

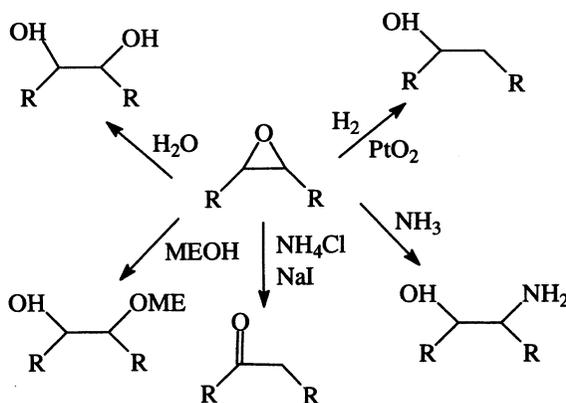
## Some Recent Advances in Epoxide Synthesis

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### Introduction

Commercial processes for preparing epoxidized oils and fatty acid epoxy esters from unsaturated oils and esters were developed in the 1940s (1). These processes use either preformed peracid or peracid prepared *in situ* by the addition of  $H_2O_2$  to acetic acid or formic acid in the presence of sulfuric acid. The resulting epoxidized fatty materials are used commercially as plasticizers. The epoxide functionality is a versatile intermediate for the production of many different chemical products. Shown in Scheme 1 are several examples of common reactions that epoxides undergo (2,3). Research on epoxide synthesis has continued for several reasons, including the following: (i) the acid present or generated by the peracid procedure catalyzes opening of the oxirane ring, causing epoxide yields to be less than quantitative; (ii) the peracid procedure shows only modest selectivity; and (iii) the spent peracid must be removed from the epoxide product and disposed of or recycled. When considering the manufacture of commodity chemicals such as those primarily produced from fats and oils, the cost of by-product disposal is often a major component of overall cost. Excellent reviews of epoxidation syntheses have been published (4-8). This chapter will review some recent advances in this area with emphasis on work using fatty substances.

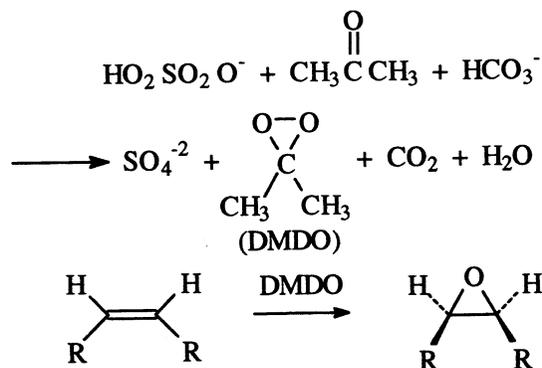


SCHEME 1. Epoxide as facile intermediate for synthesis.

## Epoxidation with Dioxiranes

A dioxirane is a three-membered ring containing two oxygen atoms. The most studied dioxirane is dimethyl dioxirane (DMDO), which is conveniently prepared by the action of potassium peroxymonosulfate with acetone in the presence of bicarbonate (Scheme 2). DMDO can be isolated by vacuum distillation, or it can be generated *in situ* in a biphasic system with a phase transfer agent (9). The main by-product formed when DMDO is used for epoxidation is acetone. In addition, a small amount of methyl acetate is formed from auto-decomposition of DMDO (10). Because DMDO epoxidations are conducted at alkaline pH, acid-sensitive epoxides can be prepared. Even when an *in situ* biphasic reaction system is used, oxirane ring opening is minimal. DMDO, like peracids, exhibits high stereoselectivity in its reactions with *cis* and *trans* alkenes. In addition, DMDO reacts with *cis*-alkenes 7–9 times faster than with *trans* alkenes (9). Allylic alcohols have the potential to promote diastereoselective epoxidation with DMDO provided that a nonpolar solvent is used; this allows hydrogen bonding between DMDO and the alcohol (11). DMDO also has the ability to oxidize methylene groups to ketones. However, its reactivity toward methylene groups is much lower than its epoxidation activity on double bonds (12).

