrotatory cyclizations are reversed.



We can now go back to the reaction that introduced this section—the photochemical electrocyclic ring opening of ergosterol to give provitamin D_2. By looking at the starting material and product we can deduce whether the reaction is conrotatory or disrotatory.

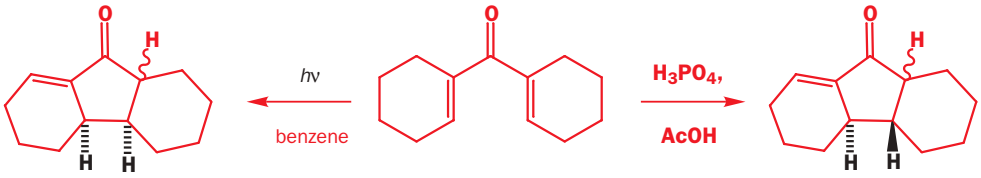


■ K.C. Nicolaou (1946–) was born in Cyprus, did his PhD in London, and has worked mainly at University of Pennsylvania and the Scripps Institute in California. His group was the first to synthesize some of the most complex natural products ever made by people.

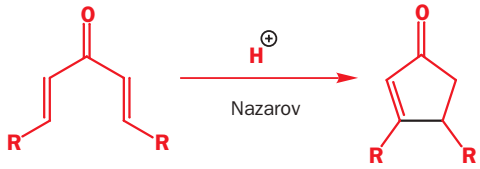
It's clearly conrotatory, and a little more thought will tell you why it has to be—a disrotatory thermal 6π cyclization would put an impossible *trans* double bond into one of the two six-membered rings. Vitamin D deficiency is endemic in those parts of the world where sunlight is scarce for many months of the year—and all because of orbital symmetry.

Cations and anions

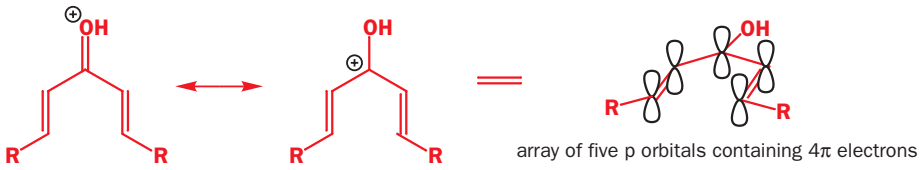
What we have just been telling you should convince you that the two reactions below are electrocyclic reactions, not least because the stereochemistry reverses on going from thermal to photochemical reaction.



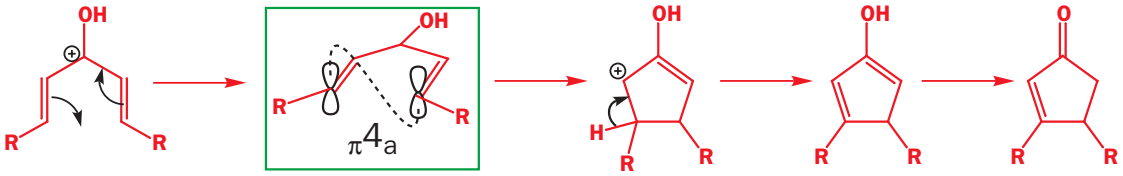
They are examples of what is known, after its Russian discoverer, as the **Nazarov cyclization**. In its simplest form, the Nazarov cyclization is the ring closure of a doubly α,β-unsaturated ketone to give a cyclopentenone.



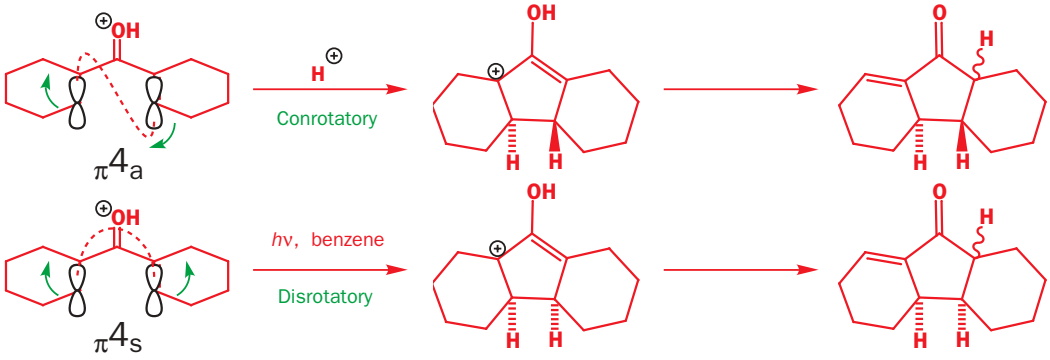
Nazarov cyclizations require acid, and protonation of the ketone sets up the conjugated π system required for an electrocyclic reaction.



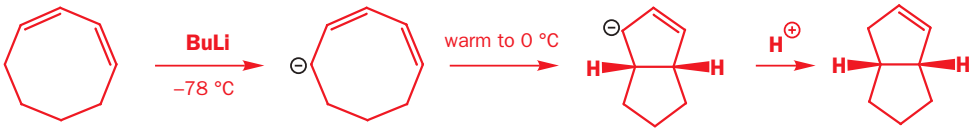
One of the five π orbitals involved is empty—so the cyclization is a 4π electrocyclic reaction, and the orbitals forming the new σ bond must interact antarafacially. Loss of a proton and tautomerism gives the cyclopentenone.



The real example above confirms that the reaction is thermally conrotatory and photochemically disrotatory.



Dienyl cations and dienyl anions both undergo electrocyclic ring closure—a nice example occurs when cyclooctadiene is deprotonated with butyllithium.



There are still five p orbitals involved in the cyclization, but now there are six π electrons, so the reaction is disrotatory.

In this case, it is the conrotatory *photochemical* cyclization that is prevented by strain (it was tried—cyclooctadienyl anion is stable for at least a week at –78 °C in broad daylight) as the product would be a 5,5 *trans*-fused system. The same strain prevents thermal electrocyclic ring closure of cyclooctadienyl cations.

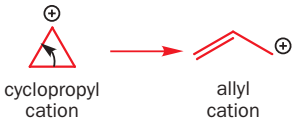
All electrocyclic reactions are allowed

It would be a good point here to remind you that, although all electrocyclic reactions are allowed both thermally and photochemically providing the rotation is right, the steric requirements for con- or disrotatory cyclization or ring opening may make one or both modes impossible.

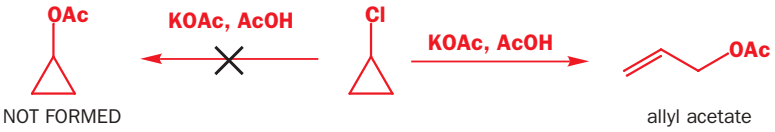
Small rings are opened by electrocyclic reactions

Ring strain is important in preventing a reaction that would otherwise change your view of a lot of the chemistry you know. Allyl cations are conjugated systems containing 2π electrons, so if you knew no other chemistry than what is in this chapter you might expect them to cyclize via disrotatory electrocyclic ring closure.

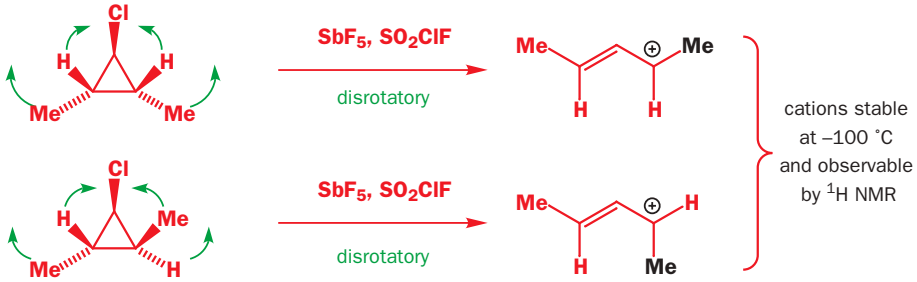
The product would be a cyclopropyl cation. Now, in fact, it is the cyclopropyl cations that undergo this reaction (very readily indeed—cyclopropyl cations are virtually unobservable) because ring strain encourages them to undergo electrocyclic ring opening to give allyl cations.



The instability of cyclopropyl cations means that, even as they start to form as intermediates, they spring open to give allyl cation-derived products. Try nucleophilic substitution on a cyclopropane ring and this happens.

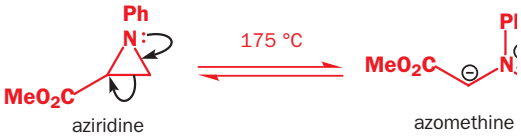


Although the initial product of the ring opening is a cation, and therefore a hard-to-observe reactive intermediate, some nice experiments in 'superacid' media (Chapters 17 and 22) have proven that cyclopropyl cation ring openings are indeed disrotatory.

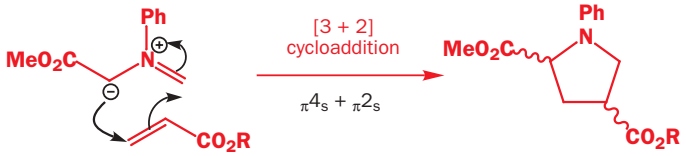


The stereochemistry of aziridine opening is predictable

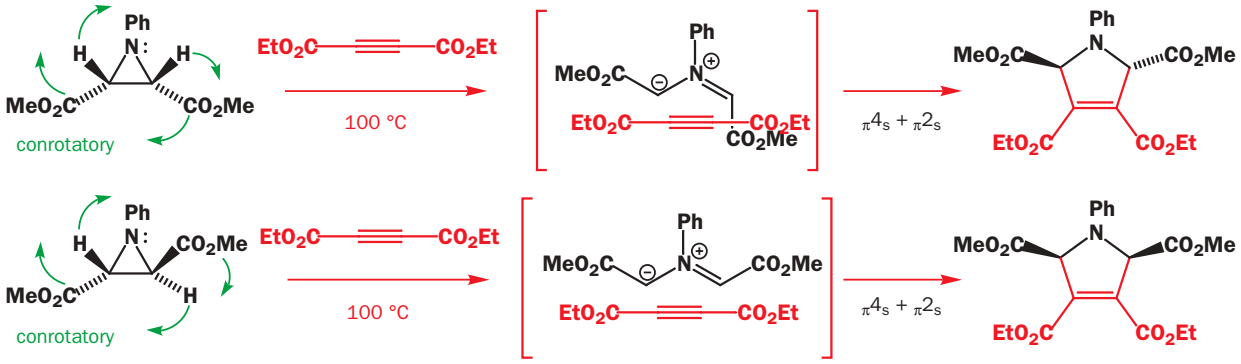
One last type of three-membered ring whose electrocyclic ring opening does tell us about the stereochemistry of the process is the aziridine. Many aziridines are stable compounds, but those bearing electron-withdrawing groups are unstable with respect to electrocyclic ring opening.

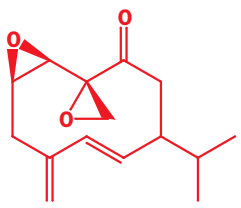


The products are azomethine ylids, and can be trapped by [3+2] cycloaddition reactions with dipolarophiles (look back at Chapter 35).



Because the cycloaddition is stereospecific (suprafacial on both components), the stereochemistry of the products can tell us the stereochemistry of the intermediate ylid, and confirms that the ring opening is conrotatory (the ylid is a 4π electron system).





periplanone B

■

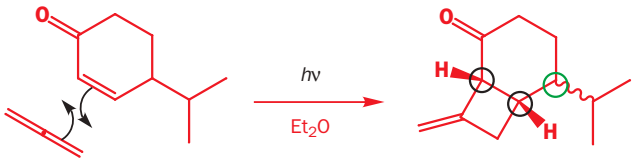
Stuart Schreiber (1956–) did his PhD at Harvard University where he is now a professor. One of the modern style of organic chemists who is equally at home with synthesis and biology.

The synthesis of a cockroach pheromone required pericyclic reactions

We finish this pair of chapters about pericyclic reactions with a synthesis whose simplicity is outclassed only by its elegance. Periplanone B is a remarkable bis-epoxide that functions as the sex pheromone of the American cockroach. Insect sex pheromones often have economic importance because they can form the key to remarkable effective traps for insect pests.

In 1984, Schreiber published a synthesis of the pheromone in which the majority of steps involve pericyclic reactions. Make sure you understand each one as it appears—re-read the appropriate part of Chapter 35 or this chapter if you have any problems.

The first step is a photochemical [2+2] cycloaddition. You could not have predicted the regiochemistry, but it is typical of the cycloaddition of allenes with unsaturated ketones.

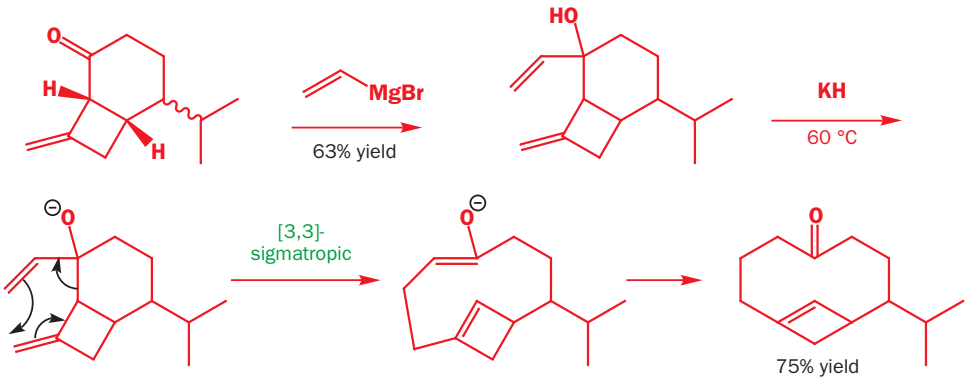


[2 + 2] cycloaddition

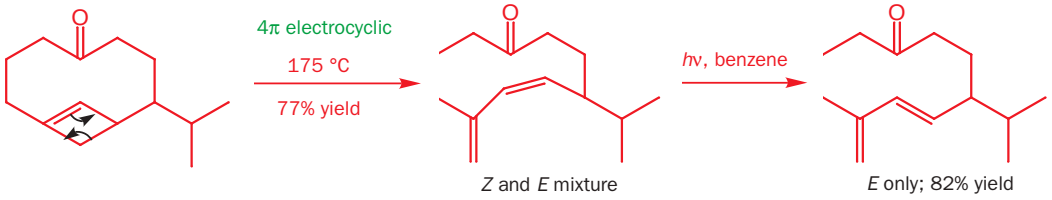
72% yield

The product is a mixture of diastereoisomers because of the chiral centre already in the molecule (ringed in green), but it is, of course, fully stereospecific for the two new black chiral centres in the four-membered ring. The next step adds vinylmagnesium bromide to the ketone—again a mixture of diastereoisomers results. Now all the carbons in the 12-membered ring are present, and they are sorted out by the two steps that follow. The first is a Cope rearrangement: a [3,3]-

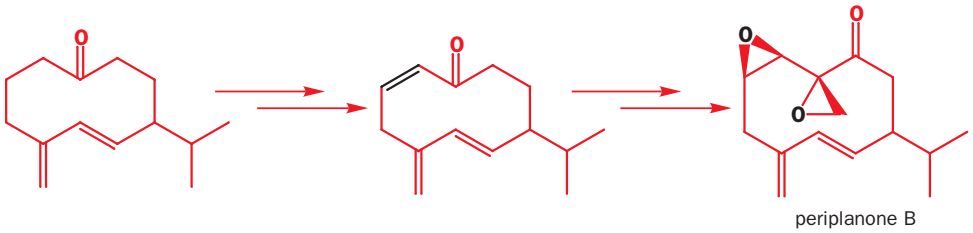
sigmatropic rearrangement, accelerated as we have described (p. 000) by the presence of an alkoxide substituent.



The six-membered ring has expanded to a ten-membered ring. Now for a second ring-expansion step—heating the compound to 175 °C makes it undergo electrocyclic ring opening of the four-membered ring, giving the 12-membered ring we want. Or rather not quite—the new double bond in the ring is formed as a mixture of *cis* and *trans* isomers, but irradiation isomerizes the less stable *cis* to the more stable *trans* double bond.



The remaining steps in the synthesis use chemistry not yet introduced in this book but involve the insertion of another (*Z*) alkene and two epoxides. Pericyclic reactions are particularly valuable in the synthesis and manipulation of rings.

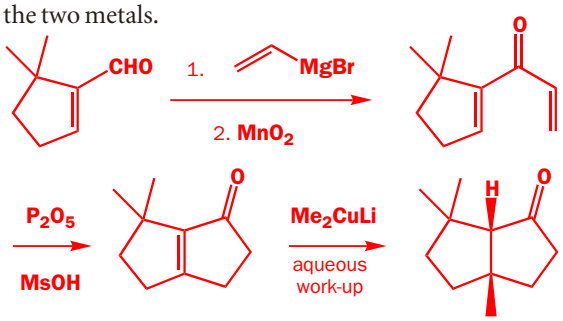


We must now take our leave of this trio of pericyclic reactions and move on to two reaction classes that have appeared frequently in these two chapters, but that involve mechanisms other than pericyclic ones and deserve chapters of their own: *rearrangements* and *fragmentations*.

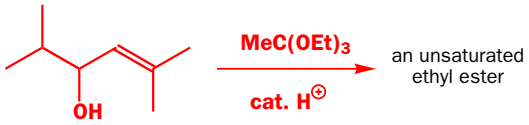
▶ There are two things to note here—firstly, the geometry of the double bond is nothing to do with whether the reaction is conrotatory or disrotatory. As you know, this 4π electron electrocyclic ring opening must be conrotatory, but as there is no substituent on the other end of the diene product we can't tell. Secondly, notice that, in this 12-membered ring, a *trans* double bond is not only possible, but probably preferred. We introduced irradiation as a means of interconverting double bond isomers in Chapter 31.

Problems

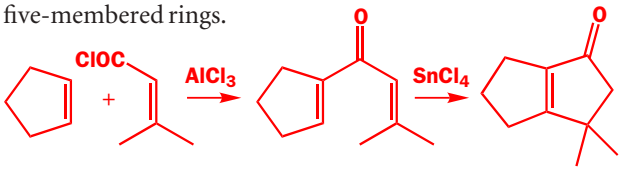
1. Give mechanisms for these steps, commenting on the regioselectivity of the pericyclic step and the different regioselectivity of the two metals.



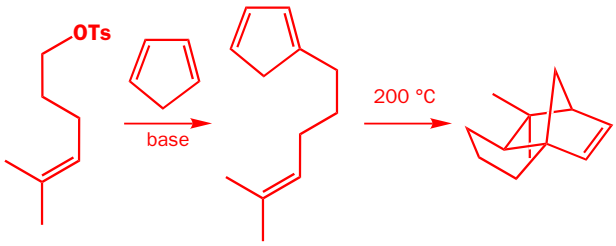
2. Predict the product of this reaction.



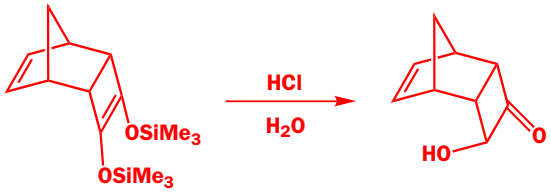
3. Give mechanisms for this alternative synthesis of two fused five-membered rings.



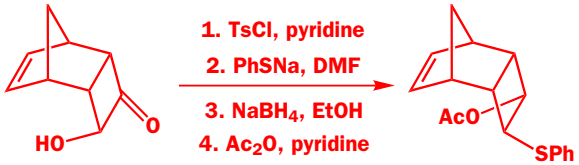
4. Explain what is going on here.



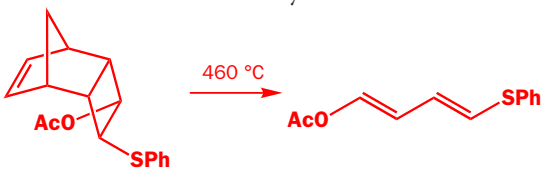
5. In Chapter 33, Problem 13, we used a tricyclic hydroxy-ketone whose stereochemistry had been wrongly assigned. Now we are going to show you how it was used and you are going to interpret the results. This is the correct result.



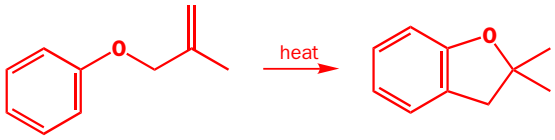
The hydroxy-ketone was first converted into a compound with PhS and OAc substituents. Explain the stereochemistry of this process.



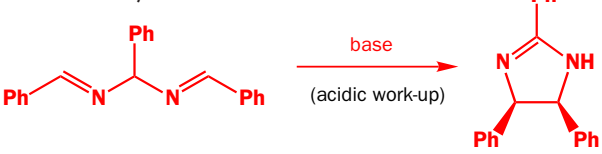
Pyrolysis of this compound at 460 °C gave a diene whose NMR spectrum included δ_H (p.p.m.) 6.06 (1H, dd, *J* 10.3, 12.1 Hz), 6.23 (1H, dd, *J* 10.3, 14.7 Hz), 6.31 (1H, d, *J* 14.7 Hz), and 7.32 (1H, d, *J* 12.1 Hz). Does this agree with the structure given? How is this diene formed and why does it have that stereochemistry?



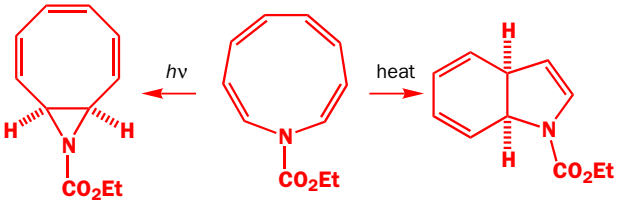
6. Careless attempts to carry out a Claisen rearrangement on this allyl ether often give the compound shown instead of the expected product. What is the expected product? How is the unwanted product formed? Addition of a small amount of a weak base, such as $PhNMe_2$ helps to prevent the unwanted reaction. How?



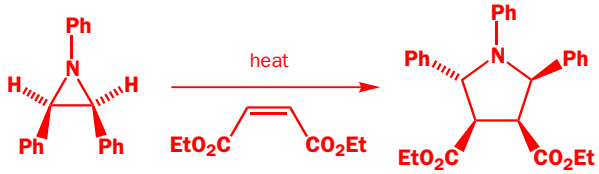
7. Treatment of this imine with base followed by an acidic work-up gives a cyclic product with two phenyl groups *cis* to one another. Why is this?



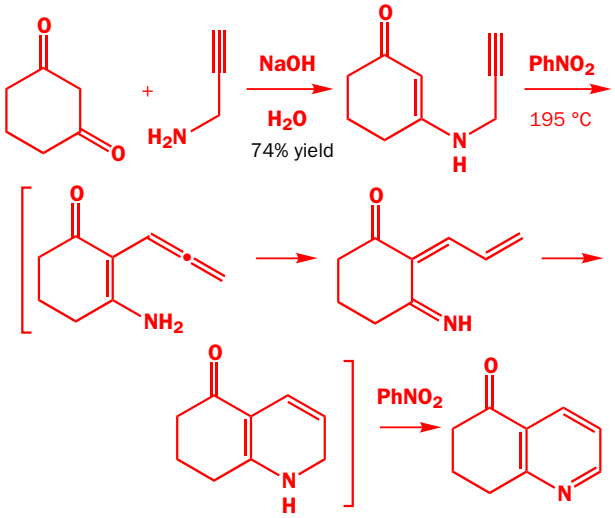
8. This question concerns the structure and chemistry of an unsaturated nine-membered ring. Comment upon its structure. Explain its different behaviour under thermal or photochemical conditions.



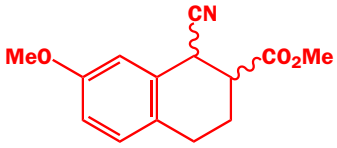
9. Propose a mechanism for this reaction that accounts for the stereochemistry of the product.



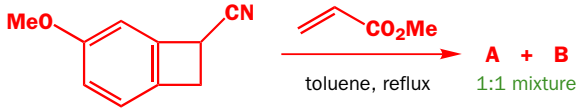
10. Treatment of cyclohexa-1,3-dione with this acetylenic amine gives a stable enamine in good yield. Refluxing this enamine in nitrobenzene gives a pyridine after a remarkable series of reactions. Fill in the details: give mechanisms for the reactions, structures for any intermediates, and suitable explanations for each pericyclic step. A mechanism is not required for the last step (nitrobenzene acts as an oxidant).



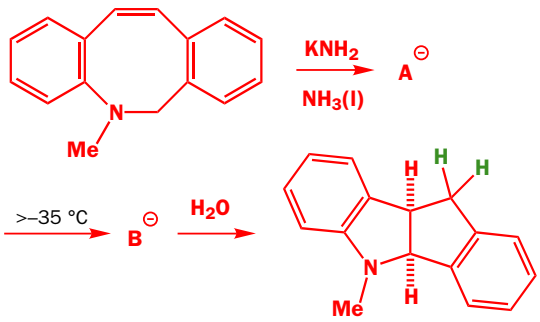
11. Problem 11 in Chapter 32 was concerned with two diastereoisomers of this compound that were formed in 'a chemical reaction'.



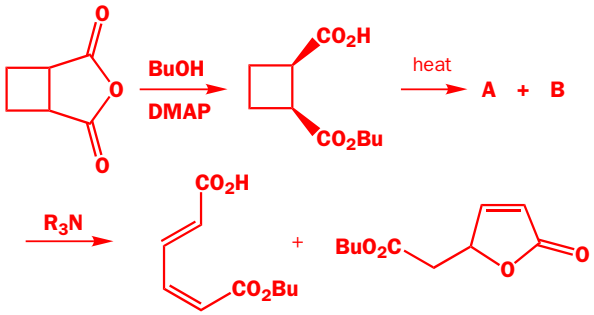
We can now let you into the secret of that 'chemical reaction'. A benzocyclobutene was heated with methyl acrylate to give a 1:1 mixture of the two isomers. What is the mechanism of the reaction and why is only one regioisomer but a mixture of stereoisomers formed? Isomer B is converted into isomer A on treatment with base. What is the stereochemistry of A and B?



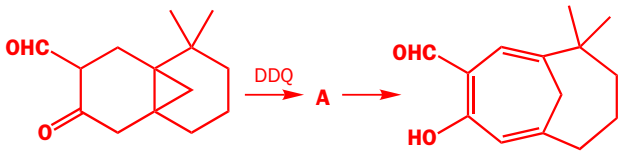
12. Treatment of this amine with base at low temperature gives an unstable anion that isomerizes to another anion above –35 °C. Aqueous work-up gives a bicyclic amine. What are the two anions? Explain the stereochemistry of the product. Revision of NMR. In the NMR spectrum of the product the two green hydrogens appear as an ABX system with J_{AB} 15.4 Hz. Comment.



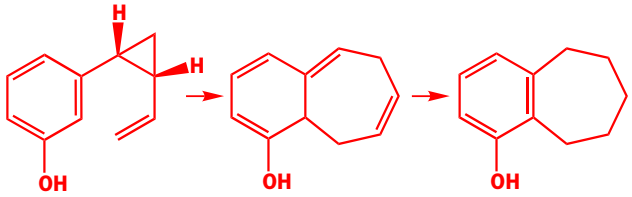
13. How would you make the starting material for these reactions? Treatment of the anhydride with butanol gives an ester that gives two inseparable compounds on heating. On treatment with an amine, an easily separable mixture of an acidic and a neutral compound is formed. What are the components of the first mixture and how are they formed?



14. Treatment of this keto-aldehyde (which exists largely as an enol) with the oxidizing agent DDQ (a quinone—see p. 000) gives an unstable compound that converts into the product shown. Explain the reactions and comment on the stereochemistry.



15. Explain the following observations. Heating this phenol brings it into rapid equilibrium with a bicyclic compound that does not spontaneously give the final aromatic product unless treated with acid.



Rearrangements

37

Connections

Building on:

- Nucleophilic substitution at saturated carbon ch17
- Conformational analysis ch18
- Elimination reactions ch19
- Electrophilic aromatic substitution ch22
- Controlling stereochemistry ch16, ch33, & ch34
- Sigmatropic rearrangements ch31

Arriving at:

- Participation: nucleophiles are more efficient if they are already part of the molecule
- Participation means acceleration and retention of stereochemistry and may mean rearrangement
- Participating groups can have lone pairs or π electrons
- Carbocations often rearrange by alkyl migration
- How to work out the mechanism of a rearrangement
- Ring expansion by rearrangement
- Controlling rearrangements
- Using rearrangements in synthesis
- Insertion of O, N, or C next to a ketone

Looking forward to:

- Fragmentations ch38
- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoelectronics ch42
- Main group chemistry ch46–ch47
- The chemistry of life ch49–ch51

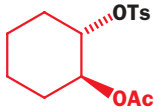
Neighbouring groups can accelerate substitution reactions

Compare the rates of the following substitution reactions. Each of these reactions is a substitution of the leaving group (OTs or Cl) by solvent, known as a **solvolysis**.

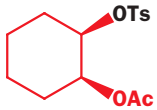
reacts with water 600 times faster than

reacts with CF_3CO_2H 3000 times faster than

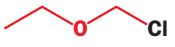
reacts with acetic acid 10^{11} times faster than



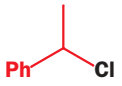
reacts with acetic acid 670 times faster than



Nearby groups can evidently increase the rate of substitution reactions significantly. Now, you may be thinking back to Chapter 17 and saying 'yes, yes, we know that'—when we were discussing the mechanisms of substitution reactions we pointed out that a cation-stabilizing group at the reaction centre makes S_N1 reactions very fast: for example—



reacts with nucleophiles 10^6 times as fast as



reacts with nucleophiles 10^5 times as fast as

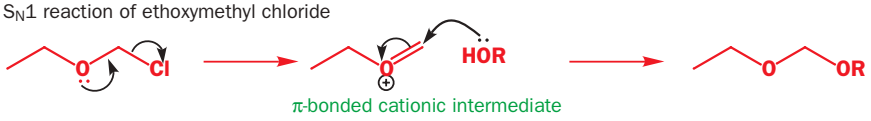
In the four examples above, though, it is not at the reaction centre itself that the functional groups change but at the carbon *next* to the reaction centre, and we call these groups **neighbouring groups**.

A solvolysis was defined in Chapter 17 as 'a reaction in which the solvent is also the nucleophile'.

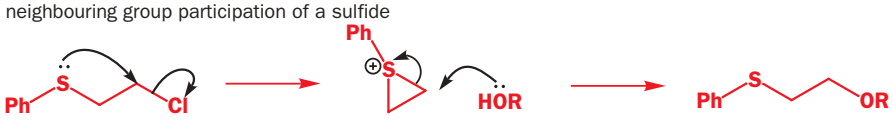
The mechanism by which they speed up the reactions is known as **neighbouring group participation**. Compare the reaction of this ether and this sulfide with an alcohol.

Neighbouring group participation is occasionally called **anchimeric assistance** (Greek *anchi* = neighbouring; *mer* = part).

S_N1 reaction of ethoxymethyl chloride



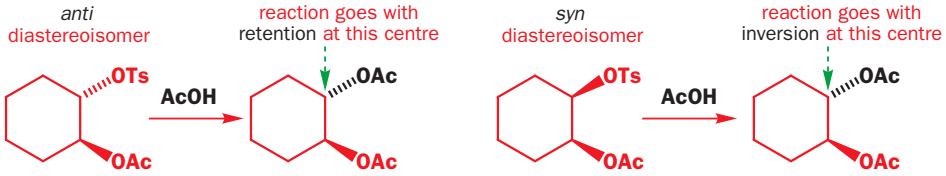
neighbouring group participation of a sulfide



In both cases, ionization of the starting material is assisted by the lone pair of an electron-rich functional group. The ether in the first example assists by forming a π bond, the sulfide assists by forming a three-membered ring, and a common feature of all mechanisms involving neighbouring group participation is the formation of a cyclic intermediate.

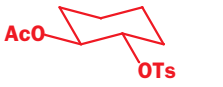
Stereochemistry can indicate neighbouring group participation

How do we know that neighbouring group participation is taking place? Well, the first bit of evidence is the *increase in rate*. The neighbouring groups will become involved only if they can increase the rate of the substitution reaction—otherwise the mechanism will just follow the ordinary S_N2 pathway. But more important information comes from reactions where stereochemistry is involved, and one of these is the last of the four examples above. Here it is again in more detail. Not only does the first of these reactions go faster than the second—its stereochemical course is different too.



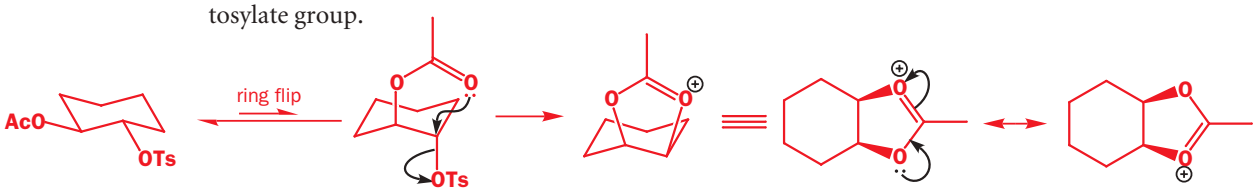
If you are unsure what we are talking about, go back and read Chapter 18 now!

Although one starting material has *syn* and the other *anti* stereochemistry, the products have the same (*anti*) stereochemistry: one substitution goes with retention and one goes with inversion. Again, neighbouring group participation is the reason. To explain this, we should first draw the six-membered rings in their real conformation. For the *anti* compound, both substituents can be equatorial.



both substituents equatorial

However, not much can happen in this conformation—but, if we allow the ring to flip, you can see immediately that the acetate substituent is ideally placed to participate in the departure of the tosylate group.



both substituents equatorial

both substituents axial

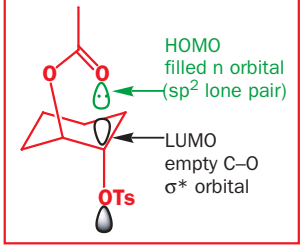
symmetrical intermediate

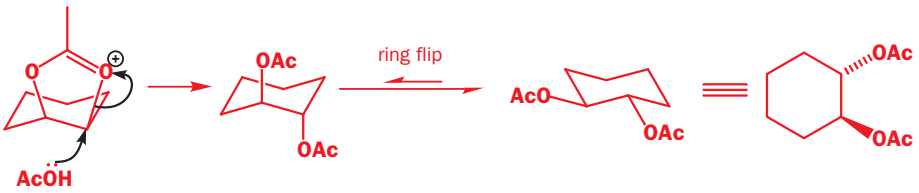
While the mechanism of this first step of the substitution reaction is S_N2 in appearance—a nucleophile (the acetate group) arrives just as a leaving group (the tosylate group) departs—it is also, of course, only unimolecular.

What results is an entirely symmetrical intermediate—the positive charge on one of the oxygens is, of course, delocalized over both of them. The intramolecular S_N2 reaction takes place with inversion, as required by the orbitals, so now the junction of the two rings is *cis*.

The next step is attack of acetic acid on the intermediate. This is another S_N2 reaction, which also proceeds with inversion and gives back a *trans* product.

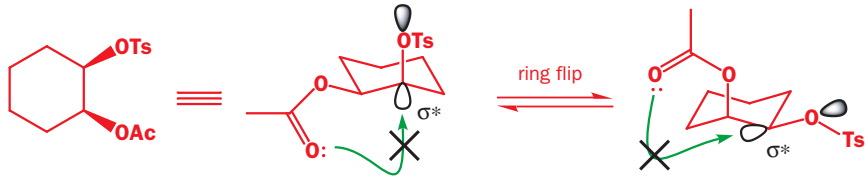
orbitals involved in participation



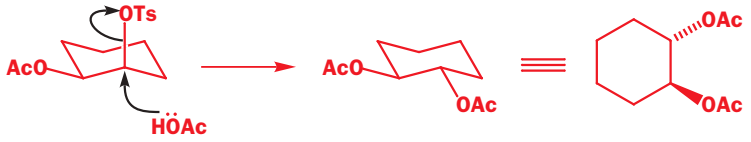


Overall, we have *retention* of stereochemistry. As you know, S_N2 reactions go with inversion, and S_N1 reactions with loss of stereochemical information—so this result is possible only if we have two sequential S_N2 reactions taking place—in other words neighbouring group participation.

Why, then, does the other diastereoisomer react with inversion of stereochemistry? Well, try drawing the mechanism for intramolecular displacement of the tosyl group. Whether you put the tosylate or the acetate group equatorial doesn't matter; there is no way in which the acetate oxygen's lone pair can reach the σ* orbital of the tosylate C–O bond.

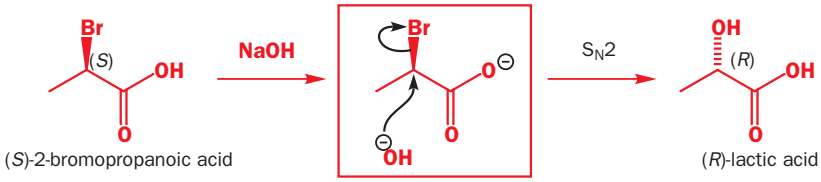


Neighbouring group participation is impossible, and substitution goes simply by intermolecular displacement of OTs by AcOH. Just one S_N2 step means overall inversion of configuration, and no participation means a slower reaction.



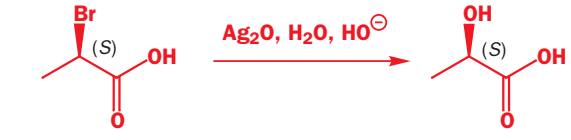
Retention of configuration is an indication of neighbouring group participation

Enantiomerically pure (*S*)-2-bromopropanoic acid reacts with concentrated sodium hydroxide to give (*R*)-lactic acid. The reaction goes with inversion and is a typical S_N2 reaction—and a good one too, since the reaction centre is adjacent to a carbonyl group (see Chapter 17).



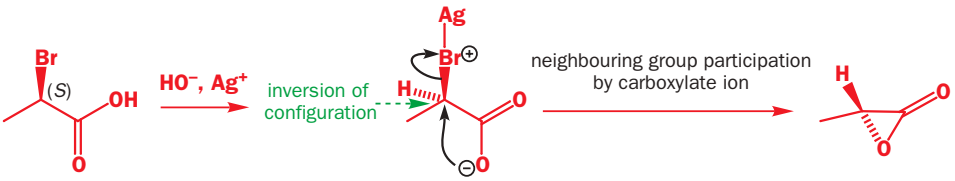
(*S*)-2-bromopropanoic acid (*R*)-lactic acid

If, on the other hand, the reaction is run using Ag_2O and a low concentration of sodium hydroxide, (*S*)-lactic acid is obtained—there is overall *retention* of stereochemistry.

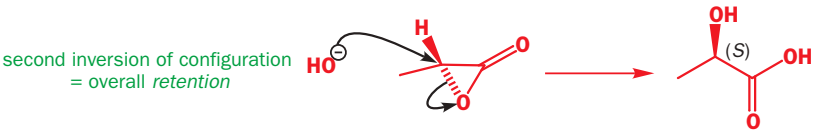


(*S*)-2-bromopropanoic acid (*S*)-lactic acid

Nucleophilic substitution reactions that go with retention of stereochemistry are rather rare and mostly go through two successive inversions with neighbouring group participation, like the example you saw in the last section. This time the neighbouring group is carboxylate: the silver oxide is important because it encourages the ionization of the starting material by acting as a halogen-selective Lewis acid.



A three-membered ring intermediate forms, which then gets opened by hydroxide in a second S_N2 step.



▶ Lactones (that is, cyclic esters) don't usually react with hydroxide by this mechanism, and you might expect this intermediate (which is a cyclic ester) to hydrolyse by attack of hydroxide at the C=O group. You might like to think about why this doesn't happen in this case.

● Retention suggests participation

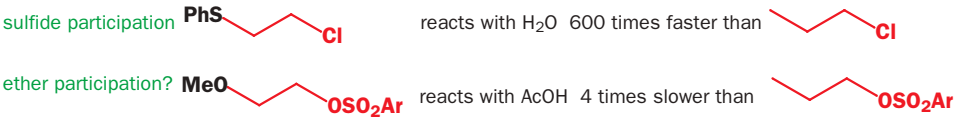
If you see a substitution reaction at a stereogenic saturated carbon atom that goes with retention of stereochemistry, look for neighbouring group participation!

Why does the carboxylate group participate only at low HO^- concentration and in the presence of Ag^+? You can think of the situation in these two reactions in terms of the factors that favour S_N1 and S_N2 reactions. In the first, we have conditions suited to an S_N2 reaction: a very good nucleophile (HO^-) and a good leaving group (Br^-). Improve the leaving group by adding Ag^+ (Ag^+ assists Br^-'s departure much as H^+ assists the departure of OH^- by allowing it to leave as H_2O), and worsen the nucleophile (H_2O instead of HO^-, of which there is now only a low concentration), and we have the sorts of conditions that *would* favour an S_N1 reaction. The trouble is, without neighbouring group participation, the cation here would be rather unstable—right next to a carbonyl group. The carboxylate saves the day by participating in the departure of the Br^- and forming the lactone. The key thing to remember is that a reaction always goes by the mechanism with the fastest rate.

● Neighbouring groups participate only if they speed up the reaction.

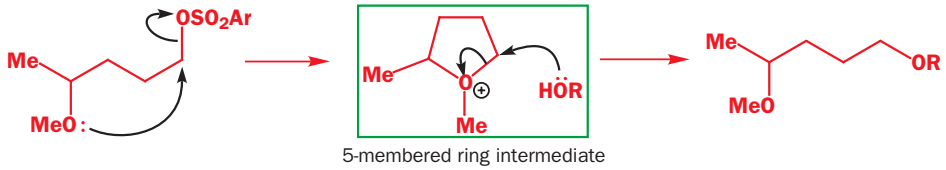
What sorts of groups can participate?

You've already met the most important ones—sulfides, esters, carboxylates. Ethers and amines (you will see some of these shortly) can also assist substitution reactions through neighbouring group participation. The important thing that they have in common is an electron-rich heteroatom with a lone pair that can be used to form the cyclic intermediate. Sulfides are rather better than ethers—this sulfide reacts with water much faster than *n*-PrCl but the ether reacts with acetic acid four times more *slowly* than *n*-$PrOSO_2Ar$.



The OMe group slows the reaction down just because it is electronegative more than it accelerates it by participation. A more distant OMe group can participate: this 4-MeO alkyl sulfonate reacts with alcohols 4000 times faster than the *n*-Bu sulfonate.

Again neighbouring group participation is involved, but this time through a five- rather than a three-membered ring. Participation is most commonly through three- and five-membered rings, less often six-membered ones, and very rarely four- or more than seven-membered ones.

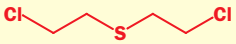


5-membered ring intermediate

▶ Why these ring sizes? Well, the underlying reasons are the same as those we discussed in Chapter 13 when we talked about the kinetics (rates) of formation and thermodynamics (stability) of different ring sizes: three- and five-membered rings form particularly rapidly in any reaction. See also Chapter 42.

Mustard gas

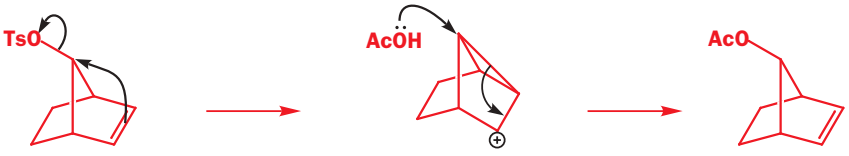
Participation of sulfides through three-membered rings was used to gruesome effect in the development of mustard gas during the Second World War. Mustard gas itself owes its toxicity to the neighbouring group participation of sulfur, which accelerates its alkylation reactions.



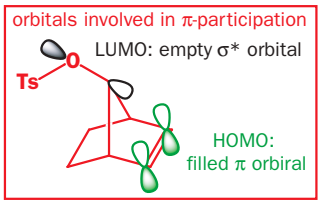
mustard gas

Not all participating groups have lone pairs

Another of the four examples we started with shows that even the π electrons of a C=C double bond can participate. Retention of stereochemistry in the product (the starting tosylate and product acetate are both *anti* to the double bond) and the extremely fast reaction (10^{11} times that of the saturated analogue) are tell-tale signs of neighbouring group participation.



just one way of representing the intermediate cation

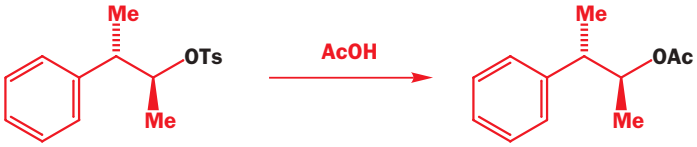


What is the structure of the intermediate?

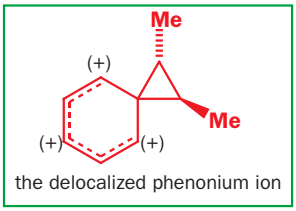
During the 1950s and 1960s, this sort of question provoked a prolonged and acrimonious debate, which we have no intention of stirring up, and all we will do is point out that the intermediate in this reaction is not fully represented by the structure we have here: it is symmetrical and could be represented by two structures with three-membered rings or by a delocalized structure in which two electrons are shared between three atoms. The difference need not concern us.

Aryl participation is more common than simple alkene participation

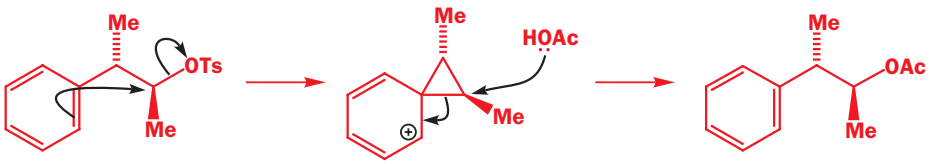
Finally, an example with a neighbouring phenyl group. Participation is hinted at by the retention of relative stereochemistry.



Again, π electrons are involved, but the reaction is now electrophilic aromatic substitution (Chapter 22) rather like an intramolecular Friedel–Crafts alkylation with a delocalized intermediate often termed a **phenonium ion**.

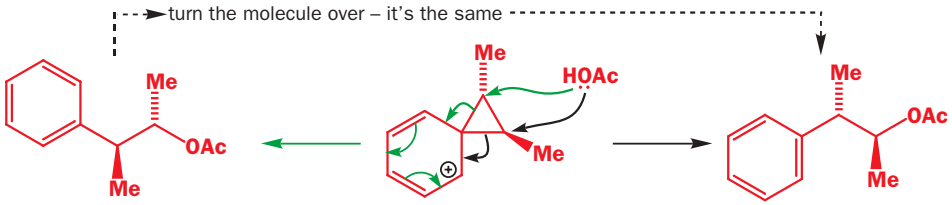


the delocalized phenonium ion

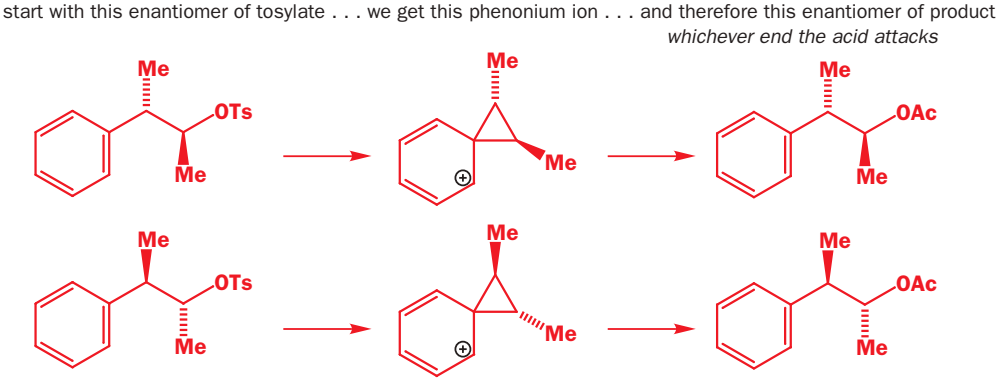


More stereochemical consequences of neighbouring group participation

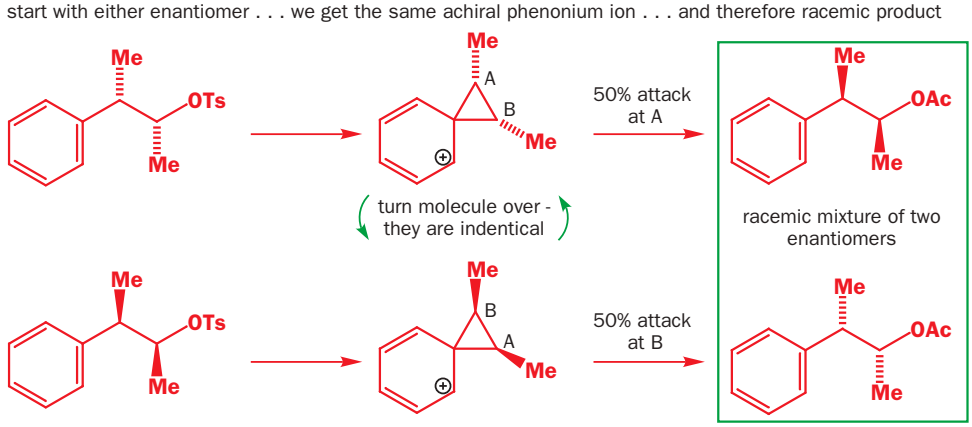
The phenonium ion is symmetrical. The acetic acid can attack either atom in the three-membered ring to give the same product.



The phenonium ion is nonetheless still chiral, since it has an axis (and not a plane or centre) of symmetry, so if we use an enantiomerically pure starting material we get an enantiomerically pure product.



Not so with the other diastereoisomer of this compound! Now, the phenonium ion is symmetrical with a plane of symmetry—it is therefore achiral, and the same whichever enantiomer we start from. Attack on each end of the phenonium ion gives a different enantiomer, so whichever enantiomer of starting material we use we get the same racemic mixture of products. You can compare this reaction with the loss of stereochemical information that occurs during an S_N1 reaction of enantiomerically pure compounds. Both reactions pass through an achiral intermediate.

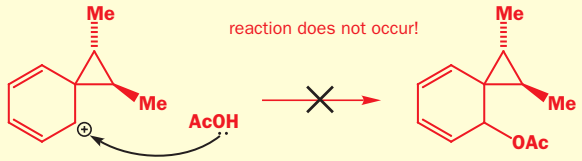


There is a subtlety here that you should not overlook and that makes this study, which was carried out by Cram in 1949, exceedingly elegant. Both of these reactions are stereospecific: the *relative* stereochemistry of the products depends on the *relative* stereochemistry of the starting materials. Yet, while the absolute stereochemistry of the starting materials is retained in one case (we get a single enantiomer of a single diastereoisomer), it is lost in the other (we get a racemic mixture of both enantiomers of a single diastereoisomer). These are important distinctions, and if you are in any doubt about them, re-read Chapters 16 and 34. Donald Cram (1919–) of UCLA was awarded the Nobel prize in 1987 jointly with Jean-Marie Lehn (1939–) of Strasbourg and Paris and Charles Pedersen (a Norwegian born in Korea in 1904) of DuPont for 'their development and use of molecules with structure-specific interactions of high selectivity'.

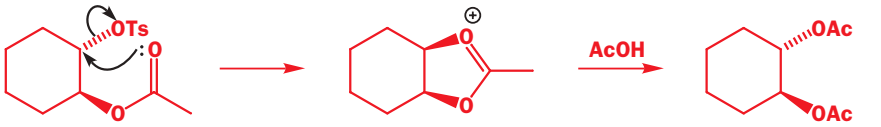
Direct cation trapping is not observed

You may be wondering why acetic acid does not intercept the phenonium ion directly at one of the positively charged carbon atoms.

The problem is that the product would not then be aromatic and would contain a strained three-membered ring. The same sort of intermediates occur in electrophilic aromatic substitution (Chapter 22) and addition to the cation does not occur there either. The reaction that does occur here is a fragmentation: a C–C bond is broken. In the next chapter we will look at fragmentations in more detail.

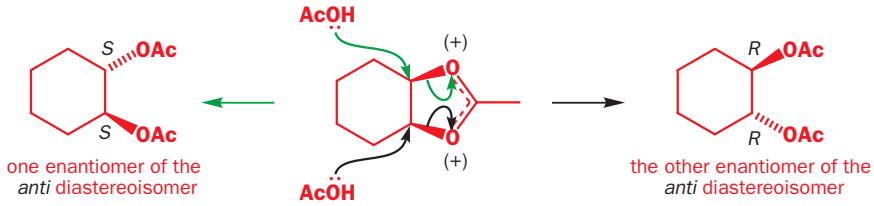


The same loss of absolute stereochemical information (but retention of relative stereochemistry) occurs in another reaction that you met at the start of this chapter. We then emphasized two features: the acceleration in rate and the retention of stereochemistry.



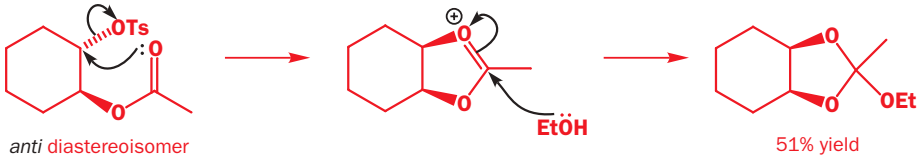
anti diastereoisomer — *anti* diastereoisomer

The intermediate oxonium ion is delocalized and achiral. If a single enantiomer of the starting material is used, racemic product is formed through this achiral intermediate. Attack at one carbon atom gives one enantiomer; attack at the other gives the mirror image.



one enantiomer of the *anti* diastereoisomer — the other enantiomer of the *anti* diastereoisomer

In this case the neighbouring group can be caught in the act—when the rearrangement is carried out in ethanol, the intermediate is trapped by attack at the central carbon atom. It is as though someone switched the light on while the acetate's fingers were in the biscuit tin (the cookie jar).



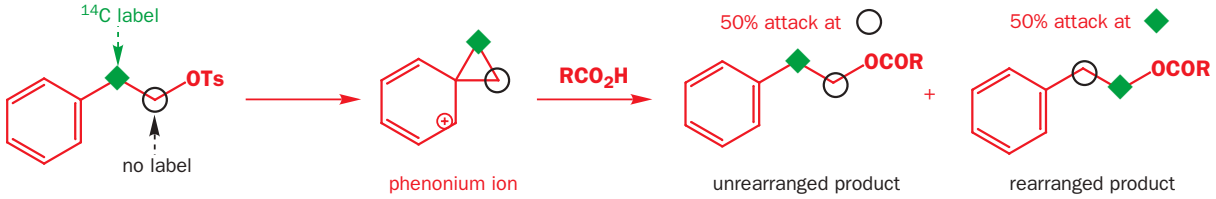
anti diastereoisomer — 51% yield

The product is an orthoester and is achiral too. This chemistry should remind you of the formation of acetals as described in Chapter 14.

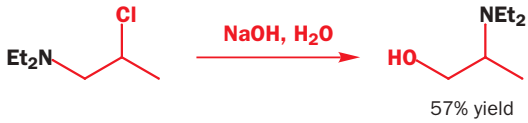
Rearrangements occur when a participating group ends up bonded to a different atom

Because the intermediates in these examples are symmetrical, 50% of the time one substituent ends up moving from one carbon atom to another during the reaction. This is clearer in the following example: the starting material is prepared such that the carbon atom carrying the phenyl group is an unusual isotope—carbon-14. This doesn't affect the chemistry, but means that the two carbon atoms are easily distinguishable. Reacting the compound with trifluoroacetic acid scrambles the label between the two positions: the intermediate is symmetrical and, in the 50% of reactions with the nucleophile that take place at the labelled carbon atom, the phenyl ends up migrating to the unlabelled carbon atom in a rearrangement reaction.

▶ Labelling an atom with an unusual isotope is a standard way to probe the details of a reaction. Radioactive ^{3}H (tritium) or ^{14}C used to be used but, with the advent of high-field NMR, non-radioactive ^{2}H (deuterium) and ^{13}C have become more popular. These methods are treated more thoroughly in Chapter 41.

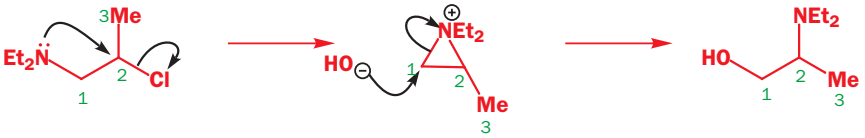


Now, consider this substitution reaction in which OH replaces Cl but with a change in the molecular structure. The substitution goes with complete rearrangement—the amine ends up attached to a different carbon atom.

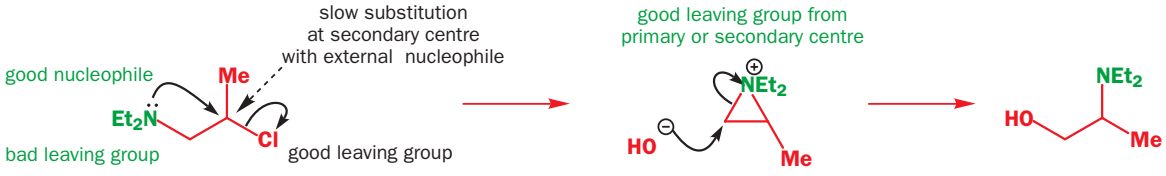


We can easily see why if we look at the mechanism. The reaction starts off looking like a neighbouring group participation of the sort you are now familiar with (the carbon atoms are numbered for identification).

The intermediate is an aziridinium ion (**aziridines** are three-membered rings containing nitrogen—the nitrogen analogues of epoxides). The hydroxide ion chooses to attack only the less hindered terminal carbon 1, and a rearrangement results—the amine has migrated from carbon 1 to carbon 2.



We should just pause here for a moment to consider why this rearrangement works. We start with a secondary alkyl chloride that contains a very bad leaving group (Et_2N) and a good one (Cl^-)—but the good one is hard for HO^- to displace because it is at a secondary centre (remember—secondary alkyl halides are slow to react by S_N1 or S_N2). But the NEt_2 can participate to make an aziridinium intermediate—now there is a good leaving group ($RNEt_2$ without the negative charge) at the primary as well as the secondary carbon, so HO^- does a fast S_N2 reaction at the primary carbon.



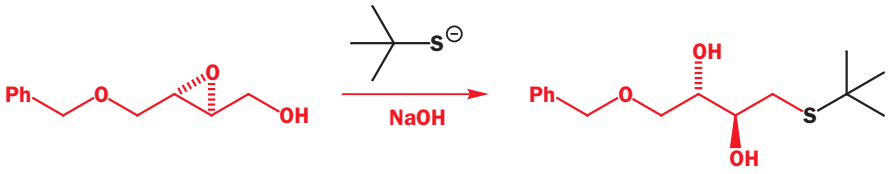
fast S_N2 at primary centre with external nucleophile

Another way to look at this reaction is to see that the good internal nucleophile Et_2N will compete successfully for the electrophile with the external nucleophile HO^-. Intramolecular reactions are usually faster than bimolecular reactions.

> ● **Intramolecular reactions, including participation, that give three-, five-, or six-membered rings are usually faster than intermolecular reactions.**

The Payne rearrangement

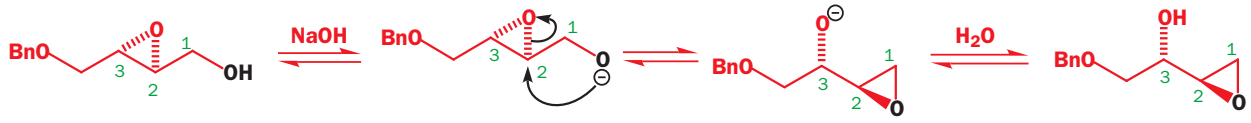
The reaction of an epoxy alcohol in base does not always give the expected product.



