Pure & Appl. Chem., Vol. 57, No. 12, pp. 1911–1916, 1985.
Printed in Great Britain.

A short route to chiral sulfoxides using titanium-mediated asymmetric oxidation

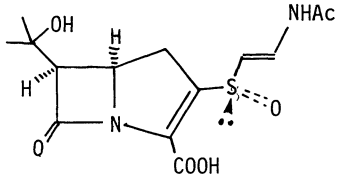
Henri B. Kagan*, Elisabet Dunach, Conception Nemecek, Philippe Pitchen, Odile Samuel and Shu-Hai Zhao.

Laboratoire de Synthèse Asymetrique, Bt 420, Université Paris-Sud, CNRS UA n°255, 91405 - Orsay, France.

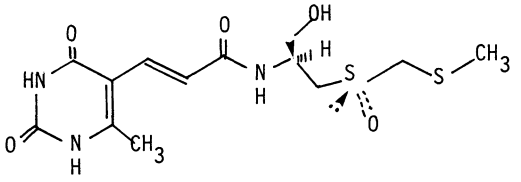
Abstract - The asymmetric oxidation of sulfides by t-BuOOH was realized in presence of one equivalent of a chiral titanium complex prepared from $Ti(OiPr)_4$/diethyl tartrate/H_2O (1:2:1). Many sulfoxides could be synthetized with ee's up to 95%. The main results are presented as well as attempts to use catalytic amounts of the chiral titanium and to the extension of the scope of the reaction.

INTRODUCTION

Chiral sulfoxides are sometimes found as natural products with a defined stereochemistry at sulfur. For example antibiotic activities were detected for Carpetimycin A 1 or Sparsomycin 2 (Refs. 1,2). Chiral sulfoxides are also frequently used as removable chiral auxiliaries in organic synthesis for the stereocontrolled formation of asymmetric centers (for some reviews see (Refs. 3,4). For example sulfoxides 3 gives aldol-type condensation with aldehydes (Fig. 1). After desulfurization products 4 were obtained in good yields with 91% ee (R = OtBu, R' = Ph) (Ref. 3) and 99% ee (R = NMe_2, R' = Me) (Ref. 5). Conjugated additions of organometallics on α-carbonyl, α,β-ethylenic sulfoxides was extensively studied by Posner and allowed to prepare an optically pure steroid by a very short route (Ref. 6) starting from sulfoxide 5 and after a two steps transformation into 6 (> 99% ee) (Fig. 1). It was found that the sulfinyl group is able to controle in many cases the stereoselectivity of a reaction occuring on a distant prochiral center. For example the reduction of sulfoxide 7 by $LiAlH_4$ or dibal and desulfurization gave in high yield (R)-8 (90% ee) or (S)-8 (90% ee) respectively (Ref. 7). Sulfoxide-mediated hydroxylation by osmium tetroxide of a remote olefin was recently established (Ref 8) allowing the clean preparation of 9 and 10. The final example which illustrates the potential of chiral sulfoxides in asymmetric synthesis is the Diels-Alder reaction. Good stereoselectivities in the cycloaddition between cyclopentadiene and some vinyl sulfoxides were recently described (Refs. 9,10).



1



2

The stereoselective preparation of chiral sulfoxides is mainly based on the method described by Andersen (Ref. 11) and studied by Mislow et al. (Ref. 12) which involves the problem of the separation of the intermediate diastereomeric menthyl sulfinates. In some specific cases (Ref. 3) procedures allow for recovery of only one diastereomer in epimerizing conditions at sulfur.
The most straightforward route to chiral sulfoxides is the direct asymmetric oxidation of a sulfide :

$$R - S - R' + [O] \longrightarrow R - \overset{*}{\underset{\underset{O}{\|}}{S}} - R'$$

