Polish J. Chem., **77**, 1703–1710 (2003)

Enantioselective Oxidation of Methyl *p*-Tolyl Sulfide Catalyzed by Chiral Schiff Base-Vanadium Complexes*

by A. Głuszyńska, K. Krajewska and M.D. Rozwadowska**

Faculty of Chemistry, A. Mickiewicz University, ul. Grunwaldzka 6, 60-780 Poznań, Poland

(Received June 16th, 2003; revised manuscript July 10th, 2003)

Oxidation of methyl *p*-tolyl sulfide with hydrogen peroxide catalyzed by VO(acac)$_2$ – Schiff base **12** complex afforded *R*-(+)-methyl *p*-tolyl sulfoxide in high yield and with 43% *e.e.* Recrystallization of the product from ethyl ether/hexane resulted in the sulfoxide enantiomerically enriched up to 99.7% [m.p. 71–74°C; $[\alpha]_D$ +144.6° (c = 2.02, acetone)].

Key words: catalytic enantioselective S-oxidation, chiral sulfoxide, Schiff bases-vanadium complexes

The utility of chiral non-racemic sulfoxides in asymmetric synthesis has been well documented [1]. Several methodologies for their preparation have been developed [2]; among them, the enantioselective oxidation of prochiral sulfides has been one of the most attractive method, resulting in sulfoxides with high enantiomeric purity. In this respect, catalytic asymmetric oxidation mediated by metal complexes with chiral ligands has become one of the most effective methods, being alternative to the well known version of the Sharpless epoxidation procedure, modified by Kagan [3] and Modena [4]. In particular, complexes of vanadium and chiral Schiff bases derived from salicylaldehydes and aminoalcohols (salen-ligands) have been applied with success.

In an earlier investigation carried out by Fujita *et al.* [5] of TBH-oxidation of methyl phenyl sulfide, catalyzed by a tridentate complexes of oxo-vanadium(V) with N-salicylidene L-aminocarboxylates **1**, *R*-methyl phenyl sulfoxide was obtained with only 8–14% *e.e.* Later [6] the selectivity was improved to 40% *e.e.* when type **2** catalysts were used (Fig. 1).

Using 30% H_2O_2 and carrying the reaction in the presence of catalysts (1 mol%) formed *in situ* from (1:1) *bis*(acetylacetonato)oxovanadium [VO(acac)$_2$] and Schiff bases **3**, derived from *S*-*tert*-leucinol and 3,5-disubstituted salicylaldehyde, Bolm and Bienewald [7] obtained alkyl-aryl sulfoxides with *e.e.* values between 50 and 70%. They have noticed that large substituents (R = *tert*-butyl) and a 5-nitro group significantly increased the enantioselectivity of the oxidation. Since that time, in most

---

* Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.
**Author for correspondence.

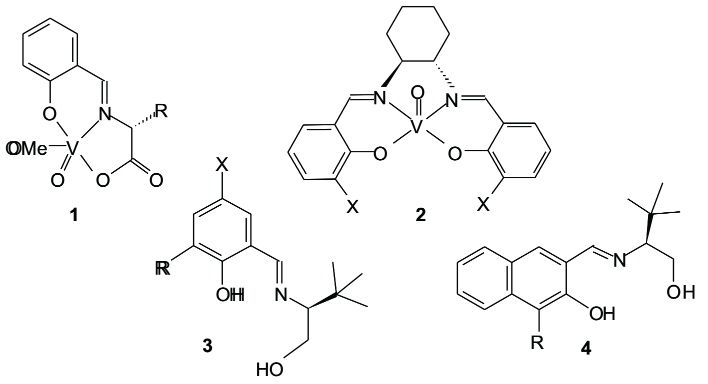


Figure 1.

