

Dedicated to Full Member of the Russian Academy of Sciences
G.A. Tolstikov on Occasion of His 70th Birthday

Metal Complexes in Asymmetric Oxidation of Sulfides

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Abstract—The review treats asymmetric oxidation of prochiral sulfides to sulfoxides catalyzed by metal complexes.

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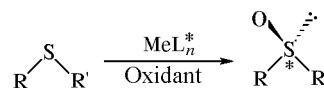
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1. INTRODUCTION

Chiral sulfoxides constitute an important class of organic compounds widely applied to asymmetric synthesis [1, 2]. The high efficiency of sulfoxides utilization in asymmetric transformations is to a large extent due to the great configurational stability of the sulfoxide group. The pronounced interest in the chiral sulfoxides is also generated by natural occurrence of compounds with asymmetric sulfoxide groups [3, 4], and by existence of biologically active sulfoxides possessing a definite configuration [5, 6].

The chiral sulfoxides of high enantiomeric purity are obtained by several approaches: optical separation of achiral sulfoxides, asymmetric synthesis introducing sulfo group into a compound already possessing optical activity, and asymmetric oxidation of appropriate sulfides. The latter approach is the most general and promising. The oxidation of prochiral sulfides can be performed, for instance, by catalysis with enzymes [7, 8], in cell cultures [9, 10], with the use of nonmetal oxidation systems (oxidation with hypervalence iodine compounds [11, 12], chiral phosphoryl chlorides [13], oxaziridines [14–16]),

and enantioselective oxidation with metal complex catalysts.



The latter method is widely spread because of its efficiency, simplicity, feasibility, and also the opportunity to vary over a broad range the process conditions and the complex metals, ligands, and oxidants. Thus a possibility is provided to choose a suitable oxidation system for efficient production of chiral sulfoxides from various sulfides, and the latter is especially important for development of industrial processes.

The first examples of asymmetric sulfides oxidation into sulfoxides catalyzed by metal complexes were published independently by two research teams in 1984 [17, 18]. The oxidation systems used were derived from the Sharpless epoxidating reagent which had been developed for allyl alcohols epoxidation. The reagent contained titanium isopropylate Ti(OP*i*-Pr)₄ and optically active diethyl tartrate (DET)

in equimolar amounts, and *tert*-butylperoxide *t*-BuO₂H as oxidant [19]. Whereas the direct application of the Sharpless system resulted only in achiral sulfoxides, the addition of one equiv of water (Kagan system) [17] or the use of 4-fold excess of diethyl tartrate with respect to Ti(OPr-*i*)₄ (Modena system) [18] provided systems affording sulfoxides of high enantiomeric purity. Therewith both modified systems turned out to be unsuitable for chiral epoxidation of allyl alcohols. As a rule, the titanium isopropylate was used in equimolar amount to the sulfide substrate, and the reaction was carried out under inert atmosphere. It was shown later that sometimes the replacement of *t*-BuO₂H by cumene hydroperoxide resulted in increased optical purity of sulfoxides obtained [20]. Further research efforts in this field were focused on raising the yield, enantioselectivity, and on applying the metal complex oxidation systems to sophisticated objects. The main results of these studies are summarized in early reviews [2, 21–27] compiling the publications up to 1995 or treating advances within a short period (1–2 years) that does not permit comprehensive consideration of the modern trends in this important field derived from a single source.

This review compiles publications on asymmetric oxidation of sulfides with the use of metal complexes appeared from 1996 to 2002. All text is divided into sections covering the application of complexes of definite metals to preparation of chiral sulfoxides.

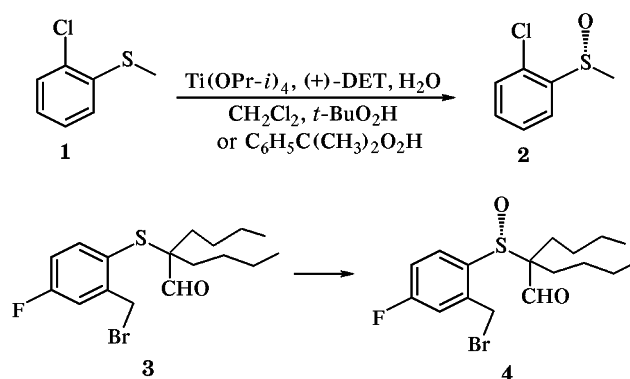
2. CATALYSTS BASED ON TITANIUM

2.1. Titanium–Diethyl Tartrate Complexes, Oxidants *t*-BuO₂H or Cumene Hydroperoxide

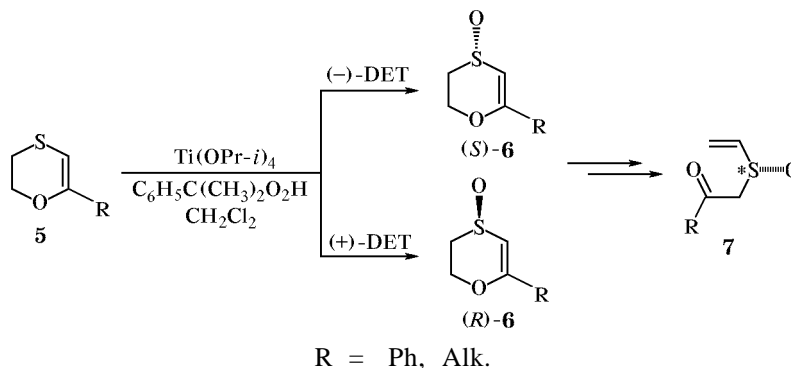
A special attention attracted recently the refinement of conditions of sulfides oxidation with the use of homogeneous catalytic systems involving esters of chiral tartaric acid, Ti(OPr-*i*)₄, and oxidant (*t*-BuO₂H or cumene hydroperoxide). Just these systems are

already used in pharmaceutical industry [28] and in the synthesis of biologically active compounds [29].

Regardless the encouraging results obtained in oxidation of prochiral aryl alkyl sulfides these systems showed low efficiency in oxidation of simple dialkyl sulfides and some halosubstituted aryl alkyl sulfides. For instance, oxidation of *o*-chlorophenyl methyl sulfide (**1**) with Kagan system [Ti(OPr-*i*)₄–DET–*t*-BuO₂H (or cumene hydroperoxide)–H₂O–CH₂Cl₂] furnished sulfoxide (**2**) in 91% yield, but the enantiomeric excess (*ee*, indicator of optical and enantiomeric purity) was only 27% at the use of cumene hydroperoxide [30]. The replacement of cumene hydroperoxide with *t*-BuO₂H resulted in increased enantiomeric purity of the product; however, the results were irreproducible, and the *ee* value varied from run to run in the range 40–88%. Poor results were also obtained with aldehydosulfide (**3**). The optical purity of sulfoxide (**4**) synthesized did not exceed 20% [31].

