Pergamon

Tetrahedron 55 (1999) 1519–1559

TETRAHEDRON

Tetrahedron report number 482

3-Acetoxyaminoquinazolinones (QNHOAc) as aziridinating agents: ring-opening of N-(Q)-substituted aziridines

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Received 8 December 1998

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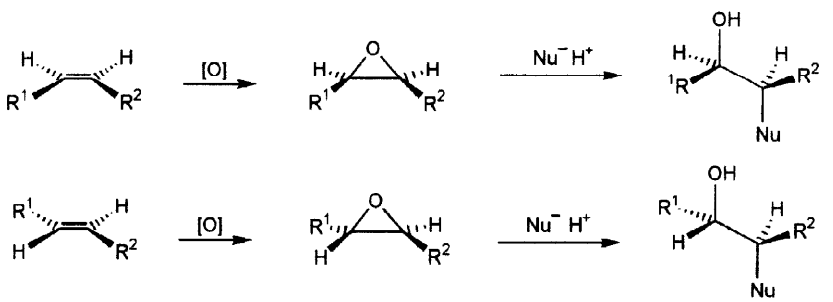
PII: S0040-4020(98)01199-5

I Aziridination: Epoxidation's poor relation

A The dearth of (stereoselective) methods for aziridination

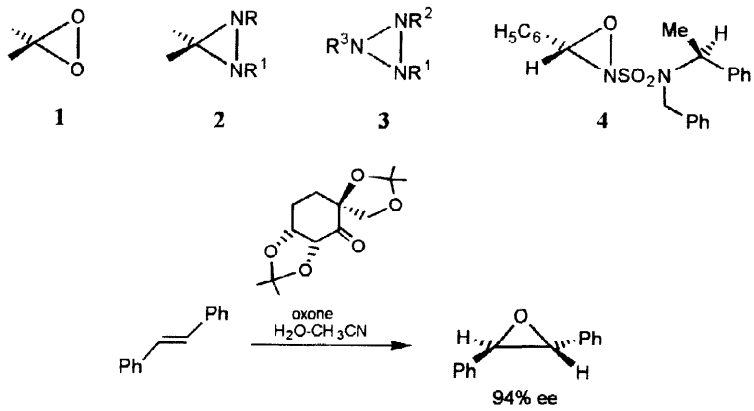
Epoxides are widely used as relay intermediates in synthesis. The sequence *E* or *Z*-alkene → epoxide → ring-opened product is an invaluable route to chiral alcohols as single diastereoisomers (Scheme 1) because methods for stereospecific epoxidation and epoxide ring-opening are available.[1] Catalytic enantioselective methods of epoxidation and particularly those of Sharpless[2] and Jacobsen[3] have made available many of these ring-opened products in high enantiopurity.



Scheme 1

By contrast, the sequence alkene → aziridine → ring-opened (amine) product enjoys nothing like the same use in synthesis in spite of the access to α- and β-amino acids, 1,2-diamines, 1,2-amino alcohols and other useful products that this route provides.[4]

It is the dearth of methods, and particularly stereoselective ones, for conversion of alkenes directly into aziridines – aziridination – which accounts for the relatively little use made of these 3-membered rings as synthetic relay intermediates by comparison with epoxides. Thus two versatile methods for stereospecific (inherently diastereoselective[5]) epoxidation of double bonds (see Scheme 1) use (a) peroxyacids and, in particular, *m*-chloroperoxybenzoic acid and (b) *tert*-butylhydroperoxide in the presence of a metal catalyst [Ti(IV), V(V), Mo(VI)].[1] Neither the nitrogen analogues of peroxyacids ($RNHOCOR^1$) nor of *tert*-butylhydroperoxide (Bu^tONHR) are aziridinating agents under the same conditions (see however below). Likewise, whereas dioxiranes **1** have found use as enantioselective epoxidising agents *e.g.* as intermediates in Scheme 2[6] the diaziridines **2**[7] (or triaziridines **3**)[8] prepared so far are not used as aziridinating agents.

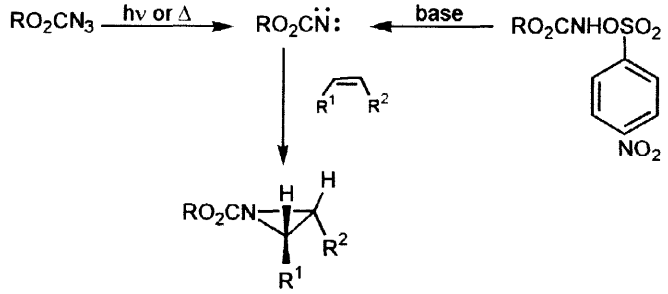


Scheme 2

The work of Davis *et al.*[9] has shown that enantiopure oxaziridines *e.g.* **4** function as highly enantioselective epoxidising agents rather than aziridinating agents.

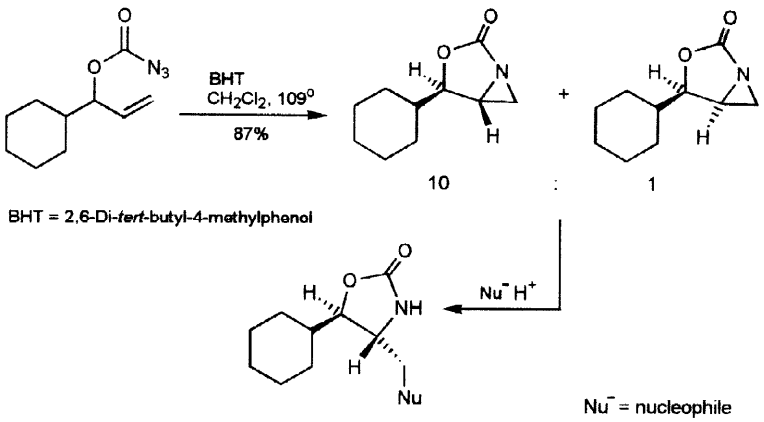
B Aziridination *via* nitrene addition to alkenes

Direct aziridination of alkenes by nitrenes is a well-studied reaction particularly using alkoxycarbonylnitrenes (Scheme 3).[10]



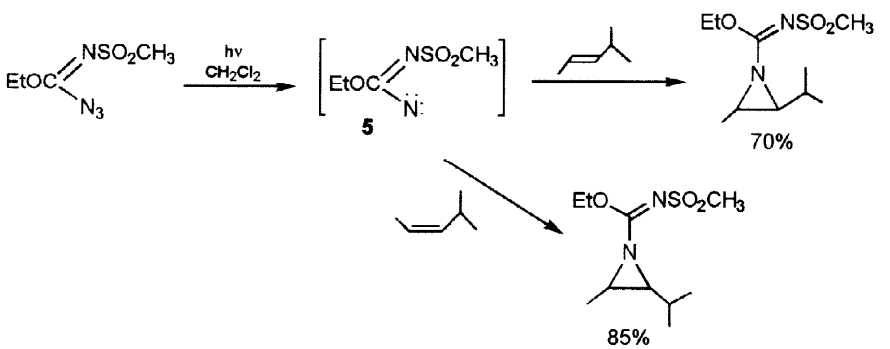
Scheme 3

However, there are severe limitations to this method in synthesis arising from competitive insertion into C–H bonds and from conversion of the initially formed singlet state of the nitrene into the triplet ground state which reacts non-stereospecifically with alkenes. Aziridinations of cyclic *cis*-alkenes[11] and intramolecular aziridination using alkoxycarbonylnitrenes (Scheme 4)[12] are more useful.



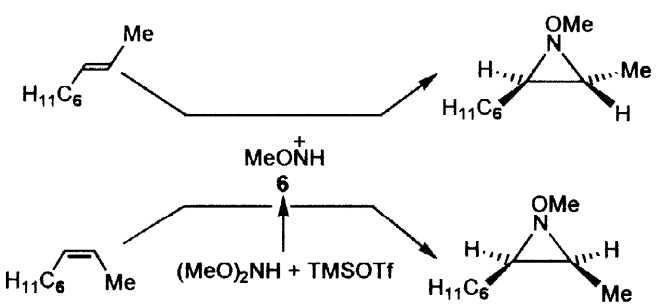
Scheme 4

Other substituents on the nitrene may reduce the reactivity, stabilise the singlet state and increase the selectivity for aziridination:[13,14] the *N*-(methanesulfonyl)ethoxycarbimidoyl nitrene **5** reacts stereospecifically with *cis*- and with *trans*-4-methylpent-2-ene.[14]



Scheme 5

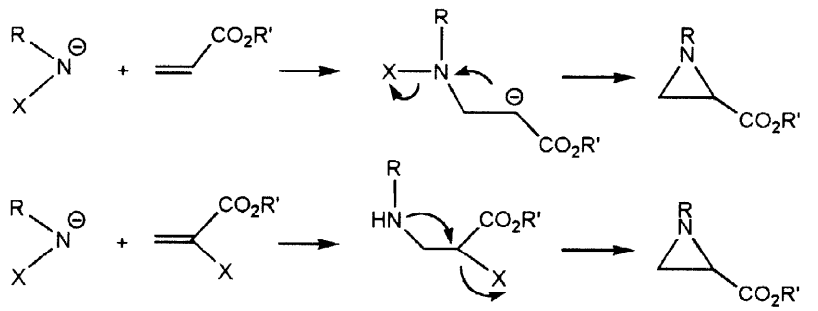
1-Methoxyaziridines are obtained stereospecifically from alkenes (Scheme 6) in a reaction mediated by the methoxynitrenium ion **6**.[15]



Scheme 6

C Aziridination *via* Michael addition

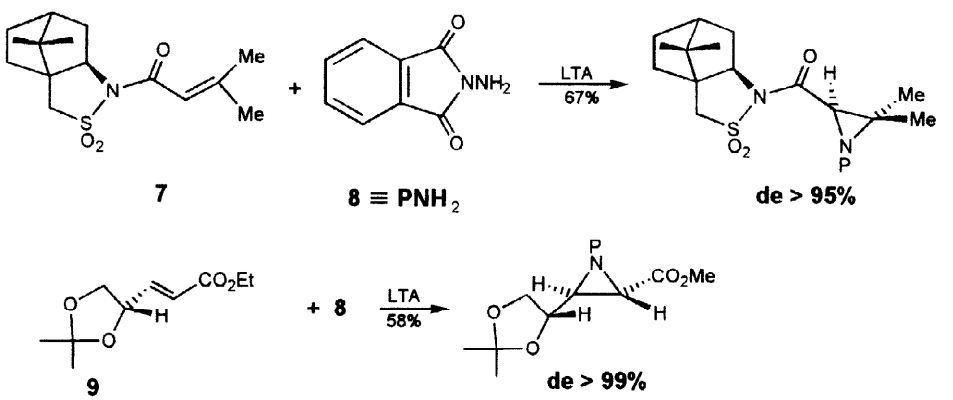
A number of methods for direct aziridination of *e.g.* α,β-unsaturated esters, ketones and nitro compounds are available which involve two step mechanisms with initial Michael addition and are not invariably stereospecific (Scheme 7).[16]



Scheme 7

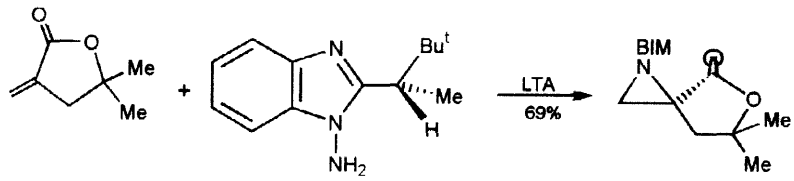
D Diastereoselective Aziridinations

There are few general methods for highly diastereoselective aziridination of alkenes with the existing chiral element (chiral centre) present in the alkene (substrate controlled diastereoselectivity)[4b,c,17] and even fewer with the chiral centre contained in the reagent (reagent-controlled diastereoselectivity). However, both the α,β-unsaturated ketone **7** bearing Oppolzer's chiral auxiliary[18] and the sugar-derived α,β-unsaturated ester **9**[19] are aziridinated by oxidative addition of *N*-aminophthalimide **8** mediated by lead tetra-acetate (LTA) with excellent diastereoselectivity (Scheme 8).



Scheme 8

A similar oxidative addition of the *N*-aminobenzimidazole **10** to an α-methylene-γ-butyrolactone gave only the aziridine diastereoisomer shown (Scheme 9) (reagent-controlled diastereoselectivity).[20]

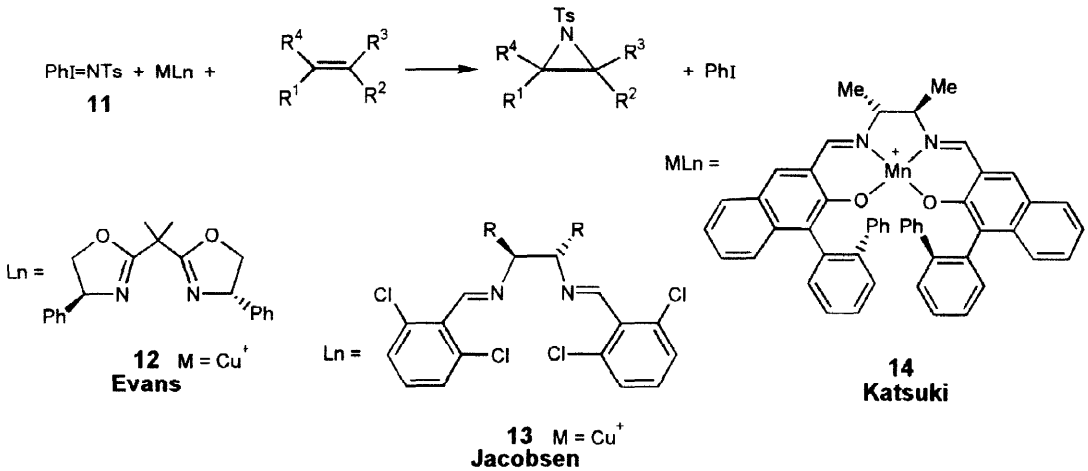


10 ≡ BIMNH$_2$ (racemic) **dr > 30:1**

Scheme 9

E Enantioselective Aziridination

The only enantioselective aziridination of alkenes of any generality is that of Evans,[21] Jacobsen[22] and Katsuki[23] and their respective co-workers. In this reaction, *N*-tosylimino-phenyliodinane **11** in the presence of a copper or manganese catalyst complexed with an enantiopure ligand (see **12-14**), aziridinates alkenes with high enantioselectivity (Scheme 10).