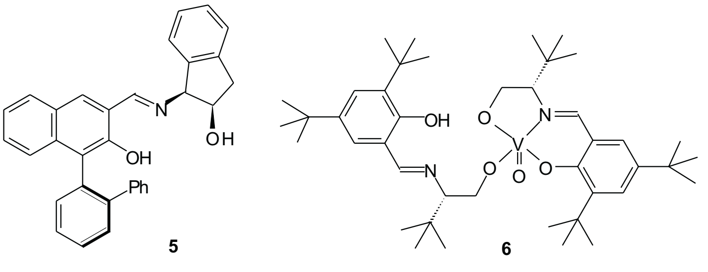
of the sulfoxidation experiments catalyzed by vanadium, hydrogen peroxide has been used as the environmentally benign oxidation agent and tridentate Schiff base of type **3** as the ligand.

Introduction of an additional element of chirality into the aldehyde component of the Schiff base, *e.g.* as 1,2-binaphthyl **4** (R = α-naphthyl), allowed Vetter and Berkessel [8] to reach *e.e.* values up to 78% in the oxidation of tioanisole. This approach was further evolved by Katsuki *et al.* [9] and extended to ligands prepared from axially chiral *o*-hydroxyaldehydes with biphenyl-naphthyl structure, particularly efficient when coupled with *S*-*tert*-leucinol (**4**, R = *o*-biphenyl) and 1*S*,2*R*-1-amino-2-indol, **5**. The best results (86–88% *e.e.*) were reached in oxidation of methyl phenyl sulfide, with these two Schiff bases in the reaction run in methylene chloride, at 0°C.

Two series of solid supported chiral salicylaldimines, which differed in substituents either in the imine side chain or aldehyde component, have been synthesized by Anson and co-workers [10] and tested in vanadium-catalyzed asymmetric oxidation of thioanisole and related alkyl aryl sulfides. The earlier observation that the selectivity of the reaction increased with increasing steric hindrance was found to apply only to the amine part of the Schiff bases and not to the influence of substituents on the aldehyde aromatic ring. As a result of systematic screening, they have established that the best enentioselectivity (90%) achieved so far in vanadium catalyzed oxidation of the model tioanisole to the corresponding *S*-oxide involved the Schiff base incorporating 3,5-diiodosalicylaldehyde and *S*-*tert*-leucine (**3**, R = X = I).

It has been observed that as a result of the chirality transfer from the chiral complex to the sulfur atom, usually the configuration at the sulfur is the same as that of the stereogenic center α- to the amine nitrogen of the ligand. The possibility of obtaining any of the enentiomeric sulfoxides by using ligands of an appropriate configuration has been demonstrated by Skarżewski *et al.* [11]. Applying Schiff bases prepared from 3-phenyl-5-nitrosalicylaldehyde and both enantiomers, D- and L-valinol, they have synthesized with satisfactory enantiomeric excess, *S*-methyl phenyl sulfoxide using ligands derived from L-valinol, and *R*-sulfoxide with the use of the enantiomer.

Recently, the mechanism of the sulfoxidation catalyzed by VO(acac)$_2$ and chiral salicylaldimine **3** (R = X = *tert*-butyl), using hydrogen peroxide as the oxidizing agent, has been investigated by a Californian group of reserchers [12]. They have isolated a crystalline 2:1 ligand to vanadium complex **6**, which used (2.5 mol%) in oxidation (H_2O_2 in $CHCl_3$) of di-*tert*-butyldisulfide, resulted in the formation of (*R*)-di-*tert*-butyl monosulfoxide in high yield and with 89% *e.e.*



