Tetrahedron: Asymmetry Vol. 3, No. 11, pp. 1317-1349, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

TETRAHEDRON: ASYMMETRY REPORT NUMBER 12

RECENT ADVANCES IN THE ASYMMETRIC DIHYDROXYLATION OF ALKENES#

Braj B. Lohray

Division of Organic Chemistry (Synthesis)
National Chemical Laboratory, Pune 411 008, **INDIA**

(*Received* 29 *September* 1992)

CONTENTS

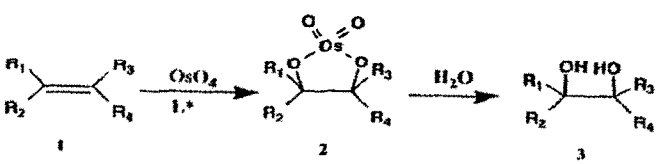
N. C. L. Commun. No. 5601.

1. Abstract:

The reaction of osmium tetroxide with alkenes is perhaps one of the most reliable and selective transformations in organic chemistry. In this article, recent advances made in the asymmetric dihydroxylation (ADH) of alkenes have been described. Chiral auxiliaries used for effecting the oxidation of olefins are mainly diamines and cinchona alkaloid derivatives. Complexes derived from osmium tetroxide with diamines do not undergo catalytic turnover whereas dihydroquinidine and dihydroquinine derivatives have been found to be very effective catalysts for the oxidation of a variety of alkenes. Kinetic resolutions of racemic olefins have been achieved. Several crystallographic studies, theoretical calculations and NMR investigations were carried out to determine the actual structure of the catalyst responsible for enantiofacial selection of alkenes. Kinetic and synthetic studies have been reported to illustrate the mechanism. Some of the most recent applications of this newly discovered methodology in the synthesis of natural products are described.

2.0 Introduction:

The property of stereospecifically embedding two hydroxyl groups in a hydrocarbon framework accounts for the popularity of osmium tetroxide in organic chemistry. Hoffmann[1] showed for the first time that osmium tetroxide could be used catalytically in the presence of a secondary oxygen donor such as sodium or potassium chlorate for the *cis*-dihydroxylation of alkenes. Criegee[2] found that osmium tetroxide could also be used in stoichiometric amount and the resultant osmate ester could be hydrolyzed reductively to give insoluble osmium salts or oxidatively to regenerate osmium tetroxide. He noticed that the addition of a nucleophilic ligand such as pyridine lead to a marked enhancement in the rate of the reaction.[2,3] This fortunate property is also shared by several other tertiary diamines. Later, several other oxidizing agents were employed in combination with osmium tetroxide for the catalytic oxidation of alkenes including, hydrogen peroxide,[4] *t*-butyl hydroperoxide,[5-7] N-methylmorpholine N-oxide,[6-8] oxygen,[9] sodium periodate,[10,11] sodium hypochlorite,[12] potassium ferricyanide[13] *etc. (vide infra).*



1 2 3 (1)

A few excellent reviews have appeared dealing with the osmium tetroxide mediated *cis*-dihydroxylation of unsaturated compounds.[14,15] The present review will be restricted to the asymmetric version of the osmium tetroxide mediated catalytic as well as noncatalytic *cis*-dihydroxylation of alkenes particularly with the recent developments. An account by Johnson and Sharpless,[16] dealing with the work carried out in Sharpless' laboratory, also describes the ADH reactions of a few *cis* olefins as well as several dienes and eneynes etc. and therefore, those topics are not covered here.

3.0 Noncatalytic Asymmetric *cis*-Dihydroxylation of Alkenes::

Criegee's[3] noted discovery of a dramatic rate enhancement in the osmylation reaction of alkenes by tertiary amines laid the foundation for the asymmetric reaction. Later, many tertiary amines were used and several of these complexes were isolated and characterized as diolatodioxabis(amine) osmium (VI) esters [OsO_2(-O-CHR^1-CHR^2-O-)L_2] [R^1=R^2 = alkyl or aryl; L=pyridine, isoquinoline, quinoline, 3-picoline, 4-picoline, 1,2-bipyridyl, 3-(pyridyl) mercuric acetate, 3-chloropyridine etc.].[3] Other nucleophilic ligands such as quinuclidine, quinidine, quinine etc. were introduced to accelerate the formation of osmium(VI) complexes, which resulted in enantioselective oxidation of olefins to vicinal diols.

3.1 Amino Alcohols as Chiral Auxiliaries:

The first attempt to effect the asymmetric *cis*-dihydroxylation (ADH) of olefins (5-82 % ee) with osmium tetroxide was reported in 1980 by Hentges and Sharpless.[17] Despite the cost and toxicity of osmium tetroxide, this reaction was commonly used in the small scale laboratory preparation of vicinal diols owing to its mildness and selectivity. Considering the acceleration of osmium (VI) ester formation by nucleophilic ligands such as pyridine, Hentges and Sharpless reasoned that if pyridine exerts its effect on the reaction by coordination to the metal center at some point along the reaction pathway, then it might lead to the stereoselective formation of the diol product by replacing pyridine with analogous chiral ligand. Initially, they used *l*-2-(2-menthyl)pyridine as a chiral ligand. However, the diols obtained in these reactions were of low enantiomeric purity (3-18 % ee). The low enantiomeric excess was attributed to the instability of the osmium tetroxide chiral pyridine complex. On account of the report of Griffith *et al.*,[18] they selected naturally occurring cinchona alkaloids *viz.* quinine and quinidine. These alkaloids were hydrogenated and acetylated to give dihydroquinine acetate and dihydroquinidine acetate[19] as chiral auxiliaries which bound with osmium tetroxide through quinuclidine nitrogen much more tightly than the chiral pyridine affording diols in reasonably high enantiomeric excess (Figure 1).

Chart A lists all the chiral auxiliaries so far used in asymmetric dihydroxylation of alkenes. Use of one molar equivalent of either quinine or quinidine derivative with osmium tetroxide in toluene

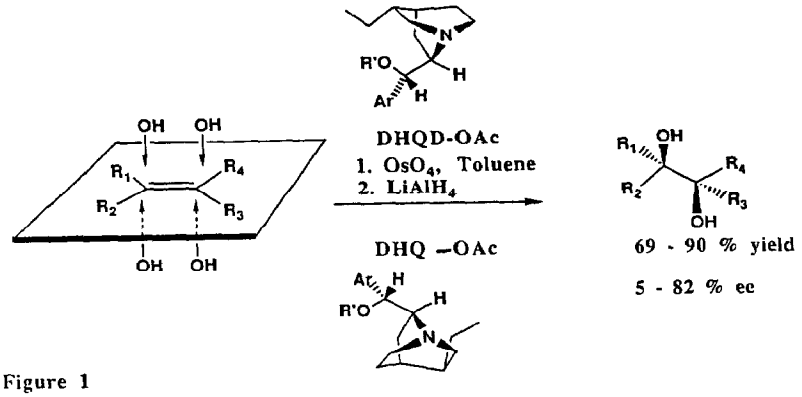
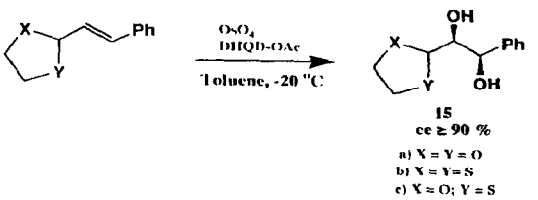


Figure 1

at room temperature with olefins gave vicinal diols of fair to high enantiomeric excess (5-82 % ee; later Sharpless corrected the *ee* of the diol to be 95 % in the case of *trans*-stilbene). Although dihydroquinidine (DHQD) and dihydroquinine (DHQ) are diastereomers, their opposite stereochemistry at carbons 8 and 9 are more characteristic of enantiomers. The quinine derived auxiliary gives one enantiomer of diol product in excess while the other enantiomer predominates when the quinidine derived auxiliary is employed. The diastereomeric nature of these two auxiliaries is reflected by a small but constant difference in the enantiomeric excess of the products (the quinine derivative always gave a lower ee of diols than the corresponding quinidine derivative).

In 1986, Italian chemists[20] carried out the stereoselective dihydroxylation of several protected α,ß-unsaturated aldehydes using dihydroquinidine acetate as a chiral auxiliary. Acetals and thioacetals of cinnamaldehyde gave dihydroxylated products in 90 % optical purity (equation 2).

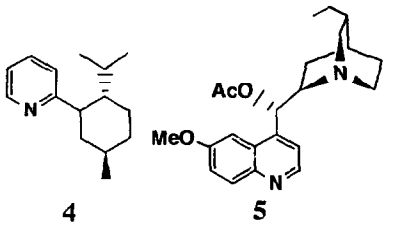


(2)

Encouraged by these results, they explored the possibility of double stereoselection[21] in which the matched pair gave higher enantiomeric excess of the diol. Their substrate controlled diastereoselection as well as double stereodifferentiation is described in Section 6.

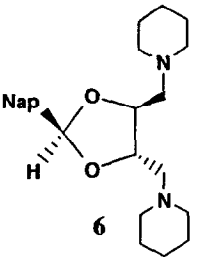
Recently, Sharpless *et al.*[22,23] have reported that 9-*O*-aryl ethers of dihydroquinidine (DHQD **12**) are excellent ligands for the asymmetric dihydroxylation (ADH) of dialkyl substituted *trans*-ole-

