Tetrahedron Vol. 43, No. 21, pp. 5135 to 5144, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

ASYMMETRIC OXIDATION OF SULFIDES MEDIATED BY CHIRAL TITANIUM COMPLEXES : MECHANISTIC AND SYNTHETIC ASPECTS

S.H.ZHAO, O.SAMUEL and H.B.KAGAN*

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

(*Received in UK* 26 *May* 1987)

Abstract -- Asymmetric oxidation of sulfides by hydroperoxides mediated by chiral titanium complexes was further developed. The effect of water was discussed as well as steric and electronic factors of aryl groups in aryl-S-alkyl oxidation. When aryl is replaced by 1-alkyne, the sulfoxide is still obtained with high ee. The enantioselectivity of oxidation is enhanced by using cumene hydroperoxide instead of *t*-butyl hydroperoxide (up to 96%). The asymmetric oxidation was also run under catalytic conditions (with respect to the titanium complex) and beneficial effects were observed in the presence of molecular sieves in the reaction medium.

INTRODUCTION

In 1984, we described a new method for the oxidation of sulfides to chiral sulfoxides (1,2). This method used tertiobutyl hydroperoxide (TBHP) as oxidant in presence of stoichiometric amounts of a modified Sharpless reagent (3). The modified reagent was obtained by the combination $Ti(O\textit{i}Pr)_4/DET/H_2O$ = 1:2:1 and showed a surprising high stereoselectivity in the oxidation of several classes of prochiral sulfides. We detailed the main features of this new method for the asymmetric oxidation of sulfides (1,2,4-6). The beneficial influence of 1 mol eq of water (with respect to titanium) on the enantioselectivity was clearly established (1), although increased amounts of DET (diethyl tartrate) with respect to Ti (from 1 to 3-4 mol eq) gave good results as it was also observed by Modena et al (7). We report here a tentative explanation of these findings. Details will be also given on the optimization of enantiomeric excesses in the oxidation of some aryl methyl sulfides. Ee's in the range of 95% are now routinely obtained at 5 to 100 mmol scale by a careful control of the experimental conditions. The mechanism as well as the stereochemical course of the reaction will be also discussed. A general picture to predict absolute configuration of the sulfoxides (including acetylenic sulfoxides) is proposed.

THE "WATER EFFECT"

We discovered by serendipity that one mol eq of water deactivates the Sharpless reagent for allylic alcohols epoxidation and promotes formation of an efficient reagent for enantioselective oxidation of sulfides (1,2). It was later found by the Sharpless group that the asymmetric epoxidation can be run catalytically (with titanium) by removing residual water with molecular sieves (8). The poisonous effect of water in epoxidation of allylic alcohols was then well demonstrated. Clearly in the sulfide oxidation the combination $Ti(O\textit{i}Pr)_4$/ 2 DET/ 1 H_2O is excellent when using *t*BuOOH as oxidant.

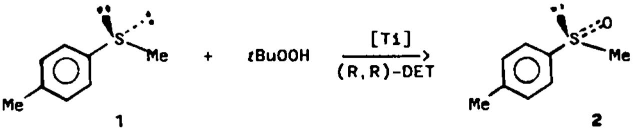


Figure 1

Dedicated to Professor H. Wynberg on the occasion of his sixty-fifth birthday.

For example (R)-methyl *p*-tolyl sulfoxide **2** was formed with 85-90% ee when (R,R)-DET was used (2)(Figure 1). The structure of the titanium complex was not established but we proposed that water promoted the formation of a Ti-O-Ti unit (2,4). We were intrigued by the fact that a large excess of diethyl tartrate gave the same effect as 1 or 2 mol eq of DET with 1 mol eq of water (2). In order to know accurately the amount of water present when preparing the reagent, diethyl tartrate was distilled and the solvent (methylene chloride) was carefully dried and stored over molecular sieves. A set of experiments (-23°C, 1 mol eq [Ti], 1 mol eq *t*BuOOH) was then performed using various amounts of DET with or without added water. Methyl *p*-tolyl sulfoxide **2** was recovered by flash chromatography. The main results are indicated in Table 1 and compared with the previous ones. By taking the modified reagent prepared as in our previous work (2) with the stoichiometry Ti/DET/H_2O = 1:2:1 but using the above conditions, we obtained very reproducible results, the isolated methyl *p*-tolyl sulfoxide having an enantiomeric excess close to 89%. This value was measured by ^1H nmr spectroccopy using a chiral shift reagent (9) but we found that more accurate data in this range of ee's could be routinely obtained by polarimetry. A flash-chromatography gives a quantitative recovery of the sulfoxide (which avoids any danger to change ee in the different fractions, as is sometimes observed in chromatography (10,11)). The maximum specific rotation of methyl *p*-tolyl sulfoxide was reexamined on a highly purified sample and found to be $[\alpha]_D$ = +146° (c=1, acetone). The enantiomeric purity of the compound was checked by ^1H nmr spectroscopy with chiral reagents and also by hplc on a chiral phase (13). The $[\alpha]_{max}$ value is in agreement with the initial report of Mislow (14) and departs from several other publications.

