



# Past and current routes to beta-hydroperoxy alcohols: A functional group with high potential in organic synthesis

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## Graphical Abstract

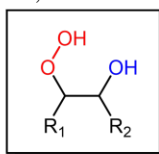
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### Past and Current Routes to $\beta$ -Hydroperoxy Alcohols: a Functional Group with High Potential in Organic Synthesis

Corentin Bordier, Vincent Escande,\* Christophe Darcel\*

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Demeta S.A.S., 6 rue Pierre-Joseph Colin, 35000 Rennes, France



This review aims to showcase the synthesis and high potential of  $\beta$ -hydroperoxy alcohols (HPA) as intermediates in molecular chemistry in both academic and industrial areas.

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Keywords:  $\beta$ -hydroxy hydroperoxides; hydrogen peroxide; singlet oxygen; perhydrolysis; 1,2,4-trioxanes

# Past and Current Routes to $\beta$ -hydroperoxy alcohols: a Functional Group with High Potential in Organic Synthesis

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**Abstract**—This review aims to showcase the high potential of  $\beta$ -hydroperoxy alcohols (HPA) as intermediates in molecular chemistry in both academic and industrial areas. In particular, these are crucial intermediates for the synthesis of 1,2,4-trioxanes, essential motifs in numerous anti-malarial drugs including the lead artemisinin. The aim of this review is to report the main pathways of preparation of HPAs, more particularly highlighting the selective opening of epoxides by hydrogen peroxide solutions or the use of singlet oxygen for the photooxygenation of allylic alcohols.

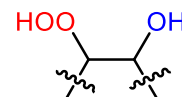
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## 1. Introduction

In molecular synthesis, organic peroxides are often key reagents both in laboratory and industrial processes as oxidizing agents and initiators for free-radical reactions. Organic peroxides are not only useful in organic synthetic chemistry, but they are also highly involved in biological

processes: indeed, their various biological activities and pharmaceutical applications have driven the recent advances in the peroxide's chemistry field as highlighted by the hundreds of publications covered in the literature concerning organic peroxides [1–3]. By contrast, the particular hydroperoxide motif of  $\beta$ -hydroperoxy alcohol was only scarcely reviewed up today, and the aim of this present review is to focus on its preparation (Figure 1) [4].



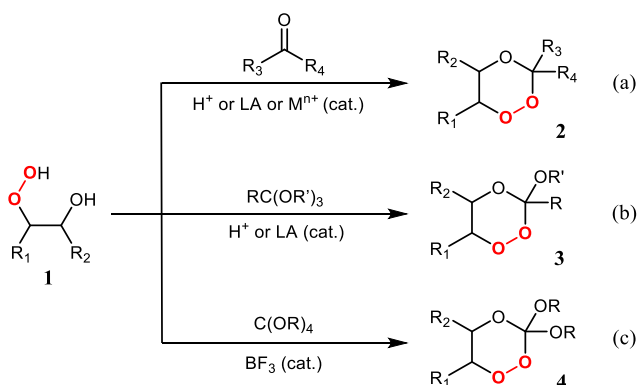
**Figure 1.**  $\beta$ -hydroperoxy alcohol motif.

$\beta$ -hydroperoxy alcohols (HPA) **1**, also known as  $\beta$ -hydroxyhydroperoxides, are important and versatile intermediates in organic synthesis. One important application of HPAs is the preparation of 1,2,4-trioxanes (Scheme 1) [1–3]. Indeed, the classical pathway to obtain efficiently 1,2,4-trioxanes **2** is the condensation of  $\beta$ -hydroperoxy alcohols **1** with carbonyl compounds (Scheme 1a) [5–8]. To promote such peroxyacetalization of  $\beta$ -hydroperoxy alcohols, the use of Brønsted acids such as tungstic acid [9], hydrochloric acid [10–12], *p*-toluenesulfonic acid (*p*-TSA) [13–21], 10-camphorsulfonic acid (CSA) [17,22,23], pyridinium or *p*-toluenesulfonate (PPTS) was required [24]. Due to the simplicity and versatility of the method, the pharmaceutical company Sanofi-Aventis patented [25] the simple Brønsted acid-catalysed condensation protocol using *p*-TSA for the preparation of various 1,2,4-trioxanes and their application as antimalarial drugs. Another widely used catalyst was the Lewis acid (LA) boron trifluoride [24,26–33] and more anecdotally transition metal catalysts such as copper(II)

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sulfate [34] or the recoverable silica-supported ferric chloride [35] were also reported.

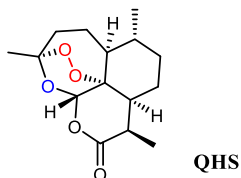
An alternative pathway for the 1,2,4-trioxanes synthesis by peroxyacetalization reaction used aliphatic and aromatic orthoesters ( $\text{RC}(\text{OR}')_3$ ) as carbonyl sources (with different catalysts such as indium triflate [24] as a Lewis acid catalyst, PPTS [36] or *p*-TSA [37] as a Brønsted acid catalyst) (Scheme 1b). Orthocarbonates ( $\text{C}(\text{OR})_4$ ) can be also used in the presence of boron trifluoride (Scheme 1c) [36].



**Scheme 1.** Synthesis of 1,2,4-trioxanes from HPAs.

1,2,4-trioxanes have aroused a great deal of interest in the scientific community due to their antimalarial properties [38,39], especially since the discovery of artemisinin by You-You Tu, Nobel Laureate in Physiology or Medicine in 2015 (Figure 2). They also displayed antitumor [30,40] as well as fasciocidal activities [41] and a lot of other various types of bioactivity [42] as recently shown by their description as possible agents to fight against coronavirus disease COVID-19 [43-45].

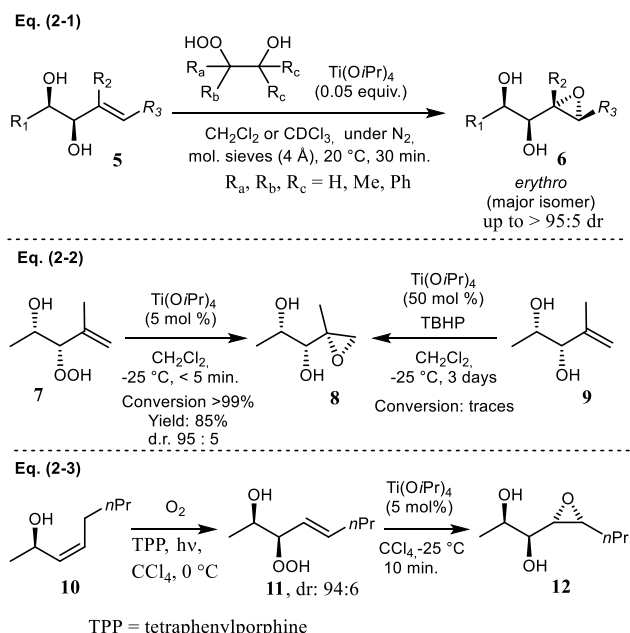
Another interest of the 1,2,4-trioxane motif is the use as an alternative to ketal protecting group of carbonyls which are stables under various conditions such as Wittig reaction, addition of Grignard reagents or reductive conditions. The deprotection leading to the corresponding carbonyl derivatives can be conducted efficiently in high yields under basic conditions at ambient temperature [46].



**Figure 2.** Chemical structure of Qinghaosu (QHS, artemisinin).

A second versatile application of HPAs is epoxidation reactions. Indeed,  $\beta$ -hydroperoxy alcohols can be used as oxygen donors in highly diastereoselective, titanium-catalysed epoxidation of ene diols [47], thus exhibiting interesting advantages over the classical Sharpless epoxidation [48]. Indeed, one advantageous practical purpose is that the reaction could be conducted at room temperature under short reaction times (*ca.* 1/2 h) with a high

stereochemical control (Eq. (2-1), Scheme 2). As a representative example, starting from an enantiomerically pure ene diol derivative **5**, the corresponding epoxy diol product **6** was obtained in an enantiomerically and diastereoisomerically pure form. In addition, HPA could play the double role of the oxygen donor and oxygen acceptor, thus avoiding the use of an external hydroperoxide, such as the classical *tert*-butyl hydroperoxide in the Sharpless epoxidation (Eq. (2-2), Scheme 2). Noticeably, an enhanced reaction rate compared to the conventional titanium-catalysed epoxidation with *tert*-butyl hydroperoxide (TBHP) was also reported (5 minutes at  $-20^\circ\text{C}$ ) [49]. Such poor reactivity of allylic alcohols bearing an additional hydroxyl functionalities in the Sharpless epoxidation with TBHP was already well-reported [50-51]. Moreover, using chiral allylic alcohols (e.g. **10**) in an one-pot epoxyhydroxylation, chiral epoxydiols (e.g. **12**) could be selectively obtained, notably with the introduction of three additional chiral centres in successive, adjacent positions (Eq. (2-3), Scheme 2) [47,52].



TPP = tetraphenylporphine

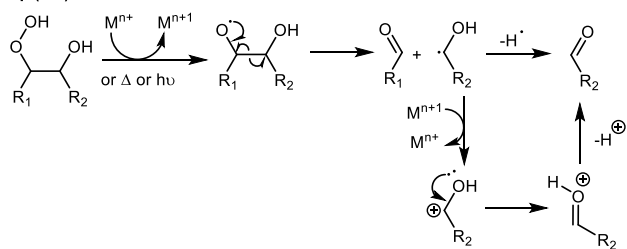
**Scheme 2.** Titanium-catalysed diastereoselective epoxidation of ene diols with  $\beta$ -hydroperoxy alcohols as oxygen donors.

Noticeably, the reduction of the HPA moiety could be performed with common reducing agents such as Pd/C-catalysed hydrogenation [34], KI [53],  $\text{Ph}_3\text{P}$  (excess) [54],  $\text{Ph}_2\text{S}$  (3 equiv.) [55], as representative examples and led to 1,2-diol, and more especially *cis*-1,2-diol.

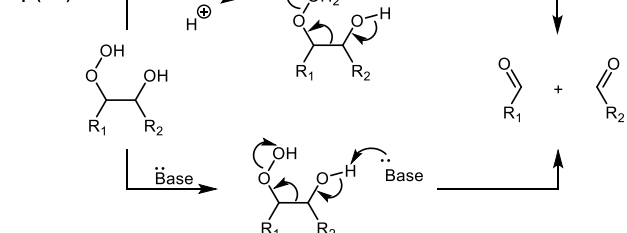
Finally, numerous studies [9,53,54,56-62] showed that HPAs can be subjected to homolytic cleavage of the O-O bond leading to the corresponding carbonyl derivatives *via* diverse pathways such as thermolysis, photolysis or transition-ion-mediated decomposition through single electron transfer (Eq. (3-1), Scheme 3) as well as acid- or base-catalysed fragmentation (Eq. (3-2), Scheme 3).

Noticeably, these fragmentation methodologies allowed easy accesses to aldehydes, ketones and carboxylic acids, which highlighted that HPA derivatives have to be seen as ideal key intermediates in the oxidative cleavage of alkenes.

Eq. (3-1)

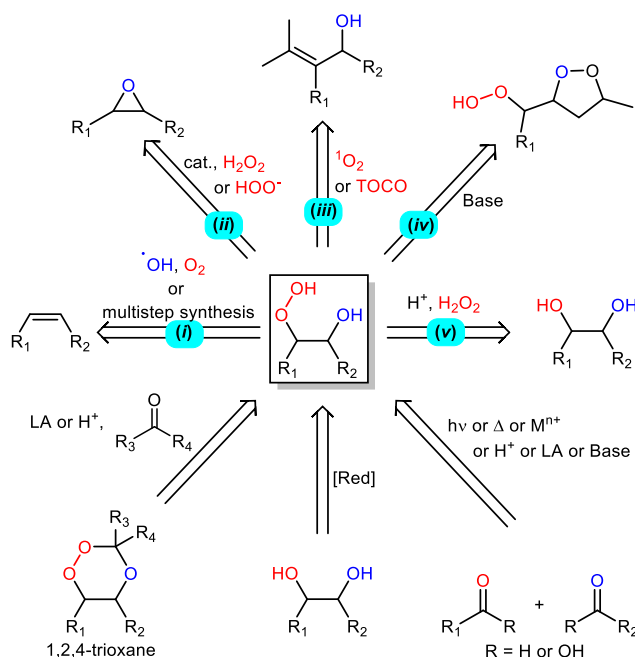


Eq. (3-2)



**Scheme 3.** Different fragmentation pathways of HPAs into carbonyl derivatives.

Currently, five main general approaches to afford HPAs were described in the literature: (i) starting from alkenes, (ii) via the epoxide opening with hydrogen peroxide, (iii) by allylic alcohol oxidation, (iv) using the Kornblum–DeLaMare rearrangement of  $\beta$ -hydroperoxy alkylperoxides and (v) using a  $\text{H}_2\text{O}_2$  mediated reaction of 1,2-diol in acidic conditions (Scheme 4).



