Organo-main-group chemistry 1: sulfur

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Connections

Building on:

- Conjugate addition ch10 & ch23
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- Oxidation ch24
- Aldol reactions ch27
- Controlling double bond geometry ch31
- Rearrangements ch36–ch37
- Radicals and carbenes ch39–ch40

Arriving at:

- Sulfur compounds have many oxidation states
- Sulfur is nucleophilic and electrophilic
- Sulfur stabilizes anions and cations
- Sulfur can be removed by reduction or oxidation
- Sulfoxides can be chiral
- Thioacetals provide d^1 reagents
- Allylic sulfides are useful in synthesis
- Epoxides can be made from sulfonium ylids
- Sulfur compounds are good at cationic and [2,3]-sigmatropic rearrangements
- Selenium compounds resemble sulfur compounds

Looking forward to:

- Main group chemistry II: B, Si, and Sn ch47
- Organometallic chemistry ch48
- Biological chemistry ch49–ch51
- Polymerization ch52

Sulfur: an element of contradictions

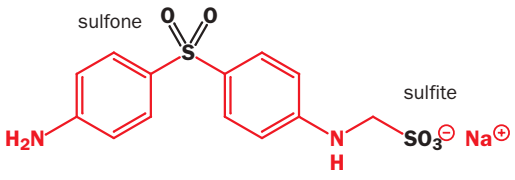
The first organosulfur compounds in this book were the dreadful smell of the skunk and the wonderful smell of the truffle, which pigs can detect through a metre of soil and which is so delightful that truffles cost more than their weight in gold.

the dreadful smell of the skunk

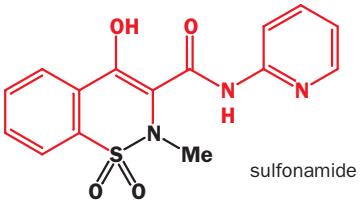
the dreadful smell of the skunk

More useful sulfur compounds have included the leprosy drug dapsone (Chapter 6), the arthritis drug Feldene (Chapter 21), glutathione (Chapter 23), a scavenger of oxidizing agents that protects most living things against oxidation and contains the natural amino acid cysteine (Chapter 49), and, of course, the famous antibiotics, the penicillins, mentioned in several chapters.

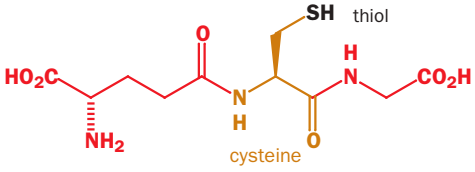
▶ If you look in the Oxford English dictionary you will see 'sulphur'. This is a peculiarly British spelling—neither the French nor the Americans for example have the 'ph'. It has recently been decided that chemists the world over should use a uniform spelling 'sulfur'.



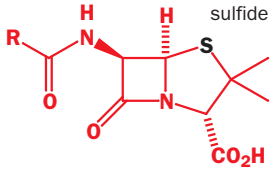
dapsone—water-soluble 'pro-drug' for leprosy



Pfizer's piroxicam or Feldene

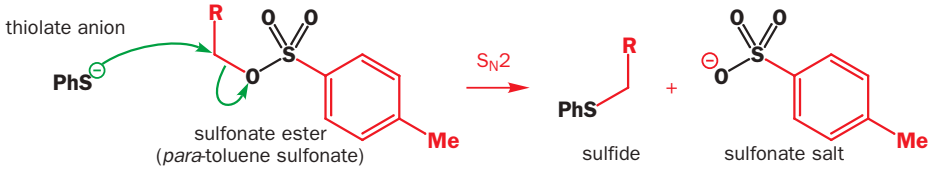


glutathione: scavenger of toxic oxidants

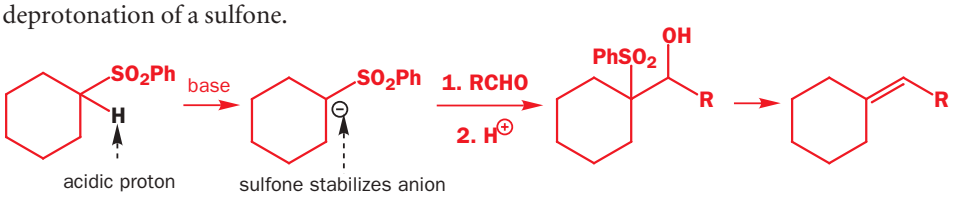


penicillin family of antibiotics

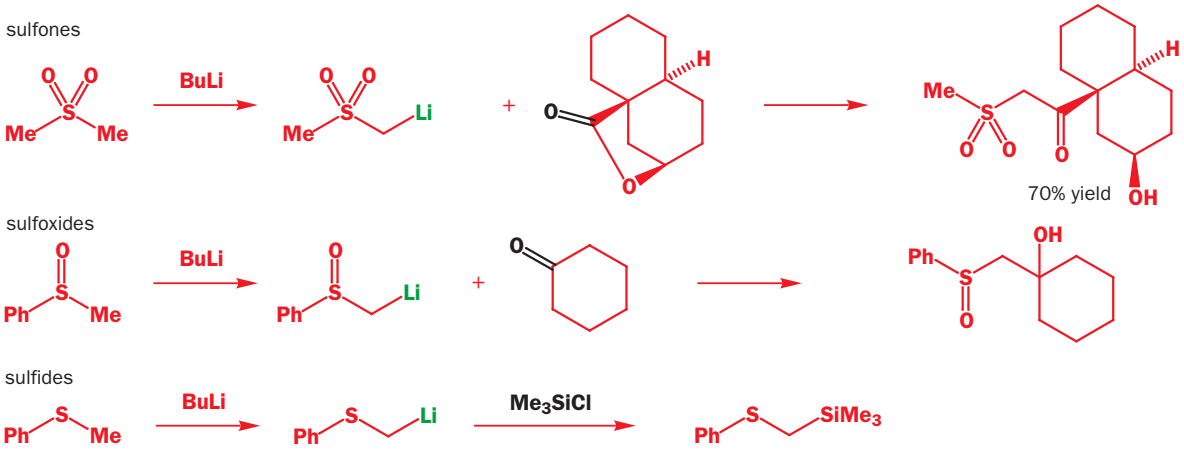
Important reactions have included sulfur as nucleophile and leaving group in the S_N2 reaction (illustrated here; see also Chapter 17), sulfonation of aromatic rings (Chapter 22), formation and reduction of thioacetals (Chapter 24), Lawesson's reagent for converting carbonyl groups to thiocarbonyl groups (Chapter 44).



This chapter gathers together the principles behind these examples together with a discussion of what makes organosulfur chemistry special and also introduces new reactions. We have a lot to explain! In Chapter 31 we introduced you to the Julia olefination, a reaction whose first step is the deprotonation of a sulfone.



Why is this proton easy to remove? This ability to stabilize an adjacent anion is a property shared by all of the most important sulfur-based functional groups. The anions (or better, lithium derivatives) will react with a variety of electrophiles and here is a selection: a sulfone reacting with a lactone, a sulfoxide with a ketone, and a sulfide with a silyl chloride.



You notice immediately the three main oxidation states of sulfur: S(VI), S(IV), and S(II). You might have expected the S(VI) sulfone and perhaps the S(IV) sulfoxide to stabilize an adjacent anion, but the S(II) sulfide? We will discuss this along with many other unusual features of sulfur chemistry. The interesting aspects are what make sulfur different.

The basic facts about sulfur

Sulfur is a p-block element in group VI (or 16 if you prefer) immediately below oxygen and between phosphorus and chlorine. It is natural for us to compare sulfur with oxygen but we will, strangely, compare it with carbon as well.

Sulfur is much less electronegative than oxygen; in fact, it has the same electronegativity as carbon, so it is no good trying to use the polarization of the C–S bond to explain anything! It forms reasonably strong bonds to carbon—strong enough for the compounds to be stable but weak enough for

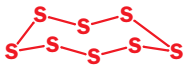
Sulfur in the periodic table (electronegativity)

C	N	O	F
(2.5)	(3.0)	(3.5)	(4.0)
Si	P	S	Cl
(1.8)	(2.1)	(2.5)	(3.0)

Bond strengths, kJ mol^{-1}

	X = C	X = H	X = F	X = S
C–X	376	418	452	362
S–X	362	349	384	301

selective cleavage in the presence of the much stronger C–O bonds. It also forms strong bonds to itself. Elemental crystalline yellow sulfur consists of S_8 molecules—eight-membered rings of sulfur atoms!



crystalline sulfur

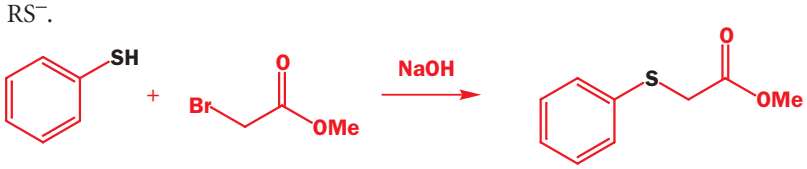
Because sulfur is in the second row of the periodic table it forms many types of compounds not available to oxygen. Compounds with S–S and S–halogen bonds are quite stable and can be isolated, unlike the unstable and often explosive O–halogen and O–O compounds. Sulfur has d orbitals so it can have oxidation states of 2, 4, or 6 and coordination numbers from 0 to 7. Here is a selection of compounds.

Compounds of sulfur

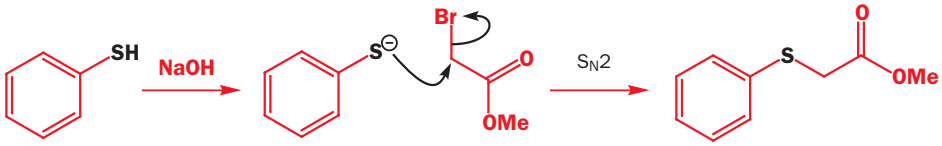
Oxidation state	S(II)			S(IV)		S(VI)		
coordination number	0	1	2	3	4	4	6	7
example	S^{2-}	RS^-	R_2S	$R_2S{=}O$	SF_4	R_2SO_2	SF_6	SF_7^-

Sulfur is a very versatile element

As well as this variety of oxidation states, sulfur shows a sometimes surprising versatility in function. Simple S(II) compounds are good nucleophiles as you would expect from the high-energy nonbonding lone pairs ($3sp^3$ rather than the $2sp^3$ of oxygen). A mixture of a thiol (RSH, the sulfur equivalent of an alcohol) and NaOH reacts with an alkyl halide to give the sulfide alone by nucleophilic attack of RS^-.



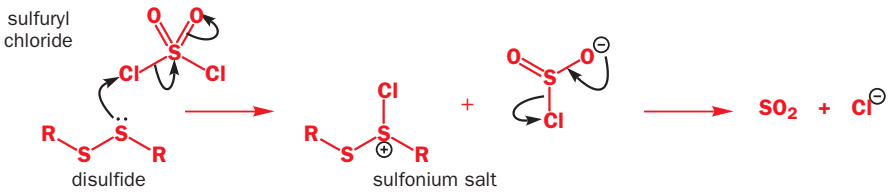
Thiols (RSH) are more acidic than alcohols so the first step is a rapid proton exchange between the thiol and hydroxide ion. The thiolate anion then carries out a very efficient S_N2 displacement on the alkyl bromide to give the sulfide.



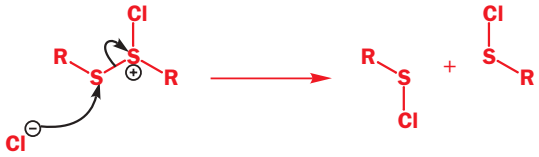
Notice that the thiolate anion does not attack the carbonyl group. Small basic oxyanions have high charge density and low-energy filled orbitals—they are hard nucleophiles that prefer to attack protons and carbonyl groups. Large, less basic thiolate anions have high-energy filled orbitals and are soft nucleophiles. They prefer to attack saturated carbon atoms. Thiols and thiolates are good soft nucleophiles.

- **Thiols (RSH) are more acidic than alcohols (ROH) but sulfur compounds are better nucleophiles than oxygen compounds towards saturated carbon atoms (S_N2).**

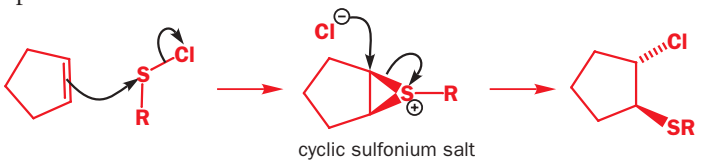
They are also good soft electrophiles. Sulfenyl chlorides (RSCl) are easily made from disulfides (RS–SR) and sulfuryl chloride (SO_2Cl_2). This S(VI) chloride has electrophilic chlorine atoms and is attacked by the nucleophilic disulfide to give two molecules of RSCl and gaseous SO_2. There's a lot of sulfur chemistry here! We start with a nucleophilic attack by one sulfur atom of the disulfide.



The intermediate contains a tricoordinate sulfur cation or sulfonium salt. The chloride ion now attacks the other sulfur atom of this intermediate and two molecules of RSCl result. Each atom of the original disulfide has formed an S–Cl bond. One sulfur atom was a nucleophile towards chlorine and the other an electrophile.

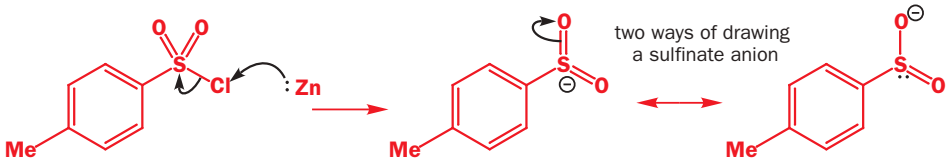


The product of this reaction, the sulfenyl chloride, is also a good soft electrophile towards carbon atoms, particularly towards alkenes. The reaction is very like bromination with a three-membered cyclic sulfonium ion intermediate replacing the bromonium ion of Chapter 20. The reaction is stereospecific and *anti*.

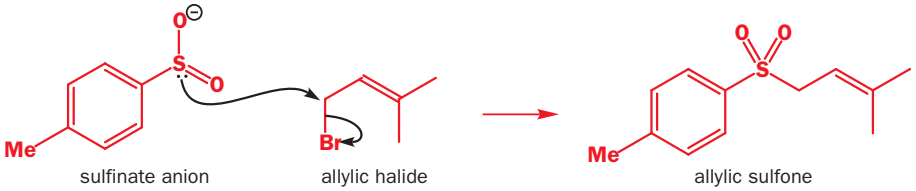


Sulfur at the S(II) oxidation state is both a good nucleophile and a good electrophile. This is also true at higher oxidation states though the compounds become harder electrophiles as the positive charge on sulfur increases. We have already mentioned tosyl (toluene-*para*-sulfonyl) chloride as an electrophile for alkoxide ions in this chapter and in earlier chapters.

At this higher oxidation state it might seem unlikely that sulfur could also be a good nucleophile, but consider the result of reacting TsCl with zinc metal. Zinc provides two electrons and turns the compound into an anion. This anion can also be drawn in two ways.



Surprisingly, this anion is also a good soft nucleophile and attacks saturated carbon atoms through the sulfur atom. In this case attack occurs at the less substituted end of an allylic bromide to give an allylic sulfone, which we will use later on.

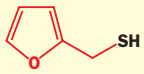
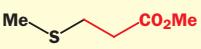
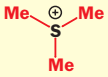
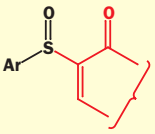


● Sulfur compounds are good nucleophiles and good electrophiles.

As this chapter develops you will see other examples of the versatility of sulfur. You will see how it takes part readily in rearrangements from the simple cationic to the sigmatropic. You will see that it can be removed from organic compounds in either an oxidative or a reductive fashion. You will see that it can stabilize anions or cations on adjacent carbon atoms, and the stabilization of anions is the first main section of the chapter.

Sulfur-based functional groups

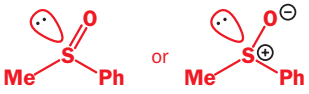
We have already met a number of sulfur-containing functional groups and it might be useful to list them for reference.

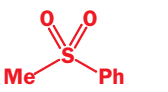
Name	Structure	Importance	Example	Example details
thiol (or mercaptan)	RSH	strong smell, usually bad, but sometimes heavenly		smell and taste of coffee
thiolate anion	RS^-	good soft nucleophiles		
disulfide	RS–SR	cross-links proteins		
sulfenyl chloride	RS–Cl	good soft electrophiles		
sulfide (or thioether)	R–S–R	molecular link		smell and taste of pineapple
sulfonium salt	R_3S^+	important reagents		ylid used in epoxidations
sulfoxide	$R_2S{=}O$ or $R_2S^+–O^-$	many reactions; can be chiral		chiral Michael acceptors
sulfone	R_2SO_2	anion-stabilizing group		
sulfonic acid	RSO_2OH	strong acids		
sulfonyl chloride	RSO_2Cl	turns alcohols into leaving groups		

Sulfur-stabilized anions

In this chapter we shall discuss some of the rich and varied chemistry of these, and other, organosulfur compounds. The stabilization of anions by sulfur is where we begin, and this theme runs right through the chapter. We will start with sulfides, sulfoxides, and sulfones. Sulfur has six electrons in its outer shell. As a sulfide, therefore, the sulfur atom carries two lone pairs. In a sulfoxide, one of these lone pairs is used in a bond to an oxygen atom—sulfoxides can be represented by at least two valence bond structures. The sulfur atom in a sulfone uses both of its lone pairs in bonding to oxygen, and is usually represented with two S=O double bonds.


methyl phenyl sulfide

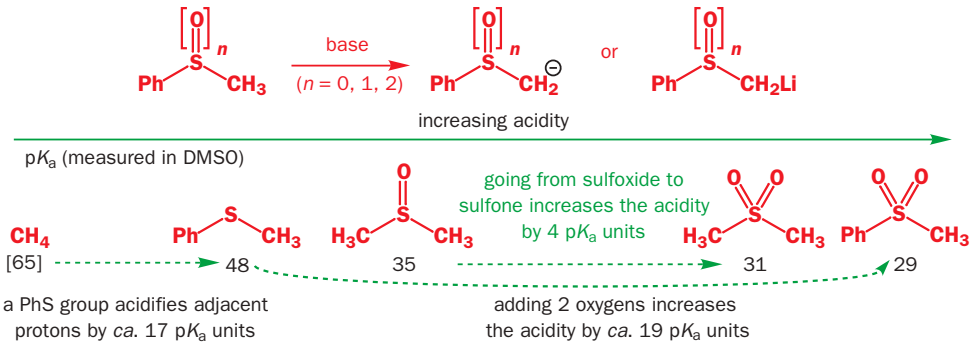

methyl phenyl sulfoxide


methyl phenyl sulfone

Treatment of any of these compounds with strong base produces an anion (or a lithium derivative if BuLi is used) on what was the methyl group. How does the sulfur stabilize the anion? This question has been the subject of many debates and we have not got space to go into the details of all of them. There are at least two factors involved, and the first is evident from this chart of pK_a values for protons next to sulfone, sulfoxide and sulfide functional groups.

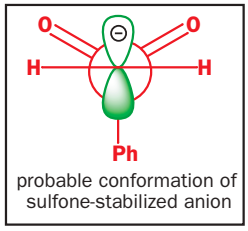
▶ Sulfoxides have the potential for chirality—the tetrahedral sulfur atom is surrounded by four different groups (here Ph, Me, O, and the lone pair) and (unlike, say, the tetrahedral nitrogen atom of an amide) has a stable tetrahedral configuration. We will revisit chirality in sulfoxides later in the chapter.

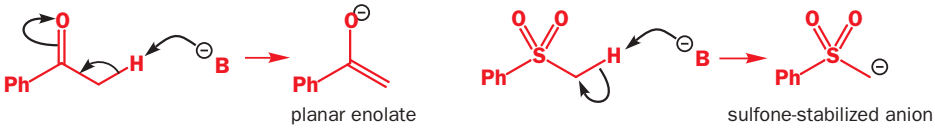

enantiomers of a chiral sulfoxide



■ If you want to read more about the elegant experiments that have been used to probe the structure of sulfonyl anions, see E. Block, *The organic chemistry of sulfur*, Academic Press, New York, 19xx.

Clearly, the oxygen atoms are important—the best anion-stabilizer is the sulfone, followed by the sulfoxide and then the sulfide. You could compare deprotonation of a sulfone with deprotonation of a ketone to give an enolate (Chapter 21). Enolates have a planar carbon atom and the anion is mainly on the oxygen atom. Sulfone-stabilized carbanions have two oxygen atoms and the anionic centre is probably planar, with the negative charge in a p orbital midway between them. Carbanions next to sulfones are planar, while anions next to sulfoxides and sulfides are believed to be pyramidal (sp^3 hybridized).

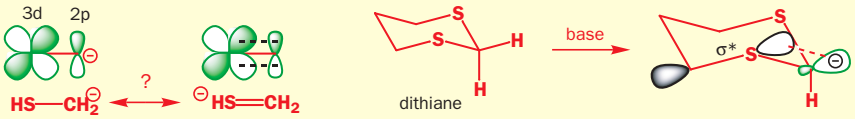

probable conformation of sulfone-stabilized anion



Yet the attached oxygen atoms cannot be the sole reason for the stability of anions next to sulfur because the sulfide functional group also acidifies an adjacent proton quite significantly. There is some controversy over exactly why this should be, but the usual explanation is that polarization of the sulfur's 3s and 3p electrons (which are more diffuse, and therefore more polarizable, than the 2s and 2p electrons of oxygen) contributes to the stabilization.

Heading

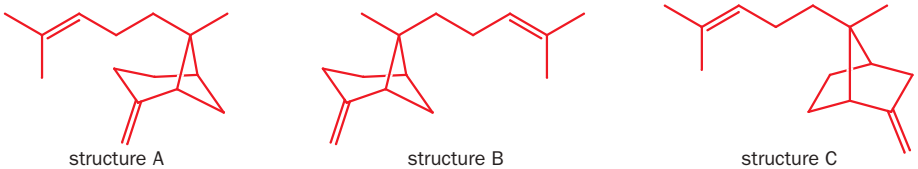
It was long thought that delocalization into sulfur's empty 3d orbitals provided the anion stabilization required, but theoretical work in the last 20 years or so suggests this may not be the case. For example, *ab initio* calculations suggest that the C–S bond in $–CH_2SH$ is longer than in CH_3SH. The converse would be true if delocalization into the sulfur's d orbitals were important. Delocalization would shorten the bond because it would have partial double bond character. More likely as an additional factor is delocalization into the σ* orbital of the C–S bond on the other side of the sulfur atom—the equatorial proton of dithiane (see p. 000 for more on dithiane) is more acidic than the axial one, and the equatorial anion is more stable because it is delocalized into the C–S bond's σ* orbital.



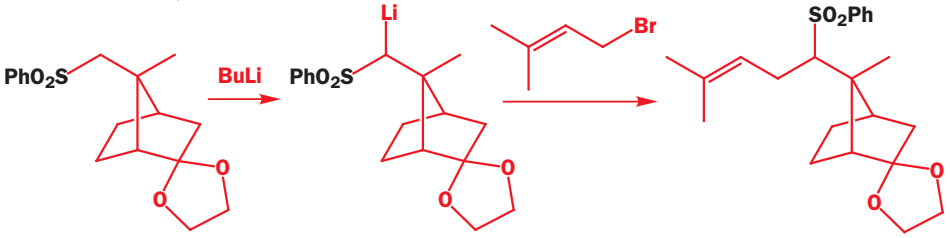
Sulfone-stabilized anions in synthesis

The terpene sesquifenchene is a constituent of Indian valerian root oil. When it was first discovered in 1963, it was assumed to have structure A, related to bergamotene, a constituent of oil of bergamot (the fragrance of Earl Grey tea).

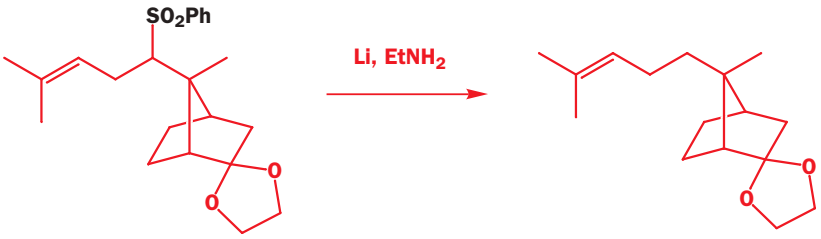
proposed structures of the natural product sesquifenchene



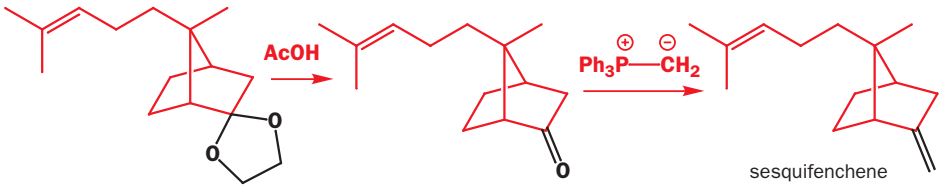
Compound A was synthesized in 1969, but was found not to be identical with sesquifenchene. A new structure was proposed, B, which was synthesized in 1971—but this compound too had different properties from those of natural sesquifenchene! A third structure was proposed, C, and it was made from a bicyclic sulfone.



The bicyclic part of the structure was available in a few steps from norbornadiene. Deprotonation of the sulfone made a nucleophile that could be alkylated with prenyl bromide—a convenient way of joining on the extra five carbon atoms needed in the target structure. Next, the sulfone group had to be got rid of—there are a number of ways of doing this, and these chemists chose a Birch reduction with $EtNH_2$ instead of liquid ammonia. They might equally have tried hydrogenation with Raney nickel (see p. 000) or a sodium–amalgam-type reduction as is used in the Julia olefination (p. 000; you will see aluminium amalgam used in this way on p. 000).



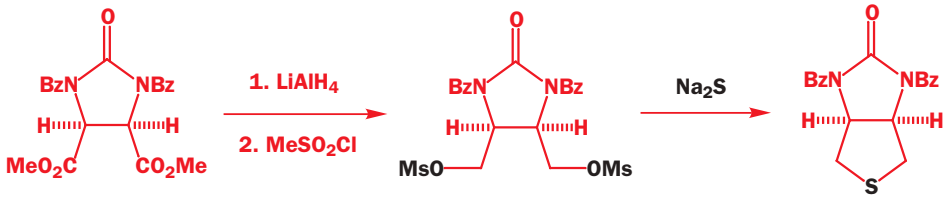
The exocyclic double bond was made by Wittig reaction on the deprotected ketone (aqueous acetic acid removed the dioxolane protecting group). This product had all the characteristics of natural sesquifenchene, confirming its true structure.



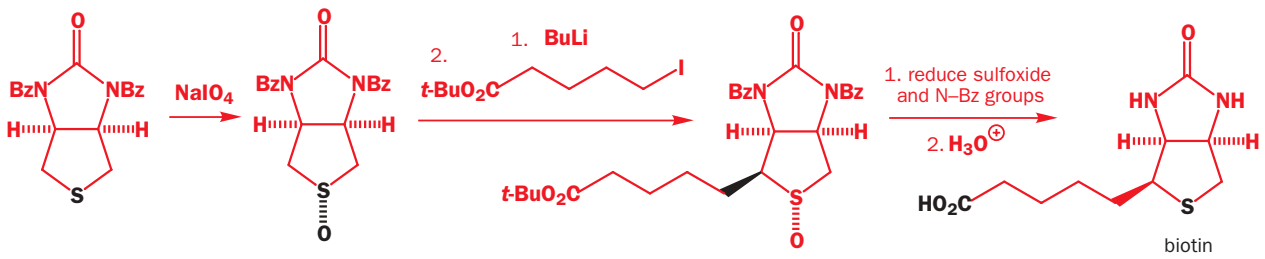
▶ Of course, with today's spectroscopic techniques it is rarely necessary to synthesize a compound to confirm its structure, but misinterpretation still takes place and it is only when the compound is synthesized that the error comes to light.

A sulfoxide-stabilized anion in a synthesis

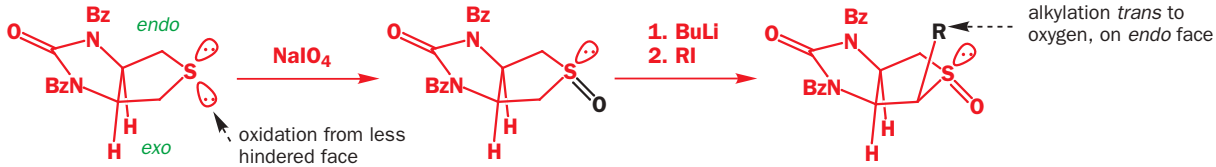
A sulfoxide alkylation formed the key step of a synthesis of the important vitamin biotin. Biotin contains a five-membered heterocyclic sulfide fused to a second five-membered ring, and the bicyclic skeleton was easy to make from a simple symmetrical ester. The vital step is a double S_N2 reaction on primary carbon atoms.



The next step was to introduce the alkyl chain—this was best done by first oxidizing the sulfide to a sulfoxide, using sodium periodate. The sulfoxide was then deprotonated with *n*-BuLi and alkylated with an alkyl iodide containing a carboxylic acid protected as its *t*-butyl ester. Reduction of the sulfoxide and hydrolysis back to the free acid gave biotin.



This synthesis involves some stereochemistry. Biotin carries the alkyl chain next to sulfur on the more hindered *endo* face of the molecule, and any successful synthesis has to address this particular problem. Here, the chemists decided to use the fact that alkylations of cyclic sulfoxides result in *trans* stereochemistry between the new alkyl group and the sulfoxide oxygen atom. As expected, oxidation of the sulfide proceeded faster from the *exo* face, giving an 8:1 ratio of *exo*:*endo* sulfoxides. Alkylation *trans* to the *exo* oxygen gave the desired (*endo*) product.

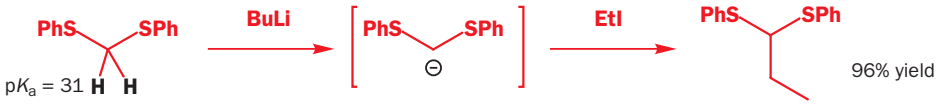


■ In Chapter 33 we talked about the ways in which cyclic compounds react stereoselectively—the stereochemistry of this sulfide oxidation is what you would expect from the examples we gave there.

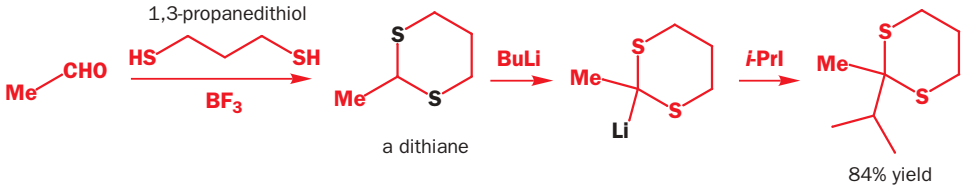
The synthesis is diastereoselective—but not enantioselective since there is no way of distinguishing the left and right sides of the symmetrical sulfoxide.

Thioacetals

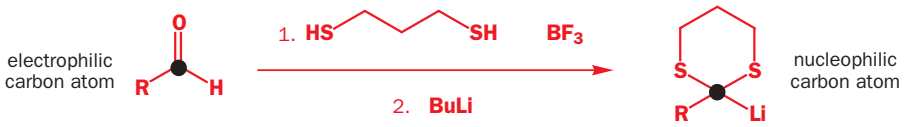
Although sulfide deprotonations are possible, the protons adjacent to *two* sulfide sulfur atoms are rather more acidic and alkylation of thioacetals is straightforward.



In general, thioacetals can be made in a similar way to 'normal' (oxygen-based) acetals–by treatment of an aldehyde or a ketone with a thiol and an acid catalyst—though a Lewis acid such as BF_3 is usually needed rather than a protic acid. The most easily made, most stable toward hydrolysis, and most reactive towards alkylation are cyclic thioacetals derived from 1,3-propanedithiol, known as **dithianes**.

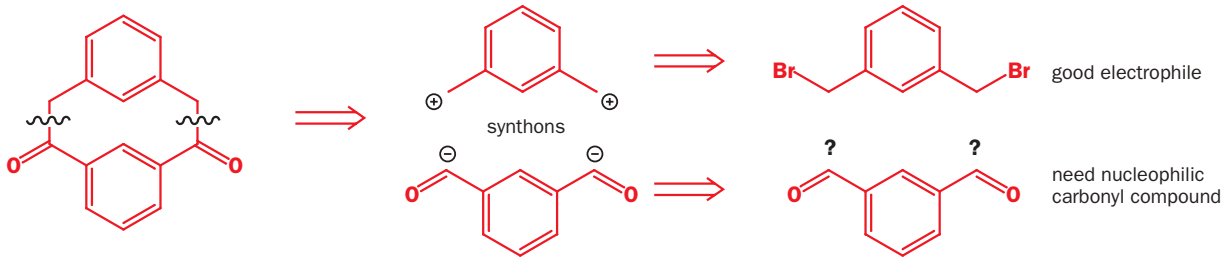


Dithianes are extremely important compounds in organic synthesis because *going from ketone to thioacetal inverts the polarity at the functionalized carbon atom.* Aldehydes, as you are well aware, are electrophiles at the C=O carbon atom, but dithioacetals, through deprotonation to an anion, are nucleophilic at this same atom.

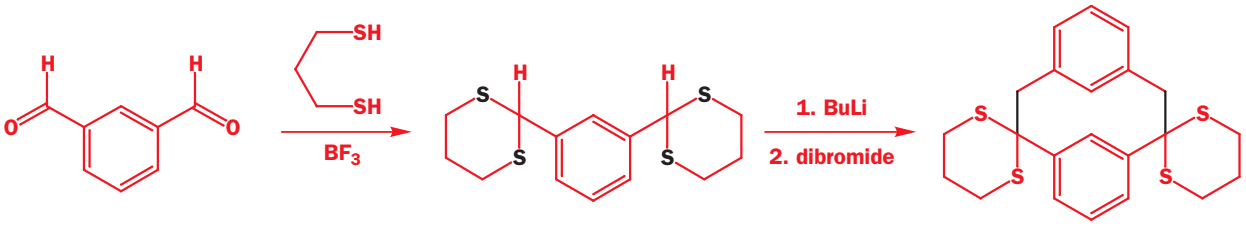


This is a case of umpolung, the concept you met in Chapter 30, and dithianes are among the most important of the umpolung reagents. An example: chemists wanted to make this compound (a

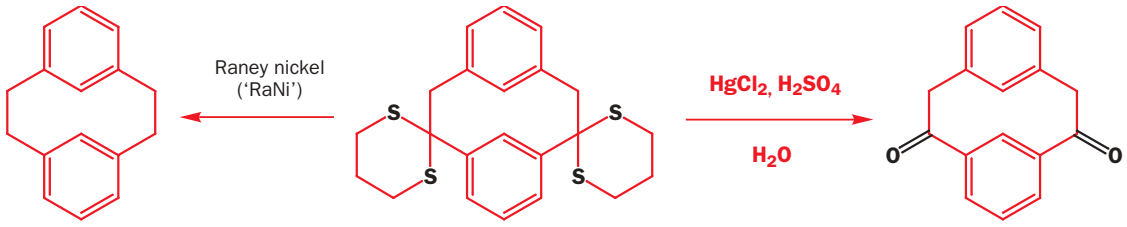
'metacyclophane') because they wanted to study the independent rotation of the two benzene rings, which is hindered in such a small ring. An ideal way would be to join electrophilic benzylic bromides to nucleophilic carbonyl groups, if that were possible.



The dibromide and dialdehyde were both available—what they really wanted was a nucleophilic equivalent of the dialdehyde to react with the dibromide. So they made the dithioacetal.

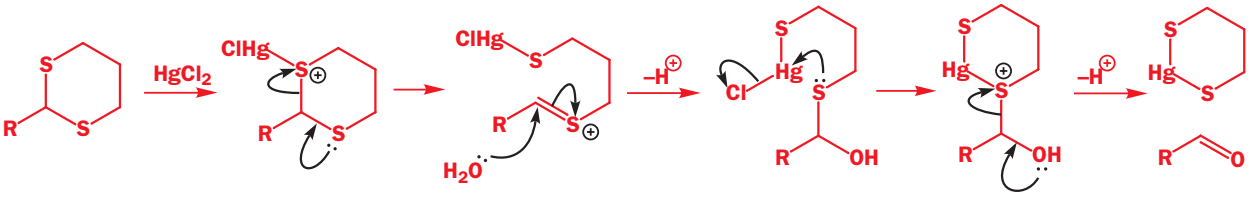


After the dithianes have been alkylated, they can be hydrolysed to give back the carbonyl groups. Alternatively, hydrogenation using Raney nickel replaces the thioacetal with a CH_2 group and gives the unsubstituted cyclophane.



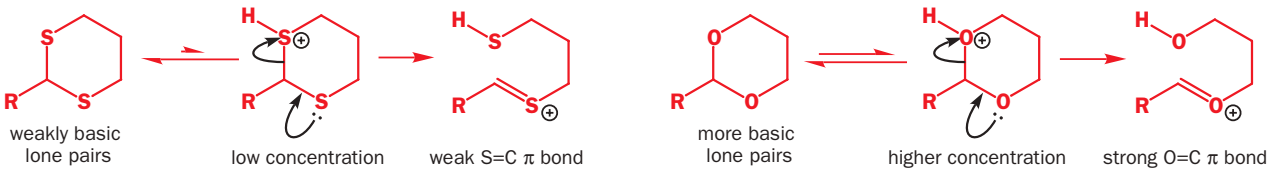
Both of these transformations deserve comment. Dithianes are rather more stable than acetals, and a mercury reagent has to be used to assist their hydrolysis. Mercury(II) and sulfides form strong coordination complexes, and the mercury catalyses the reaction by acting as a sulfur-selective Lewis acid.

■ Thiols are also known as **mercaptans** because of their propensity for 'mercury capture'.

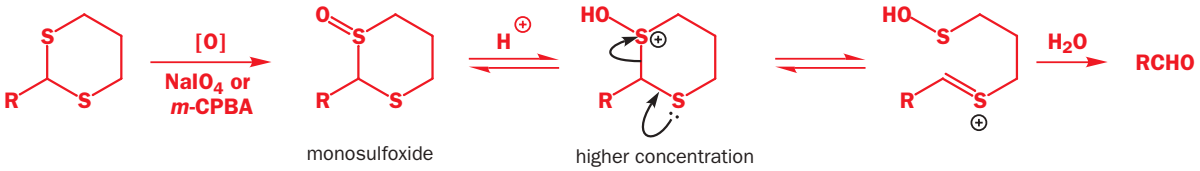


There are two reasons why the normal acid-catalysed hydrolysis of acetals usually fails with thioacetals. Sulfur is less basic than oxygen, so the protonated species is lower in concentration at a given pH, and the sulfur 3p lone pairs are less able to form a stable π bond to carbon than are the oxygen 2p lone pairs.

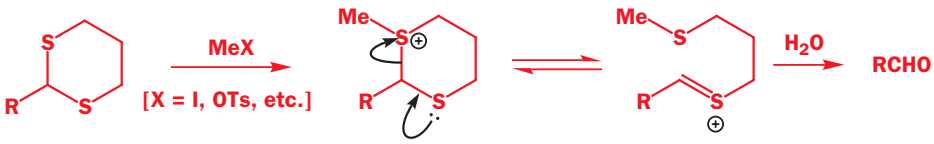
● **Sulfur compounds are less basic than oxygen compounds and C=S compounds are less stable than C=O compounds.**



The most obvious solution to this problem is to provide a better electrophile than the proton for sulfur. Mercury, Hg(II), is one solution. Another is oxidation of one sulfur to the sulfoxide, a process that would be impossible with the oxygen atoms of an ordinary acetal. Protonation can now occur on the more basic oxygen atom of the sulfoxide and the concentration of the vital intermediate is increased.



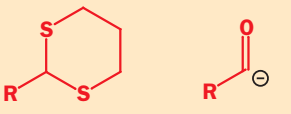
A third solution is methylation since sulfur is a better nucleophile for saturated carbon than is oxygen. The sulfonium salt can decompose in the same way to give the free aldehyde. There are many more methods for hydrolysing dithioacetals and their multiplicity should make you suspicious that none is very good. The best is probably the Hg(II) method but not everyone likes to use stoichiometric toxic mercury!



Hydrogenation of C–S bonds in both sulfides and thioacetals is often achieved with **Raney nickel**. This is a finely divided form of nickel made by dissolving away the aluminium from a powdered nickel–aluminium alloy using alkali. It can be used either as a catalyst for hydrogenation with gaseous hydrogen or as a reagent since it often contains sufficient adsorbed hydrogen (from the reaction of aluminium with alkali) to effect reductions alone. Thioacetalization followed by Raney nickel reduction is a useful way of replacing a C=O group with CH_2.

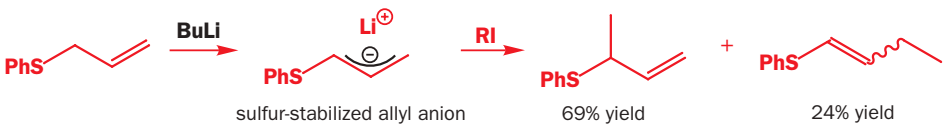
● Dithianes are d^1 reagents (acyl anion equivalents)

A sequence in which a carbonyl group has been masked as a sulfur derivative, alkylated with an electrophile, and then revealed again is a nucleophilic acylation. These nucleophilic equivalents of carbonyl compounds are known as acyl anion equivalents. In the retrosynthetic terms of Chapter 30 they are d^1 reagents corresponding to the acyl anion synthon.

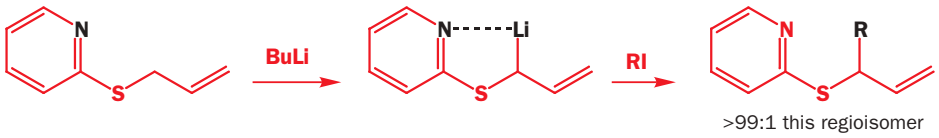


Allyl sulfides

Apart from thioacetals, allyl sulfides are among the easiest sulfides to deprotonate and alkylate because of the conjugating ability of the allyl group. However, the very delocalization that assists anion formation means that the anions often react unregioselectively: lithiated phenyl allyl sulfide, for instance, reacts with hexyl iodide to give a 3:1 ratio of regioisomers.



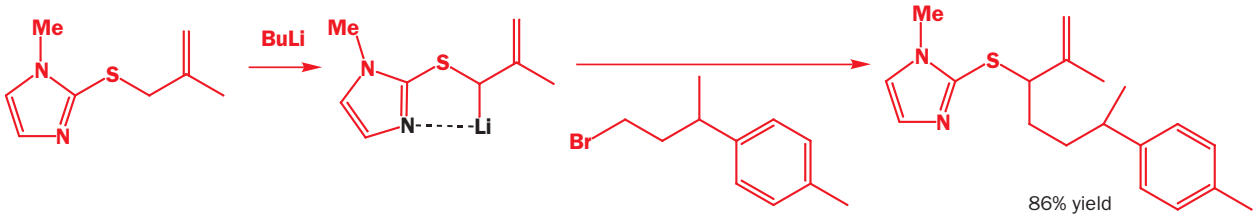
2-Pyridyl allyl sulfide, on the other hand, gives only one regioisomer in its alkylation reactions. It is sensible here to show the 'allyl anion' as a compound with a C–Li bond.



>99:1 this regioisomer

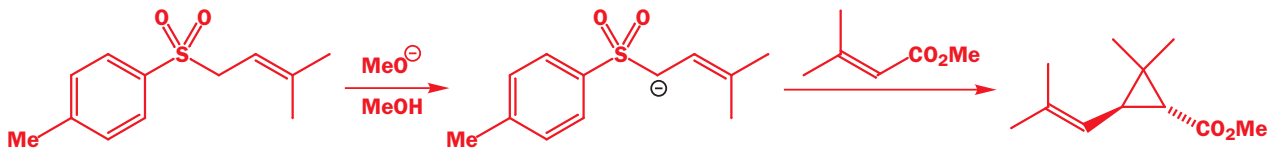
▶ The 'sulfur-stabilized allyl anion' in the previous reaction is probably a mixture of organolithium compounds in unknown proportions and the depiction as an anion avoids this

The same is true for a number of other allylic sulfur compounds in which the sulfur carries a lithium-coordinating heteroatom. Coordination encourages reaction next to sulfur (you might say it makes the lithium more at home there) and means that allyl sulfide alkylations can be made quite regioselective. The importance of this is probably not evident to you, but on p. 000 you will meet a synthesis of the natural product nuciferal in which this principle is used—the key step will be the alkylation of this allylic sulfide to give an 86% yield of the product with the alkyl group next to sulfur.



86% yield

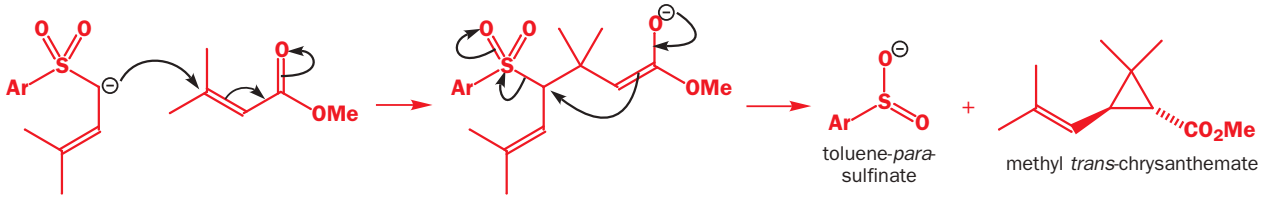
If the sulfur-based anion-stabilizing group is at a higher oxidation level, it is not usually necessary to provide chelating groups to ensure reaction next to sulfur. The allylic sulfone we made earlier in the chapter (p. 000) reacts in this way with an unsaturated ester to give a cyclopropane. Notice how much weaker a base (MeO^-) is needed here, as the anion (and it is an anion if the counterion is Na^+ or K^+) is stabilized by sulfone and alkene.



allylic sulfone | anion of allylic sulfone | methyl *trans*-chrysanthemate

The first step is conjugate addition of the highly stabilized anion. The intermediate enolate then closes the three-membered ring by favourable nucleophilic attack on the allylic carbon. The leaving group is the sulfinate anion and the stereochemistry comes from the most favourable arrangement in the transition state for this ring closure. The product is the methyl ester of the important chrysanthemic acid found in the natural pyrethrum insecticides.

■ In Chapters 10 and 23 we established that more stable nucleophiles, and hence more reversible reactions, are likely to favour conjugate addition.

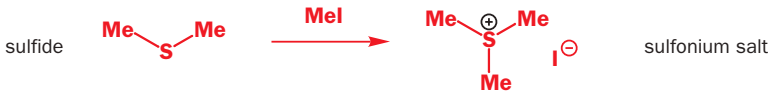


toluene-*para*-sulfinate | methyl *trans*-chrysanthemate

We shall see more reactions of this sort in which sulfur has a dual role as anion-stabilizing and leaving group in the next section.

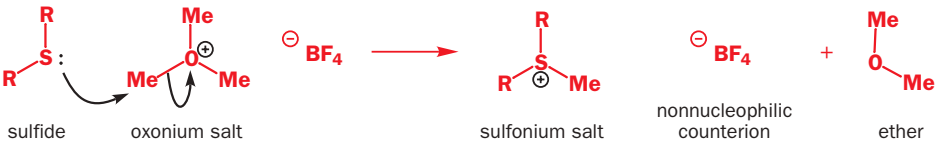
Sulfonium salts

Sulfides are nucleophiles even when not deprotonated—the sulfur atom will attack alkyl halides to form sulfonium salts. This may look strange in comparison with ethers, but it is, of course, a familiar pattern of reactivity for amines, and you have seen phosphonium salts formed in a similar way (Chapters 14 and 31).



This same principle was used in the isolation of stable carbocations described in Chapter 17.

This reaction is an equilibrium and it may be necessary in making sulfonium salts from less reactive sulfides (sterically hindered ones for example) to use more powerful alkylating agents with non-nucleophilic counterions, for example, $Me_3O^+\ BF_4^-$, trimethyloxonium fluoroborate (also known as Meerwein's salt). The sulfur atom captures a methyl group from O^+, but the reverse does not happen and the BF_4^- anion is not a nucleophile.

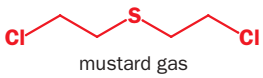


Not only is dimethyl ether a poor nucleophile, it is also a gas and is lost from the reaction mixture. The same principle is used to make sulfides from other sulfides. With that clue, and the position of this reaction in the 'sulfonium salt' section, you should be able to work out the mechanism and say why the reaction works.

The most important chemistry of sulfonium salts is based on one or both of two attributes:

1. Sulfonium salts are electrophiles: nucleophilic substitution displaces a neutral sulfide leaving group
2. Sulfonium salts can be deprotonated to give sulfonium ylids

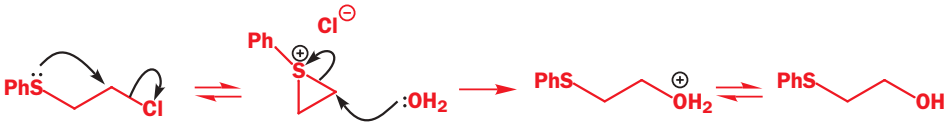
Sulfonium salts as electrophiles



mustard gas

During the First World War, mustard gas was developed as a chemical weapon—it causes the skin to blister and is an intense irritant of the respiratory tract. Its reactivity towards human tissue is related to the following observation and is gruesome testimony to the powerful electrophilic properties of sulfonium ions.

In both cases, intramolecular displacement of the chloride leaving group by the sulfur atom—or, as we should call it, **participation by sulfur** (see Chapter 37)—gives a three-membered cyclic sulfonium ion intermediate (an **episulfonium** or **thiiranium ion**). Nucleophilic attack on this electrophilic sulfonium ion, either by water or by the structural proteins of the skin, is very fast. Of course, mustard gas can react twice in this way. You will see several more examples of reactions in which a sulfonium ion intermediate acts as an electrophile in the next section.

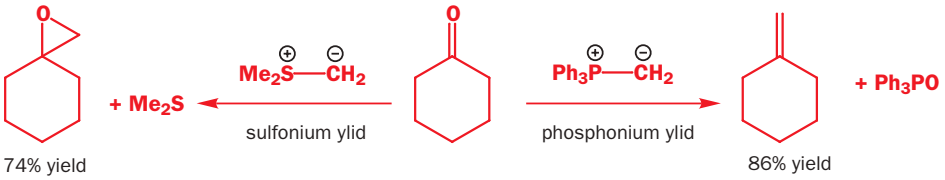


A reminder. An **ylid** is a species with positive and negative charges on adjacent atoms.

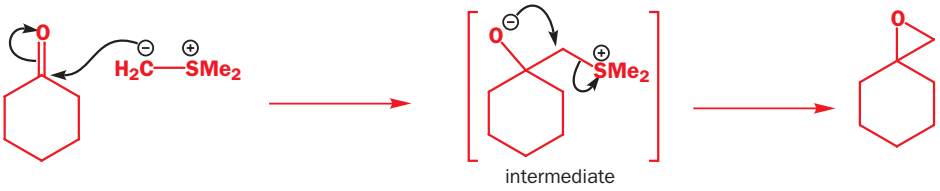
Sulfonium ylids

The positive charge carried by the sulfur atom means that the protons next to the sulfur atom in a sulfonium salt are significantly more acidic than those in a sulfide, and sulfonium salts can be deprotonated to give **sulfonium ylids**.

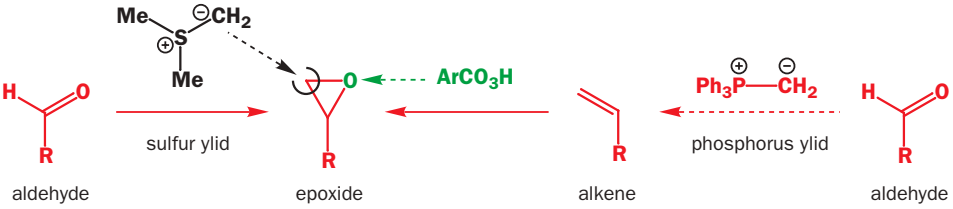
In Chapter 31 we discussed the Wittig reaction of phosphonium ylids with carbonyl compounds. Sulfonium ylids react with carbonyl compounds too, but in quite a different way—compare these two reactions.



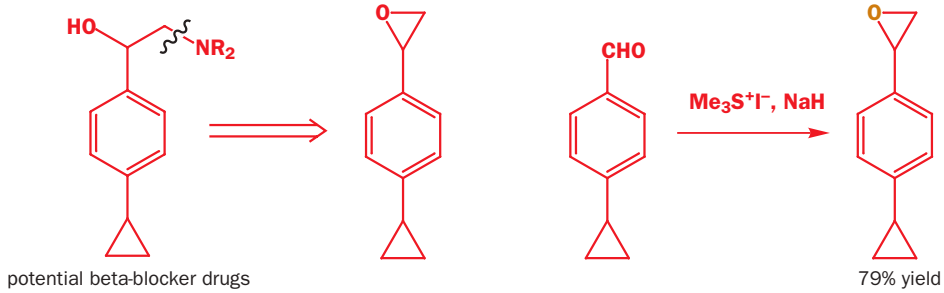
Phosphonium ylids give alkenes while sulfonium ylids give epoxides. Why should this be the case? The driving force in the Wittig reaction is formation of the strong P=O bond—that force is much less in the sulfur analogues (the P=O bond energy in Ph_3PO is 529 kJ mol^{-1}; in Ph_2SO the S=O bond energy is 367 kJ mol^{-1}). The first step is the same in both reactions: the carbanion of the ylid attacks the carbonyl group in a nucleophilic addition reaction. The intermediate in the Wittig reaction cyclizes to give a four-membered ring but this does not happen with the sulfur ylids. Instead, the intermediate decomposes by intramolecular nucleophilic substitution of Me_2S by the oxyanion.



We could compare sulfonium ylids with the carbenoids we discussed in Chapter 40—both are nucleophilic carbon atoms carrying a leaving group, and both form three-membered rings by insertion into π bonds. Sulfonium ylids are therefore useful for making epoxides from aldehydes or ketones; other ways you have met of making epoxides (Chapters 20 and 45) started with alkenes that might be made with phosphorus ylids.

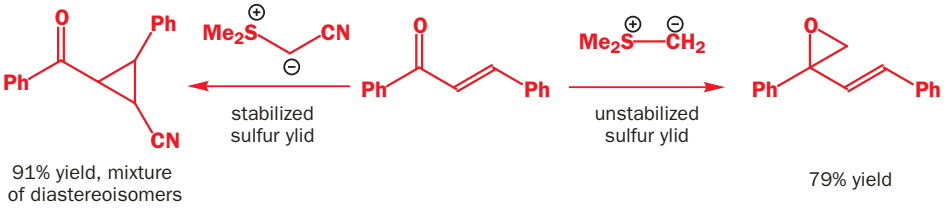


The simplest route to certain potential β-blocker drugs is from an epoxide, and the chemists working on their synthesis decided that, since 4-cyclopropylbenzaldehyde was more readily available than 4-cyclopropyl styrene, they would use the aldehyde as the starting material and make the epoxide in one step using a sulfonium ylid.



When we are talking about S ylids or P ylids, 'stabilized' refers to stabilization of the carbanion as explained in Chapter 31.

You will recall from Chapter 31 that we divided phosphorus ylids into two categories, 'stabilized' and 'unstabilized', in order to explain the stereochemistry of their alkene-forming reactions. Again, there is a similarity with sulfonium ylids: the same sort of division is needed—this time to explain the different regioselectivities displayed by different sulfonium ylids. Firstly, an example.



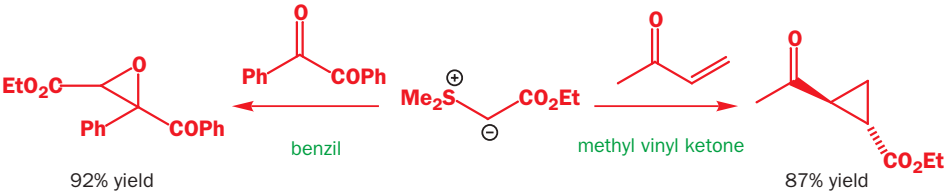
91% yield, mixture of diastereoisomers

79% yield

'Stabilized' sulfonium ylids

Changing from the simple sulfonium ylid to one bearing an anion-stabilizing substituent changes the regioselectivity of the reaction. 'Unstabilized' sulfonium ylids give epoxides from α,β-unsaturated carbonyl compounds while 'stabilized' ylids give cyclopropanes. In the absence of the double bond, both types of ylid give epoxides—the ester-stabilized ylid, for example, reacts with benzil to give an epoxide but with methyl vinyl ketone (but-3-en-2-one) to give a cyclopropane.

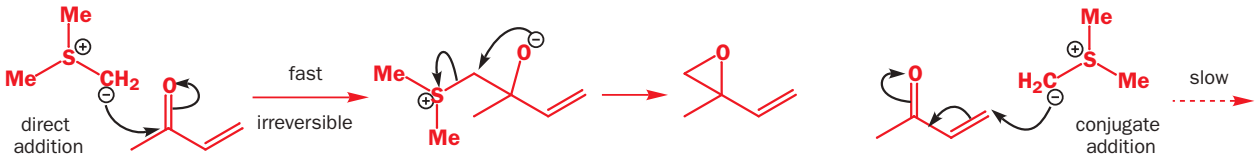
Compare this epoxidation with the Darzens reaction you met on p. 000.



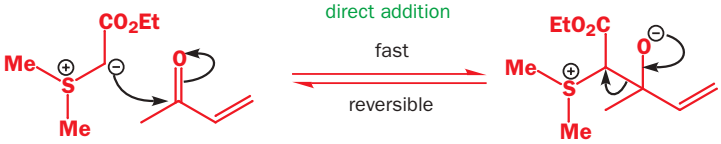
92% yield

87% yield

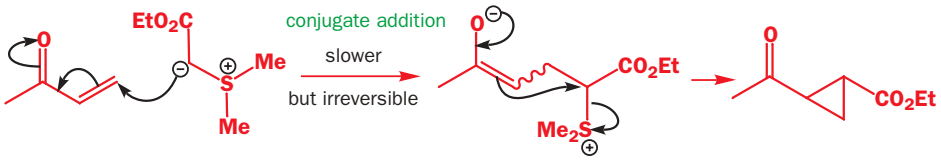
Why does the stabilized ylid prefer to react with the double bond? In order to understand this, let's consider first the reaction of a simple, unstabilized ylid with an unsaturated ketone. The enone has two electrophilic sites, but from Chapters 10 and 23, in which we discussed the regioselectivity of attack of nucleophiles on Michael acceptors like this, you would expect that direct 1,2-attack on the ketone is the faster reaction. This step is irreversible, and subsequent displacement of the sulfide leaving group by the alkoxide produces an epoxide. It's unimportant whether a cyclopropane product would have been more stable: the epoxide forms faster and is therefore the kinetic product.



With a stabilized ylid, direct addition to the carbonyl group is, in fact, probably still the faster reaction. But, in this case, the starting materials are sufficiently stable that the reaction is reversible, and the sulfonium ylid is re-expelled before the epoxide has a chance to form. Meanwhile, some ylid adds to the ketone in a 1,4 (Michael or conjugate) fashion. 1,4-Addition, although slower, is energetically more favourable because the new C–C bond is gained at the expense of a (relatively) weak C=C π bond rather than a (relatively) strong C=O π bond, and is therefore irreversible. Eventually, all the ylid ends up adding in a 1,4-fashion, generating an enolate as it does so, which cyclizes to give the cyclopropane, which is the thermodynamic product. This is another classic example of kinetic versus thermodynamic control, and you can add it to the mental list of examples you started when you first read Chapter 13.



continued opposite



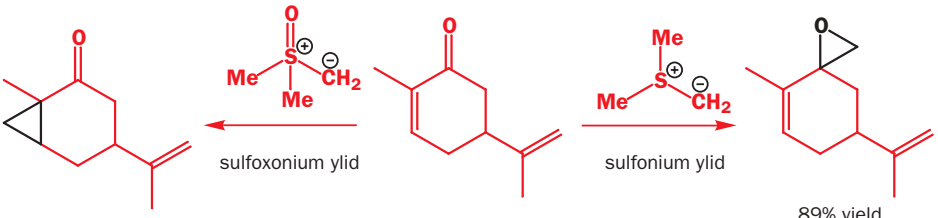
Sulfoxonium ylids

There is another, very important class of stabilized sulfur ylids that owe their stability not to an additional anion-stabilizing substituent but to a more anion-stabilizing sulfur group. These are the **sulfoxonium ylids**, made from dimethylsulfoxide by S_N2 substitution with an alkyl halide. Note that the sulfur atom is the nucleophile rather than the oxygen atom in spite of the charge distribution. The high-energy sulfur lone pair is better at S_N2 substitution at saturated carbon—a reaction that depends very little on charge attraction (Chapter 17).

dimethylsulfoxide (DMSO)

sulfoxonium ylid

Sulfoxonium ylids react with unsaturated carbonyl compounds in the same way as the stabilized ylids that you have met already do—they form cyclopropanes rather than epoxides. The example below shows one consequence of this reactivity pattern—by changing from a sulfonium to a sulfoxonium ylid, high yields of either epoxide or cyclopropane can be formed from an unsaturated carbonyl compound (this one is the terpene carvone).



81% yield

sulfoxonium ylid

carvone

sulfonium ylid

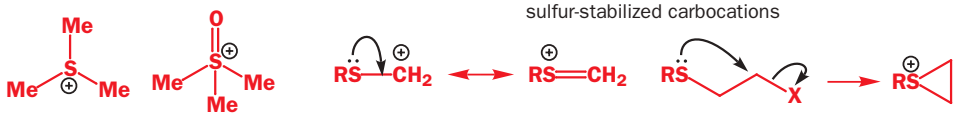
89% yield

■ The table on p. 000 introduced the idea that anion-stabilization is related to the number of oxygen atoms carried by the sulfur atom.

Sulfur-stabilized cations

We have mentioned cations in this chapter several times and now we will gather the various ideas together. Cations are stable on the sulfur atom itself, as you have just seen in sulfonium and sulfoxonium salts. They are stable on adjacent carbon atoms since the sulfur atom contributes a lone pair to form a C=S^+ π bond, and they are stable on the next carbon atom along the chain since sulfur contributes a lone pair to form a C–S^+ σ bond in a three-membered ring.

sulfur-stabilized carbocations



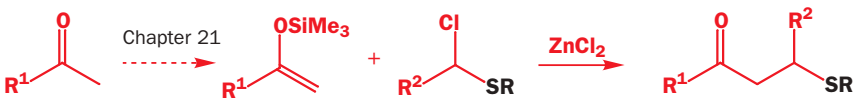
sulfonium ion

sulfoxonium ion

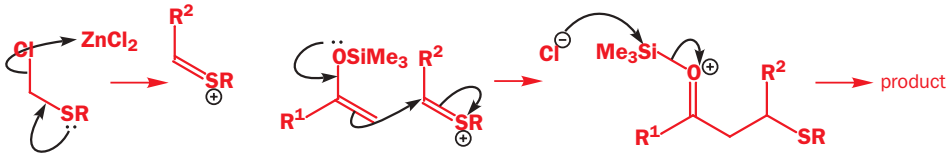
sulfur-stabilized α-cation

sulfur-stabilized β-cation

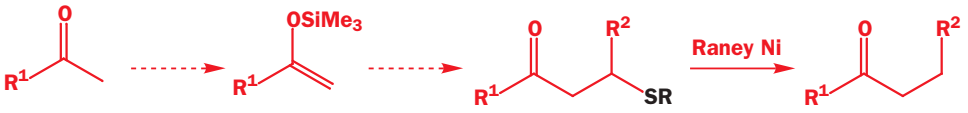
You may protest that these last two species are not *carbo*-cations at all but rather sulfonium ions, and you would be right. However, they can be used in place of carbocations as they are electrophilic at carbon so it is useful to think of them as modified carbocations as well as sulfonium ions. Sulfur-stabilized α-cations are easily made from α-chlorosulfides and are useful in alkylation of silyl enol ethers.



What is the point of this? Silyl enol ethers can be alkylated only by compounds that give carbocations in the presence of Lewis acids. The mechanism for the alkylation therefore involves the formation of a sulfur-stabilized cation.

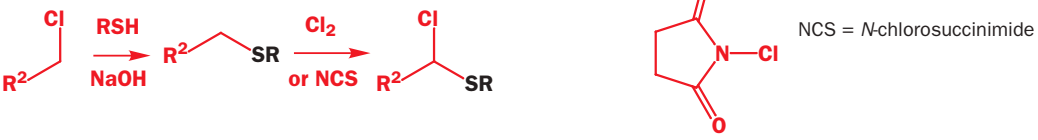


The sulfide (SR) can be removed from the product with Raney nickel to give a simple ketone. This ketone has apparently been made by the alkylation of a silyl enol ether with a primary alkyl group (R^2CH_2). This would be impossible without stabilization of the cation by the sulfur atom.



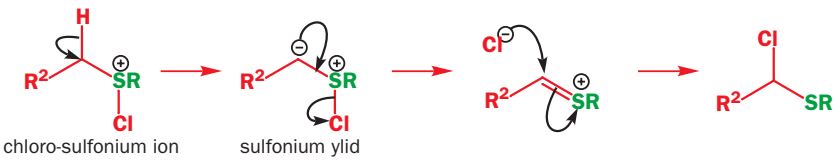
The Pummerer rearrangement

Though the stabilization of the cation by a sulfide is not as good as the stabilization by an ether (the $C{=}S^+$ bond is weaker than the $C{=}O^+$ bond), it is still good enough to make the reaction work and, of course, C–O bonds cannot be reduced by any simple reagent. One thing remains—how is the chlorosulfide made in the first place? Remarkably, it is made from the alkyl halide (R^2CH_2Cl) you would use for the (impossible) direct alkylation without sulfur.

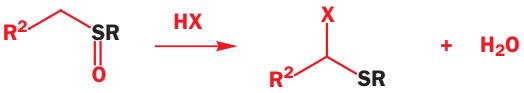


The first step is just the S_N2 displacement of Cl^- by RS^- that you have already seen. The second step actually involves chlorination at sulfur (you have also seen that sulfides are good soft nucleophiles for halogens) to form a sulfonium salt. Now a remarkable thing happens. The chlorine atom is transferred from the sulfur atom to the adjacent carbon atom by the **Pummerer rearrangement**.

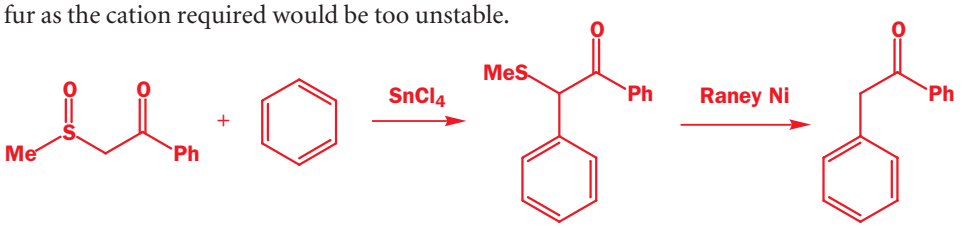
An ylid is first formed by loss of a proton—again, you have seen this—and then chloride is lost to form the same cation that we used in the alkylation reaction. In this step there is no nucleophile available except chloride ion so that adds to the carbon atom.



There are many variations on the Pummerer rearrangement but they all involve the same steps: a leaving group is lost from the sulfur atom of a sulfonium ylid to create a cationic intermediate that captures a nucleophile at the α carbon atom. Often the starting material is a sulfoxide.

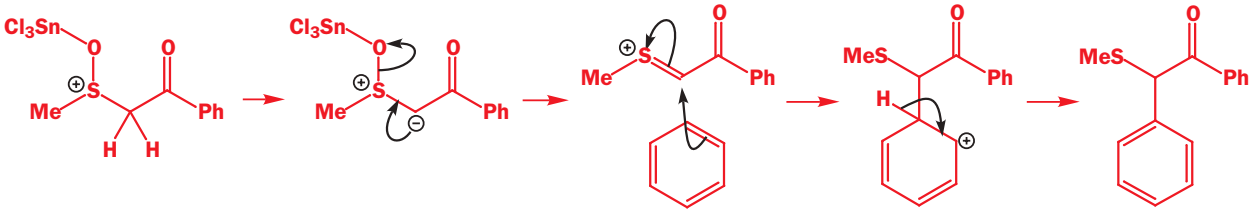


Treatment of a sulfoxide, particularly one with an anion-stabilizing substituent to help ylid formation, produces cations reactive enough to combine with nucleophiles of all sorts, even aromatic rings. The product is the result of electrophilic aromatic substitution (Chapter 22) and, after the sulfur has been removed with Raney nickel, is revealed as a ketone that could not be made without sulfur as the cation required would be too unstable.

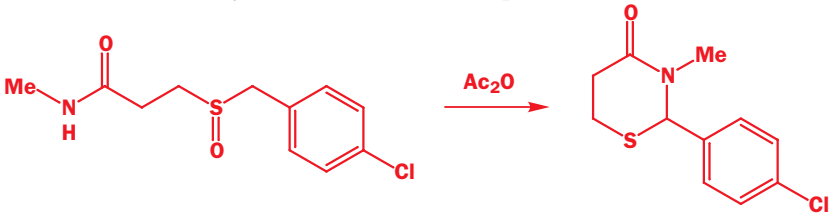


100% yield

A Lewis acid ($SnCl_4$) is used to remove the oxygen from the sulfoxide and the ketone assists ylid formation. The sulfur atom stabilizes the cation enough to counteract the destabilization by the ketone. The Lewis acid is necessary to make sure that no nucleophile competes with benzene.



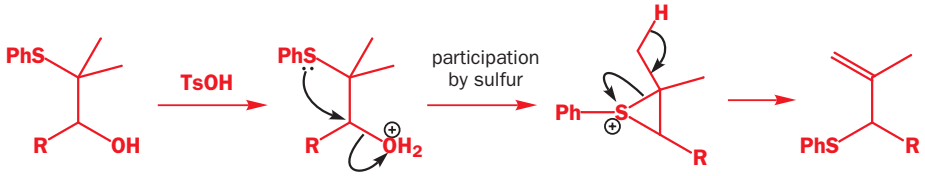
Most commonly of all, a sulfoxide is treated with acetic anhydride and the cation is captured by an internal nucleophile to form a new ring. Here the nitrogen atom of an amide is the nucleophile. The mechanism is very like that of the last example.



71% yield

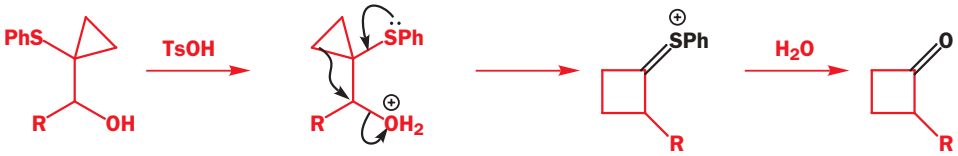
Sulfur-stabilized β-carbocations (three-membered rings)

Three-membered cyclic sulfonium ions, representing β carbocations, are often encountered in participation reactions. We have seen this already in the way mustard gas works, but almost any arrangement of a sulfide with a leaving group on the β carbon atom leads to participation and the formation of a three-membered ring. The product is formed by migration of the PhS group from one carbon atom to another (Chapter 37).



In this case, elimination of a proton from one of the methyl groups leads to an allylic sulfide—you have seen earlier in the chapter how these compounds, and the sulfoxides derived from them, can be used in synthesis. If we make a small change in the structure of the starting material—just joining up the two methyl groups into a cyclopropane—things change quite a bit. It becomes possible to make the starting material by a lithiation reaction because cyclopropyllithiums are significantly stabilized by the three-membered ring (Chapter 8) and the rearrangement goes with carbon rather than sulfur migration.

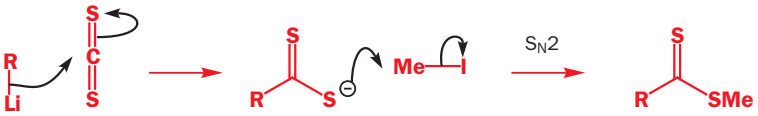
In the rearrangement, the alcohol is protonated as before but no sulfur participation occurs. Instead, a ring expansion, also assisted by sulfur, produces a four-membered ring and hydrolysis of the α cation (an intermediate you have seen several times) gives a cyclobutanone. The difference between participation through space and C=S$^+$ bond formation is not that great.



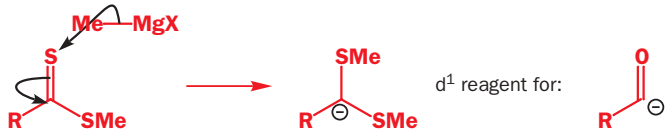
Thiocarbonyl compounds

Simple thioaldehydes and thioketones are too unstable to exist and attempts at their preparation lead to appalling smells (Chapter 1). The problem is the poor overlap between the 2sp^2 orbital on carbon and the 3sp^2 orbital on sulfur as well as the more or less equal electronegativities of the two elements. Stable thiocarbonyl compounds include dithioesters and thioamides where the extra conjugation of the oxygen or nitrogen atom helps to stabilize the weak C=S bond.

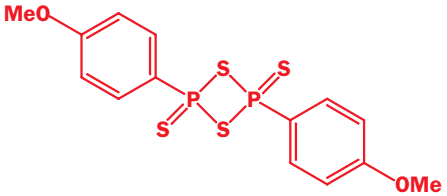
Dithioesters can be made by a method that would seem odd if you thought only of ordinary esters. Organolithium or Grignard reagents combine well with carbon disulfide (CS_2—the sulfur analogue of CO_2) to give the anion of a dithioacid. This is a much more nucleophilic species than an ordinary carboxylate anion and combines with alkyl halides to give dithioesters.



The reaction of dithioesters with Grignard reagents is even more remarkable. Because sulfur and carbon have about the same electronegativity, the Grignard reagent may add to either end of the π bond. If it adds to sulfur, the resulting anion is stabilized by two sulfur atoms, rather like the dithiane anions we have seen earlier in this chapter, and can be used as a d^1 reagent.

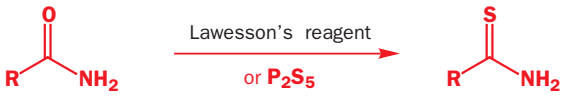


Thioamides are usually made by reaction of ordinary amides with P_2S_5 or **Lawesson's reagent**. Since C=S is so much less stable than C=O, there is a clear case to call in phosphorus to remove the oxygen. The situation is rather like that in the Wittig reaction: C=C is less stable than C=O, so phosphorus is called in to remove the oxygen because of the even greater stability of the P=O bond. Lawesson's reagent has P=S bonds and a slightly surprising structure.



Lawesson's reagent, or, if you prefer...
2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide

We can learn from this compound that sulfur has much less objection to four-membered rings than do oxygen or carbon. We have seen from the structure of sulfur itself (S_8) that it likes eight-membered rings too. Rings of almost any size are acceptable to sulfur as bond angles matter less to second-row elements that are not generally hybridized. Lawesson's reagent converts amides into thioamides and we have seen (Chapter 44) how these are used to make thiazoles.



Sulfoxides

The formation and reactions of sulfoxonium ylids demonstrate how sulfoxides occupy a useful and interesting part of the middle ground between sulfides and sulfones—they are weakly nucleophilic, like sulfides (and can be alkylated with methyl iodide to give sulfoxonium salts as we have just seen), but at the same time they stabilize anions almost as well as sulfones. However, sulfoxides are perhaps the most versatile of the three derivatives because of a good deal of chemistry that is unique to them. There are two reasons why this should be so.

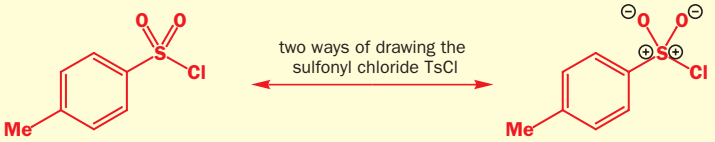
1. Sulfoxides have the potential to be chiral at sulfur
2. Sulfoxides undergo some interesting pericyclic reactions

We shall deal with each of these in turn.

Representing S=O compounds

Sulfoxides are sometimes drawn as S=O and sometimes as $S^+–O^-$. The second representation might remind you of the phosphorus ylids used in the Wittig reaction (Chapters 14 and 31), which can be drawn with a $P=CH_2$ double bond or as $P^+–CH_2^-$. All of these representations are correct—it is a matter of personal choice which you prefer.

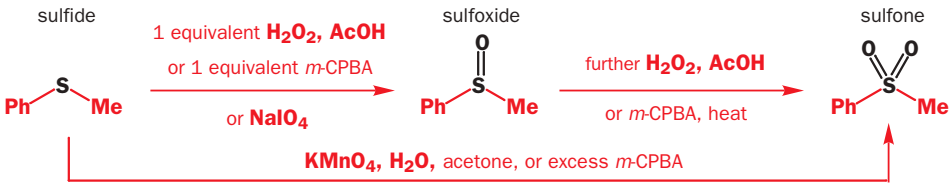
The double bonds are between 2p orbitals of O or C and 3d orbitals of S or P. But when we drew the structure of TsCl we always drew two S=O double bonds. You might think that an alternative structure with two S–O single bonds is not so good and almost nobody draws TsCl that way. Illogical but not unreasonable.



Sulfoxides are chiral

Providing the two groups attached to sulfur are different, a sulfoxide is chiral at the sulfur atom. There are two important ways of making sulfoxides as single enantiomers, both asymmetric versions of reactions otherwise used to make racemic sulfoxides: oxidation and nucleophilic substitution at sulfur.

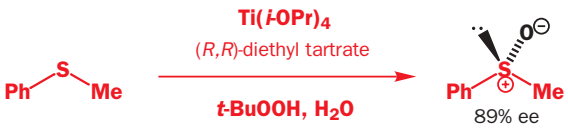
Sulfides are easy to oxidize and, depending on the type and quantity of oxidizing agent used, they can be cleanly oxidized either to sulfoxides or sulfones.



The oxidation of sulfides to sulfoxides can be made asymmetric by using one of the important reactions we introduced in the last chapter—the **Sharpless asymmetric epoxidation**. The French chemist Henri Kagan discovered in 1984 that, by treating a sulfide with the oxidant *t*-butyl hydroperoxide in the presence of Sharpless's chiral catalyst ($Ti(O^iPr)_3$ plus one enantiomer of diethyl tartrate), the oxygen atom could be directed to one of the sulfide's two enantiotopic lone pairs to give a sulfoxide in quite reasonable enantiomeric excess (ee).

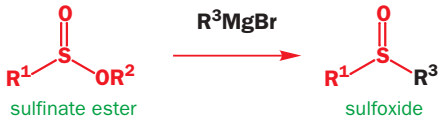
■ For a definition of 'enantiomeric excess', see Chapter 45.

▶ Here is an example where drawing a sulfoxide as $S^+–O^-$ is better.

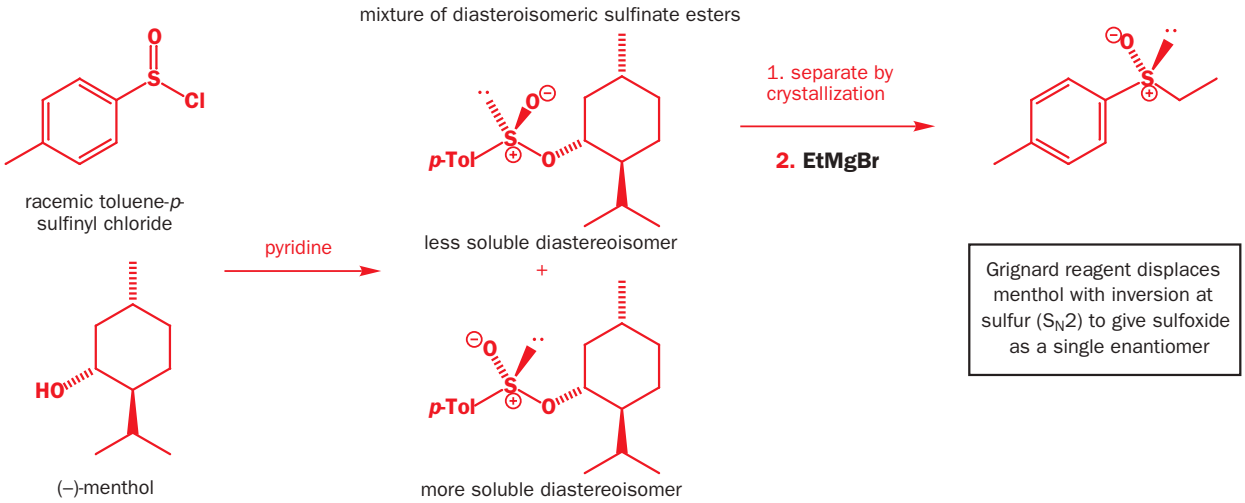


As yet, this asymmetric oxidation is successful only with simple aryl alkyl sulfoxides like this one, and the nucleophilic displacement method is much more widely used since it is more general and gives products of essentially 100% ee.

Sulfoxides can alternatively be made by displacement of RO^- from a **sulfinate ester** with a Grignard reagent.



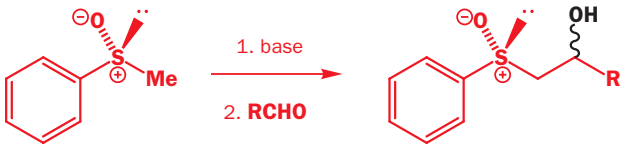
Sulfinate esters, like sulfoxides, are chiral at sulfur and, if the ester is formed from a chiral alcohol (menthol is best), they can be separated into two diastereoisomers by crystallization—this is really a resolution of the type you first met in Chapter 16. Attack by the Grignard reagent takes place with inversion of configuration at sulfur, giving a single enantiomer of the sulfoxide.



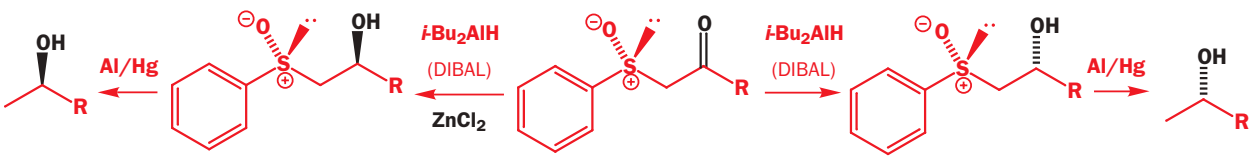
Grignard reagent displaces menthol with inversion at sulfur (S_N2) to give sulfoxide as a single enantiomer

Chiral sulfoxides in synthesis

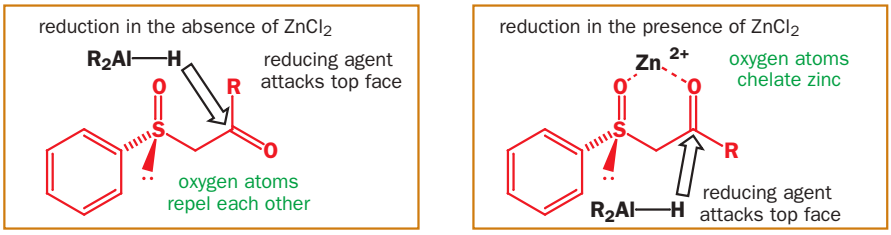
How can the chirality of sulfoxides be made useful? This area of research has received a lot of attention in the last 10–15 years, with many attempts to design reactions in which the chirality at sulfur is transferred to chirality at carbon. Unfortunately, one of the simplest reactions of sulfoxides, the addition of their anions to aldehydes, usually proceeds with no useful stereoselectivity at all.



Some more successful uses of sulfoxides to control new chiral centres at carbon have been developed in Strasbourg by Guy Solladié, and they involve stereoselective reduction of carbonyl groups directed by the sulfoxide's oxygen atom. For example, the synthesis below shows how chirality at sulfur can be transferred to chirality at carbon by using a reduction directed by the S–O bond. If this ketone is treated with the bulky reducing agent DIBAL (i-Bu_2AlH), one alcohol is formed, with less than 5% of its diastereoisomer. Remarkably, if $ZnCl_2$ is added to the mixture, the opposite diastereoisomer is obtained! Reduction of the products with aluminium amalgam removes the sulfoxide (we discussed this process earlier in the chapter) leaving behind enantiomerically enriched samples of the alcohol.

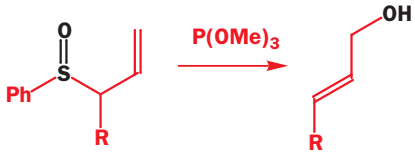


Solladié explained these results by suggesting that, in the absence of $ZnCl_2$, the sulfoxide adopts the conformation that places the two electronegative oxygen atoms as far apart as possible. DIBAL then attacks the less hindered face of the ketone, *syn* to the sulfoxide lone pair. With $ZnCl_2$, on the other hand, the sulfoxide's conformation is fixed by chelation to zinc: attack on the less hindered face of the ketone now gives the other diastereoisomer. Both compounds can be reduced with Al/Hg, which removes the sulfur group, to give opposite enantiomers of a chiral alcohol.

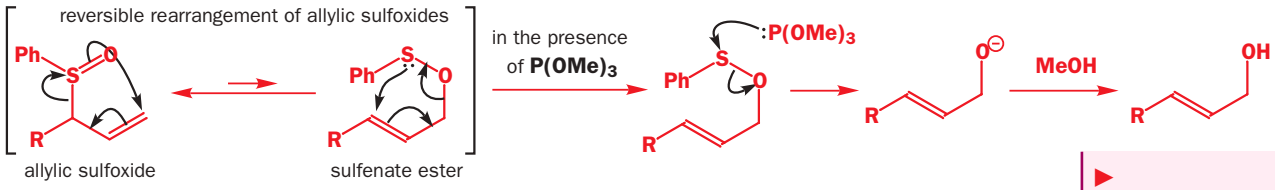


Allylic sulfoxides are not configurationally stable

Most sulfoxides will retain their configuration at sulfur up to temperatures of about 200 °C—indeed, it is estimated that the half-life for racemization of an enantiomerically pure sulfoxide is about 5000 years at room temperature. However, sulfoxides carrying allyl groups are much less stable—they racemize rapidly at about 50–70 °C. A clue to why this should be is provided by the reaction of an allylic sulfoxide with trimethyl phosphite, $P(OMe)_3$.



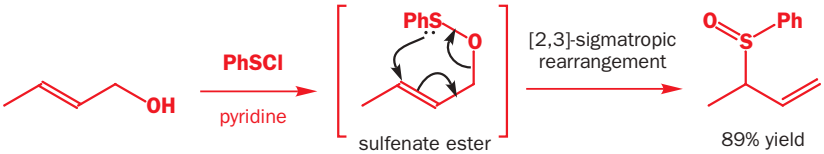
The product obtained is an allylic alcohol with the hydroxyl group at the other end of the allyl system from where the sulfur started—a rearrangement has taken place. We have observed the rearrangement in this case because the $P(OMe)_3$ has trapped the rearrangement product but, even without this reagent, allylic sulfoxides are continually and reversibly rearranging into sulfenate esters by the mechanism shown below.



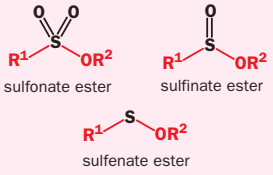
The rearrangement product, which is less stable than the sulfoxide and is therefore never observed directly, is a **sulfenate ester**. It has no chirality at sulfur so, when it rearranges back to the sulfoxide, it has no 'memory' of the configuration of the starting sulfoxide, and the sulfoxide becomes racemized.

Having read Chapter 36, you should be able to classify the pericyclic rearrangement reaction: it is a [2,3]-sigmatropic rearrangement (make sure you can see why before you read further) and as such is the first of the pericyclic rearrangements of sulfoxides that we shall talk about.

If our proposal that allylic sulfoxides rearrange reversibly to sulfenate esters is correct, then, if we make the sulfenate ester by another route, it too should rearrange to an allylic sulfoxide—and indeed it does. The sulfenate ester arising from reaction of allylic alcohols with PhSCl (phenylsulfenyl chloride) cannot be isolated: instead, the allylic sulfoxide is obtained, usually in very good yield, and this method is often used to make allylic sulfoxides.

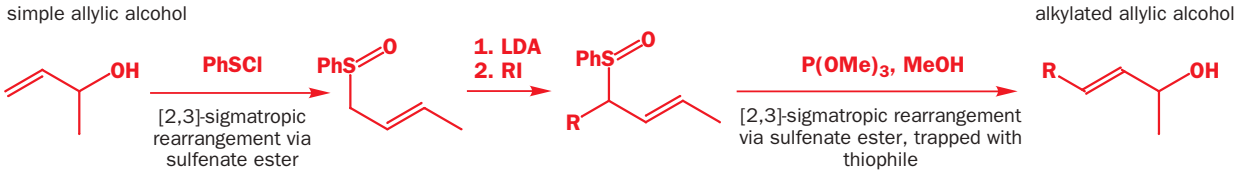


▶ You shouldn't at this stage try to learn all the names for every type of organosulfur compound—what matters is the structures. Here the names are all very similar and easily confused so, just for reference, here are the structures of a sulfonate ester (such as a tosylate or mesylate), a sulfinate ester, and a sulfenate ester.

