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Reagent-controlled Diastereoselectivity in Aziridination of Alkenes by chiral 3-Acetoxyamino-3,4-dihydroquinazolin-4-ones: 1′-(*t*-Butyldimethylsilyloxy)ethyl as the chiral 2-Substituent on the Quinazolinone

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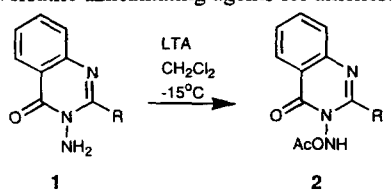
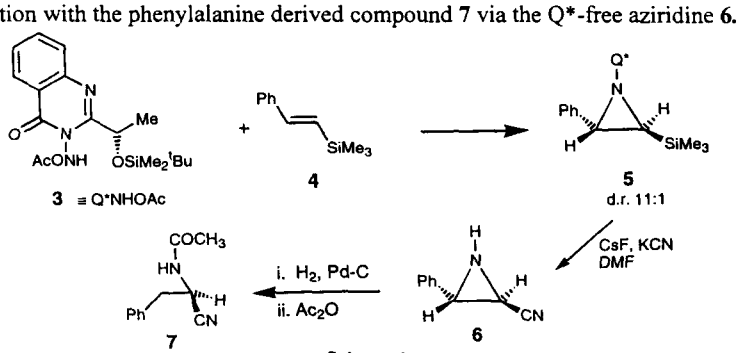
Abstract: Conformational preferences within the $^{t}BuMe_2SiOCH(Me)C{=}N$ unit in 3-acetoxyaminoquinazolinone **3** lead to well defined site preferences for H, Me and $OSiMe_2{}^{t}Bu$ in the transition state for, and hence high diastereoselectivity in, its reaction with β-trimethylsilylstyrene **4** to give aziridine **5**. Copyright © 1996 Elsevier Science Ltd

3-Acetoxyaminoquinazolinones **2**, prepared, *in situ*, by acetoxylation of 3-aminoquinazolinones **1** are versatile aziridinating agents for alkenes.[1] The presence of the heterocyclic ring has enabled us to probe into the mechanism and transition state for aziridination using **2** in a way not possible for epoxidation of alkenes using peroxyacids;[2] both 3-membered ring-forming reactions have much in common.[3] The 2-position of the quinazolinone ring also allows the introduction of a chiral centre (**2**, R=R*) which can then be used to bring about asymmetric induction in aziridination of prochiral alkenes.[4] Thus reaction of β-trimethylsilylstyrene **4** with enantiopure 3-acetoxyaminoquinazolinone **3** (Q*NHOAc), bearing a 1′-(*t*-butyldimethylsilyloxy)ethyl group in the 2-position,[5] gives a 11:1 ratio of diastereoisomers of the aziridine **5** (Scheme 1). The absolute configuration of the major diastereoisomer of **5** was proved by chemical correlation with the phenylalanine derived compound **7** via the Q*-free aziridine **6**.[6]



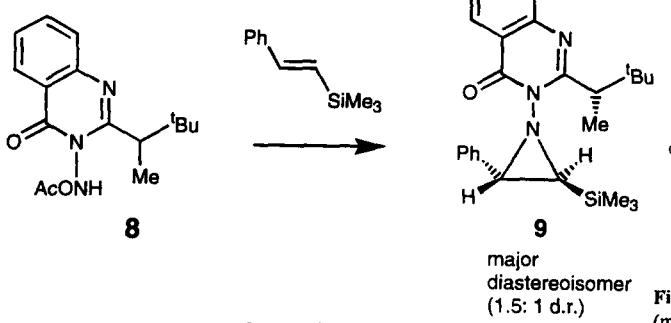
1 **2**



3 ≡ Q*NHOAc **4** **5** d.r. 11:1 **6** **7**

Scheme 1

This high diastereoselectivity in aziridination of vinylsilane **4** with Q*NHOAc **3** is superior to that using (racemic) 3-acetoxyaminoquinazolinone **8** (Scheme 2); the ratio of aziridine diastereoisomers **9** produced was 1.5:1 with the major diastereoisomer having the relative configuration shown from an X-ray crystal structure determination (Fig. 1).[7]



Scheme 2

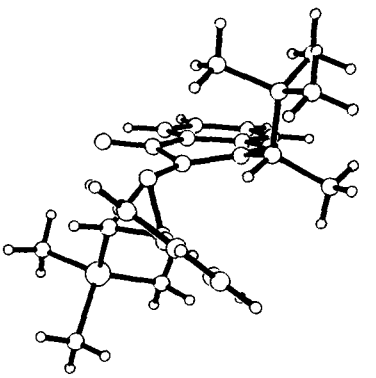


Fig. 1 X-Ray crystal structure of aziridine **9** (major diastereoisomer) (*The phenyl group on the aziridine is oriented towards the viewer*)

The poor diastereoselectivity from the aziridination in Scheme 2 suggests that the high diastereoselectivity obtained in Scheme 1 is not the result of simple steric effects arising from the substituents on the chiral centre in Q*NHOAc **3**.