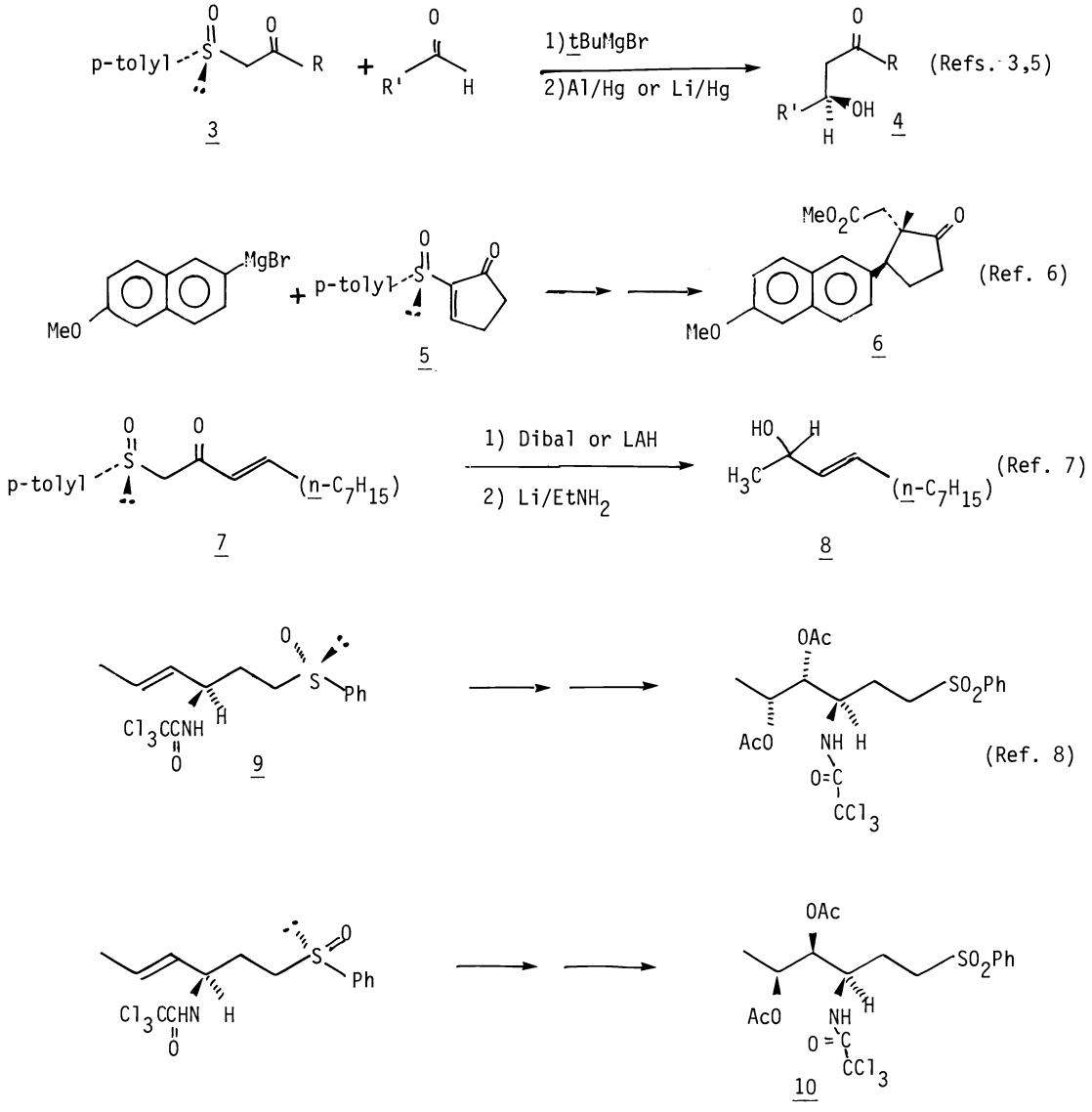


Fig. 1 Some examples of the use of a sulfinyl group to control the creation of an asymmetric center.

