3-Acetoxyaminoquinazolin-4(3*H*)-ones as aziridinating agents: relative rate of inversion at the exocyclic nitrogen

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Inversion at the exocyclic nitrogen in 3-acetoxyaminoquinazolinones, *e.g.* 2 is slow on the NMR time-scale. The associated inversion barrier could not be measured directly by NMR spectroscopy because of the thermal instability of compound 2. However, the corresponding inversion barriers for 3-isopropoxyaminoquinazolinone 5 and 3-*tert*-butoxyaminoquinazolinone 6, prepared by reaction of 3-acetoxyaminoquinazolinone 2 with titanium(IV) isopropoxide and titanium(IV) *tert*-butoxide respectively, suggest that it is sufficiently low for the rate of inversion to be fast relative to the rate of aziridination of alkenes using reagent 2. This conclusion is supported by the preparation of diastereoisomers of 3-acetoxyaminoquinazolinones 3, 16 and 21 at −20 °C and by monitoring their relative rates of aziridination of cinnamyl alcohol (by 3), and styrene (by 16) and of intramolecular aziridination (for 21) by NMR spectroscopy. In no case was there any change in the ratio of these diastereoisomers as the aziridinations progressed implying that interconversion between them was faster than the rates at which they reacted individually with the respective alkene.

N-Acetoxylation of 3-aminoquinazolinones, *e.g.* **1**, gives 3-acetoxyaminoquinazolinones, *e.g.* **2**, which are aziridinating agents for alkenes (Scheme 1) and may be considered as nitrogen analogues of peroxyacetic acid.[1] In the NMR spectrum of **2** (QNHOAc) at −20 °C, the two protons of the ethyl group are diastereotopic and so there is a chiral element present in this molecule. The presence of an additional chiral centre in analogues, *e.g.* **3** (Q^1NHOAc), leads to the observation of diastereoisomers in its NMR spectrum at −20 °C: for the case of **3** these are present in a 4:1 ratio.

This chiral element present in Q^1NHOAc **2** and the existence of diastereoisomers in Q^1NHOAc **3**, at least on the NMR time-scale, is most likely the result of slow inversion at the exocyclic nitrogen: pyramidal nitrogen atoms substituted with two electron-withdrawing but non-conjugating atoms or groups like those in QNHOAc **2** and Q^1NHOAc **3** are known to have barriers to inversion which are sufficiently high in some cases to allow isolation of stereoisomers.[2] However, we have also shown that certain 3-(substituted)aminoquinazolinones have high barriers to rotation around their N–N bonds. This is particularly so when the exocyclic (substituted) nitrogen is sp^2-hybridised as is the case when it is acylated: the *N*,*N*-diacylated 3-aminoquinazolinone **4** for example has been isolated in two diastereoisomeric forms with a barrier of $\Delta G^{\ddagger}$ 121 kJ mol^{-1} (29 kcal mol^{-1}) for rotation around the N–N bond.[3]

We have shown that aziridinations of certain prochiral alkenes using Q^1NHOAc **3** and related compounds bearing other chiral 2-substituents are highly diastereoselective.[4] To understand the origin of this reagent-controlled diastereoselectivity it is clear that the identity of the additional chiral element in compound **3**, besides the chiral centre, needs to be established. For the rational design of 2-substituted 3-acetoxyaminoquinazolinones which will maximise this diastereoselectivity it is also necessary to know the configurational stability of this chiral element on the time-scale of the aziridination. In this work we present evidence to support assignment of this chiral element to a pyramidal exocyclic nitrogen in these 3-acetoxyaminoquinazolinones which is inverting slowly on the NMR time-scale but fast on the time-scale of the aziridinations which they bring about.

Unfortunately, both compounds **2** and **3** and analogous 3-acetoxyaminoquinazolinones† begin to decompose at temperatures >0 °C and so observation of coalescence of signals from diastereotopic protons in NMR spectra run at higher temperatures, and hence measurement of the energy barriers giving rise to their diastereotopicity, is not possible. However, no coalescence of signals from the diastereotopic protons in the methylene group of a base-washed sample of QNHOAc **2** was evident in an NMR spectrum run at 40 °C (at which temperature extensive decomposition had taken place) and so the barrier to *N*-inversion or N–N bond rotation must be greater than ~63 kJ mol^{-1} (~15 kcal mol^{-1}).

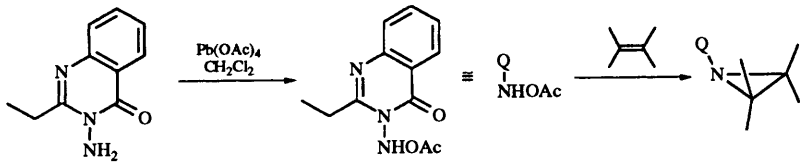
Reaction of QNHOAc **2** with titanium(IV) isopropoxide in dichloromethane gave 3-isopropoxyaminoquinazolinone **5** (QNHOPr^i) in good yield. Like QNHOAc **2**, the methylene protons of the 2-ethyl group are diastereotopic (as are the two methyl groups of the isopropyl). Unlike QNHOAc **2**, however, QNHOPr^i **5** is thermally stable: coalescence of the diastereotopic protons of the ethyl group takes place at 30 °C (T_C) and a barrier ΔG^* of 62 kJ mol^{-1} (14.7 kcal mol^{-1}) is calculated for the process which renders these two protons equivalent.

In the NMR spectrum of 3-*tert*-butoxyaminoquinazolinone **6** (QNHOBu^t), prepared analogously to the isopropoxy analogue **5** from zirconium(IV) *tert*-butoxide and QNHOAc **2** albeit in poor yield (3.6%),‡ coalescence of the diastereotopic methylene protons of the ethyl group occurs at 13 °C from which an associated barrier of 58 kJ mol^{-1} (13.9 kcal mol^{-1}) is calculated.