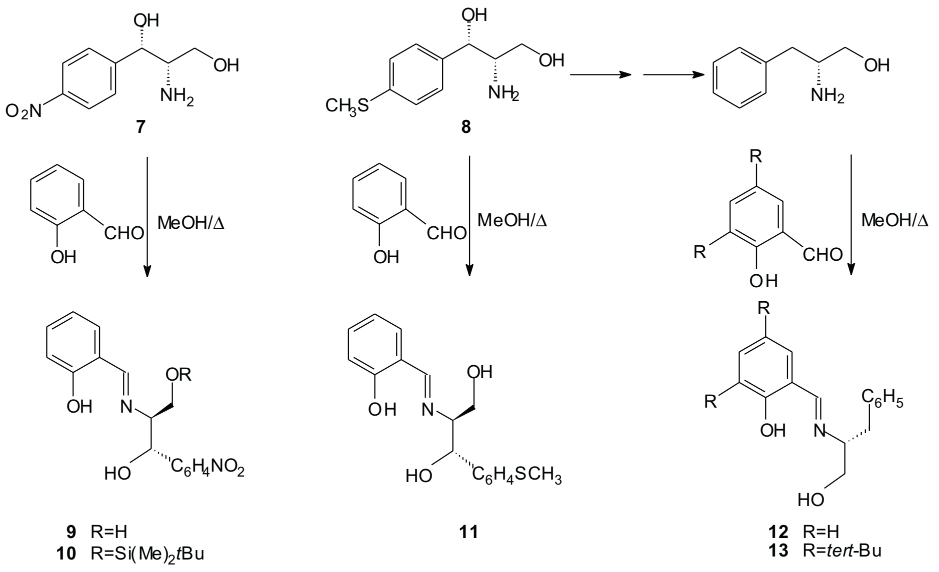
5 **6**

Figure 2.

RESULTS AND DISCUSSION

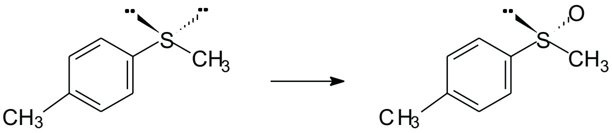
As a part of our investigation on transformation of (1*S*,2*S*)-1-aryl-2-amino-1,3-propanediols (**7** and **8**), industrial waste products, into compounds useful in organic synthesis [13,14], we have undertaken experiments to use the aminodiols for the synthesis of salen-type chiral ligands and examine their effectiveness in vanadium-catalyzed oxidation of sulfides to sulfoxides. Thus, five selected Schiff bases **9**–**13** were synthesized in satisfactory yield by coupling the corresponding aminoalcohols with salicylaldehydes, carried out in methanol at reflux (Scheme 1).

Scheme 1



Schiff bases **9** and **11** were prepared in high yield from aminodiols **7** and **8** and salicylaldehyde, respectively; imine **10**, by treatment of **9** with one molar equivalent of TBDMSiCl in DMF at –20°C, to selectively silylate the primary hydroxyl group. For preparation of benzaldimines **12** and **13**, *R*-phenylalaninol, obtained from (+)-thiomicamine (**8**) [14], was treated with salicylaldehyde and 3,5-di-*tert*-butylsalicylaldehyde, respectively. Complexes prepared *in situ* from VO(acac)$_2$ and the ligands **9–13** were used in amounts of 1.5 mol% to catalyze the oxidation of methyl *p*-tolyl sulfide to the corresponding sulfoxide (Scheme 2):

Scheme 2



This sulfide was chosen as a model compound in our experiments because its oxidation product, being a crystalline compound, could be purified and hopefully enentiomerically enriched by crystallization [15]. Indeed, it was the case.

Several factors that might influence the steric outcome of the oxidation, such as the structure of the ligand, type of solvent, reaction temperature and type of the oxidizing agent, were studied. The results of selected experiments are presented in Tables 1–4.

Table 1. Oxidation of methyl *p*-tolyl sulfide using ligands **9–13**[a].

Entry	Ligand[b]	Y [%]	*e.e.* [%][c]	abs. conf.[d]
1	**9**	11	24	(*R*)
2	**10**	82	21	(*S*)
3	**11**	65	15	(*R*)
4	**12**	97 **(39)**	43 **(100)**[e]	(*R*)
5	**13**	56	35	(*R*)

[a]Reaction conditions: CH$_2$Cl$_2$, 1.2 eq. 30% H$_2$O$_2$, 0°C, 23 h; [b]1.5 mol%; [c]determined by HPLC using CHIRALCEL OD-H column; [d]based on the sign of specific rotation; [e]after recrystallization from ethyl ether/hexane.