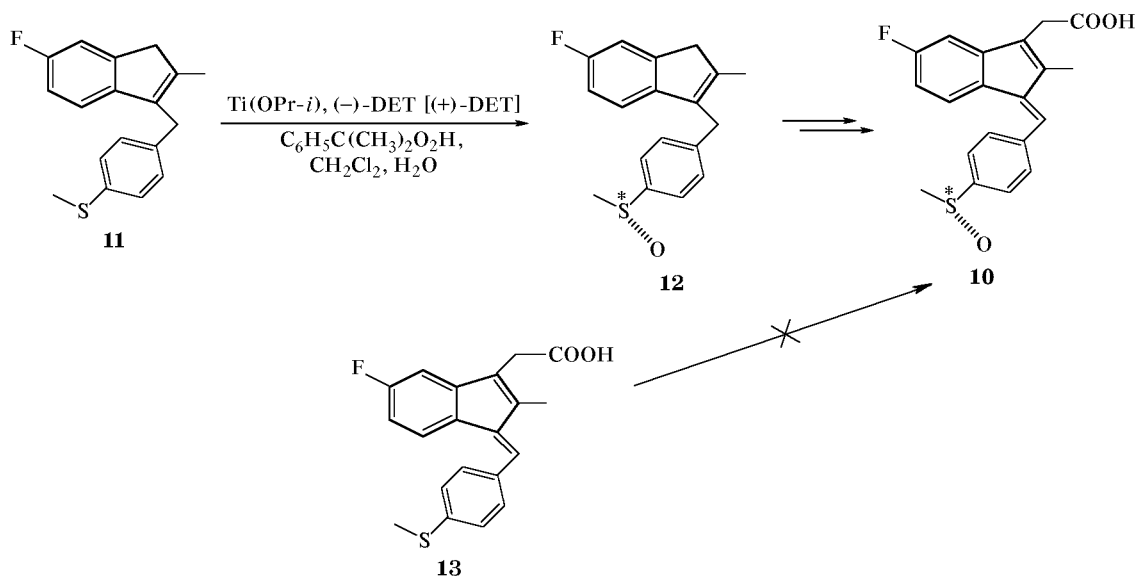
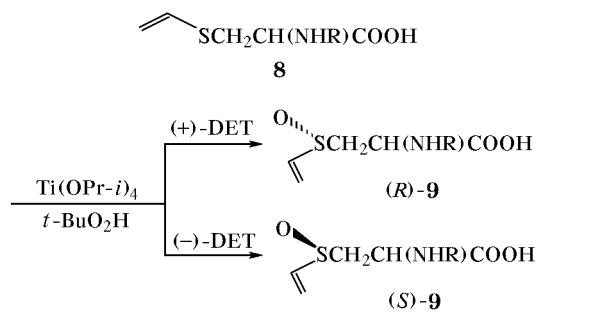


At the same time the asymmetric oxidation of 6-substituted 2,3-dihydro-1,4-oxathiines (**5**) with Modena catalytic system afforded optically active sulfoxides (*S*)-(**6**) or (*R*)-(**6**) with chemical and optical yields over 90% [32]. Here the cumene hydroperoxide served as oxidant; at the use of *t*-BuO₂H the catalytic activity and enantioselectivity of the catalyst



notably diminished. By subsequent ring opening from these sulfoxides chiral β -ketosulfoxides (**7**) were obtained which found wide application in the synthesis of naturally occurring and biologically active compounds [33].

The use of (+)- or (-)-DET in a system with $\text{Ti}(\text{OPr-}i)_4$ and $t\text{-BuO}_2\text{H}$ for selective oxidation of S-allyl-L-cysteine (**8**) with a protected amino group yielded two optical isomers of compound **9** [34].

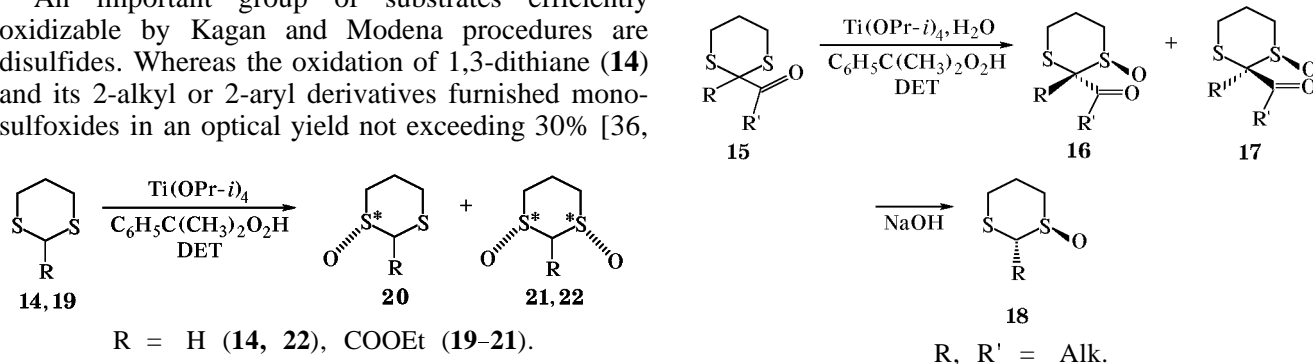


One of key stages in the synthesis of non-steroid antipyretic pharmaceutical Sulindac (**10**) is an asymmetric oxidation of sulfide (**11**) into sulfoxide (**12**). The application of Kagan procedure with the use of (+)- or (-)-DET furnished both enantiomers of compound **12** in 54–56% yield and optical purity about 90% [35]. At the same time oxidation of compound **13** containing a carboxy group afforded only racemic sulfoxide, and oxidation of the methyl ester of compound **13** resulted in almost quantitative yield of the corresponding sulfone.

An important group of substrates efficiently oxidizable by Kagan and Modena procedures are disulfides. Whereas the oxidation of 1,3-dithiane (**14**) and its 2-alkyl or 2-aryl derivatives furnished monosulfoxides in an optical yield not exceeding 30% [36,

37], an oxygen-containing substituent in position 2 of the 1,3-dithiane in a number of cases provided a possibility to obtain mono- and disulfoxides in good yield and with high enantiomeric purity.

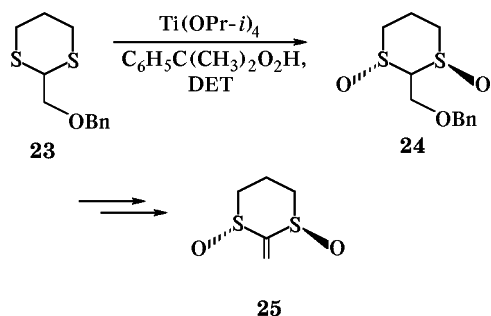
In oxidation of 2-acyl-2-alkyl-1,3-dithianes (**15**) under Kagan conditions with the use of cumene hydroperoxide monosulfoxides were prepared with optical purity from 80 to 99%. Therewith as a rule formed a mixture of *anti*-(**16**) and *syn*-(**17**) isomers with *anti*-(**16**) prevailing [36]. Deacylation of compounds **16** and **17** provided *syn*-isomers **18** in a high optical yield.



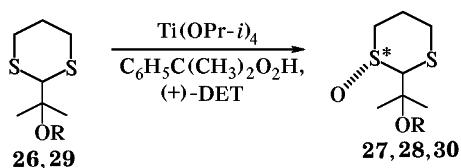
The asymmetric oxidation of ethyl 1,3-dithiane-2-carboxylate (**19**) with cumene hydroperoxide afforded mono- (**20**) and di- (**21**) sulfoxides (80–97% *ee*) [37]. At the absence of water in the reaction mixture prevailed disulfoxide, and the enantiomeric purity of the products was not affected. The increase of cumene hydroperoxide amount from 2 to 4 equiv and the excess of diethyl tartrate 2-fold also favored disulfoxide (**21**) formation in up to 66% chemical yield. On decarboxylation compound **21** gave rise to disulfoxide (**22**) of high optical purity (over 99%).

The oxidation of substituted 1,3-dithiane (**23**) under Modena conditions afforded the corresponding disulfoxide in 68% yield (98% *ee*) [38]. The latter was further used in the synthesis of chiral dienophile (**25**) for Diels–Alder reaction. An important role plays the structure of the substituent at the oxygen atom: the presence of a free hydroxy group results in low chemical and optical yield of disulfoxide (**24**), and the replacement of a benzyl group by an acetoxy group leads to decomposition of the original dithiane under the reaction conditions.

The addition to the reaction mixture of molecular sieves (4 Å) enabled the oxidation of compound **26** containing a free hydroxy group with *t*-BuO₂H to be performed with good yield of sulfoxide (**27**) (61%, mostly *trans*-isomer) and moderate enantioselectivity (up to 46% *ee*; in the absence of the molecular sieves optical yield was 33%) [39].