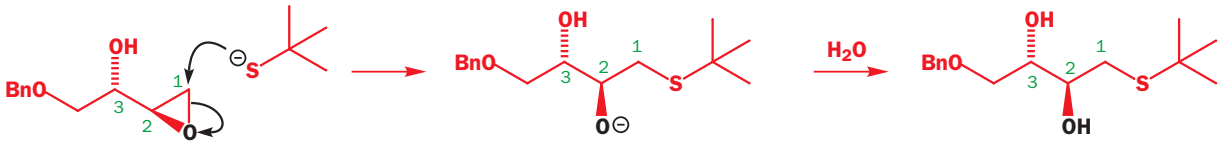
85% yield

The thiolate nucleophile has not opened the epoxide directly, but instead *appears* to have displaced HO^-—a very bad leaving group. Almost no nucleophile will displace OH^-, so we need an alternative explanation. This comes in the form of another rearrangement, this time involving oxygen, but otherwise rather similar to the ones you have just met. Again, our epoxide, though reactive as an electrophile, suffers from being secondary at both electrophilic centres. *t*-BuS^- is a bulky nucleophile, so direct attack on the epoxide is slow. Instead, under the basic conditions of the reaction, the neighbouring alkoxide group attacks intramolecularly to make a new, rearranged epoxy alcohol. This rearrangement is called the **Payne rearrangement**.

the Payne rearrangement

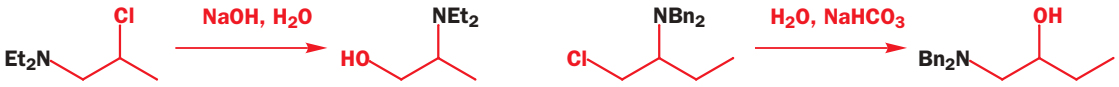


Now we do have a reactive, primary electrophilic site, which undergoes an S_N2 reaction with the *t*-BuS^- under the conditions of the rearrangement. Notice how the black OH, which started on the carbon labelled 1, has ended up on carbon 2.

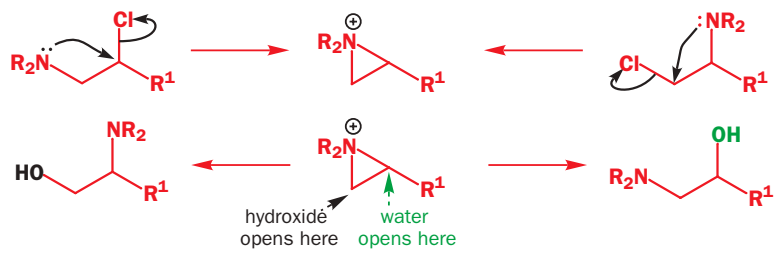


The direction of rearrangement can depend on the nucleophile

Compare these reactions: you saw the first on p. 000 but the second is new.



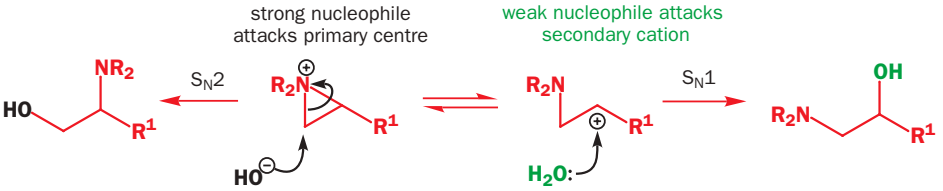
In the first reaction, the amine migrates from the primary to the secondary position; in the other from secondary to primary. Both go through very similar aziridinium intermediates, so the difference must be due to the regioselectivity with which this aziridinium opens in each case.



The only important difference is the nucleophile used in the reaction. Hydroxide opens the aziridinium at the less hindered end; water opens the aziridinium ion at the more hindered (more substituted) end. Why?

▶ When a group migrates from a primary to a secondary carbon, we say the rearrangement has a primary **migration origin** and a secondary **migration terminus**. The migrating group moves from the migration origin to the migration terminus.

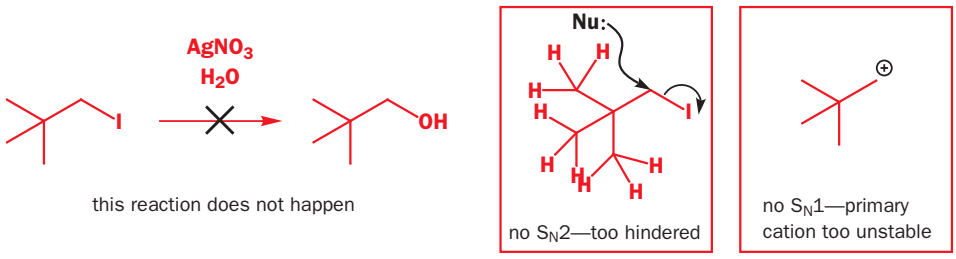
We can think of the aziridinium ion as a compound containing two alternative leaving groups—one from a primary centre and one from a secondary one. Primary centres can take part in fast S_N2 reactions, but cannot undergo S_N1. Secondary centres can undergo either S_N1 or S_N2 reactions, but, in general, do neither very well. Now, the rate of an S_N2 reaction depends on the nucleophile, so a good nucleophile (like HO^-) can do fast S_N2 reactions, while a bad one (like H_2O) cannot. The fastest reaction HO^- can do then is S_N2 at the primary centre (remember: you see only the reaction that goes by the fastest mechanism). Water, on the other hand, takes part only reluctantly in substitution reactions—but this does not matter if they are S_N1 reactions because their rates are independent of nucleophile. H_2O waits until the leaving group has left of its own accord, to give a cation, which rapidly grabs *any* nucleophile—water will do just as well as HO^-. This can happen *only* at the secondary centre because the primary cation is too unstable to form.



All the rearrangements you have met so far occurred during substitution reactions. All happened because reaction *with* rearrangement is faster than reaction *without* rearrangement—in other words, rearrangement occurs because of a kinetic preference for the rearrangement pathway. You could see these reactions as 'special case' examples of neighbouring group participation—in both participation and rearrangement, the neighbouring group speeds up the reaction, but in rearrangement reactions the neighbouring group gets rather more than it bargained for, and ends up elsewhere in the molecule. Both proceed through a cyclic transition state or intermediate, and it is simply the way in which that transition state or intermediate collapses that determines whether rearrangement occurs.

Rearrangement can involve migration of alkyl groups

You have seen reactions in which the lone pairs of N, O, and S atoms participate, and reactions in which the π orbitals of alkenes and aromatic groups participate, and participation can lead to rearrangement for any of these groups. Alkyl groups too may rearrange. This example is a nucleophilic substitution under conditions (Ag^+, H_2O) designed to encourage S_N1 reactions (excellent leaving group, poor nucleophile). First of all, this is what does not happen (and indeed without Ag^+ *nothing happens at all*).



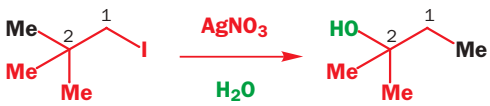
▶ The *t*-butylmethyl group is also called 'neopentyl'.

t-butylmethyl iodide
2,2-dimethyliodopropane
- neopentyl iodide

the neopentyl group

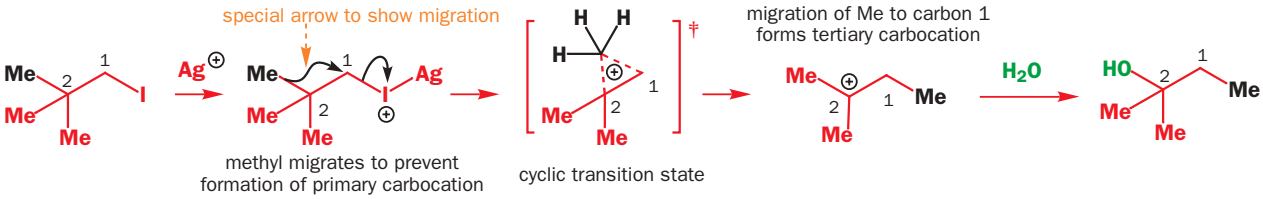
Compounds like this, with a *t*-butyl group next to the electrophilic centre, are notoriously slow to undergo substitution reactions. They can't do S_N2, they are too hindered; they can't do S_N1, the cation you would get is primary.

In fact, a rearrangement occurs. One of the methyl groups moves ('migrates') from carbon 2 to carbon 1, the new OH group taking its place at carbon 2.



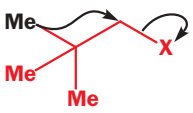
How has this happened? Well, firstly, our principle (p. 000) tells us that it has happened because S_N1 and S_N2 are both so slow that this new rearrangement mechanism is faster than either. Adding Ag^+ makes I^- desperate to leave, but unassisted this would mean the formation of a primary

carbocation. The molecule does the only thing it can to stop this happening, and uses the electrons in an adjacent C–C bond to assist the departure of I^-.

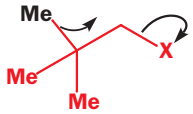


Having participated, the methyl group continues to migrate to carbon 1 because by doing so it allows the formation of a stable tertiary carbocation, which then captures water in a step reminiscent of the second half of an S_N1 reaction.

In the migration step we used a slightly unusually curved curly arrow to represent the movement of a group (Me) along a bond taking its bonding electrons with it. We shall use this type of arrow when a group migrates from one atom to another during a rearrangement.



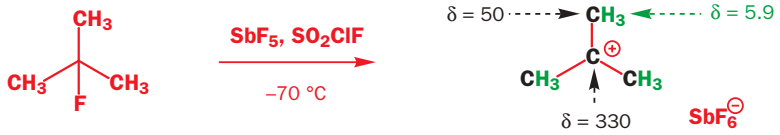
Often, you will see this rearrangement represented in a different way. Both are correct, but we feel that the first is more intuitively descriptive.



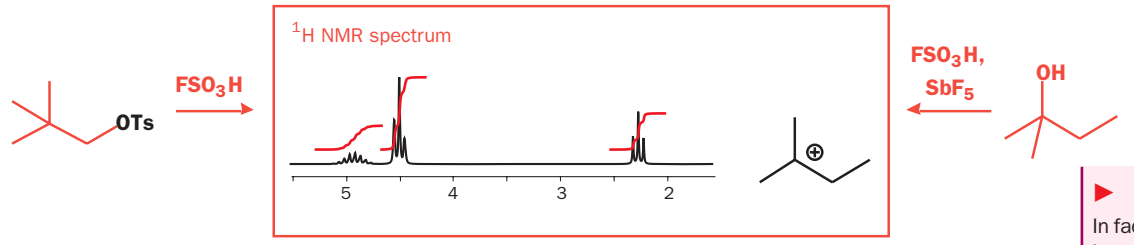
▶ Some of the cyclic species you have seen so far (aziridinium ions, epoxides) are intermediates; this cyclic species is probably only a transition state.

Carbocations readily rearrange

In Chapter 17 we showed you that it is possible to run the NMR spectra of carbocations by using a polar but nonnucleophilic solvent such as liquid SO_2 or SOClF. Treating an alkyl halide RX with the powerful Lewis acid SbF_5 under these conditions gives a solution of carbocation: the carbocation reacts neither with solvent nor the SbF_5X^- counterion because neither is nucleophilic. We know, for example, that the chemical shifts in both the ^{13}C and ^1H NMR spectra of the *t*-butyl cation are very large, particularly the ^{13}C shift at the positively charged centre.

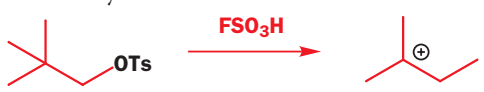


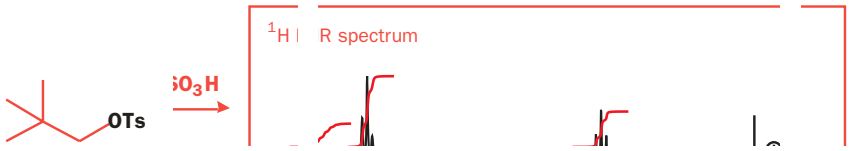
NMR can be used to follow the course of rearrangement reactions involving carbocations too. We can illustrate this with an experiment that tries to make the neopentyl cation by the substitution reaction you have just seen. This time the starting material and solvent are slightly different, but the outcome is nonetheless most revealing. Dissolving neopentyl tosylate in fluorosulfonic acid (a strong, nonnucleophilic acid) at –77 °C gives a 77% yield of a cation whose spectrum is shown below. Assigning the peaks is not hard once you know that the same spectrum is obtained when 2,2-dimethyl-2-butanol is dissolved in fluorosulfonic acid with SbF_5 added.



▶ In fact, all *seven* possible isomers of pentyl alcohol ($C_5H_{11}OH$) give this same spectrum under these conditions at temperatures greater than –30 °C.

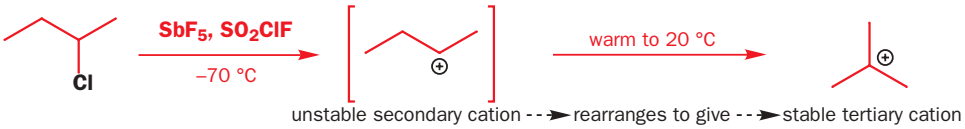
Clearly, both spectra are of the tertiary 2-methylbutyl cation and the neopentyl cation never saw the light of day. The reaction is the same rearrangement that you saw in the substitution reaction of neopentyl iodide, but here the rate of rearrangement can be measured and it is extremely fast. Neopentyl tosylate reacts to form a cation under these conditions about 10^4 times as fast as ethyl tosylate, even though both tosylates are primary. This massive rate difference shows that if migration of an alkyl group can allow rearrangement to a more stable carbocation, it will happen, and happen rapidly.





▶ The distinction here is quite subtle and need not detain us long. We know that a secondary cation is formed in this case because we can see it by NMR; it subsequently rearranges to a tertiary cation. As we can never see primary cations, we don't know that they are ever formed, and the most reasonable explanation for rearrangements of the type you saw on p. 000 is that migration of the alkyl group begins *before* the leaving group is fully gone. This has been proven in a few cases, but we will from now on not distinguish between the two alternatives.

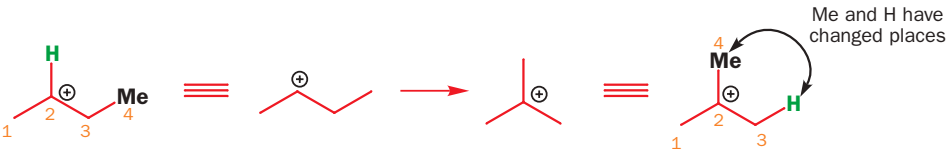
Primary cations can never be observed by NMR—they are too unstable. But secondary cations can, provided the temperature is kept low enough. *sec*-Butyl chloride in SO_2ClF at –78 °C gives a stable, observable cation. But, as the cation is warmed up, it rearranges to the *t*-butyl cation. Now this rearrangement truly is a carbocation rearrangement: the starting material is an observable carbocation, and so is the product, and we should just look at the mechanism in a little more detail.



With rearrangements like this it is best to number the C atoms so you can see clearly what moves where. If we do this, we see that the methyl group we have labelled 4 and the H on C3 have changed places. (Note that C3 starts off as a CH_2 group and ends up as CH_3.)

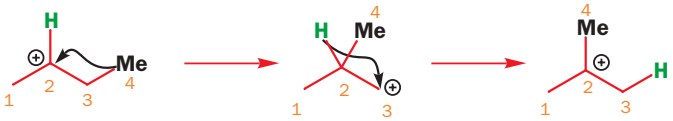
● Top tip for rearrangements

Number the carbon atoms in starting material and product before you try to work out the mechanism.

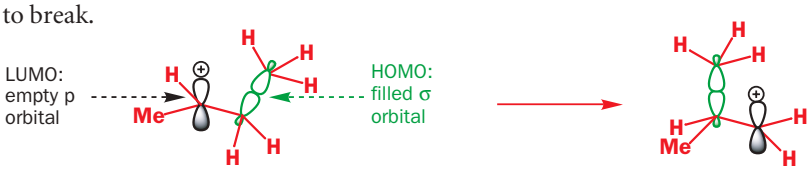


▶ You will see why Me has to migrate first if you try drawing the mechanism out with H migrating first instead.

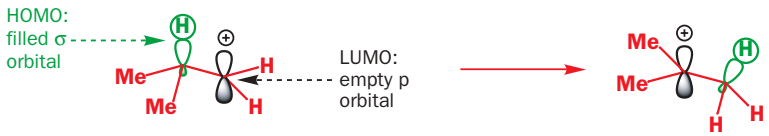
Using the sort of arrows we introduced on p. 000, we can draw a mechanism for this in which first the Me migrates, and then the hydride. We say **hydride** migration rather than *hydrogen* (or *proton*) because the H atom migrates *with* its pair of electrons.



As these rearrangements are a new type of reaction, we should just spend a moment looking at the molecular orbitals that are involved. For the first step, migration of the methyl group, the LUMO must clearly be the empty p orbital of the cation, and the HOMO is the C–C σ bond, which is about to break.



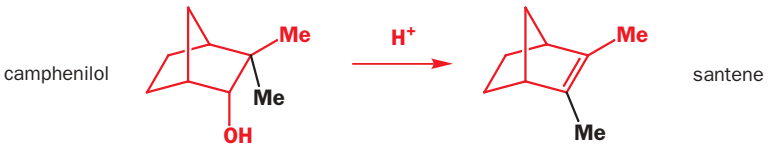
The methyl group migrates smoothly from one orbital to another—there are bonding interactions all the way. The next step, migration of H, is just the same—except that the HOMO is now a C–H σ bond. The methyl migration is unfavourable as it transforms a secondary cation into an unstable primary cation but the hydride migration puts that right as it gives a stable tertiary cation. The whole reaction is under thermodynamic control.



Wagner–Meerwein rearrangements

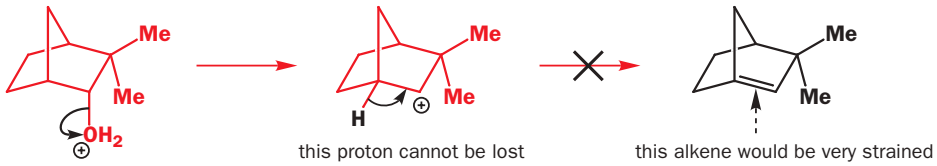
Carbocation rearrangements involving migration of H or alkyl groups don't just happen in NMR machines. They happen during normal reactions too. For example, acid-catalysed dehydration of the

natural product camphenilol gives the alkene santene (a key component of the fragrance of sandalwood oil) in a reaction involving migration of a methyl group.

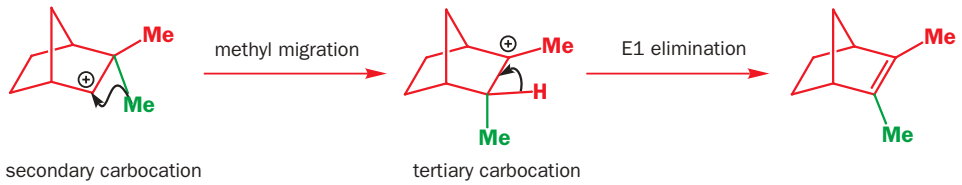


The mechanism shows why the rearrangement happens: the first-formed cation cannot eliminate H^+ in an E1 reaction because loss of the only available proton would give a very strained alkene (make a model and see!).

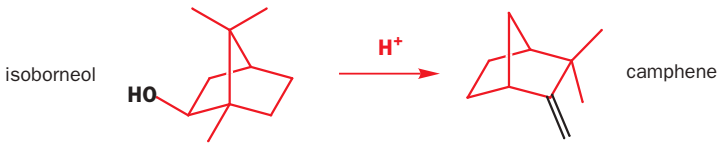
■ Bredt's rule is discussed in Chapter 19 and essentially forbids bridgehead alkenes.



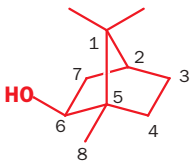
However, migration of a methyl group both stabilizes the cation—it becomes tertiary instead of secondary—and allows E1 elimination of H^+ to take place to give a stable alkene.



The migration of an alkyl group to a cationic centre is known as a **Wagner–Meerwein rearrangement** or **Wagner–Meerwein shift**, and this migration is, of course, a synthetic manifestation of the rearrangement we have just been looking at in NMR spectra. Wagner–Meerwein shifts have been studied extensively in the class of natural products to which both of these natural products belong—terpenes—and we will come back to them in Chapter 51 (natural products). For the moment, though, we will just illustrate this type of reaction with one more example—another acid-catalysed dehydration, of isoborneol to give camphene.



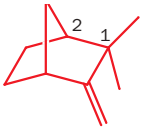
This one *seems* much more complicated—but, in fact, only one alkyl migration is involved. To see what has happened, remember the 'top tip'—number the carbons. You can number the starting material any way you choose—we've started with the *gem*-dimethyl group because it will be easy to spot in the product. The numbers just follow round the ring, with C8 being the methyl group attached to C5.



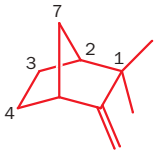
Now for the hard bit—we need to work out which carbon in the starting material becomes which carbon in the product. The best thing is just have a go—mistakes will soon become obvious, and you can always try again.

- Use the substituents to help you—some will have changed, but most will be the same or similar—for example, C1 is still easy to spot as the carbon carrying the *gem*-dimethyl group

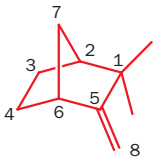
- Use connectivity to help you—again, a C–C bond or two may have broken or formed, but most of the C–C bonds in the starting material will be there in the product. C1 and C2 will probably still be next door to one another—C2 was a bridgehead carbon in the starting material, and there is a bridgehead C attached to C1 in the product; assume that's C2



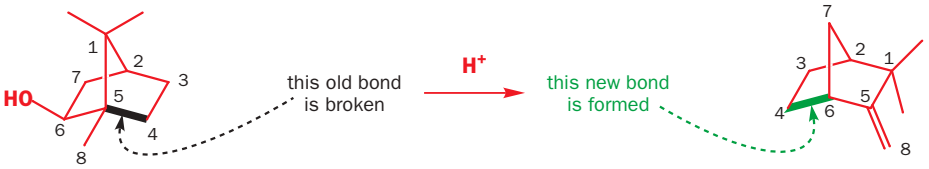
- C3 and C4 were unsubstituted carbons in the starting material, and are identifiable in the product too. The other easily spotted atom is C7—an unsubstituted C attached to C2



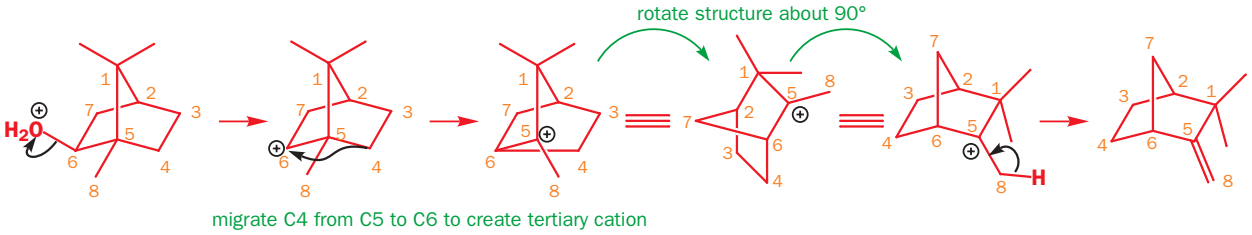
- C5, C6, and C8 are harder. We can assume that C8 is the $=CH_2$ carbon—it was a methyl group but perhaps has become involved in an elimination. C5 was attached to C1, C4, C6, and C8: one of the remaining carbons is attached to C1 and C8, so that seems more likely to be C5, which leaves C6 as the bridgehead, attached as before to C7 and C5



Now we have the whole picture and we can assess what has happened in the reaction—which old bonds have been broken and which new bonds have been formed.



Numbering the atoms this way identifies the likely point of rearrangement—the only bond broken is between C4 and C5. Instead we have a new one between C5 and C6: C4 appears to have migrated from C5 to C6. Now for the mechanism. The first step will, of course, be loss of water to generate a secondary cation at C6. The cation is next to a quaternary centre, and migration of any of three bonds could generate a more stable tertiary carbocation. But we know that the new bond in the product is between C4 and C6, so let's migrate carbon 4. Manipulating the diagrams a bit turns up a structure remarkably similar to our product, and all we need to do is lose a proton from C8.



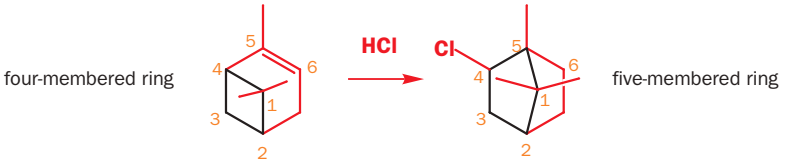
If you are observant, you may ask why the alkyl group migrated in this example and not the methyl group, or the other alkyl group—all three possibilities give similar tertiary carbocations. The reason involves the *alignment* of the orbitals involved, which we will discuss at the end of the chapter.

Although migration of an alkyl group that forms part of a ring leads to much more significant changes in structure than simple migration of a methyl group, the reason why it happens is still just the same.

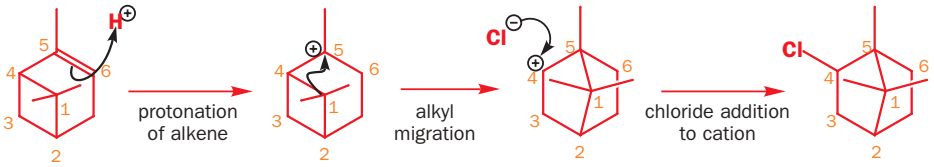
Alkyl migrations occur in order to make a carbocation more stable.

Ring expansion means rearrangement

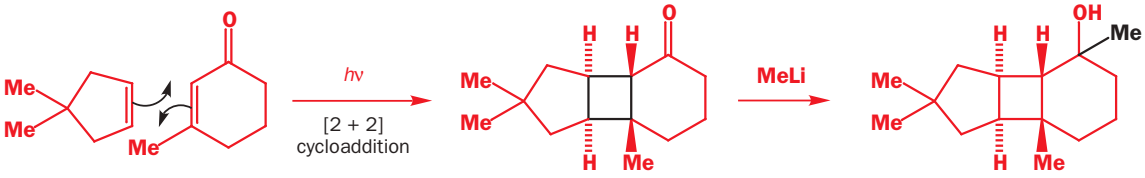
'More stable' usually means 'more substituted', but cations can also be made *more stable* if they become *less strained*. So, for example, four-membered rings adjacent to cations readily rearrange to five-membered rings in order to relieve ring strain.



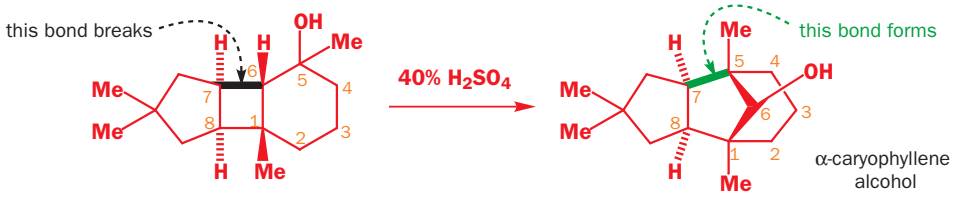
This time the cation is formed by protonation of an alkene, not departure of a leaving group, but writing a mechanism should now be a straightforward matter to you.



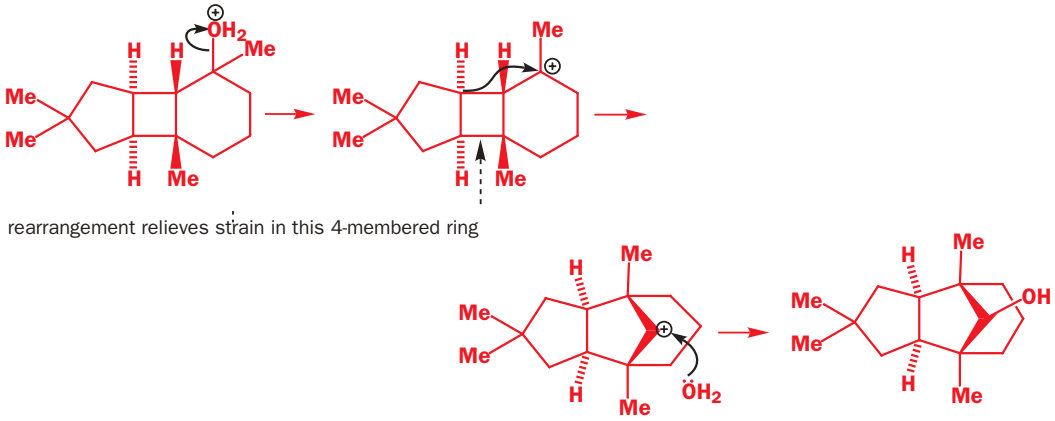
Though the rearrangement step transforms a stable tertiary cation into a less stable secondary cation, relief of strain in expansion from a four- to a five-membered ring makes the alkyl migration favourable. In 1964, E.J. Corey published a synthesis of the natural product α-caryophyllene alcohol that made use of a similar ring expansion. Notice the photochemical [2+2] cycloaddition (Chapter 35) in the synthesis of the starting material.



Rearrangement of this tertiary alcohol in acid gives the target natural product. The four-membered ring has certainly disappeared but it may not be obvious at first what has taken its place.



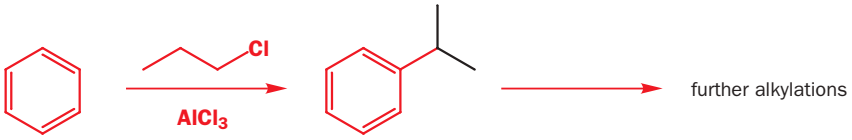
As usual, numbering the atoms makes clear what has happened: carbon 7 has migrated from carbon 6 to carbon 5. Loss of water gives a tertiary carbocation that undergoes rearrangement to a secondary carbocation with expansion of a four- to a five-membered ring.



▶ Most compounds are *kinetically* stable precisely because spontaneous rearrangements to more *thermodynamically* stable compounds do not occur—the kinetic barrier to rearrangement is too high. You did meet a few exceptions in the last chapter—cyclopentadienes, for example, undergo rapid [1,5]-sigmatropic shifts of hydrogen, and are unstable with respect to the position of the double bonds. Carbocations are probably the most important class of species that *habitually* undergo rearrangement reactions, even at low temperature.

Carbocation rearrangements: blessing or curse?

Well, that depends. You have now seen a few useful carbocation rearrangements that give single products in high yield. But you have also met at least one reaction that *cannot* be done because of carbocation rearrangements: Friedel–Crafts alkylation using primary alkyl halides.



The Friedel–Crafts alkylation illustrates the problems of trying to use carbocation rearrangements to make single products in high yield. We can give three guidelines to spotting this type of reaction.

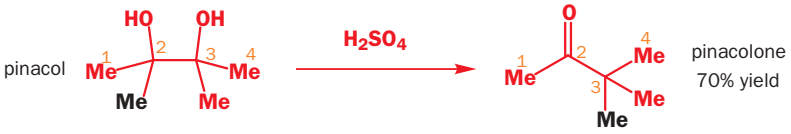
1. The rearrangement must be fast so that other reactions do not compete
2. The product cation must be sufficiently more stable than the starting one so that the rearrangement happens in high yield
3. Subsequent trapping of the product cation must be reliable: cations are high-energy intermediates, and are therefore unselective about how they react

A reaction is no good if the cation reacts in more than one way—it may react with a nucleophile, eliminate, or undergo further rearrangement—but it must do only one of these! For the rest of the chapter, we will address only reactions that, unlike this Friedel–Crafts reaction, follow these guidelines. The reactions we will talk about all happen in good yield.

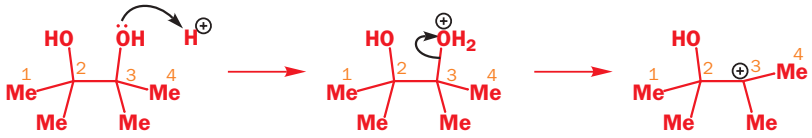
The pinacol rearrangement

Pinacol, the trivial name for the starting material, which is made from acetone by a reaction you will meet in Chapter 39, gives its name to this class of rearrangements, and to the product, 'pinacolone'.

When the 1,2-diol 'pinacol' is treated with acid, a rearrangement takes place.

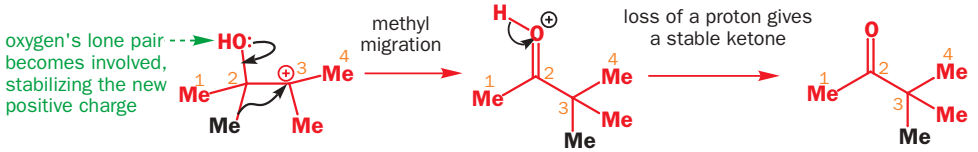


Whenever you see a rearrangement, you should now think 'carbocation'. Here, protonation of one of the hydroxyl groups allows it to leave as water, giving the carbocation.



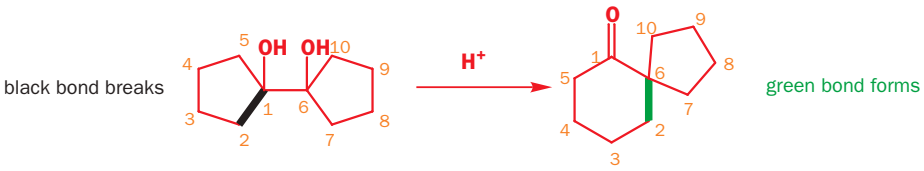
You now know that carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange? Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom. We pointed out early in the chapter that oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away. By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.

Unlike sulfur, which stabilizes a charge 2 atoms away better than it stabilizes a charge on an adjacent atom.

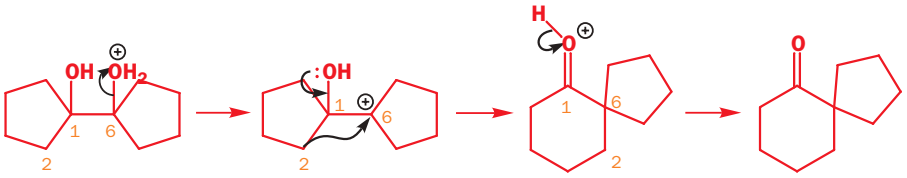


You can view the pinacol as a rearrangement with a 'push' and a 'pull'. The carbocation left by the departure of water 'pulls' the migrating group across at the same time as the oxygen's lone pair 'pushes' it. A particularly valuable type of pinacol rearrangement forms spirocyclic ring systems. You may find this one harder to follow, though the mechanism is identical with that of the last example. Our 'top tip' of numbering the atoms should help you to see what has happened: atom 2 has migrated from atom 1 to atom 6.

Spirocycles are pairs of rings joined at a single carbon atom (Chapter 33).



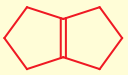
When drawing the mechanism it doesn't matter which hydroxyl group you protonate or which adjacent C–C bond migrates—they are all the same. One five-membered ring expands to a six-membered ring but the reason this reaction happens is the formation of a carbonyl group, as in all pinacol rearrangements.



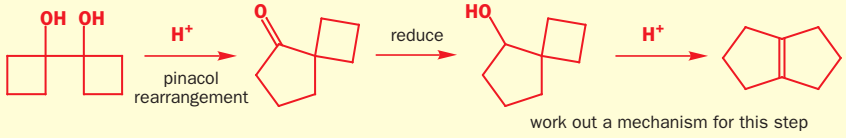
▶ Of course, it doesn't matter how you number the atoms, but the numbering must be consistent. Usually, your initial impression of a greatly changed molecule will come down to just one or two atoms changing their substitution pattern, and numbering will help you to work out which ones they are.

The pinacol reaction in synthesis

A nice synthesis of the bicyclic alkene on the right starts with a pinacol reaction.

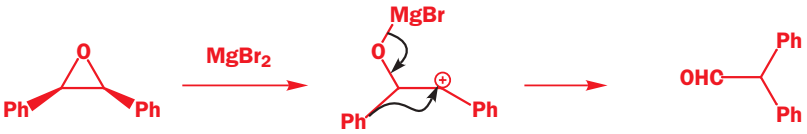


The first step is straightforward—just like the one you have just met. The 'pinacol' dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused *spiro* to the remaining four-membered ring. Reduction of the ketone then gives an alcohol that rearranges to the alkene in acid. Try working out a mechanism for this transformation—start by protonating of the alcohol and allowing water to leave to give a cation. You might also like to think about why the rearrangement happens—for a clue go back to p. 000.

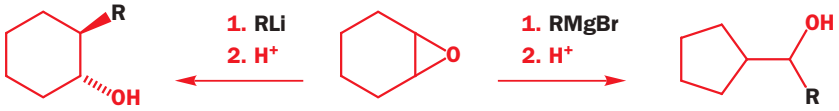


Epoxides rearrange with Lewis acids in a pinacol fashion

The intermediate cation in a pinacol rearrangement can equally well be formed from an epoxide, and treating epoxides with acid, including Lewis acids such as $MgBr_2$, promotes the same type of reaction.



Rearrangement of epoxides with magnesium salts means that opening epoxides with Grignard reagents can give surprising results.

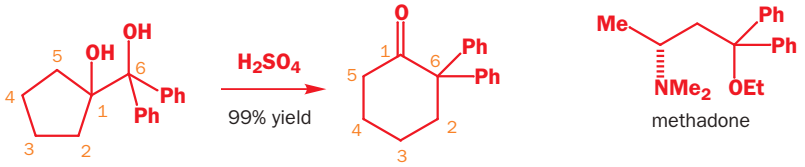


The alkyllithium reaction is quite straightforward as long as the alkyllithium is free of lithium salts. A clue to what has happened with the Grignard reagents comes from the fact that treating this epoxide with just $MgBr_2$ (no RMgBr) gives an aldehyde.

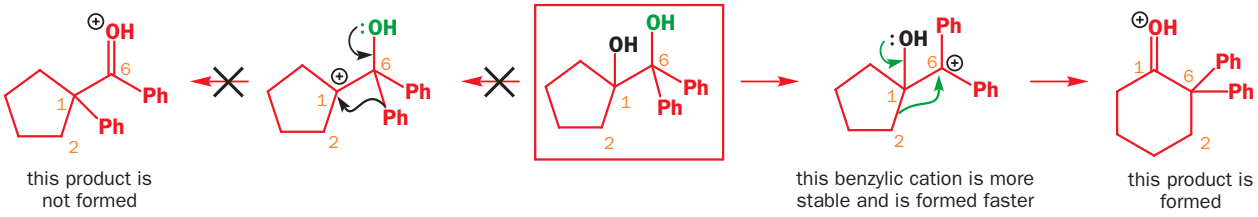
With a Grignard reagent, rearrangement occurs faster than addition to the epoxide, and then the Grignard reagent adds to the aldehyde.

Some pinacol rearrangements have a choice of migrating group

With these symmetrical diols and epoxides, it does not matter which hydroxyl group is protonated and leaves, nor which end the epoxide opens, nor which group migrates. When an unsymmetrical diol or epoxide rearranges, it *is* important which way the reaction goes. Usually, the reaction leaves behind the more stable cation. So, for example, this unsymmetrical diol gives the ring-expanded ketone, a starting material for the synthesis of analogues of the drug methadone.



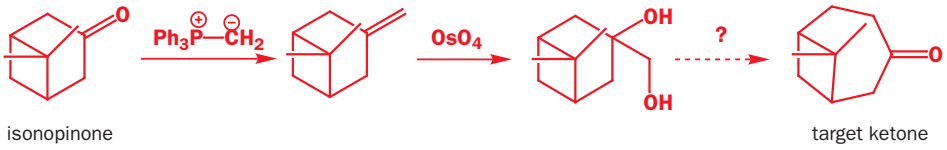
This product is formed because the green OH group leaves more readily than the black because the carbocation stabilized by two phenyl groups forms more readily than the carbocation stabilized by two alkyl groups. The migration step follows without selectivity as both alkyl groups on the black alcohol are the same.



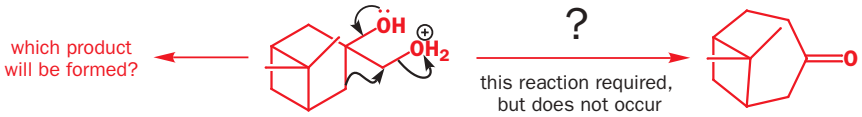
Most unsymmetrical diols or epoxides give mixtures of products upon rearrangement. The problem is that there is a choice of two leaving groups and two alternative rearrangement directions, and only for certain substitution patterns is the choice clear-cut.

Semipinacol rearrangements are pinacol reactions with no choice about which way to go

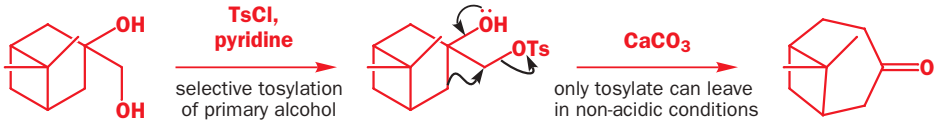
In 1971, French chemists needed this seven-membered cyclic ketone. A reasonable starting material to use is this diol, because it can be made in two steps from the natural product isonopinone.



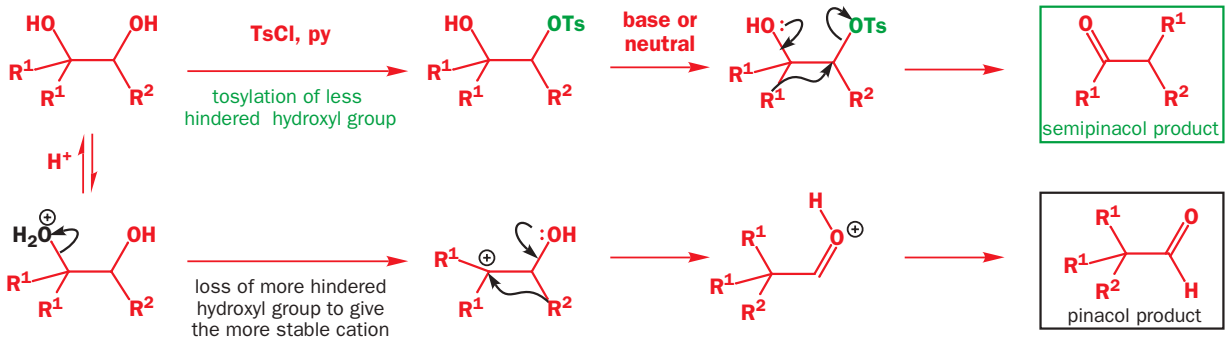
The reaction they needed for the last stage is a pinacol rearrangement—the *primary* hydroxyl group needs persuading to leave as the ring expands. The problem is, of course, that the tertiary hydroxyl group is much more likely to leave since it leaves behind a more stable carbocation.



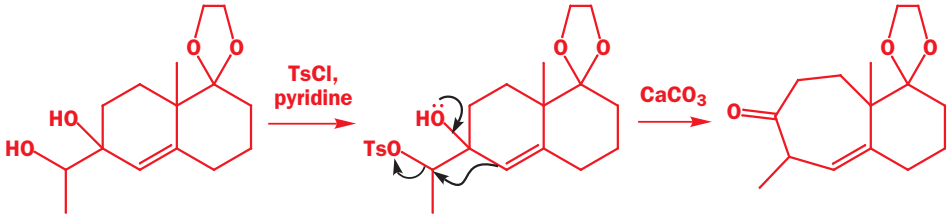
The solution to this problem is to force the primary hydroxyl group to be the leaving group by making it into a tosylate. The primary hydroxyl group reacts more rapidly with TsCl than the tertiary one because it is less hindered. A weak base is now all that is needed to make the compound rearrange in what is known as a **semipinacol rearrangement**.



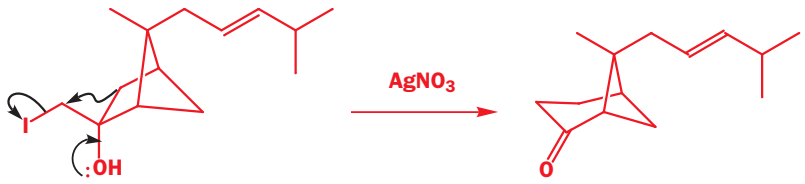
Semipinacol rearrangements are rearrangements in which a hydroxyl group provides the electrons to 'push' the migrating group across, but the 'pull' comes from the departure of leaving groups other than water—tosylate in this example, but typically also halide or nitrogen (N_2). Since tosylation occurs at the *less* hindered hydroxyl group of a diol, not only can semipinacol rearrangements be more regioselective than pinacol rearrangements, but their regioselectivity may be in the opposite direction.



Corey exploited this in a synthesis of the natural product longifolene. He needed to persuade an easily made 6,6-fused ring system to undergo rearrangement to a ring-expanded ketone. Again, a normal acid-catalysed pinacol rearrangement is no good—the tertiary, allylic hydroxyl group is much more likely to ionize, and the acid-sensitive protecting group would be hydrolysed too. Tosylation of the secondary alcohol in the presence of the tertiary is possible, and semipinacol rearrangement gives the required ketone.



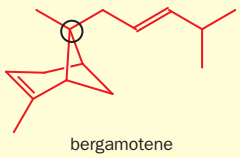
The leaving group need not be tosylate: in the following example, part of a synthesis of bergamotene (a component of valerian root oil and the aroma of Earl Grey tea), a 2-iodo alcohol rearranges.



Treating 2-halo alcohols with base is, of course, a good way to make epoxides. Using $AgNO_3$ to improve iodide's leaving ability without increasing the nucleophilicity of the hydroxyl group favours rearrangement at the expense of epoxide formation. There would certainly be a danger of epoxide formation in strong base.

The structure of bergamotene

The structure of bergamotene was, for some years during the 1960s, a matter of debate. The difficult question was the configuration of the chiral centre ringed in black. With modern spectroscopic techniques, we can now solve this type of problem simply, but the only solution then was to synthesise the two isomers and compare them with the natural material. There is more about bergamotene in Chapter 46.

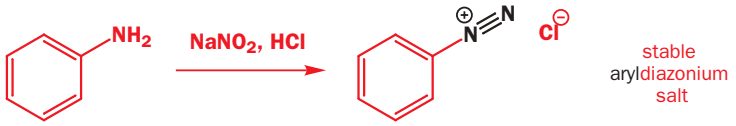


bergamotene

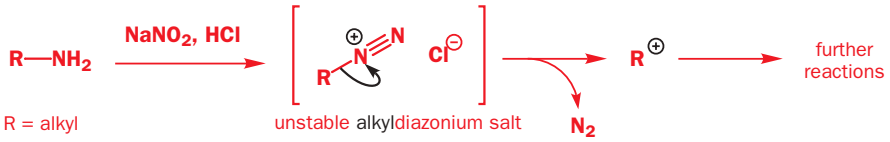
Semipinacol rearrangements of diazonium salts

You saw in Chapter 22 how aromatic amines can be converted to diazonium salts by treatment with acidic sodium nitrite.

▶ It might be an idea to review pp. 000–00 of Chapter 22 to be sure you understand the mechanism of this reaction.

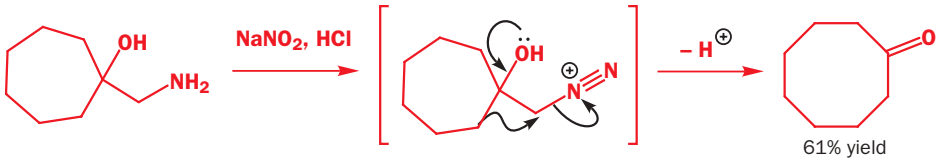


Aryldiazonium salts are stable but *alkyl*diazonium salts are not: nitrogen gas is the world's best leaving group, and, when it goes, it leaves behind a carbocation.

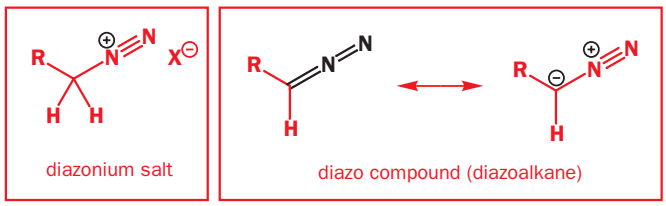


▶ Semipinacol rearrangements of diazonium salts derived from 2-amino alcohols are sometimes called **Tiffeneau–Demjanov rearrangements**.

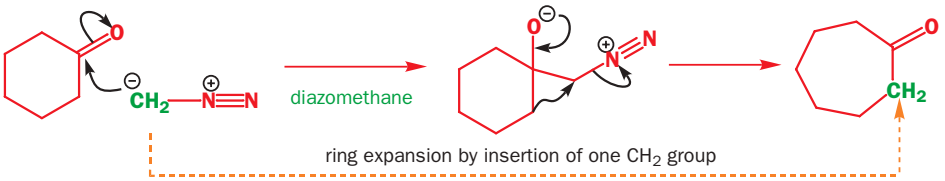
One of the 'further reactions' this carbocation can undergo is rearrangement. If the starting amine is a 2-amino alcohol, the cation can be stabilized by a semipinacol rearrangement.



While alkyldiazonium salts are unstable, their conjugate bases, diazoalkanes, are stable enough to be prepared and are nucleophilic towards carbonyl compounds. **Diazoalkanes** are neutral compounds having one fewer proton than diazonium salts and are delocalized structures with a central sp nitrogen atom.



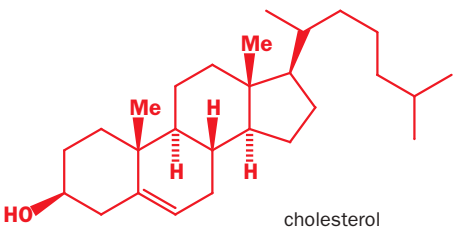
When diazomethane (a compound we will investigate in more detail in Chapter 40) adds to a ketone, the product undergoes a ring expansion by rearrangement of the same type of intermediate.



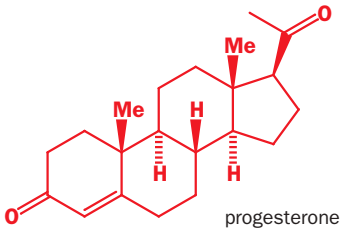
The problem with reactions like this is that both the starting material and product are ketones, so they work cleanly only if the starting material is more reactive than the product. Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone, so it ring expands cleanly to cycloheptanone. But expansion of cyclopentanone to cyclohexanone is messy and gives a mixture of products. We shall come back to diazo compounds in more detail in Chapter 40; diazonium salts will reappear in Chapter 38 where their decomposition will provide the driving force for fragmentation reactions.

The dienone–phenol rearrangement

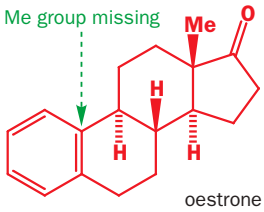
The female sex hormone oestrone is the metabolic product of another hormone, progesterone, itself made in the body from cholesterol.



cholesterol



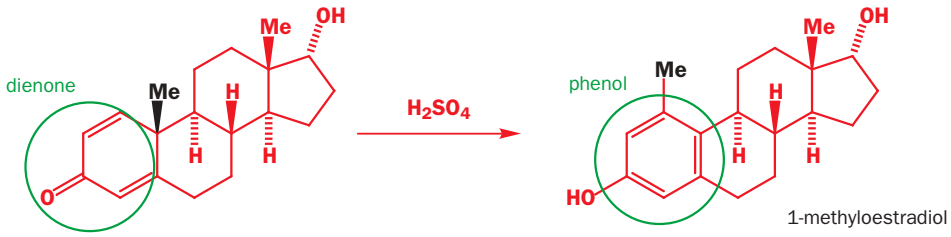
progesterone



oestrone

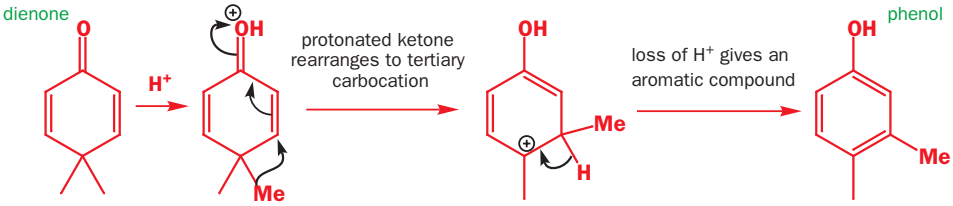
Oestrone lacks one of progesterone's methyl groups, probably removed in the body as CO_2 after oxidation. In 1946, Carl Djerassi, a man whose work led directly to the invention of the contraceptive pill, showed that another derivative of cholesterol could be rearranged to the oestrone analogue 1-methyloestradiol—notice how the methyl group has this time migrated to an adjacent carbon atom. At the same time, the dienone has become a phenol.

■ Carl Djerassi, an American born in Vienna in 1923, worked chiefly at CIBA, Syntex in Mexico, and at Stanford. He developed syntheses of human steroids from compounds in plants, was a pioneer of mass spectrometry, and is a colourful campaigner for peace and disarmament.



1-methyloestradiol

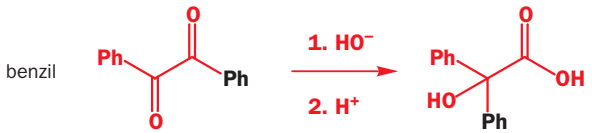
This type of rearrangement is known helpfully as a **dienone–phenol rearrangement**, and we can consider it quite simply as a type of *reverse* pinacol rearrangement. Pinacol and semipinacol rearrangements are driven by the formation of a carbonyl group. The rearranged cation is stabilized by being next to oxygen, and it can rapidly lose H^+ to give a carbonyl compound. In the key step of a dienone–phenol rearrangement, a protonated carbonyl compound rearranges to a tertiary carbocation.



The reaction is driven from dienone to phenol because the product cation can rapidly undergo elimination of H^+ to become aromatic.

The benzilic acid rearrangement

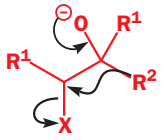
You have seen rearrangements in which carbonyl groups form at the migration origin: the migrating group in the pinacol and semipinacol rearrangements is 'pushed' by the oxygen's lone pair as it forms the new carbonyl group. You have also seen carbonyl groups being destroyed at the migration terminus: the migrating group in the dienone–phenol rearrangement is 'pulled' towards the protonated carbonyl group. The first rearrangement reaction ever to be described has both of these at once.



benzilic acid

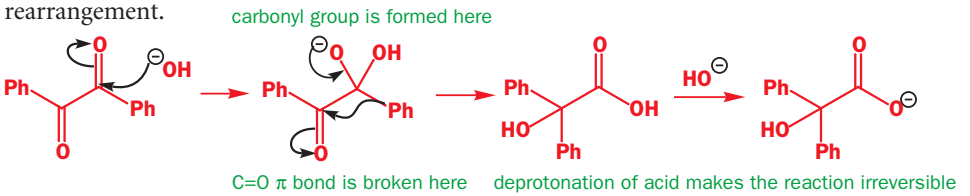
In 1838, Justus von Liebig found that treating 'benzil' (1,2-diphenylethan-1,2-dione) with hydroxide gave, after acid quench, 2-hydroxy-2,2-diphenylacetic acid, which he called 'benzilic acid'.

▶ You may find it helpful to think of the benzilic acid rearrangement as a semipinacol rearrangement in which we have a breaking C=O π bond instead of a leaving group.



compare the migration step with this semipinacol rearrangement

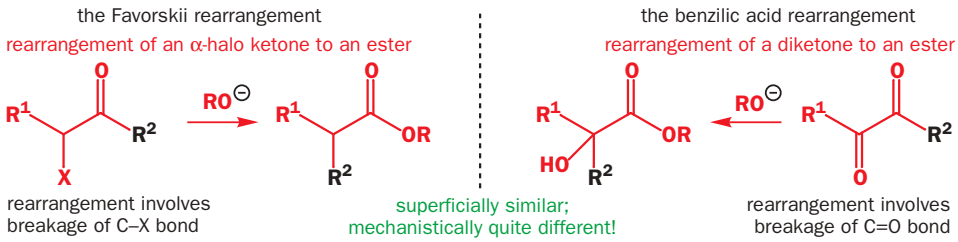
The mechanism of this **benzilic acid rearrangement** starts with attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.



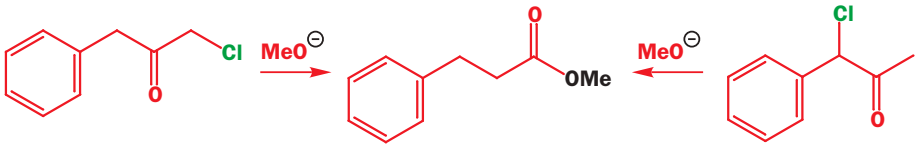
With alkoxides, the benzilic acid rearrangement can lead directly to esters by the same sort of mechanism.

The Favorskii rearrangement

We hope you have appreciated the smooth mechanistic progression so far in this chapter, from Wagner–Meerwein to pinacol and semipinacol through dienone–phenol to benzilic acid. Our aim is to help you gain an overall view of the types of rearrangements that take place (and why) and not to present you with lots of disconnected facts. It is at this point, however, that our mechanistic journey takes a hairpin bend. A surprising one, too, because, when we show you the Favorskii rearrangement, you would be forgiven for wondering what the fuss is about: surely it's rather like a variant of the benzilic acid rearrangement?

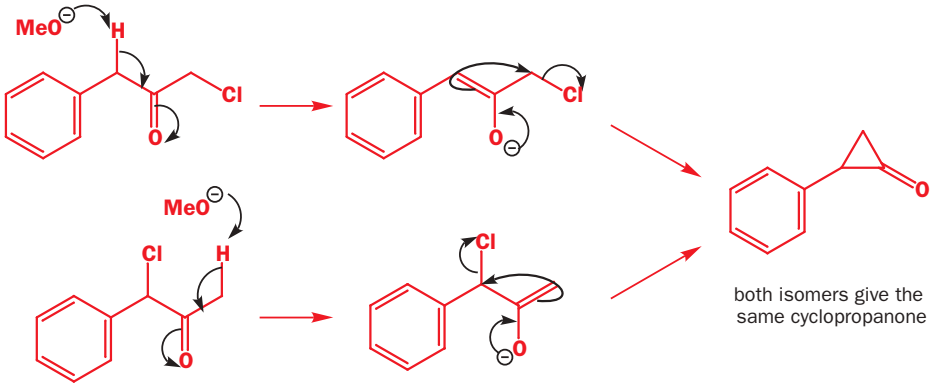


Well, this is what chemists thought until 1944, when some Americans found that two isomeric α-chloro ketones gave exactly the same product on treatment with methoxide. They suggested that both reactions went through the same intermediate.

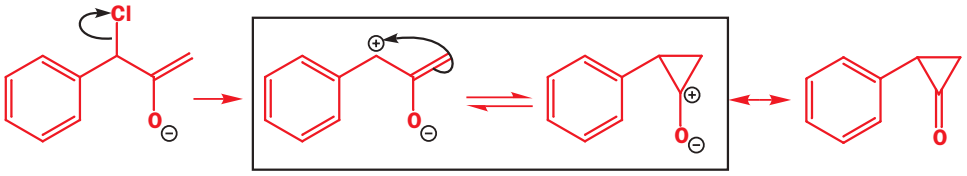


■ A full discussion of this point requires Baldwin's rules, which appear in Chapter 41.

That intermediate is a three-membered cyclic ketone, a cyclopropanone: the alkoxide acts not as a nucleophile (its role in the benzilic acid rearrangement) but as a base, enolizing the ketone. The enolate can alkylate itself intramolecularly in a reaction that looks bizarre but that many chemists think is not unreasonable. The product is the same cyclopropanone in each case.

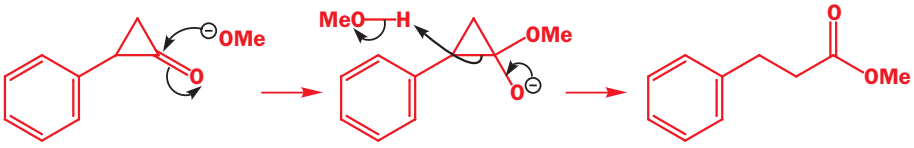


Other chemists prefer a pericyclic description of the ring-closure step. The same enolate simply loses chloride to give an 'oxyallyl cation'—a dipolar species with an oxyanion and a delocalized allylic cation. This species can cyclize in a two-electron disrotatory electrocyclic reaction (Chapter 36) to give the same cyclopropanone. We shall return to this discussion in the next chapter but, whatever the mechanism, there is no doubt that a cyclopropanone is an intermediate.

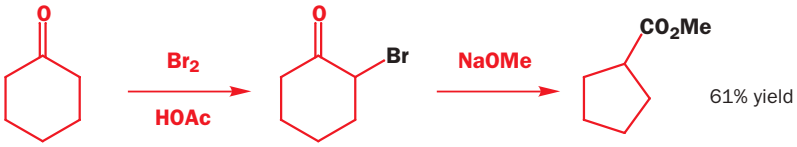


two-electron disrotatory electrocyclic reaction

Cyclopropanones are very reactive towards nucleophiles, and the tetrahedral intermediate arising from the attack of methoxide springs open to give the ester product. The more stable carbanion leaves: though the carbanion is not actually formed as a free species, there must be considerable negative charge at the carbon atom as the three-membered ring opens. Here the benzyl group is the better leaving group.



Favorskii rearrangement of cyclic 2-bromoketones leads to ring contraction and this has become one of the most fruitful uses of the rearrangement in synthesis. Bromination of cyclohexanone is a simple reaction (Chapter 21) and treatment with methoxide gives the methyl ester of cyclopentane carboxylic acid in good yield.