The lower barrier for QNHOBu^t **6** by comparison with the isopropoxy analogue **5** is evidence for *N*-inversion at the exocyclic nitrogen rather than N–N rotation as the dynamic process involved: an increase in the size of substituents on nitrogen generally lowers the barrier to *N*-inversion but is expected to raise the barrier to N–N bond rotation.[5] It is likely, therefore, that the chiral element present in QNHOAc **2** (see above) is also the result of retarded inversion at the exocyclic nitrogen, at least on the NMR time-scale. Few direct comparisons between the magnitudes of the barriers to inversion at (sp^3-hybridised) nitrogen in *N*-alkoxy and *N*-

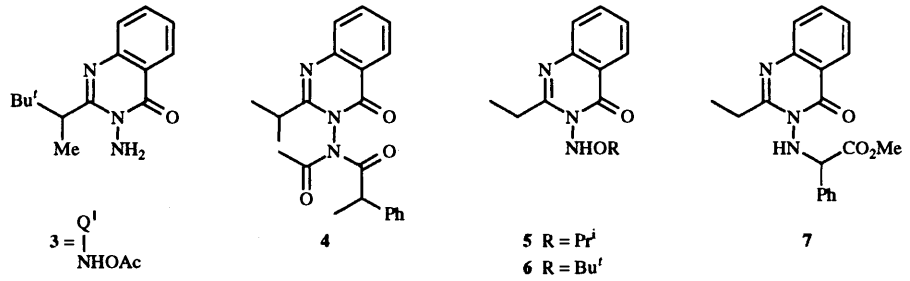
† Exceptionally, 3-acetoxyamino-2-trifluoromethylquinazolin-4(3*H*)-one is stable at room temperature (R. S. Atkinson, M. P. Coogan and C. L. Cornell, *J. Chem. Soc., Chem. Commun.*, 1993, 1215.

‡ The low yield of product in this experiment may have been the result of the lack of purity of the zirconium *tert*-butoxide used since we have obtained yields >60% using previously unopened bottles of this reagent (with other 3-acetoxyaminoquinazolinones).

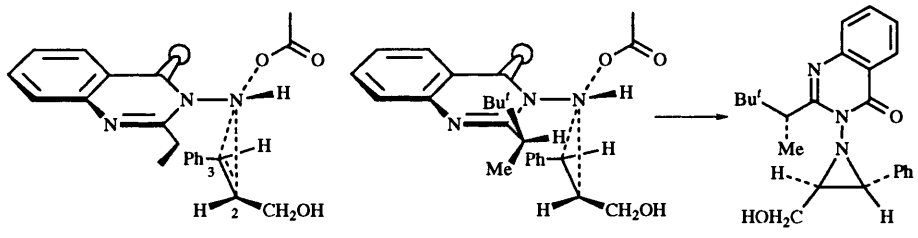


1 2

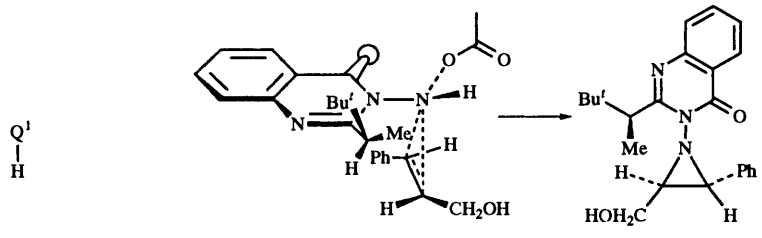
Scheme 1



3 4 5 R = Pr^i 6 R = Bu^t 7



8 9 11



13 10 12

Scheme 2

acetoxy compounds are available but one suggests that the barrier is slightly lower in the *N*-acetoxy case.[6] If the barrier to *N*-inversion in QNHOAc **2** is not substantially greater than 63 kJ mol^{-1} it will be considerably below that required (> 80 kJ mol^{-1}) for *N*-inversion to be slow on the time-scale of the aziridination.

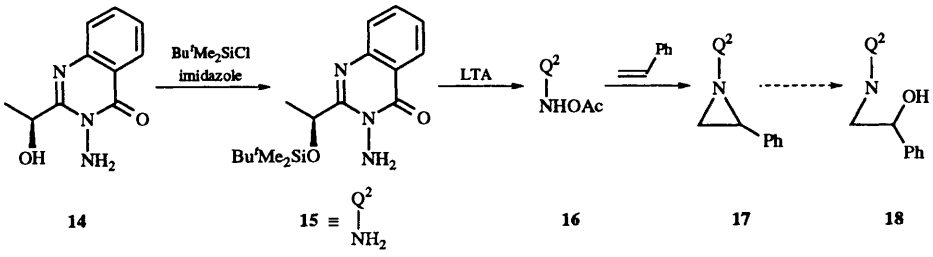
Further support for slow *N*-inversion at the exocyclic nitrogen in compounds **2**, **3**, **5** and **6** on the NMR time-scale comes from comparison with the magnitude of the barrier to N–N bond rotation in the 3-alkylaminoquinazolinone **7**.[7] The change in hybridisation of the exocyclic nitrogen to sp^3 in compound **7** from sp^2 (*cf.* **4**) dramatically decreases the N–N bond rotational barrier. Nevertheless, the bulky *N*-substituent in compound **7** hinders N–N bond rotation sufficiently for signals from both rotamers to be visible in its NMR spectrum at −90 °C in CD_2Cl_2 (ratio 3:1) with an associated barrier to rotation of 47 kJ mol^{-1}. This N–N bond rotational barrier in compound **7**, therefore, is ~12.5 kJ mol^{-1} less than that in QNHOPr^i **5** and > 12.5 kJ mol^{-1} less than that in QNHOAc **2** in spite of the bulkier *N*-substituent in compound **7** than the *N*-isopropoxy group in **5** or the *N*-acetoxy group in **2**. The relative magnitudes of these measured barriers in compounds **5**, **2** and **7** suggest that for compounds **5** and **2** they are not attributable to N–N bond rotation and are therefore the result of *N*-inversion.

The possibility that the exocyclic nitrogen atoms in compounds **2**, **3**, **5** and **6** are sp^2-hybridised thus giving rise to enhanced N–N rotational barriers (see above) can be discounted: this nitrogen is expected to respond to the electronegative demands of the OR substituent by supplying more p-character to the hybrid orbital it uses for the bonding to this substituent and sp^2-hybridisation at the exocyclic nitrogen would make this increased p-orbital provision more difficult. (It is the same increased supply of p-orbital character in bonds from the nitrogen to electronegative atoms/groups as substituents which raises the barrier to *N*-inversion.)§

Although *N*-inversion in QNHOAc **2** and Q^{1}NHOAc **3**, therefore, is slow on the NMR time-scale, the results of experiments outlined below suggest that it is fast on the time-scale for aziridination.

From a comparison of the diastereoselectivities of aziridination of chiral allylic alcohols bearing electron-withdrawing (CO_2Me) or electron-donating (Ph) groups on the double bond, we have concluded that the transition state for aziridination of *e.g.* cinnamyl alcohol with QNHOAc **2** can be represented by **8** (Scheme 2).[8,9] In this transition state, C_2–N bond formation runs ahead of N–C_3 bond formation with S_N2-type displacement of the acetoxy group on the exocyclic nitrogen. An attract-

§ A crystal structure of Q′NHQ′ [Q′ = 2-trifluoromethylquinazolin-4(3*H*)-one] shows that the nitrogen is tetrahedral (R. S. Atkinson, M. P. Coogan and C. L. Cornell, *J. Chem. Soc., Perkin Trans. 1*, 1996, 157).



