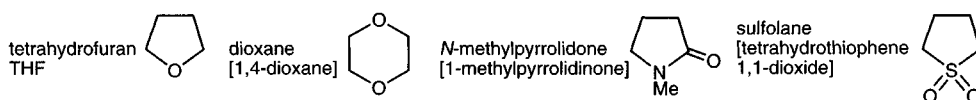


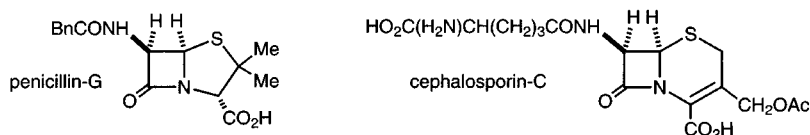
27 Saturated and partially unsaturated heterocyclic compounds: reactions and synthesis

This book is principally concerned with the chemistry of aromatic heterocycles, however mention must be made of the large body of remaining heterocycles, including those with small rings¹ (3- and 4-membered). Most of the reactions of saturated and partially unsaturated heterocyclic compounds are so closely similar to those of acyclic or non-heterocyclic analogues that a full discussion is not appropriate in this book, however in this chapter we discuss briefly those aspects in which they do differ – perhaps the most obvious aspect in which they differ from aromatic heterocycles is in having sp^3 hybridised atoms, i.e. in the exhibition of stereochemistry.²

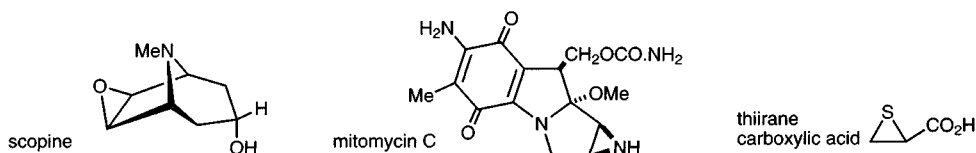
Saturated and partially unsaturated heterocycles are widely distributed as natural products. Some are used as solvents for organic reactions, notably tetrahydrofuran (THF) and dioxane, where diethyl ether is unsuitable. *N*-Methylpyrrolidone and sulfolane are useful dipolar aprotic solvents, with characteristics like those of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).



The four-membered β -lactam ring is the essential component of the penicillin and cephalosporin antibiotics.



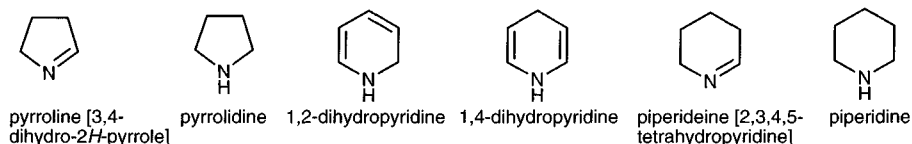
Epoxides (three-membered saturated oxygen-containing rings), are components of epoxy resins and occur in some natural products, such as the alkaloid scopine. Epoxides, because of their alkylating properties, can be carcinogenic – the biologically active metabolites of carcinogenic hydrocarbons are examples – however they are also found in some anti-tumour agents.



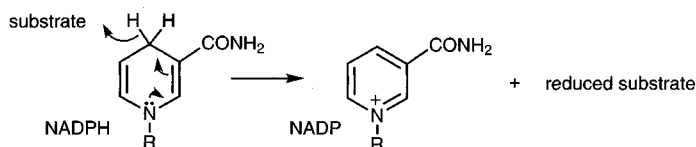
Aziridines (three-membered saturated nitrogen-containing rings) are also found in anti-tumour agents, such as the mitomycins. Thiiranes also occur naturally, as plant products such as thiirane-2-carboxylic acid, isolated from asparagus.

27.1 Five- and six-membered rings

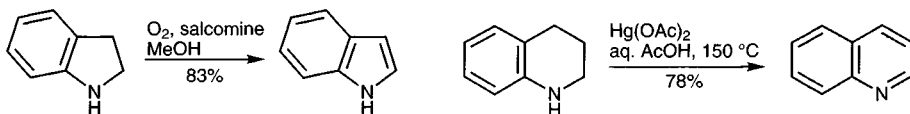
27.1.1 Pyrrolidines and piperidines



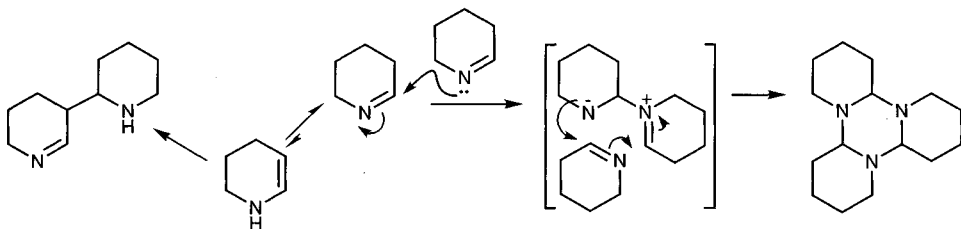
The main chemical aspect in which compounds with a nitrogen in a five- or six-membered ring differ from their acyclic counterparts is in the possibility open to them to be dehydrogenated to the corresponding aromatic system. Dihydroaromatic systems naturally show the greatest tendency to aromatise, indeed one of the important reducing coenzymes, NADPH, makes use of this tendency, as indicated below.



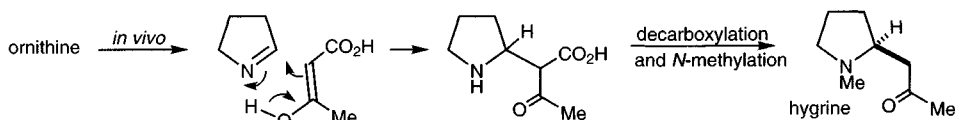
Dihydro-compounds are often useful synthetic intermediates showing different reactivity patterns to the parent, aromatic heterocycle. For example, indolines (2,3-dihydroindoles) can be used to prepare indoles³ with substituents in the carbocyclic ring, *via* electrophilic substitution then rearomatisation (section 17.16.1.8), and similarly, electrophilic substitutions of dihydropyridines, impossible in pyridines themselves, followed by rearomatisation can give substituted pyridines. Dehydrogenation of tetra- and hexahydro-derivatives requires much more vigorous conditions.