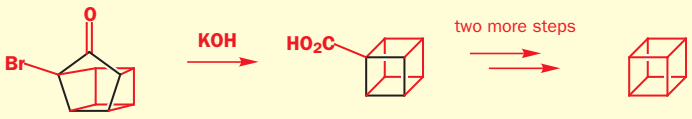
61% yield

Enolization occurs on the side of the ketone away from the bromine atom and the enolate cyclizes as before but the cyclopropanone intermediate is symmetrical so that the product is the same whichever C–C bond breaks after nucleophilic attack by the methoxide ion.

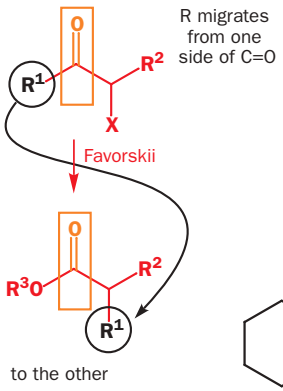
▶ Cyclopropanones and cyclobutanones are very reactive, rather like epoxides, because, while the 60° or 90° angle in the ring is nowhere near the tetrahedral angle (108°), it is nearer 108° than the 120° preferred by the sp^2 C of the C=O group. Conversely, the small ring ketones are resistant to enolization, because that would place *two* sp^2 carbon atoms in the ring.

Heading

In 1964, two American chemists synthesized for the first time a remarkable molecule, cubane. Two of the key steps were Favorskii rearrangements, which allowed the chemists to contract five-membered rings to four-membered rings. Here is one of them. Two more steps decarboxylate the product to give cubane itself.

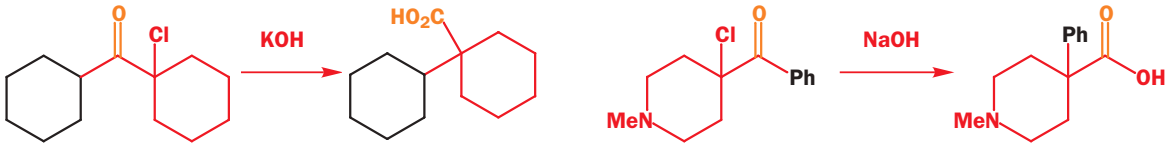


55% yield cubane



The overall consequence of the Favorskii rearrangement is that an alkyl group is transferred from one side of a carbonyl group to the other.

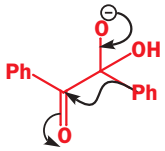
This means that it can be used to build up heavily branched esters and carboxylic acids—the sort that are hard to make by alkylation because of the problems of hindered enolates and unreactive secondary alkyl halides. Heavily substituted acids, where CO_2H is attached to a tertiary carbon atom, would be hard to make by any other method. And the Favorskii rearrangement is a key step in this synthesis of the powerful painkiller Pethidine.



Pethidine

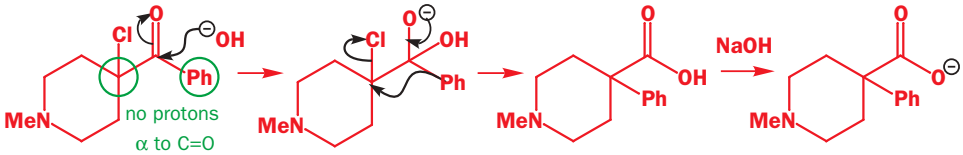
▶ The Favorskii mechanism will help you understand the Ramberg–Bäcklund reaction in Chapter 46—the two reactions have quite similar mechanisms.

Try writing a mechanism for this last reaction and you run into a problem—there are no acidic protons so the ketone cannot be enolized! Yet the Favorskii rearrangement still works. Despite our warnings against confusing the mechanisms of the Favorskii and benzilic acid rearrangements, the Favorskii rearrangement may, in fact, follow a benzilic (or 'semibenzilic', by analogy with the semipinacol) rearrangement mechanism, *if* there are no acidic hydrogens available.



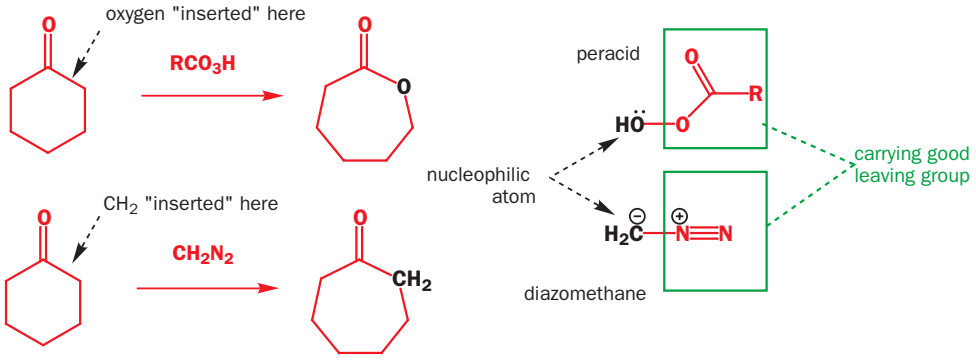
compare the migration step with this benzylic acid rearrangement

'semibenzilic' Favorskii rearrangement of nonenolisable ketones

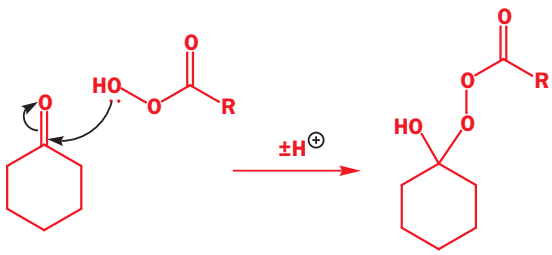


Migration to oxygen: the Baeyer–Villiger reaction

In 1899, the Germans, A. Baeyer and V. Villiger, found that treating a ketone with a peroxy-acid (RCO_3H) can produce an ester. An oxygen atom is 'inserted' next to the carbonyl group.

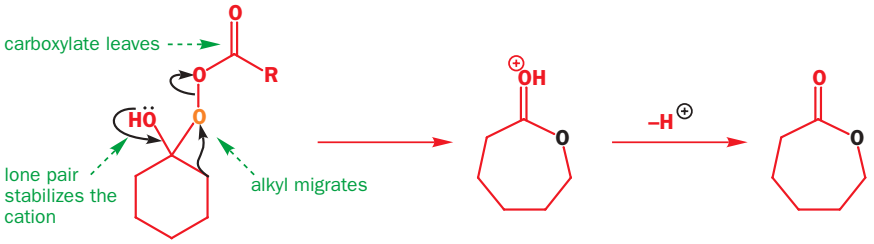


Now, you saw a similar 'insertion' reaction earlier in the chapter, and the mechanism here is not dissimilar. Both peracids and diazomethane contain a nucleophilic centre that carries a good leaving group, and addition of peracid to the carbonyl group gives a structure that should remind you of a semipinacol intermediate with one of the carbon atoms replaced by oxygen.



Carboxylates are not such good leaving groups as nitrogen, but the oxygen–oxygen single bond is very weak and monovalent oxygen cannot bear to carry a positive charge so that, once the peracid

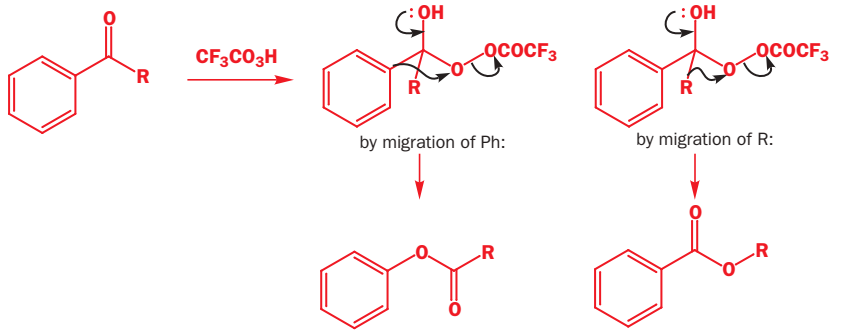
has added, loss of carboxylate is concerted with a rearrangement driven, as in the case of the pinacol and semipinacol, by formation of a carbonyl group.



Baeyer–Villiger reactions are among the most useful of all rearrangement reactions, and the most common reagent is *m*-CPBA (*meta*-chloroperbenzoic acid) because it is commercially available.

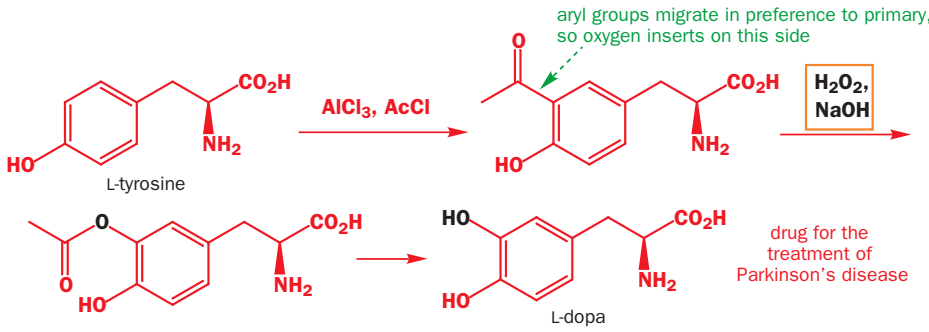
Which group migrates? (I)—the facts

A question we have deliberately avoided up to this point is this: when there is a competition between two migrating groups, *which group migrates*? This question arises in pinacol, semipinacol, and dienone–phenol rearrangements and in Baeyer–Villiger reactions (in the benzilic acid and Favorskii rearrangements, there is no choice) and the awkward fact is that the answer is different in each case! However, let's start with the Baeyer–Villiger reaction, because here the question is always valid except when the ketone being oxidized is symmetrical. Here are some examples; and you can probably begin to draw up guidelines for yourself.



R =	Yield for R (%)	Yield for R (%)
Me	90	0
Et	87	6
i-Pr	33	63
t-Bu	2	77

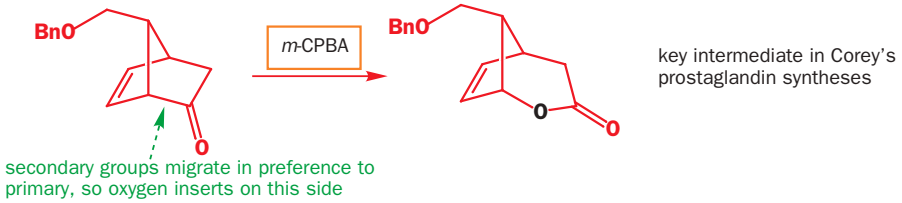
The order, with *t*-alkyl the best at migrating, then *s*-alkyl closely followed by Ph, then Et, then Me, *very roughly* follows the order in which the groups are able to stabilize a positive charge. Primary groups are much more reluctant to undergo migration than secondary ones or aryl groups, and this makes regioselective Baeyer–Villiger reactions possible.



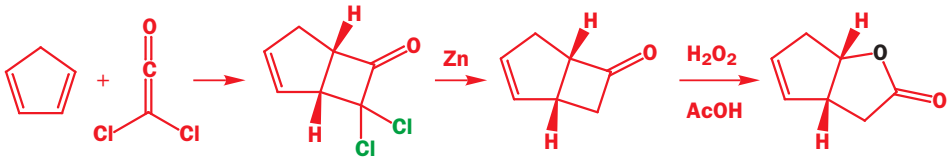
The Baeyer–Villiger reaction has solved a regioselectivity problem here. L-tyrosine, a relatively cheap amino acid, can be converted to the important drug L-dopa provided it can be hydroxylated *ortho* to the OH group. This is where electrophilic substitutions of the phenol take place, but electrophilic substitutions with 'HO^{+}' are not possible. However, after a Friedel–Crafts acylation, the acyl group can be converted to hydroxyl by the Baeyer–Villiger reaction and hydrolysis. The Baeyer–Villiger reaction means that $MeCO^{+}$ can be used as a synthetic equivalent for 'HO^{+}'. Note the unusual use of the less reactive H_2O_2 as oxidizing agent in this reaction. This is possible only when the migrating group is an electron-rich aromatic ring; these reactions are sometimes called **Dakin reactions**.

Unsaturated ketones may epoxidize or undergo Baeyer–Villiger rearrangement

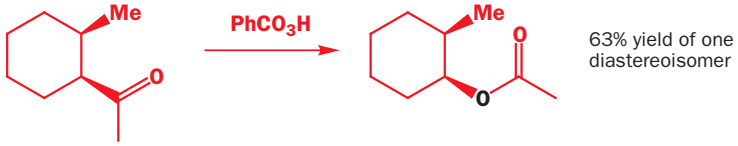
Peracids may epoxidize alkenes faster than they take part in Baeyer–Villiger reactions, so unsaturated ketones are not often good substrates for Baeyer–Villiger reactions. The balance is rather delicate. The two factors that matter are: how *electro*philic is the ketone and how *nucleo*philic is the alkene? You might like to consider why this reaction *does* work, and why the C=C double bond here is particularly unreactive.



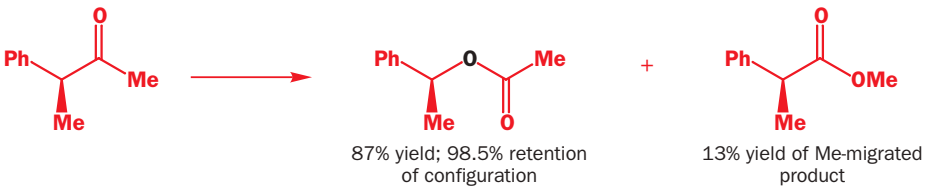
Small-ring ketones can relieve ring strain by undergoing Baeyer–Villiger reactions—this cyclobutanone (an intermediate in a synthesis of the perfumery compound *cis*-jasmone) is made by a ketene [2+2] cycloaddition, and is so reactive that it needs only H_2O_2 to rearrange. Unlike CF_3CO_3H or *m*-CPBA, H_2O_2 will not epoxidize double bonds (unless they are electron-deficient—see Chapter 23).



One point to note about both of the last two reactions is that the insertion of oxygen goes with retention of stereochemistry. You may think this is unsurprising in a cyclic system like this and, indeed, the first of the two cannot possibly go with inversion. However, this is a general feature of Baeyer–Villiger reactions, even when inversion would give a more stable product.

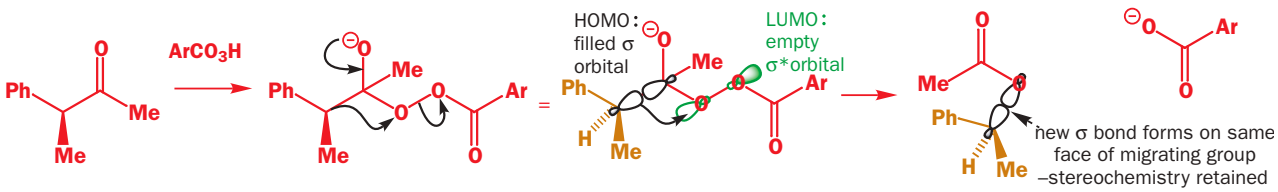


Even when you might imagine that racemization would occur, as in this benzylic ketone, retention is the rule.



By looking at the orbitals involved, you can see why this must be so. The sp^3 orbital of the migrating carbon just slips from one orbital to the next with the minimum amount of structural

reorganization. The large lobe of the sp^3 orbital is used so the new bond forms to the same face of the migrating group as the old one, and stereochemistry is retained.

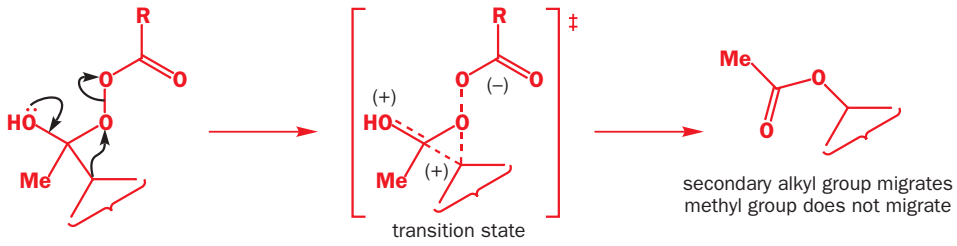


The orbital interactions in all 1,2-migrations are similar, and the migrating group retains its stereochemistry in these too. In the more familiar S_N2 reaction, inversion occurs because the antibonding σ* orbital rather than the bonding σ orbital is used. In the S_N2 reaction, carbon undergoes *nucleophilic* attack with *inversion*; in rearrangements the migrating carbon atom undergoes *electrophilic* attack with *retention* of configuration.

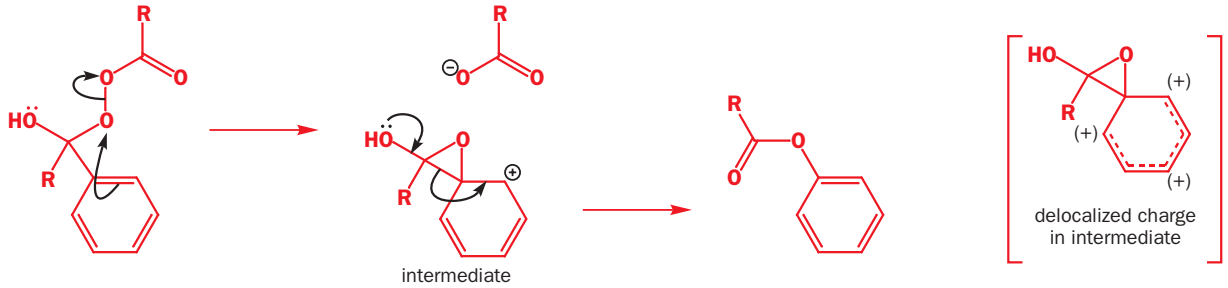
In 1,2-migrations, the migrating group retains its stereochemistry.

Which group migrates? (II)—the reasons

Why does the more substituted group migrate in the Baeyer–Villiger reaction? The transition state has a positive charge spread out over the molecule as the carboxylate leaves as an anion. If the migrating group can take some responsibility for the positive charge the transition state will be more stable. The more stable the charge, the faster the rearrangement.

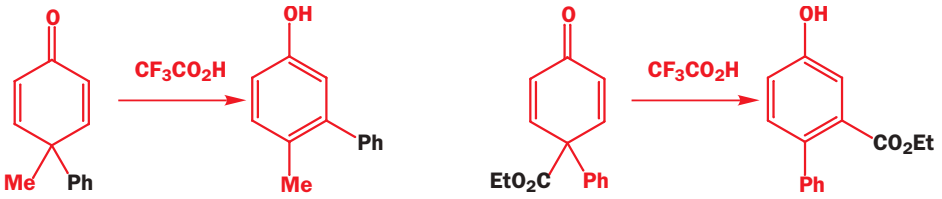


When a benzene ring migrates, π participation is involved as the benzene ring acts as a nucleophile and the positive charge can be spread out even further. Note that the Ph is stabilizing the charge here in the way that it stabilizes the intermediate in an electrophilic aromatic substitution reaction—like a pentadienyl cation rather than like a benzylic cation. What was a transition state in alkyl migration becomes an intermediate in phenyl migration.

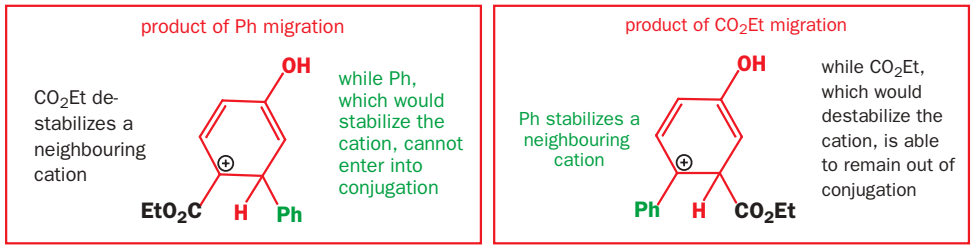


The situation in other rearrangements is much more complicated—and indeed more complicated than many textbooks would have you believe. We shall look just briefly at the dienone–phenol rearrangement again, this time considering reactions in which there is a competition between two different migrating groups. As in the Baeyer–Villiger reaction, the transition state is cationic, so you would expect cation-stabilizing groups to migrate more readily. This appears to be true for Ph versus

Me, but is most definitely not true for Ph versus CO_2Et. The cation-*destabilizing* group CO_2Et migrates even though Ph is much better at stabilizing a positive charge!

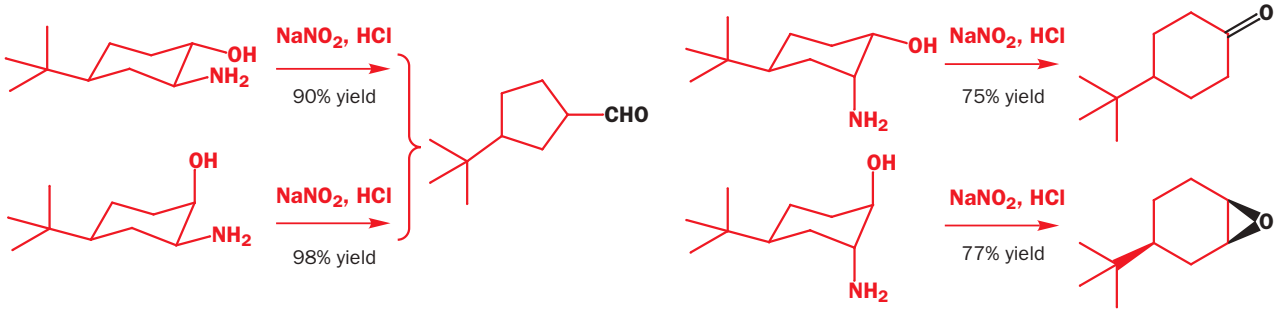


The reason is that CO_2Et is so cation-*destabilizing* that it prefers to migrate rather than be left behind next door to a cation. In this case, then, it is the cation-stabilizing ability of the group that *does not* migrate that matters most.

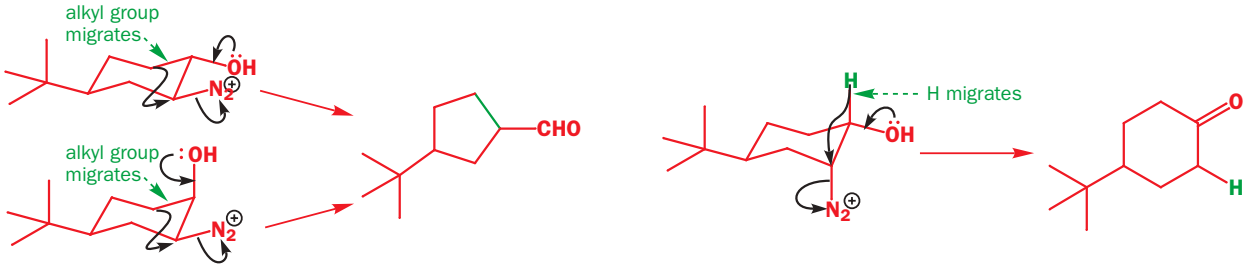


Which group migrates? (III)—stereochemistry matters too

Selectivity in rearrangement reactions is affected by the electronic nature of *both* the group that migrates *and* the group that is left behind. But there is more! *Stereochemistry* is important too. The outcome of diazotization and semipinacol rearrangement (Tiffeneau–Demjanov rearrangement) of this amino-alcohol depends entirely on the diastereoisomer you start with. There are four diastereoisomers, and we have drawn each one in the only conformation it can reasonably adopt, with the *t*-butyl group equatorial.

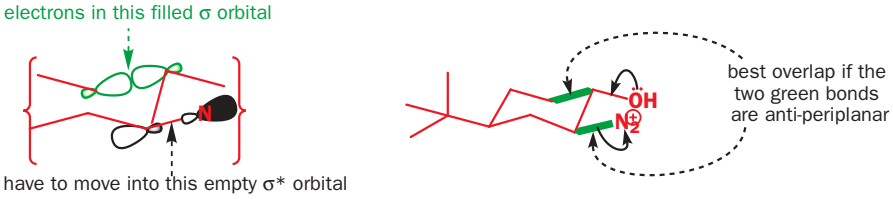


In all of these reactions, the OH group provides the electronic 'push'. In the first two reactions, the ring contracts by an alkyl migration from the secondary alcohol, while in the third it is H that migrates from the same position.

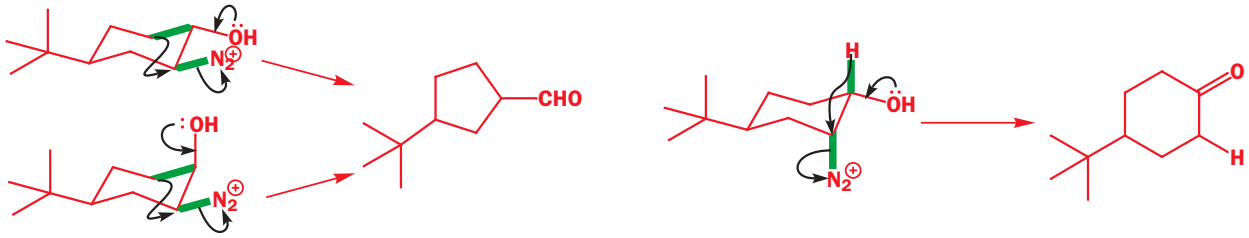


The only difference between the compounds is stereochemistry and, if we look at the orbitals involved in the reactions, we can see why this is so important. As the N_2 leaving group departs, electrons in the bond to the migrating group have to flow into the C–N σ* orbital—we discussed this on

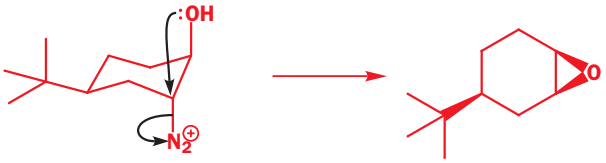
p. 000. But what we didn't talk about then was the fact that best overlap between these two orbitals (σ and σ*) occurs if they are anti-periplanar to one another—just as in an E2 elimination reaction.



For the first two compounds, with the $-N_2^+$ group equatorial, the group best placed to migrate is the alkyl group that forms the ring; for the third reaction, there is a hydrogen atom anti-periplanar to the leaving group, so H migrates.



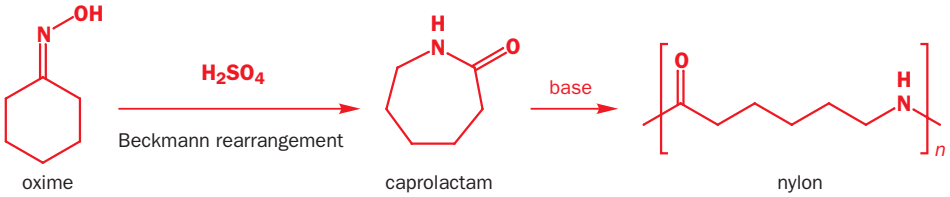
The fourth reaction has, rather than a group that might migrate, the hydroxyl group ideally placed to displace N_2 and form an epoxide—another example of participation.



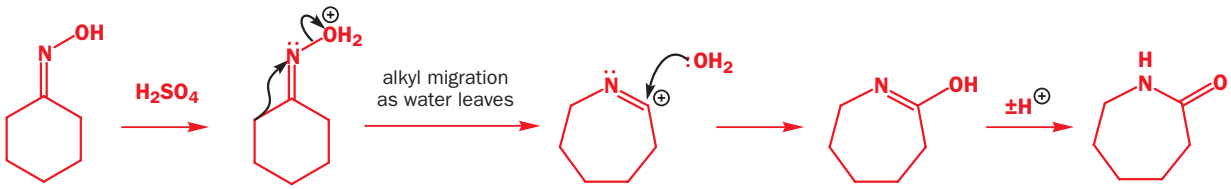
The requirement for the migrating group to be anti-periplanar to the leaving group is quite general in rearrangement reactions. The reason we haven't noticed its effect before is that most of the compounds we have considered have not been conformationally constrained in the way that these are. Free rotation means that the right geometry for rearrangement is always obtainable—stereochemistry is not a factor in the Baeyer–Villiger reaction, for example. We will come back to some more aspects of stereochemical control in the next chapter, on fragmentation reactions. Before then, we will consider one last rearrangement reaction, in which stereochemistry again plays an important controlling role.

The Beckmann rearrangement

The industrial manufacture of nylon relies upon the alkaline polymerization of a cyclic amide known trivially as caprolactam. Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the **Beckmann rearrangement**.

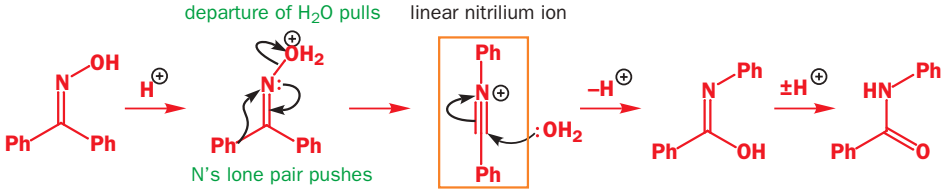


The mechanism of the Beckman rearrangement follows the same pattern as a pinacol or Baeyer–Villiger reaction—acid converts the oxime OH into a leaving group, and an alkyl group migrates on to nitrogen as water departs. The product cation is then trapped by water to give an amide.



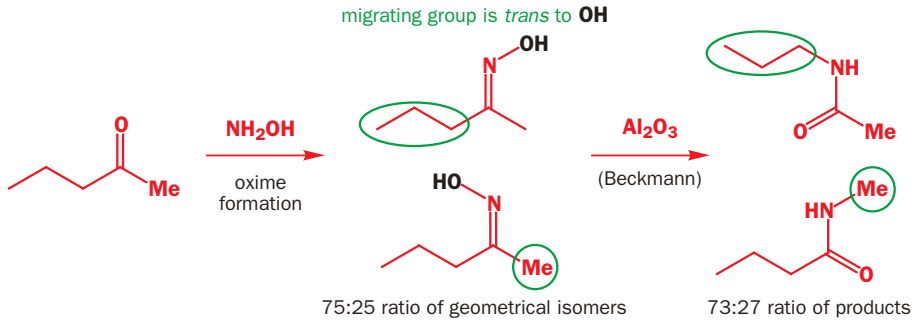
▶ A linear system like this was impossible in the seven-membered ring of the last example.

This rearrangement is not confined to cyclic oximes, and other ways of converting OH to a leaving group also work, such as PCl_5, $SOCl_2$, and other acyl or sulfonyl chlorides. In an acyclic Beckmann rearrangement, the product cation is better represented as this nitrilium ion. When we write the mechanism we can then involve the nitrogen's lone pair to 'push' the migrating group back on to N.

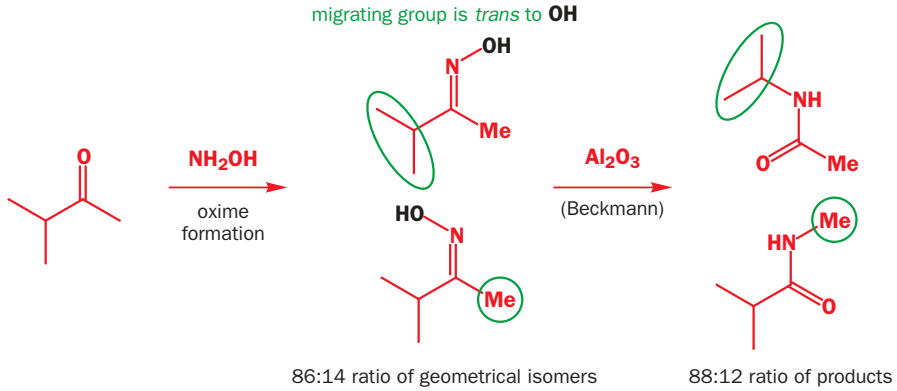


Which group migrates in the Beckmann rearrangement?

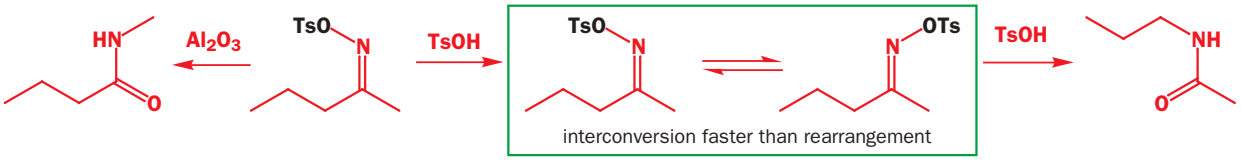
In the Beckmann rearrangement of unsymmetrical ketones there are two groups that could migrate. There are also two possible geometrical isomers of an unsymmetrical oxime: C=N double bonds can exhibit *cis/trans* isomerism just as C=C double bonds can. When mixtures of geometrical isomers of oximes are rearranged, mixtures of products result, but the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials—the group that has migrated is in each case the group *trans* to the OH in the starting material.



We have already touched on the idea that, for migration to occur, a migrating group has to be able to interact with the σ* of the bond to the leaving group, and this is the reason for the specificity here. In the example a couple of pages back the stereospecificity of the reaction was due to the starting material being constrained in a conformationally rigid ring. Here it is the C=N double bond that provides the constraint. If one of the alkyl chains is branched, more of the oxime with the OH group *anti* to that chain will be formed and correspondingly more of the branched group will migrate.



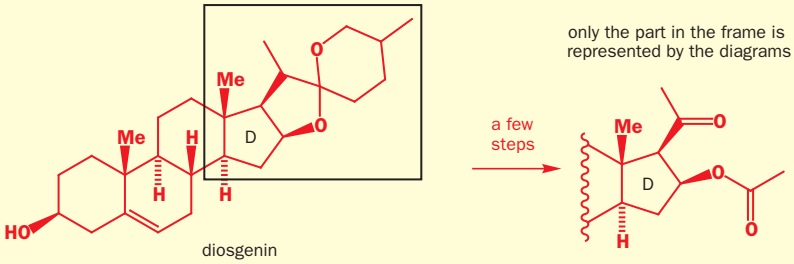
Conditions that allow those double isomers to interconvert can allow either group to migrate—which does so will then be decided, as in the Baeyer–Villiger reaction, by electronic factors. Most protic acids allow the oxime isomers to equilibrate—so, for example, this tosylated oxime rearranges with full stereospecificity in Al_2O_3 (the *anti* methyl group migrates), but with TsOH, equilibration of the oxime geometrical isomers means that either group could migrate—in the event, the propyl group (which is more able to support a positive charge) migrates faster.



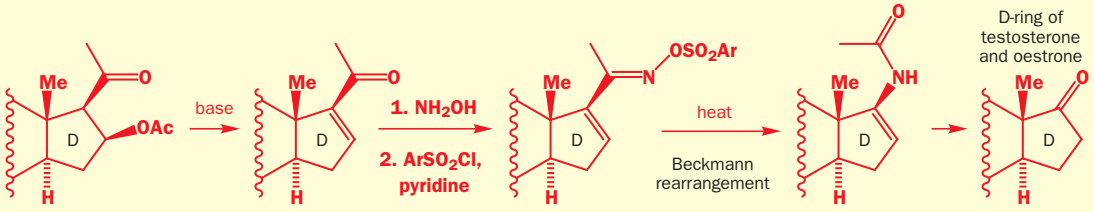
Notice that the effect of the Beckmann rearrangement is to insert a *nitrogen* atom next to the carbonyl group. It forms a useful trio with the Baeyer–Villiger *oxygen* insertion and the diazoalkane *carbon* insertion.

The diosgenin story: steroids from vegetables

Many of the human steroid hormones are available by 'semisynthesis'—in other words synthesis starting from a natural product similar in structure to the target molecule. One very important starting material for semisynthesis routes to these hormones is diosgenin, a plant sterod which makes up 5% of the dry mass of the roots of Mexican yams. Most of the chemical manipulation necessary to turn diosgenin into human steroids concerns the top right five-membered ring (the 'D' ring). A few steps convert the acetal group of the natural product into a simpler methyl ketone, present in cortisone and progesterone

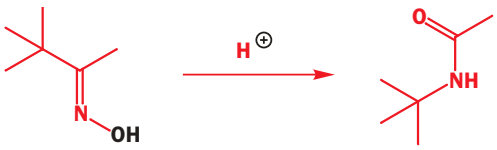


Bur for hormones such as oestrone and testerone two carbon atoms need removing to make a cyclopentanone. This is accomplished using a Beckmann rearrangement. The oxine forms with the OH group trans to the more bulky cyclic substituent. Tosylation and Beckmann rearrangement gives an acetylated enamine which hydrolises to the required cyclopentanone

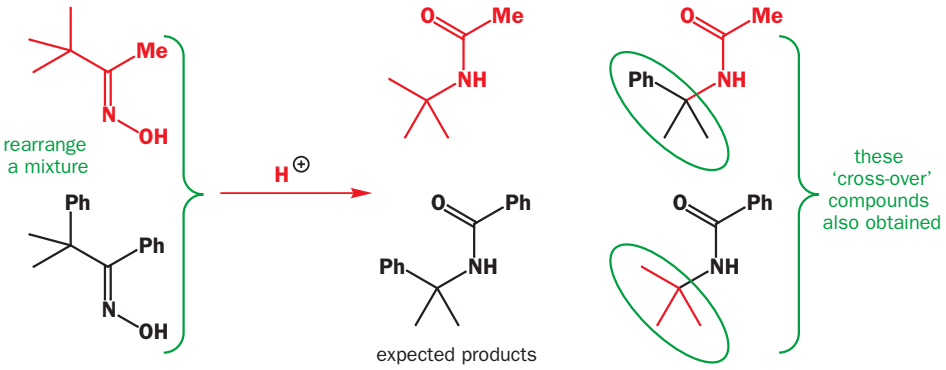


The Beckmann fragmentation

To finish this chapter, a Beckmann rearrangement that is not all that it seems. *t*-Butyl groups migrate well in the Baeyer–Villiger reaction and, indeed, Beckmann rearrangement of this compound appears to be quite normal too.

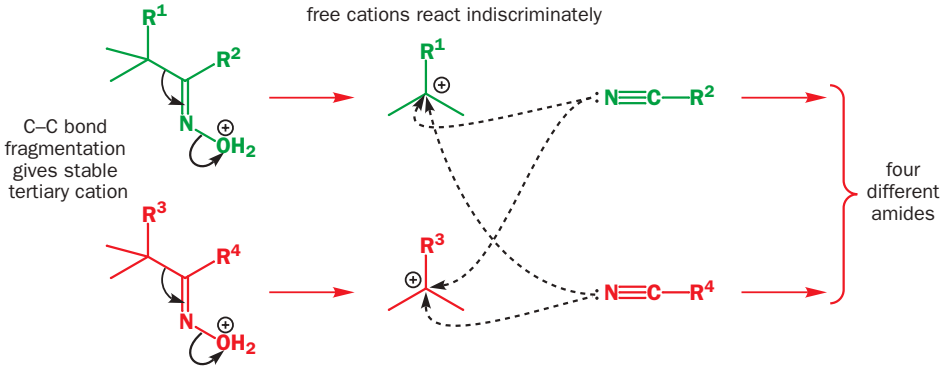


But, when this compound and another compound with a tertiary centre next to the oxime are mixed together and treated with acid, it becomes apparent that what is happening is not an intramolecular reaction.



▶ The recombination step of this reaction is really just a Ritter reaction: reaction of a nitrile with a carbocation. You came across the Ritter reaction on p. 000.

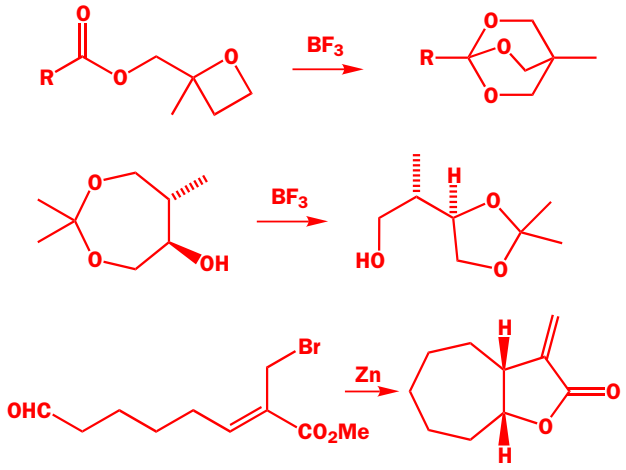
Each migrating tertiary group must have lost contact with the amide fragment it started out with. Each molecule falls to bits to give a *t*-alkyl cation and a nitrile: the Beckmann rearrangement now goes via a **fragmentation** mechanism.



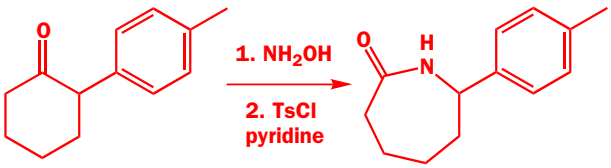
Migrating groups have to provide some degree of cation stabilization. But if they stabilize a cation too well there is a good chance that fragmentation will occur and the 'migrating group' will be lost as a carbocation. It is with this idea that we begin the next chapter.

Problems

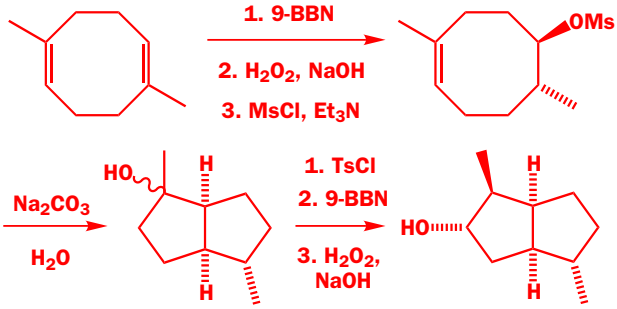
1. Rearrangements by numbers. This problem is just to help you acquire the skill of tracking down rearrangements by numbering. There are no complicated new reactions here. Just draw a mechanism.



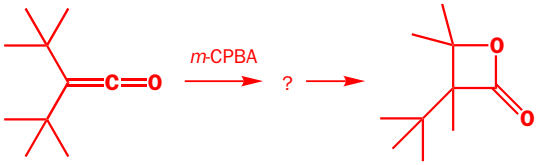
2. Explain this series of reactions.



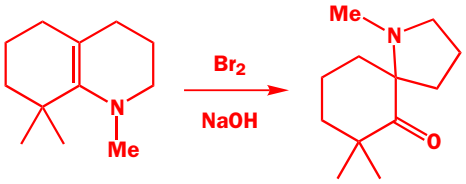
3. Draw mechanisms for the reactions and structures for the intermediates. Explain the stereochemistry, especially of the reactions involving boron. Why was 9-BBN chosen as the hydroborating agent?



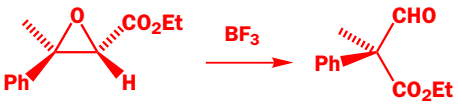
4. It is very difficult to prepare three-membered ring lactones. One attempted preparation, by the epoxidation of di-*t*-butyl ketene, gave an unstable compound with an IR stretch at 1900 cm^{-1} that decomposed rapidly to the four-membered lactone shown. Do you think they made the three-membered ring?



5. Suggest a mechanism for this rearrangement.

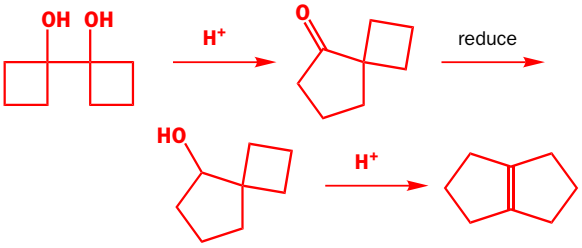


6. A single enantiomer of the epoxide below rearranges with Lewis acid catalysis to give a single enantiomer of product. Suggest a mechanism and comment on the stereochemistry.

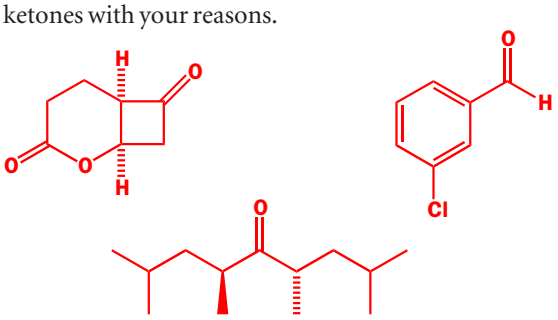


(+) (–)

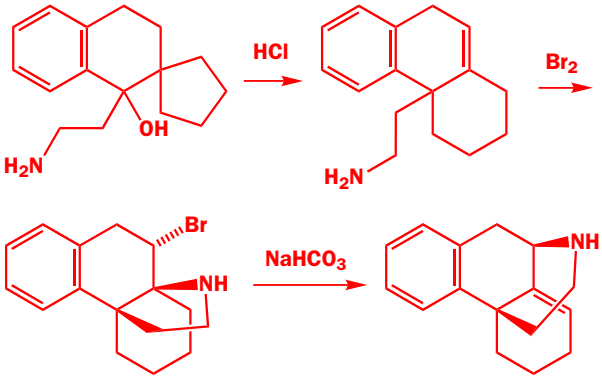
7. The 'pinacol' dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused *spiro* to the remaining four-membered ring. Draw a mechanism for this reaction. Reduction of the ketone then gives an alcohol that rearranges to the alkene in acid. Try working out a mechanism for this transformation. You might also like to think about why the rearrangement happens.



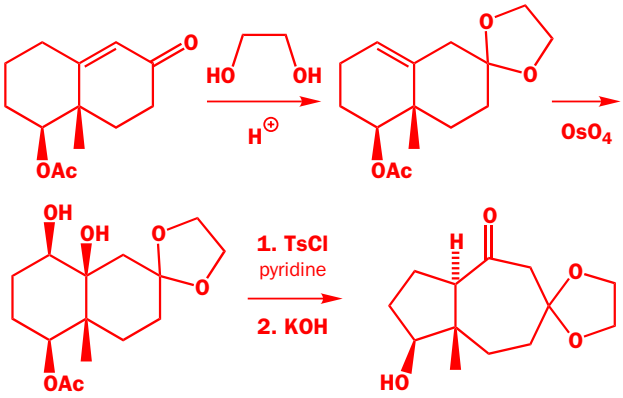
8. Give the products of Baeyer–Villiger rearrangement on these ketones with your reasons.



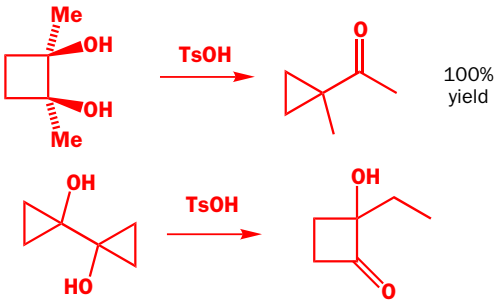
9. Suggest mechanisms for these rearrangements explaining the stereochemistry in the second example.



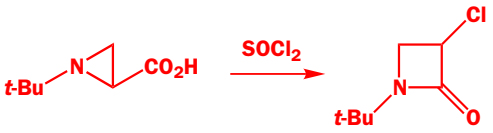
10. Give mechanisms for these reactions, commenting on any regio- and stereoselectivity. What controls the rearrangement?



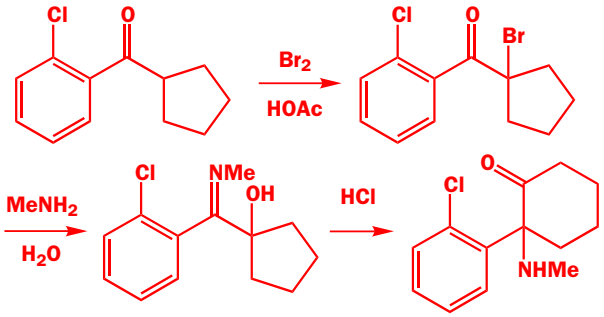
11. Suggest mechanisms for these reactions that explain any selectivity in the migration.



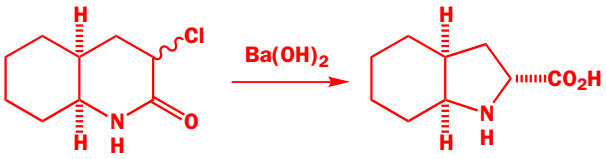
12. Attempts to produce the acid chloride from this unusual amino acid by treatment with $SOCl_2$ gave instead a β-lactam. What has happened?



13. Revision content. Suggest mechanisms for these reactions, commenting in detail on the rearrangement step.



14. Suggest a mechanism for this rearrangement, comparing it with a reaction discussed in the chapter. What controls the stereochemistry?



Fragmentation

38

Connections

Building on:

- Nucleophilic substitution at saturated carbon ch17
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling stereochemistry ch16, ch33, & ch34
- Rearrangements ch37

Arriving at:

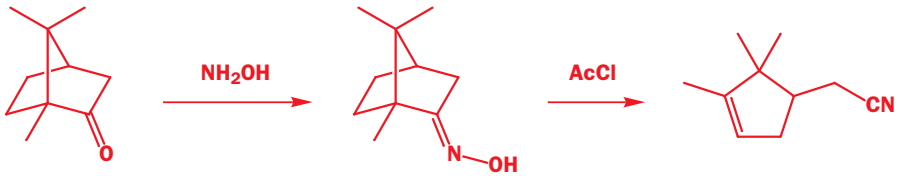
- Electron donation and electron withdrawal combine to create molecules that fragment
- Fragmentation literally means the breaking of a molecule into three by the cleavage of a C–C bond
- Reactive groups should have a 1,4 relationship
- Anti-periplanar conformation is essential
- Small rings are easy to fragment
- Medium and large rings can be made in this way
- Double bond geometry can be controlled
- Using fragmentations in synthesis

Looking forward to:

- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoelectronics ch42
- Main group chemistry ch46–ch47

Polarization of C–C bonds helps fragmentation

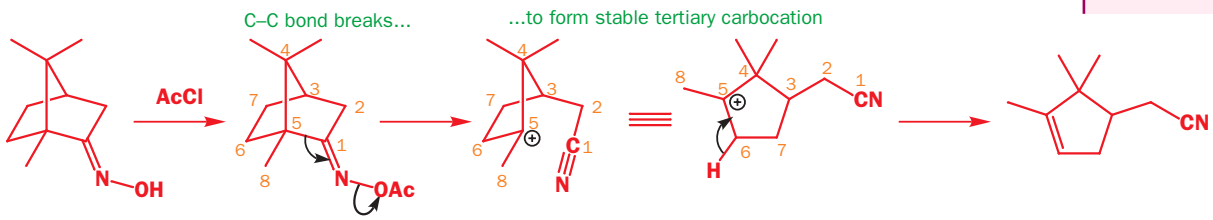
We finished the last chapter with an attempted migration that went wrong because the migrating group stabilized a cation too well. Here is a more convincing example of the same reaction: again, the conditions for, but not the result of, a Beckmann rearrangement.



camphor — *trans* oxime preferred

The starting material is bicyclic, the product monocyclic, so we have broken a C–C bond: the reaction is a **fragmentation**. The mechanism is straightforward once you know what happens to Beckmann rearrangements when the migrating group is tertiary—but hard to follow unless you number the atoms!

▶ Beckmann rearrangements that go with fragmentation are sometimes called 'anomalous' or 'second-order' Beckmann rearrangements. You should not use the second of these names and, in any case, **Beckmann fragmentation** is much better than either.



You have met few fragmentation reactions—reactions in which C–C bonds are broken—largely

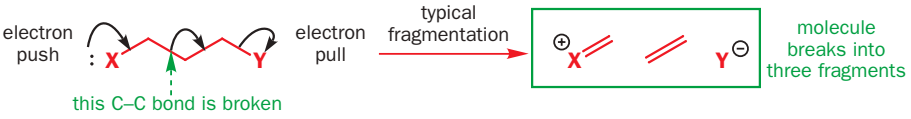
Bond	Typical bond energy, kJ mol^{-1}
C–C	339
C–O	351
C–H	418
O–H	460

▶ The bond energies listed in the table are the energies required to break the bonds **homolytically** to give two radicals, not **heterolytically** to give two ions, which is what has happened in most of the reactions we have talked about. We will look at this in much more detail in the next chapter.

because the C–C bond is so strong. Why then does this reaction work? Well, the reason C–C bonds are hard to break is not just because of their strength, as the table of bond energies indicates.

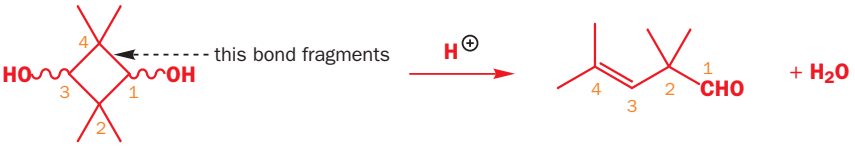
For both carbon and hydrogen, a bond to oxygen is *stronger* than a bond to carbon. Yet we have no hesitation in breaking O–H bonds (of, say, carboxylic acids) with even the weakest of bases and we have spent much of the last chapter showing C–O bonds of protonated alcohols rupturing spontaneously! What is going on?

The answer is **polarization**. Oxygen's electronegativity means that C–O and O–H bonds are polarized and are easy to break with hard nucleophiles and bases; C–C and C–H bonds are (usually) not polarized and, though weaker, are harder to break. It follows that to break a C–C bond it helps a lot if it is polarized—there needs to be a source of electrons at one end and an electron 'sink' (into which they can flow) at the other.

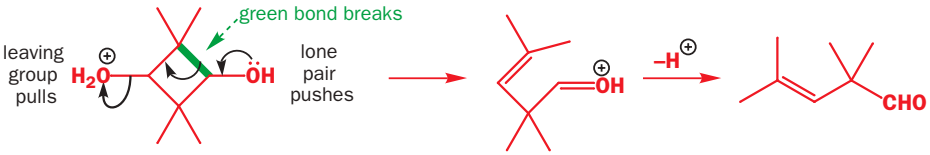


Fragmentations require electron push and electron pull

Fragmentations are reactions in which the molecule breaks into three pieces by the cleavage of a C–C single bond. Now for some examples and comparisons. The first example shows a fragmentation giving only two, not three, molecules. This is because two of the fragments were joined together in a ring. Both diastereoisomers of this cyclic diol fragment in acid to give an aldehyde. Numbering the atoms shows which bond fragments—now we need to provide a source and a sink for the electrons to polarize the bond.

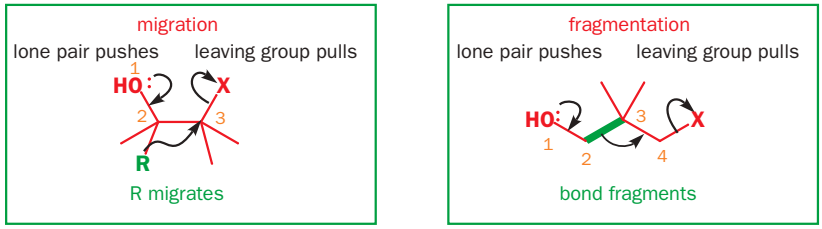


Protonation of a hydroxyl group provides the sink—it can now leave as water. And the lone pair of the other oxygen provides the source. You can think of the electrons in the C–C bond being 'pushed' by the oxygen's lone pair and 'pulled' by the departing water—until the bond breaks. A bit of extra impetus comes from release of ring strain: C–C bonds in three- and four-membered rings are weaker than usual (by about 120 kJ mol^{-1}).

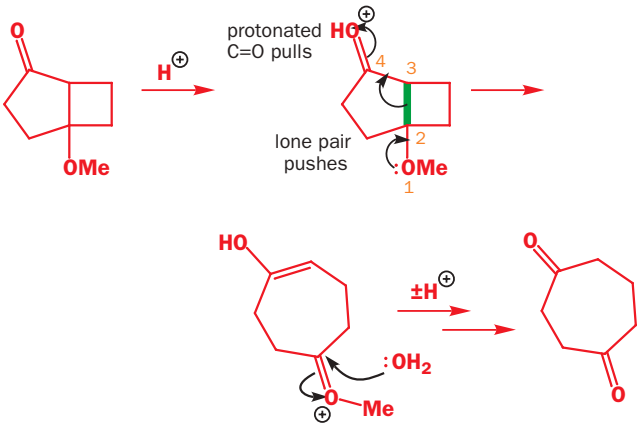


▶ Note the numbering in these diagrams: 1, 2 ,3, 4 from electron source to electron sink. We shall make use of it in many more fragmentation mechanisms.

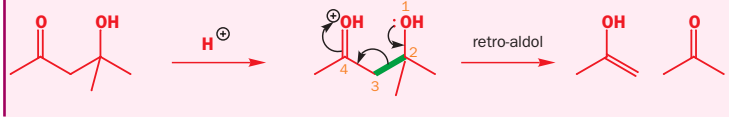
We talked about 'pushing' and 'pulling' electrons when we introduced the pinacol rearrangement, and a very similar thing is happening here *but* the electron source and sink are *separated by one atom* instead of being *adjacent*.



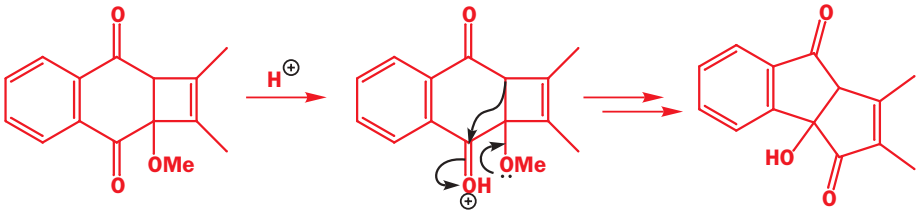
Protonated carbonyl compounds can be electron sinks too (remember the dienone–phenol rearrangement from Chapter 37?), and this bicyclic methoxy ketone fragments to a seven-membered ring in acid. Note the same 1, 2, 3, 4 arrangement, with the bond between carbon atoms 2–3 fragmenting.



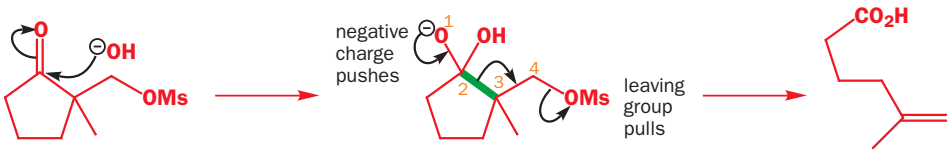
We should perhaps remind you here of the reversibility of the aldol reaction (Chapter 27): a retro-aldol is a fragmentation reaction with a carbonyl group as electron sink and OH as electron source. The aldol reaction usually goes in the other direction of course, but where steric or ring-strain factors are involved, this may not be the case.



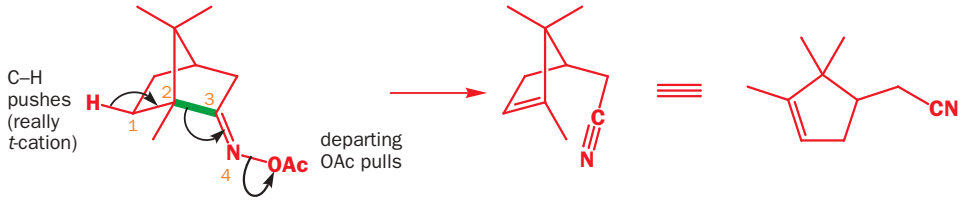
Yet a similar compound to our last example rearranges, and does not fragment because there is an alternative electron sink placed in the right place for migration.



If the MeO group is replaced by a leaving group such as MsO, it can exercise the pull and the carbonyl can provide the push after it has been attacked by a nucleophile. This next five-membered cyclic ketone fragments on treatment with base—can you detect hints of the benzylic acid rearrangement?



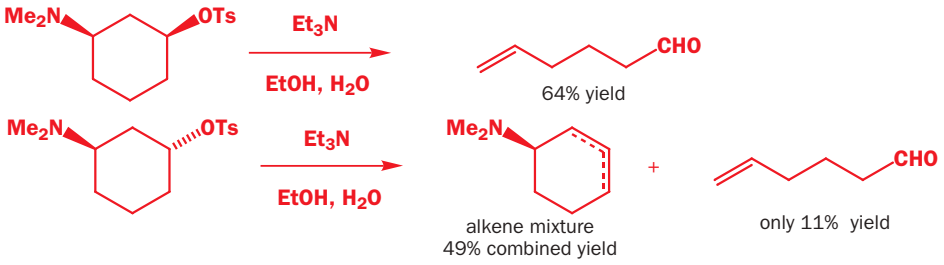
Analysing our Beckmann fragmentation (or anomalous Beckmann rearrangement) in the same way, we can identify the electron sink (the departing acetate group), though the source in this case is a little more obscure. Saying that the tertiary cation is stable is really saying that the neighbouring C–C and C–H bonds provide electrons (through σ conjugation) to stabilize it, so these are the electron sources. A good alternative is to write loss of a proton concerted with fragmentation, which gives one particular C–H bond as the source.