Dioxirane has been used to epoxidize fatty materials. The epoxidation of methyl oleate took place cleanly and completely (12). The action of DMDO/acetone on methyl ricinoleate did not give satisfactory yields of epoxy alcohol. However, when a biphasic reaction system was used with butanone to give ethylmethyldioxirane (EMDO), high yields of epoxide were obtained. Oils from several sources were subjected to the action of EMDO, prepared *in situ* in a biphasic medium (13). Generation of EMDO required two additions of peroxymonosulfate to achieve high levels of epoxide formation with oils containing higher levels of unsaturation. Yields were poor only with tung oil, which contains esters of the conjugated polyunsaturated fatty acid  $\alpha$ -eleostearic. When methyl ricinoleate was treated with an excess of EMDO,



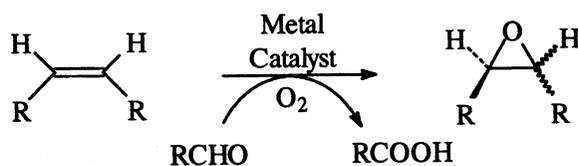
**SCHEME 2.** Synthesis of dimethyl dioxirane (DMDO) and its use for epoxidation.

the ketoepoxide, methyl (*Z*)-9,10-oxido-12-oxo-octadecanoate, was produced (14). The ketoepoxide was acid labile and rearranged to methyl 8-(5-hexylfuran-2-yl)octanoate. Dioxiranes were generated in the presence of trifluoroacetone or methyl pyruvate (15). A diepoxide could be obtained from a fatty methyl ester containing two conjugated double bonds with dioxirane, whereas with *m*-chloroperoxybenzoic acid, only the monoepoxide could be generated. Epoxy-hydroxystearate was generated by dioxirane from *iso*-ricinoleic acid, but *m*-chloroperoxybenzoic acid gave only the tetrahydrofuran derivative.

## Aldehyde and Oxygen Epoxidations

A wide variety of metal catalysts have been examined for their ability to promote epoxide formation (4–8). In most cases, these catalysts require higher energy oxidants such as hydrogen peroxide, organic peroxides, or iodobenzene. With some metal catalysts, molecular oxygen can be used as the oxidant, provided that an aldehyde is added to the reaction mixture (16,17). Epoxide formation is accompanied by co-oxidation of the aldehyde to a carboxylic acid (Scheme 3). The kinetics of oleic acid epoxidation by  $\text{Co}^{+3}$  in the presence of benzaldehyde were determined (18). The kinetics could be described by a mechanism in which the benzaldehyde donates an electron to  $\text{Co}^{+3}$ , and the resulting radical then reacts with  $\text{O}_2$  to give the peroxybenzoate radical. Reaction of the peroxybenzoate radical with oleic acid was the main source of epoxy oxygen (16). Cobalt acetate was bound to a membrane by ion exchange (19). This membrane was used as a catalyst for the epoxidation of oleic acid with benzaldehyde and oxygen. The membrane-bound cobalt catalyst could be recycled.

Synthetic metalloporphyrins are analogs of the prosthetic group of heme-containing enzymes that selectively catalyze various reactions, i.e., oxygenation, oxidation, oxidative chlorination, and dismutation (6). In recent years, the number of studies of metalloporphyrins and other organic metal complexes has increased because the organic ligands can modulate the activity and selectivity of the metal (8,16,20,21). With respect to fatty epoxide formation by benzaldehyde/ $\text{O}_2$ , there has been only one study. The epoxide of oleic acid was formed using cobalt (II) tetraphenylporphyrin as a catalyst (22). It was found that the use of 4-methoxybenzaldehyde increased the rate of epoxidation sevenfold, whereas 4-chlorobenzaldehyde decreased the rate of epoxidation compared with benzaldehyde.



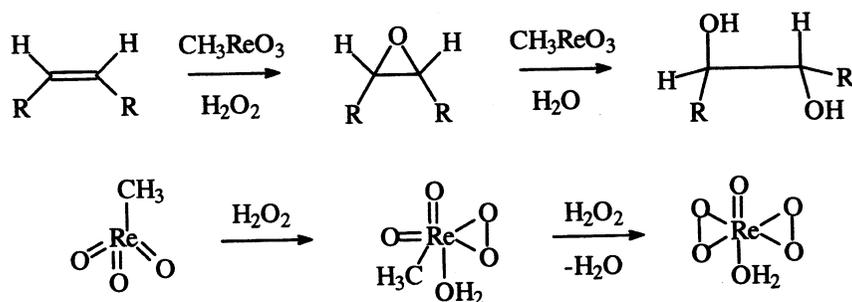
**SCHEME 3.** Epoxidation with aldehyde and  $\text{O}_2$  with a metal catalyst.