A strong stereocontrol in this process should be useful for solving two problems : i) The synthesis of chiral sulfoxides with a wide variety of R and R' groups ii) The introduction of the sulfinyl moiety with a given configuration in a chiral molecule thanks to a "reagent control" (Ref. 13). We shall discuss here only the first point, after summarizing the literature data upon asymmetric oxidation of prochiral sulfides. Chiral peracids gave very low ee, only recently it was found that some chiral oxaziridines could be of preparative value for the oxidation of sulfides into sulfoxides (Ref. 14).

Electrochemical oxidation of t-butylphenyl sulfide with platinum electrode modified by poly-(S-valine) gave the sulfoxide with 93% ee (Ref. 15). Apart the oxidation of alkyl aryl sulfides with hydrogen peroxide in presence of bovine serum albumin (Ref. 16) (ee up to 80%) it is mainly the biochemical oxidation of sulfides which has given high ee but with a strong influence of the substituents (Ref. 15).

We wish to discuss a new method that we discovered (Refs. 16-18) for the asymmetric oxidation of a wide variety of sulfides. This method is based on a modification of the Sharpless reagent for epoxidation of allylic alcohols (Ref. 19). We found that the combination $Ti(OiPr)_4$/(+)-diethyl tartrate (DET)/H_2O in the stoechiometry 1:1:1 or 1:2:1 in presence of 1 mol eq. of t-BuOOH is an excellent reagent for asymmetric oxidation of aryl methyl sulfides (80-90% ee). This reagent can be replaced by the combination $Ti(OiPr)_4$/(+)-DET (1:3 or 1:4) (Ref. 17) as found also independently by Modena et al. (Ref. 20). Because of the ease of manipulation we focussed our work on the water-modified reagent, which behaves in a complete different way from the Sharpless reagent ($Ti(OiPr)_4$/(+)-DET 1:1).

PREPARATION OF THE REAGENT (Ref. 17)

The reagent is prepared in dichloromethane at room temperature with the sequential addition of $Ti(OiPr)_4$, (+)-DET, H_2O and t-BuOOH (1:2:1:1.1). It is crucial to add water after diethyl tartrate ; a reverse order will lead to a precipitate (presumably TiO_2). A perfectly soluble species is obtained ; the yellow solution can be used at the desired temperature , usually - 20°C.

MAIN FEATURES OF THE REAGENT

An exploratory work (Refs. 16,17) on p-tolyl methyl sulfide as substrate showed that the Sharpless reagent itself lead to racemic sulfoxide and sulfone , while the addition of one mol eq. of water inhibits the sulfone formation and gives (R)-sulfoxide with 85% ee. The reagent with the 1:2:1:1.1 stoechiometry is not able to epoxidize isolate double bonds or allylic alcohols. Amines (pyridyl groups, tertiary amines), primary alcohols or phenols are not oxidized. The enantioselectivity of this reagent is highly dependent of the nature of the substituents of sulfides, but is fairly constant when families of sulfides are considered. This point will be developped shortly by selecting some representative examples (Refs 17,18).

OXIDATION OF ARYL METHYL SULFIDES (Fig. 2)

The reagent (prepared with (+)-DET) oxidizes sulfides Ar-S-CH_3 in good isolated yields at the 5 mmol scale . As shown by some representative examples in Figure 2 optical yields (80-90% ee) are fairly independent of the nature of the aryl moiety. The ee's were mostly measured by nmr methods with chiral shift reagents (Ref. 22) and the (R) configuration was found in the cases this has been established and assumed for the other examples to be also (R).