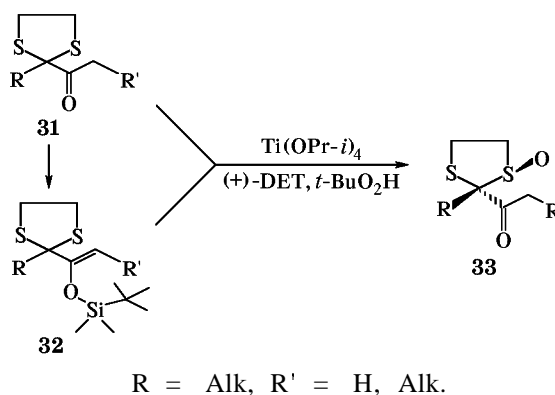
The oxidation with the use of cumene hydroperoxide provided compound **27** in 89% yield, but it was virtually racemic. The oxidation of a methoxy derivative of compound **26** gave rise to (*S*)-monosulfoxide **28** in 58% yield (over 99% *ee*). Interestingly, the



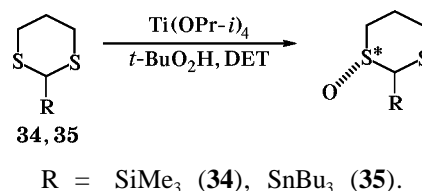
R = H (**26**, **27**); CH₃ (**28**); COCH₃ (**29**, **30**).

oxidation of compound **29** afforded mainly (*R*)-enantiomer of sulfoxide (**30**).

By an example of 2-alkyl-2-acyl-1,3-dithiolanes (**31**) oxidation an effect was studied of 2-substituent size on the yield and selectivity of the reaction [40]. The synthesis from compounds **31** of silicon-containing enol ethers **32** resulted in the change in the substituent character and therewith the enantioselectivity of reaction increased from 73–86% (depending on R and R' substituents) to 88–99% with a slight decrease in the yield of compounds **33**.

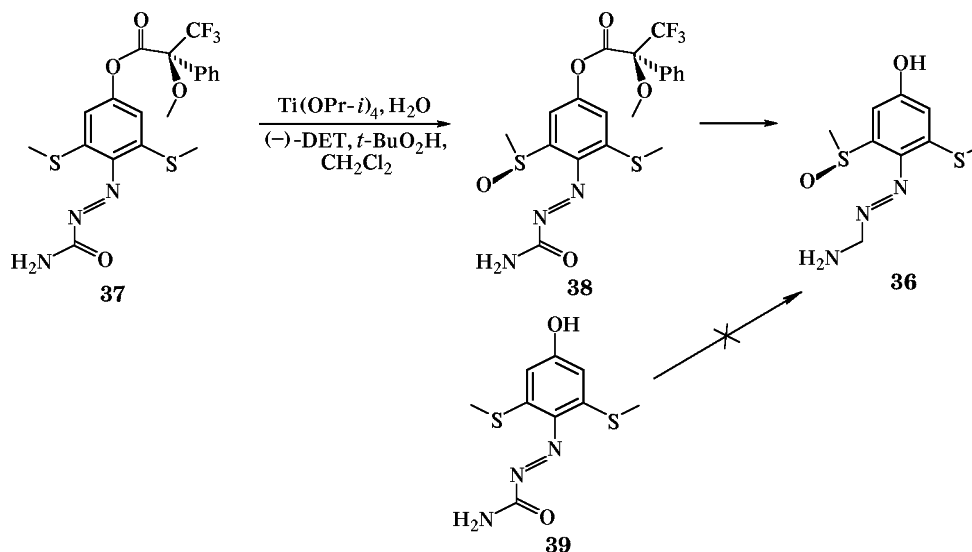


The direct bonding of a heteroatom to the heterocycle affected the oxidation process far less efficiently and led to conversion of 1,3-dithianes into monosulfoxides (**34**, **35**) with slightly over 50% *ee* [36].

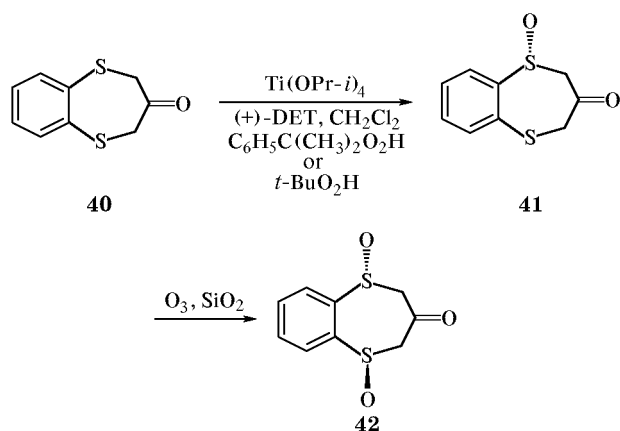


The key stage in rubroflavin pigment (**36**) synthesis turned out to be the asymmetric monooxidation of disulfide (**37**) that under Kagan conditions afforded compound **38** in 35% yield (67% *ee*) [41]. The direct oxidation of compound **39** containing a phenol group gave poor results presumably due to its low solubility in CH₂Cl₂.

The other example of a successful regio- and stereoselective oxidation of an aromatic disulfide is the conversion of 1,5-benzodithiepan-3-one (**40**) under Modena conditions [42]. From the arising monosulfoxide (**41**) disulfoxide (**42**) was further prepared which was then used for asymmetric separation of cyclic meso-1,2-diols. The oxidation with



$t\text{-Bu}_2\text{H}$ provided monosulfoxide (**41**) in higher yield than the reaction with cumene hydroperoxide (82 and 56% respectively) but in lesser optical purity (86 vs 97% *ee* at the use of the cumene hydroperoxide). The oxidation of compound **40** under Kagan conditions furnished racemic monosulfoxide in a low yield.



Kagan method turned out to be inefficient (yield 53%, *ee* ~0) for asymmetric oxidation of polymeric poly(aryl alkyl sulfides) containing sulfur atoms in the main chain [43]. Taking into consideration that water addition during oxidation of aryl disulfide (**40**) also resulted in racemic sulfoxide (**41**) [42] it was probable that in [43] was used an unsuitable catalytic system.

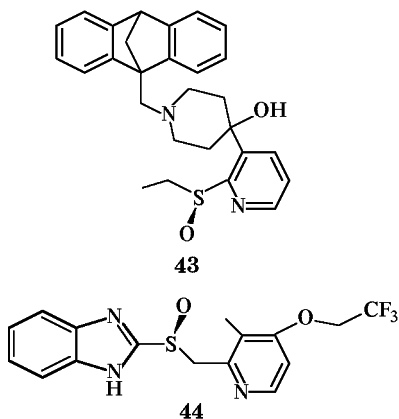
A modified Modena system was advanced for oxidation of aryl methyl sulfides which in certain cases resulted in increased yield and enantioselectivity [44, 45]. Although the classical procedure was inefficient in asymmetric oxidation of *p*-tolyl methyl

sulfide (yield 64%, *ee* 19%), the addition of molecular sieves (4 Å) and of 4-fold excess of 2-propanol into the reaction mixture enhanced the enantioselectivity to 95.6% at the chemical yield 77%; cumene hydroperoxide was used as oxidant [45]. Significant points in the procedure are the sequence of molecular sieves addition and the amount of the 2-propanol. If the molecular sieves are added after preparation of the catalytic complex of $\text{Ti(OPr-}i\text{)}_4$ with DET and not before, the *ee* value is reduced by 10%. It was found that the best ratio between $\text{Ti(OPr-}i\text{)}_4$ and 2-propanol was 1:4, the change in the ratio to 1:1 resulted in decrease in the *ee* value by 13%. The enantioselectivity diminished similarly at raising the excess of 2-propanol to 10 times. A significant advantage of the modified system as compared to the systems of Modena and Kagan consists in the possibility to use it in catalytic amounts [10 mol% of $\text{Ti(OPr-}i\text{)}_4$ with respect to sulfide].