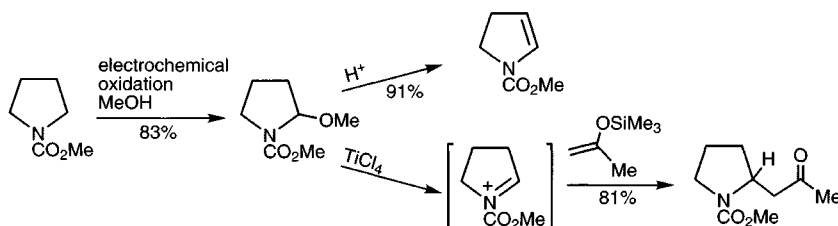
Generally speaking, piperideines and pyrrolines exist predominantly in the imine form and not in the tautomeric enamine form; *N*-alkyl analogues have no alternative but to exist as enamines. These cyclic imines are resistant to hydrolytic fission of the C=N bond, in strong contrast with acyclic imines, but nonetheless they are very susceptible to nucleophilic addition at the azomethine carbon. An example of this is that both piperideine and pyrroline exist as trimers formed by the nucleophilic addition of nitrogen of one molecule to the azomethine carbon of a second molecule, etc.



The presence of some enamine, at equilibrium, is demonstrated by the conversion of piperidine into a dimer, indeed, the ability of these two systems to serve as both imines and enamines in such aldol-like condensations is at the basis of their roles in alkaloid biosynthesis. Formed in nature by the oxidative deamination and decarboxylation of ornithine and lysine, they become incorporated into alkaloid structures by condensation with other precursor units.⁴ Hygrine is a simple example in which the 1-pyrroline, as an imine, has condensed with acetoacetate, or its equivalent.



Controlled oxidation of *N*-acylpiperidines and -pyrrolidines can be used to prepare 2-alkoxy-derivatives or the equivalent enamides, which are useful general synthetic intermediates.⁵ The former are susceptible to nucleophilic substitution under Lewis acid catalysis, *via* Mannich-type intermediates, and the latter can undergo electrophilic substitution at C-3 or addition to the double bond.

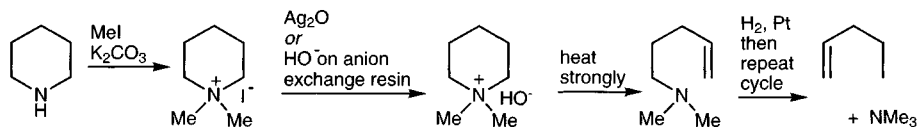


Pyrrolidine and piperidine are better nucleophiles than diethylamine, principally because the lone pair is less hindered – in the heterocycles the two alkyl ‘substituents’, i.e. the ring carbons, are constrained back and away from the nitrogen lone pair, and approach by an electrophile is thus rendered easier than in diethylamine where rotations of the C–N and C–C bonds hinder approach. The pK_a values of pyrrolidine (11.27) and piperidine (11.29) are typical of amine bases; they are slightly stronger bases than diethylamine (10.98).

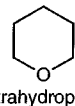
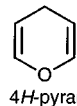
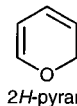
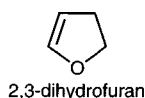
Piperidines, like cyclohexanes, adopt a preferred chair conformation. Much controversy centred over the years on the question as to whether in piperidines it is the *N*-substituent (or *N*-hydrogen) or the *N*-lone pair which adopts an equatorial or axial orientation; some confusion arose because of the results from *N*-alkylation reactions, the products from which do not necessarily reflect ground state conformational populations. Both an *N*-hydrogen and an *N*-alkyl substituent adopt an equatorial orientation, though in the former case the equatorial isomer is favoured by only a small margin.⁶

In early days, structure determination of natural products involved degradative methods. Many alkaloids incorporate saturated nitrogen rings, so degradations were used which gave information about the environment of the basic nitrogen atom. The classical method for doing this was the ‘Hofmann exhaustive methylation’ procedure. This is illustrated as it would be applied to piperidine. What the method does is to cleave N–C bonds and eventually remove the nitrogen; one repetition of the cycle, as in the example, removes the nitrogen – it was originally part of a ring; a third cycle would be necessary if the nitrogen had been originally a component of two rings. At

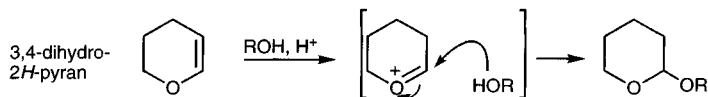
the end of the process a nitrogen-free fragment is left for study to determine the original carbon skeleton.



27.1.2 Pyrans and reduced furans

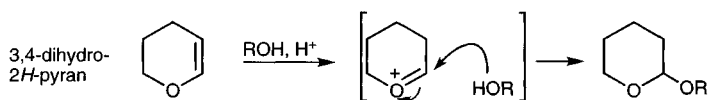


3,4-Dihydro-2H-pyran and 2,3-dihydrofuran behave as enol ethers, the former being widely used to protect alcohols⁷ with which it reacts readily under acidic catalysis, producing acetals which are stable to even strongly basic conditions but easily hydrolysed back to the alcohol under mildly acidic aqueous conditions.

