Non-Aromatic Heterocyclic Systems

The chemistry of small, strained heterocyclic molecules will be discussed. The course will cover 3- and 4-membered ring systems containing one or more heteroatoms. Synthetic strategies will be outlined for each compound class and illustrated with selected examples from the literature. Examples will include key routes into beta-lactams and multi-ring heterocyclic systems.

1. Hypertensive Molecules (Strain)

2. 3-Membered rings containing one heteroatom

2.1. Epoxides

2.1.1. Preparation

(i) Olefin and Peracid
(ii) Sulphur Ylides
(iii) Cyclisation of Halogenohydrins etc.
(iv) Sharpless Enantioselective Epoxidation of Allylic Alcohols
(v) Jacobsen-Katjuki Epoxidation

2.2. Aziridines

2.2.1. Preparation

(i) (1a) From epoxides
(ii) (1b) From azido mesylates
(iii) From olefins and iodine isocyanate
(iv) Via an azide

2.3. Thioepoxides (Thiiranes)

2.3.1. Preparation

(i) Halohydrin Method
(ii) From Sulphur Ylides
(iii) From epoxides

2.4. Reactions of Epoxides and Aziridines

(i) Ring opening to relieve strain
(ii) Ring expansion reactions
(iii) Intramolecular cyclisation via ring opening

2.5. 3-Membered Rings containing one heteroatom plus unsaturation
2.6. 3-Membered Rings containing more than one heteroatom

3. 4-Membered Rings Containing One Heteroatom

3.1. Preparation

(i) Halohydrin Method
(ii) Paterno-Büchi Reaction

3.1.1. 4-Membered Rings containing one heteroatom plus unsaturation

3.1.2. 4-Membered Rings containing more than one heteroatom

3.2. ß-Lactam Antibiotics

3.2.1. Synthesis of ß-Lactam

(1) Cyclisation of ß-amino acids
(2) π2s + π2a cycloaddition
  (i) ketene plus imine
  (ii) isocyanates
  (iii) haloamide cyclisation
  (iv) ring expansion reaction
  (v) ring contraction reaction (Wolff-Rearrangement)

3.2.2. Conversion of Penicillins into Cephalosporins

(i) Oxidation plus 2,3-sigmatropic shift
(ii) Sulfoxide stereochemistry
(iii) Stability towards base
(iv) Stability towards acid

4. **Supported Reagents** (if time allows)

(i) Epoxidation catalysts

5. **ß-Lactam Total Syntheses** (if time allows)

(i) Selected examples

Course Summary

(i) To introduce general aspects of reactivity associated with small non-aromatic heterocycles
(ii) To present synthetic strategies and appropriate reagents for the synthesis of 3-membered ring systems
(iii) To present synthetic strategies and appropriate reagents for the synthesis of 4-membered ring systems
(iv) To provide examples which demonstrate the reactivity of 3- and 4-membered non-aromatic rings containing at least one heteroatom
(v) To introduce and discuss key elements of the synthesis and reactivity of beta lactams
(vi) To exemplify transformations of beta-lactams to cephalosporins
(vii) To have been introduced to examples in which synthesis and reactivity of small ring heterocycles is aided through the use polymer supports

Aim of the course

After this course you are expected:

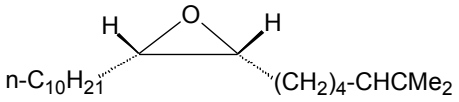
(iv) To explain with examples the special relevance of ring strain in the synthesis and reactivity of small non-aromatic heterocycles.
(v) To identify and predict syntheses in which steric and stereoelectronic effects allow the stereoselective synthesis of 3-membered rings as exemplified in cases involving a steroid skeleton.
(vi) To apply at least 3 synthetic routes (incl. mechanisms)and the corresponding reagents to the synthesis of nitrogen, oxygen and sulphur 3- and 4-membered non-aromatic heterocycles.
(vii) To apply at least 3 synthetic routes (incl. mechanisms) and the corresponding reagents to the synthesis of beta lactams
(viii) To illustrate three synthetic approaches used in the synthesis of 3- and 4-membered non-aromatic heterocycles containing two or more N, O, or S heteroatoms.
(ix) To discuss possible advantages of solid-phase chemistry in the synthesis of strained non-aromatic heterocycles.

Non-Aromatic Heterocyclic Systems

(a) *Small Ring Heterocycles*

(b) *Alkaloids*

(c) *ß-Lactams*

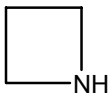
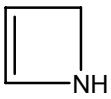
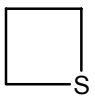
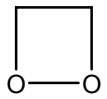


disparlure sex attractant for gypsy moth

1. Hypertensive Molecules (Strain)

2. 3-Membered rings containing one heteroatom

Nomenclature

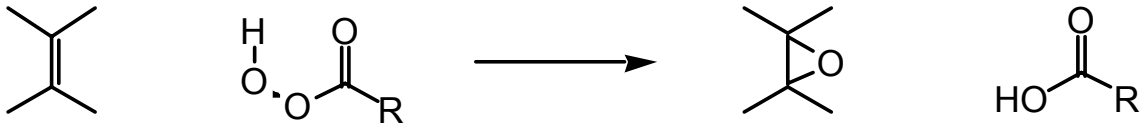
3 (t**ri**)	3 (t**ri**)	4 (t**et**ra)	4 (t**et**ra)	5 (t**et**ra)	5 (t**et**ra)
ir-ane (-) ir-dine (- + N)	ir-ene (=) ir-ine (= + N)	et-ane (-) et-idine (- + N)	et ene(=) et ene(= + N)	ol-ane (-) ol-idine (- + N)	ol ene (=) ol ene(= + N)
 oxirane	 oxirene	 azetidine	 azetene		
 aziridine		 thietane			
 thiirane		 dioxetane			
az = nitrogen		ox = oxygen		thi = sulphur	

2.1. Epoxides

- most common
- easy to prepare
- naturally occuring
- very useful synthetic intermediates

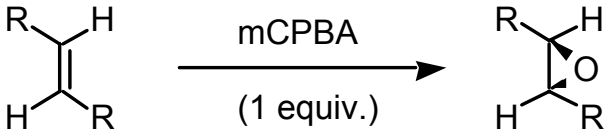
2.1.1. Preparation

(1) Olefin and Peracid



Mechanism

m-chloroperbenzoic acid (mCPBA) is the most commonly used since it is:

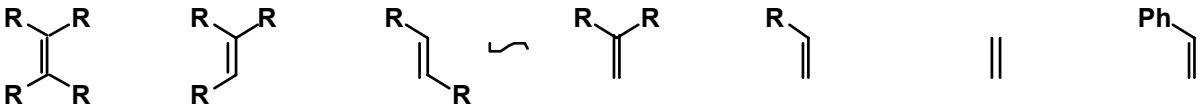


- commercially available
- crystalline
- easy to purify
- stable when pure

Since epoxides are acid sensitive the reaction may require the addition of a buffer to control pH. Solid $NaHCO_3$ is often used (alternatively $PhCN + H_2O_2$)

Since the reaction is an electrophilic addition the **most** electron rich olefins react first (subject to steric factors).

The order of reactivity



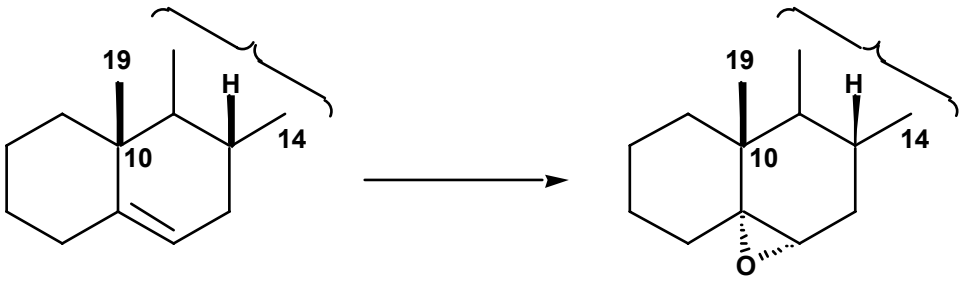
This of course results from the inductive effect of the alkyl groups.

Example: Limonene

Note ! The reaction is stereospecific. The olefin geometry is always preserved.

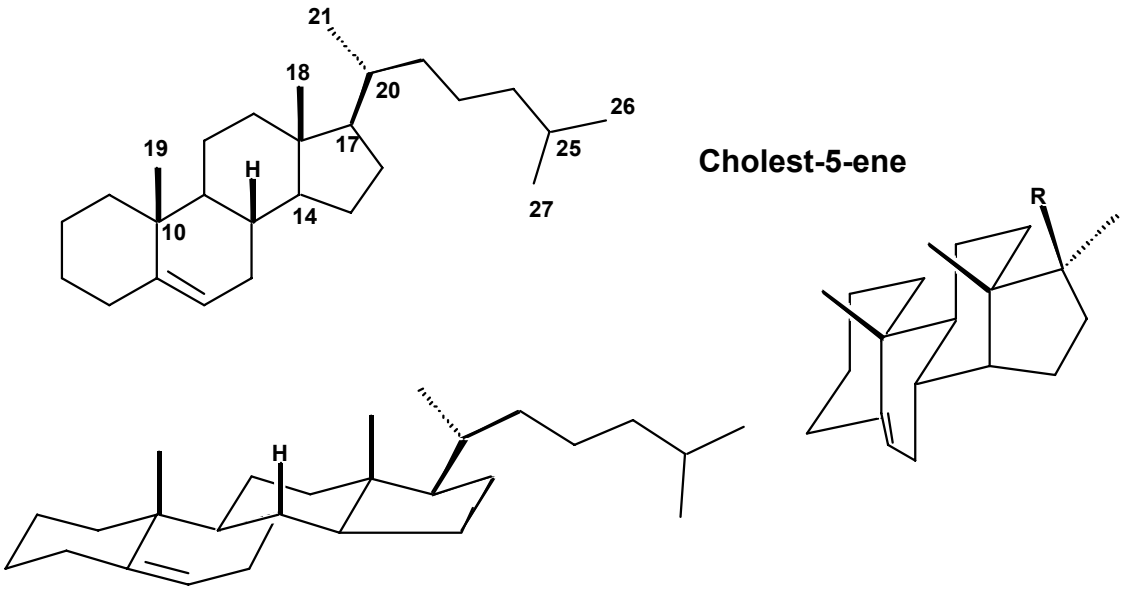
The peracid approaches the olefin from the less hindered face (STERIC APPROACH CONTROL)

This is best illustrated by an example from steroid chemistry:



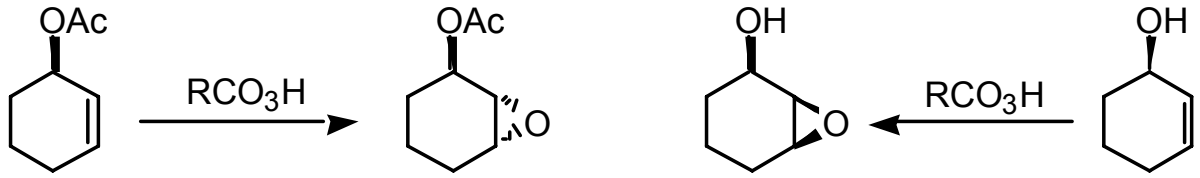
major isomer

The angular 19ß methyl group shields the top face of the steroid molecule and directs the peracid to the α face.

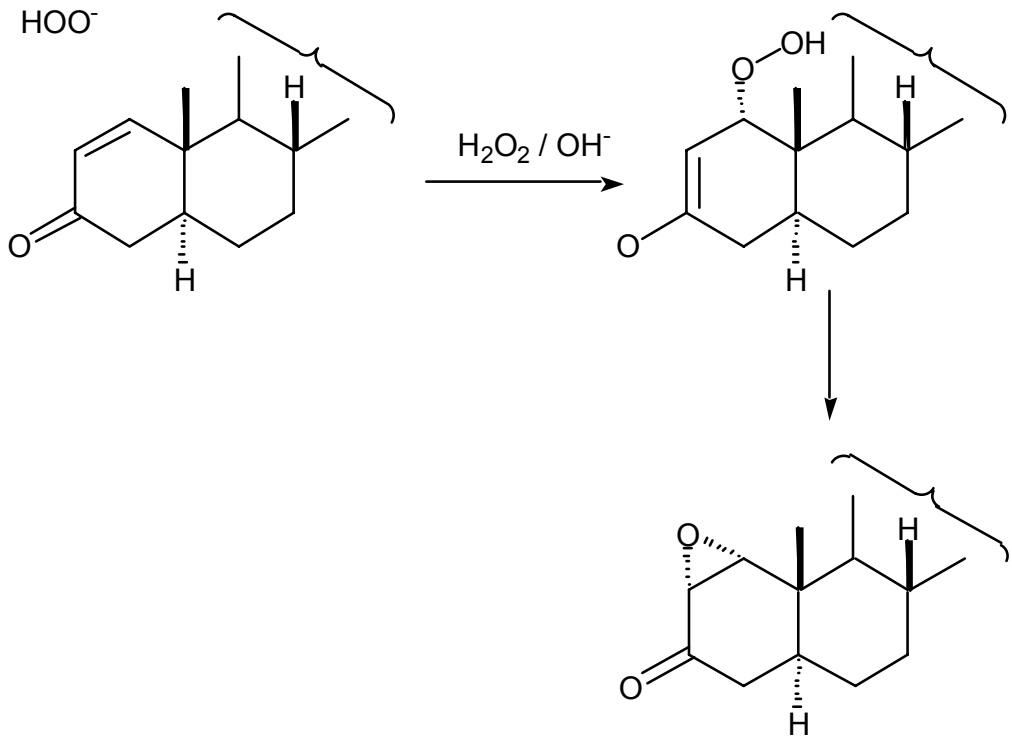


Attack from the **more** hindered face can result if NEIGHBOURING GROUP PARTICIPATION is possible:

In this case the hydroxyl group is an anchor and forms a hydrogen bond to the incoming peracid!



Electron deficient olefins can be converted into epoxides using basic hydrogen peroxide. Once again the reagent approaches from the less hindered α face

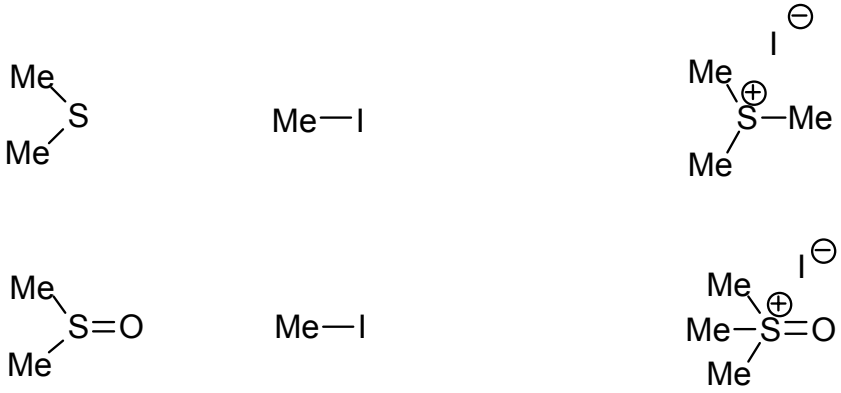


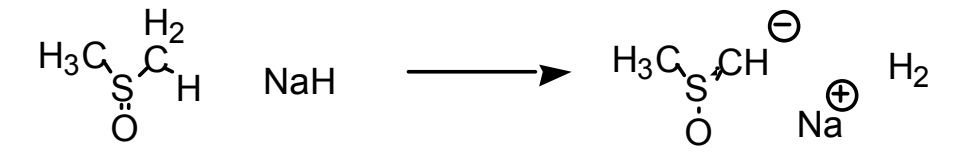
(2) Sulphur Ylides

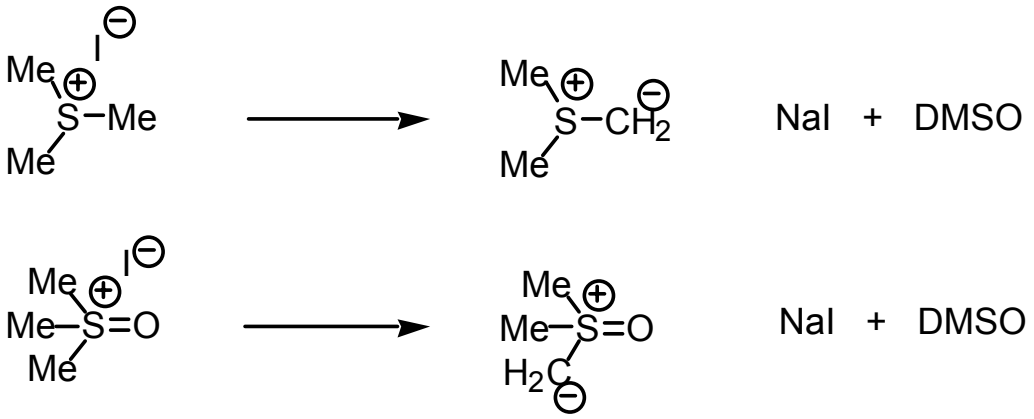
Both dimethyl sulfide and dimethylsulphoxide react with iodide to give salts which on reaction with a strong base give sulphur ylides.

Preparation

The base used is “dimsyl sodium” prepared by the reaction of DMSO with NaH

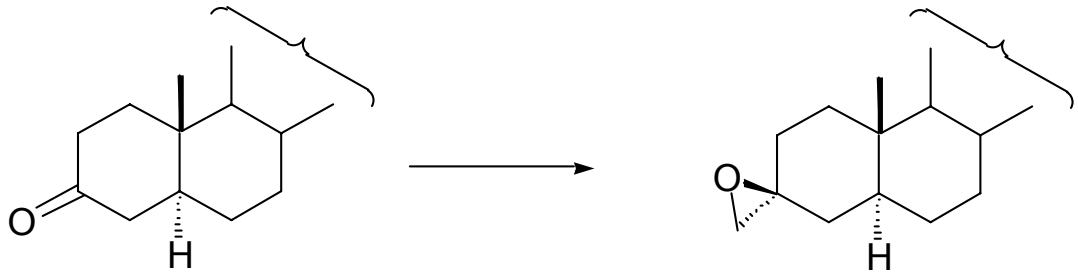




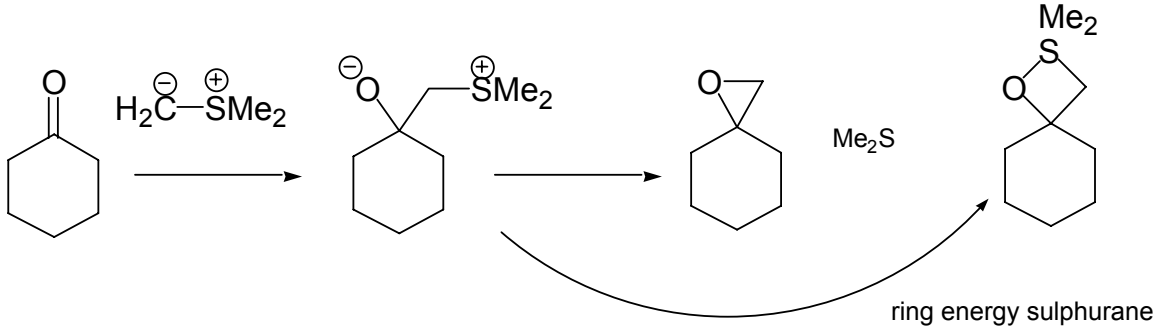


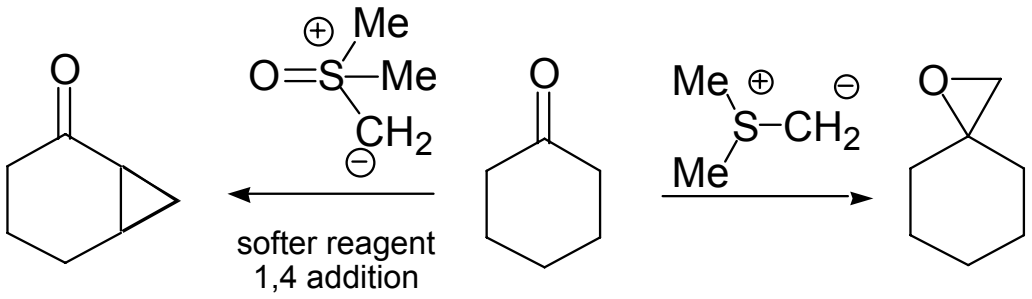
Both sulphur ylides react with ketones to give epoxides:

Mechanism (compare to phosphorus ylides; Wittig Reaction)

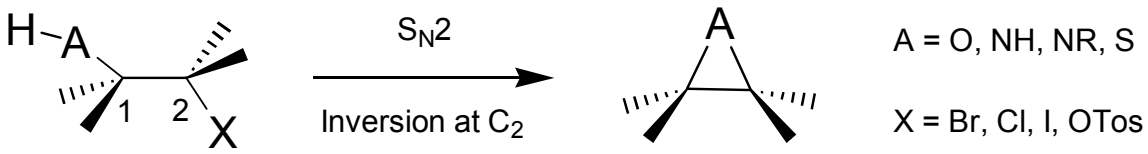


The two reagents differ in their behaviour towards α,ß-usaturated ketones

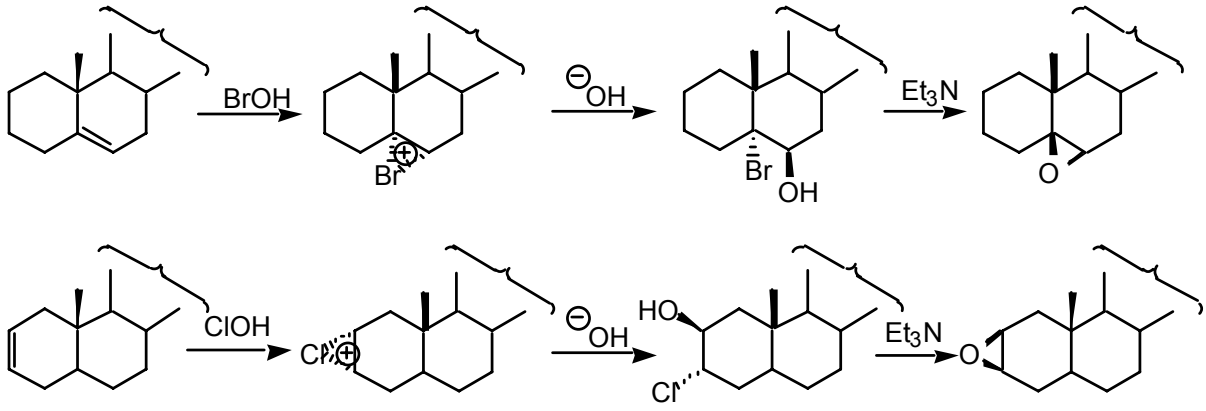




(3) Cyclisation of Halogenohydrins etc.