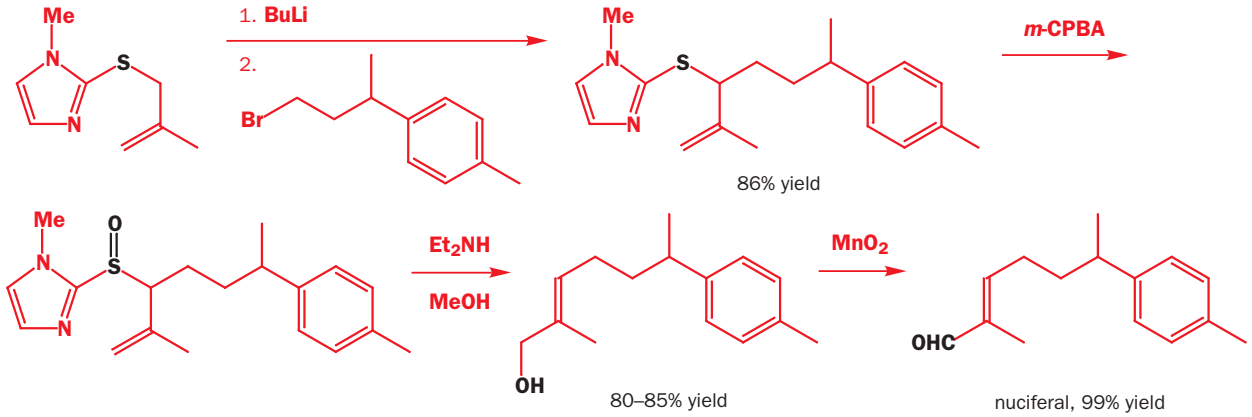


Uses for [2,3]-sigmatropic rearrangements of sulfoxides

Allylic sulfoxides exist in equilibrium with allyl sulfenate esters. The two interconvert by [2,3]-sigmatropic rearrangement, and the equilibrium lies over to the side of the sulfoxide. Allyl sulfenate esters are therefore impossible to isolate, but they can be trapped by adding a compound known as a **thiophile**—$P(OMe)_3$ was the example you just saw, but secondary amines like Et_2NH also work—which attacks the sulfur atom to give an allylic alcohol. This can be a very useful way of making allylic alcohols, particularly as the starting sulfoxides can be constructed by using sulfur's anion-stabilizing ability. What is more, the starting allylic sulfoxides can themselves be made from allylic alcohols using PhSCl—overall then we can use allylic sulfoxide to alkylate allylic alcohols! This scheme should make all this clearer.

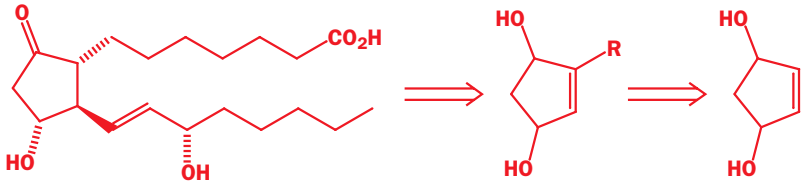


We can illustrate the synthesis of allylic alcohols from allylic sulfoxides with this synthesis of the natural product nuciferal. We mentioned this route on p. 000 because it makes use of a heterocyclic allyl sulfide to introduce an alkyl substituent regioselectively. The allyl sulfide is oxidized to the sulfoxide, which is converted to the rearranged allylic alcohol with diethylamine as the thiophile. Nuciferal is obtained by oxidizing the allylic alcohol to an aldehyde with manganese dioxide.



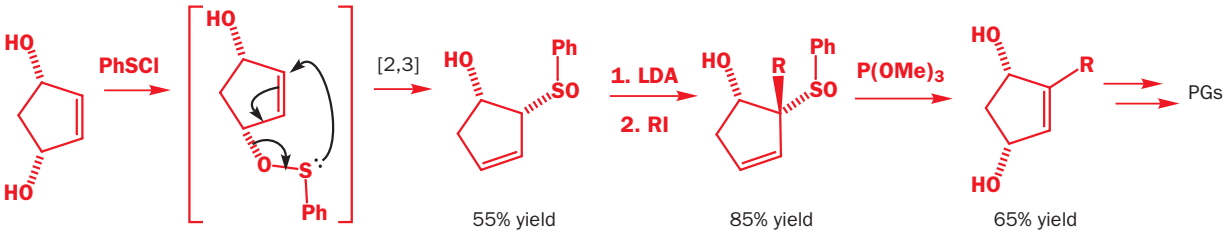
■ Prostaglandins are discussed more thoroughly in Chapter 51.

The next example makes more involved use of these [2,3]-sigmatropic allylic sulfoxide–allylic alcohol rearrangements. It comes from the work of Evans (he of the chiral auxiliary) who, in the early 1970s, first demonstrated the synthetic utility of allylic sulfoxides. Here he is using this chemistry to make precursors of the prostaglandins, a family of compounds that modulate hormone activity within the body.



PGE_1, a prostaglandin

Prostaglandins are trisubstituted cyclopentanones, and the aim was to synthesize them from available cyclopentenediol using allylic sulfoxide chemistry to introduce the long alkyl chain R group. Treating *syn*-cyclopentenediol with PhSCl gave the allylic sulfoxide (either hydroxyl can react but the product is the same). The sulfoxide was deprotonated and reacted with an alkyl halide, and then rearranged back to an allylic alcohol using $P(OMe)_3$ as the thiophile.

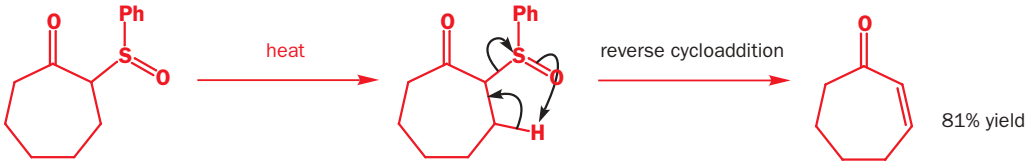


Stereochemistry of sulfoxide reactions

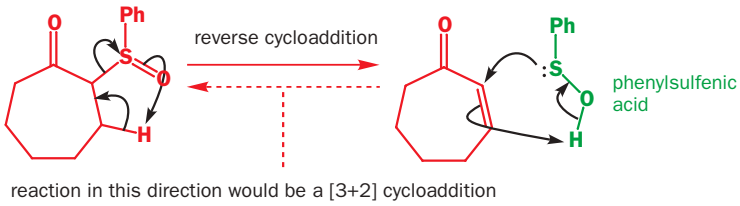
This sequence of reactions contains some interesting stereochemistry. The first rearrangement, from the cyclopentenediol to the allylic sulfoxide, is stereospecific—the *syn*-diol gives the *syn*-hydroxysulfoxide. This is typical of [2,3]-sigmatropic rearrangements—they are suprafacial with respect to the allylic component (see Chapter 36). In the next step, the R group is introduced *trans* to the hydroxyl group. This is a stereoselective reaction, not a stereospecific one, because the other diastereoisomer of the starting material, with the hydroxyl group and the sulfoxide *trans*, also gives the product with the R group *trans* to the hydroxyl group. Finally, there is another stereospecific (suprafacial) [2,3]-sigmatropic rearrangement, maintaining the *syn* relative stereochemistry of the hydroxysulfoxide in the stereochemistry of the diol product.

Sulfoxide elimination—oxidation to enones

Sulfoxides next to an electron-withdrawing or conjugating group are also unstable on heating, not because they racemize but because they decompose by an elimination process.

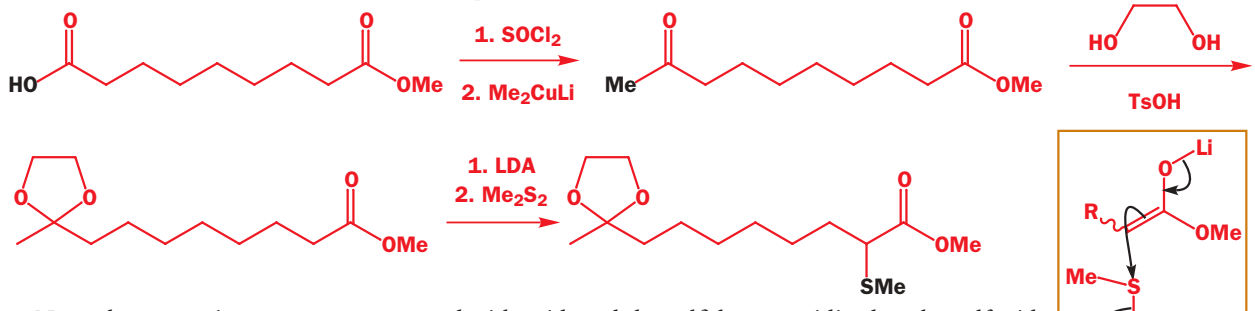


The rather unstable phenylsulfenic acid (PhS–OH) is eliminated and the reaction occurs partly because of the creation of conjugation and partly because PhSOH decomposes to volatile products. The elimination is a pericyclic reaction—it may not immediately be obvious what sort, but it is, in fact, a reverse cycloaddition. This is clearest if we draw the mechanism of the reverse reaction.

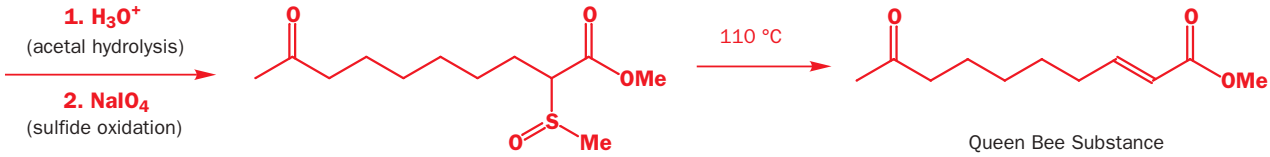


This reaction provides a useful way of introducing a double bond next to a carbonyl group. Here it is in a synthesis by Barry Trost of the Queen Bee Substance (the compound fed by the workers to those bee larvae destined to become queens). The compound is also a pheromone of the termite and is used to trap these destructive pests. Trost started with the monoester of a dicarboxylic acid, which he converted to a methyl ketone by reacting the acyl chloride with a cuprate. The ketone was then protected as a dioxolane derivative to prevent it enolizing, and the sulfur was introduced by reacting the enolate of the ester with the sulfur electrophile MeSSMe.

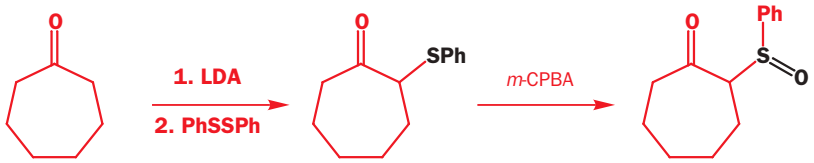
■ In Chapter 9 we discussed ways of making ketones by nucleophilic attack on carboxylic acid derivatives.



Next, the protecting group was removed with acid, and the sulfide was oxidized to the sulfoxide with sodium periodate ($NaIO_4$) ready for elimination. Heating to 110 °C then gave the Queen Bee Substance in 86% yield.

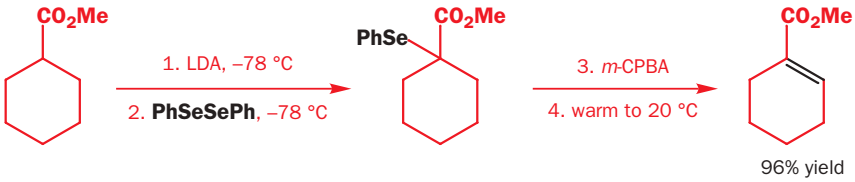


Presumably, the methyl sulfoxide was chosen here because it worked better—it is more usual to use a phenyl sulfoxide, and PhS groups can be introduced in the same way (by reacting enolates with PhSSPh or PhSCl). The cycloheptanone derivative used in our first elimination example was made from cycloheptanone in this way.



▶ Sulfur and selenium have many properties in common, and much sulfur chemistry is mirrored by selenium chemistry. In general, organoselenium compounds tend to be less stable and more reactive than organosulfur ones because the C–Se bond is even weaker than a C–S bond. They also have even fouler odours.

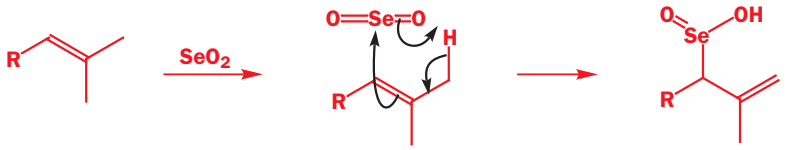
This elimination takes place more easily still when sulfur is replaced by a selenium—PhSe groups can be introduced by the same method, and oxidized to selenoxides with *m*-CPBA at low temperature. The selenoxides are rarely isolated, because the elimination takes place rapidly at room temperature.



Other oxidations with sulfur and selenium

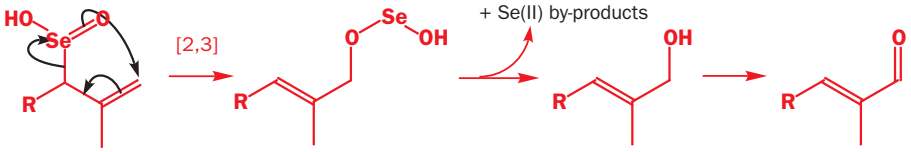
Selenium dioxide and allylic oxidation

Having introduced selenium, we should at this point mention an important reaction that is peculiar to selenium but that is closely related to these pericyclic reactions. Selenium dioxide will react with alkenes in a [4 + 2] cycloaddition reminiscent of the ene reaction.



▶ In a very few special cases, the seleninic acid intermediate has been isolated.

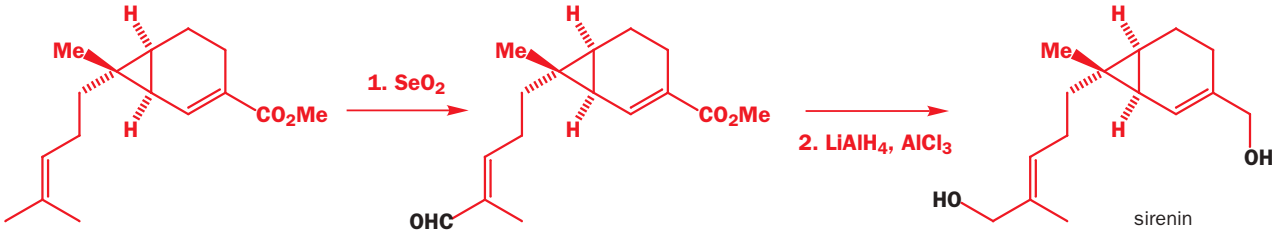
The initial product is an allylic seleninic acid—and just like an allylic sulfoxide (but more so because the C–Se bond is even weaker) it undergoes allylic rearrangement to give an unstable compound that rapidly decomposes to an allylic alcohol. In some cases, particularly this most useful oxidation of methyl groups, the oxidation continues to give an aldehyde or ketone.



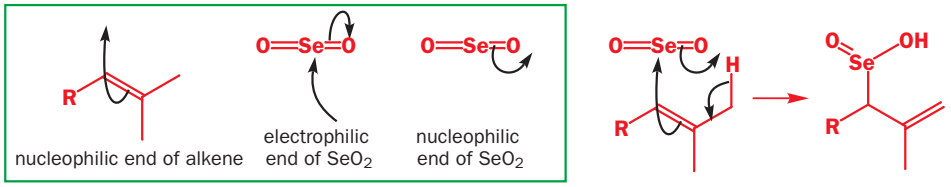
Overall, CH_3 has been replaced by CH_2OH or CH=O in an allylic position, a transformation similar to the NBS allylic bromination reaction that you met in Chapter 39, but with a very different mechanism. The by-product of the oxidation is a selenium(II) compound, and it can be more practical to carry out the reaction with only a catalytic amount of SeO_2, with a further oxidizing agent,

t-butyl hydroperoxide, to reoxidize the Se(II) after each cycle of the reaction. This eliminates the need to get rid of large amounts of selenium-containing products, which are toxic and usually smelly.

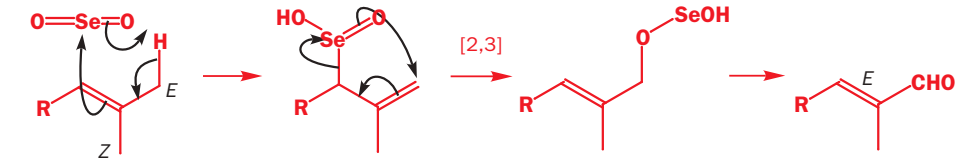
In Chapter 40 we left the synthesis of sirenin at a tantalizing stage. A carbene insertion into a double bond had formed a three-membered ring and the final stage was the oxidation of a terminal methyl group. This is how it was done.



There is some interesting selectivity in this sequence. Only one of the three groups next to the alkene is oxidized and only one (*E*-) isomer of the enal is formed. No position next to the unsaturated ester is oxidized. All these decisions are taken in the initial cycloaddition step. The most nucleophilic double bond uses its more nucleophilic end to attack SeO_2 at selenium. The cycloaddition uses the HOMO (π) of the alkene to attack the LUMO (π^* of Se=O). Meanwhile the HOMO (π) of Se=O attacks the LUMO (C–H σ^*) of the allylic system.



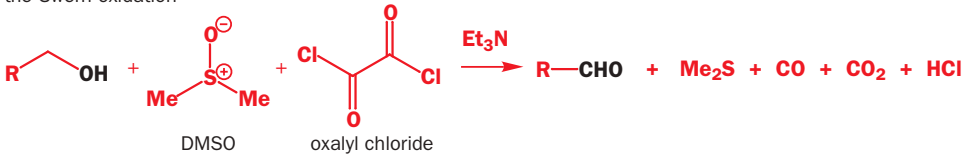
The stereoselectivity also appears to be determined in this step and it is reasonable to assume that the methyl group *trans* to the main chain will react rather than the other for simple steric reasons. Though this is true, the stereochemistry actually disappears in the intermediate and is finally fixed only in the [2,3]-sigmatropic rearrangement step. Both [2,3]- and [3,3]-sigmatropic rearrangements are usually *E*-selective for reasons discussed in Chapter 36.



The Swern oxidation

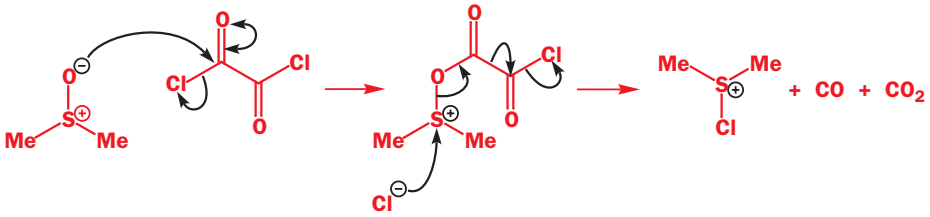
In Chapter 24 we mentioned the Swern oxidation briefly as an excellent method of converting alcohols to aldehydes. We said there that we would discuss this interesting reaction later and now is the time. The mechanism is related to the reactions that we have been discussing and it is relevant that the Swern oxidation is particularly effective at forming enals from allylic alcohols.

the Swern oxidation

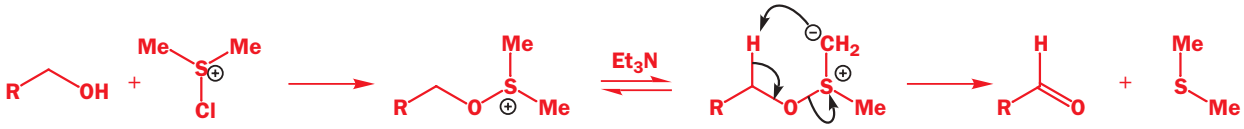


In the first step, DMSO reacts with oxalyl chloride to give an electrophilic sulfur compound. You should not be surprised that it is the charged oxygen atom that attacks the carbonyl group rather than the soft sulfur atom. Chloride is released in this acylation and it attacks the positively charge

sulfur atom expelling a remarkable leaving group, which fragments into three pieces: CO_2, CO, and a chloride ion. Entropy favours this reaction.



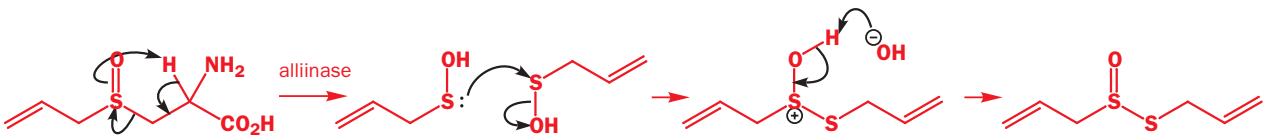
The alcohol has been a spectator of these events so far but the chlorosulfonium ion now formed can react with it to give a new sulfonium salt. This is the sole purpose of all the reactions as this new sulfonium salt is stable enough to survive and to be deprotonated by the base (Et_3N). You will recognize the final step both as the redox step and as a close relative to events in the preceding sections.



To conclude: the sulfur chemistry of onions and garlic

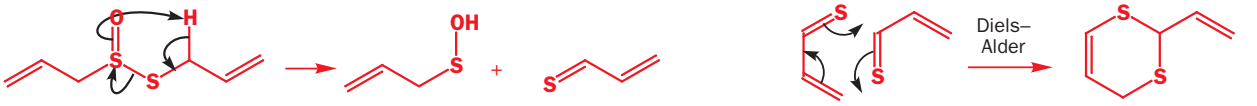
Traditional medicine suggests that onions and garlic are 'good for you' and modern chemistry has revealed some of the reasons. These bulbs of the genus *Allium* exhibit some remarkable sulfur chemistry and we will end this chapter with a few examples. Both onions and garlic are almost odourless when whole but develop powerful smells and, in the case of onions, tear gas properties when they are cut. These all result from the action of alliinase enzymes released by cell damage on unsaturated sulfoxides in the bulb.

In garlic, a simple sulfoxide elimination creates an unstable sulfenic acid. When we looked at sulfoxide eliminations before, we ignored the fate of the unstable sulfenic acid, but here it is important. It dimerizes with the formation of an S–S bond and the breaking of a weaker S–O bond.



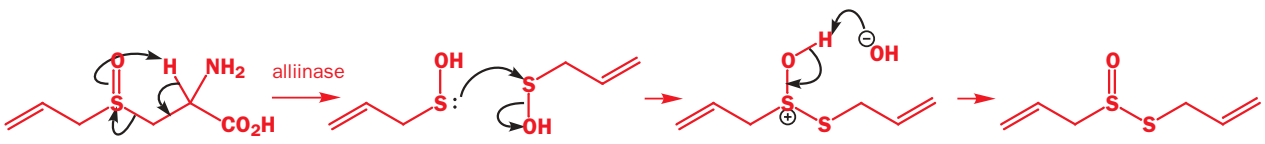
allylic sulfoxide in raw garlic — unstable sulfenic acid — thiosulfinate ester

Another simple elimination reaction on the thiosulfinate ester makes another molecule of the sulfenic acid and a highly unstable unsaturated thioaldehyde, which promptly dimerizes to give a thioacetal found in garlic as a potent platelet aggregation inhibitor.



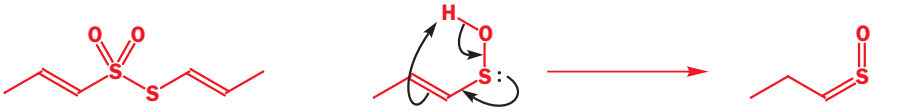
thiosulfinate ester — sulfenic acid — unstable thioaldehyde — platelet aggregation inhibitor

In onions, things start much the same way but the initial amino acid is not quite the same. The skeleton is the same as that of the garlic compound but the double bond is conjugated with the sulfoxide. Elimination and dimerization of the sulfenic acid produce an isomeric thiosulfinate.



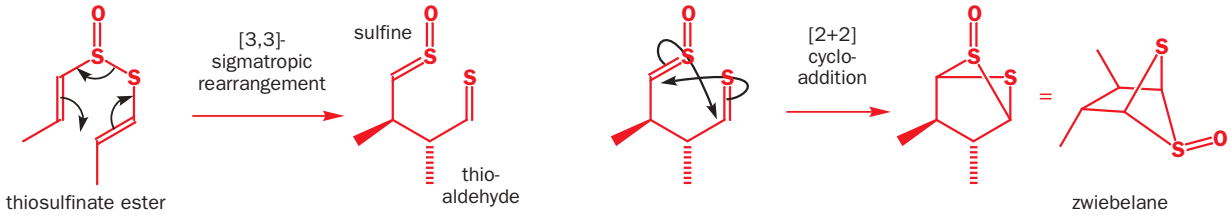
allylic sulfoxide in raw garlic — unstable sulfenic acid — thiosulfinate ester

Oxidation of the thiosulfinate ester up to the sulfonate level gives the compound responsible for the smell of raw onions, while a hydrogen shift on the conjugated sulfenic acid (not possible with the garlic compound) gives a sulfine, the sulfur analogue of a ketene. The compound has the *Z* configuration expected from the mechanism and is the lachrymator that makes you cry when you cut into a raw onion.



▶ There is still one lone pair on the sulfur atom of a sulfine so the sulfur is trigonal and not linear, rather like the nitrogen in an oxime.

Even more remarkable is the formation of the 'zwiebelanes', other compounds with potential as drugs for heart disease. They are formed in onions from the conjugated thiosulfinate ester by a [3,3]-sigmatropic rearrangement that gives a compound containing a sulfine and a thioaldehyde. We said that sulfines are the sulfur equivalents of ketenes, so you might expect them to do [2 + 2] cycloadditions (Chapter 35) but you might not expect the thioaldehyde to be the other partner. It is, and the result is a cage compound with one sulfide and one sulfoxide joined in a four-membered ring.

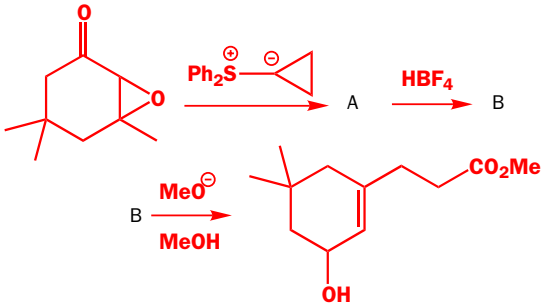


Look at onions with respect! They are not only the cornerstone of tasty cooking but are able to do amazing pericyclic reactions as soon as you cut them open. You can read more about the *Allium* family in Eric Block's review in *Angewandte Chemie* (International Edition in English), 1992, Volume 31, p. 1135.

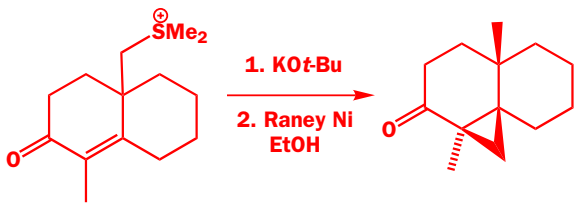
Though you have only seen a couple of examples of the latter, it is clear that organosulfur and organoselenium chemistry are closely related. In the next chapter we will look at the quite different type of chemistry exhibited by organic compounds containing three other heteroatoms—silicon, tin, and boron.

Problems

1. Suggest structures for intermediates A and B and mechanisms for the reactions.



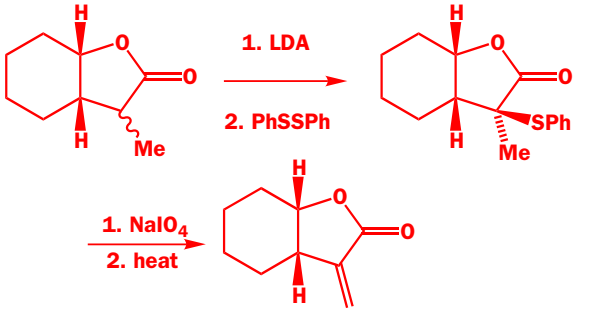
2. Suggest a mechanism for this reaction, commenting on the selectivity and the stereochemistry.



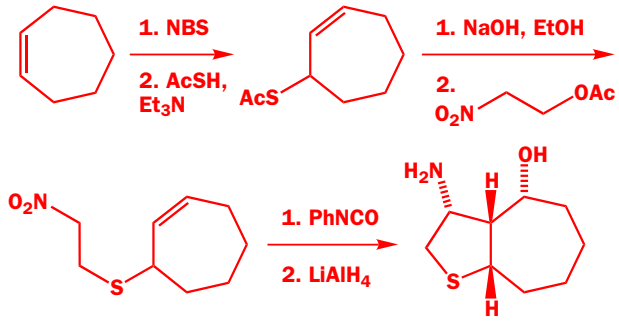
3. The product X of the following reaction has δ_H 1.28 p.p.m. (6H, s), 1.63 p.p.m. (3H, d, *J* 4.5 Hz), 2.45 p.p.m. (6H, s), 4.22 p.p.m. (1H, s), 5.41 p.p.m. (1H, d, *J* 15 Hz), and 5.63 p.p.m. (1H, dq, *J* 15, 4.5 Hz). Suggest a structure for X and a mechanism for its formation.

4. The thermal elimination of sulfoxides (example below) is a first-order reaction with almost no rate dependence on substituent at sulfur (Ar) and a modest negative entropy of activation. It is accelerated if R is a carbonyl group (that is, R = COR′). The reaction is (slightly) faster in less polar solvents. Explain.

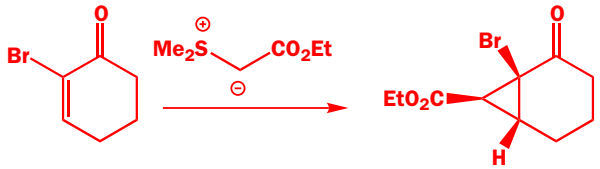
Explain the stereochemistry of the first reaction in the following scheme and the position of the double bond in the final product.



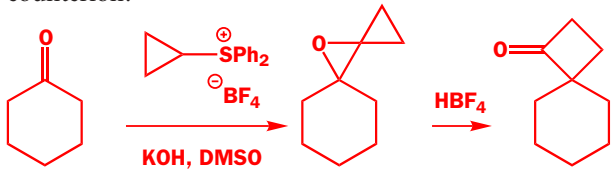
5. Revision content. Explain the reactions and the stereochemistry in these first steps in a synthesis of the B vitamin biotin.



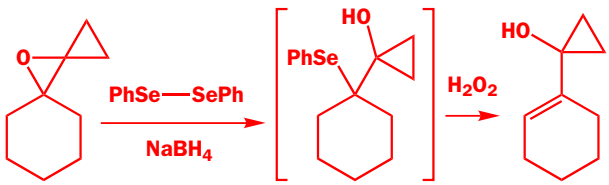
6. Explain the regio- and stereoselectivity of this reaction.



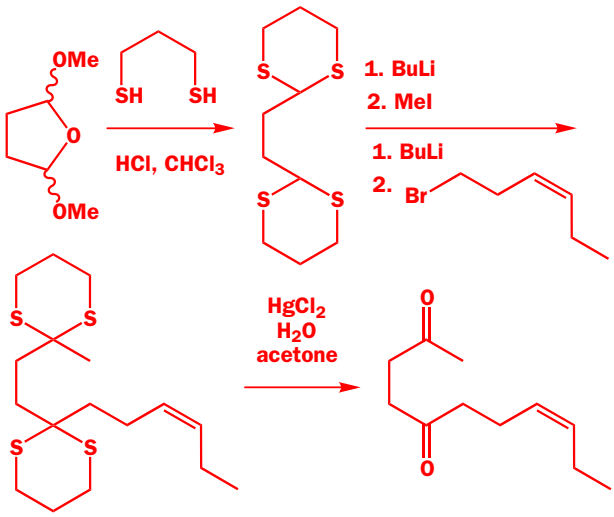
7. Draw mechanisms for these reactions of a sulfonium ylid and the rearrangement of the first product. Why is BF_4^- chosen as the counterion?



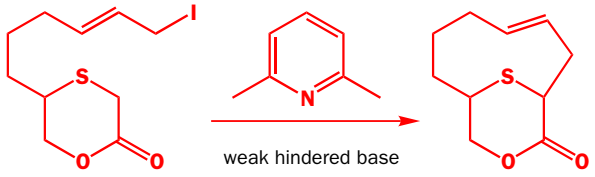
The intermediate may alternatively be reacted with a selenium compound in this sequence of reactions. Explain what is happening, commenting on the regioselectivity. Why is the intermediate in square brackets not usually isolated?



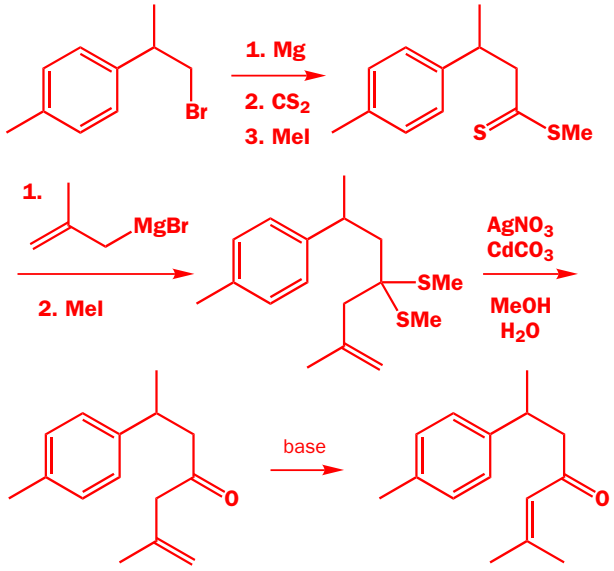
8. Give mechanisms for these reactions, explaining the role of sulfur.



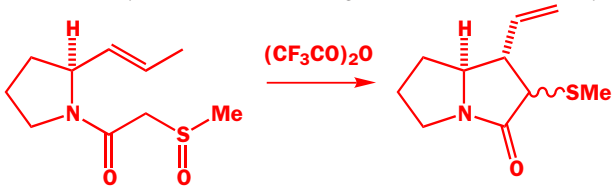
9. Suggest a mechanism for this formation of a nine-membered ring. Warning! The weak hindered base is not strong enough to form an enolate from the lactone.



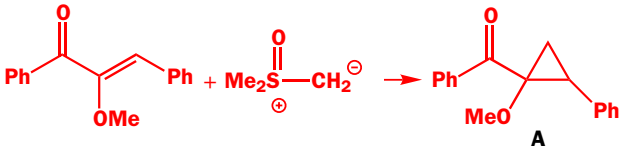
10. Comment on the role of sulfur in the steps in this synthesis of the turmeric flavour compound Ar-turmerone.



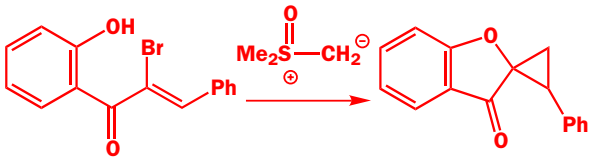
11. Explain how the presence of the sulfur-containing group allows this cyclization to occur regio- and stereoselectively.



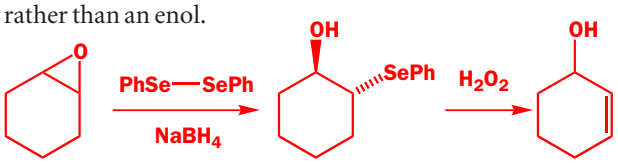
12. Problem 9 in Chapter 32 asked you to interpret the NMR spectrum of a cyclopropane (A). This compound was formed using a sulfur ylid. What is the mechanism of the reaction?



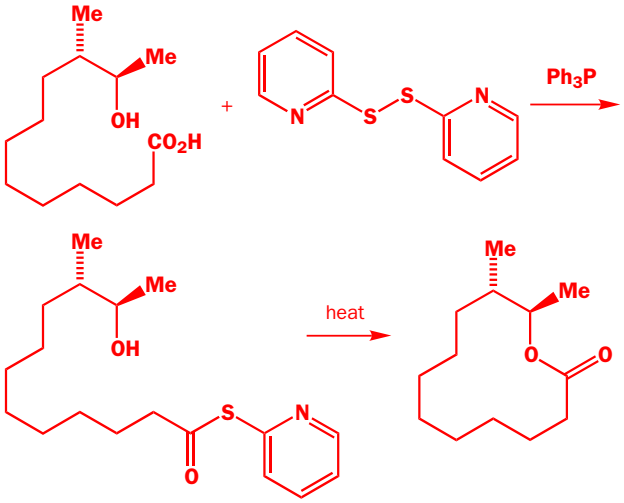
Attempts to repeat this synthesis on the bromo compound below led to a different product. What is different this time?



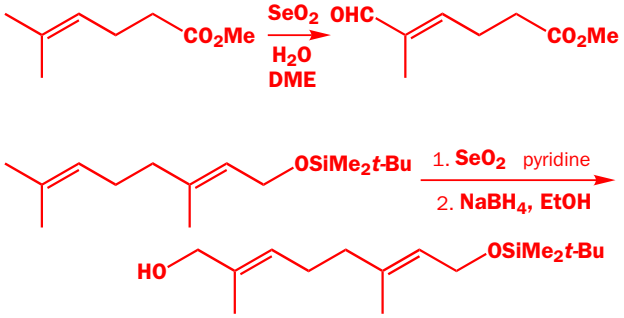
13. Epoxides may be transformed into allylic alcohols by the sequence shown here. Give mechanisms for the reactions and explain why the elimination of the selenium gives an allylic alcohol rather than an enol.



14. In a process resembling the Mitsunobu reaction (Chapter 17), alcohols and acids can be coupled to give esters, even macrocyclic lactones as shown below. In contrast to the Mitsunobu reaction, the reaction leads to retention of stereochemistry at the alcohol. Propose a mechanism that explains the stereochemistry. Why is sulfur necessary here?



15. Suggest mechanisms for these reactions, explaining any selectivity.



Organo-main-group chemistry 2: boron, silicon and tin

47

Connections

Building on:

- Conjugate addition ch10 & ch23
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- Oxidation, reduction, and protection ch24
- Aldol reactions ch27
- Controlling double bond geometry ch31
- Rearrangements ch36–ch37
- Radicals ch39
- Asymmetric synthesis ch45
- Sulfur chemistry ch46

Arriving at:

- Main group elements in organic chemistry
- Boron is electrophilic because of a vacant orbital
- Hydroboration adds boron selectively
- Oxidation removes boron selectively
- Boron chemistry uses rearrangements
- Allyl B, Si, and Sn compounds are useful in synthesis
- Organo-B, -Si, and -Sn compounds can be used in asymmetric synthesis
- Silicon is more electrophilic than carbon
- Silicon stabilizes β carbocations
- Organo-tin compounds are like Si compounds but more reactive
- Tin is easily exchanged for lithium

Looking forward to:

- Organometallic chemistry ch48
- Polymerization ch52

Organic chemists make extensive use of the periodic table

Although typical organic molecules, such as those of which all living things are composed, are constructed from only a few elements (usually C, H, O, N, S, and P and, on occasion, Cl, Br, I, and a few more), there are very many other elements that can be used as the basis for reagents, catalysts, and as components of synthetic intermediates. The metals will be discussed in the next chapter (48) but many main group (p block) elements are also important. These nonmetals bond covalently to carbon and some of their compounds are important in their own right.

More commonly, elements such as Si, P, and S are used in reagents to carry out some transformation but are not required in the final molecule and so must be removed at a later stage in the synthesis. The fact that organic chemists are prepared to tolerate this additional step demonstrates the importance of these reactions. The Julia olefination is an obvious example. The difficult conversion of aldehydes and ketones into alkenes is important enough to make it worthwhile adding a sulfur atom to the starting material and then removing it at the end of the reaction. So many elements are used like this that the list of nonmetals that are *not* used frequently in organic synthesis would be much shorter than the list of those that *are* useful.

In the previous chapter we described the special chemistry of sulfur, and you have previously met that of phosphorus. These two elements may be thought of as analogues of oxygen and nitrogen but many reactions are possible with S and P that are quite impossible with O and N. This chapter will concentrate on the organic chemistry of three other main group elements: boron, which is unusual in this context because it is a first row element, and silicon and tin, which are in the same group as

■ At the time of writing only Be, Ga, As, Sb, and Bi among the non-radioactive p-block elements are not used extensively and some would argue about As.

■ The organic chemistry of phosphorus is scattered about the book with important reactions in Chapters 14 and 31 (the Wittig reaction), 17 (various nucleophilic substitutions), 23 (conjugate addition of phosphines), and 41 (mechanisms involving phosphorus). In Chapter 48 you will see how important phosphorus compounds are as ligands for transition metals.

carbon in the periodic table but in the second and fourth rows. Here they are surrounded by other familiar elements.

Li	Be	**B**	C	N	O	F	Ne
Na	Mg	Al	**Si**	**P**	**S**	Cl	Ar
			Ge		**Se**		
			Sn				

Boron

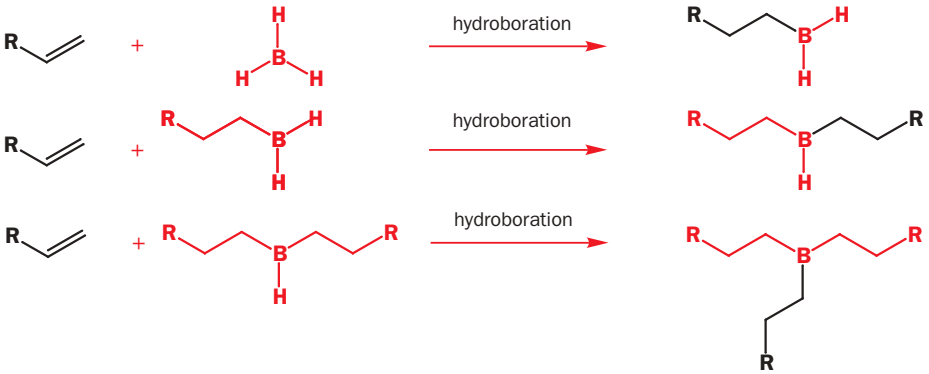
Borane has a vacant p orbital

You have already met boron in useful reagents such as sodium borohydride $NaBH_4$ and borane BH_3 (more correctly, B_2H_6). Both display the crucial feature of boron chemistry, which results directly from its position in group IIIB or 13 of the periodic table. Boron has only three electrons in the 2p shell and so typically forms three conventional two-centre two-electron bonds with other atoms in a planar structure leaving a vacant 2p orbital. Borane exists as a mixture of B_2H_6—a dimer with hydrogen bridges—and the monomer BH_3. Since most reactions occur with BH_3 and the equilibrium is fast we will not refer to this again.

The vacant orbital is able to accept a lone pair of electrons from a Lewis base to give a neutral species or can combine with a nucleophile to form a negatively charged tetrahedral anion. The reducing agent borane–dimethyl sulfide is an example of the Lewis acid behaviour while the borohydride anion would be the result of the imaginary reaction of borane with a nucleophile hydride. The vacant orbital makes borane a target for nucleophiles.

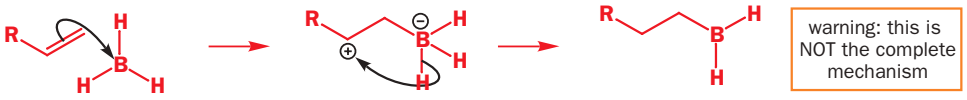
Hydroboration—the addition of boron hydrides to alkenes and alkynes

One of the simplest classes of nucleophiles that attacks borane is that of alkenes. The result, described as **hydroboration**, is an overall addition of borane across the double bond. Unlike most electrophilic additions to alkenes that occur in a stepwise manner via charged intermediates (Chapter 20), this addition is concerted so that both new bonds are formed more or less at the same time. The result is a new borane in which one of the hydrogen atoms has been replaced by an alkane. This monoalkyl borane (RBH_2) is now able to undergo addition with another molecule of the alkene to produce a dialkyl borane (R_2BH) which in turn undergoes further reaction to produce a trialkyl borane (R_3B). All these boranes have a vacant p orbital and are flat so that repeated attack to produce the trialkyl borane is easy and normal if an excess of alkene is present.

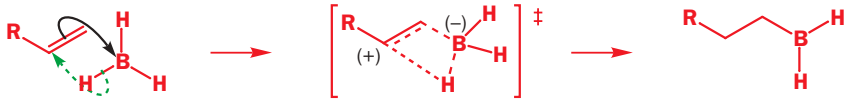


Hydroboration is regioselective

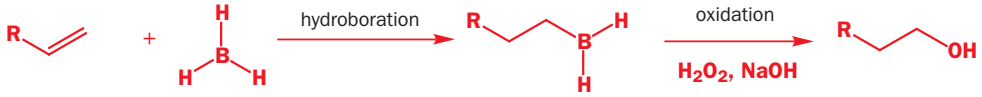
You will notice that the boron atom always adds to the *end* of the alkene. This is just as well; otherwise, three sequential additions would give rise to a complex mixture of products. The boron always becomes attached to the carbon of the double bond that is less substituted. This is what we should expect if the filled π orbital of the alkene adds to the empty orbital of the borane to give the more stable cationic intermediate.



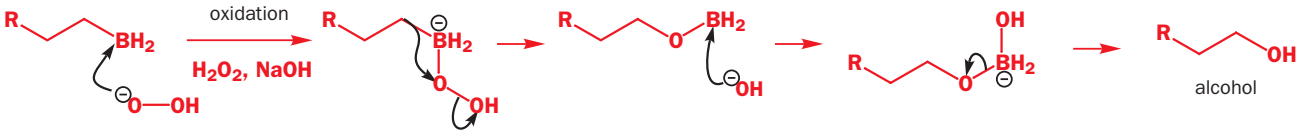
We know that this is not the whole story because of the stereochemistry. Hydroboration is a *syn* addition across the alkene. As the addition of the empty p orbital to the less substituted end of the alkene gets under way, a hydrogen atom from the boron adds, with its pair of electrons, to the carbon atom, which is becoming positively charged. The two steps shown above are concerted, but formation of the C–B bond goes ahead of formation of the C–H bond so that boron and carbon are partially charged in the four-centred transition state.



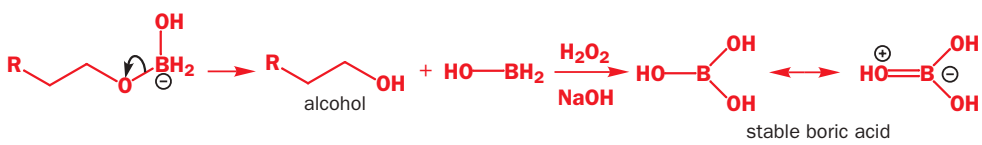
It is, of course, impossible to tell in this case whether the addition is *syn* or *anti* and in any case the alkyl borane products are rather unstable. Although organoboranes can be stored, and some are available commercially, air must be rigorously excluded as they burst into a spectacular green flame in air. A more controlled oxidation is required to remove the boron and reveal the useful organic fragment. The simplest is alkaline hydrogen peroxide, which replaces the carbon–boron bond with a carbon–oxygen bond to give an alcohol.



The oxidation occurs by nucleophilic attack of the hydroperoxide ion on the empty orbital of the boron atom followed by a migration of the alkyl chain from boron to oxygen. Do not be alarmed by hydroxide ion as leaving group. It is, of course, a bad leaving group but a very weak bond—the O–O σ bond—is being broken. Finally, hydroxide attacks the now neutral boron to cleave the B–O–alkyl bond and release the alcohol.



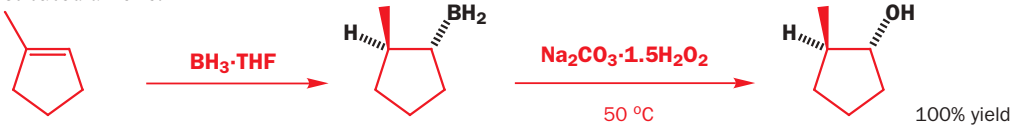
In this sequence boron goes backwards and forwards between planar neutral structures and anionic tetrahedral structures. This is typical of the organic chemistry of boron. The planar structure is neutral but boron has only six valency electrons. The tetrahedral structure gives boron eight valency electrons but it is negatively charged. Boron flits restlessly between these two types of structure, becoming content only when it has three oxygen atoms around it. Returning to the oxidation but concentrating on the boron product, we find that $B(OH)_3$ is the stable product as it is neutral and has three oxygen atoms donating electrons into the empty p orbital on boron.



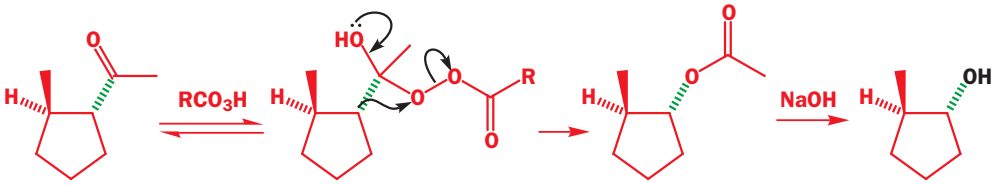
▶ The hydrogen must bond to the carbon of the alkene that had fewer hydrogens attached to it. This is a formal violation of Markovnikoff's rule, which you met in Chapter 20, and is a warning to understand the mechanisms of the reactions rather than follow a rule. Boron is less electronegative than hydrogen and so the regioselectivity is normal with the more electronegative atom becoming attached to the more substituted centre.

▶ More modern alternative reagents, which are stable, inexpensive, safe and easy to handle but achieve the same transformation under mild conditions and often in higher yield, are sodium perborate ($NaBO_3{\cdot}4H_2O$) and sodium percarbonate ($Na_2CO_3{\cdot}1.5H_2O_2$).

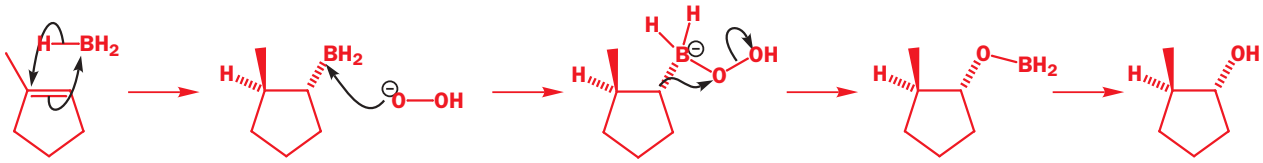
Hydroboration is mostly used for the conversion of alkenes to alcohols by the *cis* addition of water with the OH group going to the less substituted end of the alkene. This is clearest with a cyclic trisubstituted alkene.



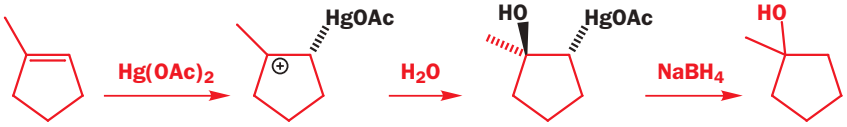
Now we can prove that *cis* addition really does occur in the hydroboration step. The migration of carbon from boron to oxygen might remind you of the Baeyer–Villiger rearrangement (Chapter 37). Both these rearrangements occur with retention of configuration at the migrating group as the bonding (C–C or C–B σ) orbital reacts. Here is the exact analogy.



The same alcohol could be made by the Baeyer–Villiger rearrangement but the stereochemistry would have to be set up before the Baeyer–Villiger step. Hydroboration has the advantage that stereochemistry is created in the hydroboration step. We have discussed the details of this step. In drawing the mechanism it is usually best to draw it as a simple concerted four-centre mechanism providing you remember that the regioselectivity is controlled by the initial interaction between the nucleophilic end of the alkene and the empty p orbital on boron.



The overall result of the hydroboration–oxidation sequence is addition of water to an alkene with the opposite regiochemistry to that expected for a conventional acid-catalysed hydration. The usual way to do such a hydration is by oxymercuration–reduction.

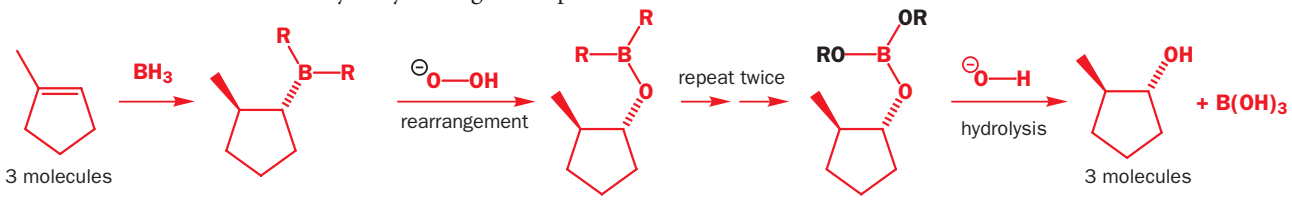


■ Chapter 20 describes the mechanisms for the addition of Hg(II) and suggests that a cyclic mercurinium ion might be involved.

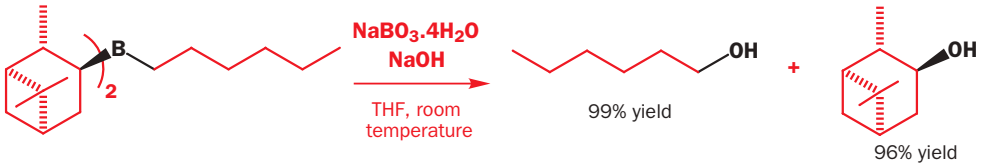
The stereochemical outcome would also be different as the hydroboration adds *syn* to the alkene, whereas oxymercuration gives the *anti* product though in this case the stereochemistry is lost in the reduction step.

Hydroboration–oxidation is normally done via the trialkyl borane

So far we have shown all reactions taking place on the monoalkyl borane. In fact, these compounds are unstable and most hydroborations actually occur via the trialkyl borane. Three molecules of alkene add to the boron atom; three oxidations and three migrations transfer three alkyl groups (R = 2-methylcyclopentyl) from boron to oxygen to give the relatively stable trialkyl borate $B(OR)_3$, which is hydrolysed to give the products.

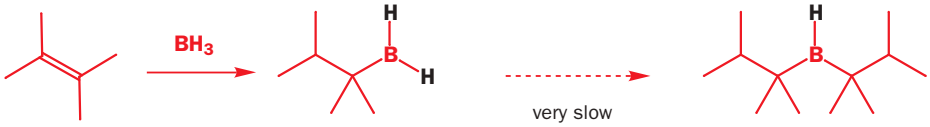


If we have a mixed trialkyl borane, you may be concerned about which of the alkyl groups migrates—the usual answer is that they all do! Oxidation proceeds until the borane is fully oxidized to the corresponding borate, which then breaks down to give the alcohols.



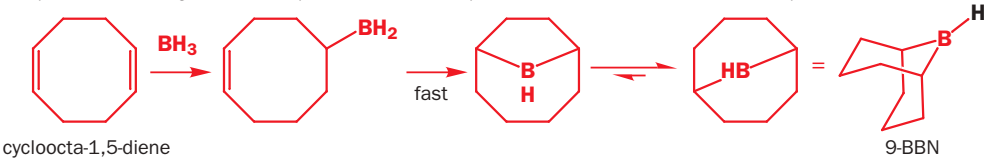
Bulky substituents improve the selectivity of hydroboration

Borane can react one, two, or even three times and this is a disadvantage in many situations so a range of hydroborating reagents has been designed to hydroborate once or twice. Dialkyl boranes R_2BH can hydroborate once only and alkyl boranes RBH_2 twice. In each case the 'dummy' group R must be designed either to migrate badly in the oxidation step or to provide an alcohol that is easily separated from other alcohols. The regioselectivity of hydroboration, good though it is with simple borane, is also improved by very bulky boranes, which explains the choice of dummy groups. Thexyl borane, so-called because the alkyl group is a 'tertiary hexyl' group (*t*-hexyl), is used when two hydroborations are required and it is easily made by hydroboration with borane since the second hydroboration with the tetrasubstituted alkene is very slow .

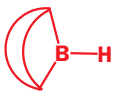


thexyl borane is often written as $ThBH_2$ and drawn as:

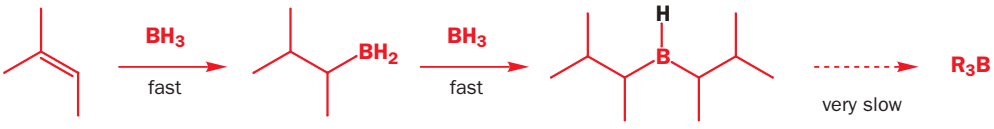
Two dialkyl boranes are in common use. The bicyclic 9-borabicyclo[3.3.1]nonane (9-BBN), introduced in Chapter 34 as a reagent for diastereoselective aldol reactions, is a stable crystalline solid. This is very unusual for an alkyl borane and makes it a popular reagent. It is made by hydroboration of cycloocta-1,5-diene. The second hydroboration is fast because it is intramolecular but the third would be very slow. The regioselectivity of the second hydroboration is under thermodynamic control.



9-BBN is often drawn as:



Disiamylborane (an abbreviation for di-*s*-isoamyl borane—not a name we should use now, but the abbreviation has stuck) is also easily made by hydroboration of a simple trialkyl alkene with borane. Two hydroborations occur easily, in contrast to the tetrasubstituted alkene above, but the third is very slow. Disiamylborane is exceptionally regioselective because of its very hindered structure. The structures of these reagents are cumbersome to draw in full and they are often abbreviated.



disiamylborane or **Sia_2BH**

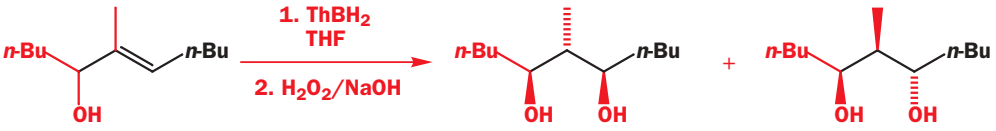
Hydroboration

- Hydroboration is a *syn* addition of a borane to an alkene
- Regioselectivity is high: the boron adds to the carbon less able to support a positive charge

Hydroboration—contd

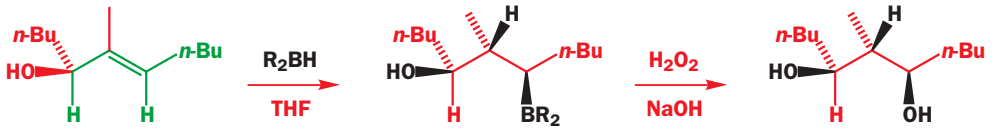
- Oxidation occurs with retention of stereochemistry
- The net result of hydroboration–oxidation is addition of water across the double bond

These bulkier boranes enhance the regioselectivity of hydroboration of trisubstituted alkenes in particular and may also lead to high diastereoselectivity when there is a stereogenic centre next to the alkene. In this next example, an allylic alcohol is hydroborated with thexyl borane. Oxidation reveals complete regioselectivity and a 9:1 stereoselectivity in favour of hydroboration on the same side as the OH group.



72 % yield 8 : 1

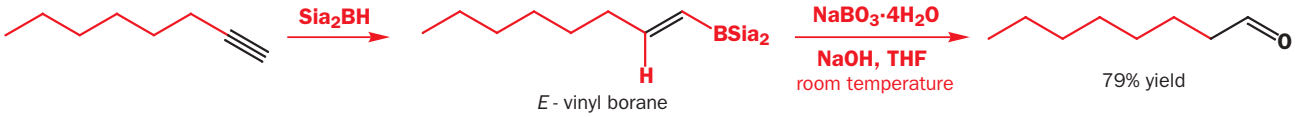
The reactive conformation of the alkene is probably the 'Houk' conformation (Chapter 34) with the hydrogen atom on the stereogenic centre eclipsing the alkene. Attack occurs *syn* to the OH group and *anti* to the larger butyl group.



most stable conformation — *syn* addition from above

Vinyl boranes, boronates, and boronic acids are important reagents in transition-metal-catalysed processes, as you will see in Chapter 48.

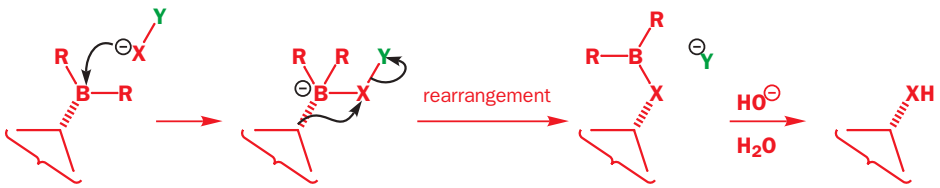
Hydroboration is not restricted to alkenes: alkynes also react well to give vinyl boranes. These may be used directly in synthesis or oxidized to the corresponding enol, which immediately tautomerizes to the aldehyde. An example of this transformation is the conversion of 1-octyne into octanal by hydroboration with disiamylborane and oxidation with sodium perborate under very mild conditions.



E - vinyl borane — 79% yield

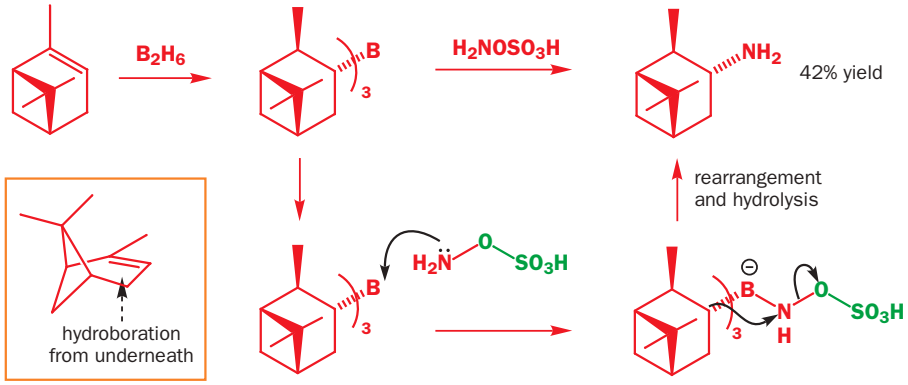
Carbon–boron bonds can be transformed stereospecifically into C–O, C–N, or C–C bonds

Although oxidation to the alcohol is the most common reaction of organoboranes in organic synthesis, the reaction with $^{-}$O–OH is just one example of a general reaction with a nucleophile of the type $^{-}$X–Y where the nucleophilic atom X can be O, N, or even C, and Y is a leaving group. We will illustrate the formation of carbon–nitrogen and carbon–carbon bonds by this reaction. The underlying principle is to use the vacant orbital on boron to attack the nucleophile and then rely on the loss of the leaving group to initiate a rearrangement of R groups from B to X similar to that observed from B to O in the hydrogen peroxide oxidation. The overall result is insertion of X into the carbon–boron bond with retention.

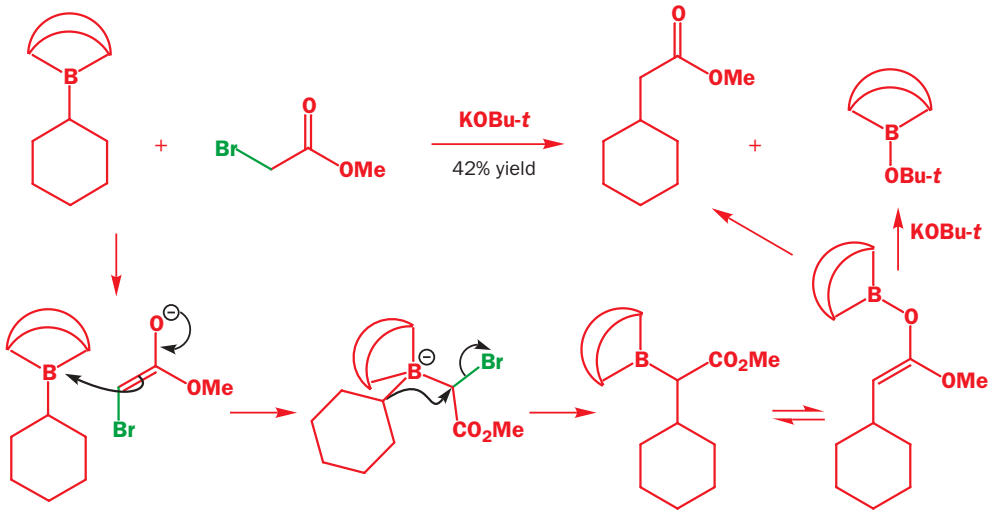


If X is nitrogen then a direct method of amination results. The required reagent is a chloramine or the rather safer *O*-hydroxylaminesulfonic acid: the leaving group is chloride or sulfonate. The overall

process of hydroboration–amination corresponds to a regioselective *syn* addition of ammonia across the alkene. In the case of pinene the two faces of the alkene are very different—one is shielded by the bridge with the geminal dimethyl group. Addition takes place exclusively from the less hindered side to give one diastereoisomer of one regioisomer of the amine.



Carbon–carbon bonds can also be made with alkyl boranes. The requirement for a carbon nucleophile that bears a suitable leaving group is met by α-halo carbonyl compounds. The halogen makes enolization of the carbonyl compound easier and then departs in the rearrangement step. The product is a boron enolate with the boron bound to carbon. Under the basic conditions of the reaction, hydrolysis to the corresponding carbonyl compound is rapid.

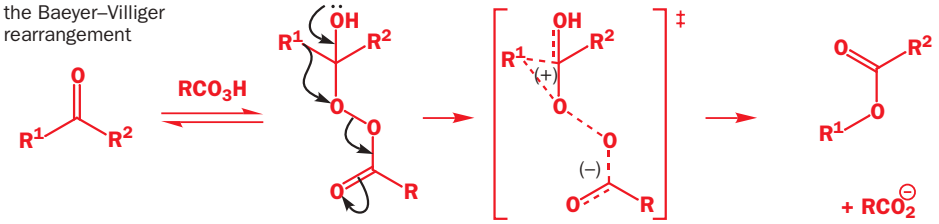


In this example it is important which group migrates from boron to carbon as that is the group that forms the new C–C bond in the product. We previously compared the oxidation of alkyl boranes with the Baeyer–Villiger reaction (Chapter 37) but the order of migrating groups is the opposite in the two reactions. In the Baeyer–Villiger reaction (migration from carbon to oxygen) the more highly substituted carbon atom migrates best so the order is *t*-alkyl > *s*-alkyl > *n*-alkyl > methyl. In organoborane rearrangements it is the reverse order: *n*-alkyl > *s*-alkyl > *t*-alkyl. Methyl does not feature as you cannot make a B–Me bond by hydroboration.

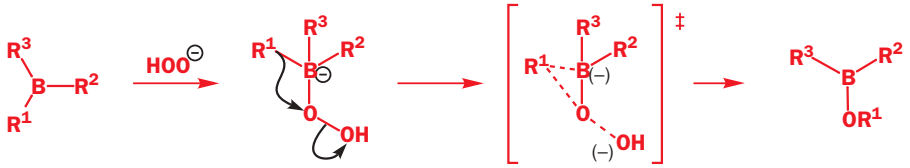
Why the difference between the Baeyer–Villiger rearrangement and boron chemistry?

The transition state for the Baeyer–Villiger rearrangement has a positive charge in the important area. Anything that can help stabilize the positive charge, such as a tertiary migrating group (R^1), stabilizes the transition state and makes the reaction go better.

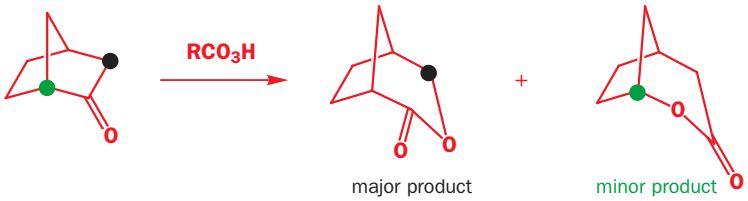
the Baeyer–Villiger rearrangement



In the boron rearrangements, by contrast, the whole transition state has a negative charge. Alkyl groups destabilize rather than stabilize negative charges, but primary alkyl groups destabilize them less than secondary ones do, and so on. This is another reason for choosing tertiary alkyl 'dummy' groups such as *t*-hexyl—they are less likely to migrate.



But what about the case we were considering? The migrating group is secondary and the groups that are left behind on the 9-BBN framework are also secondary. What is the distinction? Again we can use the Baeyer–Villiger reaction to help us. The treatment of bridged bicyclic ketones with peroxy-acids often leads to more migration of the primary alkyl group than of the secondary one.



Bridgehead atoms are bad migrating groups. When the green spot carbon migrates, it drags the whole cage structure with it and distorts the molecule a great deal. When the black spot carbon migrates, it simply slides along the O–O bond and disturbs the cage much less. It is the same with 9-BBN. Migration of the bicyclic group is also unfavourable.

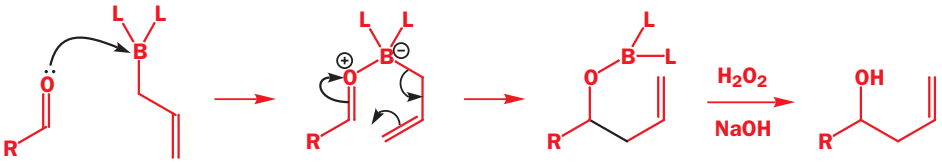
Migration preferences

- **For the Baeyer–Villiger reaction, cation-stabilizing groups migrate best: *t*-alkyl > *s*-alkyl > *n*-alkyl > methyl**
- **For boron rearrangements, cation-stabilizing groups migrate worst: *n*-alkyl > *s*-alkyl > *t*-alkyl**
- **For both, bridgehead groups migrate badly**

Allyl and crotyl boranes react using the double bond

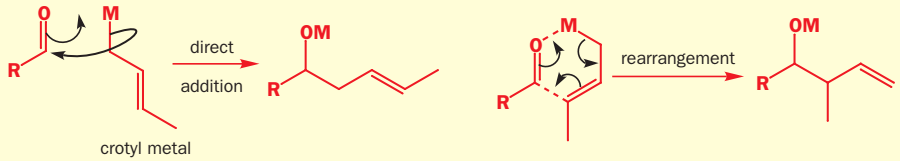
Allylic boron compounds react with aldehydes in a slightly different way. The first step is, as always, coordination of the basic carbonyl oxygen to the Lewis acid boron. This has two important effects: first, the carbonyl is made more electrophilic and, second, the carbon–boron bond in the allylic fragment is weakened so that migration is easier. The difference is that the reaction that follows is not the now familiar 1,2-rearrangement but one involving the allylic double bond as well, rather like a [3,3]-sigmatropic rearrangement (Chapter 36). The negatively charged boron increases the nucleophilicity of the double bond so that it attacks the carbonyl carbon. The result is a six-membered transition state in which transfer of boron from carbon to oxygen occurs with simultaneous carbon–carbon bond formation. Hydrolytic cleavage of the boron–oxygen bond is often accelerated by hydrogen

peroxide as in hydroboration. The precise nature of the ligands on boron is not important as this process is successful both for boranes (L = R) and boronates (L = OR).



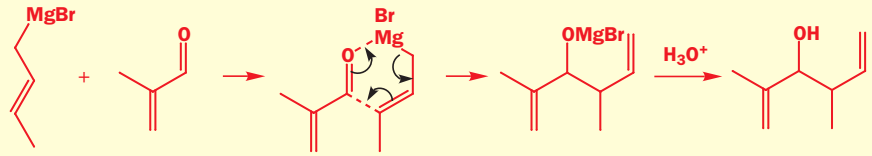
Other allylic organometallic reagents frequently react with 1,3-rearrangement

It is necessary to have a label of some sort to tell whether an allyl metal has reacted directly or by the mechanism we have just seen, a mechanism common to many metals. An isotopic label such as deuterium or ^{13}C might be used but by far the simplest is a substituent such as a methyl group. The resulting methyl allyl group is known as **crotyl**. Reaction with an aldehyde can follow two pathways; direct addition leads to one product without rearrangement while addition with rearrangement gives an isomeric product.



crotyl metal

This sort of rearrangement is often known as **allylic rearrangement**, and even simple Grignard reagents react with aldehydes in this way via a cyclic six-membered transition state (Chapter 9).



Enantioselective allylation is possible with optically pure ligands on boron

You may not think that allylating an aldehyde is much of an achievement—after all, allyl Grignard reagents would do just the same job. The interest in allyl boranes arises because enantiomerically pure ligands derived from naturally occurring chiral terpenes can easily be incorporated into the allyl borane. H.C. Brown, has investigated a range of terpenes as chiral ligands. The reagent below, B-allylbis(2-isocaranyl)borane, has two ligands resulting from hydroboration of carene and delivers the allyl group under such exquisite control that the resulting homoallylic alcohol is virtually a single enantiomer. This reaction is one of the fastest in organic chemistry even at the very low temperature of –100 °C and the product is a useful building block. This makes the process more practical as the cooling is required for only a short time.

almost enantiomerically pure

■ Herbert C. Brown (1912–) won the Nobel Prize in 1979 for his invention and development of hydroboration, mostly carried out at Purdue University, which made this new chemistry familiar to the practising organic chemist. The prize was shared with Georg Wittig, showing how important organic chemistry with main group elements had become. He vigorously opposed 'non-classical' carbocation theory.

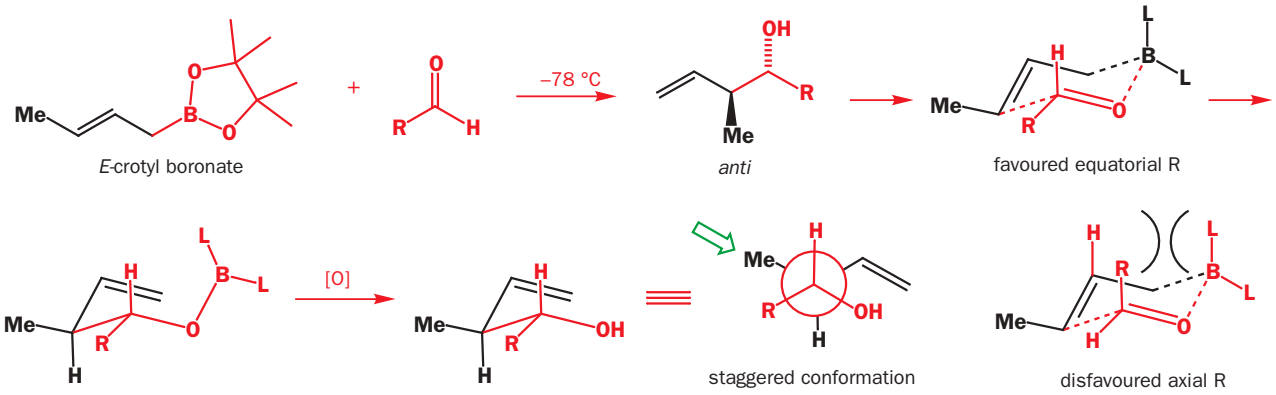
■ Asymmetric synthesis is discussed in Chapter 45.

carene

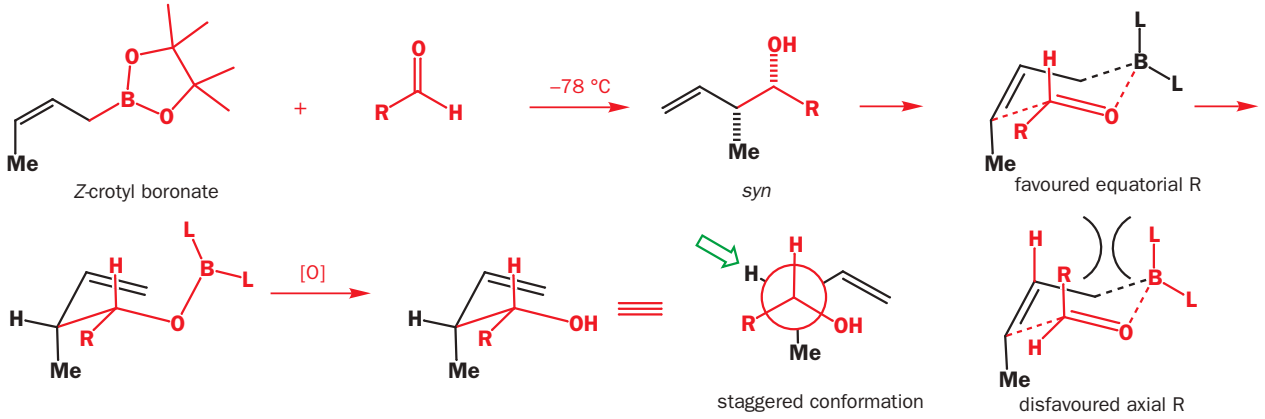
Allyl and crotyl boranes react stereospecifically

The six-membered transition state for the reaction of an allylic borane or boronate is very reminiscent of the cyclic transition state for the aldol reaction you met in Chapter 34. In this case the only change is to replace the oxygen of the enolate with a carbon to make the allyl nucleophile. The transition state for the aldol reaction was a chair and the reaction was stereospecific so that the geometry of the enolate determined the stereochemistry of the product aldol. The same is true in these reactions. *E*-Crotyl boranes (or boronates) give *anti* homoallylic alcohols and *Z*-crotyl boranes (or boronates)

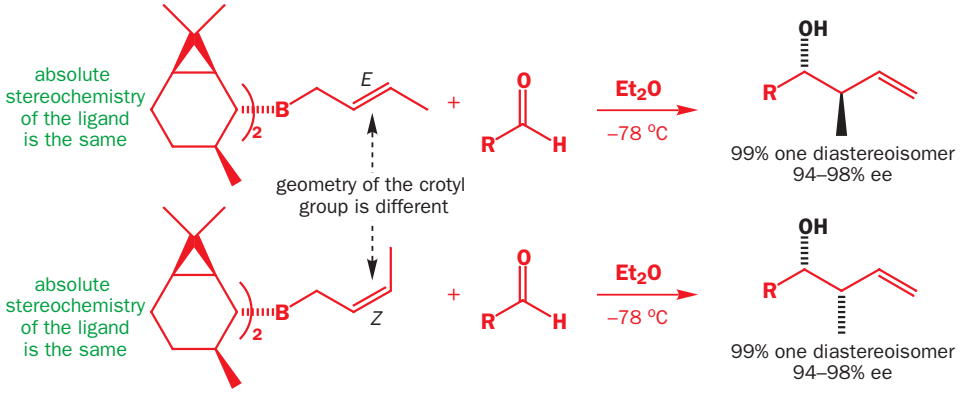
give *syn* alcohols via chair transition states in which the aldehyde R group adopts a pseudoequatorial position to minimize steric repulsion. As with the aldol reaction the short bonds to boron create a very tight transition state, which converts the two-dimensional stereochemistry of the reagent into the three-dimensional structure of the product.



The low temperature is a testament to the reactivity of the crotyl boronates and also helps minimize any isomerization of the reagents while maximizing the effect of the energy differences between the favoured and disfavoured transition states.



The dramatic diastereoselectivity of this process is noteworthy but, of course, the products are racemic—two *anti* isomers from the *E*-crotyl reagent and two *syn* isomers from the *Z* counterpart. This is inevitable as both starting materials are achiral and there is no external source of chirality. You may be wondering if the use of a chiral ligand on boron would allow the production of a single enantiomer of a single diastereoisomer. The simple answer is that it does, very nicely. In fact, there are a number of solutions to this problem using boranes and boronates but the one illustrated uses the same ligand as that used earlier for allylation derived from carene.



Though boron and aluminium form similar reducing agents, such as $NaBH_4$ and $LiAlH_4$, the reactions described so far in this chapter do not occur with aluminium compounds, and compounds with C–Al bonds, other than DIBAL and Me_3Al, are hardly used in organic chemistry. We move on to the other two elements in this chapter, Si and Sn, both members of group IVB (or 14 if you prefer)—the same group as carbon.

Special features of organoboron chemistry

- Boron is electrophilic because of its empty p orbital
- Boron forms strong B–O bonds and weak B–C bonds
- Migration of alkyl groups from boron to O, N, or C is stereospecific

Silicon and carbon compared

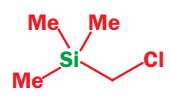
Silicon is immediately below carbon in the periodic table and the most obvious similarity is that both elements normally have a valency of four and both form tetrahedral compounds. There are important differences in the chemistry of carbon and silicon—silicon is less important and many books are devoted solely to carbon chemistry but relatively few to silicon chemistry. Carbon forms many stable trigonal and linear compounds containing π bonds; silicon forms few. The most important difference is the strength of the silicon–oxygen σ bond (368 kJ mol^{-1}) and the relative weakness of the silicon–silicon (230 kJ mol^{-1}) bond. Together these values account for the absence, in the oxygen-rich atmosphere of earth, of silicon analogues of the plethora of structures possible with a carbon skeleton.

■ Instead, silicon forms compounds containing the very stable O–Si–O linkage giving a variety of structures such as rocks and plastics.

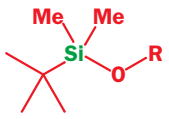
Average bond energies, kJ mol^{-1}

X	H–X	C–X	O–X	F–X	Cl–X	Br–X	I–X	Si–X
C	416	356	336	485	327	285	213	290
Si	323	290	368	582	391	310	234	230
ratio	1.29	1.23	0.91	0.83	0.84	0.92	0.91	1.26

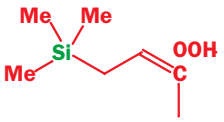
Several of the values in the table are worthy of comment as they give insight into the reactivity differences between carbon and silicon. Bonds to electronegative elements are generally stronger with silicon than with carbon; in particular, the silicon–fluorine bond is one of the strongest single bonds known, while bonds to electropositive elements are weaker. Silicon–hydrogen bonds are much weaker than their carbon counterparts and can be cleaved easily. This section of Chapter 47 is about organic silicon chemistry. We will mostly discuss compounds with four Si–C bonds. Three of these bonds will usually be the same so we will often have a Me_3Si– group attached to an organic molecule. We shall discuss reactions in which something interesting happens to the organic molecule as one of the Si–C bonds reacts to give a new Si–F or Si–O bond. We shall also discuss organosilicon compounds as reagents, such as triethylsilane (Et_3SiH), which is a reducing agent whereas Et_3C–H is not. Here are a few organosilicon compounds.



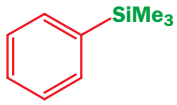
a useful electrophile



a protected alcohol



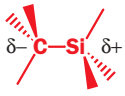
an allyl silane



a silyl benzene

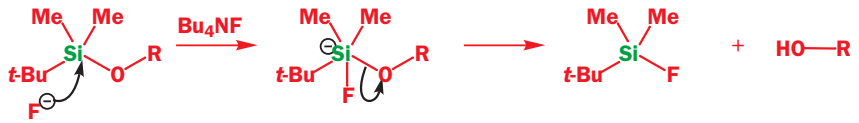
The carbon–silicon bond is strong enough for the trialkyl silyl group to survive synthetic transformations on the rest of the molecule but weak enough for it to be cleaved specifically when we want. In particular, fluoride ion is a poor nucleophile for carbon compounds but attacks silicon very readily. Another important factor is the length of the C–Si bond (1.89 Å)—it is significantly longer than a typical C–C bond (1.54 Å). Silicon has a lower electronegativity (1.8) than carbon (2.5) and therefore C–Si bonds are polarized towards the carbon. This makes the silicon susceptible to attack by nucleophiles.

▶ The strength of the C–Si bond means that alkyl silanes are stable but useful chemistry arises from carbon substituents that are not simple alkyl groups.

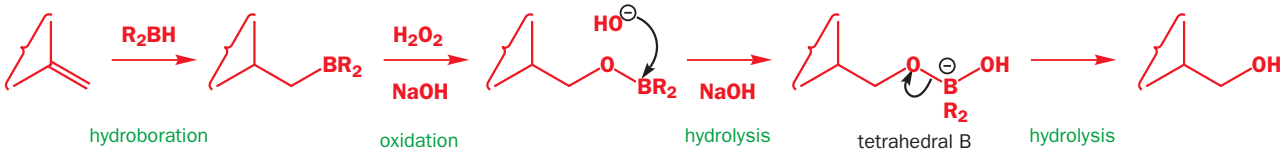


Silicon has an affinity for electronegative atoms

The most effective nucleophiles for silicon are the electronegative ones that will form strong bonds to silicon, such as those based on oxygen or halide ions with fluoride being pre-eminent. You saw this in the choice of reagent for the selective cleavage of silyl ethers in Chapter 24. Tetrabutylammonium fluoride is often used as this is an organic soluble ionic fluoride and forms a silyl fluoride as the by-product. The mechanism is not a simple S_N2 process and has no direct analogue in carbon chemistry. It looks like a substitution at a hindered tertiary centre, which ought to be virtually impossible. Two characteristics of silicon facilitate the process: first, the long silicon–carbon bonds relieve the steric interactions and, second, the d orbitals of silicon provide a target for the nucleophile that does not have the same geometric constraints as a C–O σ^* orbital. Attack of the fluoride on the d orbital leads to a negatively charged pentacoordinate intermediate that breaks down with loss of the alkoxide. There is a discrete intermediate in contrast to the pentacoordinate transition state of a carbon-based S_N2 reaction.

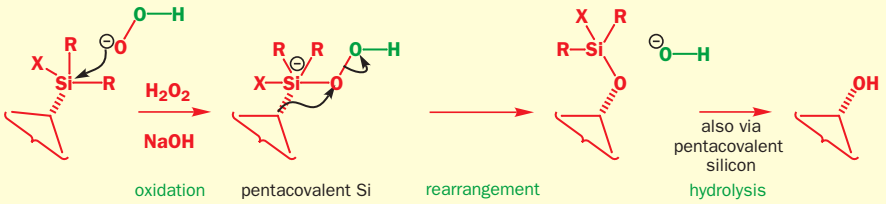


This process is sometimes abbreviated to S_N2 at silicon to save space. The intermediate is a trigonal bipyramid with negatively charged pentacovalent silicon. It is often omitted in drawings because it is formed slowly and decomposes quickly. This mechanism is similar to nucleophilic substitution at boron except that the intermediate is pentacovalent (Si) rather than tetrahedral (B). The hydrolysis of a boron ester at the end of a hydroboration–oxidation sequence would be an example.



The silicon Baeyer–Villiger rearrangement

Evidence that the 'S_N2' reaction at silicon does indeed go through a pentacovalent intermediate comes from the silicon analogue of the migration step in hydroboration–oxidation. Treatment of reactive organosilanes (that is, those with at least one heteroatom—F, OR, NR_2—attached to silicon to encourage nucleophilic attack of hydroperoxide at silicon) with the same reagent (alkaline hydrogen peroxide) also gives alkyl migration from Si to O with retention of configuration. It would be difficult to draw a mechanism for this reaction without the intermediate. This is a precise copy of the oxidative cleavage of organoboranes that works on silanes.

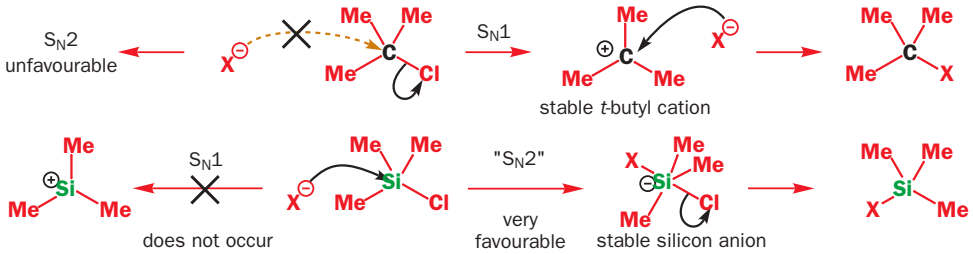


Silicon forms strong bonds with oxygen and very strong bonds with fluorine.

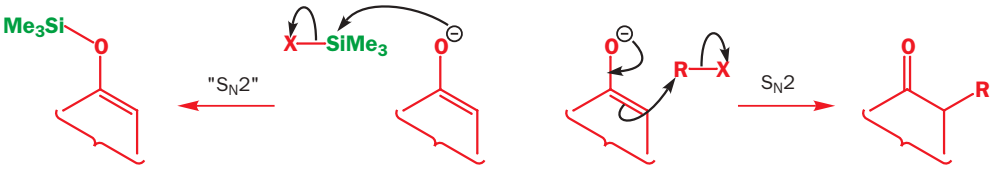
Nucleophilic substitution at silicon

You may wonder why trimethylsilyl chloride does not use the S_N1 mechanism familiar from the analogous carbon compound *t*-butyl chloride. There is, in fact, nothing wrong with the Me_3Si^+

cation—it is often observed in mass spectra, for example. The reason is that the 'S_N2' reaction at silicon is too good.



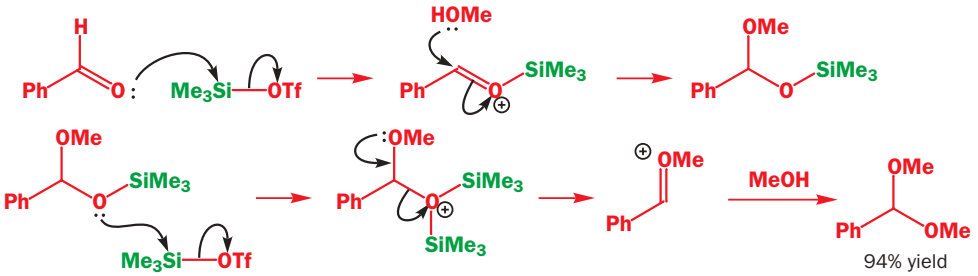
We should compare the 'S_N2' reaction at silicon with the S_N2 reaction at carbon. There are some important differences. Alkyl halides are soft electrophiles but silyl halides are hard electrophiles. Alkyl halides react only very slowly with fluoride ion but silyl halides react more rapidly with fluoride than with any other nucleophile. The best nucleophiles for saturated carbon are neutral and/or based on elements down the periodic table (S, Se, I). The best nucleophiles for silicon are charged and based on highly electronegative atoms (chiefly F, Cl, and O). A familiar example is the reaction of enolates at carbon with alkyl halides but at oxygen with silyl chlorides (Chapter 21).



When a Me_3Si group is removed from an organic molecule with hydroxide ion, the product is not the silanol as you might expect but the silyl ether 'hexamethyldisiloxane'. Di-*t*-butyl ether could not be formed under these conditions nor by this mechanism, but only by the S_N1 mechanism in acid solution.

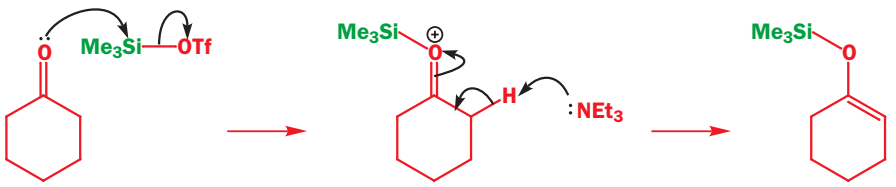
The other side of the coin is that the S_N2 reaction at carbon is *not* much affected by partial positive charge (δ+) on the carbon atom. The 'S_N2' reaction at silicon *is* affected by the charge on silicon. The most electrophilic silicon compounds are the silyl triflates and it is estimated that they react some 10^8–10^9 times faster with oxygen nucleophiles than do silyl chlorides. Trimethylsilyl triflate is, in fact, an excellent Lewis acid and can be used to form acetals or silyl enol ethers from carbonyl compounds, and to react these two together in aldol-style reactions. In all three reactions the triflate attacks an oxygen atom.

In the acetal formation, silylation occurs twice at the carbonyl oxygen atom and the final leaving group is hexamethyldisiloxane. You should compare this with the normal acid-catalysed mechanism described in Chapter 14 where the carbonyl group is twice protonated and the leaving group is water.