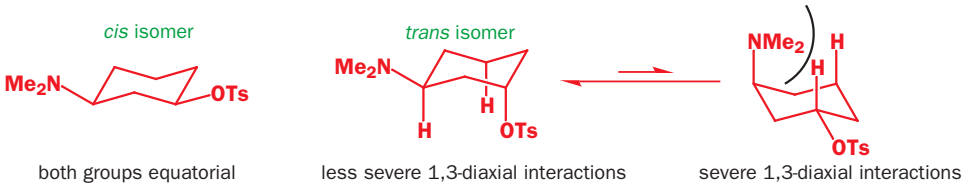
Fragmentations are controlled by stereochemistry

In the last chapter we introduced you to the idea that the control of rearrangements can be stereoelectronic in origin—if a molecule is to rearrange, orbitals have to be able to overlap. This means that, for a Beckmann *rearrangement*, the migrating group has to be *trans* to the leaving group. Not surprisingly, the same is true for Beckmann fragmentations like the one at the end of the last section, where the green fragmenting bond is *trans* to the leaving group.

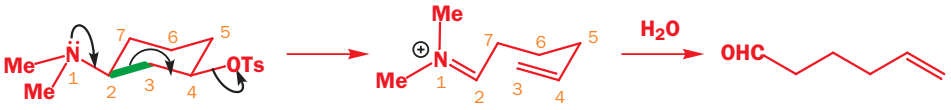
Before we extend these ideas any further, consider these two quite different reactions of quite similar compounds.



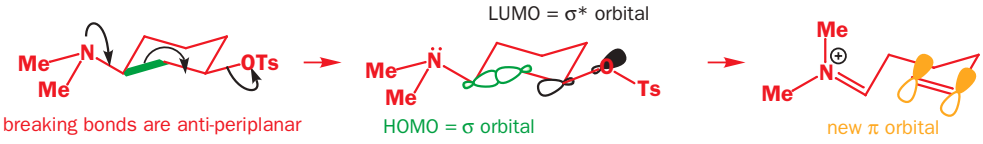
Just as with the rearrangements we looked at on p. 000, we need to draw these compounds in reasonable chair conformations in order to understand what is going on. In the *cis* isomer, both substituents can be equatorial; in the *trans* isomer one has to be axial, and this will be mainly the OTs group, since the two methyl groups of NMe_2 suffer greater 1,3-diaxial interactions.



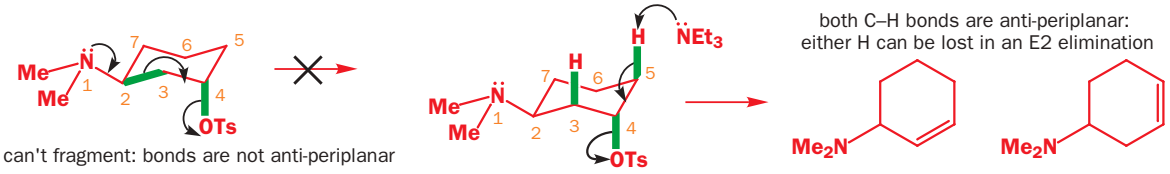
Now, the *cis* isomer has clearly undergone a fragmentation reaction and, as usual, numbering the atoms can help to identify the bond that breaks. The nitrogen lone pair pushes, the departing tosylate pulls, and the resulting iminium ion hydrolyses to the product aldehyde.



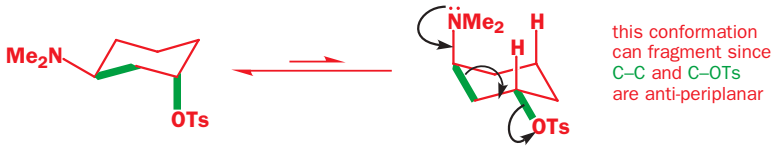
Yet the *trans* isomer only does this in very low yield. Mostly it eliminates TsOH to give a mixture of alkenes. Why? Well, notice that, in the *cis* isomer, the fragmenting bond is *trans* to the leaving group—indeed, it is both parallel and *trans*: in other words **anti-periplanar** to the leaving group. Electrons can flow smoothly from the breaking σ bond into the σ* of the C–OTs bond, forming as they do so, a new π bond.



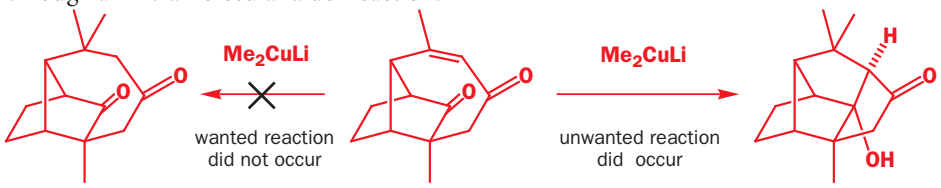
For the *trans* isomer, fragmentation of the most populated conformation is impossible because the leaving group is not anti-periplanar to any C–C bond. The only bonds anti-periplanar to OTs are C–H bonds, making this compound ideally set up for another reaction whose requirement for anti-periplanarity you have already met—E2 elimination.



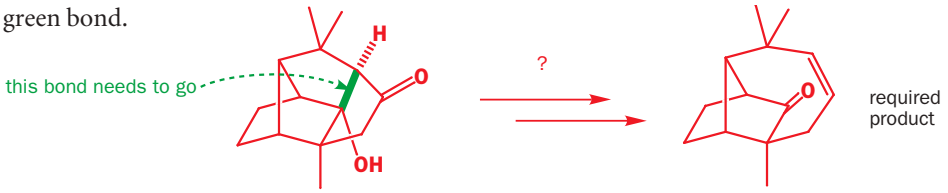
The other conformation can fragment because now the OTs is anti-periplanar to the right C–C bond, and this is probably where the 11% fragmentation product comes from.



When McMurry was making longifolene in the early 1970s, a fragmentation reaction saved the day when a conjugate addition reaction using a cuprate gave an unexpected cyclization product through an intramolecular aldol reaction.

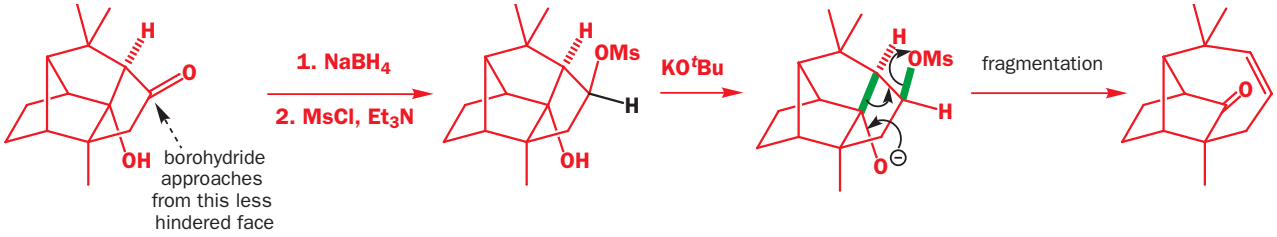


The actual compound McMurry wanted had the framework of the molecule on the left, but was to be transformed into the alkene below, so he needed to fragment the unexpected product at the green bond.



■ Another synthesis of longifolene is summarized later in this chapter.

Fortunately, reducing the carbonyl group gave a hydroxyl group anti-periplanar to the green bond and therefore set up for fragmentation. Making the hydroxyl a leaving group and treating with base gave the required compound by a fragmentation reaction.

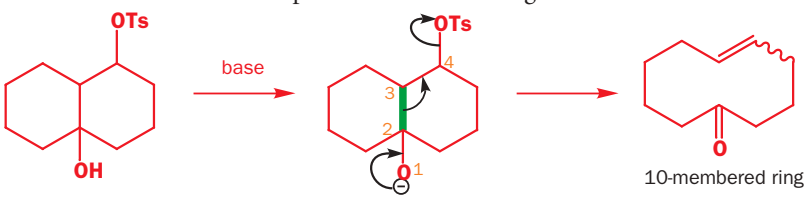


Ring expansion by fragmentation

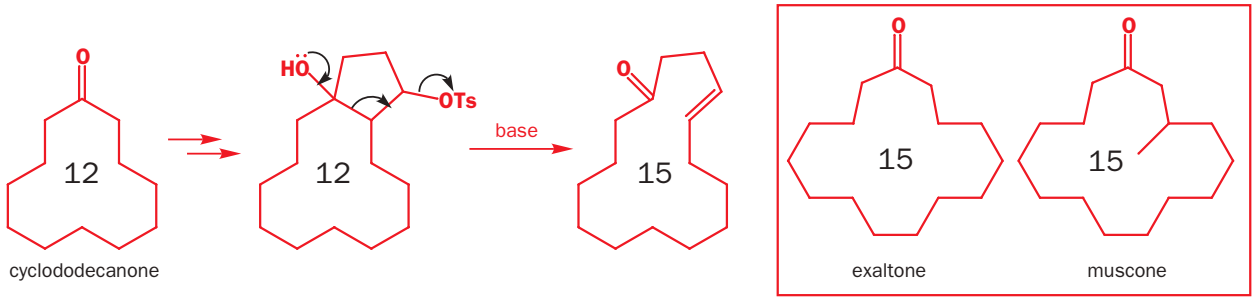
Ring sizes greater than eight are hard to make. Yet five- and six-membered rings are easy to make. Once you realize that a fused pair of six-membered rings is really a ten-membered ring with a bond across the middle, the potential for making medium rings by fragmentation becomes apparent.

■ This point was discussed in Chapter 18.

All you need to do is to make the bond to be broken the 2–3 bond in a 1, 2, 3, 4 electron source–sink arrangement and the ten-membered ring should appear out of the wreckage of the fragmentation. Here is an example—a decalin that fragments to a ten-membered ring.



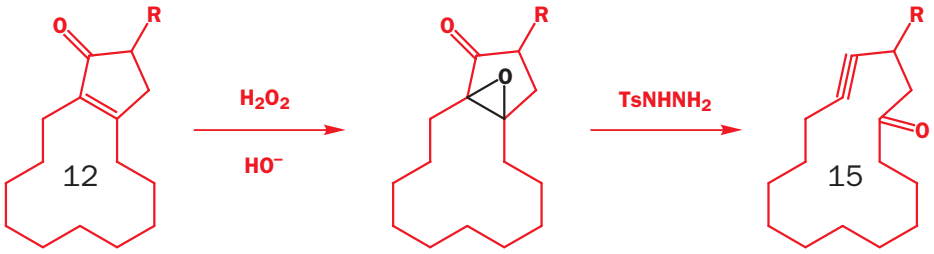
Muscone and exaltone are important perfumery compounds with hard-to-make 15-membered ring structures. Cyclododecanone is commercially available: addition of a fused five-membered ring and fragmentation of the 12,5-ring system is a useful route to these 15-membered ring compounds.



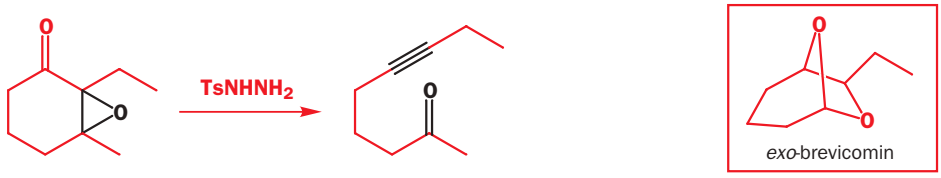
■ Albert Eschenmoser (1925–), working at the ETH in Zurich, synthesized vitamin B_{12}, a cobalt complex and at the time the most complicated molecule yet made, in an unusual international collaboration with Woodward at Harvard.

In the late 1960s, the Swiss chemist Albert Eschenmoser discovered an important reaction that can be used to achieve similar ring expansions and that now bears his name, the **Eschenmoser fragmentation**. The starting material for an Eschenmoser fragmentation is the epoxide of an α,β-unsaturated ketone. The fragmentation happens when this epoxy-ketone is treated with tosylhydrazine, and one of the remarkable things about the product is that it is an alkyne. The fragmentation happens across the epoxide (shown in black), and the product contains both a ketone (in a different place to the ketone in the starting material) and an alkyne. You can see how in this case hydrogenation of the triple bond can again give muscone (R = Me) or exaltone (R = H).

■ Electron-poor double bonds can be epoxidized with basic hydrogen peroxide. See Chapter 23.

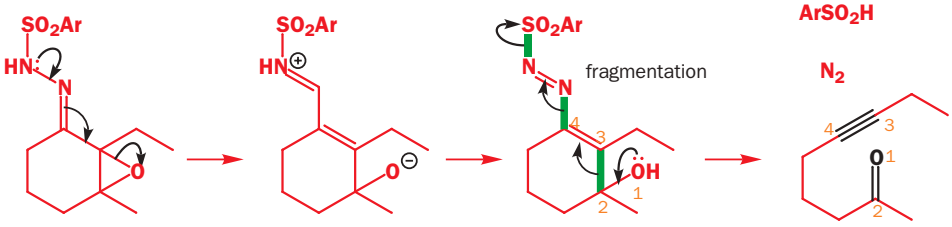


The Eschenmoser fragmentation does not have to be a ring expansion, and it is a useful synthetic method for making keto-alkynes. The following reaction, which we will use to discuss the fragmentation's mechanism, was used to make an intermediate in the synthesis of an insect pheromone, *exo*-brevicomin.



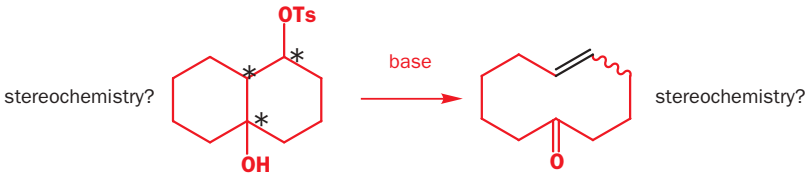
The reaction starts with formation of the tosylhydrazone from the epoxy-ketone. The tosylhydrazone is unstable with respect to opening of the epoxide in an elimination reaction, and it is this elimination that sets up the familiar 1, 2, 3, 4 system ready for fragmentation. The 'push' comes from the newly created hydroxyl group, and the 'pull' from the irresistible concerted loss of a good leaving group (Ts^-) and an even better one (N_2). Notice how all the (green) bonds that break are parallel to one another, held anti-periplanar by two double bonds. Perfect!

▶ The sulfur-containing leaving group here is not toluenesulfonate (tosylate, $ArSO_3^-$ or TsO^-) but toluenesulfinate ($ArSO_2^-$ or Ts^-), giving toluenesulfinic acid (TsH or $ArSO_2H$), not toluenesulfonic acid (TsOH or $ArSO_3H$) as a by-product.



More on stereochemistry and fragmentations

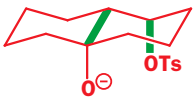
You saw, at the beginning of the last section, a ring expansion reaction of a decalin.



Now, the story of this ring expansion is a little more complex than we led you to believe, because the starting material has three stereogenic centres (*) and hence can exist as four diastereoisomers: two *trans*-decalins and two *cis*-decalins. What is more, the product has a double bond in a ten-membered ring: will it be *cis* or *trans*? (Both are possible—see Chapter 31.)

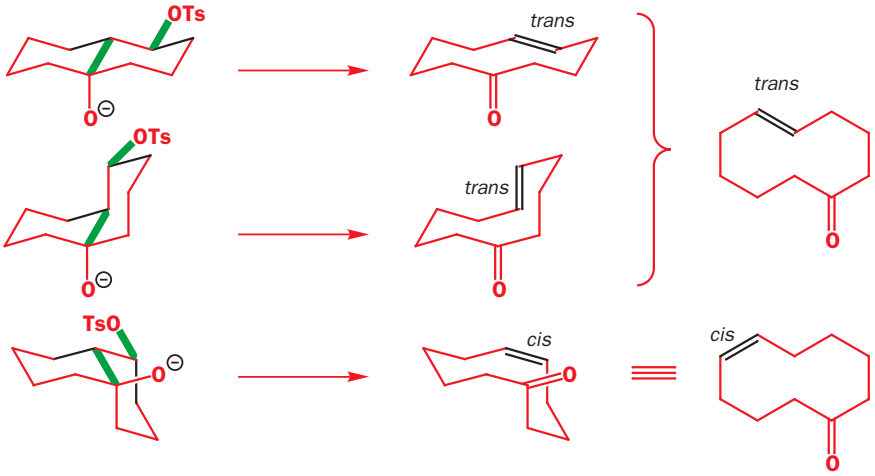
■ We discussed the conformations of decalins in Chapter 18.

One of the four diastereoisomers of starting material cannot place the tosylate anti-periplanar to the ring-fusion bond, so it can't fragment.



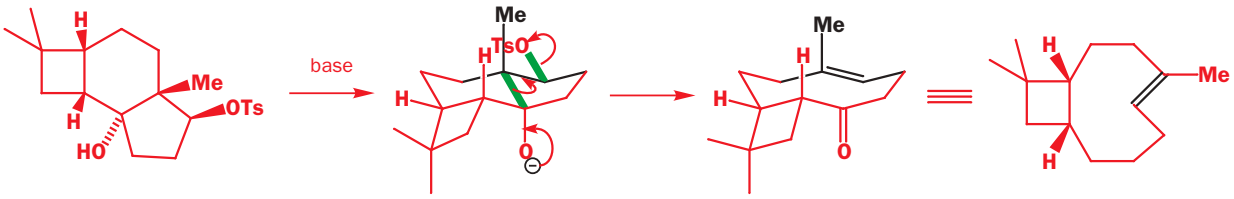
green bonds not anti-periplanar: no fragmentation possible

The other three diastereoisomers all can, but two of them give a *trans* double bond while the third gives *cis*.

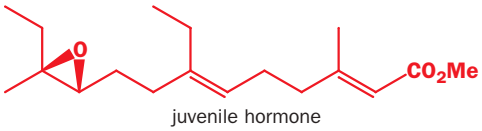


Looking at the alignment of the bonds that end up flanking the double bond in the product shows you where the geometrical isomers come from: these are the black bonds in the starting material, and are *trans* across the forming π system in the first two isomers and *cis* in the third. Fragmentations are stereospecific with regard to double bond geometry, much as E2 elimination reactions are.

Corey applied this stereospecificity in conjunction with a ring expansion reaction to make the natural product caryophyllene. Caryophyllene is a bicyclic molecule with a nine-membered ring containing an *E* trisubstituted double bond. The right relative stereochemistry in the starting material leads both to fragmentation of the right bond and to formation of the alkene with the right stereochemistry.

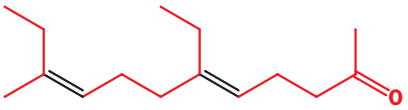


One of the most spectacular demonstrations of the use of fragmentation was the 1968 synthesis of juvenile hormone (a compound you met in Chapter 31) by chemists at Syntex, an American pharmaceutical company.

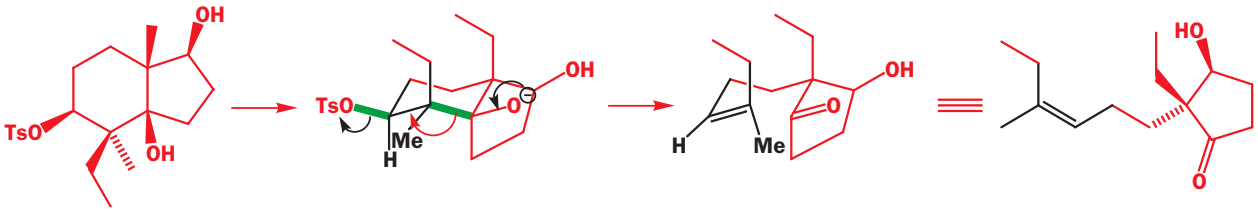


juvenile hormone

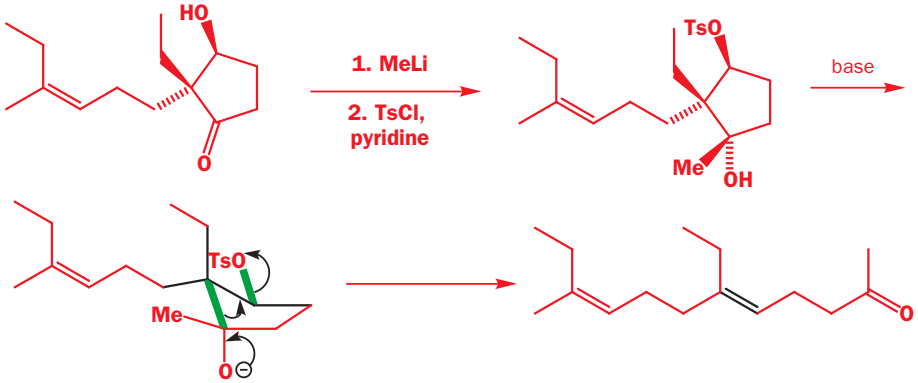
The major challenge in making juvenile hormone is the three trisubstituted double bonds (one of which ends up as an epoxide), and the initial target was to make the related aldehyde, which contains two of them.



The Syntex chemists reasoned that, if this methyl ketone could be made stereospecifically by fragmenting a cyclic starting material, the (hard-to-control) double bond stereochemistry would derive directly from the (easier-to-control) relative stereochemistry of the cyclic compound. The starting material they chose was a 5/6-fused system, which fragments to give one of the double bonds.



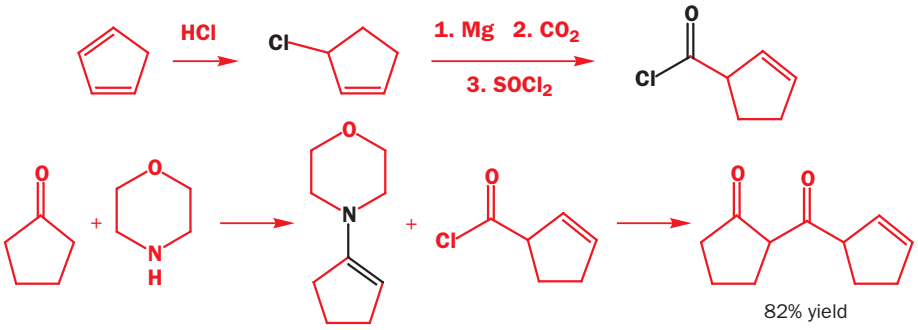
The product of this reaction is prepared for another fragmentation by addition of methyllithium (you might like to consider why you get this diastereoisomer) and tosylation of the less hindered secondary alcohol. Base promotes the second fragmentation.



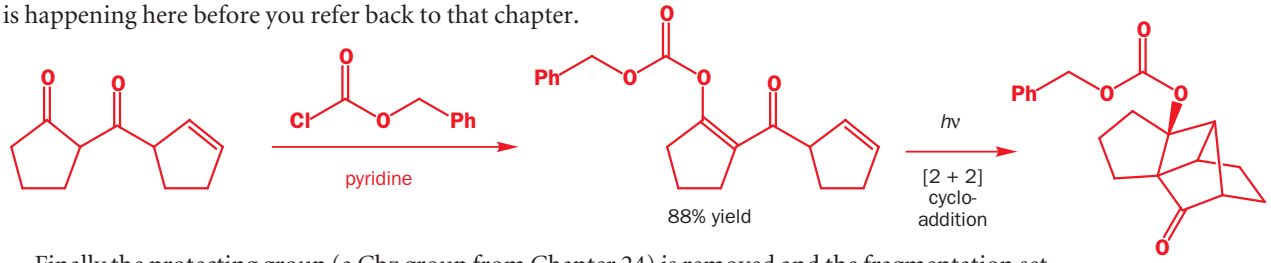
In the next chapter you will meet, among many other reactions, more fragmentations, but they will be radical fragmentations rather than ionic fragmentations, and involve homolytic cleavage of C–C bonds.

A second synthesis of longifolene

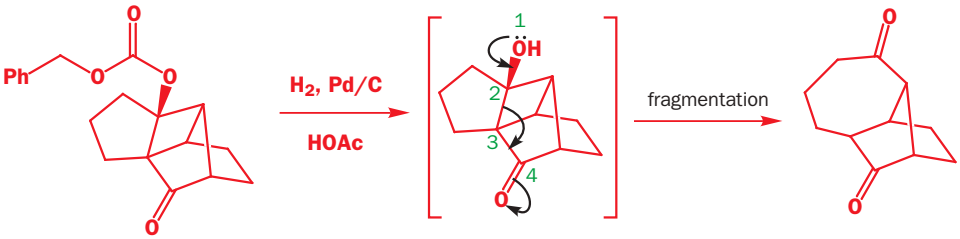
In Chapters 28 and 35 we introduced parts of Oppolzer's synthesis of longifolene. We now revise those reactions and bring the synthesis a stage further forward with a fragmentation reaction different from the one used earlier in the chapter for the same molecule. McMurry used a fragmentation to escape from a disaster. Oppolzer had planned to use one right from the start. The first stage in the synthesis involves the building of two five-membered rings into a 1,3-diketone.



Next the enol ester of the 1,3-diketone forms a new four-membered ring by a [2 + 2] photocycloaddition. This reaction appears in Chapter 35 but you are invited to work out for yourself what is happening here before you refer back to that chapter.

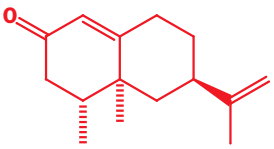


Finally the protecting group (a Cbz group from Chapter 24) is removed and the fragmentation set in motion. The four-membered ring is cleaved and the ring system of longifolene revealed. You might like to compare this route with McMurry's route described earlier in this chapter.



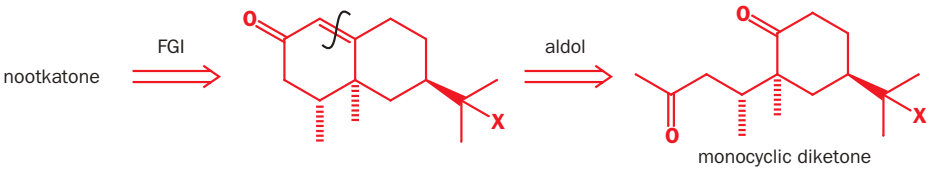
The synthesis of nootkatone

In the 1970s it was supposed that the characteristic sharp fruity scent and flavour of grapefruit came mainly if not entirely from a simple bicyclic enone called nootkatone. There was quite a rush to synthesize this compound in various laboratories and a remarkable feature of many successful syntheses was the use of fragmentation reactions. We shall describe parts of three syntheses involving the fragmentation of a six-, a four-, and a three-membered ring.



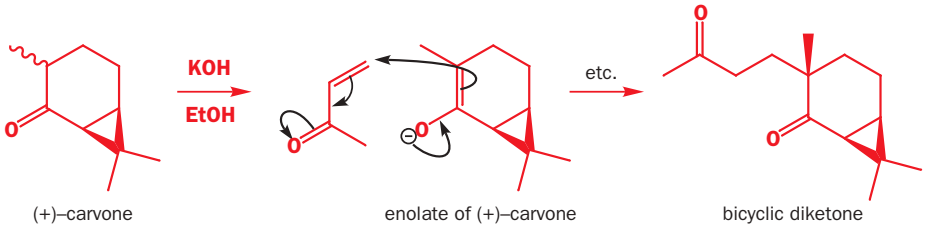
nootkatone
supposed flavour
principle of grapefruit

Most syntheses make the side-chain alkene by an elimination reaction so the first 'disconnection' is an FGI adding HX back into the alkene. The last C–C bond-forming operation in most syntheses is an intramolecular aldol reaction to make the enone so that can be disconnected next. It is the starting material for the aldol, a simple monocyclic diketone, which is usually made by a fragmentation reaction because this is a good way to set up the stereochemistry.

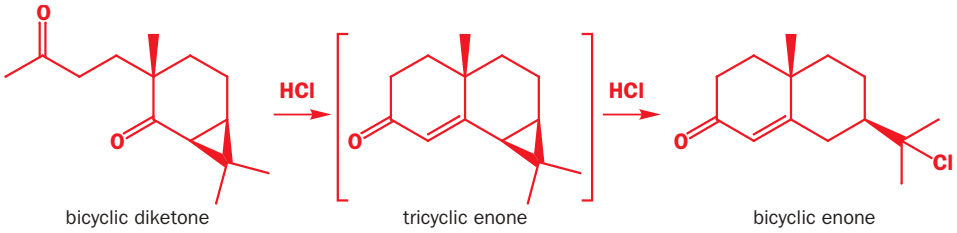


Fragmentation of a three-membered ring

This synthesis does not look as though it will lead to nootkatone because the fragmentation product requires a great deal of development. It has the advantage that the stereochemistry is correct at one centre at least. The sequence starts from natural (+)-carvone: conjugate addition of the enolate to butenone without control leads to a bicyclic diketone with one extra stereogenic centre. The enone adds to the bottom face of the enolate opposite the dimethylcyclopropane ring so the methyl group is forced upwards.

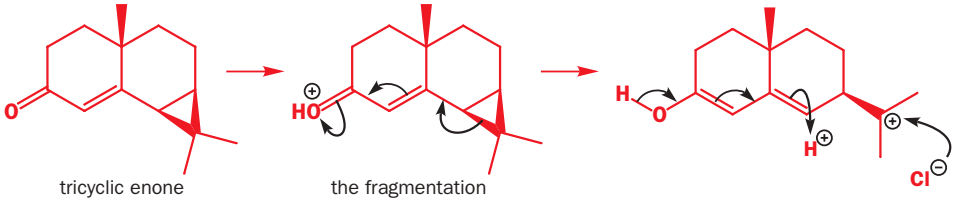


Now the diketone is cyclized in HCl to give a bicyclic enone. A new six-membered ring has been formed but the old three-membered ring has disappeared. First, an intramolecular aldol reaction closes the new six-membered ring to form an enone and then the stage is set for a fragmentation.



bicyclic diketone tricyclic enone bicyclic enone

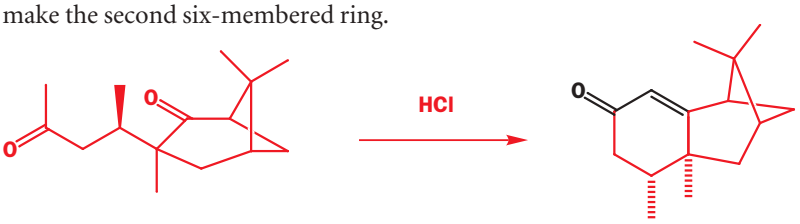
The fragmentation is pulled by the enone (with some help from the acid) and pushed by the stability of the tertiary carbocation as well as the release of strain as the single bond that is fragmented is in a three-membered ring. The fragmentation product is an enol on the left and a carbocation on the right. Addition of a proton to the end of the enol and a chloride ion to the cation gives the bicyclic enone. The chloroalkyl side chain must be on the top of the molecule because only one of the C–C bonds in the three-membered ring has been broken and the remaining bond cannot change its stereochemistry. The further development of this compound into nootkatone is beyond the scope of this book.



tricyclic enone the fragmentation

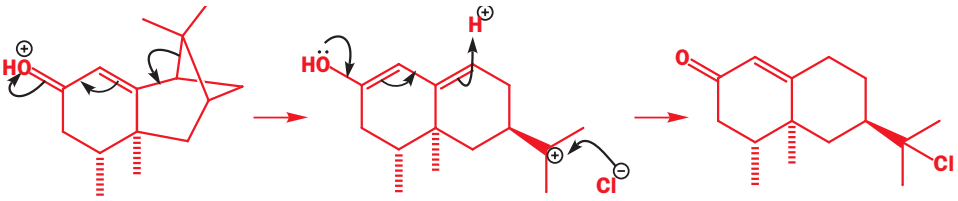
Fragmentation of a four-membered ring

This approach leads directly to the enone needed for nootkatone. A diketone prepared from a natural terpene (Chapter 51) is also treated with HCl and much the same reactions ensue except that the fragmentation now breaks open a four-membered ring. First, the intramolecular aldol reaction to make the second six-membered ring.



bicyclic diketone tricyclic enone

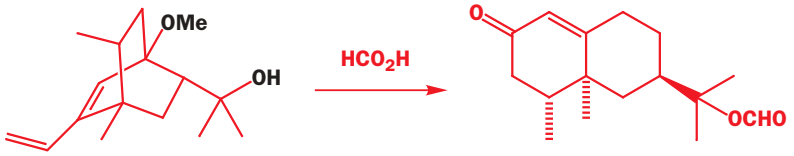
Now the fragmentation, which follows much the same course as the last one: the enone again provides the electron pull while the cleavage of a strained C–C single bond in a four-membered ring to give a tertiary carbocation provides the electron push. A simple elimination is all that is needed to make nootkatone from this bicyclic chloroenone.



Fragmentation of a six-membered ring

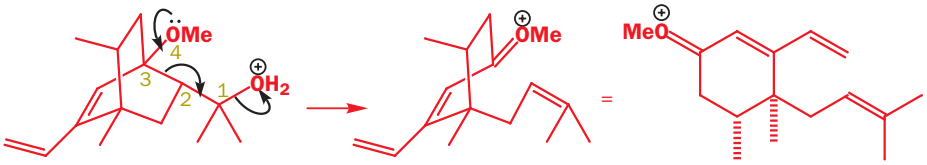
This chemistry is quite different from the examples we have just seen. The starting material has a bridged bicyclic structure and was made by a Diels–Alder reaction (Chapter 35). Fragmentation is

initiated by formic acid (HCO_2H), which protonates the tertiary alcohol and creates a tertiary carbocation. The ether provides the push. More serious electronic interactions are needed in this fragmentation as the C–C bond being broken is not in a strained ring.

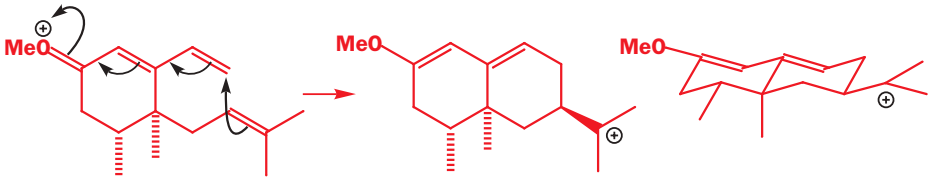


50% yield

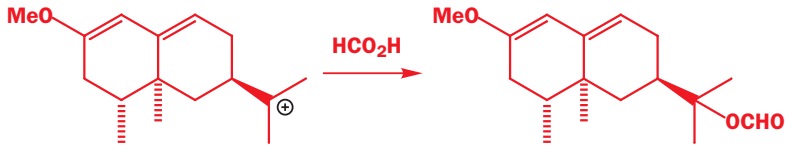
The yield of 50% is not wonderful but there is obviously a lot of chemistry going on here so it is acceptable when so much is being achieved. The first stage is the fragmentation itself. Drawing the product first of all in the same shape as the starting material and then redrawing, to ensure that we don't make a mistake, we discover that we are well on the way to nootkatone. Note that the stereochemistry of the two methyl groups comes directly from the stereochemistry of the starting materials and no new stereogenic centres are created in the fragmentation. Though one six-membered ring is fragmented, another remains.



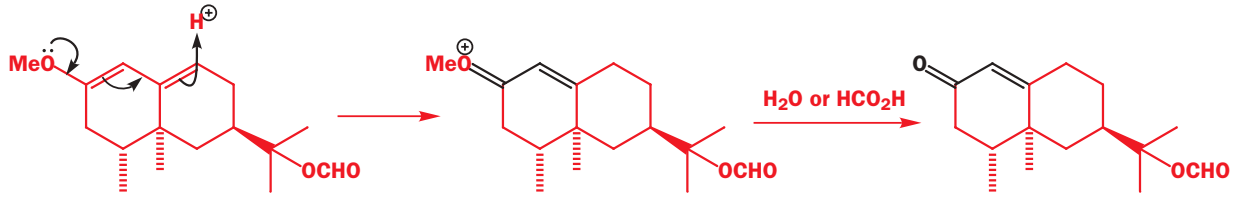
The first formed product now cyclizes to form the second six-membered ring. This recreates a carbocation at the tertiary centre like the one that set off the fragmentation as the more nucleophilic end of the isolated alkene attacks the end of the conjugate electrophile. This is a thermodynamically controlled reaction with the new stereogenic centre choosing an equatorial substituent.



The cation picks up the only nucleophile available—the very weak formic acid. This gives the product of the fragmentation, which contains two unstable functional groups—a tertiary formate ester and an enol ether—and this product is not isolated from the reaction mixture.

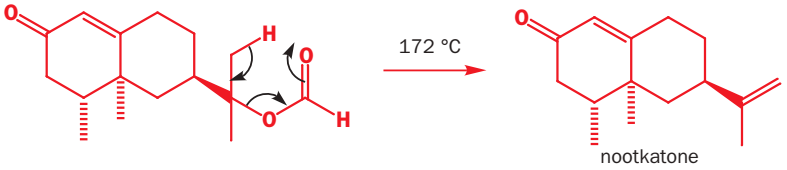


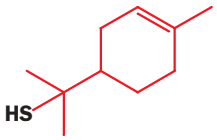
Protonation and hydrolysis of the extended enol ether to release the enone may occur during work-up and the stable enone is the first compound that can be isolated. The 50% yield of this compound represents a much better yield in four steps: fragmentation, olefin cyclization, addition of formic acid, and enol ether hydrolysis.



Completion of the synthesis of nootkatone simply requires pyrolysis of the formate ester in

refluxing 2,4,6-trimethyl pyridine (b.p. 172 °C). The reaction is a *syn* elimination by a pericyclic mechanism and it gives nootkatone in 79% yield.





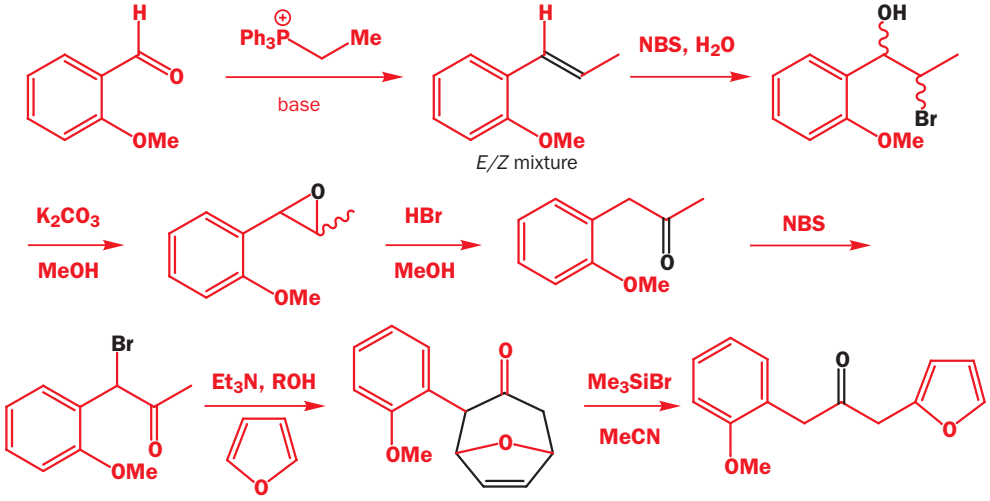
true flavouring principle of grapefruit

■ We first introduced this intense taste in Chapter 1 and we will discuss sulfur compounds in Chapter 46.

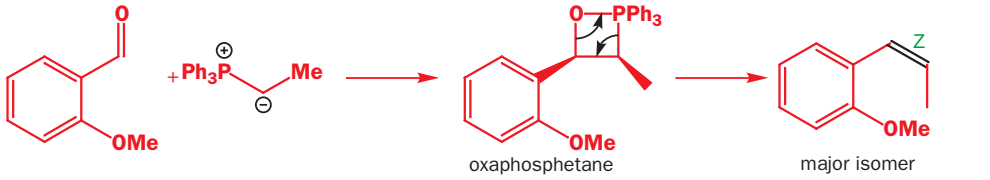
The synthesis of nootkatone occupied many chemists for some years and has given us some excellent examples of fragmentation reactions. However, the synthetic samples of nootkatone failed to deliver the intense grapefruit taste and smell of the material from grapefruits. The reason is simply that nootkatone is not the flavour principle of grapefruit! The samples of nootkatone isolated from grapefruit contained minute traces of the true flavour principle—a simple thiol. Humans can detect 2×10^{-5} p.p.b. (yes, parts per *billion*) of this compound, so even the tiniest trace is very powerful. At least the syntheses allowed chemists to correct an error.

A revision example: rearrangements and fragmentation

We shall end this chapter with an example that involves many of the reactions we have been discussing in recent chapters. It culminates in a fragmentation but takes in two different rearrangements (Chapter 37) on the way as well as a cycloaddition (Chapter 35) and an electrocyclic reaction (Chapter 36). Here is the whole scheme with the main changes in each step highlighted in black. You might cast your eye over the scheme and see in general terms what sort of reaction happens at each step (substitution, rearrangement, etc.).

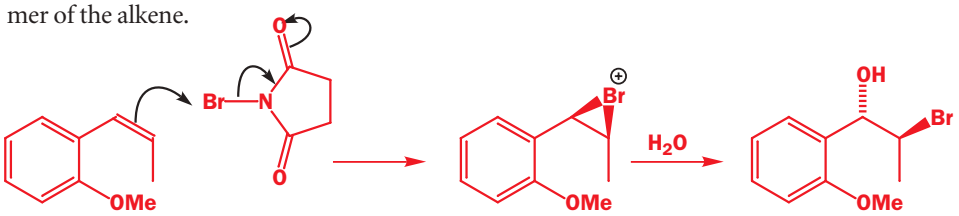


The first step is a simple Wittig reaction with an unstabilized ylid (Chapter 31), which we expect to favour the *Z*-alkene. It does but, as is common with Wittig reactions, an *E*/*Z* mixture is formed but not separated as both isomers eventually give the same compound. The reaction is kinetically controlled and the decomposition of the oxaphosphetane intermediate is in some ways like a fragmentation.



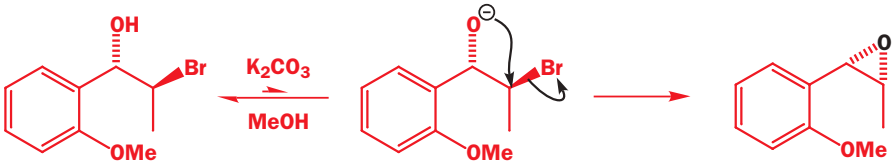
Now the alkene is converted into an epoxide by a slightly unusual sequence. Bromination with NBS (*N*-bromosuccinimide) in water gives a mixture of bromohydrins by electrophilic addition to the

double bond. The reaction occurs through a bromonium ion and is stereospecifically *anti* on each isomer of the alkene.

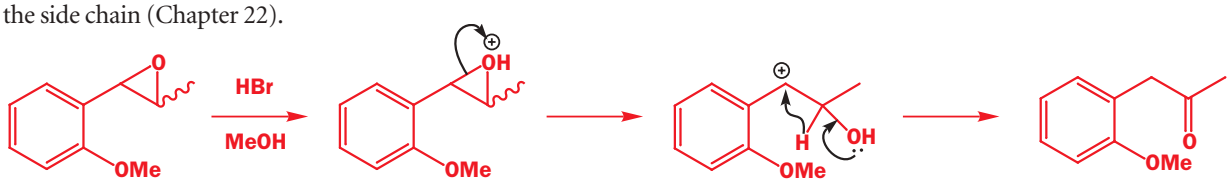


■ NBS is a radical generator in nonpolar solvents as we shall see in Chapter 40, but in polar solvents, especially water, it supplies electrophilic bromine, Chapter 20.

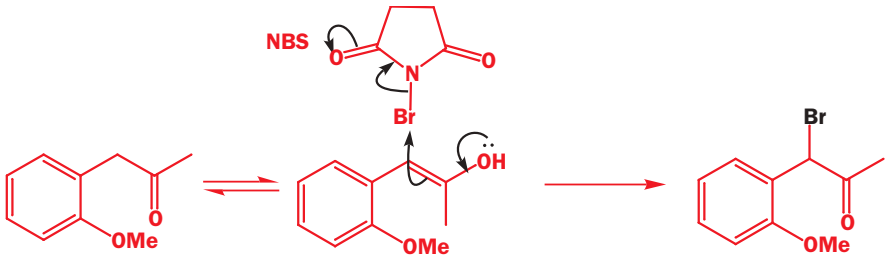
Next, the bromohydrin is treated with base and an intramolecular S_N2 reaction (Chapter 17) closes the epoxide ring. This too is stereospecific and the major isomer only is shown. The mixture of epoxides is a result of the *E/Z*-alkene mixture. Potassium carbonate is too weak a base to generate much of the alkoxide anion but the cyclization may still go this way in methanol. In Chapter 41 you will learn of an alternative type of catalysis by weak bases.



We saw some epoxide rearrangements in Chapter 37 but this reaction seems rather tame by comparison. The epoxide opens in acid to give the more stable (secondary and benzylic) of the two possible carbocations and then a hydrogen atom migrates with the pair of electrons from the C–H bond ('hydride shift') to give a ketone. The rearrangement is useful because it allows the synthesis of aryl ketones, which cannot easily be made by a Friedel–Crafts reaction since the carbonyl group is in the wrong position on the side chain (Chapter 22).

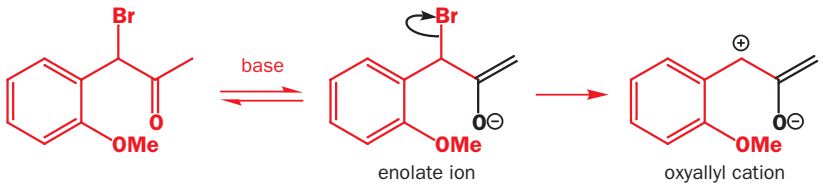


The ketone is then brominated, also with NBS, in a regioselective manner. The more conjugated enol is formed between the carbonyl group and the aromatic ring and this is attacked electrophilically by the bromine atom of the NBS (Chapter 20).

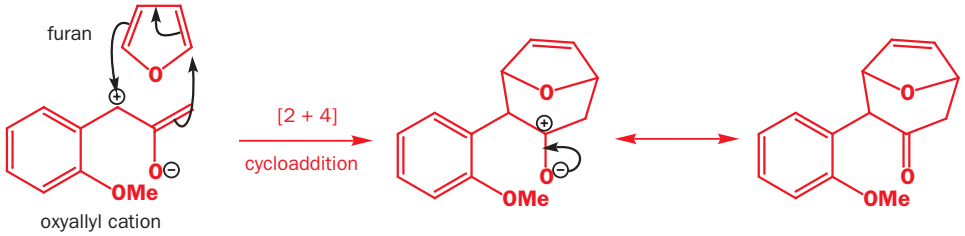


Cycloaddition and rearrangement

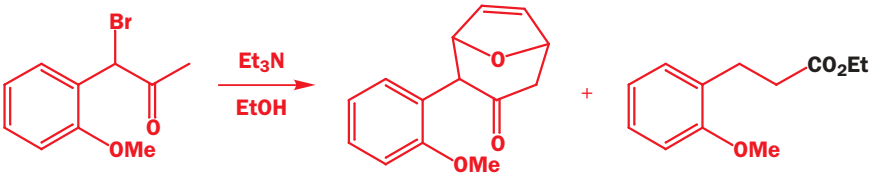
Now comes the most interesting step in the whole process—a step that unites a cycloaddition and a rearrangement and sets the scene for a fragmentation. The idea was to treat the bromoketone with base to make an oxyallyl cation as an unstable intermediate.



The oxyallyl cation with its two electrons delocalized over the allylic system would add to furan in a [2 + 4] cycloaddition to give a new cation stabilized by the oxyanion or, in more familiar guise, a ketone. The reaction was supposed to go like this.

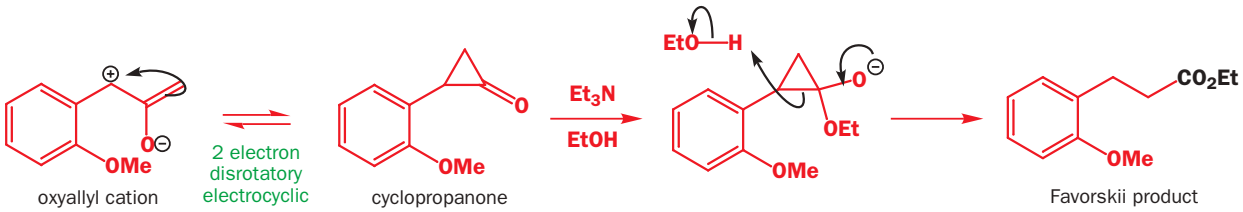


The best base turned out to be the tertiary amine Et_3N and the reaction had to be performed in alcoholic solution as alcohols were the only solvents able to keep the organic and ionic materials in solution. However, a substantial amount of a by-product was formed in ethanol—evidently the product of a Favorskii rearrangement.

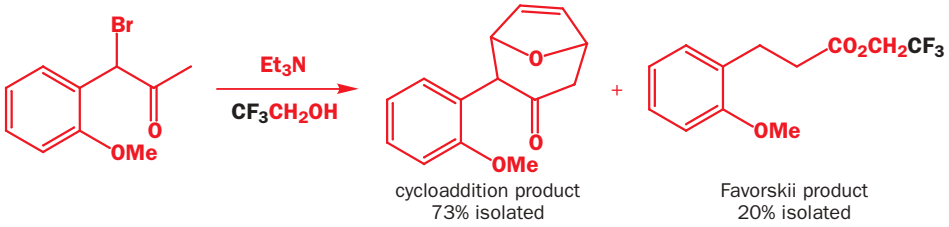


■ This is an example of GAC (general acid catalysis) as explained in Chapter 41.

What is happening here is that the oxyallyl cation is in equilibrium with the cyclopropanone by an electrocyclic reaction (Chapter 36) and the alcohol is capturing this unstable ketone by nucleophilic addition. Hemiacetals of cyclopropanones form spontaneously in alcoholic solution (Chapter 6) because of the strain in the ketone. The anion of the hemiacetal decomposes by cleavage of a C–C bond to release what would be the more stable of the two carbanions, that is, the benzylic carbanion. This carbanion is not actually formed as it is protonated by the alcohol as it leaves.



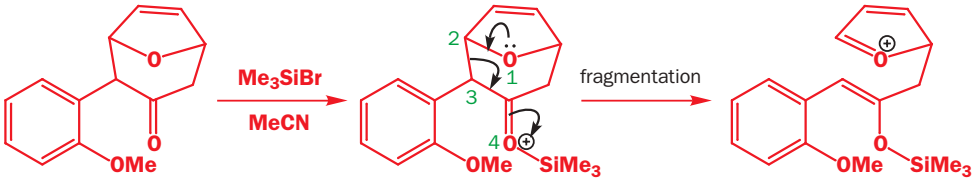
So how can the cycloaddition be promoted at the expense of the Favorskii rearrangement? Nothing can be done about the equilibrium between the oxyallyl anion and the cyclopropanone—that's a fact of life. The answer is to reduce the nucleophilicity of the alcohol by using trifluoroethanol instead of ethanol. Under these conditions the major product is the cycloadduct, which can be isolated in 73% yield.



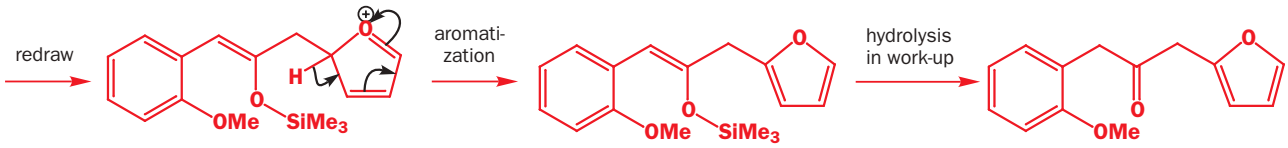
The two compounds can easily be separated as they have completely different structures and are not stereoisomers or indeed isomers of any kind. Now it is time for the fragmentation reaction on the cycloadduct.

The fragmentation reaction

The cycloadduct is fragmented with Me_3SiBr in acetonitrile. The electrophilic silicon atom attacks the ketone and the furan oxygen atom provides the electronic push. These two groups have the 1,4 relationship necessary for a fragmentation. First of all, we shall draw the product in the same way as the starting material—this is a good tip in a complicated mechanism. The product may look odd but we can redraw it more realistically in a moment.



The redrawn product is a silyl enol ether (Chapter 21) at one end and an oxonium ion at the other. Simple proton removal and hydrolysis of the silyl enol ether in the work-up reveals a furan that can be isolated in 81% yield as the true product.

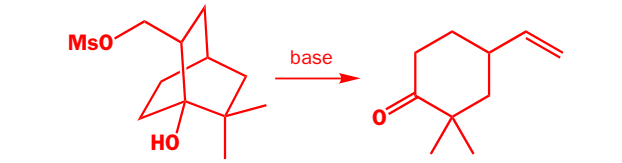


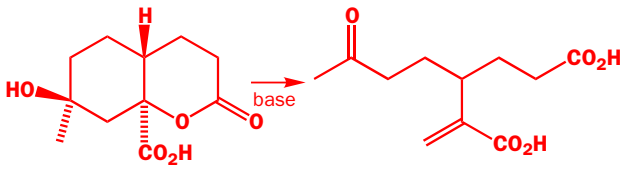
This product is worth a close look. The three-atom chain joining the two aromatic rings has the ketone on the middle carbon atom and it is therefore on C2 (β) with respect to *both* rings. This is the difficult position for a carbonyl group and so this product cannot be made by a Friedel–Crafts reaction on either ring.

Fragmentation reactions cleave C–C single bonds by a combination of electron push and electron pull so that both electrons in the bond move in the same direction as the bond breaks. In the next chapter we shall see reactions that break C–C bonds in a quite different way. No electron push or pull is required because one electron goes one way and one the other. These are radical reactions.

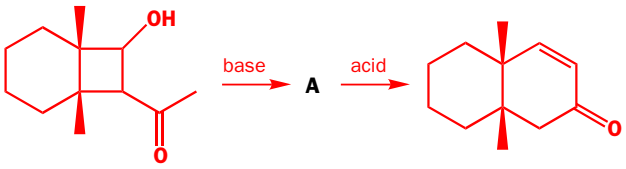
Problems

1. Just to check your skill at finding fragmentations by numbers, draw a mechanism for each of these one-step fragmentations in basic solution (with an acidic work-up).

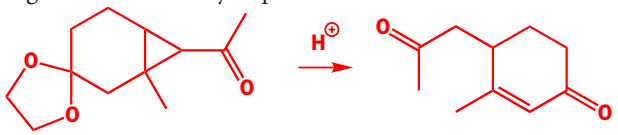




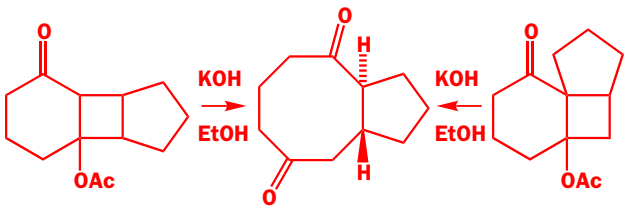
2. Treatment of this hydroxy-ketone with base followed by acid gives the enone shown. What is the structure of the intermediate A, how is it formed, and what is the mechanism of the formation of the final product?



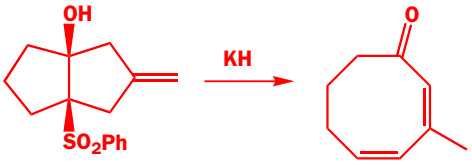
3. Suggest a mechanism for this reaction that involves a fragmentation as a key step.



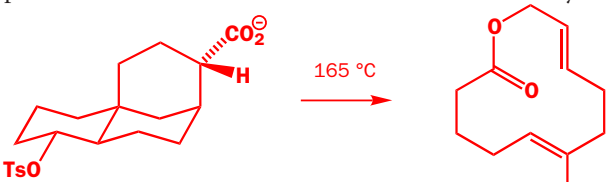
4. Explain why both of these tricyclic ketones fragment to the same diastereoisomer of the same cyclo-octadione.



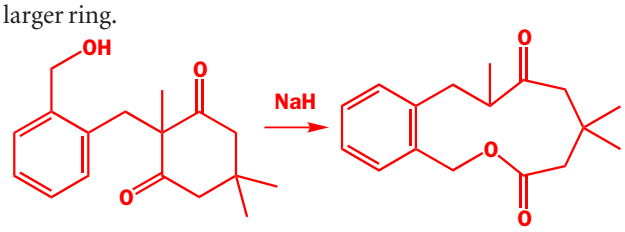
5. Suggest a mechanism for this ring expansion in which fragmentation is one step.



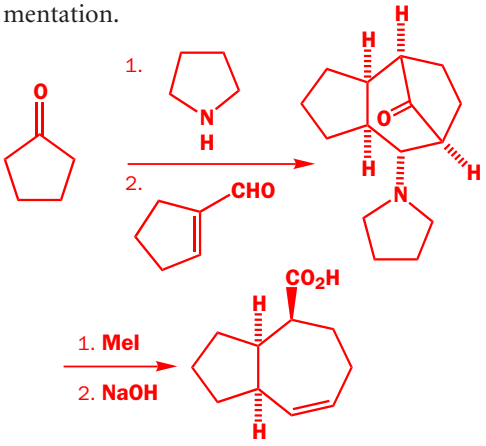
6. Suggest a mechanism for this fragmentation and explain the stereochemistry of the double bonds in the product. This is a tricky problem but find the mechanism and the stereochemistry will follow.



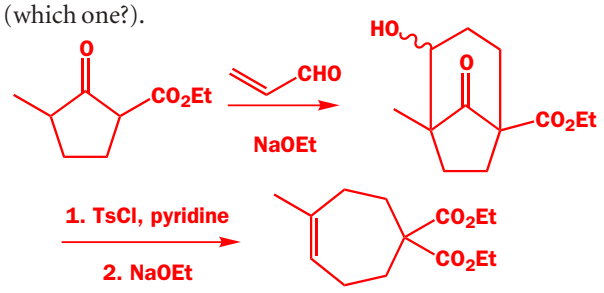
7. Suggest a mechanism for this reaction and explain why the molecule is prepared to abandon a stable six-membered ring for a larger ring.



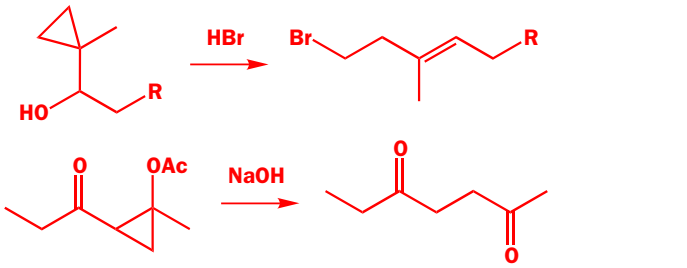
8. Give mechanisms for these reactions, commenting on the fragmentation.



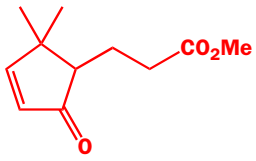
9. Propose mechanisms for the synthesis of the bicyclic intermediate and explain why only one diastereoisomer fragments (which one?).



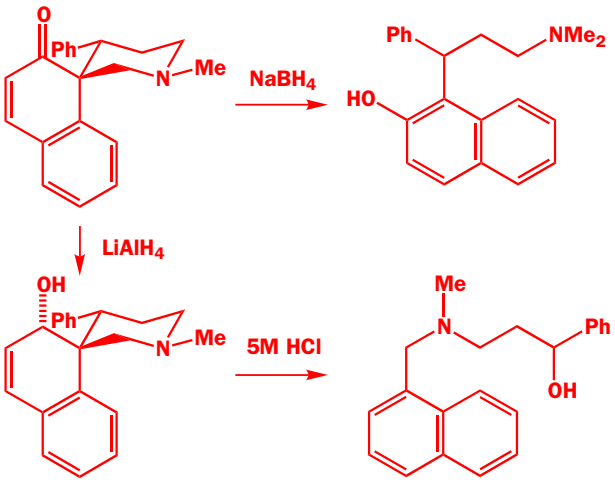
10. Suggest mechanisms for these reactions, explaining the alkene geometry in the first case. Do you consider that they are fragmentations?



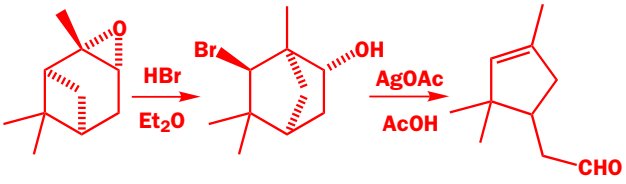
11. What steps would be necessary to carry out an Eschenmoser fragmentation on this ketone and what products would be formed?