CHART A



4 5

Hentges & Sharpless [17]
J. Am. Chem. Soc. 1980

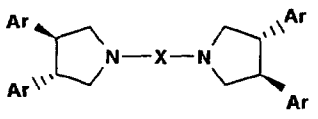


6

Yamada & Narasaka [24]
Chem. Lett. 1986

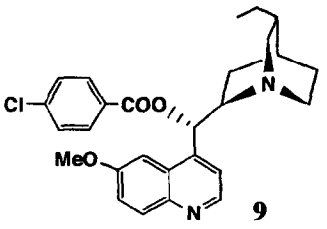
7

Tokles & Snyder [27]
Tetrahedron Lett. 1986



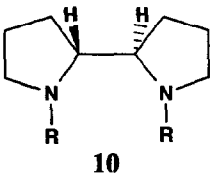
8

Tomioka, Nakajima & Koga [28]
J. Am. Chem. Soc, 1987



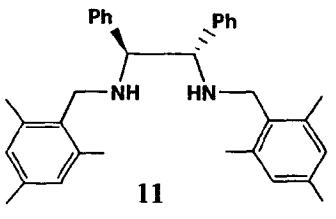
9

Sharpless *et. al.* [36]
J. Am. Chem. Soc. 1988



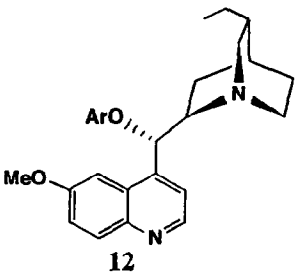
10

Hirama, Oishi & Ito [31]
Chem. Commun. 1989



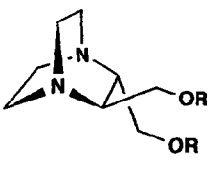
11

Corey *et. al.* [33]
J. Am. Chem. Soc. 1989



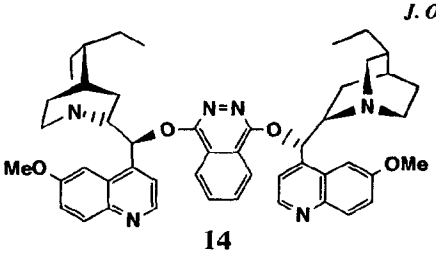
12

Sharpless *et. al.* [22,23]
Tetrahedron Lett. 1990
J. Org. Chem. 1991



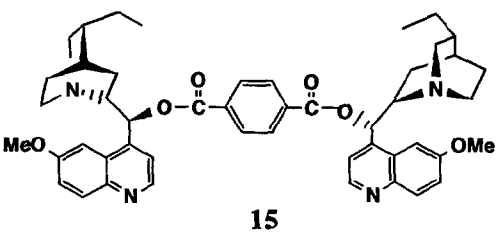
13

Hirama *et al.* [43]
Tetrahedron Lett. 1992



14

Sharpless *et. al.* [44]
J. Org. Chem. 1992



15

Lohray & Bhushan [45]
Tetrahedron Lett. 1992

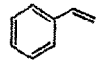
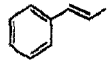
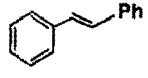
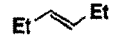
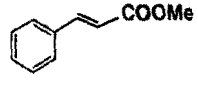
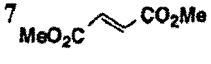
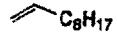
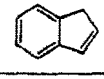
fins. A number of olefins were examined under stoichiometric conditions using aryl ethers of DHQD and DHQ as chiral auxiliaries and their ee's were compared with the ee's of the diols obtained using dihydroquinidine 4-chlorobenzoate as the chiral auxiliary. The data indicate that aryl ethers of DHQD are superior chiral auxiliaries for the ADH of *trans*-dialkyl olefins.

3.2 Diamines as Chiral Auxiliaries:

Since the discovery of the ADH reaction of alkenes mediated by osmium tetroxide-cinchona alkaloid complexes, continuous attempts have been made to improve the optical purity of the diols. Most of the chiral auxiliaries examined were based on the philosophy that higher binding properties with osmium tetroxide would result in better stability of the complex and improved enantiomeric excess of the product. Guided by these principles (*vide supra*), all the chiral auxiliaries investigated so far have been diamines. In 1986, Yamada and Narasaka[24] synthesized a number of homochiral 1,4-diamines derived from *L*-tartaric acid, and screened them in the ADH reaction. All the diamines examined had C_2-symmetry which is often effective in high enantioselection.[25,26] Surprisingly, the highest enantiomeric excess was realized with the naphthyl substituted diamine **6** which does not have C_2-symmetry, for *trans*-stilbene (90 % ee). Table 1 summarizes the ee of the diols obtained in the noncatalytic asymmetric dihydroxylation (NCADH) of alkenes using various chiral ligands.

Tokles and Snyder[27] reported the use of (*R,R*)-N,N,N',N'-tetramethyl cyclohexane-1,2-diamine **7**, as the chiral ligand. The oxidation of 1-heptene with 1.1 eq. of osmium tetroxide-diamine complex gave 86 % ee of (*R*)-1,2-heptanediol in 75 % yield, whereas *trans*-stilbene gave only 34 % ee of (*R,R*)-hydrobenzoin (69 % yield), which is in sharp contrast with the earlier observations.[17,24] These authors explained the unusual stereoselectivity by steric differentiation of osmium tetroxide-olefin complex and the approach of the chiral ligand (diamine) towards this complex. The increasing success of C_2-symmetric ligands in asymmetric reactions[26] encouraged several groups to search for new ligands. In 1987, Tomioka *et al.*[28,29] reported an unparalleled success in the asymmetric dihydroxylation of alkenes using a chiral diamine **8** (Ar = Ph; X = CH_2CH_2) of D_2 symmetry.[30] Virtually complete asymmetric induction was observed with *trans*-ß-methylstyrene (see Table 1). Both the optical antipodes of the chiral 1,4-diamine **8** were synthesized and several olefins were examined. The enantiomeric excesses of the diols were found to be in the range of 83-99 % (Table 1). They have also studied the effect of substituents on the reaction.[29] Slight structural modifications of ligand resulted in dramatic changes in both enantioselectivity and reactivity. With the chiral diamines **8** (Ar = Ph; X = $(CH_2)_3$ or 1,2-benzo or 2,2'-biphenyl), very poor enantioselectivity (*trans*-stilbene, 27 % ee; *S,S*) was observed. The most intriguing result was obtained with the 3,5-xylyl substituted diamine **8** (Ar = 3,5-xylyl, X = CH_2CH_2), which gave opposite facial selectivity for styrene (62 % ee; *R*) and stilbene (66 % ee; *R,R*). They have explained the change in selectivity *via* a four membered metallacycle

Table 1 Enantiomeric Excess (%) of a Few Selected Diols in Noncatalytic Asymmetric Dihydroxylation of Alkenes

S.No.	Alkenes	Sharpless[17]	Yamada[24]	Snyder[27]	Tomioka[28]	Hirama[31]	Corey[33]
1		64.5	—	—	90	88	92
2		45.5	—	—	99	92	93
3		83	90	34	97	100	92
4		50	—	—	90	96	98
5		68	—	—	83	—	82
6		—	—	—	—	99	92
7		—	—	48	93	98	92
8		—	—	66	—	58	—
9		—	—	86	—	91	—
10		—	35	—	—	67	—

based on steric grounds (Section 11).

Hirama[31] investigated N,N-dialkyl-2,2'-bipyrrolidine **10** as a chiral ligand and found that N,N'-dineohexyl-2,2'-bipyrrolidine[32] serves as the most effective ligand at -78 °C for the ADH reaction. However, the enantiomeric excess of the diols obtained from *cis*-disubstituted and trisubstituted olefins is not yet synthetically useful. For example, indene (67 % ee), 1,2-dihydronaphthalene (43 % ee), 1-methylcyclohexene (58 % ee) gave relatively low enantiomeric excesses.

Simultaneously, Corey and coworkers [33] have reported yet another 1,2-chiral diamine **11** derived from (1*S*,2*S*)-diphenyl-1,2-diaminoethane[34] as an effective chiral controller for the ADH reaction. The diol products were obtained in 82-98 % enantiomeric purity and 75-95 % yield. Like Hirama's bis-pyrrolidine ligand **10**, Corey's diamine **11** also afforded modest selectivity in the ADH reaction of *cis* and trisubstituted olefins. For example, the dihydroxylation of 1-phenylcyclohexene (60 % ee), methyl (*R*)-cyclohex-3-ene-1-carboxylate (50 % de), methyl 6-methyl-5-heptenoate (67 % ee), (*S*)-citronellol benzoate (76 % ee) gave relatively lower stereoselectivity.

4.0 Catalytic Asymmetric Dihydroxylation of Alkenes (CADH):

4.1 *Cis*-Dihydroxylation of Alkenes:

The first catalytic asymmetric dihydroxylation of alkenes was reported by Kokubo *et al.*[35] using Bovine Serum Albumin (BSA)-2-phenylpropane-1,2-diolatodioxo-osmium (VI) complex. It has been proved by spectroscopic methods that osmium tetroxide is bound to BSA through the amine residue. α-Methylstyrene gave its product diol with 68 % ee (*S*-configuration) using *t*-butyl hydroperoxide as co-oxidant at 25 °C. Other olefins such as 1-octene, *trans*-ß-methylstyrene gave relatively lower optical purities even though all the diols were of *S*-configuration. The major breakthrough in the CADH reaction of olefins was reported by Sharpless and coworkers in 1988.[36] Combination of 9-acetoxy dihydroquinidine **5** as the chiral auxiliary[17] with N-methylmorpholine N-oxide as the secondary oxidant in aqueous acetone was found to give efficient catalytic turnover affording from olefins optically active diols in excellent yields (Figure 2).

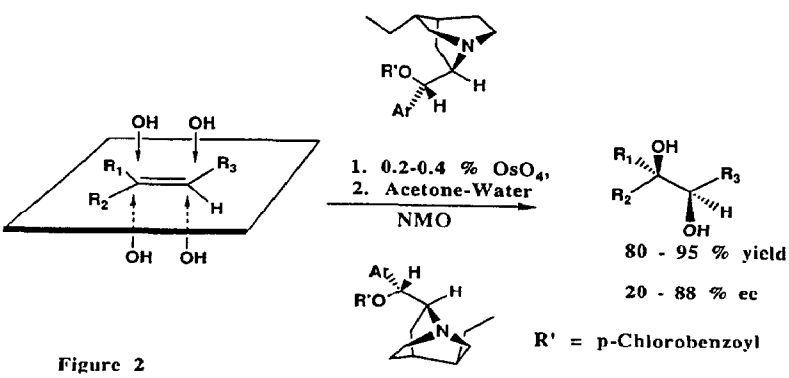
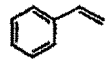
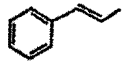
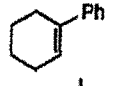
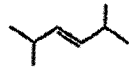
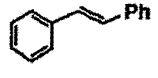
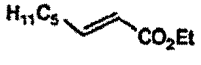
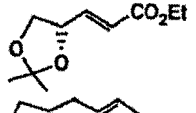
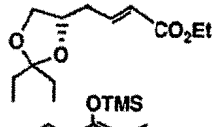
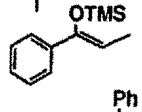
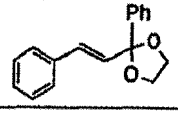


Figure 2

Table 2 Enantiomeric Excess of Diols under modified Conditions

Entry	Substrate	Stoich	Catalytic Conditions		
			Original	Acetate	Slow addition (h)
1		61	56	61	60 (5h)
2		87	65	73	86 (5h)
3		79	8	52	78 (26 h)
4		80	12	61	46 (24h) 76 (24h +TEAA)
5		69	20	64	70 (10h)
6		99	78	—	80
7		66	—	—	67 (31h)
8		77	—	—	76 de (42h)
9		54	—	—	52 de (23h)
10		85	—	—	72 (23h) 78 (23h + TEAA)
11		86	—	—	84 (20h) 87 (20h + TEAA)

Initially, a few derivatives of DHQD and DHQ were examined in order to improve the enantiomeric excess of the diol products. The 4-chlorobenzoate derivatives of dihydroquinidine (DHQD-CLB) and dihydroquinine (DHQ-CLB) were found to afford high optical purity and opposite optical antipodes of the diols. Although several aryl substituted alkenes afforded high optical purity of the corresponding diols, alkyl substituted olefins resulted in considerably lower (20 % ee) optical purities. Even lower enantiomeric excesses were realized with *cis* or cyclic olefins (4-10 % ee).