**Scheme 4.** Pathways of preparation and main synthetic uses of  $\beta$ -hydroperoxy alcohols (HPA).

This review aims to report the state of the art in this area, highlighting the advantages of the methodologies but also the possible drawbacks, such as the limited scope, the unsatisfactory efficiency, the use of toxic reagents, and the inappropriate conditions with regard to safety requirements. This review also aims to highlight the recent achievements for the synthesis of HPA avoiding the use of hazardous anhydrous and ethereal solution of hydrogen peroxide, which make them safer to be implemented in an industrial scale-up phase and stimulate a revival interest in the synthetic community.

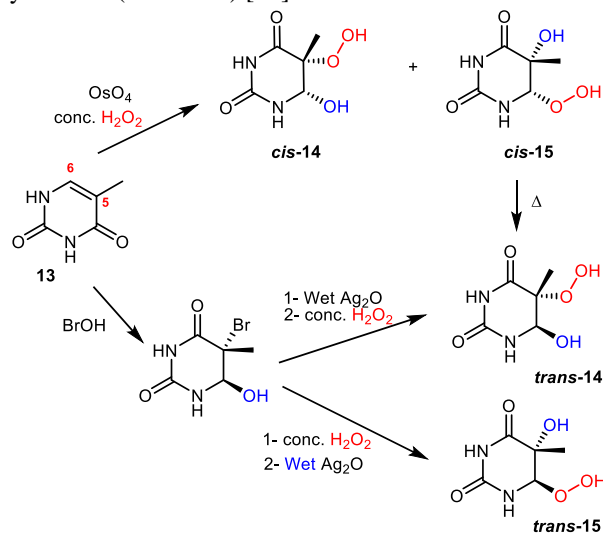
## 2. HPA synthesis starting from alkenes

This first part of this review will focus on the pioneer syntheses of HPAs using radio-induced methodologies and the chemical preparation from alkenes (other than those involving an epoxide intermediate which will be described in the following part).

### 2.1. Pioneering work on natural molecules

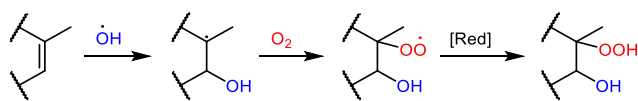
Historically, the first synthesis of the HPA motif took place directly from alkenes, by radiochemical activation. The degradation of DNA in cells induced by radiation such as  $\text{X}$ ,  $\alpha$ ,  $\beta$  or  $\gamma$ -rays had serious biological consequences such as the cell death, reproductive death, mutation and carcinogenesis. Thus, to learn more about the radio-induced modifications in DNA nucleobases, the study of pyrimidines led to the first synthesis of the HPA moiety.

Indeed, since 1956, it has been shown that the radiolysis of oxygenated aqueous solutions of thymine **13** led to the formation of peroxidized organic products, which were identified as the pyrimidine HPA **14/15** formed by saturation of the 5:6 ethylenic bond [63–65]. Two years later, in order to validate the *cis* or *trans* configuration of the HPA motif, Ekert and Monier carried out chemical syntheses of the *cis* and *trans* isomers of 5-hydroperoxy-6-hydroxydihydrothymine **14** and of 6-hydroperoxy-5-hydroxydihydrothymine **15** (Scheme 5) [66].



**Scheme 5.** First selective chemical synthesis of HPAs.

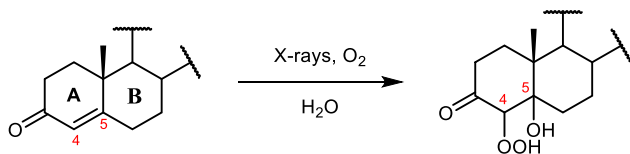
The mixture of *cis*-**14** and *cis*-**15** isomers was obtained by reaction of thymine **13** with concentrated hydrogen peroxide in the presence of a catalytic amount of OsO<sub>4</sub>. The *trans* isomers were separately prepared from **13** in a sequential pathway: first, the *trans*-4-hydroxy-5-bromothymine was prepared by reaction with hypobromous acid. By treatment with concentrated H<sub>2</sub>O<sub>2</sub> then wet Ag<sub>2</sub>O, HPA *trans*-**14** was obtained. By switching the order of the introduction of the two reactants, HPA *trans*-**15** was selectively prepared. Thus, in accordance with Latarjet's results [67], the HPA obtained by radiation of thymine was in fact a 20:80 mixture of the *cis* and *trans* isomers of **14**. The proposed reaction sequence for the HPA formation is shown in Scheme 6.



**Scheme 6.** Reaction sequence of radiation-induced formation of HPA.

In a very similar way to X-rays, hydroperoxides can be formed by the action of  $\gamma$  radiation on thymine in aerated aqueous solution as demonstrated by Téoule and Cadet [69]. Similarly, the identification of the different hydroperoxides formed during the irradiation process, (e.g. 5(6)-hydroperoxy-6(5)-hydroxydihydrothymine **14** and **15**), was based on the comparison with separately prepared compounds.

A new family of HPAs was obtained from various steroids under ionizing radiation. Indeed, as representative examples, the action of ionizing radiation on aqueous solutions of 11-deoxycorticosterone, cortisone and related steroids led to the corresponding HPA derivatives (Scheme 7). The corresponding regioisomer with the hydroxyl group on the C4 carbon and hydroperoxyl on the C5 carbon can also be formed [65,68,70].

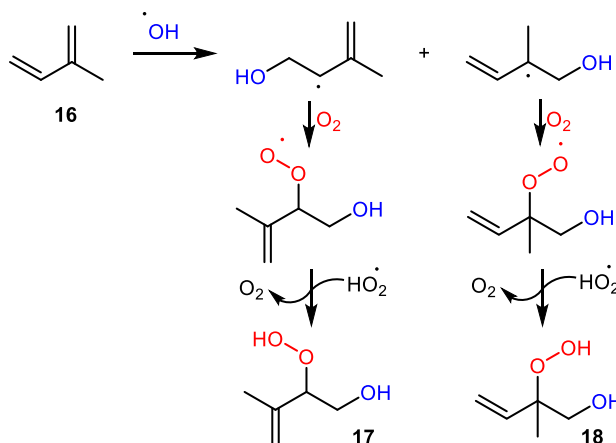


**Scheme 7.** Structure of HPAs derived from steroids (herein are represents the rings A and B of the steroids).

These radiochemical or chemical synthetic routes only had an interest in fundamental research, particularly in the field of biology. Indeed, starting from simple olefinic molecules, the radiolysis of an aqueous solutions of ethylene gave only very small amounts of stable hydroperoxides [71]. On the other hand, the formation of HPAs from the irradiation of an aqueous solution of propylene in the presence of oxygen was briefly mentioned [65,70]. Thus, the action of ionizing radiations on ethylenic systems in the presence of oxygen could lead to HPAs, although this did not constitute a viable and efficient synthetic route.

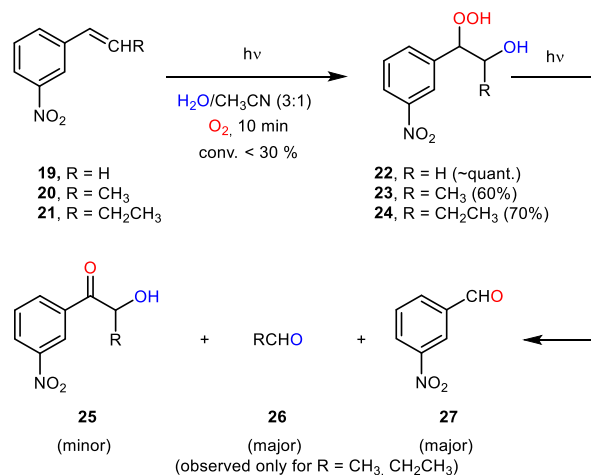
## 2.2. From tropospheric chemistry to preparative HPA synthetic methods

A similar mechanism for the formation of HPAs can take place naturally in the troposphere. These reactions were mainly initiated by hydroxyl radicals, whose primary formation results from the photo-dissociation of ozone by solar ultraviolet radiation in the presence of water vapour [72]. Thus, oxidation of isoprene **16** in certain geographic areas led to the formation of HPAs **17** and **18** (Scheme 8) [73-75]



**Scheme 8.** Formation of HPAs under tropospheric conditions.

This tropospheric type of route could also be used in the laboratory. For example, Wan and Davis had described the formation of HPAs by the photo-oxygenation of several *m*-nitrostyrenes in the presence of oxygen [76]. Although photochemical reactions in the presence of oxygen were generally not selective, the authors had shown that starting with *m*-nitrostyrene derivatives, the reaction in water in the presence of oxygen was clean and took place *via* a global tandem addition process (Scheme 9).

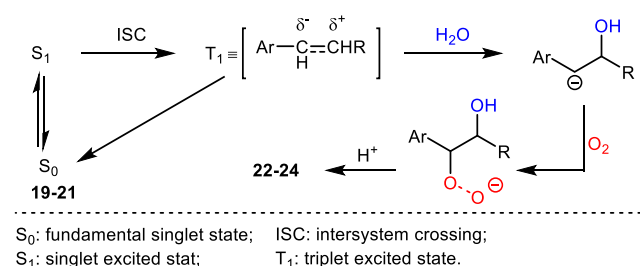


**Scheme 9.** Photo-oxygenation conversion of *m*-nitrostyrene derivatives to HPAs.



When an oxygen flow was applied in the aqueous solution of *m*-nitrostyrenes **19–21** under light irradiation, the corresponding HPAs **22–24** were selectively obtained in low conversions (< 30%). Noticeably, under similar conditions, *m*-nitrostilbene only led in the *trans*-to-*cis* photo-isomerization product [77]. Additionally, due their relative low stability, prolonged irradiation resulted in the formation of *m*-nitrobenzaldehyde **27** along with aldehyde **26**, and small amounts of  $\alpha$ -hydroxyketone **25**. These products all originated from a secondary photochemical reaction, as confirmed by an independent photolysis of HPA **22**.

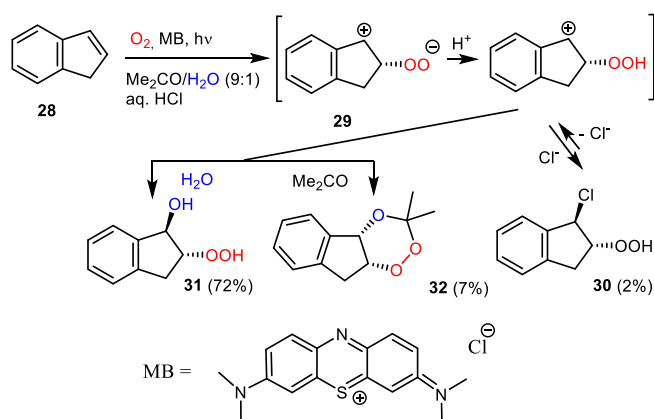
Performing sensitization experiments with rose Bengal of aqueous solution of *m*-nitrostyrenes led to no significant reaction which ruled out the implication of singlet oxygen in the process. These observations suggested that only the triplet state of oxygen was involved in the reaction pathway. A plausible mechanism for water and oxygen addition is shown in Scheme 10. Notably, water underwent nucleophilic attack of the polarized triplet excited state generating a *m*-nitrobenzyl carbanion intermediate which could be “trapped” by dissolved oxygen to give the corresponding HPAs (Scheme 10).



**Scheme 10.** Photochemical tandem addition of water and oxygen to *m*- nitrostyrene derivatives.

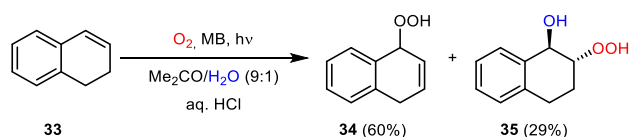
HPA **22** was fairly stable and could be purified by silica gel chromatography or crystallized from acetone. Its reduction with aqueous  $\text{Na}_2\text{SO}_3$  or KI gave the corresponding 1,2-diol and hence offered a simple overall procedure for the dihydroxylation of *m*-nitrostyrene **19**. By contrast, HPA **23** and **24** were much less stable and could easily decompose by thermolysis (at > 30 °C) or by prolonged photolysis, which make their purification difficult. It must be underlined that it represented the first and still the only example of conversion of alkenes, more particularly styrenes to HPA by photo-oxygenation using natural triplet oxygen (if excluding allylic alcohols).