Scheme 3

ive interaction between the phenyl ring and the quinazolinone ring carbonyl carbon leads to a *syn* relationship between the *N*-acetoxy group and this carbonyl group.

According to this interpretation, with a chiral centre on the 2-position of the quinazolinone ring as in Q^1NHOAc **3** and with slow interconversion between the two diastereoisomers of Q^1NHOAc **3**, the ratio of aziridines **11** and **12** formed should be identical to the ratio of Q^1NHOAc **3** diastereoisomers present. On the other hand if interconversion between the two diastereoisomers of Q^1NHOAc **3** is fast by comparison with the rates at which they individually aziridinate the alkene, the ratio of aziridines **11** and **12** will reflect the rates of reaction *via* the transition states **9** and **10** and will not just reflect the ratio of Q^1NHOAc **3** diastereoisomers present.¶

Solutions of Q^1NHOAc **3** show the presence of a 4:1 ratio of diastereoisomers (see above) from integration of the separated low field Q^1N*H*OAc signals in the NMR spectrum at −40 °C. After addition of cinnamyl alcohol (1.1 mol equiv.) the temperature of the probe was raised to −20 °C when aziridination took place at a measurable rate. The ratio of unreacted diastereoisomers of Q^1NHOAc **3** remained constant at 4:1 throughout the aziridination as did the 1.5:1 ratio of diastereoisomers of the product aziridines **11**:**12**‖ and the only by-product visible in the NMR spectrum of the crude reaction product was the 3*H*-quinazolinone **13** (~25%). The minor aziridine diastereoisomer **12** was obtained pure by crystallisation and although the major diastereoisomer was not isolated in pure form because of its decomposition upon silica chromatography, its presence in the crude reaction mixture was confirmed by signals in the crude reaction mixture *inter alia* at δ 4.09 and 3.09 (*H*C*H*OH) and 2.86 (C*H*Ph).

This lack of correlation between the ratios of diastereoisomers of aziridines **11**:**12** and those of Q^1NHOAc **3**, together with the unchanged ratio of the latter as the aziridination progressed, are most economically accounted for in terms of a fast interconversion between these two diastereoisomers of Q^1NHOAc **3** as aziridination takes place. Support for this interpretation comes from a similar experiment using the 3-acetoxyaminoquinazolinone **16** (Q^2NHOAc).

The known (enantiopure) 3-amino-2-(1-hydroxyethyl)quinazolinone **14**[7] was silylated with *tert*-butyldimethylsilyl chloride and imidazole to give 3-aminoquinazolinone **15** (Scheme 3). Reaction of the derived 3-acetoxyaminoquinazolinone **16** (Q^2NHOAc) with styrene gave a 4.6:1 ratio of diastereoisomers of aziridine **17** from the well separated respective aziridine ring proton signals in its NMR spectrum. After flash chromatography, the ratio of diastereoisomeric aziridines in the recovered material was 6:1 and further elution gave an artefact which was assigned structure **18** from spectroscopic evidence including a broadened triplet for the NH proton at δ 5.85 (D_2O exch.) and a broad singlet for the OH proton at δ 4.25 (D_2O exch.) in the NMR spectrum. It is likely that the selective ring opening of one of the diastereoisomers of aziridine **17** occurs on chromatography since this ring-opened product **18** appears to be a single diastereoisomer.

A sample of Q^2NHOAc **16** prepared in $CDCl_3$ at −20 °C and freed from acetic acid (see Experimental) showed the presence of a 1.5:1 ratio of diastereoisomers from integration of the low field Q^2N*H*OAc protons at δ 10.86 and 10.93 in its NMR spectrum. Styrene (5 mol equiv.) was added and aziridination was monitored at −5 °C. Here also, no change in the 1.5:1 ratio of diastereoisomers was detectable as the aziridination progressed as indicated by the relative intensities of the two Q^2N*H*OAc signals above. There was also no measurable change in the 4.6:1 ratio of aziridine **17** diastereoisomers produced as monitored by integration of their respective aziridine ring proton signals.

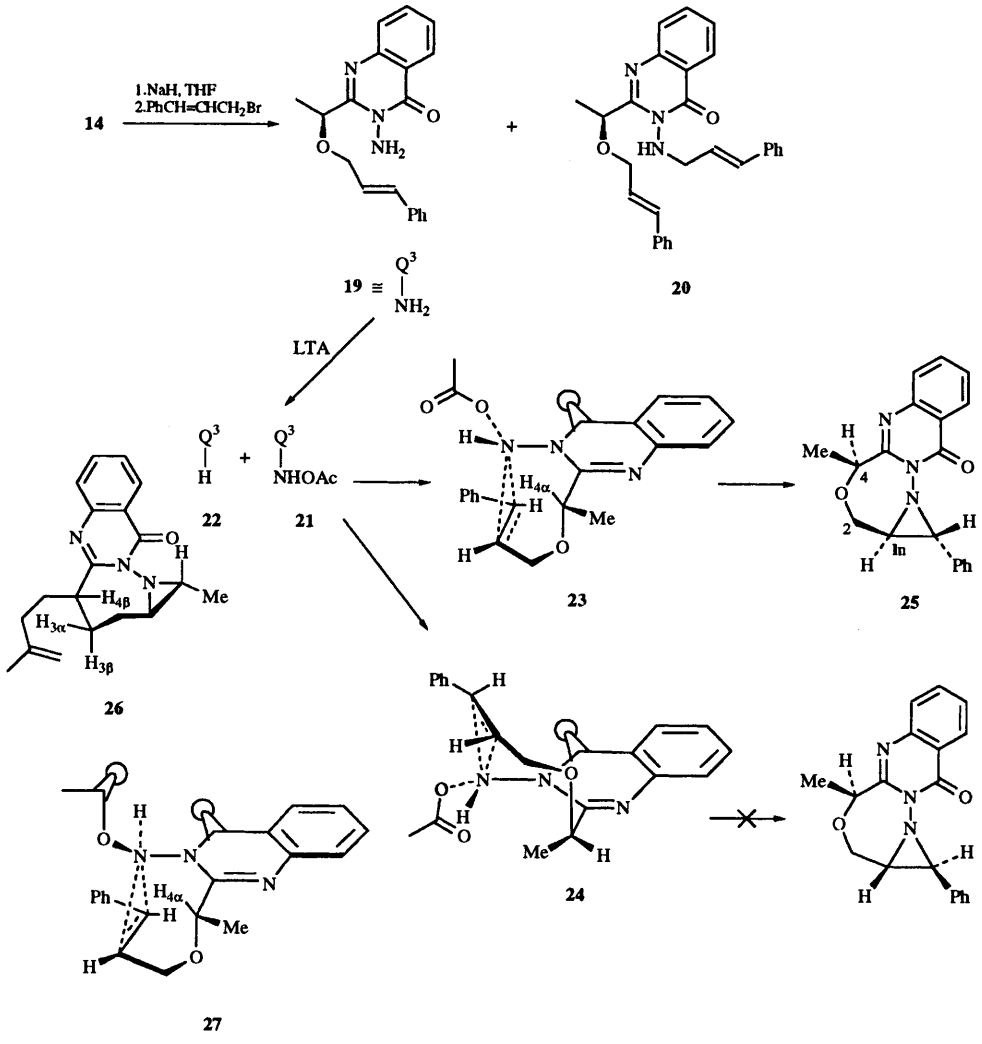
We have also followed the progress of an intramolecular aziridination (Scheme 4) using the 3-acetoxyaminoquinazolinone **21** (Q^3NHOAc) by NMR spectroscopy. Although the major product from alkylation of the 3-aminoquinazolinone **14** with cinnamyl bromide was the *N*,*O*-dialkylated product **20**, the *O*-alkylated 3-aminoquinazolinone **19** was separated by chromatography. *N*-Acetoxylation of this 3-aminoquinazolinone **19** and examination of the Q^3NHOAc **21** by NMR spectroscopy at −20 °C showed its presence as both diastereoisomers in a ratio of 1.5:1 from the intensities of the two low field Q^3N*H*OAc signals at δ 10.94 and 10.88. Also formed was ~30% of the 3*H*-quinazolinone **22**. Signals from the intramolecular aziridination product **25** slowly appeared at this temperature but there was no change in the ratio of diastereoisomers of unreacted Q^3NHOAc from monitoring the relative intensities of the Q^3N*H*OAc signals referred to above. Pure samples of aziridine **25** and 3*H* quinazolinone **22** were obtained in a separate experiment.