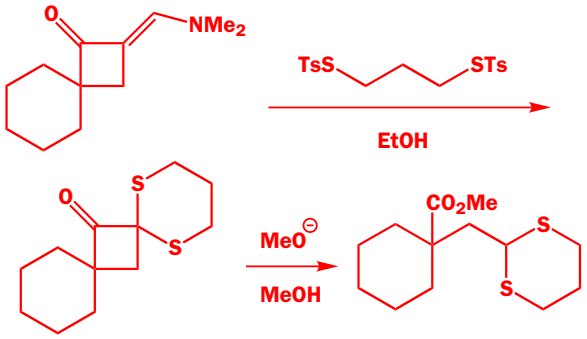
12. These related spirocyclic compounds give different naphthalenes when treated with sodium borohydride or with 5M HCl. Each reaction starts with a different fragmentation. Give mechanisms for the reactions and explain why the fragmentations are different. Treatment of the starting ketone with $LiAlH_4$ instead of $NaBH_4$ gives the alcohol below without fragmentation. Comment on the difference between the two reagents and the stereochemistry of the alcohol.



13. Revision content. Suggest mechanisms for these reactions explaining the stereochemistry.



14. You might not think that these reactions are truly fragmentations, but give the mechanisms anyway.



Radical reactions

39

Connections

Building on:

- Conjugate addition ch10 & ch23
- Energy profile diagrams ch13
- Nucleophilic substitution ch17
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling stereochemistry ch16, ch33, & ch34
- Retrosynthetic analysis ch30
- Diastereoselectivity ch33–ch34

Arriving at:

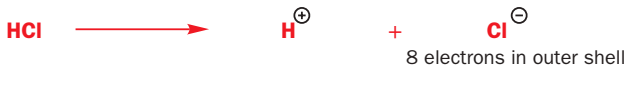
- Radicals are species with unpaired electrons
- Radical reactions follow different rules to those of ionic reactions
- Bond strength is very important
- Radicals can be formed with Br, Cl, Sn, and Hg
- Efficient radical reactions are chain reactions
- There are electrophilic and nucleophilic radicals
- Radicals favour conjugate addition
- Cyclization is easy with radical reactions

Looking forward to:

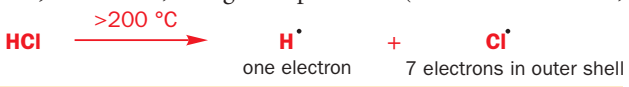
- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoelectronics ch42
- Main group chemistry ch46–ch47
- Natural products ch51
- Polymerization ch52

Radicals contain unpaired electrons

You may remember that at the beginning of Chapter 8 we said that the cleavage of H–Cl into H^+ and Cl^- is possible in solution only because the ions that are formed are solvated: in the gas phase, the reaction is endothermic with $\Delta G = +1347\ kJ\,mol^{-1}$, a value so vast that even if the whole universe were made of gaseous HCl at 273 K, not a single molecule would be dissociated into H^+ and Cl^- ions.



At temperatures above about 200 °C, however, HCl does begin to dissociate, but not into ions. Instead of the chlorine atom taking both bonding electrons with it, leaving a naked proton, the electron pair forming the H–Cl bond is shared out between the two atoms. ΔG for this reaction is a much more reasonable $+431\ kJ\,mol^{-1}$ and, at high temperatures (above about 200 °C, that is), HCl gas can be dissociated into H and Cl atoms.



▶ The single, unpaired electron possessed by each atom is represented by a dot. The Cl atom, of course, has another three pairs of electrons that are not shown.

Heterolysis and homolysis

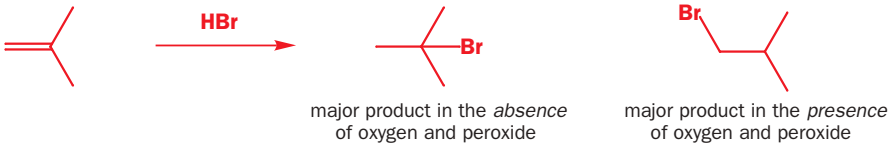
- When bonds break and one atom gets both bonding electrons, the process is called **heterolysis**

  The products of heterolysis are, of course, **ions**.
- When bonds break and the atoms get one bonding electron each, the process is called **homolysis**

  The products of homolysis are **radicals**, which may be atoms or molecules, and contain an unpaired electron.

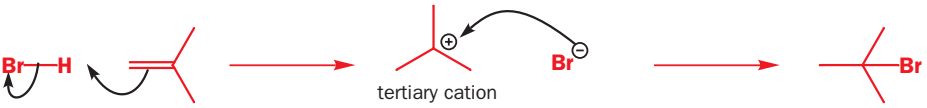
It was, in fact, a reaction of a closely related molecule, hydrogen bromide, that was among the first to alert chemists to the possibility that radicals can be formed in chemical reactions even at ambient

temperatures, and that they have a distinct pattern of reactivity. In the 1930s, Morris Kharasch found that the regioselectivity of addition of H–Br to isobutene was dependent on whether or not oxygen and peroxides were present in the reaction mixture.



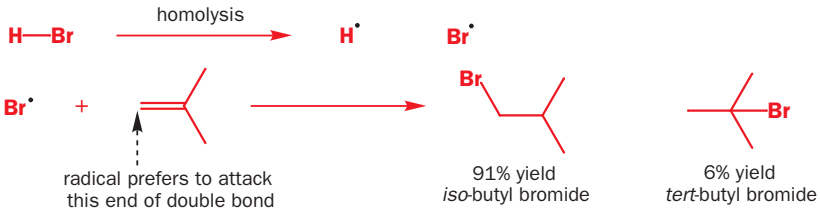
■ You should be familiar with this mechanism from Chapter 20.

It turns out that in the *absence* of peroxides the addition takes place by the type of (ionic) mechanism that you have already met. The tertiary bromide is formed because the intermediate, a tertiary cation, is more stable than the alternative primary cation.



▶ This scheme represents the process schematically: it is not the full mechanism of the reaction!

In the *presence* of peroxides, the mechanism is quite different. Homolysis of the H–Br takes place, and bromine radicals that attack the C=C double bond at its less hindered end are formed. Mostly isobutyl bromide is formed.



▶ Try to get a feel for bond strengths: we shall refer to them a lot in this chapter as they're very important to radical reactions. Compare this with the situation for ionic reactions, in which the strengths of the bonds involved are often much less important than polar effects (see the example on p. 000, for example).

What does the peroxide do? Why does its presence change the mechanism? The peroxide undergoes homolysis of the weak O–O bond extremely easily, and because of this it initiates a **radical chain reaction**. We said that H–Cl in the gas phase undergoes homolysis in preference to heterolysis: other types of bond are even more susceptible to homolysis. You can see this for yourself by looking at this table of bond dissociation energies (ΔG for X–Y → X• + Y•).

Bond X–Y	ΔG for X–Y → X• + Y•, kJ mol^{-1}	Bond X–Y	ΔG for X–Y → X• + Y•, kJ mol^{-1}
H–OH	498	CH_3–Br	293
H_3C–H	435	CH_3–I	234
H_3C–OH	383	Cl–Cl	243
H_3C–CH_3	368	Br–Br	192
H–Cl	431	I–I	151
H–Br	366	HO–OH	213
H–I	298	MeO–OMe	151
CH_3–Cl	349		

Dialkyl peroxides (dimethyl peroxide is shown in the table) contain the very weak O–O bond. The radicals formed by homolytic cleavage of these bonds, stimulated by a little heat or light, initiate what we call a 'radical chain reaction', which results in the formation of the Br• radicals, which add to the alkene's C=C double bond. We shall return to radical chain reactions and their mechanisms in detail later in this chapter.

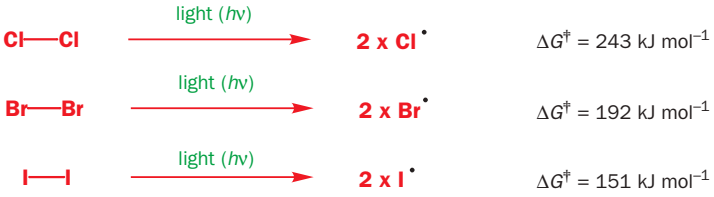
Radicals form by homolysis of weak bonds

■ It is not sufficient for light to be energetic enough to promote homolysis; the molecule must have a mechanism for absorbing that energy, and the energy must end up concentrated in the vibrational mode that leads to bond breakage. We shall not consider these points further: if you are interested, you will find detailed explanations in specialized books on photochemistry.

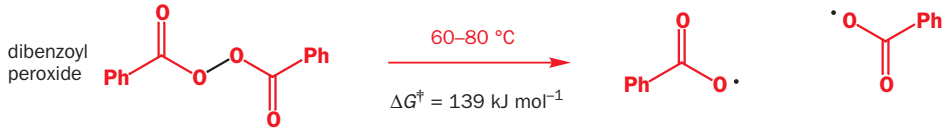
You've just met the most important way of making radicals: unpairing a pair of electrons by homolysis, making two new radicals. Temperatures of over 200 °C will homolyse most bonds; on the other hand, some weak bonds will undergo homolysis at temperatures little above room temperature. Light is a possible energy source for the homolysis of bonds too. Red light has associated with it 167 kJ mol^{-1}; blue light has about 293 kJ mol^{-1}. Ultraviolet (200 nm), with an associated energy of 586 kJ mol^{-1}, will decompose many organic compounds (including the DNA in skin cells: sunbathers beware!).

There are a number of compounds whose homolysis is particularly important to chemists, and the most important ones are discussed in turn below. They all have weak σ bonds, and generate radicals that can be put to some chemical use. The halogens are quite readily homolysed by light. These process are important in radical halogenation reactions that we shall discuss later.

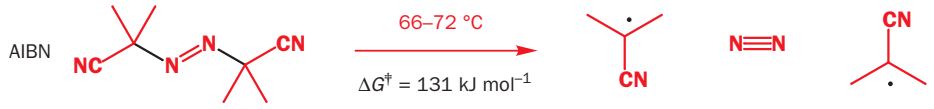
▶ $\Delta G^{\ddagger}$ is the activation energy for the reaction.



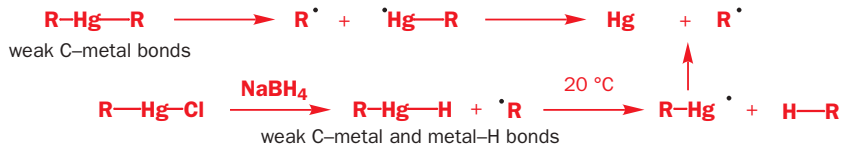
Dibenzoyl peroxide is an important compound because it can act as another initiator of radical reactions; we'll see why later. It undergoes homolysis simply on heating.



Another compound that is often used in synthetic reactions for the same reason (though it reacts with a different set of compounds) is AIBN (*azo*i*so*b*utyro*n*itrile).



Some organometallic compounds, for example organomercuries or organocobalts, have very weak carbon–metal bonds, and are easily homolysed to give carbon-centred radicals. Alkyl mercury hydrides are formed by reducing alkyl mercury halides, but they are unstable at room temperature because the Hg–H bond is very weak. Bonds to hydrogen never break to give radicals *spontaneously* because H• is too unstable to exist, but interaction with almost any radical removes the H atom and breaks the Hg–H bond. This is the process of hydrogen abstraction, which forms the next section of the chapter.



Radicals in cars

Radicals generated from another organometallic compound, tetraethyllead Et_4Pb, were the reason for adding this compound to petrol. These radicals react with other radical species involved in the pre-ignition of petrol vapour in internal combustion engines, and prevent the phenomenon known as 'knocking'. Nowadays simple organic compounds such as $MeOBu^t$ are used instead in 'green' petrol.

Radicals form by abstraction

Notice that we didn't put HBr on the list of molecules that form radicals by homolysis: relative to the weak bonds we have been talking about, the H–Br bond is quite strong (just about as strong as a C–C bond). Yet we said that Br• radicals were involved in the addition reaction we talked about on p. 000. These radicals are formed by the action of the alkoxy radicals (generated by homolysis of the peroxide) on HBr—a process known as **radical abstraction**. Here is the mechanism.

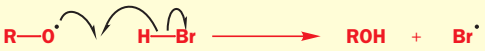
The peroxy radical RO• 'abstracts' H• from the HBr to give ROH, leaving behind a new radical Br•. We have described this process using arrows with 'half-heads' (also known as 'fish-hook arrows').

They indicate the movement of single electrons among orbitals, by analogy with our normal curly arrows, which indicate the movement of electron pairs.

Writing radical mechanisms

There is often more than one correct way of drawing a radical mechanism using half-headed arrows. For example, we could have represented the abstraction reaction shown above in either of these alternative ways.

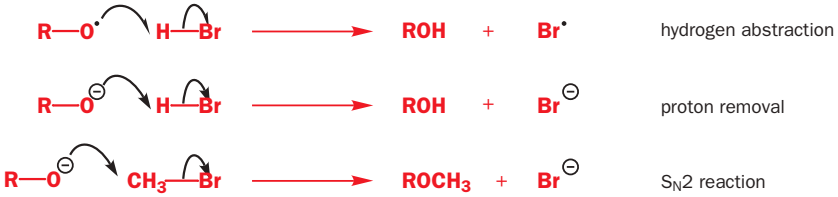
The full story shows that the odd electron on RO• pairs with one of the electrons in the H–Br bond while the other moves on to the bromine atom.



Because radical reactions always involve the reorganization of electron pairs, we can choose whether to show what happens to either or both of the members of each pair. In most examples in this book, we will draw arrows only in one direction.

▶ We use 'spin-paired molecule' to mean a 'normal' molecule, in which all the electrons are paired, in contrast with a radical, which has an unpaired electron.

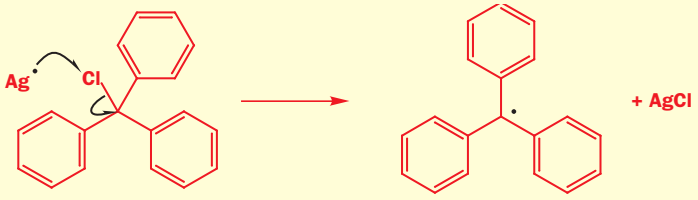
The ability of radicals to propagate by abstraction is a key feature of radical chain reactions, which we shall come to later. There is an important difference between homolysis and abstraction as a way of making radicals: homolysis is a reaction of a spin-paired molecule that produces *two* radicals; abstraction is a reaction of a radical with a spin-paired molecule that produces *one* new radical and a new spin-paired molecule. Radical abstractions like this are therefore examples of your first radical reaction mechanism: they are in fact substitution reactions at H and can be compared with proton removal or even with an S_N2 reaction.



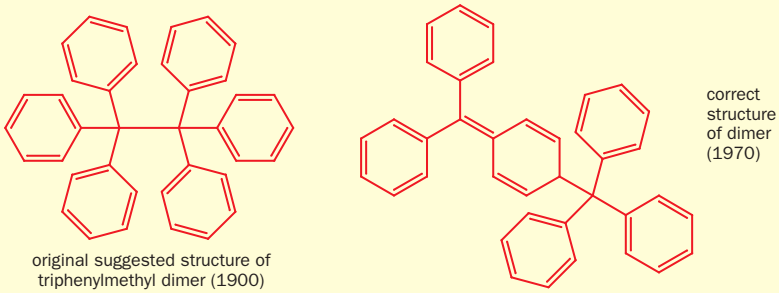
Radical substitutions differ considerably from S_N1 or S_N2 reactions: importantly, *radical substitutions almost never occur at carbon atoms.* We shall come back to radical substitutions, or abstractions (depending on whether you take the point of view of the H atom or the Br atom), later in the chapter.

First radical detected

The very first radical to be detected, the triphenylmethyl radical, was made in 1900 by abstraction of Cl• from Ph_3CCl by Ag metal.

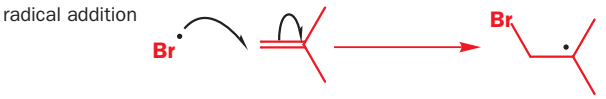


This radical is relatively stable (we shall see why shortly), but reacts with itself reversibly in solution. The product of the dimerization of triphenylmethyl was for 70 years believed to be tetraphenyl ethane but, in 1970, NMR showed that it was, in fact, an unsymmetrical dimer.



Radicals form by addition

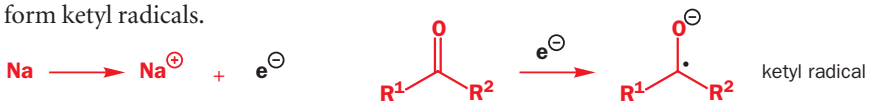
The key step in the radical reaction with which we started the chapter is the formation of a radical by **radical addition**. The Br• radical (which, you will remember, was formed by abstraction of H• from HBr by RO•) adds to the alkene to give a new, carbon-centred radical. This is the mechanism: again, notice that half-headed arrows are used to indicate the movement of single electrons.



Just as charge must be conserved through a chemical reaction, so must be the spin of the electrons involved. If a reactant carries an unpaired electron, then so must a product. Addition of a radical to a spin-paired molecule always generates a new radical. Radical addition is therefore a second type of radical-forming reaction.

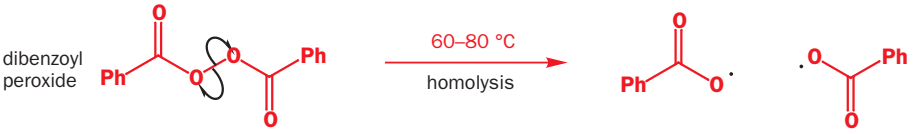
The simplest radical addition reactions occur when a single electron is added to a spin-paired molecule. This process is a reduction. You have already met some examples of single-electron reductions: Birch reductions (Chapter 24) use the single electron formed when a group I metal (sodium, usually) is dissolved in liquid ammonia to reduce organic compounds. Group I metals are common sources of single electrons: by giving up their odd s electron they form a stable M^+ ion. They will donate this electron to several classes of molecules; for example, ketones can react with sodium to form ketyl radicals.

■ We shall discuss ketyl radicals and their reactions later in the chapter.

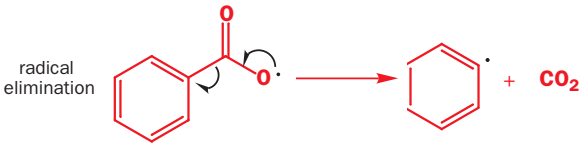


Radicals form by homolytic cleavage of weak bonds

A fourth class of radical-forming reaction is **homolytic cleavage**. For an example, we can go back to dibenzoyl peroxide, the unstable compound we considered earlier in the chapter because it readily undergoes homolysis.



The radicals formed from this homolysis are unstable and each breaks down by cleavage of a C–C bond, generating CO_2 and a phenyl radical. These homolytic bond cleavages are elimination reactions and are the reverse of radical addition reactions.

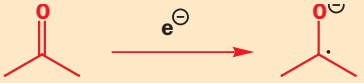


To summarize methods of radical formation

Radicals form from spin-paired molecules by:

- homolysis of weak σ bonds, e.g.

- electron transfer, that is, reduction (addition of an electron), e.g.



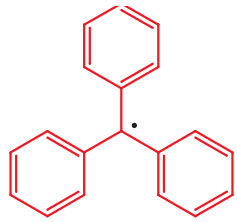
Radicals form from other radicals by:

- substitution (abstraction)

- addition

- elimination (homolysis)

▶ *Electron célibataire* is the French term for these bachelor electrons searching earnestly for a partner.



triphenylmethyl radical – stable in solution in equilibrium with its dimer

Most radicals are extremely reactive . . .

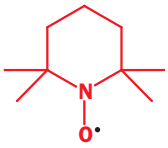
Unpaired electrons are desperate to be paired up again. This means that radicals usually have a very short lifetime; they don't survive long before undergoing a chemical reaction.

Chemists are more interested in radicals that are reactive, because they can be persuaded to do interesting and useful things. However, before we look at their reactions, we shall consider some radicals that are unreactive so that we can analyse the factors that contribute to radical reactivity.

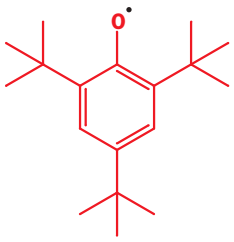
. . . but a few radicals are very unreactive

Whilst simple alkyl radicals are extremely short-lived, some other radicals survive almost indefinitely. Such radicals are known as **persistent radicals**. We mentioned the triphenylmethyl radical on p. 000: this yellow substance exists in solution in equilibrium with its dimer, but it is persistent enough to account for 2–10% of the equilibrium mixture.

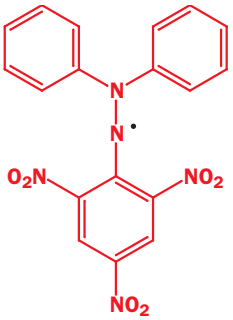
Persistent radicals with the single electron carried by an oxygen or a nitrogen atom are also known: these three radicals can all be handled as stable compounds. The first, known as TEMPO, is a commercial product and can even be sublimed.



TEMPO
TEtraMethylPiperidine *N*-Oxide
m.p. 36–38°C



dark blue solid
m.p. 97°C

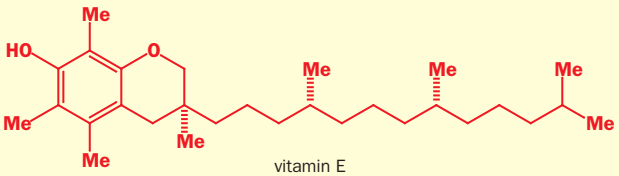


violet crystals

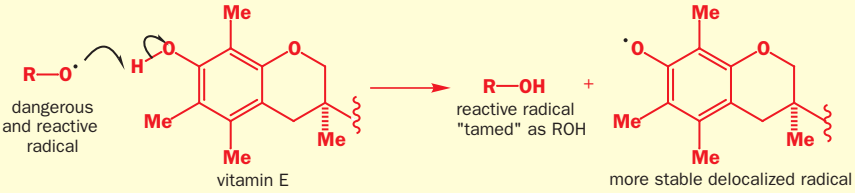
There are two reasons why some radicals are more persistent than others: (1) steric hindrance and (2) electronic stabilization. In the four extreme cases above, their exceptional stability is conferred by a mixture of these two effects. Before we can analyse the stability of other radicals, however, we need to look at what is known about the shape and electronic structure of radicals.

Vitamin E tames radicals

Many of the molecules that make up the structure of human tissue are susceptible to homolysis in intense light, and the body makes use of sophisticated chemistry to protect itself from the action of the reactive radical products. Vitamin E plays an important role in the 'taming' of these radicals: abstraction of H from the phenolic hydroxyl group produces a relatively stable radical that does no further damage.



vitamin E



dangerous and reactive radical

vitamin E

reactive radical "tamed" as ROH

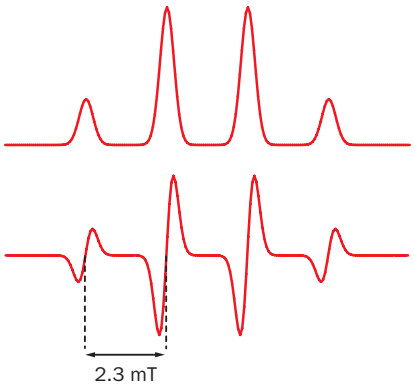
more stable delocalized radical

How to analyse the structure of radicals: electron spin resonance

For the last few pages we have been discussing the species we call radicals without offering any evidence that they actually exist. Well, there is evidence, and it comes from a spectroscopic technique known as **electron spin resonance**, or **ESR** (also known as EPR, electron paramagnetic resonance). ESR not only confirms that radicals do exist, but it can also tell us quite a lot about their structure.

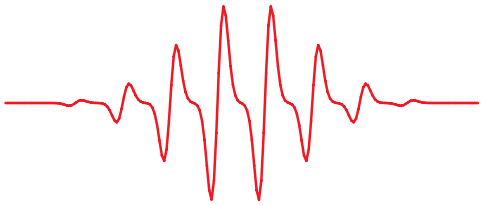
Unpaired electrons, like the nuclei of certain atoms, have a magnetic moment associated with them. Proton NMR probes the environment of hydrogen atoms by examining the energy difference between the two possible orientations of their magnetic moments in a magnetic field; ESR works in a similar way for unpaired electrons. The magnetic moment of an electron is much bigger than that of a proton, so the difference in energy between the possible quantum states in an electron field is also much bigger. This means that the magnets used in ESR spectrometers can be weaker than those in NMR spectrometers: usually about 0.3 tesla; even at this low field strength, the resonant frequency of an electron is about 9000 MHz (for comparison, the resonant frequency of a proton at 9.5 tesla is 400 MHz; in other words, a 400 MHz NMR machine has a magnetic field strength of 9.5 tesla).

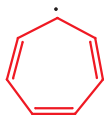
But there are strong similarities between the techniques. ESR shows us, for example, that unpaired electrons couple with protons in the radical. The spectrum below is that of the methyl radical, $CH_3^{\bullet}$. The 1:3:3:1 quartet pattern is just what you would expect for coupling to three equivalent protons; coupling in ESR is measured in millitesla (or gauss; 1 gauss = 0.1 mT), and for the methyl radical the coupling constant (called a_H) is 2.3 mT.



▶ Notice that, for historical reasons, ESR spectra are recorded in a different way from NMR spectra: the diagram shows the first derivative of the absorption spectrum (the sort of spectrum you would get from a proton NMR machine).

ESR hyperfine splittings (as the coupling patterns are known) can give quite a lot of information about a radical. For example, here is the hyperfine splitting pattern of the cycloheptatrienyl radical. The electron evidently sees all seven protons around the ring as equivalent, and must therefore be fully delocalized. A localized radical would see several different types of proton, resulting in a much more complex splitting pattern.


ESR spectrum of cycloheptatrienyl radical

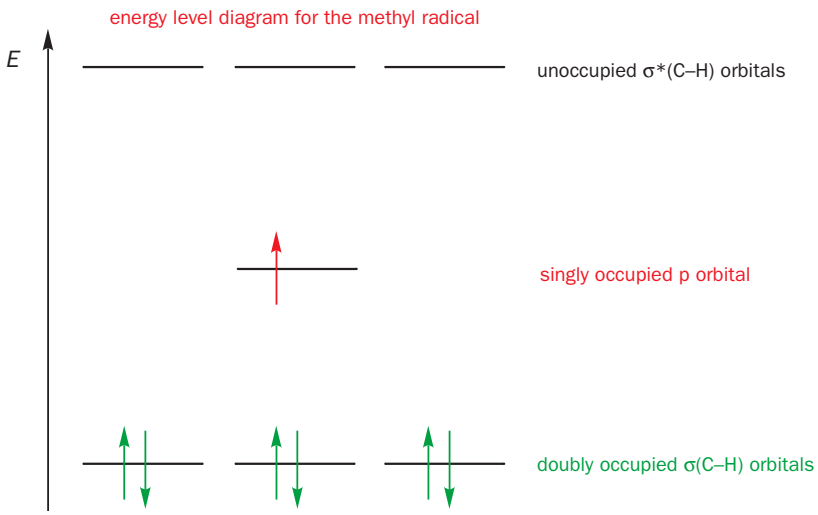

cycloheptatrienyl radical

Even the relatively simple spectrum of the methyl radical tells us quite a lot about the radical. For example, the size of the coupling constant a_H indicates that the methyl radical is planar; the trifluoromethyl radical is, on the other hand, pyramidal. The oxygenated radicals $^{\bullet}CH_2OH$ and $^{\bullet}CMe_2OH$ lie somewhere in between.

▶ The calculations that show this lie outside the scope of this book!

Radicals have singly occupied molecular orbitals

ESR tells us that the methyl radical is planar: the carbon atom must therefore be sp^2 hybridized, with the unpaired electron in a p orbital. We can represent this in an energy level diagram.

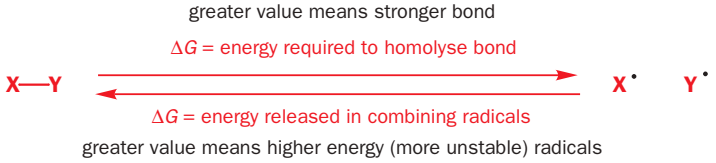


In Chapter 4 we talked about the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of organic molecules. $CH_3^{\bullet}$ (like all radicals) has an orbital containing one electron, which we call a **Singly Occupied Molecular Orbital** (**SOMO**).

As with all molecules, it is the energy of the electrons in the molecular orbitals of the radical that dictate its stability. Any interaction that can decrease the energy levels of the filled molecular orbitals increases the stability of the radical (in other words, decreases its reactivity). Before we use this energy level diagram of the methyl radical to explain the stability of radicals, we need to look at some experimental data that allow us to judge just how stable different radicals are.

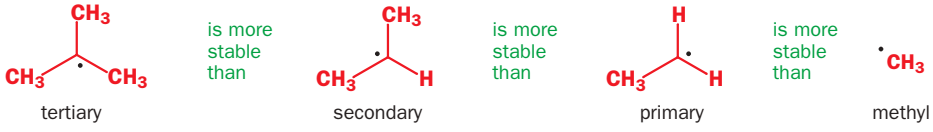
Radical stability

On p. 000 we used bond strength as a guide to the likelihood that bonds will be homolysed by heat or light. Since bond energies give us an idea of the ease with which radicals can form, they can also give us an idea of the stability of those radicals once they have formed.



This is particularly true if we compare the strengths of bonds between the same atoms, for example, carbon and hydrogen, in different molecules; the table does this.

A few simple trends are apparent. For example, C–H bonds decrease in strength in R–H when R goes from primary to secondary to tertiary. Tertiary alkyl radicals are therefore the most stable; methyl radicals the least stable.

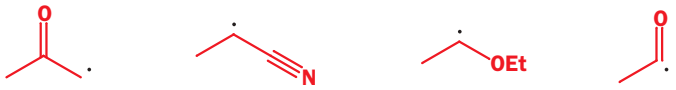


C–H bonds next to conjugating groups such as allyl or benzyl are particularly weak, so allyl and benzyl radicals are more stable. But C–H bonds to alkynyl, alkenyl, or aryl groups are strong.

▶ The absolute values in this table were determined in the gas phase, but the relative stabilities of the different radicals should mirror their relative stabilities in solution—after all this table is meant only as a guide to the relative stability of different radicals.

Bond	Dissociation energy, kJ mol^{-1}
CH_3–H	439
$MeCH_2$–H	423
Me_2CH–H	410
Me_3C–H	397
HC≡C–H	544
H_2C=CH–H	431
Ph–H	464
H_2C=CH_2CH_2–H	364
$PhCH_2$–H	372
RCO–H	364
EtOCHMe–H	385
N≡CCH_2–H	360
$MeCOCH_2$–H	385

Adjacent functional groups appear to weaken C–H bonds: radicals next to carbonyl, nitrile, or ether functional groups, or centred on a carbonyl carbon atom, are more stable than even tertiary alkyl radicals.

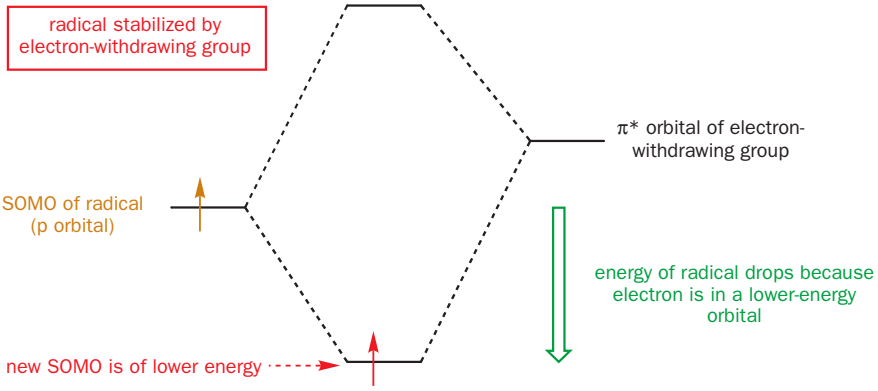


radicals stabilized by functional groups

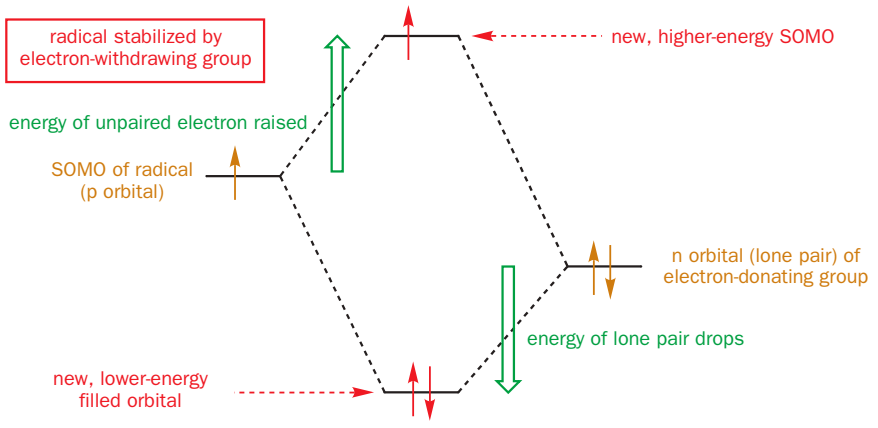
Whether the functional group is electron-withdrawing or electron-donating is clearly irrelevant here: both types seem to stabilize radicals. We can explain all of this if we look at how the different groups next to the radical centre interact electronically with the radical.

Radicals are stabilized by conjugating, electron-withdrawing, and electron-donating groups

Let's consider first what happens when a radical centre finds itself next to an electron-withdrawing group. Groups like C=O and C≡N are electron-withdrawing because they have a low-lying empty π* orbital. By overlapping with the (usually p) orbital containing the radical (the SOMO), two new molecular orbitals are generated. One electron (the one in the old SOMO) is available to fill the two new orbitals. It enters the new SOMO, which is of lower energy than the old one, and the radical experiences stabilization because this electron drops in energy.



We can analyse what happens with electron-rich groups, such as RO groups, in a similar way. Ether oxygen atoms have relatively high-energy filled n orbitals, their lone pairs. Interacting this with the SOMO again gives two new molecular orbitals. Three electrons are available to fill them. The SOMO is now higher in energy than it was to start with, but the lone pair is lower. Because two electrons have dropped in energy and only one has risen, there is an overall stabilization of the system, even though the new SOMO is of higher energy than the old one. We shall see later what effect the energy of the SOMO, rather than the overall energy of the radical, has on its reactivity.



In Chapter 17, you saw how the electrons in C–H σ bonds stabilize cations: they stabilize radicals in the same way, which is why tertiary radicals are more stable than primary ones.

Conjugation, too, is effective at stabilizing radicals. We know that radicals next to double bonds are delocalized from their ESR spectra (p. 000); that they are more stable is evident from the bond dissociation energies of allylic and benzylic C–H bonds.

- **Anything that would stabilize an anion *or* a cation will stabilize a radical:**
  - **electron-withdrawing groups**
  - **electron-donating groups (including alkyl groups with C–H σ bonds)**
  - **conjugating groups**

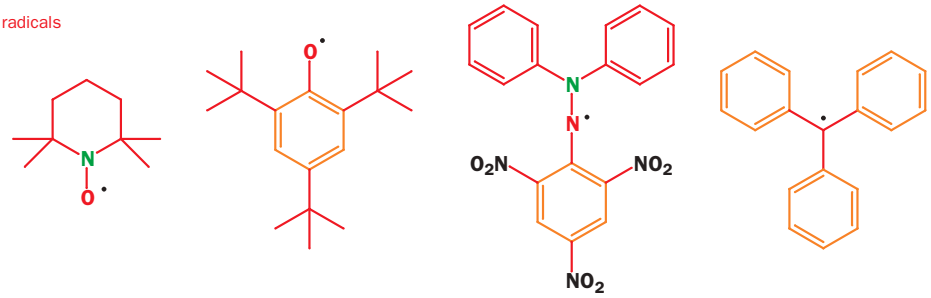
▶ Both electron-donating and electron-withdrawing effects stabilize radicals, as you have just seen. Some radicals are stabilized by an electron-withdrawing group and an electron-donating group at the same time. These radicals are known as **captodative radicals**.

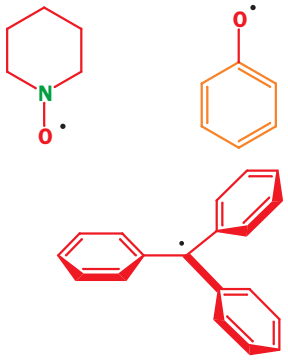
Steric hindrance makes radicals less reactive

On p. 000 we showed you some radicals that are remarkably stable (persistent): some can even be isolated and purified. You should now be able to see at least part of the reason for their exceptional stability: two of them have adjacent powerful electron-donating groups and one has a powerful electron-withdrawing group as well, and three of the four are conjugated.

some persistent (unreactive) radicals

electron-donating groups in green
electron-withdrawing groups in black
conjugating groups in orange

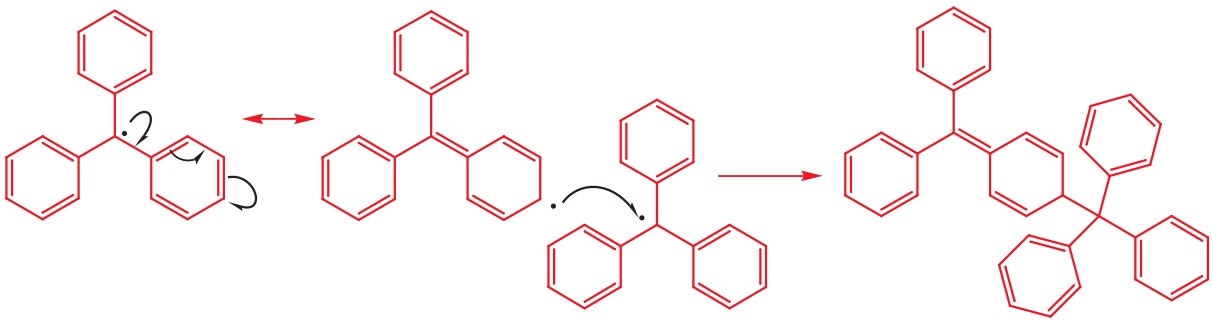




But electronic factors alone are not sufficient to explain the exceptional stability of all four radicals, since the next two radicals (in the margin) receive just about the same electronic stabilization as the first two above, but are much more reactive.

In fact, the stability of the triphenylmethyl radical we know to be due mainly to steric, rather than electronic, factors. X-ray crystallography shows that the three phenyl rings in this compound are not coplanar but are twisted out of a plane by about 30°, like a propeller. This means that the delocalization in this radical is less than ideal (we know that there is some delocalization from the ESR spectrum) and, in fact, it is little more delocalized than the diphenylmethyl or even the benzyl radical.

Yet it is much more stable than either. This must be because the central carbon, which bears most of the radical character, is sterically shielded by the twisted phenyl groups, making it very hard for the molecule to react. And when it does dimerize, we know that it does so through one of its least hindered carbon atoms.



Further evidence for the role of steric effects in helping to stabilize radicals comes from triphenyl-

methyl derivatives with *ortho* substituents: these force the phenyl rings to twist even more (at 50° or more), decreasing still further the extent of electronic stabilization through delocalization. Yet these *ortho*-substituted radicals are more stable than triphenylmethyl: this must be a steric effect. The rest of this chapter is devoted to the reactions of radicals, and you will see that the two effects we have talked about—electronic stabilization and steric hindrance—are key factors that control these reactions.

How do radicals react?

A reactive radical has a choice: it can either find another radical and combine to form a spin-paired molecule (or more than one spin-paired molecule), or it can react with a spin-paired molecule to form a new radical. Both are possible, and we shall see examples of each. A third alternative is for a radical to decompose in a unimolecular reaction, giving rise to a new radical and a spin-paired molecule.

Three possibilities

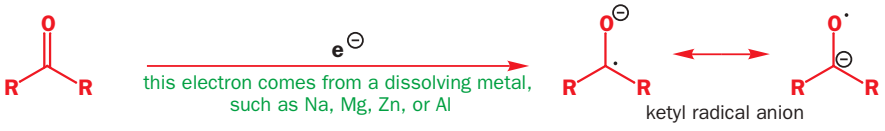
- **Radical + radical → spin-paired molecule**
- **Radical + spin-paired molecules → new radical + new spin-paired molecule**
- **Radical → new radical + spin-paired molecule**

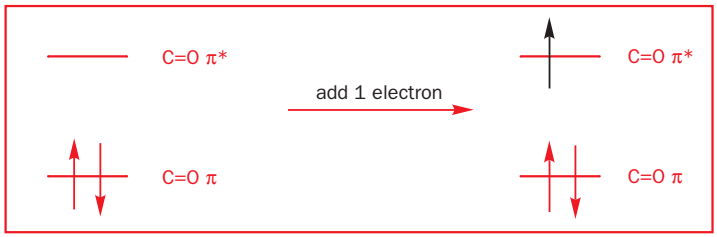
Radical–radical reactions

In view of the energy released when unpaired electrons pair up, you might expect this type of radical reaction to be more common than reaction with a spin-paired molecule, in which no net pairing of electrons takes place. Radical–radical reactions certainly do take place, but they are not the most important type of reaction involving radicals. We shall see why they are not as common as you might expect shortly, but first we can look at some examples.

The pinacol reaction is a radical dimerization

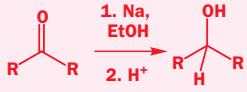
We outlined on p. 000 a way of making radicals by single electron transfer: effectively, the addition reaction of a single electron to a spin-paired molecule. The types of molecules that undergo this reaction are those with low-lying antibonding orbitals for the electron to go into, in particular, aromatic systems and carbonyl compounds. The radical anion formed by addition of an electron to a ketone is known as a **ketyl**. The single electron is in the π^* orbital, so we can represent a ketyl with the radical on oxygen or on carbon and the anion on the other atom.





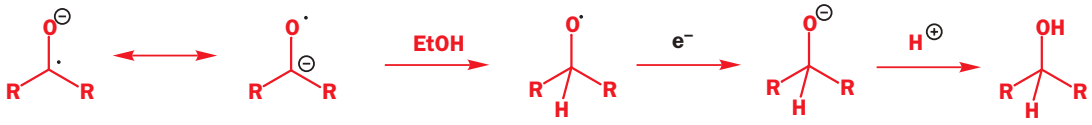
Ketyls behave in a manner that depends on the solvent that they are in. In protic solvents (ethanol, for example), the ketyl becomes protonated and then accepts a second electron from the metal (sodium is usually used in these cases). An alkoxide anion results, which, on addition of acid at the end of the reaction, gives an alcohol.

▶ This reaction, known as the **Bouveault–Blanc reduction**, used to be used to reduce carbonyl compounds to alcohols, but now aluminium hydrides and borohydrides are usually more convenient. You met an example of the Bouveault–Blanc reduction in Chapter 33 (conformational analysis–reduction of cyclohexanones).



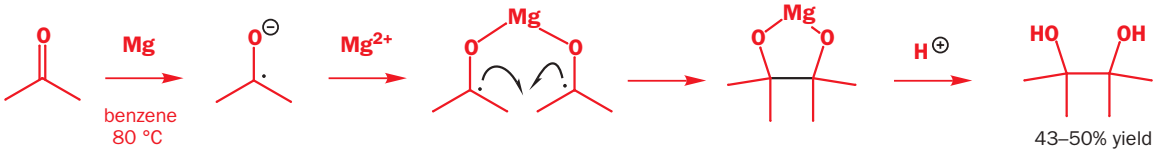
Notice that this is a reaction using sodium metal in ethanol, and not sodium ethoxide, which is the basic product that forms once sodium has dissolved in ethanol. It is important that the sodium is *dissolving* as the reaction takes place, since only then are the free electrons available.

reaction of the ketyl radical anion in protic solvents



In aprotic solvents, such as benzene or ether, no protons are available so the concentration of ketyl radical builds up significantly and the ketyl radical anions start to dimerize. As well as being a radical–radical process, this dimerization process is an anion–anion reaction, so why doesn't electrostatic repulsion between the anions prevent them from approaching one another? The key to success is to use a metal such as magnesium or aluminium that forms strong, covalent metal–oxygen bonds and that can coordinate to more than one ketyl at once. Once two ketyls are coordinated to the same metal atom, they react rapidly.

pinacol dimerization of acetone (ketyl radical reaction in hydrocarbon solvent)

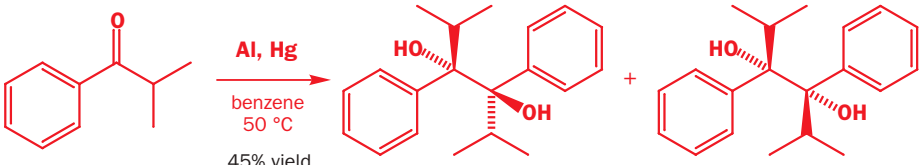


diol product known as "pinacol"

43–50% yield

The example shows the dimerization of acetone to give a diol (2,3-dimethylbutane-2,3-diol) whose trivial name, pinacol, is used as a name for this type of reaction using any ketone. Sometimes pinacol reactions create new chiral centres: in this example, the two diastereoisomeric diols are formed in a 60:40 mixture. If you want to make a single diastereoisomer of a diol, a pinacol reaction is not a good choice!

■ You would be better off using one of the methods described in Chapter 34 on diastereoselectivity.

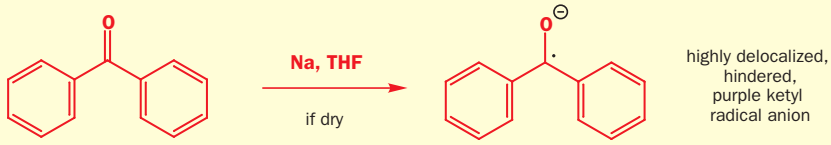


anti-diastereoisomer
60% of mixture

syn-diastereoisomer
40% of mixture

Benzophenone as an indicator in THF stills

As you should have gathered by now, THF is an important organic solvent in which many low-temperature, inert-atmosphere reactions are conducted. It has a drawback, however: it is quite hygroscopic, and often the reactions for which it is used as a solvent must be kept absolutely free of water. It is therefore always distilled immediately before use from sodium metal, which reacts with any traces of water in the THF. However, it is necessary to have an indicator to show that the THF *is* dry and that the sodium has done its job. The indicator used is a ketone, benzophenone.



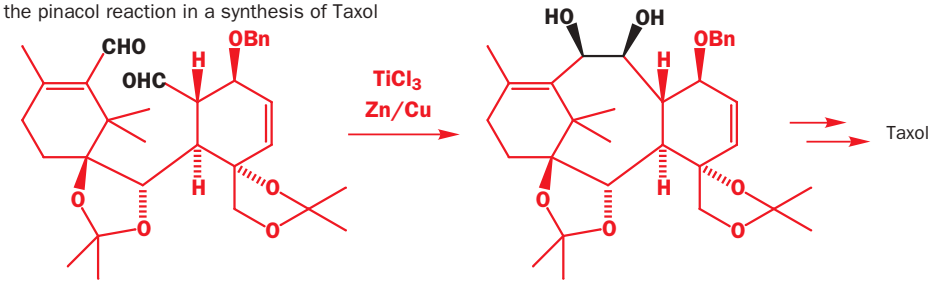
benzophenone

highly delocalized, hindered, purple ketyl radical anion

When the THF is dry, the distilling liquid containing the benzophenone becomes bright purple. This colour is due to the ketyl of benzophenone, the formation of which under these conditions should not surprise you. It should also come as no surprise that this ketyl, being stabilized by conjugation and quite hindered, is persistent (long-lived)—it does not undergo pinacol dimerization (as we explained above, you would not normally choose sodium to promote pinacols anyway). However, if water is present, the ketyl is rapidly quenched in the manner of the reduction described above to give the (colourless) alkoxide anion: only when all the water is consumed does the colour return.

Pinacol reactions can be carried out intramolecularly, from compounds containing two carbonyl groups. In fact, the key step of one of the very first syntheses of Taxol® (the important anticancer compound) was an intramolecular pinacol reaction using titanium as the source of electrons.

the pinacol reaction in a synthesis of Taxol

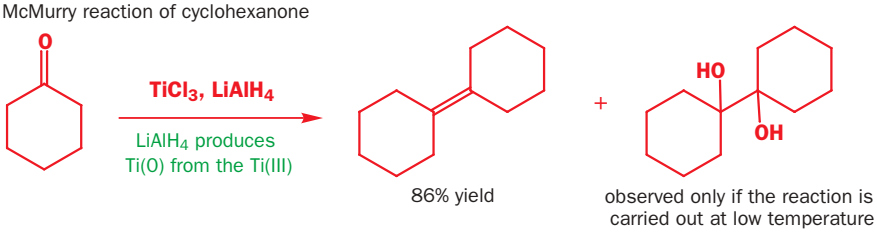


The titanium metal that is the source of electrons is produced during the reaction by reduction of $TiCl_3$ using a zinc–copper mixture. This reaction is, in fact, unusual because, as we shall see below, pinacol reactions using titanium do not normally stop at the diol, but give alkenes.

Titanium promotes the pinacol coupling and then deoxygenates the products: the McMurry reaction

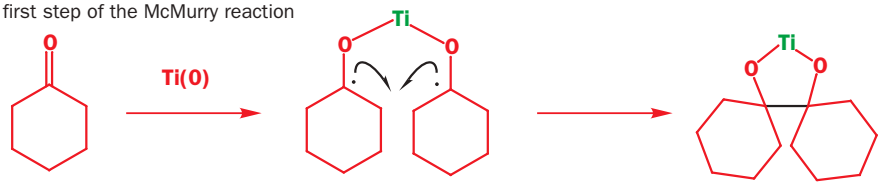
Titanium can be used as the metal source of electrons in the pinacol reaction and, provided the reaction is kept cold and not left for too long, diols can be isolated from the reaction (see the example at the end of the previous section). However, unlike magnesium or aluminium, titanium reacts further with these diol products to give alkenes in a reaction known as the **McMurry reaction**, after its inventor.

McMurry reaction of cyclohexanone



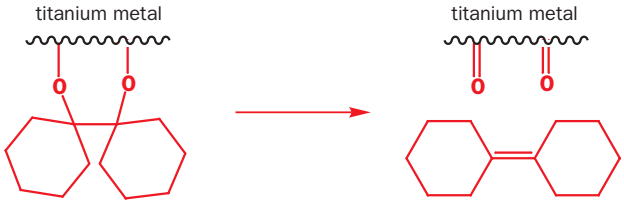
Notice that the titanium(0), which is the source of electrons in the reaction, is produced during the reaction by reacting a Ti(III) salt, usually $TiCl_3$, with a reducing agent such as $LiAlH_4$ or Zn/Cu. The reaction does not work with, say, powdered titanium metal. The McMurry reaction is believed to be a two-stage process involving firstly a pinacol radical–radical coupling. Evidence for this is that the pinacol products (diols) can be isolated from the reaction under certain conditions (you've just seen how this was done during the synthesis of Taxol).

first step of the McMurry reaction



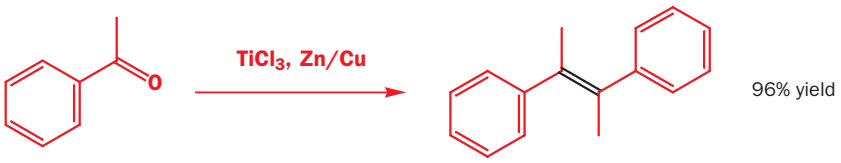
The Ti(0) then proceeds to deoxygenate the diol by a mechanism not fully understood, but thought to involve binding of the diol to the surface of the Ti(0) particles produced in the reduction of $TiCl_3$.

second step of the McMurry reaction: deoxygenation on the surface of a Ti(0) particle



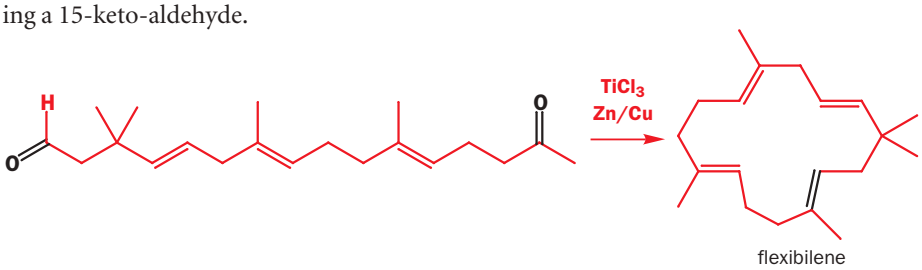
■ The evidence that it happens on a metal surface is quite nice, though, and if you're interested you can read McMurry's own account of it in *Accounts of Chemical Research*, 1983, p. 405.

We expect you to be mildly horrified by the inadequacy of the mechanism above. But, unfortunately, we can't do much better because no-one really knows quite what is happening. The McMurry reaction is very useful for making tetrasubstituted double bonds—there are few other really effective ways of doing this. However, the double bonds really need to be symmetrical (in other words, have the same substituents at each end) because McMurry reactions between two different ketones are rarely successful.



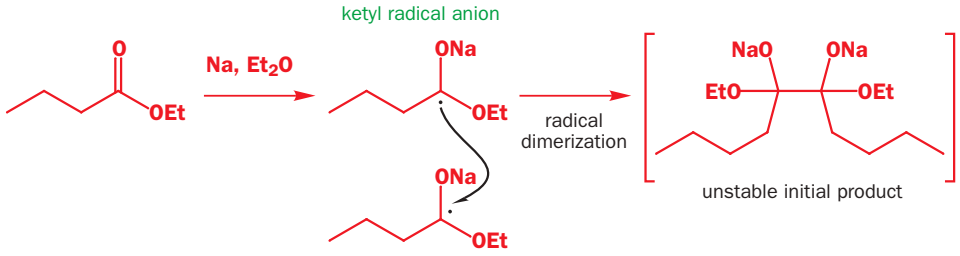
■ You saw on p. 000 how the same reagent was used to carry out an intramolecular pinacol reaction, producing an eight-membered ring. Remember that medium rings, in other words ring sizes 7 to 13, are uncommonly difficult to form by cyclization reactions—the reasons for this were discussed in Chapters 18 and 42.

McMurry reactions also work very well intramolecularly, and turn out to be quite a good way of making cyclic alkenes, especially when the ring involved is medium or large (over about eight members). For example, the natural product flexibilene, with a 15-membered ring, can be made by cyclizing a 15-keto-aldehyde.

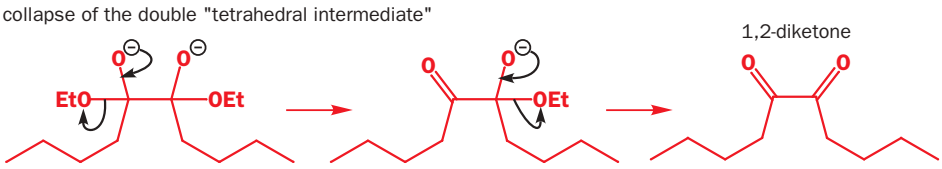


Esters undergo pinacol-type coupling: the acyloin reaction

You've seen examples of pinacol and McMurry reactions of ketones and aldehydes. What about esters? You would expect the ketyl radical anion to form from an ester in the same way, and then to undergo radical dimerization, and this is indeed what happens.



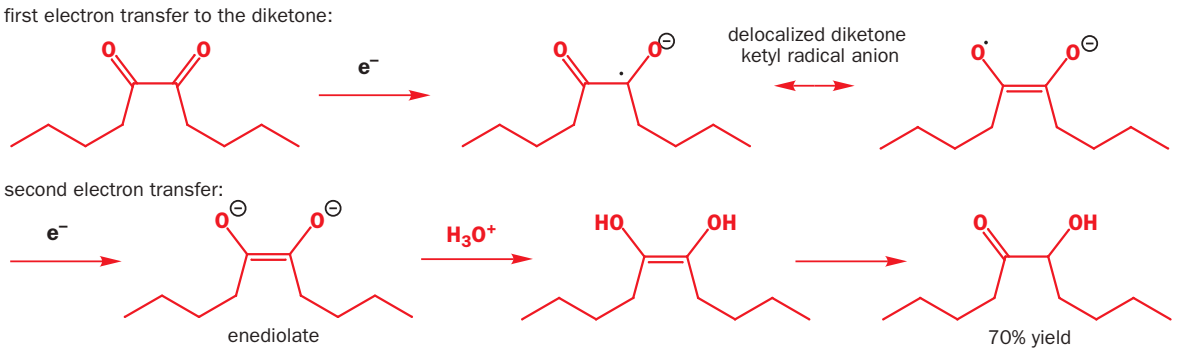
The product of the dimerization looks very much like a tetrahedral intermediate in a carbonyl addition–elimination reaction, and it collapses to give a 1,2-diketone.



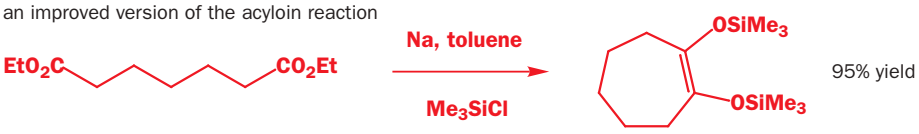
The diketone is however still reducible—in fact, 1,2-diketones are more reactive towards electrophiles and reducing agents than ketones because their π^* is lower in energy and straight away two electron transfers take place to form a molecule, which we could term an **enediolate**.

On quenching the reaction with acid, this dianion is protonated twice to give the enol of an α-hydroxy-ketone, and it is this α-hydroxy-ketone that is the final product of the acyloin reaction. The yield in this example is a quite respectable 70%. However, in many other cases, this usefulness of the acyloin reaction is hampered by the formation of by-products that arise because of the reactivity of the enediolate dianion. It is, of course, quite nucleophilic, and is likely to be formed in the presence

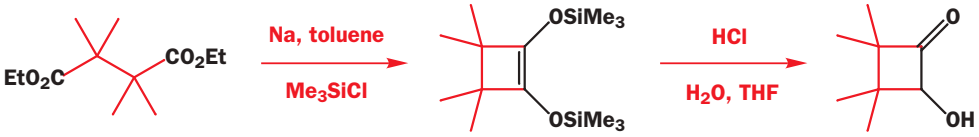
of the highly electrophilic diketone. It is also basic, and often catalyses a competing Claisen condensation of the esters being reduced.



The solution to these problems is to add trimethylsilyl chloride to the reaction mixture. The silyl chloride silylates the enediolate as it is formed, and the product of the acyloin reaction becomes a bis-silyl ether.



The silyl ethers are rarely desired as final products, and they can easily be hydrolysed to α-hydroxy-ketones with aqueous acid. This improved version makes four-membered rings efficiently.



It's not by accident that these two examples of the acyloin reaction show the formation of cyclic compounds. It is a particularly powerful method of making carbocyclic rings of from four members upwards: the energy to be gained by pairing up the two electrons in the radical–radical reaction step more than compensates for the strain that may be generated in forming the ring.

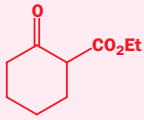
The pinacol, McMurry, and acyloin reactions are exceptional

We've already said that this type of reaction, in which two radicals dimerize, is relatively uncommon. Most radicals are simply too reactive to react with one another! This may sound nonsensical, but the reason is simply that highly reactive species are unselective about what they react with. Although it might be energetically favourable for them to find another radical and dimerize, they are much more likely to collide with a solvent molecule, or a molecule of some other compound present in the mixture, than another radical. Reactive radicals are only ever present in solution in very low concentrations, so the chances of a radical–radical collision are very low. Radical attack on spin-paired molecules is much more common and, because the product of such reaction is also a radical, they give rise to the possibility of radical chain reactions.

Radical chain reactions

In looking at how radicals form, you've already seen examples of how radicals react. In fact, we've already dealt (if only very briefly) with every step of the sequence of reactions that makes up the mechanism of the radical reaction you met at the beginning of the chapter.

▶ In the absence of the Me_3SiCl, the main product from this reaction becomes the cyclic keto-ester below, which arises from base-catalysed Dieckmann cyclization (see Chapter 28) of the diester.



■ In Chapter 8 we discussed ring strain—remember that it's not only small (three- and four-membered) rings that are strained, but medium (8 to 13 members) ones too.

■ This is known as the **reactivity–selectivity principle**—see Chapter 41.

▶ Think of radicals as smash-and-grab raiders. They pick the first shop that catches their eye, smash the window, and run off with a handful of jewellery from the front of the display. Ions in solution are stealthy burglars. They scan all the houses on the street, choose the most vulnerable, and then carefully gain entry to the room that they know contains the priceless oil painting.

Let's now consider each step in turn and in more detail.