Unlike Wan and Davis, Jefford *et al.* introduced the HPA motif *via* singlet-oxygen-mediated reaction [78]. In fact, the methylene blue (MB)-sensitized photo-oxygenation of indene **28** in aqueous acetone solution containing traces of hydrochloric acid at 10 °C for 10 h led to the *trans*-2-hydroperoxy-1-hydroxyindane **31** as the major product in 72% isolated yield (Scheme 11). Small amount of the chloro analogue **30** (2%) and the *cis*-fused 3,3-dimethyl-1,2,4-trioxane **32** (7%) were also obtained. This result indicated that a singlet oxygen molecule could be added to indene **28** to form the zwitterionic stabilized species **29**.



**Scheme 11.** Formation of HPA **31** by singlet oxygen photo-oxygenation of indene **28**.

Noticeably, when 1,2-dihydronaphthalene **33** was used under the same conditions (aqueous acetone solution, with or without addition of HCl), allylic hydroperoxide **34** was the main product (60 % yield) while HPA **35** was isolated in 29% yield (Scheme 12). Additionally, the amount of hydrochloric acid had no effect on the composition of the mixture.



**Scheme 12.** Conversion of 1,2-dihydronaphthalene **33** to HPA **35** by singlet oxygen photo-oxygenation.

This reaction was sensitive to the substituents present on the aromatic ring. Indeed, no reaction took place when a nitro group was present in position 7 of 1,2-dihydronaphthalene **33** and no HPA was formed if this position was occupied by a methoxy group since in this case a dioxetane was generated instead of the zwitterionic peroxide intermediate. Even if interesting, this methodology to prepare HPAs was substrate specific and not suitable for aliphatic olefins.

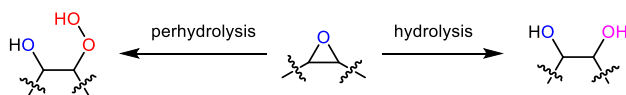
### 3. The perhydrolysis way via ring-opening of epoxides

Epoxides are versatile and important intermediates in organic synthesis [79]. No reaction of epoxides has been more thoroughly studied and more widely used in synthesis than the regio- and stereoselective ring-opening reactions with a variety of nucleophilic species leading to  $\beta$ -substituted alcohols [80–82]. In this area, the opening of epoxides with hydrogen peroxide as a nucleophile is one of the easiest and most straightforward synthetic procedures for the efficient preparation of  $\beta$ -hydroperoxy alcohols. In this paragraph, a few general features of this reaction will be first presented highlighting its main advantages and limitations and then advances made to overcome these limitations will be described.

### 3.1. Hydrolysis versus perhydrolysis: general considerations

Epoxides can be ring-opened in either neutral, basic, or acidic conditions [81,85–94]. Usually, the presence of acid accelerates the epoxide's ring opening. More interestingly, the main concern in this area is the regioselectivity of the ring opening of unsymmetrical epoxides which differs under acid-catalysed, base-catalysed or neutral conditions. Indeed, performing the reaction under basic or neutral conditions leads to regioselective nucleophilic attacks at the sterically less-hindered carbon atom according to a classical  $S_N2$  mechanism. On the other hand, the reaction is described to proceed *via* a borderline  $S_N2$  mechanism (or modified  $A_2$ ) under acidic conditions [80,83,84].

One of the most important reactions involving a nucleophile for the opening of epoxides in industrial applications is hydrolysis which results in the corresponding 1,2-diols (Scheme 13) [95]. However, hydrogen peroxide has very different chemical properties from water [96], as classically illustrated by pH meter readings of aqueous hydrogen peroxide solutions which are lower than the "real" pH value in water. Indeed, Kolczynski *et al.* have shown [97] that this behaviour appeared to have a connection with hydrogen ion activity. More precisely, it is linked to the difference in the free energy of the proton solvation in water and in hydrogen peroxide which is about 9 kcal/mol, indicating that the proton is more firmly bound to oxygen in water. As a result, undissociated hydrogen peroxide behaves as a stronger nucleophile than water. This argument was confirmed by Sanderson who indicated that hydrogen peroxide was about  $10^4$  times more nucleophilic than water [98]. Based on these observations, it becomes apparent that hydrogen peroxide can act as a nucleophile in epoxide opening reactions resulting in HPA formation *via* a perhydrolysis reaction (Scheme 13).



**Scheme 13.** Perhydrolysis vs hydrolysis of 1,2-epoxides.

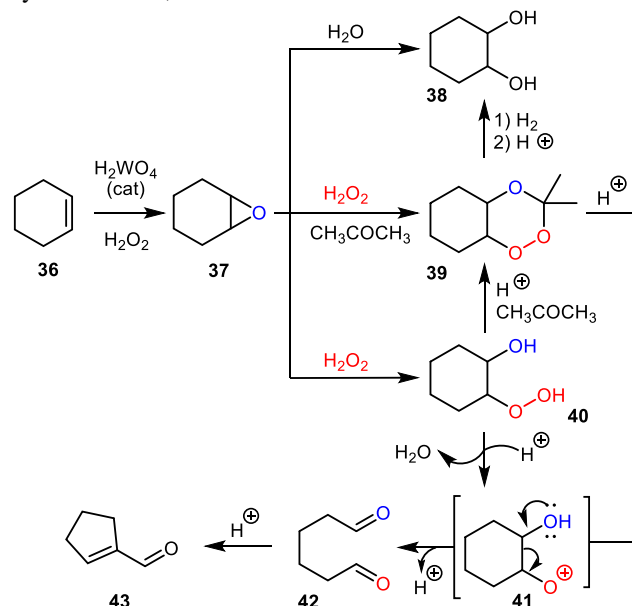
Thus, the use of aqueous hydrogen peroxide should result in a competition for the opening of epoxides by water and hydrogen peroxide nucleophiles. In the next part, in order to direct the reaction towards the selective formation of HPAs, highly concentrated hydrogen peroxide, or even anhydrous or in ethereal extracts were used, even if such reactions can represent high risks [99].

### 3.2. Use of highly concentrated, ethereal, or anhydrous $H_2O_2$

#### 3.2.1. Homogeneous catalysis

The first experimental proof of the perhydrolysis reaction of epoxides was reported in 1957 by Payne and Smith [9]. The conversion of cyclohexene **36** to its corresponding  $\alpha$ -glycol

monoether was evaluated using 3.2 mol% of tungstic acid as the catalyst and 90% hydrogen peroxide in different solvents. By contrast with methanol, in *tert*-butanol, no glycol monoether was formed and the major product was the cyclohexane-1,2-diol **38**.

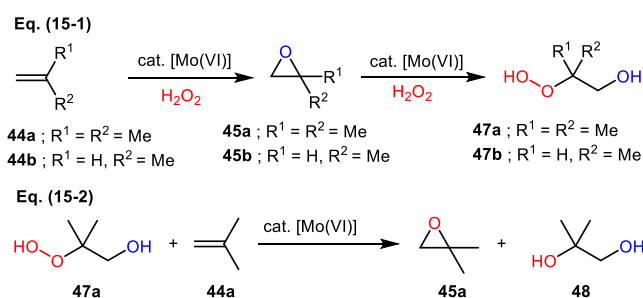


**Scheme 14.** First HPA formation by perhydrolysis of cyclohexene **36** catalysed by tungstic acid in non aqueous media.

During the investigation of the hydroxylation of cyclohexene **36** in *tert*-butanol, the *trans*-2-hydroperoxycyclohexanol **40** was identified, resulting from the ring-opening of the epoxide **37** by hydrogen peroxide. During the purification by distillation, HPA **40** underwent an acid catalysed rearrangement to adipaldehyde **42**, and 1-cyclopentenecarboxaldehyde **43** which was obtained from **42** under acidic conditions [100] (Scheme 14) (Scheme). Noticeably, 1,2,4-trioxane **39** derived from HPA **40** was isolated after the reaction with acetone. This procedure constituted the first synthesis of 1,2,4-trioxanes, but it should underlined that this procedure produced large amounts of extremely explosive triacetone triperoxide [101]. Additionally, the yields of 1,2,4-trioxane **39** were related to the concentration of hydrogen peroxide: an increase of the  $H_2O_2$  concentration from 34 to 90 % led to an increase of the yield from 23 to 49% highlighting the crucial importance of the concentration of hydrogen peroxide in the selectivity of the reaction.

Mattucci *et al.* were the first to isolate and characterize a HPA derivative by spectrometric methods [102]. Indeed, the reaction of olefins (propene and isobutene) with anhydrous  $H_2O_2$  in the presence of catalytic amount of molybdenyl acetylacetonate **46** led first to the corresponding epoxides and then to the  $\beta$ -hydroperoxy alcohols **47** (Eq. 15-1, Scheme 15). Interestingly, HPA could be used as oxygen donors, for the epoxidation of alkenes such as isoprene or cyclohexene (Eq. 15-2, Scheme 15).



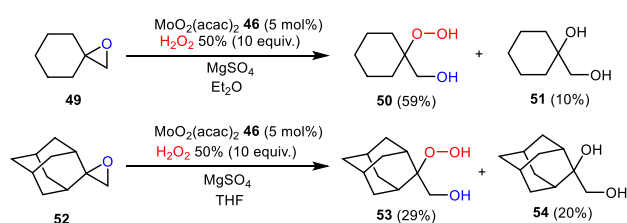


**Scheme 15.** Molybdenyl acetylacetonate **46** catalysed reaction of hydrogen peroxide with alkenes.

In addition, these results clearly showed the regioselective opening of epoxides by H<sub>2</sub>O<sub>2</sub> on the most substituted carbon centre. This pioneering work highlighted several important criteria to perform selective perhydrolysis of epoxides for the preparation of HPAs and their reactivities:

- (i) Lewis acids such as Mo(VI) are effective perhydrolysis catalysts,
- (ii) With this type of catalyst, a greater tendency for nucleophilic attack at the carbon atom which can better accommodate a positive charge in the transition state is noted,
- (iii) HPAs are reactive enough to be used as oxygen donors,
- (iv) they are subject to thermal degradation leading to carbonyl species and therefore not observable by gas chromatography.

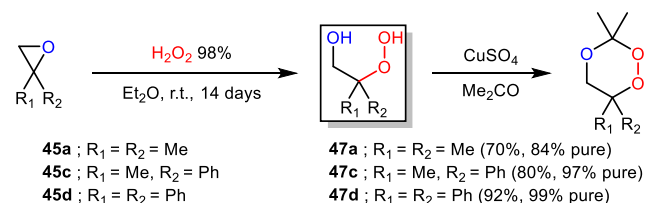
In 2005, Vennerstrom and co-workers succeeded to isolate some HPAs using a similar process [17]. Using the commercially available 50% aqueous H<sub>2</sub>O<sub>2</sub> (10 equiv.) pre-treated with anhydrous MgSO<sub>4</sub> in diethylether or THF, the perhydrolysis of two spiroepoxides **49** and **52** was performed in the presence of 5 mol% of molybdenyl acetylacetonate **46** (Scheme 16).



**Scheme 16.** Perhydrolysis of spiroepoxides **49** and **52**.

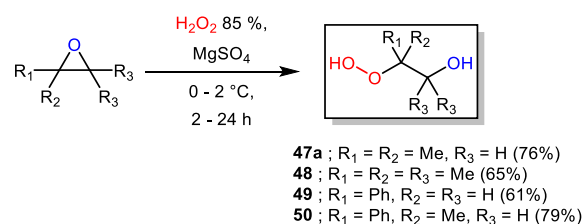
It should be underlined that the combination of *in-situ* dehydrated aqueous hydrogen peroxide with diethylether or THF does not constitute a significant improvement from a safety point of view. It should be also noticed that a recent report by An *et al.* on the study of the chemoselectivity of the reaction of ethereal H<sub>2</sub>O<sub>2</sub> with ketones, ketals and epoxides in the presence of a catalytic amount of MoO<sub>2</sub>(acac) described the decreasing reactivity order as follows: tri- or tetrasubstituted epoxides > ketones > ethylene glycol ketals > monosubstituted or 1,2-disubstituted epoxides [104a].

The first isolated yields of HPAs using perhydrolysis pathway were described in 1971 [34]. The catalyst-free reaction of an ethereal solution of epoxides **45** with 98% hydrogen peroxide for 14 days led to the corresponding HPA **47** in 70-92% isolated yields (Scheme 17).



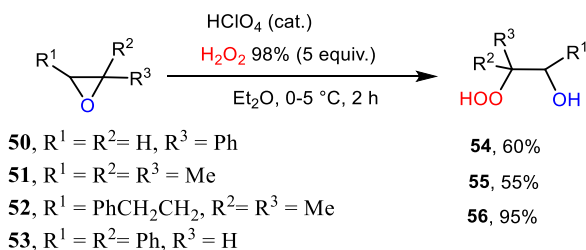
**Scheme 17.** Synthesis of HPAs by catalyst-free perhydrolysis with neat H<sub>2</sub>O<sub>2</sub>.

