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Substrate-controlled diastereoselective aziridination of alkenes using 3-acetoxyaminoquinazolinone in the presence of hexamethyldisilazane

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Abstract—8-Phenylmenthol derived α,β-unsaturated esters were aziridinated highly diastereoselectively using 3-acetoxyamino-2-ethylquinazolinone. The yields of these aziridines were greatly improved in the presence of hexamethyldisilazane.

3-Acetoxyaminoquinazolinones, for example, QNHOAc **2** are well known aziridinating agents for alkenes through the mechanism shown in[1,2] **A** (Scheme 1). The mechanism for 3-membered ring formation, at least for electron-rich alkenes (R = Ph) as in **B** resembles that by which peroxyacetic acid converts alkenes into epoxides (Bartlett mechanism).[3,4] Although peroxyacids do not convert α,β-unsaturated esters to epoxides, their counterpart, QNHOAc **2** reacts with α,β-unsaturated esters to give the corresponding aziridines in good yields (see below). The mechanism in this case has been suggested to involve Michael addition of the exocyclic nitrogen onto the β-position of the α,β-unsaturated ester followed by an S_N2 type displacement of the acetoxy group by the developing partially negative charge at Cα (see **C** in Scheme 1). In aziridine formation for both methyl acrylate and styrene, *endo* overlap between the carbonyl or the phenyl group and the quinazolinone carbonyl is also required (see **B** and **C**).

Additionally, the quinazolinone ring in the aziridinating agent offers a number of advantages: in particular, the presence of a stereogenic centre at its 2-position, as in QNHOAc **4**,[5,6] can result in high or even complete diastereoselectivity (>50:1) (reagent-controlled) in the aziridination of alkenes, for example, styrene in the presence of $Ti(OBu^t)_4$ (Scheme 2).

Despite the usefulness of aziridines for accessing α- and β-amino acids, 1,2-diamines and 1,2-aminoalcohols, there are few methods, especially diastereoselective ones, for the conversion of alkenes into aziridines.[1,7,8] Here we present our results on the substrate-controlled diastereoselective aziridination of α,β-unsaturated esters derived from the easily prepared alcohol (−)-phenylmenthol[9] (R*) using QNHOAc **2**.

The chiral esters used in our work were converted into their aziridines using lead tetraacetate (LTA) acetoxylation of 3-amino-2-ethylquinazolinone **1** (R = Et) in CH_2Cl_2 at −18 to −20 °C under various conditions (see Schemes 1 and 3 and Table 1).

During decomposition of QNHOAc **2**, or the analogous *N*-aminophthalimide derivative PNHOAc, in the presence of electron deficient alkenes, or in the absence of alkenes, the main product is deaminated quinazolinone **9** (QH) or phthalimide (PH).[10–12] However, 2 mol equiv of hexamethyldisilazane (HMDS) scavenges the acetic acid formed in the acetoxylation as well as in the aziridination steps, so prolonging the lifetime of the aziridinating agent, for example, QNHOAc **2** (stable at <0 °C), and increases the aziridine yield.[13]