Table 1

Asymmetric oxidation of methyl *p*-tolyl sulfide **1** by 1 mol eq of *t*BuOOH in presence of 1 mol eq of titanium complex ($Ti(OiPr)_4$ + xDET + yH_2O).

Entry	mol eq of (R,R)DET	mol eq of water	Isolated yield (%)	Configuration of sulfoxide **2**[c]	ee %	Ref.
1	1 [a]	1	95	R	84	(2)
2	2 [b]	1	90	R	89	
3	4 [a,e]	0	60[d]	R	88.3	(7)
4	3 [a]	0	85	R	82	(2)
5	2 [a]	0	85	R	70	(2)
6	1 [a]	0	41 (17% sulfone)		0	(2)
7	2 [e]	1	89	R	86	(4)
8	4 [b,e]	0	80	R	76	
9	4 [e,b,f]	0	47	R	31	
10	4 [e,b,g]	0	40	R	21	

a) DET was used as received from Aldrich Chemical Co. $[\alpha]_{neat}$=+7.9.
b) DET was distilled prior to use (bp=110°C / 0.1 mmHg). $[\alpha]_{neat}$=+8.8.
c) Sulfoxide was isolated by flash chromatography.
d) Sulfoxide isolated by distillation (7).
e) Oxidation carried out in $ClCH_2CH_2Cl$.
f) Activated pellet 4Å molecular sieves were added after preparation of the reagent.
g) Activated powdered 4Å molecular sieves were added after preparation of the reagent.

In Table 1 are arranged the data concerning various reports (2,7) involving oxidation in presence of the combination $Ti(OiPr)_4$/DET (1 to 4 mol eq) and in the absence of water (entries 3-4). The general trend is clear : the more DET is introduced, better is the ee of the sulfoxide. We performed a set of complementary experiments (entries 7-9, Table 1) in order to better analyze the influence of water. In very dry conditions with 4 mol eq of DET there is a decrease in ee with respect to experiments quoted in entries 3 and 4. Moreover introduction of molecular sieves after the formation of the reagent and before beginning the oxidation ensures to remove all traces of water (residual, or formed during the course of the oxidation). Experiments in entries 9 and 10 (Table 1) show under these conditions a slow down of the reactivity and a spectacular drop in the ee (to 31% and 21%) which has to be compared to 86-88% (entries 3-5). One tentative interpretation of this effect is the following : the undistilled diethyl tartrate used in the experiments of entries 3-5 could contain some water giving a beneficial effect which overlaps with the effect (if any) of a large excess of DET itself. Another explanation could be that molecular sieves interfere in some way with the titanium complex, reducing its reactivity and enantioselectivity. We do not favor this hypothesis (see later on the influence of molecular sieves). The actual water content necessary to obtain the maximum quantity of the useful chiral titanium complex remains to be clarified. Our previous investigations indicated an optimum amount close to a 1:1 composition (Ti/H_2O), but this value should be corrected for the additional residual water present in the reagents or occuring in the system. It is also possible that the beneficial quantity of water is correlated with the amount of diethyl tartrate. Whatever is the exact stoichiometry of the active chiral complex it seems clear that a controlled amount of water is a useful component, while a strictly anhydrous medium has to be avoided.

INFLUENCE OF THE STRUCTURE OF THE HYDROPEROXIDE

One feature of our system not yet investigated was the nature of the oxidant (apart from 90% H_2O_2 or MCPBA which led to very low ee's (15)). We were not encouraged to use other hydroperoxides than TBHP since it is known that Sharpless epoxidation is not very much changed by replacing TBHP by other hydroperoxides (16). We were then very surprised to see that cumene hydroperoxide ($PhC(Me)_2OOH$, CHP), a cheap and easily available compound, gives a significant increase in the ee's of many sulfoxides, without any decrease in the chemical yields. The results obtained are indicated in Table 2 ; for a preliminary report see (17). Many sulfoxides were recovered with ee's above 90% (up to 96%). The method can be performed up to 150 mmol scale, the product is cleanly separated from cumene alcohol by flash chromatography.

Because of the good results obtained by introducing one aromatic group into the peroxide we investigated the oxidation of methyl *p*-tolyl sulfide by trityl hydroperoxide (Ph_3COOH) in the conditions of Table 2. Methyl *p*-tolyl sulfoxide was isolated in 90 % yield with 20% ee (R configuration). There is a strong decrease in ee when compared with the oxidation by TBHP or cumene hydroperoxide (entry 1, Table 2). It would be interesting to study the oxidation with the intermediate hydroperoxide $Ph_2C(Me)OOH$.