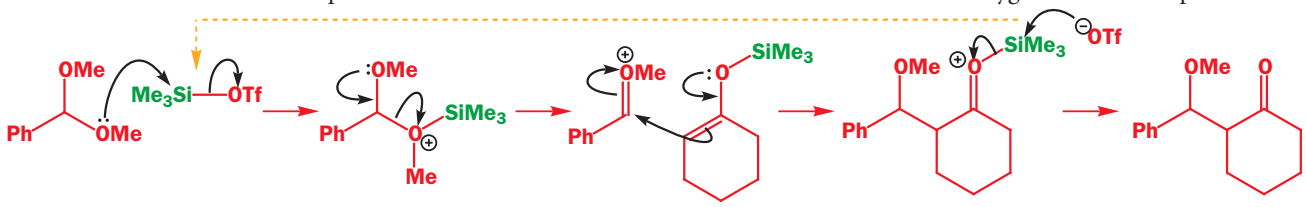
Silyl enol ether formation again results from silylation of carbonyl oxygen but this time no alcohol is added and a weak base, usually a tertiary amine, helps to remove the proton after silylation.

■ You will see in Chapter 52 that Me_2SiCl_2 polymerizes by repeating this mechanism many many times.



85% yield

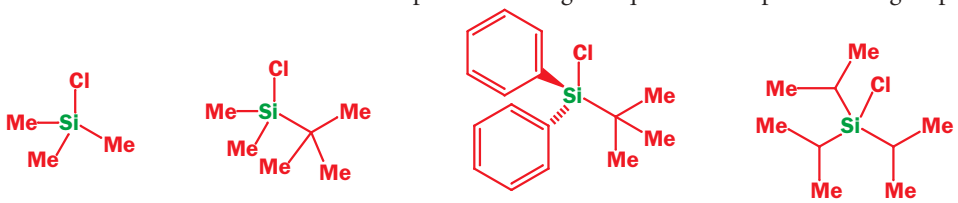
When the acetal and the silyl enol ether are mixed with the same Lewis acid catalyst, Noyori found that an efficient aldol-style condensation takes place with the acetal providing the electrophile. The reaction is successful at low temperatures and only a catalytic amount of the Lewis acid is needed. Under these conditions, with no acid or base, few side-reactions occur. Notice that the final desilylation is carried out by the triflate anion to regenerate the Lewis acid Me_3Si–OTf. Triflate would be a very poor nucleophile for saturated carbon but is reasonable for silicon because oxygen is the nucleophilic atom.



89% yield

Silyl ethers are versatile protecting groups for alcohols

Silicon-based protecting groups for alcohols are the best because they are the most versatile. They are removed by nucleophilic displacement with fluoride or oxygen nucleophiles and the rate of removal depends mostly on the steric bulk of the silyl group. The simplest is trimethylsilyl (Me_3Si or often just TMS) which is also the most easily removed as it is the least hindered. In fact, it is removed so easily by water with a trace of base or acid that special handling is required to keep this labile group in place.



Me_3SiCl TMSCl

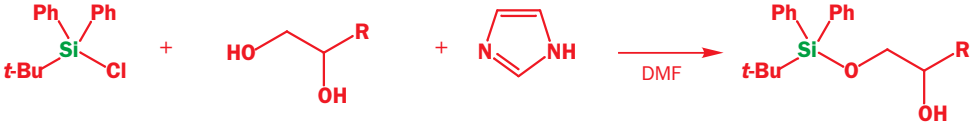
***t*-$BuMe_2SiCl$** TBDMSCl

***t*-$BuPh_2SiCl$** TBDPSCl

***i*-Pr_3SiCl** TIPSCl

Replacement of the one of the methyl groups with a much more sterically demanding tertiary butyl group gives the *t*-butyldimethylsilyl (TBDMS) group, which is stable to normal handling and survives aqueous work-up or column chromatography on silica gel. The stability to these isolation and purification conditions has made TBDMS (sometimes over-abbreviated to TBS) a very popular choice for organic synthesis. TBDMS is introduced by a substitution reaction on the corresponding silyl chloride with imidazole in DMF. Yields are usually virtually quantitative and the conditions are mild. Primary alcohols are protected in the presence of secondary alcohols. Removal relies on the strong affinity of fluoride for silicon and is usually very efficient and selective.

However, a protecting group is useful only if it can be introduced and removed in high yield without affecting the rest of the molecule and if it can survive a wide range of conditions in the course of the synthesis. The extreme steric bulk of the *t*-butyldiphenylsilyl (TBDPS) group makes it useful for selective protection of unhindered primary alcohols in the presence of secondary alcohols.



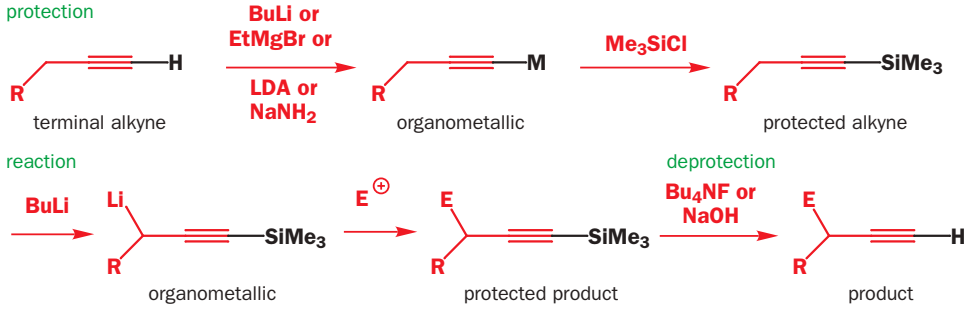
TBDPSCl diol imidazole TBDPS ether

The most stable common silyl protecting group (triisopropylsilyl or TIPS) has three branched alkyl substituents to protect the central silicon from attack by nucleophiles which would lead to cleavage. All three hindered silyl groups (TBDMS, TBDPS, and TIPS) have excellent stability but can still be removed with fluoride.

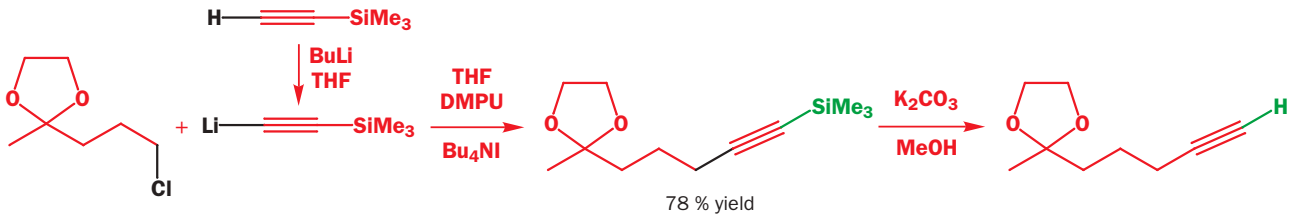
Alkynyl silanes are used for protection and activation

Terminal alkynes have an acidic proton (pK_a *ca.* 25) that can be removed by very strong bases such as organometallic reagents (Grignards, RLi, etc.). While this is often what is intended, in other circumstances it may be an unwanted side-reaction that would consume an organometallic reagent or interfere with the chosen reaction. Exchange of the terminal proton of an alkyne for a trimethylsilyl group exploits the relative acidity of the proton and provides a neat solution to these problems. The $SiMe_3$ group protects the terminus of the alkyne during the reaction but can then be removed with fluoride or sodium hydroxide. A classic case is the removal of a proton next door to a terminal alkyne.

■ Alkynyl lithiums and Grignards were made in this way in Chapter 9.

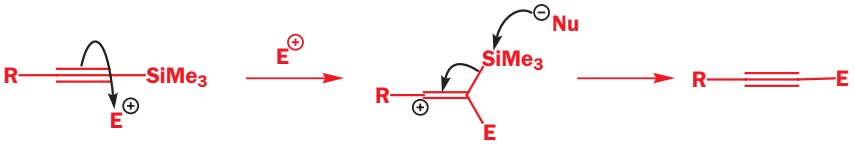


Additionally, acetylene itself is a useful two-carbon building block but is not very convenient to handle as it is an explosive gas. Trimethylsilylacetylene is a distillable liquid that is a convenient substitute for acetylene in reactions involving the lithium derivative as it has only one acidic proton. The synthesis of this alkynyl ketone is an example. Deprotonation with butyl lithium provides the alkynyl lithium that reacted with the alkyl chloride in the presence of iodide as nucleophilic catalyst (see Chapter 17). Removal of the trimethylsilyl group with potassium carbonate in methanol allowed further reaction on the other end of the alkyne.



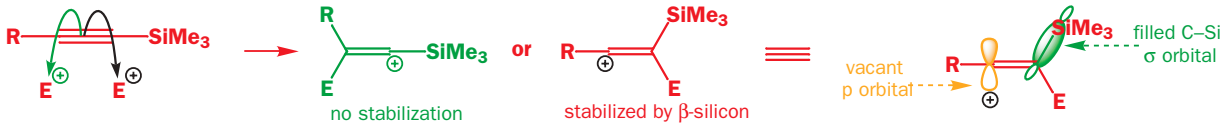
Silicon stabilizes a positive charge on the β carbon

In common with ordinary alkynes, silylated alkynes are nucleophilic towards electrophiles. The presence of the silicon has a dramatic effect on the regioselectivity of this reaction: attack occurs only at the atom directly bonded to the silicon. This must be because the intermediate cation is stabilized.



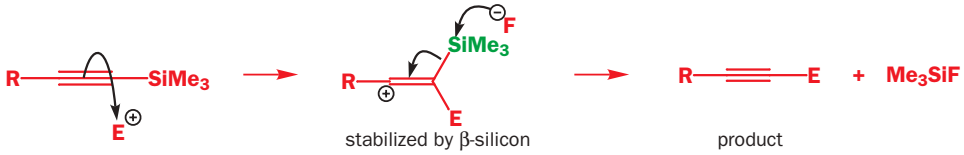
The familiar hierarchy of carbocation stability—tertiary > secondary > primary—is due to the stabilization of the positive charge by donation of electron density from adjacent C–H or C–C bonds (their filled σ orbitals to be precise) that are aligned correctly with the vacant orbital (Chapter 17). The electropositive nature of silicon makes C–Si bonds even more effective donors so that a β-silyl

group stabilizes a positive charge so effectively that the course of a reaction involving cationic intermediates is often completely controlled. This is stabilization by σ donation.

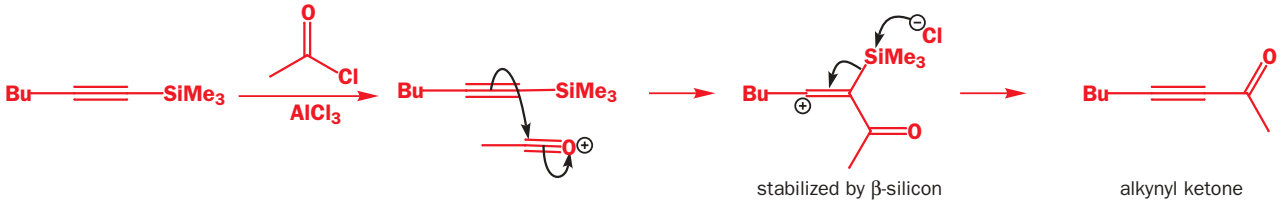


■ The nucleophile does not need to be very powerful as the C–Si bond is weakened. Many neutral molecules with a lone pair and almost any anion will do, even triflate ($CF_3SO_2O^-$).

The stabilization of the cation weakens the C–Si bond by the delocalization of electron density so that the bond is more easily broken. Attack of a nucleophile, particularly a halogen or oxygen nucleophile, on silicon removes it from the organic fragment and the net result is electrophilic substitution in which the silicon has been replaced by the electrophile.



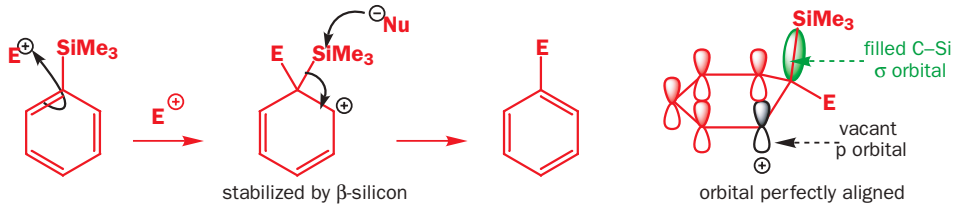
This is useful for the synthesis of alkynyl ketones, which are difficult to make directly with conventional organometallic reagents such as alkynyl–Li or –MgBr because they add to the ketone product. Alkynyl silanes react with acid chlorides in the presence of Lewis acids, such as aluminium chloride, to give the ketones.



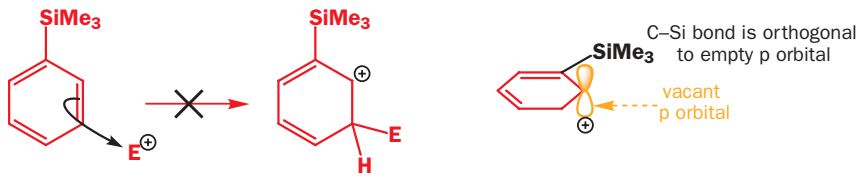
Aryl silanes undergo *ipso* substitution with electrophiles

Exactly the same sort of mechanism accounts for the reactions of aryl silanes with electrophiles under Friedel–Crafts conditions. Instead of the usual rules governing *ortho*, *meta*, and *para* substitution using the directing effects of the substituents, there is just one rule: the silyl group is replaced by the electrophile at the same atom on the ring—this is known as ***ipso* substitution.** Actually, this selectivity comes from the same principles as those used for ordinary aromatic substitution (Chapter 22): the electrophile reacts to produce the most stable cation—in this case β to silicon. Cleavage of the weakened C–Si bond by any nucleophile leads directly to the *ipso* product.

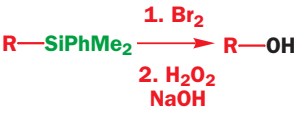
▶ The Latin word *ipso* means 'the same'—the *same* site as that occupied by the SiR_3 group.



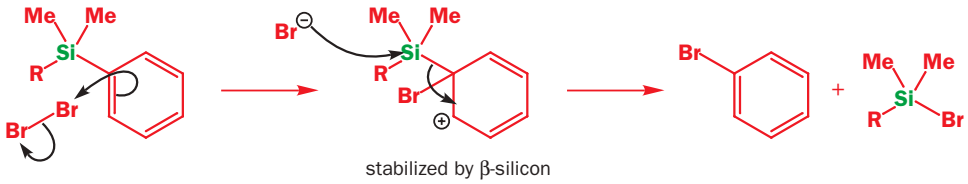
There is an alternative site of attack that would lead to a cation β to silicon, that is, *meta* to silicon. This cation is not particularly stable because the vacant p orbital is orthogonal to the C–Si bond and so cannot interact with it. This illustrates that it is more important to understand the origin of the effect based on molecular orbitals rather than simply to remember the result.



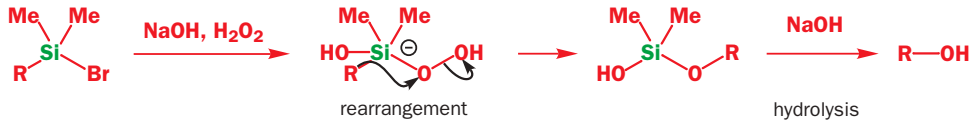
This reactivity of aryl silanes is used to convert the stable phenyl dimethylsilyl group into a more reactive form for conversion into an alcohol by the 'silyl Baeyer–Villiger' reaction described above. Overall this makes the phenyl dimethylsilyl group a bulky masked equivalent for a hydroxyl group. This is useful because the silane will survive reaction conditions that the alcohol might not and the steric bulk allows stereoselective reactions. Ian Fleming at Cambridge has made extensive use of this group and the conversion into an alcohol by several reagents all of which depend on the *ipso* substitution of the phenyl silane. The reaction with bromine is typical. Bromobenzene is produced together with a silyl bromide that is activated towards subsequent oxidation.



The mechanism of electrophilic desilylation is the same as that for electrophilic aromatic substitution except that the proton is replaced by trimethylsilyl. The important difference is that the silicon stabilizes the intermediate cation, and hence the transition state leading to it, to a dramatic extent so that the rate is much faster. This is the first step with bromine.



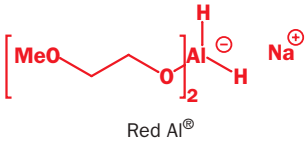
The rest of the reaction sequence involves displacement of Br– by HOO–, addition of hydroxide, rearrangement, and hydrolysis. All these steps involve the silicon atom and the details are given a few pages back.



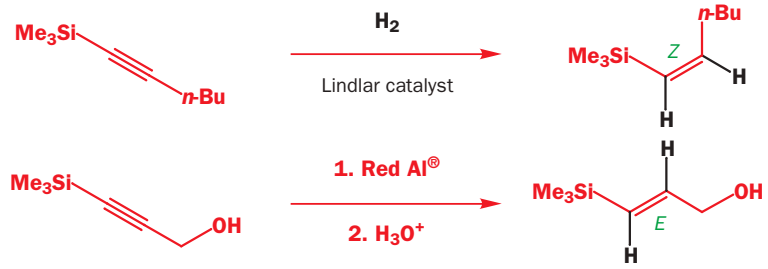
● Trimethylsilyl and other silyl groups stabilize a positive charge on a β carbon and are lost very easily. They can be thought of as very reactive protons or 'super protons'.

Vinyl silanes can be prepared stereospecifically

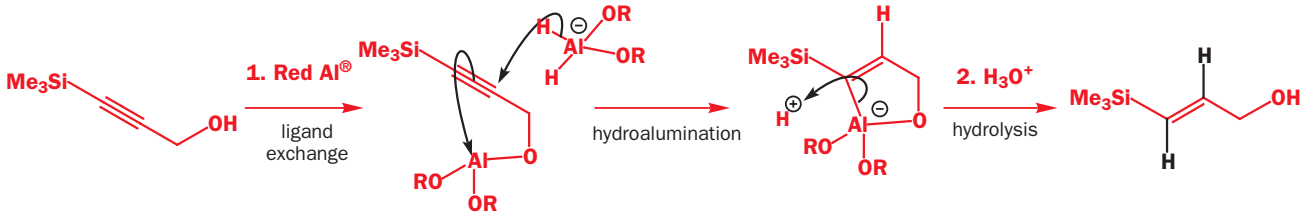
Controlled reduction of alkynyl silanes produces the corresponding vinyl silanes and the method of reduction dictates the stereochemistry. Lindlar hydrogenation adds a molecule of hydrogen across the alkyne in a *cis* fashion to produce the *Z*-vinyl silane. Red Al reduction of a propargylic alcohol leads instead to the *E*-isomer.



■ Another example of this type of reduction appears in Chapter 31.

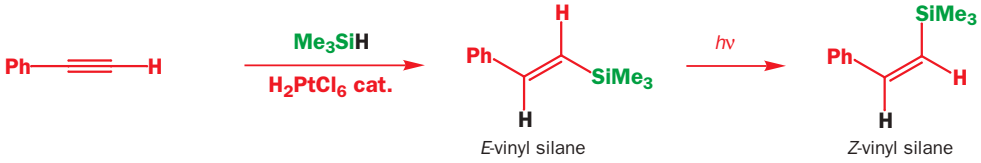


The mechanism of the second reaction is a *trans* hydroalumination helped by coordination of the alane to the triple bond and external nucleophilic attack. The regioselectivity of the hydroalumination is again determined by silicon: the electrophilic alane attacks the alkyne on the carbon bearing the silyl group (the *ipso* carbon).

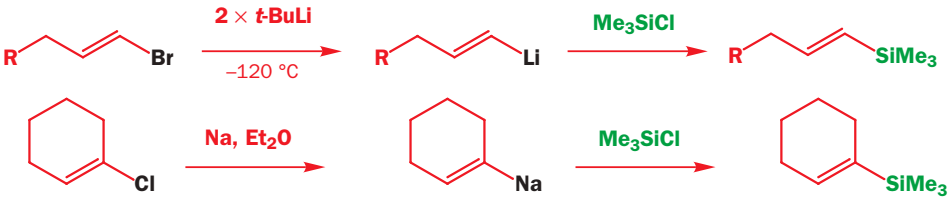


Instead of adding two hydrogen atoms to an alkynyl silane we could add H and $SiMe_3$ to a simple alkyne by hydrosilylation (addition of hydrogen and silicon). This is a *cis* addition process catalysed by transition metals and leads to a *trans* (*E*-) vinyl silane. One of the best catalysts is chloroplatinic acid (H_2PtCl_6) as in this formation of the *E*-vinyl silane from phenylacetylene. In this case photochemical isomerization to the *Z*-isomer makes both available. Other than the need for catalysis, this reaction should remind you of the hydroboration reactions earlier in the chapter. The silicon atom is the electrophilic end of the Si–H bond and is transferred to the less substituted end of the alkyne.

■ See Chapter 31 for the effect of light on alkenes.

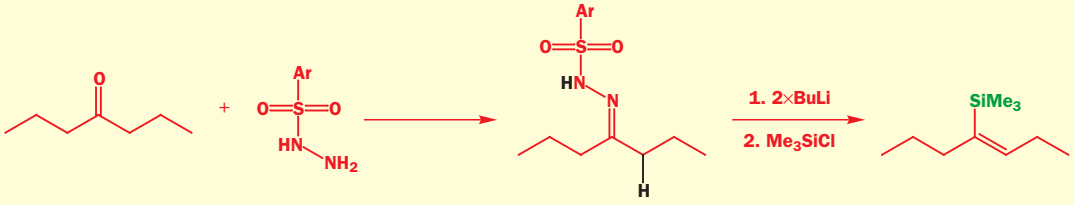


Vinyl silanes can also be prepared from vinyl halides by metal–halogen exchange to form the corresponding vinylic organometallic and coupling with a silyl chloride. Notice that both of these reactions happen with retention of configuration. This route is successful for acyclic and cyclic compounds and even vinyl chlorides, which are much less reactive, can be used with the lithium containing some of the more powerfully reducing sodium as the metal.

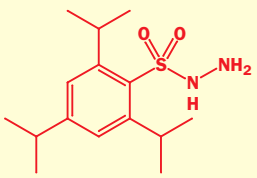


Vinyl silanes can be prepared directly from ketones using the Shapiro reaction

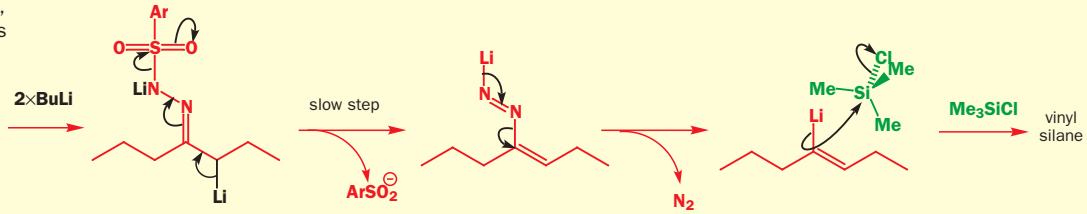
Conversion of ketones into arylsulfonylhydrazones allows preparation of the corresponding vinyl lithiums by base-promoted decomposition of the hydrazone. This is known as the **Shapiro reaction**. Trapping with trimethylsilylchloride gives vinyl silanes, which can be difficult to prepare by other methods.



The mechanism involves deprotonation with a very strong base, usually butyl lithium or LDA, to form the hydrazone aza-enolate, which then eliminates aryl sulfinate to give an unstable anion. Loss of nitrogen, which is extremely favourable, leads to the vinyl lithium.



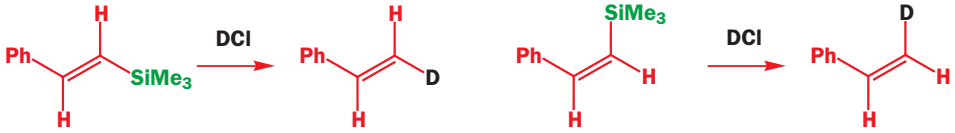
a bulky sulfonyl hydrazine for the Shapiro reaction



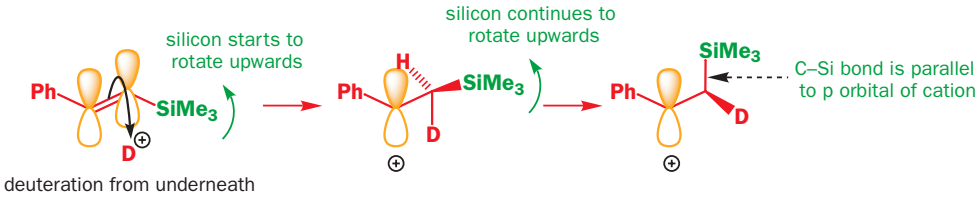
The key step is the elimination of the aryl sulfinate and this has been improved by using aryl hydrazones with bulky isopropyl groups on the 2-, 4-, and 6-positions of the aromatic ring to accelerate the elimination. The weakness of this approach to vinyl silanes is that the position of the double bond is governed by the initial site of deprotonation and so the usual problems of regioselective ketone enolate formation arise. However, in symmetrical cases or those where one side is favoured as a result of the structure of the ketone, the Shapiro reaction works well.

Vinyl silanes offer a regio- and stereoselective route to alkenes

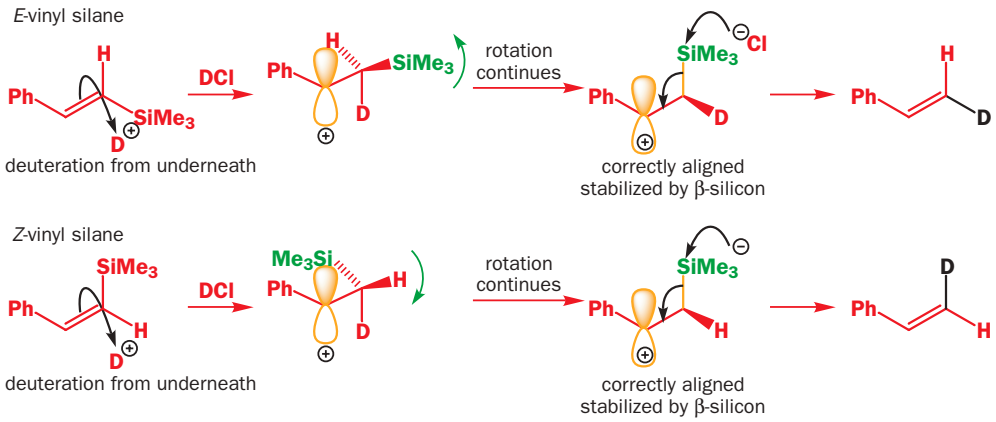
Vinyl silanes react with electrophiles in a highly regioselective process in which the silicon is replaced by the electrophile at the *ipso* carbon atom. The stereochemistry of the vinyl silane is important because this exchange usually occurs with retention of geometry as well. Consider the reaction of the two vinyl silanes derived from phenyl acetylene with the simple electrophile D^+. Deuterons are chemically very similar to protons but are, of course, distinguishable by NMR.



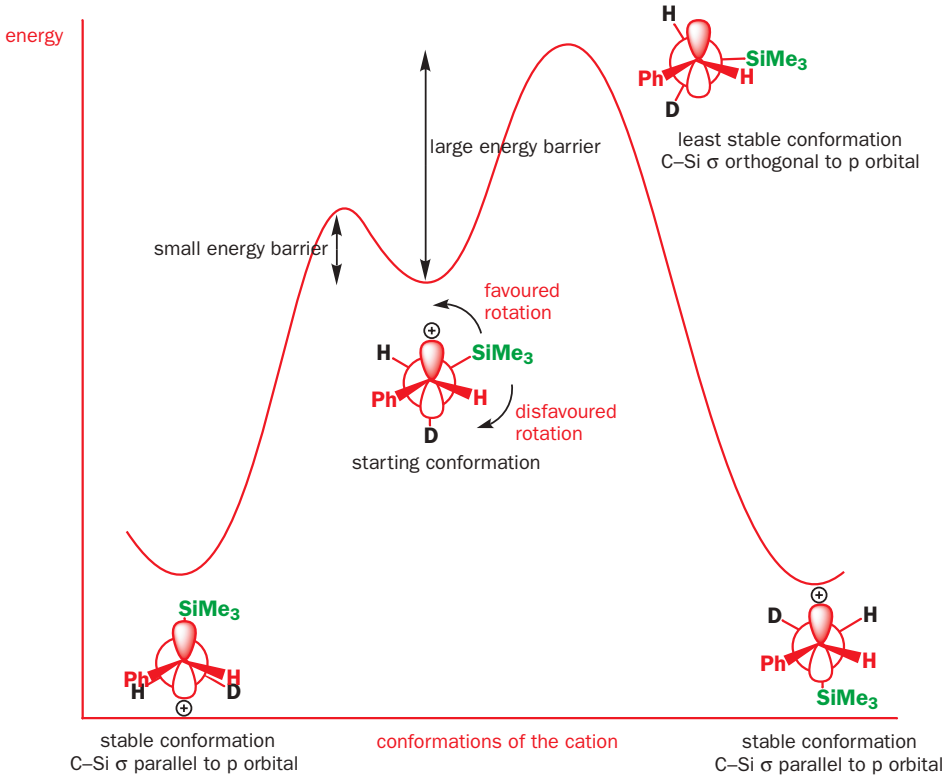
In principle, the alkenes could be protonated at either end but protonation next to silicon leads to the more stable cation β to silicon. In the vinyl silane the C–Si bond is orthogonal to the p orbitals of the π bond, but as the electrophile (D^+ here) attacks the π bond, say from underneath, the Me_3Si group starts to move upwards. As it rotates, the angle between the C–Si bond and the remaining p orbital decreases from 90°. As the angle decreases, the interaction between the C–Si bond and the empty p orbital of the cation increases. There is every reason for the rotation to continue in the same direction and no reason for it to reverse. The diagram shows that, in the resulting cation, the deuterium atom is in the position formerly occupied by the Me_3Si group, *trans* to Ph. Loss of the Me_3Si group now gives retention of stereochemistry.



The intermediate cation has only a single bond and so rotation might be expected to lead to a mixture of geometrical isomers of the product but this is not observed. The bonding interaction between the C–Si bond and the empty p orbital means that rotation is restricted. This stabilization weakens the C–Si bond and the silyl group is quickly removed before any further rotation can occur. The stabilization is effective only if the C–Si bond is correctly aligned with the vacant orbital, which means it must be in the same plane—rather like a π bond. Here is the result for both *E*- and *Z*-isomers of the vinyl silane.

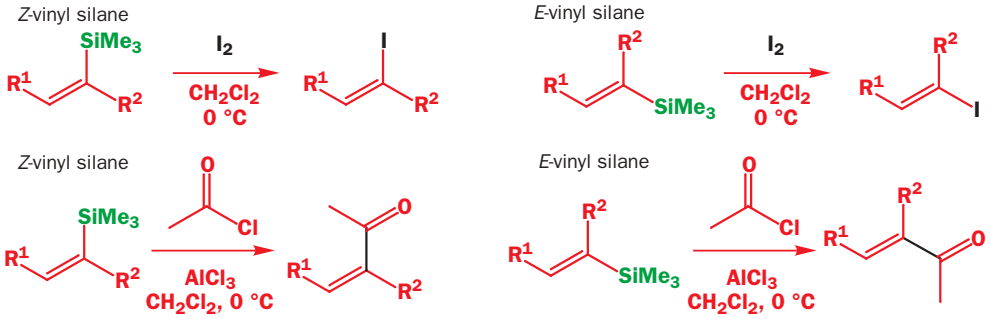


We can illustrate the two alternative rotations with an energy diagram: one rotation leads directly to a stable conformation with the C–Si bonding orbital parallel to the vacant p orbital, while the other passes through a very-high-energy conformation that has the two orbitals orthogonal and so derives no stabilization from the presence of silicon. It is this energy barrier that effectively prevents rotation and leads to electrophilic substitution with retention of double bond geometry. The favoured rotation simply continues the rotation from starting material to cation.



It is unusual for silicon to be required in the final product of a synthetic sequence and the stereospecific removal of silicon from vinyl silanes makes them useful reagents that can be regarded as rather stable vinylic organometallic reagents that will react with powerful electrophiles preserving the double bond location and geometry. **Protodesilylation**, as the process of replacing silicon with a proton is known, is one such important reaction. The halogens are also useful electrophiles while organic halides, particularly acid chlorides, in the presence of Lewis acids, form vinyl halides and unsaturated ketones of defined geometry.

■ Geometrically pure vinyl halides are important starting materials for transition-metal-catalysed alkene synthesis (Chapter 48).

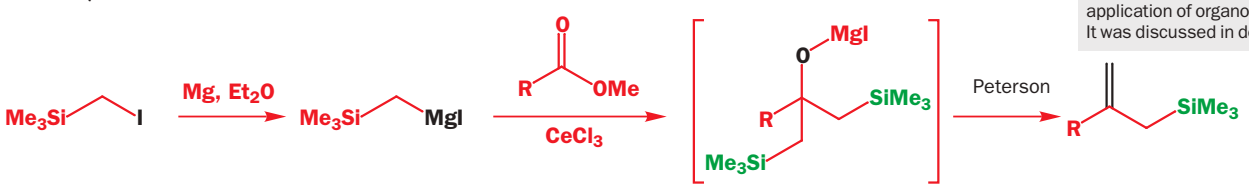


Allyl silanes are readily available

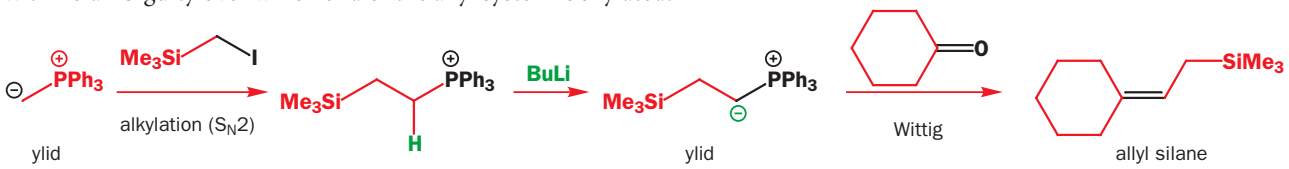
If the silyl group is moved along the carbon chain by just one atom, an allyl silane results. Allyl silanes can be produced from allyl organometallic reagents but there is often a problem over which regioisomer is produced and mixtures often result. Better methods control the position of the double bond using one of the methods introduced in Chapter 31. Two useful examples take advantage of the Wittig reaction and the Peterson olefination to construct the alkene linkage. The reagents are prepared from trimethylsilyl halides either by formation of the corresponding Grignard reagent or alkylation with a methylene Wittig reagent and deprotonation to form a new ylid. The Grignard reagent, with added cerium trichloride, adds twice to esters to give the corresponding tertiary alcohol which

loses one of its Me_3Si groups in a Peterson elimination to reveal the remaining Me_3Si group as part of an allyl silane.

■ The Peterson elimination is another application of organosilicon chemistry. It was discussed in detail in Chapter 31.

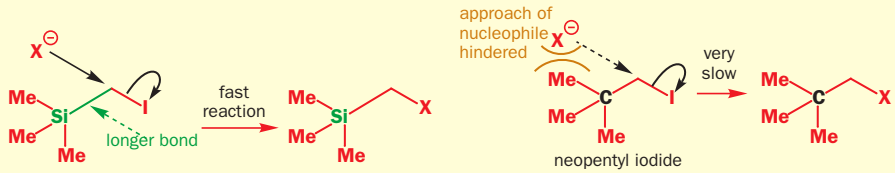


The Wittig reagent is made by alkylation of the simplest ylid with the same silicon reagent. Notice that the leaving group (iodide) is on the carbon next to silicon, not on the silicon itself. Anion formation occurs next to phosphorus, because Ph_3P^+ is much more anion-stabilizing than Me_3Si. The ylid reacts with carbonyl compounds such as cyclohexanone in the usual way to produce the allyl silane with no ambiguity over which end of the allyl system is silylated.



Silicon exerts a surprisingly small steric effect

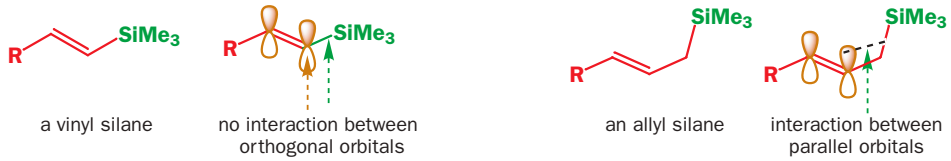
The Me_3Si group is, of course, large. But the C–Si bond is long and the Me_3Si group has a smaller steric effect than the Me_3C(*t*-butyl) group. For evidence, look at this last sequence: nucleophilic displacement at a carbon atom next to an Me_3Si group occurs normally whereas the infamous 'neopentyl' equivalent (see Chapter 17) reacts very slowly if at all. The Me_3Si group can get out of the way of the incoming nucleophile.



The carbon–silicon bond has two important effects on the adjacent alkene. The presence of a high-energy filled σ orbital of the correct symmetry to interact with the π system produces an alkene that is more reactive with electrophiles, due to the higher-energy HOMO, and the same σ orbital stabilizes the carbocation if attack occurs at the remote end of the alkene. This lowers the transition state for electrophilic addition and makes allyl silanes much more reactive than isolated alkenes.

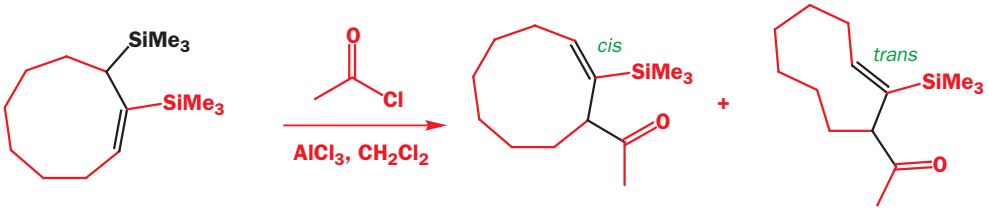
Allyl silanes are more reactive than vinyl silanes but also react through β-silyl cations

Vinyl silanes have C–Si bonds orthogonal to the p orbitals of the alkene—the C–Si bond is in the nodal plane of the π bond—so there can be no interaction between the C–Si bond and the π bond. Allyl silanes, by contrast, have C–Si bonds that can be, and normally are, parallel to the p orbitals of the π bond so that interaction is possible.

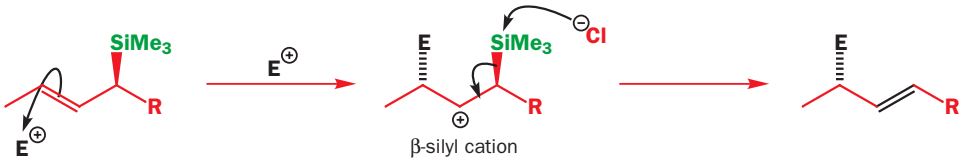


The evidence that such interaction does occur is that allyl silanes are more reactive than vinyl silanes as a result of the increased energy of the HOMO due to the interaction of the π bond with the C–Si bond. Conversely, vinyl silanes are thermodynamically more stable than the allyl isomers by

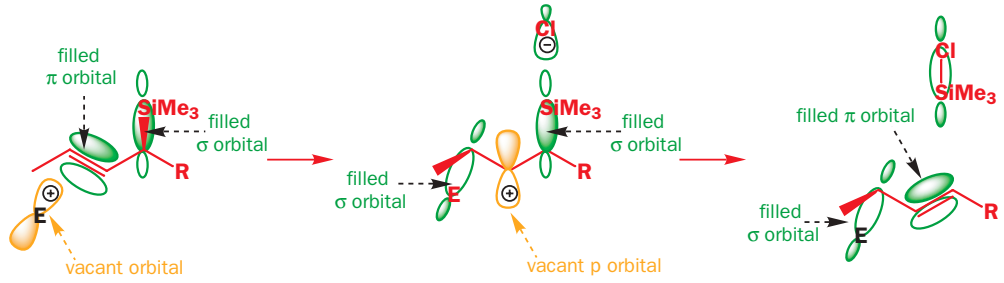
about 8 kJ mol^{-1}. This is evident from the acetylation of a compound having both vinyl silane and allyl silane functional groups. It reacts exclusively as an allyl silane, shown in black, with double bond migration to produce two double bond isomers (*cis* and *trans* cyclononenes) of the vinyl silane product. The vinylic silicon is not involved as the C–Si bond is orthogonal to the π system throughout.



Allyl silanes react with electrophiles with even greater regioselectivity than that of vinyl silanes. The cation β to the silyl group is again formed but there are two important differences. Most obviously, the electrophile attacks at the other end of the allylic system and there is no rotation necessary as the C–Si bond is already in a position to overlap efficiently with the intermediate cation. Electrophilic attack occurs on the face of the alkene *anti* to the silyl group. The process is terminated by loss of silicon in the usual way to regenerate an alkene.



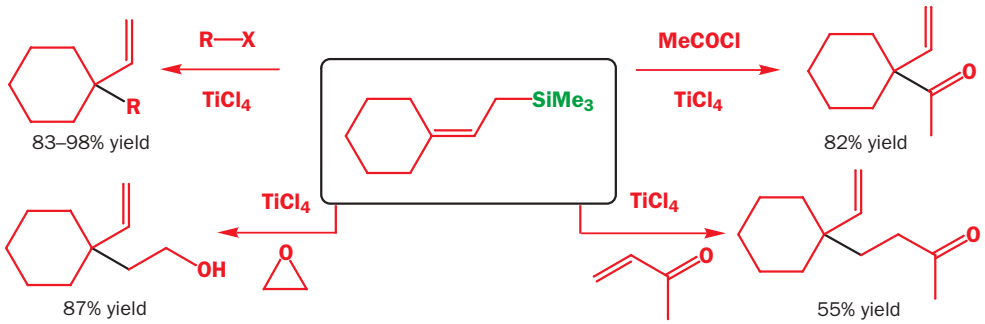
Molecular orbitals demonstrate the smooth transition from the allyl silane, which has a π bond and a C–Si σ bond, to the allylic product with a new π bond and a new σ bond to the electrophile. The intermediate cation is mainly stabilized by σ donation from the C–Si bond into the vacant p orbital but it has other σ-donating groups (C–H, C–C, and C–E) that also help. The overall process is electrophilic substitution with allylic rearrangement. Both the site of attachment of the electrophile and the position of the new double bond are dictated by the silicon.



Allyl silanes react with a wide variety of electrophiles, rather like the ones that react with silyl enol ethers, provided they are activated, usually by a Lewis acid. Titanium tetrachloride is widely used but other successful Lewis acids include boron trifluoride, aluminium chloride, and trimethylsilyl triflate. Electrophiles include the humble proton generated from acetic acid. The regiocontrol is complete. No reaction is observed at the other end of the allylic system. All our examples are on the allyl silane we prepared earlier in the chapter.

The first reaction is the general reaction with electrophiles and the second shows that even reaction with a proton occurs at the other end of the allyl system with movement of the double bond.

Other electrophiles include acylium ions produced from acid chlorides, carbocations from tertiary halides or secondary benzylic halides, activated enones, and epoxides all in the presence of Lewis acid. In each case the new bond is highlighted in black.



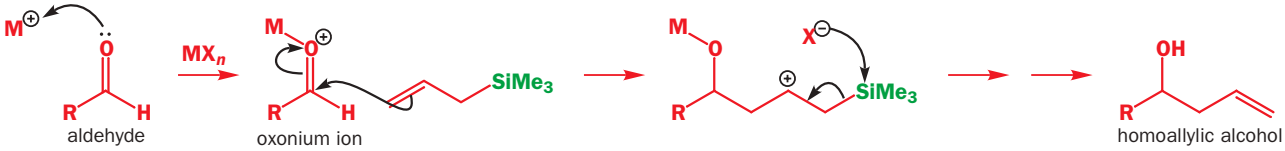
Heading

Vinyl and aryl silanes react with electrophiles at the same (*ipso* or α) atom occupied by silicon. Allyl silanes react at the end of the alkene furthest from silicon (γ). In both cases a β-silyl cation is an intermediate.

In enantiomerically pure systems one enantiomer of the allyl silane gives one enantiomer of the product. The stereogenic centre next to silicon disappears and a new one appears at the other end of the alkene. This is a consequence of the molecule reacting in a well defined conformation by a well defined mechanism. The conformation is controlled by allylic strain (Chapter 34) which compels the proton on the silyl-bearing stereogenic centre to eclipse the alkene in the reactive conformation and the electrophile attacks *anti* to silicon for both steric and stereoelectronic reasons. In these examples of Lewis-acid-promoted alkylation with a *t*-butyl group, *E*- and *Z*-isomers both react highly stereoselectively to give enantiomeric products. The reactions are completely stereospecific.

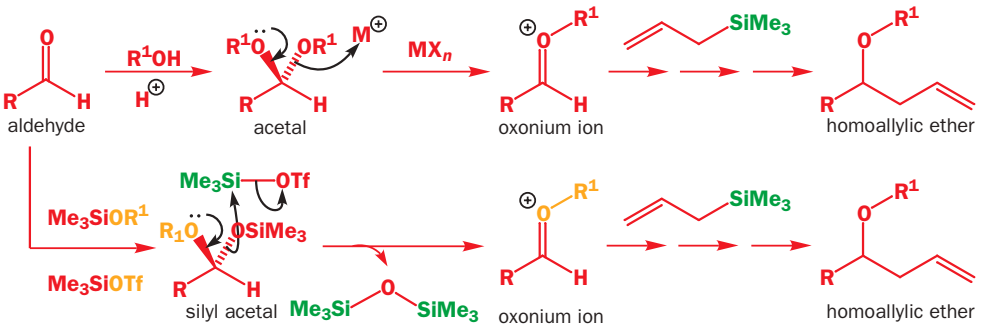
Lewis acids promote couplings via oxonium ions

Allyl silanes will also attack carbonyl compounds when they are activated by coordination of the carbonyl oxygen atom to a Lewis acid. The Lewis acid, usually a metal halide such as $TiCl_4$ or $ZnCl_2$, activates the carbonyl compound by forming an oxonium ion with a metal–oxygen bond. The allyl silane attacks in the usual way and the β-silyl cation is desilylated with the halide ion. Hydrolysis of the metal alkoxide gives a homoallylic alcohol.

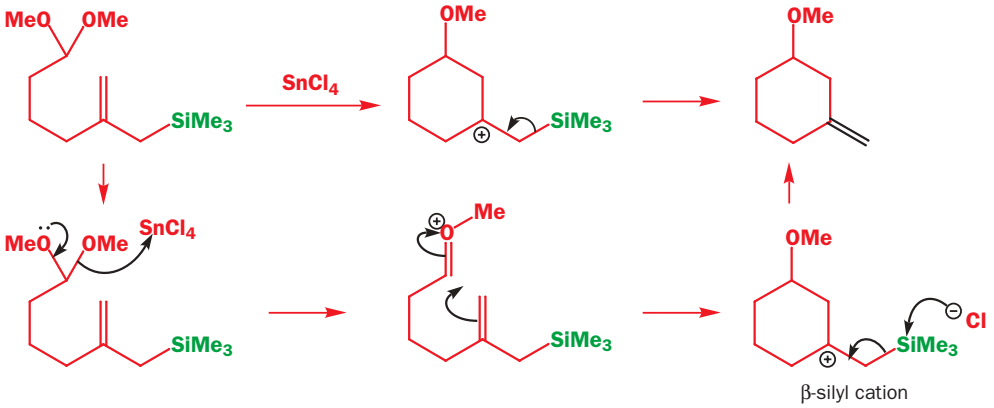


A closely related reactive oxonium ion can be prepared by Lewis-acid-catalysed breakdown of the corresponding acetal. Alternatively, especially if the acetal is at least partly a silyl acetal, the same oxonium ion can be produced *in situ* using yet more silicon in the form of TMSOTf as the Lewis acid catalyst. All these intermediate oxonium ions act as powerful electrophiles towards allyl silanes producing homoallylic alcohols or ethers.

▶ Note how the Me_3Si group mimics the behaviour of a proton even to the extent of producing $(Me_3Si)_2O$—the silicon analogue of water.

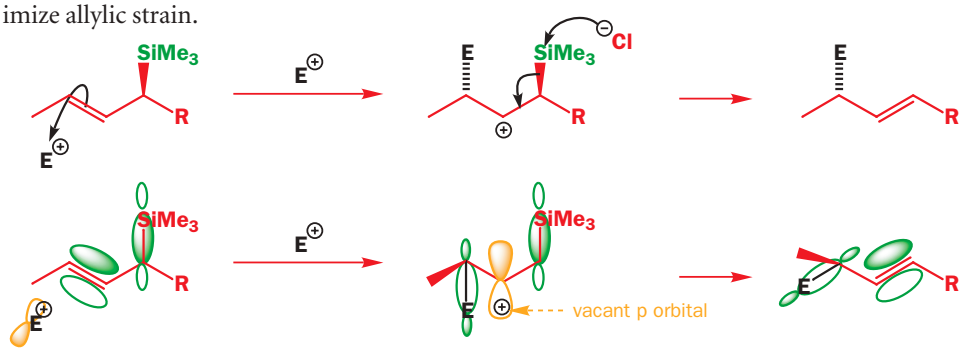


The regiocontrol that results from using an allyl silane to direct the final elimination is illustrated by this example of an intramolecular reaction on to an acetal promoted by tin tetrachloride. The same reaction can be run in the absence of silicon but the intermediate cation can then lose a range of protons to produce five different products!



Crotyl silanes are powerful reagents in stereoselective synthesis

Crotyl silanes offer the possibility of diastereoselectivity in reactions with aldehydes in the same way as the corresponding boranes. The mechanism is completely different because crotyl trialkylsilanes react via an open transition state as the silicon is not Lewis acidic enough to bind the carbonyl oxygen of the electrophile. Instead, the aldehyde has to be activated by an additional Lewis acid or by conversion into a reactive oxonium ion by one of the methods described above. The stereoelectronic demands of the allylic silane system contribute to the success of this transformation. Addition takes place in an S_E2' sense so that the electrophile is attached to the remote carbon on the opposite side of the π system to that originally occupied by silicon and the newly formed double bond is *trans* to minimize allylic strain.



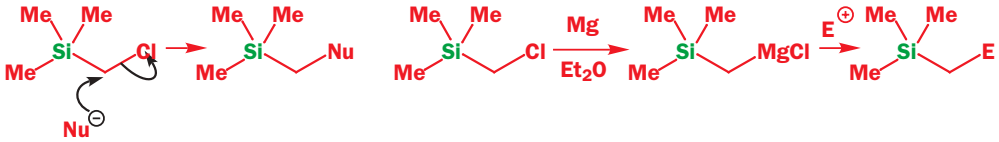
Radicals, anions, and S_N2 transition states stabilized by ailicon

In Chapter 31 we discussed the Peterson reaction, which uses carbanions next to silicon, and the reagent Me_3SiCH_2Cl was used to make a Grignard reagent for this reaction. In fact, the chloride can

be made directly from Me_4Si (tetramethylsilane used as a zero point in NMR spectra) by photochemical chlorination. A chlorine atom removes a hydrogen atom from one of the methyl groups to leave a primary radical next to silicon, which reacts in turn with a chlorine molecule, and the radical chain continues.

We might suspect that silicon stabilizes the intermediate carbon-centred radical as primary radicals are not usually stable, but we can prove nothing as there is no alternative. This chloride is a very useful reagent. It readily reacts by the S_N2 mechanism, in spite of the large Me_3Si group, which makes us suspect that silicon encourages the S_N2 reaction at neighbouring carbon. It also readily forms organometallic reagents such as Grignard reagents and lithium derivatives and these were used in the Peterson reaction. This makes us suspect that the Me_3Si group stabilizes anions. Can all this really be true?

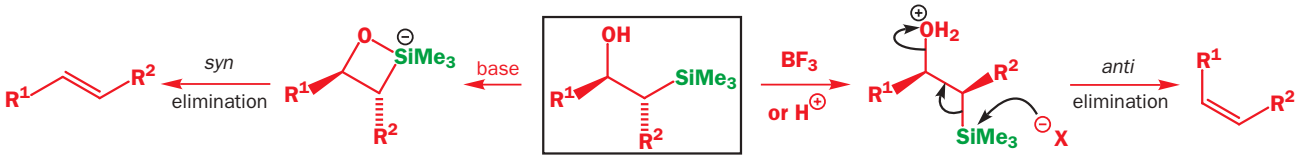
■ Radical reactions, radical chains, and the stability of radicals are discussed in Chapter 39.



It is all true. Evidence that a silyl group stabilizes the S_N2 transition state comes from the reactions of the epoxides of vinyl silanes. These compounds can be made stereospecifically with one equivalent of a buffered peroxy-acid such as *m*-CPBA. Epoxidation is as easy as the epoxidation of simple alkenes. You will see in a moment why acid must be avoided.

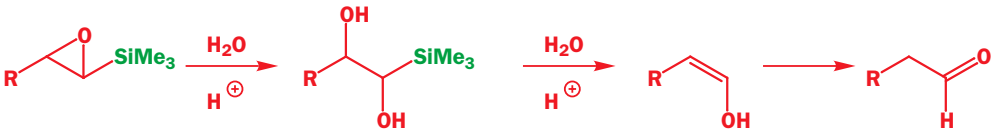
These epoxides react stereospecifically with nucleophiles to give single diastereoisomers of adducts. If a carbon nucleophile is used (cuprates are best), it is obvious from the structure of the products that nucleophilic attack has occurred at the end of the epoxide next to silicon. This is obviously an S_N2 reaction because it is stereospecific: in any case an S_N1 reaction would have occurred at the other end of the epoxide through the β-silyl cation.

When we discussed the Peterson reaction in Chapter 31, we explained that each diastereoisomer of a β-silyl alcohol can eliminate, depending on the reaction conditions, to give either geometrical isomer of the alkene but we did not explain how these diastereoisomers could be made. This is how they are made. Elimination in base is a Wittig-style *syn* process but an *anti* elimination occurs in acid. Here are the reactions on one of the diastereoisomers we have just made.



If the nucleophile is water—as it might be in the work-up of the original epoxidation in acid solution—the product is a diol, which eliminates by the *anti* mechanism in acid solution to give initially an enol and then, under the same conditions, a carbonyl compound. All these steps are often carried

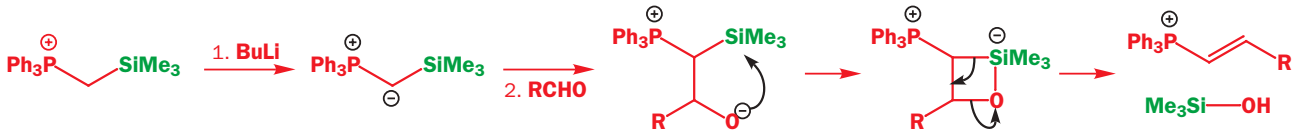
out in the one reaction to convert the epoxide to the carbonyl compound in one operation. Stereochemistry does not matter in this reaction.



Silicon-stabilized carbanions

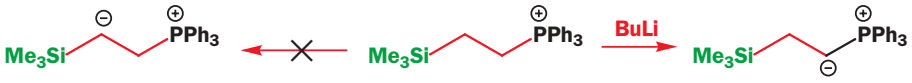
We are going to concentrate on the most important of these properties: silyl groups stabilize carbanions. We can show that this is true rather easily. Here are two reactions of carbanions with aldehydes.

The first reagent has a choice: it can do either the Wittig or the Peterson reaction; it prefers the Peterson reaction. This merely tells us that nucleophilic attack at silicon is faster than nucleophilic attack at phosphorus. The carbanion part of the ylid is next to silicon but it could be nowhere else.



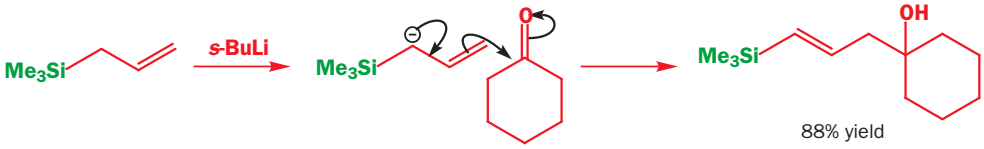
There is, however, a choice in the second reaction. There are six methyl groups on the two Me_3Si groups and one CH_2 between them. That makes eighteen methyl hydrogens and only two on the CH_2 group. Yet the base removes one of the two. It is better to have an anion stabilized by two silicon atoms. Silicon does stabilize a carbanion. There is, of course, no choice in the elimination step—O^- must attack one of the Me_3Si groups and the Peterson reaction must occur.

These reactions are also useful syntheses of vinyl phosphine oxides and of vinyl silanes. The stabilization of anions is weak—weaker than from phosphorus or sulfur—but still useful. The Wittig reagent used to make allyl silanes earlier in this chapter illustrates this point.



Si-stabilized carbanion phosphorus ylid

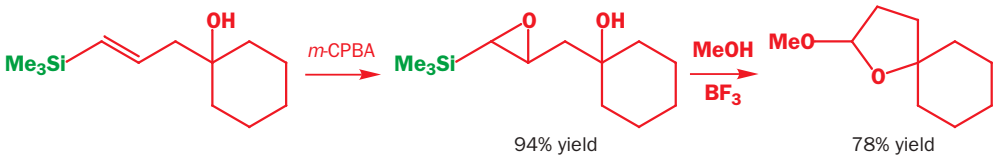
If you want to make an 'anion' stabilized by one Me_3Si group it is better to use an organolithium or organomagnesium compound made from a halide, the most important being the simplest as we have seen. But given just a little extra help—even an alkene—anions can be made with bases. So an allyl silane can give a lithium derivative (using *s*-BuLi as the very strong base) that reacts with electrophiles in the same position as do the allyl silanes themselves—the γ-position relative to the Me_3Si group. In this example the electrophile is a ketone and no Lewis acid is needed.



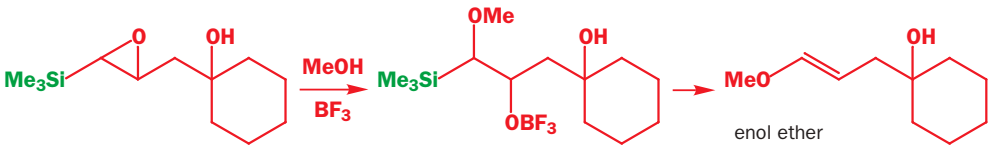
88% yield

The product is a vinyl silane as the Me_3Si group is retained in this reaction of the anion. The reaction is stereoselective in favour of the *E*-alkene as might be expected. The alkene can be epoxidized

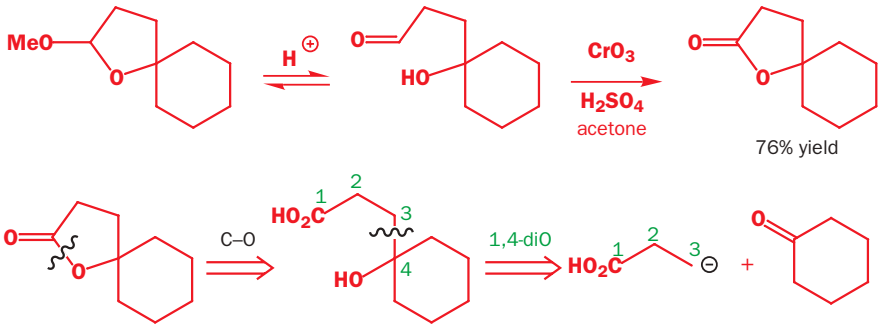
and the epoxide opened in the reaction we discussed earlier in the chapter. If methanol is used as the nucleophile with BF_3 as the Lewis acid, cyclic acetals are formed.



Nucleophilic attack occurs next to silicon and Peterson elimination gives an enol ether that cyclizes to the acetal under the acidic conditions.

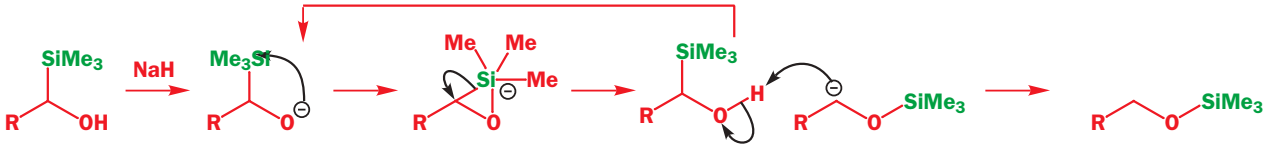


The cyclic acetal is a protected form of the hydroxy-aldehyde and oxidation under acidic conditions (CrO_3 in H_2SO_4) gives a good yield of the spirocyclic lactone. In the whole process from allyl silane to lactone, the allyl silane is behaving as a d^3 synthon or **homoenolate**.

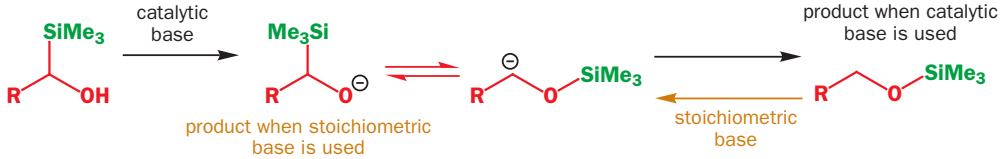


Migration of silicon from carbon to oxygen

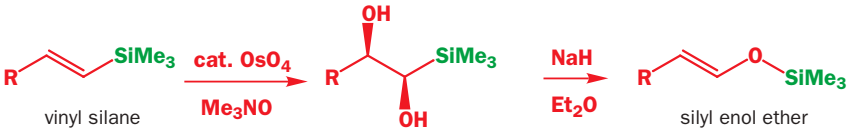
Much of silicon chemistry is dominated by the strong Si–O bond and this leads to some surprising reactions. When compounds with an OH and a silyl group on the same carbon atom are treated with a catalytic amount of base, the silyl group migrates from carbon to oxygen. That all sounds reasonable until you realize that it must go through a three-membered ring. It is, in effect, a nucleophilic substitution at silicon. The reaction is known as the **Brook rearrangement**.



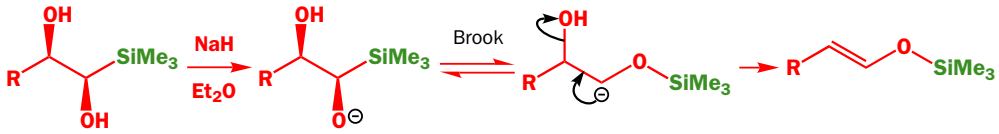
No such reaction could occur at a carbon centre (it would be impossible by Baldwin's rules; see Chapter 42), and the difference is that nucleophilic substitution at silicon goes through a pentacovalent intermediate so that a linear arrangement of nucleophile and leaving group is not required. The product anion is less stable than the oxyanion formed at the start of the reaction but removal of a proton from another molecule of starting material makes the product, with its Si–O bond, more stable than the starting material. The central reaction should really be shown as an equilibrium going to the right with catalytic base and to the left with a full equivalent of base.



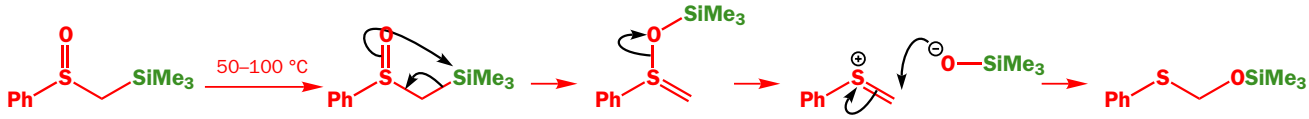
By itself, the Brook rearrangement is not very useful but, if the carbanion can do something else other than just get protonated, something useful may happen. We have seen what happens to the epoxides of vinyl silanes. Dihydroxylation of the same alkenes also gives interesting chemistry when the diols are treated with base.



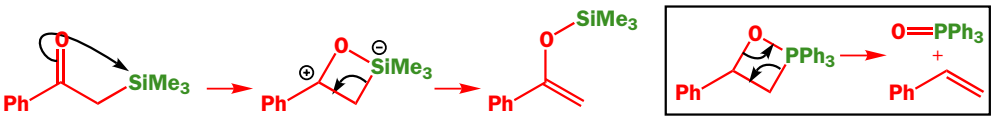
The overall reaction is the insertion of an oxygen atom between the silicon and the alkene and the product is a useful silyl enol ether (Chapter 21). The Brook rearrangement takes place first but the carbanion has a leaving group (OH) on the neighbouring carbon atom so an E1cB reaction (Chapter 19) occurs next.



It is remarkable that the other OH group does not lose a proton because a Peterson reaction could then follow. Perhaps the three-membered cyclic intermediate is formed more easily than the four-membered ring. This would be the case if carbon were the electrophilic atom. Rearrangements from carbon to oxygen through four-membered rings do occur: examples are the 'sila-Pummerer' rearrangement and the rather annoying tendency of α-silyl carbonyl compounds to rearrange to silyl enol ethers. The **sila-Pummerer rearrangement** is like the normal Pummerer rearrangement (discussed in Chapter 46) except that a silyl group rather than a proton migrates to oxygen.



We could no doubt find uses for α-silyl carbonyl compounds if they did not rearrange with C to O silyl migration simply on heating. The mechanism is similar to that of the sila-Pummerer rearrangement except that the nucleophile that attacks the silicon atom via a four-membered ring intermediate is carbonyl oxygen rather than sulfoxide oxygen. The intermediate might remind you of the intermediate in the Wittig reaction: a C–Si or C–P bond is sacrificed in both cases in favour of an Si–O or a P–O bond.



These last examples show that there is some similarity between silicon and sulfur or phosphorus. Now we shall see similarities with an element further down group IV—tin.

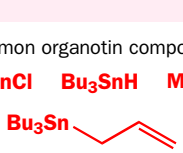
Organotin compounds

Tin is quite correctly regarded as a metal but in the +4 oxidation state it forms perfectly stable organic compounds, known as stannanes, many of which are available commercially. The tin atom is rather large, which means that it forms long covalent bonds that are easily polarized. The table of important bond lengths of the group IV (14) elements C, Si, and Sn shows that all bonds to carbon are shorter than the corresponding ones to silicon, which are in turn shorter and, as a result, stronger than those to tin.

▶ The symbol Sn for tin warns us that there are two sets of names for tin compounds. Stannanes and stannyl are often used but so are tin and, for example, tributyltin hydride. You will meet both and there is no particular significance as to which is chosen.

common organotin compounds

Bu_3SnCl Bu_3SnH Me_4Sn

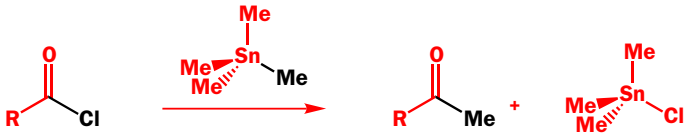


Organotin chemistry exploits the weakness of C–Sn bonds to deliver whatever is attached to the tin to another reagent. You have already seen (Chapter 39) tributyltin hydride used as a radical reducing agent because of the ease with which the Sn–H bond can be broken. Carbon substituents can be transferred by a radical mechanism too but organotins transfer the organic group intact by polar mechanisms as well. This reactivity is closest to that of a conventional organometallic reagent but the organotins are stable distillable liquids that can be stored unlike Grignard reagents. You may be concerned about the fact that there are four substituents on the central tin atom and, in principle, all of them could be transferred. In practice, alkyl groups transfer only very slowly indeed so that the tributylstannyl group (Bu_3Sn–), the most popular tin-based functional group, is generally transferred intact during reactions. The exception to this is tetramethyltin which has only methyl groups and therefore must transfer one of them. Methyl ketones may be made from tetramethyltin and acid chlorides. Contrast this with the inert NMR reference tetramethyl silane!

Bonds to carbon, silicon, and tin compared

	Bond length, nm					
X	C–X	H–X	Cl–X	O–X	S–X	Sn–X
C	0.153	0.109	0.178	0.141	0.180	0.22
Si	0.189	0.148	0.205	0.163	0.214	
Sn	0.22	0.17	0.24	0.21	0.24	0.28

▶ Tin compounds are often volatile and are usually toxic, so beware! They were very effective in 'antifouling' paints for boats but they killed too many marine creatures and are now banned.

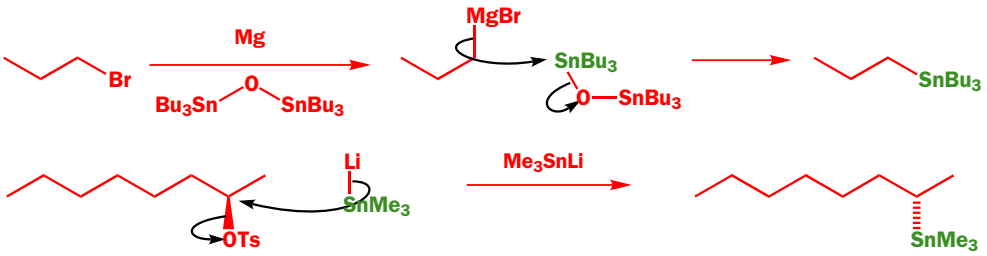


Organotin compounds are like reactive organosilicons

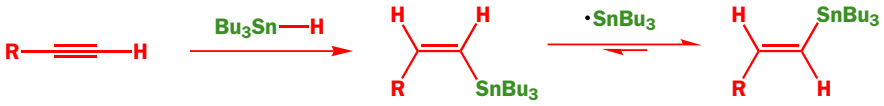
Organotin chemistry is useful because the familiar patterns of organosilicon chemistry are followed but the reactions proceed more easily because the bonds to tin are weaker and tin is more electropositive than silicon. Thus vinyl, allyl, and aryl stannanes react with electrophiles in exactly the same manner as their silicon counterparts but at a faster rate.

● Organostannanes are more reactive than organosilanes and use the same mechanisms.

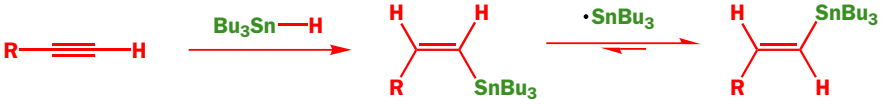
The preparation of organostannanes is also similar to that of organosilanes. Organometallic reagents react with organotin electrophiles such as the trialkyl halides or bis(tributyltin) oxide. This is one method for the preparation of alkyl tributyltin using allyl Grignard and bis(tributyltin) oxide. Alternatively, the polarity can be reversed and a stannyl lithium, generated by deprotonation of the hydride or reductive cleavage of Me_3Sn–$SnMe_3$ with lithium metal, will add to organic electrophiles such as alkyl halides and conjugate acceptors. The first reaction is S_N2 at tin (probably with a 5-valent tin anion as intermediate) and the second is S_N2 at carbon.



Direct hydrostannylation of an alkyne with a tin hydride can be radical-initiated in the way we saw in Chapter 39. The product of kinetic control is the *Z*-isomer but, if there is excess tin hydride or enough radicals are present, isomerization into the more stable *E*-isomer occurs. The regiocontrol of this process is good with terminal alkynes.

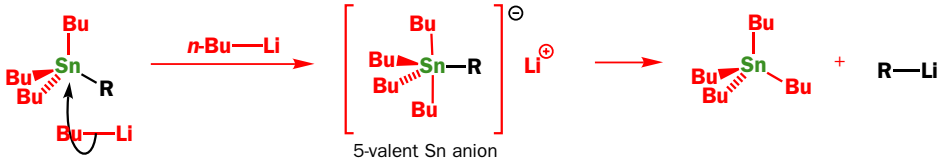


Addition of a tributyltin radical to the alkyne gives the more substituted linear (sp) vinyl radical (see Chapter 39). Addition of a hydrogen atom from another molecule of Bu_3SnH occurs preferentially from the less hindered side (the Bu_3Sn group already in the molecule is in the plane of the p orbital containing the unpaired electron) to give the *Z*-vinyl stannane. If there is more Bu_3SnH around, reversible addition of Bu_3Sn• radicals to either end of the vinyl stannane equilibrates it to the more stable *E*-isomer.



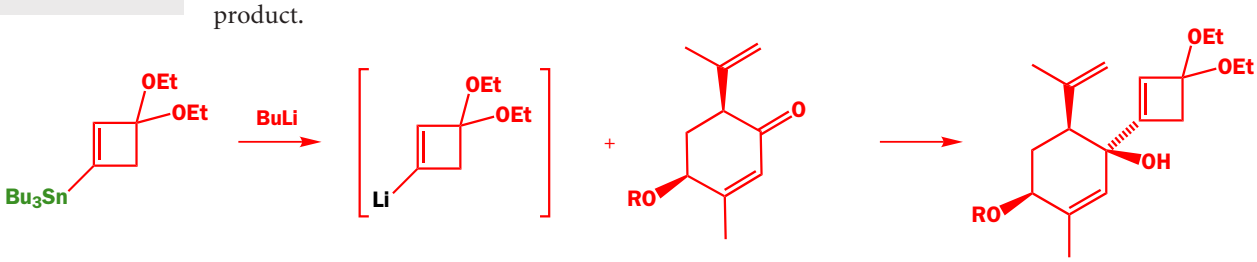
Tin–lithium exchange is rapid

Organotin compounds are usually simply not reactive enough to be useful nucleophiles. Conversion into the corresponding organolithiums provides a much more reactive reagent. This is achieved in the same way as lithium–halogen exchange described in Chapter 9 and has essentially the same mechanism. The principle is simple. A very reactive nucleophile such as butyl lithium reacts at the tin and expels an organolithium species. The process is thermodynamically controlled, so the more stable the organolithium, the more likely it is to form. By having three of the groups on tin as butyl and adding another butyl from the organolithium, the choice is between the re-formation of butyl lithium or creation of an organolithium from the fourth substituent. If this is a vinyl, allyl, aryl, or alkynyl group this emerges as the most stable organolithium and is produced without any lithium halide present. The by-product is tetrabutyltin which is nonpolar and unreactive and can usually be separated by chromatography from the product of the reaction.



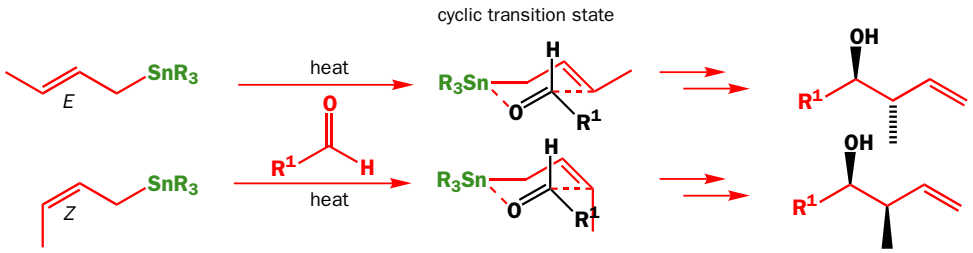
See Chapters 10 and 23 for a discussion of direct versus conjugate addition.

Such a tin–lithium exchange was the key to the preparation of a functionalized vinyl organolithium that was coupled to an enone in a synthesis of a natural product. Direct addition of the cyclobutenyllithium to the less hindered face of the carbonyl group gave one diastereoisomer of the product.



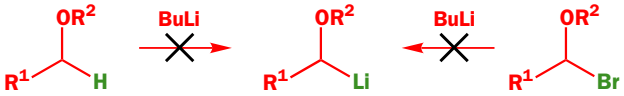
Crotyl stannanes react with good stereochemical control

Crotyl stannanes are important reagents in organic synthesis because they can be prepared with control over the double bond geometry and will tolerate the presence of additional functional groups. This allows stereoselective synthesis of functionalized acyclic molecules. The control arises from the well-defined transition states for the crotylation reaction. Tin is more electropositive than silicon and can accept a lone pair of electrons in a purely thermal reaction with no added Lewis acid. The carbonyl group of the aldehyde can coordinate to the tin and lead, through a cyclic transition state, to give *anti* products from *E*-crotyl tin reagents and *syn* products from the *Z*-crotyl isomer.



Tin–lithium exchange in action

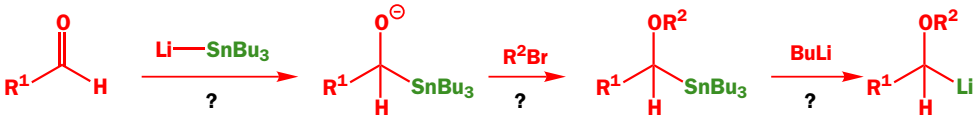
Many organolithium compounds are useful reagents and no doubt many more would be if only they could be made. Tin chemistry allows us to make organolithium compounds that cannot be made by direct lithiation. An excellent example is a lithium derivative with an oxygen atom on the same carbon. The hydrogen atom is not particularly acidic and cannot be removed by BuLi, while the bromide is unstable and will not survive treatment with BuLi.



Heading

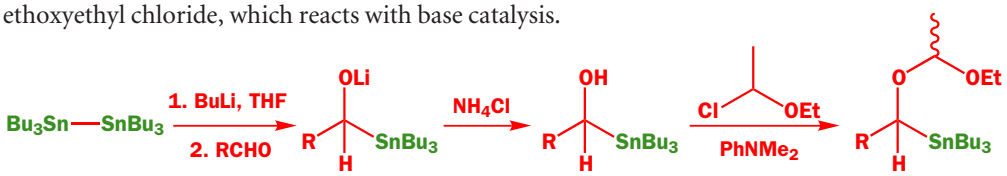
- Tin/lithium exchange occurs rapidly and stereospecifically with BuLi
- Other elements that can be replaced by Li: RX + BuLi gives RLi when X = SnR_3, Br, I, SeR

However, the problem should be easily solved with tin chemistry. The idea is to add a tributyltin lithium reagent to the aldehyde, mask the alkoxide formed, and then exchange the tributyl tin group for lithium.



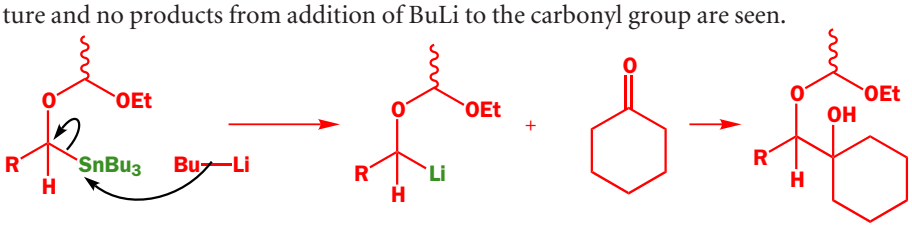
First, the Bu_3Sn–Li reagent has to be made. This can be done in two ways. Treatment of any tin compound with BuLi results in nucleophilic attack at tin but LDA is much less nucleophilic and can be used to remove a proton from tributyltin hydride. Otherwise, we can accept that BuLi will always attack tin and provide two tin atoms so that nucleophilic attack on one expels the other as the lithium derivative.

These THF solutions of Bu_3Sn–Li are stable only at low temperatures so the aldehyde must be added immediately. The lithium alkoxide adduct can be neutralized and the alcohol isolated but it is also unstable and must be quenched immediately with an alkyl halide. The preferred one is ethoxyethyl chloride, which reacts with base catalysis.



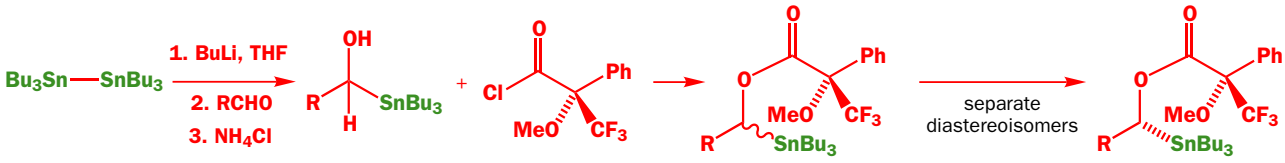
These protected hydroxystannanes are stable compounds and can even be distilled. Treatment with BuLi and an electrophile such as an aldehyde or ketone gives the product from addition of the

organolithium derivative to the carbonyl group. Tin–lithium exchange is rapid even at low temperature and no products from addition of BuLi to the carbonyl group are seen.

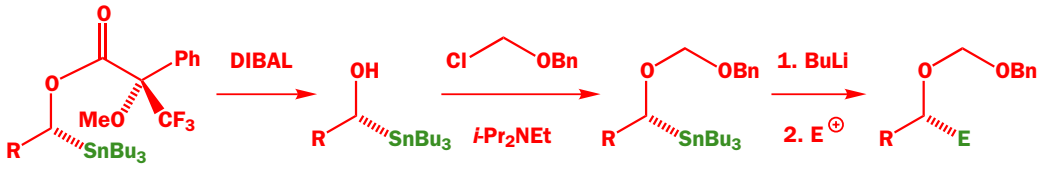


■ You may recognize this acid as 'Mosher's acid' which we introduced in Chapter 32 as a way of determining enantiomeric excess by NMR.

The most surprising thing about these reagents, invented and exploited by W. Clark Still at Columbia University, is that they can be prepared in stable enantiomerically pure forms and that the stereochemistry is preserved through exchange with lithium and reaction with electrophiles. It is very unusual for organolithium compounds to be configurationally stable. Still first quenched the Bu_3SnLi adducts with one enantiomer of an acid chloride and resolved by separating the diastereoisomers.



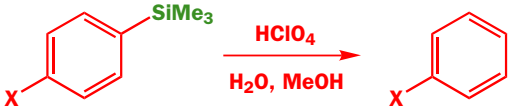
The ester was cleaved by reduction with DIBAL (*i*-Bu_2AlH) and an achiral version of the normal protecting group put in place. It would obviously be silly to create unnecessary diastereomeric mixtures in these reactions. Then the tin could be exchanged first with lithium and then with an electrophile, even an alkyl halide, with retention of configuration and without loss of enantiomeric purity. The intermediate organolithium compound must have had a stable configuration.



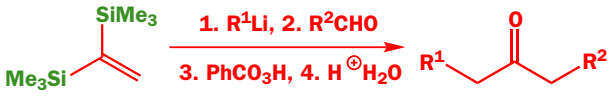
The exchange of tin for lithium or other metals is probably the most valuable job it does. Reagents such as BuLi attack tin or boron directly rather than removing a proton. Silicon is not usually attacked in this way and proton removal is more common. In the next chapter we shall see how transition metals open up a treasure chest of more exotic reactions for which the reactions in this chapter are a preparation.

Problems

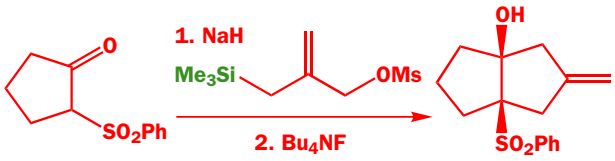
1. The Hammett ρ value for the following reaction is –4.8. Explain this in terms of a mechanism. If the reaction were carried out in deuterated solvent, would the rate change and would there be any deuterium incorporation into the product? What is the silicon-containing product?



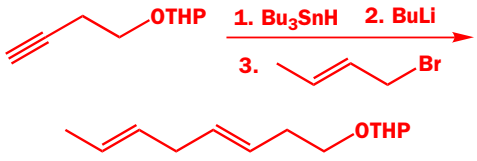
2. Identify the intermediates in this reaction sequence and draw mechanisms for the reactions, explaining the special role of the Me_3Si group.



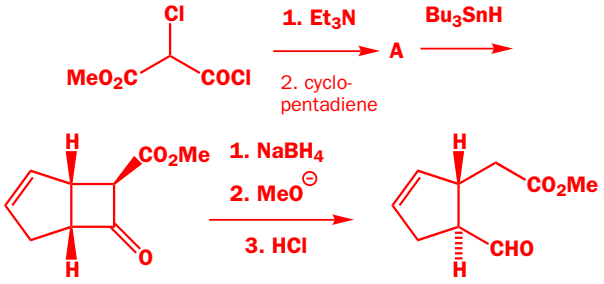
3. The synthesis of a compound used in a problem in Chapter 38 (fragmentation) is given below. Give mechanisms for the reactions explaining the role of silicon.



4. Give mechanisms for the following reactions, drawing structures for all the intermediates including stereochemistry. How would the reaction with Bu_3SnH have to be done?

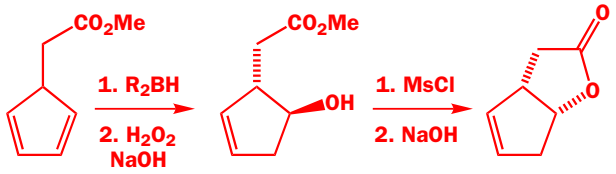


5. Explain the following reactions. In particular, explain the role of tin and why it is necessary and discuss the stereochemistry.

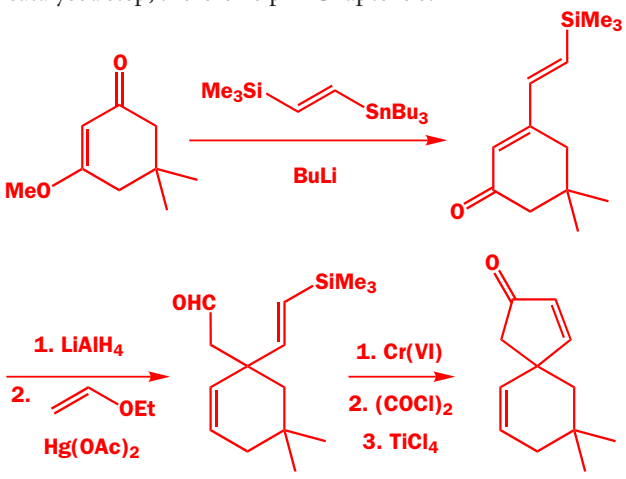


6. Explain the stereochemistry and mechanism of this hydroboration–carbonylation sequence.

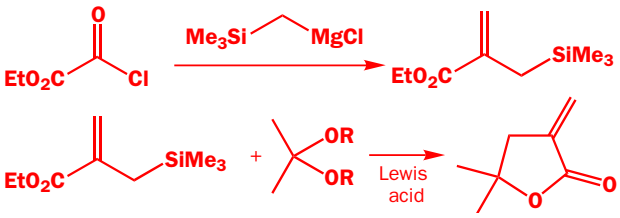
7. Give mechanisms for these reactions explaining: (a) the regio- and stereoselectivity of the hydroboration; (b) why such an odd method was used to close the lactone ring.



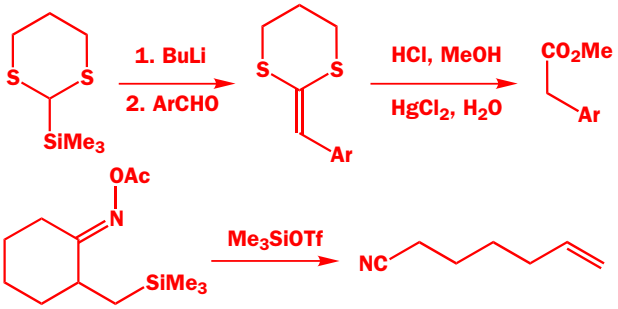
8. Revision content. Give mechanisms for these reactions, commenting on the role of silicon and the stereochemistry of the cyclization. The $LiAlH_4$ simply reduces the ketone to the corresponding alcohol. If you have trouble with the Hg(II)-catalysed step, there is help in Chapter 36.



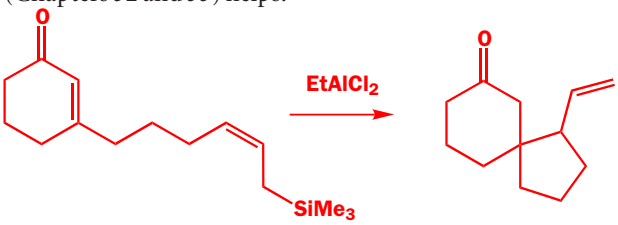
9. Give mechanisms for these reactions, explaining the role of silicon. Why is this type of lactone difficult to make by ordinary acid- or base-catalysed reactions?



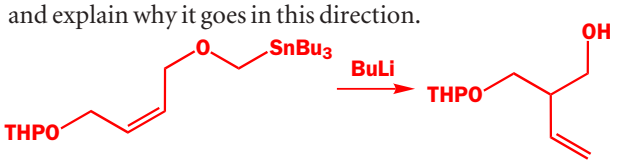
10. Revision of Chapters 38 and 46. How would you prepare the starting material for these reactions? Give mechanisms for the various steps. Why are these sequences useful?



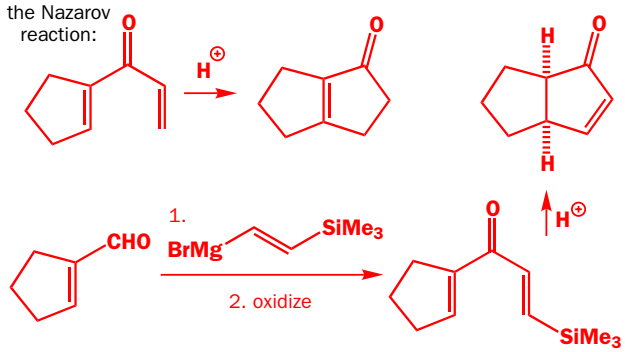
11. How would you carry out the first step in this sequence? Give a mechanism for the second step and suggest an explanation for the stereochemistry. You may find that a Newman projection (Chapters 32 and 33) helps.



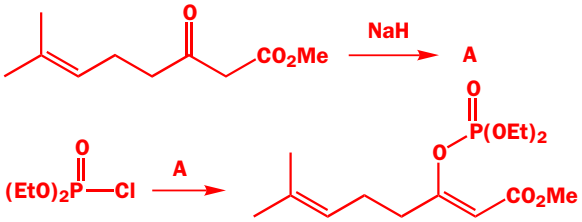
12. Revision of Chapter 36. Give a mechanism for this reaction and explain why it goes in this direction.



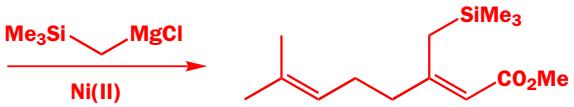
13. The Nazarov cyclization (Chapter 36) normally gives a cyclopentenone with the alkene in the more substituted position. That can be altered by the following sequence. Give a mechanism for the reaction and explain why the silicon makes all the difference.



