Reagent- and chelation-controlled diastereoselective aziridination of electron-rich alkenes by 3-acetoxyamino-2-(1-hydroxy-2,2-dimethylprop-1-yl)-quinazolin-4(3*H*)-one

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In the presence of titanium(IV) *tert*-butoxide, the title 3-acetoxyaminoquinazolinone aziridinates styrene, butadiene and indene completely diastereoselectively; the absolute configuration of the styrene-derived aziridine 6a is proven by X-ray crystallography and is consistent with a transition state model involving chelation control by titanium.

3-Acetoxyaminoquinazolinones **1** are aziridinating agents for alkenes.[1] The mechanism for the aziridine ring formation appears to resemble that by which peroxyacids convert alkenes into epoxides.[2]

The presence of the quinazolinone ring has allowed us to probe the mechanism for these aziridinations in a way which is not possible for epoxidation; its presence also allows the incorporation of a chiral centre into the 2-position of the ring (**1**; R = R*) which can then bring about reagent-controlled diastereoselective aziridination of prochiral alkenes.[3] We are engaged in the rational design of the chiral substituent R* so as to maximise the diastereoselectivity in aziridination of a range of alkenes by making use of transition state models we have derived for the reactions.[4]

Here we report the completely diastereoselective aziridination of alkenes using the chiral 3-acetoxyaminoquinazolinone **2** (Q*NHOAc) in which chelation between N-1 and a titanium alkoxide of the sidechain hydroxy group apparently controls the diastereoselectivity.

3-Aminoquinazolinone **3** {$[\alpha]_D$ = 20.2 (*c* 1, EtOH)} was prepared from (*S*)-*tert*-leucine **4** *via* the α-acetoxyacid **5** in 39% overall yield without the requirement for chromatography at any stage (Scheme 1).†

Solutions of Q*NHOAc **2** (1 equiv.), free from lead diacetate, reacted with styrene (1.2 equiv.) to give a 1:1 ratio of diastereoisomers of aziridine **6a**:**6b** (92%). When titanium(IV) *tert*-butoxide (2 equiv.) was added to the reaction mixture, a single diastereoisomer **6a** was formed as shown by NMR spectroscopic examination of the crude reaction product (60% isolated yield). The absolute configuration at the created chiral

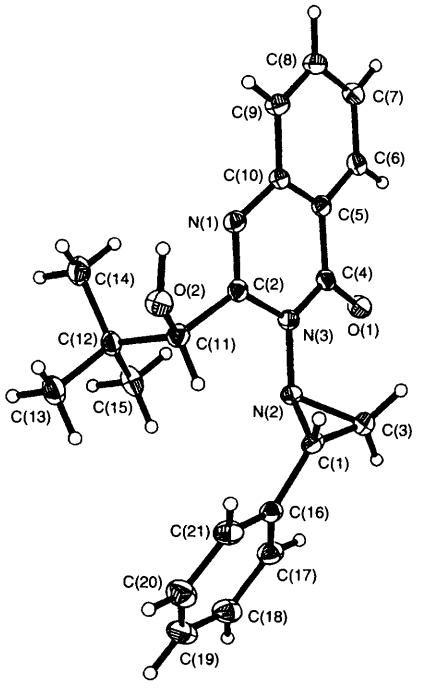
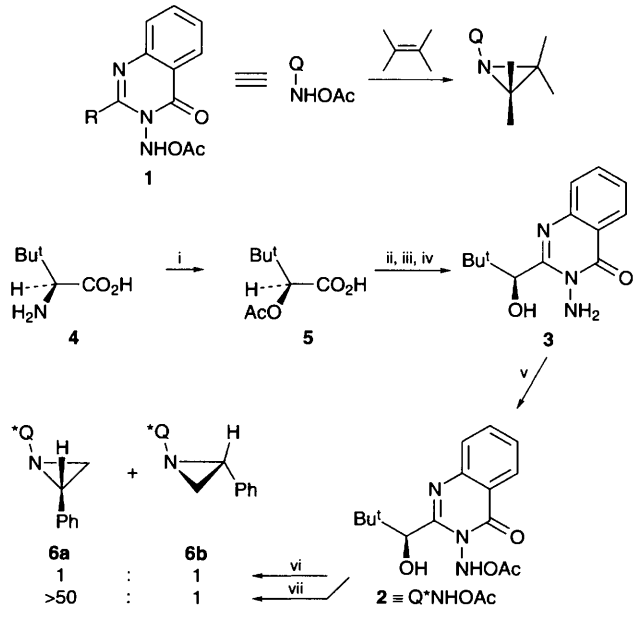
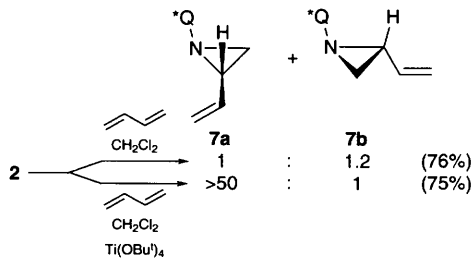


Fig. 1 X-Ray crystal structure of aziridine **6a**



Scheme 1 *Reagents and conditions*: i, HNO_2, AcOH; ii, $SOCl_2$; iii, methyl anthranilate; iv, NH_2NH_2, 140 °C; v, $Pb(OAc)_4$, CH_2Cl_2, −20 °C; vi, styrene; vii, styrene, $Ti(OBu^t)_4$



Scheme 2

centre was shown to be (*S*) by X-ray crystal structure determination (Fig. 1).‡

Similarly, aziridination of butadiene with Q*NHOAc **2** in the presence of titanium(IV) *tert*-butoxide gave a single diastereoisomer **7a** whereas in its absence there was virtually no diastereoselectivity (Scheme 2). In the NMR spectrum of aziridine **7a** there are additional signals from another minor aziridine species present (30 : 1) that are assigned to the N-invertomer of **7a** in which Q* and the vinyl group are *cis*-disposed.

