

Aziridination of styrene derivatives with 3-acetoxyaminoquinazolinones: probing transition state geometry from changes in diastereoselectivity

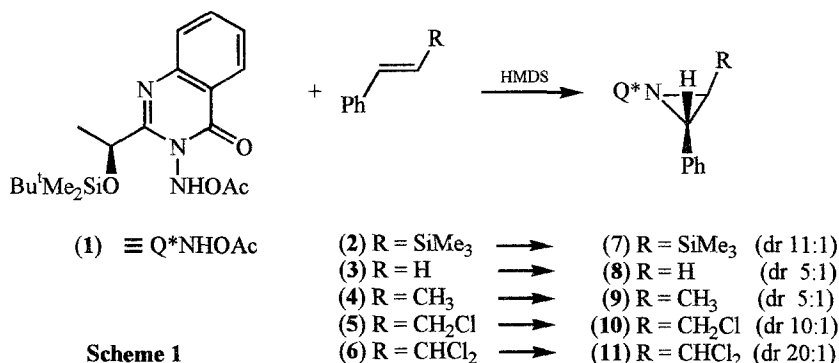
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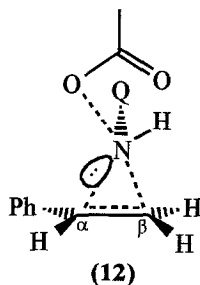
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Abstract: In aziridinations of β -substituted styrenes (**4**), (**5**) and (**6**) with the enantiopure 3-acetoxyaminoquinazolinone (**1**), diastereoselectivity (dr) increases from 5:1 (for **9**) to 10:1 (for **10**) to ~20:1 (for **11**): changes in transition state geometry which account for this increase are rationalised using Frontier Orbital Theory. © 1998 Elsevier Science Ltd. All rights reserved.

3-Acetoxyaminoquinazolinones *e.g.* Q^*NHOAc (**1**) are aziridinating agents for alkenes.¹ The mechanism for 3-membered ring formation resembles that by which peroxyacetic acid converts alkenes into epoxides² (the Bartlett mechanism); both reactions are stereospecific with retention of the alkene configuration in the product and both react highly stereoselectively with cyclohex-2-enol *syn* to the hydroxy group.³ However, the presence of the quinazolinone ring in the aziridinating agent offers a number of advantages: in particular, the presence of a chiral centre at its 2-position as in Q^*NHOAc (**1**) can result in high (reagent-controlled) diastereoselectivity in aziridination of prochiral alkenes as in Scheme 1.⁴



In the formation of aziridine (**7**) in Scheme 1, the high diastereoselectivity was ascribed to a preferred conformation for the trialkylsilyloxyethyl 2-substituent of Q^* in the transition state model previously⁵ deduced for these aziridinations (see below). The mechanism of aziridination of electron-rich alkenes such as styrene is believed to be concerted but asynchronous as in (**12**);⁶ here C_β -N bond formation runs ahead of $N-C_\alpha$ bond formation and attack by the π -electrons in the alkene on the sp^3 -hybridised nitrogen⁷ in Q^*NHOAc (**1**) occurs with S_N2 -type displacement of the acetoxy group. In terms of orbital overlap therefore, the aziridination is dominated by interaction of the HOMO (alkene) with $\sigma^*(N-OAc)$ over LUMO (alkene) with HOMO (NOAc) (the lone pair-containing orbital on nitrogen). The present work was undertaken in an attempt to understand why substitution of a β -trimethylsilyl substituent into styrene [(**3**) $\rightarrow$ (**2**)] raised the level of diastereoselectivity in aziridination by Q^*NHOAc (**1**) from 5:1 to 11:1 (Scheme 1; major diastereoisomers (**8**) and (**7**), respectively). As Scheme 1 shows, as the β -substituent becomes progressively more electron-withdrawing in the styrenes (**4**), (**5**) and (**6**), the diastereoselectivity (dr) in their aziridination by Q^*NHOAc (**1**) increases from 5:1 to 10:1 to ~20:1 respectively.