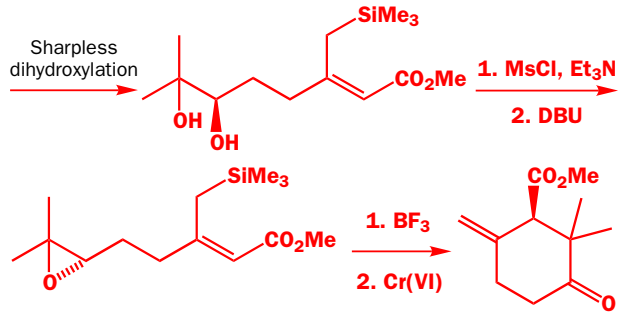
14. This is rather a long problem but it gives you the chance to see an advanced piece of chemistry involving several elements—P, Si, Sn, Mg, B, Ni, Cr, Os, and Li—and it revises material from Chapters 23, 33, and 45 at least. It starts with the synthesis of this phosphorus compound: what is the mechanism and selectivity?



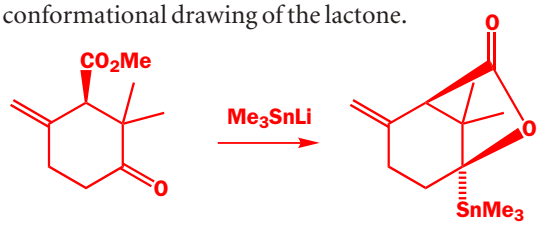
Next, reaction with a silicon-substituted Grignard reagent in the presence of Ni(II) gives an allyl silane. What kind of reaction is this, what was the role of phosphorus, and why was a metal other than sodium added? (You know nothing specific about Ni as yet but you should see the comparison with another metal. Consult Chapter 23 if you need help.)



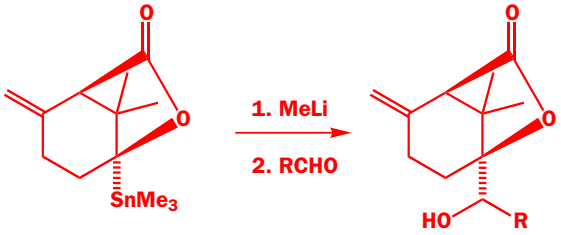
Asymmetric dihydroxylation (Chapter 45) is straightforward though you might like to comment on the chemoselectivity. The diol is converted into the epoxide and you should explain the regio- and chemoselectivity of this step. The next step is perhaps the most interesting: what is the mechanism of the cyclization, what is the role of silicon, and how is the stereochemistry controlled?



Reaction of this ketone with a stannyl-lithium reagent gives one diastereoisomer of a bridged lactone. Again, give a mechanism for this step and explain the stereochemistry. Make a good conformational drawing of the lactone.



Treatment of the tin compound with MeLi and a complex aldehyde represented as RCHO gave an adduct that was used in the synthesis of some compounds related to Taxol. What is the mechanism of the reaction, and why is tin necessary?



Organometallic chemistry

48

Connections

Building on:

- Conjugate addition ch10 & ch23
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- S_N2 and S_N2' ch23
- Oxidation and reduction ch24
- Cycloadditions ch35
- Rearrangements ch36–ch37
- Radicals and carbenes ch39–ch40
- Aromatic heterocycles ch43–ch44
- Asymmetric synthesis ch45
- Chemistry of B, Si, and Sn ch47

Arriving at:

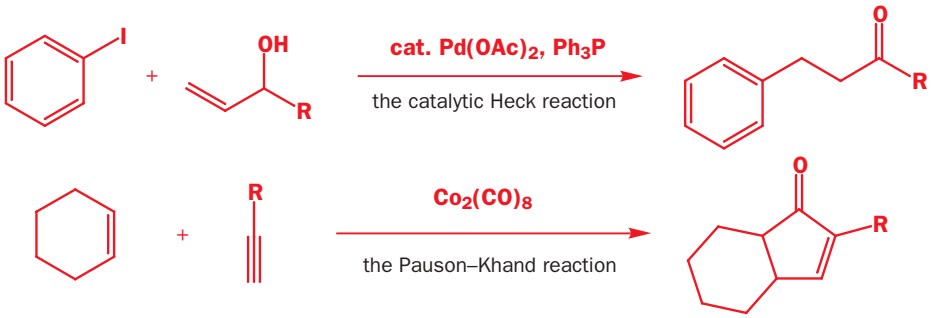
- Transition metals form organic compounds
- There are σ- and π-complexes given 'η' numbers
- The bonding is described with the usual orbitals
- Most stable complexes have 18 valency electrons
- Metals catalyse 'impossible' reactions
- Oxidative insertion, reductive elimination, and ligand migration from metal to carbon are key steps
- Carbon monoxide inserts into metal–carbon bonds
- Palladium is the most important metal
- C–C, C–O, and C–N bonds can be made with Pd catalysis
- Cross-coupling of two ligands is common
- Allyl cation complexes are useful electrophiles

Looking forward to:

- The chemistry of life, especially nucleic acids ch49
- Steroids ch51
- Polymerization ch52

Transition metals extend the range of organic reactions

Some of the most exciting reactions in organic chemistry are based on transition metals. How about these two for example? The first is the **Heck reaction**, which allows nucleophilic addition to an unactivated alkene. Catalytic palladium (Pd) is needed to make the reaction go. The second, the **Pauson–Khand reaction**, is a special method of making five-membered rings from three components: an alkene, an alkyne, and carbon monoxide (CO). It requires cobalt (Co). Neither of these reactions is possible without the metal.



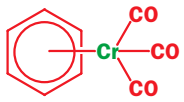
Reagents and complexes containing transition metals are important in modern organic synthesis because they allow apparently impossible reactions to occur easily. This chemistry com-

plements traditional functional-group-based chemistry and significantly broadens the scope of organic chemistry. This chapter introduces the concepts of metal–ligand interaction, describes the most important reactions that can occur while ligands are bound to the metal, and demonstrates the power of organometallic chemistry in synthesis. Many industries now use transition-metal-catalysed reactions routinely so it is important that you have a basic grounding in what they do.

There is a contradiction in what is required of a metal complex for useful synthetic behaviour. Initially, it is useful to have a stable complex that will have a significant lifetime enabling study and, ideally, storage but, once in the reaction vessel, stability is actually a disadvantage as it implies slow reactivity. An ideal catalyst is a complex that is stable in the resting state, for storage, but quickly becomes activated in solution, perhaps by loss of a ligand, allowing interaction with the substrate. Fortunately, there is a simple guide to the stability of transition metal complexes. If a complex satisfies the 18-electron rule for a stable metal complex it means that the metal at the centre of the complex has the noble gas configuration of 18 electrons in the valence shells. The total of 18 is achieved by combining the electrons that the metal already possesses with those donated by the coordinating ligands. The requirement for 18 electrons comes from the need to fill one 's' orbital, five 'd' orbitals, and three 'p' orbitals with two electrons in each. This table gives you the number of valence electrons each metal starts with before it has acquired any ligands. Notice that the 'new' group numbers 1–18 give you the answer without any calculation. The most important are highlighted.

Group	**IVB (4)**	**VB (5)**	**VIB (6)**	**VIIB (7)**	**VIIIB (8, 9, and 10)**			**1A (11)**
Number of valence electrons	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
3d	**Ti**	V	**Cr**	**Mn**	**Fe**	**Co**	**Ni**	**Cu**
4d	**Zr**	Nb	**Mo**	Tc	**Ru**	**Rh**	**Pd**	Ag
5d	Hf	Ta	**W**	Re	**Os**	Ir	**Pt**	Au

Metals to the left-hand side of this list obviously need many more electrons to make up the magic 18. Chromium, for example, forms stable complexes with a benzene ring, giving it six electrons, and three molecules of carbon monoxide, giving it two each: 6 + 6 + 2 + 2 + 2 = 18. Palladium is happy with just four triphenylphosphines (Ph_3P:) giving it two each: 10 + 2 + 2 + 2 + 2 = 18.



You may already know from your inorganic studies that there are exceptions to the 18-electron rule including complexes of Ti, Zr, Ni, Pd, and Pt, which all form stable 16-electron complexes. An important 16-electron Pd(II) complex with two chlorides and two acetonitriles (MeCN) as ligands appears in the margin. The so-called platinum metals Ni, Pd, and Pt are extremely important in catalytic processes, as you will see later on. The stable 16-electron configuration results from a high-energy vacant orbital caused by the complex adopting a square planar geometry. The benefit of this vacant orbital is that it is a site for other ligands in catalytic reactions.

a 16-electron Pd(II) complex

Ligands can be attached in many different ways

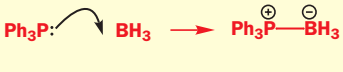
Transition metals can have a number of ligands attached to them and each ligand can be attached in more than one place. This affects the reactivity of the ligand and the metal because each additional point of attachment means the donation of more electrons. We usually show the number of atoms involved in bonding to the metal by the **hapto number** η. A simple Grignard reagent is η^1 (pronounced 'eta-one') as the magnesium is attached only to one carbon atom. A metal–alkene complex is η^2 because both carbon atoms of the alkene are equally involved in bonding to the metal. In these cases the η designation is not very useful as there are no alternatives and it is usually omitted.

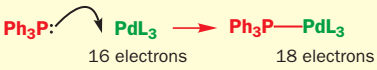
η^1


η^2

Representing bonds in transition metal complexes

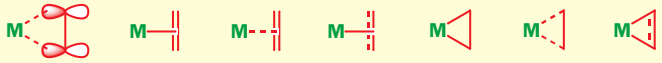
It is difficult to know exactly how to draw the bonding in metal complexes and there are often several different acceptable representations. There is no problem when the metal forms a σ bond to atoms such as Cl or C as the simple line we normally use for covalent bonds means exactly what it says. The problems arise with ligands that form σ bonds by donating both their electrons and with π complexes. Everyone writes phosphine–boron compounds with two charges but we normally draw the same sort of bond between a phosphine and, say, Pd as a simple line with no charges.



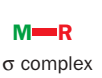


You will sometimes see π complexes drawn with simpler dotted lines going to the middle of the π bond, sometimes with dotted π bonds, and sometimes with bonds (simple or dotted) going to the ends of the old π bond. These are all acceptable as the bonding is complex as you will see. We might almost say that the ambiguity is helpful: we often don't know either the exact nature of the bonding or the number of other ligands in the complex. In the diagrams in this section we have shown the main bond from metal to ligand as a heavy line in the simplest representation but we also offer alternatives with simple and dotted bonds. Don't worry about this—things should become clearer as the chapter develops. When you have to draw the structure of a complex but you don't know the exact bonding, just draw a line from metal to ligand.

different acceptable ways to draw π complexes



The bonding in these two complexes is very different. In the first there is a simple σ bond between the metal and the alkyl group as in a Grignard reagent R–MgBr and this type of complex is called a **σ complex**. In the alkene complex, bonding is to the p orbitals only. There are no σ bonds to the metal, which sits in the middle of the π bond in between the two p orbitals. This type of complex is called a **π complex**.



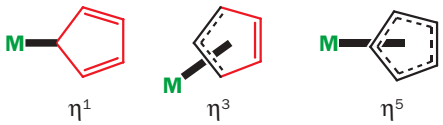
σ complex

π complex

These labels are useful where there is a choice of type of bonding as with allylic ligands. The metal can either form a σ bond to a single carbon (hence η^1), or form a π complex with the p orbitals of all three carbons of the allyl system and this would be η^3. If the π complex is made from an allyl cation, the ligand has two electrons, but it has four if it is made from an allyl anion.

η^1 σ allyl
η^3 π allyl
allyl cation complex
allyl anion complex

Similarly, cyclopentadienyl anion can act as a σ ligand (η^1), an allyl ligand (η^3), or, most usually, as a cyclopentadienyl ligand (η^5). The distinction is very important for electron counting as these three different situations contribute 2, 4, or 6 electrons, respectively, to the complex.



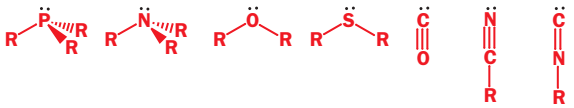
η^1 σ complex
η^3 π complex
η^5 π complex

Neutral ligands can also bond in a variety of ways. Cyclooctatetraene can act as an alkene (η^2), a diene (η^4), a triene (η^6), or a tetraene (η^8), and the reactivity of the ligand changes accordingly. These are all π complexes with the metal above or below the black portion of the ring and with the thick bond to the metal at right angles to the alkene plane.

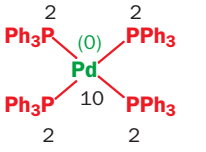
η^2 η^4 η^6 η^8

To determine the number of electrons around the transition metal in a complex the valence electrons from the metal ion are added to those contributed by all the ligands. The numbers of electrons donated by various classes of ligands are summarized in the table. Anions such as halides, cyanide, alkoxide, hydride, and alkyl donate two electrons, as do neutral ligands with a lone pair such as phosphines, amines, ethers, sulfides, carbon monoxide, nitriles, and isonitriles. Unsaturated ligands can contribute as many as eight electrons and can be neutral or negatively charged. If the overall total is eighteen, then the complex is likely to be stable.

Ligand characteristics

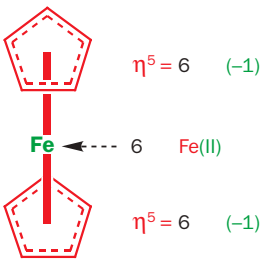
	Formal charge	Electrons donated
anionic ligands		
	–1	2
neutral σ-donor ligands		
	0	2

	Hapto number	Formal charge	Electrons donated
unsaturated σ- or π-donor ligands			
aryl, σ-allyl	η^1	–1	2
olefins	η^2	0	2
π-allyl cation	η^3	+1	2
π-allyl anion	η^3	–1	4
diene—conjugated	η^4	0	4
dienyls, cyclopentadienyls (anions)	η^5	–1	6
arenes, trienes	η^6	0	6
trienyls, cycloheptatrienyls (anions)	η^7	–1	8
cyclooctatetraene	η^8	0	8
carbene, nitrene, oxo	η^1	0	2

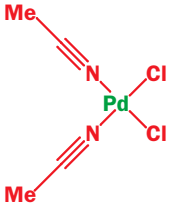


total: 4 x 2e + 10e = 18e

▶ Note that $(Ph_3P)_4Pd$ is a stable complex and is not a useful catalyst until at least one of the ligands is lost.



total: 3 x 6e = 18e



a Pd(II) complex

Electron counting helps to explain the stability of metal complexes

Counting electrons in most complexes is simple if you use the table of ligand characteristics above and the table on p. 000. Tetrakistriphenylphosphine palladium(0) is an important catalyst as you will see later in the chapter. Each neutral phosphine donates two electrons making a total of eight and palladium still has its full complement of ten valence electrons as it is in the zero oxidation state. Overall, the complex has a total of eighteen electrons and is a stable complex. In the diagrams that follow, the formal charges are highlighted in green and the numbers of electrons contributed shown in black.

All of the different classes of ligands listed in the table can be treated in this way. The cyclopentadienyl ligands contribute six electrons each and have a formal negative charge, shown in green, which means that the iron in ferrocene is in the +II oxidation state and will have six valence electrons left. The total for the complex is again eighteen and ferrocene is an extremely stable complex.

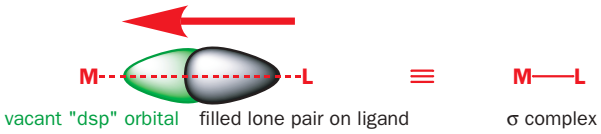
The oxidation state of metals in complexes

As well as the problem of bond drawing, there is a potential problem over oxidation states too. You can either say that ferrocene is a complex of Fe(II), having two fewer electrons than the normal eight, with two cyclopentadienyl anions contributing six electrons each, or you can say that it is a complex of Fe(0), having eight electrons, with two cyclopentadienyl ligands each contributing five electrons. The simplest approach is to say that a metal is in the (0) oxidation state unless it has σ bonds to ligands such as Cl, AcO, or Me that form bonds with shared electrons. You do not count neutral ligands such as Ph_3P that provide two of their own electrons. Grignard reagents RMgBr have two ligands that share electrons (R and Br) and a number of others, probably two ethers, that donate both their electrons. Magnesium is in the +2 oxidation state.

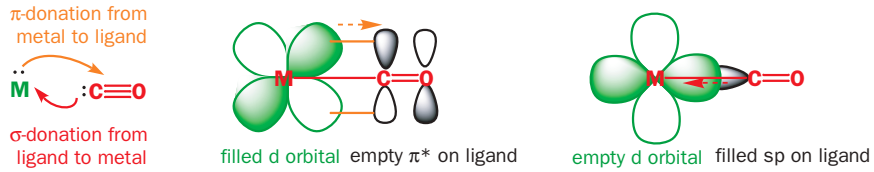
The useful complex $(MeCN)_2PdCl_2$ has palladium in the +2 oxidation state because of its two chlorine atoms and the number of electrons is 8 for the Pd(II) oxidation state and another two each from the four ligands making 16 in all. This complex does not fulfil the 18-electron rule and is reactive. You would have got the same answer if you had counted ten for the palladium, two each for the nitriles, and one each for the chlorines, but this is not so realistic.

Transition metal complexes exhibit special bonding

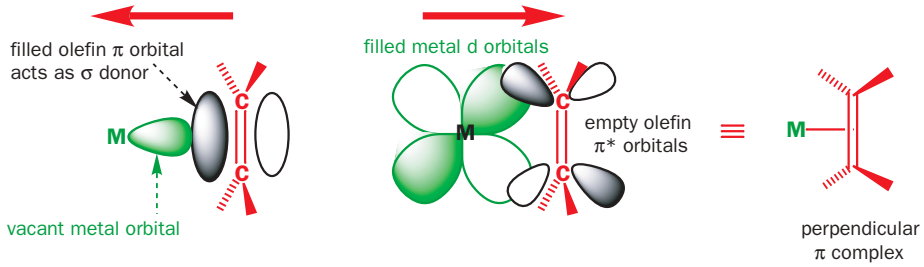
The majority of ligands have a lone pair of electrons in a filled sp^n type orbital that can overlap with a vacant metal 'dsp' orbital, derived from the vacant d, p, and s orbitals of the metal, to form a conventional two-electron two-centre σ bond. Ligands of this type increase the electron density on the central metal atom. This is the sort of bond that used to be called 'dative covalent' and represented by an arrow. Nowadays it is more common to represent all bonding to metals of whatever kind by simple lines.



A bonding interaction is also possible between any filled d orbitals on the metal and vacant ligand orbitals of appropriate symmetry such as π* orbitals. This leads to a reduction of electron density on the metal and is known as **back-bonding**. An example would be a complex with carbon monoxide. Many metals form these complexes and they are known as **metal carbonyls**. The ligand (CO) donates the lone pair on carbon into an empty orbital on the metal while the metal donates electrons into the low-energy π* orbital of CO. Direct evidence for this back-bonding is an increase in the C–O bond length and a lowering of the infrared stretching frequency from the population of the π* orbital of the carbonyl.



When an unsaturated ligand such as an alkene approaches the metal sideways to form a π complex, similar interactions lead to bonding. The filled π orbitals of the ligand bond to empty d orbitals of the metal, while filled d orbitals on the metal bond to the empty π* orbitals of the ligand. The result is a π complex with the metal–alkene bond perpendicular to the plane of the alkene. The bond has both σ and π character.

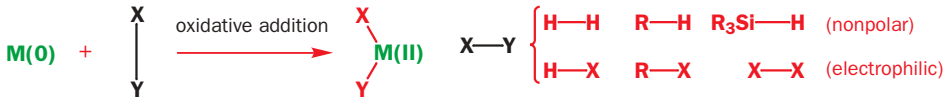


Coordination to a metal by any of these bonding methods changes the reactivity of the ligands dramatically and this is exploited in the organometallic chemistry we will be discussing in the rest of the chapter. You do not need to understand all the bonding properties of metal complexes but you need to be able to count electrons, to recognize both σ and π complexes, and to realize that complexes show a balance between electron donation and electron withdrawal by the metal.

Oxidative addition inserts metal atoms into single bonds

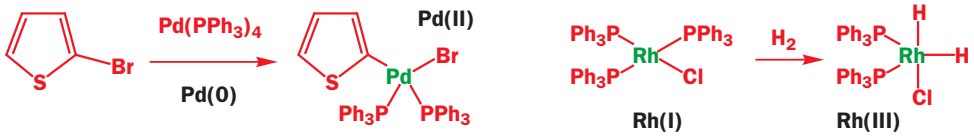
Potential ligands that do not have a lone pair or filled π type orbital are still able to interact with transition metal complexes but only by breaking a σ bond. This is the first step in a wide variety of processes and is described as **oxidative addition** because the formal oxidation state of the transition metal is raised by two, for example, M(0) to M(II), in the process. This is the result of having two extra ligands bearing a formal negative charge. You have seen this process in the formation of Grignard reagents (Chapter 9)

The number of coordinated ligands also increases by two so the starting complex is usually in low oxidation state (0 or 1; the diagram shows 0) and **coordinatively unsaturated**, that is, it has an empty site for a ligand and, say, only 16 electrons, like $(MeCN)_2PdCl_2$, whereas the product is usually **coordinatively saturated**, that is, it cannot accept another ligand unless it loses one first.



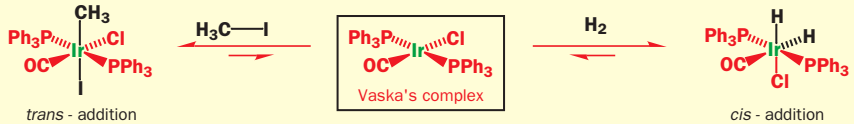
introduces new organic ligands on to metal

Oxidative addition occurs for a number of useful neutral species including hydrogen, carbon–hydrogen bonds, and silanes as well as polarized bonds containing at least one electronegative atom. The resulting species with metal–ligand bonds allow useful chemical transformations to occur. Important examples include the oxidative addition of Pd(0) to aryl iodides and the activation of Wilkinson's catalyst for hydrogenation in solution by oxidative addition to a hydrogen molecule.



Vaska's complex

There are a number of possible mechanisms for oxidative addition and the precise one followed depends on the nature of the reacting partners. Vaska's complex $[Ir(PPh_3)_2COCl]$ has been extensively studied and it reacts differently with hydrogen and methyl iodide. Hydrogen is added in a *cis* fashion, consistent with concerted formation of the two new iridium–hydrogen bonds. The 16e, d^8, Ir(I) complex becomes a new 18e, d^6, Ir(III) species. With methyl iodide the kinetic product is that of *trans* addition, which is geometrically impossible from a concerted process. Instead, an S_N2-like mechanism is followed involving nucleophilic displacement of iodide followed by ionic recombination.



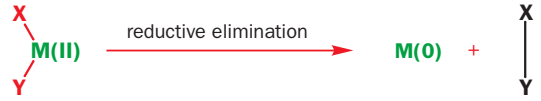
trans - addition
18 e complex
Ir(III); d^6

16 e complex
Ir(I); d^8

cis - addition
18 e complex
Ir(III); d^6

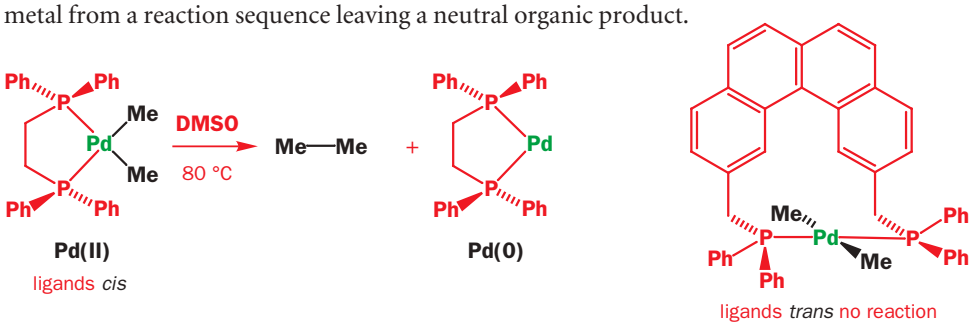
Reductive elimination removes metal atoms and forms new single bonds

If we want to use organometallic chemistry to make organic compounds other than those containing metals, we must be able to remove the ligands from the coordination sphere of the metal at the end of the reaction. Neutral organic species such as alkenes, phosphines, and carbon monoxide can simply dissociate in the presence of other suitable ligands but those that are bound to the metal with shared electrons require a more active process. Fortunately, most reactions that occur around a transition metal are reversible and so the reverse of oxidative addition, known as **reductive elimination**, provides a simple route for the release of neutral organic products from a complex. Our general reaction shows M(II) going to M(0) releasing X–Y. These two ligands were separate in the complex but are bound together in the product. A new X–Y σ bond has been formed.

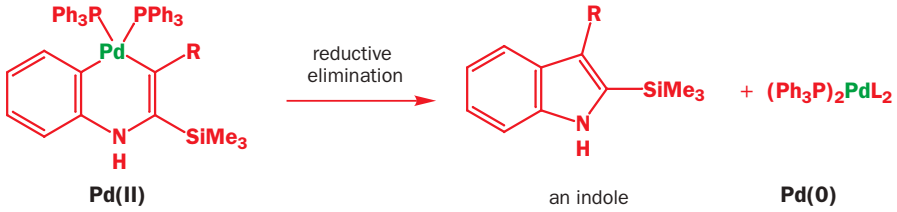


removes organic ligands from metal producing new organic product

The ligands to be eliminated must be *cis* to one another for reductive elimination to occur. This is because the process is concerted. Two examples from palladium chemistry make this point clear. Warming in DMSO causes ethane production from the first palladium complex because the two methyl groups are *cis* in the square planar complex. The more elaborate second bisphosphine forces the two methyl groups to be *trans* and reductive elimination does not occur under the same conditions. Reductive elimination is one of the most important methods for the removal of a transition metal from a reaction sequence leaving a neutral organic product.



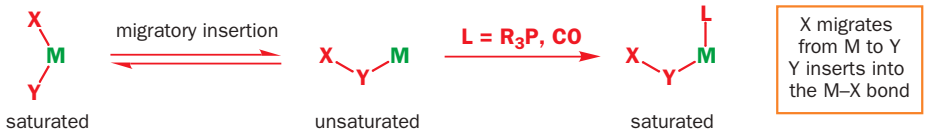
In fact, no one wants to make ethane that way (if at all) but many other pairs of ligands can be coupled by reductive elimination. We will see many examples as the chapter develops but here is an indole synthesis that depends on a reductive elimination at palladium as a last step. In the starting material, palladium has two normal σ bonds and is Pd(II). The two substituents bond together to form the indole ring and a Pd(0) species is eliminated. Notice the use of 'L' to mean an undefined ligand of the phosphine sort.



Migratory insertion builds ligand structure

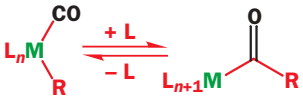
Two ligands can also react together to produce a new complex that still has the composite ligand attached to the metal ready for further modification. This process involves migration of one of the ligands from the metal to the other ligand and insertion of one of the ligands into the other metal–ligand bond and is known as **migratory insertion**. The insertion process is reversible and, as the metal effectively loses a ligand in the process, the overall insertion may be driven by the addition of extra external ligands (L) to produce a coordinatively saturated complex. As with reductive elimination, a *cis* arrangement of the ligands is required and the migrating group (X) retains its stereochemistry (if any) during the migration.

■ Migration normally occurs with retention; see Chapter 37.

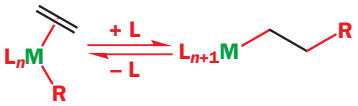


Migratory insertion is the principal way of building up the chain of a ligand before elimination. The group to be inserted must be unsaturated in order to accommodate the additional bonds and common examples include carbon monoxide, alkenes, and alkynes producing metal–acyl, metal–alkyl, and metal–alkenyl complexes, respectively. In each case the insertion is driven by additional external ligands, which may be an increased pressure of carbon monoxide in the case of carbonylation or simply excess phosphine for alkene and alkyne insertions. In principle, the chain extension process can be repeated indefinitely to produce polymers by Ziegler–Natta polymerization, which is described in Chapter 52.

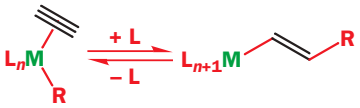
carbonylation



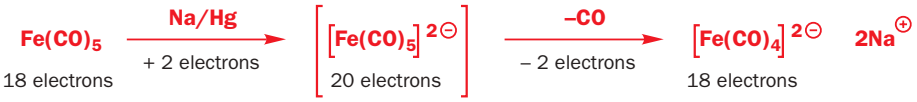
carbometallation or hydrometallation, R = H



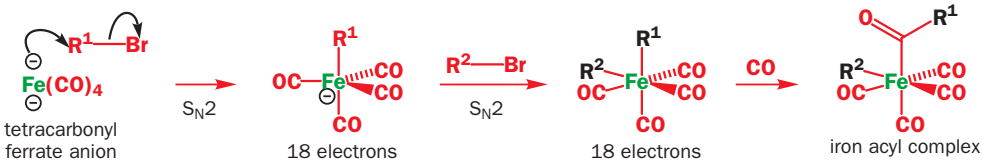
alkyne insertion



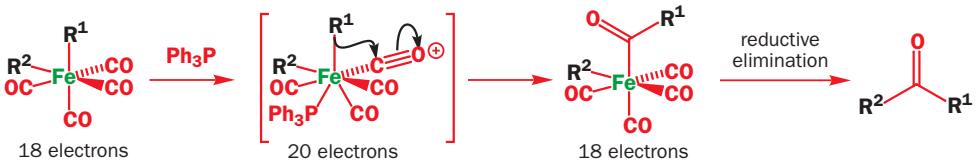
A good example of the carbonylation process is the reaction of the tetracarbonyl ferrate dianion $[Fe(CO)_4^{2-}]$ with alkyl halides. This reagent is made by dissolving metal reduction of the 18-electron Fe(0) compound $Fe(CO)_5$. Addition of two electrons would give an unstable 20-electron species but the loss of one of the ligands with its two electrons restores the stable 18-electron structure.



This iron anion is a good soft nucleophile for alkyl halides and can be used twice over to produce first a monoanion with one alkyl group and then a neutral complex with two alkyl groups and four CO ligands. Each of these complexes has 18 electrons as the electrons represented by the negative charges are retained by the iron to form the new Fe–C bonds. If extra CO is added by increasing the pressure, CO inserts into one Fe–C bond to form an iron acyl complex. Finally, reductive elimination couples the acyl group to the other alkyl group in a conceptually simple ketone synthesis. It does not matter which Fe–C bond accepts the CO molecule: the same unsymmetrical ketone is produced at the end.

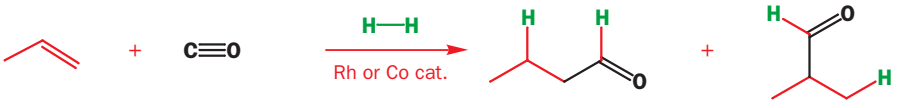


Any good two-electron ligand will cause the CO insertion: Ph_3P is often used instead of an increased CO pressure. The phosphine adds to the iron and pushes out the poorest ligand (one of the alkyl groups) on to a CO ligand in a process of **ligand migration**. In simple form it looks like this though the phosphine addition and alkyl migration may be concerted to avoid the formation of a 20-electron complex as intermediate.



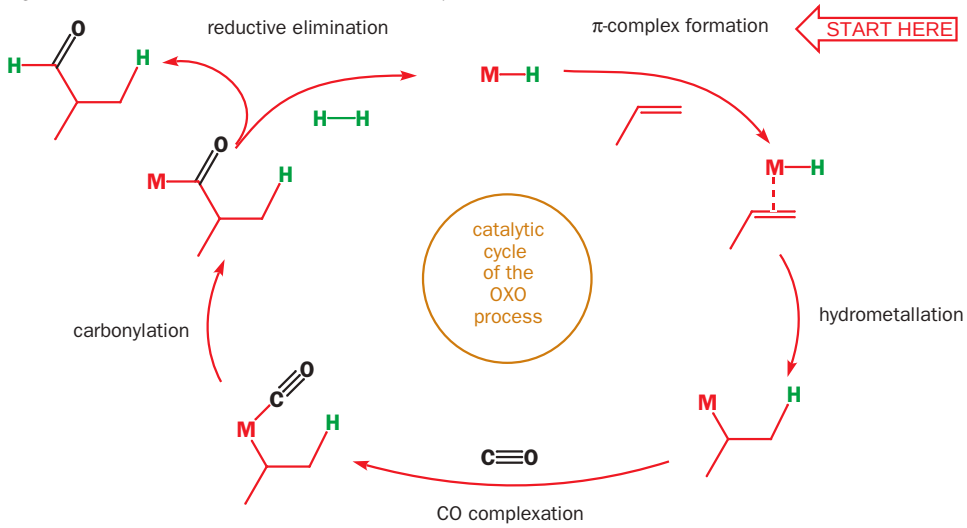
Carbon monoxide incorporation extends the carbon chain

Carbonylation (the addition of carbon monoxide to organic molecules) is an important industrial process as carbon monoxide is a convenient one-carbon feedstock and the resulting metal–acyl complexes can be converted into aldehydes, acids, and their derivatives. The **OXO process** is the hydroformylation of alkenes such as propene and uses two migratory insertions to make higher value aldehydes. Though a mixture is formed this is acceptable from very cheap starting materials.

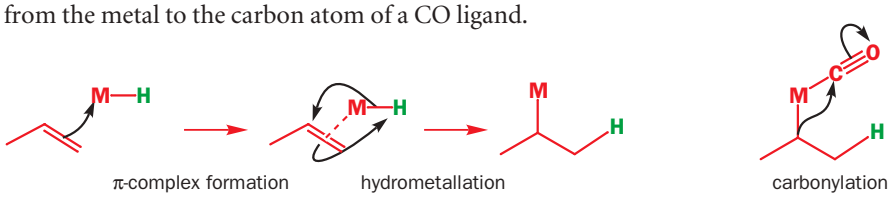


A catalytic cycle (going clockwise from the top) shows the various stages of alkene coordination, hydrometallation to produce an alkyl metal species, coordination of carbon monoxide followed by insertion, and finally reductive cleavage with hydrogen to produce the metal–hydride intermediate,

which is then ready for another cycle. The steps leading to the other regioisomeric aldehyde and the ligands on the metal are omitted for clarity.

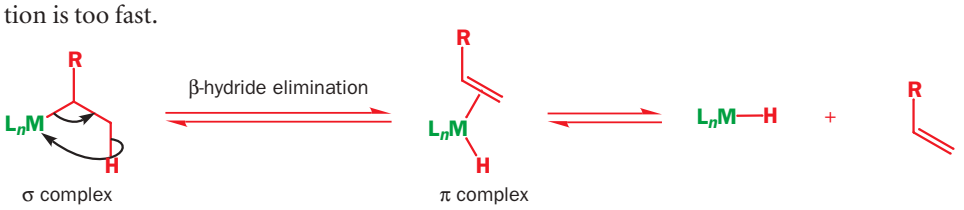


The mechanisms of the two key steps are worth discussion. **Hydrometallation** occurs by initial π-complex formation followed by addition of the metal to one end of the alkene and hydrogen to the other. Both of these regioisomers are formed. The **carbonyl insertion reaction** is another migration from the metal to the carbon atom of a CO ligand.



Insertion reactions are reversible

The reverse process, **decarbonylation**, is also fast but can be arrested by maintaining a pressure of carbon monoxide above the reaction mixture. The reverse of hydrometallation involves the elimination of a hydride from the adjacent carbon of a metal alkyl to form an alkene complex. This process is known as **β-hydride elimination** or simply **β elimination**. It requires a vacant site on the metal as the number of ligands increases in the process and so is favoured by a shortage of ligands as in 16-electron complexes. The metal and the hydride must be *syn* to each other on the carbon chain for the elimination to be possible. The product is an alkene complex that can lose the neutral alkene simply by ligand exchange. So β elimination is an important final step in a number of transition-metal-catalysed processes but can be a nuisance because, say, Pd–Et complexes cannot be used as β elimination is too fast.



Palladium(0) is most widely used in homogeneous catalysis

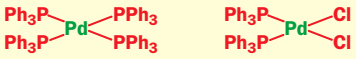
These elementary steps form the basis for organo-transition-metal chemistry and are the same regardless of which metal is present and the detailed structure of the ligands. This is an enormous and rapidly expanding field that could not be discussed here without doubling the size of the book! Instead, we will concentrate on the chemistry of the most important transition metal, palladium,

▶ Hydrogenation with homogeneous catalysis involves a soluble catalyst rather than the more common heterogeneous catalysis with, say, Pd metal dispersed on an insoluble charcoal support as in Chapter 24. In general terms **homogeneous catalysts** are those that are soluble in the reaction mixture.

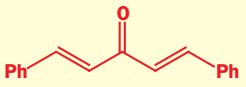
which is the most widely used both in industrial and academic laboratories on both a minute and very large scale. The variety of reactions that can be catalysed together with the range of functional groups tolerated, and usually excellent chemo- and regioselectivity, has meant that an ever increasing amount of research has gone into this area of chemistry. Most syntheses of big organic molecules now involve palladium chemistry in one or more key steps.

Choice of palladium complex

There are many available complexes of palladium(0) and palladium(II). Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, and tris(dibenzylidene-acetone)dipalladium(0), $Pd_2(dba)_3$, or the chloroform complex, $Pd_2(dba)_3{\cdot}CHCl_3$, which is air-stable, are the most common sources of palladium(0). The detailed structures of some palladium complexes, particularly the dimers, are beyond the scope of this book but we will discuss the reactions in detail.



a stable **Pd(0)** complex a stable **Pd(II)** complex



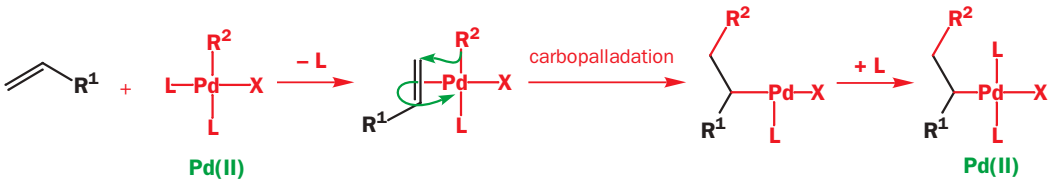
dba
dibenzylidene acetone

Palladium(II) complexes are generally more stable than their palladium(0) counterparts. The dichloride $PdCl_2$ exists as a polymer and is relatively insoluble in most organic solvents. However, $(PhCN)_2PdCl_2$ and $(MeCN)_2PdCl_2$ (both easily prepared from $PdCl_2$) are soluble forms of $PdCl_2$, as the nitrile ligands are readily displaced in solution. Bis(phosphine)palladium(II) chloride complexes are air-stable and readily prepared from $PdCl_2$. Palladium is, of course, an expensive metal—these complexes cost about £50–100 per gram—but very little is needed for a catalytic reaction.

▶ It is supposed that dba complexes the palladium atom through its alkenes.

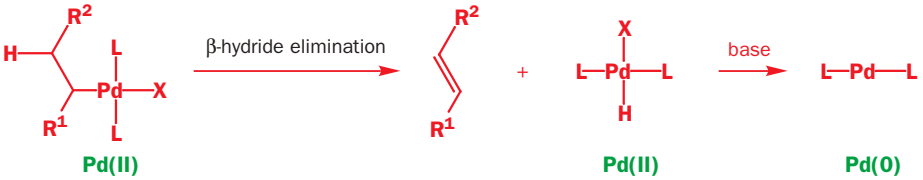
We should review the basic chemistry of palladium, as you will be seeing many more examples of these steps in specialized situations. Palladium chemistry is dominated by two oxidation states. The lower, palladium(0), present in tetrakis(triphenylphosphine)palladium, for example, is nominally electron-rich, and will undergo oxidative addition with suitable substrates such as halides and triflates ($TfO^- = CF_3SO_2O^-$), resulting in a palladium(II) complex. Oxidative addition is thought to occur on the coordinatively unsaturated 14-electron species, formed by ligand dissociation in solution.

The resulting σ alkyl bond in such complexes is very reactive, especially towards carbon–carbon π bonds. Thus an alkene in the reacting system will lead to coordination followed by migratory insertion into the palladium–carbon σ bond. This process is like hydrometallation and is called **carbopalladation** as carbon and palladium are attached to the ends of the alkene system. There is no change in oxidation state during this process, although the ligands (often phosphines) must dissociate to allow coordination of the alkene and associate to provide a stable final 16-electron product.



Theoretically, it is possible for the process of olefin coordination and insertion to continue as in Ziegler–Natta polymerization (Chapter 52) but with palladium the metal is expelled from the molecule by a β-hydride elimination reaction and the product is an alkene. For the whole process to be catalytic, a palladium(0) complex must be regenerated from the palladium(II) product of β-hydride elimination. This occurs in the presence of base which removes HX from the palladium(II) species.

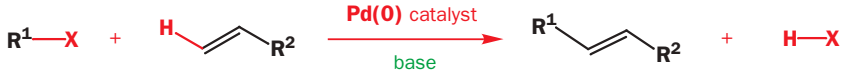
This is another example of reductive elimination: one that forms a hydrogen halide rather than a carbon–carbon or carbon–hydrogen bond as described earlier.



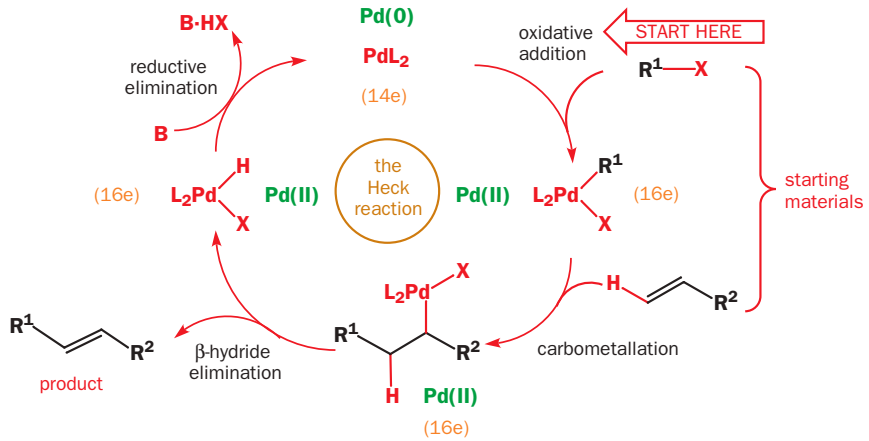
The speed of the intramolecular β-hydride elimination means that the original substrate for the oxidative addition reaction must be chosen with care—the presence of hydrogen at an sp^3 carbon in the β position must be avoided. Thus, substrates for oxidative addition reactions in palladium chemistry are frequently vinylic, allylic, or aromatic and never ethyl or *n*-propyl.

The Heck reaction couples together a halide or triflate and an alkene

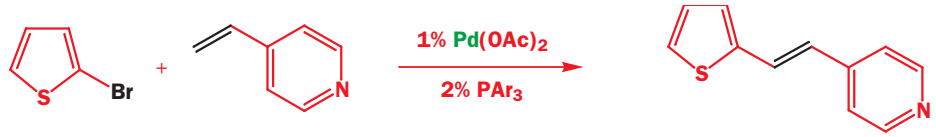
All the individual steps outlined above combine to make up the catalytic pathway in the **Heck reaction**, which couples an alkene with a halide or triflate to form a new alkene. The R^1 group in R^1X can be aryl, vinyl, or any alkyl group without β Hs on an sp^3 carbon atom. The group X can be halide (Br or I) or triflate (OSO_2CF_3). The alkene can be mono- or disubstituted and can be electron-rich, -poor, or -neutral. The base need not be at all strong and can be Et_3N, NaOAc, or aqueous Na_2CO_3. The reaction is very accommodating.



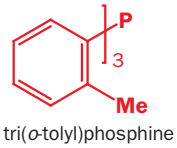
The palladium-catalysed addition of aryl, vinyl, or substituted vinyl groups to organic halides or triflates, the Heck reaction, is one of the most synthetically useful palladium-catalysed reactions. The method is very efficient, and carries out a transformation that is difficult by more traditional techniques. The mechanism involves the oxidative addition of the halide, insertion of the olefin, and elimination of the product by a β-hydride elimination process. A base then regenerates the palladium(0) catalyst. The whole process is a catalytic cycle.



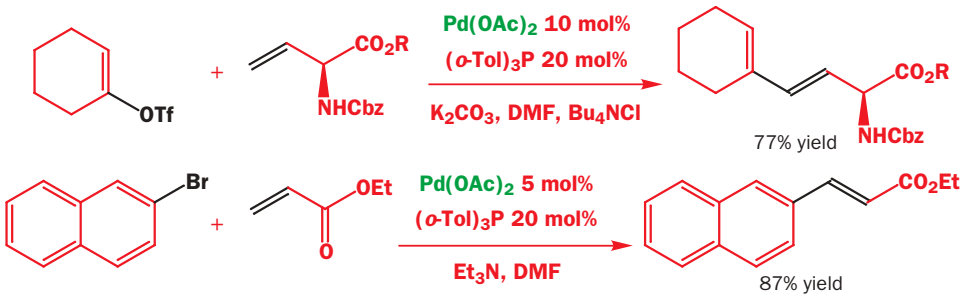
The choice of substrates is limited to aryl, heteroaryl, vinylic, and benzylic halides and triflates, as the presence of an sp^3 carbon in the β position carrying a hydrogen rapidly results in β-hydride elimination. The reaction tolerates a variety of functional groups, and works well with both electron-withdrawing and electron-donating groups on either substrate. Here is an example using a heterocyclic compound we featured earlier reacting with another heterocycle.



Protected amino acids can be made without any racemization and electron-withdrawing groups such as esters promote excellent regioselectivity in favour of terminal attack. These three examples rely on *in situ* reduction of the palladium(II) acetate by tri(*o*-tolyl)phosphine, a popular more sterically demanding aromatic phosphine.

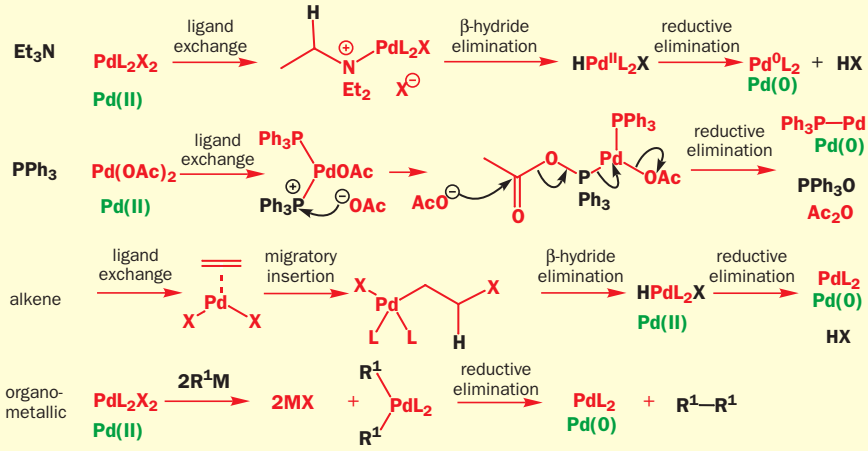


tri(*o*-tolyl)phosphine

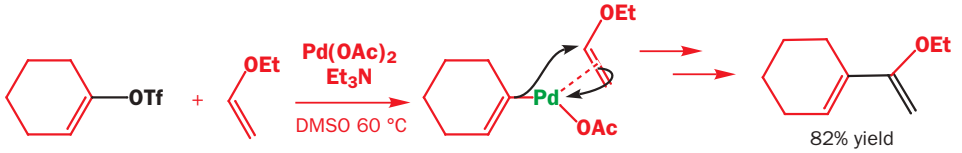


In situ formation of palladium(0) by reduction of Pd(II)

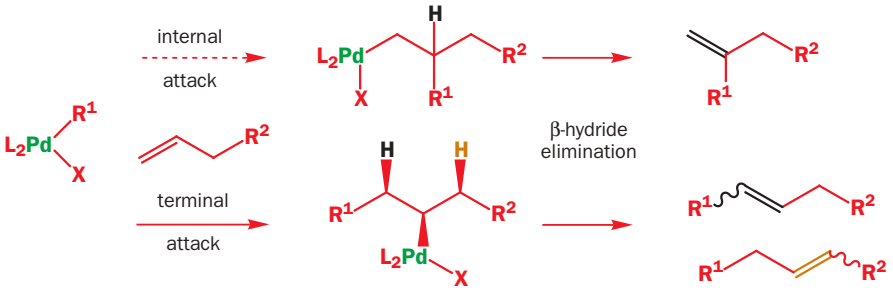
In reactions requiring palladium(0), formation of the active complex may be achieved more conveniently by reduction of a palladium(II) complex, for example, $Pd(OAc)_2$. Any phosphine may then be used in the reaction, without the need to synthesize and isolate the corresponding palladium(0)-phosphine complex. Only 2–3 equivalents of phosphine may be needed, making the palladium(0) complex coordinatively unsaturated and therefore very reactive. The reduction of palladium(II) to palladium(0) can be achieved with amines, phosphines, alkenes, and organometallics such as DIBAL-H, butyl lithium, or trialkyl aluminium. The mechanisms are worth giving as they illustrate the basic steps of organometallic chemistry.



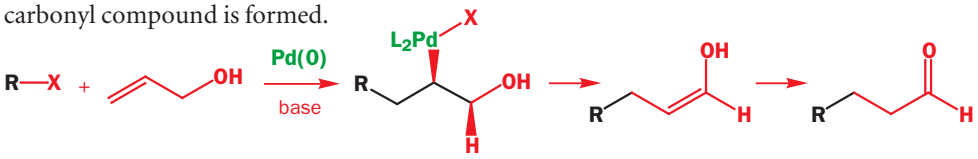
In contrast, electron-donating groups such as ethers lead to attack at the end of the alkene substituted by oxygen to produce in this case the 1,1-disubstituted product. These reactions must be dominated by the interaction of the filled p orbital of the alkene with an empty d orbital on Pd. This is an example of a Heck reaction working in the absence of a phosphine ligand.



In the β-hydride elimination step, the palladium and hydride must be coplanar for reaction to take place, as this is a *syn* elimination process. For steric reasons, the R group will tend to eclipse the smallest group on the adjacent carbon as elimination occurs, leading predominantly to a *trans* double bond in the product.

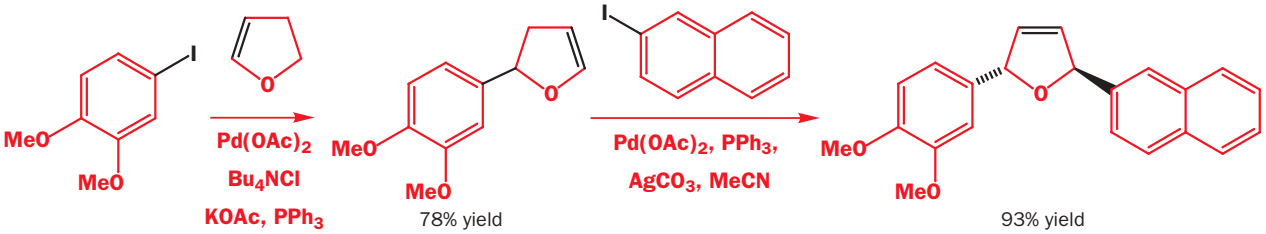


Where there is a choice as to which hydride can be lost to form the alkene, the stability of the possible product alkenes often governs the outcome as the β-hydride elimination is reversible. The reaction of allylic alcohols is particularly important as the more stable of the two alkenes is the enol and a carbonyl compound is formed.

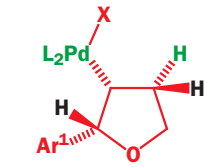


Hydropalladation–dehydropalladation can lead to alkene isomerization

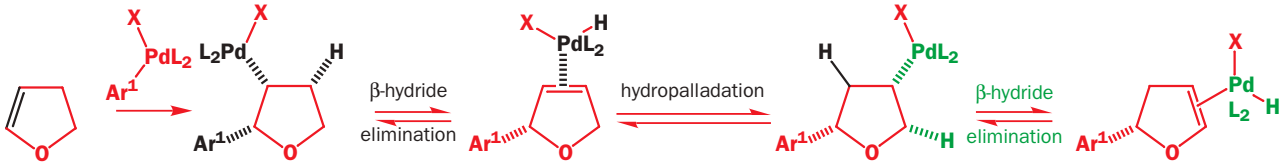
As β-hydride elimination is reversible, hydropalladation with the opposite regiochemistry provides a mechanism for forming regioisomers of the alkene. This allows the most stable alkene that is accessible by the hydropalladation–dehydropalladation sequence to dominate. The only restriction is that all of these processes are *syn*. The migration can be prevented by the addition of bases like silver carbonate, which effectively removes the hydrogen halide from the palladium complex as soon as it is formed. This synthesis of a complex *trans* dihydrofuran involves the Heck reaction followed by alkene isomerization and then a Heck reaction without migration to preserve the stereochemistry.



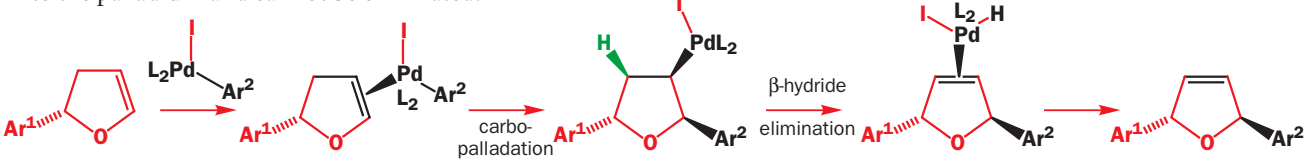
Oxidative addition of the aryl iodide (Ar^1 = 3,4-dimethoxyphenyl) to a palladium(0) complex, formed from $Pd(OAc)_2$ by reduction (with the phosphine?) gives the active palladium(II) complex $ArPdOAcL_2$. Carbopalladation occurs as expected on an electron-rich alkene to give the product of aryl addition to the oxygen end of the alkene in a *syn* fashion. β-Hydride elimination must occur away from the aryl group to give a new alkene complex as there is no *syn* H on the other side. The alkene has moved one position round the ring. Hydropalladation in the reverse sense gives a new σ complex, which could eliminate either the black or the green hydrogens. Elimination of the green H gives the enol ether, which is the most stable alkene possible due to conjugation.

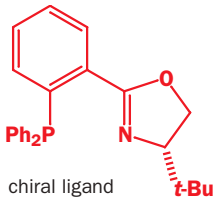


syn (green) H on one side only
anti (black) Hs on both sides



The second Heck reaction involves a naphthyl iodide (Ar^2 = 2-naphthyl) but the initial mechanism is much the same. However, the enol ether has two diastereotopic faces: *syn* or *anti* to the aromatic substituent (Ar^1) introduced in the first step. Palladium is very sensitive to steric effects and generally forms less hindered complexes where possible. Thus coordination of the palladium(II) intermediate occurs on the face of the enol ether *anti* to Ar^1. This in turn controls all the subsequent steps, which must be *syn*, leading to the *trans* product. The requirement for *syn* β-hydride elimination also explains the regiochemical preference of the elimination. In this cyclic structure there is only one hydrogen (green) that is *syn*; the one on the carbon bearing the naphthyl substituent is *anti* to the palladium and cannot be eliminated.

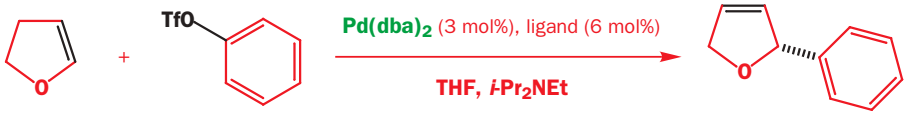




chiral ligand

Heck reactions can be enantioselective

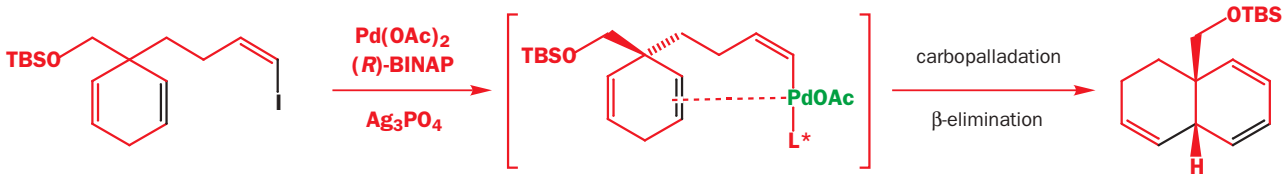
With chiral ligands the Heck reaction can be enantioselective. The amino-acid-derived phosphine ligand in the margin controls the Heck reaction of phenyl triflate with dihydrofuran. The ligand selects one enantiotopic face of the alkene (see Chapter 45 if you have forgotten this term) and the usual double bond migration and β elimination complete the reaction.



87% yield, 97% ee

■ BINAP was introduced in Chapter 45.

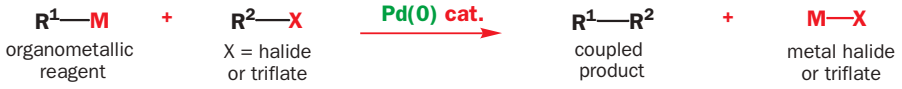
The famous ligand BINAP controls an intramolecular Heck reaction to give decalin derivatives with good enantiomeric excess. BINAP is the optically pure phosphine built into the palladium catalyst. The presence of silver ions accelerates the reaction as well as preventing double bond isomerization in the original substrate. This time the chiral ligand selects which double bond is to take part in the reaction. The vinyl palladium species is tethered to the alkene and can reach only the same face. The faces of the alkenes are diastereotopic but the two alkenes are enantiotopic and you must know your right from your left to choose one rather than the other.



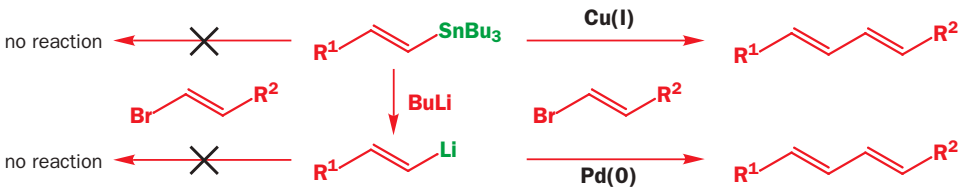
67% yield, 80% ee

Cross-coupling of organometallics and halides

Other than β-hydride elimination, another important pathway by which palladium(II) intermediates can lead to neutral organic fragments is reductive elimination. This forms the basis of the mechanism for **cross-coupling reactions** between an organometallic reagent and an organic halide or triflate.



This is a reaction that seems very attractive for synthesis but, in the absence of a transition metal catalyst, the yields are very low. We showed in the last chapter how vinyl silanes can be made with control over stereochemistry and converted into lithium derivatives with retention. Neither of these vinyl metals couple with vinyl halides alone. But in the presence of a transition metal—Cu(I) for Li and Pd(0) for Sn—coupling occurs stereospecifically and in good yield.



The mechanism involves oxidative addition of the halide or triflate to the initial palladium(0) phosphine complex to form a palladium(II) species. The key slow step is a **transmetallation**, so called because the nucleophile (R^1) is transferred from the metal in the organometallic reagent to the palladium and the counterion (X = halide or triflate) moves in the opposite direction. The new palladium(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the palladium(0) catalyst ready for another cycle.

The reaction is important because it allows the coupling of two different components (R^1 and R^2). If this is to happen, the substituents, M (metal) on R^1 and X (halide or triflate) on R^2, must be different electronically. Both components form σ complexes with Pd but the halide partner (R^2X) bonds first by oxidative addition and the R^2–Pd must survive while the metal partner (R^1M) bonds to the Pd by transmetallation. Once the two components are joined to the palladium atom, only the cross-coupled product can be formed. The essential feature is that X and M are different so that R^2X combines with Pd(0) and R^1M with Pd(II). There can then be no confusion.

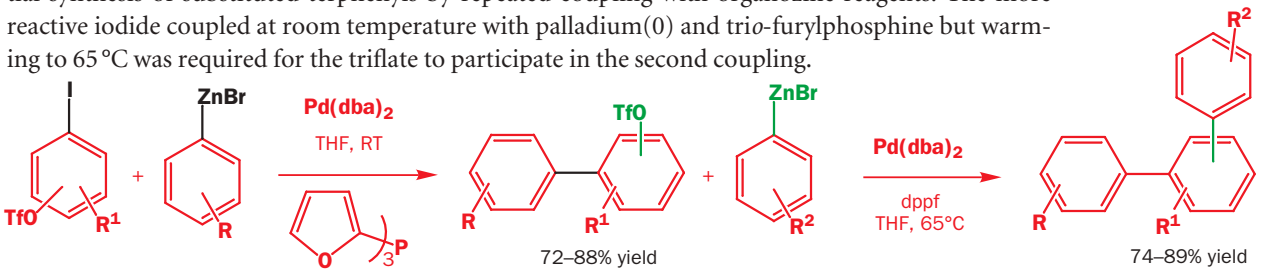
The halide partner (R^2X) must be chosen with care, as β-hydride elimination would decompose the first intermediate during the slow transmetallation step. The choice for R^2 is restricted to substituents without β-hydrogen atoms: vinyl, allyl, benzyl, and polyfluoroalkyl halides, triflates, and phosphates have all been coupled successfully. The organometallic reagent (R^1M) can be based on magnesium, zinc, copper, tin, silicon, zirconium, aluminium, or boron and the organic fragment can have a wide variety of structures as coupling is faster than β-hydride elimination.

R^1—M R^1 = almost anything including examples with β H

M = MgX, ZnX, Cu, SnR_3, SiR_3/TASF, $ZrCp_2Cl$, $AlMe_2$, $B(OR)_2$

R^2—X R^2 must not have β Hs that can eliminate X = I, Br, (Cl), OTf, $OPO(OR)_2$

The difference in relative reactivity of aromatic iodides and triflates was exploited in this sequential synthesis of substituted terphenyls by repeated coupling with organozinc reagents. The more reactive iodide coupled at room temperature with palladium(0) and tri-*o*-furylphosphine but warming to 65 °C was required for the triflate to participate in the second coupling.

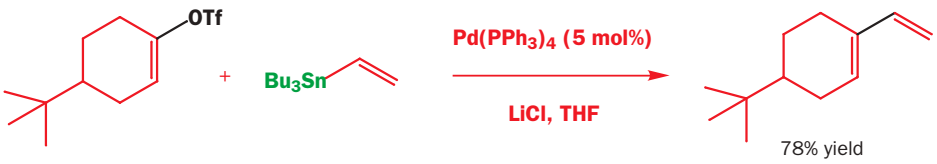


In spite of the wide range of organometallic reagents that can be used there are two classes that have proved particularly popular because they are stable intermediates in their own right and can be prepared separately before the coupling reaction. These cross-couplings are known by the names of the two chemists whose work made the reactions so valuable. The Stille coupling employs a stannane as the organometallic component (R^1M) while the Suzuki coupling relies on a boronic acid.

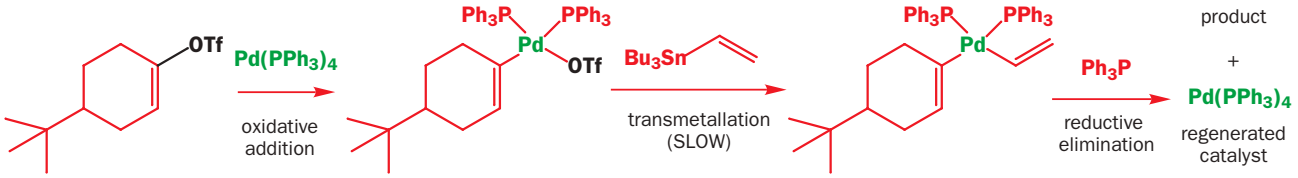
The Stille coupling uses stannanes as the organometallic component

Since the first reported use in the late 1970s, the Stille coupling has been widely used for the coupling of both aromatic and vinylic systems.

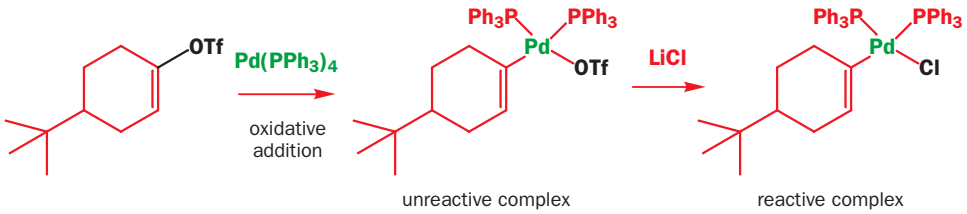
▶ There is a problem in naming the two partners. The halide partner (R^2X) is sometimes called the electrophile and the organometallic partner (R^1M) the nucleophile. These names describe the nature of the reagents rather than the mechanism of the reaction and we will not use these names.



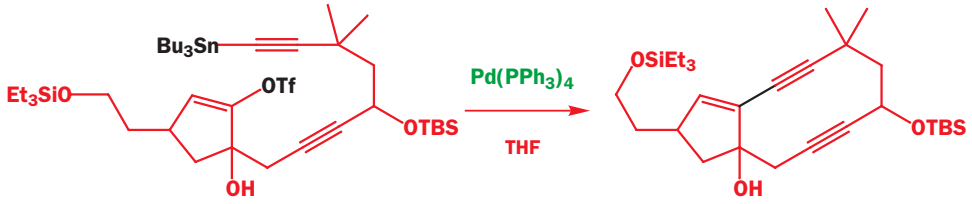
The mechanism involves the oxidative addition of the vinyl or aromatic triflate or halide to give a palladium intermediate. This then undergoes a transmetallation reaction with the organostannane, giving an organopalladium intermediate in which both components are σ-bound. This complex then undergoes a reductive elimination step, releasing the product and thereby regenerating the palladium(0) catalyst.



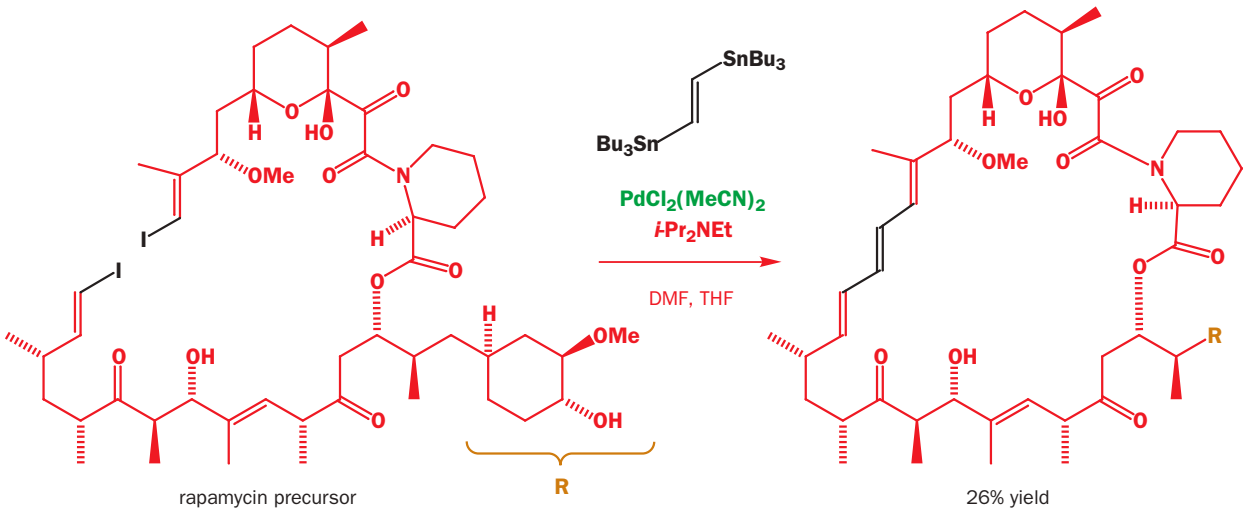
The reaction will also occur if the vinyl or aryl halide is used in place of the triflate. However, the triflates have been more widely used as they are readily prepared from phenols or enolizable aldehydes or ketones. In these reactions, the presence of a source of halide (typically LiCl) is generally required. This may be because the triflate is a counterion and is not bound to the metal as a ligand. If transmetallation is to occur some other ligand must be added to give the necessary square coplanar geometry.



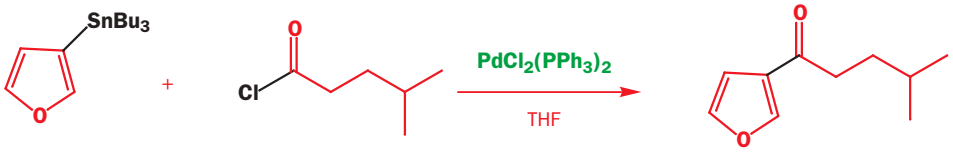
The Stille reaction, which represents over half of all current cross-coupling reactions, has been used in total synthesis with excellent results. The reaction may also be carried out intramolecularly and with alkynyl stannanes instead of the more usual aryl or vinyl stannanes, even to form medium-sized rings. This example forms a ten-membered ring containing two alkynes.



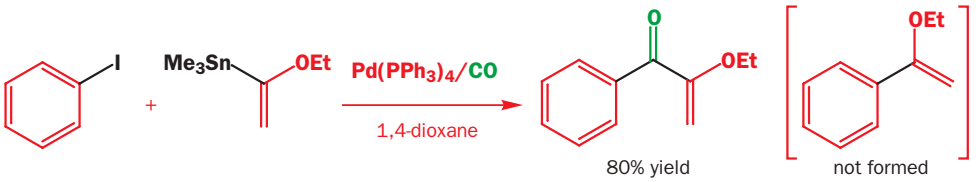
Nicolaou's synthesis of rapamycin uses the reaction twice in the **macrocyclization** (cyclization reaction to form a large ring) step. This illustrates an important feature of palladium-catalysed cross-couplings—the geometry of both double bonds involved in the coupling is preserved in the product. This seems a very complex example and the molecule *is* complex. But just inspect the black region and you will see two simple Stille couplings. These reactions work with complex molecules having many functional groups, even if the yield isn't great (26%!).



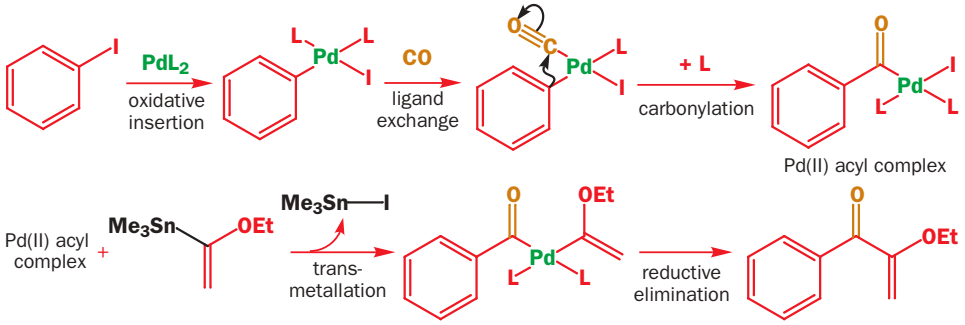
The Stille coupling may be combined with carbonylation in two ways. Acid chlorides may be used as substrates for the reaction with vinyl or aryl stannanes. However, an atmosphere of carbon monoxide is frequently required to prevent decarbonylation after the oxidative addition step.



More recently, it has been shown that performing the normal Stille reaction in the presence of carbon monoxide may also lead to carbonylated products. These reactions can take place in a CO saturated solution, under one atmosphere of pressure. Using these conditions, excellent yields of the carbonylated product can be obtained, without any of the normal coupling product being present.

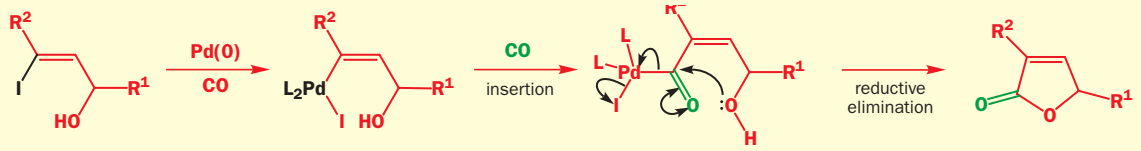


The mechanism is like that of a normal Stille coupling except that the carbon monoxide first exchanges for one of the phosphine ligands and then very rapidly inserts to produce an acyl palladium(II) complex. This then undergoes transmetallation with the vinyl stannane in the usual way forming trimethylstannyl iodide and the palladium complex with two carbon ligands. Reductive elimination gives the masked diketone and regenerates the palladium(0) catalyst. Transmetallation is the slow step in these coupling reactions so that there is time for the carbon monoxide insertion first. The final step—reductive elimination—releases the Pd(0) catalyst for the next cycle.



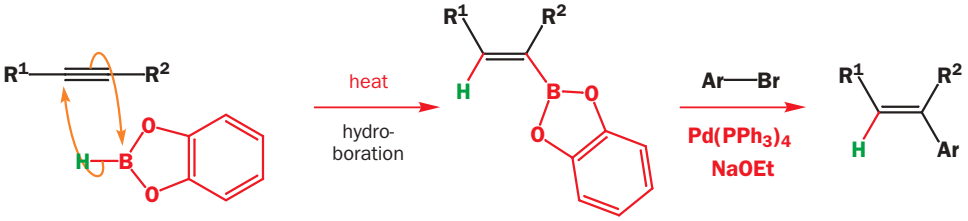
Acyl palladium species react like activated acid derivatives

Carbonylation of a halide or triflate provides a direct route to a range of chain-extended acyl derivatives. A carbonyl group substituted with PdX (X = halide or triflate) is a reactive acylating agent, rather like an acid anhydride, as PdX is a good leaving group. Reaction with alcohols and amines gives esters and amides, while reduction with tributyltin hydride gives the aldehyde. Intramolecular attack by alcohols leads to lactones as demonstrated in the conversion of a vinyl iodide into a 2H-furanone (butenolide). We will see more of these reactions later.

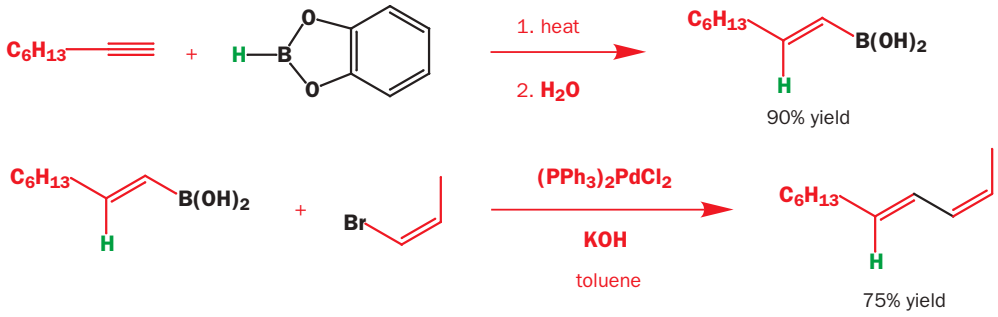


The Suzuki coupling couples boronic acids to halides

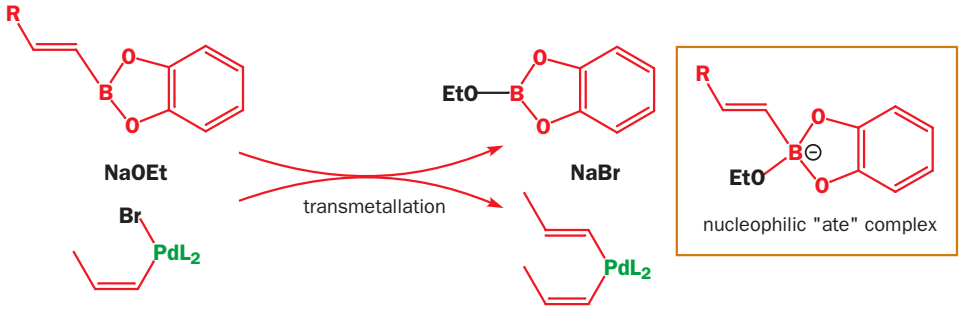
Since first being published in 1979, the Suzuki coupling of a boronic acid with a halide or triflate has developed into one of the most important cross-coupling reactions, totalling about a quarter of all current palladium-catalysed cross-coupling reactions. The original version consisted of hydroboration of an alkyne with catecholborane, followed by palladium(0)-catalysed coupling of the resulting vinyl boronate with an aromatic iodide or bromide. The hydroboration is generally regioselective for the less hindered position and addition of boron and hydrogen occurs *cis* stereospecifically.



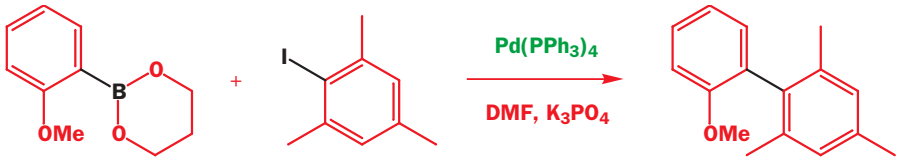
As in the Stille coupling, the geometry of both unsaturated components is preserved during the coupling so this is an excellent method for stereospecific diene synthesis. Hydroboration of octyne followed by hydrolysis of the boronate gave exclusively the *E*-vinyl boronic acid. Coupling with the *Z*-vinyl bromide in toluene with palladium(0) catalysis with potassium hydroxide as the base gave the *E,Z*-diene in good yield. These dienes are very useful in the Diels–Alder reaction (Chapter 35).



The mechanism is very similar to that of the Stille coupling. Oxidative addition of the vinylic or aromatic halide to the palladium(0) complex generates a palladium(II) intermediate. This then undergoes a transmetallation with the alkenyl boronate, from which the product is expelled by reductive elimination, regenerating the palladium(0) catalyst. The important difference is the transmetallation step, which explains the need for an additional base, usually sodium or potassium ethoxide or hydroxide, in the Suzuki coupling. The base accelerates the transmetallation step leading to the borate directly presumably via a more nucleophilic 'ate' complex.

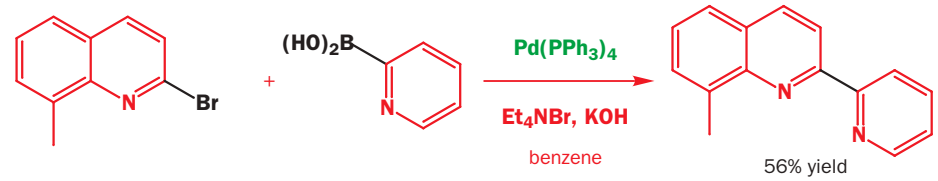


Sterically demanding substrates are tolerated well and Suzuki coupling has been used in a wide range of aryl–aryl cross-couplings. This example has three *ortho* substituents around the newly formed bond (marked in black) and still goes in excellent yield. It also shows that borate esters can be used instead of boronic acids.

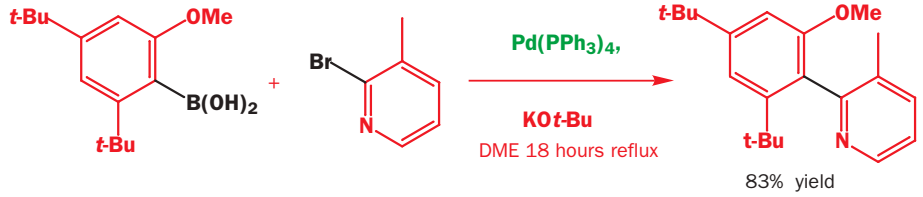


85% yield

Coupling of aromatic heterocycles goes well. The 2-position of a pyridine is very electrophilic and not at all nucleophilic (Chapter 43) but couplings at this position are fine with either the halide or the boronic acid in that position. Clearly, it is a mistake to see either of these substituents as contributing a 'nucleophilic carbon'. It is better to see the reaction as a coupling of two equal partners and the two substituents (halide and boronic acid) as a control element to ensure cross-coupling and prevent dimerization. In the second example potassium *tert*-butoxide was crucial as weaker and less hindered bases gave poor yields.

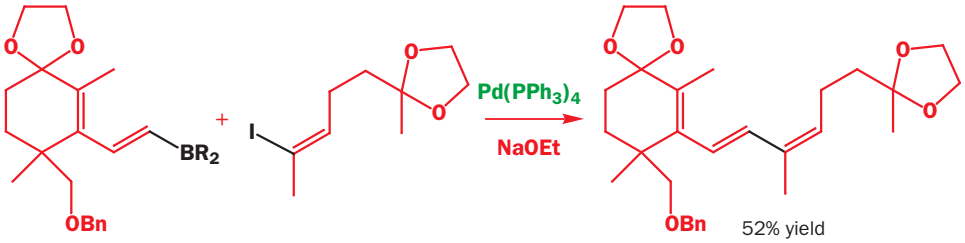


56% yield



83% yield

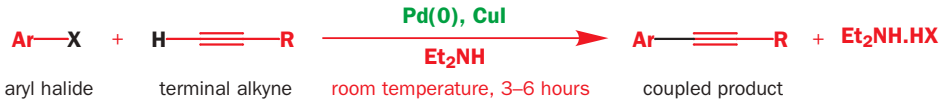
Due to the excellent stereoselectivity of the Suzuki coupling, the reaction has been used in the synthesis of the unsaturated units of a range of natural products including trisporol B. The key step is the stereocontrolled synthesis of an *E*,*Z*-diene. The geometry of both double bonds comes stereospecifically with retention of configuration from single geometrical isomers of the starting materials.



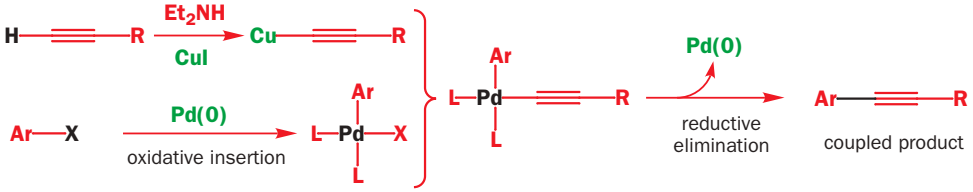
52% yield

The Sonogashira coupling uses alkynes directly

The coupling of terminal alkynes with aryl or vinyl halides under palladium catalysis is known as the Sonogashira reaction. This catalytic process requires the use of a palladium(0) complex, is performed in the presence of base, and generally uses copper iodide as a co-catalyst. One partner, the aryl or vinyl halide, is the same as in the Stille and Suzuki couplings but the other has hydrogen instead of tin or boron as the 'metal' to be exchanged for palladium.



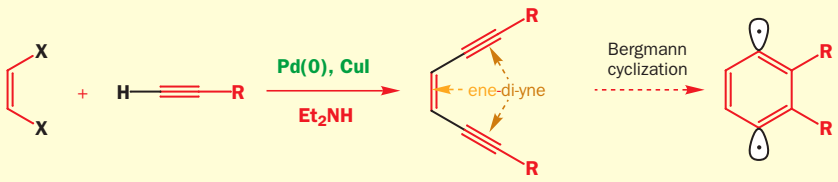
The mild conditions usually employed, frequently room temperature, mean that the reaction can be used with thermally sensitive substrates. The mechanism of the reaction is similar to that of the Stille and Suzuki couplings. Oxidative addition of the organic halide gives a palladium(II) intermediate that undergoes transmetallation with the alkynyl copper (generated from the terminal alkyne, base, and copper iodide). Reductive elimination with coupling of the two organic ligands gives the product and regenerates the palladium(0) catalyst.



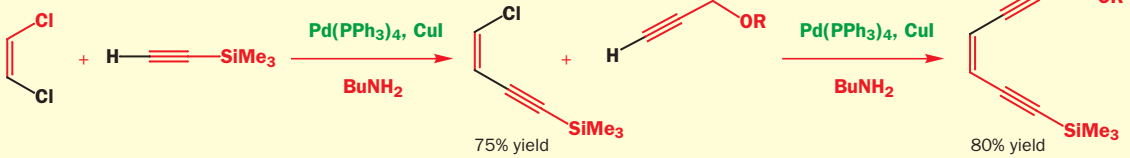
It is often more convenient, as in the Heck reaction, to use a stable and soluble Pd(II) derivative such as bis(triphenylphosphine)palladium(II) chloride instead of Pd(0). This is rapidly reduced *in situ* to give a coordinatively unsaturated, catalytically active, palladium(0) species. The geometry of the alkene is generally preserved so that *cis* (*Z*) and *trans* (*E*) dichloroethylene give the two different geometrical isomers of the enyne below in >99% stereochemical purity as well as excellent yield.

Ene-diynes and the Bergmann cyclization

The Sonogashira reaction is used a lot because of the great potential of **ene-diyne antibiotics**. Symmetrical ene-diynes may be synthesized in one step from two molecules of a terminal alkyne and *Z*-dihaloethene. The ene-diyne part of the molecule does the remarkable Bergmann cyclization to give a benzene diradical: the ene-diyne is able to penetrate DNA and the diradical is able to react with it. These compounds are anticancer drugs of some promise.



To make useful biologically active compounds, however, the reaction is performed sequentially, allowing different functionality on each of the alkyne units.

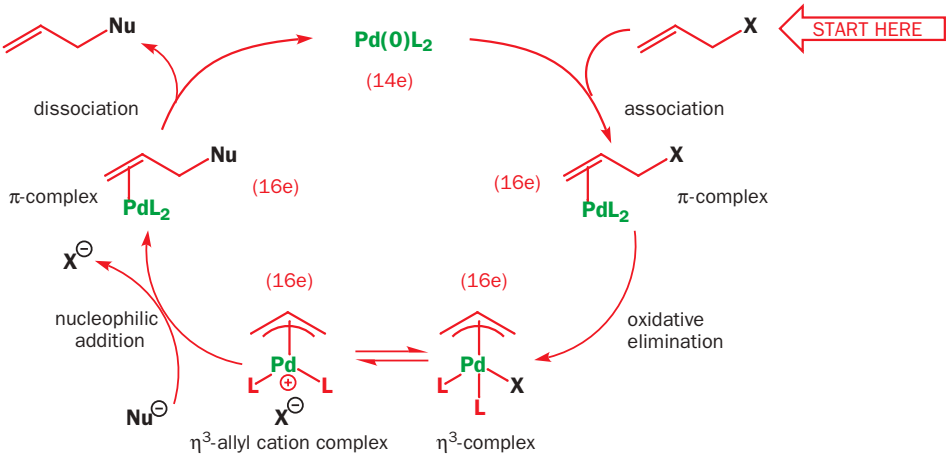


Allylic electrophiles are specifically activated by palladium(0)

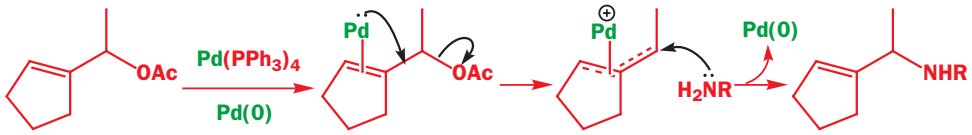
Allylic compounds with good leaving groups, such as bromide and iodide, are excellent allylating agents but they suffer from loss of regiochemistry due to competition between the direct S_N2 and

S_N2' reaction. This problem together with the associated stereochemical ambiguity was described in Chapter 23. In contrast, π-allyl cation complexes of palladium allow both the stereochemistry and regiochemistry of nucleophilic displacement reactions to be controlled.

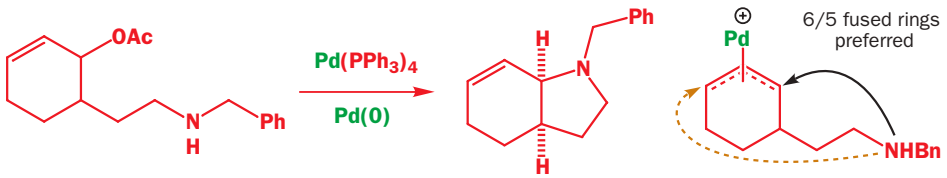
In addition, leaving groups (X) that are usually regarded as rather unreactive can be used, which means that the electrophilic partner is more stable in the absence of palladium making handling easier. Acetate (X = OAc) is the most commonly used leaving group, but a wide range of other functional groups (X = OCO_2R, $OPO(OR)_2$, Cl, Br, OPh) will perform a similar role. The full catalytic cycle is shown with the intermediate π-allyl complex in equilibrium between the neutral version, which has the leaving group coordinated to palladium, and the cationic π-allyl, in which one of the phosphine ligands has displaced the anion.



Soft nucleophiles (Nu) generally give the best results so, for carbon–carbon bond formation, stabilized enolates such as malonates are best, but for C–X (X = O, N, S) bond formation the reaction is successful with alkoxides, amines, cyanide, and thioalkoxides. This example shows an amine attacking outside the ring probably because the alkene prefers to be inside the ring.



The intramolecular reaction works well to give heterocyclic rings—the regioselectivity is usually determined by the length of the chain and how far it can reach. Here a 6/5 fused product is preferred to a bridged product containing two seven-membered rings.



The reaction usually proceeds with *retention* of configuration at the reacting centre. As in S_N2 reactions going with retention (Chapter 37), this can mean only a double inversion. Coordination of Pd to the double bond of the allylic acetate occurs on the less hindered face opposite the leaving group and the nucleophile adds to the face of the π-allyl Pd cation complex opposite the Pd. The net result is displacement of the leaving group by the nucleophile with retention. Thereafter, the

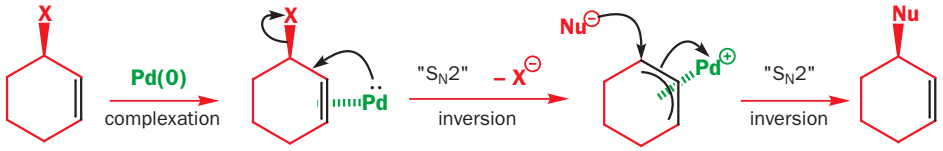
The Pd π-allyl cation complex

You can represent the palladium π-allyl cation complex in two ways. Either you draw a neutral allyl group complexed to Pd^+ or you draw an allyl cation complexed to neutral Pd. Though the counting is different (Pd^+ has only 9 electrons: the neutral allyl has 3 but the allyl cation only 2), both come out as η^3 16-electron species, which is just as well as they are different ways of drawing the same thing.

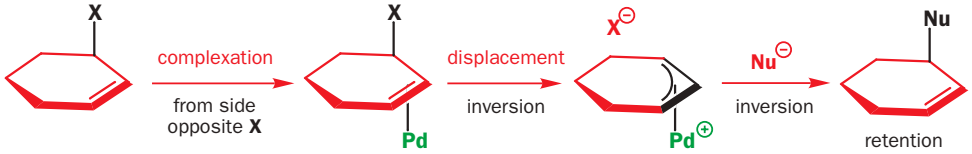
Pd π-allyl cation complex

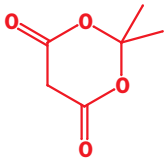
▶ The ligands around palladium are omitted for the sake of clarity.

nucleophile attacks from the less hindered face of the resulting π-allyl complex (that is, away from the metal) leading to overall retention of configuration.