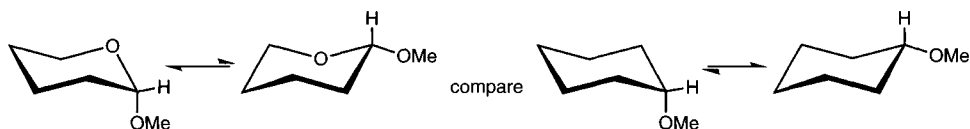


4H-Pyran appears to be somewhat less stable than dihydropyran but reacts similarly, for example it lithiates at C-2 and undergoes Diels-Alder reactions as an enol ether.⁸

A great deal is known about hydroxylated tetrahydrofurans and tetrahydropyrans because such ring systems occur in sugars and sugar-containing compounds – sucrose and RNA (section 24.1) are examples.⁹

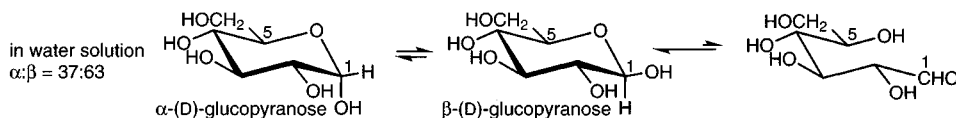


Tetrahydropyran, like piperidine, adopts a chair conformation. One of the interesting aspects to emerge from studies of alkoxy-substituted tetrahydropyrans is that when located at C-2, alkoxy groups prefer an axial orientation (the 'anomeric effect'¹⁰). The reason for this is that in an equatorial orientation there are unfavourable dipole-dipole interactions between lone pairs on the two oxygen atoms, and the energy gain, when these are relieved in a conformation with the C-2-substituent axial, more than offsets the unfavourable 1,3-diaxial interactions which are introduced at the same time.

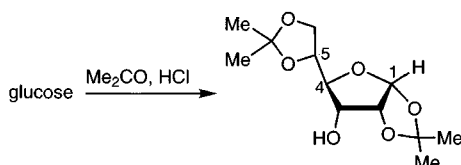


Glucose, of which many of the chemical reactions actually involve the small concentration of acyclic polyhydroxyaldehyde in equilibrium with the cyclic forms, hemiacetals containing a tetrahydropyran: this illustrates the inherent stability of

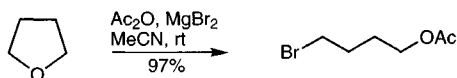
chair conformers of saturated six-membered systems. The propensity for cyclisation is a general one: 5-hydroxyaldehydes, -ketones and -acids all easily form six-membered oxygen-containing rings – lactols and lactones respectively.



Five-membered rings, too, are relatively easy to form: depending on conditions, glucose derivatives can easily be formed in the furanose form i.e. based on tetrahydrofuran.



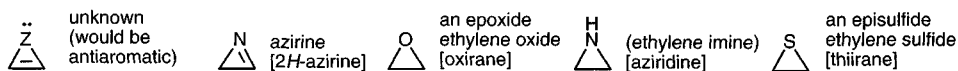
Saturated cyclic ethers are inert like acyclic ethers, requiring strong conditions for C–O bond cleavage;¹¹ this contrasts with heterocycles having smaller ring sizes (sections 27.2 and 27.3).



27.2 Three-membered rings

27.2.1 Three-membered rings with one hetero atom

Δ -2-Unsaturated three-membered systems are unknown as stable molecules because they would have a 4-electron π -system, and thus be antiaromatic.¹² 1*H*-Azirines occur as reactive intermediates and there is evidence for the existence of 2-thiirene in a low temperature matrix.¹³ Azirines,¹⁴ by contrast, are well-known stable compounds. Thiirene *S,S*-dioxides are also stable molecules, probably best likened to cyclopropanones.¹⁵ The chemistry of saturated three-membered heterocycles is, however, very extensive, in particular, epoxides (oxiranes) are vital intermediates in general synthesis.

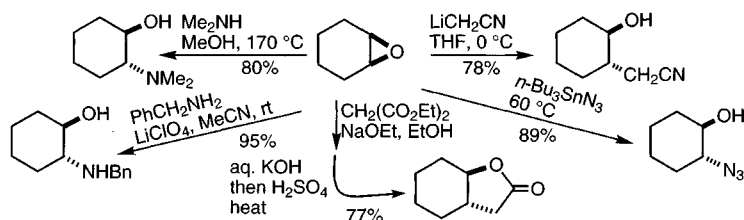


A major advance has been the development of an efficient synthesis of epoxides of high optical purity from allylic alcohols and related systems (the *Sharpless epoxidation*) (below); such epoxides have been used extensively for the synthesis of complex natural products in homochiral form.

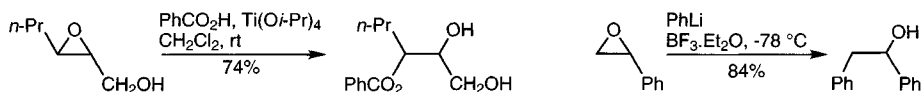
The $\text{p}K_{\text{a}}$ of aziridine (7.98) shows it to be an appreciably weaker base than azetidine (11.29), the four-membered analogue, which is 'normal' for acyclic amines and for five- and six-membered saturated amines. The low basicity is mirrored in the oxygen series, as measured by the ability of oxiranes to form hydrogen bonds. The explanation is probably associated with the strain in the three-membered compounds, meaning that the lone pair is in an orbital with less p-character than a 'normal' sp^3 nitrogen or oxygen orbital, and is therefore held more tightly. The rate

of pyramidal inversion of the 'saturated' nitrogen in azirines is very slow compared with simpler amines. This is because there is a further increase in angle strain when the nitrogen rehybridises ($\rightarrow sp^2$) in the transition state for inversion.

