ASYMMETRIC OXIDATION OF PROCHIRAL SELENIDES TO OPTICALLY ACTIVE

SELENOXIDES

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<u>Abstract</u>. Oxidation of 1,1-diphenyl-1-methoxy-2-phenylselenylethane and of 1,1-diphenyl-1-methoxy-2-(\underline{o} -methoxy)phenylselenylethane with the Sharpless reagent afforded the corresponding selenoxides with moderate optical yields.

In contrast with the corresponding sulphoxides, simple organic selenoxides are configurationally labile compounds. The facile racemization of partially optically active selenoxides has been ascribed to acid catalyzed reversible formation of tetra-coordinated achiral hydrates. In agreement with this interpretation selenoxides with sterically bulky substituents present enhanced optical stability due to steric inhibition in the formation of the hydrates. The synthesis of optically active selenoxides has been attempted in several ways, $^{1-10}$ including asymmetric oxidation of prochiral selenides. These latter experiments however were not extremely encouraging. Thus, microbial oxidation of achiral selenides failed, 10 whereas oxidation of phenyl methyl selenide with chiral 2-sulphonyloxaziridines gave the corresponding selenoxide with an e.e. lower than 10%.

We have recently investigated the oxidation of several 1-phenyl-1-methoxy-2-arylselenylethanes of type $\underline{1}$ and we have observed that the corresponding selenoxides $\underline{2}$ are thermally stable compounds which can be easily manipulated.¹¹ A mixture of diastereoisomeric selenoxides was obtained when R was different from phenyl. With R = Ph these compounds could not be easily further oxidized to the selenones. In view of these properties we thought that these latter selenides could be suitable substrates to investigate new methods of asymmetric oxidation. It has recently been reported that a mixture of t-butyl hydroperoxide, titanium

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tetraisopropoxide, and (+)- or (-)-diethyl tartrate, (Sharpless reagent), with or without added water, is a good reagent for the asymmetric oxidation of sulphides, chiral sulphoxides being obtained with satisfactory chemical yields and with moderate to good optical yields.¹²⁻¹⁴

We now report that a similar reagent, $Ti(OC_3H_7-i)_4$, L-(+)- or D-(-)diisopropyltartrate (DIPT), and <u>t</u>-BuOOH (molar ratio 1 : 2 : 1) can also be employed for the asymmetric oxidation of prochiral selenides to optically active selenoxides.



a : R = Ar = Phb : R = Ph, $Ar = o-MeOC_6H_4$ Method A : (+)-DIPT Method B : (-)-DIPT

To a solution of $\text{Ti}(\text{OC}_{3}\text{H}_{7}-i)_{4}$ (1 mmol), (+)-DIPT (Method A) or (-)-DIPT (Method B) (2 mmol), and <u>t</u>-BuOOH (1 mmol) in $\text{CH}_{2}\text{Cl}_{2}$ (10 ml), at -5°C, 1,1-diphenyl-1-methoxy-2-phenylselenylethane, <u>1a</u>, or 1,1-diphenyl-1-methoxy-2-(<u>o</u>-methoxy) phenylselenylethane, <u>1b</u>, (1 mmol) was added and the resulting mixture was stirred under argon at -5°C for 20 h. Triphenylphosphine (0.3 mmol) was then added and after 1 h the solvent was removed in vacuum. The residue was chromatographed through a deactivated alumina column using a mixture of $\text{CH}_{2}\text{Cl}_{2}$ and methanol (99.5/0.5) as eluant. Compounds <u>2a</u> and <u>2b</u> were obtained as colourless solids, mp 169-71¹¹ and 163-5°C, respectively. Pertinent data are summarized in the Table.

