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Highly Stereoselective Intramolecular Epoxidation in Unsaturated Oxaziridines

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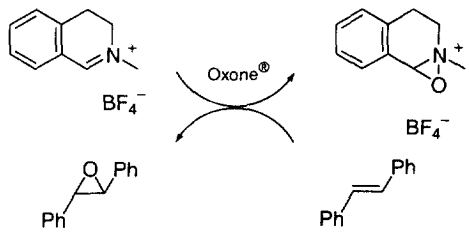
Abstract: Highly stereoselective intramolecular epoxidation is observed in unsaturated oxaziridines *via* oxaziridinium salts. The observed selectivities are consistent with a *spiro* transition state for the intramolecular epoxidation.

The efficient asymmetric epoxidation of alkenes remains a significant challenge in organic synthesis. Notable recent progress has been achieved with chiral dioxiranes derived from ketones.[1-4] We were attracted[5] to the related area of oxaziridinium epoxidation pioneered by Hanquet and Lusinchi (Scheme 1).[6] Since these early studies, chiral iminium salts have been used as catalysts in asymmetric epoxidation, yielding epoxides in moderate to good enantioselectivity.[6c,6e,7] Further progress in this area, particularly from the viewpoint of rational design of chiral catalysts, would undoubtedly be aided by knowledge of the transition state stereoelectronics. Two extreme geometries can be envisaged (Figure 1): the *planar* mode, where the three atoms of the oxaziridine ring and the two carbons of the olefin lie in the same plane; and the *spiro* mode, where the plane defined by the oxaziridine ring is perpendicular to the plane defined by the developing epoxide ring. For epoxidation by chiral dioxiranes, the observed sense of enantioselectivity provides good evidence that a *spiro* mode is preferred, in accord with calculations.[1,2,8] However, there is currently no literature evidence on the transition state geometry involved in epoxidation by oxaziridinium salts.



Scheme 1

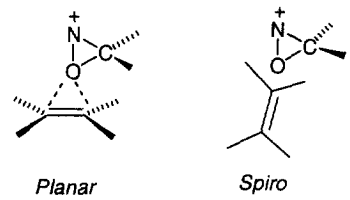


Figure 1

We have been interested in intramolecular epoxidation as a means of controlling regio- and stereochemistry, and recently reported that treatment of unsaturated oxaziridines with MeOTf results in intramolecular epoxidation, presumably *via* oxaziridinium salts.[9] We wished to investigate the effect of oxaziridine ring stereochemistry on this process and here report the first examples of highly stereoselective intramolecular epoxidation in such systems.

We reasoned that oxidation of an imine derived from an enantiomerically pure chiral primary amine and an unsaturated aldehyde could yield separable diastereomeric oxaziridines, allowing the oxygen transfer process to be studied in each. The first substrate to be studied was imine **1a** prepared from (*S*)-α-methylbenzylamine and the corresponding unsaturated aldehyde[10] (Scheme 2). Oxidation with buffered Oxone®

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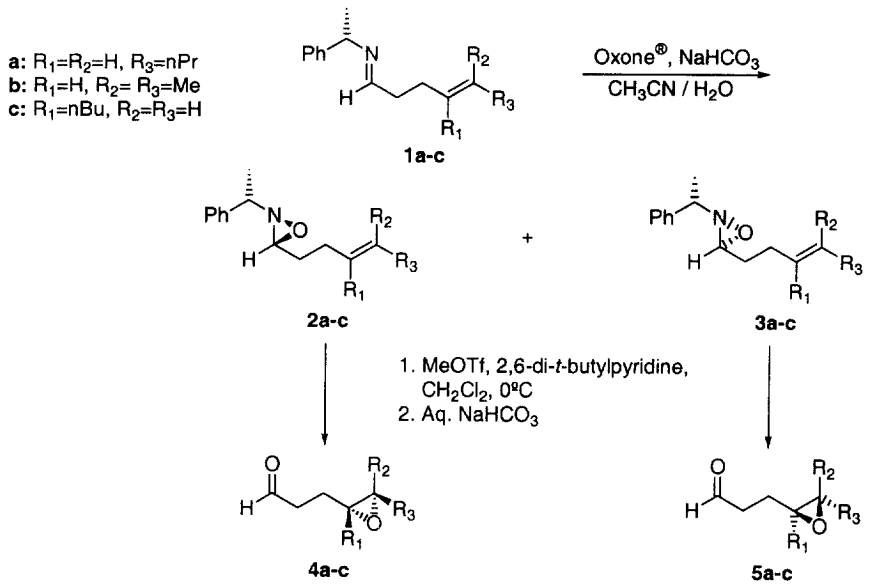
gave two products (**2a** and **3a**) in a ratio of 4:1 in good combined crude yield. The diastereomeric oxaziridines could be separated and purified (>20:1 by ^{1}H NMR), albeit in low yield due to the need for repeated column chromatography on silica.[11] The major diastereomer, **2a**, was assigned stereochemistry 2*R*,3*R* (oxaziridine numbering) following established precedent.[12] When a solution of **2a** in CH_2Cl_2 was treated with MeOTf in the presence of 2,6-di-*t*-butylpyridine, followed by hydrolysis with aqueous $NaHCO_3$, epoxyaldehyde **4a** was isolated in moderate yield (Table 1, entry 1). The minor diastereomer **3a** also underwent the sequence of intramolecular epoxidation and hydrolysis affording **5a**. We were pleased to discover that **4a** and **5a** were obtained in >90% ee as opposite enantiomers. This suggests that the configuration of the oxaziridine ring controls the stereochemistry of the intramolecular epoxidation, rather than the α-methylbenzyl chiral centre.