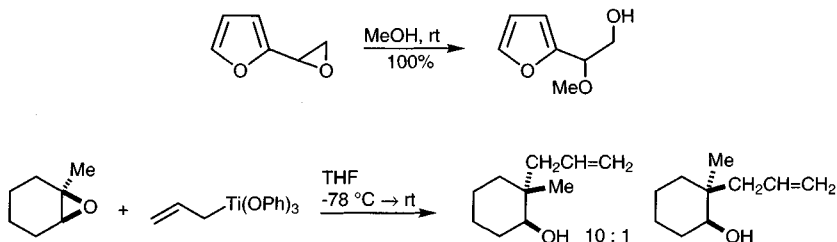
The chemical reactions of three-membered heterocycles are a direct consequence of the strain inherent in such small rings, which, combined with the ability of the heteroatom to act as a leaving group, means that most of the chemical properties involve ring-opening reactions. Most epoxide ring-openings occur by S_N2 nucleophilic displacements at carbon and a very wide range of carbanion and heteroatom nucleophiles have been shown to react in this way, including amines,¹⁶ alcohols, thiols, hydride ($LiAlH_4$), malonate anions,¹⁷ etc. Assistance by protic solvents or *O*-coordinating metal cations (Lewis acids) which help to further weaken the C–O bond can dramatically increase the rate of reaction. Additives such as alumina,¹⁸ titanium alkoxides,¹⁹ and lithium perchlorate,²⁰ and reagents such as tributyltin azide,²¹ which is itself a Lewis acid (coordination to ' Bu_3Sn^+ '), but also contains a nucleophilic function (N_3^-), are useful in this respect.



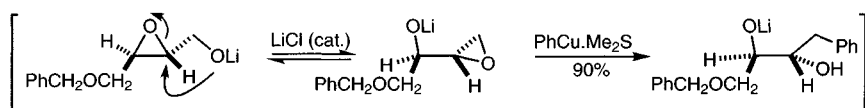
'Harder' organometallic nucleophiles such as alkyllithiums often give rise to side reactions but their combination (at $-78^\circ C$) with boron trifluoride gives very clean and efficient reactions.²²



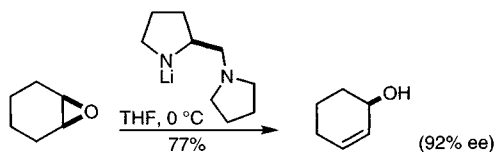
The regiochemistry of ring opening is determined mainly by steric and to a lesser extent by inductive and electronic effects. Where strong Lewis acids are used or where a highly stabilised (incipient) carbonium ion can be formed, such as when an α -aryl substituent is present, reaction can occur mainly at the most substituted position, an extreme case being the solvolysis of 2-furyloxirane in neutral methanol,²³ however, selective substitution at the most highly substituted position of even simple, alkyl epoxides has been achieved with an allyltitanium reagent.²⁴



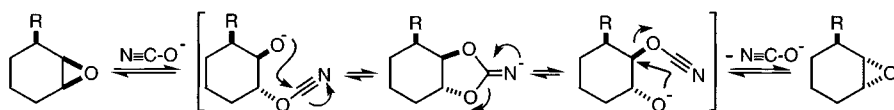
The Payne rearrangement of epoxy-alcohols is a special case of an intramolecular nucleophilic opening of epoxides and is of synthetic significance due to its application to Sharpless epoxides.²⁵



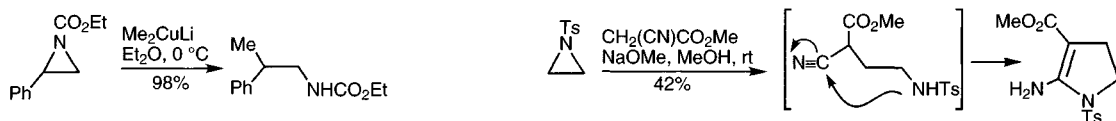
Ring-opening of epoxides by β -elimination, on reaction with strong bases such as lithium amides, or combinations of trimethylsilyl triflate with diazabicycloundecane,²⁶ is a useful synthetic method for allylic alcohols, particularly as it can be carried out enantioselectively.²⁷



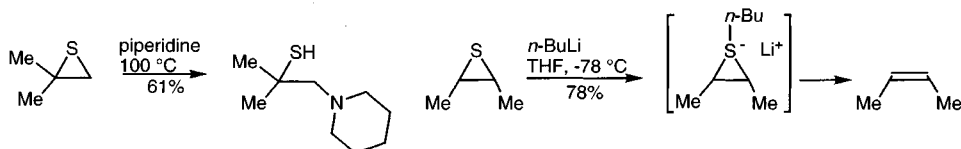
The relative stereochemistry of epoxides can be inverted by equilibration with cyanate anion, as the sequence below shows.²⁸



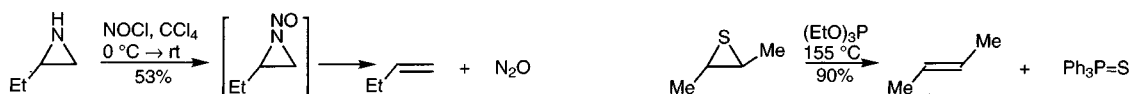
Acid-catalysed opening of aziridines is usually quite rapid, but simple nucleophilic reactions, without acid catalysis, are very slow due to the much poorer leaving ability of negatively charged nitrogen, however *N*-acyl or *N*-sulfonyl aziridines have reactivity similar to epoxides.²⁹ In the nucleophilic ring opening of aziridines with *N*-nosyl (4-nitrophenylsulfonyl) groups, the excellent leaving group ability of the nitrogen and its substituent can lead to loss of regioselectivity.³⁰



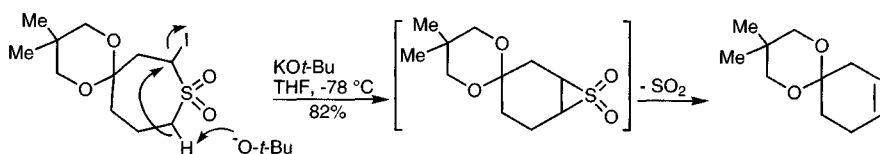
Thiiranes similarly undergo ring opening reactions with nucleophiles such as amines,³¹ but attack at sulfur can also occur with lithium reagents.³²



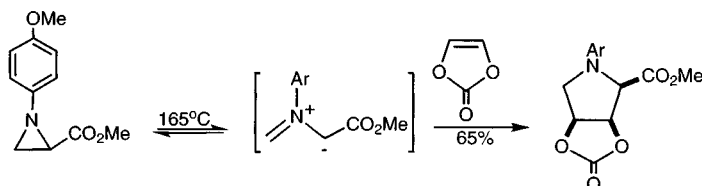
The heteroatom in a three-membered heterocycle can be eliminated *via* various cycloreversion reactions, for example by nitrosation of aziridines,³³ or by the reaction of thiiranes with trivalent phosphorus compounds.