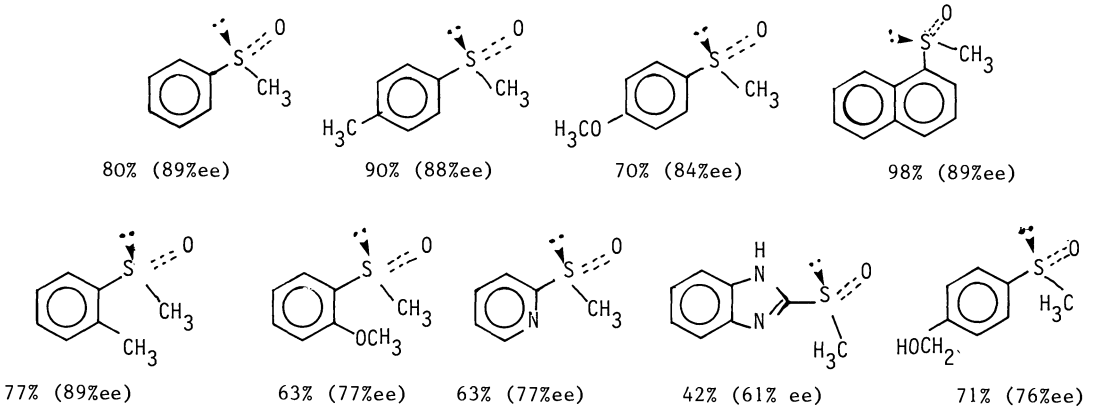


Fig. 2. Synthesis of aryl methyl sulfoxides by asymmetric oxidation ((+)-DET is the ligand in the reagent) (Refs. 17,18).

OXIDATION OF ARYL ALKYL SULFIDES (Fig. 3)

There was a drastic decrease in the ee's of sulfoxides prepared from Ar-S-R when R is changed from Me to a larger alkyl. An unexpected finding is the very high enantioselectivity (95%ee) obtained in the oxidation of cyclopropyl phenyl sulfide (Ref. 18). Phenyl vinyl sulfide is oxidized into the corresponding vinyl sulfoxide (70%ee).

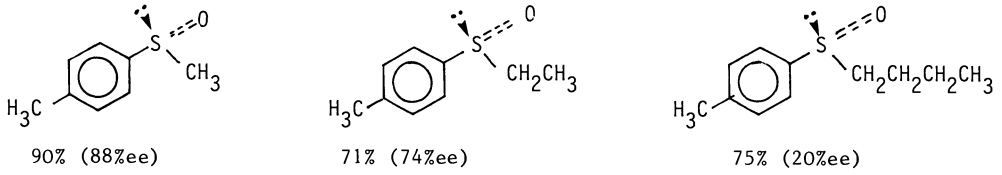


Fig. 3 Oxidation of alkyl p-tolyl sulfides ((+)-DET is the ligand in the reagent) (Ref. 17).

OXIDATION OF DIALKYL SULFIDES (Fig. 4)

We were delighted to find that our reagent was also able to give appreciable ee's in the oxidation of alkyl methyl sulfides (Refs. 17,18). Some examples are quoted in Fig. 4.

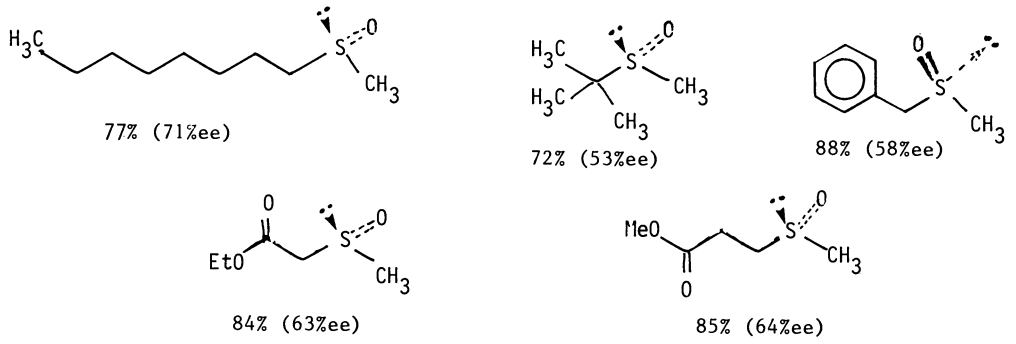


Fig. 4. Asymmetric oxidation of R-SCH_3 ((+)-DET is the chiral ligand in the reagent) (Refs. 17,18).