As expected by analogy with previous intramolecular aziridinations we have carried out,[10] aziridine **25** is formed as a single diastereoisomer. The similarity of the coupling constants for the H_{1a} signal (*J* 13.1, 5.3, 3.6) in aziridine **25** to those of analogues, *e.g.* aziridine **26** (*J* 11.9, 5.5, 3.1), suggests that the preferred conformation of the seven-membered ring is not affected by substitution of a methylene group by oxygen. It is safe to assume that, by analogy with the stereostructure of aziridine **26**** the relative (and absolute) configuration at the three chiral centres in aziridine **25** is as shown with the diastereoselectivity arising from the preference for reaction *via* transition state **23** rather than **24** because of the severe Me–H

¶ The yields of aziridines **11** and **12** from the respective diastereoisomers of Q^1NHOAc **3** are assumed to be identical.

‖ Assignments of relative configuration in aziridines **11** and **12** are tentative but correspond to those from an analogous aziridination using **3** where the relative configuration of the major diastereoisomer (**11**; Me_3Si replacing CH_2OH) has been proved by X-ray crystallography (R. S. Atkinson and I. S. T. Lochrie, unpublished work).

** Evidence for the 'equatorial' placement (4α) of the side chain in compound **26** was not explicitly given in our earlier work but was based, *inter alia*, on the absence of a *J* 1.6 coupling for H-4β (ddd, *J* 11.8, 6.6, 6.6, 6.6): a *J* 1.6 coupling from H4αH3β is present in the unsubstituted analogue of **26** (4α-H instead of the side-chain and lacking the aziridine ring methyl group). The 3-acetoxyaminoquinazolinone from which **26** is now known to be formed also aziridinates the alternative double bond in the bifurcated quinazolinone 2-substituent and this aziridine also has a 4α configuration for its side chain, *i.e.*, this aziridination is completely stereoselective in the same sense but not regiospecific.



Scheme 4

interaction in the latter. Our interpretation of the stereochemistry of this intramolecular aziridination, therefore, is that interconversion between the two diastereoisomers of Q^3NHOAc **21** takes place and aziridination occurs only *via* that depicted in transition state **23**. Even if aziridination could take place using the other diastereoisomer of Q^3NHOAc **21** *via* a transition state resembling **27** [notwithstanding our evidence which suggests that the *N*-acetoxy and carbonyl should be *syn* (see earlier)], a difference in rates of aziridination *via* transition states **23** and **27** would be anticipated arising from the more adverse $H_{4\alpha}$–*AcO*N interaction in **27** than the $H_{4\alpha}$–*H*N interaction in **23**. This would be revealed in a change in ratio of unreacted diastereoisomers of Q^3NHOAc **21** if interconversion between them was slow on the aziridination time-scale.

The conclusions to be drawn from this work, therefore, are that *N*-inversion at the exocyclic nitrogen in 3-acetoxyaminoquinazolinones, *e.g.* **2**, **3**, **16** and **21**, is slow on the NMR time-scale but fast on the time-scale for their aziridinations of electron-rich alkenes. Since we have found that aziridination of phenyl-substituted alkenes takes place at lower temperatures than other alkenes, these conclusions can be extended to less electron-rich and electron-deficient alkenes also. This result has important implications for the design of chiral aziridinating agents using 3-acetoxyaminoquinazolinones because it means that this QNHOAc chiral centre alone cannot be used to bring about asymmetric induction in aziridination of a prochiral alkene and additional chirality elsewhere in the quinazolinone will be required for reagent-controlled diastereoselectivity.

Experimental

For instrumentation and general experimental details see refs. 7 and 11. NMR spectroscopic data for compounds **2** and **3** are given in ref. 7.