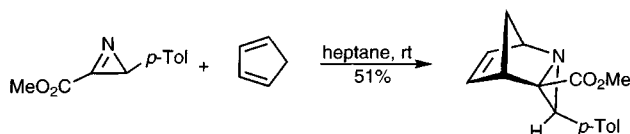
A related elimination of sulfur dioxide occurs during the Ramberg-Bäcklund synthesis³⁴ of alkenes, which generates an episulfone as a transient intermediate, although episulfones are isolable under controlled conditions.³⁵



Substituted derivatives of all three systems are able to undergo a highly stereospecific concerted thermal ring opening, generating ylides which can be utilised (trapped) in 3 + 2 cycloaddition reactions, providing a route to pyrrolidines.³⁶



Azirines with an ester group on the imine carbon, will take part in cycloadditions, with the imine unit as the dienophile, as illustrated below.³⁷

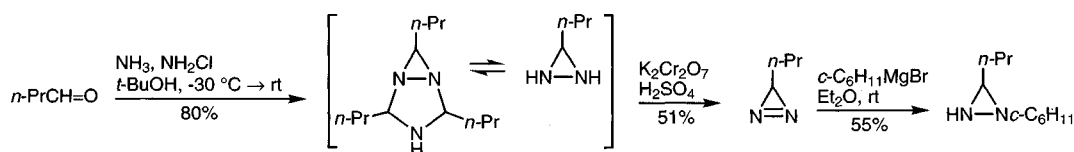


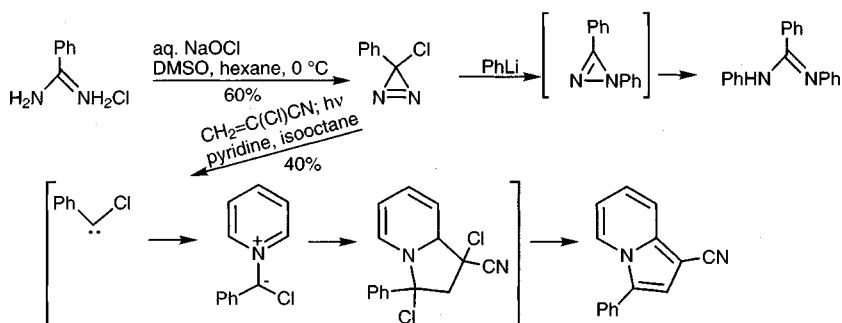
27.2.2 Three-membered rings with two hetero atoms

Diaziridines, diazirines and dioxiranes are all relatively stable isolable systems, although some dioxiranes are explosive.

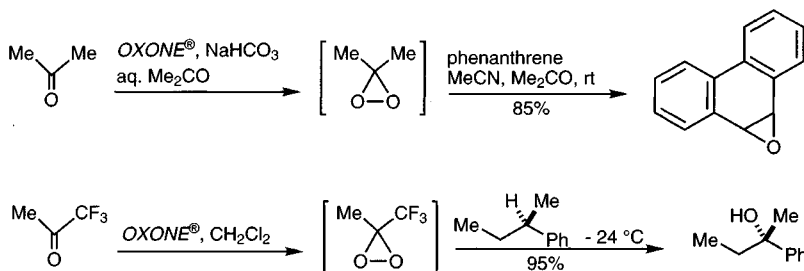


Three-membered rings with two heteroatoms are usually encountered as reagents. Diazirines are useful carbene precursors³⁸ – they are generally more stable than the equivalent isomeric diazo compounds, though they are sometimes explosive in the pure state. They can be prepared by oxidation of diaziridines which in turn are available via the condensation of a ketone or aldehyde with ammonia and chloramine.³⁹ Chlorodiazirines, from the reaction of amidines with hypochlorite, will undergo S_N2 or S_N2' displacement reactions.⁴⁰

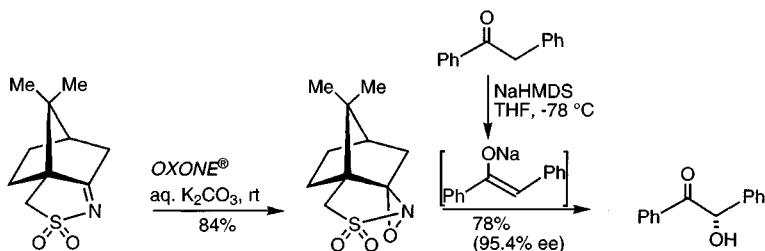




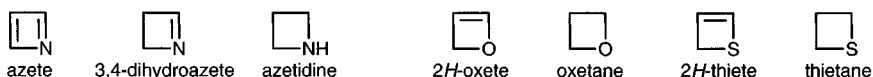
Dimethyldioxirane is a relatively strong oxidant but can show good selectivity: its reactivity is similar to that of a peracid but it has the advantage of producing a neutral byproduct (acetone). Methyl(trifluoromethyl)dioxirane is a more powerful oxidant which can insert oxygen into C–H bonds with retention of configuration, as shown below.⁴¹ Dioxiranes are obtained by reaction of ketones with *OXONE*®.⁴² NOTE: Dioxiranes are explosive and are usually handled in dilute solution.