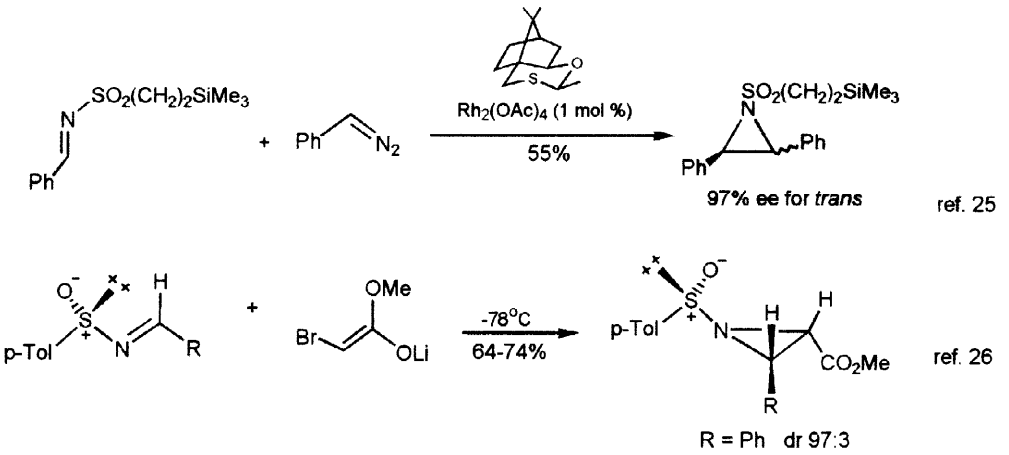


Scheme 10

Although this aziridination is in many cases highly enantioselective, it is not invariably stereospecific and aziridines derived from *cis*-alkenes may have their substituents *trans*-disposed on the aziridine ring. Consequently, application of the method is best suited to enantioselective synthesis of 2-substituted, 2,2-disubstituted or 2,3-*trans*-disubstituted aziridines or those derived from cyclic *cis*-alkenes.

II Aziridines from imines

The alternative 2 + 1 cycloaddition route to aziridines involves carbene/carbenoid or Darzens-type addition to imine double bonds.[24,4c] Some of these methods are highly stereoselective (Scheme 11).



Scheme 11

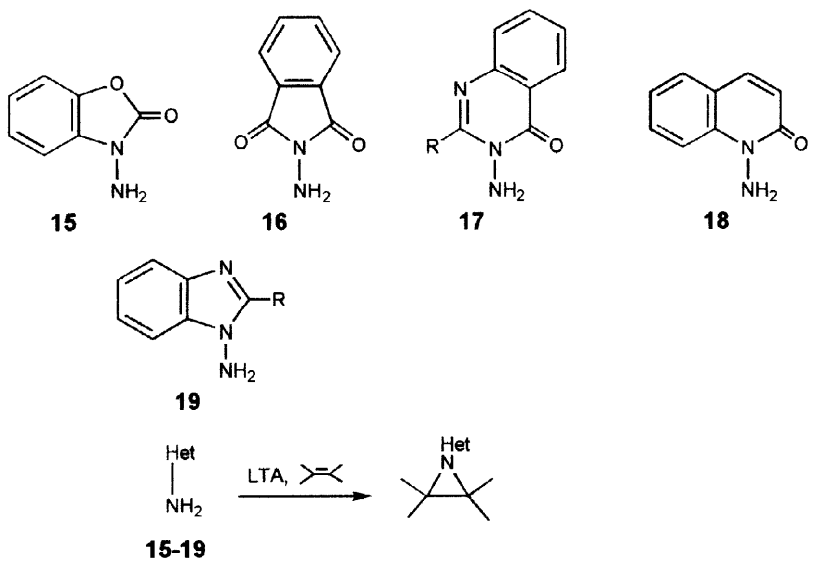
III Other routes to enantiopure aziridines

When enantiopure aziridines are required as synthetic relay intermediates they are still as often as not prepared from chiral pool available materials (amino acids,[27] sugars[28]) or from other readily available enantiopure starting materials – especially epoxides.[29]

IV Aziridination of alkenes by oxidative addition of *N*-aminoheterocycles

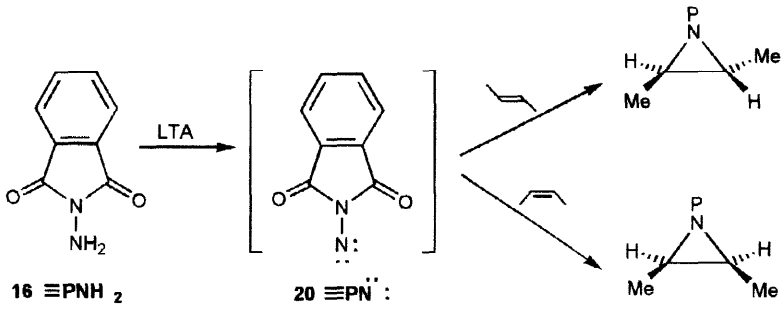
A Historical

In work carried out in Leicester University by C. W. Rees and his co-workers, it was shown that oxidation of a variety of *N*-aminoheterocyclic compounds by lead tetra-acetate (LTA) in the presence of alkenes gave aziridines, often in high yields[30,31] (Scheme 12). This family of heterocyclic compounds included the members **15-19**.



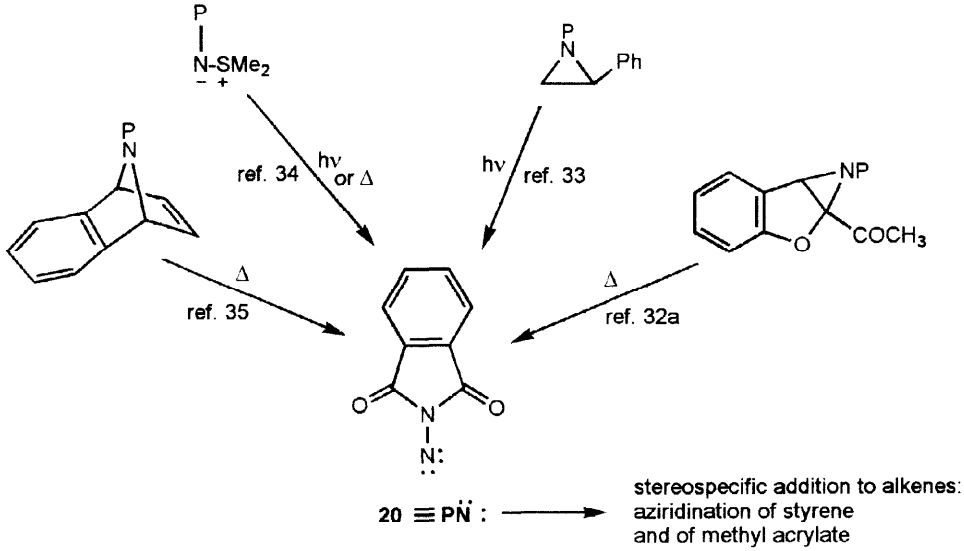
Scheme 12

Not only were aziridines in Scheme 12 obtained in good yield from electron-rich alkenes – styrene, butadiene and *trans*-but-2-ene – but also from alkenes bearing electron-withdrawing groups, *e.g.* methyl acrylate and methyl vinyl ketone. The intermediates in these aziridinations were assumed to be the corresponding *N*-nitrenes, *e.g.* **20** from oxidation of *N*-amino-phthalimide **16** (Scheme 13).



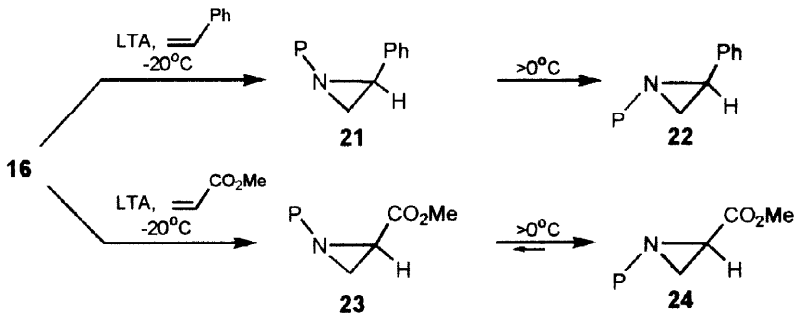
Scheme 13

It was assumed that the *N*-nitrene **20** was generated and reacted in its singlet state to account for its stereospecific addition to *cis*- and to *trans*-alkenes (Scheme 13). What appeared to be incontrovertible proof for the identity of the aziridinating species in Scheme 13 as the *N*-nitrene was its presumed generation subsequently by a number of independent routes as shown in Scheme 14.



Scheme 14

Work done subsequently in Leicester revealed that aziridinations of styrene, methyl acrylate and other alkenes using 'phthalimidonitrene' **20** generated by oxidative addition of PNH_2 **16** were completely diastereoselective in an unexpected sense (Scheme 15)[36] (occasional diastereoselectivity[37]).



Scheme 15

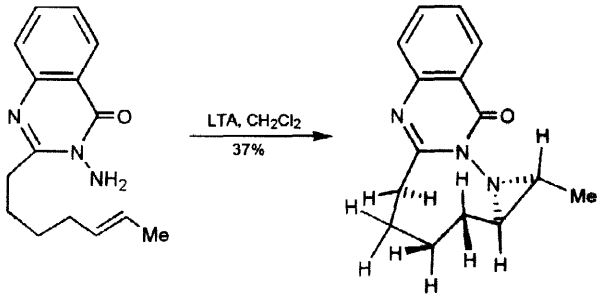
The inherently high barrier to inversion at nitrogen in aziridines is augmented by the presence of the electron-withdrawing *N*-phthalimido substituent (P) such that, at -20 °C, the rate constant for this inversion in *N*-(P) aziridines is effectively zero. Oxidation with LTA of *N*-aminophthalimide in deuterochloroform at -20 °C in the presence of *e.g.* styrene and measurement of the NMR spectrum of the reaction mixture without any intermediate warming of the solution revealed that the kinetically-formed product was exclusively aziridine **21**, the *N*-invertomer with the phenyl and phthalimide *cis* (Scheme 15). On warming above 0 °C, complete conversion of *N*-invertomer **21** to the more stable *trans*-substituted aziridine **22** occurs: signals from **21** are not observed when the spectrum was re-run at -20 °C.[36]

A similar result is found in aziridination of methyl acrylate (Scheme 15) with *cis*-aziridine **23** as the sole kinetically formed product. In this case, however, thermodynamic equilibration by warming above 0 °C gives a 5:1 ratio of aziridine invertomers **24**:**23** (unchanged on re-running the spectrum at -20 °C). Pure *cis*-aziridine **23** was crystallised from the initial cold reaction mixture and in the crystalline state at room temperature was slowly converted to the *trans*-invertomer over several weeks.

This identification of *endo* aziridines **21** and **23** as kinetically-formed products in Scheme 15 is important because it shows that in the transition state (ts$^{\#}$) for aziridination of styrene or methyl acrylate there is an attractive interaction between the phthalimide ring and the π-electron-containing substituent.

B Identification of the aziridinating agent in LTA oxidation of 3-aminoquinazolinones

3-Aminoquinazolinones **17** are particularly useful members of the family of *N*-amino-heterocyclic compounds in Scheme 12: intramolecular aziridination can be studied by incorporation of double[38-40] or triple[41] bonds into the substituent R at position 2 on the quinazolinone. Thus LTA oxidation of 3-aminoquinazolinone **25** in dilute dichloromethane solution gave aziridine **26** (Scheme 16) whose NMR spectrum at 400 MHz shows that the 8-membered ring exists in the single conformation shown with each of the anisochronous ring protons appearing as (assignable) structured multiplets.[40]

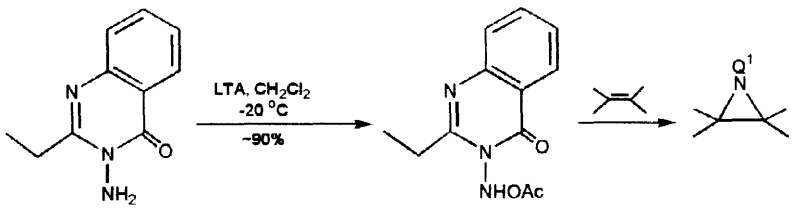


25 26

Scheme 16

Oxidation of 3-aminoquinazolinone **25** with LTA was carried out at -20 °C and the solution examined by NMR spectroscopy at -30 °C to determine whether aziridine **26** was the kinetically-formed *N*-invertomer as well as the thermodynamically favoured one (*cf.* Scheme 15). To our surprise, the NMR spectrum of the cold reaction mixture showed that no addition to the double bond in the side-chain of **25** had occurred but that the amino group protons had disappeared. Only when the temperature of the solution was raised to 0 °C did the very characteristic multiplet signals from aziridine **26** make their appearance.[42] Clearly, there was an intermediate produced by reaction of LTA with the 3-aminoquinazolinone **25** which was stable at -20 °C but effected aziridination of the double bond at higher temperature.

It was then shown that a correspondingly stable (at -20 °C) intermediate was formed by LTA oxidation of 3-amino-2-ethylquinazolinone **27** (Scheme 17) since this intermediate brought about the aziridination of alkenes added subsequently to the reaction mixture.