4.2 Improvement of the Optical Purity of Diols:

Since all alkyl substituted *cis*- or *trans*-olefins gave poor enantiomeric excess under the original ADH condition,[36] it became rather essential to explore the reason for this poor stereoselection. An interesting clue came from the osmylation reaction of 1-phenylcyclohexene, which gave the corresponding diol in 20 % yield and 8 % ee after 8 days at *ca.* 0 °C. The addition of two equivalents of tetraethyl ammonium acetate (TEAA)[6] expedited the reaction yielding diol with 52 % ee in two days.[37] The increase in the ee of the diol indicated that the osmium (VIII) ester complex **19** (Figure 3, where L = DHQD or DHQ derivatives) plays a pivotal role in determining the ee of the diols. Several olefins were examined under this condition using two equivalents of TEAA and in many cases considerable improvement in the enantiomeric excess was observed. This also shed light on the possible existence of yet another catalytic cycle (Figure 3) furnishing diols of low enantiomeric excess.[37] The two catalytic cycles also explain the role of tetraethyl ammonium acetate. The intermediacy of **17**, **18** and **20** have been proved unequivocally by isolation and characterization including X-ray studies. [38,39]

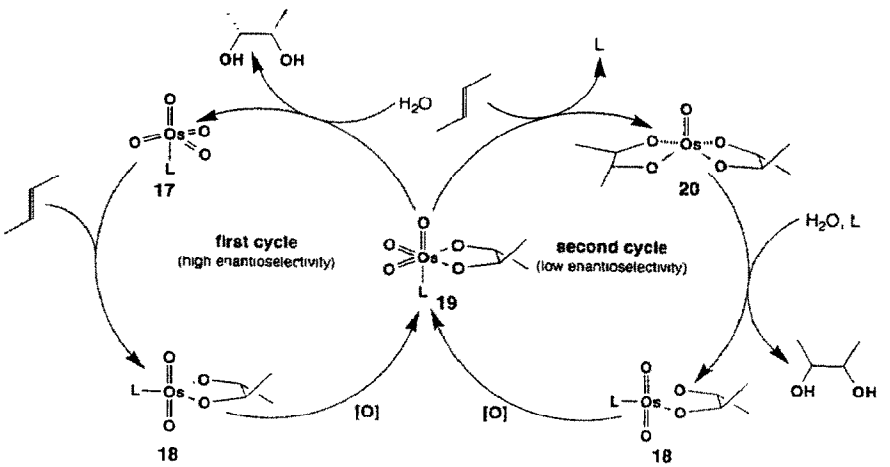


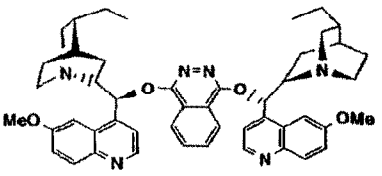
Figure 3

The key, putative intermediate osmium (VIII) trioxoglycolate complex **19** occupies a cardinal position at the junction between the two cycles and hence its properties would determine, how the enantiomeric excess of the diols would be effected by partitioning of the complex between the two cycles. Thus, reduced optical purity in any ADH process is just the counter productivity of turning on the second cycle which also reduces the turnover frequency by tieing up the catalyst. The trivial modification of adding the olefin slowly to the reaction mixture improved the rate as well as the enantiomeric excess of virtually all the diols. For example, 1-phenylcyclohexene was oxidized in 1 day and gave the diol in 95 % yield and 78 % ee. A few selected examples are reported in Table 2. The first column in the Table represents the optical purity of the diols from the reactions performed using a stoichiometric amount of the osmium tetroxide-ligand complex. This allows one to establish the ee ceiling that can be reached in the catalytic process using the DHQD-CLB ligand. The second column represents the ee of the diols under the original conditions.[36] The third and the fourth columns show that most of the olefins benefit greatly from any modification that speeds up the hydrolysis of the osmate ester **19** and in extreme cases, neither acetate nor slow addition alone is sufficient. For example, diisopropylethylene only approached its highest optical purity when both effects were used in tandem. For those olefins which reach their optimum ee's through slow addition alone, the addition times could be substantially shortened in the presence of TEAA. With this improved methodology, most of the *trans*-disubstituted aromatic olefins reached ee's in the range of 80-99 %.[40] However, for aliphatic *cis*- and *trans*-olefins, terminal, tri- and tetrasubstituted olefins, the optical purity of the diols were still not synthetically useful and the search for new chiral ligands continued.

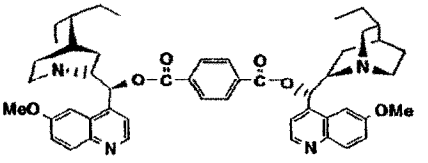
4.3 Search for New Chiral Ligands:

It has been shown that, while the enantiomeric excesses of the diols resulting from the ADH of aryl substituted olefins using DHQD-CLB were satisfactory ($\geq$ 90 % ee),[40] there was room for improvement in the enantioselectivity of the dialkyl substituted olefins. Over 250 different cinchona alkaloid derivatives were screened for the stoichiometric ADH process and the aryl ethers of DHQD were found to be excellent ligands for the dialkyl substituted olefins (*vide supra Section 3.1*).[22,23] A number of aryl ethers of DHQD were examined as chiral ligands for the ADH reaction of several terminal, di- and trisubstituted alkenes. The highest enantioselectivity was obtained with 9-*O*-(9'-phenanthryl)-dihydroquinidine **12a** and 9-*O*-(4'-methyl-2'-quinolyl)-dihydroquinidine **12b**.[23] The use of potassium ferricyanide as secondary oxidant was also examined[13,41,42] (*vide infra*) where the slow addition of olefin is not required and the reaction can be carried out at room temperature. Under these conditions, the diols were obtained in 85-90 % yield with essentially the same enantioselectivity as that obtained in the stoichiometric reaction (Section 8). More recently, Hirama *et. al.*[43] have used C_2-symmetric diazabicyclo[2,2,2]octane **13** as a chiral auxiliary in the osmium tetroxide catalyzed

ADH reaction of alkenes. Although the enantiomeric excess of the diols are less than 41 %, they have observed the change in the diastereofacical selectivity of the alkenes with increasing steric constraint of the chiral controller. Sharpless [44] and we[45] have independently developed C_2- symmetric ligands



14

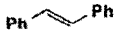
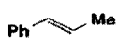
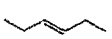
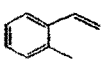
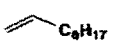
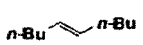
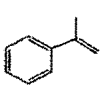


15

a) X = -
b) X = CH_2
c) X = $(CH_2)_2$
d) X = $(CH_2)_4$
e) X = 1,4-C_6H_4

Scheme A

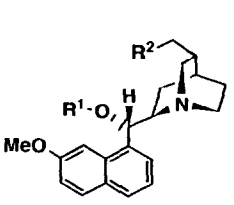
Table 3 Enantiomeric Excess of Diols in Catalytic Asymmetric Dihydroxylation of Alkenes

Entry	Substrates	$DHQD_2$-PHAL	DHQ_2-PHAL	C_2-DHQD	C_2-DHQ
1		>99.5	>99.5	>98	98
2		—	—	>98	—
3		97	97	92	85
4		—	—	93	—
5		97	95	94	—
6		—	—	76	—
7		—	—	48	—
8		84	80	45	—
9		97	93	—	—
10		94	93	—	—

derived from cinchona alkaloids. Sharpless *et.al* [44] have prepared bisdihydroquinidine and bisdihydroquinine ethers of 1,4-phthalazine **14** as chiral auxiliaries and found great improvements in the enantiomeric excess of most of the diols, especially with monosubstituted alkenes. We have examined bisdihydroquinidine and bisdihydroquinine esters of a few carboxylic acids **15a-e** especially with the view to understanding the mechanism of the ADH reaction. We have also found that bisester **15e** is an excellent chiral auxiliary for the ADH reaction of most *trans*-disubstituted alkenes. Table 3 compiles some of the results from our as well as from Sharpless' laboratory using $C_2$2-symmetric ligands in the catalytic ADH reaction. Thus, the enantioselectivity in the dihydroxylation of various substituted olefins which were previously only possible through the use of stoichiometric reagent at low temperature[27-29,31-33] can essentially be obtained in the catalytic ADH reaction using the C_2-symmetric ligands **14** and **15** at room temperature.[44,45]

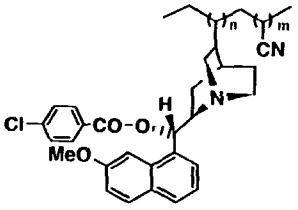
5.0 Catalytic Asymmetric Dihydroxylation on Polymer Support:

Polymer bound cinchona alkaloid have been used in a number of heterogeneous catalytic reactions.[46] To explore the possibility of recycling the alkaloid-OsO_4 complex, Kim and Sharpless [47] have synthesized four different polymers **21** for the ADH reaction of stilbene (up to 87 % ee). Salvadori *et.al*[48] have examined copolymers of acrylonitrile and substituted quinidine and quinine **22** and reported very low optical purity of the diols (up to 45 %ee) at - 15 °C.