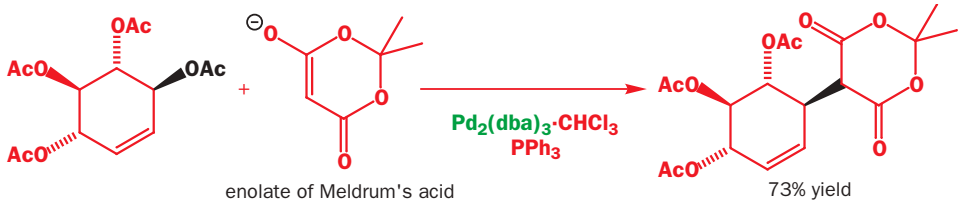


The rather vague arrows on the middle two diagrams are the best we can do to show how Pd(0) uses its electrons to get rid of the leaving group and how it accepts them back again when the nucleophile adds. They are not perfect but it is often difficult to draw precise arrows for organometallic mechanisms. The double inversion process is perhaps more apparent in a perspective view.



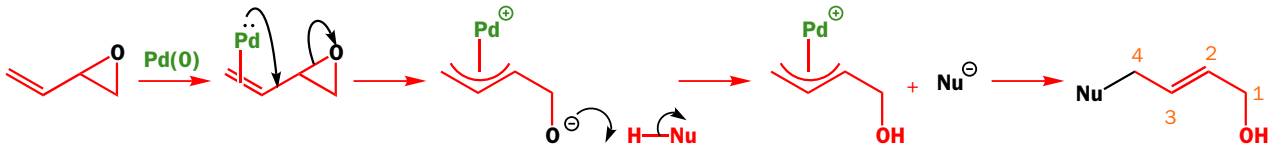

Meldrum's acid

The reaction of this allylic acetate with the sodium salt of Meldrum's acid (structure in margin) demonstrates the retention of configuration in the palladium(0)-catalysed process. The tetraacetate and the intermediate π-allyl complex are symmetrical, thus removing any ambiguity in the formation or reaction of the π-allyl complex and hence in the regiochemistry of the overall reaction.

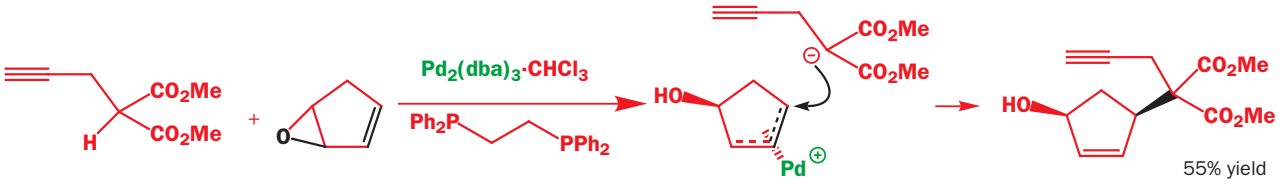


Vinyl epoxides provide their own alkoxide base

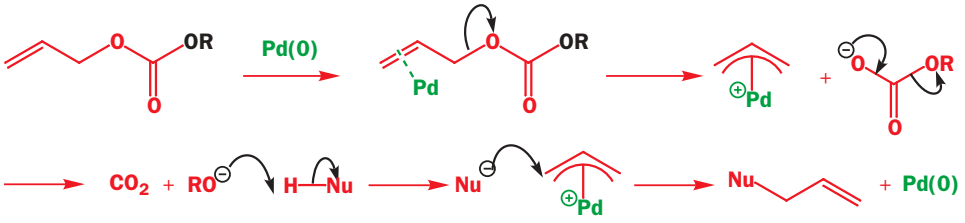
Vinyl epoxides and allylic carbonates are especially useful electrophiles because under the influence of palladium(0) they produce a catalytic amount of base since X^- is an alkoxide anion. This is sufficiently basic to deprotonate most nucleophiles that participate in allylic alkylations and thus no added base is required with these substrates. The overall reaction proceeds under almost neutral conditions, which is ideal for complex substrates. The relief of strain in the three-membered ring is responsible for the epoxide reacting with the palladium(0) to produce the zwitterionic intermediate. Attack of the negatively charged nucleophile at the less hindered end of the π-allyl palladium intermediate preferentially leads to overall 1,4-addition of the neutral nucleophile to vinyl epoxides.



Retention of stereochemistry is demonstrated by the reaction of a substituted malonate with epoxycyclopentadiene. Palladium adds to the side opposite the epoxide so the nucleophile is forced to add from the same side as the OH group. This, no doubt, helps 1,4-regioselectivity. The required palladium(0) phosphine complex was formed from a palladium(II) complex as in the Heck reaction.

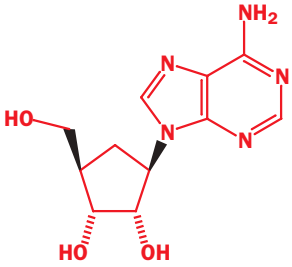


Allylic carbonates produce the required alkoxide by decarboxylation of the carbonate anion that is displaced in the formation of the π-allyl palladium intermediate. Deprotonation creates the active nucleophile, which rapidly traps the π-allyl palladium complex to give the allylated product and regenerates the palladium(0) catalyst.



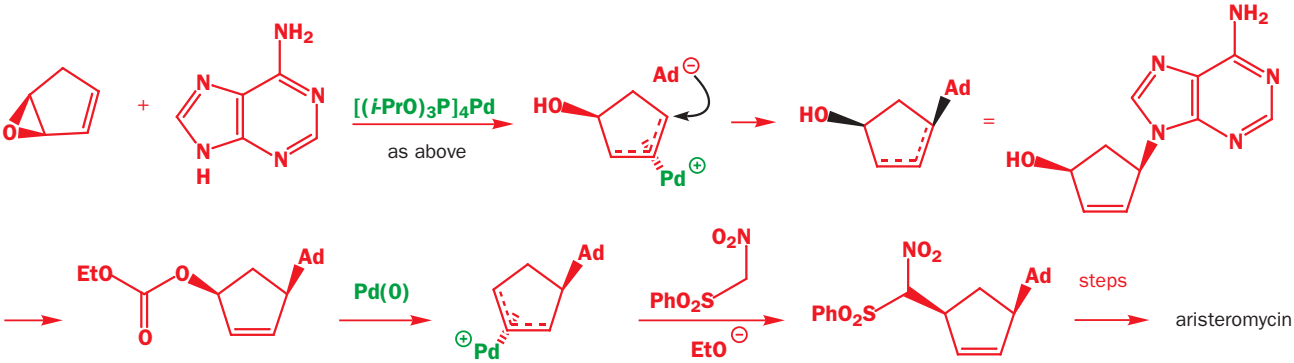
Trost and his group have used both of these palladium-catalysed alkylations in a synthesis of aristeromycin from epoxycyclopentadiene. The *cis* stereochemistry of this carbocyclic nucleotide analogue is of paramount importance and was completely controlled by retention of configuration in both substitutions.

The first reaction is between epoxycyclopentadiene and adenine, one of the heterocyclic building blocks of nucleic acids, and follows the course we have just described to give a *cis*-1,4-disubstituted cyclopentene. The alcohol is then activated by conversion into the carbonate, which reacts with phenylsulfonylnitromethane, which could later be converted into an alcohol. Once again, retention of stereochemistry during the palladium-catalysed substitution gives the *cis* product.



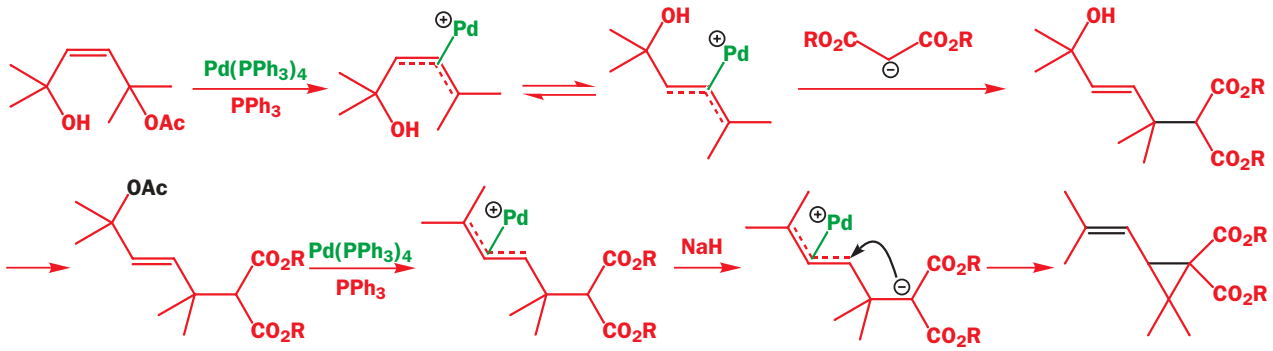
aristeromycin

■ Chapter 49 describes the importance and chemistry of nucleic acids in detail.

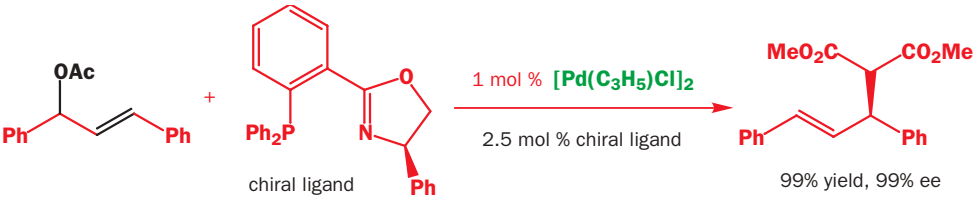


Intramolecular alkylations lead to ring synthesis

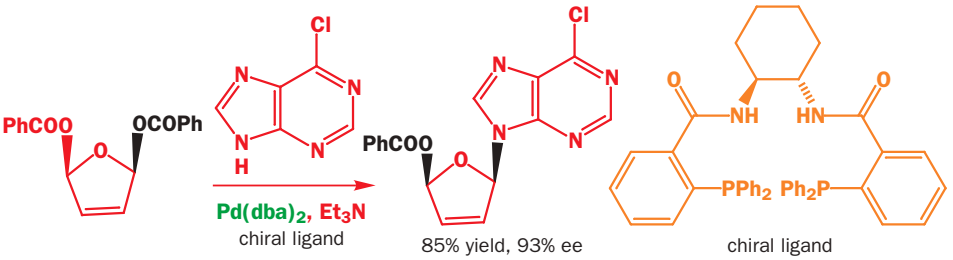
π-Allyl intermediates may also be used in cyclization reactions including the synthesis of small and medium-sized rings using an intramolecular nucleophilic displacement. Three-membered rings form surprisingly easily taking advantage of the fact that the leaving group can be remote from the nucleophile. The precursors can also be prepared by allylic alkylation. The sodium salts of malonate esters react with the monoacetate under palladium catalysis to give the allylic alcohol. Acetylation activates the second alcohol to displacement so that the combination of sodium hydride as base and palladium(0) catalyst leads to cyclization to the cyclopropane. The regioselectivity of the cyclization is presumably governed by steric hindrance as is usual for allylic alkylations with palladium(0).



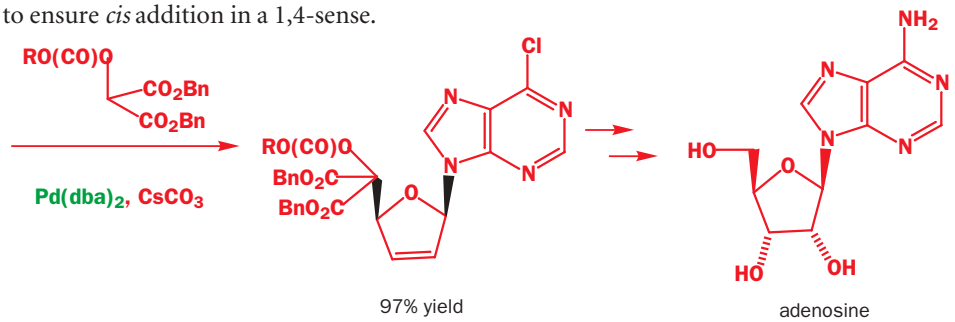
Optically pure ligands on Pd in allylic alkylation can give good enantiomeric excess. You have already seen the first chiral amino-phosphine as the ligand in a chiral Heck reaction and it also gives excellent results in this example. It has to be said, however, that this is a very well behaved example and the next one is more impressive.



A C_2 symmetric bis(amidophosphine) ligand was used by Trost to prepare the natural nucleoside adenosine (see Chapter 49 for nucleosides) in similar fashion to the carbocyclic analogue described above. The key enantioselective step was the first allylic alkylation that selected between two enantiotopic benzoates in the *meso* dihydrofuran derivative to give one enantiomer the expected *cis* product.



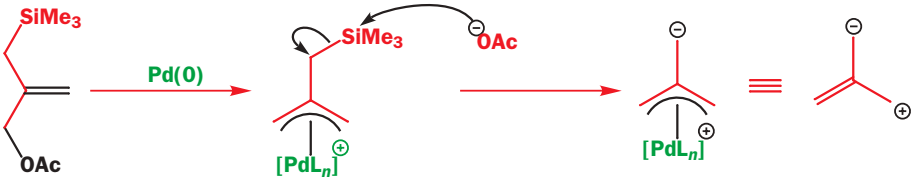
The second benzoate is displaced by a malonate anion, which allows the CH_2OH group to be added at the other side of the dihydrofuran. No enantioselectivity is needed in this step—it is enough to ensure *cis* addition in a 1,4-sense.



Palladium can catalyse cycloaddition reactions

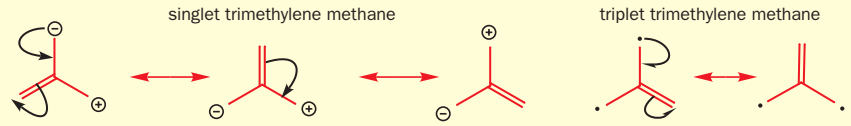
■ Cycloadditions were described in Chapter 35.

The presence of five-membered rings such as cyclopentanes, cyclopentenes, and dihydrofurans in a wide range of target molecules has led to a variety of methods for their preparation. One of the most successful of these is the use of trimethylenemethane [3 + 2] cycloaddition, catalysed by palladium(0) complexes. The trimethylenemethane unit in these reactions is derived from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate which is at the same time an allyl silane and an allylic acetate. This makes it a weak nucleophile and an electrophile in the presence of palladium(0). Formation of the palladium π-allyl complex is followed by removal of the trimethylsilyl group by nucleophilic attack of the resulting acetate ion, thus producing a zwitterionic palladium complex that can undergo cycloaddition reactions.

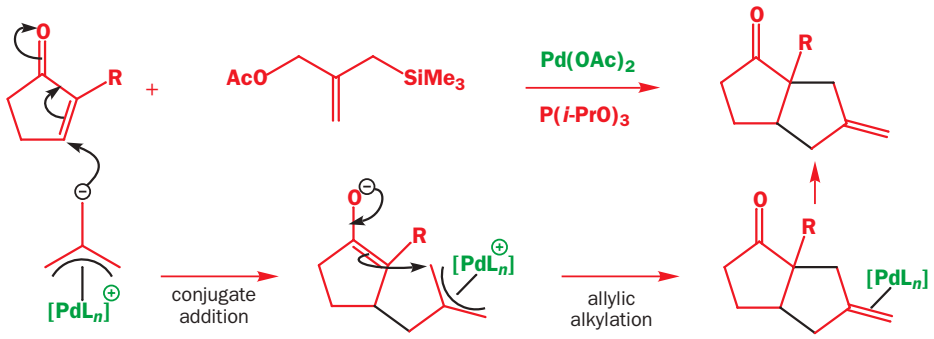


Trimethylene methane

The symmetrical molecule with three CH_2 groups arranged trigonally about a carbon atom is interesting theoretically. It could have a singlet structure with two charges, both of which can be delocalized, but no neutral form can be drawn. Alternatively, it could be a triplet with the two unpaired electrons equally delocalized over the three CH_2 groups. This form is probably preferred and the singlet form is definitely known only as the palladium complex we are now describing. You might compare the singlet and triplet structures of trimethylene methane with those of carbenes in Chapter 40.

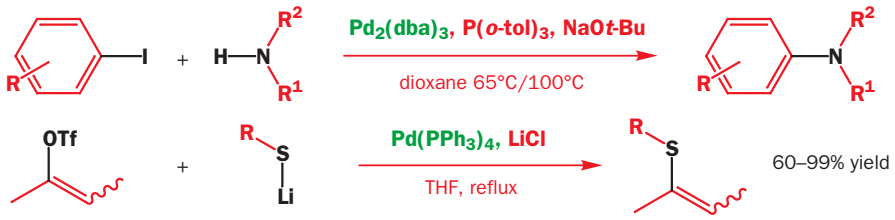


The normal course of the reaction is to react with an alkene with electron-withdrawing substituents present, which make the substrate prone to Michael-type conjugate addition. The resulting cyclization product has an *exo* methylene group. Cyclopentenones illustrate this overall 'cycloaddition' nicely. The mechanism is thought to be stepwise with conjugate addition of the carbanion followed by attack of the resulting enolate on the π-allyl palladium unit to form a five-membered ring—not a real cycloaddition at all.

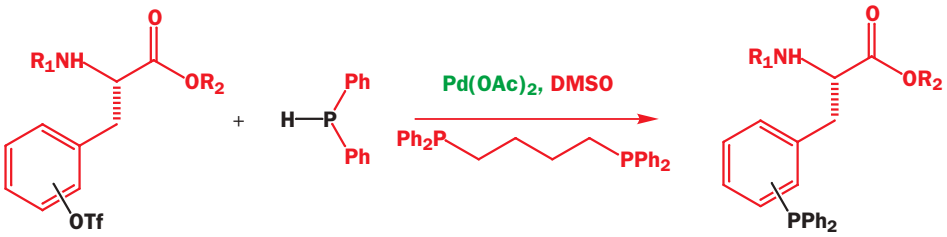


Heteroatom couplings produce aryl– or vinyl– N, –S, or –P bonds

While the major use for palladium catalysis is to make carbon–carbon bonds, which are difficult to make using conventional reactions, the success of this approach has recently led to its application to forming carbon–heteroatom bonds as well. The overall result is a nucleophilic substitution at a vinylic or aromatic centre, which would not normally be possible. A range of aromatic amines can be prepared directly from the corresponding bromides, iodides, or triflates and the required amine in the presence of palladium(0) and a strong alkoxide base. Similarly, lithium thiolates couple with vinylic triflates to give vinyl sulfides provided lithium chloride is present.



The mechanisms and choice of catalyst, usually a palladium(0) phosphine complex, are the same as those of coupling reactions involving oxidative addition, transmetallation, and reductive elimination. Phosphines do not require additional base for the coupling with aromatic triflates and the reaction has no difficulty in distinguishing the two phosphines present.

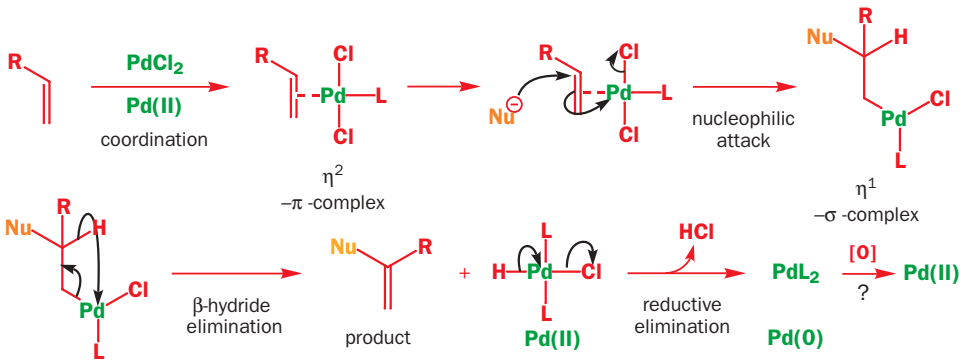


Alkenes are attacked by nucleophiles when coordinated to palladium(II)

The importance of transition-metal-catalysed reactions lies in their ability to facilitate reactions that would not occur under normal conditions. One such reaction is nucleophilic attack on an isolated double bond. While the presence of a conjugating group promotes the attack of nucleophiles, in its absence no such reaction occurs. Coordination of an alkene to a transition metal ion such as palladium(II) changes its reactivity dramatically as electron density is drawn towards the metal and away from the π orbitals of the alkene. This leads to activation towards attack by nucleophiles just as for conjugate addition and unusual chemistry follows. Unusual, that is, for the alkene; the palladium centre behaves exactly as expected.

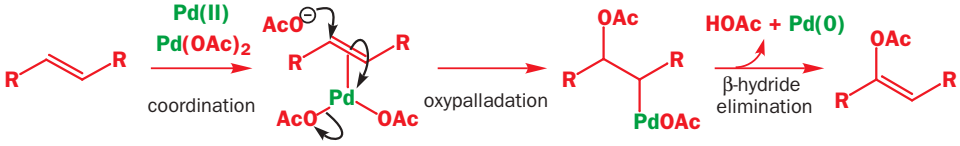
Many nucleophiles, such as water, alcohols, and carboxylates, are compatible with the Pd(II) complex and can attack the complexed alkene from the side opposite the palladium. The attack of the nucleophile is regioselective for the more substituted position. This parallels attack on bromonium ions but is probably governed by the need for the bulky palladium to be in the less hindered position. The resulting Pd(II) σ-alkyl species decomposes by β-hydride elimination to reveal the substituted alkene. Reductive elimination of a proton and the leaving group, usually chloride, leads to palladium(0). The weakness of this reaction is that the catalytic cycle is not complete: Pd(II) not Pd(0) is needed to complex the next alkene.

▶ Unfortunately, this regioselectivity is not the same as in the Heck reaction where attack mostly occurs at the end of the alkene. Internal nucleophiles transferred from the palladium to the alkene usually prefer the end of the alkene but external nucleophiles usually prefer the other end.



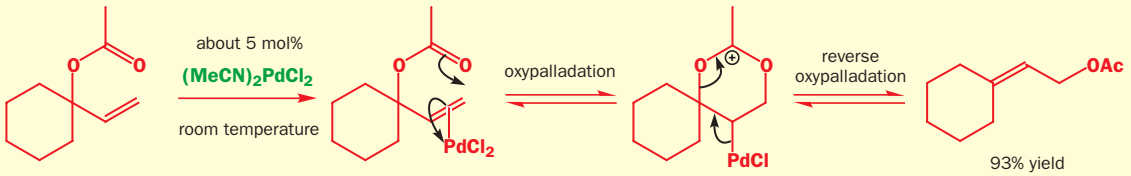
▶ Please note again that our mechanisms for organometallic steps such as oxypalladation are intended to help organic chemists' understanding and may well be disputed by experts.

A Pd(II) salt such as $Pd(OAc)_2$ adds to an alkene to give, via the π complex, a product with Pd at one end of the alkene and OAc at the other. This is oxypalladation but this product is not usually isolated as it decomposes to the substituted alkene. This reaction is occasionally used with various nucleophiles but it needs a lot of palladium.

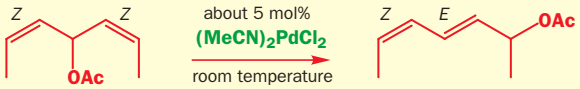


Allylic rearrangement by reversible oxypalladation

An example of catalytic oxypalladation is the rearrangement of allylic acetates with Pd(II). The reaction starts with oxypalladation of the alkene and it is the acetate already present in the molecule that provides the nucleophile to attack the alkene. The intermediate can reverse the oxypalladation in either direction and the product is whichever allylic acetate has the more substituted alkene. In this case, trisubstituted beats monosubstituted easily.

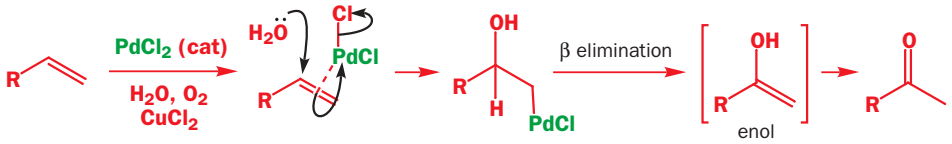


The reaction is *E*-selective, which means that a simple synthesis of an *E,Z*-diene is possible from the symmetrical acetate with two *Z*-allylic alkenes. The one that rearranges goes *E* and the one that stays behind remains *Z*. It does not matter which way the acetate goes. The driving force for this rearrangement, from one disubstituted alkene to another, is establishment of conjugation.

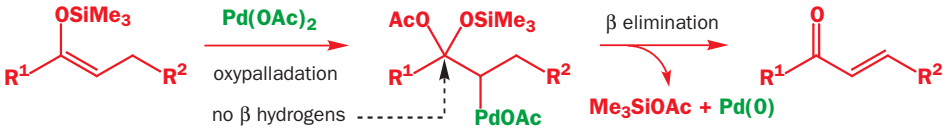


There are two solutions to this problem. We could use stoichiometric Pd(II) but this is acceptable only if the product is very valuable or the reaction is performed on a small scale. It is better to use an external oxidant to return the palladium to the Pd(II) oxidation state so that the cycle can continue. Air alone does not react fast enough (even though Pd(0) must be protected from air to avoid oxidation) but, in combination with Cu(II) chloride, oxygen completes the catalytic cycle. The Cu(II) chloride oxidizes Pd(0) to Pd(II) and is itself oxidized back to Cu(II) by oxygen, ready to oxidize more palladium.

This combination of reagents has been used to oxidize terminal vinyl groups to methyl ketones and is known as the **Wacker oxidation**. The nucleophile is simply water, which attacks the activated alkene at the more substituted end in an oxypalladation step. β-Hydride elimination from the resulting σ-alkyl palladium complex releases the enol, which is rapidly converted into the more stable keto form. Overall, the reaction is a hydration of a terminal alkene that can tolerate a range of functional groups.

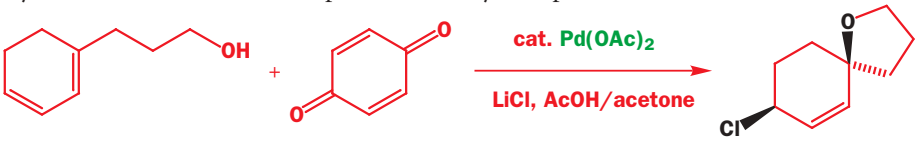


A related reaction is the oxidation of silyl enol ethers to enones. This requires stoichiometric palladium(II), though reoxidation of Pd(0) with benzoquinone can cut that down to about half an equivalent, but does ensure that the alkene is on the right side of the ketone. The first step is again oxypalladation and β elimination puts the alkene in conjugation with the ketone chiefly because there are no β hydrogens on the other side.



Alcohols and amines are excellent intramolecular nucleophiles

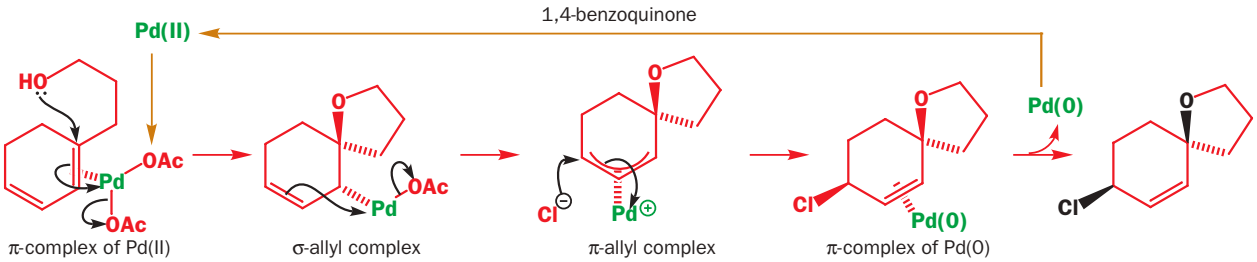
Cyclic ethers and amines can be formed if the nucleophile is an intramolecular alcohol or amine. Stoichiometric palladium can be avoided by using benzoquinone as the stoichiometric oxidant with a catalytic amount of palladium. In this example intramolecular oxypalladation of a diene is followed by attack of an external nucleophile on a π-allyl complex.



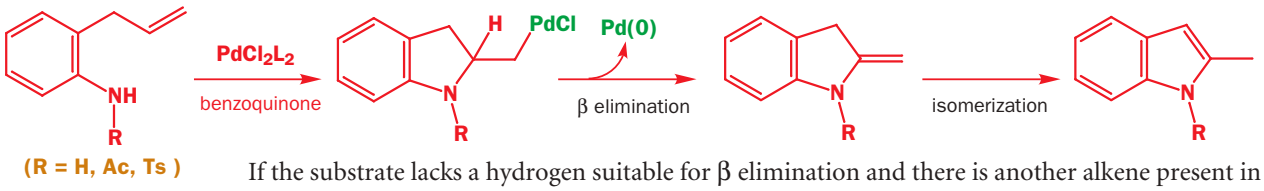
1,4-benzoquinone

73% yield; 99:1 *syn*:*anti*

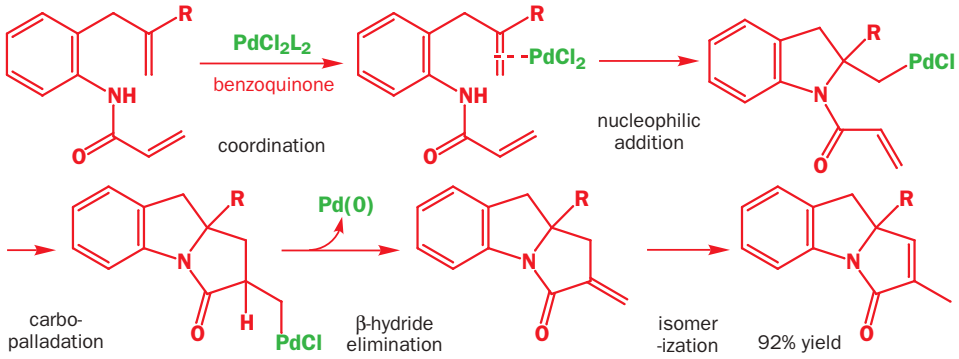
Palladium coordinates to one face of the diene promoting intramolecular attack by the alcohol on the opposite face. The resulting σ-alkyl palladium can form a π-allyl complex with the palladium on the lower face simply by sliding along to interact with the double bond. Nucleophilic attack of chloride from the lithium salt then proceeds in the usual way on the face opposite palladium. The overall addition to the diene is therefore *cis*.



Nitrogen nucleophiles also attack alkenes activated by Pd(II) and benzoquinone can again act as a reoxidant allowing the use of catalytic quantities of palladium. The mechanism follows the same pattern as for oxygen nucleophiles including the final isomerization to produce the most stable regioisomer of product. In this example the product is an aromatic indole (Chapter 43) so the double bond migrates into the five-membered ring.



If the substrate lacks a hydrogen suitable for β elimination and there is another alkene present in the molecule, the σ-alkyl palladium intermediate can follow a Heck pathway to form a bicyclic structure in a tandem reaction sequence. Once again, the final step is a palladium-hydride-mediated isomerization to give the endocyclic alkene.

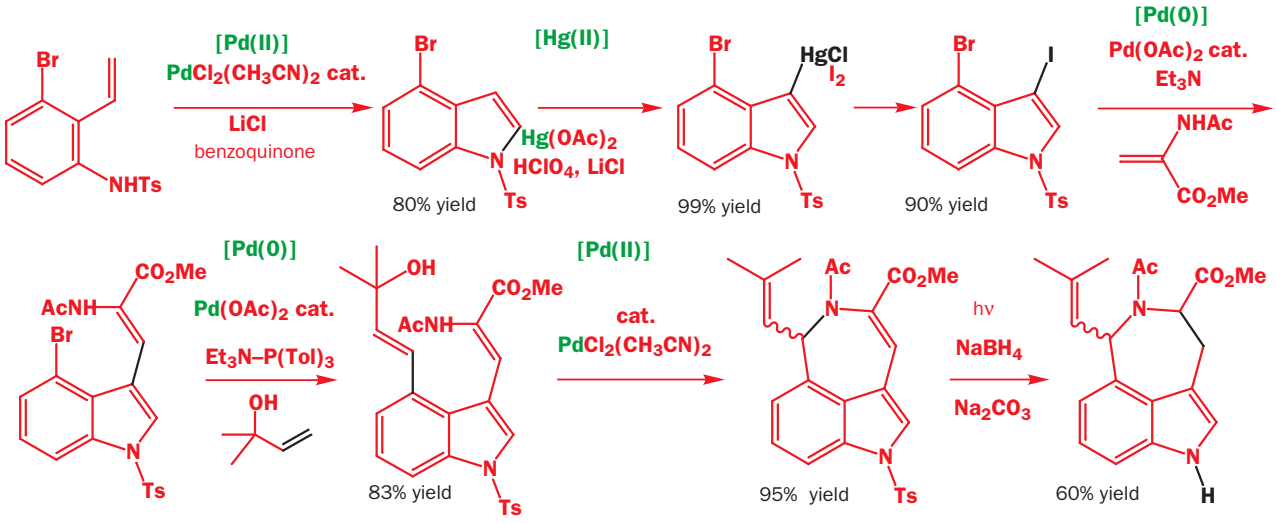


Palladium catalysis in the total synthesis of a natural alkaloid

We end this chapter with a synthesis of *N*-acetyl clavicipitic acid methyl ester, an ergot alkaloid, by Hegedus. The power of organo-transition-metal chemistry is illustrated in five steps of this seven-step process. Each of the organometallic steps catalysed by Pd(0) or Pd(II) has been described in this chapter. The overall yield is 18%, a good result for a molecule of such complexity.

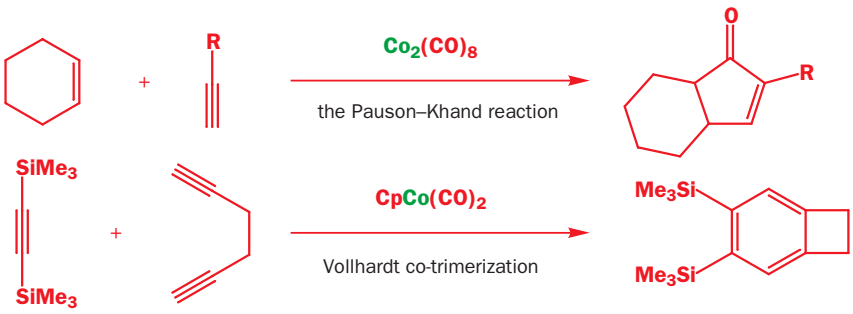
The first step is to make an indole by Pd(II)-catalysed cyclization in the presence of benzoquinone as reoxidant. The nucleophilic nature of the 3-position of the indole (Chapter 43) was exploited to introduce the required iodine functionality. Rather than direct iodination, a high yielding two-step procedure involving mercuration followed by iodination was employed. The more reactive iodide was then involved in a Heck coupling with an unsaturated side chain in the absence of phosphine

ligands. The remaining aromatic bromide then underwent a second Heck reaction with an allylic alcohol to introduce the second side chain. Cyclization of the amide on to the allylic alcohol was achieved with palladium catalysis, not as might have been expected with palladium(0) but instead with palladium(II), to produce the seven-membered ring. Finally, the conjugated double bond was reduced and the sulfonamide removed with sodium borohydride with photolysis.



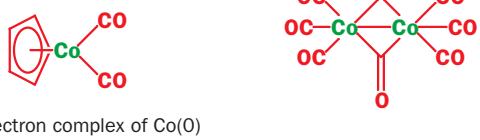
Other transition metals: cobalt

We have concentrated on palladium because it is the most important of the transition metals but we must not leave you with the idea that it is the only one. We shall end with two reactions unique to cobalt—the **Pauson–Khand reaction** that we mentioned right at the start of the chapter and the **Vollhardt co-trimerization**. You will see at once that cobalt has a special affinity with alkynes and with carbon monoxide.



▶ Take care to distinguish between Co and CO in these reactions.

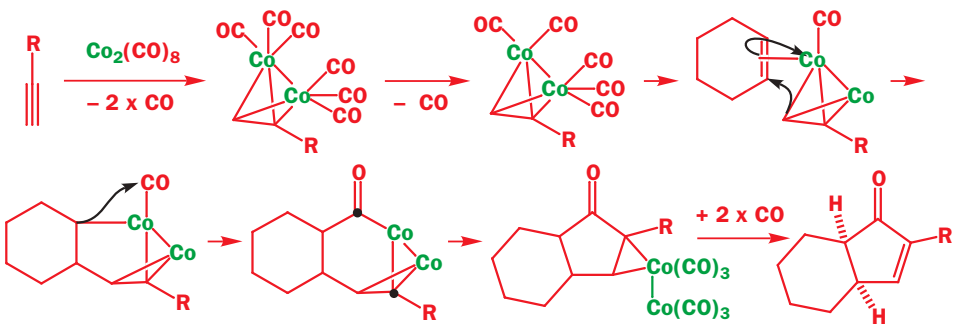
The structure of the cobalt reagents is worth a mention. Cobalt has nine electrons so the second reagent is easy: nine from Co, five from the cyclopentadienyl, and two each from the two COs giving 18 in all. But why is the first reagent a dimer? The monomer $Co(CO)_4$ would have 9 + 8 = 17 electrons.



18-electron complex of Co(0)

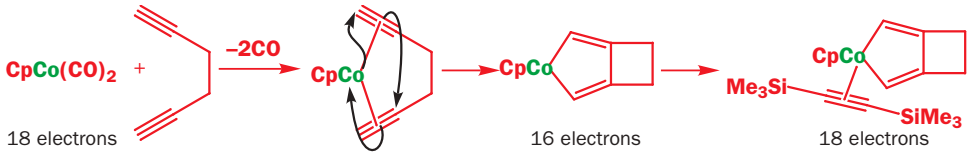
The Pauson–Khand reaction starts with the replacement of two CO molecules, one from each Co atom, with the alkyne to form a double σ complex with two C–Co σ bonds, again one to each Co atom. One CO molecule is then replaced by the alkene and this π complex in its turn gives a σ complex with one C–Co σ bond and one new C–C σ bond, and a C–Co bond is sacrificed in a ligand coupling reaction. Then a carbonyl insertion follows and reductive elimination gives the product, initially as a cobalt complex.

▶ In the middle few structures, showing the vital steps, we omit all CO molecules except the one that reacts.

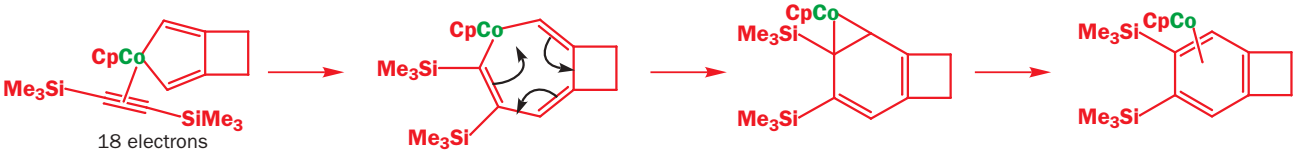


This is an extraordinary reaction because so much seems to happen with no control except the presence of the two cobalt atoms. The alkene reacts so that the more substituted end bonds to the carbonyl group. This is because the ligand coupling occurs to the less substituted end, as in other coupling reactions. The stereochemistry of the alkene is preserved because the coupling step puts the C–C and C–Co bonds in at the same time in a *syn* fashion and the migration to the CO ligand is stereospecific with retention. This is one of the most complicated mechanisms you are likely to meet and few organic chemists can draw it out without looking it up.

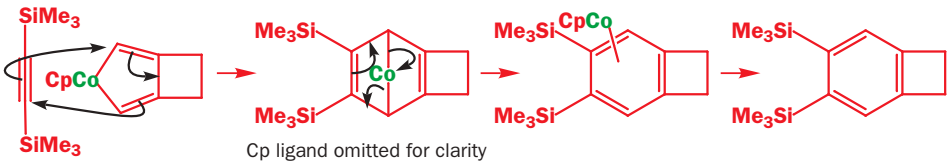
The Vollhardt co-trimerization is so-called because it uses cobalt to bring three alkynes into a ring and it is one of the rare ways of making a benzene ring in one step. First, the dialkyne complexes with the cobalt—each alkyne replaces one CO molecule. Then the double π complex rearranges to a double σ complex by a cycloaddition forming a new C–C σ bond. This new five-membered ring cobalt heterocycle has only 16 electrons so it can accept the remaining alkyne to give an 18-electron complex.



There are now two possible routes to the final product. Reductive elimination would insert the new alkyne into one of the old C–Co bonds and form a seven-membered ring heterocycle. This could close in an electrocyclic reaction to give the new six-membered ring with the cobalt fused on one side and hence the cobalt complex of the new benzene.



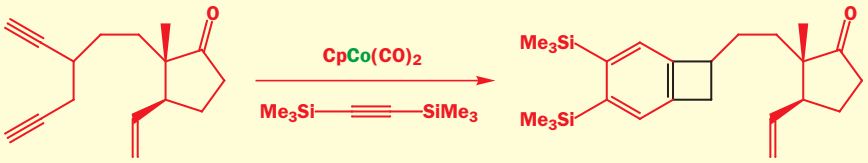
Alternatively, the new alkyne could do a Diels–Alder reaction on the five-membered cobalt heterocycle to give a bridged six-membered ring that could extrude cobalt to give the same benzene complex. The CpCo group can form a stable complex with only four of the benzene electrons and these can be profitably exchanged for two molecules of carbon monoxide to re-form the original catalyst.



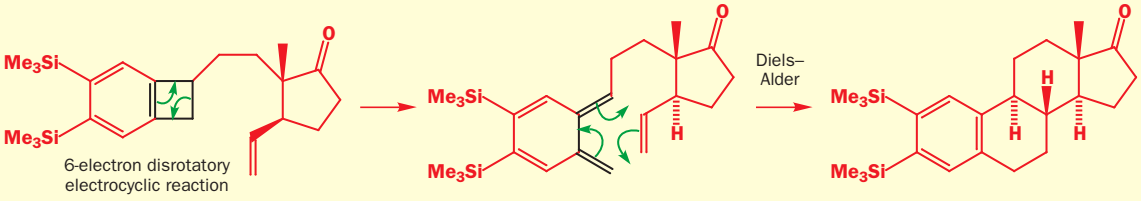
We have selected a few reactions of Co, Fe, and Cu with honourable mentions for Pt, Ir, and Cr. We could have focused on other elements—Ni, W, Ti, Zr, Mn, Ru, and Rh all have special reactions. Transition metal chemistry, particularly involving palladium catalysis, occupies a central role in modern organic synthesis because complex structures can be assembled in few steps with impressive regio- and stereochemical control. There are many books devoted entirely to this subject if you wish to take it further.

Steroid synthesis by the Vollhardt co-trimerization

This product is interesting for two further reactions that revise chemistry from Chapters 36 and 47. If the original acetylene has a special substituent this emerges from the co-trimerization on the four-membered ring.



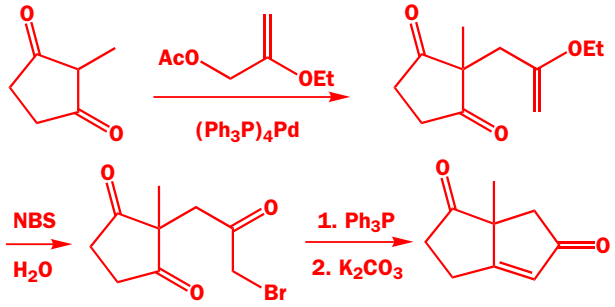
Heating the benzocyclobutene causes an electrocyclic opening (Chapter 36) of the four-membered ring to give a diene that does an intramolecular Diels–Alder rearrangement on the alkene attached to the five-membered ring. The product has the skeleton of the steroids (Chapter 51).



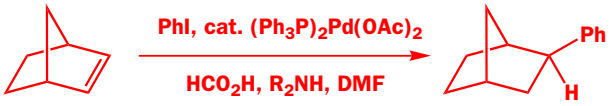
This compound is not a steroid because steroids do not have Me_3Si groups, but these can be removed (Chapter 47) by protodesilylation and this sequence is a very short synthesis of an important compound.

Problems

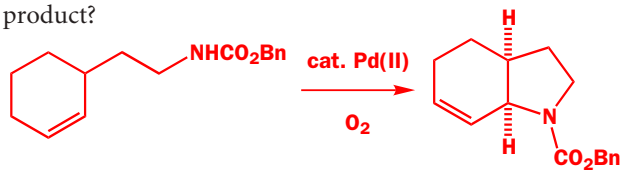
1. Suggest mechanisms for these reactions, explaining the role of palladium in the first step.



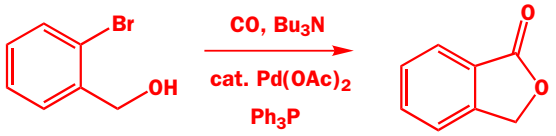
2. This Heck style reaction does not lead to regeneration of the alkene. Why not? What is the purpose of the formic acid (HCO_2H) in the reaction mixture?



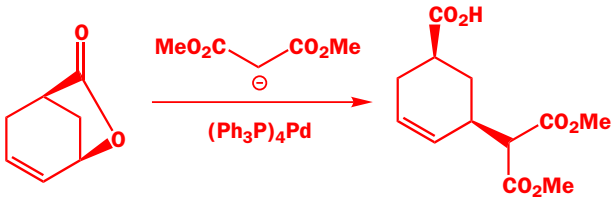
3. Cyclization of this unsaturated amine with catalytic Pd(II) under an atmosphere of oxygen gives a cyclic unsaturated amine in 95% yield. How does the reaction work? Why is the atmosphere of oxygen necessary? Explain the stereo- and regiochemistry of the reaction. How would you remove the CO_2Bn group from the product?



4. Suggest a mechanism for this lactone synthesis.



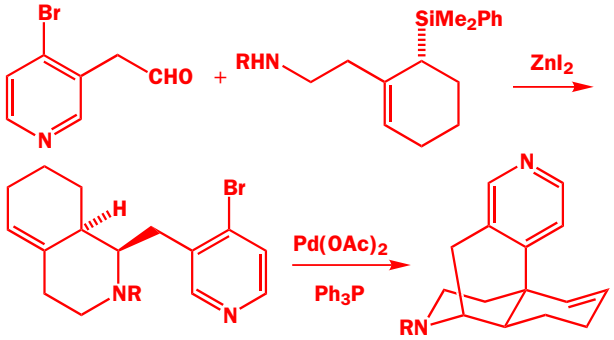
5. Explain why enantiomerically pure lactone gives all *syn* but racemic product in this palladium-catalysed reaction.



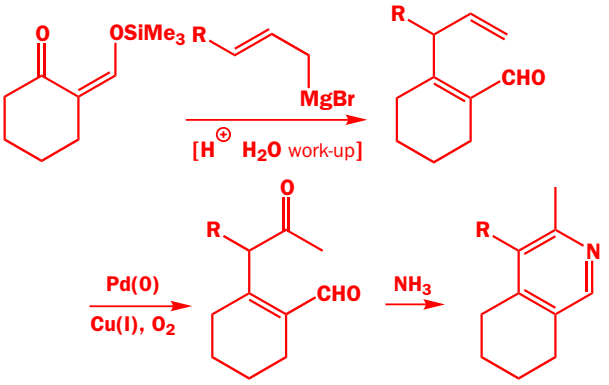
(–)-lactone

all *syn* but racemic

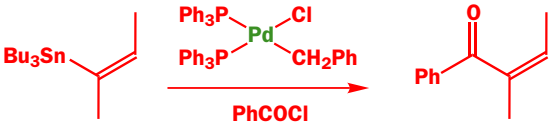
6. Revision of Chapter 47. The synthesis of a bridged tricyclic amine shown below starts with an enantiomerically pure allyl silane. Give mechanisms for the reactions, explaining how the stereochemistry is controlled in each step.



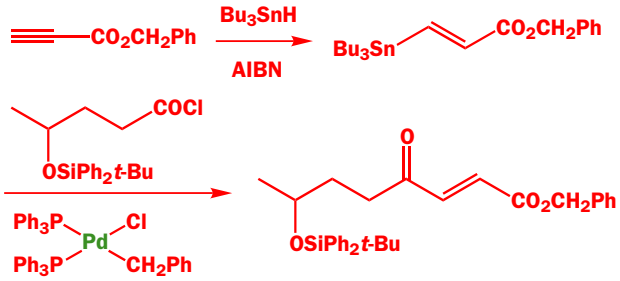
7. Revision of Chapter 44. Explain the reactions in this sequence commenting on the regioselectivity of the organometallic steps.



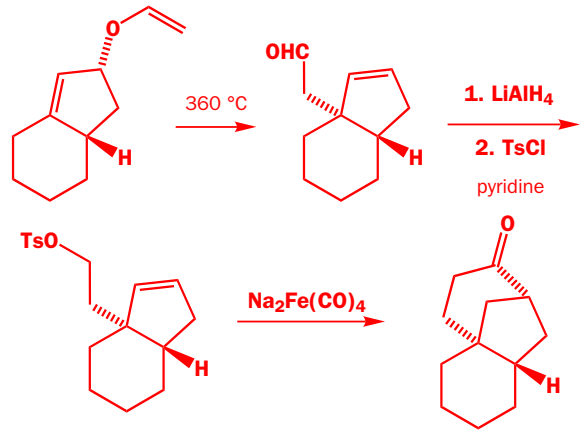
8. Give a mechanism for this carbonylation reaction. Comment on the stereochemistry and explain why the yield is higher if the reaction is carried out under a carbon monoxide atmosphere.



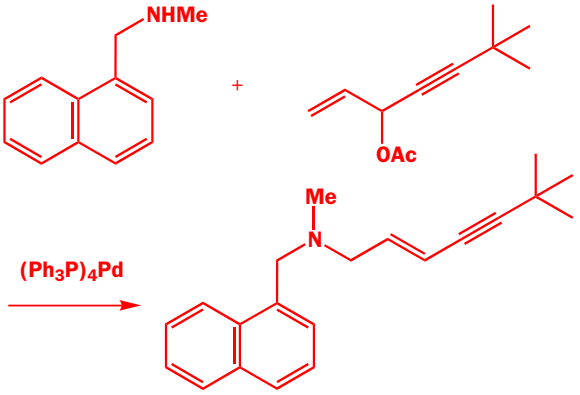
Hence explain this synthesis of part of the antifungal compound pyrenophorin.



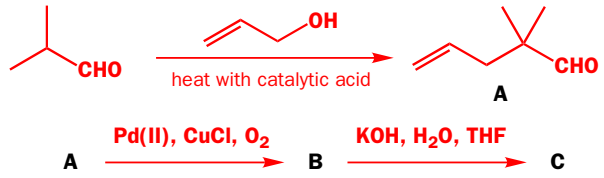
9. Explain the mechanism and stereochemistry of these reactions. The first is revision and the second is rather easy!



10. The synthesis of an antifungal drug was completed by this palladium-catalysed reaction. Give a mechanism and explain the regio- and stereoselectivity.



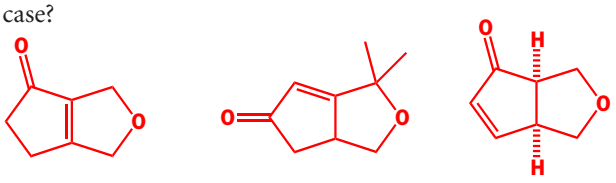
11. Some revision content. Work out the structures of the compounds in this sequence and suggest mechanisms for the reactions, explaining any selectivity.



B has IR: 1730, 1710 cm^{-1}; δ_H 9.4 p.p.m. (1H, s), 2.6 p.p.m. (2H, s), 2.0 p.p.m. (3H, s), and 1.0 p.p.m. (6H, s).

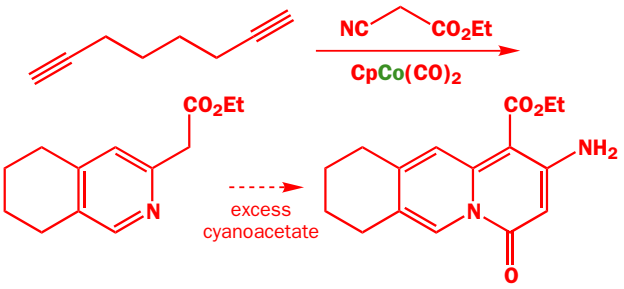
C has IR: 1710 cm^{-1}; δ_H 7.3 p.p.m. (1H, d, *J* 5.5 Hz), 6.8 p.p.m. (1H, d, *J* 5.5 Hz), 2.1 p.p.m. (2H, s), and 1.15 p.p.m. (6H, s).

12. Revision of Chapter 36. What would be the starting materials for the synthesis of these cyclopentenones by the Nazarov reaction and by the Pauson–Khand reaction? Which do you prefer in each case?

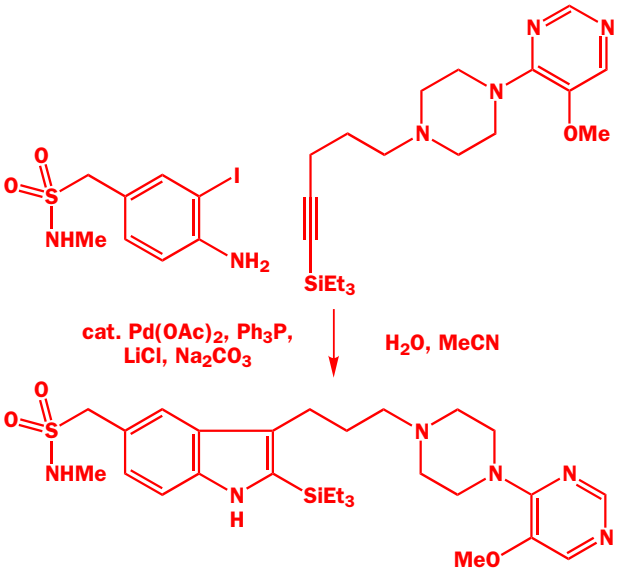


Nazarov Pauson–Khand Pauson–Khand

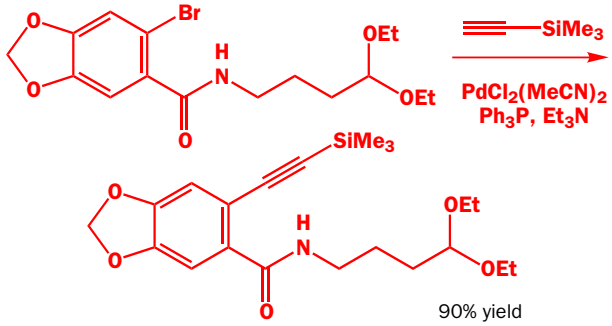
13. A variation on the Vollhardt co-trimerization allows the synthesis of substituted pyridines. Draw the structures of the intermediates in this sequence. In the presence of an excess of the cyanoacetate a second product is formed. Account for this too.



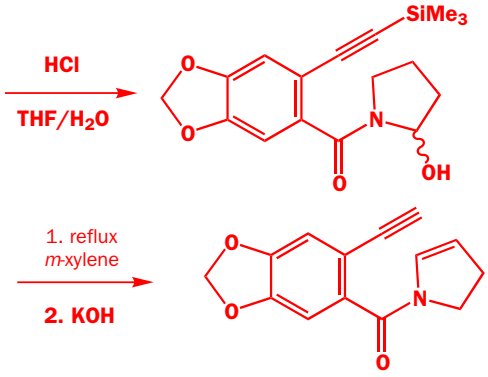
14. The synthesis of the Bristol–Myers Squibb anti-migraine drug Avitriptan (a 5-HT1D receptor antagonist) involves this palladium-catalysed indole synthesis. Suggest a mechanism and comment on the regioselectivity of the alkyne attachment.



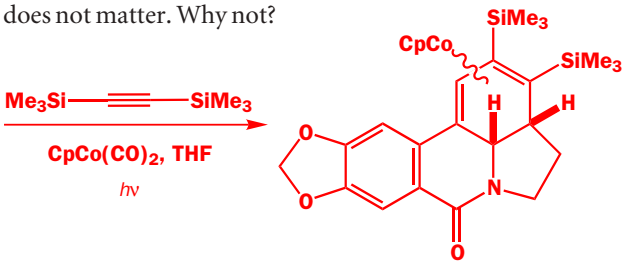
15. A synthesis of the natural product γ-lycorane starts with a palladium-catalysed reaction. What sort of a reaction is this, and how does it work?



The next two steps are a bit of revision: draw mechanisms for them and comment on the survival of the Me_3Si group.

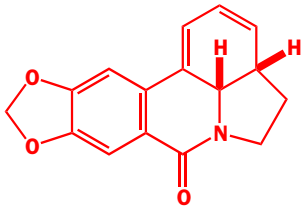


Now the key step—and you should recognize this easily. What is happening here? Though the product is a mixture of isomers, this does not matter. Why not?



65% yield, 3:2 Co up : Co down

Finally, this mixture must be converted into γ-lycorane: suggest how this might be done.



γ-lycorane

The chemistry of life

49

Connections

Building on:

- Acidity and basicity ch8
- Carbonyl chemistry ch12 & ch14
- Stereochemistry ch16
- Conformational analysis ch18
- Enolate chemistry and synthesis ch24–ch30
- Heterocycles ch42–ch44
- Asymmetric synthesis ch45
- Sulfur chemistry ch46

Arriving at:

- Nucleic acids store information for the synthesis of proteins
- Modified nucleosides can be used as antiviral drugs
- Nucleotides have a role in energy storage
- Proteins catalyse reactions and provide structure
- Other amino acid derivatives act as methylating and reducing agents
- Sugars store energy, enable recognition, and protect sensitive functional groups
- How to make and manipulate sugars and their derivatives
- Lipids form the basis of membrane structures

Looking forward to:

- Mechanisms in biological chemistry ch50
- Natural products ch51
- Polymers ch52

Life runs on chemistry, and the chemical side of biology is fascinating for that reason alone. But from the point of view of a textbook, biological chemistry's combination of structures, mechanisms, new reactions, and synthesis is also an ideal revision aid. We shall treat this chemistry of living things in three chapters.

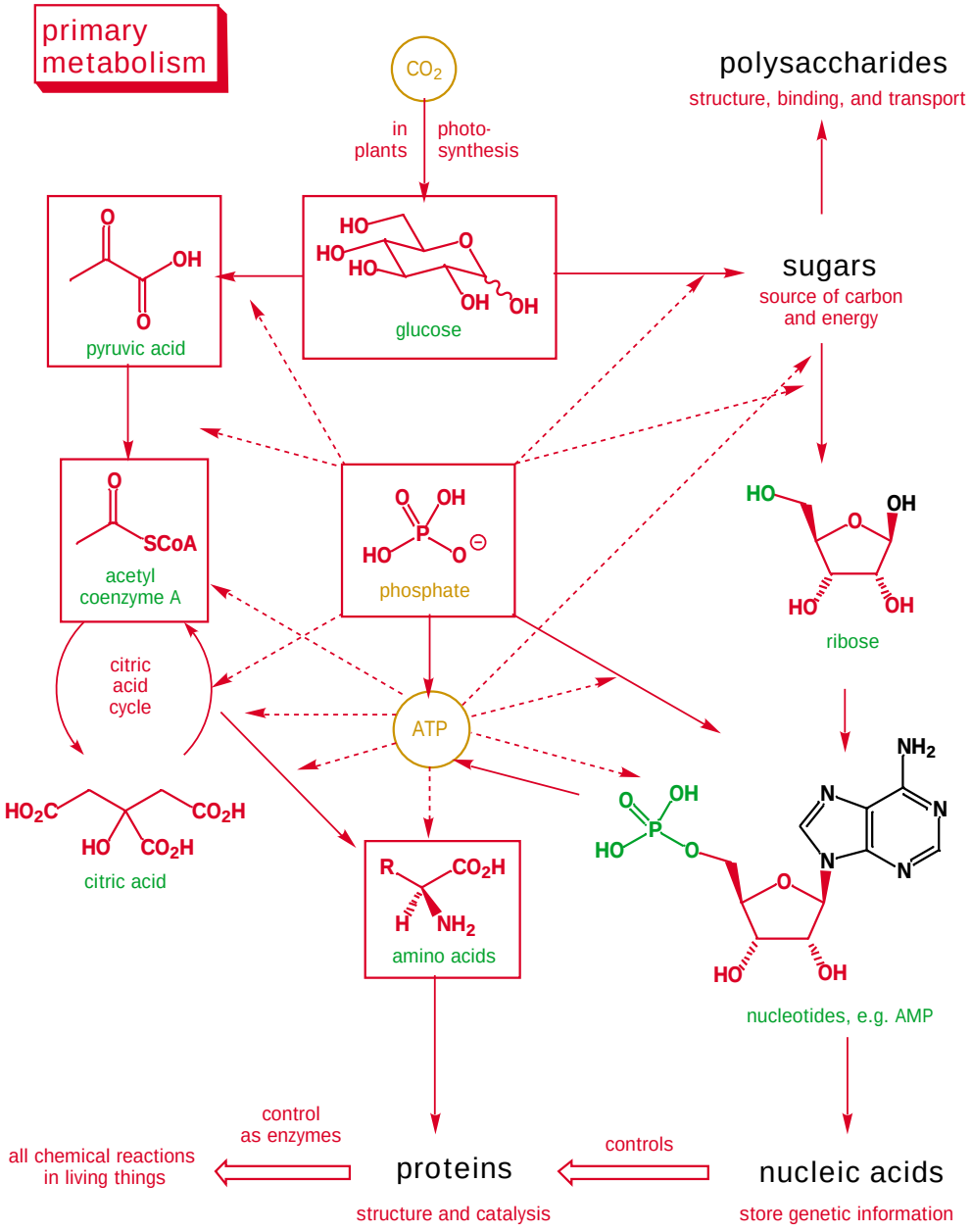
- Chapter 49 introduces the basic molecules of life and explains their roles along with some of their chemistry
- Chapter 50 discusses the mechanisms of biological reactions
- Chapter 51 develops the chemistry of compounds produced by life: natural products

We start with the most fundamental molecules and reactions in what is called primary metabolism.

Primary metabolism

It is humbling to realize that the same molecules are present in all living things from the simplest single-cell creatures to ourselves. Nucleic acids contain the genetic information of every organism, and they control the synthesis of proteins. Proteins are partly structural—as in connective tissue—and partly functional—as in enzymes, the catalysts for biological reactions. Sugars and lipids used to be the poor relations of the other two but we now realize that, as well as having a structural role in membranes, they are closely associated with proteins and have a vital part to play in recognition and transport.

The chart overleaf shows the molecules of primary metabolism and the connections between them, and needs some explanation. It shows a simplified relationship between the key structures (emphasized in large black type). It shows their origins—from CO_2 in the first instance—and picks out some important intermediates. Glucose, pyruvic acid, citric acid, acetyl coenzyme A (Acetyl CoA), and ribose are players on the centre stage of our metabolism and are built into many important molecules.



The arrows used in the chart have three functions.

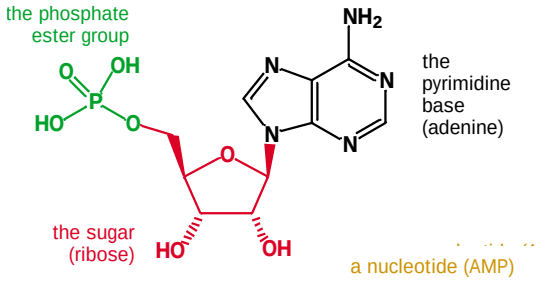
chemical reaction in the usual sense: the starting material is incorporated into the product

compound needed for the reaction but not always incorporated into the product

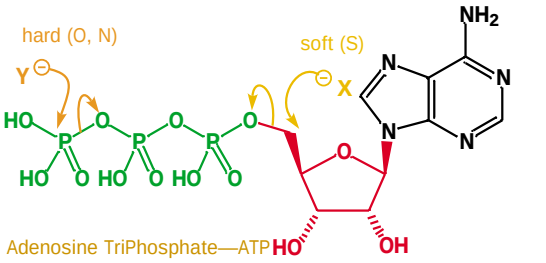
compound involved in controlling a reaction: *not* incorporated into the products

We hope that this chart will allow you to keep track of the relationships between the molecules of metabolism as you develop a more detailed understanding of them. We will now look briefly at each type of molecule.

Life begins with nucleic acids



Nucleic acids are unquestionably top level molecules because they store our genetic information. They are polymers whose building blocks (monomers) are the nucleotides, themselves made of three parts—a heterocyclic base, a sugar, and a phosphate ester. A nucleo*side* lacks the phosphate. In the example alongside, adenine is the base (black), adeno*sine* is the nucleo*side* (base and sugar), and the nucleotide is the whole molecule (base + sugar + phosphate).



This nucleotide is called AMP—Adenosine MonoPhosphate. Phosphates are key compounds in nature because they form useful stable linkages between molecules and can also be built up into reactive molecules by simply multiplying the number of phosphate residues. The most important of these nucleotides is also one of the most important molecules in nature—Adenosine TriPhosphate or ATP.

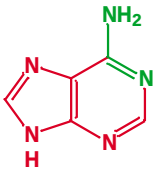
ATP is a highly reactive molecule because phosphates are stable anions and good leaving groups. It can be attacked by hard nucleophiles at a phosphate group (usually the end one) or by soft nucleophiles at the CH_2 group on the sugar. We shall see examples of both reactions soon. When a new reaction is initiated in nature, very often the first step is a reaction with ATP to make the compound more reactive. This is rather like our use of TsCl to make alcohols more reactive or converting acids to acid chlorides to make them more reactive.

There are five heterocyclic bases in DNA and RNA

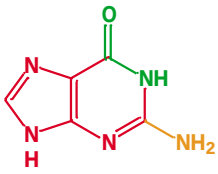
In nucleic acids there are only five bases, two sugars, and one phosphate group possible. The bases are monocyclic pyrimidines or bicyclic purines and are all aromatic.

- There are only two purine bases found in nucleic acids, adenine (A), which we have already met, and guanine (G)
- The three pyrimidine bases are the simpler and they are uracil (U), thymine (T), and cytosine (C). Cytosine is found in DNA and RNA, uracil in RNA only, and thymine in DNA only.

purine bases in nucleic acids

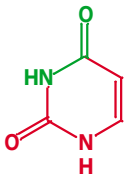


adenine

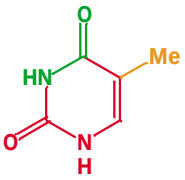


guanine

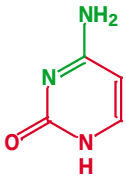
pyrimidine bases in nucleic acids



uracil



thymine



cytosine

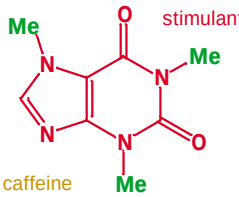
■ You met pyrimidines on p. 000 and learned how to make them on p. 000, but the purine ring system may be new to you. It isn't always easy to find the six (or ten!) electrons in these compounds. Check for yourself that you can do this. You may need to draw delocalized structures especially for U, T, and G.

The stimulants in tea and coffee are methylated nucleic acid purines

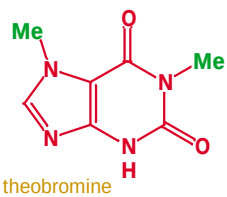
An important natural product for most of us is a fully methylated purine present in tea and coffee—caffeine. Theobromine, the partly methylated version, is present in chocolate, and both caffeine and theobromine act as stimulants. Caffeine is a crystalline substance easily extracted from coffee or tea with organic solvents. It is extracted industrially with liquid CO_2 (or if you prefer 'Nature's natural effervescence') to make decaffeinated tea and coffee.

If we, as chemists, were to add those methyl groups we should use something like MeI, but Nature uses a much more complicated reagent. There is a great deal of methylating going on in living

stimulant purines

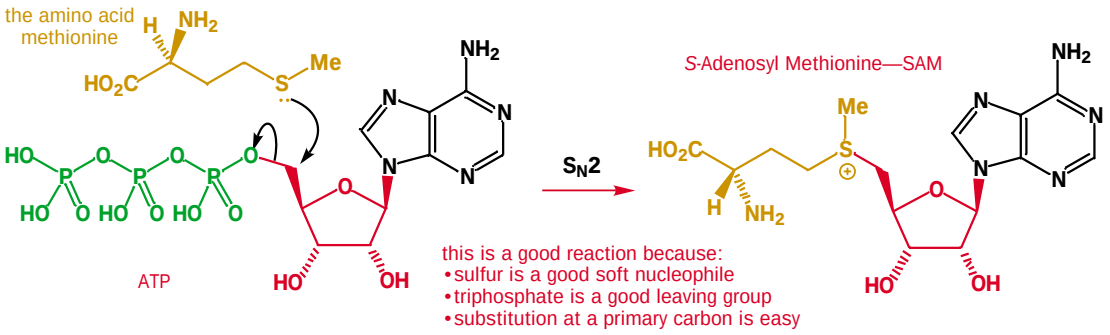


caffeine



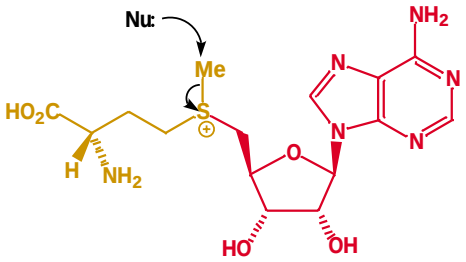
theobromine

things—and the methyl groups are usually added by *S*-adenosyl methionine (or SAM), formed by reaction of methionine with ATP.

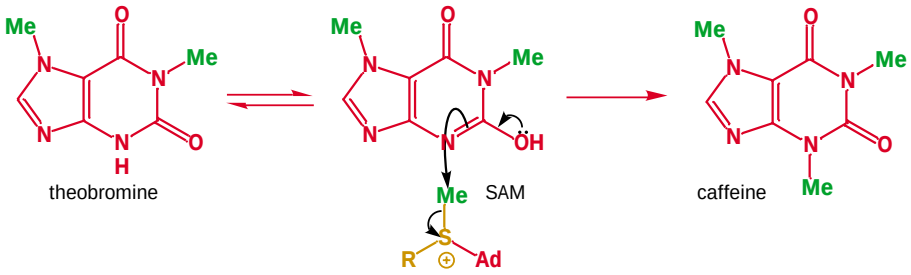


The product (SAM) is a sulfonium salt and could be attacked by nucleophiles at three different carbon atoms. Two are primary centres—good for S_N2 reactions—but the third is the methyl group, which is even better. Many nucleophiles attack SAM in this way.

nucleophilic attack on SAM, Nature's methylating agent



In the coffee plant, theobromine is converted into caffeine with a molecule of SAM. The methylation occurs on nitrogen partly because this preserves both the aromatic ring and the amide functionality and also because the enzyme involved brings the two molecules together in the right orientation for *N*-methylation.



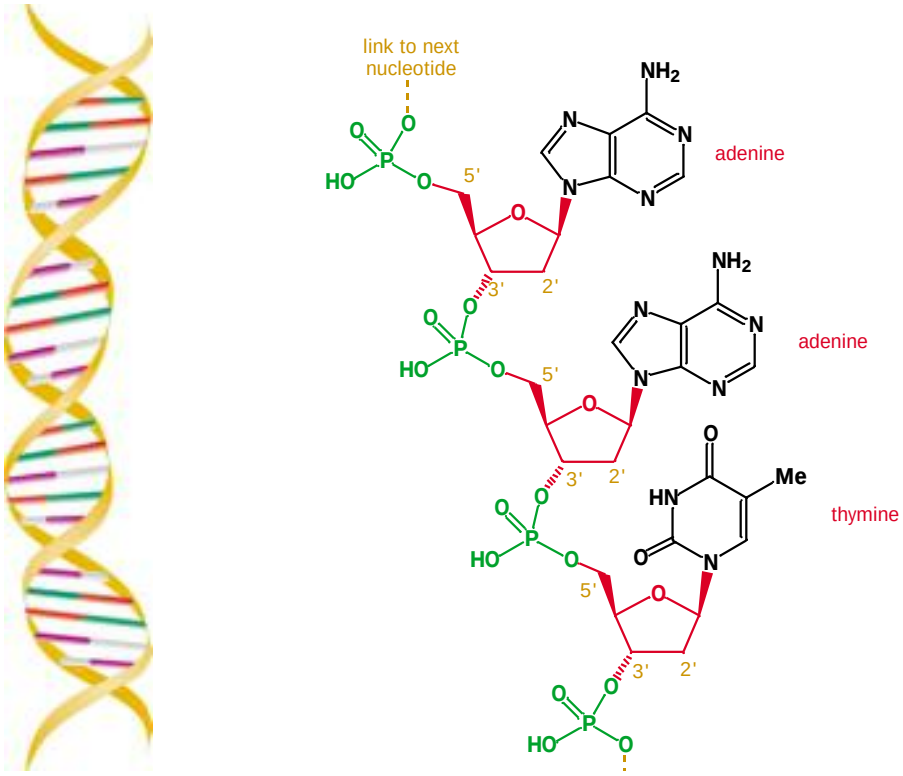
At this point we should just point out something that it's easy to forget: there is *only one chemistry*. There is no magic in biological chemistry, and Nature uses the same chemical principles as we do in the chemical laboratory. All the mechanisms that you have studied so far will help you to draw mechanisms for biological reactions and most reactions that you have met have their counterparts in nature. The difference is that Nature is very very good at chemistry, and all of us are only just learning. We still do much more sophisticated reactions *inside* our bodies without thinking about them than we can do *outside* our bodies with all the most powerful ideas available to us at the beginning of the twenty-first century.

Nucleic acids exist in a double helix

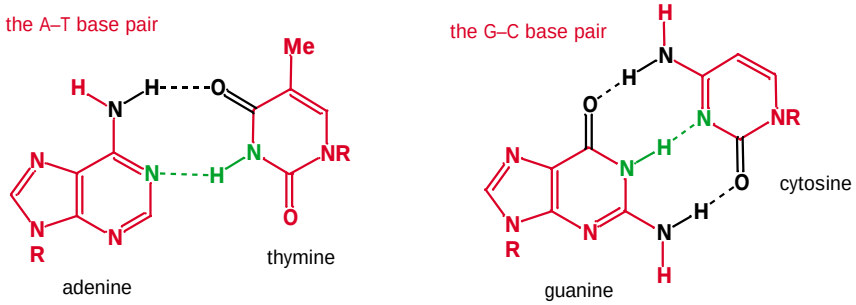
One of the most important discoveries of modern science was the elucidation of the structures of DNA and RNA as the famous double helix by Watson and Crick in 1953. They realized that the basic structure of base–sugar–phosphate was ideal for a three-dimensional coil. The structure of a small part of DNA is shown opposite.

Notice that the 2′ (pronounced 'two prime') position on the ribose ring is vacant. There is no OH group there and that is why it is called *Deoxy*ribo-*N*ucleic *A*cid (DNA). The nucleotides link the two

remaining OH groups on the ribose ring and these are called the 3′- and 5′-positions. This piece of DNA has three nucleotides (adenine, adenine, and thymine) and so would be called –AAT– for short.



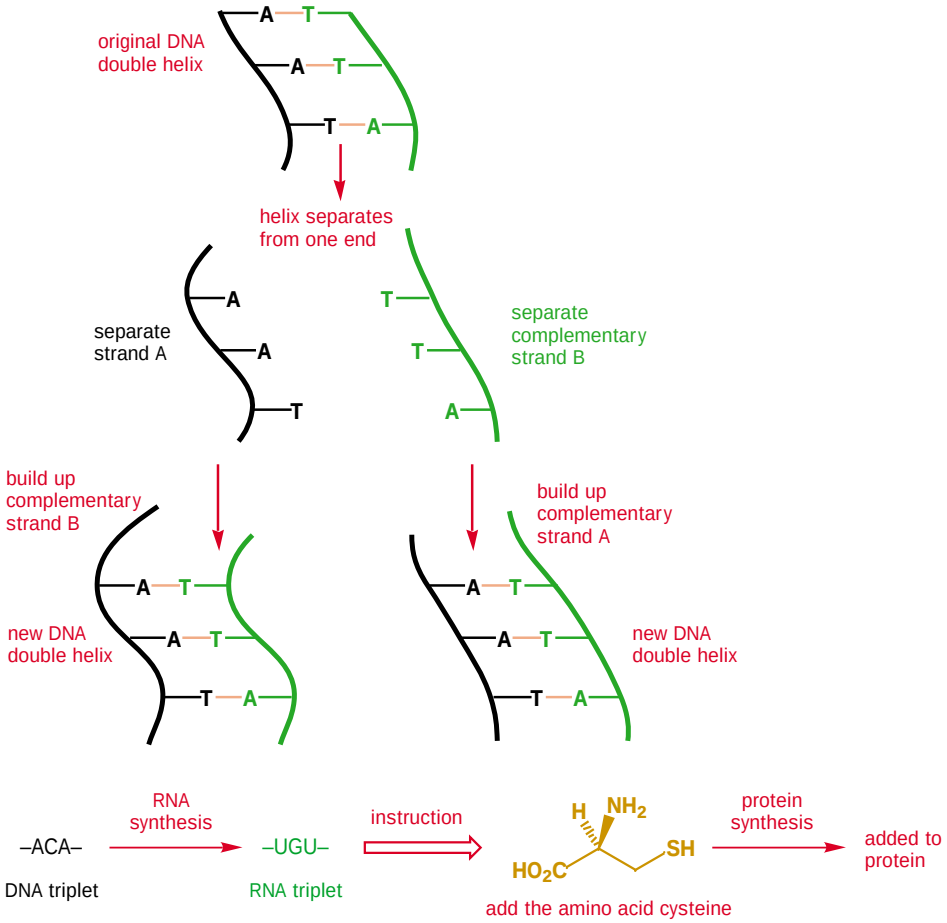
Each polymeric strand of DNA coils up into a helix and is bonded to another strand by hydrogen bonds between the bases. Each base pairs up specifically with another base —adenine with thymine (A–T) and guanine with cytosine (G–C)—like this.



There is quite a lot to notice about these structures. Each purine (A or G) is bonded specifically to one pyrimidine (T or C) by two or by three hydrogen bonds. The hydrogen bonds are of two kinds: one links an amine to a carbonyl group (black in the diagram) and one links an amine to an imine (green in the diagram). In this way, each nucleotide reliably recognizes another and reliably pairs with its partner. The short strand of DNA above (–ATT–) would pair reliably with –TTA–.

How the genetic information in DNA is passed to proteins

In the normal structure of DNA each strand is paired with another strand called the complementary strand because it has each base paired with its complementary base. When DNA replicates, the strands separate and a new strand with complementary structure grows alongside each. In this way the original double helix now becomes two identical double helices and so on.



This is a crude simplification of a beautiful process and you should turn to a biochemistry textbook for more details. The actual building up of a strand of DNA obviously involves a complex series of chemical reactions. The DNA is then used to build up a complementary strand of RNA, which *does* have the 2′ hydroxyl group, and the RNA then instructs the cell on protein synthesis using three-nucleotide codes to indicate different amino acids. Again, the details of this process are beyond the scope of this book, but the code is not.

Each set of three nucleotides (called a triplet or codon) in a DNA molecule tells the cell to do something. Some triplets tell it to start work or stop work but most represent a specific amino acid. The code UGU in RNA tells the cell 'add a molecule of cysteine to the protein you are building'. The code UGA tells the cell 'stop the protein at this point'. So a bit of RNA reading UGUUGA would produce a protein with a molecule of cysteine at the end.

There are four bases available for DNA and so there are $4^3 = 64$ different triplet codons using three bases in each codon. There are only 20 amino acids used in proteins so that gives plenty of spare codons. In fact 61 of the 64 are used as codons for amino acids and the remaining three are 'stop' signals. Thus the code ATT in DNA would produce the complementary UAA and this is another 'stop' signal.

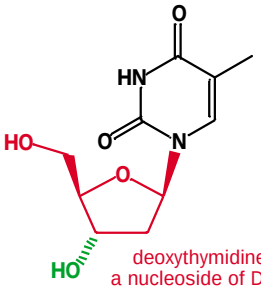
Base	Complementary base in DNA	Complementary base in RNA
A	T	U
C	G	G
G	C	C
U	*	*
T	A	a

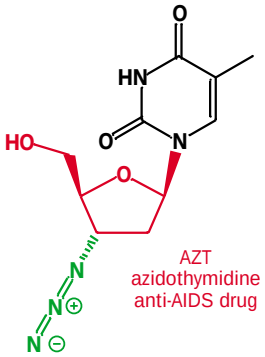
* T occurs in DNA only and is replaced by U in RNA.

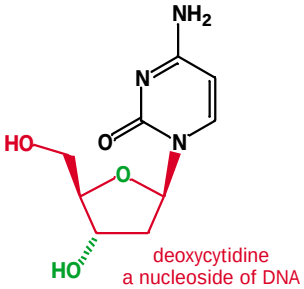
But that doesn't leave a 'start' signal! This signal is the same (TAC in DNA = AUG in RNA) as that for the amino acid methionine, which you met as a component of SAM, the biological methylating agent. In other words, all proteins start with methionine. At least, they are all made that way, though the methionine is sometimes removed by enzymes before the protein is released. These code letters are the same for all living things except for some minor variations in some microorganisms.

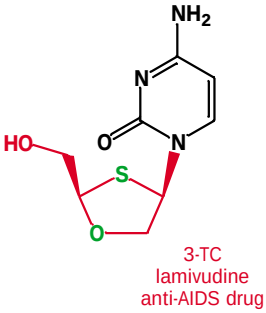
AIDS is being treated with modified nucleosides

Modified nucleosides have proved to be among the best antiviral compounds. The most famous anti-AIDS drug, AZT (zidovudine from GlaxoWellcome), is a slightly modified DNA nucleoside (3′-azidothymidine). It has an azide at C3′ instead of the hydroxyl group in the natural nucleoside.





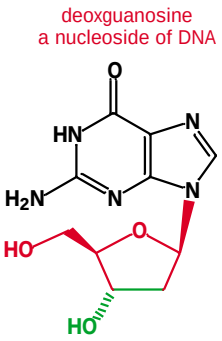


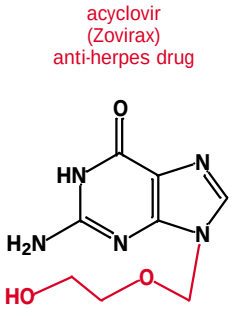


Doctors are having some spectacular success at the moment (1999) against HIV and AIDS by using a combination of AZT and a much more modified nucleoside 3-TC (lamivudine) which is active against AZT-resistant viruses. This drug is based on cytosine but the sugar has been replaced by a different heterocycle though it is recognizably similar especially in the stereochemistry.

The last drug to mention is acyclovir (Zovirax), the cold sore (herpes) treatment. Here is a modified guanosine in which only a ghost of the sugar remains. There is no ring at all and no stereochemistry.

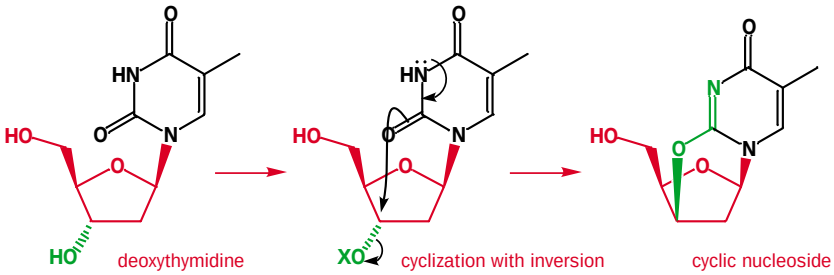
The bottom edge of the sugar ring has been done away with so that a simple alkyl chain remains. This compound has proved amazingly successful as an antiviral agent and it is highly likely that more modified nucleosides will appear in the future as important drugs.



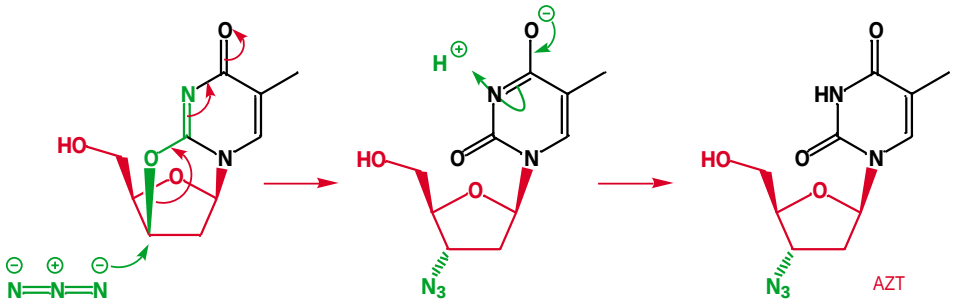


Cyclic nucleosides and stereochemistry

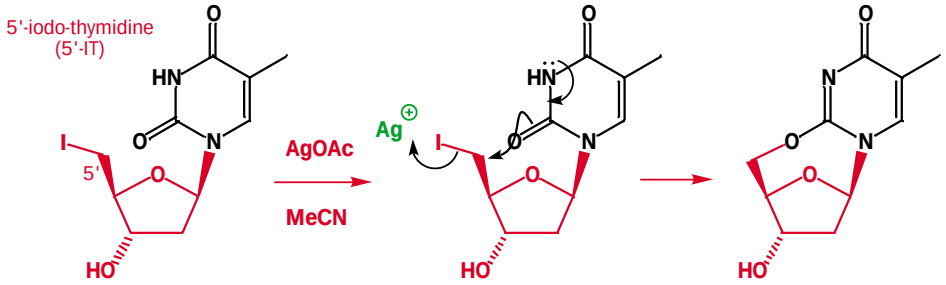
We know the relative stereochemistry around the ribose ring of the nucleosides in DNA and RNA because the bases can be persuaded to cyclize on to the ring in certain reactions. Treatment of deoxythymidine with reagents that make oxygen atoms into leaving groups leads to cyclization by intramolecular S_N2 reaction. The amide oxygen of the base attacks the 3′-position in the sugar ring.



This S_N2 reaction has to happen with inversion, proving that the base and the 3′-OH group are on opposite sides of the ribose ring. The cyclized product is useful too. If it is reacted with azide ion the ring reopens with inversion in another S_N2 reaction and AZT is formed.

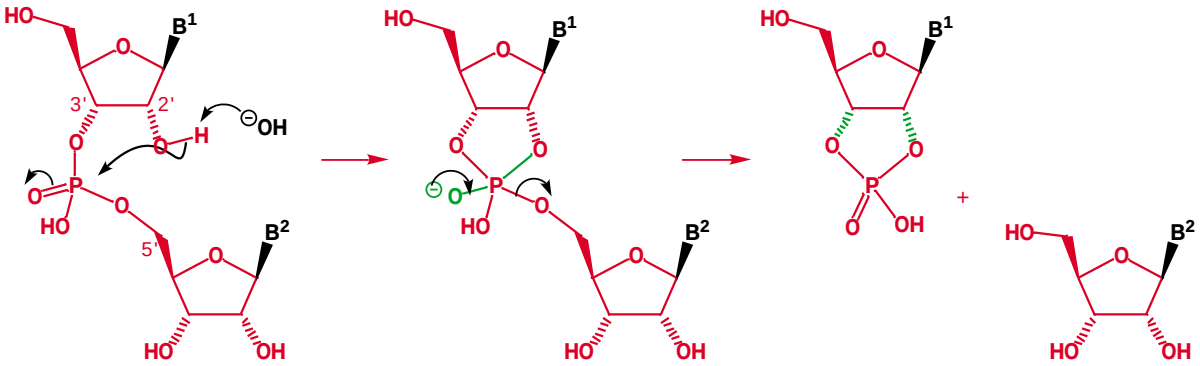


We can show that the primary alcohol is on the same side of the ring as the base by another cyclization reaction. Treatment of the related iodide with a silver(I) salt gives a new seven-membered ring. This reaction can happen only with this stereochemistry of starting material.



In ribonucleic acids, the fact that the 2′- and 3′-OH groups are on the same side of the ring makes alkaline hydrolysis of such dinucleotides exceptionally rapid by intramolecular nucleophilic catalysis.

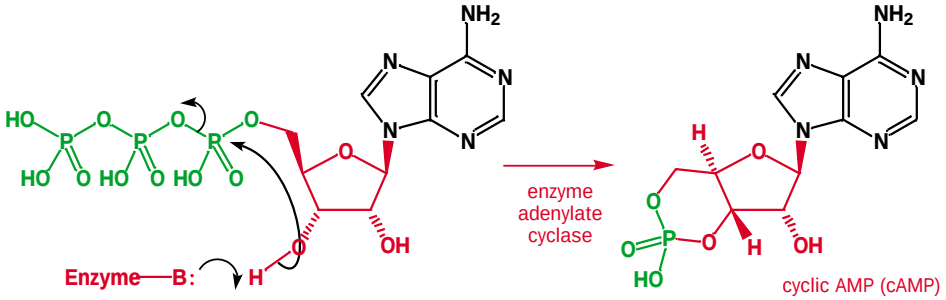
■ The substituents B^1 and B^2 represent any purine or pyrimidine base.



The alkali removes a proton from the 2′-OH group, which cyclizes on to the phosphate link—possible only if the ring fusion is *cis*. The next reaction involves breakdown of the pentacovalent phosphorus intermediate to give a cyclic phosphate. One nucleoside is released by this reaction and the second follows when the cyclic phosphate is itself cleaved by alkali.

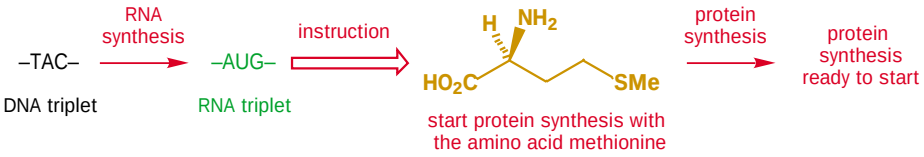
The simplest cyclic phosphate that can be formed from a nucleotide is also important biologically as it is a messenger that helps to control such processes as blood clotting and acid secretion in the stomach. It is cyclic AMP (cAMP), formed enzymatically from ATP by nucleophilic displacement of pyrophosphate by the 3′-OH group.

▶ Note that cAMP has a trans 6,5-fused ring junction.



