



Vanadium catalyzed enantioselective oxidation of sulfides: easy transformation of bis(aryltio)alkanes into C_2 symmetric chiral sulfoxides

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Abstract

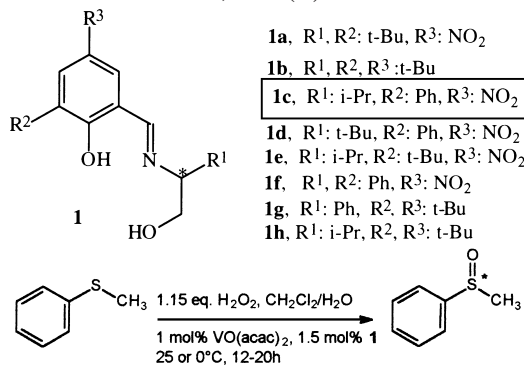
A facile and selective method for the title transformation is described. The two-phase oxidation of bis-sulfides with hydrogen peroxide catalyzed by vanadium complex of chiral Schiff base leads to the corresponding chiral mono- and bis-sulfoxides. In the case of 1,2-bis(aryltio)ethanes the respective optically active bis-sulfoxides are formed in up to over 95% e.e. © 1999 Elsevier Science Ltd. All rights reserved.

Optically active sulfoxides constitute the class of highly valuable chiral auxiliaries and reagents in asymmetric synthesis.¹ The most attractive method for their preparation is the enantioselective oxidation of the easily available prochiral sulfides.² Procedures based on the modified Katsuki–Sharpless epoxidation reagents³ and the oxaziridines of Davis⁴ are often used for this important transformation. However, there is still much interest in the development of a new, simple and truly catalytic oxidizing system. In 1995 Bolm and Bienewald described successful enantioselective oxidations catalyzed by the in situ formed vanadyl complex of the substituted salicylidene derivatives of (*S*)-*tert*-leucinol (1.5 mol%) and 30% hydrogen peroxide used as a stoichiometric oxidant.⁵ They have found that in the case of oxidation of thioanisole 3-*tert*-butyl-5-nitrosalicylidene derivative **1a** was the most effective chiral inducer, while the 3,5-di-*tert*-butylsalicylidene ligand **1b** was the best suited for the oxidation of dithioacetals and dithioketals, e.g. 2-phenyl-1,3-dithiane was converted to the respective *trans*-monosulfoxide in 85% e.e.⁶ These two chiral ligands have been chosen from the collection of 44 Schiff bases examined.⁷ Another highly successful ligand was obtained from the axially chiral 1-naphthyl-2-hydroxy-3-naphthylaldehyde and (*S*)-*tert*-leucinol: it gave some improvement in the oxidation of thioanisole (78% e.e. at 0°C and 71% e.e. at 25°C),⁸ but this seems to result rather from the decrease of reaction temperature than from the structural changes.

These results encouraged us to report our findings.⁹ We scrutinized other simple chiral Schiff bases and discovered that the ligand **1c** obtained from D- or L-valinol and 3-phenyl-5-nitrosalicylaldehyde

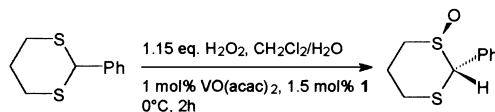
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performed under the same oxidation conditions at least as well as the previously reported ones. Moreover, this catalyst may be considered as a more versatile one because both its enantiomers are easily available and it gives relatively good enantiomeric excess in both model reactions. Also, the derivative **1d** gave good results, while the ligands **1e–h** were worse. It seems that the particular set of substituents on **1c** gives a ligand that fits better to the oxidation transition state. As was reported,^{5,6,8} the chirality transfer occurred generating the same configuration at the sulfur atom as in the catalyst, i.e. (*S*)-sulfoxide was formed using the ligands derived from L-valinol, and (*R*)-sulfoxide was obtained with that of D-valinol.



Ligand 1	Yield, %	E. e., %
a	94 ^a	70 ^a
b	73 ^a	59 ^a
c	(90) 80	(75) 58
d	(74) 78	(73) 62
e	(64)	(69)
f	74	15
g	79 ^a 50	30 ^a 34
h	58	50

^a From the work of Bolm and Binewald^{5,7}.
 Values in parentheses refer to the reaction at 0°C.