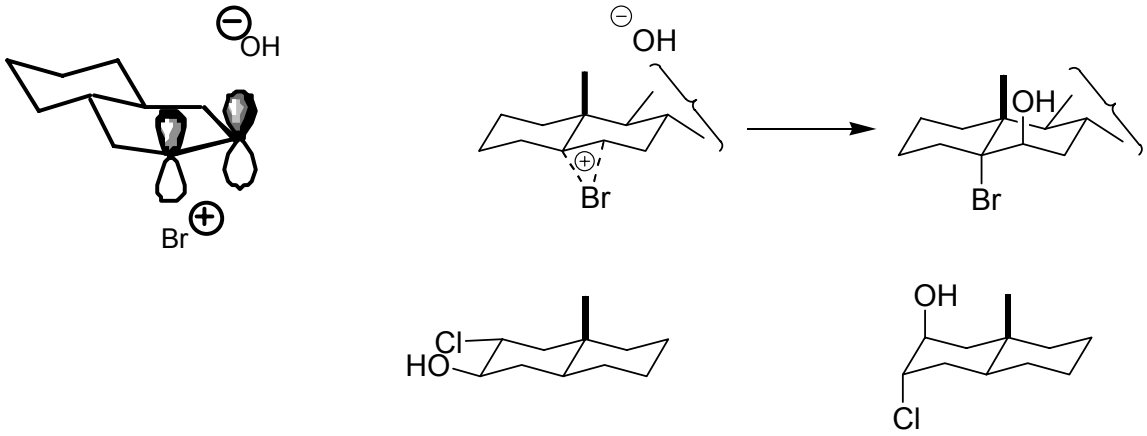
This reaction can be used to generate the opposite stereochemistry from peracids



Note

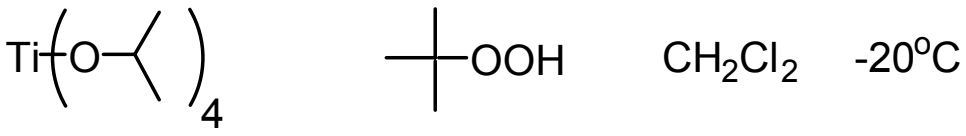
(i) The bromonium cation approaches from the less hindered α face.

(ii) The hydroxide anion attacks to give the **trans diaxial** product. This choice ensures maximum orbital overlap in the transition state for bromonium ion opening, i.e. STEREOELECTRONIC CONTROL.



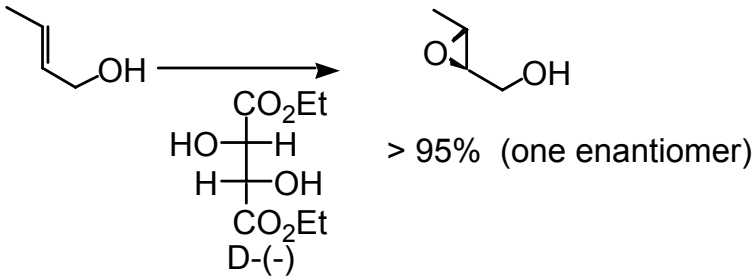
relative rates: 1 1000

(4) Sharpless Enantioselective Epoxidation of Allylic Alcohols

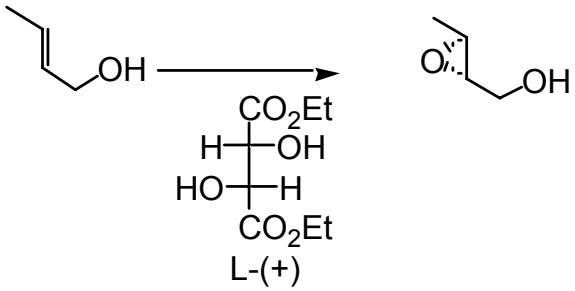


It took ten years to develop this methodology (MIT)

(i) Prochiral allylic alcohols

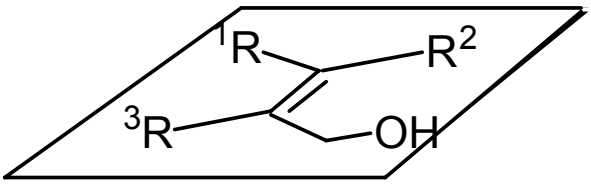


> 95% (one enantiomer)



D-(-)-diethyl tartrate

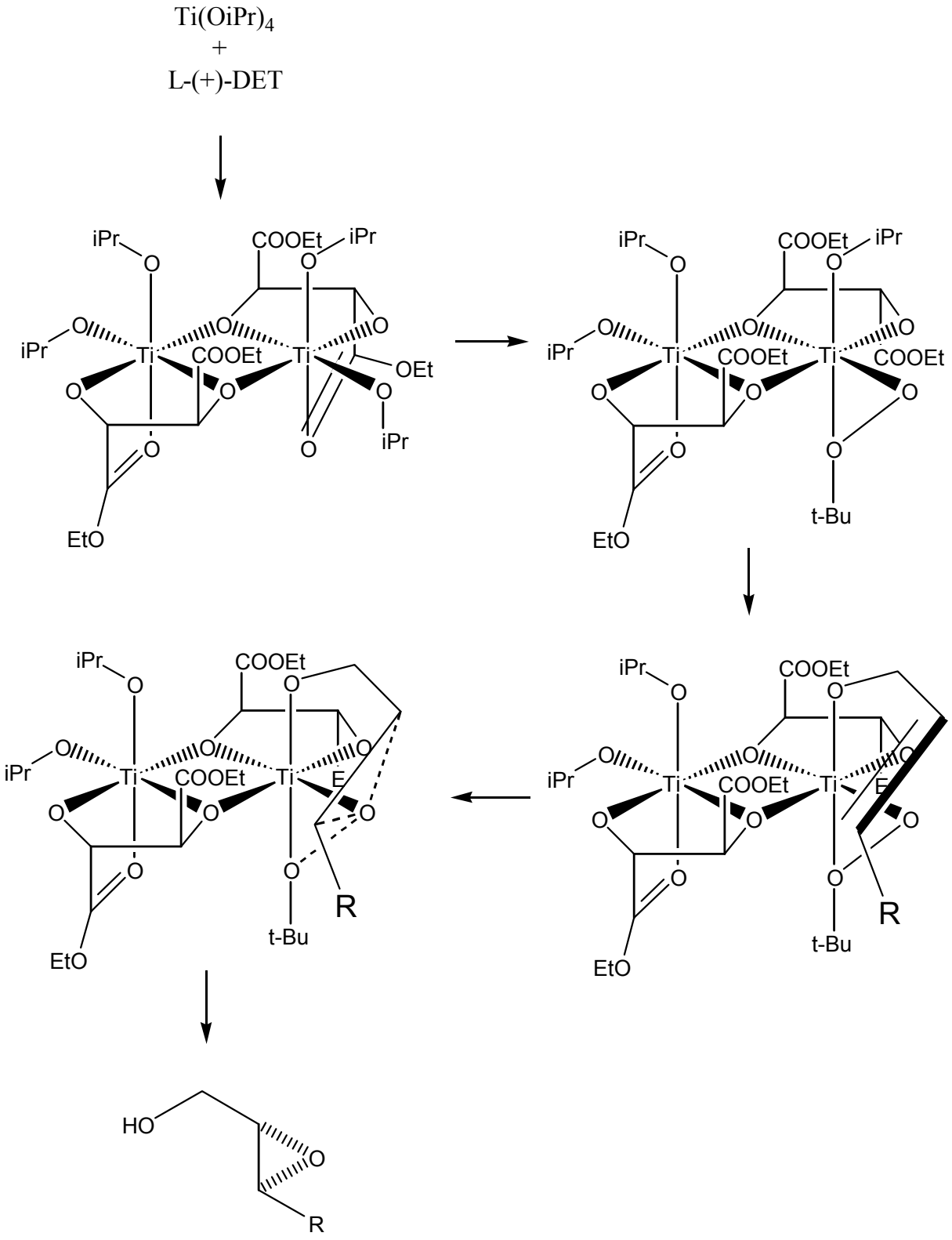
"O"

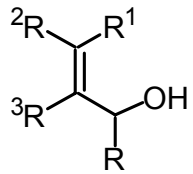


"O"

L-(+)-diethyl tartrate

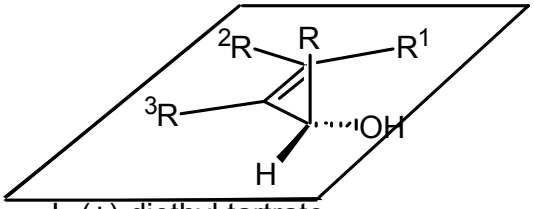
Further examples: reaction improved by using 3Å molecular sieve (use less isopropoxide!)


Ti(OiPr)4
+
L-(+)-DET
iPr
COOEt
OEt
EtO
t-Bu
R
HO



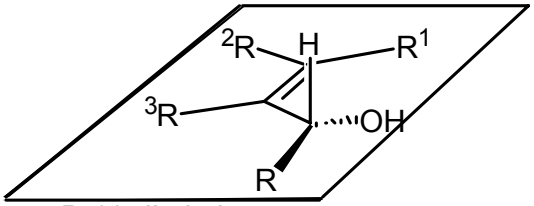
Racemic

Reacts faster with

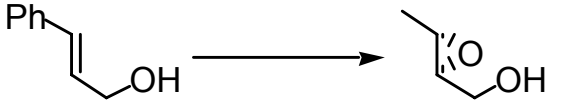


L-(+)-diethyl tartrate

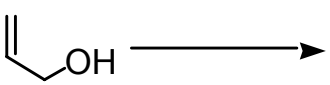
Reacts faster with



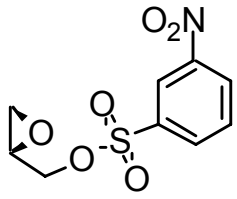
D-(-)-diethyl tartrate



92% ee

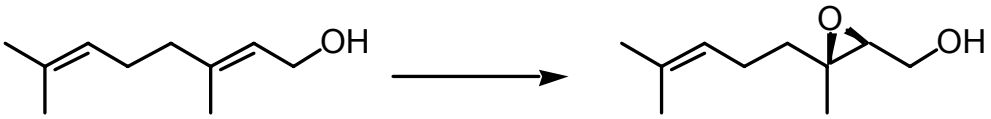


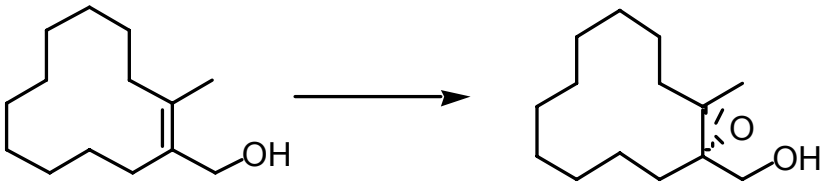
88-92% ee



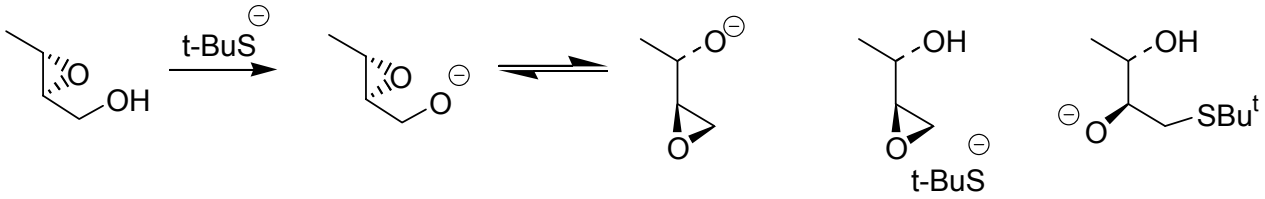
crystalline - recrystallised to > 99% ee

Selective for allylic alcohols

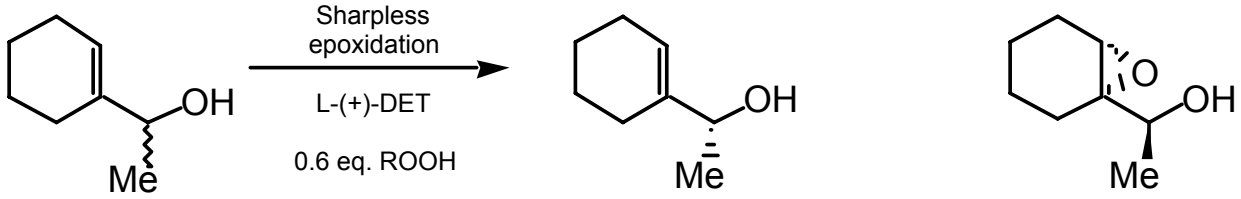




Payne rearrangement

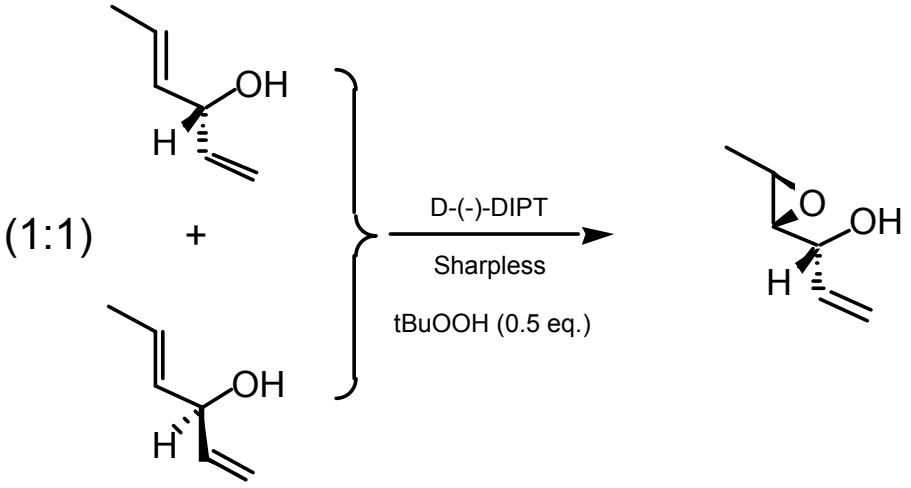


Kinetic Resolution



Racemic

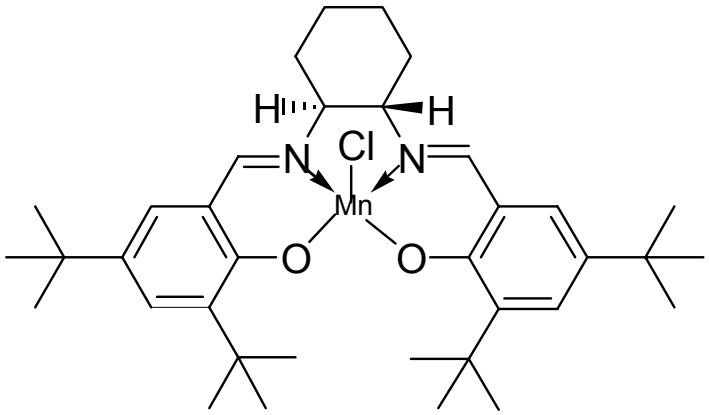
> 96% ee



- disubstituted alkene more reactive
- kinetic resolution

Jacobsen-Katjuki Epoxidation

Both were Sharpless' coworkers. They discovered this method independently.



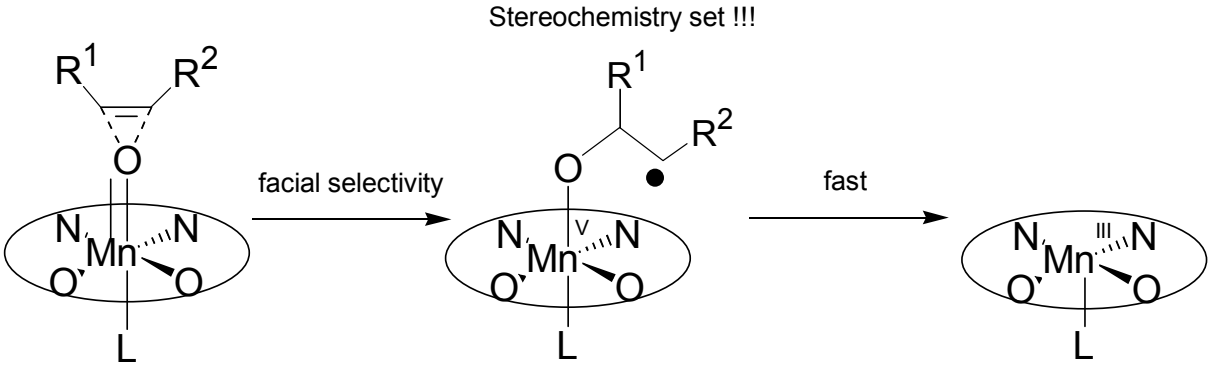
2 mol%

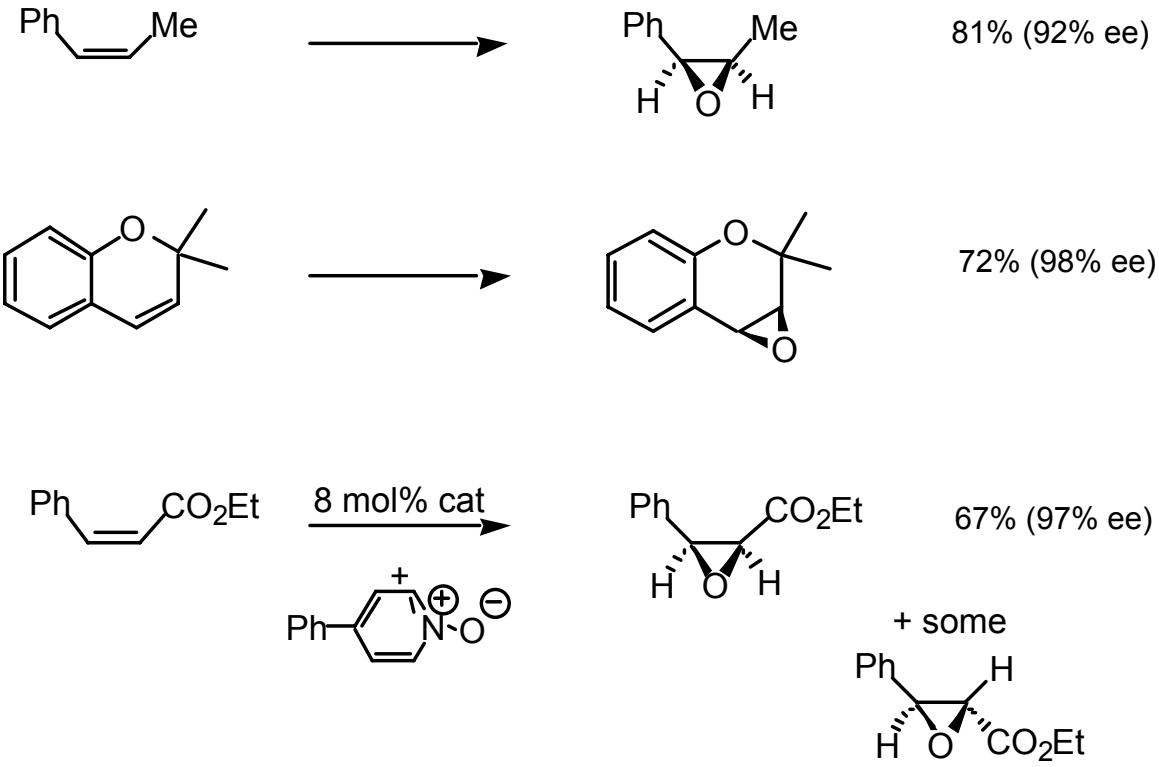
NaOCl bleach | Na_2HPO_4 buffer

pH 11.3
+
alkene in CH_2Cl_2

4^oC / 2-phase system

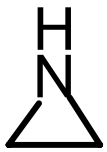
Mechanism via Mn(V):

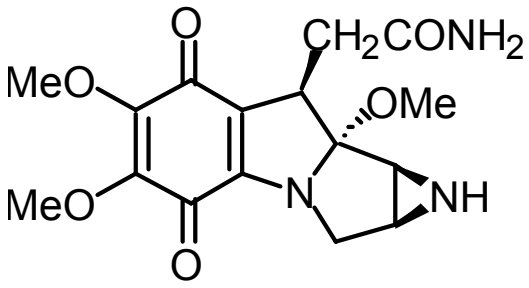



Ph
Me
81% (92% ee)
O
72% (98% ee)
Ph
CO2Et
8 mol% cat
+
Ph
N
O
67% (97% ee)
+ some
Ph
H
H
O
CO2Et

2.2. Aziridines

The nitrogen analogues of epoxides. They do crop up in natural products.



