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Asymmetric epoxidation

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ABSTRACT. **The data on asymmetric epoxidation that have been obtained in recent years are correlated. Particular attention is given to the epoxidation of allylic alcohols with Sharpless reagent, which is a chemical complex of a titanium alkoxide with dialkyl tartrate. The structure of the catalyst, a model of the transition state, and the reaction mechanism are examined.**

The bibliography includes 242 references.

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I. Introduction

In recent years the epoxidation of olefins—an important and frequently used reaction in organic synthesis—has acquired increasing significance as a method for the synthesis of chiral compounds. Enantioselective epoxidation, which results in the formation of two chiral sites in a single stage, yields optically active oxiranes, which are synthons for the preparation of natural compounds and their analogues. Of particular importance is the use of oxiranes in an optically pure form in the production of drugs, pheromones, etc.[1,2]

Chiral oxiranes play a significant role in the active processes of plants and animals. They are intermediates in biological synthesis. For example, the important function of 2,3-epoxysqualene in the biosynthesis of terpenes and steroids is well-known. By studying asymmetric epoxidation (AE) it is possible to establish the mechanism of many biological processes. Epoxidation is one of the fundamental stages during the exchange of substances in plant cells and animal organisms.[3] In many cases oxiranes participate in the catabolism of pesticides, drugs, and other xenomorphic comounds.[3,4] Hydroxylation, which is a key stage in the metabolism of aromatic amino acids, drugs, and vitamins in living organisms, occurs via an epoxidation reaction.[5] Intermediates containing an oxirane ring that are formed during the oxidation of aromatic hydrocarbons function as carcinogenic, mutagenic, and cytogenic agents.[5] Some natural epoxy compounds have juvenile hormonal activity.[6–8]

The physiological activity of many natural compounds containing an epoxide ring and the important role of oxiranes in the synthesis of natural compounds have determined the need for research into effective methods and a study of the mechanism of enantioselective epoxidation. A survey of the methods of AE is the aim of the present review, in which epoxidation using Sharpless reagent, which has been studied the most comprehensively in direct relation to the mechanism of this reaction, occupies a central position.

II. Methods of asymmetric epoxidation

AE was first reported to have been carried out by Henbest in 1965.[9,10] By epoxidising olefins with an isolated double bond with (+)-peroxycamphoric acid it was possible to obtain oxiranes with an enantiomeric excess (EE) of less than 5%. Despite the low optical purity of the compounds obtained, this reaction played an important role since for the first time the possibility of synthesising chiral oxiranes from achiral precursors was demonstrated. The attempts made subsequently to carry out AE using other peroxides were not successful in increasing the optical purity of oxiranes above 10%.[11–18] In 1977 Pirkle again studied this method and found that the peroxycamphoric acid which had been used in previous experiments was insufficiently pure.[19] As a result of purifying the oxidising agent it was possible to increase the enantioselectivity of the reaction by a factor of more than 2. By using the purified peroxyacid in the epoxidation of imines it was possible to obtain oxaziridines with an EE of >60%. In the majority of the cases mentioned above the low asymmetric induction at the stage involving oxygen transfer is probably due to the considerable distance of the electrophilic atom of the peroxide oxygen from the asymmetric centre and hence to the weak interaction between this centre and the double bond in the transition state (Fig. 1*a*).[20]

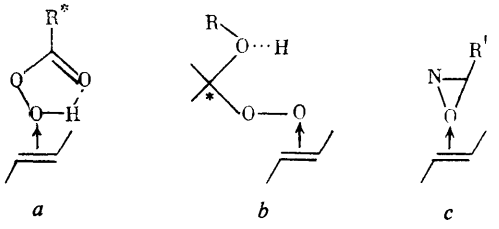


Figure 1. Transition state in the epoxidation of olefins with chiral peroxyacids (*a*), α-substituted hydroperoxyketals (*b*), oxaziridines (*c*).

The epoxidation of olefins with different chiral α-substituted hydroperoxyketals occurs with low asymmetric induction (EE <5%).[21] This value, in the opinion of Finn and Sharpless,[22]

could be increased since in this case the chiral centre is closer to the reaction site than for chiral peroxyacids (Fig. 1*b*).

Considerable success was achieved in the epoxidation of olefins with oxaziridines. In the transition state (Fig. 1*c*) the interaction between the chiral centre and the double bond is greater than when peroxyacids are used.[23–25] The maximum EE of these reactions was 65%.[24,25]

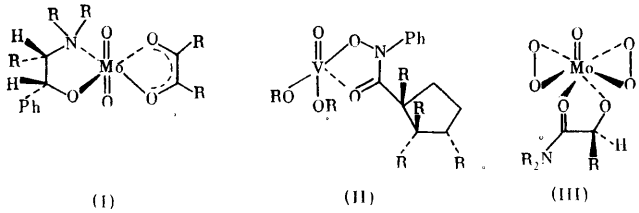
Use of the dioxiranes obtained by reaction of potassium peroxomonosulphate with chiral ketones for asymmetric induction in the epoxidation of olefins results in the formation of epoxy compounds with a low enantioselectivity (EE 4–13%).[26]

Epoxidation with hydrogen peroxide, t-butyl hydroperoxide (TBHP), or with hypochlorite of α,β-unsaturated acids, aldehydes, ketones, and other olefins whose double bond is conjugated with strongly electronegative substituents gives chiral epoxy compounds when a two-phase system and an optically active phase-transfer catalyst are used. In this case the enantioselectivity of the reaction varies from 1.2–5.4% EE (quaternary salts of quinone added to a polystyrene matrix comprise the phase-transfer catalyst),[27] 11% EE in the presence of cyclodextrins,[28–30] up to values of 55–78% EE when phase-transfer catalysts based on cinchona alkaloids[31] and quinine derivatives[32–37] are used. Much more effective phase-transfer catalysts are the so-called synthetic enzymes—polyamino acids—which can be used to epoxidise prochiral olefins with a high enantiomeric purity (EE up to 100%).[38–43] Epoxidation in this case takes place in a three-phase system—α-amino acid/aqueous phase/organic phase.

AE with hydrogen peroxide in an aqueous solution of sodium hydroxide under phase-transfer conditions using optically active solvents as the organic phase has been reported.[44] Chiral crown ethers have been used for asymmetric induction under phase-transfer conditions.[45] Epoxidation of olefins with aromatic substituents by hydrogen peroxide in the presence of (+)- or (−)-cyanoheptohelicene gives chiral oxiranes with an optical purity of 97–100%.[46]

Oxiranes with an EE of about 10% have been obtained by Darzens condensation in the presence of chiral compounds such as quinine salts.[47,48] Quinine salts have also been used for asymmetric induction in the epoxidation of prochiral olefins with molecular oxygen.[49]

During the last twenty years there has been increased interest in transition metal complexes as catalysts for AE.[50,51] One of the advantages of processes catalysed by transition metals is the possibility of varying the structure of the ligands for modifying catalytic processes. In the case of chiral ligands, the substituents will in all probability be arranged asymmetrically about the chiral centre. On the basis of this assumption, Yamada[52] and Sharpless et al.[53] used chiral complexes of molybdenum (I) and vanadium (II) for the first time in order to carry out the asymmetric epoxidation of allylic alcohols with organic hydroperoxides.



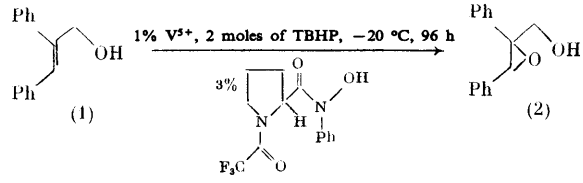
(I) (II) (III)

R = CH_3

A number of reports were later published on the epoxidation of prochiral olefins with various chiral molybdenum oxodiperoxo complexes used in stoichiometric amounts[54–59] [this reaction was carried out for the first time using complex (III)] and on the asymmetric epoxidation of olefins with organic hydroperoxides when a catalytic quantity of chiral dioxomolybdenum complexes [similar to complex (I)] were used.[60–63] On treatment of molybdenum oxodiperoxo complexes in the presence of chiral diols it was possible to obtain an oxirane with an EE of 95.4% in the epoxidation of olefins with an isolated double bond.[59] Lower asymmetric induction occurred in the epoxidation of olefins with an isolated double bond by hydrogen peroxide in the presence of chiral platinum complexes modified with diphosphines (EE 41%)[64] and also chiral complexes of iron porphyrin (EE about 51%).[65] In the latter case oxo compounds obtained by oxidation of iron porphyrin with iodosylbenzene constitute the epoxidising agent. Chiral complex iron compounds have also been used for AE of styrene derivatives (EE about 50%).[66–68]

The use of aluminium alkoxides and chiral hydroxamate ligands for carrying out the AE of allylic alcohols with TBHP has been reported (EE 30–40%).[69]

The AE of substituted allylic alcohols catalysed by vanadium complexes involving more than 20 chiral hydroxamate ligands has been studied.[70–72] The maximum enantioselectivity was achieved in the epoxidation of (*E*)-α-phenylcinnamic alcohol (1) [EE of epoxyalcohol (2) was 80%]:



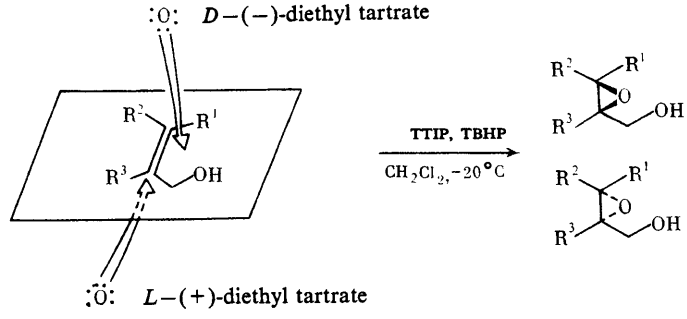


Figure 2. Asymmetric epoxidation of prochiral allylic alcohols.

In addition to chemical methods, other ways of obtaining chiral oxiranes are also known. One of these is the microbiological epoxidation of olefins.[73–82] The enantioselectivity of the reactions catalysed by the enzymes secreted by microorganisms depends on metabolic by-products of the microorganisms, which can cause inhibition of the reaction. Enzymatic epoxidation has been used to obtain oxiranes with a high EE.[83–87] For example, a high degree of enantioselectivity can be achieved when globular proteins such as bovine serum albumin (BSA) are used as catalysts.[88–91] In particular, AE of 2-substituted naphthoquinones with hydrogen peroxide and TBHP in a buffer solution containing an organic

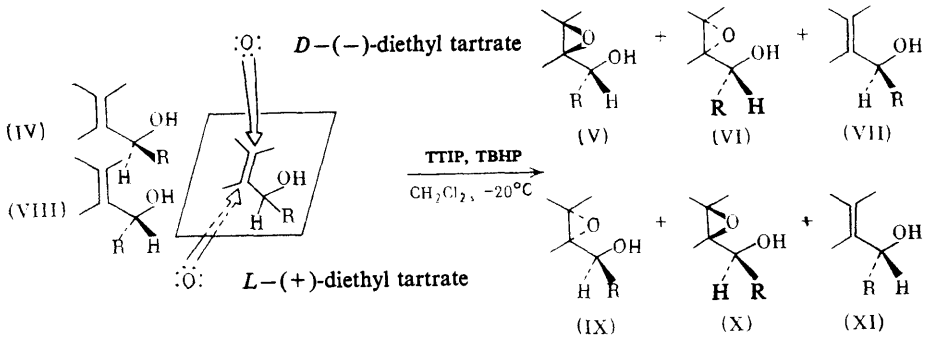


Figure 3. Kinetic resolution of racemic secondary allylic alcohols.

solvent and BSA results in the formation of chiral oxiranes with an EE of up to 100%. Asymmetric induction in this case is due to BSA occurring in the form of α-helices with hydrophobic groups capable of bonding with water-insoluble substrates situated between the helices. It should be noted that AE catalysed by enzymes is only suitable for a narrow range of substrates and its effectiveness is determined to a considerable extent by the reaction conditions.

III. Asymmetric epoxidation in the presence of a chiral titanium−tartrate complex

Directed research on chiral ligands was carried out in order to obtain an effective AE catalyst based on titanium and vanadium compounds.[71,72] This culminated in 1980 with the publication of the first report on an unusually effective method of enantioselective epoxidation that gave chiral oxiranes, the absolute configuration of which depended only on the configuration of the tartrate used and not on the structure of the substrate.[92,93] Soon afterwards Sharpless et al found that this unique combination of titanium alkoxide, optically active tartrate ester, and TBHP was sensitive to chirality existing in the substrate and could be used for the kinetic resolution of racemic allylic alcohols.[94,95]

AE has been used quite frequently and at the present time it is the most successful means of obtaining optically active oxiranes with high enantiomeric purity. Since the publication of the first report on AE using Sharpless reagent, a large number of studies and several reviews devoted to the use of this reaction and an investigation of its mechanism have been published.[20,22,96–106]

1. Reactivity of substrates and enantioselectivity of asymmetric epoxidation

A scheme for AE of allylic alcohols with Sharpless reagent is shown in Fig. 2. As a result of coordination of the titanium atom of a chiral complex consisting of titanium tetraisopropoxide (TTIP), dialkyl tartrate, and TBHP with the hydroxyl group of the compound undergoing epoxidation, the faces of the plane of the double bond become nonequivalent. For this reason attack by the oxygen atom of the peroxide occurs preferentially from one of these faces depending on the absolute configuration of the tartrate used, resulting in the preferred formation of one of the two possible enantiomers of the epoxy alcohol. By studying the stereochemical structure of a large number of α-hydroxyepoxides obtained by AE of allylic alcohols, it was possible for Sharpless et al[22] to develop a rule for the enantioselectivity of this reaction. If the allylic alcohol is drawn in a plane as shown in Fig. 3, attack by the oxygen atom on the double bond when *L*-(+)-tartrate is used occurs from below, while when *D*-(−)-tartrate is used attack occurs from above. This rule has no known exceptions amongst prochiral substrates at the present time. It can be used to predict easily and accurately the absolute configuration of the resulting epoxyalcohol, which is one of the significant merits of this reaction.

By comparing the results of epoxidation of allylic alcohols with different structures it is possible to establish the mechanism of AE.

1. The rate of the reaction, as when epoxidation is carried out by other methods, increases with an increase in electron density on the double bond of the olefin.[22,107] For example, a comparison of the rates of epoxidation of unsubstituted (4) and substituted cinnamic alcohols (Table 1) shows that the introduction of an electron-withdrawing nitro group reduces the rate of epoxidation [compound (3)] while an electron-donating methoxy or chloro group increases the rate of reaction [compounds (5) and (6)].

2. The rate of epoxidation of (*Z*)-allylic alcohols [compounds (7)−(24), Tables 2 and 3] with a substituent on the C(3)† carbon atom (Tables 2 and 3) is lower than for (*E*)-allylic alcohols [compounds (1), (4), (25)−(42), Tables 4 and 5].[108]

At the same time the enantioselectivity of the reaction is also somewhat less. For example, (*E*)-allylic alcohol (30) with a t-butyl substituent on the C(3) carbon atom is epoxidised with high optical purity, whereas the enantioselectivity of AE of (*Z*)-allylic alcohol (12) is low.

3. The optical purity of the α-hydroxyepoxides obtained from (*Z*)-allylic alcohols with a substituent on the C(3) carbon atom depends on the steric structure of the substituent (Table 2).[108] In compounds (7)−(9), (11), (15)−(20), containing an unbranched substituent, the enantioselectivity is high (EE 80−95%). In the case of compounds with a secondary [e.g. (10)] or tertiary [e.g. (12)] C(4)

† Here and subsequently, if the name of the compound according to the IUPAC nomenclature is not given, the carbon atom bearing the hydroxy group is designated C(1).

carbon atom, the optical purity of the α-hydroxyepoxide obtained is reduced. The same pattern is observed in the epoxidation of 2,3-, 3,3- and 2,3,3-substituted allylic alcohols [compounds (22)–(24), (43)–(49), Tables 3 and 6].