## Epoxidation with Hydrogen Peroxide

### Methyltrioxorhenium as Catalyst

Methyltrioxorhenium (methylrhenium trioxide),  $\text{CH}_3\text{ReO}_3$  (MTO), catalyzes the epoxidation of olefins with hydrogen peroxide (23). The catalytically active species is formed when 1 or 2 mol of  $\text{H}_2\text{O}_2$  react with MTO to give organorhenium peroxo complexes with a ligand of water (Scheme 4) (24). MTO also catalyzes the hydrolysis of the oxirane ring, leading to *trans*-configured 1,2-diols. Oxirane ring opening can be suppressed by conducting the epoxidation at temperatures as low as  $-25^\circ\text{C}$  or by adding an amine as an acid scavenger. Epoxidation of *cis*- $\beta$ -methylstyrene and *trans*- $\beta$ -methylstyrene led to the *cis* and *trans* epoxides, respectively (25). This observation appears to rule out either a radical mechanism or one involving nucleophilic attack of one of the olefinic carbon atoms on the peroxo oxygen. These studies were extended to substituted alkenes (26). Epoxidation rates increased with increasing alkyl substitution of the double bond and decreased when electron-attracting groups were present. Rates of epoxidation were about an order of magnitude greater in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  than in methanol. It was concluded that the data were consistent with a mechanism in which the double bond of the alkene attacks a peroxidic oxygen in a concerted manner. In a successful attempt to reduce oxirane ring opening, MTO was used with a urea/ $\text{H}_2\text{O}_2$  adduct, thus eliminating the presence of  $\text{H}_2\text{O}$  (27).

Diastereoselectivity was examined with a series of allylic alcohols and found to be approximately the same as that given by *m*-chloroperbenzoic acid, with the *threo* epoxy alcohol predominant in most cases. It also was found that the addition of pyridine to MTO substantially increased the degree of epoxidation and decreased ring opening of the epoxide even when aqueous  $\text{H}_2\text{O}_2$  was used as the oxidant (28). Although the mechanism by which this acceleration occurs is not known, the observation that 2-picoline cannot provide reaction acceleration eliminates a simple base effect as the origin of the rate enhancement. Epoxidation of selected cyclic dienes resulted in high diastereoselectivity in diepoxide formation. In another study of epox-



**SCHEME 4.** Epoxidation with methyltrioxorhenium/ $\text{H}_2\text{O}_2$  with subsequent oxirane ring opening in the presence of water. The second line shows the structures of the epoxidizing agents.

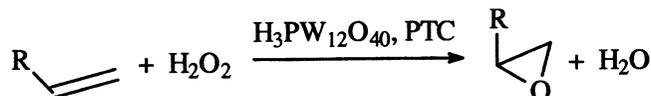
idation of conjugated dienes with MTO/aqueous  $\text{H}_2\text{O}_2$ , diols were the major product in many cases (29). When urea/ $\text{H}_2\text{O}_2$  complex was used as the oxidant, monoepoxide was the predominant product.