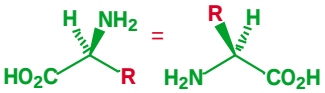
Proteins are made of amino acids

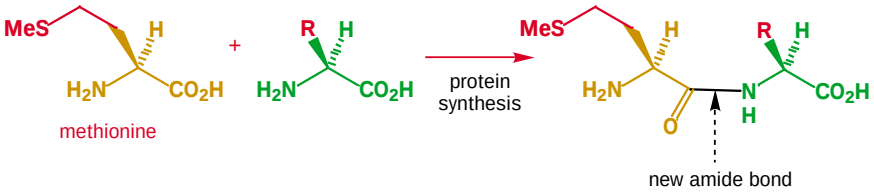
The molecule of methionine, which we met as a component of SAM, is a typical amino acid of the kind present in proteins. It is the starter unit in all proteins and is joined to the next amino acid by an amide bond. In general, we could write:



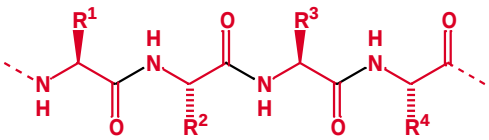
Now we can add the next amino acid using its correct codon, but we want to show the process in general so we shall use the general structure in the margin. All amino acids have the same basic structure and differ only in the group 'R'. Both structures are the same and have the same (*S*) stereochemistry.

two views of the general amino acid structure





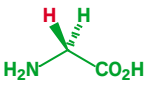
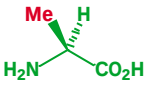
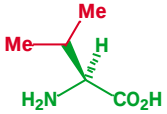
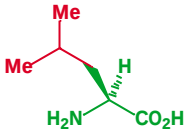
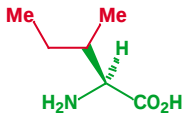
The process then continues with more amino acids added in turn to the right-hand end of the growing molecule. A section of the final protein drawn in a more realistic conformation might look like this.



The basic skeleton of the protein zig-zags up and down in the usual way; the amide bonds (shown in black) are rigid because of the amide conjugation and are held in the shape shown. Each amino acid may have a different substituent (R^1, R^2, R^3, etc.) or some may be the same.

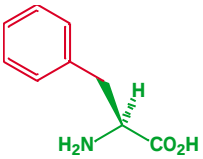
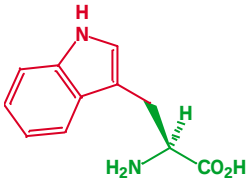
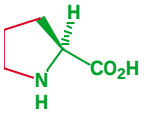
A catalogue of the amino acids

So what groups are available when proteins are being made? The simplest amino acid, glycine, has no substituents except hydrogen and is the only amino acid that is not chiral. Four other amino acids have alkyl groups without further functionality. The next table gives their structures together with two abbreviations widely used for them. The three-letter code (which has nothing to do with the codon in DNA!) is almost self-explanatory as are the one-letter codes in this group, but some of the one-letter codes for the other amino acids are not so obvious.

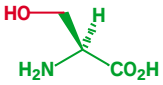
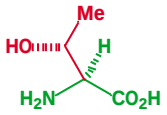
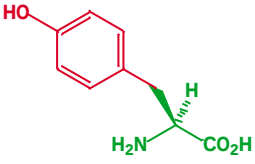
Name	Three-letter code	One-letter code	Structure
glycine	Gly	G	
alanine	Ala	A	
valine	Val	V	
leucine	Leu	L	
isoleucine	Ile	I	

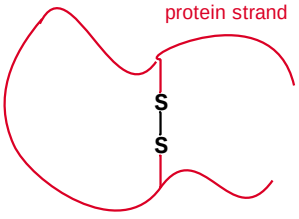
▶ Many of the compounds we discuss in this chapter will be salts under biological conditions. Most carboxylic acids will exist as anions, as will the phosphates you have just seen, and most amines as cations as they would be protonated at pH 7. Amino acids exist in biological systems as zwitterions. For simplicity, we will usually draw functional groups in the simplest and most familiar way, leaving the question of protonation to be addressed separately if required.

These amino acids form hydrophobic (water-repelling) nonpolar regions in proteins. There are three more of this kind with special roles. Phenylalanine and tryptophan have aromatic rings and, though they are still hydrophobic, they can form attractive π-stacking interactions with other aromatic molecules. Enzyme-catalysed hydrolysis of proteins often happens next to one of these residues. Proline is very special. It has its amino group inside a ring and has a different shape from all the other amino acids. It appears in proteins where a bend or a twist in the structure is needed.

Name	Three-letter code	One-letter code	Structure
phenylalanine	Phe	F	
tryptophan	Trp	W	
proline	Pro	P	

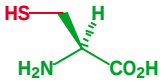
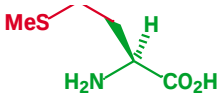
The rest of the amino acids have functional groups of various kinds and we shall deal with them by function. The simplest have hydroxyl groups and there are three of them—two alcohols and a phenol. Serine in particular is important as a reactive group in enzymatic reactions. It is a good nucleophile for carbonyl groups.

Name	Three-letter code	One-letter code	Structure
serine	Ser	S	
threonine	Thr	T	
tyrosine	Tyr	Y	



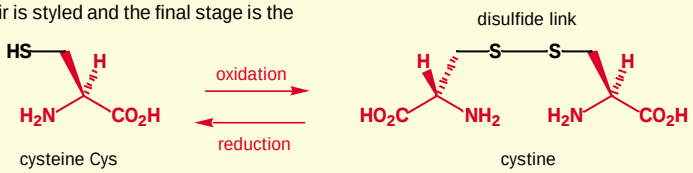
disulfide cross-link

Next come the two compounds we have already met, the sulfur-containing cysteine and methionine. Cysteine has a thiol group and methionine a sulfide. These are very important in protein structure—methionine starts off the synthesis of every new protein as its *N*-terminal amino acid, while cysteine forms S–S bridges linking two parts of a protein together. These disulfide links may be important in holding the three-dimensional shape of the molecule.

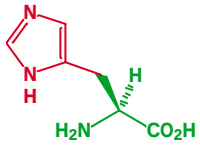
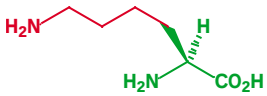
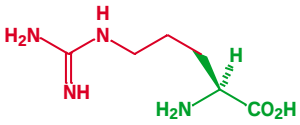
Name	Three-letter code	One-letter code	Structure
cysteine	Cys	C	
methionine	Met	M	

Cysteine and hairdressing

Thiols (RSH) are easily oxidized, by air, for example, to disulfides (RS–SR). This chemistry of cysteine is used by hairdressers to give 'perms' or permanent waves. The hair proteins are first reduced so that any disulfide (cysteine to cysteine) cross-links within each strand are reduced to thiols. Then the hair is styled and the final stage is the 'set' when the hair is oxidized so that disulfide cross-links are established to hold its shape for a good time. The disulfide resulting from cross-links between the thiol groups of *cysteine* is known as *cystine*—beware of confusing the names!



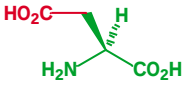
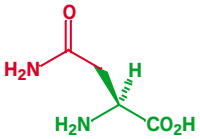
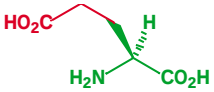
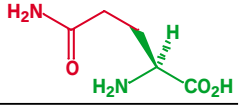
The amino acids with a second amino group are important because of their basicity and they are vital to the catalytic activity of many enzymes. Histidine has a pK_{aH} very close to neutrality (6.5) and can function as an acid or a base. Lysine and arginine are much more basic, but are normally protonated in living things. An extra column in this table gives the pK_{aH} of the extra amino groups.

Name	Three-letter code	One-letter code	pK_{aH}	Structure
histidine	His	H	6.5	
lysine	Lys	K	10.0	
arginine	Arg	R	12.0	

Essential amino acids

If you saw 'Jurassic Park' you may recall that the failsafe device was the 'lysine option'. The dinosaurs were genetically modified so as to need lysine in their diet. The idea was that they would die unless lysine was provided by their keepers. Lysine was a good choice as it is one of the 'essential' amino acids for humans. If we are not given it in our diet, we die. Of course, any normal diet, including the human beings eaten by the escaped dinosaurs, would also contain plenty of lysine. The other essential amino acids (for humans) are His, Ile, Leu, Met, Phe, Thr, Try, and Val.

Finally, we come to the acidic amino acids—those with an extra carboxylic acid group. We are going to include their amides too as they also occur in proteins. This group is again very much involved in the catalytic activity of enzymes. The two acids have pK_as for the extra CO_2H group of about 4.5.

Name	Three-letter code	One-letter code	Structure
aspartic acid	Asp	D	
asparagine	Asn	N	
glutamic acid	Glu	E	
glutamine	Gln	Q	

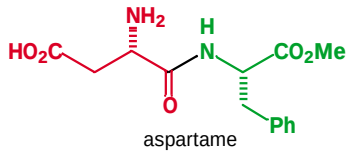
Sometimes it is not known whether the acids or their amides are present and sometimes they are present interchangeably. Aspartic acid or asparagine has the codes Asx and B while glutamic acid or glutamine is Glx or Z.

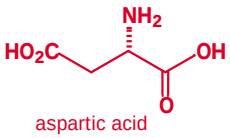
Now perhaps you can see that a protein is an assembly of many different kinds of group attached to a polyamide backbone. Some of the groups are purely structural, some control the shape of the protein, some help to bind other molecules, and some are active in chemical reactions.

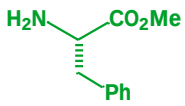
Most amino acids are readily available to chemists. If proteins are hydrolysed with, say, concentrated HCl, they are broken down into their amino acids. This mixture is tricky to separate, but the acidic ones are easy to extract with base while the aromatic ones crystallize out easily.

Amino acids combine to form peptides and proteins

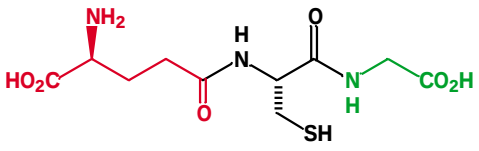
In nature, the amino acids are combined to give proteins with hundreds or even thousands of amino acids in each one. Small assemblies of amino acids are known as peptides and the amide bond that links them is called a peptide bond. One important dipeptide is the sweetening agent aspartame, whose synthesis was discussed in Chapter 25. It is composed (and made) of the amino acid aspartic acid (Asp) and the methyl ester of phenylalanine. Only this enantiomer has a sweet taste and it is very sweet indeed—about 160 times as sweet as sucrose. Only a tiny amount is needed to sweeten drinks and so it is much less fattening than sucrose and is 'safe' because it is degraded in the body to Asp and Phe, which are there in larger amounts anyway.


aspartame

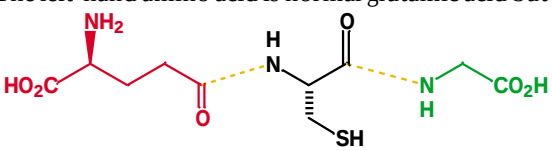

aspartic acid


phenylalanine methyl ester

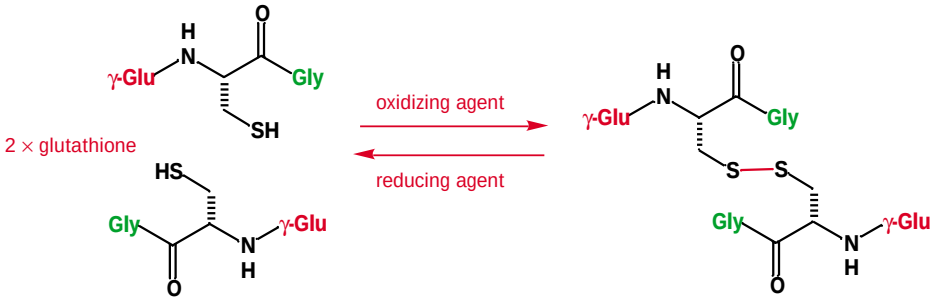
An important tripeptide is glutathione. So important is this compound that it is present in almost all tissues of most living things. It is the 'universal thiol' that removes dangerous oxidizing agents by allowing itself to be oxidized to a disulfide.


glutathione = RSH

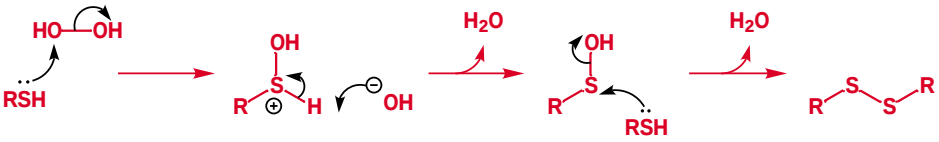
Glutathione is not quite a simple tripeptide. The left-hand amino acid is normal glutamic acid but it is joined to the next amino acid through its γ-CO_2H group instead of the more normal α-CO_2H group. The middle amino acid is the vital one for the function—cysteine with a free SH group. The *C*-terminal acid is glycine.


γ-Glu (glutamic acid joined through its γ-CO_2H group) cysteine glycine

Thiols are easily oxidized to disulfides, as we have already seen in our discussion on hairdressing (though the redox chemistry of glutathione is a matter of life or death and not merely a bad hair day), and glutathione sacrifices itself if it meets an oxidizing agent. Later, the oxidized form of glutathione is reduced back to the thiol by reagents we shall meet in the next chapter (NADH, etc.).

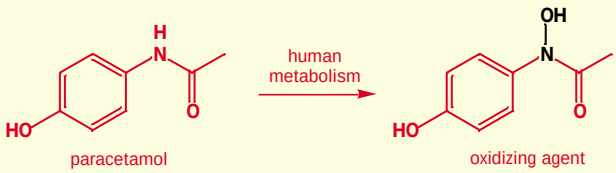


If we imagine that the stray oxidizing agent is a peroxide, say, H_2O_2, we can draw a mechanism to show how this can be reduced to water as glutathione (represented as RSH) is oxidized to a disulfide.

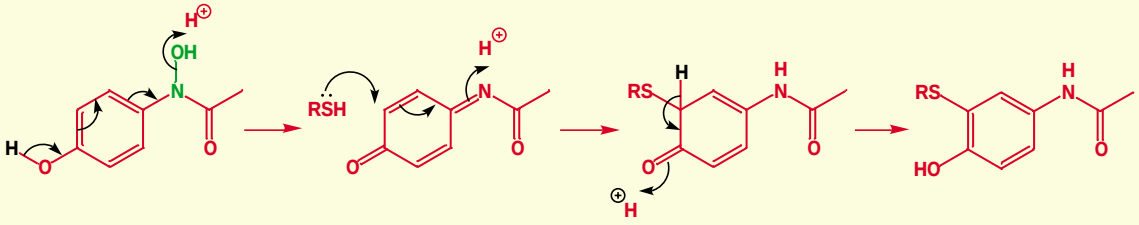


Paracetamol overdoses

Paracetamol is a popular and safe analgesic if used properly but an overdose is insidiously dangerous. The patient often seems to recover only to die later from liver failure. The problem is that paracetamol is metabolized into an oxidized compound that destroys glutathione.

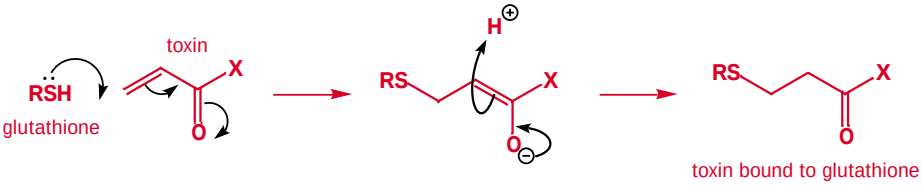


Glutathione detoxifies this oxidizing agent by a most unusual mechanism. The unstable hydroxylamine loses water to give a reactive quinone imine that is attacked by glutathione on the aromatic ring. The adduct is stable and safe but, for every molecule of paracetamol, one molecule of glutathione is consumed.



There is no problem if a normal dose is taken—there is plenty of glutathione to deal with that. But if an overdose is taken, all the glutathione may be used up and irreversible liver damage occurs.

Glutathione also detoxifies some of the compounds we have earlier described as very dangerous carcinogens such as Michael acceptors and 2,4-dinitrohalobenzenes. In both cases the thiol acts as a nucleophile for these electrophiles. Most of the time there is enough glutathione present in our cells to attack these poisons before they attack DNA or an enzyme.



The toxin is now covalently bound to glutathione and so is no longer electrophilic. It is harmless and can be excreted. More glutathione will be synthesized from glutamic acid, cysteine, and glycine to replace that which is lost.

Proteins are Nature's chemical laboratories

Longer peptides are called proteins, though where exactly the boundary occurs is difficult to say.

The structure of the hormone insulin (many diabetics lack this hormone and must inject themselves with it daily) was deduced in the 1950s by Sanger. It has two peptide chains, one of 21 amino acids and one of 30, linked by three disulfide bridges—just like the links in oxidized glutathione. This is a very small protein.

Enzymes are usually bigger. One of the smaller enzymes—ribonuclease (which hydrolyses RNA) from cows—has a chain of 124 amino acids with four internal disulfide bridges. The abundance of the various amino acids in this enzyme is given in this table.

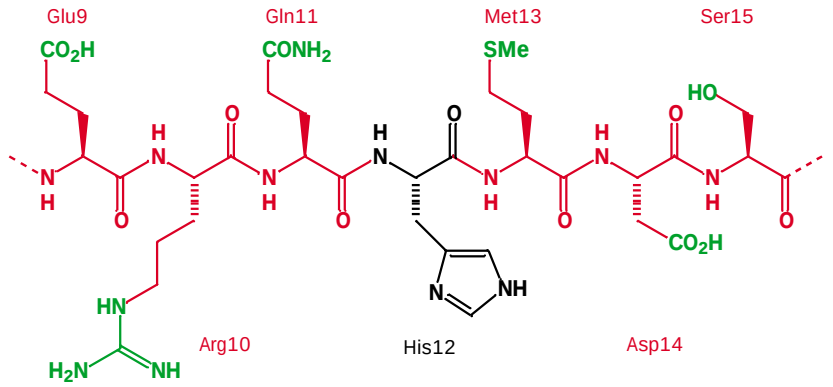
Type	Amino acid (number)[a]	Total
structural	A (12), F (3), M (4), L (2), P (4), V (9), G (3), I (3)	40
cross-linking	C (8)	8
basic	K (10), R (4), H (4)	18
acids and amides	E (5), Q (7), D (5), N (10)	27
hydroxyl	T (10), S (15), Y (6)	31

[a] See tables earlier in this section for one-letter codes of amino acids.

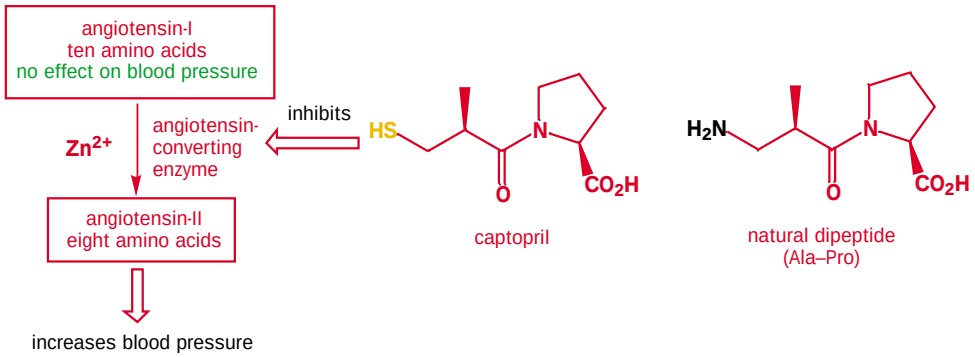
There are 48 structural and cross-linking amino acids concerned with the shape of the protein but over half of the amino acids have functional groups sticking out of the chain—amino, hydroxy, acid groups, and the like. In fact, the enzyme uses only a few of these functional groups in the reaction it catalyses (the hydrolysis of RNA)—probably only two histidines and one lysine—but it is typical of enzymes that they have a vast array of functional groups available for chemical reactions.

Below is part of the structure of ribonuclease surrounding one of the catalytic amino acids His12. There are seven amino acids in this sequence. Every one is different and every one has a functionalized side chain. This is part of a run of ten amino acids between Phe8 and Ala19. This strip of peptide has six different functional groups (two acids, one each of amide, guanidine, imidazole, sulfide, and alcohol) available for chemical reactions. Only the histidine is actually used.

▶ Proteins are conventionally drawn and described with the amino (*N*) terminus to the left and the carboxyl (*C*) terminus to the right. This section of ribonuclease would be called 'glutamyl arginyl glutaminyl histidyl methionyl aspartyl seryl…' or, more briefly, –Glu–Arg–Gln–His–Met–Asp–Ser– or, more briefly still, –ERQHMDS–. The numbers on the diagram such as 'Glu9' tell us that this glutamic acid residue is number 9 from the *N*-terminus.

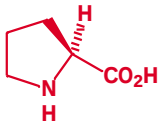


One reason for disease is that enzymes may become overactive and it may be necessary to design specific inhibitors for them to treat the disease. *A*ngiotensin-*C*onverting *E*nzyme (ACE) is a zinc-dependent enzyme that cleaves two amino acids off the end of angiotensin I to give angiotensin II, a protein that causes blood pressure to rise.

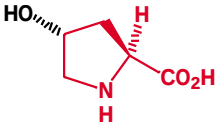


It is necessary in some situations for our blood pressure to rise (when we stand up for instance!) but too much too often is a very bad thing leading to heart attacks and strokes. Captopril is a treatment for high blood pressure called an 'ACE inhibitor' because it works by inhibiting the enzyme. It is a dipeptide mimic, having one natural amino acid and something else. The 'something else' is an SH group replacing the NH_2 group in the natural dipeptide. Captopril binds to the enzyme because it is *like* a natural dipeptide but it inhibits the enzyme because it is *not* a natural dipeptide. In particular, the SH group is a good ligand for Zn(II). Many people are alive today because of this simple deception practised on an enzyme.

glycine
Gly; G



(*S*)-proline Pro; P



(2*S*,4*R*)-hydroxyproline Hyp

Structural proteins must be tough and flexible

In contrast with the functional enzymes, there are purely structural proteins such as collagen. Collagen is the tough protein of tendons and is present in skin, bone, and teeth. It contains large amounts of glycine (every third amino acid is glycine), proline, and hydroxyproline (again about a third of the amino acids are either Pro or Hyp).

In the enzyme above there were only three glycines and four prolines and no hydroxyproline at all. Hydroxyproline is a specialized amino acid that appears almost nowhere else and, along with proline, it establishes a very strong triply coiled structure for collagen. The glycine is necessary as there is no room in the inside of the triple coil for any larger amino acid. Functionalized amino acids are rare in collagen.

Hydroxyproline and scurvy

Hydroxyproline is a very unusual amino acid. There is no genetic codon for the insertion of Hyp into a growing protein because collagen is not made that way. The collagen molecule is first assembled with Pro where Hyp ends up. Then some proline residues are oxidized to hydroxyproline. This oxidation requires vitamin C, and without it collagen cannot be formed. This is why vitamin C deficiency causes scurvy—the symptoms of scurvy (teeth falling out, sores, blisters) are caused by the inability to make collagen.

Proteins are enormously diverse in structure and function and we will be looking at a few of their reactions in the next chapter.

Sugars—just energy sources?

Sugars are the building blocks of carbohydrates. They used to be thought of as essential but rather dull molecules whose only functions were the admittedly useful provision of energy and cell wall construction. We have already noted that ribose plays an intimate role in DNA and RNA structure and function. More recently, biochemists have realized that carbohydrates are much more exciting. They are often found in intimate association with proteins and are involved in recognition of one protein by another and in adhesion processes.

That may not sound very exciting, but take two examples. How does a sperm recognize the egg and penetrate its wall? The sperm actually binds to a carbohydrate on the wall of the egg in what was the first event in all of our lives. Then how does a virus get inside a cell? If it fails to do so, it has no life. Viruses depend on host cells to reproduce. Here again, the recognition process involves specific carbohydrates. One of the ways in which AIDS is being tackled with some success is by a combination of the antiviral drugs we met earlier in this chapter with HIV protease inhibitor drugs, which aim to prevent recognition and penetration of cells by HIV.

We now know that many vital activities as diverse as healing, blood clotting, infection, prevention of infection, and fertilization all involve carbohydrates. Mysterious compounds such as 'sialyl Lewis-X', unknown a few years ago, are now known to be vital to our health and happiness. Far from being dull, carbohydrates are exciting molecules and our future depends on them. It is well worthwhile to spend some time exploring their structure and chemistry.

Sugars normally exist in cyclic forms with much stereochemistry

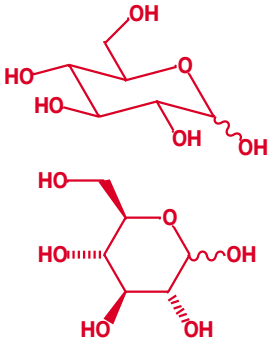
The most important sugar is glucose. It has a saturated six-membered ring containing oxygen and it is best drawn in a chair conformation with nearly all the substituents equatorial. It can also be drawn reasonably as a flat configurational diagram.

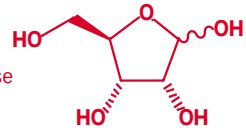
We have already met one sugar in this chapter, ribose, because it was part of the structure of nucleic acids. This sugar is a five-membered saturated oxygen heterocycle with many OH groups. Indeed, you can define a sugar as an oxygen heterocycle with every carbon atom bearing an oxygen-based functional group—usually OH, but alternatively C=O.

Both our drawings of glucose and ribose show a number of stereogenic centres and one centre undefined—the OH group is marked with a wavy line. This is because one centre in both sugars is a hemiacetal and therefore the molecule is in equilibrium with an open-chain hydroxy-aldehyde. For glucose, the open-chain form is this.

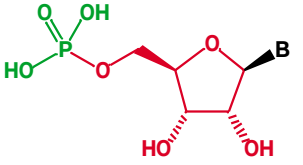
■ Sugars have had walk-on roles in a few other chapters, notably Chapter 16 on stereochemistry. They are discussed on pp. 000, 000, and 000.

two representations of glucose

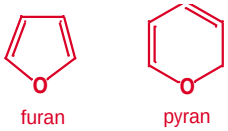




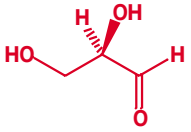
ribose



a ribonucleotide

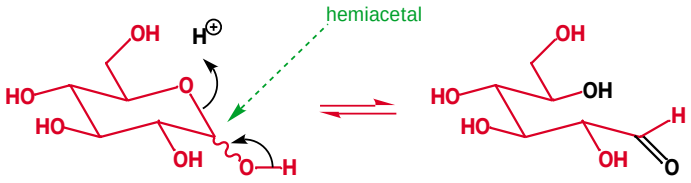


furan pyran

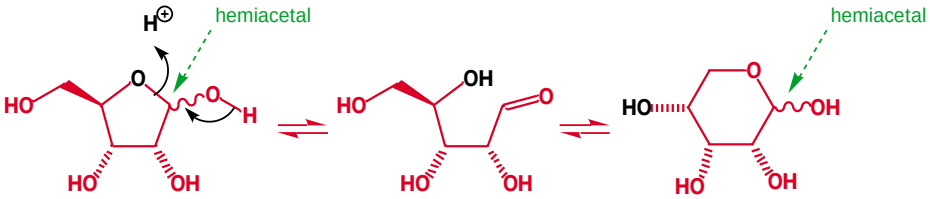


D-glyceraldehyde
(*R*)–(+)–g;yceraldehyde

■ Glyceraldehyde was the compound used to define the D and L designators before anyone knew what the real configurations of natural compounds were. See the discussion on p. 000 for more on this.



When the ring closes again, any of the OH groups could cyclize on to the aldehyde but there is no real competition—the six-membered ring is more stable than any of the alternatives (which could have three-, four-, five-, or seven-membered rings—check for yourself). However, with ribose there is a reasonable alternative.



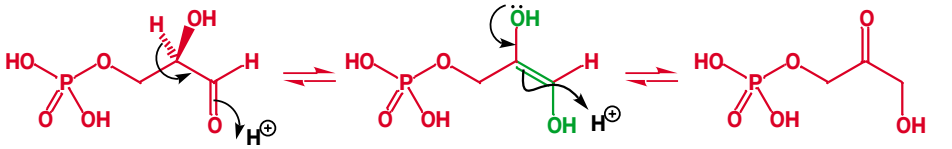
ribo-furanoside ribo-pyranoside

The most important sugars may exist in an open-chain form, as a five-membered oxygen heterocycle (called a furanoside after the aromatic furan) or a six-membered oxygen heterocycle (called a pyranoside after the compound pyran).

From triose to glucose requires doubling the number of carbon atoms

We will return to that in a moment, but let us start from the beginning. The simplest possible sugar is glyceraldehyde, a three-carbon sugar that cannot form a cyclic hemiacetal.

Glyceraldehyde is present in cells as its phosphate which is in equilibrium with dihydroxyacetone phosphate. This looks like a complicated rearrangement but it is actually very simple—the two compounds have a common enol through which they interconvert.

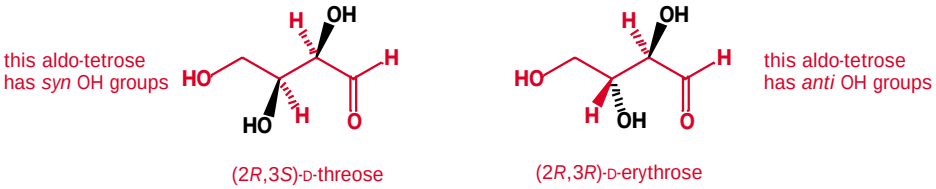


glyceraldehyde-3-phosphate common enediol dihydroxyacetone-3-phosphate

Glyceraldehyde is an aldehyde sugar or aldose and dihydroxyacetone is a keto-sugar or ketose. That ending '-ose' just refers to a sugar. These two molecules combine to form the six-carbon sugar,

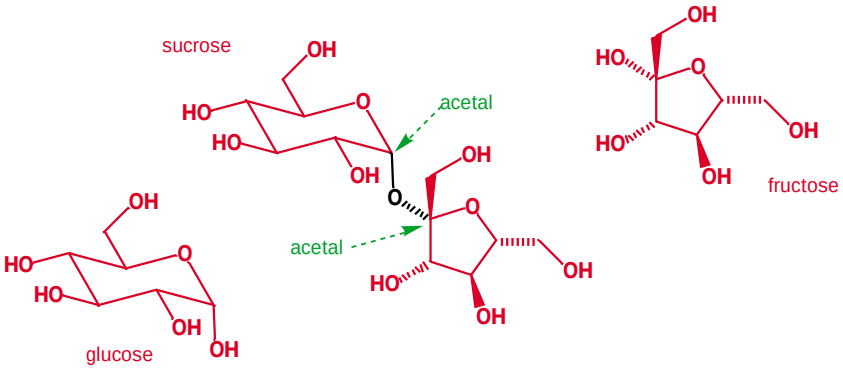
fructose, in living things and this reaction is a key step in the synthesis of organic compounds from CO_2 in plants.

When we come to the four-carbon sugars, or tetroses, two are important. They are diastereoisomers called erythrose and threose. You can see from this series that each aldose has $n - 2$ stereogenic centres in its carbon chain where n is the total number of carbon atoms in that chain.



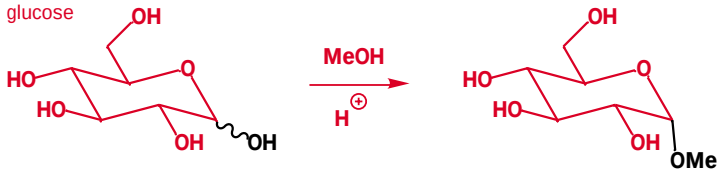
■ These sugars too have given their names to a stereochemical designation—'erythro-' and 'threo-' are used to describe diastereoisomers that resemble these two sugars. We do not use these rather ambiguous terms in this book, preferring more precise or vivid terms such as *R,R* or *anti* as appropriate.

We shall take a longer look at the stereochemistry and reactions of glucose and the important keto-hexose, fructose. These two are often found together in cells and are combined in the same molecule as sucrose—ordinary sugar. In this molecule, glucose appears as a pyranose (six-membered ring) and fructose as a furanose (five-membered ring). They are joined through an acetal at what were hemiacetal positions, and sucrose is a single diastereoisomer.



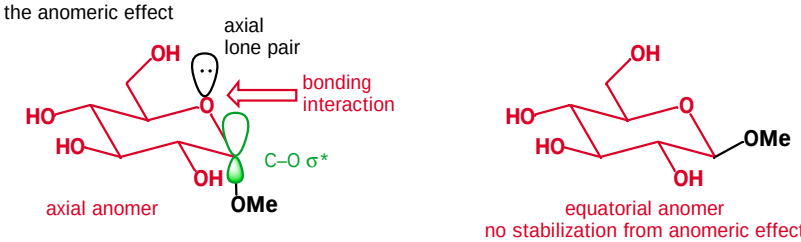
Sugars can be fixed in one shape by acetal formation

This is the simplest way to fix glucose in the pyranose form—any alcohol, methanol, for example, gives an acetal and, remarkably, the acetal has an *axial* OR group.



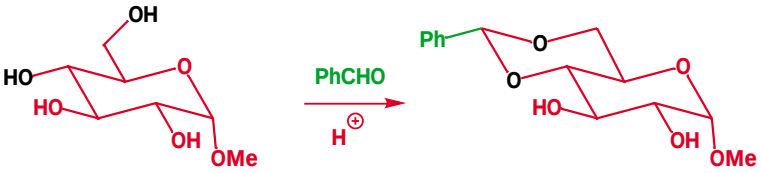
Acetal formation is under thermodynamic control (Chapter 14) so the axial compound must be the more stable. This is because of the anomeric effect—so called because this C atom is called the anomeric position and the acetal diastereoisomers are called anomers. The effect is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the σ* orbital of the OMe group.

■ The anomeric effect was discussed in Chapter 42, and you should check that you can still write down the mechanism of acetal formation you learned in Chapter 14.



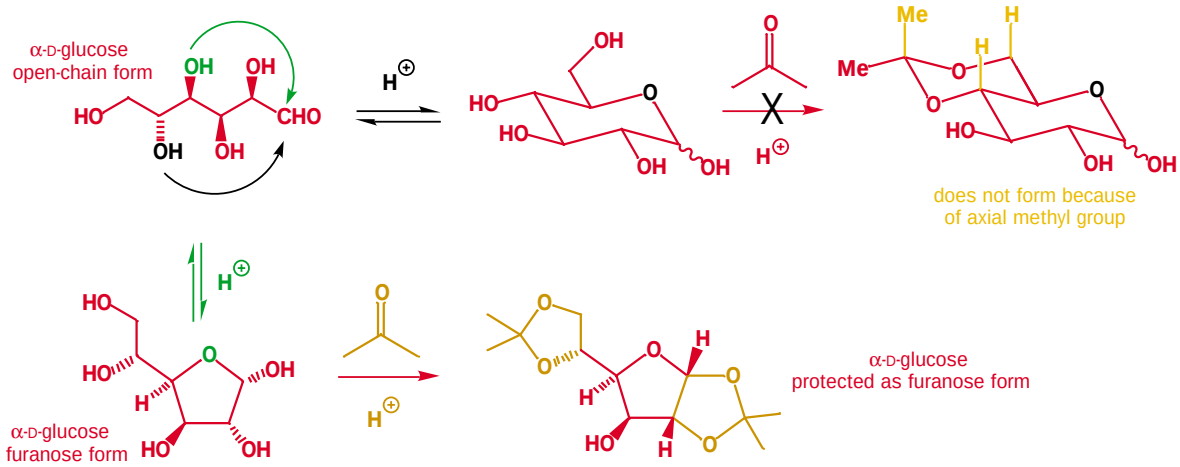
The formation of acetals allows a remarkable degree of control over the chemistry of sugars. Apart from the simple glucoside acetal we have just seen, there are three important acetals worth understanding because of the way in which they illustrate stereoelectronic effects—the interplay of

stereochemistry and mechanism. If we make an acetal from methyl glucoside, we get a single compound as a single stereoisomer.



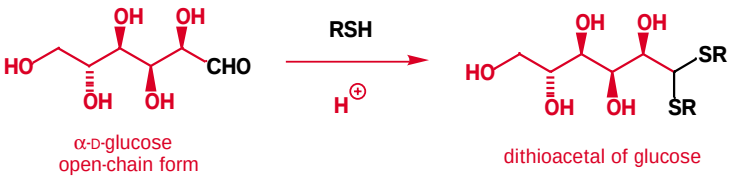
The new acetal could have been formed between any of the adjacent OH groups in the starting material but it chose the only pair (the black OH groups) to give a six-membered ring. The stereochemistry of glucose is such that the new six-membered ring is *trans*-fused on the old so that a beautifully stable all-chair bicyclic structure results, with the phenyl group in an equatorial position in the new chair acetal ring. It does not matter which OH group adds to benzaldehyde first because acetal formation is under thermodynamic control and this product is the most stable possible acetal.

Acetals formed from sugars and acetone have a quite different selectivity. For a start, cyclic acetals of acetone prefer to be five- rather than six-membered rings. In a six-membered ring, one of the acetone's methyl groups would have to be axial, so the five-membered ring is preferred. A 5/5 or 5/6 ring fusion is more stable if it is *cis*, and so acetone acetals ('acetonides') form preferentially from *cis* 1,2-diols. Glucose has no neighbouring *cis* hydroxyls in the pyranose form, but in the furanose form it can have two pairs. Formation of an acetal with acetone fixes glucose in the furanose form. This is all summarized in the scheme below.

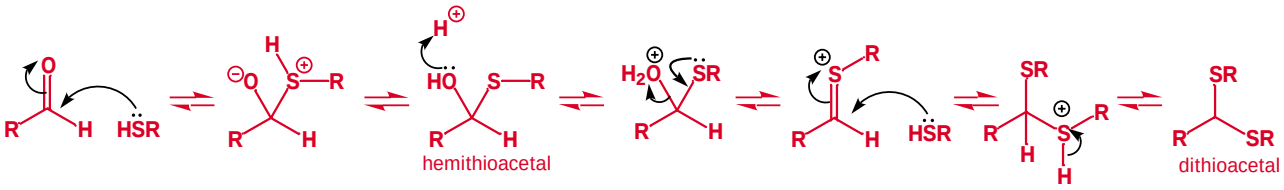


The open-chain form of glucose is in equilibrium with both pyranose and furanose forms by hemiacetal formation with the black and green OH groups, respectively. Normally, the pyranose form is preferred, but the furanose form can form a double acetal with acetone, one acetal having *cis*-fused 5/5 rings and the other being on the side chain. This is the product.

If we want to fix glucose in the open-chain form, we must make an 'acetal' of quite a different kind using a thiol (RSH) instead of an alcohol, an aldehyde, or a ketone.

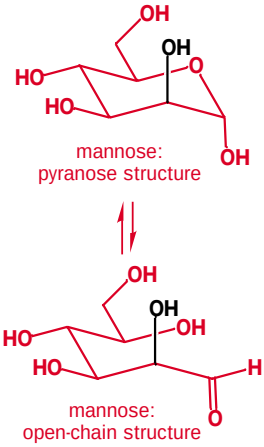


The thiol combines with the aldehyde group of the open-chain form to give a stable dithioacetal. The dithioacetal is evidently more stable than the alternative hemiacetals or monothioacetals that could be formed from the pyranose or furanose forms.

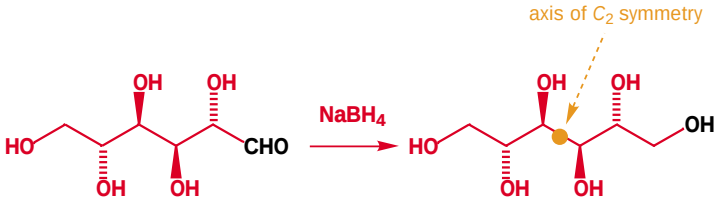


Sugar alcohols are important in food chemistry

Another reaction of the open-chain form of sugars is reduction of the aldehyde group. This leads to a series of polyols having an OH group on each carbon atom. We will use mannose as an example. Mannose is a diastereoisomer of glucose having one axial OH group (marked in black) and, like glucose, is in equilibrium with the open-chain form.

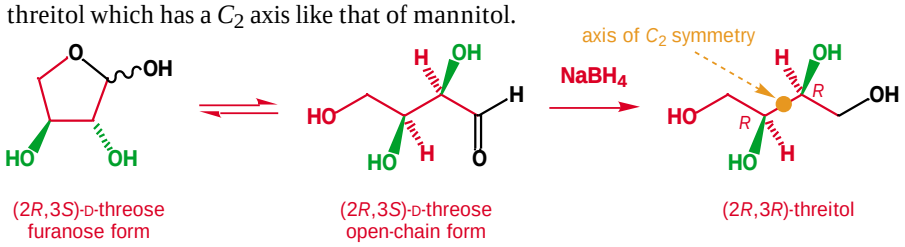


If we redraw the open-chain form in a more realistic way, and then reduce it with $NaBH_4$, the product is mannitol whose symmetry is interesting. It has C_2 symmetry with the C_2 axis at right angles to the chain and marked with the orange dot.

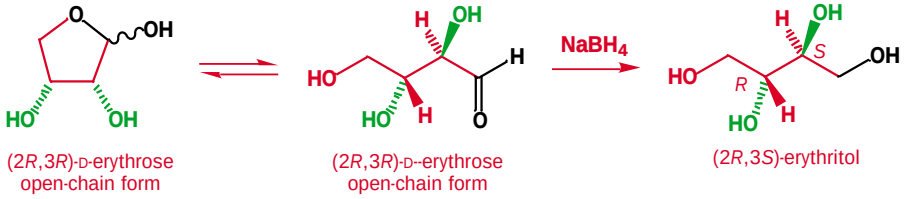


■ C_2 means that the axis of symmetry is twofold: rotating 180° gives the same structure.

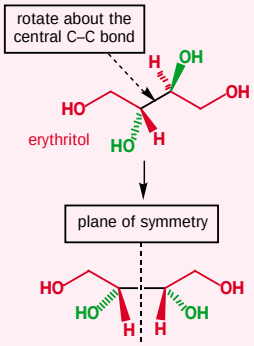
The simplification of stereochemistry results because the two ends of the sugar both now have CH_2OH groups so that the possibility of C_2 and planar symmetry arises. If we look at the two four-carbon sugars we can establish some important stereochemical correlations. Threose is reduced to threitol which has a C_2 axis like that of mannitol.



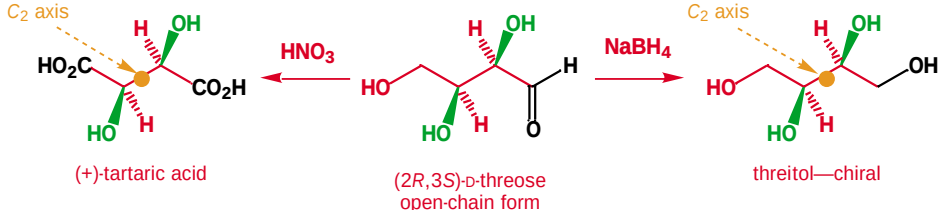
Erythrose on the other hand reduces to erythritol, which is not chiral.



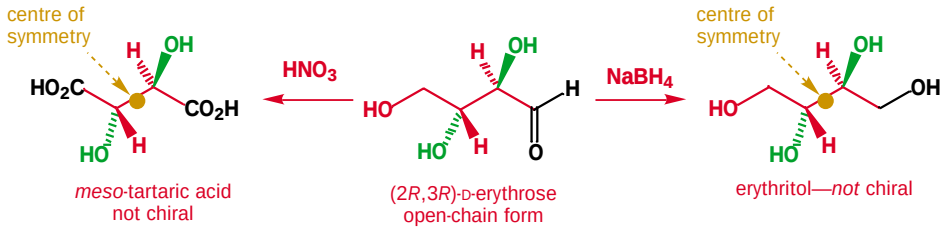
▶ This may not be obvious in the normal drawing (which has a centre of symmetry), but rotation around the central C–C bond clearly shows the plane of symmetry. Neither plane nor centre of symmetry may be present in a chiral molecule, but a C_2 axis is allowed (Chapter 16).



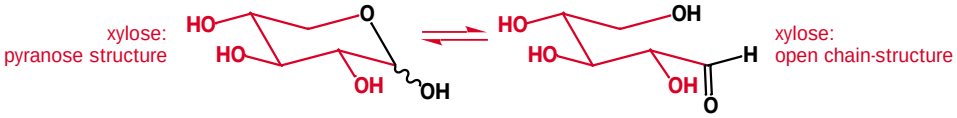
The important correlation is that threose is reduced or oxidized to chiral compounds—the oxidation product is tartaric acid—while erythrose is reduced or oxidized to *meso* compounds. This may help you to remember the labels erythro- and threo- should you need to.



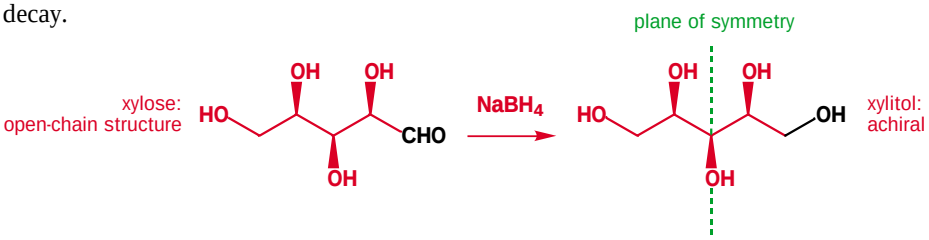
(continued overleaf)



In the pentoses and hexoses there are again sugars that are reduced to *meso* alcohols and some that are reduced to C_2 symmetric alcohols. The C_5 sugar xylose has the same stereochemistry as glucose from C2 to C4 but lacks the CH_2OH group at C6.



Xylose is reduced to the *meso* alcohol xylitol. This alcohol is more or less as sweet as sugar and, as xylose (which is not sweet) can be extracted in large quantities from waste products such as sawdust or corncobs, xylitol is used as a sweetener in foods. There is an advantage in this. Though we can digest xylitol (so it is fattening), the bacteria on teeth cannot so that xylitol does not cause tooth decay.



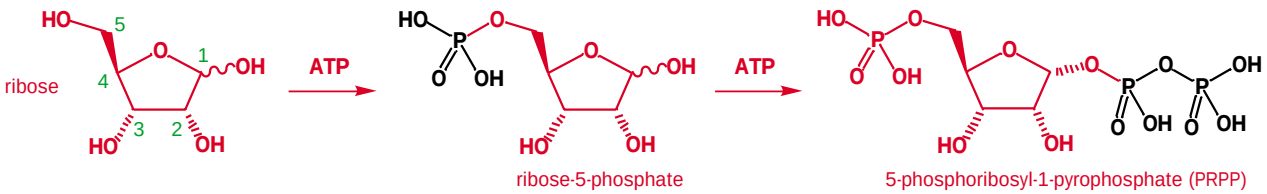
By careful manipulation of protecting groups such as acetals and reactions such as reduction and oxidation, it is possible to transform sugars into many different organic compounds retaining the natural optical activity of the sugars themselves. As some sugars are also very cheap, they are ideal starting points for the synthesis of other compounds and are widely used in this way (Chapter 45). Sucrose and glucose are very cheap indeed—probably the cheapest optically active compounds available. Here are the relative (to glucose = 1) prices of some other cheap sugars.

Sugar	Price[a]	Sugar	Price[a]
glucose	1	sorbitol	2
mannose	75	mannitol	4
galactose	8	dulcitol[b]	70
xylose	20	xylitol	15
ribose	100	sucrose	1

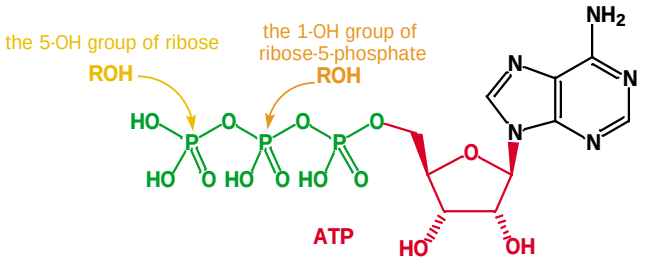
[a] Prices relative to glucose = 1.
[b] Dulcitol is the reduction product of galactose.

Chemistry of ribose—from sugars to nucleotides

We have said little about selective reactions of pentoses so we shall turn now to the synthesis of nucleotides such as AMP. In nature, ribose is phosphorylated on the primary alcohol to give ribose-5-phosphate. This is, of course, an enzyme-catalysed reaction but it shows straightforward chemoselectivity such as we should expect from a chemical reaction.

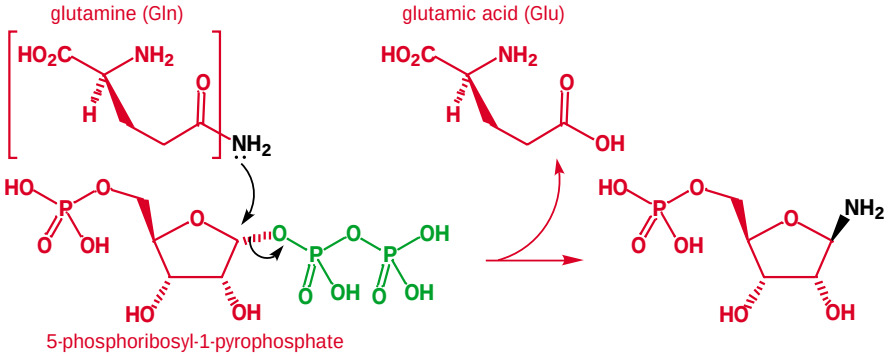


The second step is a pyrophosphorylation at the anomeric position to give PRPP. Only one diastereoisomer is produced so presumably the two anomers interconvert rapidly and only the one isomer reacts under control by the enzyme. This selectivity would be very difficult to achieve chemically.

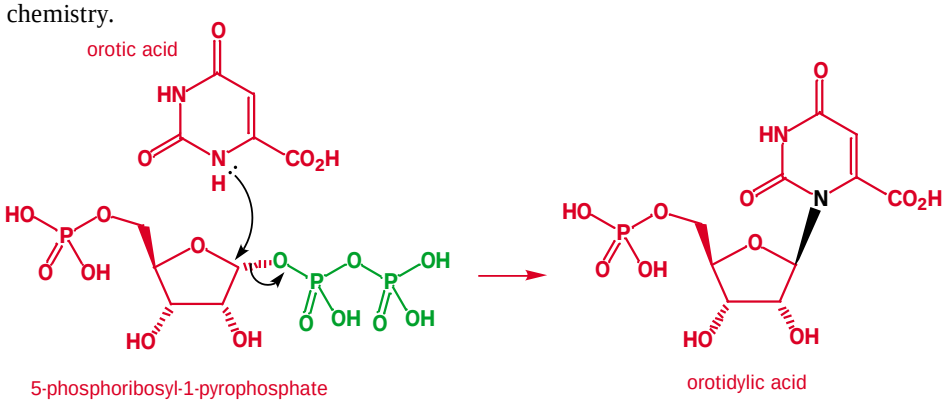


You will notice that these two reactions illustrate the flexibility with which ATP can activate biological molecules. In the first reaction, the nucleophilic OH group of ribose attacks the terminal phosphate group, but in the second the OH group must attack the middle phosphate residue. This would be impossible to control chemically.

Now the stage is set for an S_N2 reaction. The nucleophile is actually the amide group of glutamine but the amide is hydrolysed by the same enzyme in the same reaction and the result is as if a molecule of ammonia had done an S_N2 reaction displacing the pyrophosphate from the anomeric position. An NH_2 group is introduced, which is then built into the purine ring-system in a series of reactions involving simple amino acids. These reactions are too complex to describe here.



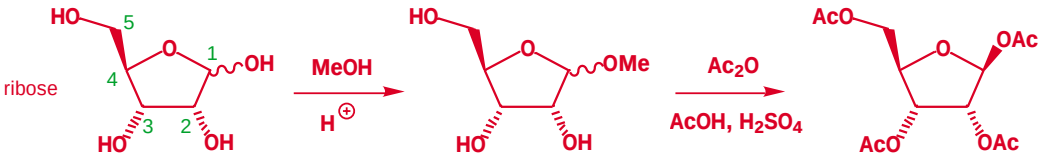
By contrast, if a pyrimidine is to be made, Nature assembles a general pyrimidine structure first and adds it in one step to the PRPP molecule, again in an S_N2 reaction using a nitrogen nucleophile. This general nucleotide, orotidylic acid, can be converted into the other pyrimidine nucleotides by simple chemistry.



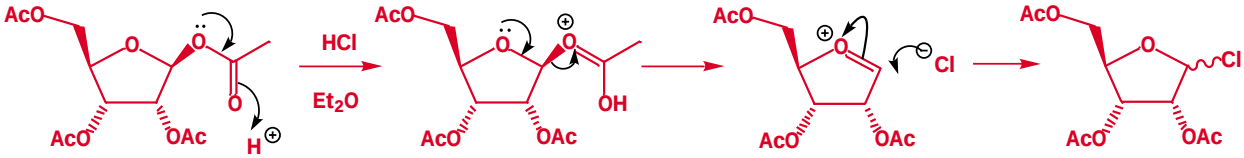
The chemical version—protection all the way

In a chemical synthesis (work that led to Alexander (Lord) Todd's Nobel prize) there are rather different problems. We cannot achieve the remarkable selectivity between the different OH groups achieved in Nature so we have to protect any OH group that is not supposed to react. We also prefer to add pre-formed purines and pyrimidines to a general electrophile derived from ribose. The first step is to form acetate esters from all the OH groups. Since ribose is rather unstable to acetylation conditions, the methyl glycoside (which is formed under very mild conditions) is used. This fixes the sugar in the furanose form. Now the tetraacetate can be made using acetic anhydride in acidic solution. All of the OH groups react by nucleophilic attack on the carbonyl group of the anhydride with retention of configuration except for the anomeric OH, which esterifies by an S_N1 mechanism. This, of course, epimerizes the anomeric centre but the crystalline diastereoisomer shown can be isolated easily.

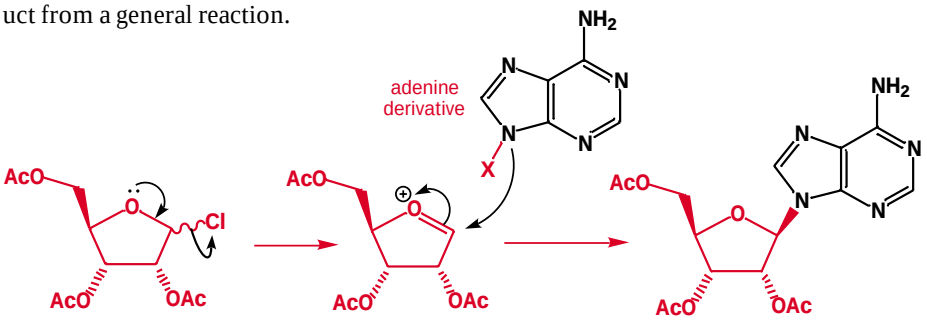
Alexander Todd (1907–97), better known as Lord Todd, was a Scot who pioneered the modern interaction between chemistry and biochemistry in his work at Frankfurt, Oxford, Edinburgh, London, CalTech, Manchester, and Cambridge. He won the Nobel prize in 1957 for his work on the synthesis of the most important coenzymes and nucleotides. This was a remarkable achievement because he had to find out how to do phosphate, ribose, and purine chemistry—none of which was known when he started, and none of which was easy as this brief excursion should show.



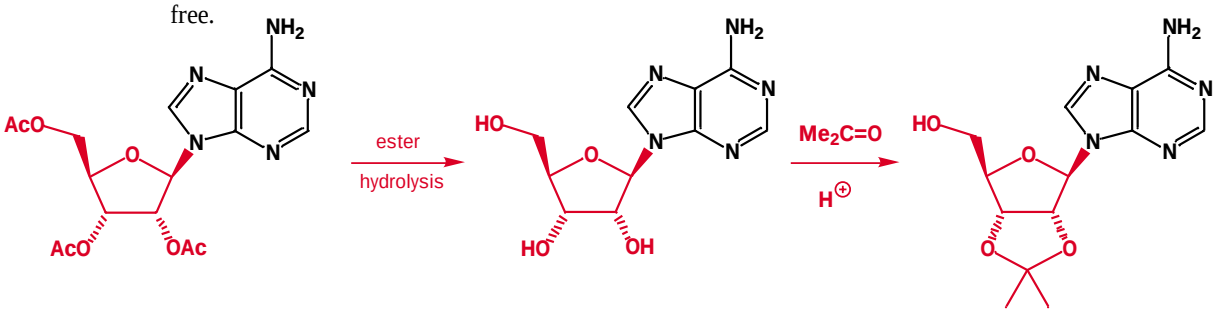
Now the anomeric centre can be activated towards nucleophilic attack by replacement of acetate by chloride. This is again an S_N1 reaction and produces a mixture of chlorides. The other esters are stable to these conditions.



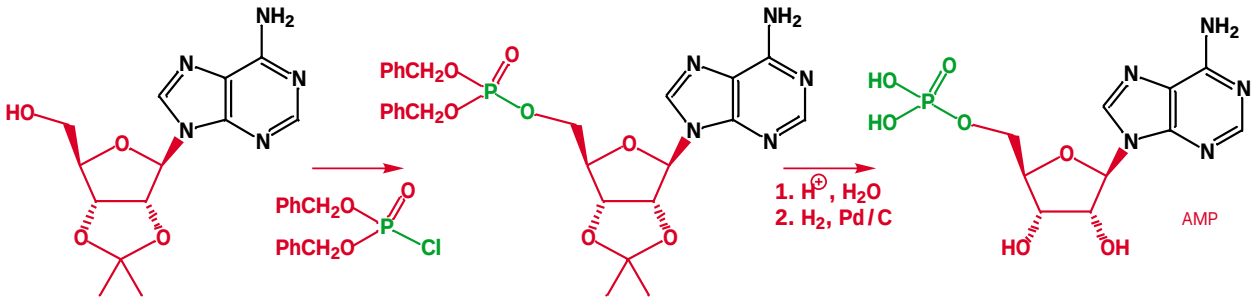
Replacement of the chlorine by the purine or pyrimidine base is sometimes quite tricky and silver or silyl derivatives are often used. Lewis acid catalysis is necessary to help the chloride ion leave in this S_N1 reaction. We shall avoid detailed technical discussion and simply draw the adenosine product from a general reaction.



Now we need to remove the acetates and put a phosphate specifically on the 5-position. The acetates can be removed with retention by ester hydrolysis and we already know how to protect the 2-OH and 3-OH groups. They are *cis* to each other so they will form an acetal with acetone leaving the 5-OH group free.



Putting on the phosphate is tricky too and more protection is necessary. This phosphorus compound with one chloride as leaving group and two benzyl esters as protecting groups proved ideal. The benzyl esters can be removed by hydrogenation (Chapter 24) and the acetal by treatment with dilute acid to give AMP.

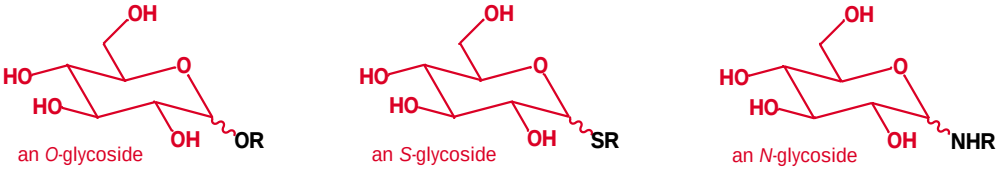


The chemical synthesis involves a lot more selective manipulation of functional groups, particularly by protection, than is necessary in the biological synthesis. However, this synthesis paved the way to the simple syntheses of nucleotides and polynucleotides carried out routinely nowadays. The usual method is to build short runs of nucleotides and then let the enzymes copy them—a real partnership between biology and chemistry.

Glycosides are everywhere in nature

Many alcohols, thiols, and amines occur in nature as glycosides, that is as *O*-, *S*-, or *N*-acetals at the anomeric position of glucose. The purpose of attaching these compounds to glucose is often to improve solubility or transport across membranes—to expel a toxin from the cell, for example. Sometimes glucose is attached in order to stabilize the compound so that glucose appears as Nature's protecting group, rather as a chemist would use a THP group (Chapter 24).

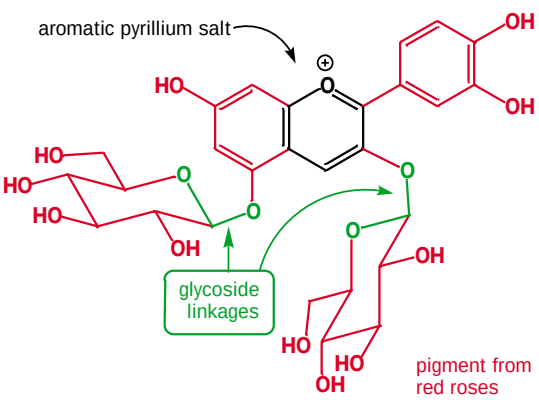
■ The most important *N*-glycosides are, of course, the nucleotides and we have already described them in some detail.

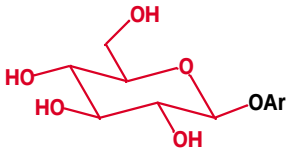


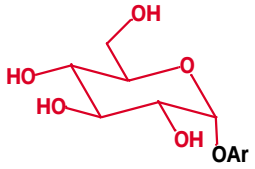
O-Glycosides occur in immense variety with glucose and other sugars being joined to the OH groups of alcohols and phenols to form acetals. The stereochemistry of these compounds is usually described by the Greek letters α and β. If the OR bond is down, we have an α-glycoside; if up, a β-glycoside.

■ We saw an example in Chapter 6 where acetone cyanohydrin is found in the cassava plant as a glucoside and suitable precautions must be taken when eating cassava to avoid poisoning by HCN.

An attractive example is the pigment of red roses, which is an interesting aromatic oxygen heterocycle (an anthocyanidin). Two of the phenolic OH groups are present as β-glycosides.



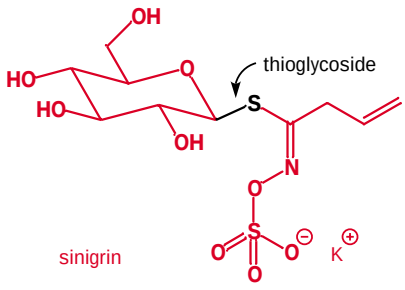




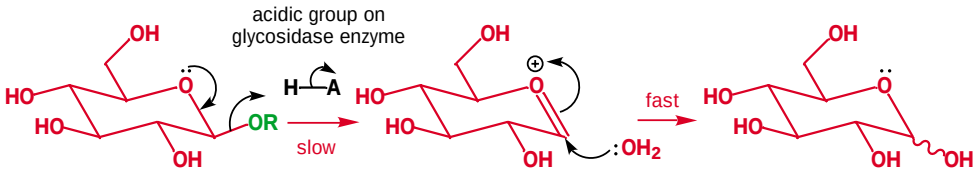
▶ It is easy to remember which is which. People who devise nomenclature are maliciously foolish and, just as *E* means *trans* and *Z* means *cis* (each letter has the shape of the *wrong* isomer), so α means *below* and β means *above*—each word begins with the *wrong* letter.

Protect yourself from cancer with green vegetables: *S*-glycosides

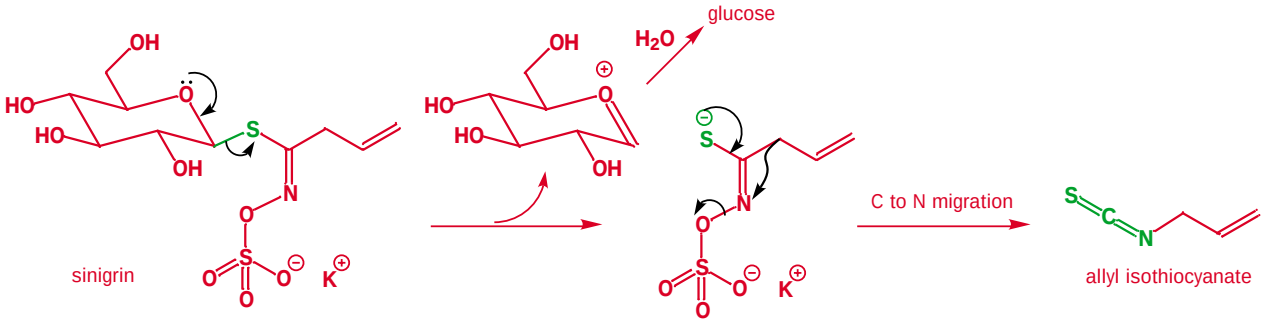
We will take an important series of *S*-glycosides for further chemical discussion in this chapter. It is clear that there are special benefits to health in eating broccoli and brussels sprouts because of their potent sulfur-containing anticancer compounds. These compounds are unstable isothiocyanates and are not, in fact, present in the plant but are released on damage by, for example, cutting or cooking when a glycosidase (an enzyme which hydrolyses glycosides) releases the sulfur compound from its glucose protection. A simple example is sinigrin.



When a glycosidase enzyme cleaves an *O*-glycoside, we should expect a simple general acid-catalysed first step followed by fast addition of water to the intermediate oxonium ion, essentially the same mechanism as is shown by the chemical reaction (Chapter 13).

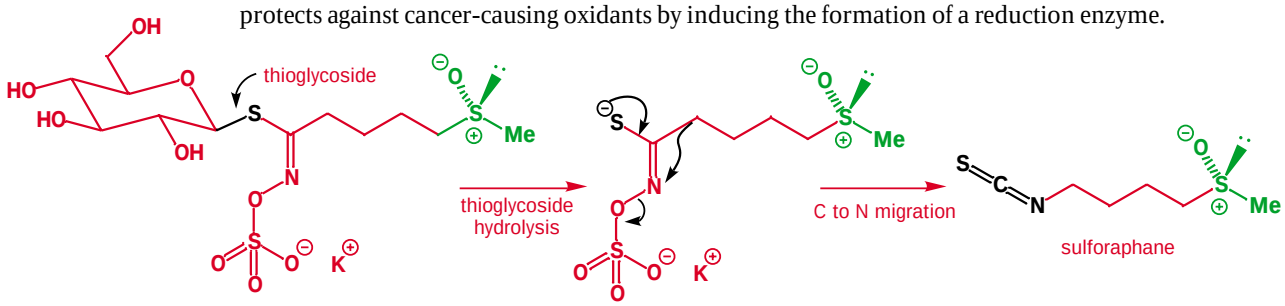


The *S*-glycosides of the sinigrin group start to hydrolyse in the same way. The sulfur atom is the better leaving group when it leaves as an anion (though worse than oxygen when the hydrolysis occurs in acidic conditions—see p. 000) and these anions are additionally stabilized by conjugation.



The next step is very surprising. A rearrangement occurs, rather similar to the Beckmann rearrangement (Chapter 37), in which the alkyl group migrates from carbon to nitrogen and an isothiocyanate (R–N=C=S) is formed. Sinigrin occurs in mustard and horseradish and it is the release of the allyl isothiocyanate that gives them their 'hot' taste. When mustard powder is mixed with water, the hot taste develops over some minutes as sinigrin is hydrolysed to the isothiocyanate.

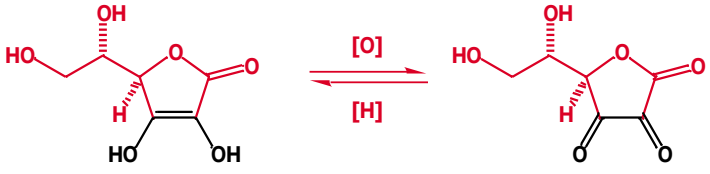
The *S*-glycoside in broccoli and brussels sprouts that protects from cancer is somewhat similar but has one more carbon atom in the chain and contains a sulfoxide group as well. Hydrolysis of the *S*-glycoside is followed by the same rearrangement, producing a molecule called sulforaphane. Sulforaphane protects against cancer-causing oxidants by inducing the formation of a reduction enzyme.



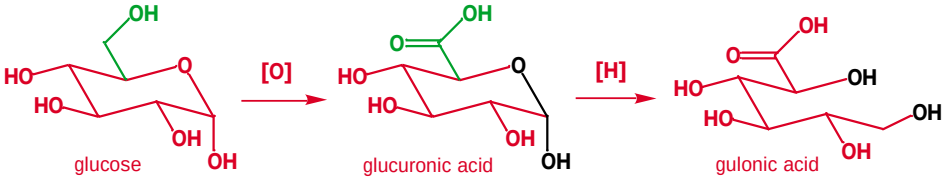
Compounds derived from sugars

Vitamin C

Nature makes some important compounds from simple sugars. Vitamin C—ascorbic acid—is one of these. Like glutathione, it protects us from stray oxidants as well as being involved in primary redox pathways (we mentioned earlier its role in collagen synthesis). Its reduced and oxidized forms are these.

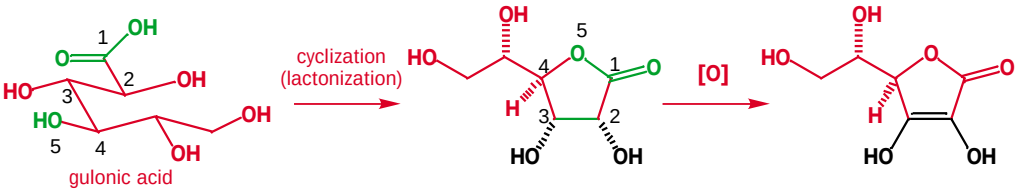


Vitamin C looks very like a sugar as it has six carbon atoms, each having an oxygen atom as substituent as well as an oxygen heterocycle, and it is no surprise that it is made in nature from glucose. We shall give just an outline of the process, which appropriately involves a lot of oxidation and reduction. The first step takes the primary alcohol of glucose to a carboxylic acid known as glucuronic acid. Next comes a reduction of the masked aldehyde to give 'gulonic acid'. Both reactions are quite reasonable in terms of laboratory chemistry.

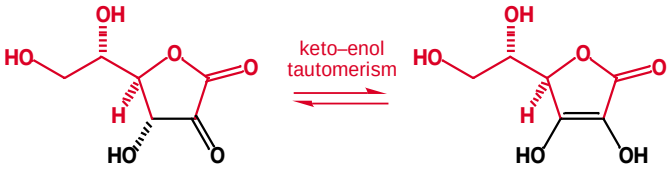


▶ We have given names for these relatively well-known sugar derivatives, but you do not need to learn them.

It is pretty obvious what will happen to this compound as it is an open-chain carboxylic acid with five OH groups. One of the OH groups will cyclize on to the acid to form a lactone. Kinetically, the most favourable cyclization will give a five-membered ring, and that is what happens. Now we are getting quite close to ascorbic acid and it is clear that oxidation must be the next step so that the double bond can be inserted between C2 and C3.

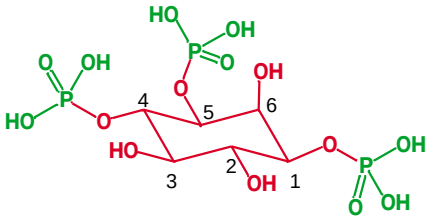


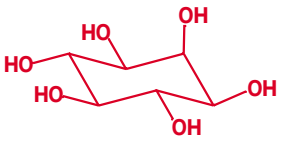
This looks a strange reaction but it is really quite logical. One of the secondary OH groups must be oxidized to a ketone. This is the 2-OH group and then the resulting ketone can simply enolize to give ascorbic acid.



Inositols

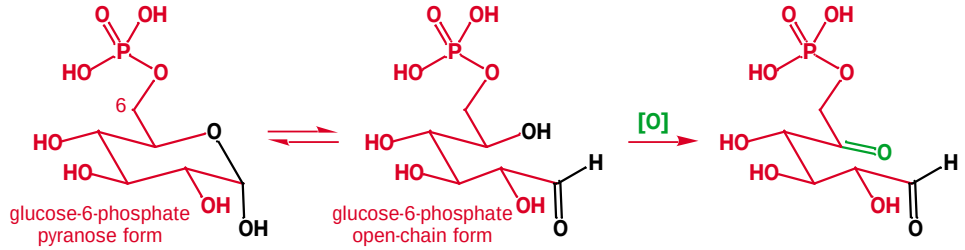
We have already discussed the widespread sugar alcohols such as mannitol but more important compounds are cyclic sugar alcohols having a carbocyclic ring (cyclitols). The most important is **inositol** which controls many aspects of our chemistry that require communication between the inside and the outside of a cell. Inositol-1,4,5-triphosphate (IP_3) can open calcium channels in cell membranes to allow calcium ions to escape from the cell.



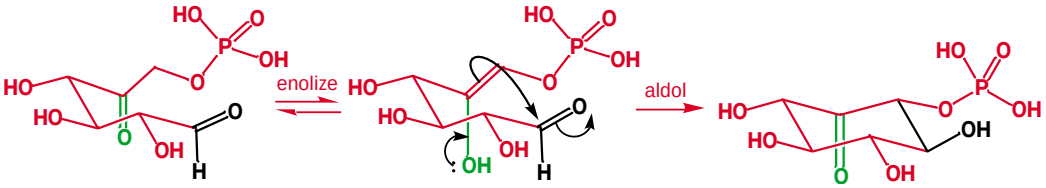


■ This inositol is known as 'myo-inositol' and is just one of many possible stereoisomers. Inositol was mentioned in Chapter 16.

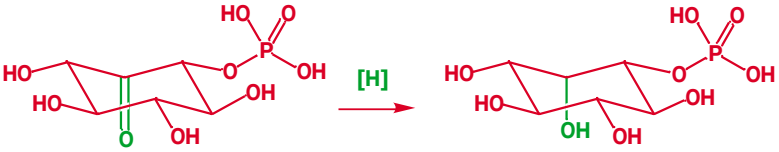
Inositol is made in nature from glucose-6-phosphate by an aldol reaction that requires preliminary ring opening and selective oxidation (this would be tricky in the lab without protecting groups!).



The resulting ketone can be enolized on the phosphate side and added to the free aldehyde group to form the cyclohexane ring. We can draw the mechanism for the aldol reaction easily if we first change the conformation.

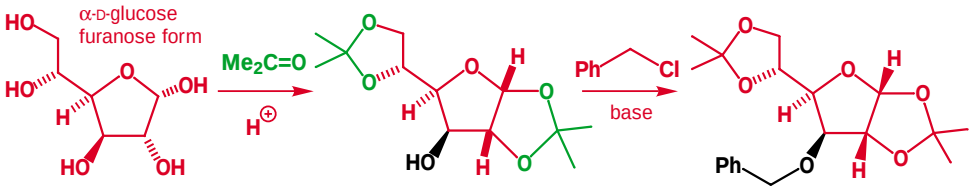


Finally, a stereochemically controlled reduction to give the axial alcohol (this would be the stereoselectivity expected with $NaBH_4$ for example: see Chapter 18) gives myo-inositol. The number and position of the phosphate esters can be controlled biochemically. This control is vital in the biological activity and would be difficult in the laboratory.

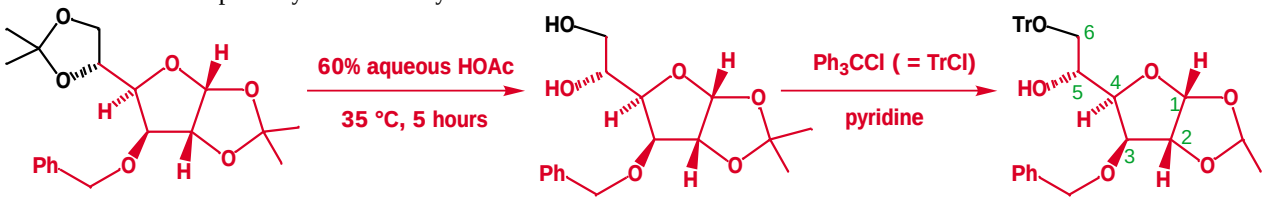


Learning from Nature—the synthesis of inositols

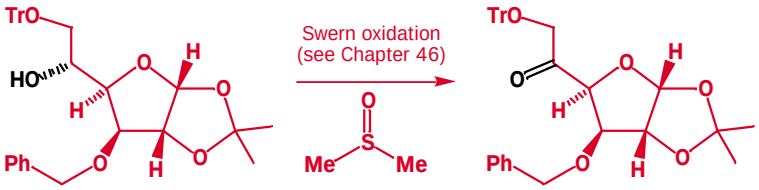
If we wish to devise a chemical version of the biosynthesis of inositols, we need to use cleverly devised protecting groups to make sure that the right OH group is oxidized to a ketone. We can start with glucose trapped in its furanose form by a double acetone acetal as we discussed above. The one remaining OH group is first blocked as a benzyl ether.



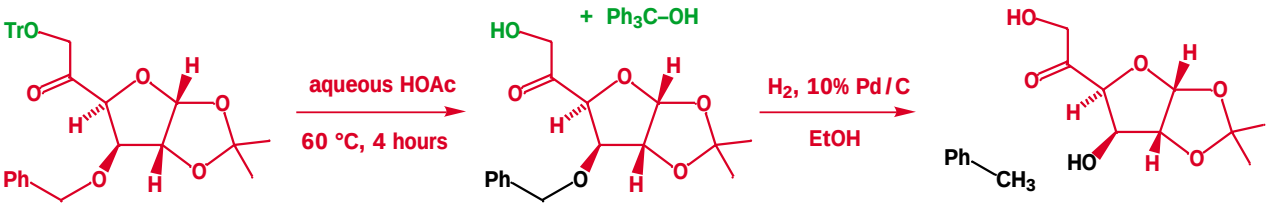
Next, one of the acetals is hydrolysed under very mild conditions, and the primary alcohol is protected as a trityl ether. This is an S_N1 reaction with an enormous electrophile—so big that it goes on primary alcohols only.



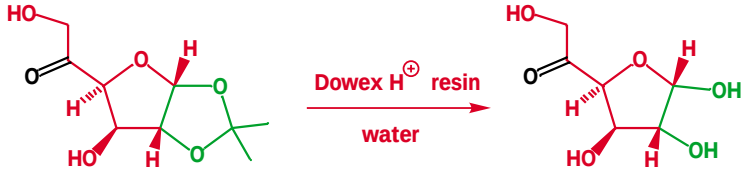
Notice that each oxygen atom in this molecule of protected glucose is now different. Only the OH at C5 is free, and its time has come: it can now be oxidized using a Swern procedure with dimethylsulfoxide as the oxidant (Chapter 46).



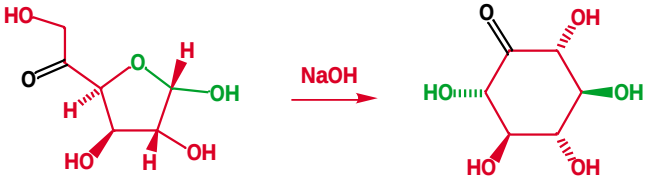
Now we can strip away the protecting groups one by one and it is instructive to see how selective these methods are. The trityl group comes off in aqueous acetic acid by another S_N1 reaction in which water captures the triphenylmethyl cation, and the benzyl group is removed by hydrogenolysis—hydrogen gas over a 10% palladium on charcoal catalyst in ethanol.



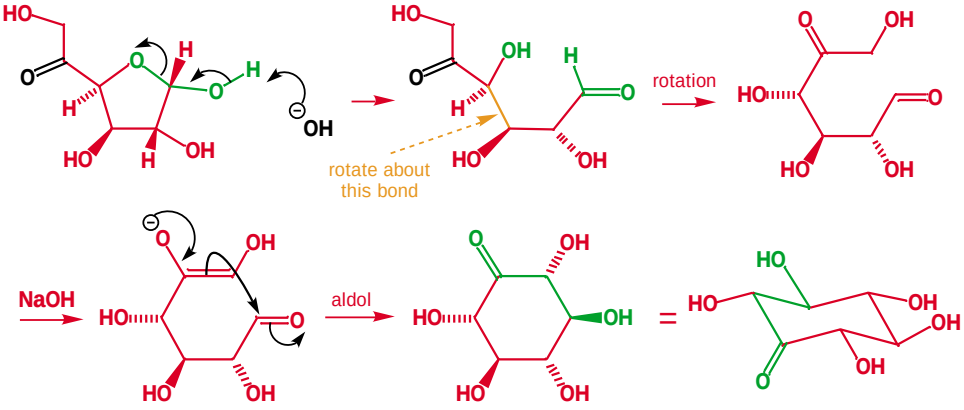
Finally, the acetone acetal is removed by acid hydrolysis. Because free sugars are difficult to isolate it is convenient to use an acidic resin known as 'Dowex'. The resin (whose polymeric structure is discussed in Chapter 52) can simply be filtered off at the end of the reaction and the solid product isolated by lyophilization—evaporation of water at low pressure below freezing point. The yield is quantitative.



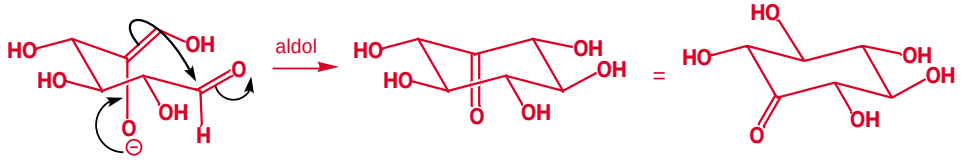
All of the hydroxyl groups are now free except the one tied up in the hemiacetal and that, of course, is in equilibrium with the open-chain hydroxy-aldehyde as we have already seen. Treatment of this free 'glucose ketone' with aqueous NaOH gives the ketone of myo-inositol as the major product together with some of the other diastereoisomers.



The simplest explanation of this result is that the chemical reaction has followed essentially the same course as the biological one. First, the hemiacetal is opened by the base to give the open-chain keto-aldehyde. Rotation about a C–C bond allows a simple aldol condensation between the enolate of the ketone as nucleophile and the aldehyde as electrophile.



The enolate must prefer to attack the aldehyde in the same way as in the biological reaction to give the all-equatorial product as the conformational drawing shows. The arrangement of the enolate in the aldol reaction itself will be the same as in the cyclization of the phosphate above.



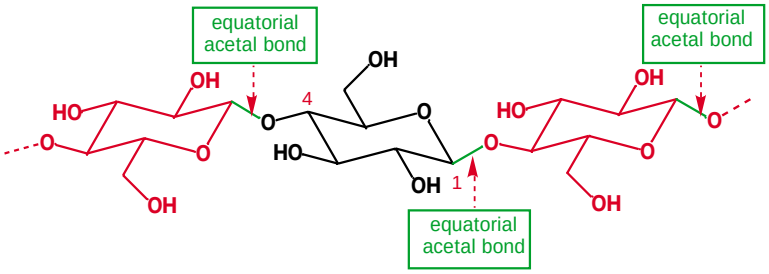
As in many other cases, by improving the rate and perfecting the stereoselectivity, the enzyme makes much better a reaction that already works.

Most sugars are embedded in carbohydrates

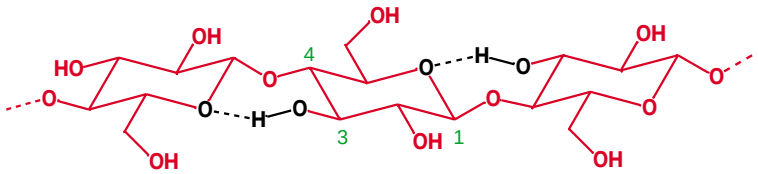
Before we leave the sugars we should say a little about the compounds formed when sugars combine together. These are the saccharides and they have the same relationship to sugars as peptides and proteins have to amino acids. We have met one simple disaccharide, sucrose, but we need to meet some more important molecules.

▶ This is literally an astronomical amount: it's about the mass of one of the moons of Mars, Deimos. Our moon weighs 10^{22} kg.

One of the most abundant compounds in nature is cellulose, the structural material of plants. It is a glucose polymer and is produced in simply enormous quantities (about 10^{15} kg per year). Each glucose molecule is joined to the next through the anomeric bond (C1) and the other end of the molecule (C4). Here is that basic arrangement.



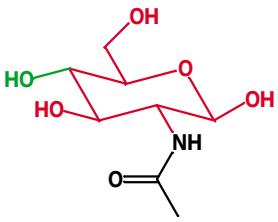
Notice that the anomeric bonds are all equatorial. This means that the cellulose molecule is linear in general outline. It is made rigid by extra hydrogen bonds between the 3-OH groups and the ring oxygen atoms—like this.



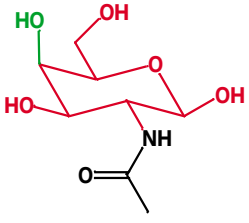
The polymer is also coiled to increase stability still further. All this makes cellulose very difficult to hydrolyse, and humans cannot digest cellulose as we do not have the necessary enzymes. Only ruminants, such as cows, whose many stomachs harbour some helpful bacteria, can manage it.

Amino sugars add versatility to saccharides

To go further in understanding the structural chemistry of life we need to know about amino sugars. These molecules allow proteins and sugars to combine and produce structures of remarkable variety and beauty. The most common amino sugars are *N*-acetyl-glucosamine and *N*-acetyl-galactosamine, which differ only in stereochemistry.

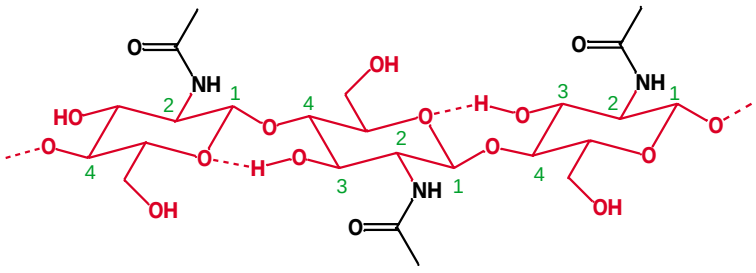


N-acetyl-glucosamine



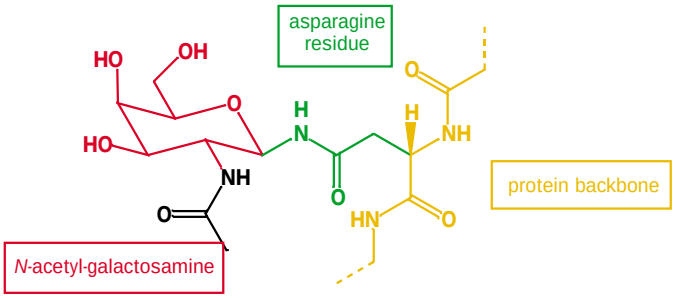
N-acetyl-galactosamine

The hard outer skeleton of insects and shellfish contains chitin, a polymer very like cellulose but made of acetyl glucosamine instead of glucose itself. It coils up in a similar way and provides the toughness of crab shells and beetle cases.



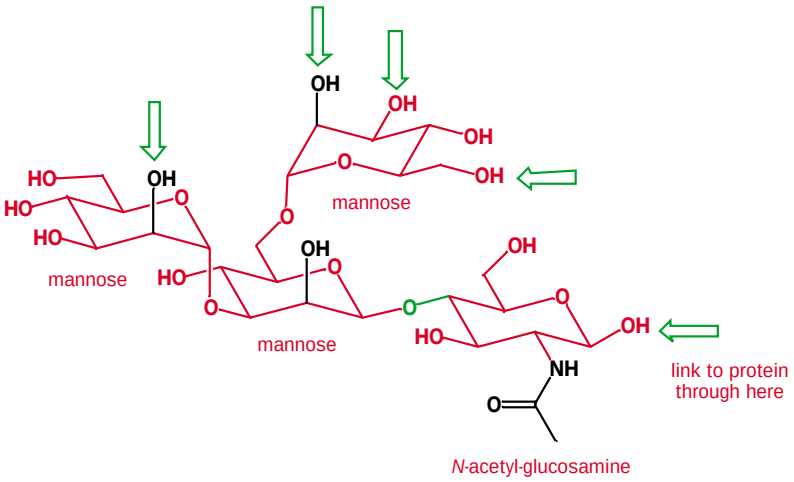
Ordinary cell membranes must not be so tough as they need to allow the passage of water and complex molecules through channels that can be opened by molecules such as inositol phosphates.

These membranes contain glycoproteins—proteins with amino-sugar residues attached to asparagine, serine, or threonine in the protein. The attachment is at the anomeric position so that these compounds are *O*- or *N*-glycosides of the amino sugars. Here is *N*-acetyl-galactosamine attached to an asparagine residue as an *N*-glycoside.

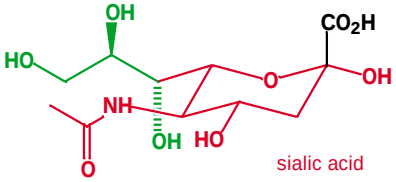


The cell membrane normally contains less than 10% of sugars but these are vital to life. Because the sugars (*N*-acetyl-glucosamine and *N*-acetyl-galactosamine) are covered with very polar groups (OH and amide) they prefer to sit outside the membrane in the aqueous extracellular fluid rather than within the nonpolar membrane itself. When two cells meet, the sugars are the first things they see. We cannot go into the details of the biological processes here, but even the structures of these saccharides dangling from the cell are very interesting. They contain amino sugars, again particularly *N*-acetyl-glucosamine and *N*-acetyl-galactosamine, and they are rich in mannose.

In addition, they are usually branched at one of the mannose residues that is joined to two other mannoses on one side and to one glucosamine on the other. The glucosamine leads back eventually to the protein through a link to asparagine like the one we have just seen. The two mannoses are linked to more sugars at positions marked by the green arrows and provide the recognition site. The structure below is a typical branchpoint.

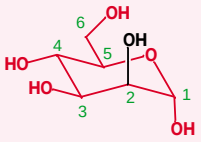


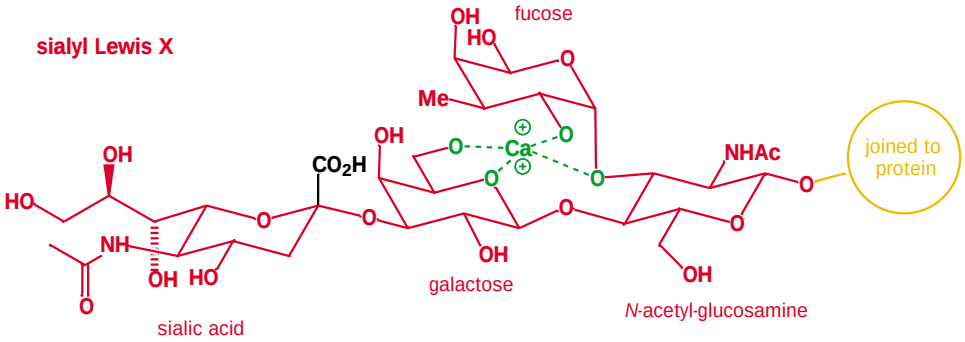
You should begin to see from structures like these just how versatile sugar molecules can be. From just four sugars we have constructed a complex molecule with up to 13 possible link sites. With more sugars added, the possibilities become enormous. It is too early to say what medical discoveries will emerge from these molecules, but one that is likely to be important is sialyl Lewis X. This tetrasaccharide is also branched but it contains a different type of molecule—a C_9 sugar with a CO_2H group, called sialic acid.