Table 1. Relative rates of asymmetric epoxidation of substituted cinnamic alcohols.[107]

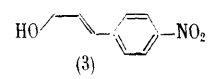
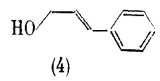
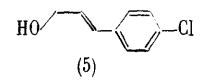
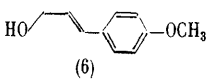
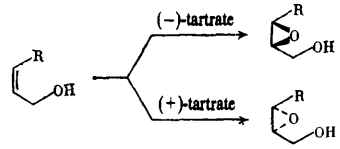
Substrate	Rate constant, s^{-1}	Relative rate
 (3)	0.579	0.42
 (4)	1.38	1.00
 (5)	1.65	1.20
 (6)	6.06	4.39

Table 2. Asymmetic epoxidation of (*Z*)-allylic alcohols with a substituent on the C(3) atom

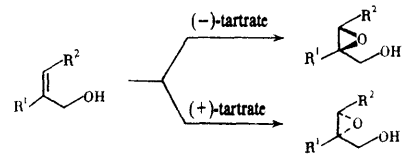


Compound	R	Catalyst: tartrate	Catalyst: Ti/tartrate, mol%	Reaction time, h	Temperature, °C	Yield, %	EE, %	Refs.
(7)	CH_3	(+)-DIPT	5/6	–	–	68	92	[109]
(8)	C_2H_5	(+)-DET	–	–	−20	60	80	[110]
(9)	n-C_3H_7	(−)-DIPT	stoichiometric	72	−20	56	80	[111, 112]
(10)	iso-C_3H_7	(+)-DET	–	–	−23	54	66	[113]
(11)	iso-C_4H_9	(+)-DET	–	–	–	80	95	[114] [115,
(12)	t-C_4H_9	(+)-DET	120/150	192	–	77	25	116]
(13)	C_5H_{11}	(−)-DET	stoichiometric	–	−20	78	–	[112]
(14)	C_6H_{13}	(+)-DET	–	–	–	64.3	80	[117]
(15)	n-C_8H_{19}	(−)-DET	100/100	–	–	80	91	[92]
(16)	n-C_7H_{15}	(+)-DET	10/14	29	−10	74	86	[109]
(17)	n-C_8H_{17}	(+)-DIPT	5/74	42	−12	63	80	[109]
(18)	$CH_2CH{=}CHC_5H_{11}$	(+)-DMT	110/110	–	–	70	94	[118]
(19)	$(CH_2)_3COOCH_3$	(+)-DET	–	–	−50 – −20	57	95	[119, 120]
(20)	CH_2OBz	(−)-DET	100/100	–	–	84	92	[121]
(20)	CH_2OBz		14/14	24	−20	–	95	[109]
(21)	Ph	(+)-DET	100/120	120	−30	61	78	[122]

DIPT = diisopropyl tartrate; DET = diethyl tartrate; DMT = dimethyl tartrate.

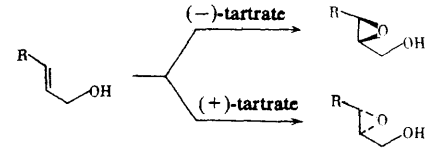
As in the case of (*Z*)-allylic alcohols with a substituent on the C(3) carbon atom, steric factors have the effect of slightly reducing the EE in the epoxidation of alcohols with a branched substituent on the C(2) carbon atom [Table 7, compounds (55) and (56)] in comparison with the results of epoxidation of alcohols [compounds (50)–(54), (58–(60)] with an unbranched substituent.[108] For the same reason the EE of stilbene α-hydroxyepoxide decreases by 20% when a chlorine atom is introduced into the *ortho*-position of the aromatic group on the C(2) carbon atom.[159]

Table 3. Asymmetric epoxidation of (*Z*)-allylic alcohols with a substituent on the C(2) and C(3) carbon atoms

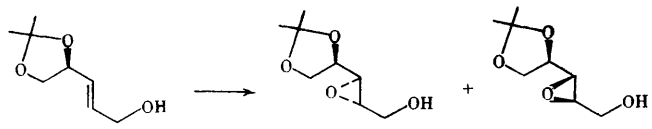


Compound	R^1	R^2	Yield, %	EE, %	Refs.
(22)	$C(CH_3)_3$	CH_3	43	60	[115, 116]
(23)	CH_3	n-C_4H_9	80	89	[92]
(24)	CH_3	CH_2Ph	90	91	[123]

Table 4. Asymmetric epoxidation of (*E*)-allylic alcohols with a substituent on the C(3) atom

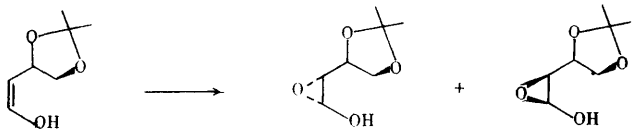


Compound	R	Catalyst: tartrate	Catalyst: Ti/tartrate, mol%	Reaction time, h	Temperature, °C	Yield, %	EE, %	Refs.
(25)	CH_3	(−)-DIPT	100/100	16	−20	48–50	95	[125–127]
(25)	CH_3	(+)-DIPT	5/6	2	−20	70	92	[109]
(26)	C_2H_5	(−)-DIPT	stoichiometric	–	–	80	>95	[128]
(27)	n-C_3H_7	(+)-DET	100/104	14	−20	64	93	[129]
(27)	n-C_3H_7	(+)-DET	5/6	2.5	−20	85	94	[109]
(28)	iso-C_3H_7	(+)-DET	100/104	–	–	66	98	[129]
(28)	iso-C_3H_7	(−)-DET	stoichiometric	–	–	59	–	[130]
(29)	n-C_4H_9	(+)-DET	»	–	−23	75	–	[131]
(30)	t-C_4H_9	(+)-DET	120/150	96	–	52	>95	[115, 116]
(31)	n-C_5H_{11}	(+)-DET	–	–	–	78	95	[134]
(4)	C_6H_{13}	(+)-DET	–	–	–	47.3	90	[117]
(32)	n-C_8H_{17}	(+)-DET	5/6	1.5	−10	78	94	[109]
(33)	n-$C_{10}H_{21}$	(+)-DET	100/100	72	−75	79	>95	[92]
(34)	Ph_3Si	(+)-DIPT	–	–	–	–	90	[138]
(34)	Ph_3Si	(−)-DIPT	–	–	–	–	90	[138]
(35)	$(CH_3)_3Si$	(−)-DIPT	–	–	–	–	95	[139]



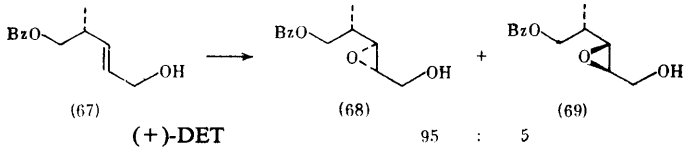
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(−)-DET 15 h, 78% 1 : 20



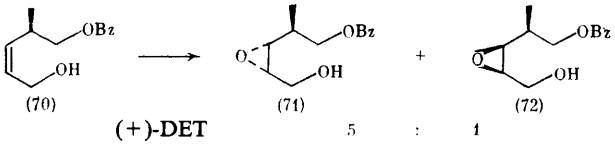
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(−)-DET 264 h 3 : 2



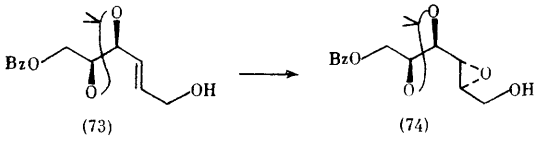
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(−)-DET 5 : 95

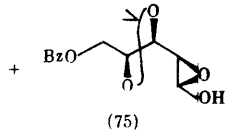


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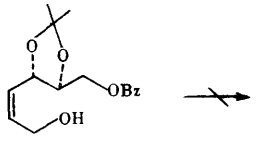


(73) (74)



(75)

(+)-DIPT 36 h, 70% 20 :
(−)-DIPT 36 h, 70% 1 :

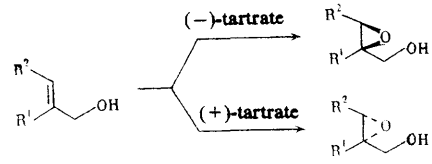


(76)

(+)-DET
(−)-DET

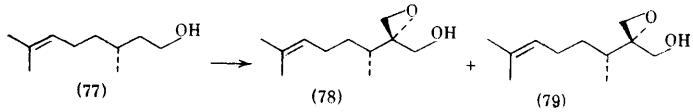
4. The results of epoxidation of optically active (*Z*)- and (*E*)-allylic alcohols with a chiral substituent on the C(3) carbon atom differ. While for (*E*)-isomers (61), (67), and (73)[121,160,161] the presence of a chiral centre has virtually no effect on the results of AE (EE is high whatever the absolute configuration of the tartrate used), in the epoxidation of a (*Z*)-isomer (64) and (70)[160,161] as a result of the interaction between the chiral substituent and the catalyst the stereoselectivity of the reaction depends on the absolute configuration of the catalyst—for one enantiomer of tartrate the diastereoselectivity is high while for the other it is virtually absent because of steric hindrance. (*Z*)-Allylic alcohol (76) is hardly epoxidised at all when either (+)- or (−)-DIPT is used,[121] since in this case the presence of a bulky substituent on the C(3) carbon atom has a substantial effect on the results of AE. It is clear from the examples given that AE of optically active (*Z*)-allylic alcohols can only be successfully achieved when the selected tartrate directs oxygen to the face of the plane of the double bond that is opposite to that in which the bond with the chiral substituent is situated.

Table 5. Asymmetric epoxidation of (*E*)-allylic alcohols with a substituent on the C(2) and C(3) atoms



Compound	R¹	R²	Tartrate	Reaction time, h	Temperature, °C	Yield, %	EE, %	Refs.
(36)	CH_3	CH_3	(+)-DET	–	–	77	94	[140]
(37)	CH_3	C_2H_5	(+)-DMT	16	−20	79	95	[125]
(38)	CH_3	CH_2OBz	(−)-DIPT	–	−15	87	90	[141]
(39)	CH_3	Ph	(+)-DIPT	2	−35	79	98	[109]
(1)	Ph	Ph	(+)-DET	–	–	70	96	[92, 109]
(40)	CH_3	$CH_2CH=C(CH_3)_2$	(+)-DET	12	−23	64	96	[144]
(40)	CH_3	$CH_2CH=C(CH_3)_2$	(−)-DET	12	−23	59	91	[144]
(41)		$-(CH_2)_3-$	(+)-DET	–	–	38	95	[145]
(42)		$-(CH_2)_4-$	(+)-DET	–	–	77	93	[109]

Like optically active (*Z*)-allylic alcohols with a substituent on the C(3) carbon atom, the diastereoselectivity of AE of an allylic alcohol with a chiral substituent on the C(2) carbon atom depends on the absolute configuration of the tartrate used, which follows from an analysis of the results of AE of (3*R*)-3,7-dimethyl-2-methylene-6-octan-1-ol (77):[162]

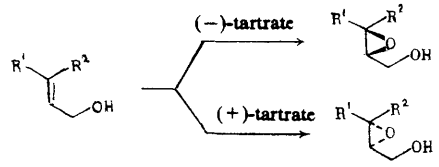


(77) (78) (79)

(+)-DIPT 96 : 1
(−)-DIPT 1 : 3

5. With an increase in reactivity of the allylic alcohols, the sensitivity of the resulting α-hydroxyepoxides towards opening of the oxirane ring increases, which in the presence of different nucleophiles (TBHP, isopropyl alcohol, titanium alkoxides) results in a decrease in effectiveness of the catalytic complex (the resulting diol is a catalyst inhibitor) and a reduction in yield of α-hydroxyepoxide.[102,107] For example, even with complete conversion of the substrate it is not possible to isolate an α-hydroxyepoxide in the AE of 4-methoxycinnamic alcohol (6), whereas 4-nitro- and 4-chlorocinnamic alcohols (4) and (5) are epoxidised in good yield. Glycidol

Table 6. Asymmetric epoxidation of (*E*)- and (*Z*)-allylic alcohols with substituents on the C(3) carbon atom



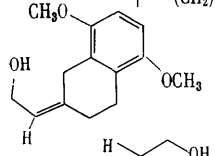
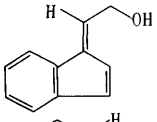
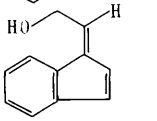
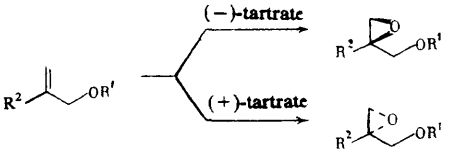
Compound	R¹	R²	Catalyst: tartrate	Catalyst: Ti/tartrate, mol%	Temperature, °C	Yield, %	EE, %	Refs.
(43)	CH_3	CH_3	(−)-DBT	100/100	−20	25	90	[147]
(44)	$CH_2CH=C(CH_3)_2$	CH_3	(+)-DET	200/200	–	67	95	[148]
(45)	$(CH_2)_2CH=C(CH_3)_2$	CH_3	(+)-DET	100/100	–	77	95	[92]
	$(CH_2)_2CH=C(CH_3)_2$	CH_3	(+)-DET	5/74	–	95	91	[109]
(46)	CH_3	$(CH_2)_2CH=C(CH_3)_2$	(+)-DET	100/100	−23	79	94	[92]
(47)			(+)-DET	10/15	–	97	93	[151]
(48)			(+)-DET	100/110	–	–	84	[152]
(49)			(+)-DET	100/110	–	–	88	[152]

Table 7. Asymmetric epoxidation of allylic alcohols with a substituent on the C(2) carbon atom

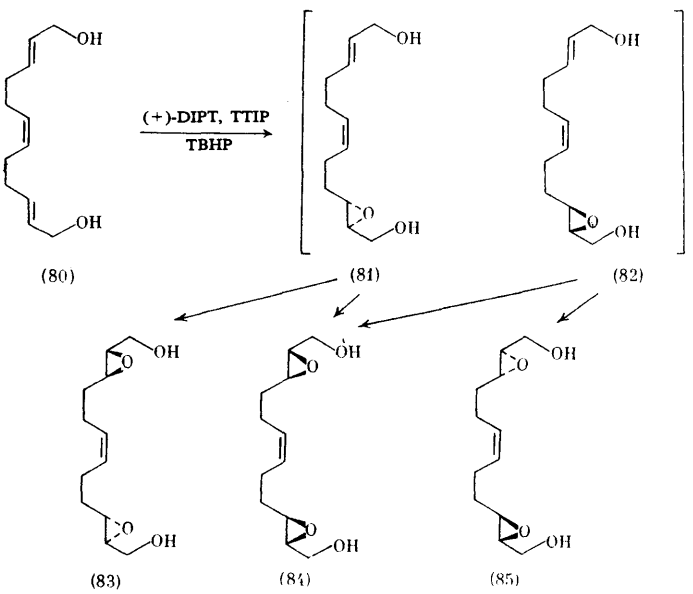


Compound	R¹	R²	Catalyst: Tartrate	Catalyst: Ti/tartrate, mol%	Reaction time, h	Temperature, °C	Yield, %	EE, %	Refs.
(50)	H	CH_3	(+)-DET	100/100[a]	72	−20	78	85	[153]
(50)	H	CH_3	(−)-DET	27/27	40	−30	32	94	[154]
(50)	H	CH_3	(−)-DET	7/6/10[a]	12	−45 ÷ −20	47	95	[155]
(51)	*p*-nitrobenzene	CH_3	(+)-DIPT	5/6	–	–	78	92 (98)[b]	[109]
(52)	tosyl	CH_3	(+)-DIPT	5/6	–	–	69	95	[109]
(53)	2-naphthalenesulphonyl	CH_3	(+)-DIPT	5/6	–	–	60	(92)[b]	[109]
(54)	H	n-C_3H_7	(+)-DET	4.7/5.9	11	−12	88	95	[109]
(55)	H	iso-C_3H_7	(+)-DET	65/120	68	−30	56	86	[156]
(56)	H	t-C_4H_9	(+)-DET	120/150[a]	15		42	86	[115, 116]
(57)	H	C_5H_{11}	(+)-DET	100/100	40	−20	81	95	[92]
(58)	H	n-C_9H_{19}	(+)-DET	100/110	–	−40	53	96	[157]
(59)	H	n-$C_{14}H_{29}$	(+)-DET	100/110[a]	–	−20	51	95	[158]
(59)	H	n-$C_{14}H_{29}$	(+)-DET	10/13	11	−12	91	96	[109]
(60)	H	CH_2OBz	(−)-DET	7.6/10[a]	12	−45 ÷ −20	74	95	[155]

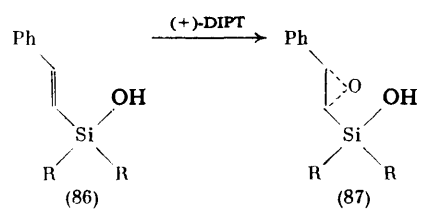
[a]Reaction carried out in the presence of Ti(O−t-C_4H_9)$_4$; [b]values of EE after recrystallisation are given in brackets.

and α-hydroxyepoxides with a substituent on the C(2) carbon atom [compounds (50), (55), (56), (58), (59), Table 7] are particularly sensitive towards opening of the epoxide ring.[92,158]

An interesting sequence of AE occurs for symmetric diallylic alcohol molecules. These results were first reported for the AE of (2*Z*, 6*E*, 10*Z*)-dodeca-2,6,10-triene-1,12-diol (80).[163,164] In the epoxidation of alcohol (80), α-hydroxyepoxide (81) is formed with high enantioselectivity together with a small quantity of epoxyalcohol (82). Epoxidation of the second double bond of enantiomers (81) and (82) occurs with the same enantioselectivity as takes place in the first epoxidation reaction. The three epoxides (83)–(85) are obtained as a result of double AE. Since the *meso*-compound (84) can be separated from the mixture and compound (85) is formed in insignificant quantity, the enantiomeric purity of the main product (83) is very high.