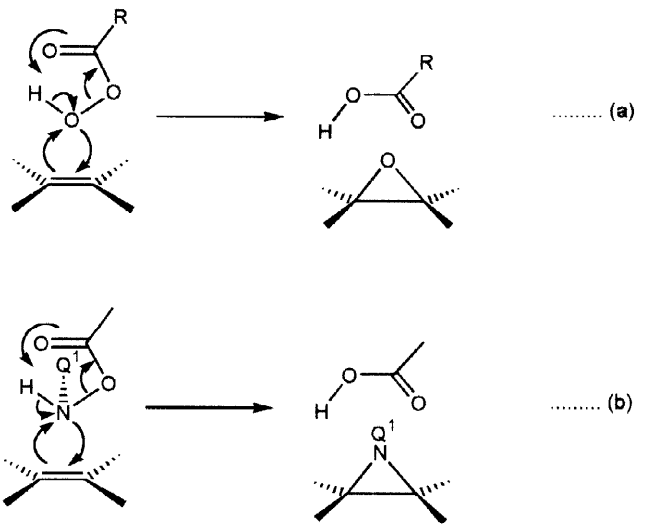
27 **28 ≡ Q^1NHOAc**

Scheme 17

The identity of this aziridinating species was revealed as the 3-acetoxyaminoquinazolinone **28** (Q^1NHOAc) by its ^1H and ^{13}C NMR spectra at -30 °C; its IR spectrum at -20 °C shows the acetoxy carbonyl stretching frequency at 1768 cm^{-1}. The rate of formation of aziridine from Q^1NHOAc **28** and the alkene is first order in each.[42]

C Comparison between aziridination by Q^1NHOAc and epoxidation by peroxyacetic acid

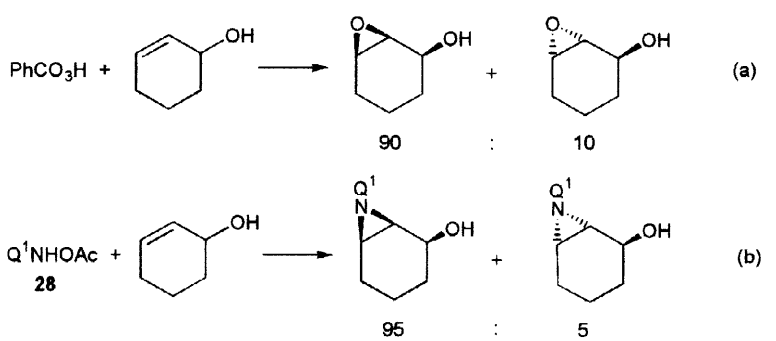
Peroxyacids are believed to epoxidise alkenes *via* the Bartlett mechanism (Scheme 18a)[43] and the mechanism for aziridination of alkenes using *e.g.* Q^1NHOAc **28** is very likely analogous (Scheme 18b).



Scheme 18

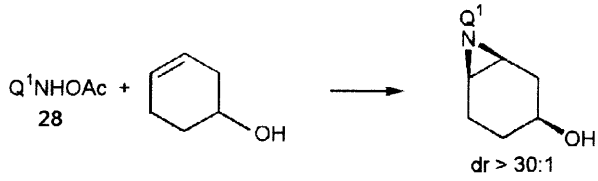
Support for the similarity between the two mechanisms comes from the similar preference for *syn*-selectivity in 3-membered ring formation from cyclohexen-3-ol (Scheme 19).[44]

There are, however, significant differences in reactivity between the two reagents: whereas Q^1NHOAc **28** aziridinates certain alkenes substituted with electron-withdrawing groups, *e.g.* methyl acrylate, in good yield, peroxyacids give poor yields of the corresponding epoxides from electron-deficient alkenes. There is also a gross difference in diastereoselectivity of 3-membered ring formation from cyclohexen-4-ol (Scheme 20);[45] peroxyacid epoxidation of this homoallylic alcohol is hardly diastereoselective at all.



Scheme 19

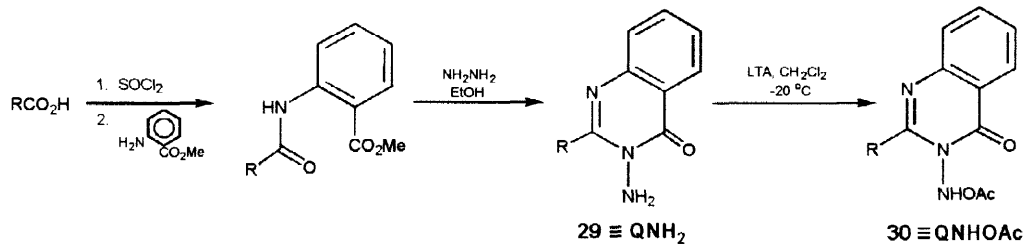
The greatest advantage in the use of 3-acetoxyaminoquinazolinones over peroxyacids is that chiral substituents can be located in the 2-substituent on the quinazolinone ring and used to induce diastereoselectivity in aziridination of prochiral alkenes (see below).



Scheme 20

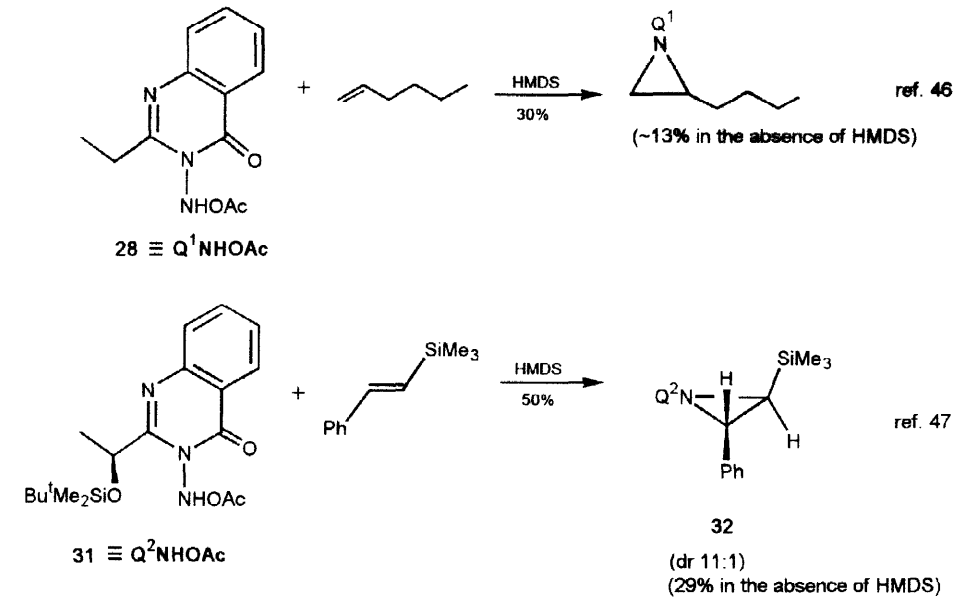
D Properties of 3-acetoxyaminoquinazolinones (QNHOAc)

Reaction of 3-amino-2-substituted-quinazolinones **29** with LTA at -20 °C in dichloromethane gives the corresponding 3-acetoxyamino derivatives QNHOAc **30** in excellent yields. Since QNH_2 **29** compounds are efficiently prepared from acids, including chiral acids (R = R*), by the route shown in Scheme 21, these aziridinating agents **30** are readily accessible.



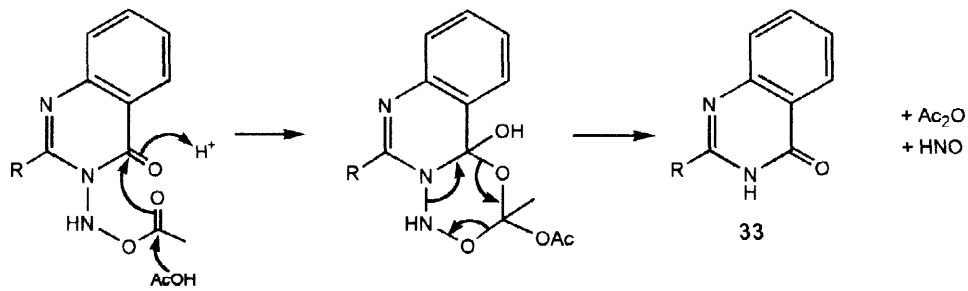
Scheme 21

2-Alkyl derivatives of QNHOAc **30** (R = alkyl) are stable for only a few minutes above 0 °C when prepared in solution as in Scheme 21 but they are stable for longer at this temperature if the acetic acid co-produced in the acetoxylation step **29** → **30** is removed. The decomposition of QNHOAc **30** by acetic acid, produced not only in the acetoxylation step but also in the aziridination itself, is an important factor in limiting yields of aziridine obtained from less reactive alkenes. A convenient method for scavenging this acetic acid is by addition of hexamethyldisilazane (HMDS) to solutions of QNHOAc **30** along with the alkene: yields of aziridines in Scheme 22 are thereby raised because competitive decomposition of Q^1NHOAc **28** and of Q^2NHOAc **31** by acetic acid is reduced.[46,47a]



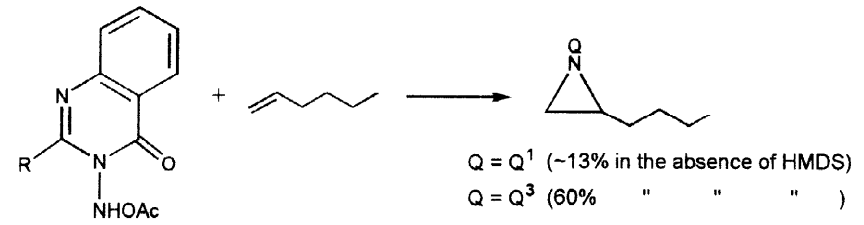
Scheme 22

Acetic acid presumably accelerates the decomposition of QNHOAc **30** by protonation of the Q group either on the carbonyl oxygen or on N–1 (Scheme 23). The major product isolated is the 3H-quinazolinone **33** which may be formed as shown.



Scheme 23

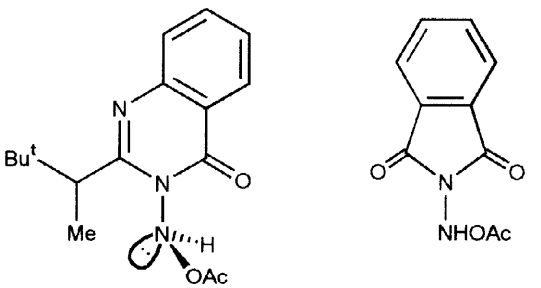
Exceptionally, 3-acetoxyamino-2-trifluoromethylquinazolinone (Q^3NHOAc) **34** is stable at room temperature in solution for several hours. Yields in aziridinations of less reactive alkenes using Q^3NHOAc **34** are superior to those using 2-alkyl-substituted analogues *e.g.* Q^1NHOAc **28** (Scheme 24).[48]



34 R = CF_3 ≡ Q^3NHOAc
28 R = Et ≡ Q^1NHOAc

Scheme 24

In the NMR spectrum of Q^1NHOAc **28** at -20 °C, the methylene protons of the ethyl group are diastereotopic and appear as an ABX_3 system. The chiral element responsible for this non-equivalence is the exocyclic nitrogen *N*HOAc which is pyramidal and is inverting slowly at least on the NMR time-scale. As expected, the presence of a chiral centre in the quinazolinone 2-substituent gives rise to diastereoisomers: in the NMR spectrum of Q^4NHOAc **35** signals from both diastereoisomers are present in a 4:1 ratio.[42]



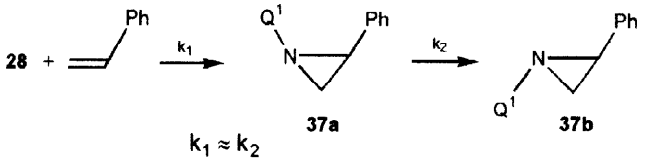
35 ≡ Q^4NHOAc (racemic) **36** ≡ PNHOAc

Attempts to separate these diastereoisomers have not been successful: a number of observations suggest that although inversion at the exocyclic nitrogen is slow on the NMR time-scale, it is fast on the time-scale of the aziridination (see below).

E Mechanisms and transition state geometries for aziridinations using QNHOAc **30** and PNHOAc **36**

In aziridination of *e.g.* styrene, butadiene, or methyl acrylate by LTA-mediated oxidative addition of *N*-aminophthalimide **16**, the initially formed product in each case is the less stable aziridine *N*-invertomer with the phthalimido and other ring substituent *cis* (Scheme 15). These aziridinations are believed to proceed *via* the intermediate *N*-acetoxyaminophthalimide **36** (PNHOAc: analogous to QNHOAc **30**[42]) in spite of the previous evidence for its identity as phthalimidonitrene **20** (Scheme 14) (see below): PNHOAc **36** is significantly less stable in solution than *e.g.* Q^1NHOAc **28** and decomposes at temperatures > -35 °C.[49]

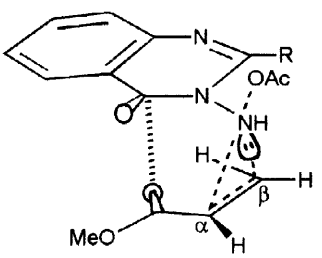
The rate of *N*-inversion of *N*-(Q)-substituted aziridines is sufficiently faster than that of the corresponding *N*-(P)-substituted analogues that it becomes comparable to the rate of aziridination with QNHOAc **30** of even reactive alkenes. Thus, using NMR spectroscopy to follow the aziridination of styrene by Q^1NHOAc **28** (Scheme 25), formation of the *cis*-aziridine *N*-invertomer **37a** was shown to be the first-formed product but, because the inversion process **37a** → **37b** is underway before aziridination is complete, it is not clear that **37a** is exclusively the initially formed product.[42]



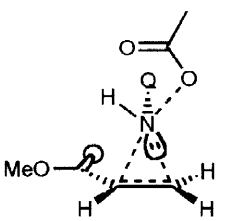
Scheme 25

We assume that, as with aziridinations using PNHOAc **36**, aziridinations at least of styrene, butadiene and methyl acrylate using QNHOAc **30** also form the corresponding *cis*-substituted *N*-invertomers exclusively as kinetically-formed products: where, exceptionally, the barrier to *N*-inversion in the *N*-(Q)-substituted aziridine product is raised (see Scheme 34), the *cis*-*N*-invertomer is found to be the sole kinetically-formed product.

What is the nature of the attractive interaction in the aziridination ts$^{\#}$ between the quinazolinone ring and the π-electron-containing substituent on the alkene which leads to formation of the *cis*-*N*-invertomer? A ts$^{\#}$ resembling **38** for aziridination of methyl acrylate allows an attractive interaction between the ester carbonyl oxygen C=*O* and the quinazolinone carbonyl carbon *C*=O (dotted line in **38a**).