Oxaziridines are selective oxygen-transfer reagents.⁴³ In particular, the camphor-derived reagent shown below is widely used for enantioselective oxygenation of enolates⁴⁴ and other nucleophiles. Oxaziridines are prepared by oxidation of imines.⁴⁵



27.3 Four-membered rings

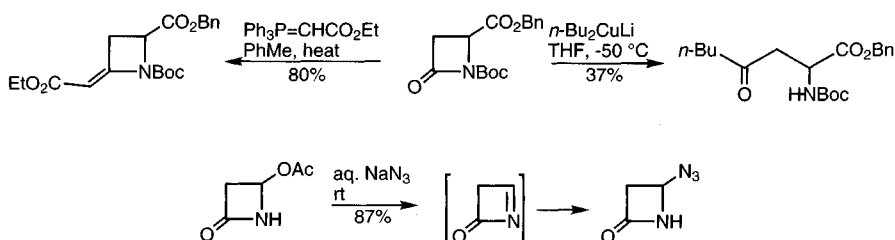


Derivatives of azete are only known as unstable reaction intermediates. Oxetane and azetidene are considerably less reactive than their three-membered counterparts (oxetane reacts with hydroxide anion 10^3 times more slowly than does oxirane), but nonetheless do undergo similar ring opening reactions, for example oxetane reacts

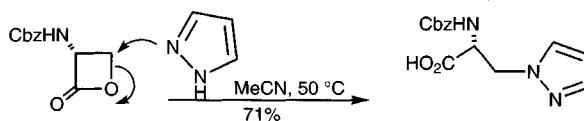
with organolithium reagents,²² in the presence of boron trifluoride, or with cuprates,⁴⁶ and azetidine is opened on heating with concentrated hydrochloric acid.



The most important four-membered system is undoubtedly the β -lactam ring⁴⁷ which is present in, and essential for the biological activity of, the penicillin and cephalosporin antibiotics. β -Lactams are very susceptible to ring-opening *via* attack at the carbonyl carbon – in stark contrast to the five-membered analogues (pyrrolidones) or acyclic amides, which are relatively resistant to nucleophilic attack at carbonyl carbon. In addition, β -lactams are hydrolysed by a specific enzyme, β -lactamase, the production of which is a mechanism by which bacteria become resistant to such antibiotics. Although the β -lactam ring is easily cleaved by nucleophiles, both *N*- and *C*-alkylation (α to carbonyl) can be achieved using bases to deprotonate; it is even possible to carry out Wittig reactions at the ‘amide’ carbonyl without ring-opening.⁴⁸ Substitution of the acetoxy group in a 4-acetoxiazetidinone by nucleophiles is an important synthetic method; the reaction proceeds *via* an imine or an iminium intermediate rather than by direct displacement.⁴⁹

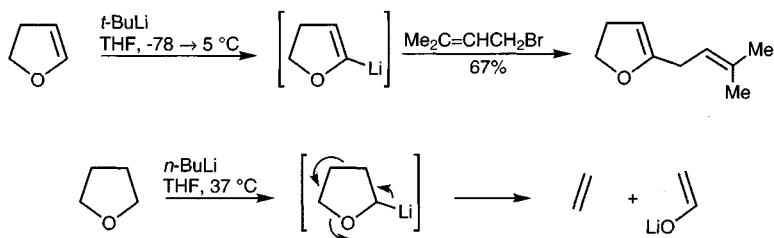


β -Lactones (propiolactones)⁵⁰ too are readily attacked at the carbonyl carbon, for example they are particularly easily hydrolysed, but a second mode of nucleophilic attack – $\text{S}_{\text{N}}2$ displacement of carboxylate *via* attack at C-4 – occurs with many nucleophiles.⁵¹ The example shows the use of a homochiral lactone, available from serine.

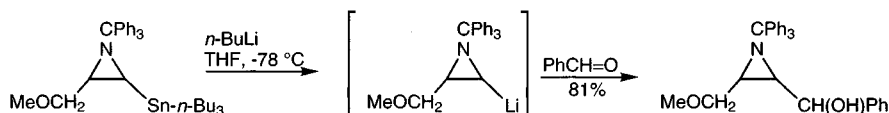


27.4 Metallation

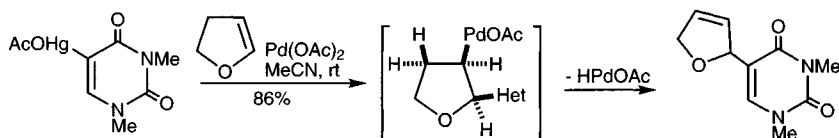
Saturated and mono-unsaturated 5-⁵² and 6-membered rings can be metallated in the same way as their acyclic analogues. In the case of tetrahydrofuran however, warming with *n*-butyllithium produces a lithio-derivative which undergoes a cycloreversion generating ethene and the lithium enolate of ethanal.⁵³ This process represents the most convenient preparation of this enolate but can also be a significant, unwanted side-reaction during lithiation reactions using tetrahydrofuran as solvent.



Three-membered rings have not been metallated directly in the absence of anion-stabilising substituents but simple lithio-derivatives of aziridines have been prepared by exchange from the corresponding stannane.⁵⁴

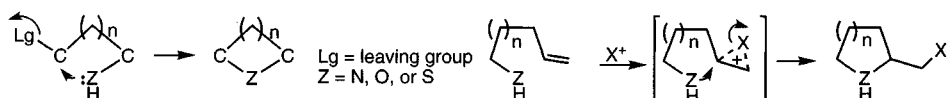


The conformationally restrained, cyclic nature of dihydrofuran (and dihydropyran) leads to an abnormal sequence during a Heck reaction. The addition of the arylpalladium halide occurs normally but rotation cannot occur so instead of syn β -hydride elimination towards the aryl substituent, elimination takes place towards C-4.⁵⁵ In some cases, particularly at higher temperatures, further migration of the double bond occurs.