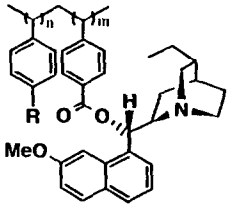
21

R^1 = p-chlorobenzoate; R^2 = polymer backbone
R^1 = polymer backbone; R^2 = H
Kim and Sharpless[47]
Tetrahedron Lett. 1990



22

Salvadori *et al*[48]
Tetrahedron Lett. 1991



23
R = H
R = Ph

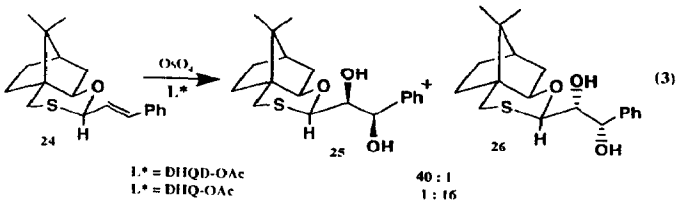
Lohray *et al*[49]
Tetrahedron Lett. 1992

Figure 4

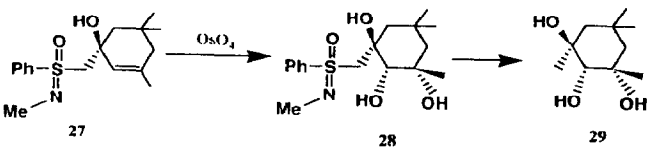
We[49] have prepared several copolymers of styrene **23a** and 4-phenylstyrene **23b** with 10 % DHQD-4-vinylbenzoate affording the most effective catalyst for the heterogeneous ADH reaction (Figure 4). Eight different olefins were examined which gave moderate to high enantiomeric excesses of the diols (22-85 %). Recovery and reuse of the polymer have also been examined and minor decreases in the rate as well as ee of the resultant diol were observed. Irrespective of the spacer or linker used for synthesizing the polymer backbone, the ones containing *ca* 10 % of the alkaloid were found to be the most effective polymer in the ADH reaction.

6.0 Double Diastereoselectivity:

The substrate controlled diastereoselectivity in the osmium tetroxide catalyzed dihydroxylation reaction is well known in the synthesis of many natural products, however, the concept of double diastereoselection in the asymmetric osmylation reaction is a recent event.[21] Annuziata *et.al* [20] used an α,ß-unsaturated thioacetal derived from camphor and cinnamaldehyde to furnish a diastereomeric mixture of diols in a 40:1 ratio when dihydroquinidine acetate is employed as chiral controller (matched pair) and a 1:16 ratio, when dihydroquinine acetate was used (mismatched pair)(equation 3). Similar diastereoselectivities have been reported with other chiral α,ß-unsaturated esters.[50] High diastereoselection has been reported in the dihydroxylation of the adduct obtained by the addition of N,S-dimethyl-S-phenylsulfoximine to 3,5,5-trimethyl-2-cyclohexanol.[51]



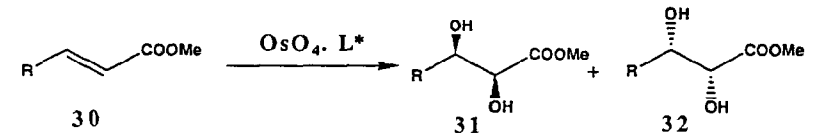
(3)



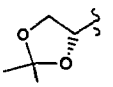
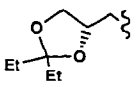
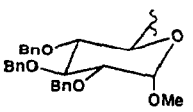
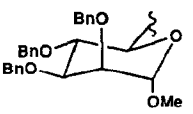
(4)

Sharpless and co-workers [16,40] have also reported the matching and mismatching of a few α,ß-unsaturated esters (Scheme B) bearing a stereogenic center (see Table 2, entries 8,9; more recently far superior stereoselectivity 39 : 1 has been reported by Sharpless *et. al.* using $DHQD_2$-PHAL).[16] Quite recently, a number of α,ß-unsaturated esters containing a pyranose ring as the chiral functional group have been studied for matched and mismatched reactions with catalysts using DHQD-CLB and DHQ-CLB as chiral ligand. In all the matched cases, higher diastereoselectivity was observed.[52,53] Even greater enhancement of selectivity was noted with stoichiometric amounts of the reagent. In recent years, the synthesis of various natural products using diastereoselective hydroxylation either in the presence or in the absence of chiral ligands have started to emerge (Section 13.0). In many cases, excellent selectivity has been observed, although even better selectivities are to be expected under the

modified experimental conditions using newer chiral ligands.



30 31 32

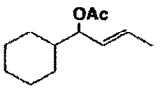
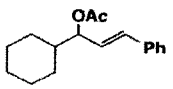
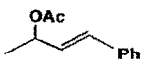
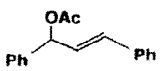
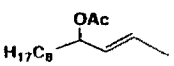
R =	L*	31 : 32
	DHQD-CLB	88 : 12
	DHQD-CLB	77 : 23
	DHQD-CLB DHQ-CLB	1.3 : 1 20.5 : 1
	DHQD-CLB DHQ-CLB	3.4 : 1 15.9 : 1

Scheme B

7.0 Kinetic Resolution:

The kinetic resolution of unfunctionalized alkenes is one of the most difficult goals to achieve by an organic chemist. Interestingly, even enzymatic resolutions of unfunctionalized alkenes are not documented in the literature. Initially, we have investigated the possibility of the kinetic resolution of allylic acetates using our C_2-DHQD-15e and C_2-DHQ-15e ligands in the osmium tetroxide catalyzed ADH reaction.[54] The purpose of choosing allylic acetates was for comparison with the well documented enzymatic catalysis as well as with titanium mediated epoxidation based kinetic resolutions of allylic alcohols. As for the asymmetric dihydroxylation of alkenes, the kinetic resolution is also highly substituent dependent. Our preliminary results summarized in the Table 4 show that in many cases highly efficient kinetic resolution of allylic acetates is possible. The enantimeric excess of allylic acetates recovered in the reactions were determined by ^1H NMR using $Eu(hfc)_3$ as shift reagent. The absolute configurations of the unreacted allylic acetates were confirmed by comparison with an authentic samples. Presently, we are investigating the possibility of the kinetic resolution of truely unfunctionalized alkenes.

Table 4 Kinetic Resolution of Allylic Acetate Using C_2-DHQD-15e[a]

Entry	Substrates Conversion(%)[c] →	Enantiomeric Excess (Configuration)[a,b] 60	70	80	90
1		47(S)	84(S)	95(S)	90(R)[d]
2		86(S)	>98(S)	—	—
3		26(S)	—	—	>98(S)
4		—	—	7(R)	33(R)
5		42(S)	62(S)		>98(S)

a) Enantiomeric excess of the recovered allylic acetate b) Absolute configuration were assigned by hydrolysis of the unreacted allylic acetate to allylic alcohol and comparison with authentic sample. c) Depending upon the conversion, the yield of the diol acetates are in the range of 70-85 % d) C_2-DHQ-13e was used as chiral auxiliary

8.0 Effect of Secondary Oxidants:

Uses of secondary oxidants in the catalytic *cis*-dihydroxylations of alkenes are well documented in the earlier review.[14] In the present section, the effect of some of the oxidants on asymmetric dihydroxylation process will be highlighted. N-Methylmorpholine N-oxide (NMO) is a commonly used secondary oxidant introduced by the Upjohn chemists.[7] Sharpless *et.al* [36] used NMO in the catalytic asymmetric dihydroxylation of alkenes, which furnished high yields and ee's of the diol products. The catalytic cycle of the ADH reaction using NMO as co-oxidant is shown in the Figure 3. Recently, we attempted to use *t*-butyl hydroperoxide (TBHP) as the source of oxygen in the ADH process using a polymer bound cinchona alkaloid as chiral auxiliary since TBHP is cheaper than N-methylmorpholine N-oxide.[49] Use of TBHP gave a considerable amount of nearly racemic α-hydroxycarbonyl compound as the side product in addition to optically active diol. We have investigated the details of the mechanism of formation of the α-hydroxyketone in the ADH reaction and found that the diol is not the precursor.[54] Details of the catalytic cycle are illustrated in the Figure 5. Tsuji *et. al.*[13] have reported the use of potassium hexacyanoferrate (III) as a cheap and convenient co-oxidant in the osmium cata-

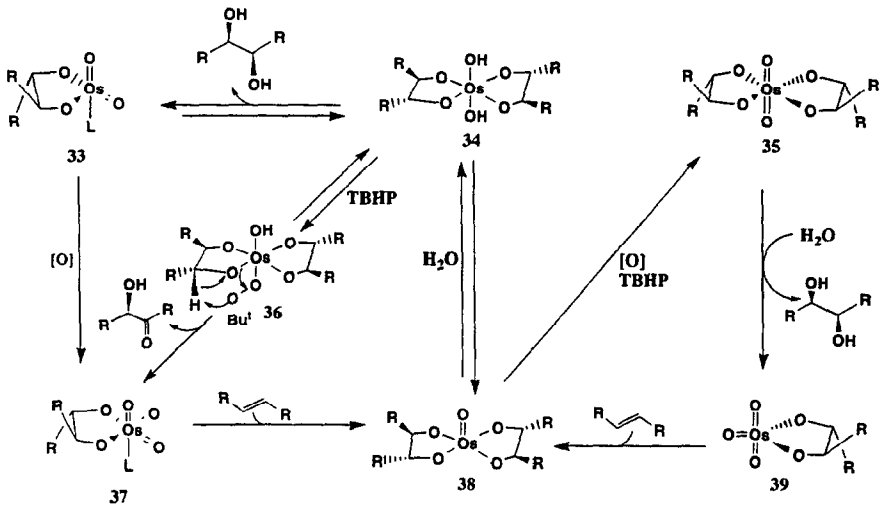


Figure 5

lyzed vicinal dihydroxylation of olefins in *tert*-butanol-water (1:1) as solvent. They believe that the oxidation of Os(VI) takes place through electron transfer mechanism.[55] Use of hexacyanoferrate (III)

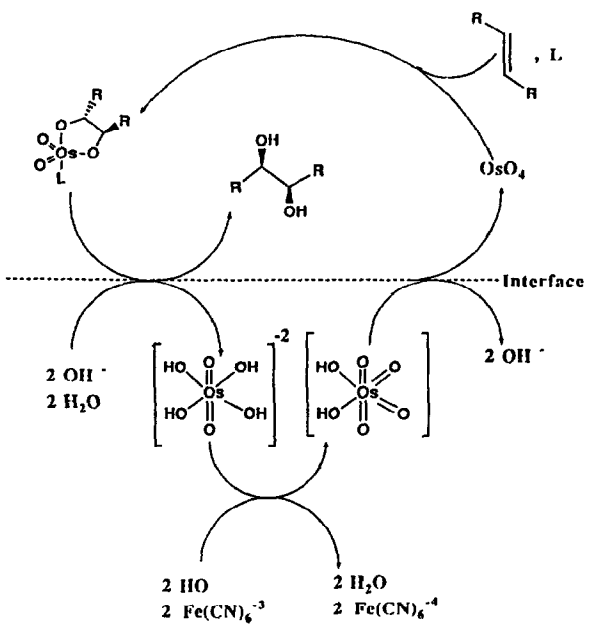
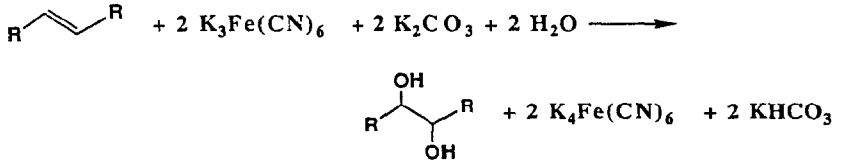


Figure 6

as a co-oxidant in the osmium catalyzed reactions is well known in studies of the kinetics and mechanism of various redox reactions.[56] Introduction of $K_3Fe(CN)_6$-K_2CO_3 as co-oxidant in the ADH reaction substantially improved the enantiomeric excess of all the diols without slow addition of alkenes at room temperature. Sharpless *et.al* [57] have figured out the details of the catalytic cycle, which appeared to be quite different from that of amine oxide (NMO) (Figure 3). When $K_3Fe(CN)_6$-K_2CO_3 is used as co-oxidant, the reactions taking place in the organic phase and aqueous phase are illustrated in the Figure 6. The overall reaction seems to be a redox reaction as shown in equation 5 which shows that in the catalytic cycle both the oxygens of diol are provided by water.