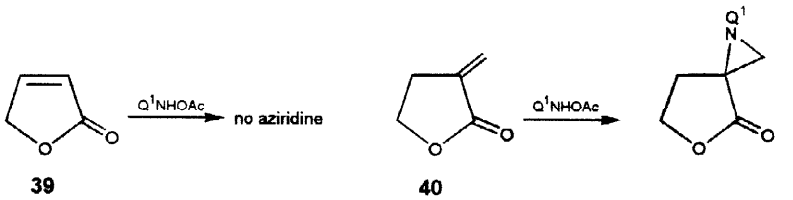


38 (a) side view



38 (b) front view

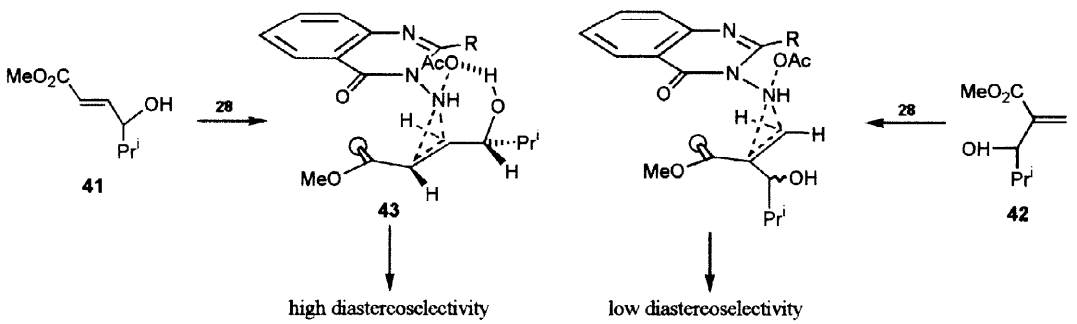
In this *endo*-ts$^{\#}$ **38a** the 'secondary' interaction between ester and Q group is only feasible if the α,β-unsaturated ester can adopt the required s-*cis* conformation. Attempted aziridination of s-*trans*-fixed α,β-unsaturated γ-lactone **39** (Scheme 26) yielded no aziridine product at all whereas the s-*cis*-fixed α-methylene-γ-lactone **40** underwent aziridination in good yield.[42]



39 40

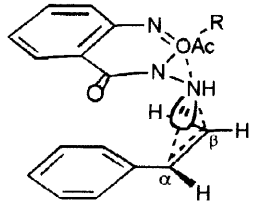
Scheme 26

Our present interpretation of ts# **38** is that, although both aziridine ring bonds are being formed, N-C_β bond formation is running ahead of C_α-N bond formation with its accompanying S_N2-type displacement of the acetoxy group from the exocyclic nitrogen. According to this interpretation, the interaction between the (ester)C=*O* and (Q)*C*=O activates the alkene towards Michael addition at C_β by the acetoxyamino nitrogen *N*HOAc. At the same time, this interaction also reduces the electrophilicity of the Q carbonyl group and, by a relay effect, increases the availability of the *N*HOAc lone pair. This mechanism specifies a particular configuration at the (stereolabile) NHOAc centre *i.e.* with the acetoxy group on this nitrogen distal to the quinazolinone carbonyl group as shown in ts# **38a**, to allow for backside S_N2 displacement. In accordance with this mechanism we have interpreted changes in the preferred sense of diastereoselectivity in aziridinations of γ-hydroxy- and α-hydroxymethyl-substituted α,β-unsaturated esters **41** and **42** respectively (and their *O*-acetates) (Scheme 27) as supporting the proposed ts# structure **38**: only with the hydroxy group in the γ-position as in ts# **43** is hydrogen bonding with the departing acetoxy group possible.[50]



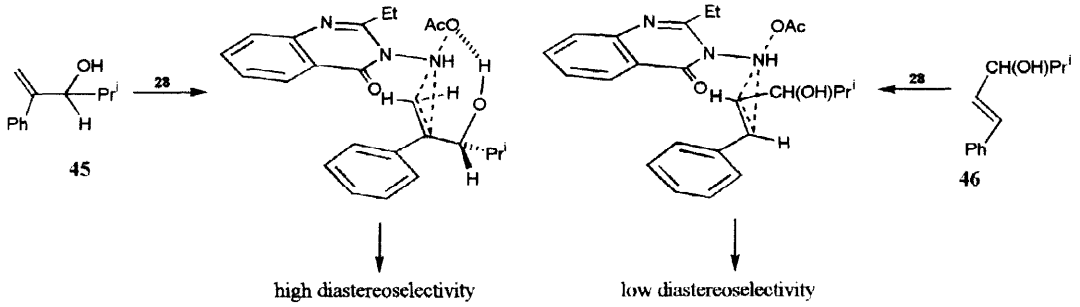
Scheme 27

With electron-rich alkenes, *e.g.* styrene, the ts# geometry **44** is assumed to be similar to that in ts# **38** but with an attractive π-π interaction[51] between the phenyl ring and the quinazolinone carbonyl group.[52]



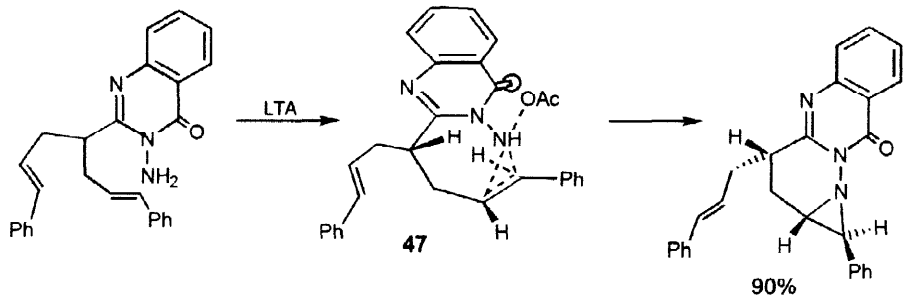
44

Here, C_β–N bond formation is thought to run ahead of N–C_α bond formation *i.e.* with partial carbocation generation at the benzylic C_α–position. Thus the order in which the ring bonds are formed is different from that in ts# **38** and in ts# **44** the acetoxy group is proximal to the quinazolinone carbonyl group. From the different orientations of the acetoxy groups in ts#s **38** and **44**, one would expect hydrogen bonding to be feasible in aziridination of α-hydroxymethylstyrene **45** (Scheme 28) but not in aziridination of γ-hydroxystyrene **46** (*i.e.* a reversal of the situation using the analogous esters in Scheme 27). The products[53] isolated from aziridination of alkenols **45** and **46** are consistent with this interpretation.



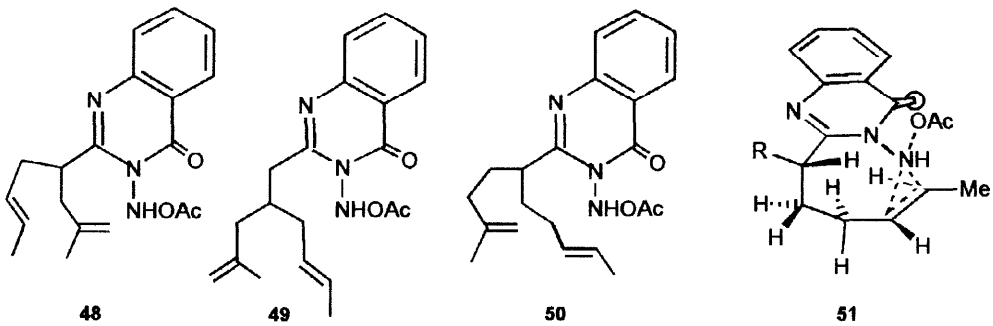
Scheme 28

Whereas *endo*-overlap of ester and quinazolinone appears to be mandatory for successful aziridination of α,β-unsaturated esters (see above), *endo*-overlap of phenyl and quinazolinone, although preferred, is not a necessity for successful aziridination of styrene derivatives: intramolecular aziridination in Scheme 29 takes place in excellent yield presumably *via* ts# **47** in which the *endo*-overlap present in ts# **44** is geometrically impossible.[38,54]



Scheme 29

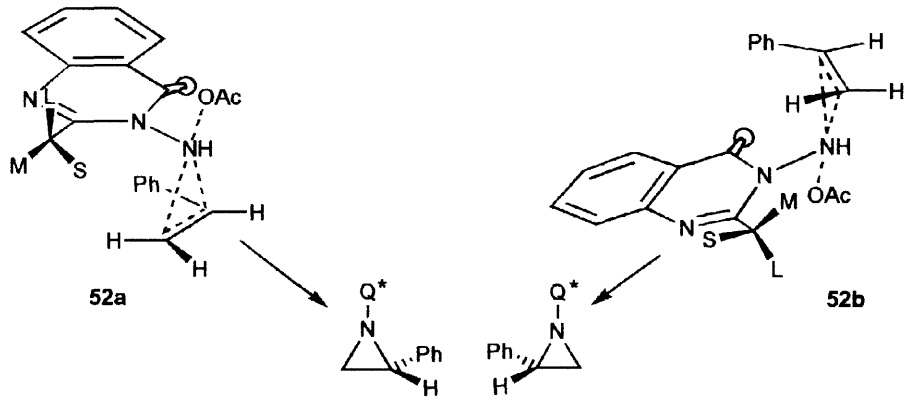
Evidence for an approach of QNHOAc **30** and the alkene double bond in nearly parallel planes with a geometry resembling that in ts# **44** comes from a study of intramolecular aziridinations using 3-acetoxyaminoquinazolinones **48**, **49** and **50**. The changes in double bond reactivity in the bifurcated side chain with tether length suggested that reaction *via* a concerted ts# was better accommodated *via* a 3-atom (rather than a 2-atom) linking tether with a ts# resembling **51** (from **50**).[39,54]



48 **49** **50** **51**

F Diastereoselectivity in aziridinations using 3-acetoxyaminoquinazolinones bearing chiral 2-substituents

The compact nature of transition states **38** and **44** suggested that the presence of a chiral 2-substituent on the quinazolinone (R = R*) might bring about reagent-controlled diastereoselectivity in aziridination of prochiral alkenes. In aziridination of styrene, for example, diastereoselectivity will be obtained if ts# **52a** is favoured over **52b** (Scheme 30).

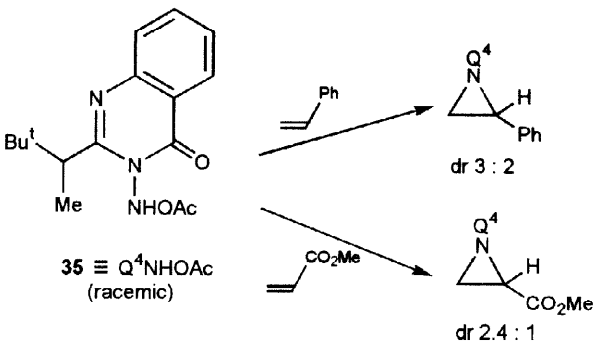


Scheme 30

In Scheme 30, approach of the alkene is assumed to take place opposite the largest group L and whether ts# **52a** is favoured over **52b** or *vice versa* depends on the site preferences of S and M in the two transition states.

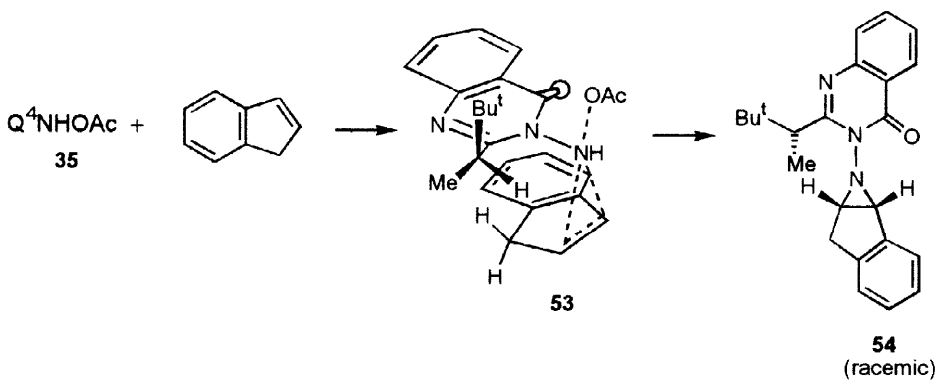
A particular example of substituents on the chiral centre whose site selectivities are presumably determined by steric effects is found in Q[4]NHOAc **35** (Scheme 31) where *tert*-butyl, methyl and hydrogen are L, M and S, respectively. With approach of the alkene

opposite the *tert*-butyl group, it is not clear that site selectivities for M and S in either ts# **52a** or **52b** will be preferred. It is not surprising, therefore, that aziridinations of styrene or of methyl acrylate with Q^4NHOAc **35** are poorly diastereoselective (Scheme 31).



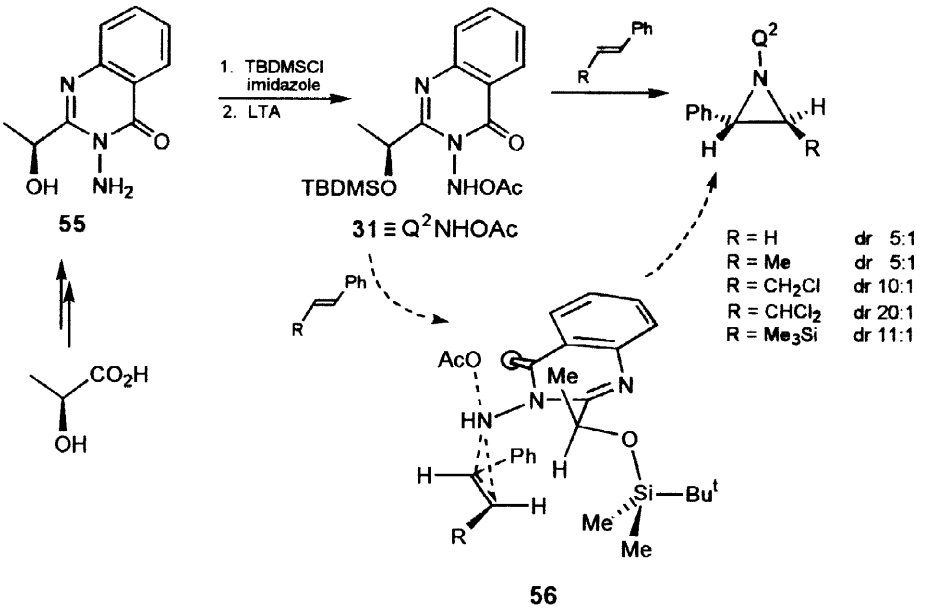
Scheme 31

However, aziridination of indene with Q^4NHOAc **35** is completely diastereoselective (Scheme 32) and the relative configuration in aziridine **54** has been confirmed by an X-ray structure determination on a product from ring-opening of the 3-membered ring.[55] In the ts# **53**, the site selectivity shown minimises steric interaction with the 'upper' proton of the methylene group.



Scheme 32

In general, the site preferences of the three substituents L, M and S in transition states **52a** and **52b** will be influenced by other factors in addition to their steric bulk. These factors will include polar/electronic interactions with neighbouring atoms/groups and with the solvent. There may be stereoelectronic effects associated with particular locations of L, M and S whose existence may not always be evident at the outset. Indeed, a highly diastereoselective outcome in the aziridination may reveal the presence of a previously unsuspected stereoelectronic effect within the (LMS)CQ ensemble. Thus Q^2NHOAc **31** is prepared as a single enantiomer from the lactic acid-derived 3-aminoquinazolinone **55** by silylation followed by *N*-acetoxylation with LTA (Scheme 33).