2-Ethyl-3-isopropoxyaminoquinazolin-4(3*H*)-one 5

To a well stirred solution of dichloromethane (4 cm^3) at −12 °C was added powdered lead tetraacetate (LTA) (2.46 g, 5.55 mmol) in one portion. After complete dissolution, the mixture was further cooled to −20 °C and 3-amino-2-ethylquinazolin-4(3*H*)-one (1 g, 5.29 mmol) added as a solution in dry dichloromethane (10 cm^3) dropwise over ~7 min, stirring throughout. The resulting slurry was stirred for 20 min at −20 °C then filtered using apparatus pre-cooled to −20 °C. The filtrate was washed rapidly once with cold (−5 °C) saturated aq. sodium hydrogen carbonate (10 cm^3), the organic layer separated, dried (−5 °C) then re-cooled to −20 °C and treated with titanium(IV) isopropoxide (1.65 cm^3, 5.55 mmol) in one portion with stirring. After removal of the cooling bath the homogeneous solution was stirred for a further 24 h at ambient temperature then washed with aq. sodium hydrogen carbonate (15 cm^3), water (12 cm^3), dried and evaporated under reduced pressure. Crystallisation of the residual solid gave the 3-isopropoxyaminoquinazolinone **5** (0.76 g, 58%) as a colourless solid mp 79–80 °C (from ethanol) (Found: M^+, 247.1321. $C_{13}H_{17}N_3O_2$ requires *M*, 247.1312); δ_H(−25 °C) 9.15 (s, NHOPr^i), 8.25 [dd, *J* 8, 1.2, 5-H(Q)], 7.8 [ddd, *J* 8, 7.1, 1.2, 7-H (Q)], 7.69 [d, *J* 8-H(Q)], 7.47 [ddd, *J* 8, 7.1, 1.2, 6-H(Q)],

4.3 [heptet, J 6.2, $CH(CH_3)_2$], 3.2 and 2.97 [2 × dq (ABX_3), J_{AB} 15.1, J_{AX} 7.6, $HCHCH_3$], 1.42 (t, J 7.6, CH_3CH_2), 1.35 (d, J 6, CH_3CHCH_3) and 1.19 (d, J 6, CH_3CHCH_3); δ_C 160.81 [C=O(Q)], 158.29 [C=N(Q)], 147.05 [C–N=C(Q)], 134.73, 128.11, 127.29, 127.01 [4 × CH(Q)], 120.17 [C–C=O(Q)], 73.95 [$CH(CH_3)_2$], 26.67 (CH_3CH_2), 21.41 [$CH(CH_3)_2$] and 11.12 (CH_3CH_2); ν_{max}/cm^{-1} 3200s, 1690s and 1600s; m/z (%) 247 (M^+, 5.3) and 175 (100). At 30 °C, the ABX_3 signals at δ_H 3.2 and 2.97 had coalesced maximally. Using $\Delta G = 19.12 \times T_C (10.32 + \log_{10} T_C/k_C)$ [12] where $k_C = \pi\Delta\nu/\sqrt{2}$, T_C = coalescence temperature, k_C = rate of nitrogen inversion at T_C, $\Delta\nu$ = frequency separation of coalescing signals in Hz, measured at −25 °C, the calculated inversion barrier ΔG = 14.7 kcal mol^{-1} (62 kJ mol^{-1}).

3-*tert*-Butoxyamino-2-ethylquinazolin-4(3*H*)-one 6

The procedure given above was followed using 3-amino-2-ethylquinazolin-4(3*H*)-one (0.6 g, 3.2 mmol), LTA (1.48 g, 3 mmol) and zirconium(IV) *tert*-butoxide (2.44 g, 6.35 mmol), in dry dichloromethane (7 cm^3). After the same work-up, the residue was chromatographed over silica using ethyl acetate–light petroleum (1:2) as eluent and the 3-*tert*-butoxyaminoquinazolinone **6** isolated as an oil (R_f 0.83) which solidified on trituration with cold dry diethyl ether (1 cm^3) and gave colourless crystals (0.03 g, 3.6%) mp 89–90 °C (from ethanol) (Found: M^+, 261.1477. $C_{14}H_{19}N_3O_2$ requires M, 261.1475); δ_H(−20 °C), 9.04 (s, NHOBu^t), 8.20 [dd, J 8, 1, 5-H(Q)], 7.81 [ddd, J 8, 7.8, 1, 7-H(Q)], 7.71 [d, J *ca.* 8, 8-H(Q)], 7.47 [ddd, J 8, *ca.* 8, 1, 6-H(Q)], 3.24 and 2.97 [2 × dq (ABX_3), J_{AB} 15.5, J_{AX} 7.8, $HCHCH_3$], 1.43 (t, J 7.8, CH_3CH_2) and 1.4 [s, $C(CH_3)_2$]; δ_C 161.10 [C=O(Q)], 158.56 [N=C(Q)], 147.15 [C–N=C(Q)], 134.75, 127.32, 127.01, 126.39 [4 × CH(Q)], 120.14 [C–C=O(Q)], 77.33 [$C(CH_3)_2$], 27.87 [$C(CH_3)_3$], 26.62 (CH_3CH_2) and 11.23 (CH_3CH_2); ν_{max}/cm^{-1} 3200s br, 1695s and 1600s; m/z (%) 261 (M^+, 1.2), 175 (100) and 130 (21). At 13 °C, the ABX_3 signals at δ 3.24 and 2.97 coalesced maximally and the inversion barrier at the exocyclic nitrogen ΔG was calculated to be 13.9 kcal mol^{-1} (58 kJ mol^{-1}) using the equation given above.

Preparation of (*S*)-3-amino-2-(1-*tert*-butyldimethylsilyloxy)-ethylquinazolin-4(3*H*)-one 15

To a stirred solution of (*S*)-3-amino-2-(1-hydroxy)-ethylquinazolin-4(3*H*)-one **14** [7] (2 g, 9.76 mmol) in dry THF (12 cm^3) was added imidazole (0.69 g, 0.01 mol) as a solution in dry THF (8 cm^3). After 30 min, *tert*-butyldimethylsilyl chloride (2.94 g, 0.019 mol) was added and the mixture stirred for a further 7 h. The bulk of the solvent was removed under reduced pressure, dichloromethane (40 cm^3) added and the solution washed with water (45 cm^3) and then dried. After evaporation under reduced pressure, the residue was triturated with cold light petroleum (5 cm^3) to give unreacted starting alcohol **14** (0.37 g). The clear oil left after evaporation of the light petroleum under reduced pressure was chromatographed over silica using ethyl acetate–light petroleum (1:2) as eluent to give the required title silyl ether **15** as a clear oil (R_f 0.55) (0.727 g, 23%); δ_H 8.05 [dd, J 8, 1 5-H(Q^2)], 7.55 [m, 7-H, 8-H(Q^2)], 7.25 [ddd, J 8, 6, 1 6-H(Q^2)], 5.65 (s, NH_2, D_2O exch.), 5.2 (q, J 6.6, CH_3CH), 1.61 (d, J 6.6, CH_3CH), 0.81 [s, $C(CH_3)_3$], 0.12 (s, CH_3SiCH_3) and 0.02 (s, CH_3SiCH_3); δ_C 159.97 [C=O(Q^2)], 155.17 [C=N(Q^2)], 146.15 [C–N=C(Q^2)], 133.51, 127.25, 126.32, 125.98 [4 × CH(Q^2)], 119.61 [C–C=O(Q^2)], 70.51 (CH_3CH), 25.62 [$C(CH_3)_3$], 20.26 (CH_3CH), 17.66 [$C(CH_3)_3$], −4.92 (CH_3SiCH_3) and −5.04 (CH_3SiCH_3); ν_{max}/cm^{-1} 3340m, 3240w, 1675s and 1600s; m/z (%) 349 (M^+, 1.3) and 262 (100).