Selenide	Selenoxide	Method	Yield(%) ^a	[α] _D ^{25^b}	e.e.(%) ^c	Conf.
1a	2a	A	82	-16	18 ^d	S
<u>1a</u>	<u>2a</u>	В	75	+14	20 ^d	R
<u>1b</u> e	<u>2b</u> f	A	72	-101	40	S
1b	2b	В	70	+85	28	R

a) Based on isolated products and calculated on the converted selenides. Conversions were of the order of 80-90%. b) Measured in 1% solutions in acetone. c) Determined by HPLC. d) Higher values were obtained in other experiments. e) Prepared from <u>o-MeO-C₆H₄SeBr</u> and $Ph_2C=CH_2$ in MeOH.¹¹ Mp 96-98°C. NMR (90 MHz, CDCl₃) 7.5-6.7 (m, 14 H), 3.9 (s, 2 H), 3.75 (s, 3 H), 3.15 (s, 3 H). f) NMR (CDCl₃) 8.1-7.0 (m, 14 H), 4.1 (d, 1 H, J=12 Hz), 3.85 (d, 1 H, J=12 Hz), 3.5 (s, 3 H, <u>o-MeO</u>), 3.25 (s, 3 H).

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The enantiomeric excess of the selenoxides 2a and 2b were determinated by HPLC using optically active columns. In the case of 2a the analysis was performed with a column packed with DNBPG/aminopropylsilica¹⁵ using hexane containing 2% (V/V) of i-propanol as the mobile phase at a flow rate of 2 ml/min; the enantioselectivity factor a was calculated to be 1.2. The analysis of 2b was instead better carried out with a DACH-DNB (R,R-(-)-1,2-diaminocyclohexane-3,5dinitrobenzoyl derivatives bonded to glycidoxypropyl silica gel)¹⁶ using a mixture of hexane, i-propanol and dichloromethane (80/6/14 Vol) as the mobile phase at a flow rate of 2 ml/min; α was calculated to be 1.19. The enantiomeric excess was also determined by proton nmr (90 MHz) using (R)-(-)-2,2,2-trifluoro,1-(9-anthryl)ethanol (TFAE) as chiral shift reagent. This reagent has already been employed in the case of sulphoxides and sulphinates ¹⁷ and it is noteworthy that it can be successfully utilized in the case of selenoxides also. The absorptions of the methoxy groups in the 1-position were diagnostic; complexation with the chiral reagent gave two singlets separated by 10 - 12 Hz for the two enantiomers of both 2a and 2b. The results observed were not significantly different from those obtained by HPLC.

The oxidation of <u>1a</u> was carried out several times with both (-)- or (+)-DIPT and in some cases considerably higher optical purities (up to 35%) were measured by nmr. Thus, it seems that the selenoxide <u>2a</u> is very sensitive to the reaction conditions and to the work up and indeed it was observed that on standing in the solid state or in solution the e.e. gradually decreases. On the contrary, the selenoxide <u>2b</u> remained unchanged for several weeks. Both <u>2a</u> and <u>2b</u> rapidly racemize in the presence of traces of acids.

In the case of the stable selenoxide $\underline{2a}$ a direct analysis of the reaction mixture (Method A) was carried out by HPLC; an enantiomeric excess of 44% was measured in this way. This value is not significantly different from that observed for the isolated selenoxide (40%) indicating that in this case the work up procedure employed does not produce racemization of the selenoxide. Thus the measured e.e. reflects the efficiency of the asymmetric oxidizing reagent employed.

Also indicated in the Table are the suggested absolute configurations of the enantiomers which are obtained in excess from the oxidation of <u>1a</u> and <u>1b</u>. These attributions are proposed on the assumption that the Pirkle's method^{15,17} for the determination of the absolute configuration of sulphoxides can be applied to the selenoxides also, i.e. that diastereoisomeric solvates are formed between the chiral TFAE and the two enantiomeric selenoxides, and that the structures of these complexes are similar to those proposed for the sulphoxides.¹⁸

The results reported in the Table indicate that a mixture of <u>t</u>-BuOOH, $Ti(OC_3H_7-i)_4$ and (+)- or (-)-DIPT represents a useful and simple reagent for the asymmetric oxidation of prochiral selenides to optically active selenoxides. As indicated by the better results obtained with <u>1b</u>, in comparison with <u>1a</u>, the presence of an <u>o</u>-methoxy group in the arylselenyl mojety seems to be beneficial for the asymmetric oxidation process probably because of a greater steric demand in the transition state leading to the selenoxide. Moreover, as already observed in other aryl selenides, ⁶ the presence of the ortho substituent increases the configurational stability of the selenoxide. Although optical yields are not exceedingly high, neverthless they are considerably higher than those so far reported for the asymmetric oxidation of selenides⁵ and encourage further researches in the hope of finding better experimental conditions which could improve the presently described procedure.

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