### Tungstate as Catalyst

This procedure is uniquely suitable for epoxide formation on terminal olefins, although internal olefins also are reactive. The original procedure for 1-octene epoxidation used  $\text{H}_2\text{O}_2$  and a  $\text{Na}_2\text{WO}_4$ - $\text{H}_3\text{PO}_4$ -quaternary ammonium chloride combined catalyst in a 1,2-dichloroethane-water biphasic system. Later work was performed with tungsten peroxo complexes (30). Both procedures were unsatisfactory in that excess olefinic substrate was used, limiting yields of epoxide to  $\leq 60\%$ . Another research group reported that tungstate ion alone could not catalyze the epoxidation of 1-octene, but that the heteropoly acid,  $\text{H}_3\text{PW}_{12}\text{O}_{40}$ , would give the epoxide in 96% yield when the reaction was conducted with cetylpyridinium chloride,  $\text{H}_2\text{O}_2$ , in  $\text{CHCl}_3/\text{H}_2\text{O}$  (Scheme 5) (31). A variety of allylic alcohols such as *trans*-2-buten-1-ol were also epoxidized in good yield with this system. In a further study of epoxidation by  $\text{H}_3\text{PW}_{12}\text{O}_{40}$  (termed Ishii-Venturello chemistry), the active catalytic epoxidation species was confirmed to be  $\{\text{PO}_4[\text{WO}(\text{O}_2)_2]_4\}^{3-}$  (32). Monitoring of gaseous products showed that  $\text{H}_2\text{O}_2$  disproportionation was the dominant side reaction. Catalysis stopped after 500 turnovers as a result of catalyst inactivation by product epoxide. Ishii-Venturello chemistry has been applied to the epoxidation of undecylenic acid (10-undecenoic acid) and its methyl ester (33). Undecylenic acid is manufactured by pyrolysis of the sodium or calcium salts of ricinoleic acid from castor oil. In terms of yield and selectivity, results were superior to those obtained with preformed and *in situ* prepared peroxyacetic acid.

In the biphasic system 1,2-dichloroethane/ $\text{H}_2\text{O}$  in the presence of methyltricaprylammonium chloride,  $[\text{WZnMn}_2(\text{ZnW}_9\text{O}_{34})_2]^{12-}$  was shown to be a very active catalyst for epoxidation of cyclohexene, cyclooctene, and several aliphatic olefins (34). The disubstituted manganese polyoxometalate was also active in toluene/ $\text{H}_2\text{O}$ , but not active under monophasic conditions in solvents such as acetonitrile or *tert*-butyl alcohol. In a subsequent study, it was shown that selectivity for epoxidation over allylic oxidation could be improved by lowering the reaction temperature to  $2^\circ\text{C}$  (35). The catalytically active species was not fully characterized, but the available data suggested that it was best described as a tungsten peroxo compound.

Another variation of this procedure used  $\text{Na}_2\text{WO}_4$ , (aminomethyl)phosphonic acid ( $\text{NH}_2\text{CH}_2\text{PO}_3\text{H}_2$ ), and methyltri-*n*-octylammonium hydrogensulfate  $\{[\text{CH}_3$

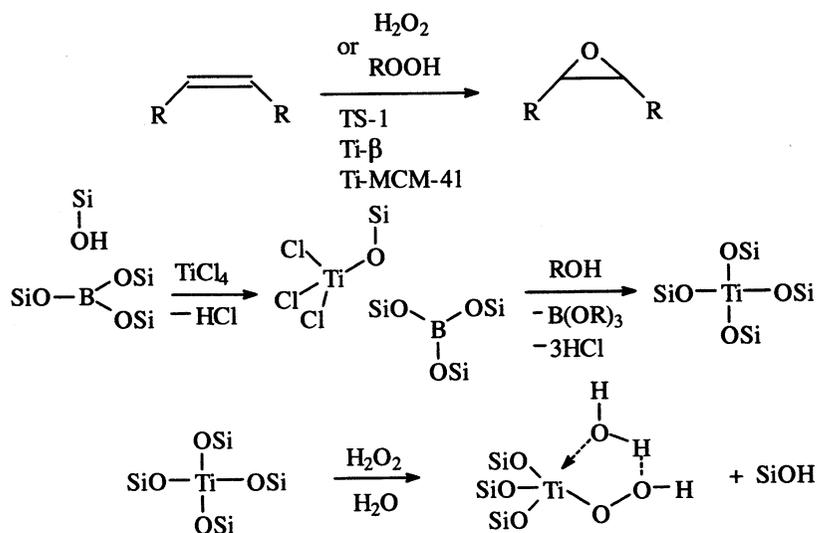


**SCHEME 5.** Epoxidation with  $\text{H}_3\text{PW}_{12}\text{O}_{40}$  with a phase-transfer catalyst (PTC).

$(n\text{-C}_8\text{H}_{17})_3\text{N]HSO}_4\}$  in a 2:1:1 molar ratio with  $\text{H}_2\text{O}_2$  as the oxidant (36). The oxidation can be performed without solvent. This procedure gave high yields except with very acid-sensitive epoxides such as that from styrene in which the yield of epoxide was <25%.