The intramolecular epoxidation procedure was further applied to the synthesis of trisubstituted epoxides **4b** and **5b** derived from unsaturated oxaziridines **2b** and **3b** respectively. Efficient transfer of chirality was again observed, with epoxide enantiomeric excess corresponding to the diastereomeric purity of the oxaziridine (Table 1, entry 2). Finally, the 1,1-disubstituted alkene substitution pattern was studied and we were delighted to discover (entry 3) that enantiomerically pure epoxide **4c** could be isolated following methylation and hydrolysis of **2c**.



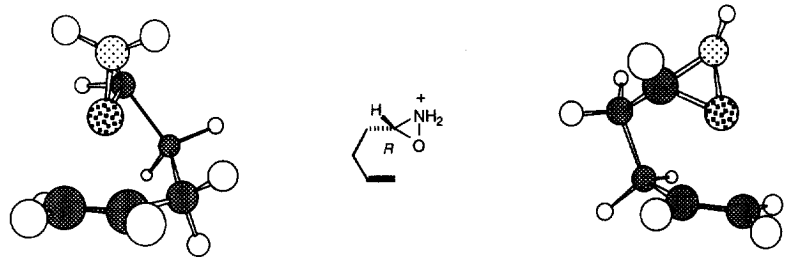
Scheme 2

Table 1 Stereoselective Epoxidation *via* Unsaturated Oxaziridines

Entry	Substrate	**2:3**[a]	**2** de (%)[b]	**4** ee (%)[c]	**4** Yield (%)	**3** de (%)[b]	**5** ee (%)[c]	**5** Yield (%)
1	**a**	4:1	>90	93	35	>90	92	47
2	**b**	3:1	~83	81	60	>90	94	40
3	**c**	3:1	>90	>98	55	[d]	84	70

[a]Estimated by ^{1}H NMR integration of the crude reaction mixtures. [b]Determined by ^{1}H NMR spectroscopic analysis of the purified oxaziridine. [c]The epoxyaldehydes were reduced ($NaBH_4$) to the epoxyalcohols and converted to the corresponding benzyl ethers, the enantiomeric purities of which were determined by chiral HPLC (Chiracel OD). The absolute configurations of the epoxides were determined by comparison to authentic samples prepared by different routes. [d]~11:1 ratio of **3c**:*cis* oxaziridine.

The high stereoselectivity in these intramolecular epoxidations, apparently determined by the oxaziridine ring stereochemistry, provides information on the likely transition state geometry. From inspection of molecular models, it is clear that a given oxaziridine diastereomer can effect intramolecular epoxidation of one face of the double bond only through a *planar* transition state, whereas the epoxide of opposite configuration can result only from a *spiro* transition state (Figure 2). Thus the intramolecular reaction of the major diastereomer **2a**, having oxaziridine stereochemistry (2*R*,3*R*), must proceed via a *spiro* transition state to yield the observed (*R*,*R*)-epoxide **4a**. All of the results in Table 1 are consistent with this *spiro* mode.



