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Asymmetric Sulfoxidation using [(3,3-Dimethoxycamphoryl)sulfonyl]oxaziridine

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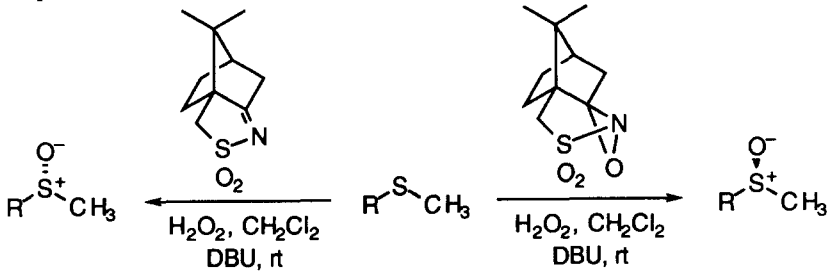
Abstract: [(3,3-Dimethoxycamphoryl)sulfonyl]oxaziridine oxidizes sulfides to sulfoxides cleanly and efficiently in up to 98% ee.

Enantiomerically pure sulfoxides have become increasingly important as chiral auxiliaries and synthons for enantioselective carbon-carbon bond formation.[1] To date there are relatively few general methods for the preparation of enantiomerically enriched sulfoxides. The most successful methods of asymmetric sulfoxidation include the modified Sharpless procedures reported independently by Kagan[2] and Modena,[3] and the enantiomerically pure oxaziridines of Davis.[4,5] In addition, we have recently shown that camphorsulfonylimines, the precursors of the Davis reagents, can be used in conjunction with hydrogen peroxide to produce chiral oxidants that oxidize dialkyl sulfides *in situ* with excellent enantioselectivity (up to ≥98% ee).[6,7] We have formulated the reactive intermediate in our system as an α-hydroperoxyamine; it should be noted that the sense of absolute stereochemistry of the sulfoxides obtained under our conditions is often different from that found when using oxaziridines derived from the same enantiomer of camphorsulfonylimine (Scheme 1). However, the nature of the chiral oxidizing species involved in our process has not been proven and we are currently undertaking a mechanistic investigation of the process.[8] In the course of this investigation we have examined both [(3,3-dimethoxycamphoryl)sulfonyl]imine **1** and the derived oxaziridine **2**, [9] which to our knowledge has not been reported as a useful reagent for asymmetric sulfoxidation. A comparison of the two systems is presented here.

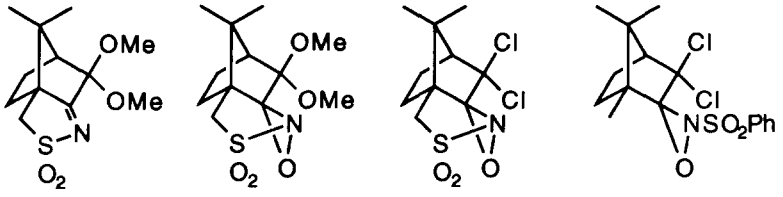


R = t-Bu, Bn, p-tolyl

Scheme 1

Results and Discussion

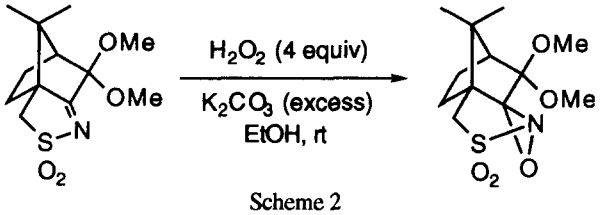
Oxaziridines are versatile reagents that can be used to carry out enolate hydroxylation, epoxidation and sulfoxidation. A major advantage of these stoicheiometric reagents is that they can oxidize substrates under neutral, aprotic conditions. [(3,3-Dimethoxycamphoryl)sulfonyl] oxaziridine **2** has previously been reported as a useful reagent for asymmetric enolate hydroxylation, although enantioselectivities were highly substrate dependent.[8,9] In some cases selectivities were better than those observed using the [(3,3-dichlorocamphoryl)sulfonyl] oxaziridine derivative **3**, but in other cases selectivities were poorer.



