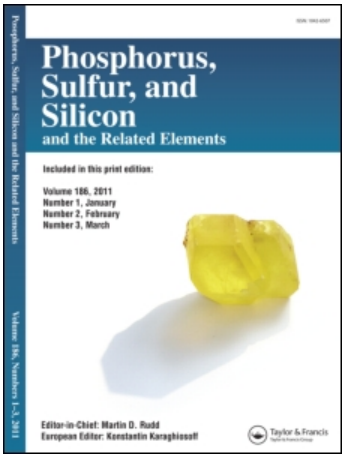

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Asymmetric Sulfur Oxidation Mediated by Camphorsulfonylimines

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Catalytic enantioselective oxidation of a range of sulfides is achieved in very high yields by treatment with hydrogen peroxide in conjunction with enantiomerically pure sulfonylimines under basic conditions. Enantioselectivities of up to ca. 98% or better were obtained using acetals of oxocamphorsulfonylimine as mediators. This process is clean, inexpensive and simple, requires minimum work up and no close monitoring. The reactive intermediate is currently formulated as an α-hydroperoxyamine.

Keywords: Organosulfur; sulfide; sulfoxide; asymmetric oxidation

INTRODUCTION

Enantiomerically pure or non-racemic chiral sulfoxides are widely used synthons and are among the most important intermediates for asymmetric carbon-carbon bond formation.[1] As a result, the search for new methods for their preparation has intensified over recent years. Indeed, the discovery of methods for the introduction of asymmetry into organic molecules remains in general a topic of great importance and excitement to synthetic chemists. Auxiliary-based approaches relying on diastereocontrol remain important, but suffer obvious disadvantages in comparison with methods which rely upon asymmetric reagents. Catalytic systems are particularly attractive, and the combination of a simple reaction system and an inexpensive reagent with a catalytic asymmetric process offers an especially desirable goal.

Non-racemic chiral sulfoxides can be obtained by the Andersen procedure and its derivatives,[2] in which resolved diastereoisomerically pure sulfinates are treated with organometallic reagents. This procedure has, however, largely been restricted to alkyl aryl sulfide substrates. A more general approach to sulfoxide preparation is by the direct oxidation of a prochiral sulfide with a chiral oxidant, which may be a pre-formed reagent or be generated *in situ*. Enantiomerically pure chiral peracids have been examined,[3] but asymmetric induction is poor, and this has been attributed to the distance of the reaction site from the controlling asymmetric centre, coupled with a lack of conformational rigidity. The most successful techniques currently available include the stoicheiometric use of enantiomerically pure oxaziridine reagents,[4,5] and chiral organometallic peroxide species such as those generated in systems derived from the Sharpless asymmetric epoxidation procedure.[6] Modification of the Sharpless procedure, first reported independently by Henri Kagan[7] and Giorgio Modena,[8] has led to some impressive enantioselectivities for the oxidation of certain sulfides, particularly aryl methyl sulfides. More recently, a catalytic titanium system using binaphthol ligands has been

reported,[9] further extending the use of organometallic species in catalytic asymmetric oxidation. Dialkyl and other non-aryl sulfides in particular have proved to be extremely testing and intractable substrates for asymmetric oxidation.

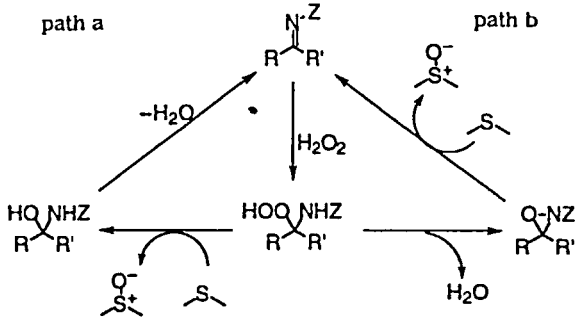
DISCUSSION

We have developed an extremely simple and remarkably clean procedure for asymmetric sulfoxidation by hydrogen peroxide which does not require the preparation and isolation of sensitive reagents or close monitoring, and which gives highest ees in the oxidation of non-aryl sulfides,[10] thus complementing other available procedures, which generally exhibit highest enantioselectivities for oxidation of aryl alkyl sulfides.