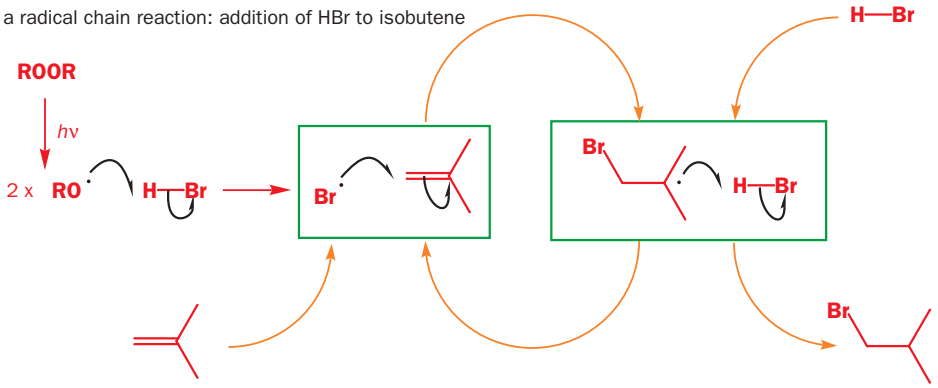
1 The dialkyl peroxide is homolysed (by heat or light) to give two alkoxy radicals

2 RO• abstracts H from HBr (radical substitution) to give Br•

3 Br• adds to isobutene to give a carbon-centred radical

4 The carbon-centred radical abstracts a hydrogen atom from H–Br to form the final addition product and regenerate Br•, which can react with another molecule of alkene

The whole process can conveniently be represented cyclically.



In each step in the cycle a radical is consumed and a new radical is formed. This type of reaction is therefore known as a **radical chain reaction**, and the two steps that form the cyclic process that keeps the chain running are known as the **chain propagation steps**. Only one molecule of peroxide **initiator** is necessary for a large number of product molecules to be formed and, indeed, the peroxide needs to be added in only catalytic quantities (about 10 mol%) for this reaction to proceed in good yield.

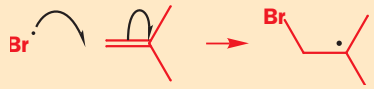
Any less than 10 mol%, however, and the yield drops. The problem is that the chain reaction is not 100% efficient. Because the concentration of radicals in the reaction mixture is low, radical–radical reactions are rare, but nonetheless they happen often enough that more peroxide keeps being needed to start the chain off again

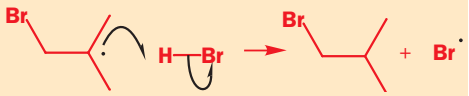
possible radical–radical chain termination steps

Reactions like this are known as **termination steps** and are actually an important part of any chain reaction; without termination steps the reaction would be uncontrollable.

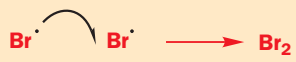
- Radical chain reactions consist of
  - **Initiation** steps

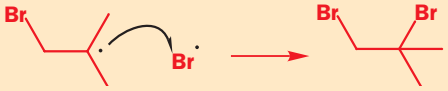
  - **Propagation** steps





  - **Termination** steps





Selectivity in radical chain reactions

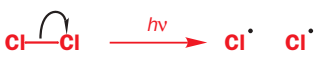
In the radical–radical reactions we looked at earlier, there was never any question of what would react with what: only one type of radical was formed and the radicals dimerized in identical pairs. Look at this chain reaction though—there are three types of radical present, $Br^{\bullet}$, $BrCH_2Me_2CH^{\bullet}$, and $RO^{\bullet}$, and they all react specifically with a chosen spin-paired partner: $Br^{\bullet}$ with the alkene, and $BrCH_2Me_2CH^{\bullet}$ and $RO^{\bullet}$ with HBr. We need to understand the factors that govern this chemoselectivity. In order to do so we shall look at another radical reaction with chemoselectivity and regioselectivity that is *measurable*.

Chlorination of alkanes

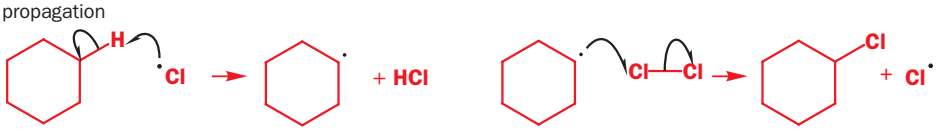
Alkanes will react with chlorine to give alkyl chlorides. For example, cyclohexane plus chlorine gas, in the presence of light, gives cyclohexyl chloride and hydrogen chloride.

This type of reaction is important industrially since it is one of the few that allows compounds containing functional groups to be made from alkanes. As you might guess, since it needs light for initiation, the process is another example of a radical chain reaction. As with the radical addition of HBr to alkenes, we can identify initiation, propagation, and termination steps in the mechanism.

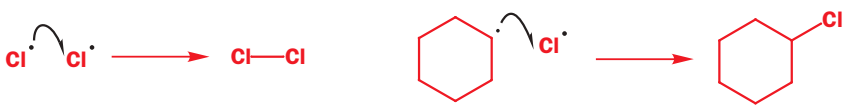
initiation



propagation



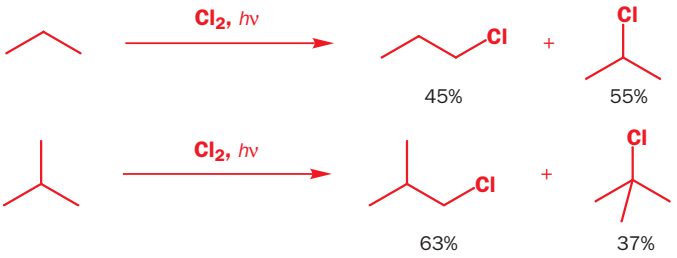
termination



In this case, the termination steps are much less important than in the last case we looked at, and typically the chain reaction can continue for 10^6 steps for each initiation event (photolysis of chlorine). Be warned: reactions like this can be explosive in sunlight.

▶ We have already suggested two reasons why the $Br^{\bullet}$ radical adds to the alkene with this characteristic regioselectivity, giving a primary alkyl bromide when the polar addition of HBr to an alkene would give a tertiary alkyl bromide: (1) attack at the unsubstituted end of the alkene is less sterically hindered; and (2) the tertiary radical thus formed is more stable than a primary radical. In fact, of all the hydrogen halides, only HBr will add to alkenes in this fashion: HCl and HI will undergo only polar addition to give the tertiary alkyl halide. Why? We need to be able to answer this type of question too.

When the chlorine radical abstracts a hydrogen atom from the cyclohexane, only one product can be formed because all 12 hydrogen atoms are equivalent. For other alkanes, this may not be the case, and mixtures of alkyl chlorides can result. For example, propane is chlorinated to give a mixture of alkyl chlorides containing 45% 1-chloropropane and 55% 2-chloropropane, and *iso*butane is chlorinated to give 63% *iso*-butyl chloride and 37% *tert*-butyl chloride.



■ These bond energies were given in the tables on pp .000 and 000.

How can we explain the ratios of products that are formed? The key is to look at the relative stabilities of the radicals involved in the reaction and the strengths of the bonds that are formed and broken. First, the chlorination of propane. A chlorine radical, produced by photolysis, can abstract either a primary hydrogen atom, from the end of the molecule, or a secondary hydrogen atom, from the middle. For the first process, we have these energy gains and losses.

First process:

	ΔH, kJ mol^{-1}
one H–Cl bond formed	–431
one primary C–H bond broken	+423
total	–8

For the second process, the energies are given in the table.

Second process:

	ΔH, kJ mol^{-1}
one H–Cl bond formed	–431
one secondary C–H bond broken	+410
total	–21

Abstraction of the secondary hydrogen atom is more exothermic than abstraction of the primary hydrogen atom, for the related reasons that: (1) secondary C–H bonds are weaker than primary ones; and (2) secondary radicals are more stable than primary ones. So, we get more 2-chloropropane than 1-chloropropane. But in this case, that isn't the only factor involved: remember that there are six primary hydrogen atoms and only two secondary ones, so the relative reactivity of the primary and secondary positions is even more different than the simple ratio of products from the reaction suggests. This statistical factor is more evident in the second example we gave above, the chlorination of isobutane. Now the choice is between formation of a tertiary radical and formation of a primary one.

abstraction of primary hydrogen

	ΔH, kJ mol^{-1}
one H–Cl bond formed	–431
one primary C–H bond broken	+423
total	–8

abstraction of tertiary hydrogen	

	ΔH, kJ mol^{-1}
one H–Cl bond formed	–431
one tertiary C–H bond broken	+397
total	–34

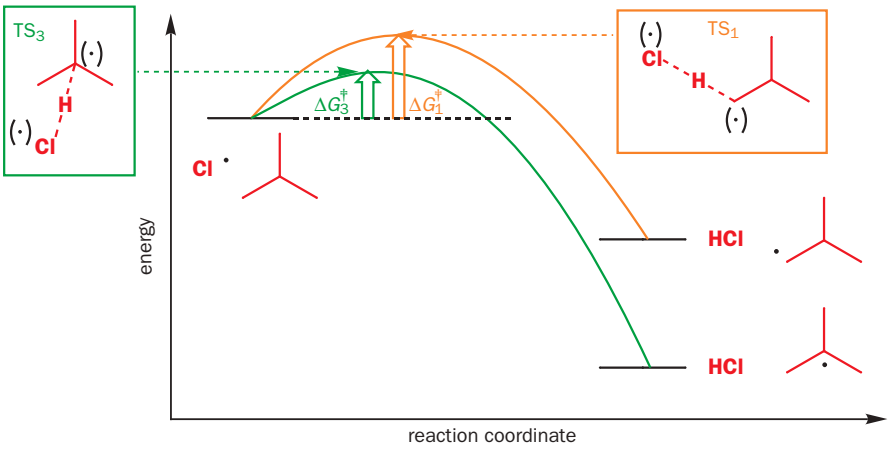
Tertiary radical formation is more exothermic, yet more primary alkyl chloride is formed than tertiary alkyl chloride. However, once the 9:1 ratio of primary to tertiary hydrogen atoms is taken into account, the relative reactivities, as determined experimentally, turn out to be as shown in the table.

ratio of products formed (tertiary:primary)	37:63
number of hydrogen atoms (tertiary:primary)	1:9
relative reactivity of each C–H bond (tertiary:primary)	37/1:63/9 = 37:7 = *ca.* 5:1

Bond strength is all-important in radical reactions

These reactions illustrate a key point about radical reactions—a very important factor affecting selectivity is the strength of the bonds being formed and broken.

The rate of attack by Cl$^{\bullet}$ on a tertiary C–H bond, then, is about five times the rate of attack by Cl$^{\bullet}$ on a primary C–H bond. We said that this is because the formation of the tertiary radical is more exothermic than the formation of the primary radical. But the rate of a reaction depends not on ΔH for that reaction but on the **activation energy** of the reaction; in other words, the energy needed to reach the transition state for the reaction. But we can still use the stability of the product radicals as a guide to the stability of the transition state, because the transition state must have significant radical character.



The energy diagram above illustrates this point. As the reactants (Cl$^{\bullet}$ plus isobutane) move towards the products, they pass through a transition state (TS_1 for formation of the primary radical, TS_3 for formation of the tertiary) in which the radical character of the Cl$^{\bullet}$ starting material is spread over both the Cl and the C centres. The greater stability of a tertiary radical compared with a primary one must be reflected to a lesser degree in these transition states: a radical shared between Cl and a tertiary centre will be more stable than a radical shared between Cl and a primary centre. The

▶ Always bear this in mind: bond strength is only a *guide* to selectivity in radical reactions. As we shall see shortly, it's not the only factor involved. Indeed, you've already seen *steric effects* in action when the Br$^{\bullet}$ radical added to the less hindered end of the alkene in the first radical reaction of this chapter, and you will later see how *frontier orbital effects* can operate too.

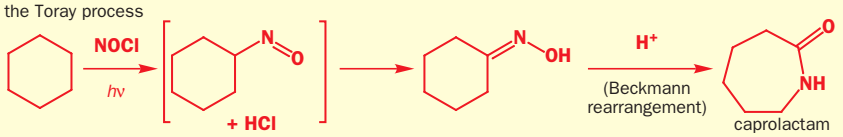
■ We use the symbol (•) to mean a partial radical; a radical that is partially centred on this atom. The symbols (–) and (+) are used to mean a similar thing when a charge is shared by more than one atom.

▶ Of course our calculations involving bond energies only gave us values for ΔH, not ΔG which is what this diagram represents. However, we can assume that the $T\Delta S$ term in the relationship $\Delta G = \Delta H - T\Delta S$ is relatively insignificant.

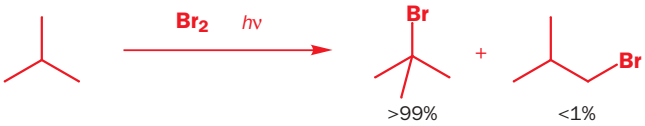
transition state TS_3 for the reaction at the tertiary C–H bond is therefore of lower energy than the transition state TS_1 for reaction at the primary C–H bond. In other words, the activation energy $\Delta G_3^{\ddagger}$ is smaller than $\Delta G_1^{\ddagger}$, so reaction at the tertiary C–H bond is faster.

The Toray process

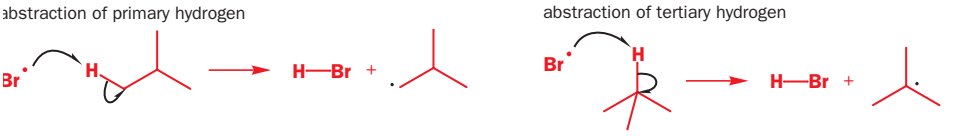
A variant of this reaction, known as the Toray process, is used on an industrial scale in Japan to produce caprolactam, a precursor to nylon. Instead of chlorine, nitrosyl chloride is used to form a nitroso compound that rapidly tautomerizes to an oxime. As you saw in Chapter 37, this oxime undergoes a Beckmann rearrangement under acid conditions to form caprolactam.



Bromine will also halogenate alkanes, and it does so much more selectively than chlorine. For example, the following reaction yields *tert*-butyl bromide with less than 1% of the primary isomer.

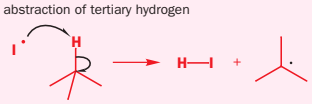


In this case, the first step of the radical chain reaction, the abstraction of H by $Br^{\bullet}$, is endothermic for both the primary and tertiary hydrogen atoms.



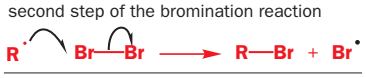
	ΔH, kJ mol^{-1}		ΔH, kJ mol^{-1}
one H–Br bond formed	–366	one H–Br bond formed	–366
one primary C–H bond broken	+423	one tertiary C–H bond broken	+397
total	+57	total	+31

▶ Of course, the overall ΔH for the reaction of an alkane with chlorine must also take into account the ΔH of this second step, which is –349 + 243 = –106 kJ mol^{-1}, making chlorination much more exothermic overall than bromination. Fluorination continues the trend, and methane–fluorine mixtures are explosive. For iodine, on the other hand, the first step becomes so endothermic, even for formation of a tertiary radical, that the second step (ΔH = –234 + 151 = –83 kJ mol^{-1}) is not exothermic enough to make reaction favourable overall. Radical iodinations therefore do not take place.



	ΔH, kJ mol^{-1}
one H–I bond formed	–298
one C–H bond broken	+397
total	+99

The second step, trapping of the alkyl radical by Br_2, is, however, sufficiently exothermic for the reaction to be exothermic overall.

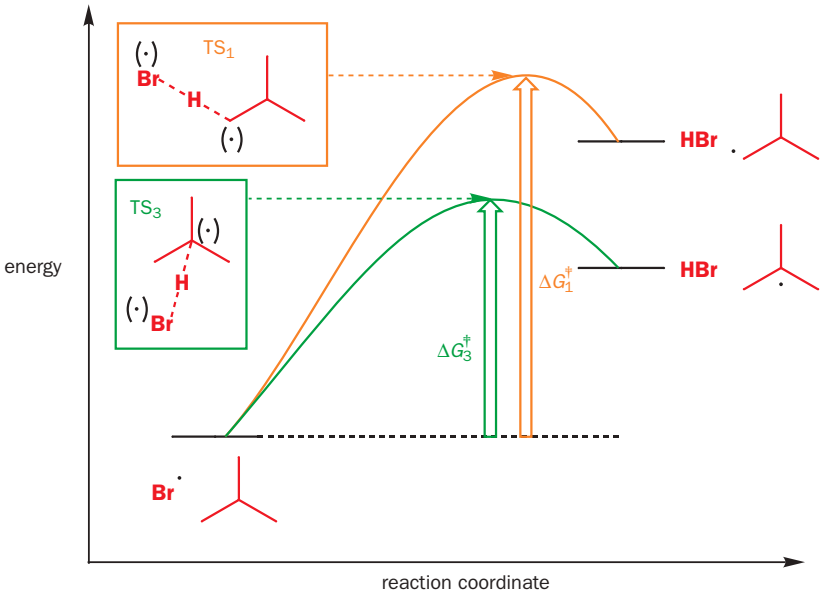


	ΔH, kJ mol^{-1}
one C–Br bond formed	–293
one Br–Br bond broken	+192
total	–101

Why is bromination so much more selective than the chlorination of alkanes? This is a good example of how the Hammond postulate applies to real chemistry. Because the products of the first step of the bromination ($R^{\bullet}$ plus HBr) are higher in energy than the starting materials, the transition state must be similar in structure and energy to that product radical; the difference in energies of the primary and tertiary product radicals should therefore be markedly reflected in the different energies of the transition states TS_1 and TS_3, and $\Delta G_1^{\ddagger}$ will be significantly larger than $\Delta G_3^{\ddagger}$. For the chlorination reaction, the products were just slightly lower in energy than the starting materials, so the transition states for the two possible reactions both resembled the starting materials rather more and the products rather less. These are the same for both tertiary and primary hydrogen abstractions, of course, so the difference in

▶ The **Hammond postulate** gives information about the structure of transition states. It says that two states that interconvert directly (are directly linked in a reaction profile diagram) and that are close in energy are also similar in structure. So a transition state will be most like the starting material, the intermediate, or the product if it is close in energy to one of these observable structures.

energy of the product radicals exerts a less pronounced effect on the difference in energy of the transition states.

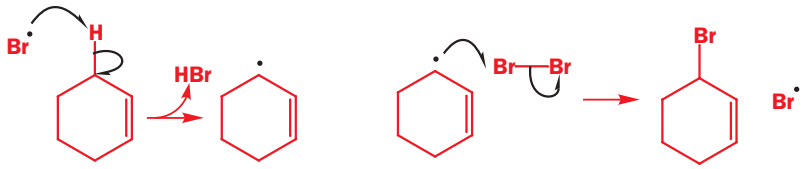


Selective radical bromination: allylic substitution of H by Br

Because radical brominations are so selective, they can be used successfully in the lab to make alkyl bromides. There are relatively few ways of functionalizing an unfunctionalized centre, but radical allylic bromination is one of these. Just as tertiary radicals are more stable than primary ones, so allylic radicals are even more stable than tertiary ones (see the table on p. 000). In the presence of a suitable initiator, bromine will therefore selectively abstract an allylic hydrogen atom to give an allylic radical that can then be trapped by a molecule of bromine to regenerate a bromine radical (chain propagation) and produce the allylic bromide.

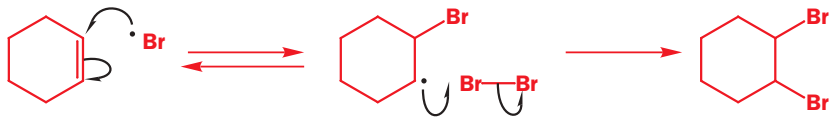
initiation $Br_2 \longrightarrow 2 \times Br^{\bullet}$

propagation

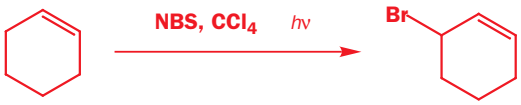


However, there is a problem with this reaction if bromine itself is used, because an alternative radical addition reaction can compete with radical abstraction.

competing addition reaction



The first step of this competing addition reaction is, in fact, reversible; the reaction is driven forward by the participation of a second molecule of bromine that traps the product alkyl radical. This side-reaction can be prevented if the concentration of Br_2 in the reaction is kept very low. One possibility is to add Br_2 very slowly to the reaction mixture, but it is better not to use bromine itself, but a compound that releases molecular bromine slowly during the reaction. That compound is *N*-bromosuccinimide, or NBS.

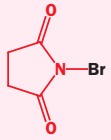


85% yield

▶ Bond energy for tertiary C–H: 364 kJ mol^{-1}. Bond energy for allylic C–H: 397 kJ mol^{-1}. Remember though that these figures were determined in the gas phase, and here our reactions are in solution. Nonetheless, because solvation effects are more or less the same for all radicals, we expect the order of the bond strengths to remain the same in both phases.

▶ This competing reaction is a radical addition across a double bond. You have also met an analogous polar addition across an alkene in Chapter 20: that reaction is suppressed here by using a nonpolar solvent, usually CCl_4.

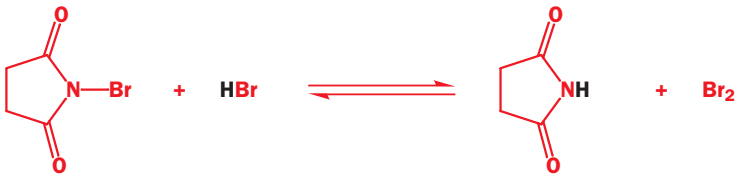
▶ NBS (*N*-Bromo Succinimide) is known to be a source of bromine because the ratios of products obtained from its reactions are identical with those obtained from reactions using small amounts of bromine.



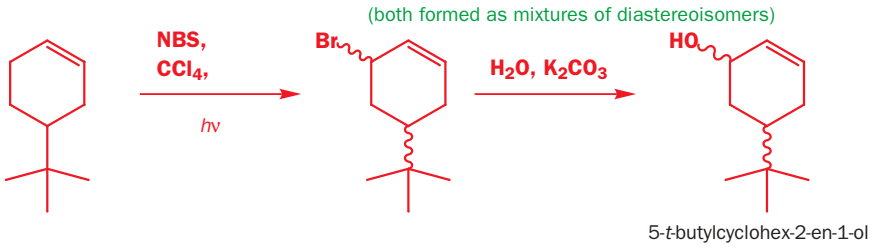
N-bromosuccinimide (NBS)

■ In this technique, the NBS acts like a turnstile, allowing only one molecule of bromine to form for every molecule of HBr produced by the reaction. The slow generation of Bu_3SnH from Bu_3SnCl and $NaBH_4$ is a very similar example and is discussed below.

The HBr produced in the substitution reaction reacts with the NBS to maintain the low concentration of bromine.



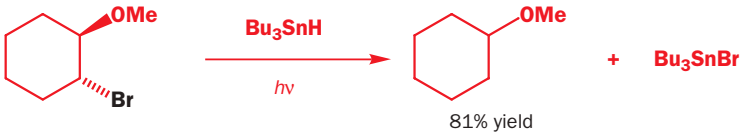
While radical halogenation of alkanes is used only rarely in the laboratory, radical allylic bromination of alkenes is a versatile and commonly used way of making allylic bromides. Nucleophilic substitution reactions can then be used to convert the bromide to other functional groups. For example, some chemists in Manchester needed to make the two diastereoisomers of 5-*tert*-butylcyclohex-2-en-1-ol to study their reactions with osmium tetroxide. *tert*-Butyl cyclohexene is readily available, so they used a radical allylic bromination to introduce the functional group in the allylic position, which they converted to a hydroxyl group using aqueous base. Steric effects play a role here in the regioselectivity of the reaction: only the less hindered allylic hydrogen atoms further from the *t*-butyl group are removed.



Reversing the selectivity: radical substitution of Br by H

■ We discussed the removal of functional groups, and why you might want to do it, in Chapter 25.

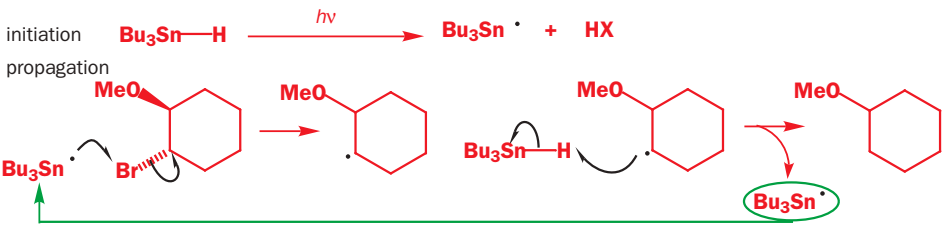
Radical substitution reactions can also be used to *remove* functional groups from molecules. A useful reagent for this (and, as you will see, for other radical reactions too) is tributyltin hydride, Bu_3SnH. The Sn–H bond is weak and Bu_3SnH will react with alkyl halides to replace the halogen atom with H, producing Bu_3SnHal as a by-product.



Bond	Representative bond energy, kJ mol^{-1}
C–Br	280
Sn–H	308
C–H	418
Sn–Br	552

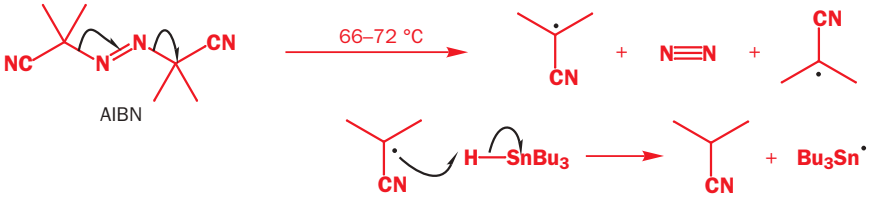
Clearly, for this reaction to be energetically favourable, new bonds formed (Sn–Br and C–H) must be stronger than the old bonds broken (Sn–H and C–halogen). Look at this table of average bond energies and you will see that this is indeed so.

The use of a tin hydride is crucial to this reaction: Sn–H bonds are weaker than Sn–Br bonds, while, for carbon, C–H bonds are stronger. Bu_3SnH is therefore an effective source of $Bu_3Sn^{\bullet}$ radicals, and the $Bu_3Sn^{\bullet}$ radical will abstract halogens, particularly I or Br, but also Cl, from organic halides, breaking a weak C–halogen (C–Hal) bond and forming a strong Sn–Hal bond. The complete mechanism of the reaction reveals a chain reaction.



Homolysis of Bu_3SnH is promoted by the initiator AIBN

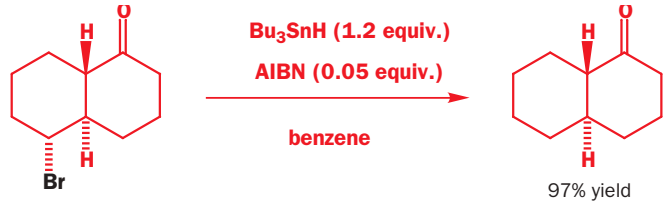
As you would imagine, the weakest C–Hal bonds are the easiest to cleave, so alkyl bromides are reduced more rapidly than alkyl chlorides, and alkyl fluorides are unreactive. With alkyl iodides and bromides, daylight can be sufficient to initiate the reaction, but with alkyl chlorides, and often with alkyl bromides as well, it is generally necessary to produce a higher concentration of $Bu_3Sn^{\bullet}$ radicals by adding an initiator to the reaction. The best choice is usually AIBN, which you met on p. 000. This compound undergoes thermal homolysis at 60 °C to give nitrile-stabilized radicals that abstract the hydrogen atom from Bu_3SnH.



Why use AIBN; why not a peroxide? (You came across peroxides as initiators of the addition of H–Br to alkenes.) Since we want to cleave only a weak Sn–H bond, we can get away with using a relatively unreactive, nitrile-stabilized radical. Peroxides, on the other hand, generate $RO^{\bullet}$ radicals. These are highly reactive and will abstract hydrogen from almost any organic molecule, not just the weakly bonded hydrogen atom of Bu_3SnH, and this would lead to side-reactions and lack of selectivity. AIBN is needed only in sufficient quantities to be an initiator of the reaction; it is the Bu_3SnH that provides the hydrogen atoms that end up in the product, so usually you need only 0.02 to 0.05 equivalents of AIBN and a slight excess (1.2 equivalents) of Bu_3SnH.

▶ The bond energy of H–CH_2CN is only 360 kJ mol^{-1}; a tertiary C–H bond next to a CN group should be even weaker.

▶ Bond energy of O–H = 460 kJ mol^{-1}; few C–H bonds are stronger than 440 kJ mol^{-1}.



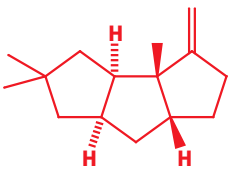
97% yield

Controlling radical chains

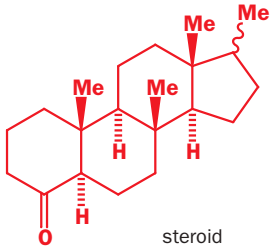
You have now met two examples of radical chain reactions:

1. radical addition of halogens to double bonds
2. radical substitution of hydrogen by halogens, or of halogens by hydrogen

You have seen how the selectivity of these reactions depends upon the bond strengths of the bond being formed or broken. Until about 1975, these reactions, with a few exceptions, were all that were expected of radicals. Since that date, however, the use of radicals in synthetic chemistry has increased tremendously, to the point where highly complex ring structures such as the natural product hirsutene and steroids can be made from simple acyclic precursors in one radical-promoted step.



hirsutene



steroid

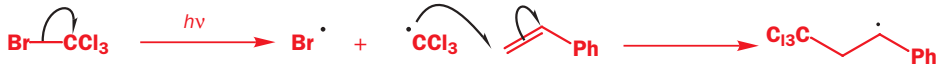
What has made this all possible is that chemists have learned how to understand the selectivity of radical reactions to such a degree that they can design starting materials and reagents to define

precisely the bonds that will break and form during the reactions. We shall now go on to look at the most important consequence of this ability to control radical reactions: they can be used to make carbon–carbon bonds.

Carbon–carbon bond formation using radicals

The following radical reaction forms a new carbon–carbon bond. The mechanism is quite similar to that of the very first radical reaction we showed you, right at the beginning of the chapter. Now, with your additional appreciation of the role of bond strength in the selectivity radical reactions, you should be able to understand why each step proceeds in the way that it does.

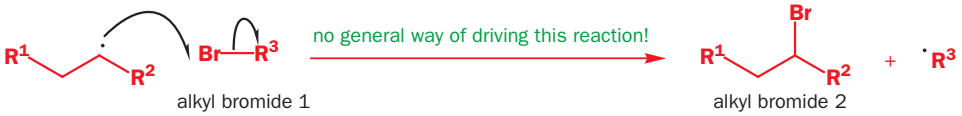
Firstly, the weakest bond, C–Br, is broken by the light being shone on to the reaction. Two radicals form, $\cdot CCl_3$ and $Br^{\bullet}$, and it is the $\cdot CCl_3$ that adds to the (less hindered) unsubstituted end of the alkene to produce a (more stable) secondary benzylic radical.



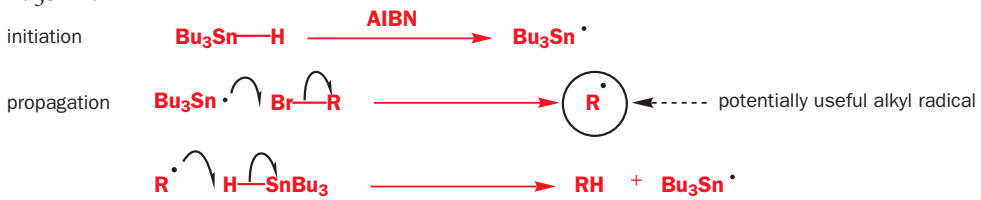
▶ It is mainly this step that produces the $\cdot CCl_3$ that undergoes addition to the alkene—the initial photolysis, of course, produces both $Br^{\bullet}$ and $\cdot CCl_3$, either of which could add, but, once the radical chain has been initiated, only $\cdot CCl_3$ is reproduced.

This radical abstracts a Br, atom from the $BrCCl_3$, breaking the (weakest) C–Br bond, forming the product and regenerating $\cdot CCl_3$, which adds to another molecule of alkene. Notice that the carbon-centred radical abstracts $Br^{\bullet}$ and not $\cdot CCl_3$ from $BrCCl_3$—to abstract $\cdot CCl_3$ would require a radical substitution at carbon—remember, radicals want the easy pickings from the front of the display; they don't go nosing round the back to see if there's anything better to be had.

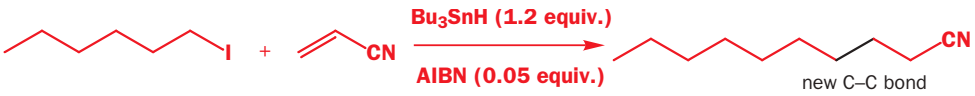
This reaction works quite well, giving 78% of the product, but it relies on the fact that the starting material, $BrCCl_3$, has an unusually weak C–Br bond (the $\cdot CCl_3$ radical is highly stabilized by those three chlorine atoms). You can't use most other alkyl bromides for a number of reasons, not least of them being that the product is also an alkyl bromide and, without the selectivity provided by the CCl_3 group, the result would be an awful mixture of polymers. The problem is that we want the product radical to abstract Br from the starting alkyl bromide to make a new alkyl bromide and a new starting radical, and there is no energetic driving force behind this transformation.



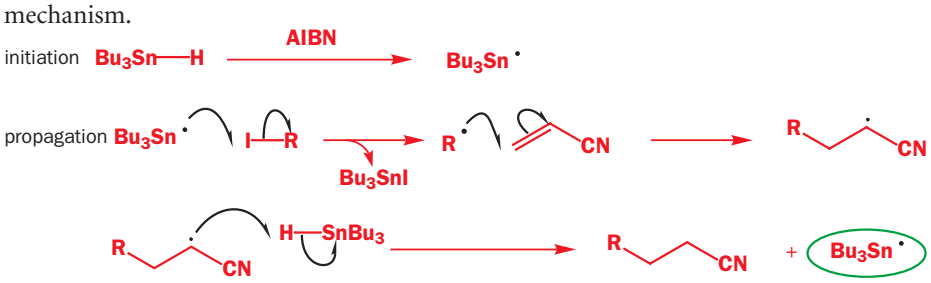
For a way of overcoming this problem, let's go back to the reaction we looked at a few pages ago, the dehalogenation of alkyl halides by Bu_3SnH. The mechanism involves formation of an alkyl (carbon-centred) radical by abstraction of Br by $Bu_3Sn^{\bullet}$. This alkyl radical then just abstracted $H^{\bullet}$ from Bu_3SnH.



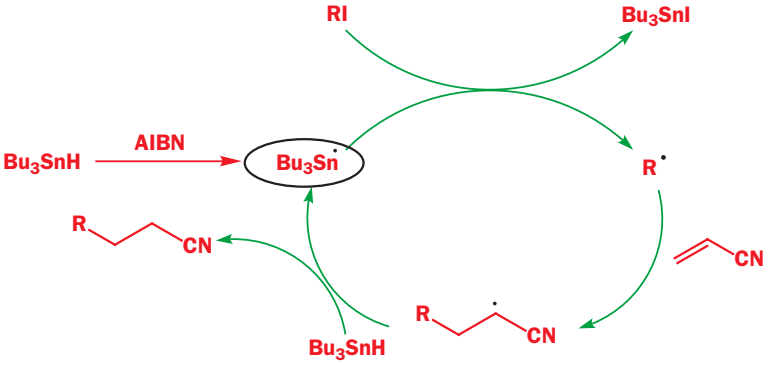
Is it not possible to use this alkyl radical more constructively, and encourage it to react with another molecule (an alkene, say, like $\cdot CCl_3$ did)? The answer is a qualified yes: look at this reaction.



We have added a carbon-centred radical to an alkene in a radical chain reaction! Here is the mechanism.



We can alternatively represent the mechanism of the reaction cyclically.

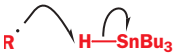
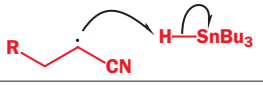
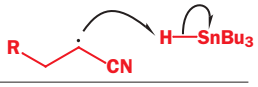
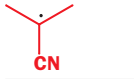


The key point is that the product radical does not have to abstract the halogen from the starting material, but H from Bu_3SnH; it is the $Bu_3Sn^•$ thus formed that then regenerates the starting radical. The driving force is provided by formation of C–H at the expense of Sn–H and then Sn–Br at the expense of C–Br.

■ We explained on p. 000 how these same favourable thermodynamics drove the Bu_3SnH-promoted reduction of alkyl halides.

The use of tin hydrides has increased the power of radical reaction in organic synthesis tremendously, and all of the steps in these radical chain processes have been studied in great detail because of the importance of the reactions. We won't dwell excessively on these details, but we need to go back and re-examine some points about this reaction because there are some further subtleties that you need to understand.

Bear in mind that we have four radicals all in the reaction mixture at the same time. Yet each reacts with its chosen partner, forsaking all others.

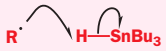
Radical	Reacts like this	Does not react like this
$Bu_3Sn^•$		
$R^•$		
		
		

Let's take each radical in turn, and look at its selectivity. Clearly bond strength has something to do with it, but how do you explain the opposing selectivities of $R^•$ and the nitrile-stabilized radicals? We will see that the origins of the selectivities impose some restrictions on the type of starting material that can be used for these C–C bond-forming reactions.

▶ For the addition of an alkyl radical to an alkene:

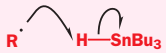
Reacts like this

Does not react like this



Yet for the radical dehalogenation:

Reacts like this



1 $Bu_3Sn^{\bullet}$. Unlike the case of the simple dehalogenation, the tin hydride radical here has a choice of reaction partners: it can either abstract the halide from the starting material or it can add to the alkene. The Sn–C bond is relatively weak, so addition to the alkene becomes a significant reaction only if:

- there is a large excess of alkene present, and
- the starting alkyl halide is relatively unreactive. This means that only alkyl bromides and iodides can be used effectively to form carbon–carbon bonds; alkyl chlorides are just too unreactive

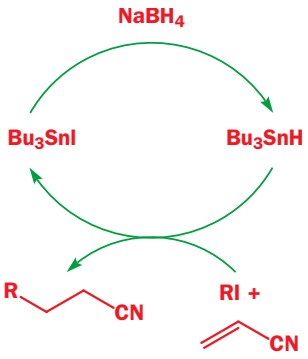
2 $R^{\bullet}$. On comparing the mechanism of this reaction with that of radical dehalogenation, you may rightly be concerned by the fact that in the dehalogenation the alkyl radical produced from the alkyl bromide was intended to abstract $H^{\bullet}$ from the Bu_3SnH, whereas now, the alkyl radical is intended to react with an alkene, despite the fact that Bu_3SnH is still a component of the reaction mixture.

Concentration effects

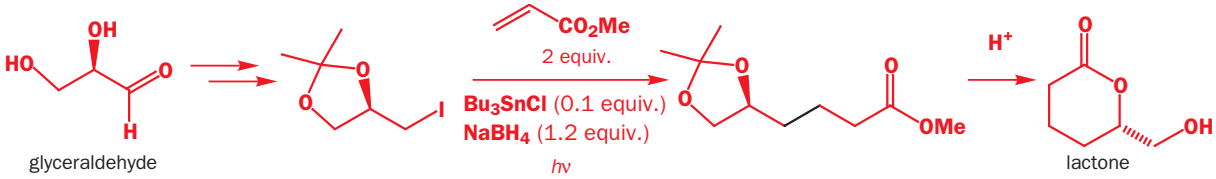
In fact, the rate *constant* for reaction of $R^{\bullet}$ with Bu_3SnH is about the same as that for reaction with acrylonitrile (CH_2=CHCN), so the only way in which good yields can be obtained is by ensuring that the concentration of acrylonitrile is always at least 10 times that of the tin hydride. The difference in rates will then be sufficient to give 10 times as much addition to the alkene as reduction by the tin hydride. Too much acrylonitrile in the reaction mixture causes problems with side-reactions, so a good way of achieving this is to add the tin hydride very slowly during the reaction—often a device known as a syringe pump is used for this. Of course, for complete reaction, a whole equivalent of hydride is necessary, but this can be added over a period of hours.

▶ A useful alternative to $NaBH_4$ as a reducing agent, particularly when there are reactive carbonyl groups in the molecule, is $NaCNBH_3$, which still reduces Bu_3SnHal but will not touch aldehydes or ketones.

An elegant alternative is to use a technique conceptually similar to the use of NBS to provide a low concentration of Br_2 for radical allylic substitution. Instead of adding one equivalent of Bu_3SnH, a catalytic amount (usually 0.1–0.2 equivalents) of Bu_3SnCl is added at the beginning of the reaction, with one equivalent of $NaBH_4$. $NaBH_4$ will reduce Bu_3SnHal to Bu_3SnH, so about 0.1 equivalent of Bu_3SnH is formed immediately. With each cycle of the chain reaction, a molecule of this Bu_3SnH is converted to Bu_3SnBr, which $NaBH_4$ can reduce back to Bu_3SnH. Only as much Bu_3SnH is produced as is needed, because the rate of production is limited by the rate of reaction.



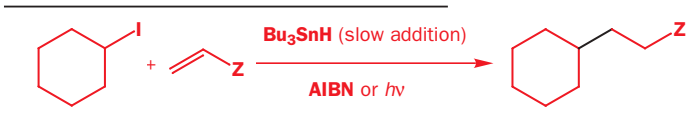
This method was used in the following example, in which an enantiomerically pure lactone, a useful synthetic building block, was made from naturally occurring glyceraldehyde.

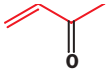
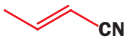
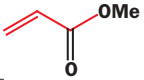
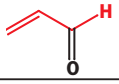


Frontier orbital effects

The second key to success in making sure that the alkyl radical behaves well is to use a reactive radical trap. In fact, this is a major limitation of intermolecular radical carbon–carbon bond-forming reactions: for the trapping of alkyl radicals only electrophilic alkenes (attached to electron-withdrawing groups such as –CN, $-CO_2Me$, –COMe) will do. This is a limitation, but nonetheless, cyclohexyl iodide adds to all these alkenes with the yields shown and the rate of addition to most of these alkenes is 10^3 to 10^4 times that of addition to 1-hexene.

To explain why, we have to go back to our analysis (on p. 000) of the electronic structure of radicals and the energy of SOMOs. We said there that, while both electron-withdrawing groups and electron-donating groups will stabilize radicals, electron-withdrawing groups tend to lower the energy of the SOMO, while electron-donating groups tend to raise the energy of the SOMO.

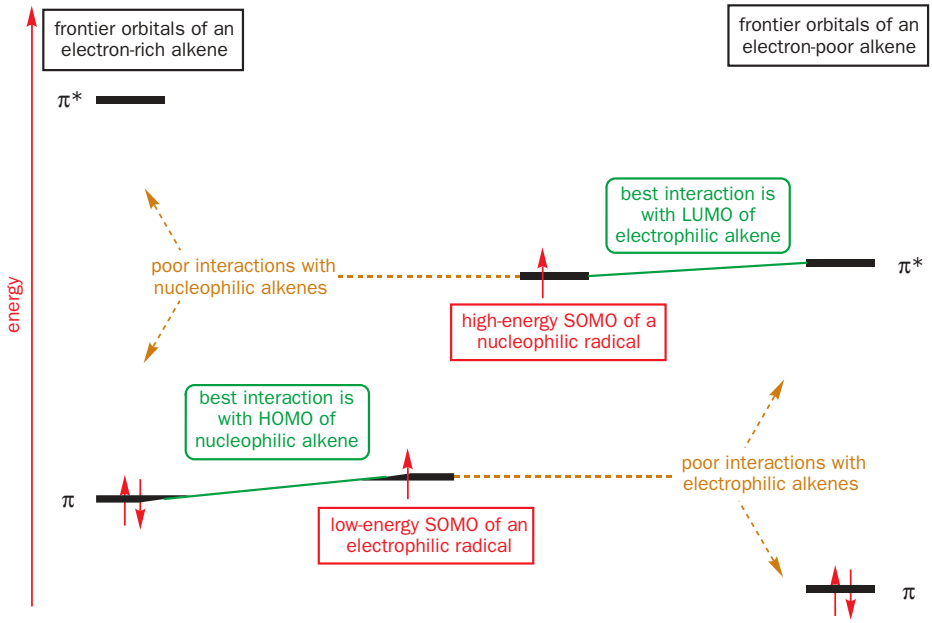


Alkene	% Yield	Alkene	% Yield
	95		85
	86		85
	72		83
	90		87

Electrophilic and nucleophilic radicals

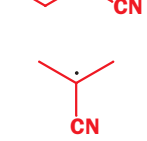
- *Low-energy* SOMOs are more willing to accept an electron than to give one up; radicals adjacent to electron-withdrawing groups are therefore *electrophilic*
- *High-energy* SOMOs are more willing to give up an electron than to accept an electron; radicals adjacent to electron-donating groups are therefore *nucleophilic*

Hence the preferred reactivity of these alkyl radicals: they are relatively nucleophilic and therefore prefer to react with electrophilic alkenes. Reaction between a nucleophilic alkyl radical and an unfunctionalized (and therefore nucleophilic) alkene is much slower. Similarly, radicals adjacent to electron-withdrawing groups do not react well with electrophilic alkenes. We can represent all this on an energy level diagram.

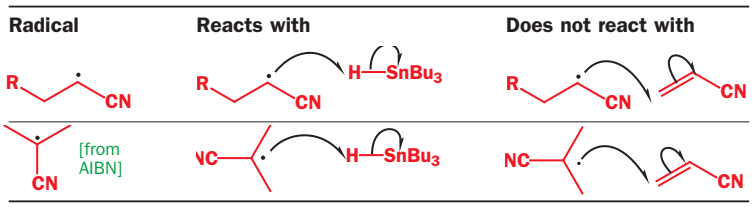


We will now consider a third type of radical—**cyanide-stabilized alkyl radicals**.

The diagram above explains the third aspect of radical chemoselectivity in this reaction: why both the product radical and the radicals produced by AIBN choose to react with Bu_3SnH and not with acrylonitrile. These radicals are electrophilic—they have an electron-withdrawing nitrile group attached to the radical centre so reaction with an electron-poor alkene is slow.



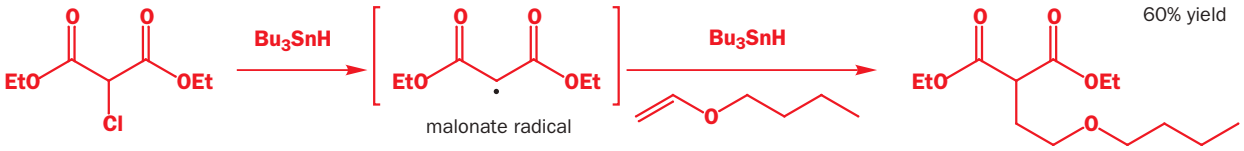
■ Radical types (1) and (2) were discussed on p. 000.



▶ Notice that this reaction works even though a C–Cl bond needs to be broken to generate the radical. Usually only C–I and C–Br bonds can be used. However, this is a very weak C–Cl bond because the radical produced is so stable.

Electrophilic radicals

Having seen the energy diagram above, you will not be surprised to learn that the malonate radical adds readily not to electrophilic alkenes, but to nucleophilic alkenes, such as this vinyl ether, which carries an electron-donating oxygen substituent. This electrophilic radical can also be formed by H-abstraction and by oxidation.



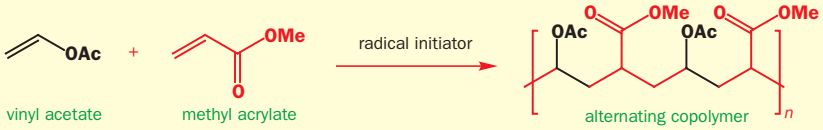
This difference in reactivity applies to non-carbon-centred radicals too. For example, the methyl radical $CH_3^{\bullet}$ and the chlorine radical $Cl^{\bullet}$ will both abstract a hydrogen atom from propionic acid. As you would expect, the methyl radical abstracts the hydrogen atom from next to the carbonyl group to form a carbonyl-stabilized radical. Perhaps surprisingly (in view of what we said earlier about the selectivity of radical chlorinations), the chlorine radical abstracts a hydrogen atom from the terminal methyl group of the acid, despite the fact that this C–H bond is stronger. The reason has to be to do with HOMO–LUMO interactions. The methyl radical is nucleophilic, with a high-energy SOMO. It therefore attacks the C–H bond with the lowest LUMO, in other words, α to the carbonyl group. The chlorine atom, on the other hand, is electrophilic: it has a low-energy SOMO (because it is an electronegative element) and attacks the C–H bonds of the terminal methyl group because they have the highest-energy HOMO. Chlorination of functionalized compounds is not as simple as we implied earlier!

● Summary of requirements for the successful use of the tin method

• Bu_3SnH	must be added or generated slowly
• R–X starting material	must contain a weak C–X bond (C–I or C–Br)
• Radical trap	must be an electrophilic alkene
	must be present in a concentration at least 10 times that of Bu_3SnH

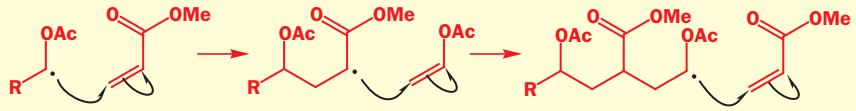
Copolymerization

Radical chain reactions are particularly suited to the synthesis of polymers, and we will look at this rather special type of radical reaction in Chapter 52. But there is one example of a polymerization that is worth including here since it demonstrates very nicely the effect of electron-withdrawing or -donating substituents on radical reactivity. When a mixture of vinyl acetate and methyl acrylate is treated with a radical initiator, a rather remarkable polymerization takes place. The polymer produced contains *alternating* vinyl acetate and methyl acrylate monomers along the length of its chain.



The mechanism of the reaction shows you why. The nucleophilic radical from vinyl acetate (adjacent to filled n orbital of OAc; high-energy SOMO) prefers to add to the electrophilic alkene (the acrylate). The new radical (adjacent to the empty π* orbital of CO_2Me; low-energy SOMO) is electrophilic and prefers to add to nucleophilic alkene (the vinyl acetate). This produces a new nucleophilic radical, which again prefers to add to the electrophilic alkene, and the whole cycle repeats endlessly.

Copolymerization—continued



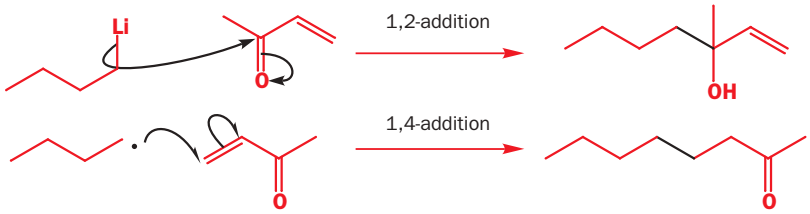
The radical produced by addition to vinyl acetate is nucleophilic, so it adds to methyl acrylate; the radical produced by addition to methyl acrylate is electrophilic, so it adds to vinyl acetate. This reaction is a clear demonstration of the power of frontier orbital theory to explain the reactivity of organic molecules—it would be hard to come up with any other convincing explanation.

The reactivity pattern of radicals is quite different from that of polar reagents

The first reaction that you met in this book, in Chapter 2, was the nucleophilic addition to a carbonyl group. Yet we have shown you no examples of radicals adding to carbonyl groups. This typical reaction of polar reagents is really quite rare with radicals.

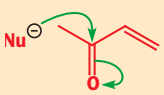
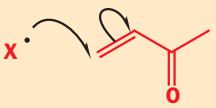
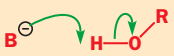
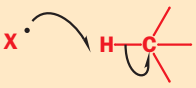
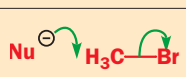
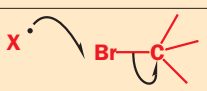
In Chapter 8 we introduced the concept of pK_a in which we saw acids and bases exchanging protons. Among the strongest organic acids are those containing O–H bonds. Yet you have seen no radical reactions in which an O–H bond is broken—in fact the reaction on p. 000 used ethanol as a solvent! Carbon acids tend to be much weaker—yet you've seen plenty of examples of C–H bonds being broken by radical attack.

In Chapter 17 we introduced nucleophilic substitution at saturated carbon, using as an example some alkyl bromides. Now, radicals do react with alkyl halides—but not at carbon! You've seen how alkyl halides undergo substitution at bromine with tin radicals. The difference in reactivity between, say, organolithiums and radicals, both of them highly reactive, is nicely illustrated by the way in which they react with enones.



We introduced the terms *hard* and *soft* in Chapters 10 and 17. From all these reactions it's evident that radicals are very soft species: their reactions are driven not by the charge density on an atom but by the coefficient and energy of the frontier orbitals at that atom.

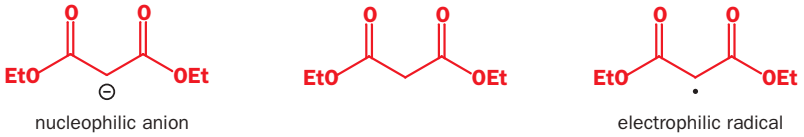
Summary of typical reactivity patterns

With	Polar nucleophiles typically react like this	Radicals typically react like this
unsaturated C=O compounds		
X–H bonds		
alkyl halides		

Umpolung

In Chapter 30, you came across the idea of **umpolung**, the inversion of the usual reactivity pattern of a molecule. You may have already noticed that radicals often have an umpolung reactivity pattern. Alkyl halides are electrophiles in polar reactions; yet they generate nucleophilic radicals that react with electrophilic alkenes.

Similarly, we consider the carbon atoms α to carbonyl groups to be nucleophilic, because enolization creates a partial negative charge there (in other words, ketones are a[1] reagents). Yet carbonyl-stabilized radicals are electrophilic.



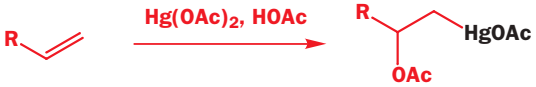
An alternative way of making alkyl radicals: the mercury method

Although the tin hydride + alkyl halide method is probably the most important way of making alkyl radicals, we should mention some other methods that are useful. We said at the beginning of the chapter that carbon–metal bonds, particularly carbon–transition metal bonds, are weak and can homolyse to form radicals. Alkyl mercuries are useful sources of alkyl radicals for this reason. They can be made by a number of routes, for example, from Grignard reagents by transmetallation.

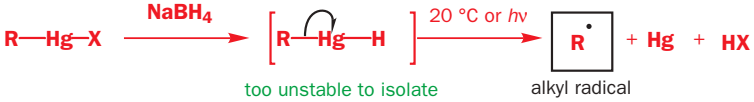
▶ This transmetallation works because mercury is softer than magnesium and therefore prefers the softer alkyl ligand.

Addition of mercury acetate to a double bond gives an alkyl mercury bearing a functional group.

■ This is an **oxymercuration reaction**. You met it in Chapter 20.

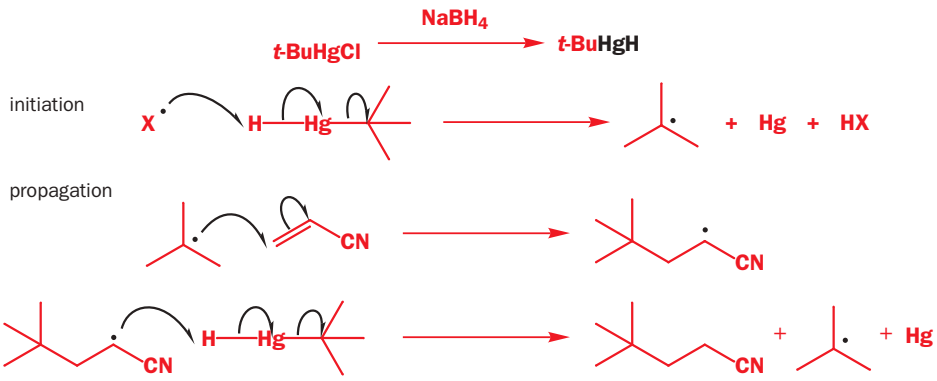


Alkyl mercury halides and alkyl mercury acetates are quite stable, but reduction with sodium borohydride leads to highly unstable alkyl mercury hydrides, which collapse at room temperature or in the presence of light to yield alkyl radicals. One other product is mercury metal and you might think you would get H• as well but this is too unstable to be formed and is captured by something else (X)—you will see what X is in a moment. This initial decomposition of RHgH initiates the chain but its propagation is by the different mechanism shown below.



In this example a *t*-butyl radical does conjugate addition on to acrylonitrile.

The key propagation step in the mechanism is abstraction of hydride from the starting alkyl mercury. In the propagation step anything will do to cleave the weak Hg–H bond but once the chain is running it is an alkyl radical that does this job, just as in tin hydride chemistry.



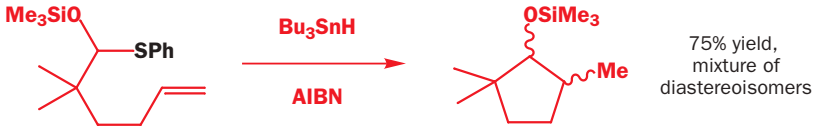
Notice that *tert*-butyl radicals add readily to electrophilic alkenes: using *tert*-butyl Grignards or *tert*-butyllithium as nucleophiles is much more problematic.

Unfortunately, radicals derived from alkylmercuries are even more limited in what they will react with than radicals made from alkyl halides by the tin hydride method. Styrene, for example, cannot be used to trap alkylmercury-derived radicals efficiently because the radicals react more rapidly with the mercury hydride (which has an even weaker metal–H bond than Bu_3SnH) than with the styrene.

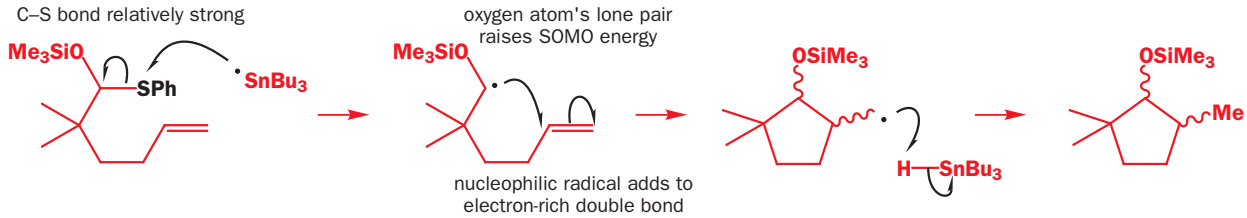
We discussed this selectivity problem as it applied to the tin hydride method on p. 000.

Intramolecular radical reactions are more efficient than intermolecular ones

All of the reactions you have met so far involve radical attack between two molecules. We've pointed out some of the drawbacks when C–C bonds are made in this way: the radical trap has to be activated (that is, electrophilic to capture nucleophilic radicals) and must often be present in excess; and the radical starting material must contain very weak C–X bonds (such as C–Br, C–I, C–Hg). The requirements are much less stringent, however, if the radical reaction is carried out intramolecularly. For example, this reaction works.



Notice that the double bond is not activated: in fact, it is nucleophilic, and the reaction still works even though the radical is also substituted with an electron-donating group. The C–S bond that is broken is also relatively strong, yet nonetheless a high yield of product is obtained. Why should this be so? What difference does it make that the reactions are intramolecular?



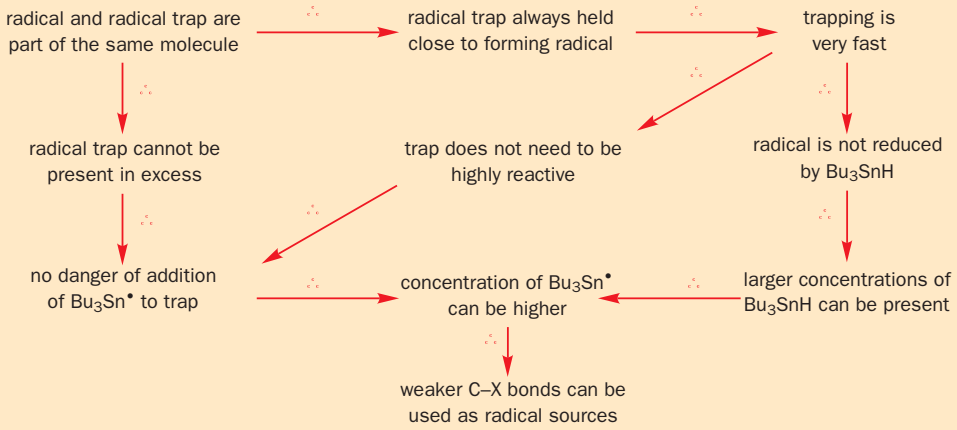
The key is that the intramolecular cyclization of the radical is now enormously favoured over other possible courses of action for the radical. Remember that when we were carrying out radical reactions *inter*molecularly, addition to the radical trap was encouraged by increasing the concentration of radical trap and decreasing the concentration of Bu_3SnH to avoid radical reduction. For *intra*molecular reactions, the double bond that acts as the radical trap is always held close to the radical, and cyclization takes place extremely rapidly, even on to unactivated double bonds. The hydride donor (Bu_3SnH) doesn't get a look in, and can be present in higher concentrations than would otherwise be possible. Moreover, as there is only one equivalent of radical trap, and the trap need not be highly reactive, there is little danger of high concentrations of $Bu_3Sn^{\bullet}$ reacting with it, so

Some useful bond strengths

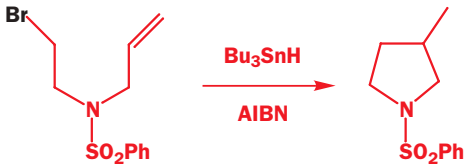
Bond	Typical bond energy, kJ mol^{-1}
C–I	238
C–Br	280
C–Cl	331
C–S	320

the concentration of $Bu_3Sn^•$ can build up to levels where the rate of abstraction of groups like Cl, SPh, and SePh is acceptable, despite their stronger C–X bonds.