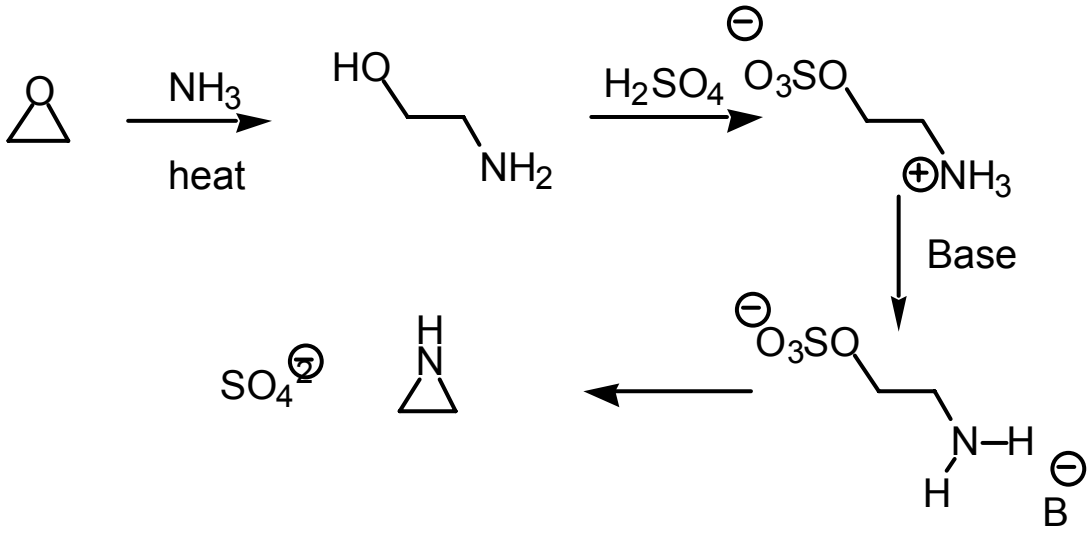


Mitomycin A

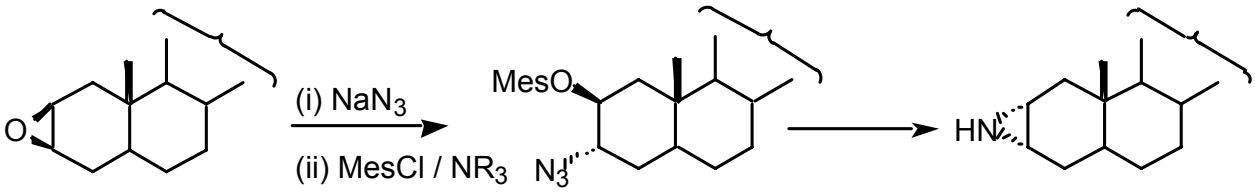
purple antitumor antibiotic from Streptomyces Verticillatus

2.2.1. Preparation

(1a) From epoxides

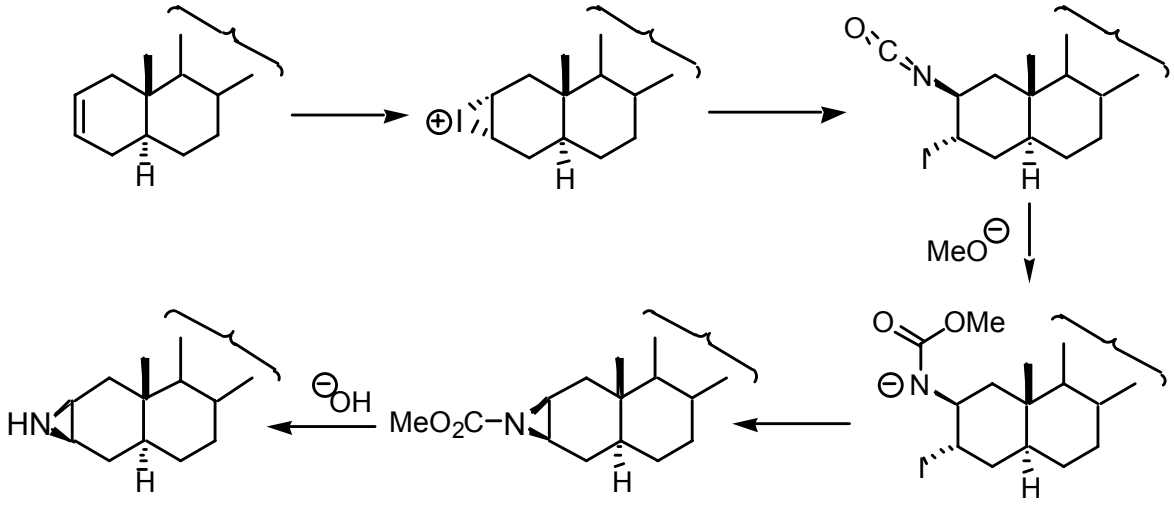


(1b) From azido mesylates



(2) From olefins and iodine isocyanate

INCO

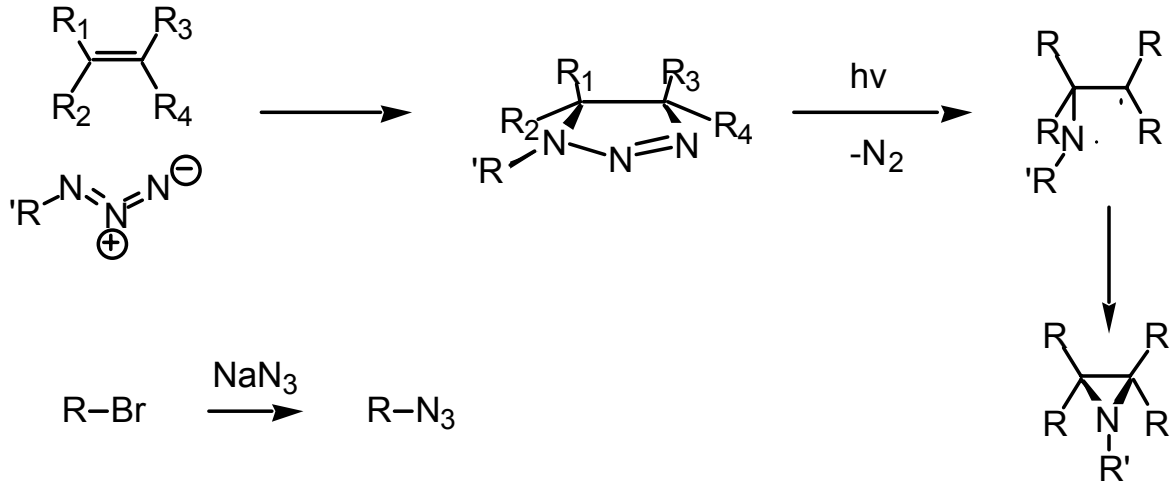


Once again STERIC APPROACH CONTROL

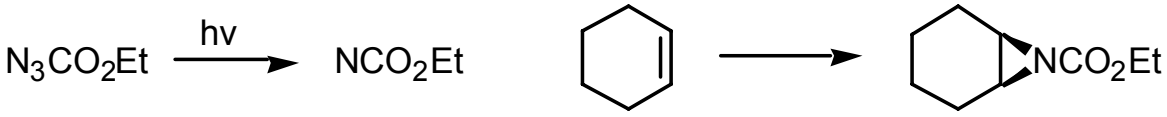
α face attack / trans diaxial ring opening / S_N2 / hydrolysis of carbamate

(3) Via an azide

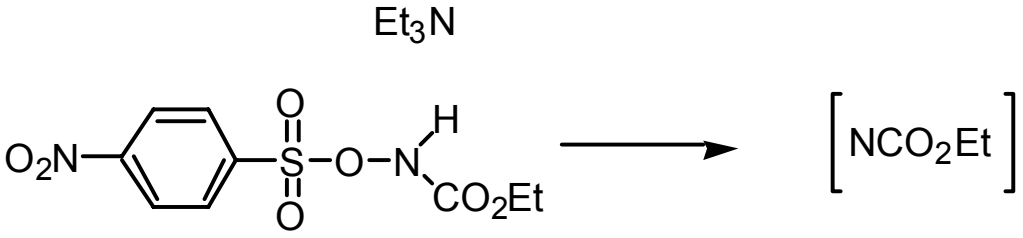
Azides are 1,3-dipoles and can cycloadd to olefins. Photolysis of the triazoline adducts leads to loss of nitrogen and aziridine formation.



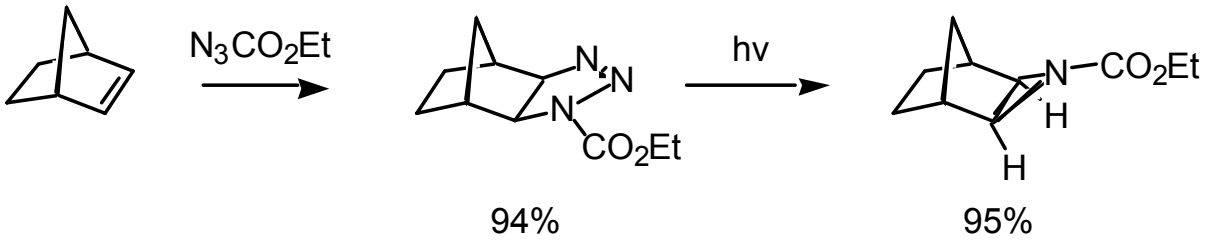
Azides may be photolysed to nitrenes e.g.



alternatively:



or via triazoline and subsequent cleavage:

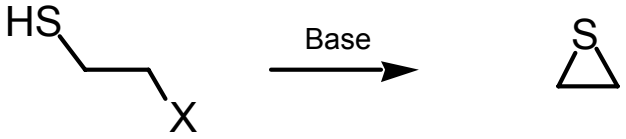


94% 95%

2.3. Thioepoxides (Thiiranes)

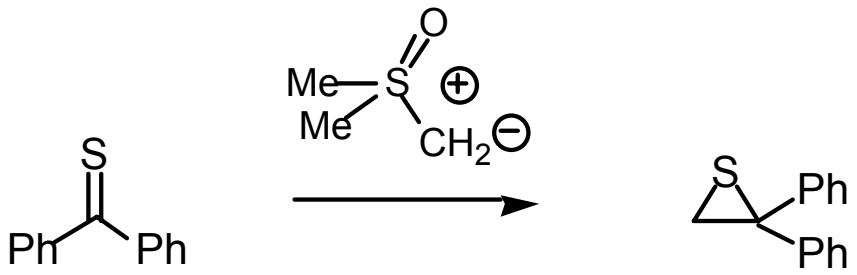
2.3.1. Preparation

(i)

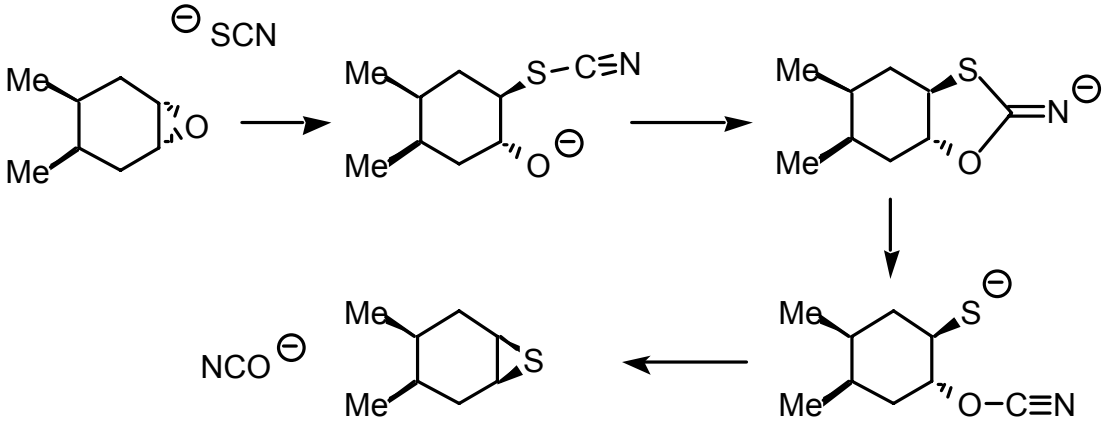


Halohydrin method

(ii)



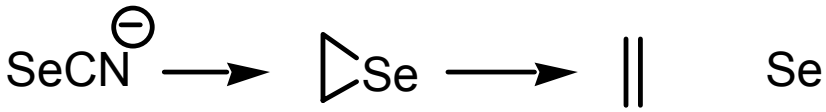
(iii) From epoxides



The driving force is the higher stability of the CNO anion.

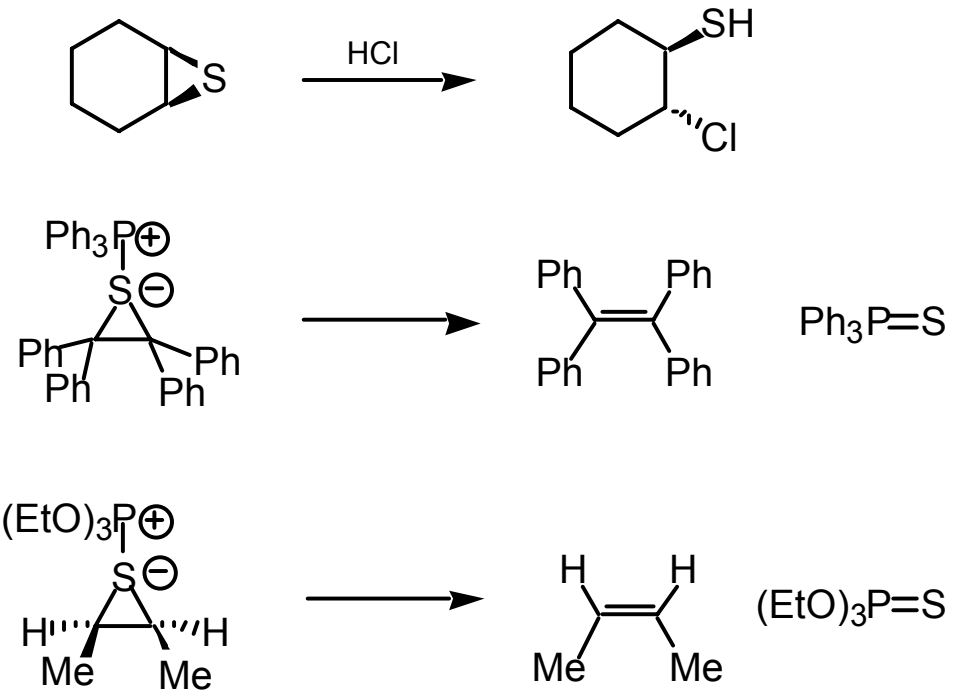
Note
(1) Reversal of stereochemistry

(2) Use of :



hence deoxygenation of epoxides!

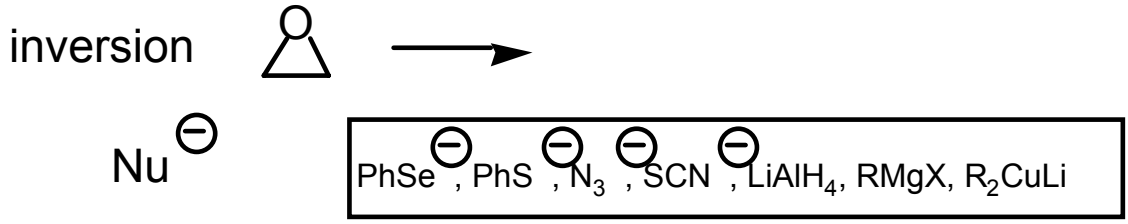
Thioepoxides may be desulphurised by reaction with triphenylphosphine in a stereospecific reaction.



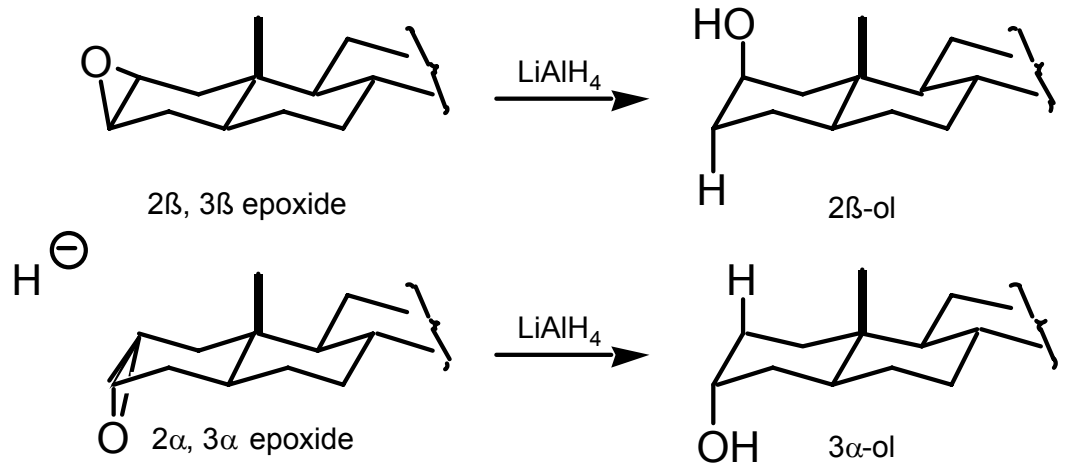
2.4. Reactions of Epoxides and Aziridines

(i) Only one: ring opening to relieve strain

(a) under neutral or alkaline conditions by good nucleophiles, S_N2 with inversion.



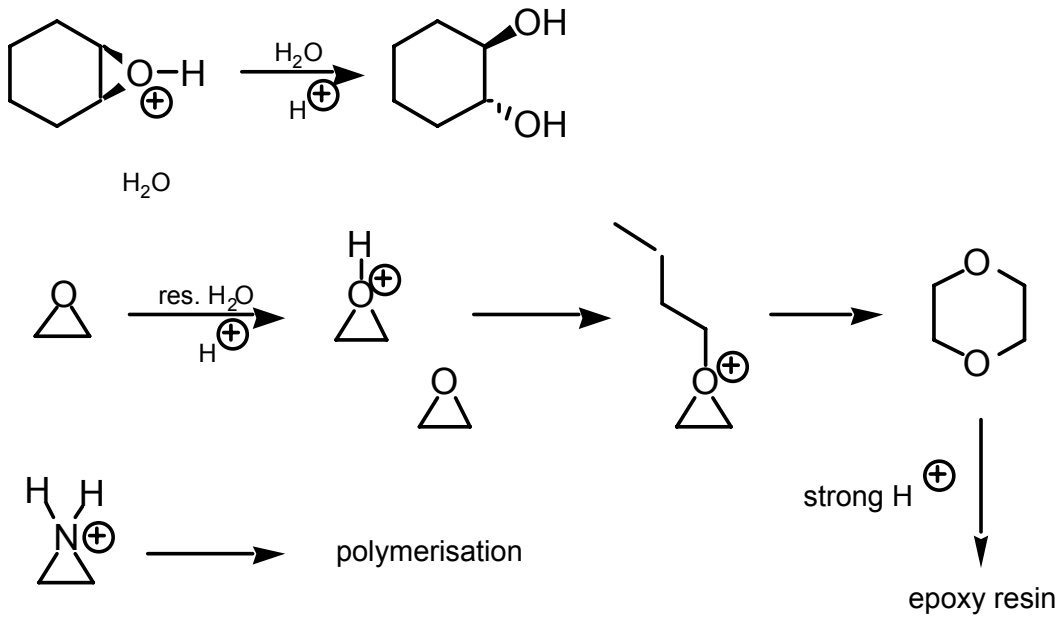
trans diaxial opening maximises orbital overlap and controls regioselectivity



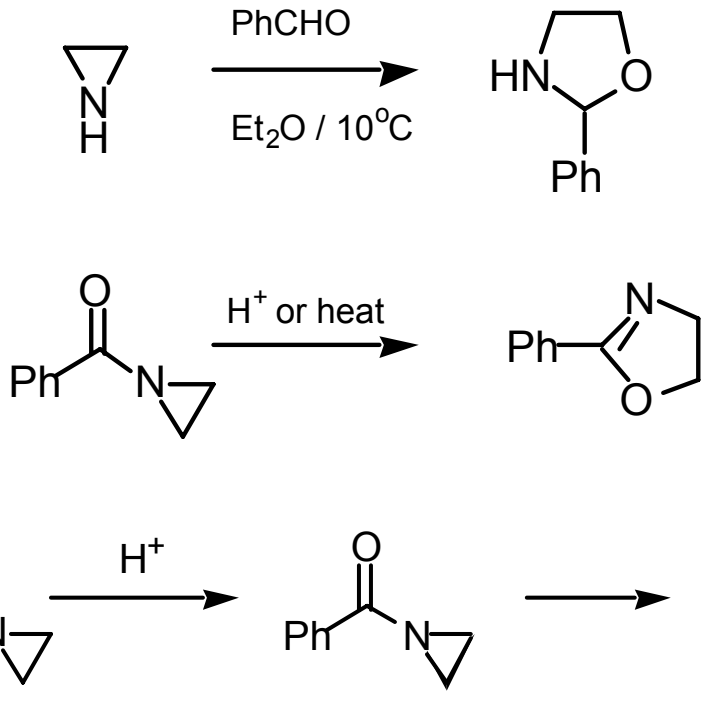
3α-ol formation in spite of the 1,3-diaxial interaction with the 19ß group.

trans-diaxial ring-opening once again.