OXIDATION OF DISULFIDES (Fig. 5)

The oxidation of symmetrical disulfides RSSR into thiosulfinates RS(O)SR is possible (Ref. 21) using the reagent in methylene chloride at - 20°C.

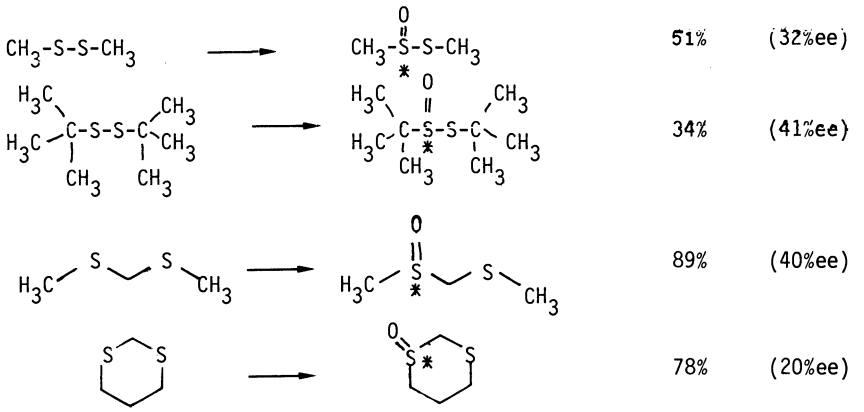


Fig. 5 Asymmetric oxidation of some disulfides (Refs. 18,21).

Isolated yields are in the range of 50%, enantiomeric excesses were measured by nmr with a chiral shift reagent (Ref. 22) when R = Me, and by nmr and polarimetry when R = t-Bu (by reference to the maximum specific rotation) (Ref. 23). Optically active thiosulfate with R = n-Bu or Ph were also isolated. The absolute configuration of the various thiosulfinates is unknown. Di-t-butyl disulfide was recently transformed into the corresponding thiosulfinate (14% ee) using a chiral 2-sulfonyloxaziridine as oxidant (Ref. 24). Thioketals are cleanly oxidized into monosulfoxides by our reagent (Ref. 18). By this method $MeSCH_2SMe$ gives rise to chiral FAMSO with 40%ee.

SOLVENT EFFECTS ON THE ENANTIOSELECTIVITY OF THE OXIDATION

In order to gain informations on the mechanism of the reaction we investigated the oxidation of methyl p-tolyl sulfide in our standard conditions (Ti/(+)-DET/H_2O/tBuOOH 1:2:1:1) with one mol eq. of reagent (0.1 M) at - 23°C in various solvents. These reactions were performed at the 5 mmol scale, results are given in Table 1 (Ref. 25).

TABLE 1. Influence of the solvent in the asymmetric oxidation of methyl p-tolyl sulfide[a].

Solvent	ε	μ (Debye)	ee %
CCl_4	2.23	0	4.5 (S)
$CHCl_3$	4.7	1.87	70 (R)
CH_2Cl_2	8.9	1.6	85 (R)
$ClCH_2CH_2Cl$	10.4	1.44	86 (R)
Toluene[b,c]	2.38	0.36	26 (R)
Acetone[b]	20.7	2.88	62 (R)

a Reactions performed at - 23°C. Experimental conditions as described in (Ref. 17) with (+)-DET.
b Some sulfone and sulfide was recovered besides sulfoxide.
c Reaction at 0°C.