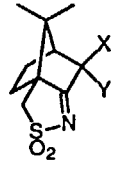
We have found that modification of the nitrile-mediated Payne epoxidation procedure [11] by use of imine derivatives in place of the nitrile allows the creation of a catalytic oxidation of sulfides. In this system, addition of hydrogen peroxide to the derivatized imine produces a highly reactive oxidative intermediate which is able to transfer oxygen to sulfide substrates with regeneration of the imine derivative under the reaction conditions, so producing a catalytic process (Scheme 1). Direct oxidation of the substrate by hydrogen peroxide is completely suppressed under the basic conditions used.

Use of the cyclic camphorsulfonylimine **1** as the mediator provides up to *ca* 50% ee in the sulfoxidation process for oxidation of a range of sulfides (Table 1). We reasoned that 3,3-dichlorocamphorsulfonylimine **2** and 3-oxocamphorsulfonylimine **3** were of high potential as mediators in our system, since oxaziridines based upon these imines have been reported to oxidize sulfides with greater enantioselectivity than does the oxaziridine derived from **1**.[4] However, under our reaction conditions, imines **2** and **3** proved to be relatively poor mediators: sulfoxides were obtained in poorer yields

and with lower enantioselectivities in every case than had been achieved using **1**.



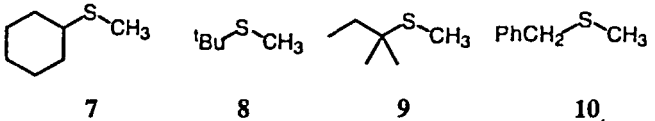
Scheme 1



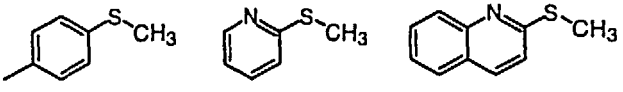
	X	Y
(–)-1	H	H
(+)-2	Cl	Cl
(–)-3	=O	
(+)-4	OCH_2CH_2O	
(+)-5	OMe	OMe
(+)-6	OEt	OEt

Acetalization of the reactive carbonyl group of **3** with simple alcohols or diols provides easy access to numerous derivatives, while avoiding the problem of *endo*/*exo* diastereoisomer formation potentially resulting from other approaches. For example, sulfonylimines **4**, **5** and **6** were prepared without chromatography in high yields from **3** (79%, 95% and 91% respectively) (Scheme 2), and were tested as mediators. While **2** and **3** proved poor mediators, remarkably high levels of enantioselectivity were achieved in some cases using **4** and **5** as mediators. It is interesting that the most enantioselective system tested, that using the dimethyl acetal **5**, is also the most reactive. In dramatic contrast to other chemical methods for

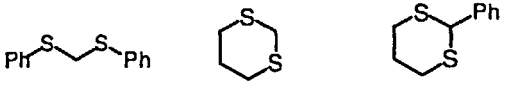
asymmetric sulfur oxidation, dialkyl and other non-aryl sulfide oxidation is particularly successful, with greater than 98% ee being observed for a simple dithiane derivative. Indeed, 4-tolyl methyl sulfide, usually the substrate of choice for asymmetric sulfur oxidation, provides one of the least impressive enantioselectivities (60%).



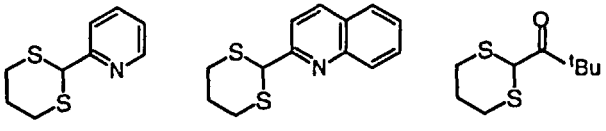
7 8 9 10



11 12 13



14 15 16

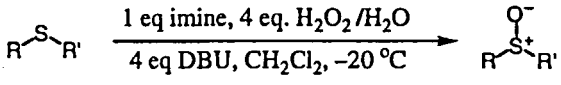


17 18 19

In this system, diastereoselective addition of hydrogen peroxide to the imine double bond would generate a single α-hydroperoxyamine diastereoisomer (Scheme 1, path a), presumably having the *endo* configuration as this is the direction of delivery of oxygen in oxaziridine formation.[3] Catalytic oxaziridine formation is in principle possible if dehydration occurs before oxygen transfer (Scheme 1, path b). Indeed, in the absence of a readily-oxidizable

substrate, we observe slow oxaziridine production from most of our imines in a remarkably clean reaction and very high yields. The reaction is easily carried out under phase-transfer conditions on a multigram scale (Scheme 3).[12]

