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Diastereoselective Oxidation of Arylsulfides

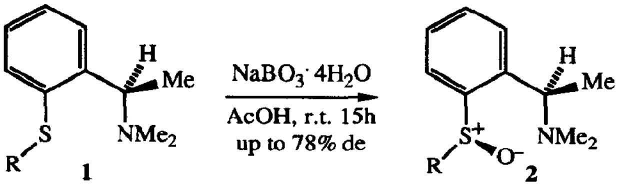
Justin F Bower and Jonathan M J Williams*

Department of Chemistry, Loughborough University of Technology,
Loughborough, Leicestershire, LE11 3TU, UK.

Abstract: Arylsulfides containing an enantiomerically pure oxazoline in the *ortho*-position have been oxidised to the corresponding sulfoxides with a variety of reagents. When the oxazoline unit contains a 4-hydroxymethyl group, good levels of diastereocontrol have been obtained using mCPBA (96:4) or t-butylhydroperoxide and titanium tetraisopropoxide (97:3) as the oxidant. This diastereocontrol provides an effective example of 1,6-asymmetric induction.

The asymmetric synthesis of sulfoxides by substrate control[1] and by reagent control[2] has received considerable attention recently. Enantiomerically pure sulfoxides have been exploited in a variety of asymmetric reactions, including; Diels Alder reactions,[3] aldol reactions,[4] and other carbon-carbon bond forming reactions.[5] Our interests lay in the application of enantiomerically pure sulfoxides as ligands for asymmetric catalysis, and recently, there have been examples of sulfoxides as ligands.[6]

Ohta and co-workers have reported the diastereoselective oxidation of the arylsulfide **1** to the sulfoxide **2** with up to 78% diastereomeric excess.[7]



Herein we report the diastereoselective oxidation of arylsulfides with an oxazoline moiety as an alternative enantiomerically pure *ortho*-substituent. Treatment of the valinol-derived oxazolines **3a** and **3b**[8] with the oxidants indicated in Table 1 afforded the corresponding sulfoxides **4a/5a** and **4b/5b** with moderate levels of diastereoselectivity.