A good correlation seems to exist between ee and the dielectric constant (ε) of the chlorinated solvents.Dichloromethane and 1,2-dichloroethane are the best solvents for the reaction. Acetone, despite its high ε, decreases the optical yield of the reaction, presumably because the solvation of the titanium reagent differes from that involved in chlorinated solvents. Toluene gives also inferior results with respect to dichloromethane or 1,2-dichloroethane (in agreement with Ref. 20). In conclusion data in Table 1 show an extraordinary sensitivity of the optical yield with the nature of the solvent, presumably because of changes in the structure of the active titanium complex. The ee (∿ 85-86% ee) was found constant between 40 and 100% conversion in the conditions of Table 1, in dichloromethane.

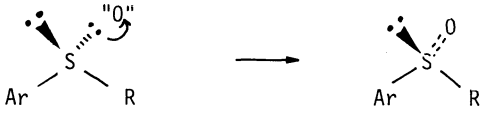
SCALE UP OF THE REACTIONS, CATALYTIC REACTIONS

In our preliminary work (Ref. 17) the reaction at the 5 mmol scale appeared to be stoechiometric by respect to titanium, because of the inhibition effect of the sulfoxide once formed. Furthermore the work-up necessitated product isolation by chromatography on silica gel. This procedure is not very convenient because of the amount of titanium and diethyl tartrate and of the final column chromatography. Nevertheless this procedure was successfully applied on 40 mmol scale with p-bromophenyl methyl sulfide (Ref. 17). More recently (Ref. 25) systematic essays on 100 mmol scale with methyl p-tolyl sulfide allowed us to use 0.5 mol eq. of the reagent ($Ti(OiPr)_4$/(+)-DET/H_2O;1:2:1) by respect to sulfide and t-BuOOH. Chemical yield and optical yield (∿ 85% ee) remain satisfactory. Isolation of the enantiomerically pure methyl p-tolyl sulfoxide (99% ee) in 60% chemical yield is very easy after crystallization of the crude product in hexane. A decrease of the amount of the reagent to 0.2 mol eq. slows down the reaction and lowers the optical yield to 50%,as previously found (Ref. 17), suggesting the competition of an achiral oxidation mechanism. We have established that a catalytic oxidation is indeed possible (total turnover number = 2) and is useful in the large scale reactions. The value of the maximum turnover number compatible with a good optical yield should be the result of rates of various competitive processes (catalyzed and uncatalyzed reactions, stability of titanium - sulfoxide complexes). It must be very much dependent of the structure of the sulfide and needs to be determined each time by a set of essays.

CONCLUSION

Our reagent is of much wider applicability that we initially believed. The scale up of the reaction (0.1 mol scale) needs some specific adjustements of the experimental procedure according to the structure of the prochiral sulfide in order to retain the ee found in the standard conditions (Ref. 17) on the 5 mmol scale.
The optimization should in many cases provide the catalytic use of the titanium complex, allowing a simple isolation of the product. The structure of the titanium complex will be not discussed here. It was tentatively assumed (Ref. 17) that a Ti-O-Ti unit is formed by partial hydrolysis of titanium/tartrate complex. A bis-μ-oxo bridge could be also envisaged. We are actively investigating the structure of the reagent and the mechanism of the reaction (external attack on the sulfur by a chiral titanium hydroperoxide or coordination of

sulfur to titanium prior to the oxidation). The following model predicts the absolute configuration of sulfoxides formed in asymmetric oxidations when (+)-(R,R)-diethyl tartrate is the chiral ligand :



(small)

This is consistent with the decrease in enantiomeric excess with the sequence : $CH_3 > CH_2CH_3 > CH_2CH_2CH_2CH_3$. It works also when Ar is replaced by t- butyl and R = CH_3. The oxidation of Ph-S-t-Bu was described (Ref. 20). The configuration of the product is given by the above model (Ar = Ph, R = t-Bu), which is an indication that the aromatic group influences the optical yield mainly by a polar effect. This was also apparent from the invariancy of optical yields when phenyl group is replaced by an ortho substituted ring or a naphthyl group (Fig.2). There are many experimental parameters which influence the enantioselectivity of the oxidation, it is also easy to modify the titanium complex by changing the titanium/DET/H_2O ratios. That gives good chances to prepare functionalized chiral sulfoxides and chiral synthons with high ee's and to control the stereochemistry of oxidation at sulfur in chiral sulfides ("reagent control" (Ref. 13)). We are currently investigating these points.

