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# Heteroatom transfer to alkenes by *N*-protected-oxaziridines: new reaction pathways and products

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**Abstract**—*N*-Alkoxycarbonyl- and *N*-carboxamido-oxaziridines are shown to react with aromatic alkenes to give epoxide, aziridine or hydro-oxidation products, in ratios depending on the oxaziridine structure. Chiral oxaziridines can effect epoxidation and hydro-oxidation with promising levels of asymmetric induction.


The high levels of asymmetric induction that have been observed in the reaction of chiral dioxiranes[1] and oxaziridinium salts[2] with alkenes suggest that the closely related oxaziridines may also have considerable potential for asymmetric heteroatom transfer. The extra stereocentre at nitrogen may allow good levels of epoxidation stereocontrol with a wider range of alkenes than is the case with dioxiranes. Additionally, there is the intriguing possibility of effecting alkene aziridination, which we have recently shown computationally to be a feasible process.[3] However, while Davis has shown that certain *N*-sulfonyloxaziridines can epoxidize alkenes with good levels of enantioselectivity,[4] there are very few other reports of effective heteroatom transfer from oxaziridines to alkenes. To date, the only report of alkene aziridination by oxaziridines has been by Schmitz,[5] who described reaction of NH-oxaziridine **1** with aromatic alkenes. Transfer of protected nitrogen would be especially interesting, but in their pioneering studies of the chemistry of *N*-alkoxycarbonyloxaziridines, Collet and co-workers indicated that **2** failed to react with cyclohexene.[6] In this letter, we report preliminary investigations on the reaction of a range of *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines with alkenes, demonstrating the first examples of productive heteroatom transfer to alkenes with this reagent class, identification of a new reaction product, and a promising initial attempt at asymmetric induction.


**1** $R^1$=H, $R^2$, $R^3$=-$(CH_2)_5$-
**2** $R^1$=Moc, $R^2$=Ph, $R^3$=H

Preliminary experiments indicated that thermal reaction of aromatic alkenes with *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines under solvent-free conditions led to productive reactions (Table 1). Due to the volatility of the simple alkenes employed, they were generally used in an excess (3 equiv), with isolated yields based on the more valuable oxaziridine as the limiting reagent. In an initial study using styrene and the *N*-carboxamido-oxaziridine **4a**, we obtained two major products (entry 1). Along with the expected epoxide **6** we obtained a significant and interesting new product, assigned spectroscopically (with support from a subsequent crystallographic structure determination—vide infra) as the imidate **5**. We were then able to probe the effect of the oxaziridine structure on the product ratio.[8] Staying with aldehyde-derived oxaziridines, but changing to the *N*-Boc series with **4b**, the proportion of the aziridine product **7** was increased (entry 2), again accompanied by epoxide **6** and imidate **5**. Our mechanistic rationale (vide infra) required the presence of the oxaziridine ring

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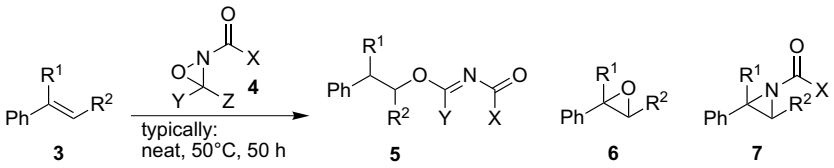
**Table 1.** Reaction of aromatic alkenes with oxaziridines[7]




