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S-Oxidation products of (+)-thiomicamine-derived oxazolines—promising substrates in the synthesis of alkyl methyl sulfoxides

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Abstract—Highly stereoselective oxidation of the 4-methylthio substituent in oxazolines **2**–**4**, derived from (+)-thiomicamine **1**, performed using the Kagan procedure and with the vanadium/chiral salen catalytic system, afforded R_S and S_S diastereomeric sulfoxides **5**–**7**, respectively. The reaction of sulfoxide R_S-**6** with *n*-butyl- and *tert*-butyllithium reagents produced the corresponding butyl methyl sulfoxides in high enantiomeric excess and with an (*S*) absolute configuration, albeit in moderate yields.

1. Introduction

Preparation of enantiomerically pure sulfoxides, a class of compounds gaining increasing importance in asymmetric synthesis,[1] has usually been performed via two general methodologies: enantioselective oxidation of prochiral sulfides[2] and stereoselective nucleophilic displacement of ligands at the stereogenic sulfur in chiral sulfinyl derivatives.[3] The latter method, based upon the classical Andersen procedure, has been extended to various sulfinyl derivatives, in which nitrogen-, oxygen- and sulfur-containing anionic species are the leaving groups. Substitution of carbanionic leaving groups in chiral nonracemic sulfoxides by organometallic reagents is another modification of this method, recently intensely studied by Naso et al.[4] Their work has encouraged us to reveal the results of our experiments on the stereoselective oxidation of sulfur of the 4-methylthio substituent in (+)-thiomicamine **1** derived oxazolines **2**–**4**, and application of the so obtained *S*-oxides **5**–**7** as chiral methylsulfinyl group transfer agents in the synthesis of butyl methyl sulfoxides with high enantiomeric purity.

2. Results and discussion

In connection with our interest in the application of (+)-thiomicamine **1**, an industrial waste product in asymmetric transformations,[5] we envisaged that the *S*-methyl substituent, after *S*-oxidation, might be useful as a source of chiral methylsulfinyl group.

To approach this problem, we have undertaken experiments in which (4*S*,5*S*) oxazolines **2**,[6] **3**[7] and **4**,[8] prepared from (+)-thiomicamine **1** to protect the two functionalities (–OH and $–NH_2$), have been chosen as the starting compounds, while the primary hydroxyl was transformed into *O*-methyl ether in **3** and *O*-tosyl ester in **4** (Scheme 1).

Since the synthetic validity of the 'carbon-for-carbon displacement' strategy[4] strongly depends upon the availability of the starting sulfoxide of high enantiomeric purity, our attention has been focused on finding an efficient and selective oxidation system for compounds **2**–**4**.

It seemed at first that because of the two stereogenic centres present in oxazolines **2**–**4**, the oxidation with achiral oxidizing agents would give sulfoxides with an acceptable degree of diastereoselectivity. Williams et al.[9] have reported *m*CPBA oxidation of oxazoline **8**, prepared from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanodiol, the analogue of (+)-thiomicamine **1**, to proceed with high diastereoselectivity. However, in our experiments with the commonly used sulfoxidation reagents:

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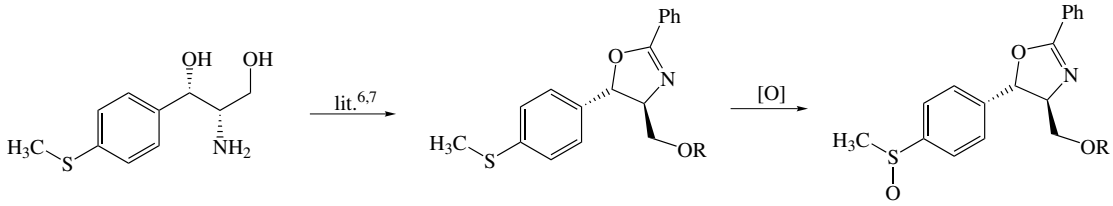


1

2 R = H
3 R = CH_3
4 R = Ts

5 R = H
6 R = CH_3
7 R = Ts

Scheme 1.

NaOCl/TEMPO,[10] bromine/H_2O/$NaHCO_3$,[11] *m*CPBA[9] the diastereoselectivities were disappointingly low (0.6–10% de) apparently because of a too distant 1,8-asymmetric induction.