27.5 Ring synthesis

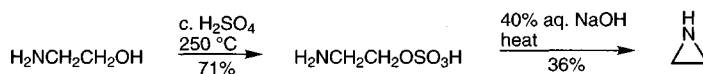
Five- and six-membered saturated rings can be prepared by reduction of the corresponding aromatic compound, but the most general method for making all ring sizes is by cyclisation of an ω -substituted amine, alcohol, or thiol *via* an intramolecular nucleophilic displacement. As an illustration, the rate of cyclisation of ω -halo-amines goes through a minimum at the four-membered ring size; the five and six-membered rings are by far the easiest to make (relative rates: 72(3-membered ring):1(4):6000(5):1000 (6)).⁵⁶ A factor which influences the rate of 3-*exo-tet* cyclisations is the degree of substitution at the carbon carrying the heteroatom: increasing substitution increases the rate of cyclisation, because in the small ring product there is some relief of steric crowding for the substituents compared with acyclic starting material.⁵⁷



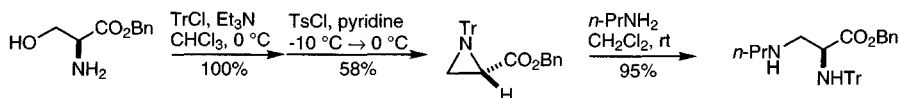
Related cyclisations involving hetero atom attachment to an alkene *via* π -complexes with cations such as Br^+ , I^+ , Hg^+ , and Pd^+ , are useful methods because they give products with functionalised side-chains for further transformations.

27.5.1 Saturated nitrogen heterocycles

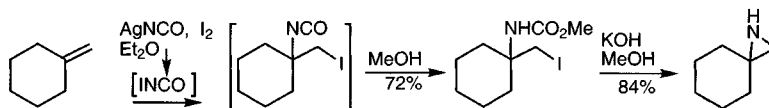
There are three main routes to aziridines: they can be prepared by alkali-catalysed cyclisation of 2-haloamines or of a 2-hydroxyamine sulfonate ester, as illustrated,⁵⁸ or by additions to alkenes or imines.



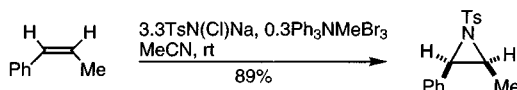
Various homochiral aziridines can be easily obtained from serine;⁵⁹ such substances can be transformed into a range of polyfunctional homochiral intermediates and products.



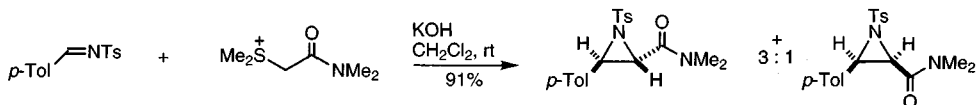
Aziridines can be obtained from alkenes using iodine isocyanate⁶⁰ or iodine azide.⁶¹ The product from the latter reaction can be converted into the aziridine *via* reduction, or into an azirine *via* elimination of hydrogen iodide and pyrolysis.⁶²



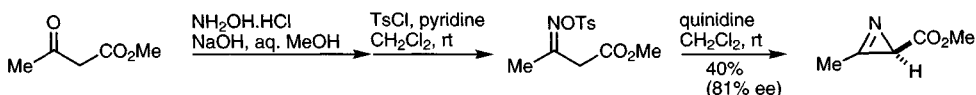
N-Tosylaziridines can be obtained directly from alkenes by reaction with Chloramine T, as shown below.⁶³



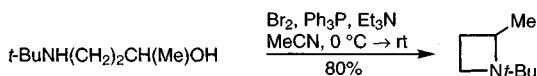
Addition to imines is the third obvious way in which to construct an aziridine, as illustrated below.⁶⁴



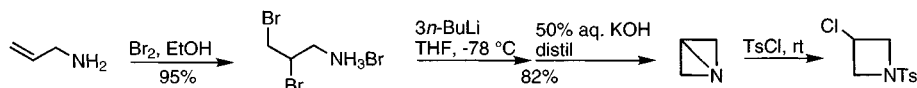
Azirines can be synthesised, enantioselectively if required using a natural alkaloid as base, from the *O*-tosyl derivatives of the oximes of 1,3-keto esters; in this synthesis the carbon is the nucleophilic centre and it is the nitrogen which is attacked with departure of tosylate.⁶⁵



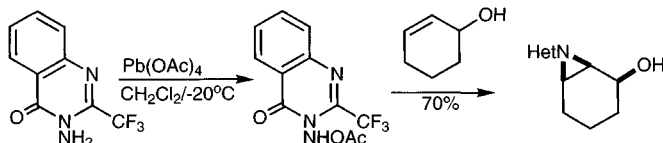
Azetidines can be obtained by cyclisations of 3-halo-amines, but yields are generally not as good as those for the formation of aziridines. The generation of the bifunctional precursors for cyclisation to azetidines has been achieved in a number of ways.⁶⁶



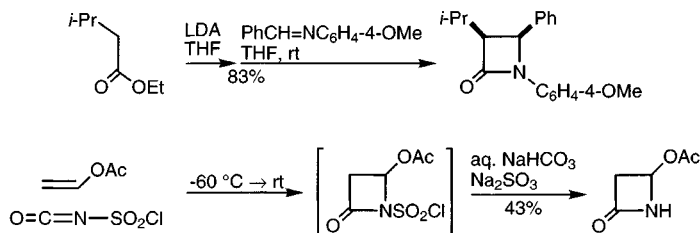
Syntheses of 1-azabicyclo[1.1.0]butane which contains both a four-membered and two three-membered nitrogen-containing rings (!) follow the general route described above.⁶⁷ As one would anticipate, ring opening reactions, one of which is illustrated, lead to products with an azetidine unit, rather than an aziridine unit.