Table 2

Asymmetric oxidation of sulfides by the modified reagent ($Ti(O\textit{i}Pr)_4$/(+)-DET/H_2O = 1:2:1) using various hydroperoxides.

Entry	Sulfide[a]	$PhC(Me)_2OOH$			Ph_3COOH	*t*BuOOH
		sulfoxide : yield (%)	ee(%)[c]	$[\alpha]_D$ in acetone	sulfoxide ee%	sulfoxide ee(%)[b]
1	Me-S-*p*-tolyl	93	96 [d,c]	+139°	16.3 [d,c]	89
2	Me-S-(*o*-anisyl)	97	93 [d]	+313°		74
3	Me-S-*p*-chlorophenyl	85	91 [c]	+114°		78
4	Me-S-phenyl	93	93 [d,c]	+135.4°		88
5	Me-S-$(CH_2)_7CH_3$	71	80 [d]	- 66.6°	32.5	53
6	Me-S-benzyl	84	61.5 [c]	- 59°[e]		35

a. Oxidations were performed at - 23°C for 20h, in CH_2Cl_2 in presence of 1 mol eq of Ti reagent prepared as (2). 1.1 Mol eq of ROOH was used. All the sulfoxides of this Table have (R) configuration.

b. Results taken from our previous publication (2). Some of the ee's quoted in (2) were reevaluated by using hplc on chiral column (13), corrected data are indicated here.

c. Calculated with maximum specifique rotation given respectively in references (14),(12),(21),(22).

d. Ee confirmed by chiral HPLC.

e. In ethanol 96%.

Another advantage of using cumene hydroperoxyde is the easiness in getting optically pure sulfoxides by means of asymmetric oxidation of sulfides followed by fractional recrystallization in appropriate solvents thanks to the high ee's of sulfoxides formed in oxidation. Thus the sulfoxides obtained after oxidation with cumene hydroperoxide were readily purified by recrystallization into optically pure ones with good yields except for the *p*-chlorophenyl methyl sulfoxide which is liquid at room temperature (Table 3).

Table 3

Obtaining of optically pure sulfoxides by recrystallization

Sulfoxide[a]	Solvent of recrystallization[b]	Yield in pure sulfoxide[c](%)	$[\alpha]_D$ of pure sulfoxide
Me-S(O)-*p*-tolyl	*n*-hexane	76	+146° acetone
Me-S(O)-*o*-anisyl	*n*-hexane	80	+339° "
Me-S(O)-phenyl	ether-pentane	60	+147° acetone
Me-S(O)-$(CH_2)_7$-CH_3	*n*-hexane	40	- 83° acetone
Me-S(O)-benzyl	cyclohexane	45	- 96° ethanol

a. Recrystallizations performed on optically active sulfoxides coming from oxidation by CHP with 1 mol eq. of Ti/(+)DET/H_2O then flash-chromatography
b. Number of recrystallizations is 2 to 3.
c. Calculated by respect to the sulfoxides obtained as a.

CATALYTIC ASYMMETRIC OXIDATION

Oxidation of methyl *p*-tolyl sulfide was taken as a model for the study of the conditions to use catalytic amounts of our chiral titanium reagent. We decreased progressively the amount of the reagent, keeping the same all the other parameters as in the stoichiometric reaction (temperature, time, TBHP,...). The results are in Table 4. They show that in the presence of 0.5 mol eq of titanium reagent the oxidation of methyl *p*-tolyl sulfide affords the same results as in the stoichiometric conditions.

Table 4

Asymmetric oxidation of methyl *p*-tolyl sulfide by hydroperoxides in presence of a catalytic amount of a chiral Ti complex ($Ti(O_iPr)_4$/(+)-DET/H_2O = 1:2:1) and additives (salts or molecular sieves pellets)

Entry	ratio(Ti/sulfide)	Additive[a]	Hydroperoxide	Sulfoxide Yield %	ee %
1	1.7	No	TBHP	86	83
2	1	"	"	88	85.5
3	0.67	"	"	90	84
4	0.54	"	"	89	84.2
5	0.4	"	"	95	75
6	0.2	"	"	68	50
7	1	No	CHP	90	96
8	0.52	"	"	82	96
9	0.25	"	"	94	84
10	1 [b]	LiCl (1) [f]	TBHP	42	25
11	0.6 [b]	KNO_3 (0.8) [f]	"	75	26
12	0.2	$LiBF_4$ (0.2) [f]	"	57	/
13	1	$Cu(Acac)_2$ (1) [f]	CHP	75	5.4
14	0.25	$Cu(Acac)_2$ (0.05) [f]	"	52	30
15	1	Molecular sieves (1) [e]	TBHP	91	82
16	0.2	" (1) [e]	"	83	77.5 [d]
17	0.2 [c]	" (1) [e]	CHP	97	88
18	0.15	" (0.7) [e]	TBHP or CHP	93	76
19	0.15	" (0.7) [f]	CHP	90	50
20	0.15	" (0.7) [g]	"	90	51
21	0.10	" (1) [e]	"	85	70
22	0.10 [h]	" (1) [e]	TBHP	90	56