ACKNOWLEDGEMENTS

We thank CNRS for its financial support. One of us (E.D.) thanks CNRS and Roussel-Uclaf for a postdoctoral fellowship.

REFERENCES

1. T. Iimori, Y. Takahashi, T. Izawa, S. Kobayashi and M. Ohno, *J.Am.Chem.Soc.*, 105, 1659-1660 (1983) and references quoted therein.
2. D.R. Hwang, P. Helquist and M.S. Shekhani, *J.Org.Chem.*, 50, 1264-1271 (1985).
3. G. Solladié, *Synthesis*, 185-196 (1981).
4. M. Mikolajczyk and J. Drabowicz, *Top.Stereochem.*, 13, 333-457 (1982).
5. R. Annunziata, M. Cinquini, F. Cozzi, F. Montanari and A. Restelli, *J.C.S.Chem.Comm.*, 1138-1139 (1963).
6. G.H. Posner, J.P. Mallamo and K. Miura, *J.Am.Chem.Soc.*, 103, 2886-2888 (1981).
7. G. Solladié, G. Demailly and C. Greck, *J.Org.Chem.*, 50, 1552-1554 (1985).
8. F.M. Hauser, S.R. Ellenberger, J.C. Clardy and L.C. Bass, *J.Am.Chem.Soc.*, 106, 2458-2459 (1984).
9. C. Maignan, A. Guessous and F. Rouessac, *Tetrehedron Lett.*, 1727-1728 (1984) and references quoted therein.
10. S.M. Proust and D.D. Ridley, *Aust.J.Chem.*, 37, 1677-1688 (1984).
11. K.K. Andersen,*Tetrahedron Lett.*, 93-96 (1962).
12. K. Mislow, M.M. Green, P. Laur, J.T. Melillo, T. Simmons and A.L. Ternay Jr., *J.Am.Chem.Soc.*, 87, 1958-1977 (1965).
13. S. Masamune, W. Choy, J.S. Peterson and L.R. Sita, *Angew.Chem.Int.Ed.Engl.*,24, 1-30 (1985)
14. F.A. Davis, J.P. McCauley Jr and M.E. Harakal, *J.Org.Chem.*, 49, 1465-1467 (1984).
15. T. Komori and T.Nonaka, *J.Am.Chem.Soc.*, 106, 2656-2659 (1984) and references quoted therein.
16. P. Pitchen and H.B. Kagan, *Tetrahedron Lett.*, 1049-1052 (1984).
17. P. Pitchen, M. Deshmukh, E. Dunach and H.B.Kagan, *J.Am.Chem.Soc.*, 106, 8188-8193 (1984).
18. E. Dunach and H.B.Kagan, *Nouv.J.Chim.*, 9, 1-3 (1985).
19. T. Katsuki, K.B.Sharpless, *J.Am.Chem.Soc.*, 102, 5974-5976 (1980).
20. F. Di Furia, G. Modena and R. Seraglia, *Synthesis*, 325-326 (1984).
21. C.Nemecek, E.Dunach and H.B.Kagan, unpublished results.
22. E. Dunach, M. Deshmukh, S. Jugé and H.B.Kagan, *Tetrahedron Lett.*, 3467-3470 (1984).
23. J.Drabowicz, P. Lyzwa and M. Mikolajczyk, *Phosphorus Sulfur*, 16, 267-270 (1983).
24. F.A. Davis, R.H. Jenkins, S.B. Awad, O.D. Stringer, W.H. Watson and J. Galloy, *J.Am.Chem.Soc.*, 104, 5412-5418 (1982).
25. S.H.Zhao, O.Samuel, E.Dunach and H.B.Kagan, manuscript in preparation.