In this context, the well known Sharpless oxidation methodology, mediated by D- or L-diethyl tartrate (DET)/titanium(IV) complexes, adapted for the enantioselective oxidation of prochiral sulfides by Kagan et al.[12] was applied. Keeping a constant ratio of the reagents Ti(O-*i*-Pr)$_4$/L-(+)-DET/H_2O (1:2:0.5),[13] using methylene chloride as the solvent and cumylhydroperoxide (CHP), (1.3 equiv), as the stoichiometric oxidant, we were able to prepare sulfoxides **5**, **6** and **7** with 95%, 96% and >99% de, respectively, in satisfactory yields (Table 1, entries 1, 4 and 5). Their (R_S) absolute configuration was later inferred from the (*S*)-configuration of the sulfoxides produced in the reaction with *n*-butyllithium and *tert*-butyllithium (Table 3) on the basis of the assumption that the nucleophilic substitution at the sulfinyl sulfur occurs with inversion of configuration.

On the other hand, the catalytic asymmetric oxidation of prochiral sulfides using vanadium/chiral salen complexes and aqueous hydrogen peroxide as the oxidant, applied by Bolm and Bienewald,[14] and further modified by others[15,16] appeared to be a more rewarding approach.

Table 1. Oxidation of sulfides **2**–**4** using the Kagan methodology[a]

Reaction conditions					Product		
Entry	Sulfide	Oxidant (equiv)	Solvent	Temperature (°C)	Sulfoxide	*Y* (%)	De (%)[b/c]
1	**2**	CHP (1.3)	CH_2Cl_2	−23	**5**	70	96
2	**3**	*t*-BuOOH (1.2)	CH_2Cl_2	−23	**6**	98	51
3	**3**	CHP (1.3)	CCl_4	−18 → −22	**6**	35	71
4	**3**	CHP (1.3)	CH_2Cl_2	−23	**6**	98	95
5	**4**	CHP (1.3)	CH_2Cl_2	−23	**7**	66	>99

[a] Reagent ratio: L-(+)-DET–Ti(O-*i*-Pr)$_4$–H_2O = 1:2:0.5.[12,13]
[b] Determined by HPLC (Chiralcel OD-H column).
[c] (R_S)-configuration inferred from the (*S*)-configuration of *n*-butyl methyl and *tert*-butyl methyl sulfoxides prepared (see Table 3).

Table 2. Catalytic oxidation of sulfides **2**–**4** using VO(acac)$_2$/Schiff base/30% H_2O_2 oxidation system[a,b]

Entry	Sulfide	Reaction conditions			Sulfoxides			
		Schiff base	H_2O_2 (equiv)	Time (h)	No.	*Y* (%)	De[c] (%)	Conf.[c,d] at sulfur
1	**2**[e]	**9**	10	48	**5**	10	14	
2	**3**	**9**	1.15	24	**6**	73	52	(*R*)
3	**3**	**13**	1.4	2.5	**6**	70	55	(*S*)
4	**3**	**10**	1.5	24	**6**	58	22	(*R*)
5	**3**	**11**	6.5	48	**6**	38	0	
6	**3**	**12**	3.9	48	**6**	43	30	(*S*)
7	**3**	**14**	1.4	23	**6**	45	41	(*S*)
8	**3**	**15**	1.4	23	**6**	67	62	(*S*)
9	**4**	**13**	1.4	4	**7**	55	63	
10	**4**	**15**[f]	1.2	25	**7**	63	82	(*S*)
11	**4**	**15**[g]	1.5	33	**7**	74	99	(*S*)

[a] Reagent ratio: VO(acac)$_2$–Schiff base–CH_2Cl_2 = 1 mol %:1.5 mol %:4 mL.
[b] At 0 °C.
[c] Determined by HPLC (Chiralcel OD-H column).
[d] Configuration at sulfur of the major diastereomer.
[e] At 0 °C → rt due to solubility problems.
[f] 0.8 mol %.
[g] 1.3 mol %.