Keywords: Aziridination; 3-Acetoxyaminoquinazolinone; 8-Phenylmenthol; Substrate-controlled diastereoselective aziridination.
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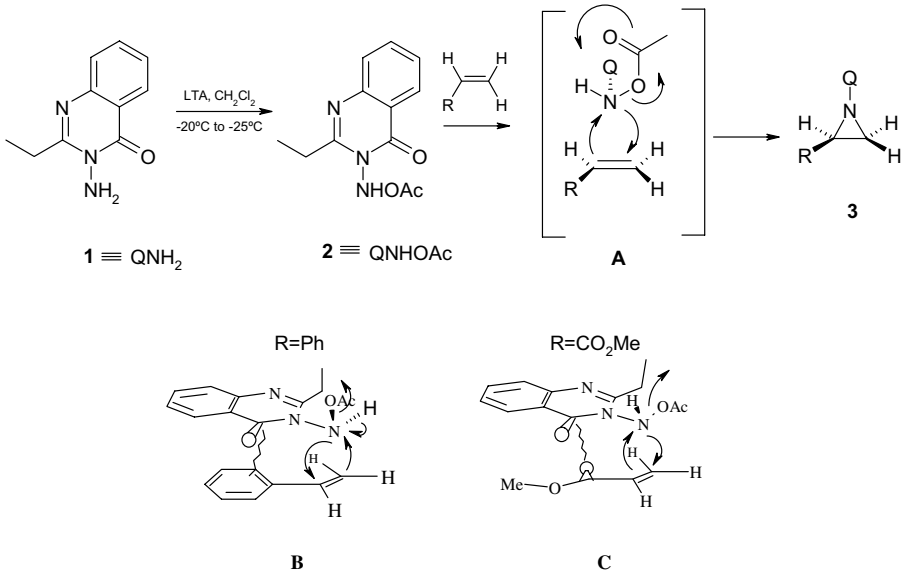
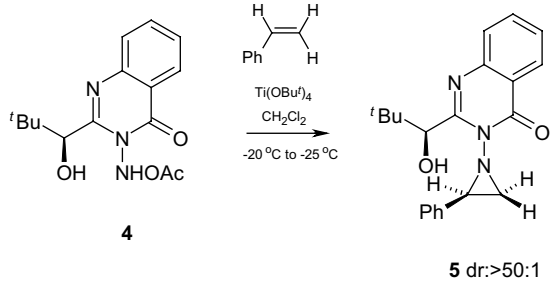


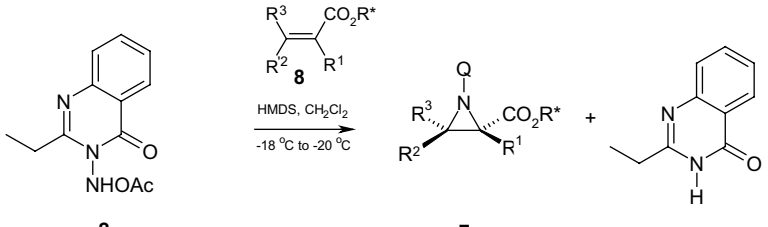
Scheme 1.



Scheme 2.

The yields of aziridine from acrylate, crotonate and methacrylate using QNHOAc **2** were 27%, 28% and 17%, respectively, (Table 1 entries 1, 5 and 7) and were raised to 72%, 79% and 66%, respectively, (Table 1, entries 3, 6 and 9) in the presence of 2 equiv of HMDS (relative to the quinazolinone). Yang and Chen[14] reported that aziridination of *N*-enoylpyrazolidinones using a slight excess of *N*-aminophthalimide (1.5 equiv) in the presence of LTA gave up to 94% of the aziridine. Therefore, we carried out aziridination of the alkenes using an excess of the aziridinating agent QNHOAc **2** (2 equiv) in the presence of HMDS (see Table 2).

In the aziridination of chiral acrylate **8a** with QNHOAc **2**, the product was shown to be a single diastereoisomer present as a mixture of *N*-invertomers (13:1) from careful ^{1}H NMR examination of the C-5 proton of the quinazolinone ring. This ratio of *N*-invertomers was not affected by chromatotron purification of the crude product as shown by re-examination of the ^{1}H NMR spectrum of the resulting oily product. The ratio of *N*-invertomers was not affected by chromatography because interconversion is fast on the real timescale in solution.[15] In the case of the crotonate derived aziridine **8b**, the ratio of *N*-invertomers (3.5:1), before and after chromatographic purification was again determined measuring the signals of the C-5 proton of the Q ring. No minor diastereoisomer was detectable ^{1}H NMR



8a R^1, R^2, R^3=H
8b R^2=CH_3, R^1 and R^3=H
8c R^1=CH_3, R^2 and R^3=H
8d R^2=Et, R^1 and R^3=H
8e R^2=Ph, R^1 and R^3=H
R*= 8-phenylmenthol

Scheme 3.