1,1-Substituted allylic alcohols are not effectively epoxidised by a titanium-tartrate complex. For example, AE of 2-methylbut-3-en-2-ol takes place very slowly and it was not possible to isolate the epoxyalcohol.[108] Epoxidation of 2-methyloct-3-en-2-ol results in the formation of the corresponding α-hydroxyepoxide in 67% yield and with an EE of 4%.[117] By replacing the C(1) carbon atom with a silicon atom it is possible to increase the optical purity of the resulting oxirane (87) because of the longer Si=C bond compared to the C=C bond.[165] The lower EE of compound (87b) compared to (87a) is probably due to the steric effect of the phenyl groups.



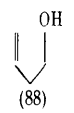
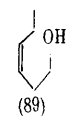
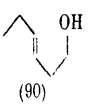
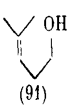
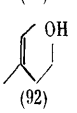
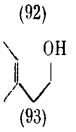
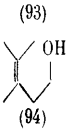
When R = CH_3, the yield of (87) is 50% and EE is 95%; when R = Ph, the yield of (87) is 70% and the EE is 20%.

The AE of homoallylic alcohols has several characteristic features when compared with the epoxidation of allylic alcohols (Table 8).[166]

1. The reactivity of homoallylic alcohols (88)–(94) is lower.

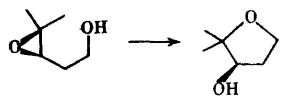
2. The absolute configurations of the hydroxyepoxides obtained by AE of allylic and homoallylic alcohols when the same tartrate ester enantiomer is used are of opposite sign.

Table 8. Asymmetic epoxidation of homoallylic alcohols.[166]

Substrate	Configuration of epoxyalcohol	Yield, %	EE, %
 (88)	(3*R*)	11–25	[55]
 (89)	(3*T*, 4*S*)	30–50	[36–50]
 (90)	(3*R*, 4*R*)	34–50	[41]
 (91)	(3*R*)	41	[27]
 (92)	–	60	[23]
 (93)	–	15	[23]
 (94)	–	62	[48]

3. The enantioselectivity of AE of homoallylic alcohols is lower than the enantioselectivity of AE of the corresponding allylic alcohols (EE 20–55%). Since the reduction in enantioselectivity of AE of homoallylic alcohols is due to the lengthening of the carbon chain by one methylene unit, in order to study the possibility of increasing the EE of an α-hydroxyepoxide chiral complexes based on zirconium, hafnium, and tantalum, which have a longer metal–oxygen bond than in a titanium complex, were used.[20] It was shown that AE of homoallylic alcohols in the presence of a zirconium tetraisopropoxide complex and (+)-dicylohexyl tartramide occurs with the same enantioselectivity as for epoxidation using the titanium–tartrate catalyst and epoxidation of a (*Z*)-homoallylic alcohol takes place with an even greater EE (up to 77%).[20]

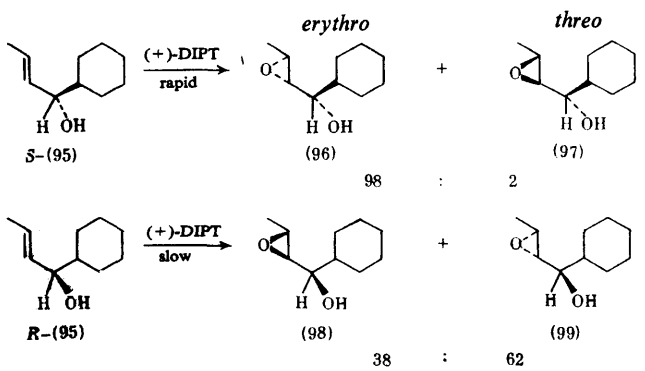
4. β-Hydroxyepoxides are more prone to isomerisation than α-hydroxyepoxides:



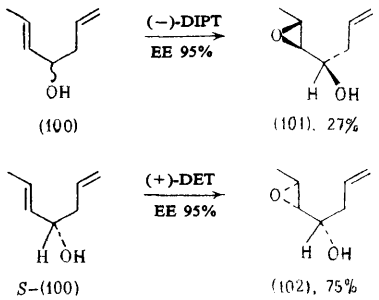
2. Kinetic resolution of racemic allylic alcohols by asymmetric epoxidation

In studying AE of racemic compounds with a secondary hydroxyl group, it is necessary to consider at the same time the enantioselectivity and diastereoselectivity of the reaction. As a result of coordination of the titanium atom of the chiral complex with the hydroxyl group of the compound undergoing epoxidation, two diastereomers of the intermediate complex are formed, AE of which occurs at a different rate, resulting in kinetic resolution of the racemate (Fig. 3).

As in the AE of prochiral allylic alcohols, the direction of attack by the oxygen atom on the double bond of the racemic allylic alcohol is determined by the absolute configuration of the tartrate selected, resulting in the preferential formation of one of the two possible *erythro*-(V) and (IX) or *threo*-(VI) and (X) diastereomers of α-hydroxyepoxide from each enantiomer of the racemate of alcohol (IV) and (VIII). However, as a result of the different orientation of the chiral substituent relative to the direction of attack by the oxygen atom the rates of epoxidation of the enantiomers differ; that enantiomer whose chiral substituent does not cause steric hindrance for attack by oxygen reacts rapidly, and hence its epoxidation leads to the formation of the *erythro*-epoxyalcohol (V) or (IX). For example, in the epoxidation of the allylic alcohol (95) in the presence of *L*-(+)-dialkyl tartrate attack on the double bond form below predominates in accordance with the proposed scheme (Fig. 3).[94,95] In this case the (*S*)-isomer of the allylic alcohol (95), whose chiral substituent does not hinder attack by the oxygen atom, reacts rapidly to form *erythro*-epoxyalcohol (96). For the (*R*)-isomer, because of the interaction between the substituent on the C(1) carbon atom and the catalyst, attack from below is inhibited so the reaction occurs slowly and with low selectivity, the *threo*-diastereomer (99) being predominant. The use of *D*-(−)-dialkyl tartrate gives the opposite result—the (*R*)-isomer of the allylic alcohol (95) is the rapidly reacting one and its epoxidation lead to the formation of *erythro*-epoxyalcohol (98).



Thus, for the reaction of AE with kinetic resolution of racemic allylic alcohols, a high *erythro* selectivity occurs since the isomer that gives an *erythro*-epoxyalcohol is the rapidly reacting one, while the isomer which forms a *threo*-diastereomer is epoxidised slowly and with a correct choice of reaction conditions remains in the mixture as unreacted (VII) and (XI) (Fig. 3). For example, the use of (−)-DIPT in the epoxidation of allylic alcohol (100) results in the formation of epoxyalcohol (101) with an EE of 95%.[167–169] The (*S*)-enantiomer of allylic alcohol (100) remains unreacted and can be epoxidised again in the presence of (+)-DET to form *erythro*-epoxyalcohol (102) with a high yield and EE.



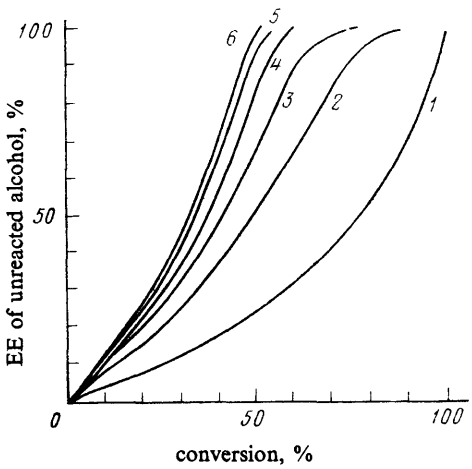
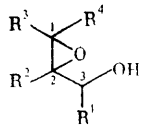


Figure 4. Graph of dependence of EE on conversion for different values of K_{rel}: *1*, 2; *2*, 5; *3*, 10; *4*, 25; *5*, 200; *6*, ∞.

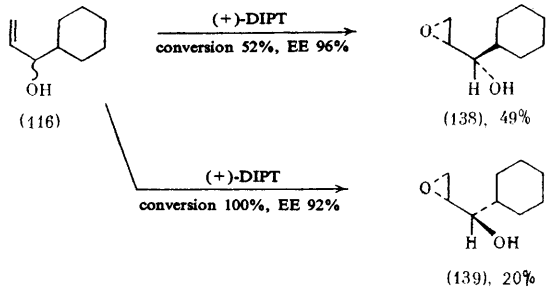
The considerable difference in the rates of epoxidation of the two enantiomers of a racemic allylic alcohol [compounds (103)–(137)] makes it possible to obtain both the α-hydroxyepoxide (Table 9) and the unreacted alcohol (Table 10) with high optical purity. The efficiency of resolution is determined by the relative rate of epoxidation of the allylic alcohols (K_{rel}), which constitutes the ratio of rates of epoxidation of the rapidly reacting to slow reacting enantiomers ($K_{rel} = K_r/K_s$) and varies over a wide range (Table 11).[22] When $K_{rel} = 100$ the reaction is almost as effective as when $K_{rel} = \infty$. Even when $K_{rel} = 15-25$ good results can be obtained.[103] The dependence of the EE of the allylic alcohol remaining in the reaction mixture on the conversion of substrate for different values of K_{rel} is shown in Fig. 4.[94] Analysis of the graph shows that when $K_{rel} = 25$, in order to reach 100% EE of unreacted alcohol, conversion should be less than 60%, which is achieved by reducing the quantity

Table 9. Asymmetric epoxidation of secondary allylic alcohols.

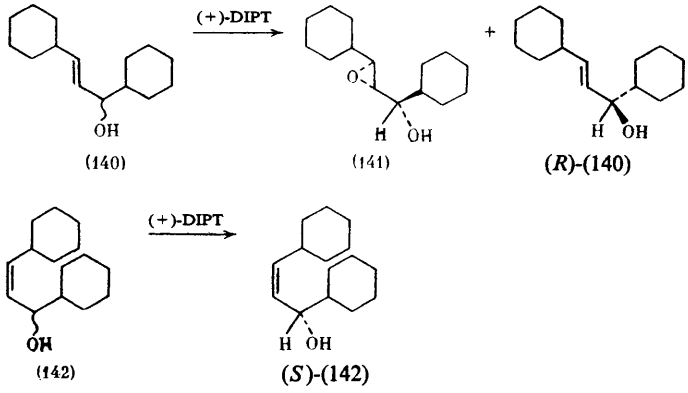


Compound	R^1	R^2	R^3	R^4	Configuration		Yield, %	EE, %	Refs.
					DIPT	epoxyalcohol			
(103)	C_2H_5	H	H	H	+	(2*R*, 3*S*)	–	–	[170]
(104)	n-C_5H_{11}	H	H	H	–	(2*S*, 3*R*)	47	91	[171]
(105)	$(CH_2)_6COOCH_3$	H	H	H	+	(2*R*, 3*S*)	36	95	[172]
(106)	$CH_2C=CSi(iso\text{-}C_3H_7)_3$	H	H	H	–	(2*S*, 3*R*)	40	90	[173]
(107)	C_2H_5	CH_3	H	H	+	(2*R*, 3*S*)	82	92	[174]
(108)	$CH(OBz)CH=CHCH_3$	H	CH_3	H	+	(1*S*, 2*S*, 3*S*)	35	95	[175]
(109)	CH_3	H	$CH_2CH=CH_2$	H	–	(1*R*, 2*R*, 3*R*)	40	90	[168]
(110)	CH_3	H	$C_2H_3(OCH_3)_2$	H	+	(1*R*, 2*S*, 3*S*)	74	98	[176]
(111)	CH_3	H	$C_2H_3(OCH_3)_2$	H	–	(1*S*, 2*R*, 3*R*)	78	97	[176]
(112)	CH_3	H	H	$C_2H_3(OCH_3)_2$	+	(1*R*, 2*S*, 3*S*)	34	97	[176]
(113)	CH_3	H	H	$C_2H_3(OCH_3)_2$	–	(1*S*, 2*R*, 3*R*)	34	96	[176]
(114)	$C_2H_3(OCH_3)_2$	H	H	CH_3	+	(1*S*, 2*R*, 3*R*)	55	93	[176]
(115)	$C_2H_3(OCH_3)_2$	H	H	CH_3	–	(1*R*, 2*S*, 3*S*)	60	95	[176]

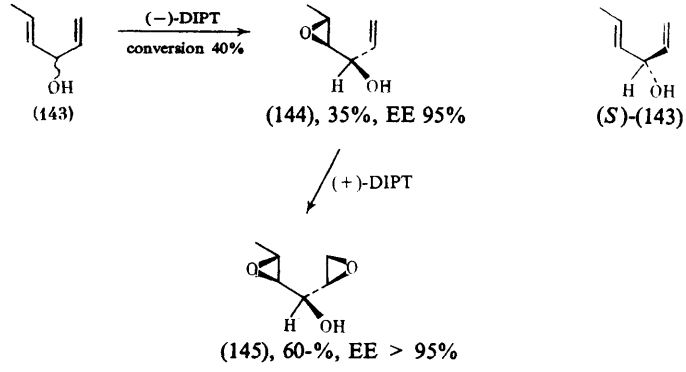
of oxidising agent. If the required reaction product is the optically active epoxyalcohol, a high EE can be achieved at 45% conversion.[108] For example, when AE with kinetic resolution of allylic alcohol (116) is carried out with a conversion of 52%, the *erythro*-epoxyalcohol (138) is formed with an EE of 96%, and with 100% conversion *threo*-epoxyalcohol (139) is isolated with an EE of 92%:[94,95]



For some substrates [compounds (126), (134), (135), and (137), Table 11] the rate of epoxidation of the rapidly reacting enantiomer is low, and the reaction takes quite a long time.[108] In the majority of cases the difference in the rates of epoxidation of the two enantiomers in the resolution of (*Z*)-allylic alcohols is less than for (*E*)-allylic alcohols and the efficiency of kinetic resolution is lower (Table 11).[94,95,107,176] In this case the optical purity of the preferentially formed (*Z*)-*erythro*-epoxyalcohol may be high, whereas (*Z*)-*threo*-epoxyalcohols are similar to racemates.[176] If the substituent on the C(3) carbon atom of the (*Z*)-allylic alcohol is branched, resolution of the enantiomers becomes virtually impossible, which is consistent with the general tendency towards a reduction in rate and enantioselectivity of AE for the analogous prochiral allylic alcohols. For example, asymmetric epoxidation with kinetic resolution of (*E*)-allylic alcohol (140) is complete after 15 h and results in the formation of α-hydroxyepoxide (141) and allylic alcohol (*R*)-(140) with a high EE (>96%), the (*Z*)-isomer (142) is ineffectively resolved (EE 10%):[94,95]



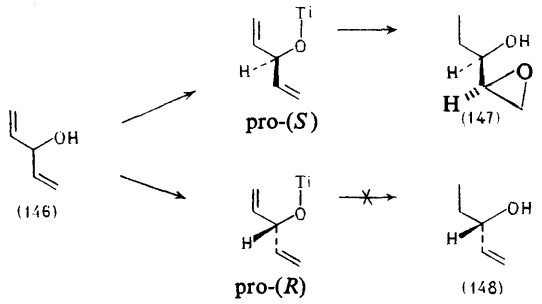
An interesting case of diastereoselectivity and enantioselectivity in AE with kinetic resolution of the racemic diene (143) using a titanium–tartrate system has been described by Sharpless:[123]



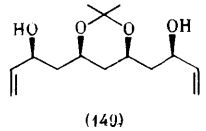
In this case it is possible to obtain eight monoepoxides. The

mechanism of AE of secondary allylic alcohols causes the preferential formation of a single monoepoxide. Firstly, from the dependence of the rate of epoxidation of allylic alcohols on the electron density of the double bond, it is to be expected that the reactivity of the disubstituted double bond is higher than that of the monosubstituted double bond. Secondly, the choice of tartrate enantiomer dictates the direction of attack on the double bond by the oxygen atom of the peroxide. And finally, the *erythro*-selectivity in AE with kinetic resolution of secondary allylic alcohols gives rise to the formation of a single monoepoxide. Thus, when (−)-DIPT is used, as a result of AE with kinetic resolution of the racemic diene (143), the (*R*)-*erythro*-epoxycarbinol (144) is mainly formed. A second asymmetric epoxidation of (144) using (+)-DIPT leads to the formation of the diepoxide (145).