Why are intramolecular radical reactions so good?

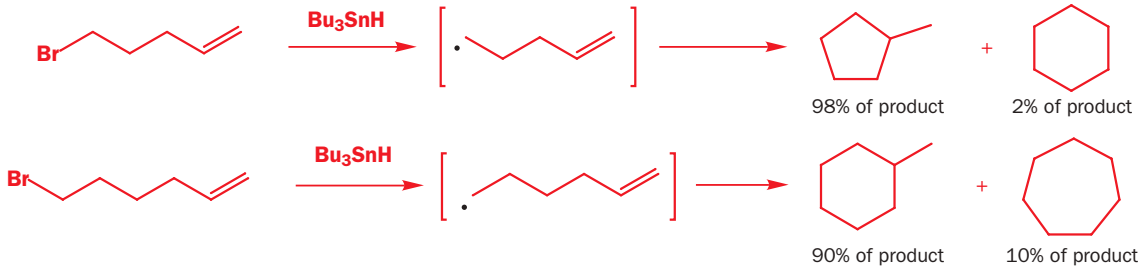


Overall then, intramolecular radical reactions are very powerful, and are often used to make five-membered rings.



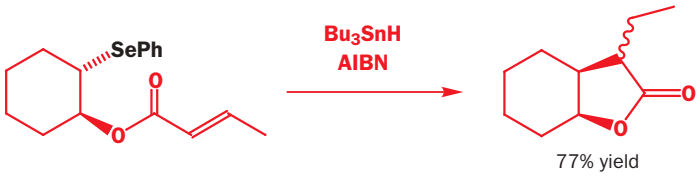
87% yield

It is possible to make other ring sizes also, but the range is rather limited. Because of ring strain, three- and four-membered rings cannot be formed by radical reactions. Otherwise, smaller rings form faster than larger ones: look at these selectivities.



■ In Chapter 41 we will learn to analyse these situations using Baldwin's rules.

The preference for formation of a smaller ring is a very powerful one: in this reaction, the five-membered ring forms and not the six-membered one, even though cyclization to give a six-membered ring would also give a stabilized radical.

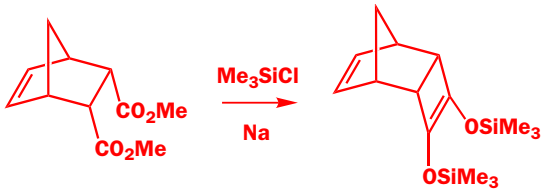


77% yield

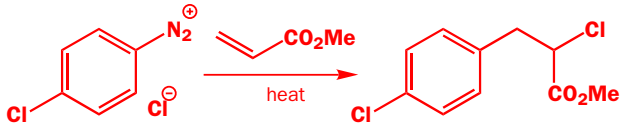
Radicals are important because they react in ways difficult to achieve with anions and cations and with different selectivity. Though radical reactions are less important than ionic reactions you need to understand their mechanisms because they are widespread in an atmosphere of the oxygen diradical. In the next chapter we will move on from carbon atoms carrying seven valence electrons to carbon atoms carrying only six valence electrons called *carbenes*.

Problems

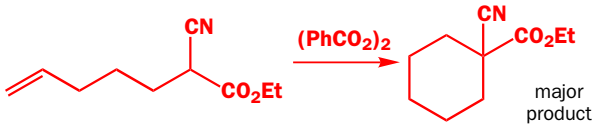
1. In Chapter 33, Problem 13, we used a silylated ene-diol that was actually made in this way. Give a mechanism for the reaction and explain why the Me_3SiCl is necessary.



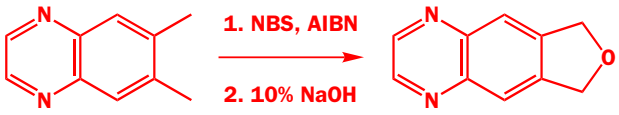
2. Heating the diazonium salt below in the presence of methyl acrylate gives a reasonable yield of a chloroacid. Why is this unlikely to be nucleophilic aromatic substitution by the S_N1 mechanism (Chapter 22)? Suggest an alternative mechanism that explains the regioselectivity.



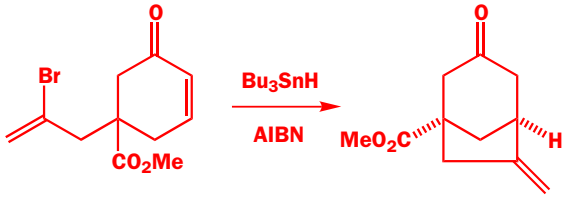
3. Suggest a mechanism for this reaction and comment on the ring size formed. What is the minor product likely to be?



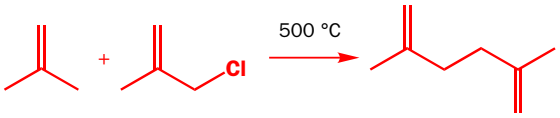
4. Treatment of this aromatic heterocycle with NBS (*N*-bromosuccinimide) and AIBN gives mainly one product but this is difficult to purify from minor impurities containing one or three bromine atoms. Further treatment with 10% aqueous NaOH gives one easily separable product in modest yield (50%). What are the mechanisms for the reactions? What might the minor products be?



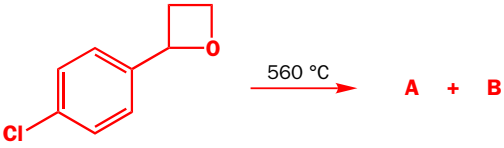
5. Propose a mechanism for this reaction accounting for the selectivity. Include a conformational drawing of the product.



6. An ICI (now AstraZeneca) process for the manufacture of the diene used to make pyrethroid insecticides involves heating these compounds to 500 °C in a flow system. Propose a radical chain mechanism for the reaction.



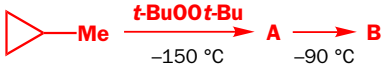
7. Heating this compound at 560°C gives two products with the spectroscopic data shown below. What are these products and how are they formed?



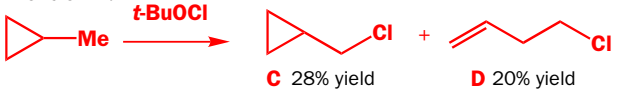
A has IR 1640 cm^{-1}; *m/z* 138 (100%), 140 (33%); δ_H 7.1 p.p.m. (4H, s), 6.5 p.p.m. (1H, dd, *J* 17, 11 Hz), 5.5 p.p.m. (1H, dd, *J* 17, 2 Hz), and 5.1 p.p.m. (1H, dd, *J* 11, 2 Hz).

B has IR 1700 cm^{-1}; *m/z* 111 (45%), 113 (15%), 139 (60%), 140 (100%), 141 (20%), and 142 (33%); δ_H 9.9 p.p.m. (1H, s), 7.75 p.p.m. (2H, d, *J* 9 Hz), and 7.43 (p.p.m. 2H, d, *J* 9 Hz).

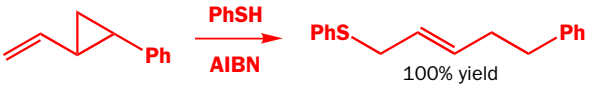
8. Treatment of methylcyclopropane with peroxides at very low temperature (–150 °C) gives an unstable species whose ESR spectrum consists of a triplet with coupling 20.7 gauss and fine splitting showing dtt coupling of 2.0, 2.6, and 3.0 gauss. Warming to a mere –90 °C gives a new species whose ESR spectrum consists of a triplet of triplets with coupling 22.2 and 28.5 gauss and fine splitting showing small ddd coupling of less than 1 gauss.



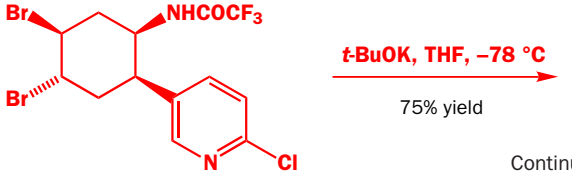
If methylcyclopropane is treated with *t*-BuOCl, various products are obtained, but the two major products are C and D. At lower temperatures more of C is formed and at higher temperatures more of D.



Treatment of the more highly substituted cyclopropane with PhSH and AIBN gives a single product in quantitative yield. Account for all of these reactions, identifying A and B and explaining the differences between the various experiments.



9. The last few stages of Corey's epibatidine synthesis are shown here. Give mechanisms for the first two reactions and suggest a reagent for the last step.



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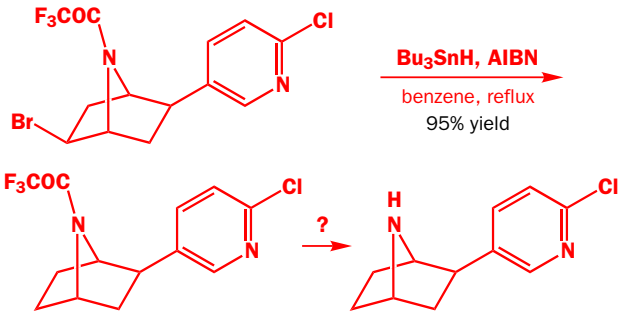
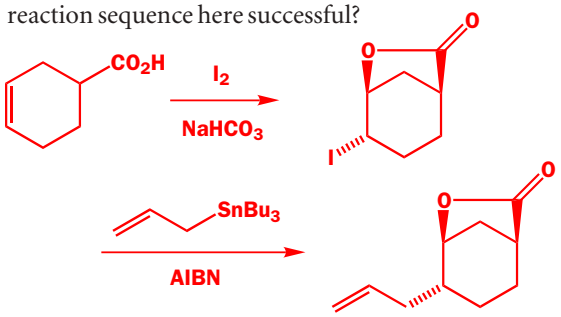
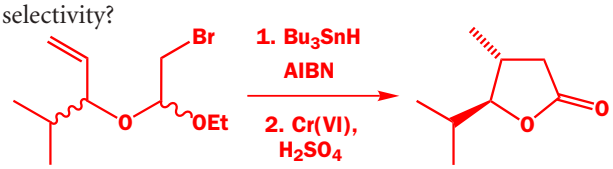


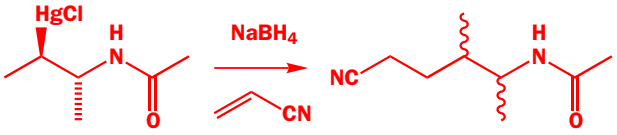
10. How would you make the starting material for this sequence of reactions? Give a mechanism for the first reaction that explains its regio- and stereoselectivity. Your answer should include a conformational drawing of the product. What is the mechanism of the last step? Attempts to carry out this last step by iodine–lithium exchange and reaction with allyl bromide fail. Why? Why is the reaction sequence here successful?



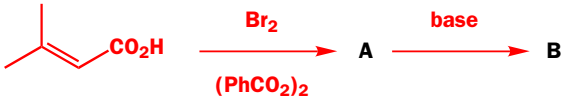
11. Suggest a mechanism for this reaction explaining why a mixture of diastereoisomers of the starting material gives a single diastereoisomer of the product. Is there any other form of selectivity?



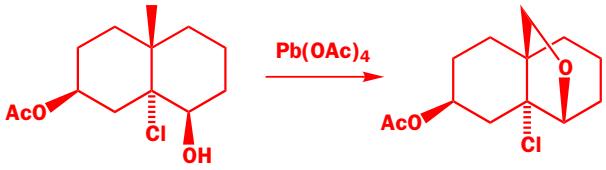
12. On the other hand, why does a single diastereoisomer of this organomercury compound give a mixture of diastereoisomers (68:32) on reduction with borohydride in the presence of acrylonitrile?



13. Reaction of this carboxylic acid ($C_5H_8O_2$) with bromine in the presence of dibenzoyl peroxide gives an unstable compound ($C_5H_6Br_2O_2$) that gives a stable compound ($C_5H_5BrO_2$) on treatment with base. The stable compound has IR 1735 and 1645 cm^{-1} and ^1H NMR δ_H 6.18 p.p.m. (1H, s), 5.00 p.p.m. (2H, s), and 4.18 p.p.m. (2H, s). What is the structure of the stable product? Deduce the structure of the unstable compound and mechanisms for the reactions.



14. The product formed in Problem 9 of Chapter 20 was actually used to make this cyclic ether. What is the mechanism?



Synthesis and reactions of carbenes

40

Connections

Building on:

- Conjugate addition ch10 & ch23
- Energy profile diagrams ch13
- Elimination reactions ch19
- Controlling stereochemistry ch16 & ch33–ch34
- Retrosynthetic analysis ch30
- Diastereoselectivity ch33–ch34
- Rearrangements ch37
- Radicals ch39

Arriving at:

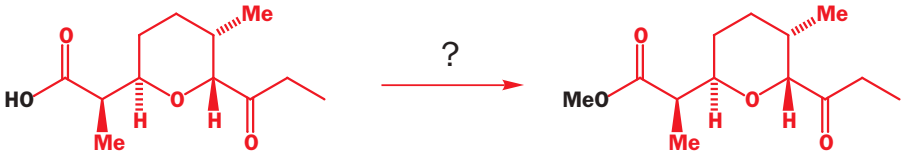
- Carbenes are neutral species with only six electrons
- Carbenes can have paired or unpaired electrons
- Carbenes are normally electrophilic
- Typical reactions include insertion into C=C bonds
- Insertion into C–H and O–H bonds is possible
- Intramolecular insertion is stereospecific
- Carbenes rearrange easily
- Carbenes are useful in synthesis

Looking forward to:

- Determination of mechanism ch41
- Heterocycles ch42–ch44
- Main group chemistry ch46–ch47
- Organometallic chemistry ch48

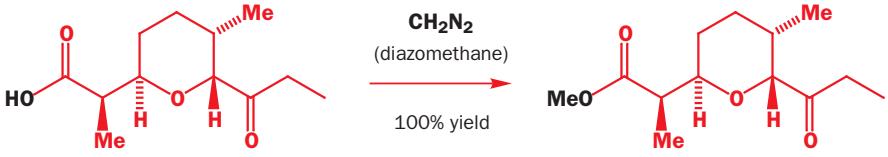
Diazomethane makes methyl esters from carboxylic acids

In 1981, some chemists in Pennsylvania needed to convert this carboxylic acid into its methyl ester as part of the synthesis of an antibiotic compound. What reagent did they choose to do the reaction?



You remember, of course, that esters can be made from carboxylic acids and alcohols under acid catalysis, so you might expect them to use this type of method. On a small scale, it's usually better to convert the acid to an acyl chloride before coupling with an alcohol, using pyridine (or DMAP + Et_3N) as a base; this type of reaction might have been a reasonable choice too.

But, in fact, they chose neither of these methods. Instead, they simply treated the carboxylic acid with a compound called diazomethane, CH_2N_2, and isolated the methyl ester.



Diazomethane, CH_2N_2, is a rather curious compound that has to be drawn as a dipole. There are several different ways of expressing its structure.

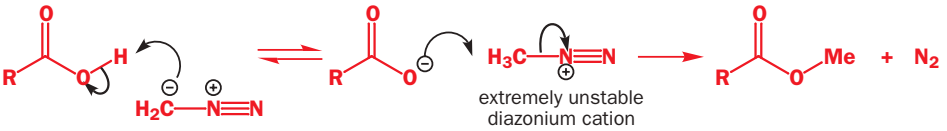
■ Look back at Chapter 12 if you need reminding of any of these reactions.

▶ You might like to think about why the alternatives would not be so suitable in this case.

■ You've met other molecules like this—carbon monoxide is one, and so are nitro compounds and the 1,3-dipoles you met in Chapter 35.

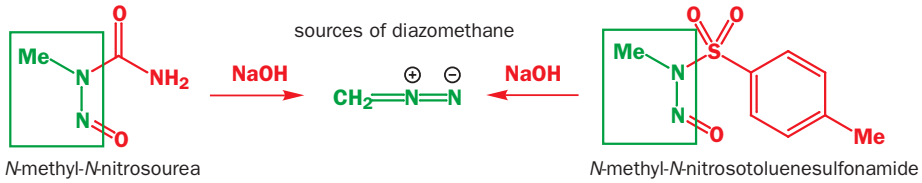
Diazomethane methylates carboxylic acids because carboxylic acids readily protonate it, giving an extremely unstable diazonium cation. This compound is desperate to lose N_2, the world's best leaving group, and so it does, with the N_2 being substituted by the carboxylate anion. The carboxylate anion is in exactly the right position to carry out an S_N2 reaction and that is what we have drawn.

▶ The exact mechanism of this step remains unclear—with such a good leaving group and a bad nucleophile you might expect S_N1, but that would require a methyl carbocation.



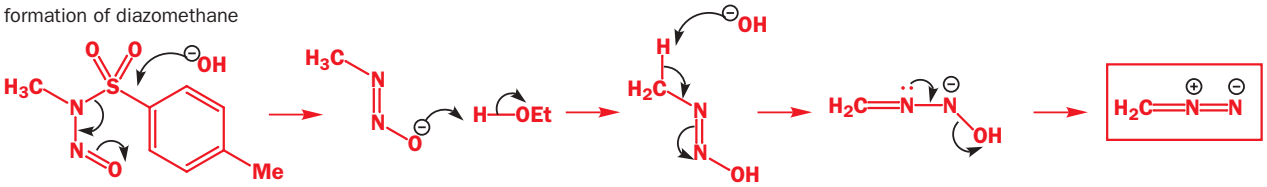
Diazomethane methylation is a good way of making methyl esters from carboxylic acids on a small scale because yields are excellent and the only by-product is nitrogen. However, there is a drawback: diazomethane has a boiling point of –24 °C, and it is a toxic and highly explosive gas. It therefore has to be used in solution, usually in ether; the solution must be dilute, because concentrated solutions of diazomethane are also explosive. It is usually produced by reaction of *N*-methyl-*N*-nitrosourea or *N*-methyl-*N*-nitrosotoluenesulfonamide with base, and distilled out of that reaction mixture as an azeotrope with ether, straight into a solution of the carboxylic acid.

▶ Conveniently, solutions containing diazomethane are yellow, so the reaction is **self-titrating**—as the carboxylic acid reacts, the yellow diazomethane is removed, but as long as excess diazomethane remains the yellow colour persists.



■ There is an alternative mechanism that starts by deprotonation at carbon: this forms one of the problems at the end of the chapter.

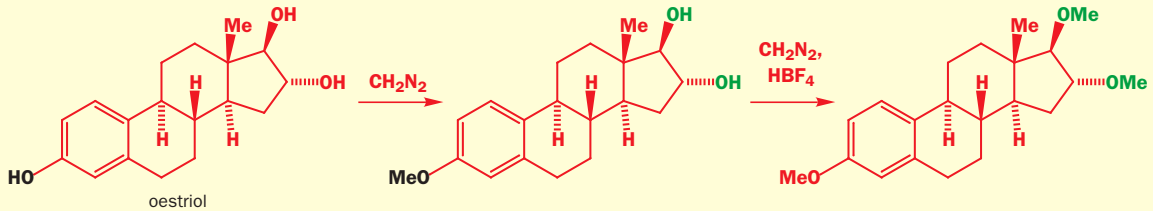
The mechanism of the reaction that forms diazomethane is shown below. The key step is base-catalysed elimination, though the curly arrows we have to draw to represent this are rather tortuous!



Diazomethane will also methylate phenols, because they too are acidic enough to protonate it. Ordinary alcohols, though, are not methylated because they are not strong enough acids to protonate diazomethane.

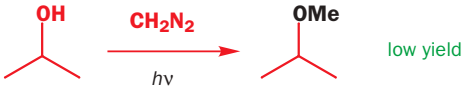
Selective methylation

Chemists studying the hormone degradation products present in the urine of pregnant women needed to methylate the phenolic hydroxyl group of the steroid oestriol. By using diazomethane, they avoided reaction at the two other hydroxylic groups. When, subsequently, they did want to methylate the other two hydroxyl groups, they had to add acid to the reaction to protonate the diazomethane.



Photolysis of diazomethane produces a carbene

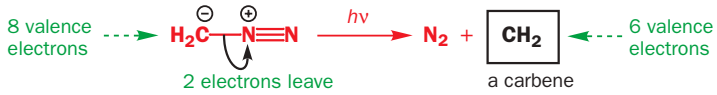
Alcohols *can* be methylated by diazomethane if the mixture is irradiated with light.



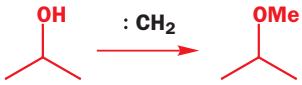
The mechanism is now totally different, because the light energy promotes loss of nitrogen (N_2) from the molecule *without protonation*. This means that what is left behind is a carbon atom carrying just two hydrogen atoms (CH_2), and having only six electrons. Species like this are called **carbenes**, and they are the subject of this chapter.

▶ Although this reaction illustrates an important point, the yield is too low, there are too many by-products, and the potential for serious explosions is too great for it ever to be useful as a way of making methyl ethers.

● Carbenes are neutral species containing a carbon atom with only six valence electrons.



Carbenes have six electrons: two in each bond and two nonbonding electrons, which are often represented as :CR_2 (as though they were a lone pair). As you will see later, this can be misleading, but :CR_2 is a widely used symbol for a carbene. This carbene is trapped by the alcohol to make an ether.



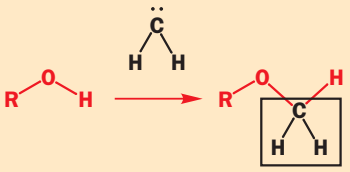
▶ Carbenium ions too have only six valence electrons, but, of course, unlike carbenes they are charged.

Like the radicals in Chapter 39, carbenes are extremely reactive species. As you have just seen, they are trapped by alcohols to make ethers, but more importantly they will react with alkenes to make cyclopropanes, and they will also insert into C–H bonds.

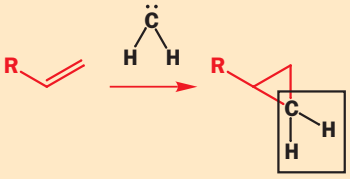
● Typical carbene reactions

- **The carbene inserts itself into a σ bond or a π bond.**

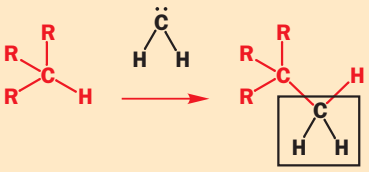
insertion in an O–H bond



insertion in a C=C bond



insertion in a C–H bond



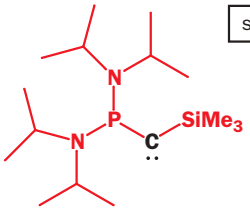
We will discuss the mechanisms of these three important reactions shortly, but we have introduced them to you now because they demonstrate that the reactions of carbenes are dominated by *insertion reactions* (here, insertion into O–H, C=C, and C–H) driven by their extreme *electrophilicity*. A carbon atom with only six electrons will do almost anything to get another two!

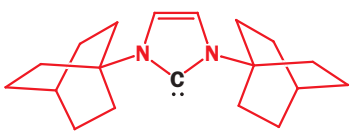
How do we know that carbenes exist?

The best evidence for the existence of carbenes comes from some very few examples that are stable compounds. An X-ray crystal structure of the second example shows the bond angle at the carbene carbon to be 102°—we will come back to the significance of this later.

stable carbenes

a red liquid





colourless crystals

But these stable carbenes are very much the exception: most carbenes are too reactive to be observed directly. Electronic and, more importantly, steric effects make these two compounds so stable.

Even reactive carbenes can be observed, however, if they are formed by irradiating precursors (often diazo compounds like diazomethane, which we have just been discussing) trapped in frozen argon at very low temperatures (less than 77 K). IR and ESR spectroscopy can then be used to determine their structure.

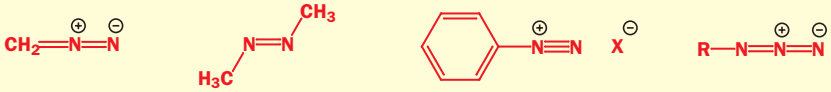
▶ You may be somewhat surprised that the structure of carbenes can be investigated by ESR—after all, we explained in Chapter 39 that ESR observes unpaired electrons, and you might expect the six valence electrons of a carbene all to be paired. Indeed, in some carbenes they are, but in many they are not. This is an important point, and we will discuss it at length later in the chapter.

How are carbenes formed?

Carbenes are usually formed from precursors by the loss of small, stable molecules. We will discuss some of the most important methods in turn, but you have already seen one in action: the loss of nitrogen from a diazo compound.

Naming azo compounds

Don't confuse *diazo* compounds with *azo* compounds. Diazomethane has twice as many nitrogen atoms per methyl group as azomethane.

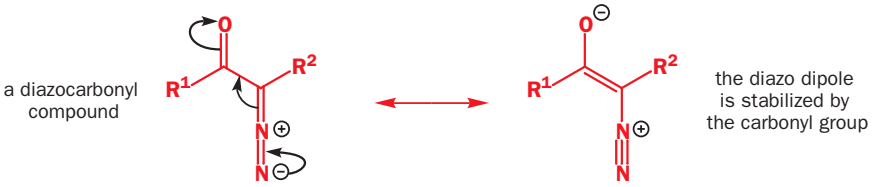


diazomethane azomethane benzenediazonium salt alkyl azide

You met *diazonium* salts in Chapter 23. Arene diazonium salts are stable compounds, but alkyl diazonium salts, which are formed by protonation of diazo compounds, are not. They decompose rapidly to carbocations—this was how the carboxylic acid got methylated at the beginning of the chapter. Other relatives of the azo and diazo compounds are alkyl azides. Alkyl azides have three nitrogen atoms and are usually stable but may explode on impact or heating.

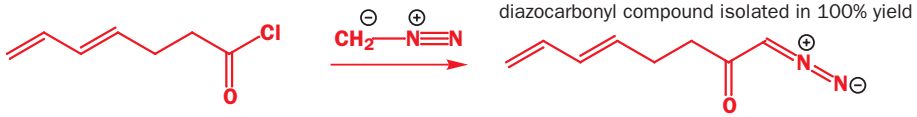
Carbenes from diazo compounds

We showed you the formation of a carbene from diazomethane to illustrate how this reaction was different from the (ionic) methylation of carboxylic acids. But this is not a very practical way of generating carbenes, not least because of the explosive nature of diazoalkanes. However, **diazocarbonyl compounds** are a different matter.

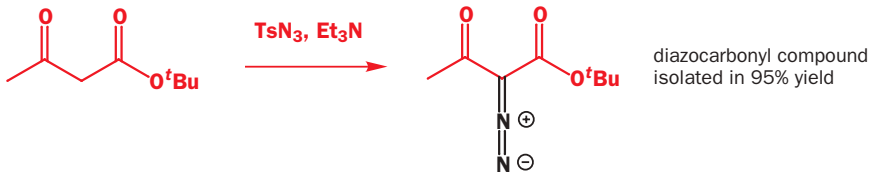


They are much more stable, because the electron-withdrawing carbonyl group stabilizes the diazo dipole, and are very useful sources of carbenes carrying a carbonyl substituent. There are two main ways of making diazocarbonyl compounds:

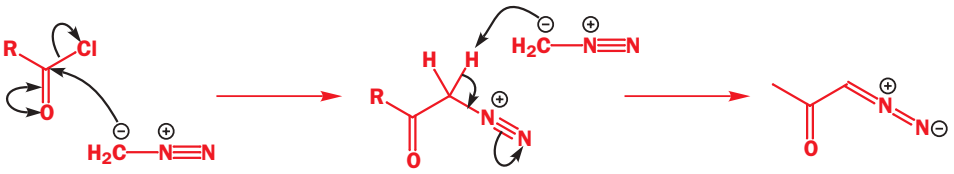
1 by reacting an acyl chloride with diazomethane



2 by reacting the parent carbonyl compound with tosyl azide, TsN_3, in the presence of base.



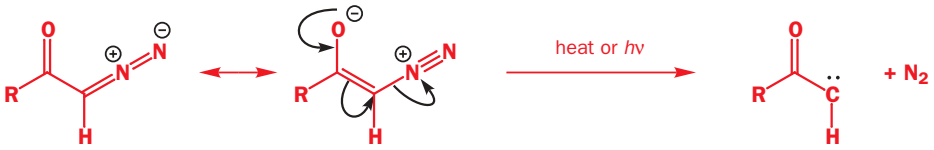
The reaction of diazomethane with acyl chlorides starts as a simple acylation to give a diazonium compound. If there is an excess of diazomethane, a second molecule acts as a base to remove a rather acidic proton between the carbonyl and the diazonium groups to give the diazocarbonyl compound.



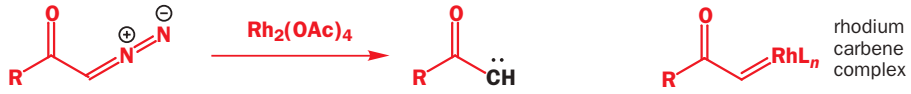
What happens to that second molecule of diazomethane? By collecting a proton it turns into the very reactive diazonium salt, which collects a chloride ion, and MeCl is given off as a gas. The second method uses tosyl azide, which is known as a **diazo transfer reagent**—it's just N_2 attached to a good leaving group.

tosyl azide, **TsN_3**

Diazocarbonyl compounds can be decomposed to carbenes by heat or light. The formation of very stable gaseous nitrogen compensates for the formation of the unstable carbene.



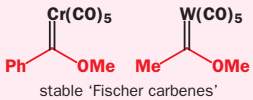
But it is much more common in modern chemistry to use a transition metal such as copper or rhodium, to promote formation of the carbene.



▶ RhL_n means rhodium with an unspecified number of unspecified ligands. This notation is common in organometallic chemistry when the nature of the carbon–metal bonding is important, but the precise structure of the metal complex is not.

Carbenes formed in this way are, in fact, not true carbenes because it appears that they remain complexed with the metal used to form them. They are known as **carbenoids**, and their reactions are discussed later in the chapter.

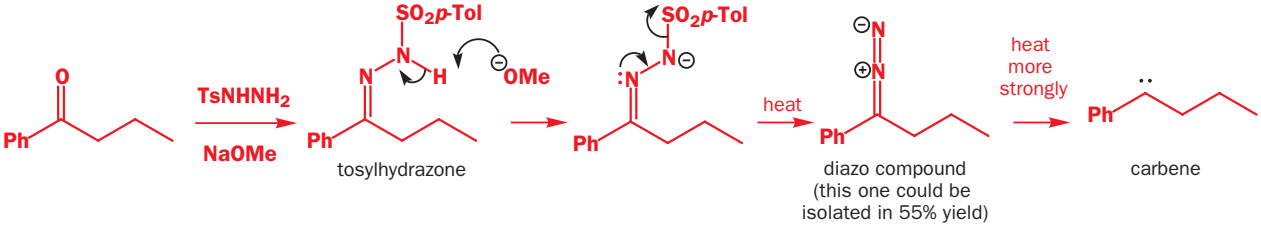
▶ While these rhodium and copper carbenoids are unstable, some transition metals such as tungsten and chromium form stable, isolable carbenoids, called **metallocarbenes** or **Fischer carbenes**.



stable 'Fischer carbenes'

Carbenes from tosylhydrazones

Many more carbenes can be made safely from diazoalkanes if the diazoalkane is just an intermediate in the reaction and not the starting material. Good starting materials for these reactions are tosylhydrazones, which produce transient diazo compounds by base-catalysed elimination of toluenesulfinate. The diazo compound is not normally isolated, and decomposes to the carbene on heating.



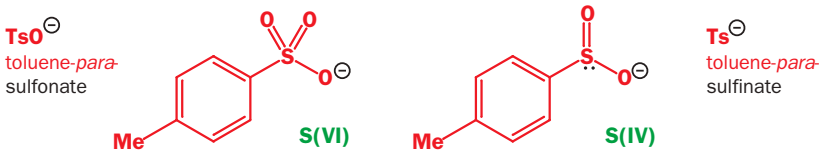
tosylhydrazone

diazo compound
(this one could be
isolated in 55% yield)

carbene

▶ This reaction is sometimes called the **Bamford–Stevens reaction**.

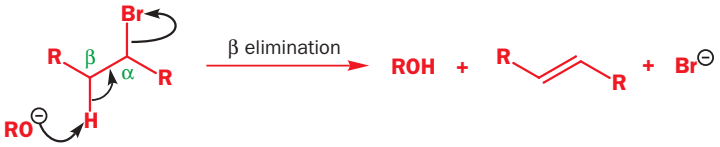
Notice that the leaving group from nitrogen is not the familiar tosylate (toluene-*p*-sulf*on*ate TsO^-) but the less familiar toluene-*p*-sulf*in*ate (Ts^-).



Carbenes are formed in a number of other similar reactions—for example, loss of carbon monoxide from ketenes or elimination of nitrogen from azirines—but these are rarely used as a way of deliberately making carbenes.

Carbene formation by α elimination

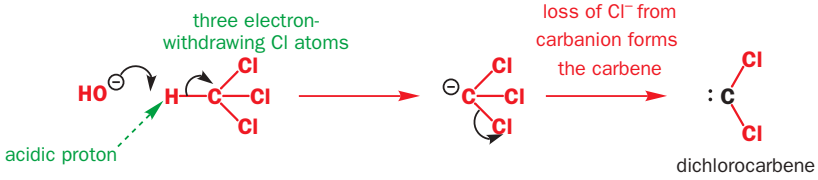
In Chapter 19 we discussed **β elimination** in detail, reactions in which a hydrogen atom is removed from the carbon atom β to the leaving group.



α Eliminations (eliminations in which both the proton and the leaving group are located on the same atom) are also possible—in fact, the reaction we've just been talking about (elimination of toluenesulfinate from tosylhydrazones) is an α elimination. α Eliminations follow a mechanism akin to an E1cB β elimination—a strong base removes an acidic proton adjacent to an electron withdrawing group to give a carbanion. Loss of a leaving group from the carbanion creates a carbene.

One of the best known α elimination reactions occurs when chloroform is treated with base. This is the most important way of making dichlorocarbene, $:CCl_2$, and other dihalocarbenes too, although it must be said that the widespread use of dichlorocarbene in chemistry is due mainly to the ease with which it can be made using this method!

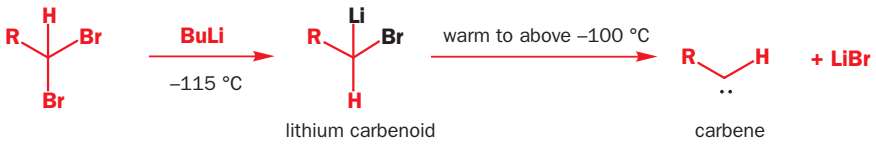
base-catalysed α elimination of HCl from chloroform



▶ The mixture *t*-BuLi/*t*-BuOK is known as **Schlosser's base**, and is one of the most powerful bases known. It will abstract protons from allylic or benzylic positions, and will even deprotonate benzene.

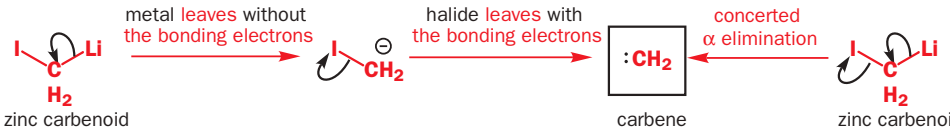
Hydroxide and alkoxide anions are strong enough bases to promote α elimination from chloroform, and from other trihalomethanes. Carbenes can be formed from dihaloalkanes by deprotonation with stronger bases such as LDA, and even from primary alkyl chlorides using the extremely powerful bases phenylsodium or *t*-BuLi/*t*-BuOK (weaker bases just cause β elimination).

When geminal dibromoalkanes are treated with BuLi, a halogen–metal exchange reaction produces a lithium carbenoid, with a metal atom and a halogen attached to the same carbon atom. Lithium carbenoids are stable at very low temperatures—they can be observed by NMR, but they decompose to carbenes at about –100 °C.

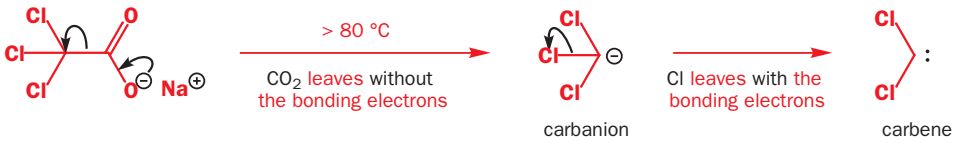


While lithium carbenoids have limited applicability in chemistry, an analogous zinc carbenoid, which can be formed by insertion of zinc into diiodomethane, is a reagent in one of the most widely used carbenoid reactions in chemistry—the Simmons–Smith reaction.

The essence of this type of carbenoid is that it should have a leaving group, such as a halogen, that can remove a pair of electrons and another, usually a metal, that can donate a pair of electrons. If the metal leaves first, a carbanion is created that can lose the halogen to make a carbene. They might also leave together. Both are α eliminations.

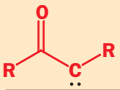
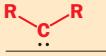


The problem with many of these reactions is that they require strong bases—either the organometallic compound itself is basic or a base must be used to create the carbanion. Carbenes are so unstable that they must be formed in the presence of the compound they are intended to react with, and this can be a problem if that compound is base-sensitive. For dichlorocarbene, a way round the problem is to make the carbanion by losing CO_2 instead of a metal or a proton. Decarboxylation of sodium trichloroacetate is ideal as it happens at about 80 °C in solution.

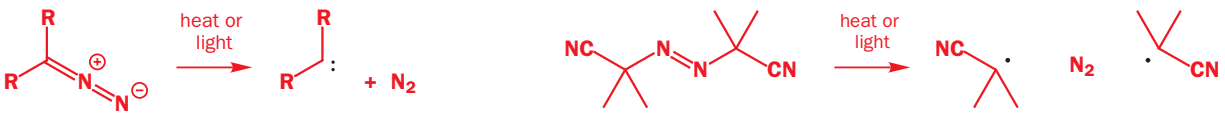


Summary: the most important ways of making carbenes

Carbenes are neutral species containing a carbon atom with only six valence electrons.

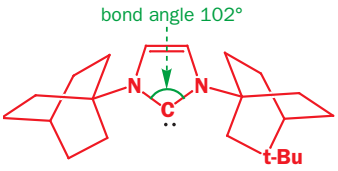
Type of carbene	Method of formation
	metal (rhodium or copper)-catalysed decomposition of diazocarbonyl compound
	thermal decomposition of diazo compound, often derived from tosylhydrazone
	α elimination of chloroform with base

This is a good point to remind you of other 'double losses' from molecules. Just as α elimination gives a carbene while β elimination gives an alkene, loss of nitrogen from a diazo compound gives a carbene but loss of nitrogen from an azo compound such as AIBN (*azo*bisisobutyronitrile) gives two radicals (Chapter 39).



▶ It is unfortunate that the term carbenoid is used for two distinct classes of molecule—usually it refers to the transition-metal bound carbene formed by metal-catalysed decomposition of diazo compounds (see p. 000)—and for this reason the carbenoids that we are discussing here are best referred to as 'lithium carbenoids', with the metal specified.

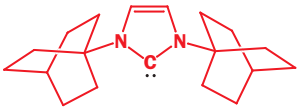
■ The Simmons–Smith reaction, one of the best ways of making cyclopropanes, is discussed later in the chapter.



Carbenes can be divided into two types

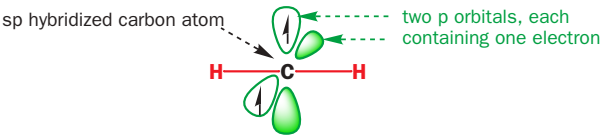
We made two important observations earlier regarding the structure of carbenes that we will now return to and seek an explanation for: firstly, we said that the X-ray crystal structure of this stable, crystalline carbene shows that the bond angle at the carbene C is 102° and, secondly, we said that many carbenes can be observed by ESR—in other words, they have unpaired electrons.

Spectroscopic investigations of a number of carbenes of differing structures have shown that they fall broadly into two groups: (1) those (which you will learn to call 'triplets') that ESR spectroscopy demonstrates have unpaired electrons and whose bond angles are 130–150°; and (2) those (like the stable crystalline carbene above which you will learn to call a 'singlet') that have bond angles of 100–110° but cannot be observed by ESR. Many carbenes, like CH_2 itself, can be found in either style, though one may be more common.

Type 1: triplet carbenes	**Type 2: singlet carbenes**
bond angle 130–150°	bond angle 100–110°
observable by ESR	all electrons paired
$:CH_2$	$:CCl_2$
:CHPh	:CHCl
:CHR	$:C(OMe)_2$
$:CPh_2$	

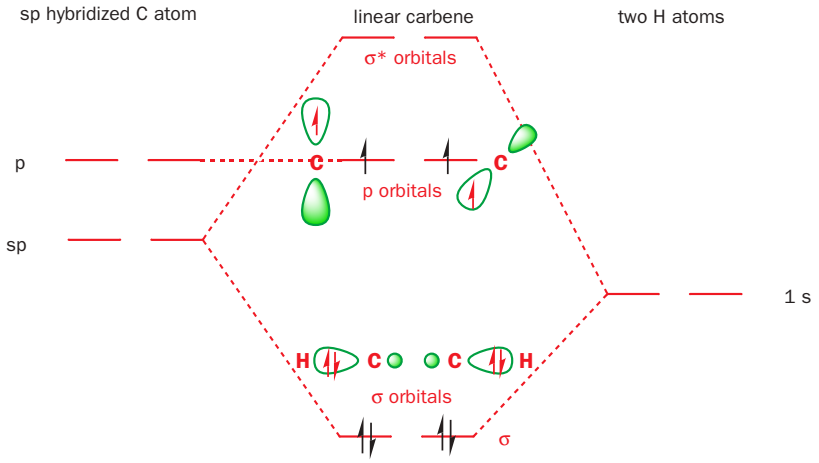
All these observations can be accounted for by considering the electronic structure of a carbene. Carbenes have 2-coordinate carbon atoms: you might therefore expect them to have a linear (diagonal) structure—like that of an alkyne—with an sp hybridized carbon atom.

▶ This diagram is for illustration only and is *not* the structure of a carbene.

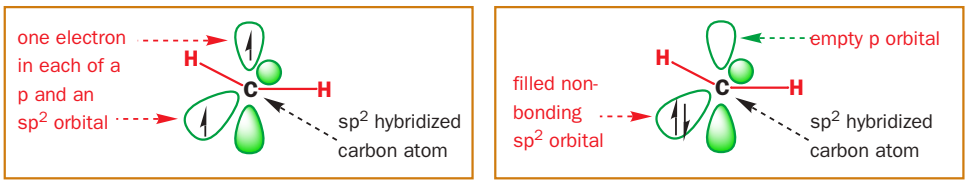


Such a linear carbene would have six electrons to distribute amongst two σ orbitals and two (higher-energy) p orbitals. The two electrons in the degenerate p orbitals would remain unpaired because of electron repulsion in the same way as in molecular oxygen •O–O•.

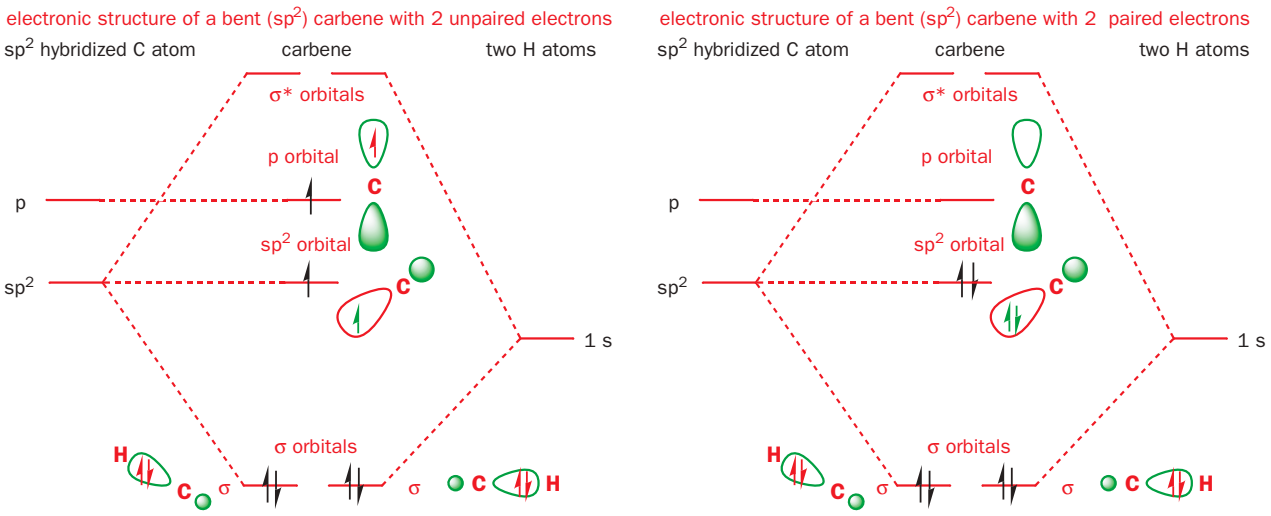
▶ We usually represent electrons, paired or unpaired, as dots. But here we are using another convention—one little arrow per electron. This allows us to define the electron's spin, up or down.



Yet few carbenes are linear: most are bent, with bond angles between 100° and 150°, suggesting a trigonal (sp^2) hybridization state. An sp^2 hybridized carbene would have three (lower-energy) sp^2 orbitals and one (high-energy) p orbital in which to distribute its six electrons. There are two ways of doing this. Either all of the electrons can be paired, with each pair occupying one of the sp^2 orbitals, or two of the electrons can remain unpaired, with one electron in each of the p orbitals and one of the sp^2 orbitals.

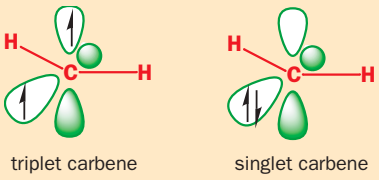


These two possibilities explain our two observed classes of carbene, and the two possible arrangements of electrons (spin states) are termed triplet and singlet. The orbitals are the same in both cases but in **triplet carbenes** we have one electron in each of two molecular orbitals and in **singlet carbenes** both electrons go into the sp^2 orbital.

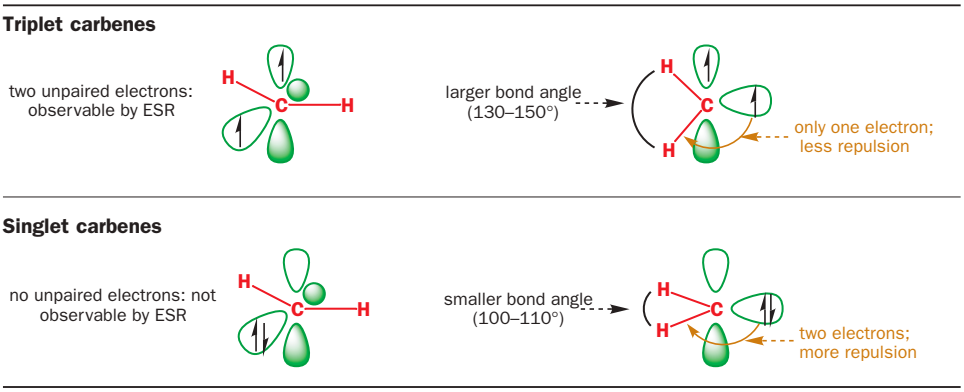


Singlet and triplet carbenes

Triplet carbenes have two unpaired electrons, one in each of an sp^2 and a p orbital, while **singlet carbenes** have a pair of electrons in a nonbonding sp^2 orbital and have an empty p orbital.



The existence of the two spin states explains the different behaviour of triplet and singlet carbenes towards ESR spectroscopy; the orbital occupancy also explains the smaller bond angle in singlet carbenes, which have an electron-repelling lone pair in an sp^2 orbital.

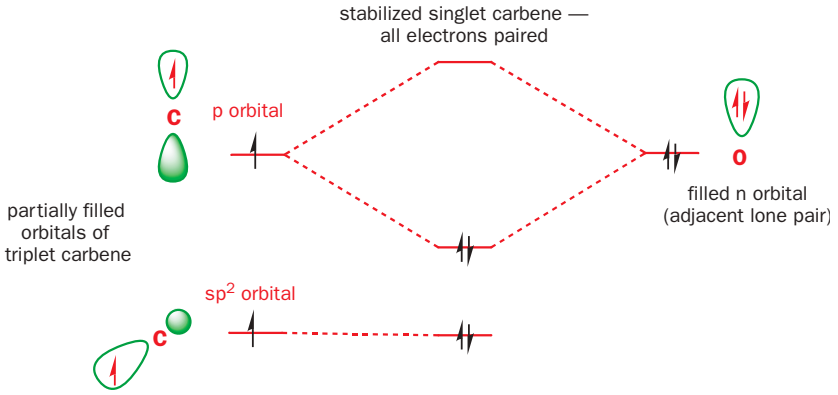


■ A manifestation of Hund's rule—see Chapter 4.

In the table on p. 000 we saw that the substituents on the carbene affect which of the two classes (which we now call singlet and triplet) it falls into. Why? Most type of carbenes are more stable as triplets because the energy to be gained by bringing the electron in the p orbital down into the sp^2 orbital is insufficient to overcome the repulsion that exists between two electrons in a single orbital.

All carbenes have the potential to exist in either the singlet or the triplet state, so what we mean when we say that a carbene such as $:CH_2$ is a 'triplet carbene' is that the triplet state for this carbene is lower in energy than the singlet state, and vice versa for $:CCl_2$. For most triplet carbenes the singlet spin state that would arise by pairing up the two electrons lies only about 40 kJ mol^{-1} above the ground (triplet) state: in other words, 40 kJ mol^{-1} is required to pair up the two electrons. When a carbene is actually formed in a chemical reaction, it may not be formed in its most stable state, as we shall see.

Carbenes that have singlet ground states (such as $:CCl_2$) all have electron-rich substituents carrying lone pairs adjacent to the carbene centre. These lone pairs can interact with the p orbital of the carbene to produce a new, lower-energy orbital which the two electrons occupy. This stabilization of the lone pair provides the incentive that the electron in the p orbital needs to pair up in the sp^2 orbital.



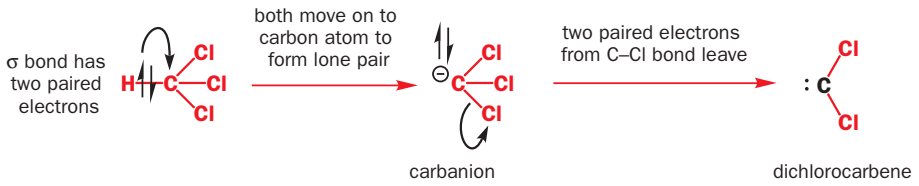
This molecular orbital formation moves electrons localized on oxygen into orbitals shared between carbon and oxygen. We can represent this in curly arrow terms as a delocalization of the lone pair electrons.

■ See p. 000 for a demonstration that $:CHCO_2Et$ is more electrophilic than $:CCl_2$.

As these arrows suggest, carbenes that have heavily electron-donating substituents are less electrophilic than other carbenes: indeed, diamino carbenes can be quite nucleophilic. The division of carbenes into two types explains their structure. It also helps to explain some of their reactions, especially those that have a stereochemical implication. We will spend the rest of this chapter discussing how carbenes react.

The structure of carbenes depends on how they are made

So far we have considered only the most stable possible structure, singlet or triplet, of a given carbene. In real life, a carbene will be formed in a chemical reaction and may well be formed as the less stable of the alternatives. If a reaction occurs by an ionic mechanism on a molecule with all electrons paired (as most molecules are!) then it must be formed as a singlet. Follow the α elimination mechanism, for example.



The starting material, a normal molecule of chloroform $CHCl_3$, has all paired electrons. The C–H σ bond breaks and the two paired electrons from it form the lone pair of the carbanion. The carbanion also has all paired electrons. The two paired electrons of one of the C–Cl bonds leaves

the carbanion and the carbene is formed. It has two paired electrons in each of the two remaining C–Cl bonds and the lone pair, also paired. It is formed as a singlet. As it happens, the singlet version of CCl_2 is also the more stable. If the carbene were instead CH_2 and if it reacted rapidly, it might not have a chance to change into the more stable triplet state. And carbenes are very reactive. In explaining their reactions in the next section we shall need to consider:

- how the carbene was formed
- how rapidly it reacts
- whether it can change into the other state (singlet or triplet)

How do carbenes react?

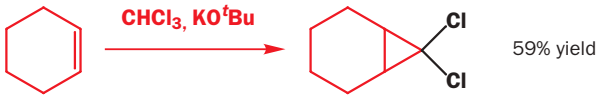
Carbenes are desperate to find another pair of electrons with which to complete their valence shell of electrons. In this respect they are like carbocations. Like carbocations, they are electrophilic but, unlike carbocations, they are uncharged. This has consequences for the type of nucleophiles carbenes choose to react with. Carbocations attack nucleophiles with high charge density—those carrying a negative or partial negative charge (think of the type of nucleophiles that will take part in S_N1 or Friedel–Crafts reactions). Carbenes, on the other hand, attack compounds we'd normally never consider as nucleophiles—even simple alkanes—by taking electrons from their HOMO. Of course, a carbocation will usually react with the HOMO of a molecule, but it will be much more selective about which HOMOs will do—usually these have to be lone pairs or electron-rich alkenes. For carbenes, any HOMO will do—a lone pair, a C=C double bond (electron-rich or -poor), or even a C–H bond.

▶ In this respect, a carbene is like an electrophilic radical—very reactive and very soft.

As you will see (and as we generalized at the beginning of the chapter), many of these reactions can be considered as **insertion reactions**—overall the carbene appears to have found a bond and inserted itself in the middle of it. It's important to remember that the term 'insertion reaction' describes the outcome of the reaction, though it isn't always an accurate description of the reaction's mechanism.

Carbenes react with alkenes to give cyclopropanes

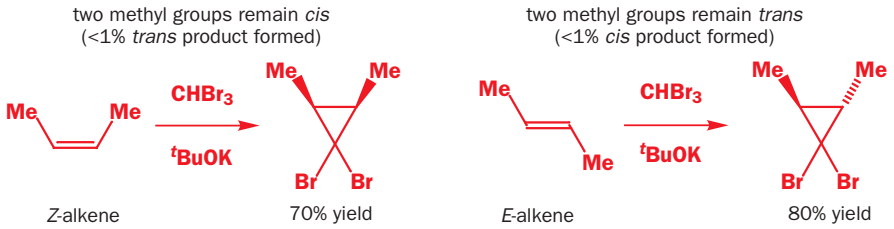
This reaction is the most important way of making cyclopropanes, and is probably the most important reaction of carbenes.



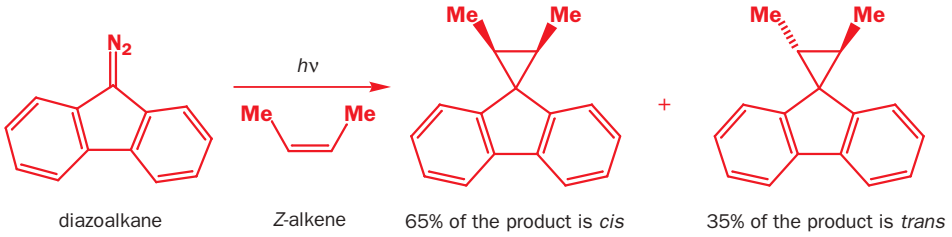
59% yield

The mechanism of this type of reaction depends on whether the carbene is a singlet or a triplet, and the outcome of the reaction can provide our first chemical test of the conclusions we came to in the previous section. Singlet carbenes, like this one here (remember that electron-rich substituents stabilize the singlet spin state), can add to alkenes in an entirely concerted manner: the curly arrows for the process can be written to show this.

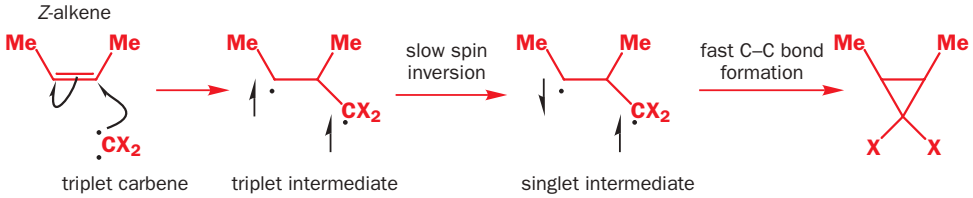
Because the process is concerted, we expect that the geometry of the alkene should be preserved in the product—the reaction ought to be *stereospecific*. The two examples below show that this is indeed the case. It is more impressive that the *Z*-alkene gives the *cis* cyclopropane as this is less stable than the *trans* cyclopropane and would change if it could.



The alkene insertion reaction is stereospecific only for singlet carbenes. For triplet carbenes, the reaction is nonstereospecific. Though carbenes formed thermally from diazoalkenes must initially be singlets, photochemistry is one way to provide the energy needed for their transformation to the more stable triplet.

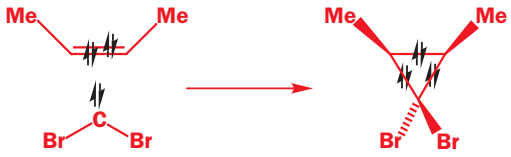


The mechanism of this nonspecific reaction must be different. In fact, a concerted reaction is impossible for triplet carbenes because of the spins of the electrons involved. After the carbene adds to the alkene in a radical reaction, the diradical (triplet) intermediate must wait until one of the spins inverts so that the second C–C bond can be formed with paired electrons. This intermediate also lives long enough for C–C bond rotation and loss of stereochemistry.

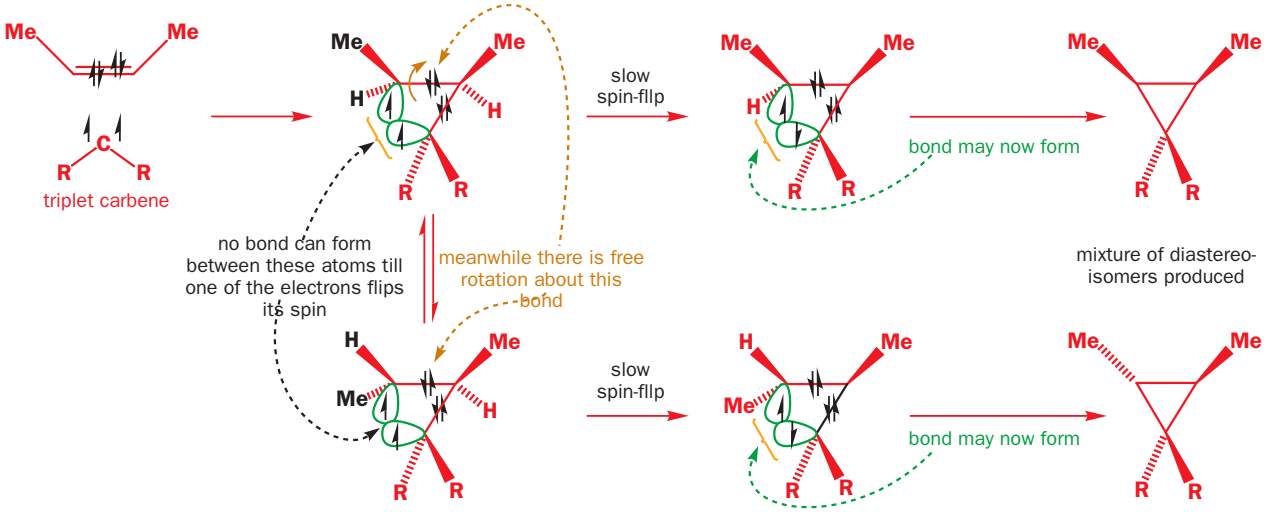


A cyclopropane has three σ bonds—in other words, six electrons, all spin-paired (three up, three down). One of these was the σ bond in the starting material; the other two electron pairs come from the π bond and from the carbene. The electrons in the π bond must have been paired, and thus they can form one of the new σ bonds. A singlet carbene (whose electrons are also paired) can then provide the second electron pair.

concerted addition of a singlet carbene is spin-allowed



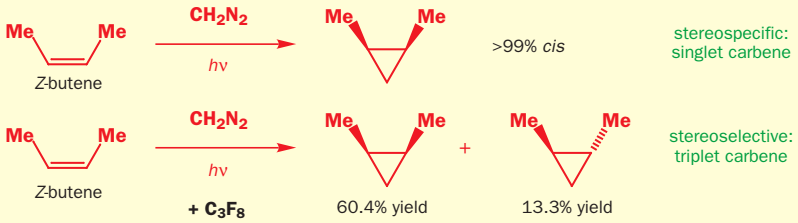
But a triplet carbene cannot, because its electrons are not paired. The second bond can only form once one of the two electrons has flipped its spin. Spin-flipping, which can only occur through collision with another molecule (of solvent, say), is relatively slow on the time-scale of molecular rotations and, by the time the electrons are in a fit state to pair up, the stereochemistry of the starting material has been scrambled by free rotation in the intermediate.