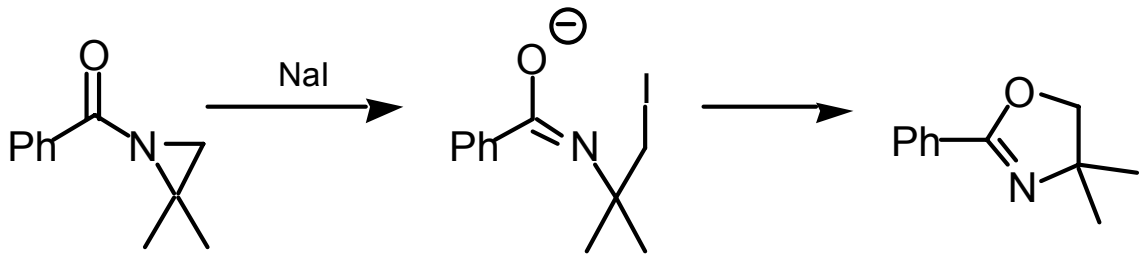
(b) For poorer nucleophiles acid or Lewis acid catalysis may be necessary.
Once again, this is generally an S_N2 like process (Nu = H_2O, MeOH etc.).



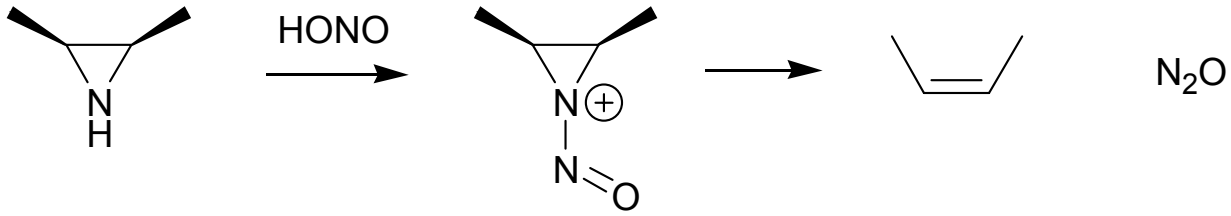
(ii) Ring expansion reactions Mechanism



also catalysed by iodide

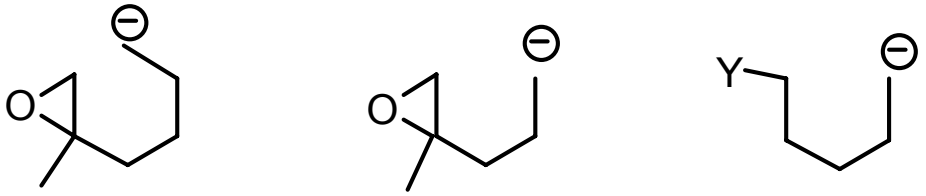


Deamination via nitrosation (stereospecific)

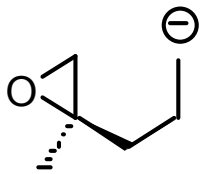


(iii) Intramolecular cyclisations via ring-opening

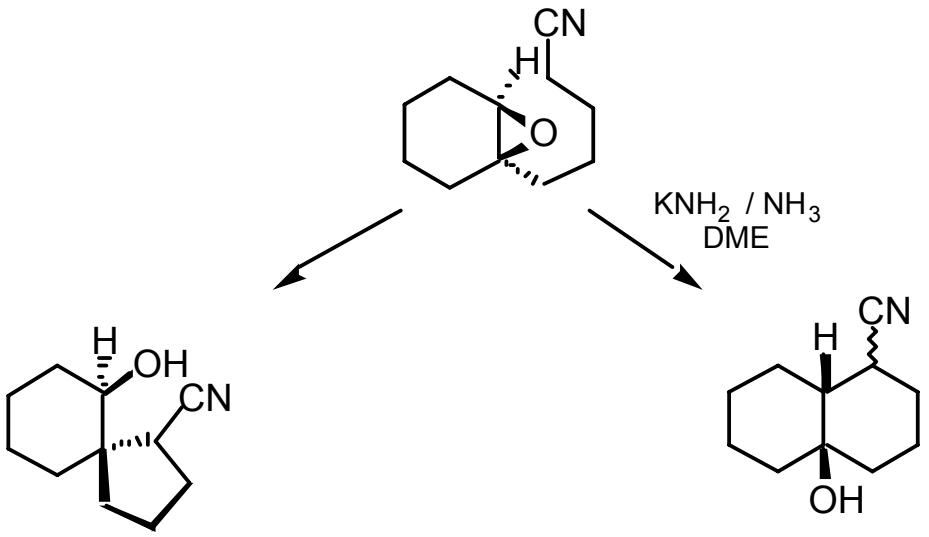
Steric limitations in intramolecular ring-opening reactions



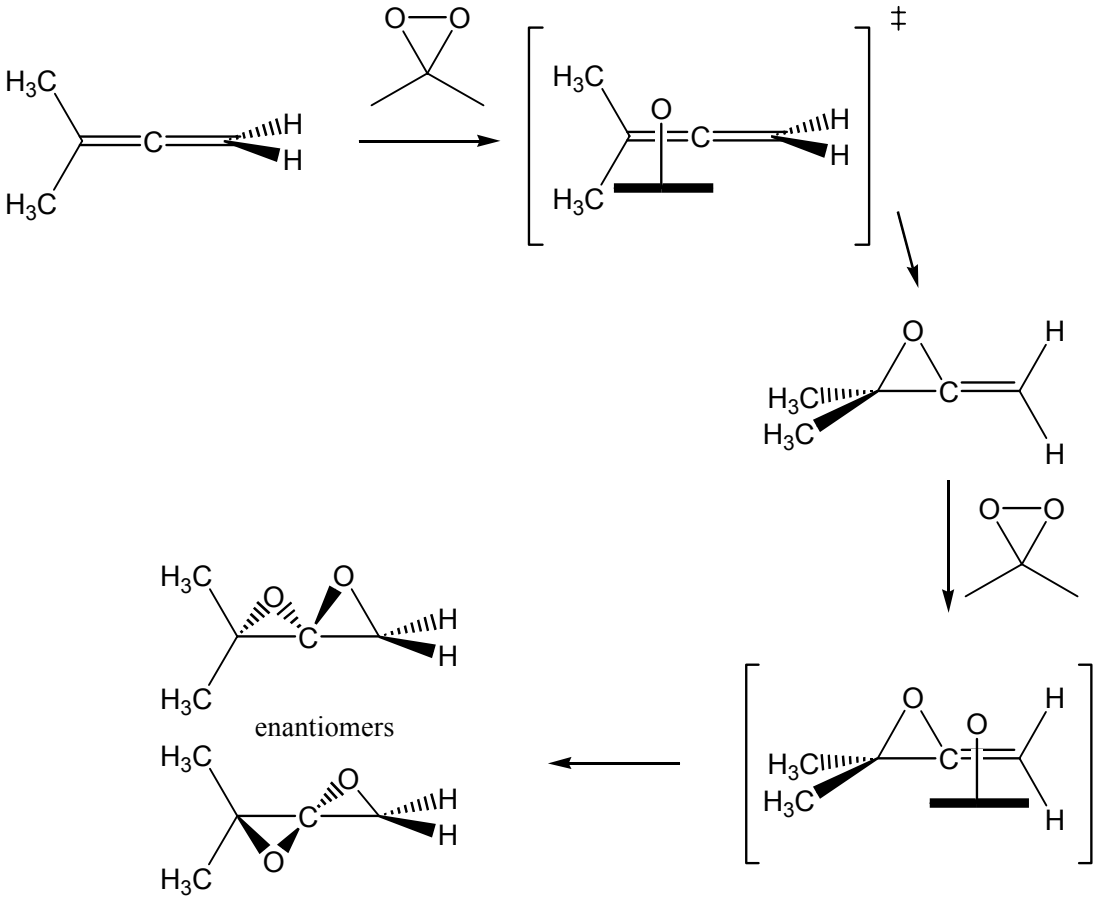
possible impossible possible



Example

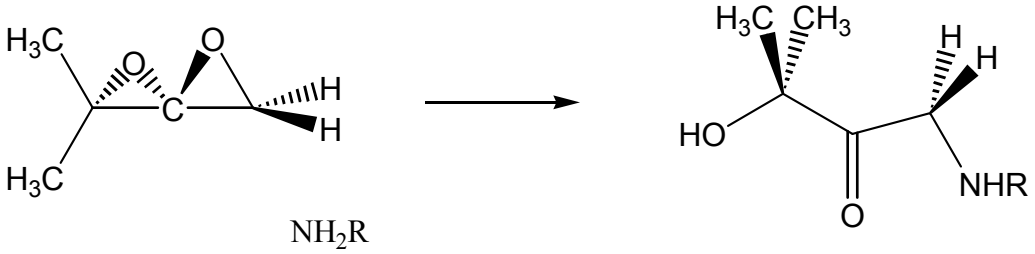


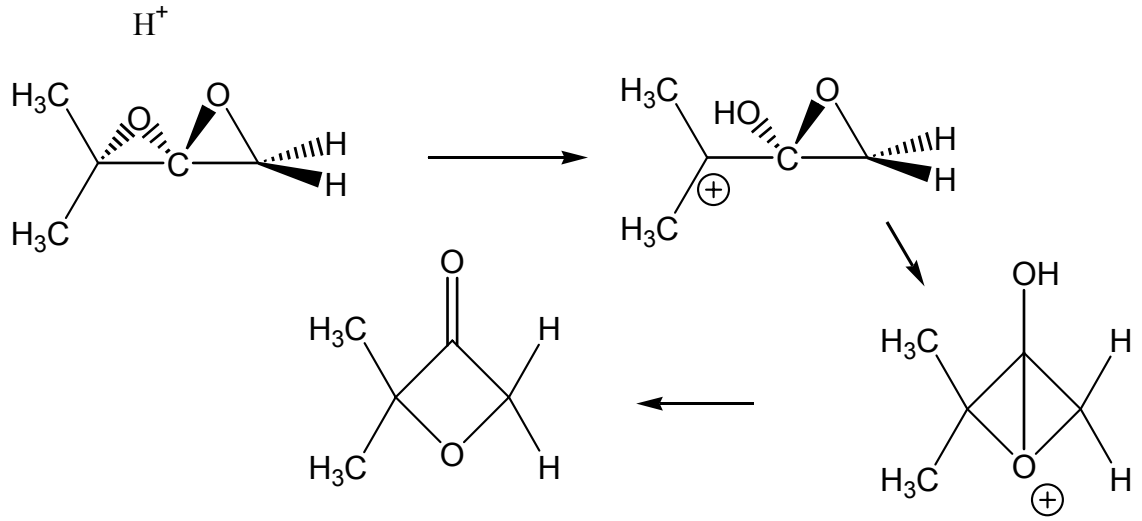
(iv) Spiro compounds



spiro compounds

Dioxirane is a powerful but mild i.e. non-acidic epoxidation reagent derived from acetone. Acetone is formed as by-product which can be easily removed.
Dioxirane reacts with the more activated C=C bond, but steric factors can alter this selectivity pattern.

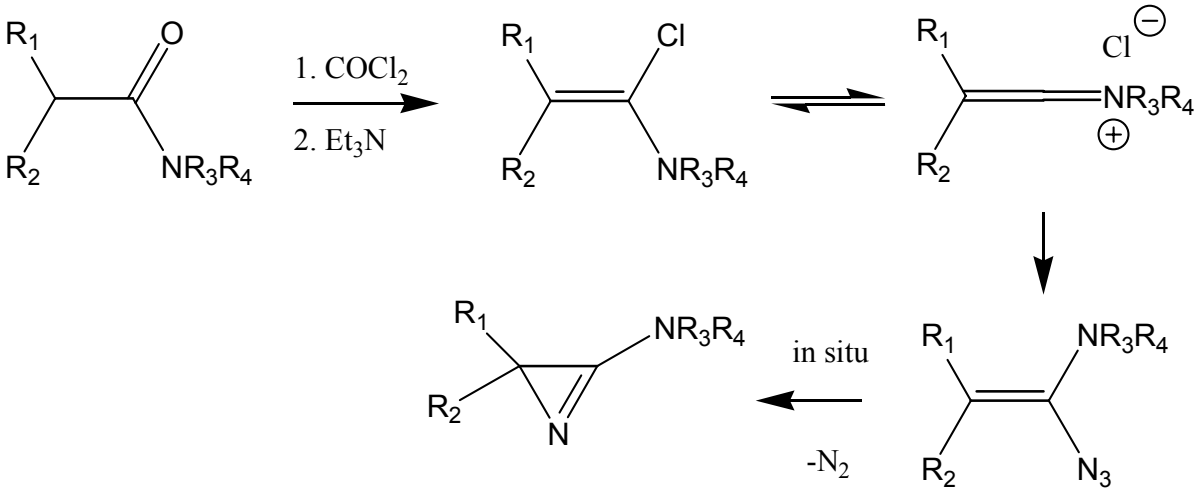




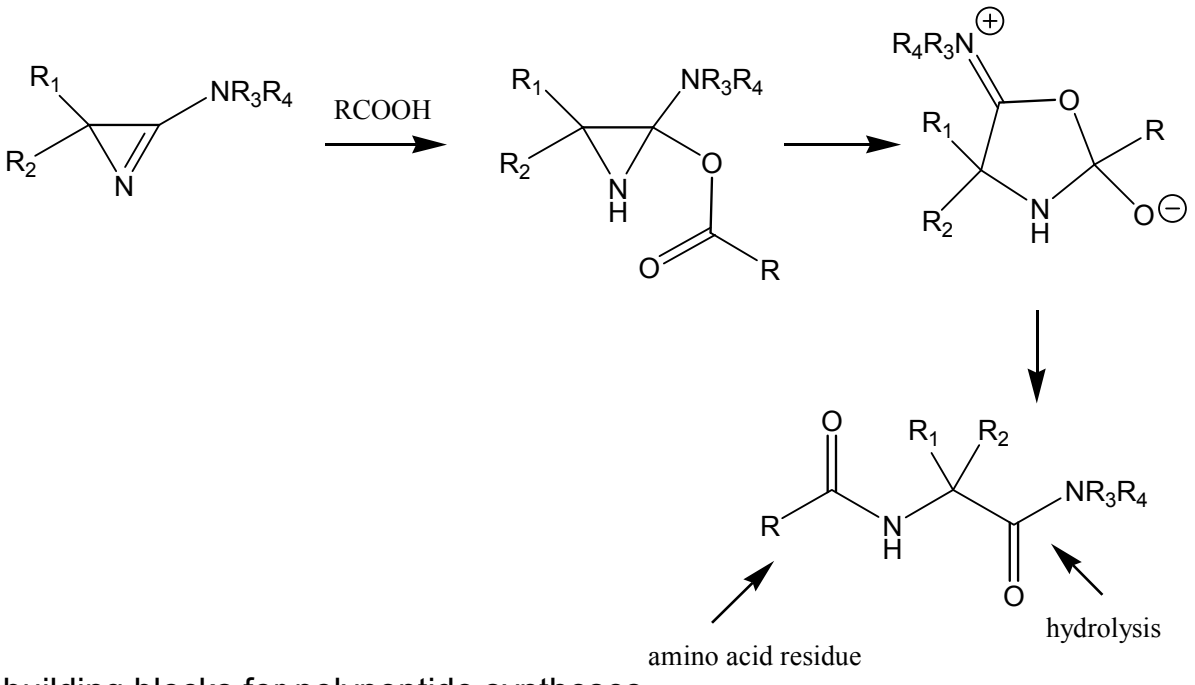
Spirooxiranes are very useful intermediates since 1,2,3-trifunctional propyl-derived building block can be prepared through nucleophilic attack of an appropriate reagent. Under acidic conditions they provide access to 2-oxetanones as shown.

2.5. 3-membered rings containing one heteroatom plus unsaturation

2.5.1. Synthesis of 2H-azirines

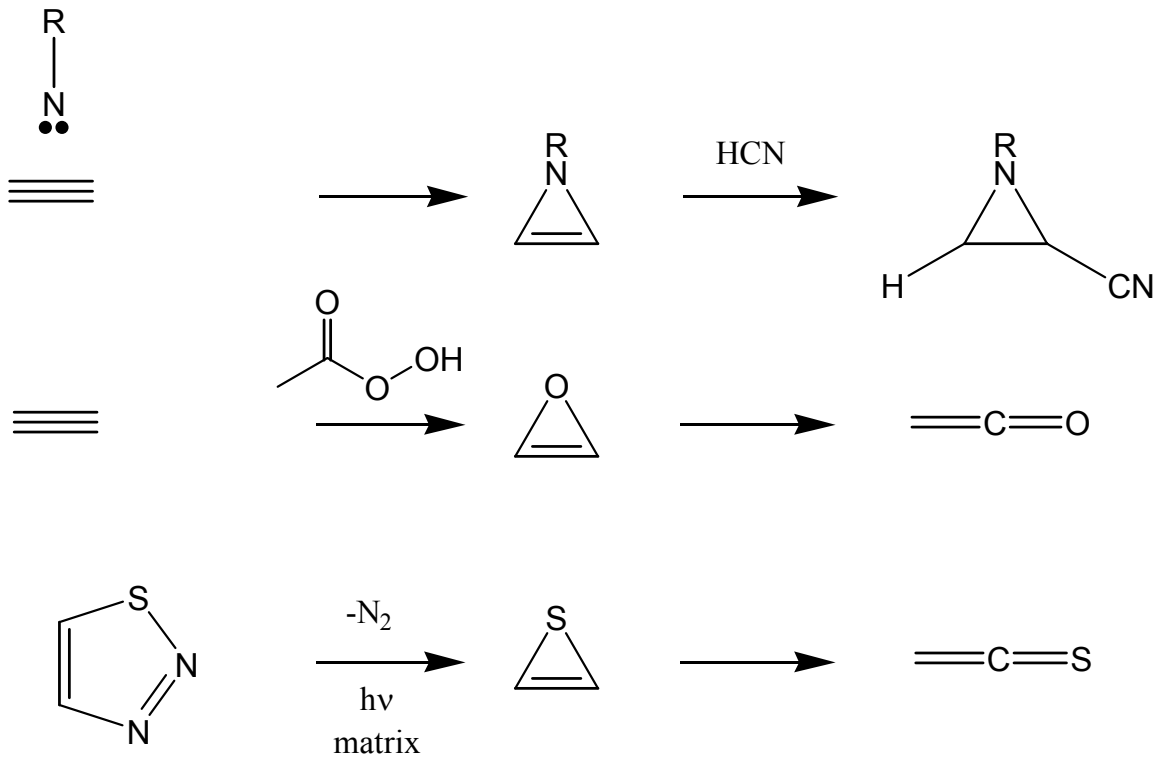


α-chloroenamine / keteniminium salt / α-azidoenamine / 2H-azirine



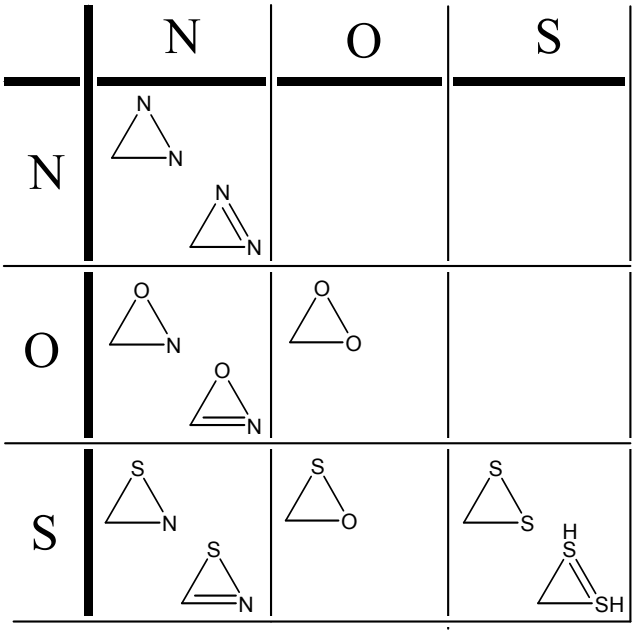
building blocks for polypeptide syntheses