Secondary allylic alcohols that have two identical substituents, such as divinylcarbinol (146), do not contain a chiral centre, but when they react with a chiral titanium complex the two double bonds become stereochemically nonequivalent (diastereotopic).[108,189–193] In this case AE occurs selectively on one double bond, the choice of which is dictated by the same factors as in the process of AE with kinetic resolution. The same factors that determine the selectivity of AE of chiral allylic alcohols cause the preferential formation of the pro-(*S*)-conformation. Hence, epoxidation of divinylcarbinol (146) gives (2*R*,3*S*)-epoxyalcohol (147).



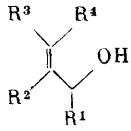
It should be noted that as a result of AE of the divinylcarbinol a small amount of epoxyalcohol (148), which is enantiomeric to the main epoxyalcohol (147), is also formed, resulting in a reduction in optical purity of the final compound. However, the configuration of the unreacted group of the allylic alcohol in this isomer is favourable for a second epoxidation to take place, and this isomer is converted to the diepoxide at a high rate, so the optical purity of α-hydroxyepoxide (147) increases as a result.[192,194] For divinylcarbinols a mathematical equation relating the optical purity of the product with the rate of epoxidation was obtained. A similar analysis can also be used in the AE of prochiral compounds such as (149).[195]



(149)

The efficiency of kinetic resolution increases when iodo-, chloro-, stannyl-, or silicon-containing substituents are present on the C(3) carbon atom of secondary (*E*)-allylic alcohols [compounds (150)–(167), Table 12].[184–188,196,197] AE of these substrates was used for the first time to obtain compounds such as (2*S*,3*S*)-3-trimethylsilylglycidol from (*E*)-3-trimethylsilylallylic alcohols and 2-trimethylsilylglycidols from 2-trimethylsilylallylic alcohols (124) and (125) (Table 10),[183] and in the latter case it was shown that it occurs with a satisfactory difference in rates of epoxidation of the two enantiomers, although it is less than in the case of kinetic resolution of (*E*)-3-trimethylsilylallylic alcohols.

Table 10. Kinetic resolution of secondary allylic alcohols



Compound	R¹	R²	R³	R⁴	Recovered allylic alcohol, %		Refs.
					yield	EE	
(109)	CH_3	H	$CH_2CH{=}CH_2$	H	39	90	[177]
(116)	cyclo-C_6H_{11}	H	H	H	32	98	[178]
(107)	C_2H_5	CH_3	H	H	–	98	[179]
(117)	n-C_4H_9	H	H	H	43	98	[180]
(118)	C_2H_5	H	Ph	H	–	99	[123]
(119)	CH_2CH_2Ph	H	H	H	–	99	[123]
(120)	n-$C_{12}H_{25}$	H	CH_3	H	44	97	[182]
(121)	CH_3	$C(CH_3)_3$	H	H	–	30	[115, 116]
(122)	$C(CH_3)_3$	H	CH_3	H	–	5	[115, 116]
(123)	$C(CH_3)_3$	H	H	H	–	10	[115, 116]
(124)	n-C_5H_{11}	$(CH_3)_3Si$	H	H	–	87.4	[183]
(125)	CH_3	$(CH_3)_3Si$	n-C_4H_9	H	–	95.4	[183]

A study of the effect of steric and electronic properties of the silyl group on the rate of epoxidation showed that the decrease in the overall rate of the process on replacing a carbon substituent by a silyl group was due to differences in the composition of the electron shells of carbon and silicon atoms while the increase in K_{rel} is due to the steric effect of the bulky trimethylsilyl group.[184] The same increase in K_{rel} occurs when a t-butyl group is introduced into the C(3)-position.[184] By studying the AE with kinetic resolution of the racemates of fluoroalkyl-(*E*)-vinylcarbinols (163)–(166) (Table 12), Hanzawa et al[198] were able to conclude that the electronegativity of the fluorine atom plays an important part in this process.

Kinetic resolution during the AE of secondary allylic alcohols with the hydroxyl group in a ring[94,108,123,200–203] occurs with lower optical purity than for acyclic allylic alcohols.

Although asymmetric epoxidation with kinetic resolution has been used most frequently for the resolution of allylic alcohols with a substituent on the C(1) atom, this reaction can be used to resolve the racemate of allylic alcohols (168)–(175) with chiral substituents on other carbon atoms (Table 13). AE of allylic alcohols with a chiral centre that is remote from the hydroxyl group can lead to results that do not conform to the general rules that apply in the epoxidation of secondary allylic alcohols. For example, the efficiency of kinetic resolution of the (*E*)-allylic alcohol (168) is low (although the enantioselectivity of epoxidation is high) while resolution of the (*Z*)-isomer (170) is effective (EE of unreacted alcohol is 95%).

Table 11. Relative rates (K_{rel}) of kinetic resolution of secondary allylic alcohols.

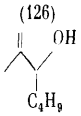
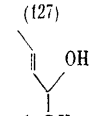
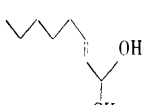
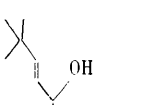
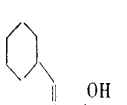
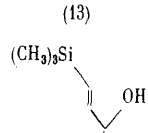
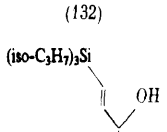
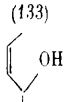
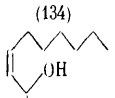
Substrate	Reaction time, h	K_{rel}, −20 °C, DIPT	EE, %	K_{rel}, 0 °C			Refs.
				DIPT	DET	DMT	
 (126)	288	83	96	60	–	–	[22, 94]
 (127)	15	138	96	96	52	–	[22, 94]
 (128)	15	104	96	74	28	15	[22, 94]
 (129)	24	160	98	–	–	–	[184]
 (130)	–	300	–	–	–	–	[184]
 (13)	–	330	–	–	–	–	[184]
 (132)	–	700	–	–	–	–	[184–188]
 (133)	–	300	–	–	–	–	[184]
 (134)	144	20	91	–	–	–	[22, 94]
 (135)	48	16	82	13	–	–	[22, 94]

Table 11 (continued).

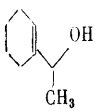
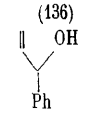
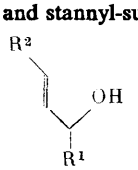
Substrate	Reaction time, h	K_{rel}, −20 °C, DIPT	EE, %	K_{rel}, 0 °C			Refs.
				DIPT	DET	DMT	
 (136)	15	83	96	60	38	–	[22, 94]
	–	4–10	–	–	–	–	[22, 94]

Table 12. Kinetic resolution during asymmetric epoxidation of silyl-, halo-, and stannyl-substituted allylic alcohols



Compound	R^1	R^2	Yield, %		EE, %		Refs.
			allylic alcohol	epoxy-alcohol	allylic alcohol	epoxy-alcohol	
(150)	n-C_5H_{11}	$(CH_3)_3Si$	42	42	99	99	[185, 186]
(151)	iso-C_3H_7	$(CH_3)_3Si$	40	41	99	99	[186]
(152)	Ph	$(CH_3)_3Si$	44	42	99	97	[186]
(153)	CH_2OPh	$(CH_3)_3Si$	47	46	99	99	[186]
(154)	CH_2OCH_2Ph	$(CH_3)_3Si$	43	48	99	99	[186]
(155)	n-C_6H_{11}	I	49	49	99	99	[196]
(156)	C_2H_5	I	40	–	98	–	[196]
(157)	cyclo-C_5H_9	I	44	–	99	–	[196]
(158)	C_6H_6	I	43	–	98	–	[196]
(159)	n-C_5H_{11}	Cl	43	–	99	–	[196]
(160)	n-C_5H_{11}	$Sn(C_4H_9)_3$	40	–	99	84	[197]
(161)	cyclo-C_6H_{11}	$Sn(C_4H_9)_3$	41	–	99	–	[197]
(162)	CH_2OPh	$Sn(C_4H_9)_3$	40	–	99	–	[197]
(163)	CF_3	n-C_6H_{13}	46	50	60	–	[198]
(164)	CF_2H	n-C_5H_{11}	39	52	98	–	[198]
(165)	CFH_2	n-C_5H_{11}	49	56	98	–	[198]
(166)	CF_3	n-C_5H_{11}	45	52	14	–	[198]

3. Mechanism of asymmetric epoxidation

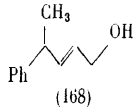
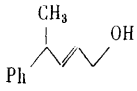
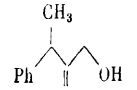
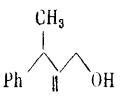
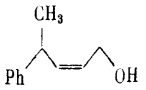
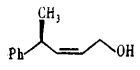
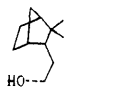
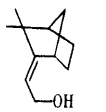
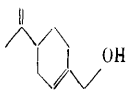
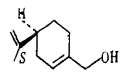
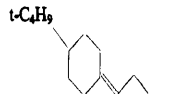
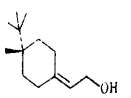
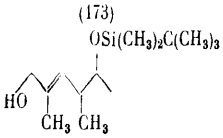
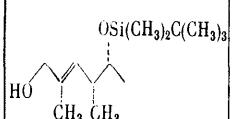
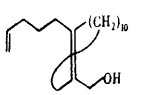
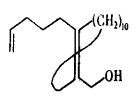
The mechanism of AE and the structural features of the catalyst that govern the high degree of enantioselectivity of reaction for allylic alcohols with different structures have been examined in several studies.[22,107,108,206]

a) Advantage of complex titanium compounds as catalysts for the asymmetric epoxidation of allylic alcohols

Asymmetric epoxidation of allylic alcohols with Sharpless reagent takes place in a similar manner to epoxidation reactions catalysed by other transition metal complexes (Fig. 5).[22,53,70,107,207–216]

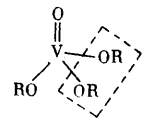
The $ML_n(OR)_m$ catalyst [L = oxo ligand, (OR) = alkoxide ligand, $n = 0-2$, $m = 2-4$ depending on the metal M][106,213,214] bonds covalently with the alkyl hydroperoxide and allylic alcohol, thus activating the peroxide. Epoxidation of the substrate occurs via the intermediate complex (XIV).[22,53,70,207–216] Although titanium alkoxides are not the most effective of the known epoxidation catalysts, these compounds have a high catalytic activity in the Sharpless method of AE. The success of AE using titanium alkoxides is determined by several properties of these systems.[107]

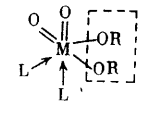
Table 13. Kinetic resolution of primary allylic alcohols.

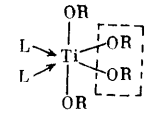
Substrate (configuration)	Recovered allylic alcohol		Refs.
	configuration	EE, %	
 (168)		6	[123]
 (169)		80	[123]
 (170)		95	[123]
 (171), (+)-enantiomer		85	[123]
 (172)		48	[123]
 (173)		70	[123]
 (174)		95	[204]
 (175), (+)-enantiomer		>95	[205]

1. Exchange of monodentate alkoxide ligands in solution takes place rapidly, which is also typical for other epoxidation catalysts such as complex compounds of vanadium, molybdenum, and tungsten.

2. In contrast to other highly active catalysts acting as complexing agents, titanium has the four covalent bonds needed for carrying out AE (two for bonding of divalent chiral tartrate, one for TBHP, and one for the allylic alcohol). Formation of a Ti=O bond is difficult, whereas the vanadium complex (XVII) is stable with one and complexes of molybdenum or tungsten (XVIII) are stable with two oxo ligands, which reduces the number of potential sites for bonding chiral ligands.[71,72]


(XVII)


(XVIII)
M = Mo, W


(XIX)

Thus, these compounds can covalently bond three (for vanadium) and two (for molybdenum and tungsten) alkoxide ligands and hence cannot be coordinated simultaneously with allylic alcohol, TBHP, and a bidentate chiral ligand, thus accounting for the low degree of enantioselectivity when AE is carried out in the presence of complexes of these metals.[52–70]

3. Titanium alkoxides are weak Lewis acids and hence to a certain extent they activate the coordinated alkylperoxo ligand for nucleophilic attack on the olefin.[210]

4. The coordination number of the titanium atom can vary.[213–215] This property is also typical for other transition metals, but when they are used as complexing agents for the preparation of chiral catalysts with dialkyl tartrates, AE of allylic alcohols using TBHP takes place slowly and with a low symmetric induction. The absolute configuration of the α-hydroxyepoxides thus obtained is usually the opposite of that which occurs when titanium is used (Table 14).[52–70,106] Evidently the formation of an effective chiral catalyst is determined by titanium's unique set of properties.

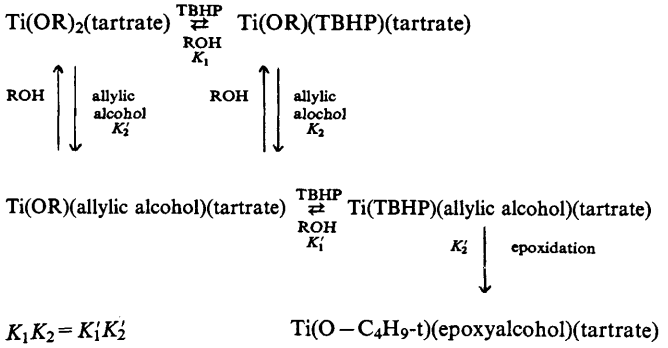
b) Reaction kinetics

On mixing equimolar solutions of titanium alkoxide and dialkyl tartrate, an equilibrium is established, as given by equation (1):[107]

$$Ti(OR)_4 + \text{tartrate} \rightleftarrows Ti(\text{tartrate})(OR)_2 + 2ROH. \quad (1)$$

In the majority of cases this system rapidly reaches equilibrium. However, when bulky alkoxides or tartrates are used to form a complex considerable time may be needed. For example, not less than 20 min is needed from a mixture of $Ti(O-C_4H_9\text{-}t)_4$ and (+)-DIPT, otherwise the EE of the epoxyalcohol obtained is significantly reduced.[22] The equilibrium in Eqn. (1) is considerably shifted to the right, since the binding constant of the diol with the titanium atom is much higher than that with monodentate alcohols. NMR spectroscopic and gas chromatographic data suggest that two moles of aliphatic alcohol occur in solution.[22,107,108] The rapid exchange of ligands continues when peroxide and allylic alcohol are introduced into the reaction medium. In this case the concentration of aliphatic alcohol increases, resulting in a shift of the equilibrium

in solution to the left [Eqn. (1)]. In the majority of cases this shift is insignificant and is suppressed by the addition of excess tartrate. On introducing the substrate and oxidising agent equilibrium is rapidly established, being represented by constants K_1 and K_2, which are equal to ~ 1 for TBHP and the majority of allylic alcohols.

