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A New System for Catalytic Asymmetric Oxidation of Sulfides using a Hydrogen Peroxide Based Reagent

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Abstract: Catalytic asymmetric oxidation of sulfides is achieved in a remarkably simple process by treatment with hydrogen peroxide and an enantiomerically pure sulfonylimine under basic conditions.

Enantiomerically pure or optically enriched chiral sulfoxides are widely used synthons and are now among the most important intermediates for asymmetric carbon-carbon bond formation.[1] Chiral sulfoxides can be obtained by the Andersen procedure,[2] in which optically resolved diastereoisomeric 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. The most successful techniques currently available include use of the enantiomerically pure oxaziridine reagents of Davis,[3] and chiral organometallic peroxide species such as those involved in the Sharpless system.[4] Modification of the Sharpless epoxidation procedure, first reported independently by Kagan[5] and Modena[6] has led to impressive enantioselectivities for the oxidation of aryl methyl sulfides. More recently, a catalytic titanium system utilizing binaphthol has been reported,[7] further extending the use of organometallic species in asymmetric oxidation. Enantiomerically pure chiral peracids have also been examined,[8] but asymmetric induction is poor, and this has been attributed to the large distance of the reaction site from the chiral centre, coupled with lack of conformational rigidity. Dialkyl sulfides in particular have proved to be extremely testing substrates for asymmetric oxidation.

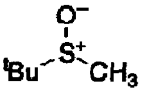
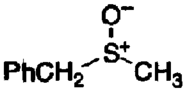
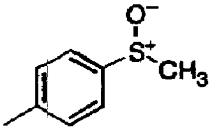
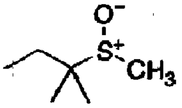
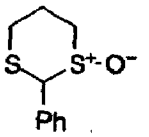
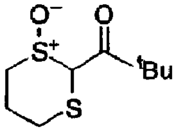
Results and Discussion

We now show that a novel imino analogue of the nitrile mediated Payne oxidation procedure[9,10] may be used to achieve catalytic oxidation of sulfides, including dialkyl sulfides, by hydrogen peroxide. In a remarkably clean and environmentally friendly process, addition of hydrogen peroxide to an imine derivative under the correct pH conditions produces a highly reactive oxidative intermediate which is able to transfer oxygen to sulfide substrates with regeneration of the imine under the reaction conditions giving overall a catalytic process.

We chose to examine imine derivatives of camphor as a convenient entry into an optically pure reagent system. Our knowledge of achiral imine systems led us to investigate a small range of electron depleted imine derivatives, including oximes and sulfonylimines.

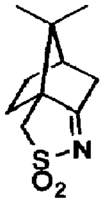
Of the imine derivatives examined, the cyclic camphorsulfonylimine (1) has proved particularly successful as a mediator.[3] Typical Payne oxidation conditions using methanol as solvent and potassium carbonate as base were used initially to investigate the temperature dependence of the stoicheiometric asymmetric sulfur oxidation. As expected, conversions were greater at higher temperature at the expense of enantioselectivity, due presumably to a combination of poorer conformational rigidity in the substrate coupled with reduced discrimination by the reactive species. Highest enantioselectivity was observed at –20 °C; at lower temperatures, reactions were slower without improving enantioselectivity. Sulfoxide yields and/or ees obtained from reactions carried out in methanol, petroleum ether, chloroform, and carbon tetrachloride were subsequently shown to be inferior to those obtained using dichloromethane as solvent, and the organic base DBU proved to be experimentally more convenient than potassium carbonate.[11] Excess base is essential to prevent direct (racemic) oxidation by hydrogen peroxide. We have shown that oxidation proceeds, albeit more slowly, with several turnovers of the mediator when present in catalytic quantities.

TABLE: Asymmetric Oxidation of Sulfides

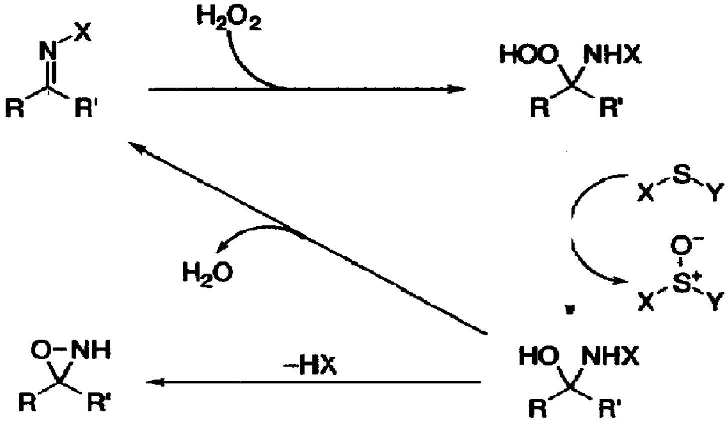
Sulphoxide	Yield/%	ee/%	Configuration at sulfur
	83	42	R
	100	35	R
	100	20	R
	87	26	
	100	44 (anti)	S
	66	49 (anti)	S

A range of sulfides was then oxidized under the standard conditions described below at –20 °C. Oxidation was achieved with moderate to good enantioselectivity (Table). Absolute configurations were determined where possible by literature precedent using the observed sign of the optical rotation. It is particularly noteworthy that dialkyl sulfides provide some of the best results.