| Entry | 3 | $R^1$ | $R^2$ | 4 | X | Y | Z | 5:6:7[d] | % 5[e] | % 6[e] | % 7[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | H | H | **4a** | $NEt_2$ | *p*-$ClC_6H_4$ | H | 46:46:8 | 40 | 21 | nd[f] |
| 2 | | | | **4b** | O$^t$Bu | *p*-$CNC_6H_4$ | H | 24:41:35 | 25 | 32 | 23 |
| 3[a] | | | | **4c** | O$^t$Bu | $CO_2Et$ | $CO_2Et$ | 0:32:68 | — | 17 | 24 |
| 4[b] | | | | **4d** | O$^t$Bu | Ph | $CO_2Me$ | 0:13:87 | — | nd[f] | 52 |
| 5[c] | **3b** | Ph | H | **4a** | $NEt_2$ | *p*-$ClC_6H_4$ | H | 50:50:0 | 39 | 50 | — |
| 6 | | | | **4b** | O$^t$Bu | *p*-$CNC_6H_4$ | H | 47:53:0 | 49 | 50 | — |
| 7[a] | | | | **4c** | O$^t$Bu | $CO_2Et$ | $CO_2Et$ | 0:100:0 | — | 82 | — |
| 8 | **3c** | H | $CH_3$ | **4a** | O$^t$Bu | *p*-$CNC_6H_4$ | H | 36:64:0 | 27 | 34 | — |
| 9 | | | | **4b** | O$^t$Bu | *p*-$CNC_6H_4$ | H | 23:73:4 | 23 | 57 | nd[f] |
| **10**[c] | | | | **4c** | O$^t$Bu | $CO_2Et$ | $CO_2Et$ | 0:96:4 | — | 79 | nd[f] |

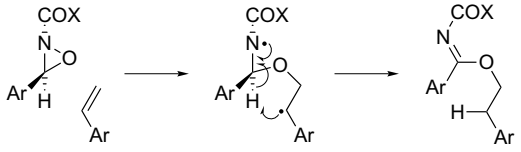
[a] Reaction at room temperature for 96 h.
[b] Reaction at room temperature for 3 weeks.
[c] 1 equiv alkene employed.
[d] Measured by integration of peaks in the $^1$H NMR spectrum of the crude product.
[e] Isolated yields.
[f] nd = not determined.

proton for formation of **5**, so we reasoned that use of 3,3-disubstituted oxaziridines should prevent this. Additionally, we reasoned that developing interactions between the *N*-Boc-substituent and the C3-substituent in the imine co-product should disfavour oxygen transfer. This strategy previously proved successful for controlling sulfide amination versus oxidation.[9] In accord with these ideas, the use of ketone-derived oxaziridine **4c** led to the aziridine for the first time being the major reaction product (entry 3), although the isolated yield was low. An alternative 3,3-disubstituted oxaziridine **4d** led to an acceptable yield of aziridine (entry 4), albeit after a long reaction time. In future studies, incorporation of further electron withdrawing substituents might be expected to provide increased reactivity.

We then probed the effect of alkene structure. In line with previous findings that steric hindrance in the nucleophile disfavours nitrogen transfer,[6,9] we did not observe any aziridine product with α-phenylstyrene **3b** (entries 5–7). With aldehyde-derived oxaziridines **4a** and **4b**, this alkene again gave a mixture of imidate **5** and epoxide **6** (entries 5 and 6). 3,3-Disubstituted oxaziridine **4c** now effected epoxidation exclusively, providing a good yield of **6** (entry 7). Similar results were obtained when a β-substituted aromatic alkene, *E*-β-methylstyrene **3c**, was used (entries 8–10). Preliminary attempts at using alkenes without an aromatic substituent in reactions with **4a** so far have led to complex product mixtures. Nevertheless, the reactions of these aromatic alkenes provided good yields of epoxide in some cases, as well as access to the novel product **5**, a process, which can be viewed as an alternative to hydroboration/oxidation. The first examples of aziridination by this class of oxaziridine have also been revealed.

Interesting mechanistic questions arise regarding all three of the observed reaction products. For the epoxidations and aziridinations, computational and experimental studies favour an asynchronous concerted process, at least for *N*-sulfonyl and *N*–H oxaziridines.[3,10] In order to determine whether the *N*-carbonyl oxaziridines studied here were also effecting concerted heteroatom transfer, the stereospecificity was probed by reaction of *cis*- and *trans*-stilbene with oxaziridine **4c**. *cis*-Stilbene (96% purity) reacted at room temperature over 114 h to afford a 20:2:1 mixture of *cis*-epoxide:*cis*-aziridine:*trans*-epoxide according to $^1$H NMR analysis. *trans*-Stilbene gave only ~10% conversion under the same conditions and only the *trans*-epoxide product could be detected. These results suggested that the epoxidation and aziridination reactions are *syn*-stereospecific and therefore likely to be concerted. For the formation of the imidates **5**, a possible mechanism involves homolytic cleavage of the oxaziridine N–O bond, subsequent addition of the oxygen-centred radical to the alkene to give a stabilised benzylic radical, and final hydrogen radical abstraction to generate the carbon–nitrogen double bond (Scheme 1). Control experiments established that **5** is not derived from opening of epoxide **6** under the reaction conditions.