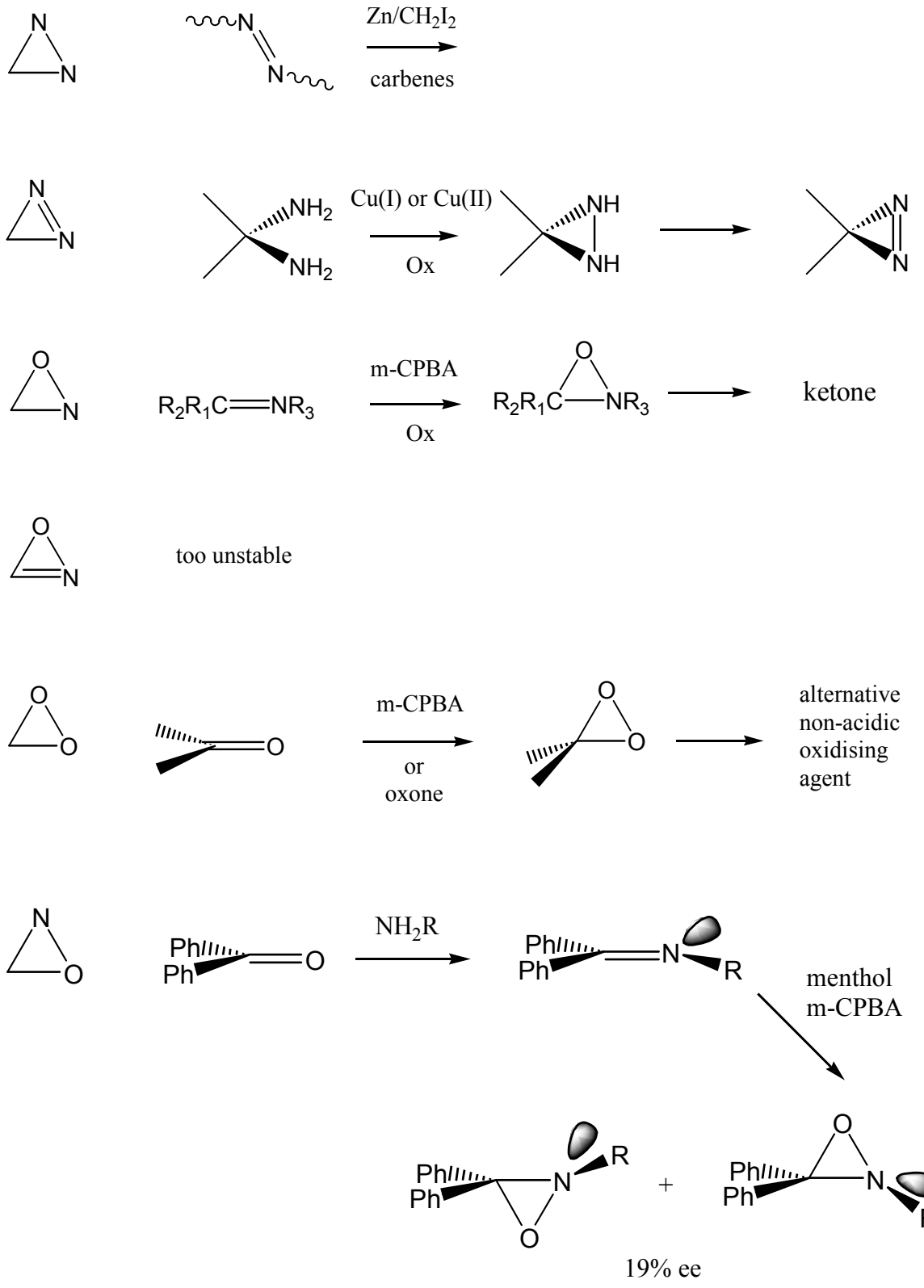
All other unsaturated 3-membered ring systems are too strained and reactive to be of widespread synthetic use.



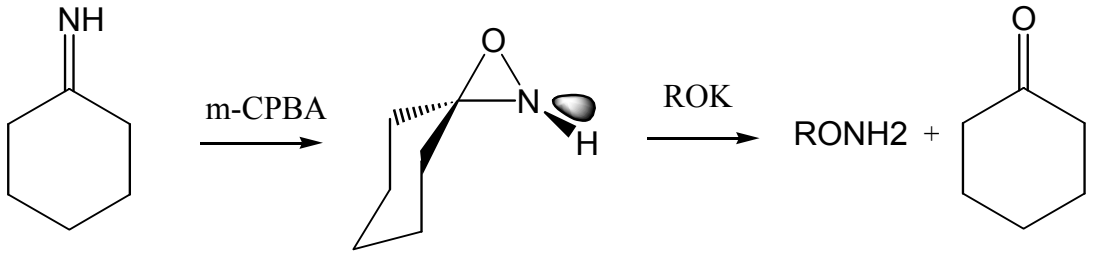
conjugation enhances thiirene stability

2.6. 3-membered rings containing more than one heteroatom




Zn/CH2I2
carbenes
Cu(I) or Cu(II)
Ox
m-CPBA
Ox
ketone
too unstable
m-CPBA
or
oxone
alternative
non-acidic
oxidising
agent
NH2R
menthol
m-CPBA
19% ee

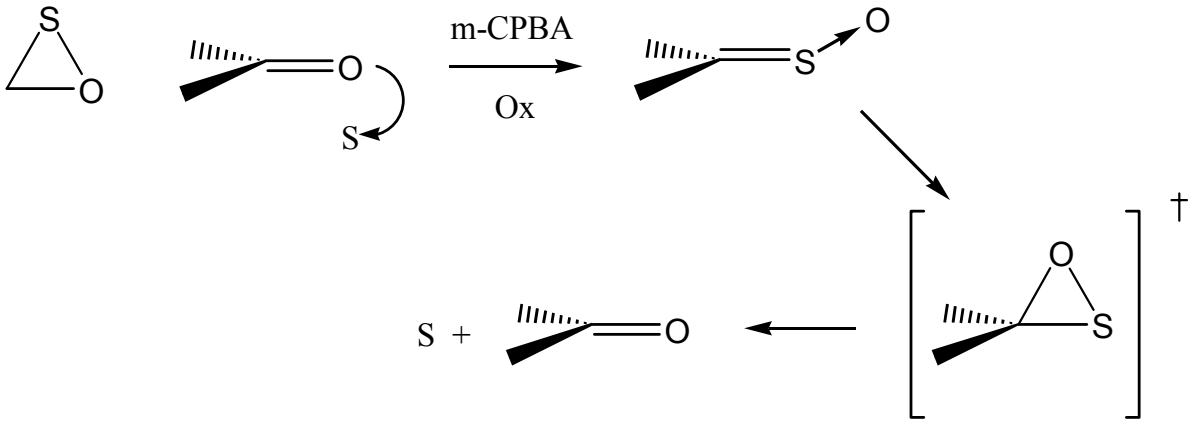
Because oxaziridines can be ring-opened selectively they have found use in synthesis. It is possible to control oxaziridine formation enantioselectively by adding an appropriate non-covalently anchored chiral “auxiliary”. Other methods involved the use of amines with alpha-positioned chiral carbon centres.

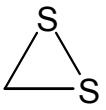


N-unsubstituted oxazirines are used to prepare O-substituted hydroxylamine derivatives.

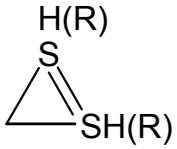
not found

too unstable

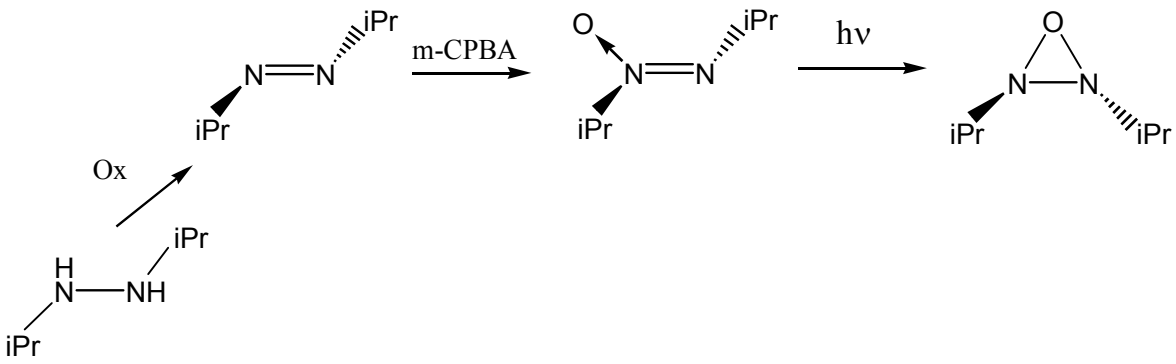




only one example, stable towards acid, but reacts with nucleophiles



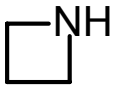
too unstable


iPr
N
N
iPr
m-CPBA
O
N
N
iPr
iPr
hν
O
N
N
iPr
iPr
Ox
iPr
H
N
NH
iPr

3. 4-Membered Rings Containing One Heteroatom

Less strained and hence less reactive than epoxides

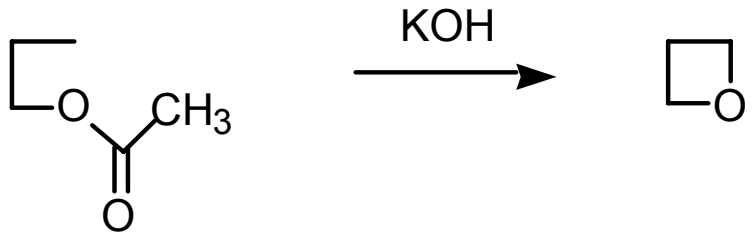
oxetan

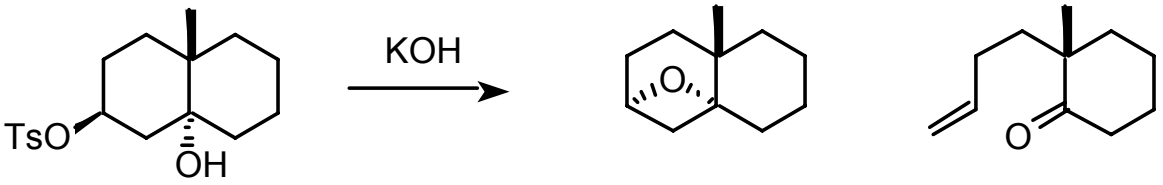


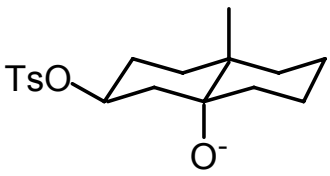
azetidine

3.1. Preparation

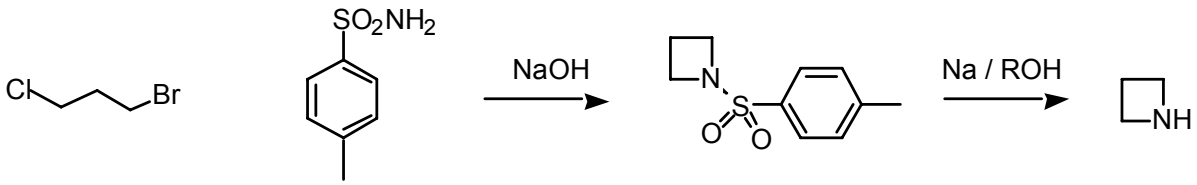
Competing reactions may pose problems



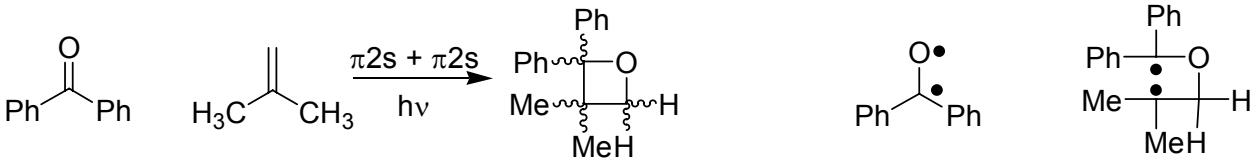




Azetidines are prepared similarly



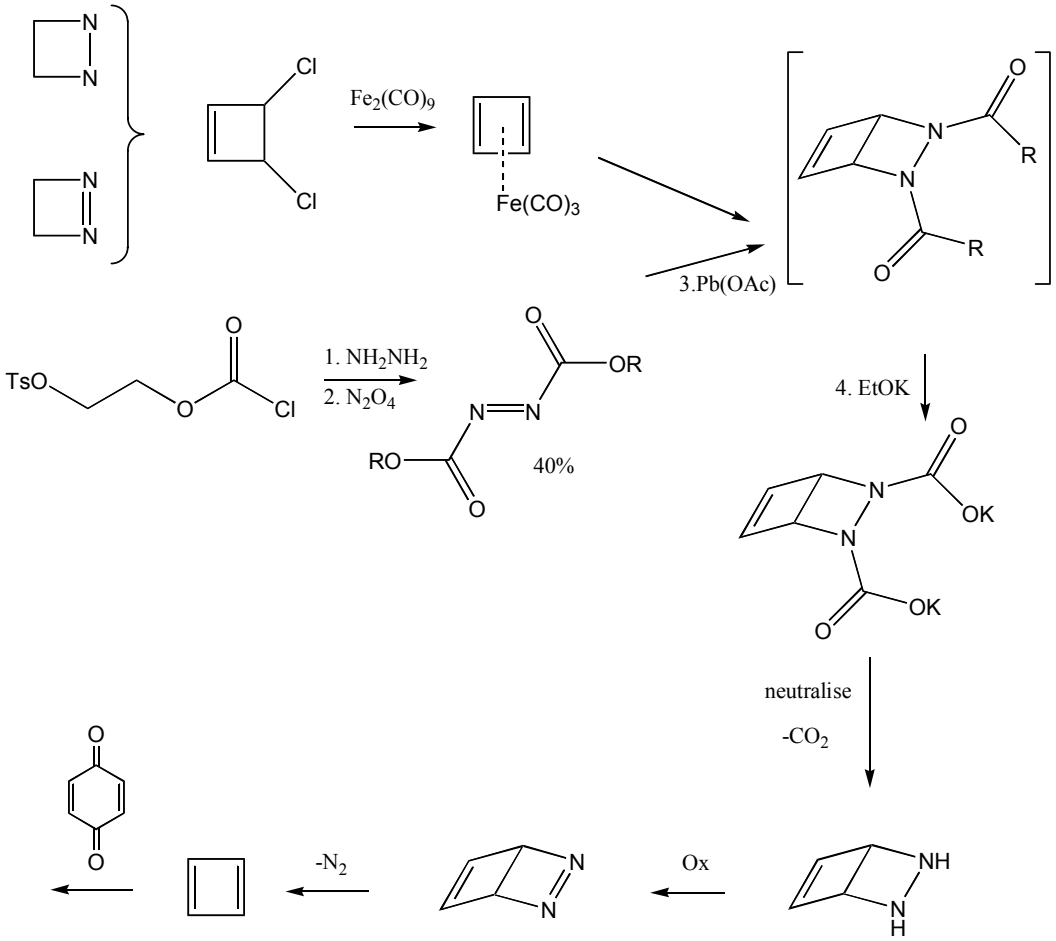
The photochemically allowed π2s + π2s cycloaddition reaction can also be used. When oxetan is formed it is known as the Paterno-Büchi reaction. It is often not concerted and hence not stereospecific:

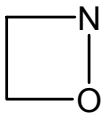


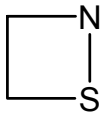
3.1.1. 4-membered rings containing one heteroatom with unsaturation

Ring strain once again limits their synthetic uses. General synthetic methods are very similar to those encountered for the preparation of saturated 4-membered ring system with one heteroatom.

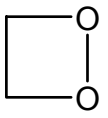
3.1.2. 4-membered rings containing more than one heteroatom

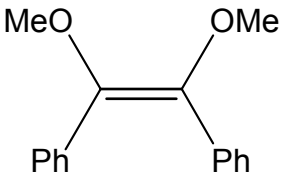






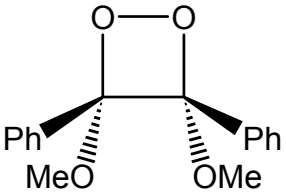
not found

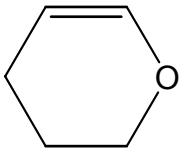




Methylene Blue

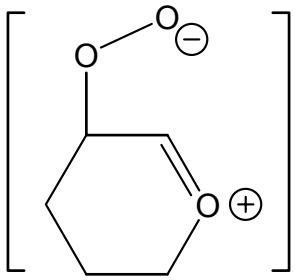
O_2
hν



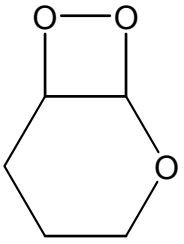


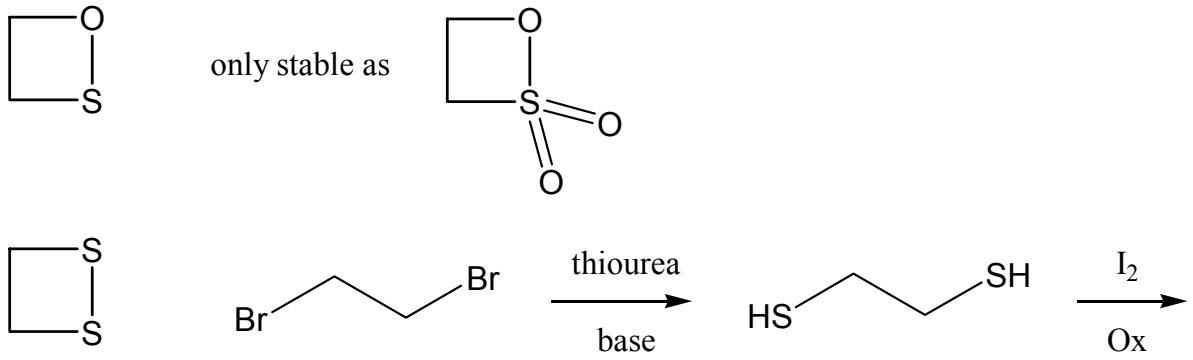
Methylene Blue

O_2
hν



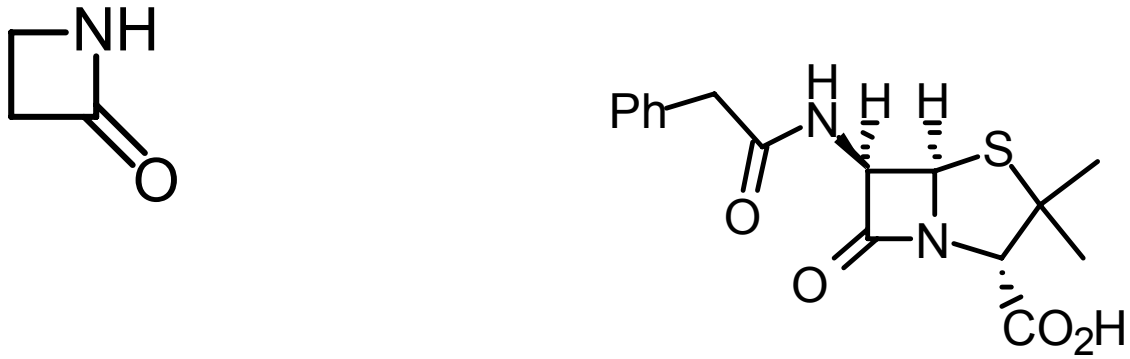
†





3.2. ß-Lactam Antibiotics

Based on the azetidinone structure are the most are the most important 4-membered heterocycles. Historically, the penicilin antibiotics were first isolated by Florey and Chain after microbial anatgonism was first obverved by Fleming in Penicillium fungi.
An example is Penicillin G:

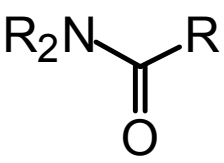


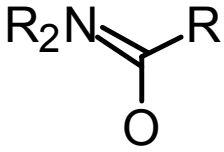
The molecule has several unusual features:

- The ß-lactam ring which is essential for biological activity.
- The second fused ring (5-membered) containing sulphur and a free carboxyl functionality
- A side chain amide with the cis stereochemistry
- Convex (concave) overall shape (i.e. V-shaped)

Unlike simple acyclic amide the ß-lactam ring is very reactive because it is strained.

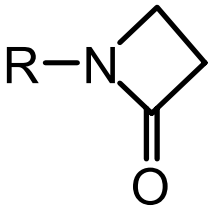
Normal amides are not readily hydrolysed because of:

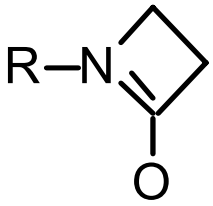




- The strong C-N bond due to nitrogen lone pair overlap
- The NCO system here is planar.