### Titanosilicates as Catalysts

Zeolites are crystalline aluminosilicate minerals that are used commercially as molecular sieves, drying agents, and catalysts (37). In the early 1980s, it was demonstrated that a zeolitic material containing titanium, known as titanosilicate (TS-1), was a good selective oxidation catalyst capable of converting propylene to propylene oxide and phenol to hydroquinone in the presence of hydrogen peroxide (Scheme 6) (38). The second coordination shell of the titanium atoms in TS-1 is silicon; clusters in the form of  $\text{TiO}_2$  are not present (39). In titanium-substituted zeolites such as TS-1, titanium is uniformly distributed in the crystalline framework by isomorphous substitution of a part of  $\text{Si}^{\text{IV}}$  with  $\text{Ti}^{\text{IV}}$  (40). The second line of Scheme 6 shows an example of how this substitution might occur in the case of a boron-containing zeolite; it is speculated that the titanium is inserted into the vacancy created by the loss of boron (39). The complexed titanium reacts either with  $\text{H}_2\text{O}_2$  or organic hydroperoxide to produce a reactive complex as shown on the third line of Scheme 6, although an alternative structure for the reactive species has been proposed (41). Because the pore size in TS-1 is small, steric restrictions do not allow



**SCHEME 6.** Epoxidation with titanosilicates. The second line shows the substitution of titanium in a borosilicate. The third line shows the formation of the epoxidizing agent.

penetration by the substrate when an alkyl hydroperoxide is used. Accordingly, TS-1 is an active epoxidation catalyst only with  $H_2O_2$  and relatively small alkenes.

Another titanosilicate catalyst is a titanium-doped zeolite (Ti- $\beta$ ), which is prepared by mixing  $TiO_2$ ,  $SiO_2$ , tetraethylammonium hydroxide, and hydrogen peroxide, followed by heating (42–44). Ti- $\beta$  has a three-dimensional pore system containing 12-membered ring apertures. This larger pore size makes Ti- $\beta$  suitable for branched and cyclic alkenes. Catalytic activity also is observed with organic hydroperoxide oxidants as well as  $H_2O_2$ .

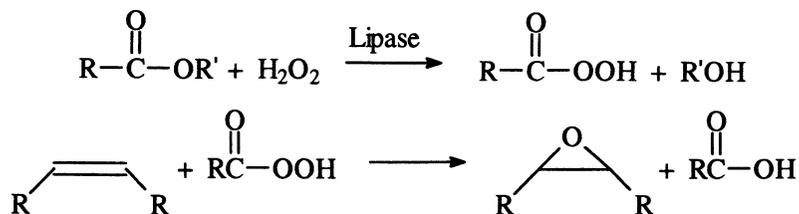
A third type of titanosilicate that will be discussed here is based upon an ordered microporous molecular (MCM) sieve (45). These were initially prepared by the calcination of aluminosilicate gels in the presence of surfactants. MCM contain uniform channels, and their dimensions can be varied through the choice of surfactant. MCM containing titanium (Ti-MCM) can be prepared in several ways. One preparation, designated as Ti $\rightarrow$ MCM41, accommodates the titanium ions within the silica walls (46,47). In another preparation, designated as Ti $\uparrow$ MCM41, tetracoordinated titanium ion was grafted onto the inner surface of the MCM channels (48).

Ti- $\beta$  and Ti $\rightarrow$ MCM41 have been used as catalysts for the epoxidation of methyl oleate with the use of  $H_2O_2$  or *tert*-butyl hydroperoxide (49). Generally Ti- $\beta$  gave better yields of epoxide than did Ti $\rightarrow$ MCM41. Acetonitrile was a better solvent than methanol, although when Al-free Ti- $\beta$  was washed with an aqueous solution of sodium cations, good yields of epoxide were obtained even in  $CH_3OH$ . Higher yields of epoxide could be obtained with Ti $\rightarrow$ MCM41 when *tert*-butyl hydroperoxide was used as the oxidant.