Reaction of (*S*)-3-amino-2-(1-hydroxy)ethylquinazolin-4(3*H*)-one 14 with sodium hydride–cinnamyl bromide

To a well-stirred slurry of sodium hydride (60% dispersion, 1.24 g, 0.031 mol) in dry THF (15 cm^3) was added the title 3-aminoquinazolinone **14** [7] (6.086 g, 0.0297 mol) as a solution in dry THF (20 cm^3) dropwise over 15 min. After a further 30 min, a solution of cinnamyl bromide (7.6 g, 0.0386 mol) in dry THF (7 cm^3) was added in one portion and the mixture stirred overnight. Water (20 cm^3) was added, the bulk of the THF removed under reduced pressure and the residue extracted with dichloromethane (30 cm^3). The dichloromethane layer was separated and washed with water, dried and evaporated under reduced pressure. Chromatography of the residue over silica using ethyl acetate–light petroleum (1:2) as eluent gave quinazolinone **20** (R_f 0.69) as colourless crystals, (3.6 g, 33%) mp 89–91 °C (from ethanol) (Found: C, 76.7; H, 6.3; N, 9.55. $C_{28}H_{27}N_3O_2$ requires C, 76.85; H, 6.2; N, 9.6%); δ_H 8.25 [dd, J 8, 1, 5-H(Q^3)], 7.85 [dd, J 8, 1, 8-H(Q^3)], 7.75 [ddd, J 8, 7 and 1, 7-H(Q^3)], 7.5 [ddd, J 8, ~7, 1, 6-H(Q^3)], 7.25 [m, 5 × CH(Ph)], 6.6 (d, J 16, CHPh), 6.5 (d, J 16, CHPh), 6.3 (dd, J 16, 6.8 and dd 16, 5.9, 2 × CH=CHPh), 5.5 [t, J 6.5, NH (D_2O exch.)], 5.27 (q, J 6.4, CH_3CH), 4.24 (ddd, J 16, 6.8, 1, OCHH), 4.15 (ddd, J 16, 6.8, 1, OCHH), 3.8 (m, NCH_2) and 1.65 (d, J 6.4, CH_3CH); ν_{max}/cm^{-1} 3300s, 1675s and 1600s. Further elution gave a mixture of compounds **20** and **19** (2.7 g) in a 1.7:1 ratio followed by 3-aminoquinazolinone **19** as colourless crystals (R_f 0.39) (2.1 g, 27%) mp 100–103 °C (from ethanol) (Found: C, 71.35; H, 6.1; N, 12.9. $C_{19}H_{19}N_3O_2$ requires C, 71.05; H, 5.95; N, 13.05%); δ_H 8.2 [dd, J 8.2, 1.2, 5-H(Q^3)], 7.7 [m, 7-H, 8-H(Q^3)], 7.4 [ddd, J *ca.* 8.2, 6.1, *ca.* 1 6-H(Q^3)], 7.2 [m, 5 × CH(Ph)], 6.55 (d, J 15.9, CHPh), 6.2 (dt, J 15.9, 8.2, CH=CHPh), 5.3 [s, NH_2, (D_2O exch.)], 5.05 (q, J 6.6, CH_3CHO), 4.2 (m, OCH_2) and 1.7 (d, J 6.6, CH_3CH); δ_C 161.92 [C=O(Q^3)], 160.66 [N=C(Q^3)], 146.89 [C–N=C(Q^3)], 137.25 [C(Ph)], 133.95, 131.65 (CH=CHPh), 130.83, 128.75, 128.24, 127.94, 127.26, 126.95, 126.22, 126.06, 125.88 [5 × CH(Ph), 4 × CH(Q^3)], 119.80 [C–C=O(Q^3)], 38.16 (OCH_2), 36.31 (CH_3CH) and 18.39 (CH_3CH); ν_{max}/cm^{-1} 3350s, 1675s and 1600s; m/z (%) 321 (M^+, 9.2), 189 (100), 173 (33), 119 (27), 117 (68) and 115 (27).

Aziridination of cinnamyl alcohol with 3

To well stirred dry dichloromethane (2 cm^3) at −12 °C was added powdered LTA (0.81 g, 1.82 mmol) in one portion. After the LTA had dissolved, the mixture was cooled further to −20 °C and then 3-amino-2-(1-methyl-2,2-dimethylprop-1-yl)quinazolin-4(3*H*)-one [13] (0.56 g, 1.73 mmol) added dropwise as a solution in dry dichloromethane (5 cm^3) over 6 min, stirring throughout. The resulting slurry was stirred at −20 °C for a further 20 min before the solution was filtered rapidly under vacuum using apparatus pre-cooled to −20 °C. After washing the filtrate rapidly with cold (0 °C) aq. saturated sodium hydrogen carbonate it was dried (−10 °C), re-cooled to −20 °C, treated with cinnamyl alcohol (0.38 g, 1.4 mol equiv.) with stirring and then the temperature of the solution allowed to rise to ambient, stirring throughout. After washing the solution with aq. saturated sodium hydrogen carbonate (15 cm^3) and then water (15 cm^3) and drying, the solvent was evaporated under reduced pressure. NMR spectroscopy of the crude product showed it to contain two aziridine diastereoisomers **11** and **12** in a 1.3:1 ratio from integration of signals at δ 0.32 (major) and δ 2.86 (minor) (see below) together with the 3*H*-quinazolinone **13** from the signal δ 2.63 (q, J 7, CHMe) (ratio **11** + **12**:**13** *ca.* 3:1). Trituration with cold ethanol gave the major diastereoisomer **11** (0.11 g, 14%) as colourless crystals mp 101–103 °C (from ethanol) (Found: M^+, 377.210. $C_{23}H_{27}N_3O_2$ requires M, 377.211); δ_H 8.26 [d, J 8, 5-H(Q^1)], 7.69 [dd, J 8.1, 8, 7-H(Q^1)], 7.55 [d, J *ca.* 8, 8-H(Q^1)], 7.44 [dd, J 8.1, 8, 6-H(Q^1)], 7.1 [m, 5 × CH(Ph)], 4.36 [d, br, J *ca.* 11, HCHOH, (D_2O exch. to dd, J 11, 1)], 4.12 (br s, CHOH, D_2O exch.), 3.73 (m, HCHOH, CHPh, azir. 3-H), 3.03 (q, J 6.9, Bu^{t}CH), 0.86 [s, $C(CH_3)_3$] and 0.32 [d, J 6.9, $CHCH_3$]; δ_C 161.35 [C=O(Q^1)], 159.09 [N=C(Q^1)], 145.46 [C–N=C(Q^1)],