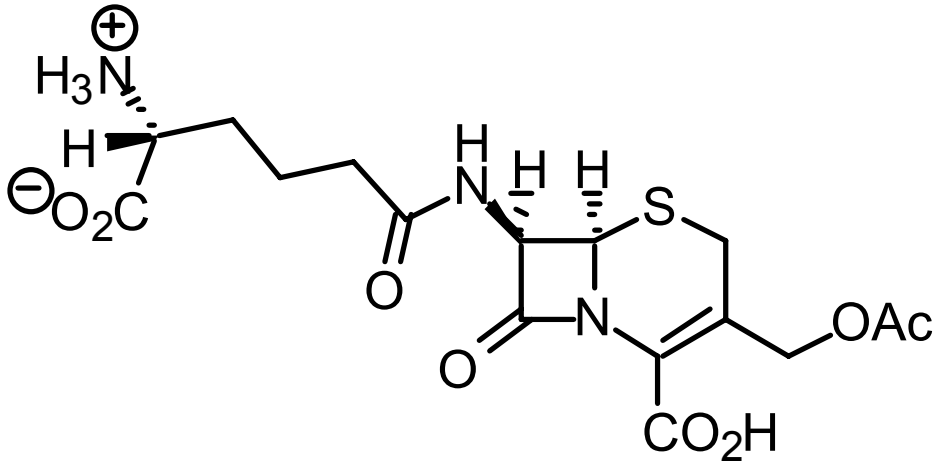
In the ß-lactam system however:



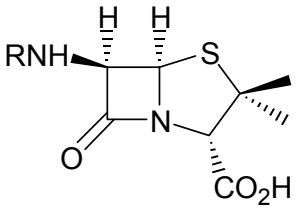


The nitrogen lone pair overlap is minimised since this introduces 2 sp2 centres into the ring. In addition the strain is introduced by the second five membered ring also diminishes nitrogen lone pair overlap. Thus the ß-lactam carbonyl is “ketonic” and susceptible to nucleophilic attack. This permits reactions with bacteria enzymes hence the antibiotic activity. Resistant bacteria produce an enzyme ß-lactamase which detsroys the ß-lactam ring.

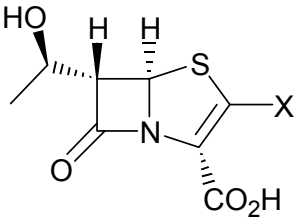
Subsequently a new class of ß-lactam antibiotics were isolated - the cephalosporins some of which showed improve activities against bacteria, for example cephalosporin C:



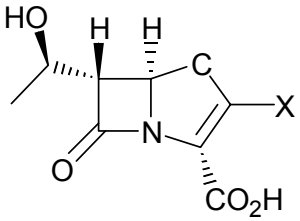
Hence there was intense interest to devise new useful syntheses of ß-lactams.



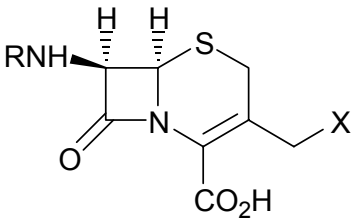
penams



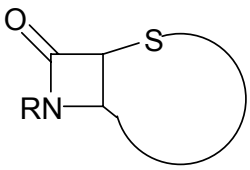
penems



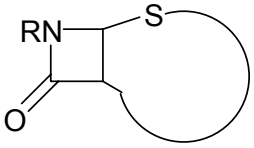
carbapenems



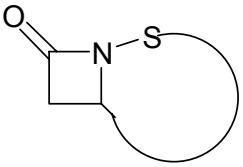
cephalosporins



penam Type I



penam Type II

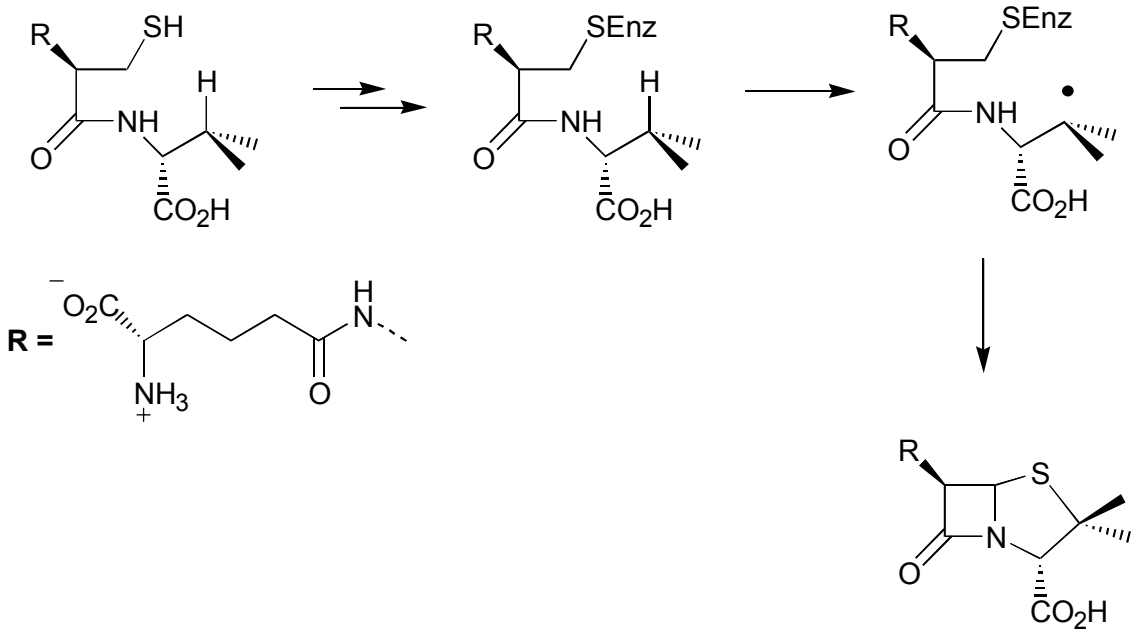


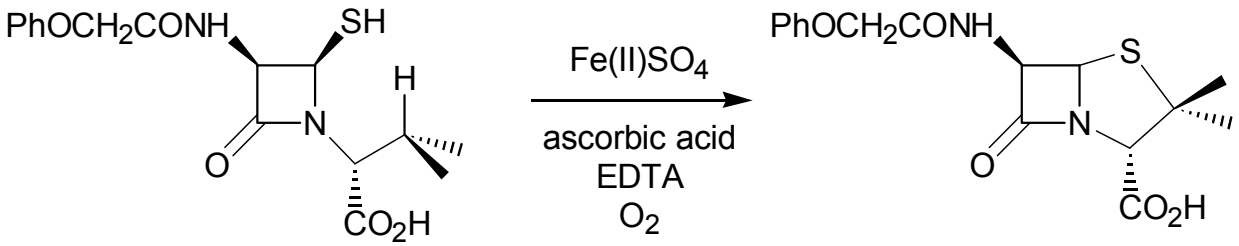
penam Type III

A selection of the most important beta-lactam ring systems and substitution patterns.

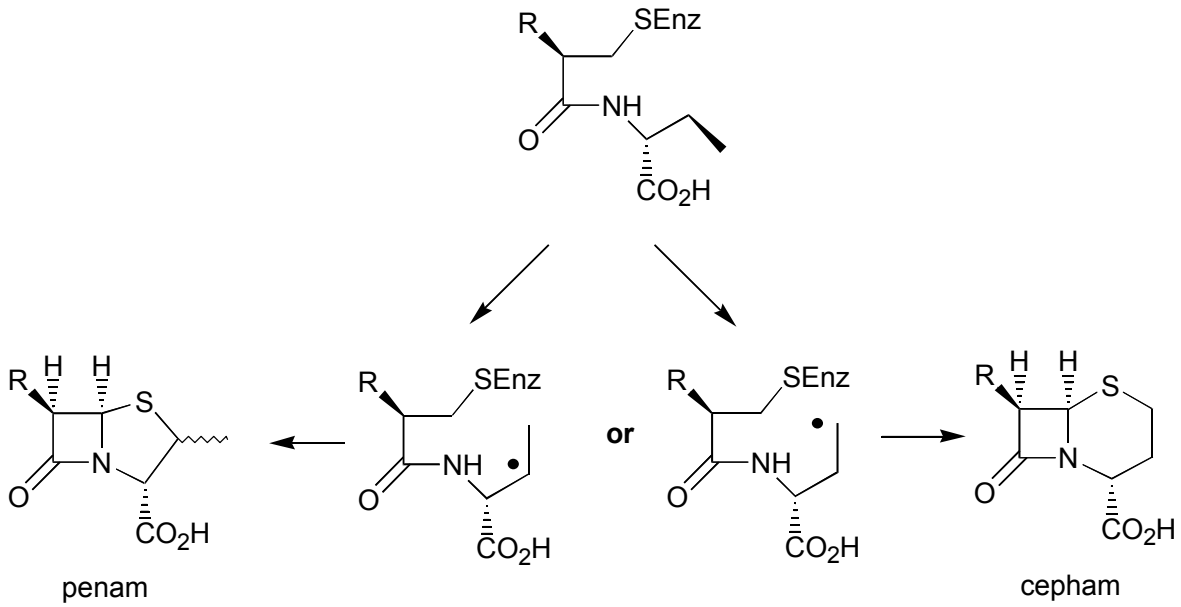
3.2.1. Synthesis of ß-lactams

Arnstein's tripeptide – the "natural" way…

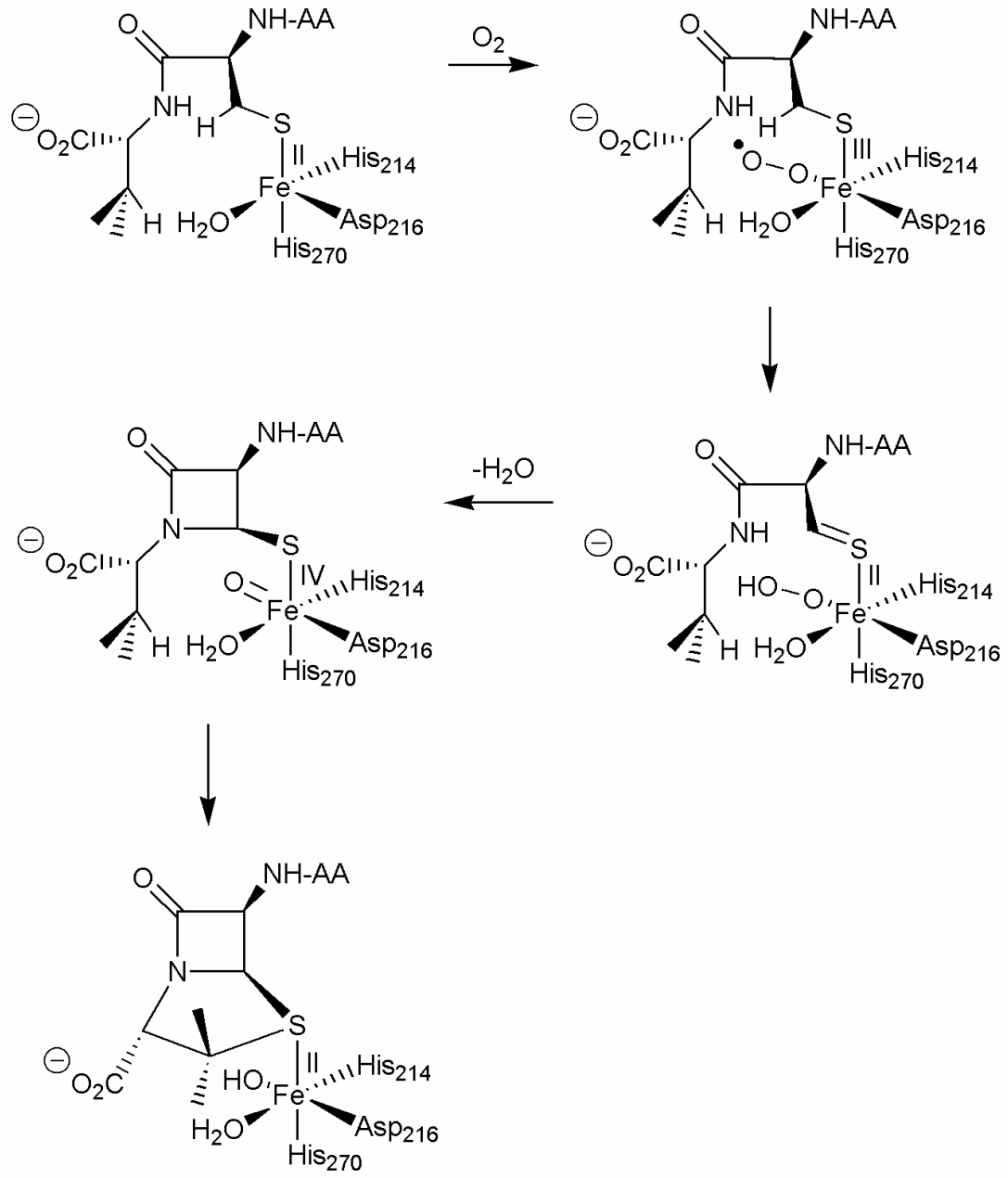




a radical reaction is involved in the biosynthetic pathway



the sequence suggests that the enzyme does NOT control stereoselectivity



Mechanism of the biosynthesis of isopenicillin N. AA = aminoadipoyl

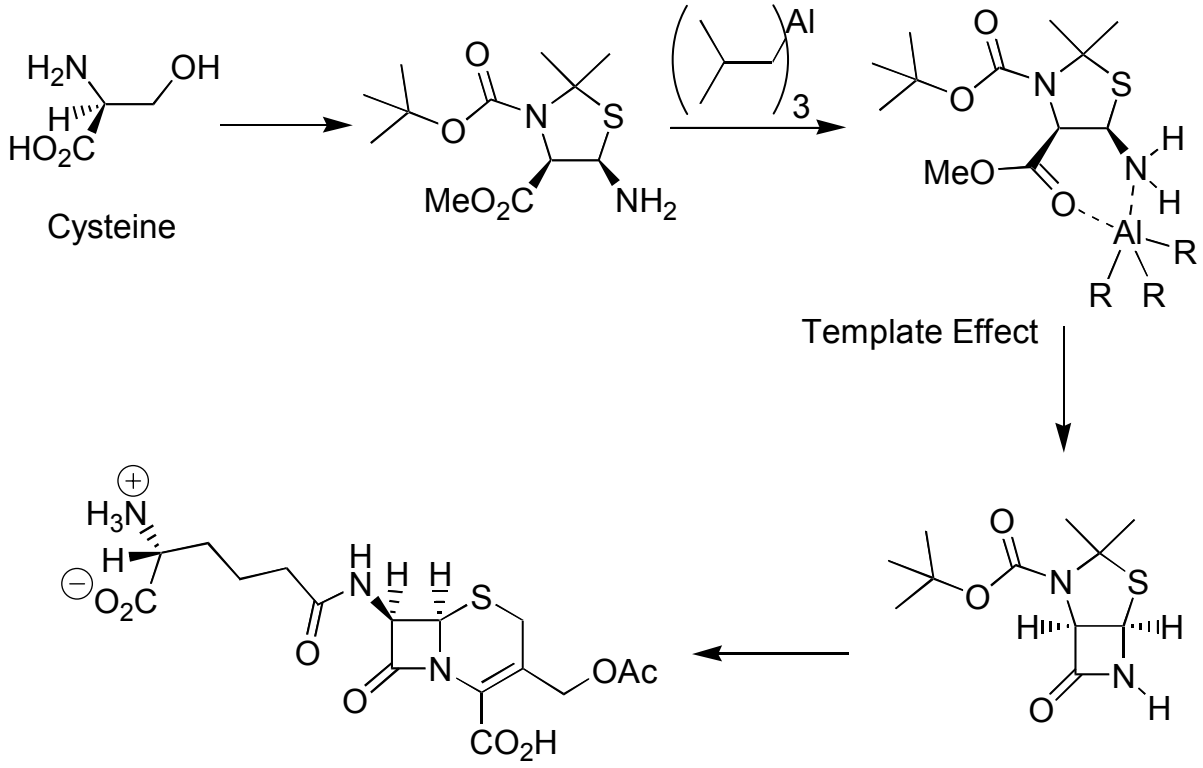
Isopenicillin N synthase (IPNS) operates as follows: Deprotonated thiol belonging to cysteine AA binds to iron centre – Iron takes up oxygen and changes oxidation state – Intramolecular hydrogen transfer Fe III to Fe II. A thioaldehyde as well as a peroxide ligand are formed. The latter deprotonates the lactam N followed by ring closure through nucelophilic attack at C=S – Second hydrogen transfer via isopropyl radical intermediate attacking the thiolate sulphure thereby producing a thiazolidine heterocycle.

(1) Cyclisation of ß-amino acids

(a) The normal outcome is polymerisation

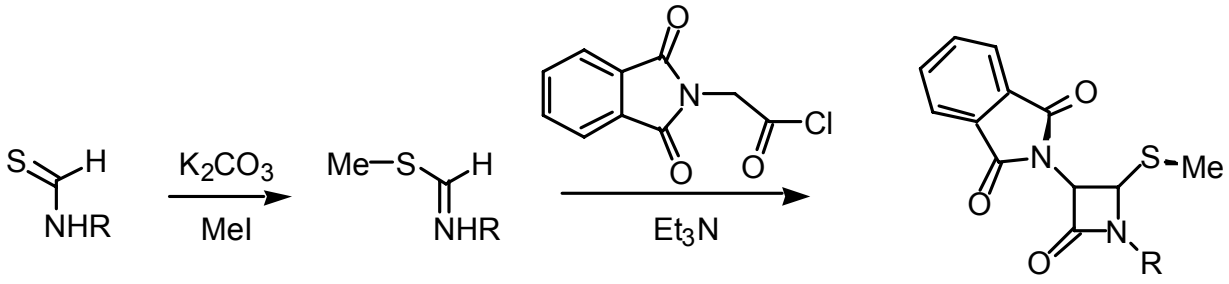
(b) ...unless the carbonyl and amino functions are held in close proximity.

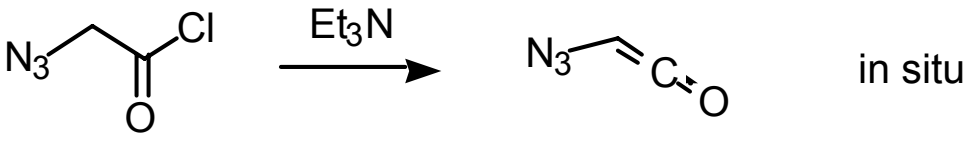
Robert Burns Woodward, of whom later, synthesised cephalosporin C using this approach:



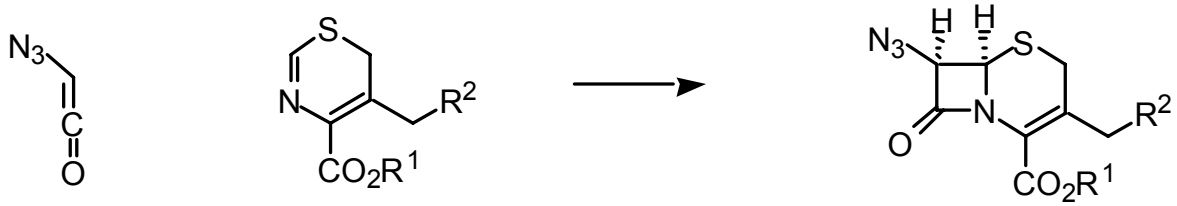
(2) π2s + π2a cycloaddition thermally allowed - base, imine and ketene

(a)

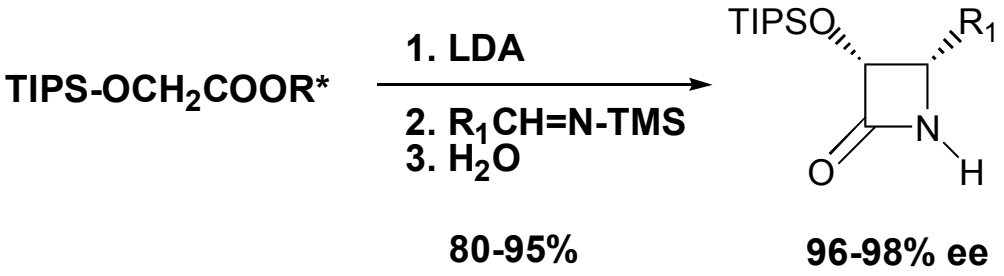


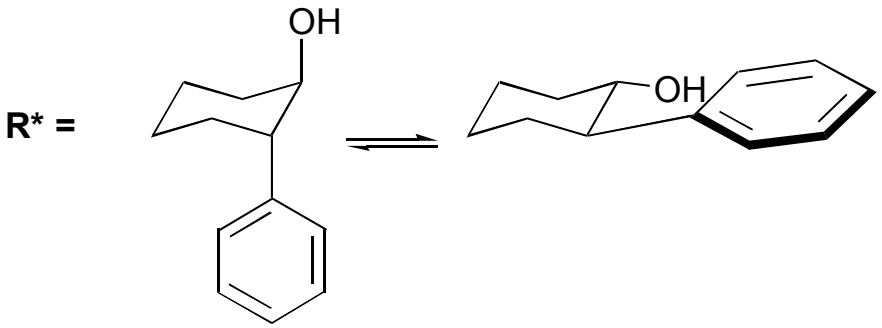


(b)

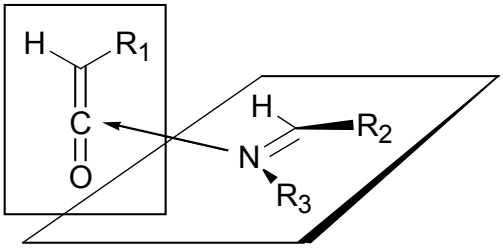


Stereoselective control is possible, very much a function of the chiral auxiliary used.