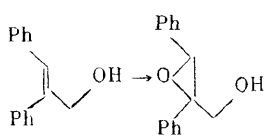


When TBHP and allyl alcohol replace the two remaining alkoxide ligands of the same titanium atom [as for example in compound (XX)],[210] the oxygen is transferred and t-butanol and a chiral epoxyalcohol are formed, which are again replaced by available allylic alcohol and TBHP. The catalytic cycle is complete when complex (XX) is regenerated.[107] A study of the kinetics of AE showed that the rate of reaction is first order with respect to the concentration of catalyst, peroxide, and allylic alcohol:[107]

$$V_{\text{reaction}} = \frac{k[\text{Ti(tartrate)(OR}_2)][\text{TBHP}][\text{allylic alcohol}]}{[\text{OR}]^2}$$

Transfer of oxygen is the rate-limiting stage.[107]

Table 14. Asymmetric epoxidation with TBHP in the presence of transition metal alkoxides



$M(OR)_n$	Configuration		EE, %
	tartrate	C(2)	
$Al(O-C_4H_9\text{-}t)_3$	(+)-DET	(*R*)	5
$MoO_2(acac)_2$	(+)-DIPT	(*R*)	15
$V(O-C_3H_7\text{-}n)_3$	(+)-DET	(*R*)	17
$Zr(O-C_3H_7\text{-}iso)_3$	(+)-DET	(*R*)	10
$Hf(O-C_3H_7\text{-}iso)_3$	(+)-DET	(*R*)	3
$Nb(O-C_2H_5)_3$	(+)-DET	(–)	0
$Ta(O-C_3H_7\text{-}iso)_5$	(+)-DIPT	(*R*)	39
$Ta(O-C_2H_5)_5$	(+)-DET	(*S*)	47
$Sr(O-C_3H_7\text{-}iso)_4$	(+)-DET	does not react	—
$Ti(O-C_3H_7\text{-}iso)_4$	(+)-DET	(*S*)	95

c) Structure of the catalytic complex

Studies on the kinetics of AE made it possible to reach general conclusions about the reaction mechanism. However, these results do not explain the high enantioselectivity of the process, since there is no information on the structure and characteristics of the titanium–tartrate complex that cause the high enantioselectivity of the reaction for a large number of substrates. A determination of the structure of the complex is, in addition to purely theoretical interest, of practical significance since it can serve as the basis for the development of novel chiral catalysts.[217] For these reasons much attention has been given to studying the structure of the titanium–tartrate complex.[22,107,108,218–225]

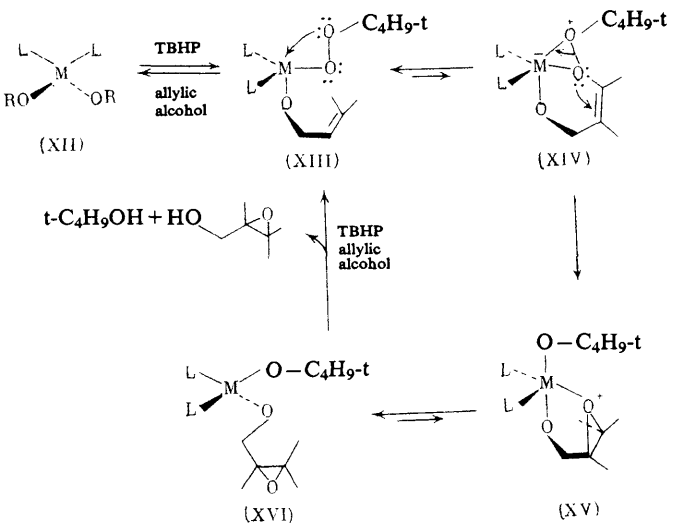


Figure 5. Epoxidation catalysed by transition metal complexes.

The complexity of the problem lies in the fact that because of the rapid exchange of ligands it is not possible to determine the structure of the titanium–tartrate complex participating in the catalytic cycle. Moreover, attempts to isolate the catalyst in crystalline form have proved unsuccessful. Some information about the structure of the complex in solution was obtained by physicochemical methods—mass spectrometry, osomometry, light dispersion, NMR and IR spectroscopy, and isopiestic methods.[22,107,108] In particular, it was shown that in solution a chiral catalyst with a 1:1 ratio of titanium alkoxide to dialkyl tartrate is mainly in the form of the dimer $Ti_2(tartrate)_2(OR)_4$. The formation of a dimeric chiral complex is supported by the nonlinear dependence of the EE of α-hydroxyepoxide on the EE of dialkyl tartrate. Since the enantiomeric purity of the epoxyalcohol is substantially higher than that expected from a linear dependence of the EE of the reaction product on the EE of the chiral ligand, it may be assumed that the high efficiency of the chiral catalyst is due to the inclusion of more than one tartrate ligand in the catalytic complex.[218] A dimeric structure for the catalyst was supported by the results obtained in a study of catalytic complexes containing novel tartrate, tartrate-like, and other ligands.[220–225] From the results of X-ray diffraction analysis of one of these complexes—Ti_2(dibenzyltartramide)$_2(OR)_4$—and assuming the similarity of this compound with the titanium–tartrate complex

$[Ti_2(tartrate)_2(OR)_4]$, the latter was suggested as having the equilibrium structure of a bisymmetric tricyclic dimer consisting of two residues of dialkyl tartrate, each of which is covalently bonded via the oxygen atom of a hydroxyl group with the two titanium atoms (Fig. 6)[224] (in contrast to the previously proposed ten-membered ring).[107] This structure has a C_2 axis of symmetry with the two titanium atoms in the same stereochemical environment. Each titanium atom (coordination number six) is bonded to six oxygen atoms: O(1) and O(2) are the oxygen atoms of the two alkoxy groups, O(3) and O(4) are the oxygen atoms of the hydroxyl groups, O(5) is from the ester group of the first tartrate ligand, and O(6) is the oxygen atom of a hydroxyl group of the second tartrate ligand. Thus, a bridging bond occurs between the two titanium atoms via the two oxygen atoms of hydroxyl groups of the two tartrate molecules, resulting in the formation of a dimeric pseudo-octahedral complex. At room temperature the signals from all of the tartrate groups in the NMR spectrum are identical. When the temperature is lowered the signals undergo a resolution that is typical of a system with asymmetrically bonded tartrate groups of a single type. From the results Finn and Sharpless[22] assumed that an equilibrium is established in solution between the two structures of the complex as depicted in Fig. 6. It should be noted that the geometric configuration of the ligands about each titanium atom in Fig. 6 is depicted for a complex with *L*-(+)-tartrate.[22] It is clear that when the *D*-(−)-enantiomer is used, the configuration of the ester groups of the tartrate will be a mirror image of the structure shown in Fig. 6. Sharpless et al.[22,108] have proposed that only one of the two titanium atoms is involved in the catalytic cycle of AE, but the possibility of both titanium atoms participting is not excluded.

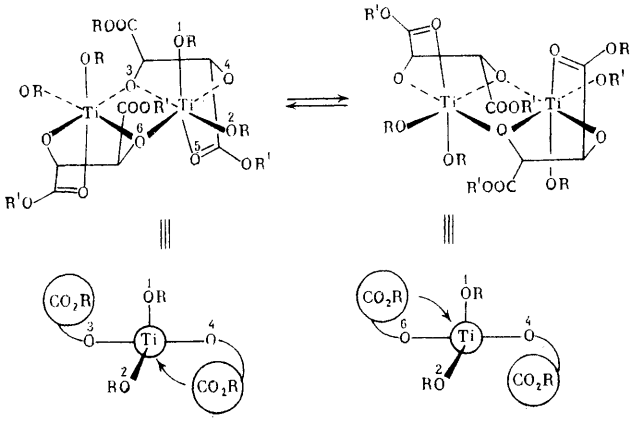


Figure 6. Equilibrium structure of a titanium–tartrate complex in solution.

d) Model of the transition state

The structure of catalyst proposed by Sharpless et al.[22,108] was the basis for a model of the transition state formed by the introduction of peroxide and substrate (Fig. 7). The frontier orbitals on the equatorial oxygen atom of the peroxide make it possible for the allylic alcohol to have four different orientations (Fig. 8).[22,219] The preferred orientation is determined by both stereochemical and stereoelectronic requirements.[22] The structures of (XXIII) and (XXIV) are sterically hindered because of the interaction between the ester group of the tartrate and the C(1) atom of the allylic alcohol. For the remaining structures (XXI) and (XXII) attack by the oxygen atom occurs from opposite sides of the plane of the double bond and hence the exclusion of conformations (XXIII) and (XXIV) does not account for the enantioselectivity of AE. However, the preferred formation of structures (XXI) and (XXII) governs the high stereoselectivity of kinetic resolution of secondary allylic alcohols. The conformation of the intermediate complex in which R^1 = H, R^2 = alkyl substituent is preferred to the conformation in which R^1 = Alk and R^2 = H because of greater steric hindrance in the latter case. For the same reason AE of tertiary allylic alcohols is ineffective.[108,117]

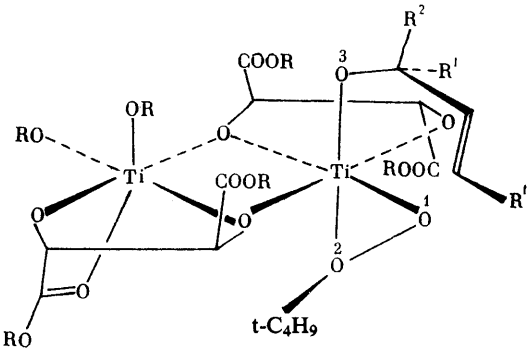


Figure 7. Model of intermediate complex; O(1) and O(2) are oxygen atoms of bidentate peroxide (by analogy with the coordination of TBHP with vanadium)[22,226] and O(3) is the oxygen atom of the allylic alcohol.

The preferred formation of one out of the two possible conformations of the intermediate complex (XXI) and (XXII), which gives rise to the high enantioselectivity of AE, is determined by stereoelectronic factors rather than by steric interactions.[22] An analysis of these factors shows that the *spiro*-orientation (XXI) of olefin and alkoxide with a small O–C/C=C dihedral angle (~30°) is the most probable one, rather than the planar orientation (XXII). The model of the transition state of complex (XXI) is confirmed by calculations using the frontier orbital method.[219] The enantioselectivity rule of AE is satisfactorily accounted for by the proposed structure of the transition state.

By choosing structure (XXI) as the preferred model of the transition state it is possible to account for the other rules of AE.[22] For example, the reduction in enantioselectivity that occurs for (*Z*)-allylic alcohols with a substituent on the C(3) atom is due to steric interactions between the substituent and the C–O bond of the allylic alcohol in conformation (XXI) (dehedral angle O–C/C=C is ~30°). This interaction is small when the substituent is hydrogen and increases as R becomes larger. When R = CH_3 or CH_2R, the

steric interactions result in a decrease in reaction rate while asymmetric induction remains high.



With a bulkier substituent (for example, R = cyclohexyl or phenyl) the rate decreases even more and there is a considerable reduction in EE.[22] The considerable efficiency of kinetic resolution of (*Z*)-allylic alcohols with a chiral substituent on the C(3) carbon atom (in contrast to a secondary (*Z*)-allylic alcohol) can be accounted for in the same way. For example, in the AE of allylic alcohol (170) (see Table 13), depending on the absolute configuration of the tartrate used the position of the phenyl and methyl groups is determined by the steric interactions when the oxygen atom of the hydroxyl group converges with the hydrogen atom on the C(4) carbon atom in the preferred conformation of the allylic alcohol in the transition complex. Thus, it is to be expected that the enantiomer remaining behind after kinetic resolution in the presence of (+)-DIPT will be the S-configuration. In the experiment this enantiomer was obtained with an EE of 95%.[123] The data given are consistent with the results on the dependence of enantioselectivity of AE of optically active (*Z*)-allylic alcohols (64) and (70) on the correspondence between the absolute configurations of the chiral substituent on the C(3) carbon atom and the tartrate used.

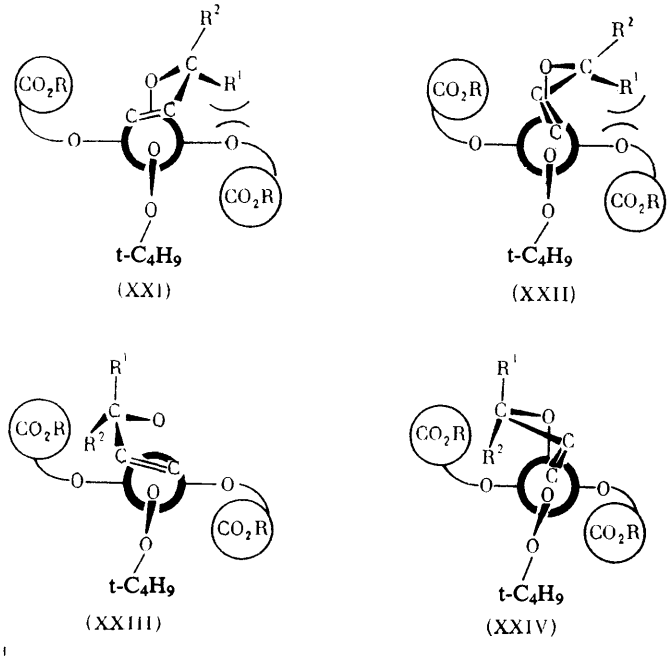


Figure 8. Possible orientations of ligands about the titanium atom in the transition state.

By using the model of the transition state (XXI) it is possible to account for other results of kinetic resolution of primary allylic alcohols with chiral substituents that are remote from the C(1) carbon atom. Thus, 2-(1′-phenylethyl)-2-propen-1-ol (169) (Table 13) in the intermediate complex exists in a conformation in which the hydrogen atom of the chiral site is directed towards the titanium–tartrate catalyst (Fig. 9).[22] By taking into account the steric interactions between the phenyl group (greater) or methyl group (smaller) with the substituent on the C(3) carbon atom of the (*E*)-allylic alcohol, a preferential formation of structure (XXV) is to be expected (Fig. 9). In fact, it was found that during AE with kinetic resolution of the racemate of (169), the (*S*)-isomer remains in the reaction mixture with 80% EE.[123]

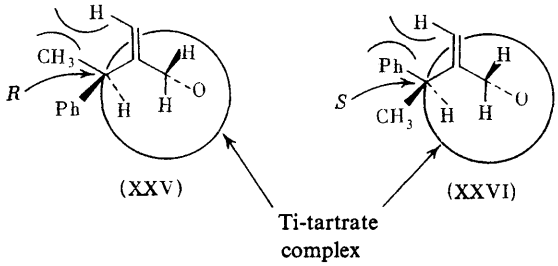


Figure 9. Kinetic resolution of 2-(1′-phenylethyl)-2-propen-1-ol.

Having created a model for the transition state similar to that given in Fig. 8, the low efficiency of kinetic resolution with high enantioselectivity of AE of the (*E*)-allylic alcohol of the α-phenylethyl group on the C(3) carbon atom (168) (Table 13) can be attributed to the spatial remoteness of this substituent from the chiral catalyst. This conclusion is consistent with the data obtained during AE of optically active alcohols when the chiral substituent on the C(3) carbon atom of (*E*)-allylic alcohols (61), (67) and (73) does not affect the results of epoxidation.

4. Reaction conditions

The unique feature of epoxidation with Sharpless reagent is the combination of high enantioselectivity of the reaction with the simplicity in carrying it out, the availability of all of the reagents, the uniformity of the reaction conditions, its preparative and technological significance, and the constancy of the results obtained. Nevertheless, in order to achieve the optimum results in each specific case it is necessary to control some process parameters. A detailed description of the conditions used in conducting AE has been given in several studies.[93,106,123,227–230]

a) Oxidising agent

TBHP is almost always used in AE as the oxidising agent; in certain cases cumyl hydroperoxide has been used.[109] Secondary hydro-peroxides such as phenyl and cyclohexyl hydroperoxides can serve as effective oxidising agents.[22] For enantioselective epoxidation of prochiral allylic alcohols and the kinetic resolution of secondary allylic alcohols, hydroperoxides with bulky tertiary groups such as trityl and tris(*p*-nitrophenyl)methyl have been successfully used.[22,130] The use of primary hydroperoxides is ineffective for AE.[22] For example, *n*-butylhydroperoxide gives rise to a substantially lower EE than does TBHP.

In order to achieve a high rate of AE of prochiral allylic alcohols, it is usual to employ 1.5–2.0 equivalents of oxidising agent. So as to ensure a large difference in the rates of epoxidation of the enantiomers of a racemic allylic alcohol during AE with kinetic resolution a smaller quantity of peroxide is used (~0.6 equivalents). Through careful control of the degree of conversion of alcohol to epoxide, it is possible to use >0.6 equivalents of peroxide, thus reducing the time of reaction.[106,108]

Normally AE using TBHP is carried out in a nonaqueous solution of methylene dichloride.[108] The absence of even trace amounts of water is an important factor, since water inhibits the rate of reaction and reduces the enantioselectivity of epoxidation.[22,53,70,208–212,227] This is because water in the presence of TBHP reacts rapidly with titanium alkoxide to form titanium peroxides and bridging compounds of the type Ti–O–Ti.[213] This results in a decrease in the number of coordination sites of the titanium atom participating in the formation of the intermediate complex and poisoning of the catalyst occurs. A study of the effect of adding water on the AE of (*E*)-α-phenylcinnamic alcohol showed that in the absence of water the EE is 99% and it decreases to 48% when one equivalent of water is added.[195] A detailed description of the methods of preparation, storage, and use of a nonaqueous solution of TBHP appears in three studies.[106,109,232]

An interesting case has been reported in which the source of oxygen for epoxidation is provided by the allyl hydroperoxide which is obtained from 2-t-butylpropene by photooxidation. The hydroperoxide is subsequently converted in the presence of the titanium–tartrate catalyst to 2-t-butoxy-2,3-epoxypropanol with an EE of 72% and yield of 79%.[116]

b) Catalyst

TTIP is used most frequently as a catalyst for AE, but other titanium compounds are used for special purposes. For example, in order to prevent the opening of an epoxide ring formed by AE which is unstable to nucleophilic attack, titanium tetraisobutoxide is used (see Table 7). Thus it was found that replacement of isopropoxide by the less nucleophilic t-butoxide makes it possible to increase the yield of hydroxyepoxide significantly (from 15–51%) in the AE of allylic alcohol (59).[153]

In certain cases $Ti(O-iso-C_3H_7)_2Cl_2$ is used instead of TTIP to obtain epoxyalcohols that are unstable under the reaction conditions.[158] In this case opening of the oxirane ring of the intermediate epoxyalcohol results in the formation of 3-chloro-1,2-diols in 60–80% yield and good regioselectivity. Treatment of the chlorodiols with a base gives epoxyalcohols with low enantioselectivity (20–70%). The absolute configuration of the intermediate epoxyalcohol is the opposite of that which occurs during traditional AE. Finn and Sharpless[22] relate the inversion of configuration of the enantiomer obtained to a strengthening of the titanium–carbonyl group interaction. The same pattern occurs when added quantities of electron-withdrawing monodentate ligands are introduced into the traditional catalyst (Table 15).[22]

The preparation and storage of a catalyst for AE has been described in three studies.[108,213,214]

Dialkyl tartrates and tartramides are used as ligands of the AE catalyst. Most frequent use is made of DMT, DET, and DIPT, which in the majority of cases are equally effective for carrying out AE.[106] It should be noted, however, that by using a tartrate with a bulkier ester group it is possible to increase the yield and rate of reaction when the epoxyalcohols formed are unstable under the reaction conditions. This is probably related to the fact that a bulkier ligand protects the epoxide ring from opening and formation of a diol.[106] For example, epoxidation of cinnamic alcohol when using DIPT occurs more rapidly and with a higher yield than when DET is used.[109] On the other hand, on changing from DIPT to DET there is a small increase in enantioselectivity (from 93 to 95%) in the epoxidation of (*E*)-substituted allylic alcohols such as (*E*)-2-hexen-1-ol.