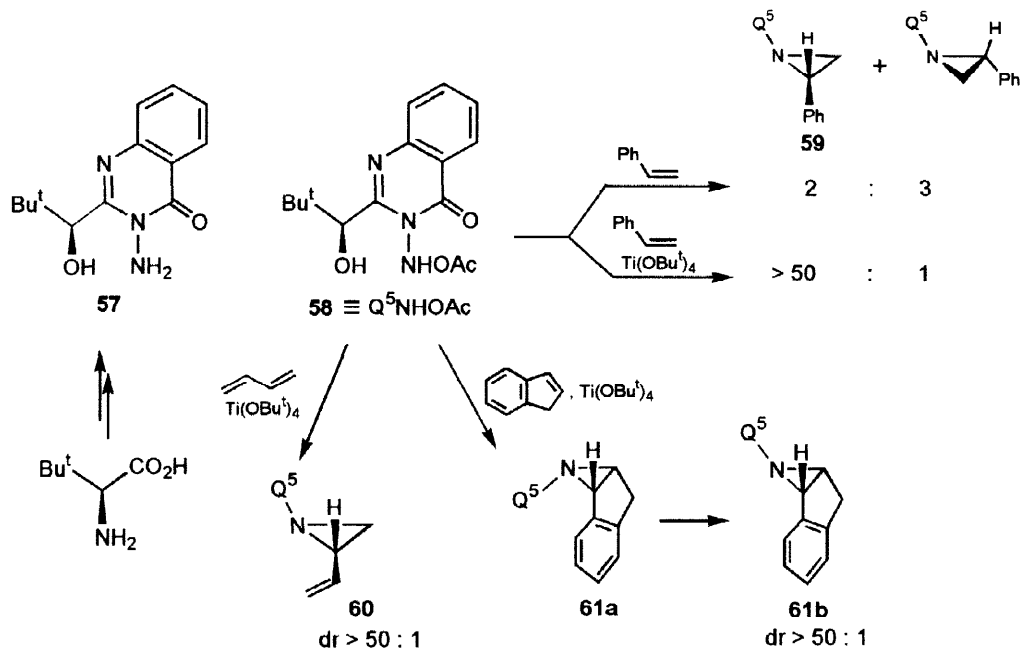
Scheme 33

Aziridination of various styrene derivatives with Q^2NHOAc **31** is surprisingly diastereoselective particularly by comparison with the corresponding aziridinations of Q^4NHOAc **35** with its better size-differentiated substituents on the chiral centre (*cf.* Scheme 31). This superior diastereoselectivity has been ascribed[56] to a conformational preference for the silyloxyalkyl group as shown in ts# **56**. Here the C–O bond of the silyloxy group lies in, or close to, the plane of the quinazolinone ring: the two methyl groups on the silicon then dictate the site preferences for methyl and hydrogen on the chiral centre and approach of the alkene is from the less hindered face of the quinazolinone *syn* to the hydrogen. Thus in this ts# **56** the site selectivities of the three substituents on the chiral centre are controlled not simply by steric effects but also accommodate a conformational preference within the side chain.

In Scheme 33 it is clear that there is another subtle electronic effect at work which results in increased diastereoselectivity with increased electronegativity of the β-substituent [H, $CH_3 \rightarrow CH_2Cl \rightarrow CHCl_2$].[57] Examination of models or even inspection of ts# **56** suggests that this increased diastereoselectivity is not the result of increased bulk of the R group. We have correlated this increased diastereoselectivity with changes in HOMO/LUMO levels and in coefficients at C_α and C_β in the β-substituted alkenes: the more electron-withdrawing R group on the alkene leads to a tighter ts# **56** and hence to higher diastereoselectivity by increasing the site preferences for methyl and hydrogen on the chiral centre.

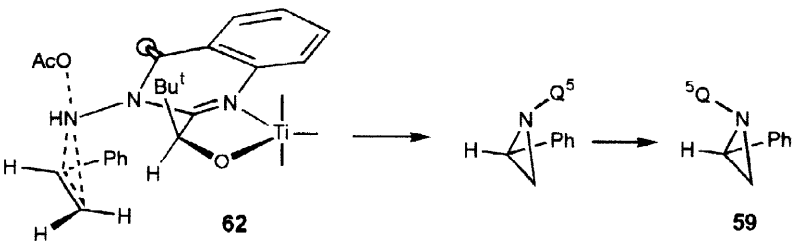
G Diastereoselectivity using chelation control of the Q-(chiral 2-substituent) bond conformation

Prediction of site preferences for the three substituents L, M and S on the chiral centre in aziridination transition states **52a** and **52b** would be greatly facilitated if their positions were fixed by restricting rotation around the Q–C(LMS) bond. Aziridination of styrene or butadiene with Q^5NHOAc **58** (Scheme 34) is hardly diastereoselective at all. However, in the presence of titanium(IV) *tert*-butoxide, the aziridination is completely diastereoselective in each case.[58] Using indene the first formed product is the expected (see earlier) *cis-N*-invertomer **61a** which is slowly converted into the *trans*-form **61b** at >5 °C and is also obtained as a single diastereoisomer.



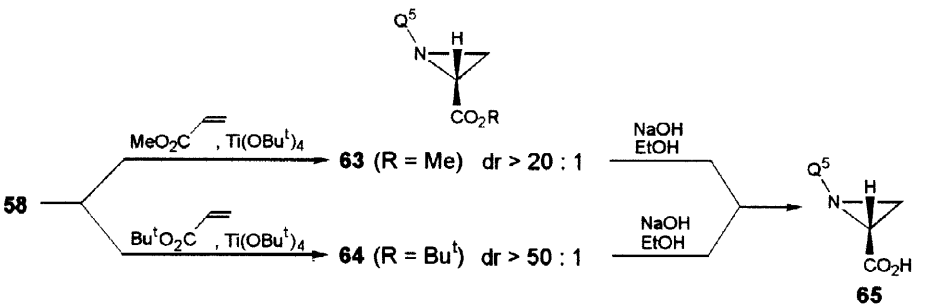
Scheme 34

Formation of a titanium alkoxide with the hydroxy group on the chiral centre in Q^5NHOAc **58** and chelation of the titanium with N–1 of the quinazolinone fixes the orientation of the *tert*-butyl and hydrogen (Scheme 35). The site preferences of these substituents are clearly best accommodated in ts# **62** and the relative configuration of the created chiral centre was confirmed by an X-ray crystal structure determination of aziridine **59**. The absolute configuration of aziridine **59** as shown follows from that of 3-amino-quinazolinone **57** which is prepared from (S)-*tert*-leucine in 45% overall yield without the need for chromatography at any stage.



Scheme 35

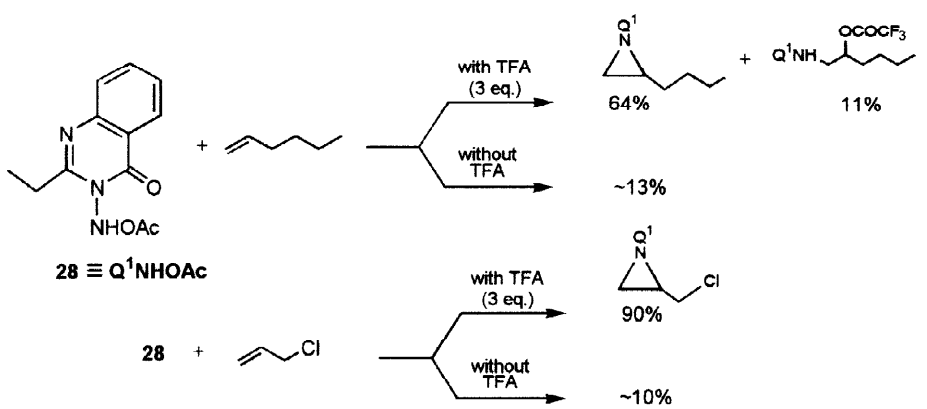
Aziridination of methyl acrylate and of *tert*-butyl acrylate using Q^{5}NHOAc **58** (Scheme 36) is also highly diastereoselective although in these cases there is evidence to suggest that the reaction does not proceed *via* a ts$^{\#}$ analogous to **62**. The preferred sense of diastereoselectivity in both cases is the same since the major aziridines **63** and **64** are both hydrolysed to the same aziridine carboxylic acid **65**.[59] An X-ray crystal structure on aziridine **64** confirms the relative and hence absolute configuration as shown.



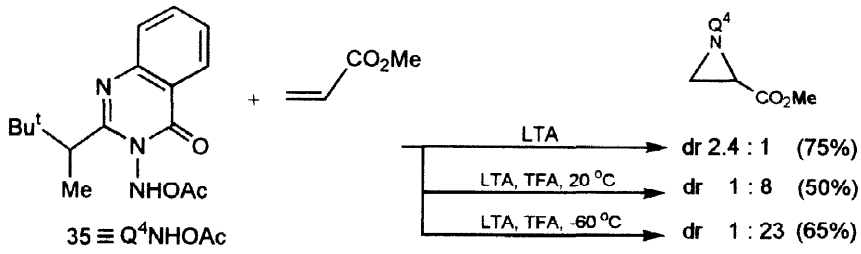
Scheme 36

H Aziridination using QNHOAc **30** – trifluoroacetic acid: evidence for a change in transition state geometry

Addition of TFA (3 eq) to aziridinations of alkenes using QNHOAc **30** has a number of beneficial effects: the yields of some otherwise less reactive alkenes are raised (Scheme 37)[60] and the diastereoselectivity in many cases is increased (Scheme 38).[61,54]



Scheme 37



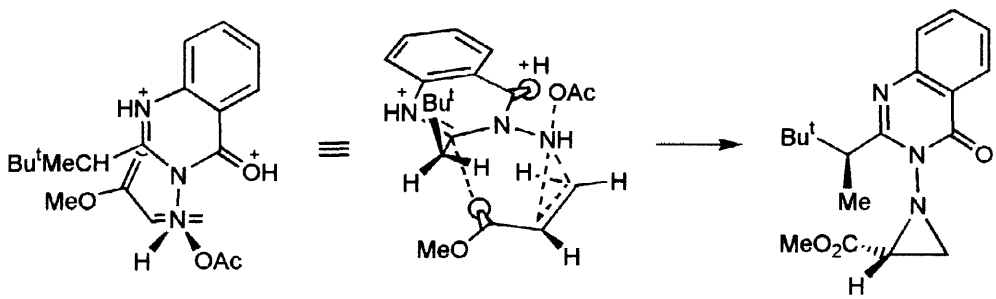
Scheme 38

The beneficial effect of TFA on yields of aziridines would seem to be at odds with our earlier conclusion that yields of aziridines are raised when acetic acid is removed from the reaction mixture (Scheme 22). However, it is necessary to use an excess (3 eq.) of TFA for its effect to be manifest which suggests that a diprotonated species may be involved whose reactivity as an aziridinating agent exceeds its rate of decomposition. Consistent with this conclusion is the finding that phthalimide (60%) is the only isolated product from oxidation of *N*-aminophthalimide **16** with LTA in the presence of TFA and either allyl chloride or hex-1-ene (*cf.* Scheme 37): *N*-aminophthalimide lacks the additional basic site at N–1 of the quinazolinone and so diprotonation will be less likely.

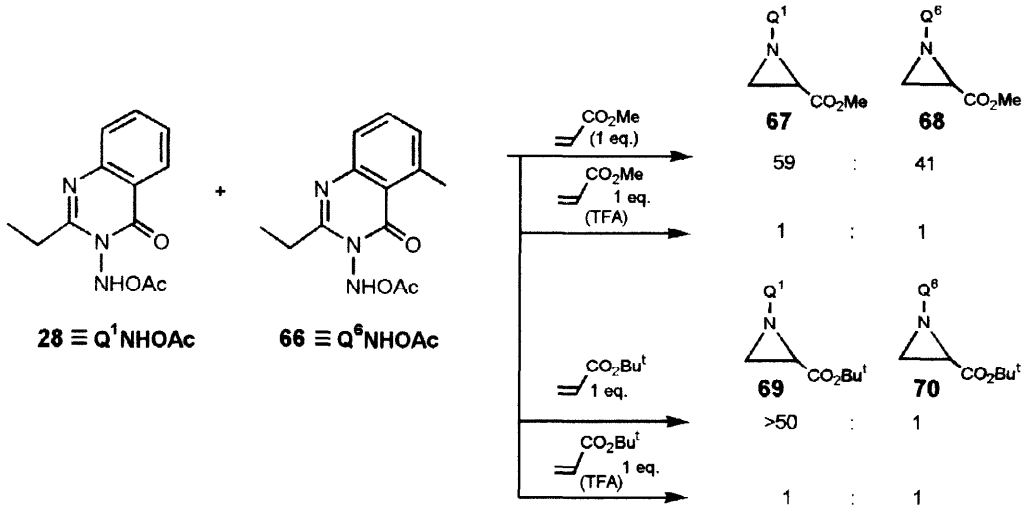
To account for the increase in *diastereoselectivity* in Scheme 38 brought about by TFA, it was proposed[61] that protonation on N–1 of the quinazolinone ring resulted in a change in ts$^{\#}$ geometry from the usual (ester)C=*O*/(Q^4)*C*=O overlap (see **38**) to (ester)C=*O*/(Q^4)*C*=NH$^+$ overlap (Scheme 39).

Thus the effect of N–1 protonation of the Q^4 group is to favour overlap of the ester with the now more electrophilic imine carbon 2 and to bring this ester into closer proximity to the chiral centre; the site preferences of the chiral 2-group substituents are thereby increased thus augmenting and changing the preferred sense of the diastereoselectivity.