The work of Gung *et al*[8] has shown that in allylic alcohols, there is a preference for a conformation having the hydroxy group eclipsed with the C=C bond (Fig. 2; R^2 = H) which is increased in γ-hydroxy-α,β-unsaturated esters (R^3 = CO_2R) and in *t*-butyldimethylsilyl ethers (R^2 = $^tBuMe_2Si$). These authors have suggested that this conformational preference may account for the sense of diastereoselectivity of addition reactions to double bonds of γ-hydroxy-α,β-unsaturated esters; there is however always the possibility that the reacting conformation is not the most stable one.

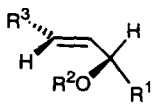


Fig. 2

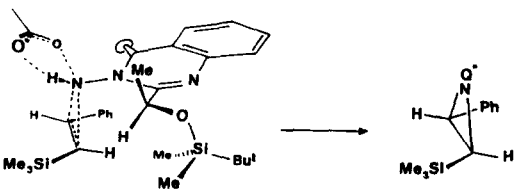
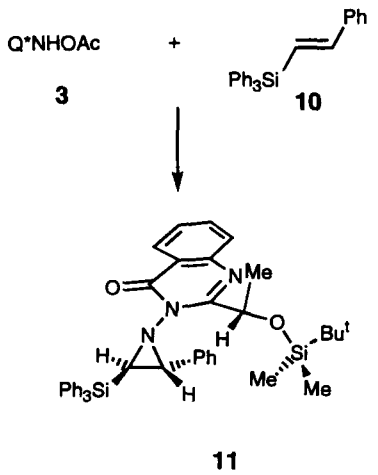


Fig. 3

We rationalise the high diastereoselectivity in the aziridination in Scheme 1 by assuming that an analogous preference also exists in Q*NHOAc **3** for a conformation of the 2-substituent having the C-O bond of the silyloxy group eclipsed with the C=N of the quinazolinone ring. Thus our transition state model[2] for the aziridination reaction in Scheme 1 is shown in Fig. 3; the Si-O bond is inclined to the plane containing the Q*CHMe-O bond and the methyl group on the chiral centre has the orientation shown to avoid adverse 1,3-interaction with the *gem*-dimethyl groups on silicon. Approach of the alkene is from the face of the quinazolinone opposite to this methyl group on the chiral centre, with the alkene and the quinazolinone in parallel planes and *endo* overlap of the phenyl ring.[9]

The presumed conformational preferences within the $^{t}BuMe_2SiOCH(Me)C=N$ sub-unit in this transition state for aziridination (Fig. 3) are reproduced in the crystal structure of aziridine **11** (Fig. 4), the minor diastereoisomer obtained in aziridination of β-triphenylsilylstyrene **10** with Q*NHOAc **3**. When viewed from the perspective shown, the orientation around the bonds to the chiral centre is as illustrated in Fig. 3 with the MeCH-O bond lying close to[10] the plane of the quinazolinone ring, the O-$SiMe_2{}^{t}Bu$ bond inclined to this plane and the $^{t}BuMe_2Si$ group *trans* to the methyl group on the chiral centre.[11]



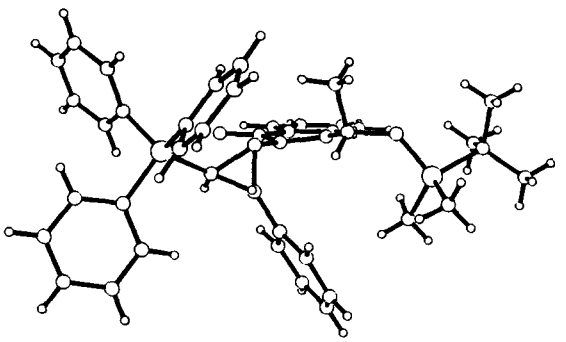


Fig. 4 X-Ray crystal structure of aziridine **11**

Gung *et al*[8] have also shown that the preference for the conformation in Fig 2 is eroded when a bulky substituent ($R^1={}^{t}Bu$) is present on the silyloxy-substituted carbon. Likewise we find (Scheme 3) that aziridination of vinylsilane **4** with 3-acetoxyaminoquinazolinone **12** having a t-butyl group instead of a methyl group on the chiral centre in Q*NHOAc **3** gives a product **13** with poorer diastereoselectivity (4:1) (51%).[12]

Scheme 3

To summarise, the magnitude and the preferred sense of diastereoselectivity in aziridination of vinylsilane **4** with 3-acetoxyaminoquinazolinone **3** can be accounted for by the conformational preferences within the (chiral) $^{t}BuMe_2SiOCH(Me)$- substituent on the 2-position of the quinazolinone. These conformational preferences are revealed in the crystal structure of aziridine **11** and are those anticipated by analogy with the work of Gung *et al* on γ-silyloxy-α,β-unsaturated esters.