The more detailed investigation of *p*-tolyl methyl sulfide oxidation catalyzed with the modified Modena system revealed that the optical purity of the resulting *p*-tolyl methyl sulfoxide nonlinearly depended on optical purity of DET used in the experiment [46]. It was established that the optical purity of the product grew with the conversion (from 68% *ee* at 13% conversion to 90% *ee* at 90% conversion), and this fact was not due to chemical separation (prevailing oxidation into sulfone of one among the enantiomeric sulfoxides that should enrich the reaction mixture with the other enantiomer), for the quantity of formed sulfone was insignificant (5% at 90% conversion). An additional proof of the absence of kinetic separation

gave a control run of racemic sulfoxide oxidation that did not afford any optically active products. Kagan *et al.* [46] suggested that the most probable cause of this effect was the change in the catalyst structure during the process.

Modification of Kagan system by adding *N,N*-diisopropylethylamine in toluene into the reaction mixture enabled to prepare practically important compounds **43** and **44** in good yield and with high optical purity [5, 47].



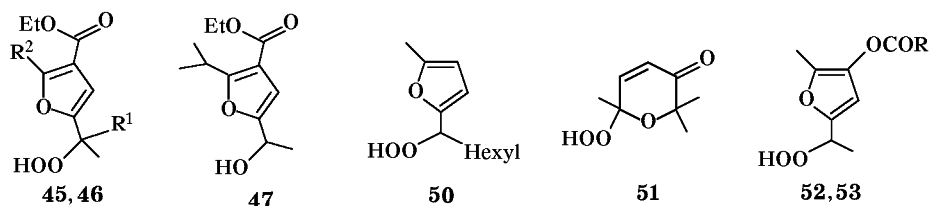
Sulfoxide (**43**) which was tested as a medicine for schizophrenia treatment was synthesized by asymmetric oxidation of an appropriate sulfide with resulting 93% *ee* and sulfone content below 1% (*t*-BuO₂H was used as oxidant) [5]. The exclusion of *N,N*-diisopropylethylamine from the system decreased the optical yield of the product to 85% and increased the sulfone content to 5%. The study of dependence of the optical purity of sulfoxide (**43**) on the quantities of Ti(OPr-*i*)₄ and DET revealed that the optimum amounts of these components are as follows: 1.45 equiv of DET, 0.95 equiv of Ti(OPr-*i*)₄, and

1 equiv of water per 1 equiv of the initial sulfide. Both increasing and decreasing of the relative amounts of DET and Ti(OPr-*i*)₄ resulted in diminished optical yield. The enantiomeric purity of sulfoxide (**43**) was successfully increased by recrystallization up to 99.5%.

Compound **44** known under the name of Omeprazole and having an outstanding antiulcer activity was prepared in 77% yield (95% *ee*) at industrial scale by oxidation of the corresponding sulfide with cumene hydroperoxide in the presence of Ti(OPr-*i*)₄, (-)-DET, H₂O, molecular sieves (4 Å), and *N,N*-diisopropylethylamine [47].

2.2. Titanium-Diethyl Tartrate Complexes, Oxidant Furyl Hydroperoxide

As already mentioned, Kagan and Modena systems show low efficiency in the dialkyl sulfides oxidation. This problem was solved by replacement of previously applied oxidants, *t*-BuO₂H and cumene hydroperoxides, by furyl hydroperoxide (**45**) [48, 49]. The system Ti(OPr-*i*)₄-(-)-DET-furyl hydroperoxide (**45**) was not only efficient for aryl methyl sulfides oxidation, but furnished sulfoxide from octyl methyl sulfide in 77% yield (78% *ee*). The use of diisopropyl tartrate instead of DET in oxidation of *p*-tolyl methyl sulfide reduced the optical yield of sulfoxide from 90% to 81% (the chemical yield in both cases being ~50%). Using as oxidant not compound **45** but furyl hydroperoxide (**46**) resulted in increasing the yield of *p*-tolyl methyl sulfoxide from 53 to 75% at 95% *ee*. Under these conditions the reaction occurred with kinetic separation of oxidant **46** proper: the unreacted furyl hydroperoxide and tertiary alcohol (**47**) isolated from the reaction mixture turned out to be optically active.

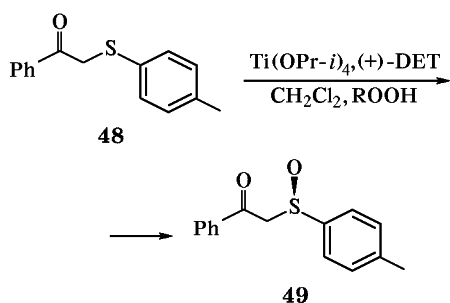


R¹ = R² = CH₃ (**45**); R¹ = H, R² = *i*-Pr (**46**); R = 5 α -cholestan-3 β -yl (**52**), (1*S*-endo)-(-)-bornyl (**53**).

A prolonged reaction time at oxidation of aryl methyl sulfides with furyl hydroperoxide (**46**) in some cases permitted a combination of asymmetric oxidation with kinetic separation and thus resulted in slight increase in the enantioselectivity of the reaction [50].

By an example of asymmetric oxidation of β -keto-sulfide (**48**) under Modena conditions the effect of oxidant was evaluated on the yield and optical purity of product **49** [51]. The application of *t*-BuO₂H instead of cumene hydroperoxide notably increased

the yield of product **49** (from 56 to 70%) at the same level of the enantioselectivity (~50% *ee*). The best results were obtained with furyl hydroperoxide **46**: the yield of sulfoxide **49** attained 89% at *ee* 62%. At the reaction time increased from 17 to 71 h the chemical yield of the β -ketosulfoxide sharply decreased (to 61%) because of sulfone formation in a significant amount. However due to kinetic separation the optical purity of the target product attained 97%.



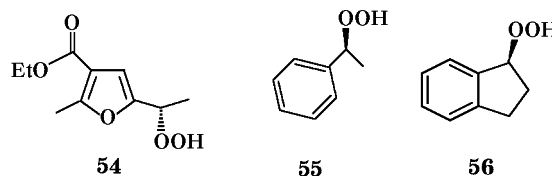
The other hydroperoxides successfully used for asymmetric oxidation under Modena conditions were compounds **50** and **51** [52]. The advantageous feature of these oxidants is their easy regeneration by reaction with hydrogen peroxide with the yield of about 70%. The more efficient was furyl hydroperoxide (**50**): in reaction of this oxidant with *p*-tolyl methyl sulfide the *p*-tolyl methyl sulfoxide was obtained in 61% yield (98% *ee*). The oxidation of the same sulfide with hydroperoxide (**51**) gave rise to the sulfoxide in the higher yield (77%), but the optical yield diminished to 68%.

The application of furyl hydroperoxide (**52**) to oxidation of aryl methyl sulfides by Modena procedure furnished the corresponding sulfoxides in 58–74% yield (84–95% *ee*) depending on the substituents in the aryl moiety [53]. In oxidation of dialkyl sulfides the system provided the corresponding sulfoxides in high yields, but with moderate optical purity (less than 40% *ee*). The replacement of compound **52** by furyl hydroperoxide (**53**) in reaction with *p*-chlorobenzyl methyl sulfide resulted in slight increase both in the yield and enantioselectivity of the oxidation. Note that hydroperoxides (**52**) and (**53**) were diastereomers mixtures and were used in the oxidation reactions without preliminary separation of isomers.