Support for this change in ts$^{\#}$ geometry comes from competitive aziridination of α,β-unsaturated esters using the two 3-acetoxyaminoquinazolinones Q^{1}NHOAc **28** and its 5-methyl congener Q^{7}NHOAc **66** (Scheme 40).[55]



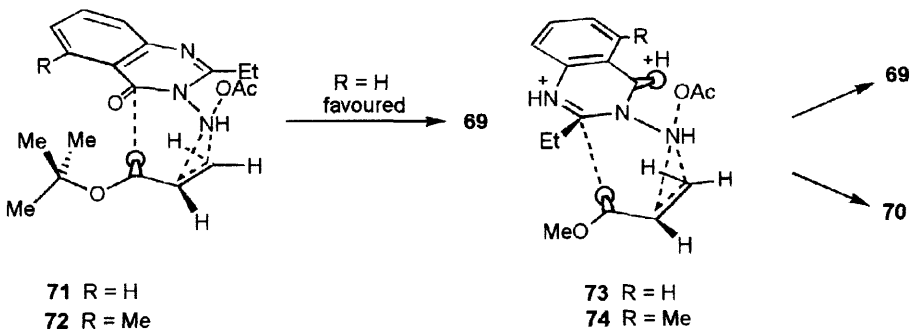
Scheme 39



Scheme 40

Thus competitive aziridination of methyl acrylate (1 eq.) by Q¹NHOAc **28** (1 eq.) and Q⁶NHOAc **66** (1 eq.) gave only a slight excess of aziridine **67** over **68**. In the competitive aziridination of *tert*-butyl acrylate (1 eq.) the proportion of aziridine **69** greatly exceeds that of **70**. However, when these competitive aziridinations of each ester (1 eq.) were carried out in the presence of TFA, the ratios of aziridines **67** : **68** and **69** : **70** present in the crude reaction mixtures were 1:1 in each case.[55]

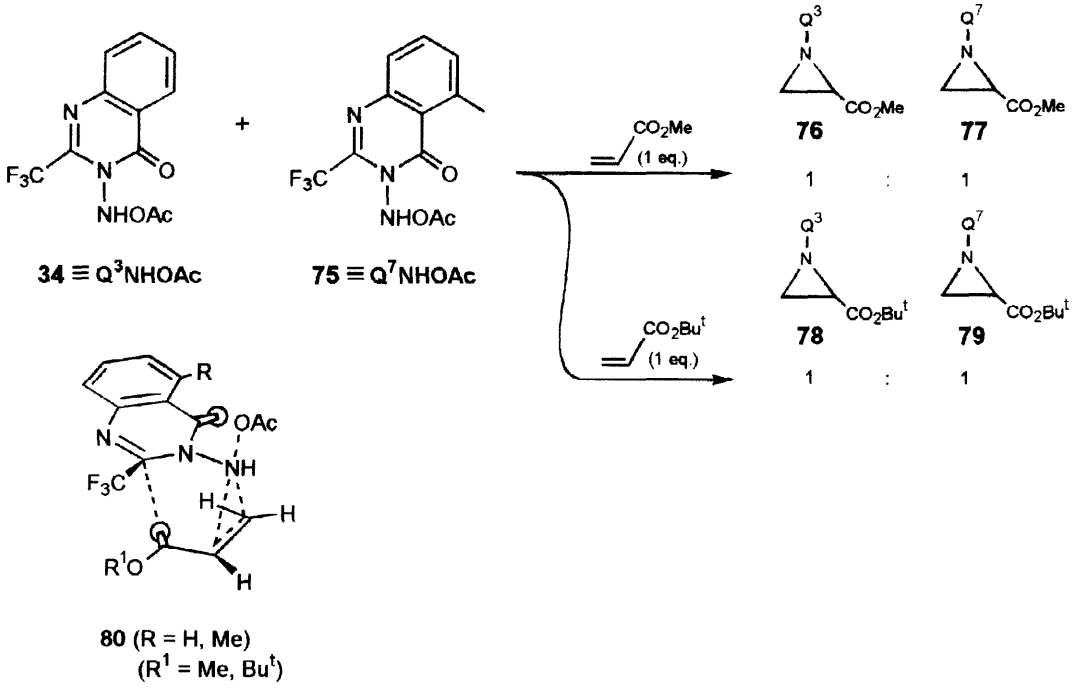
Our interpretation of these changes in ratios is that steric interaction between the 5-methyl group in Q⁶NHOAc **66** and the *tert*-butyl group in the ester destabilises ts# **72** relative to **71** (Scheme 41).



Scheme 41

However, in the presence of TFA, the switch in ts# geometry means that the presence of the methyl group in ts# **74** has no destabilising effect relative to **73** and consequently a 1:1 ratio of aziridines **69** and **70** is produced.

Similar competitive aziridinations using Q³NHOAc **34** and its 5-methyl analogue **75** (Scheme 42) reveal that C=*O*(ester)–*C*=N(Q³) overlap is preferred *even in the absence of TFA*.[55]

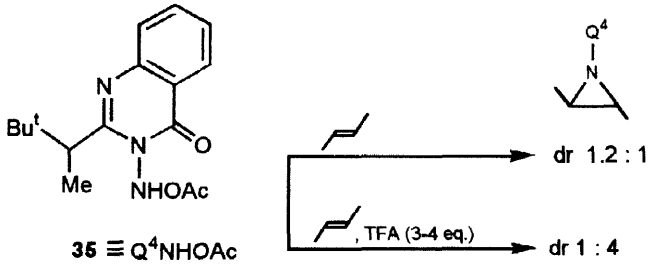


Scheme 42

Thus a 1:1 ratio of aziridines **76** and **77** is obtained from methyl acrylate and a 1:1 ratio of aziridines **78** and **79** from *tert*-butyl acrylate. Comparison of these ratios together with those in Scheme 40 suggest that a common ts# **80** is involved in each case in which no selectivity resulting from the presence of the 5-methyl group is expected.

Using a chiral electron withdrawing group to replace the trifluoromethyl in Q³NHOAc **34** would be expected to lead to enhanced diastereoselectivity in aziridination of α,β-unsaturated esters in the absence of TFA *via* a ts# resembling **80**. This possibility is under investigation.

Aziridinations using QNHOAc–TFA cannot be applied to electron-rich alkenes *e.g.* styrene which are polymerised by the acid present but the ratio of diastereoisomers obtained from aziridination of *trans*-but-2-ene with Q⁴NHOAc **35** is changed from 1.2:1 in the absence of TFA to 1:4 in its presence (Scheme 43).[62]

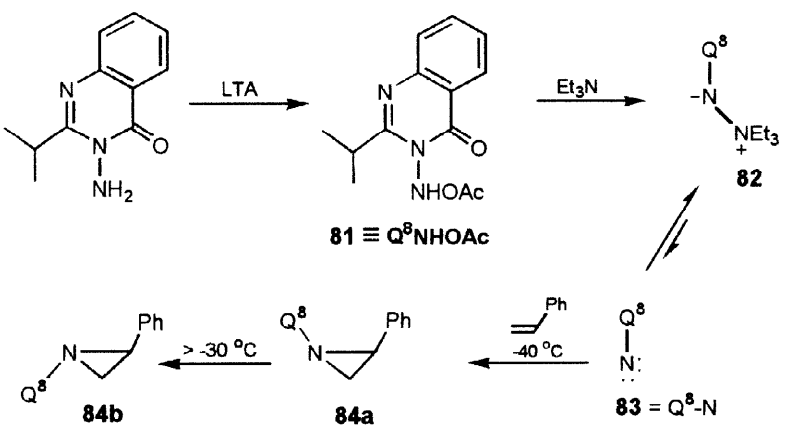


Scheme 43

V *N*-Phthalimidonitrene and (3,4-dihydro-4-oxoquinazolin-3-yl)nitrene

The apparent identification of the intermediate in aziridination of alkenes by LTA oxidation of *N*-aminophthalimide **16** as the corresponding *N*-nitrene **20** was referred to earlier (Schemes 13 and 14). Subsequently, the aziridinating species in this oxidation was formulated as *N*-acetoxyaminophthalimide **36** from the similarity of its reactions to those of the better characterised 3-acetoxyaminoquinazolinones *e.g.* Q^1NHOAc **28**.[42] Reconciliation of these contradictory conclusions came from a comparison of the *selectivity* of aziridination for two alkenes of different electron demand (styrene and methyl acrylate) using LTA oxidation of *N*-aminophthalimide and the different aziridinating methods in Scheme 14.[35a] This selectivity in reaction of styrene and methyl acrylate is the *same* (1:1.8 respectively) for the intermediate, presumably phthalimidonitrene **20**, generated in boiling benzene from the precursors shown in Scheme 14 but different (ratio 1:1.3) for the intermediate, presumably *N*-acetoxyaminophthalimide **36**, generated from *N*-aminophthalimide **16** by LTA oxidation in boiling benzene. Remarkably, therefore, there are two aziridinating species, differing only in the presence or otherwise of the elements of acetic acid on the exocyclic nitrogen which have an independent existence but a very similar reactivity profile.

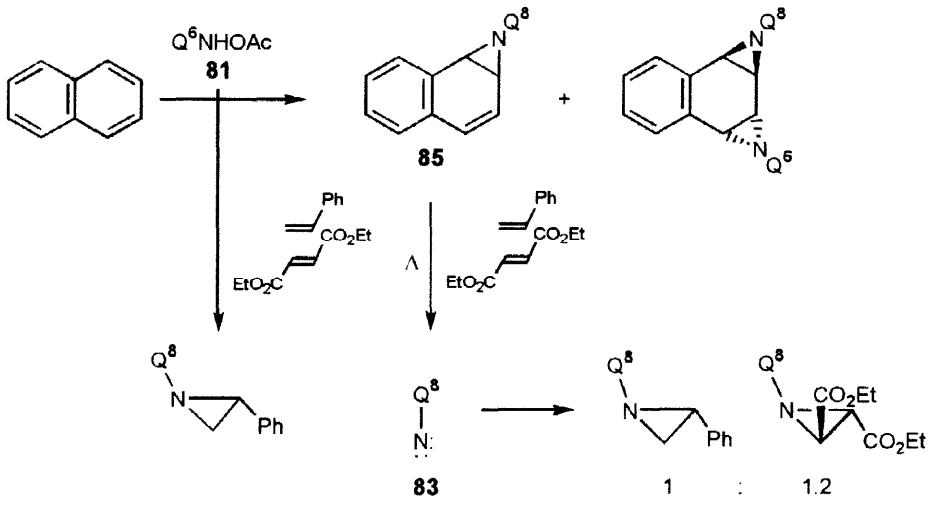
Support for this conclusion comes from identification of the analogous (3,4-dihydro-4-oxoquinazolin-3-yl)nitrene **83** (Q^6N) (Scheme 44) as an aziridinating species and *its* very similar but identifiably different reactivity profile to that of the corresponding 3-acetoxy-aminoquinazolinone Q^8NHOAc **81**. Thus, reaction of Q^8NHOAc **81** with triethylamine in dichloromethane at -30 °C gives a solution of the ammonium ylide **82**. Solutions of this ylide bring about the aziridination of alkenes at temperatures slightly lower than those required for aziridinations using the starting Q^8NHOAc **81**.[63] As a result, by using styrene and following the aziridination by NMR, *cis*-*N*-invertomer **84a** was shown to be the first formed aziridine with the onset of inversion to the *trans*-form **84b** observable at -30 °C.



Scheme 44

The nitrene Q^8N **83**, formed by reversible cleavage of ylide **82** is believed to be the aziridinating species in this conversion. Like the corresponding Q^8NHOAc **81** it adds stereospecifically to *cis*- and *trans*-but-2-ene and adds to methyl acrylate as well as to styrene. As has been mentioned previously, the corresponding aziridine *cis*-*N*-invertomer **37a** is believed to be, but was not proved to be, the sole kinetically-formed product from reaction of Q^1NHOAc **28** and styrene (Scheme 25).

An alternative route to what appears to be the same nitrene **83** is by heating the naphthalene-derived aziridine **85** (Scheme 45).[64]



Scheme 45

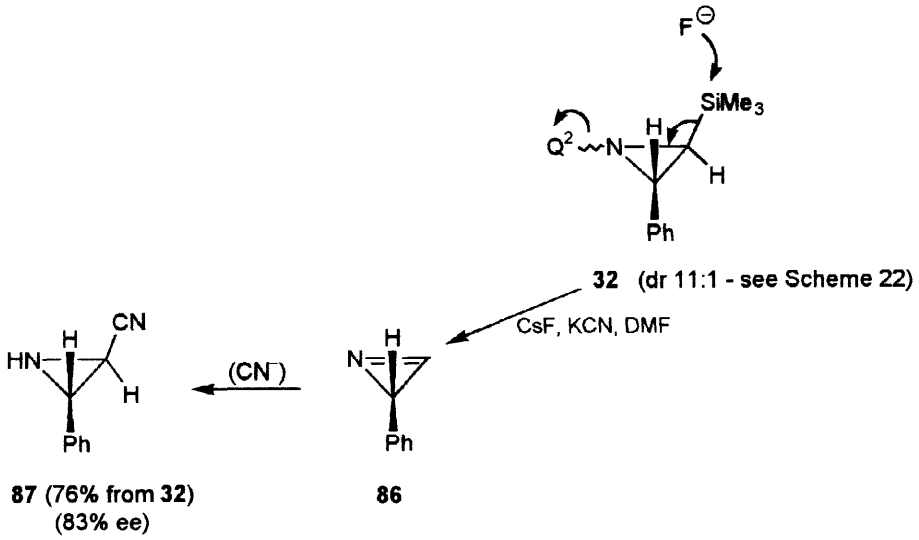
Distinction between Q^8N **83** and Q^8NHOAc **81** is again recognised by their different selectivities in aziridination of a mixture of alkenes (styrene and diethyl fumarate); Q^8NHOAc reacts exclusively with styrene **64**. Nitrene **83** (Q^8N) is revealed as a species more nucleophilic than Q^8NHOAc **81**.

It is clear that there are parallels between the behaviour of PNHOAc **36** and PN **20** and of Q^8NHOAc **81** and Q^8N **83**: both aziridinating agents in each case have an independent existence but similar reactivity.