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2. R.S. Atkinson, J. Fawcett, D.R. Russell and P.J. Williams, *J. Chem. Soc., Chem. Commun.*, 1994, 2031.
3. R.S. Atkinson and B.J. Kelly, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1515.
4. R.S. Atkinson and G. Tughan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2803.
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7. Crystal data: Data for **9** and **11** were measured on a Siemens P4 diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.7107 Å) at 190K with a ω-scan technique. The data were corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full matrix least squares using the program packages SHELXTL-PC(Sheldrick G.M.(1990), SHELXTL-PC Users Manual. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, U.S.A.) and SHELXL93(Sheldrick G.M. (1993), SHELXL93 Program for Crystal Structure Solution, University of Göttingen, Germany.)
   For **9**: $C_{25}H_{33}N_3OSi$, M = 419.63, Monoclinic space group $P2_1/c$, a = 9.977(2), b = 6.648(1), c = 37.159(6) Å, β = 94.36(2)°, V = 2457.5(7) $Å^3$, Z = 4, D_c = 1.134 Mg m^{-3}, F(000) = 904, μ = 0.115 mm^{-1}, crystal dimensions 0.60 x 0.20 x 0.06 mm. 4645 data were collected with 3202 unique reflections (R_{int} = 0.0402) of which 1990 having $F > 4\sigma(F)$ were regarded as observed. All non-hydrogen atoms were refined as anisotropic. All hydrogen atoms were included in calculated positions (C-H = 0.96 Å) with a single fixed isotropic displacement parameter (0.08 $Å^2$). Final R_1 = 0.0595 wR2 = 0.1218 (0.1104 and 0.1482 respectively for all data) for 271 variables, $(\Delta/\sigma)_{max}$ = 0.001. The final residual Fourier map was featureless (± 0.24 e $Å^{-3}$).
   For **11**: $C_{42}H_{45}N_3O_2Si$, M = 679.99, orthorhombic space group $P2_12_12_1$, a = 10.301(4), b = 14.728(2), c = 25.050(7) Å, V = 3800(2) $Å^3$, Z = 4, D_c = 1.188 Mg m^{-3}, F(000) = 1448, μ = 0.132 mm^{-1}, crystal dimensions 0.46 x 0.14 x 0.10 mm. 3827 data were collected with 3618 unique reflections (R_{int} = 0.0238) of which 2145 having $F > 4\sigma(F)$ were regarded as observed. The non-hydrogen atoms of the (*t*-butyldimethylsilyloxy)ethyl group, the triphenylsilyl group and O(1) were refined with anisotropic displacement parameters. The remaining non-hydrogen atoms were refined as isotropic. All hydrogen atoms were included in calculated positions (C-H = 0.96 Å) with a single fixed isotropic displacement parameter (0.08 $Å^2$). Final R_1 = 0.0692 wR2 = 0.1026 (0.1403 and 0.1299 respectively for all data) for 342 variables, $(\Delta/\sigma)_{max}$ = 0.001. The final residual Fourier map was featureless (±0.32 e $Å^{-3}$).
   Details of both the above structures have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge.
8. B. Gung, J.P. Melnick, M.A. Wolf and A. King, *J. Org. Chem.*, 1995, **60**, 1947; B. Gung and M.B. Francis, *Tetrahedron Lett.*, 1995, **36**, 2579 and refs. therein.
9. R.S. Atkinson and J.R. Malpass, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2242.
10. The quinazolinone ring and C-O bond are not perfectly eclipsed: the torsion angle between C-O and C=N bonds is 12.32°.
11. The crystal structure of a aziridine diastereoisomer from reaction of Q*NHOAc **3** with cyclohexen-1-ol also shows the same conformational preferences for the chiral 2-substituent (R.S. Atkinson and P.J. Williams, unpublished work).
12. The 3-aminoquinazolinone precursor of **12** was synthesised from (*S*)-*t*-leucine (W.T. Gattrell unpublished work) by a method analogous to that used for the preparation of the precursor of Q*NHOAc **3** (R.S. Atkinson, B.J. Kelly and J. Williams, *Tetrahedron*, 1992, **48**, 7713).

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