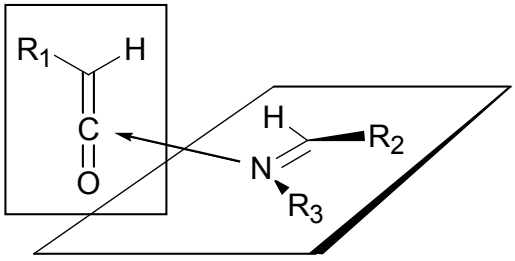




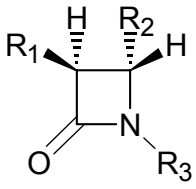
Staudinger reaction – exo-functionalisation of alkene sidechain – hydrostannylation – protiodestannylation. Cyclisation follows the Barton rules and is a 5-exo-trig process, determining the formation of the 5-membered bicycle. The reaction proceeds particularly well and regiocontrolled if R1 represents an electron withdrawing substituent such as an ester or phenyl group.



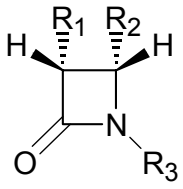
endo



exo



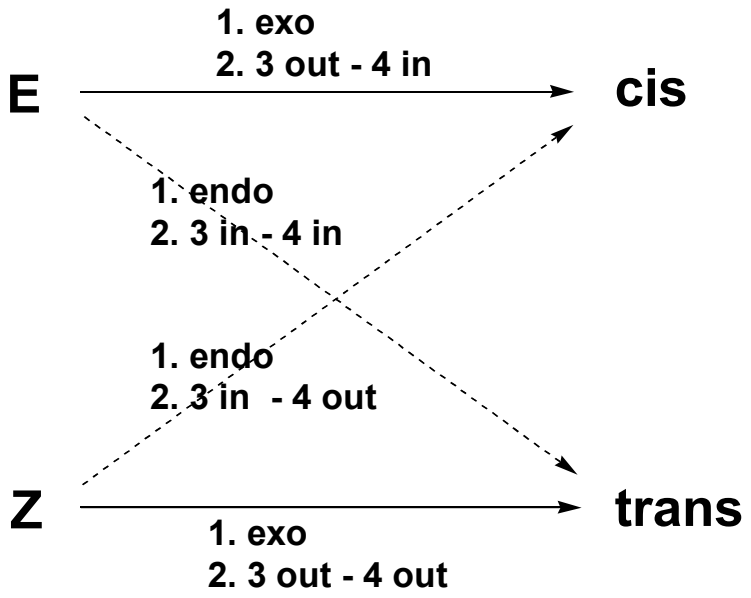
trans

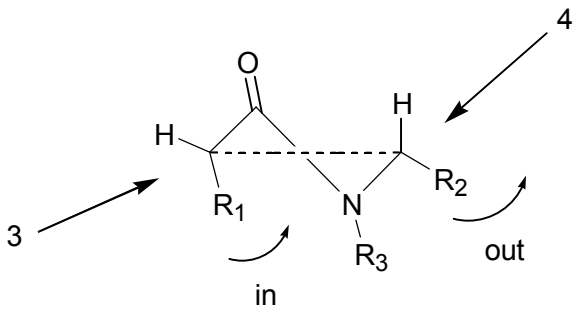


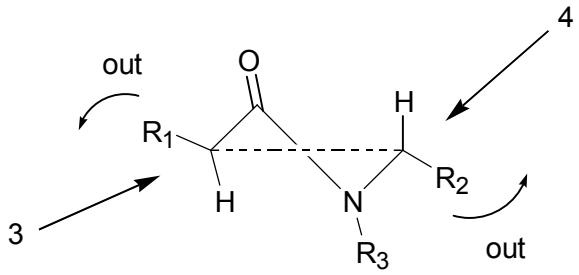
cis

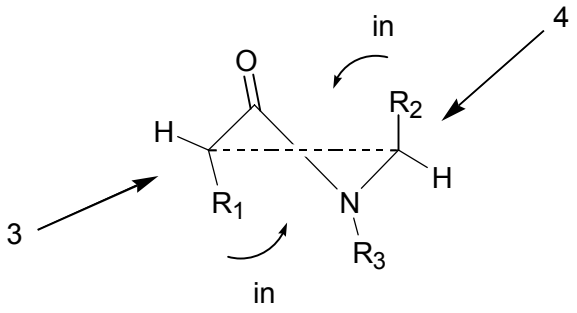
only one enantiomer shown

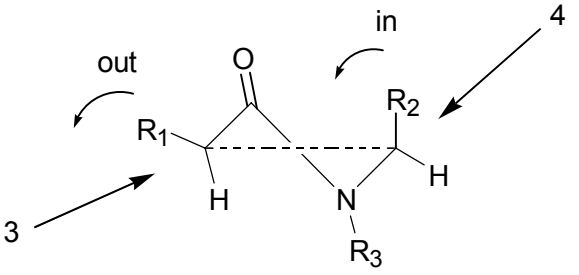
JACS **115**, 995. All permutations that arise from 4 different transition states. Formerly this reactions was believed to proceed via a [2+2] cycloaddition mechanism, but more recently experimental evidence fits better with a diene intermediate which undergoes conrotatory (thermally allowed) ring closure.





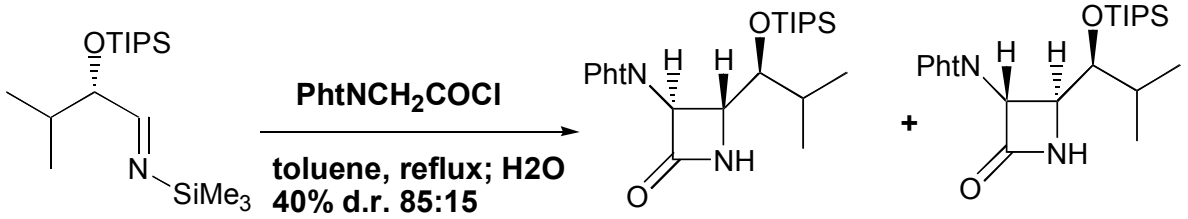


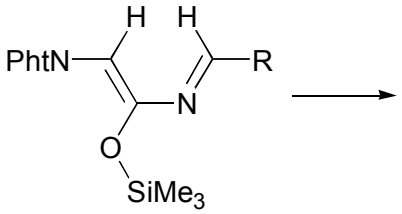




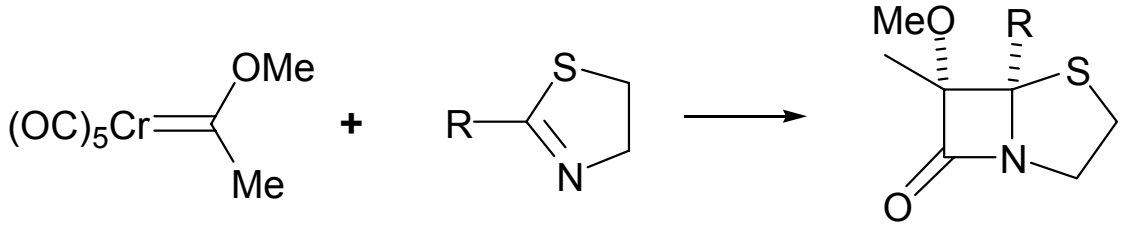
ENDO (R1) **EXO (R1)**

Trans selectivity with regards to the hydrogens on the lactam ring can be very efficient as shown: The mechanism is believed to proceed via a two-step process starting with the formation of the conjugated imineenolate followed by conrotatory [2+2} cyclisation.

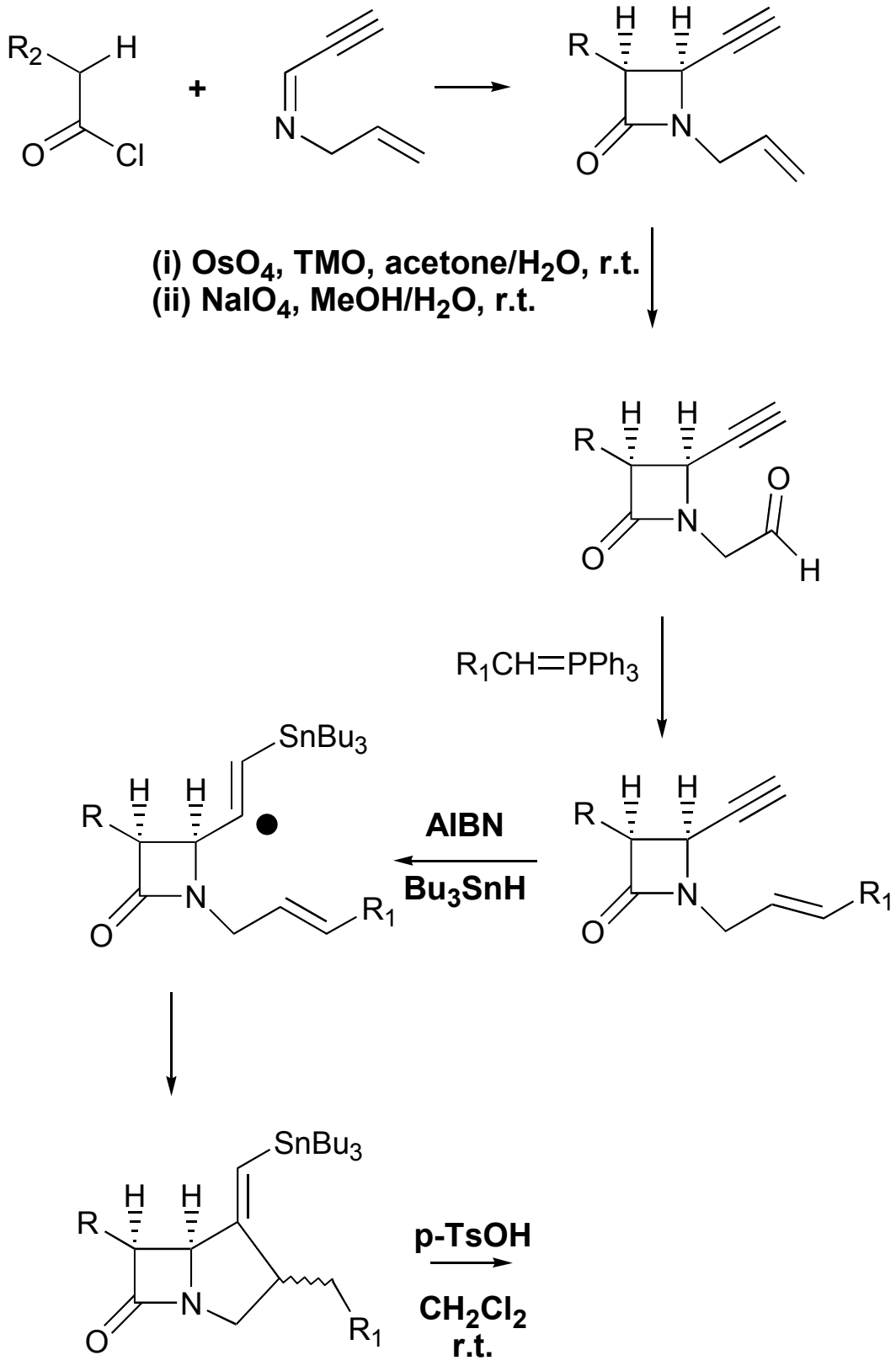




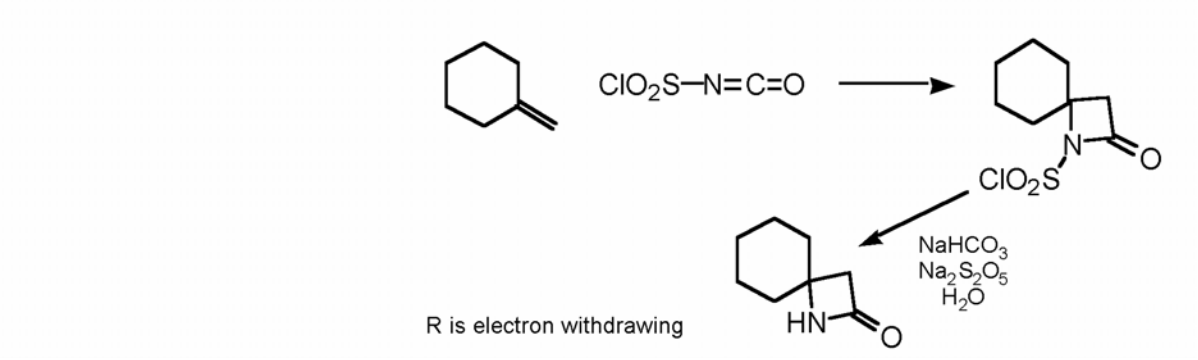
Chromium carbenes (and related transition metal alkylidenes) have also been exploited for the synthesis of the 4-membered lactam skeleton



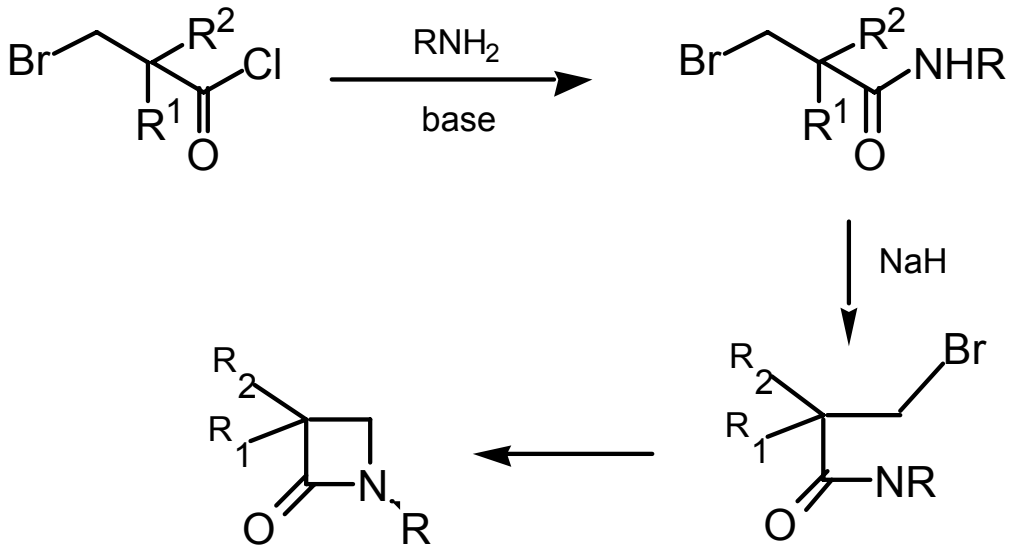
Radical cyclisation to form the annulated 5- or 6-membered ring in analogy to the biosynthetic enzymatic process has also been transformed into a controllable and quite versatile process.


R2
H
O
Cl
+
N
R
H
H
N
O
(i) OsO4, TMO, acetone/H2O, r.t.
(ii) NaIO4, MeOH/H2O, r.t.
O
H
R1CH=PPh3
SnBu3
AIBN
Bu3SnH
R1
p-TsOH
CH2Cl2
r.t.

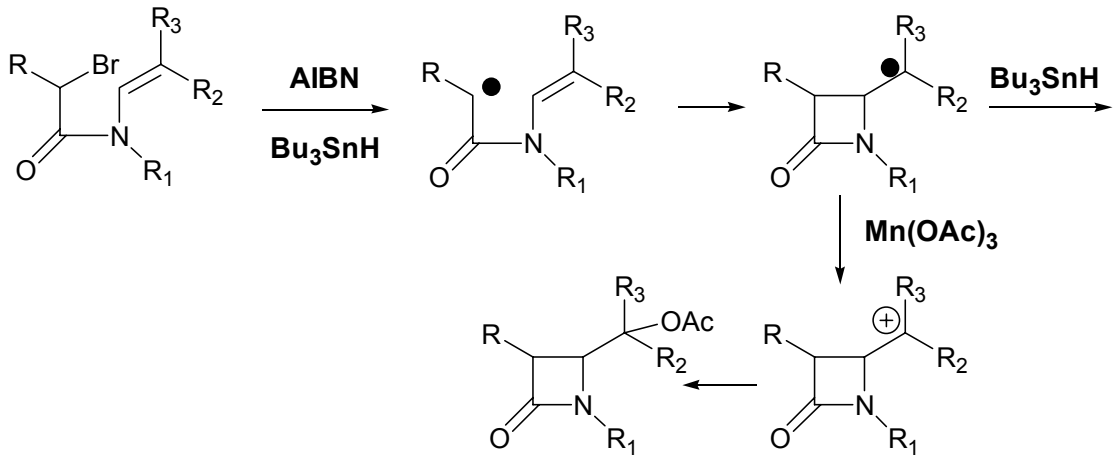
(3) Isocyanate cycloadditions



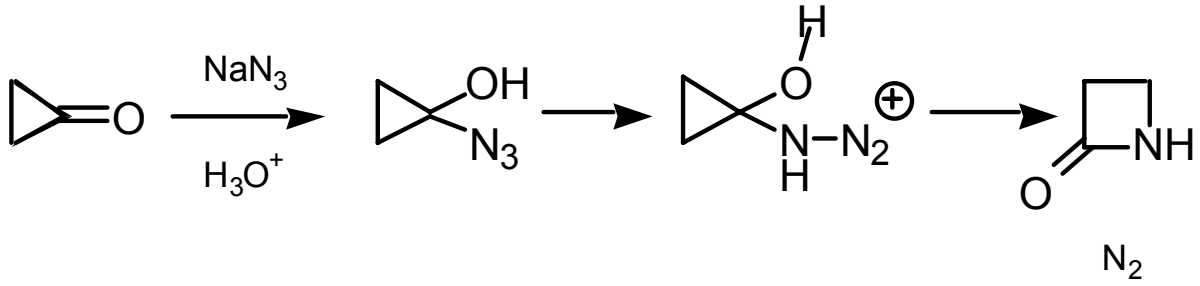
(4) Haloamide Cyclisations



It is also possible to perform these cyclisations via radical chemistry

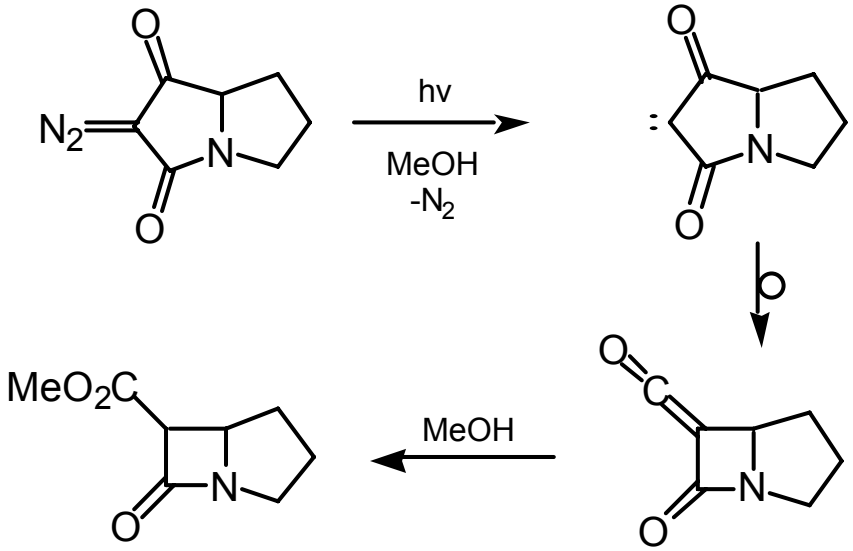


(5) Ring expansion reactions

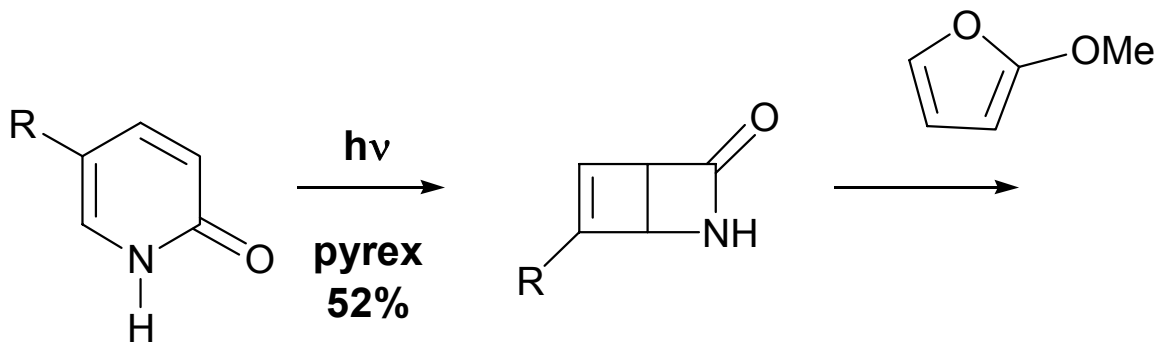


(6) Ring contraction reactions

Wolff Rearrangement

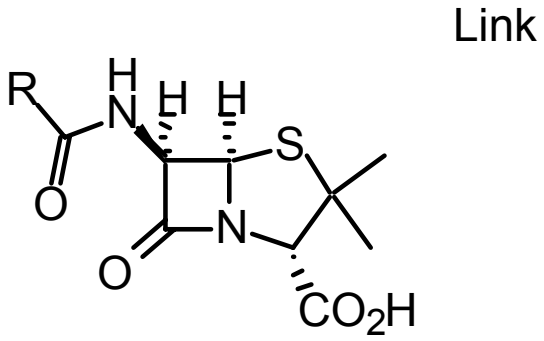


Another route via ring contraction is available via photopyridones, allowing the synthesis of strained multicyclic ring systems



3.2.2. Conversion of Penicillins into Cephalosporins

Penicillins are produced by the ton by microbiological fermentation and are very cheap. Cephalosporins are harder to obtain. They have many features in common:

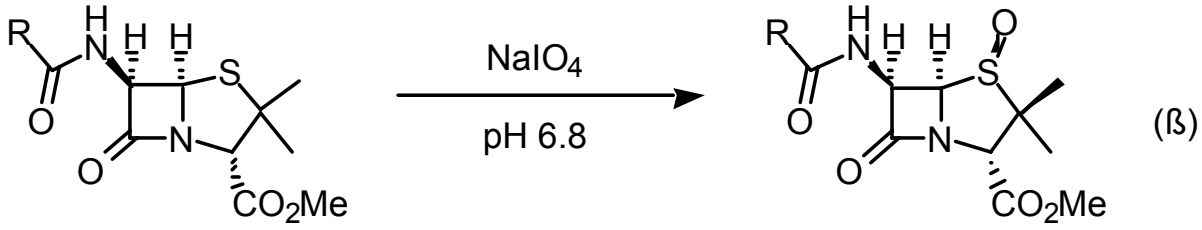


(i) same absolute stereochemistry in the ß-lactam ring; both hydrogens cis.