Later, Adam *et al.* improved this catalyst-free protocol by performing the perhydrolysis of epoxides at 0 °C with a 85% aqueous hydrogen peroxide solution, filtered over magnesium sulfate. After 2 h of reaction, Et<sub>2</sub>O and molecular sieves were added to decompose the excess of hydrogen peroxide (Scheme 18) [47]. Noticeably, the HPAs were then used for the epoxidation of ene diols in presence of Ti(OiPr)<sub>4</sub> catalyst.



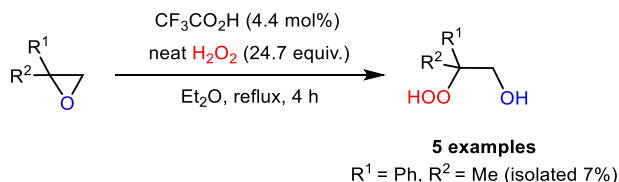
**Scheme 18.** Catalyst-free synthesis of HPAs with 85% H<sub>2</sub>O<sub>2</sub>.

One of the most efficient pathways to produce HPAs was Brønsted acid- or Lewis acid-catalysed reactions of epoxides with highly concentrated H<sub>2</sub>O<sub>2</sub> or ethereal solution of anhydrous H<sub>2</sub>O<sub>2</sub>. Thus, in 1976, a first report was dedicated to the synthesis of HPAs starting from epoxides **50-53** by reaction with 5 equiv. of 98% H<sub>2</sub>O<sub>2</sub> in ether solution at 0-5 °C for 2 h, in the presence of a catalytic amount of HClO<sub>4</sub>. HPAs **54-56** were regioselectively formed and isolated in 55-95% yields. However, benzaldehyde was the only product isolated from the reaction of stilbene oxide **53** due to the acid decomposition of the HPA intermediate under these conditions (Scheme 19) [59].



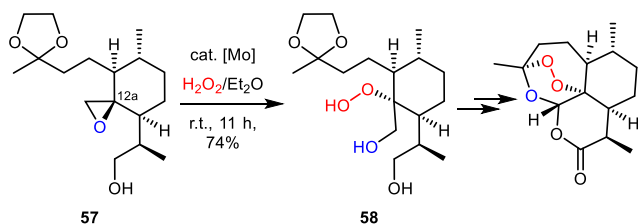
**Scheme 19.** Perchloric acid catalysed regioselective perhydrolysis of epoxides.

Another strong Brønsted acid, trifluoroacetic acid (4.4 mol%) in combination with a large excess of anhydrous  $\text{H}_2\text{O}_2$  (24.7 equiv.) (obtained by dehydration of ether solution of 90%  $\text{H}_2\text{O}_2$  by  $\text{Na}_2\text{SO}_4$ ) was also used in the synthesis of HPA from terminal epoxides [53] (Scheme 20).



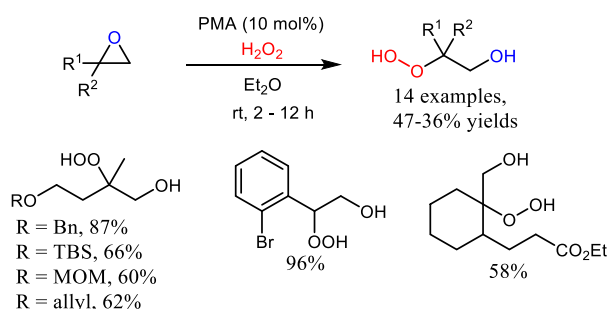
**Scheme 20.** Trifluoroacetic acid catalyzed perhydrolysis of epoxides.

Later, Wu *et al.* demonstrated that perhydrolysis of sophisticated terminal epoxides was also achievable by combining a suitable catalyst, prepared from sodium molybdate and glycine, with an ethereal  $\text{H}_2\text{O}_2$  solution [13,14]. As a representative example, the perhydrolysis of the highly hindered enantiopure spiroepoxide **57** specially designed for the synthesis of Qinghaosu (artemisinin) has been performed stereoselectively and the corresponding HPA **58** was isolated in 74% yield, using 15 mol% of the catalyst (Scheme 21).



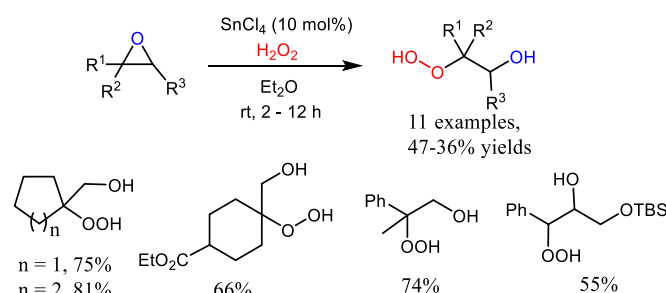
**Scheme 21.** Access to Qinghaosu (Artemisinin) via a perhydrolysis of an epoxide intermediate.

Commercially available source of molybdenum, phosphomolybdic acid (PMA, 10 mol%), was also used in association with ethereal  $\text{H}_2\text{O}_2$  solution (5 equiv.) prepared by extraction of the commercially available aqueous 30%  $\text{H}_2\text{O}_2$  with  $\text{Et}_2\text{O}$ . After reaction at rt for 2–12 h, HPA were obtained in 47–96% yields. Noticeably, an interesting scope was demonstrated with the tolerance of alcohol protecting groups such as MOM, Allyl, TBS or benzyl (Scheme 22) [103].



**Scheme 22.** PMA catalyzed perhydrolysis of epoxides.

Qiao *et al.* reported perhydrolysis of substituted epoxides using  $\text{SnCl}_4$  as a highly soluble and strong Lewis acid catalyst in the presence of 5 equiv. of ethereal  $\text{H}_2\text{O}_2$  at 0 °C to r.t. for 0.2–2 h. The corresponding HPAs were produced in 37–81% yields with similar functional groups than the previous reaction catalysed by PMA, but in substantially shortened time (0.2–2 h vs. 2–12 h) [104b]. Noticeably, using 1 equiv. of tin tetrachloride, *gem*-dihydroperoxy derivatives were exclusively obtained. Even if efficient, this procedure suffered from the use of hydrogen peroxide ethereal solution, and the toxicity of tin tetrachloride [105] (Scheme 23).

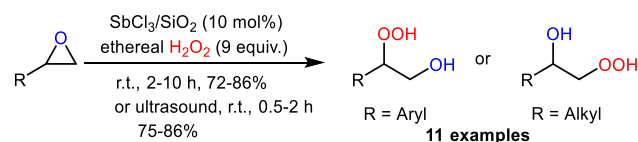


**Scheme 23.** Tin(IV) chloride catalyzed perhydrolysis of epoxides.

For all these homogeneous catalyzed perhydrolysis reactions, the question of the recovery and recycling of the catalyst have never been addressed, which contrast with the field of heterogeneous catalysis.

### 3.2.2. Heterogeneous catalysis

The first report dealing with epoxide perhydrolysis performed using a heterogeneous catalyst was reported by Zhang *et al.* [106]. Indeed, using a catalyst based on antimony trichloride/ $\text{SiO}_2$ , a mild and efficient procedure for the ring-opening of epoxides with hydrogen peroxide afforded the corresponding  $\beta$ -hydroperoxy alcohols in yields up to 86% (Scheme 24). This transformation can be conducted classically at r.t. for 2–10 h, but also under ultrasound conditions at r.t. which allowed to reduce significantly the reaction time to 0.5–2 h.

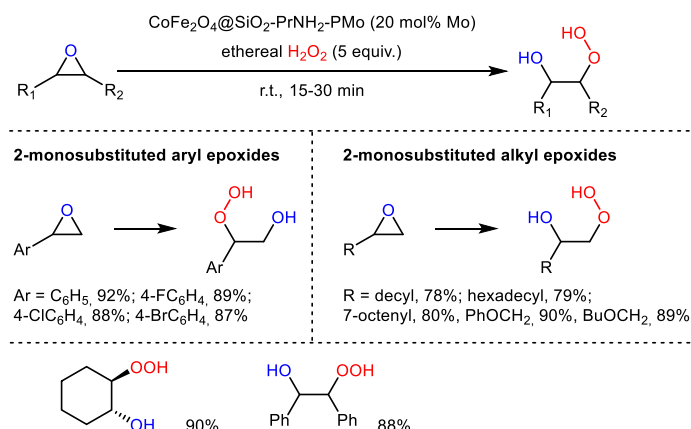


**Scheme 24.** Perhydrolysis catalyzed by antimony trichloride/ $\text{SiO}_2$  under conventional and ultrasound conditions.

Notably, after the reaction, the catalyst can be easily removed by a simple filtration. Nevertheless, no indication of its reuse was reported. The main drawbacks is still the use of ethereal hydrogen peroxide solutions, prepared by saturating a 30% aqueous hydrogen peroxide solution with sodium chloride, then extracting several times with

diethylether, and finally drying and partially condensing the ethereal solution, which involved a significant risk of explosion [107–109]. Additionally, the toxicity of  $\text{SbCl}_3$  may be also problematic [110].

Five years later, the same group described an improved procedure using a robust and reusable nano magnetically ( $\text{CoFe}_2\text{O}_4$ )-supported phosphomolybdate catalyst for ring-opening of epoxides. HPAs were obtained with a high regioselectivity at room temperature for 15–30 min. in 78–92% isolated yield (Scheme 25) [111]. The scope of the reaction showed that the substitution (aryl vs alkyl) of the epoxides have a crucial influence on the regioselectivity of the ring-opening reaction.



**Scheme 25.** Magnetic nanoparticles ( $\text{CoFe}_2\text{O}_4$ )-supported phosphomolybdate as a recyclable catalyst for the synthesis of HPAs.

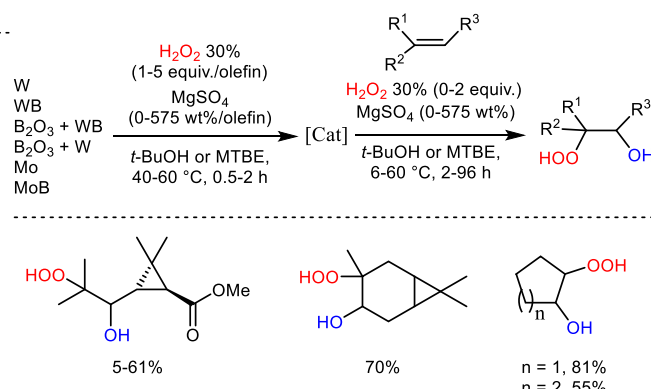
In addition, the use of magnetically recyclable nanocatalysts being an easy and efficient approach to separate and recycle a catalyst [112–114], the authors demonstrated that the ( $\text{CoFe}_2\text{O}_4$ )-supported phosphomolybdate catalyst exhibited high but slowly decreasing activity in 8 consecutive cycles (90 to 80% isolated yield), which might be attributed to the slight loss of catalyst during the reaction and recovery processes.

Later, magnetic nano-graphene oxide-supported molybdenum ( $\text{Fe}_3\text{O}_4/\text{GO-Mo}$ ) was also readily prepared and identified as an efficient and recyclable perhydrolysis catalyst (20 mol%) [114]. This catalytic system exhibited similar activity and regioselectivity (rt, 15 min., 14 examples, 78–96% yields) and the catalyst can be recycled and reused up to 8 times without significant loss of activity. These few examples clearly showed the main advantage of such nanomagnetically supported PMA in terms of easy recovery and efficient reuse in comparison to their homogeneous analogues, the use of highly concentrated hydrogen peroxide being again the main drawback.

### 3.3. Use of dilute hydrogen peroxide

#### 3.3.1. Use of non-ethereal diluted H<sub>2</sub>O<sub>2</sub>

On the reported examples in this review, until now, when a commercial diluted hydrogen peroxide solution ( $[\text{H}_2\text{O}_2] \leq 70$  wt%) was used in non-alkaline perhydrolysis, a desiccant as well as Et<sub>2</sub>O extractions were necessary in order to prepare almost neat H<sub>2</sub>O<sub>2</sub> ethereal solutions. However, the high risks involved with the use of such a solution is clearly a considerable obstacle to industrial application. In 2000, one of the first patents dealing with the synthesis of HPAs (as intermediate to carbonyl compounds) by epoxide perhydrolysis without the use of ethereal solution described the use of a metallic species (tungsten or molybdenum, in their metallic form or associated with an element of group IIb such as boron) in association with a 30% aqueous H<sub>2</sub>O<sub>2</sub> solution. After preparing the catalytic species by mixing the metallic one with 30% aqueous H<sub>2</sub>O<sub>2</sub>, the olefin and extra equiv. of H<sub>2</sub>O<sub>2</sub> were added to the solution thus leading to the corresponding HPA (Scheme 26). Noticeably, the preparation of the catalytic species prior to the alkene addition was not required. Importantly, the presence of a desiccant such as  $\text{MgSO}_4$  (for the preparation of the catalytic mixture, and/or the reaction) was desirable in order to *in-situ* dehydrate hydrogen peroxide and thus selectively produced HPA as the main product [115].