In aziridination of indene the diastereoselectivity is also greatly increased in the presence of the titanium salt (Scheme 3). For the major diastereoisomer **8a**, the inversion barrier at the aziridine ring nitrogen is significantly greater than those in aziridines **6a** and **7a**; the kinetically-formed and (at 0 °C) isolated N-invertomer is, as expected,[1] the *endo*-isomer; equilibration to give an 8 : 1 ratio of *exo*: *endo* isomers occurs at room temperature over 30 min.

The sense of diastereoselectivity in formation of aziridine **6a** is in agreement with our previously described transition state model [4b] but with titanium coordinated to the hydroxy group on the chiral centre and to N-1 of the quinazolinone ring as shown in **9** (Scheme 4).§

In this transition state **9** the phenyl and quinazolinone rings are *syn* (*cf.* addition to indene above) and approach of the alkene is from the face of the quinazolinone opposite the *tert*-butyl group.‡ Since analogous transition states for aziridinations of butadiene and of indene are anticipated, the (absolute) configurations of aziridines **7a** and **8a** are assigned accordingly.

Ring-opening of aziridines **6a–8a** and N–Q bond reduction[5] should provide access to a range of enantiopure chirons.

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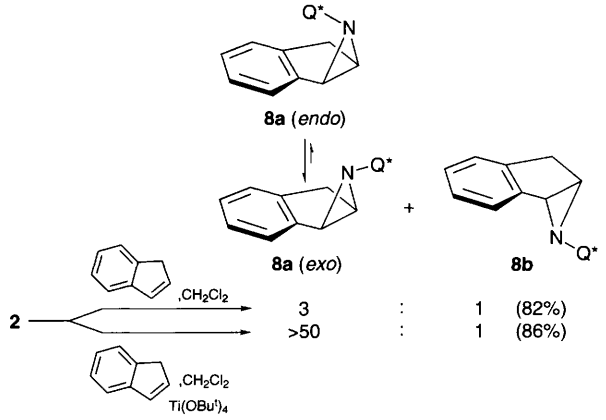
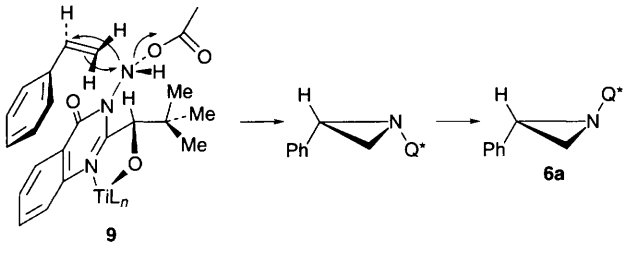


Scheme 3



Scheme 4

Footnotes

† 3-Aminoquinazolinone **3** was shown to be enantiopure based on its reaction products with *O*-acetyllactic acid chloride: its absolute configuration follows from the retention of configuration in conversion of amino acid **4** to α-acetoxyacid **5**.

‡ *Crystal data* for **6a**: $C_{21}H_{23}N_3O_2$, M = 349.42 orthorhombic, space group $P2_12_12_1$, a = 5.723(1), b = 11.908(2), c = 26.529(3) Å, V = 1807.9(5) Å^3, Z = 4, D_c = 1.284 mg m^{-3}, $F(000)$ = 744, μ = 0.084 mm^{-3}, λ(Mo-Kα) = 0.7107 Å. The crystal used for data collection was a colourless block with the approximate dimensions 0.61 × 0.36 × 0.17 mm. Unit cell parameters were determined by least-squares refinement of the optimised setting angles of 40 reflections in the range 5.2 < θ < 12.4°. Intensity data for 2559 reflections were measured on a Siemens P4 diffractometer at 190 K using an ω scan method. The reflections were corrected for Lorentz and polarisation effects to yield 2357 independent reflections (R_{int} = 0.0192). The structure was solved by direct methods using the program SHELXTL-pc (G. M. Sheldrick, SHELXTL-pc Release 4.2, Siemens Analytical X-ray Instruments, Madison, WI, 1991) and refined by full-matrix least-squares on F^2 using the program SHELXL93 (G. M. Sheldrick, SHELXL-93, Program for Crystal Structure Refinement, University of Göttingen, 1993). All hydrogen atoms were included in calculated positions (C–H = 0.96 Å) with fixed isotropic displacement parameters. All non-hydrogen atoms were refined with anisotropic displacement parameters. Final cycles of refinement of 235 parameters gave $R1$ = 0.0425, w$R2$ = 0.1131 for all data, $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, w$R2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (0.0621\ P)^2 + 0.08\ P]$ and $P = [\max(F_o^2, 0) + 2F_c^2]/3$. The maximum and minimum electron densities in the final ΔF map were 0.18 and −0.22 eÅ^{-3} respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/164.

§ The exocyclic nitrogen in **9** is sp^3-hybridised and its inversion has been shown to be fast on the time-scale of the aziridination (R. S. Atkinson and P. J. Willilams *J. Chem. Soc., Perkin Trans. 2*, 1996, 205); for the configuration assigned to this nitrogen in **9** see ref. 4(*b*).

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