Analysis by NMR spectroscopy of the crude reaction product from aziridination of β -methylstyrene (**4**) was complicated by the presence of both diastereoisomers of the aziridine product as mixtures of *N*-invertomers (1.3:1 for major (**9**); 2.1:1 for minor). However, separation by chromatography of a pure sample of the major diastereoisomer (**9**) facilitated this analysis. In the aziridination of cinnamyl chloride (**5**), separation by chromatography of the major and minor aziridine diastereoisomers and isolation of (**10**) as a crystalline solid (*N*-invertomer ratio 3.5:1) again facilitated measurement of the diastereoisomer ratio present in the crude reaction product by NMR spectroscopy.

In aziridination of cinnamyl dichloride (**6**), distinction between the *N*-invertomer ratio (7:1) and the diastereoisomer ratio (~20:1) was again possible after assignment of signals present in the NMR spectrum of the pure crystalline major diastereoisomer (**11**). The preferred sense of diastereoselectivity in aziridination of substituted styrenes (**2**)–(**6**) is the same and (**7**)–(**11**) are the respective major diastereoisomers. This conclusion for β -trimethylsilyl styrene (**7**) follows from a chemical correlation reported previously.⁴ X-ray crystal structures⁸ for aziridines (**10**) and (**11**) (Figs. 1 and 2) confirm their relative and hence absolute configurations. These crystal structures show a *cis*-relationship between quinazolinone and phenyl rings which corresponds to that of the major *N*-invertomer in solution (CDCl_3).

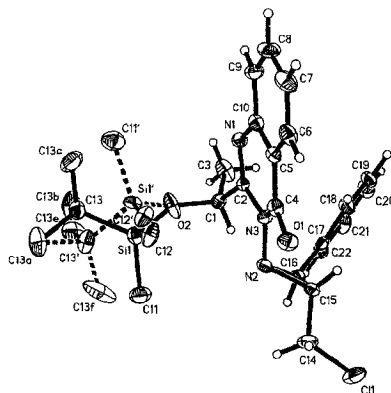


Fig. 1. X-ray crystal structure of **10**. The minor component of disorder is depicted by dashed bonds. [Displacement ellipsoids are shown at 30% probability level.]

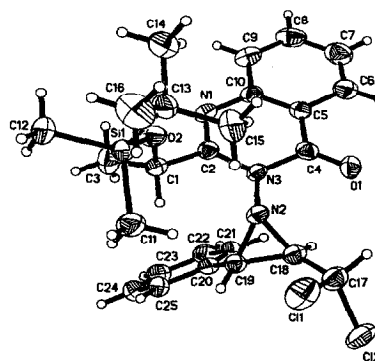
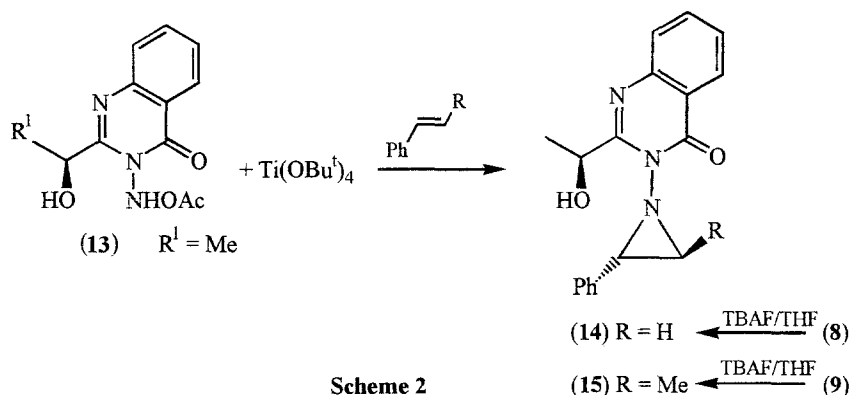


Fig. 2. X-ray crystal structure of **11** with displacement ellipsoids shown at 30% probability level.