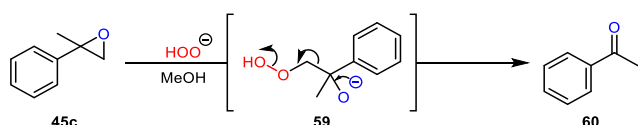
**Scheme 26.** First patented perhydrolysis of epoxides using aqueous hydrogen peroxide solution.

It must be underlined that *tert*-butanol or *tert*-butyl methyl ether (MTBE) were the recommended solvents as their combination with dehydrated hydrogen peroxide was much less hazardous than Et<sub>2</sub>O. However, the use of solvents and the desiccant in large amounts as well as the long reaction times and the lack of selectivity due to the formation of side products such as the vicinal diol hampered the industrialization of such a process.

#### 3.3.2. Reaction of epoxides with alkaline hydrogen peroxide

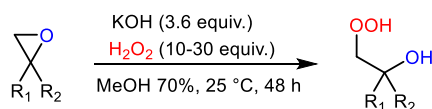
Another way to increase HPA selectivity without using a highly concentrated H<sub>2</sub>O<sub>2</sub> solution was to perform the ring-opening of epoxides with alkaline hydrogen peroxide solution. In such media, no catalyst was required, the selectivity then arose from the difference in nucleophilicity between the hydroperoxide and hydroxide anions. First,

Hoffman described a mechanism involving the formation of an anionic HPA intermediate **59** in an alkaline medium as a key step in the cleavage of  $\alpha$ -methylstyrene oxide **45c** into acetophenone **60** at room temperature with almost quantitative yield (Scheme 27) [57]. This Grob type fragmentation was then further investigated by Temple [58], which provided experimental evidence that hydroperoxide anion is a stronger nucleophile than hydroxide analogue in the opening of 1,2-epoxides.



**Scheme 27.** HPA as a key intermediate in cleavage reaction involving epoxides in alkaline aqueous  $\text{H}_2\text{O}_2$ .

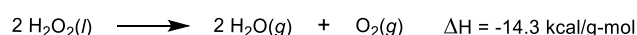
The first isolated HPAs obtained by perhydrolysis of epoxides in an alkaline medium were reported by Ogata *et al.* [53]. Performing the reaction in the presence of 10-30 equiv. of  $\text{H}_2\text{O}_2$  and 3.6 equiv. of KOH in methanol at 25 °C for 48 h, most of the epoxides led to the cleavage products due to the instability of HPAs in such conditions. However, two HPAs **47e-f** derived from epoxides **45e-f** could be isolated in 38 and 80% yields under these conditions. Noticeably, the reaction was regioselective with the hydroperoxide unit linked to the less-hindered carbon of the initial epoxide, resulting from a classic  $\text{S}_{\text{N}}2$ -type mechanism (Scheme 28).



**45e**,  $\text{R}_1 = n\text{-Pr}$ ,  $\text{R}_2 = \text{Me}$       **47e**,  $\text{R}_1 = n\text{-Pr}$ ,  $\text{R}_2 = \text{Me}$  (38%)  
**45f**,  $\text{R}_1 = n\text{-C}_7\text{H}_{15}$ ,  $\text{R}_2 = \text{H}$       **47f**,  $\text{R}_1 = n\text{-C}_7\text{H}_{15}$ ,  $\text{R}_2 = \text{H}$  (up to 80%)

**Scheme 28.** First isolation of HPAs by perhydrolysis of epoxides with alkaline aqueous hydrogen peroxide.

Although this perhydrolysis route in basic conditions permitted to avoid the use of a catalyst and anhydrous or highly concentrated ethereal hydrogen peroxide solution, bases are also well-known to be able to accelerate the decomposition of peroxide and trace heavy-metal impurities (*e.g.* iron, copper, and manganese) which are common contaminants of alkali-metal hydroxides, have also an important influence on the reaction rate [99,116–119]. The hydrogen peroxide decomposition reaction is a disproportionation reaction producing oxygen and water (Scheme 29) [120,121]. This reaction is highly exothermic and the rise in temperature can increase the rate of decomposition of HPA.



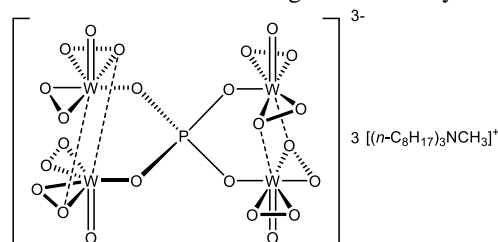
**Scheme 29.** Disproportionation of hydrogen peroxide.

As illustrative examples, over the past 2 decades, at least three bleach plants within North America experienced

catastrophic events involving the decomposition of hydrogen peroxide with serious injuries [122,123]. Thus, such hazards associated to the important amount of aqueous waste, the relative instability of HPAs under these alkaline conditions are important drawbacks for large scale applications.

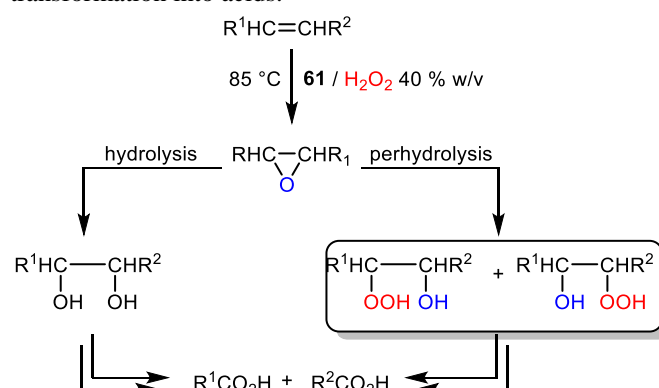
### 3.3.3. Use of highly hydrophobic substrates

The last described methodology to prepare HPAs with good selectivity using  $\text{H}_2\text{O}_2$  in safer conditions is to manage finely the hydrophilic-lipophilic balance of the reaction medium. In such context, in 1998, Venturello *et al.* published the oxidative cleavage of alkenes to carboxylic acids using 40% w/v aqueous hydrogen peroxide solution in the presence of methyltriocetylammmoniumtetrakis(oxodiperoxotungsto)-phosphate<sup>(3-)</sup> **61** as the catalyst (1-1.2%) in biphasic solvent-free medium at 85 °C for 5-7 h [54] (Figure 3). This catalytic system was applied for various alkenes including styrene, cycloalkenes and oleic acid with good efficiency.



**Figure 3.** Methyltriocetylammmonium tetrakis(oxodiperoxotungsto)phosphate<sup>(3-)</sup> **61**.

Notably, in this report, important data related to the nature of medium and long chain substrates, *i.e.* for linear alkenes with at least 8 carbon atoms on the selectivity of the transformation were given. Additionally, two main reaction pathways leading to carboxylic acids have been proposed, the first one involving a hydrolysis and the second one a perhydrolysis of the epoxide initially formed from the alkene (Scheme 30). The occurrence of the latter pathway has been proven by the isolation of intermediates HPAs and their transformation into acids.

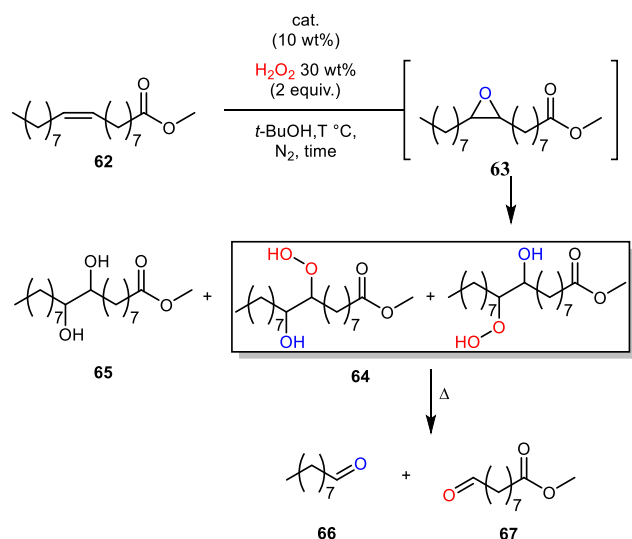


**Scheme 30.** Oxidative cleavage of medium and long chain olefins to carboxylic acids with hydrogen peroxide under two-phase conditions highlighting the course of the reaction with HPAs.



Thus, the concentration of hydrogen peroxide, the lipophilicity of the epoxide and the nature of the catalyst were the three main factors governing the reaction selectivity. The influence of the concentration of hydrogen peroxide is easily understood with regard to the perhydrolytic pathway, since the  $\text{H}_2\text{O}_2$  activity as a nucleophile in the opening of epoxides depended on its concentration. The lipophilicity of the substrate, in the perhydrolytic route was logically favoured for medium and long chain substrates since these are, by nature, more hydrophobic and therefore less subject to hydrolysis. Finally, the choice of the acid catalyst appeared also to be a very important factor since it must be able to promote a significant Brønsted acidity. In addition, its ability to form peroxo complexes appeared to directly influence the HPA formation *versus* the vicinal diol one.

Similarly, Benessere *et al.* have reported the direct oxidation of a highly lipophilic substrate, oleic acid, using an excess of 30%  $\text{H}_2\text{O}_2$  (2 or 4 equiv.) in the presence of tungstic acid (1 mol%) [61]. After 2 or 4 hours at 70 °C, the HPA and 1,2-diol were obtained, respectively in 43-45% and 47-45% NMR yields. Under these conditions, the competitive epoxidation of oleic acid by the formed HPA, with the concomitant production of vicinal diol, could occur, as described by Mattucci *et al.* [102], which could explain these modest HPA yields. The reaction temperature could also be identified as a detrimental factor as shown in the Mitsui's patent dealing with the synthesis of HPAs from methyl oleate **62** under very similar conditions (Scheme 31) [60] and their decomposition into aldehydes.

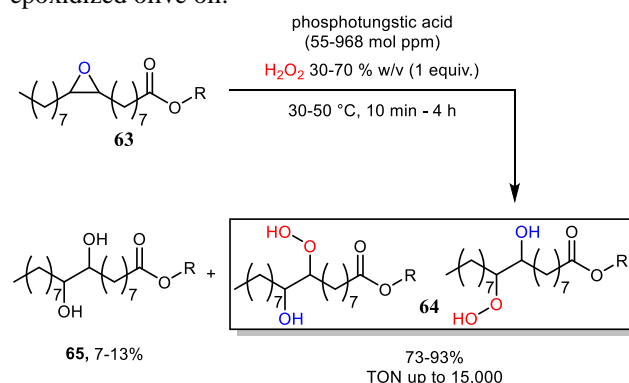


cat.	T °C	t (h)	conv. <b>62</b> (%)	<b>64</b> (%)	<b>65</b> (%)
$\text{H}_2\text{WO}_4$	35	5 h	75	50	13
$\text{H}_2\text{WO}_4$	70	1 h	>99	37	24
$\text{MoO}_3$	35	5 h	23	8	5
$\text{H}_3\text{PMo}_{12}\text{O}_{40}$	35	5 h	21	13	5
$\text{H}_2\text{MoO}_4$	35	5 h	11	4	5

**Scheme 31.** Synthesis of HPAs as key intermediates for the production of aldehydes.

The reaction had to be conducted at temperatures between 10 and 50 °C in order to suppress diol production. Indeed, when the reaction was performed at 35 °C for 5 h in the presence of 12 mol% (10 wt%) of tungstic acid in *t*-BuOH, 75% conversion of **62** was observed and the HPA **64** was produced in 50% with 13% of diol **65**. When conducting the reaction at 70 °C for 1 h, even if full conversion was observed, the selectivity decreased as only 37% of HPA **64** was detected with higher amount of diol **65** (24%), which clearly demonstrated that a high temperature was harmful for the selective formation of HPAs. Noticeably, tungstic acid was more reactive than  $\text{MoO}_3$  or  $\text{H}_3\text{PMo}_{12}\text{O}_{40}$  in such conditions.