a. In brackets are molar ratio for salts and weight ratio for sieves with respect to sulfide.
b. Sulfide is methyl phenyl sulfide.
c. 4 DET.
d. In the same experiment with powdered molecular sieves, ee is lower.
e. Molecular sieves are added before all the other additions.
f. Added after Ti complexation.
g. Non activated molecular sieves added after Ti complexation.
h. Without H_2O.

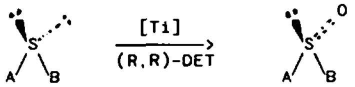
If the amount of titanium is less than 0.5 mol eq with respect to the sulfide, the oxidation occurs with a decrease in ee (entries 1-9, Table 4). This is indicative of at least one non enantioselective pathway involving catalysis by a new titanium species. The direct oxidation by TBHP has been shown to be very slow in the standard conditions (2) and does not fit with the good chemical yields quoted in Table 4. One pathway diverting from the main stereoselective route could be caused by accumulation of the sulfoxide as the reaction proceeds. It is known that sulfoxides are good ligands for titanium (18), so that one can envisage a loss of stereoselectivity for a chiral reagent bearing a coordinated sulfoxide. To test this hypothesis, catalytic reactions were performed in presence of several salts of hard metal ions which should compete with titanium for coordination of sulfoxides. $LiBF_4$, LiCl, KNO_3 were tested, without any increase in the ee's (entries 10-14, Table 4). Indeed the stoichiometric reaction (1 mol eq of Ti reagent) is severely perturbed by addition of metallic salts presumably because of a change of the structure of the modified titanium reagent. This unexpected observation deserves further investigation in heteropolymetallic species formation.

Another approach to achieve catalytic oxidation was then investigated. It appears that excess water has deleterious effects on the enantioselectivity of asymmetric oxidation by the modified reagent, as found previously for the stoichiometric reaction (2). In catalytic conditions small amounts of water present in the reaction media could be sufficient to destroy the right titanium catalyst, leading to titanium complexes of low enantioselectivity. In order to protect the desired chiral titanium catalyst ($Ti(OiPr)_4/(+)\text{-DET}/H_2O$ = 1:2:1) against excess of water a set of oxidations was undertaken in presence of 4Å molecular sieves (entries 15-22, Table 4). In most of the cases a beneficial effect was observed when the sieves were added before the other components. When the sieves (activated or not) were added after Ti complexation, they had no effect. This seems to indicate that molecular sieves regulate the amount of water in the reaction but do not act themselves as catalysts.

Result of entry 17 (Table 4) appears to be the best one dealing with catalytic asymmetric oxidation of sulfides. Recently Fujita et al (19) reported 40% ee by using a catalyst based on optically active Schiff base µ-oxo vanadium complexes. Colonna et al (20) obtained 21% ee with a catalyst prepared from chiral amino acids and titanium complex.

INFLUENCE OF AN UNSATURATED GROUP IN ASYMMETRIC OXIDATION

The presence of an aromatic ring directly connected to sulfur ensures a good ee (80-95%) in the asymmetric oxidation of sulfides such $Ar\text{-}S\text{-}CH_3$ ((2) and Table 1). Moreover these sulfoxides are formed in the (R) configuration when (R,R)-DET is taken as the chiral auxiliary. It was pointed out that a simple scheme allows to predict the steric course of most of the asymmetric oxidations (2,4) :



(A = "Large", B = "Small")

Figure 2

In this picture the A,B pairs are respectively (aryl, n-alkyl) (2), (aryl, tBu) (7), (alkyl, Me) (2), ($PhCH_2$, Me) (the absolute configuration of $PhCH_2S\text{-}Me$ given in ref.2 was erroneously written and has to be reversed), (aryl, S aryl) (6), (aryl, OMe) (6). An aromatic group stands always as A ("large"). However there is not so much difference in ee's in the series Ar-S-Me (85-90% ee) whatever is Ar (Phe, α or β-naphthyl, anthracenyl) (2,5). Moreover phenyl appears to be "larger" than tBu if we take into account results of ref.7 (for an opposite finding during the weakly enantioselective oxidation of sulfides by chiral peracids see (21)). These facts suggest that the aromatic group influences asymmetric induction by a combination of steric and electronic effects. Polar effects of an aromatic ring in asymmetric reactions have many precedents. For example charge control was found operating in asymmetric reduction of prochiral benzophenones by a chiral Grignard reagent bearing a benzene ring (23). The apparent size of a phenyl group had been discussed in several papers (23-24). A test to assess the relative importance of steric and electronic effects of a phenyl group on stereoselective transformations is to replace it by the linear acetylenic moiety which has a small bulkiness and two π-systems. In the Horeau method for assigning absolute configuration of secondary alcohols by kinetic resolution of α-phenylbutyric anhydride (26,27) it was found that the ethynyl group acts as "large" with respect to a *n*-alkyl chain in the same way a phenyl does (28). It is well known that ketones such as $\mathrm{Ar{-}\overset{O}{C}{-}alkyl}$ or $\mathrm{R{-}C{\equiv}C{-}\overset{O}{C}{-}alkyl}$ are reduced by various chiral reagents into alcohols with high ee's and often with the same stereochemical course, while $\mathrm{RCH_2CH_2\overset{O}{C}{-}alkyl}$ gives alcohols of low ee's (28-31).