Ligand 1	Yield, %	E. e., %
a	77 ^a	76 ^a
b	84 ^a	85 ^a
c	80	88 ^b
d	88	71 ^b

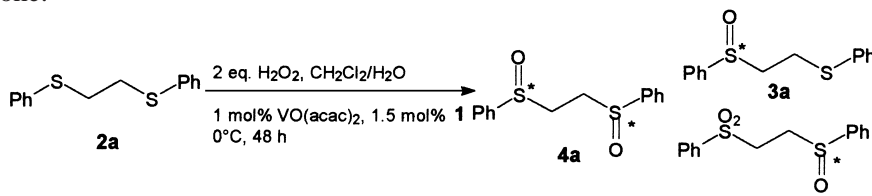
^a From the work of Bolm and Binewald^{5,6} run at 25°C.

^b The only product was *anti*-isomer and the e.e. values reported were obtained using Eu(hfc)₃, discrimination of -CH₂-S*(O)-.

Chiral synthetic building blocks of C₂ symmetry¹⁰ containing sulfoxide functions are particularly promising for the construction of various important compounds and several oxidative procedures are viable for their preparation by oxidation of sulfides. The oxidation of two prochiral centers present in a bis-sulfide molecule may lead to two diastereoisomeric products, namely a meso form and a chiral, C₂ symmetric bis-sulfoxide can be expected. To the best of our knowledge, the only reported enantioselective oxidations of substrates of this type were those of bis-methylthiobenzenes¹¹ and its cyclic analog¹² using the Modena version of the Katsuki–Sharpless oxidant. Recently, we have investigated the catalytic

oxidation of 1,x-bis(phenylthio)alkanes to the respective mono- and bis-sulfoxides;¹³ however, only the meso bis-sulfoxides were formed selectively. When we oxidized the bis-sulfide **2a** with 1.2 equiv. of cumyl hydrogen peroxide in the presence of 2:1:1 equiv. of (+)-DET, Ti(Oi-Pr)₄ and H₂O, respectively, at –20°C, racemic mono-sulfoxide **3a** (93%) and meso-bis-sulfoxide **4a** (6%) were obtained.

Now, we extend the application of the new catalytic system elaborating a selective procedure for the oxidation of 1,2-bis(arylthio)alkanes **2** and *ortho*-bis(phenylthiomethyl)benzene to the corresponding chiral bis-sulfoxides **4**. We examined several ligands for this oxidation, and again **1c** was chosen as the most suitable one.



Ligand 1	Yield of 4a , %	D.e., %	E.e., %
a	66	58	79
b	41	38	85
c	41	60	95
d	44	42	85

Although mixtures containing mono- and bis-sulfoxides were usually obtained, flash chromatography gave complete separation. All the obtained chiral bis-sulfoxides (see below) are configurationally stable and can be separated from the respective meso-forms, while the recrystallization of mono-sulfoxides **3** leads to gradual racemization. The e.e. values reported refer to the obtained chiral major-**4** or **3** (¹H NMR, 300 MHz, CCl₄ solution in the presence of Eu(hfc)₃, Δδ_(enantiomers) ca. 0.2 ppm for *ortho* hydrogens of the arylsulfinyl group). Several recrystallizations of the chromatographed **4** gave material of the highest specific rotation and no minor enantiomer could be detected by NMR with the chiral shift reagent. The absolute configuration of (+)-(*R,R*)-**4e** has already been proved¹⁴ by chemical correlation.

If the reaction was carried out with one equivalent of H₂O₂ the only products were mono- and bis-sulfoxides (no sulfonosulfoxide) in comparable yields and the stereochemical results were not much different from those expected for the same reactivity (enantioselectivity) at both centers. The same enantioselectivity in the oxidation of the prochiral sulfur atom in **2** and **3** requires, for the ratio of major enantiomer of **3**:ent-**3** being *x*:1, that the ratio of stereoisomers for **4** is *x*²:2*x*:1 for major-**4**:meso-**4**:ent-**4**, respectively. Thus the ratio of meso-**4**:dl **4** is 2*x*/*x*²+1 and this value is available from the NMR spectrum of crude **4**. When we correlated by the least squares method the calculated enantioselectivities for both oxidation steps vs the observed specific rotations of the crude samples of **3** and **4**, two lines resulted and the extrapolated [α]_D values for 100% e.e. were in acceptable agreement with the observed ones (Fig. 1). Additionally, in order to test the possibility of autocatalytic enantioselective oxidation (NLE)¹⁵ we ran the reaction with **2c** using the catalytic amount of enantiomerically pure **4c** (>95% e.e.) instead of chiral ligand **1c**. However, in this case, the products obtained were completely racemic. All these suggest that the stereoselectivity enhancement for the formation of bis-sulfoxides is due to the known statistical effects.¹⁶