For aziridines (**8**) and (**9**), assignments of configuration were carried out as shown in Scheme 2. Thus treatment of the aziridines (both 5:1 mixtures of diastereoisomers) with tributylammonium fluoride (TBAF) in THF gave the corresponding alcohols (**14**) and (**15**) as major products, respectively. These alcohol diastereoisomers are the major ones (dr 6:1 in both cases) from

aziridination of styrene (**3**) and β -methylstyrene (**4**) respectively with QNHOAc (**13**) in the presence of $\text{Ti}(\text{OBu}^t)_4$. Aziridines (**14**) and (**15**) are those predicted as the major diastereoisomers from our transition state model for these $\text{Ti}(\text{OBu}^t)_4$ -mediated reactions using QNHOAc (**13**).^{9,10}

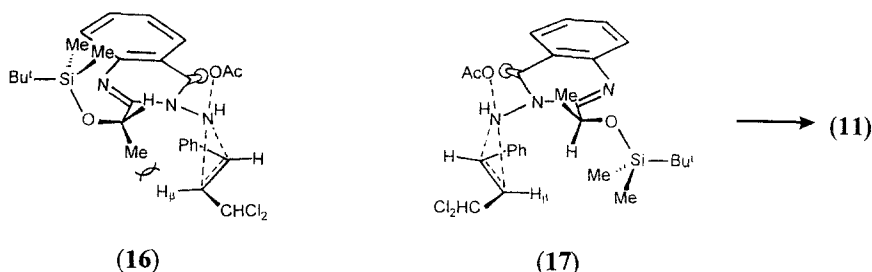
The effect of increasing the electron-withdrawing character of the β -substituent down the series (**4**), (**5**) and (**6**) is to lower both HOMO and LUMO levels of the alkene and lead to an increase in LUMO (alkene) – HOMO (Q^*NHOAc) overlap relative to that of HOMO (alkene) – LUMO (Q^*NHOAc). Additionally, there is a progressive increase in the coefficient at C_α in the LUMOs of (**4**), (**5**) and (**6**) respectively¹¹ which will also favour LUMO (alkene) – HOMO (Q^*NHOAc). Both these factors will tend to reduce the extent to which C_β -N bond formation runs ahead of N- C_α bond formation *cf.* (**12**) and hence lead to a tighter more symmetrical transition state.



Scheme 2

This change in transition state geometry is expected to increase the diastereoselectivity in formation of *e.g.* aziridine (**11**) because it brings the proton H_β on the alkene closer to the existing chiral centre in the 2-substituent on the quinazolinone ring. More specifically, using our previous derived transition state model for aziridination using Q^*NHOAc (**1**), this change brings about greater steric interaction between H_β and the CHMeOSi as shown in (**16**). Aziridination is accordingly preferred *via* transition state (**17**) with its lesser interaction between H_β and CHMeOSi .

Our calculations on the effects of β -trihydrosilyl substitution (as a model for β -trimethylsilyl) on the LUMO energy of styrene and on the change in the coefficient at the α -position suggest that a similar explanation accounts for the increased diastereoselectivity in formation of aziridine (**7**) by comparison with (**8**) (Scheme 1).