Noyori carefully analyzed the origin of enantioselectivity during the reduction of a wide variety of ketones by a chiral hydride reagent, BINAL-H(30). He concluded that unsaturated (phenyl, alkenyl, alkynyl) and saturated groups attached to a carbonyl function are differentiated primarily by their electronic properties.

It was then interesting to examine asymmetric oxidation of acetylenic sulfides such as R-C≡C-S-R' to see if the absolute configuration of the sulfoxide is in agreement with the previous A-S-B scheme (Figure 2) where A is the alkynyl moiety when B = Me. Indeed we observed asymmetric oxidation of two acetylenic sulfoxides (R = *n*-Bu) with R' = Me or Phe. These compounds **3** and **4** were prepared from 1-pentyne through its lithium derivative as depicted in Figure 3.

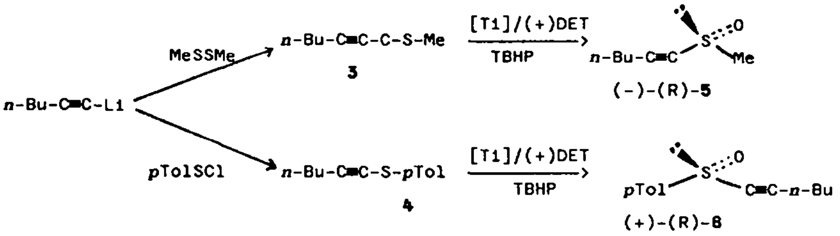


Figure 3

Oxidation of **3** by the modified reagent ((R,R)-DET) and TBHP in our standard conditions gives (R)-(-)-**5** (75% ee) in 83% yield. The absolute configuration of (-)-**5** was established by the reaction indicated in Figure 4. The known methyl *t*-butyl sulfoxide was obtained almost quantitatively (S configuration, 75% ee).

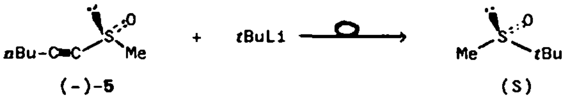


Figure 4

This efficient substitution reaction of an alkynyl group bound to a sulfinyl function seems to have no precedent in literature (although it is known on some types of alkynyl or aryl sulfides (32), it seems a general one since *n*-butyl lithium gave also the substitution reaction (*n*-butyl methyl sulfoxide (75% ee) is produced with 95% yield). This displacement reaction could be related to the report of Johnson et al (33) who obtained optically active dialkyl sulfoxides from aryl alkyl sulfoxides and alkyl lithium reagents. The exchange reaction occured with inversion of stereochemistry as in all the displacement reactions on compounds with an asymmetric sulfur atom (34). It is then very reasonable to assume inversion of configuration for the transformation in Figure 4, meaning that (-)**5** has (R)-configuration. In turn this means that asymmetric oxidations of **3** and Ar-S-Me have a similar steric course, the alkynyl group playing the same role as a phenyl ring. Similar oxidation of **4** led to the known sulfoxide **6** (29% ee) with the absolute configuration shown in Figure 4. The low ee is best explained by opposite effects of the alkynyl and tolyl groups, leading to a small predominancy of the tolyl group. The reactivity of **4** is small and obliged us to perform oxidation at + 3°C. It is interesting to recall that the modified reagent does not oxidize mesityl phenyl sulfide in the standard conditions (2).

In conclusion it seems well established that the beneficial role of an aromatic ring in sulfides is related to the aromatic π-system. In addition a route is opened to the formation of 1-alkynyl methyl sulfoxides. These compounds are not easily available by the Andersen method (14) apart from (-)-menthyl-*p*-toluene sulfinate and 1-alkynyl organometallics (35,36), which leads to 1-alkynyl-*p*-tolylsulfoxides.