In order to learn about the scope and limitations of the catalytic oxidation we examined the reaction of several different 1,2-bis(arylthio)ethanes, 1,3-bis(phenylthio)propane and *ortho*-bis(phenylthiomethyl)benzene. The oxidizing species are clearly electrophilic, so the more electron-rich system is easier to oxidize and in these cases the catalyzed enantioselective reaction leads to the highest yield and e.e., and the reverse is true for the electron-poor arylsulfinyl group **2d**. Interestingly, a

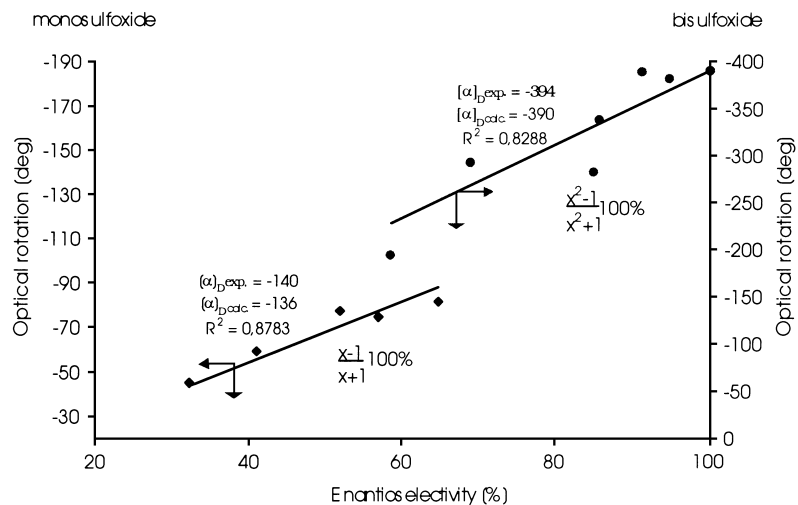
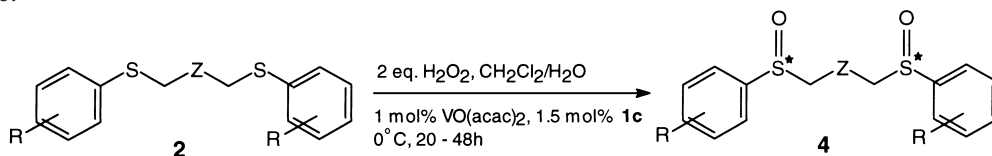


Figure 1. Plot of the measured $[\alpha]_D$ values (CHCl_3 , 25°C) vs the calculated e.e.s for **3a** and **4a** obtained under various reaction conditions

three-carbon-atom bridge in the case of **2f**, in spite of the high yield and d.e. observed in the oxidation, causes much lower e.e. values for **4f**. This result suggests low stereoselectivity in the first oxidation step. Probably, in this case, the first sulfoxide function is involved in the second oxidation step giving the high d.e. value.



2, 4	R	Z	Yield of 4 , %	D.e., %	E.e., %	$[\alpha]_D^{25^\circ}$ (CHCl_3)
a	H	-	41	60	95	-394
b	2-Me	-	62	14	91	-516
c	2-OMe	-	95	65	> 95	-596
d	2-COOMe	-	12	84	20	-98 (20% e.e)
e	4-Me	-	56	78	92	-300
f	H	CH_2	92	> 80	25	-421 (64% e.e)
g	H	1,2- C_6H_4	61	26	49 ^a	-284

^a Estimated from the specific rotation only.

Work on synthetic applications of the thus prepared chiral bis-sulfoxides is underway. We have already found that **4c** in the presence of methyllithium (THF, -30°C) underwent elimination and the respective chiral vinyl sulfoxide (ca. 75% e.e.) was formed.

In conclusion, the method described in this paper offers a convenient route to some C_2 symmetric chiral bis-sulfoxides obtained in good d.e. and often excellent e.e. from the easily available bis-sulfides.

Acknowledgements

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