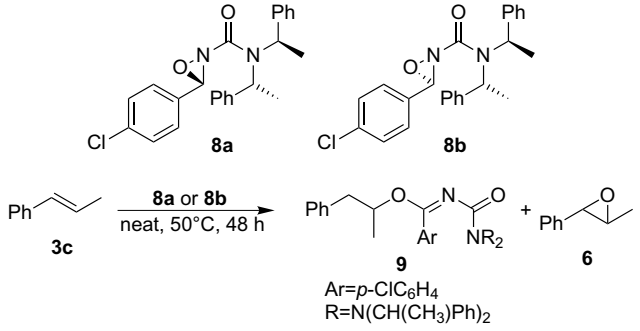
Finally, we decided to investigate the possibility of asymmetric induction in these reactions by employing enantiomerically pure, chiral oxaziridines. We employed the diastereomeric *N*-carboxamido-oxaziridines **8a** and **8b**, the synthesis and configurational assignment of




**Scheme 1.** Potential mechanisms of hydro-oxidation.

which we have previously reported,[11] and examined their reaction with *trans*-β-methylstyrene. The chemoselectivity was consistent with the trends observed for the achiral oxaziridines, with epoxidation predominating (Table 2). Promising diastereoselectivities were obtained: the benzimidate **9** was formed with 70% de and the epoxide **6** with 47 or 56% ee. The absolute configuration of **9** was assigned by X-ray crystallography of the major diastereomer ((*R*)-**9**) derived from reaction of oxaziridine **8a** (Fig. 1).[12] It is interesting to note that **8a** and **8b** gave opposite and approximately equal stereoselectivity in formation of **9** and **6**. This reinforces the observation made in the previous diastereoselective sulfimidation with these oxaziridines,[11] that the ring carbon stereocentre has greater influence than the *N*-substituent over the stereoselectivity. In addition, it is of note that for a given oxaziridine, the epoxide and imidate products have opposite configurations of the newly formed stereocentre. Possible models[10b] that can rationalise the observed stereoselectivity are shown in Figure 2 for oxaziridine **8a**. Both planar and spiro transition state models are shown, that minimise steric interactions or maximise π–π interactions.

**Table 2.** Asymmetric reaction of enantiopure oxaziridines with *trans*-β-methylstyrene




| Entry | Oxaziridine | **9**:**6**[a] | % **9**[b] | **9** dr[a] | % **6**[b] | % ee **6**[c] |
|---|---|---|---|---|---|---|
| 1 | **8a** | 30:70 | 30 | 85:15 (*R*) | 25 | 47 (*S*,*S*) |
| 2 | **8b** | 33:67 | 30 | 85:15 (*S*) | 34 | 56 (*R*,*R*) |

[a] Measured by integration of the $^1$H NMR spectrum of the crude product.
[b] Isolated yields.
[c] Determined by $^1$H NMR in the presence of Eu(hfc)$_3$.

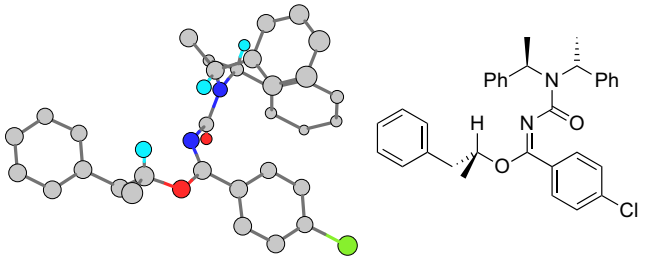



**Figure 1.** X-ray crystal structure of benzimidate (*R*)-**9**.

In conclusion, we have demonstrated for the first time that *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines can react productively with alkenes. We have also assessed the effect of oxaziridine structural modifications on product ratios, and shown that promising levels of stereocontrol are possible. While the yields of the reaction products are currently moderate-to-low, the studies suggest synthetic targets for new oxaziridine reagents offering higher levels of chemo- and stereoselectivity, as well as improving our understanding of the factors affecting these.