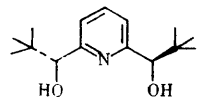
Table 15. Asymmetric epoxidation of *E*-α-phenylcinnamic alcohol.[22]

Added component	Ti	Tartrate	Added component	Configuration of epoxyalcohol	EE	Yield
	mol%				%	
–	2	2	0	(2*S*, 3*S*)	98	90
–	2	1	0	(2*S*, 3*S*)	80	90
O_2N–C$_6$H$_4$–OH	2	1	2	(2*R*, 3*R*)	80–85	50–70
$(F_3C)_2CH$–OH	2	1	2	(2*R*, 3*R*)	85	90
F_5C_6–OH	2	1	2	(2*R*, 3*R*)	90	93
PhOH	2	1	2	(2*R*, 3*R*)	6	90

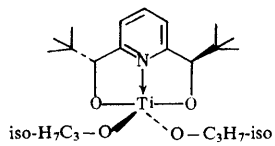
In contrast to the AE of prochiral primary allylic alcohols, the choice of dialkyl tartrate has a substantial effect on the efficiency of AE with kinetic resolution. In this case DIPT provides a better resolution in comparison with DET and DMT, which is of particular importance for substrates with only a small difference in rates of epoxidation of the enantiomers.[22] When dicyclohexyl and dicyclododecyl tartrates are used in the kinetic resolution of a number of allylic alcohols the EE of the products obtained is higher than when DIPT is used, but the yield is slightly lower.[109]

When diadamantyl and di-t-butyl tartrates are used as ligands in AE, the reaction takes place slowly and with a low EE of the resulting products.[22,106] Other dialkyl tartrates substantially reduced the efficiency of the catalytic system.[106]

Hawkins and Sharpless[225] carried out the AE of (*E*)-α-phenylcinnamic alcohol (1) in the presence of TTIP and the chiral reagent (*R*,*R*)-(XXVII).

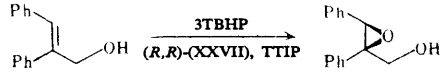


(*R*,*R*)-(XXVII)

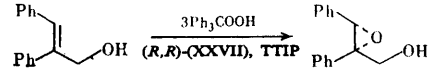


(XXVIII)

The use of TBHP resulted in the formation of the corresponding epoxyalcohol in high yield and with an EE of the predominant (2*S*)-enantiomer of ~40%.

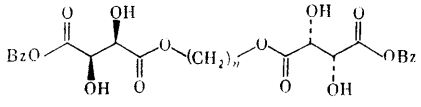


The use of trityl hydroperoxide resulted in the preferential formation of the (2*R*)-enantiomer with an EE of 64%:



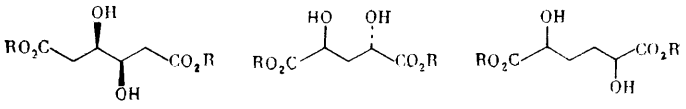
In these cases the epoxidation catalyst is the optically active complex (XXVIII), which exists in solution as a monomer.[225] Asymmetric induction during epoxidation in the presence of complex (XXVIII) depends on the size of the alkyl group of the peroxide, in contrast to reactions in the presence of the titanium–tartrate complex, in which TBHP and trityl hydroperoxide have no effect on the absolute configuration of the resulting epoxyalcohol.

Catalysts based on the novel esters of tartaric acid (XXIX) (n = 3–5) which incorporate two equivalents of titanium tetraisobutoxide provide a high enantioselectivity of AE but are ineffective for kinetic resolution.



(XXIX)

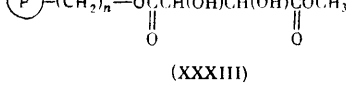
More recently the three tartrate-like ligands (XXX)–(XXXII) have been synthesised.[223] It was shown that (3*R*,4*R*)-diisopropyl 3,4-dihydroxyadipate (XXX) and (2*S*,4*S*)-diisopropyl 2,4-dihydroxyglutarate (XXXI) mainly form dimeric titanium–ligand complexes in the same way as the titanium–tartrate complex, while (2*S*,5*S*)-diisopropyl 2,5-dihydroxyadipate (XXXII) gives seven complexes.



(XXX) (XXXI) (XXXII)

Thus epoxidation in the presence of a titanium–diol (XXX) complex takes place very slowly and inactively; the titanium–diol (XXXI) complex is as effective as the titanium–tartrate complex in the epoxidation of primary allylic alcohols (EE > 93%, but is ineffective as a catalyst of kinetic resolution; and epoxidation in the presence of a titanium–diol (XXXII) complex, which probably consists of several active catalysts, occurs with low selectivity.[223]

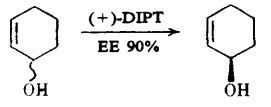
In order to establish the possibility of the repeated use of a chiral tartrate, the tartrate ester (XXXIII) was synthesised, being bonded via the ester with a hydroxymethyl (n = 1) or hydroxyethyl (n = 2) group of a polymer.[233]



(XXXIII)

The epoxidation of geraniol using TBHP in the presence of compound (XXXIII) and TTIP results in the formation of an epoxyalcohol with an EE of 49% (n = 1) and 65% (n = 2). The tartrate bonded to the polymer can be returned to the catalytic cycle and used again, although with reduced efficiency. Although the enantioselectivity of AE using (XXXIII) is less than for a homogeneous catalyst, this reaction has played an important role as it was the first attempt to use a heterogeneous catalyst that made possible the use of a chiral tartrate ester for the second time.

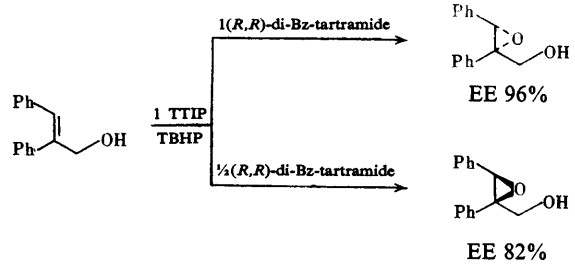
An important factor that determines the successful realisation of AE is the ratio of TTIP : tartrate in the complex catalyst. In contrast to the previously suggested ratio of 1 : 1,[92,93] in order to obtain the maximum possible EE Sharpless recommends the use of the tartrate in at least 10% excess relative to the titanium alkoxide.[94] This is because in the presence of a lesser quantity of tartrate in the system unsubstituted titanium alkoxide remains, which, like the complex Ti(tartrate)$(OR)_2$, is an active epoxidation catalyst and because of its achirality even a small percentage of it in the reaction mixture results in a reduction of enantioselectivity of AE. Of particular importance is the use of excess tartrate in AE reactions of substrates with low reactivity. For example, AE with kinetic resolution of compounds (142) and (176) does not occur when a ratio of titanium : tartrate equal to 1 : 1 is used; with a ratio of 1 : 1.5 the EE of compounds (*S*)-(142) and (*R*)-(176) is 10 and 30% respectively.[94,95]



(176) *R*-(176)

Thus, for reducing the content of titanium alkoxide to a minimum it is necessary to use more than one molecule of tartrate per titanium atom. However, when the excess of tartrate is increased by more than 10–20% the rate of reaction decreases, which is due to the formation of a $[Ti(tartrate)_2]_x$ structure, which is catalytically inactive because of the impossibility of displacing the bidentate tartrate with monodentate allylic alcohol and TBHP.[106] Hence in selecting the ratio of titanium : tartrate for carrying out AE, it is necessary to bear in mind that an increase in the tartrate content will lead simultaneously to an increase in enantioselectivity and a reduction in the rate of reaction.

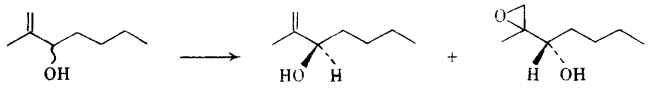
As has already been mentioned, a titanium–tartramide complex is an effective catalyst of AE. When this complex is used asymmetric induction is determined by the ratio of the components in the catalytic complex.[22] For example, AE of allylic alcohols using a TTIP–dibenzyltartramide system in the ratio 1 : 1 as the catalyst takes place with the same enantioselectivity as occurred when a titanium–tartrate complex was used.[158] It should be emphasised that on changing the ratio of titanium : dibenzyltartramide to 2 : 1 inversion of the absolute configuration of the α-hydroxyepoxide occurs:



c) Ratio of substrate to catalyst. Heterogeneous catalysis

Until 1986 a stoichiometric quantity of the catalytic system was used in the majority of cases to carry out AE, and only for a small number of allylic alcohols did AE give good results in the presence of a catalytic amount (5–10%) of titanium–tartrate complex.[106] Thus, the yield of AE of cinnamic alcohol under stoichiometric conditions was 65% and under catalytic conditions it was 80%. For epoxidation of 4-chloro- and 4-nitro-cinnamic alcohol only 5% catalyst is required. The epoxidation of less reactive substrates was also successfully carried out under catalytic conditions. For example, the epoxidation of (*Z*)-2-hexen-1-ol with < 10% catalyst takes place with high enantioselectivity, although at the same time the rate of reaction is slower than with a stoichiometric quantity of catalyst and it is difficult to achieve 100% conversion of the initial compound.[228]

Catalytic quantities of titanium–tartrate complex can also be used to carry out AE with kinetic resolution of allylic alcohols.[94,95] For example, allylic alcohol (127) is effectively resolved when 0.25 equivalents of the TTIP–(+)-DIPT complex is used. It should be noted that the enantioselectivity of kinetic resolution decreases slightly in the presence of the titanium–tartrate complex in catalytic amount as compared to a stoichiometric reaction. To obtain the best results with a catalytic quantity of complex, dicyclohexyl tartrate and dicyclododecyl tartrate are used instead of DIPT.[108]



(127)

A substantial improvement in AE was achieved by introducing molecular sieves into the reaction medium, making it possible to carry out virtually all of the reactions with catalytic quantities of titanium–tartrate complex.[109,232] For example, epoxidation of many simple allylic alcohols (such as 2-hexanol, cinnamic alcohol, 2,4-pentadien-1-ol) using a 5 mol.% titanium–tartrate complex in the absence of molecular sieves occurs with partial conversion (5–50%), while in their presence (3 or 4 Å sieves) reaction moves rapidly to complete consumption of the initial alcohols. When molecular sieves are used the EE decreases slightly (to 85–95%) but it can be increased by subsequent purification. For example, 4-nitrocinnamic alcohol is epoxidised in the presence of 2 mol.% TTIP–DIPT and molecular sieves with an EE of 90%. The resulting α-hydroxy-epoxide is crystallised to give an EE equal to 100%.[22]

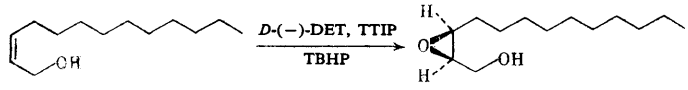
It should be noted that it is possible to reduce the concentration of catalyst to a given limit, after which a decrease in the optical purity of the resulting epoxyalcohol occurs, which is probably due to replacement of tartrate in the catalytic complex, without which asymmetric induction is impossible, by allylic alcohol or hydroxy-peroxide residues.[108] Thus, a study of the epoxidation of cinnamic alcohol showed that there was a substantial decrease in EE on reducing the catalyst content below 5 mol.% (Table 16).[108] At the present time it is recommended to use 5–10% mol.% TTIP and 6–12% mol.% tartrate to carry out AE in the presence of molecular sieves.[109]

In all probability the role of the molecular sieves is to protect the catalyst from water that could penetrate the reaction medium or could be formed in small quantities in side reactions during epoxidation.[108] A detailed description of the principles that should be followed when molecular sieves are used during AE is given in several studies.[22,106,108,109]

Asymmetric epoxidation in the presence of catalytic quantities of titanium–tartrate complex has the following advantages:[109]

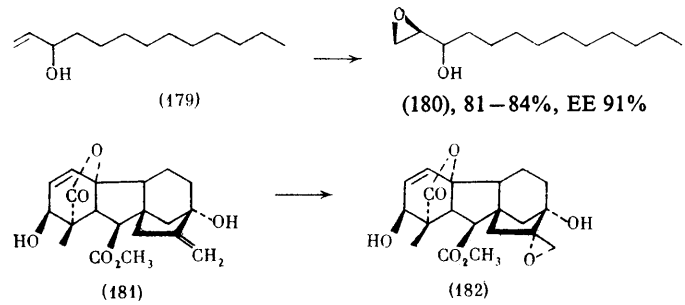
1. The quantity of reagent used is reduced while the rate of reaction is kept at the same level.
2. The reaction is carried out under milder conditions.
3. The yield of the reaction increases (Tables 4, 6, and 7).
4. In contrast to stoichiometric conditions substrates with a low molecular weight are effectively epoxidised.
5. Isolation of the reaction product is simplified.
6. The possibility of obtaining epoxyalcohol derivatives arises.
7. The concentration of substrate can be increased (as in contrast to AE with a stoichiometric amount of catalyst an increase in concentration of the allylic alcohol when there is a catalytic amount of chiral complex does not result in the increased probability of side reactions occurring).