Table 3. Reaction of sulfoxide (R_S)-**6** with butyllithium reagents[a]

Entry	Butyllithium	Butyl methyl sulfoxides	Y[b] (%)	Ee[c] (%)	$[\alpha]_D^{20}$/conf.
1	*n*-BuLi	*n*-Bu–S(O)–CH_3	52	92	+95.1 (*S*) (*c* 0.65, acetone)
2	*t*-BuLi	*t*-Bu–S(O)–CH_3	47	99	+17.3 (*S*) (*c* 0.33, MeOH)
3	*sec*-BuLi	*sec*-Bu–S(O)–CH_3[d]	50	99	—

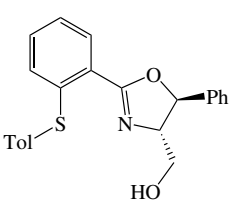
[a] Reaction conditions: **6**–BuLi = 1:3, THF, −76 °C.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR with DNBA as the chiral solvating agent.
[d] Diastereomeric ratio 1:1.

Thus, several chiral Schiff bases, **9**–**15**[15,17,18] (Fig. 1) were synthesized, using readily available chiral aminoalcohols, and screened in vanadium-catalyzed oxidation of sulfides **2**–**4** with hydrogen peroxide (Table 2).

The complex prepared in situ by reacting $VO(acac)_2$ with Schiff base **15**,[15] prepared from 3,5-diiodosalicylaldehyde and (*S*)-*tert*-leucinol was found to be the most efficient catalytic system (Table 2, entries 8, 10, 11), leading to diastereomers with the (S_S)-configuration opposite to that produced according to the Kagan et al.[12] procedure. In this way (S_S) sulfoxides **6** and **7** were prepared with 62% and >99% de, respectively, yet in moderate yield because of overoxidation to sulfones **16** and **17** often taking place before sulfoxidation was completed. Therefore, the reaction was quenched when either the sulfide was consumed or when no more sulfoxide was produced after the addition of another aliquot of H_2O_2 and/or over oxidation to sulfones **16** and **17** became a dominating process.

Sulfoxides (R)$_S$-**6**, (R)$_S$-**7** and (S)$_S$-**7**, obtained in pure form by chromatographic separation, were then subjected to the reaction with excess (3 equiv)[19] butyllithium reagents in THF solution or in suspension. Unfortunately, both diastereomeric sulfoxides **7**, obtained with the highest enantiomeric purity and in the crystalline form, afforded nonseparable mixtures of products, in which 4-methyloxazole (ca. 30%), formed apparently by the elimination–aromatization process, could be detected (^{1}H NMR). Satisfying results were obtained with sulfoxide (R_S)-**6**, whose reaction with each of the reagents: *n*-butyl-, *tert*-butyl- and *sec*-butyllithium, produced the corresponding butyl methyl sulfoxides with practically no loss of enantiomeric purity, yet in moderate yield (Table 3). In the reaction in which *sec*-butyllithium was used two enantiopure diastereomers in a 1:1 ratio were formed. The enantiomeric purity of the butyl methyl sulfoxides prepared, was determined by ^{1}H MNR spectra, recorded in the presence of the chiral solvating agent, (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)(1-phenylethyl)amine (DNBA). The absolute (*S*)-configuration of both *n*-butyl methyl sulfoxide and *tert*-butyl methyl sulfoxide was assigned on the basis of the positive sign of the specific rotation.[20,21]

The synthesis of *n*-butyl methyl sulfoxides by exchanging carbanionic groups at sulfur in chiral sulfoxides had been performed earlier. Johnson et al.[20] obtained (*R*)-(−)-*n*-butyl methyl sulfoxide and its (*S*)-(+)-enantiomer in satisfactory yield (ca. 80%) from (*S*)-(−)-methyl phenyl sulfoxide and (*R*)-(+)-methyl *p*-tolyl sulfoxide, respectively, on treatment with *n*-butyllithium. However, Naso et al.[21] by treating methyl phenyl sulfoxide with Grignard reagents obtained a mixture of products, while at the same time, under the action of long-chain



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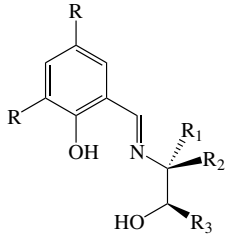
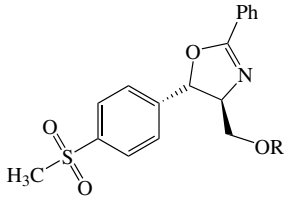


	R	R_1	R_2	R_3
9[17]	H	Bn	H	H
10	I	Bn	H	H
11[17]	*t*Bu	Bn	H	H
12	H	H	H	CH_3
13[17]	H	H	Bn	H
14[18]	H	*t*Bu	H	H
15[15]	I	*t*Bu	H	H



16 R = CH_3
17 R = Ts

Figure 1.

alkyl Grignard reagents, methoxy- and halo-phenyl methyl sulfoxides gave exchange products in satisfactory yield and with high enantioselectivity.