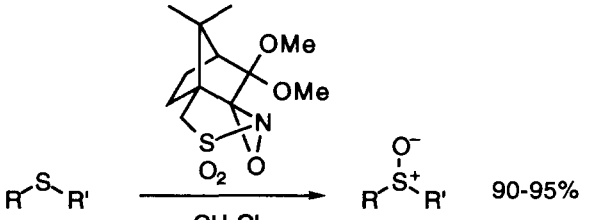
1 **2** **3** **4**

The dichloro derivative has also been shown to be useful for asymmetric sulfoxidation.[4] The most selective oxaziridine reagent for sulfoxidation previously studied is however *N*- (phenylsulfonyl)-3,3-dichlorocamphoryloxaziridine **4**,[5] which can be used to prepare aryl alkyl sulfoxides in greater than 95% enantiomeric excess. The enantioselectivities for oxidation of dialkyl sulfides, or sulfides in which an aryl group is not directly bonded to the sulfur atom, are however much more variable. For example, benzyl methyl sulfoxide is only obtained in 13% ee, although *t*-butyl methyl sulfide is oxidized with excellent selectivity (94% ee) when the oxidation is carried out in carbon tetrachloride. Oxidations in more polar solvents such as dichloromethane are less impressive. The modified Sharpless procedures are also generally most effective for aryl sulfide substrates.

The discovery of a general and selective method for the oxidation of dialkyl sulfides continues to be an important challenge. We have shown that [(3,3-dimethoxycamphoryl) sulfonyl]imine **1**, under our reaction conditions, can mediate sulfoxidation by hydrogen peroxide with excellent enantioselectivity.[7] Surprisingly, 3,3-dichlorocamphorylsulfonylimine is a poor mediator under these conditons, whereas the corresponding oxaziridine **3** fares much better. We therefore also examined [(3,3-dimethoxycamphoryl)sulfonyl]oxaziridine **2**, best prepared in our hands by reaction of the imine with hydrogen peroxide in the presence of base (Scheme 2), as a stoicheiometric oxidant, and were pleased to find that use of this oxaziridine gave sulfoxides from non-aryl sulfides with good to excellent enantioselectivity, even in dichloromethane solution (Scheme 3). A comparison of these results with those obtained using the imine/hydrogen peroxide system is given in the table.[10]

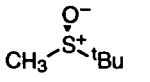
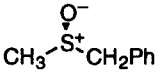
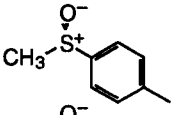
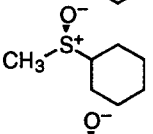
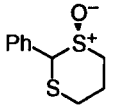
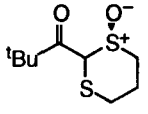
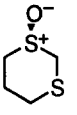


Scheme 2



Scheme 3

Table. Enantioselective Oxidation of Sulfides

	oxidation system; ee (yield)	
	imine/H_2O_2	oxaziridine
	86 S (100)	85 S (100)
	63 S (100)	49 S (100)
	60 S (96)	61 S (100)
	66 (+) (100)	53 (+) (100)
	≥98 S (100) (anti)	98 S (100) (anti)
	78 R (46) (anti)	83 R (68) (anti) 85 R (28) (syn) 2.4:1 anti:syn
	32 R (77)	36 R (96)

It should be noted that the absolute sense of stereochemical induction is the same in each system for every example. Taken together with the similarity in ees obtained in every case, this evidence suggests that the same reactive intermediate, presumably oxaziridine, is involved in both systems. This is particularly interesting because it is in direct contrast with our results obtained with the simpler cyclic sulfonylimine, where the reactive intermediate in the hydrogen peroxide driven oxidation of several sulfides cannot be oxaziridine because of the observed reversal in the absolute sense of asymmetric induction (Scheme 1).[6,7]

Conclusion

[(3,3-Dimethoxycamphoryl)sulfonyl]oxaziridine is shown to be a useful reagent for asymmetric sulfoxidation of dialkyl sulfides. Enantioselectivities are in some cases higher than those obtained using *N*-(phenylsulfonyl)-3,3-dichlorocamphoryloxaziridine. Unlike the *N*-(phenylsulfonyl) derivative, [(3,3-dimethoxycamphoryl)sulfonyl]oxaziridine can be prepared in enantiomerically pure form from inexpensive, commercially available material without the need for any column chromatography.

Acknowledgments

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10. Enantiomeric excesses were measured using ^{1}H NMR spectroscopy at 400 MHz in the presence of 5-10 molar equivalents of (+)- or (–)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Absolute configurations where given were determined by comparison of the sign of the specific rotation with that of authentic material and/or with literature values.

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