130.62 [C(Ph)], 133.59, 128.67, 128.66, 128.29, 127.23, 126.31, 126.19, 126.00 [5 × CH(Ph), 4 × CH(Q^1); one signal overlapping], 120.17 [*C*–C=O(Q^1)], 63.12 (CH_2OH), 53.62, 52.81 (*C*HPh and *C*HCH_2OH), 44.29 (Bu^{t}CH), 36.10 [*C*$(CH_3)_3$], 27.64 [C(*C*H_3)$_3$] and 13.05 (Bu^{t}CH*C*H_3); ν_{max}/cm^{-1} 3480s, 1655s and 1610w; *m*/*z* (%) 377 (M^+, 6), 347 (28), 346 (100), 174 (61), 173 (28) and 130 (26). The minor diastereoisomer **12** was not isolated by chromatography over silica but its presence in the crude reaction mixture after removal of the bulk of the major diastereoisomer **11** was inferred from signals at δ 4.09 (m, *H*CHO*H*, D_2O exch. gives dd, *J* 13, *ca.* 1 for *H*CHOD), 3.47 (ddd, *J ca.* 8, 6, 1, azir. 3-H), 3.25 (q, *J* 6.8, Bu^{t}C*H*CH$_3$), 3.09 (dd, *J* 13, 8 HC*H*OH), 2.86 (d, *J* 6.7, C*H*Ph) and 1.33 (d, *J* 6.8, CHCH_3).

Aziridination of styrene using 16

A solution of 3-acetoxyaminoquinazolinone **16** was prepared at −20 °C using dry dichloromethane (2 cm^3), powdered LTA (0.81 g, 1.82 mmol) and 3-aminoquinazolinone **15** (0.56 g, 1.75 mmol) dissolved in dichloromethane (5 cm^3), using the procedure described above and styrene (1 cm^3, 8.65 mmol) added. After the same work-up, the crude product, containing a 4.6:1 ratio of aziridine **17** diastereoisomers from signals at δ 3.75 and 3.50 in the NMR spectrum (see below) was chromatographed over silica using ethyl acetate–light petroleum (1:4) as eluent to give aziridine **17** as a clear oil (R_f = 0.32) as a 6:1 ratio of diastereoisomers (0.174 g, 24%) (Found: M^+, 421.219. $C_{24}H_{31}N_3O_2Si$ requires *M*, 421.218); δ_H(major diastereoisomer) 8.2 [dd, *J* 8, 1, H-5(Q^2)], 7.7 [m, H-7, H-8(Q^2)], 7.4 [m, H-6(Q^2), 5 × C*H*(Ph)], 5.45 (q, *J* 6.4, CH_3CH), 4.04 (dd, *J* 7.8, 5.1, azir. C*H*Ph), 3.75 (dd, *J* 7.8, 1.8, azir. *H*CH *trans* to Ph), 2.73 (dd, *J* 5.1, 1.8, azir. HC*H cis* to Ph), 1.65 (d, *J* 6.5, CH_3CH), 0.9 [s, Si$(CH_3)_2$] and 0.89 [s, C$(CH_3)_3$]; minor diastereoisomer (observable peaks) 8.23 [d, *J* 8, 5-H(Q^2)], 5.59 (q, *J* 6.4, CH_3CH), 3.5 (dd, *J* 7.2, 1.6, azir. *H*CH *trans* to Ph), 2.8 (dd, *J* 5.2, 1.6, azir. HC*H cis* to Ph), 1.57 (d, *J* 6.4, CH_3CH) and 0.05 [s, Si$(CH_3)_2$]; ν_{max}/cm^{-1} 1670s and 1600s; *m*/*z* (%) 421 (M^+, 28), 365 (24), 364 (86), 260 (24), 247 (100), 118 (58) and 91 (36). Further elution gave an artefact (R_f 0.07) (signals in its NMR spectrum (see below) were absent in the spectrum of the crude reaction mixture above) isolated as a clear oil (0.149, 19.6%) identified as amino alcohol **18** (Found: M^+, 439.229. $C_{24}H_{33}N_3O_3Si$ requires *M*, 439.229); δ_H 8.25 [d, *J* 8, 5-H(Q^2)], 7.75 [m, 7-H, 8-H(Q^2)], 7.35 [m, 5 × C*H*(Ph), 6-H(Q^2)], 5.85 (t, *J* 6.8, N*H*, D_2O exch.), 5.37 (q, *J* 6.4, CH_3CH), 4.94 (dd, *J* 6, ~6, C*H*OH), 4.25 (s br, CHO*H*, D_2O exch.), 3.31 (m br, NHCH_2), 1.64 (d, *J* 6.4, CH_3CH), 0.9 [s, C$(CH_3)_3$], 0.2 (s, CH_3SiCH_3) and 0.1 (s, CH_3SiCH_3); δ_C 162.31 [C=O(Q^2)], 158.96 [N=C(Q^2)], 146.64 [C(Ph)], 141.22 [*C*–N=C(Q)], 134.36, 128.3, 127.67, 127.63, 126.66, 126.29, 125.69, 125.6 [5 × CH(Ph), 4 × *C*H(Q) and signal overlapping], 120.52 [*C*–C=O(Q)], 71.41 (CH_3CH), 66.38 (*C*HOH), 58.73 (QNH*C*H_2), 25.79 [C(*C*H_3)$_3$], 22.42 (*C*H_3CH), 16.37 [*C*$(CH_3)_3$] and −4.47, −4.83 (*C*H_3Si*C*H_3); ν_{max}/cm^{-1} 3470s br, 3310w, 1680s and 1600s; *m*/*z* (%) 440 (M^+ + H, 0.4), 382 (42), 332 (45), 248 (70) and 247 (100%).