(ii) all substituents in analogous positions

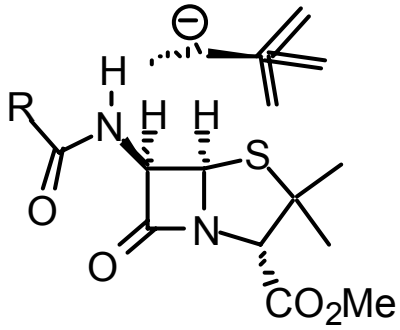
break the 5-membered ring, reform a 6-membered one!

This can be achieved via the sulphoxide. Oxidation of Penicillin G (protected as the methyl ester) with sodium periodate gives the ß-sulphoxide.

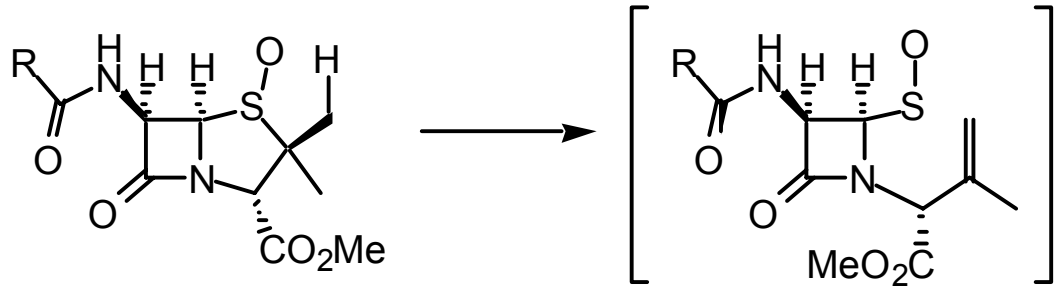


Note: Sulphoxides are **configurationally** stable.

Periodate approaches from the **more hindered** side as a result of neighbouring group participation due to H-bonding with the amide.

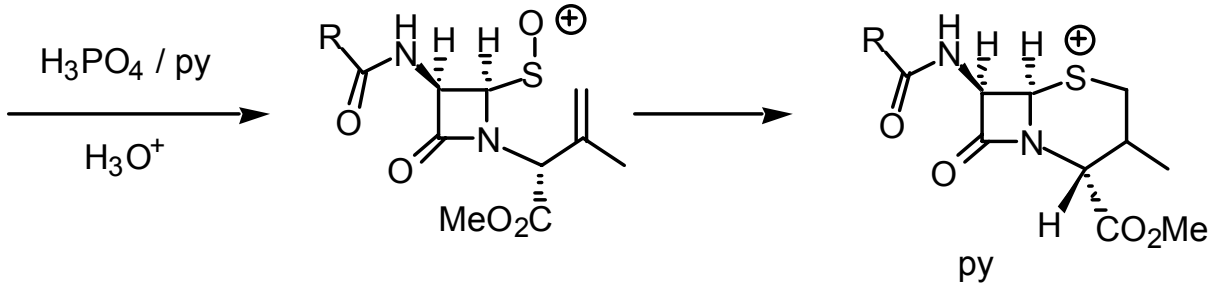


The sulphoxide ring opens on heating to give the sulphenic acid via a [2,3] sigmatropic shift.

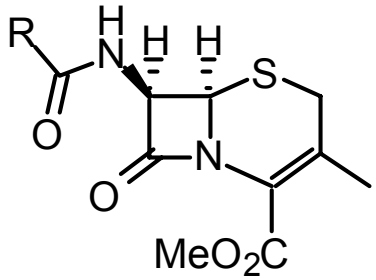


Note: The proton from the ß-Me group is stereospecifically removed **cis**.

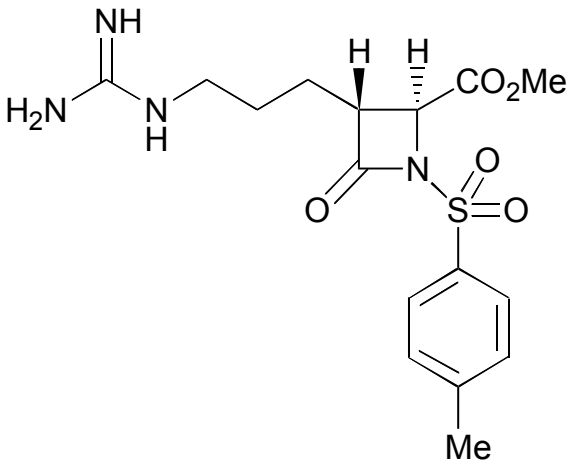
In the presence of acid the unstable sulphenic acid may be protonated and recyclise.



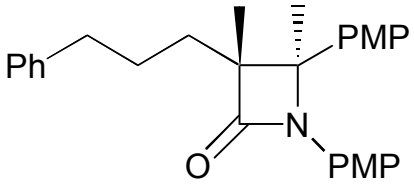
The product is an episulphonium cation that is readily opened by the base pyridine to give the Cephalosporin C ring system.



Recently beta-lactams have found additional therapeutic uses as illustrated with the following examples:

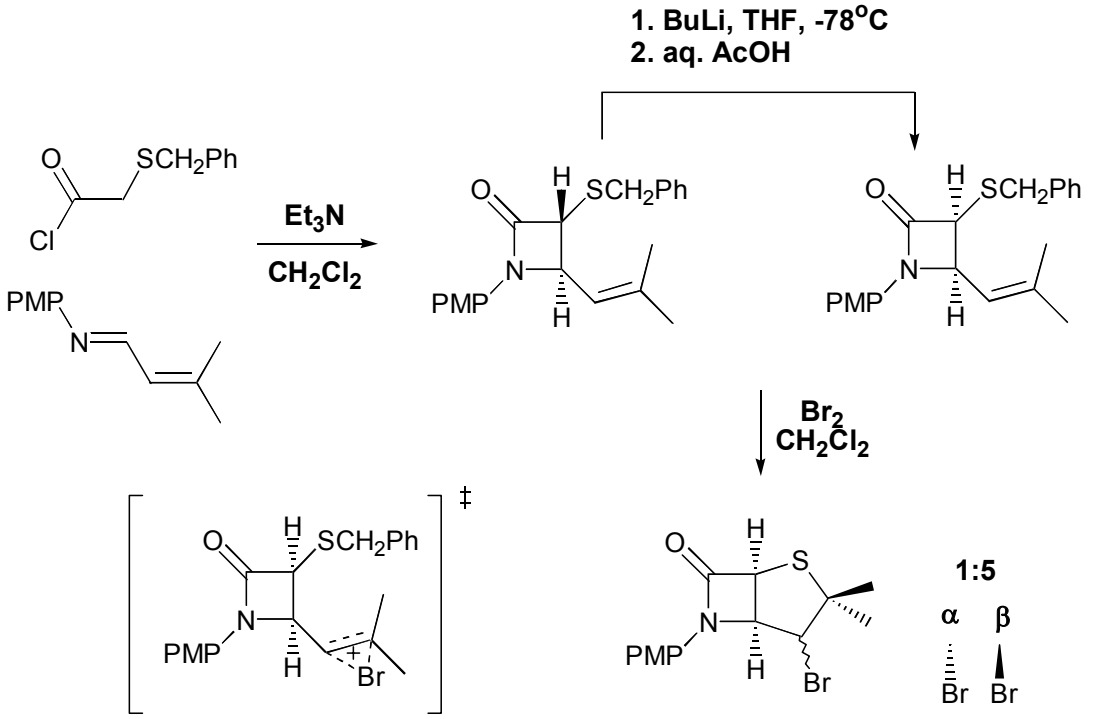


Thrombine Inhibitor



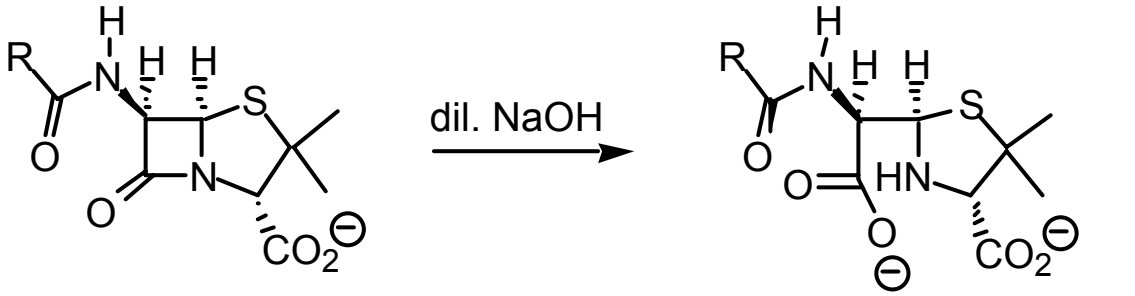
Cholesterol Absorption Inhibitor

One example of a synthesis of non-classical beta-lactam. These molecules have received a lot of attention because they open up the possibility to formulate more effective and new antibiotics. Despite the different orientation of the beta-lactam moiety, synthetically all methods applicable to classical beta lactam syntheses remain valid also for this class of compounds.



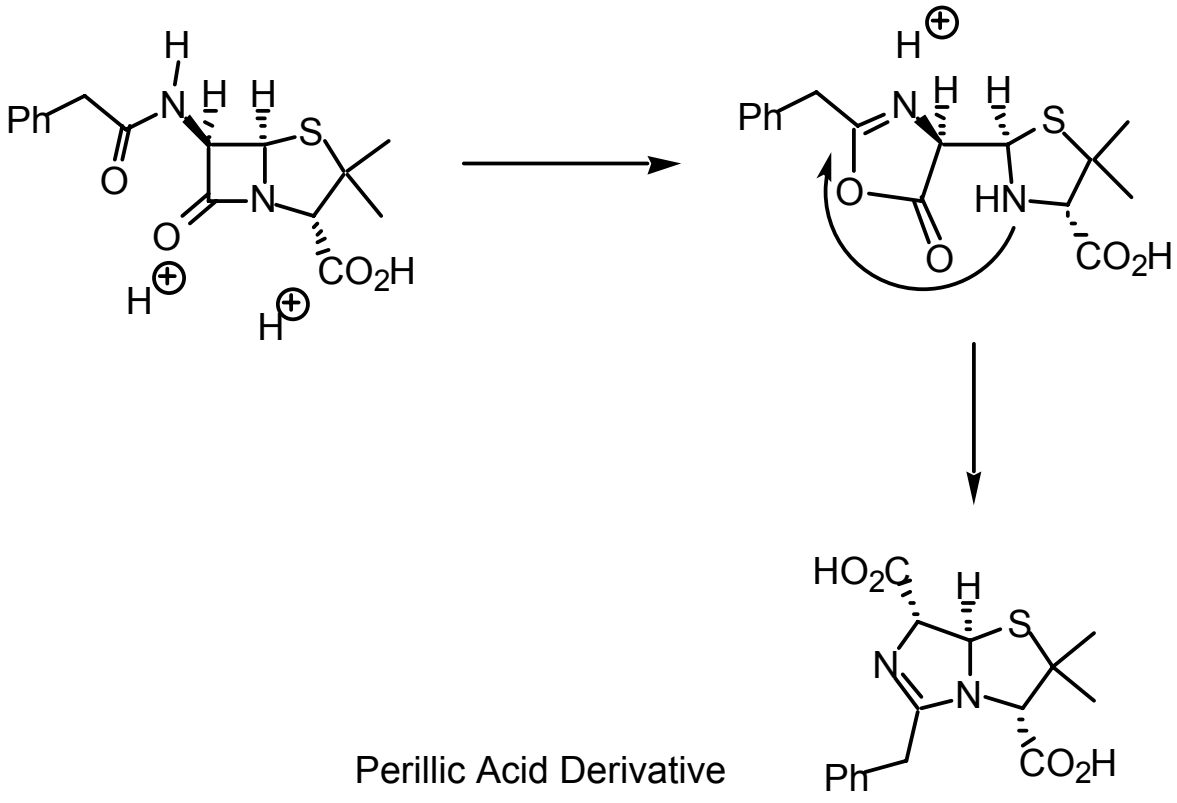
Reactions of Penicillin G

(a) Bases



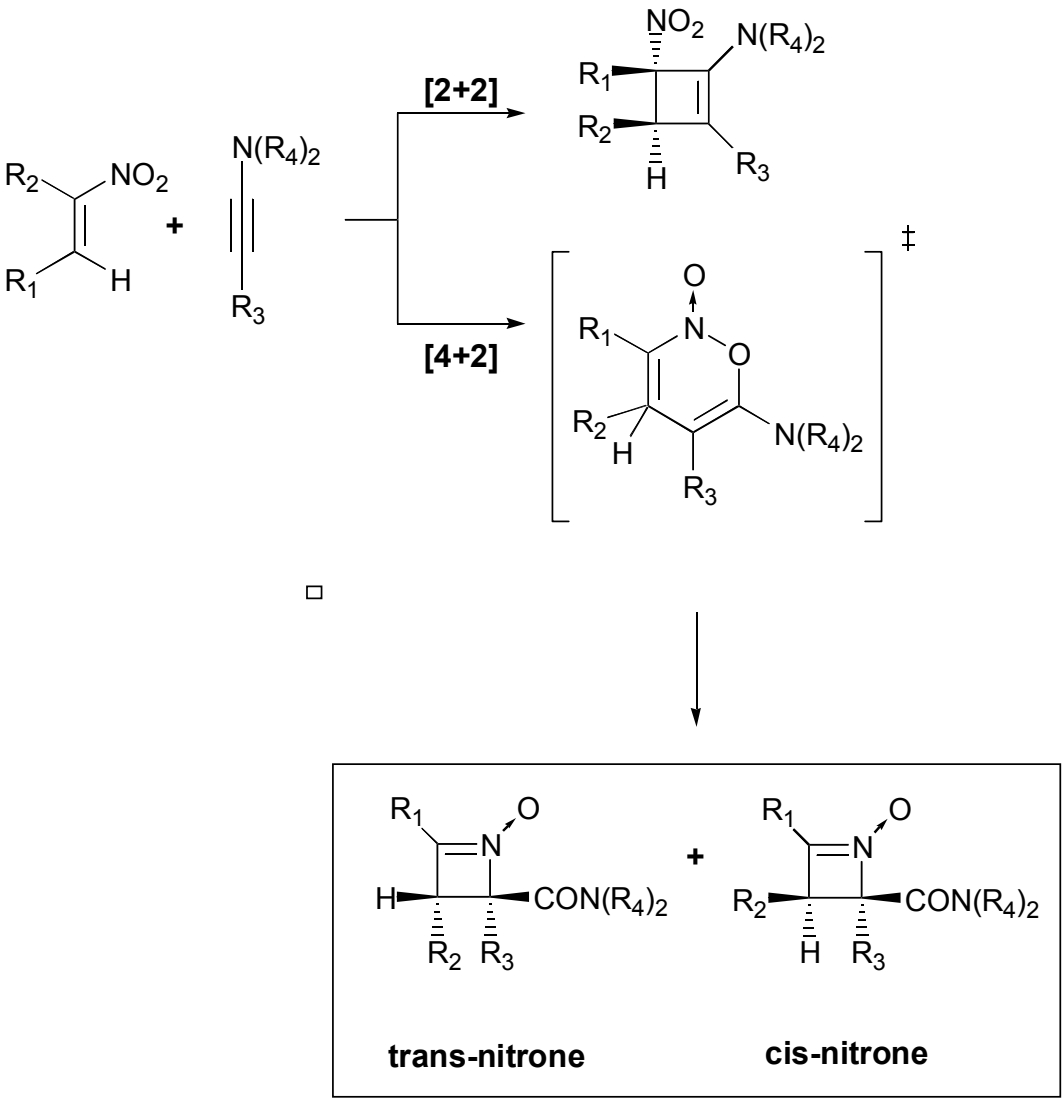
Penicilloic Acid Derivative

(b) Acids



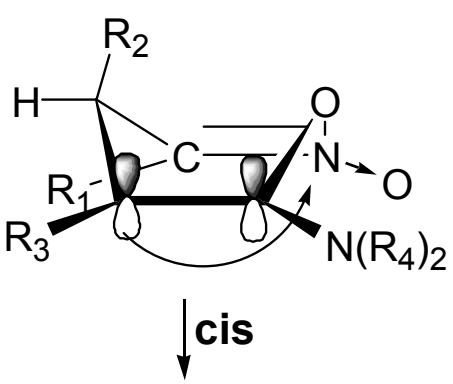
Perillic Acid Derivative

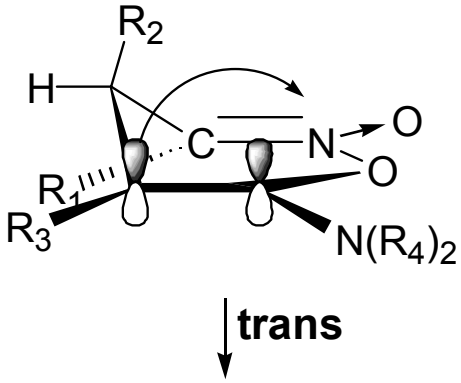
Cyclic nitrones: A useful 4-membered ring synthetic intermediate.



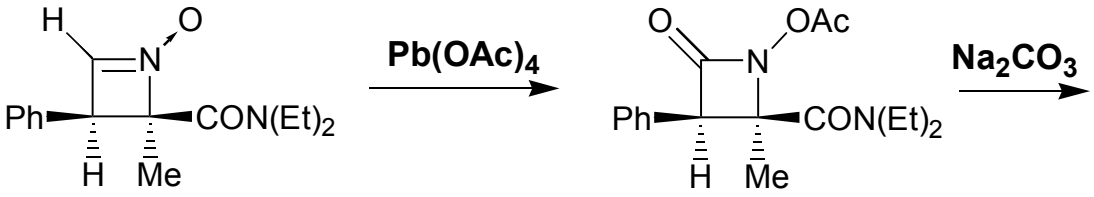
In polar solvents (e.g. AcCN) the 4+2 process is preferred.
Cis is preferred over trans nitrone formation.
Trans nitrones are only formed if the R2 substituent is bulky
Useful intermediates to built up complex ring systems via 1,3-dipolar cycloadditions.

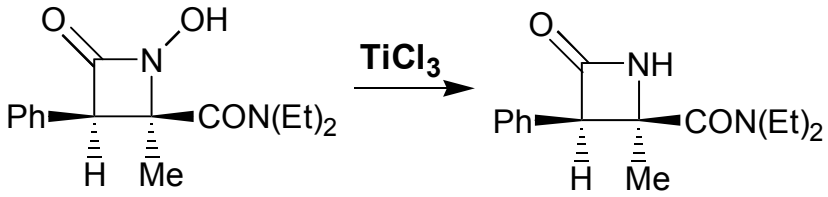
Mechanism to explain cis/trans selectivity.





Subsequent conversion into a beta-lactam derivative is possible via a sequence of Oxidation – Hydrolysis – Reduction:





Problem Sheet

Complete the scheme by entering as many different retrosynthetic pathways as you can come up with relevant to the synthesis of beta-lactams. Select 3 of your pathways and provide in each case a complete sequence of mechanisms for the synthetic route chosen.