(5)

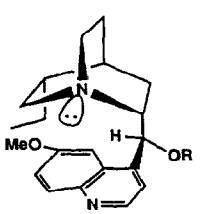
Gao *et. al.*[58] have developed an electrochemical oxidation of potassium ferrocyanide to ferricyanide in order to regenerate the co-oxidant so that the co-oxidant also becomes catalytic in nature. The equation 5 may be simplified further to equation 6 which shows that ultimately water is only adding at the alkene C=C bond to give diol.

(6)

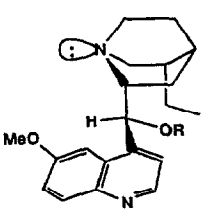
9.0 Conformational Studies of the Catalyst:

Several studies have been reported on the conformation of quinine and quinidine[59] and the general results suggest that C_8-C_9 and C_4-C_9 bonds are of considerable importance in determining the overall conformation of the molecule. Wynberg and Hiemstra[59b] proposed that the most stable conformation of quinine has the quinuclidine ring on one side of the quinoline ring and H_8 and the OH on carbon-9 on the other side. This conformation was also favored by Prelog and Meurling.[60] Dijkstra has also described the conformation of quinine and quinidine from NMR and molecular modelling.[61,62]

CHART B



CLOSED FORM



OPEN FORM

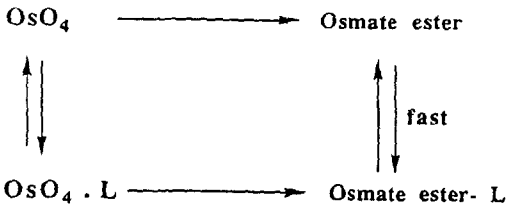
Sharpless *et al.*[38] have carried out NMR studies on various cinchona alkaloid derivatives and assigned a "closed" conformational structure for dihydroquinidine derivatives in solution as well as in solid state. In the "closed" structure the quinuclidine nitrogen lone pair points over the quinoline ring. Upon gradual addition of osmium tetroxide to a solution of the alkaloid, the quinuclidine nitrogen moves away from the quinoline ring and thus results in an "open" conformation as shown in Chart B. Despite detailed NMR studies to understand the conformational structure of alkaloid and alkaloid-osmium tetroxide complex in solution as well as in solid state, it was not clear, how chirality is being transmitted to the substrate from the catalyst, since the stereogenic centres in the ligand are quite remote from the oxo ligands. One significant point which has become clear from these studies is that the alkaloids which are effective ligands in the process, exist in a "closed" conformation in the uncomplexed state, whereas ineffective ligands (R=OH, OMe, $OSiMe_3$, H), all exist in "open" conformations. Interestingly, the methoxy derivative (R = OMe), which exists in an "open" conformation in $CDCl_3$, apparently adopts a "closed" conformation in CD_2Cl_2. In order to assess if similar conformational changes occur when the alkaloids are protonated, DHQD derivatives were treated with trifluoroacetic acid-d_1. The more basic nitrogen of the alkaloid, *viz.* the quinuclidine nitrogen gets protonated preferentially and a change in the conformation from a "closed" to an "open" form takes place. Irrespective of the nature of alkaloid derivatives, they all exist in "open" forms upon complexation with osmium tetroxide.

10.0 Kinetics of the ADH Process:

In order to understand the mechanism of the ADH process, Sharpless and coworkers[63] have studied the detailed kinetics of the ADH reaction. In addition to imparting fair to high level of asymmetric induction into the diol products, DHQD and DHQ derivatives also accelerate the rate of addition of osmium tetroxide to olefins by 1-2 orders of magnitude.

Osmium tetroxide forms coordinatively saturated 18 electron 1:1 complexes with DHQD or DHQ derivatives. For DHQD-CLB K_{eq} = 10-50 M^{-1} at 20 °C in toluene or acetone-water (10:1) and complexation occurs exclusively through the nitrogen of the quinuclidine moiety.[38,39] So far no evidence has been obtained for a bisamine adduct [32] (20 electron complex), although under stoichiometric olefin oxidation by osmium tetroxide in the presence of pyridine or ammonia, a second order rate law has been observed with respect to amine component.[64]

Tomioka *et al.*[65,66] have proposed that the rate limiting step and asymmetry inducing step in the stoichiometric osmylation of olefins involves an intramolecular attack by the second amine component. Therefore, the question of whether one or two molecules of the alkaloid ligand are involved in the rate limiting step was addressed by Sharpless *et. al.*[63] They suggested the possible pathways in the osmylation reaction as shown in equation 7. The rate expression for the outlined process involving

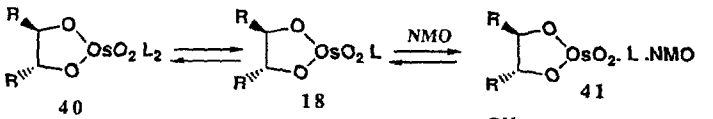


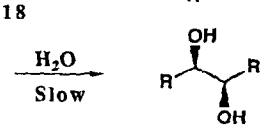
(7)

a single amine ligand is given by equation 8 where K_{eq} is the binding constant of ligand and OsO_4 and K_2 is the measured second order rate constant. They measured the rate expression for nine different olefins both for stoichiometric and catalytic processes using various concentrations of DHQD-CLB and DHQ-CLB. In all the cases, the above rate law was obeyed and the plots of $1/\Delta K$ *vs* 1/[alkaloid] were strictly linear, rigorously establishing the involvement of a single amine ligand in the rate/turnover limiting step. Enantiomeric excesses in the catalytic reaction also approached their maximum value with increasing ligand concentration, obeying equation 9, where K_f and K_s are the rate constants for the major and the minor enantiomeric pathways, respectively. At higher ligand concentration, the

$$\Delta K = K_2 - K_o = \frac{[K_1 - K_o]\, K_{eq}\ (\text{Ligand})}{K_{eq}\ [\text{Ligand}] + 1} \qquad (8)$$

$$ee = \frac{(K_f - K_s)\, K_{eq}\ [\text{Ligand}]}{K_1 . K_{eq}\ [\text{Ligand}] + K_o} \qquad (9)$$





(10)

resulting osmate ester appears to bind the second ligand (kinetically fast step; a 20 electron complex), which is in equilibrium with the coordinatively saturated 18 electron complex as shown in eq 10.

The second binding constant was measured by UV-visible spectroscopy (K_2=0.8-2.1 M^{-1} at 25°C in acetone-water). Osmate esters form octahedral bisamine complexes with pyridine[2] or chiral diamines[2,65] in the presence of high concentrations of the alkaloid. As a result of this, the rate of catalysis is retarded since the reoxidation/ hydrolysis phase of the catalytic cycle is inhibited and becomes turnover limiting. In fact, at lower levels of alkaloid concentration, the reoxidation/hydrolysis appears to be accelerated by a factor of 2-3 relative to the alkaloid free system.

Sharpless and coworkers[63] have also studied the kinetics of decomposition of an osmate ester from styrene in the presence of varying concentration of N-methylmorpholine N-oxide. The results revealed the saturation dependence on the stoichiometric oxidant, indicative of an Os(VI).NMO intermediate. They suggested that NMO binds reversibly to the alkaloid-osmate ester complex and the reoxidation-hydrolysis takes place from the resulting intermediate. Thus, an optimum amount of alkaloid is required to achieve rate saturation in the addition step. The study of saturation kinetics, revealed that the concentration of alkaloid required to achieve the maximum ee is well below that which produces rate saturation (Figure 7).

Thus, the rate becomes independent of the ligand concentration (i.e. saturation when K_{eq}[amine] > > 1). Equation 8 shows that the ee of the reaction reaches a maximum when $K_1 . K_{eq}$ > > [L] K i.e. when $(K_1/K_o)K_{eq}$[L] > > 1. Thus, when K_{obs} is plotted as a function of alkaloid concentration, the enantiomeric excess of the reaction approaches its maximum value K_1/K_o times sooner than does the rate, with K_1/K_o being the direct measure of ligand acceleration effect. Further support in favour of a single ligand complex was provided by our synthetic studies.[45] We have prepared several bis-dihydroquinidine **15** a-c (X = -, CH_2, CH_2CH_2) ligands in which two quinuclidine moieties can bind with the osmium tetroxide. Interestingly, all are very poor catalysts for the ADH process. These ligands essentially can coordinate with OsO_4 like other diamines and thus do not undergo catalytic turnover. In contrast, when two DHQD ligands are separated by a suitable spacer as in **15d** (X = $(CH_2)_4$ or **15e** (X = 1,4-benzo), they function as effective ligands for the osmylation reaction (see Section 4.3). Further, when DHQD or DHQ is immobilized on the polymer backbone,[49] the rate as well as the optical purity of the diol decreases. As the concentration of alkaloid increases on the polymer support, the rate as well as the optical purity of the diols decrease slowly with increasing concentration of DHQD and 100 % of the crosslinked DHQD did not undergo catalytic turnover at all (Section 5.0). These observations suggest that the probability of binding of two ligands in the coordination sphere of osmium tetroxide has a harmful effect on the catalytic process. Thus, the kinetic analysis and synthetic studies unequivocally establish that only one ligand is attached to the OsO_4 in the addition step, and reoxidation/hydrolysis step, which is a key feature in the catalytic turnover and ee generating steps.