In a number of cases the use of AE is limited by the long reaction time, which can amount to several weeks. It is possible to reduce the reaction time substantially by introducing a catalytic quantity of calcium hydride and silica gel into the reaction mixture.[234–237] For example, the time of epoxidation of (*Z*)-2-tridecen-1-ol (177) in the presence of 5–10 mol.% calcium hydride and 10–15 mol.% silica gel can be reduced from 96 to 8 h, whereas the yield and EE of the epoxyalcohol (178) remains unchanged.[234]



(177) (178)

The time of kinetic resolution of 1-tridecen-3-ol (179) in the presence of 5–10 mol.% calcium hydride and 10–15% mol.% silica gel decreased from 360 to 25 h.[234] AE of methyl giberellate (181) using traditional methods is ineffective. The use of calcium hydride and silica gel results in the formation of the corresponding epoxyalcohol (182) in 70–80% yield and with an EE of 75–80%.[235]



(179) (180), 81–84%, EE 91%

(181) (182)

Table 16. Effect of catalyst concentration on enantioselectivity of asymmetric epoxidation of cinnamic alcohol.[108]

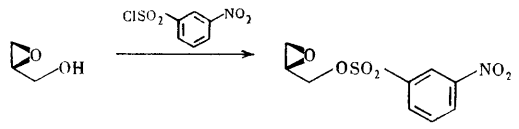
TTIP, mol%	(+)-DIPT, mol%	EE, %
5.0	6.0	92
4.0	5.2	87
2.0	2.5	69

When the reaction is carried out in the presence of calcium hydride alone (or sodium or potassium hydride), the reaction time is reduced but at the same time the optical purity of the product is also reduced. The use of silica gel alone does not reduce the enantioselectivity but shortens the time of epoxidation.[234,236]

d) Preparation of epoxyalcohol derivatives *in situ*

Because of the sensitivity of a number of epoxyalcohols to the action of nucleophiles and their solubility in water, isolation of the reaction product can be difficult. Of particular importance in this case is the preparation of epoxyalcohol derivatives *in situ*, which can be used to carry out AE with a catalyst content of 5–10 mol.%. For example, low molecular-weight alcohols such as glycidol (183) are

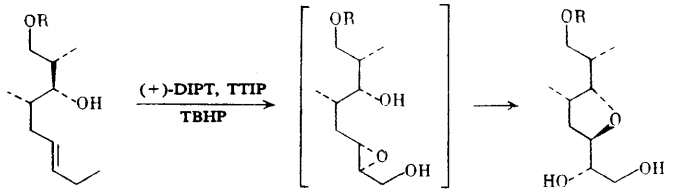
readily isolated from the reaction mixture as their ester derivatives, such as *p*-nitrobenzoate or 3-nitrobenzenesulphonate (184).[109,238]



(183) (184)

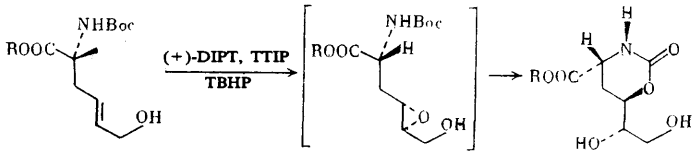
The increase in yield of 2,3-epoxypropanol in the preparation of derivatives *in situ* can be seen from the data of Table 7. With a stoichiometric quantity of titanium–tartrate complex the 2-methylallylic alcohol is epoxidised with an EE of 90% but in low yield. By carrying out the reaction under catalytic conditions and preparing derivatives *in situ* it is possible to isolate the *p*-nitrobenzoate in 70% yield and an EE of 98% and the 3-nitrobenzenesulphonate (184) in 55% yield and an EE of 93%.[108]

It is possible to obtain derivatives *in situ* by nucleophilic opening of the epoxide ring using the TTIP which is already contained in the reaction medium and is an effective reagent that accelerates regioselective attack by nucleophiles on 2,3-epoxyalcohols.[239] In this case the required compounds can be obtained with a given configuration of the functional groups relative to the double bond of the allylic alcohols. In particular, compound (187) is formed as a result of AE of allylic alcohol (185) followed by intramolecular cyclisation.[158]



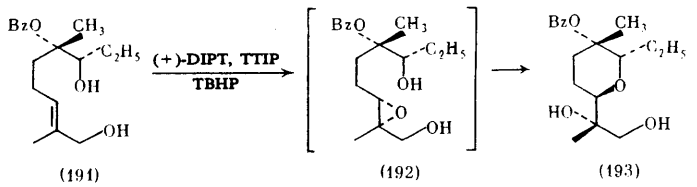
(185) (186) (187)

In the same way, in the epoxidation of alcohol (188) cyclisation of the intermediate epoxyalcohol (189) occurs during reaction and results in the formation of the cyclic urethane (190).[240]



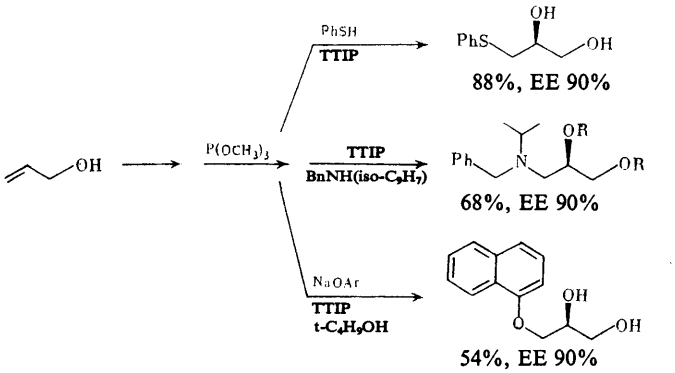
(188) (189) (190)

Epoxyalcohol (192), obtained from allylic alcohol (191), gives the ether (193) as a result of intramolecular cyclisation.[174]

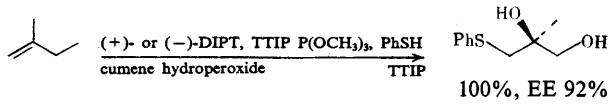


(191) (192) (193)

The preparation of derivatives *in situ* not only assists the isolation of the reaction product, but it can also be used to obtain chiral compounds in a suitable form for further synthesis. For example, *in situ* opening of the epoxide ring of glycidol using nucleophiles such as thiols, secondary amines, and phenols results in the formation of intermediates in the synthesis of adrenalin blockers, antidepressants, etc.[162,241,242]



Thus, methallylic alcohol gives a diol that is used in the synthesis of important organic compounds:



Sulphonation, silylation, and esterification *in situ* result in the formation of derivatives that are intermediates in the synthesis of natural derivatives.

- - -o0o- - -

This literature survey on AE has shown that the most effective method of obtaining optically active oxiranes is the Sharpless reaction, which has the following main advantages.

1. Simplicity, availability, and economical price of all components.
2. Reliability (AE of the majority of prochiral and optically active allylic alcohols, and also the AE with kinetic resolution of the racemate of allylic alcohols occur successfully).
3. High enantioselectivity (EE of 90–95% or more in many cases).
4. Preparation of oxiranes with a given absolute configuration.

The possibility of regioselective opening of the epoxide ring could be used for Sharpless epoxidation in a number of multistage syntheses of optically active compounds, amongst which natural compounds such as sugars, pheromones, and products used as drugs are of the greatest importance. The number of studies devoted to a directed synthesis of natural compounds using the Sharpless asymmetric epoxidation as the key stage continues to grow.

References

1. R T Coutts, O B Baker *Chirality*, 1989, **1**(2) 99
2. I R Reimmer, C P Schalbe *Entomol.*, 1977, (4) 518
3. R Croteau, P E Kolattukudy *Arch. Biochem. Biophys.*, 1975, **170**(1) 61
4. A Frigerio, M Cavo-Briones, G Belvedere *Drug Metabolism Rev.*, 1976, **5**(2) 197
5. S W May, R D Schwartz, B J Abbott, et al. *Biochim. Biophys. Acta*, 1975, **403**(1) 245
6. Yu S Tsizin, A N Drabkina *Usp. Khim.*, 1970, **39**(6) 1074 [English translation in *Russ. Chem. Rev.*, 1970(6)]
7. W C Still *J. Am. Chem. Soc.*, 1979, **101**(9) 2493
8. W H Pirkle, P L Rinaldi *J. Org. Chem.*, 1979, **44**(7) 1025

9. H B Henbest *Chem. Soc. Spec. Publ.*, 1965, **19**(1) 83
10. R C Ewins, H B Henbest, M A McKervey *J. Chem. Soc., Chem. Commun.*, 1967, (21) 1085
11. R M Bowman, J F Collins, M F Grundon *J. Chem. Soc., Chem. Commun.*, 1967, (21) 1131
12. R M Bowman, M F Grundon *J. Chem. Soc., Ser. C*, 1967, (22) 2368
13. F Montanari, I Moretti, G Torre *Boll. Sci. Fac. Chem. Ind. Bologna*, 1968, **26**(1) 113
14. F Montanari, I Moretti, G Torre *J. Chem. Soc., Chem, Commun.*, 1969, (3) 135
15. D R Boyd, D M Jerina, J W Daly *J. Org. Chem.*, 1970, **35**(9) 3170
16. R M Bowman, J F Collins, M F Grundon *J. Chem. Soc., Perkin Trans. 1*, 1973, (6) 626
17. F Montanari, I Moretti, G Torre *Gazz. Chi, Ital.*, 1974, **104**(1) 7
18. M F Grundon, I S McColl *Phytochemistry*, 1975, **14**(1) 143
19. W H Pirkle, P L Rinaldi *J. Org. Chem.*, 1977, **42**(12) 2080
20. T Katsuki *J. Syn. Org. Chem. Jpn.*, 1987, **45**(2) 90
21. J Rebek, R McCready *J. Am. Chem. Soc.*, 1980, **102**(17) 5602
22. M G Finn, K B Sharpless *Asymmetric Synthesis* (Edited by J D Morison), Academic Press, New York, 1985, Vol. 5, p. 247
23. F A Davis, M E Harakal, S B Awad *J. Am. Chem. Soc.*, 1983, **105**(10) 3123
24. F A Davis, S Chattopo *Tetrahedron Lett.*, 1986, **27**(42) 5079
25. F A Davis, A C Sheppard *Tetrahedron*, 1989, **45**(18) 5703
26. R Curci, M Tiorenti, M R Serio *J. Chem. Soc., Chem. Commun.*, 1984, (3) 155
27. N Kobayashi, K Iwai *Makromol. Chem. Rapid Commun.*, 1981, **2**(1) 105
28. S Banfi, S Colonna *Synth. Commun.*, 1983, **13**(12) 1049
29. S Colonna, S Banfi, A Papagni *Gazz. Chim. Ital.*, 1985, **115**(2) 81
30. Y Hu, A Harada, S Takahashi *Synth. Commun.*, 1988, **18**(14) 1607
31. N Baba, J Oda, M Kawaguchi *Agric. Biol. Chem.*, 1986, **50**(12) 3113
32. R Helder, J C Hummelen, R W Laane, et al. *Tetrahedron Lett.*, 1976, (21) 1831
33. H Wynberg, B Greijdanus *J. Chem. Soc., Chem. Commun.*, 1978, (10) 927
34. M Igarashi, H Midorikawa *Bull. Chem. Soc. Jpn.*, 1967, **40**(11) 2624
35. B Marsman, H Wynberg *J. Org. Chem.*, 1979, **44**(13) 2312
36. Y Harigaya, H Yamaguchi, M Onda *Heterocycles*, 1981, **15**(1) 183
37. Y Harigaya, H Yamaguchi, M Onda *Chem. Pharm. Bull.*, 1981, **29**(5) 1321
38. S Julia, J Guixer, J Masana, et al. *J. Chem. Soc., Perkin Trans. 1*, 1982, (6) 1317
39. S Julia, J Masana, J C Vega *Angew. Chem., Int. Ed. Engl.*, 1980, **19**(11) 929
40. S Colonna, H Molinari, S Banfi, et al. *Tetrahedron*, 1983, **39**(9) 1635
41. S Colonna, S Julia, H Molinari *Heterocycles*, 1984, **21**(51) 548
42. S Banfi, S Colonna, H Molinari, et al. *Tetrahedron*, 1984, **40**(24) 5207
43. S Colonna, A Manfredi, M Spadeni *Recl. Trav. Chim. Pays-Bas*, 1987, **106**(6–7) 273
44. P Singh, G Arora *Indian J. Chem., Sect. B*, 1987, **26**(12) 1121
45. Y Shida *Agric. Biol. Chem.*, 1979, **43**(8) 1797
46. B Ben Hassine, M Goisone, J Pecher, et al. *Bull. Soc. Chim. Belg.*, 1986, **95**(7) 547
47. J C Hummelen, H Wynberg *Tetrahedron Lett.*, 1978, (12) 1089
48. H Wynberg *Selectivity—a Goal for Synthetic Efficiency* (Edited by W Bartmann), Verlag Chemie, Weinheim, 1983, p. 365
49. K Nanjo, K Suzuki, M Sekiya *Chem. Lett.*, 1978, (10) 1143
50. I Ojima *J. Synth. Org. Chem. Jpn.*, 1986, **44**(6) 499
51. K A Jørgensen *Chem. Rev.*, 1989, **89**(3) 431
52. S Yamada, T Mashiko, S Terashima *J. Am. Chem. Soc.*, 1977, **99**(6) 1988
53. R C Michaelson, R E Palermo, K B Sharpless *J. Am. Chem. Soc.*, 1977, **99**(6) 1990
54. H B Kagan, H Mimoun, C Mark, et al. *Angew. Chem., Int. Ed. Engl.*, 1979, **18**(6) 485
55. U M Dzhemilev, R N Rakhretdinov, A G Telin, et al. *Khim. Prir. Soedin.*, 1981, (5) 650
56. U M Dzhemilev, R N Rakhretdinov, A G Telin, et al. *Dokl. Akad. Nauk SSSR*, 1983, **271**(2) 361
57. E Broser, K Krohn, K Hintzer, et al. *Tetrahedron Lett.*, 1984, **25**(23) 2463
58. O Bortdini, F Difuria, G Modena, et al. *J. Mol. Catal.*, 1986, **35**(1) 47
59. V Schurig, K Hintzer, U Leyrer, et al. *J. Organomet. Chem.*, 1989, **370**(1–3) 81
60. K Tani, M Hanafusa, S Otsuka *Tetrahedron Lett.*, 1979, (32) 3017
61. T Mashiko, S Terashim, S Yamada *J. Pharm. Soc. Jpn.*, 1980, **100**(3) 319
62. S Coleman-Kammula, E T Duim-Koolstra *J. Organomet. Chem.*, 1983, **246**(1) 53
63. J Tessier, J P Demonte, French Appl. 26 18 781
64. R Sinigalia, R A Michelin, F Pinna, et al. *Organometallics*, 1987, **6**(4) 728
65. J T Groves, K S Myers *J. Am. Chem. Soc.*, 1983, **105**(18) 5791
66. D Mansuy, P Battioni, J P Renaud, et al. *J. Chem. Soc., Chem. Commun.*, 1985, (3) 155
67. Y Kaku, M Otsuka, M Ohno *Chem. Lett.*, 1989, (4) 611
68. Y Naruta, F Tani, K Mazugama *Chem. Lett.*, 1989, (7) 1269
69. K Takai, K Oshima, H Nozaki *Tetrahedron Lett.*, 1980, (17) 1657
70. K B Sharpless, T R Verhoeven *Aldrichim Acta*, 1979, **12**(1) 63
71. K B Sharpless *Stereospecificity in Chemistry and Biochemistry*, Houston, 1984, Vol. 27, p. 59
72. K B Sharpless *Chem. Br.*, 1986, **22**(1) 38
73. G S Fonken, R A Johnson *Chemical Oxidation with Microorganisms*, Marcel Dekker, New York, 1972, p. 113
74. R A Johnson *Oxidation in Organic Chemistry* (Edited by W S Trahanovsky), Academic Press, New York, 1978, Part C, p. 131
75. S W May, R D Schwartz *J. Am. Chem. Soc.*, 1974, **96**(12) 4031
76. H Ohta, H Tetsukawa *J. Chem. Soc., Chem. Commun.*, 1978, (19) 849
77. K Furuhashi, A Taoka, S Uchida, et al. *Eur. J. Appl. Microbiol. Biotechnol.*, 1981, **12**(1) 39
78. K Furuhashi *Biosci Ind.*, 1988, **46**(5) 3205
79. O Takahashi, J Umezawa, K Furuhashi, et al. *Tetrahedron Lett.*, 1989, **30**(12) 1583
80. R F White, J Birnbaum, R T Meyer, et al. *Appl. Microbiol.*, 1971, **22**(1) 55