Table 1 Asymmetric Oxidation of Sulfides



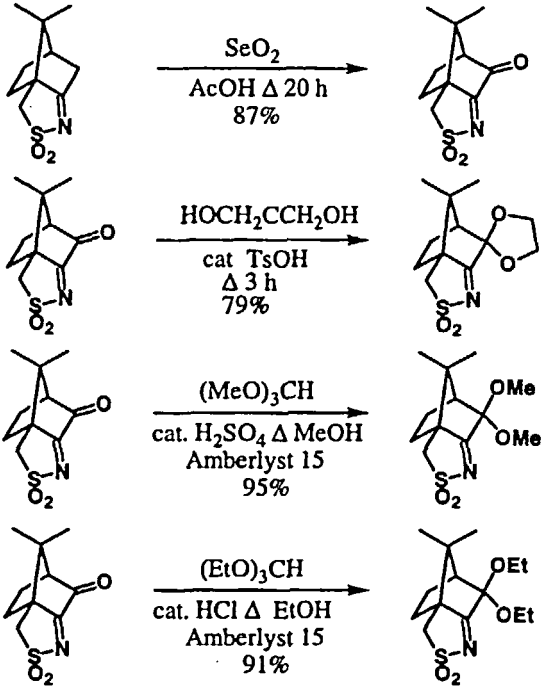
ee/%, Abs. Config., (yield/%)

Sulfide	Mediator				
	1	**2**	**3**	**4**	**5**
7	0 (100)	–	–	68 (+) (100)	66 (+) (100)
8	42 R (83)	–	–	82 S (100)	86 S (100)
9	26 (87)	–	–	–	–
10	35 R (100)	25 (100)	23 (34)	46 S (100)	63 S (100)
11	20 R (100)	–	–	37 R (100)	60 S (96)
12	–	–	–	–	38 R (75)
13	–	–	–	–	27 R (55)
14	–	–	–	–	48 S (65)
15	0 (100)	–	–	28 R (67)	32 R (77)
16*	44 S (100)	–	–	94 S (100)	≥98 S (100)
17	–	–	–	–	≥98 S (69)
18	–	–	–	–	86 S (74)
19*	49 R (66)	0 (8)	20 (23)	68 S (74)	78 S (46)

* *trans* product obtained

Using imine **1** in our sulfur oxidation system however we observe predominantly the *opposite* absolute sense of asymmetric induction in sulfoxide products from that obtained under similar conditions using as oxidant the oxaziridine prepared from the *same*

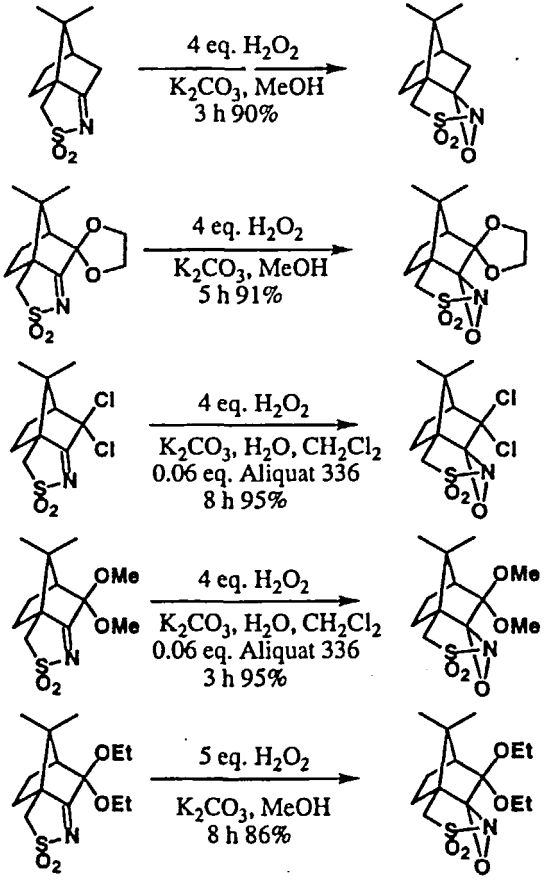
enantiomer of **1**. Oxaziridine is therefore unlikely to be the reactive oxidizing species in these cases. Further, the patterns of results obtained using imines **1** and **2** in our system are quite different from those seen using analogous pre-formed oxaziridines, and, in addition, the low enantioselectivities obtained using imines **2** and **3** would not be expected if oxaziridine were the reactive intermediate.