(*R*)-(−)-*tert*-Butyl methyl sulfoxide of high enantiomeric purity was prepared by Naso et al.[22] by exchanging the methylphosphonate substituent in (*R*)-(+)-dimethyl-(methylsulfinyl)methylphosphonate with a *tert*-butyl group.

The absolute (S_S)-configuration of the levorotatory diastereomeric sulfoxide **7**, can be postulated on the basis of the negative sign of the specific rotation of small samples of *n*-butyl- and *tert*-butyl methyl sulfoxides isolated by fractional extraction (methylene chloride) from the product mixture of reactions in which the levorotatory diastereomer **7** was treated with *n*-butyl- and *tert*-butyllithium reagents, respectively.

3. Conclusion

Enantiomerically pure sulfoxides **5**–**7** have been prepared from (+)-thiomicamine **1**, an industrial waste product, via oxazolines **2**–**4**. Stereoselective oxidation of **2**–**4** by the Kagan procedure with L-(+)-DET/Ti(O-*i*-Pr)$_4$/H_2O/CHP (1:2:0.5:1.3)[13,14] afforded (R_S)-isomers while the catalytic asymmetric oxidation with vanadium/chiral salen complexes (VO(acac)$_2$/**15**/H_2O_2)[17] led to the (S_S)-sulfoxides. The ability of sulfoxide (R_S)-**6** to act as a chiral methylsulfinyl group transfer agent was tested in the reaction with butyllithium reagents involving exchange of carbanionic group at stereogenic sulfur. In this way *n*-butyl methyl, *tert*-butyl methyl and diastereomeric *sec*-butyl methyl sulfoxides were prepared in high ee and moderate yield in a short synthesis involving simple procedures and commercially available substrates. Herein we present another example of usefulness of the 'carbanionic leaving group' strategy[4] for the synthesis of chiral nonracemic dialkyl sulfoxides.

4. Experimental

4.1. General

Melting points were determined on a Koffler block and are not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV, and FAB, *m*-nitrobenzylalcohol as the matrix. Optical rotations: Perkin–Elmer polarimeter 243B at 20 °C. Analytical HPLC: Waters HPLC system with Mallinkrodt–Baker Chiralcel OD-H column. Merck DC-Alufolien Kieselgel 60_{254} were used for TLC. (+)-Thiomicamine was purchased from the Aldrich Chemical Co and used as received.

4.2. Synthesis of Schiff bases

4.2.1. (*R*)-[(3,5-Diiodo)-2-hydroxybenzylidene]-1-hydroxy-3-phenylisopropylamine 10. A mixture of 3,5-diiodosalicylaldehyde (1.12 g, 3 mmol) and (*R*)-phenylalaninol (0.45 g, 3 mmol) in methanol (3 mL) was heated under reflux for 1 h. After evaporation of the solvent, the residue was digested with *n*-hexane to give a yellow crystalline solid (0.73 g, 48%); mp 61–64 °C, $[\alpha]_D$ = +217.5 (*c* 0.50, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1633. ^{1}H NMR ($CDCl_3/D_2O$): δ 2.84 (dd, *J* = 8.7, 13.7 Hz, 1H, PhC*H*H), 3.00 (dd, *J* = 4.8, 13.7 Hz, 1H, PhCH*H*), 3.56–3.64 (m, 1H, C=NCH), 3.72 (dd, *J* = 7.9, 11.3 Hz, 1H, C*H*HOH), 3.86 (dd, *J* = 3.6, 11.3 Hz, 1H, CH*H*OH), 7.10–7.33 (m, 6H, ArH), 7.78 (s, 1H, N=CH), 7.99 (d, *J* = 2.0 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 38.59 (CH_2), 65.43 (CH_2), 71.38 (CH), 77.94 (C), 89.55 (C), 118.50 (C), 126.75 (CH), 128.60 (2CH), 129.20 (2CH), 136.82 (C), 140.12 (CH), 148.98 (CH), 162.83 (C), 163.83 (CH). EI MS *m*/*z* (%): 508 (M^++1, 26), 507 (M^+, 100), 416 (86), 359 (54), 91 (53), 77 (10), 65 (14). HRMS (M^+) calcd for $C_{16}H_{15}I_2NO_2$: 506.91922. Found: 506.91775.