In our group, within the framework of our research aiming at the development of an industrial process based on the perhydrolysis of epoxidized fatty derivatives (triglycerides, free acids or esters derivatives), the analyses and the optimizations of all these factors allowed us to develop a process with high efficiency, as illustrated by the unprecedented TON obtained (up to 15,000) [124,125] (Scheme 32). Indeed, performing the reaction at 50 °C for 70 minutes using 112 ppm of phosphotungstic acid in the presence of 1 equiv. of 60%  $\text{H}_2\text{O}_2$  aqueous solution, methyl 9,10-epoxystearate **63** led to 93% of HPA **64** and 7% of diol **65**. Noticeably, these conditions could be applied to epoxidized olive oil.



**Scheme 32.** Efficient perhydrolysis of epoxidized fatty acid derivatives according to patent application WO2020169932A1 [125].

The catalytic loading of this solvent-free methodology using equimolar amount of commercial aqueous solution of hydrogen peroxide turned out to be an important factor. Indeed, a low loading allowed a significant gain in HPA selectivity. This was probably due to a reduction of the acid-catalysed decomposition of HPA.

Noticeably, Duguet *et al.* reported very recently similar results using 0.1 mol% of PTA in the presence of 1.1 equiv. of 50%  $\text{H}_2\text{O}_2$  aqueous solution in *t*-amyl alcohol at 10 °C for 16 h and exemplified the reaction on several fatty epoxides derived from methyl oleate, linoleate or ricinoleate, yielding the corresponding HPAs in 20-80% yields [62].

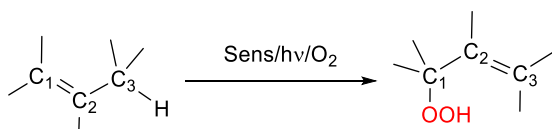
#### 4. From allylic alcohols to $\beta$ -hydroperoxy alcohols

The selective synthesis of  $\beta$ -hydroperoxy alcohols can be also achieved by regio- and diastereoselective photo-oxygenations of allylic alcohols, in particular with singlet oxygen. Such pathways are usually more efficient processes for the selective synthesis of HPAs, and will be highlighted in this section.

#### 4.1. Photo-oxygenation of allylic alcohols

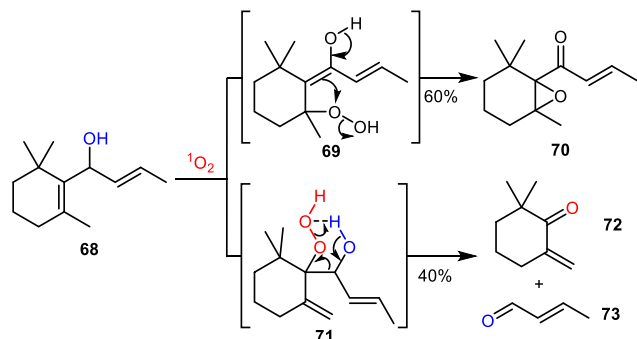
Photo-oxygenation processes are classified as different three types depending on the mechanism involved [126,127]: Type I for radical-induced oxygenation (with triplet oxygen as the transfer reagent), type II for energy-transfer oxygenation (with singlet excited oxygen as the reagent), and more scarcely encountered type III for electron-transfer oxygenation [128] (with triplet oxygen or with a superoxide anion radical as reagent).

The photooxygenation of alkenes containing at least one allylic hydrogen with singlet oxygen usually followed a type II mechanism, yielding the corresponding allylic hydroperoxide resulting from the shift of the double bond (Scheme 33).



**Scheme 33.** Mechanism of the ene reaction between singlet oxygen and olefins.

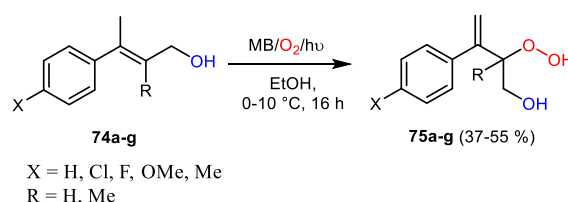
Since its discovery by Schenck in 1948 [129], this reaction has been widely used and starting from allylic alcohols, the HPA motif could be generated via the reaction with triplet oxygen from air as the reagent in the presence of an energy-transfer sensitizer (sens) (e.g. natural porphyrins or xanthene dyes) under sunlight. Photooxygenation of allylic alcohols was first studied soon after the discovery of Schenck but initially the isolation of stable HPAs was not reported [130–132]. Noticeably, Ohloff *et al.* reported the first formation of the HPA derivative during their studies on type II photooxygenation of  $\beta$ -damascol **68** (Scheme 34) [130,132].



**Scheme 34.** Type II photooxygenation of  $\beta$ -damascol **68**. By treatment of  $\beta$ -damascol with singlet oxygen, a 3:2 mixture of  $\alpha,\beta$ -epoxyketone **70** and the  $\alpha$ -methylene ketone **72**, was obtained in addition to crotonaldehyde **73**.

Noticeably, HPA **71** was stable at 0 °C, but decomposed at room temperature leading to the corresponding carbonyl derivatives, **72** and **73**. For steric reasons, the access of the singlet oxygen to the upper side of the double bond was difficult, which explained why the yield of **72** only reached 40% and why the main product was the epoxide **70**, formed via **69**.

The first work concerning the efficient preparation and isolation of HPAs obtained by allylic alcohol photooxygenation was carried out by Singh in 1990 [133] with the aim of synthesizing 1,2,4-trioxanes [134–135]. Allylic alcohols such as 3-aryl-2-butenols **74a-g** were particularly targeted as the presence of an aryl group in position 3 of the allylic alcohols should favour the regiospecific formation of the HPAs **75a-g** (Scheme 35).



**Scheme 35.** Methylene blue (MB)-sensitized photooxygenation of 3-aryl-2-butenols **74a-g**.

Thus, the reactions were carried out in ethanol under air in the presence of methylene blue (MB) as photosensitizer at a temperature between 0 and 10 °C for 16 h (Scheme 35). Under these conditions, HPAs **75a-g** were obtained in 37–55% yields after purification by silica gel chromatography and crystallization.

Additionally, due to the remarkably high regioselectivity of the singlet oxygen ene reaction with allylic alcohols, the regio- and diastereoselective photooxygenation of chiral allylic alcohols, in which the hydroxyl group acts as a directing group, was firstly reported by Adam *et al.* [136–137]. Thus, starting from chiral allylic alcohols **76**, by reaction of oxygen in the presence of tetraphenylporphine in CCl<sub>4</sub> under a 150-W sodium lamp irradiation at 0 °C, the corresponding HPA **77** were obtained regio- and diastereoselectively (up to >97:<3 and 95:5, respectively). (Table 1).

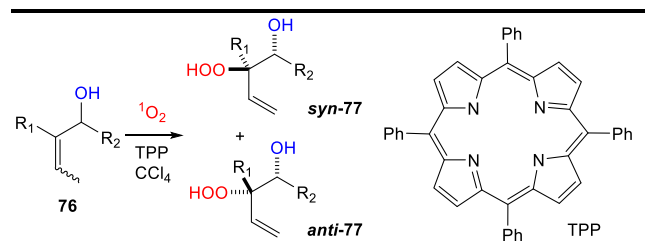
These results demonstrated that (i) (*Z*)-chiral allylic alcohols led to excellent diastereoselectivities in favour of the *syn* compound whereas (*E*) isomer led to poor *syn:anti* selectivity and (ii) that the steric effect of the aliphatic substituent attached to the stereogenic center did not influence the diastereoselectivity (entries 1–4, Table 1). Such observations seemed to confirm that the steric control and the 1,2-allylic steric strain had a weak influence on the diastereoselectivity, unlike the 1,3-allylic one (entries 1, 5–7, Table 1).

In a mechanism point of view, the interaction of singlet oxygen with the hydroxyl group in the most stable conformer, *i.e.*, not destabilized by the 1,3-allylic strain, selectively directed the approach of the electrophilic singlet



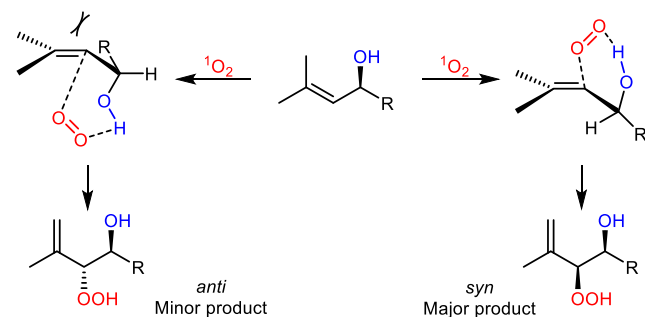
oxygen to one side of the double bond as shown in Scheme 36 providing stereoselectively the *syn* HPAs. Noticeably, the diastereoselectivity of this reaction was higher in non-polar solvents such as chloroform, dichloromethane or tetrachloromethane.

**Table 1.** Diastereoselectivity in the photooxygenation of chiral allylic alcohols.



Entry	76 Conf.	R <sub>1</sub> , R <sub>2</sub>	Yield (%)	<i>syn:anti</i>
1	(Z)	H, Me	73	93:7
2	(Z)	H, Et	92	94:6
3	(Z)	H, <i>i</i> Pr	85	94:6
4	(Z)	H, <i>t</i> Bu	79	95:5
5	(E)	H, Me	NC <sup>[a]</sup>	54:46
6	(Z)	Me, Me	92	93:7
7	(E)	Me, Me	55	66:34

<sup>[a]</sup> Not communicated in the article.



**Scheme 36.** Hydroxy-directed regio- and diastereoselective ene reaction of singlet oxygen with chiral allylic alcohols.

This regio- and diastereoselective photo-oxygenation of chiral allylic alcohols [138,139] has been extended to ester [140] or ether [141] functionalized allylic alcohols, and was applied for the synthesis of 1,2,4-trioxanes [21,142]. Noticeably, this transformation could be performed with allylic alcohols bearing di-, tri- and tetra-substituted (Z)-C=C with a vicinal substituent at the stereogenic centre. Additionally, photo-oxygenation of chiral allylic alcohols can be also performed in micro-emulsions [143] or on PS-DVB polymer matrix doped with adsorbed porphyrin sensitizers [21].

This reaction could be performed using several photosensitizers. Apart from the most widely used tetraphenylporphyrin [21,24,27,33,36,37,142b,144], a fluorinated derivative of porphyrin, 5,10,15,20-tetrakis-(hepta-fluoropropyl)porphyrin [145,146], and methylene

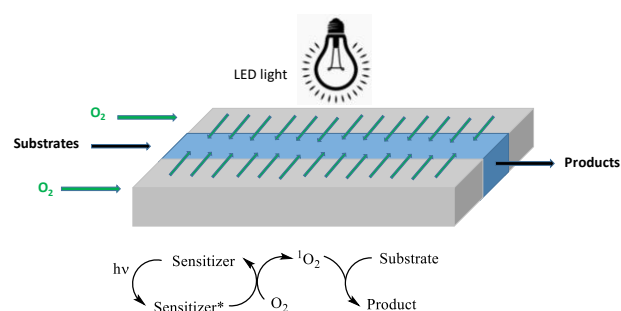
blue under homogeneous conditions [20,147–149] or incorporated in zeolite [150] were reported.

Despite the advantages of this procedure, condensed phase photo-oxygenation conditions suffered from at least five major disadvantages as reported by Griesbeck [151]:

- (i) dyes have to be soluble in the reaction mixture which is limiting the use dye-solvent combinations,
- (ii) the dye extraction from the crude mixture is often carried out by chromatography which is an important constraint in an industrial point of view,
- (iii) singlet oxygen exhibits the longest lifetime in toxic solvents such as halogenated ones (e.g. CCl<sub>4</sub>, freons, perfluorohydrocarbons) [152,153],
- (iv) in halogenated solvents, dye photobleaching often happens especially when long reaction times are required [145], and
- (v) solution purging with pure oxygen is a main drawback in both industry and laboratory.

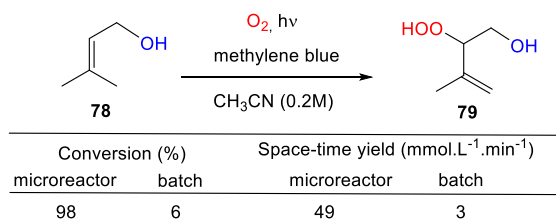
Noticeably, since the beginning of this millennium, notable progresses on the efficiency of type II photo-oxygenation were performed by Griesbeck *et al.* in the solid phase polymer matrix [29,32,142b,154–157].