## Acknowledgements

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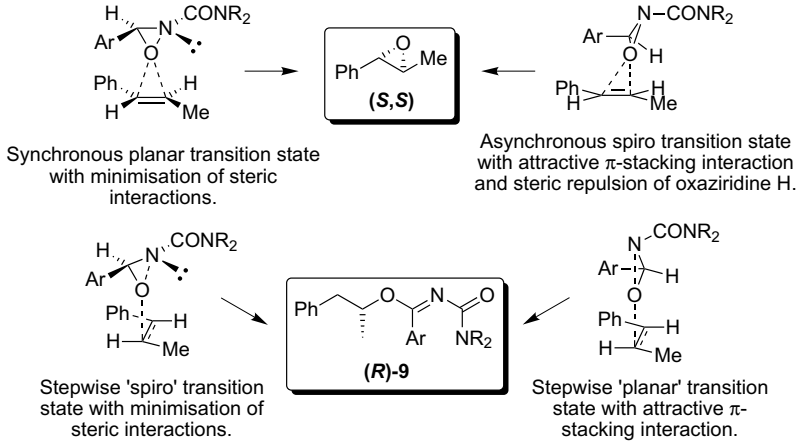


**Figure 2.** Possible models of stereoselectivity for oxaziridine **8a**.

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7. Typical procedure: Reaction between styrene and oxaziridine **4a**. A mixture of the oxaziridine **4a** (100 mg, 0.39 mmol) and styrene (140 μL, 1.22 mmol) was stirred at 50 °C under nitrogen for 50 h to afford a 46:8:46 crude ratio of **5**:**6**:**7**. Purification by flash chromatography (5–30% EtOAc in petrol) afforded epoxide **6** (10 mg, 21%) and imidate **5** (56 mg, 40%), isolated as a yellow oil, $\nu_{max}$/cm$^{-1}$ 3029, 2974, 2934, 1664, 1644, 1472, 1425, 1267, 1109, 1015, 836, 700; $\delta_H$ (250 MHz, $CDCl_3$) 7.59 (2H, d, *J* 8.5, Ar–H), 7.35–7.25 (7H, m, Ar–H), 4.48 (2H, t, *J* 7.1, $OCH_2$), 3.39 (2H, q, *J* 7.0, $NCH_2CH_3$), 3.19 (2H, q, *J* 7.0, $NCH_2CH_3$), 3.09 (2H, t, *J* 7.1, $PhCH_2$), 1.13 (3H, t, *J* 7.0, $NCH_2CH_3$), 1.03 (3H, t, *J* 7.0, $NCH_2CH_3$); $\delta_C$ (75.4 MHz, $CDCl_3$) 160.7 (C), 158.5 (C), 137.9 (C), 137.4 (C), 131.0 (C), 129.6 (CH), 128.9 (CH), 128.5 (CH), 128.5 (CH), 126.5 (CH), 67.5 ($CH_2$), 42.4 ($CH_2$), 40.5 ($CH_2$), 35.0 ($CH_2$), 13.8 ($CH_3$), 13.0 ($CH_3$); *m*/*z* (CI, $NH_3$) 359 ($[M+H]^+$, 100%); Found: $[M+H]^+$, 359.1531. $C_{20}H_{24}N_2O_2Cl$ requires: [M+H] 359.1526.
8. Oxaziridines **4a** (Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247–2251), **4b** (Ref. 6) and **4c** (Ref. 9) were prepared as described previously. Oxaziridine **4d** was prepared from *N*-Boc-phenylalanine by bromination/elimination (NBS, $CCl_4$, *hν*; 63%) followed by imine oxidation (*m*CPBA, $K_2CO_3$, $CH_2Cl_2/H_2O$; 91%).
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12. We are grateful to Dr. A. J. P. White, Dept. of Chemistry, Imperial College London, for this structure determination. Crystallographic data for **9** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258891.