Spiro mode: *4R*-epoxide predicted

Planar mode: *4S*-epoxide predicted

Figure 2: Possible Transition Structures for Intramolecular Epoxidation

In conclusion, we have demonstrated that highly stereoselective intramolecular epoxidation in diastereomerically enriched unsaturated oxaziridines is possible on treatment with MeOTf. Epoxyaldehydes **4a-c** and **5a-c** were generated in high enantiomeric purity and the observed stereochemistry is consistent with a *spiro* transition state. For this stereoselective intramolecular epoxidation process to be of real practical value, we need to find an alternative primary amine which leads to higher diastereoselectivity in the Oxone® oxidation of the derived imine, thus providing higher yields of diastereomerically pure oxaziridine. Nevertheless, we have clearly demonstrated the feasibility of the process and have gained useful information on the transition state geometry for oxaziridinium epoxidation which may be of use in the rational design of chiral iminium salts as catalysts for asymmetric epoxidation.

Acknowledgements. We thank the EPSRC for their support of this work. This work was facilitated by access to the EPSRC Chemical Database Service.[14]

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10. For the source of the unsaturated aldehydes used in this work, and the procedure for imine formation and oxidation, see reference 9.
11. Isolated yields of oxaziridines (%): **2a** 21; **3a** 15; **2b** 22; **3b** 14; **2c** 54; **3c** 15.
12. The stereochemical outcome of the oxidation of imines derived from α-methylbenzylamine by *m*CPBA has been established in the literature (ref. 13) by ^{1}H NMR work and by correlation of X-ray structures. We carried out Oxone® oxidation of the imine derived from α-methylbenzylamine and isobutyraldehyde, and obtained the same major isomer as is reported to be obtained (ref. 13g) with *m*CPBA. We therefore assume that the same sense of selectivity is obtained in the oxidation of imines **1** with Oxone® as in the literature work with *m*CPBA. Typically, the ring H-3 and the benzylic proton α-to N are at higher field in the major isomer than in the minor one.
    Data for **2a**: Colourless oil, R_f 0.48 (50% CH_2Cl_2-petrol); $[\alpha]_D^{20}$ -40.0 (*c* 0.72, $CHCl_3$); ν_{max} (film) 2958, 1494, 1452, 1373, 970, 761 and 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.31 (5H, m, Ph), 5.23-5.13 (2H, m, *H*C=C*H*), 3.82 (1H, dd, *J* 5.5, 4.5 Hz, *H*CN(O)), 3.03 (1H, q, *J* 6.5 Hz, PhC*H*(CH_3)N), 1.97-1.83 (4H, m, 2xCH_2CH=), 1.69-1.64 (1H, m, one of CH_2CHN(O)), 1.59 (3H, d, *J* 6.5 Hz, PhCH(CH_3)N), 1.56-1.50 (1H, m, one of CH_2CHN(O)), 1.29 (2H, q, *J* 7.5 Hz, CH_2CH_3), 0.84 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (68 MHz, $CDCl_3$) 140.5 (s), 131.8 (d), 129.2 (d), 128.7 (d), 128.5 (d), 127.8 (d), 81.9 (d), 71.4 (d), 35.0 (t), 32.7 (t), 27.6 (t), 23.0 (t), 22.0 (q), 14.1 (q); *m/z* (CI+) 245 (M+), 230, 140, 120, 105, 77; observed: 245.1775. $C_{16}H_{23}NO$ (M+) requires 245.1780.
    Data for **3a**: Colourless oil, R_f 0.57 (50% CH_2Cl_2-petrol); $[\alpha]_D^{20}$ -85.0 (*c* 0.72, $CHCl_3$); ν_{max} (film) 2927, 1685, 1495, 1448, 1360, 969, 758 and 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42-7.27 (5H, m, Ph), 5.54-5.41 (2H, m, *H*C=C*H*), 3.88 (1H, dd, *J* 5.5, 4.5 Hz, *H*CN(O)), 3.14 (1H, q, *J* 7.0 Hz, PhC*H*(CH_3)N), 2.25-2.20 (2H, m, one of CH_2CH=), 2.01-1.96 (2H, m, one of CH_2CH=), 1.87-1.80 (1H, m, one of CH_2CHN(O)), 1.79-1.69 (1H, m, one of CH_2CHN(O)), 1.44 (3H, d, *J* 7.0 Hz, PhCH(CH_3)N), 1.38 (2H, q, *J* 7.5 Hz, CH_2CH_3), 0.89 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (68 MHz, $CDCl_3$) 142.0 (s), 131.6 (d), 128.5 (d), 128.4 (d), 127.5 (d), 126.8 (d), 81.8 (d), 69.7 (d), 34.6 (t), 32.3 (t), 27.4 (t), 22.6 (t), 19.5. (q), 13.6 (q); *m/z* (FAB+) 246 (M+H), 176, 136, 120, 105, 77; observed: 246.1859. $C_{16}H_{24}NO$ (M+H) requires 246.1858.
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