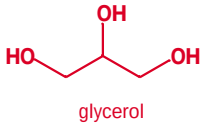
Sialic acid has the CO_2H group at the anomeric position, a typical *N*-acetyl group, and a unique side chain (in green) with three more OH groups. Sialyl Lewis X has sialic acid at the end of a branched sugar chain. The branchpoint is the familiar *N*-acetyl-glucosamine through which the molecule is eventually linked to the glycoprotein. The remaining sugars are galactose, a diastereoisomer of glucose, and a sugar we have not seen before, fucose. Fucose often appears in saccharides of this kind and is a six-carbon sugar without a primary OH group. It is like galactose with Me instead of CH_2OH.

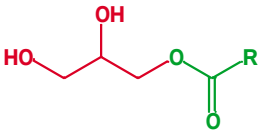
▶ Mannose is another glucose diastereoisomer and has one axial OH group at C2.

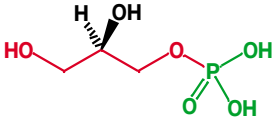




Sialyl Lewis X can also form a stable complex with calcium ions as the diagram shows and this may be vital to its activity. It is certainly involved in leukocyte adhesion to cells and is therefore vital in the prevention of infection.


glycerol


glycerol monoester

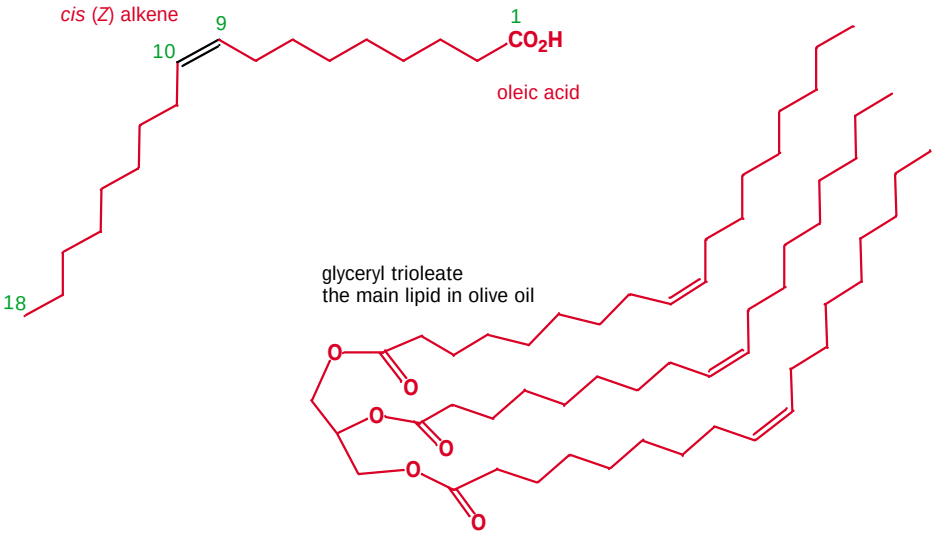

glycerol 3-phosphate

Lipids

Lipids (fats) are the other important components of cell membranes. Along with cholesterol, also a component of the cell membrane, they have acquired a bad name, but they are nonetheless essential to the function of membranes as selective barriers to the movement of molecules.

The most common types of lipids are esters of glycerol. Glycerol is just propane-1,2,3-triol but it has interesting stereochemistry. It is not chiral as it has a plane of symmetry, but the two primary OH groups are enantiotopic (Chapter 16). If one of them is changed—by esterification, for example—the molecule becomes chiral. Natural glycerol phosphate is such an ester and it is optically active.

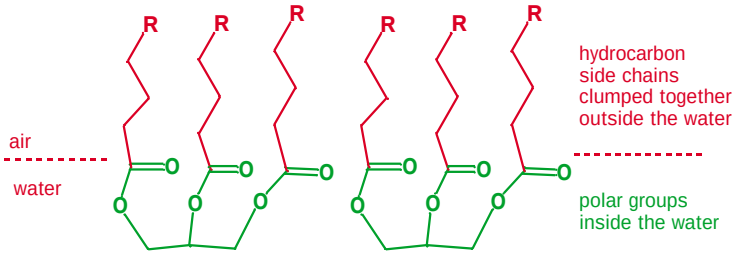
A typical lipid in foodstuffs is the triester formed from glycerol and oleic acid, which is the most abundant lipid in olive oil. Oleic acid is a 'mono-unsaturated fatty acid'—it has one *Z* double bond in the middle of the C_{18} chain. This bond gives the molecule a marked kink in the middle. The compound actually present in olive oil is the triester, also kinked.



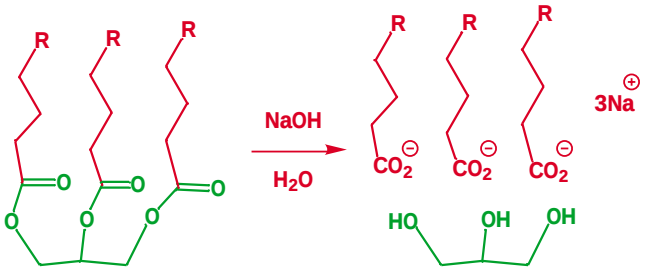
Oil and water do not mix

The lipid has, more or less, the conformation shown in the diagram with all the polar ester groups at one end and the hydrocarbon chains bunched together in a nonpolar region. Oil and water do not mix, it is said, but triglyceride lipids associate with water in a special way. A drop of oil spreads out on water in a very thin layer. It does so because the ester groups sit inside the water and the hydrocarbon side chains stick out of the water and associate with each other.

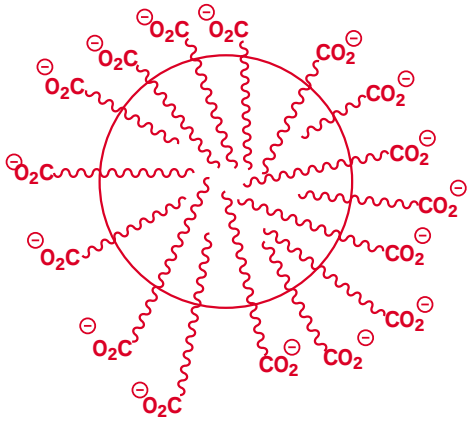
■ You may have done the 'Langmuir trough' experiment in a physical chemistry practical class. This involves measuring the size of a molecule by allowing an oil to spread on the surface of water in a unimolecular layer.



When triglycerides are boiled up with alkali, the esters are hydrolysed and a mixture of carboxylate salts and glycerol is formed. This was how soap was made—hard soap was the sodium salt and soft soap the potassium salt.

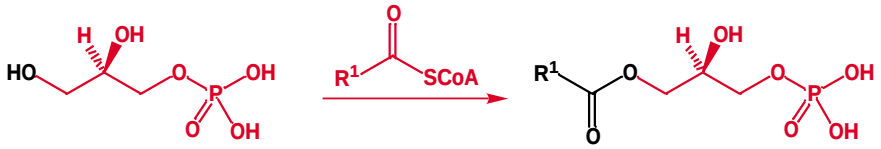


When a soap is suspended in water, the carboxylate groups have a strong affinity for the water and so oily globules or micelles are formed with the hydrocarbon side chain inside. It is these globules that remove greasy dirt from you or your clothes.



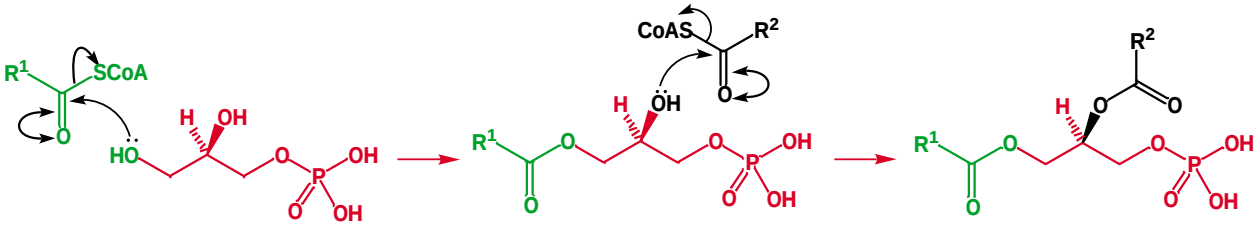
Nature uses thiol esters to make lipids

The repulsion between molecules having oily or aqueous properties is the basis for membrane construction. The lipids found in membranes are mostly based on glyceryl phosphate and normally contain three different side chains—one saturated, one unsaturated, and one very polar.



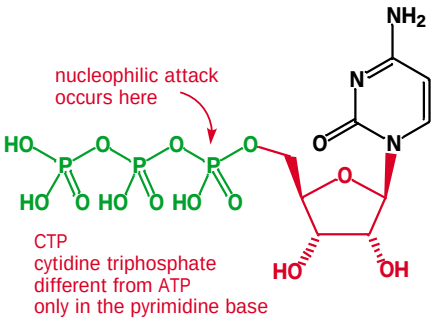
The saturated chain is added first, at C1 of glyceryl phosphate. The reagent is a thiol ester called acyl coenzyme A, whose full structure you will see in the next chapter. This reaction occurs by simple nucleophilic attack on the carbonyl group of the thiol ester followed by loss of the better leaving group, the thiolate anion. Then the process is repeated at the second OH group where an unsaturated fatty acid, perhaps oleic acid, is added by the same mechanism.

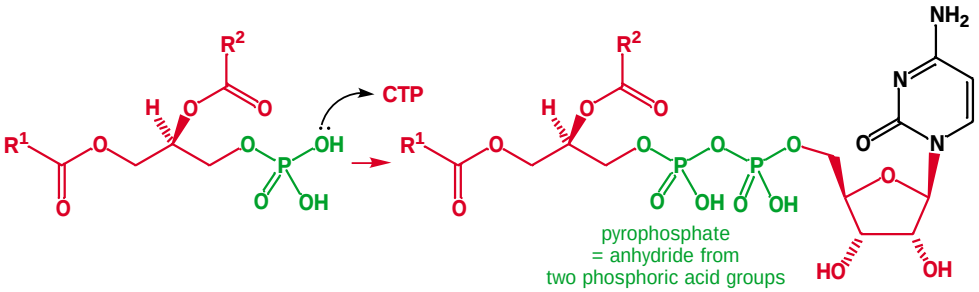
■ We discussed acylation by thioesters, the laboratory version of this reaction, in Chapter 27.



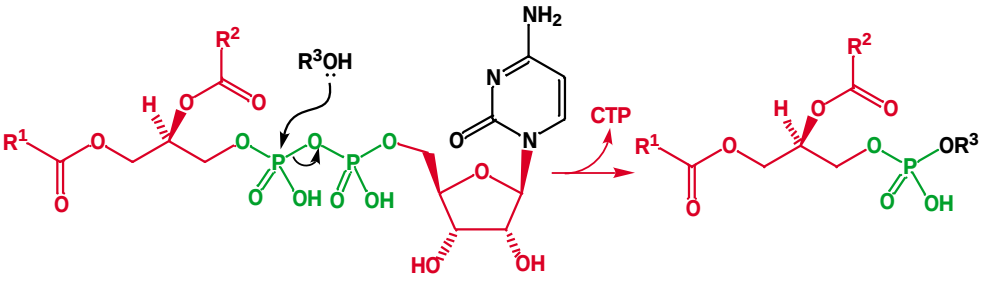
The third acylation requires the phosphate to act as the acylating agent and a polar alcohol to be introduced to form a phosphate ester. This reaction actually occurs by the activation of the phosphate as a pyrophosphate. Pyrophosphates are really acid anhydrides so it is not surprising that they act as acylating agents. The first step is a reaction with cytidine triphosphate (CTP) doing a job we might expect from ATP.

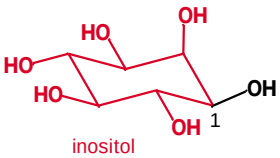
Nucleophilic attack by the phosphate group of the phosphoglyceride at the point indicated on CTP gives the pyrophosphate required for the acylation step.



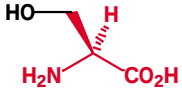


The anhydride is now attacked by an alcohol acting as a nucleophile. The attack occurs only at the electrophilic phosphorus centre further from the nucleotide. This is an impressive piece of regioselectivity and is presumably controlled by the enzyme.





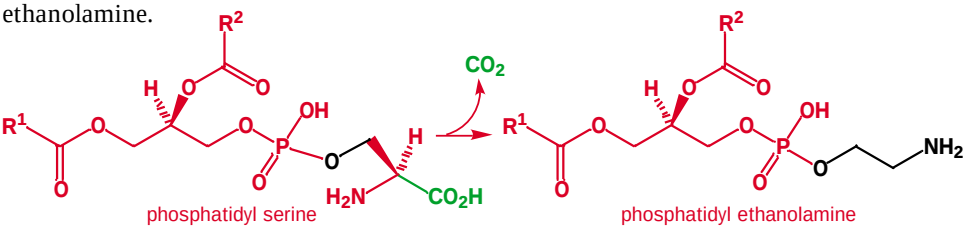
inositol



the amino acid
serine (Ser)

This third chain is rather different from the other two—it's a phosphate diester, and the alcohol portion can be inositol joined through the OH group at C1 or it can be the amino acid serine, joined through its OH group.

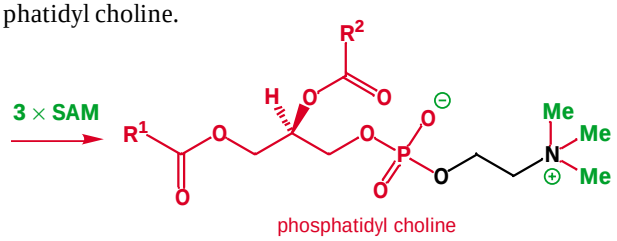
The compound formed from serine is particularly important as it can be transformed into the most dramatically contrasted of these phospholipids. A decarboxylation using a coenzyme (we shall look at the mechanism of this reaction in Chapter 51) gives a very simple molecule, phosphatidyl ethanolamine.



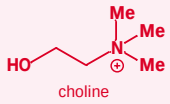
phosphatidyl serine

phosphatidyl ethanolamine

Finally, three methylations on the nitrogen atom by SAM (see p. 000) gives the zwitterion phosphatidyl choline.

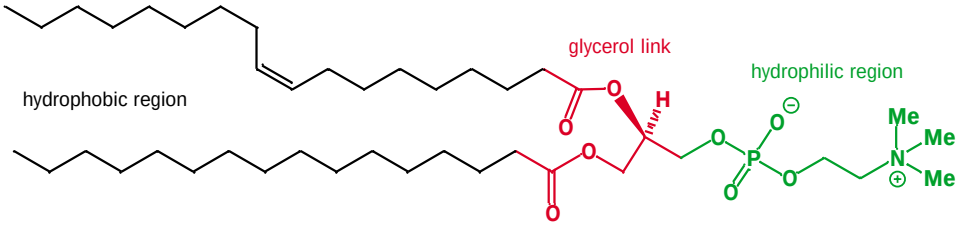


▶ Choline is a tetraalkyl ammonium salt and is important elsewhere in biology.

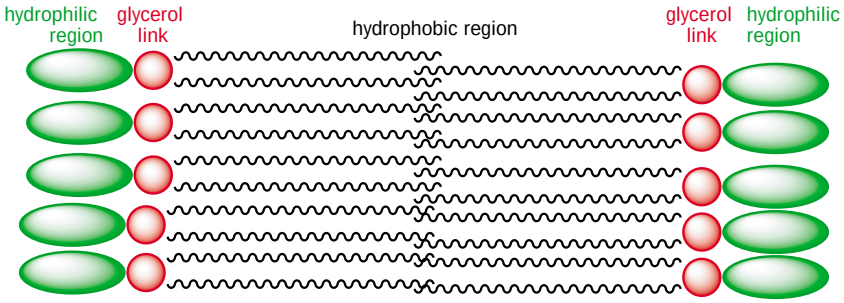


Phospholipids form membranes spontaneously

The choline terminus of the molecule is very polar indeed. Phosphatidyl choline adopts a shape with the nonpolar chains (R^1 and R^2) close together, and it should be clear that this is an ideal molecule for the construction of membranes.



We have already seen how oils such as glyceryl trioleate form thin layers on water while soaps from the alkaline hydrolysis of glycerides form micelles. Phosphatidyl choline forms yet another structure—it spontaneously forms a membrane in water. The hydrophobic hydrocarbon chains line up together on the inside of the membrane with the hydrophilic choline residues on the outside.

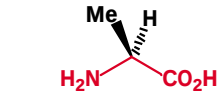


This is just a small piece of a cross-section of the membrane. These membranes are called lipid bilayers because two rows of molecules line up to form two layers back-to-back. The charged, hydrophilic region on the outside is solvated by the water and the hydrocarbon tails are repelled by the water and attracted to each other by weak forces such as van der Waals attractions.

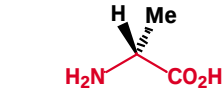
Full structural analysis of a real cell membrane reveals a chemically diverse thin sheet composed of phospholipid bilayers penetrated by glycoproteins containing the amino sugars we discussed earlier. The amount of each component varies but there is usually about 50:50 phospholipid:protein, with the protein containing about 10% sugar residues. The phospholipids' main role is as a barrier while the glycoproteins have the roles of recognition and transport.

Bacteria and people have slightly different chemistry

We have many times emphasized that all life has very similar chemistry. Indeed, in terms of biochemistry there is little need for the classifications of mammals, plants, and so on. There is only one important division—into prokaryotes and eukaryotes. Prokaryotes, which include bacteria, evolved first and have simple cells with no nucleus. Eukaryotes, which include plants, mammals, and all



(*S*)-Ala from normal proteins

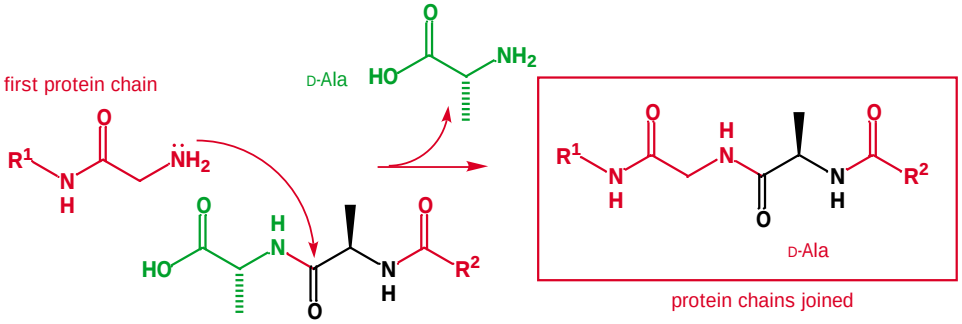


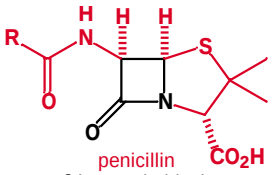
(*R*)-Ala from bacterial cell walls

other multicellular creatures, evolved later and have more complex cells including nuclei. Even so, much of the biochemistry on both sides of the divide is the same.

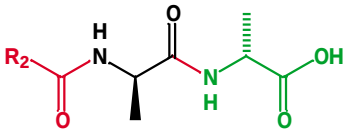
When medicinal chemists are looking for ways to attack bacteria, one approach is to interfere with chemistry carried out by prokaryotes but not by us. The most famous of these attacks is aimed at the construction of the cell walls of some bacteria that contain 'unnatural' (*R*)- (or D-) amino acids. Bacterial cell walls are made from glycopeptides of an unusual kind. Polysaccharide chains are cross-linked with short peptides containing (*R*)-alanine (D-Ala). Before they are linked up, one chain ends with a glycine molecule and the other with D-Ala–D-Ala. In the final step in the cell wall synthesis, the glycine attacks the D-Ala–D-Ala sequence to form a new peptide bond by displacing one D-Ala residue.

▶ The reason bacteria use these 'unnatural' D-amino acids in their cell walls is to protect them against the enzymes in animals and plants, which cannot digest proteins containing D-amino acids.

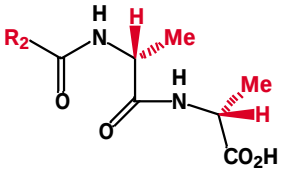




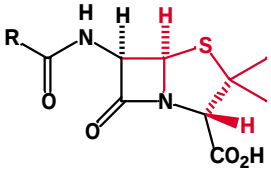
The famous molecule that interferes with this step is penicillin, though this was not even suspected when penicillin was discovered. We now know how penicillin works. It inhibits the enzyme that catalyses the D-Ala transfer in a very specific way. It first binds specifically to the enzyme, so it must be a mimic of the natural substrate, and it then reacts with the enzyme and inactivates it by blocking a vital OH group at the active site. If we emphasize the peptide nature of penicillin and compare it with D-Ala–D-Ala, the mimicry may become clearer.



acyl–D-Ala–D-Ala redrawn back to front and upside down



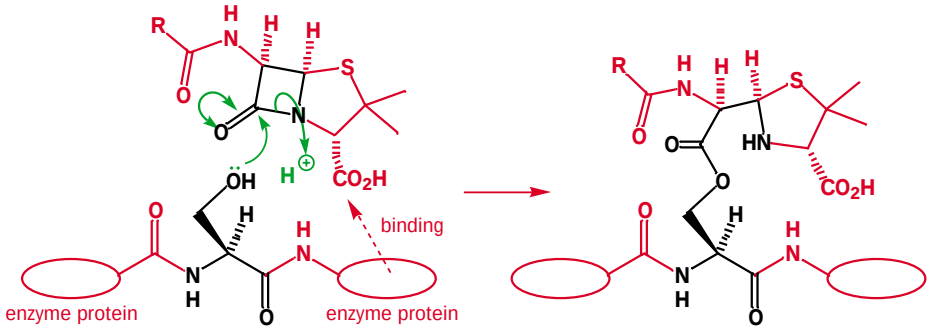
acyl–D-Ala–D-Ala redrawn in the penicilin shape



the peptide part of penicillin

Penicillin imitates D-Ala and binds to the active site of the enzyme, encouraging the OH group of a serine residue to attack the reactive, strained β-lactam. This same OH group of the same serine residue would normally be the catalyst for the D-Ala–D-Ala cleavage used in the building of the bacterial cell wall. The reaction with penicillin 'protects' the serine and irreversibly inhibits the enzyme. The bacterial cell walls cannot be completed, and the bacterial cells literally burst under the pressure of their contents. Penicillin does not kill bacteria whose cell walls are already complete but it does prevent new bacteria being formed.

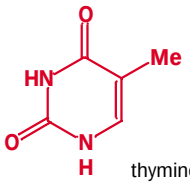
▶ Our current last line of defence against bacteria resistant to penicillin, and other antibiotics, is vancomycin. Vancomycin works by binding to the D-Ala–D-Ala sequences of the bacterial cell wall.



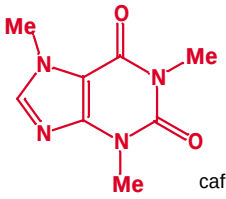
You have seen many instances in this chapter of the importance of a good understanding of both the chemistry and the biochemistry of living things if medicine is to advance: it is at the frontier of chemistry and biology that many of the most important medical advances are being made.

Problems

1. Do you consider that thymine and caffeine are aromatic compounds? Explain.

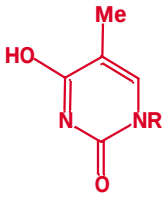


thymine

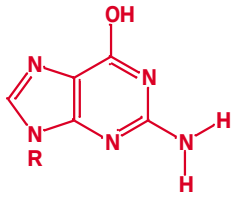


caffeine

2. It is important that we draw certain of the purine and pyrimidine bases in their preferred tautomeric forms. The correct pairings are given early in the chapter. What alternative pairings would be possible with these (minor) tautomers of thymine and guanine? Suggest reasons (referring to Chapter 43 if necessary) why the major tautomers are preferred.

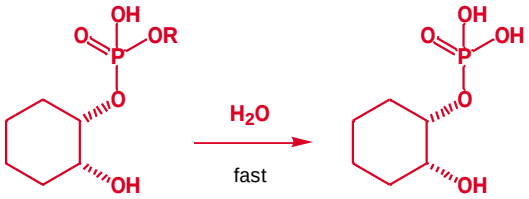


thymine tautomer



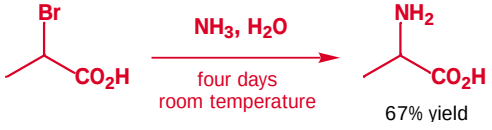
guanine tautomer

3. Dialkyl phosphates are generally hydrolysed quite slowly at near-neutral pHs but this example hydrolyses much more rapidly. What is the mechanism and what relevance has it to RNA chemistry?



Revision of Chapter 41. This reaction is subject to general base catalysis. Explain.

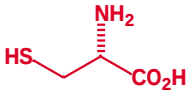
4. Primary amines are not usually made by displacement reactions on halides with ammonia. Why not? The natural amino acids can be made by this means in quite good yield. Here is an example.



67% yield

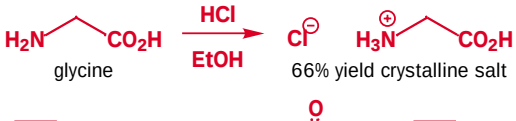
Why does this example work? Comment on the state of the reagents and products under the reaction conditions. What is the product and how does it differ from the natural amino acid?

5. Human hair is a good source of cystine, the disulfide dimer of cysteine. The hair is boiled with aqueous HCl and HCO_2H for a day, the solution concentrated, and a large amount of sodium acetate added. About 5% of the hair by weight crystallizes out as pure cystine $[\alpha]_D$ –216. How does the process work? Why is such a high proportion of hair cystine? Why is no cysteine isolated by this process? What is the stereochemistry of cystine? Make a good drawing of cystine to show its symmetry. How would you convert the cystine to cysteine?

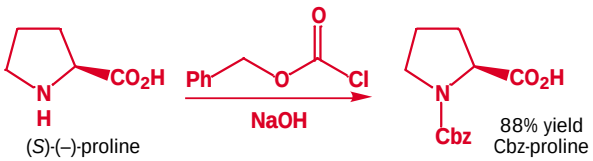


(*S*)–cysteine

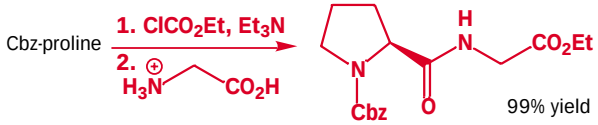
6. A simple preparation of a dipeptide is given below. Explain the reactions, drawing mechanisms for the interesting steps. Which steps are protection, activation, coupling, and deprotection? Explain the reasons for protection and the nature of the activation. Why is the glycine added to the coupling step as its hydrochloride? What reagent(s) would you use for the final deprotection step?



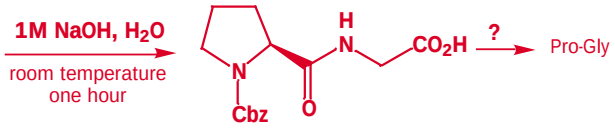
glycine — 66% yield crystalline salt



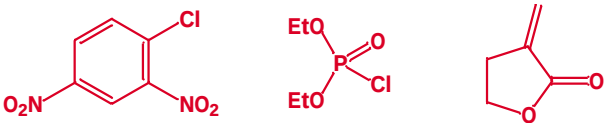
(*S*)-(–)-proline — 88% yield Cbz-proline



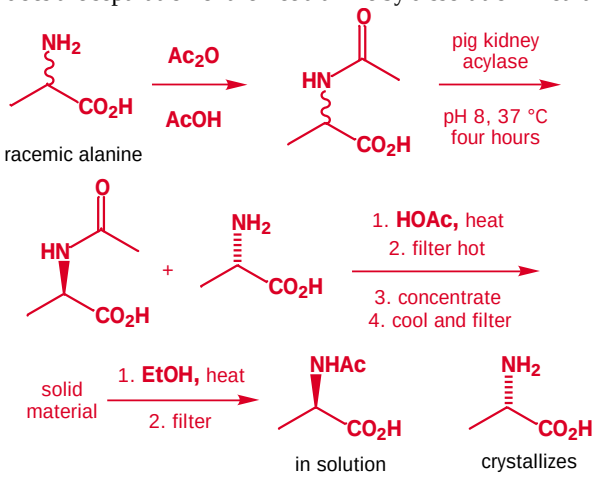
99% yield



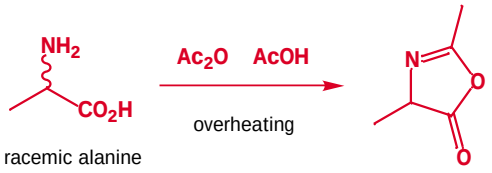
7. Suggest how glutathione might detoxify these dangerous chemicals in living things. Why are they still toxic in spite of this protection?



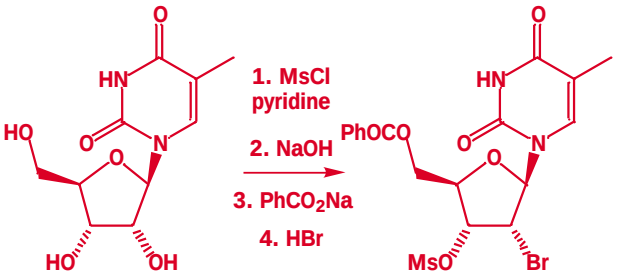
8. Alanine can be resolved by the following method, using a pig kidney acylase. Draw a mechanism for the acylation step. Which isomer of alanine acylates faster? In the enzyme-catalysed reaction, which isomer of the amide hydrolyses faster? In the separation, why is the mixture heated in acid solution, and what is filtered off? How does the separation of the free alanine by dissolution in ethanol work?



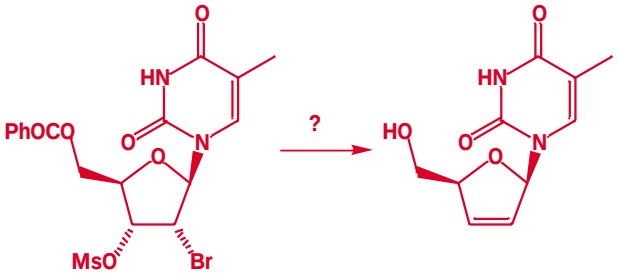
If the acylation is carried out carelessly, particularly if the heating is too long or too strong, a by-product may form that is not hydrolysed by the enzyme. How does this happen?



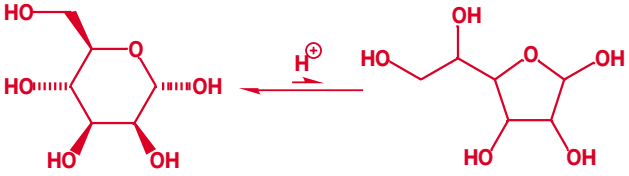
9. A patent discloses this method of making the anti-AIDS drug d4T. The first few stages involve differentiating the three hydroxyl groups of 5-methyluridine as shown below. Explain the reactions, especially the stereochemistry at the position of the bromine atom.



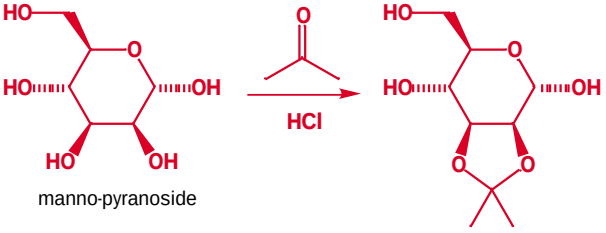
Suggest how the synthesis might be completed.



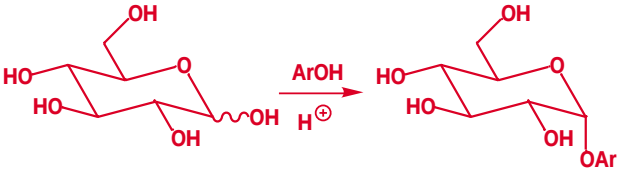
10. Mannose usually exists as the pyranoside shown below. This is in equilibrium with the furanoside. What is the conformation of the pyranoside and what is the stereochemistry of the furanoside? What other stereochemical change will occur more quickly than this isomerization?



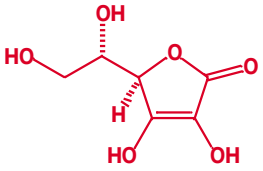
Treatment of mannose with acetone and HCl gives the acetal shown. Explain the selectivity.



11. How are glycosides formed from phenols (in Nature or in the laboratory)? Why is the stereochemistry of the glycoside not related to that of the original sugar?



12. Draw all the keto and enol forms of ascorbic acid (vitamin C). Why is the one shown the most stable?



13. 'Caustic soda' (NaOH) was used to clean ovens and clear blocked drains. Many commercial products for these jobs with fancy names still contain NaOH. Even concentrated sodium carbonate (Na_2CO_3) does quite a good job. How do these cleaners work? Why is NaOH so dangerous to humans, particularly if it gets in the eye?

14. Bacterial cell walls contain the unnatural amino acid D-alanine. If you wanted to prepare a sample of D-ala, how would you go about it? (*Hint*. There is not enough in bacteria to make that a worthwhile source, but have you done Problem 8 yet?)

Mechanisms in biological chemistry 50

Connections

Building on:

- Acidity and basicity ch8
- Carbonyl chemistry ch12 & ch14
- Stereochemistry ch16
- Conformational analysis and elimination ch18–ch19
- Enolate chemistry and synthesis ch24–ch30
- Pericyclic reactions ch35–ch36
- Determining mechanisms ch13 & ch41
- Heterocycles ch42–ch44
- Asymmetric synthesis ch45
- Sulfur chemistry ch46
- Chemistry of life ch49

Arriving at:

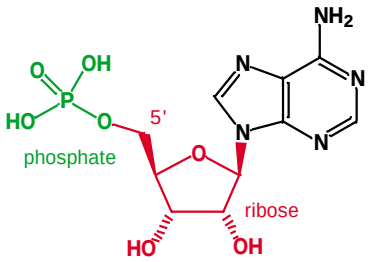
- How Nature makes small molecules using ordinary organic mechanisms
- Enzymes are Nature's catalysts, speeding up reactions by factors of 10^6 or more
- Coenzymes and vitamins are Nature's versions of common organic reagents
- Reductions with NADH
- Reductive amination, deamination, and decarboxylation with pyridoxal
- Enol chemistry with lysine enamines, with coenzyme A, and with phosphoenolpyruvate
- Umpolung chemistry with thiamine as a d^1 reagent
- Carboxylation with biotin
- Oxidations with FAD
- How Nature makes aromatic amino acids

Looking forward to:

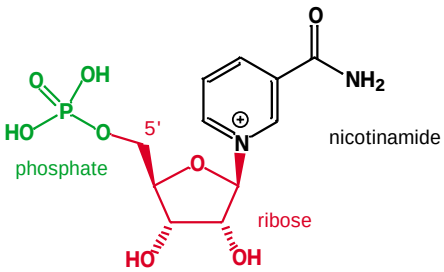
- Natural products ch51

Nature's $NaBH_4$ is a nucleotide: NADH or NADPH

In Chapter 49 we spent some time discussing the structure of nucleotides and their role as codons in protein synthesis. Now we shall see how Nature uses different nucleotides as reagents. Here is the structure of AMP, just to remind you, side by side with a new pyridine nucleotide.

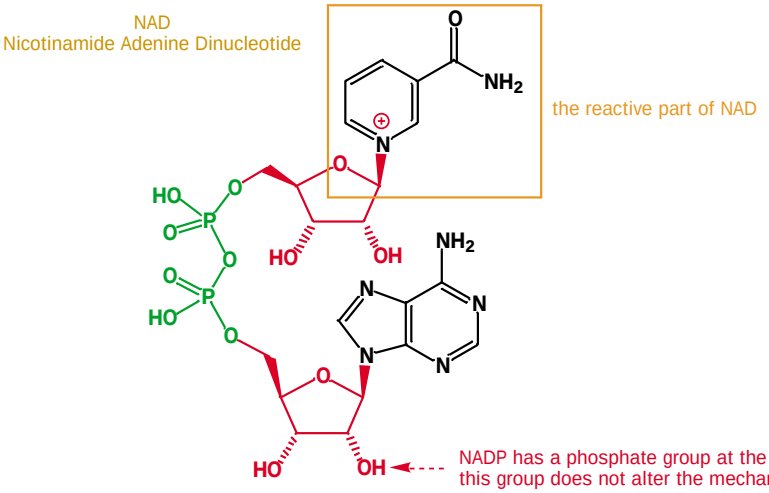


AMP—an adenine nucleotide

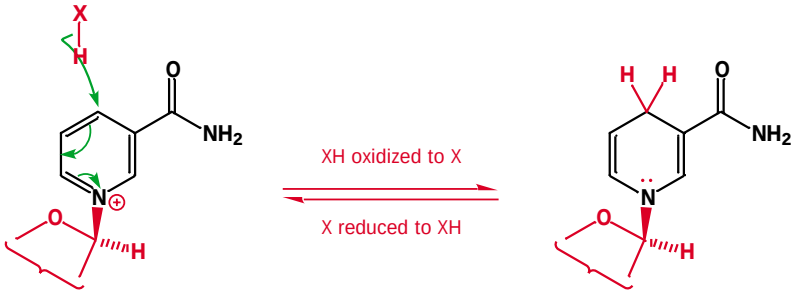


a nicotinamide nucleotide

These two nucleotides can combine together as a pyrophosphate to give a dinucleotide. Notice that the link is not at all the same as in the nucleic acids. The latter are joined by one phosphate that links the 3′–5′ positions. Here we have a *pyro*phosphate link between the two 5′-positions.



Notice also the positive charge on the nitrogen atom of the pyridine ring. This part of the molecule does all the work and from now on we will draw only the reactive part for clarity. This is NAD^+, nicotine adenine dinucleotide, and it is one of Nature's most important oxidizing agents. Some reactions use NADP instead but this differs only in having an extra phosphate group on the adenosine portion so the same part structure will do for both. NAD^+ and NADP both work by accepting a hydrogen atom and a pair of electrons from another compound. The reduced compounds are called NADH and NADPH.

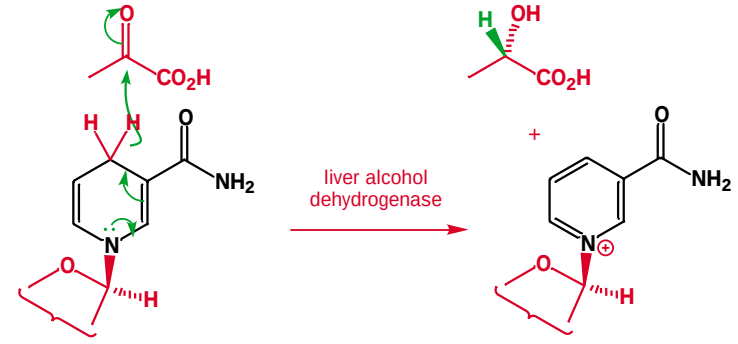


NAD^+—Nature's oxidizing agent

NADH—Nature's reducing agent

The reduction of NAD^+ (and NADP) is reversible, and NADH is itself a reducing agent. We will first look at one of its reactions: a typical reduction of a ketone. The ketone is pyruvic acid and the reduction product lactic acid, two important metabolites. The reaction is catalysed by the enzyme liver alcohol dehydrogenase.

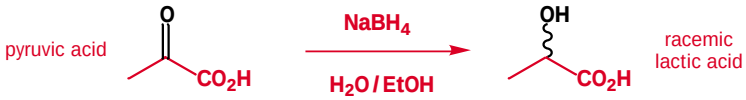
▶ The names of enzymes are usually chosen to tell us where they come from and what job they do and the name ends '-ase'. A **dehydrogenase** is clearly a redox enzyme as it removes (or adds) hydrogen.



NADH—Nature's reducing agent

NAD^+—Nature's oxidizing agent

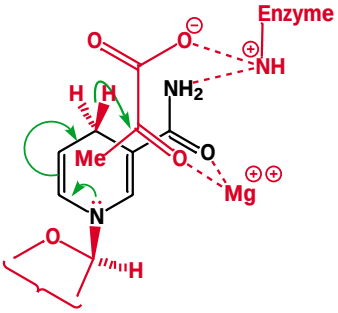
This is a reaction that would also work in the laboratory with $NaBH_4$ as the reducing agent, but there is a big difference. The product from the $NaBH_4$ reaction *must* be racemic—no optical activity has been put in from compound, reagent, or solvent.



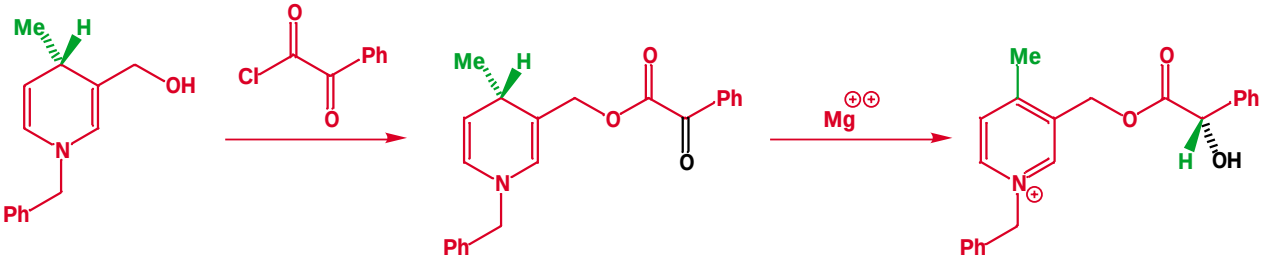
■ If you are not clear about enantioselective reactions and why $NaBH_4$ must give a racemic mixture, reread Chapter 45. If you are not clear about the terms 'enantiotopic' and 'prochiral' reread Chapters 32 and 34. If you are not clear about what enantiomers are, you must reread Chapter 16 now.

But the product from the enzymatic reaction is optically active. The two faces of pyruvic acid's carbonyl group are enantiotopic and, by controlling the addition so that it occurs from one face only, the reaction gives a single enantiomer of lactic acid.

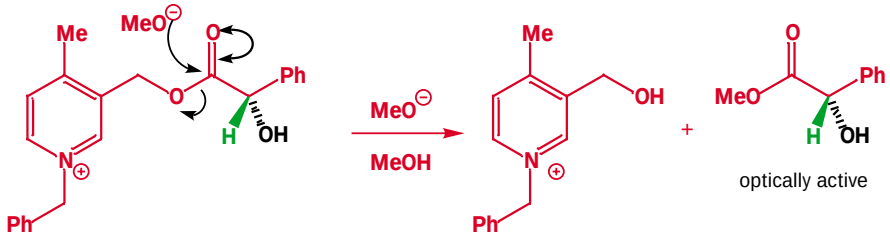
Both the enzyme and the reagent NADH are single enantiomers and they cooperate by binding. The enzyme binds both the substrate (pyruvic acid) and the reagent (NADH) in a specific way so that the hydride is delivered to one enantiotopic face of the ketone. Pyruvic acid under physiological conditions will be the anion, pyruvate, so it is held close to the positively charged amino group of a lysine residue on the enzyme that also binds the amino group of NADH. A magnesium(II) cation, also held by the enzyme, binds the carbonyl group of the amide of NADH and the ketone in pyruvate. If this model is correct, only the top H atom (as drawn) of the diastereotopic CH_2 group in NADH should be transferred to pyruvate. This has been proved by deuterium labelling.



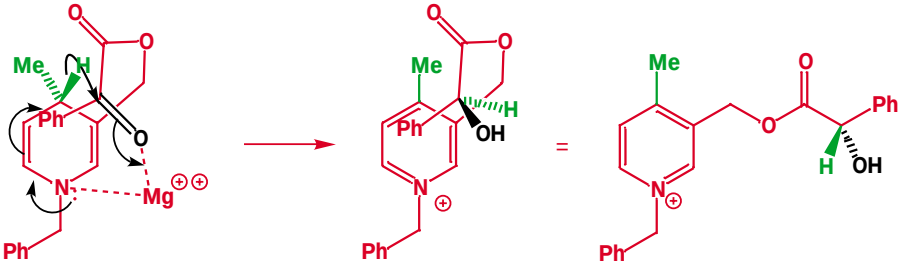
Supporting evidence comes from a model system using a much simpler reducing agent. A dihydropyridine with a primary alcohol replacing the amide group in NADH and a simple benzyl group replacing the nucleotide forms stable esters with keto-acids. As soon as the ester is treated with magnesium(II) ions, intramolecular and stereospecific reduction occurs. The hydride ion is transferred from a stereogenic centre, which replaces the diastereotopic CH_2 group in NADH.



When the ester is cleaved by transesterification with methoxide ion, the newly released hydroxy-ester is optically active.

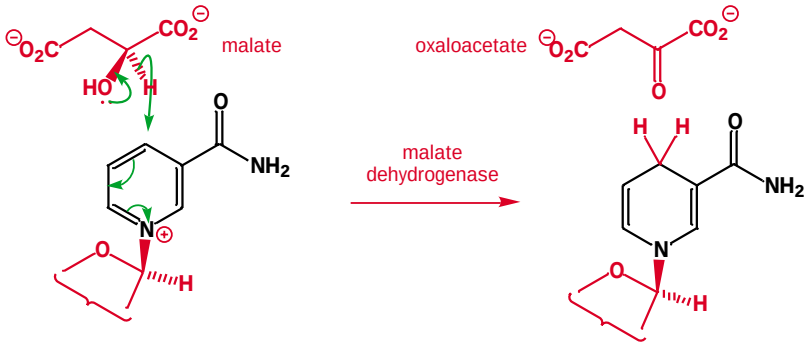


The details of the reaction are probably a good model for the NADH reaction even down to the activation by magnesium(II) ions. A possible transition state would be very similar to the NADH transition state above.



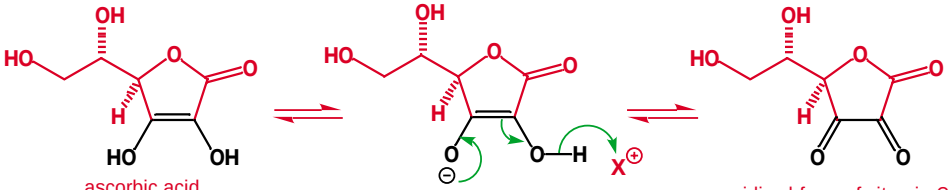
▶ The other two reactions are of a more complex type that we will meet soon when we show how acetyl coenzyme A is a key reagent in the building of carbon–carbon chains.

Many other reactions use NADH as a reducing agent or NAD^+ as oxidizing agent. Three molecules of NAD^+ are used in the citric acid cycle (see the chart on p. 000). One of these oxidations is the simple transformation of a secondary alcohol (malate) to a ketone (oxaloacetate).



▶ Ascorbic acid is usually described as an antioxidant rather than a reducing agent though mechanistically they are the same.

Other redox reagents include dinucleotides such as FAD (flavine adenine dinucleotide), lipoic acid, which we will meet when we discuss the chemistry of thiamine, and ascorbic acid (vitamin C), which you met in Chapter 49. Ascorbic acid can form a stable enolate anion that can transfer a hydride ion to a suitable oxidant.



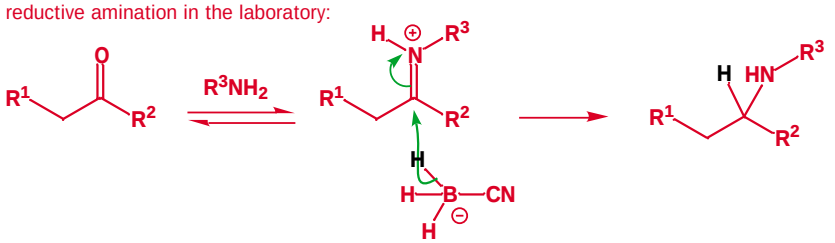
In this mechanism 'X^+' represents an oxidant—a dangerously reactive peroxide perhaps, or even Fe(III) which must be reduced to Fe(II) as part of the reaction cycle of many iron-dependent enzymes.

Reductive amination in nature

■ For more on reductive amination, see Chapter 14.

One of the best methods of amine synthesis in the laboratory is reductive amination, in which an imine (formed from a carbonyl compound and an amine) is reduced to a saturated amine. Common reducing agents include $NaCNBH_3$ and hydrogen with a catalyst.

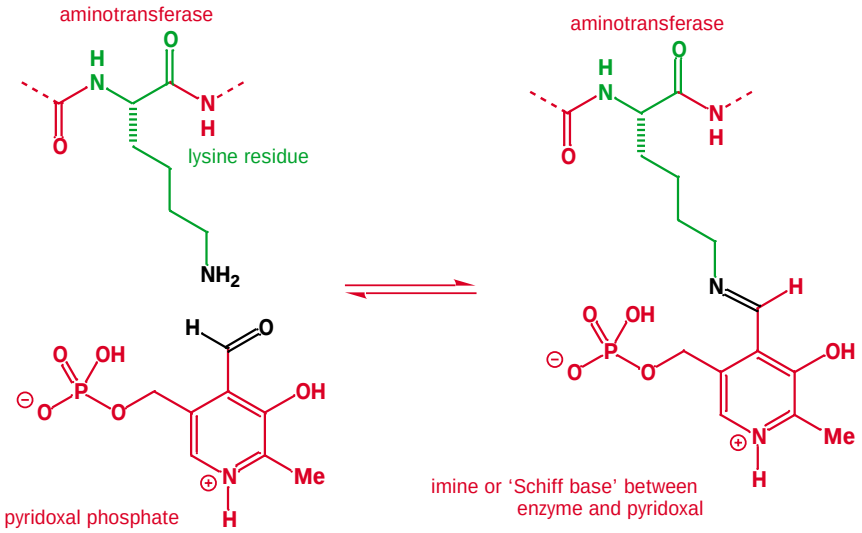
reductive amination in the laboratory:



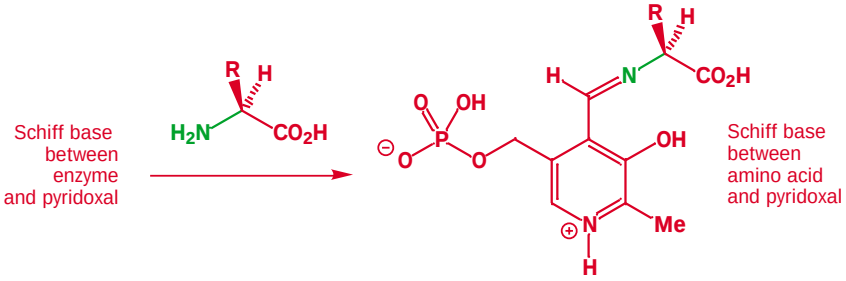
This reaction, of course, produces racemic amines. But Nature transforms this simple reaction into a stereospecific and reversible one that is beautiful in its simplicity and cleverness. The reagents are a pair of substituted pyridines called pyridoxamine and pyridoxal.

You might imagine that pyridoxamine is a product of reductive amination of pyridoxal with ammonia. In practice it doesn't work like that. Nature uses an amine transfer rather than a simple reductive amination, and the family of enzymes that catalyse the process is the family of aminotransferases.

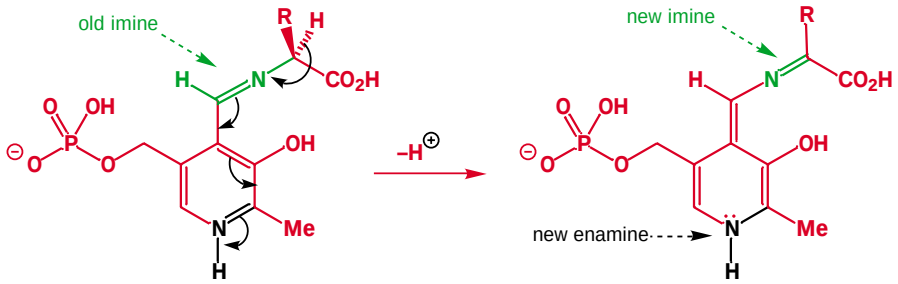
Pyridoxal is a coenzyme and it is carried around on the side chain of a lysine residue of the enzyme. Lysine has a long flexible side chain of four CH_2 groups ending with a primary amine (NH_2). This group forms an imine (what biochemists call a 'Schiff base') with pyridoxal. An imine is a good functional group for this purpose as imine formation is easily reversible.



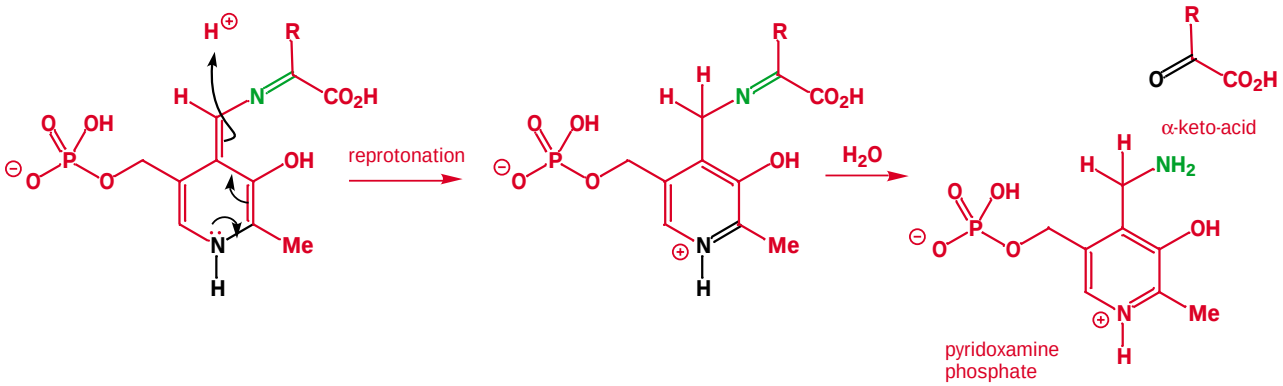
When reductive amination or its reverse is required, the pyridoxal is transferred from the lysine imine to the carbonyl group of the substrate to form a new imine of the same sort. The most important substrates are the amino acids and their equivalent α-keto-acids.



Now the simple but amazing chemistry begins. By using the protonated nitrogen atom of the pyridine as an electron sink, the α proton of the amino acid can be removed to form a new imine at the top of the molecule and an enamine in the pyridine ring.

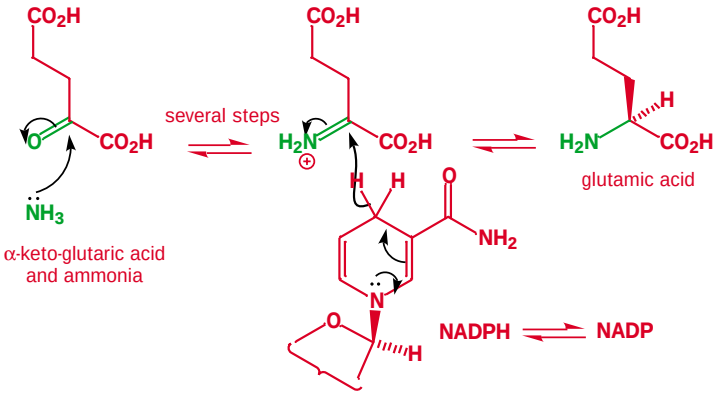


Now the electrons can return through the pyridine ring and pick up a proton at the top of the molecule. The proton can be picked up where it came from, but more fruitfully it can be picked up at the carbon atom on the other side of the nitrogen. Hydrolysis of this imine releases pyridoxamine and the keto-acid. All the natural amino acids are in equilibrium with their equivalent α-keto-acids by this mechanism, catalysed by an aminotransferase.



Reversing this reaction makes an amino acid stereospecifically out of an α-keto-acid. In fact, a complete cycle is usually set up whereby one amino acid is converted to the equivalent α-keto-acid while another α-keto-acid is converted into its equivalent amino acid. This is true transamination.

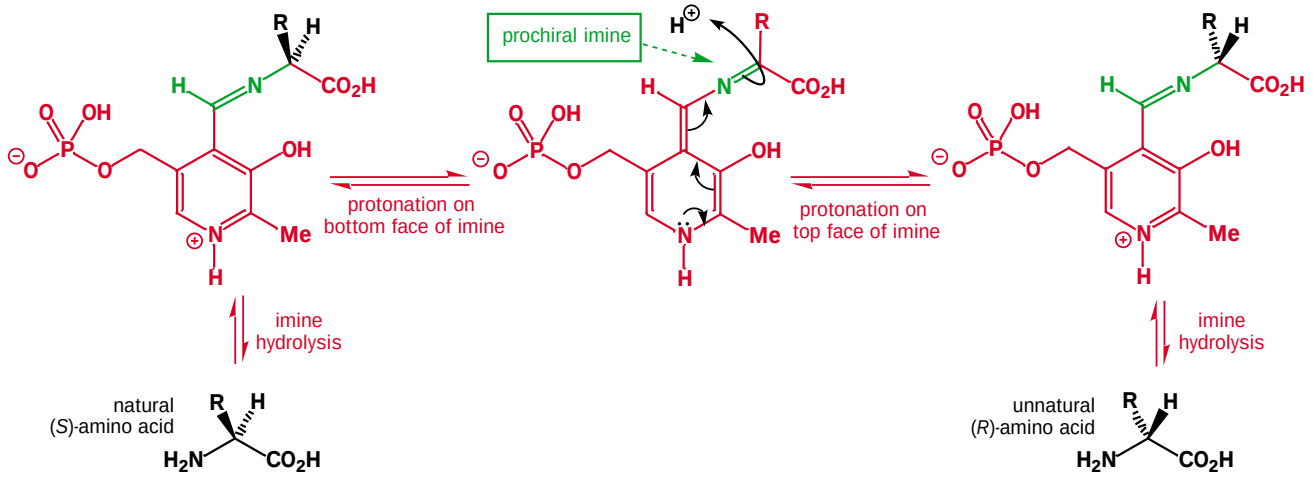
Amino acids get used up (making proteins, for example) so, to keep life going, ammonia must be brought in from somewhere. The key amino acid in this link is glutamic acid. A true reductive amination using NADPH and ammonia builds glutamic acid from α-keto-glutaric acid.



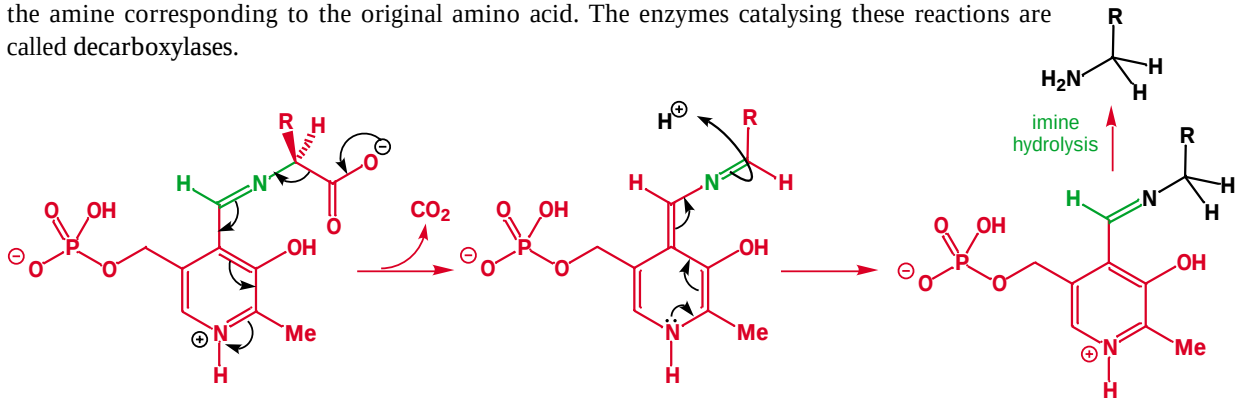
The other amino acids can now be made from glutamic acid by transamination. At the end of their useful life they are transaminated back to glutamic acid which, in mammals at least, gives its nitrogen to urea for excretion.

Pyridoxal is a versatile reagent in the biochemistry of amino acids

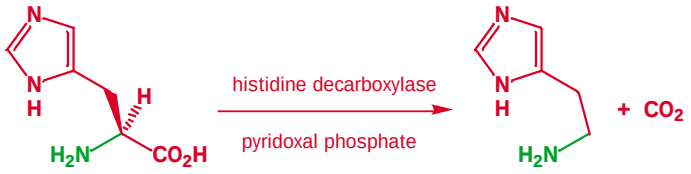
Pyridoxal is the reagent in other reactions of amino acids, all involving the imine as intermediate. The simplest is the racemization of amino acids by loss of a proton and its replacement on the other face of the enamine. The enamine, in the middle of the diagram below, can be reprotonated on either face of the prochiral imine (shown in green). Protonation on the bottom face would take us back to the natural amino acid from which the enamine was made in the first place. Protonation on the top face leads to the unnatural amino acid after 'hydrolysis' of the imine (really transfer of pyridoxal to a lysine residue of the enzyme).



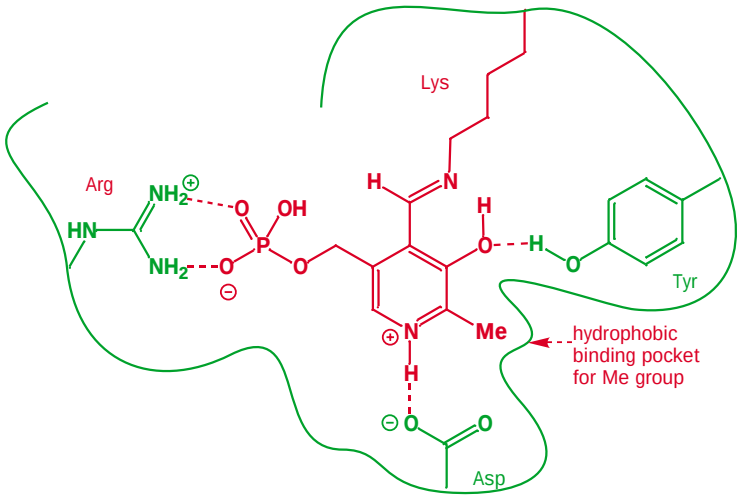
A very similar reaction is decarboxylation. Starting from the same imine we could lose carbon dioxide instead of a proton by a very similar mechanism. Reprotonation and imine transfer releases the amine corresponding to the original amino acid. The enzymes catalysing these reactions are called decarboxylases.



In Chapter 43 we mentioned the role of histamine in promoting acid secretion in the stomach, and its role in causing gastric ulcers. The drug cimetidine was designed to counteract the effect of histamine. Histamine is produced in the body by decarboxylation of histidine using the mechanism you have just seen.



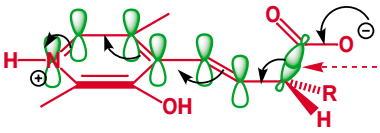
How is it possible for the same reagent operating on the same substrate (an amino acid) to do at will one of two quite different things—removal and/or exchange of a proton and decarboxylation? The answer, of course, lies in the enzymes. These hold pyridoxal exceptionally tightly by using all the available handles: the hydroxy and phosphate groups, the positively charged nitrogen atom, and even the methyl group. The diagram shows the proposed binding of the lysine imine of pyridoxal by an aminotransferase.



The green line shows an imaginary shape of the enzyme chain into which fit acidic groups and basic groups forming hydrogen bonds to groups on the coenzyme. Around the methyl group are alkyl-substituted amino acids, which form a hydrophobic region. Even when the lysine attachment is exchanged for the substrate, all these interactions remain in place. The substrate is bound by similar interactions with other groups on the enzyme.

Control over the choice of reaction arises because the different enzymes bind the substrate–pyridoxal imine in different ways. Decarboxylases bind so that the C–C bond to be broken is held orthogonal to the pyridine ring and parallel to the p orbitals in the ring. Then the bond can be broken and CO_2 can be lost.

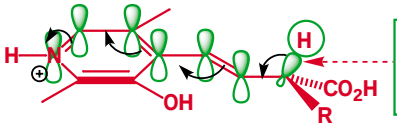
decarboxylases bind the substrate–pyridoxal imine so that the C–C bond is parallel to the p orbitals in the pyridoxal ring



the σ bond to be broken is parallel to the p orbitals in the pyridine ring

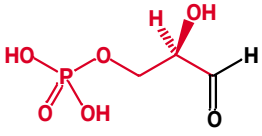
Racemases and transaminases bind the substrate–pyridoxal imine so that the C–H bond is parallel to the p orbitals in the ring so that proton removal can occur. Enzymes do not speed reactions up indiscriminately—they can selectively accelerate some reactions at the expense of others, even those involving the same reagents.

racemases and transaminases bind the substrate–pyridoxal imine so that the C–H bond is parallel to the p orbitals in the pyridoxal ring

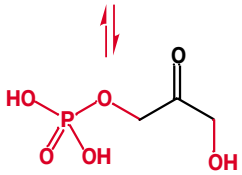


the σ bond to be broken is parallel to the p orbitals in the pyridine ring

Nature's enols—lysine enamines and coenzyme A



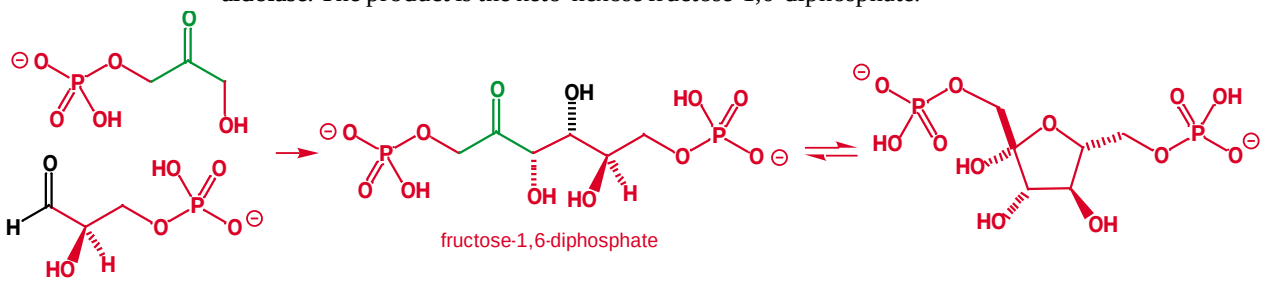
glyceraldehyde-3-phosphate



dihydroxyacetone-3-phosphate

The glycolysis pathway breaks down glucose to produce energy, and in doing so produces smaller molecules for use in the citric acid cycle. In reverse, it allows the synthesis of the six-carbon sugar fructose from two three-carbon fragments. A key reaction is the step in which these two C_3 sugars combine. They are glyceraldehyde and dihydroxyacetone and we met them and their interconversion in the last chapter.

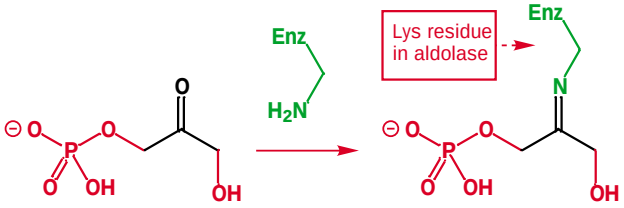
The reaction is effectively an aldol condensation between the enol of the keto-sugar phosphate and the electrophilic aldehyde of glyceraldehyde phosphate and the enzyme is named appropriately aldolase. The product is the keto-hexose fructose-1,6-diphosphate.



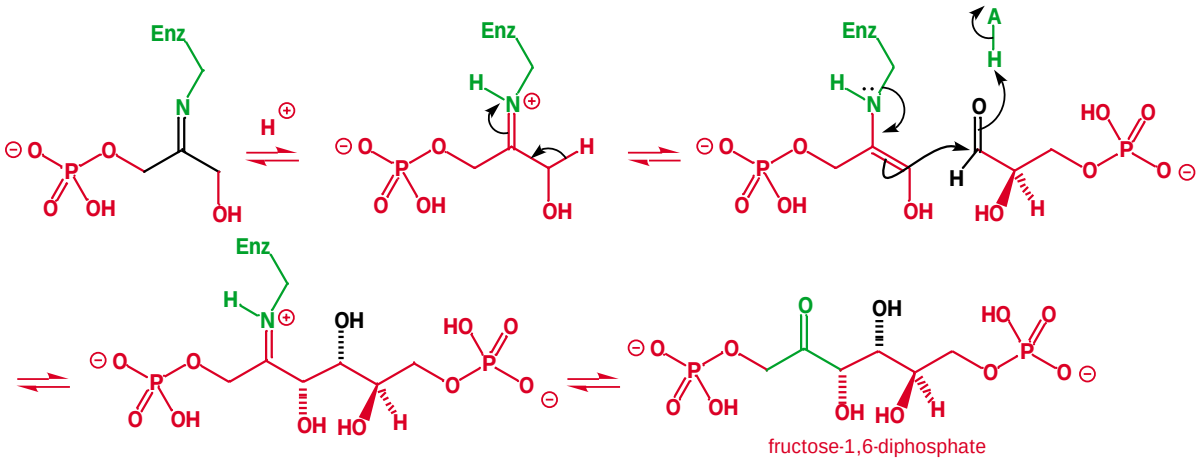
fructose-1,6-diphosphate

■ The rest of the aldolase molecule is represented by 'Enz'.

No enolate ion is formed in this aldol. Instead a lysine residue in the enzyme forms an imine with the keto-triose.



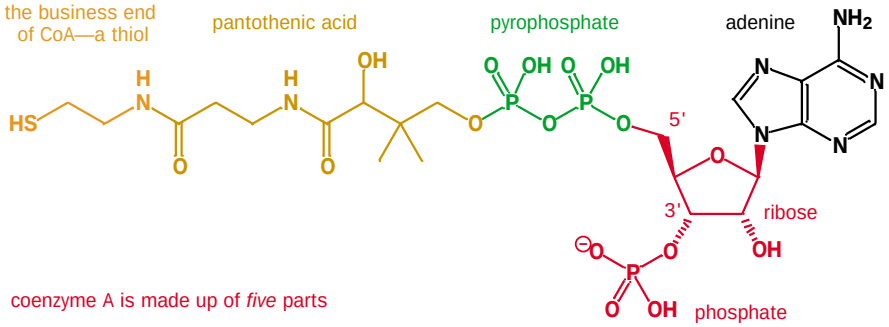
Proton transfers allow this imine to be converted into an enamine, which acts as the nucleophile in the aldol reaction. Stereochemical control (it's a *syn* aldol) comes from the way in which the two molecules are held by the enzyme as they combine. The product is the imine, which is hydrolysed to the open-chain form of fructose-1,6-diphosphate.



Many other reactions in nature use enamines, mostly those of lysine. However, a more common enol equivalent is based on thiol esters derived from coenzyme A.

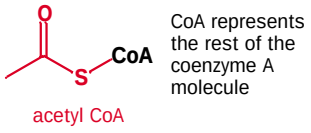
Coenzyme A and thiol esters

Coenzyme A is an adenine nucleotide at one end, linked by a 5′-pyrophosphate to pantothenic acid, a compound that looks rather like a tripeptide, and then to an amino thiol. Here is the structure broken down into its parts.

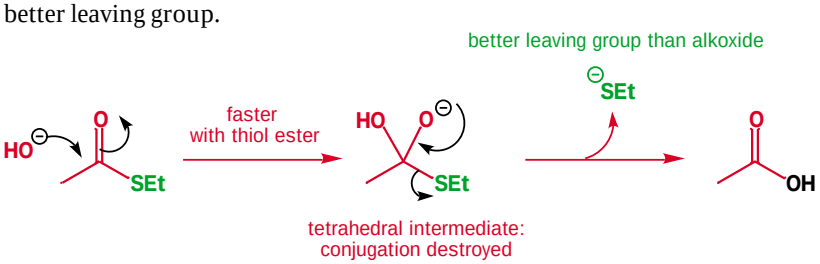


▶ Compare this structure with that of NAD—the adenine nucleotide is the same, as is the 5'-pyrophosphate link. The difference is at the other end of that link where we find this new tripeptide-like molecule and not another nucleotide. There is also a 3'-phosphate on the ribose ring not present in NAD.

By now you will realize that most of this molecule is there to allow interaction with the various enzymes that catalyse the reactions of coenzyme A. We will abbreviate it from now on as CoASH where the SH is the vital thiol functional group, and all the reactions we will be interested in are those of esters of CoASH. These are thiol esters, as opposed to normal 'alcohol esters', and the difference is worth a few comments.

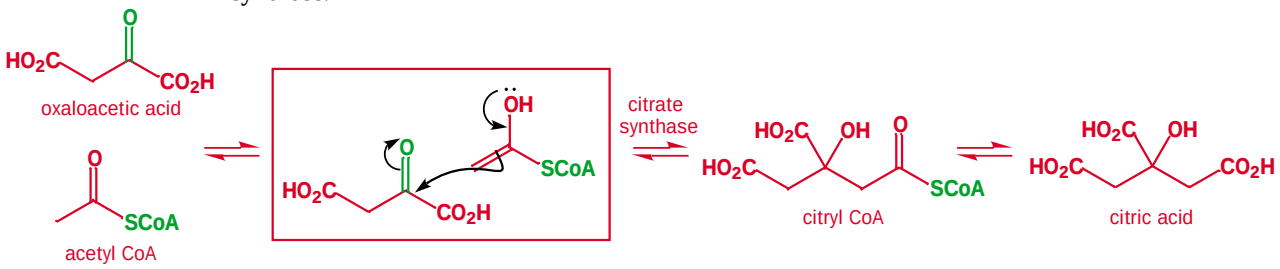


Thiol esters are less conjugated than ordinary esters (see Chapter 28, p. 000), and ester hydrolysis occurs more rapidly with thiol esters than with ordinary esters because in the rate-determining step (nucleophilic attack on the carbonyl group) there is less conjugation to destroy. The thiolate is also a better leaving group.



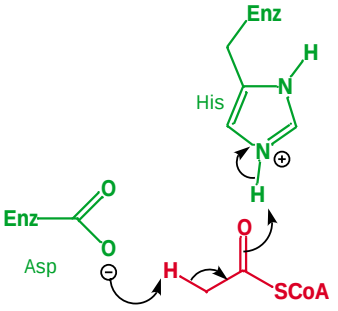
Another reaction that goes better with thiol esters than with ordinary esters is enolization. This is an equilibrium reaction and the enol has lost the conjugation present in the ester. The thiol ester has less to lose so is more enolized. This is the reaction of acetyl CoA that we are now going to discuss. We have mentioned the citric acid cycle several times and it has appeared in two

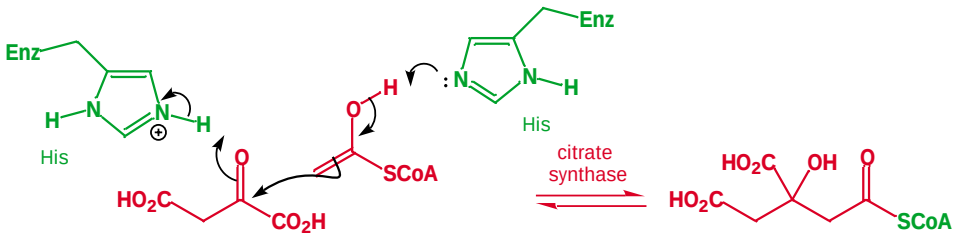
diagrams but we have not so far discussed the chemistry involved. The key step is the synthesis of citric acid from oxaloacetate and acetyl CoA. The reaction is essentially an aldol reaction between the enol of an acetate ester and an electrophilic ketone and the enzyme is known as citrate synthase.



The mechanism in the frame shows the enol of acetyl CoA attacking the reactive ketone. In nature the enolization is catalysed by a basic carboxylate group (Asp) and an acidic histidine, both part of the enzyme, so that even this easy reaction goes faster.

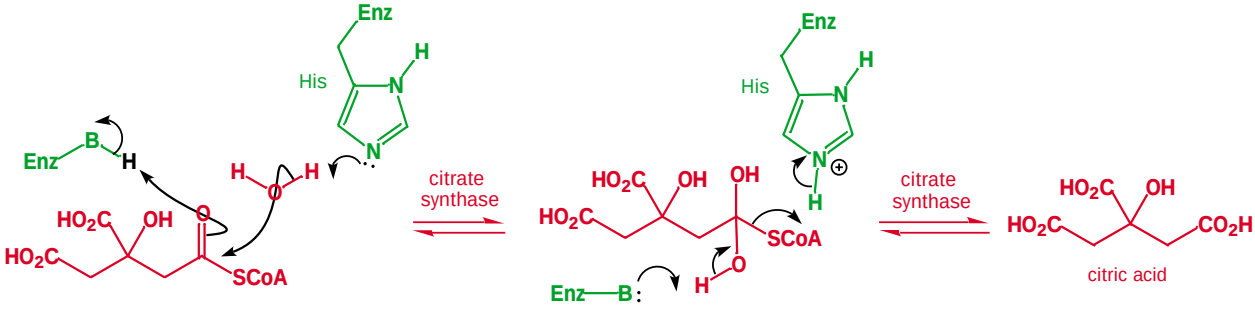
In the C–C bond-forming step, the same histidine is still there to remove the enol proton again and another histidine, in its protonated form, is placed to donate a proton to the oxygen atom of the ketone. You should see now why histidine, with a pK_{aH} of about 7, is so useful to enzymes: it can act either as an acid or as a base.





▶ This is **general acid catalysis**, as described in Chapter 41.

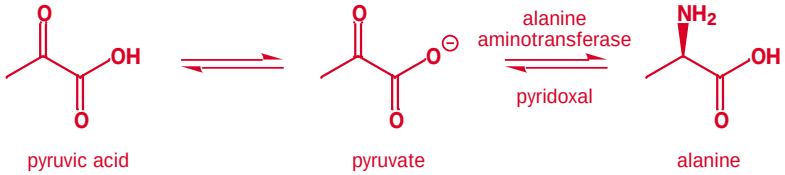
Even the hydrolysis of the reactive thiol ester is catalysed by the enzyme and the original histidine again functions as a proton donor. Acetyl CoA has played its part in all steps. The enolization and the hydrolysis in particular are better with the thiol ester.



CoA thiol esters are widely used in nature. Mostly they are acetyl CoA, but other thiol esters are also used to make enols. We will see more of this chemistry in the next chapter. The two enol equivalents that we have met so far are quite general: lysine enamines can be used for any aldehyde or ketone and CoA thiol esters for any ester. Another class of enol equivalent—the enol ester—has just one representative but it is a most important one.

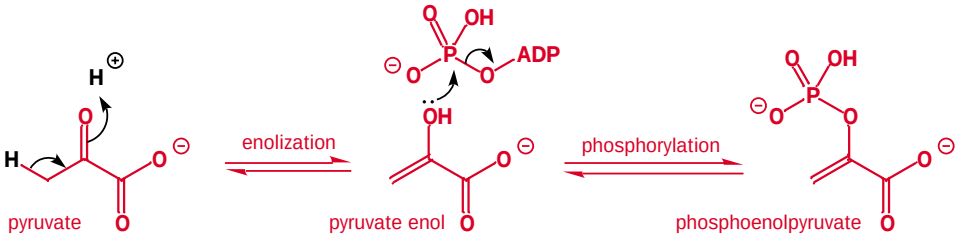
Phosphoenolpyruvate

Pyruvic acid is an important metabolite in its own right as we shall see shortly. It is the simplest α-keto-acid (2-oxopropanoic acid). Having the two carbonyl groups adjacent makes them more reactive: the ketone is more electrophilic and enolizes more readily and the acid is stronger. Pyruvate is in equilibrium with the amino acid alanine by an aminotransferase reaction catalysed by pyridoxal (above).

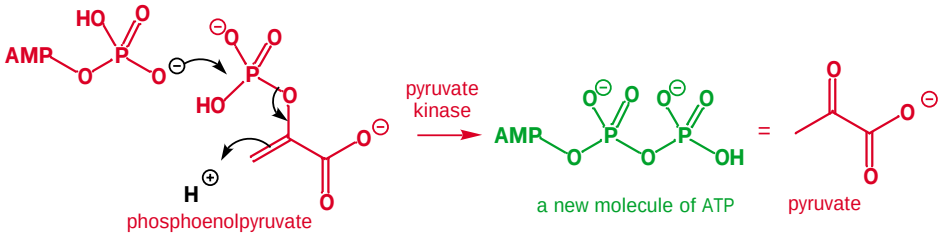


■
For an explanation of the effect of two adjacent carbonyl groups, see Chapter 28, p. 000.

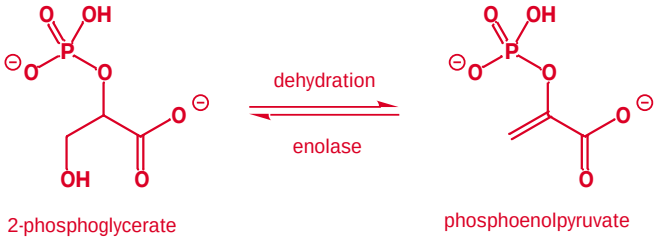
Nature uses the enol phosphate of pyruvic acid (phosphoenolpyruvate or PEP) as an important reagent. We might imagine making this compound by first forming the enol and then esterifying on oxygen by some phosphorylating agent such as ATP.



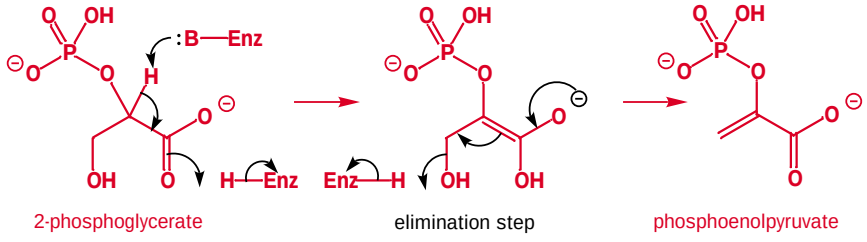
Now, in fact, this reaction does occur in nature as part of the glycolysis pathway, but it occurs almost entirely in reverse. PEP is used as a way to make ATP from ADP during the oxidation of energy-storing sugars. An enol is a better leaving group than an ordinary alcohol especially if it can be protonated at carbon. The reverse reaction might look like this.



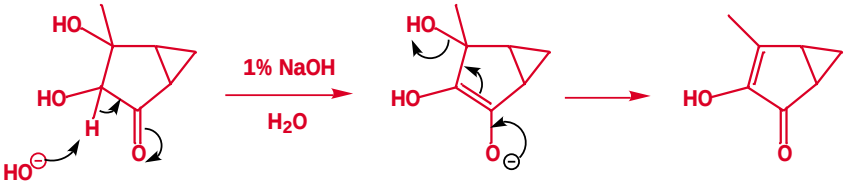
PEP is also used as an enol in the making of carbon–carbon bonds when the electrophile is a sugar molecule and we will see this reaction in the next chapter. So, if PEP is not made by enolization of pyruvate, how is it made? The answer is by dehydration. The phosphate is already in place when the dehydration occurs, catalysed by the enzyme enolase.



You saw in Chapter 19 how simple OH groups could be lost in dehydration reactions. Either the OH group was protonated by strong acid (this is not an option in living things) or an enol or enolate pushed the OH group out in an E1cB-like mechanism. This must be the case here as the better leaving group (phosphate) is ignored and the worse leaving group (OH) expelled.



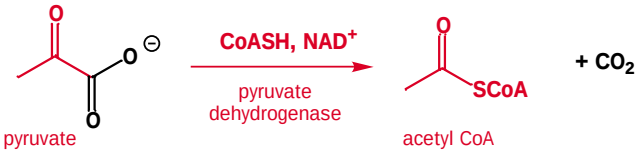
This would be an unusual way to make an enol in the laboratory but it can be used, usually to make stable enols. An example that takes place under mildly basic conditions is the dehydration of the bicyclic keto-diol in dilute sodium hydroxide—presumably by an E1cB mechanism.



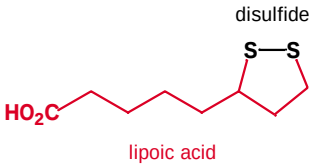
Pyruvic acid and acetyl CoA: the link between glycolysis and the citric acid cycle

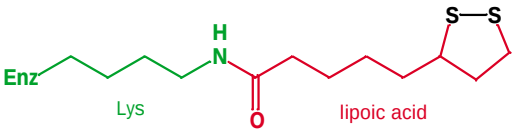
We have now examined the mechanism of several steps in glycolysis and one in the citric acid cycle and we have seen enough to look at the outline of these two important processes and the link between them (see opposite).

You have already seen that citric acid is made from acetyl CoA. The acetyl CoA comes in its turn from pyruvic acid. Pyruvic acid comes from many sources but the most important is glycolysis: acetyl CoA is the link between glycolysis and the citric acid cycle. The key reaction involves both CoASH and pyruvate and carbon dioxide is lost. This is an oxidation as well and the oxidant is NAD^+. The overall reaction is easily summarized.



This looks like a simple reaction based on very small molecules. But look again. It is a very strange reaction indeed. The molecule of CO_2 clearly comes from the carboxyl group of pyruvate, but how is the C–C bond cleaved, and how does acetyl CoA join on? If you try to draw a mechanism you will see that there must be more to this reaction than meets the eye. The extra features are two new cofactors, thiamine pyrophosphate and lipoic acid, and the reaction takes place in several stages with some interesting chemistry involved.



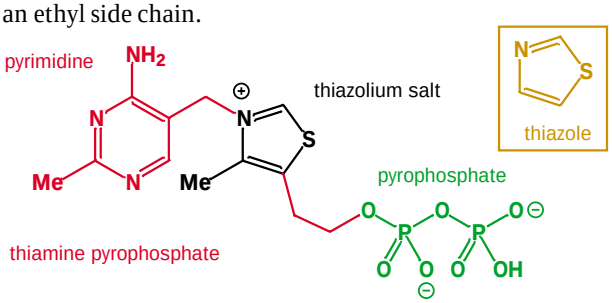


lipoic acid attached to the enzyme as a lysine amide

Lipoic acid is quite a simple molecule with a cyclic disulfide as its main feature. It is attached to the enzyme as an amide with lysine. Our first concern will be with the much more complex coenzyme thiamine pyrophosphate.

Nature's acyl anion equivalent (d^1 reagent) is thiamine pyrophosphate

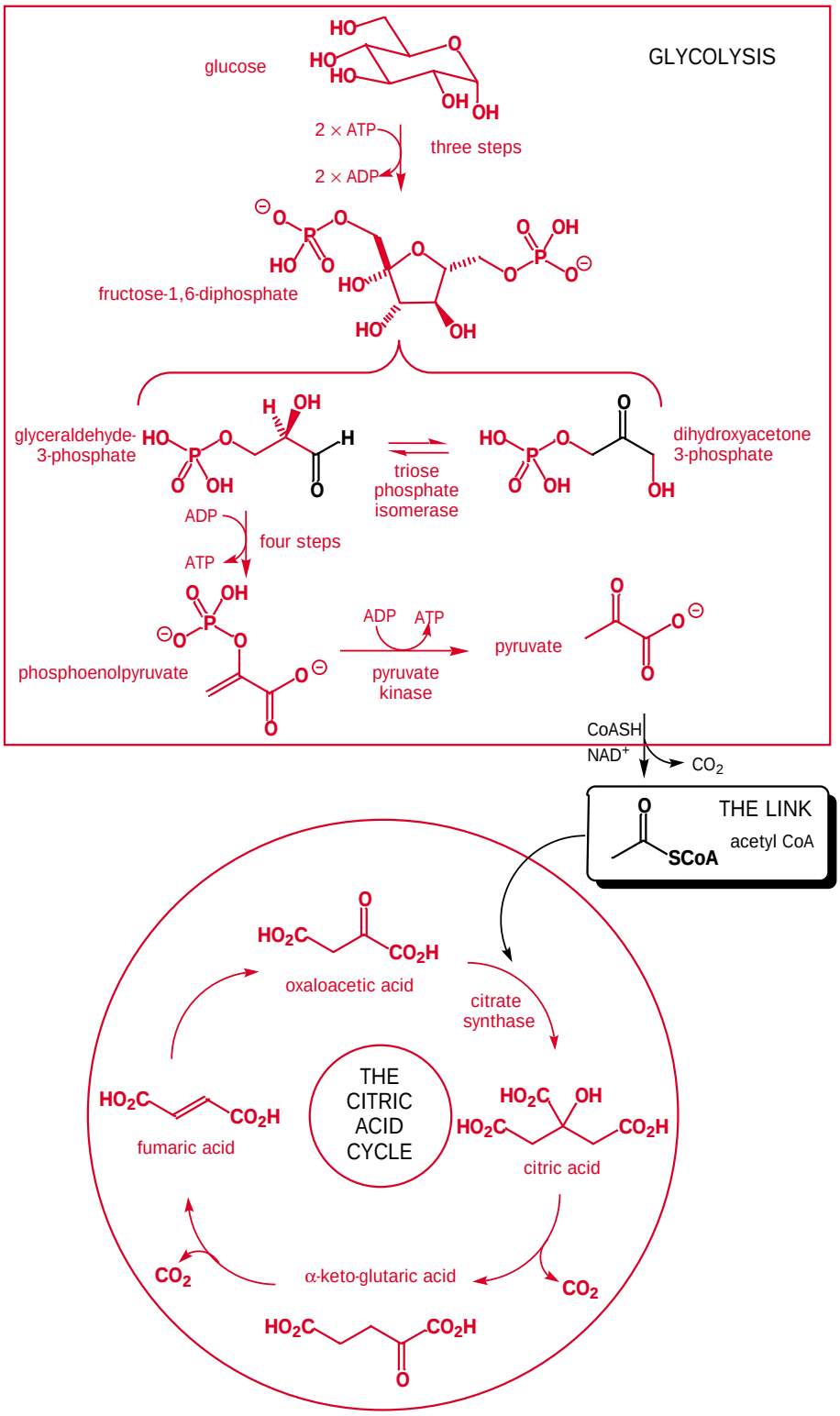
Thiamine pyrophosphate looks quite like a nucleotide. It has two heterocyclic rings, a pyrimidine similar to those found in DNA and a thiazolium salt. This ring has been alkylated on nitrogen by the pyrimidine part of the molecule. Finally, there is a pyrophosphate attached to the thiazolium salt by an ethyl side chain.