2.3. Titanium Complexes with Optically Active Oxidants

The next step in selection of oxidants for Kagan and Modena systems was the use of optically active

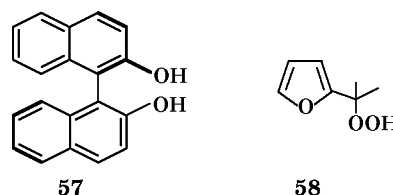
hydroperoxides that simultaneously were chiral ligands [54]. The oxidation of *p*-tolyl methyl sulfide with optically active furyl hydroperoxide (**54**) together with $\text{Ti(OPr-}i)_4$ furnished *p*-tolyl methyl sulfoxide in almost quantitative yield and extremely low optical purity (only 7% *ee*). The oxidation of the same sulfide with hydroperoxide (**55**) was more successive with respect to the optical purity of the product. Enantiomeric purity of the *p*-tolyl methyl sulfoxide obtained reached 75%, but the fraction of sulfone formed was 84%. The study of the reaction mechanism revealed that primary oxidation to sulfoxide occurred fast and with low asymmetric induction (less than 20% *ee*). The main contribution to the enantiomeric enrichment is obtained from the kinetic separation resulting in the high sulfone fraction. The use instead of hydroperoxide (**55**) of compound **56** gave comparable results, but unexpectedly instead of previously obtained (*S*)-isomer here arose (*R*)-isomer. In a control experiment of *p*-tolyl methyl sulfide oxidation with hydroperoxide (**55**) in the absence of $\text{Ti(OPr-}i)_4$ a racemic sulfoxide was obtained in low yield (9%).



Thus an attempt to use a single compound both as an oxidant and a chiral ligand turned out to be a failure, and the main attention of researchers in designing of new titanium-containing catalytic systems was focused on ligand variation.

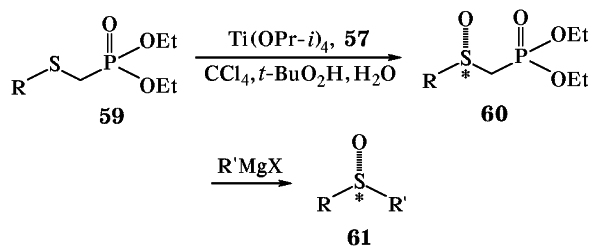
2.4. Titanium Complexes with C_2 -Symmetrical Diols

2.4.1. Titanium complexes with 1,1'-bi-2-naphthol and its derivatives. Apart the esters of D- and L-tartaric acid in the homogeneous asymmetric catalysis are successfully applied chiral derivatives of 1,1'-bi-2-naphthol, in particular, (*R*)-isomer (**57**) and its derivatives. The combination of (*R*)-diol (**57**) with $\text{Ti(OPr-}i)_4$ for oxidation of *p*-tolyl methyl sulfide by *t*-BuO₂H in the presence of water was first used in 1984 [55]; the yield of the sulfoxide obtained was 88% at 77% *ee*. An important advantage of this system was its activity in catalytic amount (10 mol%).



The oxidation with furyl hydroperoxide (**58**) instead of *t*-BuO₂H resulted in higher yield and enantiomeric purity of the *p*-tolyl methyl sulfoxide (up to 87% *ee*) [56]. Besides this oxidant is easily recovered by treating with H₂O₂. A high content of sulfone in the reaction product apparently evidences a kinetic separation.

A method was developed [57] for preparation of dialkyl sulfoxides of high enantiomeric purity. In the first stage an asymmetric oxidation of alkyl thiomethyl phosphonates (**59**) using a catalytic system [Ti(OPr-*i*)₄-(*R* or *S*)-1,1'-bi-2-naphthol-*t*-BuO₂H-H₂O] occurred in 86% yield and up to 98% *ee*. The application of diethyl tartrate instead of binaphthol was far less efficient, the optical yield was no more than 60–80% [58]. Further treatment of the arising sulfoxides (**60**) with Grignard reagent proceeded without racemization affording dialkyl sulfoxides (**61**) in 40–60%.

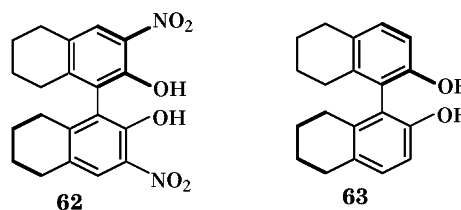


R, R' = Alk.

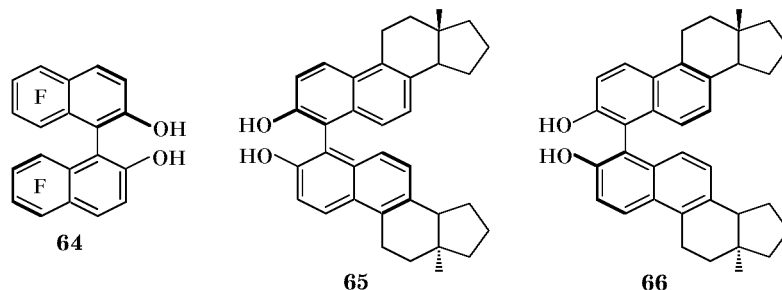
An attempt was performed to replace Ti(OPr-*i*)₄ in the system involving compound **57**, *t*-BuO₂H, and molecular sieves (4 Å) by commercially available titanocenes [bis(cyclopentadienyl)titanium dichloride or bis(cyclopentadienyl)titanium di(trifluoromethanesulfonate)], but it turned out to be unsuccessful for aryl methyl sulfides oxidation [59]. The best result

obtained with such system was an yield of 95% at 45% *ee*. The application as oxidant of the cumene hydroperoxide provided a lower yield at the same enantioselectivity, and oxidation of dialkyl sulfides furnished sulfoxides with an optical purity no more than 14%. It should be noted that in the presence of the molecular sieves the reaction was notably accelerated, whereas the water content in the sieves (0–18%) did not significantly affect the process.

The use of ligand **62** in place of compound **57** in the oxidation of *p*-tolyl methyl sulfide unexpectedly resulted in formation of (*S*)-sulfoxide in 52% yield (86% *ee*) [60] instead of the (*R*)-isomer. With a partially hydrogenated compound **63** this reaction afforded the sulfoxide enriched with (*R*)-enantiomer (10% *ee*).



A similar inversion of the optical rotation sign in the product obtained by oxidation of *p*-tolyl methyl sulfide was observed when electron-withdrawing substituents were introduced in compound **57**: it occurred at the use of the fluorinated ligand **64** [61]. In the latter case the ratio ligand to titanium plays an important role. Whereas at the 1:1 ratio a racemic sulfoxide was obtained, the raising of the ratio to 2:1 resulted in a product with optical yield of 61%; further increase in the ratio ligand–titanium did not affect the optical purity of the sulfoxide synthesized. The oxidation with cumene hydroperoxide and addition of two equiv of water into the catalytic system enabled to raise the optical yield to 86%.

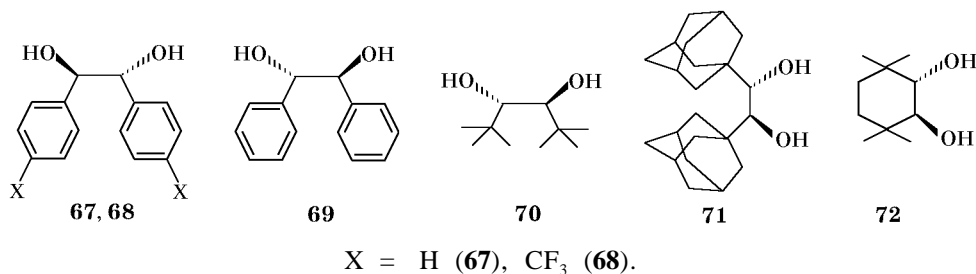


In asymmetric oxidation of phenyl methyl sulfide with *t*-BuO₂H the efficiency of compound **57** was exceeded by its analog **65**, synthesized from equilenin steroid. In the presence of compound **65** the oxidation

gave rise to virtually individual (*S*)-enantiomer in 80% yield (92% *ee*) [42]. Unlike compound **57** and its derivatives which preferably were applied in chlorine-containing solvents, the oxidation with a

system involving diol **65** the most efficiently occurred in tetrahydrofuran. The oxidation with the use of compound **66** resulted in slight excess of the (*R*)-isomer (optical yield 15%).