INFLUENCE OF THE ALREADY FORMED SULFOXIDE ON THE OPTICAL YIELD

Since once formed, the sulfoxide may react with the Ti complex, it was interesting to see if the enantioselectivity of oxidation changes with the conversion extent. The results in Table 5 show that the optical yield does not significantly vary with the conversion.

Table 5

Oxidation of methyl-*p*-tolyl sulfide as function of conversion extent.

Time (hours)	TBHP mol eq	Isolated yield (%)	ee (%)
0.25	1.1	46	82
1	1.1	57	86
2	1.1	65	85
4	1.1	80	87

CONCLUSION

A highly enantioselective system for the oxidation of many sulfides has been set up. It is based on the use of cumene hydroperoxide in the presence of a stoichiometric amount of a titanium complex ($Ti(OiPr)_4$/(+)-DET/H_2O = 1:2:1). Ee's in the range of 90-96% are often obtained. Moreover the titanium complex can work as a catalyst, without decrease in the chemical yield, but with 10% decrease in ee in the case of the oxidation of *p*-tolyl methyl sulfide. In the presence of activated molecular sieves (Pellet), the catalytic ability of the titanium reagent is improved with respect to both ee and yield of the sulfoxide obtained. Synthetic applications of this system seem promising. The absolute configuration of the sulfoxides is predictable in many cases, on the basis of a simple model which also includes oxidation of some 1-alkynyl sulfides. The electronic properties of phenyl and alkynyl groups are of great importance for achieving the preferred transition state during the enantioselective oxidation. The nature of the exact titanium species which is formed in presence of excess diethyl tartrate and water remains to be clarified.

EXPERIMENTAL SECTION

Apparatus

^1H NMR spectra were recorded on Bruker AM 250 MHz spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Chemicals

CH_2Cl_2 was distilled over calcium hydride and stored under nitrogen over molecular sieves. TBHP solutions in toluene were prepared according to ref (3) and stored over molecular sieves under nitrogen. Cumene hydroperoxide was purchased from Aldrich Co (80%) and stored over sieves. Silicagel (Merck, 230-400 mesh) was used for flash column chromatography. (+) and (-) diethyl tartrate were purchased from Janssen Co. $Ti(OiPr)_4$ was obtained from Fluka and distilled before use. Unactivated pellet 4Å molecular sieves were obtained from Aldrich Chemical Co. and activation was accomplished by heating at 250-300°C overnight.

Asymmetric oxidation with TBHP

Stoichiometric oxidation of methyl *p*-tolyl sulfide as an example is performed as follows : (R,R)-DET (1.71 ml, 10 mmol) is dissolved at room temperature in 50 ml of CH_2Cl_2 under argon ;

then, $Ti(OiPr)_4$ (1.49 ml, 5 mmol) is added through a septum via a syrynge with stirring ; similarly, H_2O (5 mmol) is introduced via a microsyringe and stirring is maintained until the yellow solution becomes homogeneous (20 min), then sulfide (0.69 g, 5 mmol) is added. The solution is cooled to -30°C and 5.5 mmol of a TBHP solution in toluene (3.6 M) are then introduced dropwise via a syringe and the whole system is kept at -23°C overnight. Water (2 ml) is added to the solution at - 23°C and a vigorous stirring is maintained for 1 h at room temperature. The white gel is filtered over celite and thoroughly washed with CH_2Cl_2. The filtrate is stirred with NaOH (5%) and brine for 1 hour in order to remove DET and then separated. The organic phase is dried over Na_2SO_4 and concentrated to give the crude product. Flash chromatography (AcOEt) on silica gel affords 0.7 g (90%) of (R)-methyl *p*-tolyl sulfoxide. α are measured in acetone (c=0.5 ≈ 2.0) and the enantiomeric excesses are calculated from $[\alpha]_{max}$ = +146°(acetone) (ref.14).

Asymmetric oxidation with CHP(cumene hydroperoxide)

CHP is used instead of TBHP in the same way. In the workup, 2-phenyl isopropanol was separated during the flash chromatography (AcOEt).

Catalytic oxidations

For entry 18 of Table 4, for exemple, the workup is the following:

2.2 g of activated molecular sieves are added in 100 ml of CH_2Cl_2 under argon, and (+)-DET (1.026 ml, 0.6 mmol) and $Ti(O\text{-}iPr)_4$ (0.894 ml, 0.3 mmol) are added. Water (54 µl, 3mmol) is then introduced via a microsyringe. The mixture is stirred at room temperature for 25 minutes before addition of methyl *p*-tolyl sulfide (2.9 g, 21 mmol). After cooling to -30°C, CHP (22 mmol) is added dropwise and the mixture is kept at -23°C overnight (28 hrs). The usual procedure of treatment (as in the stoichiometric conditions) affords 3 g of methyl *p*-tolyl sulfoxide (93%, $[\alpha]_D$=+111.3 c= 1.015 acetone, ee=76.5% for R)

Preparation of methyl-*n*-hexyn-1 sulfide

To 33 ml of *n*-BuLi under argon at -20°C in hexane (1.6 M ; 50 mmol) was added slowly a solution of 5.7 ml (50 mmol) of distilled *n*-hexyn-1 in 25 ml ether. After half an hour, a solution of 4.4 ml of dimethyldisulfide (50 mmol) in 30 ml ether is added. The temperature is allowed to raise to room temperature, then the solution is refluxed for 5 hours. After the usual workup, the methyl *n*-hexyn-1 sulfide is purified by distillation under reduced pression (Eb = 85°C/15 mmHg). Yield : 30%.