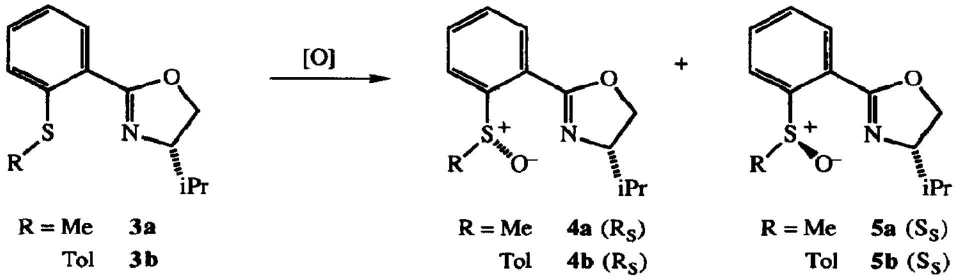


Table 1: Diastereoselective Oxidations of Arylsulfides **3a** and **3b**

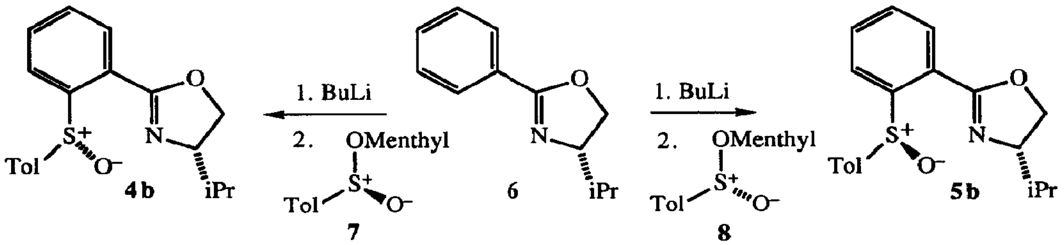
Sulfide	*Conditions*	*Product*	*Ratio*[a]	*Yield (%)*
3a	mCPBA, $CHCl_3$ -78 °C, 1.25hr	**4a:5a**	30:70	94
3a	$NaIO_4$ MeOH / H_2O (1:1), 0 °C, 1hr	**4a:5a**	65:35	91
3a	$NaBO_3 \cdot 4H_2O$, AcOH, 20 °C, 16hr	**4a:5a**	41:59	94
3a	MMPP, EtOH / H_2O (1:1), 50 °C, 1.5hr	**4a:5a**	38:62	90
3a	tBuOOH, $Ti(OiPr)_4$ CH_2Cl_2, -20 °C, 24hr	**4a:5a**	48:52	38
3a	tBuOOH, $Ti(OiPr)_4$ (+)-DET CH_2Cl_2, -20 °C, 24hr	**4a:5a**	89:11	19
3a	tBuOOH, $Ti(OiPr)_4$ (-)-DET CH_2Cl_2, -20 °C, 24hr	**4a:5a**	37:63	19
3a	tBuOOH, $VO(acac)_2$, CH_2Cl_2, -20 °C, 24hr	**4a:5a**	85:15	77
3b	mCPBA, $CHCl_3$ -78 °C, 1 hr	**4b:5b**	28:72	57

[a] Ratios were determined by capilliary gc using a BP1 column (SGE)

The sulfide **3a** was oxidised in good yields but with low selectivity by mCPBA,[8] $NaIO_4$,[9] $NaBO_3$[10] and magnesium monoperoxyphthalate (MMPP).[11] Lower yields were obtained using t-butylhydroperoxide with either titanium tetraisopropoxide or vanadyl acetylacetonate promoters, although in the latter case a reasonable selectivity is obtained in the formation of sulfoxide **4a**. The use of a titanium reagent modified by (R,R)-(+)-DET affords the product **4a** with good diastereoselectivity with the (R)-stereochemistry at sulfur predominating,[2c] whereas the use of (S,S)-(-)-DET represents affords the other diastereomer **5a** albeit with a lower selectivity.

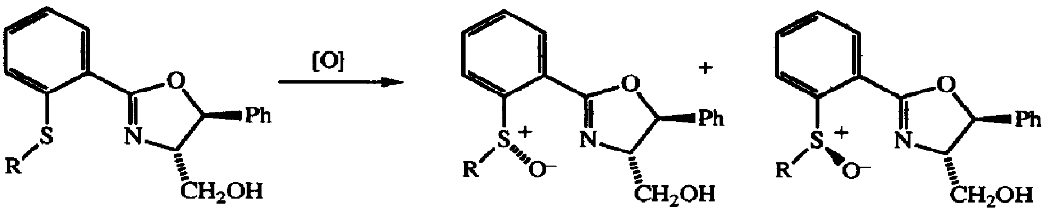
The two sulfoxide diastereomers **4b** and **5b** were prepared by an independent method, as follows: Treatment of the 2-phenyloxazoline **6**[12] with BuLi followed by quenching with the (R)-sulfinate **7** afforded sulfoxide **4b** (assuming an inversion mechanism).[13] Similarly, quenching with the (S)-sulfinate **8** afforded the other sulfoxide diastereomer **5b**.

The assignment of stereochemistry for diastereomers **4a** and **5a** is based tentatively on analogy with **4b** and **5b** (compare the diastereoselectivities obtained with mCPBA) and also on the fact that the Kagan method of oxidation with (R,R)-(+)-DET modified titanium reagents generally affords the (R)-stereochemistry of product in the oxidation of arylalkylsulfides.[2c]



4b **7** **6** **8** **5b**

The hydroxy group has been shown by other research groups to direct the oxidation of sulfides to sulfoxides.[14] We therefore examined the oxidation of the 4-hydroxymethyl substituted oxazolines **9a-c**[12] to the corresponding sulfoxides **10a-c** and **11a-c**. We were pleased to find that the oxidations were often highly diastereoselective, as indicated in Table 2.



