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ENANTIOSELECTIVE OXIDATION OF SULPHIDES BY DIOXIRANES IN THE PRESENCE OF BOVINE SERUM ALBUMIN

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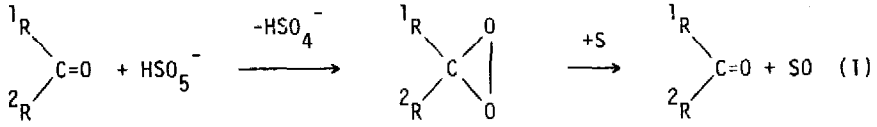
Abstract. Oxidation of sulphides by in situ generated dioxiranes in buffered (pH 7.5) aqueous solutions, using bovine serum albumin (BSA) as a chiral auxiliary, affords the corresponding sulphoxides in up to 89% enantiomeric excess (e.e.).

It has been shown that dioxiranes **1**, the smallest ring peroxides containing carbon, can be generated upon reaction of potassium peroxomonosulfate (caroate) $K^+HSO_5^-$ and ketones.[1,2] Indeed, a few volatile dioxiranes (e.g., in **1**: $^1R=^2R=CH_3$; $^1R=CH_3$, $^2R=CF_3$) could be isolated from reaction mixtures of the precursor ketone and caroate, and fully characterized spectroscopically.[2,3,4]



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Thus, a new class of powerful oxidants became available that are of unusual utility for synthetic purposes.[2]

Dioxiranes generated in situ (i.e. the ketone/caroate system) have been employed to perform efficient and selective transformations such as epoxidations of unfunctionalized alkenes,[5a] allylic alcohols,[5b] arenes,[6] as well as alkynes oxidation,[2] and the conversion of amines into nitrocompounds.[2,7]

In view of the convenience of this new class of useful oxidants, it is perhaps surprising that just one case has been reported of asymmetric epoxidation via dioxiranes.[5c] It was shown that asymmetric epoxidation of simple, unfunctionalized alkenes occurs in 9-12% e.e. when certain optically active ketones are employed as the precursors of dioxiranes (eq. 1).[2,5c] By following a different approach, we report herein the possibility of achieving high enantioselectivity in the oxygen transfer by achiral dioxiranes to prochiral sulphides using a chiral auxiliary, such as bovine serum albumin (BSA).[8a-c]

Sulphoxidations of a variety of organic sulphides (Table I) have been readly performed by the buffered (pH 7.5-8.0) ketone/caroate system in water containing BSA at 4°C. Reaction times ranged from 15 to 180 min, depending on the substrate and on the structure of the ketone employed as dioxirane precursor. Since methyl trifluoromethyl dioxirane has been shown to have a reactivity by far exceeding that of dialkyl dioxiranes,[4] it is not surprising that ketones such as CF_3COCH_3 and CF_3COPh are the most efficient oxidation catalysts, affording shortest reaction time.

The product sulphoxides have been isolated by column (silica gel Et_2O, MeOH 95:5) chromatography. The enantiomeric excesses were determined by ^1H n.m.r. spectroscopy using $Eu(tfc)_3$ as chiral shift reagent and/or by optical rotations. Chemical yields, absolute configuration and e.e. of the sulphoxides are given in Table 1.

In situ dimethyl dioxirane, (i.e., acetone:caroate), was adopted as the standard oxidizing agent for the conversion of aryl alkyl sulphides into the corresponding sulphoxides. The highest enantioselectivities were observed with phenyl isopropyl and t-butyl sulphoxide, i.e. 79% and 73% e.e., respectively (entries 2, 6). The corresponding p-tolyl derivatives presented a lower asymmetric induction (entries 12, 13). The stereoselection was less relevant also in the case of the other phenyl aryl sulphoxides (entries 1, 8). The yield of sulphones was 5%, except for the p-tolyl ^{t}butyl sulphide case, where a sizeable amount of sulphone was obtained (14%). The asymmetric induction is accompanied by a negligeable kinetic resolution (2.2% in the case of phenyl isopropyl sulphoxide).

The degree of stereoselectivity of the sulphoxidation is influenced by the structure of the dioxirane used as oxidant. In situ methyl trifluoromethyl dioxirane afforded the (+)-(R) phenyl isopropyl sulphoxide in 89% e.e. during a very short reaction time (12 min.) (entry 5). Phenyl isopropyl sulphoxide of lower optical purity (16% e.e.) was obtained with the dioxirane deriving from cyclohexanone, (entry 3). An intermediate behaviour was observed with CF_3COPh as dioxirane precursor (64% e.e.), (entry 4). All dioxiranes presented the same stereochemical course.

Table 1. Asymmetric oxidation of sulphides to sulphoxides by *in situ* dioxiranes at 4°C in the presence of bovine serum albumin.

Entry	Ar	R	Ketone catalyst	Yield[a] (%)	Absolute configuration	E.e.[b] (%)
1	Ph	Me	$(CH_3)_2CO$[c]	98	(-)-(S)	7
2	Ph	Pr^i	$(CH_3)_2CO$[c]	56	(+)-(R)	79
3	Ph	Pr^i	cyclohexanone[c]	46	(+)-(R)	16
4	Ph	Pr^i	CF_3COPh[d]	96	(+)-(R)	64
5	Ph	Pr^i	CH_3COCF_3[d]	67	(+)-(R)	89
6	Ph	Bu^t	$(CH_3)_2CO$[c]	70	(+)-(R)	73
7	Ph	Bu^t	CF_3COPh[e]	37	(+)-(R)	71
8	Ph	C_6H_{11}[c]	$(CH_3)_2CO$[c]	45	(+)-(R)	52
9	Ph	$C_6H_5CH_2$	CF_3COCH_3[e]	56	(+)-(R)	67
10	p-tolyl	Me	$(CH_3)_2CO$[c]	77	(-)-(S)	32
11	p-Tolyl	Et	$(CH_3)_2CO$[c]	68	(-)-(S)	64
12	p-Tolyl	Pr^i	$(CH_3)_2CO$[c]	50	(-)-(S)	29
13	p-Tolyl	Bu^t	$(CH_3)_2CO$[c]	40	(+)-(R)	8.5

[a] Based on the amount of sulphide reacted.

[b] Based on the observed specific rotation of isolated sulphoxides as referred to literature data of maximum specific rotation and/or determined using $Eu(tfc)_3$ as a chiral shift reagent.

[c] Sulphide/$KHSO_5$/Ketone/BSA ratio = 1: 2: 13: 0.05.

[d] " " = 1: 2: 0.44: 0.05.

[e] " " = 1: 0.5: 0.11: 0.0125.

In summary the asymmetric sulphoxidation with dioxiranes generated in situ using BSA as chiral auxiliary (1.25-5% molar equivalents) appears to be highly stereoselective and compares favourably in terms of the enantioselectivity and rate with those observed using H_2O_2 or ^tBuOOH as oxidants and a much larger amount of globular protein.[8c]

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