NMR : δ 0.9 (3H,t) ; 1.5 (4H,m) ; 2.3 (2H,t) ; 2.4 (3H,s).

MS : M^+ = 128 (m/e : 71 ; 81 ; 85 ; 113)

Oxidation of methyl *n*-hexyn-1 sulfide

The routine procedure of stoichiometric asymmetric oxidation affords the methyl-*n*-hexyn-1 sulfoxide in 83% yield and $[\alpha]_D$ = - 59.1° ($CHCl_3$, c=1.3).

NMR : δ 0.9 (3H,t) ; 1.5 (4H,m) ; 2.45 (2H,t) ; 2.95 (3H,s).

The ee is measured by RMN in the presence of a chiral shift reagent (ref.9) : 75%.

Determination of the absolute configuration of methyl-*n*-hexyn-1-sulfoxide

To a solution of 580 mg (4 mmol) of sulfoxide in 80 ml ether, at -78°C, under argon, are rapidly added 11 ml (16 mmol) of *t*-BuLi in pentane. Three hours later, water was introduced (60 ml) ; extraction with CH_2Cl_2 gives 380 mg of a yellow liquid (80% yield). The ee of methyl t-butyl sulfoxide was estimated by the use of chiral shift reagent to be 75%. The sign (+) (22) of the measured [α] and the position of nmr lines in presence of chiral shift reagent (9) prove the S configuration. Assuming that the substitution occurs with inversion of configuration at sulfur, it comes that the methyl *n*-hexyn-1 sulfide has the R-configuration. The same reaction between methyl *n*-hexyn-1 sulfoxide and *n*-BuLi carried out under the same conditions, affords *n*-butyl methyl sulfoxide with 73% yield, ee = 75% (measured by chiral shift reagent and specific rotation ($[\alpha]_{max}$ = + 108°, c=1.5, acetone, S configuration (33)).

Preparation of *p*-tolyl *n*-hexyn-1 sulfide

This is obtained by the reaction between *p*-tolyl sulfenyl chloride and *n*-hexynyllithium. *p*-Tolylsulfenyl chloride prepared in situ according to (25) from thioanisole and N-chlorosuccinimide (0.05 mol in 40 ml ether) is added to *n*-hexynyllithium in excess at 0°C and the mixture is allowed to stand at room temperature overnight. The workup gives 83% sulfide which was purified by flash chromatography (cyclohexane-AcOEt 95/5) and distillation (Eb = 115°/0.4 mmHg).

NMR : δ 0.9 (3H,t) ; 1.5 (4H,m) ; 2.3 (3H,s) ; 2.4 (2H,t) ; 7.2 (4H)

Analysis : calculated :	C 76.47	H 7.84	S 15.69
found	76.18	7.8	15.53

MS : M^+ = 204 (m/e : 81 ; 91 ; 117 ; 161)

Oxidation of *p*-tolyl *n*-hexyn-1 sulfide

This was performed at 3°C during 60 h. The sulfoxide was isolated by flash chromatography (AcOEt : cyclohexane 1:2) in 97% yield. $[\alpha]_D$ = +22.2° ($CHCl_3$, 1.5) ee = 29% ($[\alpha]_{max}$ = + 77.6° for R configuration (36)).

ACKNOWLEDGMENTS

We thank CNRS for a financial support, and one of us (S.H.Z) acknowledges the Ministry of Education of the People's Republic of China for a fellowship.

REFERENCES

(1) Pitchen,P. ; Kagan,H.B. Tetrahedron Lett., **1984**, 1049.

(2) Pitchen,P. ; Deshmukh,M. ; Duñach,E. ; Kagan,H.B. J.Am.Chem.Soc., **1984**, 106, 8188.

(3) Katsuki,T. ; Sharpless,K.B. J.Am.Chem.Soc., **1980**, 102, 5974.

(4) Kagan,H.B. ; Duñach,E. ; Nemecek,C. ; Pitchen,P. ; Samuel,O. ; Zhao,S., Pure Appl.Chem., **1985**, 57, 1911.

(5) Duñach,E. ; Kagan,H.B. Nouv.J.Chim., **1985**, 9, 1.