Research on titanosilicates as well as other forms of immobilized titanium catalysts is rapidly advancing, and novel forms of titanosilicates are still being discovered (50,51). Two recently described advances that may prove useful are the following: (i) tetra-n-pentyltitanium was reacted with surface hydroxyl groups on several types of silicas. With the use of this catalyst, epoxidation occurred with  $H_2O_2$  and *tert*-butyl hydroperoxide (52,53); (ii) Silica was reacted with  $TiF_4$ ; dropwise addition of  $H_2O_2$  to the defluorinated catalyst led to epoxidation of cyclohexene (54).

### ***Lipase-Catalyzed Peracid Formation***

Hydrogen peroxide can react with carboxylic acid to form peracid when lipase enzyme is used as a catalyst instead of inorganic acid. The peracid will epoxidize alkenes, which results in the regeneration of the carboxylic acid (Scheme 7). The best results were obtained in the nonpolar solvents toluene and hexane or when mixtures of alkene and carboxylic acid were used without solvent (55). Lipases were immobilized on cellulose, polysulfone membranes, or polypropylene beads (56). The lipases were used to convert caprylic acid to its peracid. The peracid was used to convert oleic acid to its epoxide. The best yield of epoxy stearic acid (81%) was obtained with the lipase from *Candida antartica*. Using a commercial preparation of immobilized *C. antartica* lipase, various unsaturated carboxylic acids were treated



SCHEME 7. Lipase generation of a peracid and its use for epoxidation.

with  $\text{H}_2\text{O}_2$ ; yields of epoxide varied from 0 to 91% (57). Formation of dihydroxy acids or estolides did not occur. The lipase was still active after 15 uses. Forty carboxylic acids were used as substrates for the lipase-catalyzed formation of peracids (58). Good agreement between the amount of peracid formed and epoxidation of 1-octene was obtained. Neither  $\alpha$ -substituted carboxylic acids nor aromatic acids was converted to peracids.

The perhydrolysis of carboxylic acid esters has also been studied. In this reaction,  $\text{H}_2\text{O}_2$  reacts with an ester to produce a peracid and an alcohol. Using perhydrolysis, a number of  $\alpha$ -substituted peracids could be prepared. Formation of epoxides by running the perhydrolysis procedure in isobutyric acid methyl ester was found to be less expensive than buying peracids. A one-pot synthesis of epoxyalkanolacylates using lipase and  $\text{H}_2\text{O}_2$  has been devised (59). The procedure used an unsaturated alcohol and an ethyl ester. Peracid is produced from the ester. The peracid is used for epoxidation, and the lipase also functions as a catalyst for interesterification to convert the alcohol to its corresponding ester. A notable example was the reaction of oleyl alcohol with the ethyl ester of acrylic acid to produce 9,10-epoxystearyl-acrylate, a compound that is not easily produced by chemical methods because of its tendency to polymerize.