VI N-(Q)-aziridine→azirine→N-(H)-aziridine conversion

Diastereoselective aziridination of prochiral alkenes using enantiopure QNHOAc compounds, *e.g.* Q^2NHOAc **31** (Scheme 33) and Q^5NHOAc **58** (Scheme 34) has made available a range of *N*-(Q)-substituted aziridines as single enantiomers. To make use of these aziridines requires cleavage of the Q-N bond and retrieval of only the chiral centre(s) created from the prochiral alkene. One method for elimination of Q is to take advantage of its potential as a leaving group. Treatment of the trimethylsilyl-substituted aziridine **32** (Scheme

46) with caesium fluoride-DMF generates the reactive azirine **86** which adds cyanide ion, *in situ*, to give the NH-aziridine **87**.[47]



Scheme 46

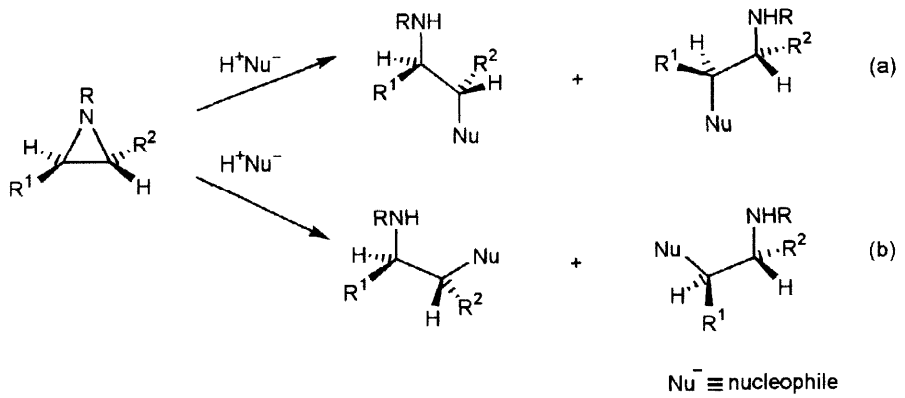
Correlation of the diastereopurity of aziridine **32** with the enantiopurity of aziridine **87** shows that the elimination-addition proceeds with no loss of configuration in the azirine **86**.

Whilst this method like others[65] provides a route to enantiopurified NH-aziridines, it removes the possibility of *using the Q group to control the regio- or stereo-chemistry of the aziridine ring opening* (see below).

VII Ring-opening of aziridines

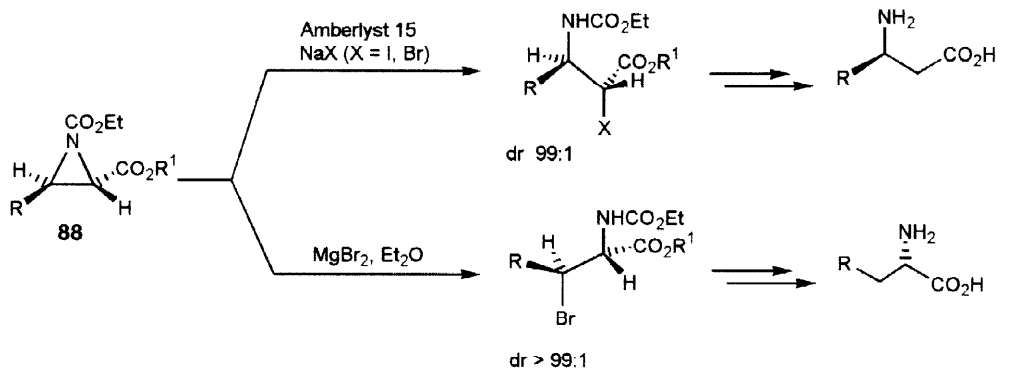
A General

The ring-opening of *e.g.* a 2,3-disubstituted aziridine can deliver two regioisomers and since each can be formed, in principle, with inversion or retention of configuration, four products are possible as shown in Scheme 47.



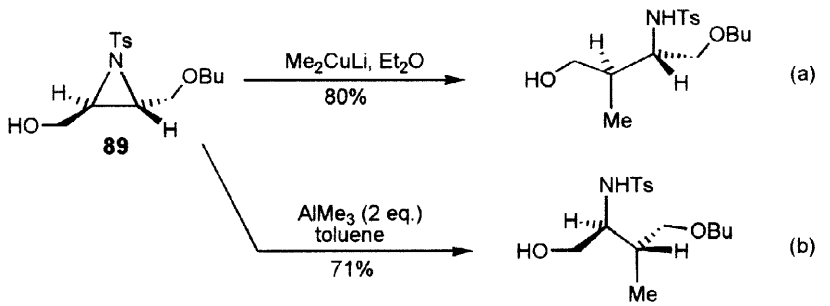
Scheme 47

In practice, complete stereoselectivity in the ring-opening almost always arises from inversion of configuration *i.e.* (a) rather than (b). Where regiospecificity in the ring-opening obtains it is seldom straightforward to achieve in the complementary sense *e.g.* by changing the reaction conditions or even the nucleophile. However, regio-complementary modes of ring-opening of aziridine esters **88** can be accomplished by metal halides under different conditions (Scheme 48); reductive dehalogenation gives the corresponding α- or β-amino acids.[66]



Scheme 48

Tanner has shown[67] (Scheme 49) that regio-complementary ring-openings of aziridine **89** can be achieved using the reagents shown. In (a), complexation of the cuprate to the hydroxy group and intramolecular delivery to the nearer aziridine ring carbon bond is thought to occur. In (b) two methylaluminium molecules are apparently involved with methyl delivery from that coordinated to the OBu group.

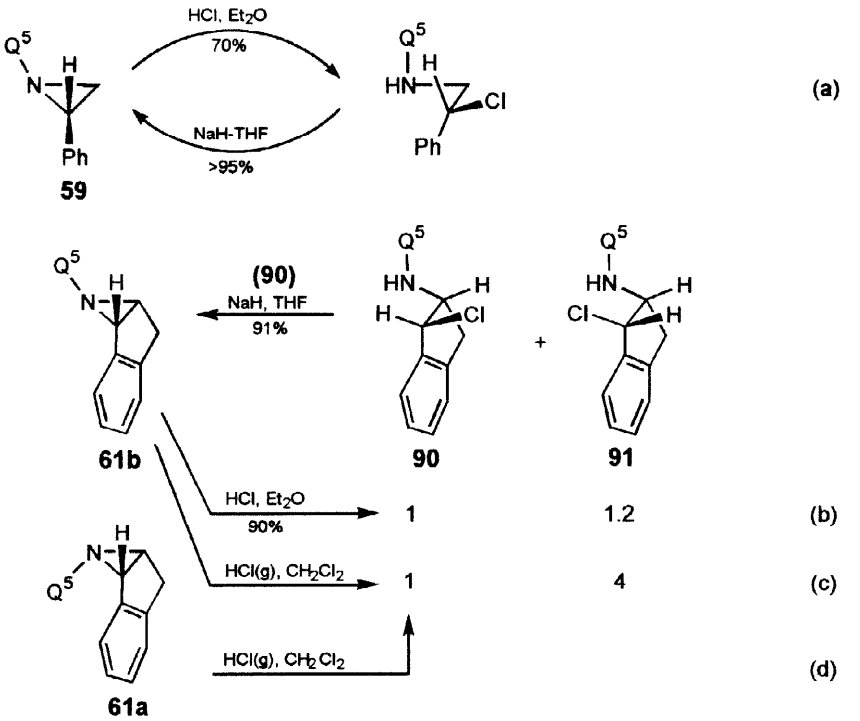


Scheme 49

However, in a completely regio- and stereoselective ring-opening of a given aziridine, there is in general no choice as to which of the four possible aziridines in Scheme 47 will be formed.

B (Lewis) Acid-catalysed ring-opening of N-Q^5-substituted aziridines

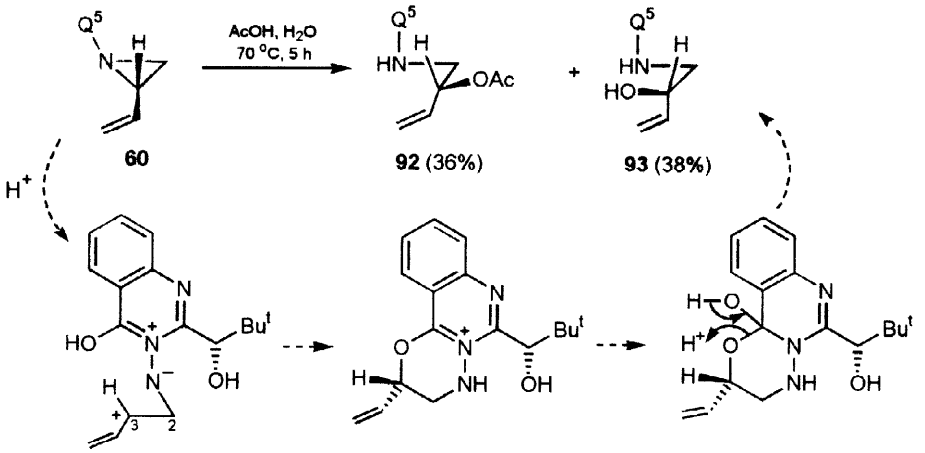
Regioselectivity in acid-catalysed ring-opening of aziridines is usually high when one of the ring-carbon substituents is carbocation stabilising *i.e.* Ph, $CH{=}CH_2$, OR etc. and this is the case with N-(Q^5)-substituted aziridines (Scheme 50).[68,69]



Scheme 50

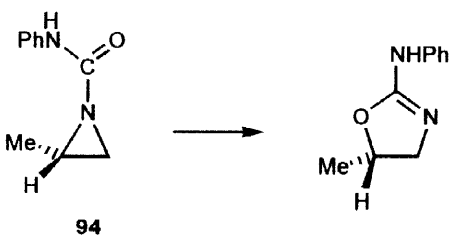
As shown in (a) (Scheme 50), ring-opening also proceeds with complete inversion of configuration since reconversion to the starting material is effected in almost quantitative yield by sodium hydride-THF. In (b), however, a mixture of stereoisomers of the ring-opened chloride was obtained under the same reaction conditions, probably as a result of the more fully-developed carbocation intermediate resulting from better stabilisation by the phenyl ring.[70] As has been mentioned previously, the *endo*-isomer **61a** is isolable by working up the aziridination of indene at <0 °C. When a solution of this *endo*-isomer in dichloromethane was treated with hydrogen chloride gas as in (d), the product was the single diastereoisomer **90** formed by inversion of configuration since it also was reconverted back to the starting aziridine by base in excellent yield. Interestingly, when the *exo*-invertomer **61b** was ring-opened under the same conditions (c), a 4:1 ratio of diastereoisomers **91** : **90** was obtained. Whatever the explanation for the changed diastereoselectivity in these reactions, it is likely that the Q^5 group is responsible either directly or indirectly for the stereochemistry.

The Q^5 ring is also directly involved in ring-opening of aziridine **60** in wet acetic acid in which allylic acetate **92** and allylic alcohol **93** are formed with inversion and retention of configuration, respectively (Scheme 51).[71]



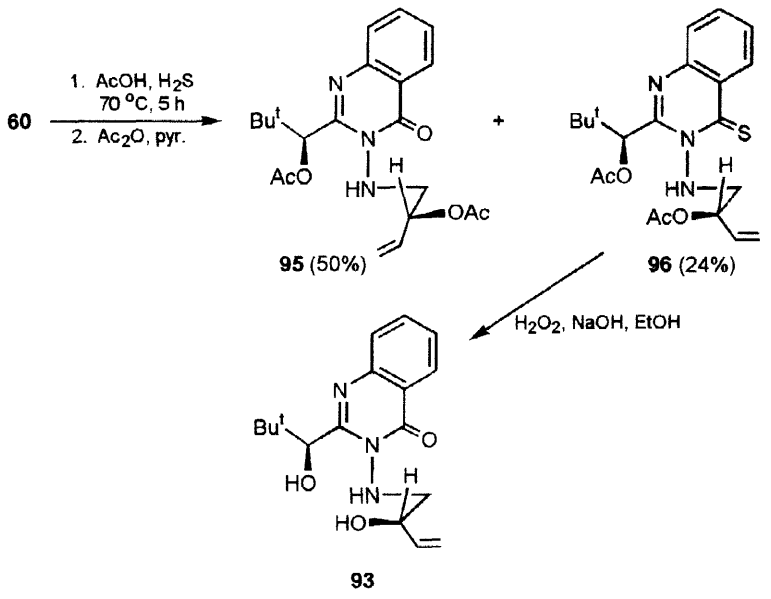
Scheme 51

A mechanism to account for the formation of allylic alcohol **93**, shown in Scheme 51, involves capture of the carbocation formed by C–N bond cleavage in aziridine **60** by the C–4 carbonyl oxygen before rotation around the C_2–C_3 bond occurs – in effect an S_Ni reaction. A similar ring-opening of aziridine **94** has been reported to proceed with complete retention of configuration (Scheme 52).[72]



Scheme 52

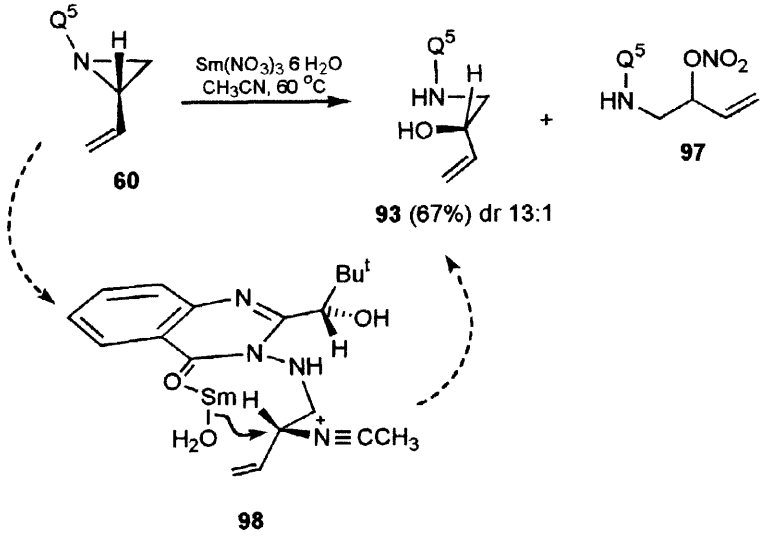
In the proposed mechanism in Scheme 51, the quinazolinone carbonyl oxygen in aziridine **60** becomes the allylic alcohol oxygen in **93** and the Q^5 carbonyl oxygen in **93** is derived from the water present in the acetic acid. To test this mechanism, the reaction was repeated in dry acetic acid saturated with hydrogen sulfide. After work-up, acetylation of the total reaction product gave the di-acetate **95** and the quinazoline-4-thione-substituted allylic alcohol **96** (Scheme 53).



Scheme 53

As expected, **96** was formed with retention of configuration as shown by conversion to the previously obtained (quinazolin-4-one)-substituted allylic alcohol **93** by treatment with basic hydrogen peroxide: the formation of di-acetate **95** in Scheme 53 shows that the Q^5-carbonyl oxygen is not directly exchanged for sulfur under the reaction conditions.