(6) Nemecek,C. ; Duñach,E. ; Kagan,H.B. Nouv.J.Chim., **1986**, 10,

(7) Di Furia,F. ; Modena,G. ; Seraglia,R. Synthesis, **1984**, 325.

(8) Hanson,R.M. ; Sharpless,K.B., J.Org.Chem., **1986**,51, 1922.

(9) Deshmukh,M. ; Duñach,E., Jugé,S. ; Kagan,H.B., Tetrahedron Lett., **1984**, 3467 ; Corrigendum Tetrahedron Lett., **1985**, 402.

(10) Charles,R. ; Gil-Av,E. J.Chromatogr., **1983**, 298, 516.

(11) Tsai,W.-L. ; Hermann,K. ; Hug,E. ; Rohde,B. ; Dreiding,A.S. Helv.Chim.Acta, **1985**, 68, 2238.

(12) Cooke,R.S. ; Hammond,G.S. ; J.Am.Chem.Soc., **1970**, 92, 2739.

(13) Dr Tambuté, personal communication.

(14) Mislow,K. ; Green,M.H. ; Laur,P. ; Melillo,J.T. ; Simmons,T. ; Ternary,A.L.,Jr. J.Am.Chem.Soc., **1965**, 87, 1958.

(15) Duñach,E. ; thèse Doctorat es Science, Université Paris-Sud, **1985**.

(16) Finn, M.G. and Sharpless, K.B. in "Asymmetric Synthesis", Vol.5, p.247, Morrison, J.P. Ed., Academic Press, New York 1985.

(17) Zhao,S.H. ; Samuel,O. ; Kagan,H.B., C.R.Acad.Sci. Paris, **1987**, 304, Serie II, 273.

(18) Bradley,D.C.; Mehrotra,R.C. ; Gaur,D.P. "Metal Alkoxides", Academic Press, New York **1978**.

(19) Nakajima,K. ; Kojima,M. and Fujita,J., Chem. Lett., **1986**, 1483.

(20) Colonna,S. ; Manfredi,A. ; Spadoni,M. ; Casella,L. ; Gullotti,M. J.Chem.Soc.Perkin Trans., **1987**, 71.

(21) Folli,U. ; Iarossi,D. ; Montanari,F. ; Torre,G., J.Chem.Soc., (C), **1968**, 1317.

(22) Axelrod,M. ; Bickart,P. ; Jacobus,J. ; Green,M.M. ; Mislow,K. J.Am.Chem.Soc., **1968**, 90, 4835.

(23) Guetté,J.P. ; Capillon,J. ; Perlat,M. ; Guetté,M , Tetrahedron Lett., **1974**, 2409.

(24) Pirkle,W.H. ; Hoekstra,M.S. ; Miller,W.H. Tetrahedron Lett., **1976**, 2109.

(25) Hopkins,P.B. ; Fuchs,P.L. J.Org.Chem. **1978**, 43, 1208.

(26) Horeau,A., Tetrahedron Lett., **1961**, 506.

(27) Horeau,A. in "Fundamentals of Stereochemistry", Kagan,H.B., Ed., Georg Thieme Verlag (Stuttgart 1977).

(28) De Marquez,M.D. ; Thaller,V; J.Chem.Res., **1986** (S), 182.

(29) Middland,M.M. in "Asymmetric Synthesis" vol. 2, Part A, p. 57 and references quoted therein, Morrison,J.D. Ed., Academic Press, New York, **1983**.

(30) Noyori,R. ; Tomiro,L. ; Tamimoto,Y. ; Nishizawa,M., J.Am.Chem.Soc., **1984**,106, 6709.

(31) Falorni,M. ; Lardicci,L. ; Rosini,C. ; Giacomelli,G., J.Org.Chem., **1986** 51, 2030.

(32) Guetté,E. ; Bibang Bi Ekogha,C. ; Julia, S.A., Bull.Soc.Chim.Fr., **1988** II, 325.

(33) Lockard,J.S. ; Schroeck,C.W. ; Johnson,C.R., Synthesis, **1973**, 485.

(34) Mikolajczyk,M. ; Drabowicz,I., Top.Stereochem., **1982** 13, 333.

(35) Kosugi,H. ; Kitoaka,M. ; Tagami,K. ; Takahashi,A. ; Uda,H., J.Org.Chem., **1987**,52, 1078.

(36) Kosugi,M. ; Kitoaka,M. ; Tagami,K. ; Uda,H., Chem.Lett., **1985**, 805.

(37) Note added after submission of the manuscript:
A recent report (F.A.Davis et al, J. Am. Chem. Soc., **1987** 109, 3370) mentionned some high enentioselectivities (≤91%) in oxidation of sulfides by chiral oxaziridines. Our procedure using cumene hydroperoxide in many cases remains superior.