R = Me 9a
Ph 9b
Tol 9c

R = Me 10a
Ph 10b
Tol 10c

R = Me 11a
Ph 11b
Tol 11c

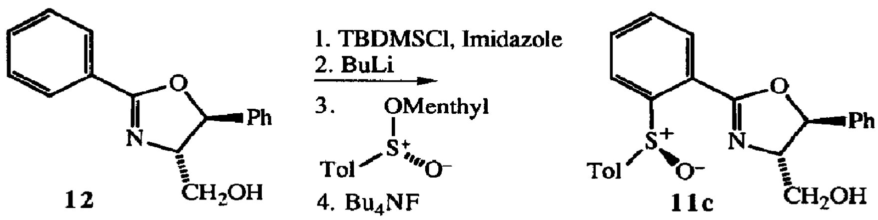
Table 2: Diastereoselective Oxidations of Aryl sulfides **9a**, **9b** and **9c**

Sulfide	*Conditions*	*Product Ratio*		*Yield (%)*
9a	mCPBA, MeOH -70 °C, 1.25hr	**10a**:**11a**[a]	57:43	76
9a	mCPBA, $CHCl_3$ -70 °C, 1hr	**10a**:**11a**	87:13	78
9a	mCPBA, Hexane/$CHCl_3$ (3:1) -70 °C, 1hr	**10a**:**11a**	96:4	76
9a	tBuOOH, $VO(acac)_2$, CH_2Cl_2, -20 °C, 3hr	**10a**:**11a**	87:13	85
9a	tBuOOH, $Ti(OiPr)_4$ CH_2Cl_2, -20 °C, 24hr	**10a**:**11a**	97:3	41
9a	tBuOOH, $Ti(OiPr)_4$ L-DET, CH_2Cl_2, -20 °C, 24hr	**10a**:**11a**	99:1	32
9b	mCPBA, $CHCl_3$ -65 °C, 2hr	**10b**:**11b**[b]	83:17	94
9b	tBuOOH, $VO(acac)_2$, CH_2Cl_2, -20 °C, 4hr	**10b**:**11b**	79:21	15
9c	mCPBA, $CHCl_3$ -20 °C, 1hr	**10c**:**11c**[a]	80:20	90

[a] Ratio determined by hplc using a bondapak C18 column (acetonitrile/water)
[b] Ratio determined by inspection of the ^1H NMR spectra

The diastereoselectivity of the mCPBA oxidation of sulfide **9a** was seen to increase dramatically on changing from a protic to an aprotic solvent, and to increase still further on reducing the polarity of the solvent. This suggests that hydrogen bonding between the hydroxyl group and the mCPBA is important for high levels of selectivity.[15] The t-butylhydroperoxide and titanium promoted oxidation of sulfide **9a** was highly diastereoselective, and the diastereoselectivity could be enhanced still further by the use of an (R,R)-(+)-DET modified titanium reagent. We believe that the high level of 1,6-asymmetric induction that we observe is made possible by the combined effect of the hydroxy group and oxazoline nitrogen both of which associate with the incoming reagent, providing more organisation in the transition state than is possible in the absence of the hydroxy group.

One of the sulfoxide diastereomers **11c** was prepared independently as follows: Oxazoline **12** was protected as the TBDMS ether, ortho-lithiated and quenched with the (S_S)-sulfinate, and the silyl protecting group removed to afford the (S_S)-sulfoxide **11c** by inversion at sulfur. The relative stereochemistry of the corresponding sulfoxides **10a**, **10b**, **11a** and **11b** was again tentatively assigned by analogy.



In conclusion, we have shown that enantiomerically pure oxazolines are able to direct the oxidation of sulfides to sulfoxides with reasonable levels of diastereocontrol.[16] When the hydroxymethyl-substituted oxazoline **9a** was treated with t-butylhydroperoxide and titanium tetraisopropoxide, the diastereocontrol was very high (97:3), and this diastereoselectivity could be enhanced still further by the co-operative effect of (R,R)-(+)-DET We will report the use of oxazoline/sulfoxide systems as ligands for asymmetric catalysis in due course.

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