It was found (Table 1) that the best enentioselectivity (43%) and chemical yield (97%) were achieved when the catalyst was formed with the Schiff base **12** (Table 1, entry 4). Lower selectivity was observed when ligands **9–11**, with an additional chiral substituent in the amine fragment were applied (Table 1, entries 1–3) as was also the case for **13**, with *tert*-butyl groups at the aldehyde part (Table 1, entry 5). In most of the experiments the dextrarotatory sulfoxide was produced, for which (*R)* configuration was established [16]. In this respect it was interesting to find that in reaction with

10, carrying the bulky silyl group, sulfoxide of opposite (*S*) configuration was obtained in 80% yield but in only 21% *e.e.* (Table 1, entry 2).

Table 2. Oxidation of methyl *p*-tolyl sulfide catalyzed by vanadium complex with Schiff base **12** (1.5 mol%); the solvent effect[a].

Entry	Solvent	Y [%]	*e.e.* [%][b]
1	Toluen	48	34
2	CCl_4	47	12
3	CH_2Cl_2/CCl_4 (3:7)	61	31
4	CH_2Cl_2	65	37

[a]Reaction conditions: CH_2Cl_2, 1.2 eq. 30% H_2O_2, r.t., 23 h; [b]established by HPLC using CHIRALCEL OD-H column.

Among the solvents used, methylene chloride was found to be the solvent of choice (Table 2), while the temperature applied, 0°C and r.t., did not effect significantly this process carried out in a biphasic system composed of methylene chloride/water solutions (Table 3).

Table 3. Oxidation of methyl *p*-tolyl sulfide at r.t. and °C[a].

Entry	Ligand[b]	T [°C]	Y [%]	*e.e.* [%][c]
1	**10**	r.t.	90	22
2	**10**	0	82	21
3	**11**	r.t.	69	16
4	**11**	0	65	15
5	**12**	r.t.	65	37
6	**12**	0	**97**	**43**
7	**13**	r.t.	66	33
8	**13**	0	56	35

[a]Reaction conditions: CH_2Cl_2, 1.2 eq. 30% H_2O_2, 23 h; [b]1.5 mol%; [c]determined by HPLC using CHIRALCEL OD-H column.

Our experiments confirmed that 30% hydrogen peroxide was the most efficient oxidizing agent, while the aqueous *tert*-butylhydroperoxide and cumylhydroperoxide led to formation of practically racemic sulfoxide (Table 4).

According to our experiments, the optimal reaction condition for oxidation of methyl *p*-tolyl sulfide involve: catalyst formed *in situ* from $VO(acac)_2$ and Schiff base **12** (1.5 mol%), methylene chloride as the solvent, 1.2 eq. of 30% hydrogen peroxide as the oxidizing agent and 0°C as the reaction temperature.

Table 4. Oxidation of methyl *p*-tolyl sulfide catalyzed by vanadium complex with Schiff base **12** (1.5 mol%) with various oxidizing agents[a].

Entry	Oxidant (eq.)	Y [%]	*e.e.* [%][b]
1	30% H_2O_2 (1.2)	65	37
2	30% H_2O_2 (2.4)	45	45
4	3% H_2O_2 (1.2)	97	40
6	aq. 70% TBHP (1.5)	97	0
7	aq. 30% CHP (1.3)	70	3
8	20% $KHCO_3/Br_2$	95	0

[a]Reaction conditions: CH_2Cl_2, r.t., 23 h; [b]determined by HPLC using CHIRALCEL OD-H column.

Though, the degree of enantioselectivity in our experiments is not as high as that resulting from oxidation according to the Kagan catalytic system [17], yet, it is comparable to those obtained by others, *e.g.* [18]. It should be emphasized that we were able to obtain methyl *p*-tolyl sulfoxide with *e.e.* up to 99.7% [m.p. 71–74°C; $[\alpha]_D$ +144.6° (c = 2.02, acetone); HPLC 100% *e.e.*] by two recrystallizations of a sample showing 43% *e.e.* from ethyl/ether hexane, in a simple reaction, carried out in the presence of catalytic amounts of vanadium complexes using enviromentally benign hydrogen peroxide.