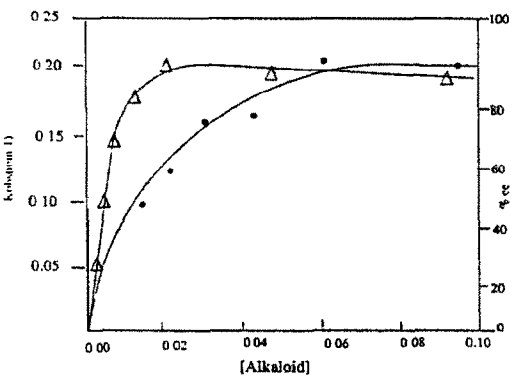
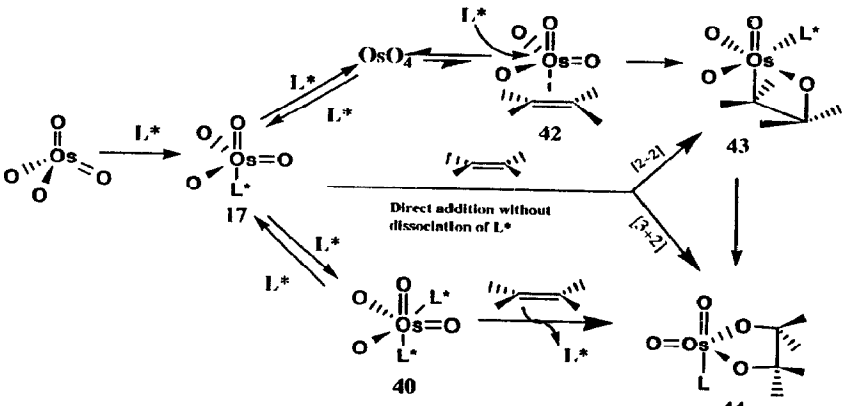


Figure 7. Plot of [Alk] vs observed rate constant & % ee (Δ) for ADH of trans-stilbene. Condition: 25 °C[OsO_4] = 3.8 x 10^{-4}M [NMO] = 0.2 M; [Stilbene] = 0.1 M

11.0 Mechanism of the ADH Process:

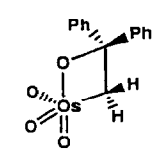
The mechanism of oxidation of olefins by osmium tetroxide to give vicinal diols has long been debated, that is whether they proceed *via* a direct oxygen attack at the unsaturated centre involving a

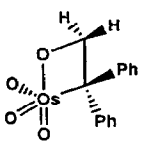


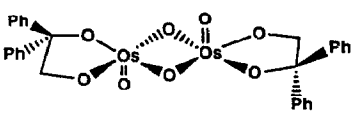
Scheme - C

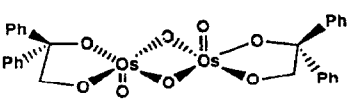
[3+2] cycloaddition[67-69] or *via* an indirect attack of olefin on OsO_4 involving [2+2] pathway[27,29,65, 66,70,71] to give four membered metallacycle, which subsequently rearranges in a rate determining step

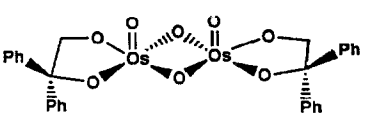
CHART C

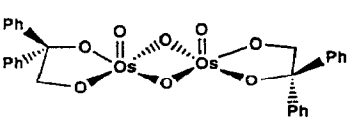

45

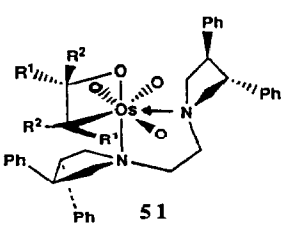

46


47


48


49


50

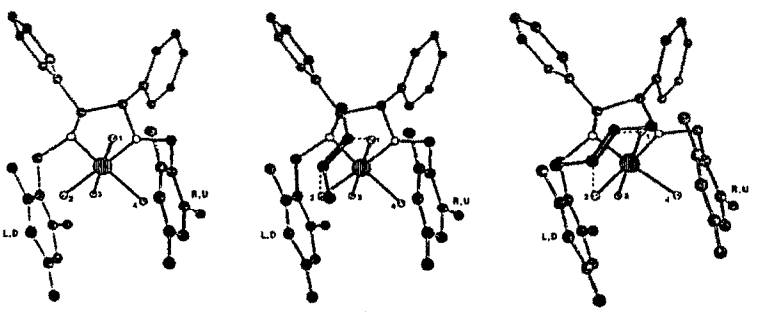

51

to a five membered cyclic osmate ester (Scheme C).[72] Evidence has been put forward in support of both the proposed mechanisms.

As early as in 1982, Schröder and Constable[73] claimed the detection of the four membered intermediates **45** and **46** by NMR studies in support of the stepwise mechanism. However, Casey[74] suggested that the structure detected by Schröder and Constable in NMR studies were not the intermediate **45** or **46** but the dimeric species **47,48,49,50** (Chart C).

Tomioka *et. al.*[28] attempted to explain the oxidation of alkenes by osmium tetroxide in the presence of chiral diamines *via* the intermediacy of a four membered organometallacycle **51**. They have characterized the complex of osmium tetroxide with diamine by X-ray crystallography[65] in which the osmium atom is coordinated to six atoms forming an octahedral coordination group. Based on molecular modelling studies and on steric grounds, they predicted the formation of the wrong diastereomer, if the (3+2) cycloaddition (a six electron transition state) pathway is operative. In contrast, (2+2) cycloaddition was predicted to give the correct stereochemical outcome.

Corey *et. al.*[33] have reported high stereoselectivities in the stoichiometric oxidation of alkenes by their osmium tetroxide-diamine complexes (Section 3.2). They have rationalized their results *via* a transition state involving the (3+2) cycloaddition mode, since the (2+2) cycloaddition pathway would involve prohibitive steric repulsions about a hexacoordinated octahedral osmium. In the transition state for cycloaddition, the geometry of the ligand approaches a C_2-symmetry structure as shown in **52**.

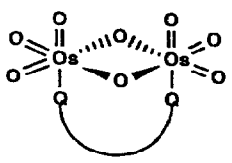


52.

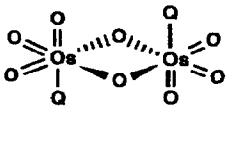
In the (3+2) cycloaddition to C=C, one of the oxygens attached to carbon is axial and the other is equatorial to the chelate ring, since the equatorial oxygens O^2 and O^4 should be electron rich (electron donation from N to σ^* of *trans* Os-O bond) relative to the axial oxygen O^3. This distinction between the four oxygens in the resulting complex with diamine provides the basis for acceleration of olefin osmylation and is essential for the phenomenon of high stereoselectivity. This model, according to Corey *et. al.*[33] leads to an unambiguous prediction of absolute enantioselectivity.

The intermediate osmium (VI) diol complex might also undergo isomerization to a structure with two axial Os=O linkages with diol and diamine chelate roughly coplanar, a geometry that has been observed in an osmate ester complex.[28] On the other hand, a mechanistic model in which the olefin is attacked by the in-plane oxygens O^2 and O^4 leads to an incorrect prediction of the reaction stereochemistry (Houk's calculation supports symmetrical five membered transition state model in which the olefin attacks at O^2 and O^4).[76] Corey[33,77] suggests that this mechanistic model can explain the stereochemical outcome of osmylation of olefins studied by Tomioka[28] and Hirama.[31] Frontier Molecular Orbitals (FMO) calculations of a ligand-osmium tetroxide complex with C_2-symmetry supports Corey hypothesis (Section 12.0).[78-80]

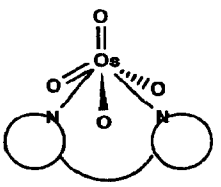
Although Corey's proposed mechanism for dihydroxylation of olefins in the presence of chiral diamines might explain the stereochemical outcome, the mechanism of catalytic dihydroxylation of olefins with osmium tetroxide-alkaloid complex is still a matter of debate. Corey and Lotto[77] have recently suggested that it is less probable for a trigonal bipyramidal osmium tetroxide-DHQD-CLB complex to undergo (3+2) cycloaddition reaction, in which osmium is pentacoordinate. They advanced an interesting suggestion that the active catalyst might not be a monomer but a dimer in which the DHQDS are occupying *trans* positions. Computer modelling studies on such a dimer were carried out and they suggested a structure **54**, in which olefin can react with one axial and one equatorial oxygen of the same osmium tetroxide as in the case of C_2-symmetry chiral diamine. With the view to



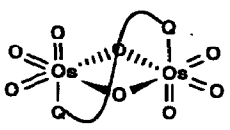
53



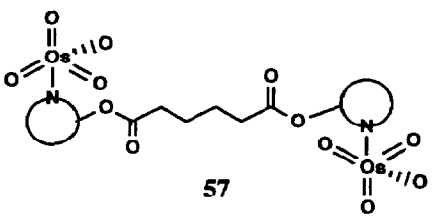
54



55



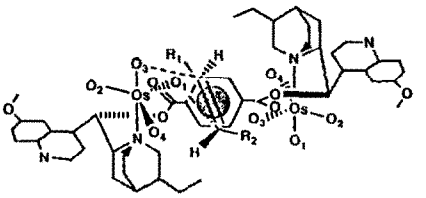
56



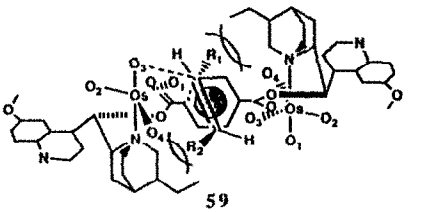
57

examining the validity of this model, we have investigated several C_2-symmetric DHQD and DHQ ligands **15**.[45] Ligands **15a-c** can only form either a very crowded *cis*-dimer **53** (which is highly improbable as suggested by Corey) or may bind to the same osmium tetroxide as a bidentate ligand as shown in **55** like other *tert*-diamines (*cf* Section 3.2). In the latter case, the reaction should not under-

go catalytic turnover (like diamine) as was found to be the case. On the other hand, in the case of **15d**, it is possible that the two quinuclidine moieties may occupy *trans* positions in the dimeric species **56** like **54** as suggested by Corey and Lotto or each quinuclidine moiety may coordinate to OsO_4 separately as indicated in the structure **57** and function as a pedestal for independent dihydroxylation.