Ring-opening with predominant retention of configuration also occurs when vinylaziridine **60** is heated in acetonitrile with samarium(III) nitrate hexahydrate (Scheme 54) with formation of allylic alcohol **93**; nitrate ester **97** is a by-product.[71]

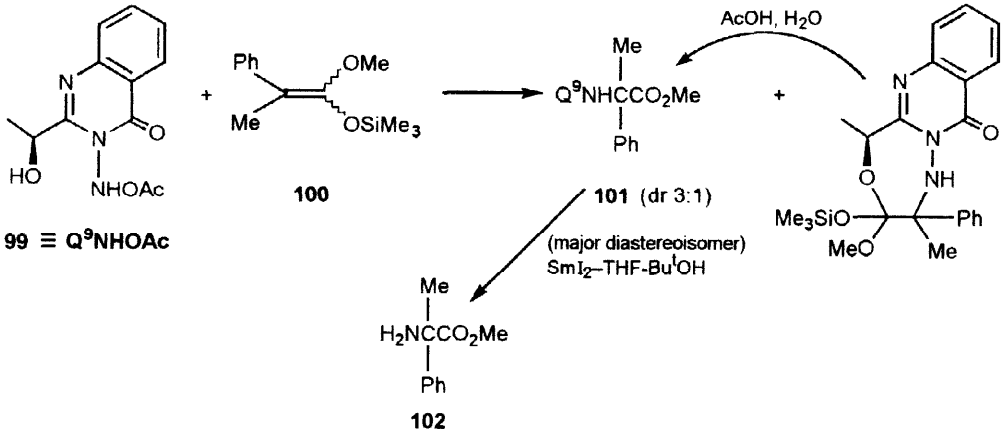


Scheme 54

The mechanism of this ring-opening is also believed to involve the Q^5 group by coordination of its C–4 carbonyl group to the oxophilic Sm(III) ion: possibly double inversion is involved *via* an intermediate resembling **98**.

C N–Q Bond cleavage in ring-opened aziridines: aziridination of silyl ketene acetals

Aziridination of silyl ketene acetals, *e.g.* **100** with Q^9NHOAc **99** (Scheme 55) leads directly to the N–(Q^9) amino acid ester **101** (dr 3:1). After separation of the major diastereoisomer, cleavage of the Q^9–N bond was accomplished in good yield by samarium(II) iodide to provide enantiopure amino acid ester **102**.[73]



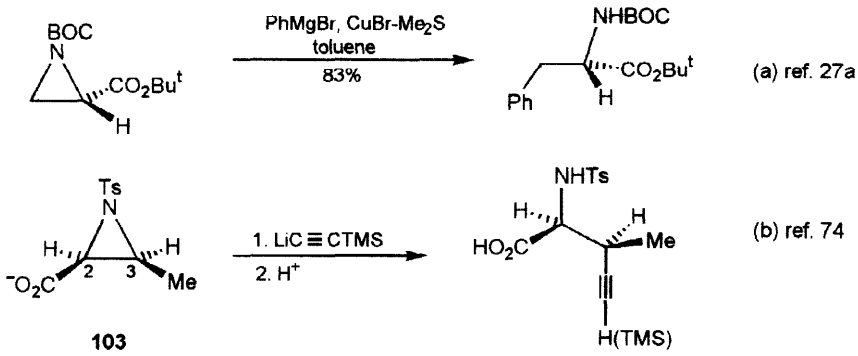
Scheme 55

Subsequently, we were able to use Sm(II) in less than mol. equivalent amounts by including magnesium in the reaction mixture to reduce the Sm(III) formed to Sm(II) (see below).

D Nucleophilic ring-opening of N-(Q^5)-aziridines: conversion to useful chirons

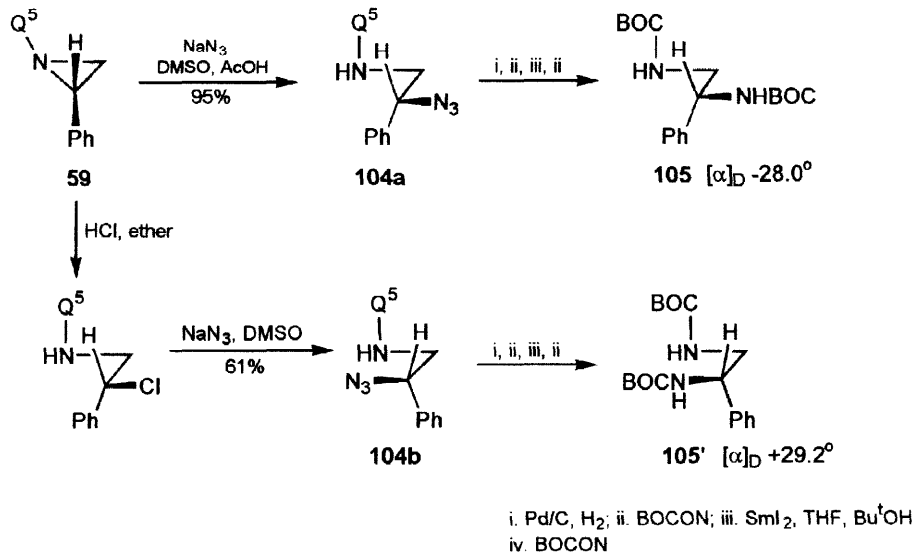
In nucleophilic ring-opening of aziridines, the mechanism is more S_N2 in type with significant nucleophile-ring carbon bond formation in the ts#. For nucleophiles of high pK_a (*e.g.* cuprates), protonation of the ring nitrogen must be avoided and an electron-withdrawing substituent (usually arene- or alkane-sulphonyl) must be present on nitrogen to stabilise its developing -ve charge in the ts#. Here, regioselectivity usually requires steric effects to direct ring-opening at the less-substituted ring carbon. The inversion of configuration which accompanies nucleophilic ring-opening is not apparent when, as is often the case, the ring carbon undergoing attack is unsubstituted (Scheme 56a).

Young *et al.* (Scheme 56b) have used the repulsive effect of a carboxylate anion to direct attack of the small and negatively charged nucleophile to the substituted 3-position of **103** with inversion of configuration.[74]



Scheme 56

The Q^5 group is sufficiently electron withdrawing to allow nucleophilic ring opening. Thus formation of azide **104a** (Scheme 57) from aziridine **59** is believed to involve significant build-up of -ve charge on the ring nitrogen in the ts# because the presence of acetic acid has such a small effect on the rate of disappearance of **59**.[68]

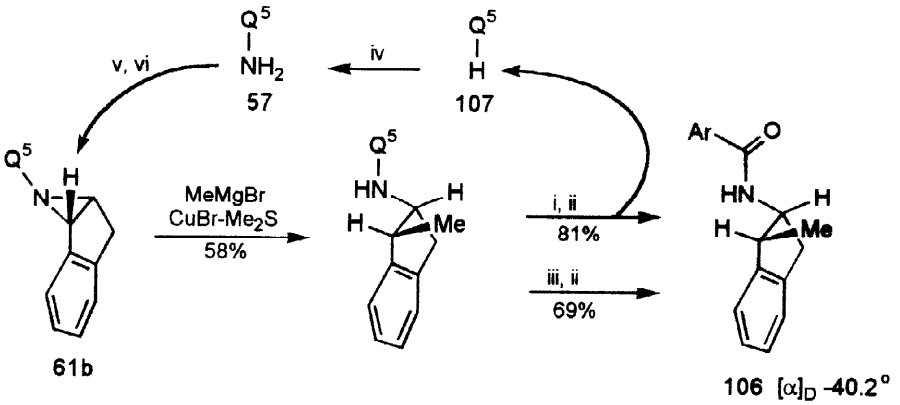


Scheme 57

As Scheme 57 shows, the diastereoisomeric azide **104b** can be obtained by a double inversion sequence and thus both enantiomeric chirons **105** and **105'** are available starting from a single enantiomer of aziridine **59**.

Nucleophilic ring-opening of aziridine **61b** also takes place with a cuprate (Scheme 58). Reductive removal of the Q^5 group gives the substituted indene **106** as a single enantiomer.[68]

As Scheme 58 shows, the expensive samarium iodide can be used in less than molar amount with only a small reduction in yield by making use of *in situ* reduction of Sm(III) → Sm(II) by magnesium.[75] Recovered 3-H-quinazolinone **107** is converted into Q^5NH_2 **57** (and thence into aziridine **61b**) with no loss of enantiopurity.

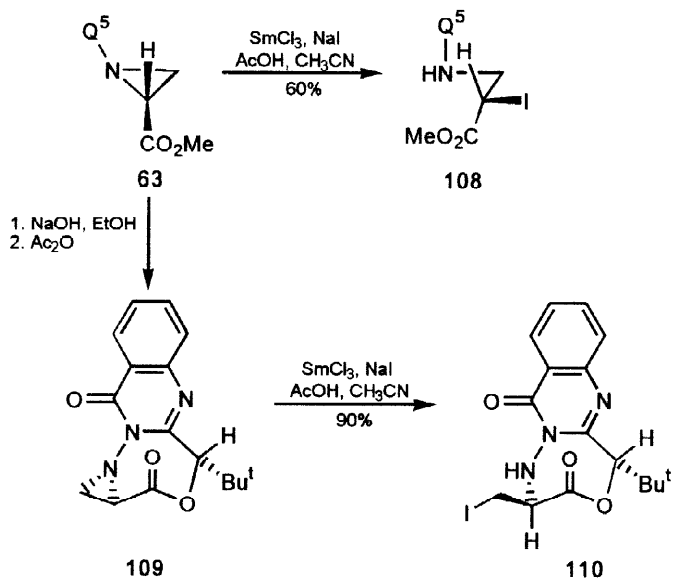


Reagents i. SmI_2(xs), THF, Bu^tOH, ii. 3,5-dinitrobenzoyl chloride (ArCOCl), pyr.
iii. SmI_2 (0.5 eq.), Mg(xs), THF, Bu^tOH, iv. $SmCl_3$, NH_2NH_2
v. LTA, CH_2Cl_2, vi. $Ti(OBu^t)_4$, indene

Scheme 58

E Control of regioselectivity in ring-opening of N-(Q^5)-aziridines

Ring-opening of aziridine **63** with iodide in the presence of Sm(III) and acetic acid gives iodide **108** as a crystalline diastereoisomer (Scheme 59). Hydrolysis of the ester group in aziridine **63** and lactonisation of the acid to **109** followed by ring-opening under the same conditions used for aziridine **63** gives the lactone **110**. Iodides **108** and **110** are formed with complementary regiosenses of ring-opening.[76]



Scheme 59

VIII Summary

3-Acetoxyaminoquinazolin-4-(3H)-ones (QNHOAc) are nitrogen analogues of peroxy-acetic acid and are efficient aziridinating agents for a range of alkenes from silyl ketene acetals to α,β-unsaturated esters. The presence of a chiral substituent in the 2-position of the quinazolinone allows complete (reagent-controlled) diastereoselective aziridination of prochiral alkenes. Greatly improved yields of aziridines from otherwise less reactive alkenes are obtained by reaction with QNHOAc in the presence of trifluoroacetic acid and this additive also greatly increases the diastereoselectivity in aziridination of some α,β-unsaturated esters.

The corresponding nitrenes (QN), formally derived from QNHOAc by removal of the elements of acetic acid, are also aziridinating agents for alkenes with a reactivity similar to, but identifiably different from that of QNHOAc.

The availability of enantiopure Q-substituted aziridines has led to an examination of their ring-opening reactions with particular emphasis on the use of the Q group to control the regio- or stereo-chemistry of the latter. Electrophilic ring-opening with inversion or with predominant retention of configuration has been demonstrated. Nucleophilic ring-opening of these aziridines is successful, *e.g.* with cuprates. Reductive cleavage of the Q group in the ring-opened products using samarium diiodide proceeds in excellent yield to allow retrieval of chirons containing only the chiral centres created in the diastereoselective aziridination: the recovered 3-H-quinazolinones (QH) can be reconverted back to 3-aminoquinazolinones (QNH_2) from which the QNHOAc are prepared in good yield, *in situ*, by acetoxylation using lead tetra-acetate. The Q group has also been used to direct the regioselectivity of ring-opening.

Acknowledgements

It is a great pleasure to acknowledge the skill and application of my coworkers in this area. I am grateful to Vicky Orson-Wright for her help in preparation of the manuscript.

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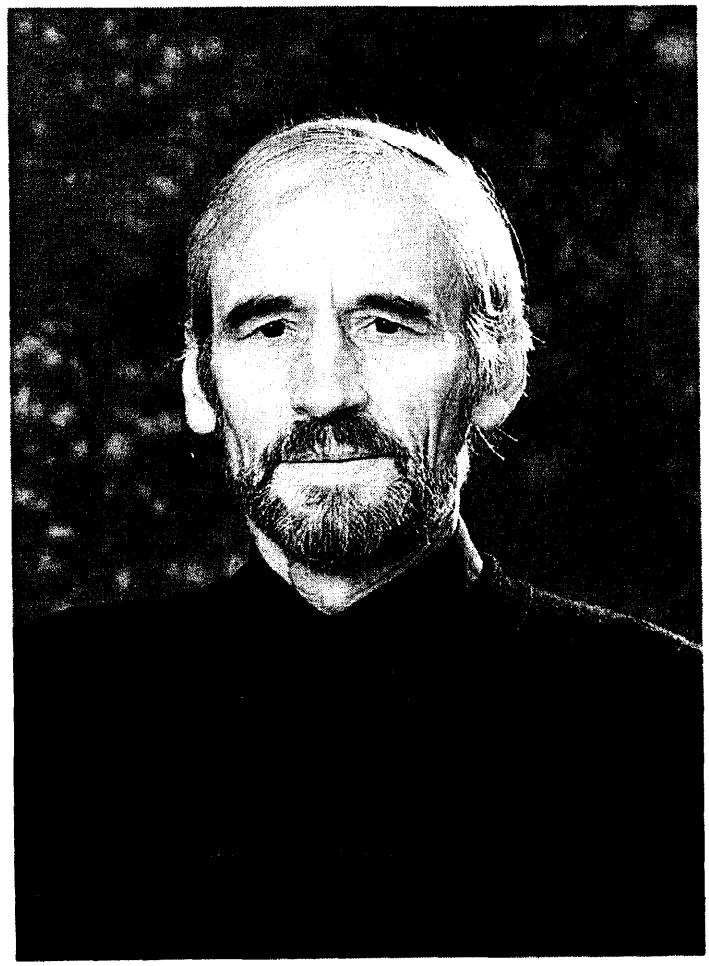
Biographical sketch



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Robert S. Atkinson was born in London. He received his B.Sc. and Ph.D. degrees in Chemistry from Nottingham University.

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