EXPERIMENTAL

General: Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin-Elmer 180 in KBr pellets and film. NMR spectra: Varian Gemini 300, in $CDCl_3$ and DMSO-d_6, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV. Specific rotation: Perkin-Elmer polarimeter 243B at 20°C. Merck DC-Alufolien Kieselgel 60_{254} was used for TLC. Analytical HPLC: Waters HPLC system with Mallinkrodt-Baker Chiralcel OD-H column. (+)-Thiomicamine and (1S,2S)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol were purchased from the Aldrich Chemical Co. and used as received.

1. Synthesis of ligands.

1.1. (1*S*,2*S*)-(2-Hydroxybenzylidene)-1,3-dihydroxy-1-(4-nitrophenyl)-isopropylamine 9. (1*S*,2*S*)-(+)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol **7** (2.12 g, 10 mmol) and salicylaldehyde (1.06 ml, 10 mmol) in methanol (10 ml) were heated at reflux for 2 h. After cooling to ambient temperature the yellow solid was filtered off, washed with hexane and dried to give 3.04 g (Y: 96%) of TLC-pure imine **9**. M.p. 173–176°C; $[\alpha]_D$ +178.3° (c = 0.51, MeOH). IR cm^{-1} (KBr): 3417, 3373 (OH), 1631 (C=N), 1521, 1347 (NO_2); ^1H NMR ($CDCl_3$+D_2O), δ (ppm): 8.29 (s, 1H, CH=N), 8.18–8.37 (m, 2H, ArH), 7.63–7.66 (m, 2H, ArH), 7.31–7.37 (m, 2H,ArH), 6.84–6.89 (m, 2H, ArH), 5.03 (d, J = 3.6 Hz, 1H, CHOHAr), 3.67–3.76 (m, 1H, CHN=C), 3.48–3.58 (m, 2H, CH_2OH); EIMS m/z (%): 316(M^+, 19), 164(100), 147(20), 134(15), 107(91), 91(11), 77(22), 51(12); HRMS: found 316.10515; calcd for $C_{16}H_{16}N_2O_5$: 316.10593.

1.2. (1*S*,2*S*)-3-[(*t*-Butyl)dimethylsilyloxy]-1-hydroxy-(2-hydroxybenzylidene)-1-(4-nitrophenyl)-isopropylamine 10. Mixture of imine **9** (2.71 g, 8.58 mmol), (*t*-Bu)Me_2SiCl (1.29 g, 8.58 mmol) and imidazole (1.17 g, 17.16 mmol) in DMF (8.58 ml) was stirred at –20°C for 72 h and next at r.t. for 1.5 h, then poured onto ice (56 g). After r.t. was reached the solid was filtered off and washed with hexane to afford 2.62 g (Y: 61%) imine **10**. An additional amount of the product was obtained from the filtrate by extraction with ethyl ether (0.4 g). Total yield 70%. M.p. 124–127°C; $[\alpha]_D$ –132.3° (c = 0.525, CH_2Cl_2). IR cm^{-1} (KBr): 3473, 3354 (OH), 2952 (CH), 1646 (C=N), 1517, 1350 (NO_2), 1234, 840 ($SiCH_3$); ^1H NMR ($CDCl_3$+D_2O), δ (ppm): 8.23 (s, 1H, CH=N), 8.19–8.22 (m, 2H, ArH), 7.55 (d, J = 8.05 Hz, 2H, ArH), 7.18–7.37 (m, 2H, ArH), 6.86–6.99 (m, 2H, ArH), 5.18 (d, J = 4.7 Hz, 1H, CHOHAr), 3.85 (dd, J = 10.4, 5.2 Hz, 1H, CHHOSi), 3.78 (dd, J = 10.4, 5.5 Hz, 1H, CHHOSi), 3.78 (ddd, J = 5.5, 5.2, 4.7 Hz, 1H, CHN=C), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); EIMS m/z (%): 430(M^+, 27), 373(100), 343(11), 325(11), 278(82), 179(59), 147(63), 132(20), 118(17), 105(24), 91(12), 73(99), 57(31); HRMS: found 430.19241; calcd for $C_{22}H_{30}N_2O_5Si$: 430.19377.