58



59

To examine this possibility, we investigated **15e** in which two units of DHQD are coupled together *via* a terephthaloyl moiety. We expected a decrease in the enantioselectivity, if Corey's suggestion that the dimer being the actual catalyst is true since **15e** cannot form dimeric species **56**. On the contrary, the enantiomeric excess of the hydrobenzoin resulting from this reaction was >98 % supporting our surmise that each quinuclidine moiety in **15e** is functioning independently during the facial discrimination of alkenes. We believe that the presence of sterically demanding and electron rich (π-cloud) substituent is playing a pivotal role, in addition to the chirality information from the alkaloid in governing the stereoselectivity of the reaction. We envisaged a model in which the olefin is held over the π-cloud of the ligand (either CO or aromatic substituents) due to π-π interactions. The osmium tetroxide coordinated to the quinuclidine moiety can approach from only one face of the alkene as shown in **58** *via* the interaction of axial oxygen O^1 and equatorial oxygen O^3.[78-80] The possibility of a π-π interaction with the other face of the olefin will suffer from severe steric repulsion as shown in **59**. This model explains the similar selectivity in the case of monosubstituted alkenes and superior selectivity in the case of *trans* disubstituted olefins than with dihydroquinidine 4-chlorobenzoate. This also accounts for the poor selectivity observed in the case of dihydroquinidine and 9-methoxy dihydroquinidine [72] as well as the excellent selectivity for 9-phenanthryl and naphthyl ether derivatives of DHQD and DHQ as reported by Sharpless and co-workers.[23,42] Any perturbation of this π-π interaction due to substituents would result in the decrease in enantiomeric excess.[42]

12.0 Theoretical Interpertation:

Recently, Frontier Molecular Orbital (FMO) calculations by Jϕrgenson and Hoffmann [81] support a [3+2] cycloaddition reaction, even though it is not possible to distinguish between the symmetrical osmium ester complex **44** and asymmetrical complex **43** (Scheme C). They argue that the frontier

orbitals in osmium tetroxide are set up for a [3+2] cycloaddition reaction. A geometric distortion of osmium tetroxide would have to take place if the reaction were a [2+2] cycloaddition process followed by a second deformation back to the symmetric osmate ester 44 which might be unfavorable due to principle of least motion. Jørgenson and Hoffmann [81] have also studied the effect of tertiary amine on the reaction of osmium tetroxide with alkenes since pyridine provides a marked increase in the reaction rate.[2,3,14] This effect has been used to support the argument for asymmetric intermediate 43.[70] They showed, based on FMO line of reasoning and the energy term from second order perturbation theory,[82] the reason for the increased reactivity of osmium tetroxide amine complex with respect to osmium tetroxide. This is due to the decrease in the difference of energy between HOMO of alkene and LUMO of osmium tetroxide amine complex. Osmium tetroxide reacts with pyridine by distortion of its geometry from T_d to C_{2v} symmetry and not from D_{4h}, which is in accordance with X-ray crystallographic investigations.[83] The X-ray analysis of osmium tetroxide quinuclidine complex[84] has suggested a trigonal bipyramidal structure in which one oxygen and quinuclidine are axial and the remaining three oxygens are in equatorial positions. Frontier orbital calculations on this geometry of osmium tetroxide has again supported a (3+2) cycloaddition mode[81] even though they have not completely ruled out the (2+2) cycloaddition mode. More recently, Jørgensen [78-80] has carried out extended Hückel calculation using FMO approach and showed that an alkene can add to one equatorial and one axial oxygen O^1 and O^3 rather than two equatorial oxygens. Frontier orbitals of OsO_4 and OsO_4 amine complexes are shown in Figure 8.

From the frontier orbitals of OsO_4 it is clear that the HOMO and LUMO of OsO_4 which would interact with alkenes are raised up and pushed down in energy when osmium tetroxide is distorted from T_d symmetry by coordination with ligands. If the interaction occurs with two equatorial oxygens O^1 and O^2 (MO of appropriate symmetry), the HOMO is raised by 0.37 eV and LUMO is lowered by 0.78 ev with respect to the molecular orbitals of osmium tetroxide with T_d symmetry. On the other hand, HOMO and LUMO located on equatorial oxygen (O^1) and axial oxygen (O^3) which have the appropriate symmetry to interact with the alkene are raised by 0.62 eV and lowered by 0.41 eV, energy with respect to osmium tetroxide with T_d symmetry. Thus, the complex becomes a better electron donor and an electron acceptor than osmium tetroxide. The distortion from T_d symmetry to C_{2v} symmetry of osmium tetroxide during interaction with amine ligands, makes the oxo-osmium bond weaker which might account for the observed increase in reactivity of osmium tetroxide in the presence of nitrogen ligands compared to osmium tetroxide. Measurement of amplitudes in the occupied and unoccupied molecular orbitals of equatorial and axial oxygens suggests that O^1 is more nucleophilic than O^3 whereas O^3 is more electrophilic than O^1 as postulated by Corey *et al.*[33] The alkene can either approach the complex through the two equatorial oxygens (O^1 and O^2) which do not account for enantioselectivity (but is in accordance with the X-ray structural characterization) or to the one equatorial (O^1) and one axial (O^3) oxygen leading to the formation of chiral diol products.

Jφrgensen's[78-80] calculation supports the latter approach. More recently, Jφrgensen and Schiott[80] have reviewed the mechanism of transfer of oxygen from osmium tetroxide to olefins in the presence of several chiral diamine ligands.

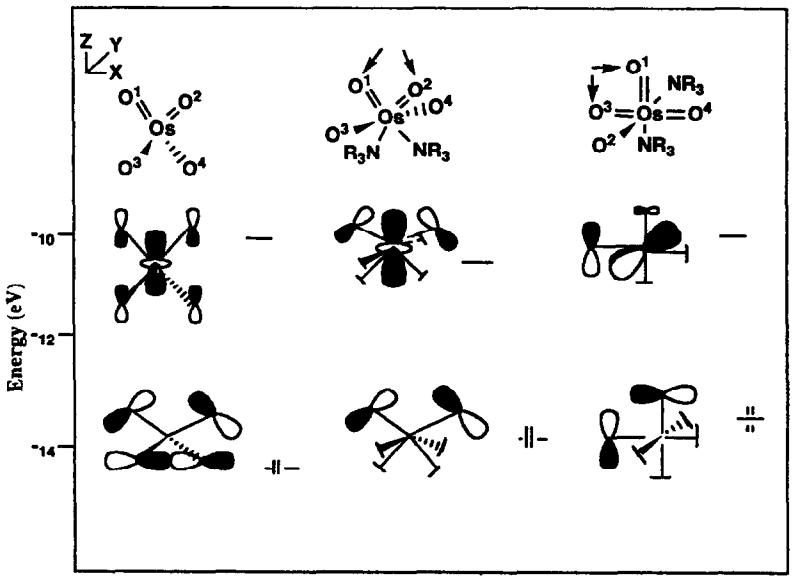


Figure 8 The frontier orbitals of osmium tetroxide with T_d symmetry(left); OsO_4-diamine complex with two equatorial oxygen (center) and with one axial and one equatorial oxygen (right)

In contrast to Jφrgensen's calculation, Houk and co-workers[76] have explained the stereochemical outcome of most of the chiral diamines based on symmetrical five membered transition state structure model using MM2 calculation. Calculation also revealed the difference in the energy for monosubstituted alkenes and disubstituted alkenes. Based on this difference in the energy, Houk argued higher selectivity for *trans*-disubstituted alkenes and also predicted for certain olefins, the possible stereochemical outcome with Tomioka's ligand. Sharpless and Gutierrez[85] have used force field calculation to support two step mechanism in which the migration of C-atom is partially bound to O and Os, however, the transition state structure model resembling four-membered intermediate does not predict the correct stereochemical outcome.

13.0 Direct Application of the ADH Process in Organic Synthesis:

The chemistry of diols have not been very well explored, though diols have been extensively used as chiral auxiliaries in various asymmetric reactions.[86] The direct application of the dihydroxyla-

tion reaction of olefins has been reviewed by Schröder.[14] In recent years, the applications of the asymmetric dihydroxylation reaction in synthesis have started to emerge. For example, Kelly *et.al.* [87] have employed asymmetric catalytic dihydroxylation process for the synthesis of pradimicinone. Similarly, Rama Rao and coworkers [88] have synthesized chiral ß-blocker drugs using the ADH process. Tomioka *et al.* [28,89] have used asymmetric dihydroxylation, though not a catalytic method, for the synthesis of anthracycline antibiotics. Chiral crown ethers are synthesized from homochiral diols.[86] Sharpless and co-workers[90] have conveniently converted several homochiral diols into cyclic sulfates, which undergo stereoselective transformations with a variety of nucleophilies such as F^-, NO_3^-, N_3^-, SCN^-, $RCOO^-$, SCN^-, RMgX and H^- to give the corresponding substituted products in excellent yields. We[34] have found that cyclic sulfites, the precursors to cyclic sulfates themselves undergo stereoselective ring opening with azide nucleophiles to afford azido alcohols, which were subsequently transformed into several aziridines, amino alcohols and diamines.[91] A detailed treatise on the stereoselective transformations of homochiral diols *via* cyclic sulfites and cyclic sulfates will appear separately.[92] Greene *et al.*[93] have synthesized the side chain of Taxol *via* stereoselective transformations of *threo*-2,3-dihydroxy esters. Watson *et. al.*[94] have reported an elegant synthesis of a potent vasodialating agent diltiazem (a calcium channel blocker) involving asymmetric dihydroxylation of methyl *p*-methoxycinnamate as the key step. Fleming and Sharpless [95] have recently reported selective transformations of *threo*-2,3-dihydroxy esters to various epoxides and other useful synthetic intermediates. Zhou *et.al.*[96] have used the ADH reaction for the synthesis of a plant growth regulator. Ireland and coworkers [97] have achieved better selectivity (5:1) using the DHQ-CLB-OsO_4 complex in the synthesis of FK 506. Similarly, Schreiber *et. al.* [98] have used the ADH reaction to get improved selectivity (12.9:1) over two isolated double bonds using the DHQ-CLB complex. Cooper and Salomon [99] have synthesized one of the intermediates in the synthesis of Halichondrin using the ADH (DHQD-CLB-osmium tetroxide) in good selectivity. These are a few isolated examples of recent application of ADH reaction which have started to appear and definitely, such examples are bound to grow in future.