## Fatty Acid Hydroperoxide as a Source of Epoxy Alcohols

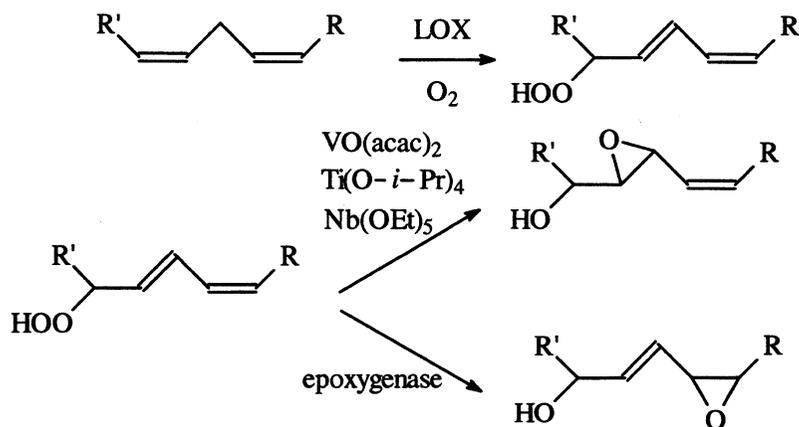
### Sources of Fatty Acid Hydroperoxide

Polyunsaturated fatty acids react with  $\text{O}_2$  to give fatty acid hydroperoxides. This reaction is catalyzed by a variety of catalysts. However, a mixture of regio- and stereoisomers is obtained. From a synthetic perspective, the best catalyst is the enzyme lipoxygenase (LOX) because under appropriate conditions, the reaction exhibits an extremely high degree of enantio- and regioselectivity and gives a product with the hydroperoxide moiety in a single position (60). Because LOX requires the presence of a (Z),(Z)-pentadiene moiety, for industrial purposes the use of LOX would be limited to linoleic acid because this fatty acid can be obtained in large amounts from several seed oils. LOX-1 from soybean catalyzes the addition of oxygen to linoleic acid to give the 13-hydroperoxide [13(S)-hydroperoxy-9(Z),11(E)-octadecadienoic acid] (61). Another class of LOX found in potato tubers

and maize kernels converts linoleic acid into the 9-hydroperoxide [9(*S*)-hydroperoxy-10(*E*),12(*Z*)-octadecadienoic acid]. Although most LOX enzymes contain ferric iron in their active state, another type of manganese-containing LOX is found in some species (62). From linoleic acid, Mn-LOX from *Gaumannomyces graminis* produced two hydroperoxides. One product was the 13-hydroperoxide with the *R* configuration [13(*R*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid]. The other product resulted from *bis*-allylic oxygenation of linoleic acid to give the 11-hydroperoxide [11(*S*)-hydroperoxy-9(*Z*),12(*Z*)-octadecadienoic acid].

### Metal Ion Catalysis of Epoxidation from Hydroperoxide

The catalysis of epoxide formation from organic hydroperoxides by transition metals has been studied extensively (7). Asymmetric epoxidation is conveniently achieved by the Sharpless epoxidation using titanium (63). The hydroperoxide of methyl linoleate [methyl 13(*S*)-hydroperoxy-9(*Z*),11(*E*)-octadecadienoate, Me-HPODE] was prepared using LOX, and Me-HPODE was subjected to the action of vanadyl acetylacetonate [VO(acac)<sub>2</sub>] (Scheme 8); only the double bond adjacent to the hydroperoxide was epoxidized (64). Treatment with titanium(IV) isopropoxide [Ti(O-*i*-Pr)<sub>4</sub>] gave predominantly the *threo* isomer, i.e., methyl 11(*R*), 12(*R*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (65). Treatment of MeHPODE with niobium(V)ethoxide [Nb(OC<sub>2</sub>H<sub>5</sub>)<sub>5</sub>] gave the *erythro* isomer, i.e., methyl 11(*S*), 12(*S*)-epoxy-13(*S*)-hydroxy-9(*Z*)-octadecenoate (66). Multiple structure epoxy alcohols can be generated from fatty hydroperoxides by Fe<sup>2+</sup> (67), hematin (68), hemoglobin (69), and myoglobin (70).



**SCHEME 8.** Formation of a fatty acid hydroperoxide with O<sub>2</sub> and lipoxygenase (LOX). The second line shows the conversion of the hydroperoxide to an epoxy alcohol with metal ion catalysts and the enzyme epoxygenase.

### Enzymatic Catalysis of Epoxidation from Hydroperoxide

Epoxy alcohol derivatives of arachidonic acids, termed hepoxilins, can have biological activity in mammalian systems. Although hepoxilins can be prepared with catalysis by hemin and hemoglobin, there is an enzymatic route to these compounds as well that has not yet been characterized (71,72). Epoxy alcohols also are obtained by the treatment of fatty acid hydroperoxide with a cytochrome P450-dependent activity (68), hydroperoxide isomerase (67,73), and epoxygenase (peroxygenase) (74). It is notable that epoxygenase acts only on *cis*-double bonds (Scheme 8).

### Conclusion

As noted in the introduction, epoxidation by the peracid procedure suffers from a number of drawbacks associated with the use of a volatile acid catalyst. Fortunately, as outlined here, research activity in this area has been vibrant, and the processor has been offered a wide variety of new alternatives for fatty epoxide production.

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