Table 1. Reactions under various conditions (absence or presence of HMDS)

Entry	Alkenes	Moleequiv of quinazolinone	Moleequiv of alkene	Moleequiv of HMDS	Yield (%)
1	Acrylate	2	1	—	27
2	Acrylate	1	2	2	68
3	Acrylate	2	1	4	72
4	Crotonate	1	2	—	<15
5	Crotonate	2	1	—	<28
6	Crotonate	2	1	4	79
7	Methacrylate	2	1	—	17
8	Methacrylate	1	2	2	48
9	Methacrylate	2	1	4	66

Table 2. All aziridinations were carried out using QNHOAc **2** (2 equiv) and alkenes (1 equiv) in the presence of HMDS (4 equiv) in dichloromethane at −18 °C to −20 °C

Entry	Substrate	Yield (%)[a]	Dr[b]
1	**8a**	72	>50:1
2	**8b**	79	>50:1
3	**8c**	73	>50:1
4	**8d**	71	>50:1
5	**8e**	66	>50:1

[a] Isolated yield (after chromatography).
[b] Determined by ^{1}H NMR and LCMS (C18-RP column with EPS + MS detection).

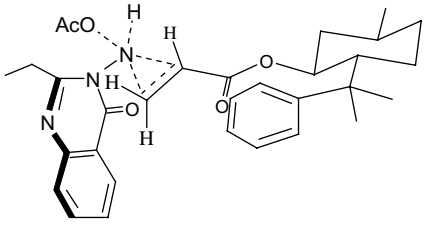


Figure 1.

analysis of the reaction product. For aziridines **7c** and **7d** no signals belonging to minor diastereoisomers were present in the ^{1}H NMR examinations of the crude mixtures. However, *N*-invertomers are present for both aziridines **7d** (mp 122–124 °C) and **7c** in ratios of 10:1 and 2:1, respectively. To confirm the diastereoselectivity for all aziridines (**7a**–**e**), LCMS analyses were carried out on crude mixtures but none of the minor diastereoismers belonging to these aziridines (**7a**–**e**) was detected.

The high diastereoselectivity using QNHOAc **2** in the aziridination of esters **8a**–**e** can be ascribed to the π-stacking effect[16] between the phenyl group and/or the double bond of the alkene in the unsaturated ester. This blocks one face of the alkene directing the exocyclic nitrogen in QNHOAc **2** to attack the other face of the alkene as in Figure 1.

Although other methods for high reagent-controlled diastereoselective aziridination of α,β-unsaturated esters or amides are known,[14] none shows the generality of the present method. It is noteworthy that crotonate and methacrylate esters give poor diastereoselectivity in reagent-controlled aziridination using QNHOAc **4**.[5]

In conclusion, we have presented herein the highly substrate-controlled diastereoselective aziridination of 8-phenylmenthol derived olefinic alkenes using 3-acetoxyamino-2-ethylquinazolinone **2** (QNHOAc). Yields obtained in these reactions were greatly improved in the presence of hexamethyldisilazane.

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References and notes

1. Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.
2. Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875.
3. Henbest, H. B.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958.
4. Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385.
5. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2783.
6. Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Chem. Commun.* **1996**, 1935.
7. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.
8. Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand.* **1996**, *50*, 361.
9. Ort, O. *Org. Synth. 8*, 522; Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908; Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610.
10. Atkinson, R. S.; Coogan, M. P.; Cornell, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 1215.
11. Atkinson, R. S.; Coogan, M. P.; Cornell, C. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 157.
12. Atkinson, R. S. In *Nitrenes and Azides, Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York, 1984; pp 247–295.
13. Atkinson, R. S.; Barker, E.; Ulukanli, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 583.
14. Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676.
15. Atkinson, R. S.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 205.
16. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.