1.3. (1*S*,2*S*)-(2-Hydroxybenzylidene)-1,3-dihydroxy-1-(4-methylthiophenyl)-isopropylamine 11. (1*S*,2*S*)-(+)-2-Amino-1-(4-methylthiophenyl)-1,3-propanediol **8** (1.066 g, 5 mmol) and salicylaldehyde (0.5 ml, 5 mmol) in methanol (5 ml) were heated at reflux for 2 h. After cooling to ambient temperature the yellow solid was filtered off, washed with hexane and dried to give 1.41 g (Y: 89%) of TLC-pure imine **11**. M.p. 151–156°C; [α]D + 340.7° (c = 1.005, MeOH). IR cm^{-1} (KBr): 3287 (OH), 1640 (C=N); ^1H NMR ($DMSO+D_2O$), δ (ppm): 8.30 (s, 1H, CH=N), 7.19–7.38 (m, 6H, ArH), 6.83–6.88 (m, 2H, ArH), 3.55–3.63 (m, 1H, CHN=C), 3.41–3.49 (m, 2H, CH_2OH), 2.43 (s, 3H, SCH_3); EIMS m/z (%): 317(M^+, 9), 165(100), 153(42), 148(23), 134(15), 118(11), 107(44), 91(10), 77(19); HRMS: found 317.10713; calcd for $C_{17}H_{19}NO_3S$: 317.10855.

1.4. (2*R*)-(2-Hydroxybenzylidene)-1-hydroxy-3-phenyl-isopropylamine 12. The mixture of (*R*)-(+)-phenyloalaninol (0.79 g, 5.3 mmol) and salicylaldehyde (0.5 ml, 5.3 mmol) in methanol (5.3 ml) was refluxed for 2.5 h. After cooling to r.t. it was concentrated under reduced pressure to give crude yellow oil. After washing with hexane yellow solid was filtered off (Y: 84%). M.p. 64–66°C; $[\alpha]_D$ + 280.6° (c = 1.005, CH_2Cl_2). IR cm^{-1} (KBr): 3354 (OH), 1632 (C=N); ^1H NMR ($CDCl_3+D_2O$), δ (ppm): 8.10 (s, 1H, CH=N), 7.13–7.35 (m, 7H, ArH), 6.83–6.98 (m, 2H, ArH), 3.84 (dd, J = 11.3, 4.4 Hz, 1H, CHHOH), 3.78 (dd, J = 11.3, 7.7 Hz, 1H, CHHOH), 3.49–3.57 (m, 1H, CHN=C), 3.00 (dd, J = 13.5, 4.9 Hz, 1H, CHHPh), 2.87 (dd, J = 13.5, 8.5 Hz, 1H, CHHPh); EIMS m/z (%): 255(M^+, 59), 224(19), 207(6), 164(100), 134(10), 120(11), 107(61), 91(41), 77(16), 65(14), 51(10); HRMS: found 255.12658; calcd for $C_{16}H_{17}NO_2$: 255.12593.

1.5. (2*R*)-[(3,5-Di-*tert*-butyl)-2-hydroxybenzylidene)]-1-hydroxy-3-phenyl-isopropylamine 13. (*R*)-(+)-Phenyloalaninol (151 mg, 1 mmol) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (234 mg, 1 mmol) was stirred in methanol (1ml) at r.t. for 4 h. The solvent was evaporated to give TLC-pure oily imine **13** (0.32 g, Y: 87%). $[\alpha]_D$ + 179.9° (c = 1.025, CH_2Cl_2). IR cm^{-1} (film): 3370 (OH), 2957 (CH), 1630 (C=N); ^1H NMR ($CDCl_3+D_2O$), δ (ppm): 8.19 (s, 1H, CH=N), 7.39 (d, J = 2.5 Hz, 1H, ArH), 7.16–7.31 (m, 5H, ArH), 7.01 (d, J = 2.5 Hz, 1H, ArH), 3.72–3.81 (m, 2H, CH_2OH), 3.49–3.54 (m, 1H, CHN=C), 2.98 (dd, J = 13.5, 5.5 Hz, 1H, CHHPh), 2.89 (dd, J = 13.5, 8.0 Hz, 1H, CHHPh), 1.45 (s, 9H, $C(CH_3)_3$), 1.28 (s, 9H, $C(CH_3)_3$); EIMS m/z (%): 367(M^+, 100), 252(90), 324(32), 310(10), 276(24), 202(10), 91(87), 65(11), 57(37); HRMS: found 367.25211; calcd for $C_{24}H_{33}NO_2$: 367.25113.