2.4.3. Complexes of titanium with diols of the other structural types. The oxidation of aryl benzyl sulfides with a system containing a complex of $\text{Ti}(\text{OPr-}i)_4$ with a chiral (*R,R*)-diol (**67**) afforded the



The introduction of CF_3 substituent into the *para*-position of aromatic fragments of ligand (**67**) [diol (**68**)] resulted in oxidation of *p*-tolyl methyl sulfide with prevailing formation of the (*R*)-sulfoxide (26% *ee*). In the oxidation of the *p*-tolyl methyl sulfide a similar dependence of the sign of optical rotation in the sulfoxide was observed also with binaphthol (**57**) derivatives as ligands [60, 61]. The oxidation of benzyl phenyl sulfide with the complex $\text{Ti}(\text{OPr-}i)_4$ -diol (**68**) gave rise to the sulfoxide enriched with the (*S*)-enantiomer (19% *ee*).

The system with compound **69**, an optical isomer of compound **68**, afforded in oxidation of aryl alkyl sulfides predominantly the expected (*R*)-sulfoxides [65]; however the yields of the latter were considerably lower due to formation of an appreciable amount of sulfones. The optical purity of the sulfoxides grew with sulfone content in the reaction mixture; thus the asymmetric oxidation was followed by kinetic separation.

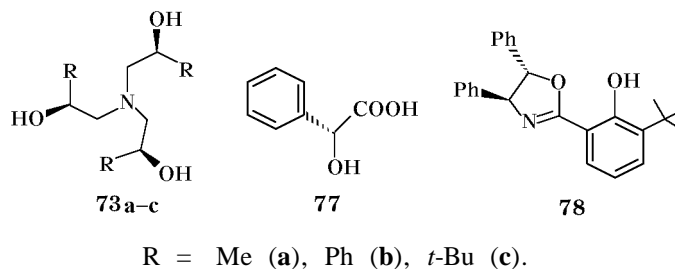
At the use of a catalytic amount of $\text{Ti}(\text{OPr-}i)_4$, diol (**70**), and cumene hydroperoxide in the presence of molecular sieves (4 Å) sulfoxide from the *p*-tolyl methyl sulfide was obtained with 95% *ee*, but a large quantity of sulfone (up to 40%) was also present [66]. The significant role of the kinetic separation was confirmed by kinetic studies.

The systems containing as ligands diols (**71**) and (**72**) were of low efficiency in the oxidation of aryl alkyl sulfides: with compound **71** the yields were moderate (up to 66%) and optical purity poor (below 15%), and in the presence of diol (**72**) formed only racemic sulfoxides [67].

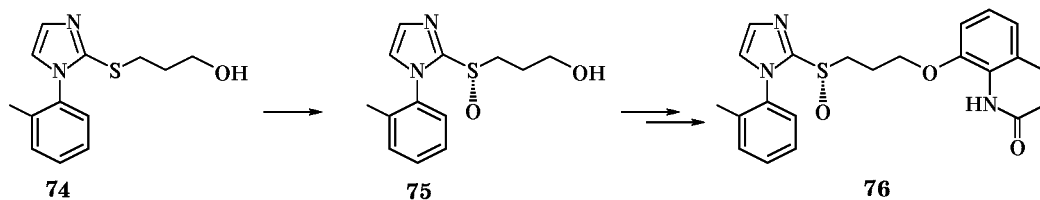
corresponding (*S*)-sulfoxides in over 60% yields and over 90% *ee* [63]. The system turned out to be nearly insensitive in oxidation of aryl alkyl sulfides to the character of substituents in the aryl moiety; yield of the (*S*)-sulfoxides was ~60%, and enantioselectivity depending on the alkyl group was 22–99%. The best solvent for oxidation of the *p*-tolyl methyl sulfide was CCl_4 . As with binaphthol **57** the system may be used in catalytic quantity (5%).

2.5. Titanium–Aminoalcohol Complexes, Salicylaldimines

The oxidation of aryl alkyl sulfides with catalytic amount (1–2 mol%) of complex $\text{Ti}(\text{OPr-}i)_4$ -cumene hydroperoxide–aminotrioles (**73a–c**) afforded sulfoxides with moderate optical yields (from 15 to 84% depending on the alkyl group and the substituent in the aromatic ring) and was accompanied with formation of a considerable sulfone quantity (up to 74%) [68, 69]. The sulfone content was reduced at the use of the ratio substrate–oxidant of 2:1, therewith also decreased the optical purity of the sulfoxide.

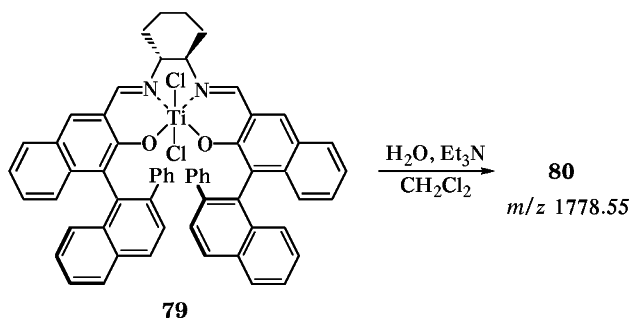


The system containing $\text{Ti}(\text{OPr-}i)_4$ and binaphthol (**57**) under conditions of Kagan or Modena showed little promise for oxidation of sulfide (**74**). Sulfoxide (**75**), the key intermediate in the synthesis of compound OPC-29003 (**76**), now under clinical tests, was obtained with optical purity not exceeding 54% [70, 71]. The trials performed with 24 ligands showed that best results with the oxidation system based on $\text{Ti}(\text{OPr-}i)_4$ gave the reaction performed in the presence of mandelic acid (**77**): compound **75** was obtained in 89% yield at 76% *ee*.



The reaction turned out to be very sensitive to the least changes in the ligand structure, and also to the character of the hydroxyalkyl substituent in sulfide (**74**). Both elongation and shortening of the aliphatic chain by a single methylene group resulted in a sharp decrease in the optical purity of the product, and the removal of the hydroxy group from compound **74** led to formation of almost racemic sulfoxide (6% *ee*) [71].

The application of titanium complexes with chiral oxazoline (**78**) made possible preparation of sulfoxide (**75**) from methyl phenyl sulfide with 95% *ee* [72, 73]. Here also the reaction rate and enantioselectivity significantly depended on the particular structure of the oxazoline used.



The oxidation of aryl methyl sulfides using complex (**79**) gave poor results [74]. At the same time a dimeric complex (**80**) with triethylamine used in amount of 2 mol% efficiently catalyzed sulfides oxidation into sulfoxides. The aqueous hydrogen peroxide can be used as oxidant, but the best results (92–99% *ee*) are obtained with urea hydroperoxide in methanol. The developed system is weakly sensitive to the character of substituent in the aryl ring.

The optical purity of a product obtained by oxidation of benzyl methyl sulfide was studied as a function of optical purity of dimeric complex (**80**). The optical purity of the latter was monitored by adding to (*S,S*)-dimer of a certain amount of (*R,R*)-dimer. A considerable positive nonlinear effect was observed, i.e., the optical purity of the product grew faster than the optical purity of the catalyst [75]. Saito and Katsuki understood the effect they observed as a

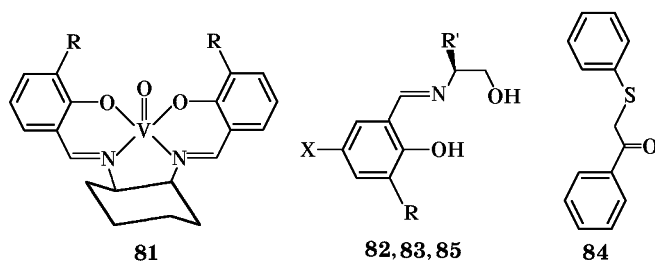
result of easy dissociation in methanol of the used (*S,S*)- and (*R,R*)-complexes with subsequent precipitation of the racemic (*R,S*)-dimer. Therefore in solution was present the excessive (*S,S*)-dimer regardless of the initial composition of the catalytic complex.