Intramolecular aziridination using reagent 19

The *N*-acetoxylation procedure described above was carried out at −20 °C using 3-aminoquinazolinone **19** (0.3 g, 0.9 mmol), LTA (0.42 g, 0.95 mmol) in dry dichloromethane (3 cm^3) and the temperature of the solution after base-washing allowed to rise to ambient without the addition of any alkene. After work-up the solid residue was crystallised to give aziridine **25** (0.18 g, 60%) mp 161–171 °C (from ethanol) (Found: C, 71.1; H, 5.5; N, 12.75. $C_{19}H_{17}N_3O_2$ requires C, 71.45; H, 5.35; N, 13.15%); δ_H 8.25 [dd, *J* 7.7, *ca.* 1, H-5(Q^3)], 7.75 [m, 7-H, 8-H(Q^3)], 7.4 [m, 6-H(Q^3), 5 × C*H*(Ph)], 5.6 (q, *J ca.* 7, CH_3CH), 4.5 (dd, *J* 13.1, 3.6, OC*H*H), 3.6 (dd, *J* 13, *ca.* 13, OCH*H*), 3.4 (d, *J* 5.3, azir. C*H*Ph), 3.25 (dd, *J* 13.1, 5.3, 3.6, azir. 3-H) and 1.75 (d, *J* 7, CH_3CH); δ_C 158.55 [C=O(Q^3)], 149.44 [N=C(Q^3)], 145.83 [*C*–N=C(Q^3)], 134.93 [*C*(Ph)], 133.04, 128.44, 128.12, 127.92, 127.28, 127.21, 127.18, 127.12, 126.0 [5 × CH(Ph), 4 × CH(Q^3)], 121.93 [*C*C=O(Q^3)], 85.25 (OCH_2), 70.14 (CH_3*C*H), 50.28, 48.89 (azir. C-2, C-3) and 17.16 (*C*H_3CH); ν_{max}/cm^{-1} 1695s, 1600s and 1575s; *m*/*z* (%) 319 (M^+, 8), 216 (68), 215 (76), 214 (29), 188 (22), 187 (22) and 176 (66). Chromatography of the residue of removal of aziridine **25** using ethyl acetate–light petroleum (2:1) as eluent gave 3*H* quinazolinone **22** as colourless crystals (60 mg, 24%) mp 122–124 °C (from ethyl acetate–light petroleum) (Found: C, 73.4; H, 6.0; N, 9.0. $C_{19}H_{18}N_2O_2$ requires C, 73.5; H, 6.05; N, 8.9%); δ_H 9.82 (s, NH), 8.3 [dd, *J* 8, 1.1, 5-H(Q^3)], 7.75 [ddd, *J ca.* 8, 7, 1, 7-H(Q^3)], 7.65 [dd, *J ca.* 8, *ca.* 1, 8-H(Q^3)], 7.45 [ddd, *J* 7.9, *ca.* 7, 1, 6-H(Q^3)], 7.3 [5 × CH(Ph)], 6.65 [d, *J* 16, PhCH), 6.3 (dt, *J* 16, 6.2, CH_2CH=), 4.6 (q, *J* 6.7, CH_3CH), 4.25 [d, *J* 6.2, OCH_2) and 1.6 (d, *J* 6.7, CH_3CH); ν_{max}/cm^{-1} 3375m, 1675s and 1610s; *m*/*z* (%) 306 (M^+, 5.5), 174 (100) and 173 (47).

Aziridination experiments monitored by NMR spectroscopy: general procedure for *N*-acetoxylation

To well stirred $CDCl_3$ (1 cm^3) at −12 °C was added powdered LTA (0.145 g, 0.327 mmol) in one portion. After dissolution, the solution was cooled to −20 °C and the 3-aminoquinazolinone (0.311 mmol) added dropwise as a solution in $CDCl_3$ (2 cm^3) over 3 min. The resulting slurry was stirred at −20 °C for 20 min before the reaction vessel was transferred to a cold box maintained at ~ −40 °C. After filtering the $CDCl_3$ solution through a small column of celite (Pasteur pipette), the filtrate was washed once rapidly with saturated aq. sodium hydrogen carbonate (5 cm^3, pre-cooled to −5 °C), dried (−20 °C) and filtered directly into an NMR tube cooled to − 35 °C. An NMR spectrum was recorded initially at −25 °C without any intermediate warming of the solution.

(a) Aziridination of cinnamyl alcohol using 3. *N*-Acetoxylation of 3-amino-2-(1-methyl-2,2-dimethylprop-1-yl)quinazolin-4(3*H*)-one by the procedure described above gave 3-acetoxyaminoquinazolinone **3** as a 4:1 ratio of diastereoisomers from the intensity of peaks at δ 11.10 and 10.89 (N*H*OAc).[7] Cinnamyl alcohol (0.046 g, 1.1 mol equiv.) was added to the NMR tube and the solution stirred (< −25 °C) using a thin glass rod. Signals from both aziridine diastereoisomers **11** and **12** slowly appeared at −20 °C in a 1.3:1 ratio respectively from comparison of the intensity of peaks at δ 0.32 (major) and δ 2.86 (minor). There was no change in the 4:1 ratio of diastereoisomers of **3** and no change in the 1.3:1 ratio of aziridine diastereoisomers **11** and **12** as the intensity of the signals at δ 11.10 and 10.89 was reduced to zero.

(b) Aziridination of styrene using 16. *N*-Acetoxylation of 3-aminoquinazolinone **15** using the procedure described above gave a solution of the 3-acetoxyaminoquinazolinone **15** as two diastereoisomers in a 1.5:1 ratio from the intensities of signals at δ 10.93 and 10.86 (N*H*OAc). After an addition of styrene (0.162 cm^3, 5 mol equiv.) to the NMR tube, the temperature of the probe was raised to −5 °C when signals from both diastereoisomers of aziridine **17** slowly appeared in a 4.7:1 ratio from the ratios of signals at δ 3.75 (major) and 3.5 (minor) (see data for **17** above). Spectra run as the temperature of the probe was gradually raised to ambient showed no change in the 1.5:1 ratio of signals at δ 10.93 and 10.86 as they gradually disappeared. There was also no change in the 4.6:1 ratio of aziridine diastereoisomers **17**.

(c) Intramolecular aziridination using 19. *N*-Acetoxylation of 3-aminoquinazolinone **19** was carried out as described above except that the slurry was stirred for 5 min. The two diastereoisomers of 3-acetoxyaminoquinazolinone **21** were present in a 1.5:1 ratio at −25 °C from comparison of intensities of the signals at δ 10.94 and 10.58 (N*H*OAc) together with ~30% 3*H*-quinazolinone **22** from the intensity of the signal at δ 4.6 (q, CH_3CH). Signals from aziridine **25** appeared

slowly at −20 °C but there was no change in the 1.5:1 ratio of diastereoisomers of **21** as the intensities of signals at δ 10.94 and 10.88 above decayed to zero.

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