81. W R Abraham, H M R Hoffman, K Kieslich, et al. *Enzymes in Organic Synthesis,* Pitman, London, 1985, p. 146
82. J O Fournezon, S A Arcela, R Furstoss *J. Org. Chem.*, 1989, **54**(19) 4686
83. J B Jones *Asymmetric Synthesis* (Edited by J D Morison), Academic Press, New York, 1985, Vol. 5, p. 309
84. G Berti *NATO Asi Ser., Ser. C*, 1986, **178**(12) 349
85. D Bianchi, W Cabri, P Cesti, et al. *Tetrahedron Lett.*, 1988, **29**(20) 2455
86. B A Marples, M Rogers-Evans *Tetrahedron Lett.*, 1989, **30**(2) 261
87. D Wistuba, H P Nowotny, O Trager, et al. *Chirality*, 1989, **1**(2) 127
88. S Colonna, A Manfredi *Tetrahedron Lett.*, 1986, **27**(3) 387
89. S Colonna, A Manfredi, M Spadoni *Tetrahedron Lett.*, 1987, **28**(14) 1577
90. S Colonna, A Manfredi, R Annunzia, et al. *Tetrahedron*, 1987, **43**(9) 2157
91. S Colonna, N Gaggera, A Manfredi *Tetrahedron*, 1988, **44**(16) 5169
92. T Katsuki, K B Sharpless *J. Am. Chem. Soc.*, 1980, **102**(18) 5374
93. T Katsuki, K B Sharpless US P. 4471130; *Chem. Abs.*, 1985, **102** 24872
94. V S Martin, S S Woodard, T Katsuki, et al. *J. Am. Chem. Soc.*, 1981, **103**(20) 6237
95. N C Gonnella, K Nakaniski, V S Martin, et al. *J. Am. Chem. Soc.*, 1982, **104**(13) 3775
96. T Katsuki *Kagaku Zokan*, 1982, (96) 105
97. J Mulzer *Nachr. Chem. Techn. Lab.*, 1984, **32**(4) 310
98. W Bigi, L Gcuqiang *Organ. Chem.*, 1984, (2) 99
99. Ganzuo Kong *Chemistry*, 1985, (11) 35
100. T Katsuki *Chem. Today*, 1985, (177) 44
101. J M Sobczak *Wiadomosci Chemiczne*, 1985, **39**(10–12) 647
102. B E Rossiter *Chemical Industries,* Marcel Dekker, New York, 1985, Vol. 22, p. 295
103. A Pfenninger *Synthesis*, 1986, (2) 89
104. W Zhou, Z Wang *Chemistry*, 1987, (10) 1
105. K P Zeller *Methoden der Organischen Chemie*, 1988, **E13**(2) 1210
106. B E Rossiter *Asymmetric Synthesis* (Edited by J D Morison), Academic Press, New York, 1985, Vol. 5, p. 193
107. K B Sharpless, S S Woodard, M G Finn *Pure Appl. Chem.*, 1983, **55**(11)
108. R A Johnson, K B Sharpless *Comprehensive Organic Synthesis*, 1990, 7 105
109. Y Gao, R M Hanson, S Y Klunder, et al. *J. Am. Chem. Soc.*, 1987, **109**(19) 5765
110. E Baker, C J Swain, J C Head *J. Chem. Soc., Chem. Commun.*, 1986, (11) 874
111. K Mori, Y Nakazono *Tetrahedron*, 1986, **42**(23) 6459
112. K C Nicolaou, S E Webber *J. Chem. Soc., Chem. Commun.*, 1985, (5) 297
113. R D Wood, B Ganem *Tetrahedron Lett.*, 1982, **23**(5) 707
114. T Takahashi, M Miyazawa, H Veno, et al. *Tetrahedron Lett.*, 1986, **27**(33) 3881
115. M J Schweiter, K B Sharpless *Tetrahedron Lett.*, 1985, **26**(21) 2543
116. W Adam, A Griesbeck, E Staab *Tetrahedron Lett.*, 1986, **27**(25) 2839
117. W Bigi, L Zhang, W Zhou *Youji Huaxul.*, 1983, (6) 440
118. L S Mills, P C North *Tetrahedron Lett.*, 1983, **24**(4) 409
119. M Suzuki, Y Norita, A Yanagisana, et al. *J. Am. Chem. Soc.*, 1986, **108**(16) 5021
120. M Suzuki, A Morita, A Yanagisawa, et al. *J. Org. Chem.*, 1988, **53**(16) 286
121. T Katsuki, A W M Lee, V S Ma, et al. *J. Org. Chem.*, 1982, **47**(7) 1373
122. J N Denis, A E Greene, A A Serra, et al. *J. Org. Chem.*, 1986, **51**(1) 46
123. K B Sharpless, C H Behrens, T Katsuki *Pure Appl. Chem.*, 1983, **55**(4) 589
124. K S Reddy, O H Ko, D Ho, et al. *Tetrahedron Lett.*, 1987, **28**(27) 3075
125. B E Rossiter, T Katsuki, K B Sharpless *J. Am. Chem. Soc.*, 1981, **103**(2) 464
126. R Baker, W J Cummings, J F Hayes, et al. *J. Chem. Soc., Chem. Commun.*, 1986, (16) 1237
127. C Kuroda, P Theramongkol, J R Engebrecht, et al. *J. Org. Chem.*, 1986, **51**(6) 956
128. M Honda, T Katsuki, Y Yamaguchi *Tetrahedron Lett.*, 1984, **25**(35) 3857
129. L A Gorthy, M Vairamani, C Djerassi *J. Org. Chem.*, 1984, **49**(9) 1511
130. R Baker, C J Swain, J C Head *J. Chem. Soc., Chem. Commun.*, 1985, (6) 309
131. L Thijs, P P Waanders, H M Stokkingreef, et al. *Recl. Trav. Chim. Pays-Bas*, 1986, **105**(9) 332
132. S Wershofen, H D Scharf *Synthesis*, 1988, (11) 854
133. R D Tung, D H Rich *Tetrahedron Lett.*, 1987, **28**(11) 1139
134. G A Molander, G Hahn *J. Org. Chem.*, 1986, **51**(3) 2596
135. J Furukawa, S Iwasaki, S Okuda *Tetrahedron Lett.*, 1983, **24**(47) 5257
136. J Kitano, Y Kobayashi, F Sato *J. Chem. Soc., Chem. Commun.*, 1985, (12) 998
137. W R Roush, M A Adam *J. Org. Chem.*, 1985, **50**(20) 3752
138. J M Schwab, C K Ho *J. Chem. Soc., Chem. Commun.*, 1986, (11) 872
139. T Katsuki *Tetrahedron Lett.*, 1984, **25**(26) 2821
140. D A Evans, J M Williams *J. Chem. Soc., Chem. Commun.*, 1988, **29**(40) 5065
141. P Garner, J M Park, V Rotello *Tetrahedron Lett.*, 1985, **26**(28) 3299
142. A I Meyers, J P Hudspeth *Tetrahedron Lett.*, 1981, **22**(40) 3925
143. N Niwa, Y Miyachi, Y Uosaki, et al. *Tetrahedron Lett.*, 1986, **27**(38) 4601
144. K Mori, H Ueda *Tetrahedron*, 1981, **37**(15) 2581
145. W C Still, H Ohmizu *J. Org. Chem.*, 1981, **46**(25) 5242
146. K Takabe, K Okisaki, Y Uchiyama, et al. *Chem. Lett.*, 1985, (5) 561
147. S Yamada, M Shiraishi, M Ohmori, et al. *Tetrahedron Lett.*, 1984, **25**(31) 3347
148. K Mori, K Okada *Tetrahedron*, 1985, **41**(3) 557
149. W R Roush, T A Bitzard *J. Org. Chem.*, 1984, **49**(23) 4332
150. F Bonadies, G Rossi, C Bonini *Tetrahedron Lett.*, 1984, **25**(47) 5431
151. M Sodeoka, T Iimori, M Shibasaki *Tetrahedron Lett.*, 1985, **26**(52) 6497
152. A G Myers, P J Porteau, T M Randel *J. Am. Chem. Soc.*, 1988, **110**(21) 7212
153. J S Gung, K W Armstrong, O P Anderson, et al. *J. Org. Chem.*, 1983, **48**(20) 3592

154. C Meister, H D Scharf *Lieb. Ann. Chem.*, 1983, (6) 913
155. D Tanner, P Somfai *Tetrahedron*, 1986, **42**(21) 5985
156. K Mori, T Ebata, S Takechi *Tetrahedron*, 1984, **40**(10) 1761
157. B Giese, R Rupaner *Liebigs Ann. Chem.*, 1987, (3) 231
158. L D Lu, R A Johnson, M G Finn, et al. *J. Org. Chem.*, 1984, **49**(4) 728
159. K Takahashi, M Ogata *J. Org. Chem.*, 1987, **52**(9) 1877
160. N Minami, S S Ko, Y Kishi *J. Am. Chem. Soc.*, 1982, **104**(4) 1169
161. H Nagaoka, Y Kishi *Tetrahedron*, 1981, **37**(23) 3873
162. Y Gao, K B Sharpless *J. Org. Chem.*, 1988, **53**(17) 4081
163. T R Hoye, J C Suhadolnik *J. Am. Chem. Soc.*, 1985, **107**(18) 5312
164. T R Hoye, J C Suhadolnik *Tetrahedron*, 1986, **42**(11) 2855
165. T H Chan, L M Chen, D Wong *J. Chem. Soc., Chem. Commun.*, 1988, (19) 1280
166. B E Rossiter, K B Sharpless *J. Org. Chem.*, 1984, **49**(20) 3707
167. W R Roush, R J Brown *J. Org. Chem.*, 1982, **47**(7) 1371
168. W R Roush, R J Brown *J. Org. Chem.*, 1983, **48**(25) 5093
169. P C Bulman-Page, J F Carefull, L H Powell, et al. *J. Chem. Soc., Chem. Commun.*, 1985, (12) 822
170. K Mori, Y B Seu *Tetrahedron*, 1985, **41**(16) 3429
171. K Mori, T Otsuka *Tetrahedron*, 1985, **41**(3) 553
172. M D Lewis, J P Duffy, J V Heck, et al. *Tetrahedron Lett.*, 1988, **29**(19) 2279
173. E J Corey, A Tramontano *J. Am. Chem. Soc.*, 1984, **106**(2) 462
174. D A Evans, S L Bender, J Morris *J. Am. Chem. Soc.*, 1988, **110**(8) 2506
175. U Kufner, R R Schmidt *Angew. Chem., Int. Ed. Engl.*, 1986, **25**(1) 89
176. Yu E Raifel'd, B M Arshava, L L Zil'berg *Zh. Org. Khim.*, 1990, **26**(3) 527
177. W R Roush, A P Spada *Tetrahedron Lett.*, 1983, **24**(35) 3693
178. P A Aristoff, P D Johnson, A W Harrison *J. Am. Chem. Soc.*, 1985, **107**(26) 7967
179. L E Overman, N H Lin *J. Org. Chem.*, 1985, **50**(19) 3669
180. S K Aggarwal, J S Bradshaw, M Eguchi, et al. *Tetrahedron Lett.*, 1987, **30**(10) 1054
181. M Ogata, H Matsumote, K Takahashi, et al. *J. Med. Chem.*, 1987, **30**(6) 1054
182. S Sugiyama, M Honda, T Komori *Liebigs Ann. Chem.*, 1988(9), 619
183. Y Kitano, T Matsumoto, Y Takeda *J. Chem. Soc., Chem. Commun.*, 1986, (23) 1732
184. P R Carlier, W S Mungall, G Schroder, et al. *J. Am. Chem. Soc.*, 1988, **110**(9) 2978
185. Y Kitano, T Matsumoto, Y Takeda, et al. *J. Chem. Soc., Chem. Commun.*, 1986, (17) 1323
186. Y Kitano, T Matsumoto, F Sato *Tetrahedron*, 1988, **44**(13) 4073
187. A T Russell, G Procter *Tetrahedron Lett.*, 1987, **28**(18) 2041
188. G Procter, A T Russell, P J Murphy, et al. *Tetrahedron*, 1988, **44**(32) 3953
189. S Hatakeyama, K Sakurai, S Takano *J. Chem. Soc., Chem. Commun.*, 1985, (24) 1759
190. B Hafele, D Schroter, V Jager *Angew. Chem., Int. Ed. Engl.*, 1986, **25**(1) 87
191. R E Babine *Tetrahedron Lett.*, 1986, **27**(48) 5791
192. S L Schreiber, T S Schreiber, D B Smith *J. Am. Chem. Soc.*, 1987, **109**(5) 1525
193. D Askin, R P Volante, R A Reamer, et al. *Tetrahedron Lett.*, 1988, **29**(3) 277
194. S Bergens, B Bosnich *Comments Inorg. Chem.*, 1987, **6**(1) 85
195. S L Schreiber, M T Goulet, G Schule *J. Am. Chem. Soc.*, 1987, **109**(15) 4718
196. Y Kitano, T Matsumoto, S Wakasu, et al. *Tetrahedron Lett.*, 1987, **28**(50) 6351
197. Y Kitano, T Matsumoto, S Okamoto, et al. *Chem. Lett.*, 1987, (8) 1523
198. Y Hanzawa, K Kawagoe, M Ito, et al. *Chem. Pharm. Bull.*, 1987, **35**(4) 1633
199. T Katsuki *Tetrahedron Lett.*, 1984, **25**(26) 2821
200. J A Marshall, K E Flynn *J. Am. Chem. Soc.*, 1982, **104**(26) 7430
201. E Alvarez, E Manta, J D Martin, et al. *Tetrahedron Lett.*, 1988, **29**(17) 2093
202. R C Ronald, S M Ruder, T S Lillie *Tetrahedron Lett.*, 1987, **28**(2) 131
203. I V Ekhato, J V Silverton, C H Robinson *J. Org. Chem.*, 1988, **53**(10) 2180
204. M Isobe, M Kitamura, S Mia *Tetrahedron Lett.*, 1982, **23**(2) 221
205. J A Marshall, K E Flynn *J. Am. Chem. Soc.*, 1983, **105**(10) 3360
206. K B Sharpless, S S Woodard, M G Finn *Selectivity—A Goal for Synthetic Efficiency* (Edited by W Bartmann, M Trost), Verlag Chemie, Weinheim, 1984, Vol. 14, p. 377
207. G A Tolstikov *Reaktsii Gidroperekisnogo Epoxidirovaniya* (Hydroperoxide Epoxidation Reactions), Nauka, Moscow, 1976
208. K B Sharpless, R C Mihaelson *J. Am. Chem. Soc.*, 1973, **95**(18) 6136
209. B E Rossiter, T F Verhoeven, K B Sharpless *Tetrahedron Lett.*, 1979, **20**(49) 4733
210. A O Chong, K B Sharpless *J. Org. Chem.*, 1977, **42**(9) 1587
211. E D Mihelich, K Daniels, D J Eickhoff *J. Am. Chem. Soc.*, 1981, **103**(26) 7690
212. T Itoh, K Jitsukawa, K Kaneda, et al. *J. Am. Chem. Soc.*, 1979, **101**(1) 159
213. D C Bradley, R C Mehrotra, D P Gaur *Metal Alkoxides*, Academic Press, New York, 1978
214. R J H Clark *The Chemistry of Titanium and Vanadium*, Elsevier, Amsterdam, 1968
215. W Russo, W Nelson *J. Am. Chem. Soc.*, 1970, **92**(6) 1521
216. R D Bach, G J Wolber, B A Coddens *J. Am. Chem. Soc.*, 1984, **106**(20) 6098
217. P G Potvin, R Gau, O C Patrick, et al. *Can. J. Chem.*, 1989, **67**(10) 1523
218. C Puchot, O Samuel, E Dunach, et al. *Can. J. Chem.*, 1986, **108**(9) 2353
219. K A Jorgensen, R A Wheeler, R Hoffman *Can. J. Chem.*, 1987, **109**(11) 3240
220. S F Pedersen, J C Dewan, R Eckman, et al. *Can. J. Chem.*, 1987, (4) 1279
221. P G Potvin, P C C Kwong, M A Brook *J. Chem. Soc., Chem. Commun.*, 1988, (12) 773
222. P R Carlier, K B Sharpless *J. Org. Chem.*, 1989, **54**(17) 4016
223. C J Burns, C A Martin, K B Sharpless *J. Org. Chem.*, 1989, **54**(12) 2826
224. I D Williams, S F Pedersen, K B Sharpless, et al. *J. Am. Chem. Soc.*, 1984, **106**(21) 6430

225. J M Hawkins, K B Sharpless *Tetrahedron Lett.*, 1987, **28**(25) 2825
226. H Mimoun, P Chaumette, M Mignard, et al. *Nouv. J. Chim.*, 1983, **7**(8–9) 467
227. J G Hill, B E Rossiter, K B Sharpless *J. Org. Chem.*, 1983, **48**(20) 3607
228. J G Hill, K B Sharpless, C M Exon, et al. *Org. Synth.*, 1984, **63**(1) 66
229. W P S Shum, US P. 4 764 628; *Chem. Abs.*, 1989, **110** 38865
230. R M Hanson, S Y Ko, K B Sharpless Europ. P. 197 766; *Chem. Abs.*, 1986, **106** 66496
231. E J Corey, D C Ha *Tetrahedron Lett.*, 1988, **29**(26) 3171
232. R M Hanson, K B Sharpless *J. Org. Chem.*, 1986, **51**(10) 1922
233. M J Farrall, M Alexis, M Trecarte *Nouv. J. Chim.*, 1983, **7**(7) 449
234. Z Wang, W Zhou, G Lin *Tetrahedron Lett.*, 1985, **26**(50) 6221
235. Z Wang, W Zhou *Tetrahedron*, 1987, **43**(13) 2935
236. W Zhou, R Wu, Z Wang *Chin. J. Org. Chem.*, 1988, **8**(6) 539
237. Z Wang, W Zhou *Synth. Commun.*, 1989, **19**(15) 2627
238. J M Klunder, T Onami, K B Sharpless *J. Org. Chem.*, 1989, **54**(6) 1295
239. M Caron, K B Sharpless *J. Org. Chem.*, 1985, **50**(9) 1557
240. J E Baldwin, A Flinn *Tetrahedron Lett.*, 1987, **28**(30) 3605
241. J M Klunder, S Y Ko, K B Sharpless *J. Org. Chem.*, 1986, **51**(19) 3710
242. S Y Ko, K B Sharpless *J. Org. Chem.*, 1986, **51**(26) 5413