4.2.2. (*R*)-2-Hydroxybenzylidene-2-hydroxy-1-propylamine 12. A mixture of salicylaldehyde (0.5 mL, 5 mmol) and (*R*)-1-amino-2-propanol (0.39 mL, 5 mmol) in toluene (50 mL) were heated under reflux for 2.5 h using a Dean–Stark water trap. The solution was then concentrated and the yellow oil was separated and digested with *n*-hexane to give a yellow solid; mp 83–86 °C, $[\alpha]_D$ = −31.3 (*c* 0.51, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1642. ^{1}H NMR ($CDCl_3$): δ 1.13 (d, *J* = 6.3 Hz, 3H, CH_3), 3.49 (ddd, *J* = 1.1, 7.1, 12.1 Hz, 1H, C=NC*H*H), 3.73 (ddd, *J* = 1.4, 3.8, 12.1 Hz, 1H, C=NCH*H*), 4.13 (m, 1H, CHOH), 6.86–6.98 (m, 2H, ArH), 7.26–7.35 (m, 2H, ArH), 8.38 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$): δ 20.20 (CH_3), 67.08 (CH_2), 67.33 (CH), 116.95 (CH), 118.56 (C), 118.59 (CH), 131.35 (CH), 132.36 (CH), 160.96 (C), 166.69 (CH). EI MS *m*/*z* (%): 179 (M^+, 61), 134 (100), 107 (71), 77 (16). HRMS (M^+) calcd for $C_{10}H_{13}NO_2$: 179.09464. Found: 179.09379.

4.3. Oxidation of sulfides 2–4 using the Kagan et al.[12,13] oxidizing system

4.3.1. General procedure. Titanium(IV) isopropoxide (1 mmol) and (*R*)-(+)-DET (2 mmol) in methylene chloride (5 mL) were stirred for 2 min at rt and then water (0.5 mmol) was added. After stirring for 20 min at rt and for 30 min at −23 °C, the sulfide (1 mmol) in methylene chloride (10 mL) was added followed by CHP (1.3 mmol) and stirring continued for 24 h at −23 °C. Water (ca. 25 mL) was then added, the mixture filtered through a pad of Celite® then the phases were separated. The organic phase was washed twice with brine, dried and the solvent evaporated. The crude reaction product was purified by column chromatography over silica gel.

4.3.2. (4*S*,5*S*,R_S)-4-Hydroxymethyl-5-(4-methylsulfinylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole 5. Yield: 70% (64% after crystallization from methanol); mp 203–205 °C; de: 96%; $[\alpha]_D$ = +173.1 (*c* 0.60, CH_2Cl_2); $[\alpha]_D$ = +196.3 (*c* 0.40, methanol); IR (KBr), *v* (cm^{-1}): 1650, 1056. ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 1H, disappears

on treatment with D_2O, OH), 2.74 (s, 3H, SCH_3), 3.94 (dABq, $J = 4.1$, 11.5 Hz, 2H, CH_2OH), 4.26 (td, $J = 4.1$, 8.0 Hz, 1H, CHN), 5.60 (d, $J = 7.4$ Hz, 1H, ArCH), 7.46–7.69 (m, 7H, ArH), 8.02 (d, $J = 7.1$ Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 44.01 (CH_3S), 63.53 (CH_2OH), 76.93 (CHN), 82.06 (ArCH), 124.03, 126.49, 128.34, 131.76 (CH), 126.68, 143.81, 145.61 (C), 164.55 (C=N). EI MS *m/z* (%): 315 (M^+, 7), 284 (100), 181 (20), 147 (24), 130 (28), 105 (28), 77 (27). HRMS (M^+) calcd for $C_{17}H_{17}NO_3S$: 315.09293. Found: 315.09160.