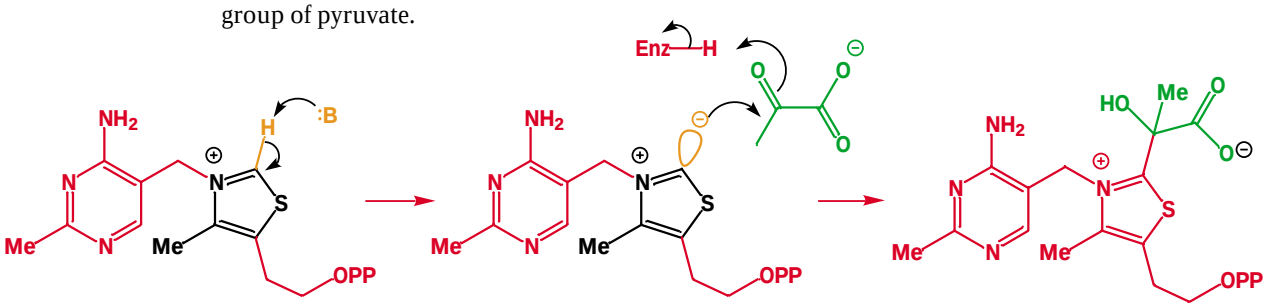
▶ We will abbreviate pyrophosphate to 'OPP' in structures.

▶ Do not confuse thiamine with thymine, one of the pyrimidine bases on DNA. The DNA base thymine is just a pyrimidine; thymidine is the corresponding nucleoside. The coenzyme thiamine is a more complicated molecule, that contains a different pyrimidine.

the link between glycolysis and the citric acid cycle

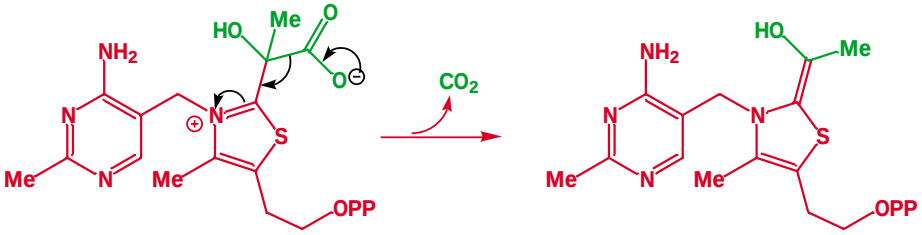


The key part of the molecule for reactivity is the thiazolium salt in the middle. The proton between the N and S atoms can be removed by quite weak bases to form an ylid. You saw sulfonium ylids in Chapter 46, and there is some resemblance here, but this ylid is an ammonium ylid with extra stabilization from the sulfur atom. The anion is in an sp^2 orbital, and it adds to the reactive carbonyl group of pyruvate.

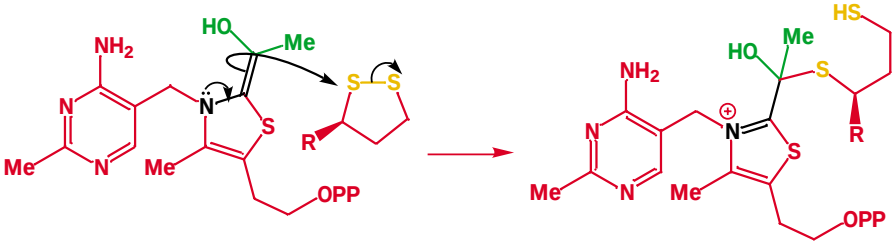


■
For more on fragmentation reactions see Chapter 38.

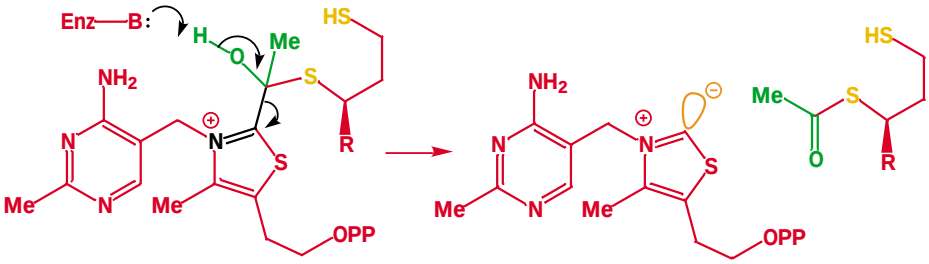
Now the carboxylate can be lost from the former pyruvate as the positively charged imine in the thiamine molecule provides a perfect electron sink to take away the electrons from the C–C bond that must be broken.



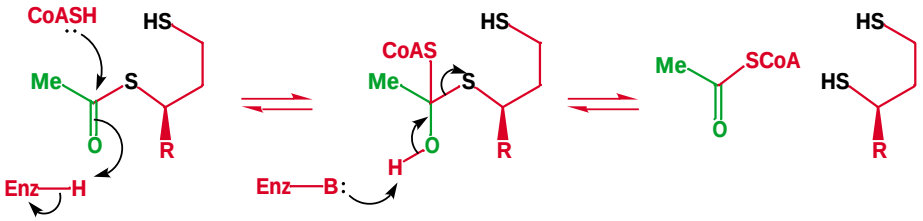
This new intermediate contains a new and strange C=C double bond. It has OH, N, and S substituents making it very electron-rich. As the nitrogen is the most electron-donating you can view it as an enamine, and it attacks the disulfide functional group of lipoic acid, the other cofactor in the reaction.



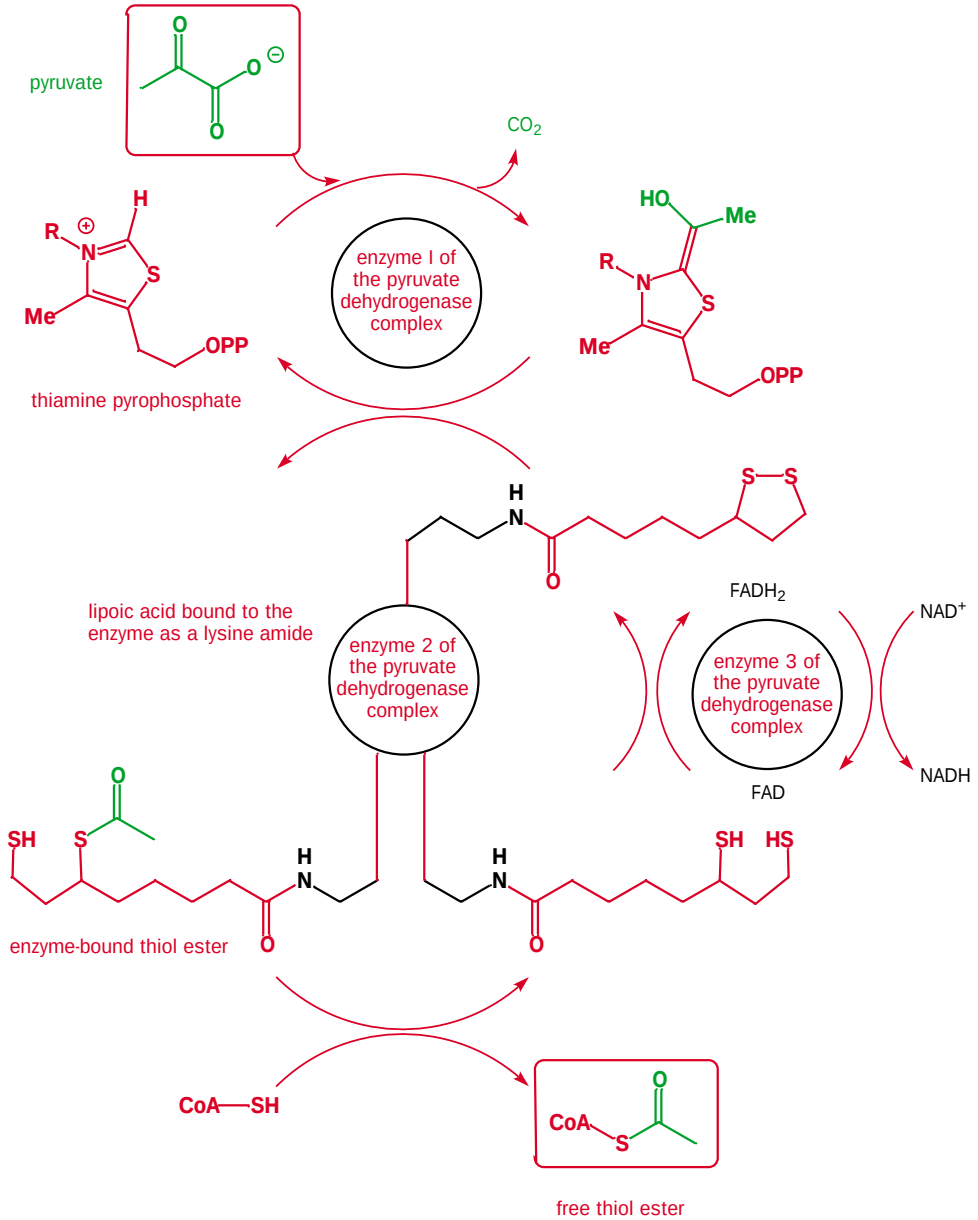
Now the thiamine can be expelled using the green OH group. The leaving group is again the ylid of thiamine, which functions as a catalyst.



The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction. This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid. All that is necessary to complete the cycle is the oxidation of the dithiol back to the disulfide. This is such an easy reaction to do that it would occur in air anyway but it is carried out in nature by FAD, a close relative of NAD^+.



This is one of the most complicated sequences of reactions that we have discussed so far. It is critical to living things because it links glycolysis and the citric acid cycle. Nature has provided not one enzyme but three enzymes to catalyse this process. In the cell they are massed together as a single protein complex.

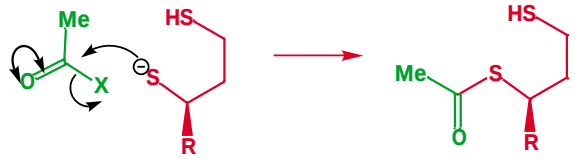


At the centre is 'enzyme 2' which binds the acetyl group through a lipoic acid–lysine amide. On the one side this acetyl group is delivered from pyruvate by the ministrations of thiamine pyrophosphate and 'enzyme 1' and on the other it is delivered to CoA as the free thiol ester. Enzyme 3 recycles

the reduced lipoic acid using FAD and then NAD^+. This remarkable assembly of proteins maintains stocks of acetyl CoA for use in the citric acid cycle and for building complex organic molecules by enol chemistry, as we will see in the next chapter.

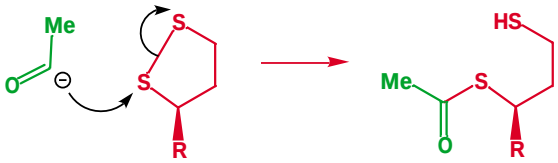
One reaction in this sequence is worth detailed analysis. The enzyme-bound lipoic thiol ester is a perfectly normal thiol ester and we would expect it to be formed by acylation of the thiol.

thiol ester formation with normal polarity: nucleophilic S electrophilic carbonyl

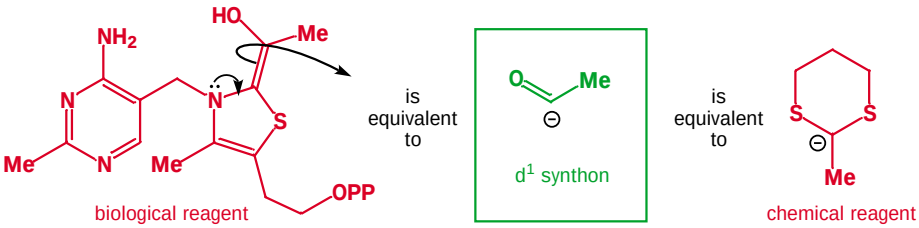


But this thiol ester is not formed by the expected mechanism in the enzymatic reaction. Thiamine delivers a *nucleo*philic acetyl group to an *electro*philic sulfur atom—the reverse polarity to normal ester formation.

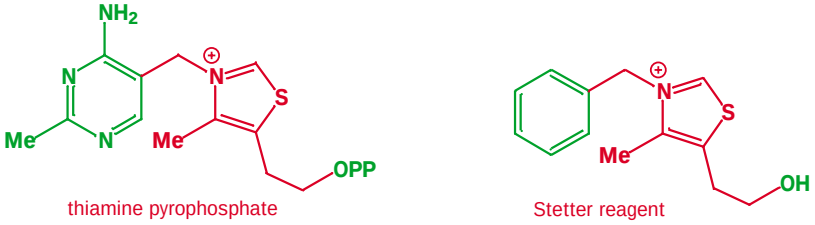
thiol ester formation with reverse polarity: electrophilic S nucleophilic carbonyl



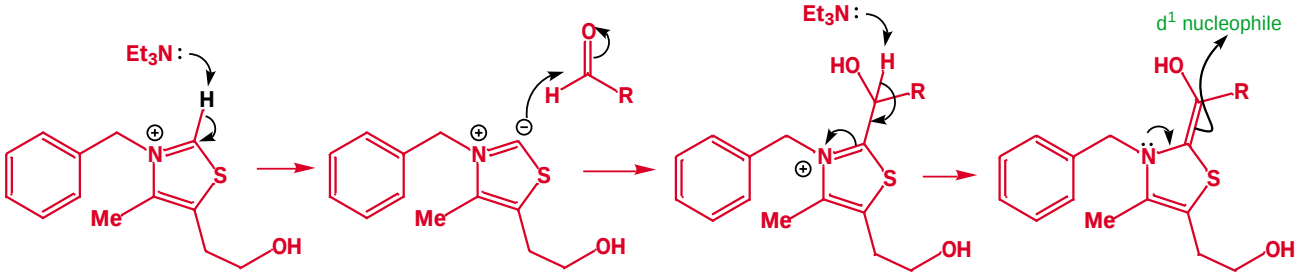
The compound formed from thiamine pyrophosphate and pyruvic acid is Nature's nucleophilic acetyl group. This is a d^1 reagent like the dithiane anion you met in Chapter 46.



If this is really true and not just a theoretical analogy, it ought to be possible to learn from Nature and design useful d^1 reagents based on thiamine. This was done by Stetter using simplified thiamines. The pyrimidine is replaced by a benzene ring and the pyrophosphate is removed. This leaves a simple thiazolium salt called a Stetter reagent.

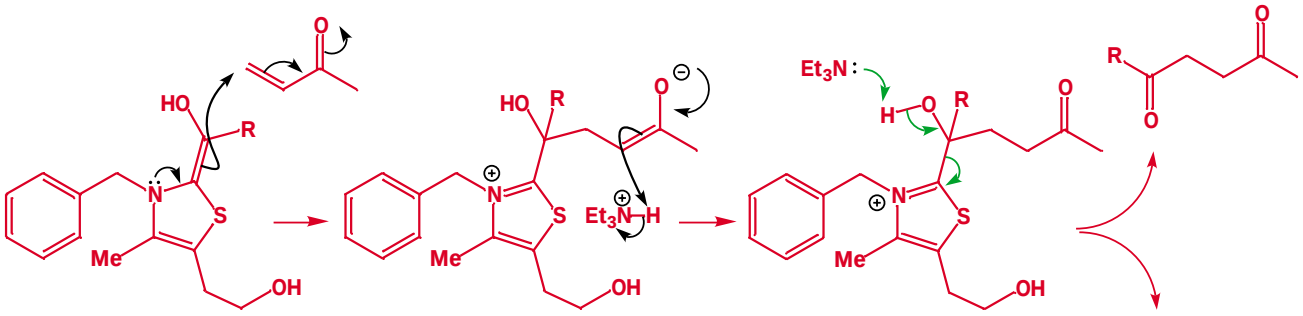


By analogy with the biological reaction, we need only a weak base (Et_3N) to make the ylid from the thiazolium salt. The ylid adds to aldehydes and creates a d^1 nucleophile equivalent to an acyl anion.

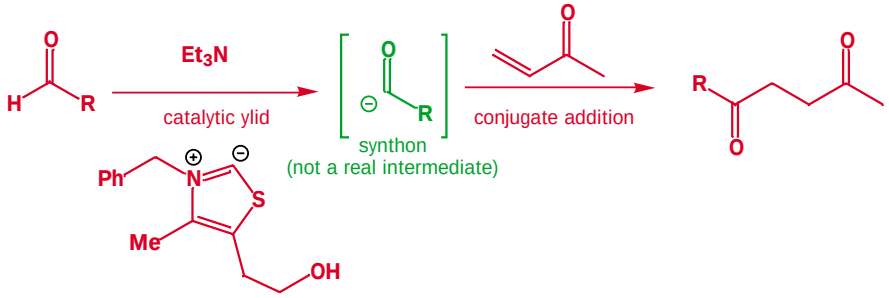


A useful application of these reagents is in conjugate addition to unsaturated carbonyl compounds. Few d^1 reagents will do this as most are very basic and prefer to add directly to the carbonyl

group. Notice that a tertiary amine, pK_{aH} about 10, is strong enough to remove both protons in this sequence.

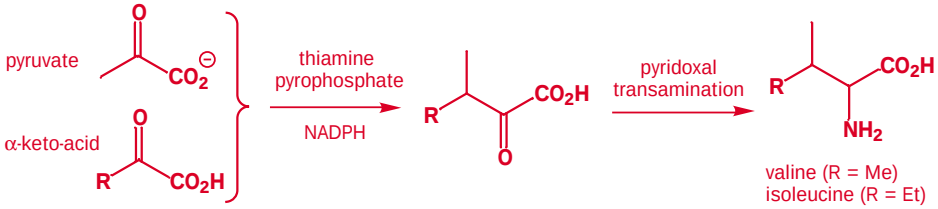


The organic product is a 1,4-diketone and the thiazolium ylid is released to continue with another cycle of the reaction. Like thiamine, the thiazolium ylid is catalyst. Processes like this, which copy nature, are called biomimetic.

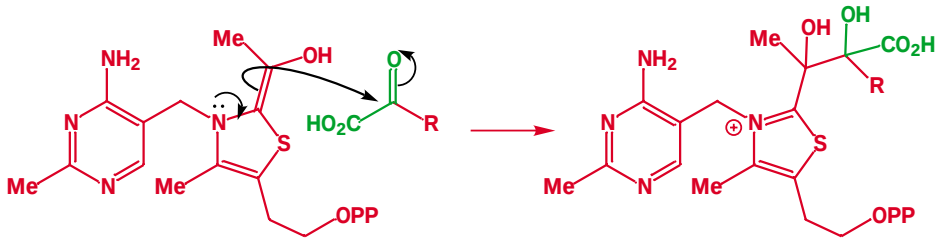


Rearrangements in the biosynthesis of valine and isoleucine

In nature, thiamine pyrophosphate also catalyses reactions of α-keto-acids other than pyruvic acid. One such sequence leads through some remarkable chemistry to the biosynthesis of the branched-chain amino acids valine and isoleucine.

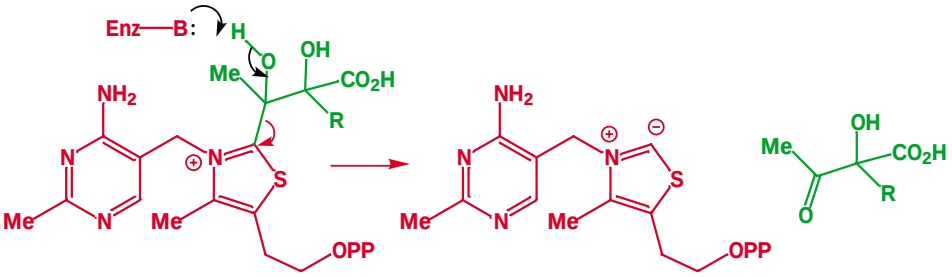


The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements (Chapter 37). The sequence starts as before and we will pick it up after the addition and decarboxylation of pyruvate and as the resulting d^1 reagent adds to the new α-keto-acid.

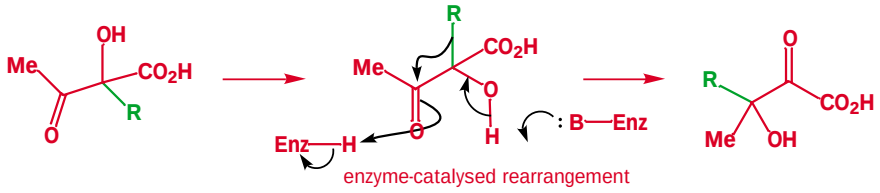


Decomposition of this product with the release of the thiazolium ylid also releases the product of coupling between the two keto-acids: a 1-hydroxy-2-keto-acid (in green). The original keto group of

the pyruvate reappears—it's clear that an acetyl anion equivalent (the d^1 reagent) has added to the keto group of the new keto-acid. The thiazolium ylid is free to catalyse the next round of the reaction.

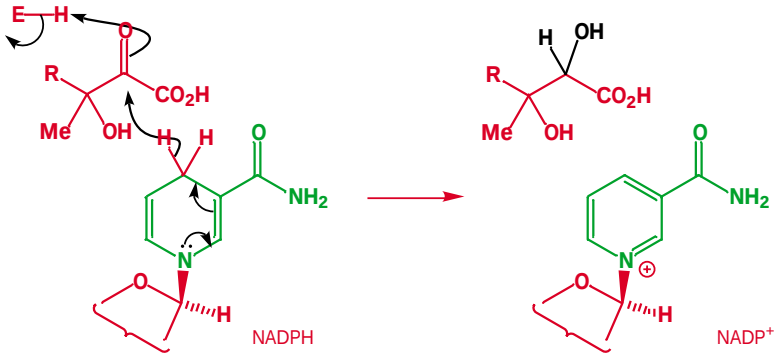


The green hydroxy-keto-acid is now primed for rearrangement. The migration of the group R is pushed by the removal of a proton from the OH group and pulled by the electron-accepting power of the keto group. Notice that the group R (Me or Et) migrates in preference to CO_2H. Usually in rearrangements the group better able to bear a positive charge migrates (Chapter 37).

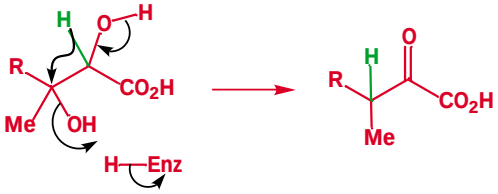


enzyme-catalysed rearrangement

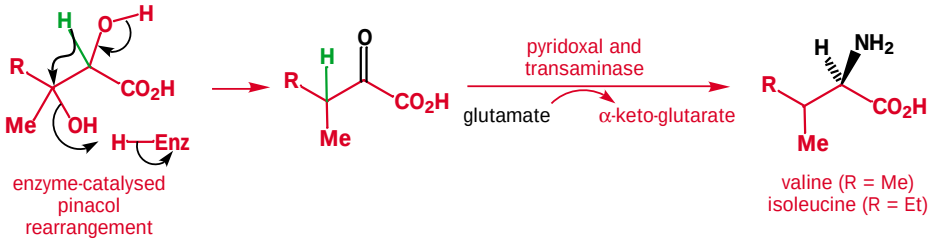
Control in this reaction is likely to be exerted stereoelectronically by the enzyme as it was in the pyridoxal reactions above. Since the C–R bond is held parallel to the p orbitals of the ketone, R migration occurs, but if the CO_2H group were to be held parallel to the p orbitals of the ketone, decarboxylation would occur. Next, a simple reduction with NADPH converts the ketone into an alcohol and prepares the way for a second rearrangement.



The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol. The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.

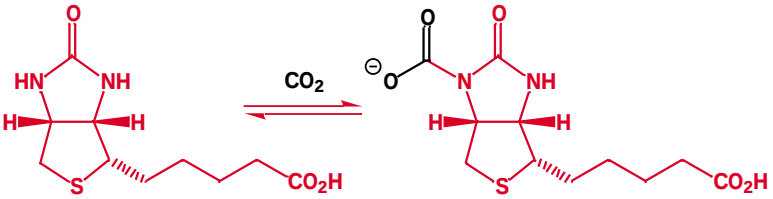


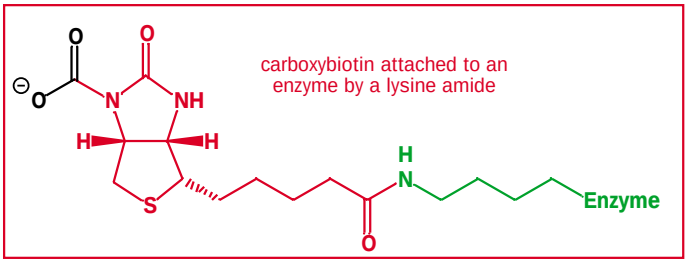
Finally, a pyridoxal transamination converts the two keto-acids stereospecifically to the corresponding amino acids, valine (R = Me) and isoleucine (R = Et). The donor amino acid is probably glutamate—it usually is in amino acid synthesis.



Carbon dioxide is carried by biotin

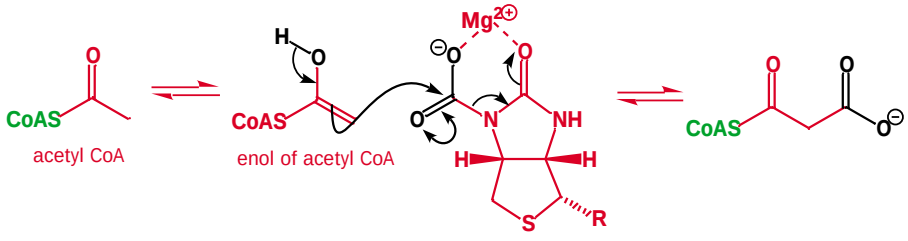
We have added and removed carbon dioxide on several occasions in this chapter and the last but we have not until now said anything about how this happens. You would not expect gaseous CO_2 to be available inside a cell: instead CO_2 is carried around as a covalent compound with another coenzyme—biotin.





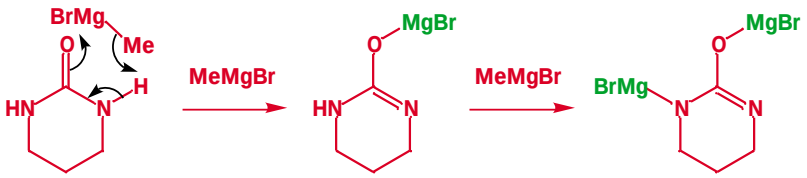
Biotin has two fused five-membered heterocyclic rings. The lower is a cyclic sulfide and has a long side chain ending in a carboxylic acid for attachment—yes, you've guessed it—to a lysine residue of a protein. The upper ring is a urea—it has a carbonyl group flanked by two nitrogen atoms. It is this ring that reversibly captures CO_2, on the nitrogen atom opposite the long side chain. The attachment to the enzyme as a lysine amide gives it an exceptionally long flexible chain and allows it to deliver CO_2 wherever it's needed.

One of the important points at which CO_2 enters as a reagent carried by biotin is in fatty acid biosynthesis where CO_2 is transferred to the enol of acetyl CoA. A magnesium(II) ion is also required and we may imagine the reaction as a nucleophilic attack of the enol on the magnesium salt of carboxybiotin. Most of the CO_2 transfers we have met take place by mechanisms of this sort: nucleophilic attack on a bound molecule of CO_2, usually involving a metal ion.

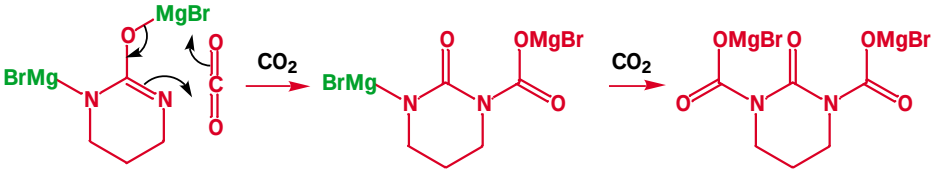


Very similar reactions can be carried out in the laboratory. This simple cyclic urea reacts twice with the Grignard reagent MeMgBr to give a dimagnesium derivative, probably having the structure shown with one O–Mg and one N–Mg bond.

■ We will see in the next chapter how acetoacetyl CoA is used in the biosynthesis of fatty acids and polyketides.

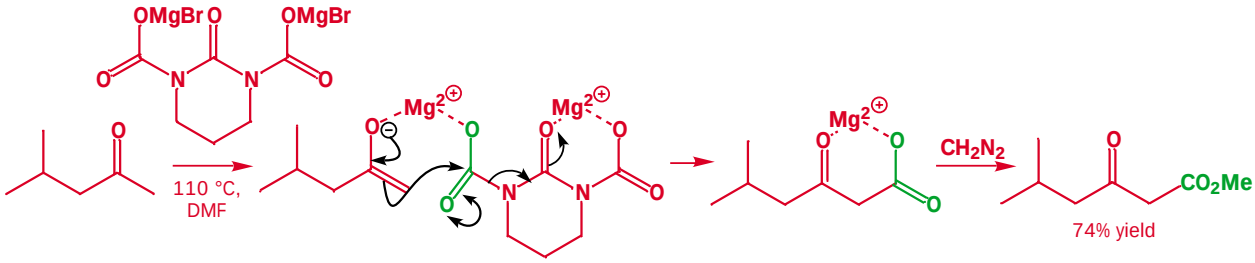


This magnesium derivative reacts with two molecules of CO_2 to give a double adduct with both nitrogens combining with CO_2. The product is stable as the double magnesium salt, which is a white powder.

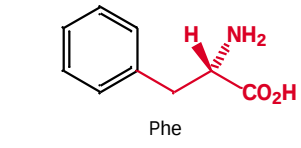


■ Diazomethane esterification appeared in Chapter 40, p. 000.

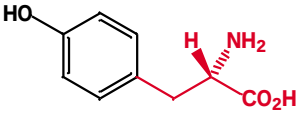
Simply heating this white powder with a ketone leads to efficient carboxylation and the unstable keto-acid may be trapped with diazomethane to form the stable methyl ester. The mechanism is presumably very like that drawn above for the transfer of CO_2 from carboxybiotin to acetyl CoA. Reactions like this *prove* nothing about the biochemical reaction but they at least show us that such reactions are possible and help us to have confidence that we are right about what Nature is doing.



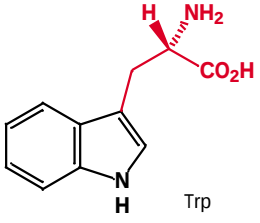
The shikimic acid pathway



Phe



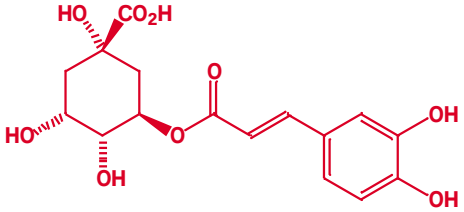
Tyr



Trp

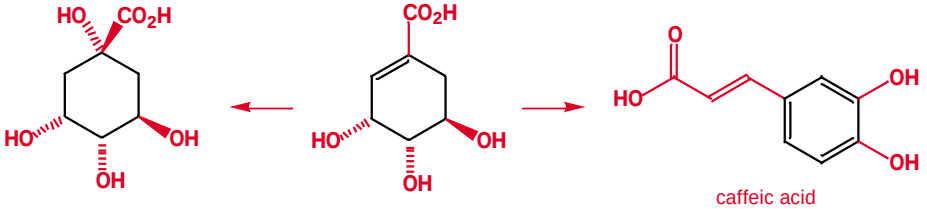
We have described reactions from various different pathways in this chapter so far, but now we are going to look at one complete pathway in detail. It is responsible for the biosynthesis of a large number of compounds, particularly in plants. Most important for us is the biosynthesis of the aromatic amino acids Phe (phenylalanine), Tyr (tyrosine), and Trp (tryptophan). These are 'essential' amino acids for humans—we have to have them in our diet as we cannot make them ourselves. We get them from plants and microorganisms.

So how do plants make aromatic rings? A clue to the chemistry involved comes from the structure of caffeyl quinic acid, a compound that is present in instant coffee in some quantity. It is usually about 13% of the soluble solids from coffee beans.



caffeyl quinic acid

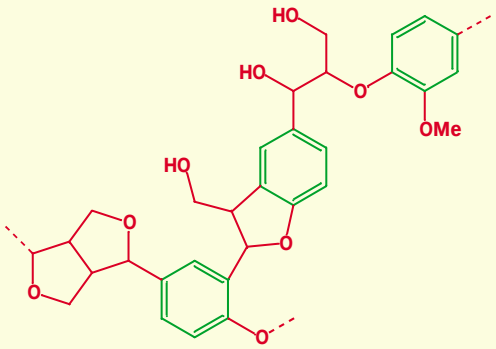
This ester has two six-membered rings—one aromatic and one rather like the sugar alcohols we were discussing in the last chapter. You might imagine making an aromatic ring by the dehydration (losing three molecules of water) of a cyclohexane triol and the saturated ring in caffeyl quinic acid looks a good candidate. It is now known that both rings come from the same intermediate, shikimic acid.



This key intermediate has given its name to Nature's general route to aromatic compounds and many other related six-membered ring compounds: the shikimic acid pathway. This pathway contains some of the most interesting reactions (from a chemist's point of view) in biology. It starts with an aldol reaction between phosphoenol pyruvate as the nucleophilic enol component and the C_4 sugar erythrose 4-phosphate as the electrophilic aldehyde.

Wood

Even the structural material of plants, lignin, comes from the shikimic acid pathway. Lignin—from which wood is made—has a variable structure according to the plant and the position in the plant. A typical splinter is shown here.

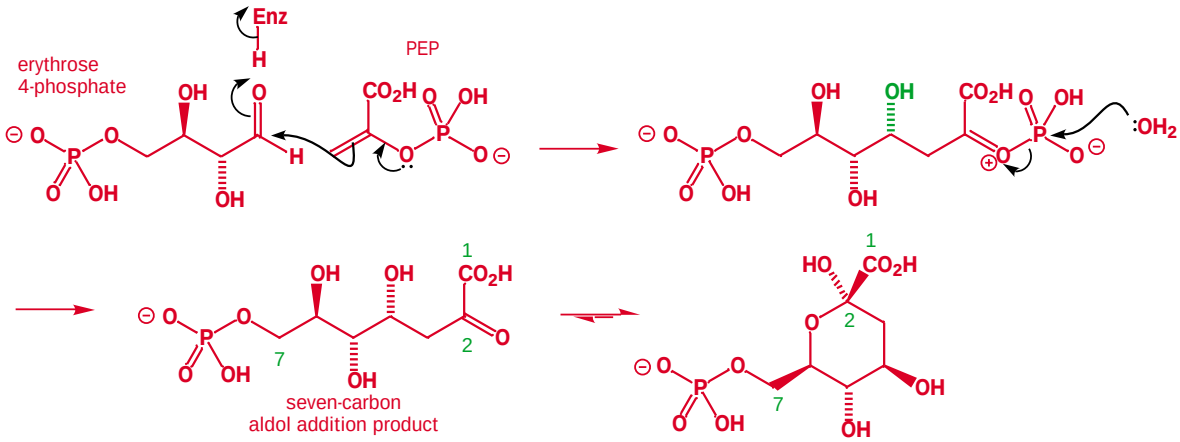


a typical lignin fragment

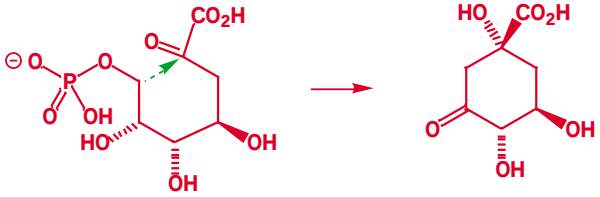
the aromatic rings are made from shikimic acid

the various structural parts and functional groups might be assembled in many different ways

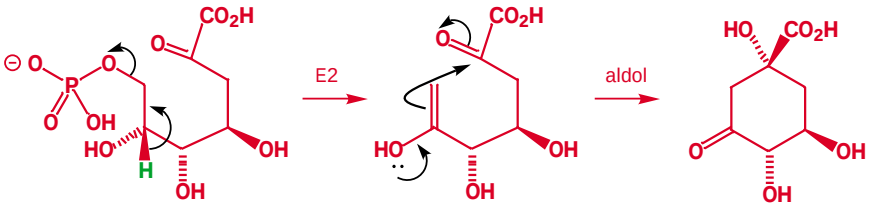
the dotted bonds show where the structure might continue



Hydrolysis of the phosphate releases the aldol product, a C_7 α-keto-acid with one new stereogenic centre, which is in equilibrium with a hemiacetal, just like a sugar. This intermediate has the right number of carbon atoms for shikimic acid and the next stage is a cyclization. If we redraw the C_7 α-keto-acid in the right shape for cyclization we can see what is needed. The green arrow shows only which bond needs to be formed.

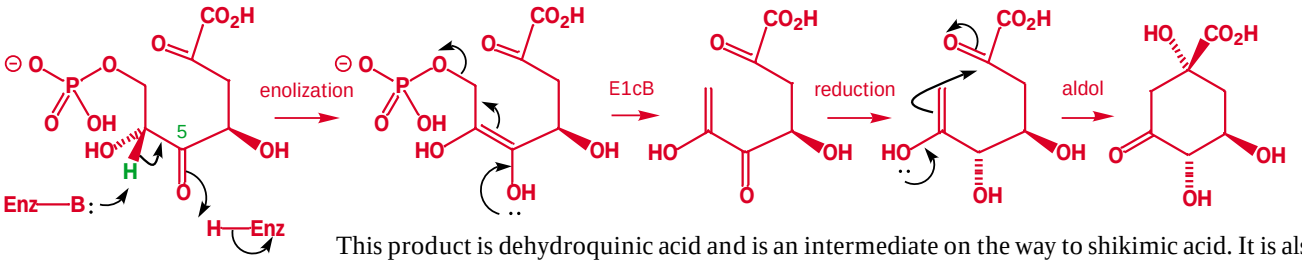


This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate. This would require the removal of a proton (green in the diagram) that is not at all acidic.

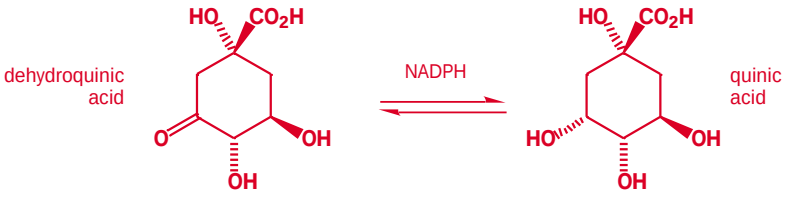


The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant). Then the green proton is much more acidic, and the elimination becomes an E1cB

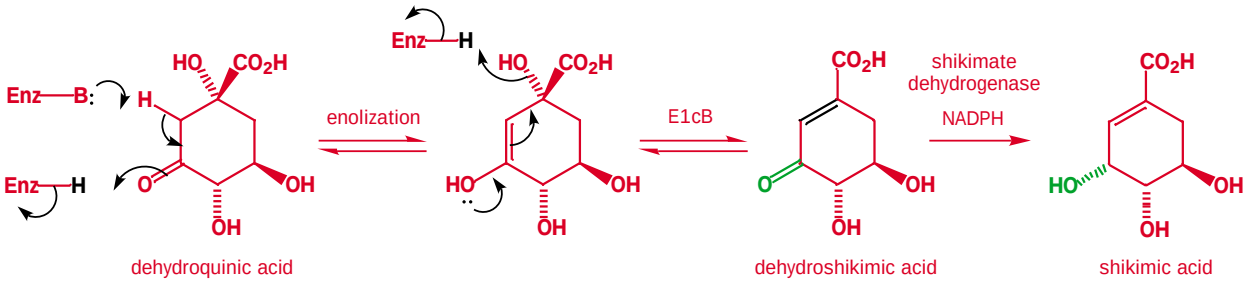
reaction, similar to the one in the synthesis of PEP. True, the ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.



This product is dehydroquinic acid and is an intermediate on the way to shikimic acid. It is also in equilibrium with quinic acid, which is not an intermediate on the pathway but which appears in some natural products like the coffee ester caffeyl quinic acid.

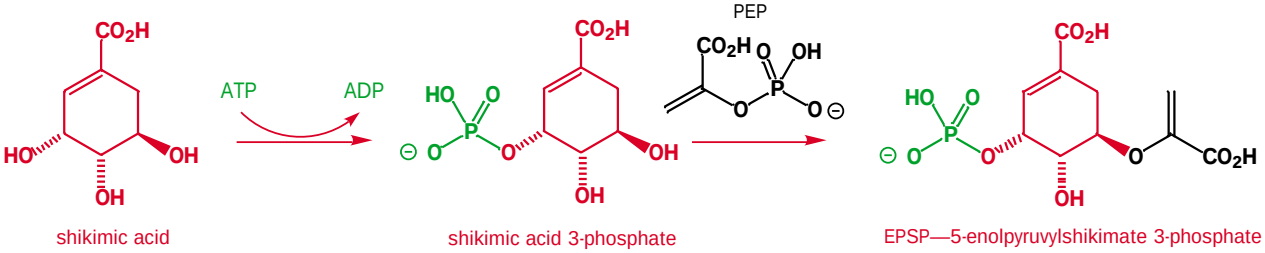


The route to shikimic acid in plants involves, as the final steps, the dehydration of dehydroquinic acid and then reduction of the carbonyl group. Doing the reactions this way round means that the dehydration can be E1cB—much preferred under biological conditions. This is what happens.

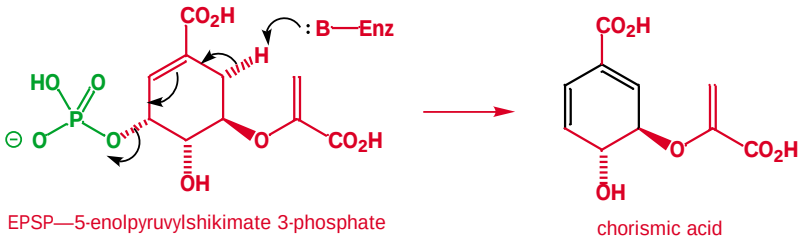


The final reduction uses NADPH as the reagent and is, of course, totally stereoselective with the hydride coming in from the top face of the green ketone as drawn. At last we have arrived at the halfway stage and the key intermediate, shikimic acid.

The most interesting chemistry comes in the second half of the pathway. The first step is a chemoselective phosphorylation of one of the three OH groups by ATP—as it happens, the OH group that has just been formed by reduction of a ketone. This step prepares that OH group for later elimination. Next, a second molecule of PEP appears and adds to the OH group at the other side of the molecule. This is PEP in its enol ether role, forming an acetal under acid catalysis. The reaction occurs with retention of stereochemistry so we know that the OH group acts as a nucleophile and that the ring–OH bond is not broken.



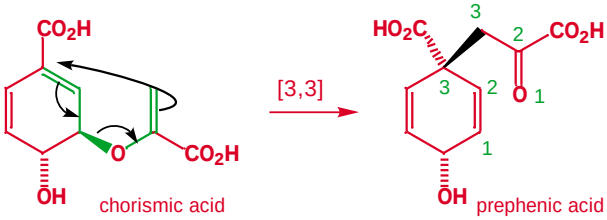
Now a 1,4 elimination occurs. This is known to be a *syn* elimination on the enzyme. When such reactions occur in the laboratory, they can be *syn* or *anti*. The leaving group is the green phosphate added two steps before.



EPSP—5-enolpyruvylshikimate 3-phosphate

chorismic acid

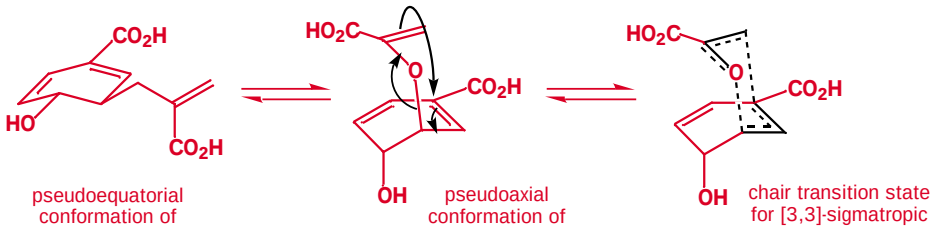
The product is chorismic acid and this undergoes the most interesting step of all—a [3,3]-sigmatropic rearrangement. Notice that the new (black) σ bond forms on the same face of the ring as the old (green) σ bond: this is, as you should expect, a suprafacial rearrangement.



chorismic acid prephenic acid

■ For more on sigmatropic rearrangements, see Chapter 36.

The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation. First, the diaxial conformation must be formed and the chair transition state achieved. Then the required orbitals will be correctly aligned.

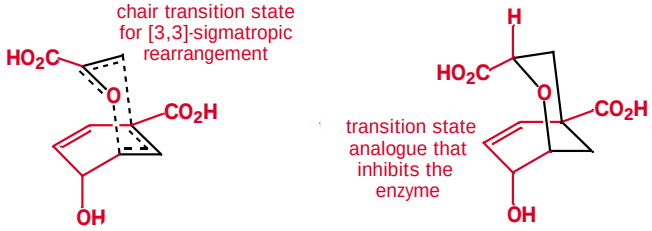


pseudoequatorial conformation of chorismic acid

pseudoaxial conformation of chorismic acid

chair transition state for [3,3]-sigmatropic rearrangement

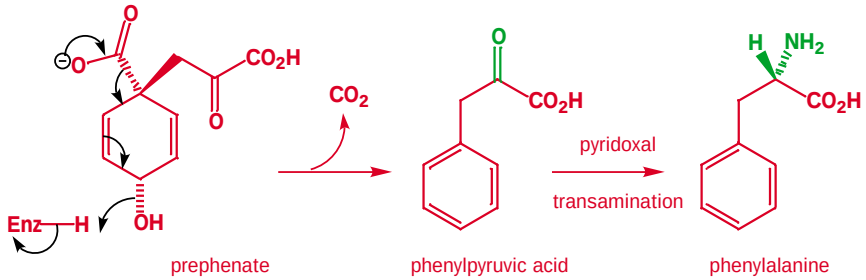
These reactions occur well without the enzyme (Chapter 36) but the enzyme accelerates this reaction by about a 10^6 increase in rate. There is no acid or base catalysis and we may suppose that the enzyme binds the transition state better than it binds the starting materials. We know this to be the case, because close structural analogues of the six-membered ring transition state also bind to the enzyme and stop it working. An example is shown alongside—a compound that resembles the transition state but can't react.



transition state analogue that inhibits the enzyme

▶ By binding the transition state (not the starting materials) strongly, the enzyme lowers the activation energy for the reaction.

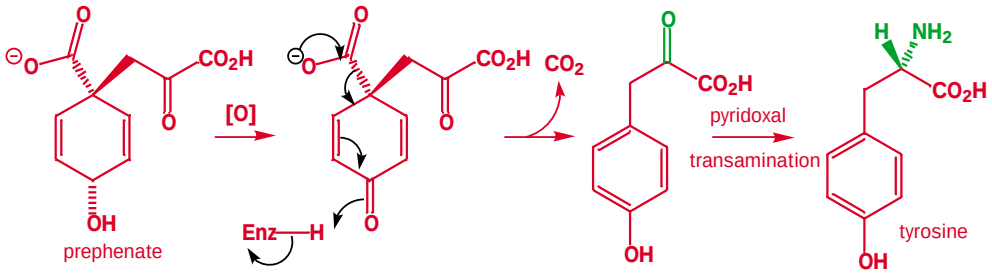
We have arrived at prephenic acid, which as its name suggests is the last compound before aromatic compounds are formed, and we may call this the end of the shikimic acid pathway. The final stages of the formation of phenylalanine and tyrosine start with aromatization. Prephenic acid is unstable and loses water and CO_2 to form phenylpyruvic acid. This α-keto-acid can be converted into the amino acid by the usual transamination with pyridoxal.



prephenate phenylpyruvic acid phenylalanine

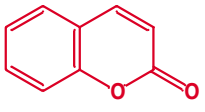
The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the

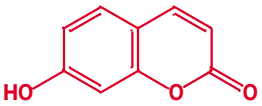
electrons of the breaking C–C bond ending up in a ketone group. Transamination again gives the amino acid.



Other shikimate products

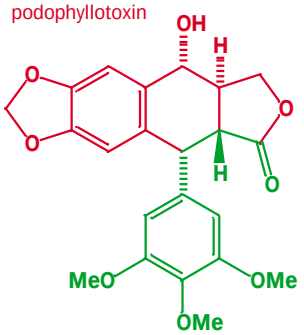
Many natural products are formed from the shikimate pathway. Most can be recognized by the aromatic ring joined to a three-carbon atom side chain. Two simple examples are coumarin, responsible for the smell of mown grass and hay, and umbelliferone, which occurs in many plants and is used in suntan oils as it absorbs UV light strongly. These compounds have the same aryl-C_3 structure as Phe and Tyr, but they have an extra oxygen atom attached to the benzene ring and an alkene in the C_3 side chain.


coumarin


umbelliferone

An important shikimate metabolite is podophyllotoxin, an antitumour compound—some podophyllotoxin derivatives are used to combat lung cancer. The compound can be split up notionally into two shikimate-derived fragments (shown in red and green). Both are quite different and there is obviously a lot of chemistry to do after the shikimic acid pathway is finished.

podophyllotoxin



Among the more interesting reactions involved in making all three of these natural products are the loss of ammonia from phenylalanine to give an alkene and the introduction of extra OH groups around the benzene rings. We know how a *para* OH of Tyr is introduced directly by the oxidation of prephenic acid before decarboxylation and it is notable that the extra oxygen functionalities appear next to that point. This is a clue to the mechanism of the oxidation.

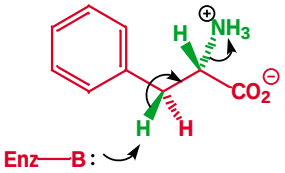
Alkenes by elimination of ammonia—phenyl ammonia lyase

Many amino acids can lose ammonia to give an unsaturated acid. The enzymes that catalyse these reactions are known as **amino acid ammonia lyases**. The one that concerns us at the end of the shikimic acid pathway is phenylalanine ammonia lyase, which catalyses the elimination of ammonia from phenylalanine to give the common metabolite cinnamic acid.

Phe
phenylalanine

cinnamic acid

▶ A *lyase* is an enzyme that catalyses *lysis*: it breaks something down.

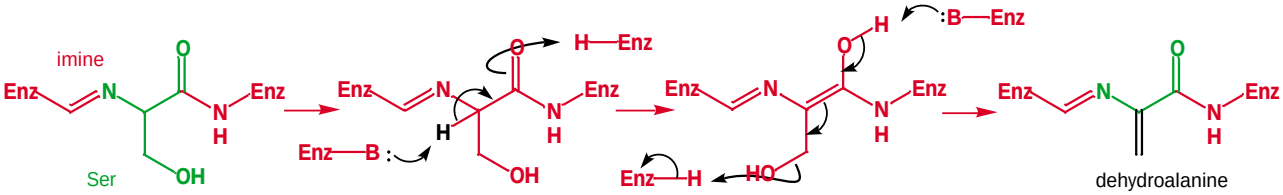


possible E2 mechanism for phenylalanine ammonia lyase?

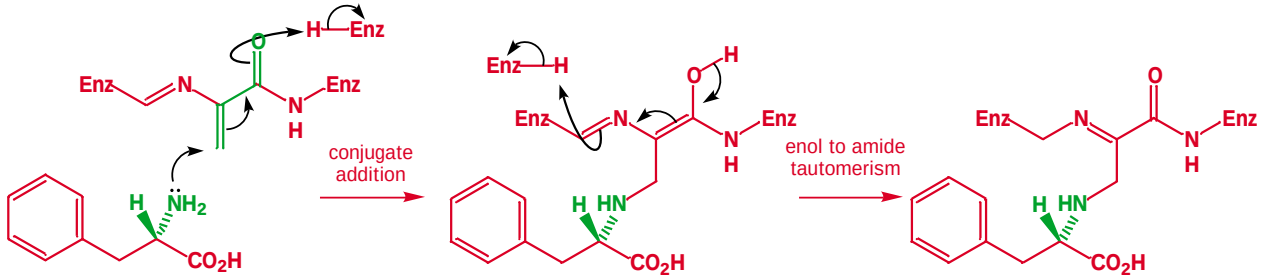
This reaction gives only *E*-cinnamic acid and the proton *anti* to the amino group is lost. This might make us think that we have an E2 reaction with a base on the enzyme removing the required proton. But a closer look at this mechanism makes it very unconvincing. The proton that is removed has no acidity and ammonia is not a good leaving group. It is very unusual for Nature to use an enzyme to make a reaction happen that doesn't happen at all otherwise. It is much more common for Nature to make a good reaction better.

▶ Eliminations of ammonium salts (Chapter 19, p. 000) require very strong bases—much stronger than those available to enzymes—and fully alkylated amines. You can't protonate an amine in the presence of strong base.

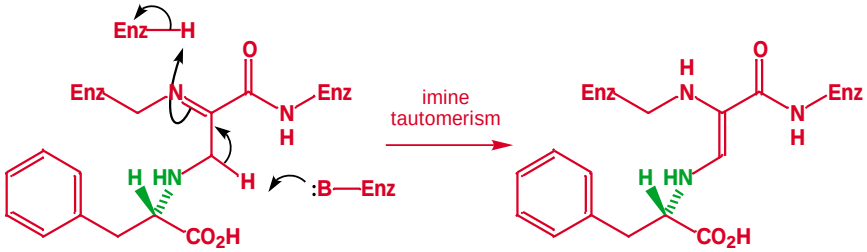
So how does an ammonia lyase work? The enzyme makes the ammonia molecule into a much better leaving group by using a serine residue. This serine is attached to the protein through its carboxyl group by the usual amide bond but its amino group is bound as an imine. This allows it to eliminate water to form a double bond before the phenylalanine gets involved. The elimination converts serine into a dehydroalanine residue. This is an E1cB elimination using only general acid and base catalysis as the proton to be lost is acidic and an enol can be an intermediate.



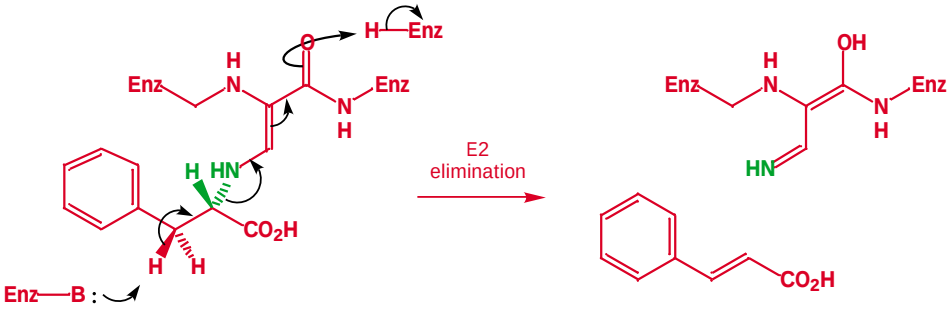
The alkene of the dehydroenzyme is conjugated with a carbonyl group—it's electrophilic and the amino group of Phe can add to it in conjugate fashion. When the enol tautomerizes back to a carbonyl compound, it can be protonated on the imine carbon because the imine is conjugated to the enol. This might remind you of pyridoxal's chemistry (p. 000).



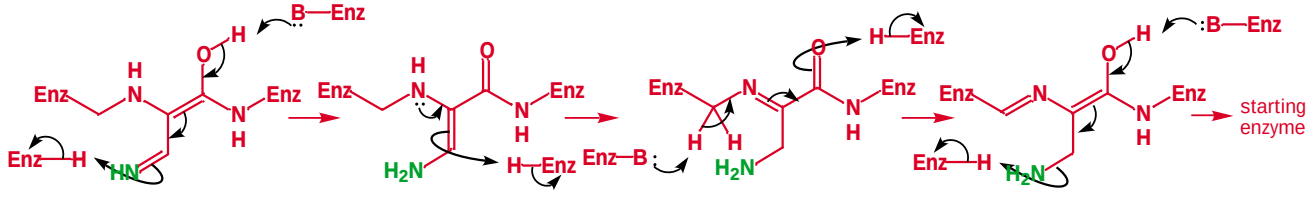
A second tautomerism makes an enamine—again very like the pyridoxal mechanisms you saw earlier.



Now at last the secret is revealed. We can break the C–N bond and use the carbonyl group as an electron sink. The acidity of the proton that must be lost is no greater but the nitrogen atom has become a very much better leaving group.

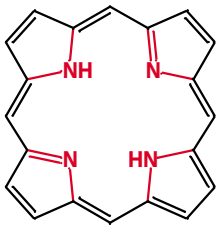


The difficult elimination is accomplished by making it an ammonia transfer reaction rather than an elimination of ammonia. Recycling the enzyme does eventually require elimination of ammonia but in an easy E1cB rather than a difficult E2 reaction. Overall, a difficult reaction—elimination of ammonia—is accomplished in steps that involve no strong acids or strong bases, and most of the steps are simple proton transfers, often tautomerisms between imines, enols, and amides.



Haemoglobin carries oxygen as an iron(II) complex

porphyrin

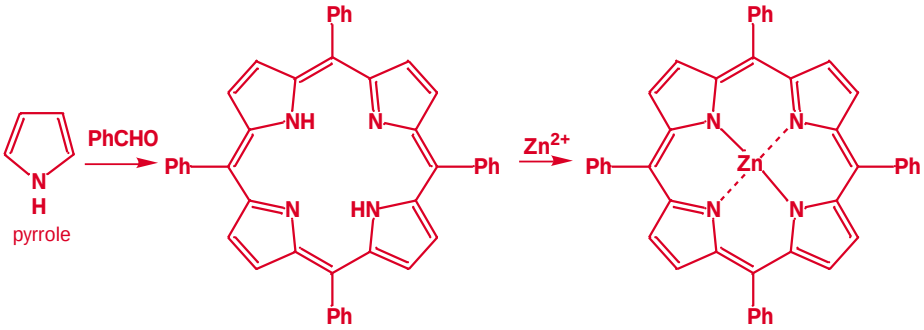


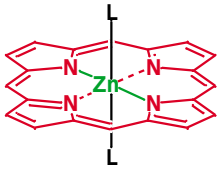
18 electrons
in a conjugated ring
= 4*n* + 2 (*n* = 4)

■
Porphyrins appeared in Chapters 43 and 44, pp. 000 and 000.

Biological oxidations are very widespread. Human metabolism depends on oxidation, and on getting oxygen, which makes up 20% of the atmosphere, into cells. The oxygen transporter, from atmosphere to cell, is **haemoglobin**.

The reactive part of haemoglobin is a **porphyrin**. These are aromatic molecules with 18 electrons around a conjugated ring formed from four molecules of a five-membered nitrogen heterocycle. Chemically, symmetrical porphyrins are easily made from pyrrole and an aldehyde.

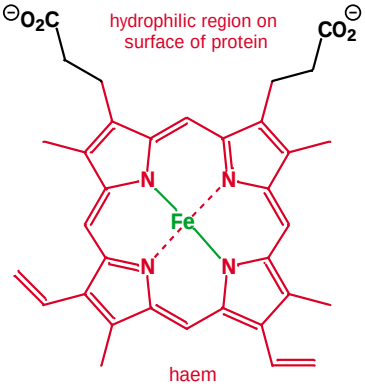




octahedral
zinc(II) porphyrin
with two extra ligands

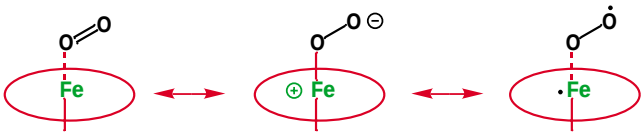
The hole in the middle of a porphyrin is just the right size to take a divalent transition metal in the first transition series, and zinc porphyrins, for example, are stable compounds. Once the metal is inside a porphyrin, it is very difficult to get out. Two of the nitrogen atoms form normal covalent bonds (the ones that were NH in the porphyrin) and the other two donate their lone pairs to make four ligands around the metal. The complexed zinc atom is square planar and still has two vacant sites—above and below the (more or less) flat ring. These can be filled with water molecules, ammonia, or other ligands.

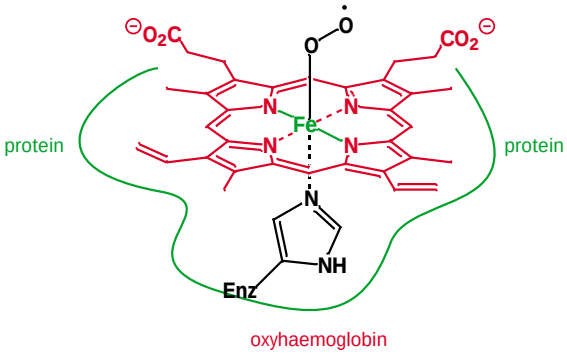
The porphyrin part of haemoglobin is called **haem**, and it is an iron(II) complex. It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other.



Haem is bound to proteins to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such a leucine and valine. The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.

The oxygen complex can be drawn like this or, alternatively, as an Fe(III) complex of an oxyanion (below).

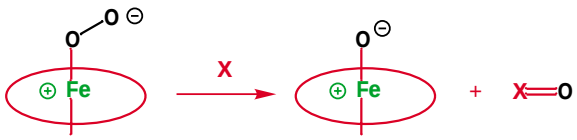




oxyhaemoglobin

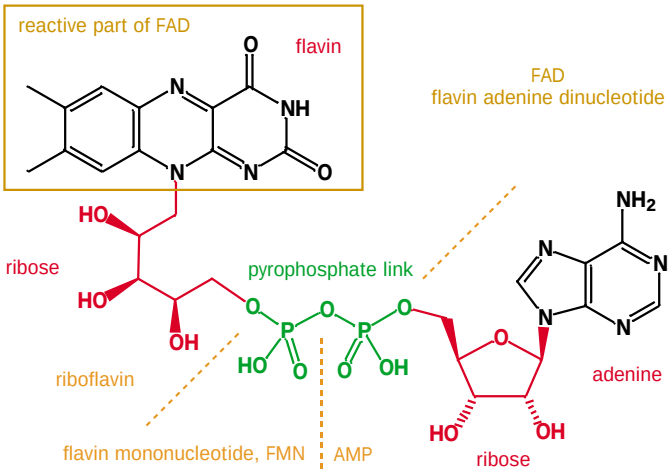
It is difficult to draw detailed mechanisms for oxidations by iron complexes but it is the oxygen atom further from Fe that reacts. You can see in principle how breakage of the weak O–O bond could deliver an oxygen atom to a substrate and leave an Fe(III)–O^- complex behind.

Oxygen molecules are transferred from haemoglobin to other haems, such as the enzyme P450, and to a wide range of oxidizing agents. Almost any molecule we ingest that isn't a nutrient—a drug molecule, for example—is destroyed by oxidation. The details of the mechanisms of these oxidations have proved very difficult to elucidate, but the hydroxylation of benzene is an exception. We do know how it happens, and it's another case of Nature using enzymes to do some really remarkable chemistry.



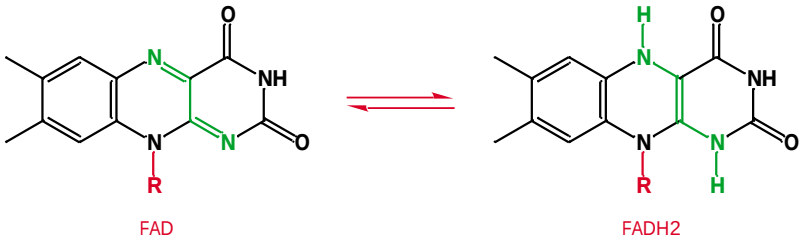
Aromatic rings are hydroxylated via an epoxide intermediate

The oxidizing agents here are related to FAD. We said little about $FADH_2$ as a reducing agent earlier in this chapter because it is rather similar to NADH which we have discussed in detail. FAD is another dinucleotide and it contains an AMP unit linked through the 5′ position by a pyrophosphate group to another nucleotide. The difference is that the other nucleotide is flavin mononucleotide. Here is the complete structure.



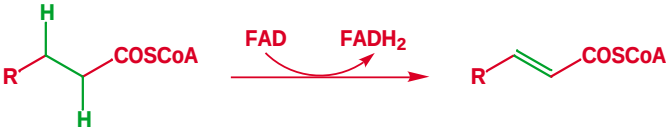
The whole thing is FAD. Cutting FAD in half down the middle of the pyrophosphate link would give us two nucleo*tides*, AMP and FMN (flavin mononucleotide). The sugar in each case is ribose (in its furanose form in AMP but in open-chain form in FMN) so the flavin nucleo*side* is riboflavin. We can abbreviate this complex structure to the reactive part, which is the flavin. The rest we shall just call 'R'.

▶ Riboflavin is also known as vitamin B_2 as you may see on the side of your cornflakes packet.

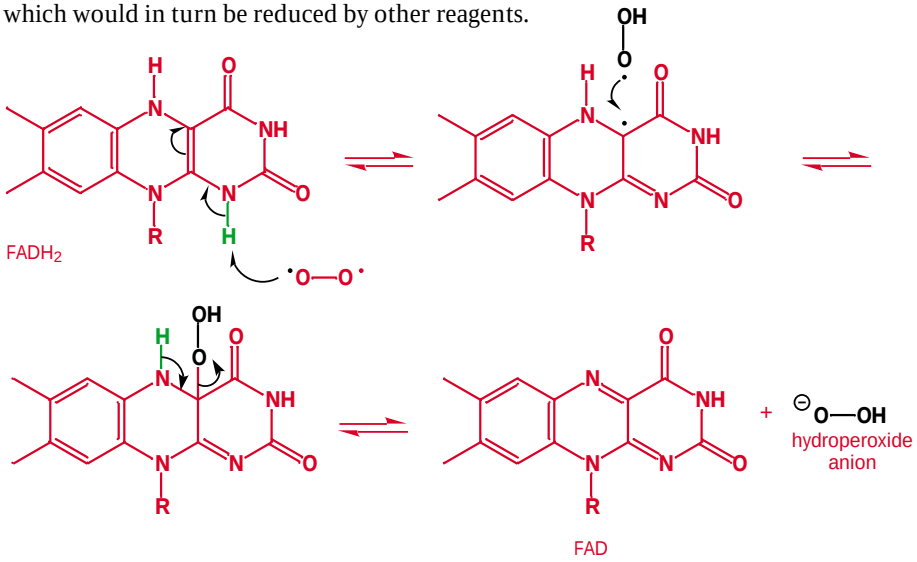


Redox reactions with FAD involve the transfer of two hydrogen atoms to the part of the molecule shown in green. Typical reactions of FAD involve dehydrogenations—as in double bond formation from single bonds. Of course, one of the H atoms can be transferred to FAD as a proton—only one need be a hydride ion H^-, though both could be transferred as radicals ($H^\bullet$).

▶ You should contrast this with the redox reactions of NAD where only one hydrogen atom is transferred.

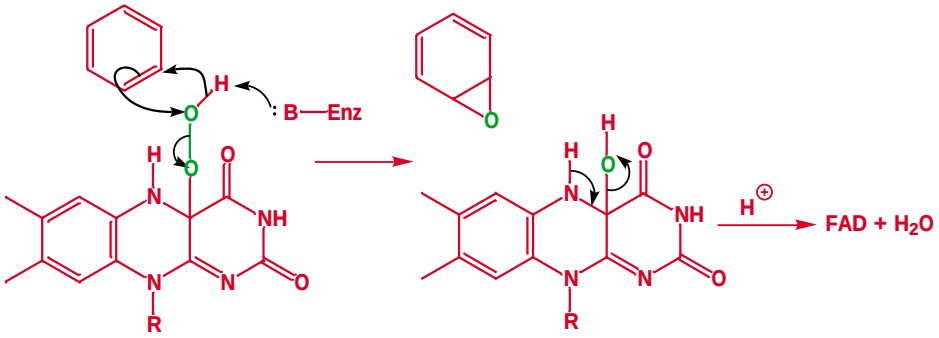


After FAD has been used as an oxidant in this fashion, the $FADH_2$ reacts with molecular oxygen to give a hydroperoxide, which decomposes back to FAD and gives an anion of hydrogen peroxide, which would in turn be reduced by other reagents.

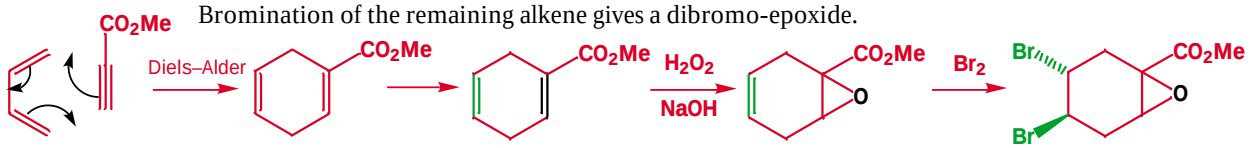


▶ Note the radical steps in this sequence. The reactions of oxygen, whose ground state is a triplet diradical (see Chapter 4), are typically radical processes.

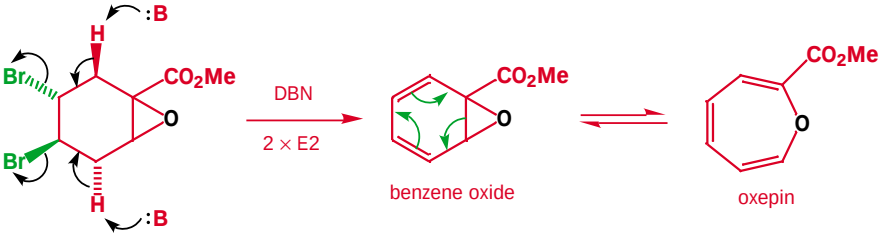
In the reactions we are now concerned with, the hydroperoxide intermediate itself is the important reagent, before it loses hydroperoxide anion. This intermediates is an oxidizing agent—for example, it reacts quite dramatically with benzene to give an epoxide.



This benzene oxide may look very dubious and unstable, but benzene oxides can be made in the laboratory by ordinary chemical reactions (though not usually by the direct oxidation of benzene). We can instead start with a Diels–Alder reaction between butadiene and an alkyne. Epoxidation with a nucleophilic reagent ($HO–O^-$ from H_2O_2 and NaOH) occurs chemoselectively on the more electrophilic double bond—the one that is conjugated to the electron-withdrawing carbonyl group. Bromination of the remaining alkene gives a dibromo-epoxide.

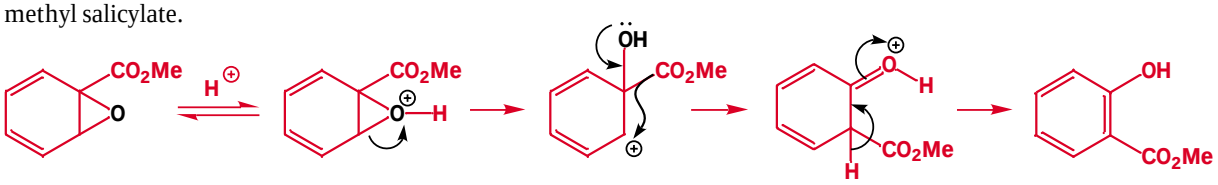


This is an ordinary electrophilic addition to an alkene so the two bromine atoms are *anti* in the product. Elimination under basic conditions with DBN gives the benzene oxide.

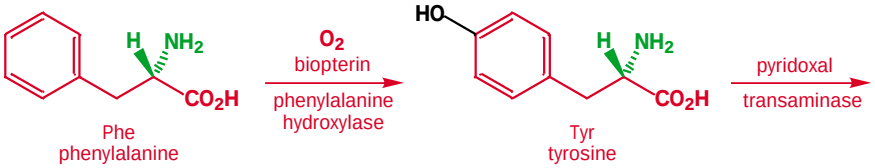


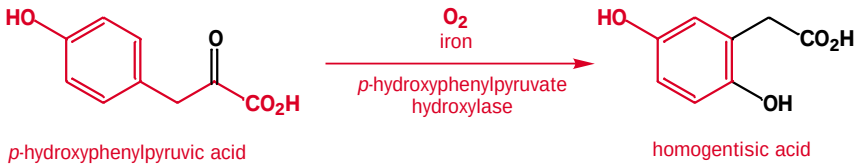
At least, it ought to have given the benzene oxide! The compound turned out to have a fluxional structure—it was a mixture of compounds that equilibrate by a reversible disrotatory electrocyclic reaction.

Treatment with acid turns the benzene oxide/oxepin into an aromatic ring by a very interesting mechanism. The epoxide opens to give the cation, which is *not* conjugated with the electron-withdrawing CO_2Me group, and then a migration of that CO_2Me group occurs. This has been proved by isotope labelling experiments. The final product is the *ortho*-hydroxy-ester, known as methyl salicylate.

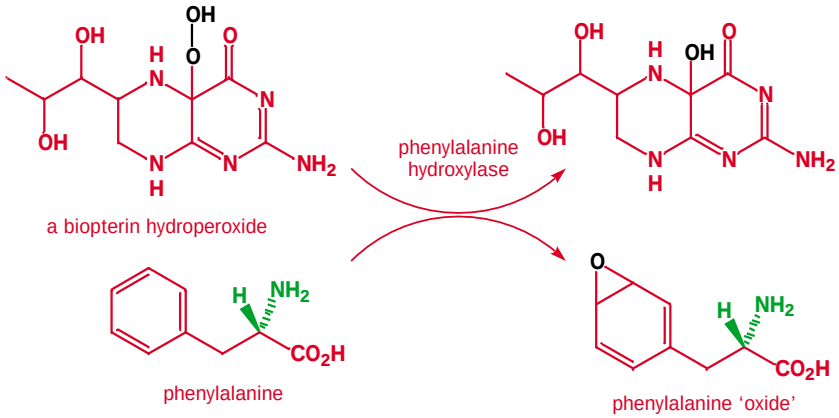


This chemistry seems rather exotic, but in the degradation of phenylalanine two benzene oxide intermediates and two such rearrangements occur one after the other. This is the initial sequence.

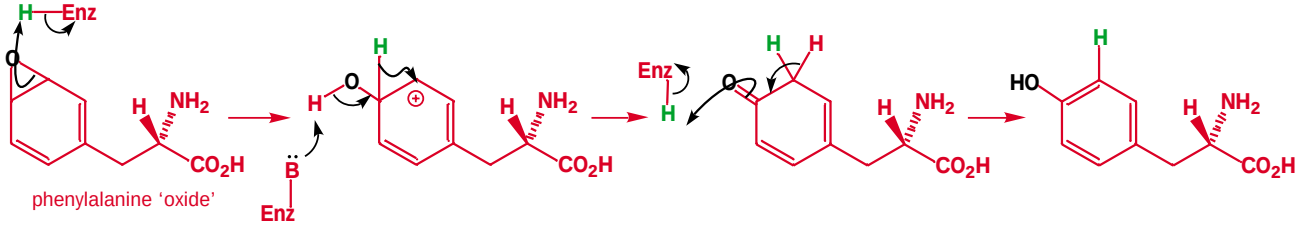




The first reaction involves a hydroperoxide related to the FAD hydroperoxide you have just seen but based on a simpler heterocyclic system, a biopterin. The reaction is essentially the same and a benzene oxide is formed.

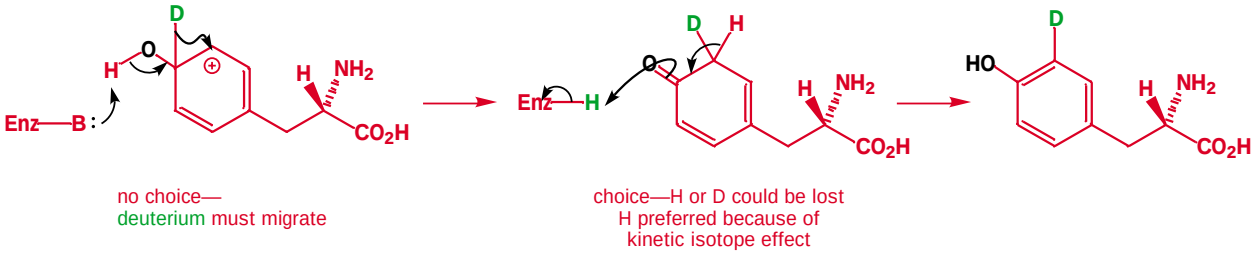


The biopterin product is recycled by elimination of water, reduction using NADPH as the reagent, and reaction with molecular oxygen. The other product, the phenylalanine oxide, rearranges with a hydride shift followed by the loss of a proton to give tyrosine.

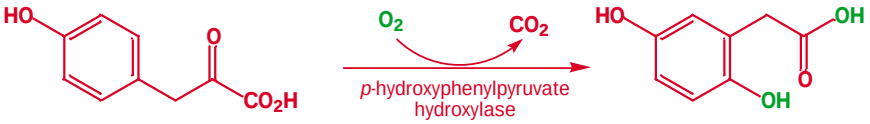


▶ This rearrangement is known as the 'NIH shift', after its discovery at the National Institutes of Health at Bethesda, Maryland.

We know that this is the mechanism because we can make the green H a deuterium atom. We then find that deuterium is present in the tyrosine product *ortho* to the phenolic hydroxyl group. When the migration occurs, the deuterium atom must go as there is no alternative, but in the next step there is a choice and H loss will be preferred to D loss because of the kinetic isotope effect (Chapter 19). Most of the D remains in the product.

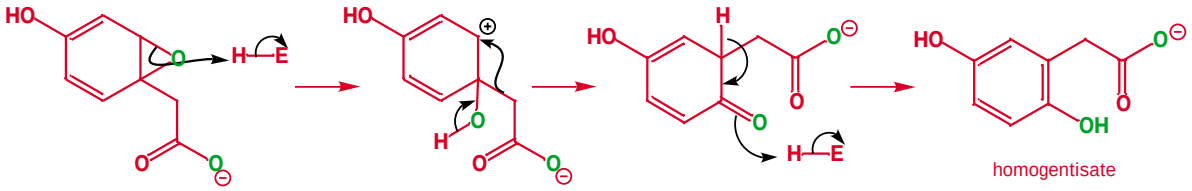


A shift of a larger group comes two steps later in the synthesis of homogentisic acid. Another labelling experiment, this time with $^{18}O_2$, shows that both atoms of oxygen end up in the product.

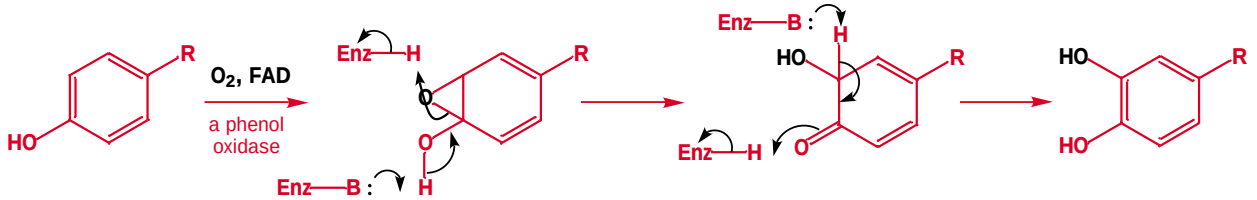


The key intermediate is a peroxy-acid formed after decarboxylation. The peroxy-acid is perfectly placed for an intramolecular epoxidation of a double bond in the benzene ring next to the side chain.

The epoxide can now rearrange with the whole side chain migrating in a reaction very similar to the laboratory rearrangement to give methyl salicylate that you saw on p. 000.



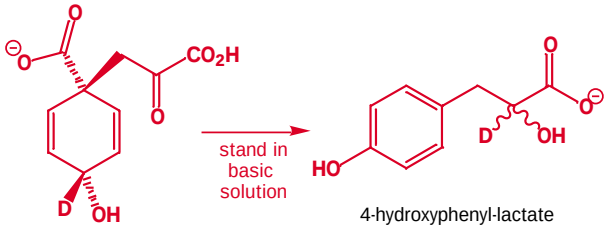
When hydroxylation occurs next to an OH group that is already there, no NIH shift occurs. This is because the epoxide is opened by the push of electrons from the OH group and there is only one H atom to be lost anyway. The cofactor for these enzymes is slightly different, being again the hydroperoxide from FAD, but the principle is the same.



In the next chapter you will see how hydroxylation of benzene rings plays an important part in the biosynthesis of alkaloids and other aromatic natural products.

Problems

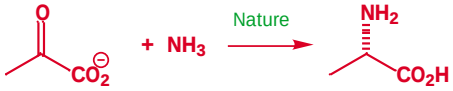
1. On standing in alkali in the laboratory, prephenic acid rearranges to 4-hydroxyphenyl-lactic acid with specific incorporation of deuterium label as shown. Suggest a mechanism, being careful to draw realistic conformations.



prephenate — 4-hydroxyphenyl-lactate

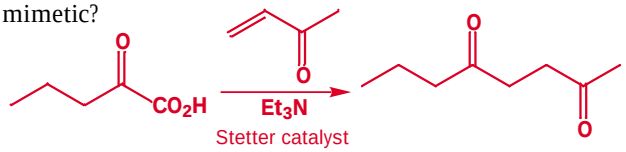
this product is racemic. why?

2. Write a full reaction scheme for the conversion of ammonia and pyruvate to alanine in living things. You will need to refer to the section of the chapter on pyridoxal to be able to give a complete answer.

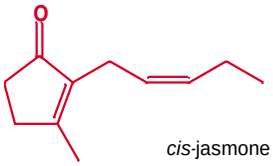


pyruvate — (*S*)-alanine

3. Give a mechanism for this reaction. You will find the Stetter catalyst described in the chapter. How is this sequence biomimetic?



What starting material would be required for formation of the natural product *cis*-jasmone by an intramolecular aldol reaction (Chapter 27). How would you make this compound using a Stetter reaction?

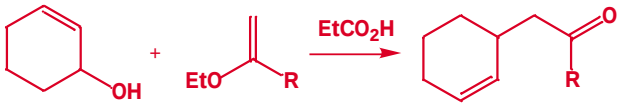


cis-jasmone

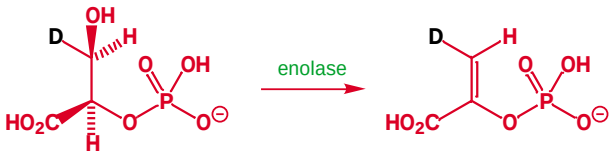
4. The amino acid cyanoalanine is found in leguminous plants (*Lathyrus*) but not in proteins. It is made in the plant from cysteine and cyanide by a two-step process catalysed by pyridoxal phosphate. Suggest a detailed mechanism.

(*S*)-cysteine — (*S*)-cyanoalanine

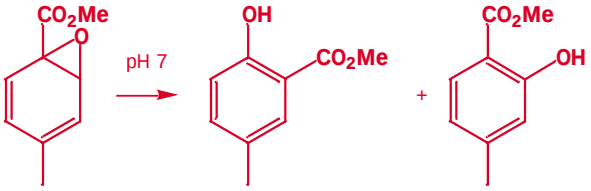
5. This chemical reaction might be said to be similar to a reaction in the shikimic acid pathway. Compare the two mechanisms and suggest how the model might be made closer and more interesting.



6. Stereospecific deuteration of the substrate for enolase, the enzyme that makes phosphoenol pyruvate, gives the results shown below. What does this tell us definitely about the reaction and what might it suggest about the mechanism?



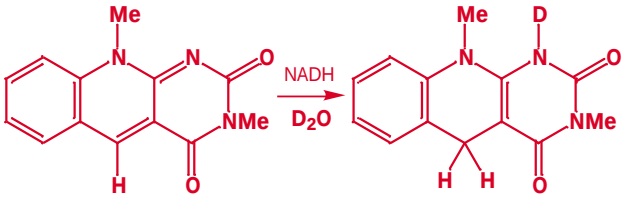
7. This rearrangement was studied as a biomimetic version of the NIH shift. Write a mechanism for the reaction. Do you consider it a good model reaction? If not, how might it be made better?



83% yield — 17% yield

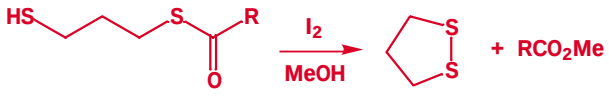
8. The following experiments relate to the chemical and biological behaviour of NADH. Explain what they tell us.

(**a**) This FAD analogue can be reduced *in vitro* with NADH in D_2O with deuterium incorporation in the product as shown.

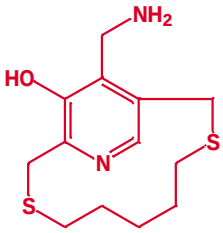


(**b**) NADH does not reduce benzaldehyde *in vitro* but it does reduce this compound.

9. Oxidation of this simple thiol ester gives a five-membered cyclic disulfide. The reaction is proposed as a model for the behaviour of lipoic acid in living things. Draw a mechanism for the reaction and make the comparison.

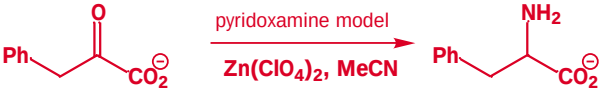


10. This curious compound is chiral—indeed it has been prepared as the (–) enantiomer. Explain the nature of the chirality.

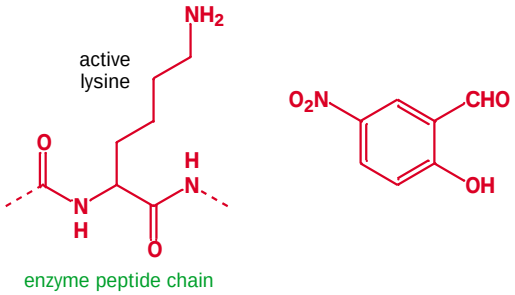


enantiomerically enriched (–) enantiomer

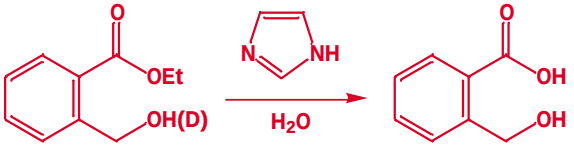
This compound has been used as a chemical model for pyridoxamine. For example, it transaminates phenylpyruvate under the conditions shown here. Comment on the analogy and the role of Zn(II). In what ways is the model compound worse and in what ways better than pyridoxamine itself?



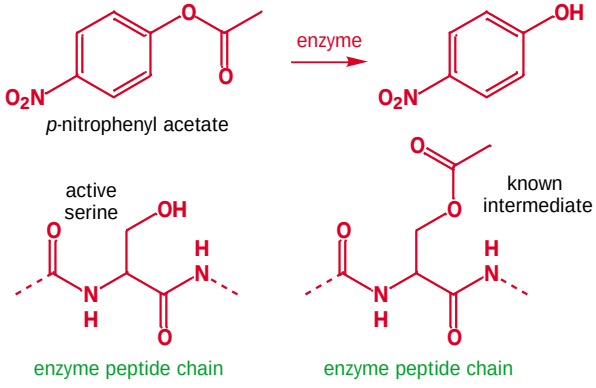
11. Enzymes such as aldolase, thought to operate by the formation of an imine and/or an enamine with a lysine in the enzyme, can be studied by adding $NaBH_4$ to a mixture of enzyme and substrate. For example, treatment of the enzyme with the aldehyde shown below and $NaBH_4$ gives a permanently inhibited enzyme that on hydrolysis reveals a modified amino acid in place of one of the lysines. What is the structure of the modified amino acid, and why is this particular aldehyde chosen?



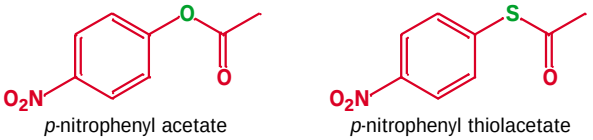
12. This question is about the hydrolysis of esters by 'serine' enzymes. First, interpret these results: The hydrolysis of this ester is very much faster than that of ethyl benzoate itself. It is catalysed by imidazole and then there is a primary isotope effect (Chapter 41) $k_{(OH)}/k_{(OD)} = 3.5$. What is the mechanism? What is the role of the histidine?



The serine enzymes have a serine residue vital for catalysis. The serine OH group is known to act as a nucleophilic catalyst. Draw out the mechanism for the hydrolysis of *p*-nitrophenyl acetate.



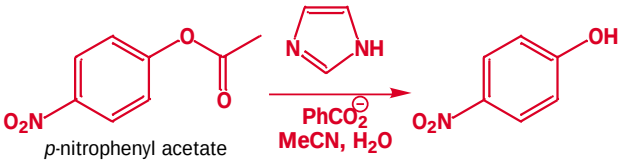
The enzyme also has a histidine residue vital for catalysis. Use your mechanism from the first part of the question to say how the histidine residue might help. The histidine residue is known to help both the formation and the hydrolysis of the intermediate. The enzyme hydrolyses both *p*-nitrophenyl acetate and *p*-nitrophenyl thiolacetate at the same rate. Which is the rate-determining step?



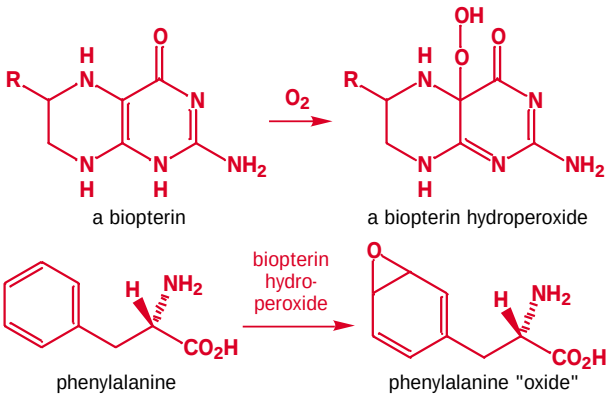
Finally, an aspartic acid residue is necessary for full catalysis and this residue is thought to use its CO_2^- group as a general base. A chemical model shows that the hydrolysis of *p*-nitrophenyl acetate in aqueous acetonitrile containing sodium benzoate and imidazole follows the rate law:

rate = k[*p*-nitrophenyl acetate] [benzoate] [imidazole].

Suggest a mechanism for the chemical reaction.



13. Give mechanisms for the biological formation of biopterin hydroperoxide and its reaction with phenylalanine. The reactions were discussed in the chapter but no details were given.



14. Revision of Chapter 48. How many electrons are there on the iron atom in the oxyhaemoglobin structure shown in the chapter? Does it matter if you consider the complex to be of Fe(II) or Fe(III)? Why do zinc porphyrins need two extra ligands and what type of ligands should they be?