2.6. Titanium-Containing Medium-Porous Silicon Catalysts

The application of silicon medium-porous catalysts MCM-41 containing titanium provided a possibility to carry out the asymmetric oxidation of *p*-tolyl methyl sulfide with hydrogen peroxide in the presence of (+)-DET and to obtain the corresponding sulfoxide in 54% yield and with moderate optical purity (30% *ee*) [76, 77]. The reaction occurred with formation of up to 37% of sulfone. The greatest advantage of the system was the heterophase condition of reaction significantly simplifying the workup of the reaction mixture.

3. COMPLEXES UTILIZING VANADIUM(IV)

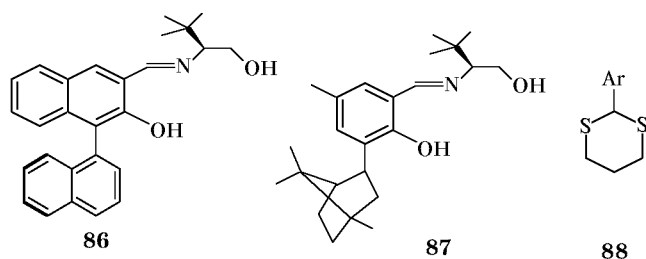
Vanadium complexes with chiral Schiff bases (**81**) were first used for asymmetric sulfides oxidation with cumene hydroperoxide [78]. Although the sulfoxides formed in good yield, the enantioselectivity of the reaction did not exceed 40%. It was found later that vanadium complexes with ligands (**82**) and (**83**) easily obtainable from the corresponding salicylaldehydes and optically active β -aminoalcohol ensured oxidation of aryl alkyl sulfides with aqueous hydrogen peroxide to afford sulfoxides in good yield (up to 94%) and with moderate enantioselectivity (commonly 50–70%) [79]: chiral complexes were used in catalytic amounts (0.01–1 mol%). It should be noted that the reaction conditions were much simpler than those required at the use of homogeneous titanium-containing systems: the reaction proceeded at room temperature, the anhydrous solvents and inert atmosphere are unnecessary. The system was suitable for oxidation of polyfunctional sulfides. For instance, β -ketosulfide (**84**) was oxidized into the corresponding sulfoxide with an optical yield 57% [80].



R = R' = *t*-Bu, X = NO₂ (**82**); R = R' = X = *t*-Bu (**83**); R = X = *t*-Bu, R' = *i*-Pr (**85**).

The asymmetric oxidation of phenyl alkyl sulfides catalyzed by complexes of ligands (**83**) and (**85**) with VO(acac)₂ was shown to afford sulfoxides of higher enantiomeric purity at addition of hydrogen peroxide by portions and not of all required amount at once [81]. This fact was rationalized by assumption that in the presence of excess H₂O₂ arose dihydroperoxy vanadium(V) complex which oxidized sulfides into achiral sulfoxides. The addition of H₂O₂ in portions with catalyst containing ligand (**85**) increased also the yield, but with ligand (**83**) an opposite effect was observed. The analysis of ⁵¹V and ¹³C NMR spectra of the vanadium-containing oxidation system suggested that in the enantioselective sulfides oxidation the active intermediates were monoperoxo vanadium(V) complexes involving one ligand per vanadium ion [82].

A wide range of ligands was assessed with VO(acac)₂ for oxidation of thioanisole, and the most efficient was vanadium complex with ligand (**86**) containing two chiral elements [83]. The application of this complex afforded methyl phenyl sulfoxide in 92% yield at 78% *ee*. Under the same conditions the vanadium complex with ligand (**83**) furnished the sulfoxide in 73% yield and 59% *ee*.

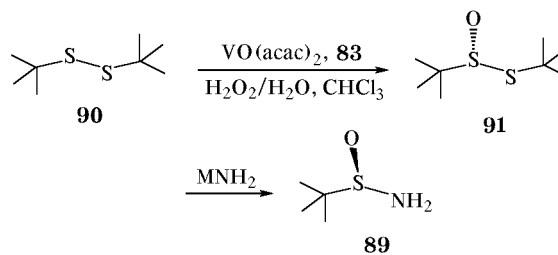


The efficiency series of ligands for *p*-bromothioanisole is quite different. The best ligand for this substrate was compound **87** which ensured the sulfoxide yield of 97% (78% *ee*).

The catalytic system including VO(acac)₂, chiral salicylaldimine (**83**), and aqueous hydrogen peroxide turned out to be active in monooxidation of 2-aryl-

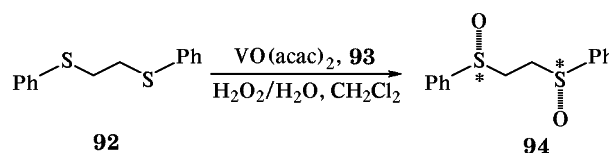
1,3-dithianes (**88**) [84]. Depending on the substituent in the aromatic ring the yield of sulfoxide varied from 60 to 87%, the optical purity from 62 to 85%. The replacement of the aromatic substituent in the 2-position by a *tert*-butyl group resulted in reduction of the optical purity to 46%. Note that oxidation of 2-alkyl or 2-aryldithianes by procedures of Kagan and Modena resulted in monosulfoxides of optical purity not exceeding 30% (see Section 2.1).

With the goal of preparation of chiral sulfinamide (**89**) used in the synthesis of chiral amines an asymmetric oxidation of *tert*-butyl disulfide (**90**) was investigated [85, 86]. This protocol for the synthesis of compound **89** was chosen because of low enantioselectivity at the oxidation of *tert*-butylsulfenamide. The testing of various Schiff bases revealed that the best results (yield 98%, 91% *ee*) provided ligand (**83**) and chloroform as solvent. The use of solvents containing no chlorine resulted in sharp decrease in the optical purity of compound **91**.



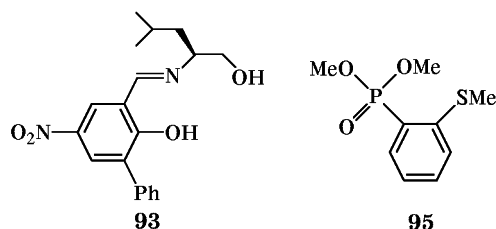
The optimum molar ratio of VO(acac)₂ to sulfide turned out to be 1:100. The reduction of the vanadium content below 1 mol% with respect to disulfide led to the yield decrease, and the increased vanadium concentration resulted in diminishing of the enantioselectivity.

The oxidation of other linear disulfide (**92**) with a system containing VO(acac)₂, aqueous H₂O₂, and



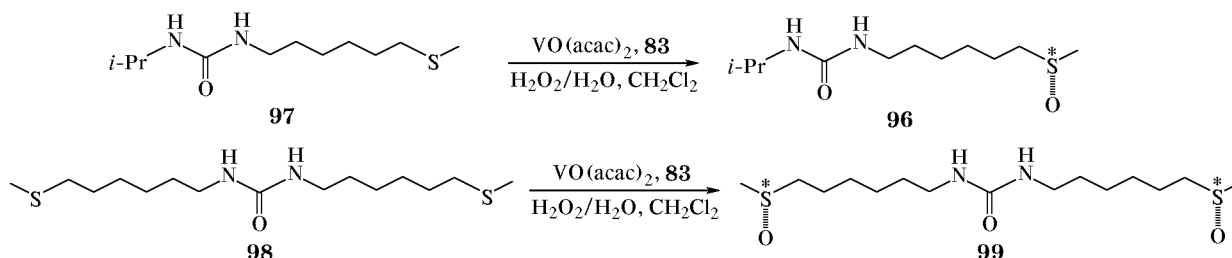
ligand **93** gave rise to disulfoxide (**94**) in 41% yield, with diastereomeric excess 60% (95% *ee*) [87].

The oxidation of compound **92** by Kagan procedure afforded only racemic monosulfoxide. The oxidation system with ligand **93** with thioanisole furnished the corresponding sulfoxide in 90% yield at 75% *ee*, the results comparable to those obtained with ligand **86**. Taking into consideration, that the synthesis of compound **93** from the corresponding salicylaldehyde may be carried out either with D- or L-valinol, it becomes possible to obtain under identical conditions both enantiomers by asymmetric oxidation of sulfides.