When performing photo-oxygenations in classical vessels, the restricted spatial illumination is one of the main drawbacks which explains the long reaction times observed. Additionally, the reaction efficiency is mainly disfavoured by the low interfacial area between the oxygen and the reaction mixture and the long molecular diffusion distances. In order to obtain a more efficient process, Kim *et al.* introduced the concept of triple-channel micro-reactors applied to photo-oxygenation [158] (Figure 4). These reactors were based on continuous-flow processing, large gas-liquid interfacial area, short molecular diffusion distances, and very high surface illumination homogeneity.



**Figure 4.** Photosensitized oxygenation in a triple-channel micro-reactor [158].

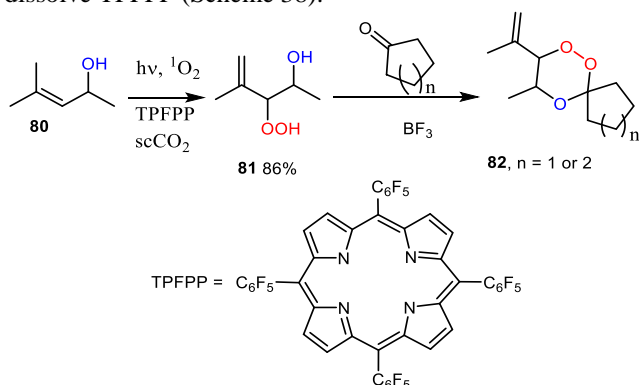
The efficiency of the methylene blue photosensitized oxygenations of allylic alcohols such as **78** using the triple-channel micro-reactor was demonstrated over the classical batch reactions (Scheme 37).



**Scheme 37.** Photo-oxygenation of allylic alcohols: triple-channel micro-reactor in comparison to the batch reactor.

Space-time yield (STY) = mmol of products/(Reactor volume × time).

Another very promising route to HPAs by photo-oxygenation of allyl alcohols without the aforementioned disadvantages was described in 2013 by Poliakov, George *et al.* [31]. In order to avoid managing problems during scale-up steps related to the high reactivity of <sup>1</sup>O<sub>2</sub>, and its quenching with solvents, the selection of the appropriate industrially acceptable non-flammable solvents was crucial. Thus, using perfluorinated photosensitiser (5,10,15,20-tetrakis-(pentafluorophenyl)porphyrin, TPFPP), photo-oxidation could be conducted continuously in scCO<sub>2</sub>, as a non-toxic and non-flammable reaction medium used close to ambient temperature (40 °C) [159–161]. The photo-oxidation proceeded faster in scCO<sub>2</sub> than in conventional solvents, probably because (i) the reaction was conducted in a single phase conditions as gaseous O<sub>2</sub> and scCO<sub>2</sub> (6% O<sub>2</sub> in CO<sub>2</sub>) were fully miscible, and (ii) the relatively long lifetime of <sup>1</sup>O<sub>2</sub> in CO<sub>2</sub> (5.1 ms at 14.7 MPa, 314 K, *vs* 59 ms for CCl<sub>4</sub>) [162,163]. Thus, using a flow system with a reduced reactor volume, a cyclic ketone was necessary for obtaining the target 1,2,4-trioxanes **82**, via the formation of the intermediate HPA **81** in a maximum of 86% yield. Noticeably the cyclic ketone acted as a suitable co-solvent to dissolve TPFPP (Scheme 38).



**Scheme 38.** Photo-oxidation of allylic alcohol **80** in scCO<sub>2</sub>.

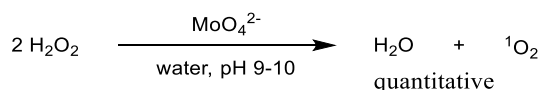
This part highlighted that photo-oxygenation of allylic alcohols is an elegant and efficient method for the synthesis of HPAs. However, photo-oxygenation in a large-scale production prospect with conventional solvents is still problematic: (i) the combination of organic compounds, pure oxygen, and light can lead to serious safety issues, (ii) lamps wearing and the progressive opacification of the photo-reactor's walls with organic deposits necessitate to adjust the

irradiation time in order to guarantee a constant conversion rate of the substrate, and (iii) photo-reactors suffer from a lack of economy of scale and are rarely available in a multipurpose chemical plant. These limitations have prompted researchers to develop methods in which the generation of singlet oxygen is not photo-induced.

## 4.2. Chemical generation of singlet oxygen

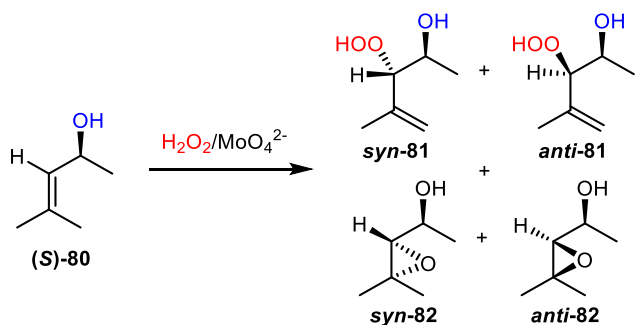
Another route to achieve the transformation of allylic alcohols into HPAs can involve singlet oxygen generated chemically [164]. In contrast, these techniques have been used mainly in mechanistic studies but more scarcely in organic synthesis. Indeed, the use of highly oxidizing inorganic agents (e.g. ClO<sup>-</sup>, BrO<sup>-</sup>) which can cause side reactions, or of organic sources such as phosphite ozonide [165] or polycyclic aromatic endoperoxides [166] which required prior preparation is the main limitation for their easy utilizations. A more significant drawback is the use of stoichiometric amount of such reagents thus generating large amounts of waste.

However, if the quantitative generation of singlet oxygen can be performed using a catalytic amount of a singlet oxygen promotor in a mild and convenient method, this chemically generated <sup>1</sup>O<sub>2</sub> can become useful in synthesis. Indeed, the disproportionation of hydrogen peroxide is promoted catalytically by sodium molybdate in alkaline aqueous medium with or without polar solvents such as methanol (Scheme 39) [167]. Noticeably, such pathway for the production of singlet oxygen was already used in an industrial scale, for example for the manufacture of rose oxide from β-citronellol by DSM [168,169]. On the other hand, it is important to underline that this reaction is exothermic and can easily lead to a thermal runaway which would obviously become problematic on a very large scale without special precautions.



**Scheme 39.** Singlet oxygen generation from H<sub>2</sub>O<sub>2</sub>/MoO<sub>4</sub><sup>2-</sup>.

First reports dealing with HPA synthesis from allylic alcohols and chemically generated <sup>1</sup>O<sub>2</sub> in micro-emulsions have been reported [143] and patented [170] by Nardello, Aubry, *et al.* Thus, reactions with allylic alcohols such as (S)-4-methylpent-3-en-2-ol (**S**)-**80** were performed in several reaction media (e.g., water, organic solvents, water-in-oil micro-emulsions (W/O)). Notably, the use of such micro-emulsions should restrict the direct interaction between allylic alcohol (**S**)-**80** and peroxomolybdate intermediates and thus minimized its epoxidation (Scheme 40).



**Scheme 40.** Chemical oxidation of (S)-4-methylpent-3-en-2-ol **80**.

The use of W/O micro-emulsions, prepared from sodium dodecylsulfate as surfactant, ethanol or *n*-butanol as co-surfactant, and dichloromethane or tetrachloromethane as continuous organic phase, formed HPAs as the major products in addition to epoxides (Table 2). The  $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$  system in micro-emulsions allows to generate singlet oxygen in short reaction times, without specific photochemical equipment. However, the major disadvantage of this system is the lack of chemoselectivity due to the formation of epoxides. Moreover, in comparison to the photo-generated singlet oxygen, the stereoselectivity *syn/anti* is lower.

**Table 2.** Comparison of the chemo- and diastereoselectivity of HPA formation by photo-chemically and chemically generated  $^1\text{O}_2$ .

Entry	$\text{R}_1, \text{R}_2, \text{R}_3$	$\text{O}_2/\text{sens}/\text{hv}^{[a]}$	$\text{H}_2\text{O}_2/\text{MoO}_4^{2- [b]}$	
		<i>syn/anti</i> (HPA)	HPA: epoxide	<i>syn/anti</i> (HPA)
1	Me, Me, H	94:6	83:17	85:15
2	H, Me, Me	88:12	89:11	86:14
3	Me, H, Me	61:39	95:5	50:50
4	Me, Me, Me	94:6	>95:<5	78:22

<sup>[a]</sup>  $\text{CDCl}_3$ , tetraphenylporphine (TPP) as sensitizer. <sup>[b]</sup> substrate (2.50 mmol),  $\text{MoO}_4^{2-}$  (0.245 mmol), 25 °C. The micro-emulsion is composed of  $\text{CH}_2\text{Cl}_2$ ,  $\text{D}_2\text{O}$ , EtOH, and SDS in the proportions 74.8:6.2:9.5:9.5 (wt %).

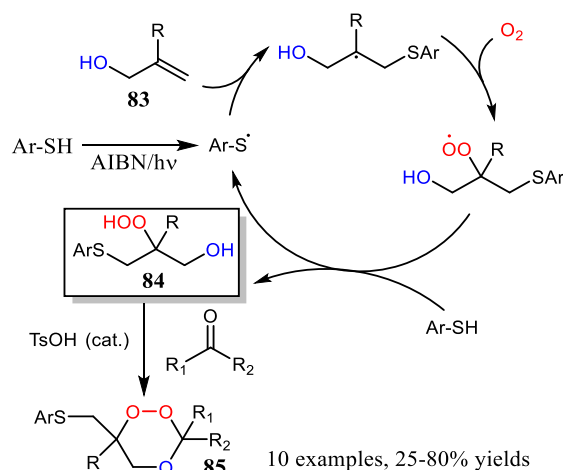
To overcome this limitation, Jacobs *et al.* have developed a similar procedure by performing hydrogen peroxide disproportionation with lanthanum(III) ions incorporated into some zeolites (2.5% wt La) [171]. The reaction was then more chemoselective because La-peroxo species themselves were poor oxidants. In addition, the incorporation of La(III) ions in zeolite was crucial for the efficiency of the singlet oxygen generation in order to avoid the appearance of a dense La-oxo/hydroxo precipitate leading to mass transfer limitations, and reducing the efficiency of the system compared to the use of molybdate ions. As a representative example, the reaction of 4-methyl-3-pentenol **80** in the

presence of 10 equiv. of  $\text{H}_2\text{O}_2$  (50%) at 40 °C for 24 h led specifically to HPA **81** in 51% conversion with a 76:24 *syn/anti* ratio.

Although the chemical generation of singlet oxygen seems easier to transpose to existing production units compared to photo-induced singlet oxygen generation, significant constraints remain associated with this process: (i) an exotherm which can be important during the hydrogen peroxide disproportionation, (ii) micro-emulsions are relatively complex reaction mixtures as they require water, an organic solvent, a surfactant and a co-surfactant, (iii) thermodynamic properties of micro-emulsions limit the amounts of hydrogen peroxide that can be used without phase separation, and (iv) the product recovery is somewhat tedious. Furthermore, the weakness of both photochemical and chemical singlet oxygen pathways is the singlet oxygen generation itself. A solution to overcome this drawback should be therefore to directly perform the reaction of allylic alcohols with natural triplet oxygen.

#### 4.3. Thio-olefin co-oxygenation (TOCO) of substituted allylic alcohols

In the aim to synthesize new anti-malarial derivatives incorporating peroxo motifs, new methodologies to create peroxide bridges were developed from allylic alcohols and oxygen, via HPA formation. Indeed, thiol-olefin co-oxygenation (TOCO) of substituted allylic alcohols **83** led to HPA **84** that can be then condensed *in-situ* with various ketones to afford a series of functionalized 1,2,4-trioxanes **85** in 25-80% yields by a simple one-pot procedure. Allylic alcohols reacted with arylthio in the presence of AIBN as activator under pure oxygen atmosphere under UV irradiation at 0 °C in order to prevent its thermal activation [16] (Scheme 41).



**Scheme 41.** Application of TOCO methodology to HPA generation for a new synthesis of the 1,2,4-trioxanes.

In this transformation, a phenylthiyl radical was first generated from thiophenol by reaction with AIBN under  $\text{h}\nu$  conditions. The phenylthiyl then attacked the C=C bond of the allylic alcohol following a Markovnikov selectivity, thus

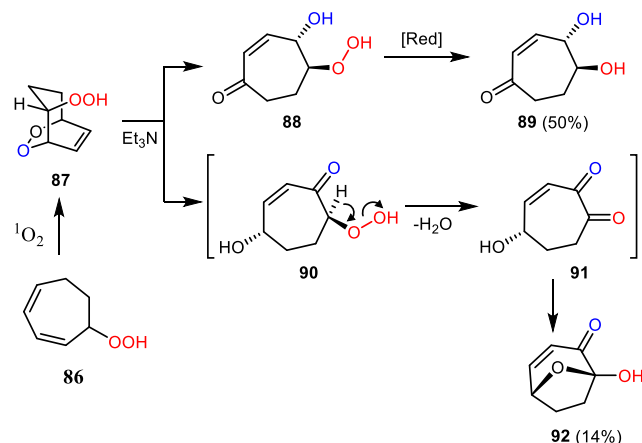
leading to a tertiary carbon radical intermediate which could be trapped by triplet oxygen. The obtained peroxy radical could perform a radical hydrogen abstraction from thiophenol giving HPA and regenerating phenylthiyl radical. However, although this article demonstrated the possibility to obtain HPAs *via* the TOCO type reaction, none of them were isolated.