14.0 Conclusion:

In the last decade, several attempts have been made to stereoselectively functionalize alkenes under catalytic conditions, however, until the discovery of asymmetric dihydroxylation of alkenes in 1988, chemists had no examples to match the catalytic activity of enzymatic processes. Success of the ADH process has already initiated further investigations of more challenging problems such as asymmetric epoxidation of nonfunctionalized alkenes as evident from the recent reports of Jacobsen[100] and Katsuki.[101] The success of *Chemzymes* is no longer dependent on a tethering group. Presently, with improved ligands for the asymmetric dihydroxylation of alkenes, useful levels of enantioselectivity have been achieved for a variety of olefins. We hope that in future with a better understanding of

the mechanism of these catalysts, even better optical purity will be achieved. In addition, the ADH process has given rebirth to the phenomenon of ligand accelerated catalysis for asymmetric reactions.

Acknowledgement: I am extremely thankful to Professor K. B. Sharpless for providing a copy of his monograph[16] which is expected to appear in early 1993. I particularly thank Drs P. K. Dhal and Vidya Bhushan for their invaluable advice and for checking the manuscript. Financial support by DST, New Delhi is gratefully acknowledged.

15.0 References:

1. Hoffmann, K. A. *Chem. Ber.* **1912**, *45*, 3329.
   Hoffmann, K. A.; Ehrhart, O.; Schneider, O. *Chem. Ber.* **1913**, *46*, 1657.
2. Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75.
3. Criegee, R.; Marchand, B; Wannwins, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.
4. a) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 1302. b) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1937**, *59*, 2345.
5. Byers, A.; Hickinbottom, J. *J. Chem. Soc.* **1948**, 1328.
6. a) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986.
   b) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.
7. Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.
8. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Grass, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.
9. Cairns, J. F.; Roberts, H. L. *J. Chem. Soc. C.* **1968**, 640.
10. Wiesner, K.; Santroch, J. *Tetrahedron Lett.* **1966**, 5939.
11. McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, N. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330.
12. Foglia, T. A.; Barr, P. A.; Malloy, A. J.; Costanzo, M. J. *J. Am. Oil Chem. Soc.* **1977**, *54*, 870A.
13. Minanto, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
14. Schröder, M. *Chem. Rev.* **1980**, *80*, 187.
15. Courtney, J. L. in *"Organic Syntheses by Oxidation with Metal Compounds"* Eds. Meijs, W. J. and de Jonge, C. R. H. I. Plenum Press, New York, 1986, 445.
16. Johnson, R. A.; Sharpless, K. B. in *"Catalytic Asymmetric Synthesis"* Ed. Ojima, I., VCH publisher, scheduled to appear in 1993.
17. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
18. Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc. Dalton Trans.* **1977**, 941.

19. Hesse,O. *Justus Liebigs Ann. Chem.* **1887**, *241*, 255.
Hesse,O. *Justus Liebigs Ann. Chem.* **1882**, *214*, 1.
20. Annunziata, R.; Cinquine, M.; Cozzi, F. *Tetrahedron Lett.* **1987**, *27*, 3139.
21. Masamune, S.; Choy, W.; Petersen, J. S.; Rita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.
22. Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3817.
23. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
24. Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131.
25. Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663.
26. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
27. Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951.
28. Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213.
29. Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741.
30. *D_2-symmetric ligands:*
Cram, D. J.; Sogah, G. D. *J. Chem. Soc. Chem. Commun.* **1981**, 625.
Mazaleyrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
31. Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc. Chem. Commun.* **1989**, 665.
32. Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834
33. Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P. W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
34. Lohray, B. B.; Ahuja, J. R. *J. Chem. Soc. Chem. Commun.* **1991**, 95.
35. Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc. Chem. Commun.* **1983**, 769.
36. Jacobsen, E. N.; Markò, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
37. Wai, J. S. M.; Markò, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
38. Svendsen, J. S.; Markò, I.; Jacobsen, E. N.; Rao, C. P.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2263.
39. Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 639.
40. Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041.
41. Kwong, H. L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**,

31, 2999.

42. Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761.
43. Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639
44. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.*, **1992**, *57*, 2768.
45. Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1992**, *33*, 5113.
46. a) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *90*, 7071. b) Kobayashi, N. Iwai, K. *J. Poly. Sci. Chem. Ed.*, **1980**, *18*, 223. c) Salvadori, P.; Rosini, C.; Pini, D.; Bertucci, C.; Altemura, P.; Vccelo-Barretta, G.; Raffaelli, A. *Tetrahedron* **1987**, *43*, 4969. d) Inagaki, M.; Iliratáka, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn* **1987**, *67*, 4121.
47. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003.
48. Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Lett.* **1991**, *32*, 5175.
49. Lohray, B. B.; Thomas, A.; Chittari, P.; Ahuja, J. R.; Dhal, P. K. *Tetrahedron Lett.* **1992**, *33*, 5453.
50. Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485.
51. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459.
52. Brimacombe, J. S.; McDonald, G.; Rahman, M. A. *Carbohydrate Res.* **1990**, *205*, 422.
53. Decamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564.
54. Lohray, B. B.; Bhushan, V. *Unpublished results.*
55. Rosenheim, L.; Speiser, D.; Haim, A. *Inorg. Chem.* **1974**, *13*, 1571.
56. Mehrotra, R. N.; Kapoor, R. C.; Vajpai, S. K. *J. Chem. Soc. Dalton Trans.* **1984**, 999. Chaudhary, P.; Nagori, R. R.; Mehrotra, R. N. *Indian J. Chem.* **1986**, *25A*, 1123 and references cited therein.
57. Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965.
58. Gao, Y. *et. al. Unpublished results; This information has been obtained from reference 16.*
59. a) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87. b) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1979**, *20*, 1215.
60. Prelog, V.; Wilhelm, H. *Helv. Chim. Acta.* **1954**, *37*, 1634. Mecurling, L. *Chem. Scr.* **1975**, *7*, 90.
61. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas*, **1989**, *108*, 195.

62. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Markò, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.
63. Jacobsen, E. N.; Markò, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.
64. Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425.
Burton, K. *Biochem. J.* **1967**, *104*, 686.
Griffith, W. P.; Rossetti, R. *J. Chem. Soc. Dalton Trans.* **1972**, 1449.
65. Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573.
66. Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741.
67. Dewar, M. J. S. *Ind. Chim. Belg.* **1950**, *15*, 181. *Chem. Zentralbl.* **1951**, *1*, 1716.
68. Dewar, M. J. S.; Longuet-Higgins, H. C. *Proc. R. Soc. London Ser. A.* **1952**, *214*, 482.
69. Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3341.
70. Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
71. Rappé, A. K.; Goddard, W. A. *J. Am. Chem. Soc.* **1982**, *104*, 3287.
72. Zelikoff, M.; Taylor, H. A. *J. Am. Chem. Soc.* **1950**, *72*, 5039.
73. Schröder, M.; Constable, E. C. *J. Chem. Soc. Chem. Commun.* **1982**, 734.
74. Casey, C. P. *J. Chem. Soc. Chem. Commun.* **1983**, 126.
75. Schröder, M.; Nielson, A. J.; Griffith, W. P. *J. Chem. Soc. Dalton Trans.* **1979**, 1607.
76. Wu, Y.-D.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 1362.
77. Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, *31*, 2665.
78. Jφrgensen, K. A. *Tetrahedron Lett.* **1990**, *31*, 6417.
79. Jφrgensen, K. A. *Tetrahedron Asymm.* **1991**, *2*, 515.
80. Jφrgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483.
81. Jφrgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867.
82. Fujimoto, H.; Fukui, K. in *Chemical Reactivity and Reaction Paths*, Ed. Klopman, G. John Wiley & Sons, New York, 1974, p 23.
83. Conn, J. F.; Kim, J. J.; Suddath, F. L.; Blattmann, P.; Rich, A. *J. Am. Chem. Soc.* **1974**, *96*, 7152.
Kistenmacher, T. J.; Marzilli, L. G.; Rossi, M. *Bioinorg. Chem.* **1976**, *6*, 347.
Neidle, S.; Stuart, D. L. *Biochem. Biophys. Acta.* **1976**, *418*, 226.
84. Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chem. Acta.* **1978**, *31*, L413.
85. Sharpless, K. B.; Gutierrez, A. *reported at 200 th National meeting of American Chemical Society, Washington D. C., Aug. 29, 1990.*
86. ***Recent examples of diols as chiral auxiliary***:
Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org.*

Chem. **1990**, *55*, 2045.
Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966.
Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515.
Eid Jr. C. N.; Konopelski, J. P. *Tetrahedron Lett.* **1990**, *31*, 305.
Konopelski, J. P. *Tetrahedron Lett.* **1991**, *32*, 465.
Commercon, M.; Mangeney, P.; Tejere, T.; Alexakis, A. *Tetrahedron Asy.*, **1990**, *1*, 287.
Precursor to chiral ether.
Crosby, J.; Fakley, M. E.; Gemmell, C.; Martin, K.; Quick, A.; Slawin, A. M. Z.; Shahriari-Zavareh, H.; Stoddart, J. F.; Willams, D. J. *Tetrahedron Lett.* **1990**, *30*, 3849.
Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.*, **1989**, *111*, 8266.
Hoffmann, R. W.; Dietrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *112*, 1783.
Stürmer, R.; Hoffmann, R. W. *Syn. Lett.* **1990**, 759.
Stürmer, R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 8089.
Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. *Tetrahedron Lett.* **1989**, *30*, 6457.
87. Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161.
88. RamaRao, A. V.; Gurjar, M. K.; Joshi, S. V. *Tetrahedron Asymmetry* **1990**, *1*, 697.
89. Tomioka, K.; Nakajima, M.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1921.
90. a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538; b) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623.
91. Pini, D.; Luliano, A.; Rosini, C.; Salvadori, P. *Synthesis*, **1990**, 1023.
92. Lohray, B. B. *Synthesis* see November issue 1992.
93. Greene, A. E.; Denis, J. N.; Correa, A. *J. Org. Chem.* **1990**, *55*, 1957.
94. Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Mattews, B. R. *J. Chem. Soc. Chem. Commun.* **1990**, 1018. Gredley M. PCT Int. Appl. WO 8902 428. *Chem. Abstr.* **1989**, *111*, 173782V.
95. Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.
96. a) Sun, L.-Q.; Zhou, W.-S.; Pan, X.-F. *Tetrahedron Asymmetry* **1991**, *2*, 973. b) Zhou, W.-S.; Huang, L.-F.; Sun, L.-Q.; Pan, X.-F. *Tetrahedron Lett.* **1991**, *32*, 6745.
97. Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284.
98. Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657.
99. Cooper, A. J.; Saloman, R. G. *Tetrahedron Lett.* **1990**, *30*, 3813.
100. Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
101. Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055.