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References

1. R. S. Atkinson, M. J. Grimshire and B. J. Kelly, *Tetrahedron*, 1989, **45**, 2875.
2. D. A. Singleton, S. R. Merrigan, J. Liu and K. N. Houk, *J. Am. Chem. Soc.*, 1997, **119**, 3385; E. Vedejs, W. H. Dent, J. T. Kendall and P. A. Oliver, *ibid.*, 1996, **118**, 3556 and references therein.
3. R. S. Atkinson and B. J. Kelly, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1515; H. B. Henbest and R. H. L. Wilson, *J. Chem. Soc.*, 1957, 1985.
4. R. S. Atkinson, M. P. Coogan and I. S. T. Lochrie, *J. Chem. Soc., Perkin Trans. 1*, 1997, 897.
5. R. S. Atkinson, M. P. Coogan and I. S. T. Lochrie, *Tetrahedron Lett.*, 1996, **37**, 5179.
6. R. S. Atkinson, J. Fawcett, D. R. Russell and P. J. Williams, *Tetrahedron Lett.*, 1995, **36**, 3241.
7. R. S. Atkinson and P. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1951.
8. **X-ray Crystallography Data for (10):** $C_{25}H_{32}ClN_3O_2Si$, $M = 470.08$, orthorhombic, space group $P2_12_12$, $a = 10.306(1)$, $b = 14.706(3)$, $c = 17.232(2)$ Å, $U = 2611.7(7)$ Å³, $Z = 4$, $D_c = 1.196$ Mg m⁻³, $\mu(Mo-K_\alpha) = 0.217$ mm⁻¹, $F(000) = 1000$, $T = 190$ K, graphite monochromated Mo-K α radiation, $\lambda = 0.71073$ Å, colourless block, dimensions $0.48 \times 0.23 \times 0.21$ mm, Siemens P4 diffractometer, ω scan. 3 standard reflections monitored every 100 scans showed no significant variation in intensity, the reflections were corrected for Lorentz and polarisation effects. 2816 data were measured ($2.6 < \theta < 27.2^\circ$), with 2678 independent reflections (merging $R_{int} = 0.042$). The structures were solved by Direct methods using the program SHELXTL-PC¹ and refined by full-matrix least squares on F^2 using the program SHELXL93.² The Si(Me)₂Bu^t group attached to O2 is disordered over two sites in the ratio 2:1. The orientation of the disordered Bu^t groups is such that it is not possible to resolve one methyl carbon (C13a) which is bonded to both C13 and C13'.
All hydrogen atoms were included in calculated positions (C-H = 0.96 Å) using a riding model. All non-hydrogen atoms were refined with anisotropic displacement parameters except those of the disordered group which were refined isotropically. Full matrix least squares based on F^2 gave $R1 = 0.057$, $wR2 = 0.146$ for all data, for 337 parameters, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.073P)^2 + 0.64P]$ where $P = [max(F_o^2, 0) + 2F_c^2]/3$ g.o.f. = 1.049, maximum $\Delta/\sigma = 0.001$, maximum $\Delta\rho = 0.85$ e Å⁻³.
Data for (11). $C_{25}H_{31}Cl_2N_3O_2Si$, $M = 504.52$, Tetragonal, space group $P4_12_12$, $a = b = 11.862(2)$, $c = 38.665(8)$ Å, $V = 5441(2)$ Å³, $Z = 8$, $D_c = 1.232$ Mg m⁻³, $\mu(Mo-K_\alpha) = 0.308$ mm⁻¹, $F(000) = 2128$, $T = 200$ K, colourless block, crystal dimensions $0.72 \times 0.37 \times 0.19$ mm. Data were collected and processed as for 10. 6516 data were measured ($2.5 < \theta < 25.0^\circ$), with 4660 independent reflections (merging $R_{int} = 0.044$). The structures were solved using the same method as 10. $R1 = 0.055$, $wR2 = 0.101$ for all data, for 298 parameters, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.07P)^2 + 4.40P]$ where $P = [max(F_o^2, 0) + 2F_c^2]/3$ g.o.f. = 1.040, maximum $\Delta/\sigma = 0.004$, maximum $\Delta\rho = 0.185$ e Å⁻³.
1. G. M. Sheldrick, SHELXTL-pc Release 4.2, Siemens Analytical X-ray Instruments, Madison, WI, 1991.
2. G. M. Sheldrick, SHELXL-93, Program for Crystal Structure Refinement, University of Göttingen, 1993.
9. The diastereoselectivity in aziridination of styrene and of β -methylstyrene by QNHOAc (**13**), mediated by Ti(OBu^t)₄, is believed to arise from chelation of a titanium alkoxide formed from the hydroxy group with N-1. In aziridinations using QNHOAc (**13**), its isopropyl ($R' = Pr^i$) and *tert*-butyl ($R' = Bu^t$) analogues in the presence of Ti(OBu^t)₄, the diastereoselectivities obtained are >50:1, 20:1 and 6:1 respectively and in each case there is a good NMR (¹H) correlation for the aziridine ring proton signals that supports major and minor diastereoisomer assignments in the sense predicted from this chelated model. The relative and hence absolute configuration of the *tert*-butyl analogue ($R' = Bu^t$) has been confirmed by an X-ray structure determination (ref. 10).
10. R. S. Atkinson, A. P. Ayscough, W. T. Gattrell and T. M. Raynham, *J. Chem. Soc., Chem. Commun.*, 1996, 1935.