4.3.3. (4*S*,5*S*,R_S)-4-Methoxymethyl-5-(4-methylsulfinylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole 6. Yield: 98%; Oil; De 95%; $[\alpha]_D = +145.9$ (*c* 1.05, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1650, 1058. ^1H NMR ($CDCl_3$): δ 2.73 (s, 3H, SCH_3), 3.46 (s, 3H, OCH_3), 3.60 (dd, $J = 7.1$, 9.6 Hz, 1H, C*H*HO), 3.80 (dd, $J = 4.4$, 9.6 Hz, 1H, CH*H*O), 4.32 (ddd, $J = 4.4$, 6.9, 7.1 Hz, 1H, CHN), 5.57 (d, $J = 6.9$ Hz, 1H, ArCH), 7.43–7.55 (m, 5H, ArH), 7.67 (d, $J = 8.2$ Hz, 2H, ArH), 8.05 (d, $J = 8.5$ Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 43.97 (CH_3S), 59.38 (CH_3O), 74.36 (CH_2O), 75.05 (CHN), 83.08 (CHAr), 123.98, 126.40, 128.44, 128.46, 131.75 (CH), 127.17, 144.32, (C), 163.99 (C=N). EI MS *m/z* (%): 329 (M^+, 7), 284 (100), 181 (48), 130 (58), 105 (46), 77 (53). HRMS (M^+) calcd for $C_{18}H_{19}NO_3S$: 329.10855. Found: 329.10745.

4.3.4. (4*S*,5*S*)-4-Methoxymethyl-5-(4-methylsulfonylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole 16. Yield: various; Oil. $[\alpha]_D = +118.8$ (*c* 0.89, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1652. ^1H NMR ($CDCl_3$): δ 3.05 (s, 3H, SCH_3), 3.46 (s, 3H, OCH_3), 3.58 (dd, $J = 7.4$, 9.3 Hz, 1H, C*H*HO), 3.81 (dd, $J = 4.3$, 9.6 Hz, 1H, CH*H*O), 4.30 (ddd, $J = 4.4$, 6.8, 7.4 Hz, 1H, CHN), 5.61 (d, $J = 6.6$ Hz, 1H, ArCH), 7.43–7.59 (m, 5H, ArH), 7.95 (d, $J = 8.5$ Hz, 2H, ArH), 8.04 (d, $J = 8.5$ Hz, 2H, ArH). EI MS *m/z* (%): 345 (M^+, 3), 300 (100), 130 (38), 118 (35), 105 (43), 77 (42). Anal. Calcd for $C_{18}H_{19}NO_4S \cdot 1/3H_2O$: C, 61.52; H, 5.45; N, 3.99; S, 9.12. Found: C, 61.46; H, 5.46; N, 3.96; S, 9.14.

4.3.5. (4*S*,5*S*,R_S)-4-Tosyloxymethyl-5-(4-methylsulfinylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (R_S)-7. Yield: 66%; mp 100–102 °C; $[\alpha]_D = +127.4$ (*c* 0.79, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1646, 1059. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3Ar), 2.73 (s, 3H, SCH_3), 4.15–4.23 (m, 1H, CHN), 4.31–4.41 (m, 2H, CH_2OTs), 5.58 (d, $J = 6.0$ Hz, 1H, CHAr), 7.31–7.34 (m, 2H, ArH), 7.42–7.49 (m, 4H, ArH), 7.52–7.58 (m, 1H, ArH), 7.64–7.68 (m, 2H, ArH), 7.77–7.80 (m, 2H, ArH), 7.94–7.98 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 21.74 (CH_3Ar) 43.99 (CH_3S), 70.20 (CH_2OTs), 73.76 (CHN), 82.49 (CHAr), 124.09, 126.32, 127.87, 128.44, 129.87, 132.06 (CH), 126.47, 132.34, 142.99, 145.109, 145.90 (C), 164.99 (C=N). EI MS *m/z* (%): 469 (M^+, 0.2), 453 (1), 297 (79), 284 (9) 282 (100), 172 (46), 130 (6), 105 (48), 91 (34), 77 (20). Anal. Calcd for $C_{24}H_{23}NO_5S_2 \cdot H_2O$: C, 59.12; H, 5.17; N, 2.87; S, 13.12. Found: C, 59.42; H, 5.06; N, 2.86; S, 13.56.

4.4. Catalytic asymmetric oxidation of sulfides 2–4

4.4.1. General procedure. A solution of the Schiff base (0.015 mmol) and VO-(acac)$_2$ (2.6 mg, 0.01 mmol) in methylene chloride (2 mL) was stirred at rt for 30 min, then the sulfide (1 mmol) in methylene chloride (2 mL) was introduced and the mixture stirred at rt for another 30 min. The mixture was cooled to 0 °C and 30% hydrogen peroxide (in amounts specified in the Table 2) was added dropwise and stirring continued at 0 °C until no more starting material was present or no more sulfoxide could be produced (TLC, 2.5–48 h, Table 2). Water was then added and the phases separated, the aqueous one was extracted additionally with methylene chloride. The combined organic extracts were washed with brine, dried and the solvent evaporated. The yield and enantiomeric purity was evaluated by HPLC of the crude reaction product (Table 2), using Chiralcel OD-H column and 20% v/v isopropanol in hexane, flow 0.5 mL/min, 224 nm; retention time: 26 min for (R_S) diastereomer, 28 min for (S_S) diastereomer and 40 min for sulfone **17**.