## 5. Miscellaneous methods

Apart alkenes, epoxides or allylic alcohols, other starting materials have also been used for the synthesis of HPA, namely  $\beta$ -hydroperoxy alkylperoxides and vicinal diols.

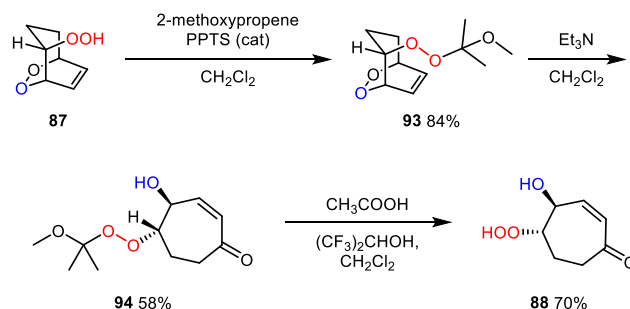
### 5.1. Kornblum-DeLaMare rearrangement of $\beta$ -hydroperoxy alkylperoxides

In 2012, Salomon *et al.* synthesized  $\beta$ -hydroperoxy alcohols using a base-catalysed disproportionation of an hydroperoxy endoperoxide [56] *via* the Kornblum-DeLaMare rearrangement [172] of  $\beta$ -hydroperoxy alkylperoxides such as **87**, obtained by singlet oxygenation of the corresponding hydroperoxy diene [173] (e.g. **86**). The disproportionation of the endoperoxide **87** was expected to produce  $\beta$ - and  $\gamma$ -hydroxyhydroperoxides **88** and **90** (Scheme 42). However, using bases such as triethylamine to catalyse the isomerization of endoperoxide **87**, no HPA was isolated, but the product resulting from their decomposition, ketodiols **89** and a bicyclic hydroxydione hemiacetal **92**, were isolated in 50 and 14% yields, respectively.



**Scheme 42.** Triethylamine-catalysed disproportionation of the endoperoxide **87**.

In order to prepare selectively the HPA **88**, before the catalysed isomerization, hydroperoxy endoperoxide **87** was first protected by an acid-catalysed treatment with 2-methoxypropene leading to methoxyisopropyl derivative **93** in 84% yield. The triethylamine catalysed isomerization of **93** then generated **94** in 58% yield and the cyclic hydroxydione hemiacetal **92** in 13% yield. Then, the deprotection of **94** under mild acidic conditions led to HPA **88** in 70% isolated yield (Scheme 43).

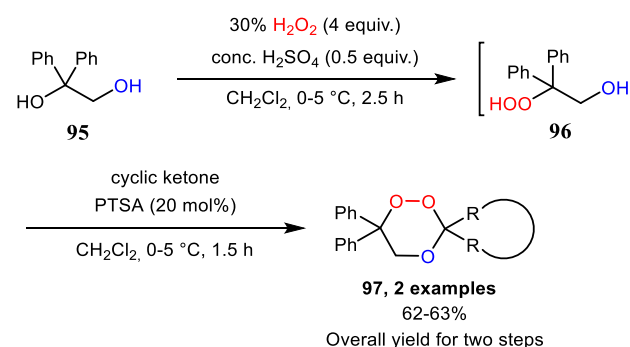


**Scheme 43.** HPA formation from endoperoxide **87** involving protection-deprotection methodology.

This protocol constitutes one of the scarce examples of synthesis of HPAs *via* a Kornblum-DeLaMare rearrangement of  $\beta$ -hydroperoxy alkylperoxides.

### 5.2. H<sub>2</sub>O<sub>2</sub>-mediated reaction of carbinols in acidic conditions

In order to prepare 1,2,4-trioxanes from different carbinols bearing cyclopropyl and phenyl substituents, Yadav *et al.* have developed a methodology *via* the formation of HPA intermediates [18]. Based on a previous report on the H<sub>2</sub>SO<sub>4</sub> catalysed reaction of 30% H<sub>2</sub>O<sub>2</sub> with cyclopropyl-substituted alcohols leading to cyclopropyl-substituted hydroperoxides [174], 1,1-diphenyl-1,3-propanediol **95** was used to prepare *in situ*, the corresponding hydroperoxides **96**, used for the synthesis of 1,2,4-trioxanes **97** (Scheme 44). Noticeably, this methodology seems to be restricted to substrates forming a highly stabilized carbocation such as diphenyl-substituted diols or cyclopropyl-substituted alcohols.

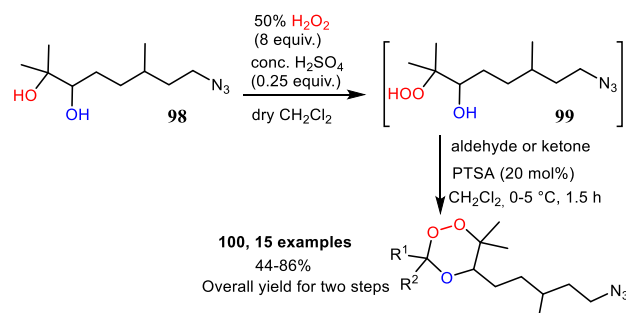


**Scheme 44.** Synthesis of HPAs from 30% H<sub>2</sub>O<sub>2</sub> mediated reaction of vicinal diol in acidic conditions.

However, other substrates lacking such substituents have also been used successfully. Indeed, recently, Das, Bez *et al.* optimized this methodology by treating 8-azido-2,6-dimethyloctane-2,3-diol **98** with 50% H<sub>2</sub>O<sub>2</sub> (8 equiv.), conc. H<sub>2</sub>SO<sub>4</sub> (0.25 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> to form *in situ* HPA **99** which upon treatment with aldehydes or ketones in the presence of *p*-TsOH yielded the corresponding 1,2,4-trioxane derivatives **100** in inseparable diastereoisomeric mixtures in 44-86% overall yields [175] (Scheme 45). Noticeably, the azido group can be tolerated under these



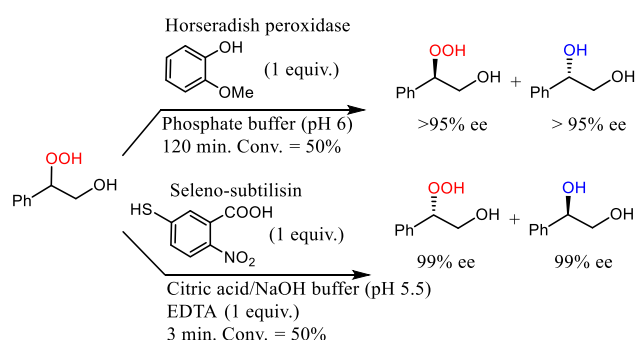
conditions, and then permitted to the synthesis of 1,2,3-triazole linker.



**Scheme 45.** Synthesis of HPAs from azido substituted 1,2-diol.

## 6. Towards optically active HPAs

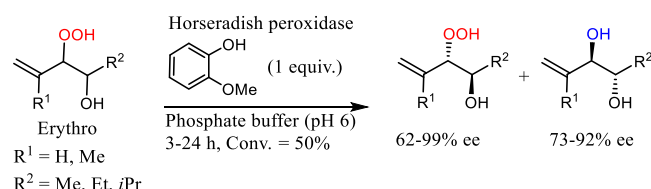
One of the most impressive applications of  $\beta$ -hydroxy hydroperoxides being the preparation of 1,2,4-trioxanes, notably for the synthesis of natural chiral compounds, the efficient preparation of optically active HPAs is then an important goal which stimulated the group of Adam. Based on pioneering contribution dealing with enzymatic technologies of synthesis of optically active hydroperoxides based on kinetic resolution via a stereoselective catalyzed reduction of the hydroperoxyl moiety to alcohol using a horseradish peroxidase (HPR) in the presence of guaiacol playing the role of sacrificial reductant, [176,177] he applied this technology for the preparation of optically active  $\beta$ -hydroxy hydroperoxides. Thus starting from racemic HPAs, a mixture of (*R*)-HPA (>95% ee) and (*S*)-diol (> 95% ee) was obtained at 50% conversion, with high enantiomeric excesses (> 95% for each product).[177] (Scheme 46)



**Scheme 46.** Preparation of optically active HPAs by kinetic resolution via enzymatic catalyzed reduction of racemic HPAs

Noticeably, using peroxidase active seleno-subtilisin, derived from serine protease subtilisin, similar reaction could be performed efficiently in a short reaction time (2 min.) leading with excellent enantiomeric excess to the optically pure HPA but with the reverse absolute configuration.[178] Coprinus peroxidase enzyme can be also used, but with lower efficiency.[179]

The kinetic resolution technique can be also used with various chiral  $\beta$ -hydroxy hydroperoxides derived from allylic alcohols. Similarly, HPAs with enantiomeric excesses up to 99% were obtained. (Scheme 47) [180] Even if this procedure is efficient for secondary HPAs, when it is applied to tertiary ones, the obtained HPA exhibited a low enantiomeric excess (9%).[181]



**Scheme 47.** Preparation of optically active HPAs using Horseradish peroxidase

## 7. Conclusion

In conclusion, the state-of-the-art reveals that miscellaneous substrates can be applied in synthesis of the useful  $\beta$ -hydroperoxy alcohol motif, an interesting and promising chemical platform. The generation of HPAs and their purification can be very challenging due to their high reactivity and easy conversion into biologically active 1,2,4-trioxane derivatives, diols or carbonyl compounds, which also constitutes their main uses and interests.

Historically and for fundamental perspectives, radical cascade reactions involving alkenes were generally used. While they allowed the synthesis of various HPAs including natural product scaffolds or simple organic molecules, these reaction conditions involved harmful ionizing radiations or were specific to aryl alkene skeletons. Additionally, sequences involving electrophilic addition of alkenes leading to bromo-alcohols then nucleophilic substitutions seemed to be a more convenient synthetic pathway. However, the low HPA yields obtained and the large excesses of reagents required made these methodologies less attractive.

In this context, application of epoxides ring-opening using  $\text{H}_2\text{O}_2$  is more effective, especially in terms of atom economy, while it allows the use of different conditions. However, in many examples, highly concentrated or even anhydrous hydrogen peroxide was required in combination with  $\text{Et}_2\text{O}$  to obtain selectively HPAs. This prerequisite can be highly dangerous and prevents any industrialization of such process. Additionally, reaction of epoxides with alkaline hydrogen peroxide solutions allowed the use of dilute  $\text{H}_2\text{O}_2$  but generated an important amount of aqueous waste and had a fairly limited scope mainly due to the fast decomposition of HPAs into carbonyls under these conditions. Once more, the use of alkaline hydrogen peroxide can be dangerous in large scale level, even if some plants (bleach plants) use it under drastic safety conditions. Nevertheless, promising safer catalytic chemoselective perhydrolysis protocols using dilute hydrogen peroxide were developed based on a fine

control of conditions with highly lipophilic starting materials.

High chemo-, regio- and diastereoselective formation of HPAs are readily accessible by oxidation of allylic alcohols. Reported works highlighted that chemically or photo-chemically generated singlet-oxygen addition to allylic alcohols can be very efficient alternatives to other known procedures, offering milder reaction conditions. However, the main drawback of this approach is the generation of the singlet-oxygen itself, which limited these processes to the synthesis of high value-added molecule. Using triplet oxygen in a radical reaction, such as TOCO for sulphur-containing molecules, could be an alternative solution to be developed.

Other starting materials such as  $\beta$ -hydroperoxy alkylperoxides or vicinal diols can be used, but their prior synthesis and the large excesses of hydrogen peroxide required explained the scarce examples reported.

To conclude, the ever-increasing importance of peroxo-containing compounds like 1,2,4-trioxanes or high added value molecules such as aldehydes make HPA an interesting and promising chemical platform. Nevertheless, more efforts are still required in order to selectively and safely produce this useful HPA intermediate, especially for non-highly lipophilic derivatives. This review showcases the high potential of this HPA motif and may encourage organic chemists to carry out future research in this area.

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