2. Oxidation of methyl-*p*-tolyl sulfide catalyzed by vanadium complex. Optimalized conditions.

The solution of ligand **12** (3.82 mg, 0.015 mmol) and $VO(acac)_2$ (2.6 mg, 0.01 mmol) in CH_2Cl_2 (4 ml) was stirred at r.t. for 30 min. The methyl *p*-tolyl sulfide (0.13 ml, 1mmol) was introduced and the mixture was stirred at r.t. for 30 min. 30% H_2O_2 (0.12 ml, 1.2 mmol) was then added dropwise and stirring was continued for 23 h until no more sulfoxide was produced (TLC). Organic solvent was evaporated, the residue was extracted with a mixture hexan/diethyl ether (6:4), to remove the unreacted sulfide, then extracted with $CHCl_3$ (3 × 20 ml). Combined $CHCl_3$ extracts were washed with 10% NaOH, dried and solvent was removed under reduced pressure. The results of the oxidation experiments are presented in Tables 1–4.

The enantiomeric excess of methyl *p*-tolyl sulfoxide produced was established by chiral HPLC of the crude reaction mixture (Chiralcel OD-H, 10% v/v 2-propanol in hexane, flow 0.5 ml/min, 224 nm. Retention times: 23 min – enantiomer (*R*), 26 min – (*S*), 28 min – sulphone).

REFERENCES

1. Carreño M.C., *Chem. Rev.*, **95**, 1717 (1995).
2. Kagan H.B. and Diter P., Organosulfur Chemistry; Page P.C.B (Ed.); Academic Press: NY 1998, vol. 2, chapter 1, p. 1.
3. Pitchen P., Dunach E., Deshmukh M.N. and Kagan H.B., *J. Am. Chem. Soc.*, **106**, 8188 (1984).
4. Di Furia F., Modena G. and Seraglia R., *Synthesis*, 404 (1984).
5. Nakajima K., Kojima M., Toriumi K., Saito K. and Fujita J., *Bull. Chem. Soc. Jpn.*, **62**, 760 (1989).
6. Nakajima K., Kojima K., Kojima M., Aoyama T. and Fujita J., *Bull. Chem. Soc., Jpn.,* **63**, 2620 (1990).
7. Bolm C. and Bienewald F., *Angew. Chem. Int. Ed. Engl.*, **34**, 2640 (1995).
8. Vetter A.H. and Berkessel A., *Tetrahedron Lett.*, **39**, 1741 (1998).
9. Ohta C., Shimizu H., Kondo A. and Katsuki T., *Synlett*, 161 (2002).
10. Pelotier B., Anson M.S., Campbell I.B., Macdonald S.J.F., Priem G. and Jackson R.F.W., *Synlett*, 1055 (2002).
11. Skarżewski J., Ostrycharz E. and Siedlecka R., *Tetrahedron: Asymmetry*, **10**, 3457 (1999).
12. Blum S.A., Bergman R.G. and Ellman J.A., *J. Org. Chem.,* **68**, 150 (2003).
13. Głuszyńska A. and Rozwadowska M.D., *Tetrahedron: Asymmetry*, **11**, 2359 (2000).
14. Rozwadowska M.D., *Tetrahedron: Asymmetry,* **9**, 1615 (1998).
15. Mikołajczyk M., Drabowicz J. and Cramer F., *J. Chem. Soc., Chem. Commun.*, 317 (1971).
16. Mislow K., Green M.M., Laur P., Melillo J.T., Simmons T. and Ternay A.L., Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965).
17. Brunel J.-M. and Kagan H.B., *Bull. Soc. Chim. France*, **133**, 1109 (1996).
18. Bohé L., Lusinchi M. and Lusinchi X., *Tetrahedron*, **55**, 155 (1999).