Scheme 2

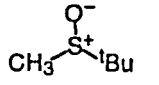
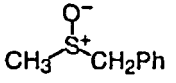
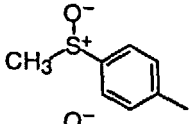
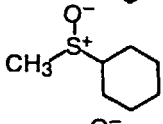
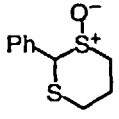
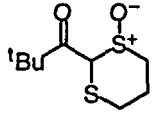
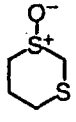
Switching from imine **1** to acetal imines **4** and **5** in our system however generally results in a change in the absolute sense of induced stereochemistry, the effect generally being greater for **5**, where the pattern of enantioselectivities parallels closely that obtained using pre-formed oxaziridine Table 2).[13] We interpret this as resulting from a

change in the mechanism favouring catalytic oxaziridine formation in these cases. Brief experimentation suggests that the oxaziridine derived from **6** provides even greater enantioselectivity than that derived from **5**, producing *S* methyl *p*-tolyl sulfoxide with 68% ee in 93% yield. Although 1,3-dithiane is itself oxidized by these systems to give the 1*R* oxide with only 36% ee at best, deacylation of the 1*S* 2-pivaloyl derivative takes place readily to provide 1*S* 1,3-dithiane 1-oxide with *ca.* 90% ee.



Scheme 3

Table 2 Comparison Between Oxidation Systems

	ee/%, abs. config. (yield/%)	
	imine/H_2O_2	oxaziridine
	86 S (100)	85 S (100)
	63 S (100)	49 S (100)
	50 S (96)	61 S (100)
	66 (+) (100)	53 (+) (100)
	≥98 S (100) (anti)	98 S (100) (anti)
	78 S (46) (anti)	83 S (68) (anti) 85 S (28) (syn) 2.4:1 anti:syn
	32 R (77)	36 R (96)

Although the identity of the oxidizing species is unproven, we currently formulate the reactive intermediates as α-hydroperoxyamines and oxaziridines, from each of which sulfonylimine is regenerated in a catalytic cycle by elimination of water and oxygen transfer to a substrate (Scheme 1).

Hydroperoxyamines are known to be oxidizing agents, but have enjoyed very limited examination in the literature. They can be generated *in situ* from hydrogen peroxide and Schiff's bases, and in a few cases they have been isolated.[14 15] Rebek investigated the use of chiral α-hydroperoxyamines to carry out epoxidation, but although moderate yields of epoxides were obtained, the asymmetric induction was poor (< 5% ee). Rebek suggested that a competing cyclization to oxaziridine may restrict the utility of chiral α-hydroperoxyamines;[14] earlier studies by Höfte and Reiche however suggest that conversion of α-hydroperoxyamine to oxaziridine requires heating in an inert solvent.[15] Neither suggestion appears to apply to our system. To our knowledge the process has not been previously been used as a method of oxaziridine synthesis. An oxaziridine-mediated catalytic oxidation using oxone was reported several years ago, but does not appear to have yet been developed into an asymmetric catalytic process.[3]

CONCLUSION

We have developed a new procedure for asymmetric sulfoxidation which is particularly effective for non-aryl sulfide substrates, complementing other known systems. The chiral mediators can be prepared in enantiomerically pure form and in high yields, without the need for chromatographic purification, in either (+) or (–) forms, from commercially available (+) or (–)-10-camphorsulfonyl chloride, and are easily recovered following use in an oxidation reaction. We would emphasise the extreme simplicity of the procedures described, the ease of preparation of a wide range of mediators without need for chromatography, and the absence of any sensitive materials. The procedure requires no close monitoring and provides remarkably clean reactions in inexpensive, simple, and rapid processes.

GENERAL EXPERIMENTAL PROCEDURE - SULFUR OXIDATION

Aqueous hydrogen peroxide (10 mmol) was added to a cooled, stirred dichloromethane or methanol solution of DBU (10 mmol) at –20 °C, followed by the camphorsulfonylimine derivative (2.5 mmol).[9] The sulfide substrate (2.5 mmol) was then added, and stirring continued until oxidation was complete (*ca* 24 hours). Work-up involved addition of aqueous sodium sulfite to destroy residual hydrogen peroxide, and simple extraction into dichloromethane (2 x 20 ml). The reactions are extremely clean, and product purification and near-quantitative recovery of imine is trivial in many cases: removal of the solvent provides the crude product which is purified by passage through a short column of silica gel (Merck 9385). Elution with dichloromethane is used to recover the imine, and elution with ethyl acetate provides clean sulfoxide.

ACKNOWLEDGMENT

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