4.4.2. (4*S*,5*S*,S_S)-4-Tosyloxymethyl-5-(4-methylsulfinylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole (S_S)-7. Yield: 74%; mp 77–80 °C (from 96% ethanol) after column chromatography separation; $[\alpha]_D = -280.0$ (*c* 0.79, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1646, 1059. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3Ts), 2.73 (s, 3H, SCH_3), 4.15–4.23 (m, 1H, CHN), 4.32–4.41 (m, 2H, CH_2OTs), 5.59 (d, $J = 6.3$ Hz, 1H, CHAr), 7.31–7.34 (m, 2H, ArH), 7.43–7.49 (m, 4H, ArH), 7.53–7.58 (m, 1H, ArH), 7.64–7.68 (m, 2H, ArH), 7.77–7.81 (m, 2H, ArH), 7.95–7.98 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 21.65 (CH_3Ar) 43.92 (CH_3S), 70.18 (CH_2OTs), 73.72 (CHN), 82.46 (CHAr), 124.17, 126.37, 127.96, 128.52, 128.53, 129.97, 132.17 (CH), 126.52, 132.38, 143.09, 145.24, 145.94 (C), 165.17 (C=N). EI MS *m/z* (%): 469 (M^+, 0.2), 453 (1), 297 (79), 284 (9) 282 (100), 172 (46), 130 (6), 105 (48), 91 (34), 77 (20). Anal. Calcd for $C_{24}H_{23}NO_5S_2H_2O$: C, 59.12; H, 5.17; N, 2.87; S, 13.12. Found: C, 59.42; H, 5.06; N, 2.86; S, 13.56.

4.4.3. (4*S*,5*S*)-4-Tosyloxymethyl-5-(4-methylsulfonylphenyl)-2-phenyl-4,5-dihydro-1,3-oxazole 17. Yield: 29%; mp 111–114 °C; (from 96% ethanol) after column chromatography separation $[\alpha]_D = +423.9$ (*c* 1.1, CH_2Cl_2). IR (KBr), *v* (cm^{-1}): 1650. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, $ArCH_3$), 3.06 (s, 3H, $ArSO_2CH_3$), 4.18 (dd, $J = 9.9$, 7.1 Hz, C*H*HOTs), 4.30–4.36 (m, 1H, CHN), 4.40 (dd, $J = 9.9$, 3.8 Hz, CH*H*OTs), 5.63 (d, $J = 6.3$ Hz, 1H, ArCH), 7.33 (d, $J = 8.00$ Hz, 2H, ArH), 7.43–9.98 (3m, 11H, ArH). EI MS *m/z* (%): 485 (M^+, 0.2), 313 (100), 299 (50), 284 (2), 130 (42), 105 (91), 91 (34), 77 (22). Anal. Calcd for $C_{24}H_{23}NO_6S_2 \cdot 1/2H_2O$: C, 58.28; H, 4.89; N, 2.83; S, 12.94. Found: C, 57.96; H, 4.76; N, 2.82; S, 13.27.

4.5. Reaction of sulfoxides 6 and 7 with butyllithium reagents

4.5.1. General procedure. Sulfoxide (R_S)-**6** (1 mmol) in freshly distilled THF was cooled to −70 °C under an argon atmosphere. Butyllithium reagent (*n*-butyllithium:

1.6 mol in hexane, *t*-butyllithium: 1.7 mol in pentane and *sec*-butyllithium: 1.4 mol in cyclohexane) (3 mmol) was then added and the mixture stirred at −70 °C for 1.5 h; during that time the initially formed green colour of the solution turned red brown. The reaction was quenched by addition of 20% NH_4Cl (25 mL) and the phases separated. The aqueous phase was extracted with ethyl ether and then three times with methylene chloride. The combined ethereal extracts were shown (HPLC) to contain mainly unreacted starting material and desulfinylated oxazoline, while in methylene chloride the sulfoxide synthesized was present.

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