Preparation of N–H aziridines in high enantiomeric excess by *in situ* aziridine–azirine–aziridine interconversion

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Aziridine 6 is produced highly diastereoselectively by treatment of enantiopure 3-acetoxyaminoquinazolinone 4 (Q*NHOAc) with β-trimethylsilylstyrene: desilylative elimination of Q* and *in situ* addition of cyanide to the intermediate azirine gives the NH-aziridine 8 of 83% ee.

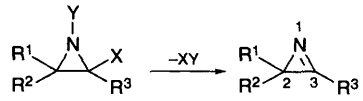
Elimination of two adjacent atoms/groups from an aziridine gives rise to an azirine (Scheme 1). This route to azirines is relatively unexplored but it is an expedient one to enantiopure compounds ($R^1 \neq R^2$) by elimination from an appropriately substituted enantiopure pure aziridine:[1] other routes to azirines do not lend themselves to the preparation of single enantiomers.[2]

The reactivity of the azirine ring system is dependent on the nature of the 3-substituent with the unsubstituted compounds (R^3 = H) being particularly reactive and difficult to isolate in pure form. We have previously shown[3] that desilylative quinazolinone (Q) ring elimination from the racemic N(Q)-substituted aziridine **1** leads to the isolation of aziridine **3** by capture of the reactive intermediate azirine **2** by Q^- (Scheme 2). This aziridine **3** was obtained as a single diastereoisomer showing the presence of a mixture of two invertomers at nitrogen in its ^{1}H NMR spectrum.

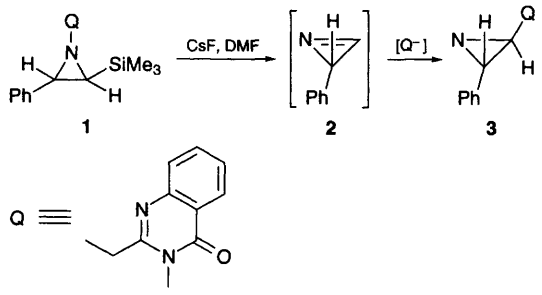
We have now shown that this aziridine–azirine–aziridine interconversion can be used to prepare a (Q-free) aziridine in high ee using reagent-controlled diastereoselective aziridination of vinylsilane **5** with an enantiopure 3-acetoxyaminoquinazolinone **4** (Q*NHOAc), by elimination of Q^*SiMe_3 from aziridine **6** and interception of the *in situ* formed intermediate azirine **7** with a nucleophile (cyanide) (Scheme 3).

The enantiopure 3-acetoxyaminoquinzolinone **4** was prepared by silylation of the corresponding 3-amino-2-hydroxyethylquinazolinone[4] in the usual way and was reacted with vinylsilane **5** in the presence of hexamethyldisilazane† to give aziridine **6** in 50% isolated yield. In the ^{1}H NMR spectrum of aziridine **6**, signals from both *N*-invertomers were present (ratio 1.6:1) with doublets at δ 3.35 and 2.90, *J* 7.6 Hz (major invertomer) and δ 3.70 and 3.35, *J* 7.2 Hz (minor invertomer). The observation of an additional small peak close to each of three of the four ^{13}C NMR signals for the aziridine ring carbons (2 invertomers) indicated the presence of a minor diastereoisomer (ratio major: minor 11:1). This minor diastereoisomer can be assumed to have the opposite configuration at both aziridine ring chiral centres since these aziridinations using 3-acetoxyaminoquinazolinones are known to be stereospecific with retention of the alkene configuration in the product.[5]