A reminder. The same constraints arising from the need for conservation of electron spin apply to the formation as well as to the reaction of carbenes. When a carbene forms by α elimination, say, from a molecule with all electrons paired, it must be formed as the singlet, whether or not the triplet state is lower in energy. Only later may the carbene undergo spin-flipping to the triplet state. Since most carbene reactions are very rapid, this means that carbenes that are known to have triplet ground states may, in fact, react in their first-formed singlet state because they don't have time to spin-flip to the triplet. This is true for $:CH_2$ produced from CH_2N_2, which adds stereospecifically to double bonds because it is formed as a singlet and because the singlet state is more reactive than the triplet.

Some evidence for triplet carbenes in cyclopropane formation

If the reaction is diluted with a large amount of an inert solvent such as C_3F_8 (perfluoropropane) then $:CH_2$ undergoes more collisions before it reacts and so the chances of spin-flipping of singlet $:CH_2$ to triplet $:CH_2$ is increased. Addition to alkenes is then less stereospecific.

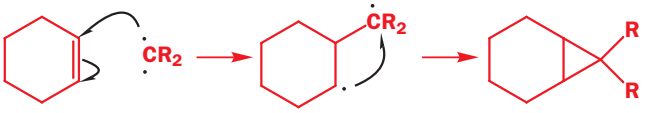


Stereospecificity (or lack of it) in the addition of a carbene to an alkene *can* be a good test of whether the carbene reacts as a singlet or triplet: lack of stereospecificity in a carbene addition almost certainly indicates that a triplet carbene is involved, but the fact that an addition *is* stereospecific doesn't mean that the carbene *must* be a singlet. In some cases, bond rotation may be quite slow, and spin-flipping rapid, leading to stereospecific addition. Notice that in this example the less stable *cis* (*Z*-) alkene was used: the reaction will give *trans*-cyclopropane if it can.

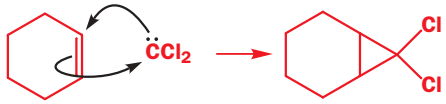
▶ Cycloadditions in which one of the components is a single atom (in other words, [1 + *n*] cycloadditions) are sometimes called **cheletropic reactions**.

The addition of a triplet carbene to an alkene can be considered to be rather like a radical addition to a double bond. The concerted addition of a singlet carbene, on the other hand, is a pericyclic reaction, and from Chapter 35 you should be able to classify it as a [1 + 2] cycloaddition.

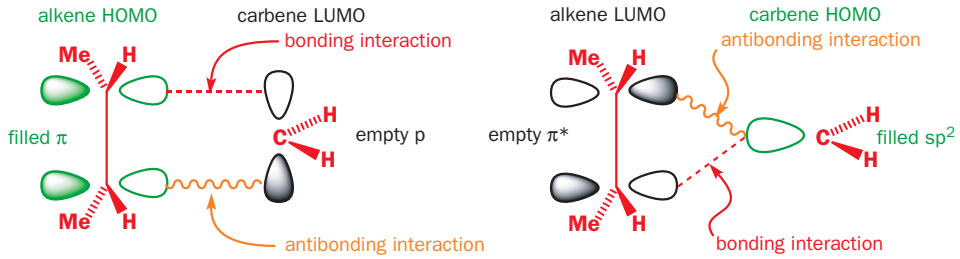
addition to alkenes of triplet carbenes is a radical reaction



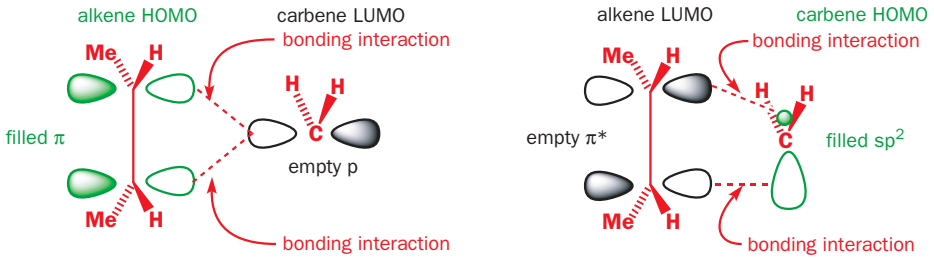
addition of singlet carbenes is a [1+2] cycloaddition



As a cycloaddition, singlet carbene addition to an alkene must obey the rules of orbital symmetry discussed in Chapters 35 and 36. We might consider the empty p orbital of the carbene (LUMO) interacting with the π bond (HOMO) of the alkene or the lone pair of the carbene in its filled sp^2 orbital (HOMO) interacting with the π* antibonding orbital of the alkene (LUMO).

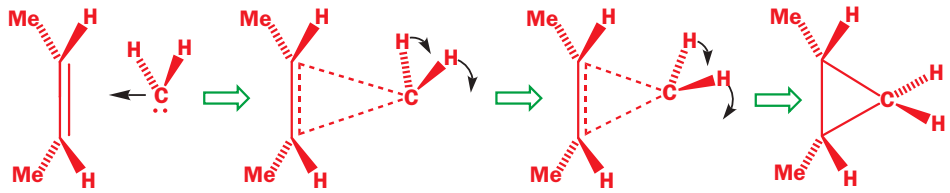


You can immediately see that there is a problem when we try to interact these orbitals constructively to build two new bonds—direct approach of the carbene to the alkene is impossible because there is always an antibonding interaction. Two new bonds can be formed, however, if the carbene approaches the alkene in a 'sideways-on' manner.



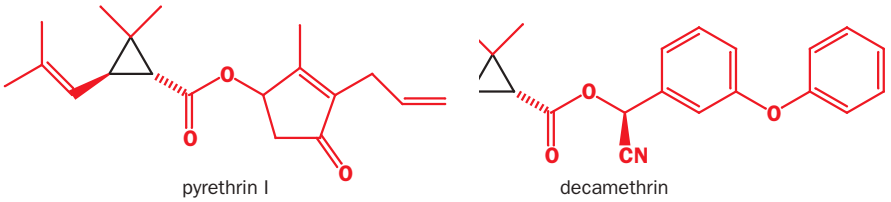
The cyclopropane product must, of course, have a more or less tetrahedral arrangement about the carbon atom that was the carbene so that, even if the carbene approaches in a sideways-on manner, it must then swing round through 90° as the bonds form.

'docking' of the carbene on to the alkene



Making cyclopropanes

Many natural products and biologically active compounds contain cyclopropane rings: we shall feature just a few. First, a most important natural insecticide, a pyrethrin from the East African pyrethrum daisy, and its synthetic analogue decamethrin, now the most important insecticide in agriculture (see Chapter 1). Very low doses of this highly active and nonpersistent insecticide are needed.

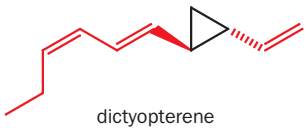


pyrethrin I

decamethrin

They told John Betjeman: 'Breathe in the ozone, John. It's iodine.' *Summoned by bells*, Murray, 1960, p. 39.

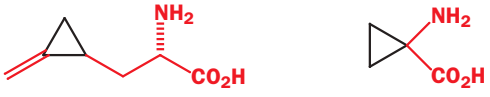
Ever heard of the 'ozone' or 'iodine' smell of the sea? Well, the smell of the sea is characteristic but has nothing to do with O_3 or I_2. It's more likely to be a dictyopterene, a family of volatile cyclopropanes used by female brown algae to attract male gametes. There is an example in the margin.



dictyopterene

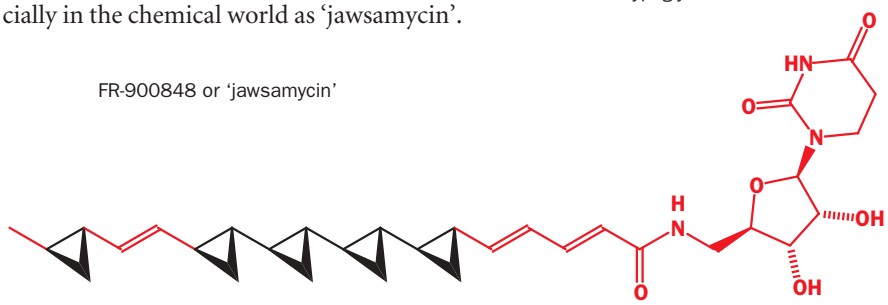
Now for two natural but highly unusual amino acids. Hypoglycidin is a blood sugar level lowering agent from the unripe fruit of the ackee tree; the causative agent of Jamaican vomiting sickness. Don't eat the green ackee. Nature makes not only strained cyclopropanes but this even more strained methylene cyclopropane with an sp^2 atom in the ring. The second and simpler amino acid is found in apples, pears, and grapefruit and encourages fruit ripening by degradation to ethylene.

Our last and most extraordinary example is an antifungal antibiotic first synthesized in 1996 and containing no less than five cyclopropanes. It has the prosaic name FR-900848 but is known unofficially in the chemical world as 'jawsamycin'.

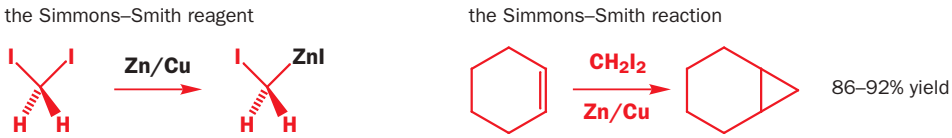


hypoglycin

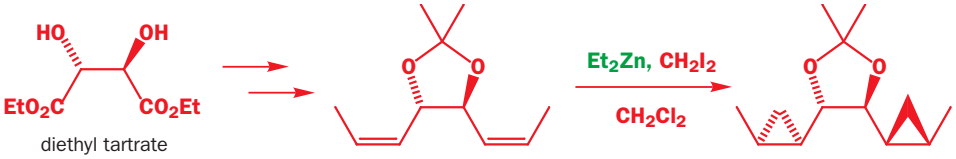
FR-900848 or 'jawsamycin'



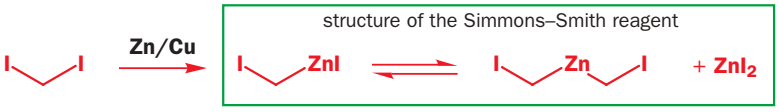
Because of these and other useful molecules containing three-membered rings, methods to make them are important as well as interesting. Most chemical syntheses of compounds containing cyclopropyl groups make use of the addition of a carbene, or carbene equivalent, to an alkene. What do we mean by **carbene equivalent**? Usually, this is a molecule that has the potential to form a carbene, though it may not actually react via a carbene intermediate. One such example is a zinc carbenoid formed when diiodomethane is reacted with zinc metal: it reacts with alkenes just as a carbene would—it undergoes addition to the π bond and produces a cyclopropane.



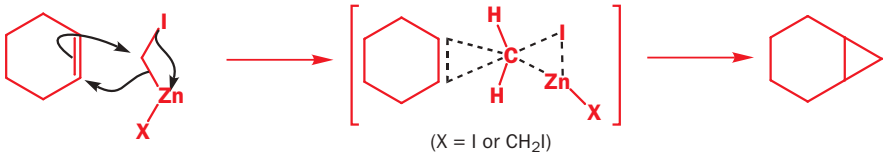
The reaction is known as the **Simmons–Smith reaction**, after the two chemists at the DuPont chemical factory who discovered it in 1958. Even after several decades, it is the most important way of making cyclopropane compounds, though nowadays a variant that uses more easily handled starting materials is often used. Diethyl zinc replaces the Zn/Cu couple of the traditional Simmons–Smith reaction. In this example, a double cyclopropanation on a C_2 symmetric diene derived from tartaric acid gives very good stereoselectivity for reasons we will soon discuss.



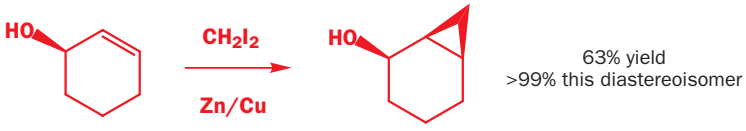
The reaction does not involve a free carbene: the zinc is still associated with the carbon atom at the time of the reaction, and the reacting species is a probably a complex of zinc that we can represent as an equilibrium between two zinc carbenoids.



The mechanism of the Simmons–Smith reaction appears to be a carbene transfer from the metal to the alkene without any free carbene being released. It may look something like this.



Some of the evidence for this comes from a reaction that not only throws light on to the mechanism of Simmons–Smith cyclopropanations, but makes them of even greater value in synthesis. When an allylic alcohol is cyclopropanated, the new methylene group adds stereoselectively to the same face of the double bond as the alcohol group.



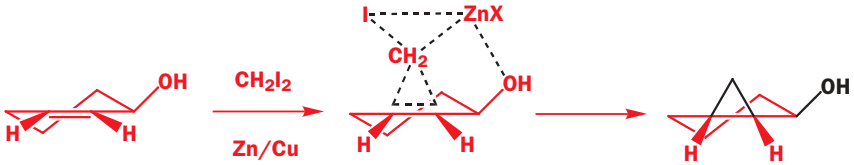
Allylic alcohols also cyclopropanate over 100 times faster than their unfunctionalized alkene equivalents. Coordination between the zinc atom and the hydroxyl group in the transition state explains both the stereoselectivity and the rate increase. Unfortunately, while the Simmons–Smith

■ You could compare this reaction with reduction by sodium borohydride (Chapter 6). Hydride is transferred from a boron atom to a carbonyl group but no free hydride is formed.

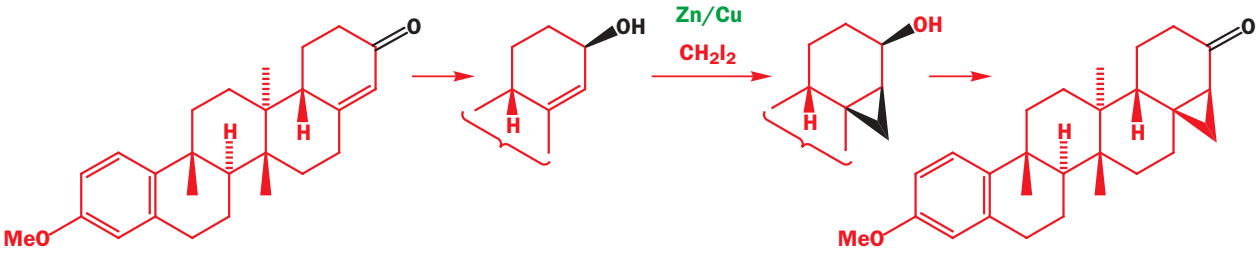
■ You might notice the similarity to the epoxidation of allylic alcohols with *m*-CPBA mentioned in Chapter 33.

▶ On the subject of stereochemistry, note that the Simmons–Smith zinc carbenoid behaves like a singlet carbene—its additions to alkenes are stereo*specific* (the product cyclopropane retains the geometry of the alkene) as well as stereo*selective* (the carbenoid adds to the same face as the hydroxyl group).

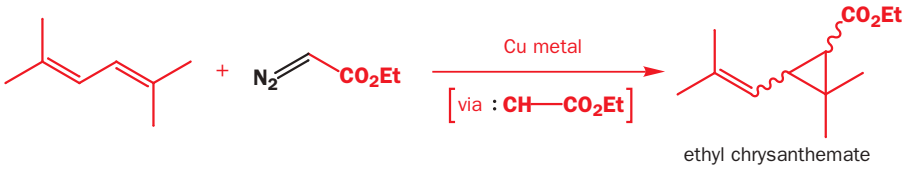
reaction works well when a methylene (CH_2) group is being transferred, it is less good with substituted methylenes (RCH: or R_2C:).



When Ireland wanted to introduce a cyclopropane ring stereoselectively into a pentacyclic system containing an enone, he first reduced the ketone to an alcohol (DIBAL gave only the equatorial alcohol) that controlled the stereochemistry of the Simmons–Smith reaction. Oxidation with Cr(VI) put back the ketone.

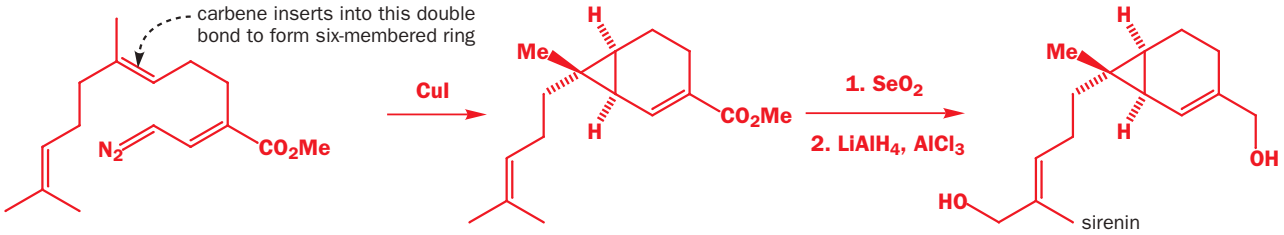


The carbene derived by metal-catalysed decomposition of ethyl diazoacetate attacks alkenes to introduce a two-carbon fragment into a cyclopropane—an industrial synthesis of ethyl chrysanthemate, a precursor to the pyrethrin insecticides (see p. 000), uses this reaction. The diene in the starting material is more nucleophilic (higher-energy HOMO; see Chapter 20) than the single alkene in the product, so the reaction can be stopped after one carbene addition.



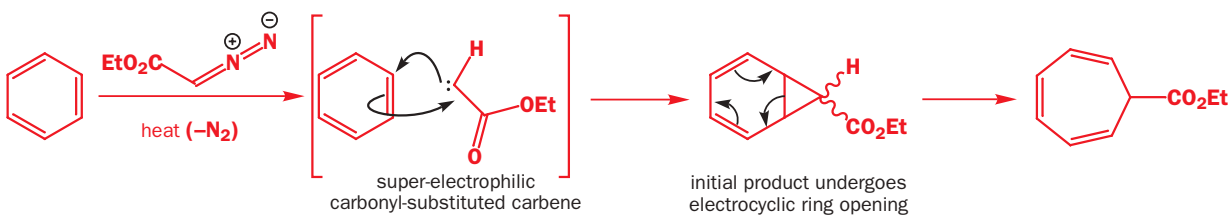
■ The selenium dioxide oxidation is discussed in Chapter 46.

The intramolecular version of this reaction is more reliable, and has often been used to make compounds containing multiply substituted cyclopropanes. Corey made use of it in a synthesis of sirenin, the sperm-attractant of a female water mould.



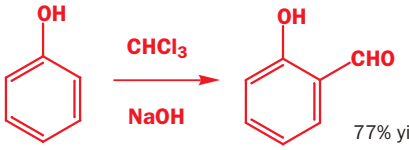
■ You met reactions like this in Chapter 36.

As you might imagine, carbenes like this, substituted with electron-withdrawing carbonyl groups, are even more powerful electrophiles than carbenes like :CCl_2, and will even add to the double bonds of benzene. The product is not stable, but immediately undergoes electrocyclic ring opening.



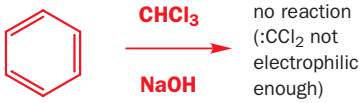
Dichlorocarbene :CCl_2 will not add to benzene, but does attack the electron-rich aromatic ring of phenol: the product is not a cyclopropane, but an aldehyde.

the Reimer–Tiemann reaction



77% yield

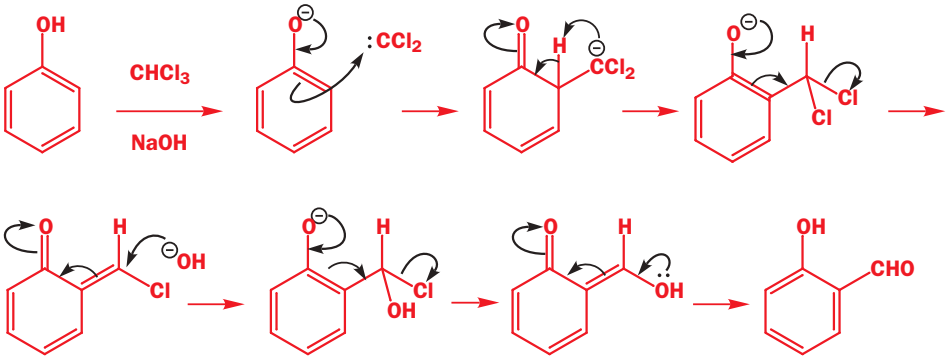
No reaction with benzene



no reaction (:CCl_2 not electrophilic enough)

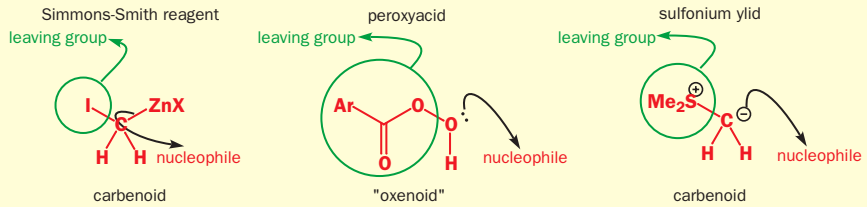
The **Reimer–Tiemann reaction** used to be an important way of making *ortho*-substituted phenols, but the yields are often poor, and modern industry is wary of using large quantities of chlorinated solvents. On a small, laboratory scale it has largely been superseded by ortholithiation (Chapter 9) and by modern methods outside the scope of this book. The mechanism probably goes something like this.

mechanism of the Reimer–Tiemann reaction



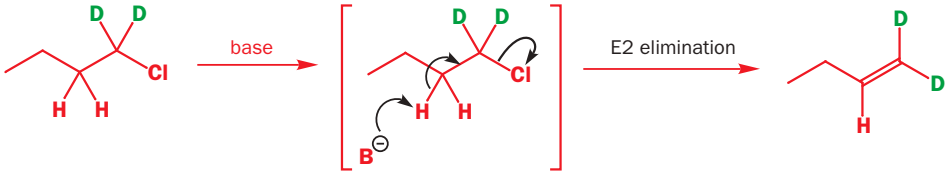
Comparison of '-enoid' reagents

Before we leave this section on cyclopropanes, we want you to take a step back from simply thinking about carbenes, and consider the types of reagents that form three-membered rings generally. They all have something in common, which we could call '-enoid' character. Cyclopropanes form when a carbene (which, in the singlet state, has an empty, electrophilic p orbital and a full, nominally nucleophilic sp^2 orbital) attacks alkenes. The Simmons–Smith carbenoid is not a carbene, but nonetheless has a carbon atom with joint nucleophilic (alkyl zinc) and electrophilic (alkyl iodide) character. When you think about it, the same is true for peracid epoxidation, which forms the oxygen analogue of a cyclopropane by attacking an alkene with an oxygen atom bearing both a lone pair (nucleophilic) and a carboxylate leaving group (electrophilic). It's an 'oxenoid'. In Chapter 46 you will meet more reagents that form cyclopropanes and epoxides by transferring CH_2—sulfonium ylids. These yet again have a schizophrenic carbon atom—carrying a negative charge and a leaving group—and, when you meet them, you can consider them to be particularly stable carbenoids.

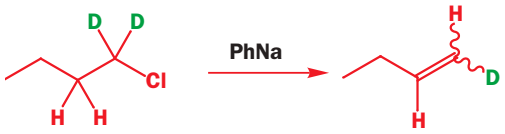


Insertion into C–H bonds

We said that the formation of cyclopropanes by addition of substituted carbenes to alkenes was rare—in fact, alkyl-substituted carbenes undergo very few intermolecular reactions at all because they decompose very rapidly. When primary alkyl halides are treated with base, alkenes are formed by elimination. Having read Chapter 19, you should expect the mechanism of this elimination to be E2 and, if you started with a deuterated compound like this, the alkene product would be labelled with two deuterium atoms at its terminus.



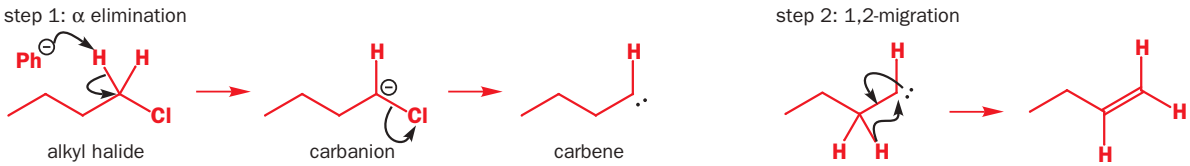
This is indeed what happens if the base is sodium methoxide (pK_a 16). If, however, it is phenylsodium (pK_a about 50), only 6% of the product is labelled in this way while 94% of the product has only one deuterium atom.



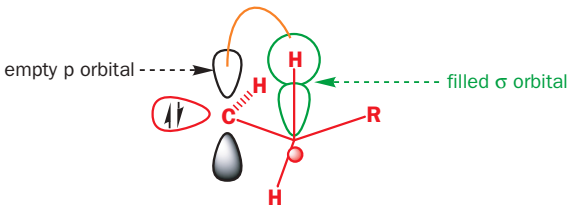
■

Migrations were covered in detail in Chapter 37. You will meet examples there of migrations on to electrophilic *carbocationic* centres, but the reactions are in essence very similar to these migrations to carbenes.

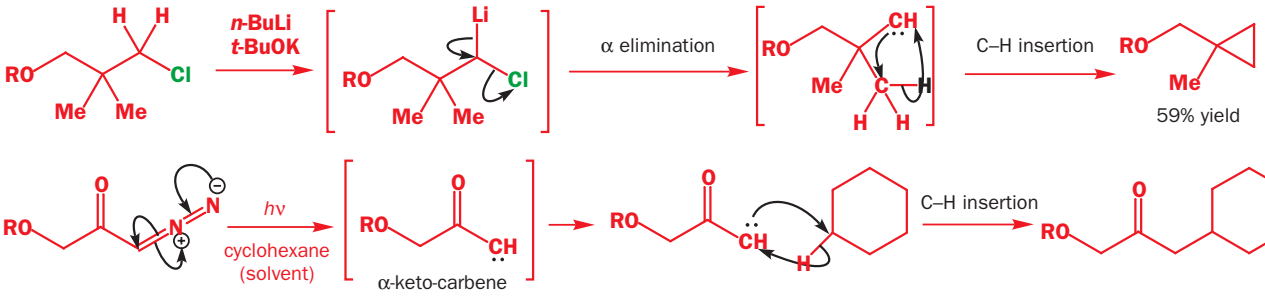
A hydrogen atom has 'migrated' from the 2-position to the 1-position. The overall mechanism of the elimination with very strong bases like phenylsodium is believed to be: (1) formation of a carbene by α elimination and then (2) 1,2-migration of a hydrogen atom on to the carbene centre. Carbenes with β hydrogens undergo extremely rapid 1,2-migration of hydrogen to the carbene centre, giving alkenes.



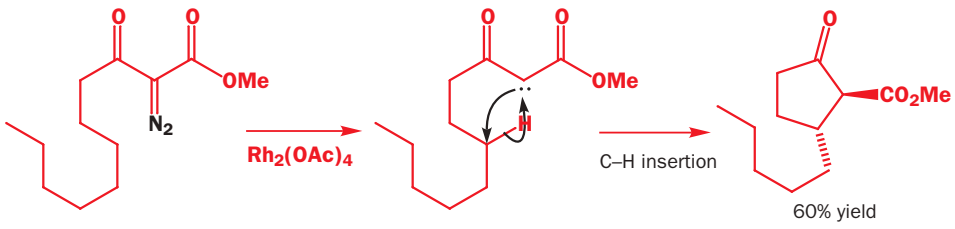
The reason for the rapid migration is that the electrophilic carbene has found a nearby source of electrons—the HOMO of the C–H bond—and it has grabbed the electrons for itself, 'inserting' into the C–H bond.



This type of reaction is better demonstrated by two examples in which the 'insertion reaction' is a bit more obvious: when there are no β hydrogens, the carbene inserts into C–H bonds a little further away in the same molecule or even in the solvent (cyclohexane in the second example). In the first case, the carbene is formed by α elimination and, in the second case, by photolysis of a diazoketone.



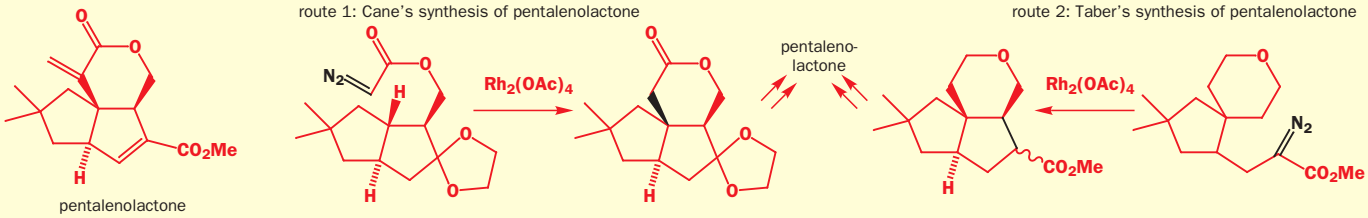
Because these insertion reactions create new bonds at completely unfunctionalized centres, they can be very useful in synthesis. This next carbene is created between two carbonyl groups from a diazocompound with rhodium catalysis and selectively inserts into a C–H bond five atoms away to form a substituted cyclopentanone.



Pentalenolactone synthesis using carbenes

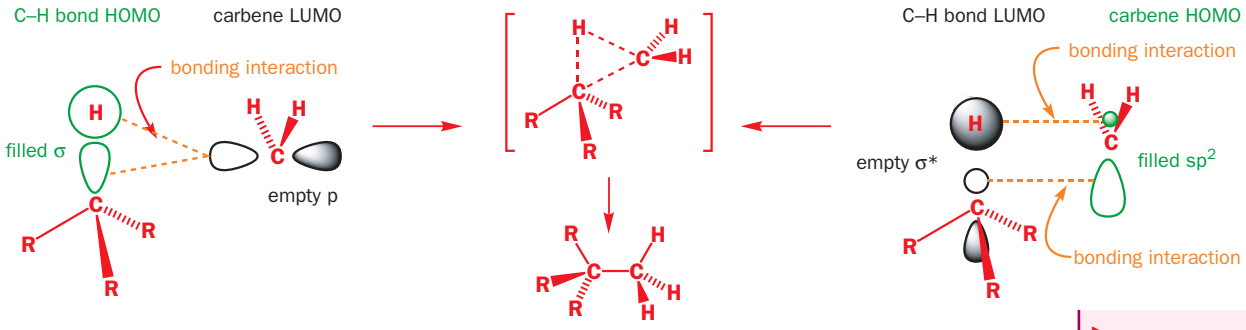
Pentalenolactone is the name given to an antibiotic extracted from *Streptomyces* fungi with an interesting tricyclic structure.

Two groups of chemists, within one year of each other, published syntheses of this compound using rhodium-promoted carbene insertions into C–H bonds. Cane's insertion reaction (route 1) proceeds stereospecifically with *retention* of stereochemistry. This is excellent evidence for a concerted singlet carbene reaction.

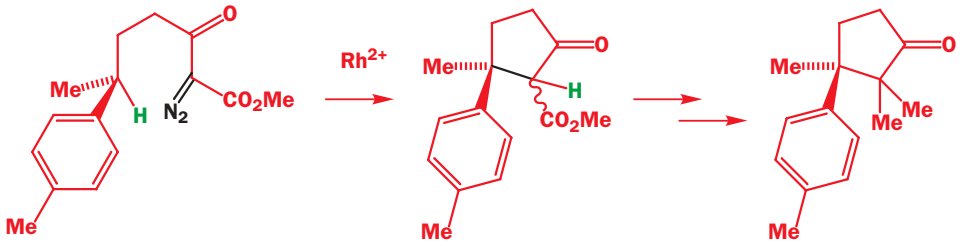


In these C–H insertion reactions, the similarity with cyclopropane formation by intramolecular cycloadditions to alkenes is clear, and the mechanisms mirror one another quite closely. As with the cyclopropanation reactions, the path of the reaction differs according to whether the carbene is a singlet or triplet. Singlet carbenes can insert in a concerted manner, with the orbitals overlapping constructively provided the carbene approaches side-on.

orbital interactions during the insertion of a singlet carbene into a C–H bond



This mechanism implies that, if the C–H bond is at a stereogenic centre, the stereochemistry at that centre will be retained through the reaction, as in Cane's synthesis of pentalenolactone. A nice example of this result is the ingenious synthesis of α-cuparenone using a stereospecific carbene insertion.

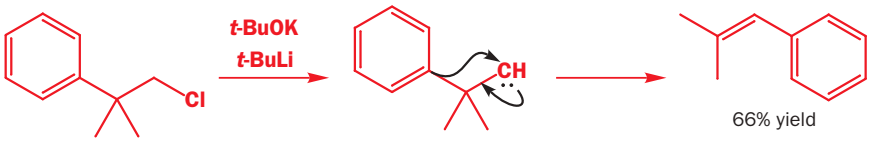


Rearrangement reactions

We talked just at the beginning of this section about migration reactions of hydrogen on to carbenes to give alkenes, and said that these reactions can be viewed as insertion reactions of carbenes into adjacent C–H bonds. Carbenes with no β hydrogens often insert into other C–H bonds in the molecule. However, carbenes with no β-hydrogen atoms can also undergo rearrangement reactions with alkyl or aryl groups migrating.

▶ In principle, triplet carbene insertions should follow a two-step radical pathway analogous to their insertion into alkenes. However, very few triplet carbene insertions into C–H bonds have been observed, and the stereochemical consequence of the two-step mechanism (which should result in mixtures of stereoisomers on insertion into a C–H bond at a stereogenic centre) has never been verified.

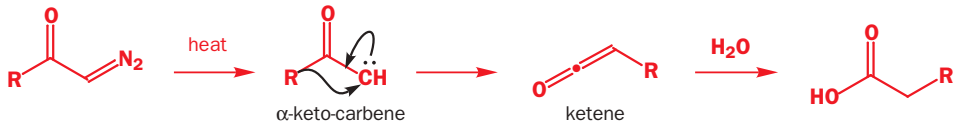
▶ The migration of alkyl groups to carbene centres has much in common with the migration of alkyl groups to cationic centres discussed in Chapter 37—after all, both carbenes and carbocations are electron-deficient species with a carbon atom carrying only six electrons in its outer shell.



■
You met ketenes in Chapter 35.

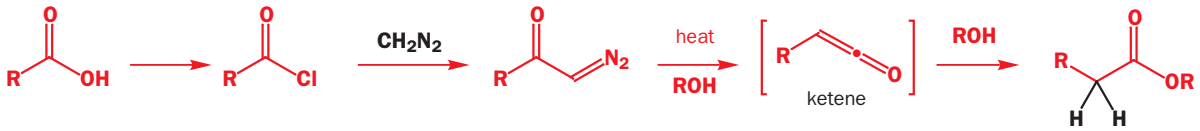
The most common example of this type of migration is that in which the carbene is adjacent to a carbonyl group. The initial product of what is known as the **Wolff rearrangement** is a ketene, which cannot be isolated but is hydrolysed to the ester in the work-up. Wolff rearrangement is a typical reaction of diazoketones on heating, though these species do also undergo intramolecular C–H insertion reactions.

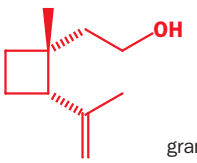
the Wolff rearrangement



One important application of this reaction is the chain extension of acyl chlorides to their homologous esters, known as the **Arndt–Eistert reaction**. Notice that the starting material for the Wolff rearrangement is easily made from RCO_2H by reaction of the acyl chloride with diazomethane; the product is RCH_2CO_2H—the carboxylic acid with one more carbon atom in the chain. A CH_2 group, marked in black, comes from diazomethane and is inserted into the C–C bond between R and the carbonyl group.

the Arndt–Eistert homologation





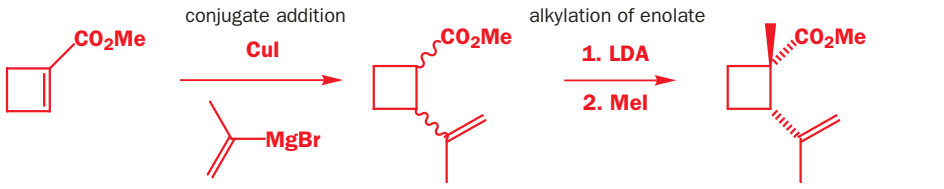
grandisol

A synthesis of grandisol using Arndt–Eistert chain extension

The boll weevil is a serious pest of cotton bushes, and it produces a sex pheromone known as grandisol.

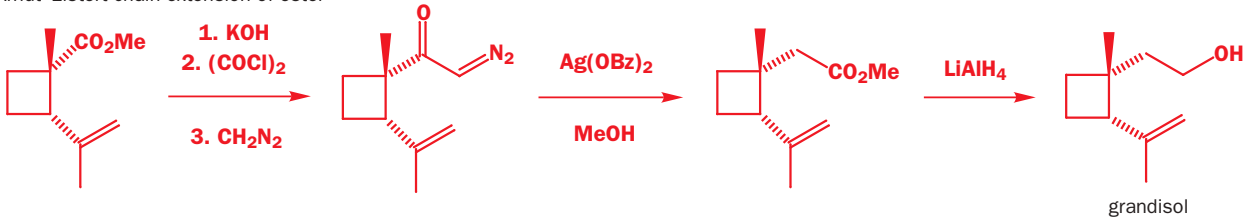
Chemists soon showed that it was an easy matter to synthesize a related ester by a conjugate addition of an organocopper derivative (Chapter 10) and then the alkylation of an ester enolate (Chapter 26). The enolate reacts with MeI on the face opposite the propenyl side chain—a good example of stereochemical control with cyclic compounds (Chapter 33).

▶
You have already met one synthesis of grandisol—in Chapter 25.



This ester is one carbon atom short of the full side chain of grandisol, so an Arndt–Eistert reaction was used to lengthen the chain by one atom. First, the ester was converted into the diazoketone with diazomethane and, then, the Wolff rearrangement was initiated by formation of the carbene with a silver compound at the Ag(II) oxidation state.

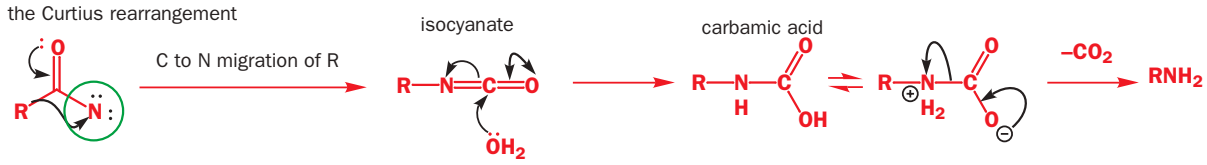
Arndt–Eistert chain extension of ester



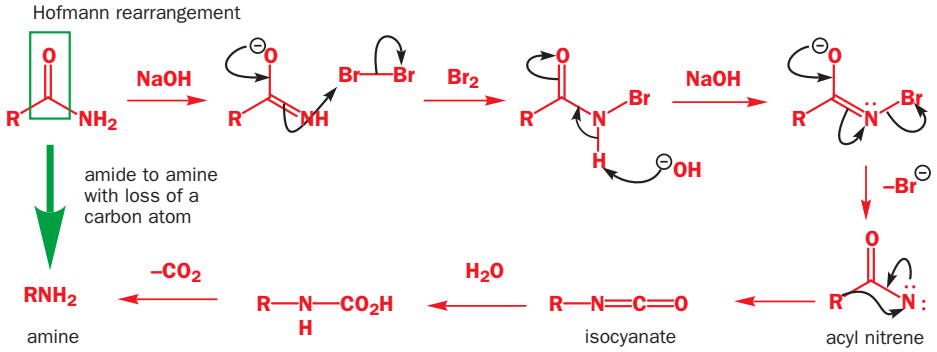
Nitrenes are the nitrogen analogues of carbenes

The Wolff rearrangement has some important cousins that we must now introduce to you—they deserve a mention because they bear a family likeness even though they do not, in fact, involve carbenes. They are a group of reactions that proceed through an intermediate **nitrene**—the nitrogen analogue of a carbene. The simplest to understand, because it is the direct nitrogen analogue of the Wolff rearrangement, is the **Curtius rearrangement**. It starts with an acyl azide—which can be made by nucleophilic substitution on an acyl chloride by sodium azide. The acyl azide is what you would get if you just replaced the $-CH=N_2$ of a diazoketone with $-N=N_2$. And, if you heat it, it is not surprising that it decomposes to release nitrogen (N_2), forming the nitrene. The nitrene has two bonds fewer (1) than a normal amine and has two lone pairs making six electrons in all.

Nitrenes, like carbenes, are immensely reactive and electrophilic, and the same Wolff-style migration takes place to give an isocyanate. The substituent R migrates from carbon to the electron-deficient nitrogen atom of the nitrene. Isocyanates are unstable to hydrolysis: attack by water on the carbonyl group gives a carbamic acid which decomposes to an amine.



Overall, then, the Curtius rearrangement converts an acid chloride to an amine with loss of a carbon atom—very useful. Also useful is the related **Hofmann rearrangement**, which turns an amide into an amine with loss of a carbon atom. This time we start with a primary amide and make a nitrene by treatment with base and bromine. Notice how close this nitrene-forming reaction is to the carbene-forming reactions we talked about on p. 000. The nitrene rearranges just as in the Curtius reaction, giving an isocyanate that can be hydrolysed to the amine.



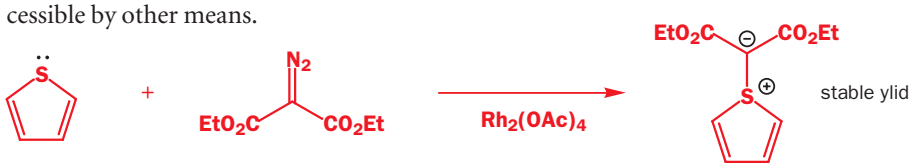
Attack of carbenes on lone pairs

Wolff rearrangements, involving shifts of alkyl groups, are effectively intramolecular insertions into C–C bonds. Carbenes will also insert into other bonds, especially O–H and N–H bonds, though the mechanism in these cases involves initial attack on the lone pair of the heteroatom.

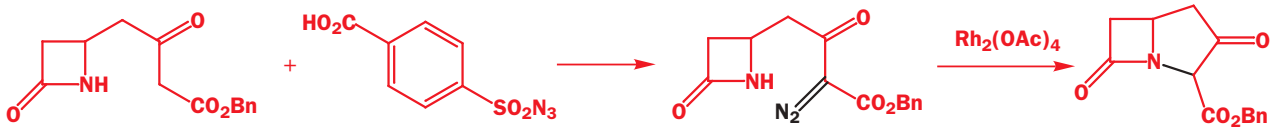
■ Ylids (or ylides) are zwitterions in which the charges are on adjacent atoms—we mentioned phosphorus ylids in Chapters 14 and 31. A whole chapter, Chapter 46, will be devoted to sulfur ylids and ylid-like species, because they have a special type of chemistry.

■ We will come back to this in Chapter 46.

Carbene attack is followed by proton transfer to generate a neutral molecule from the first formed zwitterion (or 'ylid'). However, if the heteroatom does not carry a hydrogen, attack on its lone pair generates an ylid that cannot rearrange in this way. Reaction of a carbene with a neutral nucleophile forms an ylid. This type of reaction is, in fact, a very useful way of making reactive ylids that are inaccessible by other means.

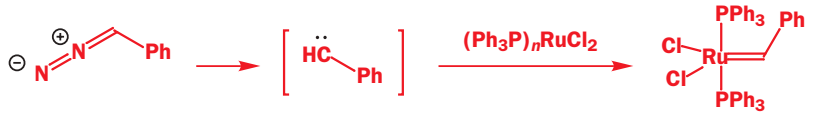


As carbonyl-substituted carbenes (like carbonyl-substituted radicals) are electrophilic, their insertion into O–H and N–H bonds can be a useful way of making bonds in an umpolung sense. Because of the difficulties in forming β-lactams (the four-membered rings found in the penicillin classes of antibiotics), Merck decided to design a synthesis of the class of compounds known as carbapenems around a rhodium-catalysed carbene insertion into an N–H bond, building the five-membered ring on to the side of the four-membered ring.



Alkene (olefin) metathesis

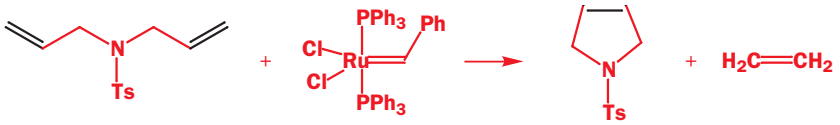
Carbenes can be stabilized as transition metal complexes: decomposition of phenyldiazomethane in the presence of a ruthenium(II) complex gives a carbene complex stable enough to be isolated and stored for months. These complexes are among the most important of carbene-derived reagents because of a remarkable reaction known as **alkene** (or more commonly **olefin**) **metathesis**.



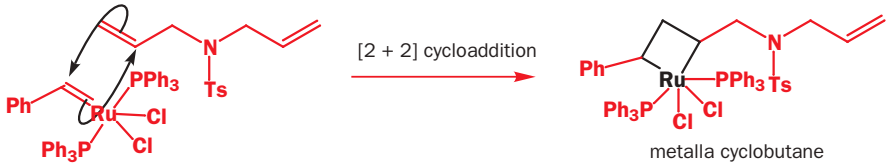
phenyldiazomethane — carbene — 'Grubb's' complex

The reaction is most easily understood when a simple diene reacts with a very small amount (in this case 2 mole per cent) of the catalyst. A cyclization reaction occurs and the product is also an alkene. It contains no atoms from the catalyst: indeed, it has lost two carbon atoms, which are given off as ethylene.

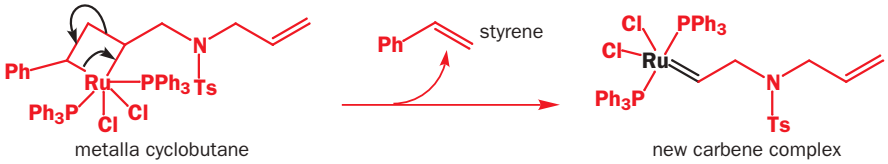
■ The stable 'Fischer carbene' complexes mentioned at the start of this chapter (p. 000) also catalyse the metathesis reaction but rather less well than these ruthenium complexes.



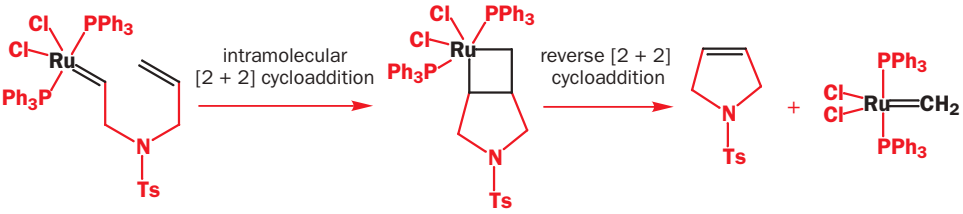
Any reaction that makes new bonds so efficiently and with so little reagent and so little waste is obviously very important. The yield is also rather good! What happens is a **metathesis**—an exchange of groups between the two arms of the molecule. First, the carbene complex adds to one of the alkenes in what can be drawn as a [2 + 2] cycloaddition (Chapter 35) to give a four-membered ring with the metal atom in the ring.



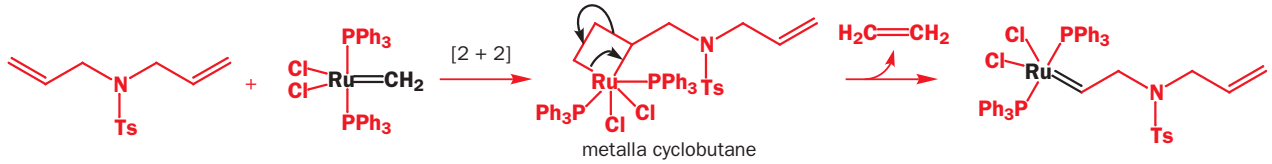
Now the same reaction happens in reverse (all cycloadditions are, in principle, reversible), either to give the starting materials or, by cleavage of the other two bonds, a new carbene complex and styrene.



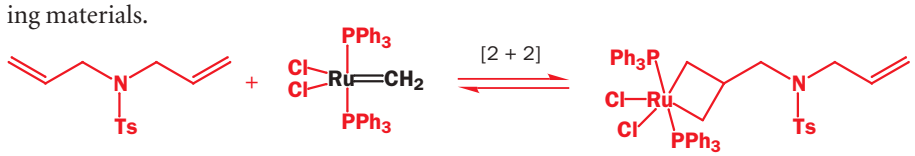
Next, an intramolecular [2 + 2] cycloaddition joins up the five-membered ring and produces a second metalla cyclobutane, which decomposes in the same way as the first one to give a third carbene complex and the product.



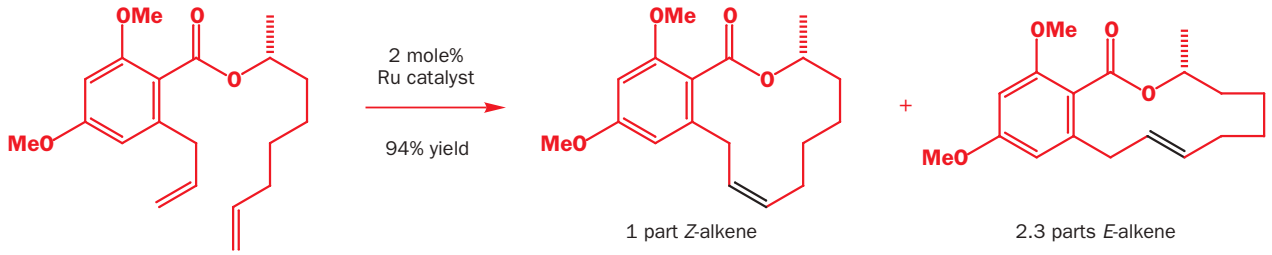
This new carbene complex then attacks another molecule of starting material and the cycle is repeated except that ethylene (ethene) is now lost instead of styrene in all the remaining cycles.



You will have noticed that the carbene complex appears to exhibit a remarkable selectivity: the ruthenium atom adds to the more substituted end of the first alkene but to the less substituted end of the second. In fact, there is no particular need for selectivity: if the second cycloaddition occurs with the opposite selectivity the metalla cyclobutane has symmetry and can decompose only to the starting materials.



One example that makes a number of points about olefin metathesis is the cyclization of this ester.



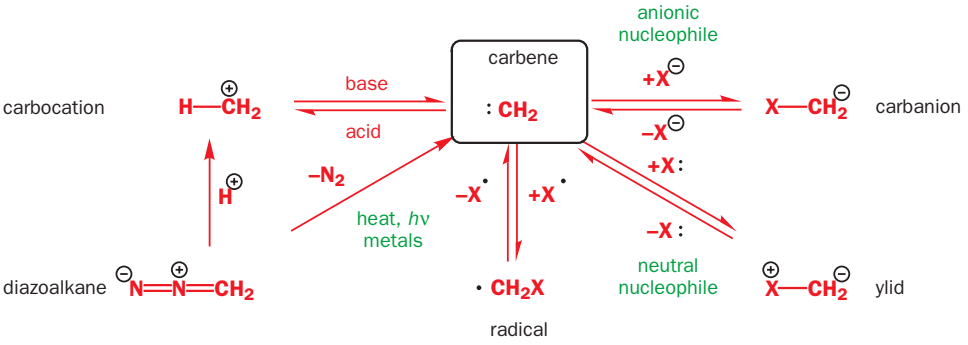
The main points are:

- Olefin metathesis is an excellent way to make difficult ring sizes—here a 12-membered ring
- It is compatible with many functional groups—here just an ester and an ether but amines, alcohols, epoxides, and many other carbonyl groups are all right
- The reaction is *E*-selective. In the previous example only a *Z*-alkene could be formed but an *E*-alkene is possible in a 12-membered ring and is the major product
- Stereogenic centres are not racemized

Alkene metathesis is one of the more important of the many new useful reactions that use transition metal complexes as catalysts. You will see more in Chapters 45 and 48.

Summary

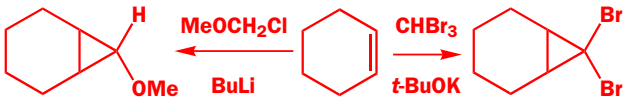
We have seen in this chapter how carbenes can be formed from many other reactive intermediates such as carbanions and diazoalkanes and how they can react to give yet more reactive intermediates such as ylids. Here is a summary of the main relationships between carbenes and these other compounds. Note that not all the reactions are reversible. Diazoalkanes lose nitrogen to give carbenes but the addition of nitrogen to carbenes is not a serious reaction.



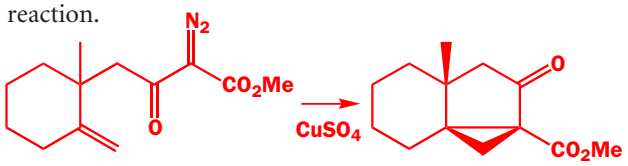
In the last few chapters we have concentrated a lot on what we call reactive intermediates, species like radicals, carbenes, or carbocations that are hard to observe but that definitely exist. Much of the evidence for their existence derives from the study of the mechanisms of reactions—we have discussed some aspects of this as we have met the species concerned, but in the next chapter we will look in detail at how mechanisms are elucidated and the methods used to determine more precisely the structure of reactive intermediates.

Problems

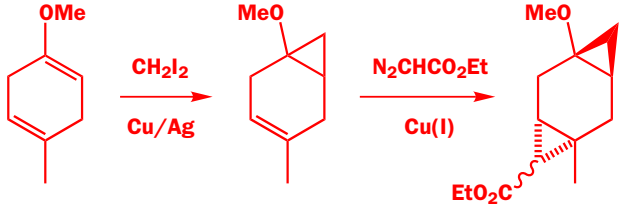
1. Suggest mechanisms for these reactions.



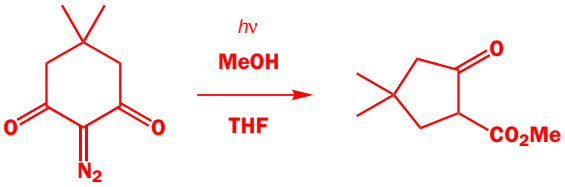
2. Suggest a mechanism and explain the stereochemistry of this reaction.



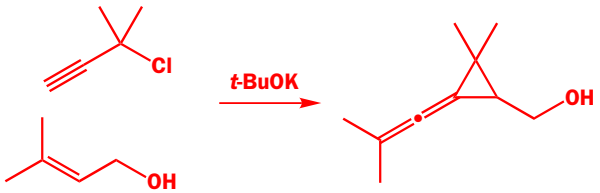
3. Comment on the selectivity shown in these two reactions.



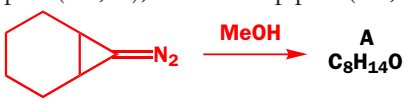
4. Suggest a mechanism for this ring contraction.



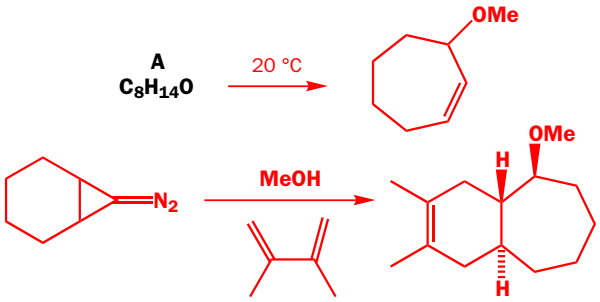
5. Suggest a mechanism for the formation of this cyclopropane.



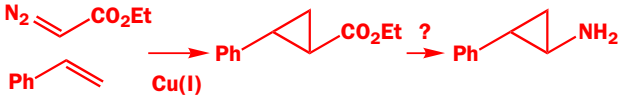
6. Problem 4 in Chapter 32 asked: 'Decomposition of this diazo compound in methanol gives an alkene A ($C_8H_{14}O$) whose NMR spectrum contains two signals in the alkene region: δ_H 3.50 p.p.m. (3H, s), 5.50 p.p.m. (1H, dd, *J* 17.9, 7.9 Hz), 5.80 p.p.m. (1H, ddd, *J* 17.9, 9.2, 4.3 Hz), 4.20 p.p.m. (1H, m), and 1.3–2.7 p.p.m. (8H, m). What is its structure and geometry?'



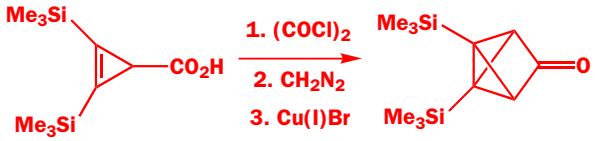
In order to work out the mechanism of the reaction you might like to take these additional facts into account. Compound A is unstable and even at 20 °C isomerizes to B. If the diazo compound is decomposed in methanol containing a diene, compound A is trapped as an adduct. Account for all of these reactions.



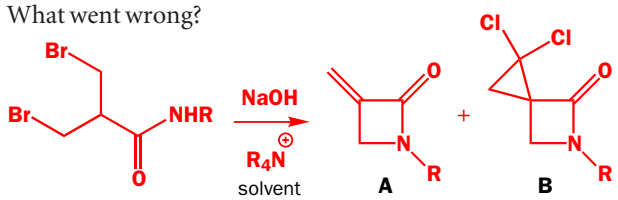
7. Give a mechanism for the formation of the three-membered ring in the first of these reactions and suggest how the ester might be converted into the amine with retention of configuration.



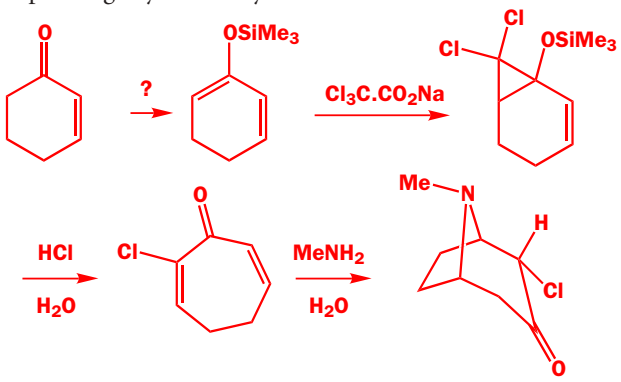
8. Explain how this highly strained ketone is produced, albeit in very low yield, by these reactions. How would you attempt to make the starting material?



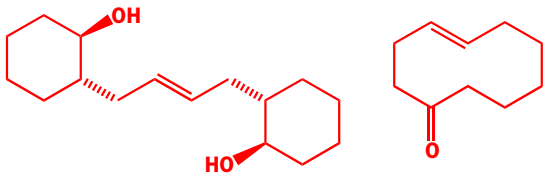
9. Attempts to prepare compound A by a phase-transfer-catalysed cyclization required a solvent immiscible with water. When chloroform ($CHCl_3$) was used, compound B was formed instead and it was necessary to use the more toxic CCl_4 for success. What went wrong?



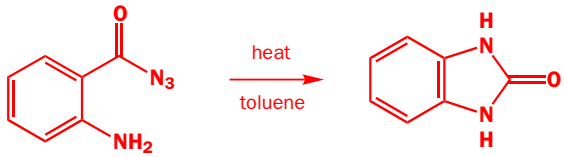
10. Revision content. How would you carry out the first step in this sequence? Propose mechanisms for the remaining steps, explaining any selectivity.



11. How would you attempt to make these alkenes by metathesis?



12. Heating this acyl azide in dry toluene under reflux for 3 hours gives a 90% yield of a heterocyclic product. Suggest a mechanism, emphasizing the involvement of any reactive intermediates.



13. Give mechanisms for the steps in this conversion of a five- to a six-membered aromatic heterocycle.