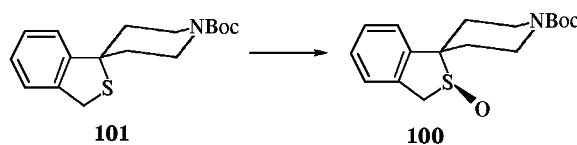
Both vanadium and titanium systems were not efficient in oxidation of dimethyl 2-(methylmercapto)-phenylphosphonate (**95**): the yield of the product was good (80%), but the optical purity low (30%) [88].

At the same time in quite a number of cases the asymmetric oxidation with vanadium-based systems turned out to be significantly more efficient than the process with titanium systems. This statement is valid for the already mentioned reactions of 2-aryl-1,3-dithianes, for oxidation of disulfide **92**, for the synthesis of alkaloid (-)-diptocarpamine (**96**) by asymmetric oxidation of compound **97** [89]. The attempts to oxidize compound **97** with the use of $\text{Ti}(\text{OPr-}i)_4$ and diisopropyl tartrate failed: in all experiments from the reaction mixture alongside the unreacted initial compound was isolated racemic sulfoxide **96** in a yield not exceeding 35%. For the lack of optical induction and low yield of the sulfoxide might be responsible the unsuitability of titanium systems for the chiral oxidation of dialkyl sulfides or a possible concurrent complex formation between $\text{Ti}(\text{OPr-}i)_4$ and the urea moiety in compound **97**.



The use of catalytic quantity of complex $\text{VO}(\text{acac})_2$ with ligand **83** furnished alkaloid **96** in 91% yield (45% *ee*). In a similar way the oxidation of disulfide (**98**) afforded alkaloid (-)-diptocarpidin (**99**) (28% *ee*) [90]. The biological assessment of both alkaloids (**96**) and (**98**) revealed their pronounced antihypoxic activity.

To obtain compound **100**, the key intermediate in the synthesis of a biologically active compound, the asymmetric oxidation of sulfide **101** [91] was carried out with the use of catalytic systems containing metal complexes: $\text{Ti}(\text{OPr-}i)_4$ with (-)-DET or 1,1'-bi-2-naphthol, and $\text{VO}(\text{acac})_2$ with ligand **56**. The best optical yield (54% *ee*) was obtained with the complex of titanium(IV) isopropylate with diethyl tartrate and with the vanadium system, but the yield of the oxidation product in the latter case was 4 times greater (20 and 80% respectively).

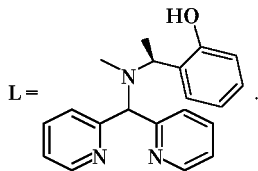
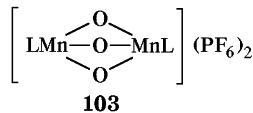
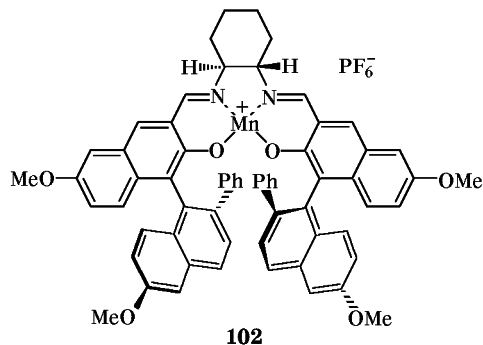


4. CATALYSTS BASED ON THE OTHER METALS

Catalytic complexes of the other metals are used a lot more seldom in the asymmetric oxidation of sulfides. The most studied system is $\text{Mn}(\text{salen})$, but the asymmetric induction with these complexes is usually relatively low, and as a rule the optical yield is no more than 25% [92]. Among the rare successful cases of asymmetric oxidation with these catalysts should be cited the oxidation of aryl alkyl sulfides in the presence of $\text{Mn}(\text{salen})$ (**102**) with an oxidant PhIO.

The *o*-nitrophenyl methyl sulfoxide prepared with this system in 94% yield was of optical purity up to 94% [93]. The enantioselectivity of the reaction strongly depended on the solvent, and the best results were obtained in acetonitrile, ethyl propionate, and chlorobenzene.

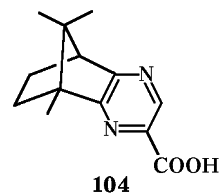
The oxidation of a number of aryl alkyl sulfides with the use of manganese-containing complex (**103**) furnished sulfoxides in ~50% yield and with very poor optical purity (from 5 to 18% *ee*) [94].



The chiral oxidation of aryl alkyl sulfides with a zirconium-containing system $\{[[Zr_2L_2(BuO)(OH)]_nH_2O\}_m$, $n = 3, 4$, L is compound **73b**, oxidant cumene hydroperoxide} gave rise to sulfoxides of 91% *ee* [95, 96]. The system is inefficient without water. The increase in the amount of the catalyst from 0.5 to 4 mol% resulted in growing optical purity of the product (from 0 to 86%) with simultaneously rising sulfone fraction (up to 75%). Thus the primary asymmetric oxidation to sulfoxide is followed by kinetic separation. Depending on aryl and alkyl groups the optical purity of sulfoxides attains 77–91%, and the sulfone fraction varies from 56 to 78%. The decrease in amount of catalyst to 0.05 mol% results in formation of sulfoxide with a reversed configuration. The oxidation of dialkyl sulfides afforded sulfoxides with a low optical yield (less than 14% *ee*) and sulfone fraction of 40%; therewith the sulfoxides obtained possessed the

opposite configuration compared to that of the oxidation products of aryl alkyl sulfides.

A moderate enantiomer excess (59%) and quantitative yield of the sulfoxide was obtained at oxidation of *p*-tolyl methyl sulfide with magnesium-containing oxidation system including (+)-dibenzoyl tartrate, $MgBr_2$, and $PhIO_2$ [97].



The system based on rhenium oxide was still less efficient. In the presence of $MeReO_3$ and a chiral ligand **104** oxidation with urea hydroperoxide afforded methyl phenyl sulfoxide with optical yield of only 15%; no sulfone formation was observed [98].

CONCLUSION

Nowadays the most well studied and versatile catalytic systems for asymmetric sulfides oxidation are those utilizing titanium and vanadium complexes. The use of Kagan and Modena reagents containing titanium(IV) isopropylate, optically active diethyl tartrate, and oxidant (commonly cumene hydroperoxide or *tert*-butyl hydroperoxide, more seldom substituted furyl hydroperoxides) enables to prepare in good yields and high enantioselectivity optically active sulfoxides from a wide range of aryl alkyl sulfides. The drawbacks of these reagents are the necessity to carry out the reactions in inert atmosphere, with controlled humidity, and frequently with equimolar amount of the oxidizing system with respect to sulfides. These systems regrettably are as a rule poorly suitable for asymmetric oxidation of dialkyl sulfides and sulfides containing functional groups. In this cases it is necessary to choose ligands from a large number (because the oxidation of each sulfide might require one definite ligand, and the slightest changes in the sulfide structure can demand looking for another ligand); or the vanadium-based systems may be usefull.

Complexes of $VO(acac)_2$ with chiral Schiff bases are used in asymmetric oxidation of sulfides in catalytic quantities (~1%), permit application of aqueous hydrogen peroxide as oxidant, and the reaction is carried out in the air presence. The system is sufficiently versatile and often is efficient where the titanium-containing systems give negative results.

However with catalytic systems utilizing vanadium the enantioselectivity as a rule is not very high (over 90%), but it is frequently attained in aryl alkyl sulfides oxidation by Kagan and Modena systems or their modifications.

Oxidation systems based on the other metal complexes are nowadays rather exotic and usually not enough efficient. They will hardly find wide application in laboratory investigations of asymmetric sulfide oxidation in the near future.

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