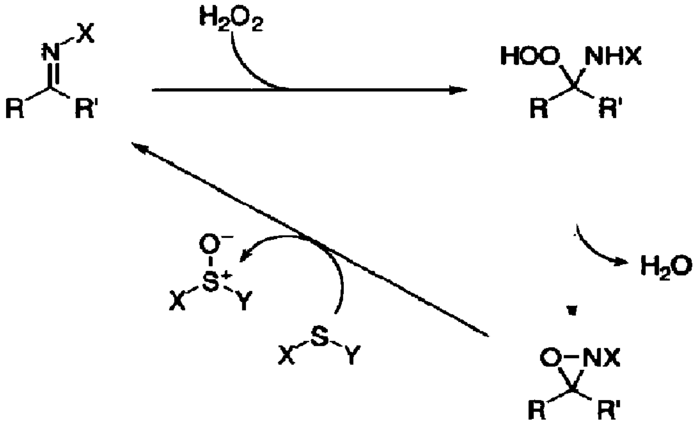
Oxidation reactions were carried out by addition of a solution of hydrogen peroxide (*ca.* 10 mmol) in ether or water to a cooled, stirred dichloromethane solution of DBU (10 mmol) at –20 °C, followed by (–)-camphorsulfonylimine (2.5 mmol).[12] The sulfide substrate (2.5 mmol) was then added and stirring continued until oxidation was complete, up to *ca.* 48 hours. Aqueous sodium sulfite solution was added, and the sulfoxide products and imine mediator were isolated by chromatography after simple work-up.



(1)



Scheme 1



Scheme 2

Currently we formulate the reactive intermediate as a hydroperoxyamine, from which, after oxygen transfer, sulphonylimine is regenerated by elimination of water (Scheme 1). Hydroperoxyamines can indeed be generated *in situ* from hydrogen peroxide and Schiff's bases;[13] unlike peroxyimidic acids, proposed as intermediates in the Payne oxidation, they were in some cases isolated, but were not considered to be useful reagents due to a reported competing cyclization giving oxaziridines.[13] This observation antedates the oxaziridine reagents of Davis,[3] and to our knowledge the reaction has not been examined as a method of oxaziridine formation. While, in our own system, oxaziridine formation with loss of group X could compete with dehydration, any oxaziridine formed would also be expected to oxidize the substrate as desired; delivery of oxygen to the substrate would then generate a different and less potent imine, and this process would therefore not be catalytic. Catalytic oxaziridine formation may however be possible by cyclodehydration of hydroperoxyamine before oxygen transfer to substrate (Scheme 2). An oxaziridine mediated catalytic oxidation using oxone was reported several years ago but does not appear to have been followed up.[3a] Although our mechanistic investigation is as yet incomplete, we believe that such a process, involving oxaziridine as the oxidizing species, does not occur in our system for the following reasons: (i) hydroxide ion is a poor leaving group; (ii) ees obtained for oxidation of various sulfides are in some cases higher than those obtained using the preformed oxaziridine reagent; and (iii) the ees obtained from a range of substrates show a different pattern and display different solvent effects and temperature profiles from those observed using preformed oxaziridine reagents. For example, Davis reports the oxidation of *p*-tolyl methyl sulfide with the oxaziridine derived from (1) at room temperature as giving 4% ee in dichloromethane as solvent and 8% ee in carbon tetrachloride (*cf* Table, entry 3); benzyl methyl sulfoxide was produced in 22% ee under the same conditions (*cf* Table, entry 2).[3b] We have however shown that the same Davis reagent oxidizes 2-pivaloyl-1,3-dithiane to the (*S*)-1-oxide with 58% ee (*cf* Table, entry 6).

Conclusion

We have developed a new catalytic procedure for asymmetric sulfide oxidation, applicable to dialkyl sulfide substrates. We would emphasise the extreme simplicity of the procedure described, which requires no preparation and isolation of sensitive reagent, no close monitoring, and which provides remarkably clean reactions in an inexpensive and environmentally friendly process. We aim to develop this method further by investigation of alternative chiral imine derivatives.

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