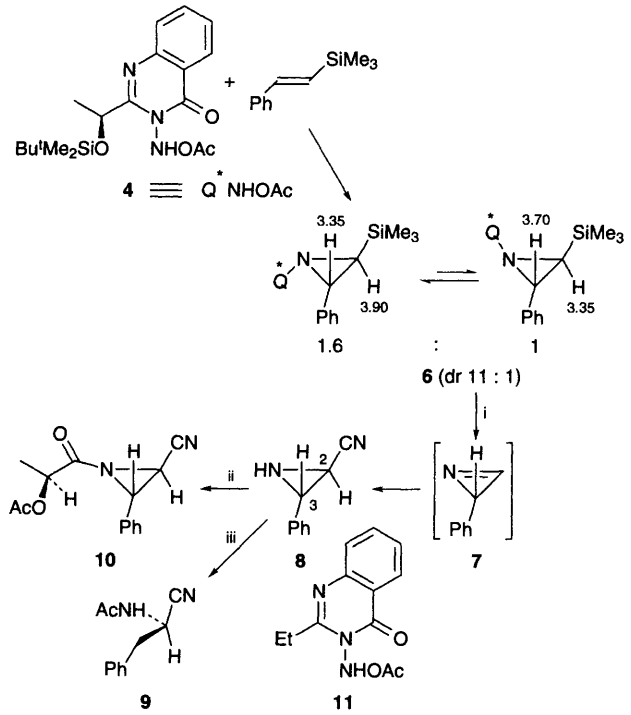
Aziridine **8**, mp 58–60 °C, $[\alpha]_D = -153.1$ (*c* = 1.0, EtOH), was isolated in 76% yield by desilylation of aziridine **6** with caesium fluoride and dimethylformamide in the presence of potassium cyanide (3 equiv.). In aziridine **8**, the magnitude of the coupling constant (2.5 Hz) between the protons at C-2 and C-3 supports the *trans*-Ph/CN assignment;[6] its absolute config-



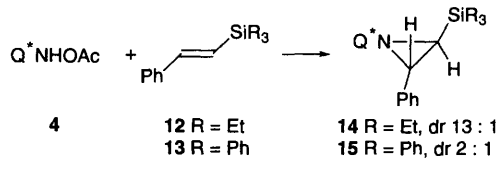
Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions:* i, CsF, DMF, KCN; ii, (*S*)-MeCH(OAc)COCl, NEt_3; iii, H_2, Pd/C, Ac_2O



Scheme 4

uration was identified as 2*R*, 3*S* by hydrogenation and *N*-acetylation to give 2-acetylamino-3-phenylpropionitrile **9**, $[\alpha]_D$ = +45.1 (*c* = 0.78, EtOH), of opposite sign to that reported $[\alpha]_D$ = −56.8,[7] $[\alpha]_D$ = −10.2 (*c* = 2.5, EtOH),[8] for a sample prepared from (*S*)-phenylalanine. The enantiopurity of the aziridine **8** (ee 83%) was determined directly by reaction with enantiopure (*S*)-α-acetoxypropionyl chloride to give the two diastereoisomers of aziridine **10** (10 : 1) by NMR comparison with a 1 : 1 mixture prepared from a sample of racemic aziridine **8**. This racemic aziridine **8** was prepared by aziridination of β-trimethylsilylstyrene **5** using 3-acetoxyamino-2-ethylquinazolinone **11** followed by the same aziridine–azirine–aziridine conversion described in Scheme 3.

We have also carried out the same procedure in Scheme 3 using β-triethylsilylstyrene **12** and β-triphenylsilylstyrene **13** instead of β-trimethylsilylstyrene **5** (Scheme 4).

The diastereoisomeric ratios (d.r.s) of aziridine **14** and the derived Q*-free aziridine **10** were slightly higher (13 : 1 d.r.) but the yield of aziridine **14** was slightly lower (40%). Using β-triphenylsilylstyrene, a 2 : 1 ratio of diastereoisomers of aziridine **15** was obtained and the minor diastereoisomer was separated by crystallisation from light petroleum. Desilylative elimination of Q* from a sample of aziridine **15** (5 : 1 d.r.) in the presence of cyanide (Scheme 3) and derivatisation of aziridine **8** gave aziridine **10** as a 5 : 1 ratio of diastereoisomers.‡

The correlation in each case between the diastereoisomeric ratios in aziridines **6, 14** and **15** and the aziridine **10** suggests that the intermediate azirine **7** is configurationally stable under the reaction conditions.

Footnotes

† The presence of hexamethyldisilazane has been found to give increased yields in this and other aziridinations (unpublished work with E. Barker); in the present case, the yield is raised from 30% (using 3 equiv. alkene) to 50% (using 1.2 equiv. alkene).

‡ Confirmation of the absolute configuration of aziridine **8** (prepared from aziridine **6**) comes from the known absolute configuration of the minor diastereoisomer of **15** (by X-ray structure determination: unpublished work) and by relating the major diastereoisomer of aziridine **15** (in a 5 : 1 mixture) to the major diastereoisomer of aziridine **10**.

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