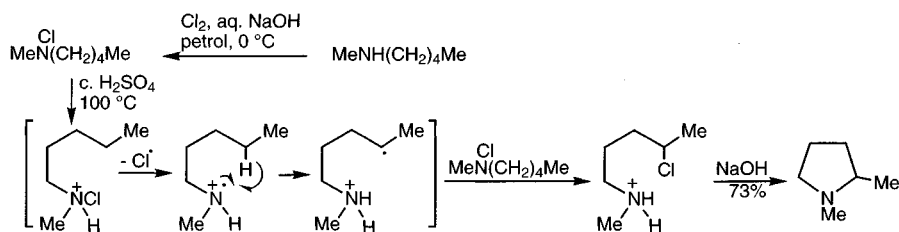
Aziridines can also be prepared by addition of nitrenes to alkenes,⁶⁸ or by the use of nitrogen-transfer agents analogous to epoxidising agents.⁶⁹



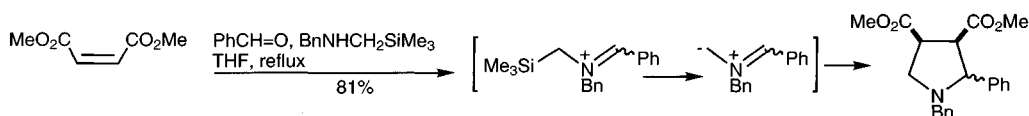
Many methods have been developed for β -lactam synthesis,^{47,70} including cyclisation of the corresponding amino acids. The most widely used methods are two-component couplings^{38,71} which occur *via* concerted cycloaddition or two-step mechanisms.



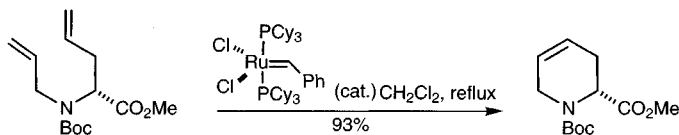
A very neat method for the synthesis of pyrrolidines does not require a difunctionalised starting material, but relies on the Hofmann-Löffler-Freytag reaction⁷² – which is a radical process – to introduce the second functional group. The six-membered size of the cyclic transition state leads selectively to a 1,4-haloamine, and thence to pyrrolidines.



The cycloaddition of azomethine ylides to alkenes is another elegant entry to pyrrolidines. The required 1,3-dipoles can be produced in a number of ways; the example below is one of the most simple wherein a trimethylsilylmethylamine, an aldehyde and the alkene are simply heated in tetrahydrofuran.⁷³

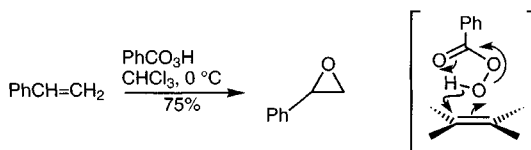


A particularly useful general method for the synthesis of 5- to 7-membered partially unsaturated heterocycles is the Grubbs olefin metathesis applied to acyclic dialkenyl amines, as illustrated by the tetrahydropyridine synthesis shown below.⁷⁴

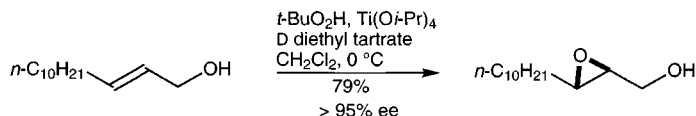


27.5.2 Saturated oxygen heterocycles

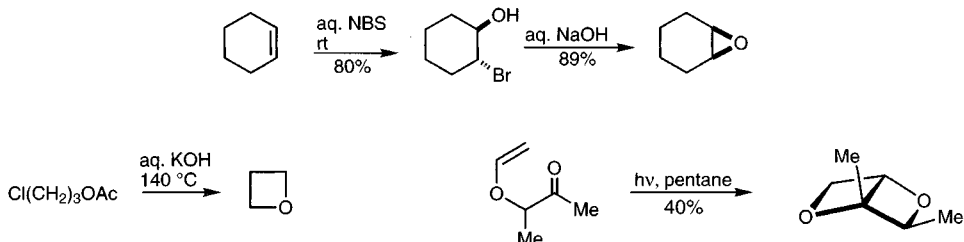
The most widely used method for the preparation of epoxides involves oxidation of an alkene by a peracid,⁷⁵ *via* a direct one-step transfer of an oxygen atom. More highly (alkyl) substituted alkenes react fastest showing that electronic effects are more important than steric effects in this reaction. Steric effects do, however, control the facial selectivity of epoxidation; conversely hydrogen-bonding groups such as OH and NH can direct the reaction to the *syn* face.



Several other direct oxygen-transfer reagents have been developed of which by far the most important is Sharpless' reagent – a mixture of a hydroperoxide with titanium isopropoxide and an alkyl tartrate.⁷⁶ The structure of the reagent is complex but it reacts readily with alkenes containing polar groups, for example allylic alcohols, which can coordinate the metal. The most important feature of this process is that when homochiral tartrate esters are used, a highly ordered asymmetric reactive site results, leading in turn to high optical induction in the product.



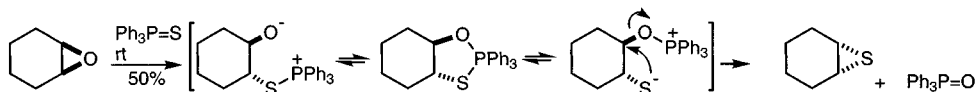
Epoxides and oxetanes can also be prepared by cyclisation of 1,2- (halohydrins) and 1,3-halo-alcohols.⁷⁷



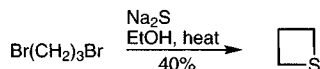
Oxetanes have often been prepared by the *Paterno-Büchi reaction*⁷⁸ in which a compound containing a carbon-carbon double bond cycloadds to an aldehyde or ketone under the influence of light.⁷⁹

27.5.3 Saturated sulfur heterocycles

Thiiranes can be prepared by cyclisation of 2-halo-thiols but the most common method is *via* reaction of an epoxide with thiocyanate⁸⁰ (cf. section 27.2), thiourea,⁸¹ a phosphine sulfide, or with dimethylthioformamide.⁸²



Thietanes, tetrahydrothiophenes and tetrahydrothiapyrans can all be prepared by the reaction of the appropriate 1, ω -dihalide with sulfide anion.



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